More can Cure Myeloma Treatment with Dr. Gareth Morgan

UAMS is the only institute in the world that claims to be Curing Myeloma since 1989. Tune in to learn the nuances of how aggressive treatment therapy for myeloma has yielded positive results from the new Director himself. At a time when the larger part of the myeloma fraternity has only recently started using the word Cure in terms of curing the disease, UAMS has been doing so since a long time!

Full Transcript:

Priya Menon : Hello, everyone, and welcome to Cure Talk for a discussion on multiple myeloma. I am Priya Menon, Scientific Media Editor at Cure Talk, joining you from India and I welcome all of you this evening. This is Cure Talk's 73rd episode. We are excited to inform our audience that henceforth we will be conducting our shows under the name of Cure Talk and we have a new website, curetalks.com. The website is a work in progress and we would really love for feedback from you. Please do check it out and mail me, priya@trialx.com, with your feedback.

On our myeloma broadcast today, we are discussing More Can Cure Myeloma treatments. My co-host for the show is myeloma survivor and editor of myelomasurvival.com, Gary Petersen. On the panel are myeloma advocates and survivors, Pat Killingsworth, Nick van Dyk, and Cynthia Chmielewski. We have a very distinguished guest with us today, Dr. Gareth Morgan, Director of the Myeloma Institute For Research And Therapy at UAMS. Welcome to the show, Dr. Morgan. Its a pleasure to have you with us.

Dr.Gareth Morgan: Thank you, Priya. It's a pleasure to be here with you and with the audience. So, hopefully, I can be informative and we can have a good discussion.

Priya Menon : Gary Petersen will introduce us to our expert and begin with the discussion. Before I hand over to Gary, I would like to tell all listeners that we will be addressing questions. towards the end of the show and if you want to ask a question to our panel, you can press 1 on your keypad and we will bring you on air to ask your question. Alternately, you can email me with your question at priya@trialx.com. With that, its over to Gary. Gary, you are on air.

Gary Petersen : – Oh, thank you again, Priya, and thank you for bringing us this forum and for updating it for a better user experience in the future. So, we all thank you for that and thank you for all that you do for the myeloma patient community. I have the pleasure of introducing Dr. Gareth Morgan, MD, PhD, FRCP, and FRCPath, somebody I think has more initials than anybody I have ever introduced in the past. Dr. Gareth Morgan is Professor of Medicine and Pathology and the Director of the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences. He is also the Deputy Director of the Winthrop P Rockefeller Cancer Institute at UAMS. He is an internationally recognized scientist-clinician in the field of molecular genetics in blood cell cancers and in particular multiple myeloma. Now, he came to The University of Arkansas for Medical Sciences from The Royal Marsden Institute of The National Health Service Foundation Trust and The Institute of Cancer Research in London and this happens to be Europe's largest and most comprehensive cancer institute, where he was a Professor of Hematology and a Director of the Center for Myeloma Research He received his Doctorate in Leukemia, actually in the genetics of leukemia, from University of London in 1991 and his Doctor's degree in 1981 from the Welsh National School of Medicine. He is a Director of the Myeloma UK, a respected UK patient organization, which is much like the IMF as well as a member of the scientific board of the IMF. He is Founding Director of The European Myeloma Network. Dr. Morgan has authored more than 450 articles appearing in leading peer journals including The New England Journal of Medicine, Black Journal, Clinical Oncology-Leukemia, Lancet Oncology, and Clinical Cancer Research. He is a member of The British Society of Hematology, The American Society of Hematology, The American Association for Cancer

Research, The Royal College of Physicians UK, and The Royal College of Pathologists in the UK. So, my point would be, is that for UAMS he was quite a great get. So, welcome to the program, Dr. Morgan.

Dr. Gareth Morgan : Thank you, Gary. I thank you for that very over-inflated introduction, but its a real pleasure to be here in the US and being in The University of Arkansas, its a kind of honor and I should say I am really enjoying it. I am looking forward to some interesting conversation and questions and discussion this afternoon.

Gary Petersen: Given your background, as I see it, you come from London, right, which is like the European capital, has all the best of the best. You headed one of the most prestigious institutions in the world for multiple myeloma and you are going to UAMS which is in Little Rock, not the capital of much and in addition, you know, I would say that if anything its been a topic of much conversation. So, I just, What were you thinking?

Dr. Gareth Morgan : was actually thinking very creatively and it was kind of good movement for me. I don't think it was a bad decision. In fact, I think it was a good decision for me and I think a good decision for the program, in that I think the access to patients and the infrastructure that we have in Little Rock is amazing for myeloma patients and we have people that look after all aspects of the myeloma patients' experience from kind of greeting them on arrival, looking after their pastoral care, to getting them educated in myeloma, to delivering the treatment, again predominantly as an outpatient and given that we are the, I think the largest myeloma center in the world, that having access to that group of patients and the facilities here will allow us to really deliver game-changing treatments for patients with myeloma and we are actually in the

Gary Petersen : Excellent to learn. I just think giving up all of that, you know, is just remarkable on your part. So, you must be seeing something that, you know, just the standard individual may not observe, you know

Dr. Gareth Morgan : Yeah, I am enthusiastic about every… We have things here and we have a team of dedicated people that really put themselves out for myeloma patients and I think we can, you know, take things to the next level really.

Gary Petersen : Okay. Great! Well, one thing I wanted to let you know for full disclosure is that you have got two people that were both treated at UAMS, myself and Nick van Dyk, and Nick happens to be, you know, very, very close with Bart and I like Bart as well, but I don't quite have the bromance that Nick has with Bart, but so, you know, I try to be as objective as I possibly can, but I am not because.

Gary Petersen : I think you guys have done a wonderful job and I think I am here 8-1/2 years later after having dialysis-dependent kidney failure, so I had left failure. Dr. Morgan, UAMS has been known as the More Can Cure Facility with exceptional survival results. Could you explain the total therapy program for us and why it has such success?

Dr. Gareth Morgan : So, I am going to start answering that question by just explaining a little bit about the background of myeloma. So, I think we are very clear now that within myeloma has more than one cancer cell or one clone, so its not homogeneous. There are cells within the cancer itself that has different behaviors and the challenge has been to kill all of those cells so that there are no cells left to lead to relapse and failure of treatment and that's where the More Can Cure comes into it. I am not sure I kind of would portray it as More Can Cure. I would say that combination treatments of drugs with different modes of action allow you to kill more of these cells and therefore cure more patients and what's kind of happening really is the whole program is moving from, you know, this more chemotherapy, more dose-intense chemotherapy can cure to more one of other total therapy. I am kind of thinking if it was total targeted therapy where we look at the patient's myeloma using the gene array sequencing, you know, all of the biological tests that we can bring to their understanding what is happening with that patient's cancer and then choosing the most appropriate treatment for those patients and this involves not just the

chemotherapy. It involves using antibody treatment, targeted therapies, and largely what we are aiming to do is to move away from a one-size-fits-all heavy chemotherapy approach to a more directed, well-thought-through, innovative, personalized approach.

Gary Petersen: Not once did I hear you say transplant. Is that something that you are shying away from or that's so integral part of the program.

Dr. Gareth Morgan : So, transplant remains one of the major tools that we have for the treatment of myeloma and for the majority of younger, fitter patients, I think we can use transplant as the backbone of our treatment but improve outcomes by adding in novel agents, antibodies, and targeted treatments.

Gary Petersen : Does that include dual transplant?

Dr. Gareth Morgan : Yeah, I was going to say so. At this point in time, I don't want to move away from the high cure rates we have got just to try new treatments and we need to work on the strategy that probably allows us to remove one of the transplants so that we move to a less dose-intense treatment, the More treatment overall, so that we not only maintain the high cure rates but move to even higher and better responses and I think this is possible, but what we don't want to do is take a step backwards by moving away from the strategy that we know to be successful.

Gary Petersen : You said monoclonal antibodies. That's currently not in the program, so that's something you are looking to?

Dr. Gareth Morgan : Yeah, very much and one of the most exciting things has been the development of the antibodies that work in myeloma and the kind of molecule on the cell surface called CD38. There are now antibodies that recognize CD38, so anti-CD38 monoclonal antibodies, and they are getting responsive in relapsed refractory disease faster than we've seen with any of the other drugs and I need to move them to the frontline into our total targeted treatment approach that will get the benefit of cures immediately for those patients. So, we are starting to plan trials for doing that now, which I think is a very innovative new direction for the program as well as to go not just single monoclonal antibodies but to go combinations that moves us away from chemotherapy totally in some respects. I am very cautious about people's long-term health and their survival, so we don't want to kind of deny people excellent treatment. So, we will do this cautiously, but it looks like a major step forward I think in the program and will improve outcomes considerably.

Gary Petersen : So, the program has provided great success and you had an opportunity to look under the covers there and see the numbers and all that stuff and from your assessment you would say that that is in fact true, but are these, unless its not, I assume that you say it is, but are there downsides to quality of life?

Dr. Gareth Morgan : Yeah. I thought you should let me answer that question because question. Yeah, I kind of looked at the data here and the patients that are in the study have been entered into the studies upfront, the data is being collected well. We have external committees that review responses on survival that is a kind of committee of people from the NCI and we have the results out as they are presented. We have excellent 15-years-and-beyond survival rates, which I think you can equate to cure in this disease. So

Gary Petersen : Its remarkable. That's fantastic.

Dr.Gareth Morgan : It is really and the other thing that I would say which you find when you come to a newer organization is what are the quality of the people like here. I would say without shadow of a doubt that I have inherited a collection of dedicated professionals that do their job really well and understand their business and deliver in a professional manner, so that's been a great discovery for me. It makes my job so much easier and I think I can concentrate on getting advantages to patients as quickly as we can, which is our aim for everybody.

Gary Petersen : And looking at the data, do you see downsides in the quality of life secondary to cancers, MDS, or any other complications which come with this more intense therapy?

Dr. Gareth Morgan : So, when you are having chemotherapy, it clearly affects your quality of life and that is kind of a period of time where your quality of life is impaired. People have to stay in Little Rock, its not such a bad place, it's actually a nice place, but during that time.

Gary Petersen : I agree, absolutely.

Dr. Gareth Morgan : Yeah, but the issue is its a tradeoff. Its like , so what you are trading off is some time at the beginning of your disease during which you have to accept being a patient, but once you are through that period of time, then you got 60% chance of being alive, cured well at beyond 10 years and that's a really important tradeoff and I think its one that people should accept because the benefits of being away from doctors for prolonged periods of time, just having followup, going back to a normal quality of life, back to your family is a really major end point or I get the concept is cure and I want to cure as many people as possible. The quality of family life and time with your family is really important to everybody and I think we give people quality family time and survival when they are well, so I don't think there is a downside on quality of life. The issue about MDS, I kind of looked at our figures for MDS here and I am not convinced that there is a problem with long-term secondary cancers or myelodysplasia. I think it was an issue giving anybody chemotherapy and any drugs together can be an issue, but I think the benefits far outweigh the minimal chances that there are of developing MDS at 10 years and beyond. When you think of what we were offering people in the past, which was 2-1/2 years of survival [end[and little else, I think its dramatic success for the program and for patients with myeloma.

Gary Petersen : Thank you, doctor. I think you have answered my next question which I won't ask then, but UAMS had participated in clinical trials, but they are generally UAMS-only trials and they seldom, you see little participation from other institutions. Will this continue to be the modus operandi or will you now participate in some of the national trials like monoclonal antibodies, etc.?

Dr. Gareth Morgan : We have always been a part of national trials and Bart was a member of SWOG and we have contributed to SWOG studies. We just completed a SWOG study of smoldering multiple myeloma, so we will continue to participate with that group and I have no problem in saying that whatsoever. Our real aim here is to bring innovative treatment strategies to patients as soon as we feasibly can and for that reason we have our own internal trial setup in which we treat people to, which gives us that facility really to kind of really push at the cutting edge of treatment and bring this to patients early on and what we are looking for are major changes in treatment now, not nuancing 2% to 3% improvement overall. I think those treatment's out there. We will need to find the major new therapies that have big effects and then to bring them to patients as soon as possible and I have told you about where we are going with monoclonal antibodies and that's a good example of how we want to get them into the frontline so we can improve cure rates further rather than going to end-stage disease and looking for all of that.

Gary Petersen : I guess one of the questions too would be why aren't other people jumping on this bandwagon, you know, why aren't total therapy 3 and 4 trials being used in other institutions, you know, because they are national. Are they UAMS only?

Dr.Gareth Morgan : So, I can't answer for the rest of the US. We bring people in from around the world who go on to these treatment protocols. They do well and I think that coming together of strategies and you would be surprised how influential this total therapy program has been. The concept implicit in it of induction and transpant one, transplant two, consolidation and maintenance and now the basis of treatment around the country and around the world and certainly in the UK, I was using these approaches for patients there and we get good approaches in the UK. I think, you know, we have quality staff here as well and I think that we do a good job by patient, whether they are interested in things like. Patients with low-risk myeloma are doing very well, but those 10% to 20% of myeloma that you can see with the gene array that we use, that have very poor outcomes where we haven't really been improving therapy for patients for the last decade

really and what we want to do is focus on those patients really trying to evaluate therapies for these guys and then translate the advantages made by kind of trying to improve the outcome of high-risk disease of all patients with myeloma and I think that really the other main thrust in change of where we are going is how do we really change the outcome of what is at least much like myeloma was 15 years ago with two years on average survival that we need to push at and really get to curing this group of patients as well. So, that's going to be a major interest.

Gary Petersen : – Doctor, one thing I wanted to say about you is that I have already seen that you have done a number of things such that here you have been on the, you know, the crowd, myeloma crowd website, of Cure Talk, they have one, you are on this one, you are on patient power, you had a myeloma blog, you had a number of other papers and it seems like you are getting on in front of a lot of people and explaining your program and that type of thing and I think that has a lot to do with my next question, which is that, you know, its Everybody has an opinion about UAMS and that opinion is usually if you are somebody who has gone there, you know, you will think that its god's gift to patients and if you haven't gone there, then it seems to be open for significant criticism and its either one or the other. There doesn't seem to be a oh, heck of a lot in between. Its kind of an I would say its an image issue, but its really not an image issue. Its an image conundrum because everybody has that opinion, you know, and its either one or the other, so my question is, you know, you get Its a lightning amount of discussion on all of the, you know, the social media pages both praise, scathing criticism and some things in between. What are your You know, now that you have just arrived, what are your purely objective observations of the reasons for such varied views of the program?

Dr. Gareth Morgan : That's a really hard question and its difficult for me to talk about the past. I think you are making good observation and clearly trying to communicate with patients from around America and the world and I want them to understand that we are a kind of cutting-edge innovative center where we look after the pastoral care of patients, make them feel welcome, and we deliver the most appropriate treatment for that patient, be it aggressive chemotherapy or be it monoclonal antibody therapy or targeted treatment and we don't want to haul everything into a one size fits all so in one level I want to bring this more to the midline, but I would like us to be named cutting edge in delivering the best of (inaudible) and because I think we do get good results and I think that's something to be proud of.

Gary Petersen : Oh, thank you very much, doctor, and continue on all your efforts to explain the program and find a way to cut through some of this bad information, at least I think its bad information, but then again I said I am somewhat… I am 8-1/2 years of continued remission. So, I am a little partial to the program. I Now, let's get on to the other questions. Pat Killingsworth, your question?

Pat Killingsworth : Thanks, Gary, and thanks for being here, doctor.

No problem.

Pat Killingsworth : I understand that its it has included a lot of attention to total therapy, but I am sure that the institute spends a great deal of time and money and effort trying to keep late-stage myeloma patients alive too, so could you take some time and explain to us some of the innovative therapies that your team has come up with to try to keep some of us alive, those of us Like Gary, I am approaching 8 years, but unlike Gary, I have now relapsed three times and eventually you run out of standard options. Could you enlighten us please?

Dr.Gareth Morgan : So, I think the antibody approach is something I talked about, which is clearly really appropriate for people with relapsed disease and building combinations of antibodies that fix different components of the immune system is going to be a really important way forward. There is antibody SLAMF7 which combines beautifully with Revlimid. There is the anti-CD38 antibodies of which there are three that will come in to clinical use. There are antibodies called anti-PD-1 and anti-PD-L1 which seem to

enhance the immune system in the presence of other antibodies and also there are antibodies which enhance the activity of cells called natural killer cells, which gobble up the myeloma cells and put people into remission. So, we have a kind of program that we will put into place along those directions together with taking cells, they are expanded in the laboratory and reintroduced into patients. The latter option is more experimental and single and combination antibodies are more kind of relevant to patients at the current time.

The really kind of cool thing is that of being interested in doing sequencing the cancer cells from myeloma patients and we found a mutation called BRAF, that's a member of the RAS family and so BRAF is mutated in 4% of cases at presentation, maybe 10% at relapse and RAS is mutated in about 50% of cases. So, we took a BRAF inhibitor and gave it to a BRAF-mutated patient and that patient went into a response. No toxicity, kind of went into a remission over a seven-day period and managed to stay in response even though they had every prior chemotherapy for six months. So, maybe that's not, you know, the duration of time wasn't good, but the fact you could show, you could get a remission even in heavily treated patients is really, really relevant. So, when I was sequencing people regularly for RAS and we have a RAS inhibitor or the downstream inhibitor of RAS called Mekinist and if a patient has a RAS mutation signature, we will treat that patient with the Mekinist and we get responses again even where we wouldn't have expected than in the past and so we are trying to build on that targeted treatment strategy by fully evaluating the Mekinist in a standardized fashion and then building combinations that enhance its activity and this is an entirely non-chemotherapy approach, but you can imagine when you build in with chemotherapy that our results will be even better. So, I think its a fascinating time and I think these targeted treatments will become more and more relevant.

Pat Killingsworth : That's very exciting. Now, the RAS mutation patients Is this a form of re-sensitization of the drugs that weren't working anymore now work or is this something Is this a completely different mechanism?

Dr. Gareth Morgan : Totally totally, the Mekinist which develops a melanoma, a skin cancer, and it turns out that I think the RAS pathway is more mutated in myeloma and so myeloma seems to be a disease where we can explore all of these RAS inhibitors and expect to see responses and it has not got much any time really in the myeloma community and I think after ASH time, its going to become more and more out there, with more and more people discussing it. It is a significant way forward.

Pat Killingsworth : – Okay. Are you working with the MMRF on that because if I am not mistaken I was having a conversation like this with several folks over there about this and it does sound really exciting.

Dr. Gareth Morgan : So, I think a patient from, I can't even remember where it is, so in the northeast Wilmington, sort of attended, was connected into the MMRF and we treated that patient with the Mekinist and they responded and so its been, you know, I think it is exciting and, you know, goes with collaborating with anybody that's in the myeloma community that wants to kind of push the outcome of myeloma patients forward and, you know, its a community effort, not just a single institution effort.

Pat Killingsworth : Well, thank you for all of your hard work and efforts and that step is very encouraging. Thank you, doctor.

Gary Petersen : – Thank you, Pat. Nick van Dyk, are you on air?

Nick van Dyk : I am. Can you hear me?

Hey doctor, its very nice to meet you telephonically. As Gary mentioned, I am a patient and dare I say a friend of your motorcycling colleague and I was treated there in 2009 under total therapy for light and I remain in stringent complete remission. I am MRD negative and I am extremely thankful for my treatment there. So, I am also a part as in and I am sort of infamous on these calls for having long questions, but I have got one for you, which is, if we think about standard-risk myeloma, there has been a debate that has

posed the question well. We know transplants and novel agents together work well, but what if novel agents do just as well by themselves and you referred to some subtle changes to the total therapy approach, even mentioning we might move away in some cases from tandems and because we all know there is nothing magical about tandems. Its just twice the novel and the work of Dr. Tiedemann in Toronto has shown at least that in vitro the progenitor cells don't have the structures required to make them susceptible to IMiDs and proteasome inhibitors. It takes alkylators to actually uproot those progenitor cells and kill them and if we are closer to home than Toronto, if we look in Little Rock, the recent article in blood that showed TT4 standard versus TT4 light, the standard arm is doing a lot better and the only difference is the standard arm got more of the alkylators. So, with all that, is it your opinion that novel agents alone can do the job or does it still take the hard core chemo for a lot of this stuff and where do the new immunotherapies and antibody therapies come into it? Do the progenitor cells exhibit CD138 or is this another exercise in culling the weeds on top of the lawn but not getting to the roots?

Dr. Gareth Morgan : Nick, you are right. You ask long questions (laughter). So, like if I start with TT4 standard versus TT4 light, I think standard arm did do better and I think the answer is your point that we should be very careful about moving away from alkylators too quickly and relying exclusively on novel agents and at one level, we should be building on the successes with alkylators using novel drugs. So, the CD38 is expressed on a myeloma precursor and so I would expect that antibody to be successful and so we are definitely not going to drop our successes and aim for transplant-free approaches. There has been a study recently from Antonio Palumbo which compared transplants versus non-transplant with the same agents other than the transplant and the transplant stayed in remission longer and lived longer. So, transplants do work and we need to be very, very careful about dropping them. There's a kind of I think for patients to say dropping in transplants makes no sense and could set us back. I think we need to move towards, you know, not doing a transplant when we show the novel agents really do work. One thing is clear. You should never see heavy transplant's mortality. We shouldn't be killing patients with chemotherapy. That is counter intuitive at so many levels and we should always remember that each patient is different and doing transplantation in frail patients is nonsense and we should move towards using antibodies and novel agents.

Nick van Dyk : No, I was just going to say that makes That makes perfect sense. I had one slightly shorter followup, which is near and dear to me.

Oh, please. I am sorry. Sorry. Didn't mean to cut you off.

Dr. Gareth Morgan : The deal with Roger is, he is my pal. That piece of work is not my most favorite piece of work and at many levels I don't believe it, not that I think he is cheating at any level, but the result is difficult for me to understand and I think we can target treatments to the biology of the myeloma stem cell which looks a lot like a myeloma plasma cell and I think its being shown reasonably conclusively that the myeloma cell itself is the target for treatment and so overall I think we have a number of ways forward which are based around targeting with what we see on the myeloma cell itself, but they seem to exist in this dynamic relationship with a smaller population of cells that don't have so much 138 on their cell surface and those cells might be epigenetically different to the mature non-myeloma stem cells and I think that we are aiming to try and understand that population and to target epigenetic drugs like defect histone methylation, DNA methylation, in order to make those cells more susceptible to chemotherapy and I think that's again a feasible approach. I guess the definite answer to your question is for now, we shouldn't move away from alkylating agents hopefully, but we should build on our successes. Ask your next question.

Nick van Dyk : Got you. Okay, so thank you. So, given that more people are achieving stringent complete remission and the MRD testing is becoming more widespread, it is both generally used for the patients and also as someone who is still MRD negative but facing the declining remission curve in the right arm, are there other tests beyond random MRD and marrow that can be done to assess outcome like deep sequencing or heavy light assays or even, you know, Bart likes to look for full resolution of focal lesions under MRI. Are you seeing other types of tests that could be useful to corroborate how durable MRD negativity might be?

Dr. Gareth Morgan : The important question that you answer patients is what was the sensitivity of the test that was used to detect your MRD because it varies from center to center and you really need a test that's sensitive to one tumor cell in the million normal cells and so if we can get people to below that level of tumor cells, I think we will then start to see the flow cytometry turning into a really clinically relevant, predictive test and there's other ways of doing it and deep down I think that the flow cytometry is very difficult to standardize across a country as big as the US and what we are kind of thinking is that the molecular PCR-based testing for MRD which is called ASO-PCR or Sequenta or Clono Sequenta Technology is more routinely applicable, more sensitive, and I actually think that we will be moving towards PCR-based assessment of MRD rather than flow cytometry. So, that's my bias in the argument, but those tests are good. We should always ask what was the sensitivity of the test because if its only sensitive to one tumor cell and 10 normal cells, you could have quite a lot of disease on board and its good advice.

Nick van Dyk : – Wonderful! Any idea when PCR-MRD tests might be put in place at Merck?

Dr. Gareth Morgan : Early in the new year. We can do them now and we are kind of collecting up all of the samples that we have to get analyzed and so I am pretty confident that early next year we will have all this stuff, we will have the data and we will have the capacity to do on patients coming for followup because following that patient is really important, you know, basically Bart has always done a good job of kind of developing and applying tests to predict relapse and so we are also working on a sort of pure signature, which I think could be really helpful if we could look at people and say that immune cells in their marrow have returned to normal. The marrow structure is normal on gene expression and I think that would be really reassuring to the patients and I think you should be reassured. I kind of think where you are is you are doing good. You are not facing the outcome of having an inferior treatment. I think you did well on it and so and I hope it continues that way.

Nick van Dyk : Thank you. Well, my hip and I will be there in January and you can have some marrow. Thank you very much.

Gary Petersen : – All right. Is Cindy in? I know she was having difficulty flying out. Did she make it online? Cindy, are you online?

Not with us. Okay. She has some travel troubles. So, I will ask her question for her. Cindy asks, I recently read your article on evolution and intraclonal heterogeneity and myeloma. You suggested that, in general, Darwinian evolutionary concept suggests that single-drug exposure may not be the best approach to treating myeloma as it may lead to the outgrowth of resistant clones and resistant clones could be overcome by either using combinations of different drugs or using cyclic approaches that employ different combinations of drugs at different times and in alternating fashion, you know, if someone has used or plans to use the cyclical approach during this. To me, this approach makes sense, especially if a combination therapy was used during induction and consolidation.

Dr. Gareth Morgan: So, I agree with Cindy. I kind of think it needs to be done and it does make sense and so one of the kind of steps we are going to do is We have been using Velcade and Revlimid for maintenance and we plan to compare that in a randomized fashion through cyclic use of the different drugs and introduce the antibody and maybe histone deacetylase inhibitors to build a combination regimen for maintenance and it does make sense and I As long as we don't increase toxicity, I think its likely to be successful. Of course, we don't know the answer to that, which is why we have to kind of set out doing a randomized comparison, but if you build these randomized comparisons with normal end points such as MRD detection and functional imaging such as PET and MRIs, I think you start to feel way forward of evaluating different approaches at the one and two-year time point rather than having to wait for 10 years to really get an answer.

Gary Petersen : Okay. Well, thank you very much, doctor. What we will do now is we will go to some of the questions from our listeners and, Priya, could you bring on anybody online right now? If not, I will go to the submitted questions.

Priya Menon : Listeners, if you have a question for Dr. Morgan, please press 1 on your keypad and we can bring you on air to ask your question live. We have a caller, um…, calling in from 917-685. You are on air. Please ask your question.

Dana Holmes : – Yes. Hi! Good afternoon, Dr. Morgan. Thank you for taking my call. This is Dana Holmes and I am a smoldering multiple myeloma patient based upon percentage of plasma cells and flow cytometry. I don't have any crab or any of the myeloma-defining events per the new International Myeloma Working Group Guidelines. I am curious to know your approach regarding early treatment intervention for smoldering patients. Will your group develop any trials or will you offer existing trials to your smoldering patients before the disease likely becomes more complex as the disease progresses? What are your feelings about treating smoldering patients?

Dr. Gareth Morgan : So, my intervention based on the behavior of smoldering myeloma and other cancers is to treat before patients develop the end-organ damage. I think its kind of true with old cancer, that if you treat early you get better outcomes. So, conceptually, that's where I am. The issue with smoldering myeloma is that its not one kind of condition in a way. Its a spectrum of disease and at one end, you have nuggets which is entirely benign and the time to change into myeloma is very, very prolonged and I think there is no indication for therapeutic intervention and the high-risk smoldering myeloma, which is a lot like early myeloma which is going to change to myeloma within a year and a half. And so, what we have been basing our strategy around is using the gene array to predict which of the patients will transform within a two-year period and so we now have a signature, a four gene signature, that predicts with high certainty patients at high risk of progression and we have kind of written a paper with, putting it in the post, but I think we have a way now that's more accurate than flow cytometry. Its more accurate than using the light chain ratio and does, you know, predict people at high risk and so what we are going to do is to offer people with high-risk disease access to the anti-CD38 antibody treatment which doesn't damage the body targeted to the tumor cells and I think we will likely see really good outcomes with such an approach. We don't have it up and running yet, but that's our plan for the new year.

Dana Holmes : Okay. Thank you, Dr. Morgan. Now, these four gene signature, it would be through gene expression profiling. Is that offered outside of MIRT? Can a patient that's not with your group get that actual test?

Dr. Gareth Morgan : There's a commercial laboratory, Signal Genetics, where people can have their doctor send the test to that company and so the answer to your question is yes, it is. Not many people take it up though and so I don't really understand that. I think the gene expression arrays actually give a lot of information and I think its pertinent to smoldering myeloma and to myeloma presentation.

Dana Holmes : Okay. Very good. Thank you so much. And you said anti-CD38 or 138?

Dr. Gareth Morgan : 38.

Dana Holmes : Okay. Very good. Thank you so much, Dr. Morgan, for taking my call. Appreciate it.

Gary Petersen : Thank you, Dana. Priya, next question.

Priya Menon : Gary, I think we can go over to some of the questions.

Gary Petersen : Okay. All right. So, we have got one question from one of our members who couldn't make it and that was Jack Aiello and Jack saw you in Houston and Jack says that in Houston he thought you said that you can or need to do better than FISH, cytogenetics, and GEP (genetic expression profiling) to learn more about an individual's myeloma and which treatment might work best for them. If Jack didn't mishear you, which is certainly possible, can you talk of I don't know Can you talk more about this or instead can you clarify where we are in using these techniques to develop precision medicine or personalized medicine?

Dr. Gareth Morgan : The issue with FISH is that a lot of people get told they have high-risk disease because they have certain FISH lesions and the bottom line is that within any FISH group some have high risk and some have low risk and the only way to sort that out is really using the gene expression signatures and so that's the most accurate way that I can see currently of defining if you are high risk or low risk and like I said before, about 20% of people are high risk and need to kind of explore novel treatments and novel approaches. The patients with low risk can be confident of good outcomes and long-term survival. The challenge is that even within low risk, there may be seven different groups and some of them benefit from certain treatments and others from other treatment and what we are trying to explore is ways of customizing treatment for each one of those seven different groups and, you know, there are possibilities of using antibodies to CD20 for instance and CD20 is only expressed in one of the groups and in certain patients we assume we are giving them anti-CD20 antibodies and they have responded. Some groups take longer to respond than others, so if you are not in the remission at three months, its important to know which group you belong to because one of the groups, it doesn't get a good remission, actually get back to remissions at three years and do well, long term do extremely well. So, you don't want to be over-treating patients and so the next decade is going to be all about understanding the biology of the tumor, its clinical behavior, and how to intervene in a personalized fashion.

Gary Petersen : Okay. Well, thank you very much. Sheri asks, can total therapy work for those with kidneys affected by MM and does it work well enough to recover kidney function or either to enable someone to receive a kidney transplant?

Dr. Gareth Morgan : So, the time to prevent a kidney damage is when you first see the patient, so its important to get in, start treatment and the sooner you reduce the paraprotein and the light chain value, it improves the chances of recovery of the kidney function. So, yes, we can improve kidney function. If its fixed, then you have it for a long time, I think that becomes difficult to improve.

Gary Petersen : Okay. But and or enough to enable someone to receive a transplant.

Dr. Gareth Morgan : I think you can take a count of the kidney function in the dose that you select at transplant and so if you have a good renal doctor as part of your unit and you discuss with them, its possible to adjust the dose and still to get good outcomes and to really improve the outcomes with people with renal disease. Its a Its a recurrent problem. It is something we have experience with.

Gary Petersen : Okay. Kate asks Following the Darwin ICH theory, if combination of drugs has led to more effective treatments of myelomas involving in variable cells, does it follow that maintenance therapy should also be combinations of drugs?

Dr. Gareth Morgan : Yeah, kind of We try to learn from infectious diseases and you know in treating bacterial infection. If people have chronic lung disease with recurrent infections, we don't put them on one antibiotic and expect it to work, rather you change between three different antibiotics, say. So, I think that's a good paradigm for what we are trying to do for myeloma patients when you have got them into complete remission. The idea is you keep the pressure on those cells so they are continually being threatened with that, until eventually until the last one and then the patient doesn't relapse and so we are not there yet totally with understanding that process, but these sensitive tests allow you to look at small numbers of cells. Its going to allow us to answer that question.

Gary Petersen : Okay. Eric asks What tests are most useful either at two years post transplant or at relapse?

Dr. Gareth Morgan : So, at two years post transplant, its important to look in the bone marrow looking for no detectable tumor cells and the flow cytometry and the PCR is the most sensitive way of doing that. You want to know that the patient doesn't have focal lesions in the bone marrow, that blood work is good and if all of those are negative, then things are looking great. Agree that you need to reassess the whole disease, re-image, MRI, diffusion weighted MRI, PET CT scans, gene expression array to check the biological

behavior of the disease and pretty soon its going to involve sequencing looking for mutations that can be targeted.

Gary Petersen : Okay. This is kind of an interesting one. How feasible is maintaining stable disease light chain only under 100 mg/L or low m spike and no crab symptoms with maintenance therapy? I guess just maintenance therapy in general, no transplant.

Dr. Gareth Morgan : Right. To say you are in a remission after your treatment and you have those conditions, the important thing is not to over treat people with those diseases or that disease

description can remain stable for years and years and years and I think maintenance can help control it at that level even if it totally doesn't eradicate, you know, the last cell. Then, you can consider patients of having achieved a (inaudible) like state, that is essentially benign and stable and what you are trying to do is prevent it transforming again to something more aggressive and so you don't want to like over treat the patients, give them symptoms, impair their quality of life just because they haven't got a complete response and that's a kind of important value judgment to be made.

Gary Petersen : Okay and Kate had another question. At this time, what are the most hopeful trials for high-risk patients?

Dr. Gareth Morgan : So, I think the targeted treatments and I think the introduction of antibodies in the background of chemotherapy is really the most hopeful. I think they are going to push the outcome and so I think these new antibodies may totally change our paradigm about who is good risk, who is bad risk and that's one of the questions that we wish to address because, you know, at one level you could argue that chemotherapy can make high-risk disease progress quicker and using the antibodies, if they are effective and they downgrade the behavior of the disease, I think that may be a very exciting way forward.

Gary Petersen : All right. Well, thank you so much. I had one last question and if you would be so kind I know in Europe you have the NHS, National Health Service, and it has some of the best data, the most robust data for myeloma and noted that one in five patients die in the first two months after diagnosis and that only 3% of the population in UK has ever heard of myeloma. How do we change this to get improved awareness and early diagnosis because we are no different than US. Almost everybody that I have ever talked to with myeloma said that when they learned about it is when they were told they had it.

Dr. Gareth Morgan : So, its a bigger scandal really. The average time for diagnosis is three to six months and more often than not, its six months and you hear these harrowing stories of people driving around in their cars with backaches, going over road bumps and being in agony and to make real inroads into myeloma, we need to get it diagnosed earlier and making family practitioners and the family doctors more aware of the condition and to do a kind of M spike and light chain value on patients makes a lot of sense to me. I think, you know, the other kind of tragedy is when somebody develops renal failure because they didn't develop that overnight and will have been present for months and months before and its just a case of sinking myeloma, do the M spike and the light chain values and refer early on for good treatments and expert advice. Its really important to get a myeloma expert on your side even if its only for a known initial consultation and the value long term improved.

Gary Petersen : Its one of the most misdiagnosed things and we had somebody here in Jacksonville who was being treated for psoriasis and then finally found out that he had myeloma but too late to save him.

Dr. Gareth Morgan : Yeah, I know. Its a tragedy and, you know, it being something that was there over a prolonged period of time as well because its a disease that doesn't come on overnight and its many years in the making.

Gary Petersen : Oh, I know that, you know, we have programs that try to do you know, to do just that, but obviously we haven't made much of an impact yet. So, you know, I have

Dr. Gareth Morgan : Patient organizations like this can make a difference. Its about all about patient empowerment and understanding the disease what they went through and making it obvious to healthcare professionals that this is something that needs to be thought about and another kind of really interesting kind of area that needs to be thought about is if you have MGUS what you do about that? Are there ways that we could investigate MGUS and give nontoxic treatment in a sort of chemoprevention fashion to prevent it turning into smoldering myeloma and then to myeloma and I think, you know, we are just touching on that now. We are treating, you know, high-risk smoldering myeloma, but the obvious place to go is to go earlier and we need to hopefully save treatments for that kind of study. I think that's where we will get to eventually, chemoprevention strategies, early diagnosis, regular screening for a paraprotein, and intervention years before there are any symptoms or signs. That's futuristic now, but its something we should aim for.

Gary Petersen : Oh, I thank you so much and I would love to see that. I think everybody would like to have enough time to do the research, become their own advocate, find a myeloma specialist to give themselves, you know like you said, 14 years at UAMS versus the four years as reported by, you know, the SEER data so that after 10 years' time, so you know, times 20,000 people a year, you know, that turns into a lot of life.

So, doctor, thank you so much. Priya, any other questions from our callers?

Priya Menon: We have a quick question from one of the callers. Person calling in from 813-997, please ask your question.

Caller : Ah, yes. I am one of Dr. Barlogie's precious ones. I am a 23-year survivor and but I have relapsed twice and so my question is that the last time I was treated with Velcade and unfortunately went into remission again, but my treatment extended of Velcade extended two years beyond the time I went into remission, that's until my bone lesion, so well, I was in Tampa and near Moffitt and I have friends that get treated with myeloma there and they, the doctors there kind of terminate therapy as soon as the person goes into remission. So, I am wondering about the length of treatment and what your thoughts are.

Dr. Gareth Morgan : I would say anything about the doctors at Moffitt who obviously However, my approach approach and I think an approach kind of justified by the evidence is if you stop treating with Velcade too early, people relapse and that makes (inaudible) and Velcade (inaudible) prolonged, gives better outcome and I think that's kind of (inaudible) around the world and there is plenty of evidence to support it and that's why I say that simple therapy approach of prolonged maintenance and exposure to drugs is becoming more generally accepted and it has, in fact, become the global standard.

Priya Menon : Thank you, doctor. Dr. Morgan, thank you so very much. It has been wonderful listening to you and thank you very much for your time. Gary, Pat, and Nick, thank you very much. Please join us again on 17th of December at 5 p.m. eastern time for our next myeloma broadcast where we will be discussing ASH 2014 myeloma updates with Dr. Parameswaran Hari. The link for today's broadcast will be shared with all the participants. Please visit curetalks.com to register for our shows. Until then, thank you.