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The BiTE® Immuno-Oncology Platform & Emerging Targets in Oncology

Announcer: You're listening to ReachMD. This medical industry feature, titled "The BiTE® Immuno-Oncology Platform and Emerging Targets in Oncology," is sponsored by Amgen Oncology. This program is intended for healthcare professionals. Your host is Dr. Matthew Birnholz.

Dr. Matt Birnholz: Despite recent advancements in the field of immuno-oncology, there are many ongoing, unmet needs for patients with hematologic malignancies and solid tumors. One emerging therapeutic approach called BiTE, short for Bi-specific T-cell Engager technology, is a promising new platform designed to engage patient's own T-cells to directly target cancers. This technology carries the potential to treat a broad range of tumor types but, before we can realize the potential, we need to understand its versatility, how BiTE molecules actually work, and where they're currently being investigated. These and other important topics, coming up on today's program.

From the ReachMD studios in Fort Washington, Pennsylvania, I'm Dr. Matt Birnholz. Joining me to share insights on the BiTE immuno-oncology platform is Dr. Ajai Chari, Associate Professor of Medicine in the Department of Hematology and Medical Oncology at Mount Sinai School of Medicine. Dr. Chari serves as Director of Clinical Research in the Multiple Myeloma Program and is Associate Director of Clinical Research at Mount Sinai's Cancer Clinical Trials office. Dr. Chari, welcome to the

program.

Dr. Chari: Thank you for having me.

Dr. Birnholz: Great to have you with us. So to start, Dr. Chari, can you give us an overview of the current therapeutic landscape for cancer and the immuno-oncology field as you see them today?

Dr. Chari: Sure. We probably started with radiation back in the early 1900s and then our first chemotherapy drugs weren't approved until approximately 1950.[1] We had some combination chemos and then some additional modifications of radiation, such as seeds, to treat prostate cancer and kind of things stayed stagnant until we started getting some targeted therapies in the late 90s into the early 2000s and then, the next kind of big class of drugs that was important for oncology, were checkpoint inhibitors in the early 2010s.[1,2] I think what's really been interesting and exciting is the most recent T-cell based therapies, and these have really changed the way we're approaching cancer.[1] And I think to understand that, we need to understand why cancer develops and, clearly, an important part of that is immunosurveillance, and so that includes both the innate and adaptive immune response.[3] But, unfortunately, cancer cells can evade all of these mechanisms and eventually escape.[4] And we've harnessed the immune system in many different ways already,[5,6] but we still have a lot of work to do in this field of immuno-oncology. First, not all patients respond.[7] Then, we don't have clear clinical criteria on whom we should be using immunotherapy on.[7] Not all tumor types have yet been addressed with immuno-oncologic approaches.[7] The management of adverse events can always be challenging.[8] There's variability in targeting mutations that are existing in oncology.[7] And, finally, we don't have clinically significant biomarkers that have been readily identified to determine who might most benefit from these approaches.[7] So, an exciting field but a lot of work to be done.

Dr. Birnholz: That's an excellent overview Dr. Chari. Thank you. So, with that background in mind, let's focus on the BiTE immuno-oncology platform that I mentioned earlier. If we look under the hood of this new therapeutic class, how does the BiTE platform and constituent BiTE molecules actually work?

Dr. Chari: The BiTE platform, it really represents a new class of targeted immuno-oncology agents.[9] And so, the BiTE molecule has two components. One is coming from the monoclonal antibody that recognizes tumor-specific antigens and then the other part has the component of the monoclonal antibody that engages with T-cells and these two components are combined by a flexible linker.[9] So, that's really the structure of the molecule and, the way these work is that when we use these BiTE molecules, we're going to have the engagement of the T-cell right up against the cancer cell and, thereby, having these T-cells engage and attack the cancer cells that might have previously learned to

evade or escape these mechanisms.[9,10] There's a lot of investigation innovation going on, and the reason there's so much excitement with this field is that we can change it up to target novel antigens.[9] We can engage the patient's own cytotoxic T-cells.[10] These are also off-the-shelf therapies, so you don't need Ex-vivo manipulation.[11] And, finally, they're being investigated not only as single agents but also as combination strategies across a lot of tumor types.[14]

Dr. Birnholz: Can you speak to where BiTE molecules are currently being studied?

Dr. Chari: They're really being studied across a lot of different settings. Both liquid and solid tumors,[9] both high and low tumor burdens are being investigated and those are slightly different because you're going to need an active agent to target somebody with high tumor burden whereas, in a low tumor burden, you might need a different mechanism to keep the tumor well-controlled.[9,10] Also, rapidly progressing disease would need to be targeted differently.[9,10] But, the entire spectrum of patients with oncologic diseases needs to be addressed and this platform is really powerful to address a lot of those needs.[9]

Dr. Birnholz: For those just joining us, this is ReachMD and I'm Dr. Matt Birnholz. Today, I'm speaking with Dr. Ajai Chari about the BiTE Immuno-Oncology platform and emerging targets in oncology.

So, Dr. Chari, let's dive in to some of these emerging targets under current investigation, and I'd like to start with multiple myeloma given your role as clinical researcher of a multiple myeloma program. Can you give us a refresher on what characterizes this hematologic malignancy and then walk us through the therapeutic approach?

Dr. Chari: Sure. Myeloma is really a debilitating disease for patients. It can present with hypercalcemia, renal failure, anemia, and bone disease, and the culprit cells, the plasma cells, are clonal cells that live in the bone marrow, although we can readily detect them in blood and urine.[15] These cells, unfortunately, while we have a lot of treatments, they learn how to evade all of these treatments and part of that is not only the chemotherapy but they also learn to evade the immune system.[16-18] And one of the challenges in treating myeloma is it is a relapse refractory pattern, so meaning the initial therapy works the longest and then patients, unfortunately, relapse and this remission duration is shorter with the second line of therapy, and then we have continued successive relapses with each remission becoming shorter and shorter and so, there is an urgent need for novel therapies.[19,20]

One of the targets that we're really interested in with myeloma is called BCMA, which stands for B-cell

membrane antigen.[21] BCMA is a transmembrane glycoprotein, it's part of the TNF tumor necrosis factor receptor super family and it's predominantly expressed on the cell membrane of late stage B-cells and plasma cells, and what this protein seems to be doing is it regulates the differentiation in survival of plasma cells.[22-24]

Dr. Birnholz: And this particular cell surface protein, is it over-expressed in myeloma cells?

Dr. Chari: It is. The highest level of BCMA expression is in untreated myeloma patients, , and it's almost undetectable in healthy controls.[25] Importantly, recent data has also shown that the increased expression of BCMA can be correlated with lower overall survival. For example, when patients had below-median expression, they had a median OS of 155 months whereas those that had more than median expression had a median overall survival of only 98 months.[26] So, I think this is an antigen that is important in myeloma genesis and likely survival.[27] We do now have some compounds that are being investigated that are BiTE molecules and what these are targeting is, basically, when these cancer cells or myeloma cells are invading the immune system, the hope is that we can get these T-cells to activate and expand using these BiTE molecule technologies, and, thereby, bringing the T-cells into proximity with the cancer and create cell death.[9,16]

These molecules come in different formulations if you will; there are some that are canonical BiTE molecules:[28] these tend to have relatively short half-life, they're small proteins;[52] and these have been studied in various pre-clinical models.[29] And there are also newer half-life extended BiTE molecules that have been studied in non-human primates and have a longer half-life of up to 112 hours,[30,31] and both of these types of molecules have actually entered clinical trials.[28]

Dr. Birnholz: Thank you Dr. Chari. That's a great overview and an exciting development. Why don't we shift to another hematologic malignancy, acute myeloid leukemia. What characterizes this cancer?

Dr. Chari: So, acute myeloid leukemia is characterized by an excessive growth of immature myeloid precursor cells in the marrow and also in the peripheral blood. As with a lot of oncologic diseases, there is a tremendous genomic heterogeneity.[32] We're learning more and more that the risk stratification of leukemia is heavily dependent on the genomic characterization of this cancer and, unfortunately, we have an unmet medical need.[33] AML cells progress very quickly with a very rapid doubling time and, when patients become relapsed or refractory to prior therapies, we really don't have effective therapies. [32]

One of the important challenges is age. In both younger and older patients, we see a clear spread as

you may move from favorable to adverse genomic features, the OS drops significantly.[34] But then we also see that younger patients and older patients have differential outcomes and, as is not uncommon in oncology, older patients, in particular, have a dire need for well tolerated therapies.[34]

Dr. Birnholz: So, with those details in mind, what targets are BiTE molecules being investigated for here?

Dr. Chari: There are a couple of molecules that are being targeted. The first is FLT3. FLT3 is a member of the class III family of tyrosine kinases.[35] It is expressed in early marrow progenitor cells and it also plays an important role in the survival and proliferation of these early hematopoietic cells.[36-38] We know that the FLT3 expression significantly increases as the percentage of bone marrow blasts increase and it's over-expressed in approximately 70% of cells from patients with AML.[36,39] Importantly, FLT3 is also much more highly expressed in AML cells,[36] which lends itself as a therapeutic target to minimize bystander toxicity. This particular antigen; therefore, is amenable and ideal for targeting with immunotherapy because leukemia cells evade immunosurveillance.[40] One of the prime candidates to help us do this would be BiTE molecules[28] because, again, they have the binding to the tumor antigen, in this case FLT3, and also binding to the CD3 component, and so, when you have this molecule, this is a great strategy to try to target these leukemia cells that are currently not being effectively targeted with current agents.[28,40]

Another target that is being studied is CD33. CD3 is another transmembrane glycoprotein expressed on the cell surface of multi-potent myeloid progenitors but also unipotent myeloid colony forming cells and maturing granulocytes and monocytes.[41,42] CD33, importantly, is expressed on nearly all AML cells and is markedly over-expressed in leukemia cells relative to healthy donors, making it, again, an ideal target.[43] And so, we have these BiTE molecules where, again, part of the BiTE molecule will bind to CD33 and the other part to the CD3.[40]

Dr. Birnholz: Now, Dr. Chari, you mentioned earlier that BiTE molecules are also being investigated in solid tumor types. Can you just walk us through an example of that?

Dr. Chari: So, one of the solid tumors that is being targeted with BiTE molecules is prostate cancer.[28] This is the second most common cancer among men.[44] There is a high mortality and it's the second most frequent cause of cancer-related deaths as well in men.[44] There is clearly an unmet need with current treatments only slowing down disease progression and we really don't know the optimal sequencing of the different treatment regimens currently available,[45,46] and there's a lot of work that

needs to be done to identify biomarkers particularly in the metastatic setting that could allow for patient specific options.[46] And so, given this unmet medical need, it represents an ideal target for immunotherapy approaches.

PSMA is a membrane protein that's over-expressed in malignant prostate tissue and it regulates nutrient uptake.[47,48] It's over-expressed in the vast majority of prostate cancer and it can be used to discriminate between BPH, benign prostatic hyperplasia, and malignant prostate cancer.[49] It gets progressively more up-regulated during disease progression and is associated with a higher risk of recurrence.[50,51] So, there are BiTE molecules that are targeting PSMA and, again, the CD3, to engage the T-cells.[9]

Dr. Birnholz: So, Dr. Chari, looking ahead, what additional targets are emerging for investigation with this BiTE platform?

Dr. Chari: Novel targets in the solid tumor field, as we discussed PSMA, but also in glioblastoma, EGFRvIII is being targeted with BiTE molecules. Another antigen that is being targeted is small-cell lung cancer with the antigen being DLL3 and BiTE technology combining with CD3. In hematologic malignancies, we discussed earlier CD33 and FLT3 for AML, but also BCMA for myeloma and one other target that's also being explored with the BiTE technology is non-Hodgkin's lymphoma with CD19. So, a lot of exciting investigational agents in phase 1 and 2 studies.[28]

Dr. Birnholz: So, before we wrap up, Dr. Chari, any takeaways on this treatment approach that you'd like our audience to come away with?

Dr. Chari: Yeah, what I think is exciting about these BiTE molecules is really we're trying to bring these T-cell innovations to more patients.[52] So, we're looking at targeting various tumor specific antigens.[52] Importantly, these are going to lead to hopefully off the shelf therapies without the need for a lot of complex Ex-vivo manipulation, which a lot of relapse refractory oncology patients do not have the time to wait.[11,52] They're being investigated, as we discussed, both as monotherapy and in combination with other treatments.[9] So, I think, in summary, we really need these immuno-oncology therapies for patients with cancer.[54,55] Clearly, the immune system is a large part of why cancer develops and why patients become refractory to current cytotoxic and targeted therapies.[3] These investigational BiTE molecules are being engineered to engage a patient's own T-cells that naturally survey the body for

malignant cells and to help eliminate detectable cancer cells.[9] Finally, the BiTE immuno-oncology platform offers the potential versatility to target different tumor-specific antigens in both hematologic malignancies and solid tumors.[9,10]

Dr. Birnholz: Well, those are excellent closing comments to round out our discussion on this new therapeutic approach in the immuno-oncology field. I very much want to thank my guest, Dr. Ajai Chari, for helping us better understand the BiTE platform today. Dr. Chari, it was great having you on the program.

Dr. Chari: Thank you for having me. It's been my pleasure.

Dr. Birnholz: For ReachMD, I'm Dr. Matt Birnholz. Thanks for listening.

Announcer: This program was brought to you by Amgen Oncology. If you missed any part of this discussion, visit ReachMD.com/BiTE. This is ReachMD. Be part of the knowledge.

USA-OCF-80678