

Exclusive Coverage of the

57th American Society of Hematology Annual Meeting and Exposition in Orlando, Florida

Changes on the Horizon for Quality Measures in Hematology

Quality Measures and Alternative Payment Models

In a session focused on quality measures in hematology and the overall effect of quality initiatives on hematology practice, Helen Burstin, MD, MPH, senior vice president for performance measures at the National Quality Forum (NQF), discussed some of the trends in quality measures. In considering quality measures and value-based remuneration, Burstin hoped to offer, in her words, “food for thought as we move forward in this new world of value-based purchasing.”

Currently, there are many limitations to implementation of quality initiatives. Among these limitations is a lack of measures applicable across various providers and settings to encourage care coordination and population health in the community, as well as the slower than anticipated rollout of information gathering via electronic health record systems.

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The Evolution of Quality Measures: A Q&A Session With Andrew Ryan, PhD, MA

In a session at the 57th American Society of Hematology Annual Meeting and Exposition in Orlando, Florida, Andrew Ryan, PhD, MA, associate professor at the School of Public Health at the University of Michigan, described his research on the effects of financial incentives on quality and cost in health care. In an exclusive interview, editors from the *American Journal of Managed Care* met with Ryan to discuss quality measures.

Q: With the Affordable Care Act (ACA), there has been a greater emphasis on quality and outcomes, as well as accountable care organizations. How is the ACA drawing attention to the issue of quality in health care?

A: I think there has been lots of attention focused on the coverage provisions in the ACA, and rightly so; however, there are major delivery system reform provisions in the ACA as

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Changes on the Horizon *(continued from page 1)*

Quality initiatives are closely linked with alternative payment models. Managed care administrators are adopting patient-centered medical homes and bundled payments as part of the move toward alternative payment models. These novel methods of care administration will be more widely implemented over time. Between 2011 and 2015, alternative payment models were used by 30% of all managed care plans, and half of all plans are expected to use these models by 2018.

Among the remaining questions is how to most effectively manage an at-risk population from acute illness management through post acute care, rehabilitation, and secondary prevention. For each of these care settings, Burstin asked, “What kinds of outcome measures could be used?” The measures will largely be related to quality of life, costs, and advanced-care planning. With respect to hematology, in each patient’s cancer journey, better transitions are required at each step of care. Palliative care and end-of-life care are key areas for quality improvement.

According to Burstin, many issues remain unsolved regarding measurement. For example, a more comprehensive set of measures that are specific to hematology is needed. Also, important questions need to be answered regarding system-level management, which is familiar and widely practiced, and more granular individual clinician-level assessment, which is more difficult to apply appropriately. Currently, a small set of system-level core measures has been developed, but specific quality measures are needed to meet the needs of different specialists in a wide variety of settings. Although a broad range of measures has been developed, most of these are applied in the disease states of leukemia and myelodysplastic syndromes. Examples of some of these quality measures are documentation of iron stores, ensuring receipt of a pathology report confirming the diagnosis, and documentation of the chemotherapeutic regimen used. NQF-developed measures in hematology are listed in the [Table¹](#).

Future hematology measures might include estimates of pain severity, lifestyle factors (eg, whether or not the patient continues to smoke), and directives related to end-of-life care. Critical in this regard is documentation of advanced directives. The patient’s pain intensity on the last 2 visits prior to death should also be documented. Hospice enrollment, the location of death, and whether or not chemo is administered in the last 2 weeks of life are additional important quality measures relevant to hematology. In the transition away from process-based quality measures toward outcome-based quality measures, quality measures may evolve to assess actual patient outcomes rather than the care a patient receives.

For instance, an outcomes-based quality measure might document the characteristics of a patient, what happened to the patient clinically, physical functioning, survival rate, and symptom control. Ultimately, these outcomes may be integrated into an overall score reflecting the quality of all care provided to a given patient at a given time. Foremost among these outcome-based measures are patient-reported outcomes, which are health status assessments obtained for a patient directly, without any interpretation. Mature tools are available for measurement of patient-reported outcomes, including the Patient-Reported Outcomes Measurement Information System (PROMIS). This set of tools enables adults and children to report outcomes that include fatigue, anxiety, depression, and physical functioning. However, many challenges remain.

Patient-reported outcomes are sometimes used in clinical trials, but this practice is not yet widespread and little is known about aggregating multiple patient-reported information sources to measure performance. Moreover, in oncology, these measures are primarily related to relief of symptoms such as pain and nausea. The limited scope of patient-reported outcome measures is another weakness in their implementation as an

Table. Hematology Measures Developed by the National Quality Forum¹

Measure #67: Myelodysplastic Syndrome	Baseline cytogenetic testing performed on bone marrow
Measure #68: Myelodysplastic Syndrome	Documentation of iron stores in patients receiving erythropoietin therapy
Measure #69: Multiple Myeloma	Treatment with bisphosphonates
Measure #70: Chronic Lymphocytic Leukemia	Baseline flow cytometry

outcomes-based quality measure. Even so, other patient-reported outcomes are more general and can be used across disease states. These include health-related quality of life, functional status, and the perceived value of treatment. Of these measures, the perceived value of treatment may be the most subjective measure of all patient-reported outcomes currently collected.²

Other challenges in measurement include persistent measurement gaps and the potential for unintended consequences of therapy. The gaps relate to standardizing performance using an overly simplistic measure. For instance, a quality measure incentivizing antibiotic use in patients suspected of having pneumonia within 4 hours of symptom onset led to many patients with congestive heart failure inappropriately receiving antibiotics. Because the symptoms of congestive heart failure exacerbations largely overlap with those of pneumonia, physicians administered antibiotics to avoid reductions in performance measure scores.

Cases where overapplication of performance measures negatively affects outcomes demonstrate the complexity of performance measurement and the need for more nuanced performance measures. “Ultimately,” noted Burstin, “performance measures are about linking cost and quality and the models clinicians use to bring those 2 things together.”

In achieving a balance of cost and quality, it is important to recognize that ideal outcomes are often not ultimately achievable in all patients, especially in hematology. It is also crucial to recognize that patient outcomes are influenced by a wide variety of factors—some that can be controlled by providers, and others that cannot. These factors have important implications for quality-based reimbursement. In quality measure design and application, patient risk factors (eg, genetics, demographics, and socioeconomic factors), as well as health-related behaviors (eg, tobacco use, diet, and attitudes toward treatment), must be taken into account. Among these, socioeconomic status is an important determinant of outcomes. As a result, hospitals and healthcare systems that provide care to patients of low socioeconomic status tend to be penalized for poor-quality outcomes more than hospitals and health care systems caring for patients with high socioeconomic status. Ultimately, this may lead to large disparities in care.

To account for this important difference, the NQF is in the process of developing socioeconomic adjustment factors that account for these disparities. However, noted Burstin, “It is important to have a conceptual basis for why disparities might exist.” For instance, for central line infection rates, there is no reason to believe that socioeconomic disparities would contribute to inferior outcomes in socioeconomically disadvantaged patients.

Along with the need to adjust for confounding factors and differences among populations in quality measurement, there is a growing need for standardization in quality measures. Many measures have been developed by multiple health plans and providers, and these measures are all slightly different. Standardization of quality measures is important, as accountable care models are becoming more commonplace. Currently, across 26 states, over 1300 measures are in use. “Even if we can clean up high-level federal measures used, there are still state-level measures to consider,” concluded Burstin. Once measures are standardized, it will also be important to integrate multiple measures into a single measure that may be compared across hospitals and health systems.

Due to the lack of standardization in these integrative measures, in some cases, hospitals may receive a very high ranking for quality under one system and a very low rating using another system. Movement toward more outcome-based quality measures will incorporate more patient-reported outcomes to measure, in Burstin’s words, “value to the patient as defined by the patient.” In addition, cost must be measured over the entire episode of care. “The intersection of these 2 variables,” added Burstin, “is the crux of the cost–quality issue.” Over time, quality measures will improve to move toward measuring the outcomes that matter the most and that are most relevant to real patient outcomes.

Pay-for-Performance: Evaluating the Evidence

Continuing with the discussion of performance measures, Andrew Ryan, PhD, MA, of the University of Michigan, reviewed the evidence supporting and refuting the use of pay-for-performance methods in optimizing care. According to Ryan, value-based purchasing in Medicare has important implications in hematology. Incentives in healthcare have an important effect on behaviors.

In one example of financial incentives driving decision making in health care, Nicholson and colleagues noted a correlation between future earning potential and residency choices. Just as earnings expectations drive career choices for physicians, financial incentives can also work to drive health systems in a desired direction. At times, these financial incentives can work counter to the benefit of patients. For instance, there are currently more than 5000 ambulatory surgical centers in the United States and an order of magnitude fewer community mental health clinics. The greater earnings potential in surgical practice versus community mental health practice is driving this trend.³

Financial incentives can also work in more subtle ways in health care. In a 2011 study, researchers reported that the likelihood of MRI scans significantly increased in practices where MRI machines were available on-site. This MRI testing may not have been driven by clinical need, but by the availability of the test. To improve the value proposition, it is important to create the right incentives.⁴

The Centers for Medicare & Medicaid Services (CMS) has been working on quality initiatives since 2003, when the agency established a hospital quality incentive demonstration program. By 2011, CMS had developed a hospital value-based purchasing and accountable care organization program; CMS continues to modify incentives to reduce costs and improve the quality of care. Value-based payment models will be assessed using 5 measures, including total per-capita costs, as well as costs related to patients with diabetes, chronic obstructive pulmonary disease, heart failure, and coronary artery disease.

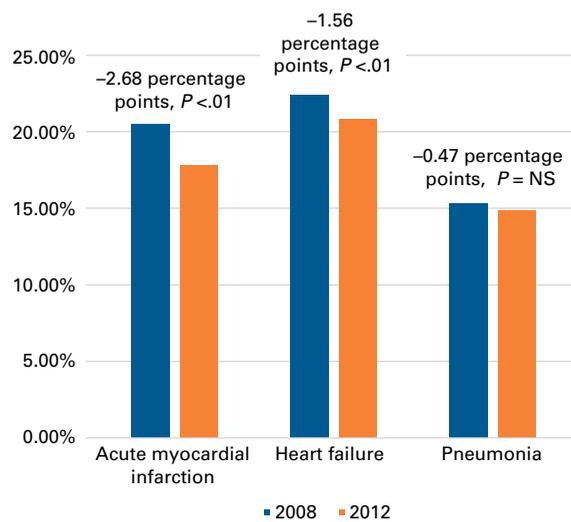
Among the most important quality measures today is the physician quality reporting system (PQRS), which uses more than 200 measures to evaluate the performance of physicians. Although most of these measures are clinical process measures rather than performance measures, the goal of PQRS is ultimately to help physicians provide the right care for the right patient at the right time. Currently, there are 4 PQRS measures related to hematology: 2 relate to myelodysplastic syndrome, 1 relates to multiple myeloma, and the last relates to leukemia. Until 2014, the PQRS program rewarded physicians for participation. CMS currently penalizes physicians who do not participate in the PQRS system.

In the PQRS program, financial incentives are determined based on cost and quality evaluations. For instance, high-quality, low-cost practices might receive a 2% increase in payments, whereas low-quality, high-cost practices would be penalized through a 1% reduction in CMS payments. These penalties are currently in place for large practices, but will soon extend to practices all over the country.

Evaluations of value-based purchasing programs have shown mixed results. Positive outcomes include increases in public reporting, such as reporting of hospital readmission rates, and reductions in 30-day readmissions following the introduction of financial incentives. Between 2008 and 2012, an analysis of Medicare data collected in New York state showed modest but significant reductions in 30-day readmission rates for acute myocardial infarction

Figure. Improvements in Selected Quality Measures Over 4 Years in New York State⁵

Reductions in 30-Day Readmissions for Selected Conditions in New York State (Medicare Data) 2008 Versus 2012



NS indicates not significant.

($P < .01$) and heart failure ($P < .05$), and a nonsignificant reduction in pneumonia-related readmissions after introduction of financial incentives (Figure⁵). Similarly, in 2007, Lindenaier and colleagues reported improvements ranging from 2.6% to 4.1% in a composite of 10 quality measures at 613 hospitals across the United States after adjustment for differences in baseline performance.⁶

Unfortunately, there are some negative aspects of quality initiatives, including the lack of a link between public reporting and outcomes improvement,⁷ attenuation of quality improvement over time, and lack of effect on mortality outcomes.^{8,9} Also, reports indicate that hospitals may send patients to observation units, rather than inpatient wards, to hide hospital readmissions and avoid penalties.⁴ This may lead to patient harm through a lack of access to an adequate level of care.

Additionally, some investigators have questioned the validity of certain performance measures. In an analysis of pressure ulcer rates as reported through claims data (used for public reporting and financial penalties) versus pressure ulcer rates based on surveillance data, there was considerable variation between the rates: 0.15% based on claims data and 2.0% based on surveillance data. This potential for variation leads many to question the validity of claims-based outcomes.¹⁰

There are also substantial concerns about unintended consequences of performance initiatives in terms of exacerbating disparities in healthcare, as hospitals caring for underserved socio-

economically disadvantaged patients tend to perform worse in readmission reduction programs than hospitals serving patients of higher socioeconomic status. By penalizing disadvantaged hospitals, these hospitals may become more disadvantaged. Notably, the NQF is developing risk-adjustment models to help take into account these differences.¹¹

In the final part of the session, Lemeneh Tefera MD, MSc, of the Department of Health and Human Services, described how changes in quality measures and incentive programs will impact clinical practice for physicians over the coming months and years. To pique the interest of the audience, Tefera stated, “In the near future, you might get a 9% bonus on your Medicare part B payments or a 9% penalty.” This change will occur as a result of legislation recently enacted known as the Medicare Act and CHIP Reauthorization Act of 2015, or MACRA.¹²

MACRA has several important effects. It repeals the 1997 sustainable growth rate law, updates physician fee schedules, and changes Medicare pay-for-performance payment rates. In addition, MACRA enacts a merit-based incentive payment system (MIPS) and incentives for participation in an alternate payment model (APM). These programs will consolidate existing disparate programs, such as the PQRS. When these programs end, physicians can choose to participate in either the MIPS or APM model. Depending on participation, a professional may receive a positive, negative, or zero payment adjustment through MIPS. A wide range of healthcare professionals are eligible for participation, including physicians, physician assistants, nurse anesthetists, nurse practitioners, and clinical nurse specialists.¹²

Through the MIPS program, these healthcare professionals will receive a composite total performance score of 0 through 100; the composite score is based on quality measures (30%), resource use measures (30%), clinical practice improvement initiatives (15%), and meaningful use of electronic health records (25%). This score will ultimately determine the payment adjustment rate of the healthcare professional. Other elements of the program will incentivize professionals to offer expanded office hours and same-day appointments.

Existing quality programs administered by CMS, including PQRS, will come to a close at the end of 2018. According to Tefera, “There has been a lot of negative feedback about some components of existing programs. [These changes] give us an opportunity to improve the programs [to provide] a better experience for providers.” One major improvement with the new program

will be elimination of duplicative reporting to different agencies. Instead, professionals will report outcomes to a single site.

With many changes in the works for quality measures and quality-based reimbursement through CMS, it is important to recognize the potential impact of these changes on the healthcare system. As the MACRA legislation is implemented, along with changes in quality measures (types and standardization), healthcare providers and systems must adapt to this fundamental shift in reimbursement policy.

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well. We have the ACO programs, which create new forms of accountability, as well as other programs throughout the sectors of care that Medicare administers—for instance, the hospital value-based purchasing program, the physician value-based pay-

ment modifier, and the Medicare advantage quality bonus program, among other programs. There are also demo projects run by Medicare. These initiatives have really accelerated the trend toward value-based care in Medicare. It is important to recognize that there are different timelines for these programs. The earliest

of these were the hospital-based programs, and now we are figuring out how to set these programs up for physicians, which is a lot more challenging given the diversity of specialties and the shorter history of measuring quality outside of primary care.

Q: Relating to adoption of quality measures for hospitals and physicians, what is your assessment of the effect of the integration of disparate systems that were introduced at different times being integrated into a single system under MACRA (the Medicare Access and CHIP [Children's Health Insurance Program] Reauthorization Act of 2015)?

A: Medicare has many different parts—part A, part B, part C—and that is how the quality improvement programs of Medicare evolved, as well. Of course, nobody thinks that having multiple disparate systems is the right way to measure and improve the overall quality of care. We want the sectors to be working in tandem toward shared goals, and the closest thing we have to that are the ACO programs right now, as well as some bundled payment programs. The idea here is that we have physicians and hospitals that are providing jointly accountable care that cuts across sectors. In essence, Medicare really has made clear that this is where they want to go. The question is how to get there. With the MACRA legislation, physicians will have to choose between participating in the MIPS stand-alone pay-for-performance program or alternative payment models. It could be much better for physicians to go the alternative payment models route. I think Medicare is really trying to have incentives that are broader and to use both carrots and sticks to get physicians to be part of alternative payment models. The way in which hospitals fit into this program is currently unclear. On the physician side, I can imagine a grand vision where everyone enters into an ACO model, and measurement is based only on what happens in that ACO, and other programs go away. I have not seen that on the hospital side. On the hospital side, there are several programs in place that are not technically related, including the hospital value-based incentives program, the hospital readmission reductions program, and the hospital-acquired condition prevention program, among others. As far as I can tell, I don't think Medicare is currently planning to integrate these programs on the hospital side, but that is something they may consider in the future.

Q: How will the consolidation of quality initiatives affect research?

A: From a research perspective, I think it is getting harder and harder to evaluate programs by themselves, and say that everything else is constant because we know that is not true. We know there are a lot of other complexities that pose challenges for researchers. Consider the example of the bundled payment

program for joint replacement that was introduced by Medicare. Instead of starting this program for all orthopedic surgeons at the same time, Medicare randomized a number of Metropolitan Service Areas (MSAs) to get the intervention early, and these MSAs will be the comparison group. This is an example of Medicare thinking thoughtfully about how we can evaluate these things in a reasonable way that benefits patients. In some ways, it is a great time to be a researcher because of all of the changes happening in the area of quality improvement, but at the same time, the complexity of evaluation is challenging. We would love help from Medicare in putting together a research-friendly implementation strategy for many of these quality initiatives.

Q: Certain current performance metrics may seem overly simplified. What progress is being made in terms of moving toward quantifiable measures that are easily measured and that physicians believe reflect actual quality of care?

A: Developing credible performance measures is a huge challenge that we face. In primary care, a handful of chronic disease performance measures are used for measuring outcomes for patients with diabetes, for example. Other performance measures relate to hypertension. We have a number of measures that people, more or less, think are reasonable, give or take the question about where the cutoffs should be. I think that it will be more of a challenge with a lot of specialty areas of practice. Medicare is trying to implement quality measures for everyone, and many specialties do not have that same history of performance measurement and accountability as primary care. Part of Medicare's effort to expand these programs is to invest in the development of appropriate measures; however, if these measures could easily be developed, they probably would have been developed already. It is very difficult to measure quality in some of these specialty areas. I am very interested in patient-reported outcomes. I think we can go a long way with these measures, but I do foresee some real problems with a lot of these measures applying to specialists. Patient-reported outcomes may be a stronger signal of patients' real response to care.

Q: There are a few measures that involve patient-reported outcomes, and the FDA is now getting involved in collecting patient-reported outcomes data in clinical trials. Is hematology a well-suited area for patient-reported outcomes?

A: The areas of care that are calling out for patient-reported outcomes are those where symptom management, pain level, and functional status are crucial. I think that relates to a lot of what hematologists do. Patient-reported outcomes may also be well suited to measuring the quality of care in orthopedics, where pain level

and functional status are important. I think there are a lot of areas of care that are well-suited to patient-reported outcomes data.

Q: What are your thoughts on the future of quality improvement programs?

A: I think that we are piecing together the effects of pay-for-performance, one study at a time. But, where do we see this actually working? Overall, the results from pay-for-performance programs are not that encouraging. However, ACO programs in Massachusetts are reporting that the Alternative Quality Contract actually improved quality of care, so that may be one of the most promising examples. The individual, practice-level per-

formance measures may be less likely to succeed. It is possible that ACO-level incentives will be an important part of the future of performance measures. Hospital readmission reduction programs that include financial penalties for hospitals are likely going to be important, as well. These are some examples of what can work, but we still don't have all the answers in terms of optimizing programs. It is always a work in progress. We need to constantly reanalyze our programs, ask what we can take out of these programs, and think more broadly about the design of quality-improvement programs. A lot of ongoing adjustment and detective work is required, but I think we are finally starting to see some glimmers of hope of which programs are going to work in the future. ●

Ixazomib in Combination With Lenalidomide and Dexamethasone Background Therapy Improves Progression-Free Survival Across Cytogenetic Risk Groups in Patients With Multiple Myeloma

In a session focused on the treatment of multiple myeloma (MM), Philippe Moreau, MD, of University Hospital in Nantes, France, discussed the results of the TOURMALINE-MM study, which evaluated ixazomib or placebo in combination with a background regimen of lenalidomide and dexamethasone. Based on the results of this study, the FDA approved the novel, oral proteasome inhibitor ixazomib (Ninlaro); when used in combination with other agents, ixazomib provides clini-

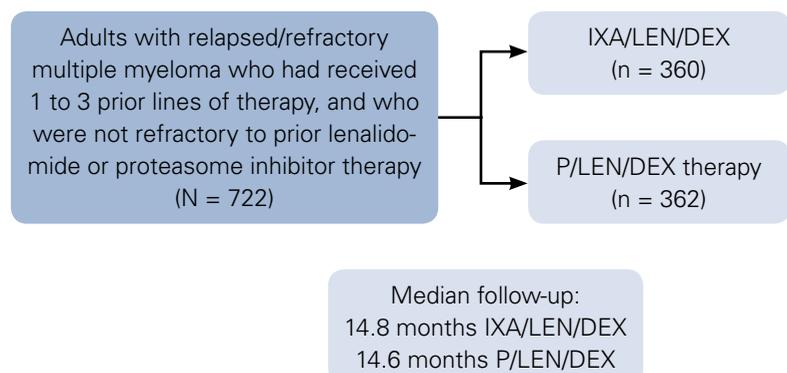
cians with an oral proteasome inhibitor-based combination therapy option for patients with MM.

Over the past 15 years, with the introduction of proteasome inhibitors and immunomodulatory drugs, treatment patterns have shifted toward combination therapy, with a backbone agent of proteasome inhibitors. Ixazomib, the first oral proteasome inhibitor, is distinct both in chemical structure and pharmacology from the injectable proteasome inhibitor bortezomib.

In early phase studies of ixazomib with lenalidomide and dexamethasone in patients with newly diagnosed MM, researchers noted a 92% overall response rate, with a tolerable and manageable safety profile enabling long-term therapy. In the TOURMALINE-MM1 trial, a total of 722 patients were randomized to receive lenalidomide and dexamethasone plus ixazomib or placebo (Figure 1¹). Patients were stratified by prior therapy and disease status. In this trial, the primary end point was progression-free survival (PFS), with secondary end points of overall survival (OS) in the entire population and OS in a subgroup of patients with negative cytogenetic markers, such as del17p and translocation 4:14.

Patients included in the study were required to have a confirmed diagnosis of MM. Eligible patients had relapsed and refractory disease. Researchers chose not to exclude patients with mild to moderate renal impair-

Figure 1. TOURMALINE-MM1 Trial Design¹



DEX indicates dexamethasone; IXA, ixazomib; LEN, lenalidomide; P, placebo; PFS, progression-free survival.

ment to improve the real-world applicability of study results. All patients with a creatinine clearance of 30 mL/min or higher were eligible to receive medication. This is an important study design choice, as many patients with MM have renal impairment.

Across the 722 enrolled patients receiving treatment at centers in 26 countries, patient characteristics were well balanced. Of note, in both treatment arms, more than half of patients (59%) had received at least 1 prior line of therapy at the time of study initiation. Furthermore, more than two-thirds (69%) of patients in each treatment arm had previously been exposed to bortezomib therapy, and more than half of patients had previously received a stem cell transplant.

On the primary end point of PFS, patients receiving ixazomib, lenalidomide, and dexamethasone experienced a progression-free interval of 20.6 months, versus 14.7 months for patients receiving placebo plus lenalidomide and dexamethasone. This result indicates a significant 26% lower likelihood of progression in patients receiving the 3-drug combination containing ixazomib, versus the background regimen plus placebo (hazard ratio [HR] of progression, 0.742 [95% CI, 0.587-0.939; $P = .012$; **Figure 2**).

These results were consistent across subgroups, including younger patients and older patients (>75 years). Notably, 15% of patients enrolled in the study belonged to this older subgroup of patients. In addition, patients with both standard-risk and high-risk cytogenetic profiles benefited from therapy, including bortezomib-naïve patients and patients who had previously been treated with proteasome inhibitors. Remarkably, PFS was identical in patients with high-risk and standard-risk cytogenetics. The benefits observed in subgroups of patients with translocation 4:14 and with del17p were similar to those observed in standard-risk patients.

Response rates were significantly increased in patients receiving ixazomib, with more than three-fourths (78.3%) of patients

receiving ixazomib responding to therapy, versus just over two-thirds (71.5%) of patients receiving placebo plus the background regimen. This improvement in response rate was both statistically ($P = .035$) and clinically significant. Although response rates favor ixazomib, an OS assessment is not yet possible. In an interim analysis at a median follow-up of 23 months, researchers reported that the OS rate could not be assessed due to an inadequate accrual of deaths in the study. Although the OS data with ixazomib are not yet mature, with a longer follow-up duration, researchers hope to see an OS benefit.

With regard to safety, 98% of patients receiving ixazomib-based treatment and 99% of patients receiving placebo plus the background regimen experienced adverse events (AEs). Grade 3 or higher AEs were mostly related to thrombocytopenia. According to Moreau, in terms of toxicity, “There is no difference in comparing these 2 arms, with no specific gastrointestinal toxicity or rash that was an issue.” Although gastrointestinal toxicity and rash were among the AEs noted in early studies, the addition of dexamethasone to the ixazomib-containing regimen may have attenuated these AEs.

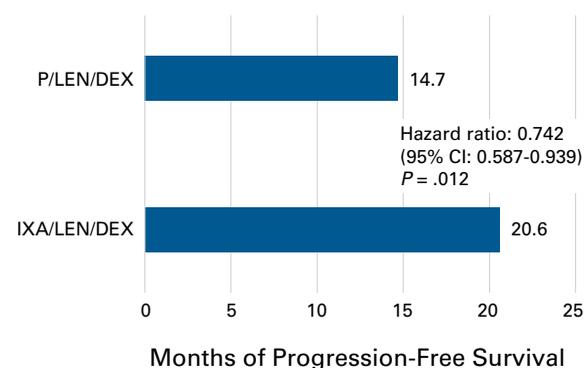
Rates of grade 3 thrombocytopenia were higher in patients receiving ixazomib, with 12% of patients receiving ixazomib-based therapy experiencing this AE with severity grade 3, versus 5% of patients in the comparator arm. More encouragingly, however, researchers found no difference between arms in terms of rates of peripheral neuropathy or deep vein thrombosis. Furthermore, noted Moreau, “No safety concerns were identified and adverse events were less frequent [with ixazomib vs placebo]. This triplet combination is a very safe one.”

Ixazomib is an oral proteasome inhibitor that significantly prolongs PFS when combined with a background regimen of lenalidomide plus dexamethasone in patients with relapsed and refractory MM. In addition to the improvement in PFS, this all-oral triplet combination significantly improves response rates, and according to Moreau, “does not substantially add to the toxicity profile of lenalidomide plus dexamethasone background therapy.” Low rates of peripheral neuropathy, and the lack of cardiovascular or renal AE signals, reinforce this favorable treatment profile. Regarding these results, Moreau concluded, “This all-oral regimen may become the new standard of care for relapsed and refractory multiple myeloma.” In the United States, ixazomib was approved on November 20, 2015, and approval in other countries is expected in 2016.

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Figure 2. Progression-Free Survival in TOURMALINE-MM1¹



DEX indicates dexamethasone; IXA, ixazomib; LEN, lenalidomide; P, placebo; PFS, progression-free survival.

R-CHOP Plus Bortezomib Unpromising in Patients With DLBCL, While an Early Trial of R-CHOP Plus Everolimus Shows Remarkable Results

Diffuse large B-cell lymphoma (DLBCL) is a disease that originates in 2 distinct lines of cells, one of which is the germinal center B-cell, which is often abbreviated GCB. Basic scientific studies indicate that this subgroup of DLBCL may rely on NF-kappa-B signaling to maintain viability, and the results of retrospective analyses suggest that patients without the GCB genotype do not do as well on combination R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisone). This finding indicates that patients without the GCB genotype may respond better to R-CHOP therapy combined with the proteasome inhibitor bortezomib, which is an inhibitor of NF-kappa-B.

Randomized Phase 2 Open-Label Study of R-CHOP ± Bortezomib in Patients With Untreated Non-GCB Subtype DLBCL: Results From the Pyramid Trial

In a phase 2 open-label trial of bortezomib (Velcade) plus R-CHOP therapy,¹ investigators tested whether the additional medication would improve response rates in patients with DLBCL of the non-BCR subtype. Investigators randomized patients who were previously untreated to receive R-CHOP (n = 95) + Velcade (VR-CHOP) or standard R-CHOP (n = 95). In both trial arms, patients received at least 6 cycles of therapy. Researcher evaluated the primary end point of progression-free survival (PFS) and secondary end points of overall survival (OS), overall response rate (ORR), complete response (CR), and safety. This study was powered to detect a 15 percentage-point difference in response rate at 2 years with VR-CHOP versus R-CHOP. Patients were evaluated at the end of cycles 2 and 6 using a fluorodeoxyglucose positron emission tomography scan and through a computed tomography (CT) scan.

Initially, 206 patients were randomized to receive treatment, with 103 patients in each arm of the trial. The modified intent-to-treat (MITT) population included patients who received at least 1 dose of study medication; 91 patients qualified for the MITT population in the R-CHOP group versus 92 patients in the VR-CHOP group. Ultimately, there were 86 evaluable patients in the R-CHOP arm and 90 evaluable patients in the VR-CHOP arm.

In terms of demographic characteristics, patients had a median age of 64 years and population characteristics were evenly balanced across the groups. Three-fourths of all patients had stage III or stage IV disease upon randomization. Of patients receiving R-CHOP, 86% completed all 6 cycles of treatment compared with 85% of patients receiving VR-CHOP who completed all 6 cycles. The median dose intensity in this trial was greater than

98% of the full therapeutic dose, indicating very few dose reductions due to adverse events (AEs). After treatment, patients received a median of 34 months of follow-up. (Note that data from 31.5 months of follow-up were published in the meeting abstract; data from 34 months of follow-up were discussed during the presentation.)

As R-CHOP is a relatively intense chemotherapeutic regimen, it is perhaps not surprising that all patients randomized to treatment with either R-CHOP or VR-CHOP experience at least one AE over the trial period. Although the incidence of AEs was generally balanced across treatment arms, there was a mildly elevated rate of grade 3 and 4 toxicities and a slightly higher rate of thrombocytopenia in patients receiving VR-CHOP versus patients receiving R-CHOP. Otherwise, there were no major differences between treatment groups in terms of the medication safety profile. Notably, rates of peripheral neuropathy were similar in both arms.

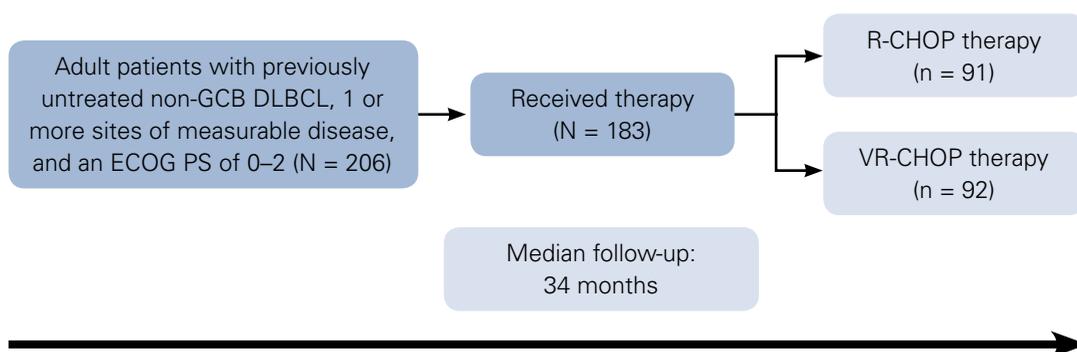
In terms of PFS, there was no significant difference between the 2 regimens. After 2 years of therapy, 78% of patients receiving R-CHOP and 82% of patients receiving VR-CHOP met the PFS end point ($P = .611$). In subanalyses of low- and high-risk groups, PFS curves were identical to those with high-risk or intermediate/high-risk disease. Similarly, OS was unaffected, with 88% of patients receiving R-CHOP and 93% of patients receiving VR-CHOP surviving at 2 years ($P = .78$). These results indicate no benefit to adding bortezomib to R-CHOP in patients with DLBCL without the GCB genotype (Figure¹).

Although this negative finding may indicate that bortezomib is not effective in these patients, it is possible that the method of selection of patients (the Hans IHC algorithm) did not adequately select patients with the non-GCB genotype. In addition, it is possible that a prospective analysis (as in this study) selects out patients with very severe disease, who tend to drop out of clinical trials. This bias in prospective studies versus retrospective studies may explain why retrospective studies show a benefit with bortezomib and prospective studies do not.

A Prospective Randomised Trial of Targeted Therapy for DLBCL Based Upon Real-Time Gene Expression Profiling: The REMoDL-B Study

In another prospective randomized controlled trial of bortezomib added to R-CHOP therapy in patients with DLBCL,² researchers from the United Kingdom reported similarly negative results. This study, known by the acronym REMoDL-B, showed the results of treatment with targeted therapy for DLBCL based on real-time gene expression profiling data.

Figure. Phase 2 Trial Design—VR-CHOP Versus R-CHOP in Patients With Non-GCB DLBCL¹



DLBCL indicates diffuse large B-cell lymphoma; ECOG, European Cooperative Oncology Group; GCB, germinal center B-cell-type; PS, performance status; R-CHOP, rituximab, cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisone; VR-CHOP, bortezomib [Velcade], rituximab, cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisone.

Rather than focusing solely on the non-GCB population, researchers separated patients into 3 groups: patients with the GCB genotype, patients with the activated B cell (ABC) genotype, and patients with DLBCL that could not be categorized. In patients with the ABC genotype, the NF-kappa-B pathway is known to be constitutively active. Due to this constitutive activity, the goal of bortezomib therapy is inhibition of this pathway to improve outcomes in patients with the ABC genotype.

Using an automated transcriptome analysis and an automatic classifier through the Illumina DASL array system, researchers were able to identify genetic subtypes of DLBCL even with partially degraded samples of RNA. Furthermore, the efficacy of this system in classifying patients with DLBCL into GCP and ABC subgroups has been validated in a 330-patient study, indicating the high reliability of the assay. To avoid delaying R-CHOP therapy, patients received R-CHOP during the genomic sequencing process and add-on bortezomib contingent on the results of the genomic assay.

Patients in this study were required to have untreated CD20-positive DLBCL, excluding primary mediastinal large B-cell lymphoma. In addition, to participate, patients were required to provide an adequate sample of formalin-fixed paraffin-embedded tissue and to have a good performance status, defined as a European Cooperative Oncology Group (ECOG) score of 0 to 2. Patients were evaluated on a primary end point of PFS at 30 months. By the second treatment cycle, the molecular profile of each patient was known after a median turnaround time of 10 days. Patients initially received a bortezomib dose of 1.3 mg per

square meter of body surface area, which was later increased to 1.6 mg per square meter of body surface area due to a perceived inadequate response with the lower dose.

A total of 1085 patients were eligible for this study and were randomized to treatment. Of patients enrolled in the study, 248 had the ABC genotype, 477 had the GCB genotype, and 201 patients were unclassifiable. For a total of 130 additional patients, screening failed for a variety of reasons and 29 patients did not receive results due to technical equipment failures. Patients with both ABC and GCB genotypes and unclassifiable patients were randomized to receive R-CHOP or VR-CHOP, and baseline demographics in each group were generally well matched.

Across treatment groups, rates of AEs of grade 3 or higher severity were similar and rates of neuropathy were broadly similar, with the exception of grade 3 or higher neuropathy, which was more common in the VR-CHOP arm than in the R-CHOP arm (3.0% vs 0.9%). CR rates as determined by CT scan were nearly equivalent in all groups treated, with response rates hovering around 60%. No significant differences were detected across groups, even after multiple subanalyses.

Over a median follow-up of 16.3 months, researchers observed 245 progression events and 138 deaths (12.7% of the population). Most of these deaths were the result of progressive disease. For the full population sample, PFS was 79.0% at 12 months and 71.7% at 24 months. Although the data from this study remain immature, the results are unpromising, with PFS curves for all patient subgroups that virtually overlap. These results confirm that real-time gene expression profiling is possible

in a clinical trial, with low failure rates due to equipment malfunction. However, based on the results of this study, the addition of bortezomib to R-CHOP chemotherapy does not appear to affect rates of early treatment failure in patients with DLBCL of any subtype.

Everolimus Plus RCHOP-21 Is Safe and Highly Effective for New Untreated DLBCL: Results of the Phase I Trial NCCTG1085

Although the results of trials with bortezomib appeared to show no benefit, a phase 1 trial of everolimus plus R-CHOP in patients with DLBCL reported more promising results. Although many targeted inhibitors have been studied in DLBCL, investigators in this analysis targeted the Akt/mTOR pathway using everolimus. mTOR, or the mammalian target of rapamycin, is an intracellular protein kinase that regulates cell proliferation. Dysregulation of mTOR can result in uncontrolled cell proliferation; thus, inhibition of mTOR has been targeted as a form of cancer therapy.

Previously, use of mTOR inhibitors has resulted in an ORR of approximately 30% in 47 patients with relapsed or refractory DLBCL. In this trial, patients experienced a median response duration of 5.7 months. The most common AE was myelosuppression, with grade 3 or 4 neutropenia occurring in 18% of patients and grade 3 or 4 thrombocytopenia occurring in 38% of patients.

In the present study, researchers evaluated the effect of everolimus with or without R-CHOP chemotherapy in patients with DLBCL.³ Patients were required to have a confirmed diagnosis of DLBCL and to have an ECOG performance status of 0 to 2. In addition, patients were required to be eligible for standard R-CHOP therapy and to lack several important lab abnormalities, including out-of-range serum creatinine levels. Each cycle of treatment lasted 21 days. As this was a phase 1 dose-finding study, researchers escalated the dose of everolimus over a period of several weeks and assessed tolerability. Researchers also assessed ORR as a secondary end point.

In terms of patient demographics, the median patient age was 58.5 years, with nearly half (46%) of patients over the age of 60 and over one-third (38%) older than 70. In addition, more than one-fourth (29%) of patients had high or intermediate/high risk scores. A total of 24 patients were treated in the trial, all of whom received everolimus plus R-CHOP therapy.

The most common AE observed in this trial was neutropenia: three-fourths of patients experience grade 4 neutropenia. Other AEs included hyperglycemia, which occurred in 4% of patients, and hypertriglyceridemia, which occurred in 13% of patients.

Over 6 cycles of treatment, 92% of patients completed all cycles, with one discontinuation due to an AE.

Over the course of the trial, patients were split into 3 cohorts. The first cohort of 3 patients experienced a CR to therapy. The next 6 patients experienced CR as well. Finally, in an expansion cohort of 15 patients, 14 experienced CR, with the sole exception being a patient who did not adhere to the treatment regimen. As a result, although the ORR was 96%, all patients in the trial who received everolimus plus R-CHOP per the treatment protocol achieved CR.

The results observed in individual patients indicate the importance of this treatment regimen, not only in improving DLBCL, but also in improving related conditions. A 71-year-old female with stage IIIB DLBCL and a history of congestive heart failure (CHF) experienced improvement in CHF symptoms after treatment with everolimus plus R-CHOP. She was able to discontinue all cardiac medications after the first cycle of treatment. After cycles 2 through 6 of treatment, the patient no longer received doxorubicin; she has had no evidence of disease for 2.7 years. Another patient, a male aged 54 years with stage IVA DLBCL, received 6 cycles of therapy and continues to have no evidence of disease 1 year later. Only 1 patient experienced a relapse of cancer, although it was not DLBCL, but a biopsy-proven follicular lymphoma.

In this trial to date, the overall survival rate has been 100%. If similar results are observed in larger clinical trials, everolimus plus R-CHOP may play a prominent role in the treatment of patients with DLBCL.

Everolimus plus R-CHOP may play a prominent role in the treatment of patients with DLBCL.

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Biosimilars: Regulatory and Practical Considerations

In a scientific session on biosimilar biologic products, Ajay Ahuja, MD, vice president of Medical Affairs at Pfizer, discussed some of the filing requirements for FDA approval of a new biosimilar drug, trends in the biosimilar market in the United States and Europe, and the potential effects of biosimilars on the healthcare market over the coming decade.

About Biologics and Biosimilars

Over the past decade, biologic drugs have improved patient care in many disease states. Particularly in the area of hematology and oncology, biologic drugs play an important role in improving outcomes. Due to their complexity, biologic drugs are relatively expensive to develop and produce. As a result, these drugs are also expensive when they reach the market.

With an explosion of newly available biologic drugs, total spending on these medications has increased dramatically, from \$46 billion in 2002 to \$106 billion in 2007, and reaching \$169 billion in 2012. By 2017, if current trends continue, researchers estimate that total spending on biologic drugs in the United States will exceed \$200 billion annually (Table 1).^{1,3}

This increase in spending is an important financial concern for physicians, patients, insurers, and for the United States government, as well. According to recent statistics reported by the Centers for Medicare & Medicaid Services, 8 of the 10 drugs that account for the largest share of Medicare spending are biologic drugs. The financial stress induced by biologics is only expected to increase far into the next decade, as approximately one-third of drugs in development are biologics. Moreover, the 2014 Express Scripts Drug Trend Report forecasts a 20% year-over-year increase in spending on these medications.^{4,5}

Biologics are generally different from small molecule compounds in several ways. Unlike small-molecule drugs, which are produced through synthetic chemistry, biologics are produced by biological organisms. Biologics are also larger in size and weight than small-molecule drugs. However, there are other differences beyond size, including the typical route of administration. Be-

cause biologic drugs are nearly always degraded in the gastrointestinal tract, these drugs are generally administered via the parenteral route. In addition, while small molecules generally do not have large differences in structure, biologics are usually proteins with complex secondary and tertiary structures.

Biosimilars are defined as highly similar successors to reference (originator) biologics. The complex structure of biologics poses an important challenge in terms of manufacturing a biosimilar product that is comparable to the originator compound.⁶

Development and Approval Process for Biosimilars

The clinical development pathway for a biosimilar product is very different from that of a typical originator biologic. Whereas, approximately 15 years of development may be required to bring an originator biologic drug to market, a biosimilar may reach market approval in less than a decade. Although some clinical trials may be necessary for the approval of a biosimilar product, these are typically much less costly than the trials involved in approval of a reference drug. In terms of the cost of development, Ahuja projected that a biosimilar product may be brought to market for around \$100 to \$200 million, versus more than \$1 billion for the reference product.

The approval pathway for small molecule drugs differs from that of biologic drugs in several important ways. For originator small-molecule medications, the FDA approves drugs based on a new drug application (NDA) review process, whereas generic forms of these medications must demonstrate bioequivalence through an abbreviated NDA, or ANDA. Analogous to the NDA and ANDA for biologic drugs are the biologic license application (BLA) and the pathway approved under the biologicals price competition and innovation act (BCPI). While the BLA demonstrates the safety and efficacy of the reference biologic, the BCPI is required to show that the biosimilar has a high degree of similarity to the reference biologic drug (Table 2).⁷

Approval of a biosimilar biologic drug through the BCPI designation means there are no clinically meaningful differences between the medications. Unlike small-molecule generics, which are considered interchangeable with the reference medication, a higher standard than the BCPI may be required to obtain interchangeability designation with biosimilar products. The FDA is currently developing a set of standards that biosimilar manufacturers must meet to obtain interchangeability with the reference product.

Originally, the biosimilar pathway became law through the Patient Protection and Affordable Care Act. However, the actual FDA regulations for biosimilar development were not finalized until early 2015, and as of this writing, no medications have yet become available through the biosimilar pathway. However, a

Table 1. Expansion in Global Biosimilar Market Value^{1,2}

Year	Global Market Value, in Billions of US Dollars
2007	\$106
2012	\$169
2017 (projected)	\$221

Table 2. Comparison of Small-Molecule Medications and Biologic Approval Pathways⁷

Medication Type	Approval Pathway	Goal
Small molecules (approved through the Food, Drug, and Cosmetic Act (FDCA))	New drug application (NDA) for innovator products	Demonstrate safety and efficacy
	Abbreviated new drug application (ANDA) for generic products	Demonstrate bioequivalence
Biologics (approved through the Public Health Service Act (PHSA))	Biologics license application (BLA) for innovator products	Demonstrate safety and efficacy
	Biosimilar biologics license application (BCPI) for biosimilar products	Demonstrate high similarity to the reference product and no clinically meaningful differences from the reference product

form of filgrastim (Zarxio) was approved through a BLA, rather than the biosimilar pathway. Even in the absence of the biosimilar pathway, companies have the option to create a version of an existing biologic drug and demonstrate safety and efficacy through the BLA process.⁸ Also, some biologic drugs have been developed and commercialized in the United States through the older NDA pathway. These medications, which are technically biosimilar products, include low molecular weight biologic drugs, such as insulins and glucagon.

A biosimilar must meet high standards for similarity to ensure no clinically meaningful differences in the safety, purity, or potency of the biosimilar product as compared with the innovator biologic product. Biologic drugs are typically produced in a drug reactor using living organisms, such as genetically modified bacteria. This relatively complex process requires several steps, including culturing of a host cell that produces a desired protein, purification of that protein, and finally formulation and packaging of the biologic product for consumption. Regulatory officials will analyze differences in manufacturing processes to ensure that manufacturing changes do not alter the clinical effectiveness of the resulting biosimilar medication.

Unlike other products, which rely on phase 3 clinical trials to demonstrate safety and efficacy, the focus with biosimilars is demonstrating the efficacy of the product with less emphasis on clinical studies. Once a biosimilar manufacturer can demonstrate that their product is very similar to an originator, confirmatory clinical trials may or may not be required (Table 3⁹). The extensiveness of these clinical trials depends on how well the product's structural and functional characteristics were validated in earlier steps. With more molecular characterization, fewer confirmatory studies are necessary. The FDA generally adopts a pragmatic "totality of evidence" approach in this regard, taking all factors into consideration.⁹

The clinical characterization of biologic products has improved exponentially over the past several years. Today, many techniques are available for characterization of a biosimilar product to ensure physicochemical similarity to an originator product. This testing involves physical testing, including validation of the product's primary sequence, purity, and consistency; functional testing, including comparative receptor binding, signal transduction effects from a mechanistic point of view, and cytotoxicity considerations; as well as immunogenicity testing.⁹

Experience With Biosimilars in Europe

Although biosimilars are a relatively new phenomenon in the United States, the European Medicines Agency (EMA) has had biosimilar guidance in place since 2005. Filgrastim was approved in Europe through a biosimilar pathway. The FDA can draw from both its own experience and European experience as the biosimilar approval pathway enters full implementation.

In Europe, 19 biosimilar products have been approved since 2006, and nearly a decade of experience has accrued (Table 4¹⁰). As experience with biosimilars in Europe has grown, the uptake and use of biosimilar products have steadily increased throughout European nations. To date, the safety and efficacy profiles of approved biosimilars have been similar to those of the original biologic drugs; no issues unique to biosimilars have been encountered.^{9,10}

Cost Savings With Biosimilars

Despite the lower cost of development with biosimilars, compared with small-molecule drugs, biosimilars are still relatively expensive. Even so, the availability of biosimilars will improve price competition, and ultimately, improve access to healthcare and benefit patients. In the European experience

with biosimilar products, the typical reduction in price with introduction of a biosimilar ranges from 10% to 35% off the cost of the originator medication. This pricing creates competition that may also result in a reduction in the price of the originator medication.

The introduction of biosimilars in Europe has resulted in substantial cost savings. For example, in the granulocyte colony stimulating factor (GSCF) category, the introduction of biosimilars resulted in decreased use of originator biologic products. Today, biosimilars account for the majority of GSCF products used in Europe. The lower price of biosimilar GSCF drugs has reduced total spending on GSCF products. According to one research group, nearly \$30 billion in healthcare dollars were saved by the end of 2010 in 8 European countries alone through the uptake of biosimilar products.¹¹

In the United States, the introduction of biosimilars is projected to reduce total United States healthcare spending by \$250 billion by 2024. This figure may be an underestimate of the potential cost savings with biologics, however, as this estimate was based on the assumption that biosimilar versions of a limited number of existing biologic medications (11) will be developed over the next decade.⁶

Immune-Mediated Adverse Events

It is important to recognize that all biologics have the potential to elicit an immune reaction. Usually these reactions are benign, with no clinical consequences. However, in some cases, these immune reactions may have detrimental results. For example, the immune system may produce neutralizing antibodies against biologic products, resulting in a loss of efficacy. This formation of antibodies may also result in allergic reactions.

Another potential immune reaction is cross-reactivity. As a general principle, the more similar a biologic drug is to an endogenous protein, the more likely it is to cross-react with the body's own endogenous proteins. In the case of 1 medication, epoetin alfa, antibodies may cross-react with the body's own endogenous epoetin, resulting in pure red cell aplasia (PRCA). Because the potential for immune-mediated adverse events like PRCA may differ between originator biologics and biosimilars, establishing comparability between reference drugs and biologics with respect to these adverse events will require close scrutiny, testing, and safety surveillance.

Interchangeability

For a biosimilar, the expectation is that its efficacy will be similar to the efficacy of the originator drug. Analogous to bioequivalence testing with generic small-molecule drugs, biosimilars will be required to meet a key clinical end point demonstrating that the biosimilar product's performance is the same as that of the original product. There are some important differences between the FDA and the EMA in terms of biosim-

Table 3. Studies and Steps Required in Biologic New Product Development and Biosimilar Development⁹

Biologic New Product Development	Biosimilar Development
<ul style="list-style-type: none"> • Discovery • Development • Preclinical studies • Phase I studies • Phase II studies • Phase III studies 	<ul style="list-style-type: none"> • Development and molecular characterization • Preclinical studies • Pharmacokinetic and pharmacodynamic studies • Clinical efficacy and safety testing • Immunogenicity testing

Table 4. Biosimilar Products Approved in the European Union¹⁰

Insulin glargine
Epoetin alfa
Filgrastim
Follitropin alfa
Infliximab
Somatropin
Epoetin zeta

ilar regulations. For instance, the FDA will consider additional testing for establishing biosimilars that are interchangeable with reference biologic products, while the EMA does not grant interchangeability status to biosimilars. In general, the FDA requires a higher level of proof of safety and efficacy for biosimilars with interchangeable status.¹²

In the United States, these interchangeability regulations have not yet been finalized, as the FDA is still evaluating what types of studies will be necessary to demonstrate product interchangeability. However, even if a biosimilar product were granted FDA-designated interchangeability with a reference biologic, state and/or local interchangeability laws for pharmacy practice will govern whether biosimilars may be substituted for reference biologics at the pharmacy level, without the approval of the physician. Currently, 31 state legislatures are evaluating this issue.

Conclusion

Biosimilar products will stimulate price competition in the biologic products market, and will reduce costs, enable better patient access, and drive competition. In addition, biosimilars

may indirectly drive innovation. With less healthcare spending on existing biologic products, there will be more dollars available for research into new biologic products. As we move into an era of cost control, it is important to consider the place of biosimilars in therapy and ensure the appropriate use of this new set of biologic medications.

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Working Toward a Cure for Multiple Myeloma: Genomic Analysis and Individualized Treatment

At the 57th American Society of Hematology Annual Meeting and Exposition in Orlando, Florida, Jonathan J. Keats, PhD, of the Translational Genomics Research Institute in Phoenix, Arizona, discussed the importance of genomic data analysis in selecting treatment for control, and ultimately, for cure of multiple myeloma (MM). According to Keats, MM is a disease with many faces. Although it is sometimes represented as a single disease,¹ it is actually a disease involving a continuum of cell types. Different molecular subtypes tend to be correlated with different phenotypes of disease.

Over time, the characteristics of these distinct phenotypes of MM have become more fully understood. For instance, since the early 1990s, MM has been classified into 2 distinct groups, based on cytogenetics: hyperdiploid and nonhyperdiploid disease. MM may also be subclassified based on pathology and the presence or absence of particular genetic markers, such as expression levels of cyclin D, MAF translocations on chromosome 16, MYC translocations, and chromosomal translocations (eg, translocation 4:14), all of which are important mutations commonly found in MM.^{2,3}

Researchers have identified at least 7, and as many as 11 different subtypes of MM. The “multiple” in MM originated from an early 1900s definition based on autopsies, in which pathol-

ogists identified multiple masses in the long bones of the body. According to Keats, the “multiple” nature of MM perhaps should be redefined to mean that there are multiple subtypes of the disease. Although many of these subtypes of MM do often respond to the same therapies, ultimately, full disease control and cure will require exact characterization of each separate subtype of MM to allow for individualized treatment.

However, to fully characterize MM subtypes, it is important to understand the pathophysiology of this disease. Fundamental to this pathophysiology is the slow accumulation of genetic errors in B cells over decades. This slow accumulation is consistent with the late onset of MM, with most patients receiving a diagnosis early in their sixth or seventh decade of life. “The hematopoietic stem cells in these patients,” noted Keats, “have been around since the egg was fertilized, slowly accumulating errors. With every division, there is a risk of error.” According to Keats, this error risk is approximately 0.6 changes per generation, resulting in 1 mutation added to the mass of a genome with each second cell division. On average, this accumulation of errors leads to the formation of approximately 20,000 new defects in cells of the body each day.⁴

A key error that occurs in B cells is an error of the class switch recombination process. However, the accumulation of these er-

rors, alone, is not enough to result in MM. Important in the persistence of these genetic errors, noted Keats, are “preexisting abnormalities that drive malignancy and allow the immune system to tolerate these defects.” The element of survival of mutated cells is an important concept, as the survival and proliferation of these cells with genetic errors has a perhaps underappreciated role in the pathogenesis of MM.

Despite the role of mutations in MM, compared with other malignancies, there are few high-level mutations in MM. “The total number of abnormalities in tumors tends to be close to the average [for all cancers],” explained Keats.⁵ However, the types of mutations in MM and the changeable nature of these mutations make MM particularly difficult to target and treat. In an important study, Keats followed a patient with MM through their entire disease course and studied how tumors evolved in relation to the therapies received.⁶

Looking at chromosome 8 specifically, Keats and colleagues noted that genetic abnormalities, “flip flopped back and forth” as patients received different lines of therapy. Despite this tendency, the total genetic burden over time remained the same, and the frequent genetic changes may have been related to the existence of multiple populations of cells (known as clones), each with distinct genetic characteristics. It is important to note that this variability is not observed in all patients. The genetic characteristics of MM remain the same at baseline and upon relapse in about one-third (35%) of patients with MM. Furthermore, although MM has often been considered a disease with a linear evolution, just over 1 in 4 (28.6%) of patients express new genetic changes, with no changes to pre-existing mutations.⁶

It is also notable that a single patient with MM may have multiple genetic abnormalities expressed in different subclonal populations of MM cells. In a study by Melchor and colleagues, researchers reported that NRAS and KRAS mutations, detectable in the same patient, existed in 2 separate types of cells in the tumor.⁷ These studies showing the multiclonal nature of MM tumors—even in an individual patient—led to the Multiple Myeloma Research Foundation CoMMpass study, which is an international multicenter study of approximately 1000 patients newly diagnosed with MM.⁸

In the CoMMpass study, patients were assigned to treatment in 1 of 3 broad treatment arms: immunomodulatory drug (IMiD)-based therapy, proteasome inhibitor-based therapy, and the combination of IMiD and proteasome inhibitor therapy. At diagnosis, at clinical remission, and when patients experienced dis-

ease progression, investigators conducted a full molecular and genomic analysis. Through gene sequencing, investigators were able to determine the number of MM cell clones in each patient. In some cases, patients had a very large population of different MM clones. For instance, in 1 patient, there were 41 different coexisting cell clones at the first progression of disease.⁸

To achieve a cure for this highly heterogeneous and complex disease, some researchers postulate that chimeric antigen receptor (CAR) T-cell therapy will be the key to advancing treatment, while others assert that the 4 therapies approved this year will ultimately lead to cure through targeted combination treatment. Regardless of the treatment regimen used, if minimal residual disease status is achieved, there will be important questions about when to withdraw therapy if a patient appears to have been cured.

Before this dilemma is a real clinical consideration, trials will have to be conducted to determine the optimal targeted regimens for the treatment of MM. Unfortunately, trials tend to be conducted only in patients with a known, relatively common genetic abnormality. To avoid this problem, future trials in MM may be designed to deliver a targeted combination of treatments that is individualized for each patient’s unique set of genetic mutations and clonal subpopulations. Specific methods of characterizing patients and tailoring treatment were discussed by Kenneth Shain, MD, PhD, of the department of malignant hematology at the Moffitt

Cancer Center in Tampa, Florida. According to Shain, mathematical models of MM will have an important role in the design of these trials.

Because MM is a disease that evolves, there is substantial uncertainty and interpatient variability in the course of disease and the optimal treatment at each stage of disease. In this way, MM shares some parallels with some other complex systems, such as hurricanes. “As we all know here in Florida,” noted Shain, “the path of hurricanes is unpredictable.” However, by using mathematical models, it is possible to predict the course of a hurricane with some degree of uncertainty; with enough data, this uncertainty may be limited.

Without an approach that involves mathematical modeling—similar to the approach used by meteorologists in predicting the course of hurricanes—oncologists will have to treat patients using highly individualized pathways of care. Otherwise, noted Shain, “No matter how we slice up groups of patients, we only have a small population of patients that do extremely well. Other patients will do poorly, and will generally die within 2 to 3 years.”

Because MM is a disease that evolves, there is substantial uncertainty and interpatient variability in the course of disease and the optimal treatment at each stage of disease.

Together with his colleagues in mathematical oncology, Shain is working to develop a mathematical model to predict the course of MM, and to effectively select the optimal regimens or combinations of regimens for each patient. However, there are at least 3 substantial challenges to achieving the goal of treating patients in a truly individualized manner. First, MM remains an all but incurable disease despite significant advances in therapy, and outcomes remain suboptimal. Second, failures are a consequence of genetic diversity, and epigenetic plasticity of a complex, dynamic, and adaptive ecosystem of heterogeneous MM cells that are constantly undergoing evolutionary-based selection. Finally, with treatment, drug-resistant clones will form. Through algorithms that model this evolutionary process, clinicians may identify which drug-resistant clones are likely to take hold in a given patient, and use treatment regimens designed to preempt the formation of those clones during remissions.

According to Shain, “This evolutionary perspective may provide a better way to understand MM.” Although it may seem very different from actual evolutionary processes, the progression of MM has actual parallels to the ebb and flow of species diversity present in the fossil record. Following each extinction-level event (analogous to treatment courses in MM), new species fill niches left by the extinction event, and diversity ultimately increases. Likewise, in MM, the diversity of MM clonal cells increases after each treatment course.^{6,9} In tracking the progression of MM, Keats and colleagues confirmed this conceptual similarity to evolutionary processes. In MM, destruction of sensitive clones with treatment ultimately leads to expansion of resistant clones. Accounting for these evolutionary processes through mathematical models may reveal methods of individualizing treatment to fully eliminate MM, or control MM for longer periods of time.

This method has already been attempted in another type of cancer—melanoma—by Thakur and colleagues. In their study, Thakur and colleagues observed that drug resistance to vemurafenib could be partially mitigated in a mouse xenograft model of human melanoma cells using a discontinuous dosing strategy that prevents drug-resistant cells from gaining full dominance among the population of cancer cells. In this way, researchers successfully forestalled the onset of drug resistance and prolonged survival in this study involving a mouse model.¹⁰

Current research in MM using retrospective data to model the results of using the current dosing strategy for several treatments, versus using adaptive therapy techniques, indicates that patients may receive less therapy with the adaptive approach and MM may remain under control for a longer period of time compared with current dosing strategies. Of course, cautioned Shain, “This is not true for all patients, as patients are unique.”

To identify patients who would benefit from an adaptive approach, Khin and colleagues created a system that used *ex vivo* modeling of the tumor microenvironment, and analyzed

the sensitivity of cells to melphalan. Using these types of assays, it may be possible to identify subpopulations of cells in MM marrow samples, and use data obtained from such assays to formulate a dosing regimen with several different drugs in a way that maintains the competition between different types of MM cells. Ultimately, with enough information, drug resistance and the appropriate treatment strategy may be determined not experimentally, but through a computer algorithm. These models are already able to predict how well a patient will respond to therapy with high reliability.¹¹

Shain and his team envision using a mathematical model to bring all of the aspects of MM biology, including ecosystems of MM cell subpopulations that change with time, to predict response. The first iteration of this model has been developed by Shain and his team. With further iterations of the model, Shain hopes to be able to predict progression-free survival, overall survival, and ultimately the optimal strategies for personalized care in patients with MM. It is hoped that the model will potentially offer longer-term remissions than have been possible in the past, or even a cure for the disease.

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Predicting Outcomes in Multiple Myeloma and Designing Individualized Regimens: A Q&A Session With Kenneth H. Shain, MD, PhD

Kenneth H. Shain, MD, PhD, is an assistant professor at the Moffitt Cancer Center in Tampa, Florida, and the scientific director of the Moffitt Myeloma Working Group. As a clinician-scientist, Shain has laboratory and clinical responsibilities, and is involved in conducting clinical trials. At the 57th American Society of Hematology Annual Meeting and Exposition in Orlando, Florida, Shain presented on the use of novel algorithms to predict the course of multiple myeloma (MM) and ultimately better manage the disease.

Q: How can evolutionary competition theories be applied to MM?

A: We are at a critical point in the disease where we have a number of drugs that are highly effective, and we must figure out how to better utilize these strategies. Evolutionary models can help us predict how patients will respond to individual drugs and better allocate therapies to maximize disease control. Treating the patient at the right time using the right strategy is critical in achieving this goal.

Q: What is the role of the CoMMpass study in providing data to predict responses in MM?

A: Although I have not directly contributed to the CoMMpass study, I recognize that the CoMMpass study is important in that it was designed to collect both phenotypic and genotypic data to help us define how the evolution of MM occurs in the context of therapy. The CoMMpass study has a great chance of providing critical information for imputation and translation to computational models using evolutionary theory.

Q: How can some of the computational models you discussed in your presentation be used to develop a novel clinical trial?

A: I think that is an important question that we are struggling with now. We need to have an understanding and acceptance of changing how we think about clinical trials, not just concerning new drugs, but how we can use existing drugs in a different way. We have designed a study based on our own phenotypic evolutionary-based model to compare therapy chosen by the oncologist versus therapy chosen as influenced by an evolutionary model, and we do better in terms of outcomes with the evolutionary model. It is also important to recognize that these types of studies would be long-term trials. One therapeutic option would not be enough to tell you whether you are improving outcomes over multiple regimens.

Q: How do you envision the current system your team has developed (the EMMA model) predicting long-term outcomes and ultimately improving long-term outcomes?

A: The EMMA platform is built to assess the patient's phenotypic clonal architecture and to predict phenotypic response to pharmacotherapy. The hope is that we can build specific predictions of response by allocating patients to the right drug regimen to maximize efficacy and, hopefully, the progression-free survival within a given regimen. If you do that correctly on multiple regimens, you will maximize your outcomes. You are not going to treat patients with drugs and regimens that they are not predicted to be sensitive to.

Q: What is the role of mathematical modeling in providing clinical support?

A: Mathematical modeling allows one to bring into context a number of different aspects of a disease state—the biology, the genotype, etc—and impute them to create an algorithm that will then facilitate the creation of clinical decision support tools.

Q: In your opinion, how will the novel therapies that have been approved in recent days and weeks impact the treatment of MM?

A: I am truly excited about the magic of our recent approvals, as well as drugs that were approved in the past. Heralding of antibody therapies in myeloma is critical, but identifying the right drugs at the right time in the right combinations is also very important. I think that all of these drugs facilitate targeting more than 1 clone or more than 2 clones at a time. This will hopefully improve on our ability to achieve longer progression-free survival with a given regimen.

Q: What is the clinical relevance of these evolutionary models for designing treatment regimens?

A: I think there are a number of levels of how they can be applied to different treatment regimens. First, can we predict what patient will respond? Second, can we identify the appropriate drug combination? Third, can we follow the patient while they use the regimen and start detecting changes early? We might detect certain aspects of the disease suggesting the growth of a resistant population and change the treatment strategy earlier.

Q: What do the next 5 years hold in terms of combination regimens?

A: An incredible amount of work needs to go into finding out how to utilize the combination regimens that we have. We have had multiple 3-drug combinations approved in the last 2 years; we need to figure out how better to utilize these therapies and what patients need to start with. We also need to find out which patients will benefit most from currently approved 2-drug and 3-drug combinations. This is a really important step—we need to figure out how to utilize the drugs we have today. In that way, we are personalizing our therapy, and I think that is a way of effecting better outcomes.

Q: What would you tell a patient with MM about the future of treatment, tempering some of these prospects for great improvement with the current state of treatment?

A: I think the future of myeloma remains outstanding. I think we have made huge jumps in the field. Some amazing new options are available for patients. Keeping that in mind, I think we need to be very careful about how we interpret this information. MM remains an all-but-incurable malignancy. Although current medications provide us with great ways of controlling disease in those who have MM, we have not yet figured out ways to utilize all of these therapies to truly cure myeloma today. ●

Rituximab as Part of Combination Therapy: A New Standard of Care in Newly Diagnosed Cases of Ph-Negative Acute Lymphoblastic Leukemia

Over the past 20 years, researchers have made important strides in the treatment of adults with acute lymphoblastic leukemia (ALL). Although novel immunotherapy approaches offer new therapeutic options for patients with relapsed and refractory ALL, treatment options remain limited for patients with newly diagnosed ALL that lacks the Philadelphia chromosome.^{1,2}

Treating these patients with rituximab, an anti-CD20 monoclonal antibody, has been proposed as a strategy for several reasons. First, at diagnosis, patients with ALL tumor cells that express CD20 antigen account for 30% to 40% of patients, and these patients have poorer outcomes than patients without the CD20 antigen marker. Rituximab may be more efficacious in patients with high baseline levels of CD20 expression. Additionally, based on experience with other cancers, rituximab may be safely added to existing chemotherapeutic regimens, with positive results. For instance, rituximab has been shown to improve outcomes in B-cell lymphomas, such as Burkitt lymphoma and leukemia.^{2,3}

To test the efficacy of rituximab in patients with ALL, researchers at MD Anderson Cancer Center initiated the Group for Research on Adult ALL (GRAAL) trial, which evaluated rituximab in addition to background therapy. In a plenary session at the 57th American Society of Hematology Annual Meeting and Exposition, Sébastien Maury, MD, discussed the results of this study.⁴ Eligible patients included patients aged 18 to 59 years with newly diagnosed and previously untreated Philadelphia chromosome–negative B-cell precursor ALL with CD20 positive status. Importantly, patients were required to have more than 20% of cells in the bone marrow expressing the CD20 marker to be considered CD20-positive.

Researchers established a primary end point of event-free survival rates. Patients received 16 infusions of rituximab, in addition to background therapy, and up to 18 rituximab infusions in the setting of salvage therapy. In patients with high-risk disease (defined by the presence of 1 or more markers of risk), patients were offered allogeneic stem cell transplant in addition to background therapy and rituximab.

A total of 220 patients were randomized to receive treatment. Following 11 exclusions due to eligibility criteria deviations and study withdrawals, the modified intent-to-treat population ultimately included 209 patients. Of these 209 patients, 105 patients received rituximab plus background therapy and 104 patients received placebo plus background therapy (Figure 1⁵). Both arms were generally well balanced with regard to pretreatment characteristics, including patient age, economic status, white blood cell counts, tumor cytogenetic features, and blast clearance rates in peripheral blood and bone marrow. A notable baseline difference was a higher proportion of allogeneic stem cell transplants among patients randomized to the rituximab-treatment arm (34% of patients) versus the placebo arm (20% of patients).⁵

In terms of event-free survival, at 2 years, investigators identified a significantly improved event-free survival rate in patients receiving rituximab (HR, 0.59 [95% CI, 0.37-0.93]; $P = .021$; Figure 2⁵). This statistically significant improvement was not explained by early response rates, which were similar in both arms (92% in the rituximab arm vs 90% in the placebo arm). In addition, investigators did not detect an effect of rituximab on rates of minimum residual disease attainment. Importantly, however, treatment with rituximab significantly reduced relapse rates (18% with rituximab vs 32% with placebo; $P = .018$).

With regard to severe adverse events (AEs), 246 severe AEs were reported in 124 patients. Rates of infectious events were slightly more frequent in the rituximab arm (n = 16) than in the placebo arm (n = 2). Although this difference was not statistically significant, it is possible that this AE imbalance may relate to the B-cell-depleting effect of rituximab.

Based on the results of this study, the addition of rituximab to an intensive chemotherapy regimen is well tolerated and prolongs event-free survival in patients who are not receiving allogeneic stem cell transplant for first-line treatment of ALL. Furthermore, multivariate analyses demonstrated that the positive effect of rituximab in delaying disease progression remained significant even after adjusting for several risk factors, including patient age and performance status. Although further studies are necessary to establish the optimal dosing strategy, according to Maury, "Addition of rituximab to background therapy in these patients should become the standard of care."

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Figure 1. Trial Design⁵

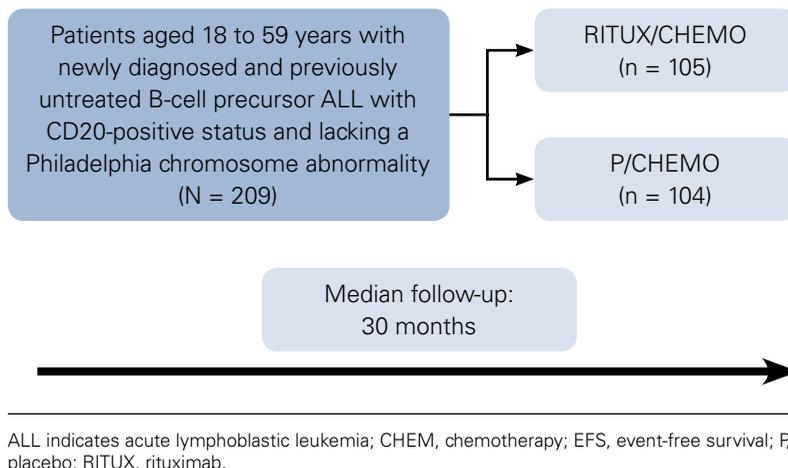
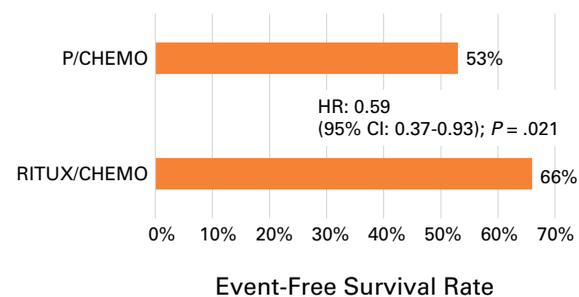


Figure 2. Event-Free Survival Outcomes⁵



CHEMO indicates chemotherapy; EFS, event-free survival; P, placebo; RITUX, rituximab.

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Trial Results Reveal Greater Risk of Inhibitor Formation in Patients With Hemophilia A Receiving Recombinant Factor VIII Than in Patients Receiving Plasma-Derived Factor VIII

Factor VIII is an important clotting factor that stimulates thrombin generation. Patients with low levels of factor VIII due to hemophilia A may experience deep-tissue and

musculoskeletal bleeding and joint bleeding that lead to serious long-term consequences.

Factor VIII replacement remains an important treatment

modality in children with hemophilia and improves outcomes for the vast majority of these patients. Two types of factor VIII treatments are currently available: (1) recombinant treatments manufactured using genetically modified bacteria, and (2) factor VIII isolated from human plasma. Over the last 25 years, a full menu of purified recombinant forms of factor VIII have been produced and used in patients with hemophilia A, resulting in improvements in safety and efficacy. Even in patients with the most severe phenotype of hemophilia A, over 90% of patients have achieved disease control through use of naturally-derived and recombinant forms of factor VIII.

Unfortunately, in 25% to 30% of patients, neutralizing antibodies (called inhibitors) to factor VIII will form after a median of 14 to 15 exposures to therapy. When these inhibitors form, they typically affect patients at a median age of 15.5 months. The formation of inhibitors to factor VIII is associated with increased morbidity and higher rates of mortality.

Although not all of the risk factors related to the development of inhibitors to factor VIII are fully understood, inhibitor development is thought to be related to both host- and treatment-related factors. Among the host-related factors are pathogenic genetic variants, such as polymorphisms of the HLA class 2 immune modulator genotypes. Additionally, the patient's circumstances and the intensity of treatment may affect the likelihood of developing inhibitor antibodies. Unfortunately, to date, scientists cannot reliably determine which patients will and will not develop inhibitors.

Treatments derived through recombinant processes have long been thought to be associated with a greater risk of inhibitor formation compared with plasma-derived products. According to some researchers, the characteristics of recombinant products alter the mode of peptide presentation to the immune system, increasing the risk of inhibitor development. However, studies have found inconsistent results. Although a meta-analysis of 13 observational studies in more than 800 patients showed that the risk of inhibitor development nearly doubled in patients treated with recombinant factor VIII versus patients treated with plasma-derived factor VIII, 2 consecutive multicenter observational studies did not confirm this finding. Unfortunately, limitations in the design of these studies led to difficulties in drawing conclusions based on study results. These limitations included heterogeneity of patient groups and possible dissimilarity of groups in observational studies.¹⁻³

To address open questions regarding inhibitor formation, in 2010, researchers initiated the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET), the first randomized controlled trial to specifically compare immunogenicity between recombinant and plasma-derived factor VIII products. This study enrolled a large international population of children with previously untreated or minimally treated hemophilia A. Researchers documented and controlled for host-related factors and recorded whether the source of factor VIII was from human plasma or from recombinant products.⁴

The primary outcome was the incidence of any inhibitor development, and the secondary outcome was the incidence of high-titer inhibitors. Inhibitors were considered present if levels were 0.4 Bethesda units (BUs) or greater, and inhibitor titers were considered high if levels were 5 BUs or greater. Children included in this study were males 6 years or older with severe hemophilia A without inhibitors upon enrollment. Patients were allocated to receive a plasma-derived factor VIII or recombinant factor VIII and were followed for 50 exposure days or until the development of inhibitors (up to 3 years). The specific treatment regimen used was left to the discretion of the local physician.

A total of 303 patients were screened, and 251 met screening criteria and were enrolled in the trial. Patients were randomized to receive plasma-derived or recombinant factor VIII in a 1:1 ratio, with 126 patients receiving recombinant factor VIII and the remaining 125 patients receiving plasma-derived products. Importantly, potential confounders were equally distributed between treatment arms at baseline.

In terms of the risk of inhibitor development, 76 patients (35.4% of the entire treatment population) developed inhibitors. Nearly 1 in 4 patients (23.2%) developed high-titer inhibitor levels. In patients receiving recombinant products, 47 patients developed inhibitors versus 39 patients in the plasma-derived therapy arm. Moreover, high-titer inhibitors developed in 30 patients receiving recombinant therapy versus 20 patients receiving plasma-derived therapy. These results indicate a significant 87% higher risk of developing inhibitors in children receiving recombinant products versus plasma-derived products (HR, 1.87 [95% CI, 1.17 to 2.96]) and a nonsignificant 70% higher risk of developing high-titer inhibitors with recombinant products compared with plasma derived products (HR, 1.70 [95% CI, 0.96 to 2.99]).

The SIPPET study investigators concluded that among patients with severe hemophilia A, recombinant factor VIII use carries a higher risk of inhibitor development than plasma-derived product use. These results are clinically important and have important implications in terms of treatment costs, morbidity, and mortality.

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Combination Therapy: The Way Forward in Multiple Myeloma

In a plenary session at the 57th American Society of Hematology (ASH) Meeting and Exposition, Sagar Lonial, MD, discussed trends and novel combination therapy approaches for treatment of multiple myeloma (MM). With 4 new drugs approved in the last 12 months, patients with MM and the physicians who treat them have a broader range of treatment options. Of these 4 new drugs, Lonial noted that 2 drugs were approved in the 3 weeks prior to the ASH meeting, and 1 drug was approved the week before the meeting (Table).¹ This growing range of therapeutic options is a result of collaboration among academia, industry, and advocacy groups. “These improvements do not occur in a vacuum,” stated Lonial. “It requires a lot of collaboration.”

With the approval of these 4 new agents, the challenge for physicians is putting together rational combinations to maximize the benefits for patients with MM. Combination therapy may be the best hope for treatment and cure of MM in the near future. Just as in other cancers where combination regimens have offered patients a potentially curative option, curative therapy in MM will likely require rounds of sequential combination treatment.

To identify effective combination regimens, one important consideration is the mechanism of action of each medication. For decades, MM has been treated with chemotherapy. Although combination therapy using traditional chemotherapy was attempted in patients with MM, these trials were unsuccessful, likely due to the similar mechanisms of action of the chemotherapeutic agents em-

ployed. “Because these medications are similar, toxicities are also similar,” commented Lonial. “That experiment was set up to fail.”²

Today, agents have evolved beyond alkylating chemotherapy and steroids. In the era of multiple novel agents with different mechanisms of action, combination therapy in MM is increasingly more common. Some 3-drug regimens have resulted in higher response rates and longer progression-free survival (PFS) intervals than 2-drug combinations in MM. These 3-drug combinations may be useful in overcoming drug resistance, and in suppressing the evolution of different clones of cells in MM.^{2,3}

One of the difficulties in managing MM is the genomic instability that is characteristic of the disease. This is most prominent in patients with high-risk forms of MM.⁴ In addition, substantial genetic instability in MM is further complicated by the diversity of cells that make up MM. As a result, effective targeted therapy will require combination treatment that not only addresses multiple targets, but also targets distinct subclones of cells.^{5,6} Existing evidence shows that upfront combination therapy is generally a successful therapeutic strategy, especially in patients with unfavorable cytogenetics, such as translocation 4:14. According to Lonial, “Combinations can achieve better depth and duration of response.”⁷

One important discovery in combination therapy for MM was that proteasome inhibitors and immunomodulatory drugs showed synergistic effects, both in primary cell lines, and in patients. Originally, basic science studies showed that the mecha-

Table. Drugs Approved by the FDA for Multiple Myeloma in 2015

Medication	Route of Administration	Indication	Approval Date
Empliciti (elotuzumab)	Intravenous	Indicated for use in combination with lenalidomide and dexamethasone for patients who have received 1 to 3 prior lines of therapy	November 30, 2015
Ninlaro (ixazomib)	Oral	Indicated for use in combination with lenalidomide and dexamethasone for patients who have received at least 1 prior line of therapy	November 20, 2015
Darzalex (daratumumab)	Intravenous	Monotherapy treatment of patients who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent, or for patients refractory to both PI and immunomodulatory therapy	November 16, 2015
Kyprolis (carfilzomib)	Intravenous	Indicated for use in combination with lenalidomide and dexamethasone for patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy	July 24, 2015
Farydak (panobinostat)	Oral	Indicated for use in combination with bortezomib and dexamethasone for treatment of patients who have received at least 2 prior lines of therapy, including bortezomib and an immunomodulatory agent	February 23, 2015

nisms of actions of treatment of proteasome inhibitors and immunomodulatory drugs might be too similar to be effective together. However, multiple trials have since shown that this combination and 3-drug regimens involving this combination improve outcomes in induction therapy.

According to Lonial, “Immunomodulatory drug and proteasome inhibitor therapy is likely the best therapeutic strategy.” To illustrate this point, Lonial discussed several studies including:

- A study showing that a 3-drug combination (carfilzomib, lenalidomide, and dexamethasone) was superior to a 2-drug combination (lenalidomide and dexamethasone) in patients with early relapsed MM (ASPIRE).⁷
- The results of the TOURMALINE study, which were presented at ASH 2015, show robust, clinically important outcomes with a combination containing ixazomib.⁸

Results of the ASPIRE study were previously reported in 2014. Researchers studied the combination of lenalidomide and dexamethasone in combination with placebo or carfilzomib in patients with relapsed MM. A total of 792 patients received treatment, with patients randomized to 3-drug therapy or placebo with a 2-drug background regimen. Results indicated a significant improvement in PFS (26.3 months in the treatment arm vs 17.6 months in the placebo arm; $P = .0001$).⁸

Similarly, results from the phase 3 TOURMALINE-MM trial, which were presented during the conference, demonstrated the efficacy of the first oral triple regimen for patients with MM. Over the course of the trial, a total of 722 patients were randomized in a 1:1 ratio to receive either ixazomib or placebo plus a background regimen of lenalidomide plus dexamethasone. In these patients, most of whom had received prior therapy, researchers noted an improvement in PFS (20.6 months vs 14.7 months in the comparator group; $P = .012$). The results showed a 26% lower likelihood of disease progression in patients receiving the 3-drug combination containing ixazomib versus patients receiving background therapy.⁹

According to Lonial, future combinations might incorporate PD-L1 inhibitors with lenalidomide and pomalidomide, as the presence or absence of checkpoint inhibitor ligands has been shown to predict response in patients with MM. With so many

avenues for treatment, and many drugs approved for MM, physicians are excited about the outlook for MM therapy.

With the approval of 4 new treatments for MM in 2015, additional research is needed to establish the optimal dosing regimens and sequences for the treatment of MM. With so many treatment options, Lonial is optimistic that the use of the right combination treatment regimens in the right patients will lead to the first cases of very long-term remission, and ultimately the cure of MM for many patients.

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Oral Hydroxyurea Noninferior to Chronic Transfusion Therapy in Reducing Stroke Risk in Children with Sickle Cell Disease

Cerebral infarction (stroke) is a devastating complication that occurs in more than 10% of children with sickle cell disease and results in long-term impairment of cognitive functioning. According to Russel Ware, MD,

PhD, from Children's Hospital Medical Center in Cincinnati, Ohio, stroke is “the most severe and catastrophic clinical event in children with sickle cell disease.” After the first occurrence of cerebral infarction, the recurrence rate is high.

Fortunately, there are ways to help reduce the risk of recurrent cerebral infarction in children with sickle cell disease, including screening using transcranial doppler and magnetic resonance imaging, and treating at-risk children with chronic red blood cell transfusions.

Previously, researchers demonstrated the efficacy of chronic transfusions in reducing the risk of primary stroke among children with high-risk characteristics in the Stroke Prevention Trial in Sickle Cell Anemia (STOP).^{1,2} Unfortunately, chronic treatment with blood transfusions is associated with risks, including iron overload, alloimmunization, and viral infection (eg, hepatitis, HIV). Although the risk of viral infection with chronic treatment has been reduced substantially through improved screening of the blood supply, chronic red blood cell transfusion remains a suboptimal treatment. The only other treatment, hematopoietic stem cell transplant, is potentially curative, but carries the risks of morbidity and mortality.

Due to the risks associated with repeat transfusions, researchers are evaluating potential alternative treatments, including hydroxyurea. Abundant preclinical evidence supports the efficacy of this oral treatment in children with sickle cell disease. Hydroxyurea, a potent inducer of fetal hemoglobin production, lowers counts of neutrophils and reticulocytes, reduces the adhesiveness of blood cells, and improves blood rheology in children with sickle cell disease. In addition, hydroxyurea assists in the release of endogenous nitric oxide, improves hemoglobin concentrations, and lowers transcranial doppler velocity. Children with a transcranial doppler reading of 200 cm/second or greater are at very high risk for stroke.

Given this data, Ware and colleagues initiated the Transcranial Doppler With Transfusions Changing to Hydroxyurea (TWiTCH) trial to investigate whether children with sickle cell disease would have less need for chronic blood transfusion if transfusions were replaced with oral hydroxyurea therapy. Additionally, researchers assessed whether stroke rates with hydroxyurea therapy were comparable with transfusion therapy.^{3,4}

Eligible children were required to have received at least 12 months of chronic transfusion treatments; exclusion criteria included a history of stroke or transient ischemic attack and evidence of stenosis detected via magnetic resonance angiography. The primary end point was change in the mean transcranial doppler velocity, and the secondary end points were neurological event rates, changes in brain magnetic resonance imaging and angiography, and liver iron concentrations.

Patients were randomized in a 1:1 ratio in an adaptive scheme to balance patient baseline ages and transcranial doppler readings between treatment groups. In children who continued monthly transfusions, iron overload was managed with daily oral chelation therapy. In children who received hydroxyurea, the dose was escalated to a maximal tolerated dose; they received overlapping transfusions until the maximal tolerable

dose was attained, and iron overload was managed through monthly phlebotomy rather than oral chelation therapy. On the primary end point, a noninferiority margin of 15 cm/second was set for the difference in transcranial doppler velocity between the control and treatment arms.

Enrollment for the TWiTCH trial started in September 2011, and ended in April 2013, with enrollment occurring at a faster-than-expected rate. A total of 61 patients received standard treatment and 60 patients were assigned to the alternate treatment with hydroxyurea. Treatment arms were well balanced for demographic characteristics, clinical characteristics, lab values, and imaging assessment results at baseline. The average age of trial participants was 9 to 10 years, with children having received an average of 3 to 4 years of transfusion before enrolling in the TWiTCH trial.

After the first interim data analyses, preliminary results indicated noninferiority between hydroxyurea therapy and chronic transfusion therapy in reducing transcranial doppler readings. In the final analysis, the standard treatment arm achieved a transcranial doppler reading of 143 cm/second versus 138 cm/second for children receiving hydroxyurea.

“The noninferiority margin of this trial was easily met,” stated Ware, “However, a post hoc superiority test was also performed.” Based on the results of this analysis, researchers determined that hydroxyurea therapy resulted in significantly better results on the primary end point of transcranial doppler velocity reduction ($P = .023$).

The noninferiority results and the results of the analysis showing superiority with hydroxyurea therapy were both important. However, clinical event rates in this study were perhaps even more important. On the primary end point, transcranial doppler velocity was maintained in both the treatment group and the transfusion group. Additionally, no deaths or new strokes occurred in either arm. Transient ischemic attacks occurred in 3 children in each treatment arm.

Based on the study results, Ware concluded, “Hydroxyurea can substitute for transfusion therapy and can prevent primary stroke in children with sickle cell disease.” These results pave the way for a transition from burdensome blood transfusion therapy to more convenient oral therapy with hydroxyurea. For many children with sickle cell disease and their caregivers, this is an important and transformative step forward in the management of sickle cell disease.

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Do Hematologists Believe Alternative Payment Models Afford Fair Value?

Alternate payment models, bundled payments, risk-sharing, value-based payments—these issues are frequently discussed at clinical oncology meetings. Initially developed for primary care or common surgical procedures, alternative payment models related to the care of patients with hematologic diseases are now being developed. At the 57th American Society of Hematology (ASH) Annual Meeting and Exposition, physicians discussed the impact of alternate payment models on clinical practice.

Moderator Steven L. Allen, MD, from the North Shore-Long Island Jewish Health System, Manhasset and New Hyde Park, NY, and chair of the ASH Committee on Practice, said, “Physicians need to be aware of how insurers pay for their services, even if their income is entirely based on salary. Our speakers will address bundled payments, using hematopoietic stem cell transplantation as the model, followed by a review of resource management, since controlling costs is crucial in all payment models, and finally, we will hear from an insurer who will discuss what is happening in this new environment and how insurers plan to handle the transfer of risk from the insurer to the provider.”

Using hematopoietic cell transplantation (HCT) as an example, Michael Lill, MD, from the Cedars-Sinai Medical Center, Los Angeles, noted that HCT is a high-cost, high-risk, and high-benefit procedure, with high resource utilization—however, this option offers patients a potential cure.

Lill listed several barriers for entry of institutions into HCT:

- Shortage of trained physicians
- Need for accreditation
- Restrictions rendered by insurance companies, such as the need to be a center of excellence and the need for outcomes data
- Substantial infrastructure needs

Providing a historical context to the evolution of payment models in HCT, Lill explained that payment models for HCT were initiated in the 1990s, but the incentives were poorly aligned, with a 100% risk on the payer. “So the concept of bundled payment came about, to share the risk between payers and providers, and to incentivize providers to be more efficient,” Lill said. This arrangement allowed HCT to remain as a profit center at most hospitals, and “helped transplant center directors focus their attention on costs of care,” he explained.

Explaining the nuances of an HCT bundled payment, Lill explained that a transplant episode is divided into the following phases: assessment, identification of donor, administration of conditioning therapy and other supportive care, and post discharge follow-up.

The bundles vary from one contract to the next, and each phase of the bundle described above involves a technical fee (for services provided by the institution) and a professional fee (for services provided by the physician). “The professional fee can be quite straightforward if it is not included in the bundle,” explained Lill. “However, inclusion in the bundle makes things complicated. What do providers bill for the overall bundle? Should they charge the Medicare rate or the preferred provider organization (PPO) rate, or the cash pay rate?” These complications create a need for negotiation and then a separate contractual arrangement with the private practice providers, Lill said.

In addition, long-term management and payment problems pop up for patients who might see a different provider 6 months after their transplant, but are still on the case rate. Providing an example of a transplant patient who might come down with pneumonia and seek care at a local emergency department, Lill said, “We need clear definitions of what is and what is not covered in the bundle.”

Provisions such as stop-loss payments add to the complication. “A typical global contract will specify payments for a well-defined episode of care, and specify a rate that will start after the contract episode ends,” Lill said, explaining that stop-loss payments help ensure that the hospital or institution does not shoulder the entire risk. The stop-loss clause, he said, states that once a certain threshold in charges is reached, the payer will pay a percentage of charges for a particular episode of care.

Lill then provided the pros and cons associated with bundled payments. The advantages of bundles, he said, include:

- Physician control over patient care plan
- Absence of preauthorization requirements
- Close attention paid to expenditures and outcomes by those in the know
- Incentive for innovation
- More predictable cost structures for insurers

The disadvantages, however, include:

- The physician is responsible for decisions made, not the payer (especially relevant when holding back care)
- Treatment strategies include cost-benefit-profit analyses
- Physicians need to be more in tune with the business of medicine
- Physicians may not be comfortable with these concepts
- Potential for conflicts of interest

“We have had 25 years of experience with this payment model in the transplant field,” said Lill, emphasizing that when cost decisions are made explicit to providers, it is important to ensure that providers are not inappropriately influenced by the payment model. “Outcomes data become very important with bundles and they can also lead to innovations in clinical practice,” he said. ●

ASH Leverages Recommendations From Other Medical Organizations, Advises Hematologists to Choose Wisely

Choosing Wisely is a national medical stewardship campaign led by the ABIM Foundation. Several professional medical organizations currently provide tips and suggestions to avoid high utilization of unnecessary tests and treatments. Following-up on last year’s recommendations, the American Society of Hematology (ASH)’s Choosing Wisely Task Force launched a first-of-its kind review of all existing Choosing Wisely recommendations to identify those published by other professional societies that are highly relevant and important to the practice of hematology, said Lisa Hicks, MD, who chairs the task force. The task force of 13 hematologists chose the top 5 of 380 recommendations listed by 70 other societies and presented them at the 57th ASH Annual Meeting and Exposition in Orlando, Florida.

The following are the 5 new recommendations that ASH is promoting among hematologists. Each recommendation was introduced by a member of the task force.

1. Don’t image for suspected pulmonary embolism (PE) without moderate or high pre-test probability of PE. – American College of Radiology
2. Don’t routinely order thrombophilia testing on patients undergoing a routine infertility evaluation. – American Society for Reproductive Medicine
3. Don’t perform repetitive complete blood count (CBC) and chemistry testing in the face of clinical and lab stability. – Society for Hospital Medicine – Adult Hospital Medicine
4. Don’t transfuse red blood cells for iron deficiency without hemodynamic instability. – American Association of Blood Banks
5. Avoid using positron emission tomography (PET) or PET-computed tomography (CT) scanning as part of routine follow-up care to monitor for a cancer recurrence in asymptomatic patients who have finished initial treatment to eliminate the cancer unless there is high-level evidence that such imaging will change the outcome. – American Society of Clinical Oncology

Using a rigorous methodology, the ASH Choosing Wisely Task Force scored 400 recommendations for relevance and importance over a series of iterations, resulting in this list of items deemed to be especially useful to hematologists. As with past ASH lists, harm avoidance was once again established as the campaign’s preeminent guiding principle, with cost, strength of evidence, frequency, relevance, and impact serving as additional factors.

“The Choosing Wisely initiative is a high visibility campaign that has increased awareness of overutilization in medicine, and at ASH we believe there is a potential for even greater impact when societies share information and work together to accomplish the same goals,” said ASH Choosing Wisely Task Force Chair, Lisa Hicks, MD, from St. Michael’s Hospital and the University of Toronto. “ASH encourages all medical groups to follow its lead by examining other Choosing Wisely lists to find applicable recommendations that will improve quality of care and avoid harm from unnecessary tests and treatments.”

“ASH has shown tremendous leadership by identifying additional Choosing Wisely recommendations relevant to hematologists and creating new ways of disseminating this important information to their members,” said Richard Baron, MD, President and CEO of the ABIM Foundation. “By increasing awareness and understanding of what tests and treatments may be overused or unnecessary across all specialties, we’ll help clinicians be better prepared to join their patients in these critical conversations about their care.

1. Don’t image for suspected PE without moderate or high pre-test probability of PE.

Recommended by the American College of Radiology.

This recommendation was introduced by Michael Bettmann, MD, a radiologist affiliated with the Bowman Gray School of Medicine of Wake Forest University. “For any test that is ordered, we have to assess the risk-benefit ratio, and especially with pulmonary embolism it’s important to make this assessment,” said Bettmann. Based on a review of the available evidence, the task force

recommends to avoid imaging for suspected PE without moderate to high pre-test probability. “Patients with low-risk can be safely excluded,” said Bettman.

2. Don’t routinely order thrombophilia testing on patients undergoing a routine infertility evaluation.

Recommended by the American Society for Reproductive Medicine.

This recommendation was introduced by Shannon Bates, MDCM, MSc, FRCP(C), a hematologist at McMaster University. “Nearly 15% couples may receive an infertility evaluation. Considering this relatively high number, there needs to be a clear association of thrombophilia and infertility or failure of assisted reproduction in these couples,” insisted Bates.

Several population-based studies have found that thrombophilia is associated with infertility, resulting in couples being referred to IVF, said Bates, and an association between thrombophilia and failure of assisted reproduction has also been shown. “However, 2 large cohort studies have shown no association between, Factor V Leiden- or prothrombin gene mutations and assisted reproduction failure or infertility,” she said. Mutations in Factor V and in the prothrombin gene have been known to result in thrombophilia.

Bates also made another point with respect to treatment in this patient population, the use of low molecular weight heparin (LMWH) treatment in assisted reproduction. “Thrombophilia is not a predictor of who will benefit from LMWH treatment with respect to assisted reproduction. There is no consistent evidence showing association between thrombophilia and assisted reproduction or infertility,” said Bates, reminding the audience that LMWH treatment is not benign and could have its own adverse effects.

3. Don’t perform repetitive CBC and chemistry testing in the face of clinical and lab stability.

Recommended by the Society for Hospital Medicine and Adult Hospital Medicine.

This recommendation was introduced by Christopher Moriates, an assistant clinical professor in the Division of Hospital Medicine at the University of California, San Francisco. Moriates began by saying that half of the testing in hospitals is unnecessary. “Ordering CBCs has become a ritual for most of us, which we now know is unnecessary,” he said.

We need to curb this because we are causing a lot of harm, explained Moriates. Critically ill patients, he said, do not have the bone marrow reserve or erythropoietin drive to compensate for iatrogenic blood loss. Also, phlebotomy is associated with risks. It’s not economical either, he explained, considering laboratory tests are not individually reimbursed and ordering too many unnecessary CBCs can be a loss to the hospital. “Disposing the

biohazard waste of the blood samples is also an avoidable cost,” Moriates said.

Moriates assured the audience that several studies have pointed out that reducing the frequency of CBC does not cause any adverse downstream effects, as is feared. “Multiple studies have shown that there’s no difference in readmission rates, length of stay, rates of adverse events, etc, when reducing unnecessary daily lab tests.”

4. Don’t transfuse red blood cells for iron deficiency without hemodynamic instability.

Recommended by the American Association of Blood Banks.

This recommendation was introduced by Jeannie Callum, MD, FRCPC, from the Sunnybrook Research Institute. “The wise options for a patient in the emergency department (ED), who has iron deficiency, are either oral iron or an intravenous infusion,” said Callum. While oral iron is cheap, it causes gastrointestinal disturbances, which are responsible for 50% adherence rates. Oral iron, however, is as effective as intravenous (IV) iron in terms of heme response at 6 to 8 weeks, she explained.

However, according to Callum, unnecessary blood transfusions are often performed to address a person’s iron deficiency. “Research has shown that 20% of blood donors are iron-deficient, so that’s another ethical challenge, at least for me.” Callum directed the audience to a podcast that encourages cautious use of transfusions, and explains why IV iron might be a much better option for certain subsets of ED patients.

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

Recommended by the American Society of Clinical Oncology.

This recommendation was introduced by Gary Lyman, MD, MPH, co-director of the Hutchinson Institute for Cancer Outcomes Research. “Until high-level evidence demonstrates that routine surveillance with PET/PET-CT prolongs life or promotes well-being, they should not be regularly performed.”

CT scans expose patients to small doses of radiation, Lyman said. Although the clinical implications of these doses may not be significant, the cost implications definitely are. Lyman concluded that high-quality evidence supporting the routine use of intensive surveillance to improve survival or enhance quality of life is lacking and he pointed out that professional organizations like the American Society of Clinical Oncology, European Society for Medical Oncology, and the National Comprehensive Cancer Network do not include surveillance PET in disease-specific guidelines. ●