Biomarker guided Phase 1: from targeted therapies to immunotherapy

Dr Christophe Massard

SIOG 2016 Milan, 19 NOV 2016
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

• 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

• I am a PI of Eli Lilly and Company trial with NOTCH inhibitor

• I will not discuss off label use in my presentation

• I will discuss investigational use in my presentation
CRPC post docetaxel treated with Ipilimumab+RTE
Outline

- Changes in the classical drug development paradigm

- Reasons for the current change in Early Clinical Trials:
  - The advent of precision medicine and molecular targeted agents
  - Trial enrichment and increased response rates
  - Immuno-stimulatory antibodies
  - Open approach of regulators
Outline

• Changes in the classical drug development paradigm

• Reasons for the current change in Early Clinical Trials:
  ✓ The advent of precision medicine and molecular targeted agents
  ✓ Trial enrichment and increased response rates
  ✓ Immuno-stimulatory antibodies
  ✓ Open approach of regulators
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
DITEP mission: give access cancer patients to innovative molecules in EDD

PORTFOLIO OF EARLY CLINICAL TRIAL MOLECULES
- Tyrosine Kinase Inhibitors: FGFR, HER2, EGFR, EGFRmut specific, ALK, ROS, MET, AKT, PI3K, ERK, MEK, BRAF, cKIT, Pleiotropic pathway modifier, VEGFR, FAK, JAK2, TrK
- Immune Checkpoints & Immunomodulators: CTLA4, PD1, PDL1, 4-1BB, CSF1R, CD27L, CD70, IL2v-CEA, Lytic peptide, Antigenic glycopeptide, TNFa inhibitor
- Antibody Drug Conjugate & Bispecific mAb: CEA-CAM5, MET, CD27L, VEGF-Ang2
- Cell Cycle & Apoptosis: FAK, MDM2, Proteasome, BCL2, CDK4/6, Chk1, IAP, ATR
- Androgen Receptor, Progesterone Receptor inhibitors
- Epigenetic inhibitors: EZH2, BET, IDH1 & 2, HDAC, LSD1
- Other: Mesothelin inhibitor

Geographical origin of patients enrolled in phase I trials at Gustave Rousy

Today the DITEP
- Largest phase I center in France
- 50% of total activity of all CLIP² centers
- All comers patients, hemato and XRT trials
> 65% come from beyond 100 km of Paris
The revolution in drug development is a change in nature and goals of early phases

<table>
<thead>
<tr>
<th>Phase I/II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PURPOSE</strong></td>
<td>Compare with SOC</td>
</tr>
<tr>
<td>Define MTD and Activity</td>
<td></td>
</tr>
<tr>
<td><strong>EMPHASIS</strong></td>
<td>Efficacy</td>
</tr>
<tr>
<td>Safety &amp; <strong>Activity</strong> &amp; Biomarkers</td>
<td></td>
</tr>
<tr>
<td><strong>ENDPOINT</strong></td>
<td>Survival (PFS, OS)</td>
</tr>
<tr>
<td>Toxicity &amp; <strong>Response</strong> (all and selected) &amp; Preliminary Survival</td>
<td></td>
</tr>
<tr>
<td><strong>N (patients)</strong></td>
<td>200-2000</td>
</tr>
<tr>
<td>100-1000 +</td>
<td></td>
</tr>
<tr>
<td><strong>Registration value</strong></td>
<td>Major (confirmatory)</td>
</tr>
<tr>
<td>Real (conditional, breakthrough)</td>
<td></td>
</tr>
</tbody>
</table>
The new trend in oncology drug development

- Phase 1
- Phase II
- Phase III

FDA approval on phase I/II data

- MPDL3280A: 334 patients
- Pembrolizumab: 1137 patients
- Nivolumab: 286 patients
- Ceritinib: 304 patients
- Crizotinib: 550 patients

Postel-Vinay S et al, Annals of Oncology 2014
Outline

• Changes in the classical drug development paradigm

• Reasons for the current change in Early Clinical Trials:
  ✓ The advent of precision medicine and molecular targeted agents
  ✓ Trial enrichment and increased response rates
  ✓ Immuno-stimulatory antibodies
  ✓ Open approach of regulators
Working Hypothesis

Drugs that target the molecular mechanisms involved in cancer progression can improve outcome.
Precision medicine aims at selecting the right therapy

Cancer Patient

Tumour type

Therapy

Wrong match

The right drug for the tumour type

Wrong match

Oncologist selects therapy based on experience, histology and tumour site

Adapted from D Weaver
Genotyping

Unselected Phase I population
ORR below 10%

Enriched Phase I population
ORR > 30%, and even > 50%

if if true mechanism-based approach
(oncogen de-addiction, synthetic lethality)
Phase I design modifications

Classical Phase I

Escalation Expansion

X 100 selected pts

Molecular enrichment

Escalation Expansion

Phase I/II trial
Histology-based clinical trial evaluating different aberrations

Histology-independent, aberration-specific clinical trial

Drug A
Drug B
Drug C

Washout period

Drug A → Drug B
Average treatment effect of drug A

Drug A → Drug B
Average treatment effect of drug B

Standard N-of-1 clinical trial design

Molecularly profiled patients with different histologies

Prior drug
Drug A

Prior drug
Drug B

Prior drug
Drug C

Modified N-of-1 clinical trial design

Bedard PB et al, Nature 2013
Number Needed to Analyze: Biomarker-Driven Clinical Research

NNS = \[ \frac{\text{frac with biomarker } \times \text{ assay specificity } \times \text{ frac trial-eligible } \times \text{ frac giving informed consent}}{1} \]

(fraction with biomarker X assay specificity X fraction trial-eligible X fraction giving informed consent)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Pt Needed to Analyze</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+ in Breast cancer</td>
<td>13</td>
</tr>
<tr>
<td>ALK fusion in NSCLC</td>
<td>63</td>
</tr>
<tr>
<td>FGFR fusion in GBM (freq 3-8%)</td>
<td>105</td>
</tr>
</tbody>
</table>
The crizotinib example

→ Crizotinib registered on the basis of phase I and II single arm data by FDA (n= 119 and n=136)

Courtesy Jessica Menis
Third generation EGFR TKI

Activating mutations in EGFR found in ~10% - 15% of caucasian NSCLC

60% of those EGFR mutant acquire T790M

~ 6% of all caucasian NSCLC

CO-1686 was designed to selectively target both the initial activating EGFR mutations as well as the T790M resistance mutation, while sparing wild-type EGFR at anticipated therapeutic doses.

Same for AZD9291
Third generation EGFR TKI

AURA Phase I / II initial study design 2013

- Phase 1 (Dose Escalation)
  - 66 patients
- Expansion Cohort
  - 92 patients

AURA Phase I / II real study

- Phase 1 (Dose Escalation)
- Expansion/Extension Cohorts
  - 20 mg (N=15) Positive
  - 40 mg (N=52) Positive, Negative
  - 80 mg (N=97) Positive, Negative, Biopsy*, First-line (n=30)*
  - 160 mg (N=74) Positive, Negative, Biopsy*, First-line (n=30)*
  - 240 mg (N=14) Positive

556 patients
March 2013-Dec 2014
ORR 66%

Courtesy Serban Ghiorghiu
Third generation EGFR TKI: the osimertinib example

2 years 8 months from FIM to FDA app

Yver A, Annals of Oncology 00: 1–6, 2016
Molecular enrichment is even possible for epigenetic modulators

**BRD4-NUT fusion**

- CREBBP / p300
- MYC
- Direct maintenance of oncogenes

**BRD4 inhibitor**

**Restored balance**

**Epigenetic imbalance**

**Normal SWI/SNF**

- **EZH2 inhibitor**
- H3K27me3

**Oncogenesis**

- SMARCB1 loss
- ARID1A loss
- SMARCA4 loss
- PBRM1 loss

SWI/SNF deficiency

Epigenetic dysregulation

**Synthetic lethal effect selectively kills**

SWI/SNF-deficient tumoral cells

**Normal SWI/SNF**

- H3K27me0

**SWI/SNF deficiency**
CR in Patient with INI1-Negative with EZH2i tazemostat

Baseline

Week 4
June 25, 2014

Week 8: CR

Week 20

55 y.o. male
800 mg BID

INI1 IHC

Diagnosis: Surgery + XRT

Tazemetostat: ongoing response week 65+

2013
CR

2014
PD

2015
Week 8: CR
Week 20: pathologic CR
Holistic molecular screening

Molecular screening with High Throughput Genomics

Target identification

Trial A
Trial B
Trial C
Trial D

Short term Goal: to develop drugs in population defined by a biomarker

Andre, Delaloge, Soria, J Clin Oncol, 2011
Ongoing precision medicine programs in France

Overall: >3,000 planned patients (all tumor types), >1,000 already included
Breast Cancer: >1,000 planned, >90 already treated (preSAFIR / SAFIR / MOSCATO)
Goal: To generate optimal algorithm for individualized therapy
The molecular portrait performed on material at time of diagnosis does not predict for the molecular portrait of the current disease.
MOSCATO 01 trial:
High through-put analysis in a high volume phase I center

- Monocentric
- Target accrual > 1000 patients

**FRESH TUMOR** → **MOLECULAR SCREENING** → **CLINICAL DECISION** → **TREATMENT**

BIOPSY → PATHOLOGICAL CONTROL

CGH Array & NGS & WES & RNAseq

Max 21 calendar days

Antoine Hollebecque et al., ASCO 2013; Charles Ferte et al, AACR 2014
Clear enthusiasm of patients and physicians for molecular screening

Kim E et al, Cancer Discovery 2011
Andre F et al, Lancet Oncol 2014
Le Tourneau C et al, BJC 2014
Outline

• Changes in the classical drug development paradigm

• Reasons for the current change in Early Clinical Trials:
  ✓ The advent of precision medicine and molecular targeted agents
  ✓ Trial enrichment and increased response rates
  ✓ Immuno-stimulatory antibodies
  ✓ Open approach of regulators
Systemic anti-cancer therapies

- Targeted Therapies
- Chemotherapy
- Immunotherapies
Big Hope— for Cancer?

Drug of the year: Programmed Death-1 receptor/Programmed Death-1 Ligand-1 receptor monoclonal antibodies

Caroline Robert, Jean-Charles Soria, Alexander M.M. Eggermont *
Paradigm shift with immuno-stimulatory Ab

Historical Paradigm: Targeting Tumor Cells

New Paradigm: Targeting Immune Cells

Lymphocyte

Tumor Cell

Adapted from A Marabelle
Immuno-stimulatory Antibodies

Mellman I et al. Nature 2011
Best response in phase I trials with Immune checkpoints at Gustave Roussy 2013-2014 (184 patients)*

- 27% PD
- 30% ORR
- 53% SD

* Many belong to expansion cohorts
Phase I design modifications

- Classical Phase I
  - Escalation
  - Expansion
  - 20-30 pts

- Multiple parallel expansion cohorts in **Phase I**
  - 100-1000 patients
  - +/- immune enrichment
  - Escalation
  - Expansion
  - Long-term follow-up
Atezolizumab (MPDL3280A): Phase Ia Study

**Ongoing dose-expansion phase**

- **UBC**
  1. PD-L1 selected
  2. All-comers

- **TNBC**
  1. PD-L1 selected
  2. All-comers

- **Melanoma**
  All-comers

- **NSCLC**
  1. All-comers
  2. PD-L1 selected

- **RCC**
  1. All-comers
  2. PD-L1 selected

- **Other Tumor Types**
  1. PD-L1 selected
  2. All-comers

ORR ranging from 10% to 80% according to PDL1 status and tumor type

N > 350 patients

NCT 01375842
Spectrum of activity of anti PD1/PDL1

Adapted from A Marabelle
US approvals

PD-1/PD-L1 Blockade

Mel
RCC
NSCLC
Bladder
HNSCC
Gastric
Hodgkin
B-Cell NHL
MSI
CRC
Ovarian
TNBC
Mesothelioma
HCC
Eosophageal
SCLC
Biliary Tract
Anal
MCC
Thymic Carcinoma
MMRd GBM
Know your Immune Checkpoint Antibodies

**Anti-CTLA-4**
- Tremelimunab (AZ)
- Ipilimumab (BMS)
- Approved

**Anti-PD-1**
- Nivolumab (BMS)
- Pembrolizumab (MSD)
- Approved

**Anti-PD-L1**
- Durvalumab (AZ/Medimmune)
- Avelumab (Pfizer)
- Atezolizumab (Roche/Genentech)
- Approved
Variable Sensitivity to Immunotherapy

Keytruda Monotherapy Has Shown Activity in 20 Tumors

Other immunotherapies

- Oral Immuno Modulator
- Oncolytic Virus
- CAR T-cells
- Bi Spe
- Cancer Vaccines
Immune Checkpoint Blockade for Therapeutic Action against Multiple Cancer Clones

αPD-1
αPD-L1
αCTLA4
αOX40
α4-1BB
αCD47
αKIR
αCD40
αLAG-3
αTIM-3
αGITR
PD1-induced psoriasis
PD1-induced psoriasis

Patient treated with topical steroids & oral retinoid
7 months after anti PD1 discontinuation
Immuno-stimulatory monoclonal antibodies: key-lessons:

- Inability to identify a maximum tolerated dose (outside CTLA4):
  - RP2D based on the maximum administered dose (MAD) (10 trials)
  - or pharmacokinetic data (2 trials)

- Dose is usually not associated with efficacy nor with toxicity
  - Concept of a minimal immunologically active dose (MIAD)

- Huge variety of doses and schedules evaluated upfront

- Optimal duration of therapy is not defined
  - should imAbs be considered as “vaccines”, with a limited nb of boost sufficient to trigger a durable immune response...
Challenge #1: How do we identify sensitive disease?

**Durvalumab efficacy in advanced bladder cancer**

- **PD-L1+** (≥25% staining on TCs or ICs)
  - Subjects with confirmed response
  - Other subjects
- **PD-L1-** (<25% staining on TCs and ICs)
  - Subjects with confirmed response
  - Other subjects

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

**ASCO ANNUAL MEETING '16**

Massard C et al
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

MSI-H prostate cancer are not so rare (5%)
Known factors that contribute to an effective anti-tumor immune response

- **Inflamed**
  - CD8+ T cells infiltrated, but non-functional
  - Mutational Load
  - Angiogenesis
  - Reactive stroma
  - MDSCs
  - Respond favorably to checkpoint inhibition
  - Convert to inflamed phenotype with combinations

- **Immune Excluded**
  - CD8+ T cells accumulated but have not efficiently infiltrated
  - TILs
  - CD8 T cells/IFNγ
  - PD-L1 & checkpoints

- **Immune Desert**
  - CD8+ T cells are absent from tumor and its periphery
  - Ki67
  - Low MHC I

Modified from Hegde PS et al., Clin Canc Res 2016

Inflamed: Melanoma, Lung, Bladder
Immune Excluded: GC, HCC, CRC, PDAC
Immune Desert: HR BC, Prostate, Ped
# PD-L1 testing

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Merck Sharp &amp; Dohme</th>
<th>Bristol-Myers Squibb</th>
<th>MedImmune/AstraZeneca</th>
<th>Genentech/Roche</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb</td>
<td>Humanized IgG4</td>
<td>Human IgG4</td>
<td>Human Fc-modified IgG1</td>
<td>Human Fc-modified IgG1</td>
</tr>
<tr>
<td>Target</td>
<td>PD-1</td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
</tr>
<tr>
<td>FDA approved</td>
<td>Melanoma</td>
<td>Melanoma, NSCLC</td>
<td>NA</td>
<td>Bladder, NSCLC^a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>coDx assay PD-L1 positive</th>
<th>Dako</th>
<th>Dako</th>
<th>Ventana</th>
<th>Ventana</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC assay developer</td>
<td>22C3 mouse</td>
<td>28-8 rabbit</td>
<td>SP263 rabbit</td>
<td>SP142</td>
</tr>
<tr>
<td>Antibody clone</td>
<td>TCs and stroma</td>
<td>TCs</td>
<td>TCs</td>
<td>TICs and TCs</td>
</tr>
<tr>
<td>Expression location</td>
<td>Melanoma, bladder, NSCLC: ≥1% TC (or any tumor stroma cell)</td>
<td>NSCLC: ≥1% to 5% TC, Renal: ≥5% TC</td>
<td>NSCLC, SCCHN: ≥25% TC</td>
<td>Bladder, NSCLC, breast: IHC2^+ ≥5% to &lt;10% TC or TIC or IHC3^+ ≥10% TC or TIC</td>
</tr>
</tbody>
</table>

Hansen et al. (2015). *JAMA Oncology*  
PD-L1 Testing in Cancer: Challenges in Companion Diagnostic Development.
Biomarkers: mutational load and TSNA?

Exomics and immunogenics
Bridging mutational load and immune checkpoints efficacy
Challenge #2: How do we overcome resistance to immune checkpoint blockade therapy?

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.
Overcoming Resistance to PD-1/PD-L1 blockade with Other Cancer Agents

**ORR = 76% (13/17)**

San Miguel et al, ASH 2015

*Lenalidomide + αPD-1 in Multiple Myeloma*

94% of patients had a reduction in M protein or free light chains

San Miguel et al, ASH 2015
Challenge #3: new patterns of response/progression?

Durvalumab efficacy in advanced bladder cancer

PD-L1\(^+\) (\(\geq 25\%\) staining on TCs or ICs)

PD-L1\(^-\) (\(< 25\%\) staining on TCs and ICs)

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

Novembre 2012

Pseudoprogression in melanoma patients

Decembre 2012

Janvier 2013

Février 2013

Mars 2013

Juillet 2013
And progression?
Hyperprogressive disease (HPD): a new pattern of progression

Champiat et al, Clin Cancer Res 2016
Hyperprogressive disease (HPD): a new pattern of progression

Champiat et al, Clin Cancer Res 2016
Outline

• Changes in the classical drug development paradigm

• Reasons for the current change in Early Clinical Trials:
  ✓ The advent of precision medicine and molecular targeted agents
  ✓ Trial enrichment and increased response rates
  ✓ Immuno-stimulatory antibodies
  ✓ Open approach of regulators
Open approach of regulators (FDA...and EMA?)

- **Food and Drug Administration (FDA) breakthrough designations based on phase I trials results:**
  - AZD9291 and Rociletinib for EGFR T790M NSCLC (May 2014, based on less than 100 patients each)
  - Atezolizumab and bladder cancer (Feb 2014, based on less than 70 patients)

- **FDA conditional approvals based on phase I/II data**
  - Accelerated approval by the FDA in August 2011 for crizotinib and in April 2014 for ceritinib (N=246)
  - Accelerated approval by the FDA in November 2015 for osimertinib (less than 3 years after 1st patient dosed in phase I)
Outline

• Changes in the classical drug development paradigm

• Reasons for the current change in Early Clinical Trials:
  ✓ The advent of precision medicine and molecular targeted agents
  ✓ Trial enrichment and increased response rates
  ✓ Immuno-stimulatory antibodies
  ✓ Open approach of regulators
  ✓ Challenges related to this new paradigm in radiation combo P1
Phase 1 and radiotherapy

• How to select the patients
  – Metastatic cancer patients
  – Localized cancer patients: Head and neck, sarcoma, glioma...

• How to select the biological hypothesis
  – IGNITION (in combo)
  – ADJUVANT (after tumor response)
  – RESCUE (after progression), and ABSCOPAL

• How to select the phase 1 design
Letter to the Editor

Abscopal effect in a Hodgkin lymphoma patient treated by an anti-programmed death 1 antibody

Jean-Marie Michot a, Renaud Mazeron b, Laurent Dercle c, Samy Ammari d, Charles Canova e,f, Aurelien Marabelle a, Shelonitda Rose a, Eric Rubin g, Eric Deutsch h,i,j, Jean-Charles Soria a, Vincent Ribrag a, Antonin Levy a,h,i,j,k,l,m
Blumenfeld et al, 2014; Deutsch et al, 2004
Phase I design modifications

Classical Phase I

20-30 pts

X 100 selected pts

Molecular enrichment +/- immune enrichment

RADIATION COMBO

Phase I/II trial
### Traditional PK
- Limited PD

### Important PK/PD modelling
- Weak PK-PD relationship

### Traditional 3+3 dose-escalation design
- 20-30 pts

### 3+3 dose-escalation design with large expansion cohorts in selected populations
- 30-300 selected pts

### Accelerated titration / adaptive design
- Multiple parallel expansion cohorts
- Long-term follow-up + Drug rechallenge

### MTD quasi-systematically reached
- MTD unconstantly reached
- MTD rarely reached

### Toxicity
- MTD -> MAD

### PK/PD - biomarkers
- Traditional PK
- Limited PD
- OBD
- Important PK/PD modelling
- MIAD?

### Patients number
- 30-50 unselected patients
- 30-200 molecularly selected patients
- 100-1000 immunologically selected patients

### Route of administration
- IV > oral
- Oral > IV
- Novel routes of administration (intra-tumoral)

### Drug development timeframe
- 10 years
- 5-8 years
- <5 years

### Drug approval
- Based on later phase 2 or 3 trials
- Conditional or accelerated approval based on large molecularly selected expansion cohorts
- Conditional or accelerated approval based on histology and immune-biomarker selected expansion cohorts

### Postel-Vinay S et al, Annals of Oncology 2016
Aknowledgements

Steering Committee
✓ Jean-Charles Soria (PI)
✓ Fabrice André
✓ Gilles Vassal
✓ Alexander Eggermont

Investigators
✓ Christophe Massard
✓ Ecaterina Ileana
✓ Antoine Hollebecque
✓ Rastislav Bahleda
✓ Eric Angevin
✓ Andreea Varga
✓ Anas Gazzah
✓ Eric Deutsch

Radiologists
✓ Thierry de Baere
✓ Frédéric Deschamps
✓ Ba Car
✓ Vania Tacher

Pathologists
✓ Philippe Vielh
✓ Jean-Yves Scoazek
✓ Cécile Charpy

Statistics
✓ Marie-Cécile Le Deley
✓ Michiels Stefan
✓ Silvia Rosellini
✓ Dorota Gajda
✓ Aljosa Celebic

Study Coordinator
✓ Claudio Nicotra
✓ Maud Ngo-Camus
✓ Lambert Lisa
✓ Fanny Wunder
✓ Aurélie Abou Lovergne
✓ Ana Lalanne

Biologists
✓ Ludovic Lacroix
✓ Etienne Rouleau
✓ Nathalie Auger
✓ Valérie Koubi-Pick
✓ Vladimir Lazar
✓ Catherine Richon
✓ Bastien Job

Funded by
✓ Philantropy and French Grants
✓ And Industrial partnerships
  • SANOFI
  • Genentech