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<<Robert Forrester, President and CEO>>

Welcome. I guess it's [the video] so hard to follow. It gets me every single time, but I think this sort of reflects how we all feel about the work that each of us do. It's really personal we've all been touched by cancer. So welcome to Verastem Oncology event. Thank you to the panelist for joining us. Thank you all for joining us. We're going to have a great day here today.

One of the words that is really important to us as a company is audacity, that means being brave and bold. So here we are in the middle of New York. We're being brave and bold. You've all got a Boston Red Sox hat and we're proud of that. So, I expect you all to walk out of here bravely and boldly wearing a Boston Red Sox hat. I agree within a block you may want to take it off because you'll be so much safer, but please try.

You also would have noticed something different. We have changed our name to Verastem Oncology and this really reflects our focus on cancer patients. We really wanted to emphasize that for everybody and so going forward we are Verastem Oncology.

Now, who knows what a TED talk is, okay, most of you know what a TED talk is. At Verastem, we have shamelessly borrowed the idea and we have VED talks and we have various different people to come and give VED talks. Nobel Laureates through to investors, through to entrepreneurs, we have had the founder of TripAdvisor, we've had incredible people come in and we often have patients come in too. And one of the patients who came in actually about three years ago is a man by name of John, who is a mesothelioma patient and as you know mesothelioma is a form of lung cancer, the really nasty form of lung cancer.

And he got mesothelioma from exposure to asbestos actually from his dad. His dad worked in a factory with asbestos and you can imagine he came home every evening with some asbestos fibers on his clothes and unfortunately John was a baby at that point and he clearly got exposed to the fibers and then 35 years later he unfortunately is diagnosed with mesothelioma and it's basically a death sentence, there is no escape. He came in and gave this most passionate and exhilarating talk at Verastem. He looks really scary. I mean he's got his big beard. He looks like he is from Middle Earth. And he is the drummer in a dark angry band. And he said, "Well I hope you and your kids never hear my music. It is really awful." And afterwards he sent us a CD and he actually is correct about his music. He also sent us a drum skin and some drumsticks. And on the drum skin he wrote "cancer sucks." Cancer sucks, but it challenges us to be our best. And I think that is what really personifies for me and for every one of us what we are doing every single day because we know cancer

sucks. It's the worse day in your life when you're told you have got cancer. And now what are you going to do, but you have to be your best, I say the best as a patient, as a caregiver, as a family and for all of us in this room we have to be in our best to develop new therapies to help these patients because we have all been touched by cancer in one way or another and I think you saw that on the video and its what drives us every day to be at our best.

I want to recognize that there were three of our team members there [in the video], who actually are all on the back here, so Mary, Kam and Ivin, just want to stand up because they're representing the whole company, but I mean just hearing them speak, really touches me very, very personally. And because we're all very dedicated and passionate to improve the survival and quality of life of cancer patients broadly.

And for me as I think about Verastem, I am reminded of a quote from Lord Saatchi, he is another Brit, he is the founder of Saatchi & Saatchi and he said, "change happens when people who care join together to make it happen."

"Change happens when people who care join together to make it happen." That for me is what Verastem is. It's a group of people, who really care. We care differently. We care passionately about what we're doing. And everybody talks about it in this industry about being patient centric, but we are really going to care and do care differently about our patients. You're going to see that now. You can see that as we rollout the commercialization of duvelisib, we're going to talk about that throughout the day, because that is Verastem. For us it is personal. We care differently.

As I am sure you've noticed we've recently filed our first new drug application. We're a 7-year-old company. So I'm really proud after seven years, only seven years, we just filed our first NDA, that is for duvelisib of course, a couple of weeks ago, we have got priority review, which is a huge step forward for us and for the drug. And we have a PDUFA date of October 5th - that's not very far away and there is a lot of work to be done. There is a lot of work to be done. We have a countdown clock in our office, counting down to October 5th and it's not many days and it's a little scary, it's a little exciting and one of the things we're going to do today is talk about how we're going to do this.

Because for these patients with CLL/SLL and follicular lymphoma, we hope to bring them a new oral therapy and we hope to do that soon and that is an exciting and amazing opportunity. So today, this is what we're going to cover and we're very fortunate to have extraordinary collection of KOLs with us and we're going to start in a moment with Dr. Koffman, who has got more letters after his name then there are actually in the alphabet, which is clearly very impressive. And he is unusual in that, he is actually a Physician, he is also the Medical Director of the CLL Society and he is also a CLL patient and he is going to talk about his experiences as a patient and as a physician. Then we're lucky to have Lori with us, Lori Kunkel, the former Chief Medical Officer of Pharmacyclics. I am sure many of you know Lori. She is going to talk a little about sort of the history, the evolution of blood cancer treatments.

Then Jen Brown, just flown down from Boston and hopefully you have got a Boston Red Sox Hat with you as well. And she's at Harvard and also at Dana-Farber Cancer Institute. And she's going to talk about the unmet needs and the role of PI3K inhibitors broadly.

Then Dr. Flinn, he has flown up here from down south and he's going to – at Sarah Cannon - and he is going to talk a little about the DUO Study and the DYNAMO Study and where Duvelisib might fit in as well.

And then we will change topic slightly, with Dr. Horwitz, he hasn't traveled very far at all and I definitely want to see you in a Red Sox Hat. And, he is going to talk about T-cell lymphomas and then finally we are going to end-up with Joe Lobacki, who joined us a few months ago, the former Chief Commercial Officer of Medivation. And he is going to talk about unlocking the potential of Duvelisib and the path to the commercial launch.

Following that, we will have a panel and everybody in the audience are able to ask questions, we've also got a number of our team here. So we got Joe, we got Julie [Feder, CFO] with Steve [Bloom, Chief Strategic Officer], Diep [Le Chief Medical Officer), Jon [Pachter, Chief Scientific Officer] and Nadeem [Mirza, SVP, Corporate Medical Affairs], all of them are available for questions as well at the end. And then probably most importantly after the panel we're going to serve you with lunch. That I know is exciting, it's reason to stay of course.

So, that is the agenda for today. So, let's get started with Dr. Koffman.

<<Brian Koffman, Physician, Medical Director-Chronic Lymphocytic Leukemia Society and CLL Patient>>

Good morning. And I want to start by thanking. I'm very grateful for the opportunity to be here. I'm grateful to Verastem, thank you for the introduction Robert. And, I'm grateful to have your attention to sort of give what I think is somewhat of a unique perspective. Everyone of us in the room has been or will be a patient. Cancer will be at everybody's kitchen table. I want to talk about my experience from kind of both sides of the table.

I have some disclosures. I'm here today because I started on a Phase 1 trial. I'm an early adapter as you'll see of a new oral drug at that time was only known by its initial PCI-32765. It's now known as ibrutinib or IMBRUVICA.

And, I'm planning to be here much longer. I got six years out of ibrutinib. A good run, but it stopped working for me and I'll go over that a little bit. On Friday, I was discharged from Seattle Cancer Care Alliance Hutch for a CAR-T therapy. Chimeric Antigen Receptor T-Cells, which is not for the faint of heart but it got me to no evidence of cancer in my blood, my marrow or my lymph nodes. So, I'm planning to be around a lot longer.

So thank you. So my bias is towards getting expert care, there's clearly survival data that suggests that. Novel therapies and I going to talk about why that in keeping your options open and I'm going to – the way I'm going to do that – let me just tell you a little bit more.

I'm a physician, a patient, an advocate, a retired professor, teacher. Writer. I have a blog that's had about a million and a half hits. I'm the Founder and the Medical Director of a small but mighty not-for-profit the CLL Society. We punched way above our weight. We have impact around the world. We have papers at ASH, EHA, ASCO. There's three people in the organization, one paid employee, and I'm not that paid employee.

And I can no longer say I am a cancer patient, because I have no evidence of cancer in my body. I'm now a cancer survivor. So our learning objectives because I have a background in med-ed is I'm going to use one case, mine, and some research that we've done, some of it's embargoed, so I can't share it with you. But some research that we've published at ASH, to illustrate how patients make decisions. What's important to patients on their journey in CLL.

We're going to recognize, what they want and don't want in therapy and we're going to weigh how patients look at novel therapies. So, this is a painting my son did of me when I was first diagnosed. I had the beard to hide the lymph nodes and stuff I had to grow it heavier later on. And, this was to remember me, because when I was diagnosed 12 years ago, the chances of me being here were single digits. Really, very low, when you look, there was no options. There was no ibrutinib, there was no venetoclax, there was no new novel therapies coming at all. There wasn't any medicine at that time, even the chemo that had shown any survival advantage at all, nothing worked, it is an incurable cancer.

So, I refused treatments, I switched around Docs, I got into clinical trials. I hired experts, I always thought about - you know going through CLL is little bit like a chess game. You got to say not just, what is my next move, what is my next move, my next move, my next move. You got to think along those lines, and not a trivial thing was getting insurance to pay for all of this stuff. And I'm very big on support groups, we have 24 different support groups around the country now, peer-to-peer support groups.

So, you talked about this, and the day that you never forget. I mean everybody knows this day when you get that result. So, I'm big on paradigm shifts. And this is what happens like you're fine and then you have cancer. So for the people who have a little bit of a science background, let me just say this is bad, very bad and worse.

These are the worst prognostics. CLL is a very interesting disease because about 25% to 30% of people will never need treatment and do fine and have a normal life expectancy. And others, are going to need immediate treatment and until the breakthrough with novel therapies didn't do very well at all, well I was in that group but there was no breakthrough in novel therapies.

So these are Kaplan Meir Curves, they're looking backwards they don't look like this anymore, but if you look down there in the yellow, you see my chances of being alive in five years was about 5%. I'm here 12 years later with no evidence of disease. I grew a big beard, my patients were starting to say what's wrong with you Dr. Koffman. You don't look so well. I grew the beard to hide my lymph nodes.

And then I was on call one night and I'd had a blood count done and I got a call and said Dr. Koffman we have a critical lab level on Dr. Koffman. And my platelets were single digits. I had ordered blood count because I'd been bruising and stuff like that. So, I ended up in hospital and I developed an auto-immune complication of CLL where my body – not only is your immune system suppressed, it's perverse and it attacks, it can attack the red cells, it can attack white blood cells and it attacked the platelets in my case.

And my platelets were just plummeting. So, I tried all different kinds of therapies, which didn't work. I ended up with an emergency splenectomy. I bled out. Lost half my blood I'm going to go through this slide quickly. I looked like I was about six months pregnant.

Then finally, I made a cold call to a CLL expert who figures – majorly in my life Dr. John Byrd out of Ohio State and I started on rituxan and cyclosporine combination. So, I'd had no chemo at this point. The CLL was growing but it wasn't killing me. The ITP was nearly killing me. My bone marrow, on these two drugs, these are not chemo drugs. Okay, one is an antibody, and one is an immune suppressant that's been shown in some minor papers to have some effect on CLL.

My bone marrow got better, my counts normalized. And it just tells you that no two CLL patients are alike. I got this tremendous response – was unexpected. So, I went for a transplant, because I was 56 years old at that point. It seemed like there was nothing around that was going to help me but a transplant was the only thing that offered a potential for cure.

And, I started to tell my story, my kid said stop emailing everybody dad. Start blogging, you are so old fashioned. So, I started to tell my story. In being a physician and being able to explain things in lay terms that got a big following and like I say it – it's now maybe a 1.5 million people have seen the blog and stuff like that.

This is a picture my son drew of me and if you count there is five different IV's running into me at the same time when you're getting the transplant. But, I relapsed, quickly I rejected the graft. I had the ITP and the CLL back. So, what do you do. So, I kind of futzed around with things.

And one thing in the CLL, world if you've ever lived in it or researched it at all, you find that, there's no agreement between any people. I mean, you go and talk to the experts at Dana-Farber who I deeply respect and then talk to the experts at UCSD, they're going to disagree

about what to do, talk to the experts at MD Anderson, but there was this brief moment in 2011 at the American Society of Hematology meeting where everybody agreed and there were these two new drugs that were just initials PCI-32765 and CAL-101 idelalisib, which was the first PI3-Kinase Inhibitors.

And everybody, said wow these drugs, I mean they're tiny numbers but they're so exciting. There was all this optimism about this that something was new and I said you know I got to get me some of that. And that's what I did. So I leveraged my advantage. There was this paradigm shift, there was again early adopters. I jumped into a Phase 1b/2 clinical trial with John Byrd at Ohio State.

Ask your doctor if taking a pill to solve all your problems is right for you. So, this really worked for me. I've now been on 71 months on ibrutinib, tremendous quality of life, I have been able to travel around the world, start this not-for-profit improved energy. Side effects, I was one of the lucky ones. Not everybody is this lucky, but the main side effects I got was some bruising and brittle fingernails.

So, cancer, brittle fingernails you make the decision. But I started to relapse, and they can test for the relapses very early. About a year and a half ago but my numbers were climbing up but they were climbing slowly first. I left the trial at Ohio State on February 19. Nine days later, I was at the Hutch because my cancer was really starting to accelerate and take-off.

And obviously I'd done prep work with insurance and other things to set step-up and again I'm honestly, levering my advantage as the physician, have the contacts to get in touch with people. But, I was in the trial at the Hutch for the CAR-T. This is the second trial that I'm in and I'm one of the last patients in that trail. They are about to close that trial.

So why did I choose CAR-T after this? Because my cancer was changing, was mutagenic. It's clonally unstable, I wanted to keep my options open because there's all these novel therapies. CAR-T has these windows where you can get in and then you can't get in. They are very small because each drug is bespoke. So if I didn't get the CAR-T now, and let's say I needed it in a year-and-a-half from now, there might not be a trial for me to do. There might be a problem with Medicare insurance paying for it because I may be on Medicare at that point.

So it seemed to me – and then there's other drugs that are in the pipeline like Duvelisib, there's drugs like Venetoclax other options that would be available for me if the CAR-T stops working but not the other way around. So that's why I say like a chess move. You got to think a couple of moves ahead.

The downside is that CAR-T keeps getting better. I mean there's been – just this week there's a couple breakthroughs and how they're looking at the memory cells and other things like that. It's still a – the art and science is still in an early phase, it's quite toxic, I had

two admissions that I wouldn't wish on anybody, I developed a blood clot, I'm giving myself shots daily now, I'm anemic, I've got inflammation. But on day 28, there was no detectable CLL in my blood, marrow or node. So it's worth it.

So during this time I've been sort of trying to give forward and talking to hematologists we set up not for profit. Last month we had 85,000 page views for this orphan disease. This is some of the things we did. I just want to emphasize quickly here the expert access program. So people, let's say who live in a rural community who don't get an access to a Dr. Jennifer Brown, or a Dr. Ian Flinn for their CLL, they can go in a HIPAA Compliance Skype type setting and have 30 minutes of face time with one of these doctors. We offer that as a free service to the patients, and Verastem is underwriting that. And that's been incredibly exciting for the patients and been life-changing for those patients.

We are doing research, we have papers at ASH, ASCO and ESA. I think one of the things, take a look in the mirror there and you take a look at the doc here, okay. We set up the CLL society here, this is the research we published at ASH. I just want to point out where patients get their information, this is based on a research of about 280-page American patients. And you can see that it's nice to know that doctors are number two on the research, where patients get their information. Websites are number one.

Are patients willing to take a medication lifelong without the potential for cure? I think this was surprising data to some people 96% of patients said they were willing to take a medicine. I think this is also surprising, are you willing to take a medication with high risk but with the potential for cure. And we can find that the numbers were pretty low for chemo, CAR-T and bone marrow transplant. We've broken that down and there'll be more data on that at ASCO.

So our minor concerns are, we don't care what happens in the infusion chairs and things like that. We think our doctors are going to get us through that. But our major concerns are once our bone marrow is damaged through chemo immunotherapy it's game over. If you don't have a good bone marrow, or if you get a secondary cancer, or if you get a life-threatening infection, it's game over. So that's what worries us and that's why we're excited about novel therapies because we're in this for the long run. I don't care if your studies show that patients don't care about response rates, they care about overall survival and progression free survival. So what we want is less toxic therapies that can be used, frontline and relapsed. We want to have more options when we do relapse because almost all the targeted therapies may not be completely durable, especially in high risk patients. And chemo immunotherapy should be reserved for the patients where it's most appropriate for.

Curative therapies may be possible, I think, with combinations either cellular or other combinations that's where I see we're going. So I have compiled my learning objectives here. We use one case report, mine, recent online survey to illustrate how patients make

decisions get our information, what patients want and don't want. And we will look at how patients weigh their risk inside and outside of the trial.

So thank you very much for your attention from the sunny beaches of California. And I'll be around after to answer questions. And I look forward to the shaking hands and meeting with most of you.

<<Robert Forrester>>

Thank you very much. That was a great way to start the session Dr. Koffman thank you very much. That was really, really inspiring. So thank you. Dr. Kunkel over to you.

<<Lori Kunkel, MD, Former Chief Medical Officer, Pharmacyclics>>

Well that is a tough act to follow. But I too am in a very unique position. I started out as a bone marrow transplantee at UCLA back in the 90s. I went into industry and I can truthfully now say I have been working decades in this area. And Ian Flinn can attest to that because we started out, he was an investigator and I was working on Rituximab back in 1997. So there's lots of us who have really dedicated our lives to bringing these therapeutics forward.

So really what I'm going to try to do is set up not only the history of where things are going, but also try to get a good understanding of why these new therapeutics matter and why there is more room for new therapeutics.

So here is a flow chart per se of the progress in the treatment with CLL. We started out in the 60s and 70s with DNA damaging agents, alkylating agents. And in the CLL we got about a 30% to 50% response rate and in CRs they're very rare. And these responses would last maybe a year or two.

In the 80s we actually developed some more selective therapeutic for lymphocytes and these are purine analyzed fludarabine, which is the most commonly used as well as pentostatin and fludarabine. Now these bumped up the response rates and actually bumped up the CRAs and improved the progression. And then with the advent in 2000 we began to combine the purine analogues and the alkylators together and really started improving the durability of responses up to about three years. Rituximab was approved in 1997 for follicular lymphoma but as a single agent in CLL it took three times the amount to see an effect, which was prohibitive. But it was very effective in combination.

And so the we had to add then a chemo immunotherapy. We added Rituximab to FCR the purine analogues and alkulators and now we're getting in frontline durabilities that were going on to about five years. So it really added an additional two years to that combination. Now FCR is relatively toxic and in randomized trials they saw that if you were an elderly

now the find is greater than 65, which is getting too close to home. But if it had comorbid conditions, it's actually prohibitive to administering that.

So we have a large group of patients who cannot get this intensive chemotherapy. So it was quite awhile actually before we saw the advent of small molecules that were really aimed at targeting the B-cell receptors or targeting B-cells signaling pathways. We had actually tried for many years with multiple products to hit the BCL2, but it really wasn't until Venetoclax came around as we develop that molecule. But the biggest breakthroughs were actually targeting the B-cell receptor and coming up with BTK is as well as PI3 kinase inhibitors.

So I'm going to group the rest of the talk into the big breakthroughs and the take home messages of why this matters. So as single agent most patients responded to these targeted agents. So you're getting response rates of 50% to 80% with a single agent. And that sometimes gets lost on people. The durability now can be years. So these patients can have PFS as the single agents that are going on three, four, five years, which is as Brian alluded to pretty remarkable when you think it's a pill a day.

The other thing that is emerging or has emerged is that each of these agents has a unique safety issue. So there is no free lunch here the BTKis we identified that they are associated with bleeding which actually they do, probably they are BTKi, but they're not have target effect. And it also has an associated atrial fibrillation. The BCL2 inhibitors, their biggest drawback is that they cause tumor lysis syndrome, they also have some other common side effects with the other agents.

And the PI3-Kinases emerge to have rare but severe colitis and pneumonitis, which are attributed to more of an auto immune effect. The other big take home message is we do know that resistance will occur. And this is through either up regulation of alternative pathways from what we're targeting. So in the case of BTK we'll go through those pathways, or you develop a specific mutation to where the TKi bind to.

So this brings us to where are the evolving unmet medical needs in CLL. And this is how a developer thinks, it's like where do we need to go next. When is and Brian you set me up amazingly is that there is a group of patients with inherent resistance to chemotherapy agents. And these are the del 17p patients or patients with a p53. They acquired resistance we identified in BTK to be a C418S point mutation. Also there is a point mutation occurs downstream. In venetoclax or BCL2 inhibitor, there's an up regulation of an alternative pathway through MCL1.

The other unmet need is and I think Jennifer is going to talk more about this is how to appropriately sequence these target therapies. They all were approved to be on the same timeframe and we're really going to need to spend some time on figuring out that sequence.

And then the fourth big bucket is the tolerability and this is because they're on drug for so long, there is a cumulative safety, we're still – there's a cumulative safety with Ibrutinib it doesn't occur in the first month they can occur over the lifetime of the drug.

And with all of these agents, we still have that inspection in this and so we have to learn to manage those as we move forward. So just a few minutes on the Del17p because this is really helped us to push these agents forward, we knew from 2000 that genetic abnormality is really influence survival in CLL, it really wasn't until we got into chemo combinations that we knew that reason so the graph on the left is different mutation with the Del17p being this one here.

And shows you in the overall survival that these patients live about 24 months so this is overall survival on average and the reason for this is because its inherently chemoresistance. So you can take a patient and give them FCR which is arguably the most potent combination of chemo that we had and their overall survival was about a year from the start of therapy.

So this really identified a population of patients that needed better therapies and we knew they could not be chemotherapy, they were going to be resistant. And so the big breakthrough when we got the initial small molecules was that we thought they were actually very active in these chemo-resistant patients.

And that enabled us to bring our development forward probably much more rapidly. Now fortunately when you're newly diagnosed these – the reasons they're only occurring about 5% of population, the relapse population is really 30%, 40% in some cases. So all of the new drugs overcome this inherent chemo-resistant, they're all active in it. And it's not that they're more active in this in patients who don't have these genetic abnormalities, the fact of the matter is they are active where chemotherapy is inactive.

So if you look at this data and this is from Susan O'Brien from early trials of Ibrutinib, if you don't have one of these 17p deletions, this is showing that this is a progression-free survival going on like you know three plus years. If you do have one of the mutations, you're showing still a relatively good progression-free survival, Brian and I just showed you a slide with FDR where half of the patients are deceased at 12 months. And so this enabled us to fast-track the development in this population. But they don't do it well if they don't have it so this is a high unmet need and the result with the PI3K and the Venetoclax they're very similar, they're all active in these patients that they do relapse.

So what are the acquired resistance mechanisms and I think this is one of the areas that we still have quite a bit of work to do. I don't even have the PI3K up here because we really have some more work to do on that. We identified relatively early what the mechanisms of resistance were with Ibrutinib, there is alternative pathway activation through NF-kappaB and PIK3-ALT, there is a specific point mutation it incurs in about half of the

patients call that C418S mutation and that makes most BTK inhibitors inactive. And then there's other downstream point mutations in the B cell receptor signaling pathway.

So with Venetoclax the major mechanism of resistance is an upregulation of Mcl-1 and Mcl-xL. Now why does this matter, once you identify the mechanisms of resistance, you can figure out which combinations are going to be more effective. So that's why it matters to figure out mechanisms of resistance. So this is work – and again Brian alluded to this is that we can pick up mutations much earlier than when the patient becomes clinically symptomatic of relapse. And so this is showing data on how the patients acquire this mutation. And really the initial clone can be detected at an estimated median of 9.3 months before relapse.

So we can identify the patients who are developing mutations, we haven't gotten there on the alternative pathways but we will begin to think about when is the best way to either switch therapy or add another therapy.

So how do we address this inherent, both inherent and acquired resistance. So one way is you preemptively target with alternative therapies before the patient becomes acutely ill with refractory disease. So in the case of relapse you could say we're going to pick this up, nine months before we're going to add something, we're going to switch something but we're not going to continue on the course until the patient becomes highly refractory. And this is being studied in clinical trials and I think we'll talk a little bit about that.

The other which is one side is moving these agents up earlier in the treatment of disease, as I mentioned Del17p only occurs in 5% in newly diagnosed patients. And we do know that the mutation rate doesn't seem to be occurring at the same rate, if they get Ibrutinib upfront as in the relapse setting. Now why is that, is it the natural history, is it because those patients are no longer getting alkylating agents and damaging your DNA? We don't know but that's under investigation right now. So that is another way of avoiding resistance.

And then the third which you're going to hear about is the combinations of novel-novel agents, for example here we know that Duvelisib really can prime apoptosis which is the main mechanism for BCL-2 inhibition and would make a really interesting novel-novel combination.

So side effect mitigation, these patients are generally over 65, they generally have co-morbid condition. So you have to take that into consideration on which therapy, so having multiple options is really an important thing. Afib occurs I think in over 65 population, my cardiologist told me like one at a five people which is remarkable. So that's a common without Ibrutinib but that's going to limit perhaps your selection of Ibrutinib in a patient.

Infections remain a risk but the importance there is if we manage this with prophylaxis we can certainly reduce that risk. And then we are really learning more about the immune-

related effects and how to manage them. So I think the more these agents get used the more we learn the more we manage them. The sequence of therapy is going to be an important determinant as we combine these different agents.

And how well they actually adhere to the regimen is also going to be very important. And I would pay attention to that because there's a big splash at ASH last year on combination that when you look closely 20% of the patients didn't make it through six months of a combination. So that is going to be a recurrency and can they actually get the combination. And then if recognition of the patient goals, are we really going to – is this curative or is this really controlling symptomatic disease?

So I'm going to switch gears and this will be much shorter because we haven't had as big of an evolution in follicular lymphoma. And so currently in follicular lymphoma, the first-line treatment remains chemoimmunotherapy. So this is either going to be a CHOP-R combination or a R-Benda and patients get generally very durable responses but they ultimately relapse. And then depending on the condition they'll switch them over if they got CHOP-R, they'll get R-Benda second line.

And then that's it, we are done. So what are the novel agents? So lagging behind CLL, the only novel agents that have been approved by the PI3-kinase inhibitors. So we have two approved, one oral, one IV and it looks like we're going to get a third approved with a dedicated company in PI3K space.

And then we have rituxan and then we have rituxan and steroids. So both again, the agents so this is a big unmet need, follicular lymphoma is not curable and I think again we need to look about the efficacy of the other agents, Ibrutinib was not particularly efficacious in follicular lymphoma.

Only 20% of patients with chemo-resistant follicular lymphoma respond to Ibrutinib monotherapy. So this is in contrast to the PI3K where you're getting over 58% responses and then median PFS is very short, it's 4.6 months. So that and the Venetoclax data is also very similar so unlike CLL, the BTK inhibitors and Venetoclax are not particularly active in follicular, which divides the biology and the use of these agents.

So the Ibrutinib targeted where are we going with this and why does it matter. The average age of patients in the U.S. is 67 years old, who are still using R-based chemotherapy. The drugs that worked in CLL are inferior to PI3K and we are still establishing treatment modalities in these chemo-refractory patients. And I think the combination therapies with PI3K are going to hold particular promise for future treatment.

So the summary is, there is little evidence today that these will be curable, hopefully CAR-T may have an impact on that. The infections and cumulative side effects remain an issue, but we are developing new management techniques. Most patients aren't going to achieve a CR and the patient goals are going to be paramount. And so we need to really be thinking

about how to maintain disease control as we evolve to safe and tolerable combination regimens that can be used earlier in the disease course.

And this is my last investor conference at Galapagos in 2014, and they didn't ask very many questions.

<<Robert Forrester>>

Thank you very much. Are you implying that investors are like lizards? I just hopefully not. No comments. Okay, we'll move right along. Just one – just one aside, all these slides will be available later today on our website. So I know some of you were taking pictures, but they will be available to you later today. This is a great setup for Dr. Jennifer Brown to come and talk more about PI3K. So Dr. Brown?

<<Jennifer Brown, Associate Professor of Medicine, Harvard Medical School Director, and Director, CLL Center of the Division of Hematologic Malignancies, Dana-Farber Cancer Institute>>

Good morning, everyone. I'm very happy to be here, have the opportunity to talk you about PI3 kinase inhibition and its important role in CLL, and Duvelisib in particular.

So as you've heard, we're moving toward a chemotherapy-free future in CLL and this has been largely because of the advent of the oral inhibitors of targets downstream of B cell receptor pathway. And these targets include BTK targeted by Ibrutinib, PI3 kinase targeted by Duvelisib and Idelalisib, and BCL-2 targeted by Venetoclax. We've heard a lot about BTK and BCL-2 inhibitors and not as much about PI3 kinase recently, but I'd like to remind you of the great importance of this pathway in this disease.

So the PI3 kinase is shown here in orange and it serves to integrate a large variety of signals both to the B cell receptor as well as from the microenvironment, including signals to CXCR4 and CD40. And all of these signals contribute to the survival and proliferation of the CLL cells leading to relapse and progression.

Now the PI3 kinase comes in four different isoforms; alpha and beta have broad expression and we knocked out in mice are lethal. Delta and gamma however have more limited expression in Leukocytes, the most important in hematopoietic cells and delta in particular is important in B cells, and gamma is important in myeloid and T cells. And Duvelisib of course inhibits both delta, targeting the CLL or follicular lymphoma cells as well B cells, and it also inhibits gamma, targeting the microenvironment that supports the survival of these cells. And we know that in the microenvironmental misuse is often where relapse and resistance are engendered.

Just a few more comments about the singular importance of the delta in B Lymphocytes from the knockout mice. We know that signaling is abrogated, downstream of the B cell

receptor, downstream of cytokine receptors and downstream of receptor tyrosine kinases in B cells. The reduced maturation of a variety of types of important B cells, lack of germinal centers in which B cells develop, reduced immunoglobulins and reduced response to infectious stimulus. Now deletion of alpha, beta, and gamma has no overt effect on B cells. But as noted, gamma is very important for myeloid and T cells, which affect the microenvironment.

Now Duvelisib in vitro will inhibit PI3 kinase signaling potently and induce selective dose dependent killing of CLL cells, as shown here. In the Phase 1 study, Duvelisib dosed in CLL is 25 milligrams twice per day was shown to completely and continuously inhibit delta and approximately 50% inhibit gamma. And this translated into an excellent progression free survival estimated at 59% at two years in this population of relapsed/refractory heavily pretreated high-risk patients.

And in this study, we had good evidence of Duvelisib inhibiting its target in patients. You can see reduction of Phospho-Akt by the drug again in patients as well as inhibition of serum factors made by the CLL cells shown here. We also know and it was shown in this study that Duvelisib also inhibits the serum factors made by the microenvironment that also support the CLL cells. And so a potent effective drug - where in CLL.

So there are different patient populations for different inhibitors. And even though these inhibitors are not chemotherapy they have very significant side effects unique to each class of drugs. For example, BTK inhibitors, Ibrutinib in particular, cardiac comorbidity is a significant problem. You've heard about atrial fibrillation, we also see congestive heart failure. And this is particularly a problem with increasing age in older patients, and we know the median age is diagnosis of CLL is 72, so most of our patients are in their 70's and 80's. Leading risk is also a significant problem and we worry about combining anticoagulation with BTK inhibitors because of the risk of bleeding. So none of that is a problem for Duvelisib.

And then for the BCL-2 inhibitors, Venetoclax, renal failure is a problem because the primary risk there is tumor lysis. And in order for us to be able to safely manage that we need the patients to have good renal function. And of course with increasing age, there is natural decline in renal function. And then the patients are not so enthusiastic about frequent clinic or even hospital monitoring for more than a month, if they can avoid it. Again, not a problem for Duvelisib.

Now for patients who are BTK or BCl-2 inhibitors, what's the natural history of that over time? So we're starting to get more data on this. These are data from the Ohio State University with their up to four-year experience with patients treated with Ibrutinib in the relapse setting. And you can see that over that time in the blue curve, about a quarter of the patients discontinued the drug for some other event, these are mostly toxicity, infections, cardiac problems, bleeding.

In the grey curve, you can see that as we observe for increasing time there's a steady increase in CLL progression, which has reached 19% at four years in this largely clinical trial based population. And so both of these categories of patients are becoming an increasing unmet need in my personal clinic, the patients who need therapies.

Here you can see that the adverse event discontinuation is much worse with increasing age. The patients over 80, 70% discontinued by a year and even those in their 70's have significantly greater discontinuation for adverse events than the younger patients. And after discontinuation, survival has not been great. You can see in the gray curve, these are patients who progress with CLL on Ibrutinib, their median survival is less than two years. So clearly new therapies are needed for these patients.

If we look at the real world experience, this is a retrospective analysis that was presented by Anthony Mato of over 600 CLL patients with a median follow-up of 17 months. And you can see that in this largely non-trial population the discontinuation rate for Ibrutinib was 42% with the median time to discontinuation of six months. And half of this is due to toxicity with 10% to 20% due to CLL progression. And so those numbers are significantly higher than in the more trial based single center data from Ohio State, indicating what is happening in the community.

And so Venetoclax is an option for these patients, but what do we see with Venetoclax in this setting? Well, the median duration of therapy with Venetoclax was 16 months in relapsed/refractory CLL patients in this pooled analysis from multiple studies, so really not very long in terms of the long-haul for patients. And the estimated progression free survival similarly was about 58% in two years. So we're looking at about two years for patients from Venetoclax, not that long, needs more therapies here too.

So role for Duvelisib in CLL. We have these emerging growing unmet need populations, in particular a large and growing population intolerant of BTK inhibitors, particularly the older patients. And my group actually has shown that the immune related toxicities of PI3 kinase inhibitors are significantly more common in younger patients and less common, less of a problem in older patients and so that works very well for Duvelisib in older patients. There's a steadily increasing population progressing on BTK inhibitors and we know that this is an unmet need population with aggressive disease.

Venetoclax has been very challenging to give in a community setting. And as you know, it has not been widely adopted since its approval likely because of the barriers to initiation. Duvelisib in contrast is easily given. There are no infusions required. It's highly effective. It has a novel mechanism adding gamma to delta. And personally, I am very much looking forward to the opportunity to use Duvelisib for my patients. Thank you.

<<Robert Forrester>>

Thank you very much. Well, hopefully we can get Duvelisib to your patients relatively soon. We are obviously working very closely with the FDA on that. Dr. Flinn, welcome. So you're now going to build on the PI3K story, build on Duvelisib. You actually treated the very first patient with Duvelisib and you want to talk a little bit about the DUO study and the DYNAMO study. So thank you.

<<Ian Flinn, Director, Blood Cancer Research Program, Sarah Cannon Research Institute, and Lead Investigator of the DUO and DYNAMO Studies>>

Thanks. Thanks for having me. I wanted to start out and then walk you through some of the data here. And then second, I wanted to start out by saying – that I think the data we're going to show today is important. It's important for all the reasons that we just heard from the previous speakers about the need for and improvement in our armamentarium [where there are new patients], who for many years in different therapies for these patients.

As Robert said, I – one of my patients, who is the first patient to be treated on the early Phase 1 study with Duvelisib. I stayed with the program through the Phase 2 and through the Phase 3 data because of the efficacy I saw and the tolerability I saw in my patients and building to bring this drug to patients in Nashville more than seven or eight years ago now. So it's been very important to have this drug available for our patients.

Before I came here yesterday, yesterday evening I had clinic, one of my – one of the patients I saw was one of the patients that was on actually went on early Phase 1b studies with Duvelisib. I didn't calculate all the number of cycles that we have given him but I think he is probably more than 4 years out and still on oral therapy, continuous therapy and today he left on a trip. I spent most of my time in clinic talking about what he is doing the rest of his life, traveling around the world and all his trips and that he is not tied to an infusion chair, he is not tied to my clinic, I see him once every three months.

So I think this is an important therapy for our patients. Earlier we heard about this is a novel both PI3K-delta and gamma inhibitor. This is just data showing that it blocks the – this is data showing that it blocks both the gamma and delta Isoforms at clinically relevant doses and why might that be important, because not only is it having an effect, a retro-effect from the malignant cell, the malignant B-cell in this case is both the delta and gamma in addition. That's working on the microenvironment, this is what sets this drug apart, it works, this microenvironment is providing a survival signals to the malignant [tumor] cells and we think this maybe an important differentiation for this drug.

The DYNAMO study was said to start a little bit over a year ago now. This is a Phase 2 study for patients with single agent Duvelisib and patients with relapsed/refractory follicular lymphoma is important from [indiscernible] (0:58:10) – it is important to note that these were [indiscernible] (0:58:14) and by that we mean, refractory to both chemotherapy and Rituxan. So different than some of the other studies that have recently been published, so very difficult to see the patient population.

The design is really pretty simple, it's 200 patients on 25 milligrams of Duvelisib given twice a day continuously until patients either progress or had unacceptable toxicity. The primary endpoint of this study was overall response rate. And, so the key secondary endpoints included duration response, progression free survival and overall survival. This is the response rates and top part of the slide we are seeing the overall response rate as judged by an independent response committee, what we saw was a 47% overall response rate that really held up amongst the different histologies, on the bottom part of the slide is the investigators' judgment of response, which was a little bit more robust than the independent response committee. These responses were rapid. So people responding by the time of their first evaluation, which was at two months.

Importantly, this data met its primary endpoint. So this was a positive study with an overall response rate of 47%. This is a waterfall plot depicting the – basically the decrease in the sum of the size of the lymph nodes. The different colors represent the different histologies. What you may note is that the overall, pretty much all patients more than the majority of patients responded in some fashion other in terms of their lymph nodes reducing. So 88% of patients had reduction of their lymph nodes and that was in again – that carried across the different histologies.

We heard earlier, some on the earlier speakers about some of the potential toxicities we know that with PI3K kinase inhibitors. There is a known toxicity profile that occurs in this class of drugs. And we – so we looked at those carefully that these are adverse events of special interest. This drug did show evidence of some pneumonitis and colitis and other adverse events that we would normally associate with PI3 kinase inhibitors, but the important point is that very few of these adverse events led to discontinuation of the drug. So most patients were able to stay on therapy.

So I think that that in a conclusion about the DYNAMO study, that this demonstrates that Duvelisib is a very active agent in patients with low grade lymphoma, about 47% of patients had a response, the vast majority of patients had reduction and some reduction in their lymph nodes. Importantly, the adverse event profile was exactly what we had seen in the Phase 1 and carried over to Phase 2. There was no surprises in the safety profile.

So and I think we also heard a little bit earlier about where does this fit in the treatment in the treatment paradigms as Dr. Kunkel, I think pointed out earlier we haven't made as much progress in follicular lymphoma as perhaps we've made in CLL. We're still largely using chemotherapy with antibody-based therapy as our frontline treatment in follicular lymphoma and low-grade lymphoma such as bendamustine, rituximab.

Maybe it's R-CHOP, the second time you may perhaps, you reverse those therapies. So someone who got BR will get R-CHOP. Unfortunately some of the other modules, BTK inhibitors, venetoclax have been disappointing in patients with follicular lymphoma. So we – so at this point, we really need new therapies for this patient population in PI3 kinase

inhibitors has demonstrated activity in this patient population. I think Duvelisib maybe an important new part of our armamentarium for these patients.

Next, I'm going to switch to the DUO trial. So the DUO trial was a randomized Phase 3 trial in patients with previously treated chronic lymphocytic leukemia. The design in the trial is actually also pretty simple on patients with at least one prior therapy were randomized to either receive Duvelisib at now standard doses of 25 milligrams twice a day continuously, until progression or they were received Ofatumumab. Ofatumumab, the anti-CD20 antibody, was given at the labeled dosing and schedule.

If patients progressed on Ofatumumab, they were able to crossover receive Duvelisib. And so 89 patients in fact did crossover from Ofatumumab to receive Duvelisib. The primary endpoint of this trial was progression free survival. We did look at overall response rate duration of response at overall survival. I think it's important to realize in a crossover study design like this, where we allow patients to crossover, really that's going to confound some of the overall survival analysis.

This is the progression free survival curves for patients that went on to this trial as judged by the independent response committee, what we see is substantial improvement in progression free survival for patients who are on the experiment of arm with Duvelisib versus Ofatumumab. This is highly statistically significant. The hazard ratio was 0.52. So it's substantial. So DUO met its primary endpoint of improvement in progression free survival.

We also looked at what investigators thought. What their impression of the progression free survival was, as you can see it reinforces what the independent response committee was. In this case, the hazard ratio was 0.4 in a little bit – in a very highly statistically P value. I guess the other thing I want to mention is that patients – those patients who were treated with Ofatumumab and then progressed and switch to Duvelisib, they did just as well as the patients who were initially treated with Duvelisib. So those 89 patients – the 73% of patients responded and the progression free survival – the median progression free survival is about 15 months. So I think that was – that's important data as well.

It looks – it turns out it really doesn't matter, if we look that all those I mean Lori went through some of the risks factors like 17p deletion and so forth. That might protect for a less response. It turns out that all the different subgroups of patients on this trial benefit from this therapy. So 17p deleted or mutated, whether you were over 65 or under 65, whether your disease was relapse or whether it was refractory, time to last anti-cancer therapy, I mean held up the Duvelisib improved things for compared over to Ofatumumab all these subgroups.

This is one of the secondary endpoints. It's looking at overall response rates. What we see is that, on the left is overall response rate, and on the right is lymph node response rate. So substantially higher overall response rate nearly 74% versus 45% that difference is even more magnified if we look at just a lymph node, so these large bulky lymph node. There

was a lymph node response in 85% of patients compared to just less than 16% with patients with Ofatumumab. Importantly, this overall response rate held up again in that hard to treat patient population to 17p deleted patients where it was on 70% versus 43%.

This is the adverse event profile. I think it looks not too dissimilar to what I showed you with the DYNAMO trial. The number that we did – we do see some of these adverse events that are associated with PI3 kinase inhibitors. Fortunately, they – this is very rarely led to discontinuation.

On the bottom lists out some of the specifics, it's important to note that there were two patients who developed Pneumocystis pneumonia. They developed Pneumocystis pneumonia, because they weren't taking the prophylaxis that was required by the protocol, so that we feel that's a preventable toxicity.

So in conclusion about the DUO study, I mean, I think this is a large randomized Phase 3 trial, it clearly demonstrates the efficacy of Duvelisib. Duvelisib works in all the different subgroups including those patients with 17p deletion at a high overall response rate compared to the control group. And I think importantly that the safety picture that we've seen since the Phase 1, since the first patient that went on the Phase 1 is consistent across the different trials and largely manageable and predictable.

And so these two trials if you think about them together I think that supports the efficacy and registration approach to Duvelisib and for patients with both CLL and low grade lymphoma, again that the safety profile is well known and well characterized and hopefully this will – hopefully the FDA will look favorably upon this application soon.

And I think we've gone through a lot of this already, but Dr. Kunkel as well as Dr. Brown talked about how these therapies may fit into the changing treatment paradigms for patients with CLL and lymphoma. We know that – in CLL, we're rapidly moving away from the combination chemotherapy regimens to more oral-based therapies. There are some issues in certain patient populations, it's hard to give some of these other therapies that we already have. Duvelisib is a potentially new therapy for these patients.

I think the same remains true in follicular lymphoma and Burkitt lymphoma that we're a little bit slower to change over from chemotherapy-based to regimens, because some of these oral therapies that work so well in CLL have really not worked, the BTK inhibitors the BCL-2 inhibitors, they've not had the same efficacy in follicular lymphoma. And so really the main theme of therapy after a chemotherapy has been a PI3 kinase inhibitor.

<<Robert Forrester>>

Dr. Flinn, thank you very much. So now we're going to change the subject a little bit. We've been talking about CLL and FL. But we see potential for Duvelisib and PI3K, more broadly

in fact. And the T-cell lymphoma, this is one of those areas. So Dr. Horwitz will talk about T-cells.

<<Steven Horwitz, MD, Medical Oncologist, Memorial Sloan Kettering Cancer Center and NYC Health + Hospitals/Bellevue>>

Thank you. Thanks. Pleasure to be here. You've heard a lot about low grade B-cell lymphoma. So we'll switch gears a little bit and moving on to T-cell lymphoma, which is a little bit of a different animal in terms of how we treat them, what the prognosis is, where the areas of unmet need.

So these are aggressive lymphomas. So where in CLL and follicular lymphoma patients often get sequential therapy over time and one of the goals of you heard about is not curative intent, but being able to manage the disease overtime and I think you've heard a lot about where the unmet needs in those diseases fit. I think in T-cell lymphoma, we're just years behind, it's just a much more basic problem, which is that – this is an aggressive disease and we really lack effective therapies.

So just to walk you through a little bit here. There's about 20 subtypes of mature T-cell lymphomas or what we broadly called peripheral T-cell lymphoma with the exception of ALK-positive anaplastic large cell lymphoma. So this is one of the subtypes, probably represents 8% or 9% of the T-cell lymphomas, these tend to be younger people more favorable characteristics with combination chemotherapy and all this data here is with upfront combination chemotherapy often with consolidation of stem cell transplant. But with that approach, with this one subtype we cure about 60% of people.

So that's certainly not good enough, but a little different than what we see with the other more common subtypes of systemic T-cell lymphomas. We're really - even with those intensive therapies only about 20% or so of patients are cured. So that either refractory in this to initial treatment or a quick relapse often followed by short overall survival.

And we do have a handful of new drugs or approved drugs in the second line in T-cell lymphomas, starting with Pralatrexate in 2009, Romidepsin and Belinostat. And most of those drugs give activity but the activities are lower sort of than what you've seen - 25% to 30% response rate, so minority of patients respond. Again the one outlier there is the anaplastic large cell lymphoma, CD30-expressing lymphoma with Brentuximab-Vedotin receive very high responses.

If you follow-up those response rates with progression free survival or durations of response, I think this even more highlights the unmet need. So this is in the relapse setting, this is older data from British Columbia Cancer Agency, where none of the new drugs were available. And they just looked at patients with first relapse of T-cell lymphoma and those patients had progression free survival of under four months. They had median overall survival of about six months. And when we look at what we do with the new drugs, if you

look at the median patient with Romidepsin, Pralatrexate, Belinostat or Brentuximab vedotin outside of the ALCL patients. We haven't really moved the needle for the median patient.

So the average patient is either a non-responder or a brief responder with quick relapse. What I think we've done is we've increased the tail on the curve. So if you look at all these curves, there are a handful of patients, probably somewhere around 8% to 10%, who really get durable benefit and clear clinical benefit with these drugs. But for the majority of patients, we have inadequate results and even if they respond to one of these drugs often quickly need additional therapies.

This is just to make a point about the Phase 1 study of Duvelisib in lymphoma. So you heard a lot about the mature – more mature days in CLL and in follicular lymphoma. And we worked with Ian as part of this dose escalation Phase 1 study. Most of the patients with indolent lymphomas were treated at 25 milligrams BID, you get high delta PI3 kinase delta inhibition and some gamma inhibition at 25. And the way that study was designed was it was a dose escalation looking at the MTD, but because of reliable activity in the low grade lymphomas at low dose, most of those patients come – came off into dose expansion and the broad experience for low grade lymphomas is with 25.

When you have low grade lymphoma patients, they can take up a spot on a clinical trial and wait for it to open. When we look at our patients with T-cell lymphoma sort of the median time from presenting them a trial to first dose of drug in our center is nine days. So those are not people who can wait for a spot for another cohort to open. So the low grade lymphoma patients came off at lower doses and most of the dose escalation with more aggressive lymphomas. And the data I'll show you with T-cell lymphoma is primarily patients treated 75 milligrams BID or which was the MTD or above the MTD at 100. At that level, you get about 90% gamma. Is that important? It might be – we don't have a pure delta PI3 kinase data in T-cell lymphoma to compare, but you are getting a lot more gamma at that level and that's where our experience in T-cell lymphoma is.

So we then went on and did a cohort expansion and if you look at the data compared to what I told you before, not a huge number of patients, 35, but overall 40% response rate and if we really focus on the aggressive or systemic T-cell lymphomas leaving aside the cutaneous T-cell lymphoma patients for now. Again in a small number of patients, 50% response rate, which certainly compares, at least equally or potentially favorably if you're going to compare cross studies to the drugs that we currently have available.

Our thought at the time was based on the mechanism is we might to be able to identify certain subtypes, maybe some on the more cytotoxic or different subtypes of T-cell lymphoma that may preferentially respond and in a bad way for correlative studies, but a good way for patients. We've really saw responses across the spectrum T-cell lymphomas. So these are T helper, these are CD8, CD4, these are cytotoxic. But really across the

spectrum, we saw responses in T-cell lymphoma, which suggests that there is some broad activity of this drug in that population.

Again if you follow up with the time to end point. So this is median progression free survival, the PTCL patients are in yellow. This patient here is now out at over four years with a relapse peripheral T-cell lymphoma on continuous with therapy. We name our studies like at Sloan Kettering this study was 12088, it was 2012, it was the 88th study through the institution in 2012. So we sort of joke that this guy won 12088, because he is over four years and remission is still doing fine on his oral therapy. But again if you look at the median, so back looking at the majority of patients, 8.5 months here small numbers but at least in the ballpark if not better of what we get with the currently approved agents.

I think as Infinity at the time was moving forward in low grade lymphomas, they were a little less clear about going forward in this and I think we'll talk about this later as a single agent in T-cell lymphoma. So there wasn't a big company sponsored effort at that time. But we did develop some preclinical data showing that patients are cell line – these are patient samples in cell lines that were resistant to PI3 kinase signatures, were in risk for these promo domain signatures. And that tells us that maybe HDAC inhibitors would be a good combination partner and we did some combination studies a lot of this is through David Weinstock's lab at Dana-Farber showing that there was synergy between Duvelisib and Romidepsin, which is the standardly approved agent relapse PTCL. So starting with Infinity and then now with Verastem we've had good support for our investigator-initiated studies looking at combination therapy.

So this is part of our combination therapy design. So it's really a Phase 2 – Phase 1 study, looking at combination with Romidepsin to see if we can build a better combination regimen. We missed an opportunity to a lot of – to do a lot of the really robust correlates in the single agent study. So we've built in a lead-in, where patients get one cycle of single agent Duvelisib. I won't show you data for that, but that's just to really get biopsies and to try to better tease out are there patients who respond more likely to Duvelisib and then really a Phase 1 and then with expansions in combination with Romidepsin.

So this is just data from our Phase 1 that Alison Moskowitz, one of my colleagues presented at ASH. The short answer is you can give full dose Duvelisib with Romidepsin at 10 milligrams per square meter, which was the highest dose we looked at really without any dose-limiting toxicities.

And if you look at the response data at least right now again comparing small numbers we're pretty enthusiastic about this. Overall 64% I would say if we look at just the systemic T-cell lymphomas over 60% response rate and 36% complete responses, so again all the caveats of small numbers. In this combination, we're seeing complete response rates that kind mirror the overall response rates that we see with the other single agent. And that's important for a couple of reasons, primarily for T-cell lymphomas, in relapse, if you have a complete response, we will likely take you to allotransplant with curative intent. And if we

can cure people, that's much better than being on long-term maintenance therapy. And we have had several patients from this study go ahead to allotransplant in response with curative intent.

The other thing that I'll show you in terms of the toxicity is this slide is notable for what's not here. So when we combine with romidepsin, we didn't really show you the Phase 1 data for transaminitis or inflammatory side effects. And those are more common at that 75 milligram BID dose. And what we see here when we combine it with romidepsin is really an absence of those inflammatory side effects. So we've seen almost no transaminitis grade three or four, low grade transaminitis when we combine with romidepsin. And our thought is that if this high response really holds up, it's allowing us to give higher doses of drug over longer-term and in a patient who we're not going to cure that may really correlate, we hope with long-term or more durable benefit or more clinical benefit. That study is ongoing, so that still remains to be proven.

So the conclusions of that are basically, preclinically, we think duvelisib has activity, we're looking at markers for response and resistance. We think combining it with romidepsin maybe a good idea. And we think this drug has legs, both as a single agent and possibly as a combination partner, primarily from romidepsin and other people. We work with – I'm just going to introduce you now to the single agent study that Verastem is now looking to take forward to look at potential approval for this drug.

So this is going to be a larger Phase 2, 100 patients and not just 35 of aggressive or systemic T cell lymphoma patients. And we're going to treat a larger number to try to more precisely define that response rate in T cell lymphoma. And again, if those numbers hold up, I think it's really in the ballpark or better to a lot of the therapies we currently have. There's going to be a dose optimization part, so we'll kind of go back and treat some patients at 25 to try to get a sense of the 75 milligrams, is that really the right dose for T cell lymphomas or might you have equivalent activity at the lower dose levels. Pin down the optimal dose and then really look at response rates in a much larger group of patients.

So I think, I'll just conclude there. Hopefully, I convince you there really is a high unmet need really across the board for patients with peripheral T cell lymphoma, our NCCN guidelines really highlight clinical trial in new therapies in terms of how we daily practice. Duvelisib is the potential new therapy for T cell lymphoma. I think that single agent activity is really quite good and we're pretty enthusiastic that we're going to get that beyond the Phase 1 dose expansion and really get a better sense of if that 50% number real and how we can translate that into an available drug.

And then I think ultimately for these more aggressive diseases, we really want to cure more patients and that means ultimately combinations moving into earlier lines of therapy. And I think we have some early signals there. So we're just excited to be part of this. Thank you.

<<Robert Forrester, LL.B., President/Chief Executive Officer>>

Thank you very much. As you can see from the work we're doing, we're really excited about the potential for duvelisib and PTCL, so looking forward to explaining both the single agent and also in combination. We've gone through a lot and so now it's up to Joe, our Chief Commercial Officer to take us through how do we actually going to optimize the opportunity for duvelisib with patients. So Joe over to you.

<<Joseph Lobacki, Chief Commercial Officer>>

Thank you, Robert. And thank you to our expert panel, who did an excellent job this morning for setting up my talk. So going through what the opportunity is for patients the unmet needs and the activity of duvelisib in those patient populations. I've had a lot of great experiences in my career and this is one of them. Joined Verastem and being part of this panel with all of you. And as I go through my career, I've always looked at things in one simple way, looking at the product is there – and is there an unmet need an opportunity for that product. And is there an opportunity to grow the market and build the company into the future.

Again I've had lots of great opportunities and been a lucky guy, whether is that got to launching Taxotere Rhone-Poulenc Rorer building a global oncology team at Genzyme or most recently as Chief Commercial Officer at Medivation. I've had times to work with great products, great people and built great businesses. The plan I'm doing that here as well.

So when Robert offered me the opportunity to help come on board and unlock the opportunity of Verastem Oncology, I jumped in very confidently. This is a great opportunity for us all at Verastem. And I think most importantly for physicians and patients. And it all starts with duvelisib. So how do we unlock the potential of duvelisib? And for me, I look at this in the way, I always look at things. One it starts with the opportunity, again is there that unmet need, is there differentiation of the product and I think we've heard today, there is differentiation of the product in this marketplace. And then we prepare the market, we get ready to go and launch this product.

And it all starts with a patient. So for all of us at Verastem, we always start with the patients. It's not what we do but it's how we do it. And by focusing on the patients and thinking of their needs and bringing that forward into our plans, we come up with novel creative ideas and we're meeting the needs of physicians who are treating patients but mostly importantly the patients themselves.

So let's take a little walk through the patient journey that we've heard about earlier from Dr. Kauffman and himself, who's been going on the journey through this. It's an older population, 65 to 75 is medium age of diagnosis. To the most part, these are people who are now planning their life ahead. They are with their spouse, the family, thinking of where do I go from here, I've been working my life, looking at retirement and planning travel and

grandchildren and marriages and everything. And I look at that myself, because I'm starting to get older.

But then one day a relatively healthy person they walk into the physician's office and they walk out a chronic cancer patient. Their life, the life of the family, the life of their friends has now changed forever. They go into this watching wait period where they have a lot of anxiety wondering what happens next. They've got the twists and turns of life that are coming at them with will my chemotherapy – if I go on chemotherapy will it work, what are the side effects that I'm looking at. And will there be other options for me down the line.

An interesting story, what I love about this business, I always get to meet interesting people in my travels. So yesterday, I was leaving Boston, I did what I always do. Go to my Uber app, call an Uber, used UberX, so it's managing my expenses just let everybody know. And then the Uber comes along, I jumped in the car and I'm headed to Logan Airport. And I start talking to the guy about the Red Sox and the Celtics and the Bruins who by the way are all doing very well. So we've got that great Red Sox hat out there.

So we're talking about that I just said, I try to stay away from all of those activities, it's too hard to drive around the city when that's happening. So he said, yes, I'm just doing this kind of part time. I do it in the morning a little bit, I got interesting. He said, yes, well I just turned to 61 years old. He said, in fact, my birthday is today. And he said, my wife and I've decided it's time to retire and kind of live life a little bit more. I said, that's great, so that's interesting to this, that a week from today, I will turn 60. So how did you make those choices in your life, what drove that.

And he said, well one day last year when I was turning 60 we had an old guy's barbecue. So he said, we got together with all his friends and they had a barbecue and he was talking to one of his friends about their plans and life and what he was planning. He said, he and his wife were talking about travel and experience things with their family and just moving on into their retirement years. He later heard from that old friend, who was one of these patients who walked into a physician's office, walked out a late-stage acute leukemia patient.

So that gentleman went on to some very high dose chemotherapy, a lot of hospitalizations and unfortunately this gentleman driving Uber lost his friend very recently. So this journey changes the patient's life, so it changes the family's life from the plan that they had but it changes everybody around them. This gentleman driving the Uber left his job, went to retirement and decided him just going to enjoy life for a while. It was just amazing for me. It was amazing that it happen to be there in that Uber as I'm coming to this event to talk about a patient journey. So there are lots of patients' stories out there.

And as we all age, as we all as baby boomers, start aging. Hopefully, we don't have these stories but the risk of us having that is upon us. So right now, there are 197,000 people

living with CLL, according to the statistics that we have. 141,000 patients living with FL, that's approximately 350,000 people living with these diseases. So we talk at times of another small markets and how many people is that affect, it affects a lot of people and it's affecting more people as the population ages.

So again increased diagnosis and increase need for new treatment options, which is happening we've heard today that there are more lives and more treatment options coming available, targeted therapies more oral therapies that help patients manage your life and that just continues on more lines of therapies. But they're still a need for increased treatment options. So let's look at the menu of therapies that exist today, it's pretty limited.

So if you are a CLL patient, you used to get – still you pretty much you get chemotherapy it's about 60%, 40%, right. Now about 40% of the patients get ibrutinib across the country, that's great. Because it's an oral monotherapy that over we've heard works well and patients can manage their life at home, why are they managing their disease? But unfortunately, we also heard that not all patients are candidates for ibrutinib. If you have cardiovascular disease or bleeding, which – remember these are 65 or 70 year olds who are being diagnosed that's probably a risk factor for that group.

They may not – their physician may feel, they are inappropriate for this therapy. So what are the other choices? Hope, PI3-Kinase we heard about idelasib which is a delta inhibitor. So it daily oral therapy, but it comes along with a need for IV toxin, so that means travel back to an infusion center or hospital. So although the patients managing their disease, their treatment starting to manage their life.

So let's look at the next product BCL-2, there is a B cell 2 inhibitor venetoclax, terrific drug, works very well. But again it comes with a dose ramp up of over five weeks to prevent against tumor lysis syndrome. It takes 1.5 to 2 liters of fluid a day and as I think I may have told many of us we've met in the past, that's a lot. So again as an older guy, if we've all been for colonoscopy taking all of that fluid the night before that, that's a lot of fluid. So to do that continuously is not an easy thing to do.

So you have the dose ramp up and most of those patients are hospitalized, just because of the risk to tumor lysis syndrome, making sure the dose ramp up is done correctly. And they can get their fluid intake. We've also heard through community advisory boards that not everybody follows this dose ramp up. And the outcome is very poor for those patients. Some physicians not familiar with venetoclax, who will go right to the 400 milligrams a day, that's a bad thing to start up. You end up with a higher risk of tumor lysis syndrome.

So some options but not many, we need few more options. When we get the FL options are even small. You have vitalism, proof of third line relapsed/refractory FL. Again, conditionally approved, daily oral monotherapy. So something that patients can manage their life with and manage their disease.

There's another PI3 kinase inhibitor copanlisib, again, nice drug PI3 kinase inhibitor, but it's a delta and alpha. So it comes with other side effects, along with hypertension, hyperglycemia. Again remember the patient population, it's an older patient population, but these are probably not things you want to be adding on top of them.

Not speaking like a physician but I'm going to assume that's probably part of what should be looking at, and there's travel required, because it's a weekly IV infusion. So now again patients have something to manage their disease. But their treatment is managing their life. So how does duvelisib fit in? Those who've heard duvelisib is a first-in-class novel dual kinase inhibitor of delta and gamma. So delta kills your B cells, gamma takes away that support of microenvironment. It's got great clinical efficacy as we have heard throughout the morning and a manageable safety profile.

It's a simple, at home, oral monotherapy. So patients can manage their disease and manage their lives. And it's accessible in the community setting, 70% of these patients are treated in the community. So they need a product that's easy to take that they don't have to travel for IV infusions. And again, they can manage and physicians can manage across patients. So whether it's CLL or FL, there's good data for duvelisib and whether it's high tumor burden or high cytogenetics. There's good data for duvelisib.

So what do we hear from people? What patients are concerned about is they're wondering as we've heard today, what's my next step? What if I can't continue to do the adverse events? So duvelisib offers that next step and therapy a novel mechanism of action. And again a convenience therapy, in case you stop responding or they can't continue on the current therapy due to adverse events.

They're wondering, how do I get this product? Again, with 70% of the patients in the community. They're looking to get an easy product to deliver to them. So it can be delivered right to their home and they can manage their disease along with their physician at home. And their lifestyle, because of that ease of administration, they can continue to manage their lifestyle by managing their disease. From research the majority of oncology patients are telling us that quality of life is as important as overall survival. So I think we've heard from the panelists, patients want to manage their disease and look at that as just with their chronic management.

So what do we hear from physicians. They're wondering who it's appropriate for. With 70% of the community oncologists treated this disease, they can – most of those physicians treating CLL and FL they can use duvelisib to cut across that patient population. They can also use it across sub populations., high tumor burden and high cytogenetics the data backs that up. And then will my patients be willing to take this drug, because it's an at home convenient, oral administered product, physicians can feel comfortable in the lots of – some follow up to make sure patients are adequately taking their drugs. But they're going

to – they don't need to travel for infusions, they don't need to make a scheduled appointment, they can take their drug at home.

So do patients believe this drug or how does this drug fit in? Well I've alluded this before in chronic diseases. So I want to talk about my time in Medivation and their product XTANDI in the prostate cancer market. Prostate cancer market is a disease of older gentlemen. Now again, who approaching their retirement years, they have a diagnosis of prostate cancer. They go in for surgery, radiation, rounds of anti-androgen therapy and then maybe chemotherapy. The population is increasing because of the aging population and they're looking for new products to use for treatment, new treatment options for them to manage their disease.

We first went to develop XTANDI, the world told us nobody needs another anti-androgen, spaces to crowd it. Well, XTANDI and ZYTIGA both came into this marketplace and they supported additional lines of therapy at growing population and the availability of patients to manage their disease. So I'm looking at this market within the first five years. These agents grew the market $5 billion about probably over $4 billion of that was ZYTIGA and XTANDI as they went into the marketplace. And there are more agents looking to come into this marketplace, because there's a need for chronic patients to manage their disease.

So at Medivation, we always talked about patients, as we do at Verastem, we have patients stories. So at Medivation, we have one patient, several patients obviously, but one patient we always talked about Graham. Graham was an elderly gentleman who was diagnosed with prostate cancer. He had gone through multiple lines of therapy, surgery, radiation and was told one day by his doctor it's time to talk to your family and get your affairs in order, because we don't have any other options for you. Well there was another option that put him on enzalutamide study, XTANDI Graham responded well. Beside the marriage of his two children, the birth of his grandchildren and he's still doing well.

In fact, I got an e-mail from Graham over the weekend, because we stay in contact about how he's doing, because he was just part of the family. So he's doing well and he is looking to reach out to say, how can I help other cancer patients? What are you doing at Verastem and is there anything I can do. So again the patients need more drugs. Yes, so I think Graham story tells us that.

So prostate cancer – with the prostate cancer market inform us what will happen in CLL and FL? I think it will, and I think it will grow the market. But it's not just me. Decision Resources is pointing out that in 2016, the market was $6 billion for CLL, FL treatments globally. It's projected due to new treatments, new lines of therapies in a growing population that will grow to $24 billion in 2026. So again that's Decision Resources. So new drugs, new therapies, new lines of treatment, increased markets.

So as we look at unlocking the potential of Verastem, that all starts with unlocking the potential of duvelisib. We're focused on providing efficacious, safe, and convenient

treatment options for patients. And for us it's personal, as Robert mentioned earlier, we're all focused on patients, we're all touched by cancer. So everybody in this room sure and everybody listening back at the Verastem offices have been touched by cancer in some way. My story is my Dad, at the age of 72, my Dad walked into his – he was planning his retirement with my mom, they just bought a small home in Florida. And they were planning to get out of the cold New Hampshire winters and go to Florida for that time period.

One day, my dad wasn't feeling well, walked-in to see his physician and walked-out as pancreatic cancer patient. That day changed my dad's life, my mom's life, the whole family and everybody around my dad. Unfortunately for pancreatic cancer patients, there were really no options available. I lost my dad five weeks after that diagnosis. So it happened very quickly. I hope one day that with great researchers like the folks who are here and their colleagues, they'll find new options for pancreatic cancer patients and pancreatic cancer patients, we come more of a chronic disease as CLL and we hope in FL of getting today. We have more work to do, a lot more work to do. But we can help patients manage their disease by managing their lifestyle, it makes a huge difference.

So again, we're here to develop duvelisib and move on and have a successful launch. So where do we start? How are we preparing this launch? And for me doing this many times before, it kind of starts in three places. The product, know your product and know your competition. The market is there an opportunity and if there is, where does that fit into the market. How does your products fit in? And then build an excellent team, which I've been fortunate to work with many great people and to build teams.

We're doing that all I guess, we're doing that today and we're well on our way to getting ready for the launch. But it all starts with the product. So back in November of 2016, small company Verastem took a bold step to acquire duvelisib. They brought it in, where the product was in the Phase 3 trial, there was kind of languishing. It wasn't due to the investigators in the trial, the product itself. The product had some good data in the early studies. It was really due to some corporate missteps and miscalculations to move this forward.

So Verastem took the bold step, brought it in, moved ahead, completed the DUO study in rapid time, presented the data last year at ASH 2017, filed an NDA in February of this year and as I think you all know in April of this year, we received acceptance of that file, prior review by the FDA with an October PDUFA date. So we're well on our way to creating value. So as we sit here today that small company Verastem, we are today and growing into Verastem Oncology, created value for duvelisib, value for patients, and value for investors.

So we've done a great job up to this point. But we've got more to do. We need to move forward. So we're getting ready to launch this product in very short period of time. And we've been working on it for several months. So we've looked at the marketplace, we've gone out to understand the opportunity to start working with community physicians and

academic physicians to see where this will fit into their practice. We are setting up a distribution system. We're working with payers and we're ready for launch.

But we're not going to stop there. We need to continue to establish ourselves in the marketplace and grow duvelisib. We've started – we've expanded our clinical development program, as we heard earlier from Dr. Horwitz, we initiated a PTCL study that's up and running now. We're expanding our IST program to listen to investigators out there to tell us what are their ideas. How can we help them develop the great ideas that they have? Most of the great ideas come from all the people out there, who are treating patients. So we want to act on that. We've also started a Verastem Steering Committee, which will be initiated very soon. That Steering Committee will guide us in duvelisib development as well as development of Verastem. Where do we go now? How do we become a larger oncology company?

And how we listen to the physicians in the field, we've been out all over the place for the last year. We've been at ASCO, ASH, talking to the physicians. We're starting medical education in fact, we're kicking up a program today that I'll speak of shortly. We've been at Ad Boards with community oncologists, payers, patients. So, we're understanding the markets and moving into those areas. We're working with patient advocacy groups, leukemia and lymphoma foundation as well as CLL society as Dr. Koffman was talking about earlier today. We want to get out and be a part of those communities and we'd be very active. And we're engaging KOLs through our medical affairs programs and education, and also our steering committee.

What are we hearing back from all these folks that were out there? We're from community oncologists, nurses in the KOL groups. They're all asking for the same things as we've been through before. They're looking for a product that can advance the treatment for the patients, that's a simple oral therapy that they can utilize. That's a new novel mechanism of actions that can move on to other therapies, and what makes us proudest, I think is when they come back and tell us people have actually told us, thank you. Thank you for developing this product, completing the dual studies and started to bring this to patients. And now they're telling us, well, get going, you've got more to do. And we're more than happy to do more. So, we're out there, we're moving forward in the marketplace.

So we're reaching out again, to really reinvigorate PI3-Kinase and start a conversation about where PI3-Kinase can fit in the current treatment in hematology in CLL and FL, but also broader then that. Going to PTCL looking at other diseases and how PI3-Kinase may change the landscape for other patients. This program is not just focused on Delta and Gamma, but the other isoforms of PI3K as well. We want a full and broad discussion of PI3K and how it may fit into the treatment. If you want to look this up, it's on PI3Kinhibition.com, I believe it's all launched today and that was started driving that discussion with physicians and started providing us with more feedback and how PI3K may move into the future.

We've also looked to start to deliver this message broader. So we're hiring a very experienced senior leadership team several of them are here today, who have been there and done that. So with over 24 years of experience each greater than 30 launches across many products, many of them on here that you probably recognize from oral oncolytics to the hematology world, again, it's an experienced team that will build their experienced teams. So, they have connections with the hematology world, with payers, with the patient groups. Again, they're ready to go and we're building for the future.

Our go-to-market plan, we're focused on our PDUFA date of October 5th, but we know it may happen sooner. So, our launch readiness state is looking at the beginning this September to be ready to go. But if by chance, we can get an earlier heads up from the FDA if I go, we'll be ready to make sure. We can deliver to patients, who were in need of duvelisib therapy. So that's our commitments to patients. We've got a broad marketing program that's already started as we talked to the disease education we'll continue to engage with physicians at the major meetings coming up and also through the MSL team that we've hired there's actually out in the field actively discussing with physicians now.

It's a group of individuals, who are again have been there done that. They've been in the industry broad experience and diverse experience. We're not hiring people from the same companies. We're looking to hire people from different companies. I want to make sure that we're getting a good conversation going on to take on all the new ideas and bring them into Verastem Oncology.

So that seems out there right now and very active. We're also gearing up for a sales organization. We've hired two very experienced area of vice presidents to start building their teams. They're actively looking to build their regional business directors now that I think they have some interviews later today to start pulling people in. Those regional business directors are planned to be on board by ASCO. So we can start building their teams. They'll look for experienced sales representatives those who know the hematology space, know oncology oral oncolytics and again, I've been there before.

People who are entrepreneurs, there's a group of sales representatives out there that love small companies. They love the challenges that are out there and those are the people that were going to go fine. There are other groups that love working for big companies and doing the same thing day-in and day-out, that's not the group we're looking to find. So we've got a lot of great sales reps, who are already contacting us, some of them through from our competitors or future competitors. So we're well on our way to building on our sales team, our marketing program we're well positioned for a strong launch.

As we look to how our field forces targeted, we want to speak with one voice. So we want to make sure that our oncology, sales representatives are aligned with market access and with our regional business directors, compliantly to make sure we're providing messages, consistent messages across the physician community. Our MSLs will back them up to make sure if there are questions physicians have that need to be answered by medical personnel

that will be there. We're going to cover with this group as we work through ZS, 95% of the high prescribing hematologists that are out there treating CLL and FL, so we're well covered.

We're also covering commercial and Medicare Part D payers now. We've already had our first advisory board back at the beginning of the year, and we're out there talking to payers now in fact, that's why the gentleman who's running our market access program is not here. He's too busy, he is going to get out there and find new market access folks even with a lot of players, because we need to be ready when doing the list of the proofs, so the patients can access the product and be reimbursed.

And again, as I talked about everything we look at starts with the patient in line. So, we were looking at our distribution systems and a support network to say how the patients want to receive their drugs. How do they want to interact in that relationship with their physician, the specialty pharmacy we make set up and all of the patient support groups, so we're wrapping that network around there, we're going to make options available to patients. So no matter how they want to interact, how they want to receive their drugs, we're going to make sure that they're taking care a seamless patient experience.

So where do we go from here. Our first step is to anchor in the opportunity that we have. So we're looking at this approval for relapsed/refractory CLL and relapsed/refractory FL. We're hopeful, we'll get that indication soon from the FDA and we'll launch our plan and that is our solid focus as a commercial organization and the medical affairs organization. We believe in this opportunity, there's the opportunity to grow to $200 million to $300 million business just in anchoring in this space.

But we're not going to stop there as I said before, we're looking to broaden our reach and as you've heard from Dr. Horwitz with the PRIMO trial, but we're moving into PTCL, we're looking to expand in earlier lines of CLL and as we've heard earlier today as well, we need to support physicians to find better options, new options for follicular lymphoma patients. We're doing all of that. And then as a bold step we took through initially bring in duvelisib. We're taking more bold steps and looking to say how do we combine that with checkpoint inhibitors, other novel standard of the cares' agents to move into other non-Hodgkin's lymphoma subtypes in terms of Richter's transformation, mantle cell patients and DLBCL.

So, we engage the community through our medical affairs and our clinical research programs to keep expanding on the opportunity of duvelisib. And if you dream along with all of us, I think there are other opportunities, because we're hearing back from the community to look at in different areas. So we think there's an opportunity to look at CAR-T therapy and other novel future therapies that will bring us out of hematology and possibly into the solid tumor world. That starts with our PI3K education program engaging the physician community, engaging our research team with those physicians and looking to see how far, how broad we can bring.

So within Verastem Oncology, I'm confident we will get this done. Why, because I've been there and I've done it before, this is my life, I love the stuff. So we will get this done. And I'm not just confident of myself, that would be foolish. I'm very confident in the team that we're hiring. I've got a very senior group of people some of them here today. We're building a more senior experience folks, who are out in the field to carry the message forward. We will get this done. Like Verastem, we care differently and we're going to focus on – we're going to focus on these patients and bring this product forward to them very successfully. So, thanks Robert. Thanks for the opportunity.

<<Robert Forrester>>

Okay. The good news is that's the end of the introduction and we've now got 250 slides to go, so hunker down.

Before we go on to the last slide, you'll be glad to hear. Much about one more patient story and last week I was interviewing one of the candidates for Joe's team. And it transpired that he had a father with CLL and this was causing a lot of family tension, because he was taking a therapy that requires a regular infusion, and he was living remote. And of course, every time, he has to go to get an infusion. It basically takes the best part of a day, so either he or his sister having to take a day of work to go and take their father to get infusion. These are the practical problems that families have. So an oral monotherapy is really important, it makes a difference, remember who these patients are.

So we'll be talking about duvelisib, I just want to take one moment and just talk a little bit about Verastem oncology, which we are launching today. And as Joe talked about the first step is to build the team. It's all about the people, when the guys and girls, who are going to make this work and we're hiring world-class people. And I'm really proud of the team that Joe is trying to go very proud to be working with Joe, it's a great honor. I'm learning so much every single day, but we're hiring incredible people and we're going to do the launch right.

And I'm absolutely, totally committed to that, and to Joe and team, we're going to do this launch right. So that's job number one. It is to anchor with the launch of our first drug duvelisib and our first indications. But as Joe showed this has been a long way to go. There are many other places, where this drug can be used both the CLL and FL earlier stage patients, single-agent combinations, higher risk patients, PTCL, DLBCL and you cause marginal zone. There's lots of places where this drug can go.

It is our obligation to do that to make sure we bring this drug effectively to the patients to all different diseases all around the world and that is our obligation when we really feel that keenly. We're going to make a difference for these patients where they might be. And then we're going to repeat. We're going to do this again, and we have defactinib in the pipeline, in fact that we've promised, we're going to update this year from one or more of the different clinical studies that are ongoing. In fact, we have some dates, early dates at

ASCO. So this is encouraging. So we'll see whether defactinib is drug that can go forward into some solid tumors.

And that's what we're going to do. We're going to need to involve, and continue to grow. We're going to bring forward new products as we develop this company over the next few years. But at the root cause or the root heart of this company, we're going to make sure that for each patient to feel like that the only patient that we're focused on. That is the company that we are. That is Verastem Oncology.

So thank you very much indeed for attending today. We're now going to bring the panelists up here, and I know we don't have an overtime left. But we thought we had given opportunity of anybody in the room, if you want to ask questions, this would be your moment. So the panelists will come up and do the answer, the chairs up there please.

Q&A

<A – Robert Forrester>: Okay, are there any questions? Susie is in charge of people quite have a lot of questions. Susie you can get to choose, who do you want to do it first. Ren?

<Q – Reni Benjamin>: Thanks, Reni Benjamin from Raymond James. I guess maybe the health center road for me is the perceptions of PI3K delta, right. And duvelisib that's out there, so panel maybe talk a little bit about you know how you go about changing those perceptions, and what really has led to the degrees in usage of PI3K delta. And then also just as the second question, prophylactic measures, how would you in the community setting be implementing prophylactic measures for some of these utilizing duvelisib? Thanks.

<A – Robert Forrester>: Dr. Brown, you want to take the first?

<A – Jennifer Brown>: Sure. I think that some of the reputation, the PI3-kinase inhibitors with idelalisib early on came from the lack of acknowledgment and lack of management of some of the toxicities that we're seeing, and that is taking a proactive approach to understand and prevent that, can actually go a long way to mitigating it, which we know. And you have to remember duvelisib is also a novel compound, inhibit not just Delta the way idelalisib does, but also Gamma, and there's scientific rationale for believing that inhibiting Gamma may also decrease, some of those immune mediated toxicities played as being the one that I think has really been what straight fear into the heart of physicians, because it happened at random to some degree it's unpredictable.

My personal experience with duvelisib I've seen less colitis much less actually, then with idelalisib, and we see from the data that patients are actually left why we need to discontinue with diarrhea for duvelisib then we have ever saw with idelalisib. And I think it's really a novel category of drug and being proactive and advising physicians on how to manage, which we do need infection prophylaxis, I think that's in all my view I feel all

patients prophylaxis against pneumocystis pneumonia and against viral infections, which did all drugs easily given in the community. And then just having the patients know what to watch out for and give a call to their physicians and maybe so the physicians are educated on what to look for, and how to take a proactive approach if someone does for example people have diarrhea or pneumonia.

<A – Robert Forrester>: That's for help, thank you. Dr. Flinn, you able to treat a lot of patients too, anything you'd like to add in terms of prophylaxis?

<A – Ian Flinn>: Yes, I think you do the same thing that the genders are used PCP and prophylaxis as well as the cycle to the normal patients.

<A – Robert Forrester>: And Joe, do you want to talk about how we're going to care differently while making sure the patients have a good experience?

<A – Joseph Lobacki>: Sure, I think it's a very comment. I agree, so it is misperception, as managing that the way Dr. Brown talked about, being proactive about what's out there and how to manage patients. So again going back to that may sound silly a times, but focusing on that patient, what do they need? And what do we need to communicate to them. So it's about a sales representative it goes out and just communicates through position that, I've got all this great data. But also as to be here the things you need to watch out for that wasn't done in the past launch of the PI3K. So we're looking for people who go out and actually own that piece of it and talk to patients about that prophylactic physicians about their prophylaxis, what to watch for this diarrhea early versus late diarrhea, what can you do about that.

Our clinical teams actually working very hard to kind of dig into that data. We're doing which specialty pharmacies – but we're doing specialty pharmacies actually going out and saying like it's important to us that they give prophylaxis. So could you help us provide patients, and physicians with prophylaxis, the best part of what we would like everybody again whether like we are not saying which you're asking. So like, if I go back to telling the stories, we want this to happen, so can you help us, can you deliver back to do that. And they're like, we never thought about that, but sure I guess we good. So again that was back to that, how do we think differently? How do we act and differently in care?

<A – Robert Forrester>: Dr. Koffman?

<A – Brian Koffman>: Just from a patients point of view, the fact that this is second, and we've learned from the first and what went wrong, there what didn't goes well if it could. But from a patients point of view, patients especially in the community hematology are often knocking on the doctor's door and saying, I want to be on prophylaxis, this isn't an issue for patients. Patients are concerned and said, can I get on prophylactic medications, I'm worried about the infections, I'm worried about these things. So I think that this won't be an issue of for the patients.

<A – Robert Forrester>: Lori?

<A – Lori Kunkel>: Yeah, I mean I was actually surprised. If you go in the NCCN guidelines, FCR is recommend the same exact prophylaxis. So this isn't a novel for these particular diseases. I think that's what you're hearing, it's not – this isn't prostate cancer where you wouldn't prophylactic cases, these patients are commonly prophylaxis, so that hurdle is probably not as big as would be in a solid tumor.

<Q – Corey Davis, Seaport>: I have two questions. I'll ask the first one first as opposed to ask the second one first. I want to get back to how big a problem the shortcomings that all of you mentioned from the other two classes really are in whether things like cardiac problems would prevent you from starting a patient on that drug, if duvelisib is approved or is it something just to be aware of in a reason that you would take them off it develops and then put them on duvelisib. And this is part two of the first one. How recent is that data and is it still do you think reliable that but about 20% of improve patients discontinue at six months.

<A – Robert Forrester>: Dr. Brown will answer you first, and then maybe Dr. Flinn.

<A – Jennifer Brown>: Sure. So – and just cardiac situation I evaluate on a patient by patient basis. I've had a lot of difficulty actually with the ibrutinib in older patients with a range that and we've reported on ventricular arrhythmia is rare, but seen with ibrutinib not just the passengers to heart failure repeatedly after starting the drug. And so I do now with someone has a history of not – AFib actually sometimes you can manage, but more serious heart problems ventricular arrhythmias or just older age and episodes of heart failure, I avoid ibrutinib in those patients.

And I've actually – yeah, so I move first-line to other not first-line therapy, but first-line novel agent to other categories of drugs. And then of course, people who do develop cardiac problems on the drug it depends on the severity of the cardiac problems. We can sometimes manage the AFib, it depends on how you feel bad and take regulations and whether it recurs or not. There are some patients who get recurrent symptomatic AFib and can be difficult to manage and have to stop.

It's the 20% discontinuation for adverse events for the ibrutinib is pretty accurate still actually and again increases with age. Trialed patients have historically been much more motivated and so the rate that we see of child patients staying on drugs are much higher, but patients who feel they have lot of options who are not on trial may not want to deal with joint pain. Joint pain is a frequent discontinuation in the upfront patients. Because it can actually be quite severe a patient in the emergency room with joint pain from BTK inhibitors. And so it remains an issue.

<A – Robert Forrester>: Dr. Flinn.

<A – Ian Flinn>: I think that's completely accurate. I think 20% is probably a low number, right. I mean, we look part of the large private practice in the community in Tennessee, maybe some doctors and we look that our pharmacy records in them and people have discontinued ibrutinib was substantial at least 25% or more, and it does it and the number one problem we run into is actually the arthrologies issue, I think, is we try to do case review of looking at all the charts and doing why people stop them, and it wasn't always clear.

But in my practice the oncologists now of course, turns the cardiac issues whether you push forward ibrutinib or not, and I really think it turns on so many factors run with the patients their age whether this is first-time therapy or second-line therapy. It's how to manage all the drugs in terms of the anticoagulantion, the antiarrhythmics which are dose reduction. And in my practice is just restricted to patients with CLL in lymphoma and it's difficult for us for the average community decision, I think there's a –we're going to move on. And I think that it's a much bigger problem for those people to don't use the drug every day.

<Q – Corey Davis>: And the second, I want to go back to the difference between being a dual and just the single inhibitor of PI3K. Dr. Brown, you said that you think you're seeing a lot less colitis with duvelisib?

<A – Jennifer Brown>: This is my personal experience. There is a certainly colitis imported in trial with both, but I think was clearly different as the discontinuation rate seemed to me significantly lower with duvelisib and your Gamma effect T-cells, and we think that these immune effects for T-cell mediated. And so by inhibiting some of the T-cells that caused the autoimmune effect to Gamma, we have a rationale for understanding why it might be better, and we're actually setting that in the lab. We're trying to understand that with samples in patients treated.

<A – Corey Davis>: So that's an intriguing differentiator that it could explain fewer side effects given that it's got dual inhibition.

<A – Jennifer Brown>: Yeah. It also could explain why it is more active in follicular lymphoma, right. Is that there may be a bigger role in the follicular microenvironment that we have no idea right now, but that that could be why it's being differentiated in follicular lymphoma.

<Q>: The patient looking at this is sometimes these quote off target effects are minor effects like some of the effects by ibrutinib may be related to its effect on the microenvironment and immune modulating when I had my CAR-T, it was important that I'd be on ibrutinib, because this is the effect on the CAR-T cells that it's just almost a doubling of the response rate when you're on ibrutinib, so these some time called off target effects are really very therapeutic.

<A>: Yeah. When we looked at the T-cell lymphoma, like the initial like nine cell lines or patients drive samples, there were no responses even though we already had this 50% response rate. So we knew there's the disconnect there and those are just cell lines. And then sort of figured out that the cell lines that expressed high levels of the pathway, keep you respond, but we see more patients responding than we do cell lines. So we're pretty confident than some of these other T-cell lymphomas, it is a microenvironment effect. It's not always on target. So I think for us that tells us in a heterogeneous disease that's probably our multiple effect.

<Q – Corey Davis>: Okay. Thank you.

<A – Robert Forrester>: Mara?

<Q Mara Goldstein, Cantor>: That's great. Thank you. I wanted to ask for the practicing physicians, who are currently treating patients today and who do use idelalisib, how you plan to transition your practice when the duvelisib will be available and what change is relative to the current patient populations that you treat. And then secondarily, just the idea around combinations and curious as to what you think might be the most compelling combinations and those that you might be willing to – you're most likely to try in your patient populations.

<A-Robert Forrester>: Great question, Mara. Okay. Dr. Flinn, why don't you go first with that?

<A – Ian Flinn>: I mean I think to answer the idelalisib question, if someone was tolerating idelalisib today, I don't think I would – as soon as duvelisib came up, I don't think I would take them off idelalisib and put them on duvelisib, just put few principle purposes. That said, I think when the news starts, I would use duvelisib and that from the combination space, we did a Phase Ib combination study looking at duvelisib with bendamustine, rituximab and duvelisib with rituximab. And I can say that there was no middle policy in this. There was no synergistic toxicity. There was no – there was also the toxicity you would think of the individual agents. There's a whole lot of work to do, and I'm really excited that this company is interested in researching some of these things about what is the best approach with combinations with getting people and perhaps to a deep remission, perhaps using different schedules, so deep remission getting people off therapy. These are things that that I think need to be explored, and hopefully will be doing that soon.

<A – Robert Forrester>: We're totally committed to doing that. So thank you for raising that.

<A – Brian Koffman>: And from the patient's perspective, especially, the treatment kind of beaten up and have the complex karyotype in a mutagenic kind of disease – I recommend to all the people, who talk to me, try to get on a combo, because the CLL was smart and it

mutates around even great drugs. So it's very exciting to see the combos of the part of the future. I think that that's the future, that's where everything is going. You were dash with all of our combos that's in CLL.

<A – Jennifer Brown>: We have actually completed a study combining duvelisib with STR actually, for very young fit patients with a very higher margin negativity rates, fairly marked and we just got in all presentation, so that you know how this is coming to. And we're launching and investigating an issue to the duvelisib with genetic facts, which is of course, very exciting based on preclinical synergy. And so we were moving toward the future without schema. So we're very excited about that.

<A – Robert Forrester>: Dr. Brown, would you use duvelisib?

<A – Jennifer Brown>: Yes. I would use – so I wouldn't transition, people are doing fine on idelalisib, but I would use duvelisib as my preferred PI3K. Again, because of the Gamma, because I have a better experience, this is the colitis and you're going to treat with the infusions.

<A- Robert Forrester>: Thank you. I think there was a couple of questions back here?

<Q>: Hi. So I know it's been discussed that unlike to be the case, duvelisib treatment can be stopped temporarily, specifically for weeks or even months and then re-challenged. And I was curious to hear based on conversations with community physicians, how big of an impact this future may have, based on their current practice. And then how you may have to educate them? And if I missed...

<A – Robert Forrester>: You missed this at the beginning. So just the question it relates to the fact that we've seen a clinical evidence that you couldn't give a dose holiday to patients on duvelisib, if you got colitis for example, you can even challenge the colitis and then re-challenge with duvelisib and if those patients continue to do quite well. I think it is the question. So maybe, hope, Dr. Flinn, you want to comment on that?

<A – Ian Flinn>: Yes, I think that's an incredibly good, but complicated question, right. The issue for us in seeing what's diarrhea and what's colitis. So very rarely, in any of the studies and in the publications you look at, you look at sometimes it's called colitis, sometimes it's called diarrhea and what we're treating really now. I do think that there's certainly, the diarrhea, you can get people often and back on transaminitis, those type of things. I think you can probably ask to do with true colitis, but my enthusiasm was very depending on that on how sick somebody was with it. If someone was mild and I can handle as an outpatient putting on some more budesonide, then I think it's reasonable to do that again. And the other thing we need do explore is, in those patients, how well can you go with the dose and still have maintained efficacy. And speaking on missing things, Robert, I'm sorry, but I'm wrapping this to my plane. So, I'm going to off to take off.

<A – Robert Forrester>: The questions are getting too tricky. Maybe, they've reached slowly even that. So thank you, Ian. Thank you very much for this. So Dr. Brown, do you want to sort of talk about, did you give a holiday whether that's helpful, not helpful, what's your experience being?

<A – Jennifer Brown>: I think if someone has development of diarrhea, colitis, so holidays are important, they get control of it. My aspiration is usually to identify you're early enough that maybe I can add a little budesonide and even keep them on drug. But I agree that certainly, one can stop and restart and maintain clinical response, usually a restart with dose reductions. And I keep the budesonide taper it. I've been able to manage probably most of the patients that's kind of got an experience with this keeping them on.

<A>: Do you – I think whether the questions is, do you see that flare – the same player that you see with ibrutinib, is it the same or is it more muted or just not enough data I mean.

<A – Jennifer Brown>: No. In the very early Phase I was a duvelisib, we can see flares like that. I think flair is less of an issue when patients they didn't respond. I think if patients have been on drug for well and good response. We tend not to see flair. If you have to stop very early or when people are progressing, say on ibrutinib, where it's been well described, that's when you see really, the marked flair. I haven't actually seen it as much and people may be starting to progress on PI3 kinase inhibitors when you stop this with ibrutinib.

<A – Robert Forrester>: That's a great question. In the clinical data, we haven't seen there is class and if that's being able to follow the patient in a good state for three to four weeks and then re-challenge again, and see this continues to be responsive, which is I think giving us a lot of flexibility to the physicians. So we've been encouraged by that. Those are great questions. Maybe, we got time for maybe, one or two more questions. RK, we have...

<Q – Ramakanth Swayampakula>: This is RK from H.C. Wainwright. Dr. Koffman, when you were giving your initial talk, you said that there are no two centers, which are able to decide or what – that's like way of therapy for the given patient. Is this based on like people have to make decisions based on how to manage the side effects or is it because they don't have proper biomarker analysis of a given patient or is it a combination of everything plus the reimbursement, which is a big gorilla out there?

<A – Brian Koffman>: So this was more true in the past when if you – some places would be very big on transplant and some people would be big on FDR, some people would be big on PCR, some people would be looking at clinical trials. There's more consensus right now, but I can guarantee if you go – whatever places you go to the workup that you'll get the prognostic testing you get, will be different at one center than the next center. Their willingness to use chemoimmunotherapy on patients will be very different. There are some centers where you don't see any chemoimmunotherapies than other centers, where they're doing that at other centers that they're doing in clinical trials in combination with novel therapies.

I think it's dependent somewhat on the research interest. I think it's dependent on the experience of the physicians and what they're comfortable with. But they're still were tremendous, I mean what I see because on a contract with the kind of patients, what they get when they go to different places, I think it's very different, and I even did one time, I did even a standup comedy routine in front of a bunch of physicians, where I said I'm going to describe the therapy gets where if they got it, and everybody could say they're on the FDR. MD Anderson, I mean everybody knew that FDR with the MD Anderson treatment. So, I mean it's better now, because of the novel agents, but it's…

<A – Jennifer Brown>: It's still little to say, we will have around different combination trials that we might favor over another, right. And I can still usually say while you're going to see so and so, and they're going to recommend this, when you're going to see so and so, and they're going to recommend this. So this is what I recommend. But to some extent, I disclosed the complexity and heterogeneity of the patients and also the fact that we used multiple therapies overtime. I think we're trying to get more of biomarkers, right now as well as more data on the novel agent areas to sort of guide some of that sequencing in those combinations. But the patients get most of the therapies and do well either way in the end.

<<Robert Forrester>

I'm just very mindful of time, and if anybody else running out to catch a plane or anything. So I think we're going to wrap it up there. We've ended with the patient's voice. So thank you very much indeed for being on the panel, it was very, very helped. It was helped with you all to. Everyone, stay around for lunch. So thank you very much.