Apports de la **biologie moléculaire** aux **traitements personnalisés.** Application dans le traitement à la carte **des sarcomes**

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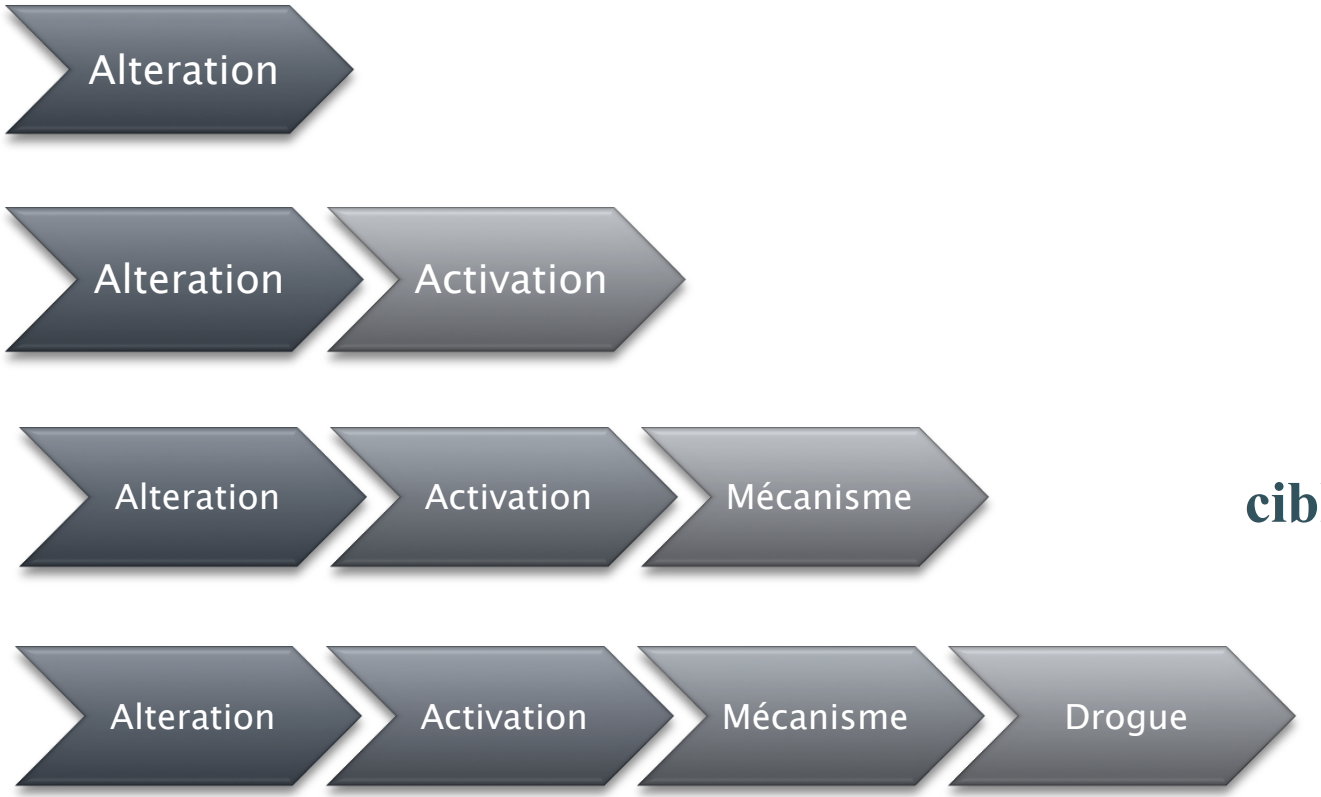
Institut Bergonié - Bordeaux

SFCO
Vendredi 26 octobre 2012

Cibles et traitements



cible possible

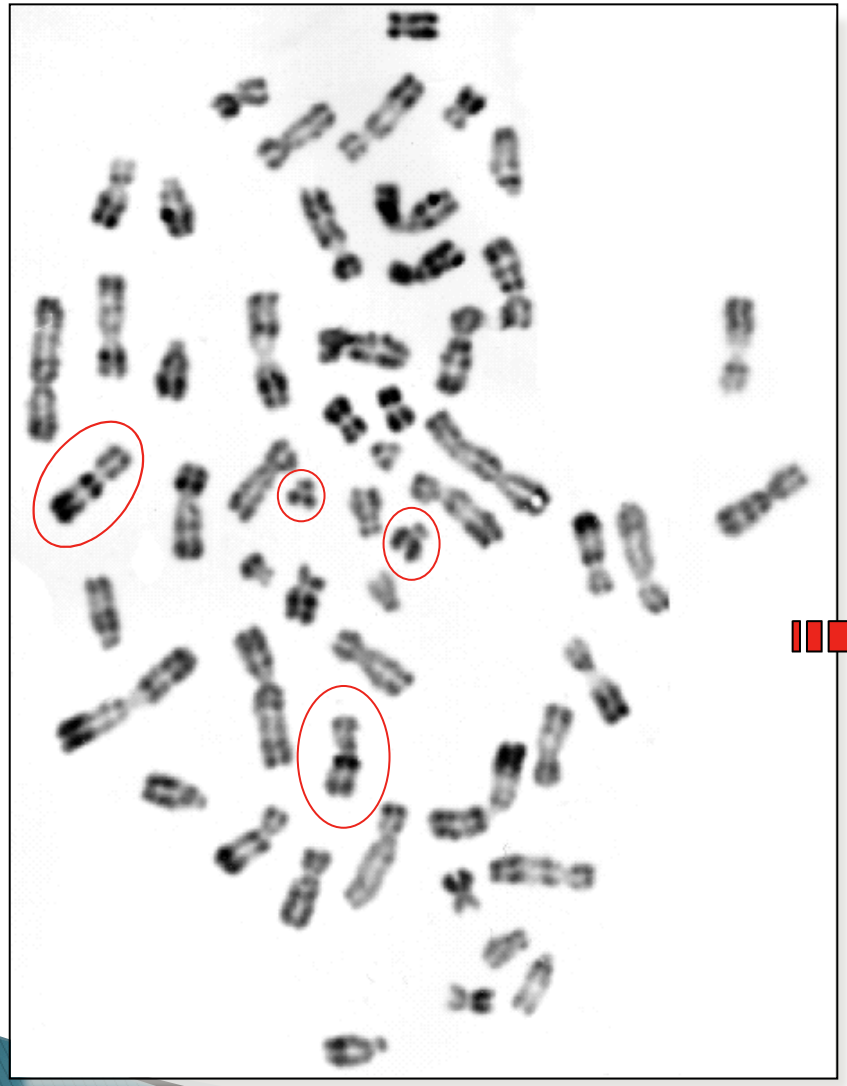
cible prometteuse

cible d'intérêt majeure

essai clinique

J. Fletcher. Sarcoma « state of the Science » Meeting, 17 june 2002, Bethesda, MD, USA

1983: La première translocation



C R Seances Acad Sci III. 1983;296(23):1105-7.

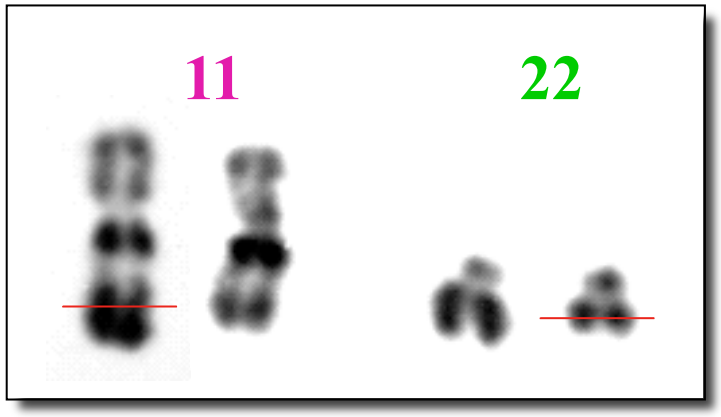
[Translocation of chromosome 22 in Ewing's sarcoma].

[Article in French]

Aurias A, Rimbaut C, Buffe D, Dubousset J, Mazabraud A.

Abstract

The chromosomal analysis of four fresh Ewing tumours shows a translocation of the band q12 of the chromosome 22 in all the clones observed. This translocation seems to preferentially involve the band q24 of the chromosome 11. These results are in favour of a consistent translocation in Ewing's sarcoma, and are to be compared with the results obtained in other malignancies. A relation between this translocation and the location of the human oncogene c-sis on the chromosome 22 should be considered.



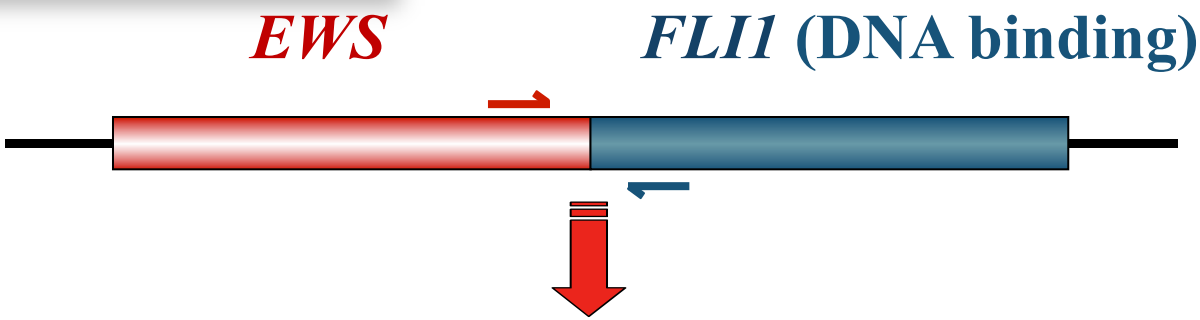
Aurias A, Rimbaut C, Buffe D, Dubousset J, Mazabraud A. Chromosomal translocations in Ewing's sarcoma. N Engl J Med 1983;309:496-7.
Turc-Carel C, Philip I, Berger M-P, Philip T, Lenoir GM. Chromosomal translocations in Ewing's sarcoma. N Engl J Med 1983;309:497-8.

1992: La biologie moléculaire….

Gene fusion with an *ETS* DNA-binding domain caused by chromosome translocation in human tumours

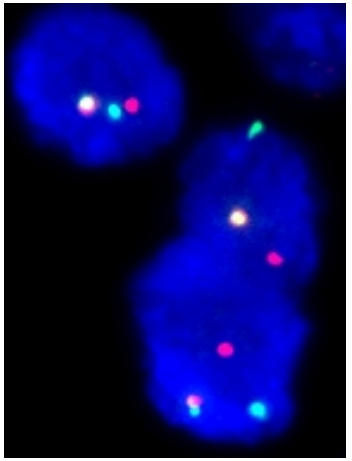
NATURE · VOL 359 · 10 SEPTEMBER 1992

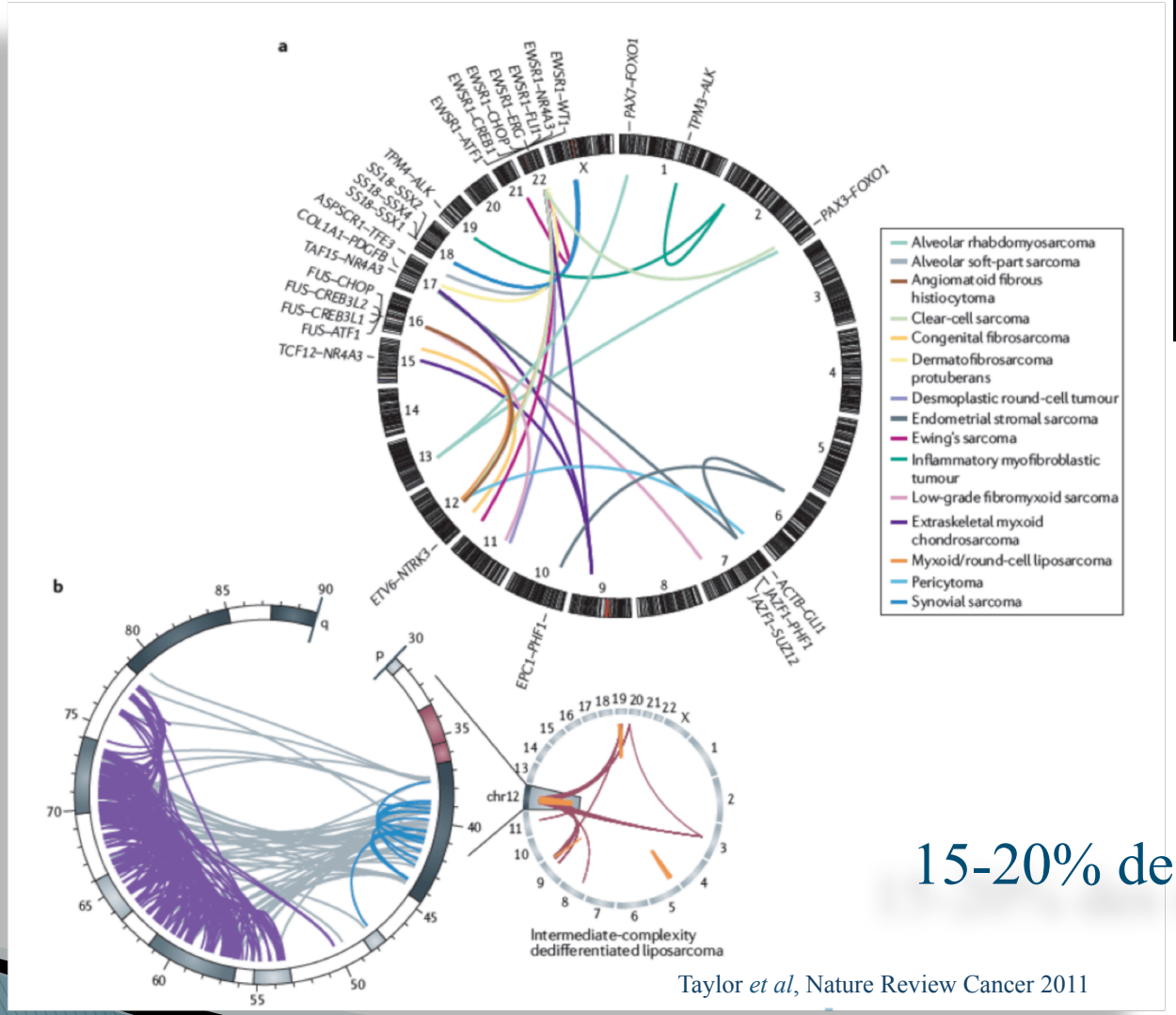
Olivier Delattre, Jessica Zucman, Béatrice Plougastel, Chantal Desmaze, Thomas Melot, Martine Peter, Heinrich Kovar*, Isabelle Joubert, Pieter de Jong†, Guy Rouleau‡, Alain Aurias & Gilles Thomas§



Nouvelle protéine chimérique
(facteur de transcription)

Les sarcomes dits « à translocation »

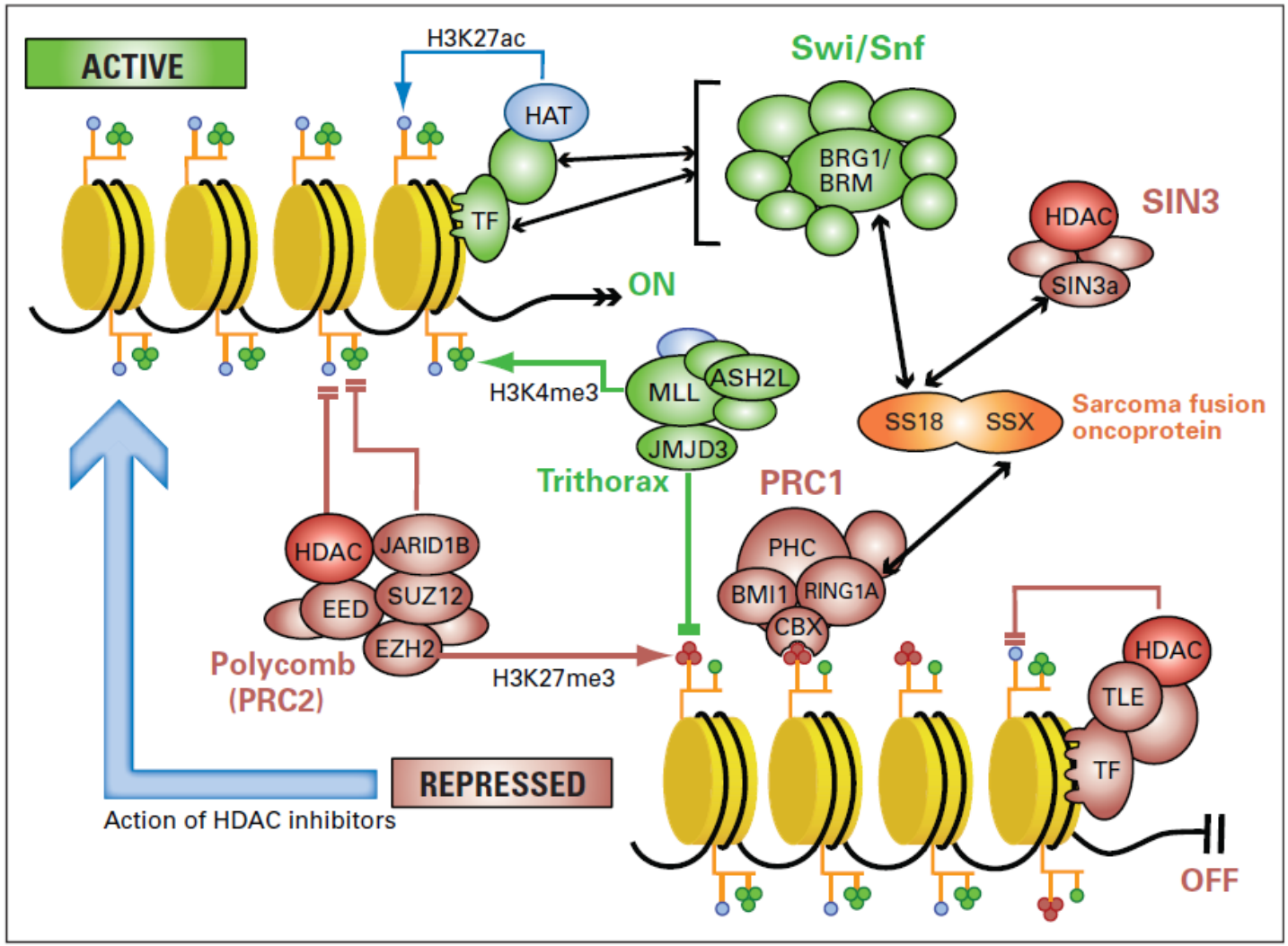




15-20% des sarcomes

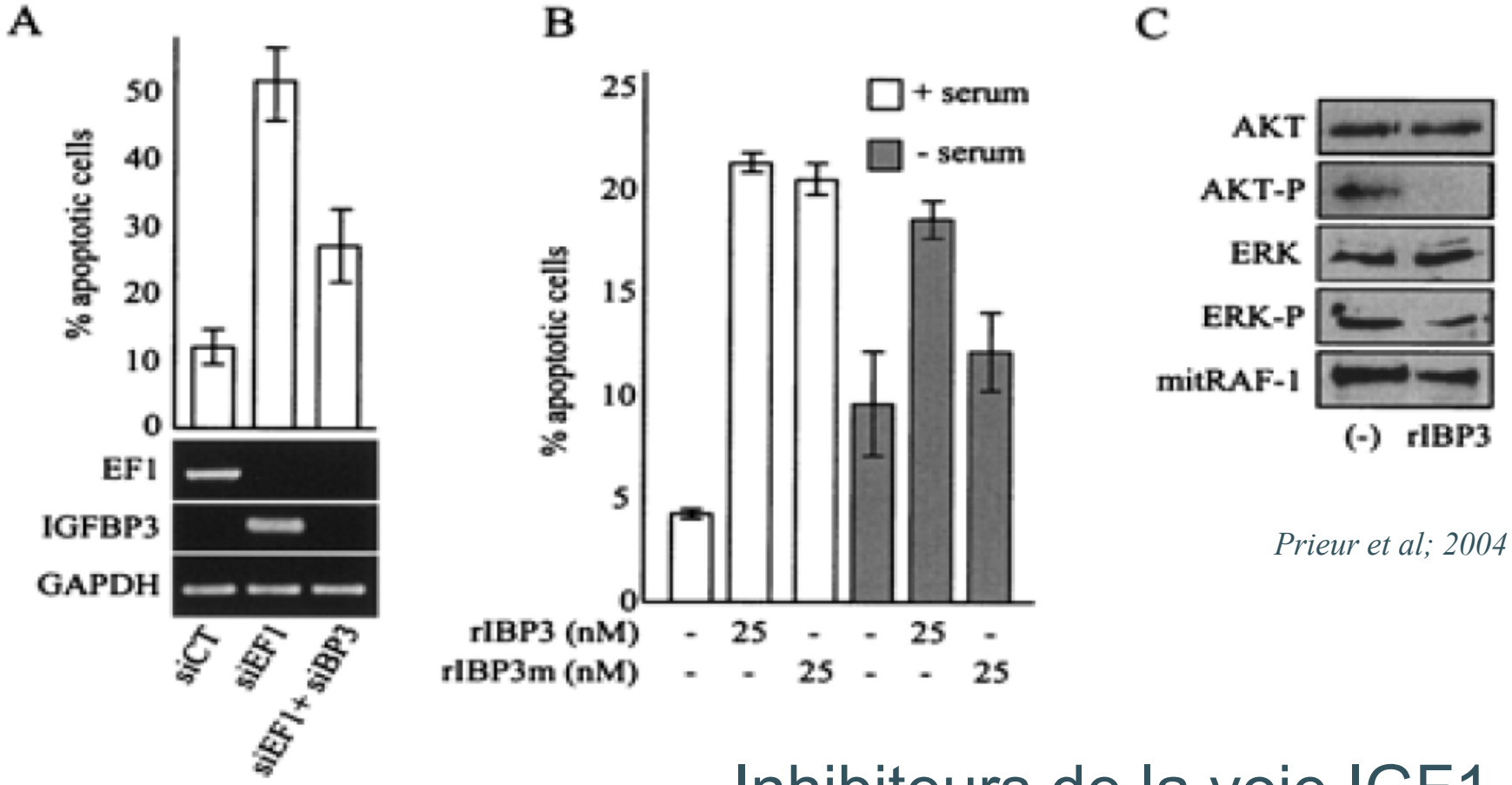
Taylor *et al*, Nature Review Cancer 2011

Synovialosarcomes et Inhibiteur de HDAC



Nielsen and West JCO 2010

IGFBP3 induit l'apoptose de cellules tumorales EWING



Prieur et al; 2004

Inhibiteurs de la voie IGF1 comme thérapie ciblée?

2001: LA thérapie ciblée des sarcomes: La « Target »

Gain-of-Function Mutations of c-*kit* in Human Gastrointestinal Stromal Tumors

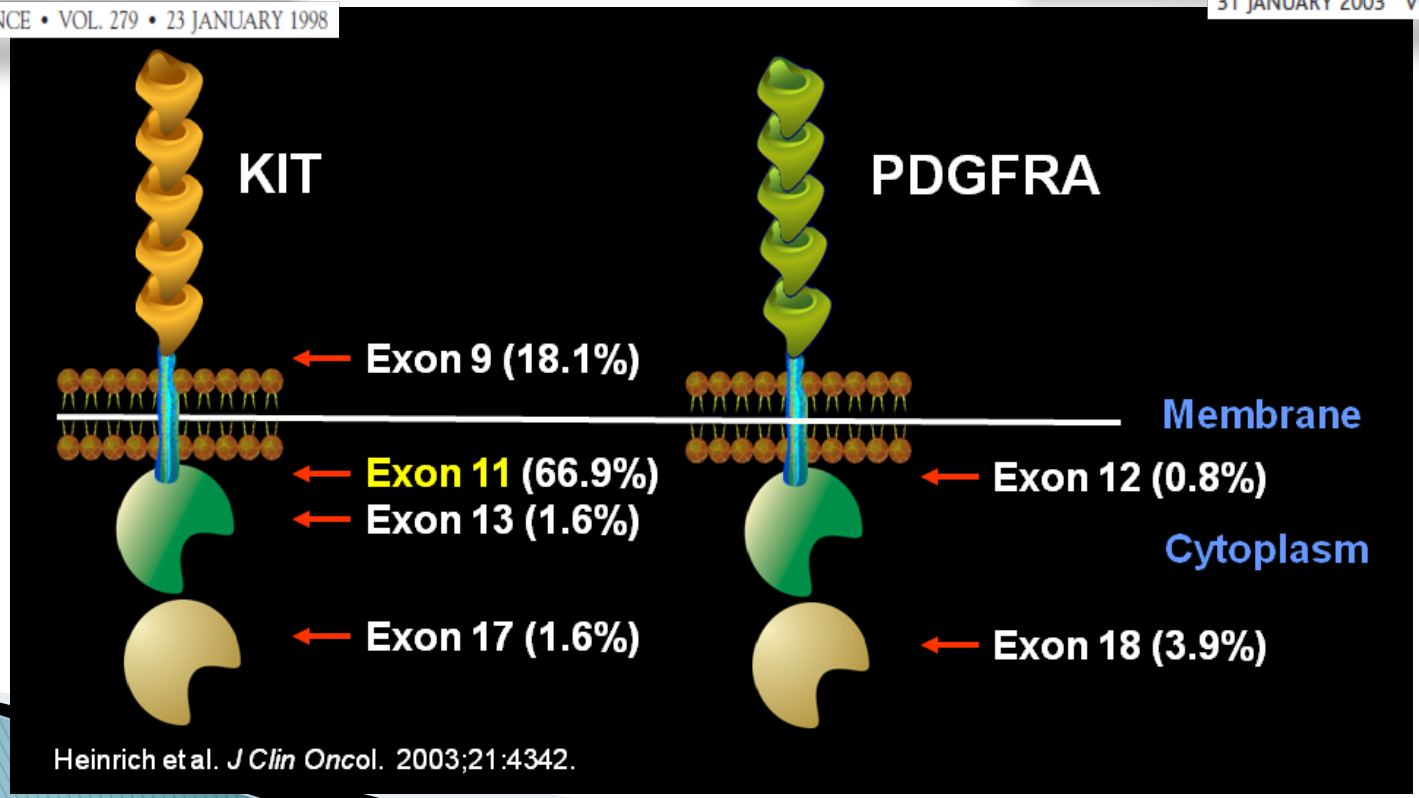
Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura†

SCIENCE • VOL. 279 • 23 JANUARY 1998

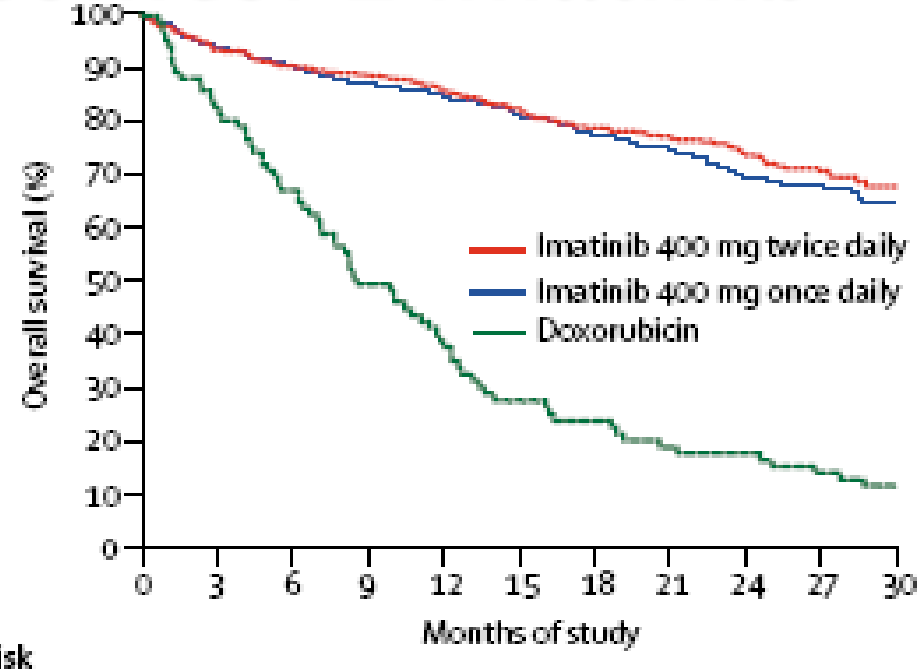
***PDGFRA* Activating Mutations in Gastrointestinal Stromal Tumors**

Michael C. Heinrich,[1]* Christopher L. Corless,[2] Anette Duensing,[3] Laura McGreevey,[1] Chang-Jie Chen,[3] Nora Joseph,[3] Samuel Singer,[4] Diana J. Griffith,[1] Andrea Haley,[1] Ajia Town,[1] George D. Demetri,[5] Christopher D. M. Fletcher,[3] Jonathan A. Fletcher[3,5]*

31 JANUARY 2003 VOL 299 SCIENCE



2001: LA thérapie ciblée des sarcomes: L'Imatinib



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Traitement ciblé

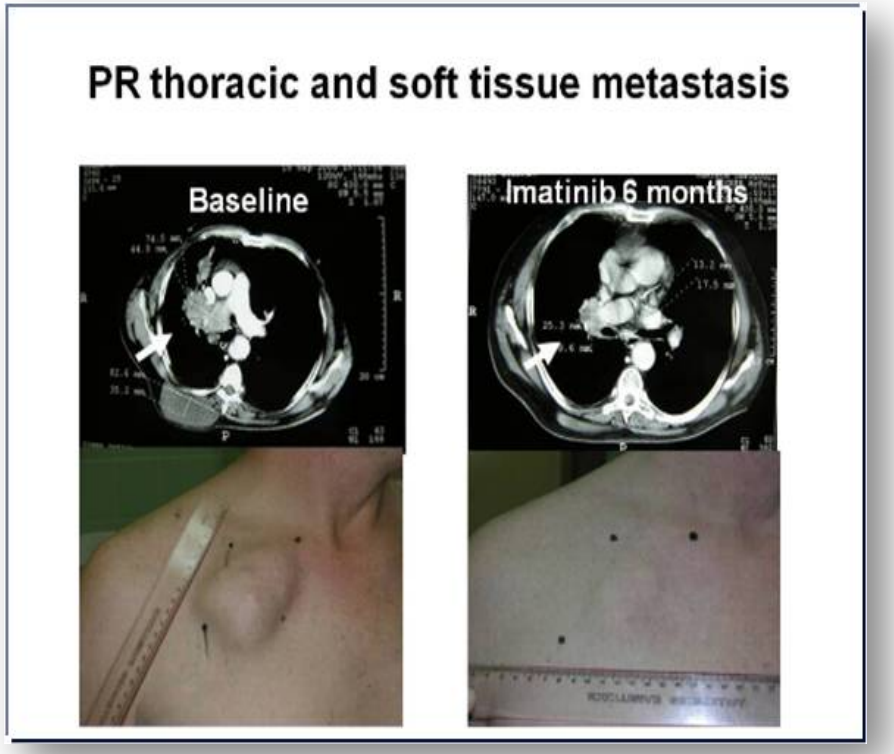
x 3 taux de survie

chimiothérapie

Verweij et al. Lancet 2004; 364: 1127-1134

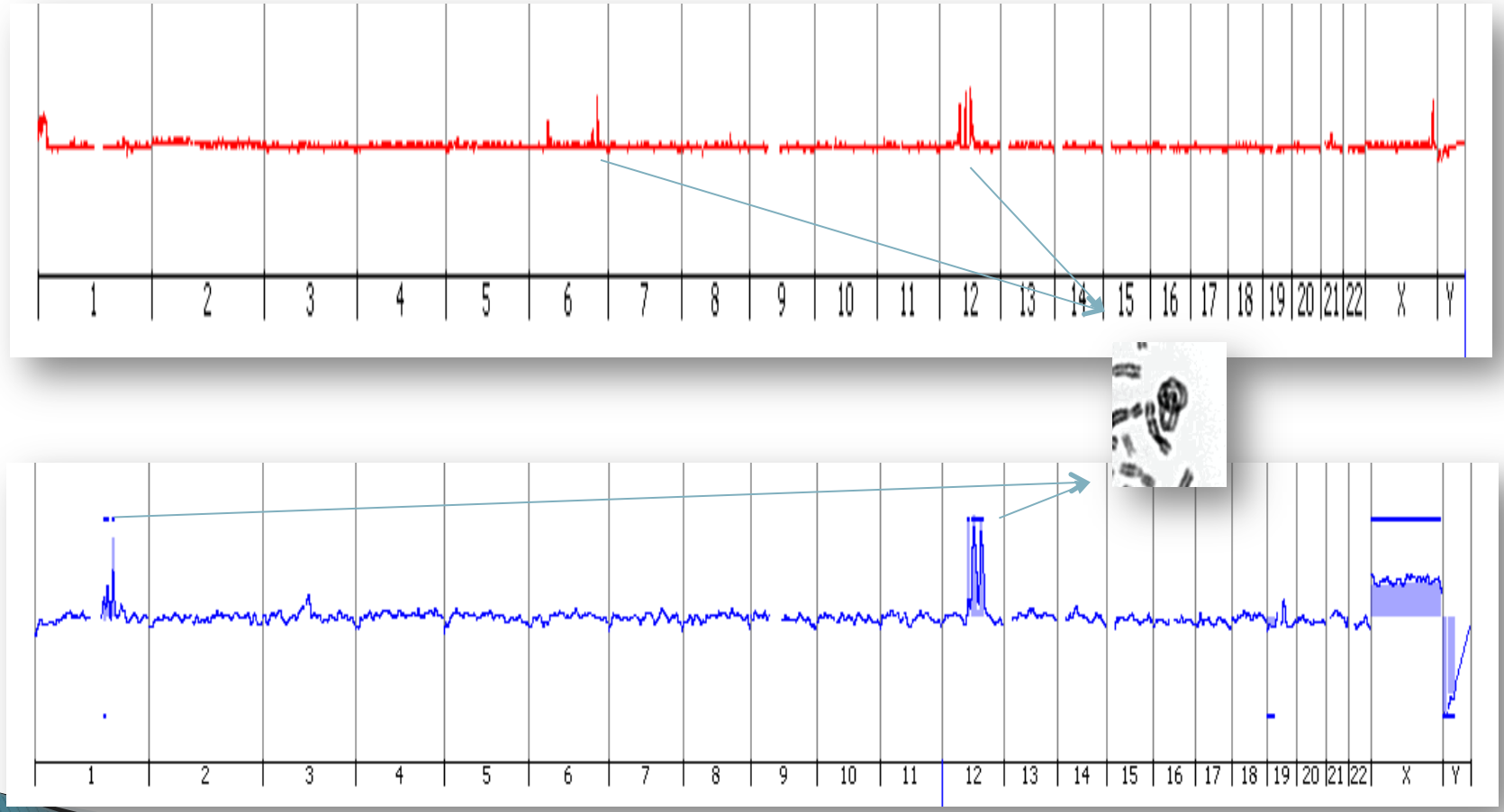
DFSP & Imatinib

- DFSP / Giant cell fibroblastoma
- t(17;12): *COL1A1* & *PDFGB*
- Autocrine loop with PDGFβ



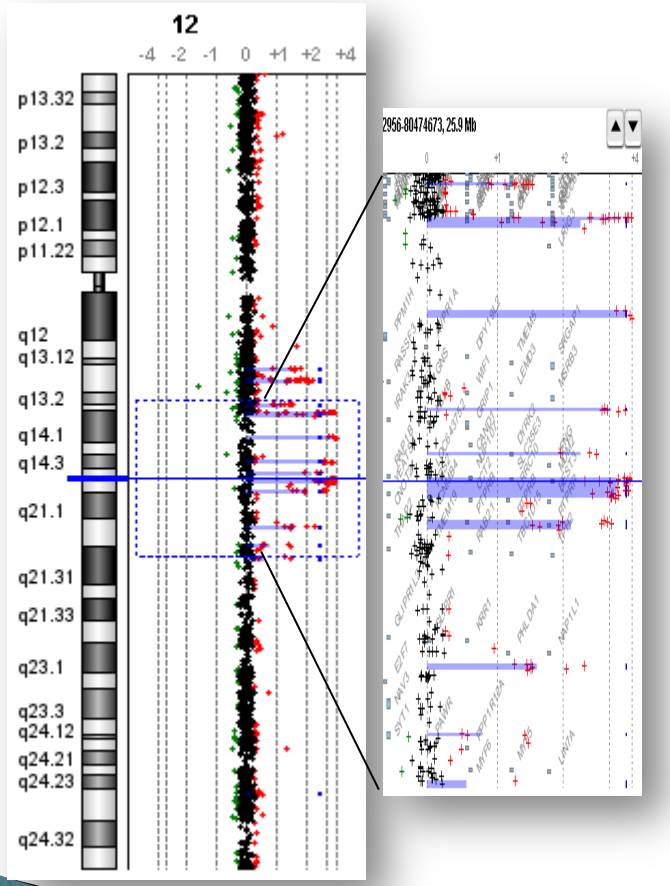
Schuetze S et al, ASCO Ann meet 2009; #10520

Génétique et Biologie des Liposarcomes dédifférenciés



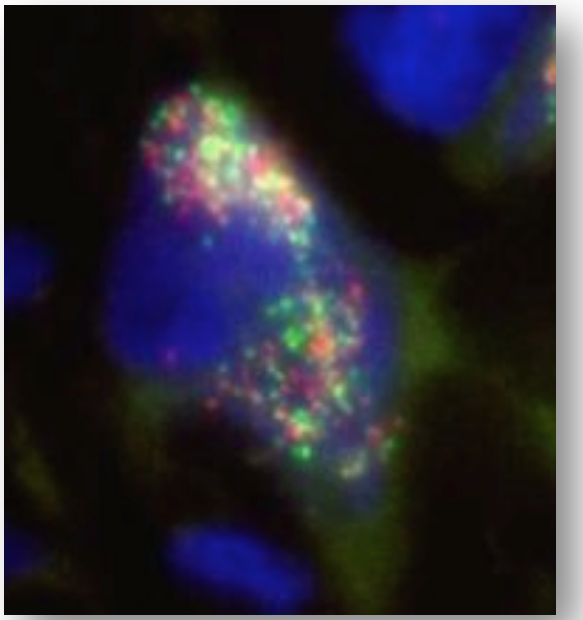
Chibon et al, Cancer Research2000

Amplification MDM2 et CDK4



CDK4

MDM2



Chibon et al, Cancer Genet Cytogenet 2003

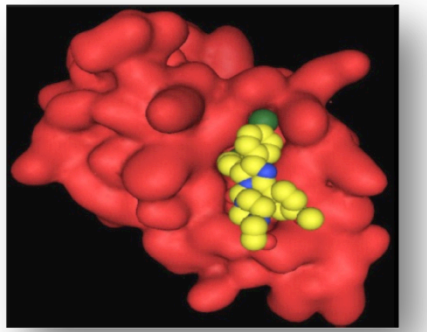
Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study.

Ray-Coquard, Lancet Oncol 2012

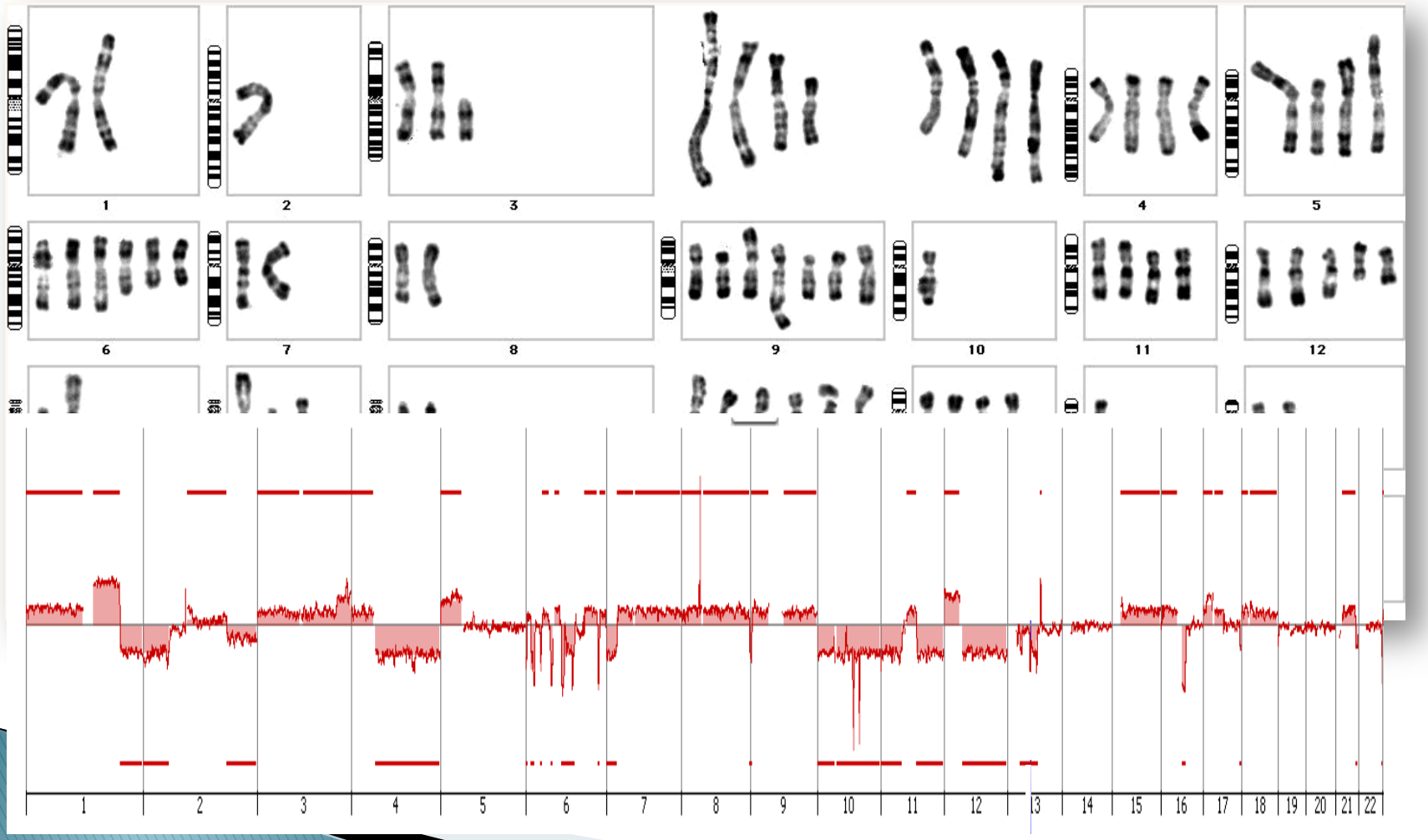
- Phase 0 / 20pts
- 1 biopsie Avant / 1 biopsie après traitement

- p53 & p21 (4,8 & 3,5 X)
- Prolifération

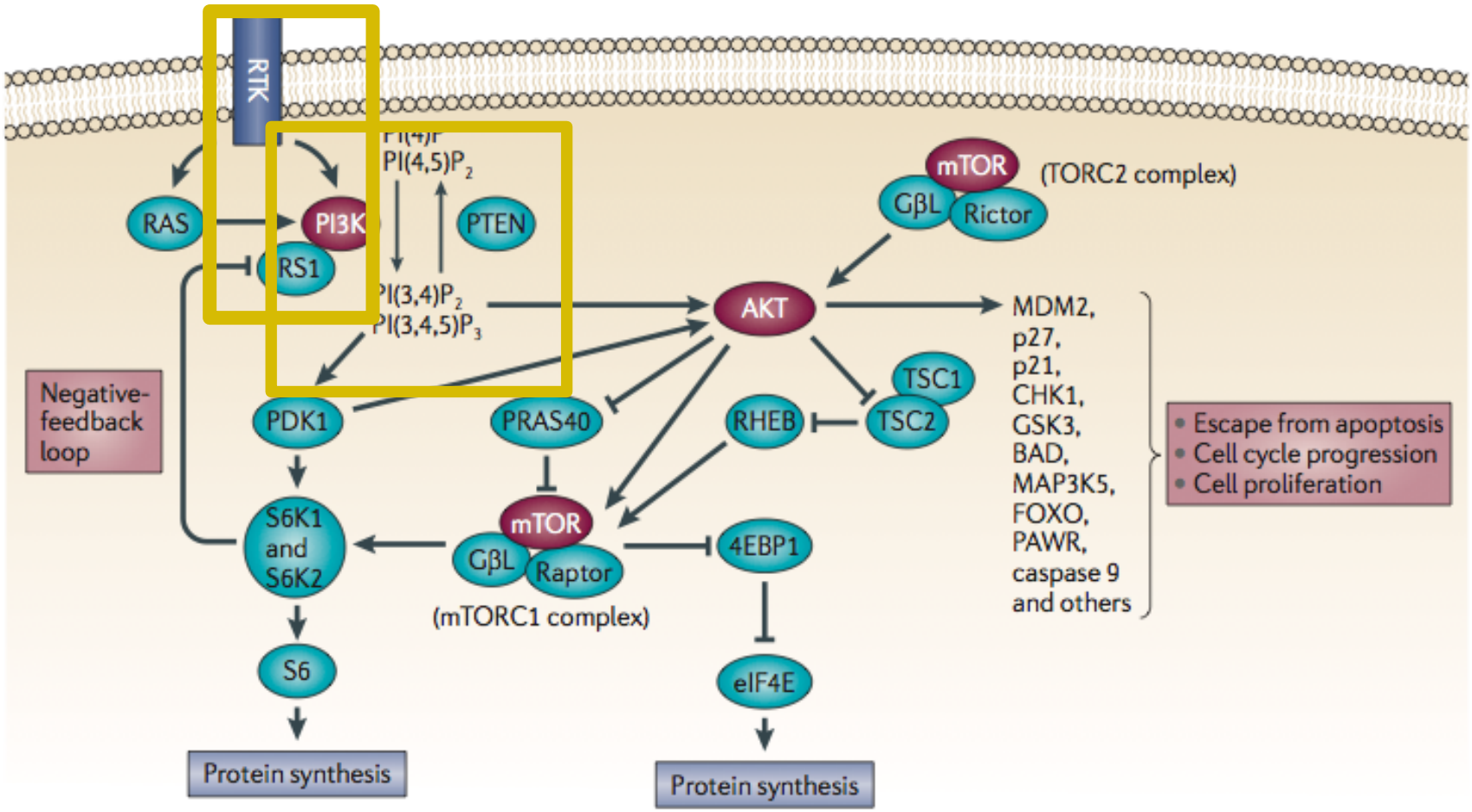
- 1 PR & 14 SD



Sarcomes à génétique complexe

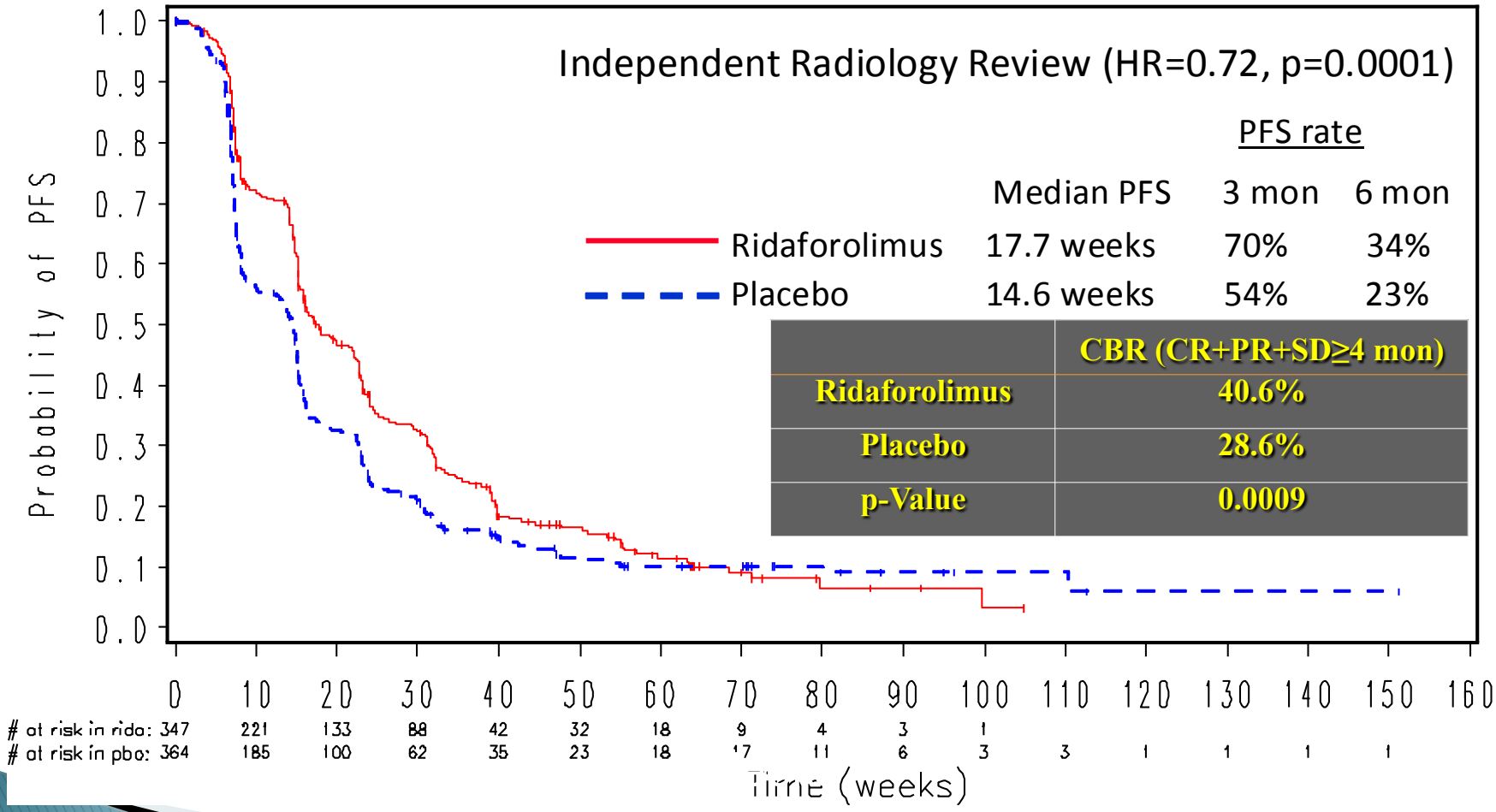


PTEN et IGF-1R contrôlent la voie PI3K



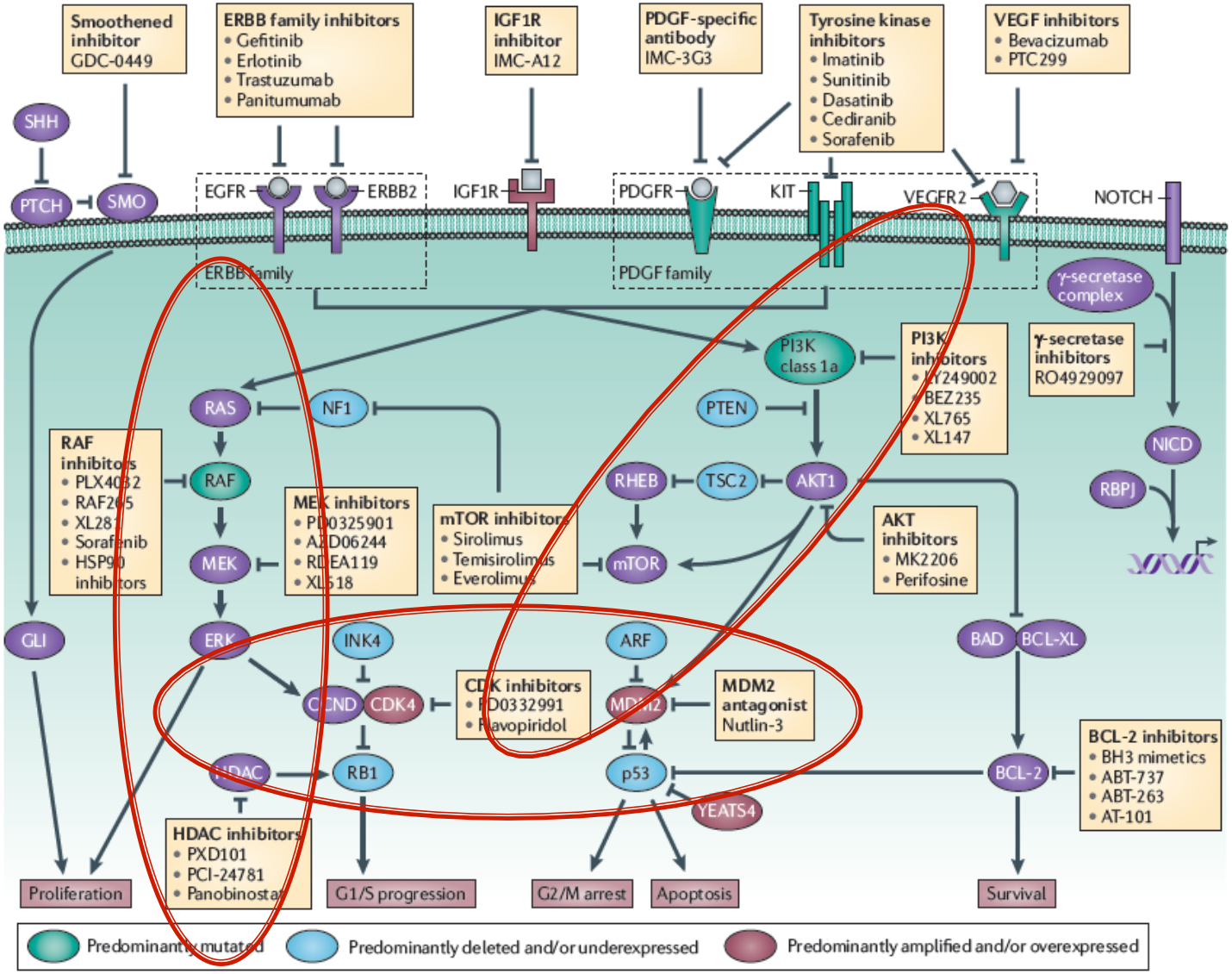
In Hollander MC and al, Nat Rev cancer, 2011;11,4 289-301.

Phase III trial (SUCCEED) ridaforolimus vs placebo as maintenance therapy



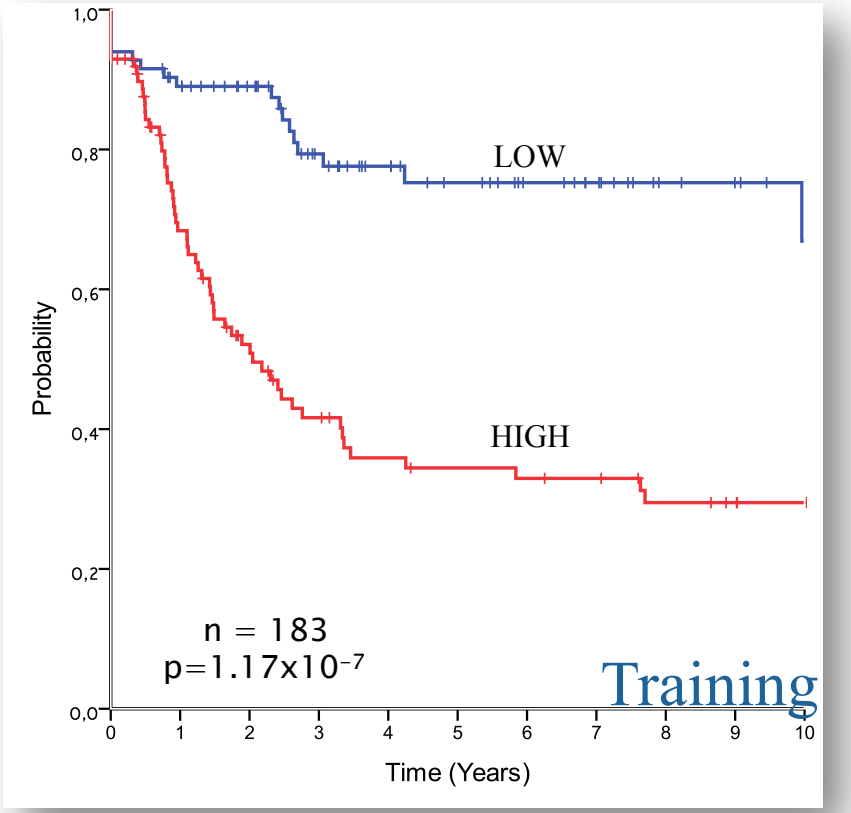
S. P. Chawla, et al, ASCO 2011

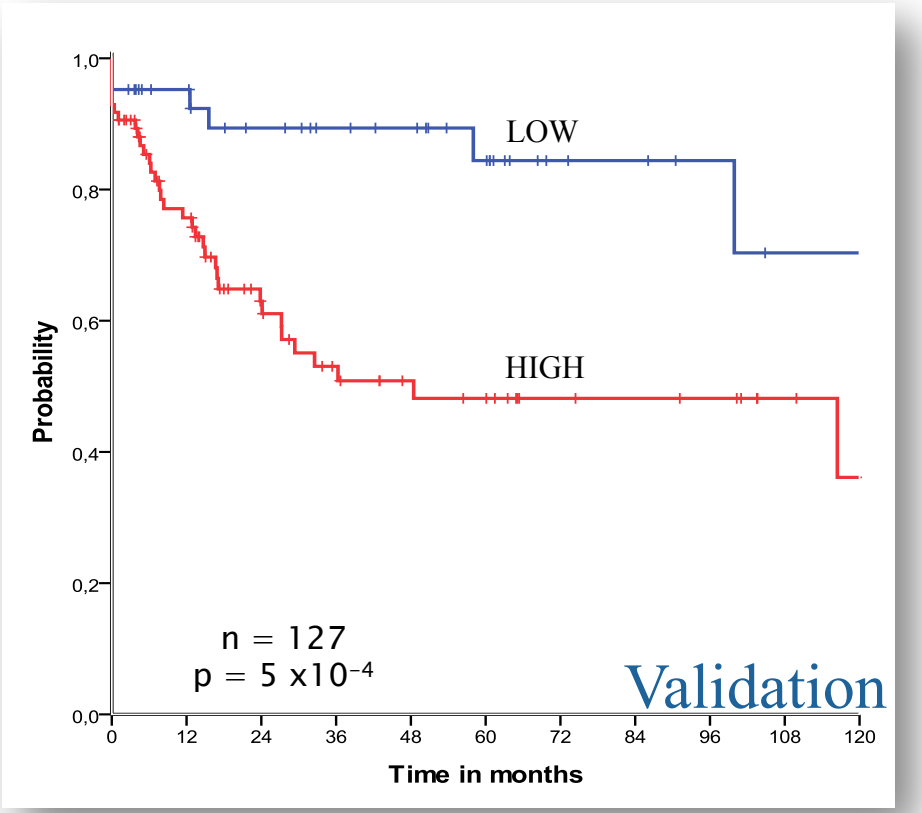
Ciblage thérapeutique dans les sarcomes



Taylor *et al*, Nature Review Cancer 2011

Sarcomas with a « Complex Genetics »
An expression prognostic signature





Metastasis-free survival

Chibon et al, Nat Med 2010

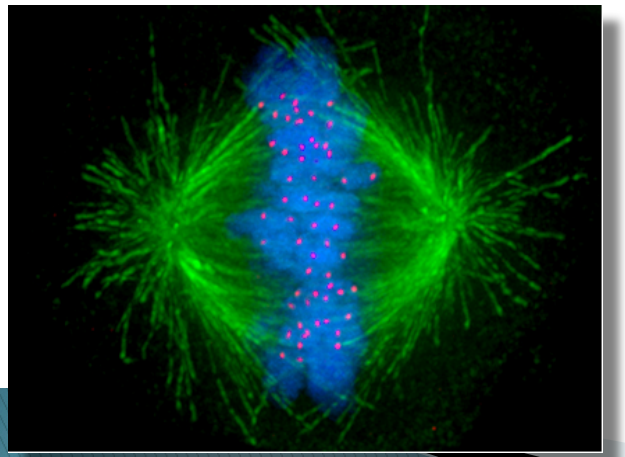
CINSARC: Complexity INdex in SARComas
Chromosome integrity and mitosis control

CYCLE CELLULAIRE: 3

Spindle Checkpoint	Cell cycle checkpoint	Exit from mitosis
ASPM	FOXM1	UBE2C

MITOSE: 9

G1/S transition	Regulation/progression CDK
CDC7	CDC20
	CDC45L
	CCNA2
	CCNB1
	CCNB2
	CKS2
	MELK
	CDCA3



CHROMOSOMES: 26

Chromosome biogenese/condensat Alignement / ségrégation / kinétochore	
NCAPH	BIRC5
HP1BP3	AURKA
CENPA	MAD2L1
KIAA1794	BUB1
SMC2	AURKB
CHEK1	BUB1B
H2AFX	SGOL2
OIP5	PTTG1
MCM2	CENPE
MCM7	NUF2
	CDCA8
	CENPL
	ZWINT
	SPBC25
	TOP2A
	ESPL1

SPINDLE: 12

Spindle µtubules	Centrosome/centriole
CDC2	PLK4
TTK	NEK2
RRM2	TPX2
SPAG5	CEP55
FBXO5	CKAP5
NDE1	
CDC6	

Kinesine complexe / µtubules motor: 8
KIF11
KIF15
KIF23
KIF4A
KIF14
KIF18A
KIF20A
KIF2C

Cytokinese: 4
ECT2
ANLN
PBK
PRC1

DNA replication / repair: 2
RAD51AP1
RNASEH2A

AUTRE indeterminé: 3

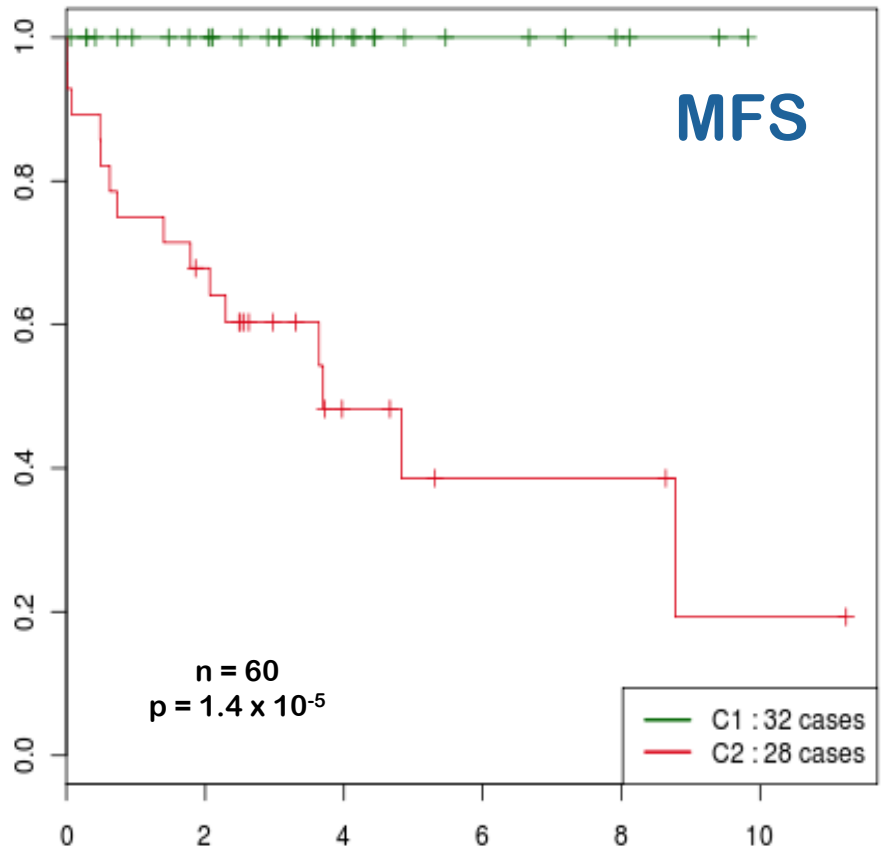
CDCA2
C13orf34
TRIP13

CINSARC & GIST

67 GISTs
(CONTICAGIST)

From frozen samples:

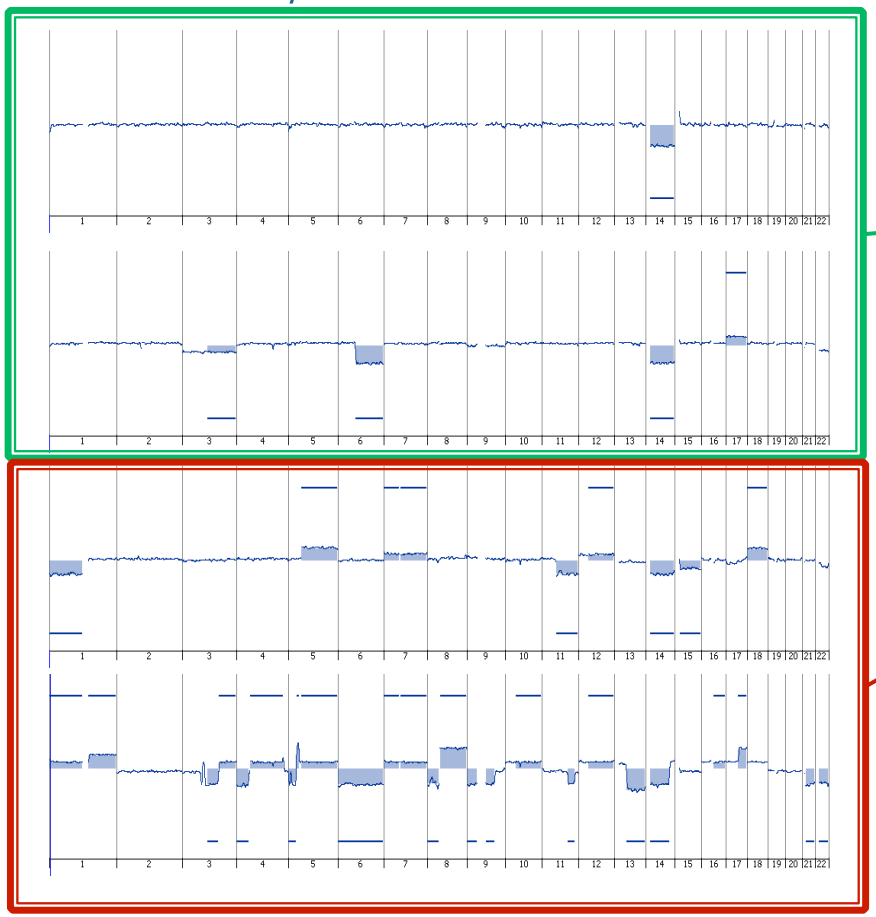
- -Expression array (60 cases)
- -aCGH (66 cases)

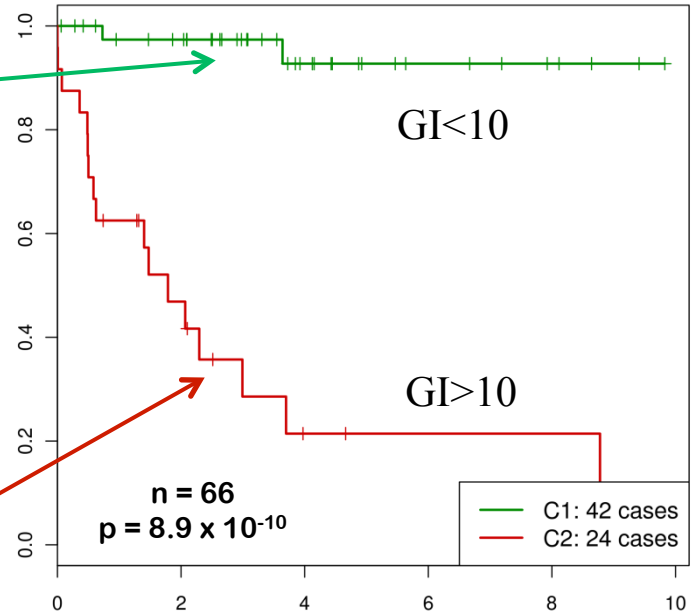


Lagarde et al, Clin Cancer Research 2012

Genomic Index (GI) is a prognostic factor in GIST

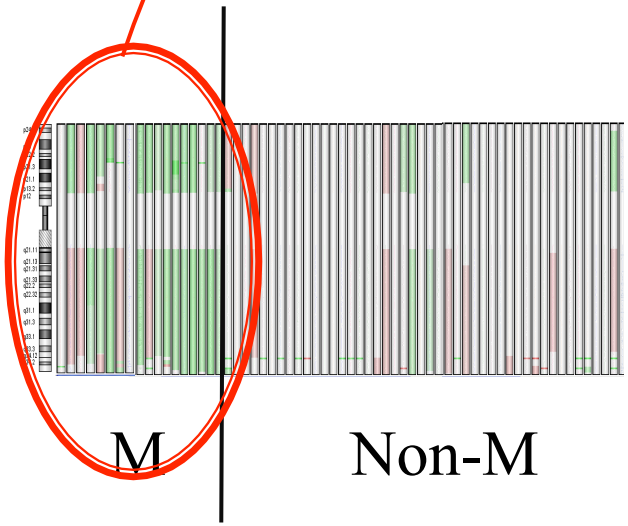
GI = Alt² / nbr of altered Chr

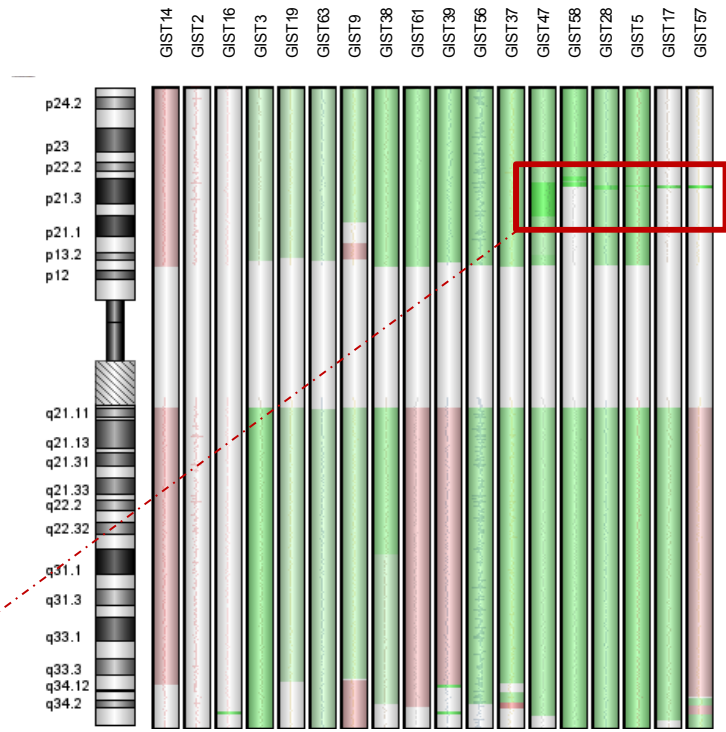


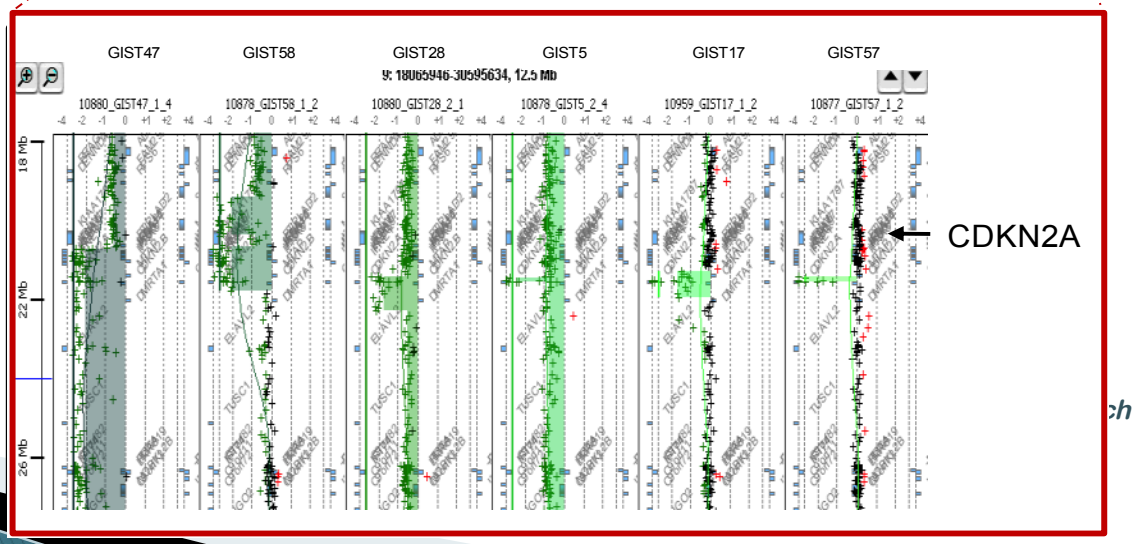


Lagarde et al, Clin Cancer Research 2012

CDKN2A deletions are associated with CINSARC and w





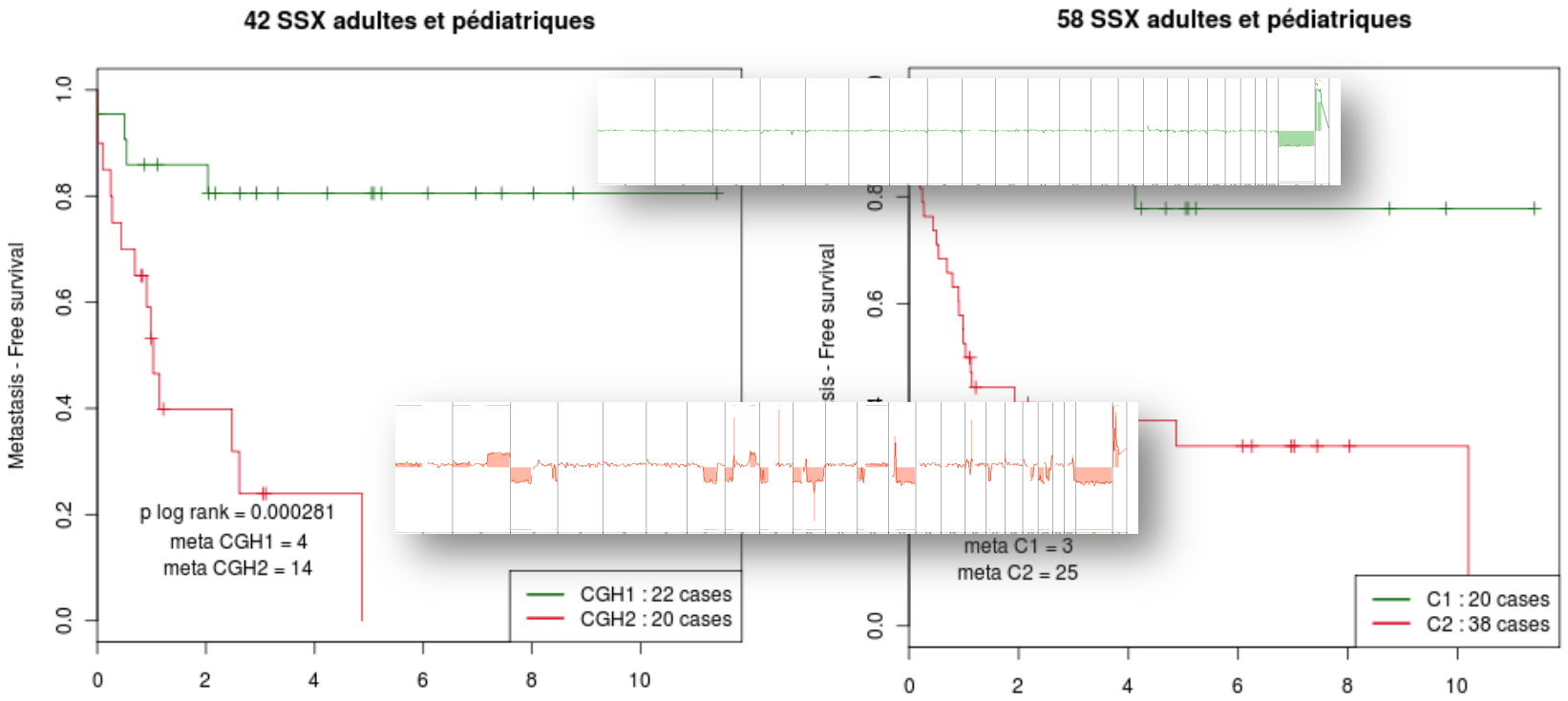


15/18 (83%) cases deleted
(6 homozygous deletions)

A “Genomic Index” (GI) for Synovial Sarcomas !

Genomic Index

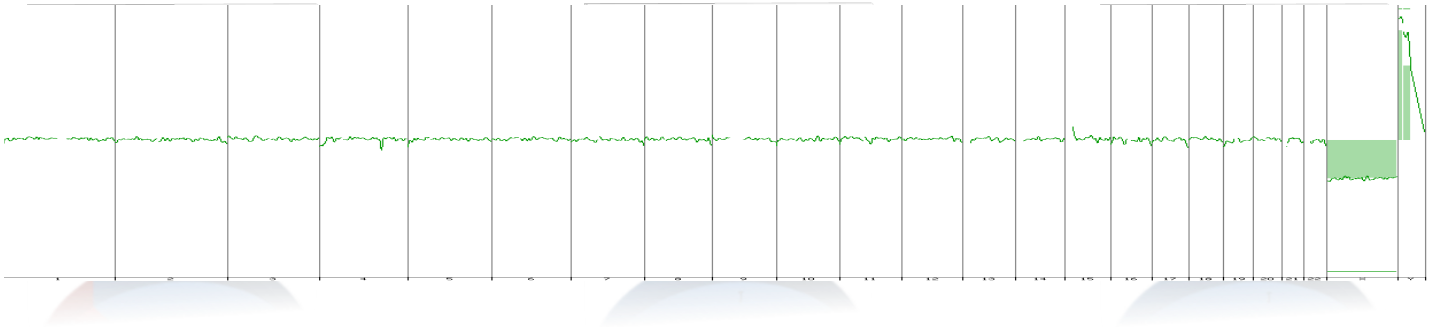
CINSARC



Chibon et al, ASCO 2012

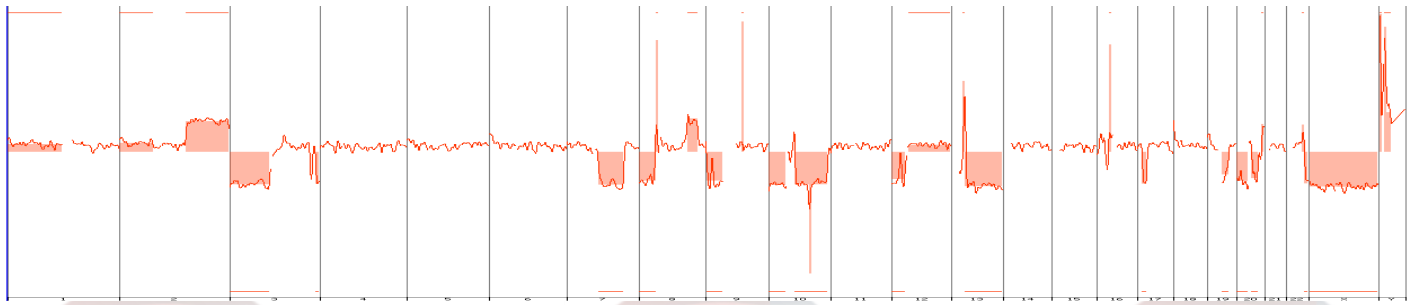
Pediatric and Adult SS…
…Same tumors?

Children



CINSARC GI Meta

Adults

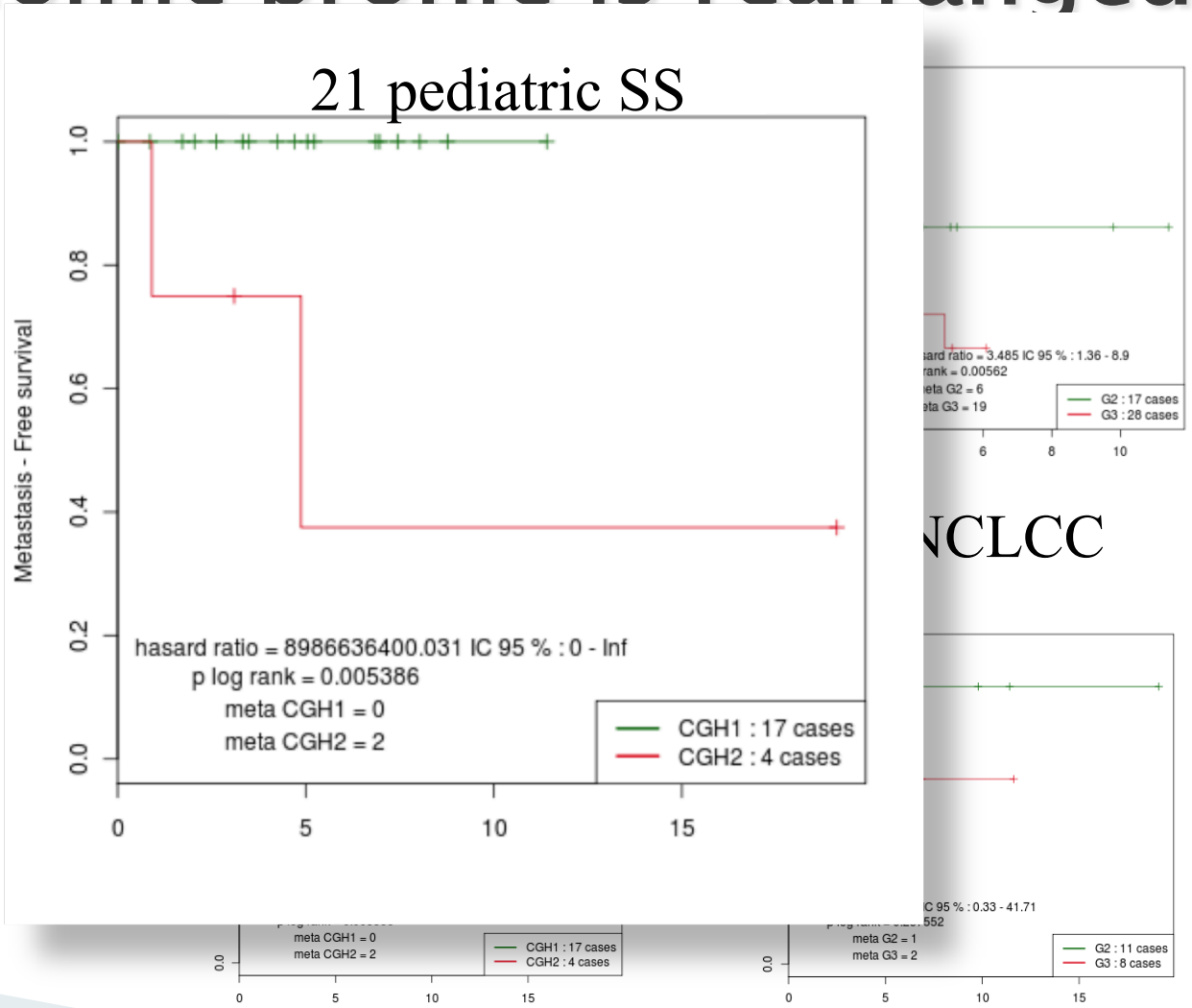


Chibon et al, ASCO 2012

Pediatric SS don't metastazise unless there genomic profile is rearranged

All cases

Pedeatric



Chibon et al, ASCO 2012

Conclusion

- Identifier les altérations « drivers » manquantes
- Comprendre la biologie sous-jacente
- Faire des tests fonctionnels / pré-cliniques
- Identifier les patients ciblés / répondeurs

Merci …