FOOD AND DRUG ADMINISTRATION

VIRTUAL PUBLIC WORKSHOP OF THE DRUG DEVELOPMENT CONSIDERATIONS FOR EMPIRIC ANTIBACTERIAL THERAPY IN FEBRILE NEUTROPENIC PATIENTS

First Session Moderated by Dr. Robert Pease and Dr. Andrea Zimmer

Second Session Moderated by Dr. Radu Botgros and Dr. Daniel Rubin

Panel Discussion Moderated by Dr. Randy Taplitz and Dr. Dmitri Iarikov

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P R O C E E D I N G S

DR. KIM: Good morning, everyone.

THE REPORTER: Who's speaking?

DR. KIM: Next slide.

THE REPORTER: One second.

DR. KIM: This is Peter Kim.

Next slide.

THE REPORTER: One instruction for everyone before you speak. Just identify yourself for the record, so I know who's speaking.

DR. KIM: Absolutely.

Next slide, please. Next slide.

Good morning. My name is Peter Kim. I'm the Director of the Division of Anti-Infectives in the Office of Infectious Diseases, OND, CDER, FDA. And I'd like to welcome you to our virtual public workshop on drug development considerations for empiric antibacterial therapy in febrile neutropenic patients.

Next slide, please.

Our workshop objectives. During today's workshop, we will bring together key

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stakeholders from academia, industry, a federal partner, and international regulators to have an open scientific discussion regarding the current state of development and need for antibacterial drugs for empiric therapy in febrile neutropenic patients.

We will also discuss design and operational challenges of clinical trials in febrile neutropenia. We note that workshops are an opportunity for stakeholders to come together to discuss ideas regarding a scientific challenge. Workshops are not advisory to the agency, and the agency will not be providing specific drug development advice.

Next slide.

Some background. Generally, febrile neutropenia is considered a medical emergency requiring early recognition and initiation of empiric systemic antibacterial therapy to avoid potential progression to sepsis or death. There are literature accounts of high mortality among febrile neutropenia patients prior to the use of empiric Carbenicillin-based treatment.

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Of note, the patients in these literature accounts were leukemia and cancer patients with Pseudomonas aeruginosa bacteremia.

Next slide, please.

Cefepime and IV Ciprofloxacin in combination with Piperacillin sodium are the only FDA-approved antibacterial drugs for empiric therapy for febrile neutropenic patients. No new antibacterials have been approved for this indication in over a quarter of a century.

No oral antibacterial drugs have been approved for this indication. There are scientific and practical challenges that affect feasibility of clinical trials in febrile neutropenia.

Next slide, please.

Some of the challenges. We note that there is heterogeneity of the patient population, such as in the characterization of febrile neutropenia episodes which may be microbiologically documented, clinically documented, or due to an unexplained etiology.

We also have questions such as how best

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to define the primary analysis population. Are there ways to enrich for patients most likely to have bacterial infections?

There are also trial design considerations. Should the trials be designed to assess for superiority of one drug versus -- care or non-inferiority? If non-inferiority, there would be a need for adequate justification of a NI margin.

Next slide, please.

There are also considerations related to the primary endpoint in these trials. Should the endpoint be mortality or a composite of clinically meaningful assessments? And there are also feasibility considerations related to sample size.

Next slide.

Now for the program overview. During session one, we will begin with a historical perspective on empiric therapy for febrile neutropenia. And that presentation will be followed by discussions related to current treatment options, diagnostic testing, antibacterial management for febrile neutropenic patients following a nuclear

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detonation incident, and an industry perspective.
Next slide.
During session two, we will hear presentations on pathways and programs to expedite drug development, regulatory considerations on clinical trial design, statistical considerations. And we will also hear from our colleagues at the European Medicines Agency and Japan's Pharmaceutical and Medical Devices Agency regarding their perspectives.
Session two will be followed by a moderated panel discussion.
Next slide, please.
During the panel session, we would like to discuss the greatest unmet needs for empiric treatment of febrile neutropenia, including comment on an ideal drug profile, strategies for enrichment of the study population, trial design consideration.
And if there's time, we'd like to discuss the potential need, utility, and feasibility of obtaining efficacy and safety data for new drugs in the treatment of neutropenic patients with defined

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systemic bacterial infections.
Next slide.
We look forward to a robust discussion. Thank you. We'll now begin with session one.
I'd like to ask Dr. Zimmer and Dr. Pease to take it away.
DR. PEASE: Great. Well, thank you, Dr. Kim.
And good morning, everyone. My name is Robert Pease, and I'm a medical officer in the Division of Anti-Infectives at the FDA, and I have the pleasure of co-moderating our first session with Dr. Andrea Zimmer from the University of Nebraska.
Our first session is on the background of clinical considerations, diagnostic testing, and challenges in the development of drugs for the treatment of febrile neutropenia. This slide depicts our session one speakers of today's workshop that will help set the stage for panel discussions at the end of today as well as our future considerations.
Some housekeeping, we are not going to be able to address questions after each presentation,

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but we'll have a discussion session with our panel this afternoon. Please feel free to type your questions into the Q&A box in Zoom. We'll try to address these in the Q&A box or during a related panel question discussion as time permits.
I'll turn it over to Dr. Zimmer, who will introduce herself and our first speaker.
DR. ZIMMER: Again, I'm Dr. Andrea Zimmer from the University of Nebraska Medical Center. I'm an associate professor and an infectious diseases physician, and I direct the oncology infectious diseases service line at the Fred and Pamela Buffett Cancer Center.
It's my pleasure to introduce our first speaker today, Dr. Randy Taplitz, who will be discussing historical perspectives on prophylaxis and empiric therapy of febrile neutropenia. Dr. Taplitz is an infectious diseases physician and chairperson of the Department of Medicine at City of Hope National Medical Center.
Her areas of interest and expertise are in the prevention, diagnosis, and treatment of

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infections in immunocompromised cancer patients.
Thank you, Dr. Taplitz.
Next slide, please.
DR. TAPLITZ: Great. Thank you.
And good morning, everyone. Thank you for joining us today.
So next slide, please.
In the next ten minutes, I'm going to really describe a historical framework of the relationship of leukemia with febrile neutropenia and infection. Here's a timeline. And basically, infection was recognized as a complication of leukemia in case reports in really the, you know, kind of mid-1800s.
But really the age of discovery really starts in the kind of the early mid-1940s to 1971 when a more clear relationship between lower white count and increased infection in the setting of leukemia was understood.
And in the '60s and '70s, there were more sort of discrete descriptions of relationships between leukopenia in the setting of cytotoxic

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chemotherapy and their infection risks. And it was really the beginning of the description of studies showing empiric antibiotics in febrile neutropenia actually reduced mortality.

In the 1980s, that period of time was characterized by a panoply of studies with the use of antibiotics in febrile neutropenia, and I will talk about that in some detail.

In the age of antibiotic glory, we had a number of different antibiotics approved, not necessarily for febrile neutropenia, but just approved for use, as well as G-CSF, granulocyte colony stimulating factor in 1991.

And really that was a period of time where there was a refinement of the understanding of risk factors that led to the development of febrile neutropenia.

Moving on into the era of the 2000s, it's really been characterized by the rise of resistant bacteria in febrile neutropenia patients. And then the development of new antibiotics for resistant gram-negative rods, not, again, for febrile

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neutropenia necessarily but just in general.

So next slide.

I'm a clinician at heart, and so I like to start with a case that's illustrative. This is a 56-year-old man who presented with progressive fatigue. He was found to have a high white count with a lot of blasts, and bone marrow biopsy showed AML.

He was started on pretty standard seven plus three induction with Cytarabine and Daunorubicin and given fairly standard prophylaxis, Levofloxacin, Posaconazole, and Acyclovir. He developed febrile neutropenia and was treated with empiric Cefepime.

So next slide.

So here what we have is some slides that sort of depict the timeline of the association of leukopenia with febrile neutropenia and really how to treat. And this was based on a lot of studies done in the 60s and 70s, but a couple of really seminal studies.

On the left you can see 1966 was really the first description of a quantitative relationship

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between the number of circulating leukocytes and infection in patients with acute leukemia. And you can look at the graph and see that infection is the major cause of death in the setting of acute leukemia.

The second slide which I like because I could never get a clear picture of it, but describes the, you know, this as a very clear quantitative relationship where when you get to a leukocyte count of less than a thousand, you increase your risk of infection.

And then the final was a seminal paper that was mentioned in the first slide set that was a study of Carbenicillin plus Gentamicin by Schimpiff et al., and then a series of other studies that were somewhat similar that shows that in the setting of febrile neutropenia, there are response rates in the 60 to 67 percent range and improved outcome in patients with febrile neutropenia.

And really, following these kinds of studies in the early 70s, empiric antibiotics in the setting of febrile neutropenic became really a generally accepted practice.

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Now, one thing to remember is that during that period of time, empirical antibiotic treatment could really not be with a single drug because there wasn't a single drug that could provide the coverage that was needed for gram-positives and gram-negatives. So combination therapy was general --

Next slide.

So in the 1980s, there was really kind of a refinement of the use of antibiotics for febrile neutropenia, and there were a lot of studies that looked at in-vitro synergy, serum bactericidal activity, concentration of antibiotics, kind of which antibiotics to use, how to use them. And a number of these studies were published in the 1980s.

But what happened in the mid-1980s was another seminal paper that showed that a single antibiotic, Ceftazidime alone versus combination therapy in cancer patients with febrile neutropenia, was equally safe and effective with failure rates that were quite low in the 5 percent and 4 percent range, respectively.

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And following that, a number of studies that affirmed that monotherapy in the setting of febrile neutropenia could be safe and effective, though, of course, patients with prolonged neutropenia or those with documented infection were likely to need an alteration of therapy.

Next slide.

I'm going to take just a minute to talk about risk assessment because this will come up in subsequent discussions.

But this was a period in the 1990s where really researchers paid a lot of attention to risk stratification. And Talcott just developed a risk prediction model that identified patients who were either at high risk or at low risk of acute medical complications based on a series of factors.

And that basically folks with lower risk potentially could be treated at home. And a multi-center randomized trial confirmed that in this particular setting, outpatient treatment could be safe. Subsequently, you'll hear more about this later. The MASCC and the CISNE scores were also

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developed and validated.

And really at this period of time, risk assessments for modification of empiric antibiotics based on specific features, do they have abdominal pain, do they need anaerobic coverage, etcetera. So there was really kind of a finetuning of this concept of febrile neutropenia treatment.

During this period of time, also newer antibiotics, as I mentioned, were developed and approved. Ciprofloxacin was developed and approved in 1987, oral, well absorbed, good gram-negative coverage, and was studied in both treatment and prophylaxis.

And then as I mentioned, G-CSF approved, and then Zosyn and Piperacillin-tazobactam and Cefepime in 1993 and 1996, respectively.

Next slide.

I just want to spend a moment talking about prophylaxis because you really can't talk about treatment without talking about prophylaxis, I think. It was recognized early on in the '60s and '70s that a majority of the infections were associated with gut

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endogenous flora.

And so during this period of time, there were a number of studies looking at non-absorbable antibiotics and whether that could decrease the incidence of febrile neutropenia and adverse outcome. And really these showed diverse outcomes, but the treatments themselves were not that well-tolerated.

And in the '60s and '70s, the Bactrim was used and studied in prophylaxis, and there were a number of studies showing that bacteremia could be prevented, and there could be reduced days of people with the use of Bactrim prophylaxis.

And then as I mentioned earlier, when Ciprofloxacin was approved, over 100 studies looking at Fluoroquinolone prophylaxis. The issue is many mixed populations, often studies are not randomized, but definitely showed a reduction in bacteremia and infection-related outcomes, but the data was not as clear for mortality benefit.

And I'm just going to say that since that time, there have been many studies. And since

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2000, a number of studies, three, one randomized controlled, one prospective observational, and an open label randomized, as well as a number of new meta-analysis of Fluoroquinolone prophylaxis, that showed that although generally well tolerated and there was a reduction in infection-related outcomes, no clear mortality benefit.

Next slide.

So really, you know, at this point for prophylaxis, there remains a variation in guidelines recommendations because of this variation of data as well as the concept of the risk of antibiotic prophylaxis. And I think by here introducing antibiotic prophylaxis -- risk of really alluding to the risks of antibiotics at -- large.

So there are toxicities with antibiotics. We know, for instance, that prophylaxis in its -- prolongation for drug interactions, but, very importantly, the consideration of antibiotic drug resistance with the use of prophylaxis.

And one thing that's become very well discussed in meetings and in the literature these

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days, is the perturbation of the microbiome which has been associated with a number of different issues, including drug-resistant infection, Clostridium Difficile, and really restricted microbiome diversity, and increased mortality in patients with acute leukemia, as well as an increased risk of graft-versus-host disease.

Next slide.

I want to move back to the treatment of febrile neutropenia. This is the NCCN guidance, and you will see slides similar to this, and I just want to just generally bring up what is done in the setting of febrile neutropenia.

The general approach is you consider the history. You do an exam. You try to localize the site of infection. And you generally start an antibiotic which is usually taken from an institutional protocol based on published guidelines such as this, and hopefully taking into account the epidemiology of your area and your antibiotic-resistant patterns.

Next slide.

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So, again, back to this case, I just want to go to scenario one, which is patient is febrile neutropenic on Cefepime, but the fever resolves. No infectious agent identified. The patient does great. So what do we do in that setting?

Next slide.

And I wanted to briefly mention de-escalation, which is kind of a follow-up approach to high-risk patients with febrile neutropenia. A number of studies have now led to a growing recognition that de-escalation of the antibiotic can be safe and decrease the burden of antibiotic use and its attendant risks.

Here, I am showing one, which I'm not going to go through it in detail, but this is one potential approach to de-escalation, where you -- in a patient who is otherwise doing well, you can change your antibiotic either to prophylaxis or to no antibiotic, or if you've identified a pathogen, you can modify your antibiotic based on susceptibility patterns.

And this is, you know, this is a

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strategy that a number of guidelines, including NCCN and a number of other guidelines, have advocated the consideration of clinical de-escalation in a patient who is otherwise stable.

Next slide.

Finally, I want to complete the scenario by talking about the patient, and we've all seen these patients where the fever did not resolve, and the patient remained febrile. Antibiotics were escalated to Meropenem. No infectious agent was found, but the patients continued on Meropenem because maybe they had a little pneumonia.

Fever resolved, ultimately, but retrogressed and then the patient grew Meropenem multidrug-resistant klebsiella. Patient was placed on Ceftazidime-tazobactam but with prolonged hypotension, multiorgan failure, the patient was made DNR, and passed away. And this is a scenario that we see all too often.

Next slide.

And just as we are aware, you know, bacteremia's changed. Initially, they were dominated

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by gram-negatives, and then in recent studies, we've seen a more equal distribution of gram-negatives and gram-positives. But one of the things that we're also seeing is a concerning rise in drug-resistant pathogens, including Carbapenem-resistant organisms.

And these are, you know, listed some of the organisms where we are seeing of these drug-resistant patterns in. And just two factors I want you to keep in mind, that colonization with multidrug-resistant organisms has been shown to lead to worse outcomes, including higher non-relapse mortality.

And infections, not just colonization, but infections with MDROs, with limited treatment options, are also associated with increased morbidity, mortality, and health care costs, a decrease in microbiota diversity, and then increase in GVHD as well as a decrease in overall survival.

Next slide.

So where are we today? And I think what I wanted to end with is, just to make clear, that in addition to increased drug-resistant organisms,

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we're also seeing just a change in the complexity of our patients. We're now treating patients with increased age, a lot of comorbidities, and with an expansion of therapeutic cancer drugs with on-target and off-tumor toxicities.

For this reason, it is even more important to consider not just neutropenia, but the next state of immunosuppression and even immune activation in the patient. And that is really what are the vulnerabilities that make our patients at risk for infection and make us really need, you know, more anti-infective options in this setting.

I'd also say we still think in terms of prevention, you know, maybe some preemptive therapy treatment, de-escalation, or escalation. I think we, to some degree, need to change our thinking about this and modernize.

And my final slide, I believe -- next slide. Yes.

I'd just like to leave you with a final consideration of the potential of the future with a more refined risk assessment, or what I like, you

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know, what we like to call precision infectious diseases, which is developing a risk score for patients which would take into account a lot of factors.

And it allowed us to individualize treatment and are based on their history, their genetics, what drugs they've been on, and all of these other features, which would really allow us to give the appropriate antimicrobial in the appropriate setting to improve outcome and limit adverse events from antibiotics.

So I will stop there and thank you very much for your attention.

DR. ZIMMER: Next slide, please.

Again, I'm Dr. Andrea Zimmer from the University of Nebraska Medical Center, and I will be talking about the current treatment options for empiric therapy of febrile neutropenia.

Next slide, please.

This is a brief outline of the topics I will cover.

Next slide, please.

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And as Dr. Taplitz mentioned, we are still trying to develop an adequate scoring and predictor system for individual patients and the individual diseases and treatments, but, in general, this is a way that we can broadly organize patients or broadly think of patients in terms of their risk for developing febrile neutropenia and bacterial infections.

We've known for a long time that the duration of neutropenia does directly correlate with risk for febrile neutropenia and subsequent bacterial infections. And so breaking these patients into high, intermediate, and low-risk categories, the highest-risk patients are going to be those that have an anticipated neutropenia of ten days or more.

This includes patients who are receiving cytotoxic chemotherapy for acute leukemias, as well as those undergoing allogeneic stem cell transplantation. Intermediate risk also includes patients with other hematologic malignancies, typically with an anticipated neutropenia period of seven to ten days.

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The depth of neutropenia also directly influences the risk for infection. And the intermediate risk category includes patients with lymphomas, chronic lymphocytic leukemias, multiple myeloma, or those receiving autologous hematopoietic cell transplantation, or CAR T cell therapy.

And then the lowest category includes those with much shorter durations of neutropenia, less than seven days, primarily solid tumor patients.

Next slide, please.

And these two scores have been around for twenty -- ten to twenty years but are still utilized today to help us determine or to predict who is at high risk for morbidity and mortality with episodes of febrile neutropenia.

These are weighted scoring systems. The mass score is a weighted score using comorbidities, age, underlying disease factors, and a higher score, above 21 or higher, predicts low risk for morbidity and mortality following febrile neutropenia.

Likewise, the CISNE score uses

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different variables but also stratifies patients into low risk if they have a CISNE score of zero, intermediate risk if they have a score of one to two, or high risk if they have a score of three or more.

Next slide, please.

So when we are evaluating somebody who's received chemotherapy within the past six weeks and presents with a fever, this is treated as a medical emergency. We want to presume they have a bacterial infection or bacterial sepsis with bacteremia and get them evaluated and started on antibiotics very rapidly.

And so as soon as they're walking in the door, we want to get blood cultures and obtain other blood work, including a comprehensive metabolic panel and a complete blood count to determine whether they are neutropenic.

And then we want to do a fairly rapid assessment, including history, physical exam, and order any symptom-directed workup. Cultures from specific sites based on underlying, you know, symptoms. If they're having urinary symptoms, sending

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urine cultures, as well as symptom-directed radiography.

And then within an hour of presentation, we want to be administering their first dose of empiric antibiotic therapy. And this first dose is usually an IV antibiotic, and the preference is generally for a broad-spectrum antipseudomonal beta-lactam antibiotic.

The choice of antibiotics will be directed by their underlying clinical signs and symptoms, history of prior infections, and prior susceptibility profiles.

We know that once patients are colonized or have had an infection with a specific organism with a particular susceptibility profile, they are at risk for recurrent infections due to gut and skin colonization, allowing translocation of those organisms, as well as we want to pay attention to the local and institutional antibiograms.

Next slide, please.

And then after their first dose of antibiotics, we're able to make our risk assessments

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using our clinical judgment and some of our scoring tools to determine if patients fall into a high or low-risk category.

High-risk patients, those with anticipated neutropenia periods that are longer or that are higher risk score by the MASCC or CISNE or clinically unstable or have an organ disease at presentation, are generally admitted to the hospital and treated with empirical IV or intravenous antibiotics.

Whereas patients that are determined to be low-risk and are clinically stable after being monitored for at least four hours can sometimes be sent home with oral antibiotic therapy if they are not already receiving oral antibiotics for prophylaxis that are included in the treatment regimen.

Next slide, please.

These are the current empirical therapies recommended for febrile neutropenia by the most recent U.S. Guidelines. And so the only agent on this list that is actually a labeled indication or FDA-approved for treatment of febrile neutropenia is

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IV Cefepime.

The other agents, both in the IV and oral categories, are recommended and utilized frequently but do not currently carry an indicated label for treatment of febrile neutropenia. And if you notice that IV antibiotic regimens are frequently dosed at least three to four times a day and so are cumbersome to do as outpatients.

In terms of the oral antibiotic therapy, it's typically recommended to be a combination of an oral Fluoroquinolone that has antipseudomonal coverage such as Ciprofloxacin or Levofloxacin plus Amoxicillin/clavulanate. And the intention is to cover for the Enterobacterales antipseudomonal coverage as well as broad gram-positive coverage.

Next slide, please.

There's been a lot of controversy and look at whether we need to be adding empiric coverage for resisting gram-positive organisms. And there's been several studies, including this one, that do not show benefit in addition of Vancomycin empirically for

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febrile neutropenia unless patients have certain characteristics including hemodynamic instability, a suspected catheter, or skin and soft-tissue infection, or concern for MRSA pneumonia.

Next slide, please.

These are some of the newer therapies that have come to market or come to availability for treatment of resisting gram-negatives. None of these have been specifically studied for use in febrile neutropenia, but they are starting to be used more commonly clinically for these organisms.

Again, none of these agents actually have a labeled indication for treatment of bacteremia. Most have been studied in the context of treatment of pneumonia, complicated UTIs, or intraabdominal infections, but we do need to broaden our tool kit.

And so antibiotics that can be used for treatment of Carbapenem-resistant Enterobacterales, which is a rising problem across the U.S. and is certainly worldwide, include Ceftazidime-avibactam, Imipenem-cilastatin-relebactum, Meropenem-vaborbactam, and Cefiderocol.

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And then, likewise, treatment of difficult-to-treat Pseudomonas multidrug-resistant include the following organisms. And then there are some combination therapies recommended including some of the newer agents for the Carbapenem-resistant Acinetobacters and Stenotrophomonas.

Next slide, please.

The epidemiology of febrile neutropenia and the bacteremia associated with this syndrome varies across the U.S. according to centers, and also varies worldwide. And so focusing on U.S. data, there is a contemporary study that looked at positive organisms of bacteremia across U.S. Cancer Centers.

The breakdown of gram-positive and gram-negative organisms are relatively equal, and so about half and half caused by gram-negative as by gram-positive. The most common gram-negative organism is E. coli, and the most common gram-positive organism is Viridans Group strep with a small number of anaerobes.

Next slide, please.

Practice patterns across the U.S.,

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Cefepime is by far and away the most commonly utilized agent for empirical treatment of febrile neutropenia followed by Piperacillin-tazobactam and then Meropenem. Additional gram-positive coverage with either Vancomycin, Daptomycin, or Linezolid was included empirically in about half of the cases of patients with Aminoglycosides combination utilizing about 6 percent.

Next slide, please.

A broad look at susceptibility profiles. On these 343 organisms isolated across these U.S. Cancer Centers demonstrated variables susceptibility patterns. Meropenem was their most reliable agent to cover all gram-negatives, particularly the Enterobacterales, but had less coverage or less reliable coverage against Pseudomonas compared to Cefepime or Piperacillin-tazobactam.

Next slide, please.

And that concludes my materials. It is my pleasure to introduce our next speaker.

Next slide, please.

So our next speaker is Dr. Kimberly

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Hanson who will be discussing diagnostic testing in febrile neutropenia. Dr. Hanson is a Professor of Medicine and Pathology at the University of Utah. Administratively, Dr. Hanson serves as the Director of the Immunocompromised Host Infectious Diseases Service, and she is the Section Chief for Clinical Microbiology within ARUP Laboratories.

Thank you, Dr. Hanson.

DR. HANSON: Thanks, Dr. Zimmer.

Good morning, everybody.

Next slide, please.

So what I'll be talking about today is trying to provide just a very high-level broad overview of current diagnostic approaches for bacterial infections in the setting of febrile neutropenia. And along the way, I also want to highlight three recent diagnostic utility studies that included neutropenic participants.

Next slide.

So febrile neutropenia is a very common complication of current cytotoxic chemotherapeutic regimens, much more common in the treatment of

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hematologic malignancies than solid tumors. But I'll note that despite, you know, very aggressive and multiple attempts at diagnostic testing, we only identify a proven infection in about half of patients who present with febrile neutropenia.

Looking across studies, bacterial infections tend to be more common than fungal or viral infections, but risk for an individual type of infection really varies by host. It depends on the duration of neutropenia, what prophylaxis may have been received, and it takes a lot of combination of thinking, looking at an individual patient to assess their risk for any given invasive infection.

Next slide.

So making the microbiologic diagnosis though of bacterial infection in the setting of febrile neutropenia is really important because it allows us then to prescribe and target infection and pick the right antibiotic for the right patient at the right time. But as I mentioned, we often don't identify infection.

There are multiple diagnostic

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challenges. These include the fact that the clinical signs and symptoms of infection in neutropenic patients are often nonspecific. The infectious differential diagnosis is quite broad. It includes common organisms, rare organisms, multidrug-resistant organisms.

And invasive testing also may not be possible in the setting of critical illness or coagulopathy that can come along with recent receive of chemotherapy. We also know that standard diagnostics that are culture-based are relatively insensitive and slow.

And so one of the major advances, I think, in the clinical microbiology laboratory in recent years is the broad availability of molecular diagnostic testing that has really improved our ability to identify bacterial infections, to do it more sensitively and more quickly relative to standard approaches that are culture-based.

Next slide.

So this schematic kind of illustrates a hypothetical patient at high risk, let's say, who

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presents to the emergency department with new onset febrile neutropenia. As was mentioned in previous presentations for current guidelines, the goal really is to identify neutropenic patients and collect blood cultures, and then initiate empiric antibiotics really within 60 minutes of that first documentation of fever and no neutropenia.

Next slide. And one more, next slide.

So along the arrow here, I've listed the diagnostic timeline and tried to group current diagnostics in terms of when we might expect to receive results from these tests. So first up would be point-of-care viral tests that are nucleic acid amplification tests or antigen tests for viruses. We can get that answer in about 30 minutes.

Next would be a group of molecular diagnostic tests that could be applied directly to clinical samples like blood or respiratory specimens, and we can get results from these assays on the order of hours. One hour, two, three, four hours. But that really assumes that the clinical laboratory can perform testing in real-time or on-demand and that the

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testing is performed near the patient.

Next up would be our more advanced sequencing-based assays which tend to take days to generate results. And then finally, that's followed by culture-based testing and phenotypic susceptibility testing, again, which is essential for targeted therapy, but that takes days.

So I show this to point out that none of our current diagnostic tests are really going to be able to inform that first dose of empiric therapy for neutropenic patients. However, the hope is after several hours, we may be able to begin to modify our regimens to be more targeted to an infection that an individual patient may have.

Next slide.

So I've mentioned that culture-based diagnostics have major limitations, but it's important to remember that standard blood cultures obtaining two sets from separate sites, really does remain the cornerstone of the diagnostic approach to neutropenic fever. And we know all comers included will identify bacteremia in about 10 to 30 percent of cases of

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new-onset febrile neutropenia.

Next slide.

One of the major advances though, I think, in the clinical microbiology lab now is the use of test methods that can be applied to positive blood culture bottles. So taking an aliquot from a bottle that is flagged positive for an organism and applying a rapid diagnostic test to quickly identify what organism is growing in that blood culture.

And many of these assays then are also linked to downstream assessments of antibiotic susceptibility or resistance which can be done either genotypically by detecting resistance genes or through newer methods that are able to generate rapid phenotypic susceptibility results.

Next slide.

A number of studies have looked at the clinical impact of rapid diagnostics from positive blood culture bottles. I show one of the studies here which I think was one of the more well-done studies because it was multicenter and is actually randomized to include several interventions.

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So the control group got the standard workup of positive blood cultures. We take an aliquot from that blood culture bottle, inoculate it onto standard solid media, incubate it for an additional period of time, and then identify that organism using methods like MALDI-TOF and perform phenotypic susceptibility testing.

But in this study, they also assessed use of a rapid multiplex PCR panel applied to the positive blood culture aliquot. That panel also included a limited amount of resistance determinants, and there were two intervention arms then.

One group randomized to receive the rapid PCR and an enhanced report from the clinical lab. So the lab issued a result that said, "This is what was detected by the rapid PCR, and here's some suggestions of what antibiotics would be recommended."

In the third arm, they used the rapid PCR, their enhanced report, and they included real-time antibiotic stewardship, where a steward called the clinical provider to say, "Hey, the test is positive, this is what was present, and here's some

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recommendations for targeted antimicrobial therapy."

You can see the results of the study here listed to the right. And not surprisingly, with the use of the rapid multiplex PCR, organism ID displayed by the red boxes was much quicker in the intervention arm versus the control. So they identified organisms about a day faster. And this really did allow more rapid escalation of antibiotics.

So escalation in a setting where the organism that was detected was predicted not to have been covered by empiric selection of antibiotics upfront in advance of the culture. The rapid testing also enabled a more rapid de-escalation, but I'll point out that was only possible with the support of antibiotic stewardship.

And most de-escalation events included dropping that extended gram-positive coverage, for instance, stopping the Vancomycin, Linezolid, or Daptomycin when a resistant gram-positive organism was not identified in the blood culture.

Next slide.

I also want to highlight another

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molecular method that can be applied directly to blood, so without the need for culture up front to amplify organisms. And the method I'll discuss today, although there are multiple that exist, is the use of unbiased metagenomic next-generation sequencing to detect and identify circulating microbial cell-free DNA that is present in plasma or in serum of patients who may have a bloodstream infection or potentially an infection at a site distant to the bloodstream.

Next slide.

So this was a study looking at the use of metagenomic next-generation sequencing for that microbial cell-free DNA in a small group of neutropenic patients. And what they did was compared the MGS result to standard of care microbiology, and then they also adjudicated with a panel of three experts, these 55 subjects who had febrile neutropenia to compare the results of the metagenomics to standard of care and then whether or not they thought the patient actually had an infection.

And high-level results I've shown here across the bottom of the slide, I want to point out

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first that the metagenomic sequencing was able to detect the majority of bloodstream infections. So, again, a small sample size, but nine of ten bacteremia patients were identified with the metagenomic assay.

But what the metagenomic test really did was in patients who were thought to have an infection identified many more potential pathogens. So standard of care microbiology identified potential pathogens in 42 percent of patients, whereas the metagenomic sequencing was able to identify organisms in 85 percent.

And the vast majority of these additional detections were polymicrobial infections and also detection of normal, endogenous GI or oral flora, many of which were anaerobes. And that made sense in a neutropenic population which had recently received chemotherapy may have significant mucositis and translocation of these organisms into the bloodstream.

Although this metagenomic test was a send-out test to a reference lab, they were able to get the metagenomic sequencing back before standard of

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care microbiology for the majority of patients, and they hypothesized that this would have changed antimicrobial management in about 50 percent of the cases.

I should have mentioned that the metagenomic sequencing result was not provided to the providers, so they were blinded to the results. So this observational study doesn't really tell us whether or not those possible antibiotic changes would have impacted clinical outcome, although it would have been possible for more rapid changes in antimicrobial therapy.

Next slide.

There are a variety of molecular diagnostics out there, many of which can be applied to sample types other than blood. And these are potentially useful for neutropenic patients where a clinical syndrome or anatomic site of infection is suspected.

I'll say that there have not been many studies looking at the performance of these tests or the clinical utility of these tests in neutropenic

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patients.

Next slide.

And then the last study I want to mention is colonization microbiome study which is really fascinating and hypothesis-generating, I think. But what this study did was look at the frequency and predictive value of colonic colonization with Fluoroquinolone-resistant Enterobacteriaceae.

So it was a single-center study. It enrolled 234 patients who were being admitted to the hospital for a stem cell transplant and they were planned to undergo Levofloxacin prophylaxis during neutropenia.

So at the time of admission and then weekly, they collected stool samples or rectal swabs from these patients to look for colonization with Fluoroquinolone-resistant Enterobacteriaceae organisms, and they tracked bacteremia.

What they found was in their cohort about 23 percent of patients were colonized with Fluoroquinolone-resistant Enterobacteriaceae. And when they compared development of bacteremia between

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those who were colonized as denoted in the gray bars to the right here versus those who were not colonized, bloodstream infections were seen in a statistically significantly increased proportion of patients who were colonized.

And interestingly, when infection did develop, the organism was the same one that was identified on the colonization cultures when they compared the two using whole genome sequencing.

Next slide.

So in summary then, I've tried to show the current kind of molecular diagnostic landscape to show you that we're able to identify organisms more quickly, and it can enable more rapid changes in targeted antibiotic therapy.

However, there have been few studies that have really shown that that change in therapy translates into improved mortality of their patient-important outcomes. I think those studies are needed.

And lastly, I've tried to show the colonization status and potentially the gut microbiome can be useful for guiding potentially prophylaxis or

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no-prophylaxis, as well as prediction of bloodstream or other invasive infections.

So with that, I'll stop, and I'll thank you for your attention.

DR. PEASE: Great. Thank you.

Next slide.

Our next speaker is Dr. Anita Sheoran. Dr. Sheoran is a health scientist in an antimicrobials program at the Center of Biomedical Advanced Research Development Authority, BARDA. She also serves as a steering committee member of Military Infectious Diseases Research Program in the wound infection prevention and management area.

DR. SHEORAN: Thanks, Dr. Pease, for the introduction.

And hello, everyone.

So looking at the names of these agencies, I thought, you know, I'll start off with a brief description of the agency that I represent and then go from there to why the focus of this workshop is of importance to us.

Next slide, please.

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So my organization, as Dr. Pease said, is BARDA. It falls under ASPR, and ASPR stands for Administration for Strategic Preparedness and Response. It is a lead federal health agency that prepares the -- that helps the nation for preparing, responding, and recovering from disasters or public health emergencies that can affect our healthcare system.

Next slide, please.

And under ASPR is BARDA, which is the largest organization under ASPR. We support advanced research and development of countermeasures against multiple threats. They can be chemical, biological, radiological, or nuclear events, or flu, influenza.

We also procure products of strategic value for national security so that, you know, if needed, ASPR can respond in a timely manner. And we do all this through our public-private partnerships providing non-dilutive funding, providing technical support, core facilities to advance the product in a faster manner.

Next slide, please.

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So this brings to my program, which is an antimicrobial program, and we fund both antifungals and antibacterials. But on the antibacterial side, we work towards providing our first responders and clinicians with options to treat not only -- pathogens but also for the opportunistic and secondary bacterial infections that can occur during the treatment course of the patients after any public health emergency.

Next slide, please.

So that brings me to the focus of this workshop and that aligns very well with our mission to have medical countermeasures available to our patients after a radiological or a nuclear event. And as you can imagine that radiation exposure, you know, it leads to complex injuries, and if there's a nuclear detonation, then we are looking at a more complex injury.

So when we are looking at the countermeasures that we need to focus on, we have to look at not only the clinical spectrum of injury but also the systems that are affected. And with respect to that, the hemopoietic system is the most sensitive.

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So we -- considering, you know, the turnover of the cells, it is so fast which makes sense, so we would expect in the case of any Rad/Nuc event, we will see the majority of the patients with these injuries.

And the typical acute radiation syndrome, you know, characteristics are, of course, neutropenia. Then, you know, hemorrhage, multiorgan failure, infection, sepsis, and might lead to death. So the products and the supportive care therapeutics that I have listed on the right here, as I mentioned earlier, the focus of my group is antibiotics and antifungals.

Next slide, please.

So I'm not going to spend any time on the antimicrobial resistance. We all heard about it, we all know about it. And antimicrobial resistance being, you know, a moving target, we do expect an increase in the rate of treatment failure in patients both for the hemopoietic acute radiation syndrome as well as the severe neutropenia in the oncology patient.

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The other factor that we had to really look into when we are evaluating the antimicrobial -- the countermeasures are that we lack robust clinical data in patients with hemopoietic acute radiation system. And so most of the data that we have are from our neutropenic cancer patients. So we've done some animal studies, and we have seen some similarities.

For example, the non-human primate acute radiation syndrome study showed that if the non-human primates are not treated in time, and what does that mean? That means if they're not treated with a broad-spectrum antibiotic prior to the -- of neutrophil decrease, then these hemopoietic ARS and the bloodstream infection and sepsis, more than 50 percent of these NHPs die.

And from the literature of what we have seen that the neutropenic cancer patients, the death rate from sepsis has been reported about 36 percent. In fact, the ASCO/IDSA 28 referenced takes this number to up to 50 percent. So kind of at par what we are seeing in the NHP study.

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The other observation was that the pattern of bacterial infection that we saw in this model in the NHPs was the same as that has been reported in the oncology neutropenic patients, the usual suspect, staph aureus, enterococcus species, Viridans Group streptococci. So we do see some similarities.

And next slide, please.

So where are we with respect to treating these neutropenic patients which have been neutropenic for a long period of time? And I'm talking about more than 30 days, putting them at higher risk of getting secondary bacterial infections. These neutropenic patients may be febrile, may not be even febrile.

So as Peter said, there are only two antibiotics that have been approved for febrile neutropenia. We are using off-label, and the ones that are approved, we have seen the resistance against them. We lack the robust clinical data for the neutropenic patients, including the hemopoietic ARS patients.

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Looking at the pipeline of the antibiotics, there are limited choices for an oral broad-spectrum antibiotic that we think we really need for this indication. And plus, there's no clear path for the product developers to develop a product for febrile neutropenia. So we certainly need more diagnostics as well as the antibacterials for this.

Next slide, please.

So looking at the gaps that I just, you know, talked about, from our perspective, we see that we can approach this by taking two treatment approaches at the same time.

One is making sure that we have antibacterial treatment options available to the patients that are febrile neutropenia. Secondly, we have to have a better understanding of the role of prophylaxis in patients that are at higher risk of neutropenia.

So what we need is the clinical consensus among different groups for both these, you know, treatment approaches. And the questions, of course, will be -- we have a better understanding of

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the clinical need for such an indication in daily practice, the feasibility of the design of the clinical development plan for these both approaches, as well as what would be the ideal type target product profile based on the clinician's experience.

Next slide, please.

So with that, I thank you for your time and look forward to discussions today.

DR. PEASE: Thank you.

Next slide.

And our next speaker is Dr. Douglas Girgenti. Dr. Girgenti is an internist and pediatrician with more than 25 years of clinical and industry experience. He currently serves as Vice President, Head of Development at Malinta Therapeutics overseeing clinical pharmacovigilance and regulatory functions.

Thank you, Dr. Girgenti.

DR. GIRGENTI: Hi, thank you.

And good morning and good afternoon and good evening to colleagues joining elsewhere.

If we could advance to the next slide.

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As noted on the slide here, I am a full-time employee of Malinta Therapeutics where I lead clinical development, as well as pharmacovigilance and regulatory functions. However, the views and opinions I'll express today are solely my own, and I have no other conflicts to disclose.

Okay, next slide. Thank you.

Okay. So thank you for the opportunity to be here for this really important event. And as noted from our earlier speakers that really, despite being quite frankly the most serious complications of chemotherapy-induced neutropenia, and what is truly a key driver of dose delay and reduction and perhaps survival in patients receiving chemotherapy.

And despite the existence of numerous guidance regarding the use of antibiotics for empiric treatment of febrile neutropenia, there really is no standardized agreed-upon study designed for clinical trial development. And this is the way I really tried to approach this discussion today.

So there are a few antibiotics that are currently recommended and even fewer licensed for

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empiric treatment, and these are largely based on, as we've seen earlier, randomized clinical trials which have been conducted in some cases more than 20 years or more prior to now.

And since that time, we've really seen great advances in the treatment of malignancy which have impacted the course of disease, microbiological considerations, and overall the course of FN, and I've highlighted some of them here.

Particularly, the microbiology, which has evolved largely due to the increased use of indwelling lines, and we also see emerging resistance patterns in both gram-negative and gram-positive populations. With regard to the population itself, a wider breadth of tumor types that are being treated, and certainly an aging population.

Treatment recommendations which are now risk-based stratified in terms of high risk and low risk. Really important ancillary treatments of chemotherapy, particularly, and most importantly, I would say, the use of G-CSF, which has had a substantial impact on outcomes as well as potential

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safety events that might be incurred in a clinical trial.

And, perhaps, most importantly, outcomes where, you know, as Dr. Taplitz earlier described, that this disease has really evolved over the last even 50 years, where at one point the mortality perhaps was greater than 50 percent and is essentially now down to 5 to 10 percent in most clinical trials that have evaluated the disease.

Okay, next slide.

So to date there are really only one or perhaps two antibacterial agents that are approved, and a small handful of drugs which are recommended for the empiric treatment of FN. Approved drugs include Cefepime and Ciprofloxacin, but only in combination with Piperacillin.

Yet, despite a lack of label indication, the antibiotics that are recommended by IDSA as well as ESMO and ASCO for empiric treatment includes Ceftazidime, Piperacillin-tazobactam, Imipenem-cilastin, and Meropenem. And, of course, none of these are really novel antibiotics, and, in

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fact, these recommendations are largely based on multicenter trials that were conducted more than 20 years ago. And the field has become, you know, somewhat stagnant.

While endpoints have not necessarily been consistent from trial to trial, in each of the cases I've shown here, the antibiotics have largely been evaluated primarily based on head-to-head clinical trials, evaluating clinical response which includes defervescence, resolution of signs and symptoms.

And if identified, clearance of the cultured organism, plus or minus the need for modification of the original antibiotic therapy chosen for empiric treatment.

So, you know, immediately evident, I think, are the challenges -- some of the challenges that we face in a randomized clinical trial design. Where looking at the clinical responses that have achieved, you know, they're not particularly robust, and really demonstrate small, if any, margin between the test and the comparative antibiotics in each

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trial.
Okay, next slide.
So this is current as of about maybe two weeks ago, where I did a search of clinicaltrials.gov based on febrile neutropenia or fever plus neutropenia which revealed in total about 162 posted trials. And merely 10 of these really represent antibiotic trials which are evaluating empiric treatment of FN. And even more importantly, only two are either ongoing or planned.
And yet, you know, as I really tried to lay out on the bottom of the slide, there are numerous beta-lactam, as well as non-beta-lactam class antibiotics, that could potentially be considered as candidates for empiric treatment.
Okay, next slide.
So where I've really started this discussion in terms of, you know, what I would do when considering whether to develop a drug for really any potential indication? You know, hypothetically, how would I address clinical development as a sponsor? What would I need to consider with regard to both

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clinical and economic impacts of development?
So first of all, on the clinical side, you know, what is really to be gained by a clinical development strategy? Is there clinical value to be added by the drug that we'd like to bring to market?
So does the drug clinically differentiate from existing therapy, either with regard to efficacy and outcomes or perhaps with improved safety and tolerability, as was seen, you know, 20 to 30 years ago with going from combination therapy to the rationale for monotherapy?
And will the results of the clinical development influence the treatment paradigm? Whether this is really top-down with respect to guidance and recommendations or even locally at the formulary level? And then, very importantly, on the economic side, you know, what impact is anticipated that could either add or detract from a value from the current treatment?
And finally, you know, realistically from a sponsor perspective, there is cost to consider. Antibiotic development is costly and realistically, we

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would really only entertain the potential to develop a drug for febrile neutropenia if the cost of development would at least be offset by commercialization.
Okay, next slide.
So where I'd like to start then, you know, in considering how to design or how I would approach clinical development. For any hypothetical drug in designing a clinical development strategy, my first step would be to understand the population and the disease as thoroughly as possible.
And really to anticipate the unique challenges that each would represent. Thus, to design a clinical efficacy trial best designed not only for success but the best potential in a label indication.
So, importantly, with regard to the FN population, we know that despite important advances in this field, there is still a substantial unmet need for novel and improved therapies. And in considering whether our previous randomized clinical trials would remain valid, despite the changes over the last two years, I think is really important.

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What we see are that there are an increased breadth of diseases which are being treated with chemotherapy and particularly late-stage diseases which were not previously treated. So the overall impact of this has been to age the population at risk. However, the breadth of diseases makes this much more disease-specific.
With regard to the breadth of solid tumors which are now being treated sometimes in combination with radiation therapy, as well as the increased use of central venous access and Fluoroquinolone prophylaxis, what used to be a disease predominated by gram-negative pathogens, this is perhaps precipitated a predominance of gram-positive pathogens responsible for febrile neutropenia.
However, we also know that patients that have hematological malignancies are generally older, more morbid, and at higher risk of febrile neutropenia, as well as poor outcomes. So the age, the morbidity, the healthcare exposures are certainly drivers of morbidity and particularly gram-negative and multidrug-resistant organisms predominating in

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this population.
And all of these really contribute to the inclusion/exclusion criteria that we might consider in a clinical trial which could potentially impact both efficacy and safety and inevitably impact what the label looks like at the conclusion of this.
Multidrug resistance and a rise of novel healthcare-associated infections, as well as fungal infections, also are to be considered pretty substantially in this population.
And really in terms of relying on historical data, the important changes in supportive care, most notably the introduction of G-CSF and prophylactic antibiotic use, have certainly contributed substantially to incidents as well as outcomes in this population. And risk-based treatment and short step-down therapy have further impacted how we might consider clinical development in the population.
So what we know at this point is that the FN population will include a substantial age range, including a substantial patient range well

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above 65 and above, which is important to the label indication. On average, the patient population remains somewhat morbid. The average mass score would represent high-risk patients.
Depending on the disease, most, if not all, patients will have central venous access. Most of patients will be prophylactically treated with Fluoroquinolones. This may be disease-specific. And we can anticipate that a large proportion of subjects will be on G-CSF therapy which may alter the natural course of neutropenia, particularly the time of neutropenia.
Okay. Let's move to the next slide.
Okay. So important for us to understand is what the microbiology looks like. This is very important to the disease, where more than half of our subjects may never declare a site of infection. And the remainder will be split evenly between those that are microbiologically defined and those that are just clinically defined based on site.
So this is really important with regard to endpoint evaluation. And does this offer us the

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opportunity to refine the population based on more recent microbiologic techniques that could either reduce a fungal -- identify those that are likely to be a fungal or a viral origin or more likely to be a bacterial origin?
And I'll move to the next slide.
Okay. So I'd like to present what I'm calling an enigma here, which is that, you know, how do we address what may be existing versions or improvements upon existing beta-lactams, beta-lactam, beta-lactamase combinations, which could certainly serve as an improvement upon existing -- the backbone beta-lactam drug.
Yet, these drugs are in the two examples I've identified here, Cefepime-enmetazobactam and Meropenem-vaborbactam, that are, in fact, indicated only for urinary tract infection due to gram-negative pathogens.
So, you know, while we know that, in fact, that these newer beta-lactam, beta-lactamase inhibitor combinations, which are only approved for gram-negative pathogens, could be a substantial

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improvement upon the existing beta-lactam drug, could this be considered in a more broad-spectrum incidence of febrile neutropenia, where the majority of bugs are anticipated to be gram-positive?
And furthermore, if we were to succeed, particularly in, say, a non-inferiority trial, what would be the value-added, particularly considering antibiotic stewardship as well as substantially higher cost?
And then finally, you know, in terms of considering everything, if I can move to the next slide with regard to clinical trial design. I've included a quote here which is now 29 years old, and I thought it was particularly relevant considering it could really well be the topic of today's workshop. So we empirically treat FN to, in fact, prevent poor outcomes in patients with regard to morbidity and mortality.
And, you know, with regard to what we should evaluate, I think it's been noted earlier whether to evaluate outcomes, potentially, say, mortality versus clinical response. And, you know,

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what we've seen is a disease which has progressed from having perhaps a 50 percent or more mortality, to now in most clinical trials 5 to 10 percent.

And in most cases where the majority of mortality is not attributable to infectious causes, which really makes this perhaps untenable as a primary outcome evaluation which really leaves us with what I believe to still be the most responsible approach to evaluate clinical and microbiologic endpoints as a primary outcome of the study.

However, you know, as for additional design considerations, we also want to consider whether to stratify based on what we know are a very heterogeneous population. For instance, solid versus hematologic malignancies, whether there's been G-CSF usage or prophylactic antibiotics. Okay.

And further considerations are, you know, really, now that we're in an environment where de-escalation to a narrow spectrum or oral treatment can be permitted relatively early in the course, where does that leave our endpoint for evaluation earlier or later in the time course?

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Okay. And I'll move on in the interest of time to the next slide.

So here I've really just laid out what a clinical trial design might look like, and I've really tried to highlight most of my considerations, most of the questions I've raised at the bottom of the slide here, so I won't reiterate those.

And I can move on to the next slide where here I've really hypothetically mapped out what this would look like. This is very hypothetical but really based on a lot of clinical trial experience.

So looking at a clinical trial response, I've assumed that for crude assumptions in a one-to-one randomized trial, that this would roughly require approximately two years to enroll at a cost of about eighty to one hundred thousand dollars per subject. And therefore, thirty to forty million dollars in total. And really in total, this would take four to five years for approval.

And in all likelihood, this would be required for -- it would be required to conduct as a post-marketing requirement, a pediatric trial, which

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may introduce another four years and approximately ten to twelve million dollars to conduct -- to achieve approval in the pediatric indication.

So in total, I would assume that for a pediatric development program for a drug which is based on a single Phase 3 trial which has already been approved in an additional indication, that this would roughly cost forty to fifty million dollars in total. And in total about a decade or so for five years of adult followed by another five years of pediatric approval.

And finally, last slide.

And really what I've shown here is that the clinical development for antibiotics treatment for febrile neutropenia presents a lot of challenges from the sponsor perspective with regard to population, disease, and microbiology, and endpoints. And it's a lengthy and costly path to licensure. So I would propose here that there are additional opportunities that could be pursued.

These could include evaluating pragmatic trials or real-world experience. And

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really, is there an opportunity to evaluate antibiotics rather than in the traditional clinical trial in more of a platform trial design where multiple antibiotics could be evaluated head-to-head against additional therapies?

Really, all of these are intended to look at ways that we can leverage and improve upon existing clinical trial designs to facilitate development and make this more attractive from the industry perspective.

Okay. Next slide, finally.

So it does take a village, and I'm grateful to my team and my colleagues who make work every day a pleasure and particularly for their contributions to this presentation. And thank you all for listening.

DR. PEASE: Thank you, Dr. Girgenti.

Next slide. Thank you. We'll now break for five minutes. Please be back at -- it's, like, 10:22 for the start of session two. Thank you.

(Off the record.)

DR. BOTGROS: It's 10:22. So I would

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like to welcome you back.
THE REPORTER: Are we back?
DR. BOTGROS: Sorry?
THE REPORTER: Are we starting? This is the court reporter.
DR. BOTGROS: Yeah -- yeah. We are starting indeed.
So again, welcome back to this workshop. My name is Radu Botgros, and I'm a physician specializing in infectious diseases. I work at the European Medicines Agency as a senior scientific officer in the Department of Public Health Threats. And I take the opportunity to thank the FDA for having invited me both to present and to moderate this session together with Dan Rubin from the FDA.
So I think, Dan, if you want to say a few words as well?
DR. RUBIN: Hello, my name is Daniel Rubin, and I'll be a co-moderator for this session. I'm from the Office of Biostatistics, CDER, FDA.
Next slide, please.
Our first speaker will be my colleague,

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Dr. Robert Pease, who introduced himself during the first session. At this point, I will turn it over to Dr. Pease.
DR. PEASE: Thank you, Dr. Rubin.
Hello. My name is Robert Pease. I am a medical officer at the FDA here in the Division of Anti-Infectives. In the next ten minutes or so, I will give you a very high-level overview of regulatory pathways that are relevant for febrile neutropenia drug development.
Next slide, please.
This is an outline for my talk today. I'll start with an overview of the approved antibacterials for the empiric treatment of febrile neutropenia and then discuss regulatory programs, pathways and designations, or incentive programs that are available.
Next slide, please.
Two antibacterial drugs have been approved for the empiric treatment of febrile neutropenic patients. Briefly summarizing, both products were available on the market with approvals

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for related indications when their sponsor subsequently performed clinical trials showing benefit in the treatment of patients with febrile neutropenia.
Cefepime monotherapy, which is administered intravenously, was the first approved antibacterial for this indication in 1997. Cefepime was approved for this indication based on the pooled results of two adequate and well-controlled trials with additional supportive studies.
Shortly following Cefepime's approval for this indication, intravenous Ciprofloxacin in combination with Piperacillin sodium was also approved for the empiric therapy of febrile neutropenia, also in 1997, based on one adequate and well-controlled trial with additional supportive studies.
So it has now been more than 25 years since the two currently approved antibacterials were approved for this indication. Additionally, there have been no oral antibacterials approved for this indication.
Next slide, please.
The statutory standards are that a

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drug's effectiveness must be established by substantial evidence defined as evidence consisting of adequate and well-controlled investigations, including clinical investigations. Historically, this was generally interpreted as requiring two adequate and well-controlled trials, each convincing on its own to establish effectiveness.
However, Section 115(a) of the Modernization Act amended the provision to make clear that FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence of effectiveness.
Next slide, please.
This slide lists the types of confirmatory evidence which are described in the reference guidance document. This includes clinical evidence from a related indication which we think is going to be the most pertinent for the indication of empiric treatment of febrile neutropenia.
Next slide.
Under certain circumstances, evidence

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of effectiveness of a drug from a clinical investigation for a particular indication can provide confirmatory evidence of effectiveness to support approval of a drug in a different but closely related indication.

An example of this approach is the submission of a new drug application or a new indication or an already approved therapy, where one adequate and well-controlled clinical investigation of the drug where the new indication is supported by the results from the clinical investigations that form the basis of the previous approval.

An example of this would be if a drug was previously approved for, say, the indication of health care or ventilator-associated bacterial pneumonia, then a single Phase 3 trial for the empiric treatment of febrile neutropenia could be supported with confirmatory evidence coming from the results formed for the basis of the previous approval and the HABP/VABP development program.

Next slide.

An overview of regulatory pathways.

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Traditional approval is based on a clinical endpoint which measures how a patient feels, functions, or survives. There's an accelerated approval pathway based on a surrogate endpoint.

Given endpoints in febrile neutropenia occur relatively quickly, we currently think that the accelerated approval pathway would not be a viable option for a febrile neutropenia drug development program.

But if you have a drug for which you would like to use a surrogate endpoint, please talk to us about it.

The LPAD pathway is for drugs that are intended to treat a serious and life-threatening infection in a limited population of patients with unmet needs. Given that treatment of febrile neutropenia is most likely to be empiric, we think that the LPAD pathway is less likely to apply for the indication of empiric treatment of febrile neutropenia.

But if you have a population in mind, we are available to help. I've included a reference

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to the LPAD guidance document.

Next slide.

Expedited programs are designations which are designed to facilitate the development, and a review of new drugs that address unmet medical needs in the treatment of a serious or life-threatening condition.

The programs include fast track, breakthrough therapy, and priority review. A drug development program may qualify for more than one of these expedited programs.

Fast track designation is intended to facilitate development and expedite review of drugs to treat serious and life-threatening conditions so that an approved product can reach the market expeditiously.

Fast track designation allows for frequent interaction with the review team, and the agency may consider a rolling review in which portions of a marketing application are reviewed before the sponsor submits the complete application.

Breakthrough therapy designation

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requires preliminary clinical evidence that the drug may demonstrate a substantial improvement over available therapy on a clinically significant endpoint.

Breakthrough therapy designation usually means that the drug -- that the effect of the drug will be large compared with available therapies, and the development program could be considerably shorter than for other drugs intended to treat the disease being studied.

The FDA will seek to ensure that a sponsor of a product designated as breakthrough therapy receives timely advice and interactive communications to help the sponsor design and conduct a drug development program beginning as early as Phase 1.

Breakthrough therapy designation is an organizational commitment from FDA, including the involvement of senior management, and it also includes all of the benefits of fast track designation, including eligibility for rolling review, and may be eligible for priority review. What priority review

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does is that it allows a shorter clock for the review of marketing application.

Next slide.

Regarding incentives for the development of drugs for febrile neutropenia, one set of incentives is the Qualified Infectious Disease Product Designation which is available for antibacterial or antifungal human drugs that are intended to treat serious or life-threatening infections.

FDA generally intends to consider a drug to be intended to treat a serious or life-threatening infection if it is intended to diagnose, prevent, or treat such an infection. The QIDP designation applies to a specific indication, meaning more than one designation may be granted for the same active ingredient.

For example, one sponsor may receive QIDP designation for multiple dosage forms of the same active ingredient or for multiple indications. QIDP provides a five-year extension for any marketing exclusivity that the application qualifies for upon

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approval.

And for the first application that's submitted to us, it's an automatic priority review even if you don't necessarily meet other criteria for priority review, and the products are also eligible for fast track designation. We have now had more than 35 QIDP-designated products approved.

Next slide.

An additional consideration is orphan drug designation for rare diseases or conditions that affect fewer than 200,000 people in the United States. Benefits of orphan drug designation include tax credits for qualified clinical trials, exemption from user fees, and the potential for seven years of market exclusivity after approval.

Orphan drugs may also use expedited programs during their development or after a review should they qualify.

Next slide.

In summary, I have provided a high-level overview for the key regulatory considerations for drug development in the empiric

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treatment of febrile neutropenia, including sources of confirmatory evidence, such as clinical evidence from a related indication. I've also reviewed regulatory pathways that are available to expedite drug development and designations or incentive programs.

We have had no new approved antibacterials for this indication in more than 25 years, and there are no oral antibacterials which have been approved for febrile neutropenia.

If you are embarking on a program for the empiric treatment of febrile neutropenia, we highly recommend that you come talk to us, so at the end of the day, we have a development program that has a high likelihood of success.

Thank you. Next slide.

DR. BOTGROS: Thank you very much, Rob, for this nice presentation as well for keeping time.

We are now having our next speaker, which is Dr. Rama Kapoor, who is currently a senior medical officer in the Division of Anti-Infectives at the FDA. Dr. Kapoor completed her internal medicine residency training from George Washington University,

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and she had a fellowship in infectious diseases from the University of Louisville.

So, Rama, over to you.

DR. KAPOOR: Thank you, Radu.

Hello. Can you hear me?

DR. BOTGROS: Yes, we can.

DR. KAPOOR: Thank you.

My name is Rama Kapoor, and I'm a medical officer at the FDA. In the next 15 to 20 minutes, I'll discuss regulatory perspective on the clinical trial design for empiric antibacterial therapy in febrile neutropenia.

Next slide.

Let's start with the roadmap of our discussion today. I'll begin by addressing general regulatory considerations for febrile neutropenia indication, delve into the challenges presented by heterogeneity, discuss primary efficacy and point considerations, comment on the unmet need in the treatment of febrile neutropenia, and conclude with the summary of our discussion.

Next slide.

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To support an indication for febrile neutropenia, one adequate and well-controlled trial is acceptable, and, as Dr. Pease noted, usually these are the situations when the test drug is already approved for another serious bacterial infection.

The FDA acknowledges unique challenges for designing an interpretable and feasible trial posed by heterogeneity among FN patients. These challenges impact both enrollment criteria and choice of the primary analysis population. Discussing ideas that may address these challenges is the focus of this workshop.

Next, I'm going to discuss characteristics of an adequate and well-controlled trial.

Next slide, please.

An adequate and well-controlled trial clearly states its objectives, methods of analysis, permits valid comparisons with a control to provide a quantitative assessment of drug effect, and ensures that the selected subjects have the disease being studied are susceptible to the condition being

Page 87

prevented.

Methods of assignment to study arms in the trial should ensure comparability between the study groups. Ordinarily, in a concurrently controlled study, assignment is by randomization. Measures to minimize bias on the part of the subject, observers, and analysts of the data, such as blinding should be taken, and methods of assessing treatment response must be well-defined and reliable.

Finally, the trial must employ statistical methods that are robust and appropriate for the data collected. This includes not just the primary analysis, but also handling any interim analysis, missing data, subgroup analysis to ensure that the conclusions drawn from the trial are valid and reliable.

With these considerations in mind, let's delve deeper into the heterogeneity challenge.

Next slide.

Based on the clinical course, FN episodes are divided into four categories. Microbiologically defined infection is characterized

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by definitive evidence of infection, either through the detection of bacteremia without a localized site of infection, or through the identification of specific site of infection with or without concurrent bacteremia.

Patients with clinically defined infection presents with signs and symptoms indicative of an infection such as pneumonia or cellulitis but lack confirmatory microbiologic evidence. Unexplained fever or possible infection includes patients with fever without clinical or microbiologic evidence of infection, and fever should not be attributed to non-infectious cause. Whereas non-infectious fever includes patients with fever that can be attributed to non-infectious causes.

Now let's look at the distribution of FN categories in previously conducted trials in next slide.

Next slide.

This slide illustrates the distribution of FN categories in previously conducted trials with consistent finding of a considerable proportion of

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patients falling into the unexplained fever category to the right, almost the rightmost column.

This confirms the heterogeneity highlighting the challenges with establishing the ideology of fever in FN patients. The resulting heterogeneity of the trial population impacts the efficacy analysis.

Also, in one study, a notable proportion of patients were categorized as having doubtful infections underscoring the difficulties in establishing the ideology of fever in febrile neutropenia.

Next, I am going to discuss further an impact of heterogeneity on efficacy analysis starting with general description of trial design in next slide.

Next slide.

In terms of an efficacy assessment, a clinical trial may aim to demonstrate that the test drug is superior or not inferior to active control. A superiority trial seek to demonstrate that the test drug is significantly better than the active control

Page 90

or standard treatment.

In general, a superiority trial provides the strongest evidence of effectiveness. A non-inferiority trial aims to show that the new treatment is not significantly worse than the established therapy by more than a pre-specified margin, which is a non-inferiority margin.

NI trials relies upon an assumption of an anticipated effect of a control based on the data from historic trials, which is the basis for NI margin. Either trial can utilize an active comparator.

Next slide.

The inclusion of patients with unexplained fever in primary analysis population will impact interpretability of superiority and a non-inferiority trial in a different way. For superiority trial, including subjects in the primary analysis population were ultimately classified as having unexplained fever does not compromise trial interpretability if superiority is demonstrated.

However, demonstrating superiority of

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an antibacterial drug may become more challenging if efficacy analysis includes patients not having a bacterial infection. For a non-inferiority trial, inclusion of patients not having a bacterial infection in the efficacy analysis population may bias the trial towards non-inferiority.

Importantly, for the trial to be interpretable, the characteristics of the patients in the primary analysis population of current trial needs to be sufficiently similar to patients in the historic placebo-controlled trials that support NI margin.

Thus, the treatment effect of the active control in FN patients with confirmed bacteriaemia seen in historically placebo-controlled trials, may not be applicable to the efficacy analysis that includes patients with unexplained fever.

This backdrop underscores the importance of precise patient selection and clear definition of primary endpoints that are robust and sensitive enough to detect differences in the mixed population. One approach to address this challenge is through the use of enrichment strategies.

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Next slide.

To improve the feasibility of FN trials, enrichment strategies may be considered to select the population in which the intervention is expected to have most significant effect thereby increasing the trials efficiency and power.

These strategies may include the use of clinical characteristics and risk factors in selecting inclusion and exclusion criteria. And as Dr. Hanson noted, use of rapid diagnostic tools such as polymerase chain reaction for bacterial DNA or advanced imaging techniques can be considered to identify patients more likely to have bacterial infection.

Today's discussion is an invitation to explore these strategies and other ideas during the panel discussion.

Next slide.

Another key consideration for efficacy analysis is the selection of an appropriate endpoint. Trial endpoints serve as predefined outcomes used to evaluate the efficacy and safety of a therapeutic

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intervention.

The chosen endpoints must be well-defined and clinically meaningful. A clinical endpoint is a variable that directly measures therapeutic benefit that is how a patient feels, functions, and survives.

Microbiologic outcomes are not considered as clinical endpoints. For non-inferiority trials, the primary endpoint should be sufficiently similar to historic trials that justify the non-inferiority margin. For instance, in febrile neutropenia, most historic trials demonstrated mortality advantage.

Next slide.

Delving into the primary endpoint considerations further, each option presents its own set of challenges. Potential endpoints of FN trials includes all-cause mortality, primary infection-related mortality, and clinical success. Each endpoint has its advantages and limitations.

All-cause mortality endpoint is objective, reliably measurable, and unequivocally

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relevant. The limitations of all-cause mortality is that mortality in FN may not be related to an infection. Also, patients who survived after modification of study therapy due to poor clinical response or adverse events may be considered success because they survived.

Furthermore, decreasing mortality rates necessitates larger sample sizes to detect any potential improvement over standard of care. The endpoint of primary infection-related mortality more directly measures the efficacy of an antibacterial therapy.

However, the challenge here lies in accurately determining the cause of death. Moreover, as compared to all-cause mortality, the use of this endpoint further lowers event rate resulting in an increase in trial sample size.

So the endpoint of clinical success, on the other hand, includes other outcomes of interest such as resolution of fever, absence of recurrent febrile episodes, eradication of the infection, or discontinuation of study therapy due to adverse

Page 95

reactions. However, it introduces variables that may be subjective or influenced by the external factors such as -- modified therapy.

Blinding and other strategies such as establishment of objective criteria could be used for assessing treatment outcomes to address the observer bias.

Now, let's examine the mortality rates observed in historic and recent trials.

Next slide.

The table here displays mortality rates observed in old and recent trials. The timing of the mortality assessment varied, but overall mortality rates in recent trials are lower as compared to historical trials.

For instance, as you can see, the studies conducted by the International Antimicrobial Therapy Cooperative Group in 1987, had a mortality rate of 26 percent which gradually went down to 8 percent by 2006. In more recent trials, mortality rate is down to as low as 2 percent.

Next slide.

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This slide looks at the different outcomes used in FN trials. Most FN trials used a composite endpoint to evaluate the response to therapy. However, the definition and timing of the assessment of these endpoints vary leading to challenges in interpreting the trial results.

Success was generally characterized by a combination of clinical and microbiologic criteria, primarily the resolution of the FN symptoms, and the eradication of infecting organism without modification of the initial treatment regimen. Failure was generally defined as death, persistence of symptoms or causative pathogens, or modification of study therapy.

Patients with fungal or viral infections or non-infectious fever, protocol violations, study drug discontinuations due to adverse events, are classified as non-accessible for response and were excluded from the primary analysis in some trials. That poses additional challenges in interpreting the trial results.

So, in general, a trial for regulatory approval purposes would be expected to use an ITT or a

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modified ITT for analyzing the trial data.

Next slide.

We are interested in discussing areas of unmet need in treatment of febrile neutropenia and would appreciate if the panel could comment on the need for novel outpatient therapies in febrile neutropenia.

For instance, in the setting of prevalence of quinolone-resistant and ESBL-producing pathogens, clinicians might be reluctant to use currently recommended oral therapies for outpatient empiric use in FN patients.

Could an oral drug with activity against drug-resistant pathogen a suitable option for developing an antibacterial drug for the outpatient management in febrile neutropenia?

Next slide.

So, in summary, a major goal of this workshop is to discuss the ideas in addressing challenges in designing FN trials. A major challenge impacting the feasibility of all trials and interpretability for an FN-NI trial is the

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heterogeneity of the population of patients with FN, and strategies to enrich the trial population with bacterial infections are needed to overcome this challenge.

With the decreasing mortality rate, choosing a primary efficacy endpoint is also challenging. While there is a greater flexibility for superiority trial designs, clinical meaningfulness of measured outcomes, strategies to address observer bias, and an ITT or a modified ITT analytic approach are important considerations.

Another goal of this workshop is to understand unmet need in the treatment of febrile neutropenia and discuss strategies to develop drug products to address these needs.

That completes my presentation. Thank you so much for your interest and attention.

DR. RUBIN: Thank you very much, Dr. Kapoor.

This is Dan Rubin, and, again, I will give the next talk on statistical considerations in clinical trials in febrile neutropenia.

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Next slide, please.

I will first discuss considerations related to superiority trial. I will then discuss non-inferiority trials and the problem of justifying a non-inferiority margin for a febrile neutropenia trial.

Next, I will describe the statistical trade-offs involved in selecting the analysis population primary endpoint and non-inferiority margin. And finally, I will discuss sample size considerations.

Next slide, please.

Suppose a sponsor plans to conduct a randomized trial to evaluate an experimental antibacterial drug by comparing it to a control antibacterial drug. In a superiority trial, the objective is to determine whether the new drug is better than the control drug.

Next slide, please.

This could be a head-to-head comparison between the experimental drug and control drug. A superiority trial could also use an add-on design in

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which all patients in both arms receive background standard of care, but patients in the treatment arm additionally receive the experimental drug.

If ethically acceptable, a superiority trial could restrict the inclusion/exclusion criteria or analysis population to patients in whom superiority may be more achievable. An example could be patients with greater certainty of bacterial infections due to resistant pathogens.

The main challenge with superiority trials relates to feasibility because it may be difficult to enroll large numbers of patients for whom a new experimental drug could greatly improve upon an optimized standard of care control antibacterial regimen in the comparator arm.

Next slide, please.

In a non-inferiority trial, the objective is to determine whether the new drug is unacceptably worse than the control according to some margin. For instance, as shown in the figure at the bottom of the slide, if the margin is 10 percent, then the trial would need to provide statistical evidence

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to rule out a difference in success rates between the new drug and active control that is 10 percent or larger in favor of the control drug.

Next slide, please.

So how should the non-inferiority margin be selected? Well, the margin should not be any larger than a value that is often called M1. This is the difference in response rates between the active control and hypothetical placebo.

The reason why the non-inferiority margin should not be larger than M1 is because otherwise demonstrating that the new drug is within M1 as the active control would not provide indirect evidence that the new drug is actually better than what could be achieved with a hypothetical placebo.

Ideally, M1 should be quantified by meta-analyzing previous placebo-controlled trials of the drug that will be used as the active comparator in the prospective trial. And the hypothetical example in this slide, the confidence limit from the meta-analysis supports an M1 of 20 percent.

Next slide, please. Next slide,

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please.

Once quantifying the M1, two additional steps are often applied to reduce the margin to a value term M2, which is the non-inferiority margin that will be used in the prospective non-inferiority trial.

The first step is that the value could be discounted based on subjective judgment if the setting of the historical data used to determine M1 was different from the expected setting of the prospective non-inferiority trial.

The second step is to reduce the margins that preserve a clinically acceptable fraction of the treatment effect to ensure that a new drug found to be non-inferior to an active control does not have clinically unacceptable efficacy compared to this control.

For example, if the non-inferiority margin M2 is 10 percent, an efficacy decrement of 10 percent or more would be clinically unacceptable.

Next slide, please.

The challenge we have encountered

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applying this framework to margin justification for febrile neutropenia trials is that we are not aware of any previous placebo-controlled randomized trials of antibacterial drugs.

Nevertheless, there is evidence that empirical antibacterial therapy would have a very large treatment effect compared to a hypothetical placebo. However, the magnitude of the treatment effect over a hypothetical placebo may depend on the analysis, population, and endpoint.

Next slide, please.

The studies from shortly after the introduction of empirical antibacterial treatment provide evidence that effective antibacterial drugs would have a large effect on key outcomes compared to a hypothetical placebo.

One study from 1971 found that in the year before use of empiric treatment with Carbenicillin and Gentamicin for leukemia patients, the survival rate for patients with Pseudomonas aeruginosa bloodstream infections was only 9 percent.

Moreover, half of the deaths were

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within 72 hours of drawing a first positive blood culture. After instituting empiric treatment, the survival rate and a subsequent cohort increased to 69 percent. Further, the rate of complete improvement increased to 62 percent.

Another study published in the same year found that in cancer patients treated with Polymyxin, the survival rate within 10 days from the onset of septicemia was only 28 percent. After introducing empiric treatment with Carbenicillin, that survival rate increased to 81 percent.

Further, the complete response in Pseudomonas aeruginosa bacteremia episodes increased to 71 percent.

Next slide, please.

Despite the small sample sizes, you can see from the -- circles in bold that if meta-analyzing the study, there is evidence that the difference in clinical response rates between empiric treatment with an active antibacterial drug and a hypothetical placebo would be at least 30 percent.

However, when considering the

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non-inferiority margin that would be used in a prospective trial to evaluate a new drug, this may need to be discounted to account for several limitations. These were non-randomized study. The studies were conducted in settings with different background standards of care than would be present today.

And additionally, patients with Pseudomonas bacteremia had a higher certainty of lethal bacterial infections than many patients with fever of unexplained origin who might be enrolled in more asthmatic trials.

Next slide, please.

I will now discuss several trade-offs that should be considered when deciding upon the analysis population endpoint and non-inferiority margin.

The trial will need to determine which categories of fever should be included in the primary analysis population among fevers of unexplained origin, clinically documented infections, microbiologically documented infections, and

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bloodstream infections.

As the analysis population becomes more restrictive to ensure bacterial infections, the trial likely becomes more sensitive for differentiating antibacterial drugs. And a non-inferiority trial, the margin justification would likely be on surer footing, but a drawback is that trial feasibility likely decreases.

And in addition, it would become harder to generalize results to an all-comer target population.

Next slide, please.

There are also trade-offs when deciding upon the primary endpoint. Consider use of a composite endpoint defined by components such as all-cause mortality, development of serious medical complications, or failure to respond to empiric antibacterial therapy as defined by persistent fever, worsening of clinical signs of infection, or the need to escalate or change the antibacterial regimen due to lack of efficacy.

As the endpoint becomes more

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restrictive to only include major events with the most extreme example being an all-cause mortality endpoint, then the endpoint may become more meaningful. The endpoint also likely would be defined more objectively.

And a non-inferiority trial, the non-inferiority margin would likely be on surer footing because the historical data I described mostly related to survival. However, with an endpoint driven by mortality or serious complications, the study population may need to be enriched to ensure participants are at high risk for major events, and this would likely decrease trial feasibility.

Next slide, please.

Finally, in a non-inferiority trial, there are important statistical trade-offs when deciding upon the non-inferiority margin. As the margin is decreased, the trial reduces the potential efficacy decrements allowed for the new investigational drug.

The margin justification would also likely be on surer footing. However, the trial

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feasibility would become more challenging.

Next slide, please.

I will now discuss sample size consideration. The slide displays sample sizes for superiority trials. The calculations assume a standard statistical significance level, 90 percent power, and one-to-one randomization. The evaluability rate is the proportion of randomized subject expected to be included in the analysis.

And this may depend on whether the trial uses an intent to treat population or is more restricted to ensure bacterial infections, such as excluding subjects without clinically or microbiologically documented infections.

The table shows evaluability rates at 100 percent, two-thirds, and one-third. The table also displays sample sizes assuming a success rate and the control arm of 65 percent, and success rates in the experimental arm that correspond to being 15 percent better, 10 percent better, or 5 percent better.

For instance, suppose the evaluability

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rate is 100 percent as might occur if the primary analysis population was an intent to treat population. If the treatment arm is 10 percent better than the control arm, so that success rates in the two arms are 75 percent and 65 percent, then a total sample size of 879 participants would be needed to power the trial or approximately 440 subjects per arm.

The sample size increases if the evaluability rate is lower or if the treatment effect is smaller.

Next slide, please.

My final slide shows sample sizes for non-inferiority trials. The sample size calculations assume success rates for the primary endpoint are equal in the control arm and experimental arm.

The table displays sample sizes for success rates of 70 percent, 65 percent, and 60 percent. The table also shows sample sizes for margins of 15 percent, 12.5 percent, or 10 percent, assuming that there would be justifications for these margins for that trial population and endpoint definitions chosen.

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You can see that, in general, non-inferiority trials for febrile neutropenia may require relatively large sample sizes. For instance, suppose the evaluability rate is 100 percent, the success rate in each arm is 70 percent, and the non-inferiority margin is 10 percent.

The table shows that the trial would need a sample size of approximately 881 total subjects or approximately 440 subjects per arm. The sample size would increase if evaluability was lower, the success rate was closer to 50 percent, or the non-inferiority margin was decreased.

Thank you very much.

DR. BOTGROS: Thank you very much, Dan, for this very nice presentation.

And the next two presentations will be actually from the EMA and the Japanese PMDA for which there will be Katsuhiko Ichimaru, who is currently a review director in the anti-infectives area at the Pharmaceuticals and Medical Devices Agency in Japan.

He works at the regulatory agency for about 20 years and has extensive experiences in review

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in anti-infectives and psychology. But first, as per the order of the slides, I will talk to you about the regulatory considerations that we have in the European Union about this indication.

Next slide, please.

As we heard today a number of times, and I won't enter into details again, febrile neutropenia is a coined entity and obviously is an entity that, you know, needs and also benefits from treatment or either preemptive treatment, prophylaxis, or real treatment.

You see here on the slide that the infections, most of them are bacterial caused by both gram-negatives and gram-positives, and we heard today what is the balance between the two. Obviously, there can be also other agents like fungal or viral, less frequent.

The next slide, please.

And in any case, we heard that mortality is much lower if the condition is treated with -- is managed with antibiotics. Obviously, I won't be telling you about, you know, what -- because

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this was addressed previously by speakers. So I will get to the regulatory side of it as we see it in the European Union.

Next slide, please.

As in the United States, some of the product information of what we call old antibiotics, that is antibiotics that have been approved some of them a long while ago, still retain the indication in period treatment of febrile neutropenia.

And you see here as a comparison, the U.S. label and one of the labels for Cefepime in the European Union, actually it's a Romanian one, and you see that -- or you can trust me that actually the indication is empiric therapy for febrile neutropenic patients.

Next slide, please.

At the EMA, we have been conducting and harmonizing product information of old antibiotics. And around 10 years ago, it was agreed that granting of the wording of the indication for an antibacterial agent for febrile neutropenia was not supported any longer.

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And our approval committee, the CHMP, agreed to replace the outdated indication at the time of harmonization to the product, so the antibiotic may be used in the management of neutropenic patients with fever that is suspected to be due to bacterial infection.

Obviously, this is more of a wording change rather than anything else, and actually it has been recognized that this condition needs to be treated with antibiotics.

What we also notice is that prospectively we had an extremely limited number of applications that were received in the European Union and, therefore, any further meaningful discussion on the design of clinical trials that would underpin such an indication has not taken place.

It was acknowledged, as I said, that the institution of antibacterial agents prior to or at the time of onset of expected neutropenia is common practice. And in some patients population center, it is done so that the rates through infections may be comparatively low compared to other patient groups.

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Next slide, please.
The study population enrolled with acute bacterial infections during neutropenia comprises, as we heard before, some ratio of patients with breakthrough infections despite prophylaxis, patients who have not received routine prophylaxis.
So you see there are at least these two subgroups which we believe may be substantially different in terms of their underlying conditions and are likely to be enrolled also at different centers with variable routine management protocols.
So on this basis, at the very least, stratification according to prior or no prophylaxis may be appropriate. The protocol should also provide clear criteria to be met in terms of neutropenia, and so what is the cutoff value? What is the expected duration of the neutropenia?
You saw that there are different risk categories and also neutropenia is, you know, undivided in a number of categories. Also, the definition of fever will require alignment across sites.

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Next slide.
So if the test agent needs to be co-administered due to its spectrum of activity, then the additional agents should be specified in the protocol, including the dose regimen and any dose adjustments. And if possible, the range of agents allowed should be standardized.
But there should be clear criteria for stopping therapy in the trial protocol pertaining to susceptibility data, clinical progress, cultural results, recovery of the granulocyte count at the very least, and also the criteria for failure need to be specified.
Next slide.
To agree on the key elements of any clinical trial which would underpin this indication, we highly recommend you to come to the EMA to discuss with us these during development. We have a number of processes and procedures that we offer to developers. I think the most important of which scientific advice and the innovation task force discussions.
And, you know, we will definitely be

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discussing all these in the panel discussion, but, you know, one may wonder if, for instance, for prophylaxis and for, you know, treatment of breakthrough infections, we need only to stratify or maybe we can think even about different endpoints.
I'll stop here. I thank you very much. And I give the floor now to our colleague from Japan. Thank you.
DR. ICHIMARU: Thank you for your kind introduction, Dr. Radu.
I'm Katsuhiko Ichimaru, Review Director in Anti-Infectives Area, PMDA. Today, I would like to -- share review of therapeutic or febrile neutropenia, etcetera, with you.
Next slide.
At first, I will touch the definition of FN in Japan and recommended -- they were developed by Japanese Society of Medical Oncology. The latest version was published in 2024. The U.S. IDSA published FN Guideline in 1990 and revised in 1997.
We find the IDSA Guideline -- Japanese FN Guideline was developed in 1998. Therefore, the

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Japanese definition of FN is very similar with the U.S. one. However, body temperature is usually measured in the armpit in Japan. Actually, temperature is approximately 0.5 degrees lower than oral temperature.
In Japanese Guideline, the criteria is written in both measurement sites. Neutrophil count is same with IDSA definition. Bottom lines are recommended empiric therapy in Japan. The upper line is approved antibiotics for FN in Japan. Bottom line is recommended antibiotics but not approved for FN in Japan. These recommended antibiotics are also similar with U.S., I think.
Next slide.
This slide shows approved anti-infectives for FN in Japan. Two antifungals and four microbials agents were approved. Right front are dosage for adult and pediatric of each drugs. I will share the data on which these are depicted and obtained regulatory approval in the next slides.
Next slide.
The first drug is Cefepime. It is the

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first antimicrobial agent approved for FN in Japan. And that product was approved in 1995 as a new active ingredient. FN was additionally approved in 2004. When the product is approved for FN in Japan, it has been already approved for FN in U.S., Sweden, and Germany.

In Japan, the product was prescribed to FN patient as off-label use before regulatory approval. Such data was published as scientific articles. Such off-label use, the data, and the clinical trial data which were submitted to U.S. FDA to obtain regulatory approval were utilized for regulatory approval in Japan.

Because Japan has a unique regulatory system that the administration of the drug or the indication is medically and pharmaceutically known, and the drug's indication is approved in a country with the same regulatory levels as Japan.

If these two conditions are met, the company can skip to conduct clinical trials to obtain regulatory approval. It means that the company can obtain an additional indication based on existing

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data. By utilizing the system, Cefepime obtained FN indication in Japan.

Next slide.

Next case is Meropenem. The antimicrobial agent was approved as a new active ingredient in 1995 in Japan. FN is approved as new indication in 2009. The data package is described here. Phase 1 and the Phase 3 trials were conducted in Japan. For pediatric indication, PK/PD analysis was utilized.

Next slide.

This slide shows clinical data package for other products. You can see most of the products utilized for clinical trial data to obtain regulatory approval in Japan. In addition to the following data, small scale of clinical trials were conducted to confirm the similarities in effectiveness between overseas and the Japanese.

Regarding the Vancomycin, FN indication was approved based on published scientific articles.

Next slide.

So far, I shared Japanese -- of FN

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approval in Japan. This is a summary of my talk. In some cases, the definition is different region by region. However, the definition of FN is the same between U.S. and Japan. Foreign data was utilized to obtain regulatory approval. So far, foreign data was utilized as kind of a separation.

However, it means possibility of multi-regional clinical trial. MRCT is one of the useful tools to obtain regulatory approval for FN. I wish that MRCT can be used efficiency obtain approval.

Thank you.

DR. RUBIN: Thank you very much to all of the session two speakers. We will now break for ten minutes and then return for a moderated panel discussion at 11:26.

(Off the record.)

DR. TAPLITZ: Hello. It's 11:26, so I think we'll go ahead and get restarted on the panel discussion. I have met you earlier. I'm Randy Taplitz from City of Hope National Medical Center joined by my co-moderator, Dmitry Iarikov, and by this august group of panelists whose affiliations you can

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see listed on this slide.

So in order to kick off this discussion, what we will do is, you know, read the questions and ask for certain individuals to sort of start a response, and then what we'll do is, we'll take comments from the panelists group. We would appreciate if you could raise your virtual hands, and we will call on you in turn from the panelists group.

Also, I know that we have, well, I saw it previously one question in the Q&A. But I think if there are questions that you specifically would like answered, please put them in the Q&A, and we can take a look at those as well.

So without further ado, why don't we move to the first -- the next slide which has the discussion questions. So the first question is "Please discuss the greatest unmet needs for empiric treatment of febrile neutropenia," and "comment on an ideal drug profile."

And to start us off, we thought we would ask Dr. Zimmer to make some comments on this.

DR. ZIMMER: Thank you, Dr. Taplitz.

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Well, to start off with, an ideal drug for empirical treatment of febrile neutropenia would have to be broad-spectrum in nature. It would need to include coverage against particularly Enterobacterales, Pseudomonas.

Ideally, those with different resistant mechanisms, ESBLs and Carbapenem resistance, to be able to most adequately treat these infections in the age of increasing antimicrobial resistance. We would also want it to have excellent coverage against gram-positive organisms, particularly the sensitive streptococcus and staphylococcus.

And then as alluded to in earlier talks, it would be very ideal if this agent -- if we had options to, apart from the oral Fluoroquinolones, to use for outpatient therapy either a novel oral antibiotic or a long-acting intravenous antibiotic that could be amenable to be arranged for outpatient transition, either to avoid admission to the hospital or to enable patients to be discharged early once they're clinically stable and improving.

And then, of course, we would want the

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agent to be well-tolerated from a side-effect profile. One of the questions that has come up sometimes in the management of febrile neutropenia, particularly with Cefepime use, is the risk of neurotoxicity or neuro-side effects with Cefepime.

And so if I'm picking my wish list, I also want it to be well-tolerated with minimal side effects.

DR. TAPLITZ: Great, thank you.

Other comments from the panelists?

Okay. Juan, and please introduce yourself if you haven't already been a speaker here today.

DR. GEA-BANACLOCHE: Yeah. My name is Juan Gea-Banacloche. I work in the infectious diseases consult service at the NIA Clinical Center, and which probably contributes to my biases because this is the place where cytotoxicity monotherapy was introduced 40 years ago or so, and we, interestingly enough, keep doing the same thing that Dr. Pitchell [ph] was doing back then.

So one thing that came to mind while

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reading -- while watching the presentations today, is that we have shifted somehow in our way of approaching the problem because with the definition of the ideal drug, why isn't Imipenem-relebactam the ideal drug as Dr. Zimmer just described?

It got great coverage against resistant organism, including resistant Pseudomonas, resistant Enterobacterales, gram-positives. We don't need to do anything else; right? And the reason is that we now are more aware of the consequences for other patients of using drugs with too broad of a spectrum. That consideration wasn't there; right?

Originally, when the first big paradigm shift was empirical treatment against Pseudomonas, no one was saying, "Well, but most people don't have Pseudomonas." No one said, "You're overtreating a lot of people who don't need this antibiotic."

Everybody said, "Yeah, we have a drug that covers the most dangerous things, and so we'll give it to everybody." And that is the way we are in the current standard of care that we are on.

And so the question about the unmet

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need in the neutropenia is really the key question. What is the problem that we need to solve? Is the problem that many patients are dying of resistant gram-negative rods?

Because if that is the problem, then the solution is we either identify the patients who need empirical treatment against those better, or we give empirical treatment against those MDR gram -- rods drugs to everybody.

But maybe that is not the problem. And I think that that is the problem that too many patients are getting exposed to too many antibiotics for too long because then the solution for that problem is a different kind of trial. We need to know how to de-escalate. And so I think that that is what we need to define.

What is the problem in the empirical management of febrile neutropenia that we need to fix? What is harming our patients, or what is harming our non-patients, future patients, our hospitals in terms of resistance? And I think that until we nail that down, it's very difficult to get anywhere.

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DR. TAPLITZ: Okay. So basically what you're saying is that we maybe need to nuance and define what the questions we need answered are, and it's not necessarily going to be go broad or go home.

DR. GEA-BANACLOCHE: Exactly.

DR. TAPLITZ: Dr. Liu from -- well, you can introduce yourself, Doctor.

DR. LIU: Good morning, everyone. My name is Catherine Liu from the Fred Hutchinson Cancer Center. So I fully agree with the comments that were just made. I do think in terms of unmet need, we need to address the growing threat of antimicrobial resistance.

But in that context really thinking about how we can move from a one-size-fits-all empiric approach to management of neutropenia fever, which I think is what we're, you know, kind of what we're doing right now, but can we move towards a more tailored approach to empiric therapy?

Really identifying those patients who are at risk for MDROs, who are at risk for colonization with ESBLs and CREs, so that we can

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provide a more nuanced approach to empiric therapy. And I think, you know, to some degree, we are doing this on a pragmatic level. We are sort of identifying patients in the clinical setting whom we think may need something other than Cefepime for empiric therapy.

But how do we study this in a randomized control trial? Can we take a more pragmatic design where patients might be risk ratified based on their, you know, risk of colonization? Can we screen folks to identify those who might be at risk for these MDROs to provide a more targeted approach with some of these broader spectrum agents?

DR. TAPLITZ: Dr. Marr?

DR. MARR: Hey, good morning, everyone. Kieren Marr here. I'm a retired prior director of Transplant and Oncology ID at Johns Hopkins and now currently affiliated with Elion Therapeutics, an antifungal company.

I want to build on the comments by my prior colleagues, and I agree with them completely, but just kind of to go back. As probably one of the

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older people here, we have to remind ourselves that fever neutropenia was classified as an indication for antibiotic therapy based on these observations, right, in the 1970s.

And what have we done in the last 50-plus years? We have incrementally decreased the risks that fever during neutropenia actually is an indicator or a reliable indicator for a bacterial infection.

And that's what we've done by choosing the hosts, our treatments even, when we use the broad categories of -- B&T, we now know that -- and we're using drugs that are really minimizing that duration and depth of risk. So we have to start thinking about fever during neutropenia as exactly what it is. It's a symptom. It's not a syndrome.

And then get to the place, in my opinion, where we define what the syndrome is, and we can do that iteratively with our multiple different kinds of diagnostics. There's limitations of diagnostics here too because the prevalence of infection is so exceedingly low.

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So, you know, it becomes very complex trial design. But in my opinion, the first thing we need to do is to acknowledge that this is a symptom. It's not a syndrome as it may have been 50 years ago. And that puts it in a very different context for studying and whether that becomes a feasible indication from my point of view.

I'll stop there for now.

DR. TAPLITZ: Kieren, how would you define a syndrome that needs to be --

DR. MARR: So what do we do? I mean, we've -- we're all on these guidelines, right? You've got fever during neutropenia, you do a CT scan, blood cultures. You do the standard diagnostics, the physical exam. Clinically, we kind of understand or have in our minds an understanding of where that infection is likely to be coming from.

If that person has a nondescript, infiltrate, nodule, etcetera, we think it's maybe an early pulmonary infection. Or if they don't, maybe we think that it's kind of an early sepsis, especially with the GI source. We can iteratively then say this

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is a presumed bacterial infection from the lung or presumed bacterial infection from the gut.

I tend towards kind of taking the approach now that our European regulators are kind of inching towards, and that fever during neutropenia itself needs to be kind of further defined in a syndromic fashion, both so that we can understand what drugs would be most important, and so that we can design a trial where there's a prevalence estimate for outcomes that will enable the feasibility of a trial design.

DR. TAPLITZ: So I think there's a question in the Q/A which I'm going to read and ask for comments on. An anonymous attendee is asking to comment on the potential role of non-small molecule products such as phage or antibodies for febrile neutropenia, and what consideration should be considered in developing such products?

Anybody want to make a comment?

DR. BOTGROS: Yeah, maybe I can start.

I mean, phages, talking about phages, so alternatives to antibiotics. I think the current

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picture is that actually phages, even for standard indications as add-ons to antibiotics, have not yet shown efficacy from, you know, well-controlled randomized clinical trials.

Actually, the trials that have been conducted have rendered negative results due to a number of issues from stability issues of manufacturing and stability and sort -- in this kind of -- but also, due to, you know, to the fact that what has been studied was most of the time a cocktail, which from the very beginning was not active for all the strains on the infection.

So when it comes to phages, while obviously if they do work, because I think safety is a bit less of an issue with phages. It's, you know, it could depend on the way they are administered and for what indication, but most of the time they are deemed to be fairly safe.

While, again, on efficacy what we have, to the best of my knowledge, are anecdotal evidence like, you know, case reports. We know that, you know, they have been used in the former space of the Soviet

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Union and some Eastern European countries.

So while I cannot exclude that they may play a role in the future, I think we first need to have the proof of concept that would reassure us that this kind of products really do work and do provide added value to the antibiotic treatment.

Thank you.

DR. TAPLITZ: Yeah. I mean, I will make a comment and then Andrea also.

So I do think that there will be work on phage therapy in the future. I know that there's some work looking at it for even for sort of preventive therapy for, you know, patients colonized with multidrug-resistant organisms, etcetera. But I agree, I'm not sure that it's necessarily ready for primetime.

Andrea, did you want to make a comment?

DR. ZIMMER: I was going to say the same thing, Dr. Taplitz, and add on to, I think this kind of crosses that border of, you know, targeted therapy versus empirical therapy. And so phage therapy most commonly has been utilized when there's

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an identified organism with a specific profile and susceptibility, you know, genetic profile.

Once that is a known organism either colonized previously and concerned to be, you know, causing reinfection or identified from a clinical isolate, that's when the phage therapy kind of comes into play.

When we're talking about empirical therapy of febrile neutropenia, we're sort of starting from that patient that is presenting in the ER or in clinic day one. And you don't know if they're going to have a bacteremia or if they're going to have, you know, develop a positive culture. You just have the data on, you know, the exam and the radiographic findings that you're working with that day.

Once we're changing therapy, once we have identified, you know, a source or a culprit organism, then we kind of move into a different category of treating a known infection or process.

DR. TAPLITZ: So we have another question that I actually think fits better into question number two. So is there any further comments

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on unmet needs from empiric treatment of febrile neutropenia from the group?

If not, then maybe what we'll do is move to the second question which is "Discuss strategies for enrichment of the study population in patients most likely to have a bacterial etiology for their fever (e.g., clinical characteristics, diagnostics, etc.)."

And I'd like to call on Dr. Hanson first for her comments.

DR. HANSON: Yeah, sure. Thanks, Dr. Taplitz.

So I'm interested in thoughts of the panelists on this as well. When I've reviewed the literature on this, there actually have been a number of studies that have looked at risk prediction models trying to look at an individual patient and assess what's the likelihood that this person with neutropenia fever actually has an invasive bacterial infection.

Most of those models have been validated in pediatric patients actually, and I

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haven't seen as much work done on the adult side. But the risk models tend to factor in a variety of things. Host factors like what is the underlying malignancy with heme malignancies, especially leukemia is being at higher risk, and relapsed leukemia is being at higher risk.

Clinical science and symptoms. So how high is the fever? Is the patient hypotensive? Hypotension is another one that tends to fall out in various models as being predictive of an invasive bacterial infection.

Also, certain findings on physical exam. Like, skin findings that are suggestive of cellulitis, for instance, is one that tends to potentially be more predictive of bacterial infection. And then this whole question about diagnostics and how might diagnostics help us.

In my talk, I really focused on pathogen directed tests, but there are a number of studies looking at host directed tests. Markers of inflammation that are non-specific. For instance, C-reactive protein, pro-calcitonin, elevations of

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those in various models have been more suggestive of bacterial infection, but pro-calcitonin is a little more controversial. Some studies suggest it's suggestive, others not.

But many analysts have said that elevated levels may be more suggestive of the presence of a bacterial infection. Elevated lactate, another marker. So again, thinking about enrollment in clinical trials, wanting to potentially stratify for some of these findings like hypotension and lactate as markers of people who are more severely ill and making sure arms are balanced.

And then the last thing I mentioned during my talk is assessments of the microbiome and how it's perturbed or is the patient known to be colonized with multidrug-resistant organisms, either in the gut or have a prior infection with a drug-resistant pathogen, might allow you then to identify individuals who are more at risk and more likely to have a bacterial infection as the cause of their fever.

Maybe I'll pause there, as some of the

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things that have fallen out in models, especially for kids that are suggestive and see what others think.

Thanks.

DR. TAPLITZ: I might actually since I'm a moderator, I get to ask a question first before going to some of the other questions, but what about other biomarkers? So if using proteomics, I mean, I think, you know, as you kind of commented, it's not all about the pathogen. It's about the response to the pathogen.

DR. HANSON: Yeah.

DR. TAPLITZ: I just wondered if you had any comments on --

DR. HANSON: You know, I'll mention a couple of --

DR. TAPLITZ: -- future technologies, genomics, proteomics, etcetera, in order --

DR. HANSON: Yeah.

DR. TAPLITZ: -- to have biomarkers to look at that.

DR. HANSON: I think in the future a number of things are being looked at. One is

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different cytokine profiles potentially. IL-10 falling out in models being more predictive. And then this whole kind of era of the genetic host response. So immune response profiles that may be more suggestive of, is this fever due to an infection or not?

If it's infection, is it bacterial versus viral versus fungal? A lot of that work is being done mostly in immunocompetent patients with neutrophils because they're looking at the signals in the gene expression profiling in neutrophils. So in a neutropenic patient that might not be as predictive or useful.

However, there's some newer work looking at gene expression profiling in plasma that may be totally separate from the neutrophil response that will be interesting to see down the road. Is this predictive for immunocompromised patients?

So I think, yeah, the wave of the future for me in terms of diagnostics is some combination of pathogen directed testing and host stress directed testing to say responding to an

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infection or not. If so, what's the broad category and can we be more targeted in our empiric approaches?

Thanks for that.

DR. TAPLITZ: Yes, thank you.

Dr. Lyman?

DR. LYMAN: Yes, thanks. Dr. Hanson already touched on this, but clearly we're victims of our own success here in the sense that with better drugs, better supportive care, better preventive measures, there's a need to, as this question has highlighted, to identify enriched population for trials moving forward.

And here, again, we run into a dilemma. There are distinctions. You know, the models that we have and that we've mentioned during this program, have their limitations. And, in fact, the test performance is not terribly good with any of them.

And we've distinguished factors that enriched for the risk of FN which appears to have gone down, but also for the serious medical complications and potential mortality from FN which is still real. Patients are still dying, as we know, from FN.

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So this brings us to the issue of how do we identify those patients who are at greatest risk from FN and make sure that they're not being missed and potentially could be enriched in the studies of new drugs or even some of the old drugs.

And things I'm thinking of are particularly things like age, older age, or comorbidities. And I can't overemphasize enough how important major comorbidities are, such as diabetes, cardiopulmonary disease, cardiovascular disease, and so forth. And, of course, patients with overt sepsis and tissue invasion with infection, so, and unfortunately, there are exceptions.

Many of these factors often become the exclusion factors we've used in the prospective studies. So what we need, it's challenging, but we need more pragmatic approach to the -- not only the inclusion but the exclusion criteria and make sure that the patients we're excluding aren't the ones who are most likely to benefit from the therapies that we're testing.

So I think there are opportunities

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here, better risk models, as Dr. Hanson said, I think are really needed. But we know enough that I think we can find ways to better enrich the eligibility for these trials.

DR. TAPLITZ: Yes. Thank you.

Yeah. So, you know, again, not necessarily excluding the better risk stratification in the inclusion group, maybe a larger inclusion group. And I think we'll probably talk a little bit more about that in trial design as well.

Kieren?

DR. MARR: Yeah. Great conversation, great questions. You know, all of our risk stratifications have, in my opinion, been too high up to the things that we can identify that we don't really understand. They have not been validated as Dr. Hanson points out.

And really what we need in order to really deploy these risk strategies is to identify the population that with fever would have a pre-test probability of bacterial infection that exceeds 30 percent.

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And the reason that I'm bringing up that number is straight up Bayesian statistics, which is you cannot have a reliable positive predictive value of any diagnostic or any symptom or any risk criteria with a prevalence or pre-test probability that is less than 30 percent.

And what we can know is that we can deploy all of these diagnostics and with the risks that we're currently in the zero to 10 percent, 20 percent is our high-risk category right now. With that, we can rely on negative predictive values and not positive predictive values just because of that driver alone.

And so I think this is the absolute bottom line on the problem of fever during neutropenia trials. You can be fever, and all clinicians on this call can and will honestly say that we can pick out of a group of ten people with fever neutropenia, the two people who are likely to have it based on things that are not going to register necessarily in our inclusion/exclusion criteria.

And the flip side, which are all of

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those predictors of, you know, when those neutrophils are going to come back. And one of the other issues that we should be hitting home, is that these criteria also impact overall mortality more so than the infection does. Relapse malignancy, the outcome of death, you just can't include those people in a trial, whether there's a documented infection or not because that's the driver.

So, with all of this said, there are some important new ways that people are approaching that. I'll just draw out the work of Carol Garcia-Vidal in Barcelona, where she's using machine learning models to validate actual risks in the setting of fever during neutropenia.

And probably, in my opinion, it's going to take a lot more data and a lot of that kind of analytic approach to actually derive a population or agreement where there's a studiable population that we can identify and to try and simulate what, as clinicians, have been looking at and labeling as high risk, low risk, because our current risk strategies aren't adequate in my opinion.

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DR. TAPLITZ: Juan?

DR. GEA-BANACLOCHE: Yeah. So one thing that I want to mention, I put it on the chat. But I think that the data on cell-free DNA suggests that most cases of fever during neutropenia reflect either active or impending bacterial infection.

And so I don't know that we're ever going to be out of the first empirical dose of antibiotic. So no matter what, the first dose of antibiotic, the patient comes with neutropenic fever, there's no way I'm going to not give them antibiotics.

And so I think that the way the thing will evolve is, how early can I de-escalate? How early can I stop my antibiotic? And I think that that may be a path forward because if we have changed from the old paradigm of, you know, keep the antibiotic until the neutropenia resolves and the fever resolves, which would be 14 days of Ceftazidime, and now you say, "Well, maybe now it's three days of Ceftazidime-lactam."

You know, I think that something like that may be helpful, because you say, you come, I get

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the carrier test, the carrier's test is back in 50 hours. So after three days, the patient is in febrile, there's no evidence of bacterial DNA in the blood, I stop my antibiotic and watch.

And overall, I am doing a service to my patient because I'm not undertreating him, and I'm being a service to the world because I'm not overusing antibiotics and creating resistance. I think that is a potential strategy to be explored. I don't know that is the thing, and that is not what I'm doing.

What I'm doing is, I'm screening all the patients to look for ESBLs and so on, but I don't know how good my screening is. You know, but the idea that I'm going to, at some point, say, "Oh, I know that you don't have a bacterial infection." I don't know that is going to be reliable enough -- that any prediction model is going to be reliable enough for me to say that.

DR. TAPLITZ: But you're talking about the concept of using the negative predictive value of certain cell-free DNA type tests in order to de-escalate and use shorter-term antibiotics.

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I see a lot of head nods for the concept here, so definitely something worth considering. Although, as you say, I'm not sure that anyone is using it in clinical practice, and nor should they without it being studied.

Yeah, Andrea, you had a comment?

DR. ZIMMER: I was just going to tag on to the last comment, is when can I stop antibiotics, and then when can I send the patient home from the hospital? When do I feel comfortable that they can go out into the world and they're not going to come back worse off than they were when they came in? Because that's, I think, a big question among our oncology colleagues too.

DR. TAPLITZ: Absolutely.

Kim, you had a comment?

DR. HANSON: Yeah. Just as it relates to de-escalation. I mean de-escalating potentially back to prophylaxis versus de-escalating from a broad empiric therapy to a more targeted therapy to complete a course of treatment. I think an unmet diagnostic need for the latter, though, is more rapid detection

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of antimicrobial resistance.

So right now, cell-free DNA, they're little pieces, and they may not, depending on how deep the sequencing is or how much of the genome is covered, give you information about antimicrobial resistance.

So additional diagnostic studies kind of linking the genotype to the phenotype and looking for platforms that can give us more in terms of, you know, targeted treatment for individuals who do need to continue a course of therapy for neutropenic fever. So I wanted to make a plug for that.

DR. TAPLITZ: Yeah. And those platforms are actively being developed; right?

DR. HANSON: Yes.

DR. TAPLITZ: Yes.

Kieren?

DR. MARR: I agree with all of this. And I just want to say out loud, though, that, you know, de-escalating is absolutely essential and probably more statistically valid in an approach for all of the reasons that we're pointing out with

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regards to probabilities.

But this isn't really what most commercial entities are going to be interested in with regards to developing a drug; right? Yeah. That's all I wanted to say. That's a real clinically relevant algorithm.

But, you know, you've got to then ask the question of it. This is our answer, is it feasible to be developing a drug for fever during neutropenia? So I'm going to go back to that.

DR. TAPLITZ: Catherine?

DR. LIU: This has all been a great discussion. And I just wanted to go back to sort of this question about enriching patients who are more likely to have a bacterial etiology as we think about outpatient, sort of, oral antibiotics, particularly for those low-risk patients or, perhaps in the context as was presented from BARDA, of a nuclear detonation event.

If we think about developing oral antibiotics, identifying those patients who are more likely -- or more likely to have bacterial etiologies

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may be more challenging in these lower risk populations. So how do we sort of enrich for this in a lower risk population that may be less likely to have microbiologic diagnoses?

This is really sort of, I think, a question, you know, do we have studies for these lower risk patients as far as bacterial etiologies? How can we enrich for those folks? These are low risk patients with -- who are younger, who have less comorbidities, less exposure to health care.

And so that, I guess, if we're trying to develop an oral antibiotic option for outpatient management, I think it's maybe a challenge at least to get sort of a group that has microbiologic confirmation of infection.

DR. TAPLITZ: I think I'm going to move -- we have a couple of questions. Number one, if anybody would like to answer, what about Citrulline as a biomarker for GI epithelial? Anybody have experience or want to comment on the use of Citrulline as a biomarker?

Yeah. Yeah. I'm not sure we have any

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takers here. I don't personally have experience with it as a biomarker. I'm not aware of the studies so --

And then I can't really, the other question is, it looks like it says, "I integrity?" Which I'm not sure what that means. I don't know, Helga, if you wanted to type in a revision of that comment or question, we'd be happy to answer it.

Okay. Dr. Hanson?

DR. HANSON: Yeah. I was just going to say looking at that question, I wonder if Citrulline is a biomarker of GI epithelial integrity got carried over onto --

DR. TAPLITZ: Yes, yes, yes -- epithelial integrity. You got it.

DR. HANSON: It's an interesting question; right? I guess it's after cytotoxic chemotherapy, you have marker of, you know, mucositis that's not clinically apparent, are you more likely to have translocation of bacterial DNA or entire organisms?

I think that's an interesting question,

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and it would be cool to kind of compare that biomarker along with all the stuff that the metagenomic cell-free DNA test is detecting in blood, which is often anaerobes from the gut. So a couple ways to get at that question.

DR. TAPLITZ: All right. Any more questions, comments regarding question number two? I think we've gotten the questions from the Q&A. And we're actually right on time, 40 minutes, almost 40 minutes into our discussion.

So maybe we'll move on to question three, Dmitri?

DR. IARIKOV: Hi, again. It's Dmitri Iarikov, Deputy Director in the Division of Anti-Infectives at FDA. And for question three, it's "Regarding trial design consideration in febrile neutropenia."

And I would ask Dr. Girgenti to start the discussion. And there are three sub-bullets under this question related to primary endpoint, primary efficacy population, and potential strategies to make these trials feasible.

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Dr. Girgenti, the floor is yours.

DR. GIRGENTI: Sure. Thank you, Dr. Iarikov.

So addressing the first point, you know, in terms of the appropriate primary endpoint, you know, and maybe this is kind of bleeding a little bit into question two as well. You know, historically, I'm a pediatrician as well as an internist, you know.

I kind of look at this population as probably, quite frankly, the closest thing to sort of the rule out sepsis protocol in newborns, you know, for a lot of very parallel reasons, in terms of a very vulnerable, susceptible population in pediatrics and a very susceptible population here in adults, where the intention, the goal of treatment, empiric treatment is really to prevent a really catastrophic outcome in a population that can succumb very quickly.

You know, so having said that, in terms of the most appropriate primary endpoint, I would normally suggest that this should, as original trials have been designed many, many years ago, you know,

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looked at outcomes, particularly in mortality and other outcomes that would reflect, you know, the true treatment effect and the intended prevention of poor outcomes in this population.

Unfortunately, for clinical trial design, very fortunate for patients, but very unfortunate for clinical trial design, this is very challenging now to evaluate mortality and morbidity in patients that are being treated empirically for FN.

Particularly, considering where the mortality rate is probably somewhere between 5 and 10 percent overall in this population, and more so, where the mortality is in the majority of cases, not infection-related, but more related to the tumor or other non-infectious reasons.

So to the first question, I would insist that probably still we are looking at, for better or for worse, clinical along with microbiological response to truly be the most appropriate primary endpoint to be evaluated.

Still, you know, as I got into in my talk and a few others did as well, it's an endpoint

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that's certainly fraught with concern in terms of clinical trial development.

You have a population which is naturally inclined so that the rule rather than the exception will be natural improvement and resolution with or without antibiotics which creates a bias towards non-inferiority, you know.

So in terms of considering type 1 and type 2 error of a clinical trial design, while in terms, you know, of the most important being type 1, that a drug is considered more efficacious than truly deserving in the clinical trial setting.

If we're looking at clinical response, there is a bias towards non-inferiority which makes it, quite frankly, a low bar to achieve non-inferiority in this case. And likewise, at the same time, makes it really challenging to achieve superiority.

So to this point in, you know, again, dialing back to question number two, how can we best refine the population? I think it really becomes hand-in-glove to refine the population in such a way

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that this primary endpoint makes sense.

You know, are we really looking at a primary endpoint of clinical response which is attributable to the antibiotic effect rather than the natural course of disease? So that's my response thus far in terms of the first bullet.

With regard to the primary efficacy population, again, you know, what I reflected on earlier, I think in any way that we can refine the population to make this a more specific endpoint would truly benefit the clinical trial population and the likelihood of demonstrating a meaningful clinical response.

Of course, you know, coming from the sponsor perspective, when I look at refining a clinical trial population, I always look at, you know, the mantra of what you evaluate in the study is what you get in the label.

And this becomes really important that if you refine a population, let's say you refine it to, you know, in extreme terms to hematologic malignancy. Will you have a label indication which is

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restricted to hematologic malignancy and not include or limit that the drug has not been evaluated in additional tumor types for instance?

And there are a number of other ways that that could play out in terms of what you study in the trial is what you get in the label. But nonetheless, I think it is truly important to refine the study population in such a way that it is far more specific what is evaluated in the clinical trial that would potentially improve the likelihood of demonstrating superiority and not just demonstrating what is, quite frankly, a relatively low bar, that being non-inferiority.

And then to the third point in terms of strategies to make this more feasible, as I alluded to at the end of my talk, you know, we've heard a number of times, I think in various talks, the term "heterogeneity." And this is a disease which is truly heterogeneous. I like Dr. Marr's reference to this as more of a symptom than a syndrome in that, you know, this is truly heterogeneity.

The heterogeneity really is not in

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favor of conducting clinical trials. Clinical trials are intended to be as homogenous as possible, minimize the variability. And in many ways, this is, quite frankly the, you know, contrary to that.

So are there opportunities for us to really kind of think outside the box from the really traditional, if you will, explanatory randomized clinical trial design to looking at more pragmatic trials?

More real-world evidence outside of the traditional inclusion/exclusion criteria in terms of how the drugs are truly being used in the clinic to evaluate both clinical and outcome efficacy endpoints.

And likewise, I think the last point that I got to in my talk was, you know, could we evaluate, again, outside of the traditional model of looking at perhaps something like a platform-based design where multiple antibiotics could be evaluated in head-to-head fashion against existing standard of care.

So I think there are a number of ways that we could look at, you know, another would be can

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we model, can we utilize, can we leverage more than we are currently doing. Modeling and simulation efforts to look at probability of target attainment in this population against these particular pathogens, extrapolating from, perhaps, an existing license indication for UTI or HABP/VABP in an existing antibiotic.

So all of these, I think, you know, potentially represent ideas that could look at clinical trial designs which are outside of the traditional randomized clinical pivotal Phase 3 design that would not only facilitate development, make it less costly and less labor intensive, time intensive, in terms of reaching licensure, the intended outcome, but also, quite frankly, generate more meaningful results.

DR. IARIKOV: Thank you. It's been very helpful and informative. I have a question as we got to primary endpoints. What do you think about the timing of assessment considering effort to de-escalate stopped earlier? What do you believe would be the optimal timing for the endpoint?

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DR. GIRGENTI: Sure. I think, you know, traditionally, and again, if we're looking at this from an outcomes perspective, if we're looking at what we're truly trying to prevent, which is the morbidity and mortality of the disease, then it would make sense to evaluate a later time point.

But as has also been discussed pretty extensively during this workshop, there is, of course, a trend towards the disease itself changing, where particularly with the introduction of ancillary treatments like G-CSF, the expectation is that neutropenia will respond a lot faster. Hospitalizations will be shorter.

Given the anticipation that we will have a bug in hand within two or three days or an indication of whether the patient is improving or not, whether step-down therapy or more narrow antibiotic therapy, you know, de-escalation could be introduced earlier.

You know, taking into account where we are in 2024 and where the disease is heading, I would suggest that the primary efficacy endpoint, the time point, primary efficacy time point, really needs to be positioned fairly early.

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And I would strongly propose that if a primary efficacy endpoint of a clinical response, an early clinical response in a traditional clinical trial setting, should probably be sitting at about the 72-hour time point.

Now, going back on what I said earlier in terms of, well, what if we explored less traditional clinical trial, you know, more novel clinical trial approaches such as pragmatic trials?

Well, a pragmatic trial would not -- an endpoint for a pragmatic trial would not necessarily fit to say a, you know, given percent response of 72 hours, would be more appropriate as a generalized response that can be easily evaluated outside of the, you know, typical Phase 3 setting.

So in a more pragmatic sense of evaluating the disease, then you would perhaps want to position this at a later time point. But I think at least with the traditional typical pivotal Phase 3 one-to-one randomized clinical trial, really

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considering all of the dynamics at play, including G-CSF, including the likelihood of de-escalation therapy, that at much like, say, UTI, that the primary efficacy endpoint should probably be positioned early in therapy. Probably at 72 hours.

DR. IARIKOV: Thank you so much.

Dr. Marr?

DR. MARR: Yeah. I want to say that we can't answer the question that you asked. How long -- when should the primary endpoint be because fever during neutropenia is not a disease? And then it's a few risks for bad infections and bad outcomes. And then beyond that, if we're using the most objective outcomes, survival, that's subjective.

These are driven by other host variables that we're not controlling by the antibiotics that we're giving or any antimicrobials. And so, you know, it's like there are far too many. We don't have a syndrome defined, so we don't even know what to measure.

And, you know, God knows how many editorials have been written about this. I've

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contributed several of them. This is why we came up with this five-point endpoint to be, you know, and antifungal studies to begin with, which was completely driven by tolerability and safety.

And the reason is that we're enrolling people that don't have a defined syndrome. They have a lot of different biases towards the outcomes we're trying to measure. And the one that we're trying to either prevent or treat is rare. And so, you know, there's, I think, no more uniquely nurturing place to have a bias towards non-inferiority because we don't even know what we're treating in that setting.

And I would even go to the point where we don't know if we're preventing the infection or treating it. And as has been absolutely indicated here, a lot of this is because of our diagnostic limitations. There's a lot of data using the more sensitive tests that are not clinically used that says that there is an infection. It's just not otherwise clinically apparent.

And so, I think that we need to roll back and say, is this feasible as an indication for a,

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you know, current drug development? That's one question that still is looming in my mind. And then start with, what are we treating with fever during neutropenia? Because I think that we can iteratively make this a more feasible environment for us to measure objective and meaningful outcomes with antibiotics.

It's not to say that they're not needed. They are absolutely needed. It's just to say that given the complexity in enrollment, heterogeneity, is host heterogeneity, and now it's been pointed out that we're enrolling a heterogeneous bag of people who have infections at different time points.

I think about the host more. We have to really re-emphasize what that's doing to the feasibility of our clinical trials as well.

DR. IARIKOV: Thank you.

Dr. Botgros, and let's make it the last question, comment for this question, and we'll move on to question four next.

DR. BOTGROS: Thank you very much,

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Dr. Iarikov.

You know, obviously I won't be able to provide definite answers to the questions, but just a few reflections. First of all, from what I heard today, you know, I don't think mortality can be a reasonable endpoint for such a trial. I think it's so low that, you know, it would be probably possible to demonstrate what needs to be demonstrated in terms of efficacy.

Now, the other thing that I was thinking about because I think in one of the presentations, I think the Melinta one, there was, and actually during more than one presentation, there was this concept of looking into those patients that have documented microbiology at baseline. So, you know, where the pathogen can be identified.

Now to me, that one is a bit of a different indication actually. It's not about empiric therapy. Actually, this is bacterium. So, you know, once you can isolate the pathogen, you know, and appreciated that it's just 15 to 30 percent, I think was the -- this is a bit of a different situations.

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We are not talking anymore in a certain sense about empiric therapy, or we shouldn't at the very least.

And then the other thing with regard to a time of collection of the endpoint and what the endpoint, the clinical endpoint could be, I was wondering if, and, you know, here I want to hear more from you.

You know, I'm wondering how far something like, you know, documented breakthrough infection after a certain period of time from start of, well, we say therapy, but actually it's preemptive therapy, I would imagine for most patients.

If such an endpoint collected maybe, and this particular one could be collected at a later time point from the start of therapy, if this could be something that developers could think about. I don't know. It's just my own reflection based on what I heard today.

Thank you.

DR. IARIKOV: Thank you.

Dr. Gea-Banacloche, I noticed that they all raised their hands. Please comment.

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DR. GEA-BANACLOCHE: Yeah. I just put it on the chat. You know, when -- studied Ceftazidime, things were all very complicated. He had a very simple design in which the patients were assessed at 72 hours and at the end of the neutropenia.

And so every episode of neutropenia could be classified as failure when the patient had died or a success with modification. If they had to modify the antibiotic or success without modification, which meant that the patient had survived without changing the antibiotic.

And that is a very pragmatic way of looking at things and avoids the issue of very slow mortality because mortality was not the key thing. And, in fact, there was no difference in mortality. But the key issue is that there was no difference either in success without modification overall.

Although, clearly, when there was a documented infection, people had to modify the Ceftazidime alone half the time. But as pragmatic studies go, there was a pragmatic study that changed

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the management of neutropenia fever.

If you want to think of what happened that -- the paradigmatic changes in neutropenic fever, one was empirical management of neutropenic fever. That was number one. Number two was monotherapy and everything after that has been incremental and trying to do it a little bit better. But those are the two things that really set the field the way the field it is right now.

And I think that, you know, trial designers can look at this, which, you know, of course, is a 40-year-old design. But, you know, think about if the answers of -- if a sponsor could consider, "Oh, maybe I can put my drug against the standard of care, and if I have to change my drug less often than the standard of care, maybe that is good enough for me to get approval."

So I don't think that is particularly crazy, but I wouldn't know.

DR. IARIKOV. Thank you. Very helpful. Thank you.

Dr. Farley?

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DR. FARLEY: Yeah. Sorry to make you late, Dmitri. I just kind of wanted to follow up on a point that Kieren had brought up.

So we're doing a fair amount of collaboration with ARLG on door endpoint development. And just to clarify, you know, for the agency, we're not at the point for a new molecular entity accepting a door endpoint as a primary endpoint, but there's a lot of utility.

And I'm just wondering if there are unanswered questions for this sort of empiric period of treatment where you have a lot of options, some of which have adverse events associated with it, whether you thought that would be helpful or not to explore further. Thanks.

DR. MARR: Can I speak? I actually think it's a great idea as more exploratory endpoints. And, you know, a lot of that has been said is really very relevant. We've got a really reposition what we're trying to do. Are we preventing an early infection from establishing?

Because as Juan says, there's ways to

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measure that with our classical microbiology, infection-free survival. I absolutely agree that we can't rely on survival alone because it's driven by too many things.

Survival in all of our infection endpoints also causes bias in this population because they die too, as well the toxicities of the drug which we've seen in these early treatment studies before. But, and as Catherine points out in the chat, I think absolutely appropriately, there's other ways to do it.

Adaptive platforms. She brings up pragmatic outcomes such as store. Absolutely. But, you know, I think that some of the framework in which we're working here is that we need to redefine what we're approaching given the contemporary population that we're dealing with.

The differences that have evolved and the lessons that we've learned based on the problems with measuring these outcomes in our historical trials. And with all of that, I think that we can probably come up with a better strategy.

For me, we're sitting in the early

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therapy land and labeling it as fever during neutropenia is not encompassing enough because that early therapy can also be someone who doesn't have a fever but has a pulmonary syndrome that is consistent with early pulmonary.

So I think that I'd like to be starting to move towards more syndromic approaches and inclusion and labeling the indication so that we can use some of these new tools and some of these new measures as you're pointing out.

DR. IARIKOV: Sorry. I was on mute. Any more comments on question three before we move to the next one? Okay, hearing none. So question four. Actually, it's not that directly related to febrile neutropenia, but as an M.D. we're very interested in discussing this subject.

So we know the data -- limited on the use of new antibacterial drugs, recently approved drugs, in your neutropenic patients, and we would greatly appreciate the discussion about the need, utility, and visibility of obtaining efficacy and safety data on new drugs in neutropenic patients with

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defined systemic bacterial infection.

Dr. Farley, please start the discussion.

DR. FARLEY: Yeah. So I just wanted to provide a little framing because actually as I've heard the discussion today, I think, in some prep for this Kieren sort of accused me of tangential thinking, which I sometimes am guilty of. But I think this is less tangential really as I learn more about sort of the state of the art from you experts.

Because my sense is that one of the possibilities during this -- after this sort of empiric period of treatment is that you're going to realize that the patient, either based on diagnostic testing fairly early, or maybe syndromic presentation clinically, really warrants treatment.

And you also have a high probability of needing to use one of a number of antibacterial drugs that have been approved during the last decade. And kind of speaking as a regulator and working with the pharmaceutical industry, the question to you all is have we given you the data that you need?

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Do you have data gaps for use of this drug, recognizing, of course, you're also working to increase the patient's neutrophil count while all of this is going on?

We have provided you as much data that we can in terms of optimizing the exposure in the setting of comorbidities like renal failure, renal compromise. We've tried -- we worked really hard during development to do that. We haven't necessarily, because of just the practicalities of getting these trials done, given you everything that you need.

And so the question is, what do you need and are there ideas for us to provide that information?

So, thanks.

DR. IARIKOV: Dr. Marr?

DR. MARR: I'll just jump out there with my answer. I think that adding neutropenic patients to other indications makes the trials more complicated and difficult to interpret. We treat for different periods of time. The diseases occur through

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a different pathobiology frequently. The example is, you know, CAP versus HAP is really irrelevant in this patient population.

And then to add to that, if you do a study in an artfully chosen population of people with community-acquired pneumonia or hospital-acquired pneumonia with the pathogen profile that we can understand, and you tell me that an antibiotic works for that pathogen profile, that's what I need to use it in my neutropenic population.

I don't need the data necessarily. I need it to be shown to be safe and effective in a population in which it can be measured. Now, if they're, you know, and you put it into a different population, we can have an endless discussion about who those other patients are. But we don't need to do studies in each of them, especially as they become more complicated.

That's my opinion.

DR. IARIKOV: So you believe that specific data on neutropenic host in a neutropenic population might not be needed because you don't

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expect any significant differences in terms of PK/PD or any other host factors that might change the efficacy, so to speak, plus-minus safety of the drug? Okay.

DR. MARR: Or at least let me clarify not due to neutropenia alone.

DR. IARIKOV: Got you.

DR. MARR: You know, other reasons that impact the PK are apparent and apply to my population as well. But neutropenia alone is another variable that we're managing that doesn't necessarily have to do with the antimicrobial. It may not work as much because the immune system is really driving so much. But that's not going to take away from my enthusiasm in translating the data that are derived from a different population.

DR. IARIKOV: Right. So basically, it's not special population as would be reflected in our labeling like, you know, geriatric patients, pregnant patients, pediatric patients, not neutropenic patients?

DR. MARR: No. Because as you've heard

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today that neutropenic population isn't even homogeneous enough to know what we're modeling for.

DR. IARIKOV: Got you. Thanks. Very helpful.

Any comments on question four?

Dr. Peter, please, and then Dr. Girgenti. Sorry, I might miss the order.

DR. KIM: Please, Dr. Girgenti, your hand was up first.

DR. GIRGENTI: Oh, by all means. That's okay.

DR. KIM: Okay. So my question is actually kind of like an add-on to what Dr. Marr was discussing and Dr. Iarikov. So of the indications that we typically grant and indications that drug developers typically conduct studies in, are there any of those indications that allow for more confidence in an antibacterial drug for use in febrile neutropenia?

Such as, if drug X has a HABP/VABP indication, then I'm more likely to use it in my febrile neutropenia patients. I have more confidence given the level of acuity of HABP/VABP versus a drug

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that's approved for complicated urinary tract infection or that really isn't relevant either. It's more about bacterial spectrum.

I don't know if you've got comments on it.

DR. MARR: I don't mean to speak for everyone and there's some tremendous clinicians and minds on this call. I will just -- I brought up the issue, and I'll give you my opinion. We don't have data that is approved in febrile neutropenic patients to guide our neutropenic syndromes.

We have neutropenic patients with pneumonia or UTIs, and we interpret the data that has been given to us with the appropriate indications anatomically and microbiologically based on what we think that our patients have.

And so I don't necessarily need to know how any -- I don't need the specific data in a neutropenic patient as much as I need that specific data in someone with my severe lung disease. It's interpreting it in the context of more clinical variables that we have to go through.

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I mean that's great ancillary data for outcomes and to understand some of the other complications that can occur. But I don't think it's necessary for -- to have that as an indication for the use of these drugs, and we currently don't. I'd be very interested in hearing other -- like Randy's opinion on this too.

DR. IARIKOV: Dr. Girgenti, you were next.

DR. GIRGENTI: Sure. Okay. I don't know -- did we want to let Dr. Taplitz respond to that first or I'd be happy to defer.

DR. TAPLITZ: Yeah. I just wanted to say, you know, again, I think the sort of the concept of the syndrome, you know, the febrile neutropenia syndrome is sort of, I think, it's just too simplistic now for what we're dealing with on a clinical level. And so we kind of need to, you know, what I think what we're sort of moving towards is we need to rethink that.

You know, again, patients have a variety of risk factors, and I think people have

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pointed out that, you know, again, it's not just neutropenia. It's, you know, everything from, you know, age to comorbidities to, you know, immunogenic or genetic risk factors to, you know, treatments.

And, you know, as ID physicians, we keep up on exactly what our immune system is being altered by the drug that they're currently, the drug du jour, and not only immune deficiency but immune activation we have to deal with and steroids.

And so I guess, you know, that's not to really answer the question, but just to sort of point out how complicated treatment of these patients has become and, you know, maybe to move past the concept of febrile neutropenia.

DR. FREIFELD: I'd like to follow up on some of this discussion. I'm sorry that I'm late. This is Dr. Alison Freifeld. And like so many clinicians, I've seen the last 40 years of this evolve.

And first of all, I'd like to agree with Kieren Marr that we don't need any specific data, I think, in answer to Peter Kim's question on these

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documented infections in neutropenic patients. Because, honestly, it's not the drugs that we use as much as it is the recovery from neutropenia that's going to really affect outcomes.

So that is yet another variable that we'd have to consider in addressing and evaluating any of these drugs. And I gather from this little bit of discussion I've heard that there's been some back and forth about whether fever neutropenia is a syndrome versus is there, you know, is it something more than that.

I think when we set out at the very beginning of treating a patient, it is a syndrome to start with. But within a pretty quick period of time, thanks to the clinical and laboratory techniques that we now have, within three days, two days often or less, it's no longer a syndrome. It's a documented infection or it's not.

And so, really, at that point, within the first three days, we're going to start making changes to any empiric regimen. So that would seem to me to be the right point as one of our panelists has

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pointed out in the chat, that would be the right point to make an evaluation as to whether or not a drug is effective or not.

I mean, clearly, no drug is going to be able to cover pneumonia or UTI sepsis. You know, that's simply not possible given the array of pathogens and syndromes and things that we have to deal with.

So, I guess, I just wanted to throw those two things out, and that the primary endpoints clearly are no longer going to be death. Mortality is simply not an appropriate endpoint as it might have been 40 or 50 years ago. So we have to certainly come up with better clinical and laboratory endpoints that are reflective of how a certain drug or regimen does in the first few days.

So sorry to be late and hope that I didn't backtrack a little too much.

DR. IARIKOV: Thank you so much. It was really helpful.

And Dr. Girgenti, thank you for waiting so patiently, please.

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DR. GIRGENTI: Thank you. I'm glad I did because I'm glad I allowed the clinical conversation to play out to Dr. Kim's question because where my, I guess, question is very much in the same territory but kind of taking this from the clinical perspective to the pharmacodynamic perspective in this population.

And, you know, to be clear, I'm a clinician, I'm not a clinical pharmacologist. But, you know, dialing back to the conversation that are there other populations, for instance, HABP/VABP versus UTI where patients with neutropenia could provide more evidence that would support an indication in febrile neutropenia.

You know, there's been some work, Imipenem-cilastin comes to mind, and I think a few others that have looked at the probability of target attainment in patients with febrile neutropenia versus other populations such as UTI and HABP/VABP, showing that there is, you know.

And whether this is attributable to augmented renal clearance or other factors, or whether

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it's something that we don't understand that's innate to the condition, the syndrome, the symptom that patients present with -- with febrile neutropenia. I strongly suspect that part of the answer is to Dr. Marr's comment that it's just too heterogeneous a population to really identify.

But, nonetheless, that the probability of target attainment in patients with febrile neutropenia may be substantially lower than similar patients, similar body weight, similar characteristics in HABP/VABP and UTI, and whether this creates itself unique challenges in this population, or whether there's something that could be learned from patients with HABP/VABP, UTI, and other indications that are likewise neutropenic.

DR. IARIKOV: Thank you. Very interesting.

Dr. Sato?

DR. SATO: Yes, thank you.

So I'm Junko Sato, Associate Executive Director, PMDA Japan. So I'd like to share what data we would like to review as a regulator. So I'd like

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to touch the possibility to utilize real-world data. There are many confounding factors such as the change of neutrophil count.

So we would like to evaluate data that excludes these influence for the purpose we are considering the possibility of using real-world data because therapeutic data is generated every day in a clinical site.

If we accumulate and analyze such data, we can obtain real-world evidence. We think such data is so helpful to review for FN product.

Thank you.

DR. IARIKOV: Thank you so much.

I have a follow-up question for Dr. Girgenti. You mentioned that PK/PD data might be different for, again, for unknown reason for now in febrile neutropenic patients. Here we come across -- does it kind of antibacterial class specific or it's hard to say at this disjuncture, and any explanation for these differences?

DR. GIRGENTI: From my perspective, again, not being the expert, I'm a clinician, not a

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clinical pharmacologist. But, you know, what I've encountered are largely single-center studies, not, you know, multi-center randomized trials, but that have proposed that, again, the two that come to mind are looking at Imipenem and Meropenem.

That evaluating specifically in the febrile neutropenia population that, and again, attributing the differences to perhaps the volume of distribution and difference in clearance that patients may have a lower probability of target attainment for similar bacterial pathogens with similar MICs than the probability of target attainment in other pathologies.

So, you know, from a sponsor perspective, I would love to be able to extrapolate and use nothing but modeling and simulation to identify that we know how the drug is going to behave in this population.

My curiosity is to whether this would complicate matters to know that we're, in fact, dealing with a different population where the PK/PD cannot be necessarily assumed to be identical as in other hospital-acquired infections.

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DR. IARIKOV: Thank you.

Dr. Marr, I see you.

DR. MARR: So you can absolutely assume that it's not identical to other hospitalized populations, but it's not the fever neutropenia that's driving it. It's the absolutely everything else. I mean the gamut of fever neutropenia patients runs from 18-year-olds with aplastic anemia to 75-year-olds with relapsed leukemia.

And there's a very, very different, and you know, a bag of variables there that's going to be driving your target attainment and your PK/PD that is not about fever and neutropenia itself. It's, again, a reflection of a very different heterogeneous population.

DR. TAPLITZ: Yeah. That's just one aspect of it.

DR. MARR: Yeah.

DR. IARIKOV: All right. Any comments on question four? Any additional comments that people might have on any questions that have been discussed or not discussed or that matter? All right. I'm not

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going to assume that we've exhausted the subject, but at least at this juncture, it seems that --

DR. TAPLITZ: Actually, I do want to bring up one thing. Kieren made the comment about machine learning, AI. And I just think that maybe that's something that we should be talking about.

I mean as we head into this burgeoning field and this new era, kind of what role, you know, machine learning can play and help with in assisting with risk stratification since we've talked about how difficult risk stratification is.

DR. IARIKOV: Any takers on artificial intelligence-related questions?

DR. TAPLITZ: I mean, I guess, perhaps the fact that nobody is answering it says something. I mean shouldn't we be at least thinking about it? We're thinking about it in so many other ways. I'm not saying that there's going to be, you know, any improvements or solutions, but probably it should be at least considered in risk stratification.

DR. IARIKOV: Dr. Lyman?

DR. LYMAN: Yeah, just a short answer.

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Obviously, there is an enormous excitement, I agree completely. We should be thinking about it, but it comes with a great deal of caution. There've been extensive studies, a lot of them outside of the cancer setting, showing the challenges of the interpretation, the methodology, the validity of models generated by machine learning techniques.

So, you know, this is clearly in our future, but I think we need to proceed cautiously and always being very vigilant as we should be with any technique we use for modeling, but very cautious about the limitations. And that the need for them to abide by the tripod statement or from machine learning, other standardized techniques, or standardized criteria and make sure all this is done.

Otherwise, we get into a quagmire because these models are black boxes, at least to most of us and certainly to clinicians. And we want to make sure if we begin to use them, which is the ultimate goal, that they are accurate, reliable, valid, and we don't do more harm than good.

DR. TAPLITZ: Yeah. And I think it's

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more -- it's not so much the idea of necessarily using them as studying them while you're studying, you know, the questions that you have. Because I think we're, many of us, I think, are very impressed with just how many different models there are out there and how can one choose.

And again, if someone is going to do a large, randomized, controlled clinical trial, then you can get so much information about that kind of modeling in the setting of doing that trial. It just seems like it's something worth considering.

DR. LYMAN: As an adjunct, I think --

DR. TAPLITZ: As an adjunct.

DR. LYMAN: -- tradition. Yes. Absolutely.

DR. TAPLITZ: Exactly. Yes, as an adjunct.

DR. IARIKOV: Dr. Marr, let me remind you that -- everyone that actually we are unfortunately nearing the end time of our panel discussion.

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Dr. Marr, please.

DR. MARR: This won't be long. I just want to say, I agree with all of that. But, you know, I think I'm thankful that we've got a technology that we are putting the guidelines around to say that we need to validate and support it with data.

Because to date, having us sitting around a table which is the genesis of most of the guidelines and models that have come up there is not validated and it's not data-driven.

And so either way, we take it with all of those bruises and warts, and in all of these analytic platforms, at least we're inching towards more validated data-driven modeling. And I think that that's a really good movement in this field.

DR. IARIKOV: Thank you so much.

And, again, unfortunately, we are nearing the end of our moderated panel discussion and I'll try to summarize today's discussion. Let me start by thanking presenters and panelists for their outstanding presentations and discussion. We've covered a lot of material in a short time. And,

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again, in the next ten minutes or so, I'll try to summarize some key points.

So during the first session following Dr. Kim's overview of the workshop objectives, Dr. Taplitz walked us through the 60 year evolution of approaches to prophylaxis and therapeutic therapy of febrile neutropenia, highlighting a rise of resistant infections, increasing complexity of febrile neutropenia patients in terms of their infectious risks, and suggesting that new treatment paradigm and effective options for febrile neutropenia are needed.

Dr. Zimmer then reviewed current febrile treatment options for various infectious risk categories and presented the causes of bacteremia and the part of the initial antibiotic use in high-risk febrile neutropenia patients in the United States showing that Cefepime remains the most commonly used antibiotic.

Then Dr. Hanson discussed diagnostic testing in febrile neutropenia indicating that while blood culture remains an essential component of the febrile neutropenia workup, culture-independent

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methods including agnostic approaches may complement the diagnostic workup.

And rapid organism and antimicrobial-resistant markers stratification from positive blood cultures have become standard of care to inform the adjustment of antimicrobial therapy. And Dr. Hanson also indicated that colonization status may inform risk for invasive infection and optimize its prophylaxis and febrile neutropenia.

And then Dr. Sheoran presented an antibiotic managements of neutropenic patients with acute radiation syndrome stressing high rates of fatal infection in this patient population as compared to neutropenic cancer patients, which in the setting of increasing rates of drug resistant infections calls for more treatment options.

Dr. Girgenti concluded session one by providing industry perspective on clinical development of antibiotic for empiric therapy febrile neutropenia. He pointed out that current recommendations for empiric treatment of febrile neutropenia are largely based on decades-old research.

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And the two key questions in his presentations were what does the current febrile neutropenia population look like, and what does the microbiology of febrile neutropenia look like? Dr. Girgenti pointed out that the heterogeneity, this is the word of the day, of febrile neutropenia patients, indicating that about 50 percent of patients will be diagnosed with fever of unknown origin.

And he questions whether there's an opportunity to use advanced testing to refine enrollment criteria in febrile neutropenia trials to increase the proportion of patients with microbiologically proven infection.

He also reviewed primary endpoints and other trial design considerations and provided outlines of a hypothetical efficacy study and clinical development program for a drug for febrile neutropenia.

And he concluded his presentations by posing questions about the possibility of a more streamlined clinical approach in febrile neutropenia, and we touched on these questions during our moderated

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panel discussion.

Session two started with Dr. Pease's presentation on regulatory considerations to expedite drug development for empiric antibacterial therapy in febrile neutropenia where he summarized applicable regulatory standards, pathways, and programs, pointing out that for febrile neutropenia no new antibacterial drugs have been approved in more than 25 years, and no oral antibiotics have ever been approved.

Then Dr. Kapoor discussed regulatory perspective on clinical trial design considerations for empiric antibacterial therapy in febrile neutropenia patients. She also noted challenges related to the inclusion of subjects whose fever remains unexplained in febrile neutropenia trials.

Dr. Kapoor noted that in a superiority trials, this will likely make demonstration of superiority more difficult. Whereas for a non-inferiority trial, it could make the justification of a non-inferiority margin challenging. Dr. Kapoor also discussed advantages and limitations of candidate efficacy and points for febrile neutropenic trials.

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Her presentation was followed by Dr. Rubin who discussed statistical consideration in clinical trials in febrile neutropenia starting with general consideration for superiority and non-inferiority trials and then described the limitations of the applicability of some historical trial information to inform the design of contemporary trials.

Dr. Rubin also described statistical trade-offs related to the selection of an analysis population and provided estimates of sample sizes for superiority and non-inferiority trials in febrile neutropenia.

Dr. Botgros provided the EU perspective for the febrile neutropenia indication. He noted that for antibacterial drugs this indication is not supported any longer in the EU and is to be replaced with the statement reading that the drug may be used in the management of neutropenic patients with fever that is suspected to be due to bacterial infection.

Dr. Botgros also noted that further discussion of clinical trial design to support such an

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indication has not taken place but would be highly recommended if the drug developer decided to pursue it.

Dr. Ichimaru concluded session two by reviewing the approval of antimicrobial drugs for febrile neutropenia in Japan. He noted that several drugs have been approved with this indication in Japan and indicated that foreign data can be utilized to obtain approval.

And during the remaining time, I'll try to summarize the panel discussion points, but, again, forgive me if I'm going to be a little bit -- I'm going to follow my notes.

So for question one regarding the greatest unmet needs for empiric treatment of febrile neutropenia, it was noted that one approach might be to develop a drug with a broad-spectrum coverage, including multidrug-resistant pathogens such as gram-negative pathogens and gram-positive pathogens.

And also a novel oral drug or a long-acting parental drug might meet an unmet need in the outpatient setting and improve safety profiles for

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this drug would be also important.

Then it was noted that other approach would be to develop targeted -- kind of to reconsider the paradigm or broad-spectrum empiric approach and maybe to develop a more targeted approach to treatment of febrile neutropenia.

And it was noted that certain drawbacks related to broad-spectrum coverage in all patients for potentially prolonged period of time and de-escalation strategies were discussed. And it was also repeatedly noted that our current understanding of febrile neutropenia needs to be revisited.

That it might not be and it's not apparently well-defined syndrome or maybe if it's not a syndrome altogether, it might be considered as a symptom of an underlying disease or condition not necessarily of infectious etiology.

And it's -- right. And it's dovetailed to question number two regarding trial design consideration, primary endpoint, and trial population, and it was a repeated theme over the discussion. The need to better define study population in trials in

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febrile neutropenia and implement potential enrichment strategies.

And this was covered by Dr. Hanson who listed several factors that might be considered, including cost factors, clinical signs for -- such as fever, clinical findings, biomarkers, predictor for bacterial infection.

And she also mentioned that this -- more novel biomarkers such as cytokine profile and immune response profile that might potentially inform and better define population in trials for febrile neutropenia. Also, the microbiome and any colonization status of course.

It was also commented that another approach would be to make these trials more pragmatic and thinking not only about inclusion criteria but maybe make exclusion criteria less excessive, again, to make this trial more generalizable to the clinical setting.

The question of de-escalation was discussed repeatedly. And, again, it seems that if trial in this space might be feasible, enrichment

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strategies would be the key for potential feasibility of the trials.

Am I good on time? Sorry. I'm just looking at my timing. So I have two minutes.

Endpoints, again, mortality does not seem to be an appropriate endpoint at this time. A competent endpoint that includes clinical and -- response would be -- seems to be more a way to go.

In regards to timing, early evaluation seems to be a better place to start maybe within the first 72 hours. By that time, we should have an understanding whether we still deal with what we're dealing with. If it's a fever of unknown origin or it's a microbiologically defined infection.

And as regards to question four, other data for febrile neutropenic patients are needed. It seems that this not necessarily -- that this population might not be that special for the lack of a better word, that data on kind of generally use of an antibacterial drug might be sufficient to inform the use of a drug in this population.

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On the other hand, there was discussion that PK/PD for multiple reason, it's very confounded, but we don't maybe fully understand why, but PK/PD might be different in febrile neutropenic patients.

We touched on artificial intelligence use over the last few minutes, but I'm not going to venture on commenting on that. And, again, it was pointed out that data to inform these models are critical to have these models meaningful.

And in conclusion, I would like to thank again speakers and panelists for taking the time to share their insights and expertise on challenges with developing drug for empiric therapy in febrile neutropenia and for making this workshop so informative and rewarding. Thank you so much.

Any last-minute comment from anyone from FDA or from outside panelists?

DR. KIM: Hi, this is Peter Kim. I would also like to thank everyone who put in the time and the effort in preparation for this workshop. This has been quite valuable to us. We'll certainly consider the discussion from this workshop in future deliberation. So thank you very much for your participation.

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THE REPORTER: Off the record? Hi, this is the reporter. Are we off the record?

DR. KIM: Yes.

THE REPORTER: Okay. We are off the record at 1:02 p.m.

(Whereupon, the meeting concluded at 1:02 p.m.)

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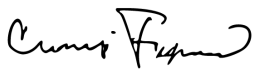
I, CHANYRI FIGUEROA MONSANTO, the officer before whom the foregoing proceedings were taken, do hereby certify that any witness(es) in the foregoing proceedings, prior to testifying, were duly sworn; that the proceedings were recorded by me and thereafter reduced to typewriting by a qualified transcriptionist; that said digital audio recording of said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



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