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Gastro Intestinal Stromal Tumours (GIST)

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Sixteen years after the first patient was treated with Imatinib (Glivec®, Gleevec®, Novartis), the enthusiasm for GIST and the concept of targeted therapies in this disease has significantly declined, if not disappeared. Very few scoops and no revolutionary communications in general. Ongoing studies were obviously not mature enough to be presented this year. The learnings of this ASCO 2016 in GIST can be summarized as follows:

1) In adjuvant setting

Still no update neither on the US ACOSOG pioneer study comparing one year of Imatinib versus 1 year of placebo, nor on the EORTC study which was presented in 2013 (ASCO 2013, Casali et al, abstract 10500), comparing two years of Imatinib versus follow-up, nor on the German-Scandinavian study (SSG-AIO) presented four years ago in plenary (ASCO 2011, Joensuu et al, abstract n° 1) but updated last year comparing three years of Imatinib in high risk GISTs (ASCO 2015, H. Joensuu et al, abstract 10505). Recall that the German-Scandinavian study has modified the therapeutic standard. The superiority of the 3 year treatment regimen is still sustained both in terms of 5 years RFS (P=0.003) and overall survival (P=0.032). The 5 year overall survival is of 93.4% for patients who received three years of Imatinib versus 86.8% for those who only received the drug for one year.

2) In relapse or advanced setting: first line treatment

This year, and for the third times in a decade, no update on the BFR14 study closed to inclusions since May 2009 (434 patients included). Patients who are long responders to Imatinib and still non-progressive under 400 mg around their tenth year of treatment should be submitted to a new randomization proposing treatment discontinuation versus continuation. This study is still under discussion.

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3) GIST and mutations

The place of mutational status is now undeniable in GISTs, both in relapse and adjuvant settings (2014 ESMO Guidelines) as :

1) The benefit of Imatinib on PFS varies according to the mutational status

2) the frequency of mutations insensitive to Imatinib is high in localized GIST (PDGFRa D842V mutation is observed in about 20% of the operated gastric GIST,

3) the optimal duration of Imatinib administration will probably expand over time in high risk GISTs (French Sarcoma Group ImadGIST ongoing trial (3 years versus 6 years), Scandinavian study (3 years versus 5 years),

4) the number of available TKIs in advanced GISTs increases in time, all with their own specific characteristics (active or not on the new mutations of the "ATP-binding pockets, KIT exon 13 and 14" area or on the "activation loop" KIT exon 17 and 18 area 5) characterization is becoming more and more complex in Wild Type GISTs (some of them now being called "quadruple negatives").

Some of the WT GISTs still benefit from a multi-platform approach (NGS sequencing, proteomic expression, amplification, detection of fusion genes). The team of M. Heinrich still continues to dissect GISTs and notably this quadruple negative WT GIST: Kit negative, PDGFR negative, no loss of expression of the complex SDH and RAS/MAPK negative. (Heinrich et al, abstract 11012). Two of these patients, out of the 5 analysed, have a fusion of ETV6-NTRK3 genes for one and of FGFR1-TACC1 genes for the other, which are already involved in some colon or small intestine cancers (non-GIST). These GISTs show genomic alterations implying new Tyrosine Kinase receptors which could be used as targets for new targeted therapies.

No communication this year regarding the detection of circulating tumour cells, containing initial mutational status as well as the mutational status of the resistant cells under treatment. This is a very complex and still expensive technique which will become more widespread in the upcoming years and will certainly be helpful for the definition of our future treatments. This would require the prospective validation of these "plasma" signatures. Do we have to switch to a second line therapy when tumour cells showing secondary mutations first appear? Even before resistant nodes can be observed on conventional imaging?

4) Beyond first line therapy Tyrosine Kinase Inhibitors

Apart from Sunitinib (Sutent®, Pfizer) and Regorafenib (Stivarga®, Bayer) which obtained a Market Authorization in 2006 and 2013 respectively, in Imatinib resistant/intolerant GISTs, what will be the future of the « ibs » in the pre-treated GISTs?

- **Sunitinib (Sutent®, Pfizer):** no communication this year
- **Pazopanib (Votrient®, GSK/Novartis):** no communication this year
- **Vandetanib (ZD6474)** is a small anti VEFR2, EGFR and RET molecule which was tested this year in Wild Type GISTs (interesting pre-clinical model of SDH deficient Wild Type GIST): 300 mg / day in adults, 100 mg/m2 in children (Glod et al abstract 11009). Nine patients included (11-52 years old): no response, two long stabilizations (Natural stabilizations of WT?). Not yet.
- **Crenolanib**: was one of the scoops of ASCO 2011. Crenolanib (CP-868596) significantly inhibits transaffected cell-lines with PDGFRa mutated genes, notably the D842V totally insensitive to Imatinib (IC50 only being of 9 nM with Crenolanib versus more than 1000 for Imatinib (ASCO 2011, Heinrich et al, abstract n°10012). Some years later, clinical outcomes were disappointing, only partially published. These metastatic patients at the time of inclusion often showed a negative initial PET-Scan (Indolent disease, few dividing cells?) and there is still a discrepancy between functional and conventional imaging (ASCO 2014, JM Matro et al, abstract 10546). Therefore, the overall results of this study were highly expected: 20 patients included, doses of Crenolanib were increased from 200 mg/d to 72 mg/m2 three times a day (van Mehren et al, abstract 11010). On the pharmacokinetic level, the daily spanned administration of Crenolanib seems to be more interesting. Gastrectomy does not influence PK dosages. Two partial responses (13%), three long tumour stabilizations (19%). To date, this is the only drug considered as «active » in this subtype of GISTs, even though the response rate is not revolutionary. A randomized study comparing Crenolanib versus placebo is ongoing. Note that two patients presenting a GIST with this D842V mutation responded to Imatinib (response by CHOI criteria) out of the 22 pre-treated patients in a retrospective study with a series of 71 patients showing a mutation on this receptor (Farag et al, abstract 11011). Therefore some genuine GISTs harbouring this mutation are sensitive to Imatinib. Note that the median PFS of non D842V mutated patients is similar to the one observed in KIT exon 11 mutated GISTs: 24.5 months. It is crucial to pay attention to the exact PDGFRa exon 18 mutation in the presence of a gastric GIST.

- **BLU**-285 (Bluprint) could be one of the GIST treatments in a near future: in transplanted murine models with Imatinib resistant mutated GIST cell lines (notably with the exon 17 mutation), BLU-285 is more potent than Regorafenib in terms of apoptosis, proliferation index and tumour shrinkage. A phase 1 study is ongoing. To be followed…