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Immunotherapy in childhood ALL

Prof Handgretinger: Good evening, good afternoon, good morning, wherever you are. I welcome you to this e-session, e-learning session of the European School of Oncology on "Immunotherapy in Childhood ALL," and it's a pleasure and an honor for me to introduce our expert, Professor Franco Locatelli. He is full Professor of pediatrics at the University Sapienza in Rome, and head of the Department of Pediatric Hematology Oncology at the Ospedale Bambino Gesù, Rome. Professor Locatelli is well-known in the field. He leads one of the largest programs of treatment of childhood cancer, and he has many, many publications in various fields, mainly on allogeneic transplantation immunotherapy in childhood ALL, malignant, non-malignant diseases treatment, and also gene therapy. So, we are lucky to have Professor Locatelli today to give us an overview and discuss with us together the immunotherapy, new approaches on immunotherapy in childhood ALL, and we all look forward to your presentation, Franco.

Dr Locatelli: So, many thanks, Rupert, for the very kind introduction. Indeed, it's a real privilege and a pleasure for me to present this lecture on "Immunotherapy in Childhood ALL," and the pleasure is certainly of mine that [Audio Not Clear] that I am introduced and chaired by you, who are a great leader in the field of the immunological approaches for treating childhood neoplasia. These are my disclosures. And I will start certainly commenting this slide that summarizes the different immunological approaches that are under investigation in childhood ALL, and in particular, during my talk, I will focus on three main topics, namely the bispecific antibodies, or bispecific T-cell engager, the antibody drug conjugate, and the CAR T-engaged frontier of immunotherapy, namely the CAR T-cells. And the reason for considering the development of immunotherapy in childhood ALL mainly stems from the observation that despite the fact that we have observed a dramatic improvement in the probability of definitive cure in this disease, leukemia recurrence still represents the main cause of treatment failure being diagnosed roughly in 15-20% of children with newly diagnosed acute lymphoblastic leukemia. And the prognosis of relapsed ALL largely depends on the time lapse in between diagnosis and recurrence, the site of relapse, and the blast immune-phenotype. And we have also to consider that more or less all children with relapsed T-ALL and 2/3 of those with B-cell precursor ALL are candidates to receive so far an allograft once that second morphological remission is achieved. And if you look at this cartoon published and presented two years ago by the Friends of the Children Oncology Group at the ASCO annual meeting, you can certainly notice that there is large room for improving the results progress in these patients, in particular for those patients experiencing leukemia recurrence within 30 months from diagnosis. The outcome is still unsatisfactory, and we need to implement innovative approaches. And as I mentioned before, immunotherapy is a very promising option in the field of B-cell precursor ALL, and I would start comment the results that have been obtained using blinatumomab, which is the prototype model of the bispecific T-cell engager. These are a category of a rather unique type of a

monoclonal antibody, because they have single-chain monoclonal antibodies creating an immunological synapsis between the leukemia cells and T-lymphocytes of the patient, and after that these immunological synapses have been created, the link of the monoclonal antibody results in the deactivation of the cytotoxic T-lymphocytes that are able to mitigate a serial lysis of multiple CD19-positive B-cells. And the drug was developed in the pediatric population initially through a Phase I and II study published in the "Journal of Clinical Oncology," demonstrating that it is an agent able to result into the achievement of complete morphological remission in roughly 40% of patients experiencing multiple relapse or refractory disease, or in patients relapsing after transplantation. And in this study, patients were eligible to be treated if they had at least 25% blast in the bone marrow. But if you concentrate your attention in the lower part of this cartoon, you can immediately appreciate that there is a better chance of responding if patients have a blast percentage below 50%. In view of this observation, an expanded access trial called RIALTO was conducted in many different centers, mainly in Europe, and it enrolled 110 patients with relapsed refractory B-cell ALL. The main difference between this trial that was published for the initial results a few months ago and the initial Phase I and II trial is that patients with more than 5% blast could be enrolled into the trial, and there was also the possibility of recruiting patients in morphological CR, but with molecularly resistant disease. Patients receive two induction courses, and up to three consolidation courses, while being offered a transplant. And this was the treatment recommended for the responding patients. And if you look at this slide, you can immediately appreciate that overall, the probability of getting a complete remission was higher in these patients with a lower leukemia burden being 63%, and that the two figures for patients with more than 5% blast, or in patients with molecularly resistant disease are 60 and 92% respectively. In most of the responding patients a complete MRD response was achieved, and remarkably, the effect of the agent was documented in patients with either constitutional or somatic abnormalities associated with the development of ALL, and this is an important information, because, for example, children with trisomy 21 are very fragile patients, and difficult to be treated if they relapse. In addition, also very good risk, cytogenetic abnormalities, like the translocation 17, 19, or rearrangement of MLL has also very good chance of responding to blinatumomab. But the evolution of the approach was that of testing the bispecific T-cell engager also in patients with first relapse high-risk relapse of BCP-ALL. And usually, these patients are treated with a cycle of induction therapy followed by two or three courses of consolidation chemotherapy before these children are transplanted, either from an HLA-identical sibling, or an unrelated donor, or an haploidentical family member. And two studies were more or less simultaneously activated. The Study 215, was mainly conducted in Europe, and they had the privilege with the PI and it had rotations between the age of 28 days and 18 years, and it recruited patients experiencing a bone marrow relapse within 30 months from diagnosis, so, the very high-risk population that I commented in the slide presented by this huge colleague. In the US, the COG cooperative group conducted a similar trial which enrolled patients up to the age of 30 years, and they recruited into the trial not only the very high-risk population, but also those patients who had initially standard risk characteristics, but showed a suboptimal response in terms of MRD again of induction therapy. And also, the study design was a little bit different, because in the European trial, after induction therapy patients who were given two consolidation courses were being then randomized to receive either blinatumomab or a third course of chemotherapy, while in the American study, patients after being treated with induction therapy were allocated to receive either two courses of blinatumomab, or two courses of chemotherapy, and they were all these patients candidates to receive, after the randomization part of the study, a stem cell transplant. And these are the key eligibility criteria and the stratification criteria of the European trial, which had the primary EFS as primary endpoint. Secondary endpoints were the probability of overall survival, MRD remission, and cumulative incidence of relapse. And both trials were discontinued prematurely, because of the manifest superiority of the immunotherapy arm in comparison to the classical consolidation chemotherapy. In particular, in this cartoon, which reproduces the figure presenting the paper published in an issue of JAMA at the beginning of this year, you can observe a much better probability of the event-free survival, and a lower incidence of leukemia recurrence in patients allocated to receive blinatumomab. And looking at the probability of event-free survival in different study subgroups, you can

observe that the advantage of having the blinatumomab was confirmed in all the subgroups of patients, including those with a high-level of minimal residual disease at the end of induction, or before stop of treatment. And more importantly, the very challenging subgroup of patients relapsing within 18 months after diagnosis had a much better probability of benefiting from treatment in comparison to patients allocated to receive chemotherapy. And the same results were observed also in the American trial. Indeed, in this cartoon you can notice that the probability of disease-free survival and overall survival was better in patients who received blinatumomab in comparison to those allocated to receive chemotherapy. So, these two studies have defined a new standard of treatment for patients with high-risk of relapse B-cell precursor ALL, and very recently the European Medical Agency has extended the indication of the approval for commercial use of blinatumomab to patients experiencing first relapse, high-risk first relapse, or BCP relapse. Inotuzumab is the prototype agent for what we can call the antibody drug conjugate. Indeed, it is a monoclonal antibody directed against CD22 in which the example is linked to calicheamicin, and once the monoclonal antibody binds to the target antigen, it is internalized and there is a lysosomal degradation of either compound, as with the activation of calicheamicin. After the initial studies conducted in adults, very recently there was a publication also in the pediatric population in particular. We treated, in a study sponsored by the Erasmus Medical University, 25 children with multiple relapse ALL, or with refractory disease, or relapsing after transplantation. And you can observe that roughly more than half of patients have had a previous transplant. In particular, the agent was tested at two dose levels, the dose level-one, which corresponded to a dosage of 1.4-milligram per meter square, and the dose level-two, which corresponds to 1.8-milligram per meter square, and the drug is administered on day plus 1, plus 8 and plus 15. And you can observe that the overall response rate is very high being 80%, even higher than 85% for those patients who were treated at the dose level-two. And it is important to note that the relevant proportion of patients were given transplantation, and despite the initial concern correlated to the use of this agent, no severe cases of veno-occlusive disease of the liver were reported. But as I mentioned before, the CAR T-engaged frontier of immunotherapy is represented by chimeric antigen receptor T-cells, and in particular, we are now using the second-generation construct, enriched into the construct there is a co-stimulatory domain, which is essential for optimizing the function of CAR T-cells. And an international trial called ELIANA demonstrated the greater efficacy of this approach, because roughly 80% of the infused patients obtained complete remission with MRD negativity. However, it tends to be underlined that if you consider the analysis on an intention-to-treat basis this proportion of response is a little bit lower being at 66%. However, we must also emphasize that the response obtained can last over time. Indeed, you can see that the one-year probability of event-free survival is in the order of 50%. And last year, Marcello Pasquini and colleagues published the initial results obtained in a real-world setting, and you can observe that also in the real-world the probability of benefiting of this treatment for patients with relapsed refractory disease is very high being in the order of 40%. It's important to emphasize that also in the setting of CAR T-cells the leukemia burden matters, like in the response to blinatumomab, as I commented a few minutes ago. Indeed, you can observe the probability of response of patients with the high leukemia burden defined as more than 5% bone marrow lymphoblasts, or presence of leukemia cells in peripheral blood, or CNS3 status is worse than that of patients with a low disease burden, or no detectable disease. And this type of probability of response is reflected by superior overall survival, event-free survival, and duration of condition. Despite these exciting results, we have to consider that we are still facing limitations on the use of CAR T-cells, represented by what can be defined as sort of iatrogenic toxicity, or treatment-related toxicity being mainly represented by the cytokine release syndrome with occurrence and severity largely dependent on the leukemia burden at the time of treatment and neurotoxicity. There is also another relevant issue to be considered, namely that that raise a small proportion of patients in which the CAR T-cells do not expand, or have a limited function, and this is the reason explaining the difference in terms of response for the ELIANA trial when we can see the intention-to-treat analysis. And to try to overcome this obstacle, some groups, in particular the colleagues of the Great Ormond Street and the University College of London invested in particular on the use of third-party CAR T-cells obtained from a healthy donor. But to avoid the risk of rejection of these third-party CAR T-cells, and also, to abolish the risk

of graft-versus-host disease induced by these allogeneic CAR T-cells, they use approach for aggregating the expression of the T-cell receptor on the surface of these CAR T-cells. And this very elegant and sophisticated approach was employed in 21 patients, which were treated with these universal CAR T-cells, and you can observe in this part of the cartoon that a relevant proportion of patients responded to the treatment, although, unfortunately, the long-term probability of progression-free survival is in the order of only 20%. The other main limitation on the use of CAR T cell is represented by the recurrence of the disease, which in many cases it is associated with the apparent loss of CD19 molecule and under cell surface of leukemia cells, and this loss of CAR-recognized epitope is the result of an alternative exon splicing forms of the CD19 gene because there is the loss of exon 2. Another mechanism of leukemia escape is represented by the myeloid switch, and loss of CD19 in patients with mixed phenotype ALL, and this occurs in particular in children with MLL rearrangement. And if you look at the data that were obtained in the ELIANA trial, you can observe that roughly 3/4 of the relapses were due to the apparent loss of CD19 molecule on the surface of leukemia cells. And it is important to emphasize that the loss of B-cell aplasia very often arouses the occurrence of leukemia recurrence, in particular with the emergence of the CD19-negative subgroup. Is there any role for the academic institution in the field of CAR T-cell? Let me spend just a few minutes commenting the results that we have obtained in our institution developing an academic program, in which we use a second-generation CAR T construct on a retroviral platform. And we decided to include a suicide gene, or a safety switch if you wish, just to improve the safety profile of the approach. And in particular, we invested on the inducible Caspase 9 as the suicide gene. And you can observe from this curve that the probability of overall survival and the event-free survival that we have obtained is absolutely comparable to that reported in the real-life world data using the commercially available CAR T-cell product that has been approved by the regulatory agency in Europe. And we didn't observe any different outcome in patients who did, or did not receive prior forms of immunotherapy, including either blinatumomab, or inotuzumab, this suggesting that the previous use of other forms of immunotherapy doesn't significantly impact on the probability of responding to CAR T-cells. But the other approach that we have developed in Rome in collaboration with a small bio company, which produces an automated system for manufacturing the CAR T-cell is that based on the use of fresh drug products, instead of the cryopreserved ones that have been developed so far. In particular, I'd like also to emphasize that through this approach the manufacturing time is reduced from four weeks to two weeks. So, there are three main advantages using this approach, namely that we are using an automated system, we can benefit from fresh T-lymphocytes, and the time elapse in between apheresis and the infusion into the patients is half of that usually needed using a cryopreserved approach. And we have activated a Phase I and II trial testing three different dose levels, one-million, two-million, and three-millions of CAR T-cells per kg. We have completed the dose level-one, and we have already treated two patients at the dose level-two. These were patients with very advanced and resistant disease, and through this approach, we have demonstrated the possibility of generating a very high number of CAR T-cells with a maximum viability and a high percentage of CAR T-cell transduction, and also, the safety profile was very good. And more importantly, this fresh CAR T-cell product have resulted into the expansion of the CAR T-lymphocyte, and all these five patients obtain a complete remission of 82 weeks after the infusion. And as a general overview of the future of the immunological approaches, let me briefly comment this slide that summarizes the new design of the study for treating patients with B-cell precursor ALL, and you can observe that either during induction therapy, or during consolidation therapy, the three approaches that I mentioned so far, namely the use of an antibody drug conjugate, a bispecific T-cell engager, or CAR T-cells are integrated with the goal of trying to improve further the chance of rescuing these patients experiencing B-cell precursor ALL relapses. So, the take-home messages can be summarized as follow. In particular, leukemia recurrence remains the main cause of treatment failure in childhood ALL, although the chance of rescuing relapsed patients is increasing over time. Immunotherapy is changing the therapeutic scenario of relapsed refractory patients with childhood B-ALL. Several immunotherapy options are now available. Novel treatment-related toxicity mainly occurring within the first six weeks of the treatment have appeared, and future studies are warranted to more precisely define the role of the immunotherapy options also considering the standard of care

consolidation therapy represented by allogeneic stem cell transplant. You have certainly noticed that I didn't comment about patients with T-ALL, because unfortunately, so far, we don't have relevant immunotherapy options, and rescue strategy for children with relapsed T-ALL still represent an unmet medical need, and we have to work all together to develop a safe and effective treatment also for rescuing and salvaging children with T-ALL. This said, I'd like to thank again for the opportunity to present this data, and we can start the question-and-answer session. Thank you so much.

Prof Handgretinger: Thank you very much, Franco, for this very comprehensive overview, and also for presenting some of your own data, which you have already achieved in the hospital in Rome. And my first question would be, again, of course, the role of the blinatumomab in replacement of chemotherapy. Of course, this is our dream of the pediatric hematologist oncologist to give as less chemotherapy as possible, and not to compromise the outcome. So, where do you see further the role of blinatumomab in even getting blinatumomab more upfront? We talked about relapse therapy. Do you also see a role for a newly treatment, a newly diagnosed patient with ALL, B-ALL?

Dr Locatelli: So many thanks, Rupert, for raising this question. Indeed, the monoclonal antibodies now tested in frontline treatment. In particular, the IR-BFM cooperative group is running two randomized clinical trials in patients with either intermediate-risk, or high-risk B-ALL. In particular, the randomized patients in the intermediate-risk population is that of evaluating whether the addition of one course of immunotherapy before starting maintenance therapy can improve the final outcome, while in the high-risk population the randomized question is that of evaluating two courses of immunotherapy with blinatumomab in substitution of two cycles of intensive myelosuppressive therapy. And both studies have already recruited a good number of patients, and we will have the answer of these two important questions in the next month. And the results are an initiative for implementing the use of blinatumomab in the treatment of children with MLL rearrange, ALL diagnosed once under the age of one year, what we call infant ALL, because the outcome of this patient is still much worse than that of older children.

Prof Handgretinger: Thank you, Franco. Another question is of course not all patients respond to blinatumomab. You have shown the data, and are there any maybe things, other therapies we can add to the, or combine with the blinatumomab treatment? There are data out that maybe the checkpoint inhibitors might play a role in combination PDL. PD-L1 is up-regulated during blinatumomab treatment. So, are there any trials going on combining and making the blinatumomab more effective?

Dr Locatelli: That's another wonderful question indeed. The idea of combining checkpoint inhibitors, drugs, just to mention nivolumab pembrolizumab, agents like these, is a very promising approach for improving the efficacy of the bispecific T-cell engager, and it must be certainly acknowledged that you were a pioneer in this field demonstrating the efficacy of the approach for improving the response rate to the bispecific T-cell engager.

Prof Handgretinger: Thank you, and another question is, again, the role of CAR T-cells, or when to use CAR T-cells, now you have shown that it's possible now with new technologies to produce them on-site in a short timeframe, so, we don't have to wait two-three months until we get them. So, would it also be possible to move this therapy at the current knowledge stage also more frontline in relapse, or maybe even in primary treatment of high-risk patients to save chemotherapy? And maybe, a second later question, would it replace at some stage bone marrow transplantation? That's always the big question, of course.

Dr Locatelli: Thank you so much, again. Very important questions. In the order. In the slide that I presented on the IntReALL study design for the future protocol, the idea is that of using CAR T-cells in what we can call very high, really, very high-risk patients, namely those having some cytogenetic or molecular abnormalities predicting a very dismal outcome, mainly children with hyperdiploid translocation of 1, 19, patients with TP53. And we will test as academic community the approach of the automated strategy for using fresh CAR T-cell products to see whether they can be useful for improving the grim prognosis of these patients. There

is another important trial, which is now ongoing. It is called the CASSIOPEIA trial, and it is sponsored by the company that has the CAR T-cell product commercially approved, and it is testing the efficacy of CAR T-cells in patients with molecularly refractory disease, namely those children with a high-level of minimal residual disease at the end of consolidation therapy. The trial has already recruited a good number of patients, and it will be completed in the next month. The key question that you mentioned as well is whether CAR T-cell therapy can replace stem cell transplant. It's an important question to be carefully addressed in future prospective trials, also because now, stem cell transplantation in particular is performed after a total-body containing conditioning regimen can offer a very high chance of leukemia-free survival. Of course, we want to spare the side effects related to the transplant procedure, but we need well-designed trial before concluding that CAR T-cells can indeed substitute allogeneic stem cell transplant.

Prof Handgretinger: Thank you, Franco. Another question I have is in your trial, local trial, most of your patients had a relapse after transplant, and then you use of course the CAR, the T-cells from the patient after transplant. So, pseudo-allogenic, so-called, have you ever considered to use directly fresh donor CAR T-cells? This has been also reported on some conferences now. Even in the absence of graft-versus-host disease what is there the experience of fresh donor CAR T-cells now you are able to produce them on-site?

Dr Locatelli: So that's another important and very stimulating question. Indeed, at the very beginning there were concerns about the feasibility manufacturing CAR T-cells directly from the stem cell donor, because of the potential risk of inducing GVHD. But more recently, data are supporting this possibility. We have treated so far two patients with CAR T-cells generated directly from the donor after asking and obtaining the authorization from the Italian regulatory agency, and I have to say that both patients have responded, and neither of them experienced GVHD. So, that's another important opportunity that can be added to the spectrum of options for treating relapsed refractory B-ALL patients.

Prof Handgretinger: And in that context of maybe donor-derived CARs, or effector CAR T-cells, what's your thinking on CAR and K-cells, or other gamma-delta T CAR cells, which might not cause, or have the risk of graft-versus-host disease? Also, we haven't seen it, but then patient number is still low. We might see it at some stage with conventional CAR T-cells, but the other cells, NK, gamma-delta CARs, what's your take about that in the future?

Dr Locatelli: The beauty of this session is that of interacting with you, because you are proposing such exciting and stimulating questions, and this is another important one. CAR NK-cells can represent the future, very attractive strategy, because there is the possibility of generating an off-the-shelf third-party allogeneic current K-cell bank immediately available to be used for treating patients, and you very rightly underline that these cells are unable to induce GVHD, and they can represent an option for treating patients. So, my personal answer is yes, it's an important field of investigation. The colleagues of the MD Anderson published at the beginning of 2020 in the New England Journal of Medicine a seminal paper on the treatment of patients with the lymphoproliferative disorders with the CAR NK-cells with promising results.

Prof Handgretinger: And maybe, my last question, Franco, is the high incidence of CD19-negative relapses after the conventional causes of concern, of course. What other new approaches to circumvent this maybe, by other targets, or what's your take about in the look in the future?

Dr Locatelli: There are some studies demonstrating the efficacy of using CD22 as target for CAR T-cells. And this offers the rationale for either implementing the dual targeting approach, namely CAR construct, and simultaneously targeting CD19 and CD22, or for infusing two types of CAR T-cells, one targeting CD19, and the other CD22, exactly for counteracting the immunological escape of CD19-negativity. And that is an important field of investigation, and we will have more robust and consistent data in the next few years.

Prof Handgretinger: Okay, so thank you very much, Franco. It seems we still have a lot to do in the future in terms of research not only to improve the treatment of B-ALL, we are not at 100% where we want to be, but

also with patients with T-ALL, I think this is still a big problem, and we have to be maybe smarter than the T-ALL, but hopefully, the future will bring us new ideas and new approaches. And with that, I thank you for your talk, and also for the discussions. And I wish you all a good time for today, or for later today. Thank you.

Dr Locatelli: Thank you so much, Rupert. It has been a great pleasure and a privilege to have this dialogue with you, and thanks to all the people attending the session. Thank you.