Transcript for Managing Patients With Other Mutations in Metastatic NSCLC and Upcoming Clinical Trials

Beth Eaby-Sandy: All right. So we're going to talk about just some other rare mutations and what is on the horizon for clinical trials. So you've seen all of these slides already. So we're going to talk about the efficacy and safety data supporting the use of targeted and immune checkpoint inhibitor therapy to treat non-small cell lung cancer. But we're going to talk about the rare ones and then our clinical trial data as well. Probably we want to go to ... there.

So a 65 year old male is currently taking dabrafenib and trametinib for his metastatic BRAF positive non-small cell lung cancer. After three weeks on the drug, he develops a fever ranging from 100.2 to 101.2 for two days that resolves with 650 milligrams of acetaminophen. He feels a little fatigued and achy, but generally is able to perform his ADLs. Given this scenario you should: hold both trametinib and dabrafenib and perform an infectious workup, hold trametinib but continue dabrafenib for a week then resume both of the same dose, continue with both drugs and monitor your temps, if the acetaminophen stops working or he begins to have significant symptoms, then hold treatment, hold both drugs for a week, then resume with a dose reduction of the dabrafenib or I'm unsure.

Okay, all right. So let's talk about it. Okay, so there's the pie chart yet again. So we covered, EGFR in the green. We covered ALK in the purple and we covered ROS1 in that olive green color. But as you can see there are a lot more. So let's talk about them. And then there's about that 31% that we don't find any driver mutations. So BRAF. So it's not just melanoma. It's also in lung cancer, about 2%, so it's uncommon in the non-squamous. Again, this is a DNA sequencing panel. So this is not going to be overexpression on IHC or FISH. You do have to do the DNA sequencing panel. Interestingly, it's more common in smokers. So all of these other ones, ALK, ROS1, EGFR, [inaudible], the non-smokers, this is why you have to test smokers too. Sometimes they have the other ones, but it's most common in smokers to have a BRAF mutation.

The most common and targetable one is that BRAF V600E like in melanoma as well. And the only drug combination right now approved is dabrafenib and trametinib. Here is the waterfall plot, so you can see that the only yellow tick up was progressive disease. And then all the ticks down on the waterfall plot are some sort of responses, though even while there's some shrinkage, some of them are considered progressive disease. That dotted line at 30 is the 30% shrinkage, which would be a resist criteria response. So you can see it has 64% first line response rates. So again, we would recommend first line treatment with dabrafenib and trametinib and it was unlikely that patients had progressive disease on this. So this is a driver mutation and this is targeted therapy for driver mutations. Same theme that we've had throughout this symposium today.

Always treat with the targeted therapy first if you find a driver mutation. So toxicities of dabrafenib and trametinib, fever, it's the most common thing. If you've used this combo with melanoma, you will know, same in lung cancer, you get fevers. It's the most common. About half of patients, a little more than half will develop grade one or two. And then about 11% will develop a grade three which means they're significantly symptomatic. You could have some GI and like nausea and

diarrhea side effects of it as well. A little bit of rash and hypertension and the oral dosing is annoyingly complicated as well. So the trametinib you only take once a day, but the Dabrafenib is twice a day and usually multiple pills of it twice a day. So this gets really confusing for patients because you're on two different targeted therapies but you don't take them the same way each day. So this takes some education for the patient as far as adherence.

So for the fever from BRAF inhibitor therapy, since it's pretty common, well over half of patients are going to develop it. The usual onset is within those first four weeks of therapy. With the median time being around nine days, you lead to a dose interruption about 32% of the time on clinical trials, and a dose reduction only about 14% of the time. So it's very interesting the first episode is usually in the first nine days and then usually you get it again and again. So even if you manage it with acetaminophen or you hold dose and restart, a lot of times it's going to happen again. So you have to counsel patients, you're probably going to get it again and then we're going to do the same thing, give you acetaminophen, whole drug, but then we're going to restart you again and it's probably going to happen again.

So annoyingly you can get subsequent episodes until you sort of peak months into it and then you stop getting them. Usually you do not need a routine infectious workup unless there's some obvious thing that the patient is saying. They sound like they have strep throat or whatever. They're not neutropenic. Generally they shouldn't be. So we don't usually recommend infectious workup unless there is an obvious sign of infection or reason for them to have infection. Otherwise it is most likely due to the BRAF inhibitor therapy. You feel like you have a fever, it's chills, headache, night sweats, you feel terrible, you feel yucky. So what's the treatment? Well, if you're going to hold a drug, Dabrafenib is the one you're going to hold. It's usually the one that's responsible. However, in my practice we don't always hold, it's a fever. We know what it's from.

If acetaminophen or NSAIDs are managing it and you don't feel terrible, we don't necessarily hold drug. You can also use corticosteroids in patients who the NSAIDs or the acetaminophen is not holding off the fever. And then usually we restart at the same dose. So I know this sounds weird, you would think, "Oh well toxicity, we should reduce the dose." But we don't usually, so the package insert, if you look at it, will tell you to reduce dose, but in multiple, in literature, there's a lot, lots of papers that have been written about this that we find that dose reduction are not usually the same rates of recurrence of fever occur. So we don't generally reduce dose. We would hold, give them maybe seven days off of the dabrafenib and then restart it at the same dose.

And then in some cases where it's debilitating fever, you feel terrible. It's happening over and over and over again. Then I would consider reducing the dose. But generally I don't always, I don't even always hold it if the patient's feeling okay. It depends on how they're feeling and how debilitating the fevers are. So skin rash or secondary malignancies is another toxicity of dabrafenib trametinib therapy, skin rashes are usually minimal, red, itchy, bumpy, not that pustular appearance that EGFR rash tends to convey. Usually we'll use anti-histamines or emollient creams, for the itching responsible. Both drugs are responsible for it. So we usually can treat that symptomatically. Oddly combining both dabrafenib and trametinib gives less secondary malignancies than with dabrafenib alone. So we don't use dabrafenib alone for multiple reasons, but the combination is better and it does give you less secondary malignancies. However, per the package insert, they do recommend that dermatology follow the patient to do an annual skin exam.

That being said, I've kind of talked to my melanoma colleagues about this and we don't always refer to dermatology because most of the secondary malignancies that can occur from dabrafenib trametinib therapy, they're on areas of the skin that are exposed. So they're prior sun exposed areas, which usually are something that you and the patient would see, number one. And they're often, usually eruptive is what I'm told. So they're not just a subtle mole. They're actually like painful, itchy, annoying, and crusting. And so these are things that are usually somewhat obvious as opposed to primary melanomas that may hide in insidious places that we would recommend derma follow-up. So you can use a dermatologist to do a skin exam. They're uncommon. They're 2% and a lot of times since they're in sun exposed areas, we don't necessarily always do that. We just warn the patient, "If you have anything like that, let us know."

So NTRK. So we just talked about entrectinib with ROS1 but this is NTRK. So there are two drugs approved for NTRK fusions, but they're really rare. They're 0.2% of lung cancer patients. But you can find NTRK in other cancers. I think the most common is like sarcoma and some brain tumors as well. So mostly pediatric brain tumors I believe. But worth mentioning because both larotrectinib and entrectinib have indications for an NTRK mutation. I have yet to find a lung cancer NTRK. Has anyone in the room had an NTRK lung cancer patient? No.

So it's really, really rare, but you can find them. Again. Only 11 patients were found on a database search. They were younger than the usual lung cancer patient. They all had adenocarcinoma and they were all never smokers. Again, gene fusion. So that that RNA gene fusion panel that we talked about earlier is where you would find this. Oh yeah, and I have it written there. The thyroid, that's the other one that's more common as well. And both of the drugs have those kind of neurocognitive side effects that Tyler spoke about. Yes, Anne.

Anne (Attendee): [inaudible] when you're finding patients that somebody said to me that is common in rare cancers. But [inaudible].

Beth Eaby-Sandy: Yeah, so that's a really good point. It's common in the rarer cancers, but even the common is probably not a good word because it's not like 50% or anything. I think it was like in the 10% to 20% range of those uncommon cancers like thyroid and sarcomas and in pediatrics GBMs but really uncommon in our common solid tumors, but two drugs approved for it. So we should technically be looking. And then KRAS. So here's KRAS. The most common mutation that we find in non-small cell lung cancer, about 25% of our adenocarcinoma patients have KRAS. The most common KRAS mutation is the G12C but there's certainly different KRAS mutations that have been identified. Again, this is a DNA sequencing panel. So this is the one that takes weeks to find. It is more in smokers though sometimes found in never smokers as well.

And it's usually mutually exclusive. So we don't see a lot of KRAS plus EGFR. KRAS often is associated with resistance to EGFR. Not that we would use EGFR with it because we don't use that outside of EGFR mutations, but it often is resistant to any target therapies. So chemotherapy plus immunotherapy is usually going to be your treatment of choice. So when we find KRAS, we say, "Okay, we found this, which means you likely don't have one of the other ones and you're going to be treated like a run of the mill chemo and immunotherapy lung cancer patient."

Now this is a new update from last week. At the world conference for lung cancer in Barcelona. So there is a new drug by Amgen. So AMG 510 a novel oral targeted therapy that targets the KRAS G12C so there's an early phase one trial now that have, 34 patients and there was a lot of responses that were

seeing with this drug and it was very, very safe and led to no adverse events that led to discontinuation, so very well tolerated with response. This has primarily been an area where we have tried multiple targeted KRAS drugs that have not worked, so this is pretty exciting to have this drug coming about.

So look for this in the future, there are also RET Rearrangements in non-small cell lung cancer. Again, rare 1% or less gender balanced, somewhat never smokers though some are smokers. This is a FISH test. Also can be found on the RNA fusion panel mostly in adenocarcinoma as the other ones. There's some phase two data on cabozantinib and vandetanib, that show clinical activity, and then there's been other drugs that have been looked at that you would think, here's just like a kind of an overview in one database review of patients that were treated on a case by case basis with these different drugs.

We definitely see some clinical activity but it's not a slam dunk like the other targeted therapies that we've seen in lung cancer. So none of these drugs have gotten an FDA approval in this setting. I would suggest if you find a patient with a RET Rearrangement look out for a clinical trial in lung cancer that is looking at one of these drugs. A lot of these are already approved so you could consider using them off study, but they don't have indications at this time. So this is all clinical activity but not great earth shattering responses.

MET exon skipping mutation. So again, this is not your run-of-the-mill MET. So this is looking for a mutation on that DNA sequencing panel as opposed to MET overexpression, which we see a lot actually on other FISH and immunochemistry panels. So this makes up about 4% to 5% of non-small cell lung cancer. It can be either in squam or adeno. So again there's that reason to test clinical pictures.

It's in both non-smokers and smokers. Crizotinib has good clinical activity actually pretty good clinical activity. It does not have an FDA indication. I suspect that's because Pfizer, the company that makes crizotinib is just like, "Yeah this is a small amount of people. Maybe they won't go for the indication." But I think the data would back it up to get an indication if they went for it. So there's technically no indication but I would never see an insurance company denying you crizotinib for a MET skipping mutation. It has really pretty good data for this use and I would consider it in first line treatment for these patients.

HER2 mutations is another thing that we find in non-small cell lung cancer. So again, this is a mutation, not an overexpression. This is not HER2 in breast cancer, which is an overexpression. This is not an amplification. This is a mutation. So if you think of EGFR, EGFR is HER1, so EGFR is HER1, so this is HER2. So there's four a housemates and there's HER1, HER2, HER3, HER4. So this is HER2 mutation in the DNA. It's uncommon, 1.7% of patients a little bit more in women than men. A lot of them again were never smokers. Trastuzumab, that you would think, "Oh well that must work because it works well in breast cancer for HER2 overexpressed patients. But it really didn't add a benefit when added to chemotherapy in these patients.

There are case studies though that have shown benefit as well as other typical HER2 treatments like lapatinib or afatinib. So there's some clinical activity with these. Again, none are earth shattering and in a randomized trial it did not add benefit with chemotherapy. So this is another subset of patients, but I'm going to show you in a second, there are some clinical trial drugs for that as well. Other pathways, the PI3 kinase pathway, there's not targeted drugs approved for it, but there are drugs in clinical trials. If you happen to stumble upon this, I would look out for a clinical trial. But in general these patients are treated with chemotherapy, immunotherapy like run of the mill patients. And you can see

some others that I've listed there that are other pathways that we're interested in, but no approved targeted therapies.

So where are we going in clinical trials? What's on the horizon? So I had looked at our University of Penn clinical trial. We have a thing that says what all of them are and I can tell you that of the novel drugs, we were looking at nine targeted therapy and 14 immunotherapies. And that included all types, not checkpoint inhibitors but vaccines, all kinds of stuff. But there were no novel chemotherapy drugs. So we had kind of had one for small cell and then that didn't work. So it's interesting because this, the future is going to be targeted and immunotherapy for sure.

So let's look at some of these drugs. So this drug poziotinib, so this is again, there was a presentation at world lung conference about this as well. Strong inhibition for not just EGFR but HER2, and that Exon 20 mutation that has been traditionally hard to target. So here's this population that we've had a really hard time targeting and at world Lung Cancer, the data presented showed really promising results on the waterfall plot for patients with, with EGFR resistance, whether it's Exon 20, whether it's HER2, that benefited with some sort of response. There is some toxicity with this. So there's certainly skin rash, which we would expect to see with these drugs that are inhibiting EGFRs. But this is a drug to look out for. And that's some exciting data. There's also another trial with a Johnson and Johnson drug, 372 it's an EGFR and cMET antibody.

So this is IV. This is a monoclonal antibody. And initially in the phase one cohort that we had had at Penn, there was a lot of reactions to this drug. It's not just infusion reactions but skin rash was certainly an issue as well. But this is a drug also that's on the move and has now moved into the phase two cohort for patients who are resistant to first and second generation EGFR inhibitors and third generation EGFR inhibitors. And then they're looking at some cMET patients with this as well. So two interesting drugs and then a third drug looking at EGFR TKI resistance is something called TAK-788. So again, here's your, those hard to treat those HER2, Exon 20s and EGFR resistance. So here's some of the phase one and two data for 26 patients that have been treated.

You can see that there was a fair amount of partial responses and stable disease. So really only one patient had progressive disease. So a lot of responses there, no complete responses. So no complete disease control, but a lot of disease control on this trial and a lot of responses. So this is promising and the adverse effects are also consistent with the other EGFR TKIs, skin rash, et cetera.

What about immunotherapy? So obviously lots and lots of immunotherapy trials, but this idea, if you haven't heard this term before, the abscopal effect. Abscopal effect is a term that looks at immunotherapy and radiation overlapping, where you would radiate using ionizing radiation to, let's say a lung tumor, but their metastatic disease would shrink. You didn't radiate their metastatic disease, but the metastatic disease shrinks based on the fact that their primary tumor was radiated and with immunotherapy on board, somehow those tumor cell antigens are recognized by dendritic cells, which then are in the circulatory system and hopefully are invoking cytotoxic T cells to kill other cancer cells.

It's like they're remembering it from here and then they're branching out and they're going to other areas to find what they saw here and finding that, that's called the abscopal effect, and we've seen this way back many years ago, but then it kind of went by the wayside and now we're kind of seeing that again with radiation and immunotherapy. So there's a lot of clinical trials now looking at overlapping immunotherapy with radiation, even though you're only radiating the primary tumor, to see if we can invoke those kinds of responses. So that'll be really interesting. And of course making sure that

this is a safe approach as well. But I think that we feel pretty good about that in the durvalumab post chemo radiation setting.

And so again, just to kind of finish up with clinical trials, immunotherapy of all types of pathways, there's too many to name vaccines, CAR T-cells in lung cancer. Problem is, is having a vector that's going to get the those CAR T-cells into the lung cancer and that's been a problem. I'm trying to figure out that in the lab, PARP inhibitors, mTOR inhibitors, vaccines, all of these things are several clinical trials. So our pearls, test all patients for these different mutations. Even if there aren't approvals, there's probably a clinical trial that they might be eligible for. Like Rashida said in our very first talk is that years later you might be able to go back and say, "Oh, they do have this or they did have this and now I'm in the future. There's something for them." And certainly immunotherapy is the future and we'll be looking at all different ways, stimulatory and suppressive ways to work with the immune system.

Okay, so let's go back to our question. A 65 year old male is currently taking dabrafenib/trametinib for his metastatic BRAF positive, non-small cell lung cancer. This is a patient of mine by the way, and he was developed this fever on my flight back on Tuesday, so this was real time. After three weeks on the drug, he's developed a fever ranging from 100.2 to 101.2 for two days, that resolves with 650 milligrams of acetaminophen. He feels a little tired and achy, but generally he's able to perform his ADLs. Given this scenario, you should: hold both trametinib and dabrafenib and perform an infectious workup, hold trametinib, but continue the dabrafenib for a week and then resume both at the same dose, continue with both drugs and monitor the temps and if the acetaminophen stops working or it begins to have significant symptoms, hold treatment, hold both drugs for a week and then resume with a dose reduction of the dabrafenib or I'm unsure.

No, they are right. Number three is the correct answer.

Right? No, the correct answer is number three.

Yeah, and they answered correctly so I'm glad. Yes, the correct answers to continue both. It's probably not an infectious process. And I mean 101 is probably an uncomfortable fever, but he's managing it okay. And he's taking the tylenol and it gets better every time he takes the tylenol. He said it goes back to 96 he feels okay until that wears off six hours later and then he gets it again. And I told him, I said, listen, if this is really making you feel terrible, we'll hold for a week. And we would probably hold the dabrafenib for a week and let them keep the trametinib maybe going and then restart him at the same dose. But for right now, he's doing okay on it. So you guys are correct, so.

Transcript for Managing Small Cell Lung Cancer

Beth Gilbert: Small cell, I'll skip through these guys. Oh, learning objective, we're going to select therapy in accordance to evidence-based best practices. Okay. A patient with extensive stage small cell received etoposide, carboplatin, and atezolizumab front line after four cycles of this regimen. The patient should then receive maintenance atezolizumab, maintenance atezolizumab plus etoposide, two additional cycles, and then maintenance atezo or take a treatment break and conduct surveillance CT scans or are you unsure? Is that a question for you guys? Did you…

All right, so a small cell, strongly associated with heavy smoking as we all know. It's very aggressive. The medium survival within weeks of diagnosis if left untreated, 13% of all lung cancers according to the 2019 American Cancer Society, facts and figures. It's 13% but I saw a range between like 10% and 15% and I guess it's dropping a little bit.

Staging and pathology of small cell, no molecular testing. Pathology often consists with neuroendocrine features. Two stages in small cell, as we all know, limited and extensive. So limited means you can confine the disease in a radiation portal site that can be treated definitively and extensive is outside the chest or in the chest but unable to fit it into a radiation portal.

The clinical presentation for these patients. Symptoms generally have bulky nodal disease, cough, chest pressure, dyspnea, superior vena cava syndrome is often an issue. Symptoms related to metastasis common with bone pain, neurological symptoms. You probably know that brain metastasis is a very high incidence with small cell. Constitutional symptoms. Fatigue, weight loss. Paraneoplastic syndrome is often seen as well, syndrome of inappropriate antidiuretic hormone secretion manifest in hyponatremia. Hyponatremia see all the time in small cell and again neurologic symptoms.

Limited stage. If found early as in there's no lymph nodes positive on bronchoscopy then resection is what is generally done. Finding a small cell this early is pretty rare though. Best management is generally chemo, radiation. Sequential chemotherapy, then radiation only in patients with poor performance status because it's a far inferior to concurrent chemo radiation. So we have a survival curve here. Stratified by no adjuvant therapy versus adjuvant therapy. That's chemotherapy with or without radiation, and you can see a definite improvement with the addition of the adjutant chemotherapy, whether or not it's given with the radiation.

So there's questions about how often you do the radiation. Do you do it once a day or do you do it twice a day? Daily radiation generally six weeks daily. It's much better tolerated. It's logistically better for the patient. Inferior overall survival, however compared to a twice daily radiation but not overwhelmingly in recent studies. And then the twice-daily radiation cuts the time in half to three weeks but it's more toxic. Esophagitis is a big issue with the b.i.d. dosing. Again, logistically more difficult. You got to hang out where you are if you do not live close, and it's a whole day affair between the radiation dose dosages, and b.i.d. radiation is superior to daily radiation in clinical studies, 19 months versus 23 months overall survival in favor of b.i.d. radiation.

That was shown in the convert trial. It looked over 500 patients randomized to chemotherapy and they did either daily or b.i.d. radiation. It was powered to be superior for daily but it was not.

Beth Eaby-Sandy: And the take home message is they're kind of the same. Twice a day is probably a little better, but the toxicity is a lot more. If you can do the twice a day, then do it. But if you're feeling at all hesitant, don't because it's not that much better. It's kind of the same way I feel about cisplatin and carboplatin. Cisplatin is slightly better but if you have any hesitation, you don't want to kill your patient with cisplatin.

Beth Gilbert: So I mean they're both usable.

Beth Eaby-Sandy: Exactly.

Beth Gilbert: PCI in limited stage, there's a definite survival advantage. So there's strong data on that and it really should be recommended and we do recommend that. And the downsides, as we all know, is cognitive deficits that can happen in real time and as a longer term side effect, alopecia, that happens we know.

For extensive stage, this is, again, the disease cannot be fit into a radiation portal. That's their designation, the cutoff line so it varies. You can have not pretty extensive disease on your TNM score, but it still would be limited if they can fit it into the radiation portal so extensive stage.

First line is backbone cisplatin or carboplatin plus etoposide or cis, carboplatin plus irinotecan. Second line, there's several options. None of them are great and topotecan is the only chemo drug that's FDA approved.

Immunotherapy in small cell, first line, etoposide platinum which is carbo or cis, standard of care has been for 20 years. So this is the first time that the addition of any drug has shown any benefit. And so it's the addition atezolizumab once every three weeks on day one to etoposide platinum showed overall survival and progression-free survival improvement versus the chemotherapy arm alone. So this was the exciting news that Beth had referred to in small cell.

And here's the IMpower133 study showing the addition of the atezolizumab with the carbo etoposide or platinum etoposide. These are all extensive stage small cell patients who were chemotherapy naïve. Endpoints were progression-free survival and overall survival, and they're treated to progressive disease.

And here's the curve for the overall survival. Just flip through these and here's the progression-free survival.

Beth Eaby-Sandy: Again, not earth-shattering but something.

Beth Gilbert: Yeah. Actually, it's, I think, what I saw… Overall survival was a 12.3 months versus 10.3 months in improvement, so it's not that much but in progression-free survival, 4.3 months versus a the 5.2 months with the addition of atezolizumab.

So second line immunotherapy. This is the complicated scheme with ipilimumab and nivolumab, the different dosings. One is would be like the melanoma dosing and the other one is like the renal dosing at lunchtime where they were talking about the three milligrams per kilogram for the ipilimumab and the one milligram per kilogram for the nivolumab. That's the renal type dosing. And the other

dosing was the melanoma type dosing and it was complex. In the end, nivolumab was the only drug FDA approved in that setting. Although there was some activity with the combination of nivo plus ipilimumab in either one of those dose, one of those doses. But the ipi at the three milligram per kilogram was much more toxic.

In fact, I just had a patient who had progressed on front line. He took topotecan, progressed on that, and then he was going to go on nivo, ipilimumab, and his insurance wasn't paying for the ipilimumab. So nivo is the only one approved so he actually came to us from New York from here and we were able to get him the drug. I think he's getting it for free but…

Beth Eaby-Sandy: Now, Beth, did that patient get the atezolizumab in the first line with etoposide and platinum?

Beth Gilbert: He did not.

Beth Eaby-Sandy: Okay.

Beth Gilbert: Yeah. It was before.

Beth Eaby-Sandy: Yeah, because I think that's the question here is that if they're getting immunotherapy in the first line, we're not really using this in the second line anymore. But for those patients who didn't get it before it was approved for the first line, this is a reasonable second or third line option for them.

Beth Gilbert: And then here's CheckMate 032. This shows the nivo and then nivo ipi curves. And then on the far side is the pembrolizumab that also was showing efficacy, and it was approved in third line for small cell.

So back to the PCI in extensive stage. In limited stage, we do recommend that. In extensive stage, I'm sorry. Yeah, so it's recommended in the guidelines. However, the data isn't as strong in extensive stage, less of a survival advantage compared to limited stage. So there's some movement towards, “Oh maybe we should just monitor them with serial MRIs given the risk-benefit of the side effects from the brain radiation that they would get.” Our practice is 0 for 2 on that. So they developed it and really went downhill without having the PCI. But would they have had that anyway? Don't really know but I don't know is anybody… Have you…

Beth Eaby-Sandy: I think it's controversial at best in extensive phase small cell.

Beth Gilbert: Yeah. It's kind of new.

Beth Eaby-Sandy: It's technically recommended but then you can get cognitive decline. But then as you see on my slide, I'm sarcastic and say, “If I won't live longer to experience going to decline anyway so…” I don't know. Tyler, your thoughts?

Tyler Beardslee: Yeah. My knowledge, there were two studies with this. The first one was that there was a survival advantage but they didn't do abdominal CT. Oh, no, no, no, sorry. They did not do brain MRIs. So they didn't. You could imagine now you have patients who are getting PCI [inaudible]. So the Japanese revealed the study and they did brain MRIs and the patients who had [inaudible] obviously got

brain radiation. In that study, the PCI would not have a survival [inaudible]. So I think the better design study which shows us that maybe PCI isn't working here, our approach has been to [inaudible]

Beth Eaby-Sandy: Okay. Yeah, I think this is controversial at best. It's in the NCCN guidelines, but there is just not strong data for it so yeah.

Beth Gilbert: So, I mean you just have conversations with the patient and lay it all out for them and try to make a shared decision giving them the option because it's really not hard and fast.

Limited stage. So what these are… These are immunotherapy trials that are ongoing. Chemotherapy and radiation followed by durvalumab or durvalumab and tremi or placebo and phase one with chemo radiation plus pembrolizumab. Tremi is a monoclonal antibody body against a CTLA-4 if you didn't know.

Okay. And other new agents for small cell that are being looked into, a whole list of them.

Beth Eaby-Sandy: It's just a long list.

Beth Gilbert: Yeah.

Beth Eaby-Sandy: You don't have to go through each one.

Tyler Beardslee: Small cell doctors suggested lurbinectedin.

Beth Eaby-Sandy: Lurbinec. I think I have a slide on it if you go to the next one.

Beth Gilbert: Oh, the lurbinectedin. I don't see it. I don't think you do.

Beth Eaby-Sandy: Maybe I don't. Yeah.

Beth Gilbert: There wasn't one that.

Beth Eaby-Sandy: That is one of the interesting ones though.

Beth Gilbert: Clinical pearls. Atezolizumab and etoposide platinum doublet is a standard first-line therapy for extensive stage small cell. Randomized trials with other checkpoint inhibitors are ongoing. Durvalumab and the doublet has been reported to improve survival compared to the doublet alone but results not yet presented or published. And NCCN guidelines approved pembrolizumab and nivo plus/minus ipi after chemo. But really the FDA, the indication is only for nivolumab. So I mean nivolumab for the single second line.

Randomized trials of immunotherapy with chemotherapy and radiation in limited stage are ongoing. And Rova-T, has anybody heard of that, Rova-T? Yeah, I know you've heard it.

Beth Eaby-Sandy: We thought it would be great and it failed.

Beth Gilbert: It's like a Trojan horse type of conjugate drug. You probably, huh?

Tyler Beardslee: [inaudible]

Beth Gilbert: Yeah.

Beth Eaby-Sandy: Yeah.

Beth Gilbert: We'd have all this promising data…

Beth Eaby-Sandy: There was a lot of promising data and it didn't pan out.

Beth Gilbert: Didn't pan out.

Beth Eaby-Sandy: There's the lurbinectedin. I knew I had it in there somewhere, it's phase III.

Beth Gilbert: Oh yeah. Phase III. Okay. All right. So we just have their response questions. So a patient with extensive stage small cell lung cancer received etoposide, carboplatin, and atezolizumab front line. After four cycles of this regiment, the patient should then receive: a maintenance atezolizumab, a maintenance atezolizumab and etoposide, C, two additional cycles and then start maintenance atezolizumab, D, take a break and conduct surveillance CT scan, or E, unsure.

Beth Eaby-Sandy: All Right.

Beth Gilbert: Okay, good.