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PD- L1 digital quantification

Prof Salto-Tellez: Hello everyone. My name is Manuel Salto Tellez. I would like to thank the ESO-ESP organizers for the opportunity to be here. The title of my talk, as you can see, is PD-L1 Digital Quantitation. I would like to give you an introduction of what I think is a very exciting, but at the same time, a pretty complex test, and a very complex digital pathology approach as well. As you know, program death 1 is a very important molecular component of immuno-oncology. PD-1 links with its main ligand PD-L1, and that link essentially inactivates the immune surveillance in relation to cancer. If we are able to block that PD-1/PD-L1 relation, then we may be able to bring the immune response back to create that potential anti-oncogenic effect. It's very important to indicate that PD-L1 is a very relevant component of what I think represents a broader picture in immuno-oncology. As you know, the presence of T-cells, the question of mutation burden, Microsatellite Instability Testing, they are all interlinked in that potential therapeutic decision-making that is very relevant to the test that we are going to describe. And in fact, what I would say today is that in our routine diagnostic laboratories, we do as much Microsatellite Instability Testing as we do PD-L1, because as you know, in some cancer types, it's the Microsatellite Instability status that carries the potential clinical relevance and predictive relevance with anti-PD-L1 therapy. PD-L1 is done on the lab, and as you know, at the beginning, there was quite a controversy on the different drugs that were associated with different monoclonals, that were associated with different scoring methods at different thresholds. It's fair to say that a degree of correlation has been established between many of these biomarkers, many of these monoclonal antibodies, and the different cancer types. Below in this image, you have one related to gastric cancer. Here, you have one of the original blueprint studies were, as you can see very nicely, the concordance between at least three of those five leading antibodies, 22C3, 28-8, and SP263 was clearly established, in this case, in the context of lung adenocarcinoma. One of the things that makes PD-L1 quite relevant, and to a certain extent, difficult test, is the scoring. As you know, there are three different scoring methods, CPS in the vast majority of the cancers, TPS in the context of non-small cell lung cancer. The description of these criteria indicate clearly that this is a complex scoring system, where the pathologists need to recognize different cell types, and provide potential percentages of expression in each of those different cellular subtypes, making these scoring probably a little bit more difficult than what we are used to in personalized medicine to date. Why should we consider digital quantitation in PD-L1? Well, first of all, because digitization is at the heart of the development of future biomarker discovery on precision medicine in cancer. We know that in any drug development from discovery to approval, and adoption, there is a component of biomarker development of companion diagnostics. We know that this is very relevant for the majority of the regulatory agencies, and we know that digital pathology, both from the point of view of the delivery of high-quality images, but also, from the point of view of creating companion algorithms that would make this process significantly more accurate and reproducible, is essential in this process. And as you know, there are companies that are actively exploring this. The other reason is clearly PD-L1 is a test that is intrinsically difficult, and obviously, we have the hope that digital pathology may be able to help us in that space. It's intrinsically difficult, because as you

know, it's very heterogeneous, or it can be very heterogeneous, in a large number of cases. And indeed, the work in Liverpool by John Gosney and others showed that that intratumoral heterogeneity is substantial, and in some degrees could affect the final scoring, and therefore, the potential therapeutic intervention associated with the test. We also know that it's a tool that can bring potential pitfalls. We are used (or we are asked) to consider weak staining to a level that perhaps we haven't considered in any other diagnostic or therapeutic tests before. We know that there are other cell lines or cell types, apart from the epithelial tumor that can express the same biomarker. We know that necrotic areas need to be considered, because they could provide false positives. We know that at least in the context of lung carcinoma, adenocarcinomas and squamous cell carcinomas can have a slightly different expression patterns, and therefore, intuitively, we look up them differently. And we know that there are many other things that we find in this slide that can make a difficult case for the scoring. The fact that sometimes the common denominator, the total number of tumor cells, is not very clear, and we may need farther immunohistochemistry for that, the same in cytology to try to understand what is the cell type that is expressing PD-L1; the, what we have called, "hugging effect" the fact that you could have a significant amount of immune cells surrounding the tumor, and it's very difficult to understand in that gray zone, what is or not epithelial expression. There are many reasons why this is a difficult test. Probably the most difficult, the reason that makes it more difficult, is the way the test has been designed. If you look for instance at the way we do HER2 testing, we know that 0 or 1+ is negative, we know that 3+ is positive, and we know that 2+, we look for other genomic approaches to decide which side of the fence we are sitting. That is not the case with PD-L1. As you know, for many of these scores, and I continue referring to lung cancer, the boundaries are very sharp, and extraordinary things can happen. For instance, here, you have a case that, let's presume the ground truth is in 53%. If I call it 97%, I'm probably right, because I am in this, in the right, or in the same therapeutic threshold, while if instead of overscoring it by more than 50%, I underscore it by 6%, I'm probably in a therapeutic framework that is not the same, and therefore, this may have implications for the patient. It's a difficult concept to characterize. And in fact, this leads to potential inter-observer variations, and several of these have been reported before. Probably the one that I like most is the Italian study led by my colleagues, Malapelle, Fraggetta and Troncone, where, as you can see, the potential discordances are quite significant, and they are related not only to the visualization and the interpretation, but also, perhaps, to other wet-lab components like the monoclonal antibody that these studies used. Other experiences like the Chinese experience on the right, or the one by the group Targos, on the left, are reporting lesser degree of discrepancies, but it's still quite significant discrepancies that may be relevant. In fact, our group has helped in the potential education in the scoring of PD-L1. On the right, you see the module that we created in the context of one of the leading digital pathology consortium in the United Kingdom, PathLAKE, of which we are a founding member; on the left, you can see a collaboration with MSD; which are essentially two ways of trying to explain the difficult areas of these tests and how to overcome them. So, we definitely need quantitation. This development of the quantitation tools happens like in any other tool in digital pathology or artificial intelligence. We, as you know, evaluate and set up our technical gold standards on the left. We also evaluate and set up our clinical gold standards on the right, and as you can see, we define the SOPs according to image capture, image analysis, subsequent analysis to produce a tool that may be clinically relevant. And the fact of the matter is that from the beginning, it was very clear that digital pathology could help in this process. This is one of the first papers by the group of Keith Steel, where, as you can see, they show a very clear prediction of response by automated image analysis. And in fact, subsequently some reviews have come to explain some of those digital pathology tools. I'll draw your attention very briefly to the middle of those studies, which is the study that Matt Humphreys led in our own laboratory. Again, these are studies that are very much driven by the same framework, a relatively small number of samples, various specific single approaches, and as you can see, always identifying the prognostic or the predictive relevance of that scoring by digital pathology means as you can see in the Kaplan-Meier curve here on the left. If you put these in a broader context, and again, this is another Chinese study supporting that, you can see that the overall impression is that indeed these approaches can help the pathologists in the assessment of PD-L1. It's very interesting. They're not saying that they can be standalone

ways of a score in PD-L1, but they can help the scoring of a PD-L1 process by a pathologist. In some ways, ~~I agreed~~ agreeing with the very recent authorization of FDA of a product by PAIGE, which, again, helps the pathologists in identifying features rather than substituting pathologists in that space. And in fact, if you want to adopt these from an off-the-shelf point of view, there are already many companies with some of these products. VISIOPHARM have several PD-L1 products in its menu. Mindpeak has its own product with a very specific platform, the delivery framework. Roche has a ~~CIBD~~ CE-IVD tool for PD-L1 scoring. Tools of Indica Labs have led to significant evaluations of PD-L1 in the discovery and translational space. There are already many tools out there that, potentially, could be adopted. The fact is that they are not adopted yet in the context of routine diagnostics. And of course, the question remains, therefore, what else do we need to do? And is there something that we can do beyond traditional immunohistochemistry? And the group that has been leading this for years in a remarkable way is always be the group of Dr. Rimm that shows us that spatial profiling can be very relevant in this scoring, and multiple immunofluorescence, as you can see in one of their last studies (Systematic Review and Meta-analysis), seems to be very relevant in creating what it seems to be the best way to minimize false positives from false negative rates in the scoring of PD-1/PD-L1 by digital pathology means. This, in a way, has been our experience as well. This was one of our earliest studies, where we essentially applied digital pathology to our very modest number of patients. Again, it was very obvious that our discrepancies were going to be at those thresholds that I described as very difficult earlier on, and multiple immunofluorescence approach, again, led in our group by Matt Humphreys, showed very clearly that the correlations between multiplex PD-L1 analysis of gold standards were extremely good, as you can see, much lower than the traditional digital pathology that I described earlier on. And interestingly, we are beginning to see the fact that perhaps these tools when they are brought together, not only can be a help for the pathologists, but in a percentage of cases, maybe, they are stand-alone tools, and they can start being used for systematic scoring of many of these patients. If this is the development, why is the use of pathology for PD-L1 still not a standard of care? Probably, there are two things that we need to consider, and I will finish with these considerations. The first one is that perhaps, as the previous studies that I was trying to show you show, we haven't done these validations in the best possible way. Maybe, we don't have well-annotated data sets; maybe, the algorithms are still not fit for purpose to run routinely ~~for~~ with proper turnaround times; maybe, the algorithms, as indicated before, are not properly validated and still have a number of unacceptable false positives of false negative results; in many cases, the health economics that are associated with these tools have not been well worked out yet. But there is another reason (and I would like to finish with this idea). The model in which we've been applying digital pathology to date in many of our studies has been very much a posteriori. In our clinical trials we stratify our patients, either because of a biomarker or through pure randomization, we are getting different groups, we start evaluating the clinical relevance of those groups, and then subsequently, the scoring of a biomarker that could be predictive, usually immunohistochemistry, and only then, we start taking that tool through the process of digital pathology analysis, trying to show with digital pathology the same paradigms that we have already generated with traditional pathology in the clinical trial material. I think that the field is already mature enough so that in some of these trials, we move directly from the clinical evidence into digital pathology tools, because I think that not only the product will be easier to score, I think also the degree of concordance and reproducibility will be significantly higher. So, with this idea, with the idea that perhaps we should be bringing digital pathology to the earliest stages of clinical trial development, I would like to conclude highlighting that clearly once the genomic revolution is established, this approach, the digital pathology approach and the applications of machine learning, artificial intelligence algorithms are probably going to be the most important challenge for the pathologists in our generation. Allow me to finish thanking you very much for your attention and thanking those that help us supporting our research and development program. Thanks a lot.