

Exclusive Coverage of the  
Academy of Managed Care Pharmacy Nexus 2021 Meeting

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## Tazemetostat Yields Fewer Safety Outcomes, Lower AE-Associated Costs vs PI3 Kinase Inhibitors

By Gianna Melillo

**A PAIR OF ABSTRACTS PRESENTED** at the Academy of Managed Care Pharmacy Nexus 2021 meeting examined the safety outcomes and health care costs associated with adverse events (AEs) among patients with lymphoma who received tazemetostat (Tazverik; Epizyme) and/or phosphoinositide 3 (PI3) kinase inhibitors.

Tazemetostat received FDA approval in 2020<sup>1</sup> for patients with relapsed/refractory follicular lymphoma (R/R FL) who received at least 2 prior systemic therapies, whereas the PI3 kinase inhibitors idelalisib, duvelisib, and copanlisib are indicated as third-line or later

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## Expert Panel Offers Insight Into Multifaceted Approach to Addressing Health Care Disparities

By Skylar Jeremias

**DISPARITIES IN HEALTH CARE** can be addressed in a multitude of fashions, including by addressing prior authorization challenges, implementing physician incentives, improving medication management, and tackling barriers to higher COVID-19 vaccination rates, according to a panel of experts at the Academy of Managed Care Pharmacy Nexus 2021 meeting.

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## Tazemetostat Yields Fewer Safety Outcomes, Lower AE-Associated Costs vs PI3 Kinase Inhibitors

(CONTINUED FROM COVER)

treatment in this patient population. Umbralisib is indicated as fourth-line or later treatment.

Because tazemetostat, idelalisib, duvelisib, copanlisib, and umbralisib were all approved based on single-arm studies, investigators compared<sup>2</sup> the treatments' safety and efficacy outcomes using an indirect treatment comparison (ITC) via a matching-adjusted indirect comparison (MAIC). The MAIC was conducted in the third-line or later ( $\geq 3L$ ) setting among those with R/R FL. After investigators concluded a systematic review to identify relevant clinical trial publications, "4 pairwise MAIC analyses were conducted by weighting data from individual patients treated with tazemetostat to baseline characteristics reported from each comparator trial."

Safety outcomes were defined as any grade 3 or higher treatment-emergent AE (TEAE) or treatment-emergent serious AE; TEAEs leading to dose reduction, drug discontinuation, or interruption; or individual grade 3 or higher TEAEs (anemia, diarrhea, neutropenia, or pneumonia), the investigators explained. Efficacy was measured via an objective response rate.

All trials included were phase 2, and patients presenting with grade 3b tumors and those with prior allogeneic sacrococcygeal teratoma tumors were excluded.

Analyses showed the relative risks of any grade 3 or higher TEAE for tazemetostat vs idelalisib, duvelisib, copanlisib, and umbralisib were 0.45, 0.35, 0.37, and 0.65, respectively.

Overall, "after adjusting for baseline population differences, results from this ITC suggest that tazemetostat is associated with lower relative risk for safety outcomes vs idelalisib, duvelisib, copanlisib, or umbralisib while achieving similar efficacy outcomes," the authors wrote.

However, some information, including the covariates of individual patient data for comparator PI3 kinase inhibitors, were unavailable, marking a limitation. A lack of data also meant the investigators could not adjust for the effect modifier of *EZH2* mutation status. In addition, "for 2 comparator trials, the populations included a minority of other non-Hodgkin lymphoma subtypes because FL-specific data were not reported."

In a separate cost analysis,<sup>3</sup> investigators sought to determine the differential cost impact arising from AEs in patients with R/R FL treated with tazemetostat compared with the PI3 kinase inhibitors, as these drugs are associated with AEs that include neutropenia, infection, and immune-mediated toxicities (see more on page 7).

Investigators used data from the MAICs of tazemetostat with each of the 4 PI3 kinase inhibitors and sourced AE-related costs from a 2018 US commercial claims analysis for patients with cancer hospitalized with AEs and the Healthcare Cost and Utilization Project.

All grade 3 or higher AEs with an incidence of at least 5% were included in the analysis, whereas "matching-adjusted AE incidence was multiplied by costs related to each AE. The AE costs per treatment episode were stratified by

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System Organ Class, per the Common Terminology Criteria for Adverse Events (CTCAE) v5.0,” the authors explained.

Cost differences were also estimated per treatment episode based on duration of exposure in the trials, and incidence rates were converted to a monthly basis, they added. For tazemetostat, patients were exposed for an average of 9.3 months vs less than 7 months for each of the 3 comparators.

Analyses revealed the following:

- PI3 kinase inhibitors were estimated to incur \$4294 to \$18,737 higher AE-related management costs per episode compared with those for tazemetostat.
- Adjusting for duration of exposure, each of the PI3 kinase inhibitors was projected to cost \$567 to \$3820 more per month than tazemetostat in AE-related costs.
- Estimates indicated the AE-related cost impact of PI3 kinase inhibitors vs tazemetostat was 3.3- to 6.1-fold higher on a per-episode basis and 3.8- to 10.4-fold higher on a monthly basis.
- By category, blood and lymphatic system disorders, such as neutropenia, were a main driver for the AE-related cost differences in all 4 cost comparisons.

The 2 sources used for cost inputs had some differences in methodology, marking a limitation to the analysis, whereas AEs below a 5% incidence rate were not included in the study and could have led to a minor underestimation of

cost differences. Furthermore, costs potentially associated with grade 1/2 AEs could yield even higher cost differences.

Taking these considerations into account, “patients with 3L+ R/R FL who are treated with tazemetostat are estimated to incur substantially lower AE-related costs compared with PI3 kinase inhibitors (idelalisib, duvelisib, copanlisib, and umbralisib) due to the more favorable safety profile of tazemetostat,” the researchers concluded.

“The main driver for these differential cost outcomes were blood and lymphatic system disorders, which occurred much more frequently among patients treated with PI3 kinase inhibitors,” they noted. “As a result, the substantially lower AE-related cost impact of tazemetostat may contribute to lower health care resource utilization and treatment management costs in R/R FL.” ♦

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## Expert Panel Offers Insight Into Multifaceted Approach to Addressing Health Care Disparities

(CONTINUED FROM COVER)

The panel explained what interventions their organizations have implemented to address health care disparities and how they have improved conditions. They also offered recommendations on how to best apply these interventions and advice on how to develop them further.

Aimee Loucks, PharmD, manager of specialty clinical pharmacy and formulary at Kaiser Permanente (KP), shared her organization's strategy for addressing the impact of rejections for prior authorization claims on Hispanic and Latinx patients, who were found to be less likely to fill a requested drug after a claim was rejected for utilization management edits than White patients (31% vs 44%).

KP launched a project aimed at creating a patient-centered solution, by hosting a focus group of Hispanic and Latinx patients to gauge whether they knew why these disparities existed, and found that not only were the patients highly aware of how prior authorizations contribute to disparities, but they also were frustrated with the system and felt that health plans did not care. Loucks suggested that plans examine the contributions of utilization management to outcome disparities to ensure that a solution is designed in partnership with patients if disparities are identified.

Kat Wolf Khachatourian, PharmD, MBA, clinical executive of MHS Employee Health Plan at MultiCare Connected

Care, offered a glimpse into how health risks affect households that make less than \$50,000, who experience a 9% greater risk of chronic disease, including diabetes, because of socioeconomic factors of zip code residence. Khachatourian's organization used a step approach that involved multistakeholder workgroups, which were conducted over Microsoft Teams because of the COVID-19 pandemic.

Results of the approach showed that observing increased pharmacy costs justifies the real-world application of clinical trial data and that aligning stakeholder goals, expectations, and incentives can be accomplished without in-person stakeholder meetings. Khachatourian said she would like to see an expansion of these processes to other disease states and broader stakeholder groups.

Edward Jai, PharmD, senior director and chief pharmacist at Inland Empire Health Plan, examined how to best address social determinants of health (SDOH) that affect health outcomes for Medicare and Medicaid beneficiaries. He talked about how medication management programs around SDOH and telephone-based medication reconciliation programs can lead to decreased hospital readmissions and significant reductions in additive adverse effects, drug-drug interactions, emergency department visits, and medication costs.

Finally, to address COVID-19 vaccination disparities, Sharon K. Jhavar, PharmD, MBA, BCGP, chief vice president and chief pharmacy officer at SCAN Health Plan, dove into the reasons some people are not getting vaccinated, including that people do not trust that the vaccines are safe and effective, do not know where to get them, or lack the savvy needed to use digital navigation and scheduling tools.

Jhavar talked about SCAN's goal to vaccinate 70% of its members, which it achieved at the end of July 2021 by creating a health equity-based outreach team, a COVID-19-specific vaccine hotline, an in-home mobile vaccination program, a COVID-19 provider task force, and a robust communication plan.

Using data and reaching out to patients, stakeholders, and providers, this panel was able to show the various ways health disparities can manifest, the multidimensional approaches that are needed to address them, and the all-hands-on-deck approach that is required for efforts to be successful over time. ♦

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## Two Posters Examine Practices to Manage Oncology Drug Costs, Drive Evidence-Based Care

By Laura Joszt, MA

AS THE COST OF ONCOLOGY DRUGS increases, there has been a growing pressure to manage oncology drug spend. In the past, this sort of management has been difficult for several reasons, including that many oral chemotherapy drugs are covered as a Medicare Part D protected class and that cancer has a greater risk of mortality if left untreated.

A new poster presented at the Academy of Managed Care Pharmacy Nexus 2021 meeting assessed payer perceptions and practices regarding oncology therapy management.<sup>1</sup> The authors utilized an online survey in 2020 and a series of interviews in 2021. Eleven payers participated in the survey and 9 in the interviews, for 14 unique respondents. These payers oversee 238 million lives.

The majority (73%) said they have the following established preferred oncology products:

- 75% have preferred therapies for breast cancer
- 75% have preferred therapies for prostate cancer
- 38% have preferred therapies for non-small cell lung cancer
- 25% have preferred therapies for hematologic malignancies
- 13% have preferred therapies for colon cancer

In addition, 67% said they have established preferred oncology biosimilars vs the originator products. "Other payers also exclude the innovator oncology product from formulary or require stepping through a biosimilar product prior to covering use of the innovator product," the investigators wrote.

Among the respondents, 2 reported that the exclusion of the innovator product resulted in up to a 30% net cost differential between the biosimilar and originator oncology drug. However, there are challenges impeding biosimilar uptake, such as a lack of interchangeable biosimilars in oncology, administrative burden associated with biosimilar utilization, and a lack of impactful price differentials.

**“The most common motivation for implementing [clinical care pathways] was to improve the quality of care...”**

In the next 1 to 3 years, 73% of respondents expect there will be greater management of oncology drugs. Some respondents said they expect their organization will increase management of oncology products in the next 2 years by utilizing such tactics as treatment pathways, site-of-care management, and contracting for favorable formulary tier positioning.

Successful oncology drug management is driven by evidence-based treatment, preventive medicine, reduced costs, and improved patient outcomes, according to the respondents. However, they admit to being only moderately successful on average when it comes to managing oncology drug spend.

Increasing cost of cancer care had the most significant influence on the decision to or the likelihood to prefer products in oncology, followed by development of clinical pathways at the point of prescribing, increased willingness of manufacturers to contract, commoditization of classes of drugs, commoditization of therapeutic areas, and advanced value frameworks. Vertical integration of the health care landscape had the least influence. Other significant influencers that affect the decision to prefer products were generic and biosimilar launches, multiple products with the same mechanism of action, and state regulations that limit health plan action, according to 3 respondents.

“To ensure effective market access and payer strategies, manufacturers of oncology products should continually assess the competitive landscape for their product(s), as well as foster their understanding of the evolution of payer management in relevant cancer types,” the authors concluded.

A second poster described the utilization of value-based frameworks (VBFs) and clinical care pathways (CCPs) at cancer centers, as well as characterized challenges and opportunities associated with their implementation.<sup>2</sup> VBFs and CCPs were developed by organizations in response to escalating prices and increased complexity of care.

VBFs assess value using health outcomes of interest, quality of evidence to measure treatment effect on identified outcomes, aggregate value of health benefit, and cost of care. CCPs are clinical guidelines that use evidence-based protocols to guide prescribers to the leading and most cost-effective treatment regimens and standardize quality of care.

The investigators created a survey after a literature review and a focus group of practicing hematologists and oncologists, quality administrators, and content experts. Between August 2020 and November 2020, oncology/hematology physicians (MDs) and quality officers (QOs) at academic and community cancer centers responded to the survey to provide insight into their center's experience with VBFs and CCPs. Thirteen academic centers and 15 community cancer centers participated.

The most commonly used VBP/CCPs were the National Comprehensive Cancer Center Evidence Blocks (77% of MDs and 92% of QOs) followed by the American Society of Clinical Oncology framework (92% of MDs and 38% of QOs), while 38% each of MDs and QOs said “other.” Community respondents were more likely to say they implemented both VBFs/CCPs (78%) compared with academic respondents (38%).

“The most common motivation for implementing CCPs was to improve the quality of care by standardization with the best evidence, enhance clinical trial availability, and adhere to payer mandates,” the authors noted. Only 1 QO and 1 MD noted their motivation for implementing CCPs was to reduce health care costs.

The incorporation of the patient experience, outcomes, and quality of care into the VBF was the most commonly cited challenge (46% of MDs and 31% of QOs) when it came to implementing VBFs. The most commonly reported challenges for implementing CCPs were substantial implementation costs (31% of MDs and 22% of QOs), provider resistance (19% of MDs and 17% of QOs), and difficulty generating performance reports (19% of MDs and 17% of QOs).

The investigators noted 2 main limitations: Recall bias may affect the responses and the results may not be generalizable outside the sample and setting of the respondents. They concluded that implementation of VBFs may be limited by resource allocation and future VBFs should include patient experience and quality of care. They added that provider acceptance of CCPs can be improved with a transparent development process that incorporates all relevant stakeholders.

“These insights on the opportunities and challenges surrounding implementation of VBFs and CCPs can help

inform the development of future frameworks as well as shape the existing ones used in clinical practice,” the authors wrote. ♦

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## Genetic Profiling in Precision Medicine Can Produce Savings, Better Clinical Outcomes

By Skylar Jeremias

**THE USE OF PHARMACOGENOMICS** in precision medicine, whereby genomic profiling is used to measure a patient’s potential response to a therapy, can produce significant savings and improved clinical outcomes in patients, said panelists during a presentation at the Academy of Managed Care Pharmacy Nexus 2021 meeting.

The presenters described the landscape of pharmacogenomics, how it can aid in treatment selection, and how precision medicine can be used in specialty pharmacy.

First, Patty Taddei-Allen, PharmD, MBA, BCACP, BCGP, vice president of clinical programs and services at WellDyne, defined pharmacogenomics, specifying that it is not used to determine a person’s genetic risk of having a disease. She explained that of the 4 billion prescriptions written each year in the United States, 720 million are affected by genetics. Also, 80% of members in a large retirement plan are on medications affected by genetics and 30% of acute hospital admissions are due to reactions to adverse effects caused by an inaccurate medication annually.

“It’s not necessarily medications that are driving health care spending. It’s really all of these hospitalizations and visits,” she said. “So if we can have tools that allow us to decrease them and make them avoidable—hospitalizations and emergency department visits—it will have a significant impact.”

Pharmacogenomics, according to Taddei-Allen, can aid in precise prescribing of therapeutics because there are several genes responsible for differences in drug

metabolism and response. Identifying patients’ genetic responses to different drugs can enable pharmacists and clinicians to better match medications to patients, and precise prescribing can improve therapeutic success and reduce the potential of drug toxicity.

**Pharmacogenomics can aid in precise prescribing of therapeutics because there are several genes responsible for differences in drug metabolism and response.**

Taddei-Allen shared that for every 4 to 5 pharmacogenomics tests conducted, at least 1 produces an actionable result and savings of \$1000 to \$3000 during the first year for every therapy change. Additionally, there could be a 38% to 50% reduction in emergency department visits and a 30% to 40% reduction in hospitalizations during the first

full year of implementation. According to Taddei-Allen, there are 261 FDA-approved medications with pharmacogenomic labeling information, as well as 362 drug/biomarker pairings.

Nick Page, PharmD, chief clinical and strategy officer at WellDyne, examined the 3 precision medicine uses in specialty care: companion diagnostics, molecular signature tests, and disease activity measures. Companion diagnostics refers to the use of a diagnostic test as a companion to a therapeutic drug to determine its applicability to a patient's individual genetic makeup. Molecular signature tests are used to identify whether a patient is likely to respond to a particular medication or therapeutic class, such as tumor necrosis factor- $\alpha$  inhibitors. Disease activity measures involve surrogate measures of outcomes, such as biomarkers for disease activity or inflammation.

Page also explained how precision medicine has affected psoriasis care by identifying patients' entire RNA transcriptome, response rate to drug classes, and optimal biologics to begin therapy. Page said that biomarker testing

prevents using a trial-and-error approach to biologics prescribing, which can lead to expected better outcomes and cost savings.

He mentioned an example of using a Vectra biomarker test for a 49-year-old engineer with rheumatoid arthritis, finding that precision medicine followed by monthly check-ins and subsequent testing can get patients on an optimal therapy regimen faster and produce \$84,000 in savings for plans during the first year by adopting precision medicine testing.

Finally, Page discussed the future of precision medicine, explaining that 66% of the phase 3 pipeline is focused on nononcology drugs, showing that precision medicine is expanding beyond cancer treatments. He also stated that a 33% increased investment in precision medicine from pharmaceutical leaders is expected over the next 5 years. ♦

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## Dr Sameh Gaballa: Tazemetostat Treatment vs PI3 Kinase Inhibitors Has Cost Benefits

Interview by Maggie L. Shaw

**A POSTER<sup>1</sup> PRESENTED** at the Academy of Managed Care Pharmacy (AMCP) Nexus 2021 meeting laid out the results of an investigation into the costs of treating adverse events (AEs) associated with relapsed/refractory follicular lymphoma (R/R FL). The investigators compared data for enhancer of zeste homolog 2 (EZH2) inhibitor tazemetostat (Tazverik; Epizyme) and the phosphoinositide 3 (PI3) kinase inhibitors idelalisib, duvelisib, copanlisib, and umbralisib.

*Evidence-Based Oncology*<sup>™</sup> (EBO) spoke with principal investigator Sameh Gaballa, MD, assistant member in the Division of Malignant Hematology at Moffitt Cancer Center of the University of South Florida, about the results of his team's investigation, why such matching-adjusted indirect comparisons are necessary, and which treatment gaps tazemetostat addresses.

*This interview has been edited for conciseness and clarity.*

**EBO:** What are the principal safety profile differences between EZH2 inhibitors and PI3 kinase inhibitors, and how does tazemetostat improve upon the outcomes of the PI3 inhibitors you included in your study, taking into account that both are indicated as third-line and beyond treatments for R/R FL?

**GABALLA:** There are a few PI3 kinase inhibitors—idelalisib, duvelisib, copanlisib, and most recently, umbralisib—and they work through inhibiting the PI3 kinase pathway. Tazemetostat is an EZH2 inhibitor; it's an oral drug and an epigenetic modifier. PI3 kinase inhibitors are mostly oral, except for copanlisib, which is given intravenously.

In terms of safety profiles, EZH2 inhibitors and PI3 kinase inhibitors are quite different in general. But even within PI3 kinase inhibitors, their safety profiles do differ significantly. For example, copanlisib which is the intravenous formulation, has fewer AEs—like pneumonitis or

colitis or hepatitis—when you compare it with idelalisib or duvelisib, but then it has unique toxicities of hypertension and hyperglycemia, which are not really seen with the other PI3 kinase inhibitors. Umbralisib has the best toxicity profile within the PI3 kinase family. And it was recently approved<sup>2</sup> based on the UNITY-NHL trial.<sup>3</sup> But if you look at the overall picture, the safety profile of tazemetostat is superior—if you are going to compare it to whichever PI3 kinase inhibitor you’re going to be looking at.

Obviously the differences [will] vary. So if you compare tazemetostat to duvelisib, idelalisib, and maybe copanlisib, there’s going to be a significant advantage with its safety profile in this setting. But if you compare tazemetostat to umbralisib, they’re going to get closer, although still tazemetostat probably will have a more favorable toxicity profile.

**EBO:** Were there gaps in the treatment of R/R FL when tazemetostat received its accelerated approval from the FDA in June of 2020,<sup>4</sup> and can you provide examples of what needs tazemetostat addresses?

**GABALLA:** There are definitely gaps in the management of R/R FL. Currently, in the frontline setting, most physicians are using chemo-immunotherapy or single agents, anti-CD20 antibodies. We’re talking about rituximab, bendamustine, and R-CHOP [rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate (Oncovin), prednisone], which are commonly used in the United States. We typically reserve R-CHOP for patients where we’re suspecting transformed disease. In the second line, based on the AUGMENT study,<sup>5</sup> we now have approval for R<sup>2</sup>, so rituximab and lenalidomide [Revlimid]. But then beyond that in the third, fourth, and beyond settings, prior to tazemetostat’s approval, we really only had PI3 kinase inhibitors: idelalisib, duvelisib, and copanlisib. At that time, umbralisib was also still not approved.

I think there’s definitely space for more treatment options, because some PI3 kinase inhibitors have some significant toxicities and the progression-free survival with most of them is still less than a year. This means that even if a patient is on a PI3 kinase inhibitor, they’re expected to relapse and more therapy options are needed. This is where tazemetostat could potentially fit in well in the relapsed setting either before or after a PI3 kinase inhibitor.

Recently, we’ve had more drugs become available. Now we have umbralisib and CAR [chimeric antigen receptor] T-cell therapy, which have been approved. And there’s probably going to be even newer things soon, such as bispecific antibodies. But at the time tazemetostat came in, there was a big unmet need.

**EBO:** Why is it important to conduct cost-related adverse-outcomes analysis on treatments, especially in the FL space, and can you discuss how need for this information spurred the study you conducted, which you presented at AMCP Nexus?

**GABALLA:** You can think about FL as a chronic disease. These patients may have been watched for many years before requiring therapy. [During] that time, they’re working and their life is going on just as usual. These patients are not used to getting a lot of toxicities, hospitalizations, and disruption in their work and their life. So in FL, we always look at the safety profile closely of any therapy—and that’s always important—because again, it’s a chronic disease and we’re not expecting to cure them.

We now have multiple therapy options available, including PI3 kinase inhibitors and EZH2 inhibitors, and their safety profiles are different. When patients have an AE, that is usually associated with cost as well to manage those AEs.

We always tend to look at the efficacy of one treatment over another, but sometimes the differences in efficacy are not substantial, and then you try to look at other factors to help you make your decision. Number 2 is usually safety, and then we look at cost of care. So [because] the safety profiles are very different and managing these AEs will trigger costs, it was important to look at that as well from that aspect—so that if you’re not looking at the efficacy or safety profile, looking at cost aspects could also help you decide on a treatment.

There are several pathways out there for institutions, and typically the general philosophy for these pathways is to try to standardize care among patients. Usually, again, they look at that sequence—efficacy and then safety and then the financial aspects—so having these data out there, not just looking at the cost of the drug but also other things such as costs associated with managing AEs, might be important as well when looking at these pathways.

**EBO:** Why might a clinician choose to treat a patient who has R/R FL with a PI3 kinase inhibitor instead of tazemetostat, despite the greater toxicities, and can you speak to any programs that may be available to help with the cost?

**GABALLA:** When we bring up these different options, if there’s more than 1 option for a patient, I usually bring up all options and go through the advantages and disadvantages, the pros and cons of each approach. Nowadays, cost is becoming more and more of an issue. Not just the safety and efficacy, but we are also looking at out-of-pocket costs. To answer your question, there are some patients—



for example, Medicare patients—who may have a lower co-pay with an intravenous medication compared with an oral one. They may, for example, opt to go with copanlisib, which is intravenous, because they would get better coverage over an oral agent, such as tazemetostat or one of the other PI3 kinase inhibitors.

Other factors, I think, are probably physician comfort and experience with different agents. Some physicians might be very comfortable with managing PI3 kinase inhibitors, because they know what to expect, over other options. Lastly, for those patients who have *EZH2* wild-type disease, the overall response for tazemetostat was lower than for *EZH2*-mutant disease. The overall response was around 35%, although another third of patients had stable disease. But if you're looking at overall response rates, those numbers were lower for *EZH2* wild-type disease. Again, it's very difficult to compare across trials without a head-to-head comparison.

These are the kinds of situations that I think may lead a physician or a patient to go with one of the PI3 kinase inhibitors over an *EZH2* inhibitor.

**EBO:** Can you extrapolate your 2020 USD cost data out 5 or 10 years?

**GABALLA:** The point of the abstract here<sup>1</sup> is to show just comparisons in costs and ratios. I don't think the ratios are going to change drastically. The absolute numbers will be higher because of inflation, but in terms of ratios, I think those are not going to change drastically. And I think that's the point of our poster here, and our research: to compare the relative cost of managing AEs with different therapy options. I think the ratios will probably stay the same.

**EBO:** Are there any treatments in development that could change your cost outcomes?

**GABALLA:** Well, you could get new approvals. We now have CAR T cells approved, which obviously is a very expensive treatment—but it's a one-time treatment and you're done. However, it's not going to be universal for all patients because not all patients are going to be either eligible for CAR T or will have access to CAR T. I think of the other agents that are going to be introduced in the mix, bispecific antibodies are probably the closest to getting indications. Antibody drug conjugates might get more data in indolent lymphomas and possibly more approvals. Novel antibody therapies might also get approvals in this setting.

I think once we have more data and more approvals, we'll have to revisit these assessments and these cost analyses to see if something has changed. Here we decided to compare

the *EZH2* inhibitor tazemetostat with PI3 kinase inhibitors because these are the 2 agents we're currently using in the third line and beyond. But if we get more and more approvals, I think we're going to need to look again.

**EBO:** Can you discuss possible influences on your results if you included the AEs that had incidence rates below the 5% threshold and why you chose 5% as a cut-off?

**GABALLA:** I don't think they're going to change the main message. If anything, there will only be minor fluctuations in the differences. Because the incidence of those AEs is low, they're probably going to have a minor impact. They're not going to change the overall results, because even if you include those less common AEs, the cost differences will still be more favorable with tazemetostat.

In terms of the 5%, when we designed the study we basically wanted to capture clinically meaningful AEs that would alter or that would be expected to have a significant impact on the cost of managing those AEs, and hence, we picked the 5%. I don't think less frequent AEs [would] have a significant impact, even if they were included.

**“You can think about FL [follicular lymphoma] as a chronic disease....So in FL, we always look at the safety profile closely of any therapy...”**

**EBO:** What if you incorporated situations beyond hospitalization?

**GABALLA:** Obviously, there are other things that are sometimes hard to measure; for example, costs associated with monitoring (eg, cytomegalovirus polymerase chain reaction monitoring), the use of prophylactic medications (eg, Bactrim or acyclovir), lost productivity, etc. I think those will have some impact but not a huge impact.

If anything, these are probably going to make the difference bigger, not smaller, because the costs associated

with monitoring and preventive measures, or prophylaxis, and office visits are probably going to be higher with the PI3 kinase inhibitors. If you look at the grade 1/2 toxicities, it's going to be the same thing. If anything, it's probably going to make the differences bigger, not smaller.

In our study, we wanted to really focus on the significant costs that we can potentially measure. Obviously, this is not a head-to-head comparison and this is not a head-to-head cost analysis. But we wanted something to give a sense of what are the cost differences associated with managing the AEs, and we thought that hospitalizations would probably be taking the lion's share in terms of costs.

We have 2 databases that we used here—a published 2018 US commercial claims analysis for patients with cancer hospitalized with AEs and the Healthcare Cost and Utilization Project for costs not included in the commercial claims analysis—to assess the toxicities associated with managing those AEs. And that's why we chose grade 3 or higher toxicities: to align with the available databases when we're translating those 2 costs.

**EBO:** What do patients and clinicians need to know about tazemetostat and the class of drugs that it belongs to?

**GABALLA:** I'd like them to know that there are more and more options now for patients with FL and there are more options coming. The toxicity profiles are different between all these agents, and you just must make sure that patients are well educated and that they know the benefits and risks of different treatment options to help make the decision.

The safety profile for EZH2 inhibitors is quite favorable, but it's always good to have more and more options. Umbralisib's recent approval also is a very welcome addition, because it has a favorable toxicity profile compared with other PI3 kinase inhibitors.

It's always good to have options. That's the bottom line. ♦

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## An Interchangeable Biosimilars vs Authorized Biologics Battle May Be Looming

By Tony Hagen

**THE FDA HAS APPROVED** 2 interchangeable biosimilars—biosimilars that pharmacists could substitute interchangeably with reference drugs—since July 2021, but manufacturer-developers are seeking interchangeable status for about 7 other biosimilars, according to Jeff Casberg, MS, RPh, vice president of clinical pharmacy for Aventura, Florida-based IPD Analytics. Casberg participated in a presentation<sup>1</sup> on interchangeable biosimilars at the recent Academy of Managed Care Pharmacy Nexus 2021 meeting.

Interchangeables are potential game changers, but also looming is the possibility of “authorized biologics,” or agents that product manufacturers develop as nonbranded copies of their original drugs, he said. The theory is that reference product manufacturers will launch authorized biologics to compete against biosimilars and prevent loss of revenues and market share.

Presumably, authorized biologics, like biosimilars, would launch at discounts to their reference products. There are

no authorized biologics yet, but that seems likely to change soon, Casberg said. The winners in this struggle may simply be the lowest-cost drugs, he said.

When it comes to pharmacy and therapeutics (P&T) committees and the choice of which drugs are used in health care institutions, the interchangeability designation has some advantage over straightforward biosimilar status, Casberg said. “Realistically, it’s going to come down to cost, but I think interchangeability could be a tiebreaker.”

For some large institutions, it won’t matter whether it is an interchangeable, he said. “If you’re in a hospital or clinic type of facility, you probably don’t need the interchangeability designation. There are policies that guide which products you can interchange as a pharmacist.”

**“...you have to start thinking about how you would manage these authorized biologics if they were introduced to the market.”**

—JEFF CASBERG, MS, RPH,

VICE PRESIDENT OF CLINICAL PHARMACY, IPD ANALYTICS

Then, there are authorized biologics. “Authorized biologics are interchangeable. They are the same drug, and we don’t call them ‘authorized biosimilars.’ We call them authorized biologics because calling them authorized biosimilars would suggest biosimilars aren’t quite the same drug,” Casberg said. “Today, we haven’t really seen brand companies have the motivation to bring these authorized products to market, but I think you’ll start to see a few in the future.”

### The Interchangeable Pipeline

The drug pipeline is stocked with more potential interchangeables. Semglee, an insulin glargine that received biosimilar and interchangeable status in July 2021, is a type of a hybrid. It was originally approved in 2020 via a new drug application rather than through the biosimilar regulatory pathway. It references Lantus.

Biocon Biologics and Viartis aim to relaunch Semglee with its interchangeable status and in vial form by the end of the year, at a 5% discount to Lantus and a wholesale acquisition

cost (WAC) of \$26.94, according to Casberg. However, the goal is also to launch Semglee as an authorized biologic in vial and prefilled syringe versions at a 65% discount to brand, or a WAC of \$9.87. That means Biocon Biologics and Viartis are playing the interchangeable and authorized biologic games with the same product, he said.

Several interchangeable biosimilars and authorized biologics could emerge for the reference insulin aspart product NovoLog, Casberg said. Those include MYL-1601D from Viartis, for which biosimilar approval is anticipated in 2021; SAR341402, a Sanofi potential interchangeable, for which no FDA application has been filed; and an “interchangeable” authorized biologic candidate from Novo Nordisk.

Limited exclusivity is awarded to the first interchangeable for a drug type, so if MYL-1601D is approved as an insulin aspart interchangeable, Sanofi’s candidate would not be launchable until 1 year has passed from the first date of marketing of MYL-1601D. The Sanofi product (SAR341402) could be approved in 2022, Casberg estimated.

There is another authorized biologic pending in the insulin category. Lilly is planning an authorized biologic to follow on its insulin lispro drug Humalog.

### Adalimumab Interchangeables

Cyltezo, a biosimilar of adalimumab, referencing Humira, was the second interchangeable approval from the FDA this fall.<sup>2</sup> Soon to follow with an interchangeable approval in the adalimumab biosimilar category could be Abrilada, a Pfizer product, Casberg said.

However, before launching as an interchangeable, Abrilada would have to wait out Cyltezo’s 1-year exclusivity award—which is more complicated than it seems. Cyltezo’s developer, Boehringer Ingelheim, has a settlement with the maker of Humira, AbbVie, not to bring the product to market until 2023, so that could affect Pfizer’s freedom to make use of the interchangeable designation with Abrilada.

Even before any interchangeable designation, Abrilada has been scheduled for launch as a biosimilar of adalimumab in November 2023. It was approved as a biosimilar in 2019.

Another product in the adalimumab biosimilar candidate category is AVT02, from Alvotect. Casberg anticipates this product will launch sometime between 2023 and 2028, given legal hurdles.

AVT02 has the advantage of being a citrate-free, high-concentration formulation version of adalimumab, which would give it footing to compete aggressively against AbbVie’s own citrate-free, high-concentration formulation, which now commands roughly 80% of the market

for adalimumab, Casberg said. The other adalimumab biosimilars lined up for US market entry in 2023 are all lower-concentration biosimilars. In addition, Alvotech is seeking interchangeable status for AVT02.

### An Authorized Adalimumab?

AbbVie has not announced any intention of launching an authorized biologic of adalimumab to compete with the biosimilar versions, but it has likely been a matter of speculation, Casberg said. “As people who manage formularies and sit on P&T committees and manage budgets, you have to start thinking about how you would manage these authorized biologics if they were introduced to market.

“If we wake up 2 weeks from now and AbbVie says they have launched an authorized Humira at a 20% discount—a year before biosimilars launch—how would you manage

that?” he asked. “How would that affect your budget? What would that do to your rebate contracts? Where would you put it on your formularies?”

Other interchangeable biosimilar candidates in the pipeline include NI-071, an infliximab drug from Nichi-Iko, for which interchangeability switching studies have been completed, and ABP 654, an Amgen ustekinumab candidate, which could launch as soon as 2023, Casberg said. ♦

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## Panel: New Medicare Part D Policies and Requirements Aim to Lower Plan Costs

By Skylar Jeremias

**UPWARD TRENDS IN ENROLLMENT** and deductibles for Medicare Part D plans create an opportunity for new policies and requirements to create more stability in the Part D space and savings for beneficiaries, explained experts during a panel discussion at the Academy of Managed Care Pharmacy Nexus 2021 meeting.

The experts described the current trends facing the Medicare Part D benefit landscape, discussed the most recent changes, explained new policies that will go into effect in 2022, and listed potential future policy changes and how they may affect managed care pharmacy, plans, beneficiaries, and manufacturers.

Enrollment in Part D plans increased substantially between 2006 and 2021, from 22 to 41 million, largely because of the baby boomer generation gradually aging into the system, explained Babette S. Edgar, PharmD, MBA, FAMCP, area senior vice president of BluePeak Advisors. Currently, 56% of total Part D enrollment is managed by 3 companies: UnitedHealthcare, CVS Health, and Humana.

Additionally, Edgar said that although premium trends have been somewhat stable, deductibles have risen from about \$100 in 2006 to \$233 in 2021 and the out-of-pocket (OOP) threshold is estimated to increase from \$6700 in

2021 to \$9800 by 2028. Edgar also went into some of the most recent policy changes, including that the Part D Payment Modernization Model will be repealed at the end of 2021 and the Senior Savings Model that went into effect on January 1, 2021.

The Part D Payment Modernization Model, enacted by the Trump administration, aimed to reduce expenditures by making available options to Part D sponsors, including Part D rewards and incentives programs, medication therapy management programs, flexibility to lower costs for beneficiaries, and cutting or removing cost sharing on generics and biosimilars for low-income subsidy (LIS) beneficiaries. In recent years, enrollment among LIS beneficiaries has significantly increased since 2006, leading the Biden administration to revoke the model, according to Edgar.

The Senior Savings Model, also enacted by the Trump administration, was designed to lower prescription drug costs and provide Medicare patients with new Part D plan choices by capping co-pays for 1-month supplies of participating insulins at \$35. Edgar explained that within the coverage gap, the 70% discount on insulins would be calculated before the co-pay is applied, which reduces the plan's

liability. Under the model, beneficiaries are estimated to save \$446 in annual OOP costs, which represents savings of 66%. Edgar said she anticipates more drugs will be added to the Senior Savings Model.

Melissa Anel, MPP, principal of CommonHealth Solutions, highlighted some of the policy changes coming in 2022, including the allowance for Part D plans to maintain 2 specialty tiers, which is expected to provide plans more flexibility in coverage for higher-cost products and to prepare the benefit for increased availability of biosimilars. Early trends showed that the approximate average difference in cost sharing between preferred and nonpreferred specialty tiers will be 5%, and 92% of plans that have signed on will use a tier design with 5 tiers or 5 tiers plus a carve-out tier.

Another change coming is the availability of real-time benefit tools (RTBTs), which will be required for all Part D plans, according to Anel. RTBTs will have to enable enrollees to view information in the prescriber RTBT system. Plans also will have to develop a new portal, and they may offer reasonable rewards and incentives to enrollees who log on to the beneficiary RTBT or seek to access the information using the plan's customer service call center.

In addition, plans will be required to implement mandatory drug management programs in 2022, through which they will have to provide information on the risks of opioids and alternative therapies to all Part D beneficiaries at the time of enrollment and on an annual basis, according to Anel.

She also discussed potential solutions to address rises in annual drug costs for beneficiaries and Part D spending on reinsurance, including eliminating legal protections for rebate negotiations between manufacturers and plans, restructuring the Part D benefit to cap OOP costs, requiring

government price controls for some drugs, and regulatory and legal reforms aimed at fast-tracking the availability for generic and biosimilar products.

**Enrollment in Part D plans has increased substantially between 2016 and 2021... largely because of the baby boomer generation gradually aging into the system, explained Babette S. Edgar, PharmD, MBA, FAMCP, area senior vice president, BluePeak Advisors.**

However, opposition by Republicans and some Democratic representatives has presented challenges in getting new drug pricing policies enacted, said Anel, leading to President Joe Biden's recent announcement that the reconciliation bill's spending target would be lowered from \$3.5 trillion to between \$1.75 and \$1.9 trillion over a 10-year period. ♦

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