Subtitles and transcriptions
Subtitles and transcriptions are available for selected materials for purpose of helping users understand the contents of the educational sessions.
Uncertain words have been indicated with ?? before and after the part. Parts that could not be understood at all have been indicated as [Audio Not Clear].

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

Are all invasive lobular cancers the same?

Prof Penault-Llorca: Hello, everyone. Hello, Simona. So, I'm going to share my screen with you and start my presentation. Simona, you want to add something?

Dr Volovat: It's a real pleasure to be here today with you, and well, I hope it's going to be a topic that will raise a lot of interesting discussions. The floor is yours, Professor Penault-Llorca.

Prof Penault-Llorca: Thank you so much. So, are all invasive lobular carcinoma the same? This is, first of all, my disclosures. So, the objective of today's webinar will be to understand the specificity of invasive lobular carcinoma, to understand the heterogeneity of invasive lobular carcinoma in terms of morphology, biology, and therapeutic opportunities. Your views are important, so, remember that you can ask questions and send comments at any time, and click on the Q&A button to send your questions and comments. First of all, lobular carcinoma is the most frequent special histopathological type of breast cancer. The major subtype, as you know, is non-specific type, the former ductal carcinoma. But in second, we have lobular carcinoma. And it's a long story since the first microscopic description in the beginning of the 20th century, then, the description of the very specific pattern, but also, the fact that we need to have pre-cancerous lesions, so, the pre-cancerous lobules, and at this time, it was mandatory to have that to give a diagnosis of lobular carcinoma. So, we had around 5% of invasive lobular carcinoma. In the seventies, with a lot of work from David Page, Rosen, they described that it was possible to have an ILC diagnosis without the pre-cancerous lesions. It was based on morphology. Then, it was described as an ER expressing breast cancer, and we were around 10 to 15% of ILC, what we have today. Then, in the 70s-80s, several variants have been described in the literature. In '95, there was evidence of the somatic loss of E-Cadherin, and the explanation, after that, that it is oncogenic, but it was later, like 20 years later. But also, in '98, the description that we can have in the family of hereditary diffuse gastric cancer also invasive lobular carcinoma because those families with germline CDH1 mutation are also at risk of lobular carcinoma. Then, comes the time after 2010 of the molecular characterization, the description of many targets, some of them are HER2 and HER3 mutations, but also, the evaluation of the immune contexture of lobular carcinoma, showing the big difference between lobular and ductal carcinoma. And a specific trial for ILC started in 2015. So, this is the most common special type of breast cancer, accounting for 10 to 15% of all breast cancer. But it's less common in Asian population, where it's around 2 to 6%. We have a different clinical presentation if we compare to a non-specific type. Patients are older, they have a larger burden of disease at presentation, larger tumour, larger node involvement. They also have a bilateral or multifocal breast cancer, and also, another representation of primary metastatic breast cancer or de novo metastatic breast cancer. But the majority of invasive lobular carcinoma are of low-histological grade, lower than NST. There is also a problem for the resection margin because of the unique pattern of extension of this tumour and also, a distinct pattern of metastatic dissemination, metastasis to the digestive tract, to the ovaries, bone, leptomeningeal, orbital, soft tissue, skin. There is less CNS or lung

metastasis than ductal carcinoma, but it was presented at San Antonio Breast Cancer yesterday, pleiomorphic lobular carcinomas, so an aggressive variant, has a high risk of brain metastasis. Altogether, there is a higher rate of multiple metastases compared to the other breast cancers. The biology is completely different from NST breast cancer, with different mutational characteristics including the hallmark, the specific feature of E-cadherin mutations, but different microenvironment, gene expression profile, and DNA copy number. And we have different subtypes, with different morphology, prognosis, molecular alterations possibly impacting therapy. So, let's go back to clinical features and histopathology. So, invasive lobular carcinoma is usually palpable, but sometimes, despite that, there is a high false-negative mammography rate because the lesions are vague, not really typical, so, most patients can be missed at the beginning. They have, as we said, larger, multifocal bilateral tumours, and also keep in mind that most patients have frequent late relapses occurring more than 10 years after diagnosis, probably because they are extremely hormone-dependent and those are the tumours with the late relapses. What are the risk factors? So, we have all the oestrogen-related risk factors as in breast, of course, for breast cancer. So, early menarche, use of hormonal replacement therapy for menopause, late age at first live birth, alcohol consumption, they are most strongly associated with the risk of developing ILC as compared to NST. Obesity was expected to be a risk factor of invasive lobular carcinoma. It's not the case in post-menopausal women. It has been documented in many studies now, so it doesn't seem to affect more the risk for lobular than NST. We have germinal mutations associated with high-risk of lobular carcinoma. CDH1, of course, germline mutation, but also BRCA2. Moderate-risk germline mutations are represented by ATM, CHEK2, and PALB2. And there is no clinically relevant risk for germline BRCA1 mutations. Another thing is that lobular carcinoma is classically absent in male, but we have seen exceptional cases in male, usually associated with germline BRCA2 or CDH1 mutations. So, this is pictures and images of a gross microscopic view of lobular carcinoma. So, first of all, you can see on the surgical specimen that you don't see any tumour. So, this is really something where pathologists have to do some palpation to find indurations. The classical pattern is with single cell infiltration, classical targetoid pattern of growth. Usually, they exclude, and the tumour cells are not invading, for instance, vessels or normal breast ducts. You can see here, on the bottom slide, that we have also an in-situ component that is associated, and I remind you that it is not mandatory. You also have another in situ component on the right, left image. So, because of this pattern of invasion, because of the fact that it's ill-defined tumour, the size of the tumour often extends the imaging findings and obtaining clear surgical margins may be challenging. So, what are the variants? The variants account for up to 70% of lobular carcinoma cases in the literature. It's not my experience and the experience of many, usually, it's around 30 to 40%, the vast majority being the classical lobular carcinoma. So, in the WHO classification of tumours of the breast, we have four different ILC variants. The solid, the alveolar, the pleomorphic, and the tubulolobular. And I'm going to describe those subtypes along with other subtypes. What you can see at first look here is that the alveolar or the solid are very monotonous, but we can have high-grade cells in those tumour types, but they have a very compact growth. The pleomorphic is really characterised by non-cohesive cells, but with really high-grade. And the tubulolobular, I will show you that we have different possibilities for this entity that is now better understood. So, as you can see in these slides, more ILC variants have been described in the literature. Some of them are named by their growth pattern, such as solid infiltrating lobular carcinoma. Others are characterised by cytologic features, like the pleomorphic carcinoma with a little atypia. Some variants are associated with distinct molecular alteration, with distinct clinical outcomes. They can be associated with mucin, as you can see here. They all share a common feature, that is, in immunohistochemistry, the loss or low expression of E-cadherin. And this is something that is very important and that will be also found in molecular biology. So, some details on subtypes. Pleomorphic invasive lobular carcinoma. So, you can see here, it's a de-differentiated variant with a high nuclear grade and usually, they are SBR3, when the classical lobular carcinomas are usually SBR2. They are E-cadherin-negative. The recurrence score can be high for them, but they are usually node positive. And you can see that they have TP53 mutation that is quite uncommon in the classical lobular carcinoma. But they can have also HER2 amplification, quiet and frequent in the classical lobular carcinoma, and HER2 mutations that is shared with invasive lobular carcinoma. But if you correct for

HER2, for nodes or stage, the survival, in many studies, is similar to ILC. A subtype that is ILC with extracellular mucin, we need to have at least 20% of signet ring cells floating in pools of extracellular mucin. The mucin is a MUC2 that is usually not found in breast, it's usually MUC1 that we have in normal breast cells. So, probably the carcinogenesis here is through a change in the mucins, but in both components, E-cadherin by immunohistochemistry is negative. It's also a tumour type with a lot of lymph nodes invasion. HER2 amplification up to 40%, and a high nuclear grade with TP53 mutation and PIK3CA mutations. Histiocytoid ILC, so, they are apocrine in terms of molecular differentiation, triple-negative, so, it's one of the triple-negative lobular carcinomas with frequent HER2 amplification, and androgen receptor expression. And they are quite known for metastasis to the eyelid. The solid ILC or the solid papillary ILC, so an extremely dense tumour with a prognosis that is usually not good. We have to exclude lymphoma because it really looks like lymphoma, and they have also TP53 alterations, ARID1A, and a gain of ESR1 copies. The signet ring cell-rich ILC, is... of course, you have to exclude a mucinous or metastasis from a gastric cancer. So, we use immunohistochemistry, but the prognosis is close to the classical ILC. And the alveolar invasive lobular carcinoma looks like a packet in situ lobular carcinoma but there is no myoepithelial cells around. And they have specific gain on chromosome 11q13.3 for the catenin and for PAK1. To finish, the tubulolobular subtype. So, it has been a lot of questions about this subtype. So, it's a subtype where we have classical single file disposition of the cells with a low-grade, and small tubes that are intermingled. So, now we have, in fact, for this morpho-molecular entity, three options. One is a true collision lesion. So, we have one former ductal carcinoma, NST, that is E-cadherin-positive, and a tubulolobular carcinoma that is E-cadherin-negative. One that is in fact ductal carcinoma or NST carcinoma but with a differentiation in single cell, but all the tumour is E-cadherin-positive, there is no alteration of E-cadherin gene. And the true tubulolobular carcinoma or ILC with tubular elements where we have a mix of single cell and small tubes and all the tumour is E-cadherin altered, E-cadherin-negative. And this is, in fact, extremely rare. So, remember that you can ask questions, and don't hesitate because we will have some time at the end of my talk. So, what is shared among all those types of lobular invasive carcinoma? The E-cadherin down regulation. So, this is really what is needed for the diagnosis of ILC. Observed in the majority of invasive lobular carcinoma caused by somatic mutation or loss of heterozygosity. You can see here that we have several areas of the genes, regions that can be altered. It's on chromosome 16, and it's in 16q22.1. That's why chromosome 16 is one of the recurrently altered genes in lobular carcinoma. In other cases, we can have an extinction of the gene by a promoter methylation. And what does occur when we have this alteration of the gene function? We have a translocation of the E-cadherin to the cytosol, and we have a translocation, sorry, of p20, usually, p20 was attached to E-cadherin, and this is really playing an important role in the discohesive cells, discohesion, and motility of the cells. Sometimes, we can have trouble in interpreting E-cadherin because some invasive lobular carcinoma can have a faint staining. So, in this case, we can use either beta-catenin that will also be lost, and we will have a negative staining, or p120, where we will have a cytoplasmic staining instead of a membrane staining. So, this can be used in difficult cases for the lobular phenotype. For the molecular signatures, we really need to have specific signatures because I remind you that the molecular signatures were not designed for lobular carcinoma. They were designed usually in non-specific type carcinoma. We have discrepancies in the percentage of high-risk cases using the different signatures and, especially with Oncotype, we have lot of low-risk tumours when you compare the same type of tumours with the other signatures. So, this is something that will be important to develop in the future. And one signature that been developed but it's still for research, by the team from Brisbane, from Sunil Lakhani and Peter Simpson. They searched database for lobular carcinoma and they found that they have kind of signature of almost 200 genes that could really be discriminant for the prognosis of lobular carcinoma. And they found that they have some high-risk tumours that are enriched in specific mutations like ERBB2, ERBB3, AKT1, ROS1. And they have also enrichment in certain type of amplification, like DIP2A and deletion of other genes like ARID1A. And the LobSig low tumours showed relatively quiet genome when the other had a lot of rearrangement. But you can see the different survival curves, but it's a good signature for the different ILC, but also, for the grade 2 and the grade 3 highly significant when, for instance, here Oncotype or MammaPrint, couldn't really separate

two prognostic groups. So, what differs? First of all, we have a different carcinogenesis with different subtypes of lobular in situ carcinoma with different molecular alterations. So, all of them start with E-cadherin loss on chromosome 16 and some gain on chromosome 1. We have atypical lobular hyperplasia and then, in situ lobular carcinoma. So, the classical one, that you can see here with E-cadherin loss and some myoepithelial cells in the periphery, doesn't have any other alterations. Then, we have two other possibilities in morphology, and also, with underlying biological alteration. It's the florid lobular in situ carcinoma that is probably precursor for alveolar, solid, and tubulolobular invasive lobular carcinoma, sorry. And TP53, dysregulation of hormone receptor, and HER2 amplification for the pleomorphic ILC that you can see here, where we can have necrosis like in situ carcinoma. In fact, now what is really important is that when we have such florid lobular in situ carcinoma or pleomorphic lobular in situ carcinoma on a biopsy, we need a surgical verification. when we don't do surgery, if we only have the classical lobular in situ carcinoma. But all those lobular in situ carcinoma are risk factors and they are a non-obligate precursor of invasive lobular carcinoma. If we see the difference, in summary, so classical ILC are grade 2, when the other ones are usually grade 3. They express hormone receptor, they are non-amplified for HER2, they are luminal A, when the other ones can be triple-negative, and they will express also androgen receptor. They have mutations for HER2 and HER3, and also, in a gene that is close to hormone receptor ESRRAm. In the classical, no amplification of HER2, low-level of HER2 mutations, and a very few or no TILs. On the other hand, you have HER2 amplification of 25% in the apocrine variants or in the mucinous. HER2 mutation also at a high level, and TILs that can be high usually in young patients. And here, something that is very important is that at the opposite of non-special type, the TILs are associated with a poor prognosis. And you can see here, on this survival curve, where in red you have high TILs, so, superior to 10 in this study. So, it's also different levels than in NST where it's more than 50. But you see that it's clearly associated with a poor prognosis. And also, with activation of different genes like ARID1A that is involved in chromatin remodelling. So, don't forget to ask questions and I'm going to finish my talks on the molecular targets. So, loss of E-cadherin, that is the step for carcinogenesis. Then, we have in this tumour type a high-level of PIK3CA alterations, but also AKT1, HER2, HER3, and this is something that is important because mutation in HER2 and HER3 are not associated with over-expression or at least in 70% of the cases, there is no over-expression of HER2. And the histologic subtype-specific association with ESR1 gain in solid subtypes, HER2 mutation in mixed non classic, and TP53 in both. One interesting paper works also to look at invasive lobular carcinoma versus invasive ductal carcinoma, and they found that there is also a specific immune-related gene expression profile in lobular carcinoma with at least three different subtypes, one being activated, and with genes involved in the oestrogen receptor signalling like FOXA1. This is in the Annals of Oncology paper looking at the genomic alteration in primary and metastatic invasive lobular carcinoma. So, as I said, PIK3CA mutation, high TMB, so in Europe, we don't have access for the moment, at least in my country, to immunotherapy for high TMB tumours. But in breast, this was something that was not expected but it is lobular carcinoma where you have the highest TMB, in 16% of the cases, in metastatic stage. Don't forget the mutation of ERBB2, ESR1 also, that can occur after hormonal treatment by aromatase inhibitors, and the ERBB3/HER3 mutations. And in this paper from Desmedt, they looked to the different subtypes of lobular carcinoma and you can see that they also confirmed that the molecular alterations are different in the different subtypes. Some of them having more frequently HER2, HER3 mutation or HER2 amplification, other having AKT1, and all of them having PIK3CA alterations. So, a lot of therapeutic possibilities. So, now, I'm at the conclusion. So, if you look at the lobular breast cancer, you can see that you have the morphology that is very specific, but you have the biology also that is different. We have the multigene classifiers that are maybe not optimal, but we have now specific molecular signature that we hope will come to put in practise. Transcriptomic subtypes with difference in different aspects including immune response. We have the E-cadherin loss that is specific and that promotes tumorigenesis, and there is an activation of ROS. So, there are now ROS inhibitors that are studied. The PIK3CA signalling pathway in half of the cases, HER2 mutations, and the alteration involved in ER-signalling, especially with ESR1 gain. So, also, we need to understand the endocrine resistance. So, what is important because of all those alterations is to have molecular profiling at metastatic stage. What is relevant for clinical practise?

Really to separate the classical lobular carcinoma, no HER2 amplification, low grade, SBR grade 2, from the high-risk, high-grade, where you can find HER2 amplification, poor prognosis, and other specific targets. Those tumours are usually luminal A, so, low chemo-sensitivity, but sensitivity to endocrine treatment and CDK4/6 inhibitors. All the HER2, HER3 with amplification and mutation in some specific cases where we can have targeted therapies; the PIK3CA pathway, and, to understand better, the immune context of those tumours that is different from the NST invasive carcinoma. And to conclude, now, we are very happy to see that we have specific clinical trials with clinical trials targeting the ER-signalling pathway, the synthetic lethality CDH1 deficiency with ROS1 inhibition with the ROLO clinical trial. Specific trials trying to target both PD-L1 and CTLA-4, and, in the metastatic setting, also targeting HER2 and HER3 mutations. You will have my presentation, but these are some papers that I have selected for you reviewing lobular carcinoma. And with that, I thank you very much for your kind attention. Thank you.

Dr Volovat: Thank you very much, Professor Penault-Llorca for the very comprehensive presentation. And we have a question in the Q&A section and it asks, "once in my laboratory we saw morphological lobular carcinoma, but it was E-cadherin-positive and the patient was 22-year-old. Have you seen lobular carcinoma in young patients, and will the treatment change if it's an E-cadherin-positive?" So, this is a very interesting question.

Prof Penault-Llorca: Yes. So, first of all, I will really send this patient to oncogenetics, and I think that's maybe something that has been considered because she's extremely young for having any type of breast cancer, and it could be germline mutation, BRCA2, or CDH1. As I said, E-cadherin can be positive, usually, it's less strong than when it's not altered, but sometimes, it's positive, and there are probably other genetic alterations that can lead to this morphologic pattern on other adhesion molecules, genes coding for other adhesion molecules. It's starting to be described for maybe the 5% where we never find anything concerning CDH1. So, my message here would be it's probably a germline mutation, BRCA1, or CDH1.

Dr Volovat: Yes, I agree. And regarding the treatment change, if it's E-cadherin-positive, actually, we don't have the data. We treat it as usual, and I agree that we need, this is actually an unmet need for lobular cancers. We need more focused data on this particular subtype of breast cancer that has different biology, different molecular alterations, and probably, different treatment responses. So, this is actually an unmet need, but for now, I think you agree that we wouldn't treat it differently depending on the E-cadherin. Okay, thank you. He said that in Peru we cannot send her to oncogenetics.

Prof Penault-Llorca: Oh, okay.

Dr Volovat: So, it's also very important to have the possibility of address.

Prof Penault-Llorca: Yes, it's not going to change our treatment, but it can change our follow-up and also for the family because if it's CDH1, there is a risk also of gastric cancer. There is a risk-reducing surgery. Same for BRCA2, but if you don't have access, you don't have access.

Dr Volovat: Yes, I agree with a very personalised monitoring for the patient and for the family, this is also very important. I actually had a patient who had breast cancer, a lobular breast cancer and a gastric cancer in the same time, and she was actually very young. She was 30-something, and with a very fast and bad prognosis. I agree. Okay, thank you. Another question. "From your point of view, what are the more interesting and promising strategies for ER-signalling pathway targeting?"

Prof Penault-Llorca: Well, I think maybe you can answer also because it's more in your field.

Dr Volovat: Yeah, so, in the ER-signalling pathway, how we target it? Of course, we have the current CDK inhibitors, that are generally done in first-line and second-line setting. So, probably, the most important strategies now are linked to patients who become resistant to CDK inhibitors, and there is a very nice focus on ESR1 mutations that we know, and we see this in clinical practise quite a lot in metastatic setting. There

are a lot of new drugs that target now this kind of mutations. And another question, "would you order any molecular tests for supporting a lobular carcinoma?"

Prof Penault-Llorca: So, maybe, I was not clear, but it's a moment to say that the diagnosis of lobular carcinoma is morphologic. So, it's not mandatory at all when the pathologist is sure about a lobular carcinoma, to perform an E-cadherin immunohistochemistry. So, just on the morphology. If there is any doubt, we perform immunohistochemistry with E-cadherin, and if it's slightly positive or if we still have a doubt, in my hospital, we have the beta-catenin. So, we will do the beta-catenin immunohistochemistry that will also be negative, and sometimes, it can be of help. But we don't use a specific molecular test because we don't have. We will find maybe an E-cadherin mutation, but you don't need it really for the management of the patient. The only thing that you could require is to know if your patient has a germline mutation, but it will be in the family, or young age, or things like that. So, the molecular testing will really be at late stages if you have access to clinical trials, because right now, at least in my country, we don't have access to specific drugs, but for the clinical trials at least.

Dr Volovat: Yes. Thank you. And this is my question. Do you usually include TILs when give histopathological report for lobular cancer?

Prof Penault-Llorca: So, TILs, it's a long story. I'm part of the International TILs group, and we are very active with Roberto Salgado in promoting TILs. But the last St. Gallen session, when we interrogated the oncologists about do you want to have TILs in the pathology reports, I think it was like 30% said yes. So, we were very, very disappointed. We know that TILs are prognostic, but as I said, in lobular, it's really different because its poor prognosis. But we are lacking large studies, we are lacking many things. So, yes, in my hospital, I give TILs, but it's more for the database, not for the oncologists, because they don't use it right now. But because I want the pathologist in my lab to be trained to score TILs. But the immune context of the lobular carcinoma is completely different from the immune complex of the NST, non-specific type tumours.

Dr Volovat: Yes, I agree, that from a practical point of view, TILs have a very limited use for now.

Prof Penault-Llorca: But there are clinical trials now for de-escalation in triple-negative breast cancer. But it's really very different types of tumours than our classical lobular carcinoma.

Dr Volovat: Yes, yes. Thank you. I agree. And we have another question. "Do you consider effectible to do an intraoperative diagnosis of free margins in the case of lobular carcinoma, doable?"

Prof Penault-Llorca: We try. It's not always easy because sometimes it looks at palpation, sometimes, we don't feel anything. But as we do frozen sections, we are here for frozen sections, in my lab, so we do that, and I think that we are wrong in maybe 10% to 15% of the cases. If there is a large involvement, we will see it. But it can be difficult, yes.

Dr Volovat: Okay. Okay, these are very, very... point on all questions. Furthermore, "what's your opinion on the discordance rate in the pathological diagnosis of invasive lobular cancers? What would your advice be maybe to improve that?"

Prof Penault-Llorca: Yes, that's a very good question because international reproducibility or inter-observer variation studies showed that for lobular carcinoma, the concordance rate are like 60, 70%. So, saying that you miss 30% of the cases, that's quite high. So, I think it's really in the way of over-diagnosing invasive lobular carcinoma because the change from ductal to lobular in those studies is rather around 2%. So, it's really more over-diagnosing. So, I think that in any doubt, using E-cadherin could be very useful. And also, the knowledge by the pathologist of the several variants that we have especially the highly pleomorphic variants. And also, if you have, for instance, a tumour with discohesive cells, but that is triple-negative and that really looks like lobular carcinoma. It's not a lobular carcinoma, it's a metastasis. And also, be very careful in some difficult presentation, or in a male, for instance, if you have a classical lobular carcinoma triple-negative, usually, it's

a metastasis. So, there are also some situations where it looks like lobular carcinoma, but it's a metastasis from a melanoma, for instance, or for a lymphoma, a localization of a lymphoma or another tumour type. So, be careful if you have a typical lobular carcinoma and, in the pathology report, it's stated classical lobular carcinoma, HER2 amplified, call the pathologist, it's not normal.

Dr Volovat: Yes, yes, I agree. Thank you very much. And what about the genomic testing in lobular cancer? You had a very nice slide stating different types of genomic tests, and in your clinical practise, are there some tests that you recommend more than others, maybe?

Prof Penault-Llorca: So, first of all, I think that something is important, is that those tumours can be with a low cellularity, and this probably can impact the molecular testing. And something that was very strange is that when you look at a series of lobular carcinoma tested with those molecular signatures, if you use a recurrence score with cut-off at 25, you have like 8 to 6% with a high-recurrence score. With MammaPrint, it's around 11 to 28. With EndoPredict, it's around 35, 37%, and 31, 32% with Prosigna. So, you see that depending on the test you use, the high-risk proportion is completely different. So, this is something that is a little scary if you must decide what treatment to give. In my hospital, we use EndoPredict a lot because we do it in the hospital and it's less expensive than running another test. And we have a lot of confidence in a low EndoPredict risk. But as for the other molecular biology test, we always look at the cellularity. And if the cellularity is less than 20, 30%, we will not run the test because we cannot be sure of the results.

Dr Volovat: Yes. Perfect. And thank you very much. I think the session is approaching to the end. It was very interesting session and discussion. Thank you very much, Professor Penault-Llorca for the presentation, and for the attendees for their questions.

Prof Penault-Llorca: Yes, thanks a lot and it was a pleasure to be with you on this session, and well, if you have any question, don't hesitate to contact us. And thank you for the questions and for attending to our webinar. Thank you so much.

Dr Volovat: Thank you.