Early Treatment of Myeloma with Dr. Irene Ghobrial

Stopping myeloma before it even gets started! Lot of work is being done in this preventative approach and Dr.

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Irene Ghobrial of Dana Farber Cancer Institute will be talking to us about the new strategies to help MGUS and smoldering patients.

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In contrast to the watch and wait approach practised by doctors for patients where disease progression is not easily discernable, this new approach to understand the patients condition and treat early may prove to be life saving.

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Full Transcript:

Priya Menon : Good evening, everyone. Hello and welcome to Cure Talk. I am Priya Menon, Scientific Media Editor at Cure Talk, joining you from India; and I welcome all of you this evening to a discussion on myeloma. This is Cure Talk's 79th episode. Please do visit us at curetalk.com and do send in your feedbacks in, priya@trialx.com. We are discussing early treatment of myeloma with Dr. Irene Ghobrial, Associate Professor of Medicine at Dana-Farber Cancer Institute at the Harvard Medical School in Boston, Massachusetts. Welcome to the show, Dr. Ghobrial. It's an honor to have you here.

Dr. Irene Ghobrial : – Thank you. Its really my honor to have everyone and to talk to everyone on this call.

Priya Menon : 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, Cynthia Chmielewski, and Matt Goldman. 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 our listeners that we will be addressing questions sent in towards the end of the show. If you have a question for our panel, you can press one on your keypad and we will bring you on air to ask your questions. Alternately, you can email me with your questions, priya@trialx.com. With that, its over to Gary. Gary, you are on air.

Gary Petersen : – Well, thank you very much and again, thank you for providing this excellent forum for all of the patients and caregivers to learn a little bit more about multiple myeloma and, you know, to give many of our best and brightest patients a chance to provide some education and leadership to this group of patients. Now, Dr. Ghobrial was on another program and Jenni Ahlstrom gave her quite an introduction and I

looked at that and I did a little plagiarism and, you know, because she did such a good job and I know that you didn't hear it all, doctor, but you are going to hear this time. Dr. Ghobrial is Associate Professor of Medicine at the Dana-Farber Cancer Institute at the Harvard Medical School in Boston, Massachusetts. She is a Physician Scientist who specializes in the field of multiple myeloma and Waldenstrom's macroglobulinemia, specifically in the precursor conditions of MGUS and smoldering myeloma. Dr. Ghobrial received her MD in 1995 from Cairo University School of Medicine in Egypt. She completed her internal medicine training at Wayne State University in Michigan, Hematology and oncology subspecialty training at a little place in Minnesota called Mayo Clinic and she is on many of Dana-Farber's and the American Society of Hematology committees. She reviews abstracts for the American Association of Cancer Research, which is the top and top publications such as Blood, Lancet, and the Journal of Clinical Oncology, just to name a few. She is on the editorial board of the American Journal of Blood Research. Dr. Ghobrial reviews grants from the National Institute of Health, the Leukemia and Lymphoma Society, and The Multiple Myeloma Research Foundation and has been awarded numerous awards including a Dana-Farber Clinical Investigator Award, the Robert Kyle Award for her work in Waldenstrom's, and many more awards. She particularly focuses on role of the malignant bone marrow niche in disease progression for early precursor conditions like MGUS, smoldering myeloma, to active myeloma. Dr. Ghobrial and her lab examines how myeloma uses a process of cell dissemination to determine biological changes that occurred during progression in myeloma. She seeks to understand that progression process from inactive to active state. In addition, her laboratory research data has been rapidly translated to innovative, investigator-initiated clinical trials. This lab is conducted over 10 phase one and two clinical trials. These studies on myeloma cell trafficking have been translated to the first chemosensitization trials in patients with myeloma. In addition, she is the co-leader of the First Consortium of Clinical Trials for Blood Cancers in collaboration with the Leukemia and Lymphoma Society to form the blood cancer research partnership, a consortium of 11 immunity oncology sites coordinated by Dana-Farber. She has initiated the Clinic for the Prevention and Progression of Blood Cancers, where patients with precursor condition such as MGUS, early MDS, and early CLL would be monitored before disease progression to see how the co- evolution happens during disease progression. She joined the MCRI or the Myeloma Crowd Research Initiative as a member of the scientific advisory board. It sounds like you have very little free time and if anything (laughter), you are a super scientist or…a super woman and that's for sure, so welcome to

Dr. Irene Ghobrial : Well, thank you for this amazing introduction.

Gary Petersen : It… Well, it wasn't real I cut some stuff out too..because, you know, and Jenni did quite a good job. I am sure you missed, so you were not able to hear a lot of it, but I make sure that I did that.

Dr. Irene Ghobrial : Oh, well, thank you. I really appreciate it.

Gary Petersen : Well, doctor, I met you at ASH and I saw your presentation and I was in a room with a lot of people and I got to say that I was truly impressed and that's why I wanted to add you on this program and if you could, could you please present our audience with your thoughts on early treatment of myeloma and why this is so important for the future of myeloma treatment and do it in a way that is a little patient friendly because I can tell you that you are so intelligent and so skilled in your field that my brain almost exploded listening to you.

Dr. Irene Ghobrial : Well, I am happy to do that. So, the whole question came along when we see patients with precursor conditions, which is MGUS and smoldering myeloma, and we all usually tell them, "Oh, don't worry, you don't have symptoms yet. We should do watch and wait. And when you have symptoms, when you have lesions in your bones, when you have anemia, when your kidneys are failing, then we will start treatment." But if you think about what we just said right now, it doesn't make sense to anyone and actually a lot of our patients would say, "Well, why are you waiting? What are you waiting for?" and many of my patients will say, "Is this watch and worry and not watch and wait?" (laughter) and if you think about the whole…, yeah, actually… If you think about what we do in other cancers, for example, take breast cancer. You see a patient with an early breast cancer lesion, a small lesion that has not done nothing more, we call it DCIS or ductal carcinoma in situ. The patient will have a mammogram. We will see that tiny lesion, and we

immediately remove the lesion and say, “Absolutely, let’s remove it.” We never say, “Oh, you are having no symptoms. Let’s watch and wait until you have lesions in your bones, until you have metastasis everywhere, and then I will treat you.” That’s what makes no sense at all for anyone, yet we do it every single day for our patients with myeloma. In fact, some people, you know, are so happy to say, “Oh, I am doing the observation, I am doing the watch and wait and that leads to problems at the end.

Dr. Irene Ghobrial : If you ask me a question, maybe why we are not curing myeloma is because we are not treating it at the right time. Maybe we are waiting too long and its too late for us to treat our patients and maybe we need to rethink the way we were all taught and we all, you know, follow it, of the watch and wait, but the question would be, well, so many people are diagnosed with MGUS, the chances of MGUS is 1% over the age of 50. It increases significantly more as we get older. You don’t want to treat all those patients because many of them will never develop myeloma. So, we need to understand better who will develop myeloma and who will not and define the patient who would progress in the next two years, in the next three or four years and you are young and healthy, why wait for them and actually why don’t we treat them early. Potentially we may cure them because they are still in very early disease and all of the changes have not happened yet, so we can actually get all those bad cells early on and maybe if we actually screen patients correctly in the future and I am thinking 5 to 10 years from now, can we define everyone and can we prevent myeloma? Think of it as a preventable disease, just like measles. We took care of it because of vaccines, although not anymore in California, but….

Dr. Irene Ghobrial : (inaudible)

Gary Petersen : …and that would be wonderful.

Dr. Irene Ghobrial : Right. The whole idea of… (inaudible)… myeloma was that prevention of progression is (1), can we screen patients and identify if it has progressed or not and do it in molecular ways, doing sequencing studies, doing actual molecular new next generation technology and (2), can we define smoldering myeloma patients who can actually benefit from treatment, so we developed clinical trials for high-risk smoldering patients with clinical agents that are well tolerated, that are known to work very well in myeloma and we are testing them right now in patients with smoldering disease to see if we can actually achieve a good remission in them. So, maybe I’ll stop here and see if you have questions for me.

Gary Petersen : Okay. Well, at ASH, I was looking at the…, your presentation on making the microenvironment inhospitable for tumor growth and what you are saying is, you know, getting it and finding it in its early stage, but then in that particular incident, it sounded like you are attempting to, I’ll say, salt the ground of, you know, of tumor soil and preventing it from blooming and this sounds like a possibility for cure. Could you please explain this in a way that this audience will understand? Can this be used for early and late-stage disease or for high and low-risk disease?

Dr. Irene Ghobrial : Yeah. So, if you look at the mutations that we have in myeloma, if you do any of the cancer cells and pull them out, we know that there are specific mutations in those patients or cytogenetic abnormalities, which we all know, and if we look carefully at patients with MGUS, we find that many of those mutations are already there, which means the seeds, the bad cancer cells, may already have acquired the bad mutations. Yet, some of them will never progress to myeloma. They are sort of stuck in there and they will never grow and proliferate, while other patients, those same mutations and same cells will go on and develop myeloma very fast. So, we are asking a question, well, maybe the soil around the seeds is the one that allows you to have progression to myeloma and in some patients it is nonpermissive, it does not allow progression. So, we are asking the questions of are we born with certain susceptibility genes or do we change something in our own bone marrow that makes us more susceptible to develop myeloma if we have this tiny mutation in some of the cancer cells, while in some others, maybe your immune system will protect you and will not allow MGUS to progress to myeloma and if we can use that to our advantage, we can develop drugs not only to kill the cancer cells but also to protect you. There are so many new drugs now for the immune system, they are called the checkpoint inhibitors. One of them just got approved for lung cancer and these are drugs that allow your immune system to go and target cancer cells. So, in this case, we can

think that, in MGUS if you have a good immune system and you will never progress, that's good. If you have a bad immune system and that will allow progression, we can give you a drug that enhances the immune system and prevents this progression.

Gary Petersen : Do you combine the drugs then as well?

Dr. Irene Ghobrial : You could. You could. It depends if we can personalize therapy, we could potentially even use drugs alone in early stages. One antibody may be enough to enhance the immune system or we may need a couple of things, one to kill the cancer cells and another one to enhance the immune system. So, it depends on the stage and it depends on the person and hopefully you will have personalized therapy where we actually profile patients, understand what's going on, and then give them the specific treatment.

Gary Petersen : Okay. One thing that people have asked me, you know, and actually Dr. Roy at Mayo Clinic here in Jacksonville once said to me, I was talking about one of the drugs that had been used in the mouse model and now you have done this on mouse models with that microenvironment, you know, being inhospitable for tumor growth and I think that, you know, these mice were actually cured but is the, you know, is the mouse model… What he had told me anyway is that if people were mice, they would all be cured, you know, (laughter) and his point being is that we are a tad bit… What works in mice didn't necessarily work in people, so as a result, you know…, but I understand that they are doing work on these mice models or mouse models that better reflect what will happen in the human being and as a result…you have more repeatability. Is that true?

Dr. Irene Ghobrial : Yeah. So, it depends on what you are using the mouse models to ask. So, you are right. The human body is very complicated and much more complicated than a mouse model and that's why we cannot predict what will happen in patients. We need to do the clinical trials with patients; however, you can ask specific questions in mouse models and you can define how something would work in mouse models before you take it to patients so that you have a good understanding of the mechanism of action of the potential problems that can happen before you take it into clinical trial.

Gary Petersen : Okay. Well, thank you very much. The American Cancer Society provides data on survival by stage of the disease, stage I at 62 months, stage II at 44 months, stage III at 29 months and these are older numbers I think and we are doing better than that, but does this prove that early treatment is more effective or more an example of late diagnosis or a combination of the both?

Dr. Irene Ghobrial : You mean like early treatments will give us like a leave bias of that we just change the numbers by treating early?

Gary Petersen : Yeah. Stage I… Right now, stage I, I assume its a little…, its an earlier diagnosis or maybe its not, you know, its just, you know, what they say is stage I, you have 62 months to live, at stage II its 44 months, stage III… This could be the proof that, you know, if you get it early, like in a stage I phase or DCIS if it were breast cancer, that, you know, you know, early treatment means longer life or does it mean that this is just example of, you know, lot of people get diagnosed late and at that point you are at stage III and its really a late diagnosis that, that this information is providing.

Dr. Irene Ghobrial : No, I think…Yeah. The International Staging System was used for patients who already have active symptomatic disease. So, when it was developed and I was at Mayo Clinic at that time when Dr. Phil Greipp developed the International Staging System which is what you are talking about, stage I, II, and III… it was for patients who already have symptoms, who already have what we call the CRAB criteria, the high calcium, the anemia, the lesions in the bone and we asked the question, well, within a group of patients who already have myeloma, which ones will have really aggressive myeloma and that's why it doesn't respond well to treatment and that's why they have a worse survival versus patients who have a very slow-growing myeloma that looks a little bit like MGUS and smoldering, very slow growing and it responds well to treatment and…within those groups of patients is the biology of myeloma. Its the type of genes that change.

Its the type of… Lots of things have changed within myeloma that can help you differentiate someone who will have worse prognosis or not. That's already after you have symptoms of myeloma, but the same applies for early MGUS and early smoldering disease. We have some classification that tells us this one will have a high risk of progression, so we call them high-risk smoldering disease or intermediate risk or low risk.

Gary Petersen : Okay. So, basically, what you are… What you are doing is well before any one of these stages, that your philosophy is to nip it in the bud before it ever gets to stage I or stage III.

Dr. Irene Ghobrial : Yes, correct, and actually there was a study that showed a huge difference in survival of patients. So, this was done by the Spanish group last year and it was presented in the New England Journal of Medicine and what they did is they took patients who have smoldering myeloma, which is before you get into stage I and II and III, and they ask the questions, should we treat them with the pill drug Revlimid or lenalidomide and dexamethasone or should we do nothing, the watch and wait, and they found a big difference in the progression-free survival and overall survival of patients who were treated. That's the first trial that shows us that if we treat early, we can make a big difference in survival.

Gary Petersen : Fantastic! When I saw… When… Dr. Morgan was on this program not too long ago and he felt the future of myeloma will be early diagnosis, safe treatments, chemoprevention strategies, regular screening for paraprotein, and early intervention, what do you see the future of myeloma care?

Dr. Irene Ghobrial : Yeah, absolutely. I agree with him. I think… The one thing that I would love to see really is can we prevent myeloma by detecting it correctly and treating it early for the right patient and again, you can think of it that the best time to treat a cancer is at the early times, before it has changed so much, before your immune system has changed, before all of the effects have occurred. If you can detect it at an earlier precursor condition or pre-cancer condition, you can prevent the disease and it would be beautiful that 10 to 20 years from now we say there is no more myeloma because we are detecting it early and we are preventing it or curing it early and that, I think, could make a huge difference for all of us.

Gary Petersen : And that's one of the reasons I found your presentation and this whole philosophy of treating it early and kind of salting the soil as being a, you know, a cure for the disease. So, yeah, fantastic!

Dr. Irene Ghobrial : We're hoping so. So, we haven't proven it yet and that's why we do need everyone to be part of it. I think the most interesting thing in patients with myeloma and smoldering and MGUS is they are very active participants. They want to be part of the effort and they want to help do it and that's the fun part, that we can all work together to understand what causes progression and how to prevent this.

Gary Petersen : One of the…., finding it early leads to a question and that question is to treat early you have to have a way to find it early…and right now, I understand that with 25% of the patients with the time from first symptoms to diagnosis of close to an year, you know, how do we… How do we get better at getting early diagnosis, you know, finding this out so that we can treat it early?

Dr. Irene Ghobrial : Yeah, great question! So, right now, we do not screen patients for the monoclonal protein, for the M spike, yet we know that every single patient who is diagnosed with myeloma today must have had an earlier stage of MGUS or smoldering for multiple years without ever being diagnosed. So, you're right. If we want to really prevent the disease, we have to start a screening study and you can think the screening studies for cancer, so mammograms for breast cancer, prostate the PSA levels, colonoscopy for colon cancer, we do a lot of screening studies to prevent 1 in a 1,000 or 1 even in 10,000 cases of cancer to happen. Yet we have probably one of the best tools, a blood test, to screen for patients with MGUS and potentially diagnose them early and we do not do that routinely. So, for us to implement a screening study for MGUS, we need to prove that indeed it will save lives if you detect it early and that's a big, huge study that we are thinking of, how to develop it, how to screen patients, what's the message we give to the patients if they are diagnosed with MGUS? So, there is a lot of work that we are thinking of to indeed ask the questions before we develop screening study for patients with myeloma.

Gary Petersen : Well, that sounds very, very exciting and that's one of the key reasons I wanted to have an opportunity for this panel to ask you some questions. So, what I would like to do now is to go on to the panel. Is Cindy online?

Cindy Chmielewski : – I am. Can you hear me?

Gary Petersen : Yeah. Cindy, your question?

Cindy Chmielewski : Hey! Thanks, doctor, for everything you're doing. Its very exciting, some out-of-the-box thinking and one thing just about the screening study, first of all, I guess to be able to do that study, you need to do some of the precursor things showing that MGUS if we treat it earlier or if we know how to identify those patients, we could start curing myeloma to justify that type of screening study, is that what you were saying?

Dr. Irene Ghobrial : Correct, yes. So, before we start the screening study, you are right, we need to show if we treat early, it will make a big difference. Can you indeed cure some patients in the smoldering condition? Can you identify which patients will actually progress or not so that you are not just screening a lot of patients and scaring a lot of patients without having the next step already. So, you're right. We are not saying we will start it today, but if all the steps we are thinking about for the next five years, 10 years, what are the steps we need to do to make this a preventable disease?

Cindy Chmielewski : Okay, great! And is this where this Blood Cancer Prevention of Progression Clinic? Is this where this comes in? Could you talk a little bit about your clinic and what's the focus of your clinic and how people could get involved in this clinical study?

Dr. Irene Ghobrial : Absolutely. So, the Prevention of Progression Clinic started with the whole initiative of us saying, we would love to see patients with MGUS, with smoldering disease, with asymptomatic disease. If you want to come to Dana-Farber, part of it is just a small one-page consent form that patients sign and whenever they are getting any blood samples, routine blood sample, or a bone marrow biopsy for any clinical study, we will ask them to participate in this so that we can understand what are the changes that happened in their bone marrow or in their blood that predict progression because right now what we are using to say MGUS will progress to myeloma, we are using just very clinical tumor burden markers that really do not predict for us well what will happen to a patient. So, the first step is understanding genomics and understanding the tumor cells and the microenvironment, what happens and why would someone progress while others do not and hopefully with that I can take a blood sample from a patient, then I tell him based on your profile, you will have a chance of progression of 2 years, 5 years, 1 year, 10 years, or you will never progress, but doing good molecular markers and not just tumor burden markers. So, that's the first step. The second step that we said we will do is the trial for clinic as we don't want patients to only come to Dana-Farber because that limits everyone from being part of it. So, we will be launching soon a crowd trial where we actually put in online to anyone who wants to participate first in the US and then hopefully we will go outside the US, where anyone who has the diagnosis of MGUS or smoldering disease go ahead and sign on on this online site, we will then get all the information, the clinical information, from your doctor and be able to get it all into one big database that people can access and then we will ask for a blood or a bone marrow sample if you have it and we will start doing profiling for patients and hopefully in the future even give them back their information. So, a lot of people are doing that now for like sites like 23 And Me or Foundation Medicine, where they are actually giving you the profile of mutations you have and you can be part of that whole initiative. We are hoping to do that also for patients where we can actually profile their information and detect mutations and give back the patient's information to them and to their doctors and say, we don't know yet if a p53 mutation will be bad or good or a KRAF mutation will be bad or good, but as we get more and more people, as we get large data set and information, we will be able to predict more accurately. Someone will be able to progress and someone will not progress. Once we have that information and we have treatment options for patients, then we can go back and do screening studies in the future to say, "I will be able to screen that much of the population and be able to detect MGUS and follow them and potentially cure them."

Cindy Chmielewski : Well, that sounds exciting. Now that cloud study, when that opened, how can we as patient advocates promote that and would it be like on my portal that people can register for free? Would it be something that your local oncologist would have to put you into or I believe just has not worked out yet?

Dr. Irene Ghobrial : No, absolutely. So, we think that patients are their best advocates for themselves. So, we will be posting it online, its free, anyone can access it. All they have to do is read the consent form, say yes, they agree, put some basic information so that we are capable of contacting them back and also giving us the approval to call their doctors and get the clinical information of their M spike, their protein, when were they diagnosed, and all of that and then we will ask for a blood sample or a bone marrow sample if they already had one or they will be planning to have one in the future. So, that will be the steps that we will have on this and we are hoping to launch it very soon and I'll send everyone the information and the more you tell people, the better we will be, you know, more successful, of course.

Cindy Chmielewski : And these are for people diagnosed with MGUS and smoldering myeloma? Is this the group of people that you are looking at?

Dr. Irene Ghobrial : Correct. Yes. So, for anyone who does not have symptoms yet, this will be designed for that.

Cindy Chmielewski : Wow! That sounds great! Now, the other thing I am hearing, there is all this talk now about smoldering myeloma and treating early and possibly once you identify which group is more likely to progress and thus we may be having a cure because of that. What information or what would you tell someone who came to your clinic, who was newly diagnosed with MGUS or smoldering myeloma, what should they be doing? I mean, especially, a lot of people who have MGUS or smoldering myeloma may be seeing their local oncologist who may not be up to date with all the new advances. So, what piece of information would you give someone who is newly diagnosed with MGUS or smoldering myeloma?

Dr. Irene Ghobrial : So, MGUS and smoldering are slightly different because the risk of progression for MGUS in general if we put everyone together is 1% per year, which is a very low risk. So, we still observe them carefully. Hopefully, we do the mutation status and genomic status to understand better, but we do not offer treatment yet, although we are thinking about, you know, gentle things and things that, you know, can we use aspirin or metformin to prevent further progression. So, these are a class of agents that are very easy and simple. When we go to smoldering myeloma and these are patients who have a little bit more disease, 10% in their bone marrow of plasma cells, the M spike is slightly higher, their light genes are higher, or they have bad cytogenetics, then we already know that the risk of progression is much higher, 10% per year. In fact, some of the patients have something called high-risk smoldering myeloma, which is 50% chance of progression over two years. That's a very high chance of developing myeloma within a very short period. These are the patients that we're telling them, "Come and consider clinical trial options, either with us or with other people." One of the trials that we just opened is something called elotuzumab plus lenalidomide, so this is a new antibody that has been tested in myeloma, and lenalidomide or Revlimid is a drug approved for myeloma and that combination gives us 90% response rate in patients who already have myeloma or relapsed myeloma. So, we are thinking probably that will give us even a higher chance of response when we use it in an earlier smoldering disease. And that's just one trial. There are multiple trials in multiple phases to consider for smoldering disease and I think the only way to know whether we can cure patients, whether we can achieve a deep response and prevent progression, is patients participating on some of those trials and seeing if they do really well, then everyone would suddenly change the way we think of treatment and start treating early because that will make a huge difference in survival.

Gary Petersen : Thank you, Cindy.

Cindy Chmielewski : So, basically if you were doing MGUS or smoldering myeloma, you probably should go see a myeloma specialist to talk about some of the next steps, not just staying locally with your oncologist, just to get a better understanding of what's available to you.

Dr. Irene Ghobrial : Yes, I mean even if you stay with your local oncologist, get in contact with one of us and I am happy to have email contacts. We are trying to make the website more informative for everyone so that people know and are informed. Its okay to see your local oncologist. In fact, we are trying to open some of those trials with the local oncologists because we know its very hard for people to travel, but what's important is to be well informed and to know your own options and to know what are the limitations of just being in the local place versus going somewhere else.

Cindy Chmielewski : Thank you so much.

Gary Petersen : Yes, thank you, Cindy. Pat, you online?

Pat Killingsworth : – I am here, Gary.

Gary Petersen : All right. Pat, your question.

Pat Killingsworth : Hi, doctor! If you remember, we met… I was at CrowdCare Foundation dinner with Gary, sitting across the table and…

Dr. Irene Ghobrial : Yes, of course, I do remember you very well.

Pat Killingsworth : I thought that was…, it was ironic because earlier in the day I had been with Gary and we attended the session that you referenced before and he was quite taken with you and if I didn't know…if I didn't know his delightful wife and know that he was happily married, I would say he had a thing for you. He just… He just sat there mesmerized, watching your presentation and it was like, my eyes were glazing over, you know, but he was just fascinated with what you had to say and I have to tell our listeners, Gary, sometimes he overdoes these introductions a little bit, but, doctor, you are very, very bright, very impressive. I love your enthusiasm. Its inspiring.

Dr. Irene Ghobrial : Oh, thank you. I really appreciate this.

Pat Killingsworth : So, if I could change gears just a little bit, this is out of left field because we have been talking about early, early diagnosis and treatment, but can you provide any insight into why a small percentage of myeloma patients end up with extramedullary, these outside-the-bone marrow tumors. I know some patients even get them early on, but a lot of late-stage patients develop them and I hear from readers all the time asking, you know, "My doctor doesn't know what to do, my doctor doesn't know what to do," because the course of Revlimid and Velcade and a lot of the similar drugs are meant to attack things in the bone marrow, correct? Do you have… Do you have any thoughts or insight into that?

Dr. Irene Ghobrial : Yeah. Great question! So, we call that extramedullary disease and the question, and we are trying to study that both in the lab and in the clinic. So, in the clinic, we have two papers that will come out very soon, looking at our experience at Dana-Farber with patients who develop the extramedullary disease, were they treated with certain drugs or not, what were their presentation, what happened, how did we treat them and so on. So, that gives oncologists all over the world an option of what are the treatment options that we have used. Then, we also looked in the lab, well, why would some cancer cells, the myeloma cells, that love to go to the bone marrow suddenly decide that they don't like the bone marrow that much anymore and they now want to go to the skin or the liver or other places, which is that extramedullary disease. And there are two options for that – either the cancer cells are so smart now that they develop new mutations and that allows them not to stick anymore to the bone marrow or it could be that the environment around them has changed enough and now they are starting to get out of the bone marrow and we did some mouse modeling and that paper is not out yet, but we have actually identified certain genes that will allow cancer cells to be able of going out of the bone marrow and sticking to other places and hopefully as we understand this better biologically, we can then develop drugs specifically for that. So, there is a lot of work ongoing on this. You are right, we don't have good treatment options for extramedullary disease, but the hope is that as we understand this better, then we can target it better.

Pat Killingsworth : Sure. So, if I am a patient and I am going through that right now, what do you do?

Dr. Irene Ghobrial : Yeah, multiple options. It depends on what they have received before, but usually we try to use combination of therapy, multiple drugs put together to really attack it better. We still use proteasome inhibitor…

Pat Killingsworth : Sure. Do you use cytoxic agents, maybe something that… Aren't they better, you know, more general chemotherapy-type drugs that aren't restricted to the bone marrow?

Dr. Irene Ghobrial : Not necessarily. We could use cytotoxic chemotherapy, like you said, but with something, with a proteasome inhibitor or with also other agents and when we put them together, can we kill enough of the cancer cells and prevent the progression? Having said that, I don't think we are doing a good job yet in developing treatments for extramedullary disease. Maybe the new antibodies that are coming out, the CD38 antibodies are obviously will be better in this, but we don't know yet.

Pat Killingsworth : Yeah, that makes a lot of sense. Its just that the spare that you read in these people's emails, you know, because their doctor is basically throwing up their hands and saying, you know, I don't know what to do and the best…I can tell them is head to a…, head to a major, you know, a place that treats and sees a lot of myeloma patients like Dana-Farber.

Dr. Irene Ghobrial : Yeah, absolutely. So, these are cases, yet absolutely go to a major center of myeloma. It doesn't have to be Dana-Farber alone. Any other center where they have a lot of options as well as new clinical trial options because this is where we can hopefully have some of those new drugs that we are developing right now.

Pat Killingsworth : Wonderful! Thank you, doctor.

Dr. Irene Ghobrial : Sure.

Pat Killingsworth : Gary, I am set. (Pause) Did we lose him? Matt, are you there?

Matt Goldman : I am here. Pat, I think you must… Pat, you must have embarrassed Gary, so he had to get off the line or something.

Pat Killingsworth : (Laughter) … He is explaining to Anita.

(Laughter)

Matt Goldman : Yeah, you got him in trouble. Yeah. Thanks for your time, doctor. I am just trying to wrap my head around the concept of curing and preventable… So, when you treat or when you talk about treatment for patients with smoldering myeloma, is it treatment that is for a fixed period of time or is it kind of like folks that have, you know, partial response or complete response, where they are still doing maintenance? Is smoldering the kind of thing where you would be treating it indefinitely?

Dr. Irene Ghobrial : Great question! So, when we were starting to design the clinical trials, we asked exactly this question. Well, if I start doing induction therapy that we do for myeloma, followed by maintenance, then all we have done for the patient is just drop everything earlier and is that really the best choice for the patient and what we have designed our trials right now is that they are a fixed period of time, that we do maybe a little bit more intensive early on to really kill as many cancer cells as possible, followed by a little bit less, but we do not do maintenance for ever. We are doing… In our trial right now, the treatment overall including maintenance is two years and the reason for that is let's achieve a good remission, follow it by some maintenance and then stop and hopefully if you really stop and you have achieved a good remission, maybe that's where you can actually see the difference. If someone is cured, then hopefully the myeloma will never come back. If someone had a good remission for years and years, then at least you prevent the progression

and you can always come back later on if progression happened to consider treatment, but we do not want to keep patient on treatment continuously, at least at that stage.

Matt Goldman : Right. So, it seems like for somebody that's not symptomatic, explaining to them that you are going to be on treatment for a while, I would imagine that there's a challenge with that, I think. Getting patients to be okay with that.

Dr. Irene Ghobrial : Exactly and regarding the other…

Matt Goldman : I am sorry. Go ahead.

Dr. Irene Ghobrial : No, I was just going to say the other options we are trying to think of is something like vaccine therapy. So, we do have a trial right now of only three months of Revlimid plus a vaccine and trying to see with the vaccine can you make the immune system attack the myeloma cells much faster. So, these are very short duration of treatment with hopefully a big effect.

Matt Goldman : So, the vaccine would be… The goal of vaccine is to help the patient's immune system as opposed to…. No, we don't really know what causes myeloma, so you are not necessarily giving someone a vaccine to kill whatever brings about the myeloma, but you are just boosting the patient's immune system. Is that correct?

Dr. Irene Ghobrial : Correct. If the immune system can attack the cancer cells, that's all you need.

Matt Goldman : Okay and in terms of causes and things, are you noticing that there are any changes in the demographics of new patients? Are they getting any younger? Are you seeing any changes over the last few years?

Dr. Irene Ghobrial : No and I think Dr. Kyle, Bob Kyle, who I trained with at Mayo Clinic and I adore him. He is 80 something years old. He is the grandfather of myeloma. He is the one who described MGUS as smoldering. One of the best people you can think of in the world and he had looked recently at whether the incidence of MGUS or smoldering has changed or whether the incidence of myeloma has changed at all and if I remember correctly, the publication showed no difference and no increase in the incidence of myeloma.

Matt Goldman : Uhmm… Okay and is there time for one more just quick question here? In terms of immune system and having a strong immune system, do you recommend that patients with MGUS or smoldering make changes to nutrition or to some of the things, lifestyle changes, that might help boost their immune system?

Dr. Irene Ghobrial : Great question and we don't know. So, we don't know what goes wrong in our immune system to allow progression. We are still studying that in the lab, so we don't know what to tell patients to take or not to take. We are actually studying right now if obesity or if we change the glucose level of the patients' insulin resistance, so if they have diabetes or if they are taking metformin, which is a diabetic drug that actually has been shown recently to have anti-cancer properties, can we prevent progression and these are the things that we are trying to see if drugs as easy as metformin or as easy as aspirin can potentially change things. So, these are the few things that we can say as potential changes early in MGUS, but I don't know the answer yet and I would not recommend anything until we have proof of it or until we have a clinical trial to ask the question.

Matt Goldman : Umm… Okay. That's all I have. Thanks. Thank you very much.

Dr. Irene Ghobrial : Thank you.

Priya Menon : Gary…Gary is online actually. Listeners…

Gary Petersen : Yes. Hello.

Priya Menon : …please press… Yes, Gary, we can hear you.

Gary Petersen : Yes. Priya, can you hear me?

Priya Menon : Yes, we can hear you, Gary.

Gary Petersen : Okay. So, I might have been muted. We have a number of questions from our callers that we can go to, but first I would like Priya, if she would see if there are any callers on line and ask questions of your doctor.

Priya Menon : We have actually a large audience listening to the panel right now. Listeners, if you have a question for our panel and you would like to ask it live here, please press 1 on your keypad and we can bring you on air to ask your question. Please let us know by pressing 1 on your keypad. Gary, we can actually move on to other questions that has been sent in to us. Yeah.

Gary Petersen : Okay. Frank sent in some questions. He said at ASH, you were part of an after act focusing on RVd light. Since patients like anything light, can you say more about this regimen and is there also a maintenance light? Are the treatment results for this regimen being used on high-risk MM patients? So, that's really almost a three-part question.

Dr. Irene Ghobrial : Yeah. So, the RVd light regimen is basically the combination of RVd, lenalidomide and Velcade and dexamethasone, that we use as the standard of care for myeloma patients and for older patients over the age of 70 or for non-transplant candidates or for someone who cannot tolerate the twice-a-week regimen we had, well, can we cut down the dose of Revlimid, cut down the dose of Velcade but still give that three-drug combination for older patients and the reason for that is older patients who are not being treated aggressive enough because everyone was saying, well, they are 80 or 85 years old or, you know, they are not going to do very well with the aggressive treatment. So, we said, well, we don't have to give very high doses and aggressive treatment, but we can still give good treatment options and this is where we came up with this RVd light option. The trial is accruing very well. We are almost done with it and it basically gives under-the-skin Velcade once a week, Revlimid at a lower dose, and dexamethasone at a lower dose and that option works very well for patients who are frail, older, who cannot tolerate the regular treatment. I would not give that option for very aggressive or high-risk myeloma because we are cutting down the dose of treatment, which means we may not be taking care of all the bad myeloma cells. So, I would be very careful when we choose options. We are choosing them for right patients and of course, the age and everything comes into account, but we are also careful that we don't under treat because that's not good either, because you'll develop resistance to therapy and then you develop really bad myeloma afterwards.

Gary Petersen : Well, thank you. Also, he asked, what test results seem to be the best indicated to determine the risk to progression, like M spike, free light chain, plasma cell percent, etc.?

Dr. Irene Ghobrial : Yeah. So, we look at several things to see if patients have poor risk features for myeloma and probably the best ones are the cytogenetics and the FISH which are the chromosomes and the mutations or the translocations that we see in the myeloma cells. We also look at the International Staging System which we just talked about earlier, the ISS Stage System and that's stage I, II, and III based on something called albumin and beta-2 microglobulin. The light chains and all the other markers usually do not predict too much the prognosis of the patients. They tell us how much tumor cells are secreting protein and how much tumor burden in general you have, but a higher light chain may not be a worse prognosis than a lower light chain.

Gary Petersen : Okay. Thank you. Is watchful waiting approach still standard protocol for smoldering myeloma or myeloma with no CRAB symptoms? What if there are no CRAB symptoms but a severely compromised immune system?

Dr. Irene Ghobrial : Yeah. So, just observation or watch and wait is still the standard of care, although that in most of us is starting to change with all the clinical trials that we are developing now for high-risk smoldering disease. For the low-risk smoldering, we still do the watch and wait or observation. Now, its a great question. What if I don't have the CRAB criteria, but I have other things? So, we are starting to redefine also smoldering disease and we are redefining what is considered symptomatic myeloma that we will treat and there was a recent publication that came out from the myeloma working group, basically all of us saying certain patients will need to be treated as active or as real myeloma even if they don't have the CRAB criteria, especially if their light chain is over 100 as a ratio, if they have lesions inside their bone by the MRI or by a PET CT scan or, you know, if they have other things that indicate that indeed they will develop myeloma very fast. So these are new changes that we have added into the CRAB criteria for myeloma. Now, if you have a really bad immune system, this is still something questionable and it will probably make the patient into the high-risk smoldering criteria by the Spanish group. So, its complicated and it needs someone who really knows what's going on with smoldering criteria and hopefully we will make them much easier to understand instead of having so many of those criteria and that's why you should go to a myeloma doctor who hopefully can look at the whole picture and decide with you.

Gary Petersen : Okay. Well, thank you. Could you elaborate on the mechanism that some of the most promising new strategies are based on? like new treatments? Treatments, uhmm….I guess, you know, like… What is it… CD38 and I think that's what…What are the mechanisms?

Dr. Irene Ghobrial : There are multiple new drugs and each of them, of course, have different mechanisms. If we are talking about the antibodies, the new antibodies, so there are two major antibody classes that are coming out. One of them is called elotuzumab, that's the one I talked about for the smoldering trial and that goes and attacks the myeloma cells because all of them carry the same antigen, something called SLAMF7 or CS1. They also can enhance your immune system by making the NK cells, which are the immune cells, go look for the myeloma cells and kill them. So, that's how it works. The nice thing about antibodies is you can think of in lymphoma, we use Rituxan all the time and that's the standard drug that has made a huge difference in the treatment of lymphoma and that's because all of the lymphoma cells carry an antigen called CD20 and Rituxan is an anti-CD20 antibody. We did not have that option in myeloma for many years. We were actually very envious of the lymphoma doctors because they have a great drug, a great antibody and we didn't. So, finally, we are getting two types of antibodies, the SLAMF71 that I told you, elotuzumab, and there is another one called anti-CD38, so again an antigen that is present on all of our myeloma cancer cells and that's one. There are two different types of them, one is called SAAR and one is called daratumumab and both of them are in each clinical trial options and hopefully we will have them FDA approved soon. So, those new antibodies are not available yet in the clinic, but they are available in clinical trials right now and they are giving us very good responses, either alone or with Revlimid or with Velcade or with other proteasome inhibitors and immunomodulators.

Gary Petersen : Okay. What is the criteria which classifies as MGUS or smoldering patients as being at high risk for progression to multiple myeloma or how do you identify which patient is more likely to transform from MGUS to full-blown myeloma?

Dr. Irene Ghobrial : So, we have certain criteria. The major ones were developed by the Mayo Clinic or by the Spanish group. For smoldering myeloma, for example, what used to be called smoldering myeloma, you have to have 10% plasma cells in the bone marrow or an M spike more than 3 grams or a light chain ratio that's abnormal and then when we start looking at what will make the patient high risk to develop myeloma very fast, the Mayo Clinic criteria said, "Well, if you have all three of those, then you're really high risk. You will develop myeloma in the next two years." So, if you have an M spike of 3 grams and 10% plasma cells and light chain ratio abnormal, you have a really high chance of developing myeloma in the next two years. The Spanish criteria was slightly different. They looked at, you know, other immunoglobulins. So, if you have an IgG type and your IgG is high, if your IgA and your IgM are low, then that's not a good sign and if your plasma cells in your bone marrow are all bad cancer cells, 95% of them, then also that's not good. Now, the problem is that these are very complicated criteria, so we are trying to change that to make it easier for us to diagnose high-risk smoldering and there will be new publications coming out saying if you have IgA

smoldering, that's bad; if you have bad cytogenetics like 17p deletion or 1q amplification, that's also bad; and so on. So, we are adding other things and trying to make sure that we unify it so that the Spanish are not doing one thing and in the US we are doing a different thing.

Gary Petersen : Okay. Well, that would be a good thing that there is some commonality. What are the signs and symptoms that an MGUS patient should show for the doctor to decide to start treatment, at least target MGUS? I know earlier it was organ damage, but that would have indicated full-blown myeloma which was used as the benchmark to initiate treatment, but it is not considered an effective one. Have there been any changes to that benchmark, but we are talking about MGUS,I am confusing it a little bit.

Dr. Irene Ghobrial : Well, MGUS by definition should not have any organ damage, should not have the CRAB criteria and should not have symptoms. So, that's why we are not treating them. If someone has a small protein in their blood, but they have symptoms, then they don't have MGUS only, they must have myeloma. However, if you have a tiny protein and someone diagnosed you with MGUS, but you do feel, "Oh, I am bleeding easily or I do have problems. I have symptoms," then they could check you for something called amyloidosis or in some cases we have patients with MGUS, but they also have numbness and tingling and neuropathy. These are rare cases where we still have MGUS, yet they have some other symptoms and that's important to differentiate from real, active, or symptomatic myeloma.

Gary Petersen : Thank you and what are the…, you best answered to this to a degree but maybe there are a few more… What are some of the more promising clinical trials that the MGUS patients can or should take part in?

Dr. Irene Ghobrial : So, again, we don't have therapeutic trial for MGUS yet, but we do have one of the trials that I talked about, the precursor clinic that we have, which is just giving samples and understanding genomic questions of evolution; however, for smoldering, we have a lot of clinical trials available. We have the vaccine trial, we have the elotuzumab and lenalidomide trials. Multiple other centers have many other trials, so there are lots of options for patients with smoldering disease.

Gary Petersen : Okay. One of my questions is on this, were you are trying to make the microenvironment less hospitable? That… When does that go into trial with humans now that…, now that we have cured a few mouses (laughter) or mice?

Dr. Irene Ghobrial : Yeah. So, we are not there yet. We are testing some of those drugs in relapsed myeloma. We have not started to test them in earlier cases and the reason for that is for you to use a drug in MGUS or smoldering, you have to make sure it stays effective, it has been tested well before we take it into earlier stages. So, we have tested already some of the CFCR for antibodies in relapsed myeloma. We have taken the SCF-1 inhibitor that I talked about in my talk in relapsed myeloma, but we have not started yet taking them into earlier smoldering disease.

Gary Petersen : Okay and in the mouse model, is that the same drug then?

Dr. Irene Ghobrial : Exactly, yes. So, we tested the same drug in earlier cases to see how it works. Absolutely. The immune checkpoint inhibitors could be also very interesting to test in earlier smoldering disease. So, we are designing a lot of trial options that will definitely affect the microenvironment as we talked about.

Gary Petersen : Yeah and these can also…, I understood, be used when you relapsed and had gone through a second, you know, remission, shall we say, and then used those drugs at tandem effect the microenvironment to prevent relapse. That also could be be coming up, right?

Dr. Irene Ghobrial : Exactly. The question would be after someone gets a complete remission, let's say post transplant or post induction therapy, is the microenvironment important to predict who will progress and who will not progress and this is what we are trying to understand also and trying to use the same drug post

transplant or post maintenance therapy to achieve a deeper remission in patients who have achieved already a complete remission.

Gary Petersen : ,Gary_Petersen] Okay. I know the… I know the company that's doing that is very small. Does that prevent them from progressing very quickly because they just don't have the resources?

Dr. Irene Ghobrial : It depends. If we are talking about the SCF-1 drug, you are right. Its a very small company. There are multiple other options that we are looking at with different companies and some of them are bigger than others, yes, but that's one of the limitations of some of the clinical trials. You are right.

Gary Petersen : That would be a great crowd for this initiative, wouldn't it?

Dr. Irene Ghobrial : Oh, yes! (Laughter) You can add that to the list.

Gary Petersen : Yeah. Okay. Early treatment is considered to be more advantageous than disadvantageous, but what about the adverse effects of all these drugs taken for long periods of time?

Dr. Irene Ghobrial : Yeah. Great question and that's why its always a balance. If we said today and I hope the message doesn't go out saying, "Oh, we should treat everyone with MGUS and smoldering," I am not advocating for that. I am saying that there are some patients who would benefit from treatment and actually it may be more harmful for them to stay without treatment because they will have more problems in the future. However, you are right. We need to have drugs that do not have bad toxicity, that will not damage their stem cells and are not given for a very long duration of treatment and that's why we are thinking of very short active therapy. Think of it more like a surgical intervention. You go in, you remove it, and its gone. You don't have to keep going on with treatment and lots of toxicity.

Gary Petersen : Okay. Fantastic! Do you have time for a couple more questions?

Dr. Irene Ghobrial : Absolutely!

Gary Petersen : Okay. Fantastic! Let me do this first. Is anybody…, Priya, that is online ready?

Priya Menon : – Yes, there is a person. Caller calling in from (503) 727-5303, please ask your question.

Dr. Irene Ghobrial : I didn't hear this question well. Sorry. Can you say it again? Your line is not as clear.

Priya Menon : Please ask your question. (Pause) Caller calling in from (503) 727-5303, please ask your question. (Pause) Gary, I think we have lost her.

Gary Petersen : Okay. I have a couple more questions… Yes. Couple more questions and then we will… If we have got the time, Priya, and then we will go…we'll sum it all up. Okay. A 29-year-old male from India detected with MM in August of 2013, 15 chemos done, auto stem cell transplant completed in 2014, now considering maintenance drug thalidomide, but I am also planning to start a family some time soon. So, the question is if I go to the thalidomide and stop it for a while before planning for a family or go to bortezomib but risk losing out on the drug in case of a relapse.

Dr. Irene Ghobrial : Umm… Yeah, so its a good question. The practice in India might be very different than the practice in the US and we do not use thalidomide for maintenance here anymore. We use lenalidomide, which is a cousin of thalidomide and has the same problems, of course. Again, it depends on the patient and the discussion with the physician. I would say you can do sperm collection and then go on on lenalidomide or on bortezomib or any of those other drugs. That could be one option. Or, you can take a small time period off from maintenance therapy to, of course, have your family and then go back on maintenance therapy, but these are things to be discussed on a personal level with your physician.

Gary Petersen : I had heard that he had an auto stem cell transplant plus 15 chemos. Doesn't that…have an impact on… Yeah.

Dr. Irene Ghobrial : Yeah. Absolutely.

Gary Petersen : Make a person sterile or no?

Dr. Irene Ghobrial : Not necessarily. It depends on the patient and again this is where sperm collections are very important.

Gary Petersen : But, before the stem cell transplant or? Or, you should be talking out this before treatment if you are a younger person, a younger patient?

Dr. Irene Ghobrial : Correct.

Gary Petersen : Okay. And one last one, its, "Hi, doctor! Do you think that treating someone with smoldering myeloma might bring a cure and is there any research going on to investigate this?

Dr. Irene Ghobrial : So, I think yes. I think we just need to find the right combination and the right time, but if we are going to cure myeloma, I think earlier treatment will probably be the place to go. We are doing clinical trials to ask that question, so until then we do not have the answer, but this is the hope.

Gary Petersen : Okay and I think with the people like yourself working out on these questions, and Pat was correct. I was enamored at what you were saying, but it was because to me what you were saying is that you have the potential in your sides to cure this thing and to find it before it ever reaches the CRAB state or reaches multiple myeloma. So, for me, its so, so exciting this possibility that I just could not keep away from our listeners.

Dr. Irene Ghobrial : Oh, thank you so much.

Gary Petersen : So, with that, Priya, could you…, could you bring it.., bring it home?

Priya Menon : Thank you, Gary. Thank you very much. Yeah, sure. Thank you, Gary. Dr. Ghobrial, it has been like amazing listening to you. You have shared so much information with our listeners today. Thank you for being with us. Matt, Pat, and Cindy, thanks a lot. Listeners, please join us again for our next myeloma episode where we would be discussing transplant with Dr. William Bensinger on March 26th at 5 p.m. eastern time. The link for today's broadcast will be shared with all our participants and will be available on Cure Talk's website by tomorrow. Please visit curetalk.com to register for our upcoming shows and thank you so very much.

Gary Petersen : Thank you very much, doctor.

Dr. Irene Ghobrial : Thank you, guys. Thanks, again. Bye, bye.