Using Clinical Data to Determine Treatments in Myeloma

Using Clinical Trial Data to Determine Treatment Options, has been successfully implemented by Dr. McCarthy and team and here he discusses the various preclinical new drug developments for myeloma treatment

Full Transcript:

Priya Menon : Hello everyone and welcome to the Cure Panel Talk Show on Myeloma. I am Priya Menon, Scientific Media Editor at Cure Panel joining you from India and I welcome all of you this evening to a discussion on multiple myeloma. This is Cure Panel's 57th episode and on our myeloma broadcast today we are discussing Using Clinical Trial Data to Determine Treatment Options. My co-host for the show today is myeloma survivor and editor of myelomasurvival.com, Gary Petersen. On the panel are Cure Panelists, Jack Aiello, Cynthia Chmielewski, Pat Killingsworth, and Lizzy Smith.

We have a very eminent expert with us today, Dr. Philip McCarthy. Welcome to the show.

Before, I hand over to Gary to introduce the expert and begin with the show…I would like to mention to the audience that if you have a question for Dr. McCarthy please press 1 on your keypad and we will bring you on-air to ask your question.

Gary will now introduce us to our expert…Gary you are live on air!

Gary Petersen : Hi Priya Thank you so much and Dr. McCarthy Thank you as well for giving us your time during this educational series that we have for multiple myeloma patients.

Priya Menon : I think we have lost Gary for a minute, so by the time he calls back. I would like to introduce our expert to audience today. Dr. McCarthy is the Director of the Blood & Marrow Transplant Program at Roswell Park Cancer Institute, and a Professor of Oncology. Dr. McCarthy has been a BMT physician and hematologist and oncologist since finishing fellowship training in 1989. He has been the BMT Director at the RPCI since 1997. Dr. McCarthy is a member of ASH and ASCO, and his research interests are devoted to developing new auto and allo treatments for hematological disorders including myeloma that will lead to improved patient outcomes and decreased toxicity. It is a great honor to have you here Dr. McCarthy. Gary if you are on air please begin with the discussion.

Gary Petersen : Ok Priya, can you hear me.

Priya Menon : Yes I can hear you loud and clear now.

Gary Petersen : well, fantastic, somehow I got cut off. So, thank you so much Priya for taking over for me. I do appreciate that, and Dr. McCarthy, thank you again for the time that you are spending with us on this program. I know that you are very much involved with a lot of clinical trials as well as, you have your own database that you work with in order to develop your treatment protocols for your patients. And also know that your organization much like Memorial Sloan Kettering and University if Arkansas for medical sciences have been a source of talent and one of those graduates is Dr. Osher Chanen Conan, Mayo, Jacksonville, who worked with you for a number of years and now runs their Mayo Southern Jacksonville operation. What I would like to ask you Dr. is how do you integrate integrate the data from Clinical Trials with your own clinical data to determine the best treatment options for your patients?

Dr. Philip McCarthy : Sure, Well that is a bright question and I would be happy to answer it. And we may

break it up, because I don't want to talk for too long. We look in a variety of options, because the first thing we do is we consider what are the most reasonable clinical trials to open for our patients. And we will focus of course on multiple myeloma today. So, I work very closely with our multiple myeloma doctor. We have a new recruit from University of Iowa Sarah Holstein, who has a lot of interesting trials. They are all preclinical looking at new drug development for the treatment of myeloma. And if you know a lot of new drugs are first tried out in patients who have relapse myeloma. So, I guess, we sort of, that is the first sort of decision tree. Is the patient newly diagnosed or is the patient, a patient who has already received therapy for multiple myeloma and then now is receiving some form of what we call salvage therapy to generate a good response after the disease is progressed after initial treatment. So we factor a lot of things in, when we make decisions regarding clinical trials. We also have mandates from the national cancer institute. The NCI does not want us to have too many trials open at once and we don't recruit enough patients because the most important thing is to get a study done and then move on to the next study. Because if you don't complete a trial in a timely manner, you may be asking a question that may be outdated. So we have a lot of these types of issue that get factored in how we make decisions about what trials we should open and also what trials we should be developing internally, so that it allows us to ask a new question. So, as you know there are different types of trials. There is phase I which look at toxicity of a new treatment, phase 2 which is looking at efficacy, phase III which is comparing your new drug or new set of drugs vs. whatever is the gold standard. And those are the three types of trials that we will be thinking about, when we are trying to develop the best approach for how we want to treat a myeloma patient. Sometimes we may adopt a standard of care approach, because the patient say, has co-morbidities or has other types of issues going on that won't allow them to go on a clinical trial. But our first thought as always when we are trying to treat a patient is if they are eligible for a trial. If they are so eligible we will offer that patient that trial as a first option, but again depending if they are newly diagnosed or receiving treatment for salvage.

Gary Petersen : You have, this is something that just kind of came to mind, you have several hundreds of patients, don't you.

Dr. Philip McCarthy : We transplant about a 150 transplants a year. So those are transplants, we see several hundreds of patients of all different types of diagnosis. For myeloma we see, I think new diagnosis we see about 60-70, I believe, but I have to talk to Dr. Holstein about that.

Gary Petersen : Ok, and on clinical trials – what % of people would be on clinical trials?

Dr. Philip McCarthy : We, do, as a institute as a whole we get about 10% of only of our patients on clinical trials which of course is disappointing. Some of our sections do better than others, and our patients are the BNP patients we put about 15% on clinical trials. And now with our myeloma patients we were a little bit low but now also around 10% on trials, and obviously we need to do better. Some of that is due to the fact the some patients don't like to go on trials. They don't like to be specially if its a randomization. We trying to get people to understand that, if we knew what we were doing, we wouldn't be doing the trial, in other words, until we cure everybody, we always be wanting to do a clinical trial that will make everybody get better. So, I think a lot of people, they don't like that. So the Europeans in the past have been much better at enrolling patients in clinical trials, primarily because the way their health care system is set up, where the patients didn't have access to new drugs unless they enroll in a trial. Here in the US it is a little different. But what people don't understand is a lot of these new drugs came about because somebody participated in a trial, 5-6-7 years ago, which then allow the truck to come into the clinic.

Gary Petersen : Ok. So one of the questions I had was, that you used not only clinical trial data which would be 10% of couple hundred patients, like 20 patients vs. the total number of patients that you had which is like 200 or so. As a result you have far more data available with your patients vs. clinical trials. SO you know, those two together, is my guess, that's the data that you use.

Dr. Philip McCarthy : Correct. WELL, yes it depends what you are using it for. So, for example and in fact, you have been very persistent in wanting us to get our stuff out there and I have to push my epidemiologist because she is very guarded, because, the on thing about data is that – there is data and there is data. So

for example, I will give you, and we are going to be posting this on our website, you will be able to access this very soon. From 2007 -2013, we have done for myeloma, 148 transplants, the 138 were first autos, and the rest were second autos, and of those 112 received full dose Melphalan, and then 18 were lower dose Melphalan and those 18 include a firm number of amyloid patients, which is little bit more complicated than multiple myeloma alone. And so what we didn't do is we didn't see what is our K100 mortality morbidity, what is our 1 year? And we have done very well. Our one year survival is 94%. And unfortunately the patients who have not done well have been those who have had recurrence of their disease, before the 1 year. So, what we then have done is, we have actually do, I will give you an example where we use our data. We have been looking at what we call Flow Cytometry. Flow Cytometry is a way of measuring markers on the cell surface of both normal and abnormal cells to tell us different cell populations are there in the blood or the bone marrow. Since myeloma is primarily a bone marrow disease, we do Flow Cytometry to look for helping us determine if the marrow contains multiple myeloma and then we often will do minimal residual disease testing, first pioneered particularly by the Spanish, but we have an excellent Flow Cytomet – he is Paul Wallace, who looks for minimal residual disease and Paul is doing the MRD testing for the BMTCTN trial, which just closed in November. It is a study looking at single transplant vs. tandem vs. single follow by consolidation, and that landmark along the way. Paul's laboratory have been measuring the presence or absence of malignant plasma cell, and then showing us, and then we are gonna look to see whether this tells us how well patients will do in the long term. And that study is still ongoing. But another thing we did which we, just talked about at the last ASH meeting – The American Society of hematology – is we are trying to look at subsets of T cells within the peripheral blood to tell us whether or not patients will do well or poorly and the Mayo Clinic has previously reported that if you look at the absolute lymphocyte recovery at day 15 and if it is above a certain level 500 cells/ microlitre, those patients do better in the long run. And we never really have been able to understand why that is? But we were able to show is that the patients who have certain T cell and natural killer cell or B cell population in the peripheral blood at pre-transplant at day 130 and day 100, those patients may do better if they are certain different types of population. Now what we are trying to figure out, Ok we have made this observation, how can we get everybody to get this type of immune signature and does that co-relate long term with overall survival. We have some data that says it does, now we have to figure out how we can get all patients to have this good overall survival.

Gary Petersen : Well, I got to say that given what you just said, which I think it was 94% for the first year survival?

Dr. Philip McCarthy : Correct.

Gary Petersen : Well, you know, given the fact that the sear data for one year survival for all myeloma patients is just 75-80% – I would say your data is downright remarkable. Why you don't want to put that out there online, I have no clue, people would be walking to you.

Dr. Philip McCarthy : No, No we have this data and there is data. Here is why? Because the sere data is all comers. So there is people on renal failure, people who have got cardiac disease, and we do, patients who want to who are transplants eligible are fit, because patients who are transplant in eligible if we were to do a stem cell transplant on them, the high dose Melphalan can be too toxic and they could die of complications. So we don't transplant everybody we see, because I don't want to cause unnecessary harm. So, we do appreciate the complement but we do have a selective population. And in fact as you may know for some studies, some studies require transplant eligible patients to pass certain criteria , they a have to have a fit heart, fit kidney function, not always, and fit lung function, because if they have too many what we call co-morbidities, they won't be able to withstand the high dose Melphalan and they would get, they would have serious complications. So I appreciate the complement again.

Gary Petersen : What percentage of patients are eliminated because of those types of issues.

Dr. Philip McCarthy : Sure. The majority of patients who we see are able to get a stem cell transplant. We use to have an upper age limit, and then say upper age limit was 65 and then was 70 and now we got rid of it. We don't do too many 80 year olds, we do patients in their 70's though, and they have to be in a

reasonable shape, so a lot of times I may not even see somebody, because if they are, say if they have bad lung disease or they have other co-morbidity terrible cardiac disease, where they are in congestive heart failure all the time, they aren't going to be a good candidate, because we will probably cause them more harm than good, because the stress of the transplant is too much. But the majority of patients, I can't give, I am just guessing if told you, probably about 75 -85 or 90% of patients we would at least consider, and if they have serious co-morbidities, we give them a dose reduction in their Melphalan. So, for example we have patients in renal failure who will get a stem cell transplant. That is not a contraindication. But if somebody has a horrible lung or heart disease, they may not be able to withstand that type of treatment.

Gary Petersen : Ok, What treatments protocols have you developed utilizing this data, your own data plus clinical trial data?

Dr. Philip McCarthy : We, well mostly we do rely on the literature. So, I will give shout out or kudos to Dr. Barlowgee and Dr. McCohen who first developed and pioneered these high dose Melphalan. Dr. McCohen in great Britain where he dose escalated Melphalan, and then found of course it get too toxic at very high levels, because it was too toxic to the marrow. But Dr. Barlowgee was the first one who showed that was a bone marrow rescue. You could get the patient through high dose Melphalan, and rescue them from the toxic effects from the marrow, and essentially he did the first autologous stem cell transplant using bone marrow. And I think it is very important to acknowledge his contribution because he pushed the field. So we use that type of information to then allow for the development of use of peripheral blood. And both investigators both in the US and the United states then found that mobilized peripheral blood first with chemotherapy mobilization and now with GCSF and this new drug Plerixafor you can mobilize stem cells and use those for the rescue from high dose Melphalan. So we continue to use Mel 200, 200mg squared as our standard. But both in clinical trials and in our patients who receive standard of care we are interested in developing a novel combination, but you need to have a lot of patients. So we have elected not to develop, say a new high dose chemothrapy regimen and participate in large clinical trials that answer those types of questions, such as the MCTN or the CLTB studies. We also will, for example with induction regimens we rely heavily on other trials. And to be quite frank, everybody talks about using triple drug induction regimens for transplant eligible patients. Ususally Lenalidomide in combination with Bortezumab and steroids dex, Decadron, or using cyclophosamide, Bortezumab and dexamethasone. And that study, there is the phase II evolution trial which Shashi Kumar was the first author on, which showed that there were very similar results. However we have not had a true phase III, and I am not sure if we will have a phase III because the induction regimens have gotten so good, that it has been hard to pick between those two regimens as to which one is better. Now the ECOG – the eastern corporative oncology group – is doing a CRD vs. VRD which is, or RVD, it is a Carfilzumab Lenalidomide Dex vs Bortezumab Lenalidomide Dex and that is probably gonna inform us as to which regimen may be better for, that is for standard myeloma patients. The South West Oncology group is now doing a trial looking at RVD, Lenalidomide Bortezumab Dexamethasone as the control group and then they are going to add Elotuzamab, The anti- CS1 antibody, and this is for high-risk myeloma patients. And then we are gonna participate in a BMTCTN trial which is an allogenic transplant or very high risk myeloma patients, say if they have deletion 17 or have a gene expression profile that is high risk. Those patients would be offered potentially if they were young and otherwise fit, an allogenic trial, it is a phase II trial, to see if we can potentially cure myeloma. So lot of what we do, we try and decide what fits at our center for development of trials and lot of what we are doing now is that Flow cytometry data that I talked about earlier. And then we want to see, can we participate in larger trials because, sometimes the only way you can answer questions is to do a very large trial, have hundreds of patients on it. Most centers don't have hundreds of patients. And so you need to cooperate with other centers to be able to ask important questions.

Gary Petersen : Ok, One of the things that I have found, in talking to a lot of doctors in very good remarkable institutions is that their data is not easily accessible, it is not easy to mine. They seem like to have to just use brute force in order to come up with simple data and Does this particular protocol have a better life expectancy than this other one or better impression free survival. Do you have a system that you are able to mine or yours is equally as outmoded.

Dr. Philip McCarthy : I wouldn't say they are outmoded, but here is the deal. Because, number 1, you have

to look, lets look at demographics. If you are looking at one study vs. another, what is the age of the patient? You will look at often the median. The median is – half the patients are above this age and half the patients are below. So for example, in our patients who have undergone the stem cell transplant the median age is 60, and our range is 28-73. We have done a patient who is 28 yrs of age and the oldest so far is 73. Although we just did somebody who is 76, but he is not yet in our database. And then you have to see, okay, what is their stage. How many of them, by ISS – The international scoring system – using beta 2 microglobulin and albumin, how many are stage one, how many are stage II, how many are stage II? And then using Durie-Salmon system that is another staging system – same thing – how many are I, II, or III? And then what was the time from when they were diagnosed to when they initiated therapy and when they initiated therapy, what is the time form initiation of therapy to time of transplant. Because somebody who is diagnosed early, gets induction, goes straight into transplant is very different, than somebody who is diagnosed who gets regular chemotherapy, say gets puts on some maintenance does not go to transplant and then relapses and then gets stem cell transplant. So I think that type of granularity is why people get very skidish about trying to compare stuff. Because sometimes you are comparing apples and oranges. You know what I am saying? And that is why people, it is not that they are trying to keep data away from you. It just that we want to make sure that it is truly a valid comparison. I can give you one more example.

Gary Petersen : Sure

Dr. Philip McCarthy : The french IFM0502 study, which is a Lenalidomide maintenance study which is Lenalidomide maintenance vs. placebo after single or tandem transplant, that has been compared a lot to CL2B100104 which is also a Lenalidomide maintenance study. And we have had numerous discussions about the differences between those two studies, even though they look on the face of it that they are, they are both transplant studies and maintenance studies. So everybody says, you should be able to compare them. Well they are really different, because both studies have showed a progression free benefit progression free survival benefit for Lenalidomide maintenance. But the French study has not shown an overall survival benefit and indeed they feel that the overall survival after progression on the Lenalidomide arm is inferior. We don't see that in CL2B100104. Now here are two studies, very similar patient population initially but their induction regimens were Vincristin Adriomycin Dexamethasone – VAD, in half the patients and the other half got Bortezumab Dex, and on 100104, 74% of patients got either a Thalidomide or a Lenalidomide based induction regimen totally different. And then one quarter of their patients get decept consolidation pre-transplant, 20% of their patients get two transplants. All of our patients only got one. They are all on 2 months Lenalidomide consolidation before randomization to Len vs. no Len. They didn't allow a crossover, we allowed a crossover once the primary end point was met and we allow the placebo patients who haven't progressed to receive Lenalidomide. So we have all these different, these differences which really we have spent months discussing this and people still are pro and con Lenalidomide, just because the studies are different.

Gary Petersen : I see. Ok. I have a got a few more questions but I am going to hold upon those because we have just, you have done an excellent job in explaining. You know the ones that are already talked about, however, we have a number of questions on the panel and I would like to get to those at this point and later on I might, if I have got time I will ask some of those questions that I have yet to cover. Jack, are you online

Jack Aiello : I am online can you hear me?

Gary Petersen : You bet I can. Your question?

Jack Aiello : Hi, Dr Mccarthy, I hope spring has sprung in Buffalow.

Dr. Philip McCarthy : It has! Finally

Jack Aiello : I have read that 25% of phase III trials close early due to lack of accruals. I wonder if yours is accurate for myeloma trials. If a trial does close early, does that mean the data isn't used at all because of insufficient numbers or it is just questioned? And I guess last week as we have patient advocates on the

phone here, is there anything you can recommend that we can do to increase accruals?

Dr. Philip McCarthy : Sure, You raised a really good point. I have had 25% of all trials. And a lot depends if you design, you have to have a really good statistician help you design a good trial, and we had an awesome one for CL2B100104. I would like to give shout out to _____who is a Duke, and he really designed a great study. But it was large study and we accrued over 400 patients on this study. So, when Enlee first opened this trial, and I will bring in this as a good lesson though, when you, you don't want to have too large national trials open up at he same time. Because there is a BMTCTN0102 trial which is two transplants vs. tanden autos, vs. an auto followed by an allo, and that was opened at the same time, so the 100104 accrual wasn't very good and 100104 came within about 6-12 months of closing, if we did not increase accrual. And what happened was that 102 closed 100104 accrual picked up and we are able and actually finish the study and answer very important question about maintenance. So a lot depends on the size of the trial, because if the trial is very large, you need to accrue patients quickly, you don't want to have a drag out for too long imperative time because this standard of care changes for when the trial was first designed and then open to say 3 or 4 or 5 yrs in. So you can have a trial that is lagging and stays open too long because the accrual will start to falter and then people may be doing different types of treatment. So, it is a really good point that, phase III trials are really good things to consider when a patient is being offered a potential clinical trial.

Jack Aiello : And something we as patient's advocates can do to may be help in accruals?

Dr Philip McCarthy : I think it is important to encourage patients to consider clinical trials, because if we don't, for the goodness of poeple's hearts, if they involve on trials, not just because they are just being altruistic they want to get good treatment and these trials are designed to give good treatment to the patients. For example, there is the French -American study, it is an IFMDFCI – DFCI is Dana Farber, IFM is International Francophone Myeloma group, it is the International Myeloma working group of France. 200 545 The French arm has closed but the American arm continues open and that is a transplant now vs. transplant later, and that is a Lenalidomide Bortezumab Dex induction, and then patients either get either 3 cycles I believe, stem cells are collected and then they go on to transplant or they continue the RVD chemo after stem cell collection. And then all patients go on Lenalidomide until progression. And that study is a little different because it is a transplant early vs. transplant late. But since most patients with myeloma get transplanted, well their disease will come back, The question is whether or not it is important to have that transplant upfront or to delay it to first progression, because at least retrospective data has shown that there is no difference. Now there are two other studies that have access in Italy, one of which, both of which have closed. One of them is Melphalan Prednisone Lenalidomide induction, sorry Lenalidomide Dexamethasone induction followed by randomization to Melphalan Prednisone Lenalidomide vs. transplant. And that study has been closed and actually submitted it for publication. And that has asked a very important question about transplant now vs. delayed transplant. So, those are the types of things that we think are important. There are some other clinical trials in development for myeloma, for example, The BMTCTN is going to be opening a vaccine trial that is very exciting. David Avigan from Beth Israel of Boston is the principal investigator. And that is gonna involve, patients being involved early so some of their cells can be taken out and a vaccine developed for with their own myeloma cells, and then there is a randomization at the end to either getting a vaccine with Lenalidomide or just giving Lenalidomide, following a stem cell transplant. And that is a really important trial which, I think hopefully will be exciting for patients. So, there are a lot of these trials which unfortunately take years sometimes to get into development. I know David has been working on this for a couple of years and hopefully it will be open by the end of this year. The fear to the 100104 study, we sent the first concept in 2001, we did not open the trial until 2005, that after 11 protocol revisions, and we did not close until 2009. It wasn't un-blinded until 2010. So that was along time to have a study from first concept to actual finishing accrual. So, I think it is important for patients advocates and patients to strongly consider clinical trials, because you get the best therapy, you are very closely monitored, you are then comparing it to a therapy that might be better or might not be better. So, usually, they are either gonna be, my feeling is, they are either gonna be the same or the new therapy may be better, but we don't know that, and we have been surprised sometimes. A good example is transplant for breast cancer, where everybody thought; everybody should get a stem cell transplant for high risk breast cancer. Well the studies were done to find out that they were equivalent to chemotherapy, so we don't do stem cell transplant for breast cancer

anymore, and now it is because patients willing to enroll in clinical trials.

Jack Aiello : Thank you very much.

Gary Petersen : Cindy are you online?

Cynthia Chemielewski : I am. Hello Dr. McCarthy. How you doing tonight?

Dr. Philip McCarthy : I am great, it is a beautiful day in Buffalow, the sun is shining.

Cynthia Chemielewski : Oh, That is great because, here in New Jersy it is windy. I can't wait for spring to show up.

Dr. Philip McCarthy : It's supposed to be here soon.

Cynthia Chemielewski : So my question is, I am hearing a lot about genomics, and it is an era where everybody is trying to get their genes sequenced. I was just wondering are there any clinical trials now being designed based on myeloma patients genomics, may be *hunting?? a* certain password for a short and small group of patients, are we getting into that type of thinking yet, or we lagging a little bit behind or what is happening there?

Dr Philip McCarthy : We are getting there. But, we at least now have at least the beginnings of it based on cytogenetics. So, as you may know, the myeloma cells sometimes have chromosome shuffling that occurs, that gives different types of chromosome deletions translocations where a piece of one chromosome is deleted. Two chromosomes may exchange information. One chromosome may gain some information and this has allowed us to re-stratify. So we know, for example, in the old days, deletion 13 was thought to be a bad prognostic feature, especially under something called metaphase karyotyping. But then Bortezumab obviated or reversed most of that risk, and the same for 4-14, that also seems to do better with the addition of Bortezumib, although it sort of somewhat controversial but pretty good evidence for that. So, now you have things that at one time were high risk and now become less high risk because of the development of proteosome inhibitor. And the same thing for the use of Lenalidomide. It helps reverse some of these high risk features based on cytogenetics. But it took a long time for people to develop the right way of doing cytogenetics so you are supposed to pull up the plasma cells and not just do metaphase karyotyping. That is where you let the cells divide and then they look at the chromosomes as they are dividing. There is something else that you may have heard of called FISH. And that is flourescence in situ hybridization. That is where you take a piece of chromosome marker and you, it is lit up with something that lights up under special light and it flouresces, and so that is the flourescence in situ hybridization. And by doing this FISH, you can then determine different, so for example, deletion 17 is much more easily seen under FISH than it is under metaphase karyotyping. Same thing with chromosome 1 abnormalities which are thought to be high risk. So that is the beginning now and most patients should have that type of level of cytogenetic analysis to help determine therapy, and patients who may be considered high risk may be offered clinical trials. Now there is gene expression profiling, that is the next generation of testing and that is being done. Again the Arkansas group pioneered that work. And GEP70 where it is a 70 chromosome signature, sorry, 70 gene signature, that Dr. Shawn has seen Dr. Barlowgee develop, which allowed for the identification of about a 13% population which is at very high risk. Problem is we don't know exactly what to do with these patients, except offer those patients high risk clinical trials. The dutch also have a high risk profile called EMC92. It is 92 gene profiling and there is some others that has been done, about 2 or 3 others. So, We don't know yet which is the best genetic profile to use. And we also don't know which is the, what to do for them, what is the best therapy to give them. So, for example, the French-American trial that I talked about early about the transplant early vs. transplant later, all those patients are getting genetics profiling done who enroll on that trial. And they will look in retrospect to see, okay who did really well, who did not do well and which patients benefitted from transplant early which ones didn't necessarily have to get it early. And then to finish up the one thing that we are discovering about the genetics of the myeloma cell is that it is complicated. So the multiple myeloma research foundation, just published something recently and there has been another one

from the Dana Farber, where they looked at the genetics if the myeloma cells, and they are complicated. So, what will happen is that you will have one set of genetic abnormality in one set of myeloma cells in the patient, and in the same patient you will genetic abnormalities that are very different. Key Stewart at the Mayo in Arizona has shown that, he tracked in a patient how there were first set of genetic abnormalities that diagnosed in this patient, patient got treated. When the disease came back, new genetic abnormalities, treated – came back again, another set of genetic abnormalities. Its sounds kind of like whack-a-ball, where you knock down one bad clone and then all of a sudden another one comes up. So we are doing this type of genetic testing and that is gonna help us make some good decisions about what is the best approach for patients. So I am encouraging patients to enroll on trials, such as the, its called the determination trial, which where all patients will have their myelomas tested for genetic abnormalities and genetic sequencing.

Cynthia Chemielewski : Ok, Another question, I am not sure of, with this FISH testing that you were talking about, I kind of remember, and I might be remembering the wrong way, Do you have to tell like what chromosome abnormalities you are looking for, is it like they are not going to find everything out there. It is more of a specific type test, like they say, look to see if this chromosome is mutated or this chromosome is mutated, as opposed to doing like a whole genome sequencing where they get everything?

Dr. Philip McCarthy : Correct. Right now we are basing our FISH analysis on previous work, which has shown that certain chromosomes are abnormal. For example, the ch 14 has the immunoglobulin gene on it, and we know that there are lot translocations 4-14, 14-16, 14-21, that are hots, because chromosomes 14 is a hotspot, and because of the immunoglobulin gene it relates to myeloma cell. So that seems to be why that occurs. Ch 17 has the p53, which is a tumor suppressor gene, and not just in myeloma, but also in chronic lymphocytic leukemia, and even in colon cancer, this tumor repressor or suppressor gene, seems to be important in a variety of different cancers for oncogenes in check. Because they are normal genes and they only become oncogenes when they are out of control. So, you are right. We have right now to look for certain abnormalities that are already established, and thus these new studies, the determination trials aren't the only ones. I know the British, the French, the Italians, as well as the investigators in US are all looking for markers, or genetic hotspots that will allow us to predict outcome and then most importantly knowing that there is a particular hotspot, what is the best treatment for these patients. And so, for example, I am very excited about the monoclonal antibodies, which we think may allow us to be able to treat myeloma in a totally different way than we have in the past with both the proteosome and the immune modulatory drugs. These antibodies attack the outside of the myeloma cell and often in combination with Lenalidomide and steroids will cull off the disease, and this is a whole new approach. In addition, there are other pathways that if we can discover mutations within them, it will allow for the development of new drugs. You probably know there is a laundry list of a variety of new pathways in the myeloma cells that we see, may be important for long term. The drug for CLL Ibrutinib, may have some efficacy through the BTK pathway. B-Raf may also be important about 10-15% of myeloma cells. But one thing we are discovering is that, it is not going to be one size fits all. Its probably gonna have to have different pathways targeted depending on the genetic mutations that are gonna be discovered in each patients' myeloma. Not just a diagnosis, but point for long the treatment continues when the disease comes back.

Cynthia Chemielewski : Ok, Sounds really complicated to me, but I am sure we are gonna get there. And the other thing that I just really can't seem to get straight in my mind and may be you can help me out – what exactly is a biomarker? I am hearing a lot of things about, we need to find biomarkers so we can get the right treatment to the right patient at the right dose at the right time. What all biomarkers, does myeloma has biomarkers or is it just in other cancers? Do we know what these biomarkers are? Can we give them to a drug company and say can we develop a drug that helps with the cure?

Dr. Philip McCarthy : Sure. Biomarkers is pretty broad. So you can use biomarkers to look at like when I mentioned earlier the immune status of our patients in terms of what T cells are present or not, that is potentially a biomarker. Because it may predict for outcome. But that pertains to the immune status of the patient. Now other biomarkers are there – Cancer markers – biomarkers that tell us this is a good cancer or a bad one, this requires, certain therapy or not. So, such generic testing is a biomarker. Serum Free Light Chains are biomarkers because they tell us what is the disease – Kappa or lambda. And then it also tells us

whether or not the patient has got a good response. And there is some thought that you may not have to do 24 hr urine for light chains because you can measure them in the serum. So biomarkers can be used to measure response and they also may be used to project outcome. There is a new biomarker that just was developed for myeloma called – you may know about this – The heavy light – which is measurement of normal and abnormal immunoglobulin. In the past we would only be able to do that by measuring only totally immunoglobulin and then looking at the M Protein or M spike that is seen on the serum protein electrophoresis, and then sort of extrapolate into see whether or not – subtracting the M protein from the total immunoglobulin to get the amount of normal immunoglobulin that is still present. It appears that this heavy light allows us to determine how much is normal gamma globulin normal immunoglobulin and how much is all the myeloma protein. And that patient at presentation – it appears whose normal immunoglobulin production is suppressed by the myeloma clone – those patients may not do as well and may require different therapy. So there is an example of how this new test may allow us to predict outcome. There is some preliminary data on this, but we need to get a lot more clinical data to make sure that this is really going to be a good biomarker. So biomarkers range from what is actually present on the cancer cell, what is in the cancer cell, how the immune system is responding, to be able to allow us to predict outcome and therapy.

Cynthia Chemielewski : Ok. Think I got it a little bit better now. Thanks so much. You know what, may be we should go on to the other questions.

Gary Petersen : Ok. Well, Thank you, and I have Pat. He was last last time. So I am gonna bring him on right now. Pat are you online?

Pat Killingsworth : I am here Gary Thanks.

Gary Petersen : Ok. Did not want to leave to till last, so, your question.

Pat Killingsworth : No, great, I have one very specific question for doctor McCarthy here, and Dr. I am glad you brought this up, because I have heard before that proteosome inhibitors help mitigate the effects of 4-14 and the 14 deletion, and my question is – Ok, so Velcade works for 2 yrs or 3 yrs or may be 4 or 5, but what then? I don't understand what changes the risk profile being somebody in the 7th year, having had 3 relapses. I mean once a PI stops working, is it used in combination? Is it somehow change..?

Dr. Philip McCarthy : You bring up a good point. Because what happens is that the cells become resistant. Then when I talked earlier about how the cells change their genetic profile, that is probably what is happening as to why they become resistant to proteosome inhibitors. And we can use the Imitz as a good example. There is that protein called Cereblon – which Keith Stewart came up with. And that is a very good marker, well it is not a perfect marker, but it is decent marker to Thalidomide and Lenalidomide and then potential response to Pomalidomide. Well, all of it turns out that Cereblon bind some Zinc finger proteins called Ikaros – which are involved with B cell development. So what probably happens is these- for example the proteosome mutates, so that it is no longer binding the Bortezumab and it is now resistant. So what are we doing to try and overcome that resistance? Well, there is a paper by Peter Voorhees – and he looked at something called an AKT inhibitor.It is another pathway. And when you combine an AKT inhibitor with Bortezumab you now make the cells sensitive. You now make the patients respond, and that is very exciting. SO what we are hoping is that an AKT inhibitor may allow us to treat patients who in the past had been resistant to Bortezumab, and now they become sensitive. It is called – A*foresitib??* – all these drugs have way too long names.

Pat Killingsworth : No, that is very helpful. Now is Panobinostat – is that an example of?

Dr. Philip McCarthy : Panobinostat! Right. H-deac (histone deacetylase inhibitor) inhibitors are another example of how you potentially combine with a drug and get activity. Another good example, if we go back to the Imitz, antibodies when combined with Imitz seem to work better. So for example, you can have a patient who is resistant for Lenalidomide, and then they get Elotuzamab with the Lenalidomide and Dex and they

can respond. And it appears that the Lenalidomide is making the antibody work better. Now that does not work for proteosome inhibitors. But we do know that when you combine, so for example, if you combine the new Proteosome inhibitor Carfilzumab and you combine it with an Imitz such as Lenalidomide or poetntially with Pomalidomide and Dex, you now can get responses. So it appears that you got to have combination agents even in relapse refractory setting that allow you to generate responses. The other drug that is now in Clinical trials well for relapse refractory is MLN9708 Ixazomib. And Ixazomib is an oral proteosome inhibitor, which you see when combined with an Imitz and Dexamethasone, shows activity in patients who have develop resistance to Velcade or Bortezomib.

Pat Killingsworth : Well, that is very helpful. So potentially_ *with* Carfilzumab *??* and now Ixazomib and there are several others coming along too, right? I can see how may be that now becomes moderate or standard risk. Very helpful. Thank you.

Dr. Philip McCarthy : Exactly, and just to give another plug, there is another antibody called Daratumamab – an Anti CD38, there is at least 1 or 2 other antiCD38 antibodies in development. There is another proteosome inhibitor called Oprozomib, there is another one called Marizomib, and these are all new drugs that potentially will offer patients new options in terms of treatment.

Pat Killingsworth : Thank You.

Gary Petersen : Lizzy, are you online?

Lizzy Smith : Hello, Can you hear me.

Gary Petersen : Your question?

Lizzy Smith : Hi thank you Dr.McCarthy for your time today. I am interested in when you were discussing genetic abnormalities and so how it can get remission and then it comes back and then you might have different genetic abnormalities, is that – And I hate to say there is anything good about myeloma – but cannot sometimes it be a good thing if you have a different myeloma, you might be more receptive to different kinds of treatments that may be you weren't originally?

Dr:[00:53:00] It depends. It depends, so sometimes patients will response to different treatment. But we don't know enough yet about this. What usually happens and unfortunately that is that the disease becomes more resistant to the standard to what the patient has seen before. And a lot of it is timing. So, in other words, if a patient relapses fairly quickly after a tenure or progresses after initial response say within 6-12 months, that is very different than if a patient have a good response, may be say a stem cell transplant and then 3,4,5 yrs later the disease comes back. Sometimes it comes back in sits there. And that is great if it just sits there. But the problem is if it starts to grow and cause problems, that is when you need to trade. So we don't know enough yet, to be able to say, whether or not a genetic abnormality is good or bad yet.

Lizzy Smith : Ok. Then I had another question going back to clinical trials. For what I have been able to tell just talking to other myeloma patients, a lot of patients get clinical trials because they can't afford it either their insurance won't cover it or they can't afford to travel. Are there programs that could help get those patients into those trials, if its finance that is stopping them?

Dr. Philip McCarthy : Yes. You bring up a really good point. Some insurance companies prohibit clinical trials, because they would only allow the standard of care. I happen to think this is crazy. And there is all kinds of politics behind this so, I am not sure how the affordable care act or the Obama care will change this, but it does, patients who do sign up for these are allowed to go on clinical trials. Now I know there is pluses and minuses to Obamacare and everything else, but I think that is a really important thing is that we need to get our companies, you know employers educated that clinical trials are not just a black hole, where money gets poured in to. We learn something from this, specially large phase III trials. So I totally in agreement that we need to change how patients are insured so that all patients are allowed to go in clinical trials. In the

mean time there is not a lot you can do about that because a lot of these trials are *purportedly..* expensive because there is a lot of supportive care that needs to be paid for by the insurance company. Now some of these trials allow for free drugs. So, for example, the determination trial – Bortezumib and Lenalidomide are provided for by the companies as part of the trials, which is fantastic, but all other supportive care needs to paid for by the insurance companies. If they don't allow it clinical trials can't be done. And then the travel thing you bring up is a really really important item, and right now the NCI is struggling with this because not everybody can travel to and stay next to a cancer center or a hospital that offers a trial. Some people just cannot afford to do that. So that means trying to come up with satellites that will be allowed administer the drug and do it on trial into all this the testing and the eligibility criteria, all the things that you need to do to make sure the patient is eligible for and can stand the trial. And that is something the NCI is wrestling with. I think we need to, if the advocates would push for a allowing a mechanism for the smaller oncology groups in veteran areas that are not large cities where there are big cancer centers to go on trial and be monitored, and that would be really important. But that is a national initiative that the NCI is gonna have to lead on.

Lizzy Smith : Ok, very good thank you very much.

Gary Petersen : Thank you Lizzy. Yes Priya, let's see if we can bring some callers on right now. if you are listening and want to ask a question to Dr. Mccarthy, please hit 1 on your keypad and will bring you online with your question. So, if you will hit 1 and ask your question, we would appreciate it.

Priya Menon : Thank you Gary. I just received a question via email for Dr. McCarthy. The listener wants to ask – I a patient has no detectable disease in the bone marrow, are there MRD or other tests that can be done to detect the presence of the disease or do they all require a bone marrow sample with malignant cells.

Dr. Philip McCarthy : Yeah. The best, right now unfortunately with myeloma the gold standard for treatment is to do a bone marrow test. There are some people who are trying to develop some blood tests that will measure cells in the peripheral blood, but they are not ready for prime time. Because having a bone marrow is no fun. I have had one done on myself for research and it wasn't, I would not want to have one done everyday. But, right now the gold standard still remains looking in the marrow under the microscope and doing flow cytometry to look for MRD. Some people are doing PCR- Polymerase Chain Reaction – but that you usually have to have the diagnostic sample to make – they are called primers to look for MRD. So, right now the gold standard is still at a flow or PCR again using the original diagnostic sample. And we are not sure yet. We know that it predicts for better progression free survival, but majority of those patients still are gonna have progression. So then the issue is what kind of strategies can we develop, some type of maintenance, consolidation, and then better salvage regimens, if and when the disease comes back, we can get the patient to get back into remission in MRD state.

Priya Menon : Thank you Dr. We have a caller online who has a question. Caller calling in from 9874359, you are on air please ask your question. I think he changed his mind. I think I have some of the panel questions remaining, may we could just get into it.

Gary Petersen : Yeah, I have one for the doctor, and it is easily…

Priya Menon : I think the caller is on air now. Yes Please, ask your question.

Caller : Yes, thank you. I am newly diagnosed multiple myeloma patient and I am 50 yrs old.

Priya Menon : Can you please mute your computer if you are listening to it live, because that brings an echo.

Caller : Sure, thank you Dr. McCarthy for this program. I said I am newly diagnosed multiple myeloma patient and I am 50 yrs old, otherwise healthy and show some induction therapy doctors are talking about RVD vs. CyborD, followed by transplant. There is also trial at Cornell with Kyprolis, Carfilzomib and Dex followed by BURD?? maintenance. Do have any advice for a nearly diagnosed patient like, should I try I

mean, things like the, consensus is around RVD for Induction therapy. I just want to hear your views on that.

Dr. Philip McCarthy : In think, for all patients, regardless of what you do, I think some form of triple drug regimen is important for induction. And I will get to specifics in a second. And then current thinking is treat to best response, collect stem cells early and get them in the freezer. So that way you have got a, and most centers collect for more than one stem cell transplant, because potentially could be used in the future and then the issue is transplant early vs. late, so starting first with RVD vs. CyborD or VCD, I think RVD is used by a lot of centers, VCD's used by lot as well, that Evolution trial I talked about earlier – they were about the same but the study wasn't powered did not have enough patients to be able to determine which one might be better. On the 100104 study, one thing we did find is those who responded to Lenalidomide containing induction regimen, and then got Lenalidomide maintenance afterwards seem to do the best. Now that was an unplanned subset analysis so that is why I am not gonna cross the limit and say, you must do that. But at least it is something in your favour. So, I usually recommend RVD as the first choice, and if there is any issue, may be CyborD as the second choice.

Priya Menon : Thank you doctor, I think we are just above our time now. I would like to thank you so much Dr. McCarthy for joining us today. I thank the panel – Pat, Jack, Cindy and Lizzy and Gary for their participation. It was an awesome discussion with lot of information shared on this. We will be sharing the link for the show via email to all the participants and you can always visit curepanel.carefeed.net for details of our upcoming shows.

On May 27 @ 6pm ET we are discussing Osteonecrosis of Jaw during myeloma with myeloma survivor and dentist Dr. John Killip. Until then thank you and have a nice day.

Thank you!