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Ovarian and uterine carcinosarcomas

Dr Amant: Hello. Thank you for attending this session on uterine and ovarian carcinosarcoma. It's a pleasure, but also an honor. And thank you for the scientific committee for inviting me here. My take-home message at the end of the session is that the monoclonal theory of carcinosarcoma, states that this is, in fact, a carcinoma where metaplasia occurs. And this is both for uterine and ovarian carcinosarcoma. The surgical staging or debulking, is similar to high-grade endometrial or ovarian cancer. And that's for both entities, paclitaxel and carboplatin results in the best efficacy, toxicity results. This is the agenda, I will start to share with you, old, but also new insights in the tumor biology of carcinosarcoma. Here, we see an epithelial component. I will see a mesenchymal component, but this is not a uterine carcinosarcoma. This is a floated desmoplastic reaction. And this is the epithelial cancer. Here we lack atypia. We lack mitotic activity. So, this may resemble carcinosarcoma, but it's not. On the contrast, this is... here we see a malignant epithelial component and a malignant mesenchymal component. So, this is a typical example of a bi-phasic tumor where both epithelial and mesenchymal components are malignant. And this is what carcinosarcoma is in fact. The big question is, of course, how does this start? Are these two separate cancers that merge/grow together? Or is one the origin of the other? And which one is, in fact, how does it start? If we look into the features of this bi-phasic tumor, the epithelial component in fact can be endometrioid, serous, clear cell, or undifferentiated. And a lot of variations in the mesenchymal component. It can be homologous, then they're round cell or spindle cell sarcomatous proliferation as we see in the uterus. Or it can be heterologous with cartridge, osteosarcoma, rhabdomyosarcoma, melanoma, liposarcoma as potential cell populations. How does this now start? And I think there is abundant evidence for the monoclonal theory. That means that it starts as a carcinoma, and then neoplasia occurs, and this results in a carcinosarcoma. So, this is more like a scheme where we see this tumor evolution is depicted. And there're, in fact, immunohistochemical arguments, clinico-pathological in-vitro, in-vivo studies and molecular findings. In the next slides, I will mainly focus on the clinico-pathologic findings and the recent molecular findings to support this monoclonal theory of carcinosarcoma histogenesis. When I was very young, I had the luck to have a pathologist who looked really in detail into all these observations. And this is like a unique case where, in fact, in one case, this monoclonal theory is depicted. This is a case where, actually, at the background, it was the intramucosal papillary serous adenosarcoma. Actually this... Then, there was a part with invasive, and then the largest cancers, in fact, with carcinosarcoma, and then, even a case with... Actually, the first case that was found

with a melanocytic differentiation. So, we see here, in one patient, how this really starts as a carcinosarcoma. From that era, actually, the most important clinical study was this study by Silverberg, where he studied metastases in 40 cases in a series of 203. And what he did see is, none of these metastases was pure. The majority was in fact pure carcinoma or they were predominant pelvic and para-aortic lymph nodes. So, this is really the metastatic spread pattern from a carcinosarcoma as we see in endometrial cancer. So, from there, we know that basically, the epithelial component is the driving force. Many other publications, immunohistochemistry showed the same staining in both components, but let's focus on more recent data of Zhao and colleagues, that wants to describe the mutational landscape of these uterine and ovarian carcinosarcomas. And what they basically did, is they dissected the carcinomatous components from the sarcomatous components by discrete laser capture microdissection, allowing them to investigate both components separately. And they looked to the single nucleotide for ions and indels in a nearly 600 gene panel. And what they did see, let's focus on this, in blue, are, in fact, the SNVs and the indels that are common for two, for both components. Green are the mutations only for the carcinoma and red for the sarcoma. And what you see is that the majority is in fact common for two, but also the driver mutations, and these are in fact, the black arrows, only are in those SNVs that are merged, that are in both components present. So, this truly supports also this clonal origin of carcinosarcoma cells. Another interesting paper. Also recently, they looked to the epithelial-mesenchymal transition by focusing on the EMT score, which was calculated based on the RNA-seq profile. And this is in fact the EMC score that you have a low-score here, or you have a high-score here. And here we see that in the carcinoma component, mainly, cancers with a low EMT score, and the sarcoma competent, mainly a high EMT score. Which again, supports this conversion theory. If we then see how this tumor further develops, and I believe this is an important slide and I will reconnect you to this slide, actually, during my last but one slide. So, what I want to show here is how this carcinosarcoma that starts as a carcinoma, how this evolves during tumor progression, with relapse. And what we did here, is to look into the composition. We are here. We have 100% carcinoma tumor composition, more than 50%. This is where the results were not so defined, more than 50% sarcoma and 100% sarcoma. In green, we see the primary tumor, in red recurrence or at autopsy. What you see in green is that in fact, most cancers are at this site. Less investigated tumors are actually mainly sarcomatous or exclusively sarcomatous. There's mainly 100% carcinoma or nearly more than 50% carcinoma. But these changes as the tumor progresses and receives treatment, we see in fact, that this tumor composition is actually less likely to be carcinoma, and it's much more likely to be more than 50% or 100% sarcoma. So, this may also add to the poor prognosis, but this may influence also the treatment that we should give these patients. But, later on about this, but try to capture this information well. So, we may say, that if we look into the histogenesis and the evolution, that maybe in the primary setting, we should focus on carcinoma directed treatment where when the disease recurs, maybe we should focus more on sarcoma-directed cancers. So, this background, I do believe we can use for both uterine and ovarian carcinosarcomas. So, let's now focus on each tumor type specifics. I proposed to separate them because some studies are quite specific for uterine and/or the ovarian counterparts. So, actually, 5% of uterine cancers are carcinosarcoma, which is more than the ovarian counterparts. Overall, survival is overall poor it arises between 8 and 26 months, in contrast to ovarian carcinosarcoma, 50% of the stage 1 disease, even stage 1 disease have only a 50% overall survival, which is much less, of course, when compared to the pure epithelial carcinomas. Basically, this figure is the same as pure sarcomas. This is an example where you clearly show also the origin. It does not originate in this case and mostly, from the muscular part, but it starts from the epithelial, endometrial lining. If we look then to the behavior, because this information is important to know how to operate these patients, we see that carcinosarcoma patients have acquired a high chance to have positive peritoneal cytology to have adnexal metastases, to have omental metastases, and to have pelvic lymph nodes. So, from this kind of studies, we do believe that we should treat these patients with a full staging. And the staging includes, actually, pelvic lymphadenectomy, omentum, peritoneal biopsies, basically, a bit similar as the serous endometrial cancer that is also staged as such. So, surgical staging for apparent early carcinosarcoma is a high-grade endometrial or ovarian cancer. Midline incision with bilateral Salpingo-oophorectomy, and then, the lymph nodes

omentectomy, and biopsy of any abnormal lesion. Of course, we can also do that by laparoscopy or endoscopy or robots, but the evidence, in fact, in high-grade cancers is not so high, but there are some data. This is a study where Amsterdam, Leuven and Paris data were merged together, specifically, for high-risk endometrial cancer, including carcinosarcomas. And there, as you can see, disease-free survival and overall survival, in fact, are actually equal when we compare laparotomy and minimally invasive surgery. Examples of that show that we can do a full exploration of the... by endoscopy and that we can also, by this procedure, remove the omentum. In contrast to epithelial cancer, Nemani and his colleagues did find a benefit of lymphadenectomy versus no lymphadenectomy in this SEER analysis in a population of 1,855 women with a significant benefit. So, in these carcinosarcomas, it is not only diagnostic but also therapeutic, at least from this paper. How do we have to subsequently treat these patients, what is the value of adjuvant chemotherapy and radiotherapy? Of course, most of you will know the important data published by Nick Reed on behalf of the EORTC, where that was a phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in uterine sarcomas. At that time, the evidence for the monochrome really was not so high, so the pure mesenchymal cancers like leiomyosarcoma were merged with uterine carcinosarcoma. So, this overall survival curve is for both entities confirming, actually, the retrospective series. But if we then look only to the carcinosarcomas, basically, in the radiotherapy arm, there was a better local control. However, these patients had a higher risk of distant metastases, the patients with the radiotherapy arm, and that, of course, explains why there was no benefits of radiotherapy in this stage 1 and 2 uterine carcinosarcomas. So, no important role for radiotherapy. What about chemotherapy, then? Well one of the... actually, the oldest randomized trial here, but again, combining pure sarcoma and carcinosarcoma where pelvic irradiation was optimal, they used doxorubicin, but there was no benefit. Of course, today we know that doxorubicin is not so commonly used, at least not in first-line. So, we have to take that into consideration, but these are the only data in the adjuvant setting, which do not show a benefit for doxorubicin. We used to check this question, let's say, 10 years ago. And we investigated the role of adjuvant chemotherapy in surgically staged serous and clear cell carcinoma and carcinosarcoma. So, these were true stage 1 and 2 cancers. And let us focus on the red, where this is on the carcinosarcoma receiving chemotherapy. These are the control groups. Numbers of course are not high, but on the other hand, the difference in the effect is actually quite high. Here we have 27% recurrence with chemotherapy, 57% in the controls. Relapse-free survival, 14 months, 7 months. Dead of disease 2, or 18%. Here's 57%. So, showing, and this is like, it's a small group, but it's a unique group because they all have been fully staged. So, this is an argument to treat these patients with adjuvant chemotherapy. There are a lot of publications then we have too much to really summarize, but let's try it in table format. And maybe, let's forget about really old studies with drugs we don't use today anymore. And we focus on the drugs we use, we see, actually, quite good response rates for the combination of paclitaxel and carboplatin. The discussion always comes back again on what about ifosfamide and BRAF data, and we can talk about that. And there is even phase III evidence, randomized control evidence of ifosfamide with or without paclitaxel. The important Homesley study, where they did see like a difference in survival, but, actually, we should not overestimate this difference in this study. Also, Sutton and colleagues, looked at ifosfamide, but then with or without cisplatin. There was a slight improvement in progression-free survival, but in fact, no survival benefits. So, ifosfamide plus paclitaxel appears to be most effective and better tolerated when compared to ifosfamide and cisplatin. But on the other hand, we need to take into consideration that we should discuss the optimal therapy looking also in this toxicity rates, especially with the use of ifosfamide. And I think that Hoskins basically summarizes best. He tested carboplatin and paclitaxel for advanced or recurrent cancers with 60% response rate, 60 and 55% with a median progression-free survival of 16 and 12 months with actually an acceptable dose toxicity. So, his conclusion was, and I think we still use this today, that carboplatin paclitaxel is effective against this uterine at that stage, mixed mullerian malignant tumors with a similar efficacy to ifosfamide combinations. We are more used to do it. It's less costly. It's easier to deliver. So, this should be the standard treatment in this population. There are recent data on the use of trastuzumab in endometrial cancer. We explored this in 2004 in carcinosarcoma. I do think that trastuzumab is not really an option, because in the cases that we investigated, the sarcoma component was ERBB-2

negative. Okay. From last week in our clinic, that basically shows the atypical behavior of uterine carcinosarcoma. They have poor prognosis, but here, we have a case that in June, 2016, we did a robot staging, stage one A. At that stage, she did not receive adjuvant treatment, and now, five years later, she presents again with unifocal umbilical port site recurrence, as you can see here. So, this is not really what we should expect. So, this shows that also the tumor biology may be heterogeneous, and maybe, there is a reason for this. And I looked into this also very recent paper by the colleagues, Travaglino and his colleagues, and they looked to the four molecular subtypes we know in endometrial cancer, and they compared them, or they also applied them in uterine carcinosarcoma. And very interesting here. And we have to focus on, here, these are the carcinosarcomas. These are the patients with endometrial cancers. And we see here, actually, the patients with carcinosarcoma with a POLE signature, mutated signature. In fact, they have a very good outcome. And then, we see the patients with carcinosarcoma, they have the worse outcome, but there are some differences according to the different molecular profiles. So, this shows that we need more data to further, to have more patients per group that may have predict the outcome. But for example, in the case that I did present, likely, we did not investigate it yet. That might be a POLE-mutated uterine carcinosarcoma. So, again, this genetic background may impact the biologic behavior, which is then not always so bad as what we believe. Recent data tests also newer drugs. In a small series, lenvatinib and pembrolizumab were tested, however, no complete or partial responses on only 28.6% stable disease. So, the authors believe that we should not further investigate this. So, if we conclude on uterine carcinosarcoma, complete surgical staging followed by systemic chemotherapy, both in early and advanced stage disease. And regarding to the chemotherapy, carboplatin and paclitaxel are most commonly used. Then we go to the ovarian carcinosarcoma counterparts. Instead of 5% endometrial cancer, this is only 1 to 3% ovarian cancers. 90% is an advanced stage. And also here, the overall survival is poor and arises between 7 and 27 months. In fact, there are not so many data on carcinosarcoma in the literature. There are some data, I will show them, but we, I think, we also need to rely on the data on uterine carcinosarcoma. Surgical staging for that 10%, which is early stage, and most of the time you don't know it, of course, pre-operatively is to have a complete surgical staging. I will not repeat it. This is fairly familiar to all of you. We do believe, however, that regarding fertility preservation, which we may do, actually, for other epithelial ovarian cancers, that there is a place for, however, given the poor prognosis, we would not recommend that for carcinosarcoma. There are actually no reports, as far as I know, we should be very careful. And I think that many of the guidelines that apply for the high-grade epithelial cancer will apply for ovarian carcinosarcoma. And certainly, regarding the value of primary surgery versus the debulking surgery, probably the same applies for these patients, since the driving force is the epithelial cancer. Also, the value of a complete debulking surgery, as Melanie Du Bois nicely showed that it's very important to leave no residual tumor. That also applies for carcinosarcoma. Data of the LION, LION's trial, showing that normal lymph nodes, removal of normal lymph nodes as debulking surgery, in fact, does not add to an improved survival. So, these patients should be treated by an expert research team and focusing on removing of all the bulk of the tumor without leaving any residual cancers. Just some examples from the clinic, just showing that despite the poor outcome, they should be treated like epithelial ovarian cancers. And with that, we should apply all the techniques that we use for these patients to get an R0 result. This is an example of how we try to prevent a thoracal drain after pleurotomy that we put a suture, dissected. We finally closed the knots and, by this, we can avoid the painful and always annoying post-op thoracal drain in the postoperative period. Regarding the chemotherapy, I think many things of what we said for endometrioid cancer can be extrapolated. This is like a very recent, actually, practice guideline, also, with information on ovarian carcinosarcomas, and also, luckily, these authors advocate paclitaxel and platin. Where I would personally prefer, actually, carboplatin that remains also, like, on a personal opinion, maybe, but I'm not in favor of the use of ifosfamide and I would try to prevent actually the neuro-toxicity of paclitaxel and cisplatin. And now, I come back to the one slide that I showed at the beginning when we discussed about the histogenesis. So, we should focus maybe more on drugs that also are active against the sarcomatous component. One of the drugs that we are very familiar with is Caelyx, and there's actually very little data on that, but luckily, Phillip Harter, from Essen, published on that, five years ago, and they looked, well, it was a

combination with carboplatin, the phase II study, where they applied this combination to patients with leiomyosarcoma, endometrial stromal sarcoma, and carcinosarcoma. In red, you see basically the difference among the three subtypes. Actually, no complete responses in the pure mesenchymal cancers, but 23% in a carcinosarcoma. Then, if you focus in green on the carcinosarcoma, in fact, 70% had at least a clinical benefit and 38% had a response rate. So, I wonder in the future, whether we should not focus more on Caelyx when the cancer recurs. So, treating actually a cancer that is more composed of sarcoma components, and that may be also parallel to that, we need to discuss these patients also in the tumor board with our soft-tissue sarcoma specialists. So, regarding ovarian carcinosarcoma, I hope I could share with you and convince you that we should treat these patients by complete staging. In most cases, a complete cytoreduction till no residual tumor. And that also, we should focus on carboplatin-paclitaxel in the adjuvant setting that probably is needed both in early and advanced stage. And then maybe focus, when the disease recurs, focus more on the sarcomatous components. And this may be a subject for further research. So, as a general conclusion, I hope I could show you that carcinosarcomas, in fact, start as a carcinosarcoma where metaplasia occurs, and this is the monoclonal theory of carcinosarcoma. That surgical staging and debulking similar to high-grade endometrial or ovarian cancer is advised. And that for both entities, at the primary setting, paclitaxel and carboplatin result in the best efficacy/toxicity balance. Thank you for your attention. Happy to tackle any questions. Thank you.