**New Drug Updates in Hematologic Malignancies: CAR T Cells, Targeted Therapeutics, and Other Agents**

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INTRODUCER Welcome back, everyone. I hope you were able to enjoy the break and got to visit with some of the exhibitors. As a gentle reminder, please be sure to silence your cell phones for our next session. This next session is the presentation of the "New Drug Updates in Hematologic Malignancies: CAR T, Targeted Therapeutics, and Other Agents." Please welcome back Dr. Donald Harvey of the Winship Cancer Institute of Emory University.

DR. HARVEY Thanks, everybody. I want to thank the organizers for having me back. I think this is continuing to be a great meeting. I want to send a shout out to the organizers for the attendance. This is growing every year, and certainly I jokingly say with my work wife, Colleen, who is probably somewhere here, she and I are better together than any oncologist in our building because we know the drugs that we deal with and I think what we actually do a better job than they do, but since there are no oncologists in the room, I can get away with that.

It has been a pretty banner year for hematologic cancers in terms of approvals, and it's not just the things that we commonly think about. I like to think of drug development and cancer in general as having two main drivers and one is personalized molecular small molecule therapies that we have that are there to really hone in on a population of patients, and then the other side is let's go

immunotherapy and really try to teach the immune system in one way, shape or another to attack what should be foreign to the body and that's cancer. The drugs that have been approved from last year to this year are absolutely indicative of those two major paradigms, and that's what we'll go through here.

We'll talk about some pharmacology, how these drugs work, we'll certainly talk about adverse events and clinical trial data, and in the end, I'll try to contextualize a little bit about where these drugs may fit into therapy overall and then what populations will be best served to receive these agents. These are my disclosures. When you look at agents and approvals, you can see that there's a list of drugs that are here and you have to put both of them in because those of you who remember the world of gemtuzumab ozogamicin know that it's been actually around for a while. It was on the market and then pulled and then came back, so it's certainly not a new agent. Similarly ibrutinib is not a new agent because it's already out there, but it represents the first drug that's been approved in a relatively difficult to treat population, those patients with steroid-refractory chronic graft-versus-host disease, and certainly rituximab we all know and love and there's a new formulation that we'll go through.

When you look at this list of drugs, again, you have sort of what I consider three main buckets. You have drugs that are very targeted for a population. As an example midostaurin for the *FLT3*-mutated AML population. You have the immunotherapy approaches, and so tisagenlecleucel—and there will be a quiz at the end to make sure you can say that word over and over in your sleep. And then finally a new formulation of drugs or a new way to deliver drugs, whether it

be with a targeted antibody targeted with a Trojan horse like ozogamicin, whether its inotuzumab or gemtuzumab ozogamicin or a new way to think about delivering conventional agents, and that's liposomal daunorubicin and cytarabine. There are additional approvals, and lenalidomide got the final approval for something that's probably been happening in many of your centers for a while already and that's maintenance treatment post-autologous stem cell transplant for patients with myeloma. I liken this approval to getting married after you've lived with somebody for a while; it was just going to happen eventually, it just took some time. Pembrolizumab is also in approval following on the heels of nivolumab. Pembro got approval in Hodgkin's lymphoma after nivolumab did as a flat dose, interestingly here compared to nivolumab, but it is also approved. Then *JAK2* testing for patients who are at potential risk for who you consider clinically who have polycythemia vera, so the FDA does approve tests as well.

Other agents that are in the heme space, but I'm not going to go into too much depth today on, one is another oral anticoagulant that directly targets factor II, betrixaban, so VTE prophylaxis in medically ill patients is its approval and indication. There's the dosing; you can see a fixed period of time post-discharge for patients who are medically ill. It's other thing that patients may come in on. L-glutamine oral powder in sickle cell disease, and so we've had hydroxyurea for a while. In sickle cell, L-glutamine at doses of 10 to 30 gm that are weight-based twice daily with liquid for adult and pediatric patients has shown to reduce the complications of acute crises. Then finally blinatumomab originally was approved for Philadelphia chromosome–negative ALL and they've just tacked on with data

for the positive population. I did want to cover ibrutinib a little bit. Again, the first drug approved in a space that has been studied for decades in an incredibly difficult population of chronic graft-versus-host disease. This is approved in patients who have failed corticosteroids, which those of you who are in allogeneic transplant settings, you'll know that after that steroid failure, there's about a 30-drug different menu you can pick from, and it kind of depends on where you practice what your next go-to drug is—420 mg daily, the same dose as it's other indications. The trial was done in 42 subjects who failed steroids and two-thirds of patients responded.

Chronic graft-versus-host disease does have a very well-defined response criteria across all organs, liver, skin, GI tract, etc., are all part of the categorization of responses. Median time can be a little bit long, and so it can take 12 weeks for patients to respond. That's median; some are early or some are much later. The bottom line is don't give up early on ibrutinib in patients who are getting it with chronic graft-versus-host disease. Let's move into the approvals. Midostaurin has been around for a little while and we'll talk about *FLT3*-positive acute leukemia and where midostaurin fits in. So *FLT3* and AML. *FLT3* is a transmembrane receptor, so it's kind of akin to a few other receptors that are out there. It's in the same tyrosine kinase family as the KIT receptor and PDGFR. So you might remember that imatinib was originally developed as a PDGFR antagonist and was found to have much more activity in the *BCR-ABL* activated structures, but this is the same type of tyrosine kinases as that. It's high expressed on early progenitors and hematopoietic cells and so you can imagine

then that if it's highly expressed, the *FLT3* is highly expressed and you're going to have potentially additional cytopenias that would be seen with inhibition of an activated mutation.

You can also think about *FLT3* a little bit like *EGFR* in lung cancer. It has to be activated to be constitutively important. It can be there, but it has to be turned on and it's turned on through mutational structures. The most common mutations seen is called the internal tandem duplication; it's basically a light switch that turns on the receptor to drive proliferation of the leukemic clone. This is the mechanism that inhibits lots of things, but most importantly it inhibits mutated *FLT3* and that's how it works. It's approved for newly diagnosed acute leukemias. As we go through a number of these drugs today, you'll see that there are a couple that are approved by the newly diagnosed and many others that are approved in the refractory and relapse setting following acute leukemia.

7+3 isn't dead yet, hopefully it will be soon, but it's still there and is still a backbone for many of our therapies in acute myeloid leukemia. It's approved in combination with a test, an FDA-approved test, and generally lots of molecular panels will have *FLT3* mutation detection and I don't suspect that there will be a problem overall with, once you identify that mutation, getting a drug approved and paid for.

Standard cytarabine and daunorubicin, and you may ask what if we use idarubicin; it really doesn't matter and so we'll talk about that a little bit and I'll tell you why it doesn't matter. This is the dose, 50 mg twice a day with food. Take it with food not for concerns of absorption or pharmacokinetics, but rather for

nausea prevention. Midostaurin has its own set of emetic potential, so it's important that patients take it with food as they can. You'll see the start date as well, so 7+3, the 7 is the week of continuous infusion cytarabine and you want to start midostaurin the day after that completes, and that's because of a potential interaction with daunorubicin, but also because you are trying to mop up the *FLT3*-positive leukemic clones. You do need prophylactic antiemetics because of the rates of nausea and vomiting seen. You don't need to change the dose in mild to moderate renal or hepatic dysfunction. If you have severe dysfunction, there's no data, but if a patient has severe dysfunction you should probably be asking yourself do you need to treat them anyway.

You need to hold for pneumonitis, which can be seen. And you'll find a common theme among a lot of small molecule tyrosine kinase inhibitors and some that are going to be presented today and that's that there can be a noninfectious pneumonitis that occurs, and this is true of erlotinib in lung cancer, it's true of everolimus in many cancers as well. You can see in a certain proportion of patients a pneumonitis that is noninfectious, it's generally pretty straightforward to see on radiograph, but the drug does need to be held should that pneumonitis occur. These are the warnings; I'm not going to go into them too much because we've already talked about it. One key clinical point is that midostaurin is a CYP3A4 substrate, and you can imagine that it becomes a bit challenging when you give drugs like the azoles like posa and vori specifically in acute leukemia antifungal prophylaxis. Because they are potent inhibitors at 3A4 and so optimally you want to try to avoid their use with midostaurin.

Now carry that a few steps forward. So what are you going to do? So the caspofungin world, the micafungin world are certainly safe to use, but they are intravenous and so there are still evolving data on how to think about azoles and midostaurin. Optimally avoiding those azoles is the best scenario if you can set up intravenous if patients need echinocandins, but it may be that you are going to take a little bit of a risk. At Emory we have begun to take a little bit of a risk, with that meaning we'll put people on azoles, put them on midostaurin, and follow them closely because we'll talk about some of the adverse events. Most of the adverse events you are going to see are adverse events that are common in patients getting induction and consolidation chemotherapy for leukemia, and so midostaurin doesn't add a whole lot to this outside of that pneumonitis concern. Most of this stuff, mucositis, neutropenia, and that's leukemia, right, for those of you who work in it, you are going to see that's garden variety kinds of stuff.

This was the trial that led to its approval, newly diagnosed AML with activating *FLT3* mutations, and they were stratified by tyrosine kinase domain and internal tandem duplication ratios up front. So 717 patients, a large study, 28-day cycles, and they got this is where the world of acute leukemia is, but cytarabine 200, 100 is fine, there's been no difference in 100 versus 200 for the development of this drug, though they elected to go with 200/$m^2$ daily of cytarabine and, at the time, standard dose daunorubicin of 16. All of that is there and then you complete those agents and then move on to midostaurin and the induction or placebo on the other side. You can see midostaurin is carried through all the way for consolidation and post-consolidation. Now post-

consolidation is a bit of a tricky story because post-consolidation is truly that. You can elect to give high-dose ara-C in however many consolidation cycles that are standard for your institution.

In this trial, it was allowed to go up to four cycles of HiDAC, but once you complete your planned consolidation, then there's this post=consolidation world, but it's not maintenance but it kind of is maintenance, and so basically continue midostaurin as long as you can and don't call it maintenance. That's really confusing, I'm sure, but that's the way the labeling and the regulatory language goes. What happened when they did this? Well, there was a survival advantage, So it's important to think about clinical trial endpoints overall. And oftentimes in solid tumor malignancies as well as some myeloma trials, you see progression-free survival as a clinical endpoint. What we are going to see today in a number of incidences is overall survival improvement, so this is an overall survival improvement with midostaurin in *FLT3*-mutated disease. That's an important point. You might argue the significance of the overall survival difference, but it is an overall survival difference, thus it has become standard of care for *FLT3*-mutated patients to receive midostaurin in combination with conventional chemotherapy. So midostaurin, yes.

Now we are going to move on, and I went sequentially based on the approvals through the years. We are going to bounce around between lymphoma, leukemia, and others. Rituximab subcu with a hyaluronidase. As a reminder, there is a reason you can only give so much volume in a subcutaneous injection and that's because of a protein in the subcutaneous tissue called

hyaluronan. Hyaluronan, think about it as a net, a fishing net, with a lot of tight junctions that are there. Hyaluronidase, back to you biochemistry, dases or enzymes, and they cleave stuff, so hyaluronidase is basically scissors for the net. It opens up the subcutaneous tissue, and that allows for the injection of larger volumes of drugs. This is already approved in IVIG therapy, so it allows for injection of larger volumes of drugs into the subcutaneous space.

Why would you want to do that? Well, it's actually more convenient. When you look at IVIG therapies, patients who get IVIG for immunodeficiencies actually can do this at home; it's a little more straightforward than starting an IV. So hyaluronan is part of that; it's cleaved by hyaluronidase, and hyaluronidase is manufactured by a company called Halozyme and it's being added to a number of drugs including IVIG and now rituximab for allowing subcutaneous administration. So again, it's both the hyaluronidase plus rituximab within the drug, and it's got the same indications that rituximab has in cancer. Not for nonmalignant disorders, so your ITP patient is not a candidate for this therapy, at least not if you want to get it paid for or you want to give it away, the agents that are there. An important point clinically although this is a little bit unfortunate, but very understandable from a safety perspective, patients have to have had one intravenous infusion of rituximab before they can begin this subcutaneous approach.

The reason is if you think about it much like daratumumab, CD20 expression and the number of CD20 cells in patients getting rituximab for the first time is up here. You give them rituximab with their chemotherapy backbone and

that CD20 population comes down, and that's what mediates the infusion reactions is the presence and the bulk of CD20 that's out there. So once you get that population down, you are then able to give the drug with much more safety involved. Premedications are the same, you inject it into the abdomen. The dosing that's here is important, that's different based on follicular lymphoma much like, again, the standard indications or CLL. It's a flat dose of rituximab at 1,400 for lymphomas and 1,600 for chronic lymphocytic leukemia, and it's with ahead of time this 23,000 or 26,000 approximately units of hyaluronidase. So again, the hyaluronidase goes in, you inject it over approximately 5 minutes and it's a dose-dependent injection and it's about 12 mL or 13 mL based on indication, and then you give the rituximab. You are there to provide both of those in a way that you are opening up the space and then giving the drug following, and then you can watch them for 15 minutes, which is very different from our usual rituximab experience and say, "Bye," and they go home.

These are the things to think about: the standard adverse events that are seen with rituximab are certainly there as well and the common adverse events are somewhat similar as well. Again, these are things that are not new based on the route of delivery. This is the data that's supported its approval. This is a 2:1 randomization of standard rituximab with CHOP chemotherapy versus the subcutaneous formulation, again 2:1 randomization. Response rates were similar in that predefined criteria, and the difference in response rate was slightly numerically better with subcutaneous, but overall really not different than standard rituximab. This provides an option for patients and institutions that want

to give rituximab a little more quickly in subsequent treatment following the first IV dose.

Moving on to enasidenib. This is like Hooked on Phonics day. So *IDH* mutations. *IDH* is isocyanine dehydrogenase; it's an enzyme that's present in a lot of different cancers. Most importantly from a drug perspective, it's present in acute myeloid leukemia. It's also important in cholangiocarcinomas as well as brain tumors and gliomas. The challenge there is you can't get drugs to cross the blood-brain barrier. It's present in about 20% of all AML cases, and it's there at the beginning. We think about mutations often and think about T790M in different places and T315I in CML, and those are mutations that evolve after treatment. *IDH* mutations are present at diagnosis, and so this drug is likely to move up in terms of where it is in its clinical use right now, but it certainly is more common in the elderly population and elderly AML certainly is a large proportion of the patients that are seen. *IDH* really regulates cellular metabolic fate, so it turns over a number of endogenous cellular products, and if you inhibit it, then the cell can't get rid of those endogenous products and then is marked for apoptosis.

It's an IDH2 inhibitor and it's approved for patients with relapsed or refractory disease, so not an up-front therapy as of today. With the *IDH2* mutation, that was identified by an FDA-approved test, the Abbott RealTime IDH2 PCR assay was approved in conjunction with this drug. There are likely others, much like PD-L1 testing that you'll find and other common molecular companion diagnostics that will evolve in this space as well. 100 mg once a day continuously, so that's dosing that's relatively straightforward for that and there

really aren't significant interactions. Because this drug is a very targeted therapy in acute leukemia, you can see a number of adverse events that are akin to differentiation syndrome, tumor lysis, for example in acute promyelocytic leukemia, and it basically teaches these cells to grow up more quickly and become productive members of the cell society. And when that happens, they can then transform and traffic into different places in the body, the lungs for example, again those of you who treat patients with acute promyelocytic leukemia know that differentiation syndrome can be challenging and can be a problem in patients with those diseases.

If you start to monitor these patients early and often and their white counts start to skyrocket, they need to be placed on good dose hydroxyurea, not weenie dose hydroxyurea, so a gram three times a day or so at least 3 to 4 gm a day of hydroxyurea should be considered. It can cause hyperbilirubinemia as well, so doses do need to be adjusted secondary to that on-target drug effect of bilirubin elevation. These are some of the adverse events: nausea, vomiting, diarrhea, so again antiemetics may be important, on-demand loperamide or other antidiarrheals need to be there as well, and all those tumor lysis syndrome watching events need to happen too. Because this is such as small number of patients within the trial or at least this is more of an orphan kind of disease, the drug was developed and delivered based on some phase I trials of dose escalation that were done early on and then the drug was moved into an expansion phase, and so from these relatively small numbers of patients initially, it moved into a phase II trial with a dose defined as 100 mg daily in the relapsed

and refractory setting. And the testing was done centrally to confirm *IDH2* within that space.

Again, these are patients with relapsed/refractory disease with this mutation, so the complete response rates are in about the 15 to 17% range overall, and the 95% confidence interval you can see here with a duration of response of about 6 months and so certainly it's a challenging population, but *IDH2* tends to be in the elderly, so you may have patients that you don't want to necessarily reinduce with a different regimen, for example, etoposide, mitoxantrone you might pick for a younger population; however, if an elderly patient is more likely to have *IDH2* mutations and cannot tolerate another induction regimen, then you might want to consider this with careful monitoring for differentiation and tumor lysis syndrome. Liposomal daunorubicin and cytarabine.: this is a nice, new package, it's a new way to deliver daunorubicin and cytarabine. I like to say that this is not your grandmother's 7+3 because if you've been in acute leukemia 7+3 was used when our grandmothers were alive, it feels like. This is a drug and a combination of drugs that are sort of wrapped in micelles and cholesterol, so it is meant to try and deliver higher concentrations of the drug to the cells of interest, improve circulation time, and hopefully improve the therapeutic index of these drugs in difficult to treat patients. The approvals for this trial and the regulatory licensing trials were done in an incredibly difficult population and that's therapy-related acute leukemia and those with MDS that have evolved into AML. So these are challenging patients to deal with, and this was a drug that was meant to come forward in that realm.

The dosing is different; talk to your local pharmacist about dosing with this drug. I want to thank whoever reviewed my slides for this because they told me that this drug is purple. I didn't know that. I think that's kind of cool. Daunorubicin is red certainly, but when you add them together in the same package it's purple. Who knew? The Barney induction. So it's induction and consolidation dosing as options, and the indications for this are kind of—they are not all over the place, but there are lots of options for this compound to be used in various AML settings. And when you think about it, and there was a lot of thought, how will this toxicity be different? And how will it compare to 7+3? And we'll go through that data, but in general it's 7+3 in a different package. So the things that you need to worry about with 7+3 extravasation if it's a peripheral IV, hopefully not, because it's really not smart in acute leukemia, but extravasation is a concern, cardiotoxicity with anthracyclines, etc., and certainly cytopenias that we all know of and love in AML.

The common adverse events, again, are very much those that are seen in the acute leukemia population with a couple of important distinctions that we'll go through. This is the data, this is a little bit of a busy slide, my apologies, but this data hasn't been fully published, so this comes out of the product information. You can see again here we have a difference in overall survival, an important endpoint for a difficult to treat population. Overall survival was improved with liposomal formulation compared to standard 7+3 with an improvement of about 3 and a half months comparatively. So it's up to you and your institution and the

clinicians you work with to think about how you fit this in, but it is an approximately 3 and a half-month survival advantage with the new formulation.

The adverse events are quite similar, and you can see if you move to the grades 3 to 5, the ones that we think about as being most severe, they are really not different, but in the all grades category, there are a few that stand out. One is hemorrhage. Why people getting the liposomal formulation would hemorrhage more is a complete mystery to me. There might be come interactions with coagulation testing and coagulation parameters, but at least in terms of thrombocytopenia rates, they are really not that different between the two groups. Similarly, there is a little more rash, which you might imagine with a new formulation of a drug, so about half of patients had some degree of a rash; generally it is self-limiting and not a problem overall, but it is more common. And similarly headache. Everything else in my eye is similar or better than 7+3, so at least in terms of adverse event profile, a couple stand out from the trials, but overall it's pretty much similar to 7+3 overall.

We'll move on to now what we call the Trojan horse category of drugs: inotuzumab ozogamicin. It was approved in August of 2017. This is the setup of inotuzumab: it's a CD22 antibody linked to calicheamicin and similarly to gemtuzumab ozogamicin, it's the same idea. The idea is that you bring the CD22 Trojan horse to the cell, it then releases its payload into the cell and then boom, the cell blows up or a few other things happen before that, but in general you are delivering a microtubule targeting agent to the cell and the cell dies. That's how I explain it to my kids. So this drug is certainly labeled with calicheamicin, it's ALL

and so there's going to be—we have this drug in trial at Emory and we jokingly called it "lymphotarg," which was not the real name by the way, and it looks very promising in a number of lymphomas, but ALL was where it came to market first, and adult ALL is certainly a challenging population of patients to treat, and so this came forward in the relapsed/refractory population. You might consider people who have failed hyper-CVAD or whatever cocktail of drugs you use in your shop for ALL treatment in the adult setting, and it does need premedication.

I won't read the dosing here. Initially cycle 1 you want to try to get more drug in in a 21-day cycle; subsequent treatment is based on the presence or absence of a complete remission or a complete remission with incomplete hematologic recovery, that's what CRi means. After that you can look at month cycles following that initial cycle. There are problems with these drugs. The ozogamicin side of these agents is hepatotoxic in certain instances; it's hepatotoxic in people certainly who have had prior busulfan conditioning for autologous stem cell transplant and the reverse is true. If you get an ozogamicin-containing drug and then you get busulfan conditioning, your rate of VOD or SOS goes up. These are combined hepatotoxicity agents. There is some degree of QT prolongation, and it's not that big of a deal to be honest, but it's in the label. The adverse events that are here are things you would expect with a drug and a cytotoxic drug that's mildly suppressive. Those are standard. LFTs need to be monitored carefully obviously for multiple reasons, but certainly the rest of these things are standard things we see in the population of interest.

This is the trial that got it onto market. CD22-positive ALL, Philadelphia positive or negative, 326 patients randomized to standard of care, which could have been dealer's choice, one of three potential options, FLAG, fludarabine, cytarabine, and GCSF, ara-C, and mitoxantrone or just straight IDAC was compared, and these are the rates of CR within the two groups. Again, this is not an overall survival, but still an important rate of response, and complete remission was certainly improved in patients getting inotuzumab; MRD negativity was improved as well. You can see the duration of response was about 3 months longer across the population in the two groups. So a 1:1 randomization another option for patients with Philadelphia chromosome–positive or –negative ALL who are adults.

Let's move into what I think is probably likely to be on the cover of *Science* at some point, and that's CAR T-cell therapy. Tisagenlecleucel was the first CAR T approved for therapy and there was one—I got these slides in really late and I still didn't get to cover two drugs that were approved, by the way, after I got these slides in, so that's how busy heme malignancies are. The other, the Kite CAR T-cell that's also been approved for adults with diffuse large B-cell lymphoma, primary mediastinal lymphoma and high-grade B-cell lymphomas I'm not going to cover today, nor am I going to cover the acalabrutinib approval, which also came out, but those are two drugs that have hit the market in the last literally two approaches in the last 2 to 3 weeks.

Let's talk through a little bit of background on tisagenlecleucel and specifically chimeric antigen receptor T cells. If you go back to your Greek, you'll

know that “chimera” is a fusion of two different things. In Greek mythology, a chimera was usually a human and an animal coming together, and so chimera really reflects the idea that you’re trying to do two things in a T-cell, and I’ll talk about what those two things are and how they can be used to target and hopefully provide a long-term disease remission or cure using this approach. This is a nice depiction of what happens in CAR T-cell therapies. In the first study, we can see the patient undergoes apheresis. A number of T cells are removed along with a bunch of other schmutz. That stuff is returned to the patient, the T cell is taken out by beads. What you’re looking for are CD4- and CD8-positive T cells, so you’ve heard a lot about immunotherapy; CD8-positive T cells are incredibly important, but you also want CD4-positive cells to come out of this apheresis product.

You then take those CD4-positive/CD8-positive populations and you try to expand them, and you expand them by adding in cytokines. So the beads on this depiction are artificial APCs are there to try to remove the cells, and then you want to grow these cells. You want to grow them like you grow anything else, and you do that from cytokines, and you do that through media and other ways to make these cells more viable. And then you want to teach them. So you’ve grown them up—think of them like children—you’ve grown them, now you want to teach them and you want to teach them in a way that will help them to go after the target of interest. That’s why CAR T cells are going to be applied at least investigationally across a number of different cancers. You can pick the antigen of interest. In myeloma, you can pick the B-cell maturation antigen or BCMA. In

solid tumors and small cell lung cancer, you can pick NY-ESO and target the cells to go after that, so it is an individualized immunotherapy based on the cancer and not on the patient.

You are teaching these cells in this instance to go after CD19-positive B cells. Those are lymphomatous B cells in ALL or leukemic cells in ALL whether lymphomatous cells and diffuse large B cell. You transduce them and you teach them with a viral particle because viruses are very good at transfecting things. You get the virus, you teach the virus what it's going to transfect, and then you do it, and you expand that column, and then they now have antigen receptors on the T cell, so they have their warhead.

That warhead is then infused back into the patient, and that's where the fun begins. After infusion, they go to the site of disease, so these T cells are very honing; they hone to what's CD19 positive. The challenge, much like CD8-positive T cells after PD-1 antagonism, is they may not know what's friend and what's foe right away, and so they want to grow and go after the cell of interest and they want to get to the target and engage it, and so it really is like an army of soldiers going after it. Then after that engagement occurs, they bring more friends to the party—cytokines, complement, natural killer cells, cytotoxic T-lymphocytes that are innate—and so there's an early phase of cellular kill that occurs after infusion of CAR T cells.

There are a couple of things that have to happen though for this to really work well. One thing is these are your cells as the patient, but they are also now a little bit foreign, so you want to try to accept these cells. It's not full-on

transplant, but you want to create an environment where these CAR T cells are going to be welcomed, and you do that through lymphodepleting chemotherapy, which we'll talk about in a second. That's one thing you want to do is to let them come in and be welcomed, and then you want them to grow and stay there and move in, and that's where the expansion of the CD8- and CD4-positive cell occurs in vivo in the patient, and that's what leads to a long-term remission after the initial infusion of the cell. It's a lot to ask of these CAR T cells, and it's impressive that the group at Penn and others have been able to do this. It was first done in 2008, so it has been a while in development. Other cellular therapies are in development, natural killer cells are in development in Europe and in other places, but in this instance, they grant a breakthrough therapy to this product's CTL019.

In August of this year, FDA granted approval to the pediatric population up to 25 years of age, and so your institution may decide how they're going to handle that, but it is in approval up to 25 and it was on a single-arm trial of 63 patients and about half of those, a little more than half, had a prior stem cell transplant. The overall remission rate was 83%, so you've got a young population who's got bad ALL, you do this procedure, and 8 out of 10 of them go into remission. That's unheard of in this place, and that's why the excitement is around this. So if 63% got into a CR, out of those eight, six of those eight went into a complete remission and 19% had complete remission with incomplete hematologic recovery. Like many times when I'm giving these talks, this does come with a price, but the payoff in my opinion is certainly worth the price for the

right patient population. So it's a CD19-directed genetically modified autologous T-cell product. There's the indication which we talked about. Patients need to get fludarabine and cyclophosphamide before they get this therapy. So if you're a patient, you come in, you get your T cells collected, and then you hang out and you wait for the product to be made. Now in new trials and later on in the development of this product, patients were allowed to get chemotherapy in the interim between when the product was being made and when it was reinfused, but if you don't have that or even if you do, you still have to get lymphodepleting chemotherapy and this is in the label: standard fludarabine, standard cyclophosphamide, and then you infuse the tisagenlecleucel 2 to 14 days after that lymphodepleting chemotherapy. I love that this is in the product label, "Verify the patient's identity." Because man, that would be a huge screw up, wouldn't it? "Oh, man, we gave Mr. Smith the T cells that we were supposed to…oh, that's too bad." So certainly verify the identity of the patient. I left this in because it is right in the product information. Premedicate with acetaminophen and diphenhydramine, which is a little bit like bringing a BB gun to a war, and then make sure you have tocilizumab. Tocilizumab is now FDA approved for complications associated with CAR T-cell therapy.

When you infuse CAR T cells, there is one cytokine, it's my favorite cytokine that just cranks up, and that's IL-6. You will get a ton of IL-6 release once you give CAR T-cell therapy. The dosing is based on the number of viable CARs that are there, so it's a weight-based dosing that you are going to infuse and it's based on weight alone, but it's a flat dose based on weight, not a per kilo

of cell infusion. These are the things that can happen; a couple of things to really point out: prolonged cytopenia. Cytopenias can be very long following these infusions. You can wipe out the marrow. Remember this is a CD19 cell. They hopefully will come back in many instances, but not necessarily all. You may have transfusion-dependent patients for an extended period of time. The other thing is hypogammaglobulinemia and you might think, “Oh, well that’s easy. We’ll just supplement them with IVIG like we do many other patients.” IVIG isn’t the only gammaglobulin, so IgA goes down, IgD goes down, IgE goes down, and those you can’t replace. So patients are at risk of infections from those types of hypogammaglobulinemia settings. So they do need—there are serious infections associated with this therapy that can be unusual in addition to your standard bacterial and fungal infections.

Common adverse events are listed here. Cytokine release syndrome I can’t talk about enough. It’s a CNS-based thing, you get a ton of cytokines released, again, IL-6 being the primary driver. You can have confusion, somnolence leading to encephalopathy, and so tocilizumab being there and being around is incredibly important. You can release bunches of cytokines, which can lead to capillary leak, which can then be a secondary acute renal failure, secondary acute hepatic insufficiency, usually though you have selected these patients well before coming on.

This is why people are excited, the swimmer’s plot here. I don’t have to tell you that these kinds of responses and these kinds of durations are what are exciting. Of the 107 screened, 88 were enrolled. This is an important point to this

trial and future products. 107 were screened, 88 were enrolled. That means you, off the bat, this is a 25 year and younger ALL population, you have a culling of the population right off the front of an otherwise healthy group, so not everyone is going to be a candidate. 68 of those 88 were treated. Why were only 68 treated? Their disease got worse, their performance status declined, and the product wasn't ready in time. Those are changing with this product and future products. The turnaround time to get these back from manufacturers has very much gone down, and in general it's usually about a 2- to 3-week process, but good communication is incredibly important. Of those 63 who were treated, 35 were men or boys, the median age was 12, 53 had gotten, did get bridging chemotherapy, and so that tells you right away the majority of patients in this trial are going to need some disease-based chemotherapy between collection of the cell and reinfusion, which is actually a good thing because you really don't—if you're going to invest in this, you want to make sure you can get the patient to the final product. 30 had a prior allogeneic stent transplant and two had two prior allogeneic transplants. So that's CAR T cells; it's an exciting area and certainly will continue to grow in terms of applications and investigations.

Let's move on now to gemtuzumab ozogamicin approved in September of this year. Gemtuzumab has been around for a while. I'm really sorry that I'm going to be over, so I'm going to try to blaze through this, but my God, there was a lot of information. CD33 antibodies, calicheamicin, newly diagnosed CD33 positive AML and relapsed/refractory-positive AML in pediatric patients. You've got to premedicate. There's a newly diagnosed regimen that can be used and

that's generally in people who are not candidates for 7+3. There's a single-agent regimen as well, so induction and consolidation. These are doses that are lower than the previous gemtuzumab label. And then finally relapsed and refractory both induction and consolidation regimens. These are the warnings, similar to inotuzumab ozogamicin; you can have hepatic insufficiency, again, the risks are the same as they were with inotuzumab. You can have infusion-related reactions, all the other stuff is stuff we see in acute leukemia patients generally and things to keep an eye on. This is the data, again, another overall survival improvement compared to daunorubicin and cytarabine in combination with gemtuzumab ozogamicin. This is a combination comparison to 7+3 alone versus gemtuzumab, and this I think the drug was evaluated correctly and I think provides a nice addition to what we have already in the armamentarium for AML. Copanlisib, a PI3-kinase, you'll know from other from idelalisib, it's an important enzyme for the regulation of proliferation and differentiation of B cells. There are four subtypes to PI3-kinase, alpha, beta, gamma, and delta. CAL-101 or idelalisib is a PI3-kinase delta primary inhibitor of that pathway, and PI3-kinase delta and alpha have slightly different activities; copanlisib inhibits both of them. It's an IV drug and so it's something that's given weekly, and it certainly has a number of important biological effects. It's approved for relapsed follicular disease who have gotten at least two prior systemic therapies, similarly to idelalisib. It's in the same follicular space as idelalisib. The drug interactions are there. It is a 3A substrate, so you want to reduce the drug to 45 from 60 in patients who have concomitant siC3a inhibitor. It's given weekly, days 1, 8, and 15 with a week off on a 28-day cycle.

These are the adverse events. A couple of key things with copanlisib: noninfectious pneumonitis, even though it's an IV drug, it's still a small molecule inhibitor, so it's still at risk for pneumonitis, and patients need to be thought about in terms of pneumonitis. PI3-kinase inhibitors have downstream effects of glucose trafficking, and you can see hyperglycemia with these drugs and certainly something to think about. You can use insulin, you can do another of other manipulations to try to improve it, you can see hypertension, you can see neutropenia, and you can see in rare instances severe rashes and cutaneous reactions.

This is the data that led to its approval, again follicular lymphoma 0-1 ECOG performance status, three prior lines, thus the two or more prior lines in patients getting it, overall response rate 60% with 14% CRs in a relatively difficult to treat population. Median time to response was about 2 months, so if you are going to respond, it usually happens fairly early. These are the conclusions I'll read and you can read on your own, and I'll stop since I'm already over and I don't know if we have time for questions. Thank you.

FEMALE Thank you very much, Dr. Harvey. Another exciting update on new medications.

**[END]**