SOFT TISSUE, BONE SARCOMAS & GIST
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This year, the most interesting communications focused on bone sarcomas and immunotherapy. Poster and parallel sessions were more attractive than the plenary.

I – Gastro Intestinal Stromal Tumours (GIST)

Sixteen years after the first patient was treated with imatinib (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.

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 (Von 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…

II- Soft Tissue and Bone sarcomas

Unlike GISTs, ASCO 2016 was an excellent year for Soft tissue and bone sarcomas, both in posters/poster discussions and plenary. A better biological/cytogenetic dismemberment of sarcomas in general, turns each histological subtype into a potential target for new therapeutic approaches which are going to widespread in the upcoming years. Intracellular signalling pathways are dissected in each histological subtype and the therapeutic trials are now based on molecular abnormalities (causal for some of them, secondary for others). Still, year 2016 gave new impetus to conventional chemotherapies, even intensified, and was notably marked by the negative results of immunotherapy based on the inhibition of PD1-PDL1 pathways.

1) Adjuvant Chemotherapy/radiotherapy

- Only one retrospective study this year on 158 patients treated over 20 years in a single centre (Greto et al, abstract 11034) suggesting that the simultaneous association of anthracycline chemotherapies combined with radiotherapy is feasible with acceptable toxicities: 12% of grade 3 cutaneous toxicities, radiotherapy discontinuation due to acute dermatitis in 12% of the cases, and delayed fibrosis in 12 of the patients (are they the same?). 20% of local relapse, 23% of metastatic relapse. In the absence of a prospective randomized study, it is difficult to pronounce on this approach and give advice especially because the patient population seemed very disparate over time as well as in the different types of adjuvant treatments.
- For the first time at ASCO, the results of the NetSarc network implemented in 2010 were reported (Blay et al, abstract 11013) : supported by INCA, the French Sarcoma Group (26 centres) established a unique database over 5 years which is going to generate, in a very near future, relevant information on the management of sarcoma patients in France: 13454 patients are in this database (all the cases reviewed by the Multi-Disciplinary Teams from January 2010 to December 2015), representing 78% of the newly diagnosed patients in France over this period. 12% of them were metastatic from the first MDT discussion. The percentage of patients with a localized disease and discussed in an MDT before any local treatment increases over time (from 41% in 2010 to 48% in 2014), the rate of initial biopsies is significantly higher in referral centres than in the non-referral ones (80% versus 36%), the percentage of patients with a R0 and R2 surgery is of 49% and 7% in the NetSarc centres versus 24% and 21% when the patients are operated in non-specialized centres, this significantly increases the PFS ($p=0.0008$) for the patients who received surgery in reference centres, and a significant decrease of wide second surgeries, often complex and expensive when these patients are initially operated in non-reference centres (6%

versus 19% of second surgery when the patients are initially operated outside reference centres). To be followed…

- On a series of 785 breast sarcomas (SEER epidemiological registry), adjuvant radiotherapy improves the overall survival of patients showing a sarcoma measuring more than 5 cm (Not those with a sarcoma under 5 cm) (Yin et al, abstract 11031). The most frequent histological subtype is angiosarcoma (252 cases). Patients presenting a sarcoma with an osteosarcomatous component have the worse prognosis whereas those with lipo/fibrosarcomas have a better outcome. Patients receiving a mastectomy are not necessarily doing better on the long term, a preservative treatment should be recommended when an R0 surgery is feasible.

2) Neo-adjuvant chemo/radiotherapy:

- The use of an induction systemic treatment and/or of an initial radiotherapy in locally advanced sarcomas is frequent in centres used to manage this kind of disease. However, the impact on survival is still to be demonstrated and the selection of patients who could benefit from this strategy still to be determined. There is still no new randomized study asking this question in STS. The Italian randomized study comparing conventional chemotherapy versus histological subtype-tailored chemotherapy is ongoing and the results should be revealed soon. Responders to chemotherapy evaluated according to the CHOI criteria have a significantly improved overall survival in the previous Italian study compared to the RECIST evaluation which discriminates far less the real "histological" responders in patients with a stabilized tumour volume under chemotherapy (5 cycles versus 3 in peri-operative) (Stacchiotti et al, abstract 11044). A new analysis of this study shows an equivalence between these two therapeutics, with 60% of patients alive after 10 years (Palassini et al, abstract 11045). Locally advanced leiomyosarcomas treated by an initial chemotherapy have an evolution which is significantly lower than in the other histological subtypes (parameter already found in the unique meta-analysis on individual data published to date on the role of adjuvant chemotherapy, Lancet 1997). Recall that ifosfamide plays a limited role in metastatic leiomyosarcomas and that this natural resistance to ifosfamide could explain these results.
- In the field of localized tumours requiring an induction therapy, Ewing Sarcomas were honoured this year, with the highly expected results of the randomized studies asking the question of therapeutic intensification. More than 15 years after the inclusion of the first patient, the 1999 Euro-Ewing trial and its R2 randomization (poor responders to VIDE-type induction chemotherapy, or locally advanced Ewing (> 200 ml) non operated, or immediately operated without any induction chemotherapy) and

comparing a Melphalan-Busulfan intensification versus 7 cycles of VAI, delivered a verdict : 216 patients (from 0.9 to 45 years old) randomized in 13 years in 112 centres and 13 countries, the Event Free Survival (EFS) and the 3 year overall survival were of 60% and 73.9% respectively (J. Whelan et al, abstract 11000), with a significant benefit for the patients who were intensified (67% versus 53.1% for the 3 year EFS (p=0.024) and 78% versus 70% for the 3 year overall survival (p=0.019)). Intensive chemotherapy is obviously more toxic than conventional one (2 deaths due to toxicity). Patients who have the best benefit with intensive chemotherapy were children and adolescent up to 18 years old. Moving forward is this a new therapeutic standard in Ewing sarcomas for young patients poor responders with a big tumour volume not feasible for surgery or resected without prior chemotherapy? According to the oral communication which followed the session, this question is still controversial because of the low number of patients who were effectively randomised (50%) compared to the initial population. This similar intensification (other part of the 1999 EuroEwing protocol) does not significantly improve the outcome of patients with lung metastases compared to conventional chemotherapy (VAI) combined with a pulmonary radiotherapy which is less and less used in metastatic Ewing sarcomas, at least in adults (Dirksen et al, abstract 11001). Like previously, only 40% of the patients who could potentially be included in the study after induction chemotherapy were randomized (mainly due to patients' refusal). Note that pelvic localized Ewing sarcomas benefiting from a more aggressive approach (surgery + radiotherapy) have less local recurrences than the others, even in good responders. Conversely, the combination of radiotherapy and surgery has no impact on the local control of Ewing sarcomas of the thoracic wall (Andreou et al, abstract 11026).

3) Chemotherapy in advanced setting:

- Last year, a retrospective analysis on 2747 patients presenting advanced STS managed in the same institution (Royal Marsden, London, UK) had been reported (ASCO 2015, S.J. Harris et al, abstract 10545): chemotherapy improves the overall survival of patients with advanced STS as the median survival of treated patients is of 19.3 months versus 12.5 in non-treated patients. Note that in England, 50% of the patients who were managed these last years do not receive any systemic treatment in advanced settings. Undifferentiated pleomorphic sarcomas (UPS) and angiosarcomas had the poorest survival rates. The French Sarcoma Group Conticabase was analysed this year on a similar population of advanced sarcomas (2225 patients) : 28% of them did not receive any treatment (especially patients >75 ans), 1600 patients receive first line

therapy, mainly with anthracyclines (poly-chemotherapy in 50% of the cases), only 950 patients receive 2nd line (42% of all metastatic patients), 650 have 3rd line, 496 have 4th, 232 have 5th and 134 have 6th (Italiano et al, abstract 11014). Then, if a patient can reach the 2nd line, the probability to receive further therapeutic lines is high. Conversely, a significant number of patients « cannot » access 2nd line therapy (down from 1600 to 950). Less than 10% of the whole population receives experimental therapy. 10% of the metastatic patients are still alive after 5 years. Unlike the locally advanced forms (eg. Previously), (22.4% of the whole population) significantly live longer than the others (higher number of active products in this disease? Higher sensitivity to anti-cancer agents in advanced setting?). UPS (19.4% of the cases) have the poorest survival (like in the pre-mentioned study), certainly because of their high chemo-resistance, to anthracyclines and to further lines of chemotherapy (Herrera et al, abstract 11066). Note that intra-tumoral injections of A1-R Salmonella typhmurium in an orthotopic xenograft model of a human UPS, followed by doxorubicin eradicate transplanted tumours (Murakami et al, abstract 11068). Are UPS the most immunogenic in general (see PD1-PDL1 and immunotherapy section) ? *(Note: UPS=undifferentiated pleomorphic sarcoma).*

■ **New drugs/targeted therapies**

1. **Olaratumab (IMC-3G3, Lilly)** is a monoclonal antibody (IgG1) against PDGFR alpha receptor, a target often involved in STS and increasing the activity of doxorubicin in sarcoma preclinical models. This was the scoop of last year! Administered at the dose of 15 mg/kg at D1 and D8, olaratumab, combined with doxorubicin (75 mg/m2 D1) and compared to doxorubicin only (phase II randomized trial) increases the objective response rates (18.2 versus 11.9%, non-significant), median PFS in a significant manner (6.6 versus 4.1 months, p=0.061, HR=0,672, unilateral statistic test, α=0,10) and overall survival (25 versus 14.7 months, p=0.0004) (ASCO 2015, Tap et al, abstract 10501). This was certainly the most interesting communication on STS of last year. A phase III registration study which inclusions are already closed is ongoing! Possible results in 2017.

2. **Pazopanib (GW786034, GSK),** VEGF, PDGF and KIT inhibitor obtained its MA both in the United States and Europe in 2012, following the results of the Palette phase III randomized study, reported at ASCO 2011 (Van Der Graaf, abstract n°LBA10002). What's new this year in this topic?

a. One of the Pazopanib mechanisms of resistance could be due to an up-regulation of its receptor to endoglin under the effect of VEGF inhibition. The TRC105, antibody directed against endoglin had been tested (from 8 to 10 mg/kg weekly) last year in association with pazopanib, 2 to 4 weeks after the beginning of its administration of pazopanib (ASCO 2015, S. Attia, abstract 10514). No increase of pazopanib toxicity, only some telangiectasies linked to TRC105. One patient with angiosarcoma (naturally expressing the endoglin receptor) was in complete response, 5 other patients out of 18 having a shrinkage of more than 10% of the tumour volume. The in extenso phase II was reported this year (Attia et al, abstract 11016): the median PFS of the 81 patients is of 3.95 months, therefore similar to the one observed with pazopanib only. Two angiosarcomas are in complete remission with the combination and 6 others benefit from a clinical improvement (8/9 in clinical benefit setting, 88%). The expression of endoglin does not seem to be a predictive factor to response/resistance in this phase 1b/2 trial. A randomized study is about to start in metastatic angiosarcomas (124 patients).

b. A randomized phase II study comparing pazopanib with the pazopanib/gemcitabine combination (Plummer et al, CCP 2013) and focusing on 90 pre-treated patients at least by anthracyclines, was orally reported this year (Schmoll et al, abstract 11004) : the primary objective has been reached with a 3 months tumour control over 60% (73.2%) for the combination versus 40% expected with pazopanib only (en fait 45.5%), p=0.005. The median PFS is of 5.6 months for the association versus 1.9 months for pazopanib (significantly lower than the one observed in the Palette study), certainly due to the presence of liposarcomas in the study. In an interesting manner, liposarcomas are precisely the ones who benefit the most from the combination! Median PFS is of 8.6 months with the combination versus 1.9 months (difference still non-significant) with pazopanib only (like in the Palette study), median survival of 25.4 months versus 11.1 months (here again the difference is not significant) in favour of the pazopanib-gemcitabine combination. Note that two patients in the combination arm died from toxicity and 37 Severe Adverse Events (SAE) (out of 42 patients) for the combination versus 9 SAE for pazopanib only (out of 44 patients). This combination deserves to be explored in the future, and notably in liposarcomas. According to a Spanish prospective phase II study: only myxoïd/round cell liposarcomas might be the most resistant to pazopanib : median PFS is of 1.9 months versus 3.5 months for dedifferentiated liposarcomas (Valverde et al, abstract 11039).

c. To be fully complete on pazopanib, an interesting communication focused on the bioavailability (absorption, PK) of pazopanib during or à after meals (as recommended) : the bioavailability of pazopanib is equivalent between 600 mg absorbed during a «fat» meal and 800 mg fasting (Lubberman et al, abstract 11040). To be followed attentively like the combination of pazopanib plus vorinostat (HDAC inhibitor) which could help to counter resistance against pazopanib (Dembla et al, abstract 11057).

3. **Regorafenib (Stivarga®, Bayer) :** the definitive results of the randomized study coordinated by the French Sarcoma Group was expected (Penel et al, abstract 11003). Only the results in leiomyosarcomas were mature enough to be presented last year (ASCO 2015, Mir et al, abstract 10504): pan-tyrosine kinase inhibiting KIT, PDGFR, FGFR, regorafenib was compared to a simple placebo in four cohorts of pre-treated patients (Liposarcomas, leiomyosarcomas, synovial sarcomas and other sarcomas) with crossing-over in case of progression (181 patients included in 18 months). These results confirm the efficacy of anti-angiogenic factors in STS (After those observed with pazopanib which obtained a Market Authorization in this indication (apart from liposarcomas) in 2012) : 4 objective responses (one Synovial Sarcoma, 2 angiosarcomas, one TFS), one partial response in the placebo arm (!), a median PFS significantly increased in the regorafenib arm in LMS (3.7 months vs 1.7), in SS (5.6 months versus 1), in other sarcomas (2.9 versus 1 months) but not in LPS (1.1 versus 1.7 months). If liposarcomas are excluded from the analysis, median PFS is of 4 months versus 1 months in the placebo arm ($p<0.0001$), benefit (3 months) similar to the one observed with pazopanib (4.5 versus 1.5 months). Despite a crossing- over performed in 76% of the patients, median survival of patients with non LPS is at the limit of significance (13.4 months for regorafenib versus 9 months in the placebo arm, $p=0.06$). The toxicities of regorafenib are similar to those observed in GIST with the same therapeutic scheme (160 mg/d, 3w/4): fatigue (63%), hypertension (36%), cutaneous toxicity (44%), mucitis (44%) and diarrhea (44%). An adaptability and a flexibility of the doses/schemes is crucial, especially in patients presenting a clinical benefit with regorafenib. Very few patients had received pazopanib before their inclusion in the study: a new cohort of patients pre-treated with this anti-VEGFR has opened, still in the frame of this study. Phase III registration trial to be followed?

4. **Anlotinib (Jiangsu Chia-Tai Tianquing Pharmaceutical)** had never been tested in advanced STS. Multi TKI (VEGFR1/2/3, FGFR1/2/3, PDGFRa/b, c-KIT, RET…), the recommended dose coming from phase I is of 12 mg /d; 2weeks/ 3.

This Chinese study on 166 patients from 15 centres has included all classical subtypes of sarcomas (mainly synovial sarcomas 47 and leiomyosarcomas 26) pre-treated with anthracyclines (Chi et al, abstract 11005) : objective response rate of 11% (13% in Synovial Sarcomas and 46% in the included 13 ASPS, highly sensitive to anti-angiogenic factors), 3 months tumour control rate is of 57.2% and median PFS of 5.6 months. Toxicities seem acceptable despite the 5 cases of pneumothorax (remarkable in Synovial sarcoma lung metastases treated with an anti-angiogenic factor), and a dose reduction to 10 mg/d in 15% of the patients. A randomized study is ongoing in China. To be followed…

5. **Sunitinib (sutent®, Pfizer)** was rarely explored in STS in general but more often in histological subtypes sensitive to anti-angiogenic factors like Alveolar Soft Tissue Sarcomas (ASTS), entity driven by a specific translocation (X-17), well-known for its initial chemo-resistance, for its immediate or delayed metastatic feature and for its sensitivity to anti-VEGF. Sunitinib (37.5 mg/j) was tested in another subtype of STS driven by a specific translocation, extra-skeletal myxoïd chondrosarcoma (EMC), (t(9 ;22), NR4A3 fusion gene) : 6 partial responses (including one post pazopanib) and 3 stabilizations, median PFS of 34 months. The EMC responding to sunitinib harbour the fusion gene EWSR1-NR4A3, whereas non responders present the TAF15-NR4A3 (Provenzano et al, abstract 11059)

6. **Anti-PD-1/PD-L1:** It was time, the first results of the ongoing studies have been reported this year and immunotherapy in sarcomas has been the subject of an outstanding scientific meeting, beside the oral session. Last year, an analysis of the PD-L1 expression (positive if >10%) had been reported on a series of 82 patients presenting five different histological subtypes of STS (ASCO 2015, C. Kin, abstract 10565): positivity in 43% of the whole analysed population, 100% in epithelioïd STS, 53% in synovial sarcomas, 38% in rhabdomyosarcomas, and 33% in Ewing sarcomas. No expression in mesenchymal chondrosarcomas.
   a. The results of the SARC study (SARC 028) testing **pembrolizumab (Keytruda®, Merck)** (200 mg IV every 3 weeks) seriously shaves some of the excitement off our dreams of immunology in sarcomas: 80 patients included, no response in leiomyosarcomas, 1 response in Synovial Sarcomas, 2 responses in Liposarcomas and 4 responses in Undedifferentiated Pleomorphic Sarcomas (4 responses out of 9, 44%). Only UPS, because of their complexity and genomic density, because of the infiltration of immuno-skilled cells and their density, receptor of the major complex of HLA histocompatibility, seem to benefit from the inhibition of this pathway (often over-expressed in IHC in UPS, parallel oral communication). In bone sarcomas, only one response out of

19 osteosarcomas, no response in Ewing sarcomas (13 in total) and one response in chondrosarcomas (17 in total) (Tawbi et al, abstract 11006).

b. Same story with **nivolumab (Obdivo®, BMS**): administered at the dose of 3 mg/kg IV every 15 days in a phase II study exclusively focused on a series of 12 patients presenting pre-treated advanced uterine leiomyosarcomas, no objective response objective was reported (George et al, abstract 11007). Note that these tumours mostly express PD-L2.

c. Some anecdotal responses in a dedifferentiated chondrosarcoma treated with nivolumab, a partial response in an epithelioïd sarcoma, as well as in an osteosarcoma treated with the nivolumab + pazopanib combination (Paoluzzi et al, abstract 11047). The enthusiasm which was observed in the inhibition of this pathway in sarcomas slightly decreased at ASCO 2016. Are we moving forward potential combinations? (anti PD1 plus anti-CTLA4, anti PD1 plus anti-VEGFR ongoing…). Are we moving forward the discovery of new pathways or of new biological markers in sarcomas?

d. This was the point of the oral communication made by the French Sarcoma Group following the two previous studies which were desperately negative. Last year, it had been mentioned that the expression of PDL1 was an independent unfavourable prognostic factor in STS (5-year overall survival of 48% versus 68%, p=0.017) (ASCO 2015, C. Kin, abstract 10565). This is not the same in the 371 studied patients from the French Sarcoma Group database (positivity in 19% of the cases). Beside classical and well-known prognostic factors in STS, the expression of kynurenine (positive in 59% of the cases) is correlated to survival in a multivariate analysis, this is not the case with Indol 2-3 dioxygenase (IDO, positive in 42% of the cases), immunological pathway inducing tolerance (Toulmonde et al, abstract 11008). A modification of the macrophagic population infiltrating the tumours (decrease of M2 at the expense of the M1 inducing a T response) by Glucopyranosyl Lipid A (G100), a TLR4 agonist directly injected in the tumour with a simultaneous administration of radiotherapy could be another pathway to explore (Pollack et al, abstract 11017). Then, a mutation on the PTEN and PI3K pathways could partially explain the mechanisms of resistance to immunotherapies involving PD1-PDL1 (Bonta et al, abstract 11049)

■ Chemotherapies

Despite the emergence of targeted therapies, conventional chemotherapy still plays an important role in the management of metastatic STS.

1. **Trabectedin (Yondelis®, Pharmamar)**

- Last year, trabectedin (1.5 mg/m2 24 hours infusion) was compared to another chemotherapy: dacarbazine (Deticene®, 1000 mg/m2) in leiomyosarcomas and advanced liposarcomas (L-sarcomas) (ASCO 2015, G. Demetri et al, abstract 10503). Median PFS was significantly increased in patients treated with trabectedin (4.2 months) versus 1.5 months with dacarbazine ($p<0.001$). The 6-months PFS is of 37% for trabectedin, 14% for dacarbazine. All the subgroups of patients benefit from yondelis® compared to deticene®. No difference was observed in overall survival with a median of 13.7 months for trabectedin and of 13.1 months for dacarbazine (final analysis), probably because of the high number of administered products after tumour progression in one or the other therapeutic arm. Even though the primary objective was not reached, the results allowed the drug registration in the United-States in L-sarcomas in 2015. Cardiac toxicity was assessed in this population of patients pre-treated with anthracyclines. (median cumulated dose of 241 mg/m2 of doxorubicin): patients who received a cumulated dose > 300 mg/m2, a limited ventricular function (< to FEVG normal value, around 13% of the patients in both of the therapeutic arms), cardiovascular history and patients over 65 years old have a significant higher risk to develop a cardiac "disorder" (0.6% for dacarbazine, 4.5% for trabectedin) (Schuetze et al, abstract 11060). No significant difference between the two therapeutic options in terms of quality of life during chemotherapy, this quality of life is obviously extended for patients treated with trabectedin (72 patients who received at least 8 cycles versus 14 for dacarbazine) (Demetri et al, abstract 11061). In an interesting manner, PFS is similar independently of grade 3-4 liver toxicity (elevation of transaminases) (Calvo et al, abstract 11064). However, trabectedin plasma level is higher in patients who initially presented liver disorders. This justifies to start the first cycle at lower doses (0.9 mg/m2) in these high-risk patients.
- It is known that trabectedin, also has activity outside L-sarcomas as demonstrated in the big US review study covering 2005 and 2015 considering several published studies (442 patients). Median PFS is even of 6.8 months in synovial sarcomas, of 4.5 months in chondrosarcomas, higher to those observed in the L-sarcomas of the same institution (Syed et al, abstract 11052)
- Trabectedin was tested in association with olaparib (PARP inhibitor) so as to increase (theoretically) definitive and non-repairable DNA breaks in an Italian phase 1-2 study (Grignani et al, abstract 11018): the recommended dose is 1.3 mg/m2 for trabectedin and 150 mg/bid for olaparib, 26 evaluable patients with pre-treated STS, 4 partial responses (18%), 5 stabilizations (23%), no pharmacokinetic interactions between the two products. To be followed.

- Results of the Spanish study (GEIS-20) comparing doxorubicin first line therapy (75 mg/m2) versus doxorubicin (60 mg/m2) plus trabectedin (1.1 mg/m2 D1, 3hours) were reported during ESMO 2013. This study on 115 patients was finally negative in terms of PFS and OS (Martín-Broto J, et al. ECCO-ESMO. 2013: Abs Nº 3800). In the group of patients who had been treated with the combination doxorubicin + trabectedin, patients with an STS expressing CUL4A (involved in cell repair) had a better PFS (8.1 months) and OS (21.8 months) than the others (1.7 and 9.4 months respectively). CUL4A expression is therefore a predictive factor for response to trabectedin (J Martin-Broto et al, abstract 11048).

2. Eribulin (ET389, Eisai)

Microtubule polymerization inhibitor, eribulin (Bolus dose 1.4 mg/m2 at D1 and D8 every 21 days) was compared to dacarbazine in L-sarcomas in a phase III randomized study on 452 pre-treated patients (beyond 2nd line treatment). The primary objective is overall survival. The results were reported last year (ASCO 2015, late-breaking abstract, P. Schoffski et al, abstract 10502). Median PFS were similar (2.6 months in both therapeutic arms) but patients treated with eribulin have an overall survival which is significantly higher, 13.5 months versus 11.5 months for dacarbazine (P=0.019). Patients with liposarcomas where those who benefit the most from eribulin compared to dacarbazine in terms of overall survival. Eribulin was first registered in the US (end of 2015), then in Europe (beginning of 2016). What's new this year with eribulin?

- One communication focused on the liposarcoma population (143 treated patients, 71 with eribulin, 72 with dacarbazine) : the PFS of the patients in the eribulin arm is significantly higher than in the dacarbazine arm (2.9 versus 1.7 months, p=0.002), median number of administered cycles (6.6 versus 3.2), all types of liposarcomas benefit from eribulin in terms of overall survival (15.6 months vs 8.4 months, HR 0.43, p=0.001), the difference is more obvious in dedifferentiated and pleomorphic liposarcomas than in myxoïd/round cell liposarcomas (Chawla et al, abstract 11037).
- Patients progressing under eribulin (209 patients) have a better quality of life (physical activity, appetite and nausea) (EORTC QLQ-C30) than patients progressing under dacarbazine (191 patients) (p=0.0083), and this, both in the leiomyosarcoma liposarcoma groups (Hudgens et al, abstract 11015)

3. Anthracyclines/alkylants

- It is and it will probably always be difficult to beat doxorubicin as first line therapy in advanced STS. This was recalled by the GeDDis trial last year (ASCO 2015, B.M Seddon, abstract 10500). Doxorubicin is superior in terms of tumour control (65.9% versus 58.6%), simplicity of administration, treatment discontinuation due to toxicity

(2% versus 16%) and overall survival (71 versus 63 weeks) compared to the combination gemcitabine + docetaxel.

- A non-cardiotoxic anthracycline (no anti-topoisomérase B activity), the 5-imino-13-deoxydoxorubicin (GPX-150) was tested in phase 2 in more than 20 patients as first line therapy (Van Tine et al, abstract 11019), initial dose 265 mgm2: 41% 4 months clinical benefits, 1 partial responses and 8 tumour control, no grade 3-4 toxicity apart from haematological toxicity, very few cardiac toxicities (some reversible decreases of FEV).
- Except in leiomyosarcomas, doxorubicin associated with dacarbazine provides interesting results in first line therapy in solitary fibrous tumours (Saponara et al, abstract 11042) with 46% of objective responses, a median PFS of 6.3 months and a median overall survival of 18.7 months.
- No communication this year on **aldoxorubicin (INNO-206, CytRx Corporation)**. Aldoxorubicin is linked to a peptide (linker) linking to albumin (ASCO 2014, Chawla et al, abstract 10502) which, theoretically, then liberates doxorubicin in intra-cellular (2% of circulating doxorubicin). Patients inclusions in this ongoing registration study are closed and the results should be revealed in 2017.

4) What's new in some histological subtypes ?

1. **Giant cell tumours :** Practically every year at ASCO, since 2008, one scientific communication focused on GCTs which management and prognosis have radically changed since the emergence of denosumab (Xgeva®, Amgen). In this benign bone tumour with risk of local malignancy, the osteoclastic giant cells over-express RANK, and the stromal cells the RANK ligand. Denosumab is a monoclonal antibody against RANKL which inactivates this possible causal abnormality of this tumour (role of this mutation on histone 8 ?). More than 500 patients were included in a worldwide phase II study which was used for the registration of the drug in this indication, in several countries. The definitive results of this trial will be known in February 2017. Still pending questions are :1) for operable patients, duration of the induction treatment (short if curettage planned, longer in case of prosthesis ?), evaluation to histological response, type of surgery to perform in responders, role of adjuvant therapy (currently 6 injections recommended); 2) for inoperable patients, life-long treatment, therapeutic de-escalation (injections spacing, dose decreases) following induction therapy (duration ?), possible discontinuation ? Note this year, an extended follow-up of 97 patients in two centres with a median administration of denosumab of 23 months

(4-94 months) for patients mainly with inoperable GCTs (Chawla et al, abstract 11021): Two thirds of the patients had complete clinical response (symptoms disappearance) after 3 months, no radiological evaluation was reported (all stable due to tumour calcifications), 6% of mandibular osteonecrosis (median time of administration 37 months, older patients (50 years) than the median (35 years), one unusual traumatic fracture: some patients asked to stop the treatment for several reasons including desire of pregnancy. It will be interesting to follow the evolution of the inoperable patients who stopped the therapy. Are we moving forward a randomized study comparing discontinuation versus continuation of denosumab, versus injections spacing after a more or less long period of treatment (3, 5 years?)

2. **Synovial sarcomas (SS) :** Apart from a constant expression of PRAME (Preferentially Expressed Antigen in Melanoma) family antigenes compared to other STS histological subtypes (Roszik et al, abstract 11067), synovial sarcomas arising from a HLA-A2 population over-express NY-ESO-1 (like myxoïd/round cells liposarcomas). Vaccination tests following cytapheresis, T lymphocytes ex vivo expension, conditioning by high doses of cyclophosphamide and fludarabine and re-injection of these T lymphocytes are currently ongoing in metastatic synovial sarcomas with quite interesting – not to say surprising – preliminary results in this population (very long responses following a single injection).

3. **Chordomas:** rarely celebrated, these chemo-resistant tumours arising from the neural crest had already been addressed, last year, in a phase II study, coordinated by the French Sarcoma Group, testing sorafenib (Nexavar®, Bayer), 800 mg/d, in advanced chordomas (ASCO 2015, N. Penel et al, abstract 10520) : 27 patients included, majority of sacral chordomas (77%), metastatic in 58% and often widely pre-treated (surgery / radiotherapy /systemic treatments). 12 months PFS was of 63% for the rare non-pre-treated patients with a partial RECIST response) and of 47.1% for pre-treated patients. The overall survival was of 86% after 12 months. This year, the same group reports a retrospective study on 79 patients: majority of males (60%), median age 59 years (12-86), sacral location 63% of the cases, skull base in 22% of the cases, 1/3 of the cases are metastatic. In first line therapy, patients received imatinib in 77% of the cases, sorafenib in 14% and Erlotinib in 5%. Note that 5 partial responses (6%) (3 with imatinib, 1 with sorafenib and 1 with erlotinib), 42% of them had less symptoms, median PFS is of 10.5 months, the average overall survival is of 59 months (Lebellec et al, abstract 11020). The multivariate analysis on survival highlights 4 independent parameters: age, sacral location of chordoma (better prognosis), symptoms requiring morphine derivatives and the absence of metastases.

4. **Chondrosarcomas :** Among all the well-known prognostic factors, the histo-prognostic grade is the only factor that really influences patients' survival. A mutation of the IDH gene has been found in 33.7% of the analysed cases, 21.2% on the IDH1 gene, 12.5% on the IDH2 gene in a series of 80 patients treated between 1966 and 2000 in Warsaw (Lugowska et al, abstract 11024). These mutations provide a lower overall survival compared to non-mutated chondrosarcomas. The combination of a HDAC inhibitor and of a proteasome inhibitor is synergetic on mutated chondrosarcoma cell-lines. (Tinoco et al, abstract 11027)

5. **Extra-skeletal osteosarcomas (ESO) :** These "osseous" tumours in "soft tissues" were presented last year through a big retrospective study on 147 patients thus highlighting the crucial aspect of local treatment quality (R0 surgery versus R1, p=0.003) (ASCO 2015, A. Longhi et al, abstract 10526). This year, it seems that patients receiving a platinum based pre-operative chemotherapy are the ones who benefit from a longer survival (Paludos et al, abstract 11025).

6. **Fibromatosis/desmoïd tumours:** A lot of communications this year on this benign tumour with risk of local malignancy compared to the previous years:
   - After the remarkable activity of sorafenib in 2011 (65% of RECIST responses, 35% of stabilization) (ASCO 2011, Gounder et al, abstract 10013) and of sunitinib in 2013 (26% of objective response, 42% of stabilization) (ASCO 2013, Jo et al, abstract n°10589), it is now the turn of navelbine (90 mg weekly total dose more or less associated with hormone therapy (LH-RH plus tamoxifen previously started in 50% of the cases) (Mir et al, abstract 11050) : 50 patients, 74% of females, median age of 35 years, 20% of intra-abdominal, median size 11 cm (3.7-29 cm) practically all progressive at the time of inclusion (88%). Median treatment duration is 10.8 months (2-26.2 months), no grade 3-4 toxicity. Symptom improvements in 80% of the cases after 3 months, RECIST objective response in 32% of the cases, stabilization in 58% of the cases, progression in 10% of the cases. 12 months PFS = 88%. Following a new progression, navelbine was restarted in 6 cases with 2 novel partial responses and 4 stable disease. Undoubtedly, one of the best treatments in desmoïd tumours (tolerance, no specific follow-up, efficacy, cost…). Are we moving forward a randomization in responders (partial response + stable disease) after 6 months between discontinuation versus continuation ? Are we moving forward a randomization in non-progressive, non pre-treated between navelbine and surveillance? New standard in desmoïd tumours?

- Preliminary reported in 2015, the results were updated this year: at the time of the last analysis, none of the 17 included patients (progressive at the time of inclusion) had progressed under the gamma-secretase inhibitor (anti-Notch, PF-03084014, 200 mg/) with 4 partial responses and 13 stable diseases (O Sullivan et al, abstract 11028). To be followed…
- Caelyx is still a therapeutic option in these aggressive fibromatosis: 36 patients of the same institution were treated with an anthracycline (Mont Sinai, New York), including 29 with caelyx: one complete response, 10 partial responses (43% of objective response), 10 stable diseases, 5 progressions (Pang et al, abstract 11032), median PFS = 41.6 months. Caelyx remains the preferred treatment in symptomatic fibromatosis which require rapid response. Then the confirmation of the efficacy of sorafenib in 79 patients treated in Brazil (including 62% in first line) on a median duration of 13.6 months (Munhoz et al, abstract 11065) : as it can be observed in other active products for desmoïd tumours, more than 50% of the patients do not re-progress after the discontinuation of sorafenib. Doses of this drug had to be reduced in 59% of the cases for toxicity reasons.

7. **Ewing sarcomas:** Ewing sarcomas in older patients (> 50 years) are rare. They mainly develop in soft tissues (76%), are often metastatic at diagnosis (27%), with a poorer prognosis than in young adults (3-years PFS and OS = 62.2 and 73.3%) according to a French Sarcoma Group retrospective study on 77 patients from 50 to 86 years old (Rochefort et al, abstract 11023). This seems to be due to a sub-optimal administration of chemotherapy in these older patients. (These patients cannot be included in the 1999 Euro-Ewing trial previously reported).

5) Miscellaneous:

- The most frequent relevant genetic abnormalities (by Next Generation Exome Sequencing, 300 analysed genes on 50ng of DNA from 100 patients) and adapted to targeted therapies currently available on the market are: CDK4 amplification (22%), mutation or loss of CDKN2A/B (16%), MDM2 amplification (21%) and more incidentally, PIK3CA, Notch2, NTRK1/3, KDR and PDGFR mutations (Groisberg et al, abstract 11046). Among those that are not necessarily "applicable" with a specific treatment, we find p53 and Rb1 mutations (Bonta et al, abstract 11049).
- Several years after the war of the histo-prognostic classifications in STS (French grading system), the hostilities are relaunched in predictive/prognostic molecular signatures: The STS profile designed by the Fox Chase Center (Thirty selected genes)

seems more relevant than the CinSarc signature in the discrimination of STS with good and poor prognosis. However, this comparison was made on a limited number of patients (Movva et al, abstract 11055). To be followed attentively.