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The forest of methods in cancer research

Dr Menis: Good evening to everyone. It is also on behalf of my co-chair that we welcome you to this e-session. We want this to be very live and attractive for all of you, so, please feel free to click on the Q&A button along the session and send your questions and comments to us. If you have any burning question that you would like to be tackled immediately and replied immediately, just raise your hand, and Luca and I will give you the reply on our presentation. In the last decades, we have made huge improvements in cancer biology. The understanding of the two different tumour types has largely improved. And this has luckily brought new advances in treatment strategies. The new compounds became more and more complex along the time, requiring the implementation of larger pharmacodynamics assessment, improvements in pharmacokinetics evaluation, the development of new predictive and prognostic biomarkers. And this has led to protocols that has become larger and more and more complex. On the other hand, though, the process of drug development has still remained more or less the same. We were starting from pre-clinical assessment leading to those finally phase-I trials, phase-II trials, and then large, very costly, phase-III trials that led to huge timing in the development of each compound. In 2013, luckily, the EROTC has promoted this W-shape that you can see below, and this represents the new treatment strategy and the new process of drug development that they have promoted through a deep connection between academia and private practise. And this would bring to new, earlier, simplified drug development processes. Still, a lot has to be done to reach the goal of more developed clinical trials. And I will leave to Luca.

Dr Bertolaccini: Thank you so much, Jessica, for having accepted my invitation to this afternoon e-ESO session. So, Albert Einstein, the most famous physicist of the last century, said that, "If we knew what we were doing, it wouldn't be called research, would it?" So, the next one, please. So, the definition of research could be different. For the Merriam-Webster, the research is the investigation or experimentation aimed at discovery and interpretation of the facts. For another dictionary, the Redman and Mory, it's a systematic effort to gain new knowledge. And for the Clifford Woody thesaurus the research is defining and redefining problems, formulating hypothesis and objective, collecting, organising, and evaluating data, making the deductions, and reaching conclusions, and testing conclusions to determine whether they fit formulating hypothesis and objective. The next, please. But why we do research? I think that all of these are valid. The desire to get a research degree along with its consequential benefit, the desire to face the challenge in solving the unresolved problems, the improvement of the desire to be of service to society or to get respectability. But I think that we do research for passion. Passion and research are similar things. The next, please. So, we have to develop a question for start research and we have to start with a clear proposal. We have to know the literature, we have to be iterative in our approach, and we try to specify the who, what, where and when of the proposed. And we have to ask to ourselves what would the answer to this question add to the literature? It's fundamental. We could perform a good paper, good research, but this research could add nothing to the research. So, the research process is the identification of the general problem. It's a literature

review. It's the specifying of question and hypothesis, determination of design and the methodology, and then, data collection, analysis, and the interpretation of the findings. The next, please. So, we have to select the research method. So, what factors to consider when choosing one research method other another? The overall applicability to meet the research objectives, the time to key planning and decision making, the resource available, the material resources, the financial resources, and the human resources, and access to the population of interest. The next, please. I have to remind that your points of views are really important for us. So, click on the Q&A button to send your comments and questions when you want. Jessica.

Dr Menis: Thank you, Luca. And I would like to let you know that when Luca invited me for this e-session that we are doing together for you, we really tried to tackle what we think is relevant in clinical trial methodology, and certainly, putting the highlight on the difference between clinical trials and clinical reality is something that you must consider when you do your research. When we have our realised patients, we know that we see in our everyday practise, of course they are patients with performance status most of the times 1 to 2 or even 3, they can be elderly. Their organ function might be not excellent, and also, they might have several comorbidities. Whereas the ones that we see in the clinical trials that are presented in the large conference or in the publications are usually PS 0 to 1 without any comorbidity. They look very much fit and their comorbidities are very low. So please bear in mind when you develop your clinical trial, try to write your inclusion and exclusion criteria in order to select the population that would best benefit of the treatment strategy you would like to bring forward. The same applies for the staging procedures in clinical trials. Try not to be too much of a specialist, try not to put too much of what you don't do in your practise and what could be difficult to be implemented in smaller hospitals. It's important, of course, to tackle at the right time, the progression, or to identify with the proper staging procedure and oligo-metastatic state, but still, bear in mind that this needs to then be implemented into practise. The same applies to treatment choices. You can see here, we have selected the perioperative treatment of non-small cell lung cancer, since this is the best example of integrated treatment strategy. As you know, a lot of trials are currently underway on the neoadjuvant treatment. Still, it is not our preferable choice in the earlier stages. It's difficult to be done in practise, unless, you have a very good surgeon, like the one that is my co-chair. For the oligo-metastatic state, again...

Dr Bertolaccini: Thank you.

Dr Menis: You're welcome. Well, Luca knows very well the oligo-metastatic, the earlier stage is very difficult. You have to not just to have a good surgeon but also, good radiation oncologist, and you have to work very well in a good and interactive manner in order to propose a local treatment in an oligo-metastatic patient. So, this is very difficult and needs a good approach to be done both in clinical trials and then, to be translated into reality, I think...

Dr Bertolaccini: Okay, Jessica. But what is, in your opinion, the oligo-metastatic lung cancer? Which is the patient?

Dr Menis: Well, for me, it's very difficult to select a good one. We have several definitions of the large societies, like ESMO, like ASCO, like the NSCLC. Still, we need to properly stage them. So, CT scan might not be enough. We have to integrate it with PET scan and we have to see the ones that actually how they perform on the systemic treatment before considering them approachable for an integrated treatment. This is the oncological way. Tell me the surgical one.

Dr Bertolaccini: The surgical one is one site of metastasis, preferable the brain or the lung. The adrenal we accept. And regarding the bones, it's a great point, it's a great question mark, because we don't know if bone oligo-metastatic state could really exist.

Dr Menis: I totally, completely agree. And this is why we need to be carefully selecting these patients and the multidisciplinary teams are really the best ones where you can discuss the patient, see if the patient is

feasible, is operable, rather than just resectable, and can be proposed to the surgeon or to the radiation oncologist.

Dr Bertolaccini: The multidisciplinary team is the keystone of our practise. Absolutely. And in the multidisciplinary team, the surgeon, the oncologist, the radiation oncologist, the biologist, the pathologist, the pulmonologist, and so on must attend.

Dr Menis: Definitely. If you have any questions, let us know. I will remind you along the session to do so. Going into depth now on the methodology. We will start from the endpoints and then move along with the design and the other practicalities in the protocol development. I am sure we know all very well what is the definition of an endpoint, which is just the way we measure our objectives. They need to be importantly, methodologically correct, but at the same time, please, pay attention that they must be clinically meaningful. You have the table on the right. This shows the typical endpoints, according to the trial design. So, for phase-I dose limiting toxicity, maximum tolerated dose, recommended phase-II dose. We have a response for the phase-II and then, disease-free survival, progression-free survival, or overall survival for the phase-III. Of course, these are the standard endpoints that we normally see in clinical trials, but the more and more we need to reduce the timing of our studies, and therefore, have earlier assessment of our endpoints. And this can come through by the use of surrogate endpoints. You can see in the bullet points, we reported some examples, like pathological complete response or major pathological response. This is free survival, or progression-free survival, and most importantly, what we don't see so much, visibility and quality of life endpoints. This is something we don't see too much because they are very difficult to be introduced in clinical trials, but still, are very important, in our opinion, for patients. Do you agree, Luca?

Dr Bertolaccini: Absolutely, I agree with you. And I want to ask, what is the PROs? The patient reported outcomes.

Dr Menis: Patient reported outcomes are very important. It's how the patients report their benefit or their feelings on the toxicity, for example, on their quality of life. So, it's a whole comprehensive type of outcome that the patient reports himself or herself. The questions that are used for the patient reporting outcomes necessarily for larger phase trials, like II or III, need to be used. They were validated ones. So, for example, the EORTC ones are the ones that most commonly are used both by academia and pharma.

Dr Bertolaccini: Okay. But are easy to use or easy to collect?

Dr Menis: As you know very well, not that much. In practical, what is difficult for us that we conduct clinical trials, are the timing that needs to be used to explain to patients these questionnaires and the time and the willingness to fulfil them. Honestly, we see more and more that they are used through apps, for examples. These are good examples for patients to have a friendly use of these patient reported outcomes and make them easier to evaluate and assess. But still, a long way has to go I believe.

Dr Bertolaccini: Okay.

Dr Menis: More for the young generation.

Dr Bertolaccini: Yeah.

Dr Menis: Here, we showed you some examples on how the classical endpoints have changed along the time. Everyone knows dose limiting toxicity has a pretty standard definition, like the toxicity that limits a further dose escalation, but the more complex the compounds we have developed in the recent years, the larger the method of evaluation has become. For example, you can see on the left, the definition that the group of Curie in Paris and the group of Gustave Roussy have developed in a common manner. As you can see, the period of assessment has become larger. Also, the reversibility needs to be taken into account as well as the severity. Also, treatment delays should be considered if, for example, a toxicity is not that much of a grade, but

requires a delay in the rescue of treatment. It should be considered in the definition of dose limiting toxicity. Of course, the more well-known example of the changes in the assessment is the modification or the implementation of the immuno-RECIST for immunotherapy. And this was because we were seeing an increase in size of the tumours, both in our clinical examination and on the CT scans. However, this was due to the tumour of the lymphocytes infiltration that was led by the treatment strategy that we were using. Also, immunotherapy. And this, Luca is seeing in the surgical theatre more and more, leads also to a whole systemic type of toxicities with the timing that is not a classical one we were used with chemotherapy. So, adverse events could be developed along the time, even several months after the treatment strategy. Since we are testing it in the neoadjuvant setting, this is also something that the multidisciplinary team needs to assess very carefully. Is this your experience as well, Luca?

Dr Bertolaccini: Absolutely. There is a change in the tissue of patients. And when we treat patients after induction immuno, we found sticky structures, difficult to dissect in hilar structure. So, the difficulty of the surgical operation really increased more and more. And this is well-defined by surgeons, like Bott, David Jones and so on, that were published in the last years about the surgery after induction immuno. It's really difficult to achieve a good surgery after immuno.

Dr Menis: And we're stressing this to you because when you develop your clinical trial, when you design your protocol, all of these factors need to be taken into account. You really need to know your treatment strategy very well because all of this needs to be defined, and so to be then studied and assessed properly. Not only immunotherapy, also target agents, which are most commonly cytostatic were leading to progressions that were not followed by clinical progressions. So, we could use the treatment beyond-progression according to iRECIST for several months, but still, keeping a clinical benefit so that endpoints like progression-free survival too, as you can see here, started to be developed along the time. But going back to the first slide on endpoints, what is a surrogate endpoint? An endpoint which is surrogate is the one that represents properly the primary and validated endpoint. You can see here; disease-free survival is a surrogate validated for overall survival with the use of chemotherapy. We are having the validation of surrogacy by the regulatory agents since that helps us in identifying which endpoints are real surrogates. And by using the surrogates, they confirm us we can achieve accelerated approval for our compounds. How do we do that? We certainly can go to the EMA or FDA website. And as you can see here, the provided definition of the endpoints, like event-free survival, disease-free survival, and others, and which one could be used as surrogate for our trials. For example, in the neoadjuvant, you can see that event-free survival might be supportive of regulatory approval by FDA if clinically meaningful, acceptable safety profile is provided by this compound and no evidence of detriment of overall survival. More challenging endpoints are pathological response or complete, or either major because we don't have yet a standard for processing and engrossing the specimens and a uniform definition that could then be confirmed in larger trials. We invite you again to do questions. If there are no burning ones, we can go along on the design. You can see here; Luca and I provided you a list of which ones are new type of designs that could be implemented in future trials. We have the window of opportunity and the surgeons like them very much because with the treatment strategy, we can cover the timing between when we see a patient and when actually a patient can go to surgery. Do you agree, Luca?

Dr Bertolaccini: Absolutely. And could you repeat this concept of the WOO?

Dr Menis: Oh, the WOO. The window of opportunity is a short treatment duration, like one or two cycles, according to what you prefer or what the type in the biology of the compound is that can be provided for about one month, one month and a half before the surgical treatment. Of course, you need to assess the tumour type, the tumour treatment before and after, before in surgery, to make sure that the patient has not been hampered by the treatment itself.

Dr Bertolaccini: Okay. Thank you so much.

Dr Menis: You're welcome. For phase-I, phase-II trials, this is a kind of way to squeeze the phase-I and the phase-II altogether to reduce the timing of ethical committee assessment, administrative assessment, and to try to have two trials in one. The phase-I and II are the ones we use more and more to get an early signal of activity and if the expected safety profile is acceptable. Of course, if you don't have any data on the safety of the compound yet, so if it's really a first in human one, then, it might be better, according to the preclinical data you have, to run a phase-I by itself. On the other hand, if you have some early security of the safety, you can actually use these trials to get some early good signals of activity, and then, promote the compound to larger phase-III trials. Moreover, you can see here, we put in some examples of adaptive designs or new model of designs where you can actually use, if you have a specific histology of a specific molecular alteration or one specific compound that you can use in several tumour types. And this is the example of the basket trials. The basket trials are really trials designed to learn. They are parallel phase-II trials, where we start from one drug that we can use for different targets or simply for different tumour types. You can see here the example of the vemurafenib, which is a BRAF inhibitor, that was tested in different tumour types.

Dr Bertolaccini: So, the basket study is a type of phase-II trials?

Dr Menis: It's a combination of different parallel phase-II trials, which are all separated. So, for example, one phase-II trial could be run in a shorter way compared to the others. For example, if we have a basket, like the one you can see here on vemurafenib, of course, recruitment of breast cancer will be much faster than the one of cholangiocarcinoma. So, you don't have to expect the end of the cholangiocarcinoma recruitment to present the results of the breast cohort, which makes it much easier and much cheaper also to run both for academic and private partners.

Dr Bertolaccini: Okay, thank you.

Dr Menis: You're welcome. Another example that we show you here are the umbrella studies. The umbrella trials are the ones designed to conclude. We start, as you can see here, from one tumour type. Of course, being us, thoracic interested, we have an example of the SAFIRO2 by the French group. So, we can start, for example, from non-small cell lung cancer, which is screened by a molecular profile evaluation. We can identify, like they did, several targets and for each one of them, we propose a drug to be tested, either as you can see here, in a randomised way or even with just simple single arm phase-II trial. The design in this part can be really easy or more complex, according to the question and the information you have on the drug itself.

Dr Bertolaccini: Okay.

Dr Menis: If everything is clear, I will leave the floor to Luca for the quality assurance in surgery.

Dr Bertolaccini: It could be evaluated, the quality in surgery, yes. And what model could we use? We could use the model proposed by Donabedian with three categories, a model for the structure, the process, and the outcome. So, for the structure, where is care provided to patients for the process? How is care provided to patients? And for the outcome, what happens to the patients? So, next, please. Regarding the structure measures, we have the famous hospital volume and surgical volume. It's really important. It's hard to say. It's difficult to say, but the hospital and surgical volume is directly correlated with the quality of life of patients, and with oncological outcome of patients. So, the centralization of patients in our hospital or in cancer centre, it's really important with multidisciplinary settings. Regarding the processes measure, the patient selection, the tissue diagnosis, the appropriate preoperative staging and the neoadjuvant chemo-radiation and the surgical approach are really the characteristics that we discuss inside a multidisciplinary team each week when we have the multidisciplinary team. And regarding the outcome measures, we have the R0 resection key-point. The number of resected lymph nodes it's directly correlated with the best outcome for patients. And there are some papers in literature that stated that more than 17 lymph nodes resected improve the prognosis of patients. So, we have the postoperative complications, the survival, and the disease recurrence

as outcome measure. The next, please. So, all of these, the preoperative indicators, intraoperative indicators, the postoperative indicators could give, improve the survival in lung cancer. The next, please. If you have some questions, please write, and we will be happy to respond to you.

Dr Menis: Actually, I have myself one. While we discussed this before now, quality assurance surgery is something we are developing more and more. When I was working at the EORTC, I was really impressed by the quality assurance in radiotherapy that the EORTC has developed and is currently using in their trials, which is a good way to standardise this radiation treatment. Also, in collaboration with ESSO, so, the surgical society, they have started doing that in surgery. For example, I have seen trials where they have implemented the Clavien-Dindo assessment of the surgical complications. Could be a good way, Luca, or is there still more to do? And this is not enough for surgery?

Dr Bertolaccini: It's not enough for surgery. The classification for complications and classification for the surgeon are hard to use, are complex, time demanding. So, really a question is a better multidisciplinary approach to the patient, with the possibility to have inside the group a data manager to take all the data from the clinical work and the clinical point of view of the patient in a database and then, discuss, and discuss more and more with the oncologist, radiation oncologist about this.

Dr Menis: I absolutely agree. And to be honest, this should be done the same for our systemic treatment. Nobody speaks about quality assurance in oncology, so in the systemic treatment, but I have seen trials where the control arm was the classical chemotherapy arm, and everybody thought there would be no need to specify how we should do some certain chemotherapy treatments. But certainly, I have seen that not everyone uses the same protocols and treatments, and this could hamper the results of your trial if it is not properly assessed, as you said, and reported.

Dr Bertolaccini: But in your opinion, who should take this part? The national society, the international society? Who should say, "Okay, we have to evaluate the quality in surgery. We have to evaluate the quality in oncology. We have to evaluate the quality of the multidisciplinary team approach."

Dr Menis: I like very much the way that, for example, our society in lung cancer, so for example, the IASLC, how they are promoting conferences or expert meetings in order to provide the standard assessment, for example, for pathological response, I think this can be a way to bring this forward, possibly, also in collaboration with the regulatory bodies. Why not? If the integrated, for example, neoadjuvant strategy or the chemo-radiation together with new compound strategy is the one that will be the new standard practise. Then, for regulatory bodies, if we show them that the treatment is done properly, this could reinforce also the evaluation of certain compound.

Dr Bertolaccini: Okay, thank you.

Dr Menis: From quality assurance to surgery, to the big basket of translational research, what we wanted clearly to highlight because translational research can mean a lot really, and Luca knows very well that tissue is definitely the issue. For him, it's very easy to get a large amount of tissue, but the analysis we do for advanced stage tumours is really difficult most of the times. So, not just the right sample, but the right approach because, at the end, the turnaround time is what matters most. And at the end, we are doing the assessment and evaluations, like the molecular profile, the immunohistochemistry, gene expression profiling, but this all will lead to a treatment choice. And at the end, the patient is the one that will ask us, "Doctor, how long is it going to take?" So, it's really important that. Luckily, we have done some advances in the role of liquid biopsy, which seemed just the future, but it has become a reality now, luckily. For example, for EGFR. But for other tests, we really need to pay attention to the accessibility of this test, the real feasibility in practise, the heterogeneity of the results that we have, and the costs. And one good example that we can translate, for example, from colorectal cancer to lung cancer is the evaluation of disease after surgical radical

treatment. So, the minimal residual disease could be something that is just exploratory now, but could be something for our future.

Dr Bertolaccini: Okay. But we, as surgeon, should have in mind that the oncologist needs tissue. So, it's normal in this time that the oncologists say, "Luca, could you take me these notes? Luca, could you take me this lesion? Because I need more and more material." It's normal in this time. And the surgeon should have in mind that our practice will really change in the next future.

Dr Menis: Definitely. Definitely very important for the surgeon, in an integrated way, in order to have a holistic approach of our patients, really comprehensive. If we translate that to a clinical trial, please, pay attention to that because Luca is an excellent surgeon, but not all sites that you select for your large, maybe phase-III trials might have the same opportunity. So, including a multidisciplinary team being present, for example, in clinical trials, is really relevant. We are very lucky, in both our institutions, this is feasible and acceptable, but when you develop your trials, pay attention to that because it could be a very good quality assurance method but at the same time, it needs to be feasible. Would you agree, Luca?

Dr Bertolaccini: Yeah. Absolutely agree.

Dr Menis: To conclude, what we wanted you to pay attention is what we think are pitfalls and temptations you might come along during your research development. The first temptation is, of course, to try to solve all questions at once. Please remember, your primary objective can be one or at least two, but shouldn't be more than that. Base your assumptions only on expert opinion or on literature data. Use the easier methodology, "Less is more," and consider the disease as a uniquum. And do not forget to be also patient- and disease-centred and not just treatment-centred. Be prepared for the unexpected, for sure. And finally, and this is the main focus of our whole presentation is sense of responsibility. This is your research, this is your project, so, it's up to you. Do not forget to collaborate and to pass information as much as possible and discuss always with your collaborators within your team, with your colleagues, like the surgeon, pathologists, radiation oncologists, everyone which is in your MDT and even beyond. Why not? And we're ready for your questions.

Dr Bertolaccini: Thank you, Jessica, for your great presentation and for a lot of key-points. There is a question from the floor about the patient reported outcomes and the importance of patient reported outcomes in the oncological study in the last two years. Why is there interest?

Dr Menis: You will comment also from the integrated, for example, trials, but for the systemic ones, what I have seen in my experience, also in registration trials, it's very important to have the view of the patient. We can see, for example, with trials with immunotherapy but also, with targeted agents that we were having this low-grade, long-lasting toxicity, which we oncologists, most of the times, don't pay too much attention about, but can be really difficult for patients. If we imagine a grade-2 diarrhoea that lasts for several weeks, this is something which can be very difficult for the patient's life. So, spotting that with the patient reported outcomes can be a way to assess better the safety profile of the drugs.

Dr Bertolaccini: Thank you, Jessica. We have another classical question when we speak about methodology, but I need to study statistics or I need to have a statistician inside my group?

Dr Menis: I have worked four years at the EORTC. I think they will kill me if I say, "I can study statistics by myself." Never, never do that. It's important to have a basic understanding of statistics, for me, but it can be just an introduction to statistics. Usually, they study mathematics. Afterwards, they do a PhD in statistics and much, much, much more time in learning and doing clinical trials. So, the best way is to have a statistician. Do you agree?

Dr Bertolaccini: Absolutely, with you. But basic statistics, it's really important because you could speak the same language with your statistician.

Dr Menis: Absolutely. Otherwise, it's impossible for them to really design the statistical plan as it is in your head. The common language is very much important. So, a close integration and an integrated discussion is the best way to have your study designed as you really wish. And at the end of the day, when you have your database closed and analysed, it leads to reply to your question.

Dr Bertolaccini: We have another question from the audience. We nowadays see many trials with similar research questions and trial design, but with different drugs, like various ICIS, and we can then do indirect comparison of results of those trials. Why not perform multi-arm trials with all the similar drugs tested at the same time, even from different pharma companies?

Dr Menis: Well, this is a million-dollar question. I will give a very academic reply. So, of course, I was working in the EORTC, which is an institution that collaborates very closely with pharma and runs purely academic trials by itself. So, of course, when you design a trial where several pharma companies have to provide the compound, it's very, very difficult to make a design and a protocol which fits everyone's opinion. But indeed, trying to pull together all trials in the same one, like the U.S. are doing, for example, in the lung master protocols, which are very nice example of collaboration between academia and private practise, is the best example we can have. So, still a lot has to be done, but we are moving in that direction. So, in Europe, we should start using the example of the U.S. In my view, I don't know, Luca, if you agree, but the reason why they are maybe a bit ahead of us is because they have a really good collaboration with the regulatory bodies. So, FDA really sat at the table together with the academic partners and the pharma partners, and they could develop this master protocol, which is, in my view, a really nice example of collaboration.

Dr Bertolaccini: I agree with you and compliment for the really academic answer to this really complex question. We have another question from the floor about the evaluation of quality in oncology, and if the quality is similar for each patient. We should have a lung cancer quality, breast cancer quality and so on.

Dr Menis: In that we have the... Well, for surgical, honestly, I don't know, you can help me in finding the reply, but for the general quality of life questionnaires, luckily there are specific ones on the different tumour types. So, for academic partners, it's very easy. You just go to the EORTC website. In the quality-of-life group, you can find all the questionnaires and they are general ones, but also the ones specific according to the tumour type.

Dr Bertolaccini: For the surgery, we have different quality report for different surgical specialties. The quality for thoracic surgeon is quite different for a general surgeon. It's completely different for a neurosurgeon.

Dr Menis: Of course.

Dr Bertolaccini: Okay. Thank you so much, Jessica. We have no other questions from the floor. So, thank you for having accepted to participate to this e-ESO oncology session this afternoon. Thank you so much.

Dr Menis: Thank you so much for inviting me, and I hope it was really nice for everyone.