GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

www.esmo.org

ESMO Hamilton Fairley Award lecture

From empirical to rational treatment of human cancers cells and their stroma

JY Blay
Lyon, France
FSG, EORTC

Major successes in clinical oncology came from an in- depth understanding of the biology of the tumor

Target the histotype?

The histotype, the driver mutation, the drug

• Leukemia	CML,CMML, HES
• Sarcoma	GIST, DFSP, PVNS, IMT, WPLPS
• Melanoma	KIT or BRAF mutations
• NSCLC	HER1 or Alk or DDR2 mutations
• BCC, Medulloblastoma	Hh pathway alterations
• Breast Carcinoma	HER2, BRCA1
• Gastric adenocarcinoma	HER2 amplification
• Renal cell carcinoma	VHL loss..
• …	

Target the primary mutation?

The histotype, the driver mutation, the drug

• KIT	GIST, Melanoma, ALL, Mast.
• PDGFR	CMML, HES, DFSP
• Alk	NSCLC, IMT, Neuroblastoma?
• HER1	NSCLC, HN?
• HER2	Breast Ca, Gastric Ca
• Hh	BCC, Medullo, chondroS
• VHL/HIF1A/VEGF	RCC, NET
• mTOR (TSC/PI3K/Akt)	RCC, NET, Breast Ca
• BRAF	MMM, other BRAF mut?

Target the primary mutation?

The disease, the driver mutation, the drug

Imatinib	KIT, PDGFR,CSF1R,+	GIST, MMM, ALL, Mast. CMML,HES,DFSP, others?
Crizotinib	Alk, Met,+	NSCLC, IMT, GC, others?
Trastuzumab	HER2	BC,GC, others?
Erlotinib	HER1	NSCLC, others?
Sunitinib	KIT,PDGFR,VEGFR,RET,+	RCC, NET, others?
Vemurafenib	BRAF	MMM, others?
Everolimus	mTOR	RCC,NET,Br.Ca, others?


Clinical research
Translational research
Basic research

Major successes in clinical oncology came from an in-depth understanding of the biology of the tumor

Vol 463|18 February 2010|doi:10.1038/nature08822 nature

ARTICLES

The landscape of somatic copy-number alteration across human cancers

Rameen Beroukhim[1,3,4,5]*, Craig H. Mermel[1,3]*, Dale Porter[8], Guo Wei[1], Soumya Raychaudhuri[1,4], Jerry Donovan[8], Jordi Barretina[1,3], Jesse S. Boehm[1], Jennifer Dobson[1,3], Mitsuyoshi Urashima[9], Kevin T. Mc Henry[8], Reid M. Pinchback[1], Azra H. Ligon[4], Yoon-Jae Cho[6], Leila Haery[1,3], Heidi Greulich[1,3,4,5], Michael Reich[1], Wendy Winckler[1], Michael S. Lawrence[1], Barbara A. Weir[1,3], Kumiko E. Tanaka[1,3], Derek Y. Chiang[1,3,13], Adam J. Bass[1,3,4], Alice Loo[8], Carter Hoffman[1,3], John Prensner[1,3], Ted Liefeld[1], Qing Gao[1], Derek Yecies[3], Sabina Signoretti[3,4], Elizabeth Maher[10], Frederic J. Kaye[11], Hidefumi Sasaki[12], Joel E. Tepper[13], Jonathan A. Fletcher[4], Josep Tabernero[14], José Baselga[14], Ming-Sound Tsao[15], Francesca Demichelis[16], Mark A. Rubin[16], Pasi A. Janne[3,4], Mark J. Daly[1,17], Carmelo Nucera[7], Ross L. Levine[18], Benjamin L. Ebert[1,4,5], Stacey Gabriel[1], Anil K. Rustgi[19], Cristina R. Antonescu[18], Marc Ladanyi[18], Anthony Letai[3], Levi A. Garraway[1,3], Massimo Loda[3,4], David G. Beer[20], Lawrence D. True[21], Aikou Okamoto[22], Scott L. Pomeroy[6], Samuel Singer[18], Todd R. Golub[1,3,23], Eric S. Lander[1,2,5], Gad Getz[1], William R. Sellers[8] & Matthew Meyerson[1,3,5]

A powerful way to discover key genes with causal roles in oncogenesis is to identify genomic regions that undergo frequent alteration in human cancers. Here we present high-resolution analyses of somatic copy-number alterations (SCNAs) from 3,131 cancer specimens, belonging largely to 26 histological types. We identify 158 regions of focal SCNA that are altered at significant frequency across several cancer types, of which 122 cannot be explained by the presence of a known cancer target gene located within these regions. Several gene families are enriched among these regions of focal SCNA, including the *BCL2* family of apoptosis regulators and the NF-κB pathway. We show that cancer cells containing amplifications surrounding the *MCL1* and *BCL2L1* anti-apoptotic genes depend on the expression of these genes for survival. Finally, we demonstrate that a large majority of SCNAs identified in individual cancer types are present in several cancer types.

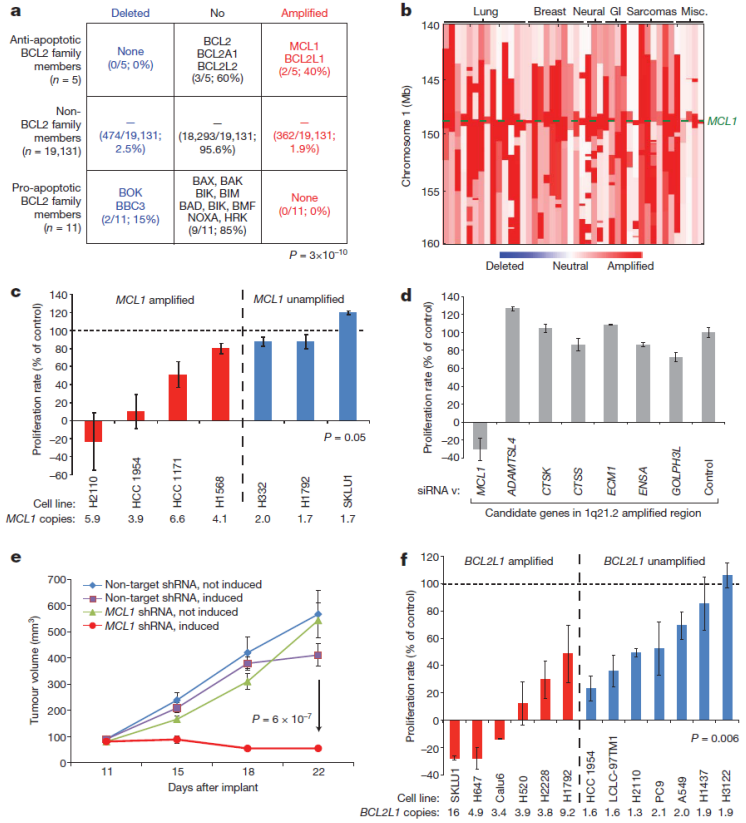


Figure 3 | Dependency of cancer cell lines on the amplified *BCL2* family members, *MCL1* and *BCL2L1*. **a**, Enrichment of pro- and anti-apoptotic

Translational research in oncology research

From empiric to cosmetic to integrated translational research

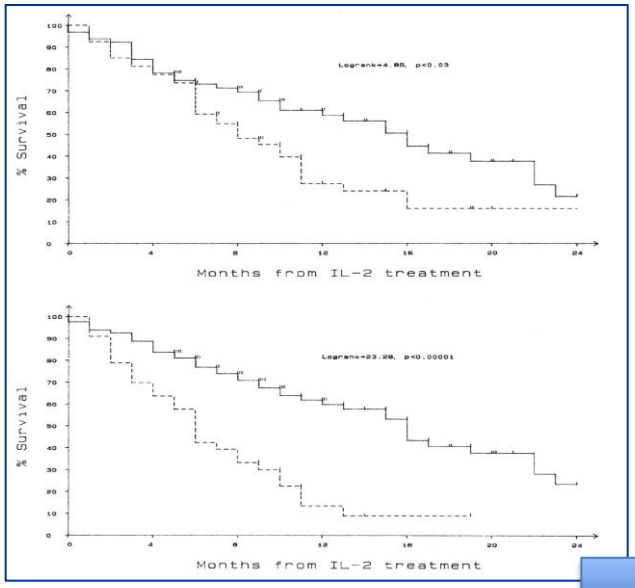
The tumor cell

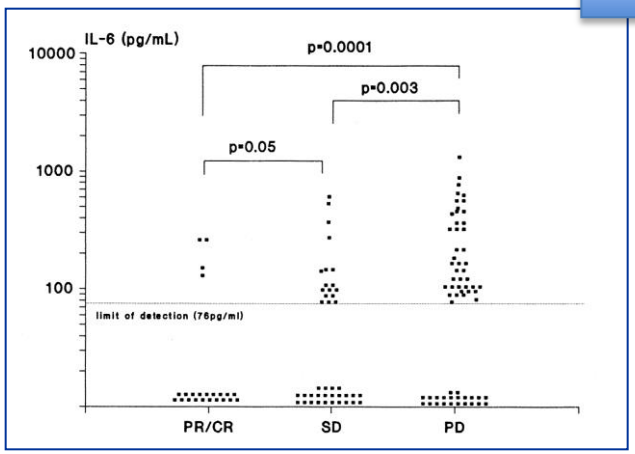
The surrounding cells

The patient

Mechanisms of response to IL-2 in RCC

Intracrine, paracrine, endocrine roles of IL-6





Endocrine?

Paracrine

Autocrine

Intracrine

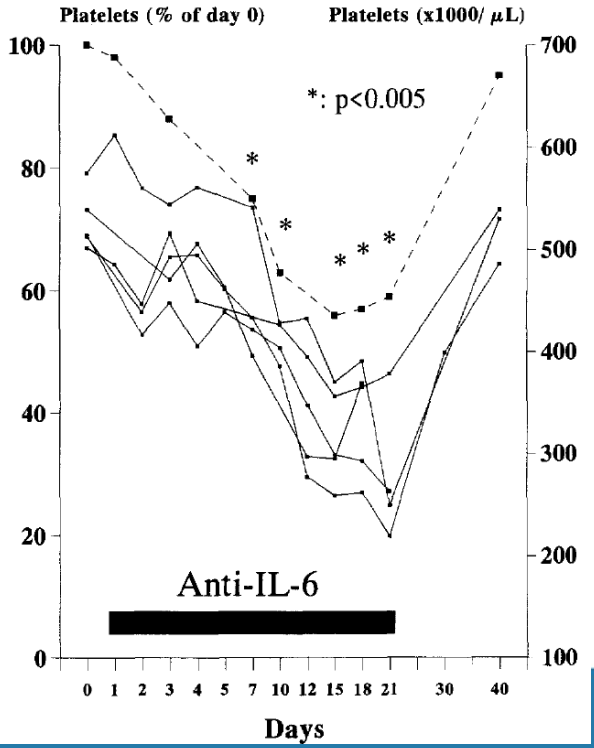
Local Production of Interleukin 6 by Renal Adenocarcinoma In Vivo

Int. J. Cancer: 72, 424–430 (1997)

Publication of the International Union Against Cancer
Publication de l'Union Internationale Contre le Cancer

ROLE OF INTERLEUKIN-6 IN THE PARANEOPLASTIC INFLAMMATORY SYNDROME ASSOCIATED WITH RENAL-CELL CARCINOMA

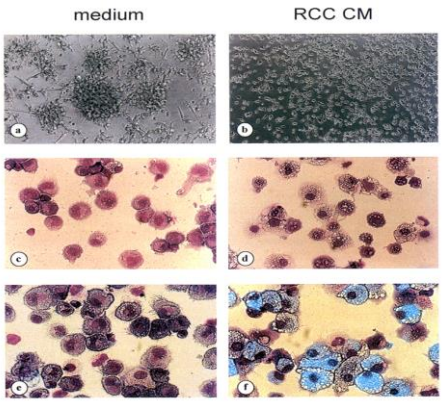
Jean-Yves BLAY[1]*, Jean-François ROSSI[2], John WIJDENES[3], Christine MENETRIER-CAUX[1], Stéphane SCHEMANN[1], Sylvie NÉGRIER[1], Thierry PHILIP[1] and Marie FAVROT[1]

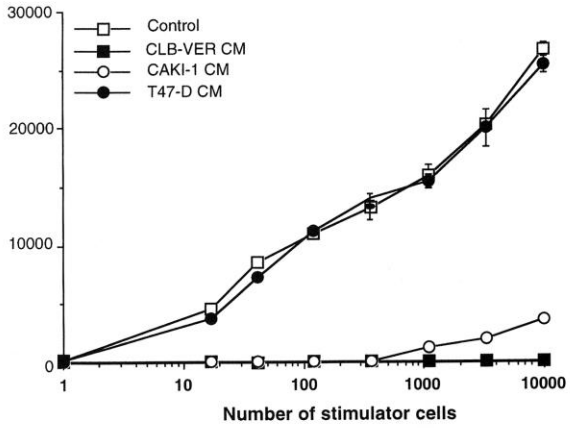


Mechanisms of response to IL-2 in RCC

Intracrine, paracrine, endocrine roles of IL-6

- Endocrine
- **Paracrine?**
- Autocrine
- Intracrine





Reversion with anti-cytokine Abs anti -IL-6 & anti M-CSF

Reversion of the Inhibitory Effect of RCC CM by Neutralizing Antibodies Against (IL-6 + IL-6R) or M-CSF

Conditions	Control	CLB-VER CM (10%)	IL-6 (20 ng/mL) (cpm × 10^{-3})	M-CSF (20 ng/mL)	IL-6 + M-CSF (20 ng/mL)
Control antibodies	29.7 ± 3.4	7.6 ± 1.4	12.9 ± 1.3	11.5 ± 1.4	11.9 ± 0.5
Anti–(IL-6 + IL-6R)	30.0 ± 2.9	13.0 ± 1.4	29.1 ± 3.0	17.9 ± 1.8	17.7 ± 3.0
Anti–M-CSF	29.6 ± 1.8	19.2 ± 3.4	15.7 ± 2.0	27.0 ± 2.4	14.8 ± 1.3
Anti–(IL-6 + IL-6R) + anti–M-CSF	29.9 ± 1.3	25.5 ± 1.5	32.1 ± 3.4	27.4 ± 1.1	25.0 ± 2.6
Anti-VEGF	30.5 ± 1.8	7.7 ± 0.9	13.1 ± 1.1	11.3 ± 0.7	12.3 ± 1.5

Correlation Between Cytokine Levels in CM and Blockade of DC Differentiation

	IL-6 pg/mL/48 h	M-CSF pg/mL/48 h
Noninhibitory		
Neuroblastoma		
CLB-CA	165 ± 24	109 ± 50
CLB-ES	<15	225 ± 31
SKNFI	<15	152 ± 32
Burkitt lymphoma		
DAUDI	<15	<3.9
RAJI	<15	<3.9
BJAB	<15	<3.9
Breast carcinoma		
CLB-SA	<15	130 ± 21
MCF-7	<15	268 ± 44
T47-D	<15	330 ± 36
Small cell lung carcinoma		
H-322	<15	<3.9
Colon carcinoma		
SW-620	<15	<3.9
Inhibitory		
Neuroblastoma		
IMR-32	<15	222 ± 30
SHEP	4,035 ± 505	2,150 ± 250
SKNAS	275 ± 10	1,032 ± 280
Melanoma		
CLB-DOR	391 ± 39	4,170 ± 348
Renal cell carcinoma		
CLB-VER	459 ± 67	3,190 ± 310
CLB-CHA	730 ± 45	8,530 ± 483
CLB-CAN	<15	1,490 ± 231
CLB-GUI	68,500 ± 1,430	14,900 ± 626
CLB-OTE	68,400 ± 1,037	4,330 ± 353
CLB-TUT	66,800 ± 948	2,613 ± 125
CLB-TUG	420 ± 31	763 ± 37
CAKI-1	2,010 ± 370	9,780 ± 512
CAKI-2	3,560 ± 426	6,500 ± 731
Colon carcinoma		
HT-29	439 ± 59	<3.9

All IL-6+tumors

Mechanisms of response to IL-2 in RCC

Intracrine, paracrine, endocrine roles of IL-6

Endocrine

Paracrine

Autocrine

Intracrine

Int. J. Cancer: **111,** 653–661 (2004)

Publication of the International Union Against Cancer

IL-6 AS AN INTRACRINE GROWTH FACTOR FOR RENAL CARCINOMA CELL LINES

Laurent ALBERTI[1], Marie Cécile THOMACHOT[1], Thomas BACHELOT[1], Christine MENETRIER-CAUX[1], Isabelle PUISIEUX[1] and Jean Yves BLAY[1,2]*

[1]*Equipe Cytokine et Cancer, Unité INSERM 590, Lyon, France*
[2]*Hôpital Edouard Herriot. Lyon. France*

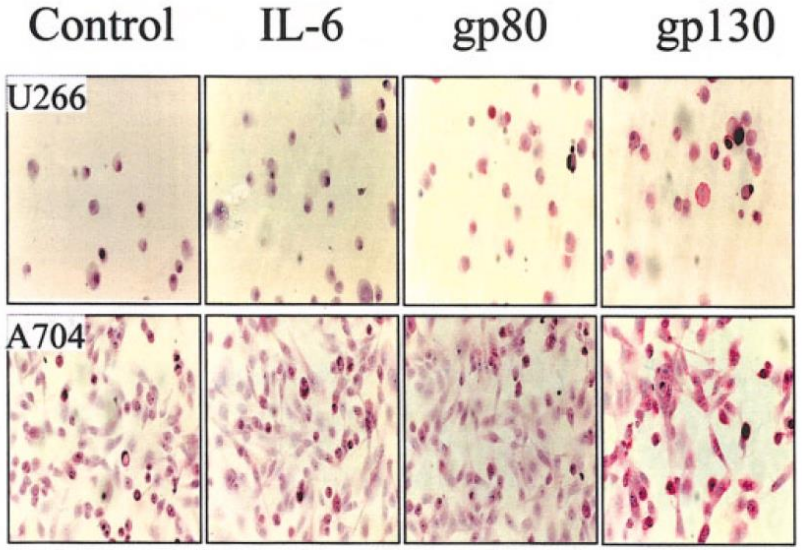


TABLE VII – ANTIPROLIFERATIVE EFFECT OF IL-6 ANTISENSE OLIGONUCLEOTIDES AND/OR IL13

	3H TdR uptake ($\times 10^3$ cpm) (% of control) Culture conditions					
Cell lines	Medium	IL-6 antisense ON (20 μM)		IL-13 (100 ng · mL^{-1})		IL-6 antisense ON (20 μM)+ IL-13 (100 ng · mL^{-1})	
A704	59.7 ± 7.1	23.6 ± 1.7	(40 %)	39.0 ± 7.5	(65 %)	15.7 ± 1.0	(26 %)
ACHN	62.1 ± 2.4	27.6 ± 2.4	(44 %)	32.1 ± 3.5	(52 %)	16.2 ± 3.9	(26 %)
CAKI1	23.0 ± 0.5	8.7 ± 0.0	(37 %)	13.9 ± 1.8	(61 %)	6.3 ± 0.1	(27 %)
CAKI2	13.9 ± 3.3	6.4 ± 1.2	(46 %)	16.3 ± 1.3	(117 %)	7.3 ± 1.1	(53 %)

Mechanisms of response to IL-2 in RCC

Intracrine, paracrine, endocrine roles of IL-6

Endocrine

Paracrine

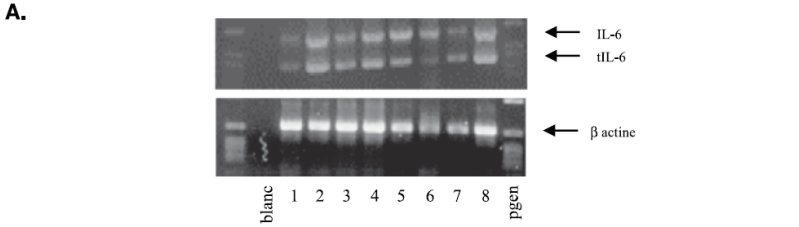
Autocrine

Intracrine

A Spliced Isoform of Interleukin 6 mRNA Produced by Renal Cell Carcinoma Encodes for an Interleukin 6 Inhibitor

Laurent Alberti,[1] Thoma Bachelot,[1] Adeline Duc,[1] Catherine Biota,[1] and Jean Yves Blay[1,2]

[1]Equipe Cytokine et Cancer, Unité Institut National de la Sante et de la Recherche Medicale, Centre Léon Bérard, Lyon, France, and [2]Hôpital Edouard Herriot, Place d'Arsonval, Lyon, France



Partial sequence chromatogram showing junction of the exon 1 and exon 3 in spliced IL-6 mRNA in RCC (E15)

C.

exon 2 for IL6 and exon 1 for SS1 and tIL-6 — exon 3

IL-6: CTCAgCCCTgAgAAAggAgACATgTAACAAgAgTAACATgTgTgAAAg
SS-1: ATgAACTCCTTCTCCACAACATgTAACAAgAgTAACATgTgTgAAAg
tIL-6 :ATgAACTCCTTCTCCACAACATgTAACAAgAgTAACATgTgTgAAAg

Comparison of partial sequence of spliced IL-6 mRNA in PBMC (clone SS-1)[14], in RCC cell line (tIL-6) and IL-6 mRNA.

```
                1 exon 1          }{                                                                100
IL-6            ATGAACTCCTTCTCCACAAGCGCCTTCGGTCCAGTTGCCTTCTCCCTGGGGCTGCTCCTGGTGTTGCCTGCTGCCTTCCCTGCCCCAGTACCCCCAGGAG
tIL-6           ----------------------------------------------------------------------------------------------------
                101                                   exon 2                                        200
IL-6            AAGATTCCAAAGATGTAGCCGCCCCACACAGACAGCCACTCACCTCTTCAGAACGAATTGACAAACAAATTCGGTACATCCTCGACGGCATCTCAGCCCT
tIL-6           ----------------------------------------------------------------------------------------ATGAACT
                201       }{                          exon 3                                          298
IL-6            GAGAAAGGAGA--CATGTAACAAGAGTAACATGTGTGAAAGCAGCAAAGAGGCACTGGCAGAAAACAACCTGAACCTTCCAAAGATGGCTGAAAAAGATG
tIL-6           CCTTCTCCACAAACATGTAACAAGAGTAACATGTGTGAAAGCAGCAAAGAGGCACTGGCAGAAAACAACCTGAACCTTCCAAAGATG CTGAAAAAGATG
                299                   }{                exon 4 and 5                                    398
IL-6            GATGCTTCCAATCTGGATTCAATGAGGAGACTTGCCTGGTGAAAATCATCACTGGTCTTTTGGAGTTTGAGGTATACCTAGAGTACCTCCAGAACAGATT
tIL-6           GATGCTTCCAATCTGGATTCAATGAGGAGACTTGCCTGGTGAAAATCATCACTGGTCTTTTGGAGTTTGAGGTATACCTAGAGTACCTCCAGAACAGATT
                399                                                                               498
IL-6            TGAGAGTAGTGAGGAACAAGCCAGAGCTGTGCAGATGAGTACAAAAGTCCTGATCCAGTTCCTGCAGAAAAAGGCAAAGAATCTAGATGCAATAACCACC
tIL-6           TGAGAGTAGTGAGGAACAAGCCAGAGCTGTGCAGATGAGTACAAAAGTCCTGATCCAGTTCCTGCAGAAAAAGGCAAAGAATCTAGATGCAATAACCACC
                499                                                                               598
IL-6            CCTGACCCAACCACAAATGCCAGCCTGCTGACGAAGCTGCAGGCACAGAACCAGTGGCTGCAGGACATGACAACTCATCTCATTCTGCGCAGCTTTAAGG
tIL-6           CCTGACCCAACCACAAATGCCAGCCTGCTGACGAAGCTGCAGGCACAGAACCAGTGGCTGCAGGACATGACAACTCATCTCATTCTGCGCAGCTTTAAGG
                599                                   639
IL-6            AGTTCCTGCAGTCCAGCCTGAGGGCTCTTCGGCAAATGTAG
tIL-6           AGTTCCTGCAGTCCAGCCTGAGGGCTCTTCGGCAAATGTAG
```

Alignment sequence of spliced IL-6 mRNA in RCC cell line (tIL-6) and IL-6 mRNA.

Mechanisms of response to IL-2 in RCC

Intracrine, paracrine, endocrine roles of IL-6

Endocrine

Paracrine

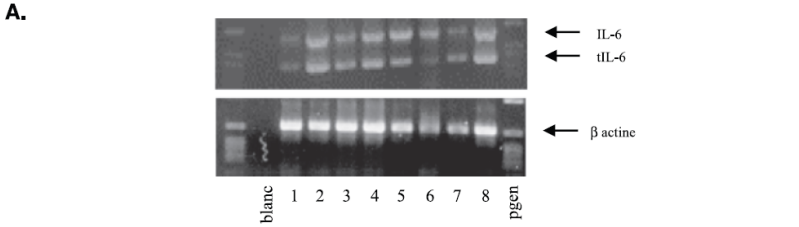
Autocrine

Intracrine

A Spliced Isoform of Interleukin 6 mRNA Produced by Renal Cell Carcinoma Encodes for an Interleukin 6 Inhibitor

Laurent Alberti,[1] Thoma Bachelot,[1] Adeline Duc,[1] Catherine Biota,[1] and Jean Yves Blay[1,2]

[1]Equipe Cytokine et Cancer, Unité Institut National de la Sante et de la Recherche Medicale, Centre Léon Bérard, Lyon, France, and [2]Hôpital Edouard Herriot, Place d'Arsonval, Lyon, France



Partial sequence chromatogram showing junction of the exon 1 and exon 3 in spliced IL-6 mRNA in RCC (E15)

C.

exon 2 for IL6 and exon 1 for SS1 and tIL-6 — exon 3

IL-6: CTCAgCCCTgAgAAAggAgACATgTAACAAgAgTAACATgTgTgAAAg
SS-1: ATgAACTCCTTCTCCACAACATgTAACAAgAgTAACATgTgTgAAAg
tIL-6 :ATgAACTCCTTCTCCACAACATgTAACAAgAgTAACATgTgTgAAAg

Comparison of partial sequence of spliced IL-6 mRNA in PBMC (clone SS-1)[14], in RCC cell line (tIL-6) and IL-6 mRNA.

```
                1 exon 1          }{                                                                100
IL-6            ATGAACTCCTTCTCCACAAGCGCCTTCGGTCCAGTTGCCTTCTCCCTGGGGCTGCTCCTGGTGTTGCCTGCTGCCTTCCCTGCCCCAGTACCCCCAGGAG
tIL-6           ----------------------------------------------------------------------------------------------------
                101                                   exon 2                                        200
IL-6            AAGATTCCAAAGATGTAGCCGCCCCACACAGACAGCCACTCACCTCTTCAGAACGAATTGACAAACAAATTCGGTACATCCTCGACGGCATCTCAGCCCT
tIL-6           ----------------------------------------------------------------------------------------ATGAACT
                201       }{                          exon 3                                          298
IL-6            GAGAAAGGAGA--CATGTAACAAGAGTAACATGTGTGAAAGCAGCAAAGAGGCACTGGCAGAAAACAACCTGAACCTTCCAAAGATGGCTGAAAAAGATG
tIL-6           CCTTCTCCACAAACATGTAACAAGAGTAACATGTGTGAAAGCAGCAAAGAGGCACTGGCAGAAAACAACCTGAACCTTCCAAAGATG CTGAAAAAGATG
                299                   }{                exon 4 and 5                                    398
IL-6            GATGCTTCCAATCTGGATTCAATGAGGAGACTTGCCTGGTGAAAATCATCACTGGTCTTTTGGAGTTTGAGGTATACCTAGAGTACCTCCAGAACAGATT
tIL-6           GATGCTTCCAATCTGGATTCAATGAGGAGACTTGCCTGGTGAAAATCATCACTGGTCTTTTGGAGTTTGAGGTATACCTAGAGTACCTCCAGAACAGATT
                399                                                                               498
IL-6            TGAGAGTAGTGAGGAACAAGCCAGAGCTGTGCAGATGAGTACAAAAGTCCTGATCCAGTTCCTGCAGAAAAAGGCAAAGAATCTAGATGCAATAACCACC
tIL-6           TGAGAGTAGTGAGGAACAAGCCAGAGCTGTGCAGATGAGTACAAAAGTCCTGATCCAGTTCCTGCAGAAAAAGGCAAAGAATCTAGATGCAATAACCACC
                499                                                                               598
IL-6            CCTGACCCAACCACAAATGCCAGCCTGCTGACGAAGCTGCAGGCACAGAACCAGTGGCTGCAGGACATGACAACTCATCTCATTCTGCGCAGCTTTAAGG
tIL-6           CCTGACCCAACCACAAATGCCAGCCTGCTGACGAAGCTGCAGGCACAGAACCAGTGGCTGCAGGACATGACAACTCATCTCATTCTGCGCAGCTTTAAGG
                599                                   639
IL-6            AGTTCCTGCAGTCCAGCCTGAGGGCTCTTCGGCAAATGTAG
tIL-6           AGTTCCTGCAGTCCAGCCTGAGGGCTCTTCGGCAAATGTAG
```

Alignment sequence of spliced IL-6 mRNA in RCC cell line (tIL-6) and IL-6 mRNA.

Mechanisms of response to IL-2 in RCC

Intracrine, paracrine, endocrine roles of IL-6 and VEGF

Endocrine

Paracrine

Autocrine

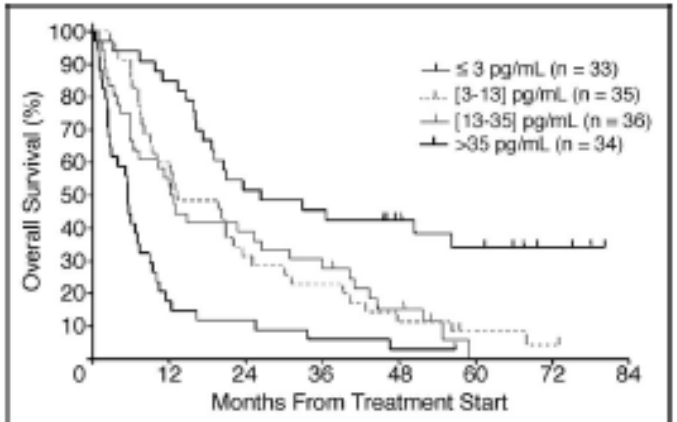
Intracrine

VOLUME 22 · NUMBER 12 · JUNE 15 2004

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

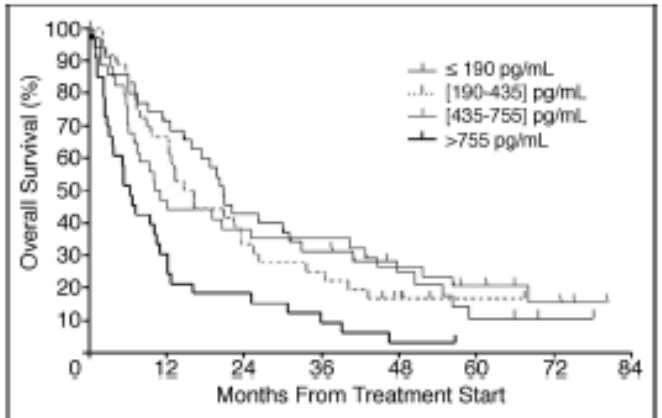
Interleukin-6, Interleukin-10, and Vascular Endothelial Growth Factor in Metastatic Renal Cell Carcinoma: Prognostic Value of Interleukin-6—From the Groupe Français d'Immunothérapie

Sylvie Negrier, David Perol, Christine Menetrier-Caux, Bernard Escudier, Michel Pallardy, Alain Ravaud, Jean-Yves Douillard, Christine Chevreau, Christine Lasset, and Jean-Yves Blay



Quartile	Q1	Q2	Q3	Q4
Limits	≤3	[3-13]	[13-35]	>35
Number	33	35	36	34
Hazard ratio	1.0	2.19	2.35	5.14
95% Confidence Interval	-	1.26-3.79	1.35-4.08	2.92-9.04

Fig 1. Results of the quartile analysis of interleukin-6 serum levels (pg/mL), with Kaplan-Meier overall survival analysis and univariate Cox proportional hazard regression model (n = 138).



Quartile	Q1	Q2	Q3	Q4
Limits	≤190	[190-435]	[435-755]	>755
Number	35	36	34	33
Hazard ratio	1.0	1.15	1.04	2.36
95% Confidence Interval	-	0.69-1.91	0.62-1.75	1.42-391

Fig 2. Results of the quartile analysis of vascular endothelial growth factor serum levels (pg/mL), with Kaplan-Meier overall survival analysis and univariate Cox proportional hazard regression model (n = 138).

Translational research in oncology research

From empiric to cosmetic to integrated translational research

The tumor cell

The surrounding cells

The patient

Cytokine as growth factors in NHL and breast Ca

[CANCER RESEARCH 56, 5499–5505, December 1, 1996]

Interleukin (IL)-10 and IL-6 Are Produced *in Vivo* by Non-Hodgkin's Lymphoma Cells and Act as Cooperative Growth Factors[1]

Nathalie Voorzanger, Robert Touitou, Eric Garcia, Henry-Jacques Delecluse, Françoise Rousset, Irène Joab, Marie C. Favrot, and Jean-Yves Blay[2]

BMC Cancer

BioMed Central

Research article

Open Access

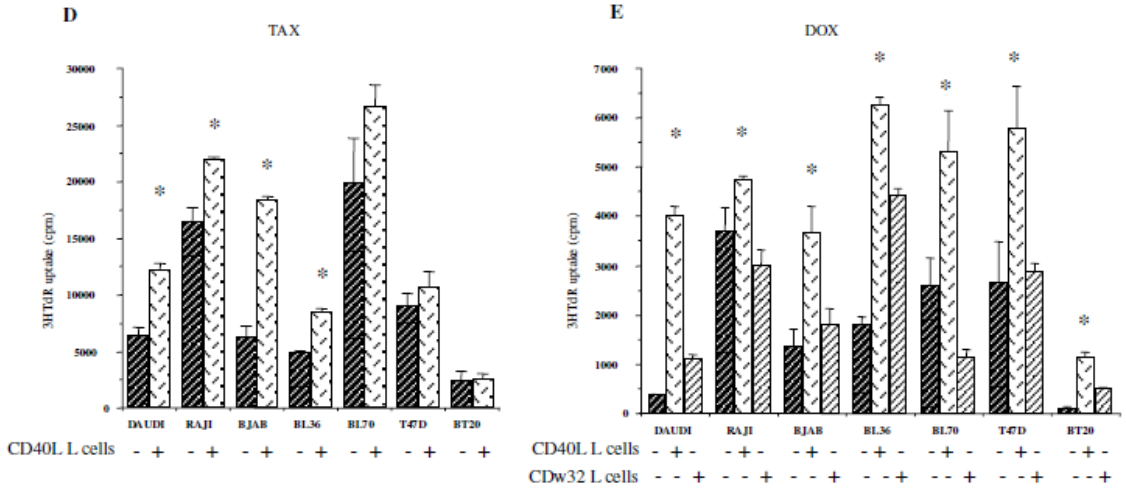
CD40L induces multidrug resistance to apoptosis in breast carcinoma and lymphoma cells through caspase independent and dependent pathways

halie Voorzanger-Rousselot, Laurent Alberti and Jean-Yves Blay*

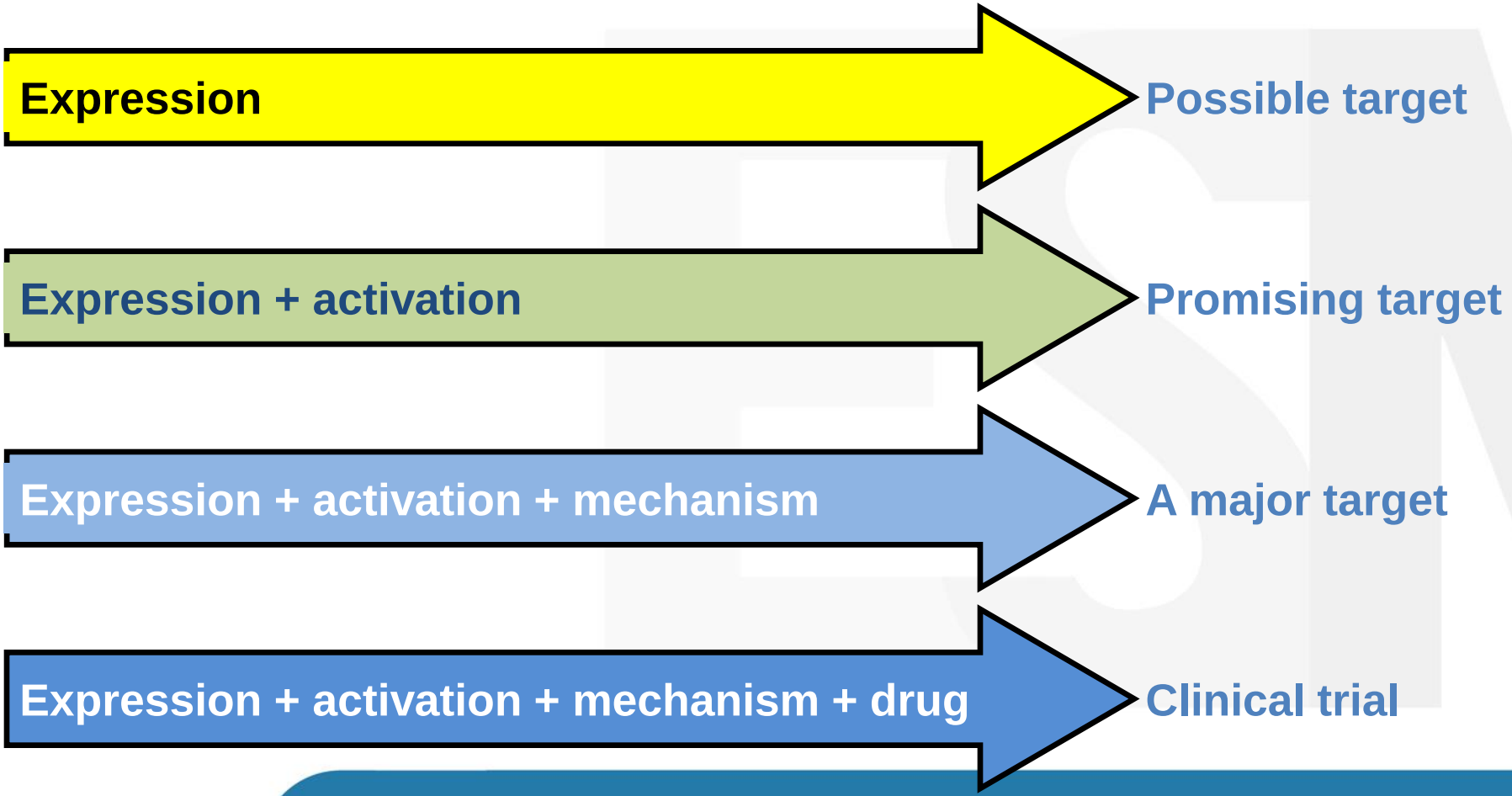
Resistance to Cytotoxic Chemotherapy Induced by CD40 Ligand in Lymphoma Cells

By Nathalie Voorzanger-Rousselot, M.-C. Favrot, and Jean-Yves Blay

Blood, Vol 92, No 9 (November 1), 1998: pp 3381-3387



What is a good target?

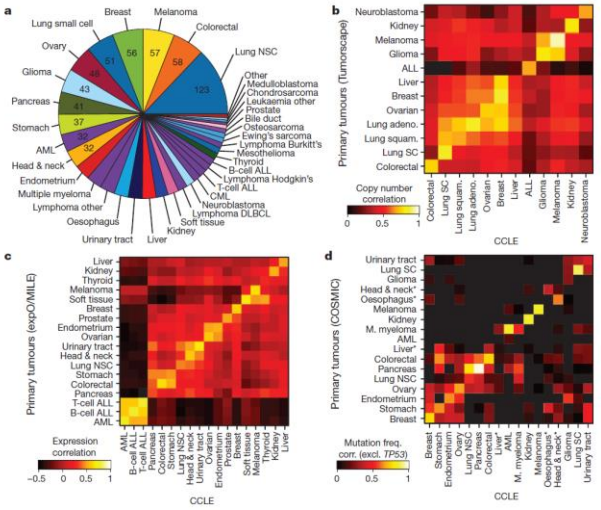


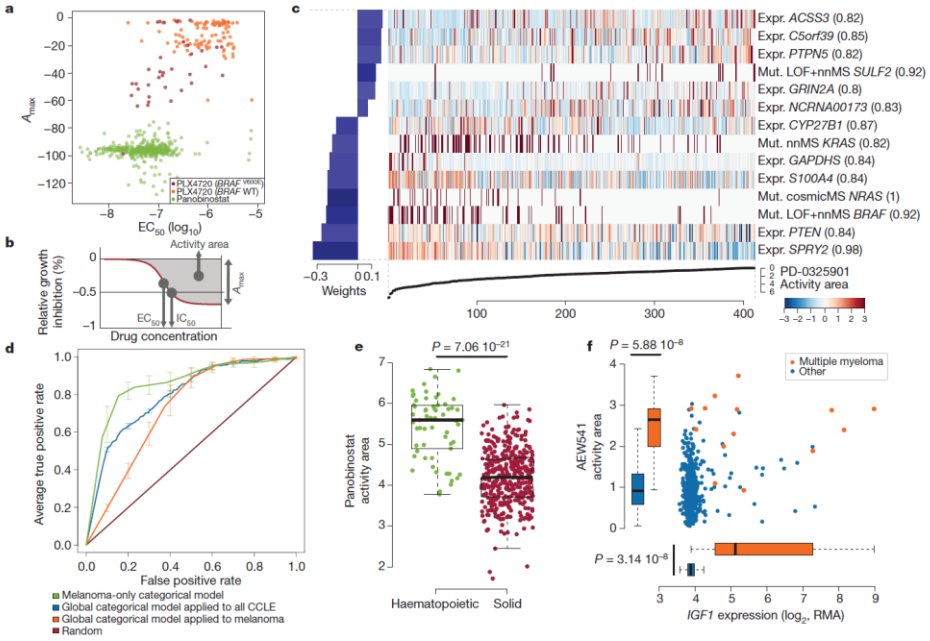
LETTER

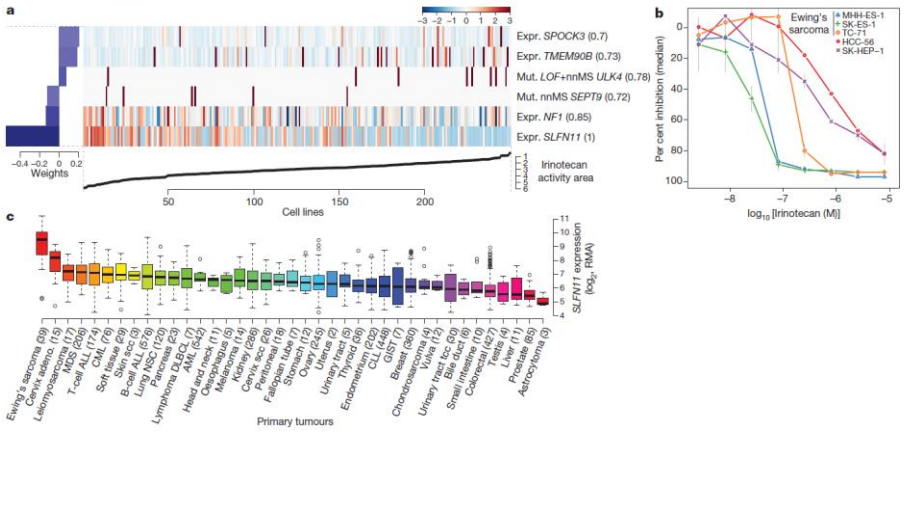
doi:10.1038/nature11003

The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity

Jordi Barretina[1,2,3]†*, Giordano Caponigro[4]*, Nicolas Stransky[1]*, Kavitha Venkatesan[4]*, Adam A. Margolin[1]†*, Sungjoon Kim[5], Christopher J. Wilson[4], Joseph Lehár[4], Gregory V. Kryukov[1], Dmitriy Sonkin[4], Anupama Reddy[4], Manway Liu[4], Lauren Murray[1], Michael F. Berger[1]†, John E. Monahan[4], Paula Morais[1], Jodi Meltzer[4], Adam Korejwa[1], Judit Jané-Valbuena[1,2], Felipa A. Mapa[4], Joseph Thibault[5], Eva Bric-Furlong[4], Pichai Raman[4], Aaron Shipway[5], Ingo H. Engels[5], Jill Cheng[6], Guoying K. Yu[6], Jianjun Yu[6], Peter Aspesi Jr[4], Melanie de Silva[4], Kalpana Jagtap[4], Michael D. Jones[4], Li Wang[4], Charles Hatton[3], Emanuele Palescandolo[3], Supriya Gupta[1], Scott Mahan[1], Carrie Sougnez[1], Robert C. Onofrio[1], Ted Liefeld[1], Laura MacConaill[3], Wendy Winckler[1], Michael Reich[1], Nanxin Li[5], Jill P. Mesirov[1], Stacey B. Gabriel[1], Gad Getz[1], Kristin Ardlie[1], Vivien Chan[6], Vic E. Myer[4], Barbara L. Weber[4], Jeff Porter[4], Markus Warmuth[4], Peter Finan[4], Jennifer L. Harris[5], Matthew Meyerson[1,2,3], Todd R. Golub[1,3,7,8], Michael P. Morrissey[4]*, William R. Sellers[4]* & Levi A. Garraway[1,2,3]*



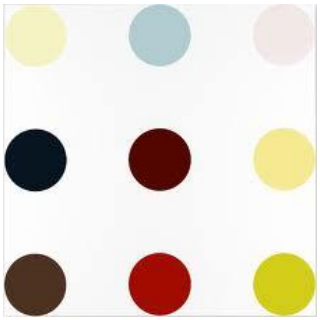


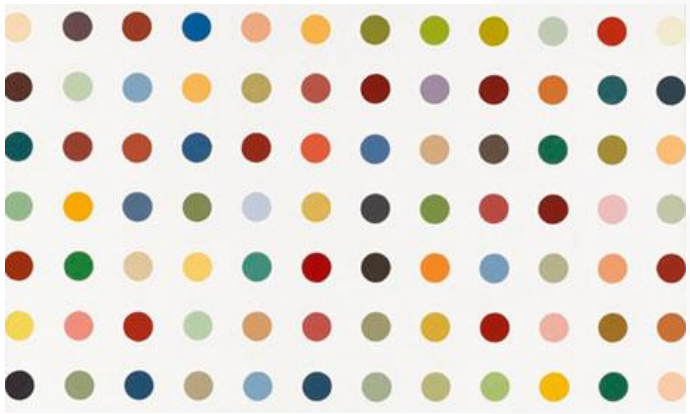


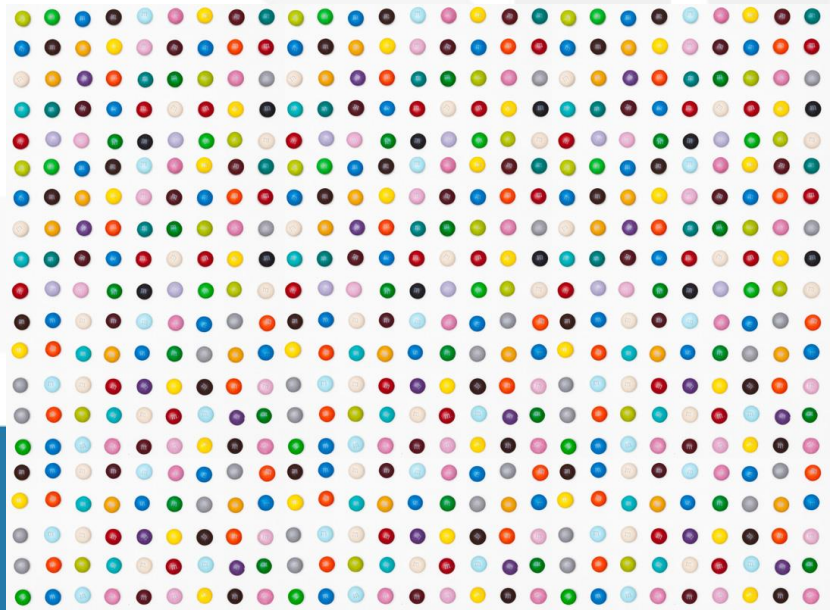
Lineage
Gene expression

Biomarkers shared across lineages

Towards a major fragmentation of nosological entities

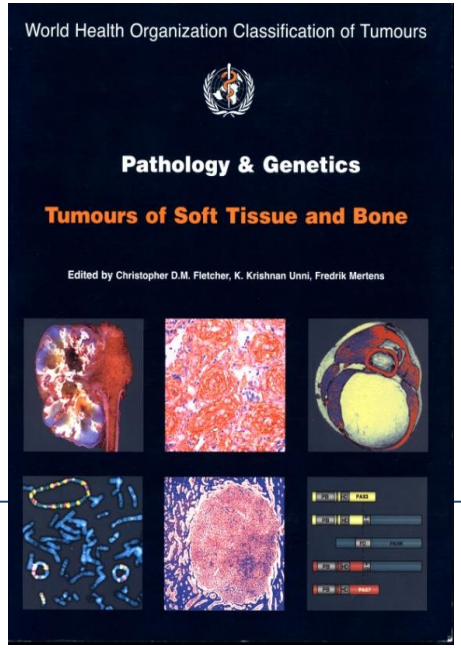






Damien Hirst
« 1-bromoadamantane »
« Acivicin »
« Arginosuccinic acid »

Even for rare tumors…



Fragmentation

>50 different histotypes

AND molecular subtypes

2013 classification

Adipocytic tumours
- Well deifferentiated / dedifferentiated liposarcoma
- Myxoid / round cell liposarcoma
- Pleomorphic liposarcoma
- …..

Fibroblastic / myofibroblastic tumours
- Fibromatosis (desmoid)
- Solitary fibrous tumour / haemangiopericytoma
- Low grade myofibroblastic tumour
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Mixofibrosarcoma
- …..

So-called fibrohistiocytic tumours
- Pleomorphic MFH / Undifferentiated pleomorphic sarcoma
- …..

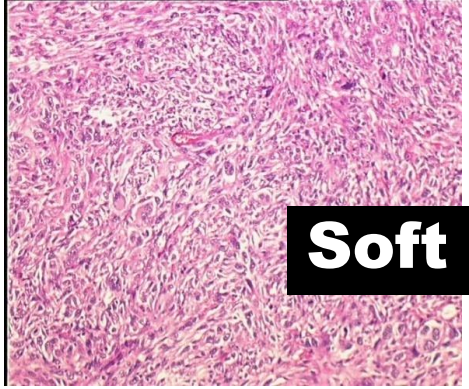
Smooth muscle tumours
- Leiomyosarcoma
- …..

Skeletal muscle tumours
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma

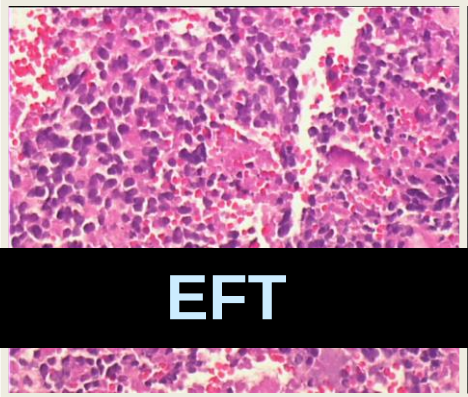
Vascular tumours
- Epithelioid haemangioendothelioma
- Angiosarcoma of soft tissue
- …..

Chondro-osseous tumours
- Mesenchymal chondrosarcoma
- Extraskeletal osteosarcoma

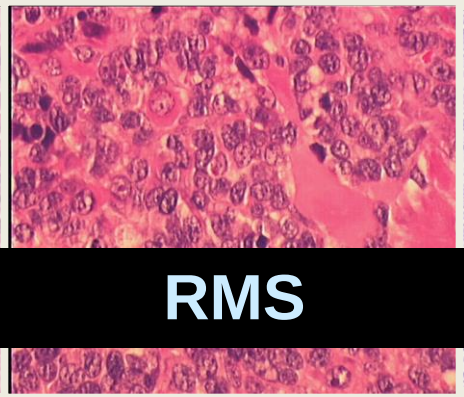
Tumours of uncertain differentiation
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal Ewing tumour
- Desmoplastic small round cell tumour
- Extra-renal rhabdoid tumour
- Malignant mesenchymoma
- Neoplasms with perivascular epithelioid cell differentiation (PEComa)
- Intimal sarcoma



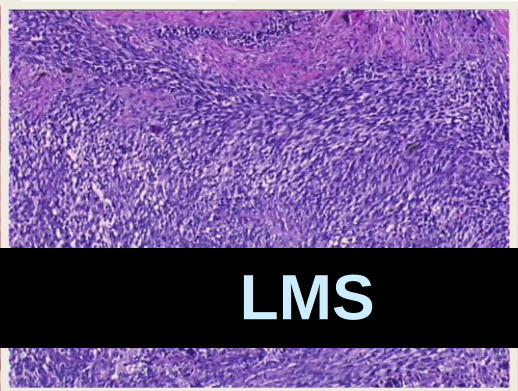
Soft Tissue Sarcomas



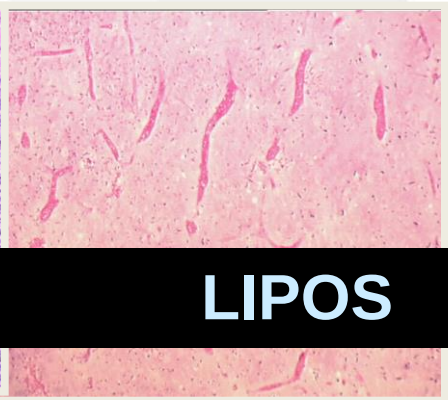
EFT



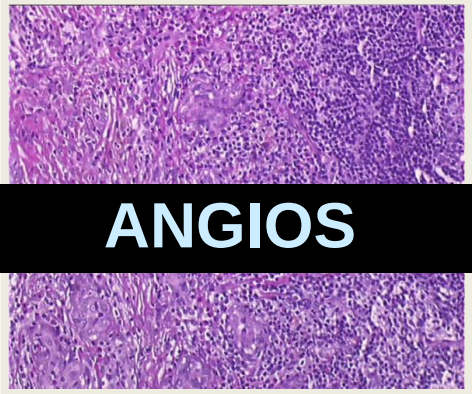
RMS



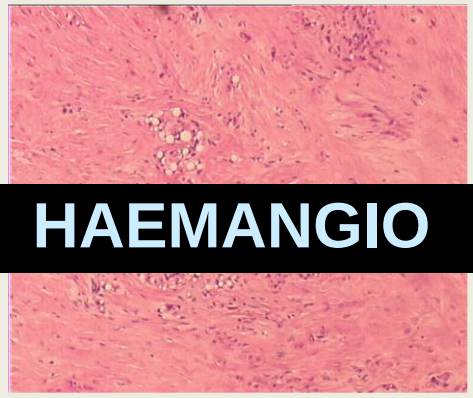
LMS



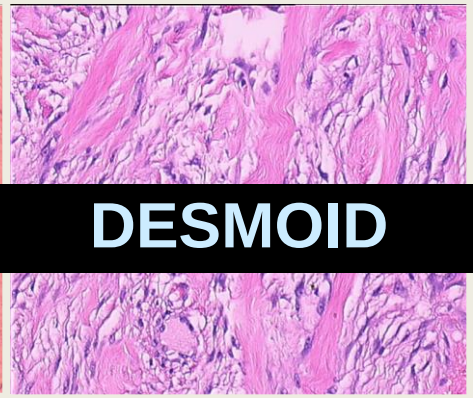
LIPOS



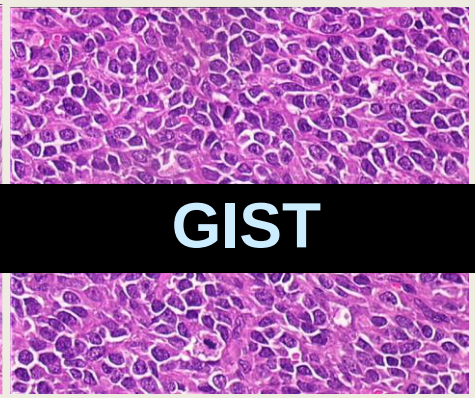
ANGIOS



HAEMANGIO



DESMOID



GIST

Connective tissue tumours

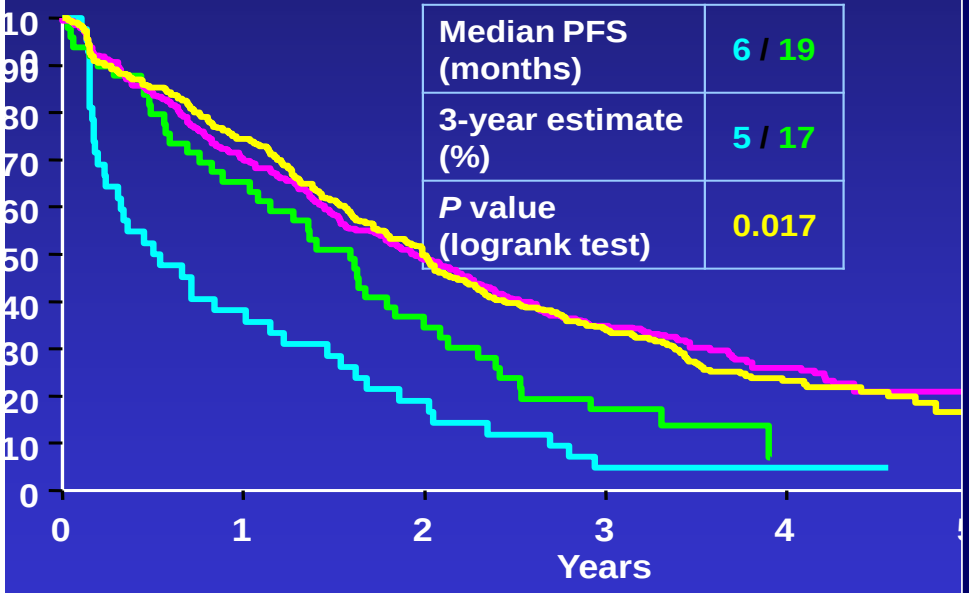
- Sarcoma with translocations ~15%
  - Ewing, DFSP, Synovial sarcomas,...
- Sarcoma with kinase mutations ~15%
  - GIST, few Angiosarcomas
- Sarcoma with tumor suppressor gene inactivation ~10%
  - MPNST NF1, Rhabdoid tumors- INI1, PEComas TSC...
- Sarcomas with chromosome 12q14-15 amplification ~15%
  - WD/DDLPS, intimal sarcomas, LG OS...
- Sarcomas with complex genetic alterations ~50%
  - Pleomorphic sarcomas, LMS, ...
- Low grade or locally agressive
  - Desmoid tumors beta catenin or APC mutation
  - Giant cell tumor of the bone ? (RANK involved)
  - Giant cell tumor of the soft part (PVNS) translocation

Fragmentation even in rare diseases

GIST are at least 10 diseases

ESMO 2012

KIT **exon 9 mutants (10% of patients)**



Median PFS (months)	6 / 19
3-year estimate (%)	5 / 17
P value (logrank test)	0.017

KIT **exon 9 mutants: 400 mg / 800 mg**
Other patients: 400 mg / 800 mg

	Dose	Adjuvant
KIT Exon 11	Im 400	+
KIT exon 9	Im 800	+
PDGFRA		
Non D842V	Im 400	+
D842V:	0	0
KIT/PDGFR WT	Im 400	+/?
NF1	?/Im 400	+/?
SDHB	?/Im 400	+/?
Raf	?	?
Pediatric	?	?

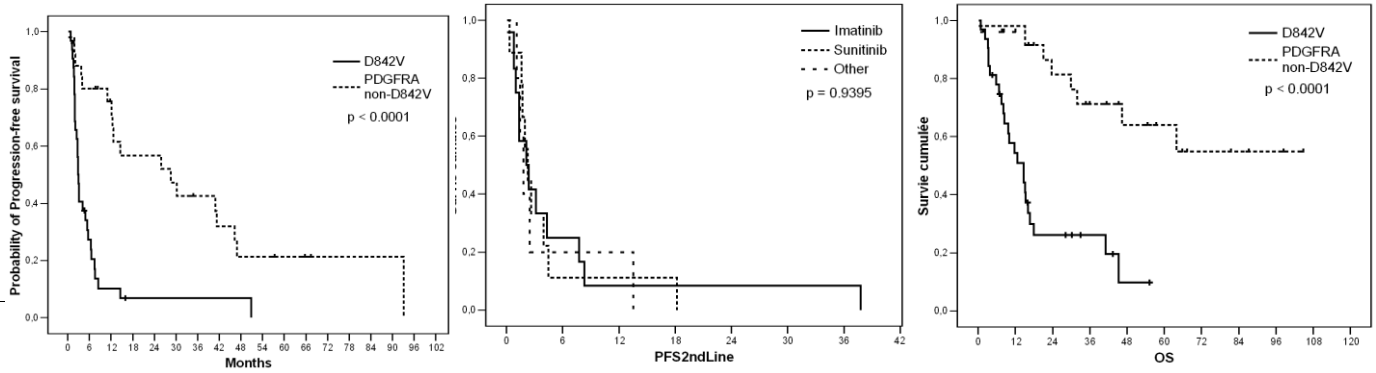
PDGFRA GIST in advanced phase

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%

Table 1: Patients' Characteristics.

Response	D842V*		Non-D842V Exon 18		Exon 12		Exon 4		Overall*	
	N	%	N	%	N	%	N	%	N	%
CR	0	0%	1	6%	1	13%	0	-	2	4%
PR	0	0%	4	24%	3	38%	1	-	8	14%
SD	10	32%	10	59%	3	38%	0	-	23	40%
PD	21	68%	2	12%	1	13%	0	-	24	42%

Table 2: response rate to imatinib per group of PDGFRA mutation and overall. (*): one patient with a D842V-mutant GIST died of gastrointestinal hemorrage before his first assessment and was therefore not evaluable for response.



P. Cassier, E Fumagalli, P Rutkowski, P Schoffski, M Van Glabbeke, M Debiec Rychter, JF Emile, F Duffaud, J Martin, B Landi, A Adenis, F Bertucci, E Bompas, S Leyvraz, I Judson, J Verweij, P Hohenberger, P Casali, JY Blay (unpublished data)

Intracellular localization of mutated & activated KIT receptors

Figure 1

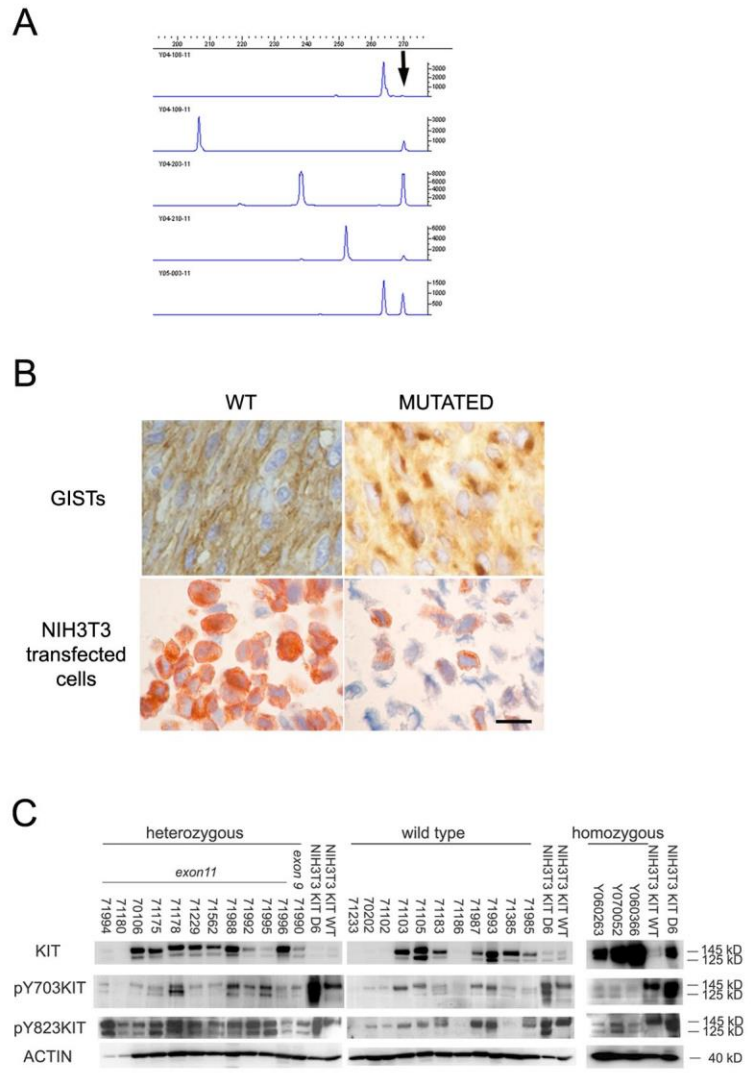
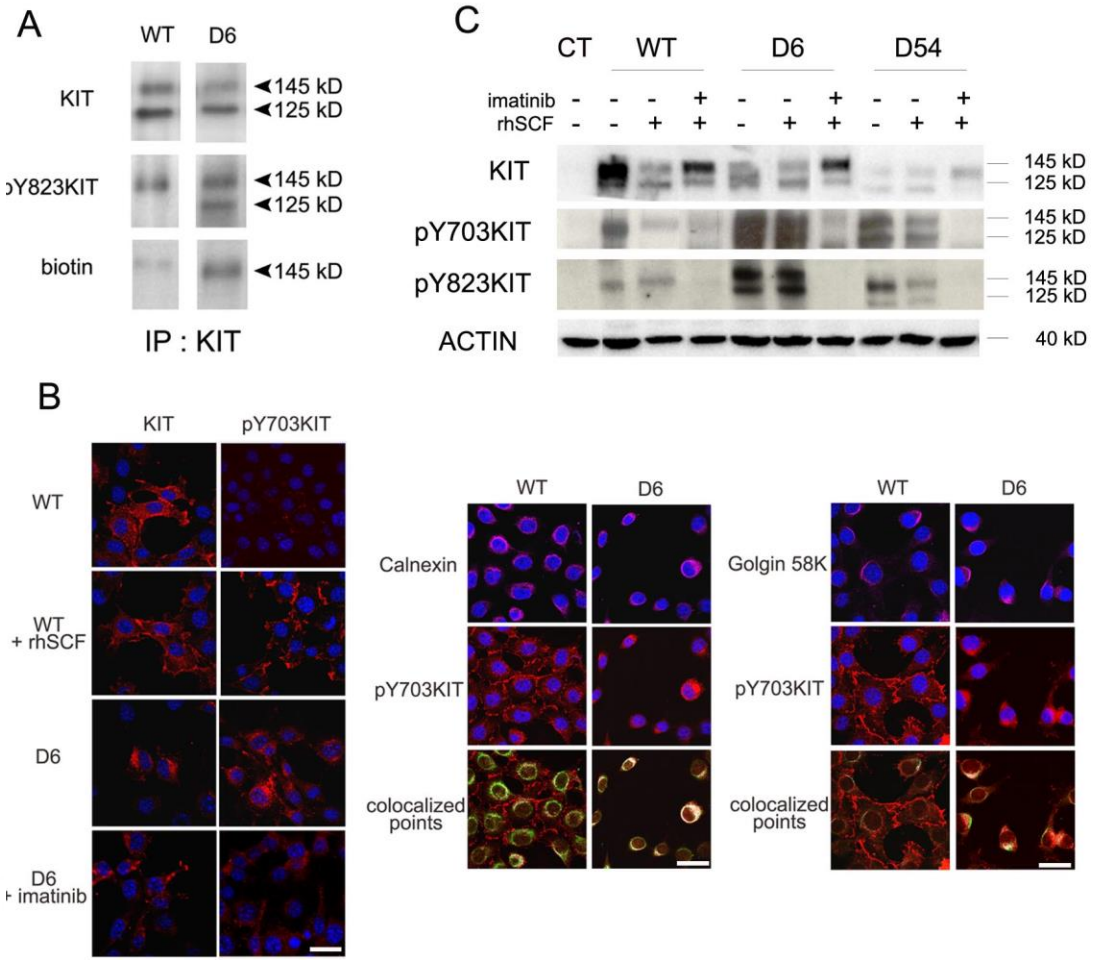


Figure 5



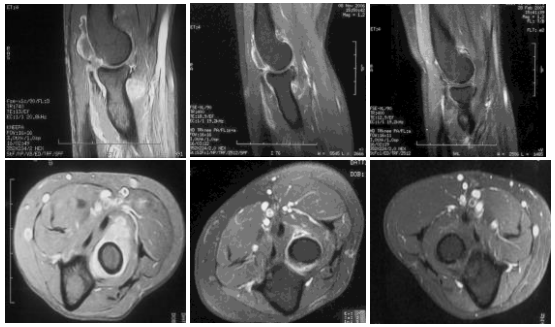
Tabone-Eglinger et al 2008

Timely proof of require international collaborations

MCSFR inhibitors in PVNS with t(1,2)

- Case report in 2008
  - (Ann Oncol 2008)
- Retrospective study 2011
  - (Cancer 2011)
- Prospective study 2012
  - (Proc ASCO 2012)

Figure: Response to imatinib in PVNS



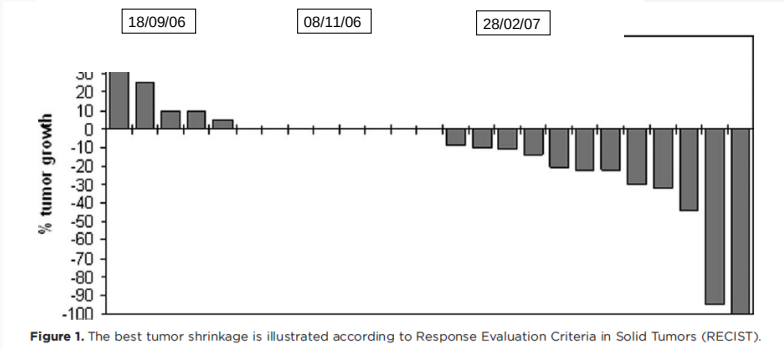
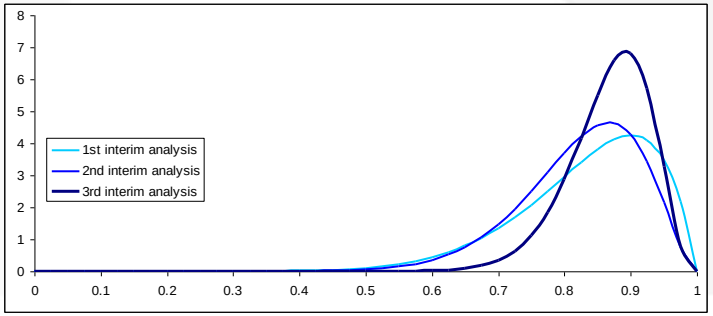
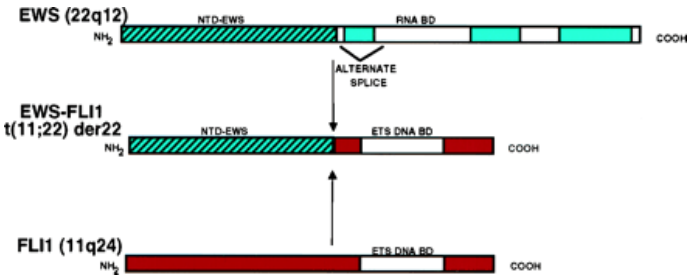


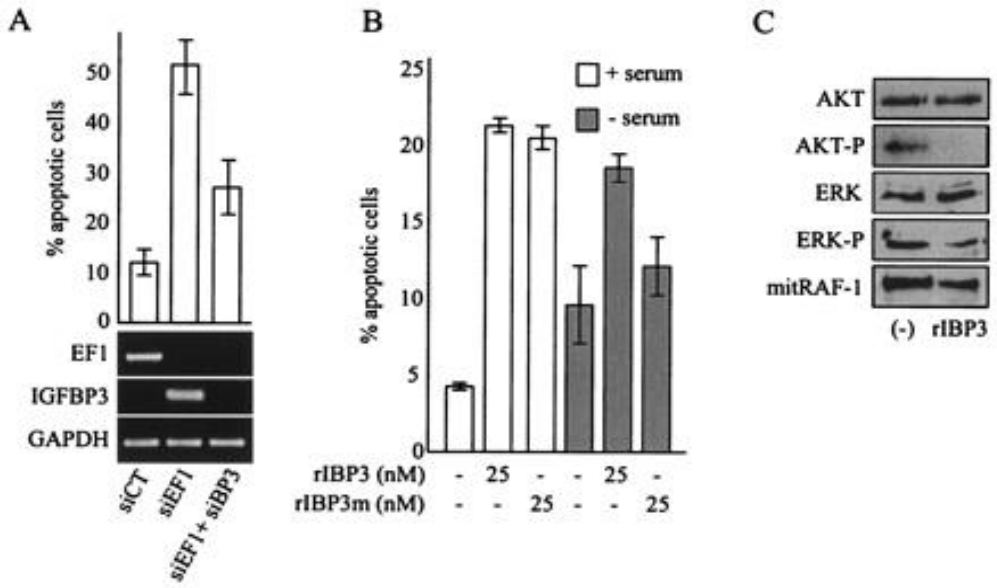
Figure 1. The best tumor shrinkage is illustrated according to Response Evaluation Criteria in Solid Tumors (RECIST).



Genomic characterisation and cellular models are required

Ewing cells depend on the IGF1 pathway

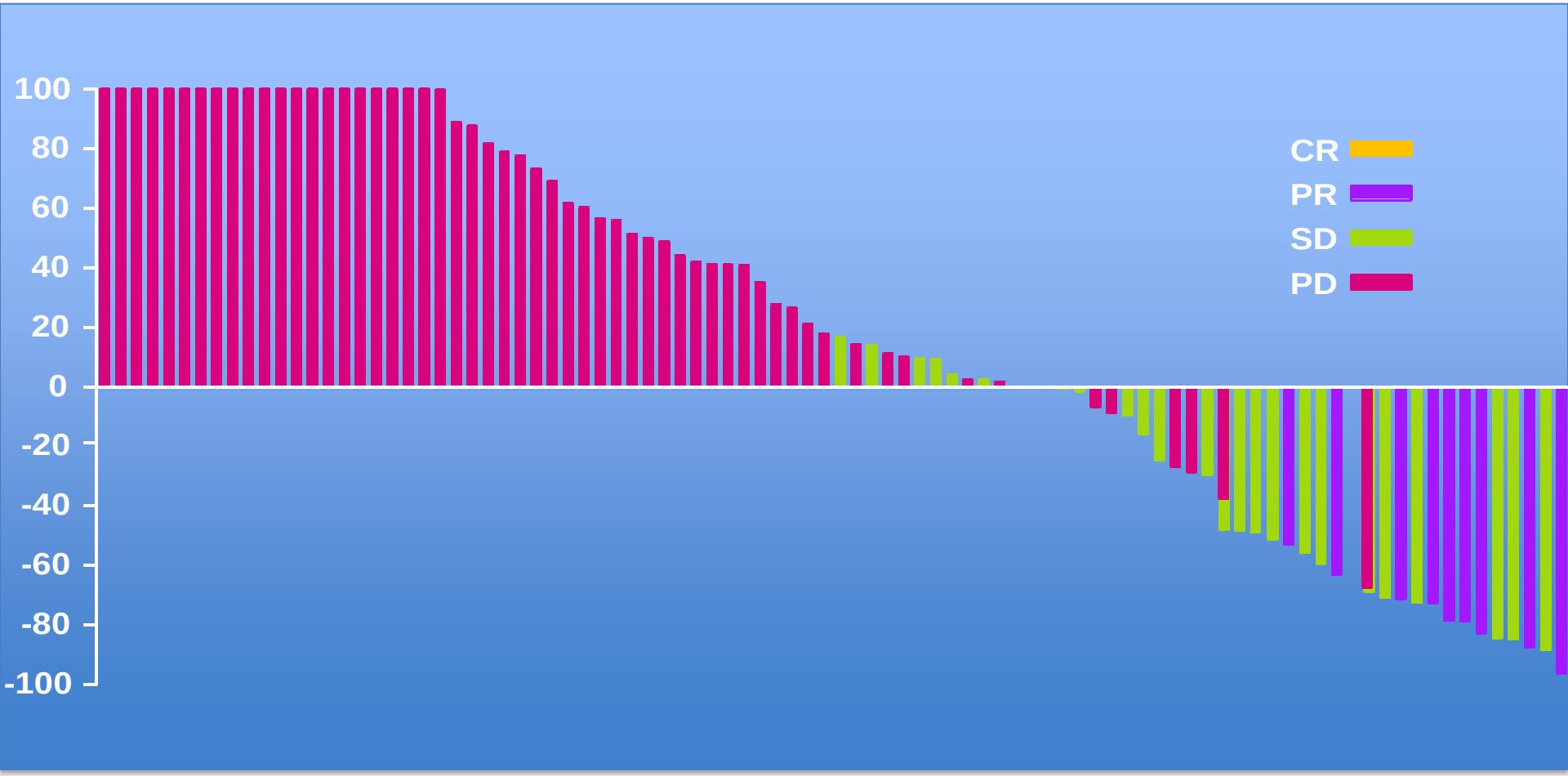




IGF1 inhibitors as potential targeted therapy in ES ?

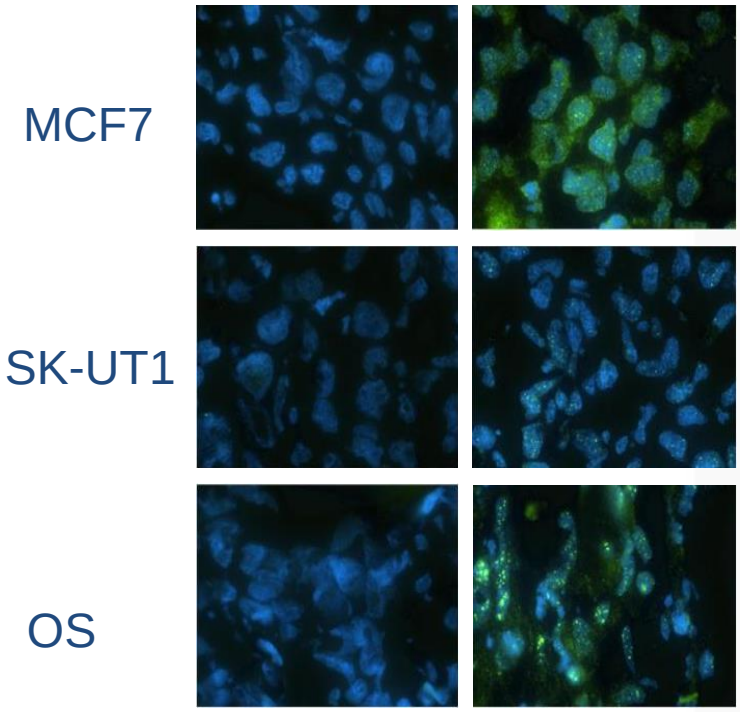
Delattre 2003, Prieur 2004

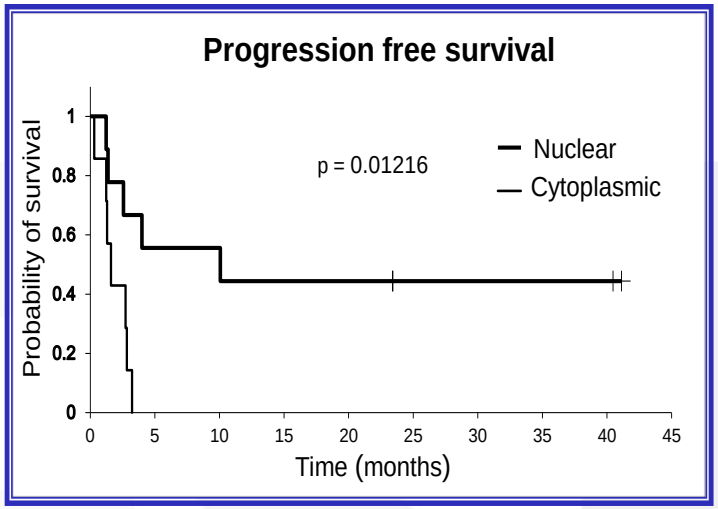
Ewing sarcoma and IGF1R Ab

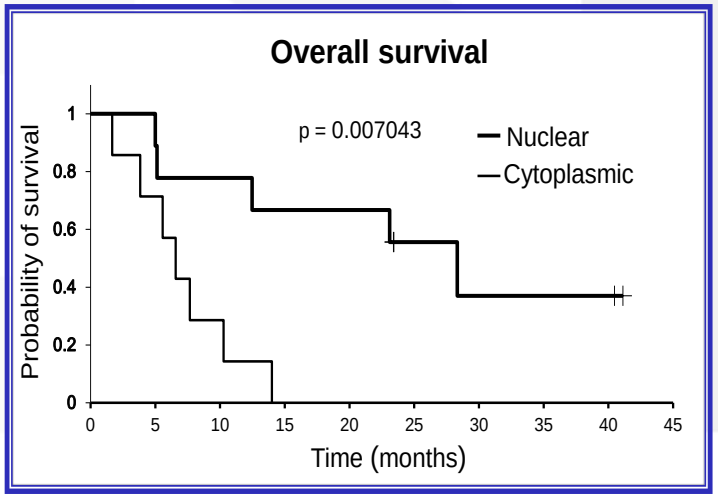


Patel 2012

Nuclear staining for IGF1R: a biomarker for response in sarcoma?

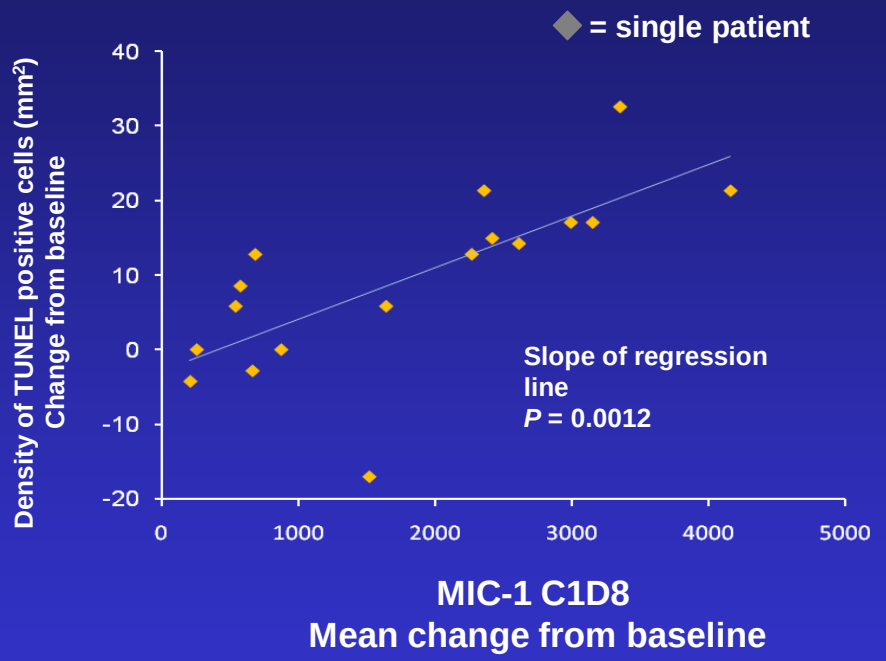






Nutlin 3a (RG7112) in Liposarcoma with MDM2 amplification

- MDM2 inhibition in human tumors activates p53, arrests cell proliferation, and induces apoptosis
- This proof of mechanism study in patients with LPS demonstrates:
  - Pharmacological p53 activation by an inhibitor of the p53-mdm2 interaction
  - Post-treatment Increases in p53, p21, and mdm2 levels
  - Exposure-related increases in MIC-1 levels
  - Post-treatment decreases proliferation as measured by change in Ki-67
  - Exposure-related induction of apoptotic signals
  - While not designed as an efficacy study, early signs of clinical activity included:
    - 1 PR after a single cycle
    - 13 SD
- This study also supports the feasibility of multiple biopsies in patients with liposarcomas eligible for surgery



Translational research in oncology research

From empiric to cosmetic to integrated translational research

The tumor cell

The surrounding cells

The patient

Lymphopenia and cancer

Lymphopenia

Survival
- Breast Ca
- Sarcoma
- NHL

Toxicity of chemotherapy

1- FN
(Blay et al JCO 1996)
- CT HR
- Lymphopenia d5 or d1

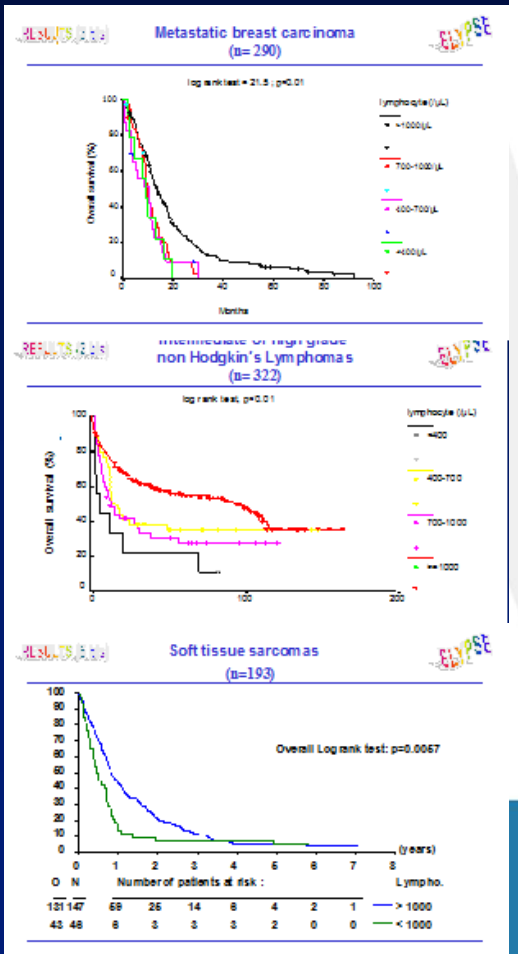
2 - Grade 4 Anemia
(Ray-Coquard et al JCO 1999)
- Hb < 12
- Lymphopenia
- PS > 1

3 - Grade 4 thrombopenia
(Ray-Coquard et al Blood 1998)
- Plt < 150
- CT HR
- PS > 1
- Lymphopenia

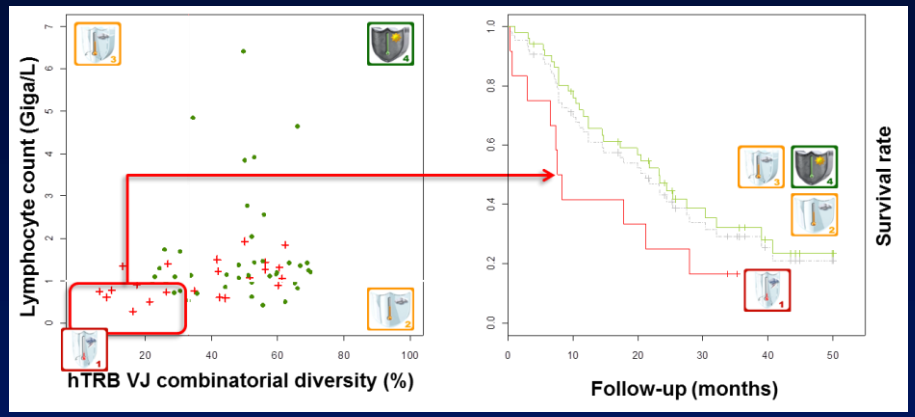
Toxic death

Death at 31 d
(Ray et al Br J Cancer 2001)
- Lymphopenia
- PS > 1

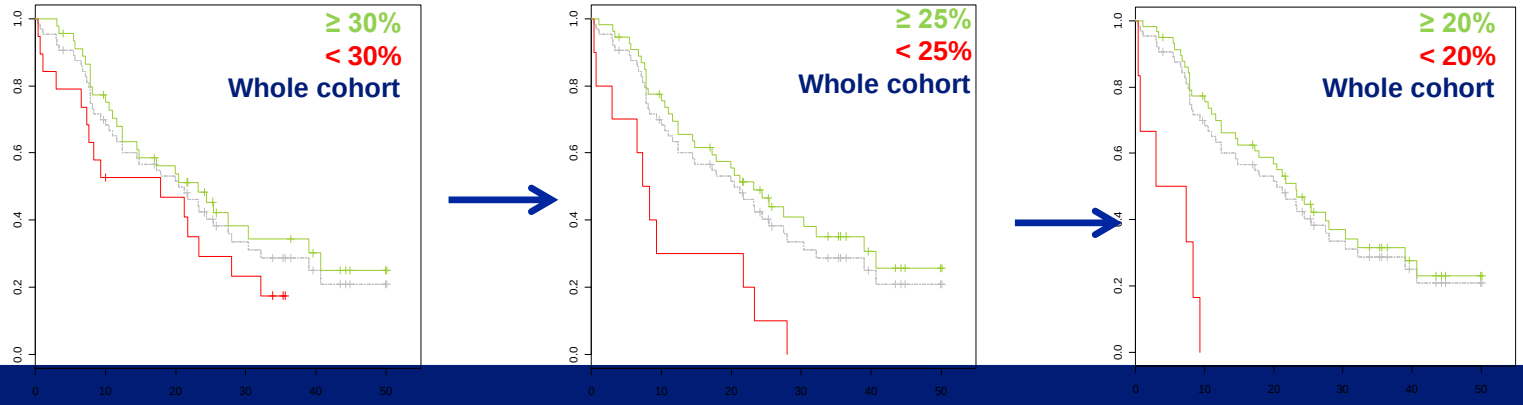
N=1997 pts
Deaths:
- 20% at 31 d
- 48% at 3 mos



Lympho-Divpenia predicts overall survival

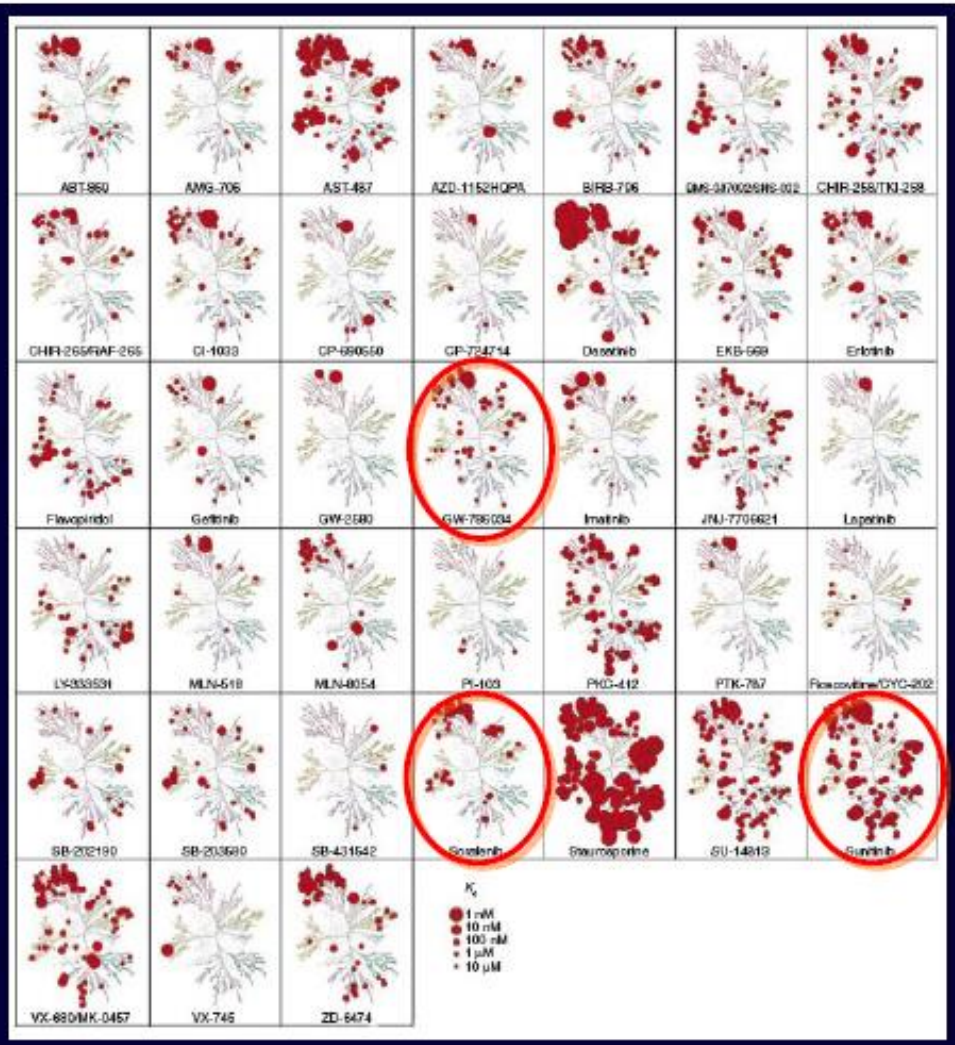


OS according to baseline diversity



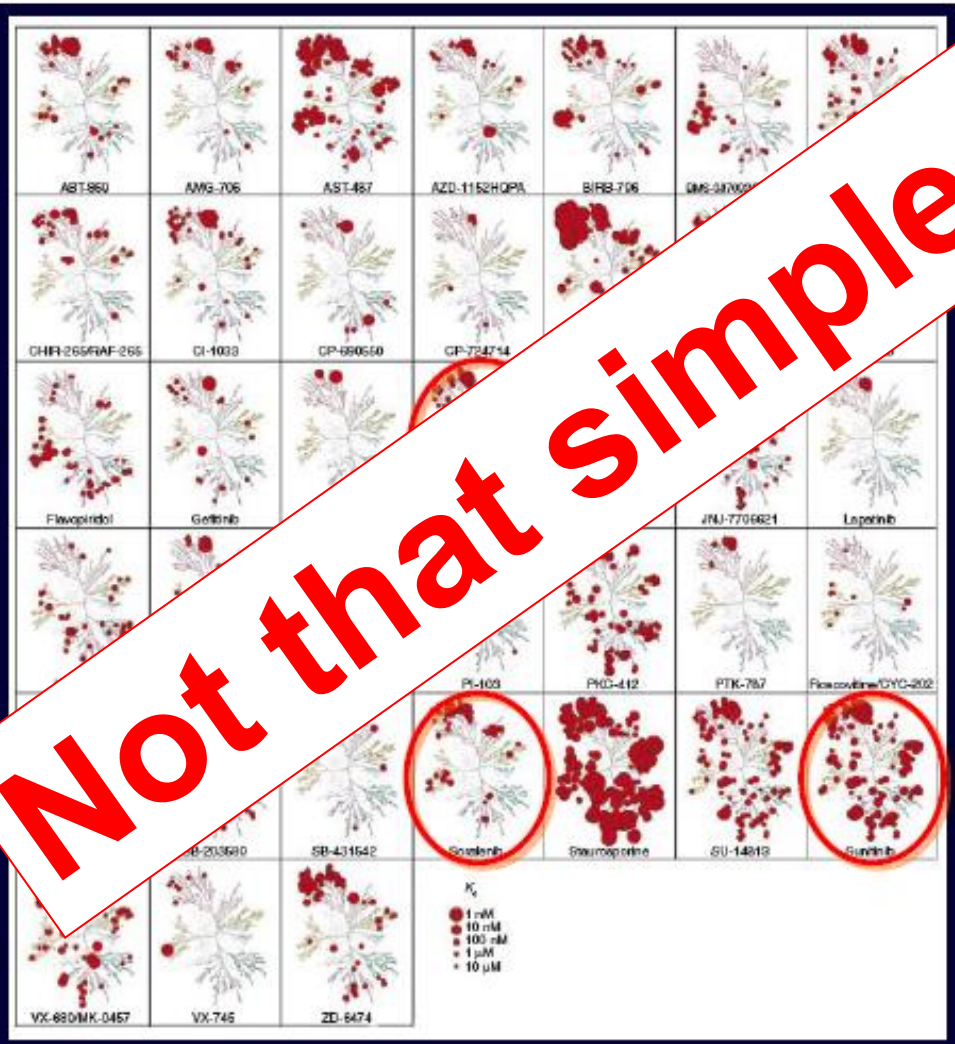
Tredan et al 2012, Manuel et al 2012

Kinase inhibitory selectivity



Karaman MW, et al.
Nature Biotech 2008

Kinase inhibitory selectivity



Not that simple

Karaman MW, et al.
Nature Biotech 2008


Clinical research
Translational research
Basic research

From empirical to rational treatment of human cancers cells and their stroma

- Genomic characterisation : opportunities and challenges
- Functional assays / in vivo models
- Fragmentation of nosological entities: lineage matters!
- The fragmented small groups of tumors are challenging for clinical research
- Novel dimensions of complexity:
    - International legal requirements
    - Health economics

Thank you

Salem Chouaib

Pierre Biron
Maud Brunat
Michel Marty
Thomas Tursz
Thierry Philip
Marie Favrot

Michel Clavel

Isabelle Ray-Coquard
Axel Le Cesne

Thomas Bachelot
Pierre Meeus
Gualter Vaz
MP Sunyach
D Ranchere
P Thiesse

Christine Caux
Christophe Caux
Laurent Alberti
Simon Baconnier
...
Alain Puisieux, Sylvie Negrier, Patrick Mehlen, M. Rousseau

Many others in the CLB & CRCL & UCC,

French Sarcoma Grp

BN Bui
JM Coindre
S. Bonvalot
N Penel
F Duffaud
F Gouin

Conticanet &
EuroboNet partners
Marta Esteban

EuroSarc partners

Netsarc partners

Many others

EORTC

F. Meunier
D. Lacombe
R. Stupp
M. Piccart

J Verweij
A van Oosterom

…

Many others

The World Sarcoma Networks: G. Demetri, P. Casali, A Gronchi, AP Dei Tos, P. Hohenberger, I Judson, V. van der Graaf, R. Maki, M. von Mehren, S.Patel, R. Benjamin,T. Nishida, D. Thomas, J. Martin, J Garcia… and many others

Thank you

Salem Chouaib

Pierre Biron
Maud Brunat
Michel Marty
Thomas Tursz
Thierry Philip
Marie Favrot

Michel Clavel

Isabelle Ray-Coquard
Axel Le Cesne

Thomas Bachelot
Pierre Meeus
Gualter Vaz

...

Alain Puisieux, Sylvie Negrier, Patrick Mehlen, M. Rousseau

Many others in the CLB & CRCL & UCC,

French Sarcoma Grp

BN Bui
JM Coindre
S. Bonvalot
N Penel

EuroSarc partners

Netsarc partners

Many others

EORTC

F. Meunier
D. Lacombe
R. Stupp
M. Piccart

J Verweij
A van Oosterom

…

Many others

ESMO

The World Sarcoma Networks: G. Demetri, P. Casali, A Gronchi, AP Dei Tos, P. Hohenberger, I Judson, V. van der Graaf, R. Maki, M. von Mehren, S.Patel, R. Benjamin, D. Thomas, J. Martin, J Garcia… and many others

Understanding the biology is as important as molecular characterisation

The examples of cytokines and growth factors

Challenges of targeted therapeutics

Ineluctable emergence of resistance?

Endless fragmentation of nosological entities.

Cells of the stroma are guilty by association and need to be treated accordingly

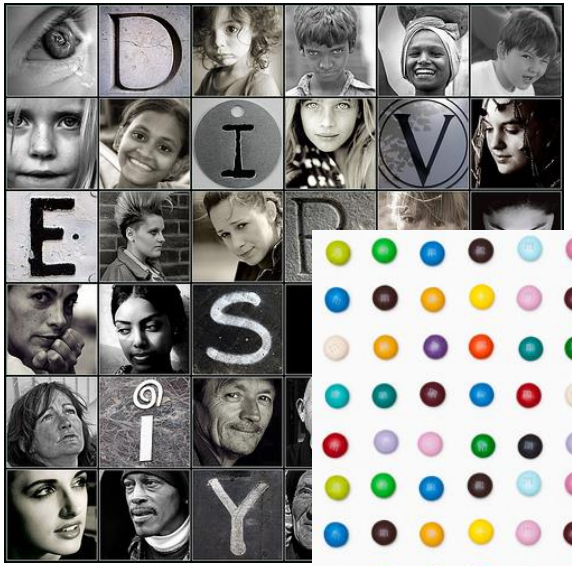
A contrasted role of the immune system

Promoting tolerance

Quantitativeluy and qualitatively altered.

Rare tumors of 2012 are models for the future rare tumors.

The fragmented small groups of tumors are challenging for clinical research


D
i
V
E
S
i
Y