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The medical therapy of STS

Prof Casali: Good morning. Today, I will talk about the principles of medical treatment of soft tissue sarcomas. I will not focus in this lesson on very rare sarcomas, which would be the subject of another lesson. These are my disclosures. I would like to start a lesson on the medical therapy of soft tissue sarcomas, saying that when you have isolated pulmonary metastasis, the standard treatment could be surgery, and not medical therapy. This is something which applies to several tumors, certainly several sarcomas and it is something that dates back to many years ago. The idea is to approach these patients or a proportion of these patients with surgery, with the aim of curing a small fraction of them, and then, being ready to do again surgery. So, with the so-called iterative surgery of lung metastasis of sarcomas. Of course, as long as you've gone, the objective of cure will probably not apply, but you can even ... You can still compare the benefits of surgery versus the benefit of chemotherapy, in practice, in prolonging the progression-free interval of your patients. Of course, in any case, there would be the decision to make, whether to do surgery or chemotherapy. In any case, recalling that the main objective of surgery of lung metastasis, which is a cure, applies, of course, to those patients who have isolated lung metastasis, those who have resectable lung metastasis, those who have relatively good prognostic factors. So, the problem might be whether to do surgery or chemotherapy, but also whether to add chemotherapy to surgery. Generally, we prefer to use chemotherapy before surgery in these cases, at least because in this way, it's apparent whether the tumor is responsive to chemotherapy, not so much to cytoreduce lung lesions, which probably will be operable or not operable. And this would not be changed by chemotherapy, because it's not just a technical issue. It's also a conceptual issue, whether to do surgery in a given case, but possibly a response to chemotherapy may help choose surgery even in some doubtful cases. The prognostic factors are the usual ones. So, the free interval before metastasis and the number of metastases. And so, you understand very well that, when these prognostic factors are not that good, one may well choose to add chemotherapy to surgery. But in essence, the aim of surgery is clearly to cure a fraction of patients. And you may also believe that chemotherapy might help, but we don't have any proof of this. But also, that clearly, I mean, surgery may prolong the progression-free interval, and chemotherapy may help surgery do so. But again, we have not saw any proof of this. So, this is one of the areas of treatment strategy of advanced soft tissue sarcomas in which actually we lack evidence. And so, the decision is too much subjective, unfortunately. This said, and coming to the medical therapy, in the introductory lesson I already recall the histological complexity of soft tissue sarcomas. They are a variegated group of diseases of several dozens of different histologies, and this is a problem, but it's also an opportunity.

I must say that years ago, for example, when Adriamycin was developed, in this paper, the authors split sarcomas into their histologies. Then, there has been a trend in the years afterwards to merge all soft tissue sarcomas together. And the idea was that grading was very important in soft tissue sarcomas. But then, histologies were much less important, at least as far as the medical therapy was concerned. And so, for example, this trial on temozolomide which means dacarbazine in the end was viewed as a negative one. Also, there were some responses and all of them had to do with leiomyosarcoma. So, if you don't split histologies you may miss something. In other words, you may miss an opportunity. They said, as of today, Adriamycin is the main drug, the most active drug in a sense, especially, across all sarcomas. However, the response frequency is low, is in the 15, 20% range. The duration of response is lower than one year generally. The median survival is in the one-two year range. There may be a tail of all these cures, the advanced disease, but in any case, the proportion of long-term survivals is low. So, this picture is quite pessimistic, clearly, about medical therapy of soft tissue sarcomas, and still, some sarcoma experts tend to see doxorubicin alone as the standard medical therapy, the standard first-line medical therapy for soft tissue sarcomas. The other drug which is active across most of them is ifosfamide, with a somewhat lower response frequency, probably, a slightly lower activity, but in essence, it may be even compared to doxorubicin. So, the problem is, and was or has been whether to resort to Doxorubicin alone, or to Doxorubicin plus ifosfamide, so, the combination in the advanced soft tissue sarcoma. So, this has been a long-lasting question, in the sarcoma ... In the medical oncologist sarcoma community. There were several trials. Last one is this, by the EORTC. So, a full dose combination of both drugs versus doxorubicin alone. And these were the results, which pointed to some benefit in progression-free survival. But this benefit is in the range of a few months, if you look at the median progression-free survival, and no convincing survival benefit was demonstrated. The response rate was a little higher, by a difference of 10%. On the other side, in this editorial, an expert like Bob Benjamin said that this trial provided convincing evidence that dose intensive doxorubicin plus ifosfamide was superior to doxorubicin alone. The sarcoma community is somewhat split about this, but I would prefer to say that, yes, clearly response is a potential surrogate endpoint, and you should look at survival and quality of life as the natural endpoints of phase III trials. But it's also true that there has always been a gap between phase II and phase III trials in advanced soft tissue sarcomas with better results in phase II. Clearly, this may be viewed as a selection bias, but also, the other way around. The selection bias might affect the population of larger phase III trials. And in any case, the problem remains, and what about the patients selected to enter phase II studies? Secondly, yes, clearly, you should validate responses to surrogate and this is not easy, but on the other hand, this patient was inoperable because of the site of his lesion, and as a response to chemotherapy and becomes operable. I mean, do you really think that, clinically speaking, response for this patient was not a surrogate for survival? Meaning at least a higher probability of surviving or being cured of this sarcoma? So, the decision may be made differently across institutions, but when you have a fit patient with some reasons why you may believe that a response might change something in terms of survival or quality of life in the individual case, I think that doxorubicin plus ifosfamide may be a reasonable choice. Of course, the toxicity is different. Myelosuppression with growth factors, wherever is tolerable in fit patients, of course. And so, for example, at our institution, many patients receive the combination. Then, when you go to the further-line chemotherapy, the ultimate problem might be whether to do a chemotherapy or not. So, whether to do just the best supportive care, but if the decision is to do a chemotherapy, that chemotherapy, that medical therapy will have to be somewhat histology-driven, much more than the first line. I must say that we generally do several lines of medical therapy in several soft tissue sarcoma patients, because there are several drugs available, and if they are used with a histology-driven approach, you might exploit them and achieve something, we believe in the individual patient who will get back to this point afterwards. But just to tell you, the drugs which are available, which are somewhat standard. One of them is trabectedin, which is a Marine-derived drug. It's a strange drug, which were shown to provide a benefit in further-line therapy, especially of patients with liposarcoma or leiomyosarcoma. And then, gemcitabine is an acute drug. Here, it was compared with gemcitabine plus docetaxel, with a benefit. However, gemcitabine and docetaxel certainly are not a substitute for a first-line of doxorubicin. Secondly, gemcitabine is more active in some

histologies, in particular leiomyosarcoma, angiosarcoma, possibly epitheloid sarcomas. But I mean, selected histologies. So, the idea of using extensively gemcitabine plus docetaxel is questionable I think, and docetaxel, on the other hand, is active only in angiosarcoma or soft tissue sarcomas. So, combining two drugs, one of which is active only in some histologies, and the other one only in one histology, which is very rare. you must really believe in a synergy between the two drugs, which is doubtful, and I will get back to this afterwards. While on the contrary, combining gemcitabine with dacarbazine in leiomyosarcoma may mean a lot, because both drugs are active in leiomyosarcoma. Then, we have pazopanib, which is an anti-angiogenic, which in non-adipogenic soft tissue sarcoma, further-line therapy, showed some benefit again over a few months in terms of medium progression-free survival, in comparison to placebo, with no survival benefit. But again, with some histologies are more sensitive during leiomyosarcoma, synovial sarcoma and others. And then, the last drug is eribulin, which was tested in liposarcoma, in leiomyosarcoma. But in the sub group of liposarcoma showed a significant survival benefit. And so, it's now used as further-line therapy in liposarcomas. Liposarcoma is the main histology, most common histology in soft tissue sarcoma. And for example, you may have high dose ifosfamide given as a continuous infusion, which may provide a convincing benefit. I'm talking about 14 days continuous infusion of 14 grams square meter of ifosfamide plus mesna. And this modality was shown retrospectively to be useful in well-differentiated, dedifferentiated liposarcomas. As you know, in particular, retroperitoneal liposarcoma fall in this category. By the way, drug like trabectedin may be possibly more active in well-differentiated, rather than less differentiated, dedifferentiated liposarcomas, and this may be somewhat the opposite as ifosfamide. Ifosfamide tends to be more active in less differentiated, dedifferentiated lipo, while trabectedin may be more active in more differentiated dedifferentiated lipo. Sorry for this wording, but this is a problem, because by definition, clearly dedifferentiate liposarcomas are dedifferentiated. So, they are at least G2 sarcomas. But you may find that a gradient in the differentiation of the dedifferentiated component. And this might be relevant to some extent also for the medical choices. You see here the long response to trabectedin of a probably more differentiated lipo, and here a patient didn't respond to standard dose ifosfamide plus epirubicin. On the contrary, responded to continuous infusion. Ifosfamide and again, a response to continuous infusion ifosfamide. You see the less differentiated component responds more than the better differentiated component. So, you may have patients who are responding to doxorubicin plus ifosfamide, to continuous infusion ifosfamide, to trabectedin in a different way. This said, I already recall eribulin in liposarcomas with a survival benefit, even more than a progression-free benefit and above all, more than a response benefit. And so, this drug may be used across the subgroups of liposarcomas. However, myxoid liposarcoma is a chromosomal translocation-related soft tissue sarcoma, so, it is completely different biology from well-dedifferentiated liposarcomas. And trabectedin in these patients has a comparatively, completely different pattern of response, especially, a higher response frequency, a longer progression-free. Some responses are really excellent. You may have a non-dimensional response at the beginning, but these are responses. So, this records patterns of response which we are used to in molecular targeted therapies. And probably, the mechanism of action of trabectedin in myxoid liposarcoma is different from the essentially alkylating mechanism that it displays in the other soft tissue sarcomas. In practice, involves some gene targeting related to the fusion task, which is typical of myxoid lipos, inducing an adipogenic differentiation, but also, exerting the kind of anti-angiogenic effect. So, the mechanism of action of trabectedin is certainly complex and may differ across histologies, even across sarcomas. Leiomyosarcoma is generally a more aggressive disease. You already recalled dacarbazine in leiomyosarcoma. Temozolomide if you want. While on the contrary, ifosfamide retrospectively seems to be less active in leiomyosarcoma, such that our first-line therapy is generally doxorubicin plus dacarbazine in spite of doxorubicin plus ifosfamide in leiomyosarcomas. And here, you see that doxorubicin plus dacarbazine seems really better than doxorubicin plus ifosfamide in leiomyosarcoma. This is a retrospective review, of course, with the problems of retrospective reviews, but it's quite convincing. Gemcitabine alone is active in leiomyosarcoma, and I already recalled the problem of whether to combine it with docetaxel. Some experts are convinced, we are much less, even because there have been conflicting trials, and gemcitabine alone clearly has a completely different tolerability profile. And

as I said, the gemcitabine plus dacarbazine maybe probably a more convincing option in leiomyosarcoma. I already recalled pazopanib saying that leiomyosarcoma is among the histologies in which it is active, maybe with patterns of response, which may be indicative of targeted agents. When I talk of leiomyosarcomas, I also include uterine leiomyosarcomas, which it's true that they may have a different biology to some extent than somatic leiomyosarcomas, but on the other side, the drugs which are active in uterine leiomyosarcoma are the same which are active in somatic leiomyosarcomas. Trabectedin is effective in leiomyosarcoma, as I showed before also in uterine leiomyosarcomas. As I said, pazopanib again. I mentioned uterine leiomyosarcomas, but I would like to recall here that uterine sarcomas include endometrial stromal sarcomas, in addition to uterine leiomyosarcomas. And the typical endometrial stromal sarcomas are receptor positive low-grade tumors, which may respond very well to progestins or aromatase inhibitors. And they may respond for long. They are a low-grade disease, with a low aggressiveness also in the metastatic phase. Their risk of giving metastasis is somewhat high, in spite of being low-grade tumors, but they may be controlled for longer with hormonal therapies, and also, clearly surgery of lung metastasis may be used liberally. Of course, I am talking about anecdotal evidence of hormonal therapy, but we are talking of a very rare subgroup, which is linked to a chromosomal translocation, which however is different from the chromosomal translocations of high-grade endometrial stromal sarcomas. And so, we should distinguish low-grade from high grade endometrial stromal sarcoma, because they are biologically different, and because clearly high grade endometrial stromal sarcomas are high grade tumors which don't respond to hormonal manipulation. They may respond to chemotherapy. They are much more aggressive, and all the more undifferentiated endometrial sarcomas are even more aggressive. They have a complex karyotype, so, again, a different biology, but also a high degree of aggressiveness. Clearly one may choose the standard regimens for high grade soft tissue sarcomas for these patients. These rare uterine sarcomas. We must make a clear distinction between these three groups and leiomyosarcomas, which are the fourth group. Then, we have also adenosarcomas, which are somewhat like low-grade endometrial stromal sarcomas, unless they become high-grade sarcomas when they have a sarcomatous overgrowth. Synovial sarcoma is an important histology. It's rarer than lipo and leiomyosarcomas, but it's important also, because it may affect young adults or even children. Ifosfamide is very effective in synovial sarcomas, like doxorubicin, of course. And in general, chemotherapy tends to be more active in synovial sarcomas, in comparison to many other histologies within the soft tissue sarcoma family. Also, trabectedin may have some activity in synovial sarcomas and definitely pazopanib. I would like to recall here a completely different subgroup, which is desmoid fibromatosis, which are tumors which may affect young patients, especially female patients. And they are a very strange disease. They may be as abdominal, abdominal desmoid fibromatosis, so, to the abdominal wall, this is the least aggressive form. The intra-abdominal desmoid fibromatosis is the mesenteric fibromatosis, is often more aggressive, and more able to imply complications for the compression, of course, so, intestinal obstructions, bleeding and so on. And then, you have the important group of extra abdominal fibromatosis, which tends to be a significant problem for the quality of life of these patients. The big joints are affected. This within a group of tumors which are, in a sense, benign because they never metastasize. So, you have a disease which doesn't give rise to metastasis, so, doesn't imply all the problems of malignant tumors. All the problems are related to the local growth of the disease. However, it's a very strange disease, because you may have a proportion of spontaneous regression, so, the course of disease is variable, with long intervals with no activity. Sometimes, the disease may become active, may become symptomatic, and may give rise to pain. It may create big problems. In a sense, surgery is not easy, it's often followed by a local relapse. And also, the surgical trauma might be relevant possibly for the tumor growth. And so, the front-line approach to most of these patients is active surveillance. Watching the evolution, the spontaneous evolution of the disease across months, and you may have stable disease or even regressions, so, sparing surgery. In case of progression, you may also resort to the medical therapy. This is the reason why I'm talking about this. So, of course, with the problem that it may be difficult to do studies, because you have these spontaneous regressions. But you may have several drugs available from non-steroidal anti-inflammatory agents, to anti-estrogens, then, low dose chemotherapy with methotrexate and vinblastine or now vinorelbine. But you must go ahead with

therapy for long intervals, for one year or so, in order to achieve something. It is active also in the familial adenomatosis polyposis-related desmoid tumors, because desmoids, due to the pathogenesis of the disease, they may also occur within FAP syndrome. Also, vinblastine, vinorelbine, and methotrexate may be useful of course in children, but also in adults, if you go ahead for sufficiently long. But also, conventional chemotherapy and other therapies may be active. Even sorafenib was shown to be active. And you see here, in a placebo-controlled study, you see the spontaneous regressions. The response rate is 20% response rate also in the non-therapy arm. Of course, sorafenib is not being developed in sarcomas. Pazopanib has been and so, pazopanib may be used, in spite of sorafenib. Generally, we have an approach, which goes from the least aggressive medical therapies to the more aggressive ones, in order to spare toxicity, not necessarily you may be willing to have the best response frequency possible in the beginning, as long as you can spare toxicity. This said, immune therapy was probably used for the first time with this Coley's toxin, several years ago, at the Memorial Sloan Kettering, and probably TNF was involved. And you may find TNF approved today as a therapy to be used however in a selected indication which is the isolation perfusion of soft tissue sarcomas of limbs. TNF really makes the difference in this approach, which is a perfusion. Is active only within the limb. But it might be useful in those few cases in which you might have to choose an amputation, and perfusion may allow you to avoid it. But aside from this, checkpoint inhibitors are not that active in soft tissue sarcomas. Also, this phase II study of pembrolizumab across many sarcoma histologies showed something, at least in some histologies, particular undifferentiated pleomorphic sarcomas, or poorly differentiated or dedifferentiated liposarcomas, with some responses which have been also somewhat lasting. On the other side, you have selected histologies, very rare histologies, like alveolar soft part sarcomas, in which we have seen something much more convincing with checkpoint inhibitors. So, clear cell sarcomas, angiosarcomas. I'm talking of very rare sarcomas, and they will be covered in another lesson. But for example, in this study, yes, you have selected rare histologies within soft tissue sarcomas, in which something more convincing was seen with checkpoint inhibitors. And with a pattern of response which is typical of checkpoint inhibitors, so they are effective. Of course, sarcomas, soft tissue sarcoma are a variegated family. If you think, for example, of the mutation alone, inevitably, it's completely different across histologies. I recall that some histologies are related to the chromosomal translocation, so, the karyotype is very simple, but any other sarcomas, like, for example, undifferentiated pleomorphic sarcomas have a complex karyotype. Probably, the microenvironment of soft tissue sarcomas is a little bit immunosuppressive. We don't have so many patients with something like microsatellite instability and the like. We have on the other side the expression of cancer testis antigens in some soft tissue sarcomas, in particular synovial sarcoma and myxoid liposarcoma. And indeed, there have been convincing demonstrations now, and ongoing studies on adoptive therapy, with engineered genetically modified cells in synovial sarcoma and myxoid lipo. Then, there is a rationale to combine checkpoint inhibitors with TKIs, with anti-angiogenics, and you have ongoing studies, and some preliminary evidence about the combination in some soft tissue sarcomas. But in particular, histologies in which, for example, anti-angiogenics may be active even alone. And so, it's different. It's left to be seen if the difference you see is due to the fact which you see is due to the combination of the checkpoint inhibitor and the anti-angiogenic, or to the anti-angiogenic alone. And so, it's not easy to study immune therapy in soft tissue sarcomas, basically because of their histological variegated nature. So, in principle, you should look at immune therapy within each of the soft tissue sarcoma histologies in a group of rare cancers. So, clearly, this is very difficult. On the other side, it's true that in the beginning I said, some are doubtful about how much to go to the single histologies, how big benefit that might be observed actually in the single histologies, but and clearly, this is a difficulty for clinical trials. But, for example, this retrospective observational series of French soft tissue sarcoma patients showed that that the survival of leiomyosarcoma is higher than other histologies. And I mean, while the number of drugs, for example, available in an undifferentiated pleomorphic sarcoma is quite limited, on the contrary in leiomyosarcoma you may have several drugs available also as maintenance therapy for some. So, it's difficult not to believe that this difference in survival was observed also thanks to medical therapies which, however, when studied as single agents in a single study, generally, didn't provide so many survival differences. But you may understand that what may make the difference for

survival is the step-wise use of these drugs. So, no study on a single line may see a difference. You should do a study comparing all these lines versus nothing, which of course, would be very unethical, and so, completely unfeasible, but probably, you should do something like that in order to demonstrate the survival benefit. So, the argument that many of these drugs were not shown to be effective in terms of survival may be questionable for this reason. At the end with chemotherapy, which is active, but not so much, at least not so much as in other cancers, in which adjuvant chemotherapy is used, you may wonder what about adjuvant chemotherapy. Whether to use it or not in localized soft tissue sarcomas as an adjuvant or neoadjuvant therapy. I must tell you that there have been a lot of trials, several meta-analyses, and you see this meta-analysis of many trials, which were, most of them, used inappropriate regimens, at least viewed today. In any case, some benefit for doxorubicin plus ifosfamide was seen overall in kind of 9-10% benefit in this meta-analysis of all randomized studies. But the problem is that some studies have been really negative, and they were the big studies. On the other hand, the Italian Sarcoma Group did this study several years ago. The study was interrupted early because of this difference in favor of adjuvant chemotherapy. Five cycles of epirubicin plus ifosfamide, full dose regimen. Unfortunately, it was closed too early. Then, the differences became a little bit lower and statistical significance was lost, but not so much if you want. The study had some problems, by the way. So, the decision was made to place chemotherapy, this regimen, preoperatively, taking into account the difficulties of localized soft tissue sarcomas. Sometimes radiation therapy must be placed before surgery for several good reasons. And so, we did a study comparing five cycles with three cycles, but three cycles were placed preoperatively, and there was no difference. And the curves overlapped the curve of the previous trial. So, this was interesting. Of course, we are talking about a proper neoadjuvant therapy, in which the first aim is clearly survival. So, we are not talking of inoperable sarcomas, in which the aim is cytoreduction, in order to achieve resectability, for example, conservative resectability, if the amputation be the choice. We are talking about properly neoadjuvant therapy, so, not a cytoreductive therapy. So, these are all operable patients. Doing chemotherapy, possibly with radiation therapy in several of these patients before surgery, with a benefit which clearly may affect also the local control, and indeed, that this was seen benefit in terms of local control for some patients with... were more problematic from the surgical point of view, even though surgery was feasible. So, we decided to go ahead, comparing this full dose epidoxorubicin plus ifosfamide regimen for three cycles preoperatively with a histology-driven approach, without doxorubicin. To our surprise, to some extent, we saw a benefit in favor of the epidoxorubicin plus ifosfamide regimen in comparison to the histology-driven approach. This doesn't mean that the histology-driven chemotherapy is not effective. We are talking about a choice which deliberately was made to avoid the doxorubicin in this arm. Basically, we interpret these results by saying that doxorubicin is still very important as an adjuvant. But also, a difference is a difference, and so a difference ... All the more, a difference versus another chemotherapy. So, in a sense, confirming the first trial of the Italian Sarcoma Group. So, to some extent, a proof of efficacy of neoadjuvant chemotherapy for three cycles. The final analysis, unfortunately, was basically ... the trend was absolutely the same, but the survival, the disease- free survival difference was lower. There was a survival difference, however. But above all, when we split our population between those patients who had a high risk, because we did our studies in a high-risk population, but the risk was lower than 40%. And those patients in whom the risk was higher than 40%, in the latter group, we saw a convincing difference. And we are comparing one chemotherapy with another chemotherapy. And also, important, I think, is that when we got back to the EORTC trial, which was that negative trial which I recalled at the beginning, and saying that the existence of big trials which were completely negative clearly was a problem. When we went to re-analyze the study, splitting between more or less the same two populations, so, a population with a high risk of relapse and a population with a low risk of relapse, we saw that indeed a difference was in place also in that study. Clearly, we are talking of an unplanned retrospective analysis, subgroup analysis, which was unplanned in a big trial, but clearly, these two results seem to confirm one another. And so, currently, if you use a nomogram, for example, to estimate the risk of relapse of your patient, we produced this circulator app, based on our series, and you have a risk, which is higher than 40%, we believe that share the clinical decision can be made with your patient to do chemotherapy. For example,

if the risk is 70%, assuming the relative risk reduction of 15%, you might have an absolute risk reduction of 10%. And so, clearly, not a big difference if you want, but definitely a difference which justifies chemotherapy in several tumors. The decision can be made on an individualized basis to do chemotherapy, possibly neoadjuvant chemotherapy, probably to maximize the benefit and also to get some benefit also at the local level, sharing the decision with your patient, because clearly, we still don't have definitive proof of efficacy of adjuvant chemotherapy or neoadjuvant chemotherapy. But we have, I would say, convincing evidence, and there is a wide consensus in the sarcoma community that there is convincing evidence of some benefit, at least. This said, I recall the need to refer these patients to expert centers, because expert centers may make some difference. And this difference may be like or even higher than the differences you may see with some medical therapies. Referring to expert centers today means more and more referring to networks. Networks are very important. I recall the European reference networks in Europe, Euracan for sarcomas and other rare adult solid cancers. Of course, I recall the guidelines, the clinical practice guidelines, the ESMO Euracan clinical practice guidelines. Now, the last edition is published now in 2021. Again, as ESMO Euracan Genturis clinical practice guidelines, with a joint effort between ESMO and the European Reference Networks. But following guidelines is not enough. You need an expert multidisciplinary panel made up of experts of a rare group of tumors which are somewhat complex because of their histologies, variegated histologies, because they arise everywhere in the body and so on. It's important to follow the state-of-the-art, but it's important also to implement state-of-the-art recommendations within an expert multidisciplinary panel, as you can find in expert centers, and in healthcare networks, focusing on sarcomas. Thank you. information on the type of cancer.