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ESGO/SIOPe guidelines in adolescents and AYA with non-epithelial ovarian cancer

Dr Morice: So, thank you very much. It's a great pleasure for us, for the ESGO and for the SIOPe to be with you. And I would like with Gabriele, to thank the ESO for the invitation to be there, to thank Fedro and to thank also Christiana Sessa, who was a very strong vice president of the ESGO, very active and deeply involved also in ESO. So, I would like to thank her and to thank all for the invitation to present you this project, that have been really fruitful, between both societies that wish to work together, to try to harmonize the management of young patients and young girls with a non-epithelial ovarian cancer. So, it was a great pleasure to work together for both societies, who has two physical meetings, where the methodologies inside the loop, of this work. And you can see here, all the guideline developments, and we have followed the same process, that we have in the ESGO since a long time, and in the SIOPE, with a methodologist involved which is ??Françoise Pérochon?? in work regularly for the ESGO as a methodologist with an evaluation of all the data published with Delphi method and the grading system that you can see here. And in term of description of the core of each of the paper that we'll analyze during this process. We have two face to face meeting in Brussels, for these guidelines. And we send all the papers and all the projects, all the proposals that you will see for validation of our criticism to 55 or 54 international reviewers, to review all the recommendations that you will see. So, with Gabriele, we will speak to in 15 minutes, I will speak about germ cells tomorrow, and Gabriele will present you sex cords and small cell carcinoma. So, about germ cells tumor, the presentation will be shorter probably because the management is, always, a conservative management in new patients. We have no place for radical treatment, meaning removal of uterus, and both ovaries is really contraindicated in this disease, whatever the stage of the disease. So, the first stage is a surgery. The choice of the approach should be done according to the aspect of the tumor on the probative imaging integrating ultrasonography and MRI that we should just use to choose adequately, the good approach, laparotomy all laparoscopic in early selected case. But the issue in these tumors and in sex cords is to avoid a rupture of the disease that is so frequent, unfortunately, in the initial management of this ovarian disease in young patients. You can have a bilateral involvement, which is infrequent in other subtypes, but for dysgerminoma and mature teratoma, you can have a risk of bilateral involvement. So, in preoperative imaging with a very good ultrasound, is very important to be sure that you have not bilateral involvement that could modify the surgical strategy. And you should have a full staging if the tumor, is recognized during the surgery integrating intraperitoneal staging with cytology and with biopsy of the peritoneal specimens and ??oophorectomy??. The key issue, you can add some questions every time when you them. You can send questions to the panel, the tool to reply with Gabriele, at the end of both presentations. Here you can add the typical aspect of dysgerminoma on the left, or can we avoid the rupture, to do a laparotomy approach. When you have this imaging, don't play with a laparoscopic approach to a cystectomy, you will add one with [Audio Not Clear] rupture, and that could modify the post-operatory strategy with indication of adjuvant chemotherapy on this context, that could be

avoided if you have a full removal of the disease without rupture. And on the right, this is also another non-epithelial tumor with a typical aspect of a teratoma. But this is very difficult to screen on MRI, between immature and mature. This is impossible. This is why, immature teratoma, this is so frequent to have initial cystectomy because the initial diagnosis is dermoid cyst. And after we will discover the immature parts of the disease during the pathology determination of the entire specimen. So, for the germ cell tumor, the restaging surgery should be considered only in the case, this is what we suggest, on the case where adjuvant chemotherapy is not indicated. If you have indication of adjuvant treatment on the basis of the histo-types, grading et cetera, there is no place for re-staging surgery. If there is no indication of adjuvant chemotherapy, and if the full stage has not been done during the initial surgery, you can consider staging surgery, if this can modify the indication of adjuvant chemotherapy. There is no place, this is the recommendation. There is no place, for routine lymphadenectomy, except if you have a big lymph node on preoperative imaging, we have long discussion inside the group but many of the colleagues agree on that. There is no demonstration on the improvement of survival, on the fact that we are removing the nodes we improve the survival, and in patients with stage 1C1 disease, meaning pre-operative rupture, you can opt for followup, or two cycles of chemo. For patient with stage 1C2 and 1C3 I remind you that it is preoperative or ??post-operative?? rupture or patient with positive cytology. You have an indication of adjuvant chemotherapy in this context. You can ask your questions, whatever you want, and we will reply to them at the end of the talk. Fertility sparing surgery is always, the key issue, even in patient with peritoneal spread of MOGCT disease, with nodal involvement, you would have no place for hysterectomy and bilateral salpingo oophorectomy. You don't need to have a systematic ovarian biopsy if the controls all seems to be normal. I remind you that you can add some bilateral involvement in dysgerminoma or in immature teratoma. In this way you can promote, a unilateral salpingo oophorectomy and contralateral cystectomy if this is technically feasible, removing all the disease microscopically. Because the high chemo sensitivity of this disease, extensive cytoreductive surgery, meaning the debulking surgical with removal of uterus and both ovaries should be avoided during initial management. Standard chemotherapy is the based on the BEP regimen or with other options with the PEI or JEB regimen that is used in pediatrician protocol. You can see here, the number of cycles of chemo that we recommend in patient with advanced stage disease. You should just consider, a very specific [Audio Not Clear] disease, which is observed in immature teratoma, but sometime in other malignant germ cells tumors, that is growing syndrome teratoma. This is a typical aspect of patients, that have initially immature teratoma with a rupture of the disease during the initial management, and that develop, thereafter, such aspects with very big masses in the abdominal cavity. In this case, you can have a huge involvement. You can see here, between the liver and the kidney, some diseases are in the peritoneal cavity, but this is never if the patient had normal blood markers. This is never the indication of the second line chemo. You should go to the surgery, if the blood markers are normal, because this is the situation, of growing some old teratoma. This recurrence is observed in between 15 to 80 percentage of patient with immature teratoma at the initial management. And you can see here the surgical aspect that we have during the surgery of growing syndrome teratoma, it's here between the bladder here and the uterus here. And here we have peeled the uterus, keeping in place the uterus, and removing the bulky, probably to prevent spread. This is why you can use exactly the same procedure that you use, in the epithelial ovarian cancer, but you should promote the fact to use, preservation of the uterus, with the peeling of the surface of the uterus if you have bulky disease, on the Ceros of the uterus. So, this is why the prognosis of growing syndrome teratoma is very good, because it is mature disease not immature, so, these patients are treated by exclusive surgery, without chemo. If you are in the case of recurrence with abnormal blood markers, this is probably a recurrence and immature disease. And this is where you can discuss the case of a second or third line of chemo. And in this case of refractory of recurrent disease, there is no defined strategy for patients who relapse after completion of chemo. So, you can discuss different option located, depending on the location of the disease, with new platinum-based chemo, or radiation therapy that could be discussed in dysgerminoma. Intensify chemo, can be considered or sometimes salvage surgery, secondary cytoreductive surgery, but we have no proof of the efficacy of such strategy. In these last slides about germ cells tumor, you can see here, the recommendation of the group

about how to follow these patients on which basis we can do it. And you can see here that we recommend, the use of clinical examination for sure, blood markers and imaging, with MRI or CT scan, but we should avoid repeated CT scan, in this very young lady that will have a very long, and that will be cured for their disease, to avoid repeat frequently CT scans. So, you can promote MRI, but an under abdominal pelvic MRI. This followup should be regular, even after five years, because you should be sure also about the key issue of the fertility issue after the initial management that could include chemotherapy. So, thank you very much for your attention for the first this part about germ cell tumor and you will have so the next part with Gabriele. Gabriele.

Dr Calaminus: Okay, so, I'll continue now with sex cord-stromal tumors. I hope you can hear me. Sex cord-stromal tumors is another disease, which is affecting, the ovary, in specifically also in AYA patients. I will talk here as Dr Morice did about the management of this disease, not about the diagnosis and the pathology. So, for the management of the earliest stage, it's important to do a very conclusive staging, because this tumor or this disease is likely to spread on the peritoneum. So, you have to be sure that the peritoneum is free of any seeding or dissemination. And you also have to have a look at the contralateral ovary to see if this is without any signs of disease. As in germ cell tumors, the systemic lymph node dissection is not recommended. You only should resect those lymph nodes, which are suspicious and either in one imaging or inter-operatively. If there is a confirmed stage 1A, figure 1A then you can only do surgery and resect the ovary and do close followup. There are some exemptions of this, and this is specifically, if other or specific different sex cord-stromal disease are appearing likes Sertoli Leydig tumors or Sertoli Leydig cell tumors which have specific retiform patterns. Because we know that these diseases or this specific sex cord-stromal tumors have not the same good prognosis as sex cord-stromal tumors in general have. If you have patients with stage higher than 1A, chemotherapy has to be discussed. As also in germ cell tumors, if there is a stage 1C granulosa cell tumor, which is also a sex cord-stromal tumor, it is possible to think about close followup, if the compliance of the patient will allow this. Differently in figure stage C2 and 1C3, juvenile granulosa cell tumors and all stages of Sertoli Leydig tumors 1C, chemotherapy is recommended. And these patients should receive, three to four cycles of cisplatin-based chemotherapy. In advanced stages, the patients have to be discussed, before touching tumor in a multidisciplinary team setting, because specifically if you have already acquired broad spread of the tumor seen in imaging, it might be considered to first start with chemotherapy. And then you do delayed surgery, to have a better attempt for complete resection because this is, should be always the goal, to have a complete resection of the tumor and all of the other dissemination or metastasis on the peritoneum. You can use either platinum or carboplatin. Also, the combination of carboplatin and paclitaxel, is good to use in such patients and they should at least receive four cycles of chemotherapy. Sometimes, even more have to be given. It is very difficult to treat patients who have a refractory disease or recurrent disease. And, the attempt of treatment is again, important to be discussed in a multidisciplinary team. And it has to be taken into account, where the site of the recurrence is the dissemination. How long was the tumor free interval? What was the previous therapy, and what is the primary histological subtype and there has been a change? So, patients with primarily stage 1A and have a progression, they can be treated easily with chemotherapy and have a far good prognosis, but all the others, if as cure is to be attempted, then you have to do quite aggressive chemotherapy and then re-surgery aiming for the maximum of cyto reduction. Also, these patients, specifically in those with advanced recurrent disease, additional treatment options has to be considered, and therefore preferentially all of the patients regardless of the stage should always be treated in clinical trials. There might be some patients, on the tumors where hormones treatment could be given and also enter any treatment or target treatment could be considered. If targets have been found in the molecule biological classification of the tumor. So, you can ask at every time questions and we will discuss them at the end of our presentation. The followup of these tumors is a bit different from those what we have shown for the germ cell tumors but what you can just notice is always that stage 1A patients need less followup than those with higher stages. In general, the interval of clinical examination is about four months in the stages in the low stages, and about two to four months in the highest stages. And it should always be clinical

examination, blood markers, and as the first possibility use ultrasound, but specifically in advanced stages, MRI is the imaging of the choice, to do the followup of these patients. It has to be also noted that patients with Sertoli Leydig tumors could germline DICER1 mutations. And if this is a fact, they have to be screened and this is important also in the long run, for other tumor diseases like thyroid cancer. So, for sex cord-stromal tumors the take home messages would be that in general, they have a good prognosis, a complete diagnostic staging is mandatory. The management of the disease in first diagnose and recurrence always should be discussed and consented in a multidisciplinary tumor board. The surgical and chemotherapy treatment has to be adapted to the stage of disease. And if possible, patients should be registered in available trials or registries, and also these patients have to have a structured followup. And I said, they should be screened for other diseases, if a germline DICER1 mutation is found. So, coming now to the last tumor entity, that we grouped under the ovarian non-epithelial tumors in AYA patients, small cell carcinoma of the ovary of the hypercalcemic type. This is a very, a rare diagnosis but the management of this disease is really-really difficult. And we have to say that if you have an advanced stage, the attempt to cure is very difficult. So, coming to the early stage, here in this disease, we are not talking about fertility sparing. It is specifically that the surgical attempt in an early stage is really radical. So, you have to try to get zero resection. Also, if you have to do a total abdomen hysterectomy and the bilateral salpingo-oophorectomy because if you want to make, to give the patient the chance of cure, you have to do it. So, adjuvant chemotherapy is also more intensive, than we have shown this for the sex cords-stromal or the germ cells tumors, and even radiotherapy is to be considered in a multi-modality would any approach. Although the role is not well defined up to now. Also, if you have a patient then after a surgery, that have no evidence of disease after then giving him initial chemotherapy, you even might consider to give does intensive chemotherapy with stem cell support, and this makes you come to the question that if you have patients with this disease, you should already in the beginning do stem cell collection to be able then after quite intense chemotherapy to give even more chemotherapy. In advanced stage, this is also something you have really to take into account what you can do for the patient. And if a complete surgical staging is done and you see that there is a chance for cure, you should try and give chemotherapy and then do another staging to see if your treatment was successful. Again, high dose chemotherapy and dose intensification with stem cell support and radiotherapy are options that might be considered. If you have a patient with refractory or recurrent disease, we can say that this is nearly not... these patients are near not to be salvaged again, there is no standard treatment, and we really need specific clinical trials with new drugs trended to the biology of the tumor. And we hope for this really difficult and mostly fatal disease there will be treatment options better than that what we have in the hand actually. Follow up is also not defined. You have to adapt it to the individual patient, and you should always discuss this as well in the multidisciplinary setting, that you have in your hospital. So, if you have questions, please answer that in the end. And coming to the take home messages, it is a disease whereas a very ??dismissive?? prognosis, complete staging again is very, very important, management of disease it's always a multidisciplinary approach. Treatment is very intense. Curation is difficult. There is no standard treatment up to now for patients with recurrence or relapses or progression. And specifically, for this disease, we need new options for treatment to improve the prognosis. So, thank you very much for your attention. And we are happy to answer your questions and you see here the group, of very enthusiastic colleagues who work together for these guidelines. This was really fun scientifically and personally, and we hope you could get something from these guidelines that help you for your daily work. And we are very happy to welcome your questions.

Dr Peccatori: So, thank you very much. I think I thank you Phillips. Thank you, Gabriele. I think that we can open up, the discussion now, and just to give some more take-home messages of these very good, presentations. Well one take home message is that of course we should rely on expert pathology assessments. These are rare tumors, and it's important to differentiate, exactly the histology of each disease. Another important message is that we should use appropriately, tumor markers, this disease tumor markers

are very important, particularly in terms of tumours. And another take home message is that always be conservative. Maybe, with the exception of small hypercalcemic tumours, conservative surgery which is the first, let's say pillar of treatment, they should be always pursued and you have seen also in advanced disease, the fact that these tumors are so chemo sensitive allows also to be conservative, whatsoever. With the exception of small cell hypercalcemic. Another important message is that these young patients, it's important to remember the fact that the late effects unfortunately remains forever and that mainly, alluding it to the late effects of chemotherapy. So, whenever it is possible to use surveillance in these group of patients, I think this makes sense. And also, on the same path, to find a balance in the surveillance programs, because you've seen they are quite intensive and they are quite a demanding for patients, they are important because the early detection of relapse is very important to be able to do a curative treatment therapies. But, you know, remember that also the effects of followup can be quite important in terms also of radiation so whenever possible use MRI or ultrasound. And the last but not least, always remember the special needs of adolescents and young adult patients. Some of these needs have been addressed. Others are as important for example the fertility issues, not only in terms of surgery, but also in terms of monitoring of the fertility after treatment, the sexuality issues that are particularly challenging in these group of patients, they returning to work or to school in this group of patients and then the access to clinical trials. That is another very sensitive issue in this group of patients that sometimes have difficulty in accessing clinical trials. So, we have a number of questions from the floor. The first one is about recurrent sex cord tumors. And do you usually, do a molecular characterization of the currents? Is there a need to biopsy the recurrence to have an up to date molecular characterization and trying then to use some of the targets that you might identify in the tumor for treatment? What do you do in your centers? What do you do in Berlin and what do you do in Paris?

Dr Calaminus: So, may I start what we would do first. I mean it is always important to have the tissue of the first and the second compared to see if there are changes in the characterization. And the characterization is starting always with the regular immunohistochemistry, but you also would look in terms of certain roles. So, it means how many mutations are appearing in the tumor. You will look at the methylation state to see we'll look at them at the mutation status and see if there are changes happening from the first to the second diagnosis. And you will also look for specific targets, that are bind to known pathways that are activated in these tumors. The point is that up to now there are not specific targets available for all the sex cord-stromal tumors. So, there might be some which might have targets that are hormone driven that you can use for the treatment in recurrence. But to say there are those targets for such a disease, this is not, available in a kind of trial up to now. Philippe would you like to-

Dr Morice: The use of characterization depends on these two types of disease because in inpatient like adult, it is really infrequent in the population that we are covering today. We're promoting the surgery and the first or second line of chemo if it is not being used during the first management of the chemotherapy being used when the first strategy. So, we don't use routinely in the adult granulosa cell and molecular characterization. But in juvenile, there is different prognosis if the patient recurred. So, we use it, even if have been said by Gabriele it's very difficult, to know exactly which kind of target we can use, in term of treatment in this kind of disease. And certainly, recurrent granulosa disease is already a nightmare. So, we use characterization for these recurrent patients because the chemo sensitivity is really poor. So, we push the patient when they're cured, to use on the phase one disease or new drugs, in this case, characterization of the disease is very important.

Dr Peccatori: And related to these questions thank you for your answers. So, related to this question, there is another question about the use of Tazemetostat. which has been approved for epithelioid sarcoma, in young adults and the adolescent. Do you have any experience, of the use of this oral drug in also non-epithelial ovarian cancer?

Dr Calaminus: I have to say I have no experience with this. No.

Dr Peccatori: Yeah, and well the question was more about small cell hypercalcemic, which of course, it is the most difficult disease to treat with the worst prognosis, and with rapid onset of resistance. By the way, it's one of those tumors where the world of genetic counseling and genetic assessment also in the family may be important because recently there's been also identified a specific mutation, which can be a germline mutation. How often do you refer your patients with germ cell tumor to the geneticist and which patients do you prefer and shall refer to the geneticist?

Dr Morice: Gabriele, ladies first.

Dr Calaminus: Yes, so, as usual, we do a very, close family examination. And if there are any other family members also in the third generation or in the first generation, in whom germ cell tumor or other ovarian tumors have been reported. And also, specifically in patients we know have syndromic abnormalities, like in patients with Swyer Syndrome or other, syndromic appearances, we always will talk to the patients and parents, for doing genetic counseling. Because we know now that there are more, even far more predispositions, issues such in such diseases, than we have known 10 years before.

Dr Peccatori: Yeah, Philippe.

Dr Morice: That is a very odd question that we covered during the two meetings, because we know the mutation, which is a marker for mutation, in the context, patient with small cell carcinoma. The main question and the main issue is that we promote probably exactly as I've been mentioned by Gabriela, genetic counseling, the question is how to manage, the other non-affected very young lady, when you find a family with this marker for, because probably prophylactic surgery should be discussing very young because the disease appear very... So, it's very difficult. There is no consensus, about the management of markers for screening, as a family screening in this population. So, it has been discussed, during our guidelines. And it's not a very easy chapter.

Dr Peccatori: Yeah, we don't know actually also the penetrance.

Dr Morice: Absolutely. Absolutely.

Dr Calaminus: Maybe, I should add one information to the first question of the discussant ??Stefan Heiby??. Nowadays in quite a lot of the European countries, there are platforms established now to test specifically patients, pediatric patients, but also AYA patients with recurrent cancers which are rare, and where no specific treatment options are available. And those platforms can be used maybe specifically for these patients to get more information about possible effective drugs. I mean, it's not something you can be sure that will work, but, it's possible to have some more information about possible treatment options, in phase two trials for example, or also as in individual treatment, in such patients.

Dr Peccatori: Yeah, and if I may add something to that, fortunately, I think that, the wind is changing and the limit of the 18 years old to access, at least some of the clinical trials, and is being gradually abandoned, even if in some trials it still remains. So, that kind of limit, particularly for the new drugs that are commonly used in adults. So, I think that it's important to know, that limit does not have any biological significance. And it's important when we characterize tumors that all patients with specific mutation might have access to clinical trials. Also, if they are in this in-between age, that is, the adolescent and young adults, still remains a gray area. I have another question about this group of patients, because AYA it's really no children but no adults. So, its, again, specific needs. How do you, do you manage to manage this group of patients? Do you think that there should be specific, wards, spaces, hospitals, departments to give these patients? Do you think that there should be a collaboration between the adult oncologists and the pediatricians? Do you think that pediatricians are better? Well, this is for you Gabriele. What do you think? I mean, it's still controversial, but I would like really to have your opinions on that.

Dr Calaminus: Well I think it depends also a bit of the system of the health care that you have. For example, I can say for pediatric oncology, it is not any more so limited in terms of the age group. So, for example, we already have, you can say, parts of the ward with a bit of a different team, was our teenagers. And patients always with, maybe you can say, pediatric tumors that are older than 18. That is specifically for the brain tumor. So, there is the already a more inter-disciplinary, exchange happening now. Because, I can say just from our approach, but I think it's the same, in most of the European countries already, that now all the patients have to be discussed and treated multidisciplinary. So, also for patients who are AYA patients, or even young adults, there is now not only the need, there is a kind of, it has to be, inter-disciplinary or multi-disciplinary approach. If we would have the chance to have AYA wards, that would also mean, that you need professionals working on this ward that are facing a tremendous amount of different diseases. So, I'm not sure if this is the solution. I'm more convinced that the solution is to have a multi-disciplinary approach for the treatment. And that you incorporate other disciplines and experts for treatment of your patients and that you do surroundings and settings for these patients which are important and interesting for them. So, that means that if there is a specific, you can say professional team, that is handling patients that are older, older than let's say 12 until 25.

Dr Peccatori: Yeah, what about you Phillip? You have a lot of experience in treating young adolescents, young girls with gynecologic malignancies. Do you face specific challenges, also related to the fact that these young ladies, I mean, have a disease that affects also their genital apparatus, we saw the investment in the future in terms of fertility sexuality, how do you manage it?

Dr Morice: I think that there is as mentioned, by Gabriele, there is regulation, in many countries in Europe, but it is the case in France. You need to have a pediatrician when you discuss of this case of AYA. The question is the age because for me 24, it's [Audio Not Clear] question, to have patients with 24, 25 it's an adult for me, it's [Audio Not Clear] patients but it's at least, at least between 15 to 18-20, the pediatrician should be there when we discussed. So, this needs to be done, cleverly in the multidisciplinary staff and we do it usually, because both communities could help the other one to bring some ideas to bring some inputs and their own experience. This is the first point. And the other point is to promote and so specific networks about rare tumor. Because these diseases are rare and you need to have, and to promote, we are very lucky in France because we are very strong networks, but where volume tumors are different in countries, in Europe try to do it in Europe. And we have a huge number of discrepancies, for example with a pathologic examination of the disease. So, we need to have experienced colleagues and we need to have also specific networks to decrease the weight of false results. Because the key issue is the pathologic resonance and the experience of pathology of the ovarian tumor. And sometimes this needs experience, but also this needs to be very, to be done very in emergency because small cell carcinoma could not wait four weeks, to have the second opinion in term of pathology. So, you need to promote us a very robust system, to have the second opinion in terms of pathologic review, very rapidly in some of this disease.

Dr Peccatori: Yes, I think that the European reference network for cancer is a good example of how really you should, make up networks that they're efficient because as you said there you cannot really wait one month to have a second opinion in terms of pathology, but also in terms of treatment and assessment. So, yeah it's a very wise. So, I think we are almost there, we're have almost finished our time, but I would like, to end our discussion now, with a question to each one of you. You are representative also of, as good as European Society of Gynecological Oncology, and COP, the Pediatric Oncology Europe, the Society of Pediatric Oncology Europe. And then this paper, this, let's say experiment, that I think it was very successful. Do you have any other plan to collaborate in this group of patients, that are in between? And what is the disease that maybe it's more, let's say, fit to collaborate?

Dr Morice: In fact, we were so happy to work together. It was really a pleasure to work together. We share different aspects, different ways to see same disease. And it was really fruitful in the kindness in the goodwill. We want to continue; the strong wish of this obvious goal is to continue with the SCIOPE. And we want to

collaborate, the next issue will be to collaborate on vaginal and to incorporate the rupture in younger baby, in young lady, in young girl, in the larger spectrum of guidelines about budget and consult. In which we will integrate. But we want to continue with Gabriele with the other colleagues from SCIOPE side, because it was a very good experience.

Dr Calaminus: Yes, I can just say, this is also the same opinion from our side. I think what is also bringing this cooperation is more of a mutual understanding, of the position of the other discipline. And also to promote this cooperation, not only on this base, but also bring the guidelines into life, into the daily work in hospitals. That would mean that colleagues from the different disciplines, if they have this guidance in their hands, they can more easily work on these platforms and be in this multidisciplinary team approaches. Then this I think it will be a growing success, and we all need throw the ball into it, to make it go further.

Dr Peccatori: Well then, thank you very-very much, for your participation, and thank you to all the, also viewers of this seminar. And you will see the next, e-ESO session on the next slide. Thank you to everybody.

Dr Morice: Thank you very much. Goodbye.

Calaminus: Thank you. Bye-bye.