Cancers bronchiques :
La personnalisation jusqu’où ?

Cours du GOLF
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INSERM U911
Marseille - France
I provided consultations for Astra-Zeneca, Bristol-Myers Squibb, Boehringer–Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre and Pfizer.
Préambule

• Médecine
  – Personnalisée
  – Individualisée

• Médecine de précision
Une question ancienne

In his book "Mounts and Medicine," Joseph Fletcher describes medicine as a "human art for human beings," and says that just as human beings increase in wisdom and stature, so must the ethics of medical care change, grow and engage in self-correction.

Without commenting on man's growth for the better, I feel it is true that few of us can remain indifferent to the climate of change around us. What future is there for family practice, and in particular, what future is there for solo practice? Is solo practice dying of innovation? Is it something that already belongs to the past? Or will it remain, like the horse and buggy doctor who typified it, into the mists of antiquity, lanterned only by rising in public esteem for their unique qualities of personal care?

We live in times of great change and it would probably be truer to say that within the span of a single lifetime, medicine has left a civilization behind it. Certainly within my medical lifetime, the advances in the science — as opposed to the art — of medicine, have been astounding. Looking back at

Can Personalized Medicine Survive?

by W.M. Gibson, MB, ChB

that our profession, especially that part of it engaged in family practice, is going through a period of evaluation not only of its ethics, but of its methods of practice. Those we serve, our patients, take a considerable interest in our doings, and we can rely on the politicians to keep them well-informed, so the sentimental few? Or will the solo practitioner's demise be welcomed, his replacement being a battery of experts in the fields of medicine, surgery, psychiatry and all the new clinical sciences? Is it not the case that we are being trained than their singleness of practice? Or will solo and family practice go from strength to strength, some of those changes over 30 years of practice helps me to predict a future for medicine. Naturally, I hope that we will retain the good, discard the bad, after an objective deliberation and analysis of our modern role as scientist-physician.

However, the essence of survived, it has been said, is adaptability, and on
Agenda

• Pharmaco-génomique
• Pharmaco-cinétique
• Pharmaco-génétique
• Perspectives
Mean number of genetic alteration / tumor

Alexandrov L, Nature 2013
Objectif de la cancérologie moderne

Caractéristique(s) génétique(s) commune(s) = traitement commun ?
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.
Examples of EU’s LC genotyping programs

- Stratified Medicine Program
- Institutions-based
- Institutions-based
- Institutions-based
Un profil moléculaire ... pour tous

- 28 platforms (2006)
- 10 biomarqueurs de routine (+ 6 émergents)

* i.e. Regional molecular genetics centers

Tableau 1. Nombre de recherches de marqueurs prédictifs de la réponse à une thérapie ciblée en 2013

<table>
<thead>
<tr>
<th>Pathologie</th>
<th>Biomarqueur</th>
<th>Nombre de tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer du sein</td>
<td>Amplification d'HER2</td>
<td>8 924</td>
</tr>
<tr>
<td>Cancer de l'estomac</td>
<td>Amplification d'HER2</td>
<td>709</td>
</tr>
<tr>
<td>Cancer colorectal</td>
<td>Mutations de KRAS</td>
<td>19 347</td>
</tr>
<tr>
<td></td>
<td>Mutations de NRAS</td>
<td>3 330</td>
</tr>
<tr>
<td>GIST</td>
<td>Mutations de KIT</td>
<td>1 105</td>
</tr>
<tr>
<td></td>
<td>Mutations de PDGFRA</td>
<td>1 005</td>
</tr>
<tr>
<td>Cancer du poumon</td>
<td>Mutations d'EGFR</td>
<td>23 336</td>
</tr>
<tr>
<td></td>
<td>Translocation d'ALK</td>
<td>18 861</td>
</tr>
<tr>
<td>Mélanome</td>
<td>Mutation de BRAF-V600</td>
<td>5 026</td>
</tr>
<tr>
<td>Leucémies</td>
<td>Détectio de BCR-ABL</td>
<td>6 750</td>
</tr>
<tr>
<td></td>
<td>Mutations d'ABL</td>
<td>861</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>89 254</strong></td>
</tr>
</tbody>
</table>

Available at www.ecancer.fr

Multidisciplinary Oncology & Therapeutic Innovations
INSERM U911 – CRO2
Marseille - France
Profil moléculaire et C. du poumon (2015)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Molecular Target</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Programme INCa</td>
<td></td>
</tr>
<tr>
<td>Non-sq NSCLC</td>
<td>EGFR mutations (activating and resistant)</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;G: EGFR-TKIs&lt;br&gt;3&lt;sup&gt;rd&lt;/sup&gt;G: AZD9291, CO1686 (ATU) &amp; trials</td>
</tr>
<tr>
<td></td>
<td>EML4-ALK transloc.</td>
<td>Crizotinib&lt;br&gt;Ceritinib (ATU), Clinical Trials</td>
</tr>
<tr>
<td></td>
<td>ROS1 rearrangement</td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td>KRAS mutations</td>
<td>Clinical trials</td>
</tr>
<tr>
<td></td>
<td>HER2 ex20 mutations</td>
<td>HER2 inhib, Clinical trials</td>
</tr>
<tr>
<td></td>
<td>BRAF mutations</td>
<td>Vemurafenib (Acsé), Clin. trials</td>
</tr>
<tr>
<td></td>
<td>MET mutations/amplification</td>
<td>Crizotinib, Clinical trials</td>
</tr>
</tbody>
</table>

Available at www.ecancer.fr
Biomarkers France

Molecular analyses sent to the database
N=19,386
- Excluded, n=525
  - Out of recruitment time, n=403
  - Other than NSCLC, n=103
  - Other, n=19

Molecular analyses available
N=18,861
- Treating physician missing, n=182

Molecular analyses considered
N=18,679
- With data available for:
  - Delays for analyses: 18,679
  - EGFR, n=17,706
  - KRAS, n=17,001
  - BRAF, n=13,906
  - HER2, n=11,723
  - PI3K, n=10,678
  - ALK, n=8,134

Corresponding patients
N=17,664
- With data available for:
  - Age, n=17,664
  - Sex, n=17,555
  - Ethnicity, n=7,350
  - Smoking history, n=8,619
  - ECOG PS, n=7,817
  - Previous familial cancer, n=7,848
  - TNM stage, n=8,637
  - Histology, n=17,664
  - Modality of diagnosis, n=17,664
  - Number samples/patient, n=17,664

Biomarkers France


HR 0.77 (0.70-0.86)
La précision jusqu’où ?

http://www.phgfoundation.org
**Sampling?**

- **Daily practice – Lung Cancers (2013)**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Number of tests</th>
<th>Non interpretable (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mut</td>
<td>23,386</td>
<td>8.0</td>
</tr>
<tr>
<td>ALK rearrang*</td>
<td>18,861</td>
<td>13.4</td>
</tr>
<tr>
<td>KRAS mut</td>
<td>22,958</td>
<td>7.9</td>
</tr>
<tr>
<td>BRAF mut</td>
<td>20,100</td>
<td>8.9</td>
</tr>
<tr>
<td>HER2 mut</td>
<td>17,843</td>
<td>10.1</td>
</tr>
<tr>
<td>PI3K mut</td>
<td>17,375</td>
<td>10.4</td>
</tr>
</tbody>
</table>

*, mainly assessed by FISH only at this time (2013)
EGFR TKI (1G) acquired resistance

Cortot A & Janne PA, Eur Respir Rev 2014;
Janne P et al, NEJM 2015
Sampling?

Antoine Hollebecque et al, EORTC NCI AACR 2013; Douillard JY et al, J Thorac Oncol 2014
Diagnostic sur ADN circulant

Patiente 76 ans, ATCD vasculaire cérébral
Etat général dégradé (PS 4), pas d’examen invasif possible
ADN circulant: mutation EGFR del 19

Tomasini et al, submitted
Profil moléculaire et C. du poumon: résultats

Molecular profiling of cancer

Non-Squamous NSCLC (n=4244)

- KRAS 25%
- wt 37%
- EGFR 13%
- Other (RET, FGFR1, MET) 4%

Squamous NSCLC (n=1498)

- wt 68%
- Other (HER-2, HRAS, RET, ALK, NRAS) 1%
- KRAS 2%
- MET 2%
- PIK3CA 4%
- DDR2 2%
- FGFR1 10%

SCLC (n=468)

- wt 94%
- FGFR1 6%

Kostenko A et al. - ESMO® 2015 – Abs.
High throughput molecular genotyping

Images: CGH and NGS analyses from the SAFIR lung Unicancer IFCT trial
PIs: JC Soria / F Barlesi
How large should be the analysis?

Ferte C et al, AACR 2014
How deep should be the analysis?

Yu HA et al, Ann Oncol 2014

<table>
<thead>
<tr>
<th>Paper</th>
<th>Method</th>
<th>Baseline EGFR T790M Among EGFR+</th>
<th>Baseline EGFR T790M Among NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al. 2013</td>
<td>Mass spectrometry (MALDI-TOF)</td>
<td>11/579 (2%)</td>
<td>11/2274 (0.5%)</td>
</tr>
<tr>
<td>Maheswaran et al. [18]</td>
<td>Mutant-enriched PCR (SAXSIS)</td>
<td>10/26 (38%)</td>
<td></td>
</tr>
<tr>
<td>Rosell et al. [13]</td>
<td>Mutant-enriched PCR (TaqMan)</td>
<td>45/129 (35%)</td>
<td>45 T790M+/129 with tissue for EGFR T790M NSCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30/78 (38%)</td>
<td>for EGFR T790M NSCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Independent cohort</td>
<td></td>
</tr>
<tr>
<td>Su et al. [11]</td>
<td>Direct sequencing</td>
<td>3/40 (8%)</td>
<td>45 T790M+/129 with tissue for EGFR T790M testing/2105 NSCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/107 (3%)</td>
<td></td>
</tr>
<tr>
<td>Pujana et al. [12]</td>
<td>Mass spectrometry (MALDI-TOF)</td>
<td>15/48 (31%)</td>
<td>15/48 (31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27/107 (25%)</td>
<td></td>
</tr>
<tr>
<td>Imokai et al. [9]</td>
<td>Mutant-enriched PCR (SAXSIS)</td>
<td>30/38 (79%)</td>
<td>30/38 (79%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10/280 (4%)</td>
<td></td>
</tr>
<tr>
<td>Sequist et al. [16]</td>
<td>Direct sequencing</td>
<td>2/34 (6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/98 (2%)</td>
<td></td>
</tr>
<tr>
<td>Wu et al. [10]</td>
<td>Direct sequencing</td>
<td>6/8 (71%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6/1261 (0.45%)</td>
<td></td>
</tr>
<tr>
<td>EGFR+, EGFR mutant NSCLC; non-small cell lung cancer; TKI, tyrosine kinase inhibitor; RR, response rate; WGT, whole genome testing</td>
<td>15/48 (31%)</td>
<td>27/107 (25%)</td>
<td></td>
</tr>
</tbody>
</table>
How deep should be the analysis?

PFS of EGFRmut patients w de novo T790M mutation by **standard sequencing** (1.5 months)

PFS of EGFRmut patients w de novo T790M mutation by **highly sensitive technics** (6.7 months)

*Yu HA et al, Ann Oncol 2014; Su KY et al, J Clin Oncol 2012*
**PD-L1 expression (example)**

PD-L1 prevalence determined with a Genentech/Roche anti-PD-L1 IHC assay

<table>
<thead>
<tr>
<th>Indication</th>
<th>n</th>
<th>Percentage of PD-L1 positive (IC)</th>
<th>Percentage of PD-L1 positive (TC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>184</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>RCC</td>
<td>88</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Melanoma</td>
<td>58</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>HNSCC</td>
<td>101</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>141</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>CRC</td>
<td>77</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>83</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

Herbst R et al, Nature 2015
## PD-L1 expression (heterogeneity)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker antibody</th>
<th>Rx line</th>
<th>Definition of ‘Positive’ #</th>
<th>N Positive %</th>
<th>Positive Predictive outcome</th>
<th>ORR % IHC pos cases</th>
<th>ORR % IHC neg cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Dako 28-8</td>
<td>1st</td>
<td>≥5% in &gt;100 cells</td>
<td>59%</td>
<td>Yes</td>
<td>31%*</td>
<td>10%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Dako 28-8</td>
<td>≥2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>≥5%</td>
<td>49%</td>
<td>No</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥1%</td>
<td>56%</td>
<td></td>
<td>13%</td>
<td>17%</td>
</tr>
<tr>
<td>Nivolumab + Ipilimumab</td>
<td>Dako 28-8</td>
<td>1st</td>
<td>≥5% in &gt;100 cells</td>
<td>42%</td>
<td>No</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Dako 28-8</td>
<td>≥2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>≥5%</td>
<td>33%##</td>
<td>Yes</td>
<td>24%</td>
<td>14%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>5H1 **</td>
<td>≥2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>≥5% Also studied TIICs</td>
<td>67%</td>
<td>Yes</td>
<td>No data For lung</td>
<td>No data For lung</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Dako 22C3</td>
<td>any</td>
<td>‘Strong’ ≥50% ‘Weak’ 1-49% %</td>
<td>25%</td>
<td>Yes</td>
<td>37%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥1%</td>
<td>70%</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Dako 22C3</td>
<td>1st</td>
<td>≥50%</td>
<td>?</td>
<td>Yes</td>
<td>47%</td>
<td>?</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>Roche Ventana SP142</td>
<td>≥2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>≥10% TIICs*** ≥5% TIICs ≥1% TIICs</td>
<td>13%</td>
<td>Yes</td>
<td>83%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Roche Ventana SP263</td>
<td>≥2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Data not available</td>
<td>41%</td>
<td>Yes</td>
<td>46%</td>
<td>18%</td>
</tr>
<tr>
<td>MEDI-4736</td>
<td>Roche Ventana SP263</td>
<td>≥2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Data not available</td>
<td>41%</td>
<td>Yes</td>
<td>31%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Kerr K et al, J Thorac Oncol (in press)*
PD-L1 expression (prediction/POPLAR)

Vansteenkiste J. et al. - ESMO® 2015 - Abs. LBA 14

<table>
<thead>
<tr>
<th>Sous-groupe</th>
<th>n(%)</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3</td>
<td>47(16%)</td>
<td>15.5 (9.8, NE)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>105(37%)</td>
<td>15.1 (8.4, NE)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>198(68%)</td>
<td>15.5 (11.0, NE)</td>
</tr>
<tr>
<td>TC0 and IC0</td>
<td>92 (32%)</td>
<td>9.7 (6.7, 12.0)</td>
</tr>
</tbody>
</table>

ITT N=287

Atezolizumab n=144

Docetaxel n=143

12.6 (9.7, 16.4) 9.7 (8.6, 12.0)
## Target(s) choice(s)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Status (M, C or F)*</th>
<th>Frequency (%)</th>
<th>Available GEMMs</th>
<th>Currently available targeted therapies</th>
<th>Selected potential targeted therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>M or C</td>
<td>10 (M)</td>
<td>L858R, Del19, T790M and Ins20</td>
<td>Erlotinib, gefitinib and afatinib</td>
<td>AZD9291, CO-1686 and HM61713</td>
</tr>
<tr>
<td>FGF1</td>
<td>C</td>
<td>N/A</td>
<td>70</td>
<td>N/A</td>
<td>Dovitinib, ponatinib, AZD4547 and BGJ390</td>
</tr>
<tr>
<td>FGF2</td>
<td>M or C</td>
<td>3 (M)</td>
<td>3</td>
<td>N/A</td>
<td>Dovitinib, ponatinib, AZD4547 and BGJ390</td>
</tr>
<tr>
<td>ALK</td>
<td>F</td>
<td>3-5</td>
<td>&lt;1</td>
<td>ALK fusion, L1196M and F1174L</td>
<td>Crizotinib and ceritinib</td>
</tr>
<tr>
<td>MET</td>
<td>C</td>
<td>2-4</td>
<td>N/A</td>
<td>Overexpression</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>ROS1</td>
<td>F</td>
<td>1-2</td>
<td>N/A</td>
<td>Crizotinib</td>
<td>Tivantinib, cabozantinib, INC280 and onartuzumab</td>
</tr>
<tr>
<td>NTRK1</td>
<td>F</td>
<td>1-2</td>
<td>N/A</td>
<td>Crizotinib and lestaurtinib</td>
<td></td>
</tr>
<tr>
<td>RET</td>
<td>F</td>
<td>1</td>
<td>N/A</td>
<td>Crizotinib and vandetanib</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>M or C</td>
<td>2-4</td>
<td>N/A</td>
<td>HER2-YVMA insertion</td>
<td>Neratinib, afatinib, lapatinib and trastuzumab</td>
</tr>
<tr>
<td>DDR2</td>
<td>M</td>
<td>N/A</td>
<td>2-3</td>
<td>N/A</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>PDGFR</td>
<td>M</td>
<td>6-7</td>
<td>4</td>
<td>N/A</td>
<td>Sunsitinib</td>
</tr>
<tr>
<td>KRAS</td>
<td>M</td>
<td>15-25</td>
<td>1-2</td>
<td>G12D, G12C and G12V</td>
<td>Selumetinib plus docetaxel combination</td>
</tr>
<tr>
<td>NF1</td>
<td>M</td>
<td>12</td>
<td>10</td>
<td>Null</td>
<td>N/A</td>
</tr>
<tr>
<td>BRAF</td>
<td>M</td>
<td>1-6</td>
<td>4-5</td>
<td>V600E</td>
<td>Vemurafenib, dabrafenib and trametinib</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>M</td>
<td>5</td>
<td>15</td>
<td>p110α</td>
<td>BEZ235, BKM120 and GDC0941</td>
</tr>
<tr>
<td>MEK1</td>
<td>M</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>Selumetinib and trametinib</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>M</td>
<td>8</td>
<td>1</td>
<td>Conditional null</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Epigenetic factors

- **MLL2** | M | 9 | 20 | N/A | N/A | N/A
- **EZH2** | M | 2 | 2 | N/A | N/A | N/A
- **TE72** | M | 3 | 2 | N/A | N/A | N/A
- **DNMT3A** | M | 4 | 1 | N/A | N/A | N/A

### Transcription factors

- **SOX2** | C | 6 | 65 | Overexpression | N/A | N/A
- **MYC** | C | 25 | N/A | Overexpression | N/A | N/A

### Proteolysis

- **KEAP1** | M | 17 | 12 | N/A | N/A | N/A

### Cell cycle

- **CDKN2A** | M | 7 | 15 | Null | N/A | N/A

### Ligand

- **NRG1** | F | <1 | N/A | N/A | N/A | N/A

### Tumour suppressor

- **TP53** | M | 52 | 79 | Conditional null and R172H | N/A | N/A
- **LKB1** | M | 9 | 2 | Conditional null | N/A | N/A
- **PTEN** | M | 2 | 8 | Conditional null | N/A | BEZ235, BKM120 and GDC0941

---

Chen Z et al, Nat Rev Cancer 2014
Target(s) choice(s)?

Molecular Profiling of Lung Cancer

Lung cancer is the leading cause of cancer-related mortality in the United States, with an estimated 221,200 new cases and 159,040 deaths anticipated in 2015 (ACS 2015). Classically, treatment decisions have been empiric and based upon histology of the tumor. Platinum-based chemotherapy remains the cornerstone of treatment. However, survival rates remain low. Novel therapies and treatment strategies are needed.

Lung cancer is comprised of two main histologic subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Over the past decade, it has become evident that subsets of NSCLC can be further defined at the molecular level by recurrent 'driver' mutations that occur in multiple oncogenes, including AKT1, ALK, BRAF, EGFR, HER2, KRAS, MEK1, MET, NRAS, PIK3CA, RET, and ROS1 (Table 1). Another altered kinase gene involves MET. 'Driver' mutations lead to constitutive activation of mutant signaling proteins that induce and sustain tumorigenesis. These mutations are rarely found concurrently in the same tumor. Mutations can be found in all NSCLC histologies (including adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma) and in current, former, and never smokers (defined by individuals who smoked less than 100 cigarettes in a lifetime). Never smokers with adenocarcinoma have the highest incidence of EGFR, HER2, ALK, RET, and ROS1 mutations. Importantly, targeted small molecule inhibitors are currently available or being developed for specific molecularly defined subsets of lung cancer patients.

Historically, efforts at characterizing the molecular underpinnings of SCC of the lung have lagged behind those of adenocarcinoma of the lung. Many of the 'driver' mutations found in lung adenocarcinoma are only rarely found in lung SCC. Moreover, newer agents, such as bevacizumab (Avastin) and pemetrexed (Alimta) are not approved for or exhibit diminished efficacy in SCC (Sandier et al. 2006; Scagliotti et al. 2008). Thus, patients with metastatic SCC have fewer treatment options than those with non-squamous NSCLC. Despite these caveats, however, 'driver' mutations that may be linked to outcomes with targeted therapies in SCC are emerging. Altered genes include FGFR1 and DDR2 as well as PIK3CA. In addition, results from a recent large genomic study in lung SCC have added a variety of potential therapeutic targets that await validation in prospective clinical trials (Hammersman et al. 2012).

The following text is meant to provide a broad overview of several of the oncogenes known to be important for lung cancer pathogenesis. Where possible, the presence of a specific mutation is correlated to clinical parameters as well as response to both conventional chemotherapy and targeted agents. At present, only data for treatment of advanced (stage IIIB/IV) disease is presented.
Target(s) choice(s)

Oncologists

Molecular
Tumor Board

Biomathematicians

Biologists

Pathologists

RCPbiomol@ap-hm.fr; Coordination F Barlesi, S Garcia, C Mascaux, L Ouafik

Multidisciplinary Oncology & Therapeutic Innovations
INSERM U911 – CRO2
Marseille - France
## Centres Labélisés INCa de Phases Précoces

### Appel à candidature 2015 "Labellisation de centres d’essais cliniques de phase précoce en cancérologie adulte/pédiatrique (CLIP<sup>3</sup> 2015-2019)"

<table>
<thead>
<tr>
<th>Centre</th>
<th>CLIP&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Site principal du CLIP&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Coordonnateur du projet CLIP&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Service ou Site Partenaire</th>
</tr>
</thead>
</table>
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Marseille - France*
IFCT – Unicancer SAPHIR02L trial

Stage IV
NSCLC
No EGFRm
No ALK

Fresh biopsy @ 2 cycles max
• CGH
• NGS

@ 4 cycles

Bioguided Rx
(AZ pipeline: AZD2014, AZD4547, AZD5363, AZD8931, selumetinib, vandetanib)

Until PRG

Standard Cx
PMX (nSQ)
ERL (SQ)

No molecular alteration or Progression

Pis JC Soria / F Barlesi
Turn around time: MOSCATO trial (G Roussy)

FRESH TUMOR
BIOPSY ➔ PATHOLOGICAL CONTROL

MOLECULAR SCREENING
CGH Array & NGS

CLINICAL DECISION

TREATMENT

Max 21 calendar days

Median 14 days (95% CI: 7-35 days)

Hollebecque A et al, ASCO 2013
Turn around time: Match trial (NCI)

- Biopsy Received
  - Tissue Fixation
  - Path Review
  - 1 DAY
  - Nucleic Acid Extraction
  - 1 DAY
  - Library/Template Prep
  - 1 DAY
  - Sequencing, QC Checks
  - 1 DAY
  - Centralized Data Analysis
  - 1 DAY
  - Clinical Laboratory aMOI Verification
  - 3 DAYS
  - Treatment Selection
  - 10-14 days

- Tumor content >70%
- DNA/RNA yields > 20 ng
- Library yield > 20 pM
- Test fragments, Total read, Reads per BC, Coverage, NTC, Positive, Negative Controls
- aMOIs identified

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Marseille - France
Turn around time: experience in France

• Daily practice (standard sequencing)
  – Bringing the sample to the lab(s): 8 days
  – Report of analyses results: 11 days

• SAFIR 02 lung trial (NGS and CGH)
  – Maximum of 6 wks to get the MTB decision
  – To date: less than 0.5% failure rate

Barlesi et al, Biomarkers France, Lancet 2015 (in press); Unicancer, data on file
Targeted drugs access

From biopsy to tumor Board
21 days (median)

Patients included
N=129

Screen Failure N=17 (13%)
- Clinical deterioration (n=13)
- Biopsy technically impossible (n=2)
- Withdraw consent (n=2)

Patients Biopsied
N=112

NGS done on N=98 (88%)
CGH done on N=94 (84%)

Actionable Target
N=53 (47%)

No Actionable Target
N=59 (53%)

Treatment matched to the Target
N=33 (29%)

No Treatment
N=20 (18%)

Hollebecque A et al, ASCO 2013
Agenda

• Pharmaco-génomique
• Pharmaco-cinétique
• Pharmaco-génétique
• Perspectives
Evidence for Therapeutic Drug Monitoring of Targeted Anticancer Therapies

Bo Gao, Shang Yeap, Arthur Clements, Bavanti Balakrishnar, Mark Wong, and Howard Gurney

Abstract

Therapeutic drug monitoring (TDM) provides valuable guidance for dose adjustment of antibiotics, immunosuppressives, antiepileptics, and other drugs, but its use for traditional anticancer therapies has been limited. Perhaps the most important obstacle is the impractical requirement of multiple blood samples to adequately define systemic exposure of drugs that have a short elimination half-life and are given by intermittent intravenous injections. However, the newer targeted anticancer therapies have different pharmacokinetic (PK) and dosing characteristics compared with traditional cytotoxic drugs, making it possible to estimate the steady-state drug exposure with a single trough-level measurement. Recent evidence indicates that certain PK parameters, including trough levels, are correlated with clinical outcomes for many of these agents, including imatinib, sunitinib, rituximab, and cetuximab. Although the current evidence is insufficient to mandate TDM in routine practice, a concerted investigation should be encouraged to determine whether the steady-state trough measurements of targeted agents will have a practical place in the clinical care of patients with cancer.

Gao et al, J Clin Oncol 2012
Impact du tabac sur la dose de médicament

*Single 150 mg Dose in Healthy Male Subjects*

- **AUC*_{0-∞} (ng·h/mL)**  
  Nonsmoker: 18726  
  Smoker: 6718  
  S/NS = 35.9%  
  \( p = 0.0001 \)

- **C*_{max} (ng/mL)**  
  Nonsmoker: 1056  
  Smoker: 689  
  S/NS = 65.2%  
  \( p = 0.0310 \)

Hamilton, CCR 2006
Impact de la dose sur la toxicité

Figure 1: Plasma Concentration-Time Profiles of Gefitinib in 31 Patients With Non–small-cell Lung Cancer Administered 250 mg of Gefitinib

Kobayashi H et al, Clin Lung Cancer 2015
**Impact de la dose sur la toxicité**

---

**Table 2**  Comparison of Pharmacokinetics Parameters of Gefitinib Among Cytochromes P450 and Drug-Transporter Genotype Groups

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Patients (n)</th>
<th>AUC_{0-24} (ng·h/mL)</th>
<th>P Value</th>
<th>C_{0} (ng/mL)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
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</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>9,794 (3247-24,726)</td>
<td>.242a</td>
<td>329 (78-813)</td>
<td>.211a</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>11,396 (4360-21,591)</td>
<td></td>
<td>389 (120-759)</td>
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<tr>
<td><strong>EGFR mutation status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19</td>
<td>14</td>
<td>10,565 (3247-21,591)</td>
<td>.710a</td>
<td>340 (78-670)</td>
<td>.710a</td>
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<tr>
<td>Exon 21</td>
<td>17</td>
<td>10,086 (3450-24,726)</td>
<td></td>
<td>334 (120-813)</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>14,246 (6226-24,726)</td>
<td>.006a</td>
<td>421 (213-813)</td>
<td>.002a</td>
</tr>
<tr>
<td>No diarrhea</td>
<td>16</td>
<td>8918 (3247-15,487)</td>
<td></td>
<td>261 (78-490)</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>20</td>
<td>11,246 (3450-24,726)</td>
<td>.476a</td>
<td>341 (120-813)</td>
<td>.761a</td>
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<tr>
<td>No skin rash</td>
<td>11</td>
<td>9433 (3247-21,338)</td>
<td></td>
<td>333 (78-607)</td>
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<tr>
<td>Hepatotoxicity (all grades)</td>
<td>17</td>
<td>12,967 (5634-21,591)</td>
<td>.024a</td>
<td>420 (182-759)</td>
<td>.002a</td>
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<td>No hepatotoxicity</td>
<td>14</td>
<td>8473 (3247-24,726)</td>
<td></td>
<td>248 (78-813)</td>
<td></td>
</tr>
</tbody>
</table>

Kobayashi H et al, Clin Lung Cancer 2015
Impact de la dose sur l’efficacité

- Variabilité (PK)

Inter-patient variability
242% (Cmax) and 133% (Ctough)

Barlesi F / Ciccolini J, en cours
Impact de la dose sur l’efficacité

Variabilité inter-patient

Variabilité intra-patient

Courtesy Joseph Ciccolini, presented at AACR 2014
Impact de la dose sur l’efficacité

- Dose optimale: drug monitoring?

Jain R, J Clin Oncol 2013
Impact de la dose sur l’efficacité

- Concept de normalisation vasculaire

H460 Lung Cancer model

Serdjebi C/Ciccolini J, Lab Pharmacocinétique SMARTc, Inserm S_911
La précision jusqu’où ?
Agenda

• Pharmaco-génomique
• Pharmaco-cinétique
• Pharmaco-génétique
• Perspectives
Avons-nous tous le même métabolisme ?

Pharmacogenomic and Pharmacokinetic Determinants of Erlotinib Toxicity


ABSTRACT

Purpose
To assess the pharmacogenomic and pharmacokinetic determinants of skin rash and diarrhea, the two primary dose-limiting toxicities of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib.

Patients and Methods
A prospective clinical study of 80 patients with non–small-cell lung cancer, head and neck cancer, and ovarian cancer was performed. Detailed pharmacokinetics and toxicity of erlotinib were assessed. Polymorphic loci in EGFR, ABCG2, CYP3A4, and CYP3A5 were genotyped, and their effects on pharmacokinetics and toxicities were evaluated.

Results
A novel diplotype of two polymorphic loci in the ABCG2 promoter involving −15622C/T and 1143C/T was identified, with alleles conferring lower ABCG2 levels associated with higher erlotinib pharmacokinetic parameters, including area under the curve (P = .019) and maximum concentration (P = .006). Variability in skin rash was best explained by a multivariate logistic regression model incorporating the trough erlotinib plasma concentration (P = .034) and the EGFR intron 1 polymorphism (P = .044). Variability in diarrhea was associated with the two linked polymorphisms in the EGFR promoter (P < .01), but not with erlotinib concentration.

Conclusion
Although exploratory in nature, this combined pharmacogenomic and pharmacokinetic model helps to define and differentiate the primary determinants of skin and gastrointestinal toxicity of erlotinib. The findings may be of use both in designing trials targeting a particular severity of rash and in considering dose and schedule modifications in patients experiencing dose-limiting toxicities of erlotinib or similarly targeted agents. Further studies of the relationship between germline polymorphisms in EGFR and the toxicity and efficacy of EGFR inhibitors are warranted.

J Clin Oncol 26:1119-1127. © 2008 by American Society of Clinical Oncology
Impact des caractéristiques génétiques

génotype 1772CC HIF1α associé à DFS

>60% de variabilité expositions sériques

Courtesy Joseph Ciccolini, presented at AACR 2014
Avons-nous tous le même métabolisme ?

Fig 1. Plasma drug monitoring of gemcitabine in mice with normal cytidine deaminase (CDA; blue circle) and inhibited CDA (gold triangle). Gemcitabine (100 mg/kg) was administered intraperitoneally. CDA inhibition was achieved by pretreating animals with tetrahydrouridine (100 mg/kg). Insert: metabolism index of gemcitabine in mice with or without cytidine deaminase (CDA) inhibition. Metabolization index was calculated as the ratio of difluorodeoxyuridine to gemcitabine × 100.

Fig 2. Distribution of cytidine deaminase (CDA) activities in patients with or without early severe toxicities in (A) subset 1 (3.9 ± 2.4 U/mg vs 1 ± 0.2 U/mg; P < .001 by Mann-Whitney rank sum test; n = 64) and in (B) subset 2 (4 ± 2.6 U/mg vs 1.2 ± 0.8 U/mg; P < .01; n = 130).

Ciccolini et al, J Clin Oncol 2010
Agenda

• Pharmaco-génomique
• Pharmaco-cinétique
• Pharmaco-génétique
• Perspectives
Améliorer encore la précision

Ciccolini et al, Nat Rev Clin Oncol 2011
Conclusions

• Médecine personnalisée
  – Faisable pour tous, partout
  – Impact réel sur la survie des patients

• Limites de développement
  – Hétérogénéité tumorale

• Prise en compte autres facteurs
  – Monitoring des médicaments ?
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