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Osteosarcoma (held in collaboration with SIOPe)

Dr Kager: So, good evening. Unfortunately, I have to give this talk today because Stefan Bielack who should have given this talk, is at the moment sick. So, I hope very much that Stefan will give the next lecture on high-grade osteosarcoma. So, I will focus on younger patients with high-grade osteosarcoma, the Pediatric Cohort and the AYA Cohort. And in this cohorts, we mainly have the conventional subtypes, the osteoblastic, condroblastic or fibroblastic subtypes, and the so-called telangiectatic subtype; secondary osteosarcomas and high-grade surface, and then Small cell osteosarcomas are rather rare in this cohort. So, I will discuss with you some aspects on the etiology, the therapy and biology of high-grade osteosarcoma. So, osteosarcoma, as you know, is typically a disease of the young, very young patients. There is a peak during the puberty growth spurt, girls have an earlier peak and have an early osteosarcoma peak, and boys have a later peak here. So, osteosarcoma development has definitely something to do with growth and this is also depicted here, because most of the growths during puberty takes place in the knee region and two-thirds of high-grade osteosarcomas are found in the knee region, in the metaphysis of the long bones, close to the growth plate. Interestingly, in preschoolers where osteosarcoma is extremely rare and most of the growth takes place in the upper extremities, the predilection site in this cohort is the upper extremity. So, we do not know exactly the mechanisms behind, but osteosarcoma definitely has something to do with growth. On the other hand, there are external factors like irradiation, and then there is the big issue of cancer predisposition. You all know the Li-Fraumeni syndrome, which is caused by heterozygous mutations in the TP53 chain that leads to decreased expression of the p53 tumor suppressor. And we know now that about 10% of patients with Li-Fraumeni syndrome will develop a high-grade osteosarcoma and in the younger group up to almost 10% of osteosarcoma patients may have TP53 germline variants. This is a very interesting novel report, just coming out on cancer predisposition. And in a high-grade osteosarcoma, you see the are more than thousand osteosarcoma patients included in more than thousand controls, and novel NGS techniques have been used, and they were able to identify pathogenic or likely pathogenic variants in almost 28% of the osteosarcoma patients, and about 18% or so were inherited autosomal dominantly, which has not just consequences for the patient but also for the families. However, this number is very high and we really have to figure out which of the tumor suppressor genes really play a role in osteosarcoma development. So, from the clinical view, we can say that about up to 20% of patients will have radiographically detectable metastases at diagnosis and these metastases are mainly found in the lungs, rarer in the bones and in the bones you can have a presentation which is called skip metastasis, where you have a metastasis that is localized within the same bone as the primary. The AJCC classification system classifies these tumors as stage-3 disease, stage-4 disease would be when you have a metastasis on the opposing side of the joint. And the stage-4 patients have a poorer outcome than stage-3 patients. So, please you should remember that you always should send

questions to Dr Attarbaschi. So, how do we treat patients with osteosarcoma? We have the neoadjuvant strategy as in most solid tumors, we do the imaging followed by the biopsy. Please keep in mind that the biopsy should be done in a center where later on tumor resection will be done. We have clear-cut data from the COSS group on more than thousand osteosarcoma patients, that when you do the biopsy outside such a center, you have a significant higher risk for local relapse and the poor outcome. So, after the diagnosis is made, you give a neoadjuvant chemotherapy, according to the protocol that you use for 10 or 13 weeks, and this is followed by the local treatment, then the local treatment is complete, microscopically, complete resection of all microscopically detectable tumors and this is followed by adjuvant chemotherapy. So, there have been significant improvements in regard to local therapy. So, currently only in about 10% of patients or so, ablative surgery has to be made and most patients can undergo limb salvage surgery, however, when you have, for example, a very big femur tumor, as we had just a couple of weeks ago in a girl, you have to go with ablative surgery. In her case, we did the rotationplasty. There has also been some progress in regard to radiotherapy of high-grade osteosarcoma. Actually, osteosarcoma in comparison to Ewing sarcoma is a rather radio resistant tumor. So, you need very high doses of radiotherapy and ideally you do some ion therapy or a proton therapy and there is a center in Heidelberg, in Germany, where there were also two trials, one is already completed, OSCAR 1, and currently they go for the OSCAR 2 trial. And we have also now a center in Austria. So, when can you considerate your therapy? When you cannot achieve a complete surgical remission, then you can think about radiotherapy, but this is not the standard of care. So, what's about the backbone chemotherapy? Most institutions use the so-called EURAMOS backbone, which was born out from the 0133 COG trial, which is MAP, high-dose methotrexate, cisplatin and doxorubicin, but when a patient does not tolerate methotrexate, you can go with protocol, the OS 99 trial from St. Jude, for example, and if a patient does not tolerate anthracyclines, there is also a protocol from the French group in younger patients. They do not use doxorubicin in good responders and young patients. So, in pediatric oncology, we always try to treat according to risk adapted strategies. And for this, you need prognostic factors, of course, we know prognostic factors in high-grade osteosarcomas. This is where multi-variate analysis in almost 2000 patients with high-grade osteosarcoma is from Stefan. I think this manuscript is now 1300 times cited and the strongest prognostic factor is the microscopic residual tumor, with the poor response to chemotherapy and primary metastasis. And we have developed over time risk adapted protocols, where we tried to deescalate therapy in the good responders with low volume tumors. However, in COSS 96, we had to close this arm early because it failed. We had seen too many relapses. We've tried to change the therapy in the poor responders with large tumors, with carboplatin VP-16. However, the number of patients was too small to draw any firm conclusions. And that's the big issue, or it was the big issuer in osteosarcoma whether with change in chemotherapy in the poor responders, that is patients whose tumor have more 10% vital tumor cells, when you change the therapy or intensify the therapy post operatively, can you improve outcome. That dates back to Gary Rosen in 1982 with his T10 protocol. And so, the EURAMOS-1 trial was launched and here we compare to MAP in the poor responders with the experimental MAPIE. All five drugs are active single agents in high-grade osteosarcoma, a very intense therapy, very much more acute toxicity in MAPIE versus MAP, and the outcome is poor, so also more long-term toxicity. So, I think we can close this chapter on intensifying chemotherapy now in high-grade osteosarcoma. This is an old slide dating back to 1965, it's from Wataru Sutow, one of the pioneers of combination chemotherapy in pediatric cancer and it's still valid after 56 years, 55 years. So, you cannot achieve cure in most solid tumors, just with drugs. There is some changes now, when you think on infantile fiber sarcoma with ntrk inhibition, but normally with chemotherapy, we cannot just achieve a significant palliation. And on the other hand, I like this cartoon, because the drugs are depicted as bombs and bombs make a lot of collateral damage. So, what's the collateral damage? What's the chronic morbidities that we see in patients with bone sarcomas? And these are data from St. Jude Lifetime Cohort, and you see patients with bone cancer survivors have the same rate in their thirties on chronic cardiovascular morbidities when compared to their counterpart controls in their fifties and this goes even up. So, as it goes up, there is room for prevention. So, look at the blood pressure, et cetera, so, to avoid other cardiac risk factors. So, there is room for improvement. On the other hand, these patients have chronic morbidities that

are much higher than when compared to the normal population, for example, in the musculoskeletal system and here there is a need for rehabilitation. On the other hand, besides cardiovascular and musculoskeletal, there is also more chronic cumulative burden on impaired neurocognitive function and that calls for a psychosocial support during long-term follow-up. And we have currently established here in Eastern Austria, Late Effects clinic, which is funded from the government for our also bone survivors and it's called the IONA, the Inter Disciplinary Oncology Late Effects Clinic and we have also established a so-called SUPA-BIO register. Here, we get the consent for the bio-bank, again, from the 18 years old patients, before transition and we get the consent to get the data back from IONA and we will establish the survivorship passport. So. where do we stand in high-grade osteosarcoma in 2000? This is data from more than 2000 COSS patients, localized, good respond, at 10-year survival, 20-year, 30-year and 10-year survival. So, it's about 80%. In the poor responders it's close to 60% or just below; primary metastatic good responders, about 50%, and the poor responders primary metastatic at about 20%. So again, please send questions to Dr. Attarbaschi. So, we have to go for novel therapies. And so, we have to identify oncogenic drivers in the tumor cells. We have to identify open pathways that drive the tumor cell development. We can focus on the tumor microenvironment, the anti-angiogenesis, the bone microenvironment, or the immune system. So, what do we know on oncogenic drivers? So, this is data from the COSS group, Mikaela Natarat and Daniel Baumer and others have provided these data. So, when you look at single nucleotide variants in cancers, which has been done in the pan-cancer analysis, In 30 different cancer-state, identified 21 signatures. And interestingly, the osteosarcoma signature in many patients resembles the signature of ovarian cancer and breast cancer in individuals with BRCA germline mutations and this is called the BRCAness signature and such tumors, at least in ovarian cancer, respond to PARP inhibition. However, the seven patients who were included in this recent trial, in the patients who received trabectedin and the PARP inhibitor olaparib, no responses were seen in these patients. So, another interesting pathway was discovered by Kathy Janeway's group in the COG trial, they identified that in subset of osteosarcoma the PI3K/mTOR pathway was activated and the ISG has also shown already that the combination of sorafenib into the mTOR inhibitor Everolimus can improve the progression-free survival in heavily pretreated osteosarcoma patients. So, obviously that works for some patients, but not of course for all. So, when we target other targets like the anti-angiogenesis or targets in tumor cells, we can also use multi kinase inhibitors, when, for example, in the tumor cell EGFR is upregulated and you have increased anti-angiogenesis, that can be targeted by regular afatinib. And in this trial, which was recently published, there was a signal coming from the multi kinase inhibitor, regular afatinib, in heavily pretreated osteosarcoma patients just to improve the progression of free survival when compared to placebo. There was another trial with a multi TKI, namely the CABONE trial, where a Cabozantinib was used. Cabozantinib also targets the MET kinase, and some osteosarcoma patients have over-expression of this path or over-activation of this MET path, and obviously some of these patients can respond to Cabozantinib. And there is already also a trial where the multi TKI lenvatinib is combined with high-dose ifosfamide and VP-16, the so-called OLIE trial, and we're currently recruiting patients. So, another strategy is to target the bone microenvironment, for example, the bisphosphonates. There were preclinical data pointing to this as a good strategy. However, the clinical data failed to show a benefit. The contrary was the case in the French OS2006 trial, patients who received zoledronate as it had even poor outcome, and there is preclinical data also for activity of the RANK inhibitor Denosumab, and this is currently tested in a COG trial. Of course, very important, we need to have this recently growing number of so-called Omics Programs, where patients with childhood cancer and relapse or progressive disease can be entered. In Germany, we have the so-called INFORM Program, and this was one of our first patients with osteosarcoma. In this INFORM Program you get the genetic results and you get trials that are open, and tracks that may work in these patients and trials that are open, and this is quite for sure an important way forward. Please ask questions. To sum up, the genomic landscape of osteosarcoma. So, in the pediatric cancer, osteosarcoma is the tumor with the highest genomic instability and in such tumors, you find a very high number of structural variances, insertions, deletions, translocations and inversions. And this is also related to the TP53 germline variance. An interesting approach was recently provided from a UCSF, where they tried to implement the Genome-Informed Targeted Therapy

program for Osteosarcoma. Here you have to copy-number alterations and this is a biopsy sample, this is a surgery sample. And you see, interestingly, that these copy-number variants do not differ between the biopsy and after neoadjuvant chemotherapy. And when you have, for example, now a chain that is over-expressed and amplified here like MYC, and such a gene can be targeted. This would be a therapeutic approach MYC can be targeted, for example, with this multi CDK inhibitor, or when you have over-expression of VEGFR, you can use a TKI sorafenib. And they used PTX models, Orthotopic patient-derived xenografts. And interestingly, when they implemented these tumors into a nude-mice, you see there was, when they had MYC over-expression, this was also present in the nude-mice tumors and when they treated with the CDK inhibitor or with sorafenib, depending on what was over-expressed, they have shown in this biological model that you can prevent the outgrow of the tumor. So, a few words at the end to the immunological approaches, immune therapy in osteosarcoma. So, why immune therapy osteosarcoma is a bone derived tumor, and there's a strong interaction between the immune system and the bones? On the other hand, there may be many tumor neo-antigens that was initially believed, because osteosarcoma has a rather high mutation-load, but in some tumors, you will not find any tumor neo-antigens, and anticancer. So, you're all familiar with the immune surveillance concept, the three Es. First E, when there is a tumor developing, and you have elimination why at the immune system, but the tumor cells become more and more resistant, and at the end they escape the surveillance. And osteosarcoma can be immunological cold or hot tumor. So, there's also a big heterogeneity. So, when it comes to the elimination-phase, certain drugs have been used, like interferon. We have done this in EURAMOS-1, we have performed an add-on interferon therapy, in the good responders, in half of the good responders, and in the intent to treat, there was no difference in outcome. However, many of the patients here randomized into the interferon, did not actually start interferon, and when we excluded these patients there was a benefit. However, you cannot get this information out from this trial. So, we cannot recommend interferon based on the results of this trial. There was another conflicting trial from, a conflicting trial, the COG group, the 0133 trial, that was a very complicated, two over two factorial design. And at the end, it was shown that the liposomal muramyl-phosphatidyl ethanolamine tripeptide or L-MTP-PE, has a significant better outcome, patients who are treated in this arm when compared to the others. But that was not accepted from the FDA, this drug was not licensed by the FDA, but was licensed by the EMA. So, you can give this drug in Europe, but COSS and many of the EURAMOS investigator did not recommend it. So, what's about immune checkpoint inhibitors. Well, the current finished trials pembrolizumab in children, there was no single responder in osteosarcoma, and there was a trial in the US from the COG and there were no responders seen on nivolumab monotherapy in osteosarcoma, unfortunately. So, this is my last slide, novel way probably on immune therapy in osteosarcoma, this is from David Thomas group in Australia. It was recently found that there was a signal in the GRM4 gene in predisposing to osteosarcoma, but no one had an idea of what GRM4 is doing, obviously GRM4 is involved in the release of IL23 and IL12 and alters to microenvironment, and probably targeting these molecules may be a novel approach. So, to sum up, osteosarcoma is an ultra-orphan disease. We have not made significant improvements in outcome during the last few decades. Intensification of chemotherapy failed to improve outcomes. So, we currently need biobanking and -omics approaches to identify novel therapies, and which will be individualized therapies at the end, probably. Cancer predisposition is an important issue, especially in the younger patients and there is a need for a long-term medical and psychosocial care for survivors. Thank you very much.

Dr Attarbaschi: Thank you, Leo, for this very nice talk, comprehensive talk and especially what is done besides of, apart from classical chemotherapy. So, if it's fine for you, I would start with the questions in the chat.

Dr Kager: Yep.

Dr Attarbaschi: And the first question, which is a little bit in line with what I would have liked to ask you too, is, what is the need of assessing histological response? If our EURAMOS trial has shown that intensification of chemotherapy does not improve prognosis.

Dr Kager: So, you have the only information at the moment, that you have a poor outcome. So, probably that may impact your surveillance, post therapy, you can cost this with the patient, but obviously currently we have no way to tailor therapy because we have no drug available for a new phase III trial.

Dr Attarbaschi: So, if I'm allowed, I would add my question. So, is there a prognostic difference in doing no chemotherapy or give them the same drugs, in a patient who had a poor response on histological basis?

Dr Kager: Thank you very much, this is a very important question. When you have a regression grade-6, and you compare this regression grade-6 data with patients who had surgery only, then the outcome in the patients treated with MAP is twice as high or other therapies. So, obviously there is some response on micrometastatic disease. I have just discussed with Thomas Künhne this week, and Thomas told me he had a patient regression, grade-1 in the resected specimen and no response at all regression grade-6 in the lung metastasis. So, it doesn't tell you everything, but very important that you keep to give the chemotherapy because the outcome is much better than just going with surgery only.

Dr Attarbaschi: Thank you, another question, if you're using targeted therapies, is it mandatory or needed to have immunohistochemical assessments before starting the specific drug.

Dr Kager: I would say, it makes sense to include these patients into Omics Programs, that you get an idea, which of the drugs you should use. So, it's much better to have the patient in a trial, like INFORM 2 and not just using the drugs based on immune histochemistry or something. We can do much more than immune histochemistry.

Dr Attarbaschi: Thank you, then we got an email before the session with a question, in the setting of limited resources, and no chance to do limp salvage, and the relatives refuse amputation, what would you recommend for such cases?

Dr Kager: What my personal opinion is to try to get this patient into a center where it is possible to do a resection. Radiotherapy is not the standard of care. It can be offered, but when you have no, no resource for good surgery, you won't have any good resource for radiotherapy that is needed, very modern radiotherapy needed either. So, unfortunately, I have no answer for this patient because we say always life before limp. So, when an amputation is necessary, we have to do it also in the high-resources country.

Dr Attarbaschi: Thank you. Another question from my side, you did not talk about the role of surgical remission concerning metastasis, especially in the lung. If I remember correctly, you once published a case where a patient underwent, I don't know, 10 lung surgeries and was cured at the end. So, my feeling was always that you suggest not to give up if there's a chance for surgical remission. Could you comment on that?

Dr Kager: Yes, thank you. Another important question. That's a single case and in this patient, he had once a lung metastasis, unfortunately the other metastases were in the bones or in the soft tissues, but it was always easy, except for one amputation of the left leg, to get into a complete surgical remission, and the parents wanted and the patient wanted, and so, therefore, we did this aggressive approach. In lung metastasis it's absolutely important that you get a complete surgical remission even when the metastasis disappear during chemotherapy. The Italian group, Stefano Ferrari and his colleagues have shown that they reoccur. So, in doubt, please go for surgery, it will probably save the life of the patient.

Dr Attarbaschi: In addition to the topic of lung metastasis, we got the question, what is the role of radiotherapy of the lungs, I suppose, after resection of lung metastasis?

Dr Kager: That depends. In the lung, when you have multiple metastases, radiotherapy has no role. You have to go for surgery because you have to apply a very high-dose, you have to apply 60 to 70 Gy and you have the heart nearby, so, I would consider the radiotherapy in the lung, it really depends on the localization. If

there is pleural metastases, or if you're in a palliative situation, then you can't go with radiotherapy, but in the curative approach, I would not say that there is much room for radiotherapy.

Dr Attarbaschi: Next question, is there any role or any data about limp chemoperfusion therapy?

Dr Kager: Yes, there is data out there. Norman [Audio Not Clear] has brought this up several times. Again, from COSS we have closed this chapter. We had the COSS-86 trial, where we did intra-arterial chemotherapy with cisplatin. However, that did not work, that was a very time-consuming approach, as you can imagine and it didn't show any big benefit. So that chapter is closed from our side.

Dr Attarbaschi: Next question, which I think is alluding to what we're doing sometimes in Ewing sarcoma of the pelvis, where we do preoperative radiation therapy, and then remove the bone with the tumor, and do an extracorporael irradiation and then re-implant the bone within the pelvis.

Dr Kager: I'm not aware on data series in osteosarcoma on this topic.

Dr Attarbaschi: Okay, I think there is a question which is not really dealing with osteosarcoma, but with chondrosarcoma. Someone is asking for it twice, how to deal with a 14-year-old patient with a chondrosarcoma of the tibia?

Dr Kager: If you really want to discuss this, I think that would be too big for now, but you can send your question via email to me and we can discuss this in our COSS group. We need to have images and to have a clear-cut histological analysis to give you a good advice, otherwise.

Dr Attarbaschi: Yes, I agree, so please send this specific case with all the important data via email to Professor Kager. So, I think that we went through all the questions in the chat, I will check my emails if there is one of the questions which have not been answered yet by you, but I think you have addressed this during your talk. I think we can take this as the last question, someone is asking, what is the percentage of patients with osteosarcoma who finally need radiotherapy? Can you estimate this?

Dr Kager: No, this is difficult, I cannot estimate, it's rare, very rare.

Dr Attarbaschi: Yeah, I agree. Yes, so I think that we are at the end. Thanks, Leo, for answering all the questions. I think there were lots of people in the audience, 33, and I expect that many people will listen to your talk afterwards. So, please tell your colleagues that the presentations are recorded and available via the ESO platform and website. So, thank you very, very much for taking part at this event, and again, Leo, thank you. It's always nice to listen to your talks, I always enjoy them very, very much. So have a good evening, bye, bye, ciao.

Dr Kager: Thank you, bye-bye.