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KPTI - Karyopharm Therapeutics Inc Corporate Analyst Meeting

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PRESENTATION

Michael Kauffman - ***Karyopharm Therapeutics - CEO***

Hello, everyone. If you could take your seats, it would be great. We are webcasting, so we have to be a little bit on time here. Plus I know everybody is at the end of ASH just about and probably at the end in general. Wow, that was efficient. People really don't have much energy left. Great. Okay, so let me just quickly mention the format of today or tonight.

I'm Michael Kauffman, I'm the CEO of Karyopharm Therapeutics and we are going to have a very fairly brief set of comments for about 15 minutes maximum. I want to review just kind of where the Company came from and where we are going and some of the highlights here at ASH. I will quickly run through the data, which were presented by some of the expert panel members here. I will not do as good a job as they did, so I strongly recommend you review their presentations, which are available through ASH.

And then we'll have an expert panel. The expert panel will come up. Daniel Auclair from the MMRF will moderate the panel. I will sit down. And the goal really is to talk about multiple myeloma and to understand where this complicated field is and where it's going. And we thought this will be the most important thing as we think about how selinexor will enter a very interesting marketplace, a place where we've done a lot of patients and we still have a lot more to do.

So without further ado, I'm going to dive in and we'll get started. We will make forward-looking statements today, so please refer to all of our various filings on the SEC, et cetera. And please recognize that these statements we make are only as good as they are tonight and as soon as we're done making them, they're effectively not good anymore.

We have a broad therapeutic pipeline, and what you see up here has been home-grown. That company is founded by Dr. Sharon Shacham who is sitting there, and really with the idea that we should inhibit nuclear export and we invented a new class of compounds called Selective Inhibitors of Nuclear Export, or SINE Compounds. And selinexor now, which has been in over 1,800 patients across many, many malignancies is moving into a late stage in development and towards regulatory approval in a couple of areas with myeloma being our major focus at the present time, but a number of other indications commensurate with its broad therapeutic activity.

This company started here in a lot of ways back in 2009 and we came to ASH, I think, the first in 2010 and we had I think three people who agreed to meet with us because they knew Sharon and they knew me. I wasn't even an employee yet. Sharon had a couple of consultants. We had a poster, which I think the same three people came by and looked at the poster about this. And really, this has grown into a very exciting area where we're conducting trials multi-nationally across the water, et cetera.

And that's a really big thing. These are completely new chemical entities; these are oral therapies for patients, initially patients that have no other options. And there are certainly, as you've heard today from some of the discussions, there are patients alive today because of this drug and other drugs like it with other targets, but we are the Company who is the leading SINE franchise with selinexor.

The BOSTON trial up there on our pipeline will start very soon in the early part of next year. I'm very happy to announce that not only has the FDA given the green light to this trial, but the EMA has given the green light to this trial, including all of the nuances and the very exciting things we're doing with this trial, which makes it very different from all of the other phase three combination studies that are being done in myeloma. And we'll review that briefly.

The STORM study is going into its second portion. We went through the first cohort. We showed very nice single-agent activity in a presentation given by Dan Vogl yesterday to high acclaim. This is, to our knowledge, the first agent that has shown robust activity in patients with penta-refractory myeloma and that's a term that we have coined and that's a term that is sticking and other people are using and now we expect it to continue. This is the paradigm now in myeloma.

So STOMP trial has the goal of saying selinexor on its own is okay, but we want to do better and we want to combine selinexor with essentially all of the major drugs in myeloma. The STOMP trial has three components, the Velcade, the Pomalyst and the Revlimid arms and you heard from Dr. Bahlis today that there is some really outstanding data, some of the best data I've seen in myeloma in my 15 years in the field today with Dr. Bahlis, including some patients that are on the drug now essentially since they started it over a year ago with some remarkable responses, including patients with Velcade refractory disease and including patients whose tumors are missing the most important guardian of the genome, that is p53. So we have seen remarkable responses here and that is tribute to the mechanism of action of selinexor and in particular in combination with Velcade. We saw similar data with Krypolis, the other proteasome inhibitor, and we've seen very interesting data now with Pomalyst with doubling the response rate, you know, in the Pomalidomide type of population from 30% expected for Pom to 60% in combination. Some very exciting data which we'll quickly review here.

In AML, you saw a lot of different studies here in combination with chemotherapy. Selinexor mechanistically should enhance the effective chemotherapy and there were a number of oral and poster presentations along those lines, exciting stuff. The SOPRA study is actually being done in elderly patients who are not chemotherapy candidates and that study is against physician's choice and that will read out with an interim analysis in the early part of 2017 with accrual on track this year, but the events haven't come in on as we expected, so early interim analysis next year and then full data mid-year.

And finally in diffuse large B-cell lymphoma, patients with relapsed refractory disease, single agent selinexor which showed a 30% robust response rate in phase one including in GCB type of DLBCL being looked at at two different doses and that trial could serve for accelerated approval in the coming months. So we'll be updating that in the early part of 2017.

A number of studies in solid tumors which I will just gloss over, a second generation compound [KPT-8602], important to remember, this is not a back-up for selinexor, this is a different compound. And we're developing that with some initial data here at ASH. And 9274, another completely novel target now from Karyopharm, an oral compound targeting the PAK4 and NAM pathway and then some other indications with some of our other selective inhibitors and nuclear exports, so lots happening in a fairly small company.

Just to remind folks about the mechanism of action, selinexor is the first of the oral selective inhibitors of nuclear export. There are eight nuclear export proteins. The reason these proteins are important is because the regulation of traffic into and out of the nucleus as you might imagine is highly regulated by cells, separately by import chaperones an export chaperones.

Exportin 1 is one of eight chaperones out of the nucleus as I've mentioned and what Dr. Shacham noticed before we picked this target was that all of the major tumor suppressors, all of the major so-called guardians of the genome, p53, p73, BRCA, FoxO, and RB and so on, all of these are exported from the nucleus by XPO-1 and every single tumor site that's been studied – every tumor cell type that's been looked at – over-expresses XPO-1 which leads to export and inactivation of these guardians of the genome. These proteins do not function when they are outside of the nucleus because they can't look at the DNA.

And tumor cells overexpress these in order to inactivate their guardian of the genome function such that the tumors can continue to proliferate. And by inhibiting XPO-1, and so far this is the only known target of selinexor or 8602, we can cause the accumulation of tumor suppressor proteins in the nucleus and that activates an apoptotic pathway in cells with damaged genomes, namely in cancer cells. So the mechanism suggests this kind of drug will work across different tumor types and that's what we've observed.

There are a couple of other mechanisms to keep in mind, glucocorticoid receptor is regulated in part through this pathway and in the presence of dexamethasone, selinexor will activate the glucocorticoid receptor by locking in the nucleus and causing it to do its job, which is why we see the synergy with steroids. And importantly, there are a set of oncoproteins namely Myc and cyclin and others whose export of their messenger RNA into the cytoplasm depends upon XPO-1, and by blocking XPO-1 we cause the messenger RNA for c-Myc and other oncoproteins to build up with a nucleus, they're never translated and the levels of these oncoproteins go down.

This is clearly a major regulatory mechanism in the cell and there are at least two known endogenous substrates that actually inhibit XPO-1 which are believed to be very important homeostatic mechanisms. So this is a very ubiquitous mechanism in cancer and suggests broad anti-tumor activity.

We're focused now on myeloma and we're branching out rapidly, but our first goal is to get this drug approved in myeloma and some of the other hematologic malignancies. We'll focus on myeloma tonight.

Now, myeloma, we all know is a crowded field. There were about 10 modern drugs approved in this disease, but only 5 of them, please remember, have single-agent activity and this is a very important distinction and then I think our panel will be covering some of this. The reason single agent activity matters in this disease is because when physicians go to choose different regimens, they like to pick drugs with single agent activities as opposed to drugs that have adjunct activity even if they're fully approved. The drugs with single-agent activity are the ones that people like to go to.

And you can see a variety of different key combinations here for these five major drugs in myeloma which consists of about three different mechanisms. So we need a new mechanism and you've seen it at this ASH, you've seen a couple of new mechanisms come through and selinexor is one of the ones that has shown clear single agent activity in patients whose disease has progressed after four or five of these different drugs. So we're quite excited that selinexor could become part of the key combinations and will be used throughout the treatment paradigm for myeloma.

In refractory myeloma, we're starting with an accelerated approval pathway. We're hopeful that this will work, but we all know that accelerated approval is very difficult. I've personally been involved in both Velcade's and Kyprolis' accelerated approval and we've managed to get those through. And I think the real excitement for both of those drugs has been in combinations and that's of course true for essentially all myeloma drugs.

We have taken the same approach here, that is to say to show single agent activity in the STORM study. You've all seen these data. We had a total of 79 patients here, 48 with quad-refractory disease, 31 with penta-refractory disease. The typical median age, some of the patients were treated continuously with at a four weeks dosing, but most of the patients actually got three out of four weeks dosing and we're going to go ahead with the four out of four weeks dosing, continuous dosing. And this is an oral drug, it's easy to give and it's easy to interrupt if you need to and certainly in patients that are this sick, it's important to monitor them very closely and adjust the dose as needed.

Importantly here the patients received a median of seven prior regimens, that's a lot of regimens. But a little bit surprisingly, it's only been a median of four years since they were diagnosed which is very short compared to many of the other studies and suggests these patients truly had very aggressive refractory myeloma. They've gone through all these great drugs that we have now in only four years.

Since the median life span of myeloma patients is over seven years, this suggested this is a particularly difficult treatment group. And you can see the patients have also received alkylating agents and glucocorticoids as well and most of them are transplanted as is typically seen in academic centers.

The treatment related adverse events have been a focus of selinexor. It's not surprising when you inhibit such an important mechanism that you might see some side effects. Some of these we believe are mediated on mechanism, in fact all of them we believe are actually through XPO1 inhibition. But importantly, the grade three events now with the dosing that we used here – 80 milligrams oral twice a week with dexamethasone and a standard dex dose from myeloma – were fairly low and most of the grade three events, constitutional events below 10% and fairly easily dealt with, with dose interruption, modification or support for these particular events.

You'll notice that 15% grade three fatigue, unfortunately, this is kind of the norm in this heavily pre-treated population and if you go back and look at some of the other drugs that have been developed in late-stage myeloma, this is not so far off from the 10% to 15% rates that you typically see here.

There is some anorexia and weight loss which is different, mostly it's anorexia. That is true satiety. This is a very different kind of anorexia than other drugs. We think it's centrally mediated and it's really -- it does go down over time, so if you can keep the patients focused on eating and if you need to give them some appetite stimulants which are prevalent in cancer anyway, it's fairly easy to do.

You'll see some of the cytopenias here, I don't think any of the doctors are surprised to see this level of grade three, four thrombocytopenia or anemia for this late-state group of patients who came in, some of them with 30,000 platelets which is grade three to begin with. And of course, the disease itself and all of the drugs from myeloma cause thrombocytopenia.

And lastly, what you will notice though is that the neutropenia rates are particularly low and the infection rates including sepsis and pneumonia which tend to be important in myeloma were really not very important with this drug, which is great news for patients seeing that infection tends to be the most common cause of death in late-stage myeloma.

The overall response rate here is 21% for the trial, really no different between quad and penta-refractory, what appears to be a slight trend of higher response although the numbers are small, with the eight doses, and we're going ahead with the eight doses per cycle.

One of the things we looked into in this trial was to see what patients had non-evaluable disease. I'll just actually take a step back and notice the far-right column over there, I think I can point. You'll notice that 16% or 21% of the patients had non-evaluable disease, which means they came into the study and were off trial within one cycle. Again, not surprising for very late stage seven prior regimens penta or quad-refractory myeloma, but we tried to look into that to see if there are any clinical predictors of early leaving the trial. And what we found out in fact was that we were a little bit too liberal if you will, too kind and permissive in our trial here and we let patients in with any level of blood counts, particularly any level of anemia.

And what we found out was the patients, you're probably not surprised, that had the lowest blood counts, that is the haemoglobin of 8.4 or less did much, much worst than the patients who had an 8.5 or higher, in fact, almost three times worse in terms of progression free survival. And that just looks at the time on study. So it's very clear that the majority of patients who came off the study early for progressive disease or clinical progression were actually patients who were anemic. And that is a sign of myeloma.

Based on this and based on the fact that essentially every other drug uses an anemia cutoff at this level or similar levels, we have modified the protocol going forward and we believe this will help focus on patients who could derive benefit from selinexor.

The other thing that's very nice and extremely important, it may seem obvious to you, but in terms of regulatory approvals, every new drug comes with the question if responses are meaningful. In myeloma we've gotten used to the idea that responses do predict clinical benefit, but every new mechanism sort of has to go through this trial and error period and will be scrutinized.

In this case what we saw was that patients that had a response to this drug did in fact live longer than the patients who didn't respond to the drug. Again, that may seem obvious, but that assumes that response always predicts good outcome. And that's not always true. And in fact there are some diseases where that doesn't necessarily happen. Myeloma, it has happened for many of the mechanisms that have been approved, but for our mechanism, it's very gratifying to see a curve where even the patients with a minor response had a survival of greater than 11 months whereas the patients who did not achieve at least some response survived less than 6 months.

The other thing that this is very important is that patients, one of the stipulations here is that the patients that have -- pardon me -- the patients that have failed or had quad-refractory or penta-refractory disease really don't have any treatment options. And what you see here is that they don't, because if they didn't respond to selinexor, they had a median survival of less than six months which is quite a dire prognosis for this disease and it's sort of more in keeping with an AML type of prognosis. So there really were no rescue therapies for these patients that could be counted on, and many of the patients went on to get multi-agent therapies including chemotherapies and some of the modern therapies and still couldn't be rescued by them.

So it's a tough prognosis group, but if you did respond to selinexor, the MR group represents about a third of the patients in this study which is a significant number.

So based on these data, we've expanded the STORM study. We're adding 122 new patients. They will be added to the 30 penta-refractory patients where we have. And we believe this is an unmet medical need. Currently, there are no drugs that have shown activity in this group of patients and assuming that accrual goes on as predicted and based on the fact that accrual went very well for the last set of 80 patients that we enrolled, we believe that we'll have potential for an NDA submission in mid '18 with top-line data in the early part to mid of '18 as well. So this is moving along.

But of course, none of us want to use drug only in isolation, nor do we want to wait until the very latest stages of disease. We want to keep patients healthy as long as we can. And so the STOMP study was started. Dr. Bahlis and others in Canada put this study together based on some beautiful pre-clinical work. Three different arms, we're going to focus on the Sel-Vel-Dex arm and in this case, these patients actually who came in had four prior regimens.

So this is a pretty heavily pre-treated group of patients, 91% had seen Velcade for the most part, some of them had seen Krypolis and 73% with clearly refractory disease to a proteasome inhibitor, 91% exposed to IMid and about 40% with prior Len and Pom as well, so a pretty heavily pre-treated group. And we looked to see whether Velcade would work in combination with selinexor in this group.

I think the most exciting thing about this study is that we are using half the dose of Velcade that is labeled and this is a very important, probably the most important take-home message for the combination of selinexor with Velcade which has shown really extraordinary synergy.

Not only have we seen extraordinary synergy which we'll look at on the efficacy slide in a minute, but the side effect profile when you use selinexor once a week with Velcade once a week really starts to look very, very appealing, and patients are able to remain on this study over a year and you've heard about this from Dr. Bahlis earlier today. But this is the recommended Phase two dose, this is the emerging toxicity profile, you can see except for nausea which where we have a third of the patients with grade two nausea, the rates of grade two side effects are very, very low and the rates of grade three and four adverse events are extraordinarily low. And in fact even with 12% and 6% thrombocytopenia, there were no bleeding events that were drug related here.

So this is an extremely well-tolerated regimen and it's great for the patients. They only have to come at the clinic once a week and they're able to really enjoy their lives for the rest of the week because they're done after Monday in terms of getting therapy. And this is really terrific when you have relapsed refractory myeloma or any myelomas.

This is a very nice regimen and I think, of course, as important is the fact that overall in 22 patients, we had a 77% response rate. And many of these responses get better over time. In fact today at the lecture you heard Dr. Bahlis mention a patient whose CR just arose from a very good partial response and that is a very nice asset for this particular regimen. So these can get better over time, but importantly, the drug showed a 67% response in patients whose disease was already refractory to Velcade and/or Kyprolis. And we believe these data are unprecedented for this kind of refractory population.

So selinexor can truly reverse proteasome inhibitor resistance, which is a growing and important medical need here. And in the patients whose disease was not refractory, they could have had exposure to a proteasome inhibitor, but if it was refractory, small number of patients but everybody responds and you're going to see that even in the expansion cohort with the very early data. So very nice efficacy here with deep responses as well as good responses and durable responses.

And this breaks out, the patients that will enter the BOSTON study, unfortunately we only got six of them onto this Phase one, two study, but of course all of them responded, and again with PRs, VGPRs and some complete responses.

And here is the swimmer plot where you can see that within one cycle, essentially every patient had a response except for two, one stable disease and a single progressive disease out of 22 patients, pretty remarkable when you think about patients with a background of four prior regimens.

We just opened an expansion trial. We have 10 patients on that study who are evaluable for efficacy and you can see that the patients that have non-refractory disease have already responded very quickly within the first cycle. This is only two months on therapy at this point. We've even got some of the patients who have refractory disease getting weekly selinexor and weekly Velcade who are responding within two months on the drug, again with very good tolerability and no progression events so far. So it's very exciting with this in terms of a progression free survival situation.

The data with Kyprolis which were presented today as well as by Dr. Jakubowiak confirmed that in patients that have Kyprolis refractory myeloma, we can still get 63% overall response rate including a quarter of the patients with very good partial responses. And we even get very good response rates in patients whose most recent regimen was refractory to Kyprolis, which tells you that it's not the selinexor and it's not the Kyprolis that's doing that; it's truly the interaction of the proteasome inhibitor in the selinexor that is leading to this 67% ORR in this patient population.

This has led us to the BOSTON trial. We've chosen Velcade because of ease of use, once a week dosing, subcutaneous administration and frankly going into next year when Velcade becomes generic, the cost of this regimen should be very competitive using half the dose of Velcade. And in combination this study will start in the early part of 2017, as I mentioned earlier, it's been approved by FDA and EMA and it will involve an SVd arm which will be the first Phase three trial that we're aware of where weekly Velcade will be used from the get go in addition with weekly selinexor and dexamethasone. So patients will be coming to the clinic 40% fewer times than they would on a standard Velcade arm. And in fact all of the approvals in combination with Velcade including with Dara in some of the on-going studies use twice weekly Velcade. We believe we can achieve the same or higher response rates with weekly Velcade which is good for everybody involved.

The control arm of course will use the standard twice weekly Velcade, but we do have another addition to this study which is unique, which is to have a crossover after the patients on the Velcade [control] arm objectively progress, we do allow them to cross over and both regulatory bodies have approved this. Again, this is will be the first Phase three study that we're aware of that allow crossover, making it a much more appealing study for lots of patients.

PFS is our primary endpoint, key secondary endpoints are standard and the statistical analysis is based on a rather conservative Vd arm of 9.4 months PFS based on the Endeavour study. Obviously some of the other studies had a shorter Vd progression. With 360 patients, we're hoping to enrol in this within about a year and a half and have data in 2019 for full approval in U.S. and Europe.

I just need to mention briefly, we also have combinations with Pomalidomide. This is a nice all oral regimen. The background of this patient population is similar to the Pomalidomide population that is dual-refractory or dual-exposed with most recently refractory disease. The expected response rate for Pom-Dex alone is about 29% to 30%, and what you can see here is a very nice side effect profile with actually less fatigue in this combination than you get with typical Pom regimens alone or selinexor regimens alone which run about 50% to 60% overall fatigue including a fair amount, more grade three fatigue than we typically see here and less of the cytopenias as well, and a response rate that is 60%, twice what you get for Pom-Dex, so very nice.

With some of the patients continuing on it, we've got some deep responses here and patients approaching the 10 month range on this study. And I mentioned already with the 60% response rate including very good partials and partial responses.

So with that, I just wanted to now move over and you've heard about the potential roles of selinexor in combination with many different drugs as well as its single-agent activity in myeloma and I want to invite the expert panel up which will be chaired by Dr. Auclair. And if you could all come up, we have Nizar Bahlis from the University of Calgary, Paul Richardson from the Dana Farber, Ravi Vij from Washington University School of Medicine and Dan Vogl from the Abramson Cancer Center in University of Pennsylvania and Dan from the MMRF, who's been a great friend and supporter, will be overseeing this. Thank you, Daniel.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Thank you. OK well, great to meet everyone and it's a pleasure and honor to be here tonight with you and we have a truly stellar cast to talk about where we are today in myeloma and maybe give an idea of the landscape of this disease and given what we've just heard about selinexor.

So maybe why don't we go around the table first and have you each introduce themselves.

Paul Richardson - ***Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research***

Hi, everyone. My name is Paul Richardson from Dana Farber.

Ravi Vij - ***Washington University School of Medicine in St. Louis - Professor for the Department of Medicine, Oncology Division***

Ravi Vij, Washington University St. Louis.

Nizar Bahlis - ***University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine***

Nizar Bhalis, University of Calgary.

Dan Vogl - ***Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor***

And Dan Vogl, University of Pennsylvania.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

So, you know, I'm from New England and an avid football fan and I like always to think that my role in many ways is kind of like the New England Patriots of the cancer world, right? No other team has won more in the last decade, but still this disease is far from being cured and there're still some real needs and real gaps here. So why don't we go around the table and ask what are these unmet medical needs that you guys can see today in multiple myeloma? Maybe first Paul.

Paul Richardson - ***Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research***

Yes. Dan, thank you very much. No, I think candidly, the important point to share with the audience tonight is that in myeloma, this is never a zero-sum game. I think we were in a therapy session at the close of today and there was a daratumumab frenzy of information and obviously having being very much involved with daratumumab's development, it was great to see.

But therefore it actually gives one a perspective, I mean we enrolled strongly to the [Fiber] one study, so we have a lot of patients who've been on daratumumab for some time. And just to share with everyone, we have plenty of daratumumab failure and I think the important message here is that we need all the drugs and what I'm very excited by and I've obviously known Mike [Kauffman] for so many years and the same time had the privilege of working with him through multiple drug development programs, really impressed this has come through. Novel mechanism of action and after some real challenges with toxicity early in this development, we're seeing some real progress.

So I think specific to tonight's discussion, the importance of having something with a completely novel mechanism of action to salvage patients after antibody failure is critical and at the same time obviously it's such an interesting target that I think bringing forward and developing further in combination will be very important.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Thanks, Paul. And yes, we'll get back to this idea of novel mechanism of action. How about you Ravi?

Ravi Vij - ***Washington University School of Medicine in St. Louis - Professor for the Department of Medicine, Oncology Division***

No, I agree with Paul that the penta-refractory is certainly an unmet medical need and I think it needs to be emphasized that a lot of these trials that have done and we say they were on patients who've had three lines of therapy and are refractory to only their last line of therapy, here, the refractory with each one of those drugs in different lines of therapy. So this is certainly an unmet medical need population. And I think high-risk myeloma defined by cytogenetics is an unmet medical need population. I think the elderly is still an unmet medical need population because we're not doing as well in the elderly yet.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Nizar?

Nizar Bahlis - ***University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine***

I guess I completely agree with Paul and Ravi. Again the need for drug that can overcome resistance to other classes of agents we use right now. We have Revlimid, we have Pomalidomide, they're pretty much the same anyway and we have Velcade kind of fills up again the same class of drugs, having a complete new approach to myeloma is very exciting. And it's important obviously to overcome resistance.

As Ravi also said, high risk disease is important that's why in my presentation today I did highlight the two high-risk myeloma that those two patients should have been dead a long time ago, but over a year still alive and doing well, so this is important as well.

Then the other important element sometimes we lose in the discussions is to have a drug that's easy to take for the patient – oral once a week is very important. Our population is elderly patients who often forget taking pills. They're actually patients that come back at the end of the month with three pills left in their bottle and you ask what happened to those, I don't know, I thought I took them. So having a pill once a week is very important as well.

And the other one is financial so to say, I mean it's important to be able to go back and reuse the drug we're currently using now becoming off patent. Velcade -- it's already off patent in Canada, I don't know about the U.S. Revlimid will soon become off patent, so to be able to combine these drugs with an agent that works will allow us to recycle those drugs is also extremely important.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Great point. Dan?

Dan Vogl - ***Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor***

So I remember being asked a couple of years ago what the biggest need that we had in myeloma therapy was and people were trying to think about do we need agents that are simpler to give, do we need more oral agents, do we need things with fewer side effects? And I think all of those are nice, but what I think we've always identified as a need is that we're not curing our patients and while it would be nice to have a cure, until we have that, what we need are more medicines with different mechanisms of action that we can use to get response after response after response. And we've gotten good at this in myeloma and our patients are now looking to us after they've been alive with this disease for 5, 6, 7, 10 years and saying "but what do you have for me now, because all of that stuff hasn't worked."

So I really think that having something that works differently and works is what we need. And if we have that, we'll use it.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Thanks. So in keeping a bit with the football analogy, you know, let's talk about compatibility, how well a drug plays with the rest of the team. And when you think about compatibility, what factors do you guys consider when combining various therapies for myeloma patients. Paul?

Paul Richardson - *Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research*

Well I think that's critical and I think was such a good move with Nizar's study which was to basically use bortezomib as a platform and combine it with selinexor. And I think the important message there is the results are quite remarkable. And what we're seeing is not only synergy in terms of activity, but we're also seeing this, I think, very important signal from side effect profile which is basically the drug is more tolerable. And so patients have been able to stay on therapy for longer and so benefit.

So my overall impression has been very favorable as a result of particularly the study in combination with bortezomib as well as the actually the signal with dexamethasone. So I think that, again, drug development is never easy, it's always challenging particularly now where we are in myeloma, I'd argue that novel mechanisms of action demand real thoughtfulness in terms of development of strategy, and I think that the fact that we now have a platform, an evidence that shows combination with bortezomib for example, which is the value proposition globally is really promising. So I think it's good news. And again, congratulations Nizar, really good work.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

Very well said. Ravi, any thoughts?

Ravi Vij - *Washington University School of Medicine in St. Louis - Professor for the Department of Medicine, Oncology Division*

I guess for combinability, you look at pre-clinical data of synergy, it doesn't always translate into what you see in humans, but you actually try to get that data, you look for non-overlapping toxicity. And sometimes you also look for some practical issues like oral regimen, also that how frequent the drug is given and how complex things get.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

Nizar?

Nizar Bahlis - *University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine*

Again, I completely agree with both of you as well, being able to combine without overlapping [toxicity] is very important and that's something that we thought about combining selinexor with Velcade is obviously a concern, but I was surprised actually the combination was better [tolerated] than selinexor as a single agent and I've had the privilege to use both as a single agent and in combination.

So that's very important because often myeloma is a disease of patients on average 65 years old and older so that we make sure the drug isn't toxic. And toxic not only about side effect but as far as ease of administration. As [benign] as daratumumab is to our patient, a lot of our elderly patients when they come to the clinic, they spend 10 hours in a chair waiting in the clinic on a weekly basis, so it's very important as Ravi, said having an oral agent as well is important.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

Dan, any thoughts?

Dan Vogl - *Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor*

Yeah. I actually think that one of the things that makes us really reassured when we're putting drugs together is to know that each drug on its own has its own anti-myeloma activity. And so medicines like elotuzumab and panobinostat which although they clearly improve progression-free survival when used on patients who are not refractory to the combination drug are turning out to have a little bit of a limited place in our armamentarium because a lot of times whenever patients who are really

refractory and we're looking for that combination that's truly going to yield a number of response, we know that those drugs don't have single agent activity in the extra oomph that you get from their combination sometimes just isn't enough to overcome resistance to the companion drugs.

And I think what we're seeing is there's no question that selinexor has single-agent activity. And then we've seen in the combination study that it clearly can in combination with the medicine that people are already refractory yield responses, and that always makes it easier and more appealing to do it in the combination.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

So I'd like to dig a little bit more on this last point, obviously single-agent activity is still important or is it. As you mentioned, drugs like elotuzumab don't have so much single-agent activity and what it's doing in combination with Revlimid and showed tremendous, expanded, increased activity. So is single-agent activity is still so important in this day and age. Or is the paradigm is slowly changing in myeloma and in cancer in general?

Paul Richardson - ***Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research***

Well it's a great question, Dan. I think it's complicated answer. I think has to just look at the science that underlies that drug. I mean, for example, elotuzumab makes complete sense. It's an immune-adjuvant. To expect it to do something on its own really demands it being used in a much earlier population. For example we saw that with smoldering myeloma. That's where we saw some activity as a single agent, not in the relapsed refractory setting where the immune system is essentially completely non-functional.

So I think in fairness one has to think mechanistically and scientifically. And I think Dan is quite right that in the context of the development of HDAC inhibition one of the challenges is being the absence of single-agent activity, but in fairness I think the HDACs are real.

We know they work and I will tell you I've had RVD pano [panabinostat] succeed in Jacob's trial when Dara has failed. So I think we have to be aware that this is not simple. So I think having said that when we think about selinexor in this extraordinary landscape of such complexity and of course the advent of the antibodies, we're seeing activity on its own. And when you put it together with the appropriate partners it's even better.

So I think it's good news, but I think we have to be careful about saying somehow that makes it in a very different category. Yes it does, but I also think it would be unwise to sort of suggest that these other drugs are somehow not useful because I don't think that's correct. But having said that, I think selinexor stands out because it has single agent activity.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Yes. That's a good sign especially --

Paul Richardson - ***Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research***

Exactly. Yes, exactly.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

It's quite active in penta-refractory [myeloma].

Paul Richardson - ***Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research***

Yes, exactly, absolutely right.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Anybody else, Nizar maybe or Ravi?

Nizar Bahlis - *University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine*

Yes, I agree with Paul that some single agent may have a role but I think a year ago probably Keith Stewart has published a paper looking at any myeloma drug that appears in the market and gets established as a myeloma drug.

The only ones that made it that had at least 15% if I recall the number correctly, single agent activity. And that's probably true, I mean, most of the drugs need to have some single agent activity to stay as a potential myeloma drug that we use. The exception as Paul mentioned are probably immuno-therapeutics because they may moderate the immune system indirectly by targeting the myeloma cells. So a single agent activity I guess is important.

And it allows you also to connect like was done with the Velcade combination with selinexor to cut back on the dose of the other drug, or the partner drug. And this will allow you to avoid some side effects because you can lower the dose of your drug, your partner drug I guess and minimize side effects.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

So we heard also a little bit earlier on the importance of novel mechanisms of action. I think myeloma may be more than many other cancers is one where drug development has been driven by modes of actions.

I think Paul and his team very early on for example, knowing that myeloma is a factory to make proteins especially all of the immunoglobulin stuff, well, if we do something to interfere with this mechanism of protein metabolism, maybe it will do something to myeloma. So I think it's more important than ever, but let's go back on this, maybe with regards to resistance or other importance of these novel mechanism of actions.

Paul maybe?

Paul Richardson - *Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research*

Well, no, I think that's what's so interesting about the mechanism of the SINE inhibitors or SINEs, rather, or SINE drugs. That essentially the thing that I really like is that it is completely novel and Mike brought this out very nicely in his talk and Sharon's work has been really ground-breaking.

But I think in that regard, this concept that these drugs influence the behavior of the guardians of the genome which is a nice term Mike used, I liked that, is really relevant because genetic instability in our disease is very real. Obviously the antibodies change that, but having said that this drug is particularly interesting in that context, and especially the synergy with other drugs.

So I think that as we think of mechanism of where this belongs, I feel personally that this particular class of drug has the promise of becoming a backbone. And I think that's the real point about the single agent activity, is that that's usually a signal then isn't it that we may have a backbone agent on their hands, which I think is, you've I think shown very nicely.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

Dan, any thoughts maybe?

Dan Vogl - *Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor*

On the mechanism of action in overcoming resistance?

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

And especially in myeloma right now where we are in almost 2017.

Dan Vogl - *Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor*

I think that having agents with clearly different mechanisms of action and being able to combine them together and seeing responses where you otherwise wouldn't expect them just makes it a lot more attractive for me to use the drug.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

And so, obviously selinexor is oral, we know that, we have a few myeloma drugs that are oral.

So what are your thoughts? We mentioned some of the advantages of oral drugs and oral drugs in myeloma. Again, as we think about where we are and almost 2017 how nice is it to have a novel agent which is oral that we can bring to the table?

Maybe Paul again first?

Paul Richardson - *Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research*

Well, obviously from a patient perspective it's huge and it's a once a week dosing which is an additional advantage and as Nizar pointed out that there is a role in the frailer patient. And we've seen the same experience like ixazomib and so forth and the appetite in terms of community practice or, ixazomib reflects that convenience I think. There's been substantial uptake.

Having said that not all oral drugs are the same, for example, I do agree with you, Dan, panobinostat, its quote, unquote, "use in the community has not been as robust as we had hoped for" frankly. So I think you're right, Dan, that the oral route is an attractive point but the critical thing about any agent is it's got to work. And I think that's I think what's so striking about this data.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

Yes. Ravi maybe?

Ravi Vij - *Washington University School of Medicine in St. Louis - Professor for the Department of Medicine, Oncology Division*

I agree that the proof is in the efficacy but being oral obviously helps.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

Okay. So I'd like now to maybe have you guys share a bit your thoughts about where we are from a regulatory perspective, what's the regulatory environment right now with regards to bringing new drugs to myeloma and especially I guess at the FDA level?

I know you guys have all been in front of the FDA multiple times in recent times, so why don't you share some of your thoughts about where we are right now to bringing new drugs to the disease? Paul?

Paul Richardson - *Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research*

Well, I think that this is an incredibly important point, Dan, and thank you for raising that. What sets selinexor apart is novel mechanism of action. And so, to be an effective inhibitor nuclear export proteins makes it really unique and that I think is a huge advantage. That's exactly what we saw with daratumumab. It's exactly what happened with elotuzumab. It's what's hopefully going to happen with other antibodies that target different epitopes and so forth. I think at the end of the day it's the novel mechanism of action that gives selinexor a real leg up. That's clear.

The other thing is isolating drug effect, in other words what does selinexor do that otherwise can't be attributed to other drugs. And I think that in that regard like in Sharon's strategy for accelerated approval and then having the confirmatory Phase three is very, very important. And so, from a regulatory point of view I think the way forward for selinexor is actually quite strong right now based on what I've seen.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Ravi?

Ravi Vij - ***Washington University School of Medicine in St. Louis - Professor for the Department of Medicine, Oncology Division***

Yes. I think that once again I personally feel the penta-refractory is an unmet medical need and possibly a way forward.

I think that otherwise the quickest way in my mind these days still is if you were there with possible synergy with pomalidomide and Dex, you can do Pom Dex, drug X versus Pom Dex, and that has the quickest readout possible. Otherwise I think in the future we should be exploring I think things like trying to target high-risk disease and trying to convince the FDA that it's getting difficult to now just continue along the same paradigm, especially if you have three drug combinations to make it a four drug combination to convince the FDA it's going to be even more difficult.

So like in CLL they've been able to target [disease with chromosome] 17p deletion. They've got a drug approved for 17p duration and we should be able to in the future do that. And then as we have further understanding of biology, hopefully at least for small subsets we will have bio-marker driven drug development as well.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Yes. And it's a great point actually, thinking back about some of the result we saw earlier, this idea that the high-risk disease is one of these unmet medical needs, 25% of patients not reaching three years often based at least on the Mayo data.

And looking at this earlier result we saw this patient having burned through all these therapies within four years. Maybe it is already a kind of a tantalizing sign that maybe something is going on even in these high-risk patients with regard to selinexor.

Paul Richardson - ***Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research***

Yes, Dan, I think that's an extremely good point because when you look at analyses of lines of prior therapy, that is a very important characteristic in patients to qualify. I think Mike did that very well because the essence is if you have 15 lines of therapy, your biology is likely to be very different and i.e., better. And so, that was what was so impressive to me about what we heard tonight.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Nizar, any point?

Nizar Bahlis - ***University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine***

Yes, a comment on something that Paul and Ravi brought up as well. Clearly we need something for penta-refractory today but I'm really thinking, this question comes up at every meeting we go to when we hear people presenting novel agents upfront first line.

I can easily see ourselves, myeloma community, in a few years from now we're going to be using daratumumab and probably carfilzomib kind of a little bit upfront to treat our patients, so when our patient relapse in even a second of therapy we're going to need to give them a novel agent. That's why the importance of the, I guess, the BOSTON trial, its early line of therapy combining Velcade, anyway, recycling Velcade with selinexor.

And today maybe we don't see the merit of the trial too much, but in three years from now I guarantee when all of us already use daratumumab and carfilzomib and Revlimid upfront and the patient relapses, we're going to need something to give them that's something different, something novel and hence the importance of this trial I think to be done.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

So maybe I will go through one last question and then I guess can we open the room for some questions, Michael or --

All right, let's do that. So one last question for this panel before we open this room for questions: What are the considerations in selecting therapies for your patient, pricing, convenience, if you could have the best of worlds, if you could, that would be the best thing you could have in selecting a drug and how would you go about doing so?

Paul?

Paul Richardson - ***Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research***

Well, I think the good news is certainly in the U.S. anyway is that whilst we're sensitive to cost, I think we have to be aware of the fact the best of value of our drugs is if they work because at the end of the day if your patient, the more the patient suffers the drug fails him or her and the patient suffers and dies, that is the least valuable drug. So at the end of the day we want drugs that work.

And frankly I'm very sensitive to this issue because there is this misunderstanding in the economics of things, I think we as physicians we need to very careful. Our job is there to advocate for our patients, number one. And the rest is secondary.

So I think in that context to have a drug that works, that's convenient, that has a manageable side effect profile, and offers the opportunity for rescue after major classes of drugs have previously failed our patients is absolutely essential. And that is why first essentially being involved in the laboratory side of things that the original work this was so appealing.

And so, I think that the excitement about selinexor is well placed. And I think today for example at the meeting, we've seen not only monoclonal antibodies do different things but most importantly we've seen selinexor stand out and venetoclax stand out. They are very different. And I would emphasize the point I made earlier, Dan, that this is never a zero sum game. The essence of it is you have to have all of these drugs available.

So I think selinexor is a brand new sort of basically different drug right there on the field right where we need it to be in penta-refractory disease. And I think Nizar nails it, you've got excitement around carfilzomib appropriately but also recognize that it partners so well with bortezomib. That's going to be a very interesting salvage strategy for the future of selinexor. So I think again I am very encouraged by what I am seeing.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Yes, maybe Nizar can bring to the (inaudible) team. Any thoughts on your end, Nizar?

Nizar Bahlis - ***University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine***

Again, I completely agree with Paul. The maximum value for a drugs is if it works, there's nothing better when your patients goes into remission and goes back to normal life. And I think if our funders and health agencies think about that, they will probably pay more upfront because the best way you can save money and health economics if one of your citizens was back to be functional, and they go back to work and not be paralyzed and being at home.

So I think it's extremely important but everything else you mentioned also we take into account, ease of administration, cost. I mean, again I practice on the other side of the border [in Canada] and again -- this is socialized medicine. And I think in the US you realize I mean it could be health economics that are challenging so you need to be able to use novel drugs but again not completely break the bank, I think is reasonable.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Dan?

Dan Vogl - *Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor*

I think we're lucky in myeloma therapy these days that we do have so many medicines that work. That creates lots of problems when you're trying to decide about sequencing of drugs, in the order in which you use them. And those are good problems to have.

But in the end I have a list of medicines in my mind that every patient with multiple myeloma should see at least once. And many of them end up getting used multiple times in different combinations, because maybe it didn't work in that combination but if it was well tolerated then there could be synergy that we see in a different one.

And I think what we're looking for is more drugs to add to that list, things that are, so obviously work and benefit at least some of our patients that they're worth trying at least once. And that we look at a patient and say I don't know if this next one is going to work, but it works for enough people and it's tolerable enough that we at least have to try it, and you can't say you've been through everything until you do this also. And I think selinexor has the potential to be one of those.

Michael Kauffman - *Karyopharm Therapeutics - CEO*

Agreed. So, Ravi, do you have a final word before we open the floor?

Ravi Vij - *Washington University School of Medicine in St. Louis - Professor for the Department of Medicine, Oncology Division*

No. I don't think I have much to add. I think that certainly efficacy, side effects, convenience, cost certainly is a thing that one considers, but that is a discussion on a different forum. When you have a patient sitting in front of you the only thing is can he afford his co-pay, after that I don't care what the cost of the drug is.

Daniel Auclair - *Multiple Myeloma Research Foundation - SVP of Research*

Okay. With this, questions?

Mike King - *JMP Securities - Analyst*

Mike King, JMP. I just wanted to ask the panel about a sort of kind of the very human emotion to dazzled by technology. We've talked about Dara today a number of times, the number of follow-ons CD-38s. I think read today that Sanofi is putting in CD-38 into trials, there's at least one or two more behind it.

We have some data last week from the BCMA [CAR-T cell] from bluebird [bio inc.], so it appears to me that the physicians in the community broadly are sort of tech freaks, they like the high-tech sexy stuff. And is that something that, is a phenomenon that you guys see and how does a company like Karyopharm kind of overcome that narrow bias?

Michael Kauffman - *Karyopharm Therapeutics - CEO*

So Paul is eager to answer that because I could see him twitching.

Paul Richardson - *Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research*

No, I'm so sorry no it's not true, I want to catch a plane, actually, that's something quite serious.

So, no, Mike, it's a great question. I love it. It's an excellent question as always. Thank you.

In our CAR-T programs I'd love the feedback especially from Dan because obviously they're on the forefront and spearhead of this. For 20 patients we put in to our CAR-Ts maybe two or three get in and get benefit. So we line up 20, we get two or three through.

Now remember you're not seeing denominators in that data. The data that you see today are numerators, not denominators, very, very important. And I think that that's the real opportunity and that Mike's team offer with selinexor. This is not a denominator issue. You're seeing a intent to treat analysis which is very important.

Now I think having said that that's not to diminish the value of CAR-T and that's not my point. My point is it's a niche business in my view. I mean I've referred multiple patients to CAR-T and I've only got one through. That's a relevant point.

We were a leading enroller into the BCMA program that you heard about from Adam today which is a great presentation of our work with the BCMA antibody and I think Hesas asked the key question, which would you want your relative to have, the monoclonal antibody or the CAR-T? But the idea is obviously of the option of both.

Again, selinexor is different. We're looking at something quite separate. So I think again, Mike, that the bottom line is the technologies are sexy, but let's be careful because at the end of the day also our case. Let me give you our case.

[This patient's treatment] was actually published by your team who took great care of her in the New England Journal [of Medicine]. She got CAR-T therapy. Do you know how long her remission was? She was published in the New England Journal and the Parade Magazine as the cure for myeloma.

Do you know what her remission was?

Mike King - ***JMP Securities - Analyst***

One year?

Paul Richardson - ***Dana Farber Cancer Institute - Clinical Program Leader and Director of Clinical Research***

No 10 months. I know that. I looked after her. And the fact is we salvaged her with radiation and a monoclonal antibody. Do you know where she is going to go next if I can persuade the powers that be, she'll get selinexor.

My point is, and she was paraded as the cure which was not a good article in my view when they say it so candidly. But the fact of the matter is, no, no, because it said she was the cure, the mouse that roared. But the reality is she was part of cohort of 10 patients. She was one of the 10 that responded, nine others didn't, and that was an uncomfortable feeling for me as a clinician. I guess the article did not say that frankly. So I think we have to be very careful and I think the technologies are one thing, the reality is another.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Anybody else wants to tackle that question?

Dan Vogl - ***Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor***

I was just going to say that I think daratumumab in some ways is a special case that gave us a treatment that has a really nice single agent response rate and almost no side effects. And the main downside is a long intravenous infusion and maybe we've got a way around that. And we would love every drug to be daratumumab but most of them aren't. They all have their downsides.

But even with daratumumab it's not a cure and our patients are all relapsing after daratumumab. And as sexy as CAR-T cells are, at least so far we have not made them work for every patient. The data that we presented now, yes, we had a couple of amazing responses. It's clear that they can work for some people. And probably as we go through iterations of the technology we'll get better and better.

But we also haven't clearly cured anybody, even our best BCMA CAR response still has a low level of residual disease, and it's likely given what we know about myeloma that at some point that will relapse as well, and that patient will need something else to bring them back, and could it be that a BCMA immune-conjugate will work then?

Adam Cohen afterwards said if he had to choose for his relative what would he pick, he'd pick both. Maybe not together, but one and then when that doesn't work try the other one because that's how we deal with myeloma these days where you try one thing. And even when it works we are pretty sure that it's going to at some point stop working.

I think the market will change when we come up with a treatment that works and cures people, and then we'll really have to, we'll all be in need of other jobs at that point. But until that one comes, I think that the market will say that we need more and more drugs to be able to string these responses along for even longer.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

So what you heard is that sexy is nice but there's nothing like reliable or small molecules like selinexor. Other questions?

Mike King - ***JMP Securities - Analyst***

Can I just ask a quick question,:are we in an era of MRD in myeloma now or if not, how far away are we from using MRD as an outcome measurement? Thank you.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Who wants to tackle that one? Ravi maybe?

Ravi Vij - ***Washington University School of Medicine in St. Louis - Professor for the Department of Medicine, Oncology Division***

Okay. Well I think it's certainly a thing that is increasingly being looked at in correlative studies. But it is something outside of a context of a clinical trial it's probably not ready for primetime use.

It is prognostic but we don't know what to do with the information in terms of informing decisions regarding therapy, whether to escalate or de-escalate based on that information is I think what we need to ultimately find out to give that test the clinical utility.

Nizar Bahlis - ***University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine***

The comment about having sexy drugs. Yes, you're right, it's appealing to have one target to go after it, but if you think about myeloma none of the drugs that we are using in the clinic today are single targeted, sexy target, why, because myeloma cells are extremely smart. And if you go at them into one approach they will outsmart you very quickly. And that's why all these novel agents as pure and as clean as they are the response don't seem to last.

I guess selinexor's advantage, Sharon I guess really banged me on the head by inhibiting this nuclear transport protein. As Michael mentioned you are affecting multiple, multiple pathway that cancer cells depend on. But at the end of the day even Revlimid affects multiple targets or bortezomib does the same way. So having a drug that can work on multiple pathways rather than a single molecule is still important in this area, especially in multiple myeloma.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

So we have a couple of questions here in the back, who has been patiently waiting I think right there. Anyway, go.

Brian Abrahams - ***Jefferies - Analyst***

Thanks. Brian Abrahams from Jeffries. Two questions. On the BOSTON trial design do you think Vel Dex is a reasonable, enrollable control arm just given the number of options that you have now today in patients, doublets, triplets in patients with one to three prior lines of therapy?

And then on the STOMP study I know responses tend to be rapid here, if you look at the spider plots of the expansion study at [selinexor] 100 mg Q weekly, at what point would you expect some of these M Protein reduction to convert to partial responses? I guess I'm trying to figure out if it's looking as good as we saw in the first

part. Maybe the Company or the investigator could comment on whether the responses in the initial part of the study were comparable with this go-forward dose as with the other twice weekly doses.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

So let's start with BOSTON, Nizar?

Nizar Bahlis - ***University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine***

Sure. I'll start with the BOSTON concept. If you think about the two sides that you heard about today - the CASTRO trial [with daratumumab] just closed within a year. The control arm was Velcade dex twice a week in limited cycles, and it did extremely well. Because if the health agencies and physicians still think Velcade dex is a control study and will always refer as a standard we have to improve on.

Now, if you're asking is Velcade dex is a standard and efficient doublet, I mean, any doublet is that the right thing to do now in any single patient. While the answer is probably, but is there still a role for a doublet with some patients? Absolutely yes as we heard today from the Pollux trial. Some patients with Rev dex they're doing extremely well just with Rev-dex.

And even in the CASTRO, trial some patient with Vel dex I mean there were probably 20% of the patients still doing well. But this is a benchmark that we set for ourselves since the – I guess Michael – in the original Apex Velcade trial that we have tried to improve on from that standard. So I think the study will accrue pretty well.

Regarding the STOMP trial and you saw my talk earlier today, I put on purpose these two cases, described them in details, will get lost in the small phase one, phase two [trial], the efficacy you see that doesn't get accounted for when you report just median PFS or median response rate.

And I think it's back again to Michael when bortezomib was initially designed. I don't know if you know, but there was only patient responding to the large phase one trial happened to have myeloma. If it wasn't for the keen observation of the investigator, it would have been lost.

So some of these patients that you say, okay, response is slow, we want to see what those patients, again, we don't capture this data, what happens to them when they go to the next therapy? I can tell you like one of those patients actually, the initial time for response was short and progressed very quickly. This patient went after that on daratumumab Pom Velcade combination and he still died.

So I think the data will look as good as the initial cohort. When the numbers are small there we get nervous that, oh, what's happening here? One of those PRs you saw today is very close to a VGPR, one of those MRs is my patient. She's going to be a PR actually, but remember with the PR to have a confirmed response you need two cycles, and most of these patients only get two cycles.

Actually I was talking to Jean [Richard, Karyopharm] that some of those patients I should put unconfirmed PR or unconfirmed VGPR, but I said, no, let's not do it because it's too early. And I emphasized that. Also I made the point in my talk today that this is a very early follow-up. I mean there's only two cycles that this patient has received. And to have a response to myeloma you have to have two parts assessment before you put response rate.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Any other talks on the panel on either BOSTON or STOMP, Ravi or Dan?

Dan Vogl - ***Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor***

I think that there's still enough patients being treated both in the United States but especially around the world with bortezomib and dexamethasone as a doublet for relapsed myeloma. That is a very reasonable comparator arm and that is still accruable.

At the University of Pennsylvania we don't treat enough patients in our center second line to make it as able to accrue to that. But out in the community our doctors do that all the time, and so, I think that there's definitely pathways to accrue well to studies like that. And I think the daratumumab study made that very clear.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Great point. I think that maybe one, go ahead, Michael.

Michael Kauffman - ***Karyopharm Therapeutics - CEO***

One of the things that we've heard feedback across the world actually on this one is very similar to what the question, along those lines but having the cross over is a fundamental change in the way that people view this study. And the reason we're able to do that is because of the 68% response rate that we saw in patients who already had PI refractory disease in the STOMP study. Now on both arms, patients can get the experimental therapy. And it really is a fundamental difference. And I think patients across the world, we are hopeful that they will be interested; with the feedback from physicians are very glad that we have to cross over. And this could really change the dynamics of accrual to the study and make it far more acceptable even in some of the prior studies.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

So maybe one last question?

Unidentified Audience Member

Your patients are very fortunate to have you as physicians and have access to a lot of drugs. How does what you do translate into real world experience in the community setting vis-a-vis the different agents that are available to treat, because my personal experience having helped a lot of patients get access to drugs is that it's not a straightforward as coming to one of you as when you are in the community setting.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Thank you for that question. They are indeed an incredible team. The myeloma community in general is just fantastic.

Ravi maybe?

Ravi Vij - ***Washington University School of Medicine in St. Louis - Professor for the Department of Medicine, Oncology Division***

No, I think with the proliferation of drugs there is actually a greater need for education in the community because they do not know how to sequence these drugs. And I think that education will format the CME and the non-CME. And the way to make that happen in the community each physician has at most a handful of myeloma patients and you can't even expect them in this era of it's rapidly changing. Therapy is not only in myeloma but all different kinds of cancers to keep up.

They can barely keep up with the trends and the major cancer is breast cancer and colon cancer, and lung cancer and prostrate cancer. And so, you can't blame them for not knowing what to do with myeloma.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

Any last final words at this point?

Dan Vogl - ***Abramson Cancer Center Research Unit, University of Pennsylvania - Director, Assistant Professor***

I think there's increasing recognition among community oncologists that this has gotten to be a complicated enough space that they generally need help. And so, I think probably the vast majority of myeloma patients at some point see not one of us in particular but one of us in general. I think most of my patients have more than one oncologist. They have their community oncologist who they see on a day to day basis and come to see me a few times a year and we're able to bring that expertise out to them and help shape their treatment.

Nizar Bahlis - ***University of Calgary, Southern Alberta Cancer Research Institute - Assistant Professor, Department of Medicine***

Just maybe I can make one comment, I mean the reason I am excited about this compound. I'm also a scientist besides being a clinician and probably more a scientist than a clinician.

When I've got my hand on this component from Sharon, any drug that kills myeloma cells in the tissue culture at the nano-molar concentration, that's a winner. I haven't seen any drug that kills myeloma cells unless it's I guess arsenic. And even though arsenic did work actually we were not -- This went on my first research with arsenic.

I mean I'm going to call it KPT but selinexor kills myeloma cells in that nano-molar range. And regardless of what cell lines you treat. And that's always a very good sign. And what other drugs have done that before, Velcade did that before, venetoclax does that in selected population, subset of myeloma cells.

But yes, selinexor got my eyes wide open and I stared emailing Sharon and Michael right away, I want to do a trial with this drug. And lucky they were thinking along the same lines so things are aligned very well. So it's a definitely exciting drug. And nothing will make me happier than see it come to fruition and be approved because I think it would help our patients eventually.

I will learn more how to use them in the future, what to combine with them in the future but I think there's definitely a place for this drug in the myeloma field, and probably many other malignancies, not just myeloma. Like myeloma is, at least what I have seen myself in the labs is impressive.

Daniel Auclair - ***Multiple Myeloma Research Foundation - SVP of Research***

So we call that dropping the mike, ladies and gentlemen. So with this, a good round of applause for our panelists, please.

Well, thank you so much and I hope you enjoyed and a great rest of the evening.