# Transforming Relapsed/Refractory MCL
## Exploring New Options for Your Patients

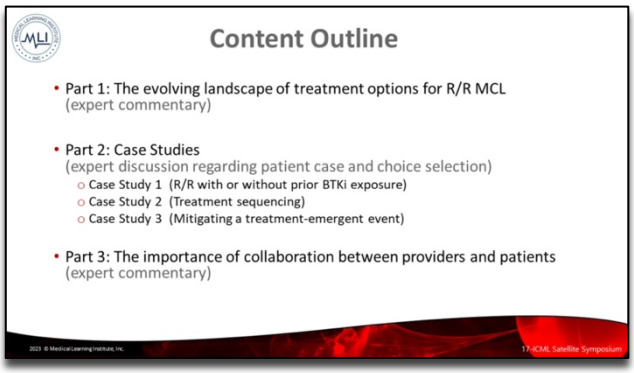
AS PRESENTED AT 17TH ANNUAL INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMAS
LUGANO, SWITZERLAND – JUNE 13, 2023


**Mats Jerkeman, MD, PhD:** So, welcome to Lugano. My name is Mats Jerkeman. I'm from Lund in Sweden, and I'm really happy to have a couple of very distinguished colleagues with me today. So please introduce yourselves. Christiane.

**Prof. Dr. Christiane Pott:** So, I'm actually traveling from the north of Germany, very close to your hospital. I'm located in, close to Denmark actually, in Kiel. I'm focusing on mantle cell lymphoma in my clinical work, and I'm happy to share with you some discussions, what I think is really important in making up the right decision for our patients. And I'm happy to do that with all and all these great people around me, and I'm leading further to Carlo.

**Carlo Visco, MD:** Hi, everybody. Welcome to this nice meeting in Lugano, the ICML 2023. My name is Carlo Visco. I'm actually working as Associate Professor at University of Verona, which is located in the Northeast of Italy. I'm the head of the Lymphoma Unit at my department, and, or I deal, specifically with mantle cell lymphoma. Thank you.

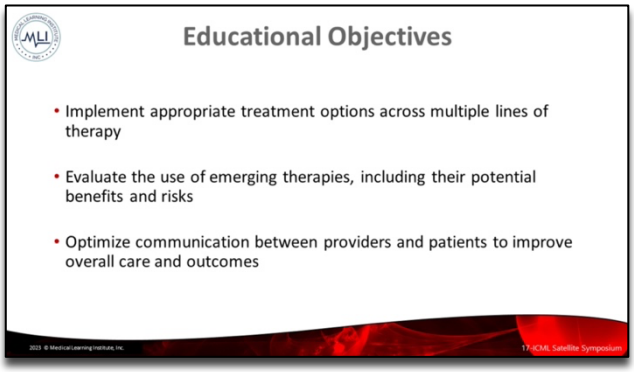
**Dr. Jerkeman:** So, thank you. And today we'll talk about the treatment of relapsed mantle cell lymphoma, where there are a number of new options available.




## CONTENT OUTLINE

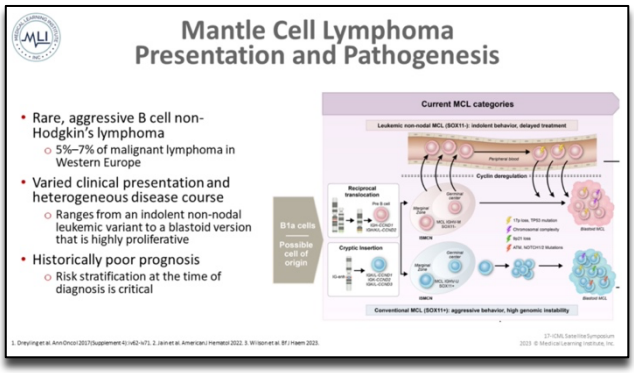
We will first have a short introduction on the, on mantle cell lymphoma and its treatment, and then we will continue with a few case studies.

So the main focus will be these case discussions. Then we will also have a discussion about shared decision-making and collaboration between patients and providers.




## EDUCATIONAL OBJECTIVES

So, the objectives of this educational session will be to learn how to implement the appropriate treatment options across multiple lines of therapy, evaluate the use of emerging therapies, including benefits and risks, and also optimize communication between providers and patients.




## MANTLE CELL LYMPHOMA PRESENTATION AND PATHOGENESIS

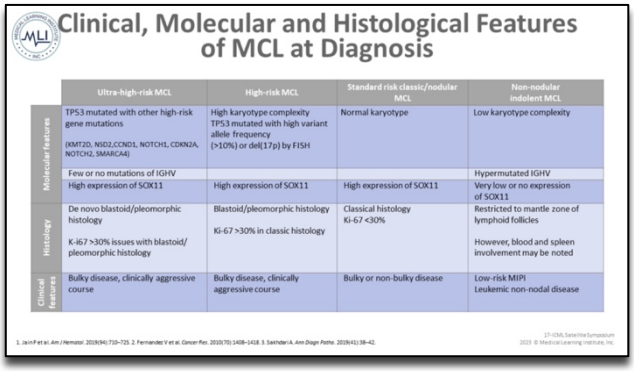
So, now to mantle cell lymphoma. This is a quite rare lymphoma, as you, I think all of you know, around 5 to 7% of all lymphomas in at least Western Europe. In Sweden, I know it's 7%, for instance. It's very, can present very differently. It can be a very indolent disease that doesn't need treatment, and it can be an extremely aggressive disease where patients can die in days without treatment.

And it's, historically, we consider this as a disease with a poor prognosis, but it's very different, I would say, and different among patients. And, but still we cannot say that it's a curable disease at least.

It's considered to be possibly originating from B1a cells that are CD5+ B-cells and, most commonly, the most common genetic aberration is the translocation between the cyclin D1 gene and the the heavy immunoglobulin gene. There's also more rare cryptic insertion of the cyclin D1 gene close to the genes for the light chain immunoglobulin genes, the blue ones.

And this can either occur in a cell that has experienced a germinal center that has a hypermutated IGHV gene, the red cells, and they develop into the indolent leukemic non-nodal form of mantle cell lymphoma, which is also characterized by being cyclin, SOX11-negative. And it's usually leukemic in this presentation. It can also acquire additional genetic aberrations and become a very aggressive disease, a blastoid disease.

The blue ones are the more classical type of mantle cell lymphoma, which is SOX11-positive. It often has unmutated IGHV genes, and it can also acquire eventually additional genetic aberrations and become aggressive blastoid type of mantle cell lymphoma.



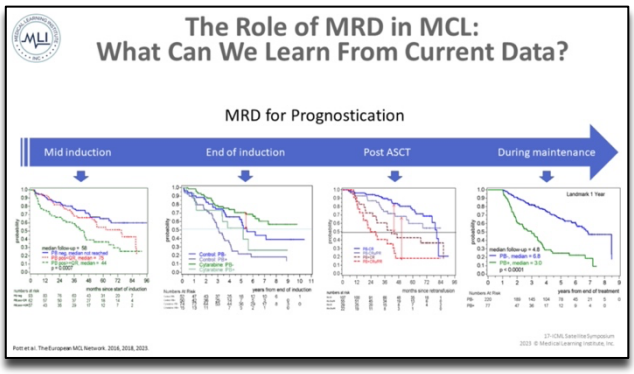

## CLINICAL, MOLECULAR AND HISTOLOGICAL FEATURES OF MCL AT DIAGNOSIS

And so we can categorize mantle cell lymphoma at diagnosis into different choice groups. It's the indolent type, which also has, often have hypermutated IGHV, low SOX11 expression, and often is leukemic and non-nodal.

The more classical and typical type of mantle cell lymphoma, we see it has high SOX11 expression, classical histology, low, lower proliferation. The disease can be bulky or non-bulky.

High-risk factors for mantle cell lymphoma include having a TP53 mutation or a 17p deletion. But TP53 mutation seems to be more important, blastoid or pleomorphic histology, and high proliferation rate, more than 30%.

We can also identify an ultra-high-risk group which has, in addition to TP53 mutation, also other high-risk gene mutation, including, for instance, NOTCH1 mutations and also CDKN2A aberrations. And also, if they have a de novo blastoid morphology, makes this an even more high-risk population.




## THE ROLE OF MRD IN MCL: WHAT CAN WE LEARN FROM THE CURRENT DATA

MRD, minimal residual disease, is a very powerful tool, also to assess efficacy of, of treatment in mantle cell lymphoma in different situations. And I know, Christiane, this is your favorite topic in a way. I don't know, do you think this is something we could use in clinical practice even?

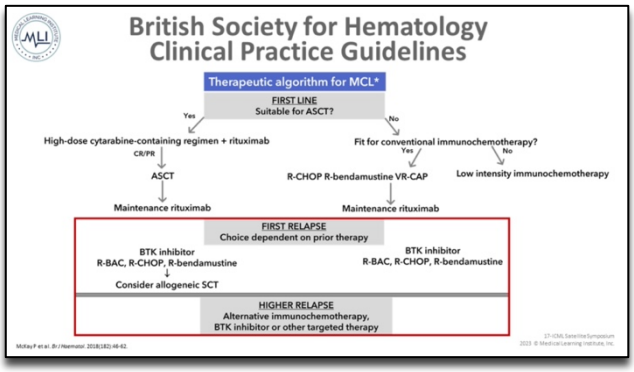
**Dr. Pott:** This data, I think, would show it only from clinical trials; and I think at that moment, it might not be justified to treat somebody according to MRD. But I think what the beauty of this approach is, as we are talking about prognostication and genetic risk factors, I think there is additionally what we don't assess at diagnosis.

Additionally, we have chemotherapy response or the, let's say, the host genetics that determines whether a patient responds to a certain treatment or not. That is not reflected by our current prognostication parameters, but MRD is a surrogate of all these genetic surroundings, let's say. I think it's a beautiful tool to assess that, to assess more deeply the quality of response; and we have seen in mantle cell lymphoma this is relevant. And also, it's a tool, I would say, in clinical trials that we can direct treatment according to an MRD response status that means induction but also maintenance treatment, and there are good data to do that in clinical trials.

But the value outside of clinical trials might be there for specific questions. What is involved with the disease or is a different aspect. Then you could use genetic diagnostics or flow to identify that. But I think for routine use, it's not, not the tool we should follow because actually we don't make any conclusion from the result we get.

**Dr. Visco:** Christiane, do you think the time has come to start thinking of replacing the, the standard MRD prognostication in the lab with the, with the liquid biopsy in mantle cell lymphoma? Is there any data on that?

**Dr. Pott:** There is. Actually, there is a session on Wednesday focusing on that, and we, we are lucky to present some data from TRIANGLE. Let's say it's not in the stage like in DLBCL where we have from several clinical situation and several trials results on that. It's more the exploratory way. But what I think is because MRD in one is addressing, I think very nicely, the leukemic part of the disease. But DNA might improve and give us a better view on what is going on in the lymph node compartment. And I think it will be additive, and then we have to plan the smart trials to use both as surrogacy for treatment decision or for more information on biology. But it's, I think, very, very necessary to explore that; and I think we are happy with the TRIANGLE trial where we have the samples and only have to do the analysis.

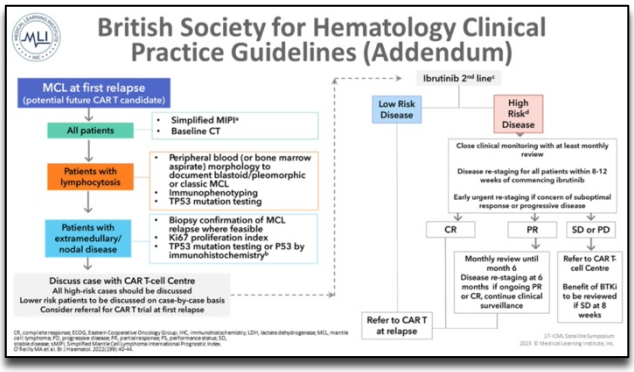



## BRITISH SOCIETY FOR HEMATOLOGY CLINICAL PRACTICE GUIDELINES

**Dr. Jerkeman:** Yes, we also have a poster from the Nordic MCL7 trial that you can come and watch on the CD data in our trial.

And about guidelines, we have chosen to use the British Guidelines because they are a little more updated than the European ESMO Guidelines, just as an introduction. And we will not talk about first-line treatment very much today; but the division line for most guidelines still is if a patient is transplant eligible or not. And patients that are transplant eligible will receive as a standard high-dose chemotherapy-containing regimen, autologous stem cell transplant, and then maintenance rituximab. Whereas more frail patients, will receive standard chemotherapy like R-CHOP, R-bendamustine, VR-CAP, and also maintenance rituximab.

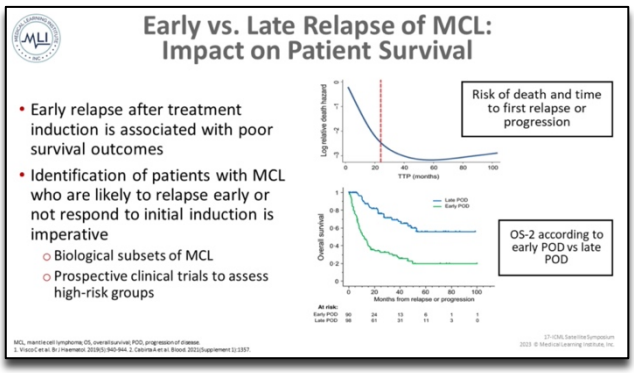
At relapse, the choice would depend on the prior regimen used or a BTK inhibitor, and then your patient would be considered for allotransplant.




## BRITISH SOCIETY FOR HEMATOLOGY CLINICAL PRACTICE GUIDELINES (ADDENDUM)

There's been an interesting addendum to this, these guidelines recently published because of the approval of CAR T-cells also in patient that have previously received a BTK inhibitor. So in these British Guidelines, they encourage more detailed workup for these patients to assess risk factors such as TP53 mutation, Ki-67 proliferation index, histological subtype and so on.

And they stratify the follow-up, depending on the presence of, these risk factors. So patients will receive ibrutinib in second line, but low-risk patients will not be so closely monitored but will be referred if they relapse. Whereas high-risk patients that have any of these biological risk factors or have an early relapse or bulky disease will be very closely monitored with restaging within two to three months. And if they don't response, will be referred early to a CAR T-cell center. So, I encourage you to have a look at these guidelines.




## EARLY VS LATE RELAPSE OF MCL: IMPACT ON PATIENT SURVIVAL

One of the risk factors in the British Guidelines was the time to relapse because this has very strong impact on overall survival. This is done, work done by Carlos, and he, colleagues showing that patients with early progression, that is within 24 months, have a much worse overall survival compared to those with a late relapse. So Carlo, how do you think we should, should, is there something we should consider in, in the clinical practice? And should we treat these patients differently if they have an early or late relapse?

**Dr. Visco:** Well, yes, I also like the British Guidelines, the addendum to the British Guidelines because it, actually, the right side of the, of the slide you've seen, it, it's actually what we are, what we use in the clinical practice, how we decide to send the patient to CAR T-cell earlier or afterwards.

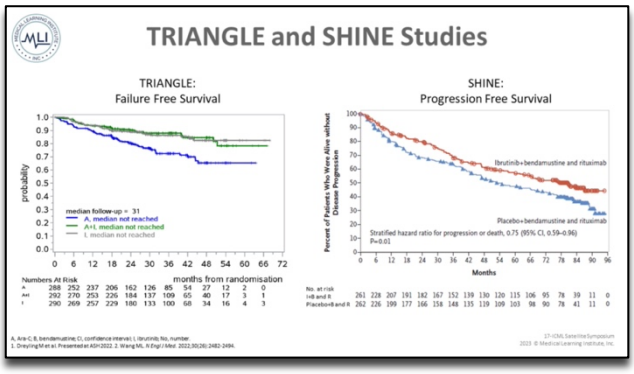
And I think among the definitions of high-risk patients, you have seen there's a molecular characterization. There's clinical characterization. But I think whenever a patient has his first relapse, it's very important to consider the time to first relapse because you can see very, very easily here how different is the, the survival of this patient. So whenever you consider to send your patient to CAR T in second line, I think you need to consider the time from first, to first relapse.

Of course, if you've given to these patients a standard treatment as first line, especially younger patients, will benefit of a very strict monitoring when they get ibrutinib as second line because these patients are very likely to be high risk because of their early relapse; and these patients are very likely to benefit of second or of third line, CAR T being monitored very closely.

**Dr. Pott:** May I ask you what, also something. Then what, what you say, I fully agree. But that would, would mean that you have to make a biopsy in any case because some people refer patients and say, "Yeah, I see an increase of the disease by flow." So that might not be, I think, good enough to say that there might be lymph nodes who are more aggressive. And, I think, at this stage, if you didn't do it at diagnosis, TP53 should be done. Would you agree with that?

**Dr. Visco:** I agree. I'm not sure we need the biopsy as we, I think we should and we are using DLBCL where we, the expression of CD19 needs to be confirmed sometimes. And also the diagnosis is sometimes very challenging between histotypes of DLBCL.

In mantle cell, I think if you have an aggressive presentation, especially in the P53 mutation subgroups, it's not that mandatory to have a new biopsy, especially when the patient relapses early. Of course, this is very true when they relapse in the peripheral blood, which is made by flow, but doesn't, doesn't mean, I mean it's, it's not a question of where it presents the relapse. It's a question of timing. You can see the, the risk of death is really dependent of time of first relapse.

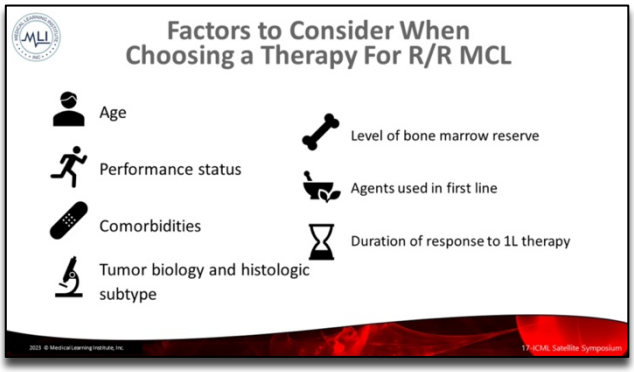



## TRIANGLE AND SHINE STUDIES

**Dr. Jerkeman:** Thank you. And we will not talk so much about first-line treatment, but I, I'd like to mention anyway that there is, there are changes now ongoing in, in first-line treatment. And I particularly want to highlight these two trials, the TRIANGLE and the SHINE study. In both these studies, at the addition of a BTK inhibitor, ibrutinib clearly improved outcome. In the TRIANGLE trial, two out of three treatment arms included ibrutinib in the induction and also as maintenance and clearly improved failure-free survival in this population of younger patients in mantle cell lymphoma.

In the SHINE trial, ibrutinib was added to R-bendamustine and improved clearly progression-free survival but not overall survival. So, we will probably see the use of BTK inhibitors frontline; so as Carlo just said, second-

line, third, what is now third-line treatment will become probably second-line treatment also. So, we had to take this also into account.




## FACTORS TO CONSIDER WHEN CHOOSING A THERAPY FOR R/R MCL

So to wrap up, there are many factors to consider when we choose treatment for patients with relapsed mantle cell lymphoma. Of course, age has an impact. Perhaps performance status is even more important than age. Comorbidities is, of course, important. We have talked about tumor biology and histological subtype, which impacts the sensitivity to chemotherapy. Bone marrow reserve is, of course, important if we want to choose chemotherapy. We have to consider what has been used already, and if it's an early or a late relapse. This will be important.

So, dear friends, how do you think we will change our guidelines now? Now, I know ESMO will probably, ESMO is working together with EHA now, which is really a step forward; and that there will be probably an update this year. So what will be the new things do you think, Christiane?

Dr. Pott: Yeah, we have already updated the German Onkopedia guidelines, but it's not yet official. But I think it reflects the topics you said with respect to CARs. It gives a similar, yeah, recommendation for the CAR T-cells. But we did not yet address pretreatment because this is really a challenge if the pretreatment was ibrutinib, in reality. I think it's not at the moment, but it will be in three, four years if we treat according to SHINE, at least the younger patients.

So, but I think, then again, coming back to your topic that maybe the time of relapse would be the most important thing, either to rechallenge somebody with ibrutinib who is in long remission, four, five years after the initial treatment. I think that, that should be an option. While I think these disastrous cases were progressive or have early relapse after this intensive induction, that might really be something where we need more, new drugs, other drugs, or whatever to make it a smart, yeah, decision. I don't know.

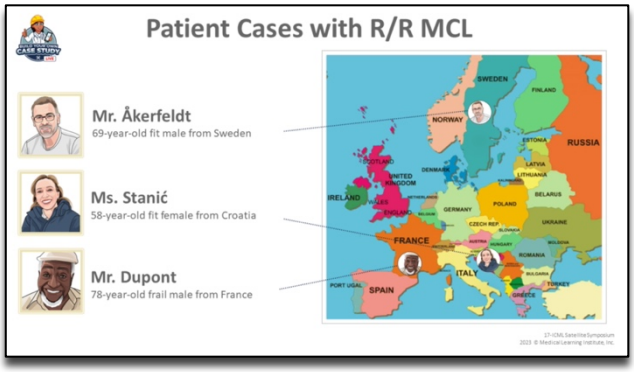
Dr. Visco: Yeah, I agree. On one side we'll have this challenge of a patient that failed ibrutinib as first line; and this, this is probably the most hot topic in mantle cell. It's going to be the most hot topic. How to manage the second line. We have non-covalent BTK. We're lucky to have those, but that's not enough. You know, if, especially if the patient is young.

So, I think the future challenge is going to be how to sequence these therapies. It's very important to acknowledge that the mantle cell lymphoma prognosis has, has improved a lot, so we have patients in the clinical practice that arrive easily to the third or fourth line, as you can see in the everyday practice. So it's going to be our challenge for us, in future trials. It's going to be what to do with second line. What is the perfect line? Probably and depending on the time to relapse, and what's going to be the third best line after you've given the second line.

So it's very challenging, very moving world of mantle cell lymphoma, especially when we take the BTK inhibitors which are, I think, the best drugs ever for this pathology to the to the first line.

I've also a comment on what you said about Mats', the guidance, the, the ESMO and, and guidelines are unifying, which is very good for clinicians, I think. And that's the opposite of what happened in the pathology where we were struggling with two different classification. We're lucky to know from Mats that this classification are going to be, will join together.

**Dr. Jerkeman:** Yeah, I agree it's a step forward. So now I will hand over to Christiane who will start discussing the patient cases.




## PATIENT CASES WITH R/R MCL

**Dr. Pott:** So, we choose three patients for you; and I go into some details.


## MR. AKERFELDT

So the first one is a male, 69-year-old. He's from Sweden. and he is a retired carpenter. He had been treated first after a watch and wait period after, for two years. He had been treated with induction of bendamustine and rituximab followed by rituximab maintenance because this is the standard, and he had a relapse three years after the start. So this is not the, like the very early and not the very late one. He's symptomatic with GI involvement, and he is in need of treatment with an elevated LDH.


## MS. STANIĆ

This is a lady from Croatia, actually. She is, she was quite young, 54 years old when she had the initial diagnosis; and she received the standard, that is rituximab-cytarabine, followed by autologous transplant, and rituximab maintenance. Her relapse was four years after start, and she already had received one treatment with ibrutinib; but now she became intolerant and she's symptomatic as well. She has neuropathy and lymphadenopathy, and she has pain. So we have to decide something for her.


## MR. DUPONT

The third patient is Mr. Dupont. He's from France. He's of older age, 78 years old; and he has a real early relapse after initial induction with R-CHOP. His, he is symptomatic. He has lymphocytosis and elevated LDH and also a suspected prostate cancer with an elevated PSA. He has rapid weight loss at presentation of, with ECOG Stage 2, so in need of treatment.


## MS. STANIĆ

So we come back to Mrs. Stanić, 58 years now. But she's, she's fit. This is the more extensive medical history. She has no real serious clinical restrictions, and she's medically fit. She's, has been marathon runner. My goodness, I would make that even without any disease. But she, she doesn't make marathon, but now she is still walking, so that's something.

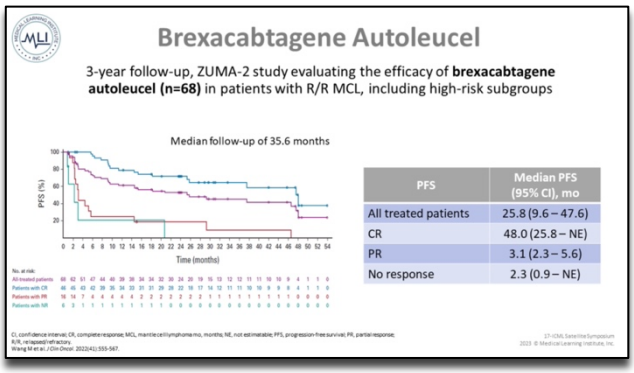
She was initially diagnosed with Stage III disease, indolent, and had an extranodal localization, what is the case in most of the patients. And we see that her genetics is not really suspicious for adverse prognosis. She has a mutated IGHV. Even if we, it's not so prognostic like in CLL, we know that these cases also in mantle cell lymphoma have a quite good prognosis. So, TP53 was unmutated, SOX11-negative, low proliferation, classic histology, and the only diagnostically relevant translocation 11;14. She was, four years ago she received the initial induction rituximab-cytarabine, autologous transplant, and had no real serious toxicity from that treatment. What I think is important information, her relapse is now four years after. In between she was fit. She received or she achieved a fully clinical recovery from the disease and the treatment.

Now, what about her symptoms? She has lymphadenopathy and neuropathy, what might influence our decision. And, but still she is fit, but she is impaired by a general weakness and a bit of the loss of reflexes and the pain.

**Dr. Visco:** Yeah, thank you, Christiane. Clinically wise, first of all, this patient was, was symptomatic. So, I think there's no doubt that she needs therapy. She needs to start the second-line therapy because, you know, sometimes some, a symptomatic relapse can be observed for a while. This is the first point.

The second point is linked with what Christiane asked before to me. So how about rebiopsy? This is a typical patient I put, yes, rebiopsy because, you know, she's a young lady. We need now four years later to know about her P53 status. We need to know about her morphology because all these factors are important for her prognosis – in terms of ibrutinib, in terms of CAR T, in terms of allogeneic transplant or whatever she will receive in second or further lines. So this to me is the typical patient I would rebiopsy.

**Dr. Pott:** Yes, thank you. That's a good, I think a very important comment.
We could first discuss the options for her if we say, "Yes, we want to put this patient into a CAR-T treatment."




BREXACABTAGENE AUTOLEUCEL

And these are the data for brexucabtagene autoleucel. This is from the ZUMA-2 trial, what everybody knows.

We had complete remission rates in, in more than 80% of the patients; and what you see here on the curve is that this is relevant, induce a very good response in these patients. And you see the curves for CR and PR. The blue curve is the complete remission curve. So we are able to queue the patients. And because she is young, I think in the clinical decision we have to do, the question is not if it's available, when to place the CARs and not whether we treat her with CARs.

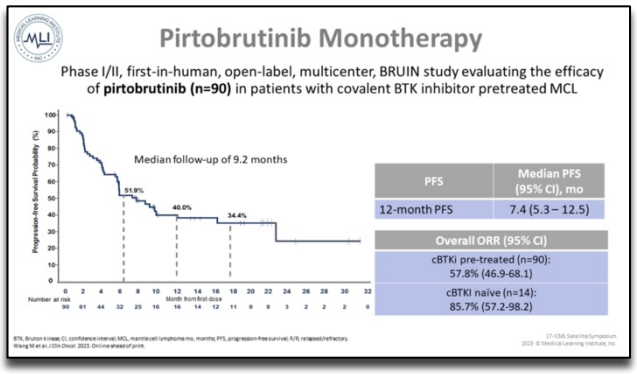
And I think what we know, also from the current treatment for DLBCL is just to do that early. The only question might be do we need the bridging in this case, and how do we do bridging? I don't know what your opinion is, Mats and Carlo, but I would follow the decision as well and try to get this lady into a CAR T-cell clinical trial or, if available, a commercial CAR-T product. What are your ideas?

**Dr. Jerkeman:** I was hoping to ask you that question how we should do the bridging, but, because I think it's real-, one of the most difficult questions right now, how we should do bridging in the situation. But, of course, a non-covalent BTK inhibitor could be, if we had access to that, that could be attractive. But we don't. But in the US, for instance, that's an option. But that, if I could choose, that would, what I would like to use. Venetoclax could be another option or chemoimmunotherapy, of course.

**Dr. Pott:** And Carlo?

**Dr. Visco:** Now, of course, this particular case, we don't have a BTK for tolerance, but we have a BTK intolerance, which makes the, makes some difference because, of course, the first choice would be the non-covalent inhibitor because it's very well tolerated and very active in this, and would be very active in this patient as a bridging therapy. But also we can consider another, with another covalent inhibitor with different toxicities because this patient is not that high risk. This patient probably is intolerant, so it means that the disease can be controlled to go forward to CAR T.

**Dr. Pott:** Maybe we can go back to the decision and to the non-covalent BTK inhibitor. This, yes, I agree. Maybe it's, we, we give her pirto for bridging, and she is receiving a complete remission or achieving a complete remission. So what to do?




PIRTOBRUTINIB MONOTHERAPY

So we know, and therefore, I want to go and discuss this slide with you again that pirto monotherapy is very effective in failure of covalent BTK inhibitors that we know from the BRUIN trial, and these are the updated results you see here.

We have a series of 90 patients, we have pretreated patients with a covalent BTK inhibitor; and we see response in these cases. And because this lady, she is not progressive on the BTK, it might be an excellent treatment for her what, where we might postpone the CARs. I don't know. It's, this is, I think, a good question. I think most of us don't have so much experience with pirto monotherapy. So, if one, if somebody wants to comment on that, I'm happy to receive your comments or questions. But it could be a very effective therapy without CARs and postpone the CARs to a later timepoint. That's something, I think we need to see in the next two or three years when pirto is available.

What we know that, in the pretreated patients who are refractory to ibrutinib, the CR rates are not so high in the trial. So that might be something where we know that the prognosis is depending on the quality of remission also in relapse in mantle cell lymphoma that might impair a bit the long-term success of pirto mono in that situation. But definitely, I think it's a, it's a good option.

Is there any comments from the audience or how do you do, how would you sequence things different from what we discuss?

Speaker: Hello, my question is if this lady had a TP53 mutation at relapse, would you then consider allogeneic transplantation maybe after bridging her with a non-covalent BTK?

Dr. Pott: That's a good question. Actually, if you ask me personally, this is something what I would postpone in the line of further treatments because I think the toxicity of CARs compared to allogeneic is something what I would like to avoid for my patients. But if there is a relapse, of course, I would put her in that direction for the second curative approach in that situation, though it would be allogeneic transplantation.

Dr. Eyre: Thank you. Yeah, I was just going to comment that the duration of remission for the pirto patients is really quite striking in the study. You may be showing this in a minute. So, in somebody who's previously covalent, BTK-intolerant, you're probably going to respond, and patients are very sensitive to pirto.

In this case, I would probably watch them. The median DOR at the moment's about 22 months or so in the study. So, as long as you watch them carefully, you may be able to safely defer CAR T. I think that's probably what I would do.

Dr. Pott: Yeah, I think this is an important point, what you say, because she's so young that you could also give her CARs to a later timepoint. That might not be the case if she has a very good remission on pirto mono. That might not be for an elderly guy, but in that situation, that could be an option; and I think we will see from the daily life, and new discussions if this is, if this is available, how we will sequence the treatment with it.

So, curation is something; and I think that's something what we need to pay attention to in the discussion with the patient. What is the treatment goal? Do you say, "Okay, I go for a curative treatment"? There are the two options, what is CARs and allogeneic, and which price am I willing to pay for that? Or is it somebody who is more reluctant to, all this modern treatments or whatever; and that, of course, I think is something what is, that could be very specific and maybe you end up with a decision pirto's nice, and we wait for the next relapse.

Dr. Visco: Well, if I can, if I can just comment on the first question and add on, of course, I agree with your response, Christiane. But, of course, if you have a P53 mutated patient after relapse, we need to keep in mind, and this is BTK-treated, already treated patient, we need to keep in mind that with the ZUMA we had some feeling that these patients were quite well-cured, even if P53-mutated CAR T-cell, but this was not the case in the real-life report and in the long-term ZUMA trial.

So, I agree with you that still allogeneic transplant might be or CAR T sometimes might become in the future some way to give the patients a true CR, a true complete response. You know, how often they do this patient independently with P53 mutation, they do achieve a good CR. So this might be where to build on for clinical trials, for allogeneic transplants, something else to give to these patients.

Dr. Pott: Yeah, I think if you, well, and probably if you have a molecule, a CR with MRD negativity, there is a high chance that you get cured. But I think that's right. We are lacking long-term data for CARs, and maybe we end up with the CARs plus maintenance in the future. I don't know.

But now the story goes further. We, she had some or an additional relapse. She responded well to the third-line treatment, and she has the preferences we just mentioned that this can be very individual. She has no specific preference for a regimen, and she wants to focus on therapy that prolongs survival. And I think this is something where we would go for a more intensive treatment, I think, in, in any case. So, in that situation. Also for allogeneic.


MR DUPONT

Dr. Visco: All right, so it looks like Mr. Dupont is going to be our second patient.

This is a 78-year-old frail man from France, retired architect, currently a volunteer gardener. His medical history is seen as hypertension, type II diabetes. There's some history of cancer in his family. He was a former, he's a former smoker. Prior to relapse, he enjoyed attending grandchildren's sporting events and gardening.

Well, he was initially diagnosed with Stage IV aggressive nodal mantle cell lymphoma; and as you can see, he had all the biological adverse factors de novo, and we're seeing how important it is to have them de novo. This means that you have a bad, a bad disease in your hands. I would say IGHV unmutated, TP53 mutated, together with deletion of, of, of the 17p, SOX11-positive, blastoid histology at presentation, high proliferation index by Ki-67. So this is a guy who has probably all the risk factors together with age, which is also a risk factor because, you know, you can't give any therapy to any age at all patients.

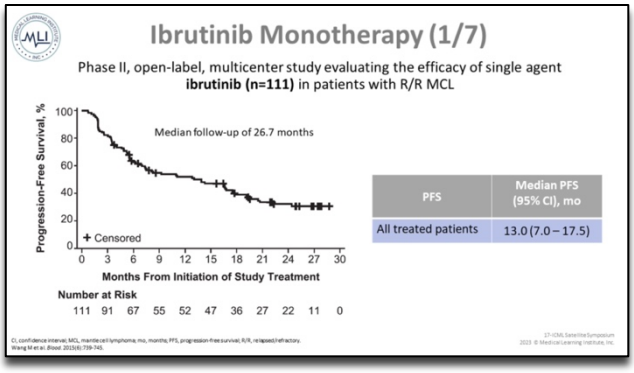
If we would have triple-positive mantle cell and each factor makes his contribution to the prognosis, to the adverse prognosis of the patient who we need to consider these biological features in the futures of course as we mentioned before.

But this guy with the, you know, R-CHOP is, is usually much useful in low-risk patients. We, as a matter of fact, this patient relapsed six months afterwards.

So, now at first relapse, six months after induction, he has lymphadenopathy, 3 centimeter nodes on axillae, which is quite relevant. Initial lymphocytosis with 3,000 per microliter, elevated LDH, elevated PSA. But clinically wise, he has a rapid weight loss and chronic fatigue with the performance status which is deteriorating, and it's a performance score of 2. He's a, so his subjective symptoms are fatigue and loss of appetite. So definitely, this is a patient we need to, we need to treat. How do we treat the patient?

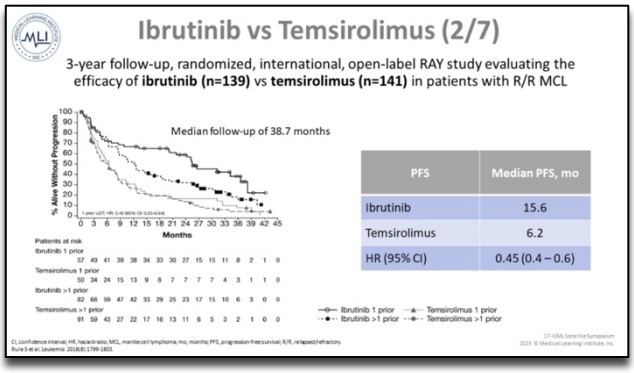
Of course, this second-line patient that's 78/9 years old, the majority of you said BTK, a covalent BTK inhibitor which is, I think, the right choice in the clinical practice.

We would also need to consider that CAR T-cell is, in most states, available 'til 80 or more years old. But then we can open a discussion, if it's ethics, to give CAR T-cell to any age in mantle cell lymphoma because this patient is becoming older and older, and the economic bargain for our states is getting important. So this is another question or this is another point we may address if we have time later on in the conclusions.



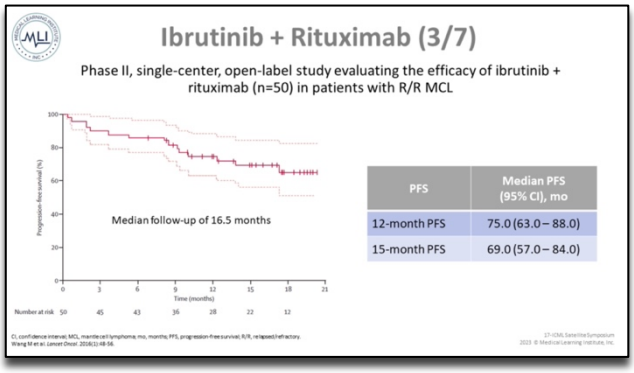

## IBRUTINIB MONOTHERAPY (1/7)

So, let's take on the data on BTK, covalent BTK inhibitors. You're all aware of this, of this initial trial which was the pivotal trial for MCL at the MD Anderson Cancer Center. This was a Phase II, open-label, multicenter study evaluating the efficacy of single-agent ibrutinib in 111 patients with relapsed/refractory mantle cell lymphoma. These patients were heavily pretreated with the median of two prior lines; and you see here the medium PFS of 13 months. This was the first trial showing how effective BTK inhibition is in these patients whose prognosis was much lower before the advent of this drug. So 13 months median PFS.




## IBRUTINIB VS TEMSIROLIMUS (2/7)

There has been also a comparison in randomized trial, a perspective trial with temsirolimus. This was some years ago. The demonstration of the drug that was available at that time, the chemo-free drug that was available at that time was largely inferior in terms of efficacy to the BTK inhibition. So ibrutinib was better than the temsirolimus was given to patient, when given to patients with relapsed/refractory mantle cell lymphoma.




IBRUTINIB + RITUXIMAB (3/7)

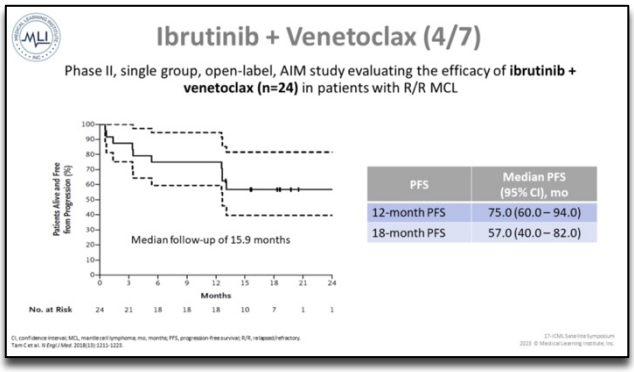
So, do we really need to associate an anti-CD20 with BTK inhibitors? And this, this is a good question for covalent but also for non-covalent inhibitors. If you think of CLL and the parallel, the addition of anti-CD20 to the BTK inhibition did not add in terms of efficacy, at least in the long term. It might add in the achievement of a good response, initially a good response; but it doesn't prolong the expected progression free survival.

So, but we had trials that the anti-CD20 can be combined with BTK safely. So what is your opinion, guys, on the, on the, if it's worth or not in the clinical practice when, whenever you can to combine the BTK with the anti-CD20?

Dr. Pott: So, what we know, especially in this case, ibrutinib monotherapy will not make the 13 months in median because it's high proliferative disease. And ibru mono is in early relapse. The, the response time is too short, so I would try to combine it if this guy's still CD20-positive. I would try to combine that, either with this or other combinations. So I would be in favor of a combination with anything else is better than ibru mono.

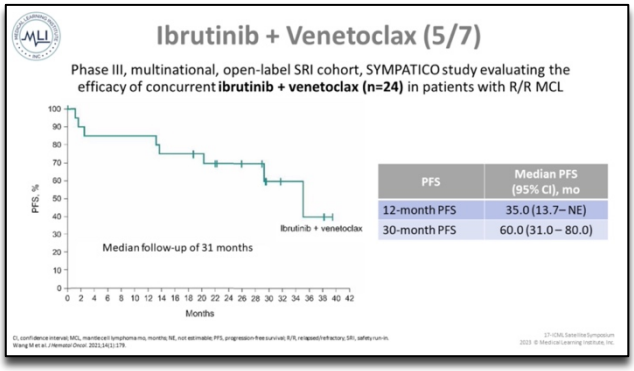
Dr. Jerkeman: Well, in general, I don't combine it with anything; but in this specific case, I think it's a good idea, yeah.

Dr. Visco: Yeah, I do agree. Actually, the data we have showed that there is likely an improvement in adding in the anti-CD20. If you see this curve, it is a little better than the one before in monotherapy. Of course, I would exclude the patient that relapsed during maintenance. Of course, these are patients that are typically anti-CD20-resistant.



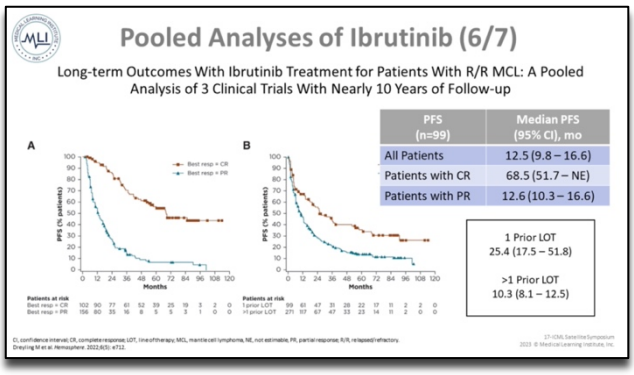

IBRUTINIB + VENETOCLAX (4/7)

So how about combining ibru with venetoclax? We have some trials already published. This was, this was a, a small bunch of patients, 24 patients. Very high preselected patients who achieved some responses, a good deep response with the combination of ibru plus venetoclax.




IBRUTINIB + VENETOCLAX (5/7) And we also have the update of the SYMPATICO study which is now being conducted; and we'll have the results soon. And this is specific, the specific arm of this Phase III multinational trial with, with the dedicated curve to the patient that had the combination arm, ibru plus venetoclax. And you see that the curve seems promising, seems much, not much, but better than what we observed with ibru monotherapy. So

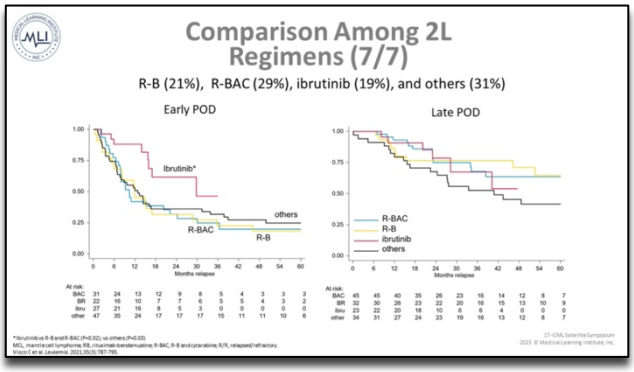
there's, I think, there's room to improve the BTK inhibition with something we can add on together with, with, with ibrutinib.




## POOLED ANALYSES OF IBRUTINIB (6/7)

And how about when to give BTK inhibition? We talked about this before. This is the pooled analysis of the, of the initial older trial, the perspective trials using ibrutinib as second and third line of therapy. And you see, of course, you have an advantage in giving in patients that achieve a CR. There are not so many, but patients that achieve a CR with ibrutinib monotherapy do have a longer expectation of progression-free survival. And especially on the curve, I want you to concentrate on the curve on the, on your right side where it shows clearly that when you give ibrutinib earlier in the, in the, in treatment scenario, you achieve a much better progression-free survival.

And you see here that 24 months, so two years, is the expected progression-free survival, median duration for an ibrutinib given in second line in patients with mantle cell lymphoma.




## COMPARISON AMONG 2L REGIMENS (7/7)

And how about the comparison with ibrutinib in second line with others? There's no direct comparison, especially in second line. There's no perspective comparison. We have, we have tried to compare them, the use of R-BAC, which is a bendamustine-based, very active regimen; the use of BR; or the use of other compounds such as cisplatinum-based therapies such as lenalidomide or other available monotherapies in Europe.

And when we can compare them in the real-life setting, dividing patient between early or late POD, we clearly showed that at least in early POD the use of ibrutinib in second line was clearly more active than any other regimen. And this made, I think, the full stop on the story of giving something else as second line to this patient. We need to give BTK earlier as second line or earlier as first line when we will have the possibility to do that.

How about late POD patients? Does patient relapse as the first patient? It relapsed late during the course of the disease. Does patient that did autologous, they relapse six or seven years later. For sure there are. late POD patients, again showing clearly that when we compare BTK inhibition, a second line also late POD, there's going to be a clear advantage in using BTK. So there's no doubt nowadays that BTK should be, when not using upfront, should be the standard second-line therapy.

Okay, combing back to our patients. So we go, you remember this 70-years-old male from France. So he had poor response to ibrutinib. He gave, he received a second-line treatment and relapsed four months later. Mr. Dupont has stated the following preferences. He's concerned relapse will occur sooner with time-limited

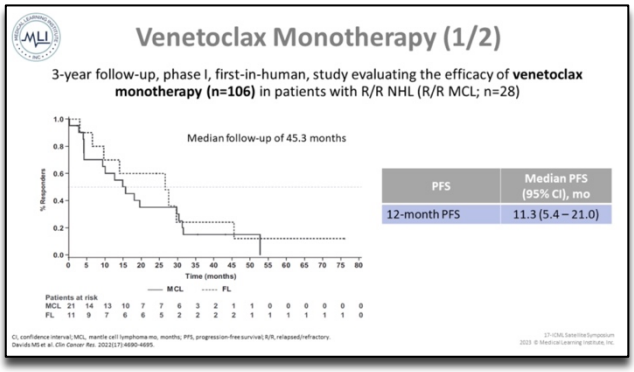
therapy. So with like chemo days, time-limited cycles. And he prefers a pill formulation that can be taken at home because of his age.

On brexucabtagene, we have commented, I think we can comment on the, on the, on the indication of giving such an expensive therapy to, to such an elderly patient with such high-risk features. But there's of course, there's room for discussion.

Lenalidomide is very, I think it's, it's not that bad. I mean in a patient like this that prefers to have a pill at his, at his home, of course, the expectation for activity of lenalidomide is very low compared to with pirto. But still, if you don't have available no-covalent inhibition, lenalidomide, I think it's a choice. It's a good choice. It's an active drug. It might be active, at least for some months.

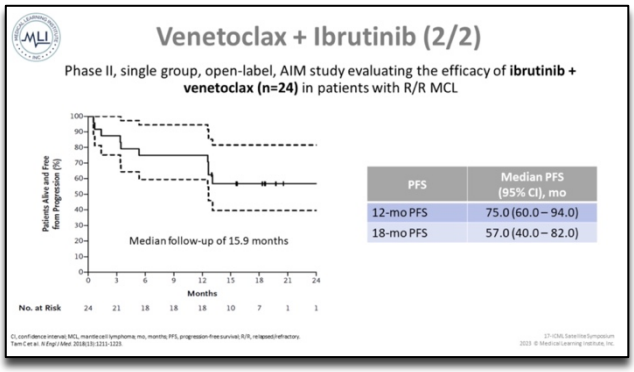
How about venetoclax? You know, venetoclax in his setting of the later relapsed patient, high-risk features, his monotherapy is not that active, I would not suggest to use venetoclax monotherapy.

This, there's someone who likes to add on to, likes to add on ibrutinib-venetoclax. This might be a better choice than to use venetoclax alone, at least, at least to me.




## VENETOCLAX MONOTHERAPY (1/2)

This is the, these are the UK data. But this is the, the initial trial that has been updated on Clinical Cancer Research later last year. You see the expectation of, of response to, to venetoclax are not that good, although this is probably the best trial ever addressing the efficacy in 28 mantle cell lymphoma, on venetoclax monotherapy.




## VENETOCLAX + IBRUTINIB (2/2)

As I was telling you, the association of venetoclax plus ibrutinib might give a chance to these patients better. I don't think allo refers to that patient, yeah.

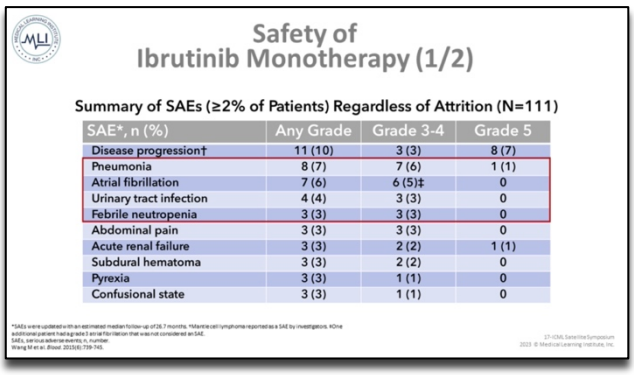
**Dr. Pott:** Just one question to you, Carlo. There are the data for Vipor and DLBCL. So this guy has a high proliferative disease. He wants some pills, and would that be something which you could envision if it's possible to give all this together or do you think-?

**Dr. Visco:** Of course, yeah. Of course, Vipor is putting together for those of you who, who are not aware of it, is pulling together all the new drugs, all the chemo-free drugs given by, by oral compounds like lena, venetoclax, ibrutinib altogether in a single regimen. Of course, this is an option. I don't think this is the, the answer, the

future answer to our patients. I think we need to sequence the therapy instead of giving everything together. But this is my opinion, of course.

What, what's of concern for you? What's more of concern for you when you give drugs to such an elderly patient? The relapsed/refractory setting, in terms of expected toxicities from, from our drugs?

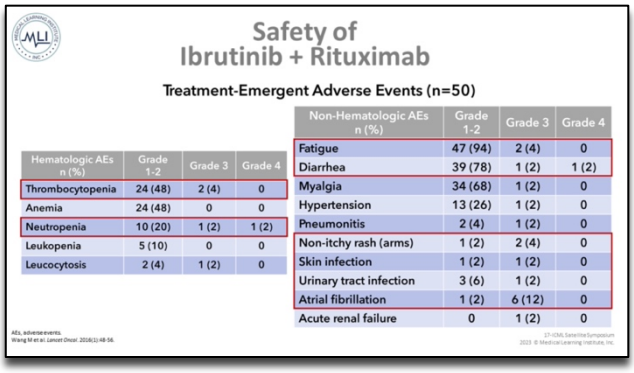
Well, I think this is actually what, this reflects the clinical practice. Atrial fibrillation is something that is of concern for our patient, especially in the elderly. This was a hypertensive patient. Probably you can have much more problems with an atrial fibrillation after your 70s than what you have earlier. So this is, this is, of course, of concern.




## SAFETY OF IBRUTINIB MONOTHERAPY (1/2)

And then infection, you know, infection is always of concern when using a BTK inhibitor. We need to consider this. Second- and third-generation non-covalent inhibitors also are associated with, with an amount, significant amount of pneumonia and infection. So we need to be aware, aware of this, yeah.

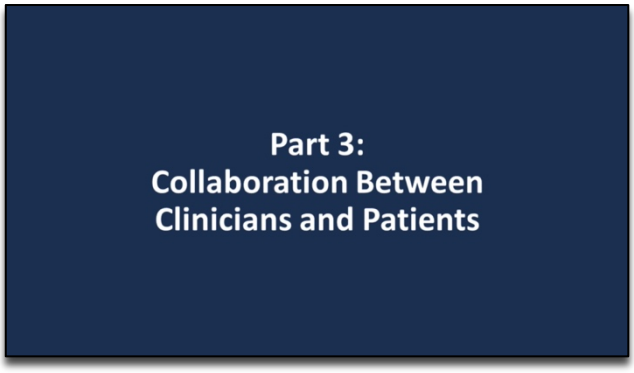
This is now the data for ibrutinib monotherapy with pneumonia, in 6% of Grade 3 or 4 and 6%. Urinary tract infection is 3%, febrile neutropenia is 3%.




## SAFETY OF IBRUTINIB + RITUXIMAB

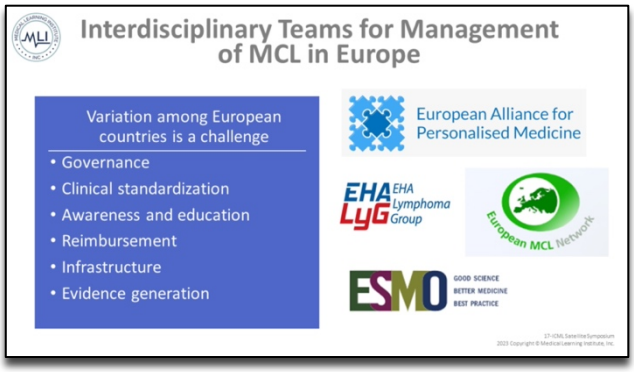
So we have 1 in 8 patients experiencing severe infections. Look at the diarrhea there. Diarrhea is not much of concern, at least in my clinical practice.

We have some, also some, some problems with cytopenias; but also I think for hematologists that's not a big deal. And I think what you responded is actually what, which reflects the real life, the real life clinical practice.




## PART 3: COLLABORATION BETWEEN CLINICIANS AND PATIENTS

So, the third part will be very quick, I think. Collaboration between the clinicians and patients. I think this is something we have already discussed. I think, of course, when choosing treatment for, for patients, of course, we have to involve the patients in these discussions.




## INTERDISCPLINARY TEAMS FOR MANAGEMENT OF MCL IN EUROPE

We have also touched upon how we can be more aligned in, in treatment guidelines. The EHA and ESMO are now developing common guidelines for hematological malignancies. The for, there have been now examples for myeloma, I think. Also, follicular lymphoma, and we will also see now common guidelines for mantle cell lymphoma and diffuse large B-cell lymphoma soon. So that's something to look forward to.

The European MCL Network, it's something where all three of us are very much involved in. It's the European platform for running clinical trials in mantle cell lymphoma. It's the, I think the only way to run Phase III trials in this quite rare disease is to collaborate many countries together.

And there are many difference between European countries in terms of reimbursement guidelines and how the healthcare is financed and so on, so which has impact on, on what treatments we can use and how easy it is to, to, to find treatments.


## DIFFERENTCE BETWEEN EUROPEAN COUNTRIES

So I live in Scandinavia, Sweden, where we have only public healthcare; and which also, of course, where we need to focus very much on, on the costs and limiting costs because everything is paid by the taxpayers.
And now, Christiane, what, what is particular with Germany do you think in terms of access to new drugs?

**Dr. Pott:** I think this is, it's a broad access to CARs. We also would consider this 79-year-old guy and probably for CARs with a curative option unless he is not, any comorbidity would exclude that. So, we have a very broad access; and I think that, that makes a big difference, especially if I think to Italy where it's difficult also with maintenance rituximab, for example. There are also basic difference in initial treatment.

**Dr. Visco:** Yeah, we, we, we used to have this problem with rituximab maintenance, which is not the case yet because we, we had recent reimbursement for rituximab maintenance. But, of course, this is a main point. In terms of CAR T-cell therapy, we of, we can give CAR T-cell therapy by law until the 80 years old patients. But as an internal policy, we usually do not consider patients elder than, older than 75 because we, we have been advised that there will be some restrictions in terms of economic pardon with the use of these, these CAR T-cells.

Instead, of course, the use of BTK inhibitors is very different. I think that we have a lot of, a lot of people from South America here. They probably, ibrutinib is becoming available everywhere, but this is not the case of other BTKs, especially in Southern America. North America has changed its policy recently. And, of course, in non-covalent, we need to wait a little bit to have them in the clinical practice.

**Speaker:** Yes, in Argentina we have approved ibrutinib, acalabrutinib, and zanubrutinib. So I was awaiting competition with the, between the, the three drugs in the talk according to effectivity. I know that there is no head to head in mantle cell. Yes, in, in Waldenström and CLL, but they, for us it's very important to know if, do you believe that there is some different, for example, for TP53 mutated?

**Dr. Jerkeman:** I don't think there is any evidence that there is a difference in efficacy between these, but in, in most parts of Europe, we don't, we can only use ibrutinib for this indication. So we have less experience of the other drugs. But, I think, the difference is mainly in the safety profile that is different, but that's the main difference.

I don't know if you want to comment some?

**Dr. Pott:** Yes, the PFS, I think, when I remembered correctly, is the best for zanubrutinib. If you just focus on PFS, I think it's 21 months or something like that; and it's increasing from ibrutinib to acala to zanubrutinib for mantle cell lymphoma.

So there, this is not, as you said, a direct head-to-head comparison; but I think it's, it's from a Phase III clinical trial so it might be valid. And then you are much more of, let's say, have a, have a better situation than in, in most countries in Europe where you can only give one because ibrutinib is the only BTK that is licensed in the most European countries. So this is, I think I would go for a newer-generation BTK if I would have the option. Also, with what Mats said was the, with the side effect profile.

**Dr. Jerkeman:** So we have, obviously, different opinions, which is inter-, interesting. Carlo, you have another opinion?

**Dr. Visco:** Well, no. I just wanted comment on, yeah, there's no direct comparison as, as it has already been said. If you look at the, if you compare different trial design seems to be better. And there's, there's some data, especially in blastoids where zanu seems better than the others. But outside these, I think they're equivalent. Yeah, they must be considered equivalent.


<u>KEY POINTS</u>
**Dr. Jerkeman:**

I think we all agree that mantle cell lymphoma is very complex, no, to treat and manage, yes? So, we can agree on this. Even if we have very, very new, a lot of new treatment options, it's still a challenge to treat. But it's becoming more interesting.

And we have, I, I think that the new treatments will improve patient outcomes; and we also have, which we didn't cover now, a lot of other agents undergoing development, like the bispecific antibodies, especially. Also, antibody drug conjugates that are really interesting in mantle cell lymphoma. And, of course, we should involve patients in the decision-making; and I think this is of focus for many of us right now. Thank you everyone for attending this activity.