Impact of personalized treatment

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Paris Saclay University

NVMO 10th anniversary – Amsterdam – April 21, 2016
Introduction
Introduction

HER-2

Trastuzumab (Herceptin®)

Lapatinib (Tykerb®)

Amplification

20%
Introduction

Pan-cancer global alteration profiles

Candidate functional alterations

Copy number alterations

Genomic coordinates

Select alterations

Tumor types

Samples

Somatic mutations

Genomic coordinates

Select alterations

1q21
3q26
MYC
CDKN2A
CCNE1

151 deleted regions

Most frequent copy number alterations

20%
15%
10%
5%

$\text{CDKN2A}$
$\text{MYC}$
$\text{CCND1}$

$\text{116 amplified regions}$

$\text{Altered samples}$

32%
24%
18%
16%
10%
6%

$\text{VHL}$
$\text{APC}$
$\text{KRAS}$
$\text{TP53}$

$\text{199 mutated genes}$
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

Introduction

HISTOLOGY-AGNOSTIC APPROACH

Molecular profile

Molecular alteration

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

Molecular profile

= TREATMENT ALGORITHM
• Treatment algorithm:
  - technology used to identify molecular alterations
  - thresholds used
  - molecular alterations/drugs matching
  - molecular alterations prioritization

Le Tourneau et al. JNCI [epub ahead of print on November 23, 2015]
Introduction

Patients receiving matched targeted therapy

Patients receiving no matched targeted therapy

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

Failure-free survival

Overall survival

Patients receiving matched targeted therapy

Patients receiving no matched targeted therapy

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

- Stratified precision medicine trials:
  - Molecular stratification
  - Histologic stratification
- Algorithm-testing trials:
  - Non-randomized trials
  - Randomized trials
- Lessons & Perspectives
Outline

• Stratified precision medicine trials:
  - Molecular stratification
  - Histologic stratification

• Algorithm-testing trials:
  - Non-randomized trials
  - Randomized trials

• Lessons & Perspectives
Outline

• Stratified precision medicine trials:
  - Molecular stratification (umbrella trials)
    - Histologic stratification
  - Algorithm-testing trials:
    - Non-randomized trials
    - Randomized trials
• Lessons & Perspectives
FOCUS4 trial (maintenance 1st-line metastatic CRC)

Molecular stratification

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

Patient selection

Standard chemotherapy for 16 weeks
=> Stable or responding disease

Registration period
(master protocol)

Molecular selection*

BRAF mutation
PIK3CA mutation and/or PTEN loss
KRAS or NRAS mutation
All wild type
Nonstratified (unclassified or when other stratifications are refused or unavailable)

Consent and random assignment

Trial period
(trial protocol)

P: BRAF + EGFR ± MEK inhibitors
P: PIK3CA ± MEK inhibitors
P: AKT + MEK inhibitors
P: HER1,2,3 inhibitor
No Rx
Capcitabine

On progression recommence first-line chemotherapy

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

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**Tumor types**

- 1

**Molecular Alterations**

- Green ▲
- Yellow ▲
- Red ▲

**Treatments**

- Green N
- Yellow N
- Pink N

**Test**
• **Stratified precision medicine trials:**
  - Molecular stratification
  - **Histologic stratification** (basket trials)
• **Algorithm-testing trials:**
  - Non-randomized trials
  - Randomized trials
• **Lessons & Perspectives**
Histologic stratification

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D.,
Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D.,
Jürgen S. Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D.,
Antoine Hollebeque, M.D., Radj Gervais, M.D.,
Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D.,
Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D.,
Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc.,
Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D.,
Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.
Histologic stratification

- Vemurafenib in BRAF-mutated tumors

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<thead>
<tr>
<th></th>
<th>Melanoma</th>
<th>NSCLC</th>
<th>ECD/LGH</th>
<th>CRC</th>
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<th>CholangioK</th>
<th>Anaplastic thyroid cancer</th>
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<tr>
<td><strong>ORR</strong></td>
<td>48%</td>
<td>42%</td>
<td>43%</td>
<td>0</td>
<td>5%</td>
<td>12%</td>
<td>29%</td>
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<td><strong>PFS</strong></td>
<td>7 mo</td>
<td>7.3 mo</td>
<td>NR</td>
<td>4.5 mo</td>
<td>2.1 mo</td>
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<tr>
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</table>

### Tumor types
- **1**

### Molecular Alterations
- **N**
- **1 or N**

### Treatments
- **N**
- **1**

### Test
- **Test drugs efficacy**
Molecular + hostologic strata

- **CUSTOM trial** (Advanced thoracic malignancies)

Lopez-Chavez et al. *JCO* 2015;20:1000-7
Outline

• Stratified precision medicine trials:
  - Molecular stratification
  - Histologic stratification

• Algorithm-testing trials:
  - Non-randomized trials
  - Randomized trials

• Lessons & Perspectives
• Stratified precision medicine trials:
  - Molecular stratification
  - Histologic stratification

• Algorithm-testing trials:
  - Non-randomized trials
  - Randomized trials

• 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
Non-randomized trials

- WINTHER trial

Selection of Individualized treatments based on biological analysis of paired tumor and normal samples

Arm A: Oncogenic events from DNA analysis
  - Matched molecular targeted therapies
  - High toxicity management/recurrence

Arm B: No oncogenic event
  - Therapeutic choice based on predictive drug efficacy scoring following RNA based analysis

Biopsies
- 200 patients with advanced malignancies
- Next Generation Sequencing (NGS)
- Comparative Genomic Hybridization (CGH)
- Copy Number Variation (CNV)
- Gene Expression (GE)
- microRNA Profiling

WIN THER
- Comprehensive Full genome investigation

WIN THER predictive drug efficacy scoring
• Stratified precision medicine trials:
  - Molecular stratification
  - Histologic stratification

• Algorithm-testing trials:
  - Non-randomized trials
  - Randomized trials

• Lessons & Perspectives
• **Question:**

![Diagram with text: Molecular profile and targeted agents leading to chemotherapy options.](image)
Patients with refractory cancer (all tumor types) → Informed consent signed → Tumor biopsy → NGS+ Cytoscan HD +IHC → Bioinformatics → Informed consent signed → Molecular biology board → Eligible patient → Specific therapy available → YES → Therapy based on molecular profiling - Approved molecularly targeted agent → Cross-over → Conventional therapy based on oncologist’s choice → NO → Non eligible patient

SHIVA01 – 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)

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<tr>
<th>Targets</th>
<th>Molecular alterations</th>
<th>MTAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER, PR</td>
<td>Protein expression ≥10% IHC</td>
<td>Tamoxifen or Letrozole</td>
</tr>
<tr>
<td>AR</td>
<td>Protein expression ≥10% IHC</td>
<td>Abiraterone</td>
</tr>
<tr>
<td>PI3KCA, AKT1, AKT2/3, mTOR, RICTOR, RAPTOR, PTEN</td>
<td>Mutation/Amplification, Amplification, Homozygous deletion, Heterozygous deletion + mutation or IHC, Homozygous deletion, Heterozygous deletion + mutation, Homozygous deletion</td>
<td>Everolimus</td>
</tr>
<tr>
<td>STK11</td>
<td>PI3K/AKT/mTOR PATHWAY</td>
<td></td>
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<tr>
<td>INPP4B</td>
<td>Mutation/Amplification</td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation/Amplification</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>KIT, ABL1/2, RET</td>
<td>Mutation/Amplification</td>
<td>Imatinib</td>
</tr>
<tr>
<td>PDGFRA/B, FLT3</td>
<td>Mutation/Amplification</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>EGFR</td>
<td>Mutation/Amplification</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>HER-2</td>
<td>Mutation/Amplification</td>
<td>Lapatinib + Trastuzumab</td>
</tr>
<tr>
<td>SRC</td>
<td>Mutation/Amplification</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>EPHA2, LCK, YES1</td>
<td>Mutation/Amplification</td>
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</table>
• 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
- Amplifications:
  - Gene copy number
    * diploid tumor: ≥6
    * tetraploid tumor: ≥7
  - Amplicon size
    * ≤1 Mb
    * ≤10 Mb if protein overexpression/or loss of expression is validated in IHC
SHIVA01

Effective accrual

Expected accrual

Effective randomizations

Expected randomizations
SHIVA01

Tumor biopsy

DNA extraction

IHC (hormone receptors determination)

Gene copy number alteration (Cytoscan HD)

Mutation analysis (AmpliSeq - Ion Torrent)

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
741 patients (pts) included

716 pts underwent a biopsy

86% ER/PR/AR: 638 pts

70% Ampliseq: 520 pts

70% Cytoscan HD: 522 pts

67% Complete: 496 pts

293 pts identified for randomization

27% 197 pts randomized / 195 pts analyzed

Experimental arm: 99 pts

99 pts treated

91 PD or † (76 PD/61 †)

Reference arm: 96 pts

92 pts treated (1 with MTA)

90 PD or † (79 PD/57 †)
**SHIVA01**

**MTA arm**

- Breast
- Ovary
- Lung
- CRC
- Cervix
- HNSCC
- Sarcoma
- Urothelial
- Pancreas
- ACUP
- Oesogastric
- ACC
- non-ACC SGT
- HCC
- Anus
- Neuroendocrine
- Biliary
- UCNT
- melanoma
- Other

**TPC arm**

- Other = mesothelioma, peritoneum (1 each)

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*Other = CNS, prostate, uveal melanoma, germline, kidney (1 each)*
<table>
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<th>TPC arm (N=96)</th>
<th>All (N=195)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Female – no. (%)</td>
<td>60 (61%)</td>
<td>69 (72%)</td>
<td>129 (66%)</td>
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<td>Male – no. (%)</td>
<td>39 (39%)</td>
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<tr>
<td>RMH score</td>
<td></td>
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<tr>
<td>0 or 1 – no. (%)</td>
<td>51 (52%)</td>
<td>48 (50%)</td>
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<td>Molecular pathway altered – no. (%)</td>
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<td>36%</td>
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<td>PI3K pathway</td>
<td>50%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>MAPK pathway</td>
<td>46%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>RMH score of 0 or 1</td>
<td>45%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>RMH score of 2 or 3</td>
<td>41%</td>
<td>44%</td>
<td></td>
</tr>
</tbody>
</table>
PFS – Hormone receptor pathway

HR 1.12 (95% CI 0.70-1.78); p=0.64

SHIVA01

PFS – PI3K/AKT/mTOR pathway

SHIVA01

- PTEN inactivations: 52%
- PIK3CA activating mutations: 33%
- PIK3CA activating mutations associated with PTEN inactivation: 7%
- STK11 inactivations: 1%
- Others: 1%
- AKT1 amplifications: 2%
- AKT1 activating mutations: 1%
PFS – MAP kinase pathway

MPACT (NCI)

Tumor biopsy from all patients for sequencing

Mutation detected

OR

Mutation not detected

RANDOMIZATION (clinical team is blinded)

Arm A

Assign treatment identified to target mutation

DISEASE PROGRESSION

Arm B

Assign treatment NOT identified to target mutation

Off Study

Kummar et al. NCI-EORTC-ASCO 2013
SAFIR02 Breast (UNICANCER)

SCREENING PHASE N=460

- Biopsy or archived frozen specimen from metastatic tumor to proceed with:
  - CGH Array
  - Next Generation Sequencing

- Metastatic Breast cancer
- Her2 negative
- Resistant to endocrine therapy if ER+
- 2 lines of chemotherapy max

RANDOMIZED PHASE N=240

Randomisation 2:1

- Targetable Molecular Aberration
- Partial response or Stable disease
- No targetable alteration, or not eligible for randomisation
- Not randomised

Arm A: Targeted treatment
- AZD2014
- AZD4547
- AZD5363
- AZD9331
- selumetinib
- vandetanib
- bicalutamide
- olaparib

Arm B: chemotherapy arm
Continue the same chemotherapy as a maintenance treatment (or no antineoplastic treatment if treatment was discontinued due to toxicity)

Chemotherapy: 6 to 8 cycles or stopped after 4 cycles for toxicity

Progression at any time or discontinuation due to intolerable toxicity before the 5th cycle

Partial response or Stable disease

université PARIS-SACLAY
SAFIR02 Lung (UNICANCER)

SCREENING PHASE N=650

- Biopsy or archived frozen specimen from primitive or metastatic tumor to proceed with:
  - CGH Array
  - Next Generation Sequencing

- Locally advanced or metastatic NSCLC
- no EGFR-activating mutation or ALK translocation
- chemo-naive or receiving 1st line platinum-based chemotherapy (2 cycles max.)

RANDOMIZED PHASE N=230

Randomisation 2:1

Arm A: Targeted treatment
- AZD2014
- AZD4547
- AZD5363
- AZD8931
- selumetinib
- vandetanib

Arm B: standard maintenance therapy
- pemetrexed in non-squamous
- erlotinib in squamous

Chemotherapy 4 cycles

Partial response or Stable disease

Targetable molecular alteration

No targetable alteration, or not eligible for randomisation

Progression or toxicity

not randomised
### Summary

#### Precision medicine trials

<table>
<thead>
<tr>
<th></th>
<th>Stratified trials</th>
<th>Algorithm-testing trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Molecularly-stratified</td>
<td>Histology-stratified</td>
</tr>
<tr>
<td>Tumor types</td>
<td>1</td>
<td>N</td>
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<tr>
<td></td>
<td></td>
<td>1 or N</td>
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<td>Treatments</td>
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<td>1</td>
</tr>
<tr>
<td>Test</td>
<td>Test <strong>drugs</strong> efficacy</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- Green triangle: Molecular alterations present
- Yellow triangle: Histology alterations present
- Red triangle: Non-randomized
- Gray square: Randomized
- Orange circle: Treatment
- Blue square: Tumor type 1
## Summary

### Precision medicine trials

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<td>N1 or N2</td>
<td>1</td>
<td>N</td>
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Outline

• Stratified precision medicine trials:
  - Molecular stratification
  - Histologic stratification

• Algorithm-based trials:
  - Non-randomized trials
  - Randomized trials

• Lessons & Perspectives
Lessons

• It is **feasible** to use **high throughput technologies** to guide therapy in **real time**
Lessons

• It is feasible to use high throughput technologies to guide therapy in real time.
• Targeted therapy is associated with substantial toxicity.
Lessons

• It is **feasible** to use **high throughput technologies** to guide therapy in **real time**

• **Targeted therapy** is associated with **substantial toxicity**

• There is **no robust data** to date suggesting that using **high throughput technologies** to guide therapy improves **patients’ outcome**
Perspectives

• Better drugs
Perspectives

- Better drugs
- Coexisting molecular alterations
• Vemurafenib in BRAF-mutated tumors

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<tr>
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<th>Melanoma</th>
<th>NSCLC</th>
<th>ECD/LGH</th>
<th>CRC</th>
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<th>CholangioK</th>
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<td><strong>ORR</strong></td>
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<td>42%</td>
<td>43%</td>
<td>0</td>
<td>5%</td>
<td>12%</td>
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<td><strong>PFS</strong></td>
<td>7 mo</td>
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**Conclusions**

BRAF V600 appears to be a targetable oncogene in some, but not all, nonmelanoma cancers. Preliminary vemurafenib activity was observed in non–small-cell lung cancer and in Erdheim–Chester disease and Langerhans’-cell histiocytosis. The histologic context is an important determinant of response in BRAF V600–mutated cancers.
• Is **histology** the real determinant of response to vemurafenib in BRAF-mutated tumors?

→ **Unidimensional treatment algorithm**
Perspectives

• Is **histology** the real determinant of response to vemurafenib in BRAF-mutated tumors?
  → **Unidimensional treatment algorithm**

• Or the **molecular landscape**?
  → **Multidimensional treatment algorithm**
Perspectives

• Better drugs
• Coexisting molecular alterations
• Drug combinations
Perspectives

- Better drugs
- Coexisting molecular alterations
- Drug combinations
- Less heavily pretreated patient population
Conclusions

- The question remains open whether oncology will move from a histology-oriented to a histology-agnostic treatment paradigm
- Treatment algorithms will need to be refined to bring the proof-of-principle
- Sharing data +++
- Systems biology approaches
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