KELVIN LEE: I am going to give-- Yans actually said that I could give a philosophical talk. So you will not hear the words progression-free survival or overall survival from me at all. And I'm going to actually approach this from more a myeloma biology standpoint. So as the mid-levels that I work with, who are huddled in the back know I am actually a very simple person.

I don't really understand things very well, unless I draw them out. So I've actually taken the concepts that actually Max presented, Yans presented, Syed presented, Phil presented, and packaged them in a little bit different way to sort of illustrate how we think about novel treatment approaches in myeloma. So I'm not going to talk about drugs, but I'm going to talk about the scientific and intellectual framework by which we think new drugs should be developed.

So my commercial disclosures and so the challenge. Again, this is something that Yans and Max have drawn. So we all think cancer is a colonial disease. You got a lot of different cancers, a lot of individual cells or lytic lesions that are all the same.

And if we had a magic bullet and we could kill them, you would wipe out the tumor. So that's great. And as you've heard from Max though and Yans and other speakers that the challenge really is that myeloma is not a single clonal disease. It's the idea of clonal heterogeneity, but what I want to talk about really is clonal heterogeneity in the context of treatment resistance.

So there are surrogates of that in terms of genetic abnormalities, but really what you have is a heterogeneous population of myeloma cells that are all different in their resistance to different therapies. So what happens? You treat myeloma.

You kill off a whole bunch of those clones. You still have clones leftover. And those clones go back. And now you have a different population of myeloma.

This is a classic clonal tiding phenomena that has been reported through really beautiful sequencing studies. And then you treat them again. And you wipe out a bunch of different other clones, but you still have clones that are left that are resistant to this therapy.

And they grow back. And then you treat this again. And you wipe out a bunch of clones, but you still have clones that are leftover that are resistant. And now you're beginning to develop new clones that have acquired resistance to the chemotherapies that you got.

And then patients relapse with chemotherapy disease, chemotherapy resistant disease. So this is the classic challenge that we face in myeloma. It's not that myeloma is our chemorefractory from the get go, much like pancreatic cancer is, very difficult to treat from the start. Myeloma is actually chemotherapy sensitive, but stuff keeps coming back. And the stuff that keeps coming back is more and more chemotherapy resistant.

So how do we tackle this with novel approaches or novel therapies? And I think that there are two ways that David alluded to by the speakers already. How do you treat that clonal heterogeneity? And how do you deal with acquired resistance?

So in my sort of simplistic thinking, there are two broad buckets that we need to go after. One are the newly diagnosed multiple myelomas, which are chemotherapy sensitive and maybe less clinically heterogeneous. And then there are refractory/relapsed myelomas that are chemotherapy resistant and perhaps are much more clonaly heterogenic.

So the idea for newly diagnosed myelomas is to try to wipe them out all at once. And you can't do it just with one-- or my feeling is that you can't do it with one therapy. In fact, you have to take an integrated combination therapy. And importantly, you have to use therapeutics that do not share common resistance mechanisms.

So if you start treating them, you don't develop resistance to the next phase. So I think of it really very much like our AML colleagues think of it. I think that there are the standard or the central framework is a three phase integrated approach, again using therapies that are not cross resistant, consisting of an induction therapy, what I would call broadly a consolidation therapy.

I think whenever you switch chemotherapies from one kind of chemotherapy to a second non-cross resistant therapy, I call that consolidation and maintenance. So I think that for induction, what we're looking at is a three to four drug combination with a deep response with the idea of induction does this, get you down to a small number of clones. You still have them, because if you stopped at this point, you would relapse, but you have a smaller number of clones. You try to get in the minimum number of clones that you can get off of the initial therapy.

And then you still have clones leftover. So at that point, you switch to something else that hopefully those residual clones are not resistant to at this point. Currently, we use high dose chemotherapy with stem cell rescue to eradicate the remaining clones, but one can consider that there may be other approaches to do consolidation.

Maybe this is where CAR T-cells come into-- we'll come back to that in a second-- but in a different therapy that has a different mechanism of killing with but the idea that at the end of consolidation, you got these guys left. So probably not going to eradicate everybody. However, if you do have a less clinically diverse population or a less heterogeneous population, in fact, you might be able to wipe all of the clones out with those two approaches. But our guess is that you will have some clones left that are resistant to what you've treated them.

And then the third phase of an integrated approach is a maintenance phase to eliminate or control residual clones. And I think that just like in AML, probably the most effective maintenance therapy is going to be something that activates the immune system for a couple of reasons, to control the remaining clones for a couple of reasons. One is that it's clear from the BMCA CAR T-cell therapies that those T-cells are capable of really wiping out the vast majority of very chemotherapy resistant disease.

So we have had patients here. Other groups have reported that somebody who has failed nine lines of therapy, is resistant to everything, IMiD, proteasome, Dara, Elo, the whole shebang. If you give them CAR T-cells, within two weeks, their disease is gone, at least from what we can detect.

Now, they do relapse. So there is still something left, but the T-cells are able to kill chemotherapy resistant disease. So that tells us that T-cells actually can kill myeloma in a way or much of myeloma in a way that is they're not resistant to. So says that T-cells are a way to go, whether or not this be may be BCMA bio-specifics or any other immunotherapy.

Len is probably doing a very similar thing, that it's activating an immuno response. The other good thing about immunotherapy, especially if it's T-cell-based or cellular-based and its persistent is that you don't have to give it all the time. So that's the advantage of allotransplant in AML is that you get a graph versus leukemia effect that persists despite the fact that you're no longer treating that patient.

So the idea is that you can get a long-term durable maintenance with an immunotherapy that you don't have to constantly treat. And aside mention, if you continually treat, which is better from a clinical standpoint, you run into the toxicity issues. Now, the important thing to remember is Syed brought this up is that there are advantages of dirty drugs, drugs that hit lots of targets, because myelomas don't become resistant to it. That is exactly the same thing for immune responses, that a very narrow immune response, such as given by a BMCA targeted T-cell, which is only going after one antigen is not nearly as good as a broad immune response.

So a broad immune response that targets lots of different myeloma antigens is likely to be better. So I think that there is still a lot to be discovered in the maintenance field for immunotherapy or myeloma immunotherapy, but there is data in MGUS and other diseases that myeloma, our immune systems are capable of keeping myeloma clones under check. So that's what I think about chemotherapy sensitive newly diagnosed disease. Well, what about chemotherapy resistant disease?

This is I think a clinically a much more complicated or much more difficult, a group of patients to deal with. And the basic questions are that we ask in the lab are basic questions. What keeps myeloma cells from dying? And what are the mechanisms of that? What are the mechanisms of resistance?

And the broad framework that we used to understand what keeps myeloma cells from dying really actually stem from this concept that my good colleague and longtime collaborator Larry Boise at Emory published. He calls it the tau of myeloma, that we all think that myeloma is a cancer, and all of its biology is a cancer, but it's very clear that myeloma biology and normal plasma cell biology have tremendous overlaps.

One example is that normal plasma cells-- so the plasma cells that you have in your body that are protecting you against measles, the measles producing plasma cells-- this was shown in humans, beautiful study in the *New England Journal of Medicine*-- they calculated the half life of that plasma cell in human beings, normal human beings. The half life of the measles plasma cell is 3,114 years. So this plasma cell, perfectly normal cell is immortal. It will live as long as you do.

So the plasma cells you generated when you got your measles vaccine are the plasma cells in your body now and will be the plasma cells in your body when you pass from this earth without proliferating. They just live forever. So they're naturally immortalized now.

That's more complicated than that, but they're naturally immortalized to begin with. So their biology is very similar to cancer biology. The other great example about this tau that Larry always gives is that we know a lot about the mutations that are in myeloma. We've sequenced lots of genomes. We've identified lots of mutations. And at the same time, we've empirically developed lots of chemotherapies or lots of drugs that kill myeloma cells-- velcade, dexamethasone. melphalan. We've developed all those too.

So if you take those two independent lines of inquiry and ask the question, how many of the drugs that we know are good for myeloma, how many of them target the mutations we find in myeloma, the answer is, none. And in fact-- maybe BRAF-- BRAF is the only one. Everything that targets myeloma actually targets normals plasma cell biology.

So under folded protein responses, BCMA is a normal plasma cell marker, all those things. So really, empirically, we've discovered drug wise, that the best drugs that we have against myeloma, in fact, target normal plasma cell biology. So we believe that there's a tremendous-- in terms of the scientific framework, there's a tremendous amount to be learned from normal plasma cell biology.

So what does that tell us? It tells us that myeloma cells are not just cells that are just floating around, doing whatever they want to do, completely independent of everything else. It's very clear that the myeloma microenvironment is, in fact, very important and critical for the survival of myeloma cells.

So if myeloma cells bad, pull them out of the bone marrow, isolate them, put them in culture, dead in 24 hours. They do not like being out of the bone marrow. And that's because there are multiple components that they need to survive, including the extracellular matrix, soluble factors, a whole bunch of other cells that interact with the myeloma cell and the plasma cell. So these cells, these normal microenvironmental cells, are critical for the survival of the myeloma. So they, in fact, identifying those interactions, might identify novel targets that confer drug resistance onto them.

So I'm going to give you an example that our lab works on. So just as an example of how we think about how to approach this, and how to identify those targets, and how to move potential drugs forward that target this. So the question is, myeloma cells depend on interaction with the microenvironment for their survival. And I'll show you a little bit of data that says that they're dependent on those interactions for acquired drug resistance.

So what are those targets? What could we finally find? So we've been thinking about there's a bazillion different genes that go up and down. But we figured that, well, all right, the genes that are important for myeloma cells or plasma cells, are the genes that go up when B cells become plasma cells.

And there are a whole bunch of them there that are important, that are involved in B cell biology, plasma cell biology, including BCMA. But one of the ones that was completely unexpected was CD28. And it's our favorite receptor. Everybody-- I won't go through this, but everybody, or a lot of people know that CD28 is a critical molecule on T cells. It's involved in T cell activation. T cells need it. And it actually enhances T cell proliferation survival and metabolic efficiency.

And CD28 for the longest time was identified in plasma cells, as up-regulated in plasma cells. And it is associated both retrospectively and prospectively with poor prognosis. And it does a couple of things in neovascular. Development. But this is the data.

So the CD28 expression, as you relapse, you start off at MGUS. It's relatively low. And as you relapse, through a medullary relapse, you get out of the bone marrow an extramedullary relapse, all the [INAUDIBLE], the amount of CD28 goes up. So expression correlates with disease progression. And it's been prognostically associated with worse outcomes-- high dose chemotherapy and a number of biological things.

But all in all, it suggests that CD28 is pro survival, and its expression is selected for under treatment pressure. So this is something that is anchored in the resistance mechanisms for multiple myeloma. So I won't bore you with all the studies that we did, but essentially this is what we have decoded from this interaction.

That CD28, up there, interacts with dendritic cells in the microenvironment. And CD28 interaction transduces a number of signaling transduction pathways that increase chemotherapy resistance to pretty much every drug that we've ever tested against myeloma and other death factors. And it does so through a number of mechanisms.

CD28 also binds to CD80 and 86. It's ligand on dendritic cells. And that induces the dendritic cell to make things, including IL6, which is a pro-survival molecule for myeloma, and Indoleamine 2,3-dioxygenase, which our melanoma colleagues will tell you is an immunosuppressive drug. And there are inhibitors for that. And that IDO converts tryptophan into kynurenine. And interestingly, kynurenine is a ligand for the aryl hydrocarbon receptor, which appears to transduce a pro-survival signal to myeloma.

So what can you do with this? So now you've identified the important interactions that seem to keep myeloma cells alive. What can you do with it? Well, this kind of a framework now allows you to identify molecules in the red that can now be used to target these interactions. So we'll go through some of them.

So CTLA4Ig-- CTLA4Ig, you've seen it on television. It's called orencia. It's used for the treatment of rheumatoid arthritis. It binds the CD80 and 86 and blocks T cell activation. So our thinking is, well, blocks T cell activation, maybe it'll block the ability of these dendritic cells to give a pro-survival signal to CD28.

So through-- actually, one of our MD-PhD students did this, took it all the way to the writing of the clinical trial. And essentially what we find-- this is a patient who has secondary PCL and had failed all those therapies in the box, was essentially having his myeloma circulating out in the blue. We had run out of everything for him. There was nothing left we could give him.

He was CD28 positive. So we treated him with carfilzomib, cytoxan and dexamethasone, three drugs that he had failed previously. Gave him Abatacept to block his CD28, to resensitize his plasma cells to chemotherapy. And we got this response, where he really had a significant reduction in his circulating plasma. So this and other studies have now served the basis for a Phase II study that's ongoing, using Abatacept to resensitize myelomas to chemotherapy that they were previously resistant to.

So what else could we do this to? And this my favorite slide, because we haven't actually tried this yet, but we think that there is a real advantage. So as Phil told you, that BCMA CAR T cells are now showing promising efficacy against myeloma. And the one component of-- so the problem with the Abatacept stuff is that, all right, you're going to give Abatacept-- you might sensitize myeloma cells to chemotherapy, but you're also going to be suppressing all the T cells, and aren't T cells important?

So the question is, are there T cells that are resistant to being blocked, having their co-stimulation blocked? It turns out that CAR T cells are. Because that little blue box up there is a piece of the CD28, or 41BB domain, that they've stuck into the CAR. So now, in addition to the CD28 from the blue Ys that you're getting, you're getting CD28 or co-stimulation from the car itself.

So we think that if you block-- you block the ability of cells to bind through CD28 with CTLA4Ig, you're going to resensitize the myeloma cells and kill them. But the CAR is resistant to this, because it's getting its DC28 co-stimulation through the CAR. So it's unaffected by the immune suppression you have with using CTLA4Ig. So we think that this is a rational combination.

The other thing that we think might happen is that, as Phil pointed out, that BCMA CAR T cells, through their cytokine release, are activating a bunch of other immune cells, maybe other T cells, to generate cytokine release syndrome. And we think that if you block CD28, through these normal cells who need CD28, you can actually potentially suppress CRS. So we think that this is a rational combination for CAR T cell therapy. As Phil mentioned, we do need to do more with CAR T cells. And I think it's going to be through rational combination.

One other target that I want to point out, that this framework has allowed us to look at, is kynurenine. So kynurenine is the endogenous oral hydrocarbon receptor. People know of the ayrl hydrocarbon receptor as the dioxin receptor. It turns out that it is highly expressed in plasma cells. And when our collaborator, Nisha McKiperov in his lab, looked at AHR expression in myeloma, saw that AHR expression was bad in multiple myeloma, in terms of overall survival.

So they, through bioinformatic magic-- I have no idea how they did this, but they figured out that there was a drug that was a previously unrecognized aryl hydrocarbon receptor inhibitor. Interestingly, this drug is called clofazimine. It is on formulary worldwide for the treatment of tuberculosis and drug resistant leprosy. And in the Philippines-- it's an oral drug you take twice a day. And in the Philippines, it cost $24 a month.

So they said, huh-- I wonder if this is a new anti myeloma drug. So they tested it in bortezomib mice, human xenografts, and they showed that clofazimine, in the blue, was just as good as single agent bortezomib in these patients. And then when we used Leif Bergsagel's spontaneous immunocompetent Vk MYC myeloma model, showed that clofazimine was just as good as bortezomib as a single agent.

So we are trying to move this drug forward. It's a lot of complications. But it's interesting, because it is inexpensive, has virtually no side effects, has a gigantic safety history. One might think that this would be useful in potentially MGUS patients, or earlier stage patients, where you would not want to incur the costs or the toxicity of more of the therapies that we have generated.

So that is just an idea of how we approach these things and how we think about them. We think about them in the context of resistance. The summary of my talk-- I'm probably droning on-- is that clonal heterogeneity in treatment-- clonal heterogeneity in terms of treatment resistance, I think, is the major challenge in multiple myeloma, that for chemotherapy resistant disease what you want is an integrated combination of non-cross resistant therapies, to eradicate as many clones as you can, with the idea that there is, I think, significant space to develop immune based therapies with broad specificity, that can keep control of the residual tumors for long-term maintenance, without the necessity of constant chemotherapy and its associated toxicities.

I think for chemotherapy resistant disease, you have to go back to the biology. And you have to understand what are the important pro-survival pathways, resistance mechanisms that will be essential for the development of new therapeutics. Because I think that that's going to be our major challenge. With that I'll stop. These all the people that did all the work. I'm just the pretty face that gets to stand up here and tell you about it. And with that, I'll take any questions or sit down.

[MUSIC PLAYING]