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Rare subtypes of non-Hodgkin's and Hodgkin's lymphoma

Prof Mellgren: Okay. So, good evening, everybody, and welcome to this session. I'm Karin Mellgren, and I will be the discussant of this session. And we will now hear the lecture from, Dr Andishe Attarbaschi, from St. Anna Hospital in Vienna.

Dr Attarbaschi: Thanks Karin, I hope that everyone can hear me. Yes, as I said before, I would like to focus this session or this presentation on rare subtypes of non-Hodgkin's lymphoma. I think before talking about rare non-Hodgkin's lymphoma, we should be aware what we mean with rare, because honestly, rare NHL has not been clearly defined. I think there are several possibilities to define rare non-Hodgkin's lymphoma. We could think about all other subtypes than Burkitt's lymphoma, diffuse large B-cell lymphoma, lymphoblastic lymphoma, and ALCL, which for example would mean that primary mediastinal large B-cell lymphoma is a rare NHL. But we could also envision that we talk about subtypes comprising less than 1%, subtypes comprising less than 5% of paediatric non-Hodgkin's lymphoma. We could even think about separating rare NHL by the lineage or by the histology, or even by the site of involvement. So, honestly, we have no clear definition of what is meant with rare paediatric non-Hodgkin's lymphoma. Today, due to the lack of time, of course, I would like to focus on four subtypes of rare NHL. I would like to talk about paediatric-type follicular lymphoma, marginal-zone lymphoma, primary CNS lymphoma, and peripheral T-cell lymphoma, which for example is a specific field of interest of my co-chair Karin Mellgren. So, I'd like to start with follicular lymphoma. You all know that follicular lymphoma is an indolent lymphoma accounting for 35% of all the NHLs in adults. But it is a very specific follicular lymphoma subtype in childhood, there accounting for 1% of all the NHLs. And you can see what we knew about this disease before we started studying it in detail. We knew that it is occurring mostly in adolescents and young adulthood. Most patients present with limited disease. The disease in childhood is usually BCL-2 negative, and in particular, negative for the translocation 14 and 18. And what was available from the literature was that these patients had a very good outcome, but most patients were or are probably treated too aggressively. So, when we started studying this disorder, one of the aims of our project was to establish a significant and secure reduction of treatment in localised disease. So, we performed a retrospective analysis by the two biggest consortia in childhood NHL in Europe, namely by EICNHL and the i-BFM NHL Committee, and we collected 63 patients. Here can see, I will not go through the details. I would just like to show you that in 2022, the WHO established a clear definition of paediatric-type follicular lymphoma, and you can see the essential diagnostic criteria and additional criteria which must be used to differentiate paediatric-type follicular lymphoma from large B-cell lymphoma with IRF4 rearrangement and reactive follicular hyperplasia. This definition was established by pathologist together with us, the paediatric oncologists, who are dealing with this rare NHL subtype. Here can see slides. And I just would like to mention the picture D, where you can see that paediatric type-follicular lymphoma is usually CD10-positive. Picture E shows the BCL6 expression and picture F, the FOXP1 expression. So, you can see now the results that we have published now one decade ago. What we saw in our analysis was the clear male

predominance with 75% of the patients being males. When it comes to age at diagnosis, you see that 72% of the patients were adolescents. What we also saw very clearly was that 87% of the patients had limited stage of disease. So, stage 1 and stage 2, defined according to the St. Jude's staging criteria. We also clearly saw that the patients almost never had elevated LDH levels. When it comes to the site of involvement, you can see that most patients had an involvement of peripheral lymph nodes usually, in the head and neck region. There was no patient with mediastinal involvement, no patient with CNS involvement. Two were reported with bone marrow involvement. Of course, at that time, when we did this study, this analysis, we did not stick to the very clear definition of the WHO, 2022. Here, can see further results with respect to the resection status. You can see that in half of the patients, a complete resection was performed. You can see in addition that 72% of the patients got systemic chemotherapy, and one got rituximab. And although, it is now more than 10 years ago, there were already patients included in this analysis, which were just for a watch-and-wait strategy. And of course, out of the 32 patients who had a complete resection, the 17 were watch-for-waiting strategy among these 32 patients. So, half of completely resected patients did not receive any further therapy. Resection according to stage of disease. As expected, we had 32 patients with a complete resection, and of course, most of them, 30 of them, had stage 1 disease. Only one patient at that time, reported to us, received local radiotherapy. Here, can see the final results of the study. As I said before, 63 patients only one relapsed, which led to an event-free survival of 94%, as the relapsed patient was rescued with chemotherapy, this was before a patient with a watch-and-wait strategy. The overall survival was 100%, and this cohort of patients had a median follow-up of 2.2 years when we published the results. So, what could we learn from our retrospective study? At that time and until now, it was by far the largest cohort of children and adolescent with follicular lymphoma, although, not all of them followed the clear definition of the WHO as I said before. But all of them had a reference histopathological review at that time reported. We see a clear association with male gender, adolescent age, limited stage of disease and low LDH level. Of course, in most patients, peripheral lymph nodes were involved. Complete resection was possible in 50% of the patients. And half of these patients, as I showed before, underwent watchful waiting. We see an excellent treatment outcome also, in particular, for those who had a watch-and-wait strategy. So, building on this analysis, we tried to develop some treatment recommendations which are valid today and used by many centres, many institutions, many countries. You can see what we recommend at the moment for paediatric-type follicular lymphoma. If it is a stage 1 patient, and the primary operation has been done, we should look for a residual tumour. If there is no residual tumour because it was a complete resection, these patients could undergo a watchful waiting strategy. If there is a residual tumour left, one could think about a second-look operation, additional surgery, the same way as we do it in lymphocyte predominant Hodgkin's lymphoma. This second-look operation should only be performed if no mutilation will be caused to the patient. So, if this is possible, and a complete resection is achieved, watchful waiting should be done, as for those patients who had a primary complete resection. If no additional surgery is possible, or in stage 2 patients, we would recommend low-dose chemotherapy. Here's just an example, it could be a BFM schema with rituximab, A4, B-block and B blocks, B4 blocks, but not giving the anthracycline in the B4 blocks. But you could always think of R-COP without anthracyclines or R-CVP without anthracyclines. Yes, this was what I wanted to say about follicular lymphoma. So, are there any questions in the chat or by you Karin?

Prof Mellgren: Thank you. This is nice. And I would now like to address to the participants to please remember to put questions in the question-and-answer box. Waiting for questions from the audience. I would like to address a few questions because I think this study that was published has really been pivotal for these patients and it has helped many patients from overtreatment. I am a bit puzzled about this disease because we have a disease that is very indolent, but we do have a very high proliferation rate in the lymphoma cells. Have you any explanation about that? How can it stay so indolent? Why doesn't this very high proliferating lymphoma spread to other parts of the body as other types of non-Hodgkin lymphoma does? Have you thought about it or do you have any ideas about it? I'm not sure there is any good explanation.

Dr Attarbaschi: I think honestly there is no good explanation why this lymphoma does not spread the same way, as you said, like Burkitt lymphoma or diffuse large B-cell lymphoma, or other non-Hodgkin's lymphoma. I think we have all to admit that the genetic characterization, so, the biology of the paediatric-type follicular lymphoma is not very well-known, or elucidated, because I think at the end usually the genetic background of a disease, the biology of the disease determines how a disease behaves, whether it spreads very rapidly, very early or it never spreads. But I think the answer to your question lies in the genetics of this disease, which until yet has not been elucidated. And I think of course the reason for that is that it is very, very rare, and all pathological institutions or countries have only very, very few patients. And as you remember this study at that time also tried to identify the reference pathologists, and to try to bring them together to bring the samples together to analyse them with more sophisticated molecular genetic methods, but we were not successful with this.

Prof Mellgren: No, I agree with you. I'm sure we are going to learn a lot more when we know more about the genetics of this disease. It was just a small comment. Thank you very much.

Dr Attarbaschi: Okay. Then, I would like to continue. I would like to continue with marginal-zone lymphoma. I will not go through all the details of this slide. But marginal-zone lymphomas are also known as indolent lymphomas, arising from post-germinal centre B-cells. And the WHO recognises three subtypes, namely the splenic marginal-zone lymphoma, the nodal marginal-zone lymphoma and marginal-zone lymphomas of mucosa-associated lymphoid tissues. Again, at the time when we developed our second retrospective study in rare NHLs, a few things were well-known. Mainly that there is, again, a male predominance. That nodal marginal-zone lymphomas usually presents with asymptomatic lymphadenopathy in the head and neck region. That in extranodal marginal-zone lymphomas, infectious agents like Helicobacter pylori may play a role and the splenic marginal-zone lymphoma is very rare. Again, recurrent genetic aberrations were not that well-known, all the few had been reported. Where recently in WHO 2022, classification, again, pathologists established a paediatric entity, namely paediatric nodal marginal-zone lymphoma, and I will talk about this in a few minutes. Yeah. Here you can see I will not go through these pathological criteria, which again are essential ones and desirable ones because I'm not a pathologist. But this has been a consensus of a very well-known pathologists in the field and we established this chapter together with them because clinical aspects are also included in this chapter on paediatric nodal marginal-zone lymphoma. Most importantly, these lymphomas are BCL6 negative. You can see again some slides. And I would like to focus on the picture B, showing the CD20 positivity. And on picture C, where you can see that BCL6 staining was negative. So, we performed a study which we called the fourth I-BFM NHL Committee EICNHL study, where we collected retrospectively patients with marginal-zone lymphoma, diagnosed by a reference pathologist between 1990 and 2016. And again, this study led to treatment recommendations which are valid now. We identified 66 patients. And you can see again that all of this lymphoma mainly occurs in the adolescent age, that there is a clear male predominance. Among the cohort that we collected, 1/3 had nodal marginal-zone lymphoma. According to St. Jude's staging system, most of the patients, so 72%, had limited stage of disease. Most patients had no elevated LDH levels. And what we saw here was that nearly 20% of the patients were reported to have a pre-existing disorder. And you can see these pre-existing disorders. And 6 out of the 12 patients had an immunodeficiency. Two had a Sjögren's syndrome, which is very well known also from the adults, that this may predispose to marginal-zone lymphoma. Now, I would like to focus on the 21 with a nodal marginal-zone lymphoma, where you can see again, very clearly the adolescent age. The predominance of male gender, all but one were males. You can see that 86% had stage 1 disease. Most of them, 90% had lymph nodes involved in the head and neck region. No one presented with an elevated LDH level. No one had a pre-existing disorder here. And already at that time when we did this analysis, this study, 20 out of the 21 underwent the watchful waiting strategy. Only one patient relapsed, he was rescued with a chemotherapy. So, overall, survival was 100%. When we come to the 44 extranodal marginal-zone lymphomas, we, of course, see again, the median age in the adolescents. We see that 57% were males, 43% were females. We see a broader distribution over the different stages of disease. We see all the different sites of involvement, lymph

nodes, ENT, gastrointestinal tract, skin, lungs and others. We see again no elevated LDH levels, but all 12 patients who had a pre-existing disorder were among these 44 patients. When it comes to chemotherapy you see that half of the patients got chemotherapy. In most cases, this chemotherapy was combined with rituximab. But we also had 27% of patients who underwent a watchful waiting. The transplant patients were patients who had a pre-existing disorder. 10 out of these 44 relapsed, but only 2 died. And you will see later on that these two patients died due to transplant-associated complications. You can see the 11 relapses, you can see the stage of disease at relapse. And as I showed before, 10 were out of the extranodal and one out of the nodal marginal-zone lymphomas. You can see the two patients who died both had a pre-existing disorder and immunodeficiency. And you can see that the reason why they died came up from complications of the transplant. Now, I come to the survival curves. The whole cohort of 66 patients event-free survival, 70%. When we look at the overall survival, it is approaching nearly 100%, because 42 patients survived, only 2 died. When you split up the event-free survival curves according to nodal or extranodal marginal-zone lymphoma, you can see that there is a significant difference, where the nodal marginal-zone lymphoma had an excellent outcome with 94%. The extranodal marginal-zone lymphoma have an event-free survival of only 64%. Overall survival is nearly the same because apart from the 2 who died, 8 of 10 relapses, or 9 relapses, were rescued. So, what did we learn from this? Again, a retrospective analysis with all the disadvantages that retrospective analyses may have, but these are the best available data that we have. So, it was again the largest cohort of children and adolescent with marginal-zone lymphoma ever analysed. We saw again, that very similar to paediatric-type follicular lymphoma, that marginal-zone lymphomas are associated with male gender, adolescent age, limited stage of disease and low LDH levels. The extranodal marginal-zone lymphomas mostly involve the ENT, skin and gastrointestinal track. Out of the whole cohort, 32 underwent a watchful waiting strategy, and these patients had an excellent outcome. So, 28 of these 32 patients who underwent a watchful waiting remained in remission. Of course, most of them were nodal marginal-zone lymphomas. So, what did we recommend afterwards to people taking care of marginal-zone lymphomas? So, we recommended the same for nodal marginal-zone lymphoma as we do for paediatric type follicular lymphoma. Namely, a watchful waiting if a complete resection has been done, or even perhaps a second look operation if there are no other sites of involvement and no mutilation will be done to the patient. For extranodal marginal-zone lymphoma, you should think about treating an infectious agent. If diagnosed, for example, Helicobacter pylori, you may think about watchful waiting in limited disease if a complete resection has been done. But for advanced disease, you should think about, again, low-dose chemotherapy like BFM blocks without anthracyclines, plus rituximab, or R-CVP or R-COP. So, now, I'm finished with the marginal-zone lymphomas. Are there any questions in the chat or by you, Karin?

Prof Mellgren: I have a question and I sometimes get the question about the use of PD-1 inhibitors in these patients. Do you have any specific opinion about if they are useful or not?

Dr Attarbaschi: I think when you look at the results that we have seen in these patients with doing nothing or low-dose chemotherapy, I think this is not an indication for checkpoint inhibitors. I think at the moment when it comes to lymphoma, we are learning that checkpoint inhibitors could be useful in anaplastic large-cell lymphomas, or in non-Hodgkin's lymphomas of patients with the constitutional mismatch repair, gene deficiency, or perhaps, in post-transplant lympho-proliferative disorders. I think the time is not ready yet to use checkpoint inhibitors in such a disease, with such an excellent outcome. So, I would never recommend to use a checkpoint inhibitor in nodal marginal-zone lymphoma, and I think I would also not recommend it for extranodal marginal-zone lymphomas, because I think in the lymphoma setting, we still have to learn that it is a secure therapy. I think in ALCL we are learning that it is working. There's an ongoing trial, you know about this trial in Paris. But for such a rare order with such good prognosis, I would not do that.

Prof Mellgren: No, I agree with you, but I know it's sometimes, I ask the question. Thank you very much for that comment. Very good.

Dr Attarbaschi: Okay. If no other questions, I would continue with a specific field of my interest, namely primary CNS lymphoma. When we talked about a transatlantic project on primary CNS lymphoma to learn also more about this rare non-Hodgkin's lymphoma, there was some literature available. As you can see, most of the things were done by a good friend of me and Karin, namely Oussama Abla, working at SickKids in Toronto. But there was also a small analysis available from us as the NHL BFM study group published in Haematologica, where we reported on the outcome of 17 patients with primary CNS lymphoma. And you can see the moderate outcome with an event-free survival of 63%. But when we excluded the 5 patients who had a pre-existing disorder, which was an immunodeficiency, outcome was excellent, 92% for the 12 patients who were treated according to their histopathological subtype. So, together with a colleague in U.S. and Oussama in Toronto, we established again a retrospective primary CNS lymphoma study. And the CNS lymphoma was defined by any newly diagnosed NHL involving exclusively the brain, the CSF, the meninges or the spinal cord. And we wanted to learn by larger number of patients about this rare NHL subtype. And here, you can see how international cooperation works. We were able to collect 75 patients in this transatlantic cooperation. And the median follow-up of these patients was quite long, 5.22 years. And you can see the results. And we can see again, when it comes to gender and male predominance. We see that 65% of the patients were adolescents. We found that 14 out of the 75 patients had a pre-existing disorder. We saw that nearly half of the patients had a diffuse large B-cell lymphoma, followed by ALCL, at the second position. Most of the patients had intracranial disease, only 2 intraspinal disease only, and 3 leptomeningeal disease only. These were the B-cell precursor lymphoblastic lymphomas. Half of the patients had only one lesion. 43% had more than one lesion within the CNS. When it comes to the initial therapy, you see different combinations. Most of the patients received chemotherapy either alone plus rituximab, plus radiotherapy, or with both of these other components. Very importantly, 76% of our patients were treated according to a paediatric NHL type protocol. But 23% of the patients were treated very, very differently and not according to a protocol. Near to a paediatric-type protocol, not an adult-type protocol. Below this, you can see the chemotherapy drugs and we focused on high-dose methotrexate, high-dose RRC, anthracyclines, alkylating agents and intrathecals. And you can see the number of patients who received these drugs. And we could also see, or you can also see that 35% of the patients received radiotherapy. So, what was the outcome? You can see that 14 out of the 75 patients had a treatment failure. You can see that 12 out of the 75 patients died, but only 6 of them died due to a relapse. But we also see 4 deaths due to treatment-related toxicity. Overall, 58 of the 75 patients are or were in a continuous complete remission at the time of reporting. And you can see that 53 of the 58 patients are in CR1 one and 5 were in CR2. Importantly, we also see that a significant number of proportion of patients had long-term side effects from the disease itself and, or the treatment. As I said before, there was a significant number of patients with a pre-existing disorder, 14 out of the 75 patients. And here's the list of the pre-existing disorders. And you can see that most of these patients had a diffuse large B-cell lymphoma. And you can also see that a significant number of them died, and not all of them died due to relapse. Most of them died due to treatment-related toxicity. Now, we come again to the survival curves. For the whole cohort event-free survival was okay or quite good. 74%. Overall survival was 85%. When we look at the event-free survival according to whether a pre-existing disorder was there or not, we can see a significant difference. 77% for those without pre-existing and 53% for the 14 patients with a pre-existing disorder. We also analysed other parameters for an association with event-free survival. We saw the trend perhaps according to the number of lesions as you can see here in figure 1D. But what we clearly saw was that those patients who received high-dose methotrexate and high-dose ara-C did significantly better than the patients who did not. Although, as you can see here with regard to the numbers, the number of patients not receiving high-dose methotrexate was very low and also low, for those not receiving high-dose ara-C. Very importantly, you can see that those patients who were treated according to their histological subtype, so, with a paediatric NHL-type therapy, that these patients did significantly better than those who were not treated according to a protocol, or I think we have to admit that those who were not treated according to a protocol were patients who had a pre-existing disorder in whom a protocol-type therapy could not be accomplished. So, what could we learn from this study? Again, it was the largest study

ever done. We saw an association with male gender and adolescent age. We saw an association with low LDH levels and diffuse large B-cell lymphoma histopathology. Nearly 1/5 of the patients had a pre-existing disorder. Most patients were treated with chemotherapy including the addition of rituximab. Most received high-dose methotrexate, ara-C, alkylating agents, anthracyclines and intrathecals. Only 1/3 received radiotherapy. If I remember the data correctly, these were in particular patients with ALCL, because within our recommendations for CNS positive ALCL, radiotherapy is still foreseen. All of this has changed with the tyrosine kinase inhibitors. What I think was also shown very nicely, that people stick to paediatric type NHL protocols, 81%. We see a good outcome in primary CNS lymphoma. However, patients with pre-existing disorders have a poor prognosis as well as those patients not treated with protocols-designed for paediatric NHL. But as I said before, there is, of course, an association between these two situations. And we see 1/3 of the patients with long-term toxicities. Yes, these are the data which are available at the moment with respect to primary CNS lymphoma. And at least in Europe, the recommendation is relatively clear at the moment. It is, follow the histological subtype directed paediatric protocols. So, any questions in the chat or by you Karin?

Prof Mellgren: I think the conclusion you find that patients with a pre-existing disorder do worse is very important and this is something we have found with all types of rare lymphomas. And I remember when I started in paediatric oncology, I was told that all the patients get odd diseases and I guess that was what we could know at that time before we knew anything about genetics of the disease, of course. But I have a more practical question and I wonder, since most of these primary CNS lymphomas are of a B-cell origin, how do you foresee the intrathecal rituximab treatment in these patients?

Dr Attarbaschi: I think there is no clear recommendation with regard to intrathecal rituximab. I think all of us have used intrathecal rituximab in different settings. We also performed an i-BFM EICNHL study on this topic. But as you know, we have this NHL-BFM NOPHO trial ongoing in which you and I are involved. And here, for primary disease so, it could also be a primary CNS lymphoma included in our trial. We are not foreseeing intrathecal rituximab, but very intensified full-dose intrathecals. You know that our first AA and BB block includes three intrathecals, full dose in six days. So, for primary disease, if you include patients in a protocol, in an ongoing trial, intrathecal or intraventricular rituximab is not foreseen. And if I look back at our very small, of course, primary CNS lymphoma collection of the NHL-BFM study group, these patients were all treated according to our protocol, and intrathecal rituximab is not foreseen in this situation. I think the situation would of course change in case of a relapse and people would use intrathecal or intraventricular rituximab. But as I said, we would recommend to follow a protocol and if we stick to our ongoing protocol, let's say, in the NOPHO and BFM countries, we would go for full-dose intrathecal triple chemotherapies and not for rituximab.

Prof Mellgren: No, I agree. And maybe, for the relapse setting we can think differently. Absolutely.

Dr Attarbaschi: Yeah. You're right.

Prof Mellgren: Yeah. Thank you.

Dr Attarbaschi: Okay. Thank you, Karin. So, I will now come to your specific field. I hope I will not say anything wrong. It's about non-anaplastic peripheral T-cell lymphoma. Why do I write non-anaplastic? Because we are not including ALCL in this topic, in this analysis. And Karin, you performed a very big trial, I remember, also nearly now one decade ago, where we tried to collect as many as possible patients with peripheral T-cell lymphoma. Lymphomas who had a national histopathological review, and yet at the end of your collection we had 143 patients who could be put into our final analysis. Here, can see again, the few histopathological slides. Here, I'm focusing on peripheral T-cell lymphoma not otherwise specified. And you can see that on picture C for example and D, that these patients or these entities are usually CD5 positive and CD7 negative, and also granzyme B negative. But when it goes to subcutaneous panniculitis, like T-cell lymphomas, you can see that these patients are usually granzyme B positive, also CD8 positive, and T-cell receptor β-positive. I hear there is a slide that I got from you, Karin, and you can see here the different subtypes of peripheral T-

cell lymphoma included in this very large analysis. And I'm already here showing outcome data. The event-free survival was, I would not say poor, but very moderate for the whole cohort of 143 patients. So, overall survival was 56%, event-free survival was 45%. These outcome data also show that the second chance for peripheral T-cell lymphoma is not very good. We also analysed or you also analysed the overall survival rates according to stage of disease where we could see a trend to a better outcome in limited stage of disease, that's compared to stage 3-4 disease. But again, if I remember the number correctly, 36 of the 143 patients with peripheral T-cell lymphoma had a pre-existing disorder. For example, you can see that 7 patients presented with Nijmegen breakage syndrome. And when we analyse the data according to whether pre-existing disorder is there or not, we found the same as for marginal-zone lymphoma. As for primary CNS lymphoma, mainly that those patients who had a pre-existing disorder get significantly worse than those without the pre-existing disorder, you can see that 36 patients had an overall survival of only 29%. What was also very important from your analysis was that there is a difference in outcome according to the histological subtype. We knew from very small analyses, but these analyses confirmed that subcutaneous panniculitis-like T-cell lymphomas do very well, here 78% overall survival. Whereas those with hepatosplenic T-cell lymphoma, all the very rare situation in childhood, do very, very bad. And those with peripheral T-cell lymphomas not otherwise specified, are in between, overall survival of only of 56%. We also try to find out what is the best therapy for these patients. In this retrospective analysis show that when it comes to peripheral T-cell lymphoma not otherwise specified, there was no advantage for the block type B-cell- derived therapy as compared to the LBL ALL-derived therapy. So, again, this was the largest study ever performed in peripheral T-cell lymphoma, and it is still the case. We saw that overall moderate outcome with respect to event-free overall survival around 50%, which however were subtype-dependent, but overall, worse than in other paediatric NHL subtypes. We saw that subcutaneous panniculitis-like T-cell lymphomas had the best outcome, but those with hepatosplenic T-cell lymphoma had the worst outcome. The NOS subtypes were in between. 1/4 of the patients had a pre-existing disorder, they had a very poor outcome, as I have shown to you by the survival curves. And of course, what we again learned from this analysis, but also from the second largest analysis which was done by the NHL-BFM study group, that the subtype directed treatment recommendation is needed by, for example, subcutaneous panniculitis-like T-cell lymphomas may benefit from B-NHL therapy. It is not so clear how to treat PTCL NOS either with B- or T-NHL type therapy. According what I've shown to you here with regard to follicular lymphoma, marginal-zone lymphoma or peripheral T-cell lymphoma, we wrote an overview and how to approach or how to treat rare NHL paper, which was published in Paediatric Blood & Cancer. And here, you can see a summary of what I have shown to you today. I will not go through the details; you will find this table in the publication. But here, you can see the treatment recommendations and not because we have done all these studies, all these analyses, but these treatment recommendations are followed by I think lots of countries all over the world. It's not only Europe, but it's also U.S., Australia, Japan, and so forth. And you can see what we recommend for paediatric-type follicular lymphoma. So, in case of localised disease, complete resection, watch-and-wait. In case of incomplete resection, a secondary operation may be done if not causing mutilation. If not, we recommend anthracycline-free, rituximab containing low-dose chemotherapy. Could be BFM blocks or other blocks like R-COP, or R-CVP. Very similar recommendations for marginal-zone lymphoma, also, for advanced and disseminated disease. For peripheral T-cell lymphoma, the recommendations are not easy, but we recommend for PTCL NOS block-like-derived, block-like ALCL-derived polychemotherapy, an alternative could be the more toxic ALL-type therapy. For hepatosplenic T-cell lymphoma, we recommend the more aggressive mature B-NHL or ALCL-derived polychemotherapy, followed by an allo-transplant in CR1. For subcutaneous panniculitis-like T-cell lymphoma, we, again, as for PTCL NOS recommend less aggressive, block like ALCL-derived chemotherapy, and alternative could be ALL-type therapy. And for the very aggressive angioimmunoblastic T-cell lymphomas, we have a very similar recommendation as for hepatosplenic T-cell lymphoma. So, more aggressive B-NHL blocks followed by either auto or allo-transplant in CR1. I think can skip this. And just to show you what international collaboration means. We performed lots of studies since 2013, now for nearly one decade. And all countries, all study groups were willing to work together to learn about rare NHL

subtypes, which is only possible by this collaboration. This led to a few publications, as you can see here and to this very clear treatment recommendations. I think we are done with my presentation. I hope it was informative. It could give you an overview on rare NHL on how international collaboration can be successful leading to treatment recommendations which are used in daily life. Thanks for listening. Thanks to you, Karin, and all the participants or the people in the chat.

Prof Mellgren: Thank you very much, Andishe.

Dr Attarbaschi: So, are there any questions left? What I can say is that this session is, of course, recorded, and available on the e-ESO website where it is included in one of our four childhood cancer pathways. We have one on supportive care, one on haematological emergencies, one on solid tumours, and one on haematological malignancies. And in this pathway on haematological malignancies, my presentation from today will be included. You can go through all the presentations and complete the pathways and get CME points.

Prof Mellgren: Okay, very good. Thank you very much.

Dr Attarbaschi: I think we are a little bit too late because we had to stop I think at seven o'clock.

Prof Mellgren: Yes.

Dr Attarbaschi: So, thanks to you, Karin, for being here and moderating the session. It is always a pleasure. And yes, I would like to wish everyone a good evening and goodnight, and hope to see most of you at meetings during the next few weeks and month. So, goodbye from my side.

Prof Mellgren: Goodbye from my side also. Bye-bye.