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
- Sarcoma
- Melanoma
- NSCLC
- BCC, Medulloblastoma
- Breast Carcinoma
- Gastric adenocarcinoma
- Renal cell carcinoma
- ...

- CML, CMML, HES
- GIST, DFSP, PVNS, IMT, WPLPS
- KIT or BRAF mutations
- HER1 or Alk or DDR2 mutations
- Hh pathway alterations
- HER2, BRCA1
- HER2 amplification
- 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?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Targeted Mutations</th>
<th>Indicated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>KIT, PDGFR, CSF1R, +</td>
<td>GIST, MMM, ALL, Mast. CMML, HES, DFSP, others?</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Alk, Met, +</td>
<td>NSCLC, IMT, GC, others?</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>BC, GC, others?</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>HER1</td>
<td>NSCLC, others?</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>KIT, PDGFR, VEGFR, RET, +</td>
<td>RCC, NET, others?</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF</td>
<td>MMM, others?</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR</td>
<td>RCC, NET, Br. Ca, others?</td>
</tr>
</tbody>
</table>

Target the primary mutation? The disease, the driver mutation, the drug
Major successes in clinical oncology came from an in-depth understanding of the biology of the tumor.

The landscape of somatic copy-number alteration across human cancers

Rameen Beroukhim1,2,4,5*, Craig H. Mermel1,2,4,5*, Dale Porter1, Guo Wei1, Soumya Raychaudhuri1,4, Jerry Donovan6, Jordi Barretina1,2, Jesse S. Boehm1, Jennifer Dobson1,5, Mitsuyoshi Urashima1,5, Kevin T. Mc Henry1,6, Reid M. Pinchback1, Azra H. Ligon1, Yoon-Jae Cho1, Leila Haery1,2, Heidi Greulich1,4,5, Michael Reich1, Wendy Winckler1, Michael S. Lawrence1, Barbara A. Weir1,3, Kumiko E. Tanaka1,3, Derek Y. Chiang1,3,11, Adam J. Bass1,3,4, Alice Loo1, Carter Hoffman1,12, John Prensner1,13, Ted Liefeld1, Qing Gao1, Derek Yecies1, Sabina Signoretti1,14, Elizabeth Maher15, Frederic J. Kaye16, Hidefumi Sasaki1,17, Joel E. Tepper1, Jonathan A. Fletcher1, Josep Tabernero1,18, Jose Baselga1,19, Ning-Sound Tsao1,19, Francesca Demichelis1,20, Mark A. Rubin1,21, Pasi A. Jänne1,22, Mark J. Daly1,23, Carmelo Nucera1, Ross L. Levine1,24, Benjamin L. Ebert1,2,25, Stacey Gabriel1, Anil K. Rustgi26, Cristina R. Antonescu1,27, Marc Ladanyi1,28, Anthony Letai1, Levi A. Garraway1,13, Massimo Loda1,29, David G. Beer20, Lawrence D. True1,18, Aikou Okamoto1, Scott L. Pomeroy1, Samuel Singer1,2, Todd R. Golub1,3,23, Eric S. Lander1,2,25, Gad Getz1, William R. Sellers1,2 & Matthew Meyerson1,3

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
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

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Control</th>
<th>CLB-VER CM</th>
<th>IL-6 (20 ng/mL)</th>
<th>M-CSF (20 ng/mL)</th>
<th>IL-6 + M-CSF (20 ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control antibodies</td>
<td>29.7 ± 3.4</td>
<td>7.6 ± 1.4</td>
<td>12.9 ± 1.3</td>
<td>11.5 ± 1.4</td>
<td>11.9 ± 0.5</td>
</tr>
<tr>
<td>Anti-(IL-6 + IL-6R)</td>
<td>30.0 ± 2.9</td>
<td>13.0 ± 1.4</td>
<td>29.1 ± 3.0</td>
<td>17.9 ± 1.8</td>
<td>17.7 ± 3.0</td>
</tr>
<tr>
<td>Anti-M-CSF</td>
<td>29.6 ± 1.8</td>
<td>19.2 ± 3.4</td>
<td>15.7 ± 2.0</td>
<td>27.0 ± 2.4</td>
<td>14.8 ± 1.3</td>
</tr>
<tr>
<td>Anti-(IL-6 + IL-6R) + anti-M-CSF</td>
<td>29.9 ± 1.3</td>
<td>25.5 ± 1.5</td>
<td>32.1 ± 3.4</td>
<td>27.4 ± 1.1</td>
<td>25.0 ± 2.6</td>
</tr>
<tr>
<td>Anti-VEGF</td>
<td>30.5 ± 1.8</td>
<td>7.7 ± 0.9</td>
<td>13.1 ± 1.1</td>
<td>11.3 ± 0.7</td>
<td>12.3 ± 1.5</td>
</tr>
</tbody>
</table>

Correlation Between Cytokine Levels in CM and Blockade of DC Differentiation

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IL-6 pg/mL/h</th>
<th>M-CSF pg/mL/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLB-CA</td>
<td>165 ± 24</td>
<td>109 ± 50</td>
</tr>
<tr>
<td>CLB-ES</td>
<td>&lt;15</td>
<td>225 ± 31</td>
</tr>
<tr>
<td>SKNF1</td>
<td>&lt;15</td>
<td>152 ± 32</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAUDI</td>
<td>&lt;15</td>
<td>&lt;3.9</td>
</tr>
<tr>
<td>RAJI</td>
<td>&lt;15</td>
<td>&lt;3.9</td>
</tr>
<tr>
<td>BJAB</td>
<td>&lt;15</td>
<td>&lt;3.9</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLB-SA</td>
<td>&lt;15</td>
<td>130 ± 21</td>
</tr>
<tr>
<td>MCF-7</td>
<td>&lt;15</td>
<td>268 ± 44</td>
</tr>
<tr>
<td>T47-D</td>
<td>&lt;15</td>
<td>330 ± 36</td>
</tr>
<tr>
<td>Small cell lung carcinoma</td>
<td>&lt;15</td>
<td>&lt;3.9</td>
</tr>
<tr>
<td>H-322</td>
<td>&lt;15</td>
<td>&lt;3.9</td>
</tr>
<tr>
<td>Coltan carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW-620</td>
<td>&lt;15</td>
<td>&lt;3.9</td>
</tr>
</tbody>
</table>

Inhibitory

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IL-6 pg/mL/h</th>
<th>M-CSF pg/mL/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM-22</td>
<td>&lt;15</td>
<td>322 ± 30</td>
</tr>
<tr>
<td>SHEP</td>
<td>4,035 ± 505</td>
<td>2,150 ± 250</td>
</tr>
<tr>
<td>SKNAS</td>
<td>275 ± 10</td>
<td>1,632 ± 280</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLB-DOR</td>
<td>391 ± 39</td>
<td>4,170 ± 348</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLB-VER</td>
<td>459 ± 67</td>
<td>3,190 ± 310</td>
</tr>
<tr>
<td>CLB-CHA</td>
<td>730 ± 46</td>
<td>8,530 ± 493</td>
</tr>
<tr>
<td>CLB-Glu</td>
<td>&lt;15</td>
<td>1,490 ± 231</td>
</tr>
<tr>
<td>CLB-GDU</td>
<td>68,600 ± 1,430</td>
<td>14,990 ± 626</td>
</tr>
<tr>
<td>CLB-DTE</td>
<td>68,400 ± 1,057</td>
<td>4,330 ± 353</td>
</tr>
<tr>
<td>CLB-TUT</td>
<td>60,800 ± 948</td>
<td>2,613 ± 125</td>
</tr>
<tr>
<td>CLB-TUG</td>
<td>420 ± 31</td>
<td>763 ± 37</td>
</tr>
<tr>
<td>CAK-1</td>
<td>2,010 ± 370</td>
<td>9,780 ± 512</td>
</tr>
<tr>
<td>CAK-2</td>
<td>3,560 ± 426</td>
<td>6,500 ± 731</td>
</tr>
<tr>
<td>Coltan carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT-29</td>
<td>439 ± 59</td>
<td>&lt;3.9</td>
</tr>
</tbody>
</table>
Mechanisms of response to IL-2 in RCC

Intracrine, paracrine, endocrine roles of IL-6

Endocrine
Paracrine
Autocrine
Intracrine
Mechanisms of response to IL-2 in RCC

Intracrine, paracrine, endocrine roles of IL-6

**A.**

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

**B.**

Comparison of partial sequence of spliced IL-6 mRNA in PBMC (clone SS-1)\(^4\), in RCC cell line (tIL-6) and IL-6 mRNA.

**C.**

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 Blay1,2

1Équipe Cytokine et Cancer, Unité Institut National de la Santé et de la Recherche Médicale, Centre Léon Bérard, Lyon, France, and 2Hôpital Edouard Herriot, Place d’Armes, Lyon, France

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

Alignment sequence of spliced IL-6 mRNA in RCC cell line (tLL-6) and IL-6 mRNA.
Mechanisms of response to IL-2 in RCC

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

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

Endocrine
Paracrine
Autocrine
Intracrine
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

Interleukin (IL)-10 and IL-6 Are Produced in Vivo by Non-Hodgkin's Lymphoma Cells and Act as Cooperative Growth Factors
Nathalie Voorzanger, Robert Touitou, Eric Garcia, Henry-Jacques Delecluse, Françoise Roussel, Irène Jaub, Marie C. Favrot, 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


BMC Cancer
Research article
CD40L induces multidrug resistance to apoptosis in breast carcinoma and lymphoma cells through caspase independent and dependent pathways
Nathalie Voorzanger-Rousselot, Laurent Alberti and Jean-Yves Blay

ESMO
What is a good target?

- Expression
- Expression + activation
- Expression + activation + mechanism
- Expression + activation + mechanism + drug

- Possible target
- Promising target
- A major target
- Clinical trial
The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity

Jordi Barrede1,2,3,*, Giordano Casponigro1, Nicolas Stransky1, Kavitha Venkatesan2, Adam A. Margolin1,*, Sungjoon Kim5, Christopher J. Wilson5, Joseph Lehar5, Gregory V. Kryukov1, Dmitriy Sonkin2, Anupama Reddy3, Manway Liu2, Lauren Murray4, Michael F. Berger2, John E. Monahan3, Paula Morin5, Jodi Meltzer5, Adam Korejwa1, Judit Jäné-Valbuena2,2, Felipa A. Mapa3, Joseph Thibault2, Eva Bric-Furlong2, Pichai Raman5, Aaron Shipway5, Ingo H. Engels2, Jill Cheng2, Guoying K. Yu6, Jianjun Yu6, Peter Aspesi Jr4, Melanie de Silva1, Kalpana Jagtap4, Michael D. Jones4, Li Wang5, Charles Hatton2, Emanuele Palecandolo3, Supriya Gupta1, Scott Mahan1, Carrie Sougne2, Robert C. Onofrio5, Ted Liefeld1, Laura MacConaill1, Wendy Winniker1, Michael Reich1, Nanzin Li5, Jill P. Mesirov4, Stacey B. Gabriel1, Gad Getz1, Kristin Ardeh1, Vivien Chan6, Vic E. Myers4, Barbara L. Weber4, Jeff Porter4, Markus Warmuth5, Peter Finan4, Jennifer L. Harris5, Matthew Meyerson5,2,3, Todd R. Golub1,2,7,8, Michael P. Morrissey4, William R. Sellers4, Robert Schlegel4, & Levi A. Garraway1,2,3,*

Lineage
Gene expression
Biomarkers shared across lineages
Towards a major fragmentation of nosological entities

Damien Hirst
« 1-bromoadamantane »
« Acivicin »
« Arginosuccinic acid »
## Adipocytic Tumours
- Well differentiated / 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

### Fragmentation
- >50 different histotypes AND molecular subtypes
- 2013 classification

**Even for rare tumors...**
Soft Tissue Sarcomas

<table>
<thead>
<tr>
<th>EFT</th>
<th>RMS</th>
<th>LMS</th>
<th>LIPOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANGIOS</td>
<td>HAEMANGIO</td>
<td>DESMOID</td>
<td>GIST</td>
</tr>
</tbody>
</table>
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 aggressive
  - 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**

- **KIT exon 9 mutants (10% of patients)**
  - Median PFS (months): 6 / 19
  - 3-year estimate (%): 5 / 17
  - P value (logrank test): 0.017

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

- **KIT exon 9 mutants:** 400 mg / 800 mg
- **Other patients:** 400 mg / 800 mg
Table 1: Patients’ Characteristics.

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

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

<table>
<thead>
<tr>
<th>Response</th>
<th>D842V*</th>
<th>Non-D842V</th>
<th>Exon 18</th>
<th>Exon 12</th>
<th>Exon 4</th>
<th>Overall*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>6%</td>
<td>1</td>
<td>13%</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0%</td>
<td>4</td>
<td>24%</td>
<td>3</td>
<td>38%</td>
</tr>
<tr>
<td>SD</td>
<td>10</td>
<td>32%</td>
<td>10</td>
<td>59%</td>
<td>3</td>
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<td>PD</td>
<td>21</td>
<td>68%</td>
<td>2</td>
<td>12%</td>
<td>1</td>
<td>13%</td>
</tr>
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</table>

Intracellular localization of mutated & activated KIT receptors

Figure 1

A

B

WT MUTATED

NIH3T3 transfected cells

Figure 5

A

WT D6

KIT 145 kD 125 kD

Y823KIT 145 kD 125 kD

biotin 145 kD

IP : KIT

B

WT p703KIT

WT + rhSCF

p703KIT

C

heterozygous wild type homozygous

KIT p703KIT pY823KIT ACTIN

D6 imatinib

colocalized points

colocalized points

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)
Genomic characterisation and cellular models are required
Ewing cells depend on the IGF1 pathway

IGF1 inhibitors as potential targeted therapy in ES?
Ewing sarcoma and IGF1R Ab

Patel 2012
Nuclear staining for IGF1R: a biomarker for response in sarcoma?

MCF7

SK-UT1

OS

Isotype

IGF-1R

Progression free survival

Overall survival

Probability of survival

Time (months)

p = 0.01216

p = 0.007043

Asmane I, Blay JY, AACR 2012
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

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

Survival
- Breast Ca
- Sarcoma
- NHL

Survival
-Breast Ca
-Sarcoma
-NHL

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

2 - Grade 4 Anemia
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- Hb < 12
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- Plt < 150
- CT HR
- PS > 1
- Lymphopenia

Deaths:
- 20% at 31 d
- 48% at 3 mos
Lympho-Divpenia predicts overall survival

Tredan et al 2012, Manuel et al 2012

Follow-up (months)

Survival rate

≥ 30% < 30%
Whole cohort

≥ 25% < 25%
Whole cohort

≥ 20% < 20%
Whole cohort

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
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

<table>
<thead>
<tr>
<th>Salem Chouaib</th>
<th>Isabelle Ray-Coquard</th>
<th>French Sarcoma Grp</th>
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<td>Pierre Biron</td>
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<td>CLB &amp; CRCL &amp; UCC,</td>
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...
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

Quantitatively 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.