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The 2021 scenario in targeted therapies for metastatic hepatobiliary and esophageal and gastric cancer

Prof Bezerra de Mello: Hello, everyone. Thank-you again for your attention here and to participate with one more e-session here, from European School of Oncology. I will share my screen right now. Dr Thereza Starling, thank-you very much to be here sharing with us a little bit about your knowledge. So, today, we will talk a little bit about, I was just sharing my screen, just to take a minute. I will, okay, you can see it here. Thereza, is this okay? Can you see here? Can you listen?

Dr Starling: It's perfect. Good afternoon to everybody here. It's a pleasure being here, today. Thank you, Dr Ramon, for the invitation.

Prof Bezerra de Mello: All right. So, today, we will talk a little bit about the scenario in 2021 regarding target therapies for metastatic hepatobiliary and esophageal and gastric cancer. Again, to people who don't know me, my name is Ramon Andrade de Mello and I'm Professor of Medical Oncology at Federal University of São Paulo and I'm also a Professor of Medicine at the Nine of July University in São Paulo and University of Algarve, in Faro, Portugal. So, going ahead, that's my disclosure and let's start the lesson today. Talk a little bit about the estimate of new cases in cancer in the world. So, we have here that prostate cancer and breast cancer, according to that publication from the National Cancer Institute in United States, is one of the most prevalent cancers in U.S. and also, in most parts of the world. However, we have here a set of two more sites of pancreas, hepatobiliary and EGC cancers that it's also important and has some higher incidents in countries like in the South Europe, Portugal, and Spain and also here in Latin America as well. These types of cancer have a very high mortality. As you can see here, liver cancer, stomach cancer, and esophageal cancer has been among the most dangerous, neoplasms in the world. And it's very important to understand that cancer it's a very complex disease and that involves a lot of cell capacities that can develop and contribute to the spread with that cells to other parts of the body So, I like very much to put on my presentation these kinds of slides because it shows the tumor microenvironment with cancer stem cells, proliferating and also, supporting other issues, that will help them to spread like in the TDO cells, also, mechanism that involve in the resistance of death, proliferative signaling. Let's see. And also, other capabilities like evading growth suppression, and so on. So, in that slide here, you have more details with the tumor microenvironment. And they think a medical oncologist should understand this very well because the mechanism of the tumor environment normally can lead us clinician to develop drugs that can help us to improve the cancer treatment outcomes today. Mainly, not only because of the angiogenesis, or tumor evading grow in capacity but also, with the tumor immune-escape mechanism also, as you can see here, is very important to contribute to the invasiveness of cancer cells. So, we starting with liver and biliary cancers. This is a disease that involves a

multidisciplinary team. Today here, we have Dr Starling, she's a Clinical Oncologist, or a radiation oncologist and I'm Medical Oncology here. So, this disease management involves a lot of specialties like hepatology, radiology, oncology, palliative care and every specialty has its role, as you can see here in the terms of outcomes for that kind of disease. The treatment of liver cancer in hepatobiliary carcinoma grew a lot during the last decades. So, you can see here in 2007 we had a first-line sorafenib regarding some trials, Asian-Pacific, Sharp trial. And after that, that one was targeted therapy so, people understood at that time that target therapy would be the secret institute to acquire the best outcomes. And through all the decades, other targeted therapies were being developing like brivanib, lenvatinib, axitinib, also, regorafenib. then, it seemed here that all kinds of these drugs are related with the anti-angiogenesis mechanism like inhibiting VEGF pathways or also VEGFR pathways as well as, you can see here. VEGF, it's difficult to write here, but so you can understand here. All right, and more centrally we have the advent of combinations of immune check points like atezolizumab plus bev. It got better on this trial here, IMbrave 150, and also, pembrolizumab as well and other trials that are involved with new drugs that change a lot a very concentrated opportunity to treat world's patient right now. So, we've explored this in the next few slides. But before we move on, so, it's important to understand the future prospects of the targeted therapy in hepatocellular carcinoma. The drug density biomarker. So, the combination of therapies and some resistance mechanisms in multi-modality treatment are key-points to get good outcomes. Today we have the use, and also, we use here in Brazil a lot, ctDNA dynamic in terms of acquiring DNA to search driver genes and also, more essentially to understand the dynamic of surveillance in early prediction in these kinds of tumors. The combination therapy. We can improve and also optimize prescription sequence of targeted therapies, choice of treatment lines and evidence of the combination. So, these are some key-points that should be taken in consideration regarding hepato-carcinoma. You remember that you can make questions in our chat during the presentation but we decided that today we will discuss the questions in the end of the presentation. So, you can just put your questions in the chat and we will make a discussion in the end. But before we start that, I would like to highlight to you the IMbrave 150 trial. There is a phase III trial involved with atezolizumab plus bev. that select patients that were submitted to surgical resection and ablation with no-residual disease, in less than 12 weeks were randomized to the combination of atezolizumab plus bevacizumab on that dose and also, just active surveillance. And then, we also had here a crossover in terms of upon recurrence, that patients who were here were randomized to active surveillance. In all trials, it's very important to figure out the table 1, table 1 is all important in the clinical trials because normally they summarize the demography and the case and also, sometimes, the results of the trial. And in that table 1 here you can see here two groups: the group with Imbrave, that shows to you here a duration of follow-up of 8.6 months and also, a median survival here very good. A median overall survival here very good when you compare atezo. plus bevacizumab versus sorafenib here. So, this table here is very important. So, you can see here this trial, IMbrave 150, for patients with unresectable disease. And here, we have an improvement because you have here eligibility of patients with advanced metastatic HCC with no-prior therapy and were stratified by that mechanism here, ECOG, performance status, macrovascular invasion, baseline and so one. And then they were randomized to atezo. plus bev. versus sorafenib until disease-progression, until loss of clinical benefit or unacceptable toxicity. The primary endpoint was overall survival. And then, the combination of atezo. plus bev. showing encouraging antitumor activity and safe in that phase I-b trial. So, in IMbrave 150, the overall survival in the metastatic disease was around 19 months versus the 13 months regarding sorafenib, which is very good because it's also two times more. And the PFS was 6.9 versus 4.3. The median duration of treatment atezo. in IMbrave regarding safety, because it's very important to discuss safety in the clinical trials. The median duration of treatment with atezo. plus bev. was around 7 months and sorafenib was around 3 months. The median dose intensity is described here. And then, I think this table is very important because it shows you something regarding the adverse events. We have here 56% of people that was submitted to atezo. plus bev. with a grade 3 or 4 adverse events versus 55.1. And so, in terms of serious advance effects, we have here, actually, something a little bit different. We haven't an increase in here, but you see, you are talking about a disease very, very aggressive and so, sometimes, it's difficult to not have adverse events with those therapies. So,

this forest-plot here shows to you some mainly adverse events and what is more favorable. So, we see, here, diarrhea, more common in sorafenib arms. Palmar-plantar erythrodysesthesia, so, more in sorafenib in that side effect it takes a lot of quality of life with the patients. Decreasing of appetite and more things noted in sorafenib. So, according to that, you can see here that we have, actually, more quality of life; faced it to that combination here with atezo. plus bev. than with sorafenib. Despite, we still have some side effects that should worry the medical oncologists. So, this is quality of life patients reported; so, no-deterioration in quality of life in this Kaplan-Meier here. And in the base here, you see the months. You see here that atezo. plus bev. showed actually a better quality of life and improved the quality of life around 37% with a hazard ratio of 0.63, which is very good and it's statistically significant. Again, you can point your questions, you can put your questions on the chat and in the end, we would discuss all the questions with everyone. Remember that in the end of this presentation, you have a CME test with five questions and you can answer the questions and it'll be good for you because you get a CME certificate. So, going ahead I would like to highlight the KEYNOTE-524: lenvatinib plus pembrolizumab in advanced HCC. This was an open-label phase I study, involving both drugs, for patients with unresectable HCC, with no-prior systemic therapy. The primary analysis set was 100 patients. Again, you can see here this table, it's very interesting because you see the overall response rate is around 36%. We had one patient with complete response which is amazing, because patients, actually, got a very good benefit. And 35 patients with partial response and more than a half of patients, more that 50% of the patients, was with stable disease. In terms of the ratio of response, the median was 12.6 months and not reach it, which means that it can provide a sustainable benefit during the time. But of course, phase II trials are rewarded for that. And the patients were treated around 3 months, could be until 7.7, all right? And you can see here with this table a very significant reduction in terms of the tumor volume. Again, overall survival by overall response. So, you can see here people with complete and partial response and people with stable disease. So, they see here that people with complete partial response had a median overall survival of 21.7 months, which is amazing considering this type of pathology and not reached; so, we need more time to understand that. In the median overall survival with the patients that had stable disease, also, were very high and then, not reached, not reached at all. So, it means that the sinenergy between anti-angiogenic drugs and immune checkpoint inhibitors could be the future of these HCC treatments for example. There is this other trial, it's LEAP-002. First-line lenvatinib plus pembrolizumab versus placebo in HCC. We have here a multicenter, double-blind phase III trial. Patients with HCC, Barcelona criteria, C or B, that was amenable to locoregional curative therapy with no previous systemic therapy. The primary endpoint was PFS and overall survival, and these are the other secondary endpoints. We have here lenvatinib with placebo and lenvatinib with pembrolizumab. Treatment until progression-disease or intolerable toxicity or until 36 cycles of pembrolizumab was the intention here. There isn't evidence that the treatment combination is meaningful or more effective than other approved treatments, this is what FDA said in September, 2020. In ASCO 2020, the result was listed here, as you can see, overall response rate of 36% with overall survival regarding 22.6%. We have another trial to highlight here, KEYNOTE-240: pembro. plus for patients with previous treated HCC. So, it's a phase II trial showing that potential efficacy of pembro. for patients with advanced HCC, previous treatment with sorafenib, so, that putting pembro, in second-line. Also, we have here a phase III trial, KEYNOTE-240 and patient was treated with advanced HCC, inoperable or to progression disease after sorafenib as well, and guess what? They had done randomization. Pembro. Versus placebo plus supportive care. The endpoint was a little bit, all is audacious because they are talking about overall survival. Efficacy was here considered the PFS. What else? And then, let's talk a little bit about the response of KEYNOTE-240. We have here, overall response rate around 18.3% which is good in the second-line. Also, we have 6 patients here with complete response, which is amazing as well, and then, make lights to future multi-modality approach. What do you do with a patient that got a complete response after the second-line? The patient is 0-disease, so, what are you going to do? So, that's an important question that rises to the scientific community. And also, you can see here, good results viewing the consideration that we are talking about, advanced HCC, not recyclable. Okay. Fail to reach prospective level of statistical significance. In terms of overall survival, we have 13.9 versus 10.6, a little bit significant. It was an actual

improvement in terms of overall survival. And then, in terms of PFS, is something also around 23% as well. But as you can analyze these curves, this is not a constant benefit, so it should be more addressed. Another trial here, we are talking about is AMEBICA PRODIGE 38, randomized phase II trial for biliary tract cancers. There is a combination chemotherapy with cisplatin, gemcitabine, CIS-GEM, is the first-line standard of care for these patients with advanced BTC. FOLFIRINOX, demonstrated as well that an overall survival improvement in metastatic pancreatic cancer compared to gemcitabine monotherapy. So, here, the aim is to compare FOLFIRINOX with CIS-GEM in advanced BTC. It was an open-label phase II-III carried out in 43 French centers. Patients with locally advanced and unresectable biliary tract cancer, good ECOG and was randomized as one-to-one to receive either modified FOLFIRINOX or CIS-GEM for 6 months. The primary endpoint in phase III was progression-free survival rate at 6 months according to RECIST 1.1. And the first chemotherapy with mFOLFIRINOX did not meet the primary endpoint. CIS-GEM remained the first-line standard of care for biliary tract cancer. So, it's an old drug and too good results. So, you can still continue to prescribe CIS-GEM that it works very well, it's what we have up-to-date. But actually, we are just suggesting it anyway, but actually, we have another trial here, RESORCE, that assesses second-line regorafenib versus placebo. Again, it was multicenter, randomized phase III trial involving patients with HCC who tolerated the first-line sorafenib but progressed with this agent. These patients should have a good ECOG, a good Barcelona classification and was randomized to regorafenib versus best supportive care. Until progression disease and acceptable toxicity or withdrawal. So, the primary endpoint again, overall survival, we are talking about a very aggressive disease, with low overall survival after the second-line. So, I think it's not too audacious to try to find out what you can have in developing impact in terms of overall survival here. But let's see here, the graph because I think the Kaplan-Meier graph will give us the answer. So, probably, of survival versus months from randomization. We have here 10.6 months versus 7.8. So, with a hazard of 0.63, meaning that regorafenib provided a benefit in terms of survival, in terms of 37%, which is very good, which is also good in terms of that scenario. And we have here median PFS, also, we have again here 3.1 month versus 1.5 but with a good hazard as well. So, it means that this drug can be used in that setting. The numbers are not too high. We are talking about incurable disease. So, if you have again terms of survival of 37% you can, depending on the type of the patient, it will be very good because a patient can be happy with that. Also, we have here some adverse events, I put this table, it's very important. So, you have here a high-rate of any grade adverse events. Hand-foot syndrome 53%, of course, placebo just 80%, diarrhea, fatigue, and hypertension are the top 4 side effects that happen with the drug regorafenib. Nothing different of what we are expecting because we use regorafenib in other tumors as well; so, it's a drug that is not so new but the indication, probably, needs to be more set up in HCC. So, this is a summary of recommendation in terms of target therapies. So, we have here, we are talking about advanced disease, not resectable. So, today, we have first-line therapy with atezo. and bev. second-line sorafenib, lenvatinib; and third-line regorafenib, cabozantinib, and nivolumab. And now, in United States, you can also do immune checkpoint inhibitors with a median overall survival not rated. In second-line, we have overall survival until 15 months and the third-line until 12 months. So, you can see here, more than three years of survival for that type of patients which is very good, taking in consideration the disease that we are talking about. Again, you can make questions any time, just pop-on the chat and we will be happy to discuss in the end. Talking about esophageal cancer and we are going to April. April is the month of esophageal cancer consultation, so, a lot of campaigns will be running out here in Brazil and in the world. And then, we start to talk that esophageal cancer corresponds according to IARC around 5.5% of the cancer cases worldwide. If you're talking about China and some Asian countries, esophageal and GC cancers and lung cancer are among the top ones, so, it's very important to understand about that disease. And so, in terms of summary, again pembro. showed promising results in HCC. Atezo. plus bev. now it's standard of care in first-line; and we have here, other chances that are coming up in the next few years to cholangiocarcinoma and also to BTC as well. Okay, talking about, again, about KEYNOTE because I think we have a slight change, but that's okay, you understand. So, KEYNOTE-590, they can come back to esophagus. So, it's a trial that randomizes again pembrolizumab plus cisplatin and then 5FU versus placebo plus cisplatin, 5FU. Primary endpoint was progression free survival and secondary endpoint

was overall survival. Again, you have here the design of the trial. It's a trial that showed to you here, we have the slide of the overall survival Kaplan-Meier curves. We see here consistent benefits during the curves and that after 12.4 months to chemo plus pembro. versus 9.8 months for chemo and 28 versus 16% of people alive after two years, which is good benefit. And you can do with other drugs, and maybe, trying to find out good outcomes. So, that slide here shows to you NCCN recommendations, systemic therapy for unresectable, recurrent esophageal cancer. So, people in United States recommend oxaliplatin generally over cisplatin due to toxicity. If you have HER2 overexpression, the combination with trastuzumab is two to one. And also, if you HER2 negative, you can combine fluoropyrimidine with oxaliplatin and maybe, an immune checkpoint inhibitor depending on the PDL1 that you have here. Other recommended regimens regarding trastuzumab should be added in the first-line to HER2 expression and others here that are listed below. In terms of second-line, NCCN recommends depending on the prior therapy that you chose in the first-line. So, we have not a consensus regarding that, but again, you can play with the chemo options and immune check point options. So, if you didn't do immune therapy in the first-line you can do nivo. for squamous, pembro. for second-line in squamous. Ramucirumab plus paclitaxel is two to one so, you can do it with a good level of recommendation. And then, other regimens like fluorouracil and irinotecan with ramucirumab for adenocarcinomas. Sometimes, you use a lot despite of the evidence. And then, in certain circumstances, a lot of entrectinib for NTRK fusions and the pembro. for TMB-high and MSI-high are other recommendations. Again, you are here paying attention to our presentation, it's a pleasure to have you here with us and giving a little bit about your attention. Just pop-up your question in the chat and then, in the end, we will discuss with Dr Starling. Now, we are almost ending. We are talking about regarding gastric cancer. Gastric cancer in terms of science changed a lot during the last years. We have estimated new cases, in 2020, of 27,000 cases, according NIH. In terms of deaths is almost, you see here the survival considering now how it extends, it's 32% in five years, so, it's something very aggressive as well. But now we have tools that can help us to understand better that disease. TCGA and ACRG are the molecular classifications that help us to understand a little bit about the gastric cancer behavior. So, you have here according to TCGA, the group of EBV-positive, MSI-high, the genomically stable, and the chromosome stability according to each characteristic. And the ACRG, you have here listed the MSS/TP53 positive, MSI-positive, EMT-positive, that is related to the expression of e-cadherin and also TP53/MSS-negative, microsatellite stable. So, these are ESMO guidelines recommendations for gastric cancer. So, we are here highlighting the metastatic setting, that one here. So, we have inoperable disease that can come up directly to palliative care or palliative chemo. So, depending of the type of the patient, if you are going to systemic treatment, you should do other HER2, in most countries, in Europe, no need to worry because the pathology report gives you all the biomarkers that you need there. That this validated like HER2, for example, NTRK. Here, in Brazil, sometimes you need to order to the pathology to have the biomarkers. HER2-negative, normally you go through platinum chemo and then HER2-positive you add trastuzumab and then clinical trials are also an option to this type of patients. Okay, in talking about clinical trials, it's very important to see here what Wainberg presented in ASCO GI this year. The FIGHT trial, that is the first-line, bemarituzumab plus mFOLFOX6 versus placebo plus FOLFOX6 in advanced gastric/GEJ cancers. This was a global, double-blind phase II trial. And if bemarituzumab, what is that? Is a first-class humanized IgG1 monoclonal antibody against FGFR2b. So, it's a new target that it's coming up to the clinical practice and then I think it will help us a lot in the near future. So, this was stratified by region, this was stratified by what type of neoadjuvant or adjuvant therapy you did. In patients with no-prior therapy for unresectable locally advanced disease, the patient should have the expression of FGFR2b by immunohistochemistry, gene amplification by ctDNA, as well, was considered. And HER2 people who were node positive. So, we have a little bit more than 150 patients randomized to the arm of the drug and the arm of placebo plus chemo, and the primary endpoint here was PFS. Let's see what happened. Again, this is one of the main tables that we have here in this trial, the patient characteristic table. So, we have here the age, 60-years age; the patient in terms of sex, well-balancing, Asian race was well-balanced. So, all characteristics here were well-balanced. And then, the possibility is to assess the FGFR2b by immunohistochemistry, by ctDNA and both overexpression and amplification; so, we have it here. Good, so, going through that Kaplan-

Meier curve we have here the PFS probability, one side, and the other side they have the months. And then, you can see here, the 9-month rate of PFS. Very good results regarding the bema. versus placebo. So, we have here 52% of patients not progressing versus 33% which is very good. And in two months, also, we have again here of bema. versus the placebo. Again, stratifying here, regarding ITT and then expression of FGFR2b. We also can keep that gain here regarding bema. arm and how much you have expressed FGFR2b, it's not influencing in terms of results but still, have good results, so, it means that ITT population, it means here that you should understand a little bit more about that, but the PFS in terms of PFS here, see people, look here. We are from more than 3 points in terms of immunohistochemistry expression. The median PFS was 7, sorry, 14.1 months versus 7 months. And the very good rate. And then, in here, still we have a gain not without an expression, but here, when have expression of this factor here, we still have a good gain, more than 50%. In terms of overall survival, we have here not reached to the people with the expression, but in 12 months we have a very good gain. 70% of the patients with the expression of FGFR2b were alive. Which can encourage a lot to prescribe this drug for its patients, if you have actually the indication and approval in your country. And here, you have some, I like this type of graphs because it gives you the idea of the reduction. In here you have a very volume area of reduction regarding the bema. versus placebo. So, in terms of adverse events, I highlighted here stomatitis that is something that decreases a lot in terms of quality of life. We have here dry eyes as of note. And then, actually, in terms of the median time of onset, 20 grades, in terms of side effects we have here an increase, in terms of corneal-related adverse effects that's decreases a lot in terms of quality of life. Our discussion should end. We are almost there. So, we have LEAP, pembro+lenvatinib in previous treated advanced gastric cancer. The population characteristics were here disclosed to you. And then, in terms of results, we have here response-rate not too good but the disease control good, around 48%. In terms of advance events, again, you have here hepatotoxicity, hemorrhage, hypertension, hypothyroidism that could aware the clinicians. In the curve here, we have 6-month overall survival rate of 46%. And again, this is not new but it's taking every time more place in gastric cancer as well. Is TAGS, trifluridine/tipiracil versus placebo. I think the problem of the trial is that because it's all versus placebo, have two arms here. Patients with unresectable disease and more than two lines, advanced disease in gastric cancer. We have here well-balanced characteristics influencing that. And then, also, here, a prior, with this is the TAGS overall survival prior therapy with or without ramucirumab. So, we can see that actually it has an influence here. See outpatient 0.69 in terms of overall. No-ramucirumab if patient did not have ramucirumab but a good response, a hazard 0.66 and depending what he did, we have benefit or not. So, here patient who did paclitaxel, also, have a good response to tipiracil. Again, PFS prior therapy with or without ramucirumab, maybe ramucirumab but have actually influence in some patients. We have good results, hazard 0.57. And then, this supergroup here, in terms of PFS also have good results. So, trying to summarize these results. In first-line, we have overall survival of 3.6 months. People that did three lines and then, of course, the overall survival has a decrease here. So, there are no clinically significant deteriorations after 5 points in terms of quality of life. The frequency of adverse events was similar in third or fourth line with the drugs. And in terms of weight loss, you can see here because weight loss is a very good clinical marker. So, questions again. Just almost the ending. We have ipi/nivo, and also, we have pembro. plus chemo as well at the KEYNOTE-062. And another trial that I think is very important is comparing trastuzumab-deruxtecan versus chemo, physician's choice. Again, we have here response of 42% versus 12%. And then, in terms of overall survival, we have trastuzumab-deruxtecan with a good impact in terms of overall survival, 12.5 months versus 8.4. In terms of toxicity-events, everything well-management. And so, that's the recommendation of NCCN to gastric cancer. You can also highlight this on the portal. And again, gastric cancer has been challenging but now we have a lot of things that is changing the life of patients with advanced gastric cancer. And in my opinion, FGFR2 gene amplification will make a difference. Again, thank-you very much for your attention. This is the reason why I choose to come back to Brazil, my nephews that are very cute. Madalena and then Joao Victor. So, I would like to thank-you then, and to thank-you all for your attention. We are happy here to discuss a little bit about the presentation, thank-you.

Dr Starling: Dr Ramon, first of all, I'd like to say that your talk today was very, very nice. I think we have a lot of recent developments in these areas and I would like to know if anyone here has any questions to make about the talk? Anyone wants to make another comment? If you don't have questions, I would like to get to ask you, can you give a little bit more of an explanation about the profile of the patients in the FIGHT trial? I think it's a very important trial that it's, I mean, it's always going to make a huge difference for these patients.

Prof Bezerra de Mello: Thereza, thank-you very much about your question. Actually, FIGHT trial brings up to us in the clinical practice new effective options in terms of target therapy with additional of anti-fibroblast growth factor receptor drugs which is also involving the endogenous drugs that it's a hallmark of cancer, very important. So, I think, we can personalize more the patient treatments and also, can improve a lot in terms of outcomes. Of course, we have some side effects, but as I show it to you in the presentation, there are many in the hands-off experience oncologists. So, it's one more weapon to help these patients get improved results.

Dr Starling: Okay, very nice. I think personalized oncology is going really to be the future for these patients, right?

Prof Bezerra de Mello: Yeah, and the issue is how to order the FGFR2b expression. Immunohistochemistry ctDNA, so, we discussed a lot in the scientific community about ctDNA on the bloods. And I think it will change a lot the practice, because it's easy to get DNA from blood then you go direct to a biopsy that is a more invasive test. So, I think it would make a difference.

Dr Starling: And Dr Ramon one more question. Do you know about the price of this therapy or having had any comments yet?

Prof Bezerra de Mello: Well, in terms of Pharmaco-economy we are still in the beginning. We need some pharmaco-economic studies to deliver you an answer, but of course depending on the country and on the willingness to pay of the national system reimbursement can be incorporated. It can be incorporated to not so easily but with subset of patients with good performance status, with the expression of the FGFR2b, depending what the number of mets. So, we should to optimize the treatment for the patient that will have a profile specific to receive that drug and get them more benefits.

Dr Starling: Very nice. We still don't have any questions here. So, would you like to make any other comments? About any other...

Prof Bezerra de Mello: I think the interaction was very good. So, wind-up our time now. It's 3:05 in Brazil, I think 7:05 in Milan. I don't know. I think, if people want to make more questions, they are happy to send us an email. And so, you also can discuss it during the next six months this presentation by email, or if you need any comments, or questions or to discuss something. That's it.

Dr Starling: Okay, so, we thank everyone for their attention, for the presence here in the session today. We hope you enjoyed. Again, Ramon, very, very good presentation about the theme. Very good sum-up of everything. And that's it. We thank-you for the invitation for the Zoom session as well.

Prof Bezerra de Mello: Thank-you also for the opportunity. See you the next time.