



Biologie moléculaire des sarcomes des tissus mous Quoi de neuf en 2023?

Réunion annuelle Sarcomes Bourgogne-Franche Comté

Sarah Watson
MD, PhD

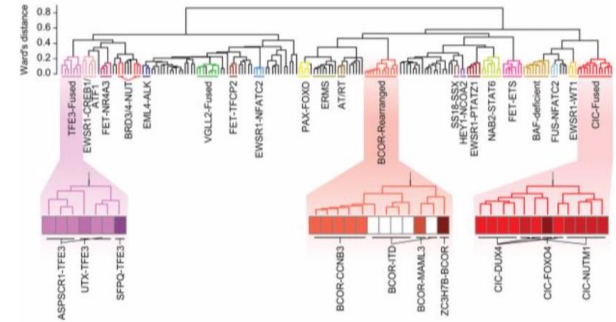
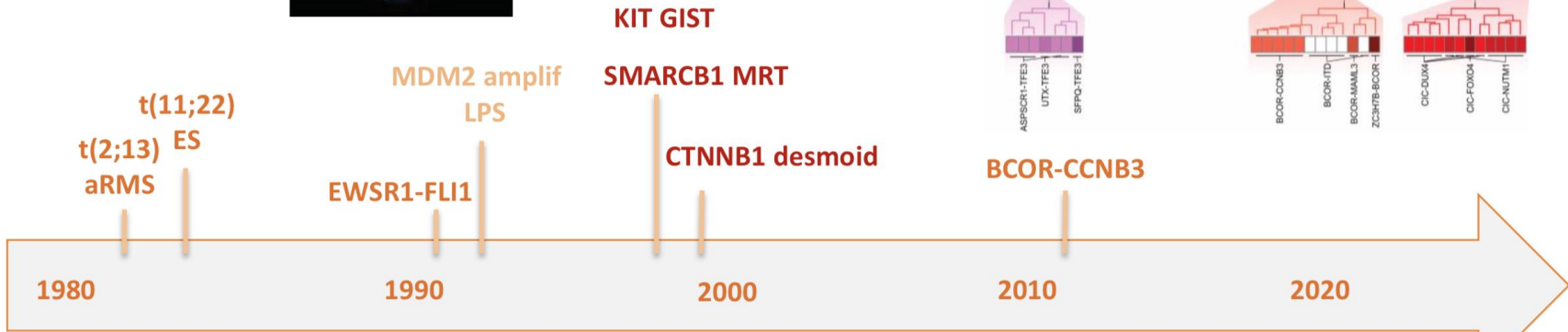
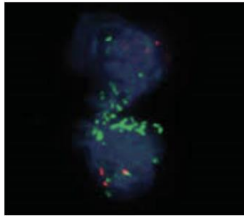
Institut Curie
Oncologie médicale, INSERM U830

Biologie moléculaire: définition(s)

- « discipline scientifique au croisement de la génétique, de la biochimie et de la physique, dont l'objet est la compréhension des mécanismes de fonctionnement de la cellule au niveau moléculaire »
- « ensemble des techniques de manipulation d'acides nucléiques (ADN, ARN), appelées aussi techniques de génie génétique »

Biologie moléculaire des STS

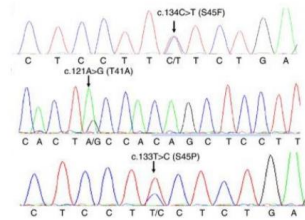
- **Quels outils en 2023?**
 - Caractérisation génomique
 - Caractérisation transcriptomique
 - Caractérisation épigénomique
- **Applications diagnostiques**
 - Classification moléculaire
 - Nouvelles entités
- **Applications thérapeutiques**
 - Sarcomes NTRK-réarrangés
 - Sarcomes MSI
 - Tumeurs musculaires lisses utérines



Banding chromosome techniques



Genomic breakpoint characterization, FISH



Sanger sequencing



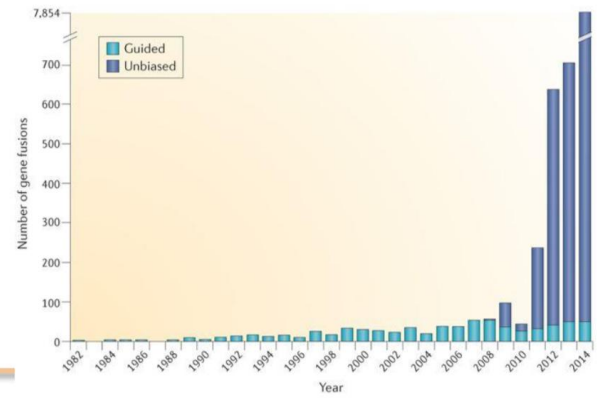
RT-PCR



Expression and copy number profiling arrays

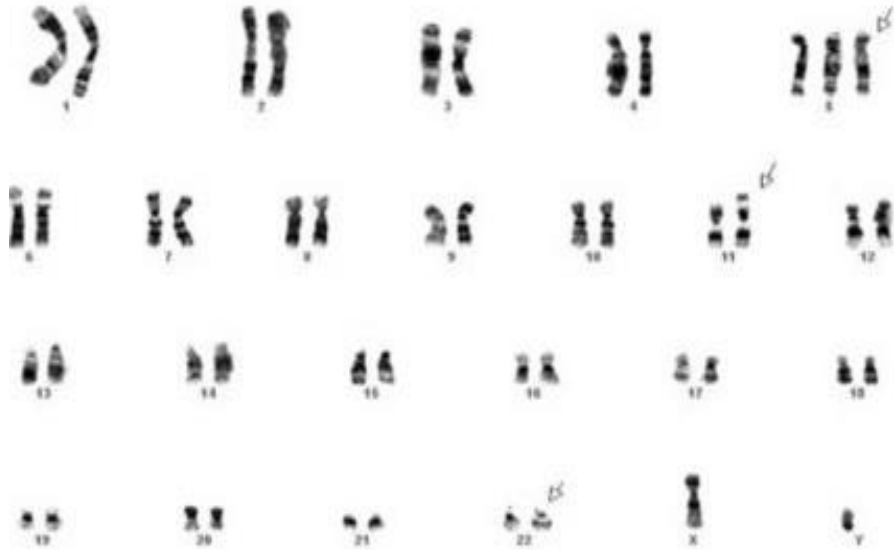


Deep sequencing approaches



Nature Reviews | Cancer

CARYOTYPE SIMPLE



$t(11;22)(p13;q12)+5$

DSRCT

CARYOTYPE COMPLEXE

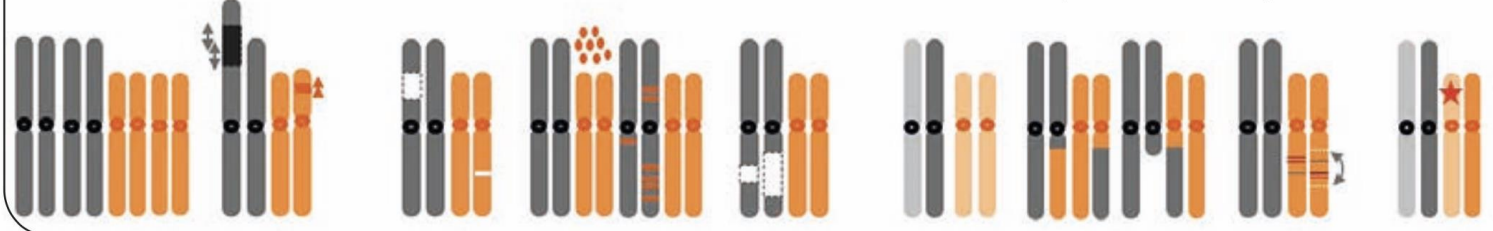


Leiomyosarcome

Génome diploïde normal



Altérations du nombre et de la structure des chromosomes, et de la séquence nucléotidique



B

Techniques	Nombre de marqueurs recherchés	Polyploïdie	Gains		Pertes		Amplifications	Délétions homozygotes	Isodisomies	Translocations	Inversions	Mutations ponctuelles
			Larges	Focaux	Larges	Focales						
Caryotype	N	+	+		+		+	+		+	±	
FISH	1	+	+		+		+	+		+	±	
PCR	1			+		+	+	+		+	+	
Séq. Sanger	1			±		±		+	+	+	+	+
QPCR	1/3			+		+	+	+				
RT-QPCR	1/3			+		+	+	+		+	+	
MLPA	N		+	+	+	+	+	+				
aCGH	N		+	+	+	+	+	+		*		
aCGH/LOH	N	+	+	+	+	+	+	+	+	*		
Panel NGS	10/50			+		+	+	+	+		+	+
RNAseq	N		+	+	+	+	+	+	+	+	+	±
WES	N	+	+	+	+	+	+	+	+	±	±	+

aCGH : array Comparative Genomic Hybridization ; FISH : Fluorescent In Situ Hybridization ; LOH : Loss Of Heterozygosity ; MLPA : Multiplex Ligation dependent Probe Amplification ; PCR : Polymerase Chain Reaction ; QPCR : Quantitative Polymerase Chain Reaction ; RT-QPCR : Reverse-Transcription Quantitative Polymerase Chain Reaction ; WES : Whole-Exome Sequencing.

Caractérisation génomique: les outils actuels (1)

Matrice: ADN



**Altérations de nombres de copies
(CNV)**

Pertes/Gains

Amplifications

Index Génomique

CGH array

WES/WGS

Panels ciblés larges (> 500 gènes)

Altérations de séquence (SNV)

Mutations ponctuelles

Signatures mutationnelles

Charge mutationnelle (TMB)

Microsatellites (MSS/MSI)

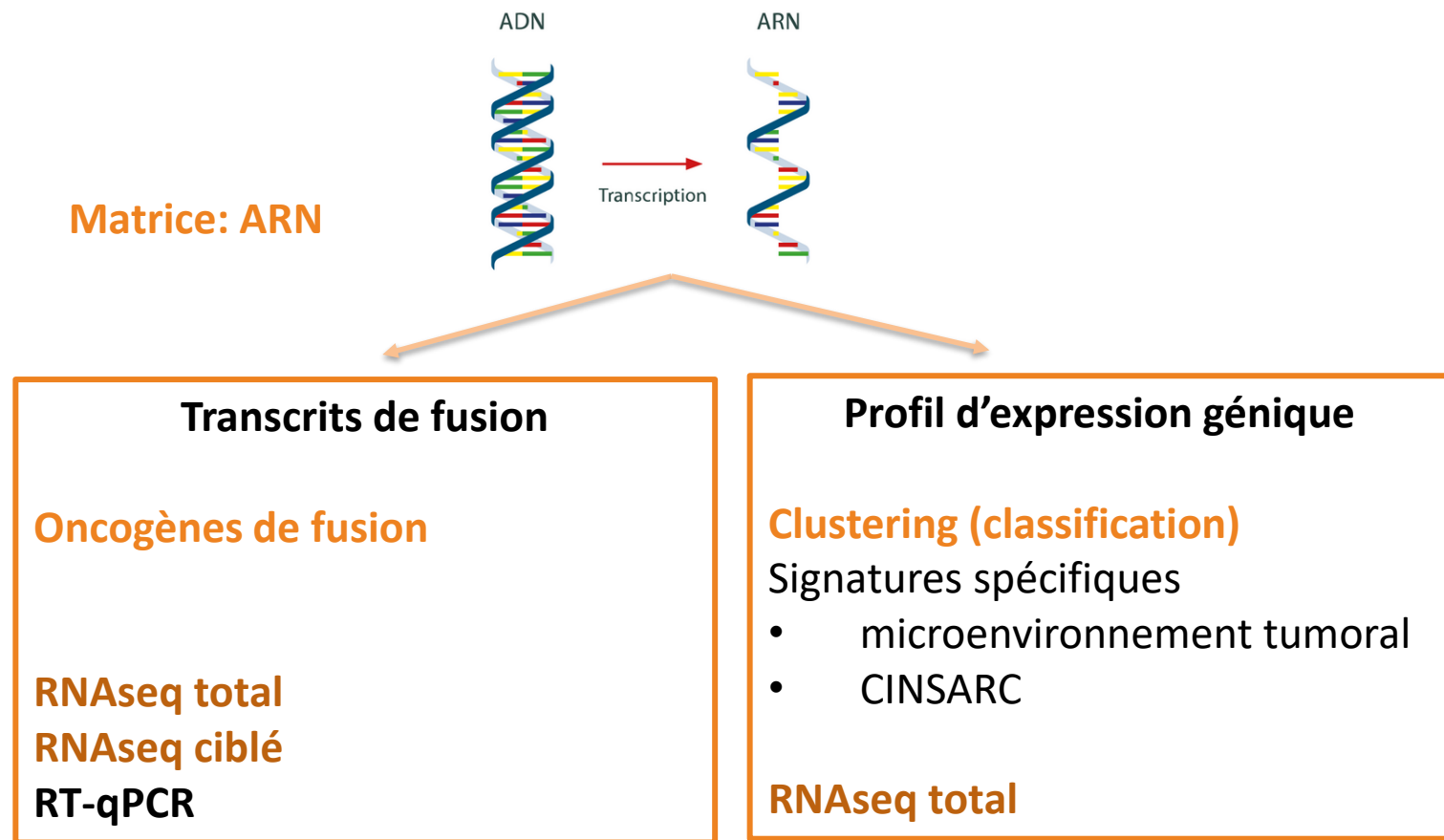
WES/WGS

Panels ciblés (10-500 gènes)

Caractérisation génomique: les outils actuels (2)

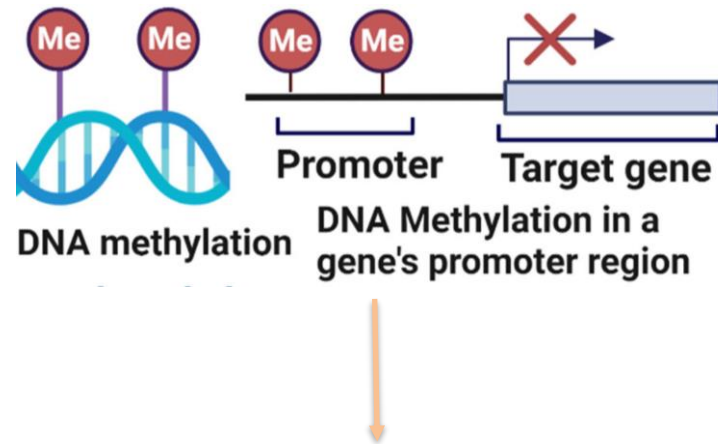
Technique	Matériel	Séquençage	Résultats	Exemples	Applications
Séquençage ciblé (panel, capture)	- FFPE - Congél	10- 500 genes; Tissu tumoral	- Mutations - +/- CNV - +/- TMB, MSI	- GIST	- Diagnostic - Thérapeutique
Whole Exome Sequencing	- Congél - FFPE	exomes; Tissus tumoral + constitutionnel	- Mutations - TMB, MSI - Signatures mutationnelles - CNV	- PFMG2025 - Essais cliniques	- Recherche - Diag/Thérapeutique - Conseil génétique
Whole Genome Sequencing	- Congél - FFPE	Exomes +ADN non codant Tissus tumoral + constitutionnel	- Mutations - TMB, MSI - Signatures mutationnelles - CNV - SNP	- PFMG 2025 - Essais cliniques	- Recherche - Diag/Thérapeutique - Conseil génétique

Caractérisation transcriptomique: les outils actuels



Caractérisation épigénétique: les outils actuels

Matrice: ADN



Profil de méthylation

450 000-850 000 CpG

Puces EPIC

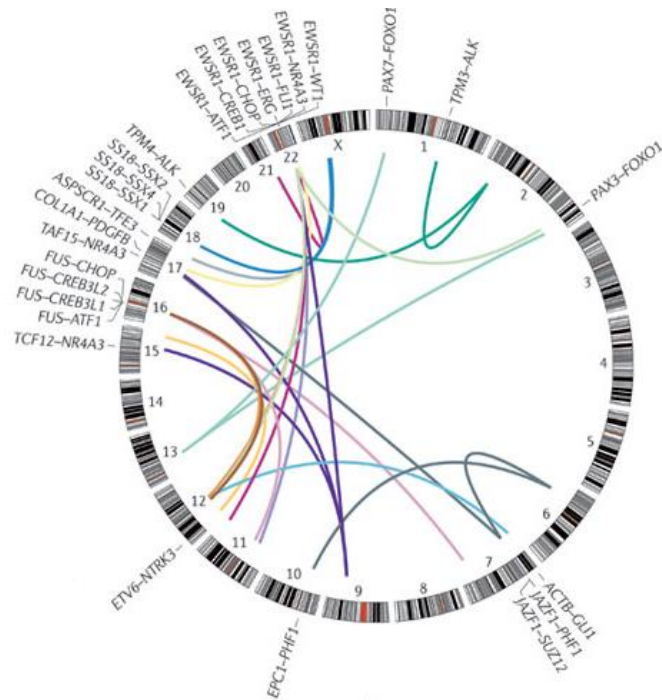
NGS, Nanopore

Biologie moléculaire des STS

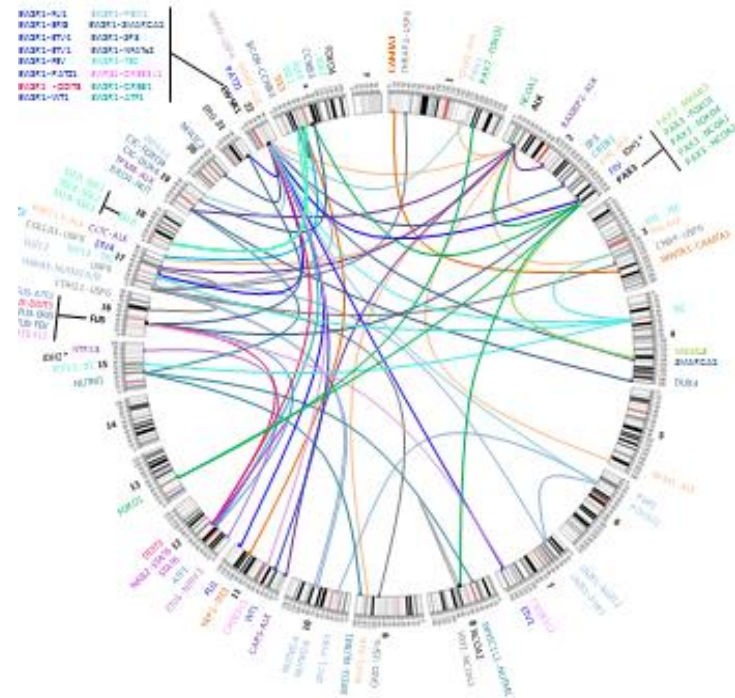
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Sarcoma subtype	Translocation	Fusion gene	Oncogenic mechanism	Prevalence
Ewing sarcoma/PNET	t(11 ;22)(q24 ;q12)	EWSR1-FL1	TF	90%
	t(21 ;22)(q22 ;q12)	EWSR1-ERG	TF	5%
Synovial sarcoma	t(X ;18)(p11 ;q11)	SS18-SSX1	TF	65%
		SS18-SSX2	TF	35%
ARMS	t(2 ;13)(q35 ;q14)	PAX3-FOXO1A	TF	80%
	t(1 ;13)(p36 ;q14)	PAX7-FOXO1A	TF	15%
DSRCT	t(11 ;22)(p13 ;q12)	EWSR1-WT1	TF	>90%
Mixoid liposarcoma	t(12 ;16)(q13 ;p11)	TLS-DDIT3	TF	95%
Clear Cell sarcoma	t(12 ;22)(q13 ;q12)	EWSR1-ATF1	TF	95%
ESMCS	t(9 ;22)(q22 ;q12)	EWSR1-NR4A3	TF	75%
	t(9 ;17)(q22 ;q11)	TAF2N-NR4A3	TF	20%
Angiomatoid fibrous histiocytoma	t(2 ;22)(q34 ;q12)	EWSR1-CREB1	TF	90%
	t(12 ;22)(q13 ;q12)	EWSR1-ATF1	TF	10%
Low grade FMS	t(7 ;16)(q32-34 ; p11)	TLS-CREB3L2	TF	90%
	t(11 ;16)(p11 ;p11)	TLS-CREB3L1	TF	10%
ASPS	t(X ;17)(p11.2 ;q25)	ASPL-TFE3	TF	>90%
Infantile fibrosarcoma	t(12 ;15)(p13 ;q25)	ETV6-NTRK3	TKI	85%
IMT	2p23 rearrangements	Various partners-ALK	TKI	60%
DFSP	t(17 ;22)(q22 ;q13)	COL1A1-PDGFB	GF	>90%

Sarcomes et gènes de fusion



2011

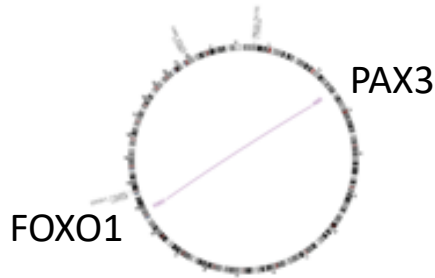


2020

L'apport du RNAseq

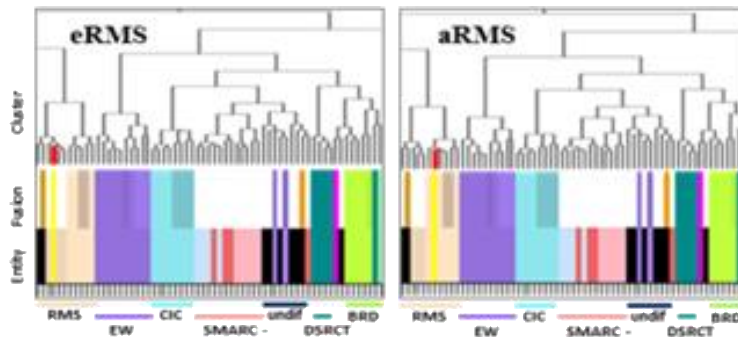
RNaseq en pratique clinique

Fusion detection

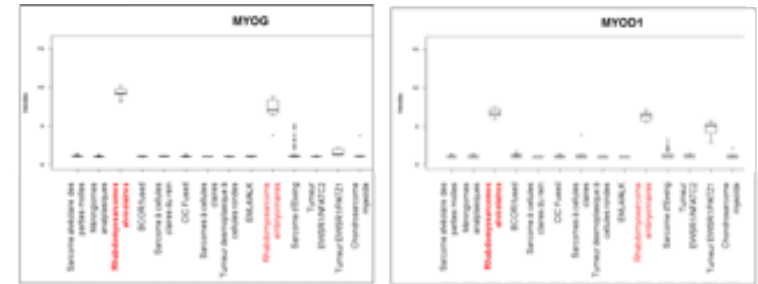


L'exemple des RMS

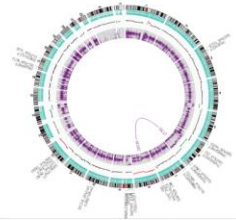
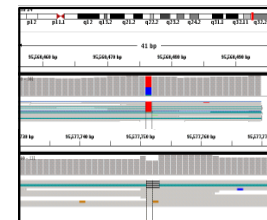
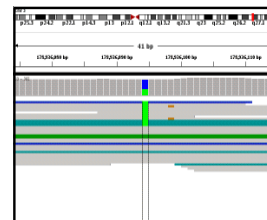
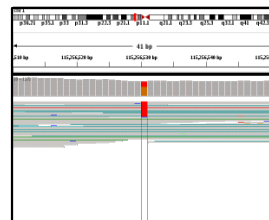
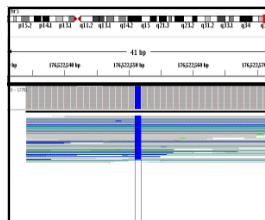
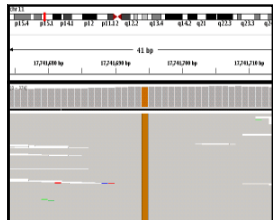
Expression Profiling



IHC Correlation



Expressed Mutation detection: therapeutic targets and markers follow up (cfDNA)



RMS spindle cell / sclerosing
MYO1 p.L122R

RMS embryonal
FGFR4 p.V550L

RMS embryonal
NRAS p.Q61K

RMS embryonal
PIK3CA p.Q546K

RMSe DICER1 (Som & Germline)
p.(D1810A) & p.(Leu345TyrFsTer8)

RMS spindle cell / sclerosing
VGLL2-NCOA2 fusion

Gaëlle Pierron



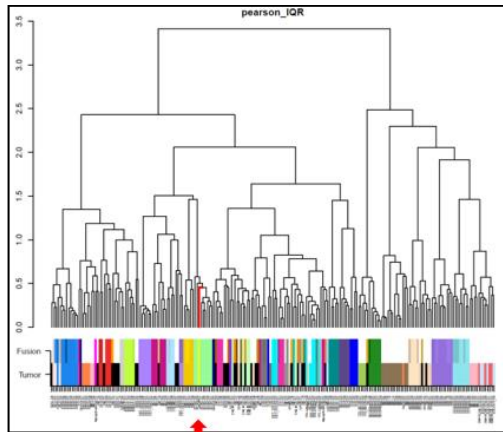
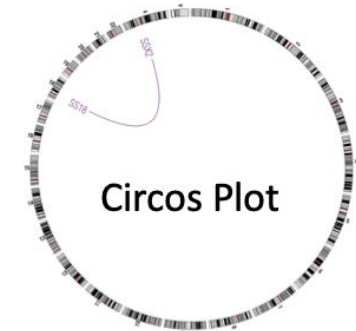
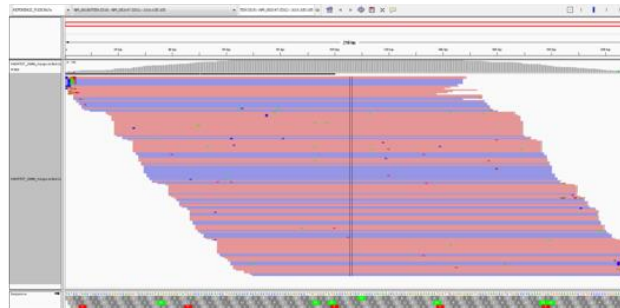
RNAseq en pratique clinique (2)

➔ For 'classical' well known fusions

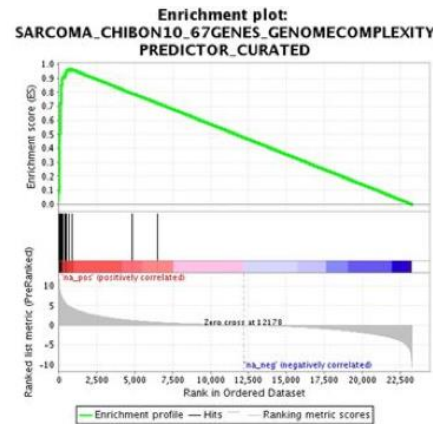
M 60 yo
Soft part sarcoma
Synovial Sarcoma vs LipoSarcoma ?
MDM2 +

➔ Fusion SYT-SSX2

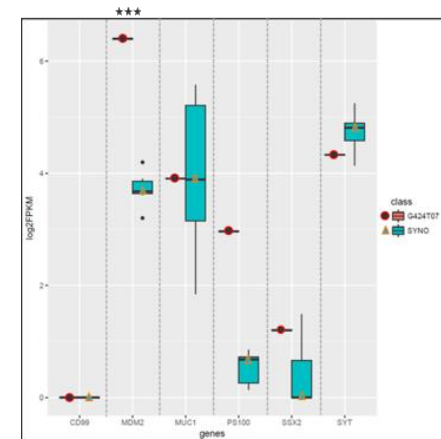
SYT ex10 / SSX2 ex6



Clustering
Within Syno+



CINSARC F. Chibon
signature assessment



Boxplot en Log2 FPKM
MDM2 overexpression vs other Syno+

➔ RNAseq for Diagnosis, Prognosis and Theranostic

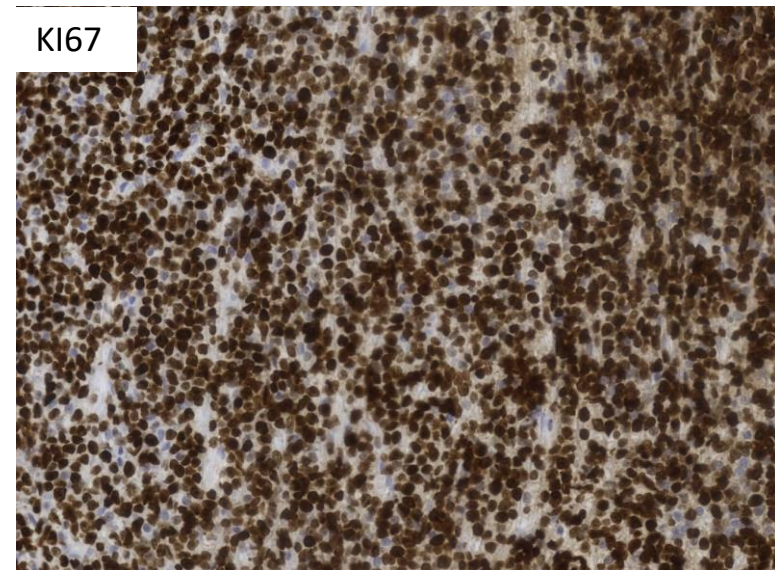
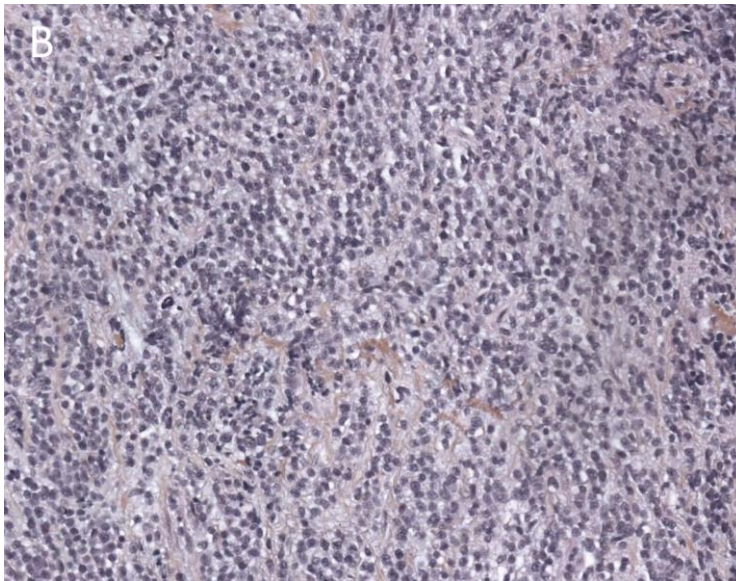
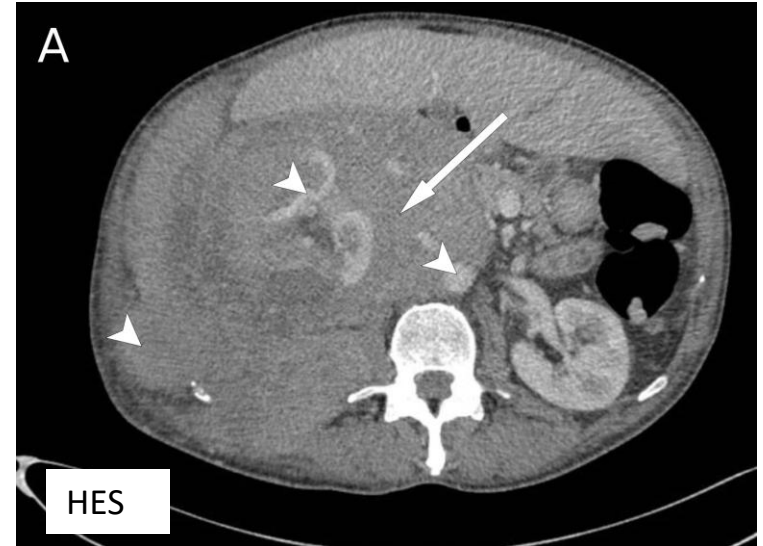
RNAseq en pratique clinique (3)

64 yo male

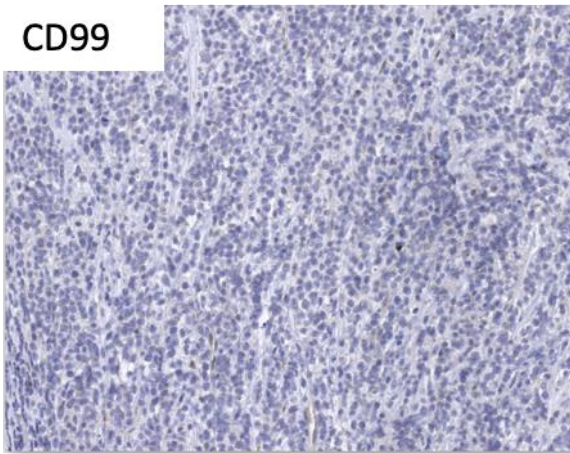
No previous medical history

Rapidly deteriorating performance status and increasing waist circumference

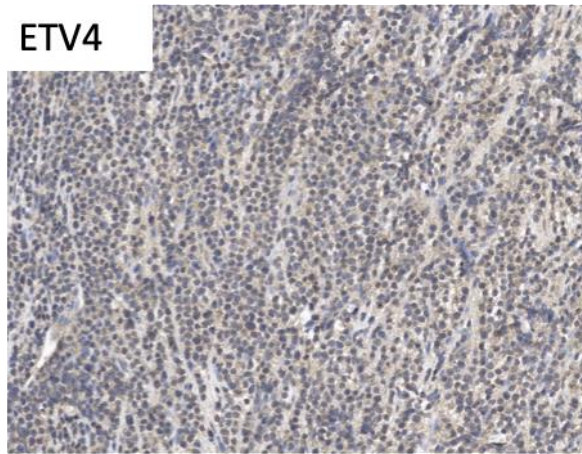
Referred to our sarcoma center for suspicion of retroperitoneal sarcoma



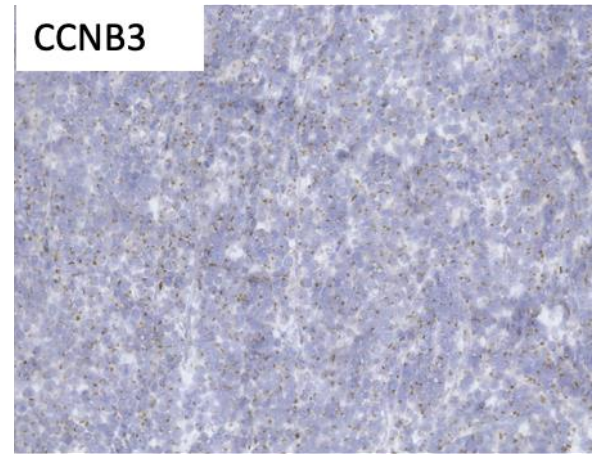
CD99



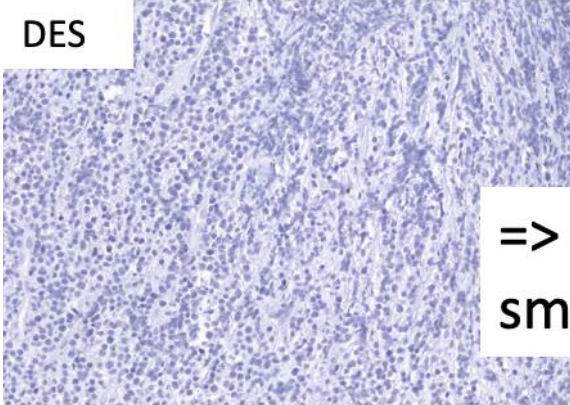
ETV4



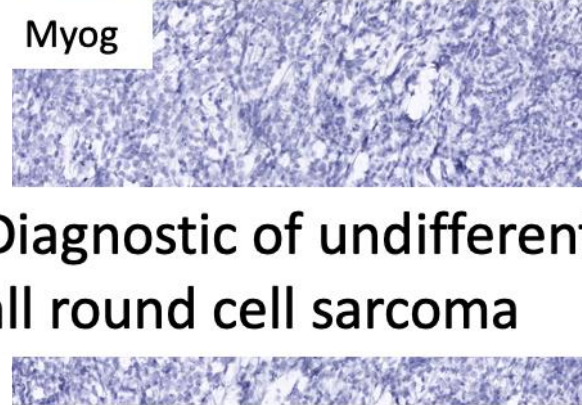
CCNB3



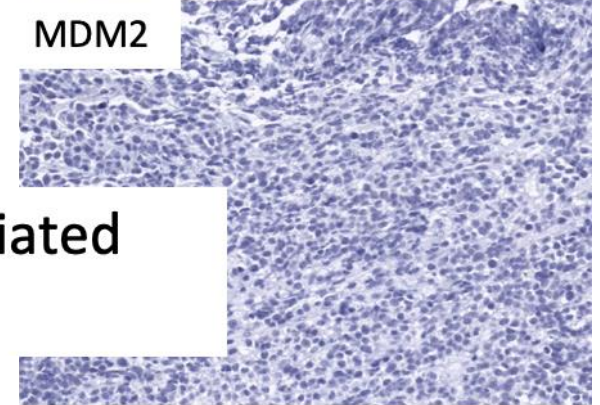
DES



Myog

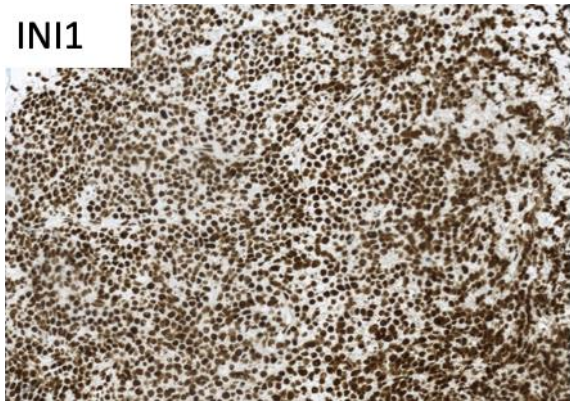


MDM2

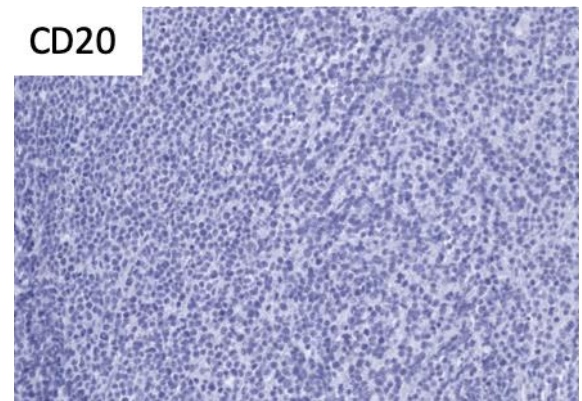


=> Diagnostic of undifferentiated
small round cell sarcoma

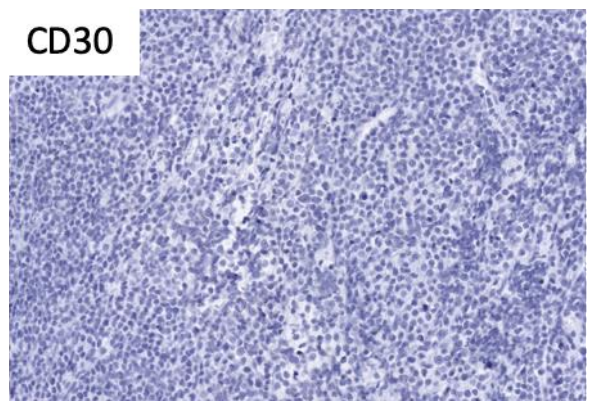
INI1



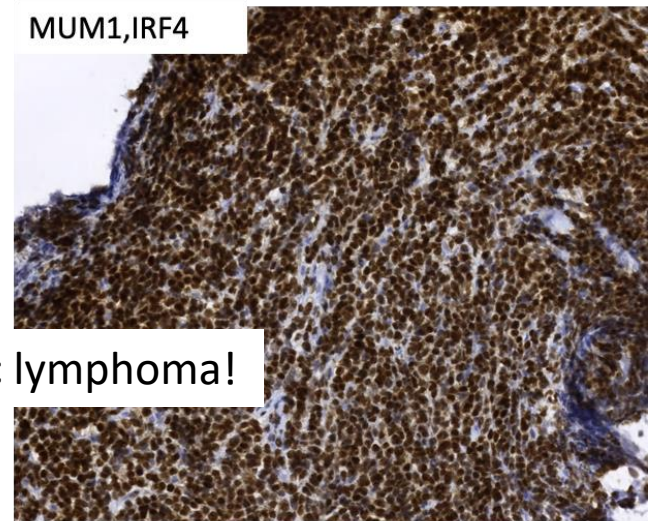
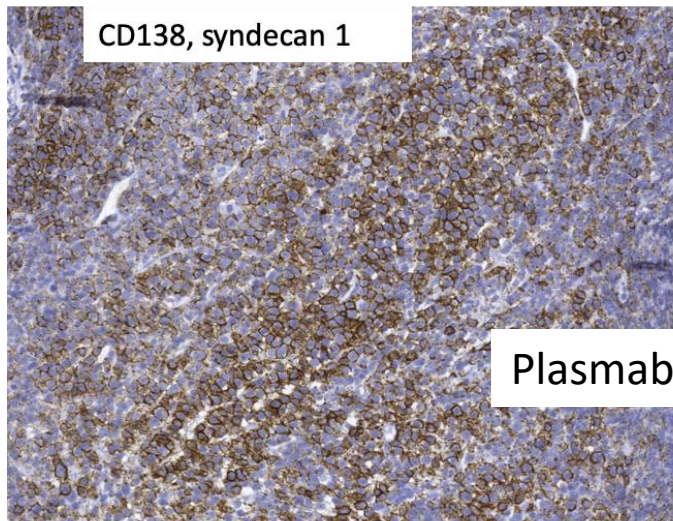
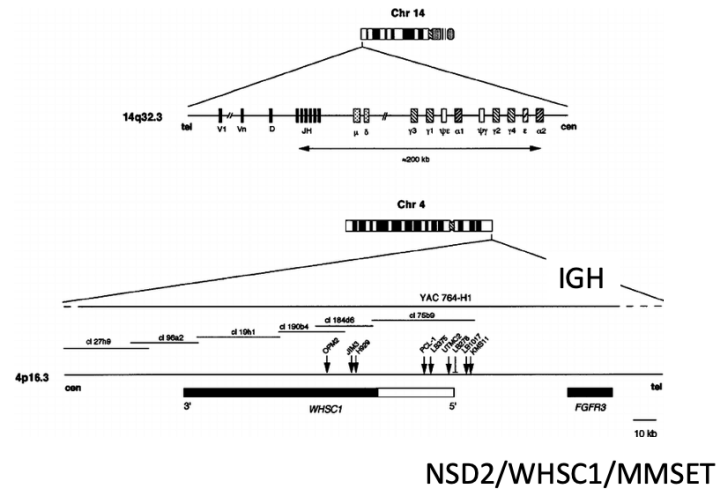
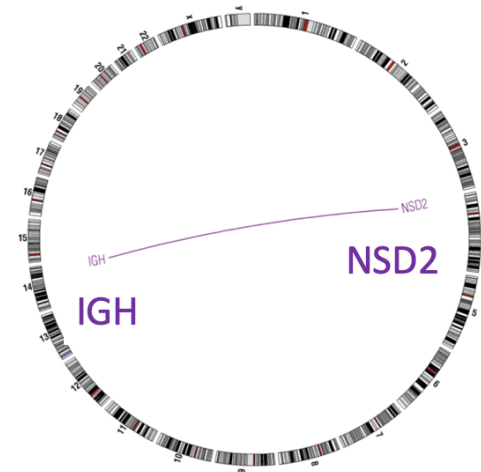
CD20



CD30

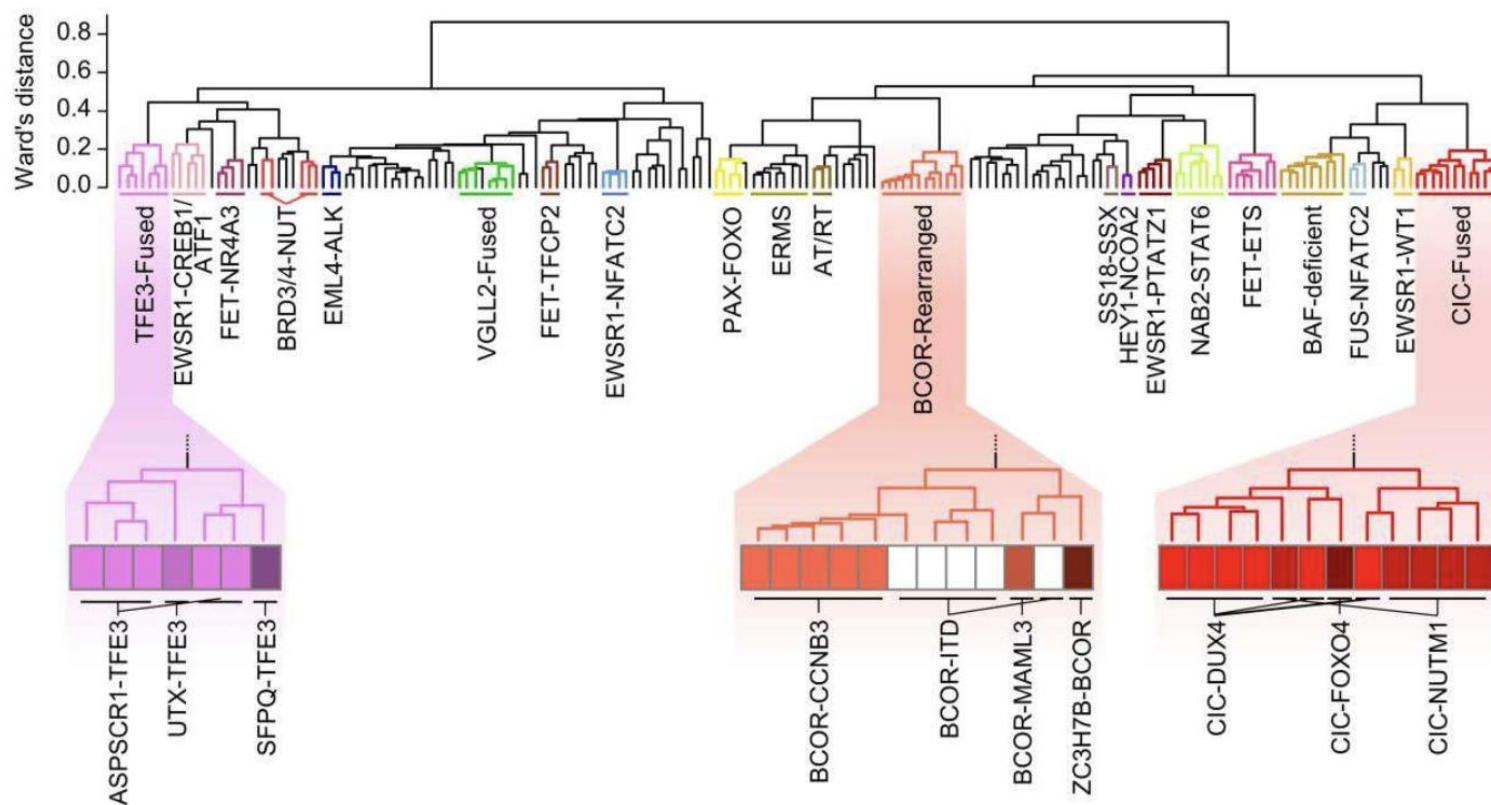


RNAseq: IGH-NSD2 fusion



Plasmablastic lymphoma!

Classification transcriptomique des sarcomes



Caractérisation des sarcomes indifférenciés par séquençage nouvelle génération (RNAseq)

- 1) Détection de nouveaux gènes de fusion
- 2) Caractérisation du profil d'expression
- 3) Corrélation clinico-pathologique

Watson et al, J Pathol 2018

Classification épigénétique

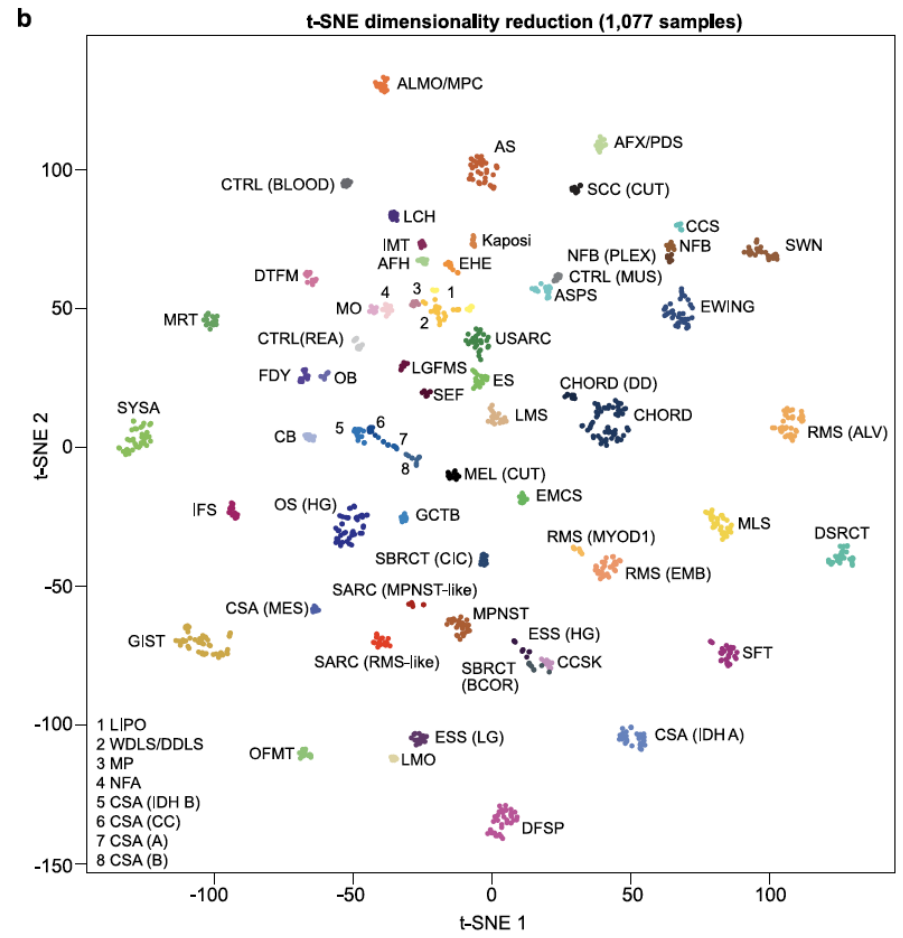
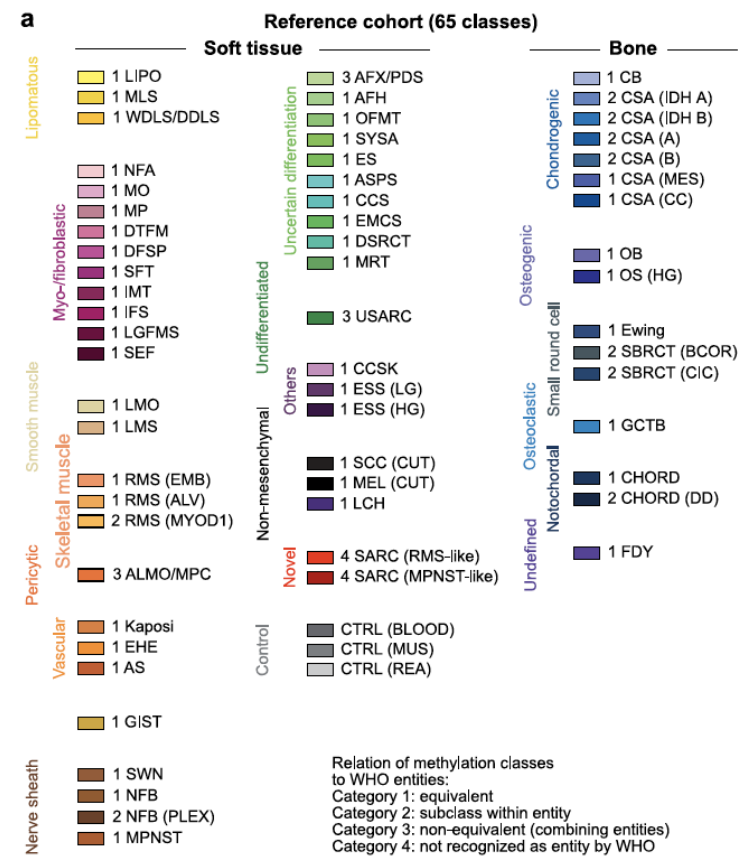
ARTICLE

<https://doi.org/10.1038/s41467-020-20603-4>

OPEN



Sarcoma classification by DNA methylation profiling



Biologie moléculaire des STS

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Sarcomes NTRK-fused

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children

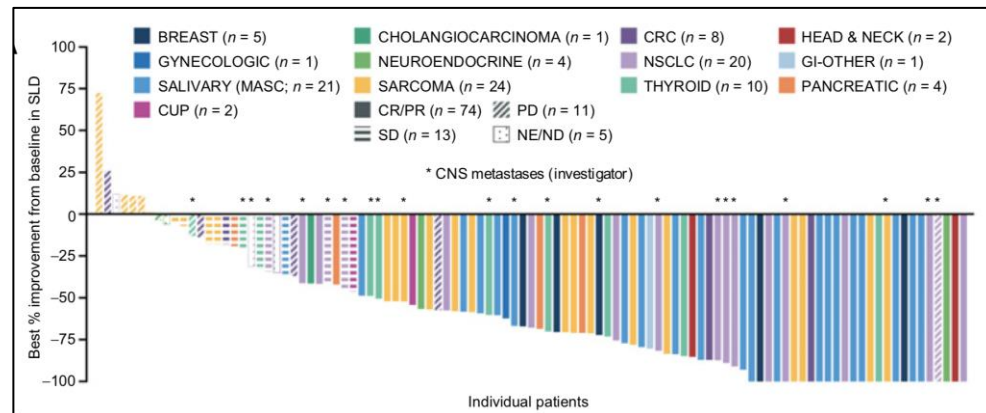
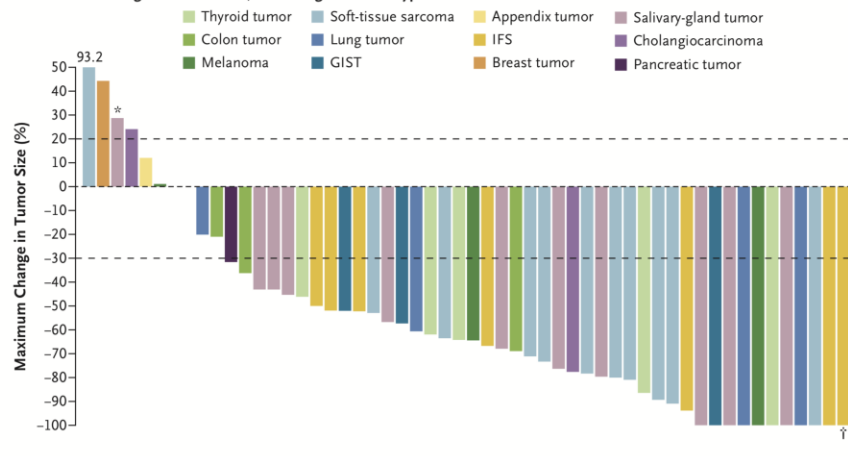
A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathanson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Patients With NTRK Fusion-Positive Solid Tumors

George D. Demetri¹, Filippo De Braud^{2,3}, Alexander Drilon⁴, Salvatore Siena^{3,5}, Manish R. Patel⁶, Byoung Chul Cho⁷, Stephen V. Liu⁸, Myung-Ju Ahn⁹, Chao-Hua Chiu¹⁰, Jessica J. Lin¹¹, Koichi Goto¹², Jeeyun Lee⁹, Lyudmila Bazhenova¹³, Thomas John¹⁴, Marwan Fakih¹⁵, Sant P. Chawla¹⁶, Rafal Dziadziuszko¹⁷, Takashi Seto¹⁸, Sebastian Heinzmann¹⁹, Bethany Pitcher²⁰, David Chen²¹, Timothy R. Wilson²¹, and Christian Rolfo²²

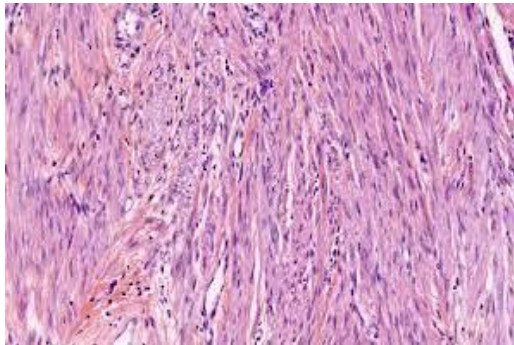
A Maximum Change in Tumor Size, According to Tumor Type



Complexité génomique: quel rôle pour la PEC des tumeurs utérines

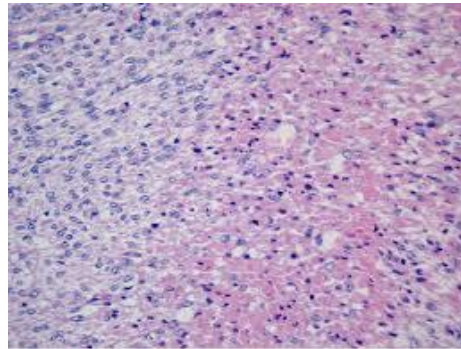
malignité

Léiomyome



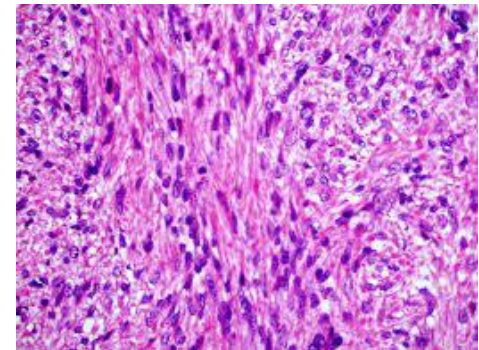
Pas de mitose
Pas d'atypie
Pas de nécrose

STUMP



Mitoses+/-
Atypies+/-
Nécrose

Léiomyosarcome



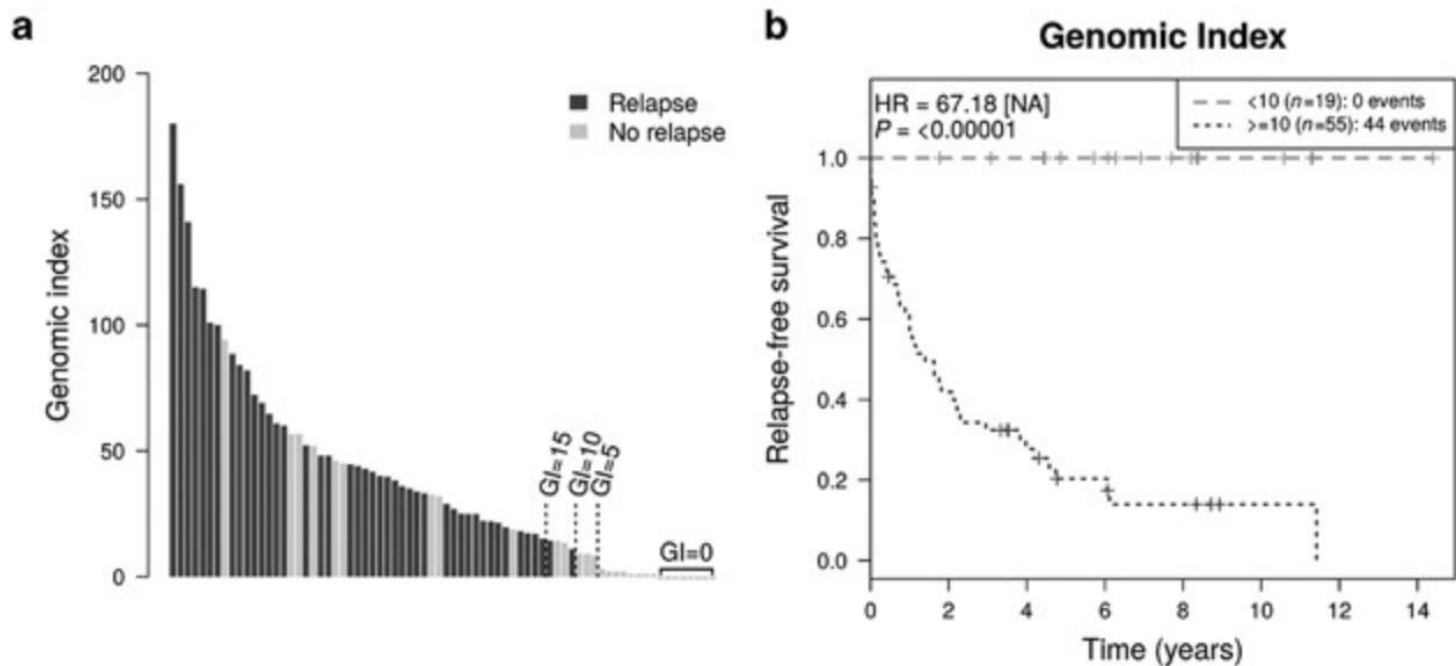
Mitoses+++
Atypies+++
Nécrose+

Limites des microbiopsies++++

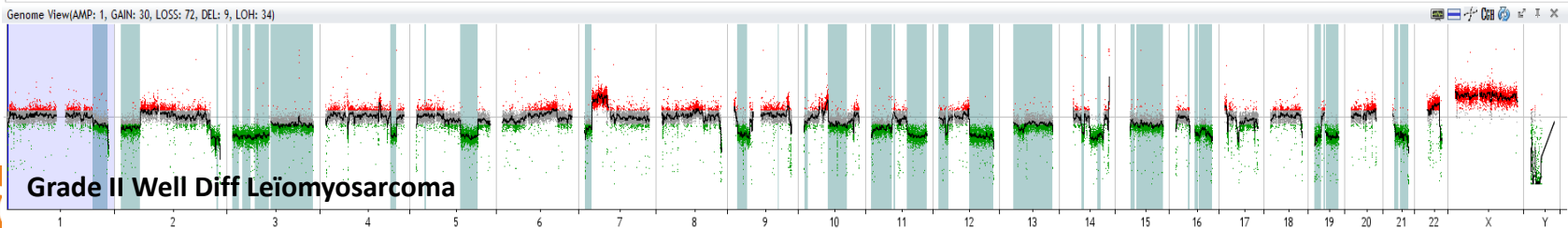
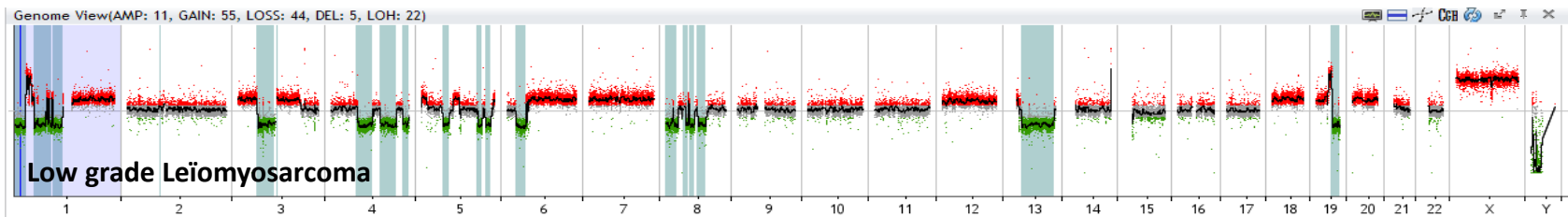
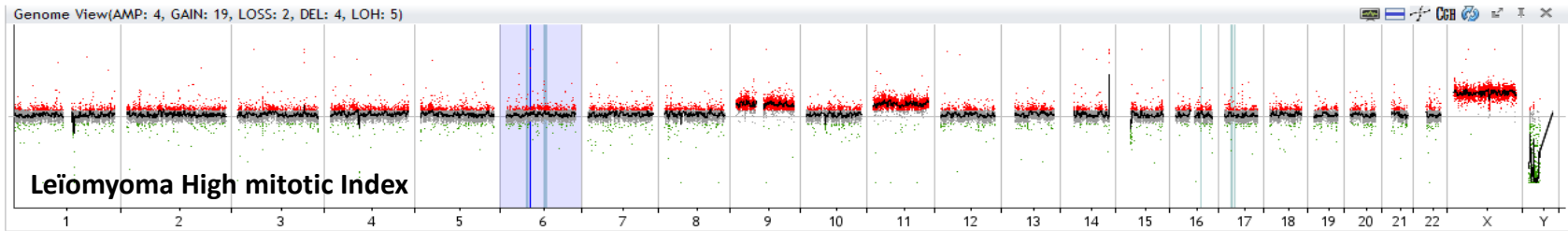
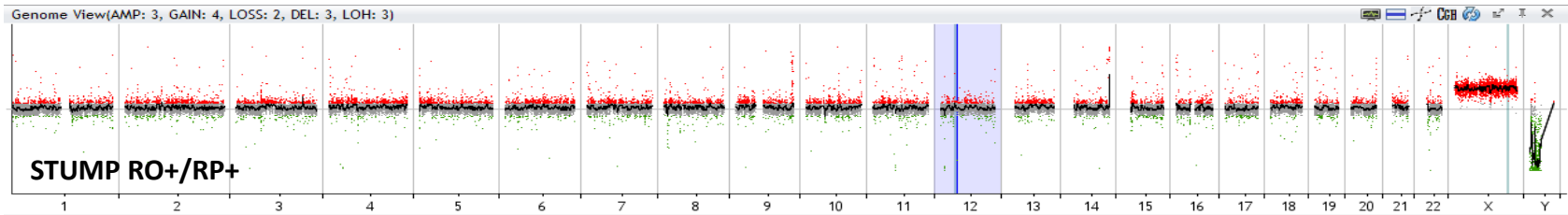
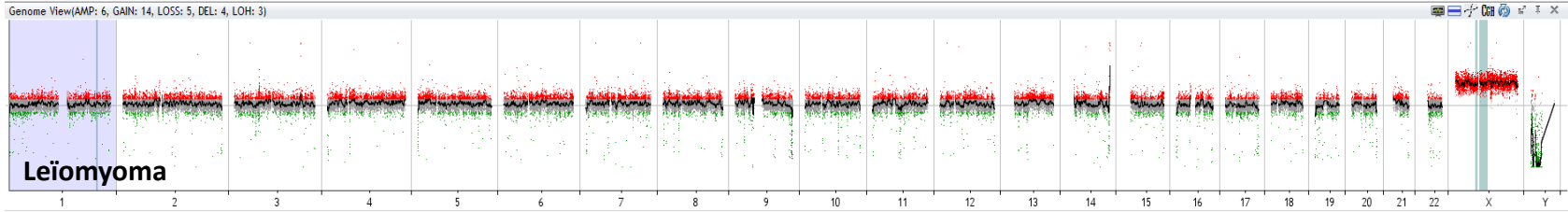
Published: 12 January 2018

Genome profiling is an efficient tool to avoid the STUMP classification of uterine smooth muscle lesions: a comprehensive array-genomic hybridization analysis of 77 tumors

Figure 2



Exemples



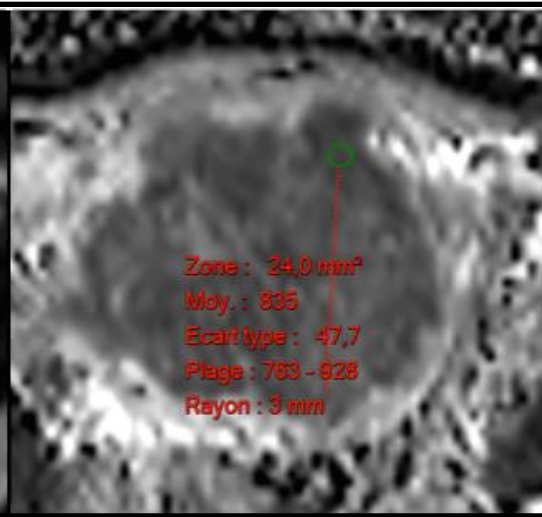
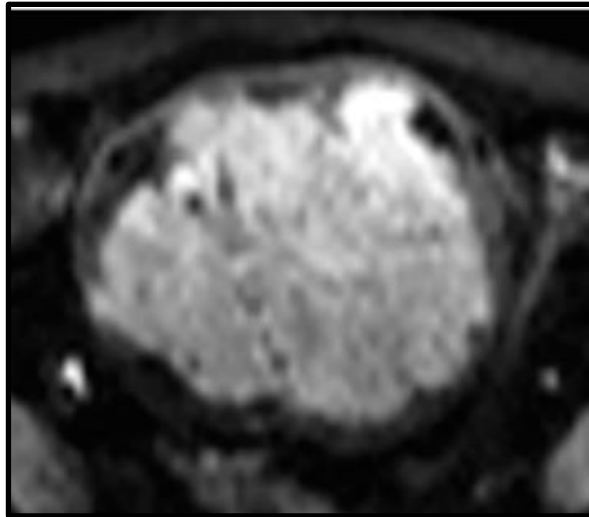
GENOMIC COMPLEXITY

Et pour guider la chirurgie?

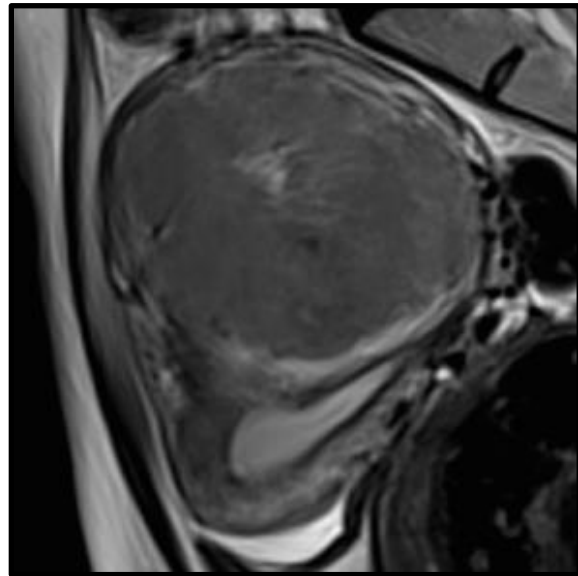
> [Ann Surg Oncol](#). 2022 Oct 26. doi: 10.1245/s10434-022-12697-5. Online ahead of print.

Percutaneous Uterine Needle Biopsy with Microscopic and Array-CGH Analyses for Preoperative Sarcoma Diagnosis in Patients with Suspicious Myometrial Tumors on MRI: A Prospective Pilot Study (SARCGYN)

Jeremy Smadja ¹, Sophie El Zein ², Gaele Pierron ³, Sarah Watson ⁴, Enora Laas ⁵,
Toulsie Ramtohol ¹, Dimitri Tzanis ⁵, Vincent Servois ¹, Sylvie Bonvalot ⁶



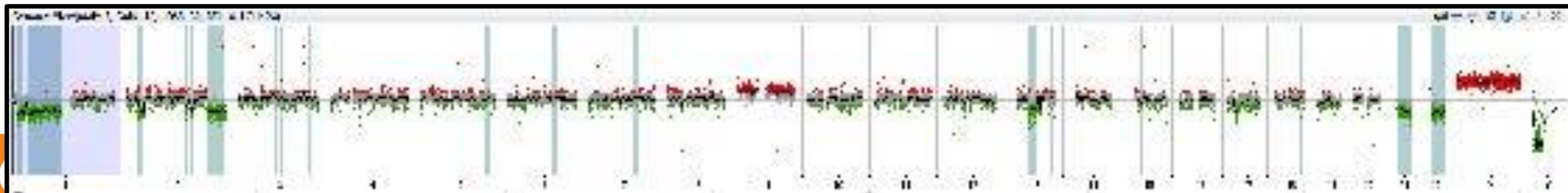
33 ans, G0,
bilan d'un
myome



Microscopie : **TML sans atypie**

CGH : G1 28 avec anomalies sur TP53 et RB1

Hystérectomie d'emblée :
Leiomyosarcome bien différencié

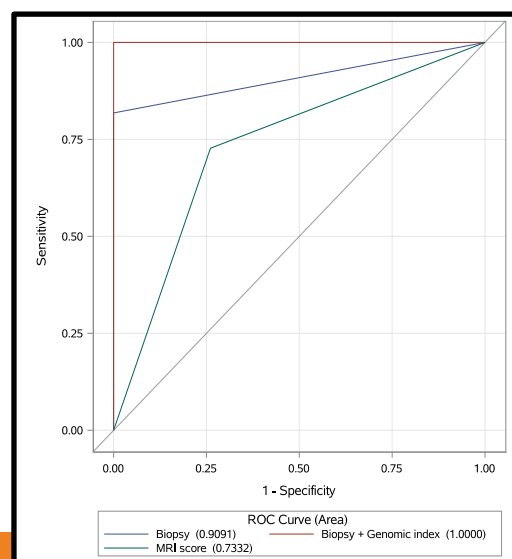
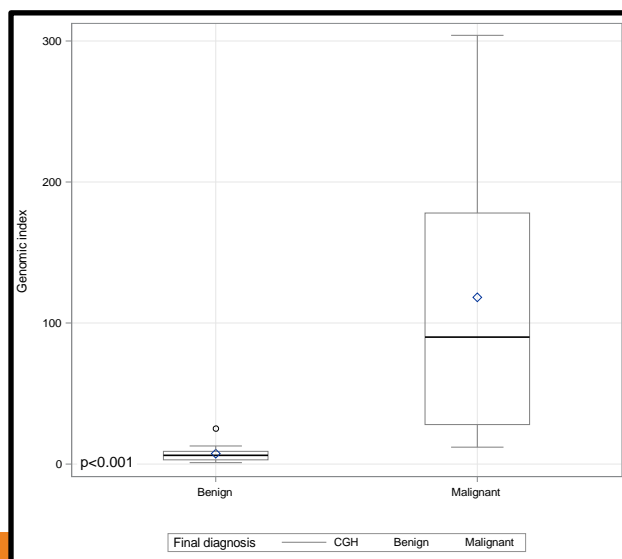


Et pour guider la chirurgie?

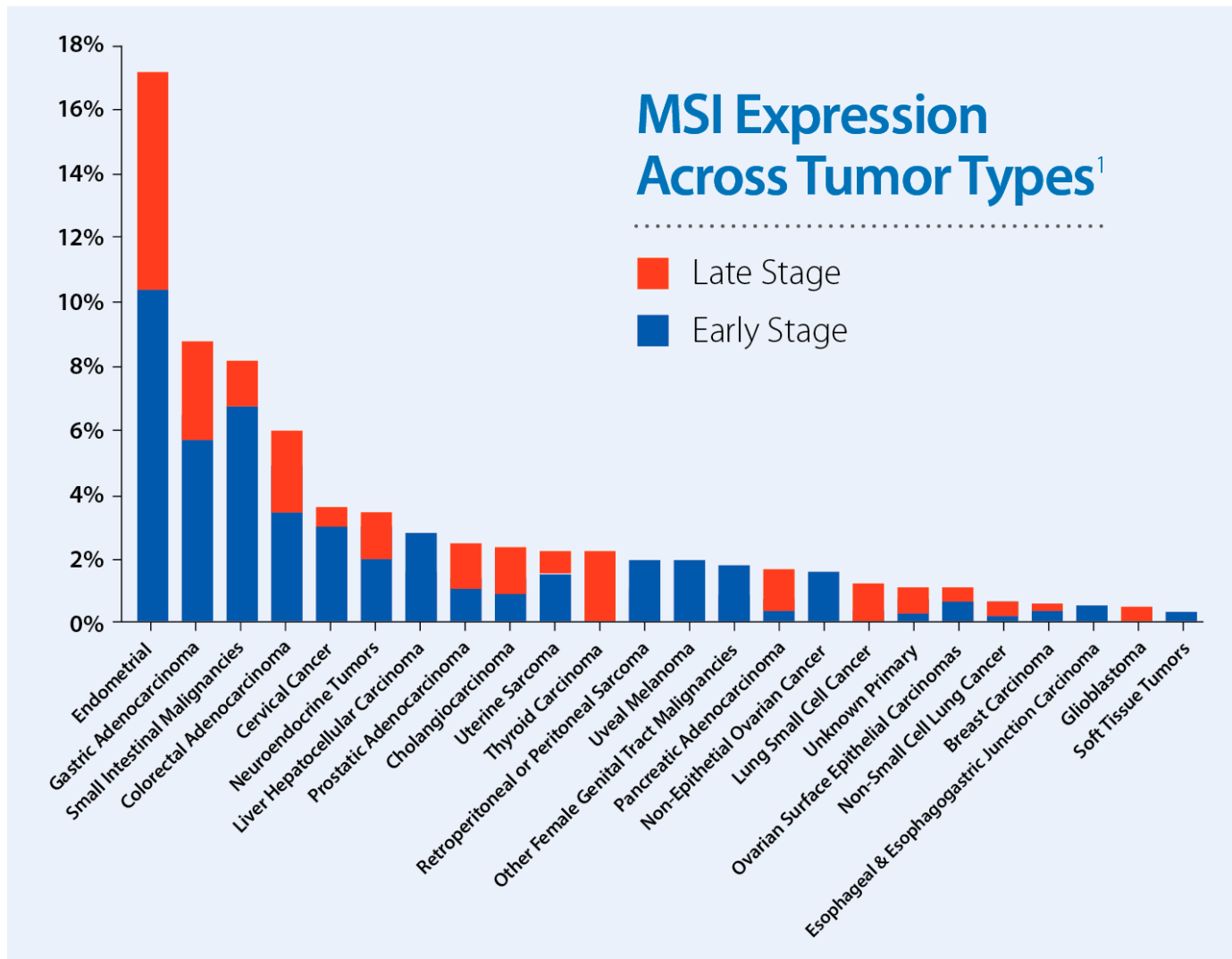
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Variables	Accuracy	Sensitivity	Specificity	PPV	PNV
Biopsy	94	92.0 (81.4-100)	100	100	81.2 (59.0-100)
Biopsy + genomic index	100	100	100	100	100
MRI score	74	85.0 (69.4-100)	57.1 (31.2-83.1)	73.9 (60.0-91.9)	72.7 (46.4-99.1)



Instabilité des microsatellites et STS

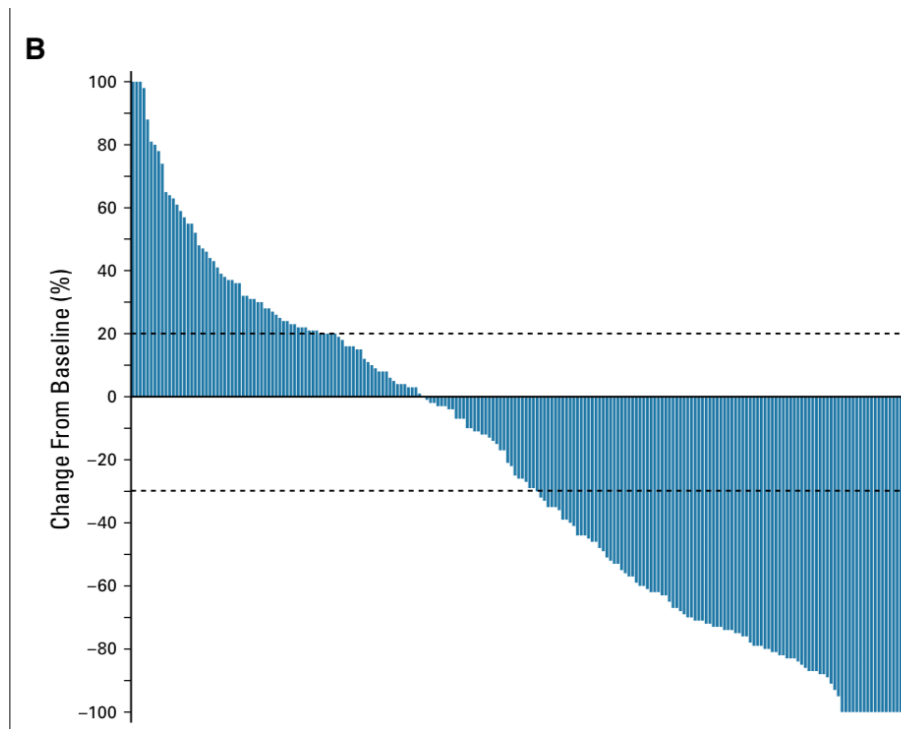


Sarcomes dMMR et immunothérapie

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

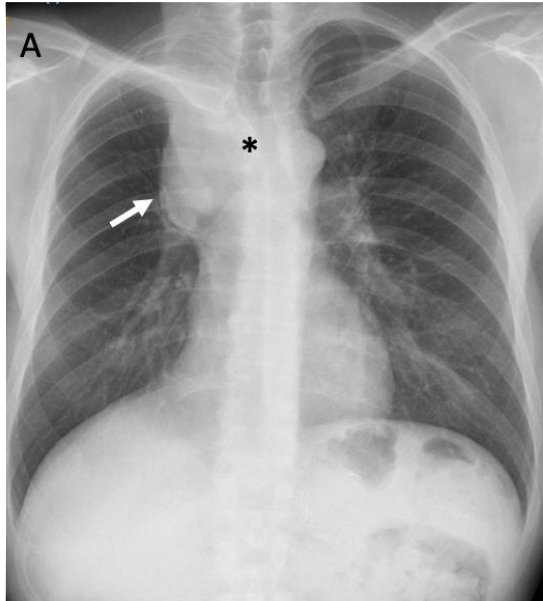
Aurelien Marabelle, MD, PhD¹; Dung T. Le, MD²; Paolo A. Ascierto, MD³; Anna Maria Di Giacomo, MD⁴; Ana De Jesus-Acosta, MD²; Jean-Pierre Delord, MD, PhD⁵; Ravit Geva, MD, MSc⁶; Maya Gottfried, MD⁷; Nicolas Penel, MD, PhD⁸; Aaron R. Hansen, MBBS⁹; Sarina A. Piha-Paul, MD¹⁰; Toshihiko Doi, MD, PhD¹¹; Bo Gao, MBBS, PhD¹²; Hyun Cheol Chung, MD, PhD¹³; Jose Lopez-Martin, MD, PhD¹⁴; Yung-Jue Bang, MD, PhD¹⁵; Ronnie Shapira Frommer, MD¹⁶; Manisha Shah, MD¹⁷; Razi Ghorri, PhD¹⁸; Andrew K. Joe, MD¹⁸; Scott K. Pruitt, MD, PhD¹⁸; and Luis A. Diaz Jr, MD¹⁹

233 patients en échec de chimiothérapie
27 histologies
9 sarcomes

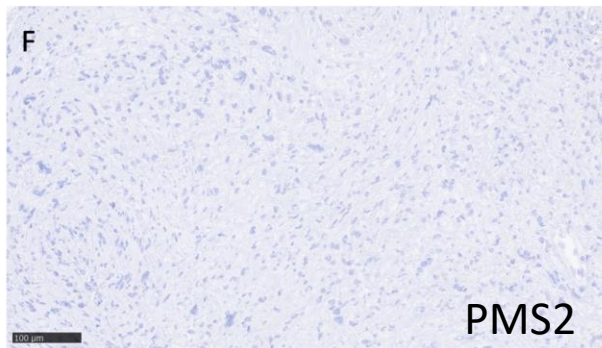
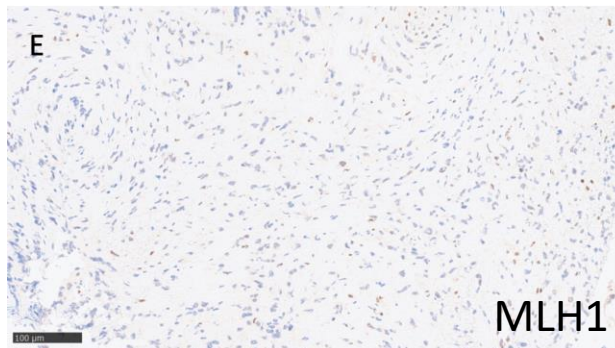
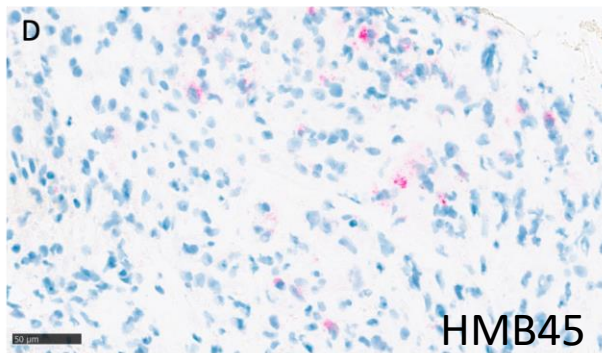
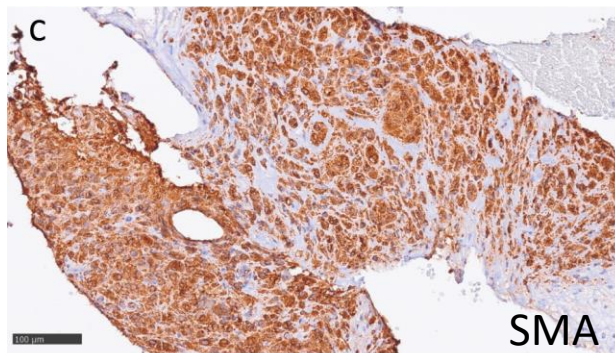
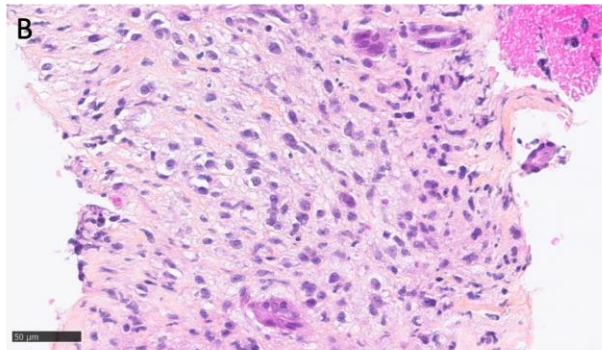
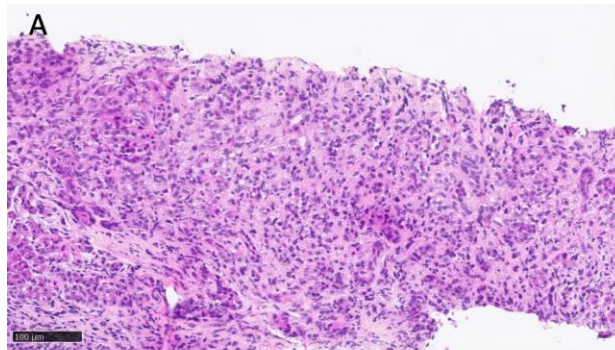


Sarcomes dMMR et immunothérapie

Homme de 45 ans
Syndrome de Lynch MLH1



Sarcomes dMMR et immunothérapie



Panel DRAGON:

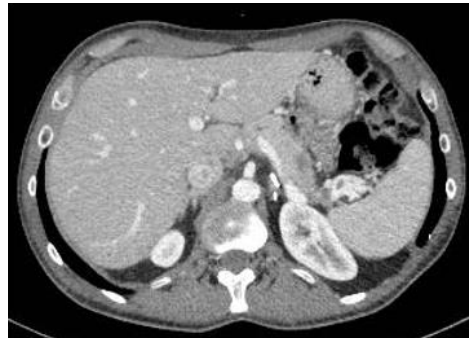
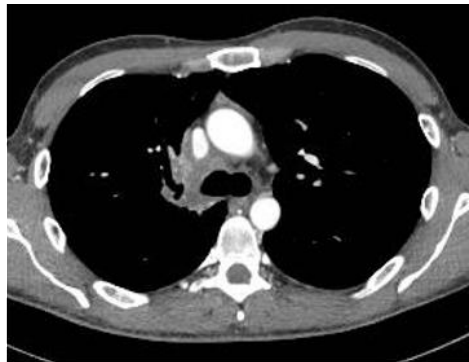
Statut MSI+

TMB: 25

Mutation MLH1

Sarcomes dMMR et immunothérapie

Traitement par Pembrolizumab



Baseline

After 2 cycles

After 4 cycles

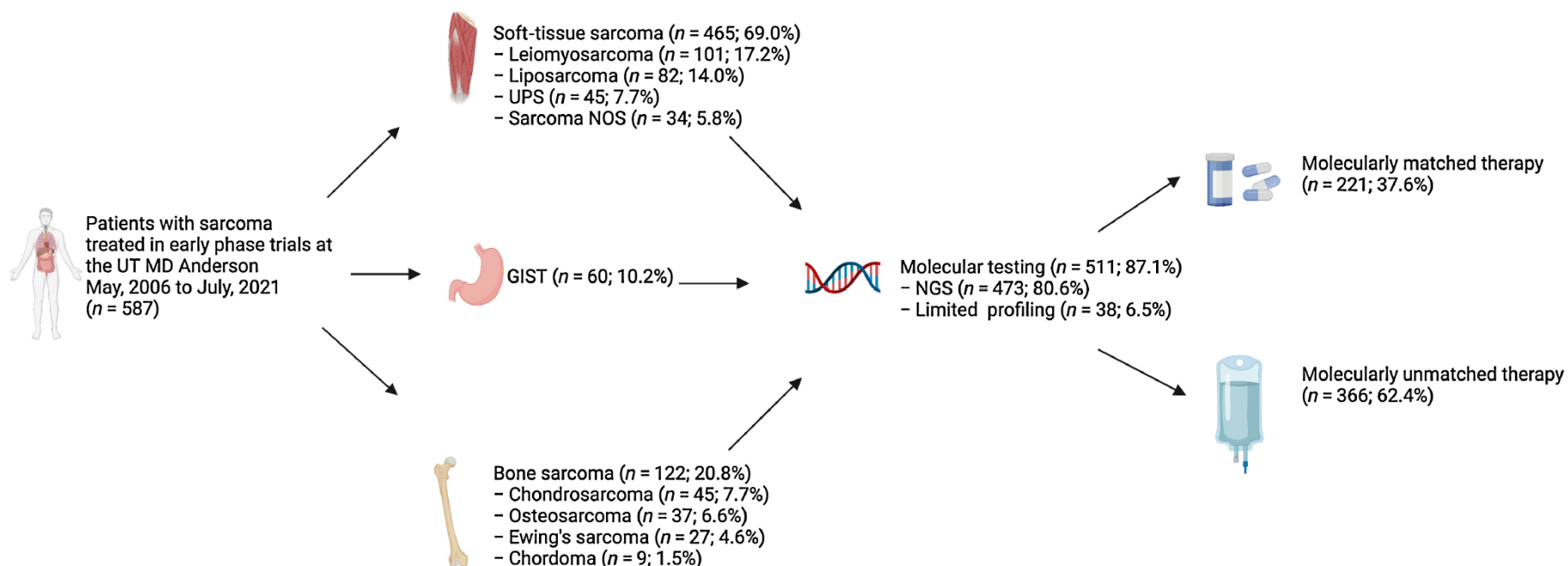
After 8 cycles

Impact of Biomarker-Matched Therapies on Outcomes in Patients with Sarcoma Enrolled in Early-Phase Clinical Trials (SAMBA 101)



Roberto Carmagnani Pestana^{1,2}, Justin T. Moyers^{1,3}, Jason Roszik⁴, Shiraj Sen⁵, David S. Hong¹, Aung Naing¹, Cynthia E. Herzog⁶, Siqing Fu¹, Sarina A. Piha-Paul¹, Jordi Rodon¹, Timothy A. Yap¹, Daniel D. Karp¹, Apostolia M. Tsimberidou¹, Shubham Pant¹, Maria A. Zazour⁷, Ravin Ratan⁷, Vinod Ravi⁷, Robert S. Benjamin⁷, Alexander J. Lazar⁸, Wei-Lien Wang⁸, Najat Daw⁶, Jonathan B. Gill⁶, Douglas J. Harrison⁶, Valerae O. Lewis⁹, Christina L. Roland¹⁰, Shreyaskumar R. Patel⁷, J. Andrew Livingston⁷, Neeta Somaiah⁷, Joseph A. Ludwig⁷, Anthony P. Conley⁷, Nelson Hamerschlak², Richard Gorlick^{6,7}, Funda Meric-Bernstam¹, and Vivek Subbiah¹

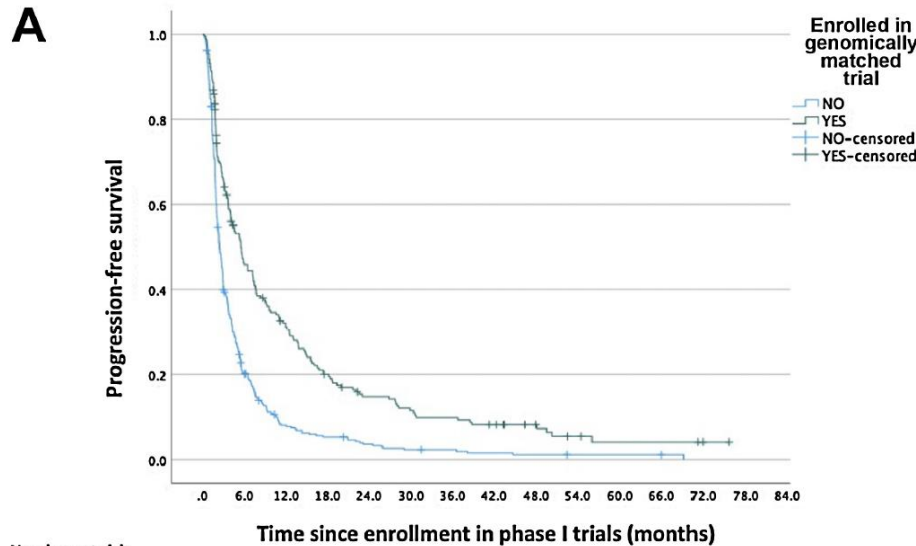
AACR 2023 and
CCR 2023



Impact of Biomarker-Matched Therapies on Outcomes in Patients with Sarcoma Enrolled in Early-Phase Clinical Trials (SAMBA 101)

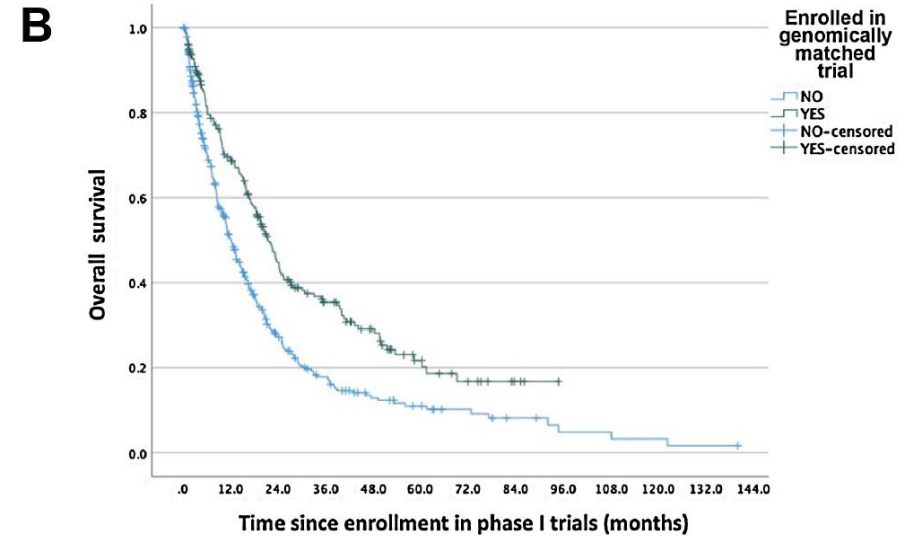


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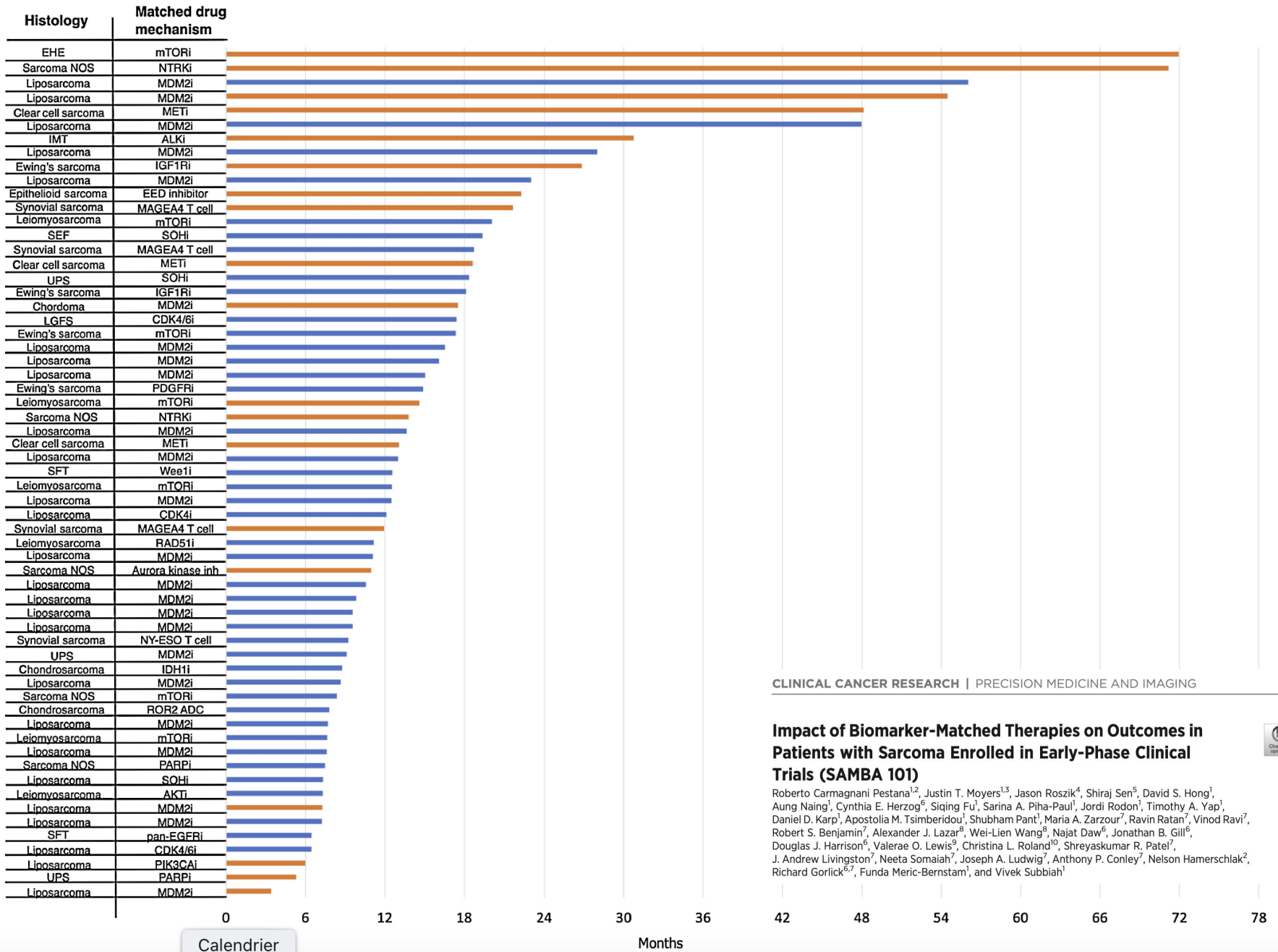
Numbers at risk	.0	6.0	12.0	18.0	24.0	30.0	36.0	42.0	48.0	54.0	60.0	66.0	72.0	78.0	84.0
Matched therapy	221	95	62	39	27	21	18	15	9	5	3	3	1	0	0
Unmatched therapy	366	70	26	17	11	7	6	4	3	2	2	2	0	0	0

5.5 vs 2.4 months (p<0.001)



Numbers at risk	.0	12.0	24.0	36.0	48.0	60.0	72.0	84.0	96.0	108.0	120.0	132.0	144.0
Matched therapy	221	135	75	48	31	15	8	3	0	0	0	0	0
Unmatched therapy	366	155	68	39	22	15	10	6	3	3	2	1	0

21 vs 12.3 months (p<0.001)



Impact of Biomarker-Matched Therapies on Outcomes in Patients with Sarcoma Enrolled in Early-Phase Clinical Trials (SAMBA 101)



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Table 2. Association between PFS and patient characteristics for advanced patients with sarcomas enrolled in early-phase trials, excluding patients with GIST.

	<i>n</i>	Univariate Cox HR (95% CI)	Univariate Cox <i>P</i> value	Multivariate Cox HR (95% CI)	Multivariate Cox <i>P</i> value
Sex					
Female	258	Ref		Ref	
Male	269	1.18 (0.99-1.41)	0.063	1.16 (0.96-1.40)	0.12
Type of sarcoma					
Soft tissue	405	Ref		Ref	
Bone	122	1.28 (1.04-1.59)	0.023	1.05 (0.62-1.78)	0.84
Sarcoma subtype					
UPS	45	Ref	<0.001	Ref	0.160
Chondrosarcoma	45	1.07 (0.70-1.64)		1.71 (0.89-3.29)	0.10
Ewing	27	0.82 (0.50-1.35)		0.89 (0.43-1.84)	0.75
Leiomyosarcoma	101	0.89 (0.62-1.28)		1.13 (0.77-1.65)	0.53
Liposarcoma	82	0.65 (0.45-0.96)		1.14 (0.76-1.72)	0.52
Osteosarcoma	37	1.60 (1.03-2.49)		1.63 (0.85-3.13)	0.14
Other	153	0.80 (0.57-1.13)		1.15 (0.80-1.65)	0.46
Sarcoma NOS	34	1.12 (0.71-1.78)		1.40 (0.88-2.25)	0.16
Prior therapies					
0	75	Ref	<0.001	Ref	<0.001
1	84	1.56 (1.12-2.20)		1.56 (1.11-2.21)	0.012
2	90	1.97 (1.42-2.73)		2.09 (1.48-2.96)	<0.001
3+	278	2.25 (1.70-2.97)		2.39 (1.74-3.27)	<0.001
Number of trials					
1	364	Ref	<0.001	Ref	<0.001
2	104	0.69 (0.56-0.87)		0.71 (0.57-0.89)	0.004
3+	59	0.47 (0.35-0.63)		0.48 (0.36-0.65)	<0.001
Matched trial					
No	361	Ref		Ref	
Yes	166	0.64 (0.52-0.77)	<0.001	0.74 (0.60-0.92)	0.006
IO trial					
No	344	Ref		—	
Yes	183	0.86 (0.72-1.04)	0.12		

Abbreviations: IO, immunotherapy; NOS, not otherwise specified; Ref, Reference; UPS, undifferentiated pleomorphic sarcoma.

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

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Perspectives

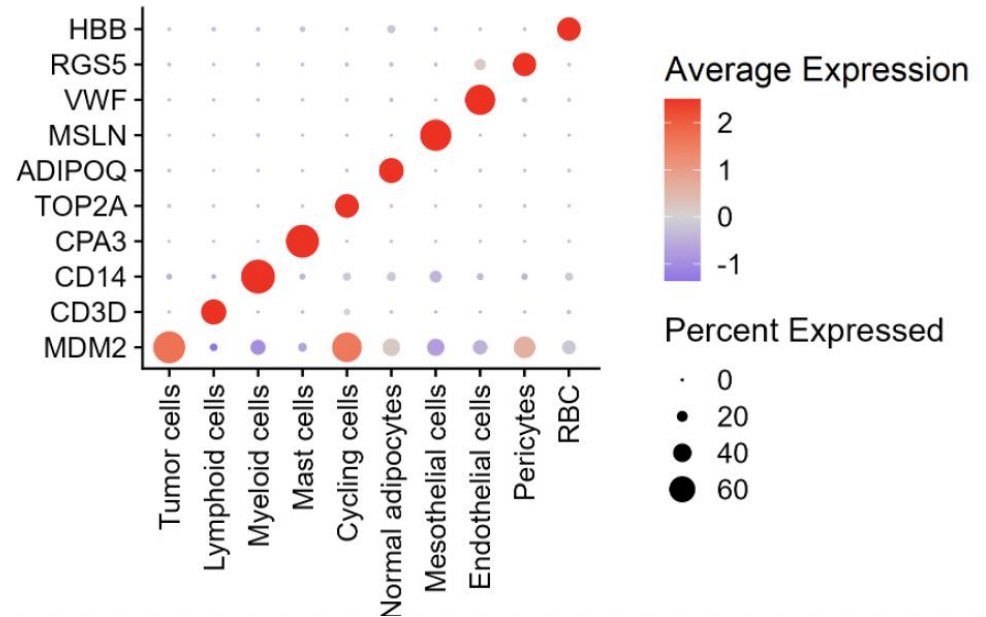
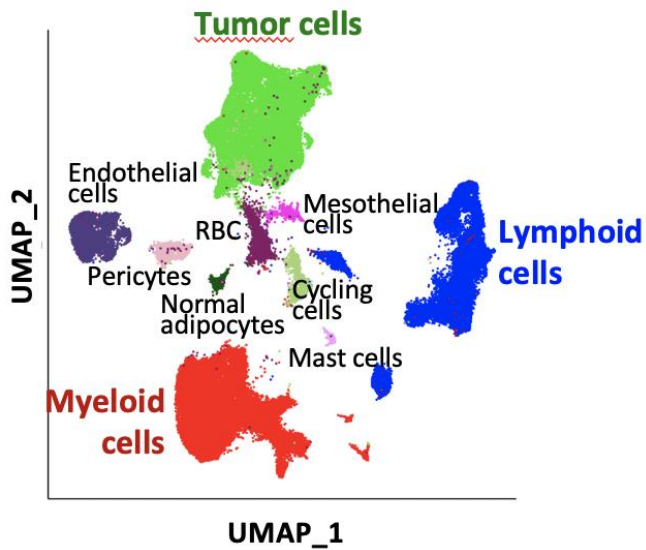
- **Intégration du profiling moléculaire en routine?**
 - Limites: rapport coût/bénéfice; anapath adaptée; matériel disponible
 - Bénéfices: médecine personnalisée, outliers, intérêt biologique
 - Phase 3 MULTISARC
 - PFMG 2025 préindication cancers rares

- **Aller plus loin**
 - Caractérisation épigénomique
 - Hétérogénéité intratumorale

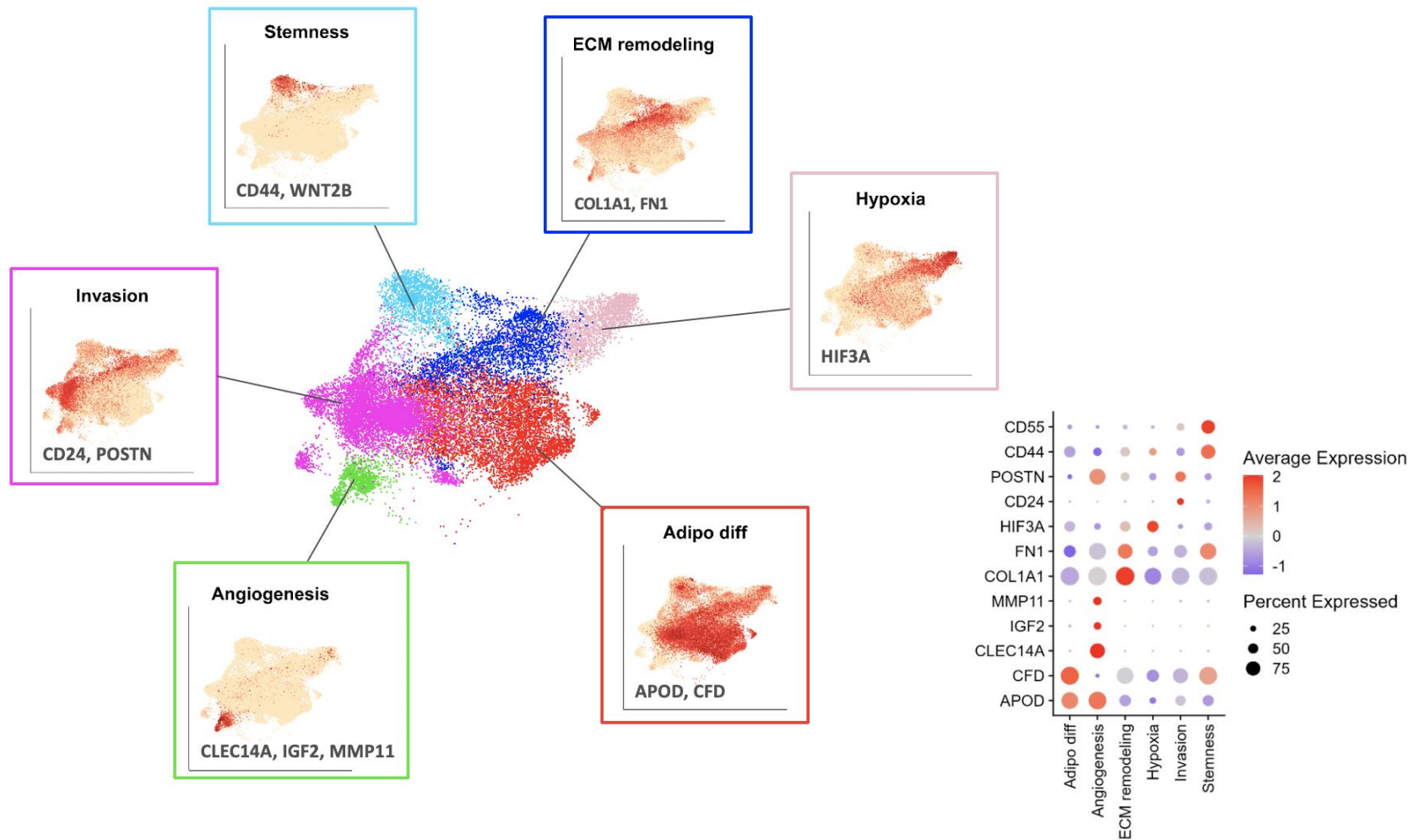
Projet SingleSARC-DDLPS

N=12 DDLPS patients

scRNAseq on WD and DD compartments of paired tumors



Projet SingleSARC-DDLPS



Conclusions

- **Révolution diagnostique**
- **Impact thérapeutique grandissant**
- **Take home messages**
 - Explorer les tumeurs avec les outils disponibles (quand?)
 - Stocker-Congeler les prélèvements
 - Tumeurs rares=projets collaboratifs++++

Remerciements

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And all collaborators

