Evolution de la méthodologie des essais cliniques

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Disclosure Slide

Consultancy fees from

- AstraZeneca, BMS, Boehringer Ingelheim, GSK, Lilly, MSD, Pfizer, Roche, Sanofi, Pierre Fabre, Merck, Novartis
Traditional clinical development

Preclinical rational → Phase I → Phase II → Phase III → Phase IV → Approval
From phase I trials to regulatory approval: climbing the Everest
Phase I cancer studies
« the most critical step from bench to bedside »
Objectives of a typical phase I trial

• **Primary objective**
  – Define the recommended phase II dose (RP2D)

• **Primary endpoint**
  – Identify the presence of dose-limiting toxicities (DLTs)
Dose-limiting toxicity (DLT)

• “Toxicity that is considered unacceptable due to severity and/or irreversibility or because it limits further dose escalation”

• Specified using standardized grading criteria, e.g. Common Terminology Criteria for Adverse Events (CTC-AE, multiple versions)

• DLT is defined in advance prior to beginning the trial and is highly protocol-specific

• Typically defined based on drug-related adverse events seen in the first treatment period (= 1 cycle)
### CTC-AE: standard methodology for assessment of adverse events and DLT

#### BLOOD/BONE MARROW

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow cellularity</td>
<td>Bone marrow cellularity</td>
<td>Mildly hypocellular or ≤25% reduction from normal cellularity for age</td>
<td>Moderately hypocellular or &gt;25 – ≤50% reduction from normal cellularity for age</td>
<td>Severely hypocellular or &gt;50 – ≤75% reduction cellularity from normal for age</td>
<td>—</td>
<td>Death</td>
</tr>
<tr>
<td>CD4 count</td>
<td>CD4 count</td>
<td>&lt;LLN – 500/mm³</td>
<td>&lt;LLN – 0.5 x 10⁹/L</td>
<td>&lt;500 – 200/mm³</td>
<td>&lt;0.5 – 0.2 x 10⁹/L</td>
<td>&lt;200 – 50/mm³</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>Haptoglobin</td>
<td>&lt;LLN</td>
<td>Absent</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Hemoglobin</td>
<td>&lt;LLN – 10.0 g/dL</td>
<td>&lt;LLN – 6.2 mmol/L</td>
<td>&lt;10.0 – 8.0 g/dL</td>
<td>&lt;6.2 – 4.9 mmol/L</td>
<td>&lt;8.0 – 6.5 g/dL</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Hemolyis</td>
<td>Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs’ test], schistocytes)</td>
<td>Evidence of red cell destruction and ≤2 gm decrease in hemoglobin, no transfusion</td>
<td>Transfusion or medical intervention (e.g., steroids) indicated</td>
<td>Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchosospasm, emergency splenectomy)</td>
<td>—</td>
</tr>
<tr>
<td>Iron overload</td>
<td>Iron overload</td>
<td>—</td>
<td>Asymptomatic iron overload, intervention not indicated</td>
<td>Iron overload, intervention indicated</td>
<td>Organ impairment (e.g., endocrinopathy, cardiopathy)</td>
<td>—</td>
</tr>
<tr>
<td>Leukocytes (total WBC)</td>
<td>Leukocytes</td>
<td>&lt;LLN – 3000/mm³</td>
<td>&lt;LLN – 3.0 x 10⁹/L</td>
<td>&lt;5000 – 2000/mm³</td>
<td>&lt;3.0 – 2.0 x 10⁹/L</td>
<td>&lt;2000 – 1000/mm³</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Lymphopenia</td>
<td>&lt;LLN – 800/mm³</td>
<td>&lt;LLN x 0.8 – 10⁹/L</td>
<td>&lt;800 – 500/mm³</td>
<td>&lt;0.8 – 0.5 x 10⁹/L</td>
<td>&lt;500 – 200/mm³</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>Myelodysplasia</td>
<td>—</td>
<td>—</td>
<td>Abnormal marrow</td>
<td>Abnormal marrow</td>
<td>RAEB or RAEB-T</td>
</tr>
</tbody>
</table>

Phase I trial design: standard 3+3 design
Traditional phase I trial assumption

- Assumes increased dose associated with increased chance of efficacy: "The higher the dose, the greater the likelihood of efficacy"
  - Dose-related acute toxicity is regarded as a surrogate for efficacy
  - The highest safe dose is the dose most likely to be efficacious

- This dose-effect assumption is primarily valid for cytotoxic agents
- May not apply to (all) molecularly targeted agents
Dose-response: relation between efficacy and toxicity
Kinetics of irAE with imAbs

RP2D: RECOMMENDED PHASE 2 DOSE

• Should encompass toxicities observed beyond cycle 1

Postel-Vinay S et al, EJC 2014
Kaehler, KC et al  Semin Oncol 2010
Kinetics of Onset and Resolution of Select Nivolumab Treatment-related AEs (Any Grade)

- Select AEs generally resolved within several weeks, apart from endocrinopathies, as some events were not considered resolved due to the continuing need for hormone replacement therapy.

The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.

Presented By Michael Postow at 2015 ASCO Annual Meeting
Special situation: Phase I trials with targeted agents

- Targeted agents differ from cytotoxic agents, as they can be therapeutically active below toxic doses
  - Conventional Phase I trial design, based on dose escalation until toxicity reached, is likely inappropriate
  - Reaching MTD may not be the goal of such Phase I since the specificity of effect may be lost at MTD

- Another potential goal: identify “biologically effective” or “optimal biologically dose”
  - Paradox: requires early development and integration of (frequently unvalidated) measures of biologic effect into Phase I trial (the so-called “surrogate endpoints”)
Responses in phase I trials

- **Classic cytotoxic agents:** response rates in studies from the 80’s and 90’s ranged from 2 – 9% (overall <5%)
  - Activity in those Phase I trials in that period suggested that the agent might find a role in oncology

- **Currently, clinical benefit rates, including prolonged stabilizations of disease, occur in aprox 1 out of 3 patients in ph1 studies**
  - Activity in these Phase I trials might lead to regulatory approval or fast track designation
Evolution of phase I study designs, after MTD achieved

- Dose confirmation
- Pharmacodynamic/Biopsy cohorts
- Signal finding expansion cohorts in a few tumor types
- Phase 1 to registration as a monotherapy in a specific tumor type
- Phase 1 to registration as a monotherapy in multiple indications
- Phase 1 to registration in combination with multiple different agents in multiple but unique indications
Early phase trials are getting larger!

Old School Phase 1 Trial
N = 20-50

Phase 1 ALK and EGFR trials
N = 150-200

Phase 1 PD1/PDL1 trials
N > 1000

Fast-track designation or even regulatory approval might be a potential goal!!

Jeffrey Infante at 2016 ASCO Annual Meeting
Anaplastic Lymphoma Kinase (ALK) Inhibition

Phase I

Part 1: toxicity, MTD, PK in non-enriched patient cohort
250mg crizotinib b.i.d., 28-day cycles
2 ALK rearranged patients reached PR
(1 myofibroblastic tumor, 1 NSCLC)

Part 2: Original plan
to assess clinical activity at the dose recommended
for phase II in the molecularly enriched cohort of
MET amplified tumors
Clinical reality
additional cohort of ALK rearranged NSCLC patients
A8081001 and PROFILE 1005 trials for patients with advanced ALK-positive NSCLC

Phase I: A8081001

Phase II: PROFILE 1005

Profile 1001: NCT00585195; PROFILE 1005: NCT00932451
Waterfall plot of best percent change in target lesions from baseline for 133 patients on the basis of investigator assessment

**Crizotinib**

Phase I dose (Profil 1001)

**ORR: 60.8%**

D Ross Camidge et al, lancet onco 2012
Response rates to ALKi crizotinib in ALK+ NSCLC patients (phase I&II)

Eunice L. Kwak et al, NEJM 2010
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
Beyong first line
Progression free survival (Profil 1007)

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=173)</th>
<th>Chemotherapy (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>127 (73)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>7.7</td>
<td>3.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.49 (0.37 to 0.64)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Interim Analysis of OS (Profil 1007)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Crizotinib (n=173)</th>
<th>Chemotherapy (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>49 (28)</td>
<td>47 (27)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>20.3</td>
<td>22.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.02 (0.68 to 1.54)</td>
<td>1.02 (0.68 to 1.54)</td>
</tr>
<tr>
<td>P</td>
<td>0.5394</td>
<td>0.5394</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Crizotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>173</td>
<td>129</td>
<td>129</td>
</tr>
<tr>
<td>174</td>
<td>83</td>
<td>84</td>
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<td>173</td>
<td>37</td>
<td>34</td>
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<td>174</td>
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<td>10</td>
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<tr>
<td>173</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>174</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

111 patients crossed over to crizotinib outside PROFILE 1007

HR adjusted for crossover using rank-preserving structural failure time method: 0.83 (0.36 to 1.35)
Discovery of EML4-ALK Fusion Gene (1)

Phase 3 Lung Cancer Trial Initiated

ASCO plenary of expanded ALK+ cohort (2)

FDA XALKORI approval

AMM France

2007 2008 2009 2010 2011 2012 2013 2014

First Clinical Responses Observed in ALK+ Tumors (phase I trial)

NEJM publication of ALK+ Cohort (3)

ACSe trial for other ALK+ solid tumors

2. Bang JY et al. Oral presentation at ASCO, 2010
First line Progression-free-Survival (PROFILE 1014)

Hazard ratio for progression or death in the crizotinib group, 0.45 (95% CI, 0.35–0.60) P<0.001 (two-sided stratified log-rank test)

10.9 (95% CI, 8.3 to 13.9) vs 7.0 months (95% CI, 6.8 to 8.2)

Benjamin J. Solomon et al, NEJM 2014
Overall Survival

Hazard ratio for death in the crizotinib group, 0.82 (95% CI, 0.54–1.26)
P=0.36 (two-sided stratified log-rank test)

Benjamin J. Solomon et al, NEJM 2014
**Crizotinib: First-in-human/patient trial**  
(Study A8081001)

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**Part 1:** Dose escalation

- **Cohort 1 (n=3):** 50 mg QD
- **Cohort 2 (n=4):** 100 mg QD
- **Cohort 3 (n=8):** 200 mg QD
- **Cohort 4 (n=7):** 200 mg BID
- **Cohort 5 (n=6):** 300 mg BID

**Part 2:** Molecularly enriched cohorts

- ALK
- METamp
- ROS1

---

NCT00585195  
BID, twice daily; QD, once daily  
RP2D, randomized phase 2 dose
Tumor Shrinkage Seen in Intermediate and High MET Cohorts

Best percent change from baseline in target tumor lesions\textsuperscript{a} by patient

<table>
<thead>
<tr>
<th>MET Group</th>
<th>n</th>
<th>Best Percent Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low MET</td>
<td>2</td>
<td><img src="chart1.png" alt="Graph showing best percent change from baseline for Low MET group with n=2." /></td>
</tr>
<tr>
<td>Intermediate MET</td>
<td>6</td>
<td><img src="chart2.png" alt="Graph showing best percent change from baseline for Intermediate MET group with n=6." /></td>
</tr>
<tr>
<td>High MET</td>
<td>6</td>
<td><img src="chart3.png" alt="Graph showing best percent change from baseline for High MET group with n=6." /></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Confirmed objective responses.

\textsuperscript{b} Based on investigator assessment.

\textsuperscript{c} Two patients in the intermediate MET group had an unconfirmed PR that was not confirmed in a second assessment.
Crizotinib and ROS1 pts

Overall response rate: 72%

Median duration of response
17.6 months
(95% CI, 14.5 to not reached [NR])

Alice T. Shaw et al., NEJM 2014
Part 1: Dose escalation

Cohort 1 (n=3) 50 mg QD
Cohort 2 (n=4) 100 mg QD
Cohort 3 (n=8) 200 mg QD
Cohort 4 (n=7) 200 mg BID
Cohort 5 (n=6) 300 mg BID
Cohort 6 (n=9) 250 mg BID MTD/RP2D

Part 2: Molecularly enriched cohorts

ALK  METamp1  ROS1

MET Exon 14

NCT00585195
BID, twice daily; QD, once daily
RP2D, randomized phase 2 dose
Antitumor Activity of Crizotinib in Patients with Advanced MET Exon 14-Altered NSCLC (PROFILE 1001 Study)

<table>
<thead>
<tr>
<th>Response-Evaluable Population (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response n (%)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
</tr>
<tr>
<td>Unconfirmed CR/PR †</td>
</tr>
<tr>
<td>Progression of Disease (PD)</td>
</tr>
<tr>
<td>Indeterminate ‡</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall response rate (ORR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44% (95% CI: 22–69), n=8/18</td>
</tr>
</tbody>
</table>

† of the 5 patients: 2 awaiting confirmation, 3 cannot be confirmed
‡ this patient discontinued therapy in cycle 1, response imaging could not be performed but response-evaluable per protocol

Alexander Drilon MD et al, ASCO 2016
Antitumor Activity

MET Exon 14 Alteration Co-Occurrence with High-Level MET Amplification

Central testing for both MET exon 14 alterations and high-level MET amplification via ThermoFisher Scientific Inc., Ion Torrent (Cancer Genetics, CA)

Alexander Drilon MD et al, ASCO 2016
Antitumor Activity

• 54 year-old female with MET exon 14-altered lung adenocarcinoma
  - metastatic disease involving lung and lymph nodes, treatment-naive
  - confirmed partial response with crizotinib (-48%), ongoing at 5+ months*

*response duration as of May 2016, Images courtesy of Ross Camidge, University of Colorado Cancer Center

Alexander Drilon MD et al, ASCO 2016
Antitumor Activity

- 87 year-old female with MET exon 14-altered sarcomatoid lung cancer
  - history of stage IIB disease, recurrent metastatic disease involving the adrenal
  - durable partial response (~60%) with crizotinib, ongoing at 8+ months*

*response duration as of May 2016, Images courtesy of Alexander Drilon, Memorial Sloan Kettering Cancer Center

Alexander Drilon MD et al, ASCO 2016
Standard precision medicine approach

- Tumor sample
- Structural DNA analysis
  - Mutational profile
- Matched targeted therapy
Genotyping

Unselected Phase I population

ORR below 10%

Enriched Phase I population

ORR > 30%, and even > 50%

if if true mechanism-based approach
(ontogen de-addiction, synthetic lethality)
MOSCATO-01 prospective molecular screening program

- Monocentric (Gustave Roussy)
- Target Accrual = 900 patients

Median 14 days (95% CI: 7-35 days)
High-throughput molecular profiling using ‘on-purpose’ biopsies

CGH array Agilent
(180K, Whole genome coverage)

Ion Torrent PGM – Life Technologies
(Ampliseq CHP2 + custom
n=74 genes, Dec 2013)

FGFR1 amplification

DNA extraction
10 – 50 ng

Multiplex PCR
1450 amplicons
IonTorrent/PGM
(> 500X coverage)

Torrent_Suite v2.2
Confirmed by Sanger Sequencing

Standardized Report
Main molecular aberrations

Mutations (17%)

Copy number alterations (83%)

“long tail phenomenon”
# The successive phases in oncology drug development

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Type of trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase I</strong></td>
<td><strong>Phase II</strong></td>
</tr>
<tr>
<td>Find maximum tolerated dose</td>
<td>Confirm clinical activity</td>
</tr>
<tr>
<td>screen for activity</td>
<td></td>
</tr>
<tr>
<td><strong>EMPHASIS</strong> (End-point)</td>
<td><strong>ACTIVITY</strong> (Response)</td>
</tr>
<tr>
<td>SAFETY/activity</td>
<td></td>
</tr>
<tr>
<td>(Toxicity/response)</td>
<td></td>
</tr>
<tr>
<td>Typical number of patients</td>
<td>30-60</td>
</tr>
<tr>
<td>Typical duration</td>
<td>12-24 Months</td>
</tr>
<tr>
<td>Randomized ?</td>
<td>Never</td>
</tr>
<tr>
<td>Multicentre ?</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Tumor-specific?</td>
<td>Sometimes</td>
</tr>
</tbody>
</table>
## The new trend of drug development in oncology

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Phase I/II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Find MTD &amp; confirm activity</td>
<td>Compare with standard therapy</td>
</tr>
<tr>
<td>EMPHASIS (End-point)</td>
<td>SAFETY/(toxicity)</td>
<td>EFFICACY (PFS, Survival)</td>
</tr>
<tr>
<td></td>
<td>ACTIVITY / (response)</td>
<td></td>
</tr>
<tr>
<td>Typical number of patients</td>
<td>50-200+</td>
<td>50-1000+</td>
</tr>
<tr>
<td>Typical duration</td>
<td>12 to 36 months</td>
<td>Years</td>
</tr>
<tr>
<td>Randomized ?</td>
<td>Rarely</td>
<td>Always</td>
</tr>
<tr>
<td>Multicentre ?</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Tumor-specific?</td>
<td>At expansion</td>
<td>Always</td>
</tr>
</tbody>
</table>
The new trend in oncology drug development:

CRIZOTINIB, CERIDINIB AND PEMBROLIZUMAB APPROVED BY FDA ON THE BASIS OF PHASE I/II TRIALS

Number of patients enrolled in recent phase 1 trials having led to breakthrough approval or breakthrough designations (based on www."

Postel-Vinay S Annals of Oncology 2014
Phase I design modifications

Etude de phase I "classique"

20-30 pts

Phase escalade de dose

Phase d'expansion

100-1000 patients

+/- enrichissement selon biomarqueurs

Etude de phase I avec multiples cohortes d’expansion
Crizotinib: First-in-human/patient trial (Study A8081001)

Part 1: Dose escalation

Cohort 1 (n=3)
50 mg QD

Cohort 2 (n=4)
100 mg QD

Cohort 3 (n=8)
200 mg QD

Cohort 4 (n=7)
200 mg BID

Cohort 5 (n=6)
300 mg BID

Cohort 6 (n=9)
250 mg BID

MTD/RP2D

Part 2: Molecularly enriched cohorts

ALK
METAmp
ROS1

MET Exon14

NCT00585195
BID, twice daily; QD, once daily
RP2D, randomized phase 2 dose
Is this the end of single-arm Phase 2 studies?

- NSCLC
- Melanoma
- Kidney
- Bladder
- HNSCC
- TNBC
- Ovarian
- CRC
- Prostate

Will single arm expansions be good enough to make a “No Go” decision?

Will single arm expansions be good enough to make a “Go” decision?

Will the future provide us with only two types of studies: Non-randomized Early (Ph1/2) Studies and Randomized Late (Ph2/3) Studies?
Atezolizumab (MPDL3280A): Phase Ia Study

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

N > 350 patients

NCT 01375842
Pembrolizumab antitumor activity

Melanoma\textsuperscript{1} (N=411) KEYNOTE-001

NSCLC\textsuperscript{2} (N=262) KEYNOTE-001

H\&N Cancer\textsuperscript{3} (N=61) KEYNOTE-012

Urothelial Cancer\textsuperscript{4} (N=33) KEYNOTE-012

Gastric Cancer\textsuperscript{5} (N=39) KEYNOTE-012

TNBC\textsuperscript{6} (N=32) KEYNOTE-012

cHL\textsuperscript{7} (N=29) KEYNOTE-013

KEYNOTE-001 NSCLC Cohorts
(N = 550)

- Pembrolizumab IV over 30 minutes until intolerable toxicity, disease progression, investigator decision, or patient withdrawal
- Primary endpoint: ORR per RECIST v1.1 by independent central review
- Secondary endpoints: PFS, OS, and duration of response
- Data cutoff: September 18, 2015
- Median follow-up: 22.2 months (range, 17.8-30.5) for treatment naive; 23.3 months (range, 14.2-40.1) for previously-treated patients

\(^a\)First 11 pts randomized to 2 mg/kg Q3W vs 10 mg/kg Q3W; 90 randomized to 10 mg/kg Q3W vs 10 mg/kg Q2W.
Vertical dotted lines represent 18 months and 24 months; the horizontal line at 50% drops vertically to the x-axis at the time of the median OS. Data cutoff: September 18, 2015.

### Overall Survival

#### Treatment Naive

<table>
<thead>
<tr>
<th>Time, months</th>
<th>No. at risk</th>
<th>OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>101</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>97</td>
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<td>10</td>
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<td>86</td>
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<td>25</td>
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<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median (95% CI), mo**

Total: 22.1 (16.8-27.2)

**18-mo Rate, %**

Total: 58.1

**24-mo Rate, %**

Total: 44.5

#### Previously Treated

<table>
<thead>
<tr>
<th>Time, months</th>
<th>No. at risk</th>
<th>OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>449</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>304</td>
<td>97</td>
</tr>
<tr>
<td>10</td>
<td>222</td>
<td>92</td>
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<tr>
<td>15</td>
<td>172</td>
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<tr>
<td>30</td>
<td>11</td>
<td>0</td>
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<tr>
<td>35</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median (95% CI), mo**

Total: 10.6 (8.6-13.3)

**18-mo Rate, %**

Total: 36.6

**24-mo Rate, %**

Total: 30.4
Patients with unknown PD-L1 TPS were excluded. Data cutoff: September 18, 2015.

OS by PD-L1 TPS ≥50%, 1%-49%, <1%

<table>
<thead>
<tr>
<th></th>
<th>Median, mo (95% CI)</th>
<th>18-mo Rate, %</th>
<th>24-mo Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS ≥50%</td>
<td>NR (22.1-NR)</td>
<td>72.7</td>
<td>60.6</td>
</tr>
<tr>
<td>TPS 1%-49%</td>
<td>19.5 (10.7-22.2)</td>
<td>50.1</td>
<td>32.5</td>
</tr>
<tr>
<td>TPS &lt;1%</td>
<td>14.7 (3.4-NR)</td>
<td>50.0</td>
<td>37.5</td>
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</table>

Treatment Naive

Previously Treated

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>27</td>
<td>25</td>
<td>24</td>
<td>22</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>52</td>
<td>42</td>
<td>36</td>
<td>29</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>138</th>
<th>100</th>
<th>81</th>
<th>65</th>
<th>34</th>
<th>13</th>
<th>3</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>168</td>
<td>112</td>
<td>77</td>
<td>57</td>
<td>33</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>57</td>
<td>36</td>
<td>28</td>
<td>21</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median, mo (95% CI) 18-mo Rate, % 24-mo Rate, %
Phase III trials

Nivolumab (SQCC)
CheckMate 017

Nivolumab vs Docetaxel

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>135</td>
<td>137</td>
</tr>
<tr>
<td>mOS, mos (95% CI)</td>
<td>2.2 (1.12, 5.2)</td>
<td>6.0 (4.29, 7.39)</td>
</tr>
<tr>
<td># events</td>
<td>103</td>
<td>122</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.62 (0.48, 0.81)</td>
<td>P = 0.0004</td>
</tr>
</tbody>
</table>

Pembrolizumab (NSCLC)
Keynote 010

Atezolizumab (NSCLC)
POPLAR

HR^ = 0.73 (0.53, 0.99)
P value = 0.040

Phase I/II dose escalation-expansion Osimertinib

Primary objective – assessment of the safety, tolerability and efficacy (ORR) of Osimertinib in patients with acquired resistance to EGFR-TKIs

Phase 1 Escalation
Not preselected by T790M status

Phase 1 Expansion
Enrolment by local testing followed by central laboratory confirmation (cobas™ EGFR Mutation Test) of T790M status or by central laboratory testing alone

# Baseline demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Escalation N=31</th>
<th>Expansion N=252</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male / Female</td>
<td>11 / 20 (35 / 65)</td>
<td>97 / 155 (38 / 62)</td>
</tr>
<tr>
<td>Age, median (range); years</td>
<td>61 (39–81)</td>
<td>60 (28–88)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian / Asian / Other / Not reported</td>
<td>5 / 21 / 1 / 4 (16 / 68 / 3 / 13)</td>
<td>84 / 152 / 5 / 11 (33 / 60 / 2 / 4)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adeno / Squamous / Other / Missing</td>
<td>29 / 1 / 1 / 0 (94 / 3 / 3 / 0)</td>
<td>TBC</td>
</tr>
<tr>
<td>Prior lines of systemic therapy, median (range)</td>
<td>3 (1–12)</td>
<td>3 (1–12)</td>
</tr>
<tr>
<td>Prior EGFR-TKIs, median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>1 (1–4)</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>22 (71)</td>
<td>150 (60)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>15 (48)</td>
<td>146 (58)</td>
</tr>
<tr>
<td>EGFR mutation type by central test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 / L858R / Other / None / Unknown, n</td>
<td>Central testing not performed for escalation</td>
<td>136 / 73 / 10 / 13 / 20</td>
</tr>
<tr>
<td>Exon 19 / L858R / Other / None / Unknown, %</td>
<td>Central testing not performed for escalation</td>
<td>54 / 29 / 4 / 5 / 8</td>
</tr>
</tbody>
</table>

Population: pre-treated, capsule-dosed patients (excluding Japanese cytology cohort). Data cut-off 2 Dec 2014

## Response rate in T790M positive cohorts (central test) - Osimertinib

### DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

<table>
<thead>
<tr>
<th></th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>160 mg</th>
<th>240 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (157)</td>
<td>10</td>
<td>32</td>
<td>61</td>
<td>41</td>
<td>13</td>
<td>157</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>50% (19, 81)</td>
<td>59% (41, 76)</td>
<td>66% (52, 77)</td>
<td>51% (35, 67)</td>
<td>54% (25, 81)</td>
<td>59% (51, 66)</td>
</tr>
</tbody>
</table>

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments.

Nine patients (seven in the 160 mg cohort) currently have a best overall response of not evaluable, as they have not yet had a 6-week follow-up RECIST assessment.

Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014.

CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Response rate in T790M negative cohorts (central test) - Osimertinib

DCR (CR+PR+SD) in patients with centrally tested T790M negative tumours was 64% (44 / 69; 95% CI 51, 75)

<table>
<thead>
<tr>
<th>ORR (95% CI)</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>160 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (69)</td>
<td>3</td>
<td>17</td>
<td>29</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>67% (9, 99)</td>
<td>12% (2, 36)</td>
<td>21% (8, 40)</td>
<td>30% (12, 54)</td>
<td>23% (14, 35)</td>
<td></td>
</tr>
</tbody>
</table>

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments

Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014

Bras T790M négatif - données non enregistrées

**Phase II dose extension**

**Primary objective** – assessment of the safety, tolerability and efficacy (ORR) of AZD9291 in patients with acquired resistance to EGFR-TKIs

**Escalation**
Not preselected by T790M status

**Expansion**
Enrolment by local testing followed by central laboratory confirmation (cobas™ EGFR Mutation Test) of T790M status or by central laboratory testing alone

**Phase 2 extension**
Enrollment by central Laboratory confirmation of T790M status

**Rolling six design**

- Cohort 1: 20 mg
  - Positive
  - Negative
- Cohort 2: 40 mg
  - Positive
  - Negative
- Cohort 3: 80 mg
  - Positive
  - Negative
  - Biopsy*
  - 1st-line EGFRm
  - Tablet***
  - Cytology§
- Cohort 4: 160 mg
  - Positive
  - Negative
  - Biopsy*
  - 1st-line EGFRm
- Cohort 5: 240 mg
  - Positive

**T790M cohorts**

**Osimertinib 80 mg once daily in patients with T790M+ NSCLC who have progressed on EGFR-TKI**
### Phase II extension

Tumor response by independent central review - Osimertinib 80mg/d

(+) 200 pts

#### Best percentage change from baseline in target lesion – all patients

![Graph showing percentage change from baseline in target lesion](image-url)

#### Confirmed objective response

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, (^{+}) % (95% CI)</td>
<td>61 (54, 68)</td>
</tr>
<tr>
<td>Complete response, (^{+}) n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, (^{+}) n (%)</td>
<td>122 (61)</td>
</tr>
<tr>
<td>Stable disease ≥6 weeks, (^{+}) n (%)</td>
<td>58 (29)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>19 (10)</td>
</tr>
<tr>
<td>DCR, % (95% CI)</td>
<td>91 (85, 94)</td>
</tr>
</tbody>
</table>

**NOTE:** Investigator-assessed ORR was 71% (95% CI 64.77)

Data cut-off: May 1, 2015. Population evaluable for response: 199/199. *Represents imputed values if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to disease progression, and/or no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%.* ORR defined as the number (%) of patients with at least one visit response of complete response or partial response that was confirmed at least 4 weeks later. *Response required confirmation after 4 weeks.* Stable disease of 6 weeks included the REGIST visit window (127 days).  

Chih-Hsin Yang et al, IASLC 2015
Study designs

**AURA Ph I/II**
Patients with T790M-positive aNSCLC whose disease has progressed following either one prior therapy with an EGFR-TKI or following treatment with both EGFR-TKI and other anticancer therapy.

**Rolling six design**
- Cohort 1: 20 mg (Positive)
- Cohort 2: 40 mg (Positive, Negative First-line Biopsy, Tablet Cytology)
- Cohort 3: 80 mg (Positive, Negative First-line Biopsy, Tablet Cytology, Biopsy)
- Cohort 4: 160 mg (Positive, Negative First-line Biopsy)
- Cohort 5: 240 mg (Positive)

**AURA2 Ph II**
Patients with confirmed EGFRm locally advanced or metastatic NSCLC who have progressed following prior therapy with an approved EGFR-TKI.

**Central T790M mutation testing** of biopsy sample collected following confirmed disease progression.
- T790M positive
- T790M negative / unknown

**AURA Phase II Extension (n=201)**
Osimertinib 80 mg qd

**AURA2 (n=210)**
Osimertinib 80 mg qd

**Pooled Phase II**

---

*The EGFR T790M mutation status of the patient’s tumour was prospectively determined by the designated central laboratory using the Cobas® EGFR Mutation Test (Roche Molecular Systems) by biopsy taken after confirmation of disease progression on the most recent treatment regimen; †Paired biopsy cohort patients with T790M positive tumours; safety and efficacy data only reported here; Data from cohorts in grayed out boxes are not included in the analyses reported here. aNSCLC, advanced NSCLC; qd, once daily

---

James C-H Yang et al, ELCC 2016, Geneva; Abstract LBA2_PR.
Tumour response to Osimertinib treatment

### AURA Ph I

- **Confirmed ORR**: 71% (95% CI 57, 82)
- **Disease control rate†**: 93% (95% CI 84, 98)

### AURA pooled Ph II

- **Confirmed ORR**: 66% (95% CI 61, 71)
- **Disease control rate†**: 91% (95% CI 88, 94)

<table>
<thead>
<tr>
<th>Best objective response</th>
<th>AURA Ph I (80 mg) N=61</th>
<th>AURA pooled Ph II (80 mg) N=397</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Partial response</td>
<td>42</td>
<td>256</td>
</tr>
<tr>
<td>Stable disease ≥6 weeks</td>
<td>14</td>
<td>99</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2</td>
<td>25</td>
</tr>
</tbody>
</table>

---

James C-H Yang et al, ELCC 2016, Geneva; Abstract LBA2_PR.
Osimertinib....

The clinical development programme for osimertinib is the most rapid to date, taking just 2 years 8 months and 1 week from the first patient dosed to the first approved indication
(FDA Approval Nov 2015)
Tagrisso in NCCN guidelines...

FDA's approval of Tagrisso
AURA 3 Study Design

Central testing of ~1540 biopsy samples

Randomise ~470 patients 2:1

18 July 2016

AstraZeneca today announced that the Phase III AURA3 trial met its primary endpoint, demonstrating superior progression-free survival (PFS) compared to standard platinum-based doublet chemotherapy.

No cross over to AZ9291 at start, now change to cross-over

PI: T Mok YL Wu

*Pemetrexed 500 mg/m² + carboplatin AUC5 or Pemetrexed 500 mg/m² + cisplatin 75 mg/m²

AUC5, area under the plasma concentration–time curve 5 mg/mL−1 per minute; EGFR+, EGFR mutation-positive; EGFR-TKI, EGFR tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; p.o., orally; qd, once daily; T790M+, T790M mutation-positive; T790M-, T790M mutation-negative
**Phase I dose escalation/expansion study design (NCT01802632)**

- For the first-line cohorts, patients with a documented EGFR-TKI-sensitising mutation and who have received no prior therapy for advanced stage NSCLC were enrolled.
- Patients received AZD9291 once daily as an 80 mg or 160 mg capsule.

### Escalation
Not preselected by T790M status

### Expansion
Enrollment by local testing followed by central laboratory confirmation (cobas EGFR Mutation Test) of T790M status or by central laboratory testing alone

*Prior therapy not permissible in this cohort. #Paired biopsy cohort patients with T790M+ tumours. ##Not selected by mutation status, US only.
PFS in osimertinib EGFRm first-line cohorts (investigator assessed)


Progression events that do not occur within 14 weeks of the last evaluable assessment (or first dose) are censored
Circles on the Kaplan-Meier plot denote censored observations

Progression-free survival is the time from date of first dosing until the date of objective disease progression or death

Calculated using the Kaplan-Meier technique

Presented by Suresh S Ramalingam at the 6th IASLC/ESMO European Lung Cancer Conference, 13–16 April 2016, Geneva, Switzerland; Abstract LBA1_PR.

<table>
<thead>
<tr>
<th>Number of patients at risk:</th>
<th>1st line 80 mg n=30</th>
<th>1st line 160 mg n=30</th>
<th>Total N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS,* months (95% CI)</td>
<td>NC (12.3, NC)</td>
<td>19.3 (11.1, 19.3)</td>
<td>19.3 (13.7, NC)</td>
</tr>
<tr>
<td>Remaining alive and progression-free, †% (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>75 (55, 88)</td>
<td>69 (49, 83)</td>
<td>72 (59, 82)</td>
</tr>
<tr>
<td>18 months</td>
<td>57 (36, 73)</td>
<td>53 (32, 70)</td>
<td>55 (41, 67)</td>
</tr>
</tbody>
</table>

*Calculated using the Kaplan-Meier technique

†Progression-free survival is the time from date of first dosing until the date of objective disease progression or death

The table shows the number of patients at risk and the progression-free survival (PFS) for different dosages of osimertinib. The Kaplan-Meier plot illustrates the survival probabilities over time.
### Etudes de développement Osimertinib

<table>
<thead>
<tr>
<th>Phase I / II</th>
<th>≥ 2ème Ligne</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AURA</strong></td>
<td></td>
</tr>
<tr>
<td>Phase I/II</td>
<td></td>
</tr>
<tr>
<td>Phase I : escalade / expansion de dose</td>
<td></td>
</tr>
<tr>
<td>Phase II : extension de dose</td>
<td></td>
</tr>
<tr>
<td>CBNPC à un stade avancé</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Phase II</th>
<th>≥ 2ème Ligne</th>
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<tbody>
<tr>
<td><strong>AURA 2</strong></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td>Etude en ouvert, monobras</td>
<td></td>
</tr>
<tr>
<td>Traitement de seconde ligne ou plus chez des patients atteints d’un CBNPC localement avancé ou métastatique avec mutations EGFRm et T790M qui ont progressé après un traitement par TKI-EGFR</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Phase III</th>
<th>2ème Ligne</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AURA3</strong></td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
</tr>
<tr>
<td>Etude randomisée, VS chimiothérapie à base de platine</td>
<td></td>
</tr>
<tr>
<td>Traitement de seconde ligne chez les patients atteints d’un CBNPC localement avancé ou métastatique avec mutations EGFRm et T790M qui ont progressé après un traitement par TKI-EGFR</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase III</th>
<th>1ère Ligne</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLAURA</strong></td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
</tr>
<tr>
<td>Etude randomisée, VS gefitinib ou erlotinib</td>
<td></td>
</tr>
<tr>
<td>CBNPC localement avancé ou métastatique avec mutation activatrice de l’EGFR</td>
<td></td>
</tr>
</tbody>
</table>

Données non enregistrées pour FLAURA ET AURA3
Marker-stratified
Progression-free survival in EGFR mutation positive and negative patients

**EGFR mutation positive**

- **Gefitinib** (n=132)
- **Carboplatin / paclitaxel** (n=129)
- HR (95% CI) = 0.48 (0.36, 0.64) \(p<0.0001\)
- No. events gefitinib, 97 (73.5%)
- No. events C / P, 111 (86.0%)

**EGFR mutation negative**

- **Gefitinib** (n=91)
- **Carboplatin / paclitaxel** (n=85)
- HR (95% CI) = 2.85 (2.05, 3.98) \(p<0.0001\)
- No. events gefitinib, 88 (96.7%)
- No. events C / P, 70 (82.4%)

**Treatment by subgroup interaction test, \(p<0.0001\)**

*ITT population
Cox analysis with covariates*

Move (staged or potentially seamlessly) from a marker-stratified to a marker-enriched design
Randomized studies on first line EGFR TKI

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>N (EGFR mut +)</th>
<th>RR</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mok et al</td>
<td>IPASS</td>
<td>132</td>
<td>71.2% vs 47.3</td>
<td>9.8 vs 6.4 months</td>
</tr>
<tr>
<td>Lee et al</td>
<td>First-SIGNAL</td>
<td>27</td>
<td>84.6% vs 37.5%</td>
<td>8.4 vs 6.7 months</td>
</tr>
<tr>
<td>Mitsudomi et al</td>
<td>WJTOG 3405</td>
<td>86</td>
<td>62.1% vs 32.2%</td>
<td>9.2 vs 6.3 months</td>
</tr>
<tr>
<td>Maemondo et al</td>
<td>NEJGSG002</td>
<td>114</td>
<td>73.7% vs 30.7%</td>
<td>10.8 vs 5.4 months</td>
</tr>
<tr>
<td>Zhou et al</td>
<td>OPTIMAL</td>
<td>154</td>
<td>83% vs 36%</td>
<td>13.1 vs 4.6 months</td>
</tr>
<tr>
<td>Rosell et al</td>
<td>EURTAC</td>
<td>135</td>
<td>56% vs 18%</td>
<td>9.2 vs 4.8 months</td>
</tr>
<tr>
<td>Yang et al</td>
<td>LUX Lung 3</td>
<td>345</td>
<td>56% vs 22%</td>
<td>11.1 vs 6.9 months</td>
</tr>
<tr>
<td>Wu et al</td>
<td>LUX Lung 6</td>
<td>364</td>
<td>67% vs 23%</td>
<td>11.0 vs 5.6 months</td>
</tr>
</tbody>
</table>

Schematic example of a basket trial:
One drug, one molecular alteration, several tumour types
Schematic illustration of the Vemurafenib basket trial

8 cohorts BRAF\textsuperscript{V600} positive cancers:
Metastatic solid tumors
Multiple myeloma

BRAF\textsuperscript{V600} testing
All BRAF\textsuperscript{V600} mutations
Tested by local routine methods
Retrospective optional evaluation with cobas 4800 BRAF mutation test

- NSCLC
- Ovarian
- Colorectal
- Cholangiocarcinoma
- Breast
- Prostate
- Multiple myeloma
- Other solid tumours

Vemurafenib
(960 mg orally twice daily)
## BASKET Trial: Vemurafenib in Multiple Non-melanoma cancers with BRAF V600 Mutations

<table>
<thead>
<tr>
<th>Variable</th>
<th>NSCLC (N=20)</th>
<th>Colorectal Cancer</th>
<th>Cholangiocarcinoma (N=8)</th>
<th>ECD or LCH (N=18)</th>
<th>Anaplastic Thyroid Cancer (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vemurafenib (N=10)</td>
<td>Vemurafenib + Cetuximab (N=27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥1 postbaseline assessment — no.</td>
<td>19</td>
<td>10</td>
<td>26</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>8 (42)</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (12)</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Stable disease — no. (%)</td>
<td>8 (42)</td>
<td>5 (50)</td>
<td>18 (69)</td>
<td>4 (50)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>2 (11)</td>
<td>5 (50)</td>
<td>7 (27)</td>
<td>3 (38)</td>
<td>0</td>
</tr>
<tr>
<td>Missing data — no. (%)†</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overall response — no. (%) [95% CI]</td>
<td>8 (42) [20–67]</td>
<td>0</td>
<td>1 (4) [&lt;1–20]</td>
<td>1 (12) [&lt;1–53]</td>
<td>6 (43) [18–71]</td>
</tr>
</tbody>
</table>

ECD/LCHErdheim–Chester disease or Langerhans’-cell histiocytosis

David M. Hyman et al., NEJM 2015
French national AcSé Program

Criblage Moléculaire
ALK, MET, RON, ROS, BRAF
10000 à 18000 patients
14000 à 25000 tests

AcSé Crizotinib
Essai
500 patients

AcSé Vemurafenib
Essai

278000 tests
144000 patients
En 2010

28 plateformes
Génétique moléculaire
INCA

promoteur

Jusqu’à 250
Centres investigateurs
Biomarker-driven access to crizotinib in ALK, MET or ROS1 positive malignancies in adults and children: the French national AcSé Program

Gilles Vassal, Denis Moro Sibilot, Marie-Cécile Le Deley, Natalie Hoog-Labouret, Frédérique Nowak, Marta Jimenez, Christophe Tournigand, Roch Houot, David Malka, Thomas Aparicio, Bernard Escudier, Isabelle Ray Coquard, Yann Godbert, Luc Taillandier, Ivan Bièche, Sylvie Lantuejoul, Gilbert Ferretti, Yves Menu, Jean-Yves Blay, Agnès Buzyn.
1 uterine leiomyosarcoma - ALK translocation,
1 pancreatic cancer - ROS1 mutation,
1 neuroblastoma - ROS1 mutation,
1 kidney cancer - ROS1 amplification,
3 NSCLC - MET mutation,
1 NSCLC - ALK mutation,
1 NSCLC - ALK amplification,
1 SCLC - MET mutation + ROS1 mutation,
1 adenoc. ovaque - MET amplification,
1 cholangiocarcinoma - MET amplification,
1 gallbladder - MET amplification,
1 B lymphoma, large cell - ALK translocation,
1 carcinoma of the esophagus - MET amplification,
1 sarcomatoid carcinoma hail - ALK translocation,
1 unknown primary carcinoma - ALK translocation.
Results: ROS1+ NSCLC

Tumor shrinkage at best response

Best response

ORR = 26/36
72 % [55% ; 86%]

DCR = 32/36
89 % [74% ; 97%]

44% PFS
at 12 months

Gilles Vassal et al, 2015
Tumor shrinkage at best response

MET<sub>AMP</sub> NSCLC

- Tumor shrinkage at best response
- **ORR = 7/25**
  - 28 % [12%; 49%]
- **DCR = 15/25**
  - 60 % [41%; 79%]

No correlation observed between the number of MET copies and best response (p=0.10).

G.Vassal et al 2015
Tumor shrinkage at best response

- No response in 13 patients
- STOP accrual at stage I
**Umbrella trial** (One disease type, multiple molecular alteration)

Note: Patients with tumors matching more than one molecular sub-study profile may be randomized to one of the studies, enrolled to the study with lowest marker prevalence or accrual, or enrolled to a study based on physician’s choice, depending on the trial protocol.
BATTLE trial in NSCLC

BATTLE Schema

Umbrella Protocol

Core Biopsy

EGFR  KRAS/BRAF
VEGF  RXR/CyclinD1

Randomization:
Equal → Adaptive

Erlotinib  Vandetanib  Erlotinib + Bexarotene  Sorafenib

Primary end point: 8 week Disease Control (DC)

SAFIR02 Lung (UNICANCER 0105-1305 / IFCT 1301)

Cancer du poumon métastatique 1ère ligne chimiothérapie

Stade IV
CBNPC
EGFR Négatif
ALK Négatif

4 cycles Chimiothérapie

Biopsies fraîches lors des 2 premiers cycles de chimiothérapie
Etude moléculaire:
• CGH
• NGS

Traitement bioguidé (AstraZeneca pipeline: AZD2014, AZD4547, AZD5363, AZD8931, selumetinib, vandetanib)

Chimiothérapie standard
Pemetrexed (Non épi)
Erlotinib (Epidermoïdes)
R2:1 jusqu'à progression

Absence de cible moléculaire ciblable

MEDI4736 (durvalumab)
R2:1

Progression

Co-principal investigateurs : Pr JC. Soria / Pr F. Barlesi
Umbrella Trials: Moving beyond one marker/drug

Phase II/III Biomarker-Driven Master Protocol for 2nd Line Therapy of Squamous Cell Lung Cancer
Adaptive designs

LUNG-MAP
Phase II/III Biomarker-Driven Master Protocol for 2nd Line Therapy of Squamous Cell Lung Cancer

Study Design Within Each Sub-study

- Assignment
- Randomization
- Phase II Analysis
  - 55 PFS events
- Phase III Interim Analyses
  - OS for efficacy
- Phase III Interim Analyses
  - PFS/OS for futility
- Complete Accrual
- Final Analysis
  - 256 OS events
  - 290 PFS events

Futility established
12 months follow-up
Stop
In Summary….Non-linear clinical development
The revolution in drug development has profound implications

Median Duration 8 to 10 years

Duration is shortened (4 years+)

Burock S, EJC 2013
Paul S, Nat rev Drug Discovery 2010
<table>
<thead>
<tr>
<th>Patients number</th>
<th>Traditional PK Limited PD</th>
<th>30-200 molecularly selected patients</th>
<th>100-1000 immunologically selected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>IV &gt; oral</td>
<td>Oral &gt; IV</td>
<td>Novel routes of administration (intra-tumoral)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>MTD quasi-systematically reached</td>
<td>MTD unconstantly reached</td>
<td>MTD rarely reached -&gt; MAD</td>
</tr>
<tr>
<td>PK/PD - biomarkers</td>
<td>Traditional PK Limited PD</td>
<td>Important PK/PD modelling</td>
<td>MIAD?</td>
</tr>
<tr>
<td>Design</td>
<td>Traditional 3+3 dose-escalation design</td>
<td>3+3 dose-escalation design with large expansion cohorts in selected populations</td>
<td>Accelerated titration / adaptive design Multiple parallel expansion cohorts Long-term follow-up + Drug rechallenge</td>
</tr>
<tr>
<td>Drug approval</td>
<td>Based on later phase 2 or 3 trials</td>
<td>Conditional or accelerated approval based on large molecularly selected</td>
<td>Conditional or accelerated approval based on histology and immune-biomarker selected</td>
</tr>
<tr>
<td>Drug development timeframe</td>
<td>10 years</td>
<td>5-8 years</td>
<td>&lt;5 years</td>
</tr>
</tbody>
</table>

**Cytotoxic chemotherapy** > **Molecularly Targeted Agents** > **Immuo-stimulatory Agents**

**Toxicity**

- DLTs
- MTD quasi-systematically reached
- MTD unconstantly reached
- MTD rarely reached -> MAD

**PK/PD - biomarkers**

- Traditional PK Limited PD
- Target enrichment
- Important PK/PD modelling
- MIAD?
- Weak PK-PD relationship

**Design**

- Traditional 3+3 dose-escalation design
- 30-50 unselected patients
- 30-200 molecularly selected patients
- 100-1000 immunologically selected patients
- Oral > IV
- Novel routes of administration (intra-tumoral)
- MTD quasi-systematically reached
- MTD unconstantly reached
- MTD rarely reached -> MAD

**Drug approval**

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

**Drug development timeframe**

- 10 years
- 5-8 years
- <5 years
Acknowledgments

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Benjamin BESSE
Thierry LE CHEVALIER

THANK YOU

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