Advances in the Use of Targeted Therapies in the Management of Non–Small Cell Lung Cancer

Heather Wakelee, MD, and Elizabeth S. Waxman, RN, MSN, AOCN®, ANP-BC
Stanford Health Care, Palo Alto, CA, and The University of Texas MD Anderson Cancer Center, Houston, TX

FEMALE Welcome, everyone, and please take your seats; I see we have a few people sneaking in. We're going to start our next presentation; "Advances in the Use of Targeted Therapies in the Management of Non–Small Cell Lung Cancer." Please welcome our talented lecturers, Dr. Heather Wakelee of Stanford Healthcare and Ms. Elizabeth Waxman of the University of Texas MD Anderson Cancer Center—a local gal.

DR. WAKELEE Welcome, everybody. We're going to be going back and forth as we go through our talk, which is going to be focusing on a lot of different aspects in the targeted treatment of lung cancer. These are the learning objectives, these are our disclosures; I do a lot of research.

We're going to focus on tumor genetic testing and then *EGFR, EGFR* T790 on the resistance mutation, *ALK, BRAF*, and then a tiny bit about a couple of the other mutations.

You all, I'm sure know this, but you can't do a talk on lung cancer anymore without showing a pie chart, which goes through some of the known driver mutations, especially in adenocarcinoma. You can see *KRAS* is a big piece; that's one we won't talk about today because we still haven't figured out how best to treat that. *EGFR*, which is really what started our understanding of the molecular drivers in lung cancer, and then *ALK*. And as you can see up along the top there, we're starting to find more and more of these, so *MET* exon 14, *BRAF,*

HER2, and then there are also still some patients where we don't find a single driver of course.

So when we're talking about targeting, there are several different strategies, and this is a cartoon talking about you can—these are tyrosine kinases, and for most of them you need to have a dimerization process once the ligand binds in order for the tyrosine kinase to actually be activated. We can block it a couple of different places: we can block at the dimerization, we can block the ligand, we can block at the tyrosine kinase. And that's what most of these drugs are doing; it's the tyrosine kinase domain that's actually blocked.

Now in order to find the mutation, you have to look for the mutation. And there are, obviously, a lot of different strategies for doing that, and I'm just going to talk through that very briefly. I think, again, most of you are aware of that and I think in our practices—I'm seeing patients in clinics, I'm not the one in the lab actually doing these myself.

But if you think about it, we've got DNA sequences and that was the first strategy, this is how we figured out about these mutations, of course. But it's very time consuming and very costly, and so there's not a lot of that being done anymore. The PCR tests are some of the fastest strategies, but that requires that you know exactly what mutation you're looking for. So for *EGFR* where we know some of the key specific mutations, that's the fastest strategy; we can get those results back in a few days and that's still done quite frequently.

FISH testing is great when you're dealing with break-apart—this is a break-apart FISH type of test. Because for some of these, it's not just a single

mutation where you can PCR it up; these are different fusions, and so when you're dealing with a fusion, you don't necessarily know exactly what it looks like. You know what part of it looks like and part of it here, but you don't know where they come together. And so the FISH strategies help us in finding those with the idea that with *ALK*—what you have is the *ALK* gene has a different gene fused to it, usually *EML4*. And so, what they do in the lab is they'll take probes that recognize the 3-prime and the 5-prime of *ALK*. Normally, if you've got normal *ALK*, they're stuck together, but if you have a fusion, one's over here and one's going to be over here. And so, they're able to see if you've got the red and the green—which are the five and the three—separated in space, you know that probably that gene's been broken apart. So that's the break-apart FISH testing.

And then immunohistochemistry. And we think, well, that's just immunohistochemistry; we've been doing that forever to look for different proteins. But we actually can now use this to look for some of the gene mutations because you can make immunohistochemistry that just recognizes the abnormal proteins. And so coming back around to that, which is a fairly fast strategy as a screening. All right, so not to bore you with that.

Where we're now taking this is that that was all from tissue testing; we now can do blood testing. And I didn't put a slide in, but basically, tumors are shedding DNA all the time and if we can find this tumor-specific DNA and find the mutations there, then we can spare the patient having to get a biopsy. And so, you've probably all heard about the liquid biopsies as they're becoming more and more frequently utilized and the sensitivity of these is increasing as well. Many of

these assays are using what we call next-gen sequencing, which is a hybrid where we know the genes of interest that are being looked at; those are amplified and then looked at in detail. So it's not just sequencing the whole genome or sequencing sections; it's amplifying up the areas that we know are of interest and then looking at those. And when that's done, you can figure out the hotspots in a tumor and then look into the blood to see if you're finding those specific mutations. So that's the strategy behind these liquid biopsies.

So what this is showing is a patient of mine who had *ROS*-positive lung cancer, and you can see in the tumor—and those pictures are pretty small—but basically the tumor's growing and shrinking over time. And in correlation with that, you can see that the fusion, the ROS1 fusion is either being detected or not. So when the tumor's big we can find it; when the tumor has shrunk, we don't find it. When the tumor starts to grow, the fusion protein starts to climb even before we can see that on the CT scan, so that's that up and down, with each of the different treatments.

The vision and actually, the reality now is that when a patient is first diagnosed with lung cancer, we can do a blood draw and from the plasma can do this testing to find a lot of the gene mutations. And I just had a patient in clinic—I think I saw him back in clinic on Thursday; I'd seen him on Monday—and he had come in, he had a new diagnosis, we did a blood draw, and I actually had a result by Thursday showing that he did, indeed, have an *EGFR* mutation. So these results can come back very, very quickly.

Now we're not always following over time, but the idea is that eventually we might be able to do the serial testing instead of, perhaps, doing CT scans or in conjunction with those. And where it's really helpful now is for patients who have developed resistance, where the tumor starts to grow and we want to find out more about why. What changed in the cancer? What changed in the tumor DNA that allowed the tumor to grow, despite therapy?

Now in the context of *EGFR*, so we're going to put it into real world. This is a case, 46-year-old woman. She has dyspnea, she has a chest x-ray, multiple small pulmonary nodules. This is a miliary pattern of growth. The bronchoscopy confirms that it's adenocarcinoma of the lung. *EGFR* shows that she has the *EGFR* exon 19 deletion, one of the most common sensitizing mutations. She started on erlotinib at 150 mg, has a partial response. She feels better, but 13 months have passed and now she's short of breath again. And at this time she, again, has regrowth of all those little pulmonary nodules. They're all small; too small to biopsy. There's an adrenal mass that's also started to grow, though, and that's 2 cm in size.

And you don't have ways to vote, so this is just a thought question. Would you consider getting a plasma assay for circulating tumor DNA to test for T790M; and remembering T790M, of course, is the most common resistance mutation when someone's been on a first- or second-generation *EGFR* drug? So we did. And, unfortunately, it does not show the T790M, but it doesn't show her primary mutation either. And so, it's important if you're doing these blood tests to realize that you have to have a tumor that's shedding DNA to be able to detect it. And

not all tumors shed as much, particularly tumors that are confined into the chest; they don't tend to shed as often. So if you do it and it's negative, it's not truly negative for T790M if you also didn't find the primary mutation; it just didn't find any of the tumor DNA.

So would you get a biopsy? Well, you need to know if she's got T790M, right? So we did. And that showed that she did have the *EGFR* exon 19. It also showed T790M. And she also, though, had high PD-L1 expression, so we'll talk about that a little bit.

What would you offer her now? Osimertinib, platinum pemetrexed, pembrolizumab, alectinib, sorafenib? If you are not recognizing some of those names, you will by the end of the talk, but hopefully you do. In this case, we gave her osimertinib, but we'll get to that.

So you probably know this; this is the IPASS data. This was the first study that helped us know about the importance of looking for the *EGFR* mutations when someone's just diagnosed. This is now old news, but it's important to kind of go back in history to understand where we are today.

When the *EGFR* targeted tyrosine kinase drugs were first developed, people recognized that about 10% of patients were having dramatic responses and so we needed to figure out why. But, before we knew, there was a phenotype that people who were never smokers, often Asian, seemed to be more likely to have these dramatic responses. So a trial was done in Asia for patients who were never smokers and they were randomized to get gefitinib, which was the first EGFR TKI, or chemo.

At the same time, people started recognizing, looking in the DNA of the tumors and found that people had mutations. And in this population of never smokers in Asia with adenocarcinoma, it's like 60% of the patients. In my practice in California, it's probably 40 to 50% of my patients with adenocarcinoma. In various parts of the country, it's going to vary based on the demographics of the lung cancer that's there.

What this is showing is that when we looked at the patients from this IPASS trial who had the mutation, so that's on the left. The green is the gefitinib. And if you have an *EGFR* mutation and you get an EGFR TKI, you do better than if you get chemo; this is a PFS curve. On the flip side, if you are a never smoker, Asian, with lung cancer and you don't have an *EGFR* mutation, you're much better off getting chemo. So the green line looks much worse than the chemo orange line on the other group.

This emphasized to us the importance that we have to test. You can't just assume based on what the patient looks like what kind of lung cancer they have; you have to actually test for it, right? So this one's was like, "Well, we all know this already." But we didn't know it until this test, until this trial, and so this was really a paradigm-shifting trial.

And since then, there have been a bunch of trials all looking at the same thing. Everybody had *EGFR* mutation in these trials. They all got chemo or an EGFR TKI, gefitinib, lorlatinib, or afatinib. And in all of them, the PFS and response rates were much better on the TKI. Overall survival, though, not changed as much and that's because of crossover.

But the PFS also, as you can see, most of those numbers are not over a year. So we're helping these patients dramatically, we're helping them really quickly, people feel better right way. But then the cancer becomes resistant and that's been a big challenge for the last decade. And as we've already alluded to, we've been able to figure out that patients who have this resistance, a lot of the time it's another *EGFR* mutation; this time T790M. It changes the biting pocket so that patients no longer are responding to the first- or second-generation drugs. There are also some other things that happened, like small cell transformation, but it's mostly T790M.

And for a long time we had nothing that worked against T790M. And then there were a bunch of drugs that were developed around the same time, but only one of them was clearly the best and that was osimertinib. This is waterfall plots showing that patients who had been on a first- or second-generation EGFR TKI and then it stopped working and they went on osimertinib. All of them for the most part—there's a few where it didn't work, but almost all of them had the tumor size shrink—so they're all on the waterfall plot. And you can see it's pretty dramatic, the percentage of people who responded. And that was regardless of dosing, but ended up coming up with this 80-mg dosing and then that went into randomized trials.

This, though, is worth looking at—well, I was talking about liquid biopsies at the beginning. Why was I doing that? Well, from the work with osimertinib if you find the T790M in the plasma or if you find the T790M in the tissue, you can still get dramatic responses. The only patients that don't seem to respond are if

the tumor is truly negative for T790M; then if the plasma's positive, they can still respond, but maybe for not quite as long. And if they're both negative, the likelihood of response is not very high. So the paradigm now is we look for the T790M usually first in the plasma if we can because that's faster and easier on the patient, and then if we don't find it, we look in the tissue.

There are a lot of different ways of looking in the plasma, so these are some of the studies, the cobas tests, ARMS, Droplet Digital PCR, beaming. And what this is showing—I know it's a really busy slide—is the sensitivity and specificities. And if you look, the sensitivities for exon 19 and for L858R, they're a little bit better than what we get for T790M, so in the 80% versus in the 70s or even lower in that one study. The specificity though is very, very, very good across it. So if you see any of these mutations in a plasma test, it's real. If you don't, you have to question whether we just missed it with the sensitivity being too low.

I presented this data at ASCO last year, 2016, where we had a trial that was being done with a different third-generation EGFR TKI that ended up not going forward, so don't worry about the name of the drug. But we had 180 patients where we had blood, tissue, and actually urine where we were able to then compare across these different ways of looking. And what that diagram is showing is that for most people if they had T790M, we found it in the blood and the urine and the tissue altogether. But there were patients where we only found it in the blood or we only found it in the tissue or we only found it in the urine. And so, again, the tumor shedding can be different and the sensitivities of the tests

are different, so if you're suspicious the patient has T790M, don't just give up after one test if you don't find it.

All right, now practice keeps shifting very quickly in the world of EGFR, so I'm showing this trial; it came out about a year ago. And in this study, patients who had been on a first- or second-generation EGFR drug—so erlotinib, gefitinib, or afatinib—at the time of progression they were tested, and if they had T790M, they were randomized and they either went to chemo—platinum pemetrexed, so very good chemo for adenocarcinoma—or they went on to this osimertinib drug and they were looking for PFS as the primary endpoint.

This is the demographics and I realize that since I can barely see it, I'm sure most of you can't read it too well. But what it's showing is that this was a study that was predominantly done in Asia, so two-thirds of the patients were Asian. Most of them had no smoking history; about 60%. Almost all of them had adenocarcinoma; many of them had brain metastases. They all had to have T790M mutation and then they either had exon 19 or L858R in a very small number with some of the other sensitizing mutations. And most had been pretty heavily pretreated. Well, they'd all been pretreated, but with either erlotinib, gefitinib, or afatinib, and most of them in the study were on gefitinib because it was done in Asia where they use a lot more gefitinib.

And these are the results. So this is a progression-free survival curve. The blue is the osimertinib; the red is the chemotherapy; and so, it's very clear that from a PFS standpoint, it was better to go on the osimertinib. And so, this actually changed practice when this result came out and that's why we test for

the T790M. It's showing response rate was strikingly higher, over 70%, and that's been pretty consistent with this drug if you have T790M versus 30% with the chemotherapy.

This is the toxicity and I'm not really going to go into that because Liz is going to soon be talking about the toxicity with the *EGFR* and TKIs. But this drug is a little different as far as there's much less rash. There are some very rare cardiac toxicities, which aren't really on this table because they're so rare, but it's just something for you all to be mindful of and Liz is going to mention that a little bit.

And then, you also can get neutropenia sometimes and thrombocytopenia. And again, that shows up on this graph as being somewhat low level, but we definitely do see it in practice, so if you have a patient on osimertinib, make sure that the CBCs are being checked. Be mindful of it; we don't necessarily have to change anything based on it. I have a lot of patients with ANCs in the 1,000 range who are just living that way and doing okay. Dose reduction can lead to less efficacy of the drug, so it's a balance.

Then one of the options I gave you when we talked about that case. She had high PD-L1; we actually do see that sometimes with *EGFR*. It's rare. It's actually fairly common with *ALK,* and we'll talk about *ALK* in a minute, but it's rare with *EGFR*. So we're trying to understand well, what do we do if we have a patient with *EGFR* who has high PD-L1? And there are just little bits of data coming out that maybe they do respond, and we have a few patients with *EGFR* who respond, but in general, if your patient has an *EGFR* mutation, the

checkpoint inhibitors don't work as well. And we know that from the three big studies that looked at for all-comers who had had chemo and maybe had had a targeted drug if they were randomized to get a checkpoint drug versus docetaxel.

So these three studies—the KEYNOTE-010, the CheckMate 057, and the OAK study—those were all very similar trials; docetaxel, standard second-line chemo versus the checkpoint drug, so nivolumab, pembrolizumab, or atezolizumab, depending on the study. And in all of those trials, if you looked at the subsets of the patients, the only group where the chemo looked like it was better than the checkpoint drug were the patients with *EGFR* mutations.

This next slide shows that and, again, it's a little busy, but here you can see—this is the line, this is nivolumab better, this is docetaxel better. And here, you can see that in this *EGFR* mutation–positive group was the group that really was looking not so good with the checkpoint drugs. When we look at the OAK trial, which was with atezolizumab, it's that same idea; this is the only group over here. And then, in the KEYNOTE with pembrolizumab, it's not on this side, but it's pretty close to it.

So there's caution still with using the checkpoint inhibitors in these patients. My usual practice is to give it, but only after they've had every *EGFR* drug I have and chemo and then we'll think about doing it. And we have a few responders, but they tend to be the people where the *EGFR* drugs weren't so good for them, so it's different.

I'm almost done and then you get to hear Liz. This is the FLORA data, so everything changes all the time. This came out a month ago and now everything I

was just telling you about the first- and second-generation drugs and T790M? You can forget about that because what we're doing now is instead of giving the first-generation and second-generation drugs first, we're going to start shifting to using osimertinib first, okay? This was a study for patients who were just diagnosed with *EGFR*-mutant lung cancer. And at this time when you're first diagnosed, you don't have T790M, you only have the activating mutation; T790M develops later.

So you don't have it, you are just getting started on an EGFR TKI to begin with. And the study looked at this osimertinib, the third-generation drug, versus erlotinib or gefitinib. And you can see if you look at the patient population, again, it's about two-thirds women; *EGFR* tends to be more in women than in men. Again, a lot of it was done in Asia, the trial, so about two-thirds of the patients were Asian. Many of the patients had never smoked; a lot of them did have brain metastases; and more of them had the exon 19 deletion than L858R. And if you look at response rates, actually whether or not you got osimertinib or you got erlotinib or gefitinib, the response rates were great, right? So they were very, very good for either group, so that doesn't help us now.

But when you look at the progression-free survival, it was actually much better with the osimertinib. And people can think about the fact, well, if you get erlotinib or gefitinib and you progress, then 60% of people can go on to get osimertinib. So if you do A plus B, you know, you're here versus if you start with osimertinib you're here, so is that really better? And if you knew someone was going to get T790M and then go on osimertinib, probably not. The challenge is

we don't know who is going to get T790M and who is going to have a different resistance mechanism. And so, for the 40% of people that get some other resistance mechanism, they were probably better off that they'd started on osimertinib because then they're going to have a longer PFS from that.

So there's a lot of controversy right now. FDA has not yet approved first-line osimertinib, but it's in NCCN Guidelines; practice is changing very quickly towards this. We're not taking people off if they're already on erlotinib or gefitinib and they're doing well with it, but in my patients that I've been seeing in the last few weeks, basically the past month, we've talked about this and most of them we've actually been starting on osimertinib, and that's being done around the country now. So things change very, very fast.

This is the data why. The survival, overall survival, is not clearly different yet, but it is definitely trending in favor of osimertinib. And if that ends up clearly positive, I think there really won't be any controversy; everyone will be shifting over. It's also a little bit better tolerated, but, again, Liz will talk about that. This is the safety summary and you can see that overall, many people did have toxicities. In general, there were fewer on the osimertinib.

I'm going to do this quick overview. Ten percent of all cases of non–small lung cancer have *EGFR* mutation, but if you're an Asian never smoking woman, it's over 50%. Within different ethnic groups we also know it's higher, so in the Hispanic population it's higher as well. We have five drugs available first line, which are first or second generation; they're very expensive. The addition of bevacizumab or ramucirumab might improve outcomes, but they are very

expensive. I didn't go into that data because we're kind of shifting away from using those drugs, from using erlotinib or gefitinib first line.

Osimertinib was clearly superior to chemo after first- or second-generation drugs. Osimertinib is the new option; it's first line. And the checkpoint inhibitors are inferior in *EGFR*-mutant lung cancer versus other types of lung cancer.

ELIZABETH I'm going to take over for a little bit on presentation, and we're going to talk about the *EGFR* toxicities and, quite frankly, on my next slides we're going to see—I feel like I'm talking to the choir because we manage these toxicities every single day, day in and day out. So the *EGFR* toxicities. Dermatologic, GI, ophthalmic, and cardiac. And there's a picture of the choir because I am speaking to the choir.

The inhibitors, as Dr. Wakelee mentioned, lapatinib, erlotinib, gefitinib, osimertinib—I don't know the fifth one—these are all very expensive; they're all about $9,000/$10,000. And if your patient's on it, you will be doing prior authorizations with their insurance. I guarantee it; my colleagues and I do it all the time.

Rash is what EGFR inhibitors are known for. It starts about a week to 10 days after they start the drug; afatinib is the worst offender. Grades 1 through 4, 80, almost 90% of patients will get it. Sixteen percent of patients will get a grade 3 or grade 4 skin rash. Erlotinib is a little bit less, but still is significant grade 3 or grade 4. Gefitinib is still less, and osimertinib has the least grade 3 or grade 4 skin rash toxicity.

The pathophysiology of the rash - EGF, epidermal growth factor, is a normal epidermal tissue and follicular keratinocytes. It regulates cell differentiation and provides protection from UV rays or other cellular damage. It hastens wound healing and inhibits inflammation. Well, guess what happens with the rash? All of the above. If inhibited, your skin begins to thin and dry. It can result in recruitment of the immune system, leading to pustular eruption and a little bit of inflammation on the skin. Sudden onset papular pustular eruption and almost looks like acne, but it's not because your skin is so dry, so it is not an acne rash usually involving the face, scalp, neck, upper chest, and back.

I have a patient who is on a different drug on a clinical trial and she's having a rash in areas I never thought possible and we've sent her to dermatology. The rash may be indicative of clinical benefit, so it may be uncomfortable for the patient, it may be hard to treat, but it may in the end show benefit to the patient; there's a paper out by Lou et al. indicating rashes of benefit.

And the low-grade rash does affect the quality of life. I had a patient who was a salesman and on one of the inhibiting agents who said, "I can't let people know I'm sick. I can't have this rash; what do I do?" And we devised something to help him keep his job, his insurance, and stay on drugs. So you have to be thinking, "Oh, it's not myeloid suppression, it's not nausea and vomiting, but it does affect quality of life."

One thing about rash—and we've been using these inhibiting agents for I don't know how many years now since they were first approved—we still do not

have solid data on what is the appropriate management for rash. I would not say we're winging it, but we're using what has become accepted as the standard. We have guidelines from MASCC and NCCN, but guidelines are recommendations, they're not based on research-driven data, so hint, hint anybody going through DNP.

Prophylaxis. There are some recommendations to moisturize the skin with a thick, alcohol-free emollient. Minimize sun exposure, so if you're living in Texas or on the west coast or in Florida, SPF, whether it's in the summer or in the winter; SPF15 or higher. Protective clothing; if your patient is like mine who likes to garden, have long sleeves, gardening gloves. Sandals; they need to wear socks. Just think about it; it's very routine, but just take a step back and think about it.

Luke warm showers as opposed to hot showers because, guess what, hot showers are going to dry the skin. Take baths in luke warm water. Avoid perfume and alcohol-containing skin products. Rash management depends on the severity. Grade 1 may be on the face, may be a little bit on the chest. You may not need to do anything—it depends on the patient—but topical antibiotic or steroid lotion, gel such as hydrocortisone or clindamycin. My physician likes clindamycin, so they'll leave my clinic with a clindamycin prescription.

Grade 2, you are going to use a steroid cream and an oral antibiotic, either doxycycline or minocycline. Grade 3 or 4, you're going to do the same thing as you do in grade 2. You might consider a methylprednisolone; you may consider a referral to Dermatology.

You may also consider a dose reduction, and since I just told you two slides ago that rash may indicate response, that's a hard sell for patients because a lot of the patients think, "I'm not going to have the same benefit at a lower dose," so it takes a lot of counseling for the patient. Quality of life, able to go to work, able to socialize at a lower dose and stay on drug versus a higher dose and deal with the rash. And, again, we lucked out at my institution because my thoracic clinic is around the corner from my dermatology clinic, so we do a lot of door knocking on Tuesday, Wednesday, and Friday when you'll find me in clinic.

GI toxicities: the main one is diarrhea. It's very common and there are EGFR inhibitors in the gut; that's where you're going to get the toxicity. Afatinib has the highest incidence of diarrhea, and I've already dose-reduced a patient twice because of diarrhea. It is dose-limiting, dose-reducing, and sometimes you just have to stop the drug. Ceritinib as the ALK inhibitors also has the highest incident of diarrhea.

So common sense; avoid foods that are going to irritate the GI tract, avoid dairy, spicy, greasy foods. Hydrate, hydrate, hydrate patients with water. Good eating habits, healthy diet. The rash, if they're erlotinib or gefitinib, is going to start within a month. On afatinib it's a faster—I'm sorry, diarrhea's going to start within a month, but afatinib it's within the week. So when a patient leaves my clinic, I tell them, "Go to a pharmacy and get loperamide, get something; just start taking it, don't call me." I say, "Call me when it doesn't work. So if you're having diarrhea on Monday, call me Tuesday if it's not slowing it down. Don't call me

Friday that you've had diarrhea all week because you're coming into the emergency room." Always do a good assessment. Is the patient on an antibiotic that may be causing C. difficile? So it may be the drug, it may be another cause; don't just focus on the inhibitor.

BRAT diet: bananas, rice, applesauce, and toast. Hydrate, electrolyte replacement, loperamide. Bump it up to diphenoxylate and atropine if the loperamide doesn't work. Intravenous hydration; I have patients coming in two or three times a week for intravenous hydration. Hold the drug, which is also a very lengthy discussion with the patient because they don't want to lose the benefit of the drug. And again possible dose reduction. I haven't stopped a drug for diarrhea unless there's been a colitis or some other cause, so it's okay to keep the patient on drug, but you have to treat them. And in Houston, you can tell we're still in summer even though it's November 5th; they need hydration.

Ophthalmic issues. There's EGF in the eyes, including the eyelids, eyelash follicles, tear glands, conjunctiva, and cornea. There is an excellent article in *ONF* by Mary Elizabeth Davis, my friend and colleague from Sloan Kettering. I recommend you read it; it's on the slide. Afatinib: patients with afatinib, 11% had conjunctivitis; it does happen. Gefitinib: conjunctivitis, blepharitis, which is an inflammation of the eyelid, dry eyes, keratitis can happen.

Eighteen percent of patients on erlotinib have reported dry eyes, eyelash growth, which is trichomegaly, and keratitis. And 19% of patients on osimertinib have also had the dry eyes, cataracts, keratitis, blurry vision, and eye irritation. So it's not something to be dismissive about. If your patients call you with an eye

problem, have them come in—and I'm not good at an eye exam. I take the ophthalmoscope and I can see the disc and that's where it ends, so I just say, "Come on in and let's take a look."

And, again, on the other side of my clinic is my ophthalmology clinic, so I'm running to them to refer a patient. But that's in a situation where it's beyond my capabilities. So I say, "Refer to an ophthalmologist." And back to Dr. Wakelee for ALK inhibitors.

DR. WAKELEE Thanks, Liz. We're going to come back to another case. RJ is a 47-year-old man; he smoked a little in the past. He's now got progressive right-sided chest pain, he had a chest x-ray, pleural thickening, and a mass. He has a right adrenal mass, a right lung mass, and pleural studding. Biopsy shows that this is adenocarcinoma. A PET, brain MRI, nothing else, it's just in that one lung. And he had an *ALK* FISH test, which was initially negative. Rapid *EGFR* is negative.

He then has a liver biopsy and that shows that he does, indeed, have an *ALK* re-arrangement when they do the next-gen sequencing. So, again, you get one test, it's negative. If you're really suspicious, think again; the next-gen sequencing is far more sensitive.

He is started on crizotinib, the first *ALK* drug. He did well for 10 months, but he then has disease progression. So he has a biopsy and now he has an *ALK* resistance mutation, the V1180L. So what do you start? Brigatinib, ceritinib, restart pemetrexed, alectinib, nivolumab, or pembrolizumab, erlotinib or ensartinib, or other on trial? So we don't really have one right answer, but I just

wanted to get you to be thinking about the fact that with *EGFR*, we've got the T790M. With *ALK* it's not a simple story; there are a lot of different resistance mutations that can come up.

This table is actually listing some of the known *ALK* resistance mutations, some of the known ALK drugs, and whether they're resistant or sensitive. It's not as easy as this, though; you can't just get your mutation, look at the table, and pick the drug. Not necessarily working quite that easily for the patient because there are a lot of other facts that play in here, too, but we're likely moving in the direction of being able to think more intelligently about which ALK drug for which patient. But for now we're in a world where there are four ALK drugs approved. They're also moving around as to which one we should use first or second or third, and they're more in development.

For *ALK*, this is also a relatively new story; it's a decade ago that we first even learned that *ALK* existed in lung cancer in about 4% of all adenocarcinoma of the lung. And I should back up and say that *ALK*, unlike *EGFR*, it's not just something that we see in never smoking Asian women, nor is *EGFR*, but *ALK*—when I think about my *ALK* patient population—African American, Asian, Hispanic, Caucasian, different ages, often young, it's equal male to female. So it can hit anybody and it also can happen to people who have a smoking history or don't. So don't just assume when you look at the patient what mutation they have; you still really have to test.

Tumor response to crizotinib. this was really big news in the past because when this drug, crizotinib, was being developed, they noticed that it would hit

ALK. So the phase I study was restricted just to people with *ALK*, and as you can see, everybody responded; you all know that. There was a randomized trial comparing crizotinib to pemetrexed-based chemotherapy in patients who were *ALK* positive. Same story as we saw with *EGFR*, you get a better response, a better progression-free survival, and so, we've all been using crizotinib for a number of years for our *ALK*-positive patients.

When development of resistance happens, we then have other options. And so, the first was ceritinib, and ceritinib works about 60% of the time when crizotinib has stopped. We have alectinib. Alectinib works 60 to 70% of the time when crizotinib works. Brigatinib: brigatinib works about 60 to 70% of the time when crizotinib stops working. Ensartinib: it's about the same; it's a drug earlier in development. And then, now, lorlatinib, which works after crizotinib, but also after some of those others. Ensartinib does too.

And so we're all looking at all these thinking, "Well, which do we use first? What's the best for our patients?" And we got some news this year from the first trial that was a comparison of crizotinib. Every one of those drugs that you see there, other than lorlatinib, is in a head-to-head trial of the drug versus crizotinib for first line. The first study that had the results was alectinib versus crizotinib. And this study showed that the response rate was a little higher with alectinib, but very high in both of them; 80% for patients who had never been treated before. Complete response rates were good, partial responses were high. And the PFS, though, was clearly in favor of alectinib with some patients staying out for quite a

while. And the most recent data is that the median time to progression is 30 months with alectinib, which is quite good, versus crizotinib.

So people are starting to think about shifting over; instead of starting on crizotinib and then going to alectinib, this idea, “Well, maybe we should give alectinib first.” There’s no clear survival difference, though, so there’s still a lot of controversy and there are patients in whom crizotinib might be a better choice. There’s cost differences, there’s toxicity differences, there are reasons to think about it. But alectinib has much, much, much better brain penetration than crizotinib, so for patients with brain metastases, we really want to think about alectinib.

First-line ALK TKI therapy is the standard of care for those with an *ALK* translocation. Crizotinib, ceritinib, alectinib are all approved for first line now. We have alectinib versus crizotinib data showing a clear PFS benefit. Second line we have ceritinib, alectinib, and brigatinib all approved. There are a lot of other ALK inhibitors in development, and so we still don’t have a clear, “Oh, we should start with this and then do this and then do this,” but you will be seeing more and more first-line alectinib as you’re in the clinics with your patients who are newly diagnosed with *ALK*-positive disease.

And the big struggles are, “What works best after that?” Brigatinib has some activity, ensartinib has some activity, lorlatinib has activity, crizotinib might actually have some activity for some of the mutations and so, there’s a lot that we’re still going to be learning; it’s a very complex world. And there’s a lot of variability in toxicity. So with crizotinib there’s the edema, the bradycardia, vision

changes, transaminitis that Liz is going to be talking about with ceritinib, nausea, vomiting, and fatigue. However, there was a recent presentation we had, a big lung conference in Japan a couple weeks ago, and one of the biggest studies was looking at ceritinib with food. So instead of giving it at the 750, at 450 dose with food and patients tolerated it much better without all of the GI toxicities - because it used to be 750 empty stomach—so 450 with food seems to be better tolerated, similar efficacy; so that's some news on ceritinib.

And then, with these other drugs, the toxicities aren't all the same; it's not like everybody gets a rash or anything like that. So with brigatinib, there's an unusual pulmonary toxicity you have to be very aware of in the first week. So with lorlatinib, there's some CNS complications that can happen; with alectinib, some myalgias; and so, each drug it's a different story and it keeps us all on our toes. We also are dealing with very expensive medications and that's a challenge for our patients.

ELIZABETH I'm going to come in on the toxicity discussion. And as Dr. Wakelee just mentioned, there are a couple that I don't have covered in my slide, but we can certainly discuss them. And the inhibitors are the alectinib, brigatinib, ceritinib, and crizotinib that we know and use. Dermatologic and GI were covered in the *EGFR* toxicities, and I'm going to cover the other three—the ophthalmic, cardiac, and hyperglycemia—now. I will add an aside on the brigatinib pulmonary complication at the end.

This slide is actually Dr. Wakelee's, and this is a nice slide showing the toxicities of crizotinib versus alectinib. And then, unlike the *EGFR* toxicities,

ophthalmic issues, especially with crizotinib, are usually that of accommodation. It's a fairly significant toxicity; 61 to 70% of patients have had it. I tell my patients I really don't want them driving if they're having light and dark accommodation issues. It's the most common side effect of crizotinib and it starts in less than 2 weeks after taking drug, so it's an immediate side effect.

They also have issues with floaters, shimmering lights, streamers, strings, overlapping shadows, and after images; like the old-fashioned flash camera when you had that after image for a couple of minutes and really couldn't see anything. You don't have to dose adjust or stop therapy, the patient can continue to take it. I say be very careful driving or have somebody drive you, whether it's to church, shopping, or to whatever. Also, a baseline ophthalmic appointment is not necessary, but the patient may feel better about getting it and then going back if these symptoms persist.

Cardiac toxicities. Now they are two-fold; there's sinus bradycardia and then there's QTc prolongation. Two retrospective studies of patients on crizotinib showed 75% of patients experienced sinus bradycardia defined as a heart rate between 50 and 59, and that was new onset. And these patients were not necessarily athletes who were in good shape, so this is a significant finding. The average decrease in heartbeat and heart rate was 25 beats per minute, and patients with baseline heart rate of less than 70 were significantly more likely to experience bradycardia. So, you know, TPR, the P is pulse; make sure you know your patient's pulse, and with electronic medical records you can do a trend and see where they are.

Patients who did have sinus bradycardia had it after 20 weeks of treatment, and patients who did not have sinus bradycardia, meaning their pulse stayed in the 70s or 80s or whatever their normal heart rate was, had some bradycardia near the third month of treatment. And I'm not sure what the mechanism is that caused that, but I thought it was an interesting finding.

Grade 1 patients stay symptomatic; they can tolerate the bradycardia, no need to change any drugs. But grades 2, 3, or 4 where there are symptoms—patient is dizzy, they have to sit down, they just don't have the stamina—hold the drug, hold the drug. That's a family patient discussion in your clinic; hold the drug, always review the medicines. The patient may be on a cardiac med or a blocker that's also contributing to the bradycardia. So make sure if you're fortunate to have a pharmacist in your clinic or nearby who can review the medications with you, that's a bonus. And make sure the patient is telling you all the medications they're on, including over-the-counter supplements, because we don't know what those drugs do with these agents.

Grade 2 and 3 sinus bradycardia. If there's no medication that's contributing, resume treatment, but at a reduced dose. And if there is a medication that is contributing, work with the cardiologist, whoever started that medication, as a way to taper the patient off of the medicine if they don't need it. And you can resume the ALK inhibitor at the full dose, the crizotinib.

Grade 4 is same thing, but permanently discontinue the ALK inhibitor if no medications are contributing to this. And I will tell you I had a patient in AFib and that's how they found his lung cancer, and we tested if he's an *ALK*. So for the

AFib, instead of getting ablation, he was on metoprolol. Metoprolol and crizotinib slowed his heart rate down to below 50, and we took him off metoprolol, but kept him on crizotinib. So be very savvy and know your patients' medications. It's tough, but you have to review them at very clinic visit.

Crizotinib, ceritinib, osimertinib all carry box warnings for QTc prolongation. Be aware of the patient's PMH, past medical history, especially if they have sinus bradycardia or skipped beats, PVCs, all medications, baseline, and periodic EKGs. And that really comes from my physician who likes to follow up and is very conscious of the patient's PMH.

Hyperglycemia is something you don't see with a lot of inhibitors; it does happen with ceritinib and alectinib. And, basically, ALK inhibitors inhibit the insulin-like growth factor receptor, so it's an inhibition of that pathway. Keep your patients on their current diabetes medications. If the hyperglycemia is 180, 200, 250, hold the drug, get the glucose under control, resume the inhibitor at a lower dose. And that's going to be a discussion with the family because they're not going to want the lower dose.

If the patient's glucose is uncontrolled, get endocrine involved and discontinue the ALK inhibitor, which will not go well with the patient and family. But you have to trade off; it's one thing or the other. If with endocrine or their primary care provider you can get the glucose back under control, maybe try the drug very slowly at a much lower dose and keep them there.

The brigatinib pulmonary toxicity that Dr. Wakelee was alluding to—and I'm sorry, I didn't create slides on this—is interstitial lung disease. For those of

you who don't use brigatinib, it's one of the newest ALK inhibitors that's approved for crizotinib failures; it's second-line for *ALK*-positive patients. So it's an escalation dose and for the first week the patient's on 90 mg and starting with the second of treatment, they're on 180 mg daily. And it comes in 30 mg tablets, so for the first week they have to take three tablets, second week and on they take six tablets a day. Well, in the clinical trials there was a proportion of patients who developed ILD within the first week and that's why the first week's dose is 90 mg; that's where the majority of patients had ILD.

ILD is biopsied; I send my patients to pulmonary if I suspect ILD, hold the drug. If you suspect ILD, send them to pulmonary and manage the ILD. I have to say, Dr. Wakelee, I'm not sure if they resume the brigatinib if ILD is documented and treated or they resume it at the lower dose; if you could help me out on that, please?

DR. WAKELEE It really depends on how severe the reaction is. Some patients can be restarted, but very cautiously with steroids and see if you can contain that 90 mg for a little bit longer. I'm hearing you go through it in such a clear way with all the different toxicities too, it's made me realize, we now have four options of ALK drugs that are approved. And since many of the toxicities as you're going through them are very unique to the different agents—we have this flexibility with our patients where if they do get one of these specific toxicities—whether it's the hyperglycemia or the pneumonitis—we have the option now of being able to switch to a different drug.

So even though the primary *ALK* mechanism was still working, that drug had unique toxicity. So I find that it's been really exciting to be able to talk to the patients about all of the different options and to be able to feel comfortable knowing that if a patient who has *ALK*-positive disease has hyperglycemia, I have another choice. If they have ILD, I have another choice.

DR. WAKELEE To close it up, we're going to talk a little bit about some of these other targets, and back to the pie chart; now we have two of the pie charts. But one of the things that's on there is that *BRAF*, which is the 3%, and you think, "Well, that's only 3%," but it matters because we now have *BRAF*-approved agents for our patients. And so we really want to be looking for the *BRAF*, we want to be looking for the *HER2*. At ASCO this year, there was a bunch of discussion about using some of the *HER2* drugs in these patients, so we want to be thinking about this for our cases.

So there's another patient, she's a 58-year-old Asian American woman, increasing dyspnea, has a pleural effusion dullness on exam and then confirmed with imaging. She has the effusions tapped, it's adenocarcinoma, and she has no other sites of disease. Cytology is used for rapid *EGFR* testing and *ALK*; they're negative; she doesn't have any tissue left. So she gets started on chemotherapy, platinum pemetrexed but does not tolerate it; she doesn't want anything else. She would consider options that are not chemo. We've all heard this in clinic, right?

But she has the systemic lupus, so she can't get immune therapy. So, what do you do now? You could repeat a biopsy, send a liquid biopsy, or initiate

hospice. And this was a real discussion I had with one of my patients. Fortunately, we're in the era where we could do a biopsy, and this actually for her found a *BRAF V600E* mutation. So if you have *BRAF V600E*, what are your options? You've got erlotinib, osimertinib, dabrafenib, trametinib, alectinib, brigatinib. Since we've just gone through all the different ALK drugs, I know you all got that one right, right? So, it's dabrafenib and trametinib.

The patient had a rapid clinical improvement; pleural effusion reduced significantly, it's well-tolerated. These drugs initially were developed in melanoma. When they were first being developed, especially the *BRAF* drug directly by itself, patients can get some unusual skin toxicities, which are actually new squamous cell carcinomas of the skin; I've had a couple patients who went through that. But when you give the combination of the MEK inhibitor plus the BRAF inhibitor, that doesn't happen. So it's one of those weird situations where two drugs is actually less toxic than one, and so patients tolerate this combination relatively well and it's approved.

And this is some of the data looking at the different dosing. And this was one of the earlier trials that led to the approval. We don't have a big phase III study with this, we only have phase II, but because the response rate's over 60% in these patients, that's enough for the approval. And these drugs now you can think about first line, second or third. It's not something where we know you have to give it first, but it is definitely an option to do that. Also, you could have started on chemo and then you can move on later.

And with these BRAF patients, they don't all behave the same way. I've had a couple patients who lived over 10 years with *BRAF* mutation lung cancer and some where it's very aggressive.

All right, so cabozantinib is another drug that you might have heard of; it's not approved in lung cancer, but it is approved in thyroid cancer. It gets a lot of different targets, and so we're starting to use it in some of our other lung cancers. I didn't talk about *ROS1* and we didn't talk about that today; *ROS1* is another mutation to look for. Some of the ALK drugs work for *ROS1*; cabozantinib also works for *ROS1*. Cabozantinib works if you find a RET rearrangement. There are a lot of other drugs that can work there as well. This is a waterfall plot with cabozantinib.

These are some of the other RET inhibitors; vandetanib is one, sunitinib, and these are VEGF drugs that also hit RET. They can cause hypertension. *MET* exon 14 is actually a bigger piece of the pie; it's about 4 to 5%. *MET* exon 14 mutation lung cancer actually responds to crizotinib. Crizotinib's not just an ALK drug, it's also a MET drug. There are other MET drugs that are in development that seem to be working also, and so this is another driver we need to be aware of and look for. There are also responses to cabozantinib. And, again, that's showing the crizotinib and cabozantinib responses.

And then, *HER2*-mutant lung cancer. We think about *HER2* amplification in breast cancer. There are actually *HER2* mutations in lung cancer, so they're usually insertion mutations in exon 20. And in some ways, they're parallel to a specific type of *EGFR* mutation in exon 20, which is a resistance mutation. It

doesn't respond to our EGFR drugs, but does respond to both of that specific kind of *EGFR* lung cancer and *HER2*-mutant lung cancer can respond to afatinib, less so with the exon 20 *EGFR* than the *HER2*. They also can respond to HER2 drugs, like trastuzumab and then TDM1; there was a lot of data about that at ASCO this year where there are some responses. It's not the "everybody responds for a long time" story, it's a "some people respond for a period of time" story, so there's more that we're learning.

And then there are a lot of new drugs, specific oral medications, tyrosine kinases, that are really focusing in on exon 20 that will be working for *HER2*-mutant lung cancer, as well as the exon 20 *EGFR*. So keep posted for those; we're just starting to get the first data about the activity of those.

And then, this is a busy slide showing that if you have a patient who's in your clinic—especially if they have a light smoking history, regardless of gender, regardless of ethnicity, light smoking history—and you don't know their driver mutation, don't give up; you've got to keep looking. This is a slide showing that for patients who are in that situation—had no known driver mutation, retested with next-gen sequencing plasma or tissue; this was a plasma assay—many of them, 39%, had a specific driver mutation identified. So we can really help our patients more if we keep looking.

And this was from one of the plasma testing companies showing that for patients who, again, already had the tissue tested, we went back and looked with the plasma testing, we were able to find actual mutations in *EGFR, ALK*, and *ROS1*, in a significant number of patients, so keep thinking about it and looking.

Once you've found a driver mutation, you know what it is. The only time to keep looking is to look for resistance; they're not going to develop a new one. But if you don't know the driver mutation, you have to assume that we just haven't found it.

So we have a lot of EGFR drugs. Osimertinib is very promising for patients with T790M, but it's probably going to be moving into first line, so we won't have to think about T790M so much. And I didn't talk about osimertinib resistance, but that's something we're trying to understand. There are other mutations that develop and we still don't have a clear path forward for that.

There are a lot of ALK drugs, first- and second-generation drugs, third-generation drugs, activity first line, second line, maybe third line, fourth line. These patients can keep going through ALK drugs, so chemo still plays a role. We're starting to understand resistance mechanisms. We know a lot, but there's more to know. Multiple other relevant targets. We need to look because we do have treatments for these patients; think about repeat testing, think about plasma testing. Many patients are living years in this setting, but we still have to challenge ourselves with drug costs and how do we help our patients in that setting?

So we have time for questions. It looks like we've got people going through with microphones. Okay, I think they're coming to you.

FEMALE Thank you so much for a great presentation. So, my question is probably directed more to you. For the *ALK* mutation, now you were talking about the hyperglycemias for holding the medication, holding the ALK meds, and then

see if it's going to resolve and then go back on a lower dose. Is that what we should be doing versus—for example, I have a patient who I held it and then restarted and the same problem occurred; at that point, should we be placing the patient on maybe an antidiabetic medicine, for example, metformin or—especially if the patient is responding to treatment, to the ALK treatment—or should we just move on to the next ALK med?

ELIZABETH Personally, I would not move on to the next ALK med unless there's clear objective data showing the ALK inhibitor is not working. So if they have disease progression on the ALK inhibitor, at that point I would say move on to a different medication; but that's a physician call to make and we'll discuss that outside.

In terms of the hyperglycemia, you need to treat the hyperglycemia. So if your patient was not diabetic when you started the ALK inhibitor, but you're monitoring and one time they come in and it's 180, I would say keep them on the drug, but they have to start checking their glucoses; get them a glucometer. If it gets to the point of 200 where you need to do medication intervention—remember in graduate school, start low and go slow? So start them on the oral hyperglycemic agent—and, again, you can keep them—if they're on diabetic management already and they are persistently hyperglycemic, then I really think you need to hold the drug, maybe discontinue the drug, come in with a different ALK inhibitor that doesn't maybe have as potent hyperglycemic side effects.

And do get internal medicine or endocrine involved to help management because sometimes it's not just metformin and escalating actually glyburide or

adding—very rarely—but sometimes patients need an insulin. That's a very rare occurrence, but I'd like the experts on management in on that call.

DR. WAKELEE We had to deal with this a lot actually when we were developing one of the other EGFR drugs, rociletinib, which is no longer in development. It was getting a lot of insulin growth factor receptor, and so patients, like half of the patients, were developing hyperglycemia, which made me have to face endocrinology again, which was not my favorite topic in medical school.

And we ended up finding that in those particular cases and with the ALK drugs—I haven't seen it yet; I think it's a pretty rare thing—the metformin was a bit more effective because it's more getting out all of the other metabolic factors that are going on as opposed to necessarily insulin; they were somewhat insulin resistant. But, yeah, supporting what Liz was saying, really, it's going to be patient dependent. I always ran to my endocrinologists right away in those settings to get help with the management. And we did have to, in that drug setting, lower the dose a lot and have everybody on metformin and rarely go to other drugs.

FEMALE Thank you so much.

ELIZABETH Sure. I should tell you that our endocrine clinic is right next door to our ophthalmology clinic, so I'm pretty well set where I have to go.

DR. WAKELEE Yeah, my dermatologists are right across the street; we're doing the same thing—

FEMALE You mentioned that the systemic lupus ruled out the use of immunotherapy, but one of our lecturers earlier in the week said that autoimmune issues did not necessarily rule out the use of immunotherapy, so I'm curious about a little more conversation on that.

DR. WAKELEE That's a great question. I think in the setting of a patient with lung cancer, regardless of mutation, if they have an underlying autoimmune disease—if it's vitiligo, if it's type 1 diabetes, if it's something where we have ways of managing it or where it's not necessarily life threatening—then, it absolutely doesn't rule it out. But for some of the other autoimmune diseases, like someone has really bad lupus, those are not patients we want to be giving these checkpoint inhibitors to because you will cause a flare.

I have had a number of patients when I'm doing my hospital time who have received checkpoint inhibitors where they had underlying autoimmune diseases where they've died of those diseases; like myocarditis is the one that we worry about a lot of, myasthenia gravis, some of the neurological complications. So we're playing with fire in the setting of people who do have underlying autoimmune diseases and giving the checkpoint drugs. There's never that you can't ever; it's just that you really have to weigh it in those discussions with the patients.

For the patients with *EGFR* and *ALK*—sorry if I was sounding a little bit too firm on that—it's not that these drugs never work, it's just the probability of them working in our patients is lower. And when they have both PD-L1 and the mutation, we don't know as much; there's very, very little data. For *EGFR*, the

small amount of data that's coming out is saying that if you have an *EGFR* mutation and high PD-L1, maybe you do actually still have some benefit from the checkpoint drugs.

For *ALK*, a very high percentage of patients have high PD-L1—probably more than 50%—but when I go to conferences and I ask all my colleagues, "Okay, *ALK* patient, checkpoint inhibitor?" There's one patient that we've heard of where that's worked. And if you think about the number of *ALK* patients and how long the checkpoint drugs have been around, they should be a much larger number. And trust me, if someone was seeing this in their clinic and a series of it, this would be out there and talked about because we're all really curious about that question.

So it's not that we can't use these drugs if there's an autoimmune disease or that we can't use them if they have *EGFR* or *ALK*, it's that we need to be cautious in our discussions with our patients and in our own expectations that we're not keeping the patient from being cured because we're not giving them a checkpoint inhibitor. The checkpoint drugs are one of our many types of options. They can help some people, but they're less likely to work in *EGFR* or *ALK* or some of the driver mutations. And they have real risks; there are definitely people who have died as complications of those drugs. And I think the public perception is still that they tend to work all the time and there's less toxicity versus chemo.

And for my clinical practice and knowledge of the literature, the likelihood of them working is fairly similar on average to chemo. Obviously, if there's high PD-L1, it's going to be higher in the absence of a mutation. The toxicities are

real; it's just that it's fewer people. Not everybody has some toxicity and some people have a lot and most people don't have much, so you have to balance it all out.

FEMALE Thank you.

FEMALE Thank you, Dr. Wakelee and Ms. Waxman. I'm sorry we don't have any more time for questions, but I'm sure they'd stick around.

DR. WAKELEE Yeah, we'll be happy to. Thank you all.

FEMALE Once again, this presentation was part of our SMARTIE program, so if you're a SMARTIE participant, please be on the lookout for an email this afternoon with questions about this session. And as always, we'd appreciate your prompt reply.

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