De la recherche aux soins en cancérologie : apport de la génomique

JY Blay
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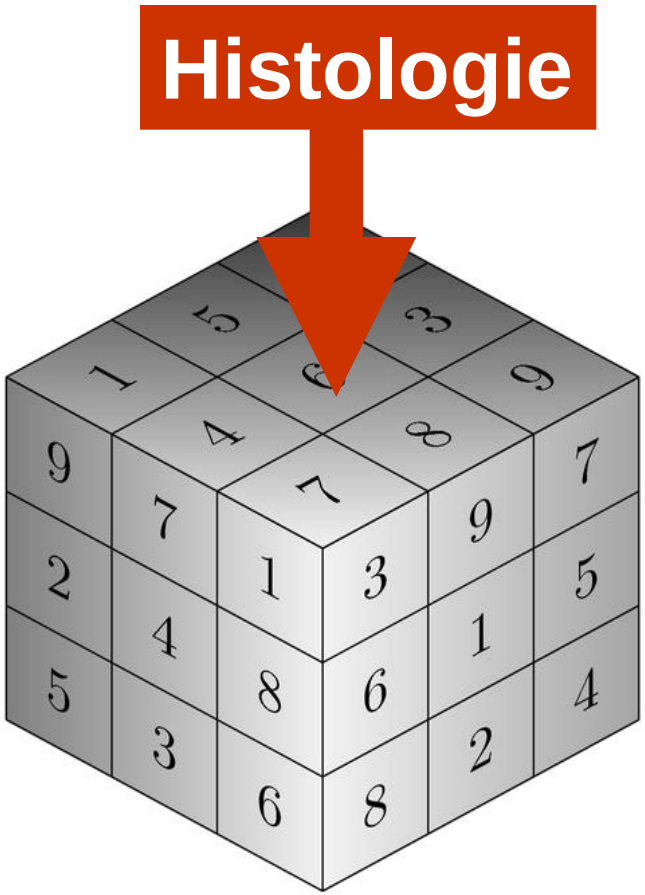
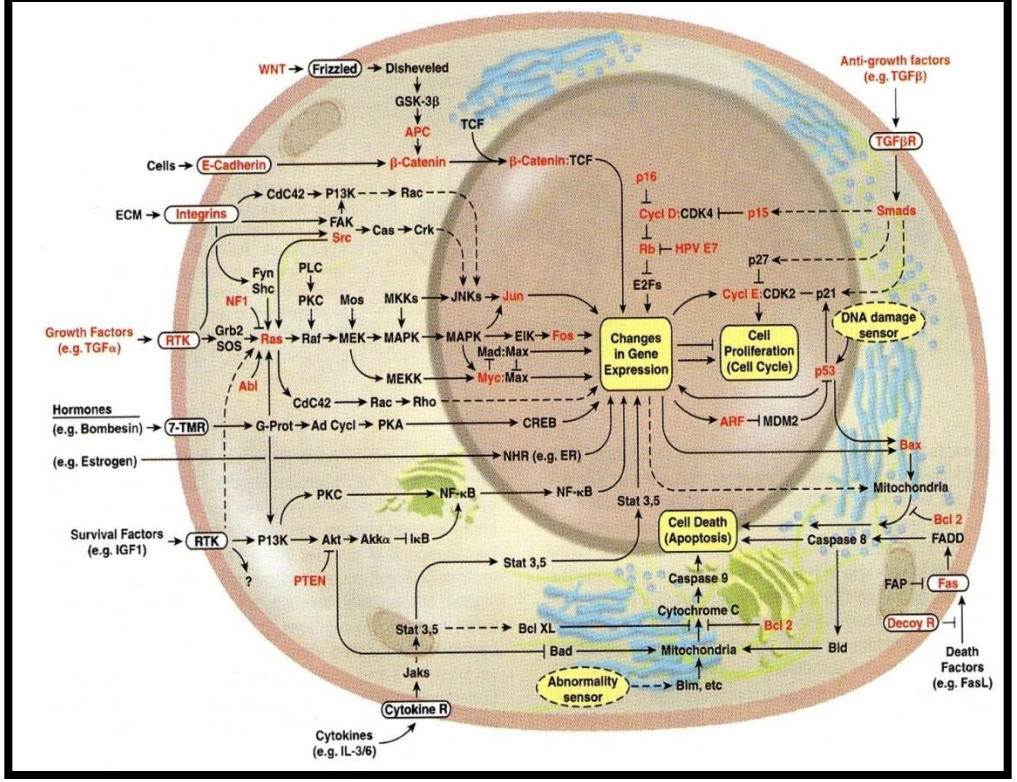
Médicaments ciblant les oncogènes

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] Lec
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

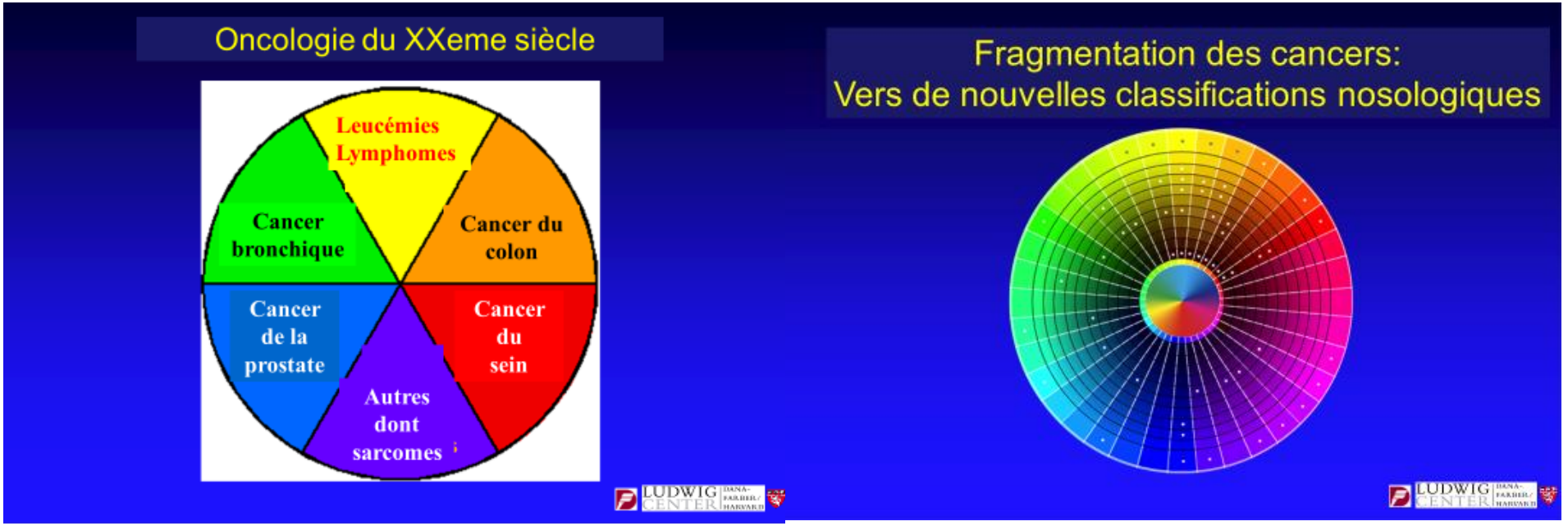
The Cancer Genome Atlas Research Network*

Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network*

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

Oncologie médicale 2017+

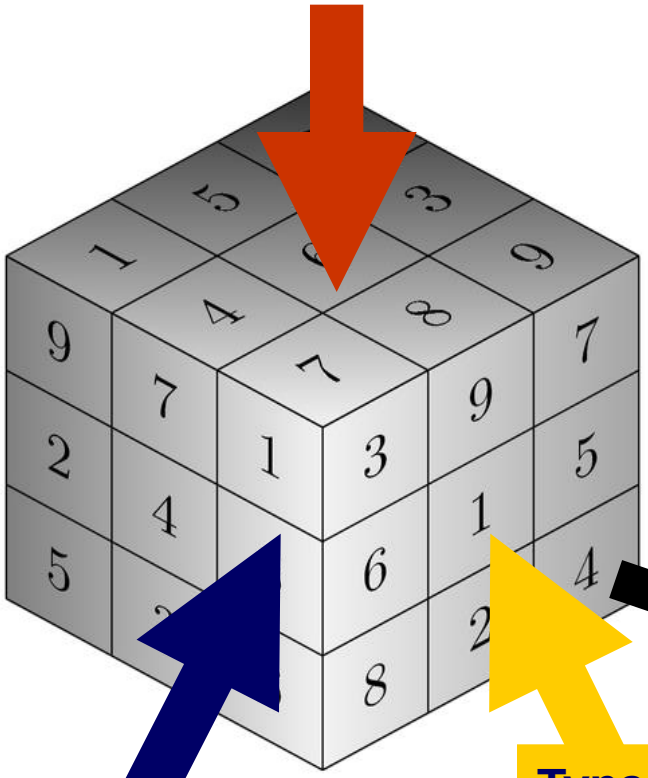


- Fragmentation nosologiques
- Biologie moléculaire en routine, à intégrer
- Bioinformatique

d'après G. Demetri

Nosologie et traitement 2017+

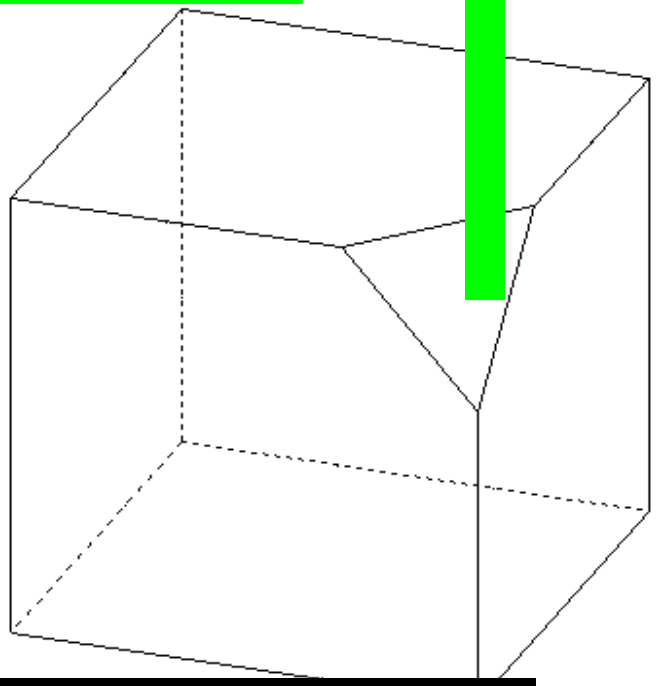
Histologie



Stroma
(cellules immune…)

Typage
Moléculaire

Essais sur
Sous groupes
histologiques
et moléculaires



Essais sur génotype?
SHIVA, SAFIR, MOST
BASKET !

Thérapeutique moléculaire et mutations pilotes

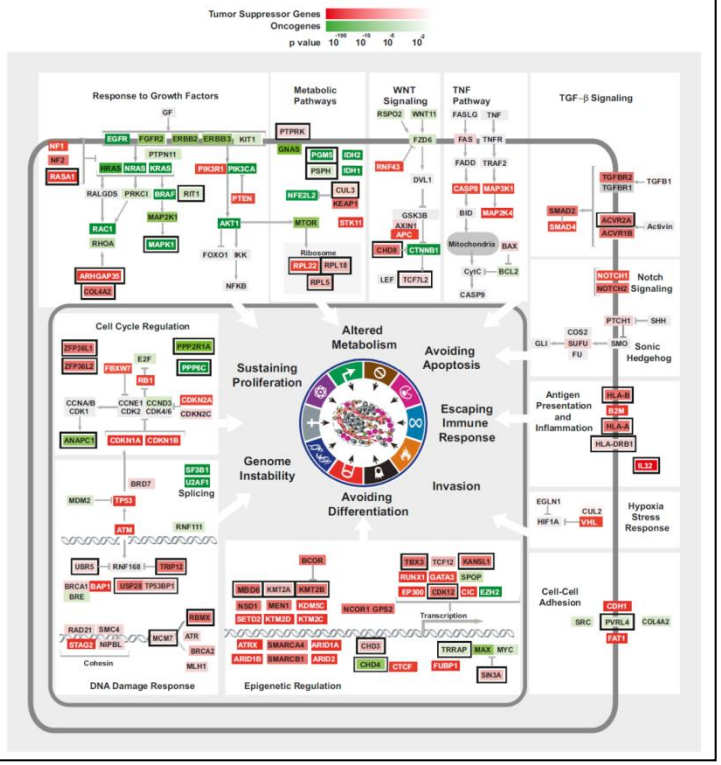
Mutations pilotes « fortes »?

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

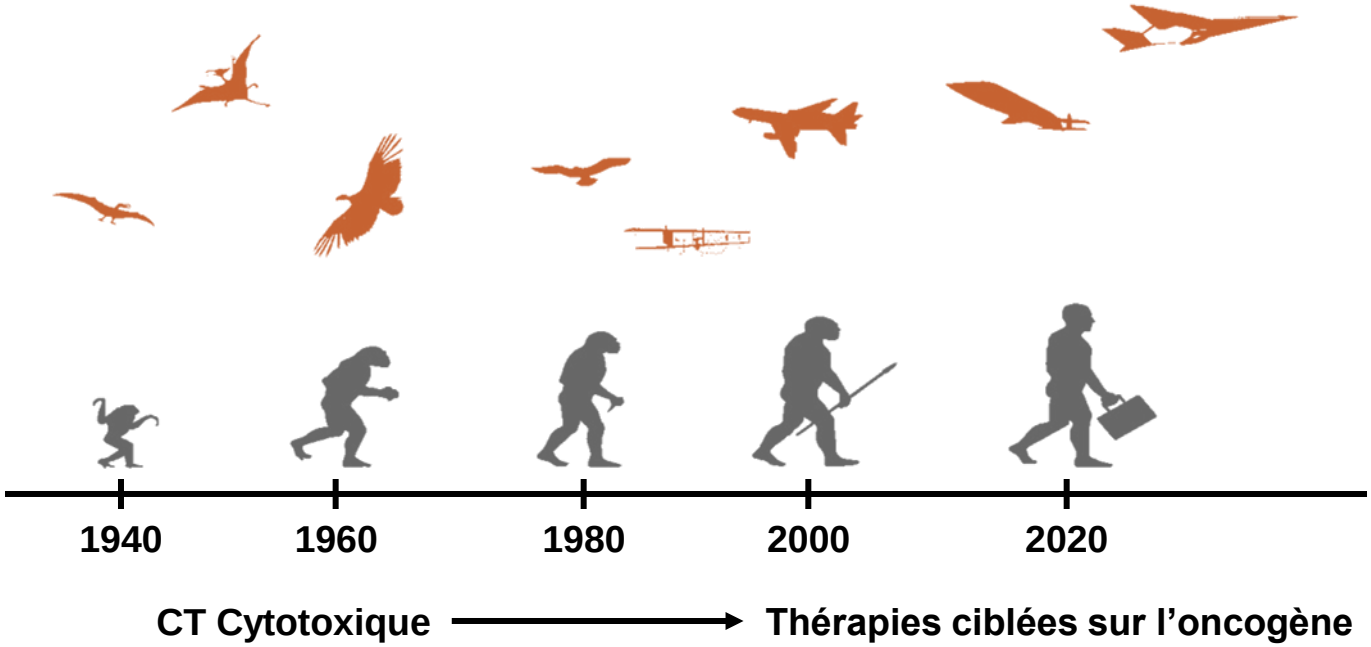
- Mutations pilotes faibles?
- La « somme » des mutations pilotes faibles?

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



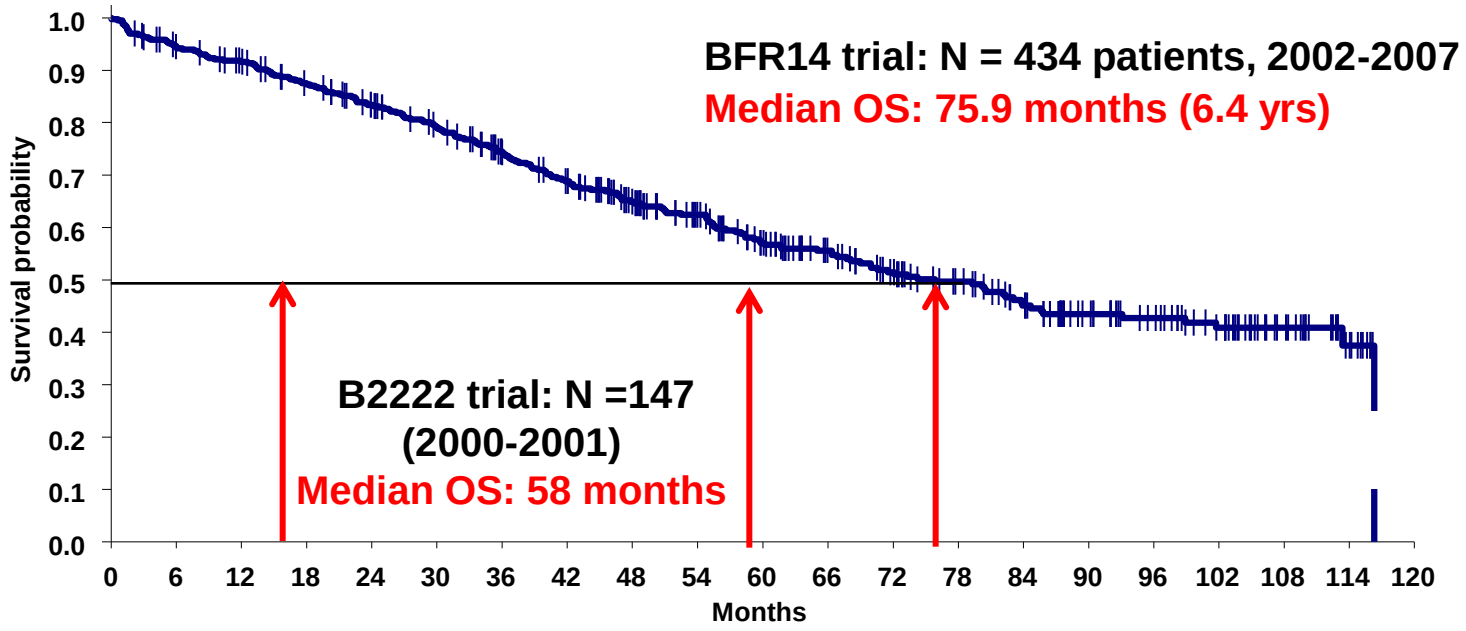
Perspective historique



La médecine moléculaire du cancer :

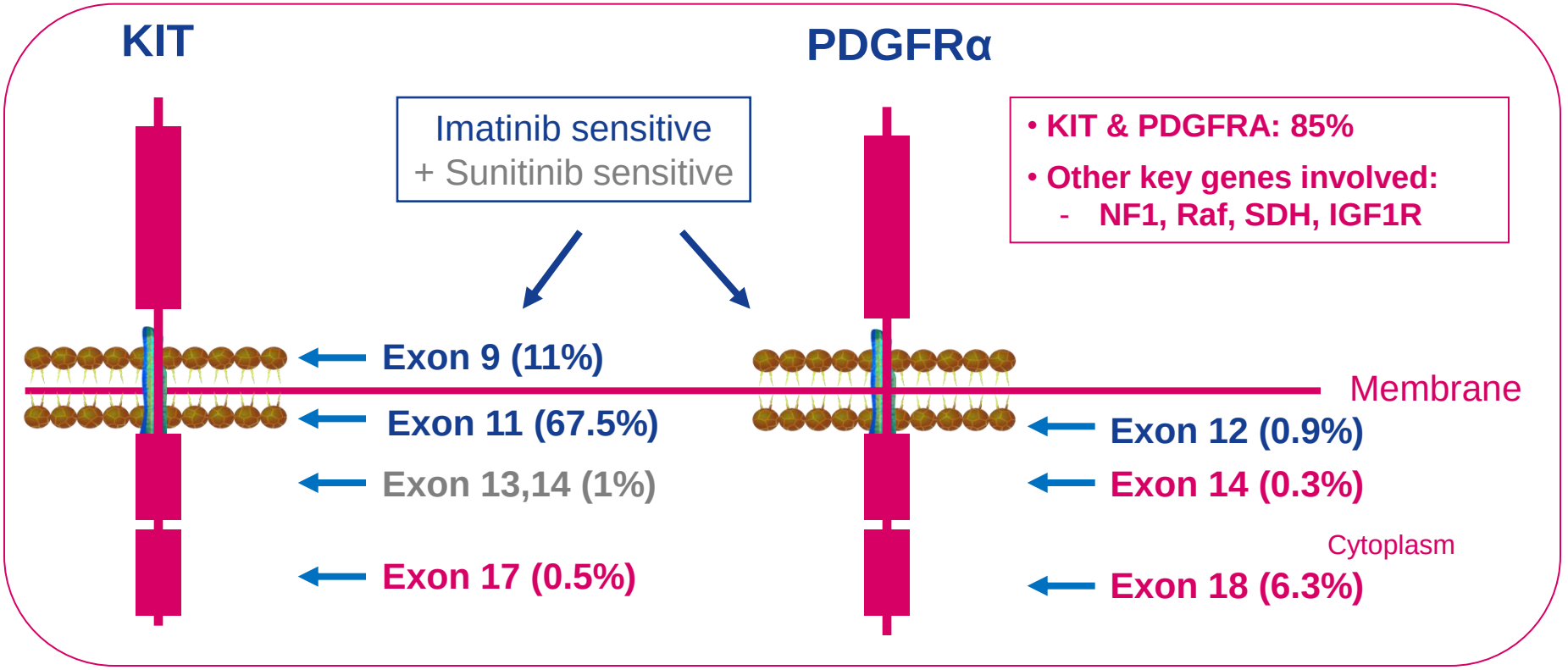
Trastuzumab et cancer du sein	adjuvant
Imatinib CML	>90% survie à 5 ans
Imatinib GIST	5% survie a 6 ans, 12% à 15 ans

GISTs: une seule maladie?



Perol M *et al.*, *J Clin Oncol.*, 2012; 30: 2516-24; Blanke CD *et al.*, *J Clin Oncol*., 2008; 26:620-25.

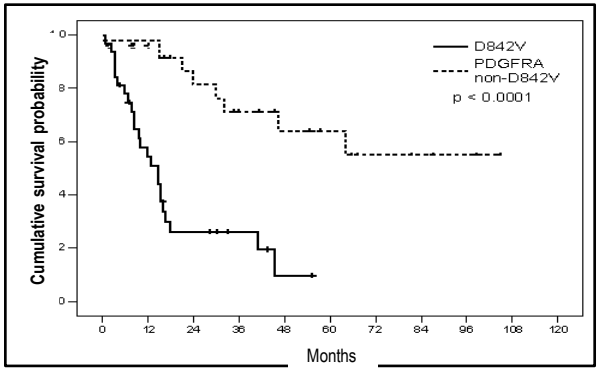
KIT & PDGFRα dans les GIST

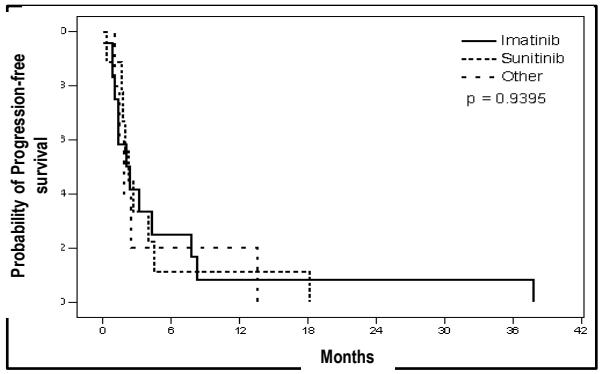


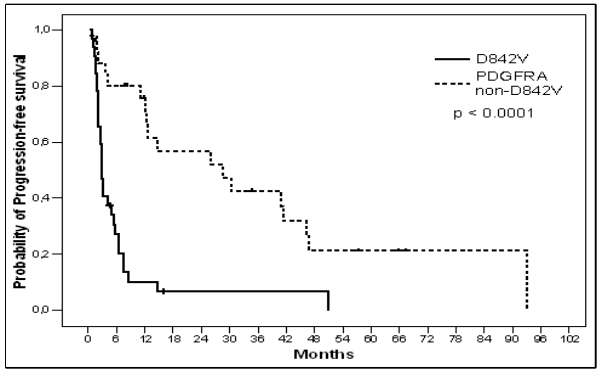
Heinrich *et al*. Hum Pathol 2002;33:484; Science 2003, Corless *et al*. Proc AACR 2003.

PDGFRA GIST en phase avancée

Characteristic	N	%
Total	**58**	**100**
Gender		
Male	34	58,6%
Female	24	41,4%
Primary tumor location		
Stomach	40	69,0%
Small bowel	7	12,1%
Peritoneum/Mesentery	2	3,4%
Rectum/Anus	1	1,7%
Other	4	6,9%
Unknown	4	6,9%
KIT/CD117 expression		
Positive	38	65,5%
Negative	7	12,1%
Unknown	13	22,4%
Type of mutation		
Exon 18 D842V substitution	32	55,2%
Other exon 18 mutation	17	29,3%
Exon 12 mutation	8	13,8%
Exon 4 mutation	1	1,7%
Metastatic sites		
Liver	36	62,1%
Peritoneum	33	56,9%
Liver & periotneum	15	25,9%
Other	15	25,9%
WHO PS		
0	28	48,3%
1	19	32,8%
2	2	3,4%
Unknown	9	15,5%







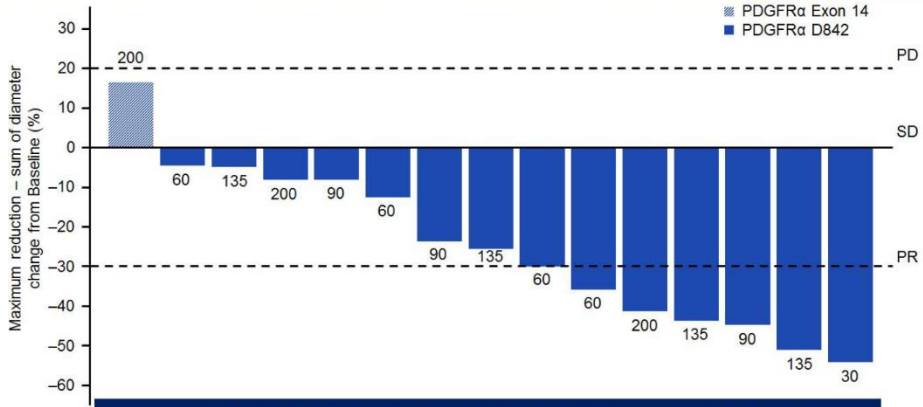
Preliminary safety and activity in a first-in-human Phase 1 study of BLU-285, a potent, highly selective inhibitor of KIT and PDGFRα activation loop mutants in advanced gastrointestinal stromal tumor (GIST)

Michael Heinrich[1], Robin Jones[2], Patrick Schoffski[3], Sebastian Bauer[4], Margaret von Mehren[5], Ferry Eskens[6], Philippe Cassier[7], Olivier Mir[8], Hongliang Shi[9], Terri Alvarez-Diez[9], Mary Ellen Healy[9], Beni Wolf[9], Suzanne George[10]

[1]Oregon Health & Sciences University, Oregon, USA; [2]Royal Marsden Hospital/Institute of Cancer Research, London, UK; [3]Leuven Cancer Institute, Leuven, Belgium; [4]University of Essen, Essen, Germany; [5]Fox Chase Cancer Center, Pennsylvania, USA; [6]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [7]Centre Leon Berard, Lyon, France; [8]Institut Gustave Roussy, Paris, France; [9]Blueprint Medicines Corporation, Massachusetts, USA; [10]Dana-Farber Cancer Institute, Massachusetts, USA

EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium, Munich, Germany, 01 Dec 2016

Strong clinical activity against PDGFRα D842-mutant GIST at all dose levels



- 14 out of 14 D842-mutant patients with tumor reductions
- All PDGFRα patients remain on treatment

GIST mute sur les codons 557-558 de KIT

Plus de rechutes,… mais plus de réponses au traitement

Deletions Affecting Codons 557-558 of the *c-KIT* Gene Indicate a Poor Prognosis in Patients With Completely Resected Gastrointestinal Stromal Tumors: A Study by the Spanish Group for Sarcoma Research (GEIS)

Javier Martín, Andrés Poveda, Antonio Llombart-Bosch, Rafael Ramos, José A. López-Guerrero, Javier García del Muro, Joan Maurel, Silvia Calabuig, Antonio Gutierrez, José L. González de Sande, Javier Martínez, Ana De Juan, Nuria Lainez, Ferrán Losa, Valentín Alija, Pilar Escudero, Antonio Casado, Pilar García, Remei Blanco, and José M. Buesa

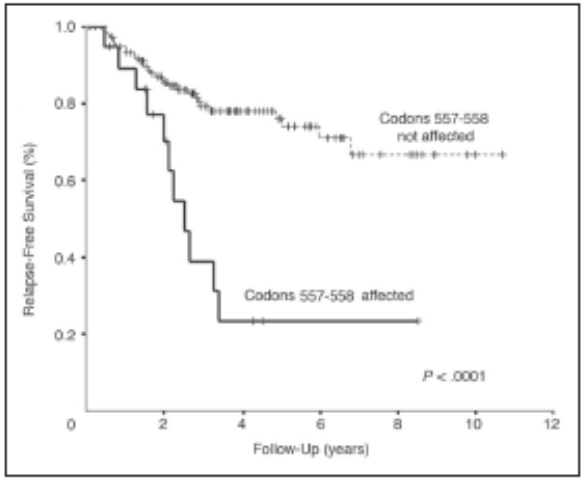
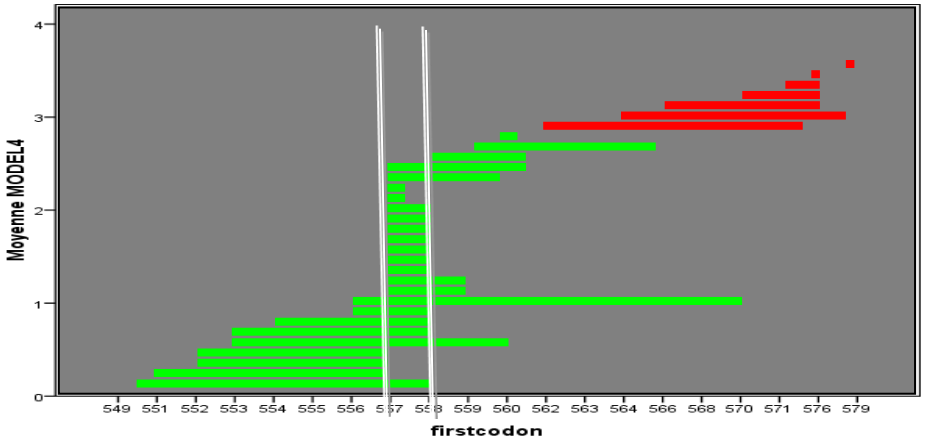


Fig 7. Kaplan-Meier curve for patients with or without deletion type mutation involving codons 557 to 558 of exon 11.



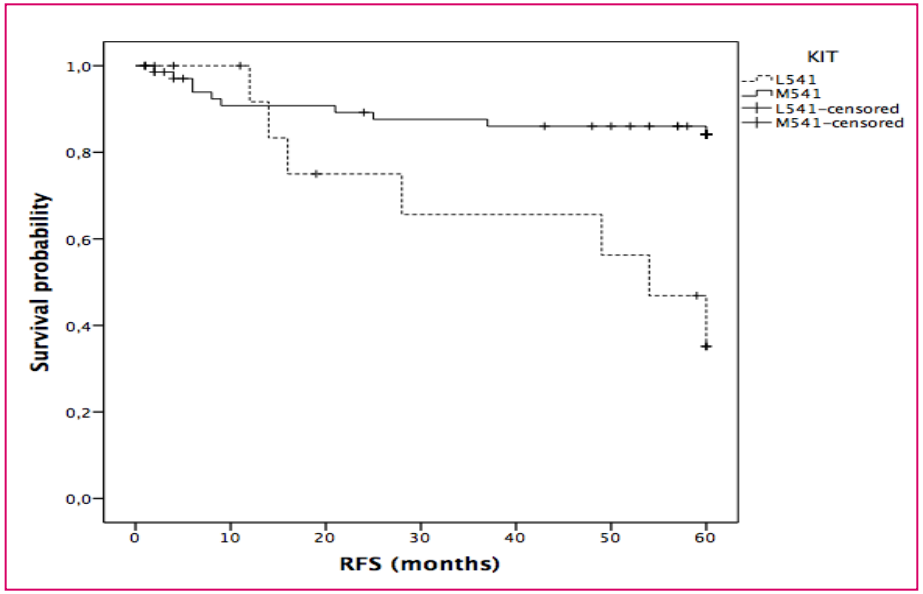
	≤ 556	557/558	≥ 559
CR	**30%**	**43.1%**	**23.5%**
PR	**57.5%**	**40.3%**	**45.1%**
SD	**10%**	**16.7%**	**31.4%**

BFR14 trial ***JF Emile et al, ASCO 2013***

P= 0.02

… et les variants génotypiques?

M541L variant in KIT
≈20% heterozygotes
≈ 4% homozygotes



Variable	HR (95% CI)	*P*
KIT^{L541}	6.1 (1.8-21)	0.004
Tumor size (< 50 mm versus ≥ 50 mm)	3.6 (1.1-12)	0.03
Location (gastric versus non gastric)	0.5 (0.1-2)	0.06
Mitotic index per 50 HPF (< 5 versus ≥5)	6.2 (1.7-23)	0.006
Mutation status (all other versus *KIT* exon 11)	1.5 (0.4-5)	0.6

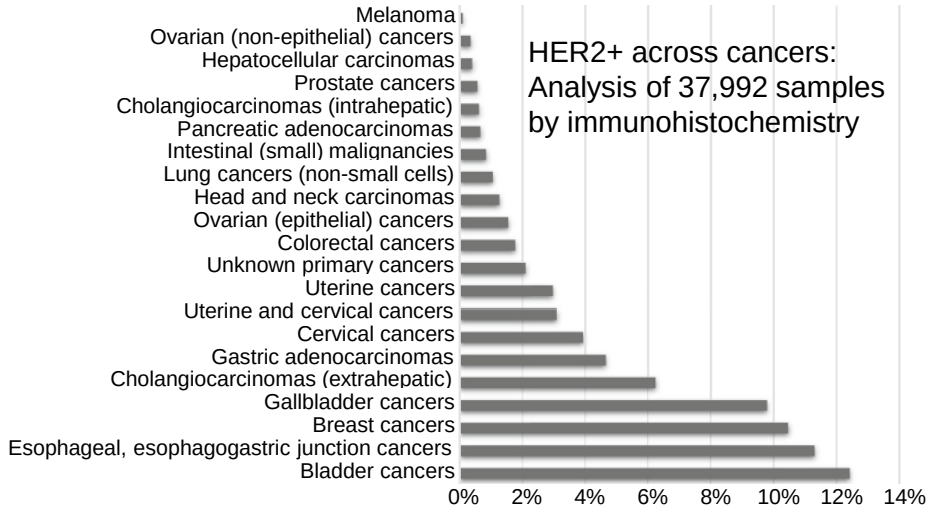
M. Brahmi, *et al 2015*.

Qu’est ce qu’un «pilote» fort?

	Médiane SSP
GIST KIT exon 11 *(70%)*	40 mois
Thymome KIT exon 11 *(?%)*	?6 mois
Melanome KIT exon 11 *(<10%)*	4 mois

Le role et l'impact des altérations moléculaires varie selon les sous-types de cancers

Une même alteration moléculaire



Un impact different en fonction des sous-types

- **Adénocarcinome du sein**
- **Cancer de la junction oesogastrique**
- **Cancers de l'ovaire**
- **Adénocarcinome colorectal**

Adapté de: Yan, M., et al. (2015) *Cancer Metastasis Rev.* 34:157-64.

Mutations de RAF

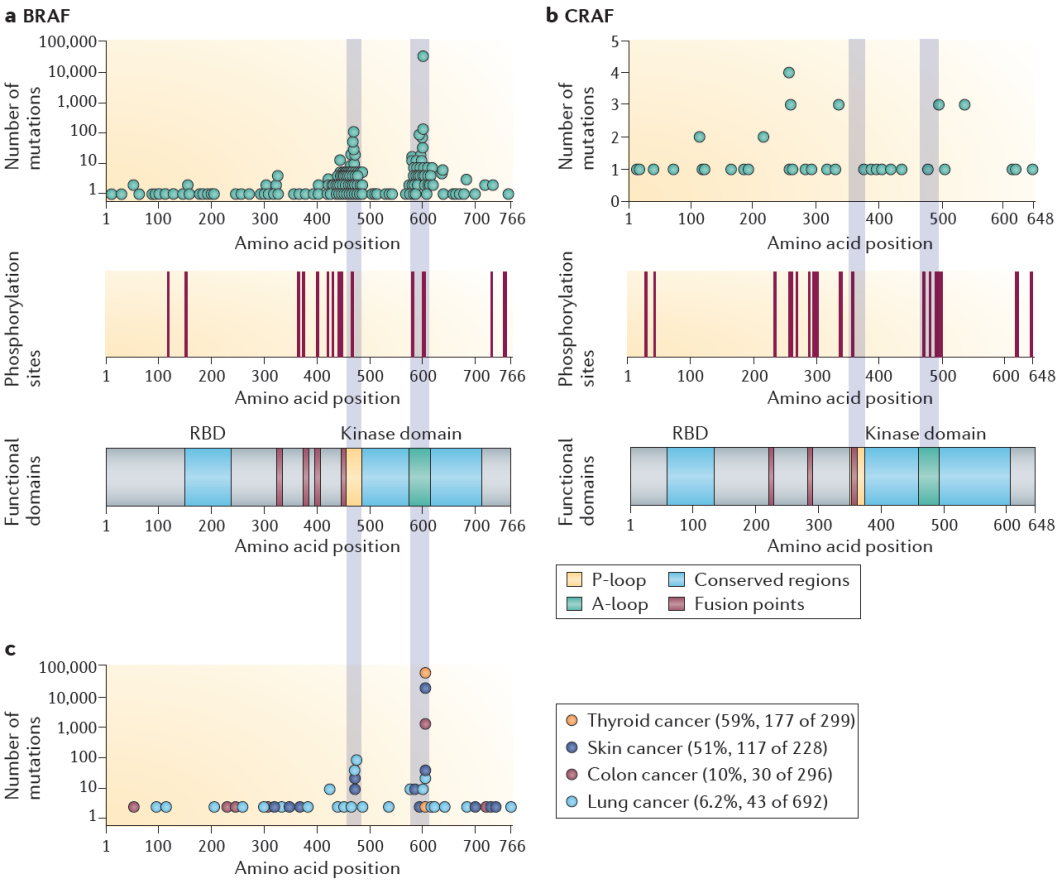
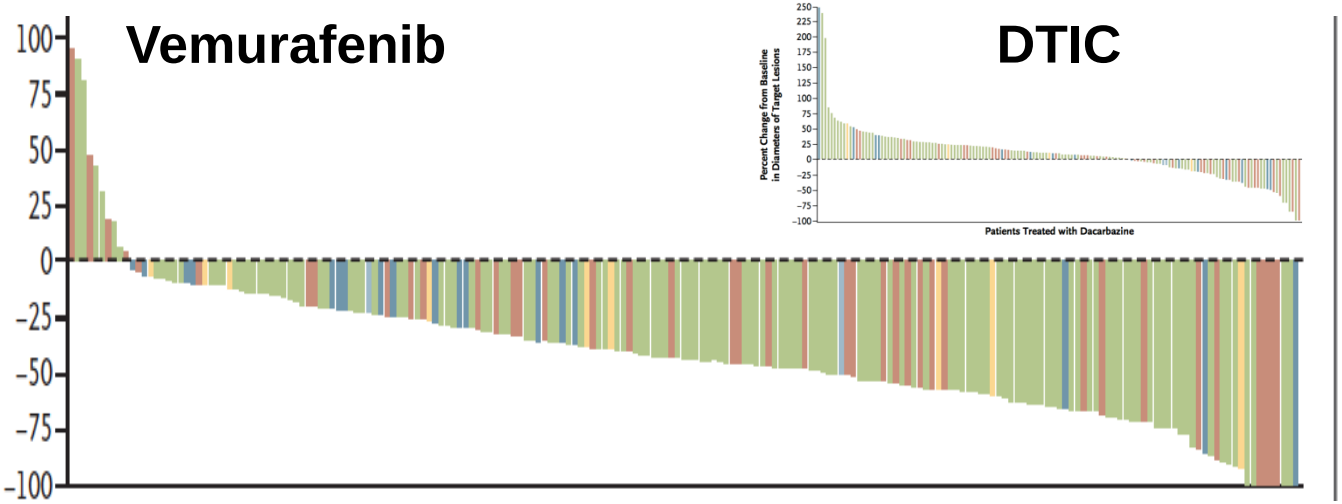


Figure 1 | **BRAF and CRAF mutations in cancer.** BRAF amino acid positions (1–766) (part **a**) and CRAF amino acid positions (1–648) (part **b**) are depicted on the x-axis. In both part **a** and part **b**, the top graphs show the number of mutations that are reported for each position[15]; the middle panels show the position of putative phosphorylation sites that are reported to have a functional consequence on kinase activity, stability or localization; and the bottom panels show BRAF and CRAF functional domains: the RAS-binding domain (RBD) and the kinase domain are highlighted in blue, the phosphate-binding loop (P-loop) is highlighted in yellow, the activation loop (A-loop) is highlighted in green and fusion points are highlighted in magenta. Part **c** shows the spectrum of BRAF mutations compiled from multiple studies[75] in thyroid[19], skin[141,142], colon[143,144] and lung[40,145,146] cancers (no equivalent graph is shown for CRAF mutations owing to their low frequency across all cancers). The sample size of the compiled sequencing data and the percentage of BRAF mutations for each indication are also shown.

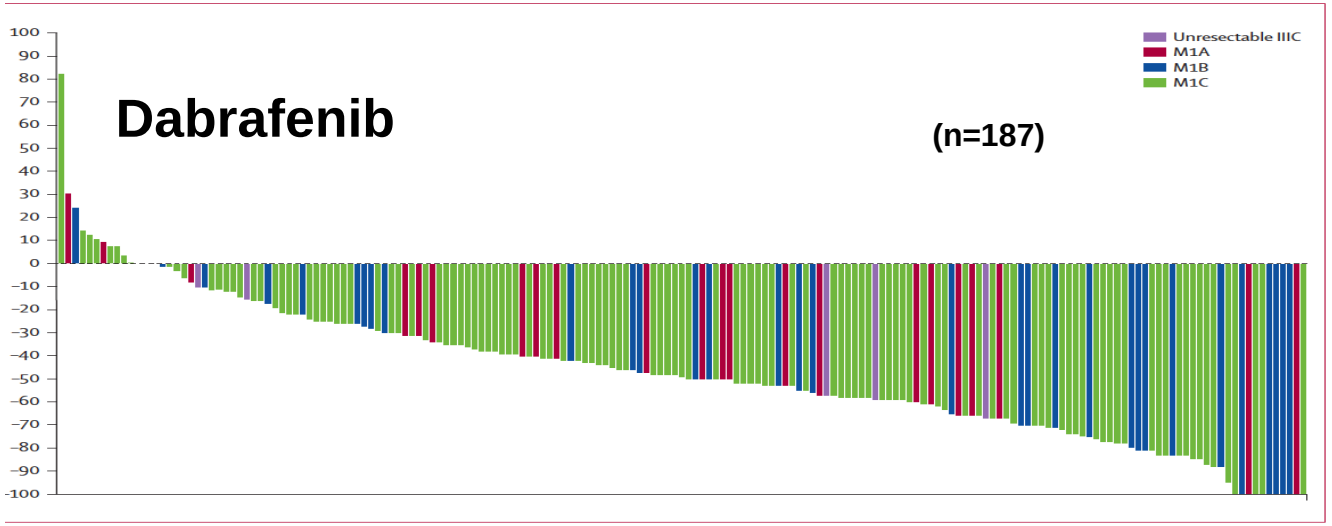
Holderfield et al Nat Rev Cancer 2014

Metastatic melanoma

Vemurafenib and Dabrafenib show similar efficacy



Chapman et al., NEJM 2011



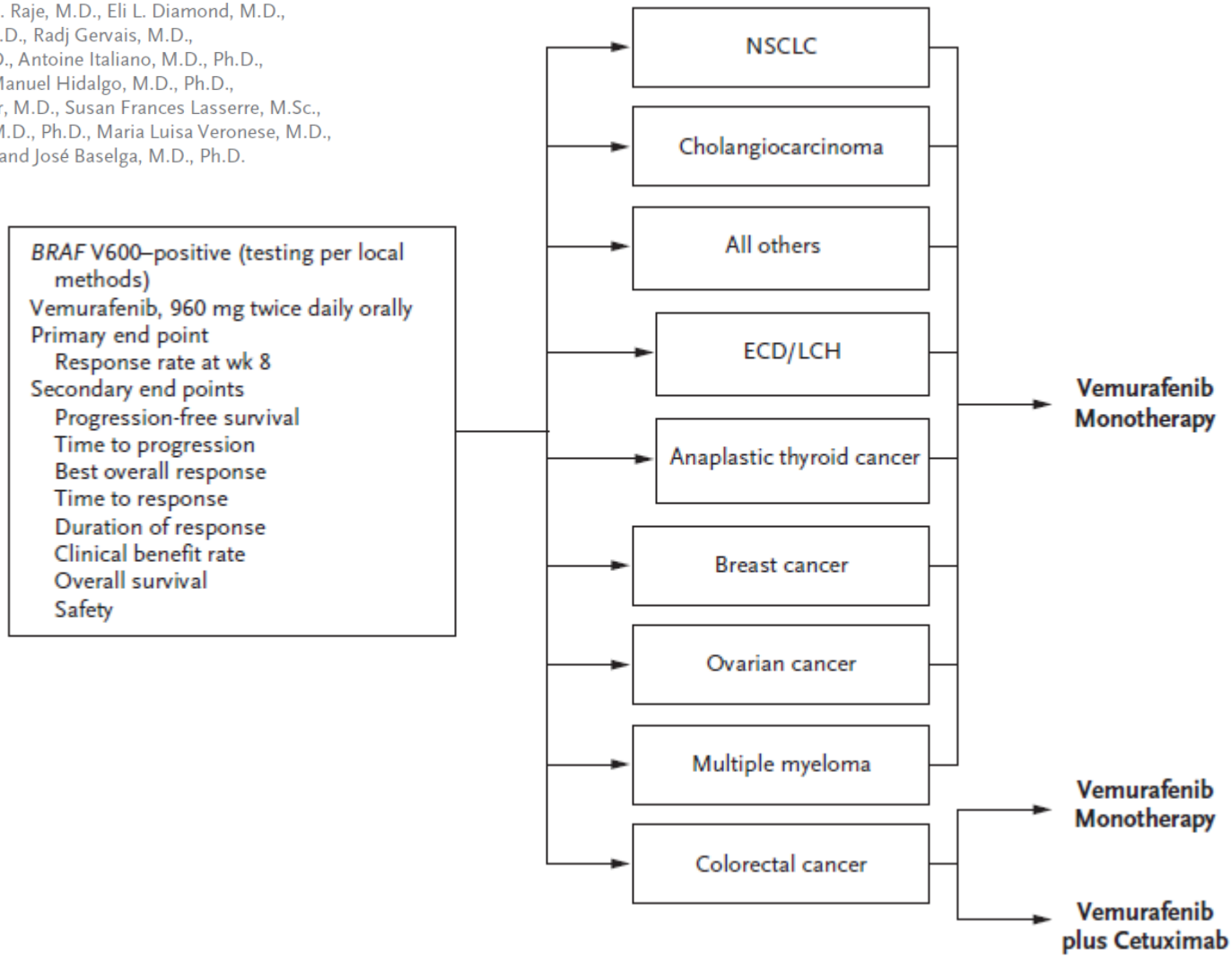
Hauschild et al., Lancet 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.



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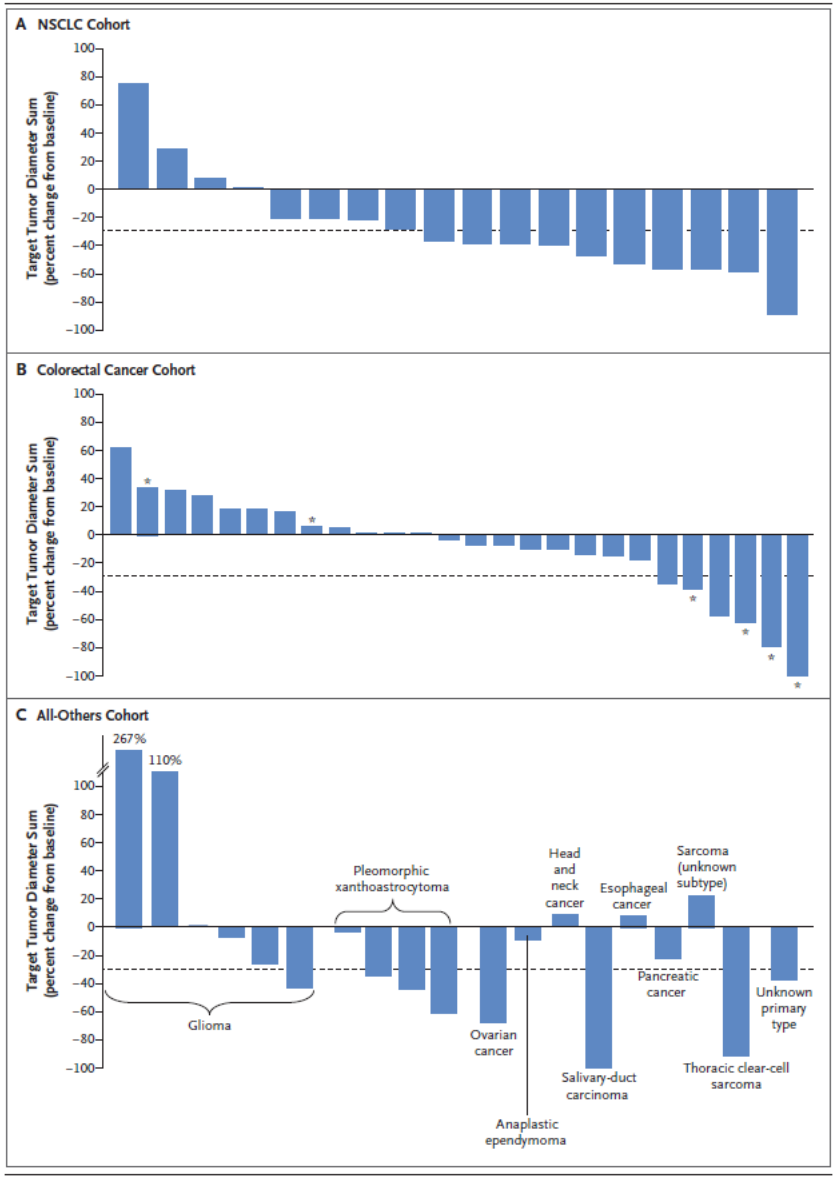
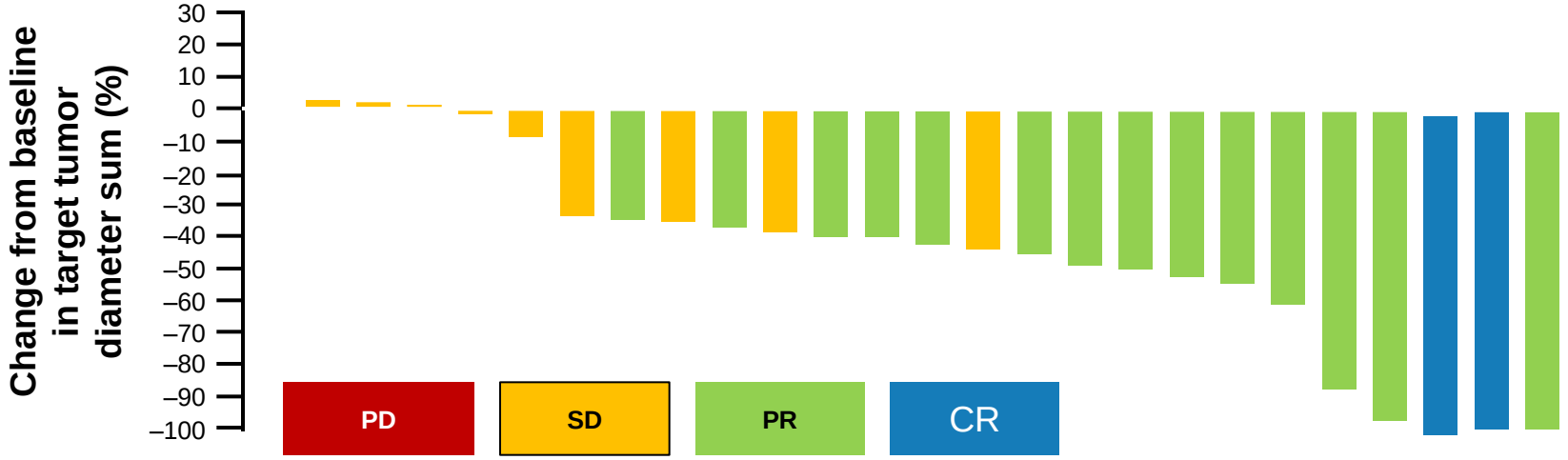


Preliminary efficacy evaluation: Best overall response (confirmed)



- 25 patients had measurable disease at baseline
  - Best overall response rate: 64% (95% CI 42.5–82.0%)
  - Clinical benefit rate: 100% (95% CI 86.3–100.0%)[a]
- 15 patients assessed by ^{18}F-FDG-PET
  - 12 had a complete metabolic response and 3 had a partial metabolic response[b]
  - Responses were confirmed in 10 patients

[a]Clinical benefit response: patients with best response of confirmed CR or sCR, confirmed VGPR or PR, or SD lasting ≥6 weeks; [b]This response was confirmed in at least 1 consecutive ^{18}F-FDG-PET assessment for 9 of the patients with a complete metabolic response and for 1 of the patients with a partial metabolic response; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Routine molecular screening of advanced refractory cancer patients: an analysis of the first 2676 patients of the ProfiLER Study.

O. Trédan[1], V. Corset[1], Q. Wang[1], R. Varnier[1,2], C. Pacaud[1,2], A. Torroja[1,2], N. Luppi[1,2], M. Ezzalfani[1], M. Myard[1], X. Jiang[1], V. Attignon[1], D. Pissaloux[1], C. Baudet[1], PA. Cassier[1], J. Fayette[1], M. Carbonnaux[1], A. Bonneville-Levard[1], A. Viari[1], D. Pérol[1] and J-Y. Blay[1,2].

[1] Centre Léon Bérard, Lyon, France; [2] University Claude Bernard Lyon1, Lyon, France

Clinicaltrial.gov Number: NCT01774409

Abstract # LBA100

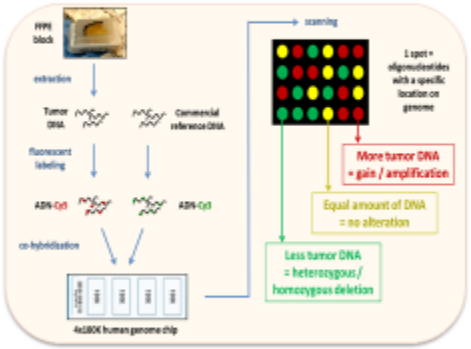
NGS (Next Generation Sequencing)

- A 69-gene panel
  - Hot-spot mutation regions for 8 genes (AKT1, BRAF, EGFR, GNAQ, HRAS, KRAS, NRAS, PIK3CA)
  - Entire coding sequences for the remaining 61 genes
- Coverage> 96%
average sequencing depth: 200X
- Variant calling:
GATK-based bioinformatics pipeline
NextGENe software
- Biological interpretation of variants
  - Hot-spot mutations in oncogenes
  - Actionable mutations if:
    - Records in databases (e.g. COSMIC)
    - Localization in functional domains
    - *In silico* prediction (SIFT, Phlyphen-2)

ABL1	CSF1	FGFR4	KIT	PDGFB	ROR1	SRC
AKT1	CSF1R	FLT1	KRAS	PDGFRA	ROR2	STK11
AKT2	DDB2	FLT3	MERTK	PDGFRB	ROS1	TEK
ALK	DDR1	FLT4	MET	PIK3CA	RYK	TIE1
APC	DDR2	GNAQ	MPL	PIK3R1	SDHAF2	TP53
AXL	EGFR	HRAS	MST1R	PTCH1	SDHB	TSC1
BRAF	ERBB2	IGF1R	MTOR	PTEN	SDHC	TSC2
BRCA1	FGFR1	JAK2	MUSK	RAF1	SDHD	TYRO3
BRCA2	FGFR2	JAK3	NRAS	RB1	SMARCB1	VHL
CDKN2A	FGFR3	KDR	PDGFA	RET	SMO	

aCGH (Comparative Genomic Hybridization)

- Analysis of somatic copy-number variation (CNV) on Agilent platform
- Detection of CNV only if:
  - No detection of balanced alterations (inversions, balanced translocations,…)
  - No detection of copy neutral loss of heterozygosity (CN-LOH)
- Fail to detect haploid or polyploid genomes



CONSORT: ProfilER Study

Enrolled
N= 2,676

Ongoing, N= 316

Tumor genomic profiles
N= 1,944

At least one actionable alterations
N= 1,004 (52%)

At least one MTA recommended
N= 676 (35%)

Patients treated with recommended MTA
N= 143 (7%)

Premature withdrawals N= 416 (16%)

- Tumor sample not exploitable, n= 339
- Less than 10% tumor cells, n= 19
- DNA extraction issues, n= 19
- aCGH or NGS failures, n= 13
- Other reasons, n= 31

No recommendation N= 328 (33%)

- MTA not available, n= 135
- MTA previously administered, n= 30
- Early death, n= 65
- Others, n= 98

Presented by: O. TREDAN

Abstract # LBA100

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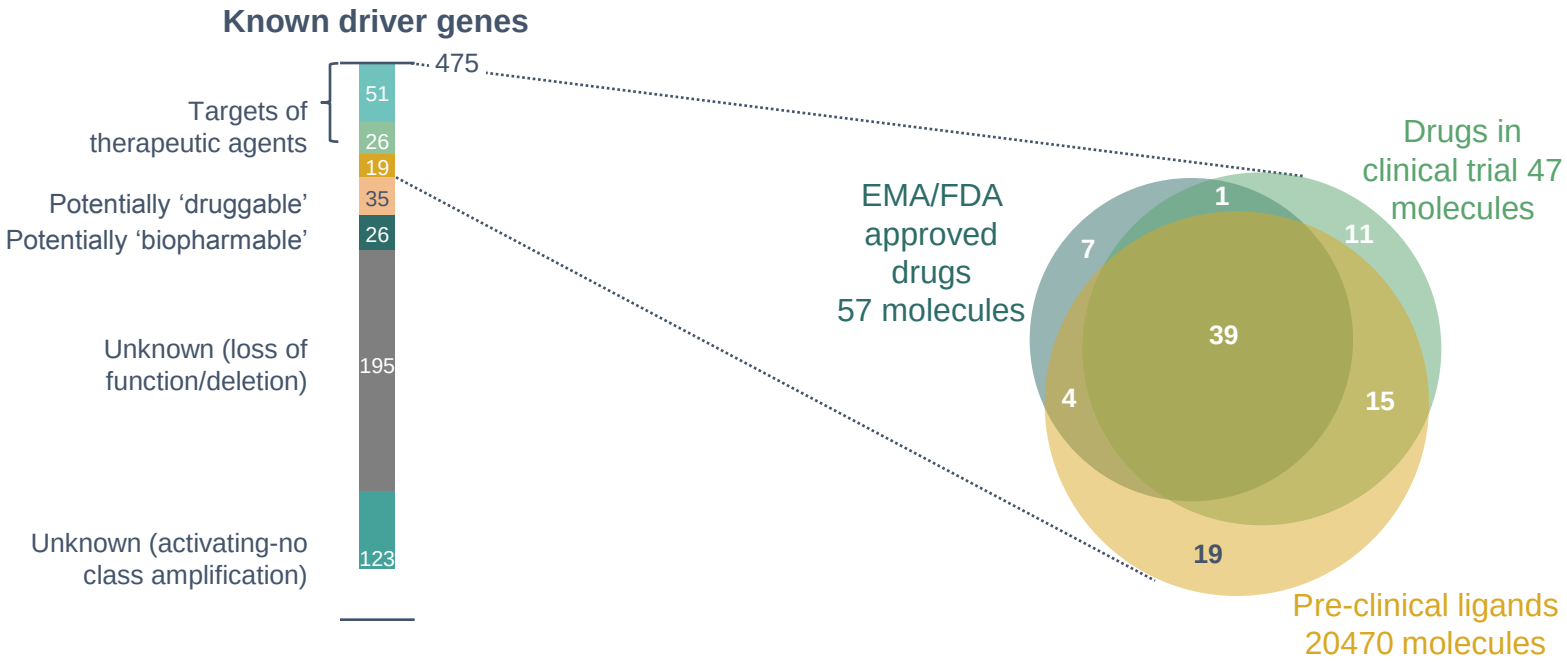
Accès aux traitements: seuls ~20% des “altérations pilotes fortes” disposent d’un medicament ciblé

Adapted from Rubio-Perez, C., et al. (2015) *Cancer Cell.* 27(3):382–96.



Immunothérapie

Réponses sous immuno thérapie vs thérapie ciblée dans le mélanome

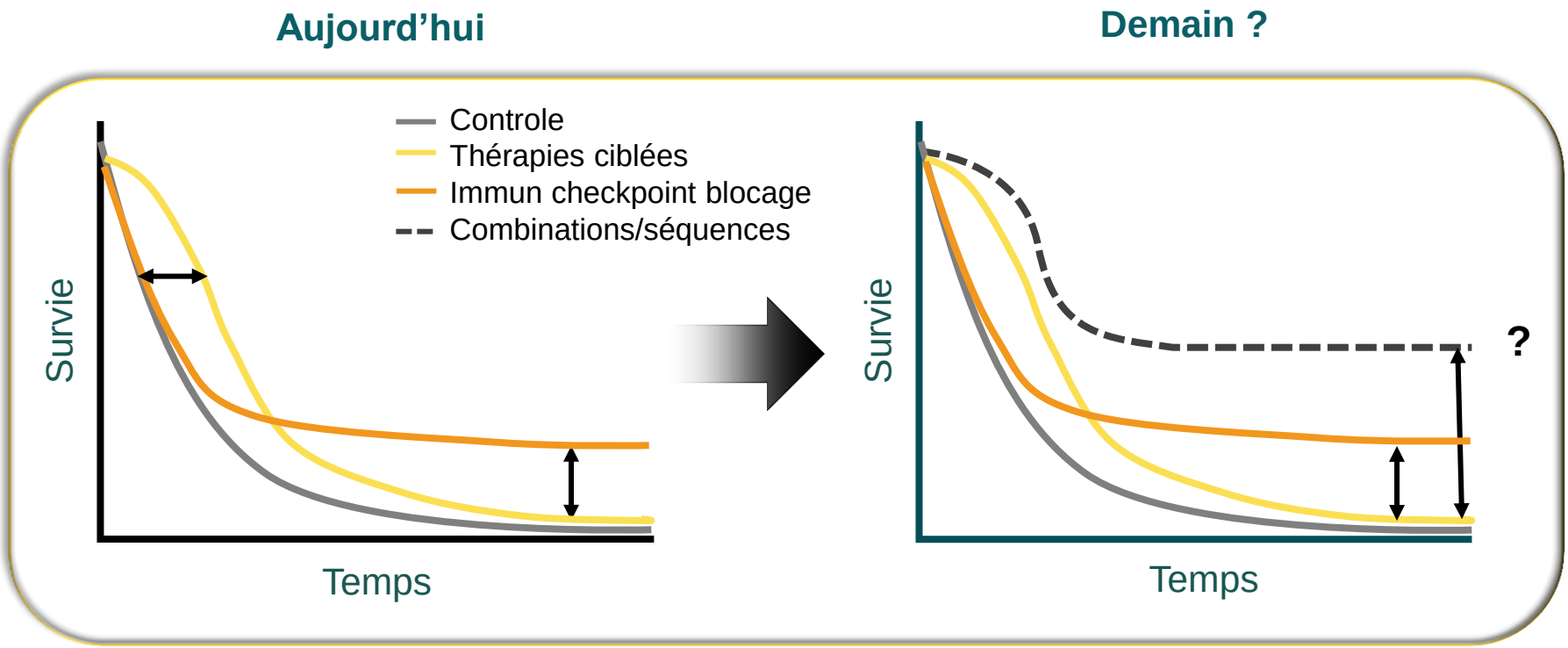
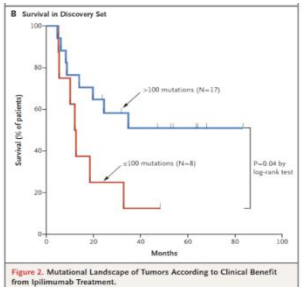


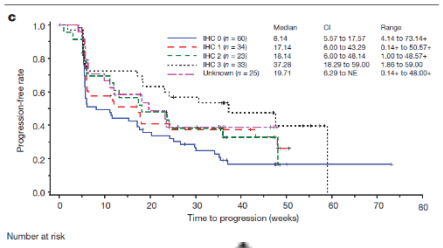
Illustration du concept scientifique et ses fondements d'après les données disponibles.
Ces éléments ne sont pas prédictifs des résultats à venir des essais cliniques.

1. Adapté de Ribas A, presenté à WCM 2013. 2. Ribas A, et al. Clin Cancer Res 2012;18:336–41. 3. Drake CG. Ann Oncol 2012;23(suppl 8):viii41–viii46.

Biomarqueurs

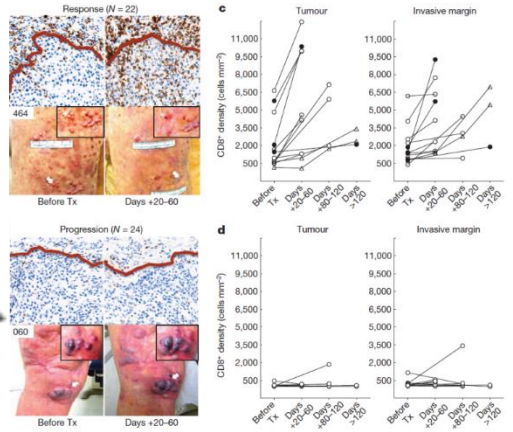
Charge en mutation



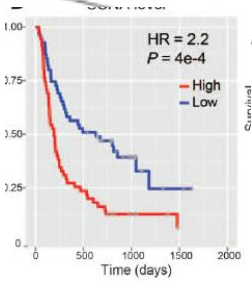


PDL1 (expression)

Infiltrats immuns



Aneuploidie

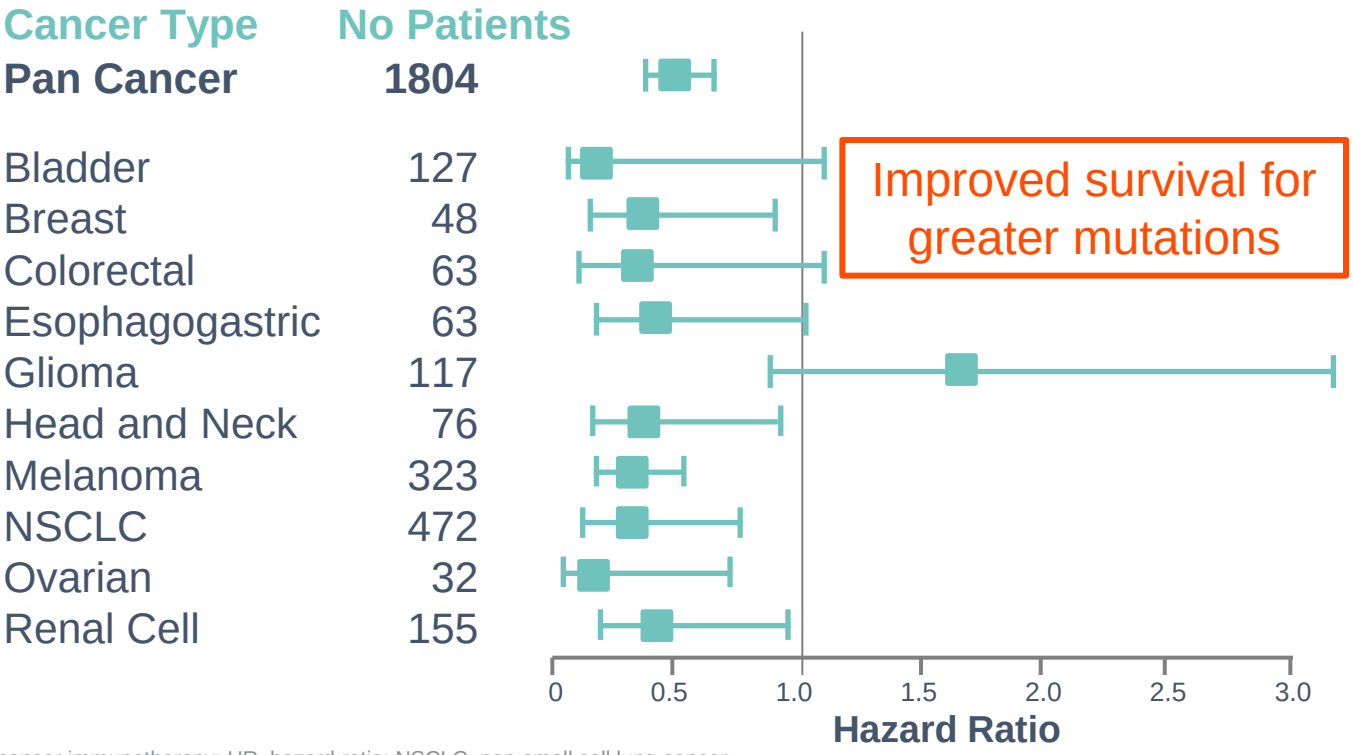


Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy

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

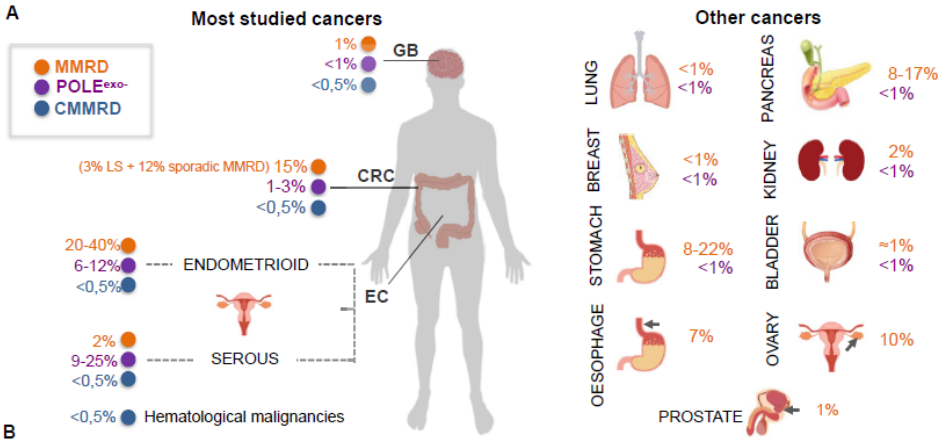
Tumor mutational burden predicts CIT response: is this the next tissue-agnostic biomarker?



CIT, cancer immunotherapy; HR, hazard ratio; NSCLC, non-small cell lung cancer.
IMPACT Platform, MSKCC.
Chan, N. (2016) *ASCO Clinical Immuno-Oncology Symposium.*

Hypermutated tumours in the era of immunotherapy: The paradigm of personalised medicine

Laetitia Nebot-Bral [a,b,c,1], David Brandao [b,c,d,1], Loic Verlingue [b,e], Etienne Rouleau [b,f], Olivier Caron [b,g], Emmanuelle Despras [a,b,c], Yolla El-Dakdouki [b,e], Stéphane Champiat [b,e,h], Said Aoufouchi [a,b,c], Alexandra Leary [b,c,g,h], Aurélien Marabelle [b,c,e,i], David Malka [b,c,g], Nathalie Chaput [a,b,j,k], Patricia L. Kannouche [a,b,c,*]



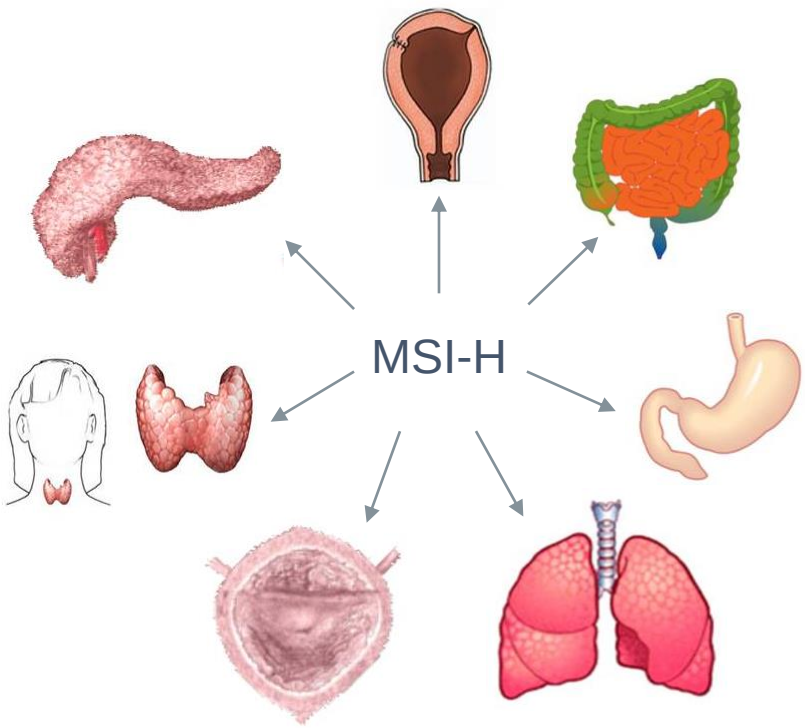
B

Cancer type	Risk		Mean age		
	general population	LS	general population	LS	CMMRD
Colon	4,3%	52-82%	65-74 years	44-61 years	8-35 years
Endometrium	2,8%	25-60%	55-64 years	48-62 years	23-31 years
Stomach	0,8%	6-13%	65-74 years	56 years	Not reported
Ovary	1,3%	4-12%	55-64 years	42,5 years	
Small bowel	0,3%	3-6%	65-74 years	49 years	
Brain/central nervous system	0,6%	1-3%	55-64 years	≈ 50 years	2-35 years

Fig. 1. Frequencies and risks of various cancers harbouring MMR deficiency (MMRD), *POLE* mutation or CMMRD syndrome. (A) Frequencies of cancers harbouring MMRD, *POLE* mutation or CMMRD syndrome. (B) Comparison of cancer risks between general population, Lynch Syndrome and CMMRD syndrome. CMMRD, constitutive mismatch repair deficiency; CRC, colorectal cancer; EC, endometrial cancer; MMRD, mismatch repair deficiency; *POLE*, mutation in the exonuclease domain of the catalytic subunit of the polymerase epsilon; GB, glioblastoma [39–43,51,55,58,65,69,77,78,117,118–136].

Pembrolizumab: approbation PDA pour les tumeurs MSI

- **Un changement de paradigme**



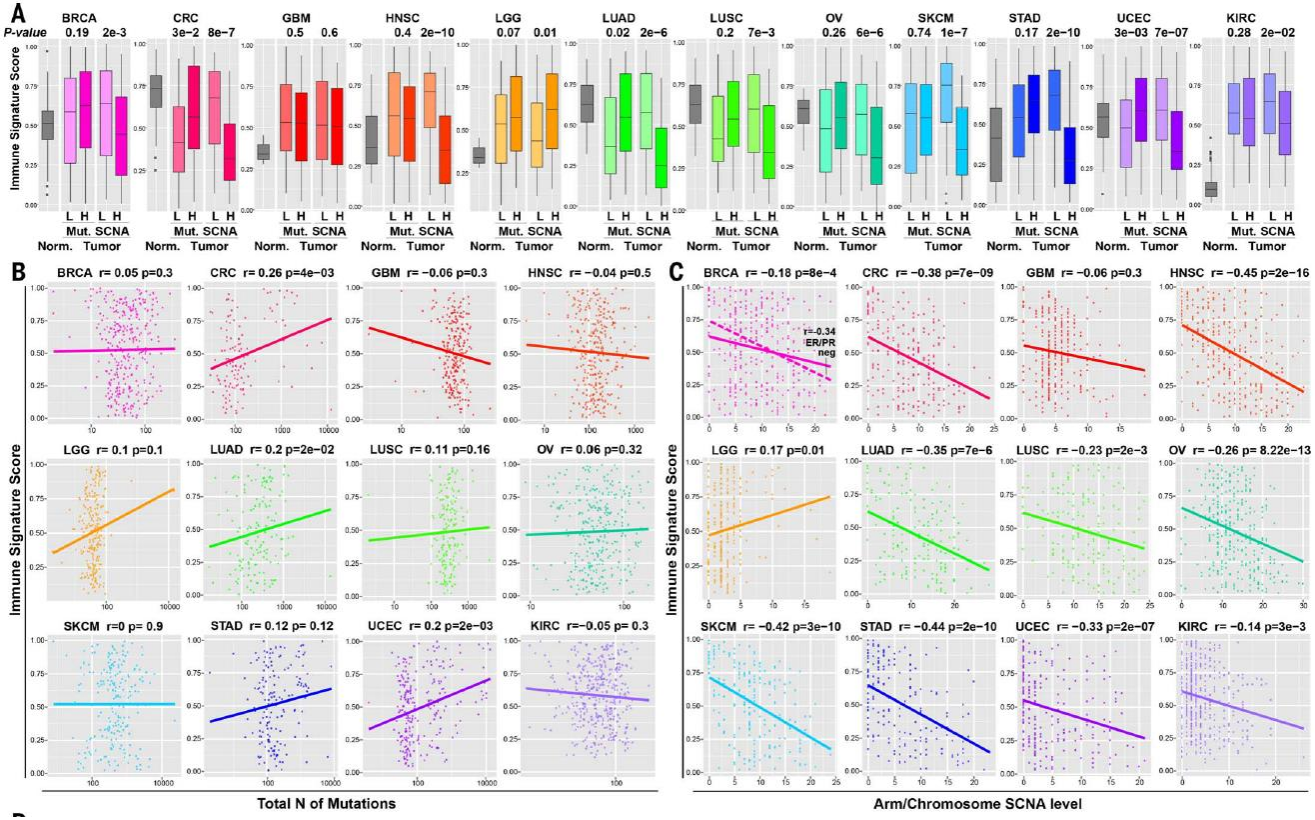
FDA news release retrieved from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm [Accessed September 2017].

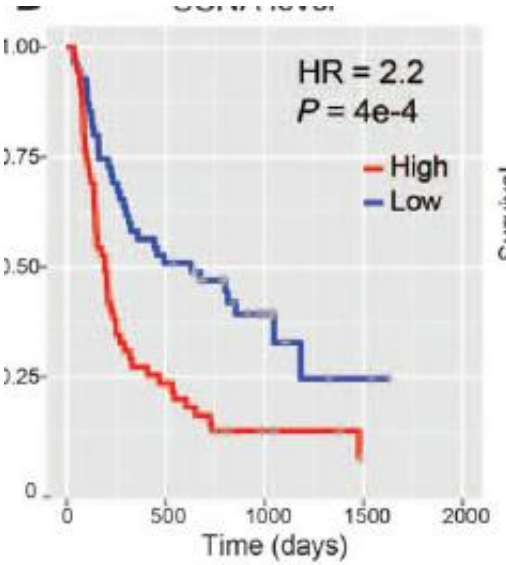
Image adapted from presentation by Steven Lemery at 2017 ASCO Annual Meeting.

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]*

Read the full article at http://dx.doi.org/10.1126/science.aaf8399





CANCER

Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance

Whijae Roh,[1,2]* Pei-Ling Chen,[1,3]* Alexandre Reuben,[4]* Christine N. Spencer,[1] Peter A. Prieto,[4] John P. Miller,[5] Vancheswaran Gopalakrishnan,[4] Feng Wang,[1] Zachary A. Cooper,[1,4] Sangeetha M. Reddy,[6] Curtis Gumbs,[1] Latasha Little,[1] Qing Chang,[1] Wei-Shen Chen,[1,3] Khalida Wani,[7] Mariana Petaccia De Macedo,[7,8] Eveline Chen,[7] Jacob L. Austin-Breneman,[4] Hong Jiang,[4] Jason Roszik,[1,9] Michael T. Tetzlaff,[3] Michael A. Davies,[9] Jeffrey E. Gershenwald,[4] Hussein Tawbi,[9] Alexander J. Lazar,[4,7] Patrick Hwu,[9] Wen-Jen Hwu,[9] Adi Diab,[9] Isabella C. Glitza,[9] Sapna P. Patel,[9] Scott E. Woodman,[9] Rodabe N. Amaria,[9] Victor G. Prieto,[3] Jianhua Hu,[10] Padmanee Sharma,[11,12] James P. Allison,[11] Lynda Chin,[13] Jianhua Zhang,[14] Jennifer A. Wargo,[1,4†‡] P. Andrew Futreal[1†‡]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

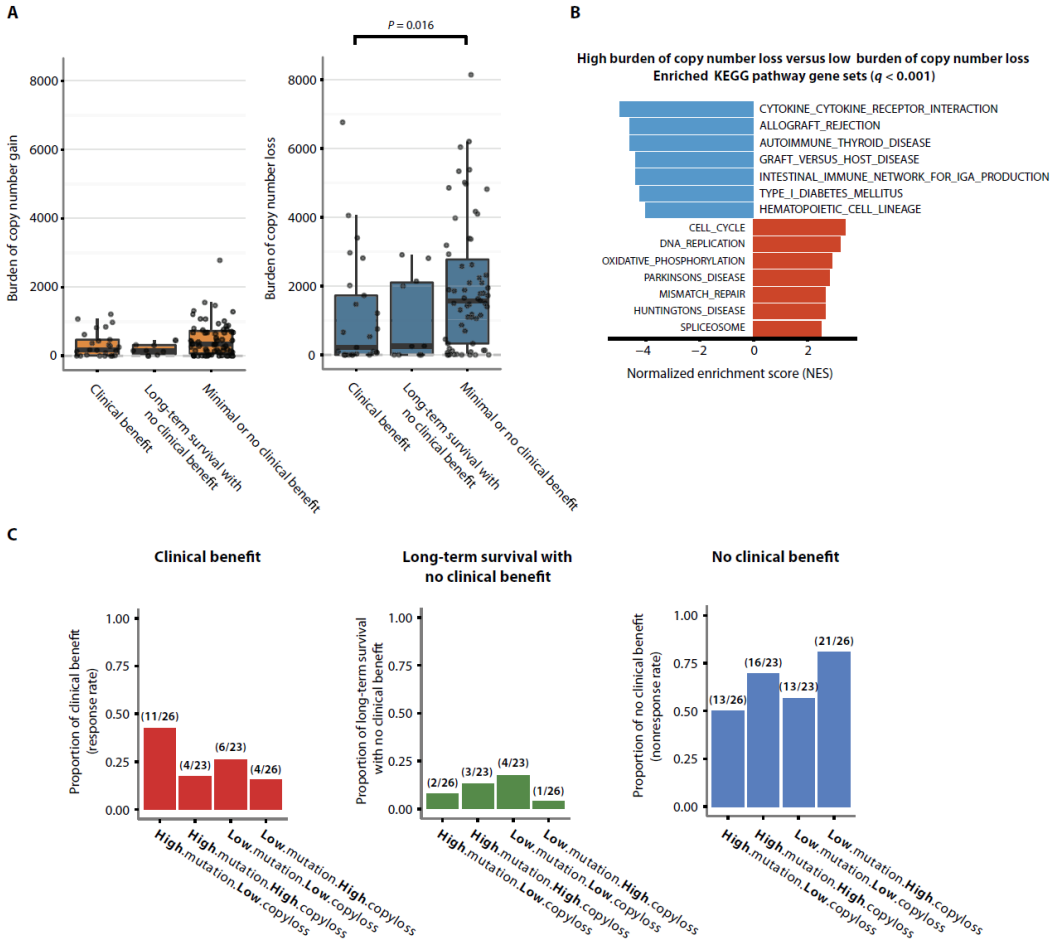
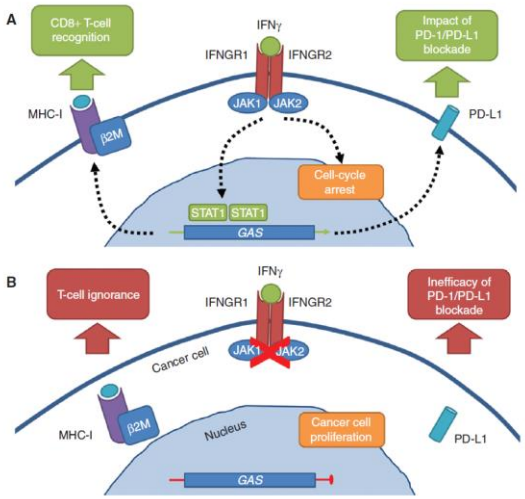


Fig. 3. Copy number loss as a potential resistance mechanism in an independent cohort. (**A**) Boxplots summarize burden of copy number gain or loss in three

Primary Resistance to PD-1 Blockade Mediated by *JAK1/2* Mutations

Daniel Sanghoon Shin[1], Jesse M. Zaretsky[1], Helena Escuin-Ordinas[1], Angel Garcia-Diaz[1], Siwen Hu-Lieskovan[1], Anusha Kalbasi[1], Catherine S. Grasso[1], Willy Hugo[1], Salemiz Sandoval[1], Davis Y. Torrejon[1], Nicolaos Palaskas[1], Gabriel Abril-Rodriguez[1], Giulia Parisi[1], Ariel Azhdam[1], Bartosz Chmielowski[1,2], Grace Cherry[1], Elizabeth Seja[1], Beata Berent-Maoz[1], I. Peter Shintaku[1], Dung T. Le[3], Drew M. Pardoll[3], Luis A. Diaz, Jr[3], Paul C. Tumeh[1], Thomas G. Graeber[1,2], Roger S. Lo[1,2], Begoña Comin-Anduix[1,2], and Antoni Ribas[1,2]



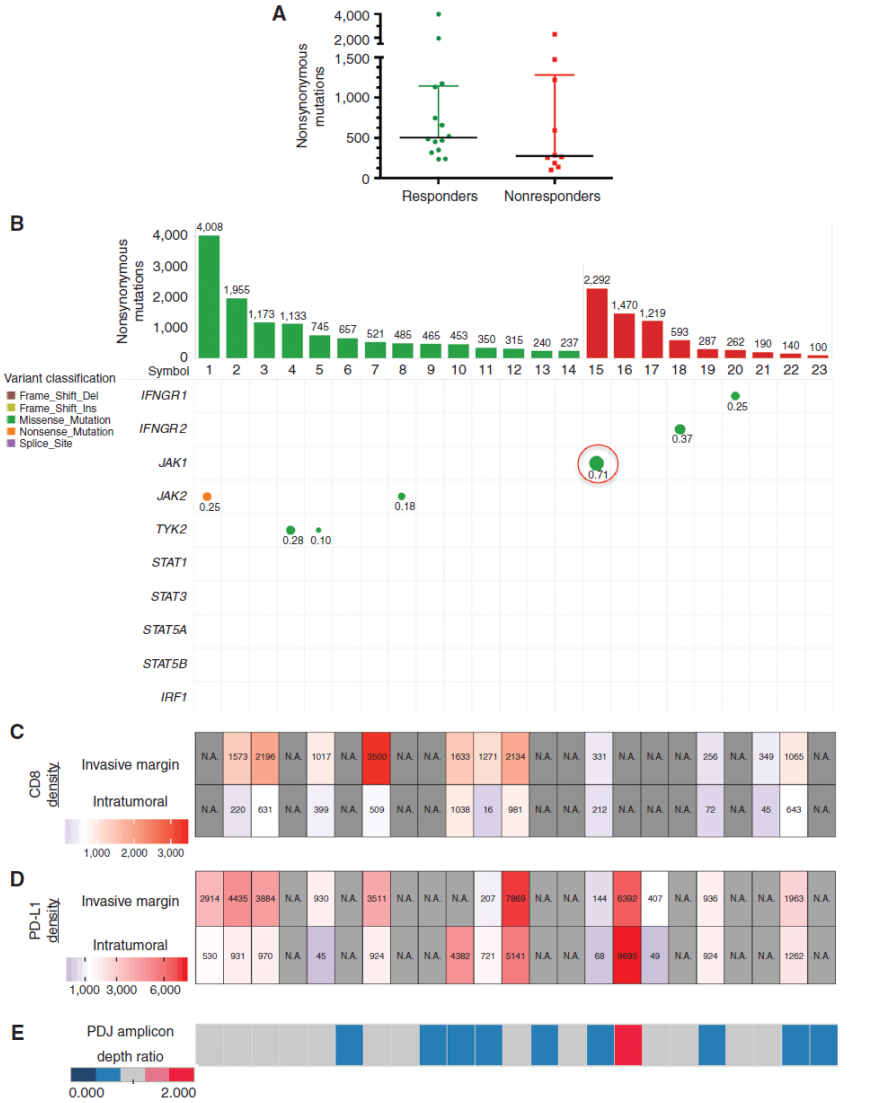


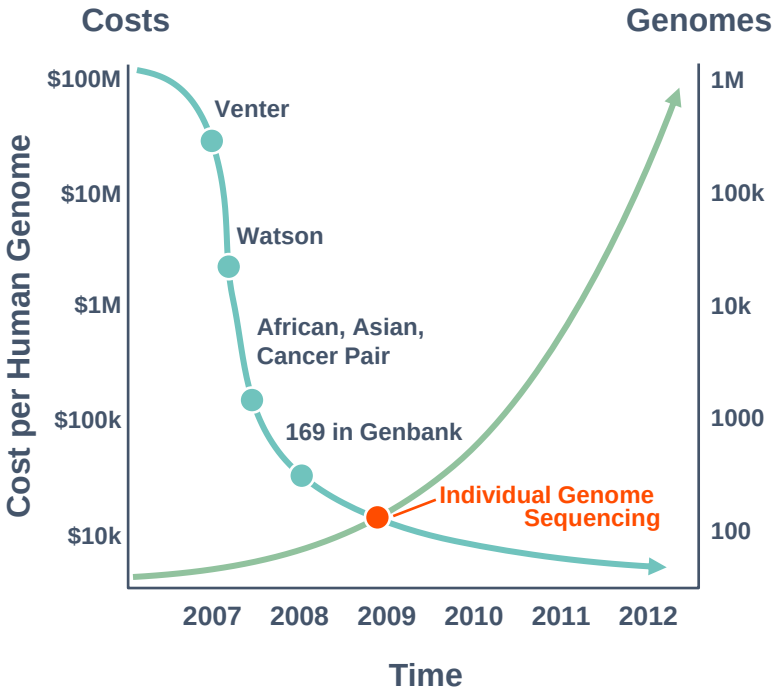
Figure 1. Mutational load and mutations in the interferon signaling pathway among patients with advanced melanoma with or without response

Published OnlineFirst November 30, 2016; DOI: 10.1158/2159-8290.CD-16-1223

Panels

Evolution du séquençage en clinique

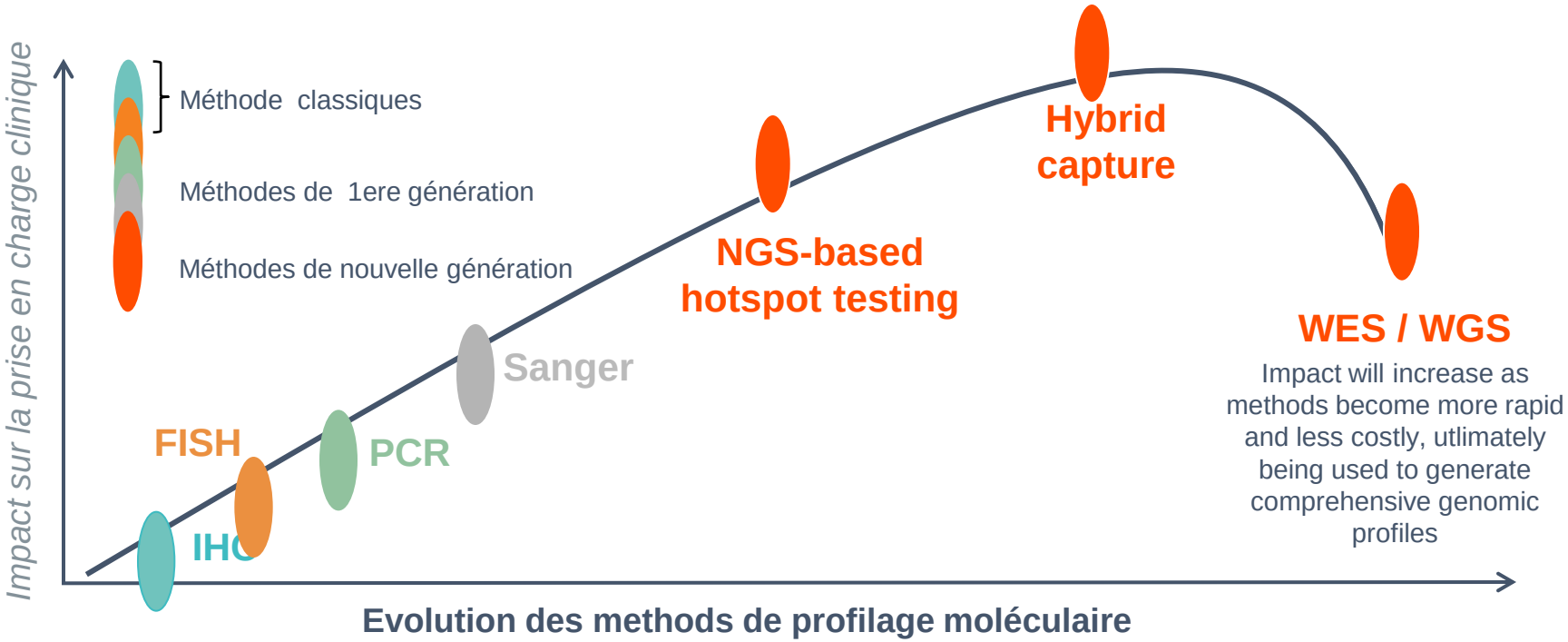
Genome sequenced (publication year)	HGP (2003)[1]	Venter (2007) [1]	Watson (2008) [1]	Current (2015) [2]
Time taken (start to finish)	13 years	4 years	4.5 months	~1 days
Number of scientists listed as authors	> 2,800	31	27	
Cost of sequencing (start to finish)	$ 2.7 billion	$ 100 million	< $ 1.5 million	~ $ 1000
Coverage	8 - 10 x	7.5 x	7.4 x	30-50 x
Number of institutes involved	16	5	2	
Number of countries involved	6	3	1	



1. Wadman, M. (2008) *Nature*. 452(7189):788.
2. Retrieved from: https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome/ [Accessed September 2017].

Evolution des outils de diagnostic moléculaire

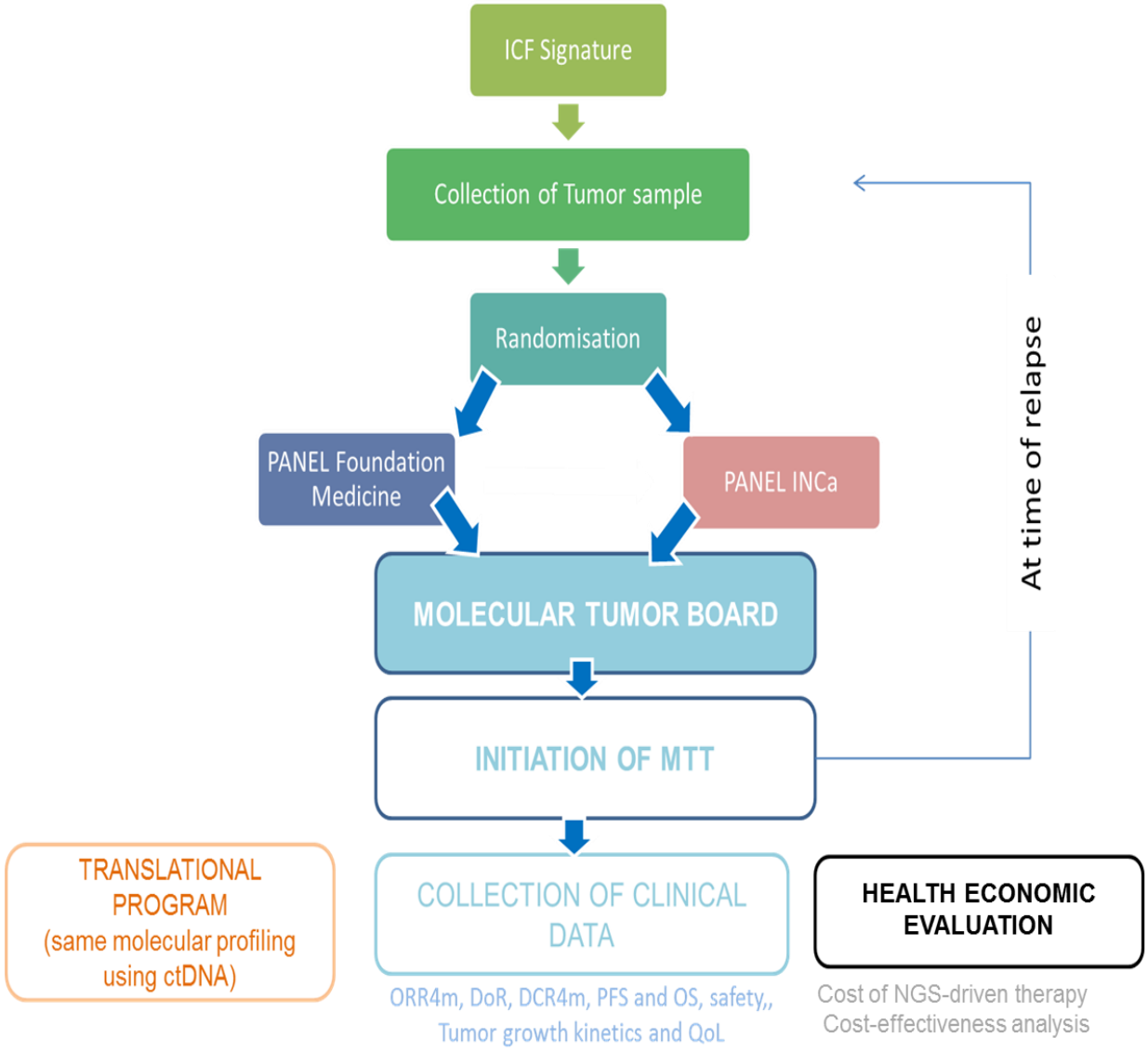
Impact sur la prise en charge clinique



FISH: fluorescence in situ hybridisation; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction; WES: whole exome sequencing; WGS: whole genome sequencing.

Netto, G.J., et al. (2003) *Proc Bayl Univ Med Cent.* 16:379-83.
de Matos, L.L., et al. (2010) *Biomark Insights.* 5:9-20.
Dong, L., et al. (2015) *Curr Genomics.* 16:253-63.

PROFILER2 STUDY

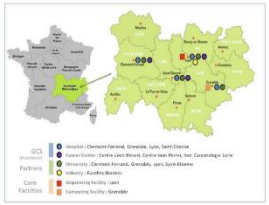


Appel d'offre France Médecine Génomique 2025

Paris le 17 juillet 2017, Matignon

AURAGEN

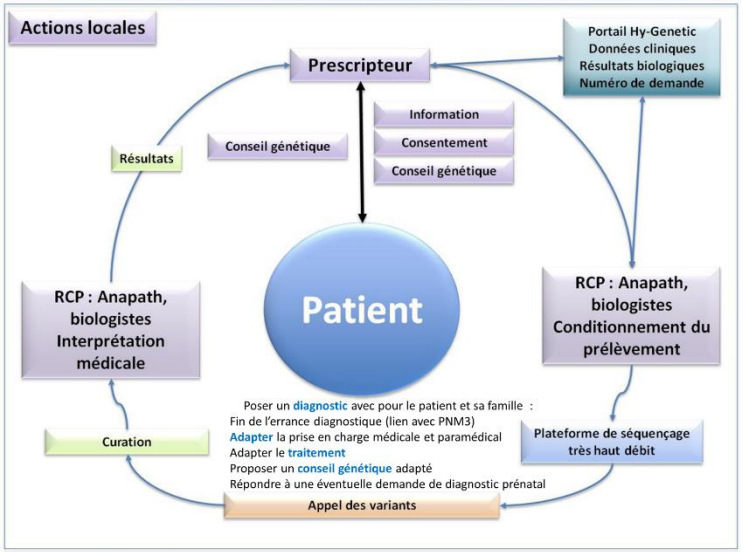
AUvergne **R**hône-**A**lpes **GEN**omique



Cancer

Maladies rares

Notre projet

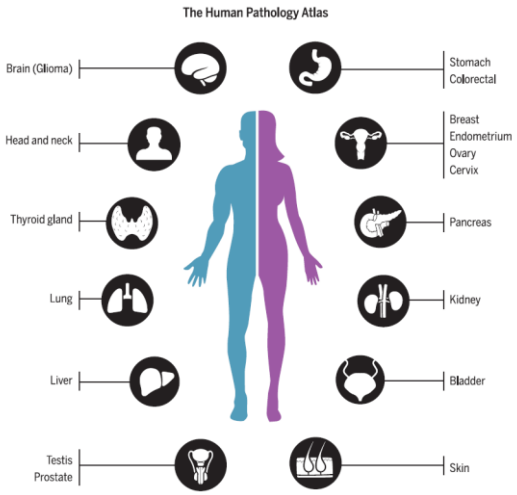


Information / discussion avec le **patient**
Production industrielle : qualité des données, productivité
Compétences en bio-informatique
Répondre à une demande **nationale**
Réunion de **C**oncertation **P**luridisciplinaire
Enseignement : augmentation des compétences
Evaluation médico-économique

Médecine Personnalisée

A pathology atlas of the human cancer transcriptome

Mathias Uhlen,* Cheng Zhang, Sunjae Lee, Evelina Sjöstedt, Linn Fagerberg, Gholamreza Bidkhori, Rui Benfeitas, Muhammad Arif, Zhengtao Liu, Fredrik Edfors, Kemal Sanli, Kalle von Feilitzen, Per Oksvold, Emma Lundberg, Sophia Hober, Peter Nilsson, Johanna Mattsson, Jochen M. Schwenk, Hans Brunnström, Bengt Glimelius, Tobias Sjöblom, Per-Henrik Edqvist, Dijana Djureinovic, Patrick Micke, Cecilia Lindskog, Adil Mardinoglu,† Fredrik Ponten†



Schematic overview of the Human Pathology Atlas. A systems-level approach enables analysis of the protein-coding genes of 17 different cancer types from ~8000 patients. Results are available in an interactive open-access database.

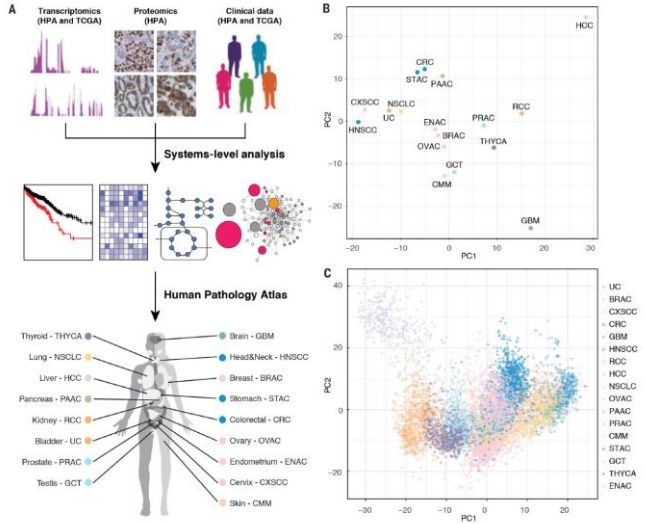
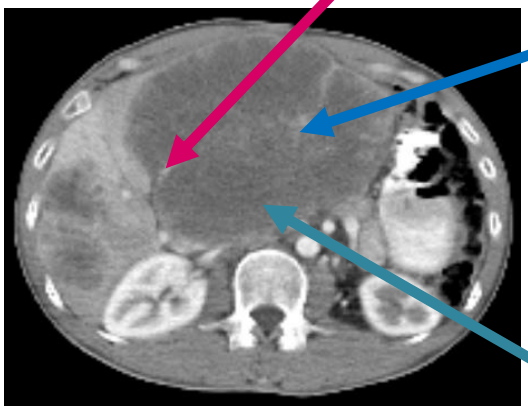


Fig. 1. Analysis of the global expression patterns of protein-coding genes in human cancers. (**A**) Schematic drawing of the Human Pathology Atlas effort described herein. (**B**) Principal components analysis (PCA) showing the similarities in expression of 19,571 protein-coding genes among 17 cancer types. See fig. S4 for additional PCA analysis with more stratified patient cohorts. (**C**) PCA plot showing the individual differences in the genome-wide global expression profiles among the 17 cancer types in 9666 individual patients.

Résistance, primaire et secondaire

Intrinsèque,
Résistance clonale,
…

Secondary GIST mutations in patients progressing on imatinib or sunitinib



DHPLC, denaturing high-pressure liquid chromatography.
Liegl B *et al*. J Pathol 2008;216(1):64-74; Wilhelm S. 2006; Patent #WO2007059154 A2, C'KIT Cytoplasmic Domain figure.

BRAF Inhibitor Resistance Mechanisms in Metastatic Melanoma: Spectrum and Clinical Impact

Helen Rizos[1], Alexander M. Menzies[4], Gulietta M. Pupo[1], Matteo S. Carlino[1,2], Carina Fung[1], Jessica Hyman[4,9], Lauren E. Haydu[4,7], Branka Mijatov[1], Therese M. Becker[1], Suzanah C. Boyd[1], Julie Howle[3,4,7], Robyn Saw[4,7,8], John F. Thompson[4,7,8], Richard F. Kefford[1,2,4,6], Richard A. Scolyer[4,5,9], and Georgina V. Long[4,6]

Clin Cancer Res; 20(7) April 1, 2014

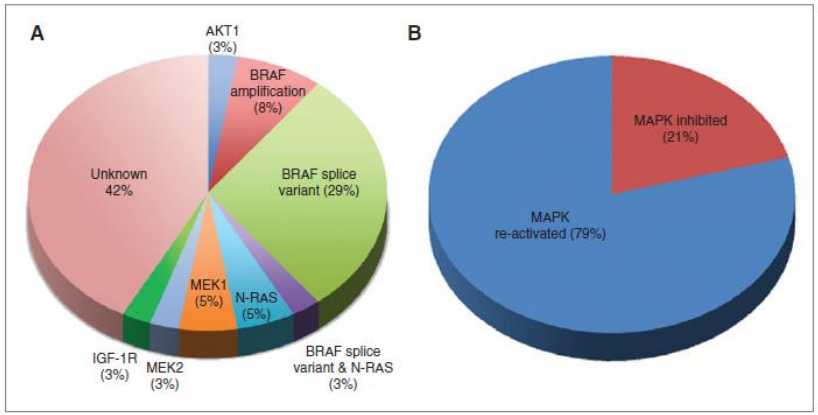


Figure 1. BRAF inhibitor resistance mechanisms. A, mechanisms of resistance in individual Prog tumors ($n = 38$). B, Prog tumor MAPK activation status relative to the pretreatment tumor, as determined by GSEA of gene expression data ($n = 29$).

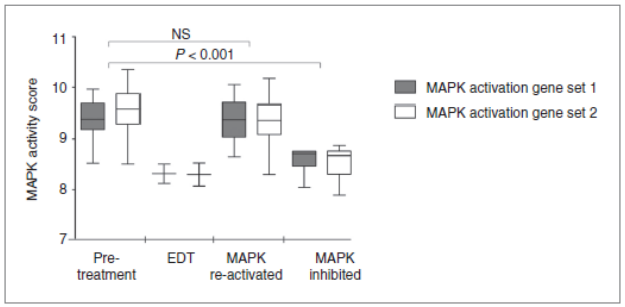


Figure 3. Loss of MAPK activation gene sets occurs in early during treatment (EDT) responding melanoma tumors and in a subset of BRAF inhibitor–resistant Prog metastases. Box plots showing significant differences in MAPK activity (mean $\log_2$-transformed expression of MAPK activation gene transcripts) between pretreatment ($n = 21$) and MAPK-inhibited Prog tumors ($n = 6$). NS, no significant differences in comparisons between pretreatment and MAPK-reactivated Prog ($n = 23$) tumors. Statistical comparisons between pretreatment and EDT MAPK activity scores were not performed because of small EDT sample size ($n = 2$). MAPK activation gene set 1 derived from (24) and gene set 2 from ref. (14).

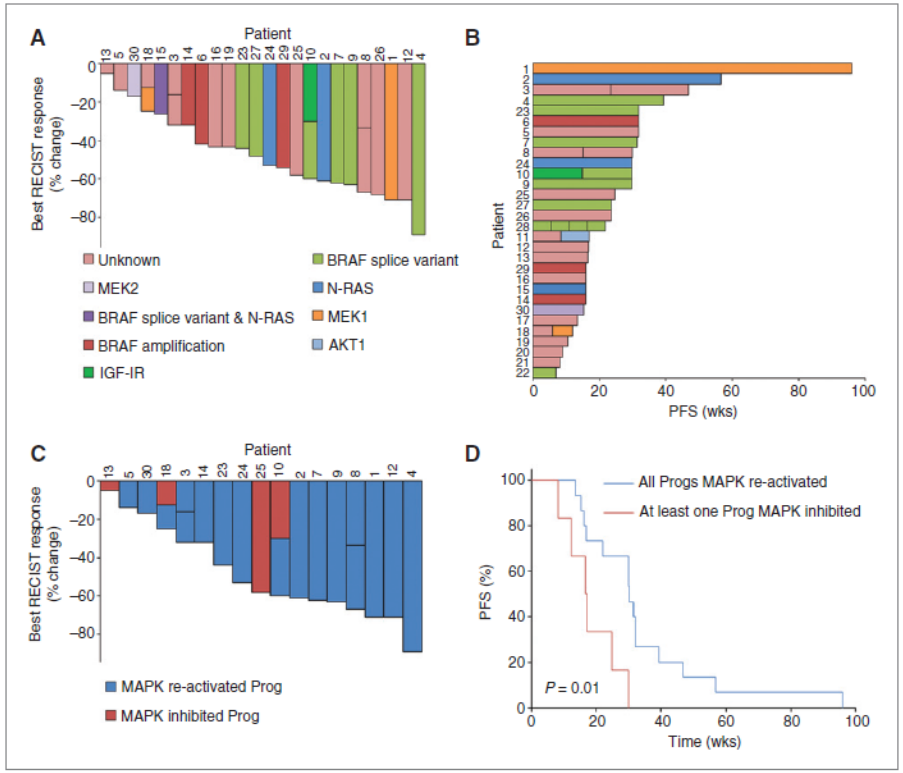


Figure 4. BRAF inhibitor resistance mechanisms and clinical correlates. A, best overall RECIST response by mechanism of resistance ($n = 24$). Six patients were excluded, as they did not have RECIST assessments. Patients with multiple Prog biopsies are shown by a divided bar, and the first biopsied Prog is closest to the x-axis. B, PFS by mechanism of resistance ($n = 30$). Patients with multiple biopsies are shown by a divided bar, and the first biopsied Prog is closest to the y-axis. C, best overall RECIST response by MAPK activity of Prog tumors ($n = 17$). Four patients were excluded, as they did not have RECIST assessments. Patients with multiple biopsies are shown by a divided bar, and the first biopsied Prog is closest to the x-axis. D, PFS by MAPK activity level of Prog tumors ($n = 21$).

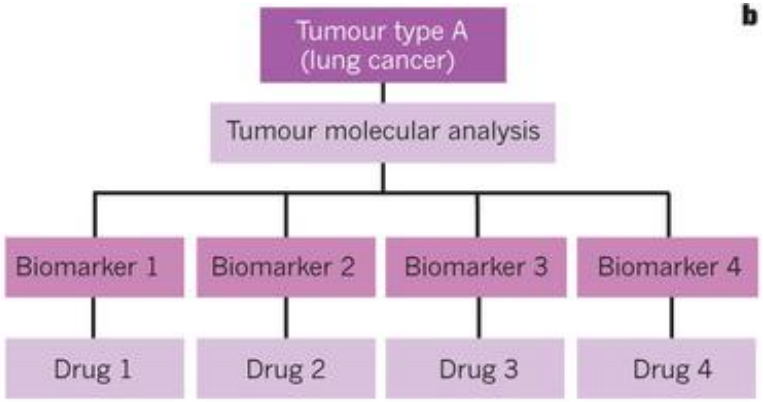
Enjeux

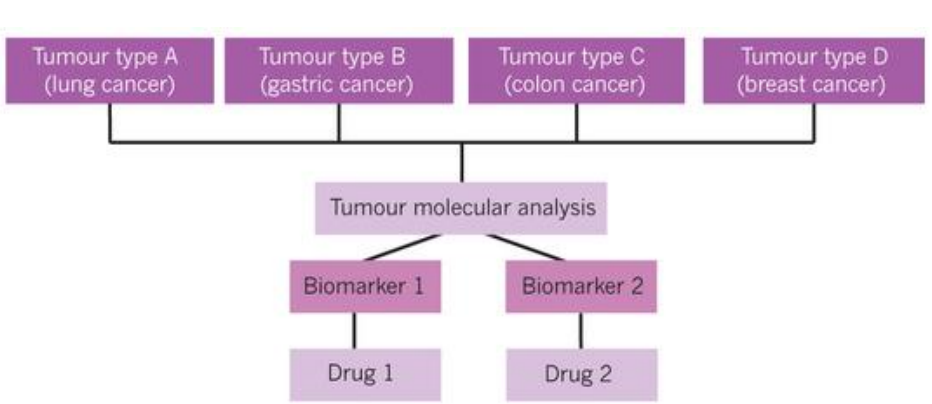
Accès à l'analyse

Réalisation des essais

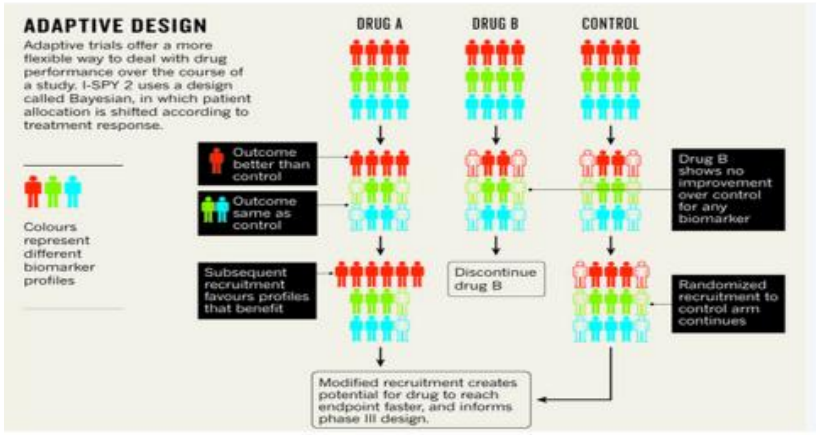
Accès au médicament

Essais parapluie/panier





Essais adaptatifs/ Adaptive trial design



Eisenstein et al , Nature , 2014

N-of-1 trials

- Recruitment of patients exposed to different experimental agents or placebo in different sequencing, with washout periods in between

- Each involved patient serves as his or her own comparator, through the comparison of the efficacy seen for the different experimental agents that the patient receives

Ce qui est simple est toujours faux.

Ce qui ne l'est pas est inutilisable.

(Paul Valéry)

Conclusion

- La médecine moléculaire du cancer en pleine croissance.
- Technologies plus rapidement évolutives que les recommandations de pratique.
- Résistance, primaire secondaire, complexité, mécanistique biologique
- Bioinformatique