Use of big data in oncology

Pr Christophe Le Tourneau
Institut Curie – Paris & Saint-Cloud – France
Department of Medical Oncology
Head of Early Phase Clinical Trials
INSERM U900 research unit

PSL University – Paris – December 1st, 2016
Introduction

HER-2

20%

Trastuzumab (Herceptin®)

Lapatinib (Tykerb®)

Amplification
Introduction

HER2+ breast cancer

Trastuzumab (Herceptin®)

→ Risk of recurrence decreased by 50%

• HER2+ breast cancer
Introduction

HER2+ metastatic breast cancer

Trastuzumab (Herceptin®)

→ Median overall survival increased from 2 to 6 years
Introduction

Ciriello et al. Nature Genet 2013;45:1127-33
Introduction

HER-2

Trastuzumab (Herceptin®)

Amplification

20%
Introduction

LUNG ADENOCARCINOMA – HER2 V659E MUTATION – LAPATINIB

March 19, 2012

June 11, 2012

PE

PLC

Introduction

Molecular profile

Molecular alteration

Targeted agent  Targeted agent  Targeted agent  Targeted agent  Targeted agent  Targeted agent  Targeted agent  Targeted agent
Introduction

Patients receiving matched targeted therapy

Patients receiving no matched targeted therapy

Tsimberidou et al. CCR 2012;18:6373-83
Introduction

Patients receiving matched targeted therapy

Patients receiving no matched targeted therapy

Tsimberidou et al. *CCR* 2012;18:6373-83
Outline

• Precision medicine trials:
  - Stratified trials
  - Algorithm-testing trials
• The SHIVA01 trial
• Molecular Biology Board
Outline

• Precision medicine trials:
  - Stratified trials
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Outline

• Precision medicine trials:
  - Stratified trials
    - Algorithm-testing trials
• The SHIVA01 trial
• Molecular Biology Board
Molecular stratification

- **FOCUS4 trial** (maintenance 1st-line metastatic CRC)

  Eligible patients
  - Advanced or metastatic CRC
  - Fit for first-line chemotherapy
  - Consent to biomarker analysis

  During first 16 weeks chemotherapy biomarker panel analysis*:
  - on FFPE tumor block
  - BRAF, PIK3CA, KRAS, NRAS mutation;
  - mRNA EREG; IHC MMR, PTEN

  Standard chemotherapy for 16 weeks
  => Stable or responding disease

  Nonstratified (unclassified or when other stratifications are refused or unavailable)

  On progression recommence first-line chemotherapy

  Kaplan et al. JCO 2013;31:4592-8
# Summary

## Precision medicine trials

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| Tumor types              |                   |                          |
|                         |                   |                          |
| Molecular Alterations    |                   |                          |
|                         |                   |                          |
| Treatments               |                   |                          |
|                         |                   |                          |
| Test                     |                   |                          |

Le Tourneau et al. Chin Clin Oncol 2014;3:13
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Le Tourneau et al. Chin Clin Oncol 2014;3:13
Histologic stratification

• 1 drug
• Multiple tumor types harbouring specific molecular alterations
Histologic stratification

- AcSé programmes
- One single **drug** given across various tumor types harbouring the target(s) of the drug
- Open in >100 centers in France
- AcSé **vemurafenib** (BRAF mutations)
- AcSé **crizotinib** (ALK/ROS1 translocations, MET amplification)
### Summary

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| **Tumor types**       |                    |                          |
| 1                    |                    |                          |

| **Molecular Alterations** | N               | 1 or N                   |
| 1 green ▲                | 1 yellow ▲       | 1 orange ▲               |

| **Treatments**         | N               | 1                         |
| 1 green ◻                | 1 yellow ◻       | 1 orange ◻                |

**Test**

Test **drugs** efficacy

---

Outline

• Precision medicine trials:
  - Stratified trials
  - Algorithm-testing trials
• The SHIVA01 trial
• Lessons & Perspectives
Non-randomized trials

- Pilot study by von Hoff et al.

von Hoff et al. JCO 2010;28:4877-83
Non-randomized trials

- 18/66 patients (27%): ratio > 1.3

von Hoff et al. *JCO* 2010;28:4877-83
SHIVA – Randomized proof-of-concept phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer (PI: Christophe Le Tourneau)

Patients with refractory cancer (all tumor types) → Informed consent signed → Tumor biopsy → NGS+ Cytoscan HD +IHC → Bioinformatics → Informed consent signed → Therapy based on molecular profiling

- Approved molecularly targeted agent

Non eligible patient → Molecular biology board → Specific therapy available

Eligible patient → Conventional therapy based on oncologist’s choice

Cross-over

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Test **drugs** efficacy

Le Tourneau *et al.* Chin Clin Oncol 2014;3:13
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<td>Tumor types: 1 or N (Purple)</td>
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<td>Molecular Alterations: N (Green), N (Yellow), N (Red)</td>
<td>Molecular Alterations: N (Green), 1 or N (Yellow), N (Red)</td>
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<td>Treatments: N (Green), N (Yellow), N (Red)</td>
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Le Tourneau *et al.* *Chin Clin Oncol* 2014;3:13
Treatment algorithm
# Treatment algorithm

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<td>Quality controls</td>
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<td>Validation of the molecular alterations identified</td>
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<td>Interpretation of the results</td>
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<td>6</td>
<td>Molecular alteration/target relation</td>
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<td>Prioritization</td>
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Treatment algorithm

Ratan et al. Plos One 2013;8
Treatment algorithm
Outline

• Precision medicine trials:
  - Stratified trials
  - Algorithm-testing trials
• The SHIVA01 trial
• Molecular Biology Board
The SHIVA01 trial

• **Mutations:**
  - Ampliseq Cancer Panel
  - Ion Torrent / PGM (Life Technologies®)

• **Gene copy number alterations:**
  - Cytoscan HD (Affymetrix®)

• **Protein expression:**
  - IHC (ER, PR, AR)
  - IHC validation of amplifications and/or losses (PTEN, EGFR, HER2, KIT, MET, BRAF, PDGFRA/B)
The SHIVA01 trial

- Variants of interest:
  - **validated hotspots mutations**
    * frequency: \( \geq 4\% \) for SNVs and \( \geq 5\% \) for indels
    * coverage: \( \geq 30X \) for SNVs and \( \geq 100X \) for indels
  - **non targeted variants**
    * outside a hotspot
    * frequency \( \geq 10\% \)
    * no synonymous mutations
    * no polymorphisms
The SHIVA01 trial

• Amplifications:
  - Gene copy number
    * diploid tumor: \( \geq 6 \)
    * tetraploid tumor: \( \geq 7 \)
  - Amplicon size
    * \( \leq 1 \) Mb
    * \( \leq 10 \) Mb if protein overexpression/or loss of expression was validated in IHC
The SHIVA01 trial

Tumor biopsy

DNA extraction

Gene copy number alteration (Cytoscan HD)

Mutation analysis (AmpliSeq - Ion Torrent)

IHC (hormone receptors determination)

Bioinformatics

IHC (validation of gene copy number alterations)

Bioinformatics report

MBB

Week 1

Week 2

Week 3

Week 4

Week 5

Le Tourneau et al. BJC 2014;111:17-24
The SHIVA01 trial

Servant et al. Front Genetics 2014;5:1-16
Outline

• Precision medicine trials:
  - Stratified trials
  - Algorithm-testing trials
• The SHIVA01 trial
• Molecular Biology Board
• Between October 2014 and Sept 2016:

- Patients discussed in the MBB: 595
- Patients with molecular analyses: 336
- Patients with druggable molecular alterations: 162
- Patients included in clinical trials: 60
Conclusions

• High throughput technologies are more and more commonly used in oncology to guide patients to targeted therapies
• Just a few targets are druggable today
• Systems biology might help demonstrating the precision medicine concept where patients are treated based on the molecular profile of their tumors
Acknowledgments

- **Direction**
  - Thierry Philip
  - Claude Huriet
  - Pierre Teillac
  - Daniel Louvard

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- **Translational research**
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- **Radiology**
  - Vincent Servois
  - Daniel Szwarc

- **Bioinformatics**
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  - Emmanuel Barillot
  - Philippe La Rosa
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  - Bruno Zeitouni
  - Alban Lermine
  - Camille Barette

- **Comunication**
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  - Cécile Charre

- **Genetics**
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  - Gaëlle Pierron
  - Etienne Rouleau
  - Céline Callens
  - Marc-Henri Stern

- **Surgery**
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  - José Rodriguez
  - Angélique Girod
  - Pascale Mariani
  - Virginie Fourchotte
  - Fabien Royal

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  - Jean-Yves Pierga
  - Véronique Diéras
  - Valérie Laurence
  - Sophie Piperno-Neumann
  - Catherine Daniel
  - Wulfran Cachoeux
  - Bruno Buecher
  - Emmanuel Mitry
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