Médecine de précision en oncologie

Académie Nationale de Pharmacie
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Gustave Roussy
Precision medicine (preferred term)/personalised medicine. A healthcare approach with the primary aim of identifying which interventions are likely to be of most benefit to which patients based upon the features of the individual and their disease. In cancer, the term usually refers to the use of therapeutics that are expected to confer benefit to a subset of patients whose cancer displays specific molecular or cellular features (most commonly genomic changes and gene or protein expression patterns). Nevertheless, the term also includes the use of prognostic markers, predictors of toxicities and any parameter such as environmental and lifestyle factors that leads to treatment tailoring. Characterisation approaches in the future are expected to encompass a wider range of technologies such as functional imaging.

Yates, Ann Oncol, 2018
Which rationale for this concept?

Genomic characterization of cancers have shown that frequent cancers include large number of genomic segments.
Impact of targeting mechanisms of cancer progression

Estimated survival of metastatic cancers according to molecular alteration (months)

Identification and targeting molecular mechanisms involved in cancer progression improves outcome.
Similar concept applies with immunotherapeutics (PDL1)
Increase efficacy

B-RAF inhibitor in NSCLC (V600E BRAF mutation)
ESMO 2014

~2% NSCLC

ALK inhibitor in NSCLC (ALK rearrangement)
NEJM 2010

~4% NSCLC

EGFR inhibitor in NSCLC (EGFR mutation)
Lancet Oncol 2012

~10% NSCLC

ROS1 inhibitor in NSCLC (ROS1 rearrangement)
NEJM 2014

~1% NSCLC
Crizotinib

**Speed-up drug development**

- **Crizotinib**

- **4 years**

- Spring 2006, initial phase I FIH trial of crizotinib initiated in patients with advanced solid tumors refractory to standard therapy.
- Summer 2007, Nature publication on EML4-ALK described as a driver mutation in 6.7% of NSCLC cases, and 1 week after first ALK+ patient enrolled onto phase I trial.
- Fall 2007, crizotinib protocol amended to include a EML4-ALK NSCLC expansion cohort.
- Summer 2008, first patient on extension cohort initiates therapy with crizotinib.
- Summer 2009, single-arm and randomized second-line studies initiated.
- Fall 2008, ALK+ patients show objective responses of 50%.
- ASCO abstract by Bang et al.: ORR of 64% (n = 76).
- NDA submission based on single-arm studies showing ORRs of 50-60%.
- 2011: Crizotinib receives accelerated approval under Subpart H along with its Vysis companion diagnostic.
- Pfizer submitted results for phase III randomized study vs. chemotherapy in second-line ALK+ advanced NSCLC.
- 2013: FDA grants conversion to full approval for ALK+ NSCLC.
Gustave Roussy molecular screening program
MOSCATO

Patients with lethal Cancer

Tumor Specimen

Molecular profiling

Targeted therapy according to the molecular profile

Intelling reports

Can molecular profiling improve patient outcome?
Design of MOSCATO

- High through-put analysis in a high volume phase I center
- Monocentric
- Target accrual => 1000 patients

Max 21 calendar days
Objectives of MOSCATO

• **Primary Objective:** To show that broad molecular screening improves outcome
  - **Statistical hypothesis:** > 25% of patients treated according to their genomic alteration will experience a clinical benefit defined by a **PFS ratio > 1.3**

- **PFS 1**
  - Standard Therapy

- **PFS 2**
  - Relevant Molecular Targeted Agent (MOSCATO)

- **PFS 2**
  - > 1.3

- **Tumor Progression**
  - PFS 1
  - PFS 2

• **Secondary Objectives**
  - To assess the feasibility of this approach
  - To improve tumor response
  - To assess the percentage of patients treated with a selected therapy
  - To assess the frequency of genomic alterations
  - To speed-up drug development through enrichment of trials in biomarker-defined patients (stratified medicine)
Methods of MOSCATO

FRESH TUMOR BIOPSY → PATHOLOGICAL CONTROL

MOLECULAR SCREENING
CGH & NGS & RNAseq & WES

CLINICAL DECISION → TREATMENT

CGH array Agilent
(180K, Whole genome coverage)

Ion Torrent PGM – Life Technologies
(Ampliseq CHP2 + custom n=75 genes, Dec 2013)

Analysis Improvement:
30 genes then 50 then 75 genes screened
then moved partially in may 2014 to WES + RNASeq
Methods of MOSCATO

- **Clinical Decision**
  - Weekly Tumor Board discussion
  - Clinicians / Biologists / Bioinformaticians

- **Treatment**
  - Phase I/II trial compounds
    - > 60 phase I trials @ Gustave Roussy
    - > 20 Actionable Targets
  - Off label use of EMA approved MTA

RESULTS of MOSCATO

Cumulative number of biopsies over time

N patients

0 100 200 300 400 500 600 700 800 900 1000


949 adults
Biopsy and decision in MOSCATO 01 are performed in *clinically* relevant timing.

Median 24 days
IC95 0-59 days

Median 25 days
IC95 12-56 days
Summary of MOSCATO results

- Patients included: n=1110
  - Adults included: n=1036
  - Molecular portrait (NGS or CGH): n=844
    - NGS+CGH: n=740 / NGS alone: n=98 / CGH alone: n=6
  - Actionable Target, n=411 (IHC alone n=1)
  - Molecular tumour board (MTB): n=949
  - Received Matched Treatment: n=199
  - Primary endpoint completed: n=193

- Pediatrics: N=74
  - Screen failure: N=87
    - No possible biopsy: n=28
    - SAE: n=25
    - Consent withdrawal: n=11
    - Clinical deterioration or death: n=5
    - Other: 11
    - Missing: n=7

- No NGS nor CGH: n=103

- No Actionable Target based on NGS or CGH: n=434
  - rapid clinical deterioration: n=62
  - waiting for treatment: n=37
  - exclusion criteria: n=18
  - trial not open: n=12
  - absence of progressive disease: n=6
  - patient refusal: n=3
  - Other: n=64, unknown: n=6

- PFS1 missing: n=5
  - PFS2<1.3*PFS1 and not yet progressed: n=1

Massard et al. Cancer Discov 2018
Results for primary endpoint

\[ \text{PFS ratio} > 1.3 = 33\% \]
\[ \text{IC95 PFS ratio} = 26\%-39\% \]
\[ H0 \text{ rejected with a p-value} < 0.001 \]

Massard et al. Cancer Discov 2018
Results for secondary endpoints

Best response rate for the MOSCATO patients

CR + PR = 11% (22/193)
CR + PR + SD = 63% (122/193)

Best percent change from baseline (RECIST1.1)

+20%  
-30%  

Massard et al. Cancer Discov 2018
Patients
N=43 (4%)

Biopsies
N=48
Fit for analysis
N=38 (79%)

No biopsy = 3
Cellularity < 10% = 6
Not realized = 1

No alteration found
N=5

Druggable molecular aberration(s)
N=25 (66%)

Treated
N=19 (76%)

Winner tumor type
e.g. cholangiocarcinoma

Verlingue et al. Eur J Cancer 2017
Winner tumor type

*e.g. cholangiocarcinoma*

Median PFS ratio = 1.52
IC95 [0.08-7.1]
PFS ratio > 1.3 = 44%

Response rates

PR+CR = 32%

Progression free survival

6-month PFS rate = 42%

Molecular targets

Altered pathway:
- EMT
- Metabolism
- TKR
- MAPK
- DNA damage
ERBB3 alterations
N=33 (3.7%)

- Amp
  N=2
- Hotspots
  N=6
- VUP
  N=13
- NPV
  N=13

1 patient with 2 alterations in ERBB3

Received therapies
N=28

- HER3 partners inhibitors
  N=11
- Other treatments
  N=17

NPV: non pathogenic variant
VUP: variant of unknown pathogenicity
Amp: amplification
HER3 partners’ inhibitors:
- Trastuzumab and/or lapatinib
- Afatinib
ERBB3

- **Ongoing treatment**
- **PFS < 100 days**
- **PFS > 200 days**

**HER2 directed monoclonal antibodies**

**HER2/pan HER directed small molecules**

**Domain Breakdown**
- **Extracellular domain**
- **Transmembrane domain**
- **Kinase domain**
- **Docking domain**

**Mutations**
- V140L
- A159T
- S846I
- E928G
- G661S
- Q865H
- K329E
- A159T
- V140L
- G661S
- Q865H
Current questions?

- Should we use large panel of genes?
- How to develop drugs in rare genomic segments?
- Prediction of sensitivity?
- Detecting subclones and monitoring clonal evolution?
Current questions?

• Should we use large panel of genes?

• How to develop drugs in rare genomic segments?

• Prediction of sensitivity?

• Detecting subclones and monitoring clonal evolution?
Should we use large panel of genes?

- Because it allows testing the few relevant genes in a single assay.
- Because it allows finding alterations in other genes for which relevance to cancer is shown but there is no drug approval.
- Because it allows having «global picture» of cancer genome and mutational processes.
- Because it allows modeling disease biology in each patient.
“FDA approved Thermo Fisher Scientific’s Oncomine™ Dx Target Test as the first next-generation sequencing (NGS)-based companion diagnostic that screens tumor samples against panels of biomarkers”
Femme 30 ans

Cholangiocarcinome intra-hépatique (Avril 2011)

En progression après:
- Mai 2011: Radioembolisation (Yttrium90)
- Mai-Sep 2011: Folfox
- Fev-Juin 2012: Folfox
- Juin-Dec 2012: Gemiinctabine-Cisplatine
- Jan-Avr 2013: Sunitinib
- Avr-Mai 2013: Paclitaxel
- Juin 2013: MOSCATO

WES et RNAseq

No mutation

Translocation FGFR2-CCAR1
Should we use large panel of genes?

Fusion FGFR2-CCAR1 → FGFR inhibitor
• Should we use large panel of genes?

• How to develop drugs in rare genomic segments?

• Prediction of sensitivity?

• Detecting subclones and monitoring clonal evolution?
Drug development in rare genomic entities

TRK fusions found in diverse cancer histologies

- Brain cancers (glioma, GBM, astrocytoma)
- Salivary (MASC)
- Thyroid cancer
- Lung cancer
- Pancreatic Cholangiocarcinoma
- GIST
- Colon Melanoma
- Sarcoma (multiple)

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

<table>
<thead>
<tr>
<th>Fusion</th>
<th>Tumor histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTRK1</td>
<td>CRC, sarcoma, Spitzoid melanoma, Congenital Infantile fibrosarcoma</td>
</tr>
<tr>
<td>LMNA-NTRK1</td>
<td></td>
</tr>
<tr>
<td>TPM3-NTRK1</td>
<td>CRC, PTC, GBM, Sarcoma, NSCLC, Breast cancer, Gallbladder cancer, Cholangiocarcinoma</td>
</tr>
<tr>
<td>SQSTM1-NTRK1</td>
<td>NSCLC, PTC, sarcoma</td>
</tr>
<tr>
<td>NTRK1-SQSTM1</td>
<td>NSCLC</td>
</tr>
<tr>
<td>NFE2L2-NTRK1</td>
<td>GBM</td>
</tr>
<tr>
<td>BANF1-NTRK1</td>
<td>GBM</td>
</tr>
<tr>
<td>PTPN11-NTRK1</td>
<td>Thyroid carcinoma</td>
</tr>
<tr>
<td>RP110N1-RTRK</td>
<td>Large cell neuroendocrine tumor of the lung</td>
</tr>
<tr>
<td>CDKN1A-NTRK1</td>
<td>NSCLC, GBM</td>
</tr>
<tr>
<td>MRRPP1-NTRK1</td>
<td>NSCLC</td>
</tr>
<tr>
<td>RBGAP11-NTRK1</td>
<td>Intrahepatic cholangiocellular carcinoma</td>
</tr>
<tr>
<td>TGF-NTRK1</td>
<td>Thyroid carcinoma</td>
</tr>
<tr>
<td>TP53-NTRK1</td>
<td>Spitzoid melanoma</td>
</tr>
<tr>
<td>MM4-NTRK1</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>TPX-NTRK1</td>
<td>PTC, CRC</td>
</tr>
<tr>
<td>CHTOP-NTRK1</td>
<td>GBM</td>
</tr>
<tr>
<td>ARM1SF2-NTRK1</td>
<td>GBM</td>
</tr>
<tr>
<td>PEAR1-NTRK1</td>
<td>Sarcoma, Breast cancer</td>
</tr>
<tr>
<td>CEL-NTRK1</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>THAP1-NTRK1</td>
<td>PTC</td>
</tr>
<tr>
<td>HSPBP2-NTRK1</td>
<td>PTC, NSCLC</td>
</tr>
<tr>
<td>GRIK5-NTRK1</td>
<td>PTC</td>
</tr>
<tr>
<td>LRRC71-NTRK1</td>
<td>NSCLC</td>
</tr>
<tr>
<td>MRPL24-NTRK1</td>
<td>NSCLC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Representative Tumors</th>
<th>TRK Fusion Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>≤1%</td>
</tr>
<tr>
<td>CRC</td>
<td>≤1%</td>
</tr>
<tr>
<td>MASC*</td>
<td>90-100%</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>1-10%</td>
</tr>
<tr>
<td>Papillary thyroid</td>
<td>1-10%</td>
</tr>
<tr>
<td>Astrocytoma/glioblastoma</td>
<td>1-5%</td>
</tr>
</tbody>
</table>

* Mammary Analog Secretory Carcinoma
Drug development in rare genomic entities

Diversity of cancers treated - 17 unique types

- Peripheral nerve sheath tumor: 4%
- Sarcoma, NOS: 4%
- Myopericytoma: 4%
- Cholangiocarcinoma: 4%
- Spindle cell sarcoma: 5%
- GIST: 5%
- Melanoma: 7%
- Lung: 7%
- Colon: 7%
- Thyroid: 9%
- Infantile fibrosarcoma (IFS): 13%
- Salivary gland: 22%
- Inflammatory myofibroblastic kidney tumor: 2%
Drug development in rare genomic entities

Larotrectinib

Efficacy regardless of tumor type

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy. **Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
Drug development in rare genomic entities

- **Drug Development and Implementation in Orphan Molecular Entities**
  - Rare genomic alterations with unmet medical need
  - Single-group practice-changing trial
  - After regulatory approval

- **Larotrectinib in Cancers with NTRK Translocation**
  - NTRK fusions in <1% of cancers
  - Oncogenic
  - No treatment available
  - Objective response rate, 80%
  - 71% of responses ongoing at 1 yr
  - After regulatory approval?

- **Milestones**
  - Decision to start a single-group registration trial
  - Interpretation of the data
  - Implementation

- **Tools Being Developed**
  - Historical controls: database to assess natural history of orphan molecular segments (e.g., GENIE)
  - Preclinical models
  - Magnitude of Clinical Benefit Scale for single-group studies (ESMO)
  - Nationwide access to multi-gene panels (e.g., France Génomique 2025)
  - Drug positioning in the existing landscape: need for prognostic biomarkers in metastatic cancers
  - Postapproval trials: objectives, design

- **Pending Issues**
  - How to define an orphan molecular entity in oncology?
  - Incidence (Orphan Drug Act?), relation of genotype and phenotype, transtumor relevance
  - Statistical tools to claim transtumor efficacy
  - Definition of the companion diagnosis in the context of multi-gene sequencing
  - New pathways of care in which few centers deliver therapy to patients with an orphan molecular entity
  - Efficacy threshold below which drugs developed in single-group trials are withdrawn from markets

Andre F, NEJM, 2018
Drug development in rare genomic entities

Basket protocol

1 molécule → 1 ou plusieurs anomalies moléculaires → plusieurs types tumoraux
Drug development in rare genomic entities

Efficacy according to histology? e.g. BRAF

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 Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, 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.

Vemurafenib Basket Study Schema

V600 BRAF Mutation Identified Locally

Lung Cancer → Ovarian Cancer → Colon Cancer → Cholangio-Carcinoma → Breast Cancer → Multiple Myeloma → Other Solid Tumors

Treatment with Vemurafenib (and Cetuximab in colorectal cancer) until progression or intolerable side effects

Primary Endpoint: Overall response rate (at 8 weeks)
Secondary Endpoint: Progression Free Survival

Centralized retrospective testing of all tumors to confirm V600 BRAF mutation

Hyman DM et al. NEJM 2015
Drug development in rare genomic entities

Mutation BRAF V600E
Mélanome

ORR ≈ 50%

Mutation BRAF V600E
Cancer du colon

ORR = 5%

## Level of evidence for actionability

<table>
<thead>
<tr>
<th>ESCAT evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical value class</th>
<th>Clinical implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ready for routine use</td>
<td>I: Alteration-drug match is associated with improved outcome in clinical trials</td>
<td>I-A: A prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point</td>
<td>Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)</td>
</tr>
<tr>
<td>Investigational</td>
<td>II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown</td>
<td>II-A: retrospective studies show patients with the specific alteration in a specific tumour type experience clinically meaningful benefit with matched drug compared with alteration-negative patients</td>
<td>Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumour type, but additional data are needed</td>
</tr>
<tr>
<td>Hypothetical target</td>
<td>III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration</td>
<td>III-A: clinical benefit demonstrated in patients with the specific alteration (at tiers I and II above) but in a different tumour type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types</td>
<td>Drug previously shown to benefit the molecularly defined subset in another tumour type (or with a different mutation in the same gene), efficacy therefore is anticipated for but not proved</td>
</tr>
<tr>
<td>Combination development</td>
<td>IV: pre-clinical evidence of actionability</td>
<td>IV-A: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical in vitro or in vivo models</td>
<td>Actionability is predicted based on preclinical studies, no conclusive clinical data available</td>
</tr>
<tr>
<td></td>
<td>V: alteration-drug match is associated with objective response, but without clinically meaningful benefit</td>
<td>V-A: activity is predicted based on preclinical studies, drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation</td>
<td>Drug combination strategies could be considered</td>
</tr>
<tr>
<td></td>
<td>VI: lack of evidence for actionability</td>
<td>VI-A: lack of evidence that the genomic alteration is therapeutically actionable</td>
<td>There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target</td>
</tr>
</tbody>
</table>

### A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

Current questions?

- Should we use large panel of genes?
- How to develop drugs in rare genomic segments?
- Prediction of sensitivity?
- Detecting subclones and monitoring clonal evolution?
Genomic predictors of sensitivity

Sensitivity to anti-PD1

Mutational burden

Number of non-synonymous mutations

Generation of neoantigens

Anti-CTLA-4 in Melanoma

Snyder et al NEJM 2014

Anti-PD-1 in NSCLC

Rizzi et al Science 2015
Genomic predictors of sensitivity

Pembrolizumab et MSI-High

A

B

% Change from Baseline SLD

Le et al. Science 2017
What is the clinical impact of multiple genomic alterations?

Co-existing mutations could be associated with resistance to single agent targeted therapies

Lefebvre & Yu, Personal data
Current questions?

- Should we use large panel of genes?
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Detecting subclones and monitoring clonal evolution?

**Baseline**
- **11 Jul 2012**

**SD (-28%)**
- **30 Aug 2012**

**PR (-36%)**
- **23 Oct 2012**

**PD (New Lesions)**
- **17 Dec 2012**

**CA19.9 Evolution**
- **12-Jul-2012 C1J1**
- **17-Dec-2012 Fin de Traitement**

**Erlotinib**
- **267**
- **59**
- **48**
- **38**
- **35**
- **47**
- **59**

**CT-scan évolution**
- **11 Jul 2012**
- **30 Aug 2012**
- **23 Oct 2012**
- **17 Dec 2012**

**CGH évolution**
- **EGFR**
- **MET**
Perspectives

• Big data

• CfDNA
Perspectives
New generation of software for target prediction & database to train

Big Data
« no amount of algorithmic finesse can squeeze out information that is not present »
(NEJM, 2017)
Integration of multicomponent predictors: example of IO
Perspectives
Multigene panels to detect genomic alterations in plasma

Performance of NGS on plasma DNA to detect actionable mutation

Approach to detect tumor-specific proteins and RNA in blood?

Jovelet, Clin Cancer Res, 2015