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Soft tissue tumors in childhood

Dr Ferrari: Hello everybody. Good evening. So, it is difficult to talk about soft tissue sarcoma, in childhood, in 30 minutes, especially because soft tissue sarcoma are a very large group of different tumors, with different biology, different clinical course, maybe, different treatment. And so, I'll try to do my best to focus on some specific aspects coming from my personal experience, from study where I was directly involved, when possible. So, this is the definition of soft tissue sarcoma, very heterogeneous group of more than 50 different histological subtypes classified on a histogenic basis according to the adult tumor they resemble; they account approximately for 4-5% of childhood cancers. And you can see here that around half of the cases are rhabdomyosarcoma, and other half of the cases are the so-called non-rhabdomyosarcomas, soft tissue sarcoma. And here, on the right part of the slide, you can see the specific characteristic of rhabdomyosarcoma and non-rhabdos. Rhabdomyosarcoma is a typical embryonal tumor of childhood, it is often, and it is always a high-grade tumor, so, high-grade of malignancy, local invasiveness, marked propensity to metastasize to the point that all rhabdomyosarcoma patients should be assumed to have micro-metastases at diagnosis, so, all the patients with rhabdomyosarcoma should be treated with chemotherapy regardless of the stage of the disease. But the good news is that this tumor generally is responsive to chemotherapy, 90% of response to chemotherapy and to radiotherapy. And in green you can see here, non-rhabdos, that's a completely different tumor, they are a rare tumor, most of these tumors are typically found in adults. There are a long list of very, extremely heterogeneous tumors and generally, they are considered to be scarcely responsive to chemotherapy. And this idea is to say that adult medical oncologists and pediatric oncologists do mean very different things when they talk about soft tissue sarcoma. You can see in this slide that the histotypes occurring in children, in green, are very different from the histotypes occurring in adolescents and young adults, and very different to those occurring in adults. In adults, we have liposarcoma, leiomyosarcoma, in children we have rhabdomyosarcoma. In adolescent and young adults, we have, for example, synovial sarcoma. So, it's important to understand that, sometimes, the experience but also, the attitude of adult medical oncology and pediatric oncology to this tumor are different for a reason. The second slide, the second figure tells us that the patient outcome is different according to the patient age. With survival rates drop when age increasing, you can see here, the outcome of pediatric patients is often better than the outcome of adult patients. I want to start with the Rhabdomyosarcoma, this slide is just to show you quite a recent review with a lot of discussion on the biology of the tumor, clinical aspect and treatment, and so, you can find these on PubMed, for example. And these are the four main key-aspects of the treatment, the management of Rhabdomyosarcoma. First, the centralization of care in very specialized centers and wide cooperation on national and international level that is strictly linked to the concept of high-rate of inclusion in cooperative multi-institutional clinical trials in order to collect a large number of the cases. This figure tells you that we are talking about a rare disease and you can see here, just an example, in red, German protocols, in green, Italian protocols, in blue, French and UK protocols, and you can see that these protocols merged in 2005, in the so-called EpSSG, we'll talk later, and in yellow, the North American protocol, and you can see the

number of the patients enrolled in randomized clinical trials starting from the '17, up to today. And this is just to say that we're talking, again, Rhabdomyosarcoma, very rare tumor, more than 10,000 patients were treated within randomized clinical trials, so, a huge number that characterized the attitude of pediatric oncology in general and in particular, of experts on soft tissue sarcoma, to work together and to include the patients in randomized clinical trials. The only way to really understand how to better treat our patients with this disease. And then, the concept of the high-rate of inclusion in clinical trials, this is a more recent study, we published within EpSSG, you can see just this number, it is the observed expected patient, that means the number of patients really enrolled in EpSSG trials and the number of patients expected to be seen according to the incidence rate. If we talk about Rhabdomyosarcoma, and if we talk about patients from 0 to 14-years-old, 77% of the patients, accrued in Europe, were enrolled in clinical trials, that's an incredible number of patients. And the other point is the concept of using a risk-adaptive treatment strategy, that means the idea to identify different prognostic factors, different variable, able to stratify the patients in order to give more intensive treatment for the patients with more risk of relapse, while to try to give less intensive therapy to avoiding over-treatment and containing side effects with the patients, with more favorable disease. And you can here, on the right part of the slide, the different prognostic factor, and so, factor related to the patients, the age of the patients, we know that patients less than 10-years-old have a better outcome compared to the patients of more than 10-years-old. Factor related to tumor, so, the histology, we know that embryonal tumors have a better outcome as compared to alveolar tumor; the size of the tumor, this is clear; the site of the tumor, because you can see here different tumor sites, paratesticular site, parameningeal site and tumor arising in the abdomen, a bladder and prostate tumor, a tumor in the limbs, and different sites have different prognoses. Paratesticular tumor or tumor of the orbit, or tumor of the vagina have a better outcome as compared to tumor of the limbs, for example, and then, of course, we have some factors that can be related to the treatment. That means the modality used in the treatment, if we treat our patient the best way, of course, the outcome may be better and the response to therapy. And according to this different variable, we were able over the years to identify a multi-disciplinary approach and a multi-variable stratification, and you can see here that it is the approach we used in the last EpSSG protocol, we'll come back later on this point, and you can see that we were able to identify eight different risk groups, eight to each, according to the histology, the stage of the disease, the nodal status, the tumor site, the tumor size, the patient age, and you can see that the outcome of the patient, the predicted outcome of the patient, changes according to the different risk group. And so, we will see how we treated these patients and how we treat these patients. And this is just to remember you can send the questions and if you have some burning questions on this point, on Rhabdomyosarcoma, please, you can interrupt me without any problem. And so, again, we are talking about this, this is the EpSSG, just to show you what are the countries involved in this very large group that includes more than 15 countries and more than 100 centers enrolling patients. And as I told you, patients with a favorable risk group, so, the so-called group-A, were treated just with a very mild chemotherapy, the combination of Vincristine and Actinomycin, so, no alkylating agents, very short treatment and outcome was excellent, with probably, really, less probability to have late sequelae in the future. Then, we have the standard treatment, the IVA treatment, we'll talk later about this, for the patients with an outcome between 80-85 and 90%. And I want to stay on this group of patients, the patients so-called to be at high-risk, the patients for which the protocol tried to intensify the treatment, with two randomized studies, to try to improve the survival. And these are the two randomized studies, we tried to discuss in the 2005 protocols. First randomization, the so-called anthracycline questions, the question was if a patient with rhabdomyosarcoma may benefit from a greater doxorubicin dose-intensity in the initial part of the treatment; and you can see here, the IVA, the IVA is the standard treatment that we use in Europe for more than 30, 40 years, that is a combination of ifosfamide, vincristine, and actinomycin, given for nine courses, and on the other side of the Atlantic, the treatment was very similar, instead of the IVA, we have the VAC that is exactly the same, with cyclophosphamide used instead of ifosfamide. While in the protocol, we tried to randomize patients to receive IVA, versus IVADo, that means the same regimen with addition of doxorubicin. We know that doxorubicin is effective in Rhabdomyosarcoma, but we did not know if adding

doxorubicin to the IVA regimen may really increase the outcome of our patients. And after the conclusion of the nine courses of chemotherapy, we have the second randomization, a very novel strategy. The idea was to stop the treatment, that was what we did before to stratify or to try to give a maintenance therapy after completing the conventional chemotherapy, so, a treatment that gives regular and frequent low-dose of drug with the idea to have a metronomic therapy, to try to have an anti-angiogenic effect, and it was based of two conceptive studies we developed in Milano, in Italy, with the use of Vinorelbine and the use of Vinorelbine combined with low-dose of Cyclophosphamide. And this is in some way the idea, to have a first randomization, IVA versus IVADo and the second randomization stop therapy versus maintenance question. And so, the result of our 2005 protocols, the first randomization, the addition of doxorubicin to IVA, you can see here the response rate, IVADo versus IVA and you can see here the two courses that were exactly the same. And so, the first randomization says that doxorubicin does not add any significant anti-rhabdomyosarcoma activity to the standard multi-drug regimen, the so-called IVA therapy. And what happened with the second randomization, stop therapy versus maintenance therapy? You can see the number of patients enrolled, 186 versus 185. And you can see here the course, it was an incredible success, the event-free survival, but in particular, the overall survival of the patients increased in the arm receiving the maintenance therapy from 73.7% to 86.5%. So, you can see that the P was statistically significant. So, this study demonstrated that adding maintenance treatment, with vinorelbine and low-dose of cyclophosphamide to patients with high-risk rhabdomyosarcoma in complete remission after the first nine courses of treatment was first, well-tolerated and second, improved survival. This was the first randomized study to demonstrate a survival benefit related to an experimental chemotherapy regimen in rhabdomyosarcoma over the past three decades. And this is just an example, a list of the different randomized studies performed by the Children Oncology Group, the North American group, that used to have a long list of historical studies to be compared to VAC. VAC was the standard treatment, and you can see VAC versus VAC plus doxorubicin and cisplatin. VAC versus VAC plus doxorubicin, cisplatin and etoposide. Or VAC plus IVA, or VAC plus VA, and then, the introducing of topotecan, and then, introducing of Irinotecan, and all these studies were exactly the same, not any of these alternative regimens increased the outcome of the patients as compared to those receiving VAC. And so, the result of our EpSSG maintenance trial was really considered a home-run Rhabdomyosarcoma after 30 years. You can see also how the mass media was really surprised for these results, and though, in some way, we can say the maintenance chemotherapy in rhabdomyosarcoma became the new standard of care. This was the standard of care before 2005 in Europe, nine courses of IVA and now, this is the standard of care, IVA plus six months of maintenance therapy. And then, the same for North American, the North America and France closed their study, the ongoing study, amended then to introduce the concept of maintenance therapy also in their treatment. It remained to be clarified of course if these great results were related to the effectiveness of the drug involved, in particular, vinorelbine, vinorelbine was the new drug we added to maintenance therapy or maybe, it could be simply the prolongation of the chemotherapy, cured a larger number of patients as compared to patients that completed the treatment. So, just related to the increase of the duration of the treatment, or both. And now, we're trying to understand what is the real reason for these great results. For example, this is our idea, in our Milan group, to try to use vinorelbine, that is our drug, we tried to really demonstrate if it is vinorelbine to be the real effective part of the maintenance therapy; the idea is to use vinorelbine not only in the maintenance, but to use in the advanced part of the treatment. And so, this is a concept that tries to introduce vinorelbine in the middle of the different IVA courses. So, on some way, to use a new drug, vinorelbine, and another way to give a more intensification of the treatment, a dose-density, to give an effective treatment in a period shorter than the usual three interval weeks. On the other side, we tried to understand if it is a problem of the prolongation of the therapy, and so, in the future protocol, this is just a schema, you don't have to understand about this, that in the future protocol, in Europe, we try to develop a randomization between six months of maintenance therapy versus 12 months in patients with localized high-risk disease, while in patients with metastatic disease, we try to randomize patient between 12 months versus 2 years of maintenance therapy. So, this is direction we are going after the results of the maintenance

therapy. So, again, if you have some questions, it's better to do, to ask some questions now if you want to do some questions about rhabdomyosarcoma and the EpSSG protocols, so, no problem to do...

Dr Attarbaschi: Andrea, may I ask you one question?

Dr Ferrari: Yes, of course.

Dr Attarbaschi: Concerning your talks to the scene randomization, was there any difference between alveolar and embryonal rhabdomyosarcoma? Taking doxorubicin or not?

Dr Ferrari: No. Not, because we tried to stratify the patients also according to the response of the treatment, because sometimes happened that, just, a promise, we treat in the same basket of rhabdomyosarcoma tumors that are probably different from a biological point of view, patients have alveolar rhabdomyosarcoma or as we call today, fusion positive rhabdomyosarcoma has a different biology as compared to patients with embryonal or fusion negative rhabdomyosarcoma. So, it's possible that a specific treatment, a given treatment may be effective in alveolar and not in embryonal rhabdomyosarcoma. So, the question is correct, but the results, the negative result of doxorubicin was exactly the same for embryonal or for alveolar rhabdomyosarcoma.

Dr Attarbaschi: Thank you.

Dr Ferrari: You're welcome. Other questions or comments?

Dr Attarbaschi: Not from the audience, no.

Dr Ferrari: Okay, while waiting, I'll go forward. And I've shown you some very good results, we discussed tumors that are 75%, 80%, 65%, but we were talking about patients with localized disease. The situation for rhabdomyosarcoma patients is completely different if we talk about patients with metastatic disease or patients that relapsed. So, patients with metastatic disease or relapsing tumor, remain patients with a poor outcome. So, you can see here a couple of cures, that suggest that we absolutely need to find novel treatment to increase the outcome of these patients. So, without the strategy we developed in the last years, this is the strategy used by the Children Oncology Group for metastatic disease, the concept of the dose-compression, to give full doses of chemotherapy administered not every three weeks, but every one or two weeks. So, as I showed you before for the IVA regimen, the intensification of the treatment to try to increase the dose-density. This trial demonstrates that this very intensive treatment is feasible, and it can be effective in some particular specific subsets of the patients, not for all metastatic patients. And this is to show that alternative ideas are ongoing using the concept of dose-compression, again the VIVA regimen, that gives vinorelbine in the middle of the different IVA courses; this is another strategy, again, an Italian study we recently published, to use irinotecan, that is an effective drug, we use irinotecan in Europe as first-line after relapse and the idea is to use irinotecan in front-line, in patients with a high-risk disease, and you can see the concept to give IVA in day one and two, and then, we'll have after three weeks, the second IVA course, and irinotecan is given during the second week of the treatment. The results of this part of study are very promising, but of course, we need to try to understand in a more large study if the IrIVA regimen may really increase the outcome of our patients. And the next EpSSG protocol will use the IrIVA regimen as part of their treatment strategy. Then, of course, the concept to try to have a new drug, a new drug that can be added to the classic IVAC or VAC regimen. And this for example is a study we developed with bevacizumab; it was the so-called BERNIE protocols. Metastatic patients with rhabdomyosarcoma and also with some specific non-rhabdomyosarcoma, soft tissue sarcoma. The patients received the IVADo treatment, the one we consider our standard in metastatic patients in Europe, while half of the patients received IVADo, half of the patients received IVADo plus bevacizumab and, unfortunately, the outcome was exactly the same, to say that bevacizumab was a good idea, try to have a target therapy, anti-VEGF therapy for our patients, that are currently not increased. This is another concept to have a new chemotherapy drug, temozolomide, this is a

treatment we used for a patient at relapse in Europe, vincristine and irinotecan, as I told you before, was our standard therapy at relapse; we tried to randomize patients to receiving vincristine and irinotecan with, with or without temozolomide, while the patients receiving VIT regimen, vincristine irinotecan and temozolomide, have a clearly better outcome as compared to the patients receiving VI only. So, the idea is that today, our standard treatment at relapse is VIT and not only VI. And then, of course, the idea to look to target therapy, to a new agent, a novel agent, and these are the results of the treatment schema in the North American Group with mTOR inhibitor and the concept is that mTOR inhibitor may be seen as a new drug that can in some way improve the outcome of the patients. A look into biologies of fundamental importance, for many, many reasons. Of course, for diagnosis, to try to have diagnostic biomarkers. Of course, to have prognostic biomarkers, to identify according to the different biology of a tumor high-risk and low-risk patients, but in particular, to try to identify target and clinically relevant novel agents, and to combine them in the future with the standard chemotherapy. It's just the figure to show the possible pathway. And this is the list of possible target therapy we can use. One of... just to, one of the targets we are focusing on our group is the potential role of regorafenib. Again, do you have some questions?

Dr Attarbaschi: Yes, Andrea, there are, there are...

Dr Ferrari: Exactly, because... Then, we will go to non-rhabdo. Okay, perfect.

Dr Attarbaschi: From a colleague, the first question is dealing with the importance of age in metastatic rhabdomyosarcoma, something we know very well, but you may comment?

Dr Ferrari: Yes, of course, we said we don't have time for talking about everything but when I show you the very poor curve of metastatic patients, around 20% of overall survival, there are also some curves that demonstrate that not all metastatic patients are the same. We know that the clinical factor used to be important in patients with localized disease, it may be important also in patients with metastatic disease. And so, age is one of the factors. If you have a metastatic patient with age less than 10, with only metastasis at the lung, for example, with embryonal rhabdomyosarcoma, we know that the overall survival may be around 45-50%, quite close to the outcome observed in patients with localized disease, while, on the contrary, if we have patients of 18-years-old with alveolar rhabdomyosarcoma with metastasis not only in the lung but also, in the bone, for example, in the bone rhabdomyo the outcome is close to 0. So, age is one of the factors we can use also to stratify patients in metastatic setting.

Dr Attarbaschi: And the second question is would you consider temozolomide as a drug which could make the tumor more sensitive to radiotherapy?

Dr Ferrari: I believe yes, not totally sure. I think that it can be used also to have a radio-sensitization of the tumors.

Dr Attarbaschi: Thank you.

Dr Ferrari: Other comments on rhabdo? Otherwise, I will pass on the second part of my talk, talking about non-rhabdos. Okay.

Dr Attarbaschi: Yes, thank you, no questions, 15 minutes left.

Dr Ferrari: Okay. I told you before, non-rhabdo are rare tumors, most of the tumors are entities typically found in adults, extremely heterogeneous. Scarcely sensitive to chemotherapy. This is just to show the heterogeneity of the tumor is related to the different histology, synovial sarcoma, liposarcoma, leiomyosarcoma, epithelioid sarcoma and so on, to the different biology, because we know today that the CT molecular finding on the different isotype we can have, you can see this table, you can see them, the table with more time after the conclusion of the presentation, but we know the different characteristics of the different tumors and different biology, the different clinical aspects, again, tumor arising in the limbs or in

the abdomen or in the lung, and also, different outcome. Because under the umbrella of non-rhabdo, under this definition we have patients with this outcome and patients with this completely different outcome. And I like to remember that in the past non-rhabdo were considered quite awful diseases, we have very few trials, just a couple of trials from North America with a few patients enrolled and the largest reported series of pediatric non-rhabdo before 2005 were two single institutional experiences, they were from St. Jude and the other one from our centers. And the major problem was that, at least in Europe, we often treat non-rhabdo patients, according to the rhabdomyosarcoma protocols and the different tumor entities were put together in different studies, in different analyses, for example, including together in the same group, truly malignant tumors or soft tissue with intermediate malignancies. And the situation changed at 2005 because in the North American group and in the EpSSG group we started quite in the same times two trials completely dedicated to non-rhabdo. And these two trials were very, very similar in term of the rationale, patient stratification, treatment programs and beside they were very recently published and represent the benchmark for this tumor and defining a risk adaptive treatment as standard of care. And now, we can also... the second generation of North American trials, that it was the first trial in cooperation with adults that can use also a target therapy. And this is the EpSSG trial, as I said, I would talk about our experience. The EpSSG 2005 trial dedicated to non-rhabdo included two prospective non-randomized historically-controlled trials, one of synovial sarcoma and the other on the so-called adult-type of tissue sarcoma and we gave a very precise definition of adult types of tissue sarcoma to separate this tumor from this tumor, the so-called other histotypes from which we provided just guideline, and you can see here, infantile fibrosarcoma, excellent outcome. Desmoplastic small round cell tumors, a completely different outcome, but also, a completely different biology and clinical history as compared to other subtypes and then, other tumors like the malignant ectomesenchymoma, epithelioid hemangioendothelioma or a tumor like desmoid-type fibromatosis and inflammatory myofibroblastic tumors, extracranial rhabdo tumor and so on. And in the last years the EpSSG published the different series for the different histotype, try to understand that it's better to analyze histotype by histotype, and you can find this in literature, and this is just to show how the outcome and the response to therapy for example was completely different in these different tumor types. And I want to use my residual time to talk about this last publication, 2021, that was in some way the analysis of the whole non-rhabdo EpSSG series, this is the diagram of the number of patients we enrolled, the number of patients excluded, because they had a different histology. The number of patients excluded because they had the so-called other category, you can see, as I said, infantile fibrosarcoma, desmoid tumors, rhabdoid tumors, and so on. Patients with missing data and then, the patients we analyzed. 569 patients, some were synovial sarcoma, some were adult type non-rhabdo, here, you can see the different history, and the different histotypes included to say that for some histotypes the number of the patients was really very small, 19 alveolar soft part sarcoma, 13 angiosarcoma, 17 clear cell sarcoma and so on. And we differentiated the patients according to the treatment category. This is the treatment category we have, according to the clinical variable that was the NRS-group, that means the resectability of the tumor of one, two and three according if the patients were resectable or not at the diagnosis. The tumor sites, less or more than five-centimeter, the tumor grade and for synovial sarcoma, also, the tumor site, because we know that synovial sarcoma may rise in the access site, and they may have a completely different outcome compared to the tumor of the limb. And according to this category, patients were treated with surgery alone, patients treated with adjuvant radiotherapy alone, patients that received adjuvant chemotherapy after initial resection, and patients with unresected tumor that received neoadjuvant chemotherapy. And this is just to briefly show the general outcome of our series and the outcome according to the different risk group. And these are in some way the conclusion of our trials. The study demonstrated that adjuvant chemotherapy and radiotherapy can be safely omitted in low-risk non-rhabdo. You can see here the blue curve is excellent outcome with surgery only. The chance to investigate in the role of adjuvant chemotherapy in patients resected at diagnosis was very limited because of the limited number of the sample. Our study however confirmed that despite the global good prognosis of resected non-rhabdo, patients with a high-grade and large tumors remained at risk of metastatic spread, and then, patients with resected cases, we demonstrated that neoadjuvant ifosfamide-doxorubicin

chemotherapy improved the resectability rate compared to previous studies and got better results compared to the past. So, I believe I've a few minutes, if I'm able to survive, so, again, these are the lists of challenges for non-rhabdo that we have to face for the future. Very briefly, to find a way to improve the outcome for patients with high-risk, to better use the standard therapy we have, the combination of ifosfamide and doxorubicin, and the idea is to have a better patient selection according to the prognostic variable, in order to give chemotherapy to the patients at major risk of metastatic spread. According to the histology, patients that have more probability to respond to chemotherapy, alveolar soft part sarcoma, clear cell sarcoma, rarely respond to chemotherapy, while synovial sarcoma has a better response to chemotherapy, but also, today, according to tumor biology. We understand that for example the genomic index can be a predicting variable that can in some way suggest if the patient may respond or not to chemotherapy. As I said, the idea to study non-rhabdo together or single histotype by singe histotype remain important because we have very few cases for some specific subtypes. There are patients with adolescent and young adults; these are exactly the same study I showed you before for rhabdomyosarcoma, but if we talk about non-rhabdo, if we talk about adolescents, you can see here that only less than 20% of the patients recover in Europe with a non-rhabdo in an adolescent group were enrolled in our protocols. So, we need to find a way to enroll AYA in our group. This means better cooperation with the adult sarcoma community, pull our resources together and create international cooperation. Developing biological studies because we need the new biomarkers to improve risk stratification, but also, to novel therapies, and this is just to show you what would be the next EpSSG protocol for the future, a protocol that is called MYCKIDS. This mainly focuses on the biology of the tumor more than on the treatment. The concept to the access to new drugs, because there are a lot of new drugs coming in from the world of adult sarcoma, but we know also that the access to new drugs for children and adolescent may be more difficult as compared to adults and the impact of target agents in the pediatric population has not parallel progress seen in adult patients. We have many barriers, but the best way is to try to better cooperate with adult experts. And also, if we will be able to have target therapy, we need to understand how to use this target therapy, just a few examples, we know for example that, in infantile fibrosarcoma, together, the inhibitor of NTRK may have a wonderful efficacy in this tumor, but we know also that this tumor, infantile fibrosarcoma, has an excellent outcome, more than 95% of the patients survive at five years. With just very mild vincristine and actinomycin chemotherapy. So, here we have a new drug, but we don't know if we want to use it instead of chemotherapy or only after relapse. Or the same in inflammatory myofibroblastic tumor, the rule of ALK inhibitor, for example, or for example the use of tyrosine kinase inhibitors in the treatment of pediatric desmoid-type tumor, two tumors of intermediate malignancy that have very good outcome without target therapy, how we can use target therapies... So, many, many... And I suppose this was my slide. Short and clear take-home message. What I can say? A lot of things, a lot of different tumors, a lot of trials, my message may be that only with the cooperative, multi-institutional work together we can really improve the outcome of the patients and only with real experts of the disease we can really try to change the outcome of these heterogeneous difficult patients. Thank you and sorry for the time I spent with...

Dr Attarbaschi: Thank you, Andrea, for this great insight into rhabdomyosarcoma and non-rhabdomyosarcoma of tissue tumors. I think we have time for two or three questions. One question from the audience is, what is your experience with the treatment of triton tumors, I think it's a subtype of malignant peripheral nervous tumors, could you comment on that?

Dr Ferrari: It's a difficult question because what is triton tumor is difficult to say, probably, we now consider triton tumor a tumor that is part of MPNST, that means malignant peripheral nerve sheath tumor, it's a tumor that responds not so well to chemotherapy, for example, but also with a rhabdomyosarcoma differentiation and what we think today is to treat the triton tumor as rhabdomyosarcoma because it's the most aggressive part and probably the part that may have more probability to respond to chemotherapy. I'm not totally sure that it is really the solution for the question. Today, we treat triton tumor as rhabdos, but we know that we need a new drug, and new strategy.

Dr Attarbaschi: Thank you. Perhaps, I can ask the next question, due to the length of time you could not comment on the role of surgery, what I'm personally very much interested in is what is your opinion on mutilating operations after main courses of chemotherapy if there is a significant residual tumor, before starting oral continuation therapy?

Dr Ferrari: Surgery is a critical part of the treatment for rhabdo and for non-rhabdo, more than for non-rhabdo, if I can say. I believe that today in the new era of the treatment for rhabdomyosarcoma, that remains a tumor that can receive different level of effective chemotherapy, that can receive radiotherapy, it is difficult to propose motivating surgery in front-line. A different issue at relapse, but to be honest, after the nine-course of chemotherapy, thinking to mutilating surgery is probably too much. The only situation may be when you have very small children that cannot receive radiotherapy, although, I can imagine a child of one-year-old with a very huge rhabdomyosarcoma of the limb that do not respond to chemotherapy. Otherwise, I would leave mutilating surgery for example at relapse, not as first part of the treatment.

Dr Attarbaschi: I was thinking of tumors of the bladder when you have for example really an embryonal rhabdomyosarcoma with a significant residual in the bladder after chemotherapy and radiation.

Dr Ferrari: Sorry, I run down to the concept of amputation and not mutilating in the term of, yes, bladder and prostate tumor is a big problem and I believe that there are more situations when this kind of surgery may be acceptable. Again, I'm thinking of small children, two-years-old, three-years-old, we know that giving radiotherapy may be probably a cause of severe future sequelae more than a mutilating surgery on the bladder. And we know that, today, in the future for the child, when they grow up, we can have a good way to reconstruct the bladder and so on. In this case, mutilating surgery may be of course an option that you can consider, yes.

Dr Attarbaschi: Thank you, Andrea. I think if there are no more questions left in the audience, I would really like to thank you for your time, I know that you're very, very busy with different things at your institution. But it was all the pleasure for me, personally, to listen to your talk and yes.

Dr Ferrari: I was able to rub the hands. So, that's the best thing for me, sorry gain.

Dr Attarbaschi: Thanks a lot. And I wish all a very nice evening and hope to see people from the audience again at the next session, which is advertised here now on the next slide. But the whole program of the ESO Pediatric Oncology pathway is also visible on the website of ESO. So, have a nice evening, bye, bye! Ciao.

Dr Ferrari: Thank you, goodbye, to everybody.

Dr Attarbaschi: Ciao, Andrea.

Dr Ferrari: Ciao!