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The medical therapy of GIST

Prof Blay: Good morning, good afternoon. My name is Jean-Yves Blay, I'm working in the comprehensive cancer in in Lyon, Centre Léon Berard. And I have the pleasure today to share with you a presentation on Gastrointestinal Stromal Tumor. Should we say gastrointestinal stromal tumors in the plural. These are my disclosures as an investigator as well as within the institution. Starting maybe with epidemiology. Gastrointestinal stromal tumors are the most frequent sarcoma. They represent about 10 to 12% of all sarcoma, and overall, the incidence of gastrointestinal stromal tumors is in the range of 12 new cases per million per year. As we can see on this slide, this is a tumor which is being diagnosed at all ages, women and men. We can see pediatric forms and we can also see that this is a tumor which is affecting all the digestive tract. The majority of gastrointestinal stromal tumors are arising in the stomach, here in green. But you also have tumors affecting the duodenum, the small bowel, colorectal, and more rarely oesophagus. So, this is a tumor which is occurring at all ages, in all genders and at all sites of the gastrointestinal tract. This is a tumor which is presenting somewhat quite differently depending on the nature of the molecular alterations that we are going to see. There is not a single GIST, there are a multiple GISTs with histological presentation which can vary from one molecular subtype to another. The majority of gastrointestinal stromal tumors are presenting with mutation of the KIT genes in about 70% of the cases and several mutations in different parts of the KIT gene and KIT molecule are being observed. Which leads, sometimes, to a slightly different natural history. But there are also other GISTs involving mutations of a cousin receptor, PDGF receptor alpha, and a smaller group of other GISTs with mutation on other genes such as succinate dehydrogenase NF1 and several other genes. The histological presentation is somewhat different as we can see on the slide. And this is actually reflecting the nature of the different mutations that we observed in these different GISTs. So, again, KIT is the most frequently mutated gene in gastrointestinal stromal tumor, and the majority of mutations are occurring in Exon 11. More rarely in Exon 9, and very rarely in Exons 13, 14, and 17. These mutations encode for a protein which is activated without the presence of the ligand. And the same is true for PDGF-receptor-alpha, which can also be mutated, even though, the mutations are mutually exclusive with KIT. So, it's either KIT or PDGF-receptor-alpha. It's never the two receptors being mutated, it's one or the other. And for PDGF-receptor-alpha, there are mutations which are occurring also in similar parts of the molecule, very similar to what is being observed in KIT, but a big difference, as we see on this slide, is that the majority of mutations are occurring in Exon 18 in PDGF-receptor-alpha. And one of the mutations called D842V, a point mutation, is quite frequent and also, encodes for protein which is quite resistant to the classical treatment of

gastrointestinal stromal tumors. This is not the only mutation that we are seeing. These are not the only genes. Again, there are genes which can be mutated in other parts of the cells. And again, they are mutually exclusive. Genes encoded by the genes of the mitochondria called succinate dehydrogenase can also be mutated in the so-called wild-type GIST. The name wild-type, it refers to wild-type KIT and wild-type PDGF-receptor-alpha. But mutations of this protein, which are in the membrane of the mitochondria, are frequently involved in gastrointestinal stromal tumors, in particular in those arising in young adults or pediatric population, as well as in young female patients. Quite often occurring in the gastric region. And then, there are even rarer forms of GISTs with mutation on the NF1 gene, which are arising as part of the neurofibromatosis type 1 syndrome, and sometimes, BRAF, and very, very rarely, mutations affecting other receptor tyrosine kinase, in the form of translocation involving the track genes, one of the track genes, and sometimes, even rarely, FGF-receptor-1. So, we can see here that we have a wide variety of different mutations in a wide variety of genes and these are different diseases with a slightly different natural history. And then, probably this fragmentation that we see is even more pronounced. If we look at the experience of our colleagues from the pediatric world, we can see that there are probably even rarer and much less frequent mutations arising in other gastrointestinal stromal tumors occurring at this age. So, what is the incidence of these different molecular subtypes? Are a few data sets which enable us to recapitulate the true incidence of these different molecular forms of GIST, but the two are quite consistent, as we can see. Experience from the Netherlands, experience from France which confirmed the frequency of KIT mutation, that the majority of KIT mutations are occurring in Exon 11, less frequently in Exon 9, second one being PDGF-receptor-alpha mutation with incidents close to 14%. And the majority are on Exon 18. And all the rest in about 17% of the patients, are the so-called wild-type GIST with the different sub-forms, sub-molecular forms that we have been discussing in the previous slide. All together and slightly different incidents in these different data sets, we see that we have between 10 per million and 14 per million new cases per year of gastrointestinal stromal tumors. This is, importantly, probably quite consistent across all the countries in the world. And interestingly, this anatomical heterogeneity of GIST which can arise from the stomach to the large bowel is also associated with heterogeneity in the terms of molecular alteration. Gastric GISTs are frequently equipped with KIT Exon 11 mutation, but they are also the most frequent site for PDGF-receptor-alpha Exon 18 mutations. Conversely, for small bowel GIST, we observe also KIT Exon 11 mutations, but this is a frequent site. It is not the exclusive site for KIT Exon 9 mutation. Why is that happening? Nobody really knows, but this is an interesting parallel between the anatomical and the molecular distribution of the mutations which is being observed in all the series presented so far. All right. So, we see that we have a group of diseases called GIST with different mutations. How should they be treated? And I will be discussing mostly the guidelines prepared by the ESMO, which are very consistent to those available all around the world. The basic principle is that surgery is a mainstay of the treatment of localized GIST. Surgery is most often the only treatment procedure which is being proposed in patients with a low-risk of a relapse. But in the case of a patient presenting with features associated with a poor prognosis and increased risk of relapse, adjuvant treatment may be needed as we are going to see in the subsequent slides. All those tumors, conversely, which are still localized, but where the surgery, which could be performed, would either be mutilating or not be deemed feasible as a complete resection in umbilical resection. Then new adjuvant treatment with Tyrosine kinase inhibitor may be recommended in this case, for 6 to 12 months, pre-neoadjuvant treatment which would facilitate subsequently the removal of the primary tumor followed on that by adjuvant treatment. Why adjuvant treatment? Well, there are three randomized studies which have investigated the administration of adjuvant imatinib during one year, two years and three years. And I show you here, the results of the study which has established three years as a standard treatment for patients with a localized GIST at high-risk of relapse. And this was a study which was conducted by the Scandinavian Sarcoma Group together with the German Sarcoma Group comparing one year versus three years of adjuvant imatinib, in patients at high-risk of relapse. The results were reported some five years ago, showing an improvement in recurrence-free survival in this patient population with a hazard ratio of 0.6 with a benefit which is being observed in all subgroups tested so far. And importantly, and as confirmed subsequently in a follow-up report, with a longer

follow-up, overall survival was also improved by a three-year administration of adjuvant imatinib as compared to a one-year treatment. This important study is a basis of the international recommendation of three-year adjuvant imatinib, for the treatment of patients with high-risk GIST. There is no demonstration that the treatment with adjuvant imatinib for one, two or three years improve survival for patients with lower risk of relapse in particular tumors with so-called intermediate-risk of relapse, that we are going to see. There is no evidence either that a shorter duration of treatment with adjuvant imatinib should be of shorter duration than three years. So, it's three years as a standard of care. Who are the patients who should benefit for this treatment? There are different types of criteria to identify patients at high-risk. And the criteria are based on the size of the tumor, on the mitotic count, on the standard 50 High Power Field, and on the primary site of the tumor, overall stomach being associated with a better outcome. And you can see here the risk of relapse in different groups of tumors, depending on the site, depending on size and depending on the mitotic count. And usually, what is considered to be a high-risk tumor, is a tumor with a risk which is above 50% of relapse, that you can see here, very distinct population of patients with lower-risk of relapse, in particular, in small size and low mitotic count in sites such as duodenum. Our colleagues from the Scandinavian Sarcoma Group together with a multinational consortium, Dr Joensuu, distinguished different type of risk classification which could be based on continuous factors. Again, this is based on tumor size, this is based on mitotic count, on the site of the tumor, but also, on the presence or absence of fracture. And we can see with this height map our capacity to investigate which subset of disease GIST should be receiving as a qualification of high-risk GIST, intermediate-risk GIST or low-risk GIST. And this is, probably, a classification which is as accurate as possible as we speak. You notice that we have not identified so far molecular characteristics, which is associated with a specific, high or low-risk, even though, as we are going to see, this is going to have an impact on the decision of the treatment. And this is probably worth noting at the present time, that those treatments with adjuvant imatinib should be given only on patients with sensitive mutation of the driver gene, whether it's a KIT or PDGF-receptor-alpha, and not with a mutation rupture which are not sensitive to imatinib, as we are going to see in the subsequent slides. Three-year is a standard. Is it the final question? Possibly not. There is one uncontrolled study which was nicely done testing five years of adjuvant imatinib in high-risk patient population showing very favorable results, but no control arm. Two ongoing studies are exploring a longer duration of adjuvant imatinib after two or three years of additional treatment, following the three years being given a standard. So, the ImadGIST study is randomizing three additional years versus interruption after three years. The Scandinavian Sarcoma Group XXII study is randomizing two additional years after three years of adjuvant treatment, in both cases, in patients with high-risk GIST. The studies are accruing, and we'll have the results presumably in the years to come. All right. So, we have seen that the management of gastrointestinal stromal tumor in localized phase is based on surgery and could involve adjuvant treatment with tyrosine kinase inhibitor imatinib in patients with high-risk GIST, for localized tumors which are difficult to resect upon the approval of an expert multidisciplinary tumor board, neoadjuvant treatment could be proposed. What about now the standard treatment in advanced phase in patients who has been relapsing in the metastatic setting who were initially metastatic at diagnosis, which represents about 10% of the patients? We can have a look back now at the historical studies which were conducted in the beginning of the two-year 2000 testing in this presentation slide that I'm showing. Two doses of imatinib, 400-milligram per day as compared to 800-milligram per day in GIST all comers. And these were patients which probably not really exist anymore. These were patients heavily pretreated, the prevalent patient population. And the outcome of these patients is probably less favorable than what we see right now. But with the advantage of having a long follow-up, we can see a very important information. The first one is at the progression-free survival of patients treated with 800-milligram per day is slightly superior to 400-milligram per day. But the difference, the magnitude of the difference is not really significant. The second important piece of information is that we see that we have patients at 10, 12 and longer years, who have not relapsed after a decade of treatment. And we still all have in our centers, patients who have been receiving imatinib since the year 2001, without any progression, which points to the fact that probably these patients are going to enjoy a prolonged progression-free survival if they maintain this treatment. Can we speak of

cure of a fraction of patients with advanced gastrointestinal stromal tumor? Nobody really knows, what is quite clear is that we do not have exactly the same results, depending on the nature of the mutation. And again, this is dependent on the nature of the mutation and the sensitivity of this mutation to the first-line tyrosine kinase inhibitor, which is imatinib. KIT mutations, the majority; PDGF- receptor-alpha mutations, in second ranking are mostly sensitive to imatinib, even though the DH42V mutation for PDGF-receptor-alpha is known to be resistant. For the others SDH mutation, BRAF, NF1 or TRK fusions, they are resistant to imatinib. But for Exon 9, if we look at the data, a subgroup analysis of the data of the previous clinical study, which was mentioned in the previous slide, we can see that interestingly the double dose of imatinib, 800-milligram per day is associated with a better outcome in terms of progression-free survival, not overall survival. In this study conducted by the EORTC Italian Sarcoma Group and Australian Sarcoma Group and also in the meta-analysis, which was conducted by merging the data from both sides of the Atlantic. So, not all subsets of GISTs should receive exactly the same dose and exactly the same treatment upfront. But what is quite clear is that when we start treatment with imatinib in the advanced phase and if the treatment is active, it should not be interrupted at least in the first five years. Within the French Sarcoma Group conducted several randomized studies, testing treatment interruption at one year, three years and five years, which are shown on this diagram, which are quite unambiguous in showing that the majority of patients who stopped treatment with imatinib in advanced phase after one, three or five years will relapse. Probably, not all patients will relapse as now know with longer follow-up. But certainly, a minority of patients do not relapse. And therefore, this treatment should be continued for a longer period of time. Probably, at least five years, probably longer. We are currently evaluating a treatment interruption for patients who have been receiving more than 10 years. What is also quite clear is that not all patients are presenting with a sensitive disease and that the exact nature of the mutation is important. This was a retrospective multinational study investigating the outcome of PDGF-receptor-alpha gastrointestinal stromal tumors in the advanced phase, distinguishing the limitations the D842V mutations as compared to the other group of patients with other types of mutations. And what you can see on this overall and relapse-free survival curve is that the outcome is very different in the two groups of patients. A patient with PDGF-receptor-alpha mutations outside the D842V, enjoy progression-free survival and overall survival, which is very similar to that observed in KIT mutated GIST. While patients with D842V mutations do not respond. Actually, have a progression-free survival to imatinib and sunitinib, which is close to two months, very close to what we had before aside, before TKIs with the classical cyto-toxic. And an overall survival which is here in the study with a median of 12 months, which is as bad as in the pre-TKI era. So, not all GISTs are sensitive, and this rare form is particularly resistant. All right, imatinib is a standard treatment in first-line setting. Is there something which we can do better? We are going to see the treatment in second and third-line in a few minutes. One of the important treatments in GIST is regorafenib. There were several in third line. There were several studies which attempted to beat imatinib in the first-line setting, by comparing imatinib versus an alternative, a tyrosine kinase inhibitor. And one of these studies tested nilotinib, which is used in chronic myelogenous leukemia with some successes in first-line. And this study failed to demonstrate priority of nilotinib which was actually slightly inferior in particular in Exon 9 patient population. So, to try to improve the outcome of these patients, there is a completely different type of strategy, was tested in the in the ALT-GIST study, which used the rotation of the standard treatment, imatinib, with a sideline treatment, regorafenib over a period of one month. And the idea with this rotational would be to eliminate the clonal resistance emerging from Darwinian selection of resistance clone and the pressure of imatinib. This study has been reported previously and failed to demonstrate superiority of the rotation as compared to the standard treatment of imatinib which remains the standard therefore. It's surgery useful? Actually, there is only one published randomized trial exploring surgical removal of metastasis in metastatic GIST. This was reported in European Journal of Cancer, 2014. There were two studies conducted. One in the EORTC, one from this Chinese group. And both studies actually failed to reach the accrual. The EORTC study was stopped, the Chinese study was published with an incomplete accrual and provided some interesting information. Showing, as you can see on this slide, that patients who have been operated while non-progressing, on imatinib, tend to have a slightly better

progression-free survival and overall survival. This is still as we speak in 2021 an open question. What is the value of surgical removal of all metastases in a patient controlled with the standard treatment of imatinib in first-line GIST? From these data set, published by our Chinese colleague, it may well be a question which deserves to be further explored, either in the form of a registry or maybe, if we are brave enough, in the form of a subsequent randomized study. But it is as we have seen, quite complicated to be achieved. All right. So, for first-line treatment, we will remain with imatinib 400-milligram per day for all GIST, 800-milligram per day for Exon 9 KIT mutated GIST, but the majority of patients, as we have seen on the previous slide, do relapse. What are the treatments in second and third line? We all know sunitinib and regorafenib as the respective demonstrate treatment in second and third-line on the basis of two randomized studies. This one for sunitinib, , comparing sunitinib versus placebo and demonstrating in all groups of patients an improvement in progression-free survival and trend for improvement for overall survival. The same was observed for regorafenib. Again, the GRID study, is a randomized phase III study, demonstrating basically the same type of benefit from the TKI given in third-line regorafenib as compared to placebo; in both cases, across over was allowed enabling to, in this case, to control tumor progression in patients with crossover, probably explaining the absence of benefit for overall survival. Also, both patients seem to benefit from this treatment including all molecular subgroups of patients. So, we have a standard treatment in second and a third-line, which are respectively sunitinib and regorafenib. These patients are however progressing after first-line, second-line and third-line. And we now understand better what is the driving force which explains this progression. Resistance, secondary resistance to this treatment arises through this clonal selection of mutated clones equipped with additional mutation on the driver alterative gene, whether it's KIT or PDGF-receptor-alpha; in this case KIT. Through a selection pressure, emerging clones with putting expressing additional mutations which encode for resistance to the different tyrosine and kinase inhibitor are emerging not only one, but multiple subgroups are emerging in a single patient, sometimes, in a single metastasis. And this is explaining the clonal heterogeneity of resistance which is arising in the secondary resistance for these patients. So, do we have additional treatment to propose to these patients? Yes, we have many other drugs and it's quite interesting to look at the last two years in the publications in international journals to see that several very interesting agents were reported. We are going to conclude this presentation by showing these different agents, starting with ripretinib, which was recently published in a randomized phase III study in patients in fourth or more line, having progressed after imatinib, sunitinib and regorafenib. This was a randomized, double blind, placebo-controlled, phase III study with a crossover with well-balanced population of patients and using an agent which is a switch-control inhibitor with multiple capacity to block all resistance mutations. And this is probably something which distinguishes this new generation of inhibitors from the first generation of inhibitors, in that it blocks the kinase in an inactive state therefore, enabling to block all resistant mutations. These are the characteristics of the patients. You can see that they were quite heavily pre-treated. You can also see that all mutations were observed in the different subgroups, ripretinib and placebo subgroups. And this is a primary endpoint, progression-free survival on the upper panel showing a major reduction in the risk of progression favoring the ripretinib arm with a hazard ratio which is remarkably low, as you can see here, hazard ratio of 0.15. The statistical analysis precluded the comparison of the overall survival, which is shown on the lower panel but we can see here, that the impact on overall survival is also, clinically quite significant. The responses were observed in about 9% of the patients and the responses, as we can see, on this slide were observed only in the ripretinib group and had a quite long duration. What about the side effect profile? There were few side effects, in particular a few grade 3 and 4 side effects in both arms. Maybe, one of the specific side effects which needs to be acknowledged is alopecia for the ripretinib group, alopecia of grade 1 and 2 observed in about 50% of the population of grade 2, which is significant alopecia being visible in about 20% of the patients. For the rest, minimal side effects, and in particular, none of the side effects which are observed with the second, third-line inhibitor related to the multi-kinase inhibitory effect on VGFR2, in particular. So, a treatment which was overall well-tolerated and interestingly, shown on this slide, the duration of response shown here on the spider plot, is quite prolonged with an update reported at the ESMO Congress last year, which showed an even better impact on the overall

survival. Interestingly and again, as was done with imatinib some two decades ago, it was possible in this study to dose-escalate patients with ripretinib 150-milligram QD to the same dose BID. And we can see here, the outcome of those patients who were dose-escalated at progression, comparing the blue versus the yellow bars, and showing that actually a large proportion of patients enjoy progression-free survival after progressing under 150-milligram QD, showing that probably escalating the dose could be an interesting strategy for the treatment of these patients. A bit like what was done initially with imatinib. So, ripretinib is an agent which is now approved in the US and evaluated in Europe. The second agent, which was very much of interest in the recent past two years was avapritinib, which was tested in phase I and phase II studies, in patients with GIST equipped with a mutation of Exon 18 PDGF-receptor-alpha, as well as in other GISTs. So, this was a study which actually explored different groups of patients, patients in all-comers situation fourth-line GIST, and also the focus population of patients with Exon 18 PDGF-receptor-alpha GIST, that we have described already as being quite resistant to the standard treatment. And this is probably, in this patient population, that the results are more interesting, in particular in the D842V patient population, where we can see here that the outcome at all those tested is very superior to what was previously shown to you and reported with imatinib and sunitinib and also regorafenib that was not shown. We can see here, very high response-rate, response-rate in the range of 80+ percent, close to 90% in a population of patients where the response-rate was 0 with imatinib. We can see here the progression-free survival at a dose of 300 and 400-milligram per day of avapritinib, which is quite impressive. Median progression-free survival 24 months. It was two months as we recall with imatinib. And as this translates, of course, in a prolonged progression-free and overall survival at later time points. Actually, the side effect profile of avapritinib is somewhat different to that of other tyrosine kinase inhibitors of the same class, with a central nervous system toxicity which is sometimes requiring treatment interruption or dose de-escalation, and which requires a careful monitoring by expert center. But for this patient population of PDGF-receptor-alpha Exon 18, in particular, the D842V mutated GIST, this is a treatment which has no equivalent in our medical treatment for this group of patients. And you can see here, the outcome of patients presenting in the format of a waterfall plot, which is really quite impressive, as compared to the very limited activity of the classical first-generation tyrosine kinase inhibitors. There is activity also, but the treatment is not approved for patients in fourth-line + treatment. We can see here, the waterfall plot of this patient population; after, avapritinib was tested in a phase III study versus regorafenib in the third-line setting, and failed to reach its primary endpoint. So, the treatment is indicated in US in Exon 18, and in Europe was approved for the 842V mutated GIST. So, the agent of interest cabozantinib, which was tested in the EORTC study, 1317, the CaboGIST study, in patients failing imatinib and sunitinib. And here, again, we have interesting results in uncontrolled study, again for avapritinib, showing a median progression-free survival of 5.5 months, and interestingly, an activity which was being observed in all molecular subset of patients, using an agent, which is able to block, to a large scale, the different mutations of KIT. And also, as we know, able to block other tyrosine kinase such as VGFR2, and MET as well. The activity of cabozantinib is quite significant. And this is observed in the majority of molecular subset of GIST. And this is an agent worth considering in this setting. This patient population was treated in this case in third-line setting. And we end up with the latest studies on the narrowest population of patients. You remember that we have, in the wild type, so-called wild-type GIST population, probably 1 to 2% of the population where the tumor is equipped with a translocation involving NTRK. And we know that these histo-agnostic treatments which are the NTRK inhibitors, such as larotrectinib, in this slide and also entrectinib, and several others in new generation, are able to block specifically the cancers in general not only sarcomas, equipped with this fusion protein. This is one of the specificities of this molecular alteration, which can be observed in all disease sites, almost all disease sites, even though, it is at a very, very low frequency, inferior to 1% for breast cancer, lung cancer and so on. This is true also for gastrointestinal stromal tumors. So, showing only here the results in sarcoma and in gray, you can see the gastrointestinal stromal tumor. It is that a very rare patient population seems to benefit from this treatment here. We have four GISTs being reported, treated with larotrectinib and they seem to respond as well as other sarcomas subtypes. They are soft or infantile fibrosarcoma, or even bone sarcoma response to GIST equipped with this fusion protein is as good as other tumors and other

sarcomas, with an impact on all sarcomas on the duration of response progression-free survival and overall survival, which is quite impressive. Remember that this is a population of patients which is not sensitive to any of the classical tyrosine kinase inhibitors being used IN GIST. So, this is the end of the story. Several other studies are ongoing to explore, to be explored in gastrointestinal stromal tumors. We are now in fifth-line or more. We have studies testing lenvatinib versus placebo. We have studies testing immunotherapy in combination with tyrosine kinase inhibitors and several tyrosine kinase inhibitors of new generation in phase I and phase II. So, we can certainly presume that in the future we'll have more to speak about in the armamentarium of GIST. I will conclude here by saying that there are multiple gastrointestinal stromal tumors but that after we described them carefully using histological classification and molecular classification and risk classification in localized phase, the treatment is quite simple. It's surgery following the rules of sarcoma management, with adjuvant medical treatment with imatinib for three years, for patients with high-risk. In advanced phase, medical treatment prevails. We have imatinib, sunitinib, regorafenib being approved as well as more recently avapritinib and possibly ripretinib in Europe, in the future, or ready-to agents' approval on the other side of the Atlantic. Medical treatment upfront, surgery being debated. And we have many more new agents which are being developed. So, GISTs are still a fascinating paradigmatic medic model of precision medicine in oncology. And will need to be investigated further in the future. Thank you very much for your attention.