2007 ASCO-REPORT
SOFT TISSUE & BONE SARCOMAS

Author (French): Axel Le Cesne, Gustave Roussy, Villejuif
Translation (English): Estelle Lecointe-Artzner
Review (English): Roger Wilson

ASCO 2017 was a very good event for soft tissue sarcomas and GISTs. A better biological/ cytogenetic understanding in general turns of each histological subtype identifying a potential target for new therapeutic approaches that will appear in the coming years. The intra-cellular signalling pathways are being unravelled in each histological subtype and molecular biology techniques are booming. Clinical trials are now based on molecular abnormalities (causative for some of them, secondary for others). Just this once, the most interesting communications dealt with biology and immunotherapy in sarcomas, with poster sessions as well as parallel sessions (like the one on GISTs) and the plenary have caught everyone's attention.

Sarcoma biology

Sarcoma biology was undoubtedly the star of this ASCO which offered many papers of great importance and high level science on this topic. Last year, the arrival of NGS (Next Generation Sequencing, 300 analysed genes on 50ng of DNA of 100 analysed patients had already allowed the detection of relevant gene abnormalities which could be matched to the targeted therapies which were currently available on the market: CDK4 amplification, loss or mutation of CDKN2A/B, mdm2 amplification and, more incidentally, PIK3CA, Notch2, NTRK1/3, KDR and PDGFR mutations (ASCO 2016, Groisberg et al, abstract 11046). Among the not necessarily «actionable» mutations with a specific treatment, p53 and Rb1 mutations could be found (ASCO 2016, Bonta et al, abstract 11049).

New this year: two brilliant papers focused on this technical approach which could be integrated in our future clinical decision-making process. One focused on 5749 patients (between 2012 - 2016), 56 different histologies, and more than 300 genes tested (M.M. Gounder et al, abstract 11001), the second one focused on 587 patients, and more than 300 genes had also been tested (A. Italiano et al, abstract 11002). What are the key messages uncovered by such approaches in soft tissue sarcoma?

Besides immuno-histo-chemistry (IHC) and clinical understanding, the input of genomics has allowed us to refine diagnosis and/or to modify it in about 5-10% of STS cases. Still, genomics cannot be, for any case, a substitute for a pathologist specialized in STS.

- In about 40 to 50% of cases, «actionable» mutations have been identified. Half of them could benefit from a «personalized» treatment in an ongoing study evaluating a specific drug active for one of these detected gene mutations/alterations.
- A full clinical-biological match is still missing in this type of approach (only 2% of the patients were tested in the American study).
- More than 60.000 mutations and 1.200 fusion genes could be identified with this technique, 8% of them could benefit from a treatment with market authorization, 10% from a treatment with a market authorization in another indication than sarcoma, 40% from a drug being evaluated in an ongoing phase I clinical trial.
- About 10% of the patients with STS harbour germ-line mutations.

- Alterations in genes involved in the cell repair process were identified in 5% of the sarcoma cases and fusion genes notably involving ROS, ALK, BRAF, NTRK, IDH1, SMARCB1, PI3K and FGF, all of which open up huge therapeutic prospects.
- Desmoïd tumours, epithelioïd hemangioendotheliomas, rhabdoïd tumours and chondrosarcomas show lower mutational change than LMS, MPNST, UPS, GIST and osteosarcomas, 5% of all STS have a mutational change superior to 10 mutations per mega base.
- However, there is still a need to prove that the identification of a gene alteration associated with an appropriate and specific treatment can prolong patients' survival. This is the aim of the Multisarc study - presented in discussion – which randomizes patients between «standard» and «adaptive» approaches. In the event that there would be no evidence of longer survival with this very expensive technique (4.000 Euro/Patient), all the therapeutic approaches and considerations listed above would then become obsolete and useless.

Localized soft tissue sarcomas: adjuvant setting

No session on this topic this year. At most, two studies on cost-effectiveness regarding optimal follow-up of patients operated for a localized STS and the frequency of surveillance of these patients. Which radiological checks are really useful for better detection of potential lung metastasis for which early identification could lead to a survival benefit by anticipating their radical resection? A retrospective study assessing the cost-effectiveness of each radiological method according to a mathematical formula, clearly demonstrates that a simple standard Chest X-ray imaging is the simplest, the more effective and the least expensive radiological tool compared to Chest CT Scan and even more to PET-Scan (T. J. Royce et al, abstract 11021). More surprisingly, an optimal follow-up (CT Scan/MRI of the tumour site every 6 months) does not allow more «curative» surgeries for lung metastasis in our patients than in those who were followed by a non-optimal imaging (> 6 months), or even than in those who never receive routine imaging ! (Lim et al, abstract 11069). The Chest CT-Scan could be justified only in high-risk STS. Who are they?

A simple app called «sarculator» can be downloaded for free on the internet (http://ww.sarculator.com/). Based on the characteristics of the tumour, sarculator evaluates the risk of tumour recurrence (reliability gap of 5%) in patients with localized, resected STS. This app facilitates the individualization of the therapeutic strategy for patients in a population identified as high risk. The nomogram is based on the Italian trial which compared 3 cycles of pre-operative chemotherapy versus +/- 2 cycles in the adjuvant setting. There are 3 categories of patients: low risk, intermediate risk and high risk of metastatic relapse (S. Pasquali et al, abstract 11016). It is interesting to note that patients included in this Italian study and who all received 3 or 5 cycles of chemotherapy, 1/3 had a low risk of metastatic relapse (26%, 78% of survival), 1/3 had an intermediate risk (31%, 63% of survival) and 1/3 – obviously the one who really needed peri-operative chemotherapy – had a high risk of recurrence (48%, 46% of survival). Are we moving to

adopt and integrate the Sarculator in our therapeutic decisions when considering a systemic treatment in peri-operative setting for a high grade sarcoma? Other prognostic classifications, like the ones of Miettinen/Joensuu, are very useful when an imatinib adjuvant treatment is considered in resected localized GISTs. The same could be expected in high grade STS with this type of nomogram.

In a series of 212 malignant phyllodes tumours (mammary sarcomas), a radical treatment based on mastectomy is the gold standard for these tumours which are often large at diagnosis (median size 5.8 cm) arising at the median age of 52 years. Mastectomy could not be avoided in 41% of the cases at initial surgery and it was necessary in 72% of cases (on the whole patient population) mainly because of inappropriate/incomplete initial surgery (40% of R1/R2 resections). A very large mastectomy (around 1 cm of margin) does not make any difference compared to a standard «R0» mastectomy. R0 mastectomy is often performed when a biopsy has been done pre-operatively (86% of the cases in this French Sarcoma Group retrospective series). Adjuvant radiotherapy or chemotherapy were given in 43% and 13% of cases respectively, their impact on overall survival still needs to be proven (M. Neron et al, abstract 11055)

Localized Soft Tissue Sarcomas: the neo-adjuvant setting

Induction systemic treatment and/or radiotherapy in first line are frequently used by specialized centres to treat locally advanced sarcomas. The Italian randomized study comparing conventional chemotherapy (Epirubicine: 120 mg/m2 D1 plus ifosfamide: 9 g/m2 total dose) to chemotherapy adapted to the histological sub-type was reported at ESMO in 2016 and has just been published (Gronchi et al, Lancet Oncol 2017). Three cycles chemotherapy based on anthracycline and ifosfomide could then become a therapeutic standard (in the absence of other scientifically proven alternatives) in neo-adjuvant setting in high risk STS of the extremities and of the chest wall (50-70% according to Sarculator) if surgery can be facilitated by such an approach. The 90% rate of R0 resection with an induction conventional chemotherapy could partially explain the 62% rate of 5 year-progression free survival which was observed in this study. This rate is superior to the 44% of PFS which can be obtained when this chemotherapy is administered in post-operative setting (around 50% of R0 resections) in the same patient population in an earlier study. Some ancillary studies are currently ongoing in order to try and better identify the population which could benefit the most from this therapeutic approach. The results of this study allow the systematic referral of patients with localized STS (90% of patients present with localized disease at diagnosis and are therefore potentially curable) to sarcoma specialized multidisciplinary teams to: 1) discuss the utility of any induction chemotherapy for each individual 2) organize planned surgery preceded by appropriate imaging 3) confirm the histological subtype of the STS with more and more sophisticated molecular biology techniques, thus permitting the optimization of the initial management of sarcoma patients with a significant benefit on their outcomes (Blay et al, ESMO 2016).

Some important papers reported this year on the same topic:

- A better definition of good histological responders to neo-adjuvant chemotherapy (S. Cousin et al, abstract 11014): in a mono centric series on 150 patients, the 40 patients (26.7%) with good histological response (< 10% of identifiable tumour cells on the surgical samples) have a better overall survival than the poor responders. Undifferentiated sarcomas and locally advanced tumours present the highest good histological response rates. The functional MRI performed after two cycles of chemotherapy allows a better prediction of differential histological response between good and poor responders, just like the evaluation according to CHOI criteria which was reported last year, in contrast to RECIST criteria (ASCO 2017, Stacchiotti et al, abstract 11044).
- The Radiation Therapy Oncology Group has evaluated the impact of complete histological responses (pCR) in its two consecutive pioneer studies, the first one exclusively using induction radiotherapy (RTOG 0630, 51 patients), the second one combining chemotherapy with radiotherapy (RTOG 9514, 72 patients (D Wang et al, abstract 11012). In the radiotherapy study 20% of patients obtained pCR together with 27% of the patients who received combined therapies. All pCR patients show a significantly increased 5 year survival with no local recurrences and 2 year overall survival was 100% vs 76.5% at 5 years for the non pCR patients in the RTE+CT study and 56.4% in the study with radiotherapy alone.
- Patients presenting a neutrophils ratio on lymphocytes > 2.5 (58% of the patients in this series of 529 patients with localized STS) have a lower survival (multivariate analysis). Should this be integrated in future peri-operative systemic studies?

Systemic treatments in advanced setting

New drugs >>> targeted therapies:

1. **Olaratumab (Lartruvo®, IMC-3G3, Lilly)** is a monoclonal anti-body (IgG1) against PDGFR alpha receptor – a target which is often involved in STS and increases the activity of Doxorubicin in pre-clinical models of sarcoma. It was the scoop of last year! Administered at the dose of 15 mg/kg on Day1 and Day8, olaratumab combined with doxorubicin (75 mg/m2 D1) and compared to doxorubicin only (randomized phase II) increases the rate of objective responses (18.2 vs 11.9%, non significant), Significantly, the median PFS (6.6 vs 4.1 months, p=0.061, HR=0,672, unilateral statistic test, α=0,10) and overall survival (25 vs 14.7 months, p=0.0004) (ASCO 2015, Tap et al, abstract 10501). It was certainly the most interesting research paper in STS last year. A registration phase III study is ongoing in first line treatment and is already closed to recruitment. Expected results in 2018. Olaratumab is currently being tested in combination with gemcitabine docetaxel (+/- olaratumab) and in association with pembrolizumab (phase I).

2. **Pazopanib (Votrient®, GW786034, GSK/Novartis),** VEGF, PDGF and KIT inhibitor obtained its market authorization in the US and in Europe in 2012, following the results of the PALETTE phase III randomized study, reported during ASCO 2011 (Van Der Graaf, abstract no. LBA10002). What's up this year on this topic?
   a. A multicentre phase II trial testing pazopanib in Solitary Fibrous Tumours (SFT), a population of STS showing sensitivity to anti-VEGFR - (JM Broto et al, abstract 11003) – maybe their more malignant form is more highly vascularized than the typical SFT, all expressing STAT6 (with IHC or FISH): 34 patients included, median age 61 years, median size at diagnosis 77 mm. The objective response rate according to CHOI criteria is of 52% (22% of stable disease) vs 3% (61% of stable disease) according to RECIST criteria, median PFS is 5.5 months and the 18 months survival rate is 72%. The very dedifferentiated forms of SFT seems to show poorest prognosis than the others. The evaluation of pazopanib in typical SFT (sometimes also called benign) is ongoing in this study which confirms the efficacy of anti-angiogenesis factors in these subtypes of STS, better evaluated with CHOI criteria than with RECIST.
   b. Pazopanib was also tested in Extraskeletal Myxoïd Chondrosarcomas (EMC) in a French-Italian-Spanish phase II study (S. Stacchiotti et al, abstract 11062): 24 patients included, most of them in first line (86%), centralized pathological review and confirmation of the NR4A3 gene rearrangement. One partial response (5%), 75% of stabilized diseases, 2 progressions, clinical benefit of 65%, 13 months median PFS, and 29% of non progression at 18 months. Three partial responses were necessary to consider this trial as a success, however, some patients seemed to benefit from pazopanib.
   c. One of the pazopanib mechanisms of resistance could be due to an up-regulation of the endoglin receptor under the effect of VEGF inhibition. The TRC105 – antibody against endoglin had been tested (from 8 to 10 mg/kg weekly) in association with pazopanib in a phase II which was reported last year (ASCO 2016, Attia et al, abstract 11016). Two angiosarcomas were in complete remission with the combination and 6 others had clinical improvements (8/9 with clinical benefit, 88%). A randomized study in metastatic angiosarcomas has started (200 patients) in several countries (RL Jones et al, abstract TPS11081)

3. **Regorafenib (Stivarga®, Bayer):** The results of the randomized trial coordinated by the French Sarcoma Group (Regosarc) in STS which had been reported last year. (ASCO 2016, Penel et al, abstract 11003) could be fully compared to the ones obtained with pazopanib, already registered in this indication. The follow-up of this study shows that the benefit of regorafenib in patients initially randomized in the placebo arm (81% could cross-over) is similar, in terms of median PFS, than the one observed in patients who initially received regorafenib (Kotecki et al, abstract 11052). This year, regorafenib has been tested (Study SARC024) in adult Ewing sarcomas and related (> 18 years) (S Attia et al, abstract 11005):

30 patients included, median age 32 years, median number of prior therapeutic lines of 5 (1-10). The more frequent toxicities were: hypophosphoremy, decrease of the dose for 40% of the patients. The objective response rate (RECIST) is 10%, the median response duration of 5.5 months, and median PFS 3.6 months, with 18/30 non progressive patients after 2 months (primary endpoint). The French Sarcoma Group Regobone study, currently recruiting, will help to clarify the efficacy of regorafenib in bone tumours (vs placebo with cross-over in case of progression).

4. **Cediranib (Recentin®, Astra-Zeneca)**: potent selective antagonist of the VEGF pathway (anti-VEGF1, 2 and 3) and KIT, cediranib had been tested (30 mg/d) in 36 patients affected by alveolar soft part sarcomas (ASTS), an entity driven by a specific translocation (X-17) (ASPL-TFE3), characterized by a well-known initial chemoresistance, by an immediate or delayed metastatic setting, and by its already well-known sensitivity to anti-VEGF (ASCO 2011, Kummar et al, abstract 10001). Practically all the patients have a decrease of their targeted lesions when under treatment (some rare exceptions), 40% of them reaching significant radiological partial responses (RECIST), some others showing non-significant decrease for a 6-months clinical benefit of 78%. Practically all the patients benefit from a metabolic improvement (FDG-PET or functional MRI) when under treatment which down-regulates the expression of the genes involved in the vascularization like FLT1, KDR, ESM1 or the angiopoiétine 2. The CASPS randomized study was expected: cediranib vs placebo, ratio 2 :1, progressive patients before inclusion, 48 patients included between 7/2011 and 7/2016 in 12 sites, median age 31 years (IR Judson et al, abstract 11004). The remarkable activity of cediranib is fully confirmed compared to placebo : decrease of the tumour volume (p=0.0013), objective response (p=0.053), median PFS 10.3 months vs 3.7 months, 1 year survival 96% vs 64.3%. This study notably highlights the feasibility of organizing a randomized study in an extremely rare STS (incidence about 1% of STS, about 40 cases per year in France).

5. **Tazemetostat (Epizyme™),** potent inhibitor of the EZH2 pathway is tested in 4 cohorts of patients affected by STS in which the INI1 pathway is inactivated, whatever the mechanism of inactivation. The results were reported in 2 cohorts: 1) synovial sarcomas in which SS18-SSX translocation induces an exclusion of INI1 from the complex SWI/SNF: 33 pre-treated patients included, no objective response, 30% of stabilized disease. The main secondary side effects are cough, dyspnoea, fatigue. Are we moving forward a combination tazemetostat/doxorubicin where a synergy can be observed in a pre-clinical context? (Schoffski et al, abstract 11057); 2) Epithelioid sarcomas (ES) presenting a loss of the INIl expression: 31 pre-treated patients included, 4 partial responses, (13%), 6 stable diseases (19%). Given the relative chemo-resistance of these tumours with the classical drugs prescribed in STS, pazopanib included (0/20 responses) (AM. Frezza, et al, abstract 11065), these promising results have led the investigators to increase the number of patients in

this cohort (M. Gounder et al, abstract 11058). The other open cohorts are rhabdoïd tumours, medullar renal carcinomas and all the other INIl negative sarcomas.

6. Anti-PD-1/PD-L1: It was about time! Several communications dealt with immunotherapy in soft tissue and bone sarcomas. This is not the expected revolution yet…

a. The definitive results of the SARC study (SARC 028) testing **pembrolizumab (Keytruda®, Merck)** (200 mg IV every 3 weeks) were reported: 86 patients included, 80 patients evaluable for response. The overall rate of objective response is 18% and the 3-months PFS 55%: 4 responses in the UPS (4 responses including one complete response on 10, 40%), 2 responses/10 in liposarcomas, 1 response/10 in synovial sarcoma, no response in leiomyosarcomas (MA Burgess et al, abstract 11008). Because of their complexity and of their genomic density, the UPS seem to be the only ones to benefit from the inhibition of this pathway (more often over-expressed in IHC in UPS). An extension cohort has been planned in UPS and LPS.
In bone sarcomas, the overall response rate is 5% and the 3-months PFS 28%: Only 1/22 response in osteosarcomas, 1 response/5 in chondrosarcomas, no response/13 in Ewing sarcomas. Over the 70 samples tested before any treatment, only 3 patients over-expressed PD-L1, they were all affected by UPS, all responders to pembrolizumab (including complete response) and all presented lymphocytes T CD8+ infiltration. Are we moving toward an «immunologic» treatment with anti-PD-L1 only in rare sarcoma subtypes over-expressing this pathway? The addition of oral cyclophosphamide (50 mg twice a day, one week out of 2) with pembrolizumab (PembroSarc study) does not modify in any case the disappointing results of the PD-1 inhibitors in STS (M. Toulmonde et al, abstract 11053): Only one objective response in 50 evaluable patients, no non-progressive patient after 6 months in the cohort of patients with LMS or UPS. The only responder was the only patient harbouring PD-L1 positivity in more than 10% of the tumour cells. The IDO1/kynurénine immunosuppressive pathway activated by PD-1 inhibitors could explain the disappointing results of these approaches exclusively based on PD-1/PD-L1inhibitors in STS. Note that the expression of PD-L1 confers a poorer prognosis in localized osteosarcomas than in the others, in contrast to the infiltration of the CD8 in an Italian study on 86 patients (Palmerini et al, abstract 11025). Are we moving forward to anti PD-1 plus IDO1 inhibitors combinations?

b. Same story with **nivolumab (Opdivo®, BMS**), 3 mg/kg IV every 15 days more or less combined with **iplimumab (Yervoy®, BMS)** (1 mg/kg every 3 weeks) in the frame of a phase II study of the Alliance programme (SP d'Angelo et al, abstract 11007): 85 patients included, all pre-treated, all STS subtypes and bone tumours. The objective response rate is of 5% (2/38) and median PFS of 2.6 months with nivolumab alone, 16% with the combination (6/38) and a median PFS of 4.5 months and a 6 months PFS

of 36%. Note that 14% of the patients had to stop the combination treatment because of toxicities. Ancillary studies are ongoing to better define the group(s) who could benefit from the combination.

c. Alveolar Soft Part Sarcomas (ASPS) which are particularly sensitive to anti-angiogenic factors certainly represent a niche (1% of all STS) in which anti PD-1/PD-L1 inhibitors could develop. On 4 treated patients, 1 complete response, 2 partial response and 1 stable disease (S. Salh et al, abstract 11059), but not necessarily correlated to PD-1/PD-L1 status but to mutations in the domain of Mismatch Repair (MMR). To be closely followed.

Chemotherapy

Despite the rise of targeted therapeutics, of personalized medicine, of molecular biology, conventional chemotherapy still occupies a prominent place in the armoury for metastatic STS.

1. **Trabectedin (Yondelis®, PharmaMar):** few communications on the topic this year:
   The administration of trabectedin in association with radiotherapy is feasible and efficient (Gronchi et al, abstract 11061): in an Italian-Spanish phase I study (TRASTS trial), in which doses of trabectedin were progressively increased from 1.1 mg/m2 to 1.5 mg/m2 (24h infusion) for a fixed dose of radiotherapy (45 Gy, 25 fractions, 1.8 Gy/fraction), the results are interesting in terms of tolerability (no DLT to the maximal dose routinely used in STS) and efficacy (40% of objective response in a population exclusively composed of locally advanced, operable round cell/myxoid liposarcomas. Note that a complete histological response was obtained in 25% of the patients.

- If the expression of CUL4A (involved in cellular repair) was highly predictive of trabectedin response in first line chemotherapy (doxorubicin-trabectedin combination, GEIS20 study) last year (ASCO 2016, J. Martin-Broto et al, abstract 11048), the expression of FAS (identified on the primary tumour) significantly induce a poorer PFS, especially in the L-STS population (liposarcomas and leiomyosarcomas), and a lower median of overall survival (11.9 months in FAS+ STS vs 21.7 months in FAS- STS) (J.M. Broto et al, abstract 11071). The Spanish Sarcoma Group also defined a prognostic score (GEISTRA) to distinguish good and poor responders to trabectedin based on: the histological subtype (L vs non L-STS), the performance status, the free interval between diagnosis and metastatic relapse. The median survival varies from 2.5 months to 25.7 months with this tool (J. Martinez-Trufero et al, abstract 11070)

2. **Anthracyclines/alkylants**

- The results of the randomized trial evaluating **aldoxorubicin (INNO-206, CytRx Corporation)** were expected (S.P. Chawla et al, abstract 11000). Recall that aldoxorubicin could easily be compared to doxorubicin in first line therapy in a phase II study which was reported in 2014 (ASCO 2014, Chawla et al, abstract 10502) in terms of response rates and median PFS.

Aldoxorubicin is attached to a peptide (linker) binding to albumin which, theoretically, then release doxorubicin in intracellular in an acid environment (2% of circulating doxorubicin). In this phase III study, Aldoxorubicin (350 mg/m2 D1 corresponds to a dose of 260 mg/m2 of doxorubicin) was compared to one of the 5 protocols chosen by the investigators: pazopanib, dacarbazine, doxorubicin, ifosfamide, gemcitabine plus docetaxel. The study enrolled 433 patients in 79 countries and L-sarcomas represented 57.5% of the included patients: no significant differences in terms of median PFS. 4.1 months with aldoxorubicin, 2.96 months with the other systemic treatments (p=0.12), significant difference on the population of L-STS, significant difference on the US and Australian cohorts of patients (4.21 months vs 2.96, p=0.007) vague interpretation. More tumour control in the aldoxorubicin arm (30.3% vs 20.9%) to the detriment of a higher grade 3-4 toxicity (61% vs 46.4%) survival? It is a pity to build a phase III validation trial (superiority compared to doxorubicin) on bases so far from the initial phase II pattern. 2/3 of the patients included in this study had received doxorubicin before their inclusion in the protocol! We can single out a « re-challenge », but in patients who progressed or relapsed after doxorubicin. There is no better way to kill a promising drug!

- Supplanting **doxorubicin** in first line therapy in advanced STS still remains a challenge, either administered in bolus or in continuous infusion (L.D Cranmer et al, abstract 11023)

Histological subtypes

Giant Cell Tumours: Almost each year at ASCO, since 2008, a scientific communication dealt with GCTs for which management and prognosis have been radically changed with the rise of denosumab (Xgeva®, Amgen). In this benign bone tumour with local malignancy, osteoclastic giant cells over-express RANK and the RANK ligand for the tumour cells. Denosumab is a monoclonal antibody against RANKL which therefore inactivates this pathway, apparently secondary to an epigenetic mutation on H3F3A histone (found in 80-90% of the cases). This year, a communication reported on 87 patients with GCT operated after an induction treatment with denosumab (P. Rutkowski et al, abstract 11026). The median duration of administration of denosumab is 7 months (range 1.5-35 mths), 45% of patients have had radical surgery (en bloc resection with more or less orthopedic prosthesis) and 55% had simple curettage, 17 patients received adjuvant denosumab. All the patients respond to denosumab, 15 patients have locally relapsed (13/15 following scaling), but they all respond once denosumab was re-introduced. The median duration of administration of denosumab is longer in patients who underwent radical surgery than in the patients who had curettage. The 1-year PFS (since surgery) is 92% for the first group (radical resection) vs 76% for the group of patients treated by curettage (P=0.01). Are we moving forward a longer treatment (in adjuvant setting) for patients who undergo curettage?

Pigmented Villonodular Synovites (PVNS): Recall that the 4th therapeutic proof of concept (after imatinib in GIST and the Darier-Ferrand Dermatofibromatosis, and denosumab in giant cell tumours) was reported in 2014 with two CSF1R inhibitors in PVNS also known as Giant Cells Tumours of the

tendons (PVNS/GCTT) induced by a specific chromosomic translocation t(1-2) (CSF1-COL6A3) in 2/3 of the cases : **PLX3397 (Plexicon®, Daiichi)** small molecule (TKI) specifically inhibiting CSF1R, KIT and Flt3 (ASCO 2014, W. Tap et al, abstract 10503). And **RG7155 (Roche)**, monoclonal antibody against CSF1R (ASCO 2014, Cassier et al, abstract 10504). The results were remarkable. PLX3397 is pursuing its development with a randomized study (PLX3397 vs placebo, randomisation 2:1 which results will be revealed soon. Some liver toxicities (increase in bilirubin level in 3 patients) explain that the initial dose (1000 mg for 2 weeks then 800 mg/day) could be modified in the future. This study integrates sophisticated surveys (PRO: Patient Reported Outcomes), critical and relevant tools evaluating all the subjective and functional inconveniences related to this disease but difficult to measure with the conventional radiological means (C. Peterfy et al, abstract 11048) H. Gelhorn et al, abstract 10521). Another monoclonal antibody against CSF1 receptor (cabiraluzimab, Cabira®) was administered in 22 patients in an ongoing phase I-II trial (recommended dose, 4 mg/kg) also showing a remarkable activity in a large majority of patients (KK Sankala et al, abstract 11078). Note that an increase of CPK was observed in 46% of the patients and 36% of the cases experienced a skin rash. To be closely followed.

Angiosarcomas: The addition of bevacizumab to the weekly taxol had no impact on pre-treated advanced in a non-comparative randomized phase II study reported in 2014 (ASCO 2014, Penel et al, abstract 10501). In a recent ancillary study, a high level of VEGF-C circulating at D1 and a decrease of FGF circulating between D1 and D8 during the first cycle of taxol +/- bevacizumab) confers patients a lower PFS in both of the therapeutic arms (Lebellec L et al, abstract 11024).

Chordomas: A retrospective series of 38 Chinese pre-treated patients included between 2003 and 2015 reveals that an adjuvant radiotherapy by IMRT (radiotherapy with intensity modulation, 60 gy in median) allows a better tumour control than gamma knife (6-8 sessions) in operated localized chordomas with a 5-year local control of 35.5% with IMRT vs 22.2% (S. Lu et al, abstract 11033).

Osteosarcomas (OS): Several communications this year in osteosarcomas:
1) The interesting efficacy of **apatinib** (anti-VEGFR2) in a small series of 26 metastatic pre-treated patients with 42% of objective response, a median PFS of 8 months, a 1-year PFS of 51.3% for patients who received apatinib in 2nd line therapy in advanced setting and a median survival of 68.7% (W. Yu et al, abstract 11031);
2) Radiation-induced localized osteosarcomas (in median 11.5 years after radiotherapy, 60 Gy of median dose) present poorer prognosis than sporadic osteosarcomas in terms of PFS (median 12.2 months), overall survival (27.6 months) which could be explained by their axial predominance and a more advanced age (61 years in median) despite a similar sensitivity to induction chemotherapy and a smaller median size at diagnosis (B. Siontis et al, abstract 11018). A retrospective analysis performed on 419 cases of secondary sarcomas highlights the following: regarding STS developing in a previously irradiated area (median time delay of 11 years), the fact they have also received chemotherapy (of any kind) at the time of the primary tumour (of any kind) significantly decreases (p=0.009) this median

time delay between the treatment of the primary tumour and the development of the sarcoma (A.Y. Zhang et al, abstract 11046);
3) The identification of the «activatable» targets in osteosarcomas is limited to some PI3KCA mutations in chondroblastic osteosarcoma, one GNAS mutation in osteoblastic osteosarcoma and a KRAS mutation in fibroblastic osteosarcoma. Only 2% of the analysed patients could be included in a study of personalized medicine. The more mutated gene is p53 (J.A. Livingston et al, abstract 11019). The genetic alterations of osteosarcoma metastasis are different from those observed in primary tumours (J. Wang et al, abstract 11029) which remain a very heterogeneous group of tumours. Finally, to be fully complete on the topic, osteosarcomas expressing PD-L1 (according to initial biopsy) have a poorer prognosis than the others, in an Italian series of 86 patients included in the same prospective protocol. A good histological response and a rich initial lymphocyte infiltration (CD8 and cytotoxic Tia lymphocytes) confers a significantly superior survival (5-years 81% vs 45% if CD8-Tia negative) (E. Palmerini et al, abstract 11025).

Small Round Cell Desmoplastic Tumours (SRCDT) (also DSRCT): belonging to the family of PNET (Peripheral Neuro-Ectodermal Tumours) and presenting a specific chromosomic translocation (t11-22) different from the one in Ewing Sarcomas (fusion EWS-WT1), SRCDT is a terrible disease with 60% of metastatic patients at diagnosis and very few survivors over 10 years. Note this year that a small study (15 patients) combining irinotecan, temozolamide and bevacizumab for 2 cycles before a standard treatment based on anthracyclines and alkylant (H.D. Magnan et al, abstract 11050): 27% of objective response at the first tumour evaluation before switching with classical induction therapies. Hard to say anything about this kind of sequential approach. News is urgently needed in this disease where tumour cells over-express Topo2, PTEN and androgen receptors in about 60% of the cases (only 3% in Ewing sarcomas, to be explored?), and the EGFR pathway in 40% of the cases. No expression of PD-L1 (like in Ewing sarcomas) and few tumour mutational load in these tumours (5-6 mutations per mega base) that explains the limited interest on these tumours for a immunotherapy/targeted therapies type of approach (J. Xiu et al, abstract 11066).

Fibromatosis/Desmoid Tumours: three interesting communications this year.
1) The potential integration of a QOL scale in the future prospective studies on this topic, symptoms described by patients being generally too rare in these studies. (J. Paty et al, abstract 11022). Patients affected by desmoid tumours are painful at the tumour site in 65% of the cases, suffer from «neurological pain» in 73% of the cases with an impact on the daily life in 65% of the cases and sleep disorders in 77% of the cases. The integration of these 11 items (symptoms) and of the 17 others (impact on daily life) could be useful for a better definition of our therapeutic strategies which are too frequently influenced by the tumour volume;
2) the largest study ever reported on this topic is a French one (T. Ryckewaert et al, abstract 11047): 771 patients, 552 females, 219 males, median age 39 years, median size at diagnosis 57 mm, presence of a beta-catenin mutation in 71% of the cases, initial surgery of primary tumour in 44% of the cases, simple surveillance in 48% of the cases and systemic treatment in 3% of the cases. The key messages

could be summarized as following: 17% of the patients with simple surveillance require treatment for progressive disease (generally systemic treatment), versus 32% of the patients who received first line surgery (these relapses are often monitored), surgical biopsies are not recommended (progression after a median of 15 months vs 31 months with needle biopsy). Finally, the most important parameter regarding the initial localization of the tumour: favourable if abdominal wall (the most frequent, 236 patients), intra-abdominal, breast, and digestive; unfavourable if chest wall (2nd more frequent localization, 206 patients) limb, pelvis, head and neck. In unfavourable localizations, the monitoring option is the most beneficial for patients (HR 0.74 compared to surgery), this is not the case in favourable localizations (HR 0.89);
3) about 20% of the patients with mutated desmoid tumours (CTNNB1) have «positive» liquid biopsies, some circulating cDNA was found with this technics (S. Salas et al, abstract 11063), especially in progressing patients. The number of copies (quantity of circulating cDNA circulated) could be a predictive factor of their evolution or not. To be followed…

Synovial Sarcomas (SS) and Myxoid Liposarcomas (MLPS): apart from a constant expression of antigens from the PRAME (Preferentially Expressed Antigen in Melanoma) family compared to the other histological subtypes of STS (ASCO 2016, Roszik et al, abstract 11067), SS appearing in HLA-A2 population over-express NY-ESO-1, just like myxoid/round cells liposarcomas (MLPS). Some vaccination testing following cytapheresis, ex vivo expansion of T lymphocytes - conditioning with high doses of cyclophosphamide and fludarabine, then re-injection of these T lymphocytes – are ongoing in metastatic SS with quite interesting/surprising results in this population (very long responses following one single injection). Note that on a population of STS patients (all types of STS), (137 patients), 20% of them over-express NY-ESO-1 (Y. Komarov et al, abstract 11075). CMB305 (4 intradermic injections of dendritic cells coding NY-ESO1), an active immunotherapy potentially boosting anti-NY-ESO1 cytotoxic lymphocytes has been tested in a phase I (first in man) including 25 patients with SS and MLPS (N. Somaiah, abstract 11006): about 2/3 of the patients develop anti-NY-ESO1 antibodies, prolonged stabilizations could be observed in a majority of these pre-treated patients. The 3-months PFS is 75% and the 1-year overall survival are 86% and 100% for SS and MLPS respectively. To be closely followed.

Synovial Sarcomas also over-express FZD10 (Frizzled homolog10). A phase I study tested a radio-guided antibody (Ytrium) targeting this protein in 20 patients with pre-treated advanced SS (P. A Cassier et al, abstract 11054). Patients who could receive the active product had to fix the indium 111 in their tumour (selection phase). Only 8 of them could be included in the therapeutic phase: no tumour response, one long stabilization.