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► To cite this version:

Florent Petitprez, Aurélien de Reynies, Emily Z Keung, Tom Wei-Wu Chen, Cheng-Ming Sun, et al.. B cells are associated with survival and immunotherapy response in sarcoma. *Nature*, 2020, 577 (7791), pp.556-560. 10.1038/s41586-019-1906-8 . hal-02456340

HAL Id: hal-02456340

<https://hal.sorbonne-universite.fr/hal-02456340v1>

Submitted on 27 Jan 2020

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1 **B cells are associated with sarcoma survival and immunotherapy response**

2 **Authors**

3 F. Petitprez^{1,2,3,4}, A. de Reyniès^{4,*}, E. Z. Keung^{5,*}, T.W. Chen^{6,7,8,9}, C.M. Sun^{1,2,3}, J. Calderaro^{1,10,11}, Y.M. Jeng^{9,12},
4 L.P. Hsiao⁷, L. Lacroix^{1,2,3}, A. Bougoüin^{1,2,3}, M. Moreira^{1,2,3}, G. Lacroix^{1,2,3}, I. Natario^{1,2,3}, J. Adam¹³, C.
5 Lucchesi^{14,15}, Y. Laizet^{14,15}, M. Toulmonde^{14,16}, M. A. Burgess¹⁷, V. Bolejack¹⁸, D. Reinke¹⁹, K. M. Wani²⁰, W.L.
6 Wang²⁰, A. J. Lazar^{20,21}, C. L. Roland⁵, J. A. Wargo^{5,21}, A. Italiano^{14,16,22}, C. Sautès-Fridman^{1,2,3}, H. A. Tawbi^{23,‡}
7 and W.H. Fridman^{1,2,3,‡}.

8 ¹ INSERM, UMR_S 1138, Cordeliers Research Center, Team Cancer, immune control and escape, Paris, France

9 ² Université de Paris, Sorbonne Paris Cite, UMR_S 1138, Centre de Recherche des Cordeliers, Paris, France

10 ³ Sorbonne University, UMR_S 1138, Centre de Recherche des Cordeliers, Paris, France

11 ⁴ Programme Cartes d'Identité des Tumeurs, Ligue Nationale Contre le Cancer, Paris, France

12 ⁵ Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

13 ⁶ Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan

14 ⁷ Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

15 ⁸ National Taiwan University Cancer Center, Taipei, Taiwan

16 ⁹ Centers of Genomic and Precision Medicine, National Taiwan University, Taipei, Taiwan

17 ¹⁰ Département de Pathologie, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Henri Mondor, Créteil, France

18 ¹¹ Inserm U955, Equipe 18, Institut Mondor de Recherche Biomédicale, Créteil, France

19 ¹² Department of Pathology, National Taiwan University, Taipei, Taiwan

20 ¹³ Department of Biology and Pathology, Gustave Roussy, Villejuif, France

21 ¹⁴ INSERM U1218, Institut Bergonié, F-33000, Bordeaux, France

22 ¹⁵ Bioinformatics Unit, Institut Bergonié, F-33000 Bordeaux, France

23 ¹⁶ Department of Medical Oncology, Institut Bergonié, F-33000 Bordeaux, France

24 ¹⁷ Department of Medicine, Division of Hematology/Oncology, University of Pittsburgh, Pittsburgh, PA, USA

25 ¹⁸ Cancer Research and Biostatistics, Seattle, WA, USA.

26 ¹⁹ Sarcoma Alliance for Research Through Collaboration, Ann Arbor, MI, USA.

27 ²⁰ Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

28 ²¹ Department of Genomic Medicine The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

29 ²² University of Bordeaux, Bordeaux, France

30 ²³ Department of Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

31 * Equal contribution

32 ‡ Corresponding authors

33 **First paragraph (185 words)**

34

35 **Soft-tissue sarcomas (STS) represent a heterogeneous group of cancer, with over 50**
36 **histologic subtypes^{1,2}. They show variable clinical behaviours and response to therapy,**
37 **including immune checkpoint blockade^{3,4}. To explain this clinical variability, we studied**
38 **gene expression profiles in 608 tumours across STS subtypes, establishing an immune-**
39 **based classification based on the composition of the tumour microenvironment and**
40 **identified five distinct phenotypes: immune-low (A, B), immune-high (D, E), and highly**
41 **vascularised (C) groups. In situ analysis of an independent validation cohort showed that**
42 **class E was also characterized by the presence of tertiary lymphoid structures (TLS)**
43 **containing T cells, follicular dendritic cells and particularly rich in B cells. B cells are the**
44 **strongest prognostic factor even in the context of high or low CD8⁺ and cytotoxic contents.**
45 **The immune-high E group demonstrated improved survival and a high response rate to**
46 **PD-1 blockade by pembrolizumab in a phase 2 clinical trial. Altogether, this work**
47 **provides novel evidence regarding the presence of immune subtypes in STS patients, and**
48 **unravels the potential of B cell rich TLS to guide clinical decision-making and treatment,**
49 **which could have broader applications beyond STS.**

50 **Main text (2210 words)**

51 Soft-tissue sarcomas (STS) comprise many histologic subtypes with distinct clinical and
52 biological behaviours. Genetically “simple” STS are characterized by translocations resulting
53 in fusion-proteins and few if any other genomic lesions, while “complex” STS have an
54 unbalanced karyotype and multiple genomic aberrations¹. STS are considered “non-
55 immunogenic” with low mutational burden². Among complex tumours, undifferentiated
56 pleomorphic sarcoma (UPS), dedifferentiated liposarcoma (DDLPS), and to a lesser extent
57 leiomyosarcoma (LMS), can exhibit durable responses to immune checkpoint blockade,
58 whereas simple tumours do not respond to PD-1 monotherapy or combination anti-PD1/anti-
59 CTLA4^{3,4}. Few reports investigating the composition of the tumour microenvironment (TME)
60 composition in different STS histologies have been published⁵⁻⁷, but a recent study from the
61 Cancer Genome Atlas (TCGA) consortium suggested an association with prognosis⁸.

62 Here, we developed a novel classification of STS, based on the composition of the tumour
63 microenvironment in large cohorts of STS, using the MCP-counter method⁹. We found that the
64 B lineage signature, a hallmark of an immune-high class we called E, correlated with an
65 improved survival of STS patients, in tumours with both high or low CD8⁺ T cells infiltration.
66 In an independent cohort, we validated by immunohistochemistry the high density of B cells
67 and presence of tertiary lymphoid structures (TLS) in class E. Finally, we showed that class E
68 exhibited the highest response rate to PD-1 blockade therapy and improved progression-free
69 survival in a multi-centre phase 2 clinical trial of pembrolizumab in STS (SARC028)^{4,10}.

70

71 **RESULTS**

72 **Immune classification of STS: Histology-independent microenvironment composition and**
73 **functional orientation**

74 The TME compositions from 4 independent discovery primary STS datasets (TCGA SARC,
75 GSE21050, GSE21122 and GSE30929, Extended Data Table 1) with publicly available gene
76 expression profiles were analysed with MCP-counter, a gene-expression-based TME
77 deconvolution tool⁹. An immune-based classification of STS was developed from this analysis
78 (Methods, Extended Data Fig. 1) and tumours were assigned to one of five Sarcoma Immune
79 Classes (SICs), labelled A, B, C, D and E, with highly distinct profiles (Fig. 1). We compared
80 the SIC distribution across histologic subtypes and found that most LMS tumours were
81 classified to SICs A and B (Fig. 1a). DDLPS accounted for half of SIC C tumours. Tumours
82 classified as SICs D and E were more evenly distributed across histologic subtypes. Application
83 of the predictor of the immune classes (Methods) to other STS histologies from French Sarcoma
84 Group (FSG) cohort (Extended Data Table 1) revealed that all SICs could be identified in each
85 histology (Extended Data Fig. 2a).

86 The TME composition differs significantly between SICs (Fig. 1b). Three SICs showed
87 homogeneous profiles. SIC A, “immune desert”, was characterised by the lowest expression of
88 gene signatures related to immune cells, as well as low vasculature. SIC C, “vascularised”, was
89 dominated by a high expression of endothelial cell-related genes. SIC E, “immune and TLS
90 high”, was characterized by the highest expression of genes specific to immune populations
91 such as T cells, CD8⁺ T cells, NK cells, cytotoxic lymphocytes. Strikingly, a key determinant
92 of SIC E was the high expression of the B lineage signature ($p=1.8e-29$). SICs B and D were
93 characterized by heterogeneous but generally “Immune low” and “Immune high” profiles,
94 respectively.

95 Expression of genes associated with T cell/myeloid cell chemotaxis, T cell activation and
96 survival, expression of major histocompatibility complex (MHC) class I, and regulatory gene
97 signatures were high in SICs D and E, intermediate in SICs B and C, and very low in SIC A
98 (Fig. 1c). Expression of the lymphoid structures-associated B cell chemo-attractant chemokine

99 CXCL13 was remarkably high in E tumours, moderate in D tumours, generally low in B and C
100 tumours, and negligible in A tumours.

101 Immune checkpoint-related genes expression (Fig. 1d) followed that of immune infiltrates, with
102 high expression of genes encoding PD-1, PD-L2, CTLA-4 and TIM3 (*PDCD1*, *PDCD1LG2*,
103 *CTLA4* and *HAVCR2*, respectively) in SIC E followed by SIC D tumours, and low to very low
104 expression in SIC C, B and A tumours. *CD274* (PD-L1) was heterogeneously expressed across
105 SICs while *LAG3* was only expressed at high levels in SIC E tumours with low expression in
106 all other classes. The above findings were consistent across the four discovery cohorts
107 (Extended Data Fig. 3).

108 **SICs are associated with survival of STS patients**

109 After verification that the two cohorts with available survival data (TCGA SARC, n=213;
110 GSE21050, n=283) exhibited similar survival patterns (data not shown), these were pooled to
111 study the clinical outcome of the five SICs (Fig. 2a). SIC A patients exhibited the shortest
112 overall survival (OS) compared to D or E patients ($p=0.048$ and $p=0.025$, respectively).
113 Similarly, among the other STS histologies from FSG cohort, SIC A patients had a shorter OS
114 compared to SIC E patients (Extended Data Fig. 2b). In a multivariate model with classical
115 prognostic factors (Fig. 2b), SICs were found to be significantly associated with prognosis,
116 independent of other clinical parameters (as compared to SIC A, $p=0.011$ and $p=0.029$, for SIC
117 D and SIC E, respectively). Tumours were separated between high and low expression of CD8⁺
118 T cells, cytotoxic lymphocytes and B lineage signatures based on the observation of the MCP-
119 counter scores distribution (Extended Data Fig. 4). Detailed analysis of the impact of these
120 immune cell population signatures revealed that whereas neither CD8⁺ T cells (Fig. 2c,
121 $p=0.277$) nor cytotoxic lymphocytes (Extended Data Fig. 5a, $p=0.0513$) significantly correlated
122 with survival, the B lineage signature was significantly associated with improved overall
123 survival (Fig. 2d, $p=4.25e-04$). When analysed in the context of high or low infiltration by CD8⁺

124 T cells (Fig. 2e), cytotoxic lymphocytes or expression of *PDCDI* (PD-1), *CD274* (PD-L1) or
125 *FOXP3* (Extended Data Fig. 5b-e), the B lineage signature was the dominant parameter for
126 improved survival, regardless of other immune factors expression. Additionally, SIC E tumours
127 demonstrate high expression of both *IGJ* and *TNFRSF17* (encoding BCMA) (data not shown),
128 indicating that plasma cells¹¹ may contribute to improve prognosis.

129 **Mutational landscape of SICs in TCGA SARC**

130 Overall Tumour Mutational Burden (TMB) was low across the studied cohorts (median: 32
131 non-synonymous mutations [NSM]) and appeared to be similar across all SICs (Extended Data
132 Fig. 6a). However, a few highly mutated tumours (each with over 250 NSM) were found in the
133 D and E groups. Qualitative mutational analysis revealed several commonly mutated genes
134 across the cohort, including *TP53* (35.2%), *ATRX* (16.0%), *TTN* (9.9%), *RBI* (8.9%), *MUC16*
135 (8.0%), *PCLO* (6.1%), *DNAH5*, *MUC17* and *USH2A* (5.2% each) (Extended Data Fig. 6b).
136 *TP53* was more frequently mutated among SICs D and E tumours (Extended Data Fig. 6c,
137 p=0.01).

138 The landscape of copy-number variations, assessed on the TCGA SARC cohort, revealed
139 differences between histologies, consistent with previously been described observations⁸.
140 However, no notable CNV difference was found between SICs (data not shown).

141 ***In situ* validation of SIC profiles in tumours**

142 To validate *in situ* the TME profiles of SICs, we analysed an independent cohort of 93 STS
143 cases (NTUH cohort, Extended Data Table 1). 73 samples passed quality control for
144 transcriptomic analysis using Nanostring nCounter technology. We classified this cohort into
145 the same 5 SICs (see methods) with the following distribution: A: 16 (21.9%), B: 19 (26.0%),
146 C: 10 (13.7%), D: 17 (23.3%), E: 11 (15.1%). The NTUH cohort samples exhibited gene-

147 expression-based TME profiles similar to that of TCGA SARC and GSE21050 cohorts
148 (Extended Data Fig. 7a).

149 By quantitative immunohistochemistry (IHC), “Immune desert” SIC A was characterized by
150 very low densities of CD3⁺, CD8⁺ or CD20⁺ cells, whereas “Immune and TLS high” SIC E
151 exhibited high densities of these cells (pairwise comparison, p=4.01e-06, p=6.64e-06 and
152 p=9.90e-07, respectively). The “vascularised” SIC C exhibited a moderate infiltration by
153 immune cells and high density of CD34⁺ endothelial cells (Extended Data Fig. 7b-c).

154 **Tertiary lymphoid structures are a feature of SIC E tumours**

155 The B cell-specific chemotactic cytokine CXCL13, which is associated with the presence of
156 TLS¹², was strongly expressed in SIC E tumours (Fig. 1c, Extended Data Fig. 2c). Its expression
157 highly correlated with that of the TLS-associated 12-chemokine signature¹³ (Extended Data
158 Fig. 8a), suggesting that TLS could be a marker of SIC E. TLS were defined as a CD20⁺ B cells
159 follicle juxtaposed to a CD3⁺ T cells aggregate containing at least one DC-Lamp⁺ mature
160 dendritic cell^{12,14-16} (Fig. 3a, left). A strong association between SICs and the presence of TLS
161 was identified (p=3.13e-06, Fig. 3c). No TLS were observed in tumours from SICs A, C and D,
162 and only one tumour from SIC B had one TLS. Conversely, nine out of eleven (82%) SIC E
163 tumours exhibited one or more TLS. All TLS were intratumoural (Extended Data Fig. 8b), and
164 found at the periphery and in the centre of the tumour in all histologies (Extended Data Fig. 8c-
165 d).

166 We observed the presence of CD3⁺PD-1⁺ T cells (Fig. 3a, right) in the germinal centre (GC) of
167 TLS with characteristics of follicular helper T cells (positive for CD4, PD-1 and the CXCL13
168 receptor CXCR5, Fig. 3b, left)^{17,18}, CD23⁺CD21⁺ cells with reticular morphology characteristic
169 of follicular dendritic cells and PNAd⁺ structures with high endothelial venules morphology
170 (Fig. 3b, right). GC are a hallmark of secondary follicle-like TLS (SFL-TLS), the final

171 maturation step of TLS, the earlier steps being early TLS (E-TLS), and primary follicle-like
172 TLS (PFL-TLS)^{15,16}. E-TLS, PFL-TLS and SFL-TLS represented respectively 60.5%, 21.1%
173 and 18.3% of all TLS analysed (Extended Data Fig. 8e-f). This differed between histologies
174 ($p=7.76e-05$), with UPS having only 16.7% of E-TLS.

175 Tumours with TLS (11.8%, 11/93) had significantly higher densities of tumour-infiltrating
176 CD3⁺ T cells ($p=4.0e-05$), CD8⁺ T cells ($p=1.8e-04$) and CD20⁺ B cells ($p=1.5e-05$) (Fig. 3d).
177 This association persisted even if T and B cells within TLS were excluded from the analysis
178 ($p=1.5e-04$, $p=3.8e-04$ and $p=7.9e-07$, respectively, Fig. 3d), reflecting that high immune cell
179 infiltration is not limited to TLS.

180 **SICs predict response to PD-1 blockade in STS patients**

181 We examined if SICs can predict patient response to checkpoint blockade therapy. We obtained
182 47 pre-treatment STS metastasis biopsies from patients enrolled in the SARC028 clinical trial⁴
183 and its expansion cohort¹⁰ (Extended Data Table 1), which evaluated the efficacy of
184 pembrolizumab (an anti-PD-1 monoclonal antibody) in patients with metastatic STS. Of these
185 47 patients, 1 achieved a complete response (CR), 9 partial response (PR), 17 stable disease
186 (SD) and 20 had progressive disease (PD) (Fig. 4a). Pre-treatment tumours were classified into
187 SICs based on gene expression data. The Objective Response Rate (ORR, accounting for
188 complete and partial responses) as evaluated by RECIST criteria was 21.2 % in the overall
189 cohort. SICs however showed substantial variation in ORR, with SIC E patients exhibiting the
190 highest ORR (50%, 5/10), followed by SIC D (25%, 3/12) and SIC C (22%, 2/9) (Fig. 4a). CR
191 were only found in SIC E, as well as one patient who had 100% change in target lesions but
192 non-CR in non-target lesions and thus not qualifying for CR. Strikingly, there were no
193 responders within the SIC A (0/5) and B (0/11) groups (Fig. 4a). Overall, SIC E tumours were
194 associated with the highest response rate to pembrolizumab in comparison with tumours from
195 other SICs ($p=0.026$, Fig. 4b). Patients with SIC E tumours also exhibited improved

196 progression-free survival than patients with SIC A or B tumours ($p=0.023$ and $p=0.0069$,
197 respectively, Fig. 4c).

198 **DISCUSSION AND CONCLUSION**

199 This study is the most comprehensive analysis of STS immune tumour microenvironment and
200 the first to evaluate the prognostic impact of immune infiltrates by simultaneously integrating
201 multiple immune cell populations and malignant cell characteristics. There have been prior
202 efforts to examine the immune profile of STS tumours, although the significance of the B cells
203 and TLS were not investigated. The clinical impact of CD8⁺ T cells and PD-1 expression has
204 yielded controversial results^{7,8,19–25}. Here, we found CD8⁺ T cells signature and PD-1 to be
205 expressed in D and E SICs, which are associated with favourable outcomes, providing high B
206 cell infiltrate. The present integrative analysis demonstrates that infiltration by B cells is a key
207 discriminative feature of a group of patients with improved survival. This B cell-high group
208 was, in particular, found to respond better to PD-1 blockade therapy, although this should be
209 validated on a larger cohort.

210 The field of immuno-oncology is rapidly expanding and it is critical to accurately identify
211 patients likely to respond. Here, we propose a new classification for STS that is immune-centric
212 with prognostic impact. It defines a group with better response to anti-PD-1 therapy marked by
213 B cells and TLS. This finding may have broad applications. Indeed, sarcomas are considered
214 as immune quiescent tumours, with a low mutational burden. Nevertheless, our data show that
215 some STS are immunogenic and that this is driven by B cells. Further work is needed to extend
216 these findings to all STS histologies and other cancers. Similarly, the underlying mechanisms
217 require further investigation, but a possible explanation is that TLS are sites where anti-tumoral
218 immunity is generated with B cells instructing T cells, in particular CD8⁺ T cells, to recognize
219 tumour-associated antigens²⁶. It is indeed striking that TLS-rich tumours are more infiltrated by
220 CD8⁺ T cells. These T cells can become exhausted, explaining the correlation of expression of

221 immune checkpoints (PD-1, Lag-3, ...) with TLS, and why treatment with checkpoint inhibitors
222 may allow productive anti-tumour immunity in TLS-rich tumours. Overall, our findings lay the
223 foundation for a tool to risk-stratify STS patients and identify those who may be more likely to
224 benefit from immunotherapies, and may be broadly applicable to other malignancies²⁶⁻³⁰.

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297 blockade response. *Nature* (2019).
298

299 **Figure legends**

300

301 **Figure 1: The Sarcoma Immune Classes exhibit strongly different tumour**
302 **microenvironments.**

303 This figure refers to the TCGA SARC cohort (n=213). **a** Composition of the TCGA SARC
304 cohort by SIC, and histology. **b** Composition of the TME by sarcoma immune class (SIC) as
305 defined by the MCP-counter Z-scores. **c** Expression of gene signatures related to the functional
306 orientation of the immune TME by SIC. **d** Expression of genes related to immune checkpoints
307 by SIC. Adjusted p-values are obtained from Benjamini-Hochberg correction of two-sided
308 Kruskal-Wallis tests p-values.

309

310 **Figure 2: SICs and B cells are predictive of STS patients' survival**

311 This figure refers to TCGA SARC and GSE21050 pooled cohorts (n=496). **a** Overall survival
312 of STS patients by SIC of their tumour. **b** Multivariate Cox proportional regression outcome,
313 with all included variables represented. For each variable, the reference level is the first one. A
314 grey bar indicates a p-value above 0.05, and variables indicated by green and red bars
315 significantly associated with prognosis in this multivariate model, respectively positively and
316 negatively. Error bars represent 95% confidence interval. **c-d** Overall survival of STS patients
317 according to MCP-counter scores for CD8⁺ T cells (**c**) or B lineage (**d**). **e** Overall survival of
318 patients based on the tumoural infiltration by B lineage cells and CD8⁺ T cells. The analyses
319 were performed with the Kaplan-Meier estimates and two-sided logrank tests. Tumours were
320 considered high for CD8⁺ T cells if their score was above median, and for cytotoxic
321 lymphocytes and B lineage if their score was above the third quartile, in each cohort. FNCLCC:
322 Fédération Nationale des Centres de Lutte Contre le Cancer.

323

324 **Figure 3: Tertiary lymphoid structures (TLS) are a distinguishing feature of the immune-**
325 **high class of STS.**

326 This figure refers to the NTUH cohort (n=93). **a** Populational characterization of tertiary
327 lymphoid structures. Left, examples of two tertiary lymphoid structures by IHC, identified as
328 CD3⁺ T cell (blue) aggregates containing DC-Lamp⁺ mature dendritic cells (red, red arrows)
329 and juxtaposing CD20⁺ B cell aggregates (brown). Right, representative immunofluorescence
330 staining of a TLS for CD3 (magenta), CD20 (green) and PD-1 (cyan). DAPI staining is shown
331 in blue. The multispectral image shows CD3⁺PD-1⁺ double positive cells (yellow arrows). **b**
332 Functionality of tertiary lymphoid structures. Left, CXCR5⁺ (magenta), CD4⁺ (yellow) and PD-
333 1⁺ (green) cells in zones 3 and 4 of the same TLS. Multispectral fluorescence images of zones
334 3 and 4 show CXCR5⁺CD4⁺PD-1⁺ triple positive cells (red arrows) characteristic of T follicular
335 helper cells. Right, CD20⁺ cells stained in pink (left) on consecutive sections of a TLS. CD23
336 (green on left) and CD21 (brown on right) positive cells with reticular morphology
337 characteristic of follicular dendritic cells (yellow arrow, zone 1). PNA⁺ structures (brown,
338 green arrow) with high endothelial venule morphology are also detectable nearby (zone 2). **c**
339 Number of TLS among 5 SICs of 73 tumours of NTUH cohort (n=73). **d** Characterization of
340 the immune infiltrate in tumours according to TLS presence (TLS⁻ n=82, TLS⁺ n=11, total
341 n=93). Densities of CD3⁺ (left), CD8⁺ (centre) and CD20⁺ (right) cells in tumours lacking TLS
342 (TLS⁻) or containing TLS (TLS⁺); densities including (total) or excluding (excl) TLS are
343 indicated for the TLS⁺ tumours. Boxplots represent median (larger bar) and interquartile range
344 (IQR). Upper whisker extends to whichever is minimal, maximum or 3rd quartile plus 1.5*IQR.
345 Lower whisker extends to whichever is maximal, minimum or first quartile minus 1.5*IQR.
346 For panel **d**, p-values were computed with two-sided Mann-Whitney tests.

347

348 **Figure 4: SICs are strongly associated with STS response to PD-1 blockade therapy.**

349 This figure refers to the SARC028 cohort (n=47). **a** Relationship between SIC, histology and
350 response to treatment in the SARC028 cohort. **b** Waterfall plot showing the best response to
351 pembrolizumab as percentage change in size of target lesions from baseline (n=45). Tumour
352 sizes were calculated as the sum of target lesion diameters. The colours indicate the SIC to
353 which each tumour was assigned. Dashed lines indicate +20%, -30% and -100% change from
354 baseline levels. SIC E vs other comparison was performed using a two-sided Mann-Whitney
355 test. **c** Progression-free survival of patients by tumour SIC (n=47). DDLPS: dedifferentiated
356 liposarcoma, LMS: leiomyosarcoma, UPS: undifferentiated pleomorphic sarcoma, SS: synovial
357 sarcoma.

358 **METHODS (2039 words)**

359 **Ethics and patients**

360 Patients diagnosed with dedifferentiated liposarcoma, leiomyosarcoma, and undifferentiated
361 pleomorphic sarcoma were identified and the pathology diagnosis confirmed by a certified
362 pathologist in National Taiwan University Hospital. The research was approved by the
363 Research Ethics Committee of NTUH (201605061RINA). Informed consent was obtained from
364 all subjects. Formalin-fixed paraffin embedded (FFPE) blocks were retrieved and 4-5 μm
365 thickness slides were taken for immunohistochemistry staining and RNA extraction for
366 Nanostring testing. Other cohorts were previously published^{4,8,31-35}.

367 **Establishing the immune classification of STS**

368 To establish a robust immune classification of STS, publicly available transcriptomic data from
369 The Cancer Genome Atlas (TCGA) data portal and Gene Expression Omnibus (GEO)
370 repository representing 4 large and independent patient cohorts were included. Only tumours
371 from the most common histologies of genomically complex STS were included:
372 leiomyosarcoma (LMS), undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated
373 liposarcoma (DDLPS). We analysed data from the TCGA SARC⁸ (n = 213), GSE21050³¹ (n =
374 283), GSE21122³² (n = 72) and GSE30929³³ (n = 40) cohorts.

375 *Public transcriptomic data pre-processing*

376 Transcriptomic data was downloaded from the TCGA data portal (SARC cohort) and Gene
377 Expression Omnibus (Accession codes: GSE21050, GSE21122 and GSE30929). TCGA SARC
378 was restricted to complex genomics sarcomas (UPS, DDLPS and LMS). Normalized TCGA
379 SARC RNA-Seq data was log₂-transformed. Micro-array data was normalized using frozen-
380 RMA method³⁶ from the R package frma. Batch effect was corrected across series using
381 ComBat³⁷, with histology as covariate.

382 *Estimation of the TME composition*

383 TME composition of each tumour was assessed with the MCP-counter tool⁹, which provides
384 abundance scores for 8 immune (T cells, CD8⁺ T cells, cytotoxic lymphocytes, NK cells, B cell
385 lineage, monocytic lineage, myeloid dendritic cells and neutrophils), and 2 stromal populations
386 (endothelial cells and fibroblasts). The scores are based on analysis of transcriptomic markers,
387 i.e. transcriptomic features that are strongly, specifically and stably expressed in a unique cell
388 population. These scores are proportional to each cell population's abundance in the tumour,
389 therefore allowing inter-sample comparison and large cohort analyses³⁸. The MCP-counter
390 signatures composition are as follows: T cells: *CD28, CD3D, CD3G, CD5, CD6, CHRM3-AS2,*
391 *CTLA4, FLT3LG, ICOS, MAL, MGC40069, PBX4, SIRPG, THEMIS, TNFRSF25, TRAT1;*
392 CD8⁺ T cells: *CD8B*, cytotoxic lymphocytes: *CD8A, EOMES, FGFBP2, GNLY, KLRC3,*
393 *KLRC4, KLRD1*; B lineage: *BANK1, CD19, CD22, CD79A, CR2, FCRL2, IGKC, MS4A1,*
394 *PAX5*; NK cells: *CD160, KIR2DL1, KIR2DL3, KIR2DL4, KIR3DL1, KIR3DS1, NCR1,*
395 *PTGDR, SH2D1B*; monocytic lineage: *ADAP2, CSF1R, FPR3, KYNU, PLA2G7, RASSF4,*
396 *TFEC*; myeloid dendritic cells: *CD1A, CD1B, CD1E, CLEC10A, CLIC2, WFDC21P*;
397 neutrophils: *CA4, CEACAM3, CXCR1, CXCR2, CYP4F3, FCGR3B, HAL, KCNJ15, MEGF9,*
398 *SLC25A37, STEAP4, TECPR2, TLE3, TNFRSF10C, VNN3*; endothelial cells: *ACVRL1, APLN,*
399 *BCL6B, BMP6, BMX, CDH5, CLEC14A, CXorf36, EDN1, ELTD1, EMCN, ESAM, ESM1,*
400 *FAM124B, HECW2, HHIP, KDR, MMRN1, MMRN2, MYCT1, PALMD, PEAR1, PGF,*
401 *PLXNA2, PTPRB, ROBO4, SDPR, SHANK3, SHE, TEK, TIE1, VEPHI, VWF.*

402 *Intra-cohort immune classifications*

403 Fibroblasts signature was removed from this analysis as all STS tumours exhibited high and
404 homogeneous scores for this cell population, which is consistent with the mesenchymal origin
405 of STS. The signature for CD8 T cells was removed from the analysis for GSE21050,
406 GSE21122 and GSE30929 as it showed very small variation across all samples in these

407 microarray-based cohorts. Unsupervised clustering of samples in each cohort was performed
408 based on the metagene Z-score for the included populations of MCP-counter (Extended Data
409 Fig. 9a-d) using R software, with the Euclidian distance and Ward's linkage criterion, using the
410 gplots package. The TCGA SARC, GSE21050, GSE21122 and GSE30929 cohorts were
411 respectively separated into 6, 9, 7 and 6 groups. The number of clusters was chosen empirically
412 following the dendrograms shown in Extended data Fig. 9a-d. Analysis of the inter-sample
413 variance revealed that much of the explainable variance was already attained at the chosen
414 number of clusters as visualized in Extended Data Fig. 9e-h.

415 *Pan-cohort immune classes*

416 To aggregate the above four intra-cohort classifications, the transcriptome matrix of each cohort
417 was independently zero-centred for each gene across all samples. Then we computed the
418 centroids of each class over the whole transcriptome and analysed the Pearson correlations
419 between all the centroids on the set of genes shared across the four cohorts (Extended Data Fig.
420 9i). From these correlations, we deduced 5 Sarcoma Immune Classes (SICs). The tumours from
421 6 remaining cohort-specific clusters shared intermediate/weak correlation patterns to other
422 clusters and were temporarily labelled as "Unclassified".

423 *Prediction of the immune classes*

424 Centroids of SICs were computed on MCP-counter intra-series Z-scores for T cells, cytotoxic
425 lymphocytes, B cell lineage, NK cells, monocytic lineage, myeloid dendritic cells, neutrophils
426 and endothelial cells, on all cohorts. To predict *de novo* the immune classes of each of the
427 cohorts, MCP-counter Z-scores were computed, and each sample was assigned to the closest
428 immune class based on its Euclidian distance to the related centroids. The SICs labels used in
429 the article are the ones predicted using this method. Principal component analysis of the 608
430 samples on the MCP-counter scores shows that the intra-SIC homogeneity was improved by

431 this prediction step (Extended Data Fig. 9j-k), as confirmed by supervised tests across SICs
432 (Extended Data Fig. 9l-m).

433 **Gene signatures for the functional orientation**

434 The signatures used to determine the functional orientation of the TME were derived from the
435 literature³⁹. The signatures were the following: Immunosuppression (*CXCL12*, *TGFB1*,
436 *TGFB3*, *LGALS1*), T cell activation (*CXCL9*, *CXCL10*, *CXCL16*, *IFNG*, *IL15*), T cell survival
437 (*CD70*, *CD27*), regulatory T cells (*FOXP3*, *TNFRSF18*), major histocompatibility complex I
438 (*HLA-A*, *HLA-B*, *HLA-C*, *HLA-E*, *HLA-F*, *HLA-G*, *B2M*), myeloid cell chemotaxis (*CCL2*), and
439 tertiary lymphoid structures (*CXCL13*). For each signature, scores were computed as the
440 geometric mean signature expression.

441 **De novo prediction of the SICs of additional cohorts and other platforms**

442 *Prediction of the immune classes on new samples*

443 The predictor described above was adapted to analyse new and independent samples, from
444 Nanostring-analysed FFPE samples. In a first step, SICs were estimated on the NTUH cohort
445 by sorting samples on the B lineage signature, T cells signature then Endothelial cell signature
446 and assigning each sample according to the SIC it resembled the most. Similarly to what was
447 done above, centroids of each SIC on Nanostring data MCP-counter scores Z-scores were
448 computed and samples were reassigned to the SIC they were closest to the centroid of. For new
449 samples from the SARC028 cohort, MCP-counter scores for T cells, Cytotoxic lymphocytes, B
450 lineage and Endothelial cells were computed and transformed as Z-scores. Distances with
451 Nanostring-defined centroids presented above were computed with Euclidian metric, and
452 samples were assigned to the SIC with the lowest distance.

453 *RNA extraction from FFPE tumours*

454 Human FFPE tumour specimens were cut into 3 μm thick sections and were reviewed under
455 microscope for tumour histology. Non-tumour tissues were excluded and tumour tissues were
456 deparaffinized by deparaffinization solution (Qiagen cat. # 19093) and RNA were extracted by
457 RNeasy FFPE kit (Qiagen cat. # 73504) according to the manufacturer's protocol. RNA quality
458 and size distribution was determined by the Agilent 2100 Bioanalyzer with RNA analysis kits
459 (RNA 6000 nano kit cat. # 5067-1511, RNA 6000 nano reagent cat. # 5067-1512, RNA 6000
460 nano ladder cat. # 5067-1529, RNA 6000 pico kit cat. # 5067-1513, RNA 6000 pico reagents
461 cat. # 5067-1514, RNA 6000 pico ladder cat. # 5067-1535) for cohorts NTUH core and NTUH
462 whole, and by the Agilent RNA ScreenTape assay (catalogue # : RNA ScreenTape 5067-5576,
463 RNA ScreenTape sample buffer 5067-5577, RNA ScreenTape ladder 5067-5578) and Agilent
464 2200 TapeStation for cohort SARC028. The samples from SAR028 were separately quality
465 controlled by the sarcoma pathology group at MD Anderson Cancer Center.

466 *Nanostring nCounter analysis*

467 The RNA was analysed using the nCounter Technology (Nanostring Technologies) as per the
468 manufacturer's protocol. Data were normalized using the nSolver software (Nanostring
469 Technologies).

470 **Enzymatic and fluorescent multiplexed immunohistochemistry**

471 The FFPE human tumour and control specimens were cut into 3- μm -thick sections. Human
472 FFPE tonsil sections were used as positive controls for CD3, CD4, CD8, CD20, CD21, CD23,
473 CD34, CXCR5, DC-Lamp, PD1, PD-L1 and PNA_d, placenta sections were used in addition for
474 PD-L1 and cerebral cortex tissue was used as a negative control. The specificity of all the
475 antibodies were tested by the manufacturers and the specificity of anti-PD-1 antibodies was
476 validated in our laboratory on overexpressing cells pellets as previously reported⁴⁰. Antigen
477 retrieval was carried out on a PT-link (Dako) using the EnVision FLEX Target Retrieval

478 Solutions at High pH (Dako, K8004) or Low pH (Dako, K8005). Endogenous peroxidase
479 activity and non-specific Fc receptor binding were blocked with H₂O₂ 3% (Gifrer, 10603051)
480 and Protein Block (Dako, X0909) respectively. The primary and secondary antibodies used for
481 IHC and IF are summarized in Extended data table 2. IHC and IF images were independently
482 analysed by three observers (LL, CSF, GL).

483 *Enzymatic immunohistochemistry*

484 The stainings were performed with an Autostainer Link 48 (Dako). Chromogenic detection was
485 performed using 3,3'-diaminobenzidine (Dako, K3468) for CD8, CD20, CD21, PD-L1 and
486 PNAd, 3-amino-9-ethylcarbazole substrate (Vector Laboratories, SK-4200) for DC-Lamp, Blue
487 Alkaline Phosphatase Substrate (Vector Laboratories, SK5300) for CD3, HighDef red IHC
488 chromogen (AP) (Enzo, ADI-950-140-0030) for CD20 and Permanent HRP Green (Zytomed
489 Systems, ZUC070-100) for CD23 and CD34. The nuclei were counterstained with
490 haematoxylin (Dako, S3301). After mounting with Glycergel Mounting Medium (Dako,
491 C056330-2) or EcoMount (Biocare Medical, EM897L), the slides were scanned with a
492 Nanozoomer (Hamamatsu). For CD3, CD8, CD20 and DC-Lamp markers, the density of
493 positive cells/mm² was quantified with Calopix Software (Tribvn). For CD34 marker, the
494 density of positive vessels/mm² was quantified with Halo10 software (Indica labs). TLS were
495 identified using the registration module to fit one slide on the other (Halo10 software, Indica
496 labs). Tumours were considered TLS-positive when a CD3 aggregate with DC-Lamp staining
497 was found juxtaposing a CD20 aggregate. Only aggregates with surface above 60,000 μm²,
498 containing at least 700 cells and at least 350 CD20⁺ cells were considered.

499 *Fluorescent multiplexed immunohistochemistry*

500 For the PD1/CD20/CD3 3-plex staining, a tyramide system amplification (TSA) was used. The
501 stainings were performed with a Leica Bond RX. The incubation with TSA reagent was

502 performed after the incubation of the HRP-conjugated polymer and was followed by antibody
503 stripping at 97°C for 10 minutes. This protocol was repeated for the second and third primary
504 antibodies and corresponding polymer incubations. The dilutions used for the TSA are 1:400
505 for TSA AF488, 1:800 for TSA AF594 and 1:200 for TSA AF647 following the manufacturer's
506 recommendations. For the CXCR5/CD4/PD-1 3-plex staining, we used a conventional
507 fluorescent-dye conjugated secondary antibody system performed manually (all secondary
508 antibodies were diluted at 1:100). For all the fluorescent stainings, the nuclei were stained with
509 DAPI Solution (Thermo Fisher, 62248) at 2µg/ml for 10 minutes. After mounting with
510 ProLong™ Gold Antifade Mountant (Thermofisher, P36934), the slides were scanned with a
511 Zeiss Axio Scan.Z1.

512 **Statistical analysis**

513 All statistical analyses were performed using the R software (version 3.4.4) and the packages
514 survival, gplots, dunn.test and FactoMineR. The relationship between two categorical variables
515 was estimated with the chi-square test. The relationship between a categorical variable and a
516 quantitative variable was estimated with the Mann-Whitney U test (2 categories) or the
517 Kruskal-Wallis test (3 or more categories). All tests were two-sided. In cases with 3 or more
518 categories, pairwise comparisons were carried with Dunn tests. The relationship between two
519 quantitative variables was estimated with the Pearson correlation. When appropriate, p-values
520 were corrected for multiple hypothesis testing with the Bonferroni or Benjamini-Hochberg
521 methods, as specified in the text or figure legends. Survival was analysed with Kaplan-Meier
522 estimates and logrank tests. Box plots represent median (larger bar) and interquartile range
523 (IQR). Upper whisker extends to whichever is minimal, the maximum of the data or the 3rd
524 quartile plus 1.5*IQR. Lower whisker extends to whichever is maximal, the minimum of the
525 data or the first quartile minus 1.5*IQR.

526 **Data and Code Availability statement**

527 The transcriptomic datasets analysed in this study can be accessed on the GDC Portal
528 (portal.gdc.cancer.gov, cohort TCGA SARC) and the Gene Expression Omnibus repository
529 (www.ncbi.nlm.nih.gov/geo, accession numbers GSE21050, GSE21122, GSE30929). FSG
530 cohort data is publicly available from ArrayExpress for GIST (www.ebi.ac.uk/arrayexpress,
531 accession code E-MTAB-373) and from Gene Expression Omnibus for synovial sarcomas
532 (www.ncbi.nlm.nih.gov/geo, accession number GSE40021). Myxoid liposarcomas from the
533 FSG cohort are available upon reasonable request to the authors. Immunohistochemistry and
534 gene expression data related to NTUH cohort (Fig. 3, Extended Data Figs. 7 and 8) are available
535 upon reasonable request to WHF (herve.fridman@crc.jussieu.fr). The data that support the
536 findings related to Fig. 4 are available from SARC but restrictions apply to the availability of
537 these data, which were used under license for the study. Data are however available upon
538 reasonable request to HAT (HTawbi@mdanderson.org) and with permission of SARC. All
539 code used in this study is available from the authors upon reasonable request.

540

541 **Additional references for methods**

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564 the Microenvironment of Primary and Metastatic Renal Cell Cancer. *Clin. Cancer Res.* **21**,
565 3031–3040 (2015).

566 **Acknowledgements**

567 This work was supported by the Institut National de la Santé et de la Recherche Médicale, the
568 Université de Paris, Sorbonne University, the Programme Cartes d'Identité des Tumeurs (CIT)
569 from the Ligue Nationale Contre le Cancer, grants from Institut National du Cancer (HTE-
570 INSERM plan cancer, C16082DS), Association pour la Recherche sur le Cancer (ARC), Cancer
571 Research for Personalized Medecine programme (CARPEM T8), French Sarcoma Group, the
572 European Connective Tissue Cancer Network (CONTICANET, FP6-018806), "FONCER
573 contre le cancer" programme, Labex Immuno-Oncology (LAXE62_9UMRS972 FRIDMAN),
574 the National Institutes of Health (EZK is supported by T32CA0095999) and the Moon Shot
575 program at MD Anderson Cancer Center. Grants from the Ministry of Education (NTU-
576 107L9014) and Ministry of Science and Technology (MOST 107-3017-F-002 -002-), Taiwan
577 and from the National Taiwan University (YongLin Chair Grant S-01 and S-03) also supported
578 this study. SARC028 was jointly funded by Merck, Inc, SARC, Sarcoma Foundation of
579 America, and the QuadW Foundation. FP is supported by CARPEM doctorate fellowship. CLR
580 is recipient of the Paul Calabresi Clinical Oncology Award (K12 CA088084).

581 The slides stained for IF were scanned and analysed at the "Centre d'Histologie, d'Imagerie et
582 de Cytométrie" (CHIC), Centre de Recherche des Cordeliers UMRS1138 (Paris, France). CHIC
583 is a member of the Sorbonne University Flow Cytometry Network (RECYF). We thank
584 Christophe Klein, Kevin Garbin and Estelle Devevre from the CHIC for their support with the
585 imaging. The nanostring analysis of the NTUH core cohort was performed by the "Plateforme
586 Génomique" of the Institut Curie (Paris, France). We thank David Gentien and Emilie Henry
587 for their support. We acknowledge the help of He Yan and Bhavana Singh from the Department
588 of Pathology of the MD Anderson Cancer Center.

589

590 **Author contributions**

591 FP, WHF, CSF, AdR, TWC, HAT, and AI designed the study and experiments. FP, AdR, CL
592 and YL performed the bioinformatics analysis. LL, GL, IN, LPH, AB, MM and FP carried the
593 immunohistochemistry experiments. JC, YMJ and JA performed anatomo-pathology revision
594 on the samples. EZK, CMS, WLW and KMW performed the RNA extraction and nanostring
595 experiments. TWC, AI, MT and HAT provided clinical guidance. TWC, MT, AI, EZK, AJL,
596 CLR, MAB, VB, DR and HAT cared for the patients and provided patient materials or clinical
597 data. FP, WHF, CSF, HAT, AdR, EZK, CLR, AJL, TWC, CMS, JAW and AI discussed the
598 data and wrote the text. WHF, CSF, AdR and HAT supervised the study and all authors
599 commented on the manuscript and approved the submission.

600

601 **Competing interest declaration**

602 WHF is a consultant for AstraZeneca, Novartis, Servier and Pierre Fabre. AI serves in the
603 advisory board of Bayer, Daiichi, Epizyme, Lilly, Novartis, Roche and Springworks, and
604 received research funding from Astra Zeneca, Bayer, Chugai, Merck, MSD, Novartis and
605 Pharmamar. JA is a consultant for AstraZeneca, Bayer, BMS, MSD and Roche and received
606 research funding from MSD, Pfizer and Pierre Fabre. JAW participated on advisory boards for
607 Merck, BMS, Novartis, Astra Zeneca, Roche Genentech and Illumina. MAB is a consultant for
608 EMD Serono, Immune Design, Eisai. HAT serves on advisory boards and receives consulting
609 fees from BMS, Merck and Genentech, and received research funding from BMS, Merck,
610 Celgene, GSK, and Genentech. TWC participated in advisory boards for Eisai and Lilly and
611 received research funds from Eisai. CLR received research funding from BMS. The other
612 authors declare no conflict of interest.

613

614 Correspondence and requests for materials should be addressed to WHF:
615 herve.fridman@crc.jussieu.fr.

616 **Extended Data Figure Legends**

617

618 **Extended Data Fig. 1: Diagram representation of analytic workflow**

619

620 **Extended Data Fig. 2: SICs in various STS histologies.**

621 **a** Repartition of the SICs in various histologies of TCGA SARC and GSE21050
622 (leiomyosarcoma [LMS], undifferentiated pleomorphic sarcoma [UPS], dedifferentiated
623 liposarcoma [DDLPS]), and FSG cohort (synovial sarcoma, myxoid liposarcoma,
624 gastrointestinal stromal tumour [GIST]).

625 **b** Survival of patients from the FSG cohort (n=136) according to SIC classification. Patients
626 with synovial sarcoma, myxoid liposarcoma and GIST were pooled. The analysis was
627 performed with the Kaplan-Meier estimates and two-sided logrank tests.

628

629 **Extended Data Fig. 3: The Sarcoma Immune Classes exhibit strongly different tumour**
630 **microenvironments.**

631 This figure refers to the GSE21050 cohort (n=283). **a** Composition of the GSE21050 cohort by
632 SIC, histology and site of disease. **b** Composition of the TME by sarcoma immune class (SIC)
633 as defined by the MCP-counter Z-scores. **c** Expression of gene signatures related to the
634 functional orientation of the immune TME by SIC. **d** Expression of genes related to immune
635 checkpoints by SIC. Adjusted p-values are obtained from Benjamini-Hochberg correction of
636 two-sided Kruskal-Wallis tests p-values. These observations stand for cohorts GSE21122 and
637 GSE30929 (not shown).

638

639 **Extended Data Fig. 4: Distribution of MCP-counter scores** in TCGA SARC (n=213) (**a,c,e**)
640 and GSE21050 (n=283) (**b,d,e**), for CD8⁺ T cells (**a,b**), cytotoxic lymphocytes (**c,d**) and B
641 lineage (**e,f**). The blue line indicates the density curve. The red dotted line indicates the cut-off
642 chosen to segregate high or low values, set at the median for CD8⁺ T cells and at the third
643 quartile for cytotoxic lymphocytes and B lineage, in each cohort. These values were chosen
644 since the CD8 T cells scores present a normal distribution, while the cytotoxic lymphocytes and
645 B lineage scores distribution exhibit a long right tail.

646

647 **Extended Data Fig. 5: B cell infiltration of STS is the key factor associated with overall**
648 **survival**

649 This figure refers to TCGA SARC and GSE21050 pooled cohorts (n=496). **a** Overall survival
650 of STS patients according to MCP-counter scores for cytotoxic lymphocytes. **b** Overall survival
651 of patients based on the infiltration level of their tumours by B lineage cells and cytotoxic
652 lymphocytes. **c-e** Overall survival of patients based on degree of tumour infiltration by B
653 lineage cells and expression of (**c**) *PDCDI*, (**d**) *CD274* and (**e**) *FOXP3*. The analyses were
654 performed with the Kaplan-Meier estimates and two-sided log-rank tests. Tumours were
655 considered high for expression of *PDCDI*, *CD274* and *FOXP3* if their expression was above
656 median, and high for B lineage and cytotoxic lymphocytes if the MCP-counter score was above
657 the third quartile.

658

659 **Extended Data Fig. 6: The mutational landscape of STS tumours does not vary**
660 **significantly between SICs.**

661 This figure refers to the TCGA SARC cohort (n=213). **a** Mutational burden according to the
662 SIC of the tumours, expressed in number of non-silent mutations. P-value was computed with

663 a Kruskal-Wallis test. Boxplots represent median (larger bar) and interquartile range (IQR).
664 Upper whisker extends to whichever is minimal, maximum or 3rd quartile plus 1.5*IQR. Lower
665 whisker extends to whichever is maximal, minimum or first quartile minus 1.5*IQR. **b** Mutation
666 frequency of all genes that are mutated in greater than 2.5% of tumours. **c** Mutation frequency
667 for genes that are mutated in more than 5% of tumours, according to SICs in the TCGA SARC
668 cohort. The dashed lines indicate the overall mutation frequency. P-values were obtained
669 through one-sample two-sided t-tests, corrected for multiple testing with the Bonferroni
670 method. This was applied only to samples which had mutations on the considered genes (TP53:
671 n=75; ATRX: n=34; TTN: n=21; RB1: n=19; MUC16, n=17; PCLO, n=13; DNAH5, MUC17
672 and USH2A: n=11, PTEN, n=6; KRAS, n=2; BRAF, n=1).

673

674 **Extended Data Figure 7: Validation of SIC profiles by immunohistochemistry.**

675 This figure refers to the NTUH cohort **a** SIC attribution as defined by gene expression using
676 the MCP-counter Z-scores in 73 cases **b** Cell density counts showing the differences in TME
677 composition according to SIC identification of the 73 cases (SIC A: n=16; SIC C: n=10; SIC
678 E: n=11). P-values labelled KW are derived from two-sided Kruskal-Wallis tests. Pairwise
679 comparisons are derived from the Dunn test. Boxplots represent median (larger bar) and
680 interquartile range (IQR). Upper whisker extends to whichever is minimal, maximum or 3rd
681 quartile plus 1.5*IQR. Lower whisker extends to whichever is maximal, minimum or first
682 quartile minus 1.5*IQR. **c** Representative images of CD3 (green)/CD20 (pink), CD8 (brown)
683 and CD34 (green) expression by immunohistochemistry of SIC A, C and E tumours. The same
684 area of the tumour is represented (0.05 mm²) in each image. Similar results were observed on
685 the other tumours from the same SICs (SIC A: n=16; SIC C: n=10; SIC E: n=11).

686

687 **Extended Data Fig. 8: Location and maturation of TLS**

688 **a** Pearson correlation between the expression of CXCL13 and the 12-chemokine signature of
689 TLS in TCGA SARC cohort (n=213). Samples are coloured according to SICs. **b** Intratumoural
690 location of TLS in three different examples from the NTUH cohort, respectively DDLPS, UPS
691 and LMS. TLS are observed by the presence of CD20⁺ B cells aggregates (brown, surrounded
692 by blue shapes). The red line delineates the tumoural zone. Similar findings were observed on
693 the 11 tumours with TLS. **c** Definition of peripheral, medium and central zones, accounting for
694 25%, 25% and 50% of the total tumour area, respectively. **d** Distribution of TLS in the various
695 zones. Each bar represents one tumour. The letters above bars indicates the SIC of the tumour
696 when the sample passed quality control of Nanostring nCounter hybridization. Dots indicate
697 tumours in which SIC could not be determined because of RNA quality control. Similar images
698 were observed over 66 E-TLS, 23 PFL-TLS and 20 SFL-TLS. **e** Illustration of diverse degrees
699 of TLS maturation in STS tumours. Consistent with maturation events occurring in secondary
700 lymphoid organs, three maturation steps have been described for TLS: early follicle (E-TLS,
701 bottom), primary follicle-like (PFL-TLS, middle) and secondary follicle-like with germinal
702 centre (SFL-TLS, top) which differ in the presence of follicular dendritic cells (FDC) and in
703 their markers. E-TLS contain aggregates of CD20⁺ B cells and CD3⁺ T cells without FDC, PFL-
704 TLS contain CD21⁺ FDC (red dotted zones) and SFL-TLS contain a germinal centre, notably
705 visible through the presence of CD21⁺CD23⁺ FDC (yellow dotted zone). DAPI staining is
706 shown in white. DAPI-negative green dots correspond to fluorescent erythrocytes. **f**
707 Distribution of TLS maturation steps in a subset of tumours. Each bar represents one tumour.
708 Differences between the number of TLS observed here and in other figures can be explained by
709 use of non-consecutive slides or a different tumour block for some samples.

710

711 **Extended Data Fig. 9: Pan-cohort immune classification**

712 This figure refers to the four discovery cohorts: TCGA SARC (n=213), GSE21050 (n=283),
713 GSE21122 (n=72) and GSE30929 (n=40). **a-d** Heatmap and unsupervised hierarchical
714 clustering of the MCP-counter scores describing the tumour microenvironment. Each of the
715 population is represented by the Z-scores of the signature. **a** TCGA SARC. **b** GSE21050. **c**
716 GSE21122. **d** GSE30929. **e-h** Evolution of the variance explained by the clusters as a function
717 of the number of clusters. The red dots indicate the number of clusters that was retained in this
718 study. Each graph corresponds to the heatmap that is situated on its left. **i** Heatmap of the
719 Pearson correlation of centroids from each SIC class of discovery cohorts (TCGA SARC,
720 GSE21050, GSE21122, GSE30929, n=608), with 5 immune classes and 2 groups of
721 unclassified samples. **j-k** Principal component analysis of samples from the four discovery
722 cohorts (n=608), based on their normalized and merged MCP-counter scores. (**j** is coloured
723 according to the original classes, **k** is coloured according to the predicted immune classes,
724 showing a heightened homogeneity within each SIC class). **l-m** Composition of the TME with
725 classes defined as in **j** and **k** for the four discovery cohorts (n=608), expressed in cohort-specific
726 row Z-scores.

727 **Extended Data Tables titles and footnotes**

728

729 **Extended Data Table 1: Clinicopathological composition of the cohorts included in this**
730 **study.** For cohort GSE21050, sex information could not be retrieved for 14 patients. For cohort
731 NTUH, SIC could be determined for 73 patients only. NA: Not Available

732

733 **Extended Data Table 2: Antibodies used for immunohistochemistry and**
734 **immunofluorescence**

Sujet : Authors change

Date : Wed, 6 Nov 2019 17:09:45 +0100

De : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Pour : Florent Petitprez <Florent.petitprez@ligue-cancer.net>

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

to

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano , C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

--

Florent Petitprez, PhD

Ligue Nationale Contre le Cancer

Programme Cartes d'Identité des Tumeurs

Sujet : RE: ****URGENT**** Agreement needed for publication

Date : Tue, 5 Nov 2019 10:28:13 +0100

De : Aurélien De Reynies <Aurelien.DeReynies@ligue-cancer.net>

Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>, Keung, Emily <ekeung@mdanderson.org>, Wei-Wu (Tom) Chen <saxotomy@gmail.com>, Cheng-Ming Sun <cheng-ming.sun@crc.jussieu.fr>, Julien Calderaro <julien.calderaro@hmn.aphp.fr>, liippiil@yahoo.com.tw <liippiil@yahoo.com.tw>, mRNA0912@yahoo.com.tw <mRNA0912@yahoo.com.tw>, laetitia.lacroix@inserm.fr <laetitia.lacroix@inserm.fr>, antoine.bougouin@crc.jussieu.fr <antoine.bougouin@crc.jussieu.fr>, guillaume.lacroix@crc.jussieu.fr <guillaume.lacroix@crc.jussieu.fr>, Ivo Gameiro Natario <ivo.natario@gmail.com>, ADAM Julien <julien.adam@gustaveroussy.fr>, Lucchesi Carlo <c.lucchesi@bordeaux.unicancer.fr>, Laizet Yechan <y.laizet@bordeaux.unicancer.fr>, Toulmonde Maud <m.toulmonde@bordeaux.unicancer.fr>, Burgess, Melissa <burgessma@upmc.edu>, vanessab@crab.org <vanessab@crab.org>, Reinke, Denise <DReinke@sarctrials.org>, Kwani@mdanderson.org <Kwani@mdanderson.org>, Lazar, Alexander <alazar@mdanderson.org>, Roland, Christina Lynn <CLRoland@mdanderson.org>, Wargo, Jennifer <JWargo@mdanderson.org>, Italiano Antoine <A.Italiano@bordeaux.unicancer.fr>, catherine.fridman <catherine.fridman@crc.jussieu.fr>, Tawbi, Hussein <HTawbi@mdanderson.org>, FRIDMAN Hervé <herve.fridman@crc.jussieu.fr>, marco.moreira <Marco.moreira@outlook.fr>, wllwang@mdanderson.org <wllwang@mdanderson.org>

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to

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(addition of authors A. Bougouïn, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Best regards,

Aurélien de Reyniès

Sujet : Re: [EXT] ****URGENT**** Agreement needed for publication

Date : Tue, 5 Nov 2019 12:34:33 +0000

De : Keung,Emily Z. <EKeung@mdanderson.org>

Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Copie à : Echeverry,Lisa R <LEcheverry@mdanderson.org>

Hi Florent,

>

> "The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

>

> F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

>

> to

>

> F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano , C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

>

> (addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

>

> I agree with these changes."

>

> Thank you!

-Emily

Sujet : Re: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 17:14:00 +0800
De : Tom Chen <saxotomy@gmail.com>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

I agree with the author changes
Tom Wei-Wu Chen

Sujet : Re: ****URGENT**** Agreement needed for publication

Date : Tue, 5 Nov 2019 14:58:36 +0100

De : Cheng-Ming Sun <cheng-ming.sun@crc.jussieu.fr>

Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Copie à : Aurélien De Reynies <Aurelien.DeReynies@ligue-cancer.net>, Keung,Emily <ekeung@mdanderson.org>, Wei-Wu (Tom) Chen <saxotomy@gmail.com>, Julien Calderaro <julien.calderaro@hmn.aphp.fr>, liippiil@yahoo.com.tw <liippiil@yahoo.com.tw>, mRNA0912@yahoo.com.tw <mRNA0912@yahoo.com.tw>, laetitia.lacroix@inserm.fr, Antoine Bougouin <antoine.bougouin@crc.jussieu.fr>, Guillaume Lacroix (guillaume.lacroix@crc.jussieu.fr) <guillaume.lacroix@crc.jussieu.fr>, Ivo Gameiro Natario <ivo.natario@gmail.com>, ADAM Julien <julien.adam@gustaveroussy.fr>, Lucchesi Carlo <c.lucchesi@bordeaux.unicancer.fr>, Laizet Yechan <y.laizet@bordeaux.unicancer.fr>, Toulmonde Maud <m.toulmonde@bordeaux.unicancer.fr>, Burgess, Melissa <burgessma@upmc.edu>, vanessab@crab.org <vanessab@crab.org>, Reinke, Denise <DReinke@sarctrials.org>, Kwani@mdanderson.org, Lazar,Alexander <alazar@mdanderson.org>, Roland,Christina Lynn <CLRoland@mdanderson.org>, Wargo,Jennifer <JWargo@mdanderson.org>, Antoine Italiano <A.Italiano@bordeaux.unicancer.fr>, Catherine Sautès-Fridman <catherine.fridman@crc.jussieu.fr>, Tawbi,Hussein <HTawbi@mdanderson.org>, Hervé Fridman <herve.fridman@crc.jussieu.fr>, Marco Moreira <Marco.moreira@outlook.fr>, wlwang@mdanderson.org

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(addition of authors A. Bougouin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Thank you very much

--

Cheng-Ming Sun, PhD

Cordeliers Research Center

UMRS 1138

Team 13, Cancer, Immune Control and Escape

15 Rue de l'Ecole de Médecine

75006 PARIS

cheng-ming.sun@crc.jussieu.fr

Sujet : Re: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 10:05:09 +0100
De : Julien Calderaro <julien.calderaro@gmail.com>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

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to

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes

Best

Julien

Sujet : Email of agreement for Nature

Date : Thu, 7 Nov 2019 16:26:28 +0800

De : Yung-Ming Jeng <mrna0912@gmail.com>

Pour : Florent.Petitprez@ligue-cancer.net

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Best Regards

Yung-Ming Jeng

Sujet : Re: RE : **URGENT** Agreement needed for publication

Date : Tue, 5 Nov 2019 19:55:58 +0800

De : 莉萍 蕭 <liippiil@yahoo.com.tw>

Pour : Ivo Gameiro Natario <ivo.natario@gmail.com>

Copie à : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>, Aurélien De Reynies <Aurelien.DeReynies@ligue-cancer.net>, Keung,Emily <ekeung@mdanderson.org>, Wei-Wu (Tom) Chen <saxotomy@gmail.com>, Cheng-Ming Sun <cheng-ming.sun@crc.jussieu.fr>, Julien Calderaro <julien.calderaro@hmn.aphp.fr>, mRNA0912@yahoo.com.tw <mRNA0912@yahoo.com.tw>, laetitia.lacroix@inserm.fr <laetitia.lacroix@inserm.fr>, antoine.bougouin@crc.jussieu.fr <antoine.bougouin@crc.jussieu.fr>, guillaume.lacroix@crc.jussieu.fr <guillaume.lacroix@crc.jussieu.fr>, ADAM Julien <julien.adam@gustaveroussy.fr>, Lucchesi Carlo <c.lucchesi@bordeaux.unicancer.fr>, Laizet Yechan <y.laizet@bordeaux.unicancer.fr>, Toulmonde Maud <m.toulmonde@bordeaux.unicancer.fr>, Burgess, Melissa <burgessma@upmc.edu>, vanessab@crab.org <vanessab@crab.org>, Reinke, Denise <DReinke@sarctrials.org>, Kwani@mdanderson.org <Kwani@mdanderson.org>, Lazar,Alexander <alazar@mdanderson.org>, Roland,Christina Lynn <CLRoland@mdanderson.org>, Wargo,Jennifer <JWargo@mdanderson.org>, Italiano Antoine <A.Italiano@bordeaux.unicancer.fr>, catherine fridman <catherine.fridman@crc.jussieu.fr>, Tawbi,Hussein <HTawbi@mdanderson.org>, FRIDMAN Hervé <herve.fridman@crc.jussieu.fr>, marco moreira <Marco.moreira@outlook.fr>, wllwang@mdanderson.org <wllwang@mdanderson.org>

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to

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes."

Best Regards,

Li-Ping Hsiao

Sujet : RE: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 10:05:44 +0100
De : laetitia.lacroix@inserm.fr
Pour : 'Florent Petitprez' <Florent.Petitprez@ligue-cancer.net>

"The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes."

Laetitia Lacroix

IMRB-U955-Equipe 9

"Immunologie et oncogénèse des tumeurs lymphoïdes"

Hôpital Henri Mondor

51 avenue du Mal De Lattre de Tassigny

94010 CRETEIL

Tél. : 01 49 81 37 68

Sujet : Agreement needed for publication
Date : Tue, 5 Nov 2019 10:15:50 +0100
De : Antoine BOUGOUIN <antoine.bougouin@upmc.fr>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

"The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano , C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman
(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes."

Antoine BOUGOUIN

Antoine BOUGOUIN - Ingénieur d'études
Centre de recherche des Cordeliers
Equipe 13 - Complément, Inflammation et Cancer
Esc E - 3e étage
15 rue de l'école de médecine
75006 PARIS
antoine.bougouin@crc.jussieu.fr
06.84.20.00.23

Sujet : Re: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 09:39:49 +0000
De : marco moreira <marco.moreira@outlook.fr>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Dear Florent,

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from
F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

to

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman
(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Best regards,

Moreira Marco

Cordeliers Research Center
UMR_S1138
Team 13, Inflammation, Complement and Cancer
15 Rue de l'Ecole de Médecine
75006 PARIS

marco.moreira@outlook.fr
+33 659096912

Sujet : Re: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 10:09:48 +0100
De : Guillaume LACROIX <guillaume.lacroix@upmc.fr>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Guillaume Lacroix
Assistant Engineer

Cordeliers Research Center
UMR_S1138
Team 13, Inflammation, Complement and Cancer
15 Rue de l'Ecole de Médecine
75006 PARIS
guillaume.lacroix@crc.jussieu.fr

Sujet : RE : ****URGENT**** Agreement needed for publication

Date : Tue, 5 Nov 2019 11:51:06 +0100

De : Ivo Gameiro Natario <ivo.natario@gmail.com>

Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>, Aurélien De Reynies <Aurelien.DeReynies@ligue-cancer.net>, Keung,Emily <ekeung@mdanderson.org>, Wei-Wu (Tom) Chen <saxotomy@gmail.com>, Cheng-Ming Sun <cheng-ming.sun@crc.jussieu.fr>, Julien Calderaro <julien.calderaro@hmn.aphp.fr>, liippiil@yahoo.com.tw <liippiil@yahoo.com.tw>, mRNA0912@yahoo.com.tw <mRNA0912@yahoo.com.tw>, laetitia.lacroix@inserm.fr <laetitia.lacroix@inserm.fr>, antoine.bougouin@crc.jussieu.fr <antoine.bougouin@crc.jussieu.fr>, guillaume.lacroix@crc.jussieu.fr <guillaume.lacroix@crc.jussieu.fr>, ADAM Julien <julien.adam@gustaveroussy.fr>, Lucchesi Carlo <c.lucchesi@bordeaux.unicancer.fr>, Laizet Yechan <y.laizet@bordeaux.unicancer.fr>, Toulmonde Maud <m.toulmonde@bordeaux.unicancer.fr>, Burgess, Melissa <burgessma@upmc.edu>, vanessab@crab.org <vanessab@crab.org>, Reinke, Denise <DReinke@sarctrials.org>, Kwani@mdanderson.org <Kwani@mdanderson.org>, Lazar,Alexander <alazar@mdanderson.org>, Roland,Christina Lynn <CLRoland@mdanderson.org>, Wargo,Jennifer <JWargo@mdanderson.org>, Italiano Antoine <A.Italiano@bordeaux.unicancer.fr>, catherine.fridman <catherine.fridman@crc.jussieu.fr>, Tawbi,Hussein <HTawbi@mdanderson.org>, FRIDMAN Hervé <herve.fridman@crc.jussieu.fr>, marco moreira <Marco.moreira@outlook.fr>, wllwang@mdanderson.org <wllwang@mdanderson.org>

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Best regards,

Ivo Natario

Sujet : RE:**URGENT** Agreement needed for publication
Date : Tue, 5 Nov 2019 20:33:31 +0000
De : ADAM Julien <Julien.ADAM@gustaveroussy.fr>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Dear Florent,

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Julien Adam

Sujet : Re: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 15:04:28 +0000
De : Lucchesi Carlo <c.lucchesi@bordeaux.unicancer.fr>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Sujet : RE:**URGENT** Agreement needed for publication

Date : Tue, 5 Nov 2019 09:47:08 +0000

De : Laizet Yechan <y.laizet@bordeaux.unicancer.fr>

Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>, Aurélien De Reynies <Aurelien.DeReynies@ligue-cancer.net>, Keung,Emily <ekeung@mdanderson.org>, Wei-Wu (Tom) Chen <saxotomy@gmail.com>, Cheng-Ming Sun <cheng-ming.sun@crc.jussieu.fr>, Julien Calderaro <julien.calderaro@hmn.aphp.fr>, liippiil@yahoo.com.tw <liippiil@yahoo.com.tw>, mRNA0912@yahoo.com.tw <mRNA0912@yahoo.com.tw>, laetitia.lacroix@inserm.fr <laetitia.lacroix@inserm.fr>, antoine.bougouin@crc.jussieu.fr <antoine.bougouin@crc.jussieu.fr>, guillaume.lacroix@crc.jussieu.fr <guillaume.lacroix@crc.jussieu.fr>, Ivo Gameiro Natario <ivo.natario@gmail.com>, ADAM Julien <julien.adam@gustaveroussy.fr>, Lucchesi Carlo <c.lucchesi@bordeaux.unicancer.fr>, Toulmonde Maud <m.toulmonde@bordeaux.unicancer.fr>, Burgess, Melissa <burgessma@upmc.edu>, vanessab@crab.org <vanessab@crab.org>, Reinke, Denise <DReinke@sarctrials.org>, Kwani@mdanderson.org <Kwani@mdanderson.org>, Lazar,Alexander <alazar@mdanderson.org>, Roland,Christina Lynn <CLRoland@mdanderson.org>, Wargo,Jennifer <JWargo@mdanderson.org>, Italiano Antoine <A.Italiano@bordeaux.unicancer.fr>, catherine.fridman <catherine.fridman@crc.jussieu.fr>, Tawbi,Hussein <HTawbi@mdanderson.org>, FRIDMAN Hervé <herve.fridman@crc.jussieu.fr>, marco moreira <Marco.moreira@outlook.fr>, wllwang@mdanderson.org <wllwang@mdanderson.org>

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Regards.

Yec'han

Yec'han LAIZET

Institut Bergonié, Bioinformatics

y.laizet@bordeaux.unicancer.fr

Poste : 44 24

Tel : +33 (0)5 56 33 04 24

229, cours de l'Argonne, 33000 BORDEAUX

Sujet : RE: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 14:43:57 +0000
De : Toulmonde Maud <m.toulmonde@bordeaux.unicancer.fr>
Pour : 'Florent Petitprez' <Florent.Petitprez@ligue-cancer.net>

Dear Florent,

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Maud TOULMONDE, MD

Institut Bergonié, Medical Oncology Dept

Early Phase Trials and Sarcoma Units

229 cours de l'Argonne

33076 Bordeaux Cedex France

Tel : + 33 5 47 30 60 88

+ 33 6 18 47 19 79

Fax : + 33 5 47 30 60 83

m.toulmonde@bordeaux.unicancer.fr

Sujet : RE: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 11:53:23 +0000
De : Burgess, Melissa <burgessma@upmc.edu>
Pour : 'Florent Petitprez' <Florent.Petitprez@ligue-cancer.net>

Dear Florent,

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Sincerely,

Melissa

Melissa Burgess

Assistant Professor of Medicine
University of Pittsburgh, Department of Medicine, Division of Hematology/Oncology

5150 Centre Avenue, Fifth Floor
Pittsburgh, PA 15232
T 412-623-7277

F 412-648-6579

Email burgessma@upmc.edu

Sujet : RE: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 15:44:01 +0000
De : vanessab (Vanessa Bolejack) <vanessab@crab.org>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Hello,

Regarding the following,

"The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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to

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano , C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Best Regards,

Vanessa Bolejack

Vanessa Bolejack, MPH

Biostatistician Consultant

Cancer Research and Biostatistics

Sujet : RE: ****URGENT**** Agreement needed for publication

Date : Tue, 5 Nov 2019 12:23:02 +0000

De : Reinke, Denise <DReinke@sarctrials.org>

Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>, Aurélien De Reynies <Aurelien.DeReynies@ligue-cancer.net>, Keung,Emily <ekeung@mdanderson.org>, Wei-Wu (Tom) Chen <saxotomy@gmail.com>, Cheng-Ming Sun <cheng-ming.sun@crc.jussieu.fr>, Julien Calderaro <julien.calderaro@hmn.aphp.fr>, liippiil@yahoo.com.tw <liippiil@yahoo.com.tw>, mRNA0912@yahoo.com.tw <mRNA0912@yahoo.com.tw>, laetitia.lacroix@inserm.fr <laetitia.lacroix@inserm.fr>, antoine.bougouin@crc.jussieu.fr <antoine.bougouin@crc.jussieu.fr>, guillaume.lacroix@crc.jussieu.fr <guillaume.lacroix@crc.jussieu.fr>, Ivo Gameiro Natario <ivo.natario@gmail.com>, ADAM Julien <julien.adam@gustaveroussy.fr>, Lucchesi Carlo <c.lucchesi@bordeaux.unicancer.fr>, Laizet Yechan <y.laizet@bordeaux.unicancer.fr>, Toulmonde Maud <m.toulmonde@bordeaux.unicancer.fr>, Burgess, Melissa <burgessma@upmc.edu>, vanessab@crab.org <vanessab@crab.org>, Kwani@mdanderson.org <Kwani@mdanderson.org>, Lazar,Alexander <alazar@mdanderson.org>, Roland,Christina Lynn <CLRoland@mdanderson.org>, Wargo,Jennifer <JWargo@mdanderson.org>, Italiano Antoine <A.Italiano@bordeaux.unicancer.fr>, catherine.fridman <catherine.fridman@crc.jussieu.fr>, Tawbi,Hussein <HTawbi@mdanderson.org>, FRIDMAN Hervé <herve.fridman@crc.jussieu.fr>, marco moreira <Marco.moreira@outlook.fr>, wlwang@mdanderson.org <wlwang@mdanderson.org>

I am in agreement with the change

Kindly,

Denise Reinke

Sujet : RE: [EXT] Re: ****URGENT**** Agreement needed for publication

Date : Wed, 6 Nov 2019 16:56:25 +0000

De : Wani,Khalida M <KWani@mdanderson.org>

Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>, Wang,Wei-Lien <wlwang@mdanderson.org>

Dear Florent,

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to

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano , C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Best regards,

Khalida Wani

Sujet : RE: [EXT] ****URGENT**** Agreement needed for publication

Date : Thu, 7 Nov 2019 13:23:22 +0000

De : Wang,Wei-Lien <wlwang@mdanderson.org>

Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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to

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano , C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Sujet : Alteration of Author list

Date : Tue, 5 Nov 2019 14:43:10 +0000

De : Lazar,Alexander <alazar@mdanderson.org>

Pour : 'Florent Petitprez' <Florent.Petitprez@ligue-cancer.net>

Hi Florent:

The list of authors of our manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response" was changed from:

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

to:

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougoüin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, K. M. Wani, W.L. Wang, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano , C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes as these four authors made important contributions and also have reviewed and approved of the final accepted version of the manuscript.

Best,

Alex

Sujet : Re: [EXT] ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 11:51:56 +0000
De : Roland,Christina Lynn <CLRoland@mdanderson.org>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Dear Florent,

"The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes."

Best Regards,

Christina Roland

Sujet : FW: [EXT] Re: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 14:45:47 +0000
De : Wargo, Jennifer <JWargo@mdanderson.org>
Pour : 'Florent Petitprez' <Florent.Petitprez@ligue-cancer.net>

Dear Florent

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Thank you very much

Jennifer Wargo

Sujet : RE:**URGENT** Agreement needed for publication
Date : Tue, 5 Nov 2019 09:44:42 +0000
De : Italiano Antoine <A.Italiano@bordeaux.unicancer.fr>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes."

Pr Antoine Italiano, MD, PhD
Institut Bergonie
Early Phase Trials and Sarcoma Units
229 cours de l'Argonne
33000 Bordeaux
Phone: + 33 5 47 30 60 88
Fax: + 33 5 47 30 60 83
E-mail: a.italiano@bordeaux.unicancer.fr

Sujet : Re: ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 12:44:51 +0100
De : Catherine Sautès Fridman <catherine.fridman@crc.jussieu.fr>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Dear Florent

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes."

Best Regards,

catherine sautès-Fridman

Sujet : Re: [EXT] ****URGENT**** Agreement needed for publication
Date : Tue, 5 Nov 2019 14:04:28 +0000
De : Tawbi,Hussein <HTawbi@mdanderson.org>
Pour : Florent Petitprez <Florent.Petitprez@ligue-cancer.net>

Dear Florent,

The list of authors of manuscript 2018-06-08855D, titled "B cells are associated with sarcoma survival and immunotherapy response", was changed from

F. Petitprez, A. de Reyniès, E. Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y. Laizet, M. Toulmonde, M. A. Burgess, V. Bolejack, D. Reinke, A. J. Lazar, C. L. Roland, J. A. Wargo, A. Italiano, C. Sautès-Fridman, H. A. Tawbi and W.H. Fridman

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(addition of authors A. Bougoüin, M. Moreira, K. M. Wani and W.L. Wang)

I agree with these changes.

Best,

Hussein

Hussein Tawbi, MD, PhD | Associate Professor

Deputy Chair, Department of Melanoma Medical Oncology

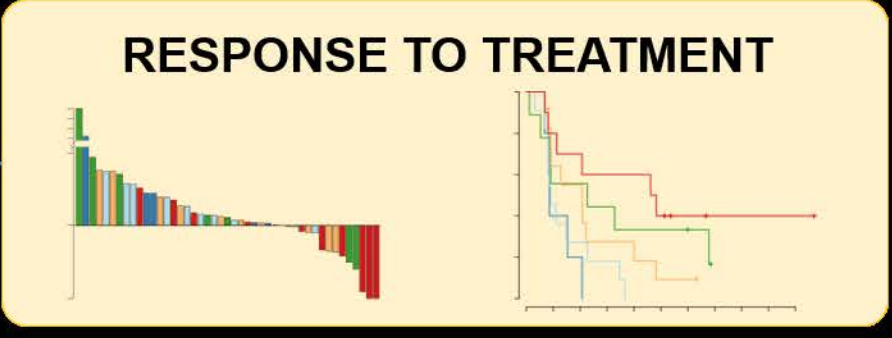
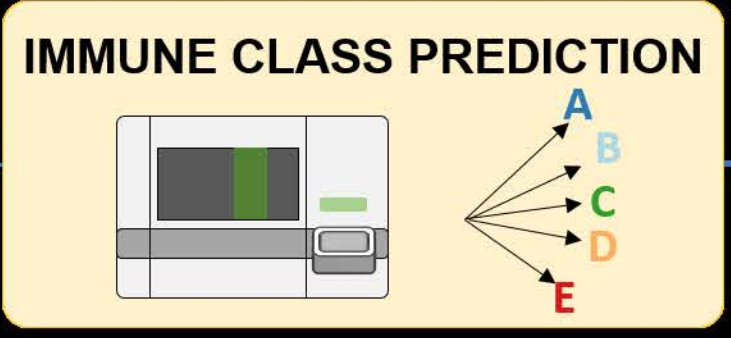
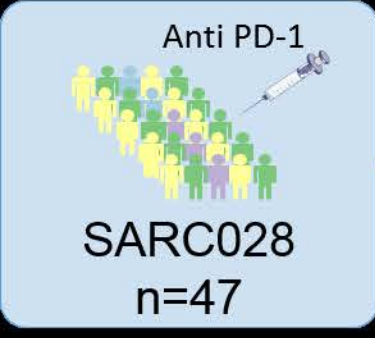
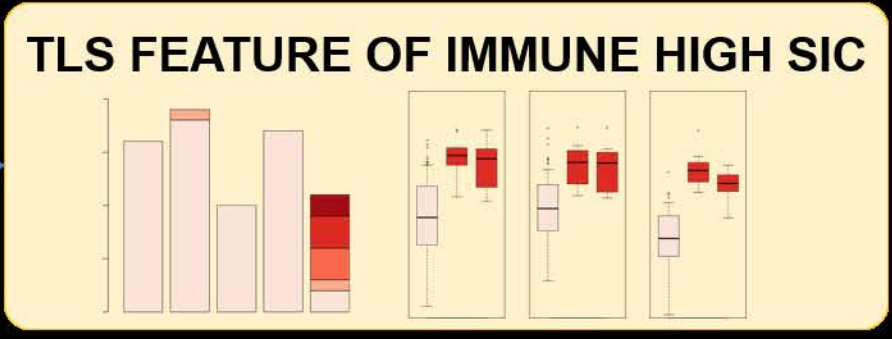
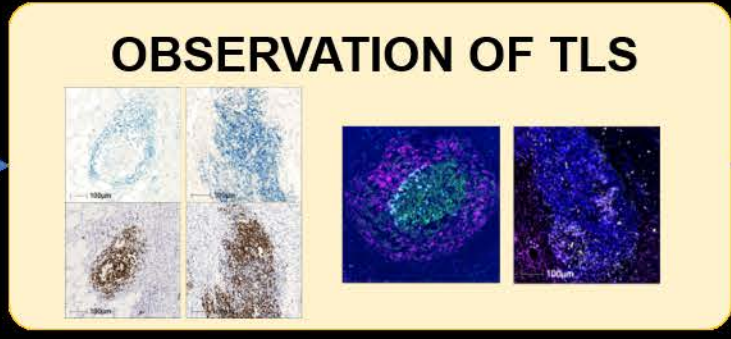
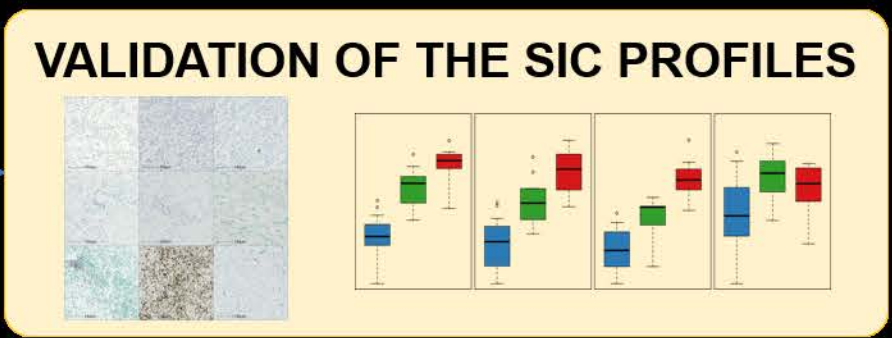
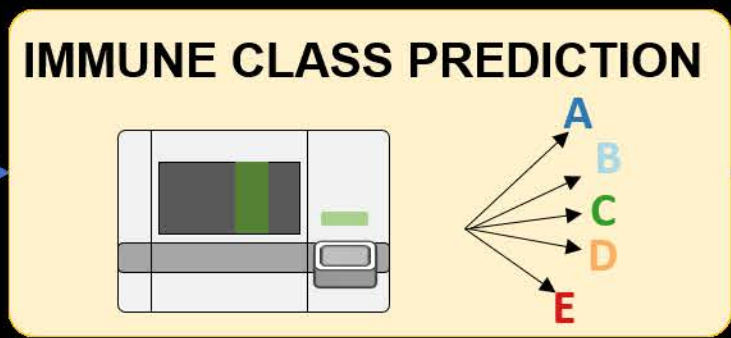
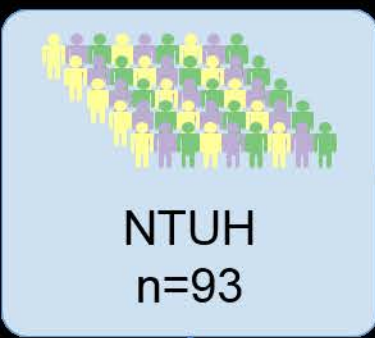
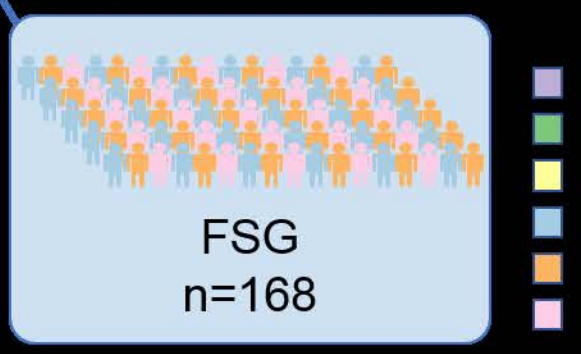
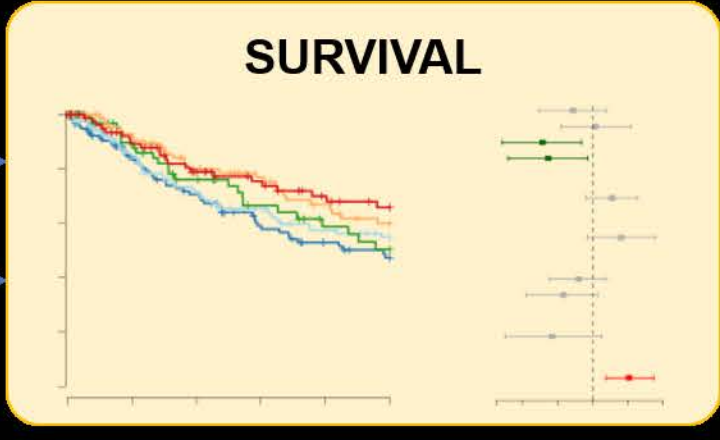
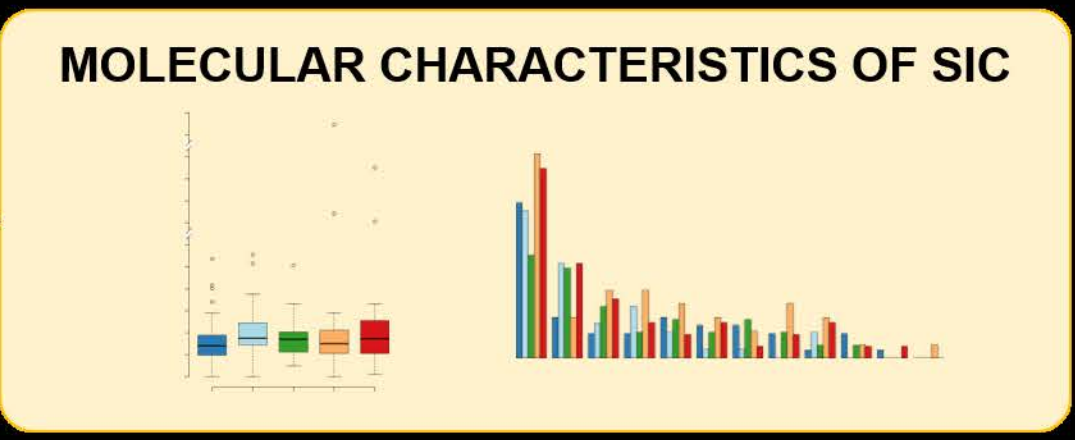
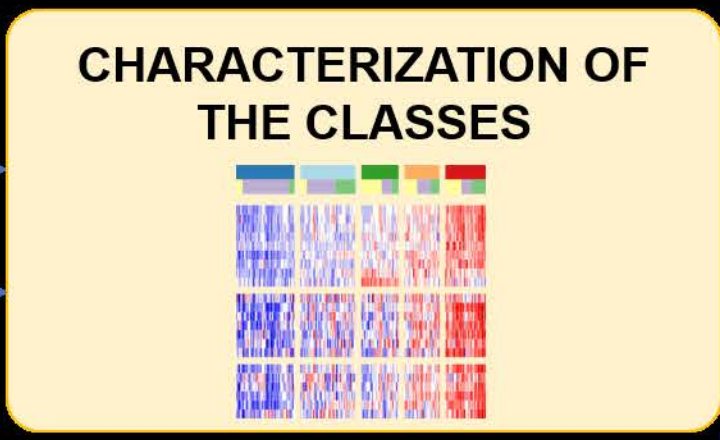
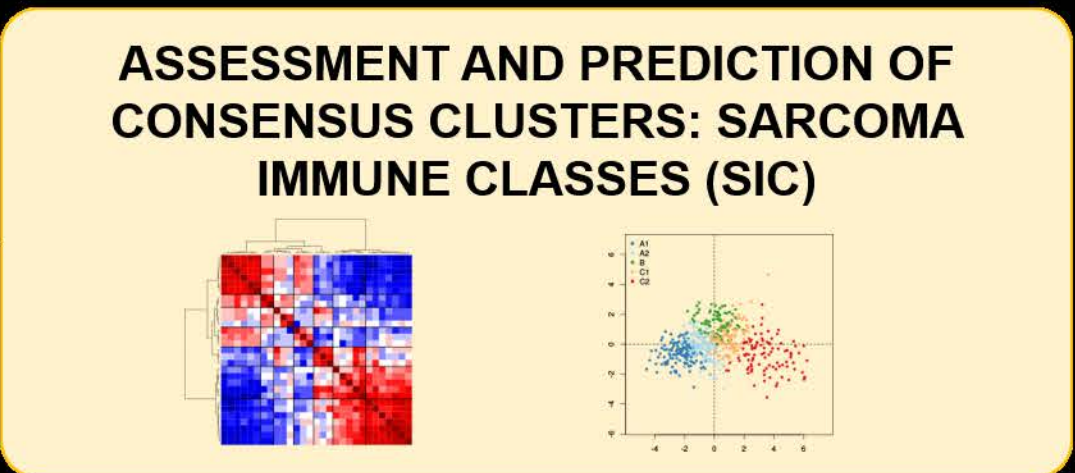
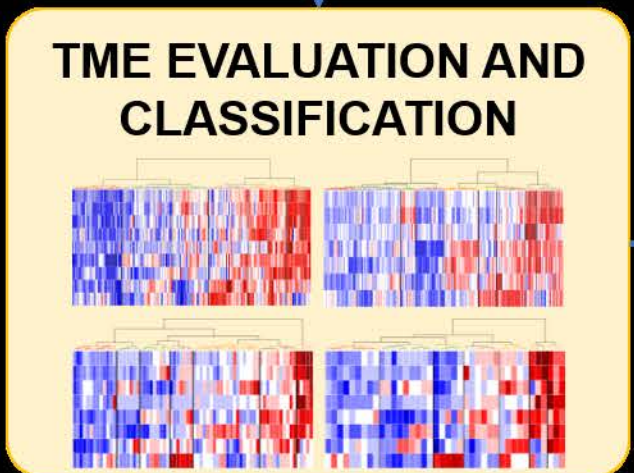
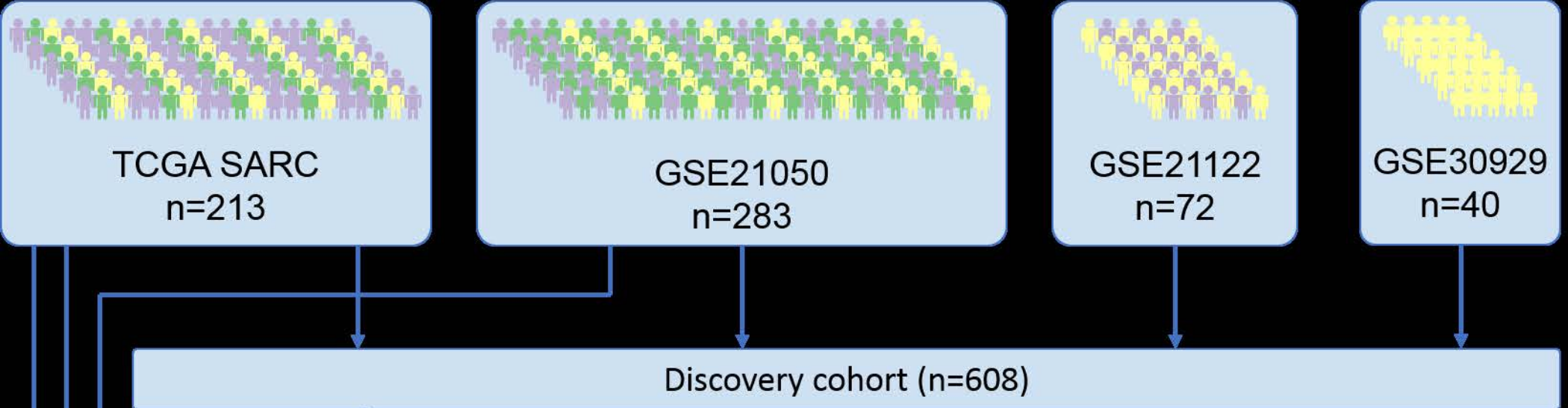
Director of Melanoma Clinical Research & Early Drug Development

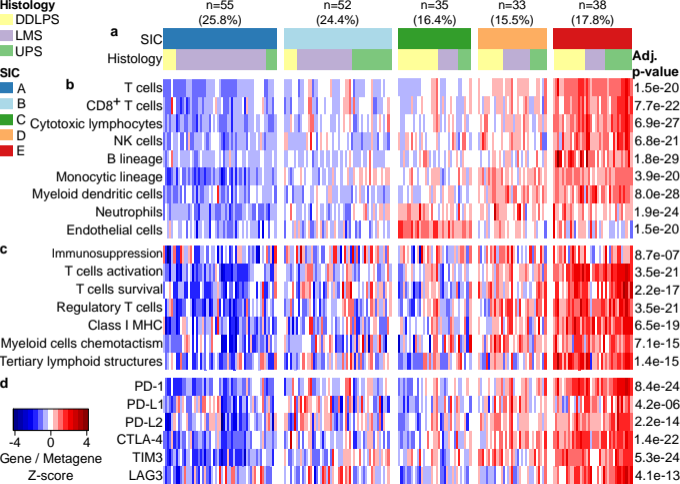
Co-Director, MD Anderson Brain Metastasis Clinic

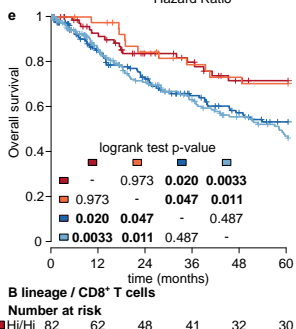
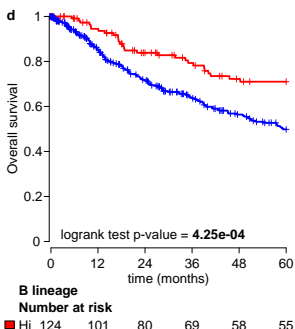
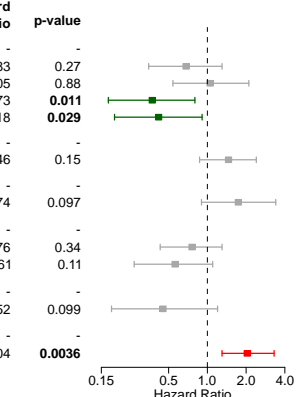
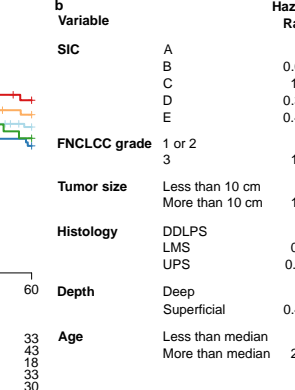
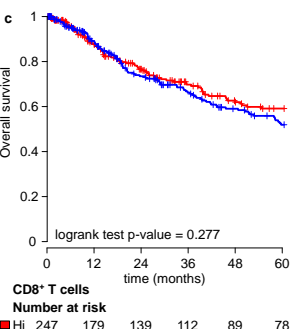
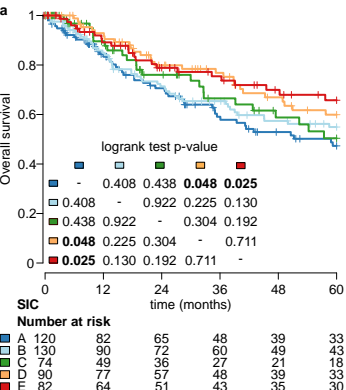
Melanoma Medical Oncology | Investigational Cancer Therapeutics

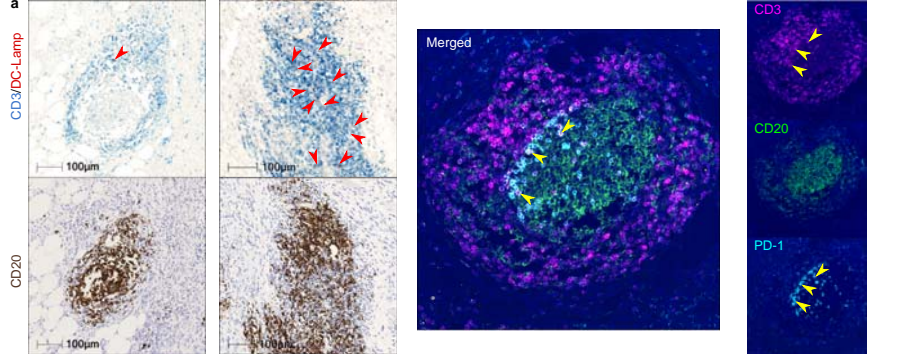
UT MD Anderson Cancer Center | 1400 Holcombe Blvd. | Houston, TX 77030

HTawbi@mdanderson.org (713-745-7763 phone | 6 713-745-1046 fax

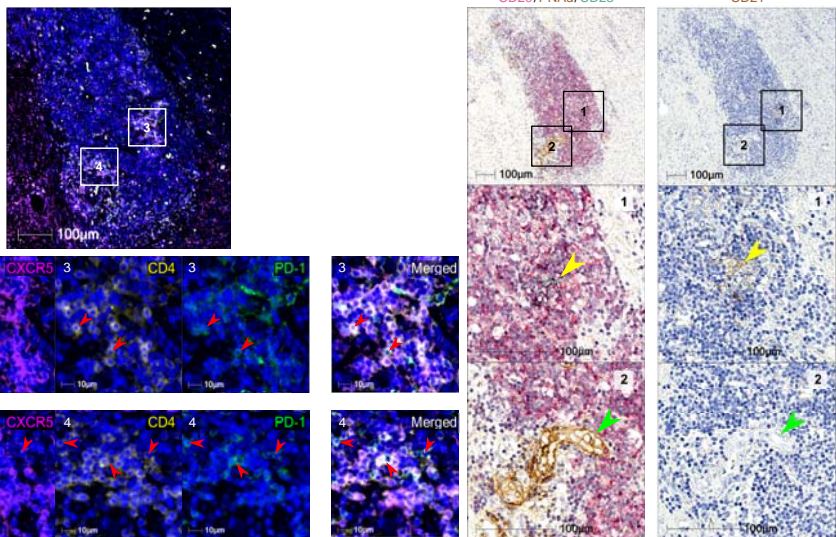




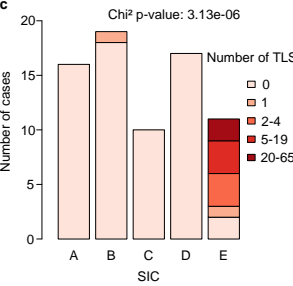




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