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Principles of treatment of rhabdomyosarcoma

Prof Minard-Colin: I am very happy to present to you some slides on data on treatment of rhabdomyosarcoma in 2021, and I'm very honored to participate to this European School of Oncology online course. So, if we look at this figure on soft tissue tumors through the lifecycle, you know that the incidence of soft tissue sarcoma is really different along the life. About 60% of patients less than 18 years do have rhabdomyosarcoma, and about 40% in children and adolescents do have so-called other soft tissue sarcoma, non-rhabdo. But if you look more carefully, you would see that rhabdomyosarcoma have a bimodal incident. Why? For example, you observe some tumors with similar histology, such as fibrosarcoma but very different biology and varying when compared with adults. Another very nice example is synovial sarcoma. We have incidents through the adolescent and young adults but we report recently that you, even if you have the same fusion, you have different biology between the adults and the young ones. Anyway, about 60% of patients do have rhabdomyosarcoma at the pediatric age. And if we look at the general characteristic of pediatric type rhabdomyosarcoma, about 60% are boys. So, median age at diagnosis is around six years, but with a bimodal incidence. And we observe about five new case per year per million for children and adolescent less than 18 years. And if you look above 18 years in adult, it's about two per million per year, so, it's a very rare tumor. Of course, if we exclude a pleiomorphic rhabdo which we do not consider, and I would not talk about that histotype, I would just focus on so-called pediatric type of rhabdomyosarcoma. I really like this workshop we performed with our colleagues from North America and Europe on Paratesticular rhabdo. And you see very well this bimodal repartition, you have Paratesticular Rhabdo in the varying ones with a very good outcome. And Paratesticular Rhabdomyosarcoma in the older ones, adolescent, young adults and with more severe outcome even if this proliferation is very chemo-sensitive and highly curable. If we think about histology, I would not share with you so many slides. You know this proliferation in the rhabdomyosarcoma is a malignant proliferation of soft tissue cells from muscle origin, which are characterized by Desmin, and myogenic immunochemistry with some of their markers. There are different histology subtypes of such embryonal rhabdo with different subtypes, alveolar rhabdo, which is about 15 to 20% of rhabdomyosarcoma, and more frequent in adolescent and young adult. On some new subtypes, such as spindle cell, sclerosing rhabdo, about 5%, we will talk about that. Pleiomorphic rhabdo, about 1% at the pediatric age, with about 50% in the adult age. And there are some new entities, and I will share with you some of that. We very nicely showed in the 2010 years, that patients with rhabdomyosarcoma FOXO1+ disease, FOXO1 or FKHR fusion have an adverse outcome. They were called before alveolar rhabdo, some

were fusion positive on an adverse outcome. And some alveolar rhabdo are FOXO1 fusion negative with a very similar outcome when compared with embryonal rhabdo. Today, in 2021, we should make sure when we diagnose about alveolar rhabdo, to have FOXO1 fusion, even if some very rare cases of true alveolar rhabdo have variant fusion that do not implicate FOXO1. But we learn much more than FOXO1, and I will not have time to share with you some of these publications. We observed some new fusion. We had very nice work in rhabdomyosarcoma in infants, less than 6-months-old with a fusion variant with VGLL2, NCOA2 and very good outcome. Some others reported more aggressive cases with different grading, et cetera, et cetera. There are more fusions in some very specific epithelioid and spindle cell rhabdo, with TCFP2 fusion on ALK upregulation when we have at least one case of very nice response to ALK inhibition. So, you have really different fusions, new fusions, in addition to FOXO1, and we are more and more doing a so-called a rela-SEC analysis, with some clustering analysis that may also help to better stratify the disease. Today, we are really at the time in rhabdo to integrate biology for diagnostic, theranostic, but also prognostic purpose. So, if we think about etiology of rhabdomyosarcoma, in the vast majority of cases, about 90%, we don't know anything about the etiology, but we observe in some cases frequent association with malformations, especially, in the young ones, in the brain, or in the urinary organ. We know about some syndromes that may be associated with rhabdomyosarcoma incidents, such as neurofibromatosis, of course, PTCH mutations, and Rasopathies. We know more about genetic predisposition to cancer, such as Li Fraumeni Syndrome, with P53 germinal mutation on DICER1. I think it's important to think about any predisposition to rhabdo. If we observe some specific subtypes such as pleiomorphic or anaplastic rhabdo early in life that made us think about P53 germinal mutation. Of course, if you have different cancer, a family history of cancer or malformation, you have to think about predisposition. More importantly, if we think about late relapse, when we have discussions with our others colleagues, they do observe some patients with relapse 10, 15, 20 years after a first rhabdo in childhood. I would think we should consider second rhabdo. And we have to think about the predisposition syndromes, such as DICER1 mutation in gynecologic female rhabdo. The impact of the genetic testing is very important for family testing, of course, for follow-up, maybe for some therapeutic adaptation, if we have to think, when we have children with rhabdo and Li Fraumeni, if we may avoid radiation therapy but there are still some signs for new drugs introduction especially in some very specific rhabdo. I just want to share with you this very nice observation of this 19-years-old boy with a very rare subtype of rhabdo so-called epithelioid rhabdo. He had a large tumor in the limb, that did progress with some metastatic disease on chemotherapy. We performed biologic testing and observed MLH1 mutation, suggested of Lynch syndrome, and he had a complete response with more than four years of follow-up with nivolumab, pazopanib, plus radiation therapy. He is in complete remission, which is really nice. So, again, think about genetic testing. If we think about the clinical presentation, we know very well, about 40% of cases are in the head and neck area. About 30% are in the genital-urinary area. About 15%, and it's more frequent in young adults, are in the limbs, and about 15% may be anywhere in the body, from the head to the toe. It could be in the liver. It could be the wall. It can be in the pelvic outside of the bladder, et cetera, et cetera. So, the main principle of therapy treatment is that this tumor is highly chemo-sensitive. And if we compare these pediatric types, rhabdos, embryonal, alveolar, they are very chemo-sensitive. We use different molecules, such as alkylating agents, actinomycin, alkaloids, anthracycline, et cetera, et cetera. We used a lot of different combo of chemotherapy. I listed some here, but we never found any better combo since 1974, when the VAC, vincristine, actino, cyclophosphamide, has been developed, or IVA in Europe. Of course, at diagnosis, the surgery should be performed only if the tumor could be completely removed with microscopically clear margins and no mutilation. So, biopsy is crucial first. And if you think about the local therapy in rhabdo, it's very interesting because as always in sarcoma, it's really a multidisciplinary discussion. We have to think about surgery. We have to think about radiation therapy, of course. It could be external or brachytherapy. It has to be discussed at diagnosis and planned within the tumor, with MTB, with oncologists, radiologists, radiotherapists, brachy physicians, and in children, we have to take into consideration, of course, the activity on the tumor, but also, into consideration the long-term sequelae of therapy. This tumor is also very radio-sensitive, with about 45 to 55 Gy usually is delivered. It could be by EBRT, by proton, photon or brachytherapy

and, of course, if you think about the long-term effect, I didn't have too many pictures, we have to think about the age at radiation therapy, the radiotherapy field and the organ at risk, the site, the modality of the radiation therapy. And of course, a combination of surgery or chemotherapy plus radiation therapy. Very importantly, if we think about the long-term effect of the radiation therapy, we have to think at the end of puberty, because before, it's very difficult to evaluate the long-term effect of the radiation therapy. One very interesting technique for such rhabdomyosarcoma in the young ones, but also, in some older patients, it could be conservative surgery plus brachytherapy or brachytherapy alone for some vaginal rhabdo in children, adolescent and young adult. It is very well indicative and developed for bladder, prostate rhabdo in the young ones, for vaginal rhabdo, or for any wall disease such as very nicely shown in this picture. The main principle of therapy, especially, in prostate rhabdo, with bladder prostate rhabdo is to allow a microscopic residue perform additional brachytherapy to avoid erectile dysfunction. The brachytherapy tubes are posed during the surgical procedure, but I think something very important is to make sure about the expertise of the brachytherapy team on such a routine. We are in the... We just report our experience in Gustave Roussy, with patients everywhere in the world, coming everywhere in the world. About 305 patients have been tutelated in experienced, with more patients from the international recruitment the last year here in Gustave Roussy by our surgical and brachytherapy team. The five-year local control for patients with rhabdo is 92.4%, which is an outstanding local control for such disease. So, the general scheme of therapy, first, we perform a biopsy, initial surgery, again, it's very, very rare, only if complex and conservative. And I'll say, it mainly concerns para-testicular rhabdo. We may think about primary re-excision, especially for small tumors in the legs. Here, you see an example of rhabdo developed in the cervix with a large tumor, and we start chemotherapy. And at the end of four or six cycles, we just have a very small tumor that is remaining. Adapt the chemotherapy intensity to the prognostic factors, we discussed about that. And then, after four, six courses of chemotherapy, we consider local therapy that is always indicated except for some tumors, such as female genital tract, that can be cured for 40% of patients with chemotherapy only after biopsy. In the majority of cases, patient do have surgery, followed by radiation therapy with some adaptation in the young ones. And then, we perform additional chemotherapy after and during, after local therapy. The main prognostic factor for localized rhabdo are bio-pathologies, such as FOXO1 fusion. It could be also some additional biology markers that we didn't investigate very well in the international trials. But this is very important. I will share with you some data reported by a colleague from North America with MYOD1 mutation, P53 mutation and some new fusions I showed you before. The quality of the initial resection, the sites, some sites such as orbit, paratesticular, head and neck, non-parameningeal and bladder-prostate are considered today favorable sites with local therapy. That is, of course, difficult, and this needs an MTB discussion with a high-level of expertise, and some sites do have more difficult disease with more poor outcomes, such as head and neck, parameningeal rhabdo, limbs, or other sites. We have to work on these sites. Of course, there is a challenge with local therapy but also, we may think about a different biology. Nodes, of course, and size and age are additional prognostic factors. American colleagues very nicely reported in ASCO 2018, the adverse outcome in patients with MYOD1 mutations and rhabdomyosarcoma. The number of patients were quite small. We have the same experience, and I think it's very important to all share our data with MYOD1 mutation in rhabdo, and confirm that these patients do have poor outcome and discuss together how to develop new strategy for such disease. The question about P53 mutation that is very well known to be an adverse prognostic marker in a lot of cancers should also to be addressed, since our data are still very limited. We also work on some new fusions, such as pGL2 fusions and other variant fusions, especially in the new ones with some very good outcome for the majority of patients. So, in Europe, we do have an international collaboration within the European Soft Tissue Sarcoma group. So-called EPSSG. And we include all patients with rhabdomyosarcoma, aged from 0 to 21 years in the trial RMS 2005. The therapy was stratified according to the pathology, the quality of initial resection, the site, the nodal stage, and the size and age. If we look at event-free survival, in a large cohort of about 800 patients, the EFS is very well-stratified, based out on these different prognostic factors with patients with low risk rhabdo do have about 91% of EFS and 97% of overall survival, which is quite outstanding. By contrast, patients with alveolar rhabdo,

N1 disease do have only 40% of EFS and survival. We have now a new stratification, based on fusion status, FOXO1 fusion status, and we have some change for favorable sites, and we include patients with bladder-prostate, even if C site is a challenging site for local therapy, especially for the expertise of brachytherapy. That is here the new stratification. And if we think, if we look at the stratification, based mainly on FOXO1, instead of alveolar status, again, we stratify very well the disease. In RMS2005, in patients with high-risk rhabdo, so, patients with embryonal rhabdo in unfavorable sites with large tumor or adolescents, or patients with embryonal rhabdo and N1 disease, or patients with alveolar rhabdo, we did perform two randomizations. The first was to randomize IVA, so, ifosfamide, vincristine, actinomycin, and IVA plus doxorubicin. Of course, you know very well that doxorubicin was a major drug in the majority of sarcoma. The second randomization was a combination of maintenance therapy with low-dose cyclophosphamide plus vinorelbine for six months, and randomized to stop therapy after nine courses of chemotherapy. And then, the first question was IVA versus IVADO. There was no benefit of IVADO, since if we compared the event-free survival, there is no statistical difference, and this is the same in overall survival. But we observed, as expected, a larger toxicity and a higher toxicity on IVADO when compared with IVA. So, our standard in Europe is still IVA. The second question was maintenance therapy for six months versus standard, which was to stop of therapy after nine courses of IVA. And in this case, we observed in term of disease-free survival some benefit of the maintenance therapy, even if it was not statistically significant at the P-value of 00.5. But if we look at survival, overall survival, we observe a clear benefit of about 30% of gain of survival in the arm with maintenance therapy, and it was an HR ratio of 0.5, with a highly significant P-value. So, this trial was published in Lancet Oncology, in 2019, and it's a very nice collaboration in different countries in Europe, and this is the first positive trial with chemotherapy in rhabdo since 1974 when the VAC combination was developed in US. What happened in US in parallel? We have a very good collaboration and discussions with our American colleagues. They did randomize VAC as a standard, versus VAC plus vincristine topotecan and cyclophosphamide, and they didn't observe any benefit of VAC/VTC. They did randomize VAC versus VAC combined with vincristine irinotecan, with lower dose of cyclophosphamide. They didn't observe any benefit in VAC/VI, but less toxicity and less gonadic toxicity at long-term was, as expected, with VAC/VI, because of the lower dose of cyclophosphamide. So, the American colleagues, the standard backbone of chemo is VAC/VI, and they're now running a randomized trial, plus and minus temsirolimus, which is an mTOR inhibitor in rhabdo in high-risk new patients with high-risk rhabdo. I really hope we should have results of these randomized trials quite soon. So, here it was localized rhabdo. What do we know about metastatic rhabdo? We know that the prognostic is still, as all metastatic sarcoma, very poor. We know that this disease has a high chemo-sensitivity but very poor outcome, and I would say almost no progress since the '80s. We know very well the prognostic factors. It's worse in the old ones, in patients with metastases on the bone and the bone marrow, in patients with more than two sites, with two metastatic sites, with unfavorable sites, and FOXO1+ disease. The outcome and survival are less than 30%. And if you look at the score, so-called Oberlin score, Odile Oberlin was an outstanding pediatric oncologist. Patients with two or more adverse prognostic markers have less than 15% of survival. Our American colleague did perform very similar analysis, but in the modern era of FOXO1 fusion, and they confirmed the very poor outcome of metastatic rhabdo and even poorer, with an EFS of only 6% in patients with FOXO1 fusion positive. We performed different trials in metastatic rhabdo, and the first one that had been published a few years ago, is European trial with Roche collaboration, an ITCC collaboration. We randomized the standard, which is metastatic rhabdo IVADO IVA, plus or minus bevacizumab-Avastin, then, performed local therapy. And then, these patients did receive maintenance therapy for one year. However, we didn't observe any benefit in term of event-free survival in the arm with bevacizumab, when compared in the arm with chemotherapy only. That has been published in 2017 in European Journal of Cancer. In parallel, our American colleagues ran a trial with all drugs that are very active in rhabdomyosarcoma and a dose-dense chemotherapy backbone, with chemotherapy every two weeks. However, when we look at the research published in JCO, in patients with a few risk factors, but number of patients was quite limited. We may think that this patient has some gain with this very dose-dense chemotherapy backbone, but in patients with more than two ... two or more adverse prognostic factors,

about 66, we didn't observe any benefit. Of course, in new patients, less than 10-years-old with embryonal rhabdo, so-called good prognostic metastatic rhabdo, with an EFS about 50, 60% in previous trial, we may think about some benefit of this dose-dense chemotherapy backbone, also, it's not clear very well, because, again, the number of patients was quite limited. We hear about metastatic rhabdo. To finalize my discussion, I want to talk about relapse and refractory rhabdo. We ran a trial, so-called VIT. It was an international trial. The first one was a randomized phase II trial in European Center in EPSSG, with a collaboration with the ITCC Innovative Therapy Children with Cancer. When we compared by randomization the VIT combination with vincristine and irinotecan combination alone. This trial was sponsored by the Oscar Lambret Centre in Lille and the coordinating team investigator was Anne-Sophie Defachelles. The chemotherapy was, as shown here, with vincristine, temozolomide, irinotecan. So-called the VIT combination, compared with vincristine irinotecan alone. It has been reported in the ASCO 2019. Here is a progression-free survival. If you compare in adjusted hazard ratio, relapse versus refractory, locoregional versus metastatic, alveolar versus non-alveolar, you see some benefit; also, it didn't reach a P-value of 00.5 in the VIT arm, when compared with the VI-only arm. However, when we look at overall survival, we observe a clear benefit of VIT when compared with VI. So, the VIT combination, vincristine, irinotecan, temozolomide, is superior to VI, and this is a new standard of combination in Europe for relapse refractory patients with rhabdomyosarcoma. In parallel, our colleagues in North America run a trial, a phase II trial of bevacizumab. Remember, no benefit of bevacizumab in metastatic patients upfront in Europe or temsirolimus in combination with chemotherapy in first relapse rhabdomyosarcoma. They observed some benefit, and it was statistically significant in PFS in the arm with temsirolimus, when compared in the arm with bevacizumab. It is why they did select temsirolimus in first-line high-risk localized rhabdomyosarcoma patients. If we think about chemotherapy, I really feel that in rhabdo, we reached a level that we will not develop new combinations that may be more active in rhabdomyosarcoma. In localized disease, in metastatic disease, or even in relapse, again VIT is our standard in relapse. But the aim in the next year, is to be able to introduce targeted therapy, new therapy, instead of new chemotherapy in combination with VIT. So, I do not have so many times to discuss with you about recurrent alteration in rhabdomyosarcoma. Very importantly, there are different alterations if you compare alveolar FOXO1 rhabdo with a very potent driver, so-called FOXO1 fusion, on embryonal rhabdo with hedgehog pathway that drive the rhabdomyosarcoma initiation in FOXO1 fusion negative embryonal rhabdo. Our American colleagues just reported the prioritization of adjuncts for patients with rhabdo. And I think we do have exactly the same list of drugs that we really want to develop in this disease. Of course, DNA damage/repair, so such as PARP inhibitors. So, epigenetic target, mainly in embryonal FOXO1 negative disease. The immune target, and we have a lot of data that unfortunately report very limited activity in the vast majority of rhabdomyosarcoma or of anti-PD1, anti-PDL1. But we know that this disease do express B7-H3, so, we have to develop such therapy. Also, we have a regular alteration in FGR4, and we really want to develop also some tyrosine kinase inhibitors, and I will share with you some data after. Some very early proof of concept of CAR-T cell therapy in such disease, it has been reported by our American colleagues, from Baylor College Hospital. You know that patients with rhabdo do have, in some cases, HER2 positive disease. In these cases, these patients with metastatic rhabdo and HER2 positive disease, the did develop CAR-T cell therapy, targeted on HER2. They included patients with osteosarcoma, Ewing sarcoma, rhabdo and synovial sarcoma. And they report one patient with metastatic rhabdo on the complete remission in the bone marrow disease 24 months after first HER2 CAR-T cell infusion. Again, proof of concept of activity of some CAR in rhabdomyosarcoma disease. The next trial in rhabdo in Europe will be the FaR-RMS trial, a multi-arm, multi-stage, MAMS study, for children and adults with localized metastatic frontline and relapsed rhabdomyosarcoma. Overall, we expect to include 1,260 patients from the whole FaR-RMS trial, 800 in frontline, 400 in relapse. It has opened in UK first in 2020. Inclusion criteria are quite simple. All patients with rhabdo, except pleiomorphic rhabdo, which are more similar to high-grade sarcoma in adults, or age from birth with no limitation of age. So, very important to have our adult colleague with pediatric type rhabdo onboard, with some, of course, written informed consent, and medically fit to receive therapy. Here is the FaR-RMS design. With new agents that I really hope we'll be able to introduce in frontline in metastatic

patients, but also in relapse. And the good news is we will be able to add to VTI, vincristine irinotecan regorafenib, compared with a VIT combination, which is the standard in Europe. We also ask still some questions about chemotherapy backbone. We'll ask very important questions, especially in localized disease about pre- versus post-surgery radiation therapy and some dose escalation in patients with high-risk of local failure. We also ask about the maintenance therapy duration. As I showed you, we reported clear benefit of six months of maintenance therapy, and we'll compare with 12 months in localized high-risk disease. And we will randomize 12 versus 24 months in very high-risk metastatic disease. This design is very interesting because it's a multi-arm, multi-stage, MAMS design, that may allow to stop some combination with new agents or some new chemotherapy combination early, when, at the first look, we observed some futility, or even at second look. And then, we will go to phase III only if these different steps have been positively enriched. Thank you very much for your attention and I will be very happy to take any questions by e-mail, please. You have my e-mail address. I'm happy to discuss with you by phone or by e-mail. Thank you very much.