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Follow-up in testicular cancer

Prof Banna: Hi to everyone, it's a pleasure to be here this evening. I'm Giuseppe Banna, I am a consultant Medical Oncologist, and I look after patients with thoracic and urology cancer. And tonight, we'll be discussing about the follow-up of testicular cancer patients. These are my disclosures. Let's start with some facts and figures about testicular cancer, which is the most common malignancy in young males, between 16 and 34-years, with an incidence which has been increasing for the last two decades. About 50% of all testicular cancers are seminomas by histology, the other 50% are non-seminomas. And most of our patients with testicular cancer will present a stage I disease, about 80 to 85% of all patients. Testicular cancer is the paradigm of a curable neoplasm. Indeed, in the last 40 years, there has been a steady increase in the cure-rate in both histologies, so, in the seminomas and in the non-seminomas, and this was due mainly to the appropriate use of cisplatin-based chemotherapy, but also to the radiotherapy, of course. This means that almost all patients become long-term survivors, which is important for the follow-up of our survivors in terms of the prediction of the disease relapse and the long-term effects of the treatments. So, my speech today will be on, and our discussion, will be on four key-topics. So, the relapse risk, the treatment-related long-term effects, the surveillance and follow-up recommendations, and the management of treatment-related effects. Let's start with the first topic. So, as I said before, especially in the early stage, the cure-rate of testicular cancer is around 100%. And the problem is of course the disease relapse. So, especially in the stage I disease where we can opt for a surveillance strategy instead of a chemotherapy after the surgery. Especially, in the non-seminoma disease, we can go for a surveillance strategy, but also in the seminoma disease. And we can consider some risk factors, which could predict the risk of the relapse, especially in the non-seminoma, the presence of vascular invasion is particularly important, and presence of embryonal carcinoma as well. The risk factors for the stage I seminoma have been recently questioned, but they are still the tumour sites, more than 4 cm and invasion of the rete testis. For the stage II disease, actually we use the size of the lymph nodes, the number of the lymph nodes to decide to offer the patients radiotherapy or a chemotherapy. So, it's an important risk factor. And in the stage II non-seminoma disease, the level of the serum markers is also important because in the negative marker, in the normal markers, we could still propose to our patients a surveillance strategy or a surgery. Instead of a surgery followed by a chemotherapy, or a chemotherapy. So, the prognosis has improved particularly in the late-stage disease. So, in advance stage, or stage IIC and III. But there are some, still, there are still some risk factors that could help us to identify those patients who are most likely to relapse. And those factors are the histology. So, patients with a non-seminoma histology, of course, are at higher risk than the seminoma. The primary site with a worst prognosis by the extragonadal germ cell tumour, particularly if the mediastinum is the primary site. The presence of non-pulmonary visceral metastases. And of course, the level of the serum tumour markers. Recently, in the update of the international classification which has actually showed that there is an improvement in the progression-free and the overall survival of our patients, again, because we use the chemotherapy better than in the past. Some new factors, especially the age, and the lung, the presence of lung metastases have been identified as

other possible risk factors. We have also risk factors for the disease, which will relapse despite our treatment, so, will be refractory to our treatments. And there are five factors. Again, the primary site, the prior response to the treatment, the interval, the disease was under control in terms of, of course, of time. The level of the alpha-fetoprotein and HCG, and the presence of liver, brain and bone metastasis. Of course, those patients who, despite the disease relapse or progression, have none of those factors will have the best prognosis, and also with all the factors, have really the worst prognosis. Another factor that we need to consider for the relapse, is the possibility of late relapse, after five years, it's a rare occurrence. Actually is a... the late relapses are described in about 1.5 to 3% of all our patients. And usually, especially if they have received a previous chemotherapy, these relapses tend to be chemo-refractory, so, the best treatment would be surgery. But what I want to highlight for these late relapses is that up to 72% at least in the Indiana University series, could be diagnosed just with symptoms, or the markers possibly. So, it is not needed a tight follow-up with a CT scan for those patients. But anyways, it's a challenge for the timing of our follow-up period. And finally, about the relapse, what is important is, of course, that we should rely and hopefully really, in the future, in the near future, we could rely on some novel biomarkers, like the miRNA-371, which is expressed from active germ cell malignancy, and whose ROC curves have over-performed the CT scan and the serum tumour marker. So, there are some ongoing studies and this could be the novel biomarker we could use in the future to detect an early relapse of the disease. I don't know if there are any questions, otherwise, I could carry on with the second topic which is the long-term effects of treatment. So, this is another thing that we need to consider for our follow-up strategies. So, of course, the most concerning long-term effects of our treatments are secondary malignancy, which could be related to the radiotherapy, especially if the subdiaphragmatic field is included or/and is also dose-dependent. Of course, the radiotherapy could increase the risk of leukaemia and other solid tumours. But there could be also, there is also an increased risk of secondary malignancy, including the leukaemias and gastrointestinal cancers for patients receiving a chemotherapy with etoposide especially if we exceeded the dose of 2000 mg as a cumulative dose, which we reach with four BEP cycles for the etoposide. And it's also dependent on the dose, especially for the gastrointestinal cancer, of the chemotherapy or with a cisplatin. It is important to know that the risk remains after 20 to 30 years. And today there is no other risk by the CT scan in terms of secondary malignancy. The other factor are the cardiovascular effects in terms of hypertension and ischemic heart disease. They could be related to the chemotherapy but also, to the radiotherapy, and especially the hypertension. And there is a 6% risk of ischemic heart disease after cisplatin, which has been described. We need also to consider about the cardiovascular disease that possibly even the tumour volume is important, because it will increase the risk of thromboembolic events. And also, the metabolic syndrome is another possibility, another late-term effect of both the chemotherapy but also, of the tumour. Because the tumour could cause, of course, a condition of hypogonadism. There are other long-term effects we need to be worried about. Hormonal late effects, like infertility, hypogonadism, sexual dysfunction, and generally ageing. Either hormonal ageing and physiological ageing, there is a 30% reduction in paternity, in testicular cancer survivors. What about the renal and pulmonary toxicity? Which of course are related to the cisplatin and bleomycin respectably. They tend to be stable after the acute phase as long-term effects. There are some neurological effects we know very well, related especially to the cisplatin and the taxanes, which are, of course, dose-dependent, and they involve the ototoxicity, the paraesthesia and the Raynaud's. And it has been also described an increased rate of anxiety in testicular cancer survivors. So, in 20% of testicular cancer survivors as compared to the 12% of the general population. It has been also described an increased depression, but we do not know in the general population which is the rate. Of course, this late-term effects of the treatment could result, and actually result in mortality, in non-testicular cancer mortality. And there is a 23 to 40% excess in non-testicular cancer mortality as compared to the general population, which is related to the use of cisplatin-based chemotherapy, or to the radiotherapy with the dose more than 20 Gy. It happens especially to younger survivors. So, those whose diagnosis of the disease has occurred before, prior the 20-year of age. And the cumulative mortality is of 9.6% in a 25-year period. As expected, the causes of non-testicular cancer mortality, the most common causes are the secondary malignancies, the cardiovascular disease which occurs, especially, in the first year.

And there is also, a suicide risk with a 20% increase in this kind of mortality. Other causes of non-testicular cancer mortality are infections after surgery, genital-urinary diseases after platinum-based chemotherapy, and digestive disease after radiotherapy. Even in this field, we are looking for some genetic biomarkers of genetic susceptibility to this kind of toxicity. Actually, we have some of these genetic alterations or polymorphism that we could assess for the prediction of the pulmonary toxicity, the neuropathy, or the ototoxicity. The problem with these biomarkers that instead of the miRNA, they are not still validated for clinical use. They require expensive tests, and specialised labs and often, eventually, are not very helpful because we need to treat patients to guarantee the high cure-rate of treatment. So, sometimes, could be considered like slightly useless. Again, if you have any questions, you can interrupt me whenever. Let's go ahead with the third part of this discussion, which is, given this risk of relapse we should look after at late-term effects. Which could be our strategies in terms of follow-up? So, firstly, there is not a standard definition even in the follow-up word. So, some authors have suggested that we should mean with surveillance, a strategy which is more focused on the early diagnosis of the relapse, using the term active surveillance, indicating a strategy as an alternative option to an active treatment like the chemotherapy for the stage I disease. And with the follow-up word, with the follow-up term, something which aims more at detecting the medium, and the long-term consequences of the treatment, the later effects. And the second important thing is actually is a field where there is no strong evidence supporting the modalities, and the timing of examination. Which does not mean that we do not have some practical guidelines we could follow actually. Which come from some scientific societies, like the EIU, or the ESMO or some other societies like the NCCN, which have been also reported. This kind of strategy often consider the risk factors. They give some indication about the radiological examination type and the timing, and the follow-up, intensity and duration. I would like to mention some examples, which have been actually reported about the follow-up strategy. The first one which has been reported was about the UK guidelines for the follow-up. Seven scenarios actually were drawn based on the disease stage and treatments. So, for instance, for the stage I seminoma, where active surveillance is the option instead of the chemotherapy, dose recommendations, also, 5 CT scans which should be performed every six months for the first two years and then, yearly for five years. What is important is the UK guidelines stress the concept that the CT scan should be of the abdomen only, because it's very unlikely that the disease will spread to other organs skipping the abdominal lymph nodes. So, for the study of the chest, is enough a chest X-ray, not a CT scan, to spare, of course, radiations by CT scan. And for the seminoma, the follow-up should last for 10 years. But after the year-5, could consist only on clinical visits and markers. Another important advice is to follow patients for the late effects of treatment at the year 2, 5 and 10. And it does mean that we should follow patients with clinical examination, blood pressure measurements, item weight for the metabolic syndrome, some lab tests, including the lipid and hormone profile. Similarly, for the stage I seminoma, which has been treated with carboplatin, where the likelihood of having a disease relapse is very low. Of course, the number of CT scan is reduced to three CT scans. And, similarly it happens for the stage II disease, if our patients are treated with carboplatin or radiotherapy. So, no need to perform too many CT scans, if they have been treated with a chemotherapy. And again, the same recommendation applies for the use of CT scan of the abdomen only, and the duration of the follow-up. In the non-seminoma disease, there is something different. So, for those patients we will refer to the surveillance strategy, so no chemotherapy, they suggest to go for three CT scans. Specifically, two CT scans are performed within the first year and just one CT scan on the year-2. So, from the year-3, there are no CT scans to be performed. This is why there is strong evidence, that the disease relapse in the non-seminoma will occur in the first two years. Almost all the disease relapse in the non-seminoma, the stage I, will occur in the first two years. So, no need to perform further CT scans later on. Furthermore, we could follow these patients with the markers as well. Of course, when these are patients at the stage I are treated with an active treatment, it is enough to go for one CT scan. Another difference as compared to the seminoma, is that in these patients, we can complete the follow-up, or at least the UK guidelines suggest to complete the follow-up at five years. In the case of the advanced disease, where a disease remission, a complete remission is achieved, is enough to go for one CT scan. And to carry on without a five-years, if it is a seminoma, because it's very unlikely that after three cycles

of BEP, patients will have a disease relapse. Or, up to 10 years in this case for the non-seminoma, if, of course, in case of disease histology and, again, carry on with a delayed effects assessment at year- 2, 5, and 10, There are many recommendations from different societies, scientific societies but also, cancer centres, on the specific topic of the active surveillance for the clinical stage I disease. But I want to focus just on two concepts, again, on two published papers, that one, with the Danish guidelines, which was focused on the stage I non-seminoma. And I want to focus on this because, in this case, they adopt a different strategy. They based their follow-up on more frequent serum tumour markers assessment than CT scans. And indeed, the most of the relapses were early relapses, 80% within the first year, as we said before, and those were detected by increased markers than the CT scan. So, in the non-seminoma, we could increase markers. We could use markers for our follow-up. Furthermore, the most of the disease relapses are the International Classification Good Prognosis Group. So, we don't need to be worried about that. And the late relapse was very rare. Similarly, in a similar strategy used by the Canadian group, but on the clinical stage I disease, so, both either seminoma and the non-seminoma, they went for more CT scans than tumour markers assessment. But what they found was that identification of disease relapse in the non-seminoma, especially, if the vascular invasion was present, was detected from the tumour markers, as well as by the CT scan. Similarly, to the CT scan. So, again, a confirmation that in non-seminoma, we could spare our patients a little bit more from CT scan by using the tumour markers. And again, they confirmed that most of the relapses was a relapse in the good prognosis group. I want to mention also our Italian experience. So, in 2017, the IAMO, which is the Italian Association of Medical Oncology, and the IGG, which is our testicular cancer group in Italy, performed a Consensus Conference, with 42 experts from 14 scientific societies. And the important thing, we included also three testicular cancer survivors in these recommendations. And differently from the UK guidelines, we decide to modulate our strategy based on the risk factors we have mentioned at the beginning of our presentation. So, for instance, in the stage I seminoma, we consider tumour sites, the invasion of the rete testis. If those patients with those factors wouldn't go for a chemotherapy, they were considered as high-risk, whilst those receiving chemotherapy, of course, were considered as low-risk. Apart from this strategy based on the risk in the seminoma and we'll see also in the other histology and stage. We proposed to use the MRI of the abdomen and pelvis instead of the CT scan, of course, to spare the radiation of the CT scan. And to use also the ultrasound only when the CT scan and MRI was not foreseen. So, we suggested for instance, in the low-risk group, only two abdomen images, with either, of course, the MRI or the CT scan. We included study of metabolism as the UK guidelines. And we introduced also psychological counselling because of the anxiety and depression we mentioned before at the beginning, and in case of any signs of distress. Similarly, for the stage I non-seminoma, we considered the vascular invasion of course, as a risk factor. And of course, if we offered or not, a patient an adjuvant treatment. So, we identified three risks groups. And again, we proposed MRI of the abdomen instead of the CT scan. And a maximum of eight CT scans in the high-risk group. In the advanced stage disease, we used the risk groups both from the international classification, in the case of the disease as advanced stage, at the disease onset. Or the IPFSG classification, which was the classification I showed you before for the relapse refractory disease. Based on this identification, we identify the three risk groups, and again, we proposed a different follow-up based... and timing, and examination based on the risk group of these patients. We think that our suggestion to use the MRI, was then confirmed just recently at the last ASCO of 2021, ASCO GU. It was reported the results of the TRISST study, which was limited at stage I seminoma, which compared two strategies. The first strategy was with less abdominal imaging, CT scan or MRI, so three instead of seven. And the second strategy was to use the MRI instead of the CT scan, in these four arms design. The results reported favoured the strategy, the less invasive strategy, so less imaging, CT scan or MRI. And the use of MRI, as compared to the CT scan was absolutely identical, in terms of identification of disease relapse. So, there is also the possibility to use the abdominopelvic ultrasound, which might be preferred after three years of follow-up. And anyway, the indication and the advice is to use low-dose CT scan and using also the novel model-based iterative reconstruction, which of course will spare our patients anyway radiations. Another important concept, sometimes we could miss, is to use and to propose to our patients also a contralateral testis ultrasound,

because we need to acknowledge there is a 3 to 4% risk at 15-years, for our patients to have a contralateral testicular cancer. So, I move to the last part of my presentation, which is about the management of treatment-related complications. So, there are some general recommendations, actually, those are from the NCCN. So, it's, of course, it's a common sense. So, aim to reduce the treatment burden, and it's is very important. I will stress a little bit with the next slide, to administer intense hydration, when we use cisplatin, to assess and monitor if needed the pulmonary function, where we use bleomycin. To discuss with patient the sperm cryopreservation, to avoid the infertility. To implement effective coping strategies. Monitor hormonal status, we have discussed that for the hypogonadism. And also, because of the increased risk of secondary malignancies, to advise our patients particularly to adhere to the national screening guidelines. And then, because of the increased risk of cardiovascular disease, to counsel our patients about CVD risk-factor modification, including smoking, and to end the use of sympathomimetic drugs for the hypertension. And to avoid using ototoxic drugs because of the neurotoxicity. For the pain, unfortunately, we can't do more than suggesting some painkillers, like the duloxetine. But in the future, our efforts should be to avoid, if possible, the therapeutic radiation, we have avoided to offer to our patients the radiotherapy in the stage I. To use the appropriate number of cycles of BEP chemotherapy, which means to avoid the fourth cycle, if it is not needed in the good prognosis group. And to avoid also as we stressed much in this presentation, extensive imaging. So, possibly, in the stage I disease, when possible, based on the risk factors we have discussed, we should prefer to go for the surveillance strategy, in the stage II possibly, we could also consider in specialised centre to go for the lymph node dissection, rather than using the chemotherapy. And what I said before, in the advance stage, to use a risk-adapted strategy. In the future, what we expect is that the use of miRNA-371 will direct our personalised approach to offer adjuvant treatment only to those patients who really need, and also in the stage II disease. And actually, this goes in the same direction we, actually, we did during the pandemic. So, of course, our patients need the best treatment despite the pandemic, despite everything, the bleomycin should not be omitted, but in some stage of disease, as it has emerged by a survey of three comparative groups, we could go for a surveillance when it is possible. So, finally, my take-home messages about the follow-up and the surveillance for testicular cancer is that, actually they start from the beginning. So, with a careful assessment of our patients, appropriate treatment and counselling, and then, of course, evidence on modalities and timing of examination is limited. But if we follow the clinical recommendations which exist, this could result in optimising the risk-benefit ratio for individual patients, and also, to an economic use of our resources. The open issues of course remain about the length of the follow-up and the surveillance, the examinations and also, the professionals to be involved, especially, in the long-term follow-up. And as I said before, the future is possibly, especially for the detection of diseases relapse is based on a precision medicine approach with the use of novel biomarkers. We rely on the miRNA studies. And these, of course, will help us to reduce the treatment burden as well, and develop risk-based targeted prevention and intervention. Hopefully, in the future, we'll be able also to set up a longitudinal cohort study, to follow our testicular cancer survivors for life. And this will help us to, of course, to get the information we need about the morbidity, and the latency trends of late adverse outcomes. Thank you for your attention. I'm, of course, open to discuss any of these topics.

Dr De Bari: Thank you very much, Giuseppe, for instance, there are no questions. So, in order to open a bit the discussion, I'd make one comment and some questions for you. I'm a Radiation Oncologist, do you know So, the first question, direct question is, is there still a place for radiation oncology in testicular cancer patients?

Prof Banna: So, in the clinical guidelines, there is still a place for the radiotherapy, actually, the stage I for patients who are more than 40-years of age. So actually, but it's still a very, very limited indication. So, actually, but we are not happy with this indication, I would say. Because, of course, the risk of a secondary malignancy after the radiotherapy is quite high. So, the radiotherapy has a little bit banned from the treatment of testicular cancer. Also, because the only space, the radiotherapy still has probably is the stage 2A disease and the stage 2A seminoma, when the lymph node sizes are less than 2 cm. In that case, I still can

see an advantage to give some radiotherapy to the lymph nodes instead of three cycles of BEP chemotherapy. But in the stage I disease, I would say that one cycle of carboplatin, even if the high-dose of AUC 7 is probably better in terms of late-term effects of secondary malignancy, than the radiotherapy. So, possibly, the last role of the radiotherapy in the testicular cancer, is just in the stage II disease, the stage II seminoma disease, where the lymph nodes are less than 2 cm. But again, is something that we are discussing. Someone still suggests the use of the radiotherapy in the residual disease of the seminoma. When, of course, there is a positivity on the PET scan. So, after a treatment, for instance, with three cycles of chemotherapy, for an advanced stage, if there is still a retroperitoneal lymph node, and is PET positive because it's a seminoma, so, we could go for the PET. Someone could suggest to go for radiotherapy instead of residual surgery. But again, residual surgery would be safer in terms of late-term effects and secondary malignancy.

Dr De Bari: I completely agree with you. Probably, I missed it, I don't know if you gave this kind of information, I apologise for that. Could you give me the rates of secondary malignancies after three cycles of BEP?

Prof Banna: So, actually, there is not a clear rate, but it is dependent on the dose of the etoposide, for instance. So, what we know is that if we exceed that 2000 ... I'm getting the number exactly. So, if we... is here. All right, so, if we exceed the 2000 cumulative dose of etoposide, there is a 2% cumulative risk of leukaemias. And what we know about the cisplatin-based chemotherapy is that there is an increase in the gastrointestinal cancer risk by 53%, with each additional 100 mg of cisplatin-based chemotherapy. So, these are the numbers. What we know in terms of relative risk, is that there is an increased risk of 1.5 approximately after the chemotherapy. So, of course, it's dose dependent.

Dr De Bari: So, I didn't miss the information. What I did not understand, so, consider that I correctly understood. Could you explain me why in your recommendation, I don't know if you can go back with your slides, on the slide where you showed that you should not deliver more than four cycles of chemotherapy.

Prof Banna: Ah, all right, so.

Dr De Bari: In any case, in one of the slides, there is a sort of recommendation telling us that you should not deliver four cycles of chemotherapy, and it is better to deliver three cycles of chemotherapy.

Prof Banna: All right. yeah.

Dr De Bari: My question is, looking at the secondary malignancies related to chemotherapy because we are not discussing about the secondary malignancies of radiotherapy. I consider it as a data, and I don't want to come back on that. I want just to say, and considering the potential risk of delivering BEP in patients presenting a relapse, is it still ethic? I don't know if we can use this very...

Prof Banna: Yeah.

Dr De Bari: Hard word to suggest the surveillance. What I want to say is that carboplatin, AUC7 carboplatin is well-tolerated. It's one or two cycles. The long-term risks with such a kind of chemotherapy are quite low. We can say that side effects of one or two cycles of carboplatin are negligible, I think, or something like that. But if we propose surveillance, there is a risk of relapse. And in this case, you would not deliver carboplatin, you would deliver BEP.

Prof Banna: Yeah, of course. Yeah, sure.

Dr De Bari: So, what I want to say is, is it better to spare one cycle of carboplatin? Or, on the other sense, it is better to deliver to everybody, one cycle of carboplatin, and reduce at the maximum the risk of relapse in order to avoid the potential risk of secondary malignancies? Or we should still consider surveillance because it's an option and etcetera, et cetera? I think that...

Prof Banna: Yeah, yeah. You know, yes, your question is great, actually, thank you very much. So, firstly, just to clarify, my indication and also the discussion we had, was to use a risk-adapted strategy. So, according to all the recommendations, international recommendations, including the ESMO guidelines, in patients, I'll show it here. In patients with advanced diseases, so the stage 2C and 3 which are at a good prognosis, we should go for three cycles not four. But for those patients who are in the intermediate and poor prognosis, we should go for four. What happens often because with our association, we still have contact with many centres, is that sometimes even good prognosis patients are offered four cycles, and this is not good. So, those patients with seminoma, with advanced disease stage, with seminoma or non-seminoma, at the good prognosis group according to the international classification should be offered only three cycles. But I agree, that intermediate and poor prognosis should be offered the four cycles. This is the first question. The second question is great. Actually, it's very true. And it's a problem, especially for the stage I seminoma, because for the stage I non-seminoma, what we should adopt, is a strategy based on the risk factors. So, in those patients, I will show this slide. So, in those patients with a vascular invasion where the risk of relapse is 50%, it's better to go for one cycle of BEP chemotherapy, of course, because otherwise, as you said, these patients will have in 50% of cases a disease relapse, and they will get three cycles of BEP chemotherapy. But in those without a vascular invasion, the risk of relapse is only 1.5 every 10 patients. So, we could suggest our patients to go for surveillance in this case, because the likelihood to have a relapse is very low. And so, in that case, we will spare our patients two cycles of BEP, of course. The problem is then stage I seminoma. And that is really a problem, as you mentioned before. Because, the risk factors that we have in the stage I seminoma, are not as reliable as for the stage I non-seminoma. Because the tumour sites more than 3 cm and the invasion of the rete testis, which in the past had been demonstrated to be an important risk factor recently, but two meta-analyses showed that they are not very reliable. And actually, they are not as discriminating as the vascular invasion. So, in this case, is true that it's more difficult to go for a decision-based on the risk factors. However, of course, if we got a tumour which has a huge size with invasion of the rete testis, with vascular invasion, with many of these factors, is very likely that this tumour will have a high likelihood of disease relapse. So, in that case, I wouldn't be ... really, I would go for one cycle of carboplatin. Otherwise, as you said, these patients, when will relapse, will have three cycles of BEP, at least. So definitely, I do agree with you.

Dr De Bari: Okay, thank you. So, there are no other questions. It's 7:00 pm, so, I think that we can close this very interesting session. Giuseppe, thank you very much, for your very great presentation, for any explanation. And so, have a nice day. Nice evening, sorry.

Prof Banna: So, thank you very much Berardino. It was a pleasure to share with you this discussion. Thank you for your questions. And if anyone has any comments now, or even later, you could write to me, and my Twitter account is GBanna74. For any questions, I am always available. Thank you. Thank you to the e-ESO, to the e-ESO team for this organisation.

Dr De Bari: Thank very much.