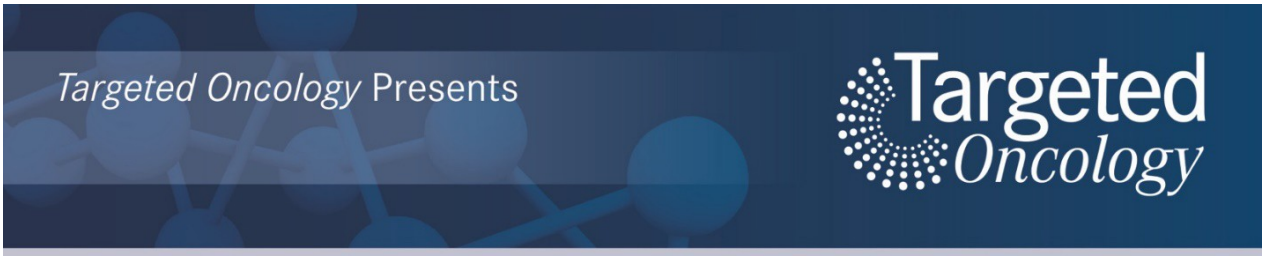

Targeted Oncology
Chronic Lymphocytic Leukemia
Virtual Tumor Board

Segment 1

Segment Title: Case 1: An Elderly Patient With Newly Diagnosed High-Risk CLL

Segment Description: William Wierda, MD, PhD, and Adam Bagg, MD, discuss the presentation of a 75-year-old woman with weight loss and upper-quadrant fullness.

William Wierda, MD, PhD: Thank you for joining us today for this *Targeted Oncology™ Virtual Tumor Board,* which is focused on chronic lymphocytic leukemia. Novel small molecule targeted therapies and chemoimmunotherapy regimens for CLL have drastically improved outcomes, but they have also increased the complexity of treating symptomatic patients. In addition, there remains to be a substantial unmet need for many patients with relapsed or refractory CLL. In today's *Targeted Oncology™* Virtual Tumor Board presentation, my colleagues and I will look at 4 clinical cases. We will discuss the individualized approach to treatment for each of these patients and will review the data considered in our decision making.

I'm William Wierda, professor of medicine at the University of Texas MD Anderson Cancer Center in Houston, Texas. Today, I am joined by Dr. Adam Bagg, professor of pathology and laboratory medicine at the University of Pennsylvania Perelman School of Medicine, in Philadelphia; medical oncologist Dr. Matt Davids, assistant professor of medicine at Harvard Medical School in Boston; and Dr. Nitin Jain, associate professor of medicine, also from MD Anderson Cancer Center. So, let's get started with the first case.

The first case is a 75-year-old female with reported symptoms of weight loss and fullness in her left upper quadrant. Her past medical history is significant for hypertension and hypercholesterolemia, both of which are medically controlled. Her physical exam shows moderate axillary lymphadenopathy. Her spleen is palpable at 4 cm below her left costal margin. Otherwise, she's well appearing and continues with her daily activities.

Her laboratory findings are significant for an elevated white blood count at 48,000; 73% are lymphocytes, her hemoglobin is 9.1, platelets are 125, the absolute neutrophil count is 1800, her LDH is 250, and her beta2 microglobulin is 4.2. A flow cytometry shows a monoclonal population of cells that are also expressing CD5, CD19, and CD23. FISH is done, and results show deletion 11q. A molecular analysis shows an unmutated immunoglobulin heavy-chain variable gene, and sequencing of *TP53* shows wild-type *TP53*. A bone marrow biopsy shows diffuse infiltration by CLL.

This is a previously untreated patient. She is diagnosed with chronic lymphocytic leukemia. She has Rai stage III disease, with a hemoglobin of 9.1 and some disease features that have some implications in a prognosis for this patient. So, why don't we start with you, Dr. Bagg. May you comment on the diagnostic workup and the molecular findings for this patient?

Adam Bagg, MD: Thanks very much, Dr. Wierda. Obviously, the flow cytometry is important in the characterization and diagnosis of CLL. Although it is not likely to be an issue in this case, it's important to be aware of the percentage of cells with the clonal immunophenotype. In some cases, the total number of clonal B cells may actually fall below $5x10^9$/L, which, by definition, is not CLL. Of course, in this

patient, who has a very elevated absolute neutrophil count–73% lymphocytes and 48,000 white cells—that's unlikely to be an issue.

Another important point, from a diagnostic point of view, is that although we all know that the co-expression of CD5 and CD19, together with CD23, is fairly pathognomonic of chronic lymphocytic leukemia, it's sometimes useful to look at other immunophenotypic markers, such as CD20, CD22, CD79B, and surface immunoglobulin—all of which are decreased in intensity in CLL—to build a portrait of the diagnosis of chronic lymphocytic leukemia.

FISH panels, nowadays, usually look at 5 or 6 abnormalities. In this individual, deletion of 11q, presumably 11q22.3, was detected. In most studies, this is believed to be an adverse prognosticator, presumably targeting the *ATM* gene. With regard to additional molecular studies, the distinction of whether the B cell has or has not transited the germinal sensor, with the indication of the immunoglobulin heavy-chain variable region being mutated or unmutated, is an important prognostic factor. In this patient, the immunoglobulin heavy-chain variable region is unmutated, which is a poorer prognostic factor.

The only gene that seems to have been investigated in this patient is *TP53*, which was reported to be wild-type, or negative. A caution to the interpretation of a *TP53* mutation analysis, for the practitioner, is to know which exons have been evaluated. Some laboratories will do a more widespread exonic analysis, looking, for example, at exons 2 through 11. Others may have a more restrictive analysis, looking at exons 4 through 10, which may miss some mutations. So, it's worth looking at the fine prints in a mutational analysis to be sure that there has been reasonable coverage of the gene of interest.

Finally, the bone marrow biopsy notes that the infiltration in the marrow is diffuse. Historically, before the advent of genetic-based prognostication, diffuse infiltration was considered to be an adverse variable as compared with those with a nodular infiltration.

Segment 2

Segment Title: Case 1: Prognostic Features and Chemoimmunotherapy Treatment Options

Segment Description: William Wierda, MD, PhD; Adam Bagg, MD; and Nitin Jain, MD, discuss the prognosis of the 75-year-old woman with chronic lymphocytic leukemia and review data available for chemoimmunotherapy use in this patient.

William Wierda, MD, PhD: For diagnostic purposes, could you comment on bone marrow versus blood workup? What's essential to have to make a diagnosis of CLL?

Adam Bagg, MD: In most instances, we get by with doing a peripheral blood analysis. As long as the patient has greater than $5x10^9$/L monoclonal B cells with an immunophenotype characteristic of CLL, that, in my opinion, is sufficient to make a diagnosis. In a patient with cytopenias, it might be important to do a marrow to ascertain the basis of the cytopenias. Is it due to extensive marrow involvement? Are there pure red cell aplasia and other considerations that might be contributing to the cytopenias? Certainly, bone marrow is useful in many cases. I'm not sure that it's required in all cases. It depends on the complete blood count.

William Wierda, MD, PhD: In terms of the prognostic significance of these markers, maybe we'll start with you, Nitin. Can you comment on the prognostic features for this patient and how they may relate to the outcomes for this patient?

Nitin Jain, MD: For this particular patient, given that the patient has deletion 11q, studies have shown this to be a high-risk prognostic marker for patients with CLL—with lower progression-free survival and overall survival, in the context of chemoimmunotherapy. Also, the patient has unmutated *V* gene status. Again, this has been associated with a high-risk prognosis for decreased progression-free survival and overall survival compared with the mutated *V* gene. With these 2 prognostic markers, which tend to go hand-in-hand, most of the time, deletion 11q and unmutated *V* gene, I think this patient is certainly at high risk for disease progression. She has already shown signs of disease progression with anemia, and I think we should consider treatment for this patient.

William Wierda, MD, PhD: Based on what you just indicated, we should be talking to this patient about treatment. This is an older patient. This patient is in their 70s. We really have 2 different approaches to treating this patient. We can approach treatment in terms of chemoimmunotherapy and then we have the new small molecule inhibitors that we need to discuss. Maybe we could start out with the chemoimmunotherapy, since we have a lot of long-term data for chemoimmunotherapy. Maybe you can summarize, for us, the studies that have been done, that are relevant for the older population, with regard to chemoimmunotherapy regimens and the outcomes associated with these options.

Nitin Jain, MD: Sure. The study I wanted to highlight is the CLL10 trial, which is actually a trial for younger patients for CLL, generally less than 65 years of age. These patients were treatment naive, fit patients. Patients above age 65 were also treated in the study. In this particular trial, patients were randomized to receive either FCR (fludarabine/cyclophosphamide/rituximab) versus bendamustine/rituximab (BR). This was done by the German CLL Study Group. The primary endpoint was progression-free survival. The study showed that in older patients—approximately one-third of

these patients—when they compared FCR versus BR, there was a similar progression-free survival. However, when they looked at the study, overall, the FCR arm had a superior progression-free survival. Above 65 years of age, the FCR regimen led to increased cytopenias, neutropenia, and infection risk. So, I think that study may tell us that if you have an older patient in whom you are thinking about chemoimmunotherapy, bendamustine/rituximab may be a reasonable alternative to FCR.

However, there is another trial, the CLL11 study, which was really designed for patients who were older or who had comorbidities. These patients were randomized to receive either chlorambucil, as a monotherapy or chlorambucil plus obinutuzumab or chlorambucil plus rituximab. The study showed that the arm with the chlorambucil plus obinutuzumab regimen was the most superior, in terms of progression-free survival and overall survival, compared with the other arms. This particular study led to the approval of this regimen, chlorambucil plus obinutuzumab, as the standard of care for frontline therapy for older patients with CLL. So, that's another option that we have available.

William Wierda, MD, PhD: You reviewed a couple of chemoimmunotherapy regimen options for the patient. The choice between the options is driven more by…

Nitin Jain, MD: I think it's driven more by the overall performance status of the patient's comorbidities. Bendamustine/rituximab is likely going to be a more myelosuppressive regimen than chlorambucil plus obinutuzumab. So, if you have a patient who is maybe 65 to 70 years of age, who has a good performance status, and you are thinking about chemoimmunotherapy, I think BR may be a reasonable alternative. However, for a patient such as this patient, at 75 years of age, obinutuzumab/chlorambucil might be a better option.

William Wierda, MD, PhD: And the expected progression-free survival with chlorambucil/obinutuzumab, in this patient population, would be?

Nitin Jain, MD: In the CLL11 trial, the median progression-free survival of this patient population was 31 months, just over 2.5 years or so.

William Wierda, MD, PhD: In terms of relapse, with this type of treatment, with the patient characteristics that this particular patient has, maybe you can comment on the expectations for long-term outcomes for this patient?

Nitin Jain, MD: This patient has deletion 11q, as well as unmutated *V* gene. Both of these have been shown to be high-risk prognostic markers with chemoimmunotherapy. What I mentioned, the 31 months of progression-free survival, would be applicable to an all-patient population, where you look at everyone, together. Because this patient is high risk, I would expect the median progression-free survival to certainly be less than that—probably on the order of 1 to 2 years. Certainly, I think that remains to be suboptimal, with the chemoimmunotherapy, but that's what you could potentially achieve with chlorambucil/obinutuzumab.

William Wierda, MD, PhD: So, we would likely be talking to this patient, in a relatively short period of time, about relapse and retreatment?

Nitin Jain, MD: Yes.

Segment 3

Segment Title: Case 1: Targeted Therapy: Ibrutinib for Newly Diagnosed CLL

Segment Description: William Wierda, MD, PhD, and Matthew S. Davids, MD, MMSc, review data for the use of ibrutinib in newly diagnosed chronic lymphocytic leukemia and discuss the appropriateness in this particular 75-year-old patient.

William Wierda, MD, PhD: Moving on to the small molecule inhibitor options for this patient, there's a trial that was reported relatively recently, referred to as the RESONATE-2 trial. This was a frontline trial that studied patients over 65 years of age. These patients were randomized to ibrutinib versus chlorambucil. Matt, you could highlight, for us, the outcomes of that trial? What important features of that trial are particularly related to the management of this patient?

Matthew S. Davids, MD, MMSc: The 2 standards that we might consider for a patient like this would be bendamustine and rituximab or chlorambucil in combination with a CD20 antibody like obinutuzumab. In the RESONATE-2 study, we see a comparison with chlorambucil monotherapy, which we're not typically using as a standard approach. When this study was designed, that was still a standard approach, particularly in Europe where a lot of patients were put on this study. So, I think it makes it a little bit challenging to compare, across this population, RESONATE-2 with some of the other data sets that we just saw. But nonetheless, I do think RESONATE-2 is a very valuable data set. It was a large randomized phase III trial of over 265 patients. In total, there were 269 patients. These patients were randomized (1:1) to ibrutinib or chlorambucil, with a primary endpoint of progression-free survival.

There are several important findings from this trial. In particular, looking at the ibrutinib arm, we saw a very nice progression-free survival at 24 months. It was in the range of 85% or so, which I think is very encouraging for this population. As expected, chlorambucil had a much shorter progression-free survival. That's not a major surprise to us. One of the things that I took away from the RESONATE-2 study was that patients with some of the higher-risk markers, in particular those with deletion 11q and the unmutated IGHV, had very nice progression-free survivals.

William Wierda, MD, PhD: So, the presence of deletion 11q and the unmutated V gene, in terms of chemoimmunotherapy-based treatment, puts this patient at higher risk for shorter progression-free survival, relapse, and the need for re-treatment. How does that factor in, in terms of small molecule inhibitor-based therapy? What's the relevance of deletion 11q and the unmutated V gene, in terms of ibrutinib-based therapy?

Matthew S. Davids, MD, MMSc: For unmutated IGHV, we're seeing equivalence (in terms of the progression-free survival in patients treated on ibrutinib), irrespective of unmutated versus mutated *IGHV* status. It's important to note that this has historically been very different with chemoimmunotherapy-based regimens, where we've always seen a shorter progression-free survival with patients with unmutated *IGHV*. So, I think this is a very encouraging development in the field—with ibrutinib.

Now, I think the deletion 11q story is also very interesting. We had seen, from the relapsed/refractory studies—the PCYC-1102 study, for example—that there was a hint of a shorter progression-free survival

in patients with deletion 11q. In the RESONATE-2 study, this is a little different. We're actually seeing, perhaps, a slightly better progression-free survival in patients who have deletion 11q—or at least equivalence. That was specifically seen in the RESONATE-2 study. Tom Kipps and colleagues put together an integrated analysis, where they looked at several different studies pooled together. In that population, there was a significant improvement in progression-free survival at 24 months in the patients with deletion 11q compared with patients without. I think this suggests that ibrutinib, and perhaps drugs like it, may help to overcome some of these traditional poor prognostic factors.

William Wierda, MD, PhD: Maybe you can comment on the quality of remission with small molecule-based therapy as monotherapy? What does this mean, in terms of duration of treatment, etc?

Matthew S. Davids, MD, MMSc: So far, these studies, that we've been discussing, have been designed with ongoing continuous therapy. They require this ongoing therapy to achieve the progression-free survival numbers that we've seen. We don't know what would happen if patients were to stop, but we have a sense that they would likely progress because most of these patients are not achieving a complete remission, let alone without MRD detectability. If patients are in a partial remission and they stop a kinase inhibitor, we're probably not very confident that they're going to have a durable response. That's why, as we'll discuss, some of the future regimens are combinations that try to achieve deeper responses and allow for time-limited therapy.

William Wierda, MD, PhD: CD20 antibodies are highly important in chemoimmunotherapy regimens. Clearly, the addition of a CD20 antibody has improved overall survival in the FCR (fludarabine/cyclophosphamide/rituximab) regimen. In terms of the small molecule inhibitors, particularly ibrutinib, looking first at the frontline setting, do we think about a CD20 antibody with ibrutinib, for example? Are there data that gives us some insight into that combination?

Matthew S. Davids, MD, MMSc: We have thought about this question—looking at the combination of ibrutinib and rituximab versus ibrutinib alone. A study was led by Jan Burger and colleagues, MD Anderson Cancer Center. In this randomized study, we certainly did see a more rapid improvement in lymphocytosis, as we see with ibrutinib, but this did not translate into improved progression-free survival at this point. Certainly, there are cosmetic benefits to adding the antibody. But whether that's going to actually benefit the patients, I think, remains unclear. There are some ongoing randomized studies that may help to answer this question, including the ALLIANCE study, in the frontline setting. In addition to comparing ibrutinib-based regimens to chemoimmunotherapy with BR, there is also a comparison of ibrutinib versus ibrutinib/rituximab. I think that's going to be an important study to look out for.

Segment 4

Segment Title: Case 1: Treatment Decision: Ibrutinib Monotherapy

Segment Description: William Wierda, MD, PhD; Matthew S. Davids, MD, MMSc; and Nitin Jain, MD, discuss the final treatment decision and toxicity management for the 75-year-old patient with newly diagnosed high-risk chronic lymphocytic leukemia.

William Wierda, MD, PhD: What is your preference for treatment for this particular patient?

Matthew S. Davids, MD, MMSc: For this particular patient, I prefer ibrutinib monotherapy. Especially given the age of the patient, the comorbidities, and the high-risk disease, I think that would offer the most durable benefit.

William Wierda, MD, PhD: How about you, Nitin?

Nitin Jain, MD: I agree. I think ibrutinib would be my treatment choice, for her, as monotherapy.

William Wierda, MD, PhD: In terms of going on ibrutinib therapy, in the older population, there is a little bit of data that clarify toxicities and the profile for toxicities. And perhaps the incidence of toxicity is a bit higher in the older population. Nitin, may you please review the toxicities that we think about with ibrutinib? What do we watch for?

Nitin Jain, MD: Sure. The common ones that I tell my patients to look out for are loose stools and arthralgia. Patients can get skin rashes, like petechia. Those are quite common toxicities in patients who start on ibrutinib. The less common, but more worrisome, events include atrial fibrillation, which I think is seen in up to 10% of patients who are started on ibrutinib. That's something that you have to tell the patient about, so that they are aware of that. Again, atrial fibrillation can be managed with the use of anticoagulation and, maybe, dose reductions.

And then there is also an increased risk of bleeding associated with ibrutinib. So, if a patient is going for a procedure, there are guidelines that recommend holding ibrutinib, pre- and post-procedure, in these patients. The other important aspect is to tell patients about reactive lymphocytosis. They may get this, once they start ibrutinib, for the first few months and should understand that it is not disease progression. They should keep going with the ibrutinib, without any interruption. The lymphocytosis generally resolves with time, without any side effects. So, those are the things that I tell patients about when they are starting on ibrutinib.

William Wierda, MD, PhD: Do you stop treatment for patients who develop atrial fibrillation?

Nitin Jain, MD: In our practice, we generally hold the drug. We get them seen by a cardiologist, to either control the rate or rhythm, depending on how the cardiologist feels about that. Then there is the issue of anticoagulation. This should be discussed. Depending on the CHADS2 score, the cardiology team will decide whether the patient needs an aspirin-like anticoagulant or full anticoagulation. In terms of ibrutinib, we typically hold the drug for a week or so and then we generally restart the drug at 1 dose level lower. Many times, if it's a first episode, you can resume the drug at the same dose level. If the episode were to recur, then the recommendation would be to go down by 1 dose level.

William Wierda, MD, PhD: We avoid the use of warfarin in these patients. Warfarin is contraindicated. There's really no safety data with regard to warfarin, so we're talking about other methods for anticoagulation. If we have patients who develop things like microscopic hematuria, how do you manage them?

Nitin Jain, MD: I haven't seen a lot of microscopic hematuria, per se, in patients who are on ibrutinib. As I mentioned, ibrutinib has an aspirin-like effect and it can lead to increased risk of bleeding. For those patients, I guess one option would be to decrease the dose of ibrutinib.

William Wierda, MD, PhD: How about you, Matt?

Matthew S. Davids, MD, MMSc: We've had a couple of cases like this. We will typically reduce the dose, temporarily, and watch to see if it gets better. Then we do try to rechallenge with the higher dose. If it does come back, we'll sometimes get our urology colleagues involved and do a cystoscopy, just to make sure there's no lesion in the bladder that is bringing out bleeding, for example. But in general, it's quite manageable.

William Wierda, MD, PhD: Are there any other treatment-limiting toxicities associated with ibrutinib that you've run into, Matt?

Matthew S. Davids, MD, MMSc: I think the bleeding issue is a real one, especially as we look at the real-world population. I worry when I have patients who are on anticoagulation and ibrutinib, particularly if they're also on an antiplatelet agent for cardiac issues. Unfortunately, I have run into a couple of issues with central nervous system bleeding. It is usually manageable, but it is certainly worrisome when it happens.

Nitin Jain, MD: Another thing I would like to highlight is hypertension. This is an issue. In several patients, after starting ibrutinib, we have seen their blood pressure rise. Many times, we have to either introduce a new drug or change the dose of the antihypertensive. So, that's another issue with ibrutinib that we commonly see.

William Wierda, MD, PhD: So, this patient was treated with ibrutinib monotherapy. She went on a dose of 420 mg daily, which is the standard dose. The patient did well, subsequently, and remains on the drug.

Segment 5

Segment Title: Case 2: 17p-Deleted CLL Progressing on Ibrutinib Therapy

Segment Description: William Wierda, MD, PhD; Nitin Jain, MD; Adam Bagg, MD; and Matthew S. Davids, MD, MMSc, review the case of a 62-year-old man with relapsed 17p-deleted chronic lymphocytic leukemia.

William Wierda, MD, PhD: Welcome back to our program. Now we're going to go to case No. 2. Dr. Jain?

Nitin Jain, MD: Case 2 is a 62-year-old gentleman who was diagnosed with CLL 6 years ago and was noted to have increased fatigue on routine follow-up. He has now been on ibrutinib for 4 years and has achieved a stable partial remission. Of note, at the time of original diagnosis, the flow cytometry showed a monoclonal B-cell population that was positive for CD5, CD19, and CD23. The FISH results show presence of deletion 17p. A molecular analysis showed that the patient is *IGVH* mutated, and the TP53 was wild-type. On physical examination, the patient currently has cervical lymphadenopathy, approximately 4 cm. His spleen is palpable; 5 cm below the costal margin. The white blood cell count is currently 153,000, with 73% lymphocytes. The patient is anemic, with a hemoglobin of 9.1. His platelet count is 125, his LDH is 250, and his beta2 microglobulin is 4.2.

So, looking at this case, a patient who has been ibrutinib for 4 years, it now appears that this patient may be progressing. Dr. Bagg, what other additional testing would you recommend at this time? And what comments do you have about the pathology in the initial diagnostic workup for this patient?

Adam Bagg, MD: As is standard practice, in the workup of a patient with chronic lymphocytic leukemia, it's important, obviously, to confirm the classical immunophenotype of co-expression of CD5 and CD23 in monoclonal B cells, which was what was noted at diagnosis. At the time of presentation, a FISH panel will typically look at 5 or 6 different abnormalities. Trisomy 12, 13q14 deletion, deletion 11q22.3, and 11p deletions are found in most panels. Some other panels look at the 6q abnormalities or immunoglobulin translocations. In this particular patient, only deletion 17p was found, which is, as you know, a poor prognosticator. With regard to the immunoglobulin heavy-chain gene variable region, for somatic hypermutation analysis, in this patient, it was hypermutated. That, of course, is a good prognosticator, indicating a CLL cell that has transited through the germinal center.

The mutational panel that's looked at in patients with CLL can contain a handful of genes, including *TP53*. A number of other genes may also be looked at, although I think it's accepted that the most important one is *TP53*. Others that could be looked at, that may be relevant to a prognosis, are things like *NOTCH1*, *SF3B1*, *XPO1*, and so on and so forth.

Interestingly, in most patients who have deletion 17p, greater than 90% who have the FISH-detected deletion of the *TP53* gene are accompanied by a *TP53* mutation. This is a little bit unusual, to find the deletion without the mutation on the other allele. So, this seems like a straightforward diagnosis of chronic lymphocytic leukemia with some good prognostic things, like mutated IgH, and some bad prognostic things, like deletion 17p. Of note, this was only performed at the time of diagnosis. It is now 6 years later. Even though the diagnosis was well established 6 years ago, and it may not be necessary to

confirm the diagnosis, some of these assays should be repeated. I think FISH should be repeated. The mutational analysis should also be repeated. It is probably not necessary to repeat the immunoglobulin heavy-chain mutation analysis. That usually remains stable. But I think the patient would benefit from repeat FISH analysis and repeat mutational testing.

William Wierda, MD, PhD: *TP53* mutation analysis, in particular.

Adam Bagg, MD: But depending on the nature of your practice, the other genes could be looked at as well.

Matthew S. Davids, MD, MMSc: How commonly do you see mutated *IGHV* with deletion 17p? It seems like it is less common….

Adam Bagg, MD: I think it is unusual. As you know, most bad things go together with other bad things. So, this sort of discordance is unusual, but it happens.

Nitin Jain, MD: This patient, who has been on ibrutinib for 4 years, which was the appropriate frontline treatment because the patient has deletion 17p, has relapsed. Are there mutations, such as *BTK* mutations and other mutations, that we haven't described, which may be evaluated for in this particular patient?

Adam Bagg, MD: Absolutely. If the assumption is that this patient has become resistant to therapy—in particular, *BTK* inhibition therapy— the leading causes are mutations, not only in the *BTK* gene preventing the drug from binding to the kinase but also mutations downstream of *BTK* that may make the *BTK* inhibition redundant. So, in a patient like this, it's appropriate to look for mutations of not only *BTK*, but of phospholipase C-gamma 2.

Segment 6

Segment Title: Case 2: Treatment Options: Venetoclax +/- Rituximab

Segment Description: Nitin Jain, MD; William Wierda, MD, PhD; and Matthew S. Davids, MD, MMSc, discuss available second-line treatment options for the 62-year-old man with high-risk chronic lymphocytic leukemia.

Nitin Jain, MD: In terms of the therapy, Dr. Wierda, what therapy would you use in this patient who has failed ibrutinib, who has deletion 17p? What are your thoughts, at this time?

William Wierda, MD, PhD: The patient has had frontline ibrutinib and has high-risk features—particularly 17p deletion. And now, the patient is clearly progressing. I think that is reflective of the rise in the white count. The patient has a high white count, at this point, and clearly has progressive adenopathy and splenomegaly. So, we need a new treatment option for this patient. In this type of patient, I like to check *BTK* mutation status and PLC gamma 2, just to confirm that those mutations are there. There probably are some additional BTK inhibitors, that are coming down the line, that don't work by the same mechanism as ibrutinib and acalabrutinib. So, in the future, we may have additional treatment options for patients who have clinical progression on ibrutinib.

Right now, we have drugs that work by other mechanisms of action. Because of the presence of 17p deletion for this patient, chemotherapy is really not an option. That will potentially make things worse for the patient, giving the patient toxicity with no benefit. So, I don't consider chemotherapy to be a reasonable option for this patient.

We have a drug that's been recently approved. A small molecule inhibitor of BCL-2, formerly known as ABT-199, is now known as venetoclax (Venclexta). It's currently approved in the United States for patients who have relapsed disease and 17p deletion. The approval was based on a phase II clinical trial that was reported on recently. Results of the trial showed the activity of venetoclax monotherapy in 107 relapsed patients with 17p deletion. The response rate, in that population, was about 80%. There were about 20% complete remissions among patients who were treated with venetoclax monotherapy, including patients who achieved an MRD–negative complete remission. To me, that speaks to the potency and efficacy of this monotherapy, even in a high-risk group. And, clearly, there's activity by a TP53 independent mechanism of action.

Today, we have a treatment option for this patient who is progressing on ibrutinib. Venetoclax monotherapy, again, is approved, and I would put this patient on venetoclax as their next treatment.

I think there are a couple of clinical considerations in this scenario. The patient is progressing. He is on ibrutinib. We have seen patients who have explosive disease when you stop the ibrutinib. So, we need to be cautious in converting them or transitioning these types of patients, who are developing resistance, over to a new treatment. We have overlapped therapy, where we're continuing the BTK inhibitor while we're initiating venetoclax. That can be safely done. Other groups, and our group have also looked at accelerated escalation of venetoclax. One of the toxicities that we worry about with venetoclax has been fatal tumor lysis syndrome. That can be mitigated by initiating it at a low dose and

escalating the dose over about 4 weeks of therapy. If you do it as it's been recommended in the package insert, it's safe. But that is a concern.

Nitin Jain, MD: So, maybe at that line there is tumor lysis syndrome, despite the fact that the patient has a white count of 153,000. Would you be worried about it? How would you manage this patient, in your practice, to start venetoclax?

William Wierda, MD, PhD: I would absolutely be worried about tumor lysis in this patient, who has a high white blood cell count. The factors that have been correlated with risk for tumor lysis are high white counts, particularly over 25,000, and lymph nodes. The bigger the lymph node cluster, or group, the higher the risk for tumor lysis. The other feature that we have to think about and take into consideration is kidney function. Patients who have compromised renal function will also have difficulty managing the electrolyte abnormalities that happen when we have a large number of cells undergoing apoptosis.

Nitin Jain, MD: Matt, at the ASH [American Society of Hematology] meeting, there was a presentation on the MURANO trial, where venetoclax was combined with rituximab. Maybe you can tell us about some of the highlights of this trial?

Matthew S. Davids, MD, MMSc: Sure. Dr Wierda just went through the data that led to the initial approval of venetoclax, which is actually an accelerated approval specifically for patients with relapsed CLL with deletion 17p. And so, the agency required a confirmatory study. The MURANO study is that registrational study in the relapsed/refractory CLL population. Part of the inspiration for the design of the MURANO trial came from a phase IB study where venetoclax was combined with rituximab. Strikingly higher rates of complete remission were seen, in the 50% range, with good tolerability. Even some patients who electively discontinued venetoclax in an MRD-undetectable state continued to remain in a good remission for a period of time.

So, that led to the development of the MURANO study, which was a randomized phase III trial of venetoclax with rituximab versus bendamustine with rituximab, which is a standard regimen for relapsed/refractory patients. The trial required 1 to 3 prior lines of therapy, a good performance status, and the patients were randomized (1:1) to the 2 arms. Patients with deletion 17p were included in this study, which is interesting because we just heard that we would not consider bendamustine and rituximab as a current standard-of-care option for these patients. I think this does highlight, again, the challenges with these large phase III international trials. When this trial was designed, that was still a regimen that was being used in some of the countries where this trial took place.

Nonetheless, it included a pretty diverse population of CLL patients. The patients were treated with either 6 months of standard bendamustine/rituximab or a 2-year regimen of venetoclax; the first 6 months contained a combination with rituximab. Some of the progression-free survival results were really quite striking. We see that the median progression-free survival for the venetoclax/rituximab group has not been reached at a now close-to-2-year follow up. Whereas with bendamustine and rituximab, there was about a 17-month progression-free survival, which is actually pretty reasonable, considering that the trial included patients with deletion 17p.

Looking across the different subgroups in the MURANO study, the venetoclax/rituximab group had an advantage across all of the different groups, in particular in the deletion 17p patients. And so, that really

highlights this as an option for patients with relapsed CLL with any of the different risk abnormalities. Now, this trial did not include patients who had progressed on ibrutinib, like our patient, in this case, so it's not as informative for that particular population. Nonetheless, I would think that it would be largely applicable to that population.

In this larger phase III setting, with a lot of different centers included, the toxicity profile of venetoclax and rituximab looked quite favorable. There were slightly higher rates of neutropenia seen with venetoclax and rituximab versus with bendamustine and rituximab. But there was not a significant increase in infections. That's really important. Dialing into some of the secondary endpoints in this study, we really saw dramatic improvements in the complete remission rate. At least, by the investigator-assessment, there was a 27% CR rate with the venetoclax regimen and there were MRD-negativity rates of 83% in the blood. This is something that was preserved over the study. There were high rates seen after 6 months. Looking at 12 months, 18 months, and even 24 months, these MRD-negative rates were quite high. Remember, though, that this is a 2-year regimen with venetoclax. So, one of the key questions with MURANO, going forward, is, at the end of the therapy, at 2 years, are these deep responses maintained? Or do we start to see patients progressing relatively soon after therapy finishes?

Nitin Jain, MD: If you look at the progression-free survival curve for the venetoclax arm in the MURANO trial, at the 2-year mark there is a drop in the curve for some patients. So, there are patients who are progressing possibly soon after stopping venetoclax or around the time of stopping venetoclax. Is that because they were MRD positive at that time? Is it because they had active disease? How does that possibly play into the appropriate duration of venetoclax, in your mind?

Matthew S. Davids, MD, MMSc: We haven't seen the details, yet. That population is a relatively small group, in this study. But as we see future data cuts, I think this picture will become a little bit clearer. You're probably right. These are probably patients who are not MRD negative at the end of treatment. Certainly, that could become a decision-making point in these patients, in terms of deciding whether to continue or stop therapy.

Nitin Jain, MD: So, for this patient—a patient who has deletion 17p, who has failed ibrutinib—I think treatment with venetoclax may be appropriate.

Nitin Jain, MD: One other drug that is approved in the relapsed setting is idelalisib. Idelalisib is a PI3-kinase delta inhibitor. The trial that led to the approval of idelalisib was a randomized controlled trial that randomized patients who had relapsed/refractory CLL. The patients were randomized to idelalisib plus rituximab versus rituximab alone. In that particular trial, there was a significantly improved progression-free survival in the idelalisib arm compared with the placebo plus rituximab arm. The 12-month overall survival was higher: 92% for the idelalisib/rituximab arm versus 80% for the placebo-plus-rituximab arm. So, that's another option that is currently available. This regimen is approved, in the United States, for patients with relapsed CLL. And it could potentially be a consideration for patients in whom you may not want to use venetoclax. So, that's another option for our patients who have failed ibrutinib.

William Wierda, MD, PhD: This is a relatively young patient who's failed ibrutinib in the frontline setting. Now he is going on to salvage treatment. It's probably important to have a discussion about allogeneic stem cell transplantation. In my mind, for a patient with a 17p deletion who has failed first-

line ibrutinib and is now going on to salvage treatment with venetoclax, that's probably something that we should be thinking about. We should at least be sending the patient for a transplant consult, to see what the transplant options are for that patient. The other issue is that clinical trials and investigational therapies are also important considerations. Certainly, we would love to have this type of patient referred to our center, to be put on a clinical trial. For example, we're working on a CAR T-cell trial. This may be a great opportunity for patients who have very-high-risk disease, and I would put this patient into that category.