# The treatment of gastrointestinal stromal tumours (GIST)

A better understanding of the different mutations that drive GIST is leading to new paradigms of tailored treatment that break many of the traditional norms of chemotherapy, particularly with respect to management of progression.

Gastrointestinal stromal tumours (GIST) are rare tumours, with an incidence of 10 new cases per million population per year, giving 4000–5000 new cases in the European Union each year. GIST was thought to be extremely rare, but the discovery of the specific molecular alteration that was driving these tumours in the late 1990s revealed it was slightly less rare than had been thought. This work showed that a mutation in the KIT gene drives the tumour. The molecular characterisation of GIST is at the centre of this review.

GIST can be detected in all organs of the digestive tract: the stomach, the small bowel, the rectum, the oesophagus and, in some rare cases, the mesentery. Mutation can occur in different parts of the KIT gene, and this can affect where the tumour develops. KIT exon 9 mutations occur most often in the small bowel lesions. Mutations in the PDGF receptor-alpha (PDGFRα) gene occur most often in gastric lesions. This interesting parallel between the molecular anatomy of this tumour and the location of GIST needs to be kept in mind, because it will drive the treatment of patients in the future.

**European School of Oncology**
**e-grandround**

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these will be selected for publication in each issue of *Cancer World*.

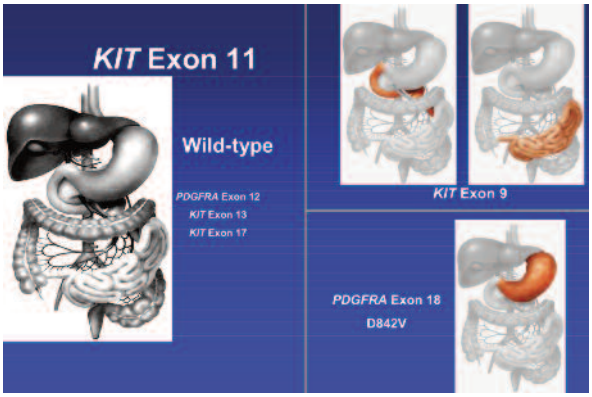
In this issue, Jean-Yves Blay, of the Centre Léon Bérard, Lyon, France, who is director of the Conticanet network of excellence and president of the EORTC, provides an update on the latest evidence for the treatment of GIST. Daniel Helbling, of the Onkozentrum Zurich, Switzerland, poses questions that explore the issues further. The presentation is summarised by Susan Mayor.

**The recorded version of this and other e-grandrounds is available at www.e-eso.net/home.do**

The majority of GIST lesions have mutations in KIT, with most occurring in the juxtamembrane region of the kinase (just inside the cell membrane). These mutations have functional consequences, including a constitutional activation of the kinase, which can be blocked by tyrosine kinase inhibitors (TKIs).

More recently, it was discovered that another gene – PDGFRα – can be mutated in this tumour. This occurs less frequently than KIT mutations – approximately 5% in the metastatic setting but probably 20% in localised tumours. The two mutations are mutually exclusive, with a GIST tumour having only one mutation to start with. However, additional mutations occur in the case of resistance.

**MUTATIONS VARY BY SITE**




**Understanding which gene mutation drives the GIST in a given patient will determine treatment choice in the future**

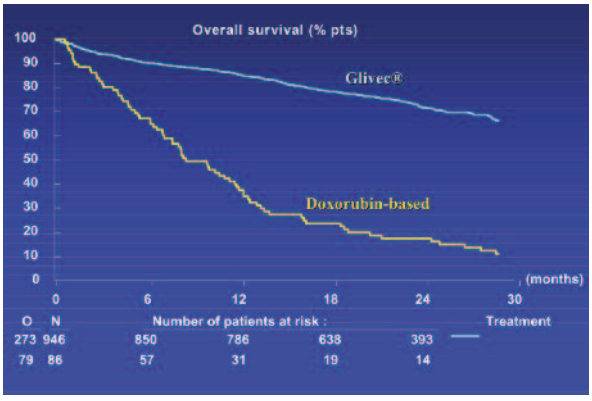
*Source:* C Corless, Presentation at the GOLS meeting 2008

## The impact of imatinib on survival

The introduction of imatinib (Glivec) for the treatment of metastatic GIST substantially increased overall survival, showing the most dramatic impact of a novel treatment on the outcome of patients with solid tumours in the last 20 years. Imatinib significantly improved survival compared to the previous treatment, doxorubicin. The large increase in overall survival led to the approval of imatinib for GIST without the usual requirement for a randomised controlled trial.

Results from the Conticanet network's series of GIST patients show the overall median survival in GIST patients treated with imatinib is around five years, while the median progression-free survival is approximately 24 months. This is of interest because it is the longest series we have to date on the treatment of GIST, and includes patients from before the imatinib era. It shows that imatinib is able to improve not only progression-free survival but also overall survival even beyond the time of progression. This is very important for the treatment strategy for GIST.

**IMATINIB GREATLY IMPROVED SURVIVAL IN GIST**




**Results from the Conticanet series of GIST patients demonstrated the huge survival benefit conferred by the new therapy**

*Source:* Adapted from J Verweij et al. *The Lancet* 2004, 364:1127–1134

**Question:** *The curve is not flat at the end, so does this mean that there is no cure in GIST with Glivec?*

**Answer:** *We do not have a final answer to this question. We do not know whether there will be a plateau at the end. We know that some patients have not progressed after 10 years of treatment, so that is reassuring, but this proportion of patients is relatively small, at less than 25%. However, this takes into consideration different GISTs with different mutations, and survival is probably different between mutations.*

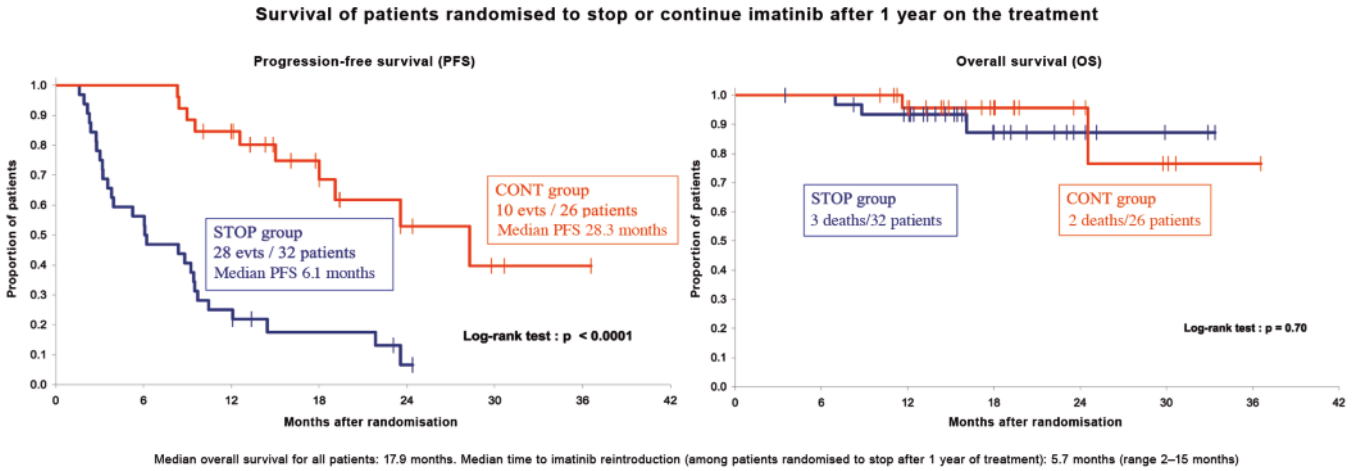
The development of a new treatment that is extremely effective in improving outcomes for these patients has led to a number of evolving paradigms.

## Evolving paradigm 1

### Double the imatinib dose for a patient progressing on the standard dose

The best treatment for a patient with metastatic GIST who is progressing on 400 mg/day of imatinib is probably to double the dose. This is, to my knowledge, the only example in oncology of a treatment where the dose is increased in the case of progression. This approach was tested in the EORTC 62005–S0033 trial, which compared 400 mg/day with 800 mg/day in advanced GIST, with patients on the lower dose being given the opportunity to cross over to 800 mg/day on signs of tumour progression.

## ONE YEAR IS NOT ENOUGH




**The BFR14 trial showed much shorter progression-free survival in patients randomised to stop imatinib therapy after one year**

*Source:* Based on JY Blay, A Le Cesne et al. *JCO* 2007, 25:1107–1113

The results showed that about one-third of patients achieve tumour control simply by doubling the dose of imatinib. Approximately 20% of the patients will not progress in the years following a dose escalation. Why is that?

Investigation of the pharmacokinetics of the drug measured the trough level of imatinib after one month of treatment and showed that patients in the lower quartile of exposure had a lower response rate and a higher risk of progression than those in the upper three quartiles (GD Demetri et al. 2008, ASCO Gastrointestinal Cancers Symposium, abstract 3). This suggested that exposure to the agent is correlated to the outcome. This has previously been observed in the treatment of chronic myeloid leukaemia, which is the other disease targeted by imatinib. There was a trend to higher rates of clinical benefit with higher imatinib exposure (67% in the first quartile vs 84% in the fourth quartile), with greater clinical benefit for patients with the KIT exon 11 mutation, which is particularly sensitive to imatinib (100% for the fourth quartile, *P*=0.009).

Question: *This is the only situation where a dose increase is recommended in oncology. Is that because the tolerance of the drug is good?*

Answer: *Tolerance to dose escalation of imatinib is good compared to usual cytotoxic agents, but it is not always very easy. Even though you have fewer side-effects by escalating the dose rather than starting with 800 mg/day, some patients have difficulty maintaining the 800 mg/day dose.*

Question: *How long do patients benefit from the dose increase?*

Answer: *The median progression-free survival after dose escalation is probably in the range of 3–4 months, and only 20% of the patients have not progressed at one year. However, we still have some patients on an escalated dose who are doing well after several years. This is very rare compared to other treatments. Some patients have shown sustained tumour control on 800 mg/day for more than two years after progression on 400 mg/day. This shows that exposure of the tumour to the agent is critical in understanding why these patients are responding.*

## EVOLVING PARADIGM 2

### Never stop systemic treatment in the advanced phase

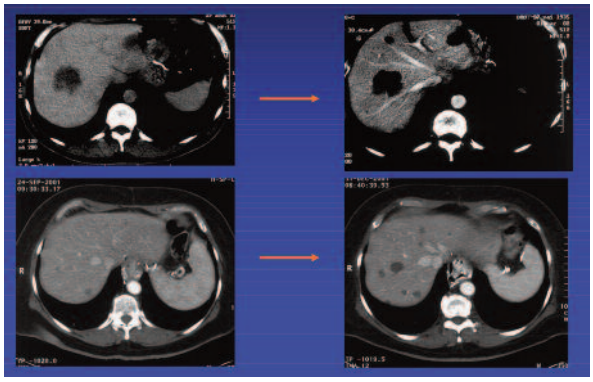
How long should we continue to treat with imatinib? This is an important question, and one that patients often ask after three to four years of treatment. To address this question, the French Sarcoma Group BFR14 trial randomised GIST patients to imatinib that was either stopped after one year and then restarted on progression or treatment was continued until progression. Results showed the median progression-free survival for patients stopping treatment at one year was six months, which was very significantly inferior to that in patients continuing treatment. The good news is that all patients, apart from one who died

from an unrelated side-effect, responded to restarting imatinib. This showed that treatment for one year does not kill all tumour cells, because all patients who stopped imatinib relapsed, although this occurred after three years in one patient.

The same trial went on to randomise patients to stop or continue at three years, with the same result. The median progression-free survival is six months, which was significantly inferior to the continuation arm. Again, all patients responded to restarting imatinib, which is reassuring.

What is more worrying is that the median progression-free survival is exactly the same in groups stopping after one year as after three years, showing that during the first three years the treatment is simply delaying progression. It is stopping the proliferation of cells, and not killing the last cancer cell. Therefore, we should probably treat with imatinib for more than three years. We are just completing a five-year randomised trial, with results being presented this year.

**FALSE PROGRESSION ON CT SCAN**



The new hypodense lesions visible on the right-hand scans do not represent tumour progression, but are caused by the treatment

*Source:* Courtesy of JY Blay, Centre Léon Bérard, Lyon

## Evolving paradigm 3

### Response does not equal reduction in tumour volume

The idea that response cannot be equated with a reduction in tumour volume is a very important change in the way we are used to seeing responses to cancer treatment. We are used to thinking that to have a response we need the patient's tumour to shrink, and that the tumour increases in volume when progression occurs. This is probably not true for the treatment of GIST with imatinib, and is probably not true for other targeted agents in other cancers. Response does not necessarily mean reduction in tumour volume, and progression does not necessarily mean a volume increase.

False progression can be seen in GIST patients treated with imatinib. The figure above shows CT scans for a patient treated in the early days of imatinib. After three months, there appears to be new lesions. However, these are hypointense lesions caused by the treatment, typical of a false progression. Conversely, you can also have a false response. Even though the patient has a response according to RECIST criteria, the disease is continuing to progress. We should be aware of this, as we should probably be ready to change our practice in years to come.

We should assume that a CT scan is the gold standard. It is also important to listen to the patient. If a patient has a partial response but is feeling unwell, we have to suspect that a partial or limited progression may possibly be occurring. On the other hand, if despite an increase in tumour volume on a scan they say they are feeling well and have no more pain, this could be a false progression. In such a case, it is important to weigh up the level of suspicion.

Question: *If you have a patient who is doing clinically better but you see on the CT scan that the lesion is increasing, do you continue with the same treatment or are you suspicious?*
Answer: *It depends on the level of the suspicion. One of the aspects that is very important to take into account is the density of the tumour measured in Hounsfield units. Most of the responding lesions have decreasing Hounsfield units. An index based on the so-called 'Choi criteria' enables you to distinguish responding from non-responding tumours. This needs to be reproduced, but it is quite convincing, and it is quite well accepted that hypointense lesions are responding lesions.*

*Concerning treatment, yes, we could continue. If I had doubts, I would probably explore with a PET scan. If I have no doubts, I would simply see the patient again within six weeks with a new CT scan and clinical evaluation, instead of the usual three-month follow-up.*
Question: *So you do not do PET scans straightaway, you reserve them for investigating areas of uncertainty?*
Answer: *Correct. There is another indication for PET scan in the ESMO guideline, which is when you start new adjuvant treatment in large tumours before resection, and you want to make sure the tumour is responding rapidly and is not a primary resistant tumour, which is rare – only 5%.*

## Evolving paradigm 4

### Understanding the molecular biology of tumour resistance is important for routine treatment of the patient

The molecular biology of resistance is a very important issue. There are different subtypes of mutation, with different

sites of mutation of KIT: exon 9 and exon 11. A meta-analysis of the two large trials mentioned – the US S0033 and the EORTC 62005 trials (1640 patients) – showed significantly different progression-free survival treating exon 9 patients with 400 mg/day (see below, *blue line*), compared to 800 mg/day (*green line*). This does not occur in exon 11 patients (*red and yellow lines*). Information on which mutation a patient has is important because we need to double the imatinib dose in a patient with an exon 9 mutation. This strategy is recommended by the ESMO and the NCCN guidelines in the US.

The difference in progression free survival does not translate into overall survival, although the number of patients in each group was quite limited. However, 800 mg/day is the standard dose for exon 9 patients, and this means that we need information on the patient's mutation when treating in the metastatic setting. This is not easy because information on the type of mutation is available in less than 50% of patients, and testing for mutation type is not available everywhere. Testing requires complex technology and good reproducibility, but this is the way to go forward, certainly for exon 9.

**Question:** *Do we need to test only for exon 9, or for the other mutations as well?*
**Answer:** *We certainly have to test for exon 9. We suspect that different mutations in PDGFRα or exon 11 may also be associated with different prognoses and we are expecting data on this at ASCO this year. If this is the case, then we should have a more exhaustive evaluation of the nature of the mutation than just a single evaluation of exon 9.*

## What strategy should be adopted at progression?

There are several things we should do if a patient progresses.

### Check adherence with therapy

The first thing to check is whether a progression is related to non-adherence to imatinib. A study on the number of packs of imatinib bought by patients in the US showed that this was only 75% of the amount prescribed, which indicates that the adherence is, at best, three-quarters. This is not very high, and we know that the exposure to imatinib correlates to the outcome. It is not simple to take a pill every day for the rest of your life. We need to try to improve patient adherence, and we have to listen to the experience from other fields, such as HIV, where adherence to long-term treatment has been studied extensively.

### Check exposure

The pharmacokinetic levels of imatinib are important, as mentioned previously.

### Consider surgery

Surgical treatment is very interesting, but still experimental. A small study by CP Raut and co-workers found that patients operated on while they had limited progression showed a longer time to secondary progression than those who had surgery at general progression, and those operated on with stable disease showed even better outcomes (*JCO* 2006, 24:2325–2331) This is of interest, but it is not yet proven to be superior to treatment with sunitinib.

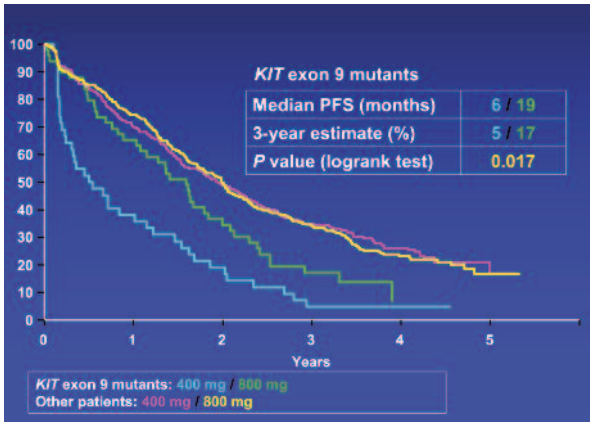
We have started a trial randomising patients with metastatic GIST responding to imatinib either to imatinib plus resection of their lesion at the time of best response (within one year) or to continue with imatinib, with surgery delayed until the time of progression. This is an extremely important study, but very difficult.

### Switch to another TKI

Sunitinib has a broader spectrum of activity in terms of kinase inhibition than imatinib, so we expected that it could have an additional effect. This additional effect was demonstrated in a trial comparing sunitinib with placebo in imatinib-resistant patients, showing an improvement in progression-free survival. Both blinded and open phases showed improved time to progression with sunitinib (P Casali et al. ASCO 2006, abstract 9513; IR Judson et al ESMO 2006, abstract 506). Some would argue that placebo was not the appropriate control arm, but the trial is very important because it demonstrates the activity of sunitinib.

Progression-free survival with sunitinib differs in patients with exon 9

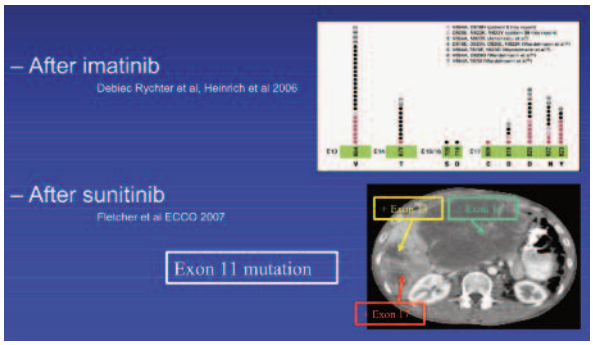
**THE MUTATION DICTATES THE RESPONSE**




**Doubling the dose for imatinib-resistant tumours is effective, but only for tumours with the exon 9 mutation**

*Source:* Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Presented at ASCO 2007

**MOLECULAR HETEROGENEITY AT PROGRESSION**




**Though GIST starts with only one mutation, multiple mutations can develop within a single tumour after treatment with imatinib and/or sunitinib, which we must learn how best to manage**

*Source:* CT scan: courtesy of JY Blay, Centre Léon Bérard, Lyon

mutations compared to other mutations. In relapse, patients with exon 9 and wild type seem to have a better outcome, so this is the opposite to what is seen with imatinib. The finding does not mean that sunitinib is inactive on exon 11, but rather that we have possibly selected a resistant clone with additional mutations.

At the time of progression, we have observed the emergence of resistant clones which are associated with additional mutations of the kinase. This mutation codes for a protein that is resistant to imatinib and/or to sunitinib. These additional mutations are located on exon 13, 14, 17 and 18 of the same kinase. There is a high level of heterogeneity in these tumours – with mutation of exon 13 and 14 in one region, and mutation of 17 in another place. This is a level of complexity that has not been addressed previously and which we do not yet know how to handle, but it needs to be characterised because outcomes differ according to the nature of the secondary mutation.

Unfortunately, a lot of patients progress on sunitinib, so what is the next step? There are several other TKIs, in addition to other strategies. Nilotinib (Tasigna) is a TKI that blocks the BCR-ABL. It has been tested in a phase I/II trial in patients with resistant GIST. The outcome of patients treated with a combination of imatinib and nilotinib, or with nilotinib as a single agent for intolerant patients, was not bad in terms of tumour control, as evaluated by complete response (CR) + partial response (PR) + stable disease rate. Progression-free survival was comparable with that of patients treated with second-line sunitinib.

Is nilotinib really useful? This is being explored in a pragmatic trial to be presented at ASCO 2010, comparing nilotinib versus 'doctor's choice': either best supportive care alone, imatinib or sunitinib. This was a very interesting trial, but it was complex because maintaining TKI pressure using a kinase inhibitor that has been failing in the past cannot be described simply in the protocol – it is the investigator's judgement. Results during 2010 will show whether nilotinib is an active agent.

**Question:** *Do some patients respond after imatinib and sunitinib to being given imatinib again?*

**Answer:** *Yes, this happens in third, fourth, fifth and sixth line. When we say response, we do not always mean tumour shrinkage, but it may be prolonged tumour control and clinical benefit for the patient and no progression according to RECIST.*

A fourth agent, sorafenib (Nexavar), was tested in a phase II and compassionate use programme for patients who had failed on imatinib and sunitinib. It showed a similar control rate of approximately two-thirds of the patients, with a median progression-free survival of four to five months. This kinase inhibitor has a profile similar to sunitinib, but has some activity in the third- or fourth-line setting in imatinib- and sunitinib-resistant GIST (HS Nimeiri et al., ASCO Gastrointestinal Cancers Symposium 2008, abstract 7). Unfortunately, there will be no prospective trial addressing this question from the pharmaceutical company, but we may be in a position to try to explore this in the academic setting.

The fifth drug being explored is the heat shock protein 90 (HSB90) inhibitor IPI 504. A phase I study showed some level of tumour control in a substantial proportion of patients with GIST. On the basis of this, the HSB90 inhibitor was tested in a phase III trial, but unfortunately this was stopped because of toxicity in the treatment arm. This is definitely a strategy that needs to be further explored.

Another pathway that is critical for the development of resistance is mTOR inhibition. A trial is exploring the combination of imatinib, sunitinib and sorafenib with RAD 001 – everolimus – which shows long-term tumour control in some patients. About 20% of patients greatly benefit from the treatment at six months. These data were presented at ASCO 2008, but have not yet been published. The combination is not standard yet, but should be further explored.

The figure opposite shows one of my patients with a huge liver metastasis who progressed after treatment with 800 mg/day imatinib. He was included in the RAD 001 trial and is still alive more than three years after resection. This patient would not have been operated on without this treatment.

## Evolving paradigm 5

### Continuing TKI therapy in case of progression under TKI

How to respond to progression of a tumour being treated with a TKI is still a changing paradigm. There is no other situation where we would maintain a treatment demonstrated to be inactive. However, in this case, the rationale for doing just this is that survival after progression on imatinib is much longer than expected from previous experience with GIST (median overall survival: 58 months versus 26 months). The second issue is focal resistance, where the majority of cell clones remain sensitive, so it is not logical to stop a treatment that is still active in a large proportion of clones. Maintenance of KIT blockade is probably very logical, based on these two observations.

What about treatment in the adjuvant setting? This question was addressed in the phase II trial ACOSOG Z9000. Imatinib treatment after surgery showed overall survival of 99% at one year and 97% at three years. The ACOSOG phase III Z9001 trial demonstrated that exposure to one year of treatment with adjuvant imatinib substantially reduced the risk of progression during and after this time period. The magnitude of risk reduction is in the range of two-thirds in all populations of patients.

Even though patients have delayed relapse, the majority will relapse after the end of the treatment. There is a high degree of suspicion that one year of treatment may not be enough. This needs to be further explored, but the basic message is that we do not yet know for how long we should treat. The Scandinavian trial, SSG/AIO, randomised patients to one year versus three years of treatment in the adjuvant setting, while an EORTC trial (62024) is studying two years of treatment. Results will be available in 2011.

The questions on adjuvant treatment that remain include:

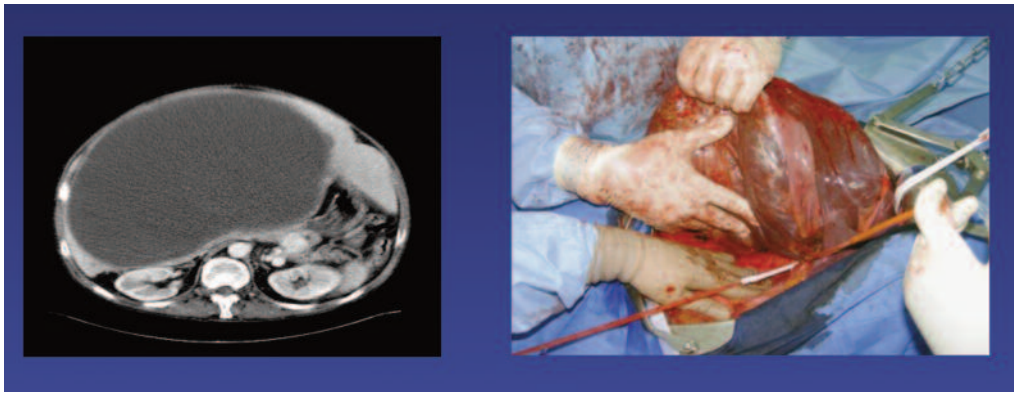
- Whom should we treat?
- What risk level?
- What duration?
- What mutational type?
- What is the impact on secondary resistance?
- What will be the impact on overall survival?

## Conclusions

Surgery and adjuvant imatinib can be considered standard treatment in localised GIST, but a lot of questions remain about adjuvant treatment. First-line imatinib is the only standard, at a 400 mg/day dose for non-exon 9, and at 800 mg/day for exon 9 patients. We should continue treatment until progression or intolerance, because patients will experience a recurrence if treatment is stopped. Molecular biology is becoming increasingly important for prognostic and treatment selection.

The evaluation of response to imatinib is not simple, and can be determined using the RECIST criteria, WHO criteria, and Choi criteria. However, we know there are false progressions and false responses and that we should integrate not only reduction in volume but also density and prolonged stabilisation as useful criteria. Surgery is not of proven benefit in the metastatic phase; it needs to be explored, and I encourage everybody to participate in the EORTC Intergroup study testing surgery in the randomised setting. The final question is whether we should maintain treatment in patients where everything has failed. The expert opinion from ESMO and the NCCN is that we should maintain treatment at least to control sensitive clones.

**THE ROLE OF mTOR INHIBITION**



**This imatinib-resistant GIST patient had a huge liver metastasis resected after treatment with the mTOR inhibitor everolimus**

*Source:* Courtesy of Pierre Meeus, Centre Léon Bérard, Lyon