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CD20 X CD3 Bispecifics—Redefining Treatment for Patients with R/R DLBCL/LBCL in the Community Setting

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Dr. Lunning:
Hello and welcome to this educational activity.

I am Dr. Matthew Lunning, Associate Professor at the University of Nebraska Medical Center in Omaha. Today we'll be reviewing CD20 x CD3 bispecific antibodies for the treatment of relapsed/refractory diffuse large B-cell lymphoma. So, let's begin.

There's been a lot of chaos recently, and unfortunately that chaos has been driven by clinical trials in the relapsed/refractory diffuse large B-cell lymphoma space.

As you can see here by this cartoon by my colleague Dr. Weston, the algorithm for second line therapy in large B-cell lymphoma has really been changed quite a bit. And what's changing it? Well, CAR T-cell therapy and a massive amount of new therapies in the large B-cell lymphoma space.

We know that the majority of those patients who have large B-cell lymphoma, if they're going to relapse, that relapse will happen within the first year. I think now with ZUMA-7 and TRANSFORM data in the second-line, high-risk population of those patients who are primary refractory or who have relapsed within 1 year of therapy really drives the left side of this cartoon before the discussion of CAR T-cell eligibility. We know that a minority will relapse from large B-cell lymphoma and those relapses are going to occur greater than 1 year.

And here's where the classical auto transplant paradigm still is in play with second-line chemotherapy. If felt to be transplant eligible, and if a response is seen, then transplant can occur. But again, sometimes the middle of those therapies that you see here below but whether or not it is immunochemotherapy, CAR T-cell, polatuzumab + bendamustine and rituximab, tafasitamab plus lenalidomide, selinexor, loncastuximab tesirine, or even newly approved bispecifics. And that's what we're going to talk about today is our CD3 + CD20 bispecific antibodies.

So, let's talk about what factors differentiate these new bispecific classes. And so, I often think that it should be kept very simple, and keep it patient-facing because it's very complex in how these are engineered. I like to use the analogy of spaghetti and the kiss of death.

So, the antibodies are bringing the CD3 T-cell together with that CD20 antibody and then, that kiss of death does happen, you can see here through them coming together for cytotoxicity. But I also see this as a spaghetti noodle. And you can see the 2-fork analogy here, where you're winding them together, bringing them together before the lymphoma cell gets eaten.

But I think that there are many different types of spaghetti just like there are many different types of bispecifics. And this technology is just blossoming to where there are multiple antigens that are being directed at these T-cells and you can see it not only in B-cell lymphomas, but also in other myeloid disorders and including solid tumors. And so really this space is just emerging in multiple different areas.

But at the end, at this synapse of when you're bringing the malignant B-cell and the T-cell together, you can see here based on the cartoon of glofitamab, engaging a CD20 antigen and bringing it next to that CD3 TCR leading to perforin and granzyme B, release of the activated T-cell, which leads to hopeful apoptosis of the B-cell.

Now there are many bispecific T-cell engagers out there and I love this review from Dr. Lusana really highlighting one of the first ones that we knew about that has relevance in acute lymphoblastic leukemia, engages CD3 to CD19. And then that is blinatumomab which is a tandem single-chain variable fragment-based T-cell engager. The ones that have come about in large B-cell lymphoma that we'll highlight today include glofitamab, mosunetuzumab, odronextamab, and epcoritamab. And I think what you can see here is that they all have different caveats that really try to make their technology differentiating, concluded in the knob-and-hole technology, which is seen in mosunetuzumab and glofitamab. In regard to odronextamab, exploits differences and affinities immunoglobulin isotypes for protein-A coupled with the use of common light chains allowing efficient large purification. As well as looking at the dual-body technology with epcoritamab, which leads to single point mutations in the constant region of the heavy chain domains, which allow for correct assembly after in vitro separation. And so, I really think that there's just some fascinating science occurring here leading to some similar targets, but potentially different designs.

And you also see this in the application of these bispecific T-cell engagers. You can see here the configuration may be different with glofitamab having a 2-arm to 1 ratio CD20 to CD3, whereas the other ones are a 1-to-1. Some of these may be subcutaneous dosing, like epcoritamab or mosunetuzumab, which is being developed with both IV and sub-q administration, versus others like glofitamab and odronextamab and plamotamab, which are primarily intravenous. All of these have step-up dosing to risk mitigate cytokine release syndrome and ICANS. The majority of them do not have a CD20 monoclonal antibody as part of their step-up dosing, whereas glofitamab uses obinutuzumab as a Cycle 1 Day 1 lead-in before the step-up dosing occurs at Cycle 1 Day 8. Also unique is whether or not it's a fixed duration or continuous duration. And you can see here epcoritamab, odronextamab and plamotamab were designed as a continuous dosing strategy, at least in the clinical trials, and glofitamab and mosunetuzumab has fixed duration. And we'll go through some of this data later in this talk. Also, kind of looking at how you're mitigating risk for CRS and ICANS with post-dose steroids, which is employed in epcoritamab, but not with the other agents. Some of them may require inpatient stays, both as part of the clinical trials and now with commercial availability with epcoritamab and glofitamab. And so, really, a lot of movement in the bispecific space. And this chaos really appreciates tables like this which help kind of differentiate these bispecifics, which have never been compared head-to-head in a clinical trial.

So, what are some of the advantages of bispecifics? Well, I think one of those is that it's readily available. It's a quote, unquote off-the-shelf product. We know that CAR T-cell therapies don't grow on trees, and they can lead to treatment delays as there is time not only to get to a CAR T-cell center, but there is also time needed between leukapheresis to actual infusion. Bispecifics don't require bridging therapy, and as I alluded to on the prior slide, they can be administered as a subcutaneous dosing or intravenously.

CAR T-cell therapies have been associated with cytokine release syndrome and neurologic symptoms at different frequencies as well as severities, and there have been improvements over time in therapeutics based upon utilization of tocilizumab or prophylactic steroids, but this may limit their use in older or more advanced age individuals, including those who are more clinically vulnerable patient populations.

With regards to bispecifics, as I'll show, the rates of Grade 3 or higher CRS and neurologic toxicities are lower and may be easily discontinued in the case of severe toxicity. Some of the attributes also of bispecifics is that they may be more available to patients, potentially with advanced age, or with those who have multiple prior lines of therapy, and those prior lines of therapy could include CAR T-cell. And I'll show you just in the upper bounds of some of the prospective trials getting all the way up to 11 prior lines of therapy before introduction of bispecifics. And there may be those individuals who logistically just may not be able to get to an authorized treatment center for CAR T-cells where this may be a particularly important option for those patients.

But bispecifics do have their challenges. I think that there is some logistics still that can happen with bispecifics where you may start as an outpatient, need to go inpatient, and then go back out to outpatient dosing. There can be that transition to not having CAR T-cell availability and having to go to an academic institution from the community or starting in academia and then moving out to the community. And so those logistics need to be discussed, I think very early on. I think dosing, with the step-up dosing strategy, that can be something to get used to from that standpoint, as well as supportive measures, as I alluded to, may be different depending upon which bispecific you're using. And then also having tocilizumab, our IL-6 antagonist, available; but also, kind of going through who buys

the tocilizumab and where is it stored? And then also thinking about toxicity management where each of them may be different. There may be different pre-medications and also post-dose supportive measures. And then also understanding what is the time of the specific event. Is it going to happen if it's intravenously at the time or near the time of administration versus subcutaneous, which may be delayed? And then what to expect and what are the signs, potentially, of severity of the event? And where is the patient going to be located? Are they close to the treatment center or are they going to be at a distance?

So, I think one of the biggest advantages of CD3 + CD20 bispecifics is their off-the-shelf capabilities. I think with CAR T-cell, yes, you may want to do CAR T-cell, but there can be a lot of challenges even in what I call the brain to vein time from when I want to do CAR T-cell to actually getting them apheresed and then, within the vein-to-vein time, which is actually after apheresis to infusion. And that timeframe can be measured, not necessarily in days, but could be measured in the amounts of weeks, versus bispecifics, which are often readily available and can be used kind of in an off-the-shelf, meaning, can be ordered through a pharmacy. But again, you have to have the right setup in order to do this. And I'm going to show you in the relapsed/refractory large B-cell lymphoma setting data that I think supports the utilization of bispecifics in aggressive lymphomas.

I think some of the challenges to adoption of bispecifics in community practice really is around kind of having a full understanding of this class of medications and what supportive therapies are necessary in order to implement them, as well as having the touchpoint for if there is toxicity. If that toxicity were to occur out of classical working hours, what is the next approach and who's going to be available and knowledgeable of the bispecific toxicities in management plan. Whether or not that is a local urgent care, an ER, or an after practice closure on-call individual. And so, with all of these, I think that we're going to talk through some of the strategies for bispecific management.

But let's first look at the clinical efficacy of some of those that are already approved versus some that are in development. So, the first that I'll highlight is epcoritamab, and this was approved on a Phase 2 single-agent trial of 157 subjects. The median age being 64. But I look at this, the upper-bound of being 83. The median prior lines of therapy was 3, again with the upper-bound of 11 prior lines of therapy. I think what is unique in this patient population is that a vast majority were refractory to their last therapy, and this is in large-cell lymphoma only, and it did include 39% of the population having had prior CAR T, with 75% of those refractory to their prior CAR T, and that means progressed within 6 months of their CAR T-cell. Epcoritamab is a continuous dosing strategy. You can see the dosing scheduled here.

The CR rate in this study was 39%, with a median time to response of 1.4 months. The median time to CR was around 3 months, and the median duration of response was 12 months.

The median PFS was 4.4 months, with a median overall survival in this population of 19 months.

Epcoritamab did have CRS occurring in 50% of the patients, with Grade 1 representing the majority of the patients at 32%. You can see to the right the CRS events were most commonly at Cycle 1 Day 15, or the first full dose at 48 milligrams, and then a substantial drop-off of CRS risk.

There can be adverse events beyond CRS, mainly hematologic in regards to neutropenia, but fatigue, nausea, and diarrhea can be seen, but most commonly at lower grades.

So, epcoritamab is FDA approved as of May of 2023. You can see here that there are black box warnings with regard to serious or life-threatening CRS and life threatening or fatal ICANS. And in regard to the label, it should be the consideration of hospitalization for 24 hours after Cycle 1 Day 15, dosage of 48 milligram.

Moving to the second FDA approved bispecific is glofitamab, and glofitamab was approved on a Phase 2 single-arm trial of 154 subjects. Again, median age was 66, but again the upper-bound was at 90 years old. Here, like the prior study, 85% of them were refractory to their last therapy. This did include prior CAR T-cell patients, representing about a third of the population with 90% of them being refractory to their prior CAR T.

You can see this, unlike epcoritamab, obinutuzumab lead-in is required at Cycle 1 Day 1, and then the step-up dosing is given. Again, this is IV, but this is fixed duration whereas epcoritamab is continuous duration.

You can see here it broken down by those who had relapsed/refractory large-cell lymphoma or transformed follicular lymphoma, versus those with prior CAR T. And you can see in the total population the CR is around 40%, and the duration of CR was a little over 2 years for those who obtained a CR. You did see some mild differences in duration of CR at 24 months between the population who did not have prior CAR T, versus those who did have CAR T. What I did discuss is that glofitamab is a fixed-duration therapy, and so you can see at the PFS at the end of therapy, if you're on a CR, there can be the capability for durability, but if you had not achieved a CR by the end of therapy, the progression free survival was relatively short.

Glofitamab has a PFS of 4.9 months with an overall of median survival of 11.5 months.

Glofitamab also, all-grade CRS at 64% with the majority of the CRS events being Grade 1. You can see here that there may be, higher baseline total metabolic tumor volume may be prognostic for those at increased risk for experiencing Grade 2 or higher CRS events, as well as lower progression-free survival.

Beyond CRS, again here there can be hematologic effects of neutropenia, anemia, and thrombocytopenia seen with glofitamab.

Glofitamab was also approved in June of 2023, shortly thereafter the epcoritamab approval. Again, this does have an obinutuzumab lead-in followed by glofitamab step-up dosing. And because of black box warnings, serious or fatal cytokine release syndrome, because of the CRS risks, patients should be hospitalized for 24-hours after the first step-up dose with caveats if CRS happens after that dosing.

The third bispecific that I'll talk about that is in the large B-cell lymphoma space, but is approved in the follicular lymphoma space, is mosunetuzumab. Mosunetuzumab was studied in large B-cell lymphoma as a fixed-duration strategy. In this 88 subject study the median age was 67. Median prior lines of therapy was 3 with an upper-bound of 13. So, you can argue that all 3 of these studies that I've discussed have a very heavily pretreated population.

Here, in this study, the CR was slightly lower than the prior 2 at 24%, with the median duration of CR at about 26 months. The median 24-month duration of CR was 55%.

Mosunetuzumab had a median PFS of 2.2 months and a median overall survival at 11.5 months.

All-grade CRS was 26% with the majority, again, being Grade 1.

Mosunetuzumab is not FDA approved in large B-cell lymphoma, but is approved in relapsed/refractory follicular lymphoma after 2 or more lines of systemic therapy.

Talking next about odronextamab, which is not FDA-approved for large B-cell lymphoma, but does have single-arm Phase 2 data also, and this is given in a continuous dosing strategy based upon their trial of 127 subjects, with the median of 66. Again, the upper-bound in the upper 80s here with a median of 2 prior lines of therapy.

You can see that there may have been some dose response. Here looking at CAR T-cell-naive patients treated at 80 mg or greater, the CR is 53%, and those who were CAR T exposed, the CR rate did lower to 23%.

Odronextamab, again had 55% all-grade CRS with 98% of them being Grade 1 or Grade 2.

So, that's kind of a run-through of some of our more advanced utilization of bispecifics in large B-cell lymphoma. But what are some of the proposed mechanisms of resistance? You can have tumor cell intrinsic mechanisms, such as antigen loss and activation of immune evasive gene expression programs, as noted in A. In B, talking about T-cell intrinsic mechanisms, including activation of regulatory T-cells, down-regulation of the T-cell receptor, and development of T-cell exhaustion, as alluded to in B. As well as C, which is T-cell extrinsic mechanisms, including recruitment of immunosuppressive myeloid and/or stromal cells. And so, multiple different mechanisms of resistance.

And so, from a contextualization of this evidence for a community practice standpoint, really trying to sort through this clinical trial data. And I think the first key point is that this was a heavily pretreated large B-cell lymphoma patient population, one that may live in your community practice, and some of them may return to your community practice after having failed CAR T-cell. And I think that there is evidence here in each of these Phase 2 trials that I alluded to for efficacy of the bispecific in the post-CAR T-cells space. There's also efficacy in those individuals who cannot get to a CAR T-cell, with either a continuous dosing approach with epcoritamab, or with a fixed-duration approach with glofitamab in an FDA-approved environment. So, I think that both of the approved bispecifics can be integrated into the community oncology setting. I think what needs to be discerned is, with the toxicity being mostly upfront, and a lot of the heavy lifting of the logistics with pre-medications, and really getting through that first month of step-up dosing, really the question is, is can this be done in academia and then transitioned out to community, or a community center who sees a higher volume of lymphoma patients perhaps could on-board and come up with standard operating procedures on how to do this safely within the community setting. And I know that all community practices may not be built equally.

So, when trying to think about patient selection, I think what is important here is a multidisciplinary treatment team as well as, thinking about where you're going to sequence the patients. So, in regard to patient selection, who's not eligible for a CAR T-cell? I think it's becoming harder and harder to discern, but there may be comorbid conditions that may preclude CAR T-cell. There may be access constraints to having a caregiver or getting to an authorized treatment center. And then there may be the fast-paced disease, which is large B-cell lymphoma, which may constrain getting to a CAR T-cell center. And then, I think if you look in the post-CAR T-cell environment, I think you have to focus on there may be some super refractory patients, those that are relapsing within 100 days, where

there is very little data in the clinical trial population being that these may have been excluded from clinical trials. There are those who are refractory or relapsed within 6 months of their CAR T-cell, and those patients were included in the epcoritamab and the glofitamab trial. And then, those who are relapsed greater than 6 months from CAR T, which represented a minority of the post-CAR T-cell population.

So, I think when considering bispecifics, it's about site readiness. Not only do you have to have a team that's willing and able to manage the patients, and that can include caregivers, nurse champion, APPs, physicians, pharmacists and also speaking to your administrators because there can be some logistics about having appropriate timing and of administration, and having access to tocilizumab.

So, being bispecific specific, knowing when it can be delivered outpatient, when it is recommended to go inpatient. What is the timing of monitoring between IV and sub-Q? Educating the patient and their caregivers when to call. Is the time to call with a fever, and how are they going to have access to that? Whether or not there's a thermometer at home, do they have blood pressure cuffs, as well as pulse oximetry accessibility? And then, how frequently are you going to follow laboratory evaluation?

And then, also, a facility logistics, thinking about those places and how you're going to communicate with the hospital, and who at your hospital to communicate with, whether that's ER, inpatient unit and your on-call team. And then, having supportive meds available, whether or not it's take-home steroids, and having access to tocilizumab and at which distance. And so, really it is becoming a patient-specific plan as well as having a system plan.

So, I think there are many different situations where you can consider, and what is the treatment sequencing? I'm starting to get into this population of where the disease is really bad, and I'm calling them a quad refractory large B-cell lymphoma, which is those who are CD79b antibody-drug conjugate like polatuzumab, rituximab, as well as anthracycline-refractory. And so those patients are progressing through a regimen like Pola-R-CHP [polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisone] and then their disease is saying that they can't wait to get through a CAR T-cell, so then they're getting platinum-based therapy like R-ICE [rituximab plus ifosfamide, carboplatin, and etoposide]. So, you have platinum-refractory, anthracycline-refractory, rituximab or CD20-refractory, as well as CD79b refractory. Those patients can be very difficult to get to a CAR T-cell and have had 2 prior lines of therapy and may be available for bispecifics. Then you have the early CAR T who are getting Pola-R-CHP but can wait and get second-line lisocabtagene maraleucel or axicabtagene ciloleucel based upon the data from TRANSFORM and ZUMA-7, respectively. And then, those late relapses who get R-CHOP [rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone] and then get standard-of-care R-ICE and have a response amenable to transplant, but then relapse and go on to get CAR T-cell. Maybe those patients, if they relapse post-CAR T, may get epcoritamab. And then the novel no CAR T. So, you get mini-R-CHOP, followed by tafasitamab plus lenalidomide, followed by loncastuximab tesirine. You know, those can be situations where bispecifics may be able to insert themselves.

So, what should community centers know about transition from inpatient to outpatient administration of bispecifics? I think the biggest thing is to know when they need to be inpatient is therapy dependent and based upon whether or not they have CRS, and may need to be admitted a second time based upon if they do have CRS. Or outpatient can continue if they are tolerated. I think really the importance of coordinating referrals to academic or tertiary to community settings is planning ahead. I think if you're starting at academia, but know that they are going to want to get into the community, reaching out early. Or if you're in the community and you have a patient and you want to work with academia, really engaging them early to have that approach.

I certainly think that it is a team-based management approach, and I think that this review by Dr. Crombie and colleagues really sums it up nicely, going through the patient selection, patient education, knowing which drug your administering. Really educating for self-monitoring but knowing when inpatient monitoring is appropriate. And then, what are truly the signs and assessment that you're going to have at the hand, not only of the patient and the caregivers, but of your team for CRS and ICAN assessment, and then knowing how you're going to manage CRS and neurotoxicity in this situation.

With regard to CRS, I think that there are several supportive care management strategies of either steroids or tocilizumab that are product-specific and can also be institutionally specific.

But I think in most regards, strategies to reduce the risk of CRS is really following the step-up dosing strategies, knowing the premedication strategies associated with each product, not leaving out the obinutuzumab if you're planning to give glofitamab. If you're getting epcoritamab, co- and post-administration of steroids is appropriate for Cycle 1. Coordinating with local facilities and having a central repository of treatment standard operating procedures and algorithms to help guide your team if after-hours communication is needed. And then, thoroughly educating patients and caregivers to the signs and symptoms of cytokine release syndrome, as well as neurotoxicity.

And you can see here this may be higher with the incidence of CD19-directed agents, but it still can occur with our CD 20 agents. And knowing that steroids are the mainstay of treatment and tocilizumab could be used, or should be used, if concurrent with CRS and

antiepileptic medications for prophylaxis could be utilized.

So, how would you set up success in a community-based practice for managing side effects? I really think it starts not only with educating the patient and their caregiver on when is appropriate to call, but what to do if a patient does call, and when to bring them in and when to administer supportive medicines like steroids or tocilizumab, and for further monitoring is a must in order to do this successfully.

So, there is a downloadable resource available to you to serve as a point-of-care reference, and a patient education tool to help facilitate equitable patient education, within this presentation.

And so, now we're going to divert to a practical application as a case-based learning lab. And this case that I'm going to present to you is a 78-year-old gentleman who presents with low back pain and diffuse adenopathy on exam. He has an excisional biopsy that shows large-cell lymphoma. By immunohistochemistry, it is felt to be a non-GCB subtype. Their FISH is negative for MYC rearrangement. Based upon PET/CT, they have Stage 4 disease based upon avid bone lesions. The bone marrow is deferred because the CBC is normal. They have an elevated LDH at 250, and the ECOG performance status is 1. This patient has an IPI score of 3 with limited comorbidities of hypertension.

And so, in this case study, what would be your initial induction therapy? R-CHOP, mini-R-CHOP, Pola-R-CHP, dose-adjusted EPOCH-R [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab], or unsure?

In my assessment, I would recommend Pola-R-CHP based upon the POLAR-X trial. You can see this was a randomized double-blinded trial that was in favor of the primary endpoint of Pola-R-CHP versus R-CHOP at the 24-month mark of primary endpoint of PFS. What I think supports this even further is the subtype analysis showing that ABC did derive more of a benefit compared to R-CHOP who had an ABC subtype in the POLAR-X trial.

Other caveats that could be looked at here that go beyond the cell of origin could be advanced stage disease, as well as an IPI 3 to 5, of which our patient did. And the POLAR-X trial did accrue those patients who had an IPI of 2 or greater.

So, at our case follow-up, the patient tolerates Pola-R-CHP for 6 cycles and has resulting Grade 1 peripheral neuropathy. The end-of-treatment evaluation notes PET/CT is consistent with a metabolic complete response. But we do MRD assessment and the patient does have positive MRD. The patient's monitored for 5 months but has recurrence of low back pain with PET/CT findings concerning for relapse. This is confirmed by biopsy. Creatinine clearance is less than 50, LVEF is 50 to 55%, and he has an oxygen saturation of 90% still with a good performance status.

So, how would you manage this patient now? Tafasitamab plus lenalidomide, loncastuximab tesirine, lisocabtagene maraleucel, or R-GemOx [gemcitabine-oxaliplatin plus rituximab]?

Well, I would argue that giving lisocabtagene maraleucel, based upon the PILOT trial, not only the TRANSFORM or the ZUMA-7 trial, but this individual having some comorbid conditions, having some mild renal insufficiency. But otherwise, a good performance status, over the age of 70. The PILOT trial really looked at those individuals who had advanced age and comorbidities, as you can see here in the Venn diagram. And those patients that got lisocabtagene maraleucel could derive benefits, especially in those patients who obtained a CR. And so, while others like tafasitamab plus lenalidomide could be used in the second-line setting, I do think that CAR T-cell would be an opportunity for this patient.

So, this patient tolerates lisocabtagene maraleucel with Grade 1 CRS. Has no ICANS. However, at Day 100, the patient has evidence of progression of disease. Biopsy confirms diffuse large B-cell lymphoma, but now is CD19 negative by flow cytometry and IHC, but remains CD20-positive and has a maintained performance status.

So, how would you manage this patient?

So, tafasitamab plus lenalidomide yes, could be an option. But the CD19 negativity does concern me for tafasitamab plus lenalidomide. Loncastuximab could be an option. It has shown to have some ability for response at lower CD19 exposures. R-chemotherapy or epcoritamab? So, in this situation, I think epcoritamab following CAR T would be a reasonable option. I do think that, as alluded to here, that heavy pretreated populations were studied in the Phase 2. I would be concerned because of the relapse within 6 months. I'm not sure I would pull off and stop a bispecific if I could get them into a CR, just because of how relapsed they would be. I might consider that based upon the data shown here, that if I could achieve MRD negativity then maybe I would consider pulling away the bispecific from that standpoint. But again, epcoritamab is delivered as a continuous dosing strategy.

So, the key takeaway is I think large B-cell lymphoma remains a curable disease in first-line, second-line, and I think it's extending into third-line but with diminished odds. There are a plethora now of marketed targeted therapies, either as single agents and in

combination. And, more combinations coming in clinical trials. I think strategic considerations are necessary in the relapsed/refractory large B-cell lymphoma space regarding the timing of CAR T-cell CD19-engaging agents, as well as our new class of CD3 + CD20 bispecifics. But I think it is also important to consider the capabilities for local administration versus shared administration versus early referral for administration of CD3 + CD20 bispecifics.

And with that, I'd like to thank you for your attention and for participating in this activity.

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