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Advances in the treatment of nasopharyngeal cancer

Prof Blanchard: Hi, everyone. As the introduction has been made immediately, we'll start right away, and Professor Paolo Bossi from the University of Brescia will give us the first talk on advances in the treatment of nasopharyngeal cancer, Paolo.

Prof Bossi: Thanks, Pierre. Thanks to ESO. So, my topic of today is speaking about the diagnosis and medical treatments in nasopharyngeal cancer. So, basically, my topics will be speaking about the role of medical treatments and let's start from the early disease. So, in the early disease, we do know that the treatment with intensity modulated radiation therapy should be reserved to Stage I, why the radiation should be performed or only intensity modulated radiotherapy. The suggestion is to tailor the treatment, according to the stage, and according to other prognostic factors like EBV-DNA load, circulating EBV-DNA and the size and the site of the nodes. For what concerned locally advanced phase of disease, we do know, as you can see in the left part of the slides, the beneficial effect of chemotherapy, and from this, we know that chemotherapy added to radiation, concurrently to radiation is able to increase overall survival of about 10%. And this is a long-term result obtained both at 5 years and at 10 years. The other thing that we know is that the dose of cisplatin should be at least 200 milligrams per square metre. And this is according to a multivariate analysis, well performed by this trial in radiotherapy oncology. So, these are two main messages for the locally advanced phase of disease. But what about induction chemotherapy? This is a meta-analysis that clearly and elegantly showed the beneficial effect of induction chemotherapy, both on overall survival and on progression-free survival. And it should be stressed the fact that after this meta-analysis, other papers have been published in particular, this paper represents the long-term results by this trial that randomised patients to induction platinum plus 5FU or directly concurrent chemo-radiation. And the beneficial effect of induction chemotherapy has been confirmed in disease-free survival, distant metastasis free-survival and overall survival. The only outcome that did not reach a benefit with induction chemotherapy was the locoregional free-survival. After that, another trial has been recently published that clearly showed the benefit of cisplatin plus gemcitabine as induction treatment in the stage 3 and 4 nasopharyngeal cancers. You can see here, the benefit in the five-year overall survival, about 10% and this trial showed us two other things. The first one is that patient obtained a good response to induction chemotherapy performed better, obviously. And the other thing is that differentiating the patients according to the baseline value of EBV-DNA, the highest benefit has been reached in patients with a high EBV-DNA load of more than 4000 copies, while in patients with less than this cut-off of EBV there was no impact and no benefit for induction chemotherapy. These have been performed in endemic areas. So, what about non-endemic areas of disease? According to this paper that we have published last year, where we studied in a retrospective way more than 1000 patients, we were able to show that in low incidence areas, nasopharyngeal cancer patients treated with induction chemotherapy followed by concurrent IMRT and platinum-based chemotherapy achieved the highest disease free-survival rate. And the benefit of this that we called intensive treatment was however, restricted to EBV positive

cancers. So, suggesting that maybe additional therapy offers new advantages in EBV negative nasopharyngeal cancer, that as you know, are quite more frequent in non-endemic areas. So, please remember that you can ask questions and send comments and any time with the Q&A button. Let's move to the adjuvant discussion. Two trials, two randomised trials have been presented recently, the first one with capecitabine with higher dose with the shorter time, six months and randomised to concurrent chemotherapy alone. And the other trial included patients also treated with induction chemotherapy that was randomised after the end of the treatment to capecitabine at a lower dose, a so-called metronomic capecitabine for one year or to standard clinical observation. The results of this trial showed that both the capecitabine doses were able to increase the failure-free survival in both the trial as you can see in this slide. However, it remains a doubt about the fact if all the patients should need adjuvant capecitabine or if we should restrict this adjuvant treatment to patients with a higher risk profile. At the moment there is another trial that is ongoing with immunotherapy as an adjuvant treatment that has been... is offered in a tailored way only to patients who have an EBV-DNA positive at the end of the treatment. We know that having circulating EBV-DNA positive circulating EBV-DNA after the end of the treatment is this male prognostic factor. So, the rational is quite strong about using this treatment as adjuvant in the adjuvant phase. Let's move to the other side of the moon. The trials performed in recurrent metastatic setting. In the first-line therapy, we have the results of three randomised trials evaluating the addition of immunotherapy to standard chemotherapy with cisplatin and gemcitabine. The designs of these three trials are quite similar, and you can see that the patients have been treated with six cycles of chemotherapy or the same chemotherapy with immunotherapy followed by maintenance with immunotherapy. So, the drugs that have been studied are toripalimab, camerlizumab, and tislelizumab. The only difference of this tislelizumab trial was the fact that this trial allowed a crossover in case of progression after chemotherapy, a crossover with two tislelizumab monotherapy. This trial showed that although the response rate was quite high with the addition of immunotherapy, so, 77% or 88% are really generous and great response rate, and there was a benefit in progression- free survival in all these trials. The tislelizumab trial was also presented with the forced, even if premature, data of overall survival showing a benefit, even if not statistically significant and a benefit in particular in the PFS2, that is a quite interesting outcome indicating that maybe this treatment should be offered as early as possible in order to make the best benefit to nasopharyngeal cancer in recurrent patients. So, what we learned from these three trials? The advantage in a response rate in PFS, the advantage in PFS2 in the tislelizumab trial, we have only premature data of overall survival only for the toripalimab trial and for the tislelizumab trial. And you can see signs of benefit even if not really strong, but we have to wait time in order to really evaluate the beneficial effect. The real question is, which is the role of maintenance therapy? As in all the three trials patients in the standard, in the control arm did not receive any maintenance therapy even not with chemotherapy. So, it is possible that the real benefit is adjuvant to the maintenance therapy. So, this is a factor that should be controlled. Please ask questions and comments, and let's come to the last part of this discussion. What about the second-line in case we had a recurrent metastatic patient with a platinum-resistant disease, what we can offer? The Keynote122 trial randomised patients to pembrolizumab alone or to the investigator choice chemotherapy in platinum-resistant patients. And this was a negative trial as there was no benefit in overall survival with a similar objective response rate, 21-23%, even if at the price of less toxicities with immunotherapy as compared to chemotherapy. The message that I received from this trial is that immunotherapy is not better than chemo, but it is another possible weapon that we have in our hands in nasopharyngeal cancer patients. Obviously in case we had performed no immunotherapy in the first-line as unfortunately is the case in most of the non-endemic countries as, as of today. For the second-line of treatment, and I've taken these slides thanks to Bridget Ma, just presented to the last ESMO congress. The future can be offered thanks to the results of this trials, with the compounds acting on the EGFR pathway or on multi-kinase anti-vascular, or thanks to this TKI or employing drugs acting on at the epigenetic level like HDAC inhibitor or, or with signal inhibitors like Somatostatin Receptor-2 or for drugs acting as a PARP inhibitor as combined with immunotherapy. So, these are my take-home messages. For early-stage of disease, stage 1 IMRT, stage 2, IMRT plus chemotherapy, in case of high-risk factors for locally advance disease, chemo-radiation with

cisplatin and concurrent cisplatin at dose of at least 200-milligramme per square metre is the key. There is a strong rational for the use of induction chemotherapy. We have evaluated the improvement of overall survival. There is a possible role for adjuvant capecitabine to be more studied in the future. Maybe, the most important message should be that we need to tailor the treatment according to risk factors. And for the recurrent metastatic setting, the first-line is becoming chemotherapy plus immunotherapy with a question mark about the role of maintenance treatment. And the second-line is chemotherapy or immunotherapy, or, and this is my favourite choice, participation to clinical trials. Thanks.

Prof Blanchard: Thank you Paolo very much for this very clear talk on the topic that has evolved very, very importantly in the recent years. We'll take the questions at the end of the second talk, but feel free to ask questions in the Q&A box. So, please ask questions if you have, I'm sure you have questions and now it's my pleasure to give the floor to Dr Orlandi. Who's a radiation oncologist like I am, and because radiotherapy is a very important tool in the treatment of nasopharyngeal cancer. And she'll talk about the advances in the treatment of NPC on the radiotherapy standpoint. Ester, please, we are listening.

Dr Orlandi: Thank you. Thank you, Pierre, thank you ESO and good afternoon, everybody. So, this is my agenda. At first, I would like to speak very quickly about the current role of IMRT intensity-modulated radiation therapy. After this, we'll focus on late toxicity and quality of life after IMRT treatments. So, the third issue... in the third issue I will see how planning optimization in terms of prioritisation and dose constraints for target volumes is essential for treatment outcome. I will do a little digression on the role of locoregional treatment in patients with de-novo metastatic disease. And finally, although IMRC represents the standard RT technique for nasopharyngeal cancer, in the recent year, protons are gaining popularity based on its physical dosimetric advantages. We will go through its properties, clinical experiences to date, and current methodology and strategies for qualifying patients to receive protons. IMRT represents the main stay in our treatment for nasopharyngeal cancer patients. A couple of years ago, a panel of experts have published a recommendation on target volume definition and contouring for nasopharyngeal cancer patients. In general, it was a dose of 70 Gy to macroscopic disease and 50-60 Gy for the treatment of potential at risk sites. Low-risk and intermediate-risk sites is usually given conventional or moderated accelerated RT is used. No hyperfractionation schemes are used for nasopharyngeal cancers at first diagnosis for the primary treatment. IMRT has demonstrated a significant reduction in terms of toxicity compared to older techniques. I mean, tri-dimensional RT technique. A recent meta-analysis by Zhang has a reported that IMRT on more than 3000 patients reported that IMRT was beneficial to reduce toxicity but a significant impact on outcome, the outcome was reported. We have to pay attention to these data because in these meta-analysis, randomised trial, three randomised trials, and a retrospective cohort were analysed. If we focus only on randomised trials, we are not able to find a significant impact of IMRT on local control and on the outcome. So, IMRT is beneficial as a significant impact in reducing toxicity, acute and late toxicity. So far, we have no evidence about the best radiotherapy schemes. I mean that sequential and simultaneous integrated boost are similar in terms of pattern of toxicity and outcomes. Okay. Despite the implementation of IMRT survivors of nasopharyngeal cancer, still experience many physical symptoms and that can affect several domains of quality of life for many years after the treatment. You can see the two largest series in endemic regions in the left side and in non-endemic regions, all patients in both cohorts received IMRT boost with or without chemotherapy, there were advanced locoregional stages, and you can see late complications, endocrinopathy symptomatic late complications, endocrinopathy, and hearing impairment was affected in high percentage of patients, respectively 13 and 70% of patients. And also, in these cohorts from non-endemic regions, you can see that the percentage of G2 and G3 toxicity was high. In addition, depression, anxiety and fatigue were reported in a 9% of cases and toxicities were strongly correlated with quality of life. These can imply the need to set up a timely and accurate survivorship care programme. Okay. With regard to the target, with regard to the target coverage, recently, a panel of experts have published a guideline on dose prioritisation and acceptance criteria for nasopharyngeal cancer plans. They recommended a minimum dose to gross target volume at least of 78 Gy. And with an acceptable minimum dose set at 76.5 Gy. And a PTB coverage with more than 95% of

the prescribing dose to the entire volume or 93% of the prescribed dose to at least 99% of the volume. This is because a proper RT target coverage proves to significantly improve the outcome, both local control and survival. This is in Italian experience. The authors were able to find a cut-off value for specific dose volume parameters impacting on the survival on the local control. Similar data were reported from endemic regions. Moving on, the scenario of de-novo metastatic patients we can underline the role of locoregional radiotherapy in chemotherapy sensitive patients with metastatic carcinoma. This is a randomised trial in which patients were randomised to receive... metastatic at diagnosis, were randomised to receive chemotherapy, palliative chemotherapy with PF and chemotherapy plus locoregional radiotherapy when patients were randomised, if after induction, if after three cycles of chemotherapy a partial complete response was obtained. And you can see that overall survival, progression-free survival, patients are receiving a chemo-radiation. So, radiotherapy also to primary tumours and nodes performed better than patients receiving only chemotherapy. So, patients with metastatic disease are managed with attention from the diagnosis and after response to induction chemo, they should receive curative radiotherapy on primary tumour and nodes. So, IMRT represents the standard radiotherapy technique, but from a ballistic and dosimetric point of view, photon therapy is likely to have reached a plateau. There is unavoidable radiation on normal tissue from low to moderate doses, even at substantial distances from the target, such a beam property invariability leads to higher complication and particle beam, especially protons, have gained a significant attention due to their physical property. You can see that protons, you can see the deep dose distribution obtained with protons compared to photons radiotherapy. The greatest part of their energy is given at a defined depth called black peak. Now dose will be deposited downstream of the Bragg peak, a combination of a number of beams with different energies, leads to spread out Bragg peak. And if we combine different intensity, we can obtain advantageous dose distribution compared with photons. So far, the radio-biological effectiveness of protons is comparable to photons. Although, protons are more sensitive to geometric variation during treatment compared to photons, but the radio-biological effectiveness is similar. Okay. Several dosimetric comparative studies have reported substantial benefits in terms of sparing dose to normal tissues including several radio-sensitive structures like parotids, brain stems, spinal cords oral mucosa, constrictor muscles. And these, we need to verify if these dosimetric benefits could be translated in a clinical impact. There are so far two retrospective cohorts, enough numerous. This is a cohort from an American cohort, considering 77 patients treated with intensity modulated proton therapy with or without chemotherapy. And within this retrospective cohort, 48 patients with ABB-related tumours were included in a one-to-one propensity score metric analysis for survival outcome. Considering all population, you can see that proton therapy was able to significantly reduce several patterns of toxicity, dysphagia, fatigue, xerostomia, dysgeusia. There are acute toxicities. Consider only patients with ixempra-related tumour. You can see that no difference, statistical difference, was found in terms of outcome. This is because proton therapy is beneficial in reducing toxicity. This is a recent meta-analysis, including not testing the role of particle beam including not only protons, but also carbon-ions. Carbon-ions have different biological properties. They are able to determine very clustered DNA damages. So, there are particularly useful in treating radio-resistant tumours. So, for nasopharyngeal cancer, we consider so far proton therapy, but in this analysis, in which protons was given for considering a full course of proton therapy or with a mixed-beam approach, you can see that the protons was able to obtain excellent survival outcomes at one-year, two-years, three-years, and at five-years with low toxicity. We need to qualify patients to protons because the costs of protons are higher compared to photons, and we have a low number of proton facilities. A model-based approach is one of the methods with a high-level of evidence comparable to randomised trial used to estimate the potential clinical benefit for proton over photon established a cut-off of toxicity if data or cut-off of toxicity, if this cut-off was over a certain percentage, patients were qualified to protons. This methodology was recently applied in European experience. And overall, about 35% of patients were qualified to receive protons. In this study, only a little percentage of patients had nasopharyngeal cancer. Recently, we test the same methodology only on nasopharyngeal cancer patients. And we are able to find that 40% of patients should be qualified for protons. In summary, attention should be paid to recognition of late

treatment complications, survivorship care, and individualised follow-up strategy should be taken into account. IMRT represents the standard RT technique, and we need to proper cover target volumes to obtain a significant outcome. Radiotherapy added to chemotherapy significantly improve overall survival in chemotherapy- sensitive patients with metastatic nasopharyngeal cancer and proton therapy shows excellent short-term results with nasopharyngeal cancer. And we can use a model-based approach to qualify patients, so to guide our clinical decision, to qualify patients for protons. Thank you.

Prof Blanchard: Okay. Thank you, Ester. Thank you also Paolo for the great talks. So, it's now time for the questions. We don't have questions so far in the chat, in the Q&A, but feel free to ask them and I will read them out loud. I think for us in Europe, we have to acknowledge that nasopharyngeal cancer is a rare disease; in France, it's for 65 to 70 million people, it's about 250 new cases per year. So, it's really low. And I think this should be really recognised and patients should be treated in centres at high-volume. The question is what is a centre of high-volume? Because as you said, Ester, the treatment has considerable, acute and late toxicity. And it has been shown that adherence to guidelines in terms of contouring, in terms of dosimetry, improved outcomes and probably could reduce also late toxicity. Before I ask the first question, I would like to remind the audience that there are guidelines for contouring that they have been published. I think, Anne Lee was the first author, the guidelines for contouring and also guidelines for dosimetry. We should all use and follow these guidelines to treat the patients, sorry. The problem with the dosimetry analyses that you've shown that when you see that the PTV is well-covered, the outcome is better, but of course, large tumours, for example, T4 diseases are always more difficult to cover due to normal tissue constraints. And then, the big question occurs when you need to make compromises. And sometimes, we need probably to push the limit a little bit and that's why also it's important to be at a high-centre. So, my question, my first question to you, Ester, would be in smaller tumours it's not that difficult, but what would you do for say like a T4 disease that goes close to the optic nerve, or that's a little bit posterior that comes close to the brain stem, if you were to treat with conventional IMAT, I think proton therapy is great in the future, but due to access, I think it's important for us to focus also on the treatment that most of us will be able to give. So, what would you do? And second question is, if you answer is induction chemo, what type of volumes do you treat after induction chemo?

Dr Orlandi: Thank you. Thank you for your questions. T4 are very challenging from a radiation oncologist community. We can consider that the first point is to try to use, in my experience, to try to use strong, hard constraints and to discuss with the patient about the opportunity to sacrifice, for example, a monocular vision. But the first point is to use hard constraints and to try to optimise plan in that direction. We can consider that recently two, one retrospective and one prospective study reported that patients with a good response after induction chemo, so, in T4 tumours, we usually give induction chemo, in these patients with a good response after chemo, we can consider to irradiate with 70 Gy. This is a total dose to macroscopic disease, 70Gy, the tumour burden after chemo response, and to give a dose about 60-64 Gy to the extension of disease at diagnosis. These studies have demonstrated that the local control is similar, but the toxicity profile can be reduced. So, we can consider in certain cases to reduce the total dose, but not the target volumes. The target dose in cases showing a good response after induction chemo, considering 70 Gy for the extension after induction chemo, while guaranteeing 70-74 Gy to the initial extension of disease.

Prof Blanchard: Okay. Okay. Thank you. So, discussion with the patient very important. And then, also, I think what's been published is to try to give to the GTV, at least 60, like 95% of the dose. So, 66.5 Gy to the GTV after induction chemo, it's always very difficult for infiltrative disease in the base of skull to define what is the response. So, it's easy in the nasal cavity, for example, there was tumour, now there's air inside the base of scull. It's always very challenging. But I agree for induction chemo. We, at least in France, I think we are not there yet for harmonisation of EBV-DNA measurement, because we know that from one lab to another one, it is difficult to get good results and reproducible results. So, I think it's, at least in Europe, it's pretty difficult to use EBV DNA for a patient selection for treatment. I don't know if you agree, especially Paolo, but

then, my question would be, I think the meta-analyses have shown that the more chemo you give the better the outcomes, so you improve, especially in distant metastasis control, but also, clearly, you increased toxicity and you can have long-term neuropathy due to the increased use of cisplatin. So, when you give induction chemo to those patients, you give induction to everyone, and you are not sure how to select the ones who will really need induction chemo. So, what would be your recommendation in terms of localised disease, large volume, localised disease. Do you think that the future should be chemo-radiation up front with a treatment that would be adapted to the response after treatment, or you think that we will stay with induction chemo and maybe in the future, for example, de-escalate local treatment in good responders? It's a bit of a prediction I give you not very easy question, sorry.

Prof Bossi: No, thanks. Not easy at all. You're right. So, basically, I would say that nasopharyngeal cancer is a chemo-sensitive disease. This is the first point that we have. So, having this in mind, we usually perform, we usually suggest induction chemotherapy to two types of patients. The first one is the patient with a large tumour. The large T as Esther was mentioning before, where this induction chemotherapy maybe can allow a de-escalation of the treatment in order to prevent late toxicities. This is the first group of patients for whom I would be more confident to perform induction chemotherapy. The second group of patients are the patients that have a higher risk of distant metastasis, therefore, patients with a high burden of disease in the neck, with low-neck nodes in the neck that are positive, or with a high EBV-DNA. It is true we have not standardization, normalisation on EBV-DNA test. However, what we know is that is possible that the commercial tests that are available can be somewhat reproducible and can be used, on obviously European market test can be used in order to evaluate the burden of disease as a strong surrogate marker of what is the risk for the patient of having distant metastasis. So, large node, high EBV-DNA load. So, that obviously is quite artificial the cut-off of 4.000 copies. However, if I see a patient with 20.000 copies, or I've seen also patients with 100.000 of copies, this is a very, very high-risk patient, and I'm more confident to perform chemotherapy, induction chemotherapy in this patient. The other part is adjunct chemotherapy in case we do not perform induction chemotherapy we have this option with capecitabine that I have shown before.

Prof Blanchard: Okay. Lots of questions. But time passes. Do you have a preferred concomitant schedule for cisplatin, Paolo?

Prof Bossi: No, as in my education, I'm quite used to perform three-weekly cisplatin, but we do know that there are papers showing also in nasopharyngeal cancer, that the weekly schedule is easy to be performed provided the fact that we give the patient at least a 200-milligramme per square metre.

Prof Blanchard: Okay. So, total dose is what matters. Ester, if we move on to deep, also important messages in terms of IMRT to reduce toxicity, we can also reduce prophylactic volumes sometimes. So, in which patients would you treat with smaller volumes, especially, in terms of prophylactic treatment?

Dr Orlandi: Okay. So, prophylactic volume, there are recently a couple of papers of randomised trials testing the opportunity to exclude low neck in patients, low neck radiation in patients with N0 or N1 disease, in particular retropharyngeal nodes. This is because among late toxicity although the main toxicities are a neuropalsis, endocrinopathy but for the involvement of skull base hypothesis, but hypothyroidism, could be hypothyroidism, fibrosis could be observed and they can be related to irradiation to the low neck. So, these trials have demonstrated that the omission of the low neck could be safe in patients with N0, N1 disease, this is in endemic regions. Also, the previous data on the possibility to reduce target volume dose to primary target volume. If a response is obtained after induction chemo comes from endemic regions. So, these studies on these results on de-escalation experiences, both on primary tumour and the neck, we need to pay or to reserve caution and attention because they come from endemic regions. So, we have another epidemiological situation, and maybe we cannot translate the results of de-escalation. I think that this is the message. This is possible and particularly on a primary tumour after induction, after response to induction chemo, but for the neck we need to have to pay attention.

Prof Blanchard: Okay. Thank you, Ester I think it's a very careful message. We don't have maybe not exactly the same disease. I agree, not the same expertise because we treat much less patients. So, maybe, not the same confidence in de-escalation. However, probably in patients with very low nodal burden, reducing a little bit, the nodal areas in the low neck or in the medium retropharyngeal space is reasonable. And you comment on the ethnicity and endemic and non-endemic area is a good comment, but unfortunately, almost all the trials come from Southeast Asia. And we've tried with the Gulf Tech in France to do a randomised trial on induction chemo with our friends and colleagues in Indonesia. And that was, well, the trial was completed, but it took a lot of time. I think, we won't be able to do randomised trials in Western countries. And we would love to support and help our friends from North Africa to do those trials. But until that time we will have to rely on the data from China. Very, very briefly, just to emphasise the message, Paolo, what would be, because we don't have a market approval for immune checkpoint inhibitors in NPC. So, what would be your first-line chemotherapy, treatment, and if you had and had-not access to immune checkpoint inhibitors, so, on and off like label, what would you do ideally in Europe and what do you do in patients where you cannot use ICIS?

Prof Bossi: Ideally, I would perform cisplatin plus gemcitabine plus any checkpoint inhibitor that would be approved, followed by the maintenance treatment with immunotherapy. In practise, what I can do at least in Italy, but I know that is the same issue in the other countries in Europe, I perform, so I administer cisplatin and gemcitabine and I continue to go with gemcitabine as maintenance treatment. This is really key message. This is a chemo-sensitive disease. Please, do not stop the treatment after six cycles, perform or gemcitabine as a maintenance or capecitabine as a maintenance, there is a trial on Jama that showed that maintenance treatment is of benefit. Then I have the immune checkpoint inhibitor as a second-line.

Prof Blanchard: Okay. I think it's time for us to stop because it's already five past seven. So, I would like to thank you both, Dr Orlandi, Dr Bossi, a lot for your time and your expertise. And with that, we close the session.

Dr Orlandi: Thank you.

Prof Bossi: Thanks.