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Principles of treatment of Ewing's sarcoma

Dr Strauss: Hello, good morning everybody, my name is Sandra Strauss. I'm a Consultant Medical Oncologist and Senior Clinical Lecturer at UCL in London. And today, I'm going to talk to you about the principles of management of Ewing's sarcoma. I have no disclosures. So, today's lecture, I'm going to focus on really the multidisciplinary management of newly diagnosed patients. I'm going to talk you through the evidence for chemotherapy, and I'm going to talk to you about local therapy, both radiotherapy and surgery, and some areas of controversy. Then, I'll move on to discuss the management of relapsed or recurrent disease and some novel and emerging therapies. So, to start with, I'm sure many of you know, Ewing's sarcoma is a rare tumor. It's the second most common primary bone tumor seen in children and teenagers, and the majority arise in bone, but they can also arise in soft tissue. Here is some evidence from an epidemiological study done in the UK. Ewing's is the yellow band here. You can see the peak incidents in adolescents and how rare it is over the age of 50. The most common primary sites are around the knee or in the femur and proximal fibula, but about 20% of tumors occur in the chest wall, and nearly a quarter of them arise in the pelvis with a small percentage in the spine as well. The majority of patients are diagnosed with a localized disease, but about 25% have metastatic disease, most commonly the lung or bone or bone marrow or a combination thereof. Ewing's sarcoma is characterized morphologically by small round blue cells. Here is an H and E stain, you can see on the right-hand side of the screen demonstrating this. Immunohistochemistry demonstrates them to be CD99 positive. But of course, they're characterized by specific rearrangement, the EWSR1 translocation with one of the ETS family of genes. Most commonly, this is with FLI1. So, 80% of Ewing sarcoma patients have an EWS-FLI1 translocation. And then, another 10% have an EWS-ERG translocation. And then, there's some further rare translocation-partners that are seen. But essentially, this translocation sets up an aberrant transcription factor with many downstream targets and is pathognomonic of Ewing's sarcoma. So, how do we manage Ewing's sarcoma? So, first of all it is complex and involves multi-modality treatment. We use intensive chemotherapy and local control that may involve surgery with or without radiotherapy or radiotherapy alone. Patients are generally stratified according to whether they have localized or metastatic disease. And more so, in Europe particularly, patients have been risk-stratified according to some other parameters. So, we, in previous studies, have called patients R1, which are a standard risk, so, those are with localized and small tumors. R2 are patients with lung metastases alone, or R2-loc which are patients with localized disease but a poor response to chemotherapy, and I'll come back to that later. And R3 are patients with extra pulmonary metastases, so, those with bone and/or bone marrow that may be including lung

metastases but have sites of disease in addition to lung metastases. And these are the patients that have the poorest prognosis, and I'll come back to show you a little bit of information about that. The evolution of treatment or chemotherapy for Ewing's sarcoma patients has been through collaborative, international clinical trials. So, I'm gonna take you through some of these to give you an idea about how we've come to give the treatment that we do. So, here is a list of studies going back to the 1990s when EICESS-92 was setup. So, this was one of the first European studies that looked at different cohorts of patients, but essentially, used treatment based on anthracyclines, vincristine, ifosfamide and cyclophosphamide. On the right-hand side, you can see survival outcomes, so, around a three-year event-free survival for patients, particularly, with this regime. These were localized patients with small tumors. So, about 3/4 of the patients, event-free at three years in this situation. Following on that, the Euro-Ewing99 protocol was set up. And that published, again, looking at standard or good-risk patients, patients under the age of 50 with localized disease and a good response to chemotherapy, and/or a small tumor. This used six cycles of VIDE chemotherapy, and then, patients were randomized to either have VIDE, continue with the ifosfamide, or switching to cyclophosphamide. Found in this group of patients, they were pretty much equivalent, and here, you could see the event-free survival of about 3/4, again, at three years. Conversely, in the USA, some other scheduling of these same active agents was performed. And Holcombe Grier, in the 1990s, looked at standards of VACA chemotherapy versus, VACA, so, that's adriamycin and actinomycin, and adding ifosfamide and etoposide. Here they found for all patients, so, this is not just, oh no, sorry, this is for localized patients, a five-year, event-free survival of 54% and overall survival of 69% versus 61 and 72% adding the ifosfamide and etoposide. So, this study showed the value of ifosfamide specifically. And then, the next 10 years or so, the Children's Oncology Group focused on intensifying the treatment and lengthening the treatment to see if that altered outcome. So, first of all, they looked at a shortened and a long version of VDC/IE and showed that patients with a dose intensified, so, longer chemotherapy, had a better five-year overall survival. And on the basis of that, they took the next step and then, said that if you were giving the chemotherapy every three weeks and we think that intensification is going to be of benefit, why can't we try and give it every two weeks? And this is alternating the VDC and IE and using growth factor support to enable that. And in fact, they found it was tolerable and possible to do and found that there was an overall survival benefit, so, again, about 3/4 of the patients being event-free at three years. So, quite similar to the results that we've seen with the VIDE chemotherapy in these patients. So, then what about other risk? So, what about patients who have more what the Europeans, what we've classified as high-risk, localized disease, and what about patients with metastatic disease? So, when the Euro-Ewing99 protocol was set up, it was felt that patients with large tumors, we know that they do have worse outcome. And also, those who have... it's thought that those who had a poor response to chemotherapy, this also impacts on outcome. So, the protocol randomized patients who either have a large tumor or a poor response to investigate the effect of high-dose chemotherapy. Now, high-dose chemotherapy has been around for a long time in Ewing's sarcoma, primarily when used with patients with metastatic disease. And this remains a controversial area, which I'll come back to. But essentially, this study looked at patients on Euro-Ewing99 using the VIDE chemotherapy, and they randomized those to continuing the VIDE or having busulfan and melphalan. And in fact, the high-dose chemotherapy in this circumstance showed a survival advantage, that you can see there, so, an eight-year event-free survival, difference of approximately 13% and nearly a 10% overall survival advantage. So, actually, this is the first evidence from a randomized clinical trial to show that patients benefiting from high-dose chemotherapy. One of the challenges, however, was establishing the acceptability of this treatment for patients, particularly due to women being rendered infertile by it. And so, in fact, the number of patients that were actually randomized compared to denominated was only, it was quite a small percentage, only about 20 or 30%. But for a select group of patients who had that treatment, there was a survival advantage. Euro-Ewing99 also investigated the role of high-dose chemotherapy in those with lung metastases only, and there, no survival benefit was found. So, here, looking at the three-year event-free survival, it was around 50% of patients and no additional advantage for high-dose and a three-year overall survival of about 60, 70%. So, you can see from these figures what the outcome of patients is with these groups of patients. So, we're

looking at those with standardized risk, localized disease of maybe 75% event-free survival, those with lung metastases between 50 and 60%. But what Euro-Ewing99 showed us and as we've been shown on many studies, is that if you've got multi-metastatic disease, so, i.e. if you've got metastases to the lung, or the bone and bone marrow with or without lung, eventually, survival is very poor. So, this was not a randomized study. In this situation, the patients were treated with VAI, or VIDE and then VAI plus or minus high-dose chemotherapy, but the event-free survival was under 30% for that group of patients, so, a very poor prognosis. And it was not a randomized study, so, unfortunately, can't prove the benefit of high-dose chemotherapy in that setting. Although, it did appear that younger patients had more benefit, so, those under the age of 14 had more benefit, but again, no randomized evidence to support high-dose chemotherapy. So, probably about 10 years ago now, the Euro Ewing Consortium was set up on the basis of an FP7 grant, really to conduct clinical trials in Ewing's sarcoma and thereby, improve outcome for patients. And so, the first study that was set up through that access was a first-line randomized trial of adjuvant therapy in Ewing's sarcoma. And simply, it determined, it was set out to compare the European standard treatment, which is VIDE, VIDE and VAI, versus VDC/IE that the Americans use. There was also a second randomization against zoledronic acid and still, some questions about high-dose chemotherapy. Just to say, so, this study was run across Europe and beyond and recruited over 600 patients over just 5.5 years and used a Bayesian approach that allowed the results to be collected more quickly with presentation of hazard ratios and looking at the probability of one treatment as better than another. And these are the results that were presented at ASCO last year, but essentially, showed that VDC/IE was a superior treatment. So, it showed that there's almost a 99% probability that VDC/IE is superior to VIDE and VAI chemotherapy both for overall survival and event-free survival. Now, these curves don't show quite that good, 75, 80%, 85% survival for local disease, because this study, in fact, recruited patients with all subtypes, so, localized pulmonary metastases and multi-metastatic disease. And in subgroup analysis, all groups benefited. So, this is a really important study because it establishes VDC/IE chemotherapy as the standard of care for Ewing's sarcoma across all risk groups. The results of the zoledronic randomization are awaited. So, just to pause for a moment to just talk a little bit more about high-dose chemotherapy because this certainly is one of the areas of controversy, as I said, the Euro-Ewing99 protocol showed that there was some benefit in patients with high-risk, localized disease. However, it's really difficult to extrapolate the findings of that from using the new standard of care VDC/IE. So, because the outcome of VDC/IE is better than VIDE, we don't really know what the addition of high-dose chemotherapy is to that regimen. One of the other challenges that I'll talk about a little bit later is that one of the prerequisites for recommendation of high-dose chemotherapy is a poor response to chemotherapy on pathology. And increasingly, not only is preoperative chemo given but also, preoperative radiotherapy which does not enable that same parameter to be used. So, in fact, we're finding it quite difficult to consider high-dose chemotherapy in patients who are having VDC/IE because it's really difficult to say there's going to be an advantage for it. As I stated before, patients with lung metastases, there's no role defined. And for multi-metastatic disease, again, there was no randomized evidence in Euro-Ewing99. In the Euro-Ewing's 2008 protocol run by the GPOH, there were patients who were randomized between VDC, VAI, and treosulfan and melphalan with multi-metastatic disease. Quite a small number of patients did not show statistical difference, but there was a trend to improvement for patients under 14. So, I do understand that some pediatric oncologists across Europe may consider this in younger children. Although, we would rarely use high-dose chemotherapy in the UK. In recurrent Ewing's sarcoma, there is also quite a lot of data from retrospective analyses, but again, no randomized evidence. But it is something we sometimes consider in patients. We found retrospectively an improved outcome in patients who've got a good disease-free interval and are able to achieve a second remission either through the use of chemotherapy with or without further surgery or radiotherapy. So, it is something that we consider in a small subset of patients. Right, so, I'm now gonna move on to talk about local therapy because this is a very important aspect of treatment as well. I think one of the first points to raise and must be remembered that this has to be individualized treatment and must be through discussion at an expert specialist MDT or tumor board. The local therapy depends on many factors, patient age, primary site, size of the tumor, and local extension of the tumor. The local therapy

must be discussed early on, and then, patients brought back to the MDT following chemotherapy to make a final decision. There's very little data comparing surgery and radiotherapy in randomized studies, but overall, there is a survival advantage for patients having surgery. So, the first point of discussion is the tumor resectable? And so, for extremity tumors and such like, which are reasonably straightforward, well, then of course, the patient will be recommended an operation. But for there are many challenging sites, particularly, in the pelvis and the spine, where the risk of local recurrence needs to be weighed against the functional outcome and late effects. And when you're looking at the margins for surgery, despite the fact that patients respond well to chemotherapy, when you often see a reduction in the extra osseous soft tissue mass, you really need to factor-in the tumor volume at diagnosis as patients are at risk of local recurrence in that tumor bed even if there's been a response to chemotherapy, so, making quite complex pelvic surgery still complex despite that response. So, the decision about local management needs to be taken using diagnostic scans and then confirmed once patients have had some chemotherapy. So, the surgery, in principle, of course, is a complete excision. There's no role for debulking surgery in Ewing's sarcoma. Amputation is now avoided in the majority of patients. Though patients with distal tibial Ewing's sarcoma, we would recommend an amputation as the functional outcome is better. There are more and more novel techniques being used including intraoperative navigation and personalized jigs to guide bone resections and provide the most optimal outcome. Here's some examples of some of these on the screen here. This is a complex navigational plan really trying to outline the tumor to be able to get the optimal margins but also, to preserve function as much as possible. But what about radiotherapy? So, radiotherapy is either used in combination with surgery. It's used as definitive treatment for inoperable tumors. And so, I'm gonna talk you through those and also, a little bit about proton beam therapy. So, why do we give radiotherapy in Ewing's sarcoma or in sarcoma in general? We give it to reduce local recurrence. This is some data from a retrospective analysis of patients treated on the Euro-Ewing99 protocol looking at the outcome of patients who have a local recurrence. So, if a tumor recurs at the primary site, outcome is poor, so, we really need to optimize treatments at diagnosis. So, here's the Kaplan-Meier curve. You can see that, so if you have a local recurrence, overall, there's a 21% chance of being alive at three years. If you've got a local cancer without metastases, you've got a 31%. So, if you have a local occurrence, you've got more than a... you've got about a 70% chance of dying of your disease. And so, what this analysis did was looked at the patterns of use of radiotherapy across Europe and in Euro-Ewing99. And what they found was that about a quarter of patients received post-operative radiotherapy, and across all groups of patients, there was a statistical reduction in local recurrence if post-operative radiotherapy was used. So, it pretty much halved the rate of local recurrence. The effects were most marked for large tumors. However, they seem pretty much across the board. And what was found in this analysis that in the UK, we use less radiotherapy than others. And in fact, we had poor outcomes as a consequence. So, here you can see in this forest plot on the right-hand side. There was probably a more marked effect in patients over the age of 14. The effect was seen in soft tissue and bone and probably, more marked, as you can see, in these sacral or pelvic tumors that are harder to treat and more marked in the larger tumor. What was also interesting that even if you see a complete necrosis on the pathology, there was an impact of radiotherapy. So, overall, it halves the risk of local recurrence. And so, in our MDTs, we now recommend it for all patients apart from those with small tumors with a good response to chemotherapy. And if we are now saying that patients are definitely going to have radiotherapy, we prefer to give it preoperatively because you can give a lower dose. And so, our practice has really changed over the last 10 years as a consequence of this study. What about definitive radiotherapy? So, that's used, of course, for patients with inoperable tumors. There's no randomized trial on the optimal dose, radiotherapy doses from about 45 to 66 Gray. And actually, this will be the subject of an upcoming trial. It's used for inoperable tumors, e.g. the sacrum and pelvic tumors, where the morbidity of resection is too great. Also, in spinal tumors, patients often undergo decompressive surgery at diagnosis and further surgery has not been shown to improve outcomes, so, they will get definitive radiotherapy. And radiotherapy is also used, whole lung radiotherapy is often given to consolidate treatment at the end of chemotherapy for patients of lung metastases. It's pretty much established as standard of care. Although, to be honest, there is no randomized evidence for this. What about

proton beam therapy? So, this is also increasingly used for patients with difficult to treat tumors, so, pelvic tumors, spinal tumors and chest wall disease. This is something that's available in the NHS and in the UK, and I'm sure in many countries across Europe. And this essentially allows you to give the highest optimal dose and protect critical structures like in this example, particularly, the spine. So, the conclusion of this is that we know the standard of care, chemotherapy, for this. We've got joint decision making for local therapy, but there's still some unanswered questions for patients with newly diagnosed disease. And so, these are some of the ones that have been discussed at the Euro Ewing Consortium and are the subject of an upcoming trial. First of all, what is the optimal dose of radiotherapy for patients receiving definitive treatment and post-operatively? And then, also, is there a role for maintenance chemotherapy, such has been proven to be of benefit in patients with rhabdomyosarcoma? And then, is there any benefit of adding any new agents to VDC/IE, and I'll come back to that later. So, what about patients with relapsed or recurrent Ewing sarcoma? Well, I think the first thing to say is long-term survival for these patients is poor. Multiple treatments are used at progression, and previously, there was no prospective evidence to say what was the best treatment for these patients. The outcome depends on local recurrence, on whether patients have metastatic disease in the lung versus other, and disease-free interval. But here's a slide from the German, the GPOH, showing that the median overall survival for patients with recurrent disease is between 5 and 15 months. You can see a local recurrence do better than systemic, and then, combined have the poorest outcome. So, the second trial I'm gonna talk to you about is rEECur, which is the second trial from the Euro Ewing Consortium, which was an international randomized trial really, essentially, that set up to compare all the standard of care chemotherapies given for Ewing's sarcoma, cyclophosphamide and topotecan, irinotecan and temozolomide, gemcitabine and docetaxel, and high-dose ifosfamide. And this was a multi-arm, multi-stage trial which essentially, we could have four drugs to start with, and you could drop the loser, and it was flexible that we could add new arms as we go along. What was interesting about this trial, first of all, it recruited very well. And it used, again, Bayesian design that allowed us to have this flexibility. And the first treatment that showed to be inferior to the others was gemcitabine and docetaxel. So, that was published in ASCO, or presented in ASCO 2019. And that arm was dropped leaving three arms left for comparison. And then interestingly, last year, it was represented and found that irinotecan and temozolomide was inferior to ifosfamide and topotecan cyclophosphamide. So, not that these are inactive agents but perhaps, they're not the most active agent in this. So, irinotecan and temozolomide has also been dropped from rEECur. What's important to note however, the number of patients that have been recruited. So, bearing in mind there was no previous randomized controlled trials in this setting. There's now over 400 have been recruited. But what was also found, so, this is the, sorry, this is the outcome looking in ASCO last year. So, here you can see, so, that was the gemcitabine and docetaxel dropped out first. And then, you can see irinotecan and temozolomide just slightly inferior to the other two, so, not to say they're inactive but perhaps just not quite the same efficacy. But what you could also see that how poor the overall survival for this group was at just over a year, and that the median progression-free survival for all patients on all the treatments was just under five months. So, that would be the general follow-up of standard chemotherapy. So, what's happening now is that carboplatin etoposide has been added as a standard arm, and there's discussion about adding some novel therapies in combination with chemotherapy to make the use of this multi-arm, multi-stage design. But what are those novel agents, and how are they being integrated into care? So, I'm just gonna spend the next 10 or 15 minutes talking about some of the new targets for therapy for Ewing's sarcoma. So, the first thing to say is, as I'm sure you're most aware, that Ewing's sarcoma mutationally are very quiet tumors. They are driven by the translocation, so, you don't see many somatic mutations in this disease, but you do see TP53 mutations in about 20% of patients and also STAG2. Now, these are poor prognostic factors. So, patients with these mutations have a worse outcome here. You can see STAG2 mutations versus non-STAG2 mutations on the left and then, if you add a TP53. So, if you have a TP53 and a STAG2 mutation, you have a very, very poor, poor outcome. However, these drugs are not, these markers, unfortunately, are not currently druggable, so, they can be used as prognostic markers, but they can't, unfortunately, be used as predictive biomarkers for clinical trials. But just to say that to date, there isn't really any role for immunotherapy, and certainly,

checkpoint inhibitors do not have any activity in this disease. So, what other agents or things have been investigated? I'm just gonna talk you through three groups, the PARP inhibitors, tyrosine kinase inhibitors, and then, a novel agent targeting the fusion, TK216. So, first of all, PARP inhibitors were first identified as potential target in Ewing's sarcoma nearly 10 years ago. Really lovely data pre-clinically showing that they are sensitive to PARP inhibitors as BRCA-mutated breast cancer. So, there's a huge amount of hope that this could be an answer for Ewing's sarcoma, but the first clinical trial of olaparib was singularly disappointing. But there's a lot of data pre-clinically showing the in-vitro and in-vivo benefit of combining PARP inhibitors with chemotherapy. They synergize extremely well, particularly with some of the drugs that we use in Ewing's sarcoma. And so, a whole host of clinical trials were set up to try and investigate these. Here are three of them. The third one was a trial that I was involved with, essentially, using different PARP inhibitors combining with temozolomide. And what all of them found was that you get quite profound myelosuppression, and it appears that the PARP inhibitors exacerbate the myelosuppression as well as synergizing potentially for chemotherapy, so you're unable to get to very high-doses of temozolomide and certainly, not at the levels that we're seeing with other treatments. A few stable diseases found, but no overt responses. What about irinotecan? So, the treatment was better tolerated hematologically. However, it was found that you still see the irinotecan-related GI toxicity. And certainly, in the trial that I was involved with, we had to drop the dose of irinotecan down to about 40% of what you would give normally. We did have one partial response and some prolonged stable disease with a median progression-free survival of 3.8 months. So, not that much worse than standard chemotherapy but not better than standard chemotherapy. And so, I think that the bottom line is that these combinations have been associated with significant toxicity that limit the dose and are unlikely to offer any efficacy over standard chemotherapy unless, there are particular biomarkers that we can find that can predict response for those patients such as those we've just seen. And what about tyrosine kinase inhibitors? So, this is the other group of drugs that have been very much studied in Ewing's sarcoma, and there've been three studies, two using regorafenib, one run by the French sarcoma group, and one run by SARC in the US and cabozantinib as well. So, here's some results of these studies using different populations, but as you can see, all trying to investigate in TYA populations. And they all showed some benefit for patients, and the REGOBONE and the SARC024 were randomized studies. And certainly, what you saw was that patients had a longer progression-free survival than those who did not receive the drug, and the median is about four months. So, again, quite similar to chemotherapy. It's not the answer. However, these are certainly very interesting drugs. And so, there's a lot of discussion about, with pharma about now moving this forward into adjuvant therapy either as maintenance treatment or combining them with chemotherapy to try improve outcome. And to the final drug I'm just gonna talk about is TK216 which is a drug that was developed by Jeff Toretsky in the University of Washington where he really designed something to try and get straight to the heart of the problem by targeting the fusion protein. And the drug works by blocking the binding of EWS-FLI1 to a helicase that is required to activate the transcription factor. Many, many years of work in the laboratory to design the protein. Lots of preclinical studies showing that it worked well pre-clinically alone and in combination with vincristine. And so, then, the clinical grade product was found and tested in animals. And then, just over the last year or two, phase I clinical trial was set up. And essentially, there've been a number of patients that have been treated with this drug now in combination, and they've found a tolerable dose. The drug is given via an infusion pump over 14 days. It's got a short half- life and been given with vincristine. The latest update of these results, just in ASCO, in fact, last week, showed that there's evidence of activity. There were two patients who achieved a complete response. One who had a very small amount of disease resected surgically, and then, more recently, another patient with an unconfirmed partial response and the rest of the patients' stable disease. So, they have a disease control rate of about 40% but a quite short progression-free survival for the whole group. So, this is a very exciting drug because it's the first target for Ewing's sarcoma, but it doesn't feel like we've quite got there to know who best to use this on. So, there's a lot of associated biomarker-work ongoing to try and work out who best to use it with and on and also, more preclinical studies to put it in combination with other chemotherapies that may increase the activity. So, that brings me to my concluding slide. I think the real messages for you are, as you're aware,

Ewing's sarcoma's a rare malignancy, and it primarily affects children and young people, and it requires an expert multidisciplinary team. VDC/IE is now the standard of care for patients under 50 years, which makes life and opportunities for learning from and collaborating with others to learn from our patients more simple than having more than one protocol being used across Europe or more widely. Local therapy, just again the message, must be discussed in multidisciplinary meetings with experts, surgeons, and radiation oncologists. But I think the other main message is that if we want to improve outcome in patients with Ewing's sarcoma, we must do this through collaboration. I think the Euro Ewing Consortium opportunities really have pulled us all together to do that. And now there are more opportunities to even collaborate more widely with the US and even further on. But the questions that we're now sitting with are how do we add novel agents to intense chemotherapy in first-line relapse setting? And how do we determine the patients most likely to benefit with these treatments to improve the outcome for all going forward? So, that brings me to the end of my presentation. Thank you very much for listening. I'm very happy to be contacted if anyone has any questions after the lecture. Thank you very much and have a lovely day.