NEW DRUG UPDATES IN HEMATOLOGIC MALIGNANCIES

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MS. NELSON [*Audio begins in middle of sentence*] – talking about any of their medications throughout this presentation.

So before I actually go into this previous year's new updates, I can't proceed any further without talking about the past year. So, we had a fundamental new landscape of new drugs that came out in 2016 and 2017, that I just want to really quickly highlight.

So for AML, we had four big drugs. We had our daunorubicin, gemtuzumab in our CD33, specifically favorable risk, in AML. We had midostaurin and alecitinib as well for our oral agents. In ALL, we had our big CAR T approval, tisagenlecleucel, as well as inotuzumab and ozogamicin in our ALL relapsed/refractory indication.

We had two formulary differences. We had copanlisib that came out with our PI3K inhibitor, as well as rituximab/hyaluronidase human. So rituximab/hyaluronidase human actually gave another alternative formulation to give rituximab to a subset of our patients. And then lastly, ibrutinib. So ibrutinib also gave an extended indication – a couple extended indications.

So, all of those actually paved the way to a new landscape, but they left a few holes. And some of those holes were actually taken care of this year with some recent approvals. I'm going to first go over the monoclonal antibodies and some of our new CAR T cells. The new approvals that we have is the moxetumomab pasudotox, which is our CD22 inhibitor; mogamulizumab;

axicabtagene; and then I'll go through some of the expanded indications for drugs that we already have out on the market. Pembrolizumab, tisagenlecleucel, blinatumomab. Brentuximab actually had two expanded indications, as well as obinutuzumab.

So, first let's get started with moxetumomab pasudotox. So, moxetumomab's mechanism of action is as a CD22-directed antibody fused to a truncated bacterial or pseudomonal toxin. This inhibits protein synthesis and triggers apoptotic cell death. It's indicated for adult patients with relapsed/refractory hairy cell leukemia who have received two systemic therapies, including treatment with a purine nucleotide. So this is likely going to be cladribine in most of our patients.

So the dose is 0.04 mg/kg IV over 30 minutes on days 1, 3, and 5 every 4 weeks for up to six cycles disease progression or unacceptable toxicity.

Now, the study, the 1053 trial that actually got this approval, was a phase 3 single-arm, open-label trial. They actually showed an overall response rate of 75%, a complete response of 41%, and hematologic remission of 80%. Now, the hematologic remission was defined as an ANC greater than 1,500, platelet count greater than 100,000, hemoglobin greater than 11, and no growth factor and no blood transfusions for up to 4 weeks. So 80% of patients actually met this criteria. For the durable complete response, they actually took that criteria and those patients that actually met that criteria for 180 days. That was about 30% of patients. So they definitely showed improvement with the addition of moxetumomab.

Now, this is what I want to focus on, and actually, at my institution now, we've been highlighting this drug. Moxetumomab pasudotox in this phase 3 trial did have some interesting adverse events that I want to focus on.

So hypertension febrile neutropenia was over grade 3 or grade 4, over 5% incidence. However, capillary leak and hemolytic uremic syndrome were also seen with these patients. Why is this important to know? We know in hematology, a lot of patients actually have both of these, or they can have both of these indications or side effects. But a lot of the patients will actually be receiving this medication out in the clinics and the infusion center versus inpatient. So it is very, very important that a lot of you know some of these toxicities, as well as educate our nursing staff about some of these toxicities.

So, grade 3/grade 4 capillary leak and HUS was seen in about 2 to 3% of these patients. So because of that, it's important to know, are they hypertensive? Look at their albumin, look at their bilirubin. What are their platelets doing? So, looking at these labs.

The other thing is the adverse – or other adverse reactions, the infusion-related reactions. This occurred in up to 50% of these patients. What's important to note is, a lot of monoclonal antibodies do have those reactions in the first couple of cycles, but with this drug specifically, you can see this throughout any treatment phase. So, you could see this eight lines down, you could see it in the first. So it is important to keep in mind that infusion reactions can be seen throughout treatment of this drug.

The other thing, and because I created the order sets and did a lot of the education at my institution, the fluids are vitally important to these patients. So these patients actually required 2 to 3 liters of fluids with each dose of drug. They also require the fluid intermittently between those days of treatment.

The other thing to keep note is the CLS and HUS does actually occur typically within the first 8 days of treatment. In the study, they did resolve within 2 weeks. There was death associated with HUS, and a lot of those patients didn't receive enough fluids. And so I just want to press the importance here about making sure that we're monitoring these patients, that we're looking at their weights. We're looking to see if they're febrile. And we're making sure that we give them a lot of fluids. We are going to be doing this outpatient, and so patients who are not receiving the treatment that day, we will require them to drink fluids when they're at home, and so that's very, very important that you educate patients about that as well.

Mogamulizumab is the next drug that I'm going to talk about, and this is indicated for relapsed/refractory mycosis fungoides and Sezary syndrome. It's mechanism of action – it's a humanized IgG kappa monoclonal antibody that binds to CCR4, and CCR4 is on our T cells. This hones in the trafficking to different lymphocytes, brings in those cytokines, which then ultimately kills the cell.

It is indicated for adult patients with relapsed/refractory mycosis fungoides or Sezary syndrome after at least one systemic therapy. It's dosed at 1 mg/kg over an hour weekly for 4 weeks, and then every subsequent cycle every 2

weeks. It's recommended that we do premedicate these patients for infusion-related reactions. It's recommended only the first cycle, although most of us use monoclonal antibodies all the time, and we do premedicate most of our monoclonal antibodies. So I would probably recommend giving everybody Tylenol/Benadryl that receives this infusion.

Dose modifications – I'll try to highlight dose modifications throughout this presentation, because it is important to know whether we need to make a call to the physician or the pharmacist, or you need to be aware of the different side effects or things that are occurring so that we need to make a judgment call and whether we need to make that dose adjustment.

So mogamulizumab – it is recommended that we do dose adjustments for dermatologic toxicity. SGAF and TEN were actually seen in the clinical trial. There was actually associated mortality with this. So because it was seen in the clinical trial, it's definitely a possibility. So it is really, really important that we keep this in mind. If this does occur, we obviously want to discontinue the drug and we don't want to give it again.

Grade 2 and grade 3 rash, it's recommended that you interrupt the treatment for about 2 weeks and apply topical steroids. And then a grade 1 rash, you could continue treatment but also the need for applying topical steroids.

Infusion reactions – with any monoclonal antibody, infusion reactions can occur. So it is important to assess this. Obviously, if it's an anaphylactic-type reaction, we probably don't want to continue the drug. So we would discontinue and not recontinue. However, if it's a temporary – and we see this all the time in

the infusion center – temporary reaction, we would treat it, treat that reaction. Symptomatic care. And as long the patient goes down to baseline, we generally can restart that medication, normally at 50% of the rate and then titrate as they tolerate it.

Other common adverse reactions – so I mentioned rash. So, a lot of these patients obviously are going to have dermatologic effects. You're going to see rash. So how are you going to know? How are you going to know the difference between the drug rash versus the disease? Well, there's a couple ways. Obviously, you can look at timing. So, when did we see the rash? When did the rash appear? Maybe it's associated with the actual infusion of the drug. But the other thing, the only way to ever really know, is to biopsy. So biopsy would be the only way to know the difference between whether it was from the drug or whether it's the disease.

Infusion-related reactions – with any monoclonal antibody, you're going to see this. What I wanted to note here is that in the studies, it was 90% incidence. Actually over 90% incidence. So it's very common. However, you generally see this within the first couple of cycles. So daratumumab is very similar to this, where it's more common in the first few cycles, whereas moxetumomab, the last drug I talked about, you could actually see that in any cycle.

So, other adverse events, musculoskeletal pain, upper respiratory tract infections, grade 3 and grade 4 adverse reactions, edema, constipation, thrombocytopenia, hypertension, and cough.

The other thing that I don't have on this slide that I want to note is autoimmune toxicity. So, there was an association with an increased mortality in patients who had graft-versus-host disease that went on to allogeneic stem cell transplant. So, keeping that in mind, not that you shouldn't give this drug in the patient population, but depending on the timing – so, because this drug does affect your T cells, we know that that's really important for allogeneic stem cell transplant patients. And so, looking at the patient population and seeing if that patient does need to proceed on to transplant, and then maybe looking at that time frame in which you give this drug and starting the actual transplant itself. And so that's something that I've talked to some of our physicians at my institution about, and that's something that they have brought up that they are considering, and something that does factor in when they're considering treating with this agent.

So, the MAVERICK trial. The MAVERICK trial, which got the approval for mogamulizumab looked at vorinostat versus mogamulizumab, and they actually showed a statistically significant, actually 4-month improvement, in progressive-free survival. They actually also focused on the fact that even though there is an approval for mycosis fungoides and Sezary syndrome, it tended to favor Sezary syndrome over, a little bit over, mycosis fungoides. The other part is that it tended to favor stage III and stage IV disease, although you will look and see that in the indication, they only required to see one prior line.

So, the other thing is that a lot of these patients are presented with skin lesions. They have some kind of skin involvement, and so they actually looked at

this, and they looked to see if there was any complete response or partial response in their skin involvement. Because you can have involvement in the blood and in the skin and in the viscera. So specifically, skin involvement – you can see there in green, complete response and partial response was pretty significant over vorinostat.

And then overall, to kind of summarize these results, is that it was – it did show improvement in mycosis fungoides and Sezary syndrome, mostly grade 2 and grade 3, but you can see that it definitely favored Sezary syndrome. Also, the duration of response was a little bit longer in Sezary syndrome versus mycosis fungoides.

And then lastly, looking at all the different compartments that you can see that there could be involvement – the skin, the blood, the lymph nodes – the blood is where they seem to have the best efficacy. So, I think looking at our current treatments and where you would see this fit in, is mostly patients with Sezary syndrome over maybe mycosis fungoides, and then maybe patients that have more blood involvement versus skin. Although, that being said, you can see that it's definitely effective and is FDA indicated for all of those indications.

Okay. So, expanded indications. So, these are all drugs that are already currently approved, but now we've expanded them into different indications. Pembrolizumab was indicated for adult and pediatric patients with refractory primary mediastinal B-cell lymphoma, or who have had relapsed after two or more prior lines of therapy. The approval was based off a study of 53 patients with relapsed or refractory primary mediastinal disease. This was a multicenter,

open-label, single trial. The pembrolizumab was given at 200 mg IV every 3 weeks until unacceptable toxicity, disease progression, for up to 2 years. Common adverse events that were seen were musculoskeletal pain, upper respiratory tract infections, cough, dyspnea, diarrhea, and even arrhythmias.

So, the KEYNOTE-170 trial showed an overall response of 45%, 11% complete response, about 34% partial response. Now, the median duration was actually not met at the end of that trial of 10 months, but the onset of that first objective response was about 3 months. So, why is that important for us to know? It is recommended that patients that need immediate treatment and need cytoreductive treatment probably shouldn't get and start with pembrolizumab. They probably should be getting cytoreductive chemotherapy first. And then pembrolizumab would be an option later. And mostly this is because of that onset of action, you don't see response for about 2 to 3 months.

All right, blinatumomab. Blinatumomab. So, blinatumomab now has an expanded indication for treatment of adult patients and pediatric patients with B-cell ALL in their first or second complete remission with MRD greater than 0.1%. The BLAST trial looked at this. It was an open-label, multicenter, single-arm trial of patients that had received three chemotherapy lines prior to this of standard ALL therapy. All of these patients were in complete hematologic remission. They only had MRD-positive disease. So, why do we care about this patient population? Well, we care because there is definitely an association of patients that have MRD-positive disease and higher risk of relapse, and so that's what this study was tackling.

So, in the study, the patients received blinatumomab 28 mcg per day for all treatment cycles. And this is also important to note. So, right now, relapsed/refractory ALL, we know that we start our patients typically in the hospital at 9 mcg per day for about a week, and then we increase them to 28 mcg a day. They do that in the hospital, and then they're discharged. This is different. So, these are patients who do not have hematologic-positive disease. They only are MRD-positive. So, you can actually start these patients at 28 mcg a day. That's important to know. So, the dosing is different.

The other thing that's important to note is the duration of hospital stay. So, normally we would give them about a week of hospital, and then we would discharge them to receive subsequent treatments outpatient. In this case, you only have to keep them in the hospital for 3 days. All subsequent cycles, it's only required to keep them in the hospital for 2 days.

So, in the BLAST trial, they actually took these patients and they had four cycles of therapy. The first cycle would be induction, the three subsequent cycles would be consolidation. The frequency is very similar to how we give ALL and relapsed/refractory, where we would do four continuous weeks of the 28 mcg a day, followed by a 2-week break. So it would be 6-week cycles for up to four cycles.

The BLAST trial had a total of 116 patients. They actually showed, after patients received their first cycle of blinatumomab, about 80% of those patients actually became MRD-negative, which is great. So, these would be the MRD responders versus the other percentage of patients that were nonresponders.

The trial actually showed that that was a statistically significant difference in these patients that had MRD-negative after that first cycle. Overall survival benefit, hematologic relapse-free survival benefit and duration of hematologic remission.

As far as the toxicity profile, it was pretty similar, and it would be pretty similar, to what we would normally see now with blinatumomab. So, obviously, fevers, neutropenia, can be seen. We do see that now in practice with either indication of blinatumomab. Tremors, aphasia can also be seen. We had a case recently in the hospital where they did start with the 28 mcg, and a lot of people actually thought that these patients wouldn't have as much toxicity, maybe because they didn't have as much active disease and not as much disease in the bloodstream. However, we – all three patients – we actually saw all of them had neurotoxicity. Which is not what we would have thought. So, kind of to go with what the study is saying here with safety, you can actually still see the same amount of neurotoxicity and fevers with patients that only have MRD-positive disease.

Okay. So, brentuximab. Brentuximab actually expanded to two different indications. I'm going to talk about the first one now, which is the ECHELON-1 trial. So, brentuximab is now indicated for treatment of adult patients with previously untreated stage III/IV classical Hodgkin's lymphoma. And this is in combination with chemotherapy. So, this approval was based off the ECHELON-1 randomized, open-label, two-arm trial that compared standard ABVD to ABD with brentuximab. This brentuximab dose was a smaller dose of 1.2 mg/kg with a

max of 120 mg. So really, all we're doing here is getting our standard ABVD and substituting it with brentuximab with the bleomycin.

These patients were randomized for up to six cycles on day 1 and day 15 of a 28-day cycle, which is similar to how we do our standard ABVD.

So they actually showed progressive-free survival that was statistically significantly better in the brentuximab arm versus standard ABVD, which is important to note. They actually noted this not only in the investigator-initiated committee, but also the independent review committee.

But what about toxicities? We definitely saw, and what we would probably see, is that there was an increase in elevated toxicity level in patients that received brentuximab. So you can see across the board that there were toxicities, more toxicities, but most notably, neutropenia, and neuropathy. And so there's a couple things I want to talk about. One is that the patients in the brentuximab arm did receive growth factor. We don't standardly give growth factor for ABVD patients. The other part is that the brentuximab patients also had more hospitalization, which is also important to note.

So, where does this fit into therapy, and how do we know where they're going to give the brentuximab ABD versus ABVD? It is now in NCCN guidelines for stage III or stage IV. They do recommend patients that aren't able to receive bleomycin that you would switch them over to this. Also, we need to keep in mind, because of the increases in neuropathy that these patients obviously shouldn't have pre-existing neuropathy prior to starting this regimen.

The other thing, and I don't really want to talk about cost, but the cost of this medication, giving brentuximab and the additional growth factor, is about $100,000 more than the treatment of ABVD. And that's not an exaggeration. So, I think it's important to keep this in mind, and if you actually look this up, you'll see a lot of dialogue about this, about, is it worth it? And I'm not saying – there's clearly progression-free survival difference, it clearly benefits a subset of patients. So I think in a subset of patients, it certainly is worth it. But I think all of these factors need to come into play when you're looking at your patient, and even the cost of the treatment.

So, the other trial, the ALCANZA trial, is brentuximab's other indication. So this is treatment of adult patients with primary cutaneous anaplastic large cell and CD30-expressing mycosis fungoides who have received prior systemic therapy. This was a phase 3 randomized, open-label, multicenter clinical trial of brentuximab patients, over 100 patients, who actually received this therapy compared to physician's choice. The physician's choice was either methotrexate or bexarotene.

Adverse reactions were very similar to the study I just presented, because we're talking about brentuximab, so you saw very similar adverse reactions, most notably primary – or peripheral central neuropathy, diarrhea, fatigue, and again, neutropenia. Most common cause of discontinuation was going to be the peripheral neuropathy.

This dose, it is single agent, so it's the larger dose of the 1.8 mg/kg every 3 weeks up to 16 cycles disease progression or unacceptable toxicity.

So, you can see here that there was actually another statistically significant, greater-than-10-month progressive-free survival with giving brentuximab over its counterparts, methotrexate and bexarotene. The other part to note is that it was more favored in patients with an ECOG of 0, and patients less than 65.

Now, the next one is the obinutuzumab, and this is kind of similar to the study I talked about, the ECHELON-1 trial, but a different disease state. So, obinutuzumab in this GALLIUM-1 trial. So, the indication and what it expanded is the treatment of adult patients with previously untreated stage II, III, or IV follicular lymphoma. This was based off a multicenter, open-label, randomized phase III trial of patients who had previously untreated non-Hodgkin's lymphoma, including 1,200 patients with follicular lymphoma.

So, what were the randomization of the arms? What we're really doing here is we're comparing obinutuzumab to rituximab. They're both CD20-targeted. They looked at CVP, CHOP, in combination of bendamustine. And so, they compared obinutuzumab to rituximab in those three different arms of treatment.

So, what they actually saw was progressive-free survival in the arm with the bendamustine versus rituximab. However, they did not see a difference in overall survival.

This is important to keep in mind, and I'll talk about the toxicities first, and then we'll talk about when we kind of maybe use this in practice. So, in the GALLIUM trial, even though obinutuzumab did show progressive-free survival, they did see a higher incidence of toxicity. Most notably, serious adverse events,

especially more than rituximab, 50% versus 43%, grade 3 reactions 79% versus 72%, and fatal infections. I think the take-home point here too to keep in mind is the bendamustine combination.

So, they did see a higher incidence of serious infections with obinutuzumab in combination with bendamustine versus the CHOP and the CVP. These patients previously received untreated – that were untreated follicular lymphoma – were recommended to get a dose of 1,000 mg days 1, 8, and 15, followed by 1,000 mg on day 1 for each subsequent cycle.

So, this is another question that we pose, of when do we substitute with obinutuzumab versus rituximab? And I think a lot of that depends on the patient characteristics, their ECOG status, and their current comorbidities. And I think, as I talk to different physicians about when they use obinutuzumab, I'm getting all kinds of answers. I have some that think it's great, there's progressive-free survival, Rebecca, why would we not use this? And he only uses it in a subset of patients, where I have other doctors that absolutely think that this is bogus, and they don't want to use this in any other patients, because they see the increase in toxicities, and they're concerned about the cost.

I think it will be interesting at this year's ASH, because they may talk about maybe where this may be more applicable in some patient populations over others.

Okay, now I'm switching gears completely, to talk about chimeric antigen receptor T cells, or our CAR T cells. So, we know that these are T cells that are genetically modified to target the patient's own tumor cells. And specifically, in

the two that I'll talk about today, and the only two that are FDA approved, is CD19.

So, axicabtagene is the first one I'll talk about. It's mechanism of action, it's modified CD19, which I just mentioned that it targets. It's reprogrammed to identify and eliminate CD19-expressing malignant and normal cells. It's made from a murine single-chain antibody fused to a CD28 and CD3 zeta. The CD3 zeta is what's critical for initiating that T-cell activation in secretion of those inflammatory cytokines and chemokines, which leads to cell death.

It's currently indicated for treatment of adult patients with relapsed or refractory large B-cell lymphoma after two more lines of systemic therapy, including diffuse large B cell not otherwise specified, and I won't read off all of those. But pretty much every formulation of diffuse large B cell, and if they have had two prior lines, are able to get this. There's a lot of other factors that come into play as far as toxicities, and we'll get there.

So the ZUMA-1 study – so the ZUMA-1 study is actually what got their approval. What they showed is sustained response – about 30 to 40% of patients had sustained progressive-free and overall survival. The ratio of response was also sustained in patients that actually had complete response, but you'll notice that patients who had partial response, it was only about 4 months.

What about the toxicity profile? And this is what we hear about all the time in our hospital is CRS, so common grade 3 or higher adverse events – febrile neutropenia, cytokine release syndrome, encephalopathy, infections, hypoxia, hypotension. The most common things that we obviously see are going to be our

CRS effects. Also infections. Infections is something else that we have seen in practice.

Because of the fatal CRS and the concern for that, it is recommended that these patients undergo a REMS program after the FDA mandated a REMS program for these patients.

As far as the dose, it is a single IV infusion of these cells. All of these patients will have had lymphodepleting chemotherapy prior to receiving their CAR T cells, and because of the CNS effects and the encephalopathy, it is not recommended that these patients be treated with, or any patient with primary central nervous system lymphoma, be treated at this time with CAR T cells.

Now following right behind this is tisagenlecleucel, which had already been out there in the market for relapsed ALL. So the JULIET trial. So this is again targeting CD19, and I'm saying that because a lot of our new CAR T-cell agents coming out are not targeting CD19 anymore, but these two still are.

So, CD19-directed genetically modified autologous T-cell immunotherapy. Again, relapsed/refractory diffuse large B cell – I won't read off all of those indications, but they're exactly the same as the last drug. This was actually based, the JULIET trial, was based off a multicenter phase 2 of 46 patients that had diffuse large B cell. These patients did receive the drug and had received lymphodepleting chemotherapy prior to the infusion of their CAR T cells.

Overall response for these 68 patients was 50%. You can see complete response is about 32%, median follow-up time was 9.4 months, but most notably in the slide is looking at the duration of response. These are almost identical to

what we saw in axicabtagene. So, duration of response was not met in those patients that actually had complete response. And then duration of response for patients that had a partial response was only about 3 to 4 months.

Again, common adverse events almost identical – CRS, infection risk, nausea, fatigue, hypotension. And because of all of this, they do recommend a REMS program.

So, the big question I had after learning about all of this is, how do you know which one to use? They're both indicated for the exact same thing. They both cost just about the exact same amount of money, for the most part. And so I asked a lot of questions about this to a lot of the providers I work with, and their general consensus is that, no one knows. We don't know. Maybe in ASH they'll probably tell us. Maybe not. But two of the things that they do look at is, tisagenlecleucel apparently is associated with less CRS effects. This could be argued probably, but if you ask a bunch of doctors that treat – that do this, a lot of them will say that. They've seen less CRS effects with tisagenlecleucel.

But the other thing to keep in mind is that a lot of these patients that get tisagenlecleucel, the turnaround time of those cells is actually about a week to a week and a half longer than axicabtagene. And so, that can play a point. If the patient has aggressive disease or they're very concerned that the patient's going to relapse, they might not have a week and a half to wait.

So, these are – they're typically the things that they do consider in their patients, whether they have pre-existing issues, but at the end of the day, these are all hypothetical things, and we don't really know.

Okay. So we're going to switch gears and talk about small molecular inhibitors. The two that I'm going to start with is ivosidenib and acalabrutinib, and then I'll go into expansion of some indications for nilotinib. It actually is not an expansion of an indication. We're actually going to be talking about when we can discontinue nilotinib. Now it's okay to do that. And then venetoclax. And then we'll talk about two indications of expansion in CML for bosutinib and dasatinib.

So, ivosidenib, IDH1 inhibitor – we already have an IDH2 inhibitor out there in AML now. So now we have an IDH1 inhibitor. It's indicated for treatment of adult patients with relapsed or refractory AML with susceptible IDH1 mutation as detected by the FDA-approved test. So, of course I asked this. I'm like, so, do all the hospitals have this test? I don't know if all the hospitals have this test, and that's important to know.

The other thing is that, just because the patient has a mutation on primary diagnosis doesn't mean they're going have the mutation during relapse. So it is important to make sure that we are checking this, and we're definitely checking this prior to starting the drug, in that relapsed/refractory setting.

The mechanism of action, which I've kind of already stated, but it's a molecular inhibitor that targets the mutant isocitrate dehydrogenase 1, IDH1 enzyme, and reduces the 2-hydroxyglutarate, the blast cells, and induces differentiation.

The dose is 500 mg once a day, with or without food, up until disease progression or unacceptable toxicities. It is recommended to avoid high-fat meals. If they take a high-fat meal, it will increase the concentrations of the drug.

And it is supplied at 250 mg, which I don't always put in these slides, but this is important to note, because it means that you can actually adjust the drug if you need to for dose adjustments.

Drug interaction – I feel like every oral chemo has drug interactions, especially with a lot of our anti-infectives. So, this is no different. So, strong 3A4 inhibitor and inducer, and it also is sensitive to a 3A4 substrate. So, those patients who have fungal infections, who are on voriconazole, fluconazole, isavuconazonium – these will be things that we need to consider when starting this drug or starting an antifungal.

Also QTc. QTc is also an issue, so patients who are on other QT-prolonging drugs, we need to monitor. And I'll talk about that.

So, black box warning is differentiation syndrome. I've seen this several times already. This can be fatal. This is very important, and I actually know a lot of providers that I practice with, physicians, that are not aware of this. They are not aware that it causes this, they don't know what the symptoms are, they don't know what it looks like, which surprised me. So I think it's important if you are aware that you do educate and let them know that it can cause differentiation syndrome.

The other thing to keep in mind is that you can actually treat this with corticosteroids. It's recommended – dexamethasone 10 mg twice a day for 3 days, is the recommended treatment. You can extend that, but generally, you don't need to.

Also important to note is to monitor for hemodynamic monitoring for symptom resolution.

The other warnings, and I talked about QTc prolongation. And so it is recommended when you start patients that you get an initial EKG, and then you get one every week for 3 weeks, and then subsequently every month. That is the recommendation. A lot of these patients may be on QT-prolonging drugs, so it is important to monitor that.

Ondansetron, if this causes nausea. Some patients might be on ondansetron. So all of this is important to note.

I get this question a lot in clinic about looking at this, and as long as you're routinely monitoring these patients, and there are no QT prolongations happening, then it is okay to continue these drugs.

Guillain-Barre syndrome, monitoring patients for signs and symptoms of new or central findings, permanently discontinuing if patients are found to actually have this diagnosis.

And then the most common adverse events, I've already kind of honed in on some of these – fatigue, leukocytosis. So patients who have leukocytosis, you actually can start hydroxyurea. White blood cell count greater than 25,000 is generally recommended. We start hydroxyurea, and you can give it concurrently, which is a question I have been asked. It is – and they actually recommend doing that. Obviously making sure that you monitor, because we'll want to stop it at some point.

Diarrhea, dyspnea, edema, nausea, mucositis. EKG, I mentioned this. Monitoring those EKGs. Rash, pyrexia, cough, and constipation.

Okay. So looking at the trial, you can see here that complete response or hematologic complete response was seen in about 30 to 40% of patients, and this was sustained. The other thing in this trial that noted is all the things that I've already mentioned that I will mention again, is the QT prolongation that we need to monitor for, the differentiation syndrome that we can give dex 10 mg twice a day for 3 subsequent days, as well as leukocytosis, which we can use hydroxyurea in combination with ivosidenib.

How about acalabrutinib? So this is our Bruton tyrosine kinase inhibitor for mantle cell lymphoma. It's mechanism, it's a selective irreversible second-generation BTK inhibitor that decreases malignant B-cell proliferation and survival. It's treatment is for mantle cell lymphoma, those patients who have received at least one prior therapy. It is dosed at 100 mg twice a day until disease progression or unacceptable toxicity.

Drug interactions – again, oral chemo, lots of drug interactions. Strong 3A4 inhibitor, moderate 3A4 inhibitor, and strong 3A4 inhibitor. So, all of these have dose recommendations. If patients are going to be started on voriconazole, and I'm going to use that, because a lot of our patients are on that drug and it is a strong inhibitor, it is recommended that you don't even start acalabrutinib in those patients, unless you're only going to give vori for maybe 5 days.

If it's a moderate inhibitor, so let's say fluconazole, we may recommend that you can actually start fluconazole with acalabrutinib, but maybe lower it to 100 mg once a day.

And then for any strong 3A4 inducers, it actually says to avoid this. So what is this going to do? It's actually going to decrease the concentration of acalabrutinib.

The other recommendation is to give a higher dose, which I don't know if I would recommend that. But it says to give a higher dose of 200 mg every 12 hours, so both possibilities. So you can either avoid and wait until they're ending their fluconazole, or you can give a higher dose of the acalabrutinib, depending on how much treatment they need and the duration of treatment that they needed.

The other recommendation, kind of similar to ibrutinib, due to potential risk of bleeding, consider interrupting treatment for 3 to 7 days prior to and after surgery.

Other dose adjustments – so this is unique to acalabrutinib, is occurrences of hematologic and nonhematologic toxicities. If it's the first or second occurrence of one of the two of these, then you would actually hold treatment until it's a grade 1, and then resume at that standard 100 mg twice a day dosing. If it's the third occurrence of this actually occurring, you would still want to hold the drug, wait until you're down to a grade 1, and then maybe restart at half the dose, the 100 mg once a day. If it's the first occurrence of this, then you would recommend,

or we recommend, or the package insert recommends, that you would discontinue the medication.

Other adverse effects seen – headaches, skin rashes, diarrhea, nausea, anemia, and myalgias. So the acalabrutinib study was a phase 2, open-label, single-arm clinical trial of 124 patients. These were adult patients with relapsed or refractory mantle cell lymphoma. Overall response rate was about 80%. Complete response was about 40% with 40% partial response. Acalabrutinib actually in practice seems to be doing really well. A lot of our providers are actually using this in place of ibrutinib. They're also seeing slightly less toxicities with acalabrutinib versus ibrutinib. So, I think it will be interesting, especially at this year's ASH, to see what else is coming out there. I think we can probably foresee that acalabrutinib is going to be indicated and used in multiple other settings. I can tell you in my institution, it is being used in other settings, but right now, the mantle cell approval, it seems to be working very well.

Okay. So, this is actually looking at nilotinib. In patients that receive nilotinib, in – looking at discontinuations. So this is two different trials – the ENESTfreedom and the ENESTop trial. Both of them have a similar number of patients, very similar results, which is why I have them paired up next to each other.

So, all of these patients actually received 3 years of nilotinib. After 3 years of nilotinib, they're in sustainable molecular response. These patients were actually able to discontinue their nilotinib after that 3-year period, and then they took a look at these patients. And they showed, not only after the first year, but

the second year, they were in treatment-free remission. At the 96-week cutoff in both of these trials, those patients that actually lost their molecular response, so they got their disease back, and they started back on their treatment, nearly 100% of those patients were able to regain molecular remission, which is very important to know.

And this also is interesting because it will – after the study and after the FDA approval of this, it kind of makes you wonder if they're going to start extrapolating this into other TKIs, and maybe even other disease states.

So in these two trials, they showed that none of these patients progressed to accelerated or blast phase in CML during this treatment-free remission. So while these patients were not receiving nilotinib, none of them progressed to accelerated or blast phase.

Common adverse effects – and these are not common adverse events of nilotinib but not taking nilotinib. So these patients have been on nilotinib for 3 years, at least 3 years, and then they just all of a sudden stopped it. And so that's what we're talking about. What are those side effects? So these patients had musculoskeletal symptoms, body aches, bone pain, extremity pain. But overall, there's been no long-term outcomes looking at discontinuing versus continuing treatments. And so we don't really know what this is going to look like in the long term. However, this was enough information for the FDA to actually expand the labeling and what's on the package insert, saying that it is okay. It's okay to discontinue nilotinib in your patients, as long as they've met certain criteria. And

a lot of that is the duration – it's been at least 3 years and they had sustained molecular response.

If the patient were to have – and obviously, after you stop it, you would still want to bring the patient back to monitor these patients – if the patient's disease does start to come back, you would obviously want to continue nilotinib within 4 weeks at this previously started – the previous dose that they were on.

Now, the BFORE trial – so this is bosutinib in the BFORE trial. So this is the indication for treatment of patients with newly diagnosed chronic-phase Ph-positive CML. The approval was based on data from an open-label, randomized, multicenter trial of 487 patients with Ph-positive newly diagnosed CML who were randomized to receive bosutinib or imatinib at 400 mg once a day. And so what we're looking at is bosutinib in the front-line setting.

The efficacy outcomes of major molecular response at 12 months is what was measured. And so you can see here, the major molecular response at 12 months was statistically significantly in favor of bosutinib at 47% versus imatinib, around 37%. Common adverse events were diarrhea, nausea, thrombocytopenia, rash, increased LFTs, abdominal pain. So obviously this now says to us that we can start bosutinib as front line in CML. There are some other options, so a lot of this is based off of what are the current side effects of the patient, what's going on with the patient, and is this a valuable option for the patient to start bosutinib front line?

Now dasatinib, again we're talking about CML patients. This is looking at pediatric patients. So, this is dasatinib in a phase 1 or phase 2 clinical trial,

approved for treatment of pediatric patient with Ph-positive CML. This was 97 pediatric patients with chronic-phase CML in two different studies. The first one was a phase 1 open-label, non-randomized, dose ranging trial, and a phase 2 open-label, nonrandomized trial. This was 51 patients exclusively who were newly diagnosed, and 46 patients who were resistant or intolerant to imatinib. In these patients, after those 24 months, you could see that 96% of those patients had complete cytogenetic response, whereas 82% of the resistant or intolerant to imatinib patients also had complete cytogenetic response.

They also looked at medium duration of cytogenetic response, as well as major outcomes in response and major molecular response overall, and they actually show that they couldn't estimate this because half of the responding patients had not progressed after that 5-year mark. So this actually expanded the indication to dasatinib in that pediatric population.

Adverse effects – a lot of us use dasatinib, so it's very similar to what we would see in dasatinib – headache, nausea, skin rash, pain in extremities, fatigue, arthralgias.

Now we'll talk about venetoclax. So this is the MURANO trial. I'm going to talk about venetoclax in a couple different settings. So this is expanding venetoclax in its indication for CLL or SLL with our without 17p deletion who have received at least one prior line of therapy. So, this is comparing venetoclax with rituximab to bendamustine and rituximab. And what they did is, they took venetoclax and did the ramp up over 5 weeks, staring at 20 mg and ending at 400 mg, and then followed by rituximab. So rituximab was given after the

venetoclax. And this was compared to bendamustine/rituximab that was standard dosing for up to six cycles.

The venetoclax/rituximab arm was statistically significantly improved with progressive-free survival over the bendamustine arm, which you can also see relayed over to overall survival as well. So it was very effective.

The MURANO trial also looked at MRD-negative patients. So they looked at MRD-negative in these patients of venetoclax versus bendamustine, and you can see there in the green, and that's the most important thing to see, is in the green you can see it was pretty substantial for patients that were able to achieve MRD-negative status.

The other thing is the side effect profile. We know that venetoclax has concerns for tumor lysis, specifically in our CLL population. We also know that there's a concern for neutropenia. So you can see here, a lot of these patients actually didn't come in with high counts, and so tumor lysis wasn't a huge issue. However, they did see a higher incidence of neutropenia.

The other thing is with the bendamustine arm, even though they saw higher neutropenia in venetoclax, the bendamustine arm had higher febrile neutropenia, and also had higher incidence of infections.

And so the other indication that I want to talk about is actually not FDA indicated, but we are using this all the time, and I'm sure that a lot of you are probably seeing this in your practices, is the addition of decitabine and azacitidine with venetoclax in AML.

So we know that BCL2 is a poor-risk predictor in our AML population, which is sort of where this idea came from. And so, this is actually a study, a multicenter, open-label, phase 1, dose-escalation study that looked at venetoclax at different dosing schemes. You have here in this chart, you can see, 400 and 700 mg, but some of these patients also receive the 1,200-mg dose. They looked at patients that received azacitidine versus decitabine, as well as if they're in complete response or CRi, and then looked at the risk stratification. And I can summarize that in the next slide.

So, multicenter, open-label, phase I study – so venetoclax plus decitabine and azacitidine was well-tolerated with deep, durable responses in elderly patients with previously untreated AML. You can see the CR and the CRi rate was about almost 70% of these patients. The overall response rate was about 80% in this trial. So, when the actually split it up and they looked at poor risk disease, secondary AML, and greater than 75 years of age, it was almost 70% of patients.

The median overall survival was about 17.5 months in all of the patients, so about 50% 1-year overall survival. And MRD-negative was observed in 45% of these patients. Overall, the study actually supported the use of venetoclax 400 mg every day, or daily, in combination with decitabine and azacitidine.

What I do want to say is that, when they looked at the different dosing schemes, obviously 1,200 had higher toxicities, and I don't have this on here, but the 800 actually showed very similar efficacy to the 400. However, a lot of people thought, well, why would we give a higher dose if there's no benefit to it? And all

now you have is an increased risk of toxicities. So the 400-mg dose has been the recommended dose in combination with azacitidine and decitabine.

Okay. So, this is my last slide. This is the pipeline drugs. So, these are drugs that are going to be coming out, and some of these actually have – duvelisib, our PI3K inhibitor, already has come out, and I didn't talk about that today. But I think the important things that I want to note here, is what are we going to do with this information?

So we have all these new drugs coming out, and what do we do with that? We have these biosimilars coming out, and a lot of the biosimilars are very similar to these drugs. And so, I think that poses a lot of questions of what we're going to do. Some of these are Me Too drugs. And so, what we say in pharmacy as Me Too drugs, it's like having 50 ACE inhibitors, is that we're not going to have all of them on formulary. And so, now we really need to start looking at these, and which ones are actually beneficial to the patients.

Looking at the toxicity profile of these agents, some of them claim that they have less toxicities than the other, and all of that needs to be compared. But the biosimilars that are coming out as well are just as great as these ones. And so, you'll probably see at ASH that we're going to be looking at a lot of this in a more big picture.

So I think the whole idea, in my take-home message, was – this whole presentation, is to keep an open mind and know your drugs. Know your targets. If you know what those targets are – because a lot of these FDA approvals are going to continuously be expanding to all of these different targets – so if you

know the drug and you know the target, you can probably start to foresee where we might start using some of these agents in the future.

The other thing in your practice settings is keeping in mind supportive care. So the doctor may decide to start one of these agents, but the supportive care is almost the more important part in some cases. So, antifungals, antivirals. Do we know if it's going to deplete their lymphocytes? Do we know if they're going to be neutropenic for more than 2 weeks? Are they going to need growth factor support? Were there growth factors used in those trials? All of these things are so pivotal and important to a lot of these drugs, and the lifeline of these patients.

And I think I'm running out of time, so I'm going to go ahead and answer any questions anybody has.

[Applause]

INTRODUCER Wow, that was a wonderful presentation. Thank you very much, Dr. Nelson.

[END]