Managing Myeloma

Targeting B-cell Maturation Antigen in Relapsed/Refractory Multiple Myeloma: New Findings in Clinical Context

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Dr. Orlowski: Good evening. I wanted to thank all of you for joining us for this event *Targeting B-cell Maturation Antigen (BCMA) in Relapsed Refractory Multiple Myeloma: New Findings in Clinical Context.* I also wanted to thank the folks in the audience who are watching on the internet in simulcast and wanted to encourage them to also submit their questions online as well as those of you who are here live because we have a really great panel to ask questions about this area.

Here are the faculty, we have Nina Shah, who is over at the University of California, San Francisco, who is a top-notch immuno-therapist and cell therapist in the clinic. We have Nikhil Munshi, who in addition to being a great clinician also runs a wonderful laboratory group and has really pioneered a lot of great things in multiple myeloma preclinically, and I am happy to serve as the moderator for this event as well.

So with that preamble, I am going to turn the podium over to Dr. Nikhil Munshi, who is a Professor of Medicine and Oncology at the Dana-Farber Cancer Institute and he is going to give you a presentation about why we should be targeting BCMA to begin with, and I cannot think of anybody who would be better at that than he.

Dr. Munshi: Thank you so much, Bob. It is a pleasure being here and discussing this very important topic. As you will see at the end of this whole symposium that the center of myeloma is BCMA currently, and of course it changes but right now we will all focus on it. Let's talk about BCMA as a target in relapsed refractory patients.

First, if you look at the population that we are targeting here, that population has changed quite a bit in the last few years and it is mainly because there are so many new

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developments in myeloma. In the last five years there are five drugs that have been approved for this disease. If you look at patients who are newly diagnosed, the response rate with the three-drug regimen let alone four-drug regimen reaches 100% with almost one-third of the patients achieving complete remission. If you look at the changes over time, patients are living much longer, instead of a median three years now the survival is eight to ten years and increasing by the month. So, a significant change in this patient population.

When the patient after the initial treatment relapses, we have many, many options. We have three proteasome inhibitors, we have three immunomodulators, we have two antibodies, and then an HDAC inhibitor, an alkylating agent, the most recently approved exportin inhibitor, and then there are many other existing drugs. Together there are almost 15 drugs we can use to treat myeloma. Many more in the research setting, and that is going to be the focus for our discussion today. All these drug can be used in some formulation combination as a two-drug, three-drug, and sometimes four-drug regimens. So many, many options are available and there is a method to the madness in terms of how do we pick it. It goes by personal biases, but also goes by some other features. So when you have a three-drug regimen, we can look at whether the patient has a pre-existing neuropathy, has the patient relapsed and/or been responsive to a proteasome inhibitor or immunomodulator, do they have preexisting cardiovascular disease, do they prefer oral drug versus IV drug, insurance coverage versus not, and all this goes into deciding which combination should be the first, second, and third in the relapsed/refractory patient population.

However, we know that most of the patients, if not all, do relapse at some point and they do relapse because of presence of the residual disease. So on the left side you see the various level of responses, and you could see that deeper the response the longer time to progression, which is well known. If you get MRD negativity that is better than just getting a CR, and the patients relapse but they relapse at a later time. And in the interim the other consolidation are maintenance treatment, which also drives what treatments we use in relapsed/refractory patients.

However, something that is very clearly known is that when patients relapse their survival is less than what they started with. So if you look at patients in the initial relapse, their overall survival is around 36 months and the progression-free survival is 13 months. However, if the patient has a refractory disease, then the PFS becomes five months, OS becomes 15 months, it shrinks over time. Very clearly if you look at the number of months on therapy from the first regimen to the second to third, it very dramatically decreases. From five coming to almost two cycles, and you can see the percentage of responses go down. So in the subsequent line of treatment patients have lesser duration of response and lesser frequency of response, and these numbers are quite important because as you see the data that is going to be shown after my talk, where does these two months of response duration compare to one of the newer treatments which are under development with BCMA as a target.

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Now, we had performed, this was around 15 years ago it really looks like all these and we used to do the DNA microarray and we are looking at gene expression profile in myeloma cell and trying to find out what is unique in myeloma. We identified 57 genes to be uniquely different within myeloma and normal plasma cells. And then factored in a lot of functional significance, what is expressed on normal tissue or not, what is really myeloma specific, not normal plasma cells were not included but not any other cell type. We identified nine targets which we have followed in the lab to look for developing some vaccination strategies. One of the top ones at that time was BCMA and that has now born the fruits which is what you will hear today, that it is one of the very important targets. The reason that it is important is its specific expression on myeloma cells. You could see this expression starts in germinal center B cells, late B cell population, plasma blasts, and then mature plasma cells. That is where it is predominantly expressed, and the ligands for it are APRIL and BAFF, and that leads to significant signaling, leads to myeloma cell growth and survival for the long-lived plasma cell. There are two components in normal plasma cells, it helps with the Ig class switching and antibody production, and supports the survival of these long-lived plasma cells. Plasma cells live forever in the body, those were memory cells. But it translates into a not so good thing in myeloma. It provides proliferation signals, survival signals, and also the soluble fraction of BCMA which is produced, it represents a number of things about the disease biology and disease phenotype. This being a TNF receptor superfamily member, it has specific functions in regards to cell signaling. As I mentioned, the BAFF and APRIL are the two molecules, leads to signals which targets NF capability, which targets MAPK and ERK pathways and eventually leads to various function including class with long survival and they are driven by which of the ligands are used. Whether it is BAFF assays predominantly used, or APRIL is used. But almost all the cells are positive and by multiple method it has been shown that myeloma cells express BCMA irrespective of its characteristics, differentiation, or proliferation phenotype.

Now, when we look at all other cell types and these are the three very common myeloma-specific targets for which drugs have been developed, this is elotuzumab, very predominant in myeloma, this is CD38, also daratumumab and newer antibodies. There is cetuximab and other coming about myeloma as a top target and you could see that BCMA very similarly is the top target for myeloma cells and mainly expression in B-cell malignancies to some extent, but nothing else. It much even cleaner than these two well-validated targets. Now, soluble BCMA that comes out of the cell are expressed and detectable and you could see that they are significantly elevated in myeloma cells. A little less in smoldering and then it is much lower in healthy donors. The healthy donor soluble BCMA comes from normal plasma cells because it also expresses the same molecule. If you look at what is the impact of soluble BCMA on outcome and survival, you could see that when the level of BCMA is below the median the PFS is better compared to higher than median, and the same thing goes for overall survival. So do low BCMA predict for better outcome in this patient population? You could see 9 versus 3.6 months and 155 months versus 98 months, so a huge big difference when the level

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is high and it may indirectly reflect the disease biology but quite importantly it also reflects the disease bulk, the amount of the plasma cell burden that may be present. The soluble BCMA really tracks very well with the M-protein, we measure the immunoglobulin, we measure or light chain. We can see that both of them, the red being soluble BCMA and blue being M-protein, they are both move very similarly in this four-patient example. This is seen across every patient population, and so the important part is that we can also now begin to consider soluble BCMA as one of the molecules to measure the disease. When a patient is non-secretory we do not have much to follow, we can use BCMA for following the disease burden in response to the treatment. It is elevated in all plasma cell disorders, modern active myeloma compared to MGUS. The baseline level predicts for response to treatment, and changes in soluble BCMA may be a biomarker or the myeloma tumor marker for practical purposes. It enables us to look at patients who are non-secretors, also for clinical purpose, and hopefully they could be included in our investigational protocols, and they both have a connection with PFS and OS, so soluble BCMA baseline level can predict the outcome. Its level is independent of renal function, so any patients with renal failure, it can become a better biomarker and it may have something to do with level of immunodeficiency patients may have. So we may have to keep that in mind.

Now BCMA being so myeloma specific or plasma cell specific it has now become an important target, and there are four different angles that are being applied for targeting BCMA or using BCMA as a target to kill myeloma cells. One of the important one is BCMA BiTE. I will describe that in detail. Also BCMA TNK related antibodies that can be utilized. BCMA is very important target for CAR-T cells, and BCMA related antigen drug conjugates are also important target, and then BCMA is also used by developing adaptive T-cell therapy or T-cell responses using peptide as a mechanism.

So if you look at first the ADC, the one which is going to be described is the BCMA conjugated with auristatin. So this drug conjugate specifically delivers auristatin to myeloma cells and it provides a number of things. Auristatin is a very important molecule to induce apoptosis. So when antibodies bind to myeloma cells it releases auristatin in the cells and kills myeloma cells. It kills through signaling molecule. It kills through direct apoptosis which is most common and also releasing of some of the lysosomes and other molecules. Very important killing of myeloma cells. The second effect of the conjugate is that it also induces antigen-dependent cellular toxicities, so it leads to ADCC-mediated myeloma cell killing through again multiple mechanisms including one that involves macrophages and leads to myeloma cell killing. There is a dual killing which leads to greater amount of cell kill.

Tai and our group has done and published a few years ago results in vitro preclinical results using this antibody and shown that there is a significant induction of apoptosis both in myeloma cells and myeloma cell in presence of stroma, but no on the stroma cells. So the cells which do not carry the target are not killed by this molecule. Again, you can see also the same molecule leads to killing by ADCC and you can see

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apoptosis in primary tumor cells. If you look at more focus on the multiple patient tumor cells, the molecule itself has a significant killing, the free drug has a killing, but the antibody itself has a limited amount of efficacy. So the BCMA ADCC kills the tumor cells very, very effectively and this is what Tai's work was. Now this drug has been taken to clinic, keeping focus on its cytotoxic activity the effects on ADCC as well as its stable presence when injected in the patients, and these four mechanisms are used to look at how does this drug affect the treatment. It is a phase 1 study. I am not going to show the data because that is what my colleagues are going to show, something about this phase 1, 2 study. But suffice it to say that the results are exciting enough that this is going to be one of the important molecules to be looked for for approval in next couple of years as the phase 3 study is already on the way and the results are expected in some near future time.

The second way of targeting BCMA is the BiTE. What it means is that it is a bispecific antibody. One component of antibody would target T-cells, the other component of antibody would target myeloma cells, bringing these two cells together so that T-cell is able to now kill the tumor cells. It is a very well-known old concept but now it has come to practice in recent past for lymphoma but also for myeloma using these kind of conjugates. The linker here, the whole molecule has one end that is a monoclonal antibody that is targeting CD3 which is present on the T-cells. The other end of the molecule is a monoclonal antibody which targets BCMA, and there is a linker which connects these two. So this is the whole molecule or the BiTE. When T-cells are present by themselves the BiTEs do not have much activity, but when the myeloma cell also is present then it brings the T-cells, plasma cells, conjugates them, leads to toxicity, killing tumor cells, also providing signals to T-cells to proliferate. So there is an increase in T-cell number to some extent and also killing of the plasma cells. This is the whole concept. The molecule that is in clinic is AMG 420 which is exactly the molecule that I described here.

Now again, Tai in our group has done part of this assay and this study and what basically chose is that in presence of the BiTE molecule there is a CD4 T-cell and CD8 T-cell mediated myeloma cell lysis as described in the cartoon here. It leads to apoptosis, the immune related apoptosis, by showing here by annexin V expression. In mice, no effect of antibody alone but when it is a conjugate BiTE, when the BiTE is infused, 4 out of 9 mice had disappearance of the tumor increasing their survival. So it is stable in mice, it provides anti-tumor activity.

This has led to first-in-human evaluation of this molecule AMG 420, patients have received up to 10 cycles and have shown very impressive results which again you will see very soon based on all these preclinical data for the activity. And finally, the last and the most important component of BCMA, most well-known is it is used as a target for CAR-T cells and so for those of you who may not be so familiar with CAR T-cell it is a method where patient's T-cells are obtained and then using a viral vector the T-cells are transfused which leads to production of this chimeric molecule. This molecule

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expresses the BCMA-containing component on the surface, binds to the tumor cell, and leads to apoptosis of the tumor cells. At the same time, the CAR-T cell itself divides further. So there is a tremendous growth of CAR-T cells at the same time killing of the tumor cell, and this is the whole concept of how CAR-T cells function.

I mentioned four CAR-T cell studies here. There are 20 CAR-T cell BCMA target directed studies done across the world, mainly in United States and in China, and they all have shown very similar result, of very significant, very quick activity and I think you will hear a lot about this CAR-T cell approach, the activity, the toxicity, and how to manage that. One important fact I would like to bring about is that all myeloma cells express BCMA. In this particular study when BCMA receptor density was measured, it varied from 387 molecules to over 4000 molecules. In a separate study when this particular BB2121 CARs were evaluated for their efficacy, a cell line with 222 BCMA molecules was quite effectively killed by these CAR-T cells. So this tells us that even the lowest BCMA expressing myeloma patient cell are good target for these CAR-T cells, and so we are to keep in mind that there are studies done to look at the expression of BCMA, and not the expression of BCMA, in the end every patient is a potential target for BCMA directed therapy including CAR-T cell therapy.

Then finally, the evolving use of BCMA is into developing a peptide-based vaccination. So Jooeun Bae and group has developed an HLA A2 targeting BCMA peptide and using this peptide we can generates T-cells which can very effectively kill the tumor cells. She has looked at it in myeloma cells. She has looked at smoldering myeloma. She generates the BCMA directed T-cells using this peptide mainly for HLA-2, now she has for HLA-24, and using this we can generate T-cells. We can use the peptide and the proposed study would be something to the effect that patients can be vaccinated, T-cell can be obtained and generated for peptide-specific or BCMA specific T-cells which can be adoptive or transferred or vaccinated further for clinical efficacy. So we can have peptide based vaccination studies that can come up.

Dr. Orlowski: All right, so thanks very much Nikhil that was a great presentation as expected and gave you a great rationale for why BCMA is such a wonderful target, and I get the opportunity to tell you a little bit about some of the clinical trial data with the various therapies that you have heard about. Mostly I am going to focus on the antibody drug conjugate which you saw a little bit on the bispecifics and then a lot more on the CAR-T cells because that is where a lot of the data are. The GSK 916 which you saw from Nikhil's group that they validated preclinically by the way is now called belantamab mafodotin. The data in the clinic comes in part from a phase 1 trial but had a number of different dosing cohorts. If we look at the patient population here you can see that these are folks that had a lot prior therapy, a 100% of them had gotten proteasome inhibitors and 97% were PI refractory, 100% had gotten IMiDs and 91% were PI refractory, and a lot of them had had daratumumab and were daratumumab refractory as well. So a difficult patient population in terms of few remaining therapeutic options and yet here

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you can see that the overall response rate was 60% with quite a few very good partial remissions and a couple of complete remissions as well.

If you look at the subgroup data, this shows you a graph of the response rate and you can see that different age groups did not really matter male or female responses were the same. I think the one area where there was a lower response rate is in patients who had had daratumumab before and this is an emerging concept in the field that we saw from last year's annual meeting of ASH where patients who have daratumumab refractory disease have particularly aggressive myeloma. The toxicity data are presented here. The main thing to note is that there are very few grade 3 and grade 4 toxicities, for example compared to other monoclonal antibodies there are very few infusion reactions. The administration usually is without corticosteroids. It is an IV given once every three weeks. The major things to watch out for, and you will hear a lot of this from Nina, is about thrombocytopenia as well as corneal toxicity where you can have blurry vision and other changes in visual acuity.

More recently, there were updated data presented about this study and published. You can see that in some patients they are able to stay on this for two or three years in some cases, and that shows you that not only is there a high response rate but the durability of the responses are quite good as well. And here you can see the progression-free survival which are around seven to nine months in range, which is very good for patients who were essentially what we would call quad- or penta-refractory, meaning that their myeloma had progressed on two proteasome inhibitors, two IMiDs and daratumumab, and here is the duration of response, so those patients who benefit have a long-term benefit, not just for a couple of months and then progression.

Here is a little bit more about the toxicity, I mentioned earlier that there is blurry vision, 52% had that at one grade or another, 43% were grade 2, and 3% were grade 3, 37% had dry eyes, and 29% had photophobia. I did want to mention that there are other antibody drug conjugates targeting BCMA that may be coming to the clinic as well and we at last year's ASH had a presentation on a different molecule called HDP-101 that has amanitin attached to a BCMA antibody, and you can see in the right column that the mice that got treated with that are quite happy with no myeloma, whereas the other sad mice in the left and the middle column have quite a bit of myeloma.

Moving on to the BiTEs which you saw Nikhil present the rationale for where you essentially bring a T-cell and activate it right next to a target and in this case a myeloma cell, and you heard about AMG-420 which is the first BiTE that we have substantial data about in myeloma. You did hear that this is a continuous infusion given over a four-week period followed by a two-week break, and the data that I am going to present to you were from the recent ASCO meeting where there was an update of 42 patients with up to five cycles of therapy allowed, although you could continue beyond that if there was a feeling that there was a clinical benefit. You can see the median prior lines of therapy in these patients was 4 with a range of 2 to 13, so these are patients that probably were

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not quite as refractory as the people who got the ADC, so that is important when you are comparing the responses. But here you can see that 70% of patients at the recommended dose which was 400 mcg, 7 out of 10 patients had responses and those included MRD negative complete remissions. Not only are you getting a high response, but the depth and quality of the response is quite good, and you can see median time to response is only one month, so you get a very rapid response as well, and you can see three patients completing 10 cycles, so like the ADC there are people who can stay on this regimen for quite a good period of time. In terms of some of the toxicities, I mentioned in the middle bullet point that 400 mcg per day was what was recommended for further study and the dose-limiting toxicities included grade 3 peripheral neuropathy, although that later did get better. At higher doses, there was cytokine released syndrome and Nina will tell us all about what that looks like and how to manage it, but it is a complication of both therapy with BiTEs as well as with CAR-T cells. There also were some infections that were seen in these patients, and remember that these drugs are not just killing the myeloma plasma cells but also the normal plasma cells because they also express BCMA, so it is not surprising that there may be some immune deficiency occurring as a result.

Here again are the safety data in a different format. You can see cytokine release syndrome in 16 out of 42, or 38%, almost all of those were grade 1, but there were some that were grade 2 and grade 3, 31% of patients with infection and 5% with peripheral neuropathy. Moving on now to CAR-T cells which again Nikhil gave you a great rationale for using. The first study that reported this came out of the National Cancer Institute and you can see in this PET scan in one of the patients who did particularly well, on the left you have got a patient with lots of bony involvement in addition to the expected positive uptake in the brain as well as in the kidneys and the bladder, and on the right two weeks after treatment in the same patient you can see just the normal expected physiological uptake, and there were other patients that did well including a stringent complete remission and a couple of very good partial remissions with this particular construct.

That launched the BB2121 study and these were data presented and published earlier this year in the *New England Journal of Medicine* by one of Nikhil's colleagues in the Harvard System, Noopur Raje. You can see that this was a phase 1, so there were patients who got dose escalation with lower doses of cells to start with and then moving up in the dose, and then there was an expansion cohort which included patients who got the dose that was recommended for further study. The main thing to look at here is that these were patients who were quite a ways out, meaning they had lots of prior therapy. You can see 58% in the expansion cohort had high-risk cytogenetic therapy previously, also a large proportion having prior stem cell transplant. Here you can see 100% of patients had bortezomib, 92% had carfilzomib, all of them had lenalidomide and pomalidomide and all of them had daratumumab and the vast majority of them were refractory to all of these drugs. So really people who would not have had very many other options at this time.

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The response by dose is shown here and you can see that as you go up on the dose, especially over 150 x 10^6 CAR-T cells you start seeing 63%, 80%, and even 100% response rates, and you can see from the swimmer's plot that many of these responses were quite durable and many of them were complete responses as well as some very good partial remissions as well. In looking at the subgroup data, once again the overall response rate is quite consistent among different groups, although the higher-risk cytogenetic patients down at the bottom had a slightly lower response rate and here you can see the progression free survival again if you got at least 150 x 10^6 your median progression-free survival was almost one year at 11.8 months, whereas it was much shorter if you got some of the earlier dose levels.

Here you can see information about cell expansion, so these cells really as you heard from Nikhil once they find the tumor antigen against which they are directed they proliferate like crazy. Their numbers go way up and then they do persist over time, but then as there fewer and fewer tumor cells for them to detect, the persistence does go down below the limit of detection. In terms of toxicities which again you will hear a lot about from Nina, and these are a little bit mixed because all of these patients also get cyclophosphamide and fludarabine as a lympho depletion because although the patients do get their CAR-T cells that are autologous, the CAR itself is a new protein and therefore could be antigenic, so the immune suppression or lympho depletion reduces the chances of early rejection, if you will. You can see hematologic toxicities which include neutropenia, which would be expected considering the therapy, but when you get into the GI and other effects there is not that much, and cytokine release syndrome although it was seen in 70 or so percent of patients overall, most of those were grade 1 or 2 with only a couple of grade 3.

Another large data set for targeting BCMA with CAR-T cells comes from the Nanjing Legend folks from China who they have now teamed up with the Janssen folks, and the main difference between their CAR and the typical CAR is that it actually has two different binding domains for BCMA and may therefore have some theoretical advantage compared to a CAR that only has one binding domain. Like other studies, essentially you screen patients, you collect their T-cells, you do some kind of lympho depletion. Here it was mostly single agent cyclophosphamide, sometimes you have to do a bridging therapy if their myeloma is really growing very rapidly and they cannot wait because it can take up to four weeks to manufacture the cells, and in this case this study gave the cells in divided doses, although in a lot of the studies they get only a single dose.

The patient population here had a median of 3 prior lines of therapy. You can see that although they had a lot of PIs and a lot IMiDs, these were probably less heavily pretreated in part because some of the novel drugs that we are used to using here in the US are not yet routinely available in China, like daratumumab for example. Nonetheless, you can see a 90% overall response rate most of which were complete

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responses with MRD negativity, and even at lower dose levels those responses were quite robust, and quite a few of these patients had extramedullary disease outside of the bone marrow, which is usually difficult to treat, and they nonetheless had good responses in that regard.

If you look at the progression-free survival and the overall survival for all patients you can see the median PFS of 15 months so it is similar to the 12 months with BB2121. This again may be a little bit longer because the patients were not quite as heavily pretreated and patients who are MRD negative of course do better, although they still seem to be relapsing, albeit not as rapidly. Adverse events are shown here. Cytokine release syndrome again is something that comes up and pyrexia or fever is part of that, most of these were grade 1 or 2 with very few grade 3 or 4 events, and thrombocytopenia and others can be seen as well. Here is just a focus in particular about cytokine release with about half of patients having grade 1, 35% with grade 2, and 7% with grade 3 and along with that you can have problems like a transaminitis, you can have some hypotension, and other complications which again you will hear about from Nina.

Unfortunately, there were some grade 5 toxicities as well, which mean deaths, most of these were from progressive disease although there were some other causes as well. University of Pennsylvania has also a large experience with BCMA CAR-T's, here is just the brief outline of how they did their study, the main differences being that they use single-agents cyclophosphamide as a lympho depletion and also did split dosing. These patients were also heavily pretreated five years out on average, and 96% of them had high-risk cytogenetics including almost 70% with deletion of 17P which is a particularly difficult patient population in terms of prognosis. Then you can see in several cohorts they had very good partial remissions as well as complete remissions, some of which lasted for quite a long period of time.

And then one other product I thought to mention which was interesting was this P-BCMA-101. The reason it is of interest is most of the CAR-T cells that we have presented and most of them that are being done right now, the gene for the chimeric antigen receptor is introduced with a viral vector, and that is great but viruses can only pack so much nucleic acid into them and if you want to introduce several genes, let us say in the future we may want to target more than just BCMA, as you saw from Nikhil we may want to target also CD38 or SLAMF7 at the same time. These folks used a piggyBac transposase which allows you to put more DNA in so you could target more than one antigen, and there also may be a greater ability to impact on stem cell memory T-cells which may hang around longer in the patient which therefore could mean longer immune surveillance, and these data were presented by Krina Patel from MD Anderson at last year's ASH. You can see a relatively low level on the left panel of cytokine release syndrome, such that you could probably give this on an outpatient basis in the vast majority of people, which of course would be great because then the cost would be

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lower. And high levels of responses including on the right you can see both bony and extramedullary disease responding in a patient who got this particular product.
Here is just an overview of some of the other studies that are out there. We went over 2121. There is also BB21217 which maybe Nina will talk a little bit about because she actually is one of the leaders of that effort and great data coming out from there. There are other also BCMA targeting therapies including some of those that are mentioned here.

So I think the conclusions are that BCMA directed therapies in all three of the formats that have so far gotten into the clinic are showing strong activity in very advanced patients. These are higher and better and more durable responses than we have ever seen before. They are also very rapid, and although there is some cytokine release syndrome, it seems in general to be of lesser severity than in the lymphoma experience where they targeted CD19. Concerns are, unlike in lymphoma were at least some patients with DLBCL and related disorders appear to be cured, so far that does not seem to be the case in myeloma. It seems that in the advanced setting, all of the patients ultimately do relapse, maybe if we give it earlier that would be different and part of the relapses could be because of the highly refractory nature of the disease, possibly the patient's T-cells have been through more chemotherapy and therefore may not be as strong if you will, and also you may get BCMA negative antigen escape with myeloma cells that do not have BCMA on the surface, and we do not yet know for sure whether BCMA is on the stem cells. So one of the concerns is we do not yet know whether myeloma will be cured by CAR tease or whether these therapies would just be a CAR Tease.

Future approaches, again we may try to target BCMA earlier in the disease, those studies are already underway. One of Nikhil's slides showed that gamma secretase cuts off BCMA on the plasma cell and releases it. If you inhibit that the plasma cells have more BCMA and therefore may be more sensitive. Combinations could be interesting like adding an IMiD to the CAR-T cells targeting more than one antigen and figuring out whether some type of T-cells are better to use in this setting than others.

I do have a couple of cases of my own just to show you how these things are working. The first is a 53-year-old lady who was originally diagnosed now seven years ago almost with stage 2 kappa light chain myeloma, had a large thoracic mass with vertebral collapse and spinal cord impingement, got radiation, and with VRd that is supposed to have a 100% response rate and usually does, unfortunately only had stable disease. Fortunately, did respond to CyBorD and then got a single auto transplant. Nice response to transplant but still had residual disease so we did a second transplant, and then we actually did consolidation KRd because still there was myeloma left over. As you might expect given how difficult it was to get the disease down, progression occurred in less than one year and over the course of a couple of years this is actually just a partial list of some of the therapies that we gave this patient, including dara/pom/dex, elo/pom/dex, Car with bendamustine/dex, bortezomib with

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panobinostat/dex and other therapies, and fortunately they all showed some benefit with an initial reduction, but unfortunately that reduction was not durable and this patient actually never achieved a complete remission.

So here is a question, Do you think this patient is a good candidate for enrollment in a CAR-T clinical trial. 1.) Yes, 2.) No, and 3.) You are not sure. So 71% of you said yes, and certainly as long as this patient's counts and liver function and renal function and so forth would qualify then this would be a great patient because clearly we do not have many options left over.

Here is just a quick overview of the eligibility for the phase 2 KarMMa trial which was the BB2121 study, and these patients had to have undergone at least two consecutive cycles of treatment for each regimen that they had before. They had to have three prior regimens or more. They had to have had a proteasome inhibitor, an IMiD, and an anti-CD38 antibody. So certainly this patient did qualify based on those criteria. The patient was enrolled, underwent apheresis, got some radiation and bridging therapy, had her T-cells reinfused which was complicated by grade 2 cytokine-release syndrome, and actually achieve a complete remission and was MRD negative with also a normal PET scan, first time ever in the course of this patient's disease to achieve a complete remission.

So here is the second question. In this patient who got BB2121, what would you expect to be the median progression-free survival? Would it be 6 months, 9 months, 12 months or 15 months. So 29% of you picked 12 months and that is actually the median progression-free survival. Although for those who achieve a CR and are MRD negative, it can be a little bit longer.

Moving on now to the second case, this is a 64-year-old male who started out with stage 1 R-ISS myeloma and was followed initially because had smoldering disease but then developed bony lesions and got VRd induction followed by tandem stem cell transplant. This was part of the BMT CTN trial where one of the arms for consolidation after upfront therapy was a tandem transplant and actually got a PR which was followed by len maintenance. Two-and-a-half years out the patient progressed and received a number of therapies including a trial of pembrolizumab with len and dex that had stable disease, and then had carfilzomib with pomalidomide and dex which gave a minor response. Once again this patient had a lot of different therapies, all of which produced some benefit but nothing that unfortunately was very durable. You can see dara/pom/dex, the panobinostat/bortez/dex, elo/len/dex, car/benda/dex, ixazomib/cyclophosphamide/dex, and dara/pom/bortezomib/dex. You can get tired just hearing about all of those regimens. You can imagine how these patients feel actually having to go through all of this. The patient did qualify for and enrolled onto the phase 2 BB2121 study, got apheresis manufacturing and reinfusion, also received grade 2 cytokine release syndrome as a result, but even though as you saw this has an 85% to 95% overall response rate, unfortunately, only stable disease was seen and the only

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reduction in the M-protein actually came after the fludarabine and cyclophosphamide lympho depletion, and then unfortunately the protein popped right back up.

One question to ask you now, you have seen other BCMA targeting therapies, do you think this patient should be switched to a different BCMA targeted therapy considering only stable disease with a CAR-T cell? And your options are yes, no or unsure. Very evenly split I wonder we can take an early poll of the panel. Nina, Nikhil what do you think about doing another BCMA targeted therapy in a patient who has not had a great response to one BCMA targeted therapy?

Dr. Munshi: So I think BCMA not having responses not because the patient does not have BCMA, that is a presumption. But I would biologically think the patient still has BCMA. For this patient, immune mechanism has not worked very well. so BiTE may not be my choice but I think BCMA can still be tried and could be successful.

Dr. Orlowski: Nina, what do you think?

Dr. Shah: So I think that I agree if it did not respond initially to BCMA immune therapy it is not probably not worth going there and I think the difference would have been if the patient had initially responded and then later had progressed, then I would say that is okay because maybe these T-cells went away and could be the BCMA could still be targeted.

Dr. Orlowski: Okay, so now I do not feel quite so dumb because what I did for the patient, if we can get to the next slide. There are actually at least a couple of case reports of people who can have responses to BCMA targeted therapy after prior benefit, but what I did in this patient, I actually was able to get belantamab mafodotin for this patient on a compassionate IND and did treat the patient. He did get five cycles, had some blurry vision but did not require dose reduction but unfortunately stable disease was the best response that I was able to get out of that. So we certainly need more data than just a couple of anecdotes, but I would agree with the panel that there is a rationale at least for trying some of these more than once in the appropriate biological sequence. So with that, I will now turn the podium over to Dr. Nina Shah from UCSF who is going to tell us about safety of these therapies and also how to manage some of the BCMA-directed therapies in light of the safety and efficacy.

Dr. Shah: Thanks. Thank you everyone who is here and thank you for the organizers for having me. Now that we have heard how great all of these therapies can be, now we can talk about what are the side effects or maybe some of the lesser good things that can happen, but the good news is that these are manageable. We will move on to the therapies. This is actually is a slide similar to what Nikhil showed about how we are using immunotherapy in various ways and this sort of explains why we have different ways to target BCMA and actually there are more coming down the line. So the good news is we have done some work on this but there is a lot more to go and there are

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other opportunities to target these proteins and other new proteins that are being discovered.

For immunotherapy options and also the toxicities associated with this, I wanted to break it up similarly to how Bob did with CAR-T cells, bispecifics, and antibody drug conjugates. We really want to focus initially on CAR-T associated toxicities, again because we probably have the most experience with this as far as different trials and also experiences from our lymphoma colleagues and leukemia colleagues that probably helped to set the stage and inform us as we began these trials initially.

So what is cytokine release syndrome? Simply it is a systemic inflammatory response occurring after CAR-T cells activate and expand, and I usually explain this to my patients it is like the worst flu you ever had. And it is characterized by high levels of CRP and ferritin as well as IL-6 and IL-10. Typically it does occur 1 to 14 days after infusion, and I will say in the myeloma scene it seems to be closer to the beginning aspects of when the T-cells are delivered, but that is not true for all products necessarily so it is important to watch patients during this entire time. It can be mild, although it can be severe as I'll tell you. It looks like, it seems like flu-like symptoms and the hallmark of this is fever and almost every patient has CRS the first defining role is fever. Now the most important thing is that it can progress to a life threatening hypotension, hypoxia and death and this is why we try to jump on it as soon as possible and I will say again that we learned a lot from our CD19 CAR-T colleagues beforehand, and not all diseases are the same but it is important to know how these can progress. Now, we think that this may be associated, the severity at least of the CRS, with high disease burden, although it is not to say that with zero disease burden you would not have any CRS and just because you have CRS does not necessarily always correlate with disease burden, but it is one of the things that we think may be related to how much the T-cells expand and activate, which seems logical since the T-cells are expanding and activating in response to tumor antigen.

This slide I simply call the GBH slide of CRS because it basically tells you that almost any organ can be affected by CRS and it is important to think about that because these patients are so sick. They have always already been treated with so many things, in addition you are giving them fludarabine and Cytoxan and then anything can happen. So it is important to look at all of their labs, look at them, ask them a lot of questions, see what kind of symptoms they are having because any of these things can be associated with CRS and it is important to jump on it before one of them develops into a higher grade toxicity.

As you can imagine, since a lot of people have been studying CAR-T and this is actually primarily from the lymphoma/leukemia space, CD19 space, there was a lot of talk about how you should grade CRS. Now there are various ways that you can grade this, various toxicities schemes, and the most common that were always associated with is with CTCAE. It is great for our usual clinical trials, but this does not really capture the

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hallmarks of CRS like we want it to, and because of that people who had more experience, like Dr. Lee and then people at Penn and Sloan-Kettering and MD Anderson, developed other ways of grading CARTOX or CAR-related toxicity and I think what is important about this is this was all related to what they were seeing in their practices, so then when we looked at clinical trials and try to compare it, it really was apples and oranges, and only recently because all of us have come together can we really have a more consensus way of approaching this. So there is a revised ASTCT or what used to be ASBMT grading system and this is related to really what the hallmarks are of CARTOX or CAR-related toxicity, and one of the things I want to point out as we already discussed is fever is necessary. Basically to say a person has CRS related to CAR-T you must have fever and that is why it is included in all of these, and the rest of the toxicities are related to other vital signs including hypotension, hypoxia, and it's just important to note all of these because if we use the same grading system across studies then it is more likely that we will be able to come together for consensus treatment, not just grading, and understand how studies compare with each other, how products compare with each other and how we are doing as far as an algorithm of management. Because eventually what is going to happen is it is not going to be just the study PI managing this, this is going to be all of us just like we do in transplant and other immunotherapies. So we want to make this digestible for the entire myeloma community.

If you look at the BB2121 data and actually this has been updated as you know in the *New England Journal of Medicine*, you can see that the CRS rate initially was presented at 63, but it is closer to three-quarters, closer to 75%. And the reason I just point this out is as I mentioned before all of the data we had before for which those criteria and grading systems were made on is related to CD19 CAR-T, so as myeloma physicians we really have to think okay is that really reflecting what we are seeing? So just to see what we were looking at for the product for which we have the most lengthiest data we can see here 63% to 75% of patients had CRS and so it is important to know that because it is something that is prevalent in these trials and if you look at all the trials you can see it is actually kind of varied. There are some like the Poseida which actually had very low CRS but you can see all the way have 90%, some trials had even 100% CRS, some of the ones from China, but what is important here is to know that it can happen and you have to be ready for it and I think I like to give us some credit with the most credit going to the CD19 folks who have taught us how to manage this, but it is manageable as I will show you.

There are various ways you can progress with managing them and I only showed the slide to show you that you have to look at everything but it is really hard to do that in the middle of the night, so it is very important to know what kind of grade they have with the simple criteria and how you manage this.

So how do you manage CRS? If you have what we would call a grade 1 or something that is just starting out as a fever the first thing to do is supportive care, and I say this

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because it is not only that the patient is having a fever after these T-cells, but remember that they are very ill and they have had other therapies and they just had fludarabine and Cytoxan. Some of them have very low counts and you do not want to forget about the normal things that can happen like fever and neutropenia due to an infection, etc. So you want to make sure you give them Tylenol. You want to make sure you give them antibiotics whatever they need, but if this continues and we really try to look at this very quickly. If a patient is not getting better with regular supportive medications like IV fluids, then we quickly move to tocilizumab. Tocilizumab, as you can see here on the right-hand side, is an antibody to the IL-6 receptor and so this allows for the IL-6 to be sort of siphoned off and not being able to affect the body as much by their receptor, and this actually is really great at reducing CRS symptoms in many of our patients. However, some will not respond to tocilizumab and so what is the next step? In this case we really want to be more active about turning off the T-cells, in which case we will give dexamethasone. Now a lot of us will start with the dose of 10 mg every 12 hours but can escalate that dose to every six hours or even if that is not getting better really bring in the big guns and give a higher dose of methylprednisolone, more steroids basically, and if it is really not getting better then we really have to talk to each other and sometimes people can use other anti T-cell therapies, for example cyclophosphamide. It is pretty rare, but if that is going on it is something that we all put our heads together for and say okay what is worth risk and benefit to turn off the CRS right now?

What is another CAR T related toxicity? I would say is neurotoxicity or what we now call ICANS or immune effector cell associated neurotoxicity syndrome. I just cannot even say so I will just say neurotox, but we do have a little bit more concise way of going about this, again because we have learned from our friends from CD19 and we have put a lot of heads together to look at this.

What are the manifestations of ICANS? I think a lot of us have gotten a little more experience with this and I would say one of the key criteria here as you can see there is many delirium, encephalopathy, aphasia, lethargy etc. I would say aphasia is one of the first things and if I could describe this the best way possible to patients when I consent them it is like a little drunk and it is a little bit subtle. Because if you do not talk to the patient for at least 5 minutes you are not going to pick up on it, and a lot of times the first people who pick up on this are the caregivers, for example the spouse or maybe the child that comes to visit or somebody who has been there for 24 hours. They will say, “you know they were just a little confused,” and a lot of patients will sort of have this circumlocutory talking and try to say, “oh yeah, yeah, yeah I know that you were saying this, yeah, yeah,” and try to you know act like they were not really drunk or something like that. They know something is off but they are not quite able to pinpoint it, and so it is really important for us as clinicians to be patient when we talked to the patient and think about what they are saying and talk to the caregiver to know exactly how they are acting and if it is a little bit off, but these symptoms can progress as you can see to tremor and seizures and even cerebral edema, headache is sort of one of those difficult ones because it might be related to neurotoxicity, but actually a lot of times people have

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headache because they have fever or you know they are otherwise ill in the hospital, and one thing to note is that it usually comes a little bit after the CRS. So again, it makes it a little bit complicated because it can happen after a fever. This was actually described in the paper as an awake patient who is mute and does not respond verbally or physically to an examiner. That person for sure has neurotoxicity and should be treated as such. Now what is the pathophysiology of this ICANS? So we do not really know because first of all we do not have enough data and second of all it is hard to biopsy and do LPs on every single patient who has this, but we think it may be related to endothelial activation which may cause the blood-brain barrier disruption, and I think this is probably one of the reasons that the neurotoxicity that we saw in the CD19, particularly ALL situation, was different than we are seeing in myeloma because they are two different diseases with different blood-brain barrier components. Now this is may be related to excitatory levels, elevated excitatory, NMDA levels or agonist or pro inflammatory cytokines. We know those are already being experienced by the patient because of the CAR-T, and then the T-cells themselves and myeloid cells may be more activated and possibly in the micro-environment of the CNS and that might also contribute to the CNS toxicity, although I think it is probably different between different diseases.

Again, the assessment tools have evolved. One of the easiest assessment tools that we have seen before was the CARTOX 10 which really talked to the patient about orientation, naming, writing, and attention. And as you can see here each of those yielded a certain number of points and then you would be able to tell a patient okay they have this many points or just drop that many points. One of the good things about the CARTOX was that it was easy to administer, and what has happened now for a lot of the centers is that nurses are administering them as part of the vital signs and recording that in the record and that is actually helping us to learn that, but of course we wanted to put our heads together and get a more nuanced CARTOX if you will and so we have the new ICE criteria which looks at orientation, naming, writing, and attention, but also following commands. So this is really important because of this cognitive aspect. Again, patients have to be able to focus and that is one of the things that is lost when they have this neurotoxicity. Again, here you get points for achieving each of that so the higher points you have, the less likely you are to have neurotox, and if you look at the scale here the the fewer points you have in the ICE score then you have a higher grade of neurotoxicity and you can actually then put that together with their depressed level of consciousness, seizure of course puts you already at a grade 3 or motor findings or elevated intracranial pressure. These are all symptoms that basically increase the severity of the neurotox either this way or that way and they really let you know that you need to do something about this in order to make this not worsen to become a seizure or to become something with increased intracranial pressure.

Let’s talk about what happens at myeloma CAR-T trials because again, all of these data is really based, or all of these recommendations are really based on the CD19 experience. As you can see in the BB2121 initially it was reported as 33%. In the paper

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this was reported as 42% of neurotox. I just caution because a lot of those were headaches and like I said before we do not know that headache is actually neurotoxicity but the investigators were being conservative.

As you can see here in the JCARH125 study, they also had several patients with neurotoxicity, about 30% in their most studied dose, so I think that sort of really hanging at 25% to 40% something like that and if you look here in the red you can see it ranges somewhere around there. Some of them have very little neurotox. For example, in the LCAR experience, and then as we talked about in the Bluebird experience and the Bluebird 2127, those patients had 25% neurotox so it can range, but I think part of this and even the numbers in between there that variability maybe explained by differences in diagnosis and differences in interpretation and a lot of differences in experience of the investigators who are giving these therapies.

What are the contributing factors? I think it is important to realize these patients are going through a lot and so what we are calling neurotoxicity may or may not be that and what we are doing to them it may not just be the CAR-T cells but other things that are happening. So they have concomitant fever and that is very difficult for a patient who may be 72 years old and we know that fever alone can cause people to have some delirium. Being in the hospital for two weeks straight can also cause delirium. Dexamethasone which they may have gotten as a result of CRS can also cause some delirium, and finally something that we do not talk about a lot but fludarabine actually in elderly population can cause delirium or neurotoxicity that is very subtle and is actually worsened by worsening renal insufficiency, another factor in myeloma patients. So it is something to consider and make sure you really look at that creatinine clearance and dose fludarabine appropriately because you do not want people to get more fludarabine than they need or than they can handle, especially if you do not want them to proceed to neurotoxicity.

Again, lengthy algorithms to try to see what happens and again, this is always a 2 a.m. page right, so who is going to open this and read this? You kind of have to know how the patient is doing, and the management is a little bit different than CRS. Really we look at seizure prophylaxis, that is the way to prevent it, and most of our patients who are going to CAR-T, and I will say our myeloma patients are on prophylactic Keppra, we do this so that we can try to eliminate the likelihood that they will have a seizure. It makes them a little bit loopy in the beginning, so I like to start up while they are on their lympho depleting chemotherapy, not necessarily the day of the CAR-T. The hallmark of management here is really steroids and that is dexamethasone, and usually after at least one or two days doses of dex they are getting better. They become clearer. Their caregiver will say oh, okay, now I know who you are. You know that is my dad, that is the person I know, and that is important because they should turn it around by the first one or two doses and if they do not, sometimes people will increase the steroids or change the steroids similarly to CRS management or again, if they are really, really having this unsurpassed T-cell activation, maybe they need something to get to this T-

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cell sooner, an anti-T cell therapy. Again, considering things like chemotherapy after much discussion within your group or if it is a trial within the investigators. But usually with steroids we can get to most of it, and there is not quite data yet or we do not think there is enough data to show that adverse events are more than the benefit of the steroids. Meaning that the risk of steroids has always been okay, maybe we are going to turn off those T-cells and they won't work, but we really have not seen that to be a correlative if the CAR-T cell patients have success or not and certainly we do not have enough data yet in myeloma to make that statement and you have really, really want to adhere to your first Hippocratic oath of do no harm. So if you have to do it, you have to give the steroids it is okay to do.

So what are some other CAR-T toxicities? Now, these have not been talked as much but they are real and they are important especially if we are going to move this as a transition from the academic centers to the community centers. Cytopenias I think is a huge thing and just on the right-hand side you can see that about 3/4 of the patients had recovered their ANC by day 32. But that means you know 20% did not and what does that mean? Those people need to be watched, they go back to their homes, they go back to their communities and they need to be given Neupogen sometimes, they need to be having prophylaxis sometimes, so you cannot just turn them loose. More importantly, half the patients really had not recovered their platelets by a month out. Again, something that needs to be watched as you communicate with their community physician or if you are the community physician that these people can have some prolonged cytopenias, they need weekly blood draws, sometimes twice weekly, and it is really important to not let that go and think that yeah it is okay. We do not know the exact mechanism of it, but we think it might be related to some bone marrow mediated inflammation which is probably not a wild idea considering the T-cells go to the bone marrow and they eat the myeloma cells so they are producing a lot of cytokines there, so it make sense that there is some sort of suppression of counts, and similarly sort of as a link to that, one of the other CAR-T toxicities that I think is becoming more apparent is this macrophage activation-like syndrome. So not true HLH. If you look at the bone marrow it is not going to be a bunch of phagocytosis ,but they have some of the clinical features of this MAS like syndrome, for example high ferritin. They will have abnormalities in IL-2 receptor and case cell activation. They will have fibrinogens that are low, elevated D-dimer, all of these things are important to look for and actually commonly what I might see is someone had CRS that looked okay, then they had a little neurotox. They were just not getting better, they got a little better, next thing you know their ferritins is 40,000 and that is sort of it and their counts are not getting any better and those people I think that we have to jump on them and one of the things we have been using is anakinra which is an IL-1 receptor antagonist and that can actually block the IL-1 signaling pathway and actually for an anecdotal evidence has shown some responses in the situation, but we do not know what the true mechanism is and we do not know what the true antidote is and we want to make sure that we explore within our community to get better answers for this. Other CAR-T toxicities that are really important especially as patients get long-term is the immunosuppression as Nikhil

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explained to you, it is not just the plasma cells but some of the other B cell components that may have this BCMA and so patients basically have this B cell aplasia and so a lot of them have immunoglobulins of under 400 for which we often give IVIg, although now there is a national shortage, maybe because of us, I do not know, and we really have to be good about antimicrobial prophylaxis. These people need their PCP prophylaxis, they need their Valtrex, they need all of these things and we should remember that they are just as immunosuppressed as some of our transplant patients. And tell them that, because some of them actually feel great and go back to teaching and their jobs and everything and we want to make sure watching all of those things.

I want to quickly cover bispecifics, we already talked about what they are as I call them the e-harmony of immunotherapy bringing together the myeloma cells and the T-cells to get some good outcome. As it was mentioned already the BiTE therapy from AMG 420 from Amgen was presented. I want to focus on the DLTs here. So as we mentioned the 400 mcg dose was the DLT and the reason the 800 mcg did not make it through was because of grade 3 CRS and this peripheral polyneuropathy, which incidentally also occurred as a DLT in the 400 but they were able to expand that dosing and call it their MDT. Now what is this polyneuropathy? This is a strange thing and we were all a little bit perplexed by it because it is not this Velcade based neuropathy that people have, it is sort of like a Guillen-Barre type situation and so because of that we do not know if it is related to antigen similarities between the BCMA and the neurons or what, but these were interesting side effects and something that you know is obviously very scary for both the patient and the provider. So something to keep an eye on for. Another thing to remember is you know CRS I think we know how to deal with that, but infections were something pertinent here and they were kind of strange infections, some pneumonia, some aspergillus, and adenovirus, and important to remember that these patients are very immunocompromised. They are heavily pretreated, but there is something to watch out for as a result of the therapies themselves. Thankfully actually, there was very minimal CNS toxicity, so I think that is a little bit different than what we have been seeing with CAR-T.

A little bit more about the peripheral polyneuropathy. There were two cases, both of them eventually resolved by month one and month two, but they did require steroids and IVIg I think similar to what we would use to treat Guillen-Barre. So something different going on and just peripheral poly sensory neuropathy that we often see with the Velcade.

How do you manage these toxicities? Well they also prophylax, a lot of the BiTEs have steroid pretreatment and that is sort of standard now. You can give tocilizumab be we do give tocilizumab if we see that the patient has a rapidly rising fever. Sometimes we will just give it at that time. Steroids afterwards are also a treatment. Really important after these patients start on BiTE, especially depending on what the schedule is and how often you see them for continuous effusion or the more longer acting being developed, you have to observe them for infections because these can happen at any

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time and they can manifest as any symptom, cytopenias, viruses whatever it is and you have to keep a close eye on them because remember, they are also undergoing a treatment where the T-cells are going to their bone marrow and causing all these disarray. So they may not have an intact immune system.

Real briefly I wanted to touch about ADCs. We talked about the mechanism of action whereby this is a way to deliver a toxic payload in a targeted way against BCMA or BCMA containing cells in this case myeloma, and GSK is the company that has been being at the forefront of this. What I want to show here is that the A's of interest the thrombocytopenia we talked about briefly and 26% of patients had grade 3 thrombocytopenia I think you know as a hematologist I kind of oh okay thrombocytopenia like I will take that because that is something we expect with a lot of our therapies. I think it's something that is a little bit more unexpected, although we would expect with ADCs because of the toxin, is the corneal events and so in here almost 70% of patients had some corneal event, mostly grade 1 and 2, but if anybody here has ever scratched their cornea, they know that it is very uncomfortable, so it is something that is clinically significant I think and did require some changes. They managed this by giving steroid eye drops consistently. A lot of patients did require a dose reduction for the blurred vision and they are really working on how to make this more palatable for the patient and particularly how to make this outpatient friendly because this is something that may be available in the communities. So cooling eye masks or increasing the duration of steroid drops may be to a week, and maybe some dose modifications, stretching it out or making the doses smaller in order to make this more manageable, and I think as we learn more about the drug and the drug teaches us more about the toxicities we will get better at this.

I just want to talk about comparing options, because we have talked a lot about the different BCMA targeted therapies and what are we going to do because all of these are sort of coming to the end of the race at the same time and how we are going to manage them and how are we going to choose between them? Something that is really important is that now we may have more options, and just like the rest of myeloma, every treatment does not fit every patient and so this is where the art comes in because you can think of different ways that you may want to approach these therapies. There are differences in logistics, obviously CAR-T right now requires a specialized center, kind of like transplant. You have to wait for production, so there is the apheresis and then the waiting time and then the infusion, bispecifics probably going to be community friendly maybe off the shelf, definitely off the shelf but probably community friendly, there are longer-acting BiTEs in development and ADCs as I mentioned community friendly, off the shelf. Length of treatment though, this is where I think the CAR-T may win because if you are done in two months that is great. People love being off therapies. We do not know how long people are going to be on bispecifics, as we mentioned people got up to 10 cycles in the study, but we do not know what that means for long-term treatment, and then the ADCs, I commend them. They actually limited the cycle to 16 although some people continue, but you can see whatever benefit they got was

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related to that fixed number of cycles. Toxicities are also to be considered and I think that is where you have to consider what the patient comes into the clinical scenario with, CRS, neurotoxicities, cytopenias versus possible polyneuropathy versus corneal, I mean all these things are important, and then of course something very important for us is going to be cost. If we take our cue from the CD19 folks, that cost is $300 to $400,000 which seems like a lot of money, but if you think that that person maybe in the future could have 15 or 17 months and weigh that against the cost of extended BiTE therapy or ADC therapy, maybe it is all going to come out to be the same. It is kind of like we think about transplant or four cycles of KRd, maybe that is going to be all the same. We do not know. So these are things that we should think about and I think everything is negotiable here and we have to really look at the patient and the patient's profile to figure it out.

So what would you do? You have a 72-year-old male relapsed/refractory myeloma, great performance status, candidate for BCMA directed therapy, past medical history includes glaucoma, high blood pressure, grade 2 neuropathy from prior treatment. There are no audience response answer here, I just wanted to talk about this a little bit because you could see why there are some aspects of this case particularly maybe like glaucoma, maybe it would sway you away from the ADC and the neuropathy might sway you away from BiTE, but the patient is also 72, so it would depend on what other factors are there right? And I think this is where we really do have to take a good social history as well. So in this case the guy was married, his wife was a very devoted caregiver. They live within 30 minutes of a major medical center. For them it really was no big deal to come to get specialized cell therapy if it was available on trial at this point because they were willing to make those drives back and forth and it would be okay or even they were willing to do a bispecific because they were close enough to do so. But if there was a different social history, for example if the patient was widowed, live 45 minutes away and just did not want to come and pay for parking basically and did not want to deal with anything, then maybe it is more important for him to get a therapy that is community friendly and maybe in that particular a case could get bispecifics if they were longer acting and were FDA approved or maybe an ADC. And then you have to consider the personal goals. Maybe this guy is widow but the daughter says she will be a great caregiver for two months, lives within 45 minutes of the major medical center and his personal goals he wants to spend as little time as possible getting treatment, no more visits to the oncologist, in this case maybe CAR-T therapy is the better solution. You do not know if it is going to work or for how long, but he seems like he could tolerate it is worth a shot, maybe if you could avoid you know 20 other trips to the oncologist in the future. So there are really are no right answers I think this is always you know a question and really part of the fun and art of treating myeloma.

Dr. Orlowski: All right, great job Nina. Thanks very much. So we have got time for a panel discussion and a summary of things. I wanted may be just to start off while people here and maybe also on the internet are formulating questions by asking one of either Nikhil or Nina or both. You know in the days of allotransplant it used to be said that you

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had to have some GVH in order to have some graft versus tumor. Do you need to have some cytokine release syndrome with a CAR-T cell or with a BiTE in order to see a benefit with reduction in myeloma in our case? What are your thoughts about that?

Dr. Nina Shah: I think for the relapsed/refractory population I would say you almost have to have the CRS. I am at 90% on that. I do not know what the answer is going to be for when we bring the CAR earlier.

Dr. Munshi: Patients are very much when they are going through this, they are very well educated. They all know this treatment and they are praying that they get the fever and they say "I haven't got a fever yet it's the third day, what is wrong" But if you look at the data the *New England* paper and others, there are around 25% of the patients who had no CRS and they still responded. I am with Nina in the sense that you need CRS because that reflects T-cell proliferation and that reflects then activities. So biologically, how can you not have CRS and still respond? Clinically, I think we have not depicted as much and so there is some disconnection with what we see clinically versus what biologically and medically we would expect, but there had been patients who I did not have any patients who had did have a fever in the response, but in the reported literature the patients who did not have CRS and still responded. Your patient that you presented had a grade 2 CRS and still had just stable disease, so CRS does not guarantee response.

Dr. Shah: That is right.

Dr. Munshi: The other opposite may not be true always.

Dr. Shah: And sometimes you know the CRS we say fever is the hallmark but sometimes people are really tired and so like Nikhil was saying that you did not pick up on the database but fatigue is there.

Dr. Munshi: I think that is very good point that what CRS you need to have response. It does not have to be fever. It can be some other subtle manifestation of IL-6 that we are not picking up but is there.

Dr. Orlowski: Are there questions from the audience or from the group on the internet?

Dr. Munshi: Yes, I can ask a question.

Dr. Orlowski: Sure.

Dr. Munshi: So currently the patients are not considered eligible if there are any CNS condition for this CAR-T cells and I think as a group what do we think about that because the patient had a remote one history of seizure for whatever reason he is not eligible today. We do not see as much myeloma involving CNS although advance

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disease patients do have some myeloma involvement and do you think, either of you, whether that should continue to be the case in excluding patients?

Dr. Shah: I think that is really tough because once you exclude them from all these trials, first of all it is horrible for patients, and secondly when we get disapproved we are not going to be able to do with patients who had a remote TIA or remote seizure which may have been related to alcohol or something, so I really feel like if there is no, it is sort of like the cancer thing, no cancer in the five years, no CNS issues in the past year then I think it is fair and actually I am not even sure we should be excluding all the CNS myeloma people. I do not know because there are a non-study population.

Dr. Munshi: Yeah, I agree. I think in so there has been a second question and maybe we combine. The CNS toxicity is so much more in the lymphoma setting. In myeloma we have very minimal and like you said maybe it is 25, 30% but there are very vague headaches for really no reason and it is not really CNS toxicity so in lymphoma it was okay to exclude them for the fear that neurotoxicity may be a problem they are being excluded and I think we need to rethink that strategy.

Dr. Shah: Because we know how to manage better now.

Dr. Orlowski: I would agree. I think certainly it is reasonable at the beginning until you get a better idea of the toxicities to be very careful, but now that the numbers of patients that have been treated are higher and we know a little bit more about how to manage them, I think it is reasonable to loosen the eligibility a little bit and make sure that a wider population can benefit. You know one question that comes up also oh sorry. Please, could you maybe go to the microphone and ask your question so that the folks on the internet can hear as well.

Audience Member 1: So my question is once that you start tocilizumab, what is the maximum dose or duration, and what is the indication for adding the steroid or the other like anakinra or secondary steroid therapy, what is the indication for that?

Dr. Shah: Yes, so actually this is really a good point because the tocilizumab, which is 8 mg/kg, and sometimes people will give a repeat dose of tocilizumab, but you have to be very careful because we are pretty sure that precipitates often neurotoxicity. You may hear this, okay they got a repeat dose of tocilizumab and then low-and-behold the fever went away but then the next day the patient was confused. And the reason is you are grabbing onto the IL-6 receptor, now where is all these IL-6 going to go, right? So it can maybe go into the CNS, so usually if they have not responded to the tocilizumab the first time and they are still having CRS I will go straight to the dexamethasone. I do not know Nikhil if you will do that.

Dr. Munshi: Similar, similar. Very rarely I do not remember using it a second time.

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Dr. Shah: Yeah, the one time I did it the person had neurotox.

Dr. Orlowski: So the question I was going to ask, Nikhil you showed some nice data about soluble BCMA levels to some extent tracking with disease and I know there has been a debate about whether high soluble BCMA levels predict for response or not and whether we should screen patients, it almost seems that if you have a high BCMA level, if it is high enough it should block activity, especially of an antibody drug conjugate. What are your thoughts about that?

Dr. Munshi: I think the good news is that although soluble BCMA does track with the disease burden and the disease data, etc., it has not been shown so far to interfere with any of the BCMA directed treatment. So CAR-T cells, none of the studies have shown, and there have been preclinical studies showing that the target of the molecule antibody is not somehow binding to the soluble BCMA. In the majority of the patients, I am sure there would be a patient where there may be something different. But same thing also I was surprised but happily that the ADC also does not bind to the soluble BCMA to the same extent that it would be any better treatment and so I think soluble BCMA is not necessarily driving the patients selection or response. I do not think we have done enough studies to know whether related level may have related difference low level people have more CRs versus high has less CR, I do not know enough that we have done it. So at the moment I think everybody is eligible, soluble BCMA does reflect patient is expressing it. What is interesting is that when patients respond the soluble BCMA goes down because the tumor burden goes down. So in CAR-T cell for example the normal plasma cell disappear also as Nina very clearly said that patients in IVIg because there are no plasma cells. When patients starts recovering their plasma cell the soluble BCMA comes up and it becomes a marker of recovery of the normal plasma cell and at some point it becomes recovery of myeloma cells also. So it reflects the disease versus plasma cell versus absence.

Dr. Shah: So could you ever see for oligosecretory patients, could you see us using that?

Dr. Munshi: I think so.

Dr. Nina Shah: That way you would have a baseline and you know what they are.

Dr. Munshi: Yes if you know where the starting point is I think we can and if the level is really high, say more than 70 or 100, we know it is really from tumor not from normal plasma cells and that may be helpful.

Dr. Orlowski: So Nina I will put you on the spot this time. We reviewed all of the data about relapsed/refractory and there is going to be more coming, but there are already trials ongoing in earlier lines of therapy with CAR-T cells and some studies that are being planned even for frontline patients, for example with high risk disease. On the one

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hand you could think maybe the CAR-T cells will work better because the patient's T-cells will be healthier and there will be less myeloma because they will have gotten for example in the frontline setting some kind of induction and maybe the myeloma cells will be less drug refractory, but on the other hand there will be fewer myeloma cells to stimulate CAR-T cell proliferation and activation. What is your thought about the efficacy that we are going to see in let's say 1 to 3 prior lines and frontline therapy, and particularly in the duration of benefit compared with what we have seen in relapsed/refractory disease and will we be curing myeloma with BCMA CAR-Ts? We will start with Nina and then we will go to Nikhil.

Dr. Shah: Yes, I think the history of myeloma therapy has always been when you take the therapies you move them more proximal, they get a better response rate, if you combine them there is a better response rate, so I would not expect this to be much more different in the setting of a BCMA CAR-T therapy, but of course the history has also always that we have not cured myeloma yet and so if we can somehow bring these therapies more proximal, getting longer duration of response, really pushing the 10 years during which time we may find other types of therapies that will be better, I am really hoping that we can find a type of BCMA cell or BCMA-directed cell that is able to be sort of activated on demand and that persist or some sort of clone because then as soon as, even if the myeloma "stem cell" is not gone, as soon as it starts to make a problem then that cell is just there ready to attack. That would sort of be an ideal way for this to work.

Dr. Munshi: I think it is going to be used in earlier disease setting, there is no question. The response rate with relapse is so super, it is 90% so I do not how much more better we can do. The depth may be more but when we get 16 out of 17 MRD negative patients, so I think that is there. The one thing I do not know and I do not know if we have good understanding is that if you do use CAR-T cell in patients with really low disease burden would it work as well?

Dr. Shah: Right we do not know that.

Dr. Munshi: Do we need stimulation of the CAR-T cells for it to work well? I think we do not know that. So although intuitively thinking earlier would be a better response, can we partially earlier know less response because there is not enough myeloma after the good induction treatment. So I think we need to do it to know where to go.

Dr. Shah: And I think response rate is really kind of not the most appropriate way to judge the CAR-Ts because we were so used to drugs have single agent 25% response rate having a party over that, but now it is just one thing it is 80% response rate but that does not mean it is any better as far as PFS or it does not mean that is cured. I mean the PFS is really the important part so that is going to be I think where we get our data, although we have to be patient which just dislike being.

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Dr. Orlowski: So I think in terms of the questions that we have on these slide we probably covered all of these both in the presentations as well as in the discussion and questions. Are there other questions, please.

Audience Member 2: I have one question. In regards to the anti BCMA antibodies as they continue to be further developed, how do you think existing monoclonal antibodies or are they going to be combined with them going forward and as a preclinical rationale to combine say elo/dara with the anti BCMAs?

Dr. Orlowski: Nikhil, you are our preclinical expert here.

Dr. Munshi: I think we combine any new treatment with existing drugs. So theoretically yes it will be combined with, but what is biologically logical? I think if you look at CAR-T cell, any immune stimulation is going to be important. So CAR-T cell with lenalidomide or pomalidomide is going to be an important combination. Similarly, now if you look at daratumumab or elotuzumab which work through different mechanisms not necessarily T-cell, theoretically could have some additive effect probably because they work through two different mechanisms and two different cell types, etc. Will there be a real synergism would either of these drugs allow the CAR-T cell to work better? I do not know. Would CD38 and daratumumab effect the CD38 on T-cells? We do not know. So I think we will have to do preclinical work to see whether this additive affect synergism or there is akinetic effect. That does not mean they cannot be combined, they can be given in a successive fashion, I might give dara first and then give this or the other way around and see how they can be combined better. So they will be evaluated together in some fashion, but we may need some preclinical work to know how they may work.

Dr. Orlowski: I think the other challenge will of course be the cost of regimens when you are adding for example daratumumab and belantamab together, I am sure they will work better together. The question is whether the incremental clinical benefit will be worth the large incremental cost, that is something for society to decide. If we can cure myeloma patients with it then of course that is great. If you get a few extra months then the debate will be on. Although, please give a round of applause to our panelists, Dr. Munshi and Dr. Shah, who I think did a great job and could not have done any better I do not think. So thanks again very much for joining us this evening and I hope this information would be of help for you in managing your myeloma patients.

Dr. Munshi: Okay, thank you very much.

Dr. Shah: Thank you.

Dr. Orlowski: Thank you.

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