Treatments for Early Stage Plasma Cell Disorders

Plasma cell disorders like multiple myeloma, plasmacytoma, smoldering myeloma, MGUS are diseases in which the body makes too many plasma cells. These disorders have different symptoms, treatments, and prognoses.

The myeloma panel is talking to Dr. Craig Hofmeister from Winship Cancer Institute on advances in treatments for early stage plasma cell disorders.

The discussion would cover smoldering myeloma, focusing on updates from ECOG trial discussed at ASCO2019, treatments of newly diagnosed myeloma based on the results of CASSIOPEIA trial and use of precision medicine to treat patients in the first relapse, highlighting MYDRUG trial.

Follow reference slides HERE.

Full Transcript:

Priya Menon: Good morning and welcome to another episode of CureTalks. I'm Priya Menon, your host and today we are discussing plasma cell disorders. We are joined by Dr. Craig Hofmeister from Winship Cancer Institute of Emory University. On the patient panel, to discuss the patient perspective, we have patient advocates, Gary Peterson, Jack Aeillo, Cynthia Chmielewski and Yelak Biru. A warm welcome to the panel and the audience. Those of you who are listening to the show on our website can follow slides via link provided on the page as well. So to get the show started, we have with us Dr Craig Hofmeister who is associate professor of Department of Hematology and Medical Oncology at Winship Cancer Institute. Dr Hofmeister's work focuses on plasma cell cancer. Dr Hofmeister, great to have you here with us, welcome to cure talks.

Dr Craig Hofmeister: Thank you so much. Looking forward to it.

Priya: So I have a few questions for you to begin with the discussion after which I will hand over to Gary Petersen to lead the patient panel discussion and towards the end we can take some audience questions as

well. My first question to you Dr Hofmeister is about the recent ECOG trial, which now confirms the benefit of early therapy with lenalidomide in smoldering Myeloma. So it'd be great if you could talk about the trial and how would these findings support a change in clinical practice?

Dr Craig Hofmeister: Excellent. Thank you so much. So this, we had the American Society of Clinical Oncology meeting in June earlier this month. And my boss, Dr Lonial, described the ECOG 3806 trial. This was a randomized phase three trial of lenalidomide alone or Revlimid versus observation. And it was, in patients enrolled in this had asymptomatic high risk smoldering Myeloma. Now the definitions for high risk smoldering Myeloma are very confusing and different based on the protocol. In this protocol, patients had to have smoldering Myeloma which is greater than 10% clonal plasma cells and bone marrow biopsy or greater than three grams of monoclonal protein in their blood. And they had to have a sufficiently abnormal serum free light chain ratio in their blood. This is what got them into the trial and that's sometimes different than other smoldering myeloma trials that you see.

And it should be always mentioned in a setting where both, potential physicians and doctors are listening, that the words high risk that physicians use here are talking about high risk for the patient's smoldering Myeloma to develop into clinically symptomatic active multiple Myeloma. And once the patient develops multiple Myeloma, then we use the words high risk to basically describe whether the patient is a relatively treatment resistant and differentiate those patients with high risk from standard risk patients that are thought to be more treatment responsive and have a longer overall survival. But back to the smoldering Myeloma ECOG trial that Dr Lonial presented here in June, it looked primarily at 90 patients who are on lenalidomide in the phase three portion of the trial, and 92 patients that were not treated with anything. And not surprisingly, the patients that didn't get treated with anything didn't have any response from the smoldering Myeloma.

But those patients who had lenalidomide or received that had about 50% of them had a partial response or better. And, that's in line with what you'd expect from single agent, lenalidomide. Interestingly, the quality of life parameters didn't seem to change in what was presented at the meeting. And the second primary malignancies, those patients who developed a different cancer during the period of observation and the trial, were very small so it's just a couple cases, four cases in the lenalidomide group, two cases in the observation group. And I'm not sure really what to make of that yet because none of these patients had received any other chemotherapy. The story of the presentation was primarily the fact that those patients with high risk smoldering Myeloma as defined by the current Mayo Clinic criteria that 20-2-20 criteria, which is greater than two grams per deciliter, monoclonal protein, greater than 20% plasma cells in the bone marrow biopsy and a serum free light chain ratio greater than 20.

Those patients had a clear benefit in terms of their progression free survival, meaning how long their smoldering myeloma stayed quiet before developing into active multiple Myeloma and that benefit was not really seen in patients with low risk disease or intermediate risk disease. So we took away from this, hey, if you have somebody who has high risk smoldering myeloma patients who are exceedingly likely to move towards active Myeloma, these patients seem to benefit from early therapy and benefit as described here means delay before they develop symptomatic Myeloma. We don't know yet whether they live longer overall and that's going to be years away from getting that type of data. But these patients certainly delay before developing symptomatic Myeloma. So that's the story with smoldering Myeloma. It's new. The only previous big trial on smoldering Myeloma was the Spanish trial, the QUIREDEX trial that use Revlimid and Dexamethasone. There were numerous kinds of critiques about that trial regarding patient access and the evaluation of Myeloma bone disease. That trial also showed a progression free survival benefit and it showed an overall survival benefit. So Dr Lonial's trial kind of showed us that we're likely to show a progression free survival benefit in the high risk patients and we don't know yet whether we'll see an overall survival benefit.

Priya: Thank you Dr. I'm going to be jumping to another trial right now – the one where Daratumumab in addition to the VTd regimen, showed longer PFS and a higher response rate as well, the CASSIOPEIA trial. So probably you could talk about this as well.

Dr Craig Hofmeister: Absolutely. So this was a huge phase three trial looking at a three drug standard in Europe, Velcade-thalidomide and dexamethasone and versus Velcade-thalidomide-dexamethasone with the addition of Daratumumab or Darzalex which is an active monoclonal antibody targeted toward CD38 used primarily in the US in relapsed Myeloma. Philippe Moreau presented this data at ASCO again earlier in June. It involved approximately a thousand patients and these were all young fit patients who were thinking about autologous stem cell transplant. So in Europe, that generally means those patients who don't have a significant other disease and are less than 65 years old, they were randomized to receive VTd which is the standard or to receive VTd with Daratumumab.

They then went on to receive autologous transplant, consolidated with VTd for two more months or cycles of treatment and then randomized to receive Daratumumab alone or observation. So, and I glossed over this point and it's worth mentioning is that at diagnosis and at the beginning of the trial, patients were randomized one to one to receive Daratumumab with induction transplant and consolidation or not to receive Daratumumab with induction transplant and consolidation. And then there was a second randomization, meaning that no matter whether you received Daratumumab with your initial treatment or not, you were randomized again, had a 50-50 chance of either having Daratumumab as part of your maintenance or having no maintenance. And so there's two parts to this and they only presented data for the first part of the trial. And what they showed is that the addition of Daratumumab didn't really change the overall response rate at all.

The majority of patients who have generally stage one and two revised ISS Myeloma had about a 90 or 93% chance of an overall response. There were more stringent complete responses in those patients who had more effective therapy, meaning effective for drug therapy led to a higher response proportion. Then those patients who had three drug therapy. And if you look at the subgroups of this, you see that most of the patients responded very well. But those patients who had ISS stage three disease and those patients who had high risk cytogenetics at diagnosis, their benefit was unclear with the addition of Daratumumab in terms of the odds that they would achieve a stringent complete response. The overall survival for this trial as well was not statistically significantly different between the groups. And that's not unusual because this trial only has had follow up for about 18 months.

So overall, this is a very large thousand patient plus trial in Europe using their standard three drug regimen their VTd and asking a question does Daratumumab add to it. And the answer is that Daratumumab slightly increases the response rate. It definitely improves the progression free survival. But the improvement in the response was not really enjoyed by patients who had high risk disease. And we don't know whether the addition of Daratumumab as part of induction therapy will prolong overall survival. It's not unexpected to see an improvement in progression free survival. In other words, how long if your myeloma stays quiet because you're adding four effective drug you're using four effective drugs versus three effective drugs. So that's not uncommon, but the real question is whether this will lead to an overall survival benefit.

And certainly we'll be waiting to see a median follow up duration as it gets presented at subsequent meetings over the next two to five years. So I think the question about whether to incorporate Daratumumab in patients who are newly diagnosed with multiple Myeloma, even if everyone was to do a Velcade-Thalidomide-Dexamethasone induction seems to be very appealing in those patients who have standard risk disease because they have a longer progression free survival, they have a better response proportion, meaning more patients went into a stringent CR. And, as far as toxicities went in this large trial, they didn't see a signal that was significant that they were having a lot more side effects although it did appear that those patients who got Daratumumab did have more infections than those patients who had a three drug therapy alone. So I think people will wait for this trial to show an overall survival benefit. But clearly regulatory agencies or are going to get submissions about adding Daratumumab to upfront therapy with VTd.

Priya: Dr, my last question before I hand it over to Gary in the panel, they have a lot of questions for you. It would be great if you could talk about the role of precision medicine and developing Myeloma treatment regimens especially with a focus on the MyDrug master protocol?

Dr Craig Hofmeister: Thank you so much. So this precision medicine has had a tremendous amount of hype and hope that we could target specific genetic abnormalities in patients with all types of cancers to specific therapies targeted towards that genetic mutation that is, people understand this, it makes sense to them. But it's been hard to really show benefit because many times these specific DNA mutations are in only a very small number of patients and then showing that patients respond better or live longer requires sometimes very large and very complex, so called umbrella trials to show that they're doing better. So there are umbrella trials in numerous solid tumors. The beat AML trial is an umbrella trial for patients with acute myelogenous leukemia trying to precisely treat those patients with characteristic abnormalities in a reasonable way.

And the MMRF is sponsoring a large umbrella trial called MyDrug, and it's really the first Myeloma umbrella study. And what they're looking for is to see patients early on in their disease course, meaning patients who've received initial therapy, whether it be just chemotherapy, whether it be chemotherapy and transplant, whatever they had initially to treat their myeloma. And then at the time of their relapse, if they have a relapse early on in their disease course and they have evidence of high risk disease, meaning they've relapsed early and they're not too sick, then these patients go on to get a bone marrow biopsy to essentially functionally target them to see what exactly genetic lesions defined their Myeloma from a large panel of known genetic lesions that are known to influence disease biology. And then depending on what abnormalities are seen on that bone marrow biopsy, they then get pushed into a particular arm of the trial. So if they have activating mutations of all different types, they are then pushed to an arm of the trial where they both get therapy that is fitting and targets plasma cells, plus they get therapy that is a genetically targeted therapy for that particular type of mutation. Now a lot of these mutations are not easy to talk about. They don't show up on your standard FISH or fluorescent in-situ hybridization panel that you can get at any oncologist's office. Many of these mutations, they really need to be tested by sequencing DNA so they're not available unless you're at a larger center and specifically unless you have access to this study and you can then, and so, the whole concept is to both attack the plasma cell with things that plasma cells are known to be susceptible to. So they're getting things like proteasome inhibitor, an IMiD, dexamethasone.

That's the core skeleton. And then adding on a genetically targeted therapy known to help specific genetic lesions. Now there are really four main pathways here. The fifth one is on hold for the moment. This is a translocation between chromosomes 11 and 14, where previously Venetoclax has shown significant benefit in this patient population. And at the moment, due to previous clinical trial results with Venetoclax suggesting that some safety concerns need to be addressed first before we can add that fifth pathway into this protocol. There's really four main pathways and if this genetic sequencing doesn't reveal that you have a specific abnormality where you'd fit in one of those main pathways, then you go to a standard grab bucket of, Hey, there's no detectable alteration. Let's just do Darzalex or Daratumumab plus Ninlaro or Ixazomib POMALYST and Dexamethasone and give that four drug therapy both as and learn about the activities for that control arm and compare all the genetically targeted arms against that main control arm. But we hope that even if we don't find that these four drugs or these four arms are the ones to use, we can in essence in the future swap out ones that aren't working, plug in another drug that might work better and test it in this ongoing trial. As people talk about these drugs as being cassettes that you can pull out of the protocol and then plug in. And that's what we hope to see here and be able to really bring precision medicine and into the early relapsed myeloma patient population. So that's the goal. This trial had a number of patients be screened. I'm not sure if the first patient has been treated yet. I know it's opening up soon to accrual at my home institution at Emory university. So looking forward to that. And that's what, I'm hoping that one of the successful future clinical trials is in Myeloma.

Priya: Thank you doctor. With that I'm going to hand over to Gary to begin with his questions. Gary you are on the air.

Gary Petersen: Doctor Hofmeister. I wanted to thank you for all your help, when I first started my website, you are one of the first to recognize the importance of places providing survival data. So I thank you for that. And I look back and you and I had conversations back in 2012.

Dr Craig Hofmeister: Yup. And I love your website and I love the idea of advocating for patients to be able to be seen by people that focus in Myeloma. And as I predicted at the time, there is now data in leukemia, now in Myeloma suggesting that if you have access to doctors that do Myeloma specifically, that things go better. I appreciate all your advocacy work today.

Gary: Well, thank you very much. And obviously you have joined a very strong team at Emory. Amazingly strong team. At the European Hematology Association meeting – EHA, myeloma specialist, Maria Victoria Mateos from Spain discuss the latest news from the Gem Cesar trial of a curative treatment when the strategy for high risk smoldering Myeloma. It's KRDS induction followed by a high dose chemotherapy, KRD consolidation and maintenance with RD. So far excellent results. Is this the early treatment end game?

Dr Craig Hofmeister: I don't think it's the end game because you really have to be kind of at the end to really know this is the end game. And I don't think we're yet curing patients with these regimens. And I don't expect cure with this trial or these regimens. But what we see from this trial is that there are many, many patients who have a great response. And I think Maria V described 93% overall response rates and those patients who were MRD negative in about a third of patients after induction therapy. I think that's impressive. And then after transplant it's about half of patients. And then after consolidation, it's 60% of patients on average, that's very active plasma cell therapy.

And you'd expect that patients with intermediate and high risk smoldering Myeloma, these patients are gonna respond to a plasma cell directed therapy and KRD and transplant and KRD consolidation and KRD maintenance. I think this is all effective plasma cell therapy. And if you're one of those patients, your Myeloma is probably – your smoldering myeloma is very well controlled. But if you're one of those patients you paid for it. You had significant infections, fatigue, counts, therapies, financial challenges, visits to the doctor. You underwent a transplant for something that is not yet described as a clear or not shown itself to be as a clear cancer. And this really highlights one of the things I think Daniel Auclair at the MMRF, points out is one of the things we really want is we need to improve our diagnostics to be able to get to where most patients with breast cancer, lung cancer, colon cancer are. So that when you do a biopsy or a diagnostic procedure, you know whether somebody has cancer or not and you can make appropriate decisions based on that. And in my world, you do a bone marrow biopsy and the pathologist calls you and tells you what percent plasma cells, hangs up the phone and says, good luck. And we really need to be able to get to where most epithelial based tumors are to be able to call it cancer or not. And many of these smoldering myeloma patients are going to develop active multiple Myeloma and interceding early like this prevents the development of fractures and anemia and kidney failure. So hats off to Dr Mateos for leading this trial. It's important work and we look forward to seeing a continuation of this thread as well as other novel interventions to potentially intercede at the Myeloma genesis phase and to diagnose smoldering versus active Myeloma to know who has an MGUS phenotype and who has a phenotype that's going to develop myeloma bone disease in six months. So let's intercede early and save somebody compression fractures. I love this area of research and can't wait to see it move on.

Gary: Fantastic. Thank you. Also in this, talking about early intervention, if you look at the data just on stage one through stage three, if you find Myeloma in Stage one, you're going to live three times longer than if you find it in Stage three. So early treatment is great and it seems like if you can find it, even when you're smoldering, it might even be better than that. But it's great, but only if you can find it early. But the majority are found when the disease is already reached stage two or stage three. So how do we better find these people in the early stage – is iStopMM the answer?

Dr Craig Hofmeister: iStopMM, it is a huge Icelandic effort to try to push us farther along into getting an early intervention, earlier diagnosis, answer a host of epidemiologic and potentially pathophysiology questions is what I'm hoping for here. At the moment what you and I can probably see is, wow, maybe we could further restratify and for those patients who you're guessing have this and this and this, well then we can go ahead and do some Myeloma labs, a protein electrophoresis, serum free light chains as their screening in those patients who are predicted to have a likelihood of a plasma cell disorder. That's what you see now. And I am so excited to think about what is just around the corner. The ability to do a so-called liquid

biopsy, that may be able through looking at DNA and RNA circulating in the blood and be able to then say, well listen, your blood test shows you're likely to have early stage colon cancer and could open the door for Myeloma.

Let's make sure you have your colonoscopy and check some Myeloma labs. This is the world that I don't think is that far away. And I think the technology is there and I don't know yet if we are able to target patients who have a really high risk yet other than those patients with familial Myeloma or Gaucher's disease or other things that put you at incredibly high risk. But I think the risk stratification in combination with some relatively iterative technological advances will be able to get us to a spot where we can screen intelligently because something with an incidence of 4 to 12 per hundred thousand, screening is going to be a challenge and we need to do better at reaching for the patients who are at highest risk.

Gary: And one of the big things, I think if you can find it early, is that you can actually prevent some of the CRAB affects. For example, I've had kidney failure. A lot of people have a lot of bone issues or I know a woman who had a stroke and because of her high calcium. So early intervention is not only gives you a longer life, but it gives you a better life. So I'm really excited about it. I'm going to break off my questions at this point because I want to make sure that everybody has an opportunity. So, let's go with Yelak Biru. Yelak, are you online?

Yelak Biru: I am. Thank you. Thanks for your time today. You have answered some of my questions in your introductory discussion. So I'm going to modify my questions a little bit. So can you talk about the role of MRD to help accelerate regulatory approval of drugs, especially as it's becoming a surrogate for PFS. I think one of the things that you outlined, we need time for the Beta to mature and would having MRD incorporated into clinical trials help us get the answers sooner, so patients can have a modified or updated treatment algorithms?

Dr Craig Hofmeister: I absolutely think they can. I think that I don't know if MRD analysis, will speed up the pace where drugs move from third line setting for front line. But I absolutely do agree that in the relapse refractory setting using MRD as a surrogate for response and activity of the agent will absolutely speed up drug development. Because I think in the relapse refractory patient population showing somebody as MRD negative is a huge bar to get over and using that to justify that the drug should be approved I think is getting closer and closer to being a reality. I should also comment that I really do want to see people report MRD in a reasonable fashion. I want to know exactly how many cells there are per hundred thousand or per million.

So is it a 10 to the minus five, 10 to the minus six. How in depth are you looking at the marrow? And I only want to be talking about that in patients who are in complete remission otherwise because I'm not interested in those patients who are MRD negative in their left hip. And the right hip on the other hand is a complete mess and unresponsive to treatment. And I think that right now there's a little too much lack of oversight in how MRD is presented. And now IMWG has clearly laid this out, but yet many people in these early abstract presentations do not clearly lay out in the patients who are in a CR this is they're MRD status, which is exactly how the IMWG appropriately laid it out to be able to well understand patients overall response. And then what's showing up by the sensitive assays with bone marrow biopsy. I don't know if MRD analysis is really going to accelerate the development, the move from approved agents in the third line setting, getting to the first line setting, as these patients, the drug is already out there. It's available for patients that relapse. But if you're using it frontline, you really need a very close assessment of toxicities and the potential for harm. And it's hard to get at this data without having a survival signal and close or at least long survival follow up. So I think that these randomized clinical trials in the early stages of Myeloma treatment are going to be very helpful. And I don't know if MRD will accelerate the move from third line to first line, but I absolutely think MRD analysis will accelerate the move from an unapproved agent to an approval.

Yelak: Interesting. Okay, thank you for that. So one of the things you also discussed earlier was for standard risk patients, Dara seems to have a PFS and potentially down the line an Ox benefit for those standard risk patients. And I think one of the things we heard during ASH and last year in ASCO, there is this move to go to giving the best drugs early. And I guess two questions, in your mind, what are the best drug combinations

and if you are moving your best drugs early, does sequencing of how you treat your patients really matter?

Dr Craig Hofmeister: Well this is an age old question, right? I've been talking about this and we've been talking about this as a community in Myeloma for decades. It's, hey, if we have better drugs, do we use them early? Because you know that they're the ones that are refractory to that, you won't be able to use that good drug early. And my boss Dr Lonial, I love his view. He's like, if I've got a great drug, use it now. Don't think about what's going on, potentially years from now, very few of us can predict what's going on next week much sometimes not even tomorrow. Use your best drugs early, keep them going and push the can down the road because the options available in the future may be better than the options available today.

And especially for those patients with difficult to treat Myeloma, those patients with so called high risk Myeloma, you're looking for anything you can to keep their myeloma quiet, to get it quiet and keep it quiet. So I think the best drug that you have today, you're looking at proteasome inhibition is a part of the skeleton of effective drug therapy. You're looking for the highest dose and frequency of dosing at a tolerable level. And you can't really dose intensify Ninlaro without significant difficulties. You have very little movement to dose increased Velcade. So you're basically left with carfilzomib as the one proteasome inhibitor that you can escalate up should you need to and that's sometimes has cardiopulmonary side effects that are unmanageable, but that's probably the proteasome inhibitor with the most flexibility. The current most effective IMiD is POMALYST that whereas CC220 is not currently approved and you know, the best steroids is still probably dexamethasone, although there's really been no rigorous testing.

The best monoclonal antibody, naked monoclonal antibody that's likely to be that's approved is Darzalex, although you don't know whether it's Isatuximab and moreover, really are all that different. And I have not seen data for what happens to patients who are Dara refractory and get Isatuximab or Isatuximab refractory who get Dara, they're hard to imagine those patients would respond. So that's really the best for four-drug therapy I'm aware of and it ignores the cellular therapy, the CAR-Ts and the antibody drug conjugates that are not going at the approval door. Thank goodness.

Yelak: All right. Thank you for your answers. I'm going to ask Jack to ask his questions now.

Jack Aiello: Hi Dr Hofmeister, how are you? I wanted to ask you questions specifically about how you treat your patients with the thought of helping patients who are listening to this conversation know what to ask their doctors. So with all the good information you provided about the high risk smoldering myeloma patients, how do you personally assess whether or not to treat them today? And if you determine treatment is warranted, what treatments do you select? And by the way, does insurance cover that?

Dr Craig Hofmeister: So, for the high risk smoldering patient population, I frequently discuss the current Mayo Clinic criteria of 20-2-20 as to specify those patients who are high risk to develop multiple Myeloma. Those patients who have greater than two grams monoclonal protein, greater than 20% plasma cells, greater than 20 serum free light chain ratio, those patients are likely to benefit from lenalidomide as described by Dr Lonial. And I found that data very reasonable, very compelling in those patients who have high risk disease, I think being on Lenalidomide makes good sense. And as for the question does everyone approves that – I don't think so. And the ICD 10 code for smoldering Myeloma and the ICD 10 code for Myeloma are exactly the same. So some people don't even pay much attention to it. I think treatment in those high risk patients is very reasonable. And I again, it's not like my clinic is blowing up with a high risk smoldering Myeloma. My clinic is filled with people who have fractures, anemia and kidney failure from active disease. And that's what I spend most of my time with.

Jack: So my next question is when being treated for Myeloma, how often should patients get imaging scans? Do you prefer MRI or PET-CT or both? And by the way, it should also be included for any kind of MRD analysis, right?

Dr Craig Hofmeister: Yes, I think that's very reasonable. I think imaging in patients who have

oligosecretory or non secretory disease is one group. Those patients get a lot more imaging, a lot more regularly because you're using it to assess the status of their Myeloma. So every two months they may be getting CAT-CTs or MRIs. And so that's a separate group for your average Myeloma patient that has plenty of protein to measure, I use imaging really if I have questions, if I want to know if their smoldering Myeloma has evidence of Myeloma bone disease etcetera. I do not do PET scans to evaluate if somebody has presence or absence of Myeloma bone disease. As I have seen too many patients who've had lytic bone disease that wasn't picked up on a PET and that drives me crazy. And because many radiologists, they'll just talk about the areas that were PET positive and they'll ignore the areas that are PET negative. So while it's true that most of the bone disease for 90% of Myeloma patients should be PET positive, 10% are not going to be a PET positive. And then there's a proportion of patients who have some lesions that are PET positive and some are negative for whatever reason. So I don't like using PET CTs to assess the status or if a patient has myeloma bone disease and tend to use MRIs of the spine and pelvis to try to figure that out. I use MRD analysis on clinical trial and rarely use it in clinical practice and use it primarily in clinical practice to figure out if somebody should stay on toxic maintenance therapy.

Jack: Thank you very much. And my last question, do you treat high risk myeloma patients differently than standard risk? And if so, how?

Dr Craig Hofmeister: Absolutely. In patients who are newly diagnosed, my current practice is to give patients with high risk Myeloma KRD because I can dose escalate the Carfilzomib or the Kyprolis, for those patients with standard risk disease who are newly diagnosed, giving them Daratumumab and RVD is a very reasonable kind of extrapolation based on data from CASSIOPEIA. And then at second, third, fourth line therapy, those patients with high risk disease go under the mantra that it's the Myeloma until proven otherwise. So they're followed differently. The labs are different and my prejudice is different. I always think that any complaints in a patient with high risk Myeloma is somehow related to the Myeloma. I just have to figure it out. Whereas those patients with standard risk disease, I'm willing to accept that some may not be related to the Myeloma and whereas those patients with high risk disease I'm not.

Jack: Thanks so much doctor, onto Cindy Chmielewski.

Cynthia Chmielewski: Hi. Good morning Dr Hofmeister. Thanks for taking time to answer our questions. My first question is, can you explain to us what a CELMoD is? Is it any different from an IMiD? Isn't going to be the new name for IMiD, and a little bit about the new CELMoD IBER?

Dr Craig Hofmeister: Yep. I thought I might get this comment. So I think that CC-220 and CC-92480 are two drugs that Celgene has recently created to help us treat patients with relapsed Myeloma. And I am not 100% certain that this is really a whole new line of therapy or whether it's just significantly better, much the way that POMALYST was significantly better than Revlimid. So I think that CC-220 is clinically and pre-clinically superior to POMALYST. And it seems to go along a nice trend, which is as Revlimid goes to POMALYST, you have more efficacy and less toxicity as POMALYST goes to Iberdomide or CC-220, it seems that you have improved efficacy and less toxicity and that's a nice trend and I'm hoping that continues.

Cynthia Chmielewski: Using your crystal ball, I guess, you were saying using the best treatment up front if that trend continues, you think that the CC-220 might be the part of the induction therapy as opposed to Revlimid or do you think you could tell?

Dr Craig Hofmeister: From a clinician perspective, right as I'm here sitting with a patient, I want the patient to get the best therapy. And so yeah, if I could have a magic wand, absolutely, that is likely to be the best cereblon targeting agent we have. But is that likely to happen in the future? Probably not. I still have to go through Revlimid to get to POMALYST so I'm not really all that assured that I'm going to be able to use CC-220 in the upfront setting acknowledging of course it, what just got reported was the first phase one two trial of CC-220 in the relapsed refractory setting. It's a long road to get from there to upfront therapy.

Cynthia Chmielewski: Fair enough. Okay. You answered a lot of my questions and about the MyDrug trial.

Clearly that it's basically the target audience is early relapsed high risk multiple myeloma patients. What about those patients who're out of treatment option? Would having a test such as next generation sequencing test that may identify some of those target mutations and then trying those drugs be something that they should consider? I realized it until just recently that it wasn't for that group of patients, it's for patients earlier in relapse.

Dr Craig Hofmeister: Right, right. I mean you're, you point to an absolute area of need, those patients who have been through, been there, done that. What do you have for me now doc? That's what I spend 80% of my time doing. Those are the patients where we really want to have new and novel agents in the relapse setting to be able to assist them. And the number of those patients who do some type of next generation sequencing via foundation medicine or other such tests, the number of them who've then gone on to get that novel agents and then get a response. Yeah. I just feel like it's a very, very small number of people and I kind of wish that everyone with relapsed disease who's at your second or your third relapse, it would be great to try if it's within reach to get to a Myeloma Center to consider a clinical trial therapy. And I think part of the reason we haven't cured Myeloma is that we have as physicians not been able to offer enough patients clinical trial options. And so if you have a patient who is savvy to their Myeloma, I'd much prefer them to consider going to a center with clinical trials rather than trying to figure out what to do with a KRAS mutation.

Cynthia Chmielewski : Do you think there maybe myeloma specific mutations out there that we haven't found yet? And there hasn't been enough patients gone through this next generation sequencing – anything about that?

Dr Craig Hofmeister: Absolutely. My colleagues here, two fabulous gene jockeys, Dr Ben Barwick and Larry Boise, they recently published a fabulous paper looking at a so called IgL translocation that they found through a number of ways, but all through validated thus far in the MMRF CoMMpass study. And that's a translocation that seems to be very significant, seems to, it's suggestive now that these patients don't respond well to IMiD therapy and you can't find that on a FISH. It's just not going to happen. They don't have that. You're only going to find it on karyotype and who finds anything on karyotype half the time karyotype doesn't grow and you don't get any results in Myeloma. It's a small number of patients. So I think that there are certainly many genetic abnormalities that have not been discovered. And that I ideally we hope will be targetable and that we can do better in those patients because, just ask anyone who has so-called standard risk disease and relapses early, well obviously they all, they don't have standard risk disease and we had no idea why. And I saw patients like that just yesterday in clinic who've done terribly and I don't know why it drives me crazy. So I think there's much to learn right there.

Cynthia Chmielewski: Okay, there are clinically high risk patients, they don't have their markers but respond that way. Could you just tell the people that are listening in, explain what karyotyping, it is a term many are not familiar with?

Dr Craig Hofmeister: Absolutely. My apologies. So normally a bone marrow biopsy if you don't know anything about what a patient has, you'll first look to see what's, what kind of cells are in there. That's the morphology that's the pathologist looking at it. Many people, and I think if you don't have a diagnosis you should send for flow cytometry. And that's looking for specific markers on the outer surface of the cells to see, oh yeah, I have B cells that is a clone of them or T-cells or whatever that's in there. Flow cytometry makes good sense. Then you can take the aspirate, just throw it in a dish and wait 24 hours and 48 hours and see what grows, and that's karyotype. They do that in newborns, as part of newborn screening and they do it on bone marrow biopsies. It is very difficult or it's rare to get a positive karyotype, just your chromosomes because you are visually just hoping that these myeloma cells survive outside of the bone marrow and only 20% of Myeloma cells do. And then there's FISH, which is actually staining the patient's bone marrow with fluorescent probes, looking for specific mutations. And most of the time bone marrow is a sent for morphology flow. Sometimes they do karyotypes, sometimes they do FISH. And it makes good sense at least in the patient with an ongoing diagnosis of Myeloma to send a full panel of FISH at least one point along the way. And karyotype is a way to look for genetic abnormalities that you didn't know would be

there, but it is very small number of patients have myeloma that is able to grow in a dish.

Gary: Priya, could you please turn this over to our audience for questions?

Priya: Yes. Thank you Gary. We have some questions sent in by the audience Dr Hofmeister. There were 2 questions on the 20-2-20 rule/criteria. The first one is what is the 20-2-20 rule and to whom does this apply and what is the difference between 2-20-20 criteria and 20-2-20 criteria? I'm so confused.

Dr Craig Hofmeister: My apologies. I'm not trying to flip the numbers. It's basically based out of Mayo Clinic retrospective for patients with smoldering Myeloma, trying to find those patients who don't yet have a myeloma defining event, which is greater than 60% plasma cells, serum free light chain ratio, greater than a hundred or greater than one focal lesion on MRI. So it's trying to look at those smoldering, their retrospective panel of patients and then saying, wait a minute, we don't want to just find the people who have CRAB criteria. We also don't want to find those people with the so called Myeloma defining events, the serum free light chain ratio greater than 100, etc. We're looking to see is there are a high risk group of patients with smoldering Myeloma and they did find those and publish that. And really it's patients who have a monoclonal approaching greater than two grams. Those patients who have a serum free light chain ratio greater than 20 and those patients who have a greater than 20% plasma cells in the bone marrow. So that's the rule. And I don't think it matters whether you call it 20-2-20 or 20-20-2, either way, it's just flipping the numbers.

Priya: Okay. The next question is, is more better than less in treating high risk smoldering Myeloma?

Dr Craig Hofmeister: That's a great question. And active clinical trials are trying to answer that question. Just in this call we talked about Dr Lonial's ECOG trial looking at Revlimid versus observation. We also talked about that Dr Mateos' trial looking at KRD autologous transplant followed by KRD maintenance. Both of those were in patients who had smoldering Myeloma. It'll be at slightly different groups of smoldering myeloma patients, but absolutely one of them is just a single drug and one is three drugs, transplant and three drugs. And clearly we need to both look at response. We need to look at toxicities, we need to look at second primary malignancies, and ultimately an overall survival signal to help us find our way towards choosing the right patients to treat with the right drugs.

Priya: Thank you Dr. One last question before we wrap up. I think you already defined high risk smoldering multiple Myeloma, but we still have a question – what is the current accepted definition of high risk smoldering multiple Myeloma? So probably we could just stop with that.

Dr Craig Hofmeister: So I think a very reasonable definition of high risk smoldering Myeloma is the greater than two grams monoclonal protein, serum free light chain ratio greater than 20 and 20% plasma cells or greater. I think that is a very reasonable definition of the high risks. I think where it gets super complicated is where somebody says, wow, that's great, but I want to know what are the intermediate risks and I'm in Spain so I can use our fabulous flow cytometry techniques to find the greater than 95% abnormal plasma cells versus, no, I'm in Mayo Clinic, I can use other techniques to find intermediate and high risk. So I think the 20% plasma cells, the two grams of monoclonal protein and the light chain ratio greater than 20 is probably a very reasonable way to get the patients who are high risk smoldering Myeloma.

Priya: Thank you doctor. The treatment of smoldering Myeloma is advancing based on what Myeloma researchers are learning in recent study, one of the most important points discussed at the recent ASCO conference was how to better risk stratify smoldering myeloma patients. And we've just heard the results of some of the key studies that can have significant clinical impact. Dr Hofmeister, thank you so very much for sharing insights and advances in treatment and research of smoldering multiple Myeloma. Gary, Jack, Cindy and Yelak thank you for participating and bringing the patient's perspective into this discussion. We also thank the Winship Cancer Institute of Emory University. The talk will be available on curetalks.com, please visit our website for details and all upcoming talks. Thank you everyone and have a great day.