Melflufen for Myeloma: A Deep Dive

The FDA recently granted priority review to a new drug application for melflufen (INN melphalan flufenamide), in combination with dexamethasone. Melflufen is intended for use as a first choice for patients with multiple myeloma whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody (triple-class refractory).

Melflufen is a peptide-drug conjugate (PDC) that targets aminopeptidases and rapidly releases alkylating agents into tumor cells. The combination treatment demonstrated encouraging efficacy and a manageable safety profile in heavily pretreated patients. The myeloma panel is taking a deep dive on melflufen with Dr. Paul G. Richardson from Dana Farber Cancer Institute and will touch upon the details of the trials, side effects and treatment regimen.

Full Transcript:

Priya Menon: Hello everyone and welcome to CureTalks. I'm Priya Menon and today we are discussing a new drug called Melflufen, which has been granted priority review by the FDA in combination with dexamethasone for use in patients with multiple myeloma. And we have with us a very distinguished myeloma specialist, Dr. Paul Richardson. Dr. Richardson is R.J. Corman Professor of medicine at Harvard Medical School, the attending physician in the division of Haematology-Oncology and the multiple myeloma and bone marrow transplant service at the Dana-Farber Cancer Institute. He is a Clinical Program Leader and Director of Clinical Research for Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute. Welcome to cure talks Dr. Richardson.

Dr. Paul Richardson: Priya it's a pleasure to be with you and it's wonderful to be with you and Gary and Cynthia.

Priya Menon: So, as Dr. Richardson mentioned the myeloma panel today consisting of advocates and survivors, your very own Gary Peterson, Cynthia Chmielewski and Yelak Biru, so everybody thanks for joining in today. To all those people who are watching us live, we will be taking in questions at the end of the discussion based on availability of the time. Please add your questions to the comment section of the page or you can also email me at priya@trialx.com. Dr. Richardson let's just get started with the discussion. And my first question which I've been asking consistently on Cure Talks this season is what everybody wants to hear- on covid vaccines. So, what are you telling your myeloma patients about the vaccine? Should they take it considering the fact that they already immunocompromised?

Dr. Paul Richardson: Oh, no, we're all recommending vaccination be our top priority for our patients. There are some broad guidelines that have come both from the IMF and the IMS actually. The IMF guidelines are basically driven by the IMS which is the International Myeloma Society guidelines. So, I think when you look at these guidelines, you have to realize that they are generated for U.S. patients from an international perspective. So that reflects the fact that there are different vaccine platforms in different countries. The very good news for the United States is that we have the RNA based vaccines in the form of the Pfizer platform and Moderna platform and to my mind these are an extraordinarily impressive technologies where I think we've seen vaccination protection rates in the excess of 90% in normal volunteers. So that being the case in our own patient population. We have to recognize that's probably going to be a bit lower to give people a frame of reference if you have an influenza vaccination as a normal, as an ordinary person your coverage is around 50-60 percent. In myeloma patients, we know that's a little bit lower. Probably the same applies to Moderna and to Pfizer but nonetheless, we don't absolutely no but it's probably going to be still a

remarkable degree of protection. So, we're encouraging all our patients to vaccinate. But at the same time once they're vaccinated still not to let their guard down. You still have to be sensible to distance, to mask and follow all the precautions. Some of my patients have been checking themselves for antibodies after they've been vaccinated. I don't think we really just don't know how to interpret that information. So, I'd caution patients about getting depressed if they then have an antibody test and it doesn't get the requisite number. I think we just don't know what that exactly means. What we do know is that the RNA platform generates not only a humoral response Priya, but it also generates an innate response and that's the beauty of the RNA platforms because essentially it's not just your antibody response to the virus, it's the other parts of your immune system that are very important as well. Now the question then becomes is what about your treatment? Well, I think the IMS and IMF guidelines are very good, but I think one just has to encourage each patient to talk to their provider for the following reasons. Whilst we know that avoiding exposure close to steroids make sense. Really when it comes to drugs like Immunomodulators, the concern might be not so much that it would suppress response to the vaccine but might magnify side effects. So being on an image, we know from studies we've done with other vaccines actually enhances your response to the vaccine. The only caution would be that you don't want to actually magnify it to the extent that you have a side effect. So, our advice is generally been if you're on three weeks on and one week off of your immunomodulatory drug, be it lenalidomide or Pomalidomide perhaps having it on your week off makes the most sense. Avoiding being too close to a steroid and again its practicality not perfection, if you've gotten steroid a couple of weeks before and you get your slot for your vaccine don't waste that slot, get the vaccine. It's far better to do that than be puritanical and say I just got my steroid just a few days ago, I can't possibly do this. Remember the vaccine effect takes about a week to be on board. One area that has been a source of confusion and I would say the same applies to Proteosome Inhibition, we have no evidence that Proteosome Inhibition actually blunts the ability to amount of vaccine response. So, I wouldn't get too concerned about when you've had your bortezomib or your Carfilzomib therapy. One area to be a little careful of is antibodies because obviously when you get Daratumumab when you Isatuximab, Elotuzumab, Belantamab mafodotin whichever of the antibodies you receive, you probably get a little steroid with it. So perhaps being a little bit away from the antibody makes sense and that I think is reasonable. So, a common-sense rule is been a week or two at least two weeks if you can. The other way we've approached this is to look at the things like IVIG. Now if you're giving an attenuated virus to a patient as your vaccine platform, that would be for example AstraZeneca, you have to be careful about IVIG because it blocks an FC receptor which allows the immune system to grab things and learn from them. So, if you're getting an AstraZeneca vaccine that may not be a smart idea to be group close to IVIG. Interestingly for the RNA platforms, the same immunological mechanism does not apply. So, whilst we're encouraging people to be away from their IVIG, couple of weeks perhaps it's not an absolute rule and I'm a little bit concerned because some patients may say I'm going to stop my IVIG for three months whilst I get vaccinated. Probably not the best idea, just simply common sense and working with your providers. Now one class of drug to definitely be away from when you get your vaccine is chemotherapy.

We know that alkylated based therapy is potentially a blunt to immune response. And so therefore being far away from chemotherapies, you can probably does make sense. And we know that from studies done for example with flu vaccines where when flu vaccines and their responses were tested of all the drug classes that were the most suppressive to vaccine response interestingly, it wasn't actually even steroids, IMiDs, Proteasome Inhibitors there weren't a lot of antibody expose patients in the study, but it was the chemotherapy, the Alkylators that were the most immune suppressive. So, a lot to digest for the audience there, but I hope those guidelines are helpful.

Priya Menon: Definitely. So, talk to your provider and get your vaccine. I think that's the message that is given here.

Dr. Paul Richardson: And don't be afraid if you are on treatment, don't be afraid of I can't have my treatment because I'm going to be vaccinated or vice versa.

Priya Menon: Thank you. That's very helpful Dr. Richardson. Now, although we are still dealing with the complexities of the coronavirus, I believe myeloma progress is still happening. And we have the new drug

which has been granted priority review. Dr. Richardson, what is Melflufen and why is it so exciting and what do you predict will be the change in the myeloma treatment scenario with the addition of this new drug to the already existing treatment protocols, the myeloma armamentarium?

Dr. Paul Richardson: Well Priya, I think the excitement around Melflufen is built on the fact that it's adapting a very key platform that we've just alluding to alkylator therapy into a very new and novel targeted approach that provides greater efficacy, which reflects not only greater activity but also better tolerability. And so, Melflufen is what we call a peptide drug conjugate. It's a very clever way of delivering the alkylator warhead to where it needs to be. So, they help patients understand it. If you think of very exciting antibody like Belantamab mafodotin, the antibody is Belantamab and the warhead is mafodotin. That's a Belamaf or Blenrep for people who may know it under a different name. So, it's a similar principle in a sense, except you're not using an antibody, you're using a delivery system flufenamide that allows you to get the warhead where it needs to be. So, how does this happen? Well, basically Melflufen which has got the chemical name Melphalan flufenamide, but it would be a mistake to think of it as isn't this just glorified Melphalan, no absolutely not. It's very different. It's a lipophilic drug and if you may think of your bone marrow is packed with fat so you need when you need to get to your myeloma, you need drugs that are like to go into fat like of interesting enough Melphalan is lipophobic so that immediately tells you is quite different. And second of all when it gets into the bone marrow environment, it's only turned on by things called Amino peptidases. So, what happens is this peptide drug conjugate drops into the bone marrow, it's lipophilic, so likes to go there and then this key enzyme called an amino peptidase, which is markedly over expressed in myeloma, when the chemical drug conjugate enters the cell, the amino peptidase, preps it, clears it, the warhead shoots where it's supposed to be which is the nucleus of the myeloma cell. And because Amina peptidases are not expressed anything like the same degree in normal tissues, you have literally a targeted delivery of your warhead. And what happens is that the warhead is trapped in the myeloma. So, if you go through a normal cell, the peptide drug contra just scoots through and if you go into the tumour cell, it stops- warhead delivered and there we are. So, that's the rationale behind it and preclinically I want to specially acknowledge my colleague Dr. Dharminder Chauhan who really demonstrated very elegantly in preclinical models of myeloma both on the bench and in our rodent models that this was a real effect. So, when he compared the behaviour of tumour cells exposed to chemotherapeutics completely different to when exposed to Melflufen, with much more effects in Melflufen. And the same thing was seen when he compared it to other drugs that we typically use. The very exciting thing is that he also showed that there were anti-angiogenic effects and all sorts of things that make Melflufen very interesting. You may say, what about the anti-angiogenic piece? Well, when we give Melflufen to patients, it works in what we call extra medullary disease which are lumps of tumour. Those are very angiogenesis dependent, mostly depend on these new blood vessels to feed them. So, we think there are differences the way Melflufen works to contribute to actually its efficacy. One very interesting aspect of its biology is its ability to target high risk disease. It targets the sort of stemness of myeloma and it targets in particular in elegant preclinical work which has been demonstrated 17p diluted disease. So, there are effects that make it attractive as a drug beyond just traditional chemotherapy. From a patient perspective which is key is the tolerability, you don't lose your hair, you don't get mouth sores and what it does cause suppression of blood counts and we are very careful about that and we're also investigating very carefully the potential risks of some of the side effects we see with other chemotherapies. Nonetheless generally speaking and it appears to be well tolerated and manageable and we don't see the same rates of infections that we see with other drugs classes and we similarly because it's a very simple infusion once a month. It has the real attractiveness of not requiring too many visits to the clinic. You just come once a month, that's it. There's no cardiac issue, no ocular issue, there is no neuropathy. We are very careful about blood cancer. That's one thing we have to watch and the impact of that but beyond that is generally well tolerated.

Priya Menon: Thank you, Dr. Richardson. And now I'm going to invite the panel. Gary, you can start with your questions.

Gary Peterson: Thank you. First of all, I'd like to thank you, Dr. Richardson for all you do for and you for putting this whole thing together Priya. For all the work that you do and your leadership and the development of new classes of drug and then also, new treatment paradigms, for example, I know that you were integral

and coming up with state-of-the-art care called VRD or Velcade Revlimid Dex, you did a lot of work on that. Also, recently Selinexor was another one which you and a number of people worked very hard against a lot of say ignorance on the part of the FDA because they didn't understand how to deal with the side effects. And the same thing goes true with this one Melflufen, it's a brand new class of drug and in the last 16 years, we've had 10 new drugs, 10 new classes of drugs all of which had dual designations by the FDA meaning it was on priority review, fast Track and as well as being orphan drug designation. So, I just wanted to thank you for all that you do for that. Right now, we have 7 new drugs, which we've talked about and 4 of them were CAR T, one was in the cell or BB 2121 and 3 others that we did. Another was CLR 131 which is very similar to what you're talking about, but they use lipid rafts, but it's a whole new delivery process and just like Melflufen is a whole new delivery process which seems to be irrespective of others. You don't have to have BCMA, you don't have to have CD38, you don't have to have all these things. You have a whole different mechanism for targeting which I think is fantastic. So, Dr. Richardson, some people confuse Melflufen for Melphalan but that is much like saying this highly targeted approach is the same as using a shotgun. But can you explain why this is so different and few of the target issues of say Melphalan or Cytoxan or anything like that?

Dr. Paul Richardson: These are great questions Gary. First and foremost thank you for your very kind words, but I want to especially acknowledge that it's a real team effort and it's been my privilege to work with a great group of clinical investigators, laboratory scientists and actually it's wonderful to have you and Yelak Biru on the call and Cynthia too because we've had great patient advocacy and participation in our trials which has led to this incredible team effort. I do want to qualify one thing you said just to be very clear FDA have always been, we're very lucky we work with a myeloma team at the FDA. They are outstanding and it's been a privilege to work with them. I think sometimes it's more difficult to deal with when you're in very tough study, populations are very resistant disease where you are maximizing your therapy because that's the only way you're going to get a response, side effect profiles and magnified. So, FDA have a have a really important job of addressing safety and I found them incredibly collaborative in that role. But I do agree with you, outside of the FDA with Selinexor there was some uninformed comments being made by people aren't used to drug a lot, to some say it was far too toxic. It's a challenging drug Selinexor but especially when you combine it and use it just once a week, the results we are seeing are remarkable. So, I appreciate your comments about that.

Gary Peterson: I told you I like the FDA because they have given us 16 or so drugs where we have 500 drugs for all 7000 diseases and we got more than our fair share.

Dr. Paul Richardson: I agree and I think that's you hit the nail on my head and I think it's to sort of be very clear. We've got the drugs you've mentioned are coming. We have 12 actual novel drugs approved over the last since 2003. So, you're absolutely right. We're in a very very sweet spot, there are many more combinations approved just to explain to the audience. So, that's why there are approximately 30 approvals. But there are actually 12 drugs currently approved Melflufen would be number 13 either so hopefully number 14. ___ and others are coming, plus all those that you kindly mentioned. So, I think an incredible team effort, but I also want to bring you back to a point you made about RVD because this was where we bought drugs together and formed by the laboratory, build the platform, but what was very important about RVD is that we not only saw synergy in terms of its effect, but very importantly we saw excellent tolerability. And for example, when we try to look at say KRD versus RVD, frankly, I was expecting KRD to knock the socks off RVD, it actually didn't because guess what the side effects matter. So, for that reason we really think sort of broadly about how to manage things. So, that's why when we come back to Melflufen and I want to emphasize it really isn't just, as I say glorified Melphalan and it really isn't. We've deliberately sought to exploit a therapeutic index by being more targeted, we can deliver that much more of the warhead to the tumour and minimize the surrounding damage to normal tissue. It sounds very simple, but it's actually very complex and what that actually results in and what we've been able to show is that this delivery of the peptide drug conjugate and the trapping of the cytotoxic motive within the cell very similar in the sense to Belantamab mafodotin in a different context that's Blenrep. This results in a very different pattern of killing in the myeloma and as a result of that in the clinical trials we've done, we've been very strong that Melflufen as a single agent just simply combined with dexamethasone once a week has generated about a third

response rate, by the thirty percent response rate in patients in whom all other treatments have failed them. And very importantly in those patients with extra medullary disease, which is such a challenge, we are seeing responses of the order of around 25% just with the drug alone in a setting where really the best we see from other agents is much less than that. So, with that in mind the future of Melflufen, frankly in my view is going to be in combination and there's some very nice data to share with you Gary where we combined Melflufen with daratumumab, would combine Melflufen with bortezomib and again always with the view of being practical, simple also frankly cost-effective. That's why Melflufen-Velcade is a good platform. We can actually engender great responses and it's fair to say there's around an 80% response rate when you combine Melflufen with daratumumab and a little bit less but comparable with Melflufen Velcade even if you've had prior velcade. So, for that reason, we're very excited by the promise of Melflufen.

Gary Peterson: Well, you just have just jumped all over my second and third question. So, I thank you very much. He has run through them all in a very short time, saved me a lot of talking. So, with that let's go to Cindy and see what she has to say. Cindy, you online?

Cynthia Chmielewski: So, Dr. Richardson provided so much information into almost took all my questions too, but I guess I'm kind of curious about this peptide drug conjugate as opposed to an antibody. What's the difference? What are peptides and why choose one? With antibodies you either target at CD38 or BCMA and things like that. With peptides, do you target them?

Dr. Paul Richardson: Yeah, Cindy that's a very good question and Gary touched on it. Obviously, we're very lucky that we have specifically targeted approaches like CD38 and BCMA. CD38 is a marker expressed on all myeloma cells, BCMA B-cell Maturation Antigens are also expressed on myeloma cells, but they reflect part of a line of development in the myeloma ontogeny. So, remember in myeloma, it's not just one line, it's an incredibly heterogeneous, multiclonal neoplasm. So, I think one of the advantages potentially of Melflufen is it targets the tumour broadly. Amino peptidases are expressed throughout myeloma whether it is expressed BCMA or has less expression, whether it's CD38 overexpressing or for any reason if CD38 expression is down regulated because of prior treatment with CD38 antibody. The reality is that Melflufen in an indiscriminate fashion, if you will, targets the disease and I would argue that this is the advantage potentially of the drug because it offers an ability to target what I call stemness. Now, stemness isn't just one cell, the complexity of myeloma biology is such that stemness is a composite. But this is I think a very important target we've known from the benefits that Melphalan has delivered, the targeting stemness is important. The Challenge from Melphalan is that it obviously has some side effect profile and the drug delivery challenge because you have to dose escalated to get it to what we need to do that makes it more difficult in the long term. In the short to medium term always seemed that Melphalan's toxicity is manageable but long-term issues we are coming to learn about not least of which secondary cancers. Other things include really very important recent data showing that the genetic signature of cancer that survives Melphalan is much more adverse than if you don't get Melphalan. And so what we're hoping with Melflufen is by being more targeted, taking advantage of stemness, but at the same time avoiding the side effect profile the Melflufen has that we will in many ways be able to overcome some of those challenges. My personal belief Cindy is that you need to use Melflufen best in combination because I think that's where we'll really get the maximum benefit of the drug and we're working to figure out how best to make sure that it doesn't carry with it in the longer term some of the challenges that we see from Melphalan.

Cynthia Chmielewski: So, right now it's being used as a single agent or in combination with dexamethasone or how's it being studied?

Dr. Paul Richardson: Right. So, in the FDA approval will be Melflufen with dexamethasone and we know that's important. We know that dexamethasone matters, even if you've had dexamethasone before and even if you become resistant to dexamethasone because that's actually part of the biology of the way it works within the cells. So, we know that's important what's really exciting and Dharminder was sort of first preclinically to show this but when you combine it with other drugs things go into a very different level of attacking the myeloma and the really good news is that the combination studies led by my colleague ____, it's an international study group, the Anchor study. ___ has provided fine leadership with ___ as one of the

senior investigators on that study. Basically, we've been able to show any anchor trial that when you combine it with other drugs, things really go into a new level of activity. So, the way to think of it is that it could become a very viable alternative to traditional chemotherapy because it would offer the promise of being more targeted and having fewer side effects.

Cynthia Chmielewski: So, if I'm understanding correctly, then I know one of the things that people are concerned about the other cytotoxic drugs is sometimes it causes damage to the DNA and that was a concern in the myeloma community about damage to the DNA with the stem cell transplant. The Melflufen since it's more directed may not cause that damage. Is that what you're saying?

Dr. Paul Richardson: We're hoping so. That always remains an area of important study, but I think it's very important to note that a lot of the drugs we give be they chemo like Melphalan and cytotoxin or even drugs like immunomodulator drugs can cause damage to DNA. They do, it's part of the challenge of exploiting the therapeutic index in cancer medicine. You have to deliver enough firepower to eliminate the tumour cell but hopefully minimize surrounding damage to other cells. So, I hope in Melflufen is by having a more targeted approach that therapeutic index will be better. In other words will be able to spare potentially some of the side effects that we see more typically from other chemotherapeutics, but I would emphasize this is an area of active study and we clearly shown from our studies that —-exist with Melflufen. And we also know from our experiences with prior chemotherapies that prolonged exposure to these drugs over time may enhance the risk of secondary leukaemia, for example. With all of that in mind, that's why I'm particularly personally excited about Melflufen and in combined with other drugs. I could foresee for example, where we would use Melflufen and bortezomib and then CD38 antibody achieve a fantastic response. It's just outpatient therapy, no hospitalizations needed and then you would then go into a maintenance phase with drugs that we know unless associated with what you're just to describing. So you can imagine how we would use this intelligently to exploit what I call therapeutic index.

Cynthia Chmielewski: Great. And something you said earlier that caught my attention that you saw some activity with Melflufen in extramedullary disease more so than other types of drugs that we have?

Dr. Paul Richardson: Yes, that's it. That's an excellent question and Cindy appreciate you emphasizing it. So, extramedullary disease is a challenge for us. This is where the myelomas escape the bone marrow, is sitting outside of the bone marrow besides the liver, the lymph nodes ,the pulmonary area, be within the lung or outside of the lung. These are very challenging manifestations of myeloma spread and what we've come to realize is that all our drugs work against it initially, the problem is that over time resistance characterized by escape in extramedullary compartment is becoming a real problem and we're seeing this particularly after say antibody treatment has failed. So, what we were very impressed by in our study was that we were enriched for patients in whom antibody treatment had failed them and they had extramedullary disease. And obviously if you have extramedullary disease in the first place and you receive an antibody, the response rates around 20%. But once an antibody has actually failed you and you have extramedullary disease, obviously that represents an even more difficult situation. Remarkably in that population, we're seeing about 25% of patients responding to just Melflufen and Dex. Why I'm so excited about that is I think if we simply add a proteosome inhibitor or add other drugs to that we could see this go up a notch. So, we now have a real potential answer to the challenge of extramedullary disease.

Cynthia Chmielewski: It's great. Wonderful to hear and one last question. Does it cross the blood-brain barrier? Have you seen it in after meningeal myeloma, like that's another area?

Dr. Paul Richardson: Cindy, such a great question. I'm so grateful for you raising that. No, we would not expect that based on the biochemistry, but we have other drugs that do cross the blood-brain barrier. Selinexor is one of them. We know that some of the immunomodulatory drugs like pomalidomide can do it and there's a great proteasome inhibitor that in my mind ___ much better study called Marizomib, which we know crosses the blood-brain barrier. In fact, it was tested in paediatric brain tumours and in glioblastoma. Interestingly in paediatric tumours, it's active. In glioblastoma, the phase 2 studies were very interesting. The large phase 3 that was launched has been fully enrolled and my understanding from it is that just like a

lot of glioblastoma trials, the results are not very clear cut, that we're not entirely surprised because remember glioblastoma is a very different set of diseases to myeloma. But, we're on the cusp of launching a study led by my colleague, Dr. Clifton Mo of Marizomib with pomalidomide in CNS myeloma to address your point. But I see promise for CNS myeloma by virtue of combination strategies like Selinexor for example, hopefully Marizomib if we can get that across the goal line another approaches like it. But Melflufen might be part of an approach that we would use in a CNS affected patient, but specifically crossing the blood-brain barrier, we would not expect.

Cynthia Chmielewski: Is Marizomib to targeting CD38 too like the others?

Dr. Paul Richardson: No, it's actually a very interesting drug Cindy. Marizomib is a proteasome inhibitor. It's the most powerful proteasome inhibitor we have. It is more power from carfilzomib and is more powerful than bortezomib and more powerful than Ixazomib. It is derived originally from a marine source. And what's so interesting about it is, it targets what's called the beta 5 subunits of the proteasome, but also beta 1 and beta 2. These are the mechanisms by which proteasome inhibitor resistance occurs. And we've actually done wonderful preclinical studies again Dharminder Chauhan, my colleague has been on the forefront of that and then at the same time we did clinical trials and I'm really hoping the drug will continue to have momentum. Because for a variety of reasons not really scientific necessarily, it hasn't seen as much study in my opinion as it should have done.

Gary Peterson: Is that the one that has been approved for use in myeloma in Australia?

Dr. Paul Richardson: No, the one approved in Australia is very interesting. That's also from a sea source, from the sea squirt that's called Aplidin and the Aplidin we've also studied a constant team on CRD at our Center did the preclinical work and we did a phase 2 trial, we've got ____. The reason it is not approved in the U.S. is because the sponsor at the time of generating the phase 3 studies didn't engage with the FDA particularly well and had randomized trials where Aplidin was been given with dexamethasone compared to dexamethasone alone. Obviously in the U.S. we said folks that doesn't make sense. So to me, it's paradoxical that Australia has had approved because the Australians have a regulatory apparatus with the greatest of respect, I thank God for our FDA is but what I would say is that basically it that's why it's approved idiosyncratically in Australia, because , it works but no surprise because dexamethasone we know now is a drug from 20 years ago, it's not now. But nonetheless, I don't think it diminishes in any way the promise of Aplidin and I rather hope that drug too gets his day in the sun because it clearly has effects but it's not a proteasome inhibitor. Marizomib is a proteasome inhibitor and it's what's called a beta lactone proteasome inhibitor. It's in my opinion one that really does warrant further study because I think honestly people thought with Ixazomib, with bortezomib, with carfilzomib we don't need any more proteasome Inhibitors, what we all know now that that's not true. Ixazomib is a lovely drug, it's not as powerful as Carfilzomib and Bortezomib which is in the main state but as our patients live 15 and 20 years, we need the PIs later as well as earlier, right? And so I'm very hopeful that Marizomib, we are going to do our best to try and bring it to patients.

Cynthia Chmielewski: Thank you so much. Yelak?

Yelak Biru: Yes. Hi, Dr. Richardson ____ is given the orphan drug and priority review designation by the FDA, right. So I want to double click on that and the new drug application review is expected I believe still this the end of this month. What happens during that meeting? I want patients to understand the mechanics of that.

Dr. Paul Richardson: I understand this. There are no old actors. No, this is going through the traditional regulatory process that the FDA apply for an accelerated approval and the date of declaration is supposed to be by the end of this month. My expectation is that we'll have that approval at any time because again in great credit to the FDA, they always understand cytotoxic drugs. But when drugs have challenging and different toxicities and the best example of that is Belantamab Mafodotin with the eye issues which are very real, but fortunately we can manage them. The FDA are obliged and rightly so to say we'll wait a second

let's try and figure this out and Gary alluded to it when we had one with Selinexor some real challenges from the GI standpoint for side effects, the FDA guys want to hear about this so we can really go through a process to be very sure that the accelerated approval is warranted. And in great credit to that process, we then had the Boston trial where clearly Selinexor performed extremely well against the control arm and hence the approval. So, I think that you're going to see at the end of this month, hopefully from the FDA a green light to say Melflufen is there for use in accelerated approval. We then have a very important study called the Ocean study, Horizon is the study that's informed accelerated approval, Ocean is to study led by my colleague Dr. ___ who is a very prominent leader in myeloma research in Europe and he's actually the president of the European Haematology Association to boot and a really great person and he has led this phenomenal trial of comparing Melflufen to Pomalidomide index and we will hopefully have a readout from that study fairly soon. And if that comes through say later this year or next year probably more likely next year to be fair. Then we will have it be in a position to get full approval for Melflufen and in the same way as Selinexor got full approval in December.

Yelak Biru: Nice. Okay, one of the challenges that you mention in previous meetings was what to do for patients that end up progressing on CD38? How do you see Melflufen fitting in that algorithm? If I come to you as a patient and present myself, what is the mental algorithm you go through to say Melflufen maybe for you?

Dr. Paul Richardson: Excellent question. I would simply say that the CD38 failure in a patient daratumumab fails a patient or say Isatuximab does, this is a major challenge for us here like and I think that this drug class adds to our ability to meet that challenge with additional combination approaches. So, I think we'll be in a position to meet that challenge for these additional drugs. So for example Melflufen in combination with something might be an ideal combination to do that.

Yelak Biru: Okay.

Dr. Paul Richardson: My friends, I must apologize but I have to sign off because I've just been paged but it's been an absolute pleasure to work with you and it's a great pleasure to see everyone and I just want to wish you well and just say thank you so much for your interest in Melflufen and we greatly look forward to continuing our dialogue as we bring exciting new advances this year as well as in the future. So, Priya thank you so much and I apologise, I've just been paged urgently. So I must jump off if you don't mind.

Priya Menon: Thank you.

Dr. Paul Richardson: Thank you. God bless and take care.

Priya Menon: I think he covered a lot of information in such a short time. So, I think this is definitely a talk I need to listen to again from the very beginning. So, thanks everyone for joining in and Cindy, Gary and Yelak thanks so much for your questions. We already have a lot of listeners actually on the stop now. So, thanks everybody for listening in. This talk will be available on Cure Talks website and along with its transcript. So, thanks, everyone. Stay tuned for more discussions on curetalks.com and stay safe. Thank you.

Thank you. See you soon.