Cancer Bronchique Non à Petites Cellules
Les nouvelles stratégies thérapeutiques
2016-2020

Cours du GOLF
Lyon – 21 Septembre 2016

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Multidisciplinary Oncology
& Therapeutic Innovations Dept
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.
2016-2020 …
2016-2020 …

• **Nouveauté(s) ?**
  – Connaissances scientifiques
  – Progrès technologiques
  – Classes thérapeutiques (Ph II ou III)

• **Aspects économiques**
  – Business
  – Contraintes économiques
Le cancer du poumon

- **45,222** nouveaux cas (**3ème**)  
  - 90% C. NAPC  
  - 2/3 stades IV

- **30,555** décès (**1er**)  

- 2 x C. colon (**17,833**)  

- 3 x C. sein (**11,913**)  

*Les cancers en France en 2015, INCa 2016*
Agenda

• Le whole genome pour tous ?
  • L’immunothérapie, le graal ?
  • Faire du neuf avec du vieux ?
LC genotyping program: France

- 28 platforms (2006)
- 10 routine biomarkers (+ 6 emerging bm)

* i.e. Regional molecular genetics centers

Available at www.ecancer.fr
Back to the basics first?

<table>
<thead>
<tr>
<th></th>
<th>EGFR mutation – no. (%)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Unknown</td>
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<tr>
<td></td>
<td>42 (9.9)</td>
<td>318 (74.8)</td>
<td>65 (15.3)</td>
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<tr>
<td></td>
<td>43 (10.1)</td>
<td>310 (72.9)</td>
<td>72 (16.9)</td>
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<tr>
<td></td>
<td>85 (10.0)</td>
<td>628 (73.9)</td>
<td>137 (16.1)</td>
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<tr>
<td></td>
<td><strong>EMLA-ALK</strong> translocation — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>2 (0.5)</td>
<td>223 (52.5)</td>
<td>200 (47.1)</td>
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<tr>
<td></td>
<td>0</td>
<td>201 (47.3)</td>
<td>224 (52.7)</td>
</tr>
<tr>
<td></td>
<td>2 (0.2)</td>
<td><strong>424 (49.9)</strong></td>
<td><strong>424 (49.9)</strong></td>
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<tr>
<td></td>
<td><strong>KRAS</strong> mutation — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>26 (6.1)</td>
<td>99 (23.3)</td>
<td>300 (70.6)</td>
</tr>
<tr>
<td></td>
<td>33 (7.8)</td>
<td>104 (24.5)</td>
<td>288 (67.8)</td>
</tr>
<tr>
<td></td>
<td>59 (6.9)</td>
<td>203 (23.9)</td>
<td>588 (69.2)</td>
</tr>
</tbody>
</table>

Example from a large phase III trial in NSCLC
Impact of routine molecular profiling

Barlesi et al, Biomarkers France, Lancet 2016

Median OS (months)
Gene alteration present: 16.5
IC95% 15.0-18.3
Gene alteration absent: 11.8
IC95% 10.1-13.5
P<0.001

17,664 pts

Number at risk
Driver +: 9498
Driver -: 1126

Barlesi et al, Biomarkers France, Lancet 2016
High throughput molecular genotyping

Images: NGS analyses from the SAFIR lung Unicancer IFCT trial
**Larger genomic profiling (NGS)**

<table>
<thead>
<tr>
<th>gène</th>
<th>Exons / hotspots</th>
<th>Molécule associée</th>
<th>utilité clinique</th>
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</thead>
<tbody>
<tr>
<td>AKT1</td>
<td>3</td>
<td>AKT inhibitors</td>
<td>essais cliniques</td>
</tr>
<tr>
<td>ALK</td>
<td>23+24+25</td>
<td>crizotinib, ALK inhibitors</td>
<td>AcSé, essais cliniques</td>
</tr>
<tr>
<td>BRAF</td>
<td>11+15</td>
<td>vemurafenib, dabrafenib</td>
<td>AMM</td>
</tr>
<tr>
<td>EGFR</td>
<td>18+19+20+21</td>
<td>anti EGFR</td>
<td>AMM</td>
</tr>
<tr>
<td>ERBB2 (HER2)</td>
<td>20</td>
<td>trastuzumab, neratinib</td>
<td>essais cliniques</td>
</tr>
<tr>
<td>ERBB4</td>
<td>E452K et R393W</td>
<td>Afatinib</td>
<td>essais cliniques</td>
</tr>
<tr>
<td>FGFR2</td>
<td>S252, N549, K659</td>
<td>FGFR inhibitors</td>
<td>essais cliniques</td>
</tr>
<tr>
<td>FGFR3</td>
<td>7+9+14 (R248 àS249 et G370 à Y)</td>
<td>FGFR inhibitors</td>
<td>essais cliniques</td>
</tr>
<tr>
<td>HRAS</td>
<td>2+3+4</td>
<td>inhibiteurs de MEK</td>
<td>essais cliniques</td>
</tr>
<tr>
<td>KIT</td>
<td>8+9+11+13+17+18</td>
<td>imatinib</td>
<td>AMM</td>
</tr>
<tr>
<td>KRAS</td>
<td>2+3+4</td>
<td>panitumumab et cetuximab</td>
<td>AMM</td>
</tr>
<tr>
<td>MAP2K1 (MEK1)</td>
<td>2</td>
<td>inhibiteurs de MEK</td>
<td>essais cliniques</td>
</tr>
<tr>
<td>MET</td>
<td>2 + 14 à 20</td>
<td>crizotinib</td>
<td>AcSé</td>
</tr>
<tr>
<td>NRAS</td>
<td>2+3+4</td>
<td>panitumumab, MEK inhibitors, BRAF inhibitors</td>
<td>pré-AMM, essais cliniques</td>
</tr>
<tr>
<td>PDGFR A</td>
<td>12+14+18</td>
<td>imatinib</td>
<td>AMM</td>
</tr>
<tr>
<td>PI3KCA</td>
<td>9 + 20</td>
<td>PI3K inhibitors</td>
<td>essais cliniques</td>
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</tbody>
</table>
High throughput molecular genotyping

Images: NGS analyses from the NIH website
Enjeux et perspectives

• Evolutions des plateformes
France (Biomarkers France)

How large should be the analysis?

Ferte C et al, AACR 2014
Precision medicine for increased survival?

420 pts enrolled from Dec 2011 to Dec 2013

368 pts Underwent a tumor biopsy

284 pts (77%) CGH

315 pts (86%) Sequencing

283 pts (77%) CGH + Sequencing

161 pts (44%) Oriented to a treatment based on an actionable target

85 pts (19%) Treated according to the molecular profile

51 pts (12%) Screening failure

Ferte et al, AACR 2014
Trial status (April 2nd, 2016)

393 patients enrolled

244 w analyses done

152 w an actionable target

Absence of target, n=76

Drug outside SAFIR, n=16
# cfDNA for molecular genotyping

<table>
<thead>
<tr>
<th></th>
<th>T790M</th>
<th>Tissue</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Plasma (BEAMing)</strong></td>
<td></td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>313</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74</td>
<td>17</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>387</td>
<td>40</td>
</tr>
</tbody>
</table>

- **T790M-positive cases (n=181)**

- Total positive by tissue: 146 of 181
- Total positive by plasma: 145 of 181
- Total positive by urine: 144 of 181

104 (57%) were positive by all 3 sample types

Wakelee H et al, ASCO 2016 (abst 9001)
cfDNA as solution to monitor biomarkers?

Tsuy DW et al, Clin Cancer Res (in press)
ddPCR development

Droplet Digital PCR

The sample is partitioned into 20,000 droplets, with target and background DNA randomly distributed among the droplets.

After PCR amplification, each droplet provides a fluorescent positive or negative signal indicating the target DNA was present or not present after partitioning. Each droplet provides an independent digital measurement.

Downloaded from biodiscover.com
PFS by tumour and plasma T790M status

- In plasma T790M negative patients, tumour genotyping can distinguish those patients with better and worse outcomes.
- Interestingly, a difference based on tumour genotype is also seen in plasma T790M positive cases.

Data cutoff: 1 May 2015. Multiple doses included.
T790M heterogeneity in plasma “false positives”

- We hypothesised that cases T790M negative in tumour and T790M positive in plasma might have heterogeneous presence of T790M
- Relative T790M AF was calculated as a proportion of EGFR sensitising AF:
  - T790M AF / sensitising AF
- Relative T790M AF was lower in cases with T790M negative in tumour, suggesting T790M may be present as a minor clone
- There was a trend toward lower response magnitude in the group with relative T790M AF <10% (p=0.08)

Data cutoff: 1 May 2015

Oxnard G, et al. ELCC 2016; Abstract 1350_PR
Lung cancer EGFRm on 1G targeted therapy

Rosell R et al, Lancet Oncol 2012
Where comes the resistance from?

Tumor cells can follow distinct evolutionary paths to become resistant to epidermal growth factor receptor inhibition

Aaron N Hata\textsuperscript{1,2,14}, Matthew J Niederst\textsuperscript{1,2,14}, Hannah L Archibald\textsuperscript{1}, Maria Gomez-Caraballo\textsuperscript{1}, Faria M Siddiqui\textsuperscript{1}, Hillary E Mulvey\textsuperscript{1}, Yosef E Maruvka\textsuperscript{1,3}, Fei Ji\textsuperscript{4}, Hyo-eun C Bhang\textsuperscript{5}, Viveksagar Krishnamurthy Radhakrishna\textsuperscript{5}, Giulia Siravegna\textsuperscript{6,7}, Haichuan Hu\textsuperscript{1}, Sana Raoof\textsuperscript{1,2}, Elizabeth Lockerman\textsuperscript{1}, Anuj Kalsy\textsuperscript{1}, Dana Lee\textsuperscript{1}, Celina L Keating\textsuperscript{5}, David A Ruddy\textsuperscript{8}, Leah J Damon\textsuperscript{1}, Adam S Crystal\textsuperscript{1,13}, Carlotta Costa\textsuperscript{1,2}, Zofia Piotrowska\textsuperscript{1,2}, Alberto Bardelli\textsuperscript{6,7}, Anthony J Iafrate\textsuperscript{9}, Ruslan I Sadreyev\textsuperscript{4,9}, Frank Stegmeier\textsuperscript{5}, Gad Getz\textsuperscript{1,3,9,10}, Lecia V Sequist\textsuperscript{1,2}, Anthony C Faber\textsuperscript{11,12} & Jeffrey A Engelman\textsuperscript{1,2}

Although mechanisms of acquired resistance of epidermal growth factor receptor (EGFR)-mutant non-small-cell lung cancers to EGFR inhibitors have been identified, little is known about how resistant clones evolve during drug therapy. Here we observe that acquired resistance caused by the $\text{EGFR}^{T790M}$ gatekeeper mutation can occur either by selection of pre-existing $\text{EGFR}^{T790M}$-positive clones or via genetic evolution of initially $\text{EGFR}^{T790M}$-negative drug-tolerant cells. The path to resistance impacts the biology of the resistant clone, as those that evolved from drug-tolerant cells had a diminished apoptotic response to third-generation EGFR inhibitors that target $\text{EGFR}^{T790M}$; treatment with navitoclax, an inhibitor of the anti-apoptotic factors BCL-xL and BCL-2 restored sensitivity. We corroborated these findings using cultures derived directly from EGFR inhibitor–resistant patient tumors. These findings provide evidence that clinically relevant drug-resistant cancer cells can both pre-exist and evolve from drug-tolerant cells, and they point to therapeutic opportunities to prevent or overcome resistance in the clinic.
Résistance acquise aux EGFR TKI (1G)

Cortot A & Janne PA, Eur Respir Rev 2014
Résistance acquise au crizotinib

## ALK mutations: frequencies

<table>
<thead>
<tr>
<th>ALK inhibitor</th>
<th>Crizotinib</th>
<th>Ceritinib</th>
<th>Alectinib</th>
<th>PF-06463922</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resistance mutation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1123S</td>
<td></td>
<td>Resistant [113]</td>
<td>Sensitive [113]</td>
<td></td>
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<tr>
<td>I1151Tins</td>
<td>Resistant [79, 90]</td>
<td>Resistant [90]</td>
<td>Resistant [79]</td>
<td>Sensitive [87]</td>
</tr>
<tr>
<td>L1152P/R</td>
<td>Resistant [90]</td>
<td>Resistant [90]</td>
<td>Sensitive [114]</td>
<td>Sensitive [87]</td>
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<tr>
<td>C1156Y/T</td>
<td>Resistant [90]</td>
<td>Resistant [90]</td>
<td>Sensitive [87]</td>
<td>Sensitive [87]</td>
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<tr>
<td>F1174L/C</td>
<td>Resistant [90]</td>
<td>Resistant [90]</td>
<td>Sensitive [115]</td>
<td>Sensitive [87]</td>
</tr>
<tr>
<td>G1202R</td>
<td>Resistant [79, 90]</td>
<td>Resistant [84, 90]</td>
<td>Resistant [79]</td>
<td>Sensitive [72, 87]</td>
</tr>
<tr>
<td>S1206Y</td>
<td>Resistant [79, 90]</td>
<td>Sensitive [90]</td>
<td>Sensitive [79]</td>
<td>Sensitive [87]</td>
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<tr>
<td>G1269A/S</td>
<td>Resistant [90]</td>
<td>Sensitive [90]</td>
<td>Sensitive [114]</td>
<td>Sensitive [87]</td>
</tr>
</tbody>
</table>

*Bayliss R et al, Cell Mol Life Sci 2016*
Lung cancer ROS1 on targeted therapy

Shaw A et al, NEJM 2014; Mazieres et al, J Clin Oncol 2015
Lung cancer BRAFm on targeted therapy

Lung cancer EGFRm on targeted therapy

Janne P, NEJM 2015

AZD9291
Osimertinib
Lung cancer ALKrearr on targeted therapy

Seto et al, Lancet Oncol 2013; Shaw A et al, NEJM 2014
3G EGFR-TKI in 1st line (AURA program)

Number of patients at risk:
- 1st line 80 mg: 30, 26, 23, 22, 20, 16, 14, 7, 0
- 1st line 160 mg: 30, 29, 27, 23, 20, 19, 7, 0

<table>
<thead>
<tr>
<th>Time</th>
<th>80 mg n=30</th>
<th>160 mg n=30</th>
<th>Total N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, * months (95% CI)</td>
<td>NC (12.3, NC)</td>
<td>19.3 (11.1, 19.3)</td>
<td>19.3 (13.7, NC)</td>
</tr>
<tr>
<td>Remaining alive and progression-free, † % (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>75 (55, 88)</td>
<td>69 (49, 83)</td>
<td>72 (59, 82)</td>
</tr>
<tr>
<td>18 months</td>
<td>57 (36, 73)</td>
<td>53 (32, 70)</td>
<td>55 (41, 67)</td>
</tr>
</tbody>
</table>

Ramalingam S, et al. ELCC 2016; Abstract LBA1_PR
3G ALKi Alectinib in 1st line

Nokihara H et al, Abst #9008 ASCO 2016

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>25 (24.3%)</td>
<td>58 (55.8%)</td>
</tr>
<tr>
<td>Median, mo [95% CI]</td>
<td>NR [20.3 - NR]</td>
<td>10.2 [8.2 - 12.0]</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HR [95% CI]</td>
<td>0.34 [0.17 - 0.71]</td>
<td></td>
</tr>
</tbody>
</table>
En résumé … 2020

• Poussée technologique

• Réorganisation (régionale)

• Peu de nouvelles cibles actionnables
  – KRAS: untargetetable target?
  – Process décision (plus) complexe

• Passage en 1ère ligne TKI 3G
Les attentes ne sont pas là ...
US Cancer Moonshot

"For the loved ones we’ve all lost, for the family we can still save, let’s make America the country that cures cancer once and for all.”

Obama, January 2016
Agenda

• Le whole genome pour tous ?

• L’immunothérapie, le graal ?

• Faire du neuf avec du vieux ?
Consequences
PD1 inhibitor 2L: Nivolumab (PhIII)

Nsq-NSCLC

Sq-NSCLC


Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.
PD1 inhibitor 2L: Pembrolizumab (PhIII)

**All NSCLC**

HR for OS (doc vs 2): 0.71 (0.58-0.88)
HR for OS (doc vs 10): 0.61 (0.49-0.75)

**NSCLC w PD-L1+ >50%**

HR for OS (doc vs 2): 0.54 (0.38-0.77)
HR for OS (doc vs 10): 0.50 (0.36-0.70)

*Herbst R et al., Lancet 2016*
Wednesday, Aug 31, 2016

Phase III Study Showed Genentech’s Cancer Immunotherapy TECENTRIQ™ (Atezolizumab) Helped People with a Specific Type of Lung Cancer Live Significantly Longer Compared to Chemotherapy

- TECENTRIQ showed significant improvement in overall survival for people regardless of their PD-L1 status

To be presented at ESMO (Presidential session, Sunday 9th)
## Intégration immunothérapie

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approval</th>
<th>EMEA Approval</th>
<th>Price (France)</th>
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<tbody>
<tr>
<td>Nivolumab (Sq) 2L</td>
<td>Mar 2015</td>
<td>Jul 2015</td>
<td></td>
</tr>
<tr>
<td>Nivolumab (Nsq) 2L</td>
<td>Oct 2015</td>
<td>Apr 2016</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (All PD-L1+) 2L</td>
<td>Oct 2015</td>
<td>Submitted</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab (All) 2L</td>
<td>2017?</td>
<td>2018?</td>
<td></td>
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</table>
Bristol-Myers Squibb Announces Top-Line Results from CheckMate -026, a Phase 3 Study of Opdivo (nivolumab) in Treatment-Naïve Patients with Advanced Non-Small Cell Lung Cancer

08/05/2016

Opdivo did not meet trial primary endpoint of progression-free survival in patients expressing PD-L1 ≥ 5%.

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol-Myers Squibb Company (NYSE:BMY) announced today that CheckMate -026, a trial investigating the use of Opdivo (nivolumab) as monotherapy, did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed PD-L1 at ≥ 5%. The company will complete a full evaluation of the CheckMate -026 data and work with investigators on the future presentation of the results.

To be presented at ESMO (Presidential session)
Merck’s KEYTRUDA® (pembrolizumab) Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

June 16, 2016 06:45 AM Eastern Daylight Time

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the KEYNOTE-024 trial investigating the use of KEYTRUDA® (pembrolizumab), in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint. In this trial, KEYTRUDA was superior compared to chemotherapy for both the primary endpoint of progression-free survival (PFS), and the secondary endpoint of overall survival (OS). Based on these results, an independent Data Monitoring Committee (DMC) has recommended that the trial be stopped, and that patients receiving chemotherapy in KEYNOTE-024 be offered the opportunity to receive KEYTRUDA.

To be presented at ESMO (Presidential session)
En 1ère ligne dès 2017 !

Essai combinaison

Cx +/- ICI

To be possibly presented at ESMO (Presidential session)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker</th>
<th>Rx line</th>
<th>Definition of ‘Positive’ #</th>
<th>%</th>
<th>N</th>
<th>Positive Predictive outcome</th>
<th>ORR % IHC pos cases</th>
<th>ORR % IHC neg cases</th>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>Dako 28-8</td>
<td>1st</td>
<td>≥5% in &gt;100 cells</td>
<td>59%</td>
<td>59%</td>
<td>Yes</td>
<td>31%*</td>
<td>10%</td>
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<tr>
<td>Nivolumab</td>
<td>Dako 28-8</td>
<td>≥2nd</td>
<td>≥5% ≤1%</td>
<td>49%</td>
<td>49%</td>
<td>No</td>
<td>15%</td>
<td>14%</td>
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<tr>
<td>Nivolumab</td>
<td>5H1 **</td>
<td>1st</td>
<td>≥5% in &gt;100 cells</td>
<td>32%</td>
<td>32%</td>
<td>No</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Dako 28-8</td>
<td>≥2nd</td>
<td>≥5%</td>
<td>33%##</td>
<td>33%##</td>
<td>Yes</td>
<td>24%</td>
<td>14%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Dako 22C3</td>
<td>any</td>
<td>‘Strong’ ≥50%, ‘Weak’ 1-49%</td>
<td>25%</td>
<td>25%</td>
<td>Yes</td>
<td>37%</td>
<td>17%</td>
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<tr>
<td>Pembrolizumab</td>
<td>Dako 22C3</td>
<td>1st</td>
<td>≥50% ≥1%</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
<td>47%</td>
<td>?</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>Roche Ventana SP142</td>
<td>≥2nd</td>
<td>≥10% TIIcs***</td>
<td>13%</td>
<td>13%</td>
<td>Yes</td>
<td>83%</td>
<td>18%</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>Roche Ventana SP142</td>
<td>≥2nd</td>
<td>≥5% TIIcs ≥1% TIIcs</td>
<td>28%</td>
<td>28%</td>
<td>Yes</td>
<td>46%</td>
<td>18%</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>Roche Ventana SP142</td>
<td>≥2nd</td>
<td>Data not available</td>
<td>6%</td>
<td>6%</td>
<td>Yes</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>MEDI-4736</td>
<td>Roche Ventana SP263</td>
<td>≥2nd</td>
<td>Data not available</td>
<td>41%</td>
<td>41%</td>
<td>Yes</td>
<td>25%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Kerr K et al, J Thorac Oncol (in press)
Personnalized IO? > 2020

*Evaluate Tumour Immunology*

**Inflamed**
- Strong PD-L1 & high mutational load
  - Anti-PDL1/PD1
- Weak PD-L1 expression
  - Anti-PDL1/PD1 + Other CIT (IDO, aTIGIT, aCSF1R, TCBs, IL2v)
- No identified target
  - Anti-PDL1/PD1 + Chemo /targeted therapy/XRT

**Excluded**
- T-Cells at Periphery
  - Anti-PDL1/PD1 + antiangiogenic + anti-stromal agents
- No Identified target
  - Anti-PDL1/PD1 + Chemo /targeted therapy/XRT

**Immune Desert**
- No Effectors
  - Anti-PDL1/PD1 + aOX40 (or aCD40, aCTLA4, IL2v, vaccine)
- MHC Loss
  - Anti-PDL1/PD1 + TCBs (or IFN, CART, MEKi)

Modified from Kim and Chen, Ann Oncol 2016
Enjeux et Perspectives

COMBINATORIAL EXPLOSION

Ipiplimumab, the first approved checkpoint inhibitor, has been tested in dozens of clinical trials since 2001. And like many other drugs in its class, it is increasingly being tested in combination with other therapies.

- Combination therapy
- Single-drug therapy

US regulators approve ipilimumab for treatment of advanced melanoma.

Studies show improved survival in people with advanced melanoma.

« There will be not enough money on this earth to test all the possible combinations »

Ira Mellman, Vice-President, Cancer Immunology, Genentech Inc.
AACR, New Orleans April 2016
PD-1 inhibitor 1L: Nivolumab

Key patient inclusion criteria
- Stage IIIIB/IV NSCLC
- No prior chemotherapy for advanced disease
- ECOG PS 0–1 (n=77)

Primary endpoint
- Safety/tolerability

Secondary endpoints
- ORR, PFS, OS, efficacy by PD-L1 expression

Hellman et al., ASCO 2016 (abst 3001)
### PD-1 inhibitor 1L: Nivolumab/Ipilimumab

<table>
<thead>
<tr>
<th>Nivo 3 q2w + Ipi 1 q12w (n=38)</th>
<th>Nivo 3 q2w + Ipi 1 q6w (n=39)</th>
<th>Nivo 3 q2w (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR, %</strong></td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td><strong>Median DOR, months (95%CI)</strong></td>
<td>NR (11.3, NR)</td>
<td>NR (8.4, NR)</td>
</tr>
<tr>
<td><strong>Median follow-up, months (95%CI)</strong></td>
<td>12.9 (0.9, 18.0)</td>
<td>11.8 (1.1, 18.2)</td>
</tr>
<tr>
<td><strong>mPFS, months (95%CI)</strong></td>
<td>8.1 (5.6, 13.6)</td>
<td>3.9 (2.6, 13.2)</td>
</tr>
<tr>
<td><strong>1-year OS rate, % (95%CI)</strong></td>
<td>NC</td>
<td>69 (52, 81)</td>
</tr>
</tbody>
</table>

Efficacy is enhanced with increasing PD-L1 expression:

≥1% tumour PD-L1 expression: **57% ORR**; 83–90% 1-year OS rate

≥50% tumour PD-L1 expression: **92% (12/13) ORR**

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*Hellman et al., ASCO 2016 (abst 3001)*
En résumé … 2020

- ICI 1ère ligne 2017-2018 (20% ?)
- ICI 2ème ligne 2016 (sans sélection)
- Combinaisons
  - ICIs (2018-2020)
  - ICI + CT (2018-2020)
Agenda

• Le whole genome pour tous ?

• L’immunothérapie, le graal ?

• Faire du neuf avec du vieux ?
Angiogenics (BUCIL)

OS of all eligible patients (n=113)

Median OS, IC95%: 17.7 [13.1-21.6]

OS of patients receiving sequence 2 (n=65)

Median OS, IC95%: 20.5 [16.9 - 26.9]

Barlesi F et al, Abst #9077 ASCO 2016
Angiogenics (ULTIMATE)

wPB Median PFS: 5.4 mo, 95%CI: [4.6-7.1]
DOC Median PFS: 3.9 mo, 95%CI: [2.7-5.3]
HR adj. = 0.62 [0.44-0.87]
$p = 0.006$

Cortot A et al, Abst #9077 ASCO 2016
Enjeux et Perspectives

Key patient inclusion criteria
- Histologically confirmed NSCLC
- Stage IV disease
- \( \leq 3 \) metastases
- No RECIST progression after FLST* (n=49)

Primary endpoint(s)
- PFS

Secondary endpoints
- OS, safety

Stratification
- Nodal status, EGFR/EML4-ALK status, response to FLST, CNS metastases, number of metastases

Primary endpoint(s)
- PFS

Secondary endpoints
- OS, safety

LCT\(^+\) +/- ST (n=25)

ST alone (n=24)

Crossover to LCT allowed at progression

Gomez et al, ASCO 2016 (abst 9004)
Enjeux et Perspectives

Gomez et al, ASCO 2016 (abst 9004)

LCT
No LCT

p=0.005

mPFS, months
No-LCT arm: 3.9 (95%CI 2.2, 6.6)
LCT arm: 11.9 (95%CI 5.4, NA)

Gomez et al, ASCO 2016 (abst 9004)
IFCT-UNICANCER SAFIR 02 lung trial

Stage IV NSCLC
No EGFRm
No ALK

Fresh biopsy @ 2 cycles max
- CGH
- NGS
cDNA
FFPE

@ 4 cycles

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

R2:1

N=230

Absence d’alt. mol. activable

N=180

Standard Cx
PMX (nSQ)
ERL (SQ)

R2:1

Until PRG

Co-PIs
JC Soria / F Barlesi

Progression

MEDI4736
(durvalumab)

Until PRG

Multidisciplinary Oncology & Therapeutic Innovations
INSERM U911 – CRO2
Marseille - France
Conclusions

• 2017-2018:
  – « NGS » accessible facilement
  – TKI 3G 1L
  – ROS1, BRAF, MET activables
  – Complexification décision (RCP bio mol)
  – Peu d’autres cibles (essais précoces)
  – ICI (mono PD-L1 high+ et combo?) 1L
Conclusions

• 2019-2020:
  – Profils prédictifs (Cx, ICI, etc) ?
  – Nouveaux réarrangements
  – Nouveaux TKI 3G ou 4G (paninhib)
  – Nouveaux inhibiteurs (CDK, JAK) ?
  – IO: ICI mono vs combo (ICI, Cx, AA)
  – Impact contraintes économiques ??
Conclusions

Les dépenses de santé en 2015 - Résultats des comptes de la santé

publié le : 05.09.16

En 2015, la consommation de soins et de biens médicaux (CSBM) est de 194,6 milliards d'euros. Elle progresse de 1,8 %, soit légèrement moins rapidement que le PIB en valeur (+1,9 %), contrairement à la période 2012-2014 où sa croissance était supérieure à celle du PIB. La France consacre, au total, 11 % de son PIB à la santé, tout comme la Suède, l'Allemagne et les Pays-Bas.

La Sécurité sociale finance plus des trois quarts de la CSBM et les organismes complémentaires 13,3 %. La part restant à la charge des ménages recule pour la quatrième année consécutive et atteint 8,4 % en 2015. Les ménages consacrent ainsi un peu moins de 250 euros par habitant à leur consommation de santé, soit moins que la plupart de leurs voisins européens.

Les dépenses de santé en 2015 – édition 2016 présentent également un éclairage sur les dépenses de prévention sanitaire, qui représenteraient plus de 4,8 % de la
• Laurent Greillier
• Pascale Tomasini
• Celine Mascaux
• Marjorie Baciuchka
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