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ESO project with Kyrgyzstan

Prof Pruneri: Hello, everyone. It's a pleasure for me to talk about the European School of Oncology project with Kyrgyzstan. My name is Giancarlo Pruneri. And I'm actually currently serving as the Head of the Department of Pathology at the National Cancer Institute of Milan. And I have been a collaborator of the European School of Oncology since many years. So where is Kyrgyzstan and what is Kyrgyzstan? Because possibly many of you haven't been, heard about it in the past. Kyrgyzstan is a country in Central Asia. There are approximately six million of inhabitants there. And they are living in a territory above 3000 meters, for at least half of them. And as you see, the estimated gross national income is quite low, ranging from 1,000 to $4,000 per capita per year in 2016. And the life expectancy is low as well, 65 years for men and 73 for women. With regard to breast cancer, its incidence is low but there is no registry there. And of course, as you know, in those countries the mortality is quite high. So, this is why the European School of Oncology with a couple of partners, set up a project. That was called Setting up Breast Services Improvements and Learning Bridges in Kyrgyzstan, the so called the SILK project. This was a pilot project to improve quality in the diagnosis and treatment of breast cancer for patients from Kyrgyzstan. And as I mentioned, this project was performed in a partnership with the Swiss Cancer League, the ERGENE Non-Governmental Organization, and the Ministry of Health. We thought that we should push through a very pragmatic approach, that was based on a close cooperation with local Non-Governative Organizations and health authorities. With the goal to get education for health providers, by improving local resources, for example, mammography and pathology. And we pushed that implementation of an efficient quality-controlled pathway. And our goal was to set a sustained long-term collaboration. So, the objectives for the first years were to get a quality control and training for the radiological diagnosis, mammography and echography. You see that of course, the tools for get this kind of analysis were quite old fashioned. And in order to get also an implementation for oestrogen receptor, progesterone receptor, HER2 with Ki67, in the pathology labs of two centres, the Osh centres and the Bishkek Cancer Centre. Osh is the capital and Bishkek is a very, you know, big city in Kyrgyzstan. And we also, you know, try to get shared guidelines for systemic treatment with Russian translation. Because this is very important for that population. Russian is a language that is used quite, you know, commonly in that country. In order to focus on the objective of the ER/PgR/HER2 and Ki67 implementation in the pathology labs, as you see, this is an archive of the pathology lab. This is a very well-maintained archive but as you see, of course, there are no software. There are no, you know, automated procedures. This is, you know, completely, you know, manual. And this is just, you know, a sustained thing to the commitment of the people working there. Of course, we started from the analysis of the situation there. Taking into account that there were a lot of, you know, flaws in the organization of the pathology labs. But the flaws were specifically, you know, due to,

you know, problems in the infrastructure, in the organization, the lack of a multi-disciplinary teamwork, and so on and so forth. By contrast, the strength of that lab was, you know, the people. The fact that the people had quite a good, I would say, a very good, you know, know-how. They were quite well educated. Of course, we provided, you know, papers and books as well. But they were quite well educated. And of course, they were super committed. And their willingness to improve their procedures was fantastic. So, what we did is get, I mean, now we are focusing on the HER2 story. We got data sheet instructions for the people. We provide polyclonal rabbit anti-human c-erb oncoprotein. We also provide a positive control that was a DCIS HER2 3+ plus, from Locarno. And we also, you know, identified four potential positive controls from the Bishkek lab. They were DCIS fully differentiated, with HER2 that was not previously analysed. It is important to underline the fact that ER/PgR/HER2, were never analysed in a pathology lab in Kyrgyzstan since 2018. Of course, we got also the titration of the antibody within the pre-specified range, three different solutions, dilution, sorry, in each of the five controls. And our best results were obtained with this solution, 1:700. And we also of course, used the validation with the new UK/NEQAS cell lines, 0, 1+ and 3+. And we also used the negative control serum in place of the primary antibody. So, we set all the procedures for, you know, a validated clinical lab. And we start with our analysis. This, as I mentioned already, these were, you know, what we found there, was that, you know, it was quite unbalanced between the infrastructure, the procedure, the tracking system that was completely absent. And the safety also for the, you know, for the sample cell. So, for the personnel. But it was, you know, counterbalanced by the fact that the know-how, the skills and the commitment and the teamwork of the people working there were absolutely fine. So, these are, so we set a sort of, you know, clinical study. We get, we stained 18 consecutive patients with breast disease. Each sample was coupled with the pre-specified positive control from Bishkek lab. It was, you know, previously validated. And we previously discussed the 2013 and then the 2018 ASCO/CAP guidelines. A report definition. The type and prevalence of staining, coupled with the tiers. And of course, we focused on the clinical relevance HER2 results. Together with the oncologists in particular with Olivia Pagani that was the, she was the oncologist, you know, in charge of the oncologist expedition there. Especially, with emphasis on the 2+ issue. And we think that the next steps would be to, you know, to get the, you know, new education related to the low HER2 issue. And we evaluated, three of us evaluated the 18 cases independently by each operator blinded of the results of the others. And this is what we did. This is one of my, you know, favourite activities. So, talking while the other people is working. But as I told you, I evaluated the cases as well. And these are some of the results. You see that, you know, these are the negative tissues, 2+ and 3+. You see that for the 3+ cases, the staining was not that intense. But probably this was, you know, due to the pre-analytical phase, especially probably fixation. Of course, we try to modify this kind of fixation, especially, you know, the time that the specimens are left without any kind of fixation, but this is not that easy. But at the end of the day, we obtained that all the tissues should be received by the lab as fresh tissue in order to, you know, to improve the quality of the pre-analytical phases. These are images which were obtained, you know, just by using a smartphone with, you know, applied to the microscope of the camera. But of course, we are willing as we will discuss the last part of my discussion, we are planning to get, you know, a telepathology network with Bishkek. These are the results. Results were quite good. You see that there was a complete clinical reproducibility. There were some problems in the analytical reproducibility. But, you know, but the results were very satisfying in my opinion. And that they confirmed the fact that the people were, you know, the pathologists were very well educated. And they were, you know, very committed to, you know, to be, to improve their knowledge, related to of course, HER2 and all the other features of the pathology, of the breast cancer pathology. You see that there were just one case in which there was, you know, in this case, there was, this was stain, sorry, scored as 3+, with heterogeneity. But two of us, the other observer scored a higher, a significantly higher level of 3+. But as we mentioned, the clinical reproducibility was the same. Because all the scoring were, you know, above the threshold. Just, you know, this was the only case in which there was, in my opinion, you know, there could be a problem. The reproducibility, because this case was scored as 1+ by one observer and 2+ by the other. But with regard to the others, you see this is 2+ with, you know, different scoring. But, you know, all, you know, the results were very, very, you know, promising. So, we decided the

next steps for HER2 in Bishkek lab. So, what we are willing to do now is to get ISH for HER2 cases. So we are planning to, you know, to get the procedures and the reagents to perform ISH. At least for HER2 in the first phases for just for breast cancer. Then we are of course planning to, you know, to expand the analysis to other types of tumours, including lung cancer for example. Then of course we are willing to, you know, to get more pragmatic and more technical improvements. Including of course, a furniture of wash buffer to be increased. The tissue processor for automation and personnel workload reduction. You know, reducing the workload from 30 to 13 hours. Then we also, we are going to provide a cool plate for the histolab, the paraffin dispenser, and so on and so forth. And of course, we are willing to get a, you know, a study. A prospective study for the analytical and clinical validation. Because as I told you, it is very important for us. And you know, we are very proud that the Bishkek lab was able, you know, for the first time to get a, you know, a complete diagnosis in breast cancer, including of course the histopathological diagnosis. But, you know, added with, adapt with the, at least the basic, immunophenotypical characteristics. And this, regarding the telepathology. And we are, you know, planning to going there in February, 2022. You know, if COVID will allow us to get there. And we are willing to get a telepathology program, with an Hub&spoke model with a very, you know, small scanner there. And we are going to set the weekly histopathologic, histopathology life session, at least for troublesome cases. And we think that we can get more education by using of course, with regard to histopathology, immunohistochemistry. And we are thinking, especially, you know, about for example, PD-L1. Or, you know, other possible biomarkers in other settings, including of course, lung cancer as I mentioned. And we are willing to get, you know, a complete training in In Situ Hybridization. Because, as I mentioned, one of our next goal is going to implement a complete, you know, a lab with a complete facility for getting In Situ Hybridization testing. And then of course, this is very important because, I mean, this is my opinion is, telepathology is just the first level of analysis. Then, of course, we have to set it but this is quite common also in Europe, in wealthier countries. The problem in some cases, the second and third level. For second levels, I, you know, thinking about the cases, that, you know, deserve to be completed with more, you know, more deeper immunohistochemical evaluation. For example, soft tissue tumours. And the third level would be for example, NGS, or at least gene sequencing. And of course, we will be proceeding to get the centralized analysis in our lab in these cases. This will be absolutely for free for in this program. And we are also planning to, you know, train the people in, within our institution. In order for them to be able to set their own lab whenever they get back in Kyrgyzstan. So, this is my final talk. Let me just, you know, underline the fact that, of course, as pathologists we can do a lot of things, in my opinion, in order to improve the procedures in low-income countries. Kyrgyzstan was, you know, such an experience for us. But of course, there are, you know, all the, you know, there is all the system that has to be improved. Let me just give you an example. The problem there is that the drugs are not provided by the the national health system. So, most of patients have to, you know, to get the drugs out of pocket. And this is a problem for a low-income country. So, what we're willing to do is of course, try to at least to build the awareness for and the know-how for the medical, the oncologists working there. And this is just the first step but of course there are a lot of other steps that must be done. Finally, let me thank, of course, all the patients. They were fantastic. And the caregivers. And all the SILK project companions. This is Olivia Pagani here. She's an oncologist, she's very committed. And this is the pathology lab. And with these, you know, names which are very difficult to pronounce for me. Let me just mention Olga. Olga was absolutely fantastic. She also came in Italy, and Switzerland in order to be trained in different kinds of pathology settings. And also, you know, of course, Ludmila. She was a, no, Ludmila is a technician. And Gulzar is the head of the department of the pathology lab. Finally, let me also thank of course, Lara Mattei. She is the technician, and she did everything. I was just involved in the teaching, and it was absolutely an experience. So, I think that telepathology would be a fantastic way to get, you know, a continuous training and education for, you know, less lucky people all over the world. Thank you for your attention and see you then.