Novel Cancer Immunotherapies with SELLAS Life Sciences

The second episode of CureTalks with Gary discusses new immunotherapies with Sellas Life Sciences. Talking to Gary Petersen is Dr Angelos M. Stergiou CEO and President of Sellas Life Sciences and Senior Advisor for Sellas, Dr. Nicholas J Sarlis.

Sellas Life Sciences is focused on the development of novel cancer immunotherapies for a broad range of cancer indications. Their Galinpepimut-S (GPS) is an engineered immunotherapy targeting the Wilms Tumor 1 (WT1) antigen. GPS has an ongoing Phase 3 trial for AML in patients achieving second complete remission. Sellas also has developed an HER-2 directed cancer immunotherapy (Nelipepimut-S) with potential for treatment of patients in the maintenance setting with triple negative breast cancer. Take a deep dive with Gary on these life saving treatments in this episode.

Full Transcript:

Gary Petersen: Welcome to Cure Talks with Gary today. We'll be discussing Novel Cancer Therapies for Immunotherapy with Sellas life sciences. Representing Sellas is Dr. Angelos M. Stergiou, CEO and President of the company as well as Former Chief Medical Officer, Dr. Nick Sarlis who will be covering their robust product pipeline. Now, I have had multiple myeloma, and I've had it now for a number of years and I followed it religiously and what I have found, is that small biotech has been the Genesis for every biotech drug for myeloma and something with dual designations from the FDA which is like orphan drug and fast-track, anything like that. All of those which represent new classes of drug and each new class of drug provides you with an extra year of life and when you're talking about when I was first given the diagnosis I had 33 months to live, that obviously each new year is important.

Now, these FDA designations are an offshoot of what we call the Orphan Drug Act of 1983, which was introduced to provide incentives for the development of Orphan drugs. These programs have provided over 450 drugs, new drugs where prior to the Orphan Drug Act there was just 38 for the over 7,000 orphan diseases. So, as you can see even now although there's been a heck of a lot of progress there's still only 450 for 7,000 diseases. This is still such an unmet need and small biotech fills this need.

Sellas has 3 dual designations for their drug GPS and to fast-track designations for another drug of theirs called NPS. GPS is a new class of drugs with application across a lot of different cancers. I am pleased to be able to discuss these life-saving developments with the senior level manager of Sellas. Welcome Dr. Angelos M. Stergiou. We are so pleased to have you here and we welcome you to provide some talk about the background of the company as well as its history. So, welcome.

Dr. Angelos M. Stergiou: Thank you Gary very much and firstly I'm glad that despite your initial diagnosis you're doing extremely well and you're up in good spirits. That's always exciting and I think it's tribute I believe to I think where the science and the medicine has gone over the last years. Thank you very much for hosting us today. Well, firstly I really hope through your platform here Gary to convey an exciting theme of growth and transformation of our company. Our core mission is really to prolong patients' lives and I'm particularly grateful that despite Covid-19, which is obviously in the Center off the news and rightfully, so we really remain clear in our mission and vision to develop and deliver complex and innovative treatments for patients battling cancer.

We're doing really our best to manage those elements of our business that we believe we can control during this pandemic, that is progressing our assets, generating clinically immune biological data and executing really new clinical development and progressing with the business development opportunities. So, about the company, we're late stage immuno oncology and immunotherapy company and our focus is really the development of Galinpepimut-S or GPS, which is an Innovative and potentially first in class Wilms' Tumour 1 or WT1 targeting at our clinic immunotherapy. What's interesting Gary is that the Wilms' Tumour 1 antigen in the fetal stage.

Dr. Angelos M. Stergiou: So, before we are born, it's responsible among others for kidney formation. Once we are born it disappears and then it comes back again as a true oncogene. So, basically it causes cancer. It's a validated target, the National Cancer Institute actually ranked it as the number one immunotherapy target to go after via a priority selected criterion. And we have licensed this technology from Memorial Sloan-Kettering Cancer Center here in New York, which is one of the world renowned Cancer Centres and which is very exciting to have such a pivotal partner and collaborator right next to us and have advanced GPS through Phase 1 and 2 studies across various indications with compelling translational and clinical data as well as regulatory designation. So, we are indeed excited Gary that we have commenced the pivotal registration enabling Phase 3 Acute Myeloid Leukaemia study which we call the Regal study in patients after the second complete remission. Additionally, we have a phase 1, 2 study that is ongoing with Merck as a collaboration partner. And that's where we combine GPS with Pembrolizumab as well as having a phase 1, 2 IST study, which is ongoing with Memorial Sloan-Kettering and Bristol-Myers combining GPS with Bristol-Myers PD-1 that is Nivolumab in relapsed/refractory mesothelioma patients.

Dr. Angelos M. Stergiou: I think we're really excited of where we got as a matter of fact it's interesting that this month actually marks the 10th anniversary of Sellas Life Sciences, and interestingly Gary Sellas, the wording comes from the ancient Greek that means truth and wisdom. And when I founded the company about 10 years ago, my vision was really that through clinical development, through clinical research we can gain more insight, more wisdom, more truth and then hopefully get to the finish point, which is to get such an exciting drug approved. My passionate love if you will over the last 15 years actually has been in the immunotherapy and cancer vaccine space, having developed one of the first cancer vaccines in lymphoma. And so that is a passion of mine in the whole immunotherapy space and I'm just really excited that with our regal trial that is the phase 3 study that is ongoing in Acute Myeloid Leukaemia and the primary endpoint being overall survival. For this study we expect Gary, by the end of next year by the end of 21, our interim analysis and our previously conducted Phase 2 study in this particular indication showed close to a 16-month median overall survival difference in strong favour of GPS.

And that was 21 months versus 5.4 months in the control arm with a p-value of 0.02 and we have fast-tracked and orphan designation for GPS and AML by the FDA, by the European medicines agency, but what really got us excited just briefly about GPS and why we entered in this collaboration agreement or the license agreement with Memorial Sloan-Kettering with, is the fact that there are about 2 tumour types that express WT1. So, indications like Acute Myeloid Leukaemia or Mesothelioma, inevitably the majority, if not all patients express WT1. And then we have other indications such as ovarian cancer, glioblastoma and many other types. That anywhere between 30 to 80 percent of the patients express WT1.

Dr. Angelos M. Stergiou: So, GPS in its core is really a mixture of engineered and artificially mutated peptides and we utilize something called the heteroclitic technology. Back in the 90s Gary, this heteroclitic concept was used in HIV AIDS vaccine work. Memorial Sloan-Kettering was one of the first if not the first institution to utilize that concept and to basically use it in immunotherapy and Cancer Treatments. And again, its by designed mutation of the sequence that basically makes the asset that compound the drug more potent and more immunogenic. So, basically it drives more of a stronger immune response that you ultimately need. As I mentioned, we have —- peptides, we address 25 WT1 optimally selected epitopes that elicits CD4 and cd8 immune responses. So, the CD4 and CD8 immune response is very important many other immunotherapies that are out there typically target and illicit what's called a CD8 cytotoxic immune response. And that's typically short-lived and we do both we do a CD4 and the CD8. So, the CDA if you will, those are the soldiers in the front line. They go after the bad guys, in this case the cancerous cells and as I

said, they do the work, but unfortunately, it's short-lived.

Now, what we have is we also have a second wave which are the CD4 helper and memory cells. Basically, the helper cells, they boost the CD8-the cytotoxic guys, but they also do the work in fighting the disease. And then we have the memory cells, which basically remember what the bad guys look like. So, if it comes back, they can fight them off. So basically, where we come in Gary is that once a patient is in remission with administered WT1 and now your immune system knows what those cancerous WT1 cells look like so if in fact that come back the CD8 guys and CD4 immune response, they can go back and fight it off. And basically, that prolongs progression-free survival and ultimately overall survival.

And what's interesting is we've done a number of studies in leukaemia, in multiple myeloma, in ovarian cancer and mesothelioma, and we have shown really intriguing and exciting both immune biological and clinical data. And again what we're very excited about is the fact that we're now in Acute Myeloid Leukaemia, we actually are in a phase 3 study.

Dr. Angelos M. Stergiou: I think maybe one more comment if I may is that WT1, it resides inside the nucleus so basically inside the cell and it's not druggable if you will with standard pharmacological approaches such as small molecules or antibodies. And our mechanism of action is quite unique the way we work, and I think that's the reason among others why we have seen such exciting clinical and immune biological data. So, again, the genesis of the companies that we're focusing on GPS and over the last 10 years when we started the company, we in license the technology about 6-7 years ago, and we've done a lot of work to progress our leader asset again in interface 3 for leukaemia, but we also have a couple other studies on going. One is in mesothelioma right now as I mentioned with Nivolumab Bristol-Myers PD-1. We're going after mesothelioma patients, and then we have a basket study in collaboration with Merck where we are initially focusing right now on ovarian cancer. So, it's been a long road but we're very excited that we've progressed the asset, progressed indications and as I mentioned before we've also shown exciting data in multiple myeloma as well as other indications, but we're a small company, a small team. If we had all the resources in the world, we would go after many other indications, but we want to stay laser focused and I think leukaemia right now is really our prime focus. because that's where we have really the bulk of the our data if you want to date.

Gary Peterson: Well, thank you so much. And obviously I think when I was looking earlier about mesothelioma, their life expectancy is like 8-9 months and there's really no drugs available. So, talk about an unmet need. Now, what I have found is that the FDA has a remarkable history of picking winners in the orphan drug space. Sellas currently has three FDA dual designations orphan drug and Fast Track, you mentioned those multiple myeloma, AML as well as the mesothelioma. So, that's great. Now this is just a remarkable accomplishment for small biotech. How have you been able to accomplish so much because you don't have a huge company. I mean of the 6 small biotech that have eight drugs for multiple myeloma, you and Cellectar have the smallest market value of any of them. So, you guys, you're doing so much more. You two companies are doing so much more with so little. So, how do you do that?

Dr. Angelos M. Stergiou: I appreciate your comment and I think firstly I have to say that I am in deep privileged and honoured being surrounded by such a strong and smart intelligent team around me from legal to clinical to regulatory and so forth. And I think kudos to all of my team. They're really doing such a phenomenal job. I cannot overemphasize the fact that we've had a lot of sleepless nights and I think our core vision and mission is really to do the best that we can to prolong patients' lives. And I think there's an ethical rationale behind it, obviously because all of us in drug development at the end of the day, that's what we care about. It's really to hopefully put our name next to something that's going to be meaningful to patients and everything else is secondary or tertiary. So, again, I really want to thank my entire team and obviously all of our key opinion leaders and the scientific advisors that we have, the clinical advisors the developers really push our asset forward.

I think to your point or Gary is when we look at GPS, we wanted to make sure that the differentiating factors that has versus other potential modalities is indeed. So, I think one is as I mentioned before we target the

Wilms' Tumour 1 or WT1 antigen and we've done this precisely and deliberately because we took fragments from the WT1 whole length protein and then basically in the lab with the in silico work in vivo and in vitro to come up with a best sequence. The sequences that would very likely have a strong clinical effect in patients, ultimately began using the heteroclitic concept as well.

I think the second piece is that by using that approach and having utilized 25 carefully selected WT1 epitopes and we have predicted that those have an optimal MHC class 1 and 2 presentation. That ultimately leads to what I said before the CD4 and CD8 immune response is very important. The tumour microenvironment Gary's very important. So, as a mono therapy we go after patients who are in complete remission. I do not believe that drugs like ours are there to debulk disease. That's where you need sort of CAR-T technology, for example where if you have a kill off a tumour you need to kill lymphocytes to basically debulk the disease. We come in as a mono therapy once patients are in remission to them basically prolong progression-free survival and overall survival. But now in combination with example of PD-1 we can administer GPS front line as well as then in the maintenance setting. The other important thing is that we're not HLA restrictive. So, anyone walking through the door who tests WT1 positive is eligible to get treated. So, be Caucasian, African American Hispanic, whatever the ethnicity or background of the HLA maybe, those patients are eligible to get treated. And what we've also shown is that we have involved a multi epitope broad cross-reactivity along the full length WT1 Protein, that's truly suggestive of immunologically mediated cancer cell destruction, which are Hallmarks of an effective cancer vaccine. So, I think we have sort of put all the right pieces together. But you're absolutely right I think a company like ours, we're sort of been under the radar and I think now with the advancement of the phase 3 we're emerging up. Unfortunately, once you sort of fall to the small cap bucket, a lot of folks may not pay as much of attention to you, as perhaps they should.

Gary Peterson: Well that was supposed to be my next question frankly. You just did an excellent job of introducing it for me. So, thanks. You have one drug in Phase 3 trial for AML and for Acute Myeloid Leukaemia and you therefore have based on the data that I've seen about a 75% percent chance of Phase 3 approval. Once you're in Phase 3 you got a 75% chance of it being finally approved. That's the data. Also, there's another one that says if you're an orphan drug, you have a 73% chance if you have this phase 3 drug to get it to the finish line. So, in my opinion, I look at your SLS and this is not reflected in the potential and opportunity and the value of your company. So, I can't understand it. I am confused why that isn't represented. Are there any challenges confronting a small biotech which can be helped to explain this and like you said is small biotech just invisible to the market?

Dr. Angelos M. Stergiou: Yeah. I think the small biotech arena may be somewhat invisible. I think to Sellas in particular I think some of the challenges that we have is that we became public by the mere fact of doing a reverse merger, so that had its own sort of issues that we have to sort of go through. But I think for a small biotech company to raise capital is a more challenging act versus being a large cap company and that's just the mere truth to it. But I think what is important is that companies like Sellas like ourselves, we just stick to our two-core mission and vision and we don't deviate from that. I think one thing that we're very clear and have been very clear is that, we set our goals and we really execute along those. And I think the other thing is also that you will see from our management team that we're not going to go out and just for the lack of better word just blur out news just for the sake of it. We're very cautious and careful and I know that our shareholders and investors would love to hear more and more news. I am very sympathetic to that. At the same time, I hope that everyone can appreciate being a public company.

We don't want to put news out that we don't feel a hundred percent certain that we can indeed at the end of the day back up. So, we're very cautious about that. And I think it's also for the benefit of all our shareholders. So, I think when we have news, we'll announce it. But one thing is certain that our team is working very diligently not only to optimize shareholder value but more importantly if you really as I said prolong a patient's life.

Dr. Angelos M. Stergiou: So, I think to your point though Gary, Yes, it is more challenging being in the small cap company because raising capital is more expensive being a small capper than being a large cap.

At the same time though I think it's those small companies that at the end of the day focus on rare diseases as you correctly stated that can potentially move the needle in and provide a treatment that otherwise wouldn't be able to be developed. So, I think on the points that you mentioned, although my mind is very analytical very well that the oncology haematology space in the rare diseases, it's more challenging to get drugs approved because of the mere fact that it's a difficult disease state.

But I think on the data that we have seen to date, we're very excited I have to say and we just really hope for the best that our ongoing phase 3 trial and all the other indications we are seeking in going after, will have positive results. And then again, I cannot stress the fact that between our team and our Advisory Board, we have been there, down there we know the challenges, we know exactly how to go about that. So, unfortunately there is a discrepancy between the value of the asset that the company and what the market cap stipulates right now and hopefully over time we'll be able to sort of reverse that what we what we really have.

Gary Peterson: Like I said I'm so confused that at this point, especially when you have a phase 3 asset. I can see it in the first year, second year, third year when you're in Phase 1, but when you can see the challenges that makes me think that maybe I shouldn't have gone to business school at NYU because there's no logic or statistics or math that can make me understand why it's not reflected. I thank you so much for everything that you've provided today. But I think we need to move on now with Nick if you don't mind.

Dr. Angelos M. Stergiou: Thank you again. Thanks Gary. Thank you.

Gary Peterson: Now that we've talked with Angelos about the background of the company. We want to get into a little bit more detail as to the discussion of the product pipeline for Sellas Life Sciences. Dr. Sarlis, GPS is a drug, which has obtained the majority of the FDA dual designations and its target is the Wilms' Tumour 1 antigen on the surface of cancer cells. Is this a new class of drugs and why has WT1 gotten so much attention from the FDA as an outstanding target?

Dr. Sarlis: Well Gary, first of all, thank you for having me here today and I will try to follow on from Angelos's excellent introduction of the asset pipeline.

Gary Peterson: That doesn't sound like a Jersey accent.

Dr. Sarlis: No, it's a North Western Greece accent with a lot of for instance in London, Houston and the Upper and the Northeast Corridors. So, I think as Angelos mentioned the vision in Sellas is to build on the promise of cancer vaccines and we're trying to do that with peptide novel and sophisticated therapeutics that are targeting major antigens or major targets for immune response to tumours. And one of them is WT1, obviously Wilms' Tumour 1 and the other one I'm going to talk in the moment is, it would be a miss not to mention our second asset in the pipeline, which is NELIPEPIMUT-S or NPS, which is a peptide vaccine targeting tool in various cancers particularly breast cancer for which we also have fast track designation and we have a couple of trials that are still ongoing and are going to report in the next few months. So, but again, I'm just going to go back to GPS. And as you mentioned there has been a lot of attention in this particular asset. So, before I do that, I would like to kind of mention a few things about why have cancer vaccines up until recently have been largely unsuccessful in oncology. And there are many factors and I think the cardinal factors is that you have had poor selection of the antigen, right? You had the wrong target. Another factor is that a lot of investigators targeted only one type of HLA molecule primarily molecules that induce a CD8 immune responses as Angelos mentioned which is unfortunately evanescent and relatively weak, especially if the antigen is a self-antigen like WT1. Meaning that is expressed in early on in normal tissues.

The other problem is that a lot of vaccine trials have been using mono valent vaccines meaning that they're targeting only one or just a few epitopes and I think a major problem in previous clinical trials with cancer vaccines is that they tried to use the vaccine to really kill tumour, right. And they have been using it in the setting of bulky disease or what we call in hematologic malignancies blastic disease. Especially in myeloid

malignancies or fervent myeloma or whatever have you as a single agent. And we know now through at least a decade or more of clinical Immunology working cancer that you need a lot of lymphocytes to kill established microscopic disease that is basically visible on scans and whatever have you.

Dr. Sarlis: And I think the rationale to use monotherapy vaccines has changed and is now focusing on maintaining a remission or maintaining a complete response and we're going to talk about this in the moment. So, WT1 has a number of interesting properties and if you want to attack this particular protein in cancer cells, it is indeed the number one ranked antigen by a large study that was done by a Consortium of the NCI led by ….probably more than 10 years now. And it has literally all the properties to be the optimal target for active vaccine immunotherapy in cancer. And one of the things that is very important is that it's not found in an appreciable amount in adult tissues and about normal tissues. And this is important because one of the problems that vaccines have had in the past is that you can have On Target off Tumour effect meaning that you're going to start attacking normal cells in the body be it cardiovascular, be it kidney, be it liver cells or whatever have you and then you can have toxicities. And this is not the case with GPS, we actually have an excellent toxicity profile which is basically relevant to immune reactions or local reactions that we see at the site of injection. Basically, when you get vaccines for example against the flu or against the pneumococcal pneumonia.

So, we haven't seen any systemic reactions that they are worrisome or and off-target toxicity, which is actually very important. The other thing about WT1 is that unlike many other proteins that are targeted in cancer through non-immune type of avenues. It does not down-regulate. One of the huge problems that we have in cancer on target therapies on which I personally have probably spent half of my career and then the other half was on immunotherapies. With targeted enzyme inhibitors, kinase inhibitors and monoclonal antibodies, you have eventually problems with down-regulation of the target and the tumour escapes from the therapeutic attack that you have with this type of molecules. And therefore, with WT1 new immune therapies, another peptide immune therapies such as GPS, you actually do not have the problem of down regulation and I think WT1 is a unique target because it really doesn't down-regulate and doesn't get mutated very frequently, once the therapy starts.

Dr. Sarlis: Finally, WT1 is also expressed on cancer stem cells and perhaps some of your audience have heard about leukaemia cancer stem cells or even in myeloma plasma sites stem cells and of course cancer stem cells in general in solid malignancies, and these are the resistant cells that eventually recur and end up killing the patient. And so, I think one of the attractive theoretical advantages of GPS is that it can attack not only the proliferating or the progressing cells that are basically continuing to create the bulk of the disease. But it also can attack these cancer stem cells which is less than 1% of the actual cancer bulk but is responsible for all the relapses. So, I think that's one of the key reasons and I think also Angelos summarized it very nicely. I'm not going repeat all this, the fact that it is a highly differentiated type of immunotherapy. We have induction of both CD4 and CD8 responses, you have a hetero critic technology, which means that you have a unique mutated fragments of the WT1 protein that can be much more immuno genic than the native sequences that are expressed on the tumour. And importantly we are working across a very broad repertoire of HLA backgrounds in human populations in essence, we cover probably around about 90% of the Caucasian North American as well as about 80 to 85% of the Asian Pacific Basin a two-day. So, this is truly a globally applied product and we also don't need a companion diagnostic because in essence once you have a tumour that expresses the ability through standard immunohistochemistry, you can use the drag.

And finally one of the practical considerations that makes the WT1 peptide immunotherapy with GPS very attractive, is the fact that this is an off the shelf product and as there is a lot of immunotherapy that is now directed through new epitopes or the new antigens as well as the CART cells and TRT cells and whatever have you. These technologies are very powerful in their very promising. However, they are highly individualized, and they have a lot of manufacturing challenges and a lot of obstacles as far as distribution and cost of goods. and whatever have you. I think one of the practical differentiating factors with GPS that makes it very attractive is that it's an off the shelf product with very large applicability.

Gary Peterson: So, it sounds like it's a brand-new target. So, it's a new class of drug, which is great. You have a phase 3 trial for AML and it's the closest to approval. Could you provide some of the details behind the trial and the currently available results?

Dr. Sarlis: Yes. Absolutely, I mean before we go actually to the current phase 3 trial which I'm going to describe in a moment. I think we need to look a little bit historically how we ended up with AML being as a kind of flagship indication, so to speak, for GPS. So, way back then when David Steinberg who's the one of the inventors of the vaccine when he was Head of leukaemia at Memorial Sloan-Kettering. Currently Dr. Sheinberg is the Head of the Development of Therapeutics in the same institution. So, when he incepted and conceptualized GPS, he obviously had a great interest himself in myeloid malignancies both chronic and acute myeloid leukaemia and one of the interesting things about AML is that not only WT 1 is expressed almost universally in AML, it also is expressed very densely. It means that most of the proliferating cells that myeloid blasts in AML express very densely WT1. And on top of that the leukemic stem cells are also expressing WT1.

So, I think it was almost the model hematologic disease to target with GPS. So, more than 10 years ago, there was a pilot early study phase 1, phase 2 study that showed that there was significant activity in the pilot setting in adult patients with AML who had their first hematologic or morphologic complete remission or CR1. A phase 2 trial was also performed which took a number of years to complete and published back in 2018 by Peter ____ and his team at Sloan-Kettering and quite recently we actually did kind of an internal meta-analysis, which means kind of merging of two data sets together and the results were quite impressive. And I will go over them very briefly. So, in the CR1 setting, which is the first complete remission setting we have treated over the years 31 patients with GPS. This were all patients that had fairly significant disease. They got standard anti-leukemic therapy. And ended up having minimal residual disease which means that they all had molecular evidence of residual disease despite having achieved complete remission under the microscope. And they were fairly standard for AML spanning with a median age of 64 years and fairly consistent type of mix of cytogenetics as far as risk classification.

Dr. Sarlis: And what we saw in the pooled analysis, we saw a median of overall survival of four to five years for both trials. The more recent trial was 67 points some months of overall survival and also particularly in elderly patients with AML, patients that were 60 years and above. We also saw a remarkable overall survival at 34 Point some months, which is several folds above what you get with standard treatment. And even in the presence of a low transplant with the elderly patients, we have typically a median overall survival round about 15-16 months and we saw 35 point three months or at least doubling of that survival. Also, we had a lot of evidence which is again, very important from a biological standpoint I mean, it's one thing to see these responses in the clinic, but people may say it's a statistical fluke or it's the small number of patients but importantly in all our trials and this included also these AML trials within the lot of immunological survey and so to speak. To look at antigen-specific or basically WT1 specific immuno responses and you can do that in peripheral blood and blood that you can take from the vein of the patients by measuring what Angelos mentioned in CD4 and CD8 cells. And by doing that we found that 88% of our AML patients that were vaccinated, ended up having the immune response measurable by this type of the clicks. We also didn't see any effect, any influence on the HLA type which makes perfect sense because this should work across all HLA types and importantly we really didn't see any grade 3 or more systemic adverse events, which as I mentioned is important to have a vaccine that is tolerable and can be given with relative safety.

Dr. Sarlis: So, this kind of completes the package of the CR1 setting. So several years ago, we also did the study at the Moffitt Cancer Center, which is another world-renowned centre with Dr Pineodon in Tampa and Dr Peniola and colleagues. In fact, Dr. Peniloa was working initially at MSK under Dr. Steinberg and then got his professorship at Moffitt and did a very interesting trial where he took two cohorts of patients that had second complete remission. So, this was very advance stage leukaemia patients that had already taken their leukemic therapy. They entered their CR1 or First Complete remission, and then unfortunately relapsed and so what happens is they got something called Salvage therapy or second-line therapy, which as in myeloma is multiple this line of therapy is almost the norm today. But in leukaemia, unfortunately anything after second line is very rare because unfortunately the disease tends to relapse and develops very vigorously and end up

having a developing type of tempo and kills the patient. So, in this very tough population, which is basically second remission population, they did the study where they took 10 patients on GPS and 15 patients that were contemporaneously treated. So, this would not historically control, this were patients that were up the same institution treated by the same team and what he found is that the median survival of Patients that were treated with GPS was 21 months versus 5.4 months in the control group. And of course, this was highly statistically significant with the median follow-up of 30.8 months.

So, this is remarkable because again, in this world median age was 73 and all the particular study to be fair was not blinded or randomized. In a post hoc analysis, the patient demographics in the disease characteristics, in the type of chemotherapy that these patients had received were highly comparable. So, we believe that there was no specific kind of fudge factor there or confounding factor rather that would produce these results. And again, we found very strong indications of specific anti WT1 or antigen specific T-cells and in and immunization of these patients. Of interest about the third of patients treated with GPS experienced sustained responses. And in fact, had progression-free intervals that were at least equal to the progression-free intervals that they had in their first remission, which is again unheard of and of course this study was published back in 2015. And we were very lucky that earlier this year to have the long-term analysis with the follow-up as I mentioned of 30.8 months and we saw this remarkable kind of difference between the two groups.

Dr. Sarlis: So, to cut a long story short when we put together the phase 3 program, we had a lot of advice both from our Scientific Advisory board, but also by external top-line leukaemia specialists around the world on how to proceed from regulatory and clinical perspective to a phase 3 setting. And so, with the background of the two CR1 studies and the CR 2 study we decided to go ahead on a pivotal registration enabling phase 3 study in AML, in patients with CR2 or their second complete remission with leukaemia with GPS monotherapy. This is called the Regal study. It is designed and I'm going to answer basically your question after it. I looked at me long but answers, so it is designed to randomize 1 on 1, 116 patients. So, it's half of the patients will get GPS and half of the patients will get what is called "best available therapy," which is basically clinicians' choice of the modern therapies that patients typically get in this setting. Especially when they're ineligible for or unable to undergo an allogenic stem cell transplant.

So, the study is opening in 50 centres across the world. We have about 25 centres in the in the US and the other half is in the European Union. We have several certification factors that are important for this particular disease. So, it's a very elegantly designed study. We recently got approval from the French Authority to run the study in France, and we are expecting any moment now approval from German Ministry of Health to run the study in Germany. And of course, we have a number of European investigators that are very interested, suffice it to say we have had the support of Dr Hagop Kantarjian, who is the head of leukaemia at the MD Anderson Cancer Center where absolutely I was associate professor for 4 or 5 years, a few moons back and Hagop Kantarjian has been responsible for the approval through his clinical trials that he has led both globally and at MD Anderson for more than 8 anti-leukemic and other chemical logic malignancy drugs. So, we are in good hands as far as running the trial and his leadership has been truly instrumental. And I will mention that although he's just retired Dr. Hagop Kantarjian in the Netherlands has been of particular help in designing the trial and helping the looking also some molecular endpoints and trying to understand the biology of the immune response.

And quite frankly, I believe that the trial, the way it's designed the weights going to be operationalized and run and eventually hopefully completed, will be most hopefully a positive trial based on everything we know about how GPS performs in leukaemia and how It should be performing in this particular kind of Niche, orphan and very high unmet medical need population. So, we are obviously expecting the results and we're obviously going to look at them very carefully, but the thing we have maximized the opportunity for success here and again, it's been several years of effort and perhaps several dozen people both in Academia and some of our industry Consultants that have instrumental in getting us there.

Gary Peterson: Well, thank you so much. Thank you so much for the highlights for small biotech and how it plays such a crucial role in drug development for Orphan diseases. What is also amazing to me is the fact

that GPS at least in 20 cancers is a universal application which is something that and I found it with a lot of cancer or of drugs that are for specific Cancers if you look at like Revlimid, for example, it not only plays a role in myeloma, it seems to be playing a role in dozens of other cancers as well. And I think the same thing would apply to you that once you get it for an orphan disease all of a sudden it opens up the market and the opportunity in many other diseases and you already shown that you've got that. In addition, it's a new class of drug and each new class of drug has always been revolutionary not evolutionary and what I mean by that is that you can have thalidomide and then incrementally better as Revlimid and incrementally better as pomalidomide and on and on we go. But when you get a Protostome inhibitor and IMiD like for myeloma, it creates far better combination. So, you're talking about those kinds of things as well.

Dr. Sarlis: If I could also interject here. I think you're bringing an excellent point and just want to kind of perhaps finish this on my end with a little hint of myeloma, which obviously is of high importance to you. So, myeloma, I think is one of the tumour types or one of the areas of hematologic cancer medicine where we have actually seen this in practice what you just mentioned, right. So, yes, we have the IMiDs right and then you have the proteasome Inhibitors, right. And then you start having the combinations of the two and now everybody God bless at least in the U.S. Its most of the western world gets triplets for induction and maybe getting quadruplets for induction, right. And I think as you mentioned, and I will corroborate highly on what you just said, the main advances that we've seen in the last 3 to 4 years and what are the advances. They're basically the CS1 Inhibitors.

We have seen the CD38 that they're very important. We have seen the trail Inhibitors that are coming now very vigorously and phase 2 studies and we have seen the BCMA targets, right. And you have the new CAR-T cells you have the new monoclonal. We have a number of approvals of that are kind of galloping and the FDA has done a tremendous job. And I will also tip my hat off to the European medical agency that is very rapidly following this, so that we can make this new medication available to very broad population. And I will finish that as you probably know we had a phase 2 study also with GPS in myeloma, which we found that is very nicely combinable with Lenalidomide maintenance and in this particular trial we not only found excellent immune responses but we actually found a median PFS in a very high risk population of 23.6 months in comparable population you get about 14 months PFS. So, we are already signalling myeloma, which is obviously early, but it is something that we would really like at some point to think about especially not that we have combinations with Elotuzumab and daratumumab and other interesting medications that come in the induction phase and perhaps we can follow them up with combination of lenalidomide, base maintenance plus GPS plus another drug.

I think we could really potentially move the timing of the relapse much further along because once you have the relapse you can take the therapies but every time you get the second or third or fouth or fifth line therapy, the progression free intervals happens to shorten over time. I think we have a phenomenal opportunity especially because as you also know the check point inhibitors did not combine very well with IMiDs and I think it is what it is and it has probably to do so with some unique biological characteristics of being in response in myeloma which you know is a very complex issue of how people respond to immune therapies and to several advantages in myeloma. Now that we know that check point inhibitors cannot be combined with with lenalidomide maintenance or protostome inhibitor maintenance in early stage disease and upfront disease and newly diagnosed myeloma. Perhaps it could be another immunotherapy and one of this candidate immuno therapists could be GPS. And so, that's the future will show but I just wanted to ensure that I do not miss in not mentioning the fact that we did have some early signal in myeloma as well.

Gary Peterson: For us, you know, 12 months of additional life is a pretty important when you start 3 years. You don't know we're at close to 6 and what you're saying is that you got a drug for myeloma in any way that would provide another year at least, initial data shows that and for us that's pretty important. Another year of life is very important, and it's the people in small biotech that do all the heavy lifting, then and you do the heavy lifting and then somebody comes along and gives you a payoff and then they take credit for as it happened with thalidomide, which became Revlimid which became pomalidomide, which took out a little company the size of yours, which was a cell gene and made it 20 million dollar company losing money hand over faith but to a being bought for 80 Billion dollars. So, little companies can grow up become big

companies and I think that’s when your late stage like you guys it’s almost a given. But thank you so much to both of you for an excellent cure talks with Gary.