



## PART I: INTERNATIONAL HEMATOLOGIC ONCOLOGY TUMOR BOARD

# Practical Perspectives on Current Challenging Cases of Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Friday, December 9, 2011

**DR LOVE:**

Welcome to International Tumor Board, and I'm honored and excited to be able to be able to listen to our faculty today. On the far side of the podium, Dr Andy Zelenetz, my co-chair, who helped plan this crazy event, Dr Stephanie Gregory, Dr Martin Dreyling, Dr Alessandra Ferrajoli, Dr Julie Vose and Dr Pier Luigi Zinzani.

Now, our mission in doing continuing education is to focus on physicians in practice. And, if you've ever attended any of our events, that's always what our emphasis is and that's our emphasis today.

And what we did today really is a demonstration — I think a principle — is we actually worked with several oncologists in different countries and put together cases. Here are the 4 oncologists from the United States, Canada, France and India, who recruited their colleagues — pathologists, radiologists and, in some cases, other oncologists — and worked with us to select cases that they wanted to present to our faculty. None of these people are here at the ASH meeting today; they're all out there taking care of patients today and probably seeing breast cancer, colon cancer, HCC, who knows what in clinical practice. And we have the utmost respect for these people and are really happy — there are hundreds of physicians like this who presented cases to us in meetings like this and have kind of exposed their own practice in sort of public view, and they do this because they want to learn how to take care of the patients better.

Now, here are actually the 6 cases that we're going to be talking about today.

So, first, Andy's going to talk about a really fascinating case of diffuse large B-cell lymphoma. It's interesting, we were talking before that — we were at the San Antonio meeting this week, and on Wednesday the first case we presented was a woman who presented with breast cancer and diffuse large B-cell simultaneously. And we were kind of talking about how to manage that. And this patient actually presented with what was thought to be breast cancer; it turned out to be diffuse large B-cell. So interesting.

You can see the other cases that we're talking about today. We're going to try to address the common questions that oncologists in practice have about these different diseases.

Now here are the 4 tumor boards that'll be presenting cases: first, from Sandusky, Ohio, in the United States; from Canada, in Ontario; the — several physicians from Nice, France; and finally, 4 physicians from Bangalore, India. And just out of interest, people I guess in India are really into, like, production and stuff. Here are the people who were actually present at this recording that we did. I was in Miami and all these people are over in India, and we somehow managed to pull this off.

So each of you has a PDA; hopefully, you've taken the survey that we've given that relate to these cases, and we're going to talk about them today. And if you have any questions you want to see the faculty address just type them in there and we'll try to address them.

We also are videoing this event, so if you find it useful and want to recommend it to your colleagues, we'll send you out an email when it's posted and they'll be able to experience what happened here today.

If you like what we did today, come back tonight at 6:00 and we're doing the same thing pretty much with multiple myeloma.

So I will first ask Andy to come to the podium and we'll talk about the first case. And as you heard, kind of an interesting, unusual situation, Andy, a young woman, 42 years old, feels a breast mass, gets it biopsied. ER-positive/HER-negative infiltrating carcinoma —typically what might be seen. I'm sorry, triple-negative breast cancer. And she actually ends up having a modified mastectomy. And the oncologist that you will hear was actually consulted to do adjuvant chemotherapy for this lady, thinking she had a triple-negative infiltrating lobular cancer. He was suspicious that this might not be actually breast cancer and had some tests done and this lady's currently on R-CHOP.

So, Andy, here is the physician and his team talking about this patient.

**DR GUPTA:** This is a very interesting case and a sad story, also. I saw her essentially as a second opinion consult. The medical oncologist who works and visits the hospital had recommended chemotherapy with TAC.

Now, here is where it's really tricky. I have not seen a triple-negative lobular. Lobulars are usually ER-positive, HER2-negative. I requested a review from pathology and our pathologist called back frantically the next day, saying, "Gee. I think this is not a breast cancer. This looks like either a poorly differentiated carcinoma or it's a lymphoma. I need to do some more markers. Do I have your permission?" And I said, "Absolutely. Go ahead." And lo and behold, they called me back one day later, after the IHCs were back, that this is diffuse large B-cell lymphoma. I was stunned.

So we called the family the next day and we really had to break this news.

**DR MALLARAJAPATNA:** In this case, we're seeing small areas of activity on CT scan, which were not forming any moth-like structures, although all they were thought to be were probably postsurgical changes, because immediate postsurgical changes cause inflammation, which takes up FDG and shows this kind of activity.

**DR PRABHUDESAI:** Yes. We got this case and the form said that she had undergone radical mastectomy with axillary clearance for carcinoma breast elsewhere and that it was for review. And we put the slides under the microscope and we said this doesn't really look like carcinoma. So the immediate reaction is a kind of panic, because some woman has lost her breasts. So we called Dr Vineet and said that this looks like a lymphoma and shall we do IHC.

And this case, really, had sheets of CD20-positive large cells. And this lady had a nongerminal-center type of lymphoma.

**DR GUPTA:** My question for the faculty was: What about CNS prophylaxis? I didn't give it. This is like a rare case for me, breast lymphoma. So in testes, in sinuses, I end up giving a CNS prophylaxis, but for breast, do you? Should we?

**DR LOVE:** So, before we actually look at this poll question, I'm just kind of curious, Andy, have you seen a case like this or have you seen breast lymphoma, and have you seen it misdiagnosed as breast cancer?

**DR ZELENETZ:** I've never seen it misdiagnosed as breast cancer, but I certainly have seen a significant number of breast lymphomas. And as I'll mention, diffuse large B-cell is the most common, but we do see a number of other lymphomas of the breast, including marginal zone and follicular.

**DR LOVE:** So, Julie, this lady apparently did not have — had the disease removed in this surgical procedure on her breast, had no other evidence of disease. We asked the audience what they thought, after this lady was treated, what her chance of relapse was. How would you answer that question?

**DR VOSE:** I would actually agree with what the audience said and the risk maybe being in the range of 10 to 20% with a fairly localized lymphoma, not a lot of other risk factors.

**DR LOVE:** And Dr Zinzani, we're going to talk a little bit about CNS prophylaxis, but just to get a little ahead of the game here, we also asked the audience, "Would you generally give CNS prophylaxis to a patient like this?"

**DR ZINZANI:**

Absolutely, yes. For breast in women, like for testes, it's very important. It is important to have a prophylaxis of CNS.

**DR LOVE:**

Okay. So we asked Andy to review some of the science related to this question. Andy?

**DR ZELENETZ:**

So here are my disclosures. And — so first about histopathology. As I mentioned, this is a large number of series of 300 — amounting to 305 cases of lymphoma of the breast. Many of these series predate the WHO classification so were really not classifiable with the current classification schema. But if you use those cases, which are classifiable by the WHO, clearly, the most common histology is diffuse large B-cell lymphoma and data that I'll show in a second, the — it's most commonly by immunohistochemistry of nongerminal-center origin. But we do see extranodal marginal zone lymphoma as a relative entity, as well as follicular lymphoma of the breast.

One of the things that is very common is the presentation of an abnormal mammogram, with a smooth mass in the axillary tail, which often leads to a diagnosis of lymphoma.

So one of the things about breast lymphoma is how do patients fail? And what is this — is there really an increased risk of CNS disease or not? So there have been several studies looking at the patterns of failure in patients with diffuse large B-cell of the breast. In this study of 84 consecutive breast lymphomas, the vast majority presented with early-stage disease. The most common presentation is Stage IE or Stage IIE disease; advanced-stage disease is relatively uncommon at presentation.

In this series, the treatment was variable. The one thing that was clear is that surgery alone is not adequate for the management of this disease. But about half the patients in this series — and this is a prerituximab-era series — about half the patients failed systemically, and 12 of the patients failed with CNS disease, both a combination of leptomeningeal and parenchymal brain disease.

In a series from Australia, they saw 19 patients achieve a complete response. Two patients had primary refractory disease with leptomeningeal disease, and an additional 4 patients failed in the CNS.

So one of the things that is emerging, as we can see, is that there's common failure in the CNS.

So — but what about with modern therapy with rituximab and CHOP-based therapy? And, in this Korean series, they looked at a group of patients with diffuse large B-cell lymphoma of the breast and actually matched them with sex, age and stage-matched controls — 3 to 1 — of a nodal diffuse large B-cell lymphoma.

One of the big differences, as you can see, is cell of origin. Overwhelmingly, primary breast lymphoma is a disease of the nongerminal center, as can be seen by the Hans classifier.

The outcome is actually quite similar to what you'd expect for other early-stage disease. However, if one looks at what some of the risk factors are, the only risk factor that was significant in a multivariate analysis was the stage-modified IPI, and that was significant for both progression-free and overall survival.

If one looks at the patterns of failure, again CNS disease, it was common with 4 CNS events among these 25 patients.

So what do we know about CNS disease and the reduction of risk with rituximab-based therapy? There have been a number of retrospective series that have tried to analyze this. The Japanese series included 1,221 patients looking at the risk of CNS events in the R-CHOP era, and the risk was about 6.7%. This is actually not that different from the historical controls with CHOP-based treatment.

So if one looks at the series where one can compare CHOP-based therapy to rituximab and CHOP-based therapy, most of the series, interestingly, have shown no benefit for the inclusion of rituximab. Two series are in contradistinction — the RICOVER-60 trial, the retrospective analysis of that did demonstrate that there was an advantage for rituximab and CHOP-based therapy with a reduction in the risk of CNS events that was significant. And, in the Vancouver experience, in a multivariate analysis, one of the predictors for reduction in CNS events was inclusion of rituximab into treatment.

So, what about prophylaxis? So if we look at the RICOVER-60 trial, and we look at the prophylaxis, in the patients who received rituximab, IT prophylaxis did not seem to make much of a difference. If the patients did not receive rituximab, then there was a protective effect from intrathecal prophylaxis.

If we look at another series, again looking at CNS events in rituximab and CHOP-treated patients, and looking at CNS prophylaxis versus not, the actual risk of developing CNS events was not impacted by the administration of intrathecal prophylaxis.

So, what about our patient here? Clearly, diffuse large B-cell lymphoma is the most common lymphoma of the breast. Breast involvement is a risk factor for CNS events. Even in the rituximab era where that

risk still — there's a relative risk of about 10-fold when there's breast involvement. Rituximab may have some, but not an enormous impact on the reduction and IT prophylaxis remains controversial. And, despite the variable data, I actually still would give IT prophylaxis in this patient.

Just a couple of things, there's nothing about breast lymphoma at the meeting, but there are a couple of interesting abstracts that are relevant to this case that will be presented that are really focused on the risk of CNS involvement. And with that, I'm going to throw it out to the panel here.

**DR LOVE:** Thanks a lot, Andy. Let's start with Stephanie. In terms of the issue of CNS prophylaxis in general, and in this kind of a case, what do you actually say to your patients? And what's your — I'm actually almost a little confused about exactly how much CNS prophylaxis helps.

**DR GREGORY:** Right.

**DR LOVE:** What do you say to your patients?

**DR GREGORY:** And breast is such an unusual presentation. It's — certainly testicular needs prophylaxis. We know that the involvement of paraspinal, extending into the epidural space, perhaps in the paranasal area, you give prophylaxis. There are certain parameters of how many extranodal sites, how high the LDH is. Those are patients you may consider for CNS prophylaxis. I have not routinely given it in limited-stage breast disease. And I, again, I think it's controversial. I don't even look at a spinal tap in these patients. I mean, that may be the wrong approach. But I don't think there is really a standard for localized breast lymphoma for CNS prophylaxis.

**DR LOVE:** So, Andy, what about this very basic question: Does CNS prophylaxis work and how much?

**DR ZELENETZ:** So we have the common wisdom, and the common wisdom is that there are risk sites — testes, paranasal, sinus, bone marrow, high IPI, high FLIPI — and so we've all been trained to give intrathecal prophylaxis. Typically, it's 6 to 8 doses, oftentimes 1 with each cycle of chemotherapy. But the major question has been actually: What is the risk reduction with this therapy? And that's actually been where it's been really difficult to clearly and unequivocally demonstrate that we reduce the risk of CNS events with the prophylaxis. And in the rituximab era, I think the data is even a little bit less clear as to whether we know that there's a risk of CNS events, but whether we can reduce that risk is the question.

**DR LOVE:** Martin, and then Pier Luigi.

**DR DREYLING:** I would also just add on your comments, I agree 100%, but we in Germany, based on the data you also showed, are a little bit reluctant to perform intrathecal prophylaxis. And, therefore, in this case, we would probably have to perform the diagnostic LP. But we more or less gave up on the intrathecal prophylaxis and only give systemic methotrexate in the cases where we really foresee some risk.

**DR LOVE:** Pier Luigi.

**DR ZINZANI:** I totally agree with Martin. There are some data from the GILA group from France, concerning the important role of 1 or 2 dose of — intermediate doses of methotrexate, to reduce the risk of CNS involvement during the follow-up after the induction phase.

**DR LOVE:** It kind of has a little better intuitive feel to it too. And every time I used to think — I can remember back as a fellow, intrathecal treatment, and kind of saying, "Hmm. Kind of strange." Anyhow, let's finish up in terms of this case, and one of the things we want to try to do today is kind of get our alerts up for what's happening in the next few days at this incredible meeting. There are so many things to go to. And we want to ask the faculty to kind of point us in the right direction in terms of what's happening at this meeting. In some cases, we'll talk about some stuff that's we have the abstracts on, but really, in terms of what to look forward toward. How about in diffuse large B-cell, Andy? You mentioned a couple of papers. What — just going beyond that, what else is happening at this meeting, Andy, or has happened in the last year in the field that you think people should be focused on?

**DR ZELENETZ:** Actually, at this meeting I don't think we're going to see a lot that's really new in diffuse large B-cell lymphoma. My colleagues can disagree, but I — and really, the biggest single change in the practice of diffuse large B-cell lymphoma occurred with the introduction of rituximab to the CHOP regimen. And we have been working hard to further improve things, and there are a number of ongoing trials. There have been trials in higher-risk groups. And still, it's been hard to really clearly demonstrate that we can alter the outcome much beyond what we've done with addition of rituximab to the treatment paradigm.

**DR LOVE:** Alessandra, what about new agents? And we're hearing about some new agents in B-cell neoplasia. What's out there right now that you're excited about, and specifically, also, in diffuse large B-cell?

**DR FERRAJOLI:** In terms of the new agents, definitely the combined antibodies. Very exciting. We have had great results in ALL that can be considered similar to diffuse large B-cell lymphoma. We did this new monoclonal antibody that is being developed.

**DR LOVE:** Julie?

**DR VOSE:** I think the other area that's really exciting is the work in trying to understand the different types of diffuse large B-cell lymphoma.

**DR FERRAJOLI:** Yes.

**DR VOSE:** So, rudimentary, we know now that there's 3 major subtypes: the ABC, GCB, mediastinal. We don't actually know what to do about that, however. And so that's kind of the next role, is to try to understand some of the newer agents and are they more active in certain subtypes of diffuse large B-cell. We have a lot of preliminary information that shows they might be, but we don't actually have the clinical trials yet.

So I think a lot of the new pathway-driven agents are the ones that are going to be tested. The B-cell pathway and JAK2 inhibitors and other pathway agents are going to be tested in those subtypes.

**DR LOVE:** JAK2 inhibitors. Now that's something that's exciting. But what's the tie-in there to diffuse large B-cell?

**DR VOSE:** Actually, that pathway is very important in certain subtypes of diffuse large B-cell. So I think the way of the future is to identify the different subtypes of lymphomas, look at some of their pathways and try to select the patients for certain types of treatments on clinical trials.

**DR LOVE:** Have patients actually been treated with JAK2 inhibitor monotherapy with diffuse large B-cell?

**DR VOSE:** Actually, we just have a new clinical trial that we've just started recently in that and based upon some pathway analysis.

**DR LOVE:** It'd be nice to see something like that and what happened to the myelofibrosis happening in diffuse large B-cell, a common disease.

Final comment from Andy. Again, what do you see happening? What are trials cooking out there that we ought to be keeping our eyes on in terms of this disease?

**DR ZELENETZ:** In terms of trying to understand more about the molecular biology of the disease, about to complete, after a number of years, is the CALGB trial comparing rituximab and CHOP to dose-adjusted EPOCH-R. This actually had it embedded, the primary endpoint of actually molecular diagnosis. All the tumors have been profiled by gene expression — will be profiled by gene expression profiling. This is going to be done in a batch at the end. And from that, we should actually learn a lot more about the parameters that predict response to these treatments. But that's almost an older generation approach. Because I think that Julie's absolutely right, the next generation is going to be to break these diseases apart into their component subtypes, and it's going to be activated B-cell. But it won't be just activated B-cell, it's going to be activated B-cell, part 11 mutation, activated B-cell, CD79 mutation. And then we're going to take these subgroups and actually use treatments that are most appropriate for that subgroup.

**DR LOVE:** Sounds like personalized oncology.

**DR ZELENETZ:** That's where it's going.

**DR VOSE:** That's where it's going.

**DR LOVE:** One final issue that does come up. We were talking — we're not really going to focus today on international differences and access to care. We really just presented patients from around the world to really just more to kind of create a subliminal thought about how cancer really is a human condition. I mean, obviously, the treatments that are available are different. But it's part of the human condition, and hopefully the advances that occur in this disease are going to affect all of humankind, but we do have to deal with practical issues. And one more I just want to throw back out there, Stephanie, is the issue of repeat PET scanning, because we get a lot of questions from docs in practice about that. There is a trial looking at this. Where are we today with that?

**DR GREGORY:** Yes. I think that we have to remember that the PET scan still is used at the end of therapy for curative cancers, that's Hodgkin lymphoma and diffuse large B-cell lymphoma. There are the guidelines. Midcycle PET scans in diffuse large B-cell are still being studied in clinical trials. There are many trials that show a lot of false-positives that have to be biopsied, and they end up being negative. So the answer is not out there yet, and we're not changing therapy on midcycle PET scans.

- DR LOVE:** I'll ask Stephanie to go to the podium for the next case, but while she is, Martin, do you agree with that? I mean, it's awfully tempting to get an interim PET scan. I kind of wonder if it were me, I maybe want to kind of take a peek at it. Is it really a bad idea?
- DR DREYLING:** Well, specifically, in Germany we are on a somewhat third-world country limbo, in the way that PET is not reimbursed at all. So our setting is totally different. However, I would completely follow what Stephanie said. We do have strong data that PET after completion of induction is a very strong prognostic marker. Still, when it comes to changing the treatment, I think in the vast majority of cases you have to perform a biopsy to really reconfirm that it's really relapsed disease.
- DR LOVE:** So the next case comes from the heartlands of America. And, in fact, the patient actually works in the agriculture industry, which sort of ties into the story. A 54-year-old man who works in the produce industry and presents with diffuse bilateral cervical adenopathy. On biopsy, which you'll see, he has a Grade I/II follicular lymphoma, has 10% bone marrow involvement. And he actually receives treatment —and you'll hear kind of why — with bendamustine/rituximab. Clinically, he has a CR, and he's currently on R maintenance. So kind of like a pretty common case, but there's an awful lot of patients like this and there are a lot of questions. And I have a feeling there are going to be a lot more questions by Monday or Tuesday of this week. But, Stephanie, here's Dr Lobins talking about this patient with his team.
- DR LOBINS:** He had a FLIPI score of two, but he had extensive disease, both above and below his diaphragm. So we talked about options, which would include observation versus R-CHOP versus R-bendamustine. But because he wanted to work, and he wanted treatment, that's how we chose R-bendamustine as the initial treatment.
- DR LOVE:** What happened on the first evaluation?
- DR LOBINS:** I did CT scans to see how his disease was, and his disease was entirely gone by CT scan. And so he was pretty happy with me and pretty confident. So, by the time we talked about rituximab maintenance and the most up-to-date data on the PRIMA trial, he was very happy to — whatever I suggested, he was going to do.
- DR ZIEBER:** The initial image is a CT study of the neck, showing a sagittal slice through the neck. What we see is multiple enlarged but separate lymph nodes, posterior to the sternocleidomastoid muscle, level 5 area. You also see an enlarged node anterior to the sternocleidomastoid muscle, which would be a level 2 enlarged lymph node.
- This is a CT, and then on the right-hand side of the screen is a PET-CT fused image. What we see is, again, multiple prominent but separate lymph nodes deep to the sternocleidomastoid muscle in the level 2 area. We also see 2 separate enlarged lymph nodes.
- This is a left cervical lymph node biopsy. The thing that really strikes your eye is there are follicular and/or nodular areas, which are synonymous, and they're all about the same size. When you look at a normal node, the nodules are almost always variable.
- When you get close on those areas of nodularity, it's a very monotonous population of small, variably angulated cells. If this were a normal nodular area, you'd have a mix of cells. So this tells me I have a node that's — most of the architecture is replaced. It has a nodular or follicular pattern, and they're small cells.
- In today's world, you put immunostains on it because that really helps characterize the cells more fully. These cells were CD20-positive, CD10 and BCL-2- and 6-positive. So, pathologically, we have a follicular lymphoma. It's Grade I to II.
- DR LOBINS:** Well, the duration of maintenance rituximab has been 2 years, but we don't know if 2 years is the optimal duration versus 3 years or 4 years. The RESORT trial is going to go for indefinite therapy. Are there any trials that are looking at other durations?
- DR LOVE:** So before Stephanie talks, let's just see what the audience said in terms of a couple of issues about this patient. So, first of all, in terms of the question of rituximab maintenance, it looks like, by far, people would use 2 years.
- The other question we threw out there, and I didn't even think about this, but Dr Lobins actually brought this up when I chatted with him — you didn't see this part of the video — was: Does this history of insecticide exposure affect the way you treat him? He was like, "Should I think about longer maintenance or more aggressive follow-up?" Is it a factor? So we asked the audience and it looks like people are a little bit split, but look at these answers and a fair amount of the audience thinks maybe you approach the patient a little bit differently. And Stephanie's going to address these points. Before

she does, I think we have to do a quick faculty poll. So this will be induction FL 2 years later. It's been 2 years, right, since Dr Rummel presented the BR data that you're going to comment on? But there was a lot of kind of shaking out that went on there, particularly in the first few months, and we've been tracking this over the last couple of years in terms of what people are doing. So I just want to start down here with you, Pier Luigi. When you have a patient who has FL that requires treatment, right now, outside a protocol setting, what tends to be your first therapy in the younger patient like this, 50, 60 years old? What tends to be your induction therapy if they're 75, 80?

**DR ZINZANI:** So, for a young patient, the induction treatment is CHOP plus rituximab, but I think bendamustine plus rituximab, in the future, will be the front-line treatment. So far, in Europe, and, of course, in Italy, it's impossible using induction in front-line treatment. But bendamustine is a quite active result and kind of extra hematological toxicity if you compare with CHOP. And Dr Rummel presented this data, as you say. And this is very important for the patients. So we have the efficacy without any kind of extra hematological toxicity.

In terms of hematological toxicity, it's quite the same. I think, also for the elderly patients, it's more important to have bendamustine because it's less toxic than in the young patients, if you compare with CHOP plus rituximab.

**DR LOVE:** Okay. So just instant poll, very, very briefly, what's your treatment? Julie?

**DR VOSE:** In this patient, I think that bendamustine plus rituximab is very appropriate and I think I would choose that. And more and more people are choosing that. I will just add one thing. If they have a follicular Grade III or a diffuse component, I would more go toward the CHOP-R.

**DR LOVE:** Interesting. Alessandra?

**DR FERRAJOLI:** I would go with the CHOP/rituximab, because bendamustine/rituximab is an excellent treatment strategy, but we don't know what are going to be the long-term complications. We do not have as long follow-up as we have with CHOP/rituximab. And, second, myelodysplastic syndromes will be something to keep in consideration.

**DR LOVE:** Age 75?

**DR FERRAJOLI:** Age 75, practicality is what counts. So I would definitely fit to the specific situation, and I may use bendamustine in that light.

**DR LOVE:** Martin?

**DR DREYLING:** My first choice would be still R-CHOP, but that is because we do believe in the role of autologous transplantation first relapse. However, it's fair to say, in Germany, where we have experience with bendamustine already since decades, that, specifically after the ASH data have been presented 2 years ago, there's a major shift. And now it is probably also the younger patients, quite a remarkable part is being treated with bendamustine.

If this would be an elderly patient, I would probably only go for 4 cycles BR.

**DR LOVE:** It kind of reminds me a little bit of breast cancer. We had — TC came along. It was better than AC, and nobody kind of believed it. But it ended up with better results. Andy, where are you today with this decision?

**DR ZELENETZ:** So in the elderly patient I would use R-bendamustine. I might, in fact, restage after 2, and if there's a really good response, stop after 4. I'm concerned about long-term toxicity, ability to retreat and to mobilize stem cells. The data suggest that we can mobilize stem cells after first-line bendamustine, but it's based on a very limited number of patients. So I would actually — I'm going to be the outlier here; I would actually still treat this patient, with this presentation, with R-CVP.

**DR LOVE:** CVP. All right!

**DR ZELENETZ:** And so we do have a prospective randomized trial from Italy, showing that there is no survival difference. There is a difference in progression free and time to treatment failure. But it does not impact overall survival, and it maintains the ability to use doxorubicin later, when the disease is more aggressive.

So I actually think that — a lot of people think R-CVP is dead. I think, without a survival disadvantage, it's really hard to say that it's there. And —

**DR ZINZANI:** And remember the Martin data.

**DR ZELENETZ:** Well, remember, that's not even CVP.

**DR ZINZANI:** Okay.

**DR ZELENETZ:** That's CVP — that's CHOP-lite.

**DR LOVE:** Stephanie, you're always our co-chair of this and you work with us on other programs. And we've been hearing these things go on now for 2 years.

**DR GREGORY:** Same story!

**DR LOVE:** Same thing.

**DR LOVE:** Get 6 other people up there, there are going to be some R-CHOP people, although not too many R-CVP. Where are you today, Stephanie, outside a protocol setting?

**DR GREGORY:** Okay. Well, I really think we have to address — we were talking yesterday at an Advisory Board, that the follicular lymphoma patient is probably the patient that you have to spend the most time with. And, actually, Andy mentioned that, but all of us know that. Because there are so many choices. There's no standard of care. And you really need to determine whether that patient has low tumor burden or high tumor burden, because I didn't get a good feel for the tumor burden in this patient, except to know that he had lymph nodes all over, which doesn't necessarily mean he had high tumor burden. And so the real question is, "Did he need treatment even and could single-agent rituximab have been used?"

So I think there a lot of issues that need to be addressed when you have —

**DR LOVE:** I just have to come back to Martin, just for a second, because, again, it really is analogous to breast cancer. We had 1 study, TC versus AC. Nobody knew whether to believe it. I mean, what do you think about the German trial? It was done in your country. It showed that BR was better. Not that it was the same and less toxic. Better. I mean, do you believe that that's the case?

**DR DREYLING:** I think it's very challenging, these data. Because this is based on a large study. It's quite convincing. And the only caveat, as I said, is the potential of myelotoxicity on the long range. And this is what we experience always — are the rates previously in our decades of experience. Otherwise, I think these data are very reliable. Yes.

**DR LOVE:** Okay, Stephanie, why don't you go through some of the science.

**DR GREGORY:** Let's go. These are my disclosures.

This is the case. It's a male who's worked in the produce industry, with exposure to pesticides, had diffuse adenopathy. We heard he was a FLIPI, so sort of low FLIPI. It's a standard follicular lymphoma. There's some bone marrow involvement. And a PET was done rather than a CT, so I refer you to an abstract about the role of PET now in follicular lymphoma. As you know, it's really not been the standard of care, but we are getting more information on PETs in these patients.

I'm going to address those questions on that slide.

Risk factors for NHL: These are the ones that we all know about, and the question of pesticide exposure is certainly there. We have lots of patients who come to us, talking about exposure to toxins, pesticides, fertilizers. We know there's an increased incidence in Julie's state because of farming, and that's why she sees all those lymphomas in Nebraska.

These are very few references I was able to pull out on the exposure and cause of lymphomas, well documented in a lot of situations. I'm not even going into details of this. I don't know if this man got his lymphoma because of his exposure.

So we're talking about the most common indolent lymphoma. We know it's not curable in general, although some people would argue with me. Rituximab's been a major advance, but it certainly has not cured patients. There is no standard of care and I think you really need to decide, with your patient, what is the best treatment. And that's really important as far as low tumor burden/high tumor burden.

We need reliable biomarkers. These are some of the biomarkers that are out there right now. We know about the BCL-6, CD10. Andy, actually, I think at Sloan-Kettering, is looking at the Ki-67, the MIB-1. These are proliferation index. Maybe if you have a low proliferation index you don't have to be treated. If you have a higher proliferation index, you can be treated.

The LAMs, or the lymphoma-associated macrophages, are also something that are being evaluated. And I refer you to abstract 90, I believe it is, looking at the absolute monocyte count in patients with follicular lymphoma and whether it might imply some prognostic factors.

These are what all of you know. I'm not going to spend time. This is a single agent, watch and wait, chemotherapy, various modalities. And perhaps someone should mention R-chemotherapy followed by radioimmunotherapy, which I haven't heard talked about at all yet.

Now, when is it okay to watch and wait? And I think that's very important. I don't use the FLIPI as



really a decision as to whether I'm going to treat a patient or not. And I think that the GELF criteria are a very important way of looking at patients as to whether or not they need treatment. And you can defer treatment in a patient with follicular lymphoma if they have less than 3 lymph nodes that measure 3 centimeters, if they don't have 1 lymph node that's more than 7 centimeters, if they don't have a big spleen, if they don't have compression symptoms, if they don't have cytopenias. So these are just some of the GELF criteria that I urge to think about when you're talking to your patient.

This was a very controversial abstract last year at ASH presented in the plenary session, randomizing patients who had very low tumor burden to 3 arms, watch and wait, rituximab for 4 weeks, or rituximab for 4 weeks and then 2 years of maintenance. And you can see from this study, the author got up and said that it's very wise to give rituximab to these patients because look at the progression-free survival. It is much improved. And the time to actually needing chemotherapy is not reached in patients who receive rituximab therapy.

If you didn't need treatment at all, I mean why give them something? So I think this is still a controversial area.

We all know about the National LymphoCare study. There are many, many abstracts at ASH now looking at certain parts of this LymphoCare study. There are abstracts looking at which patients did better if they got R-CHOP or the R- CVP. So I ask you to look at some of those abstracts at this meeting.

You can see that from the National LymphoCare study in the United States, 18% of the doctors were watching their patients. And about 14% were putting patients on rituximab monotherapy.

This was before the era of bendamustine, so that's why you don't see the bendamustine up there.

Now, treatment of advanced-stage follicular lymphoma. Again, I've talked to you mainly about low tumor burden and high tumor burden. So low tumor burden, you can decide to watch and wait or you can give them single-agent rituximab. If they relapse, they can be used — that same drug can be used again.

These are the results with all the chemotherapy regimens that we know. And the regimens with asterisks have actually shown improvement in overall survival. And, actually, in patients who were previously treated there are also 2 trials that showed improved overall survival. Both of those previously treated trials had rituximab maintenance in them.

This is the bendamustine versus the R-CHOP trial that we talked about already. I think most of you know this has been presented 2 years in an abstract form. Overall responses, complete response rates, the complete response rates is better in the bendamustine/rituximab arm, progression-free survival better in the bendamustine/rituximab arm, and fewer side effects without alopecia.

Now, this has not been published and we keep talking about that. It has been submitted and I did talk to Dr Rummel yesterday. And so hopefully, we will see this in publication shortly.

This is a very important trial. This is one of the newer ECOG trials. And we are really trying to get away from toxic — for patients with higher tumor burden, we are trying to add immunomodulating agents, biologics, and treating these patients with combinations of drugs that we know are very effective. And so this is the most recent ECOG trial for high-risk follicular lymphoma, advanced stage. It's a BR arm, a BVR arm and a BR arm followed by different maintenance — rituximab maintenance in 2 arms and rituximab and lenalidomide maintenance in another arm. This is active and accruing.

So how about rituximab maintenance? Most of you obviously are using that after an R-chemo regimen. Which patients do we use that in? What are the long-term toxicities? This was all based on the GELA trial, which was published last year in *Lancet*, and this led to the FDA approval for 2 years of rituximab maintenance after patients who received R-chemo. So that's the approval for maintenance rituximab today.

This is the results of the PRIMA study, showing improved progression-free survival in those patients who had rituximab maintenance. There is no difference in overall survival.

This is the late-breaking abstract. I suggest, if you are around on Tuesday, try to see this. This is a study that we've been waiting for, the results of the Eastern Cooperative study, the RESORT trial, which is rituximab extended scheduling, which means maintenance or re-treatment at the time of relapse. And I think you're going to be surprised at the results. They actually found no difference between the 2 arms as far as a significant difference. So you can either use maintenance rituximab or you can use re-treatment at the time of relapse. And I think the recommendations from the author may be that

rituximab re-treatment is probably what we should do in patients who have been treated initially with rituximab.

I want you to remember that the FIT trial also was chemotherapy followed by radioimmunotherapy, and we now have a 7-year follow up of these patients. The progression-free survival is dramatically improved in those patients who had consolidation with radioimmunotherapy. And, actually, if you look at the patients that were in complete remission after their induction therapy, they are still in a progression-free remission at 107 months compared to only 32 months of the patients who were observed only after chemotherapy. So radioimmunotherapy still has a role.

This is my algorithm for patients with follicular lymphoma. Low tumor burden, you can watch and wait. Some people will put those patients on rituximab. I'm not sure of the need for rituximab maintenance in those low tumor burden patients. If they have high tumor burden, BR, R-CHOP and rituximab maintenance or RIT consolidation is certainly acceptable. You have to decide about comorbidities.

So emerging therapies are new CD20 monoclonal antibodies, bortezomib and lenalidomide. And if may just have the next slide, we'll show you that there are very nice responses with lenalidomide and rituximab in the relapsed setting and that's why these drugs are being moved up in the ECOG trial to front line.

These are some additions with bortezomib and rituximab in the relapsed setting. Again, this is why bortezomib is now being moved up to the front-line setting. Some very impressive responses.

I've pointed to a few of the abstracts at ASH this meeting. Dr Zinzani, on our panel, is going to give us follow up of RFN followed by radioimmunotherapy and rituximab maintenance. There are some very important trials listed here. And a lot of radioimmunotherapy abstracts at this meeting.

On Monday, there are a lot of trials looking at bortezomib/lenalidomide/rituximab and some of the newer monoclonal antibodies. The one that's probably most advanced in studies is GA101. It's a humanized monoclonal anti-CD20 antibody and is being looked at in combination with bendamustine. At this meeting, you'll see studies of the single agent in relapsed lymphoma and also combined with rituximab.

So I thank you. Patients with follicular lymphoma are living longer. Lots of new options. A lot of new novel combinations can be used. I think there's no decision as to whether rituximab maintenance or RIT should be used after chemoimmunotherapy. I think that the RESORT trial is really an impressive finding after low tumor burden and rituximab. Probably maintenance is not the thing to do. And I think that we need to remember to please accrue patients to these clinical trials.

Thank you very much.

**DR LOVE:**

So let's pick up on a few of the things that Stephanie talked about. And, of course, I think one of the most anticipated presentations is going to be the RESORT trial data. I am getting a little bit of a flashback to Wednesday when I was San Antonio, because there they presented the much-awaited NSABP-34 clodronate adjuvant trial. We've been waiting for that for a long time. And it's "negative," except if you actually sat there and watched it it was kind of interesting. Over age 50 it was not negative, so things are not always as straightforward as they would seem. And we don't want to kind of steal the thunder of what's going to be presented here, but I am curious — I'll start with Martin — in terms of where you think things are heading with maintenance. One of the things that I see here in this abstract, Martin, that I find kind of interesting, is it says that at 3 years, 95% of the people who got the extended rituximab were free of cytotoxic therapy, kind of like that watch and wait study last year, as opposed to 86% in the ones who just got the initial R. So I flipped that around and say, well, it sounds like there's a 5% chance they got chemo at 3 years versus a 14% chance. Is that valid — again, this came up last year with the watch and wait — is that a valid thing to look at? And what do you think about, and we're going to talk about R maintenance in mantle cell, but what about in follicular?

**DR DREYLING:**

I can just agree with Stephanie that also in our daily clinical practice, 2 years maintenance is standard full scope. There's — this is rather clear. And the question is whether this has to be like this for all patients. We don't know yet, but this is our current standard approach.

Now, when it comes to rituximab monotherapy, and to challenge the question "Is it not worthwhile for the patient not to suffer under subsequent chemo?" I would absolutely agree that it's of value, per se. However, I think we have to have a closer look at the data. I just would refer to the additional data. We do have to know what happens with the patients when — the way of relapse under rituximab maintenance. And as soon as we have these data we will be able to really evaluate the benefit of ongoing maintenance.

**DR LOVE:** And Stephanie, you pointed out the RESORT trial looks at low tumor burden patients. Now this patient, who's a higher tumor burden, who got chemo —

**DR GREGORY:** I don't know if he is a high tumor burden, because I don't have any measurement of lymph nodes on him. I don't see mass of splenomegaly. I didn't hear about cytopenias.

**DR LOVE:** Well, he has more than 3 areas, right? Anyhow...

**DR GREGORY:** No. More than 3 centimeters in 3 —

**DR LOVE:** Ah, okay. So if you have a patient who has high-risk disease and is getting R-chemo, what is your approach in terms of maintenance or not, and what do you do at 2 years?

**DR GREGORY:** The PRIMA trial has at least given the approval to use rituximab maintenance. It improves progression-free survival. There is no difference in overall survival. So I still think that clinicians make their own choice about that. It is not a dictum, that if you get R-chemo you need to get R maintenance. Do I do that in all patients? No, I don't.

**DR LOVE:** Do you do it in most?

**DR GREGORY:** I do it in most patients.

**DR LOVE:** Andy?

**DR ZELENETZ:** When you get follicular lymphoma you're in it for the long term and you're in it for survival. The quality-of-life data is difficult to interpret and is incomplete at this point. But rituximab maintenance has not altered survival. If we look where rituximab has altered survival, every single time when rituximab has altered survival in follicular lymphoma a trend has emerged by 18 months. At 24 months, the curves are absolutely 100% overlapping. That's one issue. The other is, just extending a observation from one study to another may not always be the correct thing to do. Rituximab maintenance was shown after R-CVP, after R-CHOP. It was not shown after bendamustine/rituximab. You already pointed out bendamustine and rituximab is the superior regimen; do you show an advantage for maintenance? In the ECOG study that looked at FC versus CVP, FC was a superior — it killed more people, that's why it was closed — but it had a super long-term, if you didn't die of complications, long-term remission and it there was no benefit for maintenance in that group of patients. So what you get induced with actually has a big factor potentially in whether maintenance works.

**DR LOVE:** So before Martin comments, I still have to come back to you, Andy, about practical issues. What actually happens in your practice when you decide to give R-chemo, when they're done, do they usually get maintenance? Do they never get it? What do you do?

**DR ZELENETZ:** I would say about a about quarter or less get maintenance.

**DR LOVE:** Martin?

**DR DREYLING:** I would just comment on your point that there are no data on overall survival, and I would strongly object that, yes, there are and they are based, for example, on the Cochrane analysis which has been just updated recently. So that's based on a reasonable number of studies of 8 or so. But I would like to pick up really, your point you said about the fludarabine combinations and Stephanie, you didn't address this point. Now, fludarabine combinations, based on the recent Italian data also, and Andrew mentioned R becoming less popular for first-line treatment in Europe. And I just wonder about your perspective.

**DR GREGORY:** We are moving away from fludarabine. We just had that conversation. I'm just getting concerned about the cytotoxic, long-term side effects of fludarabine. So I'd rather have Dr Zinzani discuss the fludarabine and that data.

**DR LOVE:** Julie?

**DR VOSE:** Do you want discuss that first?

**DR ZINZANI:** Yes. So I use this fludarabine-containing regimen in front-line treatment, in particular, fludarabine plus mitoxantrone and rituximab. There was also was rituximab in several patients with follicular lymphoma and also in follicular lymphoma. I think the result in terms of activity, like maximum percent of the last meeting, are quite the same if you compare with CHOP plus rituximab, probably bendamustine plus rituximab.

There is an important neurotoxicity and there is a high risk to have secondary myelodysplastic syndrome. I saw only 1 patient with this particular complication, but I know there are some data from Stephanie in Chicago and also from MD Anderson.

Another factor, bendamustine, in terms of pharmacokinetics, is very close to fludarabine.

**DR GREGORY:** Yes.

**DR ZINZANI:** You have to remember that for the future.

**DR LOVE:** So, Julie, sorry to keep hammering on what people do, but we do a lot of surveying, as you know, you've participated, of both physicians in practice and investigators. And I would say that Andy's answer would be unusual in both groups. How do you approach outside a protocol setting, the decision of R maintenance after R-chemo?

**DR VOSE:** I just want to bring up that this type of patient we're going to be treating off and on for many years. Remember, this patient is going to be alive 10, 15, 20 years, so we have to keep that in mind for long term. What we do now makes a big difference with what's going to happen with this patient in the future. So with that in mind, we have to remember that maintenance rituximab is not totally without side effects in some patients, and there are a number of patients — a small percentage — but some patients that have multiple infectious complications and sinopulmonary complications. And so there are a number of patients that cannot get it.

I would say in our practice that, up until the PRIMA study, we didn't do maintenance at all in the first line. After the PRIMA study came out and the FIT study came out, we do talk about that with patients and offer them an option to do one or another, depending on their situation.

I would say, as far as my patients, probably the number of patients I give it to would be maybe about 50%.

**DR LOVE:** So just a word about radioimmunotherapy. Stephanie, we are seeing a study we've been hearing about for a long time presented at this meeting, the SWOG study. Again, without kind of going into the details of what they're going to present, what's the trial and what do you think it's going to mean?

**DR GREGORY:** Well, the SWOG study — all these trials get reported after we've moved on to newer therapies, so that was a CHOP with rituximab or CHOP followed by radioimmunotherapy, and the results were comparable. But that was — again, another study is now in place and already accrued and that's looking at R-CHOP followed by radioimmunotherapy followed by rituximab maintenance. So you need to sort of look at all the parameters now and address those issues again. That trial was the next trial that SWOG did. It's a Phase II trial. It's already accrued. And I should mention that there is an ongoing international trial now, looking at R-chemotherapy, 1 arm randomized to rituximab maintenance and another arm randomized to radioimmunotherapy. And that, hopefully, will give us some information about: Is radioimmunotherapy, 1 week of treatment, as good as 2 years of rituximab maintenance or 4 years or 6 years of rituximab maintenance? So these are questions that have to be answered.

**DR LOVE:** Also, Alessandra, would, as in this SWOG trial that's referred to, if you look at the abstract, at the end of it they refer to this study that's already completed — they're waiting for results — where you get R-chemo, radioimmunotherapy and then R maintenance. And, interesting, I just pulled this off the web, and if I'm reading this correctly they get the R maintenance for 4 years.

**DR GREGORY:** Hopefully.

**DR LOVE:** And I'm not sure where that came from. But anyhow, Alessandra, where do you think things are heading in terms of long-term therapy in terms of follicular lymphoma and integrating these sort of longer-term concepts?

**DR FERRAJOLI:** It's probably going to go from — the initial therapy is definitely a combination chemo monotherapy, but for long-term therapy and maintenance, I see possibly a role for an alternating of agents with different mechanisms of action, with patients transitioning from rituximab maintenance to another type of maintenance and then a subsequent type of maintenance. And I totally agree with the panel, there is a lot of discussion that needs to be done with the patient. There are some patients that are able to take the survival as the right endpoint and they are able to decline the maintenance and have an earlier relapse. There is a type of patient that is not able to accept the idea of having active disease, and that type of patient is going to be interested in any kind of maintenance that will keep their remission longer even if the length of the remission may not necessarily affect the overall survival.

**DR LOVE:** So, Stephanie, high-risk patient gets R-chemo, does well. Gets 2 years of R maintenance, is doing great. Comes in and says, "Can I keep it going?" Do you say, "Absolutely not"?

**DR GREGORY:** No, I don't say "Absolutely not." We talk about it.

**DR LOVE:** So you will continue it?

**DR GREGORY:** Yes. I mean — I've participated in the RESORT trial. I have three patients on rituximab maintenance for 6 years, in complete remission. And talking about — now, I have to tell them that the study is equal and I bet they're going to want stay on the rituximab maintenance.

- DR LOVE:** So we're getting great cases presented by the PDAs; keep putting them in here. We'll present them all to the faculty afterward. Andy, I've got a great one for you here in a second. But one other point about RAI I want to ask Pier Luigi. One of the things about RAI in the patient with follicular lymphoma, we're talking about how long these people hopefully are going to live, is the issue of AML/MDS. And I note that in this SWOG abstract, in the graphic that they have here, that there were 7 cases of AML/MDS in the CHOP radioimmunotherapy versus 3 — 1.1 versus 2.7, p 0.34 — so it's not statistically significant. What do you say to your patients about MDS and AML with RAI?
- DR ZINZANI:** So I was involved with the FIT trial and treated at my institute more than 250 patients with radioimmunotherapy therapy. And I think that the risk of myelodysplastic syndrome or secondary acute leukemia is quite the same when you compare with historical data, because the most part of those patients were treated. So it's so difficult to understand the real role of radioimmunotherapy. By the end of the day, there are no statically significant differences so far. And the follow up, the median follow-up is more than 6, 7 years.
- DR LOVE:** Andy, agree, disagree or in between?
- DR ZELENETZ:** I think that the — when we look at the overall risk of AML/MDS in patients with follicular lymphoma historically, it does not seem to be dramatically influenced specifically by radioimmunotherapy. We — it would be naïve to think that radioimmunotherapy isn't a contributing factor, but so is the multiple courses of cyclophosphamide, so is the etoposide that patients get. So, right now, with our paradigm over the last 4 or 5 decades, having been chemotherapy, an alkylator and radiation based, we are giving treatments that unfortunately contribute to the risk.
- If we move to more targeted therapy and with less generalized DNA damage, will we see a decline and then the relative risk of radioimmunotherapy might increase? It might, but that data is yet to be generated. I think radioimmunotherapy is a contributing factor to the overall lifetime risk follicular lymphoma patients unfortunately have for developing AML/MDS.
- DR LOVE:** Final comment from Martin.
- DR DREYLING:** Just a short point. We are talking about the cost or risk of radioimmunotherapy, but we have also to talk about the gains and when do we apply it. And I think in our daily clinic it's that way. That, after completion of immunochemotherapy there's a large residual mass, you consider radioimmunotherapy. If it's very low residual tumor mass, you're more in favor of rituximab maintenance, just to split up between these 2 options.
- DR LOVE:** So I'm going to ask you to come to the podium, and while you do, Pier Luigi, you had a point.
- DR ZINZANI:** Yes. You have to remember the difference between the conversion rates. If you compare the PRIMA data after rituximab for 2 years, 52% the conversion went from PR to CR. In the FIT trial, a conversion rate after one shot of ibritumomab tiuxetan was 78%. You have to remember that.
- DR DREYLING:** Yes.
- DR ZINZANI:** And, in particular, for the high tumor burden subset said before, Martin.
- DR LOVE:** So, as I said, we're getting some awesome cases and questions. And, Julie, just maybe take a quick crack at this one: How would you treat a 56-year-old woman with diffuse large B-cell, Stage IIIB and previous breast cancer, who had significant epirubicin chemotherapy exposure? Kind of getting to this whole question of anthracyclines, older patients, et cetera, but how would you deal with this situation?
- DR VOSE:** Well, obviously, you — she's still curable for the lymphoma, so you want to try to do that as much as possible. So you want to add up the prior anthracycline exposure, see if there's any room for any additional anthracycline exposure, make sure the current cardiac function is adequate. If they are able to get additional anthracycline, I still would try to do that to the maximum amount. And when you get to that point, typically in such a patient we would substitute etoposide for that.
- DR LOVE:** Okay. Let's go on to the next case, and this is from Canada, Martin. And it's a 67-year-old man who has a left axillary lymph node. Goes through a workup and is diagnosed with mantle-cell lymphoma, has diffuse lymphadenopathy and splenomegaly, bone marrow involvement. You can see the treatment that he received, because a couple of years ago, he — FCMR and achieved a clinical CR. And, actually, the patient ended up going on maintenance. And it's interesting, he didn't go on the maintenance right away, he went on some time — a few months later when this physician heard about the maintenance data that you put out there. And then — and he actually was wondering "Did I do the right thing?" because it wasn't, like, right after, but he is on maintenance today. In any event, here is Dr Sehdev and his team talking about this man.

- DR SEHDEV:** This was a sort of a middle-aged gentleman, 67 years old, and really had an incidental finding on physical examination with a quite small axillary node.
- At the onset, his picture was almost in keeping with a CLL presentation, but it was found to be a mantle-cell lymphoma, based upon flow cytometry, pathology and marrow involvement.
- In his case, I think the real question is: How do we approach mantle-cell lymphoma optimally in today's era? The treatments historically have varied. The prognosis of this condition can be unpredictable. We generally think of it as an aggressive histology of lymphoma, and yet some patients have very indolent disease. We generally refer patients afterward for consideration of autologous transplant. Should that be done in every case? How can we select patients who perhaps do and don't need transplantation?
- DR CARVALHO:** This was admission CT, and it shows adenopathy in both axillary regions and in the right paratracheal region and anterior mediastinum. And here we see adenopathy in the left and right cervical regions posterior to the internal jugular veins and also in the submental region. And here we see quite large-volume bulky adenopathy in the pelvis, both in the right and left inguinal regions and also in the obturator region.
- This is the post-treatment CAT scan, and it shows a marked improvement in the abdomen with no enlarged lymph nodes present.
- DR RUIJS:** These lymphocytes are slightly enlarged, fairly monomorphic, which you do not see in a normal lymph node. We have all different types of populations in a follicular architecture, so this is diffuse infiltrate and, actually, right in the center, and just below that, you can see 2 mitotic figures. So this is obviously some kind of non-Hodgkin lymphoma, based on the morphology alone.
- This is an immunostain for CD5. And on this staining we can actually see that there is CD5 expression diffusely, but quite heterogeneously. And then just to illustrate an image of a bone marrow biopsy on this patient, and the patient had multiple of these sort of nodule infiltrates. So I would still do the immunostains or flow cytometry to confirm that this is involvement by mantle-cell lymphoma, which is clearly compatible.
- DR SEHDEV:** He was afterward treated with maintenance, when the maintenance data were coming out, although there had been a significant gap between his finishing his FCMR and starting his maintenance. So, if someone's finished their initial therapy and it comes afterwards, after a period of gap, is maintenance still reasonable? And how effective is maintenance in the setting, particularly, of mantle-cell lymphoma?
- DR LOVE:** Any other questions for the faculty?
- DR SEHDEV:** In an older patient, perhaps, who might not be a good candidate for a stronger, standard cytotoxic induction regimen, would there be a role to consider an approach such as bendamustine/rituximab as up-front therapy?
- DR LOVE:** So I want to see what the faculty said about these things, Martin, but first let me just ask you about this thing, about delayed maintenance. It kind of reminds me of when adjuvant trastuzumab came out in 2005 and women had — maybe they were a year later and we were trying to figure out do we give it to them or not. How long is too long or how — within what period of time do you think it would be reasonable to start maintenance?
- DR DREYLING:** Short answer, I have no clue. I can only provide you some eminence-based data, so a gut feeling essentially, and I would say, let's say up to 3, 4 months might be absolutely reasonable. When it extends 6 months, I would doubt that we really have solid data and then I would skip it.
- DR LOVE:** So here are some thoughts from the audience, Martin. First of all, about initial therapy of a patient like this. Sixty-seven is kind of an interesting age in terms of whether or not transplant's on the table. And you can see a lot of heterogeneity in what people are doing, which always tells me that there's maybe more data needed. A fair amount of transplant coming after R-hyper-CVAD and R-CHOP.
- We can look at the next question that we asked, which was: Would you use maintenance? And it looks like there's kind of an interesting split there. We probably ought to repeat this after your talk. And finally, and Alessandra you might find this interesting because of your work in lenalidomide, we asked the audience: What about lenalidomide in mantle cell? Is that something in an advanced-disease situation that you would like to be able use, assuming you can get a hold of it? And you can, again, kind of see the spectrum of response there.
- So Martin's going to bring in some of the science that addresses these and other questions.

Thank you very much. And, in fact, what I will present is probably a minority vote, if I've seen your votes, but I will guide you through that.

Now we're talking about a 67-year-old patient and of course we don't know the biological status of this patient. But I would guess, at least, that this is a typical 65-year-old patient with some kind of comorbidities and this is what my discussion is based on.

Here is a list of my disclosures. And I'm not going to wait for 20 seconds but move on in the interest of time.

At first point, why are we talking about mantle-cell lymphoma, a rare disease, why don't we care at all? Well, first of all, it's a very challenging disease because of diagnosis. And, in fact, only since a couple of years that we really are able to reliably diagnose mantle-cell lymphoma and that it's mostly based on the overexpression of cyclin D1. And only then we learn that we're not talking about one disease, but really a mixed bag of different diseases. And just to allude of that, the indolent mantle-cell lymphoma represents only 15% of the cases. So, really, the minority of cases, but all of us would agree on the podium that there is something like indolent mantle-cell lymphoma.

On the other hand, the vast majority of cases, around 80, 85% of cases, in fact, are somewhat follicular lymphoma, clinical course in speed motion, which means initially high response rates but rather quick relapses.

And then finally we come up with the transformed mantle cell lymphoma, the blastoid ones. And these cases, in fact, do behave like a real aggressive lymphoma.

So how do we approach these different kinds of diseases? How can we differentiate them up front? And we do know a couple of molecular markers, some of them also updated at this meeting. Really what has been generally accepted for daily care, first of all, is cell proliferation, Ki-67. And you can even analyze that quantitatively and come up with different risk groups.

Secondly, the so-called MIPI mantle-cell lymphoma, International Prognostic Index. And, again, a simplified IPI by some performance status, age, LDH, leukocyte counts, here validated in almost 1,000 patients and almost confirmed in almost every clinical trial worldwide.

Now let's get back to our patient. We're talking about 60-year-old male, LDH is slightly elevated, and this is what I made up to challenge you, leukocytes around 18,000, with lymphocytosis, and the typical Stage IV mantle-cell lymphoma. So what kind of risk factor are we talking about?

If you really apply MIPI, you come up with a high-risk patient. So, really, this is my first message — if we're talking about elderly patients, the vast majority of these are high-risk patients. So the ones where you, first of all, would like to delay treatment, these are probably the ones who need treatment most urgently. And in this patient, I would argue it's probably definite — to start up treatment because of the bulky disease in the lower abdomen.

Now, the addition of rituximab did increase at least initial response rates in the vast majority of cases, also PFS and, again, in a Cochrane analysis, overall survival, but what kind of chemotherapy? And here we are, based on a randomized trial of almost 600 patients, comparing R-CHOP and R-FC, and a fludarabine combination is resulting in significantly reduced progression-free survival and overall survival.

Now, of course in Germany, and I showed you this trendy picture, we have had bendamustine for quite a while. In fact, bendamustine did show some very promising data in mantle-cell lymphoma. And this is the data we also talked about for follicular lymphoma, just the same for mantle-cell lymphoma, bendamustine did show some high efficacy. But it's far to say, people still tend to relapse. They relapse 6 months or so later, but then after 3 years or so, the vast majority has relapsed. So we need something in addition.

So let's go back to this one trial where we already had a look at the R-CHOP and R-FC data. We also had a second randomization, comparing interferon maintenance, which is also efficient in mantle cell, versus rituximab maintenance.

And what are the results? These are just preliminary data. These data are being updated at this meeting, and I can just tell you it's worthwhile to listen to them because the overall survival data are very interesting. But anyway, when it comes to remission duration, definitely rituximab maintenance does change the clinical course of the disease, at least doubling the duration of remission from about 2 years. And that is what we have observed in previous trials, up to 6 years or so for the patients who did receive rituximab maintenance.

Having a look at these data, it's fair to say — and I should emphasize that that was unlimited rituximab maintenance, and we might come back to this point in the podium discussion.

Now, what about the comparison of different moleculars? What is the impact in mantle-cell lymphoma? And it's far to say, if we only go for immunotherapy, at least for the registered drugs, you come up with a response rate about 30, 40% and a duration of remission or PFS in the range of 6 months. When you move on to bendamustine, which is the lower lines, here we're talking about response rates in the range of 80% and a duration of remission of 20 months.

So I would argue, in fact, chemotherapy still remains one part of the package in contrast to follicular lymphoma, by the way.

Now, here we are, what we have learned about the moleculars, because I think it's very intuitive if we want to further improve outcome, and that is a short look into the future. We're really not talking about some different kind of chemotherapies, but we really discuss about adding new moleculars.

And here, I highlighted the different ones, and specifically, the yellow one I would like to refer for, which is the bortezomib, registered in the US for relapsed disease, and temsirolimus, registered in Europe.

How are the results? This is the long-term follow-up of the pivotal trial with bortezomib in relapsed mantle-cell lymphoma by Andre Goy. And this, in fact, resulted in a 40% response rate. However, duration of remission on median PFS was more in the range of 6 months. So it's definitely efficient but probably not sufficient for the majority of patients.

And based on some in vitro data and also first clinical experience, we could show there is some synergism between high-dose Ara-C plus bortezomib. And this is the ratio for this European trial we have just started a couple of months ago, comparing high-dose Ara-C plus/minus bortezomib.

Here are the complementary data for the temsirolimus. Again, this is registered in Europe for relapsed mantle-cell lymphoma. And you can see, the monotherapy is superior to monotherapy, but still duration of remission on median progression-free survival is in the range of 4 to 6 months.

How can we improve? Again, by some in vitro data, we combined bendamustine plus temsirolimus and some of the preliminary data will be presented at this meeting, and the results are very satisfying so far. Just to mention that, as long as the audience knows who of these 2 guys is Bert, I'm satisfied that I'm not that old.

Moving on to lenalidomide that has been also mentioned and, again, I can build on the MD Anderson experience. We do have some data that lenalidomide is efficient, specifically in combination with rituximab. And just to build on that, also on the oral availability of this approach, we're just starting a randomized trial for elderly patients, where we took over the concept of the younger patients, meaning for induction, we challenge the CHOP by high-dose Ara-C. Whereas, for the maintenance question, we compare our current standard-care rituximab maintenance versus rituximab plus lenalidomide.

Finally, this is the one exception. So far, I've told you molecular monotherapy is not sufficient in mantle-cell lymphoma. Well, these 2 compounds might make the difference, which is they are attacking either the PI3K delta or BTK, and they are 2 small molecules. Also, these are being updated at this meeting.

And I just would like to refer to the results in mantle cell. This is based on the Phase I trial. If you just have a look at the green bars, what you can see is, in fact, that just with 1 or, better said, 4 pills a day, you can overcome this disease in the majority of cases. Very thoughtfully, and I can just address the presentation at this ASH, where these high response rates hold up also in the Phase II setting.

With that, I would like to finish. This is my quick overview of our current care in mantle-cell lymphoma in elderly patients, and I put this patient in the basket of elderly patients. I would say, starting with R-chemo, either R-CHOP or BR, and then followed by rituximab maintenance is for us now a standard. For the younger patients, definitely high-dose Ara-C should be added to induction. And then for relapsed disease, really the setting is for molecular approaches. Also, outside of clinical trials, however, if you apply that you should do that in combination with chemotherapy or other compounds.

Thank you very much.

**DR LOVE:**

Let's talk a little bit about the clinical management of mantle cell. I'm curious, in terms of the entire faculty, and, again, here's the way the audience approaches it in general. Julie, one question that we get a lot is, when people see bortezomib having activity in advanced disease, they know there are trials looking at it, combined up front, and there's a lot of temptation. In fact, not rarely I've seen



people actually try it outside a trial setting. Where do you think things are heading in terms of earlier bortezomib? And what about outside a protocol setting?

**DR VOSE:** In the US, anyway, bortezomib is only approved for relapsed patients. So it would perhaps be a little bit more difficult to give in the up-front setting. I think, as a single agent, not necessarily would it have an adequate response rate that I would use it up front. In a combination it has fairly good activity. There's some good clinical trials for relapsed patients combining with bendamustine/rituximab and bortezomib, with fairly good activity. And that's going to be looked at, more in the up-front setting, in clinical trials.

**DR LOVE:** Pier Luigi, tonight we have — in our myeloma session, we're going to talk a lot about new ways to give bortezomib: giving it weekly, giving it sub-q, really exciting. What about bortezomib use in lymphomas and in mantle cell, these alternative ways?

**DR ZINZANI:** I agree with Julie. The real problem is that they — also in Europe, it is possible to use only in relapsed patients. But I think that we need more data concerning the combination with bendamustine and rituximab, and also what about with lenalidomide? Because I think it would be a very important, specific drug for the treatment of mantle-cell lymphoma.

**DR LOVE:** Martin, what about this issue of delivery of bortezomib in mantle cell? It has apparently less neurotoxic things that we're seeing in myeloma.

**DR DREYLING:** First of all, let me just get back to your question before. There's an ongoing randomized trial, which is, in fact, comparing R-chemo plus/minus bortezomib in first-line treatment. And the recruitment is completed, and I hope we'll see the data probably next year or so.

Now the question: Which schedule or dose to combine with chemotherapy? And there, I think there's somewhat of a consensus that you not prefer the ongoing regimen as in multiple myeloma, but most groups, in fact, add bortezomib, just a 1 and 4, in addition to chemotherapy, based on a presumed synergism. And by that, in fact, you can also avoid neurotoxicity.

**DR LOVE:** Do you feel comfortable that it's a safe approach? And it's always, "If it were you or somebody in your family," would you ever consider doing it off protocol, bringing bortezomib up front?

**DR DREYLING:** For up front, probably not yet, but for relapsed disease, I would definitely say yes. In fact, we have treated already quite a couple of patients with this combination — high-dose Ara-C plus bortezomib — and some of them really with striking responses. And, therefore, I think there's something in this combination.

**DR LOVE:** You can have a seat, and just a couple more points. Stephanie?

**DR GREGORY:** Could I just ask Martin about the role of Ara-C in the treatment of mantle cell? It appears that there are many people who feel it's a very important drug.

**DR DREYLING:** I think it's very interesting. When we started our randomized trial in younger patients, a lot of my colleagues said, "Just comparing another chemotherapy drug we know for decades. So what is it about?" But, in fact, in younger patients it not only significantly improves progression-free survival but there's already now, after a rather short follow-up, a strong tendency toward improved overall survival. So yes, I do believe, and this is why I put high-dose Ara-C as part of a standard treatment in younger patients. It does improve the long-term outcome of the disease.

**DR LOVE:** So with that comment, what do you think about the ongoing trial — I think it's actually been launched in the US — of people going to transplant but being randomized to BR versus R-hyper-CVAD before?

**DR DREYLING:** I think it's very challenging. If I have the data from our own consortium, and, again, this is somewhat representing more than 1,000 patients. In the younger patients, we do definitely do know that high-dose Ara-C does result in improved PFS and also borderline overall survival. We don't have the same data for the bendamustine. So I think it will be a very challenging trial.

**DR LOVE:** I'm going to ask Alessandra to go to the podium, and while she does, Pier Luigi, what do you think about that study? Pretty interesting to contemplate somebody randomized between BR and R-hyper-CVAD, pretty different experiences.

**DR ZINZANI:** I'll come back just a moment concerning the role of Ara-C. The first demonstration was done by Massimo Gianni, with the high-dose sequential treatment using high-dose Ara-C in a particular sequential treatment in mantle-cell lymphoma. And I think it's a very important step forward for the treatment to try to cure the most part of, of course, younger patients.

Hyper-CVAD, I think this is the same concept. I think it's very important to use, in particular in high-risk patients. But remember the real goal of Ara-C in the treatment of mantle-cell lymphoma.

- DR LOVE:** So Martin, does that mean that you would not likely be putting patients on a study like that? Sorry to put you on the spot.
- DR DREYLING:** I mean, if I believe in my own data, which I do, of course, based on the randomized trial, I would be a little bit reluctant. This would be, for me, a study really we left for patients who would not like to go for intensive treatment. And there, bendamustine really has the major advantage. On the other hand, it's been followed anyway by autologous transplantation. So you could argue it both ways.
- DR LOVE:** One of the common comments we get from physicians who listen to our audio programs or come to these things is they really feel comfortable when people say different things and aren't really sure what to do, because they're feeling that way all the time. And I've been fantasizing all night, if there were different people up here — I mean, there are people who you ask about that trial and they go, "Oh, yes. No problem." Anyhow, interesting.
- DR DREYLING:** But having said generally, it's always better to put patients on clinical trials than treat them outside of clinical trials. That's clear cut.
- DR LOVE:** Maybe we should just talk for a second, Julie, maybe you want to comment on this too, in terms of where things are heading, and Martin talked a little bit about it, in terms of new agents. When you and I chatted not too long ago, you were talking about some of the exciting, new agents: CAL-101, et cetera. What about these kinds of — and we'll talk about that later, but what about these kinds of agents in mantle cell?
- DR VOSE:** I just want to comment on the clinical trial first. Actually, I was sort of involved in that clinical trial, so — and it is going to be open in the US very shortly. So I think it's actually a very good trial. And the reason is, R-hyper-CVAD, we know that it does have very good activity, but it's very toxic. And if we can have an alternative therapy that doesn't have that toxicity and we can still get the patient to transplant and the outcomes are equivalent, then I think that we've done those patients a favor. So I actually think it's a very good trial, and we're going to support that.
- DR LOVE:** I'm just kind of imaging, what are you going to say to a patient? "Okay, here's option A, here's what's going to happen, and here's option B."
- DR VOSE:** Normally in clinical practice right now, we do R-hyper-CVAD. So that would be the alternative if they don't go on the study — they're still going to get the more toxic therapy. So I actually think it's a good design, but it will be difficult to explain to patients.
- DR LOVE:** Martin, what about new agents, like CAL-101, in mantle cell?
- DR DREYLING:** I think it's quite striking. Both of the compounds, CAL-101 as well as the BTK inhibitor, and as I said, I think these are really the drugs which will change the field in, let's say, 5 years from now. And I'm very much looking forward to the first randomized trial that's applying these compounds.
- DR LOVE:** So let's go on to the next case, a patient with CLL, from India. A 68-year-old man who was asymptomatic, and you see the numbers there. Now, the physician felt that he did need to be treated, but — and we don't want to go into huge detail about this, but in this situation there was a major financial obstacle in that the patient was going to have pay out of pocket for his treatment. And this physician, a very educated oncologist, decided to use chlorambucil on this patient and was very open about — he understood that that's not maybe what would be ideal, but here he is, and his team, asking the faculty what they think about this case.
- DR SHAH:** We have a lot of people being treated still with chlorambucil because of the ease of the regimen and the outpatient regimen, the lesser use of resources from family and everybody else. And what I would like to know from the faculty is what kind of patients — or, is this a right candidate to treat with chlorambucil in the first line? Would it alter the outcome? Would you use a bendamustine-based regimen in the first line in this patient if he was, say, able to afford this kind of regimen?
- DR MALLARAJAPATNA:** First one is in the abdominal set, showing splenomegaly and some lymph nodes. They tell us where exactly the disease is, and we can actually use these modalities for biopsy gradings, as personal gradings.
- And the second set shows the high-resolution ultrasound of the submental region, where the nodes were identified, and that could be done from that using ultrasound grading.
- DR PRABHUDESAI:** This patient had initially flow cytometry, which was done on the peripheral blood. And that was a BCLL. Later, when he relapsed, the lymph nodes were biopsied. We again did immunohistochemistry on this, and the morphology and IHC were both consistent with relapse of CLL/SLL.
- DR LOVE:** Any questions, in general, about CLL that you'd want to ask these investigators?

**DR SHAH:** For an elderly patient, maybe a frail elderly, would you consider FCR or a bendamustine-based regimen? Because we think that FCR still has much longer data and probably a better molecular clearance rate, suggesting that some of these patients at least would have a longer disease control rate with FCR.

**DR LOVE:** So, before you talk about some of the science involved, Alessandra, let's look at the audience. And one question we had was, in this situation, suppose you were seeing this patient as a second opinion, same situation, and the first opinion suggested just chlorambucil alone. How would you respond to it? And would you say, "This is really something you shouldn't do?" Or, "This is okay"? And you can see again a little bit of a split, certainly everybody feeling that it's not as effective, but in terms of how strongly they feel about not using it. We'll see what the faculty thinks.

And the next question we asked the audience: "What likely would you have recommended to a patient like this?" And it looks like the most common — the answer there is FCR, a little bit of BR. It's kind of interesting, if I'm seeing that correctly. And then finally, and this relates to a lot of your work, Alessandra, is the question of lenalidomide. You've been presenting some really fascinating information over the last couple of years on lenalidomide in CLL. We wanted to know from the audience, "How would you — have you utilized it? And if you haven't utilized it, is it because you can't get it paid for it or you just don't think...?" And you can see most people have not utilized it, but there are a fraction who would if they could.

So with that, and we'll kind of poll the faculty a little bit about these and other questions related to CLL, but maybe we can bring out a little bit of the science first.

**DR FERRAJOLI:** So thank you very much for the invitation to discuss this case in these interesting international tumor boards.

Those are my disclosures. I have clinical trials with these companies.

And the first situation that we all face, and the situation that my colleagues faced, was to determine whether the patient is in need of therapy. Once I have determined whether the patient is in need for therapy, there is other information that I would like to know, and that is what are their prognostic factors? Because their prognostic factors are going to help me in defining treatment expectations.

On the decision of therapy, and which therapy to use, I will be looking at other components, mainly the performance status, comorbidities, age as a factor, and very relevant will be the information, if I could have it, of genomic abnormality by fluorescence in situ hybridization status. If this patient, we don't know, but if this patient is a go-go patient, we often see them in our tertiary medical center. They bike for 3 hours every day, even if they are older, even if they are 68 or 70 or 71. They are totally functional. They have no comorbidities, and they have intact organ function, in particular, renal function. Then, and for these types of patients, my go-go patients, the most relevant data that I will be discussing, are the ones from the CLL8 trial.

This is a trial conducted by the German Study Group. This was published last year by Dr Hallek and collaborators. It's a large trial, more than 800 patients. They were patients that had to have — they could be of any age, but they have to have a good performance status, a low comorbidity score and intact renal function. Those patients were randomized to receive chemotherapy with fludarabine and cyclophosphamide and then in conjunction either the FC treatment alone or rituximab chemoimmunotherapy.

Here, we see the characteristics for this patient. The median age is younger than the one of the patient that we discussed. They are mainly Stage B and C patients. And, as expected in front-line therapy, the number of patients with deletion 17p is quite low.

The results. We see that they are a junction of rituximab, so the chemoimmunotherapy combination increases overall response rate, and even more significantly, exactly doubles the complete response rate.

Response duration is longer, with a longer progression-free survival for the patients that were randomized to the fludarabine/cyclophosphamide and rituximab arm. And probably for the first time in a randomized trial in chronic lymphocytic leukemia, there is an overall survival benefit that was demonstrated for the patients receiving treatment on the FCR arm.

As you probably know, our center is experienced with FCR. This experience has been really conducted by Dr Keating, and we have been treating patients with CLL with FCR for over a decade. When we look at FCR as a single-center experience, we have very high overall response rate, very high complete response rate and a very low mortality with this treatment. But, as I said at the beginning, I really would like to know what the patient prognostic factors were. In particular, at this point I would be

wondering what is the immunoglobulin, heavy chain mutation status? This is because when we look back in our experience with FCR, and we divided patients according to mutated or unmutated immunoglobulin and heavy chain gene, there is no difference in terms of overall response, complete response or achievement of negativity for minimal residual disease by flow cytometry. This work was published by Dr Lin in 2008. But what we see that is very interesting is that the mutation status affects the duration of response. In particular, I would like to focus the attention on the blue line.

Those are patients that achieved complete response. They were mutated. And the progression-free survival at 5 years is 93%. Therefore, I will be very optimistic discussing what the chance of remission duration with FCR is in a patient that is mutated.

We don't know the fitness of our patient, so he could be a 68-year-old patient, the common patient with CLL. I just want to remind you that the median age at diagnosis for this disease is 72 years, and he may be a slow-go patient, a slow go based on performance status, comorbidities. The German Study Group, Dr Eichhorst, defined a number of comorbidities in 2 parallel studies, the CLL4 and the CLL5. And in this slide we see depicted how the patient with a significant number of comorbidities, more than 2 comorbidities, increased steadily with age. Therefore, we should design — and this is the focus of our center, as well as my personal interest, clinical trials that are specifically designed for elderly patients.

One of the earlier trials is the CLL5 trial. In this trial, patients older than 65 were randomized to receive single-agent chlorambucil or single-agent fludarabine. We see that their response rate and the overall response rate and complete response rate was higher with fludarabine, but this did not translate in a survival advantage. Those data were discussed extensively. We do not know why we see these effects with a more active agent but no improvement in survival. There is the possibility that the subsequent salvage therapy may be part of the explanation for this result, with patients treated with fludarabine receiving subsequent therapy with a palliative intent, whereas patients that had received chlorambucil are then treated with a purine analog or other combination chemotherapies.

Nevertheless, age is important and on Monday morning, at 7:00 in the morning for whoever has jet lag or has changed time zones, there will be the first CLL clinical sessions. And Dr Woyach will present his experience, the combined experience of the CALGB, looking at the impact of age on the results of chemotherapy and chemoimmunotherapy trials.

Last year at ASH, we discussed the experience of the CLL-208 trial. This is a Phase II trial of 100 elderly patients that were treated with the combination of chlorambucil and rituximab. The data last year showed that the overall response rate and complete response rate that are shown in these slides were superior to the same group, a historical experience with single-agent chlorambucil. They also showed that there was an increase in myelosuppression when rituximab is added to chlorambucil therapy.

The progression-free survival was reached, with a median duration of response of 24 months in this Phase II trial.

To have a good definition of what is the benefit of combining rituximab with chlorambucil, this should be tested in a randomized trial. The CLL11 trial from the German Cooperative Group will provide interesting data.

This is trial that has accrued extremely fast, and patients that were elderly or had comorbidities were randomized to receive single-agent chlorambucil, chlorambucil plus rituximab or chlorambucil plus GA-101, that we know is a Type II anti-CD20 monoclonal antibody.

The Italian Group, the GIMEMA group, will discuss again on Monday morning the results of their experience with rituximab plus chlorambucil in the treatment of elderly patients with CLL.

In our center, we have done a number of trials for elderly patients. The one that we most recently completed, and very recently published, is the one with lenalidomide as a single agent. It was a Phase II trial, and patients were treated with single-agent lenalidomide, 5 milligrams initial dose and then dose escalation treatment with a continuous schedule. It's very important to remember that when treatment with lenalidomide is initiated in patients with CLL, we do need to use tumor lysis prophylaxis with allopurinol.

We are proud to say that the characteristics of these patients were the ones of the average patient with the CLL, with the median age of 71 years, high beta-2 microglobulin also as a risk factor. The overall response was 65%, and combining CR and CRi, the complete response rate was 15%.

The most interesting data are from the overall survival, a very encouraging overall survival at median follow-up of 31 months, so 88%, and also progression-free survival of 57%.

The panel rightfully brought up bendamustine as a possible alternative. So I reviewed the data from Dr Knauf that were published in JCO in 2009, where patients were randomized to receive either bendamustine or chlorambucil. This was not the study for elderly patients, and therefore a direct comparison and the applicability of these data to our patients is a little bit different. The median age in the bendamustine trial was 63 years and in chlorambucil was 66. Nevertheless, bendamustine had a higher overall response rate and a higher complete response rate.

When looking though at progression-free survival, I would define both not very exciting, in particular, the chlorambucil arm had only a median progression-free survival of 10 months, and the bendamustine had better progression-free survival, but this was 22 months.

And in conclusion, what I would say is that I think nowadays the future is toward individualized therapy, therapy based on the characteristics of the patients, on their prognostic factors, on their age, level of fitness. Initial therapy should be with a combination, and then the maintenance could be discussed. What is really exciting is that this overcrowded slide represents the new agents that are available now for CLL, not only new monoclonal antibodies but targeted therapy to BTK, to PI-kinase inhibitor. And, also, everybody probably heard the exciting reports of the CARs. That is an immunotherapy with chimeric antigen receptor transduced T-cells that have hit big time in the news lately in the United States.

Thank you.

**DR LOVE:** So, Andy, can you talk a little bit about what your thoughts are about the approach to CLL, particularly in the older patient, where you hear a lot of questions — Alessandra, you can have a seat — the FCR/FR debate, and this physician's question, which is: Is chlorambucil totally out of the question?

**DR ZELENETZ:** Well, I don't think — certainly, if we look at the NCCN guidelines, if we look at the elderly unfit, in fact chlorambucil is the recommended treatment. Whether this was an elderly unfit patient, that's a different question. But it's not that chlorambucil should never be written, though I will be honest, I don't think I can remember the last time I wrote a chlorambucil prescription. So it's been a while. But I think one of the things that becomes important in the elderly CLL patient is, actually, make the punishment fit the crime. And that is to start to integrate information we know about the genetics up front and pay attention to the fact that is someone a 17p up front, it's pretty uncommon and it's relatively rare, but a deletion 11 is actually pretty common. And in that patient, chlorambucil is not probably the best treatment. There, you might want to use bendamustine, or FCR can be tougher in these older patients, but you will want to definitely include a stronger alkylator.

But in an otherwise run-of-the mill patient, rituximab, rituximab/chlorambucil, rituximab/fludarabine is not an unreasonable way to go. We have to be realistic. Things have to be done within the resources that are available. And we saw the comparative trial, chlorambucil did not have an inferior survival, and it was a completely appropriate choice here given all the considerations, and I think it's reasonable to do. Would it be something I would do? Probably I would use a different treatment in this patient, but it's not a wrong treatment.

**DR LOVE:** So I'm going to ask Julie to come to the podium. We're going to talk about the next case in a second. But, Martin, we asked the audience about maintenance, and most people said we really don't have enough information. But what about maintenance R in CLL? Where do you think things are heading?

**DR DREYLING:** Well, I think it's very suggestive that it might work, but we don't really have the proof. And so far, at least in our institution, we don't apply it in general. However, there are at least 2 major studies going on: the French one is probably the larger one, which is almost completed. We also have an Italian one. And so I hope we will get a definite answer in 2 years or so.

**DR LOVE:** Alessandra?

**DR FERRAJOLI:** Yes. Just to bring the attention, on Tuesday, Francesc Bosch will present the experience with rituximab maintenance in CLL, patients that were treated with FCM treatment. And, actually, the toxicity in CLL of rituximab maintenance is not negligible with cytopenias and infectious complications following that type of chemo monotherapy. So I think the issue of maintenance in CLL is quite different. We cannot apply the rule of being an NHL — we can give maintenance.

**DR LOVE:** What about the patient with 17p deletion? What do we know about that at this point, Alessandra?

**DR FERRAJOLI:** For initial therapy?

**DR LOVE:** No. Initial, but more in relapse.

**DR FERRAJOLI:** In relapse, I would fit it to the patient characteristics. If he's a patient that has no lymphadenopathy, but this is in the bone marrow and in the peripheral blood, alemtuzumab is still a valid option. For a

patient that has large lymphadenopathy, I will be looking more into high-dose steroids, rituximab, even FCR, if the patient does not receive it before, and then a very strong indication for an allogeneic transplant. As the data with allogeneic transplant have shown, that 17p patients do not behave any different after transplant than the rest of the abnormalities.

- DR LOVE:** So a couple of quick questions from the audience before we go on to T-cell lymphoma. Pier Luigi, a number of people asked, getting back to the first case we've talked about of diffuse large B-cell of the breast, what about radiation therapy?
- DR ZINZANI:** So I don't think it's a real issue in this case. Probably in the past, but right now, the best treatment is chemo plus immunotherapy. And, of course, the prophylaxis for the CNS.
- DR LOVE:** Anybody here who would radiate the breast? Andy?
- DR ZELENETZ:** I think, based on the SWOG data of R-CHOP followed by radiation, the results are really actually quite good. It would limit the exposure to chemotherapy. This patient could have easily been managed with R-CHOP followed by radiation. I think that would be an appropriate treatment.
- DR LOVE:** Okay, Martin. A 70-year-old, mantle-cell lymphoma, GI involvement, perforation postsurgery. Gets bortezomib/rituximab, has a CR. Has been on rituximab maintenance for 3 years. How long would you continue rituximab? The patient is reluctant to stop.
- DR DREYLING:** Well, let me say this is quite an unusual case, because normally GI involvement in mantle-cell lymphoma, in fact, is more a tendency of low-risk patients. So there is — that perforation occurrence is quite unusual, which brings me to the point that this is probably more aggressive disease. Would I have treated this patient with bortezomib/rituximab? Probably not, because of this estimation of a higher biological activity. However, should one now go on with maintenance after 3 years? If I believe in the data I showed you, these data were recruited based on an unlimited maintenance. Would I do that outside of clinical trials? Definitely not. Because I think we still have to learn more about the feasibility and side effects. For the time being, outside of clinical trials, I would still remain for a limited maintenance.
- DR LOVE:** Real quick. A lot of questions about in what specific situations will you hold off any treatment in mantle cell?
- DR DREYLING:** Very distinct cases. Very few cases, and that's based, first, on biology, Ki-67 very low. That is based on cases almost as similar as the one discussed, with only GI involvement, no bone marrow involvement. These tend to be more indolent and, also, the cases with pure leukemic manifestation, more a CLL-like type. And these normally also have low MIPI risk score.
- DR LOVE:** So, Julie, let's talk about this next case from France, a 56-year-old healthy, bulky construction worker presents with pretty symptomatic peripheral T-cell lymphoma and given an IPI of 3. He receives, and I guess an intensive regimen was given there, ACVBP and DHAP for 4 cycles, and transplant is being discussed. Pretty vexing situation no matter where it occurs in the world. Here's what the Nice doctors had to say about this patient.
- DR MOUNIER:** He had the large T-cell lymphoma, not otherwise specified. He had Stage IV disease, and he was a worker in building construction, very, very healthy and very strong man.
- We used the most intensive treatment we have in France — he received the high-dose CHOP. The name is ACVBP.
- DR VIAU:** Here we can see adenopathy above and subdiaphragmatic. And to complete the staging, we made FDG PET. And we can see that the surdity of the patient is due to cavum and amygdala hypertrophy with FDG uptake.
- DR BENCHETRIT:** This is an inguinal lymph node biopsy. The normal picture is destroyed by nodular proliferation. These nodules are of irregular style and shape. They are composed of large cells with irregular nuclei contours with a large cell coexpressed CD3 and CD5 and is consistent with T-cell lymphoma.
- DR MOUNIER:** The main question is: What is the best induction treatment for this type of patient? He's young. He had very bad disease. Another way is to combine with a small molecule like romidepsin or pralatrexate. But at the present time, we have no good standard to go to the first line and achieve the CR.
- DR LOVE:** So, Julie, we asked the audience a couple of questions. One, how many new patients with T-cell lymphoma came in your practice the last year? And I think a lot more than we would see if it was in general practice. People are particularly interested, I hear, at this ASH meeting. So, actually, a fair amount of experience.
- We asked: What would your likely therapy be of a patient like this one? And most people said, "CHOP

followed by transplant.” And it was also curious. We asked them about the 2 new agents that you’re going to be commenting on, romidepsin and pralatrexate, and how many patients they’ve treated with these agents. And, actually, most people in this room have not used either one of these agents. That I find pretty interesting.

This is romidepsin. And here’s pralatrexate. So I’ll be curious what the faculty’s experience is with these 2 agents, and Julie, what your thoughts are about approaching a patient like this?

**DR VOSE:**

This is a pretty typical patient with peripheral T-cell lymphoma, very advanced disease, high IPI. And is something that is pretty uncommon. There aren’t a lot of patients with T-cell lymphoma, so any one physician may not see a huge number of patients. So one thing is very important, to try to get information from every patient we have with T-cell lymphoma, because there’s so few of them.

So I’m going to talk a little bit about the up-front treatment for these patients. And I think — these are my disclosures as far as clinical research that I do.

One very important part of T-cell lymphoma is the classification. And this is something that we’re understanding more and more of over the past few years as we’ve done larger studies. But it’s a very rare disease, and there are multiple different types and subtypes, mostly into the different categories that you see here.

Now this patient had peripheral T-cell lymphoma not otherwise specified, and that’s under the nodal category, which is the most common type that we see in Western developed countries. Even within this type of lymphoma, there’s probably multiple different subtypes that we’re starting to understand, based upon our genetic analysis and pathway analysis. And over the upcoming years, I think we’ll understand a little bit better how to treat these patients based upon this information. But, as of yet, and from past analysis, we still don’t have very good treatments for these patients, unfortunately.

So what we do know from a large international study that we did several years ago now, looking at about 1,300 patients with different types of T-cell lymphomas, unfortunately, standard therapy, for the most part, does not do very well for the vast majority of our patients other than anaplastic large cell ALK-positive.

You can see there the subtypes of PTCL, the most common types, and the outcomes for 5-year overall survival. This patient, as far as the overall subtype PTCL NOS, would be about a 30%, 5-year overall survival, because he has a high IPI, high-intermediate IPI. He would actually have even a worse outcome, and that was standard therapy. So we have a long ways to go in trying to improve this.

This just looks at prognostic indices, and there are several different that have been applied to different types of T-cell lymphoma. The standard IPI that we use for diffuse large B-cell and has been applied to T-cell you can see on the left. And then on the right, one that has been more specifically applied for patients with PTCL, the PIT index, is a little bit better in prognosticating our patients and looks at the different risk factors and outcomes as you see there.

So as far as treatment, what should we treat this patient with? We know from the international study that patients that are treated with standard therapy, either an anthracycline or, in some cases, a non-anthracycline regimen, for PTCL NOS, such as this patient or other types, such as angioimmunoblastic lymphoma, had very poor outcomes. And, unlike diffuse large B-cell, the anthracycline does not appear to add a huge amount to the treatment for these patients. So we need different options.

So the paradigm for treatment for aggressive B-cell lymphoma does not really work very well for T-cell lymphoma. And, obviously, R-CHOP is not something that we can use very well and does not appear to look for a cure.

Stem cell transplantation for relapsed patients, there’s always been a question, “And what should we do for different salvage regimens?” So we really need a new conceptual framework for T-cell lymphoma, including different options for newly diagnosed patients for induction, perhaps a non-anthracycline-containing regimen, substituting other agents or putting some of our newer agents up front. Perhaps consolidation and transplantation is always something that comes up in this context, either allo or auto transplant. And we may even need some maintenance therapy to try to keep patients in remission, because it’s very difficult not only to get them into remission but to have them remain in remission.

So as far as relapsed patients, again transplant comes up and novel therapeutics.

What’s the information that we have? What does work better than a standard anthracycline regimen? There’s not a lot of data out there, actually, that show us what does work better. This is one example that was published a couple of years ago by Dr Schmitz, looking at the German Lymphoma Study

Group, and looking at the addition of etoposide to a standard CHOP regimen, or the CHOEP regimen, and it has been used in Germany. And what he looked at was the patients that were treated with the etoposide-containing regimen — you can see on the right — do appear to have an improvement in outcome. And this has led to some concern that perhaps, if we're using a nonetoposide-containing regimen, that this may be not beneficial to our patients.

So some of the new trials are adding etoposide, a potential agent, to the up-front therapy to improve the outcome. But we have lots of targets for T-cell lymphoma and that's where the research really lies right now, looking at either new antigens on the surface, possible microenvironmental factors and some of our new agents that address that, or particular cellular pathways and survival mechanisms. And a lot of the new therapies address this as well.

We do have two agents that have been approved over the past couple of years in the US for patients with relapsed peripheral T-cell lymphoma, pralatrexate, which is a selected antifolate. It was approved a few years ago.

This is the bar graph for that. And looking at the waterfall plot, that about 75% of patients had a decrease in tumor sites to some extent.

Toxicity for pralatrexate. It does have some very specific toxicities. It does cause mucositis, even with vitamin replacement pretreatment beforehand, and does cause some cytopenias.

Romidepsin is the second agent that has been approved in the US, and this is an HDAC inhibitor, also perhaps has some anti-angiogenesis factors and has also been approved recently for PTCL. It's given for 2 weeks out 4 intravenously.

Toxicity and overall response rate. Overall response rate for this one is also about 30%, as it is with pralatrexate. You can see the data there.

Brentuximab vedotin is an antibody that is anti-CD30. And then attached to that is the potent antitubulin agent, and this really recently has been approved for patients with anaplastic large cell that are CD30-positive in relapse, as well as Hodgkin's disease. And for a small number of patients with PTCL, about 30% are CD30-positive, as well. And that's being studied currently with this agent.

This is the waterfall plot for the anaplastic large cell lymphomas that are CD30-positive and has very high activity in the relapsed setting.

So the question is, "How can we try to gather more information and treat these patients?" And there's a lot of research going on looking at different subtypes of PTCL NOS. There's probably many different subtypes within this "wastebasket" term, so to speak. Using gene expression profiling, they've looked at at least 3 types that, perhaps, different gene signatures and perhaps different pathways we can try to address with some of our clinical trials and targeted agents.

And there are certain types of T-cell lymphomas that, for example, the NF-kappa-B pathway appears to be important, and those are the types of patients where, perhaps, bortezomib or other NF-kappa-B inhibitors may be a potential treatment.

And then there's another type that appears to have overexpression of genes involved in the JAK/Stat pathways as well, and that's a clinical trial that's going on as well.

So this type of research will help us in the future to try to suggest treatments for specific types of patients.

What about transplantation? There are not large randomized trials for transplantation in T-cell lymphoma. These trials, of course, are very difficult to do. Probably the best information available was this CIBMTR abstract that looked at allogeneic or autologous transplant for patients with T-cell lymphoma, presented by Dr Smith a couple of years ago, looking at 241 patients that were treated with transplant, about 115 autologous and 126 allogeneic. Some of those were either matched and related or related patients, and some of them were ablative and some were nonmyeloablative. So it's kind of a mixed bag.

But looking at this information overall, for all patients, you can see that — actually, for all patients — progression-free survival, autologous transplant came out on top of allogeneic for progression-free/overall survival, and that was mostly due to increased nonrelapse mortality for allo patients.

If you look at patients that are — excluding CR1 patients, the allotransplant still comes out on top, although it's not clinically significant in any of these graphs. Again, due to increased nonrelapse mortality.



So even though a lot of us consider that allotransplant for relapsed peripheral T-cell lymphoma may be a consideration, there's no data necessarily at this point to say that's a better consideration.

The regimen intensity did not appear to make a difference, myeloablative versus nonmyeloablative, so that you could still use the reduced intensity regimen, which would have a decrease in nonrelapse mortality in some patients.

So what's the future for PTCL therapy? I think standard CHOP does not work well and, although that's kind of the standard I would say in the US, it's not a very good standard and we need to put patients on clinical trials, trying to test some of these new treatments or sequential therapies or other things that we're looking at. We need to identify these novel agents and, perhaps, try to use those in combinations for these up-front clinical trials and look at relapsed patients as well, of course. And try to use our information for gene expression profiling and pathways to try to identify specific targets in specific patients. So personalized medicine.

We also need a combination of, not only good induction, but also consolidation. Transplantation may be an option. And maintenance therapy may be an option as well in clinical trials.

Consider transplant for selected younger patients. I think the patient that was presented today is a good option for a transplant in first remission, and also consider novel therapies added to transplant or after transplant, to try to keep the patient in remission.

So these are some abstracts that are going to be presented at ASH this year looking at PTCL, looking at some of the treatments we discussed today and updated some of the clinical trials and the use of transplantation, as well. So I'll draw your attention to those.

And thank you very much. I'd be happy to answer any questions.

**DR LOVE:** Thanks, Julie. I'm actually going to ask Pier Luigi to go to the podium so we can get to our last case. But while we do, Andy, we had your colleague Craig Moskowitz down in our neck of the woods for some education a few weeks ago. My favorite slides of last year's ASH were the 2 waterfall plots on B-vedotin — the one from ACL — anaplastic large cell and Hodgkin's disease. Any experience on the faculty with this agent? Andy, have you treated anybody with this drug?

**DR ZELENETZ:** Yes. We've treated a number of patients. We have a couple of trials open. We've also dosed now some patients actually with commercial drug. And this is a drug with some toxicity. And people need to be aware and used to using it. But particularly, if there's any preexisting neuropathy, there is a clear potential to exacerbate neuropathy with this. But one of the things, and a good way to sort of judge the risk-benefit, it works pretty quickly. So if there's no early response, the chance of response is very small. You don't keep going to 6, 7, 8, 9 cycles and run the risk of the neuropathy. You will see a response, typically by the third or fourth dose. And if you haven't seen that response, you don't keep going because you won't see it.

**DR LOVE:** Julie, where do you think things are heading in general, in terms of antibody-drug conjugates? In the breast cancer meeting, we were talking about the T-DM1 trastuzumab maytansine. Really exciting. They actually — we hardly see any toxicity there. What about B-vedotin and other antibody-drug conjugates, Julie?

**DR VOSE:** I think for a lot of our lymphomas, the antibody-drug conjugates are going to be very potent. We are going to have to be able to use them in very specific patient populations. They're not going to be for all of our patients. And we're going to have to try to identify which patients that they're going to be useful in. In the anaplastic large cell patients that are CD30-positive, this agent is very active. And I agree with Andy, if it's going to work it works fairly quickly and is very impressive, actually.

**DR LOVE:** So you've seen clinically useful responses?

**DR VOSE:** We've seen very useful responses. I've used it in patients that have multiply relapsed. And we're trying to get ready for allotransplant after failing an autotransplant. And it's been successful in a number of different patients in that category.

**DR LOVE:** Again, we heard a bunch of stories about T-DM1 on Wednesday, same situation.

So Pier Luigi, let's go on to our last case. We're back to the US of A. And this is a young man, 43 years old, with right flank pain. Found to have massive adenopathy. On biopsy is found to have diffuse large B-cell, but in the bone marrow actually has low-grade disease. The patient gets R-CHOP and has a complete remission. And in fact, later on, the doc kind of was going back and forth about — we were talking about R maintenance, whether to use R maintenance in this situation. Very controversial. A lot of docs in practice ask us about that. Unfortunately, this patient did relapse, and he relapsed with follicular lymphoma. Here's the team talking about the patient.

**DR MURPHY:** So, in fact, I repeated his bone marrow after his R-CHOP was completed and he was in remission as far as restaging went, and his second bone marrow was normal. We kind of somewhat warned him that he may actually have underlying low grade, and that may be what recurs. And I don't typically give rituximab maintenance after large cell. Is there a role for that? Especially if we're wondering maybe he does have an underlying low grade that may have transformed.

**DR ZIEBER:** On the left side of the screen, we see a PET image showing a left submandibular lymph node, which is abnormal, increased glucose uptake.

The image on the right side of the screen is a corresponding CT study axial image to the area showing a lymph node, which corresponds to the area of that abnormal activity, although the lymph node is not significantly enlarged.

**DR CRABTREE:** In this case, we have a right flank mass biopsy. When we look at the slide it's diffusely blue, which tells us, "Hey, it's bad." If you look centrally down it, there's that pink area, which is an area of fibrous tissue.

When we get up close on this, the cells are very undifferentiated. They're large and pleomorphic. They're scattered individually, and it's hard to get individual cytoplasmic detail.

This gentleman subsequently apparently had a left submandibular gland mass. In the lower right-hand edge of the slide we have a normal-appearing salivary gland. All the rest of the slide is lymphoid tissue. It's essentially diffusely replacing the gland.

When you look at other areas, you get a very subtle nodularity to the cells. Over at 3:00, there's a nodule; over at 9:00 there's a pinch nodule, even a better one down toward 8:00. And so you have nodules in this. When you go up close on these nodules, they are not composed of a mixture of variable cell sizes or variable cell configuration. They're all a monotonous cell population of relatively small, angulated cells. So this is a follicular lymphoma and it's a Grade II, which is intermediate grade.

**DR LOVE:** What about after he recurred with essentially a follicular lymphoma?

**DR MURPHY:** I had discussed bendamustine/rituximab second line once his follicular lymphoma developed, but wanted to avoid any potential that we might burn out his stem cell, so to speak. So we decided to give rituximab single agent. Would it have been more appropriate to give something more aggressive at that point? Knowing he's only in his forties and knowing he probably may need a transplant down the road, he did not want to take any risk against something that could...So would there have been an agent — would it have been reasonable to give bendamustine/rituximab, which we tend to like second line? What other options would they choose?

I'm not sure at this point as to what his best choices would be. If he's doing well with no signs of disease, tolerating rituximab well, keep him on every 2 months? And for how long? If he does well after 1 year, after 2 years. If he's in remission at 2 years, do we stop it if he's tolerating it well? Do we keep it going? I don't know if there's an end point as to when we have to stop it.

If he does relapse, at what point do you consider something like a stem cell transplant in a follicular lymphoma in a young person?

**DR LOVE:** So before Pier Luigi goes into some of the science and whether this is transformed disease or mixed disease, to start, just a couple of basic clinical things. I'll start with Stephanie. What about this issue of maintenance R in patients like this? It looks like the audience would be favoring actually using it for a couple of years. How would you have thought through that, Stephanie? Also, what about his question in terms of treatment on relapse?

**DR GREGORY:** First of all, there's no data as far as maintenance rituximab in this type of person. And I think the real question also is, what is his lymphoma? I mean, he has a follicular in one area, he has a diffuse large B-cell in another. And do you call that transformed? Do you call it a composite, a discordant? So I think you'll discuss that, perhaps, a little bit.

At relapse it depends on how bulky his disease was. It sounds like it was localized. I probably would have used rituximab at that point if it were follicular, after restaging, making sure that he had nothing else.

**DR LOVE:** And, Martin, what about the question here about transplant in FL?

**DR DREYLING:** We just had a Consensus Meeting of the EBMT earlier this day, and we exactly discussed this point. And I would probably argue, specifically in such a young guy with quickly relapsing disease, although it's still follicular lymphoma, obviously clinical wise it was more aggressive. And, therefore, in fact, in this young chap I would have preferred to go on to autologous transplantation.

**DR LOVE:**

Okay, Pier Luigi, we'd like to hear your thoughts on this. And then we're going to close with a few more questions from the audience.

**DR ZINZANI:**

Thank you very much for the invitation. And these are my disclosures.

I want to define, first of all, the concept of transformed lymphoma. This probably is a composite lymphoma, but I think it's very important to do an update concerning the situation on transformed lymphoma. All of you know that there is a rise from follicular lymphoma Grade I or Grade II to the diffuse large B-cell lymphoma or the Burkitt or another situation could be 2 different steps from follicular lymphoma Grade I or II to Grade III and then to diffuse large B-cell lymphoma.

And how to define, in this case, in terms of evaluation of a biopsy. Transformed lymphoma usually maintains a GC phenotype, germinal center phenotype. The most common phenotype is CD10-positive, BCL-6-positive, and there are changes in antigenic pattern, that this change is quite common.

And, at the same time, in terms of clinical situations, so sometimes it's so difficult to have a second biopsy in this subset of patients, are out to series one from Canada, from Vancouver; another one from France in Europe, from Lyon in particular. And this is quite easy to select and to identify the patient with a potential transformed lymphoma with a sudden rise in LDH, with rapid discordant and localized nodal growth, with new or unusual extranodal sites and with new B symptoms or new hypercalcemia. At the same time, for the French group, it was possible to have the idea concerning the rapidly growing bulky disease, poor performance status plus B symptoms. And also in this case, a high level of LDH.

And in terms of transformation rate, in terms of what is the risk in the follicular lymphoma patient to rise to a transformed lymphoma, it's roughly 30% at 10 years. There are data from France. There are data from London, and those are from Canada again.

In terms of: Does the risk of transformation present a plateau? Probably yes. There are data from Lyon at 6 years. There is a plateau from Saint Bart's in London. At roughly 15 years, there is a plateau. On the contrary, there are some different data from Canada and also from Stanford in the United States that is so difficult to find the plateau also after more than 15 years.

And in terms of biopathology, molecular biology, this transformation is associated with a gene special profile that is at least in genes expressed in embryonic stem cells. And the transformations likely arise not from a true hematopoietic stem cell but from a more differentiated follicular lymphoma or follicular lymphoma progenitor cells that acquire a stem cell-like expression pattern.

There are several molecular events in this transformation, but there are actual changes that you can see: multiple alternative mechanisms involved in patients with transformed lymphoma. At the same time, there are, of course, 2 different points and the clinical variables predictive for transformed lymphoma. There are others predictive for transformation, in particular, advanced stage at diagnosis, high IPI or FLIPI, high beta-2 microglobulin. At the same, also, there is a dynamic variable predictive for transformed lymphoma, in particular not achieving CR after the front-line treatment for follicular lymphoma. And the requirement of more than 2 courses, 2 different chemotherapy regimens of treatment to manage initial follicular lymphoma.

And another important question is: Does early treatment versus watch and wait alter the risk of transformation? Probably not. There are data from Stanford. There are data from Vancouver on the contrary, from London. There was more transformation patients in the watch and wait subset instead of the patients treated at diagnosis.

And another question is: Does the type of initial treatment alter the risk of transformation? There are data from Vancouver concerning the real risk, if you use an alkylating agent or, in particular, fludarabine, also in the case. But it would be inappropriate to read this observation solely to a specific agent included in the chemotherapy or the use of local radiotherapy.

Another important concept is the outcome for the patient with transformed lymphoma. There are data from France, from London and, again, from Vancouver, concerning that the median duration of the survival range is between 1 and 2 years.

In terms of treatment options. So we need prospective trials concerning the best treatment for this subset of patients. But all of you don't know that it's a disease, so it's so difficult to have a randomized trial. At the same time, concerning the role of CHOP plus rituximab. It's in this data published by the British Columbia Group concerning the real role of CHOP plus rituximab in transformed patients versus CHOP without rituximab. You can see a real statistical difference. With CHOP plus rituximab, the 5-year overall survival is 61%. This is only roughly 30% in CHOP treatment in transformed lymphoma.

There are data, several data concerning the role of autologous bone marrow transplantation in these

specific patients. And the data are quite interesting. The overall survival range in between 40 to 70%. The event-free survival is in the range between 25 to 35, 40%. And there is a risk of myelodysplastic syndromes, a second acute leukemia, range in between seven to 15%. And, also allogeneic. There are a few data. Now all the studies suggested a poor outcome, but there are a few recent studies that may suggest a benefit, but, of course, these therapeutic approaches should be limited to clinical trials.

And why not also in this subset of patients, radioimmunotherapy? There is an official indication by FDA, by EMA, for ibritumomab tiuxetan in transformed patients – in relapsed-refractory transformed patients, but there are also data using tositumomab. And you can see the result in terms of CR rate is a range between 30 to 50%.

And what about rituximab? There is a very interesting case published a few months ago by the Spanish Group concerning the role of sustained rituximab in terms of sustained complete response with single-agent rituximab in relapsed follicular lymphoma as transformed disease after an unrelated reduced intensity conditioning regimen — allogeneic stem cell transplantation. Very interesting data resulting in kind of toxicity. Can a have a complete response after allogeneic stem cell transplantation, using the conventional dose of rituximab.

And, also, a few months ago, Friedberg and colleagues published this data on leukemia and lymphoma concerning again the role of rituximab in transformed patients. So they treated 18 patients with autologous transplantation. Six patients did not receive the rituximab pretransformation, and this group had a significantly better progression-free survival after 2 years. Postautologous transplantation compared to the 12 patients who were exposed before transformation to rituximab. And the  $p$  was statistically significant.

So high dose with a vascular autologous stem cell. And it's an effective therapeutic option for transformed NHL in the rituximab era. However, patients positive to rituximab pretransplantation appeared to have inferior outcomes.

And a slide concerning a few new agents, also from this subset. Again, bendamustine and again lenalidomide. There are a few data concerning the role of bendamustine in 15 patients, published a few years ago by Friedberg and colleagues, the overall response rate was roughly 70%, and 13% of the patients obtained a CR.

The same for lenalidomide from an interventional Phase II trial. Czuczman extrapolated 23 patients. The overall response rate was 57%, and 25% of the patients obtained a CR.

And this last slide, you can have the legend concerning the abstract on transformed patients presented at this ASH in the next few days.

Thank you very much.

**DR LOVE:**

Luigi. You can have a seat here. And we're going to close out with a little thing we've developed recently called "Rapid-Fire Questions." So we want to see how many questions from the audience I can get your answers to in just about 5 minutes.

So, Andy, I don't know if this is a typo or not, 110-year-old gentleman. Do people live to 110 with diffuse — let's just skip that one.

Okay. We were — what's the best CNS prophylaxis? We talked a little bit about this, but there have been a lot of questions trickling in during this about if you're going to use high-dose methotrexate, how do you integrate with R-CHOP?

**DR ZELENETZ:**

I use MR CHOP, which is high-dose methotrexate, 3.5 grams/m<sup>2</sup>, given on day 15, but you support the first 14 days with growth factor. So you're actually treating at the time of count recovery. So you do R-CHOP and then you start in with high-dose methotrexate. It actually is less — there are fewer complications than if you give it at day 10.

**DR LOVE:**

Stephanie, what patient subgroup did RESORT include?

**DR GREGORY:**

It was the low tumor burden/low GELF tumor burden. And it was both follicular and other indolents, but what's being reported at ASH is only on the follicular.

**DR LOVE:**

Another low-grade question, Stephanie. What role does PET scanning have in initial management?

**DR GREGORY:**

We thought it didn't have any role, but from the PRIMA trial there were some very nice data that PET scans at the end of the PRIMA trial showed that those who were PET-negative had a longer progression-free survival. So maybe there's a role. And there are many, many abstracts on PET in follicular lymphoma at this meeting. Please look at them.

- DR LOVE:** Martin, can bendamustine be used in patients with significant renal insufficiency?
- DR DREYLING:** Yes. Definitely yes. We do have unpublished data on these patients. It's still well tolerated and gone to a creatinine clearance of 30 or less. You don't have to reduce the dose.
- DR LOVE:** A follow-up, another bendamustine question for you, Martin. Due to the risk of Stevens-Johnson syndrome when allopurinol is used, what do you use to prevent tumor lysis syndrome with CLL and bendamustine/rituximab?
- DR DREYLING:** This is based on few cases, but still we follow the general guidelines, which is stop allopurinol simultaneously to bendamustine and then move on after completion of the 2-day treatment. And with that you're still able to avoid tumor lysis. But really, also, try to skip this danger of Stevens-Johnson Syndrome.
- DR LOVE:** Alessandra, in CLL I use bendamustine with rituximab in a majority of my relapsed patients. The results have been very good. So I'd like to use bendamustine/rituximab first line, but I don't know what to do when patients relapse after bendamustine/rituximab. Do I retreat with bendamustine?
- DR FERRAJOLI:** A few things. First of all, we use rasburicase sometimes, to prevent the tumor lysis syndrome and we have no problem with that. Then, to use bendamustine/rituximab as front line we need to wait for the results of the randomized trials that the Germans have completed accrual. I expect it will be presented next year or the year after, where they're randomizing patients with BR versus FCR. And what do I use for patients that relapse after bendamustine? Again, it depends on their genomic abnormalities, but I would say enrollment in clinical trials with Btk or CAL-101 or similar.
- DR LOVE:** Julie, does R-CHOP reduce the rate of transformation of indolent disease?
- DR VOSE:** Well, there's conflicting data on that. In some studies, it's stated that it does reduce that and in others it does not. So I think this question is still out there.
- DR LOVE:** Julie, another question about R maintenance with R-CVP, "the PRIMA subgroup analysis did not show statistical difference." Is that just numbers?
- DR VOSE:** Yes. The problem was with the PRIMA study that most of the patients got R-CHOP, and so the other data with the other drugs is really very minimal.
- DR LOVE:** Pier Luigi, gastric MALT lymphoma, Stage I, biopsy negative for H pylori times 2. Do you still treat with antibiotics? What do you do?
- DR ZINZANI:** Yes. There are some data concerning the role of antibiotics, so in HP-negative. And it's possible to obtain a response in terms of CR FL lymphoma in roughly 50, 60% of the patients.
- DR LOVE:** So please fill out your CME forms. Tell us what you liked, what you didn't like. And if you liked what we did, come back tonight and we'll do the same thing with multiple myeloma. Thanks so much to our faculty and thank you for coming today.