Gary Shelton (Moderator): Welcome back, Tyler. Dr. Beardslee. Identifying and avoiding drug interactions.

Tyler Beardslee: All right, thanks for having me back and thanks everyone for coming back here. So we're going to talk a little bit about drug interactions. I'm going to see if I can get y'alls brain working like a pharmacist brain. We shall see. So here we go. So in general we're going to go through and understand the metabolism and the elimination of various compounds used to treat drug cancer. This is kind of where the bulk of drug interactions happen. We're going to identify a pertinent common drug-drug interactions involving chemotherapy, targeted therapy, and immunotherapy. So we're going to talk about a lot of the drugs we've been talking about so far today. And as well as we want to avoid drug disease interactions, so we'll be talking a little bit about that, mostly with immunotherapy. We've touched on it briefly thus far.

Tyler Beardslee: There we go.

Tyler Beardslee: So the following statement is true about taking proton pump inhibitors or H2 blockers with EGFR tyrosine kinase inhibitors. It should be avoided at all costs due to potential to interfere with absorption. They should be spaced out by 12 hours to improve the absorption of the EGFR TKI. Patients who took PPIs or H2 blockers with EGFR TKIs had decreased efficacy of the EGFR inhibitor on their cancer. Or there was little to no effect on the pharmacokinetics when giving a PPI or H2 blocker within EGFR TKI. Or are you unsure, which you might be.

Tyler Beardslee: Cool. All right. Pretty. That's like, it looks like a bell curve to me.

Beth Eaby-Sandy: Yeah.

Tyler Beardslee: A 62 year old female patient with non-small cell lung cancer and a history of cardiac ischemia is to be treated with a 5HT3 receptor antagonist. Which drug would you consider that would have the least risk of prolonging the QT interval?

Beth Eaby-Sandy: Read the answers.

Tyler Beardslee: I'll sorry, ondansetron, palonosetron, dolasetron, or are you unsure?

All right. A pretty good distribution here. So we'll talk a little bit about this later.

So to get started, when we're talking about drug interactions, we're really talking about pharmacokinetics of drugs. So pharmacokinetics refers to the ADME of drugs. It's what the body does to the drugs, not what the drugs do to the body. So it's the absorption of the drug. It's the metabolism of the drug. How is this drug broken down or is it broken down? The distribution of the drug, is it a highly bound to protein, does it penetrate the blood brain barrier? As well as excretion. The majority of drug-drug interactions are going to happen with metabolism, however they can happen with absorption, excretion, or distribution really.

So talking a little bit about kind of some generalizations of the pharmacokinetics of our different treatments. I just kind of want to go through and give you some broad generalizations about these things. So when talking about TKIs, almost all of these are going to be hepatically metabolized by CYP

enzymes. And in fact, the majority of them are going to be CYP3A4. About 75% of all drugs are metabolized by CYP3A4 and that is kind of true here as well. Immunotherapy and other monoclonal antibodies for the most part are not hepatically metabolized or renally excreted. So they are gotten rid of through a number of different rep mechanisms that I won't get into. Things like you can imagine, a PD-L or a PD-1 inhibitor would go and beyond the PD-1 on the cancer cell and that cancer cell now gets phagocytized by a macrophage. Now that antibody is completely gone. It didn't go through hepatic metabolism or renal excretion. So there's a number of different mechanisms there. Then we have chemotherapy, which can either be hepatically metabolized or renally excreted. I've given you some examples there. And then etoposide actually has both, which is kind of interesting.

So we're going to talk a little bit starting off with a drug that has a drug interaction based on absorption. So you guys have kind of already seen all this stuff about EGFRs so I won't belabor that, those points there. I'm talking about gefitinib and erlotinib pharmacokinetics. They have a pretty decent bioavailability of about 60%. They can be affected by the presence of food. So look, once again go back and look at the dosing. But the important thing I want to harp on here is the fact that there's pH dependent solubility with decreased solubility at high pH. So low pH is meaning a more acidic environment, we have better absorption of these drugs. This is going back a little bit to chemistry. I also have a chemistry degree, so I have to do this type of stuff, every once in a while to just show myself that I can.

So it has a pK of 5.42, which means that below a pH of 5.42 this thing is going to be protonated. So it has a maximum solubility at a pH of two. And when something is protonated, it has better dissolution in an aqueous solution. So that when it has better dissolution, that means that it's better absorbed. Okay, so that's going way back to your chemistry more than you ever wanted to know. But the key point here is that a lower pH, a more acidic environment, these drugs are better absorbed. You see the AUC decrease here with different acid suppressing medications and this is based off of the package insert. Okay?

Looking a little bit more about the package insert. So we've talked about the decrease in absorption with the AUC and Cmax going down with both of these drugs. There are some different recommendations for what to do. So they say if you administer, for example erlotinib, if you administer an H2 blocker, you can do that, but you need to have the drug taken at least two hours before or 10 hours after an erlotinib dose. This is quite cumbersome for patients. So basically it's 10 hours after their last dose or two hours before their next dose of H2 blocker. They can take their erlotinib and it's going to be okay absorption. This is based on what the package insert is showing you. Now I'm going to show you some data that this acid suppression mechanism may not have as great of an effect as we might think based on some of this data.

Oops, I was hitting the, was lighting you up out there. So this was a retrospective study. It compared the pharmacokinetic efficacy of safety of erlotinib in patients who had either acid suppression or no acid suppression. So this is a real analysis looking back at some patients, this is real world analysis. If you look at the efficacy here, there was no apparent difference in the overall survival and progression free survival between the patients that were on acid suppression versus those who are not on acid suppression. And this is also supported by the safety data here. So we see that acid suppression patients had more rash so you would imagine if they're absorbing, if there's going to be drug in there you would expect more rash. So this is kind of opposite of what we would have thought actually in some of the safety data. The take home point here is the efficacy and the safety, with acid suppression along with

erlotinib, tells us that it might actually be okay to have acid suppression with erlotinib based on this real world data.

This was another single center study and they compared, once again, acid suppression and non acid suppression in patients receiving concomitant gefitinib. We see here, once again, the response rates were almost the same between... Ooh, how do I go back? I don't know how to do that.

Beth Eaby-Sandy: See the back arrow on there?

Tyler Beardslee: Oh, there it is. Okay, great. I was like, I can't go back. That's bad.

But what we were seeing there, let's try that again, is basically no difference in the PFS or the response rates. So this is basically two studies and there's actually more data out there than this. I just showed you two. So what this is telling us is that in the real world, acid oppression has really minimal impact erlotinib and gefitinib absorption in the real world setting. Who knows why this really is, I don't have great hypotheses here. I could give you a long talk about the design of TKI phase one trials and how we're probably actually the using doses that are too high for the TKIs. So what's probably happening is they might be absorbing less, but it's still far more than enough TKI to inhibit the EGFR that we need to.

Beth Eaby-Sandy: I think that probably makes the most sense.

Tyler Beardslee: Yeah. I mean there's studies looking at erlotinib all the way down at doses of 25 milligrams and they saw like no difference in the efficacy of the drug. So you can severely dose reduce. Where I do get concerned about this is in patients who have had to have lots of dose reductions with like going down to a low dose and then they're on acid suppression. That's the one place I might worry a little bit about it and I might harbor more back towards those H2 blockers and doing that spacing appropriately.

Beth Eaby-Sandy: This brings up another point. What about patients who've had surgery on their stomach, like these gastric bypasses and things like that? I mean I'm probably getting into a whole other world here, but I mean are they absorbing these oral cancer drugs okay?

Tyler Beardslee: That's a great question. They don't look at those patients in trials, that's for sure. I think that'd be a very interesting probably PK study. I need to talk to Donald Harvey at my institution. He's our phase one oncology pharmacist. He would probably have some better thoughts on that.

Beth Eaby-Sandy: I just think because it's becoming so common now, the bariatric surgeries for obesity, that I think that 10, 15, 20 years down the road when these patients are of age in their sixties and seventies, and they're developing cancers, this is going to be an issue for oral cancer treatments and absorption. I don't know.

Tyler Beardslee: Yeah, that's an interesting point.

Beth Eaby-Sandy: By then, it'll be topical.

Tyler Beardslee: Yes, exactly right. So talking a little bit about other absorption issues. So I was talking about this earlier, harping on the point that you really just need to check the package insert for

administration instructions for all these oral anticancer treatments. Alectinib should be taken with food or erlotinib without food. So food can affect absorption quite significantly in some cases.

Beth Eaby-Sandy: And I think that's where we as providers rely on our pharmacist to put these things on the bottles because-

Tyler Beardslee: Yes it should be on, that's exceedingly important. Needs to be on the bottle because if I can't remember it, there's no chance a patient's going to remember it. So, yeah, here's where, like I said, it's the bulk of the drug interactions is the metabolism of drugs. Drugs, other drugs that interfere with the drug that you're looking at, the metabolism of it leading to a build-up of the drug or maybe it increases the metabolism of the drug leading to a decrease in the levels of the drug in your system.

So I'm just going to kind of go through some of the recommendations. Some of these slides are a little bit wordy but I'll kind of hit on some of the high points here. So erlotinib is metabolized by both CYP3A4 and 1A2. In patients who have inhibitors, once again, this increases their exposure to erlotinib, so we would expect them to have more toxicity. So that's what they recommend, is basically if you have an inhibitor, a strong inhibitor, that you should probably monitor them for toxicity. And if they're having a lot of toxicity you can decrease in increments of 50 milligrams. In patients who have concomitant CYP3A4 and 1A2 inhibitor, which important, ciprofloxacin, which we use quite a bit in oncology land can increase exposure to erlotinib. So I would pretty much probably avoid this one because you know it's probably going to increase your levels quite a bit because it's inhibiting both of the metabolic pathways. But they also have recommendations for dose reduction here if you see toxicity.

For inducers, they actually have recommendations for increasing the dosage. This is not something you see with a lot of drugs, but they've actually done PK studies on this and shown that with these inducers CYP3A4 enzyme, this decreases your exposure to erlotinib. So if you increase the dose, you get it back up to that level where you are with a normal patient who's not on an inducer. And then another very interesting one we mentioned there are some smokers that have these EGFR mutations and CYP1A2 is an enzyme that's actually induced by smoking. So this means you're chewing up your erlotinib faster, decreasing your erlotinib exposure. They've actually done a peak PK trials in these patients too. And they show that a dose of 300 actually is the right dose for smokers. And I've actually done this before for one, I've only had one guy, but this was a long time ago.

Back to gefitinib. These ones don't, does not have the same dose, kind of thing where it says, monitor for toxicity. They say just to avoid it and CYP3A4 inhibitors. For inducers, you can increase the dose here.

Osimertinib, so this is kind of our drug of choice here in EGFR. Looking at the inhibitors, really this is where they say you should just avoid the use of it. And I'm going to go through later and show you kind of a list of some CYP inhibitors and what are some alternative therapies. You usually can get away with something else other than a CYP inhibitor. For inducers, also, definitely avoid use. Okay. Mmm. There are some other substrates of some of the enzymes that metabolize this drug that they say you should avoid. Drugs that have a narrow therapeutic index. And I have those listed there for you.

I'm looking at ALK inhibitor metabolism, this is actually a very interesting one with alectinib. This is kind of one of those things where you wouldn't really be expected. So it's metabolized by CYP3A4 too. An active metabolite, so both the parent compound and the metabolite M4 are active. So a strong

CYP3A4 inhibiter and strong CYP3A4 inducers don't really have any clinically meaningful expect on the combined exposure. And it's probably because if you induce it, you're just inducing it to an active metabolite. If you inhibit it, you're building up the parent drug, that's just an active drug. That's my kind of thought there. So despite it having a hepatic metabolism, you can really not have to dose adjusted it for inducers and inhibitors.

For lorlatinib, this is kind of what you see, which is similar to osimertinib, that you really should probably avoid the use of CYP inducers and inhibitors.

Now we're going to move on to chemotherapy and I'm going to give you a couple of examples of some drug interactions with chemotherapy. So we're going to go through two here. With pemetrexed, which you guys are probably using in your lung cancer patients. This is a folate antagonist. It undergoes extensive renal excretion. And in fact if you look in the package insert, it'll say that it's contraindicated in patients with a creatinine clearance less than 45. This is because they had a couple of deaths in patients with febrile neutropenia and low renal function. However, in our clinic we do a dose adjustment at less than 40, between 45 and 30. Below 30 that's where we have our cutoff. We dose reduce 20%.

The drug interaction here, since it's renally excreted, is NSAIDs, as you can imagine. So NSAIDs can cause some AKI. And so you might get a less excretion of the chemotherapy if you have NSAIDs around the time that you're giving chemo. So this is a big counseling point for me. NSAIDs are available over the counter. We want them to avoid it about two days before and after treatment with Pemetrexed.

Beth Eaby-Sandy: Do you have a question, Beth?

Beth Gilbert: What about naproxen?

Tyler Beardslee: Yeah, so for, for some of the longer ones, naproxen has a longer half life, and so I would say five days. Yeah.

Beth Gilbert: I mean I think, I've had the discussion with our pharmacists and they told me that ibuprofen was the main thing to avoid. [inaudible] Naproxen was okay.

Tyler Beardslee: Yeah. I'll have to look-

Beth Gilbert: [inaudible] have to space out.

Tyler Beardslee: Yeah. I might have to look more into that.

Beth Eaby-Sandy: If anybody didn't hear Beth's question was saying there was some thought that maybe ibuprofen was more the culprit here. And that maybe Naproxen, aspirin may not be as much of an effect.

Tyler Beardslee: Yeah. I go by what was in the clinical trial, which as I said, to avoid this stuff, but I think there are some like nitty-gritty mechanistic things that are responsible for this. And that, like you said, Naproxen may be okay. I would just avoid it though. You can get away with acetaminophen. It's only a couple of days around treatment. Right? And why risk it? That's my thought.

So taxanes are kind of our more broad spectrum chemo option. I always joke with our residents, if I'm pimping you on a question and you don't know the answer, if you guess CarboTaxol you might be right. So that's a good guess, in any scenario, for this whole year is what I tell them.

The two taxanes that we have is paclitaxel and docetaxel. These undergo CYP3A4 and CYP2C8 metabolism. You should really avoid CYP3A4 inhibitors inducers in this setting. It's not well-studied. And in the studies that they have done, it's hard to predict what the actual outcome would be in that patient. For example, you might read that with a CYP3A4 inhibitor we saw two fold increase in the drug levels. What if in your patients a three fold increase? That's not okay with chemotherapy. And I'm going to show you an example of that.

So this is a 62 year old male with newly diagnosed stage four squamous cell carcinoma of the lung. This is a real thing that happened. Of note, during a recent hospital visit, he was found to have a AFib or a flutter. He was started on diltiazem for this while he was admitted to the hospital. And he presented to the clinic for consideration of starting Cycle 1, Day 1 of carboplatin, paclitaxel, and pembro. So he's on the diltiazem. He has some other drugs here. What drug-drug interactions should you be concerned about? Does anyone know?

So it's the diltiazem that he started, it's a moderate CYP inhibitor, and it's kind of one of the ones that goes under appreciated as far as drug interactions go. This is a pretty common drug for people. So I looked it up and there actually were, like I said, some studies saying that maybe there's a twofold increase in the drug levels when you have a moderate CYP3A4 inhibitor and a taxane. So I said, "Well, let's dose decrease by 50% and see what happens." So he got his dose here on 1/10. With Abraxane, you come back on week two and get your dose. His platelets were already low and I was like, "Okay, well that happens sometimes." And then he comes back to the third week and his platelets are 18. This is not typical of what we see in most of our patients. I think it even got lower than-

Beth Eaby-Sandy: And that was first cycle?

Tyler Beardslee: Yeah. This is first cycle. First dose of the drug. So needless to say we did not do that again.

So this is where I was going to tell you a little bit about some of the alternative therapies. So strong CYP3A4 inhibitors, a lot of times, are antifungals. And our patient population, they're getting radiation to this area. Sometimes they get some candidiasis, for those patients you can do nistatin. Nistatin doesn't interact. Whereas all of your azole antifungals are going to have some CYP inhibition.

Beth Eaby-Sandy: I definitely gave fluconazole one time to one of erlotinib patients. She had, I don't remember what, but she had some kind of candidiasis infection, and she broke out in the worst rash, EGFR rash.

Tyler Beardslee: Yeah.

Beth Eaby-Sandy: But at that, and then I mean, then I kind of put two and two together and figured it out. We stopped the fluconazole but I didn't want to stop the erlotinib, I guess I could have held it because she probably had like four fold dosing of it at that point. And we just kind of pushed through it

and waited till the fluconazole got out of her system. And her rash did improve but it was really bad rash.

Tyler Beardslee: And you also have to, and we won't get into the nitty gritty with that, but I was going to say, if you're doing something like a 10 day course of fluconazole that's a higher risk than if you know you're doing something like vaginal [crosstalk]-

Beth Eaby-Sandy: Like one day?

Tyler Beardslee: ... that's one dose. That's probably be okay. But that's a little bit in the nitty gritty there. Antiseizure medications, brain meds, patients get seizures. They might go to some neurologist who uses some of these more older-school things and they are CYP3A4 inducers. And as you've seen, this can have a great effect on some of our drugs. So if we would want to avoid this, we can use levetiracetam, which I would say the brand name, but I don't want to.

Antiretrovirals. We have a number of antiretrovirals used for the treatment of HIV that are strong CYP3A4 inhibitors, and their entire purpose in these HIV regimens is to boost the levels of the other drugs that they're used with. So alternative therapies, I usually say console your ID specialist. Because you don't want go mucking around with somebody's HIV meds when you don't know the resistance that their disease has had in the past. So I always say refer to their ID specialists, who you should be able to talk to you pretty easily.

And then grapefruit and grapefruit juice for all of our patients getting counseled on TKIs, they all get the blanket statement, no grapefruit, no grapefruit juice. Not even Fresca because I don't know what's in there. So there's all kinds of stuff that has grapefruit in it.

As far as checking for drug interactions, use your Lexicomp, use your micromedics. This little interaction checker is fantastic. So not only will it give you kind of the level of concern, it'll be like ABCDX do not do. It also will give you the data that supports that rating. So you can read into it and make some kind of soft calls yourself by reading the data if you find an interaction that you're concerned about.

You guys have kind of seen how immunotherapy works. So I don't think I want to go into the mechanism here just because you guys have gotten that and I'm probably-

Beth Eaby-Sandy: Down to five minutes.

Tyler Beardslee: I was about to say, I know I'm running short on time here. We've talked about the potential for immune related adverse events. And I'm kind of highlighting some of the more common ones that we know happen in lung cancer. So this goes back to the question, we've talked a little bit about this before, immunotherapy in autoimmune disease. So let's just say drug disease interaction. Clinical trials for the most part have excluded these patients with preexisting autoimmune disease. So what we're relying on really is a lot of retrospective case series here to see what happens to these patients if we put them on immunotherapy.

Really the type of immunotherapy, type of autoimmune disease, how well it's treated, and how active their autoimmune disease is, has an effect on whether or not we should be able to do this. This is looking at the irAE rates for patients without preexisting autoimmune disease. And what you see here is

the grade three or greater, we'd go anywhere from like 10% all the way up to a little bit higher percentage in the patients who are getting CTLA4 therapy, all the way up to maybe 40, 50, 60%. Especially in combination treatment.

What we see here is the data for whether or not there's irAE in patients with autoimmune disease. So first I showed you without, this is with, so these are all retrospective studies, like I said. What you see in general is that the irAE rate is somewhat similar, maybe a little bit higher for the patients in these PD1, PDL1 treatments. What you do see as well is that CTLA4 seems to have a pretty high rate of both disease flare... So they split this up into autoimmune disease flare as well as irAE rate. So in general I would say probably CTLA-4 might not be a great idea for patients with autoimmune disease. Although, like I said, you can take into account how well their disease is controlled, what immunosuppressive drugs they're on, and also what type of autoimmune disease it is.

Let's kind of skip this. So let's go back to the recommendations here. So immunotherapy, and this is from the NCCN, immunotherapy can be considered obviously in patients with a low level of immunosuppression or with really good control of their autoimmune disorder. Or for things like, I would say lupus, rheumatoid arthritis. You get a little bit more concerned with colitis because if you have really bad ulcerative colitis, and then you give them immunotherapy, that's probably going to flare and that can be potentially life threatening. And especially neurologic or neuromuscular diseases, or any patients with poor control, those are the patients you should avoid immunotherapy in.

Drug herb interactions. Let me just say that there are a number of herbs that interact. You can look these up by going to MSK's website about herbs. You just go to Google and type in about herbs. Really great website. If your institution has it, the Natural Medicines database is even better I would say. Just look these things up. I usually just say don't do it because these things are very poorly characterized and extremely poorly regulated, actually not regulated at all.

QT prolonging agents, this is what I kind of wanted to get to. So there are a lot of drugs that prolong the QT, and I would say that we kind of freak out about it a little bit sometimes. So a lot of these drugs are our 5HT3 inhibitors, and our other antiemetics, which I've listed here, but we've kind of gone through some of our TKIs that are QT prolonging. So the question is what is too much and who should we be concerned about? The people who should be concerned about are patients with additional risk factors. So whether they have a congenital long QT syndrome, CHF, bradycardia, or other cardiovascular disease, these are the ones that were specifically listed. You might want to do a baseline EKG and if they're QT interval is extended and we'll go, actually, let me get back because I want to make one more point here. It won't go back. We'll just keep it.

So here's what the normal QT interval for patients is. For men, it's 440. For women, it's 450. So patients with longer QTs than that, And if you're going to put them... My rule is if they go on 2 and they have a long QT interval, then I want to maybe do QT monitoring, kind of serial QTs on them. For patients who have a QT interval that's extended to greater than 500 seconds, or they were at baseline and now it's greater than 60 seconds from their baseline, this significantly increases their risk for Torsades. And I would be concerned in maybe trying to start peeling off some of those QT prolonging drugs at this point. As far as the 5HT3 inhibitors that have lower risk, granisetron and palonosetron have less QT prolongation, although route, as well as dose can play a role. So IV is more than PO, and obviously higher dose has higher risk.

So going back to our questions, the following statement is true about taking proton pump inhibitors or H2 blockers with an EGFR TKI. It should be avoided at all costs due to potential to interfere with absorption. They should be spaced out by 12 hours to improve the absorption of the EGFR TKI. Patients who took PPIs or H2 blockers with ETFR TKIs had decreased efficacy of the EGFR inhibitor on their cancer. Or, there was little or there was little to no effect on the pharmacokinetics when giving a PPI or H2 blocker with an EGFR TKI. Or are you unsure still? Please don't be unsure. Well, you can be unsure.

Beth Eaby-Sandy: Yeah.

Tyler Beardslee: All right, so there was some improvement here. So I did go through some data showing that the drug, in the package insert shared, that it had decreased absorption. But in the real world data, we really haven't seen that it has any effect on efficacy or safety really. So I say we don't really have too much of a concern of PPIs or H2 blockers with an EGFR TKI.

A 62 year old female patient with non-small cell lung cancer and a history of cardiac ischemia is to be treated with a 5HT3 receptor antagonist. Which drug would you consider that would have the least risk of prolonging the QT interval? Is it ondansetron? Palonosetron? Dolasetron? Or are you unsure? I mentioned this briefly.

All right. Good job, guys. So there's one thing, I want to make a point about Palonosetron. Palonosetron actually has some data showing that it's better for delayed nausea, and this is because it has a very long half life of about 40 hours. However, that 40 hour half life means the drugs really in your system for two, three, four days. So when you're giving patients PRN anti emetics and they're getting a dose of Palonosetron, you might want to be a little bit more cautious with using 5HT3 inhibitors for a few days after you give Palonosetron. That's a safety point I'd like to harp on.

All right. Any questions?

Beth Eaby-Sandy: Okay.

Tyler Beardslee: Excellent. Thanks y'all.