Precision medicine in 2017

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Disclosure

- Participation to advisory boards, speaker or investigator for: Amgen, Astellas, Astra Zeneca, Bayer, Celgene, Genentech, Ipsen, Jansen, Lilly, Novartis, Pfizer, Roche, Sanofi, Orion, MedImmune, New Oncology, DebioPharm
Disclosure

• I am a medical oncologist

• I am a Phase 1 PI, and a strong believer in Precision medicine programs

Outline

• Precision medicine
• Genotype-based clinical trial
• Challenges and perspective
Outline

• Precision medicine
  – We are still believers
• Genotype-based clinical trial
• Challenges and perspective
Conceptual evolution of Cancer treatment

- Few therapeutic options to treat tumors:
  - Surgery
  - Radiotherapy
  - Few chemotherapies

- Increase on therapeutic options allowed specific treatments for different tumor types:
  - Combined chemo-radiation
  - Specific protocols

- Targeted agents that work in specific molecular alterations:
  - Broad knowledge of molecular tumor biology and immune context

Disease guided approach → Pathological guided approach → Molecular & immune approach

Technology has improved...

- SANGER sequencing
- RT-PCR
- Sequenom/SNAPshot
- NGS
- WES/RNAseq

Decreasing costs

Decreasing costs

Decreasing costs

MacConaill L E, Garraway L A JCO 2010;28:5219-5228
We believe in precision medicine...

...and we need to biopsy patients and discuss phase I trials

Courtesy Pr T DeBaere, Gustave Roussy
The molecular portrait performed on material at time of diagnosis

Does not predict for the molecular portrait of the current disease

S Vignot, JC Soria

Precision Medicine: To identify and hit the target

A virtuous circle (I)

Targeted therapy according to the molecular profile

Identification of the molecular alteration

Can molecular profiling improve patient outcome?

MOSCATO: MOlecular Screening for CAncer Treatment Optimization
The revolution in drug development is a change in nature and goals of early phases.

Classical drug development paradigm before 2000

**Phase I**
- **PURPOSE**: Find MTD
- **EMPHASIS**: Safety
- **ENDPOINT**: Toxicity (DLT)
- **N (patients)**: 20-60
- **Registration value**: Null

**Phase II**
- **PURPOSE**: Define Activity
- **EMPHASIS**: Activity
- **ENDPOINT**: Response (ORR)
- **N (patients)**: 20-200
- **Registration value**: Limited

**Phase III**
- **PURPOSE**: Compare with SOC
- **EMPHASIS**: Efficacy
- **ENDPOINT**: Survival (PFS, OS)
- **N (patients)**: 200-2000
- **Registration value**: Major

The revolution in drug development is a change in nature and goals of early phases.

**Phase I/II**
- **PURPOSE**: Define MTD and Activity
- **EMPHASIS**: Safety & Activity & Biomarkers
- **ENDPOINT**: Toxicity & Response (all and selected) & Preliminary Survival
- **N (patients)**: 100-1000 +
- **Registration value**: Real (conditional, breakthrough)

**Phase III**
- **PURPOSE**: Compare with SOC
- **EMPHASIS**: Efficacy
- **ENDPOINT**: Survival (PFS, OS)
- **N (patients)**: 200-2000
- **Registration value**: Major (confirmatory)
DITEP mission: give access cancer patients to innovative molecules in EDD

- Today the DITEP
  ✓ Largest phase I center in France
  ✓ 50% of total activity of all CLIP² centers
  ✓ All comers patients, hemato and XRT trials

PORTFOLIO OF EARLY CLINICAL TRIAL MOLECULES
- Tyrosine Kinase inhibitors (BIBR, BIBR, GSK21, Bibraxicisopropyls, A.A, BRD, MET, A17, PD1, ERK, MDM, BRAF, IAP, Phenolhexane, pharma, HCL, LPA, T.1)
- Inverse CTAK20 inhibitors & Interferon receptors (IFN1, IFN2, E1, 100, CTESFR, CEFHR, CEFHR, CEFHR, CEFHR, CEFHR, CEFHR, CEFHR, CEFHR, CEFHR, CEFHR)
- Antibody Drug Conjugates & Bispecifics: (CD3-GAG, MET, CD20, VEGF-A, ICI)
- Cell Cycle & Apoptosis: (DM, MDM, Proteasome, BCL2, CDK4, Erb-1, AIP, IAP)
- Androgen Receptors, Progesterone Receptor inhibitors
- Synthetic inhibitors (CDK4, BCC, ENT, 9.3, HSGC, IBD)
- Other: Monoclonal antibodies

Precision Medicine: To identify and hit the target
A virtuous circle (II)
Outline

• Precision medicine
• **Genotype-based clinical trial**
  - Basket-trials
    - VE-basket
    - Basket of basket: CAPTURE
  - Umbrella trials
• Challenges and perspective
Design of MOSCATO

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

Max 21 calendar days

Antoine Hollebecque et al., ASCO 2013; Charles Ferte et al, AACR 2014

Selected Molecular Profiling Initiatives and Genotype-Matching to Clinical Trials

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample Size</th>
<th>Platform</th>
<th>Fresh Biopsy vs FFPE</th>
<th>Germ-line Control</th>
<th>Number and % of “Matched” Patients in Genotype-Matched Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustave Roussy MOSCATO</td>
<td>1,035</td>
<td>40-75 gene panels (Life) + CGH (Agilent) + RNA Seq</td>
<td>Fresh biopsy</td>
<td>Yes</td>
<td>199/1035 = 19%</td>
</tr>
<tr>
<td>Institut Curie</td>
<td>741</td>
<td>46 gene panel (Life) + CNA (Affymetrix) + IHC</td>
<td>Fresh biopsy</td>
<td>No</td>
<td>195 randomized/741 = 26%</td>
</tr>
<tr>
<td>BCCA</td>
<td>100</td>
<td>Whole genome</td>
<td>Fresh biopsy</td>
<td>Yes</td>
<td>1/100 = 1%</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>2,000</td>
<td>11-50 gene panels (Life)</td>
<td>FFPE</td>
<td>No</td>
<td>83/2000 = 4%</td>
</tr>
<tr>
<td>Princess Margaret</td>
<td>1,640</td>
<td>23-48 gene panels (Illumina, Life)</td>
<td>FFPE</td>
<td>Yes</td>
<td>92/1640 = 5.6%</td>
</tr>
</tbody>
</table>

CNA = Copy number alterations; IHC = Immunohistochemistry

Molecularly profiled patients with different histologies

Histology-independent, aberration-specific clinical trial design (“basket” of basket trials)

Sleijfer S, Bogaerts J, Siu LL, J Clin Oncol 2013

Three categories

- (One drug, several tumor types)
- One drug, one molecular alteration, several tumor types
- One drug, several molecular alterations, several tumor types

Importance of Basket Studies


Courtesy J Rodon
One drug -> Several molecular alteration -> Several tumor types

Phase II: secured access to crizotinib

Statistical design
- Marked clinical objective response (OR, PR) after 2 cycles. TTG is changed to the best response for cohorts that are displaying relevant responses.
- Three statistical 2-stage designs are considered for cohorts to anticipate 3 prescriptions in terms of expected response rate and incidence. Actual p-value is calculated for each cohort based on the data of the second stage.
- General cohort: major OR ≥5%.
- Combination therapy: OR ≥5% in combination and IASLC consensus.
- We compare between arm studies.

Clinicaltrials.gov. NCT02034981.

Cancer Core Europe: Study Design

STUDY CHAIR: Jordi Rodon
Histology-based clinical trial design to evaluate multiple molecular aberrations ("umbrella" trials)

Sleijfer S, Bogaerts J, Siu LL, J Clin Oncol 2013

SAFIR 02lung-IFCT1301

Biopsy metastatic site:
Next generation sequencing
Array CGH

Molecular alteration
Excluding EGFR mut and ALK t

Chemotherapy 4-6 cycles

No PD

Followed up but not included

N= 650

N= 230

Ethics approval sept 2013; ANSM approval oct 2013, FPI april 2014
Outline

• Precision medicine
• Genotype-based clinical trial
• Challenges and perspective
  – “Finding trials for patients” (J Rodon)
  – Precision medicine and immunotherapy
  – DNA repair

Building a Molecular Prescreening program

- No prescreening
- Prescreening per trial ("Finding patients for trials")
  - preferred by Pharma
  - ok for small sites without diagnostic capabilities
  - ok for sites with a small portfolio

- Broad prescreening ("Finding trials for patients")
  - preferred by patients and by investigators
  - ok for large sites/large portfolios/cooperative groups.
Challenge #1: How do we identify sensitive disease?

Durvalumab efficacy in advanced bladder cancer

Three patients have ongoing, unconfirmed responses and 19 patients are ongoing and not evaluable. Data cutoff on November 20, 2015.


PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Challenge #2: How do we overcome resistance to immune checkpoint blockade therapy?

**Durvalumab efficacy in advanced bladder cancer**

![Graph showing Durvalumab efficacy in advanced bladder cancer](image)

Three patients have ongoing, unconfirmed responses and 19 patients are ongoing and not evaluable. Data cutoff on November 20, 2015.

Challenge #3: new patterns of response/progression?

**Durvalumab efficacy in advanced bladder cancer**

![Graph showing Durvalumab efficacy in advanced bladder cancer](image)

Three patients have ongoing, unconfirmed responses and 19 patients are ongoing and not evaluable. Data cutoff on November 20, 2015.
Pseudoprogression in melanoma patients

And progression?
Hyperprogressive disease (HPD): a new pattern of progression

Champiat et al, Clin Cancer Res 2016
DNA repair defects in PCa
Treatment opportunities

Platinum-based chemotherapy

Deficient HR-FA pathway:
- PARPi
- DNA-Pki

Deficient DNA damage response
- ATRi
- CHEK1/2i

Deficient MMR
- Hypermutator phenotype
- Novel neoantigens
- Immune-Chekpoints inhibitors

mCRPC & prevalence of germline DNA repair mutations

Spanish Prospective study in mCRPC

<table>
<thead>
<tr>
<th>Gene</th>
<th>N=431</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>8</td>
<td>1.9%</td>
</tr>
<tr>
<td>BRCA1</td>
<td>4</td>
<td>0.9%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>13</td>
<td>3.0%</td>
</tr>
<tr>
<td>BRIP1</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>CHEK2</td>
<td>4</td>
<td>0.9%</td>
</tr>
<tr>
<td>MRE11A</td>
<td>2</td>
<td>0.5%</td>
</tr>
<tr>
<td>MSH2</td>
<td>2</td>
<td>0.5%</td>
</tr>
<tr>
<td>MSH6</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>35</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

- 12% vs 8%
- Different population may have different backgrounds:
  Anglo-American study:
  -50% and 24% of the BRCA1 and BRCA2 mutations were founder Ashkenazi mutations
  - 55% of CHEK2 were the Eastern European founder mutation c.1100delC

Pritchard et al. NEJM 2016; Castro & Olmos (PROCURE studies network) Unpublished
Histologies of patients with DNA repair genes’ alterations

Landscape of DNA Damage Response (DDR) Genes Alterations in Prospective MOSCATO and MATCH R Trials; Yolla El Dakdouki et al, ESMO 2017

DDR genes alterations occur in almost 10% in metastatic solid tumors

MOSCATO 02:
Integrating immune markers and non-invasive biomarkers to select patients for phase I trials

IGR
MOSCATO 02:
NGS (updated panel)
CGH
Immune profile
(300 / year)

WES
RNA-seq

ctDNA

Soria JC, Marabelle A, Hollebecque A, Lacroix L
Lung cancer management, timelines

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