CONFÉRENCE NATIONALE DES COMITÉS DE PROTECTION DES PERSONNES

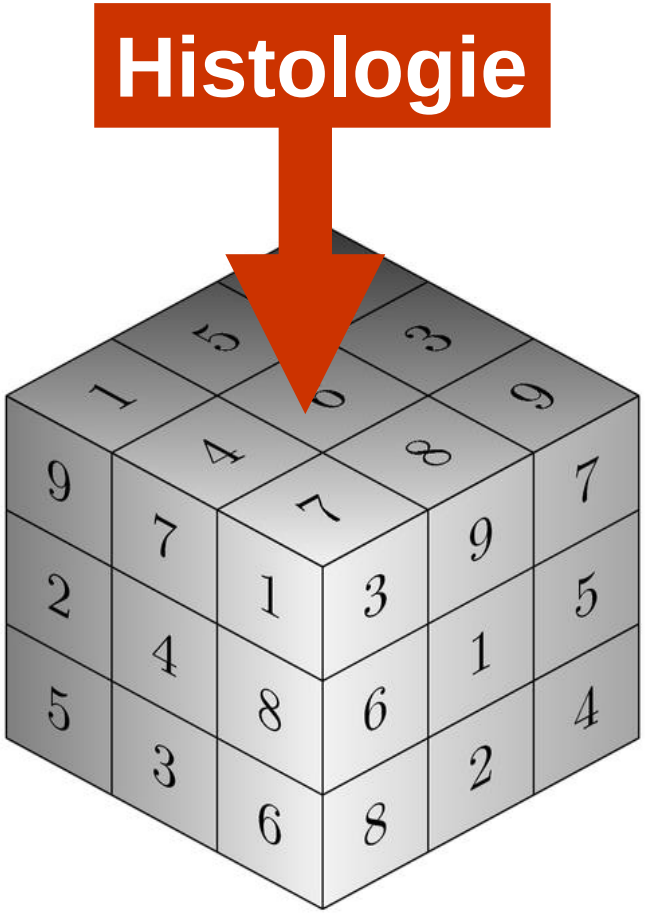
Les innovations de rupture en cancérologie

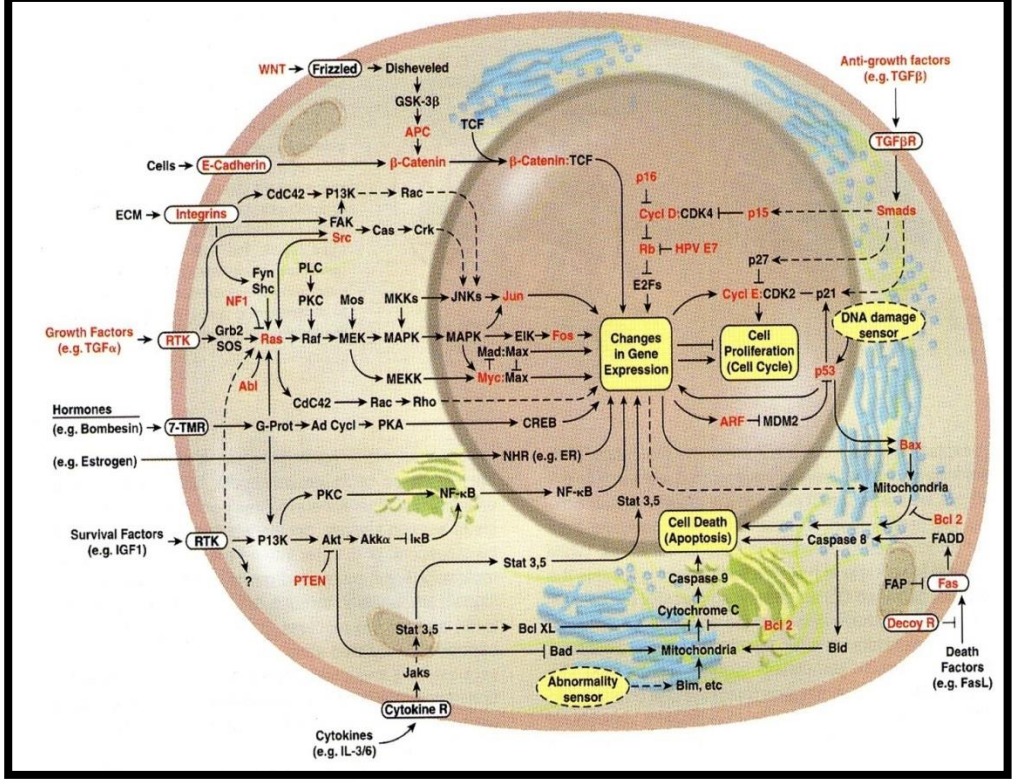
JY Blay
Centre Léon Bérard
Université Claude Bernard Lyon I
LYRICAN
Académie de Médecine

Liens d'intérêt

Company	Scientific advice	Scientific works	Symposia & oral communication
Abbvie	x	x	
Amgen	x	x	x
ARIAD	x	x	
AstraZeneca		x	x
Bayer	x	x	x
BMS	x	x	x
Deciphera	x	x	
DDB	x	x	
EISAI	x	x	x
Genomic Health		x	x
Gilead		x	x
GSK		x	x
INNATE PHARMA	X (member of the Supervisory committee)		
INCYTE		x	
IQVIA	x	x	x
Jansenn		x	x
LILLY		x	x
Merck Serono		x	x
MSD		x	x
Nanobiotix	x	x	
Novartis	x	x	x
Novex		x	x
Onxeo	x		
Pfizer		x	x
Pharmamar	x	x	
PRA		x	
Roche		x	x
Sanofi Aventis		x	x
Swedish Orphan		x	x
Takeda		x	
Toray		x	

Nosologie et traitement





Sciencexpress Research Art

The Consensus Coding Sequences of Human Breast and Colorectal Cancers

Tobias Sjöblom,[1]* Siân Jones,[1]* Laura D. Wood,[1]* D. Williams Parsons,[1]* Jimmy Lin,[1] Thomas Barber,[1] Diana Ma
Rebecca J. Leary,[1] Janine Ptak,[1] Natalie Silliman,[1] Steve Szabo,[1] Phillip Buckhaults,[2] Christopher Farrell,[2] Paul Mee
D. Markowitz,[3] Joseph Willis,[4] Dawn Dawson,[4] James K. V. Willson,[5] Adi F. Gazdar,[6] James Hartigan,[7] Leo
Liu,[8] Giovanni Parmigiani,[9] Ben Ho Park,[10] Kurtis E. Bachman,[11] Nickolas Papadopoulos,[1] Bert Vogelstein,[1]
Kinzler,[1]† Victor E. Velculescu[1]†

Mutational landscape and significance across 12 major cancer types

Cyriac Kandoth[1]*, Michael D. McLellan[1]*, Fabio Vandin[2], Kai Ye[1,3], Beifang Niu[1], Charles Lu[1], Mingchao Xie[1], Qunyuan Zhang[1,3], Joshua F. McMichael[1], Matthew A. Wyczalkowski[1], Mark D. M. Leiserson[2], Christopher A. Miller[1], John S. Welch[4,5], Matthew J. Walter[4,5], Michael C. Wendl[1,3,6], Timothy J. Ley[1,3,4,5], Richard K. Wilson[1,3,5], Benjamin J. Raphael[2] & Li Ding[1,3,4,5]

TP53 loss creates therapeutic vulnerability in colorectal cancer

Yunhua Liu[1], Xinna Zhang[2,3], Cecil Han[1], Guohui Wan[1], Xingxu Huang[4], Cristina Ivan[2,3], Dahai Jiang[2,3], Cristian Rodriguez-Aguayo[3,5], Gabriel Lopez-Berestein[3,5], Pulivarthi H. Rao[6], Dipen M. Maru[7], Andreas Pahl[8], Xiaoming He[9], Anil K. Sood[1,2,3], Lee M. Ellis[10], Jan Anderl[8] & Xiongbin Lu[1,3]

Comprehensive genomic characte defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network*

Vol 455|23 October 2008|doi:10.1038/nature07385

Thérapeutique moléculaire et mutations pilotes

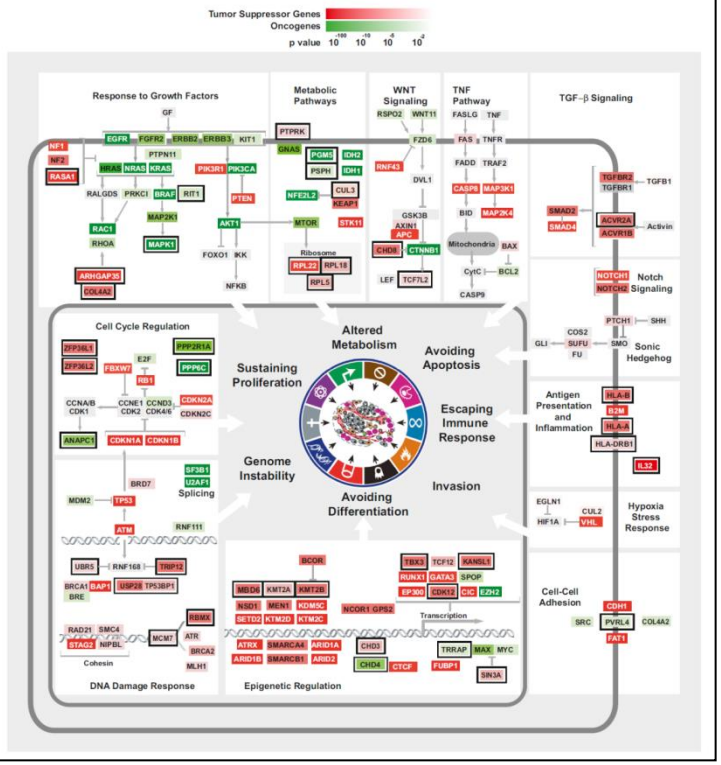
Mutations pilotes « fortes »?

- La cellule tumorale
- Le stroma
- Hétérogénéité
- L'hôte, le patient
- Evolution dans le temps

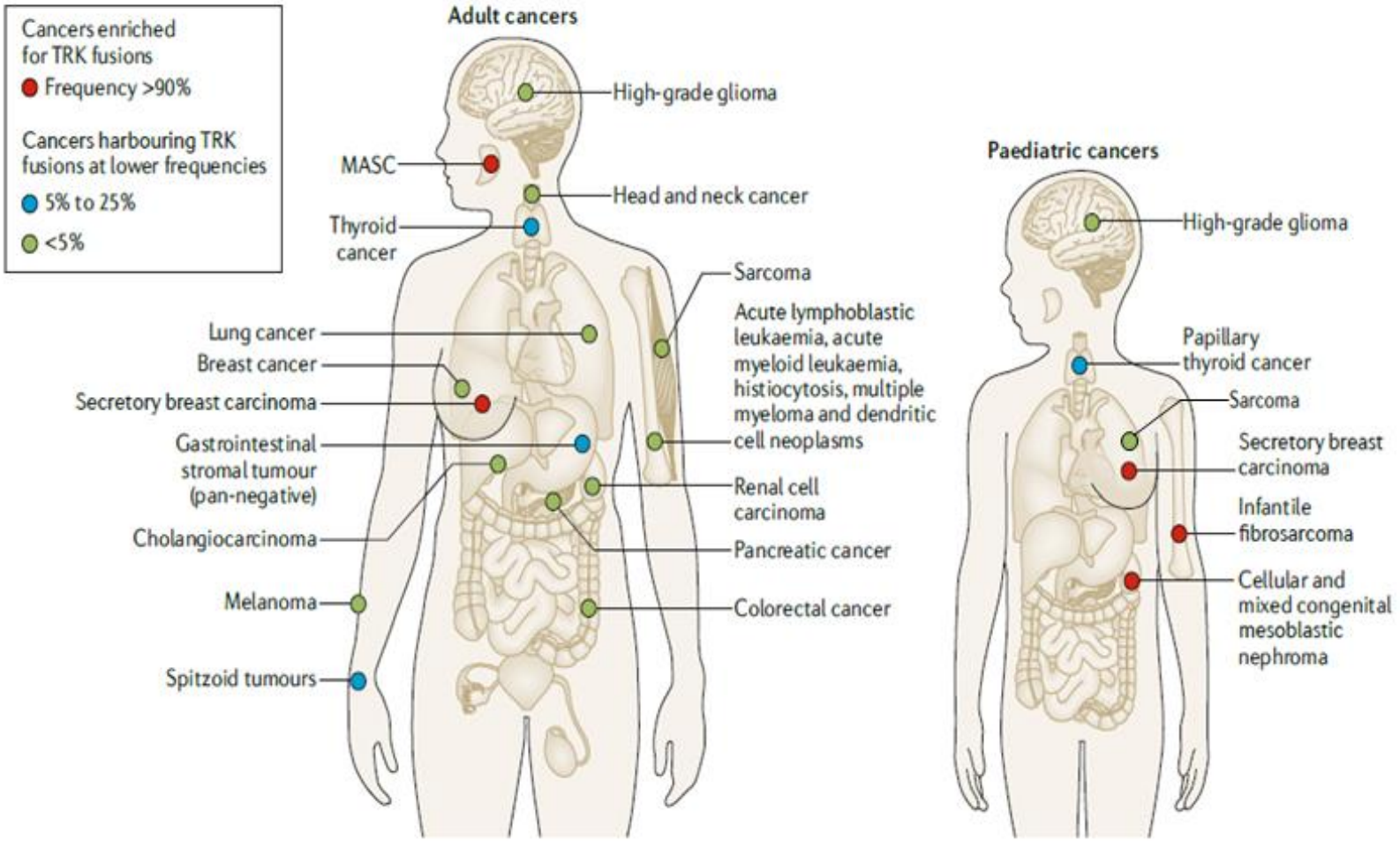
- Mutations pilotes faibles?
- La « somme » des mutations pilotes faibles?

Cumulative Haploinsufficiency and Triplosensitivity Drive Aneuploidy Patterns and Shape the Cancer Genome

Teresa Davoli,[1,2,5] Andrew Wei Xu,[2,4,5] Kristen E. Mengwasser,[1,2] Laura M. Sack,[1,2] John C. Yoon,[2,3] Peter J. Park,[2,4] and Stephen J. Elledge[1,2,*]
[1]Howard Hughes Medical Institute, Department of Genetics, Harvard Medical School, Boston, MA 02115, USA
[2]Division of Genetics, Brigham and Women's Hospital, Boston, MA 02115, USA
[3]Department of Medicine, Massachusetts General Hospital, Boston, MA 02114, USA
[4]Center for Biomedical Informatics, Harvard Medical School, Boston, MA 02115, USA
[5]These authors contributed equally to this work
*Correspondence: selledge@genetics.med.harvard.edu
http://dx.doi.org/10.1016/j.cell.2013.10.011



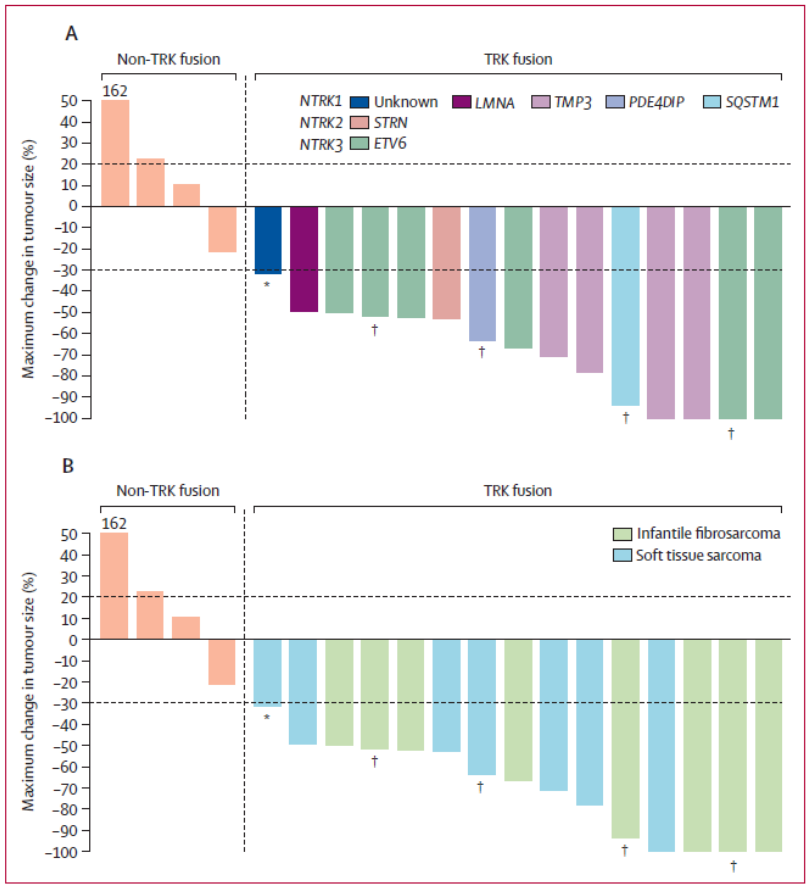
NTRK fusions across cancers



Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study

Theodore W Laetsch, Steven G DuBois*, Leo Mascarenhas, Brian Turpin, Noah Federman, Catherine M Albert, Ramamoorthy Nagasubramanian, Jessica L Davis, Erin Rudzinski, Angela M Feraco, Brian B Tuch, Kevin T Ebata, Mark Reynolds, Steven Smith, Scott Cruickshank, Michael C Cox, Alberto S Pappo*, Douglas S Hawkins**

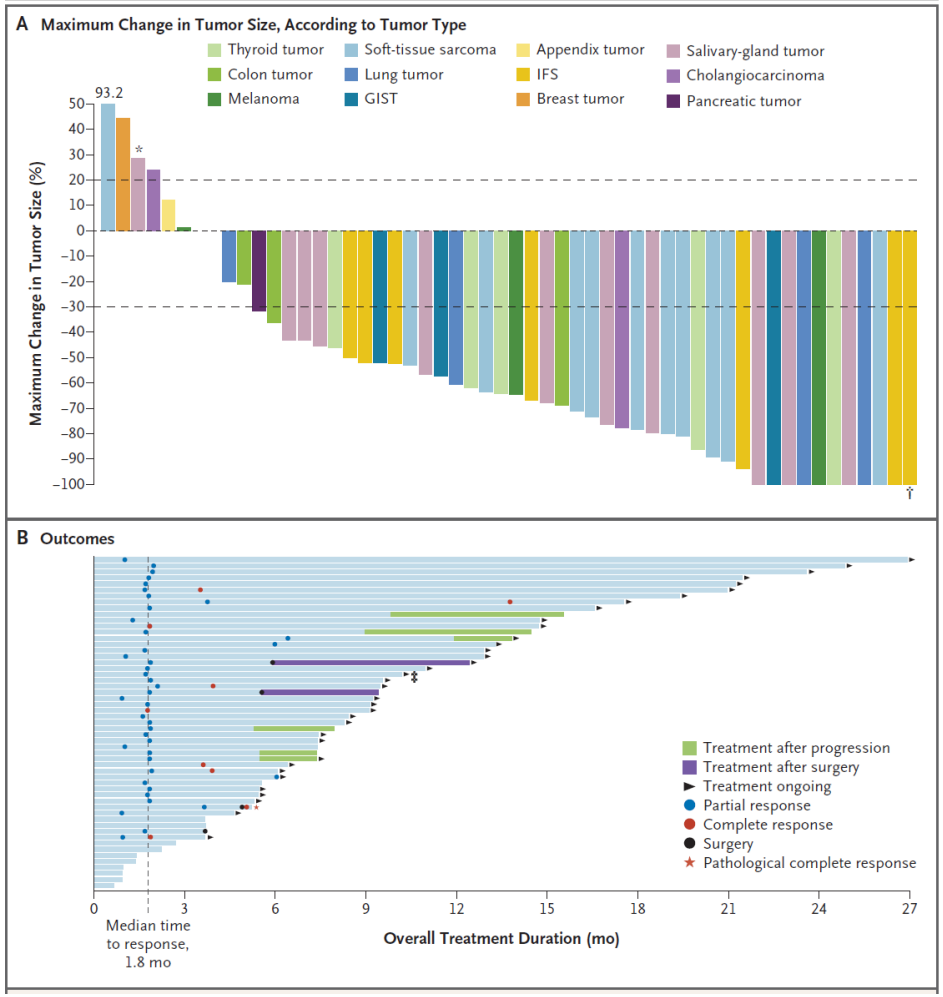
Lancet Oncol 2018; 19: 705–14



Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

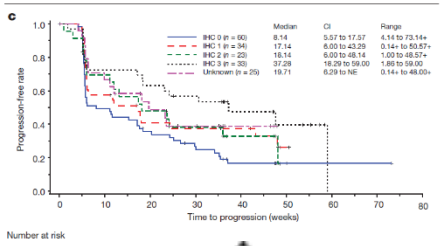
A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, 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

N Engl J Med 2018;378:731-9.
DOI: 10.1056/NEJMoa1714448

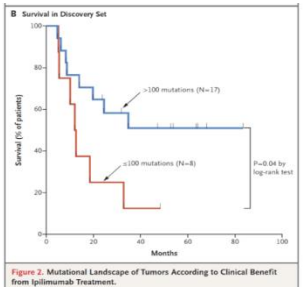


Predictive immune markers

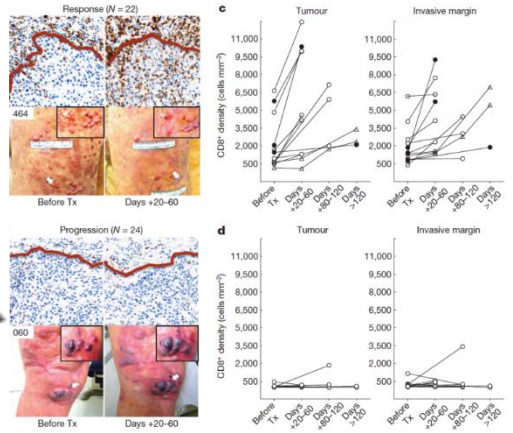
PDL1 expression



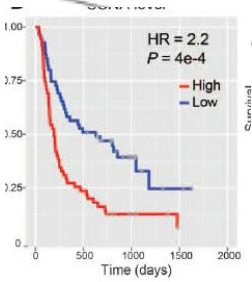
Mutation load



Immune infiltrates



Aneuploidy



Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy

Teresa Davoli,[1] Hajime Uno,[2] Eric C. Wooten,[1] Stephen J. Elledge[1]*

Herbst Nature 2014, Tumeh Nature 2014, Snyder NEJM 2014, Davoli et al, Sciance 2017

La méthodologie des essais cliniques doit évoluer

Basket/Panier
Un gène: plusieurs histologies

Umbrella/Parapluie
Une histologie: plusieurs gènes

Octopus/Pieuvre
Une study: Bras multiples

PRECISION MEDICINE TRIALS in the CLB

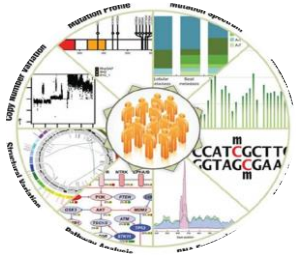
MOLECULAR SCREENING PROGRAMS

Profiler 01 et Profiler 02

Home-based and FoundationOne panels (≈ 70 molecular portrait / months)

illumina Agilent Technologies FOUNDATIONONE

WEEKLY MOLECULAR BOARD

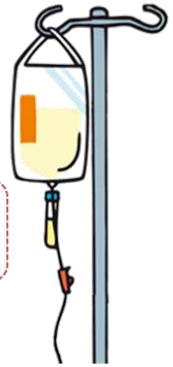


MOLECULAR BASED RECOMMANDED THERAPIES

PRECISION MEDICINE INVESTIGATOR INITIATED TRIALS

- **PI3K - mTOR** Buparlisib (PIK-ORL), Everolimus (MOST), AZD2014 (VICTORIA)
- **CDK4 / CDK6** Abemaciclib (ABORL), *Ribociclib (MEGAMOST)*
- **RTK** Sorafenib, Lapatinib, Pazopanib (MOST)
- **HER2** *Pertuzumab+ Trastuzumab (MegaMOST)*
- **MAPK** *Trametinib (TRADH)*
- **MDM2** *HDM201 (TRADH, MegaMOST)*
- **PARP** *Olaparib (MOST-Plus)*

Un nouveau paradigme de la cancérologie porté par une révolution scientifique et technologique



Caractérisation des tumeurs

Chirurgie ambulatoire

Les traitements médicamenteux

Quelles ruptures ?
Pour quelles tumeurs ?

La radiothérapie hypofractionnée

Radiologie interventionnelle

Soins de support

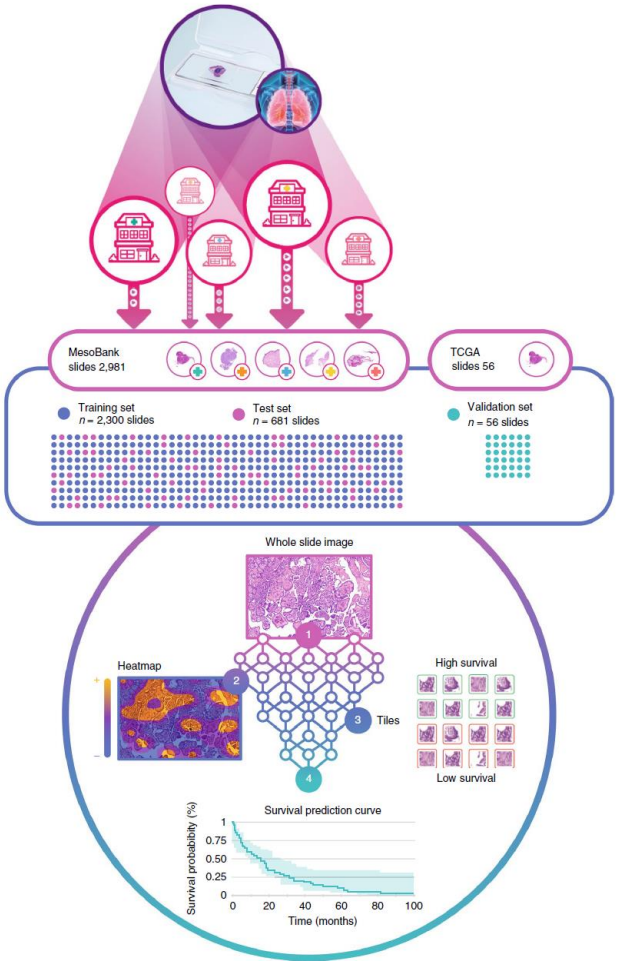
Conséquences : capacité, métiers, finance

Projet DI-A-GNOSE

Diagnostic using artificial intelligence for the novel nosological classification of human cancers: a proof of concept study

Francoise Galateau, Marie Karanian

J-Y Blay, Gilles Wainrib



nature medicine

LETTERS

https://doi.org/10.1038/s41591-019-0583-3

Deep learning-based classification of mesothelioma improves prediction of patient outcome

Pierre Courtiol[1,8], Charles Maussion[1,8], Matahi Moarii[1], Elodie Pronier[1], Samuel Pilcer[1], Meriem Sefta[1], Pierre Manceron[1], Sylvain Toldo[1], Mikhail Zaslavskiy[1], Nolwenn Le Stang[2], Nicolas Girard[3,4], Olivier Elemento[5], Andrew G. Nicholson[6], Jean-Yves Blay[7], Françoise Galateau-Sallé[2,8], Gilles Wainrib[1,8] and Thomas Clozel[1,8]*

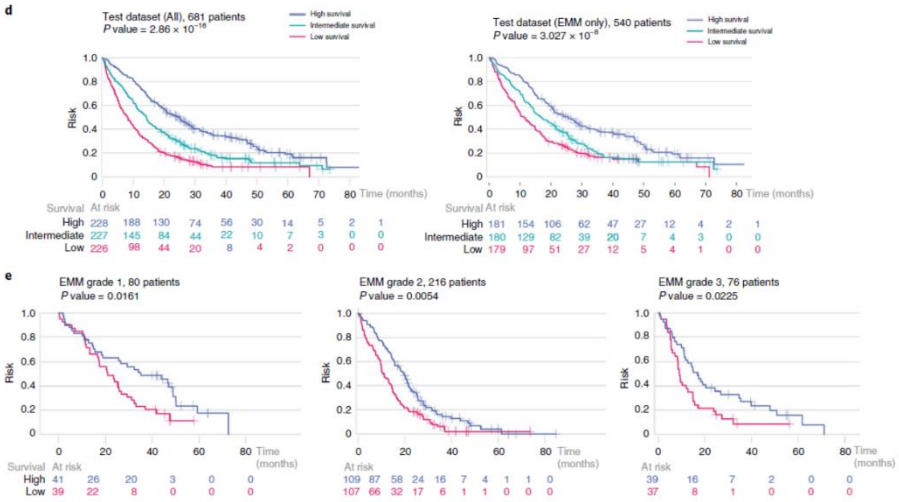
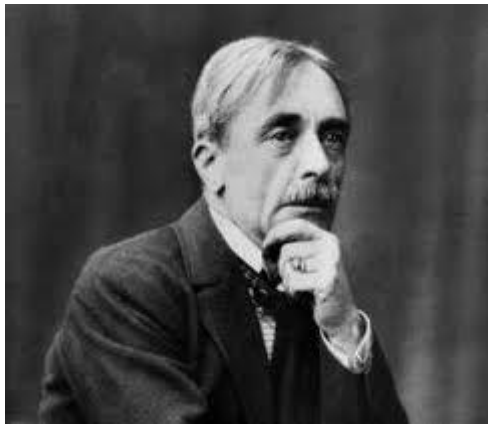


Fig. 2 | Comparison of the performance between MesoNet and other histology-based models to predict MM patient overall survival. a, Distribution of the



Ce qui est simple est toujours faux
What is simple is always false

Ce qui ne l'est pas est inutilisable
What is not simple is unusable

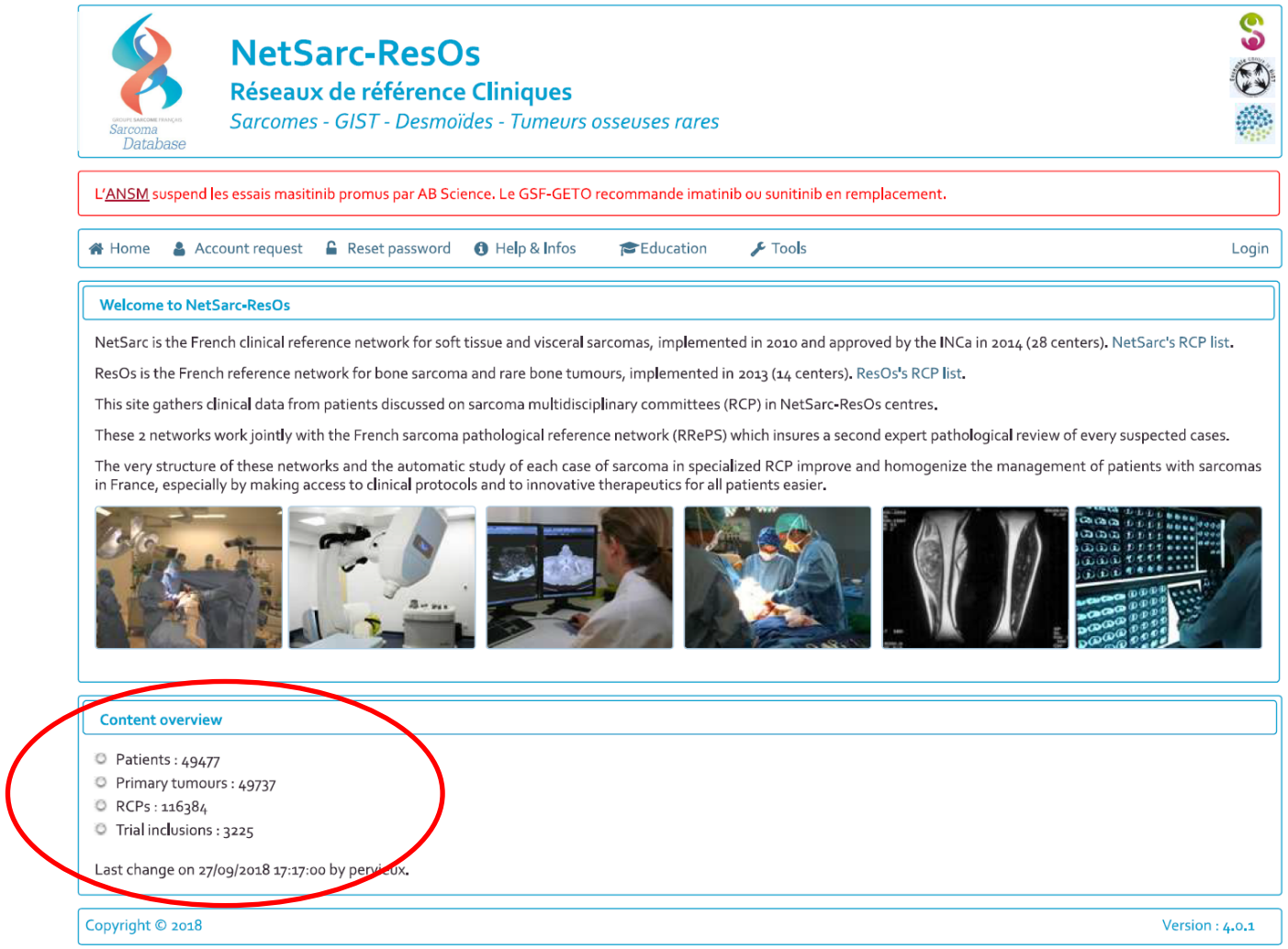
Paul Valéry

Conclusions

- Fragmentation des cancers : surtout des maladies rares
- Mutations somatiques : en routine, à mieux utiliser et à refaire
- Caractéristiques immunologiques et immunothérapie des cancers
- AI, mégadonnées..
- Thérapeutiques locales

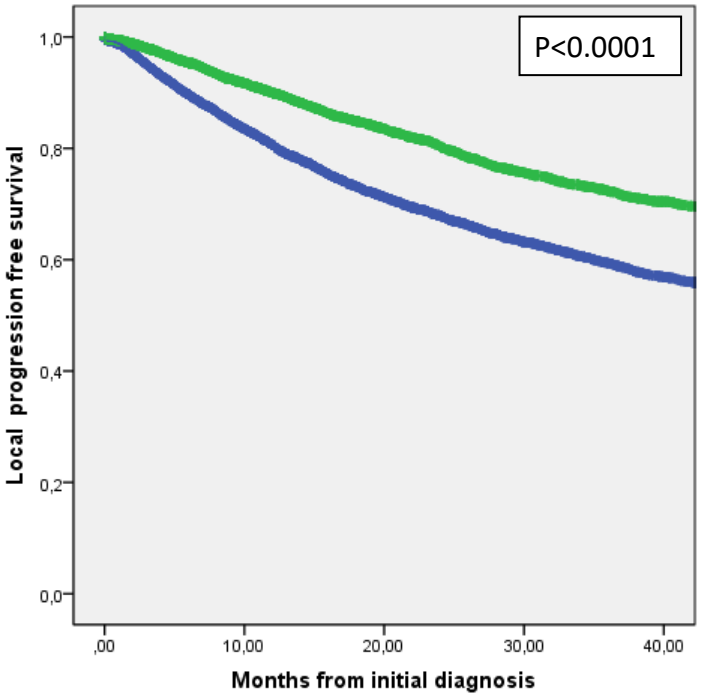
Websites

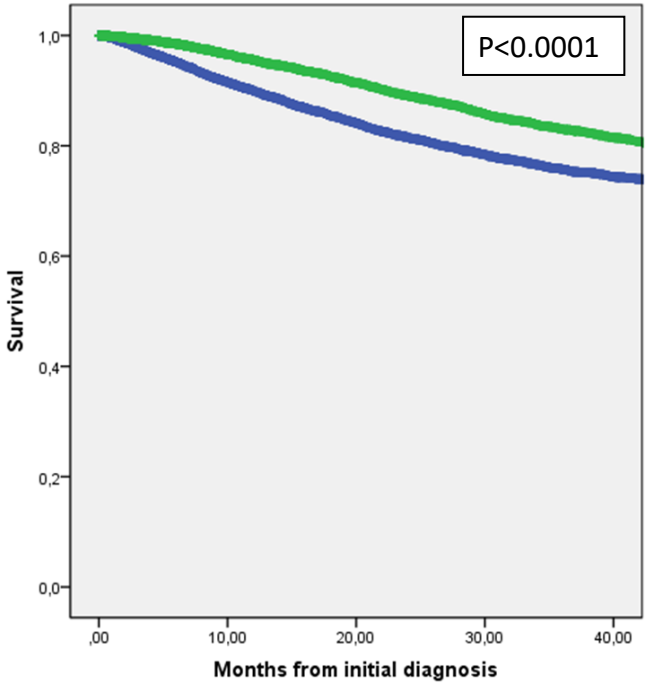
- netsarc.org
- rreps.org
- resos.org



MUNICH 2018 ESMO congress

LRFS & OS : incident patient population





Operated
- In NETSARC, N=9910 (33.9%)
- Outside NETSARC or
  no data, N=19307 (66.1%)

Ann Surg Oncol
https://doi.org/10.1245/s10434-019-07421-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – SARCOMA

Survival Benefit of the Surgical Management of Retroperitoneal Sarcoma in a Reference Center: A Nationwide Study of the French Sarcoma Group from the NetSarc Database

S. Bonvalot, MD, PhD[1], E. Gaignard, MD[1], E. Stoeckle, MD[2], P. Meeus, MD[3], G. Decanter, MD[4], S. Carrere, MD[5], C. Honore, MD, PhD[6], J. B. Delhorme, MD[7], M. Fau, MD[8], D. Tzanis, MD[1], S. Causeret, MD[9], P. Gimbergues, MD[10], J. M. Guillois, MD[11], B. Meunier, MD[12], A. Le Cesne, MD[13], F. Ducimetiere, PhD[14], M. Toulmonde, MD, PhD[15], and J. Y. Blay, MD, PhD[16]

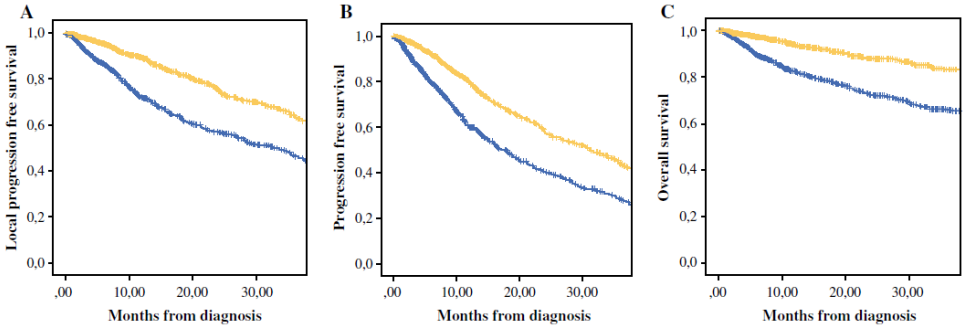


FIG. 1 Local progression-free survival (**a**), progression-free survival (**b**), and overall survival (**c**) of the retroperitoneal sarcoma patients in the NetSarc database. In blue: patients operated on outside of the NetSarc network. In yellow: patients operated on at a NetSarc center. Log-rank $p < 0.0001$ for LRFS, PFS, and OS

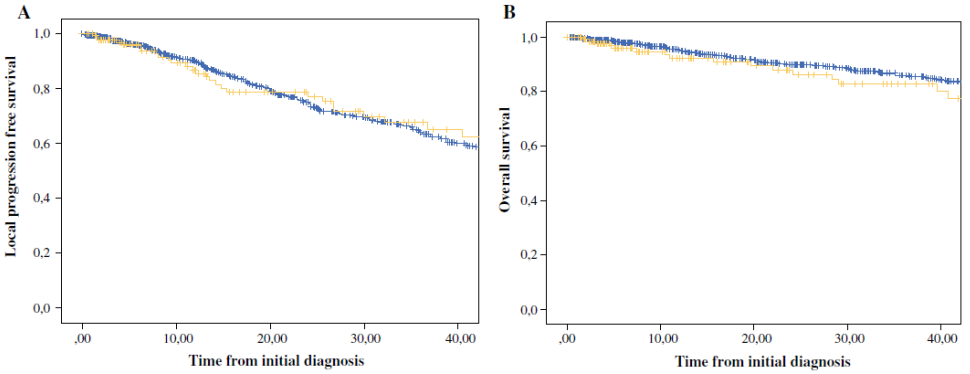
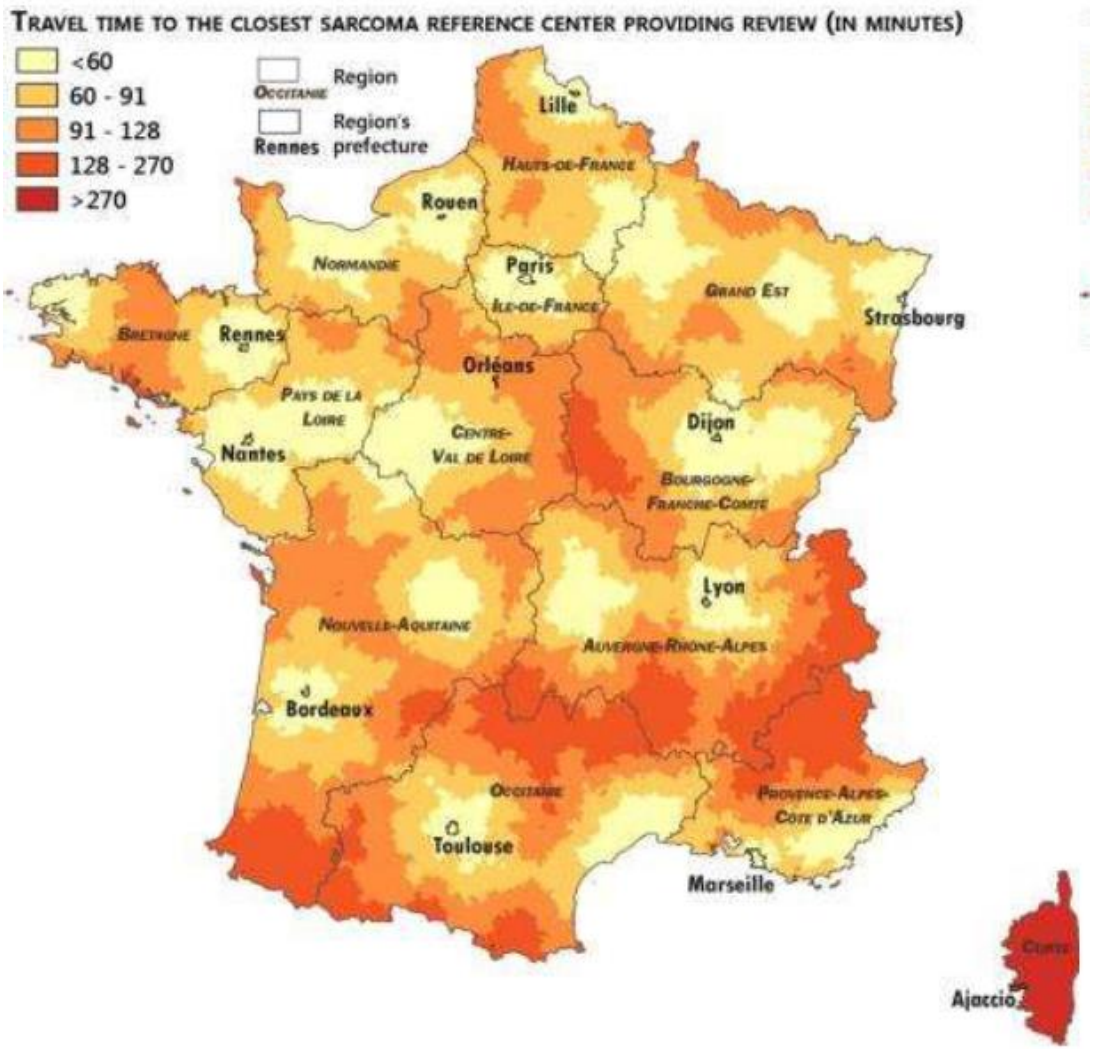


FIG. 2 Local progression-free survival (**a**) and overall survival (**b**) of patients operated on at NetSarc centers. In blue: patients operated on at the 13 NetSarc centers with the largest accrual of RPS patients. In yellow: patients operated on at the 13 NetSarc centers with the smallest accrual of RPS patients. Log-rank $p > 0.05$

Time to the closest reference center



Yohann Fayet et al