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Rare and ultrarare soft tissue and bone sarcomas

Prof Casali: Hello everybody. This lesson will be about rare and ultrarare subgroups within soft tissue and bone sarcomas. These are my disclosures. In this lesson I will touch some rare sarcomas therefore, and this means some rare and ultrarare subgroups within a family of rare cancers. This is important to stress. And I will mention those aspects, which may make these tumors deviate from the general principles of medical therapy of tissue sarcomas which I recall in my other lesson. I will also touch a couple of ultrarare bone sarcomas. Let's start from angiosarcoma, which is rare a subgroup, not ultrarare. Its sensitivity profile overlaps the spectrum of medical therapy in soft tissue sarcomas but that goes somewhat beyond. So, the drug is sensitive to Doxorubicin, of course, it's sensitive to Ifosfamide including a high dose Ifosfamide but it's also sensitive to Gemcitabine like leiomyosarcoma in particular. It's also sensitive to taxanes even to low dose weekly taxanes and this way it's actually the only subgroup in soft tissue sarcomas, which is sensitive to taxanes. So, the more, it may be sensitive to Gemtax, we may have doubts over the superiority of Gemtax over gem alone in leiomyosarcoma but clearly if they intent is tumor response or if you are in, I mean, however in a setting in which maximizing the benefit from therapy is important, the Gemtax clearly combines two drugs which are even alone active in angiosarcoma. It is also sensitive to anti-angiogenics like pazopanib which is the only anti-angiogenic to be approved for soft tissue sarcomas at the moment. So, in practice, the problem with the medical therapy of angiosarcoma is that its sensitivity spectrum is wider. The response frequency is higher on average than the other tissue sarcomas but the duration of response may be limited. Angiosarcoma has an aggressive histology. Of course, there are cases in which the duration of response may be long and in particular being available such drugs that one can use them sequentially in order to maximize their benefit. Even though, one by one, they may become resistant to such an aggressive histology. On the completely other side of the spectrum epithelioid haemangioendothelioma is a vascular ultrarare subgroup of low-grade malignances. They may present as unifocal lesions to soft tissues but also to other organs, in particular the lungs, the liver and the bone. And they may also present as multifocal within a single organ or as a multi-organ disease which may be labeled as metastatic clearly but in such a low-grade disease the impression is something like a systemic disease affecting several organs. And the, I mean, the disease evolution may well be the evolution of a low-grade malignancy in spite of extension. So, this is a very important concept and surgery is the standard treatment, of course, for limited disease. It may be questionable what is limited disease within a multifocal organ-based disease, but even more important active surveillance should be the choice in the asymptomatic patients and in medical therapy would be needed, of

course, in progressive cases. Unfortunately, we don't have so much at the moment. And unfortunately, the conventional chemotherapy for sarcomas is basically ineffective or so. There are signs of activity of Sirolimus, so mTOR inhibitors in progressive epithelioid haemangioendothelioma. But clearly, we would need much more medical therapy with this disease, which may well go very well in spite of its extension in a substantial proportion of these patients even without any therapy, I mean, but clearly, in another proportion would require medical therapy. Particularly, there are some cases in which, for example, there is a pleural effusion, patient is highly asymptomatic in which the disease may follow a much more aggressive course. Indeed, this is a really variegated disease, very different presentations, as I have mentioned. And it's also followed by several specialists depending on the different primary site. Sometimes, the clinical approach to the disease has been described amongst them. So, an effort was made recently to let some of the specialists, this ultrarare disease in the ward, talk with each-other and this is the consensus paper resulting from this effort, which sets what we know and what we don't know and the time being with such a complex disease. Solitary fibrous tumor is not an ultrarare tumor among the soft tissue sarcomas, it's an important histology now. Sometimes, it's called hemangiopericytoma especially for meningeal primaries, can present as the classical malignant forms often with a benign course for the classic forms. Then there is a prognostic score. There are some prognostic scores at the moment which try to provide the risk of relapse of these tumors. Then there is a dedifferentiated solitary fibrous tumor which basically behaves as a high-grade sarcoma. By the way, distant relapse of the classic and malignant forms may come even after a while, after several years. This disease is responsive to chemotherapy, used in soft tissue sarcomas, including the dacarbazine and possibly trabectedin. But also, anti-angiogenics maybe especially active, among them sunitinib but also others. By the way, they must not necessarily be active the same way. So, you may have a response also after failure of another of them. You know pazopanib is the only anti-angiogenic approved in soft tissue sarcomas. And it was proven to be active in solitary fibrous tumors as well. Alveolar soft part sarcoma is another soft tissue sarcoma in which anti-angiogenics may be active. This is an ultrarare sarcoma marked by chromosomal translocation activating met. It is a low-grade sarcoma which indeed is often an indolent disease. But the risk of metastasis is high in spite of this, even though with possible indolent behavior also the metastatic disease. And by the way, one of the few sarcomas which may metastasize to the brain. It is typically refractory to chemotherapy. But as I said it was shown to respond to several anti-angiogenics which may also be active one after resistance to another, so, that they can be used sequentially thus impacting on survival. So, the natural history of the disease is such that a response maybe all the more beneficial. So, with long-lasting responses in a disease which may not necessarily be that aggressive. By the way, as I said in the other lesson, alveolar soft part sarcoma, is one of the few soft tissue sarcomas in which there have been clear signs of activity of checkpoint inhibitors, and clearly, studies are ongoing. Another histology, again, a translocation related sarcoma, is extraskeletal myxoid chondrosarcoma which is an intermediate low-grade sarcoma if you want, in the sense that it may relapse but relapses may take place after a while. And it is sensitive to chemotherapy. It's reasonably sensitive, I mean, as a soft tissue sarcoma but it's also sensitive to anti-angiogenics, like sunitinib and also pazopanib. Possibly with a gradient of sensitivity depending on the kind of transcript, but this is work in progress. Another highly peculiar translocation related sarcoma is inflammatory myofibroblastic tumor, which is generally treated with surgery being of an indolent and rarely metastasizing disease, but which kind of occasionally requires medical therapy due to its extent, its spread, also due to its location to primary sites which may be very challenging from the surgical point of view. And the big opportunities that a proportion of these tumors are ALK-rearranged, the range of 50-60%, so that the anti-ALK drugs may work in ALK-rearranged inflammatory myofibroblastic tumors. So, this was the CREATE study, which proves this very clearly. By the way the disease may be responsive to anthracyclines as well but also, to low-dose chemotherapy, such as methotrexate vinorelbine, as used for example in desmoids and anecdotally even to steroids or non-steroidal anti-inflammatory agents, by the way. While some inflammatory myofibroblastic tumors may have an NTRK-rearrangement and can respond to NTRK-inhibitors. Clearly there are some sarcomas which show an NTRK-rearrangement, but they are not so many, they are a small proportion but it seems that there are some peculiar subgroups which tentatively are defined

currently and practically rearrange the spindle cell neoplasms. And that, of course, it's left to see how much they not only responded to NTRK-inhibitors but also, make up a tumor entity. I believe that a tumor entity in some way should correspond to a peculiar natural history or in any case some clinical characteristics which may parallel a biomolecular marker or in any case a phenotype, even a molecular phenotype, of course. So, in any case, as I said, there is a small proportion of sarcomas, which aside from these, which would be marked by an NTRK-rearrangement. And so clearly, would be obvious candidate for NTRK-inhibitors. There is, also, there is a small proportion of soft tissue sarcomas which are even an NTRK-rearrangement. And so, they may benefit from the activity in a histologically agnostic way of NTRK inhibitors which have been approved in a histological agnostic way. By the way, one shouldn't forget that infantile fibrosarcoma is marked by an NTRK-rearrangement that clearly has a completely peculiar natural history. So, it's clearly a tumor entity and these tumors are clearly responsive to NTRK-inhibitors. Dermatofibrosarcoma is rare, not an ultrarare sarcoma, again, it's a translocation related soft tissue sarcoma, with a fusion transcript leads to an over expression of PDGF beta driving the pathogenesis of this tumor. And so, this histology is clearly sensitive to imatinib PDGF receptor beta inhibitor, which displays a high response frequency. So basically, this is a, in most cases, this is a surgical disease which must be cured by means of appropriate surgeon. There are instances, however, in which a medical therapy can be useful because the tumor relapses or because the tumor becomes locally advanced, which may also give rise to metastasis and the medical therapy, may help the surgeon in several ways, not necessarily to shrink the tumor because of the surgical margins then, probably, will not be able to be so much improved by tumor shrinkage in a disease which typically is a locally challenging, may be locally challenging. But in any case, the medical therapy may help in some cases, even indirectly, time is useful. By the way, one should distinguish the typical dermatofibrosarcoma from the fibrosarcomatose dermatofibrosarcoma, where imatinib is still active but the duration of response may well be short. Okay. Then, I would like to recall another subset, which are malignant PEComas so, the perivascular epithelial cell tumors which display both a melanocytic and smooth muscle differentiation. They belong to a family of tumors and even malignant PEComas like lymphangioleiomyomatosis, in a more clear-cut way, they have some disruption of their mTOR pathway. And so, they may benefit from mTOR inhibitors. In this retrospective analysis, this is a retrospective international analysis of these rare tumors, the response frequently was 40% so. much higher than with chemotherapy fortunately, or even anti-angiogenics. And there is a subgroup of patients with possibly long-lasting responses. So, studies on mTOR inhibitors, even new ones, are ongoing at the moment. Tenosynovial giant cell tumor, diffuse-type is a group of benign conditions. These tumors typically originate from the synovial of joint, of tendon sheath, they tend to have a slow growth over years, most are localized and typically affect the hands and the fingers, are often cured by surgery, of course, but in a proportion of cases may relapse over years. And this is truer for the diffuse-type tumors which have a diffuse pattern of growths which can be intra-articular or peri-articular or even to those tissues. And sometimes, the clinical implications and the implications of the quality of life of these patients may be substantial, as you can understand. So, in practice, these tumors may have a high relapse risk. They may become not amenable anymore to surgery or at least to conservative surgery. Fortunately, the tumor is marked by, again, a chromosomal translocation which leads the neoplastic cells of this tumor to activate... at the macrophage colony stimulating factor 1 and thereby recruiting mononuclear phagocytes which...are CSF1 positive. So, which have the receptor for CSF1. And this is the mechanism by which these tumors' masses, these tumors' lesions go up. So, is a non-neoplastic component which is important. And clearly, for this reason, the tumor is sensitive to drugs like imatinib which may inhibit the CSF1 receptor. Also, there are new drugs available and which have been proved, for example, in this phase III randomized trial in such a rare disease, this trial tested Pexidartinib. So, it's a small molecule, which has a selective activity against CSF1 receptor. So, that in these patients may have some substantial quality of life issues, even though is a benign disease theoretically may benefit from a medical therapy. The giant cell tumor of bone, sometimes called osteoclastoma, was called osteoclastoma, it's a completely different disease. Is a locally aggressive bone tumor. Has a low potential of metastasizing, so, it's a kind of borderline tumor. Even though in all that high-grade sarcoma may grow up in a classical giant cell tumor of bone. And even possibly after radiation therapy

sometimes; other times, there may be a differential diagnosis between the giant cell tumor of bone and some osteosarcomas, which may be rich in giant cells. So, one should pay attention to a poor guidance of the diagnosis. This tumor typically affects the end of the long bone. Possibly the axis of skeletal. And in giant cell tumor bone, the neoplastic cells express the RANKL ligand which gives rise to the accumulation of non-neoplastic cells which are giant osteoclastic-alike multinucleate cells. And clearly, denosumab may display novels therapeutic effect, this being the also genetic mechanism which leads to the growing of the lesions and the maintenance of the lesions. So, denosumab has been studied in patients with giant cell tumor of bone. This was a multicentered, open-label phase II study, big study, which proved that the treatment with denosumab is highly effective in most cases. And it may be useful in two senses. I mean, it controls the disease, improving the quality of life of patients unamenable to surgery or metastatic patients who are not amenable to surgery or lung metastases or otherwise the medical treatment may help surgery. Clearly the treatment doesn't target the neoplastic cells. So, it needs to be a chronic therapy without surgery; if stopped the disease grows again. Histologically the responses in terms of a big lesion of the giant cells along with substantial formation of bone. Clearly, the challenging issue may be how to best explain these tumors' responses from the surgical point of view, if possible. This is a method for a multidisciplinary team work which may be challenging sometimes. And also, for some kind of patient-physician shared decision making. Treatment is well-tolerated but one should pay attention to the risk of the osteonecrosis of the jaw. This needs to be checked during a chronic treatment. Okay. In general, I like to stress that settings like tenosynovial giant cell tumors, so, giant cell tumor of bone, first ones to be treated with inhibitors, so CFS1 receptor, second one with denosumab, are, in a sense, ideal conditions for the targeted therapy, because, you know very well, that the limiting factor of targeted therapies is secondary resistance due to the genomic instability of the tumor. And the more malignant the tumor is, of course, the most likely there will be a selection of clones resistant to the targeted therapy under a chronic targeted treatment. Okay. These tumors being low-grade have much less genomic instability. And so, tumor responses, at least, may be much longer. They're less likely to be back of secondary resistance but of course, one should look at long interval and then a secondary resistance may happen all the same. So, these treatments cannot substitute for surgery when surgery is feasible; they may help surgery. Clearly, there is a problem for non-conservative surgical indications. As I said this is a matter of multi-disciplinary decision-making and shared decision-making, of course. I'm going to bone tumors, to rare bone tumors. Chordomas are low-grade malignancies, which have a notochordal differentiation. And so, have a dual mesenchymal and epithelial phenotype. They are low-grade malignancies which typically affect the sacrum and the skull base, but clearly cannot also grow on the spinal cord. I mean, the rest of the spinal cord. They are marked by the expression of brachyury. They're low-grade malignancies, but, first of all, there are two kinds of chordomas, which are different, they are dedifferentiated chordomas, which are biphasic tumors with a high-grade sarcomatose component. May also curve after radiation therapy, but in any case, it's a high-grade sarcoma. And then there are the poorly differentiated chordomas which are high-grade notochordal neoplasms which are more typical of children. Okay. Both have much worse prognosis than conventional chordomas but also, conventional chordomas has a prognosis which, first of all, must be looked at on the long run. So, even after complete surgery, one should look at relapses after several years, even after more than 10 years. And secondly, these are diseases which may give rise to metastasis. This was not completely known even in the recent past but as many as one third of chordoma patients they become metastatic, all the more, the bulk the disease, clinically speaking, is the local diseases. These patients happen to die of locoregional disease. And again, we tried to build the consensus on chordomas some years ago with this position paper which you may look at trying to set the state of the art of what we know, not only about treatments, but also, about the diseases itself. And surgery is the standard treatment, of course. Clearly relapses may take place easily, obviously, because of the extent of these tumors, but also because of the primary location, the primary site. So, clearly surgery faces obvious problems in the skull base, but also in the in the sacrum for chordomas arising above S3 and the quality of life, impairment, after surgery may be substantial, depending on visceral organs resected, with fecal incontinence and neurological bladder is a possible consequence, also motor sensitive neurological limb

problems. So, this is the reason why radiation therapy has been resorted to substitute for surgery trying to maximize the dose while sparing of the normal structure, which is not easy both in thei skull base and in the sacrum. And this is the reason why proton beam radiation therapy or carbon-ion radiation therapy has been used and is routinely used as possible because clearly all the physical advantages of hadrons in this difficult location, so for such a difficult tumor. In any case there is a substantial proportion of chordoma patients in whom a medical therapy would be very useful at least. And some years ago, we proved that imatinib maybe active, unfortunately, chemotherapy is poorly active though dedifferentiated chordoma, they respond to conventional sarcoma chemotherapy being high-grade sarcomas to some extent. Among cytotoxic one may use cisplatin, even low-dose weekly cisplatin, but clearly the results are limited. Targeted therapy was very interesting and is very interesting. Imatinib has some activity, may give rise not to tumor shrinkage in general, but to some clear radiological signs, so the tumor response, so, like targeted therapy we do and here, you see how many drugs are indeed being used over the years within the molecular targeted therapy area to try to treat chordoma from the medical point of view. So, both imatinib, anti-angiogenic, EGFR-inhibitors, even considering this dual phenotype of chordomas and the results with some of these molecular targeted therapies have been quite encouraging in a disease, by the way, in which natural history may be quite bland. And so, any medical therapy should be started in case of progression, of course, not in a non-progressing setting, of course. So, you see, in addition to imatinib anti-angiogenics, like sorafenib, or pazopanib and sunitinib, and also EGFR inhibitors like lapatinib or even others which are currently subject of studies. What immune therapy seems to be interesting in chordoma, was the study on a brachyury vaccine was negative unfortunately. So, in conclusion, I would like to give you a general comment on this, because I talked about rare and ultrarare soft tissue and bone sarcomas. We made an attempt recently to better define what an ultrarare soft tissue and bone sarcoma may be. And there was a consensus process, which finally set the threshold around 0.1 per 100,000 each year. So, an incidence threshold which is lower by more than a factor-10; then, the threshold which was to define rare cancer is such, you know, it's a 6 per 100,000 per year. So, was this definition, which is quite conservative, you see here that 20% of sarcomas also soft tissue and bone sarcomas are ultrarare. I think the ultrarare concept is important not because ultrarare cancers are a different problem than rare cancers from the point of view of the organization of healthcare because clearly healthcare is problematic when the tumor is rare; but ultrarare tumors add to this, also, additional problems in terms of knowledge generation. So, in terms of quality of evidence. And so, I think that in terms of quantity of evidence the distinction between ultrarare cancers and less rare cancers as though they are still rare, may be useful because, clearly, this variegated composition of sarcomas, maybe viewed as a weakness and it is a weakness because they are so rare that we find it difficult to generate new evidence. But on the other side, if we miss this variegated composition of sarcomas, in soft tissue sarcomas, we might well say that doxorubicin alone is the standard treatment for all soft tissue sarcomas. I hope that in this course we've been able to show to you that this is not the case, provided you are able to consider this variegated composition of sarcomas not as a weakness, but as an added value because you will have in the end, biologically speaking, you will have inevitably so many biological mechanisms which can be targeted. Okay. Of course, this means a lot of problems also on the methodology of the research and clearly regulator implications, and, in fact, when that paper was published on the methodology of clinical research in rare cancers, we discussed its recommendations also with regulatory bodies, because clearly this means that these patients may not have access to new agents even though these new agents may be available just because they have an ultrarare cancer. And the problem in the end is an ethical problem because unless we accept a higher degree of uncertainty in rare cancers in general, but all the more in ultrarare cancers, unless we do this, these patients will be discriminated against. So, I mean that it's not just a research issue. So, of course, it's a clinical issue for all those who try to take care of sarcoma patients. Clearly all this is not easy but it is an ethical problem. Because, as I said, especially in the case of ultrarare cancers and sarcomas, the risk is discriminated against some of our patients just because of the extreme rarity of their condition. Thank you.