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2021 Top 10 scientific highlights in paediatric oncology

Dr de Rojas: Hello, everyone. And thank you for the introduction. This is a session that we have jointly organised between Young SIOPE and the ESO School of Oncology. I'm very thankful that they have allowed us to have this very interesting session, and well, I am Teresa de Rojas. I am part of the Young SIOPE Steering Committee, which is why I'm involved in this session, and I will be discussing the presentation with Professor Michel Zwaan, who very joyfully accepted the invitation to present this. We are ending the year, so I think it's a very nice session to present some of the scientific highlights that happened in paediatric oncology in 2021. Professor Zwaan doesn't need much of an introduction because he's one of those big names in paediatric oncology, as you know, but, well, he's a paediatric oncologist working at Princess Maxima Centre in Utrecht, in the Netherlands. There, he's the chair of the Trial and Data Centre, and he's also a professor at the university, in the Erasmus University. He's also chairing the ITCC group of hematologic malignancies, among many other activities. So, without further introduction, I will give the word to Professor Zwaan. Please feel free to write any questions also during his presentation. I will be happy to interrupt him if there are interesting questions to comment with him.

Prof Zwaan: So, thank you, Teresa, for the very kind introduction. I'm actually quite honoured that I was invited to give this talk here, which came sort of surprising. So, thank you very much. As Teresa already said, we are sort of approaching the end of the year, so it's an ideal moment to look back and forth to 2022, but of course, we will start looking back. This talk will be slightly biased because I'm a haematologist by training more so than from the solid tumour field or the brain tumour field, but my main interest is holding phase clinical trials in myeloid leukaemia. So again, sorry that the presentation is somewhat biased to that end. So, we will first look through the retrospect scope, and I can, of course, only look a little bit at the iceberg above the water. This is what we usually all see, of course, many things happen that are not so visible because we also all have our failures and so on, but I guess that in a presentation like this, you usually focus on the successes. So, if you talk about the history of paediatric oncology, I think you have to realise that anything in medicine is actually not very old. I mean, the first clinical trial in history was only in 1747, related to Scurvy, and you can see the probably a rather underpowered study randomised approach that he took to look at if something could actually cure this horrible disease where many people of course in those days, were dying from. But you can realise that it's only a very short while ago, in fact, that this whole area of clinical research started, and we are still making a lot of progress, I think, in how trials should be run, especially, in paediatric oncology, because we only picked up about 20 years ago, I think, to really do early-phase clinical trials in paediatric oncology. So, one of the highlights that I, at least found in my personal career was this agnostic EMA approval on a drug called Larotrectinib, which was given for NTRK fusion rearranged malignancies, and that was an agnostic, tumour agnostic approval from the European Medicines Agency, and it was special actually in two ways. First of all, because it was tumour agnostic. But also, secondly, because there were paediatric data collected right from the start, and there was actually also an on-label dose for children with cancer right in the first version of the SPC that was released, which I think is actually quite remarkable. So,

we were all very delighted that this happened, and this took place in July 2019. But now, something that is slightly disappointing, that is two years down the road, from July 2019, at least in the Netherlands, this drug is still not reimbursed, and this is because there are issues with comparison that our HTA, so, the people that actually decide on re-endorsement of drugs in the Netherlands, in this case, they say there are no comparative data, and the problem is that this is a dossier where paediatrics and adults are in together because the approval is across all age ranges, and a lot is unknown about the true frequency of this mutation across all cancer subtypes, including all the adults, and not all adults are screened, so, basically, there is no reimbursement status. So, what you can see is that even if you progress the early clinical trial development through an own label access to children, you still end up that, the last part of the chain is apparently not intact or the access data is not well-arranged, and Gilles Vassal has started a project together with SIOPE to actually look at these HTA evaluations, and there is a paper forthcoming with a few anticancer medicines that are studied in that respect. Larotrectinib is not one of them, but I just wanted to share that sometimes you start off with a very positive message, and then two years down the line, you are still in a sort of a blurry situation how you get access to a drug in any given country. And this is actually very different across Europe between member states, which is also important to understand. So, specifically, on Larotrectinib, all the questions and the COG has already done this perfectly. They have immediately written a protocol where they are assessing how long patients should be treated for, to find out whether you can actually get cures with Larotrectinib alone, without surgery, and there are some data that will probably appear next year about that approach, showing that you can actually get cures where you find no abnormalities anymore in any surgery that was done. So, you can probably get cured with Larotrectinib. Out of the 16 patients, 12 were cured for hyper-local relapse, that where nothing was found with surgery anymore, and, of course, in all the cases where you perform surgery, and there is a complete resection, these patients also tend to be cured. So, I think it's a very important asset to our portfolio, but we need to make sure that we do not only get a label, but also get reimbursement. So, we then move to something where I feel much more comfortable, and the person you see talking here, is Pat Brown on the right top of the slide. So, this is about immunotherapy, this was actually presented at ASH. So, earlier this year, results were published in JAMA about high-risk relapse refractory ALL and the use of Blina in consolidation and at the ASH meeting, the results in low-risk patients were so low-risk for relapse ALL were released, where you can see the control arm and the experimental arm, where there was basically a substitution of chemotherapy for several blocks of Blina, so this is again in low-risk patients. And if you look at the results, if you look at the two top panel Kaplan-Meier curves, you can clearly see that there is a difference in disease-free and overall survival, but this appears to only to be true for patients with bone marrow disease. So, if you have bone marrow disease, Blina is superior over conventional chemotherapy, like in the high-risk patients. However, the disappointing part is that in patients with isolated extramedullary disease, and most of these in fact had CNS disease, as you can appreciate from the bottom two panels, that there was no difference at all. And in fact, the idea is that this is mainly due to isolated CNS relapse, where apparently, we are not improving with given Blina consolidation. So, this is clearly still an unmet medical need. And this is one of the important things we discussed at the ITCC meeting in November, whether we need a specific approach for patients with this problem and what it should look like. And of course, it's easy to think that CAR T-Cells play a role there, but we also know of patients where you can actually demonstrate CAR T-Cells in the CSF, and you still have circulating tumour cells. And it's poorly understood how that in fact works. And it's also, of course not so easy to characterise these cells biologically, because sometimes these are very few tumour cells. So, the second thing I think that really became apparent is that Blina is a drug to use in minimal residual disease setting, that it is very efficacious. We have now two trials in high-risk ALL, and one trial in standard-risk ALL, showing a clear benefit of Blina in consolidations. So, in the low-disease setting, I would say, if you use Blina in re-induction, you'll only get a 40% CR rate with about 50% MRD negative CR rate, 50% of that 40%. So, altogether, only 20% MRD negative CR, which is of course not sufficient. So, Blina is clearly a drug to use in consolidation and not in remission induction. So, this is once more also shown by this Infant Blina pilot that actually ended up in the best of ASH session, this is a study from Willem Van de Sluis, which was run off the Maxima, where Blina was given straight after the

induction course in infants, this was a small study with only 40 patients. The primary endpoint of the study was safety. And actually, it appeared that the drug was safe. There were a few SAEs, but nothing too, let's say impressive. There were mainly no neurological SAEs, there were also no SUSARs in these infants. So, that's actually quite important, but the bottom slide shows you a comparison, which is historical. So, it's not randomised; it's historical data where the Interfant of 6 treated patients were compared with the Blina infant-patients. And you can see that there is an enormous difference in outcome between these two groups, where there's one block of Blina, we do have to say that, of course, in the Blina-treated patients, the follow-up was relatively short. So, it might be that you are just postponing some of the relapses to a later time-point and that the curve was still dropped down because this difference is so big that you can actually hardly imagine that one block of Blina can make this difference, but still, this is what the data at the moment suggest, although, longer follow-up is needed. Now, the same approach with this Blina block will be taken forward to the Interfant 21 protocol, which in fact will probably only open in 2022. And that also will be run out of the Maxima. We are quite far along the line to prepare this new protocol. So, then, Inotuzumab, this Inotuzumab is in fact often quality immunotherapy, but in reality, it's an antibody drug conjugate, where, if you look at this blue structure here in the left-top graph with the two eyes, this is the two bullets of calcimycin, it binds to CD 22, gets internalised. Then the calcimycin, is surprised, too often, it causes apoptosis. And we just published this year, the paediatric phase I study results where we basically showed that the recommended phase II dose was the same as in adults, but there was a very huge overall response rate of 80%, which in a phase I study is really enormously high. And out of these 80% responders, 84% were MRD negative. So, all in all, roughly 60% of patients experienced MRD negative CR, which is of course incredibly high if you realise that this is a population of multiple relapsed ALL, that are usually quite resistant to all sorts of chemotherapy. So, you can see the individual patient affect in the bottom graph, for patients who are sometimes consolidated with transplant and/or CAR T-Cells, the safety profile was favourable. It was mainly some VODs and they usually occur during the subsequent transplantation. And at the bottom part, you see the EFS, the lowest curve, of this particular population. Now I got a slide that I don't understand. Your views are important, it says. Teresa, what is this for slide? Should I do something?

Dr De Rojas: No, no. This is just to remind people that they can post any questions at any time using the Q&A section. And we will address them.

Prof Zwaan: Okay. Thank you for doing this part of the presentation.

Dr De Rojas: You are welcome.

Prof Zwaan: Okay. So, then, I will continue. Right? Okay. So, I think another highlight of the last year was the Accelerate meeting on CAR T-Cells. So, Accelerate is basically a multi-stakeholder strategy forum discussion where we either take a particular class of drugs or a particular disease, and we discuss drug development for that particular drug or that particular disease. And I shouldn't say particular drug, I should probably say particular targets. And usually, we have a paediatric strategy for a meeting under our... And when there is a target with multiple drugs and we don't know which one to take forward, and then, we want to look at the characteristics of these compounds and make a selection and then, decide which structure will be taken forward, how these meetings are joint by the FDA and by the European Medicines Agency by patient advocates, by pharma. So, this is also really interesting. Often, you have multiple pharma in the room who are sharing confidential data with the other parties in the room, which I think is in itself would be an interesting endeavour because this is not something that normally happens. So, these are actually quite unique meetings and this one was held on the CAR T-Cells. So, I have a few summary slides. First of all, we all know that Tisagenlecleucel is of course approved that in adults, that the CART product is approved and that there are PIPs mainly to be on custody. And the CASSIOPEIA study that are currently ongoing in many of the centres in Europe. And then, as you can see, there are a few other products in development, but I won't go into details here. So, I think where we are currently with the CAR T-Cell field is that we have two questions. First of all, in the ELIANA study, which is of course the study that led to the approval, roughly 50% of the

patients benefited. If you're not looking at real-world data from the CB MTR registry, you can see that also roughly 50% of the patients benefit. And this is the commercial use of this particular compound. So, in terms of activity, 50% is, of course, on one hand spectacular, on the other hand not enough. So, the question is this product related and do we need to improve the products? And the second main question in the field is, of course, can we replace Allo transplant? And that is of course I have a debate because nobody wants to randomise. And when we talk to the patient that for God's hell say that you do not want to randomise, they want to be treated with CAR T-Cells and reserve transplantation in case they relapse, or the CAR-T fails in a sort of a sequential approach. But of course, this is still also an issue of debate and sometimes, done differently and different centres, I would say. So, in terms of safety outcomes, the real-world data actually look better, which I think is our learning curve in the ELIANA trial, people treated the overall disease. I think we all now use some sort of cyto-reduction before we infuse CAR T-Cells so that we have much less CRS as you can see in this graph, but also less neuro toxicity, as you can also appreciate in this real-world data, which basically showed that the CAR T-Cells are used more differently than during the ELIANA trial. So, one of the things to basically avoid antigen escape, and I think at this ITCC Accelerate meeting we defined this as one of the most important questions to answer, is that we need to develop CD19, CD22, either dual-specific-CARTs or sometimes, people infuse CD19 CARTs, and CD22 CARTs. So, the rest can have two drugs with different transduced products that they are infusing. And this is just a very small example of something that was published. But the real question is can combine CD19, CD22 approach avoid antigen escape, and will that improve our results from 50% to, let's say, 60, 70, 80% success rate of CAR T-Cell therapy. So, we all identified that these products are there and that this is probably one of the most important questions at the moment to address. And this is of course a sort of provocative slide. We all know now that we actually bother these children with very long therapy during two years with a lot of toxicity, which as paediatric oncologists, to be honest, we're often blind to see the toxicity which children have problems with vincristine, they have pain, they have constipation, they have obesity, they lose their hair, they cannot participate in many activities. So, I think that the treatment is actually much more, let's say, disabling that we often admit ourselves. And of course, the cure-rates are excellent. So, I mean, that's the positive side, but yeah, the real question is, later-on are we cyto-reducing inpatients and give them CART very early on and see what the result is. And I guess people are also sort of scared to do this. So, the first approach is of course, the CASSIOPEIA study, where instead of giving patients transplant, we tried to consolidate with CART and see if that is efficacious. But in the end, we will need to get to this question-mark, at some stage in order to answer that question, I think.

Dr De Rojas: Professor Zwaan. We have a question before we move on about CAR T therapy, Evangelia Antoniou is asking whether there were any patients that were not eligible for transplantation and were treated only with CAR T-Cells therapy until now. And if there were any, what was the outcome of that?

Prof Zwaan: Yeah, so, in the ELIANA trial in principle, patients were not treated with an additional bone marrow transplant. So, out of the 50% rates we are showing here, it's the salvage rate in most cases without transplant. So, there are certainly durable responses without a consolidation, I guess most people nowadays use Allo transplant. If they, for instance, see early loss of CAR T-Cells, really quite early after infusing the CAR T-Cells, if you see MRD coming back where your CB cell loss after four weeks or six weeks, then, usually people have a patient that has very low MRD and can then be rescued with stem-cell transplantation. So, I guess it's more reserved for specific indications, personally, I don't think we should do CAR T-Cells always followed by transplant because for me, the main part is to actually avoid the transplant because of all the long-term toxicity. So, we are looking for something that is efficacious, but doesn't have the long-term toxicity. At the same time, I have to admit that we don't know the long-term toxicity of CAR T-Cells yet. I mean, we induce a state of, again, often immunological, immuno-deficient patient that needs to get immunoglobulin therapy. We don't know, are probable whether these patients will, I don't know, develop other late effects that currently are unforeseen. So, we really also need to follow these patients for 20, 40 years, but this is done in the context of long-term follow-up commitment that was actually, no further was

obliged to do, to follow these questions for a long time, provide these data to the regulatory authorities as well. I hope that answers the question.

Dr De Rojas: Yes. Very much so, thank you.

Prof Zwaan: Yeah. So, this is the conclusion of the Accelerate meeting. So, for B-ALL I already basically mentioned the CD19, CD22. The other thing we realised is that it's unlikely that companies will keep developing products for many of our paediatric oncology indications, which sometimes are tiny, where you have selected targets that do not occur in let's say adult diseases. So, the idea was also that we should have academic multi-centre trials to pilot products, for instance, for solid tumours, but maybe also for AML. So for rare disease types. And then, if they are successful, we can hand them off to industry to make sure that they are sustainable because of course, academia suffers to make these products available in the long-run, or you have to produce them without label on an hospital exemption basis, but then, you cannot export them to other countries. You cannot provide access to patients in other countries under that kind of mechanism. So, this was also an important endpoint of the accelerate meeting, sort of a strategy, how to move forward. And I'm just mentioning, this was an abstract at ASH about CD7 CAR T-Cells for T-cell ALL showing that in fact, you can get the permissions with CAR T-Cells also in TALL, there was not much information on the product, to be honest, they have different products that they tested, but choose one of these products to take forward. But at least you could see here that there were the permissions and all these patients were in fact transplanted after the CAR T-Cell therapy. Also, in Europe, we will in the next year, have CAR T-Cells available for T-ALL at CD7 through commercial company, a different one than the one that is on the slide here, because this was a Chinese company. We will have a US company running a clinical trial for T-ALL in Europe next year. And then, something completely different. We're not talking about optimization of CAR T-Cell products and CD19, CD22 combinations. This is all about, let's say, tweaking the CAR T-Cells themselves to make them better. But the other idea is that you can look at the microenvironment trying to influence the microenvironment, but here, we have data where we looked at Fludarabine exposure, quite to our surprise that was a big difference in outcome between the patients with high-Fludarabine Exposure, and low-Fludarabine Exposure, who were all treated with the same dose. So, this is clearly pharmacokinetics and it shows that precision dosing may matter. So, patients who have sufficient exposure to Fludarabine have a better outcome. And the question is, should we not then do a pharmacokinetic analysis of these patients, measure their serum levels and titrate them to the level of Fludarabine that they actually need to achieve sufficient exposure? Or can we calculate a starting dose that is probably a little bit higher than what we are doing now to make sure that CAR T-Cells can engraft a lot better. And then, in the past, and sometimes, you don't think of these things because these regimens are there and everybody's using them. But then, when you look, go back to the details, there's often no real rationale behind it. And I just wanted to point out, there are a lot of situations I think around transplantation as well, where precision dosing could play a major role. So, just to people that have something to do at home and create their own studies in these kinds of things. And I felt this was also a very interesting presentation because I think it contains an important lesson for all of us. So, this is on the internal protocol, was a presentation from Charite Berlin where they looked at the cumulative incidence of protocol deviations. And that's not something we usually look at. I think this was an unusual paper, that's why I liked it. So, 15% cumulative incidence of protocol deviations over time, as you can see, this is probably a reality and most of our phase III trials that people do deviate from the protocol for all sorts of reasons. But as you can see, it impacts on outcome so, the patients who were getting deviations get worse than the patients where a protocol therapy was followed. And of course, sometimes there are good reasons. I mean, if you are a high-risk patient and you have excessive toxicity and you cannot follow the protocol; but she was also mentioning that there were deviations that were not so obvious during maintenance therapy where the clear medical reason was not so evident. And that result actually also important outcomes. So, I thought that an important eye-catcher, if you write a protocol, or if you use a protocol, you got to stick to it unless, the patient can really not tolerate it. But I think thinkers like this are important to convince us that protocol therapy

works and that the protocol is there for a reason and not something that you can easily deviate from. So, okay, sorry, we have one of these slides again. Any other questions?

Dr De Rojas: No, not so far. Go ahead.

Prof Zwaan: Nobody wants to deviate from the presentation. That's good, okay.

Dr De Rojas: Exactly

Prof Zwaan: Then, the future. So, the past year I have struggled a lot trying to set up complex clinical trials. And so, there are basically three versions, that is the Basket Trial, the Umbrella Trial, and the Platform Trial. And these are all different of course. So, in a Basket you have multiple diseases, but one targeted intervention. So, for instance, if you have an ALK inhibitor that will target inflammatory myofibroblastic tumours, but also large anaplastic lymphoma, and you combine them in one protocol, this would typically be a Basket Trial. Then, you can have the Umbrella Trial. You don't have a single disease and multiple interventions. And I'm going to show you at least three examples of Umbrella Trials that are set up in Europe at this moment, and that hopefully will open next year. And then, you have the Platform Trial. The good thing of a Platform Trial is that you have a continuous standard of care arm running in the background, but then, you need to have a defined standard of care, of course, otherwise, you cannot do this. And then, you can bring in interventions and you can do a sort of pick-the-winner approach that is if they are not successful, you drop the arm. And unlike that if you have a successful intervention that can then become the standard of care and so on and so forth. So, this can be a sort of ongoing platform. Now, in fact, regulators don't like this because it's complicated because they have multiple drugs in one trial, multiple safety issues, multiple amendments. So, they don't like it very much. And in order to at least make sure that some basic principles are laid down, the competent authorities who work together in the CTFG as you can see on the right here, affecting a recommendation paper. So, if you any time want to start writing a protocol that has any of these aspects, you really need to dive into the matter and read this paper with the recommendations, because otherwise you try on like it rejected. And there are really a couple of things that you have to take into account when you write such a protocol. Now, do the strategy for a meetings work? Well, I think they do because two of the strategy for a meeting, as you can see, we're in 2017 and 2019 and both will open an Umbrella Trial next year, as a result I think of this forum meetings. I mean that's why the discussion started and the decision was made that we need such an Umbrella Trial. So, here are the examples, and I'll go into a little bit more detail in a moment. So, we will have GloB NHL for non-Hodgkin's lymphoma. This is run out of this year CTU by Pam Kearns and Amos Burke, in Birmingham, due to open next year, we will have the PedAL initiative, which is a Transatlantic initiative, just like GloB NHL. This is run out of Maxima and the Leukaemia-Lymphoma Society in North America together with CLG. And then, the Maxima is preparing the so-called HemiSMART trial for T-ALL and BCP-ALL, which will start as a European endeavour, but we may export it across the ocean at a later stage. So, that will be free basically short of master trials, running in Europe, hopefully next year, covering almost all aspects of the haematological malignancies, which I think completely will change the landscape and will hopefully provide access to a lot of new agents in the near future. So, to start with the PedAL initiatives, Leukaemia Lymphoma Society did an adult programme called Beat AML. And this was mainly focused on elderly unfit AML patients. And they have now translated this to a paediatric initiative, and we've jumped on that to trying to be the European representative and make sure that all these trials are going on two sides of the ocean. And this was the slide from the... the frustrating slide from the strategy for a meeting where all these compounds were approved in adults. And actually, none of these compounds currently is approved for children. So, that's the frustrating situation where we started with that there are many new compounds available, but not for children. So, this is the overview slide of the PedAL projects. The current, you see, this grey box down here, this is the trial that has just been submitted to regulatory authorities on two sides of the ocean. So, this is Mylotarg Flat-course with or without Venetoclax. So, this will be a question for patients in second relapse or first relapse AML, who cannot tolerate Anthracyclines anymore. And this trial will open, but we are currently working very hard on Flotetuzumab an immune

inhibitor and AMGN 632, which is a CD123 directed-antibody drug conjugate. And all these sub-trials I presume will actually open next year, so we will have a massive portfolio of experimental agents available, for relapsed refractory acute myeloid leukaemia in this programme. I'll skip, well, I can just say this is a complicated project where you can see a division of tasks between the European sponsor and the US sponsor, and with a global working CRO in the middle, who's taking care of the database and drug distribution and so on and so forth. And you can imagine the number of contracts that you need in such a trial to make it work. So, it's one of the most complex things to be honest I have ever looked at. This is also the interesting part of the PedAL trial that we have young investigators, early-career investigators on two sides of the ocean, so, there are points of the European investigators, in the other colour are the North American investigators. So, we always have two investigators. Early career investigators working on any of these sub-trials. So that will also educate people to take home for in the future and make sure that we have sufficient people in Europe who can run such trials. So, then, the Hem-iSMART initiative, as I said, this is an Umbrella Trial actually for two new relapse categories that we have identified. First of all, the post-CAR T-cell relapses, where of course currently often these patients now have also been transplanted, of course, but the post-CART, the post-transplant BCP ALL is really a new sort of relapse indication, which may have different characteristics. To be honest, we don't really know. And T-ALL with high MRD after reduction. So, this is first relapse T-ALL, if they fail re-induction, the outcome is really poor. And then, we want to enter them into this protocol. And here, you see the approach, again, an Umbrella approach, one disease, T-ALL, multiple different interventions I am not going through all these interventions, but you can see these arms. And here, the requirement is that you have next generation sequencing dome at the moment of relapse, drug results of response profiling done, and flow cytometry, of course, and at the basis of these gene alterations that we identify, there will be a molecular tumour-board assigning these patients to any of these specific arms. So, this is molecularly stratified whereas the PedAL project is more disease-stratified. And then, the last one, GLOBNHL, you can appreciate the number of patients. They are thinking that there will be around 40 in Europe, sorry, globally to enrol in this such a trial by year. And here, you can see the principle lay out of these trials. So, they don't allow me to show the compound yet, but there is a bi-specific antibody. There is an antibody drug conjugate, and there are CAR T-Cells. So, again, the whole immunotherapy repertoire for [Audio Not Clear] disease, which we all know is extremely poor. When you relapse, we only have to have R-ICE available for these patients. So, I think this is my last slide. This is not something to look forward to, but next year, there will be a new clinical trials regulation, which hopefully will benefit us in the end. But if we have to learn how to work with this in the beginning, it's difficult. Basically, there is a centralised European portal where if you have a drug trial, you have to submit your dossier including mainly the product information, whereas the local ethics committee procedure, which is called Part-2, here, on the right, is still done, let's say, locally and on a country-specific level, yet you have to submit everything for the EU portal, and there are extremely tight timelines. So, if you submit your trial, you will get within 45 days, your initial answer, then, you have to respond within 12 days. So, if you are the PI of the study, you better mark your calendar, that you have to do other things than patient care on these 12 days. And then, you get your final yes or no, when you'll get a yes or no, you don't get the option to go back again. So, you cannot sort of negotiate, it is a yes or no. You get an approval or not. And the other thing is that there is this new category that where we have to learn if our phase III protocols actually fall under this category, which is called low-intervention clinical trial, where the, let's say, the requirements are diminished, but we don't know exactly how much diminished, especially concerning the labelling. And we also don't really yet, I think fully understand if most of our, let's say, phase III treatment protocols will be seen as a low-intervention clinical trial. So, we also have to learn to work with this new system, which I think is a lot of work, but very important for all of us to understand. So, this was my last slide. I do need to thank all these people that I collaborate with, collaborate with me in all these trials, especially, the ITCC, but also, the IBM new agents and resistant-disease group, and many other colleagues that actually recruit patients actively into all these studies. So, thank you for listening, and I'm happy to take any questions.

Dr De Rojas: Many thanks, Professor Zwaan, that was an excellent presentation. I see no further questions so far in the chat. Please feel free to write any questions down. But in the meantime, I would like to ask you about the histology agnostic approval of drugs, you highlighted a Larotrectinib this happened two years ago, and you stressed out that there is a negative outcome of that because taking into the practise, there is some issues with HDA approval and so on. I want to focus on the positive because it is a huge landmark to have histology agnostic drugs approved. Do you think this is the way forward? And if so, how can we push regulators into that direction more? I know this is a very complex question but go ahead.

Prof Zwaan: Yeah. So, I think one of the... it answers a couple of potential answers here, first of all, in a way it would be nice if you can submit paediatric data separately from adult data. I mean, this happened in the CAR T-Cell dossier, for instance in the Netherlands, where CAR T-cells were approved for children under 25-years of age. But the adult indication for non-Hodgkin lymphoma was not, is not yet approved for reimbursement. So, if you can splice out the paediatric patients from an HDI application and you can work with the company to sort of set them apart or agree with the HDI to set them apart, you can probably make a better case. Here we have a very well-defined infant disease, which is this particular subtype of sarcoma with these NTRK fusions that the infantile fibrosarcoma, they could have been set apart and as a specific group have been registered, but then, of course, you lose the agnostic principle. The other part is that sometimes, apparently Europe doesn't like the agnostic approvals because it happened of course before the checkpoint inhibitors in North America for hyper-mutant disease. And this is still something that we're also lacking in Europe and that doesn't happen. The other thing is very well-documented historical data will also help to provide evidence that this is better than what we have historically. And I think we don't probably have really good matching historical treatment data of infantile fibrosarcoma to provide the registration authorities with. And the problem is if you have an agnostic drug, they have to do that on 40/40 different disease indications. So, that's where the problem comes from.

Dr De Rojas: Yeah, exactly. It's a very complex thing. Well, with the fibrosarcoma, you may argue that if you apply only for that given indication, it would have been impossible to recruit sufficient numbers in a timely manner and have this clearly beneficial drug approved for children. So, it's a bit of a catch-22 situation.

Prof Zwaan: No, I mean, more that you run this trial, but if you spliced them out in an HTA dossier as a specific entity and then, submit that with historical data to prove to the HTA that's a clear benefit over the historical situation to get the reimbursement status. I wouldn't suggest to indeed split up to trial, because I agree with you there, that we would never get to that.

Dr De Rojas: Okay, thank you very much. A different question. Also, looking into the future, you mentioned the involvement of young investigators, and since I'm representing Young SIOPE, I want to ask you, I know you're an advocate, and you have really involved early-career investigators in your trials, but I have the feeling and it's shared with other young investigators that it's becoming a bit of a tick-the-box situation, where it is nice to include young investigators, but then, they don't really have a crucial or very active role in certain groups or trials. How can we change that? How can we involve early-career investigators more?

Prof Zwaan: Yeah, so I'm actually trying to change that. I don't know if it will work, so, what we are trying to do is that we hook up early career investigators from various institutions. So, not just a Maxima, but also, there are people from France, from Austria, from Italy, what you are seeing. Nowadays, I think we're also used to work with Zoom that most of the meetings can be online, but they actually have to write protocols and look at safety data and participate in all the tele-conferences. The problem I experience is that I don't always have the time because of the clinical duties. So, it's really important that for these people, we even actually provide them with a contract to cover their liability and our liability. But in that contract, it also states that our own institution should provide them with sufficient time, because don't underestimate, you may work two days a week or so on such early clinical trial, in times that it is busy, maybe even more. And that

means you are not available for the clinic. So, you need to be a good negotiator with your boss and with your education training path to make sure that you can actually spend the time that you're asking for.

Dr De Rojas: Yes. And you may, of course, I'm biased because I'm very research-focused, but you may argue that you can't understand a good paediatric oncology education without research education. So, yeah, it's difficult to find a balance with the clinics.

Prof Zwaan: Yeah, well doing phase I-II studies and writing protocols and that kind of stuff is quite, I would say, we don't need every paediatric oncologist to do that, for every paediatric oncologist to really understand clinical trials, but you don't need to go to that level of detail. That's really for people who want to become, let's say, early clinical trialists, but in general, there are not enough early clinical trialists in Europe on the whole also to actually recruit patients and to ensure that they are treated in a safe manner, according to the GCP guidelines. So, I guess that, yes knowledge on clinical trials is a key-aspect I think of the training of every paediatric oncologist and should be incorporated much more than what we've done in the past, because I'm more or less an autodidact because there was nothing back then, apart from a couple of phase III studies when I started and now there is this huge portfolio. But yeah, it would be really great if we can train people to take over and keep doing this in the future.

Dr De Rojas: Okay. We don't have time for more. It's seven now, but well, there is a popping question from Alba. Perhaps, we can still take it if it's not, Dr Alba Rubio is asking, which are the most relevant obstacles in your opinion to perform a transatlantic trial, because there are different regulatory issues between FDA and EMA, the pharma interests, resources and so on. This is a very hot topic.

Prof Zwaan: You've mentioned already a few. It depends. So, first of all, if it's a phase I-II trial, you need one single database because you need real-time oversight over all the safety issues. If that one single database, if it is a COG lab trial, you are in trouble because it means that it is done under the NCI, and that means that for instance, the database has to be the COG database that is not easy to get access from Europe to that database, because you need to be an NCI-approved institution. Like in PedAL we are trying to solve that by actually putting the database at the CRO. And I think in the PedAL programme, we have realised for the first time that NCI is accepting that this database is at the CRO, but that the data will later be synchronised with the COG database so that the COG database is not the primary source. So, I think that we will actually manage to do this for the very first time, which I think is really a milestone. So, that's really important. And the second really important thing is that our protocol templates are really different. So, we are now working in this PedAL Initiative. We have tried to come up with a sort of a global protocol format, but when a trial is developed by COG, they go back to their own sort of template. And when we define a trial, we go back to our own template. So, these things need to be resolved in order to make this much more feasible. In general, exporting a trial from Europe to North America is much easier than when it is a COG lab study export into Europe.

Dr de Rojas: Okay, yeah. This sums up some of the big issues, but it's a very complex topic. Unfortunately, we do have to stop now. I want to thank you very much for this excellent presentation and accepting our invitation from Young SIOPE. And we are looking forward to the new year, to 2022 and all new, exciting, scientific discoveries in paediatric oncology. Thank you very much.

Prof Zwaan: Thank you very much and thank you for listening.