Gene Expression Profiling of Desmoid Tumors by cDNA Microarrays and Correlation with Progression-Free Survival

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Abstract

Purpose: Because desmoid tumors exhibit an unpredictable clinical course, translational research is crucial to identify the predictive factors of progression in addition to the clinical parameters. The main issue is to detect patients who are at a higher risk of progression. The aim of this work was to identify molecular markers that can predict progression-free survival (PFS).

Experimental Design: Gene-expression screening was conducted on 115 available independent untreated primary desmoid tumors using cDNA microarray. We established a prognostic gene-expression signature composed of 36 genes. To test robustness, we randomly generated 1,000 36-gene signatures and compared their outcome association to our 36-gene molecular signature. PPV and NPV were high (75.58% and 81.82%, respectively).

Conclusions: By analyzing expression profiles, we have identified a gene-expression signature that is able to predict PFS. This tool may be useful for prospective clinical studies.

Introduction

Desmoid tumors are mesenchymal fibroblastic/myofibroblastic proliferations. The major obstacle in the management of desmoid tumors is their high propensity for local recurrence even after complete surgical removal. Currently, an initial “wait-and-see” policy is explored as a possible standard of care (1, 2), but because desmoid tumors exhibit an unpredictable clinical course and an indistinguishable morphology, translational research is crucial to identify the predictive factors of progression in addition to the clinical parameters. A significant improvement would be to be able to detect patients who are at a higher risk of progression and those with no risk of progression.

Biologically, alterations of the APC (mutation or loss of the entire locus) and CTNNB1 mutation might constitute an initial mutually exclusive alteration (3, 4). Moreover, Salas and colleagues described three recurrent and relevant alterations of chromosomes 8, 20, and 6 by array comparative genomic hybridization (CGH) array. These alterations could be involved in the same pathway or could confer a selective advantage. Patients harboring CTNNB1 mutations, in particular CTNNB1 (45F) mutations, are at risk of recurrence and the wild-type appears to be a good prognostic marker (5, 6). There have been only a few reports concerning gene-expression analysis in desmoid tumors. One of them demonstrated that a gene-expression signature could distinguish desmoid tumors from nodular fasciitis and suggested that selected tyrosine kinases, transcription factors, and members of the Wnt, TGFβ, IFN, and TNF signaling pathways could distinguish these two entities (7). Another study has shown that it was identified genes, in particular ADAM12, WISP-1, and SOX1, which were uniquely overexpressed in 12 cases of aggressive fibromatosis compared with expression in normal skeletal tissues and a variety of normal tissues. The authors concluded that gene-expression patterns may be useful in the classification of subtypes of aggressive fibromatosis (8). Finally, Colombo and colleagues...
Expression Data from 115 Desmoid Tumors

Translational Relevance

The aim of this study was to identify molecular markers that can predict progression-free-survival (PFS) and thus to distinguish those desmoid tumors for which the use of aggressive treatment is justified rather than a "wait-and-see" strategy. This study clearly demonstrates that there is prognostic molecular signature of desmoid tumors that could benefit from different therapeutic strategies. The main question raised is how patients should be managed. Should patients with poor prognostic molecular signature be operated straightforward in a curative intent and/or benefit from early medical treatment? This study is the starting point for prospective studies, the only way to answer these questions and optimize the management of desmoid tumors. Prospective validation of the molecular signature is under way in France through a clinical trial evaluating the "wait-and-see" strategy (ClinicalTrials.gov identifier NCT01801176).

Materials and Methods

Patients and samples

From February 1, 1987 to March 6, 2008, 115 consecutive patients with sporadic aggressive fibromatoses were diagnosed for their first tumor event in 16 participating cancer centers. Among tumors in the 115 patients, 66 formed the training samples. The diagnosis of desmoid tumors was confirmed in each case by collegial histologic analysis (mesenchymal fibroblast/myofibroblastic proliferations). The following clinical data were collected: gender, age at diagnosis, location (intra-abdominal, abdominal wall, and extra-abdominal), size of tumor, and follow-up (Table 1). All patients had an initial surgical resection. Histologic evaluation of surgical margins was available in 91 (79%) cases. Forty-seven patients (41%) had R0 resection, 32 (28%) had R1 resection, and 12 (10%) had R2 resection (macroscopic incomplete as R2 resection; microscopic incomplete resection as R1 resection; microscopic complete resection as R0 resection). Radiotherapy generally included photons or electrons with a median dose of 50 Gray. Forty-three patients received radiotherapy. Surgery was followed by radiotherapy in 16 patients. Clinical and histologic data were entered into a centralized computerized database (www.canticbase.org). All samples were obtained after informed consent from patients.

Pathology review

Histologic slides of all patients entered in this study were reviewed by the pathology subcommittee of the French Sarcoma Group (GSF). This subcommittee included 20 pathologists and a monthly slide review session was performed. For each tumor, one to eight slides were reviewed collegially. Histologic typing was based on the World Health Organization (WHO) histologic typing of soft tissue tumors. Histopathologic diagnosis was confirmed by the search for CTNNB1 mutations. All training samples had the CTNNB1 mutation.

RNA extraction and cDNA array

Total RNAs were extracted from frozen tumor samples with TRizol reagent (Life Technologies, Inc.) and purified using the RNeasy Min Elute TM Cleanup Kit (Qiagen) according to the manufacturer's procedures. RNA quality was checked on an Agilent 2100 bioanalyzer (Agilent Technologies). Samples were then analyzed on Human Genome U133 Plus 2.0 array (Affymetrix), according to the manufacturer's procedures. All microarray data were simultaneously normalized using the GCRMA algorithm (Wu J and Gentry (2014) RiwcfJMJ. GRCMA: Background Adjustment Using Sequence Information. R package version 2.40.0). Minimum information about a microarray experiment–compliant data have been deposited at Gene Expression Omnibus under accession number GSE58697.

Gene-expression analysis

Differential expression was established using the limma R package and P values were adjusted using the Benjamini–Hochberg procedure (10). Analysis of variance was performed by using GeneSpring GX software (Agilent Technologies) one-way ANOVA test and P values were adjusted by using the Benjamini–Hochberg procedure.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort A (n = 66)</th>
<th>Cohort B (n = 49)</th>
<th>Cohort A + B (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (years) (IC 95)</td>
<td>2.36 (0.03–12.04)</td>
<td>1.43 (0.33–11.07)</td>
<td>1.82 (0.08–11.97)</td>
</tr>
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<td>Age at diagnosis (%)</td>
<td></td>
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<tr>
<td>&lt;37 years</td>
<td>27 (41)</td>
<td>25 (50)</td>
<td>52 (45)</td>
</tr>
<tr>
<td>≥37 years</td>
<td>37 (56)</td>
<td>24 (50)</td>
<td>61 (53)</td>
</tr>
<tr>
<td>Nd</td>
<td>2 (3)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>23 (35)</td>
<td>20 (41)</td>
<td>43 (37)</td>
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<tr>
<td>Location (%)</td>
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<td></td>
<td></td>
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<td>4 (6)</td>
<td>8 (16)</td>
<td>12 (10)</td>
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<td>Abdominal wall</td>
<td>13 (20)</td>
<td>9 (18)</td>
<td>22 (18)</td>
</tr>
<tr>
<td>Extra-abdominal</td>
<td>49 (74)</td>
<td>32 (66)</td>
<td>71 (62)</td>
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<td>Size (%)</td>
<td></td>
<td></td>
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<tr>
<td>&gt;7 cm</td>
<td>35 (53)</td>
<td>20 (41)</td>
<td>55 (48)</td>
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<tr>
<td>≤7 cm</td>
<td>17 (26)</td>
<td>22 (45)</td>
<td>39 (34)</td>
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<tr>
<td>Nd</td>
<td>14 (21)</td>
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<td>21 (18)</td>
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<tr>
<td>Progression number (%)</td>
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<tr>
<td>0</td>
<td>48 (72)</td>
<td>14 (29)</td>
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<tr>
<td>1</td>
<td>0</td>
<td>30 (61)</td>
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<td>2</td>
<td>13 (20)</td>
<td>1 (2)</td>
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<td>3</td>
<td>5 (8)</td>
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<td>6 (5)</td>
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<tr>
<td>&gt;3</td>
<td>0</td>
<td>3 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Mutations CTNNB1 (%)</td>
<td>66 (100)</td>
<td>29 (60)</td>
<td>95 (82)</td>
</tr>
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</table>
Statistical analysis

PFS is defined as time from the date of initial diagnosis to the date of progression or recurrence or last follow-up. Local recurrence-free survival (LRFS) is defined as time from the date of initial diagnosis to the date of recurrence or last follow-up. We chose to study PFS because the validation cohort consisted of patients who underwent surgery that was not only R0 and R1 but also R2. Survival curves were obtained by the Kaplan–Meier method and compared with the log-rank test. All survival analyses were performed by using R software, version 2.14.1 (R development Core Team, Vienna Austria, 2009) and survival package (Therneau T [2013]). A Package for Survival Analysis in S. R package version 2.37-4. The Cox proportional hazards model was used to calculate adjusted hazard ratios (HR) and their 95% confidence intervals (95% CI). Variables with a P value less than 0.05 in univariate analyses were tested in the multivariate analysis. Multivariate analysis was performed by using Cox regression with Firth’s correction (R by Meinhard Ploner and Foruran by Georg Heinze, 2012; coxphf: Cox regression for the group with a good prognostic signature, or R package version 1.09). The positive predictive value (PPV) is the ratio of the number of patients having neither a recurrence nor progression at the end of follow-up and classified in the group with a good prognostic molecular signature over the total number of patients classified as having a good prognostic signature. The negative predictive value (NPV) is the ratio of the number of patients whose disease recurred or progressed and were classified as having a poor prognostic signature over the total number of patients classified as having a poor prognostic signature. Sensitivity, specificity, and accuracy were also calculated for the molecular signature.

Results

Establishing molecular signature

In unsupervised analysis, no molecular signature could be identified. To identify molecular markers that can predict PFS of desmoid tumors, we compared expression profiles in supervised analyses of 48 patients without recurrence versus 18 patients with two or three local recurrences. We identified 18 genes upregulated in recurrence samples and 18 genes downregulated in recurrence samples (Table 2). The supervised analysis comparing patients without recurrence with those having one or more recurrences did not identify any prognostic molecular signature. Classification based on biologic process categories from GO (www.geneontology.org) of the 36 genes demonstrated four enriched GO process terms: cellular component organization or biogenesis (GO:0006430), cellular component organization (GO:0016043), single-organism organelle organization (GO:1902589), organelle organization (GO:0006996), which include 16, 16, 10, and 12 genes, respectively (Table 3). The interaction of the lists of genes from the ANOVA analysis comparing 0-versus-2, 0-versus-3, and 2-versus-3 recurrences identified three genes as shown in the Venn diagram (Fig. 1): FECH, STOML2, and TRIP6. TRIP6 was overexpressed in the good outcome group unlike STOML2 and FECH, which were overexpressed in the poor outcome group.

Prognostic factors for PFS and molecular signature validation

To test whether clinical factors can predict PFS, we performed univariate analysis for age at diagnosis (cutoff, 37 years), tumor site (intra-abdominal versus abdominal wall versus extra-abdominal) and tumor size (cutoff, 7 cm) in the whole cohort. Tumor site and tumor size were not significant but age at diagnosis (P = 4.1e10^-6) had a significant impact on PFS. Survival analysis was also established for a 36-gene molecular signature with centroid defined on cohort A (n = 66) and classification and validation defined on the whole cohort (n = 115). Univariate analysis showed that the molecular signature predicted PFS (P = 1.7e10^-5; Fig. 2). The molecular signature also has a prognostic value in LRFS (only the recurrence is considered as an event) in the validation cohort.
36-gene signatures versus random signatures

To test its robustness, we randomly generated 1,000 36-gene signatures and compared their outcome-association to our defined 36-gene molecular signature. Exactly the same procedure was used with centroid definition on cohort A and validation in the whole cohort. Among the 1,000 random signatures generated, 56.7% were significant ($P < 0.05$) and none was more significant ($P < 1.7 \times 10^{-7}$) than our 36-gene molecular signature. Finally, the following values were obtained for our 36-gene molecular signature: PPV, 75.58%; NPV, 81.82%; specificity, 72.58%; sensitivity, 81.82%; and accuracy, 78.26%.

Prognostic value of the signature in myxofibrosarcomas

The signature was also tested in 42 myxofibrosarcomas. These cases were previously published by Chibon and colleagues (12). In this cohort, we found a prognostic value in metastasis-free survival but not in LRFS (respectively $P = 0.007$ and $P = 0.47$).

Discussion

One of the main problems in managing desmoid tumors is their locoregional aggressiveness and their propensity to recur after initial treatment. The aim of this study was to identify molecular markers that can predict PFS and thus to distinguish those desmoid tumors for which the use of aggressive treatment is justified rather than a “wait-and-see” strategy. A few studies to date have tried to correlate biologic prognostic markers with outcome, but the clinical impact was limited as a result of low robustness (5, 6). Here, we performed the largest gene-expression analysis of sporadic desmoid tumors from the French Sarcoma Group tumor bank ever published. By analyzing expression profiles, we have identified a gene-expression signature that is able to predict PFS. This molecular signature identified two groups with clearly distinct PFS in the two sets of subjects. Patients in the good prognostic group had achieved a 2-year PFS rate of 86% while those in the poor prognostic group had a 2-year PFS rate of 44%.

The top two genes upregulated in the recurrence group were $\text{FECH}$ and $\text{STOML2}$ and the top gene upregulated in the non-recurrence was $\text{TRIP6}$. These genes corresponded to the interaction of the lists of genes obtained from ANOVA analysis comparing 0-versus-2, 0-versus-3, and 2-versus-3 recurrences. The function of these genes of interest is detailed below.

The last step of the heme synthetic pathway, which is essential for the cellular energy metabolism, is the incorporation of iron into protoporphyrin IX (PpIX) by the FECH enzyme. 5-Aminolevulinic acid (ALA) is a small-molecule precursor for the synthesis of (PpIX; ref. 13). Loss of FECH enzyme activity might be responsible for enhanced PpIX accumulation in human carcinomas (14). Van Hillegersberg and colleagues (15) have shown that oral administration of ALA resulted in progressive accumulation of protoporphyrin in a rat colon carcinoma but not in the surrounding liver tissue. This team and others suggested that PpIX formation in human cancers, especially as a response to ALA medication, might be related to lowered FECH enzyme activity. Moreover, Kemmner and colleagues (16) were able to demonstrate a significant downregulation of FECH mRNA

\[(P = 1.0 \times 10^{-3})\]. The prognostic value of the three-gene molecular signature ($\text{FECH}, \text{STOML2}, \text{and TRIP6}$) was lower than that of the 36-gene molecular signature (respectively $P = 0.025$ and $P = 1.7 \times 10^{-07}$). Multivariate analysis comparing age at diagnosis to the 36-gene molecular signature demonstrated that the latter ($P = 7.9 \times 10^{-07}$) was more predictive than age at diagnosis, which was not significant (Table 4). The molecular signature had also prognostic value in mutated cases whatever the type of mutation ($P = 4 \times 10^{-08}$), in S45 cases ($P = 3 \times 10^{-03}$), T41 cases ($P = 1.3 \times 10^{-04}$), and S45 and T41 cases ($P = 2.5 \times 10^{-10}$) but molecular signature has no prognostic value in nonmutated cases ($P = 0.59$).
expression in gastric, colonic, and rectal carcinomas. These data were used as a rationale for the use of photodynamic therapy (PDT) supplemented with exogenously added ALA in particular on urothelial carcinoma (17). In our study, FECH was overexpressed in more aggressive forms of desmoid tumors.

Recent evidence indicates that stomatin-like protein 2 (STOML2) regulates mitochondrial functions (i.e., energy production, calcium buffering, and apoptosis) by organizing mitochondrial membranes into defined cardiolipin-enriched microdomains, which then facilitate the optimal assembly of membrane-associated molecular complexes (18). STOML2 has been identified as an oncogenic-related protein and found to be upregulated in multi-cancers. First, STOML2 might serve as a prognostic marker especially in human gallbladder cancer, gastric cancer, glioma, colorectal cancer, breast cancer, and pulmonary squamous cell carcinoma (19–24). STOML2 is also involved in invasion, regulating cell growth and cell adhesion in human esophageal squamous cell carcinoma, glioma, and human endometrial adenocarcinoma (21, 25–27). In desmoid tumor that behaves aggressively by infiltrating tissues deeply, STOML2 overexpression is clinically related to PFS.

Thyroid hormone receptor-interacting protein 6 (TRIP6) is a zyxin-related adaptor protein and focal adhesion molecule (28). TRIP6 associates with a variety of molecules from the cell surface to the nucleus, regulates actin reorganization, focal adhesion assembly/disassembly, cell migration/invasion, anti-apoptotic signaling, and transcriptional control. Notably, TRIP6 binds to lysophosphatidic acid (LPA) receptor 2 (LPA2) and the Fas/CD95 receptor to promote LPA- and Fas ligand-induced cell migration in a c-Src-dependent manner. TRIP6 can also regulate prosurvival signaling via activation of NF-κB, extracellular signal–regulated kinase (ERK), and phosphatidylinositol 3-kinase (PI3K)/AKT, and nuclear TRIP6 acts as a transcriptional coregulator of AP-1 and NF-κB. These data suggest that TRIP6 functions at a point of convergence of multiple signaling pathways critical for cancer development (29). Thus, TRIP6 acts as an oncogene that partially accounts for the autonomous migratory, invasive, and proliferative properties of Ewing sarcoma cells. Although short-term proliferation was not considerably affected by TRIP6 knockdown, silencing of the protein significantly reduced migration, invasion, long-term proliferation, and clonogenicity of Ewing sarcoma cells in vitro as well as tumorigenicity in vivo (30). Moreover, in nasopharyngeal cancer cells (NPC), TRIP6 overexpression/knockdown results in significant enhancement/inhibition of NPC cell migration, respectively (31). Finally, knockdown of TRIP6 in glioblastoma or ovarian cancer xenografts restores nuclear p27 (KIP1) expression and impairs tumor proliferation and may have a significant impact on enhanced NF-κB activity, resistance to apoptosis, and Fas-mediated cell invasion in glioblastomas (29, 32). Paradoxically, in desmoid tumors, TRIP 6 was overexpressed in the good outcome group. However, unlike STOML2 and FECH, TRIP6 is connected to β-catenin in the literature, the main signaling pathway in desmoid tumors. Indeed, TRIP6 might compete with β-catenin for binding with the MAGI-1b/PTEN signalsosome to destabilize E-cadherin junctional complexes and to promote cell motility through the regulation of Akt/NF-κB targets and/or effectors of focal adhesion (33). STOML2 and FECH are likely β-catenin transcriptional targets.
Expression Data from 115 Desmoid Tumors

Table 4. Univariate and multivariate analysis for prognostic factors in PFS

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Molecular signature</td>
<td>1.7e10^-27</td>
<td>5.3 (2.64-10.58)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>4.3e10^-02</td>
<td>1.7 (1.02-3.08)</td>
</tr>
</tbody>
</table>

Classification based on biologic process categories from GO of the 36 genes principally demonstrated four clusters composed of 16, 16, 10, and 12 genes, respectively. These clusters relate to general biologic processes. Validation of the molecular signature analysis was obtained from the whole population including a part of the training. Even though the validation cohort was not totally independent, the prognostic value of this molecular signature was highly significant in this rare disease. In multivariate analysis, only the 36-gene molecular signature was prognostic of PFS, unlike any classical clinical prognostic factor, such as tumor size, tumor site, or age. Moreover, PPVs and NPVs were high, suggesting that this molecular test could be used at the time of diagnosis to stratify patients enrolled in randomized trials. Finally, to test its robustness, we compared its prognostic value to that of randomly generated signatures according to the methodology published in the article by Venet and colleagues. By comparing 47 published breast cancer outcome signatures to signatures of identical size constructed from random genes, they showed that 60% of the published signatures were not significantly better outcome predictors than random signatures (34). In soft tissue sarcoma, the CINSARC signature is particularly robust with only two random signatures more significantly associated with outcomes (35). In this study, our signature was always more significant than random signatures, thus demonstrating the high reliability of our results. Moreover, the fact that the molecular signature had prognostic value in another fibroblastic entity such as myxofibrosarcoma reinforces our idea that this signature is robust and that this signature probably reflects a biologic property.

Although considered nonmalignant owing to their inability to metastasize, the locoregional recurrence rate of desmoid tumors after resection is nearly 50% and the likelihood of accelerating the evolution of the disease with surgery is still debated. This shows that there is an unpredictable clinical course in desmoid tumors and justifies a "wait-and-see" policy as initial strategy. It is therefore necessary to identify patients who are at a higher risk of progression and the search for molecular markers may be a way forward (1, 2).

This study clearly demonstrates that there is prognostic molecular signature of desmoid tumors that could benefit from different therapeutic strategies. The main question raised is how patients should be managed. Should patients with poor prognostic molecular signature be operated straightforward in a curative intent and/or benefit from early medical treatment?

This study is the starting point for prospective studies, the only way to answer these questions and optimize the management of desmoid tumors.

Prospective validation of the molecular signature is under way in France through a clinical trial evaluating the "wait-and-see" strategy (ClinicalTrials.gov identifier NCT01801176). However, our work concerns surgical patients and not those in a "wait-and-see" strategy. Thus, we cannot affirm that this molecular signature who predicts progression after surgery, will predict progression before surgery.

Finally, somatic markers are not the only factors to be considered because desmoid tumors may completely shrink spontaneously and undergo a change in size over time according to external events (pregnancy, trauma, surgery performed at another site, etc.). The host environment is doubtlessly involved.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: S. Salas, J.-Y. Blay, J.-M. Coindre, F. Chibon
Development of methodology: S. Salas, A. Aurias, J.-M. Coindre, F. Chibon
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Salas, F. Terrier, D. Ranchere-Vince, A. Nevirle, L. Guillou, M. Lae, A. Leroux, O. Verola, K. Jean-Emmanuel, S. Bonvalot, J.-Y. Blay, A. Le Cesne, J.-M. Coindre, F. Chibon
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Salas, C. Brulard, L. Guillou, J.-Y. Blay, A. Le Cesne, F. Chibon
Writing, review, and/or revision of the manuscript: S. Salas, C. Brulard, A. Nevirle, M. Lae, A. Leroux, S. Bonvalot, J.-Y. Blay, J.-M. Coindre, F. Chibon
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Salas, F. Terrier, L. Guillou, J.-Y. Blay, J.-M. Coindre, F. Chibon
Study supervision: S. Salas, A. Aurias, J.-M. Coindre, F. Chibon

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