Subtitles and transcriptions

Subtitles and transcriptions are available for selected materials for purpose of helping users understand the contents of the educational sessions.

Uncertain words have been indicated with ?? before and after the part. Parts that could not be understood at all have been indicated as [Audio Not Clear].

Every effort has been made to faithfully reproduce the audio of the sessions as recorded. However, no responsibility is accepted for mistakes or omissions. ESO does not endorse any opinions expressed in the presentations.

Low and high risk gestational trophoblastic neoplasia

Prof Seckl: Well, hello everybody, hope that you have enjoyed the festive season, and this is now, I guess, the end of January. I'm going to talk to you about the management of low, high and ultra-high risk gestational trophoblastic neoplasia, and there's a lecture to follow on placental site trophoblastic and epithelial trophoblastic tumors. So, to remind you that for a low and high-risk disease, we use a scoring system. This does not apply to PSTT and epithelial trophoblastic tumors, and this scoring system is pretty intuitive. So, if you have a lot of disease onboard or represented by a very high hCG or lots of metastases or disease in difficult areas to reach, you score more points on the system and this tells us that you're less likely to be cured with single-agent treatment. Whereas if you have very little hCG and no metastases or only metastases in easy sites, then, you score less points. And so, you're likely to have disease that could be treated successfully with single-agent treatment. And essentially, when you add your scores together, if you score 0 to 6 you're low-risk, so, single-agent treatment should work quite nicely. Whereas if you score 7 and above, you're high-risk, and then there's this new ultra-high-risk group, which is those patients scoring 13 and above, which we will discuss in a bit. So, for the regular low-risk patients, remember most of these patients will be women who've had a complete or partial mole where the hCG instead of returning to normal has plateaued or is rising consistently. Then, they're called up to the clinic where after taking a simple history, then, very simple investigations are required and that's blood test, principally to confirm that the hCG is plateaued and rising. We don't want to start treatment if the hCG is suddenly falling and obviously, to do other bloods that you would need before starting chemotherapy. In addition, we we'll do a ultrasound of the pelvis. And the reason for this is, obviously, you don't want to start chemotherapy if the patient has fallen pregnant with a new healthy pregnancy. And you certainly don't want to do a chest x-ray or any other imaging investigation that involves radiation, if they're having a healthy pregnancy. We like Doppler to be turned on because this can add useful additional prognostic information, which is still work in progress for the international community. So, if the ultrasound just shows suspected molar disease or doesn't show anything in particular, then a test x-ray can be done. And if that shows nothing, then, you don't need any further investigations. If there are possible mets, then, it's worth getting a CT test properly document these and measure them metastases centimeter or a bigger accounted in the scoring system, less than a centimeter or not. And if they're a significant lung mets, then the patient needs an MRI head because they're at risk for brain disease, once the disease has spread into the chest. So, most patients need no further investigations than simple

blood tests, Doppler ultrasound pelvis and a chest x-ray when they have low-risk disease. So, for low-risk treatment, the two most frequently used drugs are methotrexate, usually with folinic acid rescue or actinomycin D. We favor methotrexate and folinic acid in this particular regime because it's simple and pragmatics deliver. And we find it to be less toxic than the actinomycin D which tends to cause a bit more in the way of nausea and thickness and ulceration and some hair loss, but some centers prefer the actinomycin D because it's simpler to give for their healthcare setting, intravenously every two weeks. In our healthcare setting, we can actually deliver the methotrexate and folinic acid at home, with our district nurse system in the UK. The patients who are admitted for the first week of treatment because of the risk of bleeding. So these are highly vascular tumors about one in 50, will bleed very heavily. And of course, if they're at home, they might not get back to hospital in time. We are a bit rubbish at predicting who is going to bleed and who isn't. So, which of these regimens is better? The answer is we don't know, we only study comparing them head-to-head. We did not have enough patients to make a conclusion. So, this just shows you a patient who had a mole and flat at hCG, started on methotrexate, folinic acid because these could be a risk, had a lovely response and then, had three consolidation cycles. So, that's six weeks of consolidation because the treatment is given for a week with a week of rest. So, that's two-weekly cycle. And on that, the risk of relapse is 4%. If you only give two consolidation cycles, the risk of relapse is 8%. But how are we doing overall? Well, this old study published in 2002 in The Journal of Clinical Oncology, looking at 485 low-risk patients started on methotrexate and folinic acid. Those that roughly two thirds of them go into remission on this very simple treatment. One third developed toxicity or resistance for treatment. Most of them resistance to the treatment, about 3 or 4% developed toxicity. If the hCG was 100 or less at the point of resistance, then they got the single-agent actinomycin D as a second-line therapy. And virtually all of these went into remission, but a small proportion without resistance to actinomycin D and they needed the combination agent chemotherapy. If the hCG was more than a hundred, then they went on to the combination agent chemotherapy. And the bottom dollar is, that all of these patients had 100% cure rate. So, that's great news for patients, but clearly, it would be nice to spare more people, the toxicity of combination agent chemotherapy. So, to do this, we increased the hCG cutoff initially to 300 and still showed 100% cure rate and spared more patients EMA/CO. We then went up to 1,000 hCG cutoff, same result, less people needing EMA/CO, but we did notice that the success rate with single-agent actinomycin D was starting to fall, once the hCG was close to 1000 IU per liter. So, we've now increased the hCG cutoff to 3000. And the question is, will that still be the same? People often ask me, is it worth exploring other single-agents such as carboplatin? And the answer is, this is being explored and has been explored. And the jury is out as to whether or not this is a sensible thing to do. My own hunch, looking at the preliminary UK data, suggests that it's probably not right next step. So, obviously, as the FIGO score increases from 0 to 6 within the low-risk group, your chances of being cured with single-agent therapies previously being suggested to fall. And indeed, when you score 5 or 6, it's thought that only 30% of patients will actually have a complete response to a single-agent chemotherapy. And on this basis, some centers in the world have advocated that those patients should simply be getting on with multi-agent chemotherapy from the outset, but this is clearly much more toxic. And since our overall survival rate is 100%, is it really necessary to start all of those 5 and 6 patients on multi-agent chemotherapy from the outset? So, and can we identify some patients that could start EMA/CO whilst the rest didn't need to? And the answer is, there were some previous reports that suggested a couple of things that you could do if the hCG was more than 400,000 IU per liter and that will be a way to select patients upfront for EMA/CO. And if you had low-risk metastatic choriocarcinoma, then, those patients nearly always need EMA/CO, so, you might just as well give them EMA/CO. But this was based on small numbers of cases. So, we then set up an international collaborative retrospective analysis of low-risk 5-6 patients between ourselves, Brazil and Boston and identifying 351 FIGO risk 5-6 cases who were all initially treated with methotrexate and folinic acid. And the first surprising result was that 60% of these patients, were actually going into remission with either methotrexate alone or followed by actinomycin D. So, that means that only 40% actually required EMA/CO So, then the question is, well could you identify in that 40% patients who should just get on with EMA/CO? Is there a way to select those patients in advance? And there were three

groups identified upfront EMA/CO, those patients with chorio who had metastases and score 5 or 6. So, we confirmed the previous report, more than 70% are gonna need EMA/CO. So, you might just as well start those, potentially on EMA/CO treatment. And then, there was another group, those patients who had choriocarcinoma, histological diagnosis with no metastases and scored of five or six, or had a post-molar trophoblastic tumor with metastasis and their hCG was greater than 150,000. So, these patients, either of these two patient groups could've get on with EMA/CO. In fact, there were 12 such patients in our series and all 12 of them ended up needing EMA/CO. So, no point wasting time with single-agent therapy. And then, there was a third group, post-molar patients with no metastases and an hCG greater than 410,000. So, rather like that McGrath paper that we published before suggesting over 400,000 was bad news. Well, this confirmed it. And it nails it down to 410,000, using these different essays between the centers listed above. And they were 6 of 7 of those patients who ended up needing EMA/CO chemotherapy in this series. So, we've made a little headway in identifying which FIGO 5-6 patients should get upfront EMA/CO but clearly the majority should stop single-agent treatment. And most of them will still be cured with either one or two sequential single-agent. So, the scoring system, as we mentioned earlier, it does determine whether you're high-risk or ultra-high risk of disease resistant single-agent therapy, and therefore, should start combination agent chemotherapy. To just to remind us a little bit about the difference between these groups, regular high-risk score seven to 12, the ultra-high risk is 13 and above. Why this discrepancy? Well, in the regular high-risk, there's no risk of early deaths in the first four weeks, remission, whereas in the ultra-high risk, there is a risk of early death within the first four weeks, principally because of bleeding complications, organ failure, and metabolic health threat. There's also a difference in late risk of death from multi-drug resistance in the regular high-risk group, it doesn't seem to be an increased risk, but in the ultra-high risk, there is a higher risk of multi-drug resistant deaths later on. There are some features associated with these two different groups, interval from the causative pregnancy, less than 2.8 years, but regular high-risk more than 2.8 years. Ultra-high risk, advanced disease in the liver and the brain or advanced disease elsewhere is a bad prognostic factor. And there are ways in which we should manage the ultra-high risk group to avoid the early deaths. And one of these is to use low dose induction of etoposide and cisplatin and to consider adapting ongoing chemotherapy. So, how does high-risk disease present? And the answer is in many different ways, this particular patient presented with a lesion in her gum, thinking that this was a dental abscess. As you can see, it's a vascular lesion in the gum margin. And she was looked at by her dentist who said, this doesn't look like an abscess and sent the patient in for a emergency review. And in the emergency room, the team looking at her did an hCG test and found that it was very high before doing a chest x-ray. And indeed, the chest x-ray showed multiple lung metastases and subsequent investigation showed that she had extensive disease in the brain, the lungs, the liver, the pancreas, kidneys, nothing actually in the uterus. A third of these high-risk patients have nothing left abnormal in the uterus at the time of presentation. And this is the appearance after chemotherapy. So, this all went away and all the rest of her disease disappeared. Well, for any woman of childbearing age, who presents with unexplained metastases, measure the hCG. Certainly, don't go sticking needles into biopsy these lesions, unless you can control the bleeding directly because they are highly vascular and you might promote life threatening hemorrhage. So, this is a lady presented with convulsions and headaches and had multiple brain metastases. And you can see afterwards, brain has completely resolved following chemotherapy. She did not require whole brain radiotherapy, or indeed any stereotactic radiotherapy to achieve this result, all done through chemotherapy. This woman presented with a history of having had her previous child a couple of years earlier, and was busily trying to conceive and just simply couldn't conceive her second child. And when she was investigated, it was found to have unexplained elevated hCG. She was locally looked at for the causes of this, but nobody could explain it. And so, she was sent to us for a review. And what you can see on the CT scan is an area of plural irregularity thickening. And that was really the only thing that we found on her initial imaging, PET of this whole body did not show that there was any increased activity, at the time her hCG was around 100. And so, we placed her on monitoring and her hCG over the next year gradually creeped up and we repeated her imaging and this area of irregularity didn't really change. But PET certainly did, this had now become positive in the plural margin.

And so, we sent the thoracic surgeons and I got a call from this, saying I can see some vascular lesions. What should I do? And I said, now if you can control the bleeding, take one of them out. And let's look at it under the microscope. And you can see this classical looking choriocarcinoma with syncytiotrophoblast cells and it stains very richly for hCG. Now, the question is, is this a gestational tumor, or is this a non-gestational tumor? Because any type of epithelial cancer and for any other cancer can turn on the right genetic signature to histologically give the appearance of a choriocarcinoma and indeed secrete hCG. The pathologist can't tell the difference, but the genetics can, and this is microsatellite allele polymorphism. And what we've done is we've taken DNA from the tumor, DNA from the patients and DNA from the partner. And you'll see that in this particular microsatellite there is in the tumor an allele, this has come from patient, but there is also another allele in the tumor that has come from the partner. So, this is a gestational tumor. So, it's a little bit like who committed the crime in forensic notes. And you do this across multiple microsatellite allele polymorphisms to prove the point. So, it follows from this preamble that you need a broad spectrum of investigations, and that should include a CT chest/abdo, MRI brain and pelvis all with contrast, if the brain is involved, you might need to image the spine, Doppler ultrasound pelvis, and add information to the diagnostic pathway. If the brain is clear, then it's still worth doing an LP to measure the CSF serum, CSF serum hCG ratio, which should be 1:60 or less if it's 1:50 or 1:40. Then you know you might have a problem. PET imaging is actually best saved until patient's relapsed and you're not sure which is the active site of disease that affect. We don't find it particularly useful in the upfront setting. Remember histopathology is nice if you can safely get it, but don't stick needles into liver lesions because you might cause the patient to die from hemorrhage. And as you see in genetics is a useful thing to try and do to confirm if the patient has a gestational tumor, as opposed to a non-gestational tumor. This is the treatment that is widely used around the world to treat these high-risk patients. With the regular high-risk patients, it's etoposide, methotrexate, dactinomycin D on day 1. Followed by further actinomycin D and etoposide dose on day 2, so, this is an overnight stay in hospital. And a week later, an outpatient trip with vincristine and cyclophosphamide. But rather like the low-risk treatment, we admit patients for the first week or so of the treatment to make sure there are no bleeding complications that could place the patient in very grave danger. But then, after that, it's either an overnight stay in hospital or an outpatient treatment alternating weeks. And this treatment is very intensive. It does require weekly GCSF support to maintain treatment intensity, but very effective as you can see here. So, these are the high-risk patients, including some ultra-high risk cases who started on EMA/CO. And what you can see is that the overall survival is running just under 95% and this was in 2013. The new analysis for some of the new treatments that we now have to offer for salvaging these patients is pushing the survival curve up closer to 100%. For non-gestational tumors, like the lung cancers, the stomach cancers, the bladder cancers, that look just like choriocarcinoma to pathologists under microscope but genetics tells the truth, avoiding it causes you badly treat at home. And the low-risk patients who end up needing EMA/CO, 100% survival apart from one death in the series, which was a patient who couldn't stop smoking and died of lung cancer. And we don't cure all these 95% of patients with EMA/CO, 20% of them develop resistance either on treatment or relapse after treatment is finished, so, how do we salvage them? Well, two commonly used regimens, although there are others around the world, is this EP/EMA. So, notice that this is also weekly alternating regime here, we've introduced cisplatin as another active agent, but the EMA is not the same as the EMA in EMA/CO because we've omitted the second day of etoposide and actinomycin D. If you try to give that second day, patients will simply fall to pieces. Though a very tough regime as it sounds, close attention needs to be paid to liver and renal function and DCSF support is required weekly. An alternative and much less toxic regime is the TE/TP regimen. And this is a two weekly alternating regime. And we find that salvage rate with either EP/EMA OR TE/TP is very similar for EMA/CO failures. And because TE/TP is much less toxic, we favor that regime today, rather than EP/EMA, the salvaging EMA/CO failures. There are a number of other salvage regimens used in China. Our colleagues prefer this FAEV, here so FAEV regime, containing regime. Some people like to use some gem cell tumor regimens like BEP, TIP and Gem-TIP So, I personally don't like that because the three-weekly regime and some toxicity of bleomycin, probably, isn't terribly active in this disease. And any three-weekly regime in a fast-growing cancer is perhaps

not as attractive as a regime that you're giving every week or every two weeks in trying to stop tumor regrow between cycles of therapy. There are other alternatives, of course, if you're failing all these treatments. And that is that if a basis chemotherapy is working, why not use high dose chemotherapy? So, this is concept where you give a massive amount of chemotherapy with a target as bone marrow support, and this will salvage directly about 20% of cases and contribute to saving a further 20%. So, overall, probably helps up to 40% of patients. Gemcitabine, pemetrexed and capecitabine have all been shown to have some activity, although I've never succeeded in curing anybody with these drugs, either alone or in combination. Surgery must never be forgotten. This can save patient's lives. And then, there are other agents, people consider in addition to radiotherapy. We would certainly recommend stereotactic brain treatment, any residual deep-seated brain lesion, but avoid whole brain radiotherapy. This in my view, just adds toxicity. And there is no randomized evidence that suggest that it is superior to just simply giving chemotherapy and saving your stereotactic radiotherapy to the end if there's something left to treat. So, this just exemplifies a patient whose surgical salvage was clearly very important. And you'll see that they went through a lot of prior treatment with remitting, relapsing course, including going through high-dose chemotherapy. And eventually, when they relapse here with lots of lung disease, they went through further treatments, including high-dose chemotherapy, but we didn't succeed in getting the disease into remission. And there were still multiple lung metastases so, the patient went through a series of thoracotomies to remove as many of those lung mets as we could. We thought we got them all out, but no, the disease relapsed, there's more disease in the chest and also in the brain. At this point, we put her onto, escalated etoposide and cisplatin regime, which is 500 milligrams per meter square of etoposide and 20-meter square of cisplatin, given sorry not 20 it's 500 milligrams per meter square of etoposide and 60 milligrams per meter square of cisplatin, given all on day one, repeated every two weeks. And she goes into remission. The brain disease appears to melt away. There's this one residual little bit left, but they want to know what that means, but there was still one lung lesion. So, we got the surgeons to take it out and that showed active choriocarcinoma. So, clearly, the surgery here is being very important, and then just to be safe, we gave some stereotactic radiotherapy throughout one, tiny query thing left in the brain. And this lady has remained in remission ever since. So, surgery can play a very important part in saving patients. What about other new agents? Well, there are lots of things you could potentially consider, but I'd really like to focus on the immune checkpoint inhibitors, because I think that is the big news in GTN at the moment. So, you probably know a lot about immune checkpoint inhibitors, but just to remind you that a tumor's now including T-blood-cells can express molecules that are recognized as foreign. And in fact, in trophoblastic disease, at least 50% of the genes will be foreign to the maternal host and can be recognized by the T-cells of the mother. But why is it that the patient then doesn't reject cancer? Well, like in normal pregnancy, there are many mechanisms to stop that. And amongst them is the expression of a molecule called PD-L1, which binds to its receptor to PD-1 on the immune cell and suppresses this T-cell activation. In any piece of biology obviously, you can design things to interrupt this interaction with PD-L1 and its factor and the antibodies to PD-1, nivolumab and pembrolizumab, for example, will do this all nicely. Now, you get full T-cell activation and disruption of human cell, in theory, does this work out in patients? Well, we know that trophoblastic tumors very, very nicely express PD-1 at very high levels. So, this is an ultra-high-risk patients who had a disease in the brain and the liver and many other places, and started low dose induction of etoposide and cisplatin to avoid killing the patient in the first four weeks, then went on to EMA. So, adjusting the EMA to a gram, per meter square, Methotrexate to ensure CNS penetration and giving alternating weekly with etoposide and cisplatin. And she went into remission on this therapy, which was fabulous, but then she relapsed, especially, when had TET Methotrexate-Etoposide from the effects of cisplatin, followed by tandem high-dose procedure. And she went into a further remission, but then she relapsed, and then she had the escalated etoposide cisplatin regime, but she only got a partial response. And then she was progressing on gemcitabine, eto, ifosfamide and cisplatin but the gem cell tumor regimes. So, what could we do? Well, she'd run out of all the standard options. And so, at this point, we found a charity willing to support trying pembrolizumab. And you can see that on the pembrolizumab, immunotherapy, the disease went into remission by hCG and indeed the visible disease in her liver and lungs disappeared too.

And after six months in total of treatment, we stopped therapy and she remains in remission from that date. So, we set up a multicenter international collaboration trial and examined whether or not this is just a manic case or not. And the last round of analysis of these data, we've had 20 treated patients, 13 in the UK, 7 from non-UK and centers, and of those 20 patients, 15 had measurable disease and 12 of those 15 has had complete responses and that's not just choriocarcinomas like this lady, but also, some patients who had the central placental site trophoblastic and epithelioid trophoblastic tumors. We also had five patients who received immunotherapy as an adjuvant treatment after existing treatment, because we deemed them at very high risk of recurrence. And these patients remain in remission to date. Can we predict response? And the short answer to this is no, these treatments all express PD-L1 extremely well. And so, that's not going to be a biomarker of response. We're looking at tumor infiltrating lymphocytes. We're looking at HCGs and a number of other things, but I don't yet have the answer for how to predict responders versus non-responders so, watch this space. Should we be considering immunotherapy and other settings in GTN? Well, the TROPHIMMUN trial actually has tried to address this question. So, our French colleagues in Lyon, set up a study using a different immunotherapy agent, this is adalimumab, which targets anti, that's PDL-1, so it's the ligand, rather than the T-cell receptor. And they looked both in low-risk and high-risk patients failing their first-line of therapy. So, at low-risk disease, the patients who received high methotrexate or actinomycin D as their first single-agent, and as soon as they became resistant to that, they were then put on to adalimumab and in the high-risk cohort, that's cohort B if they became resistant to either EMA/CO or EMA/EP, then they'd be put on to adalimumab. They presented their low-risk findings in the JCO in 2020 and they showed that in 15 treated patients, 53%, 8 of the 15 achieved a complete response to adalimumab. So, not bad, but maybe not as good as just getting on with another single-agent in that setting and in the high-risk group, they showed that in fact of the 7 patients, they needed to close the study because of futility. And I believe there was any one patient who'd had a complete response and all the others had been progressing. So, or run into other problems. So, clearly quite discrepant from our own preliminary data with pembrolizumab. And there's plenty of work now to try and understand why there may be this difference. Is it simply because it's a different setting or is it because it's different agents or a combination of these things? And the answer is we simply don't know yet. So, if a single immunotherapy agent has worked well, should we perhaps think about combining it with another immunotherapy agent, that targets, for example, CTLA-4 ipilimumab. If you look at melanoma, for example, it's quite clear that the combination of an anti PD-1 with an anti CTLA-4 targeting agent, is better than using single-agent alone, but it's much more toxic. And of course, it is much more expensive. So, we don't know the answers to these things yet in trophoblastic disease. There's also evidence in, for example, lung cancer, combining immunotherapy with chemotherapy is better than either the chemotherapy or the immunotherapy alone. So, that might be another thing that's worth exploring. So, these are things for the future. So, what about ultra-high risk GTN management? So, we've said it needs to be treated differently. We mentioned that the low dose etoposide and cisplatin is a way of eliminating the early deaths. And that's been shown now by several groups. Obviously, if you've got brain involvement, then it's going to need adaptive care, patients might need an emergency operation when they first presented their bleeding into their heads or they've got pressure problems in the head to raise a skull flap, so, that the brain bulges upwards rather than downwards through the foramen magnum. They might need embolization of a nasty bleeding blood vessels to stop the patient hemorrhaging to death. And then, after you got them through the acute period, then they're going to probably need adapted ongoing therapy, adjusted treatment for brain disease, adapt to adjusted treatments if they've got brain and liver or liver disease, because these are poor prognosis patients, more likely to develop multi-drug resistance late to form. And then maybe you need to consolidate these patients for longer. The routine six weeks of consolidation may simply not be enough. And we favored eight weeks, but we don't have hard data, but that's better than six. So, and of course, for residual disease in difficult areas in the brain, stereotactic radiotherapy might be a very simple thing to do, and we mentioned earlier trying to avoid whole brain radiotherapy. So, what happens after we finished all the treatment? Well, six weeks after treatment is finished, we then do a post treatment review. But during the six weeks, the patient's continuing to send us samples to measure the hCG weekly. So, we

repeat any previously abnormal imaging. We give them advice about chemotherapy effect, almost screening sun-exposure. So, avoiding this for a year after chemotherapy, we talk about when to have future pregnancies and ideally if they can wait a year. That's terrific. But if their biological clock is ticking, we tell them about what happens to the 500 patients who did get pregnant in the first year and how any all goes away with a very successful result. And we talk about contraception that can be used and any form of contraception is fine. But obviously, if you still got a persistent vascular lesion at the bottom of the uterus, then sticking an intrauterine device through the cervix may not be in your best interest. We talk about the risk of relapse and hCG monitoring. And we talk about the fact that a lot of patients experienced psychosexual problems, some weeks or months, and even longer than that after the chemotherapy and offer them ongoing counseling. So, this is how we monitor patients in the UK for hCG after treatment is completed. But I accept that lots of you will be doing different things and nobody has an exactly right answer. We were doing this for life. So, you'll see it here in monitoring, every six months for life. We've stopped that now. We now only monitor up to 10 years, except in the ultra-high-risk patient or patients who have high-dose chemotherapy, where we're still collecting the data. So, the reason why we stopped, is because of this set of results, which show in low-risk disease that most of the relapses actually occur in the first two years. There's still a few that take place in the third year. And after that is vanishingly rare and there are no relapses after second year and in the high-risk patients, you'll see again, most of the relapses happened in the first two years and vanishingly rare to have relapses beyond that now after seven years. So, you could argue, you could stop quite happily after one or two years of monitoring. It's all about risk and perception of risk, and also about being able to collect more data so we can report more for you in future years. So, we are still monitoring the patients that I set up to 10 years. What's the long-term outlook? Well, it's excellent. 83% will have successful pregnancies after they've gone through chemotherapy. We do know that EMA/CO hastens the menopause by three years, so important to warn these women, that they may not be able to recover their ovarian function if they're undergoing chemotherapy in their late '30s or early '40s, but otherwise the vast majority will do. There's no increased risk of second tumors, providing you keep the chemotherapy to no more than six months. Early pregnancies, our data in more than 500 women who've got pregnant in first year is there's no increase in having an abnormal baby, no increase risk in the relapse rate. And of course, there were the usual second mode of pregnancies, but nothing over and above what we would expect. So, in summary, low-risk survival rate running at 100%, high-risk in excess of 95% biopsy is not mandatory. EMA/CO is widely used, but in the ultra-high-risk patients, you need to consider adaptive therapy, low dose of etoposide and cisplatin seems to eliminate the early deaths. And after that, you might want to consider how you adapt ongoing treatment. Do you just give EMA/CO or should you consider an EMA for example, and how to adapt disease and the diseases in the brain and then for salvage. But if you have regular EMA/CO you could use either EP/EMA or TE/TP. We favor now TE/TP because it's simply much less toxic and easier to deliver, but there are other salvage regimens out there as we discussed. A high dose seems to directly say 20% of the patients and contributes to a further 20% going to remission. But there's now an addition to surgery, immunotherapy, to consider giving way before high doses, it's much less toxic and seems to have a complete response rate somewhere between 70 to 80%, which I think is very encouraging, certainly for pembrolizumab. So, I think I'd like to stop there and thank you for listening to me and to acknowledge I don't work alone, but have a very large group of people that I work with and many international collaborators and the Sheffield trophoblastic disease team as well. So, thank you very much.