Late Drug Development (Molecular Targeted Therapy)

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Cornerstone for clinical trial design

- Phase I: on dose and toxicity
- Phase II: on efficacy
- Phase III: on comparison with standard therapy
- Phase IV: on general population

Early development → late development
Study objectives

• Early development
  – Pharmacokinetic and dosing
  – Proof of concept
  – Identification of biomarker

• Late development
  – Prove to be better than standard treatment
  – Drug approval by regulatory bodies
Study objectives

• Early development
  – Pharmacokinetic and dosing
  – Proof of concept
  – Identification of biomarker

• Late development
  – Prove to be better than standard treatment
  – Drug approval by regulatory bodies
A classic late drug development study on targeted therapy

Hazard ratio: 0.871 (95% CI 0.762–0.996)
p = 0.044

Number at risk
Chemotherapy 557
Chemotherapy plus cetuximab 568

Pirker R et al. Lancet 2009, 373, 1525
Basic assumptions on phase III design

• All patients enrolled to study share similar characteristics (clinically and genonically)

• Stratification by few clinical criteria trying to assure similarity between the two arms

• Impact of the study drug at first line would influence the overall survival, ie assuming both the exposure and outcome from subsequent therapy to be similar between the two arms

• Minimal cross over to the other arm
Histology similarity ≠ Genomic similarity

NSCLC as one disease

Histology-based Subtyping

Adenocarcinoma
- EGFR
- KRAS
- Unknown

Squamous Cell Cancer
- FGFR1 Amp
- EGFRvIII
- PI3KCA
- EGFR
- DDR2
- Unknown

Li, Gandara et al: JCO (in press) adapted from Pao et al
# Oncogene in Chinese Patients with NSCLC

<table>
<thead>
<tr>
<th>Group</th>
<th>EGFR % (n)</th>
<th>PTEN % (n)</th>
<th>STK11 % (n)</th>
<th>ALK % (n)</th>
<th>KRAS % (n)</th>
<th>c-Met % (n)</th>
<th>PIK3CA % (n)</th>
<th>BRAF % (n)</th>
<th>DDR2 % (n)</th>
<th>FGFR2 % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>28.4% (147/517)</td>
<td>9.5% (21/220)</td>
<td>7.9% (8/101)</td>
<td>6.3% (15/239)</td>
<td>5.4% (27/498)</td>
<td>4.5% (20/448)</td>
<td>4.4% (20/452)</td>
<td>1.5% (7/452)</td>
<td>1.2% (2/166)</td>
<td>0.6% (1/165)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>40.9% (119/291)</td>
<td>6.3% (7/112)</td>
<td>2.1% (1/48)</td>
<td>6.4% (8/125)</td>
<td>3.6% (10/279)</td>
<td>4.3% (11/255)</td>
<td>4.6% (12/260)</td>
<td>1.5% (4/260)</td>
<td>0% (0/91)</td>
<td>0% (0/90)</td>
</tr>
<tr>
<td>Smokers</td>
<td>12.4% (28/226)</td>
<td>13.0% (14/108)</td>
<td>13.2% (7/53)</td>
<td>6.1% (7/114)</td>
<td>7.8% (17/219)</td>
<td>4.7% (9/193)</td>
<td>4.2% (8/192)</td>
<td>1.6% (3/192)</td>
<td>2.7% (2/75)</td>
<td>1.3% (1/75)</td>
</tr>
<tr>
<td>AC</td>
<td>40.3% (140/347)</td>
<td>7.0% (8/115)</td>
<td>8.6% (5/58)</td>
<td>7.7% (10/130)</td>
<td>7.1% (24/340)</td>
<td>4.5% (14/308)</td>
<td>4.2% (13/307)</td>
<td>2.3% (7/307)</td>
<td>0% (0/97)</td>
<td>0% (0/96)</td>
</tr>
<tr>
<td>SCC</td>
<td>4.4% (6/144)</td>
<td>10.6% (10/94)</td>
<td>6.1% (2/33)</td>
<td>4.1% (4/93)</td>
<td>1.5% (2/132)</td>
<td>5.2% (6/116)</td>
<td>5.8% (7/121)</td>
<td>0.0% (0/121)</td>
<td>3.3% (2/61)</td>
<td>1.6% (1/61)</td>
</tr>
<tr>
<td>LCC</td>
<td>3.8% (1/26)</td>
<td>27.3% (3/11)</td>
<td>10.0% (1/10)</td>
<td>8.3% (1/12)</td>
<td>3.8% (1/26)</td>
<td>0.0% (0/24)</td>
<td>0.0% (0/24)</td>
<td>0.0% (0/24)</td>
<td>0% (0/8)</td>
<td>0% (0/8)</td>
</tr>
<tr>
<td>NS with AC</td>
<td>49.8% (114/229)</td>
<td>9.1% (7/77)</td>
<td>2.7% (1/37)</td>
<td>9.3% (8/86)</td>
<td>4.5% (10/223)</td>
<td>4.8% (10/207)</td>
<td>5.2% (11/210)</td>
<td>1.9% (4/210)</td>
<td>0% (0/71)</td>
<td>0% (0/70)</td>
</tr>
<tr>
<td>S with AC</td>
<td>22.0% (26/118)</td>
<td>2.6% (1/38)</td>
<td>19.0% (4/21)</td>
<td>4.5% (2/44)</td>
<td>12.0% (14/117)</td>
<td>4.0% (4/101)</td>
<td>2.1% (2/97)</td>
<td>3.1% (3/97)</td>
<td>0% (0/26)</td>
<td>0% (0/26)</td>
</tr>
<tr>
<td>NS with SCC</td>
<td>8.0% (4/50)</td>
<td>0.0% (0/32)</td>
<td>0.0% (0/9)</td>
<td>0.0% (0/35)</td>
<td>0.0% (0/44)</td>
<td>2.8% (1/36)</td>
<td>2.6% (1/38)</td>
<td>0.0% (0/38)</td>
<td>0.0% (0/16)</td>
<td>0.0% (0/16)</td>
</tr>
<tr>
<td>S with SCC</td>
<td>2.1% (2/94)</td>
<td>16.1% (10/62)</td>
<td>8.3% (2/24)</td>
<td>6.5% (4/62)</td>
<td>2.3% (2/88)</td>
<td>6.3% (5/80)</td>
<td>7.2% (6/83)</td>
<td>0% (0/94)</td>
<td>4.4% (2/45)</td>
<td>2.2% (1/45)</td>
</tr>
</tbody>
</table>
Lung cancer is a heterogenous disease

- Different genomic profile between ethnicity
- Different genomic profile between smoker and non-smoker
- Different genomic profile between histologic cell type
Cross-over rate in NEJ002

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>CBDCA/PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR-TKI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>100%</td>
<td>98.2%</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>27.2%</td>
<td>28.9%</td>
</tr>
<tr>
<td>BIBW2992</td>
<td>0</td>
<td>1.8%</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum based</td>
<td>64.9%</td>
<td>100%</td>
</tr>
<tr>
<td>CBDCA/PTX</td>
<td>50.0%</td>
<td>100%</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>28.9%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>24.6%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Others</td>
<td>23.7%</td>
<td>22.8%</td>
</tr>
</tbody>
</table>

Maemondo et al NEJM 2010
The old day late-drug development model may not be applicable to modern day molecular targeted therapy
New strategy on drug development

Haber et al. Cell 2011
### Integrated New Drug-New Biomarker Development Paradigm:

**Phases of Development of a New Drug**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Participants</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical</td>
<td>N=30</td>
<td>~18 mo.</td>
</tr>
<tr>
<td>Phase I</td>
<td>N=300</td>
<td>~18 mo.</td>
</tr>
<tr>
<td>Phase II</td>
<td>N=1600</td>
<td>~36 mos</td>
</tr>
</tbody>
</table>

**Total Time**

- ~90 mos (7.5 years)

**Phases of Development of New Biomarker linked to New Drug**

- Confirm Target
- Integrate Biomarker
- Biomarker Informative?
- Clinical Validation
- Clinical Application of Biomarker

*from Gandara et al: Clin Lung Cancer, 2012*
Biomarker selection design

- Clinical selection with retrospective biomarker study
- Biomarker selection upfront
Phase III biomarker-based study design

Marker-by-treatment-interaction Design

Marker-based Strategy Design


How prevalent is the positive biomarker?

How accurate is the cut-off (threshold between positive and negative)?
When to use which design?

from Redman, Gandara et al: Clin Cancer Res 2012
& Gandara et al: Clin Lung Cancer 2012
IPASS

Patients
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
  - Life expectancy ≥12 weeks
  - PS 0-2
  - Measurable stage IIIIB / IV disease

1:1 randomisation

Gefitinib (250 mg / day)

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m²) 3 weekly#

Endpoints
Primary
- Progression-free survival (non-inferiority)

Secondary
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

Mok et al NEJM 361:947 2009
IPASS: EGFR Mutation and Progression-free survival

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

Mok et al NEJM 361:947 2009
Validation of the biomarker

- **Retrospective study**
  - Existing clinical data base
  - Un-intended retrospective evaluation of biomarker

- **Prospective single arm study**
  - Able to study the prognostic value only

- **Prospective randomized study**
  - Intended retrospective biomarker analysis
  - Biomarker selected study
  - Interaction test
Validation of biomarker trial

- **Retrospective study**
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- **Prospective randomized study**
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  - Interaction test
Interaction test

Study population

Treatment A

Treatment B

Patients With biomarker

Treatment A

Treatment B

Patient without biomarker

Treatment A

Treatment B
Interaction test

Study population

Treatment A

Patients With biomarker

Treatment A

HR <1.0

Treatment B

Patient without biomarker

Treatment A

HR >1.0

Treatment B
Progression-free survival in EGFR mutation positive and negative patients

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Mok et al NEJM 361:947 2009
Phase III study design

Marker-by-treatment-interaction Design

Marker-based Strategy Design

When to use which design?

PROFILE 1007

Key entry criteria
- ALK+ by central FISH testing
- Stage IIIB/IV NSCLC
- 1 prior chemotherapy (platinum-based)
- ECOG PS 0–2
- Measurable disease
- Treated brain metastases allowed

N=318

Crizotinib 250 mg BID PO, 21-day cycle (n=159)

Pemetrexed 500 mg/m² or Docetaxel 75 mg/m² IV, day 1, 21-day cycle (n=159)

CROSSOVER TO CRIZOTINIB ON PROFILE 1005

Endpoints
- Primary
  - PFS (RECIST 1.1, independent radiology review)
- Secondary
  - ORR, DCR, DR
  - OS
  - Safety
  - Patient reported outcomes (EORTC QLQ-C30, LC13)

\(^a\) ALK status determined using standard ALK break-apart FISH assay
\(^b\) Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)
PROFILE 1007: PFS

1. Clear cut qualitative biomarker
2. Low prevalence of biomarker
# PROFILE 1014: First line study

## Trial design
- World-wide, multicenter, randomized, open-label, focused screening

## Endpoints
- **Primary:** PFS*  
  Secondary: 6- and 12-month OS; OS; ORR*; DCR; DR; Safety; HRQoL; Lung cancer-specific symptoms; General health status; Biomarkers; TTD; HCRU

## Stratification
- ECOG PS (0/1 vs 2)  
- Ethnicity (Asian vs non-Asian)  
- Brain metastases

## Key entry criteria
- Diagnosis of locally advanced/metastatic non-squamous NSCLC; ECOG 0-2  
- Positive for ALK  
- No prior treatment for advanced disease  
- Brain metastases allowed

*Based on RECIST v 1.1 and confirmed by independent radiology review

## Trial design details

### Arm A: Crizotinib 250 mg BID administered on a continuous dosing schedule

- N=160

### Arm B: Pemetrexed/ cisplatin or pemetrexed/ carboplatin

- N=160  
- Day 1 of a 21-day cycle  
- Patients in Arm B who have RECIST-defined PD as determined by the independent radiology review will be allowed to cross over to Arm A

PI: Mok T and Blackhall F
Common factors in positive trials

• Proven driver oncogenic
• Known incidence of the driver oncogene in population
• Convincing waterfall plot
• Established predictive biomarker prior to phase III study
Common factors in negative trial

- Unselected population
- Limited translational research from lab to clinic
- Lack of a known potential predictive biomarker before engagement in phase III study
- Chemotherapy +/- targeted drug in unselected population
Can we predict outcome of late drug development trial?
**MetLung**: global phase III study of onartuzumab (MetMAb) in Met-positive NSCLC

- **Primary endpoint**
  - OS

- **Secondary endpoints**
  - PFS, ORR, QoL, safety

- **Stratification**
  - *EGFR* Mut status
  - Met 2+ or 3+ score
  - Number of prior lines of therapy
  - Histology

- Erlotinib 150mg/day
- Onartuzumab (MetMAb) 15mg/kg iv q3w

- Target HR=0.71
- 90% power at alpha 0.05

- Erlotinib + onartuzumab (MetMAb) n=490 (recruiting globally)
- Erlotinib + placebo

- Treat until PD

- Survival follow-up

- No crossover
Positive factors

- Known C-MET pathway and its importance to cell proliferation
- Incidence of Met-Positive is known
- Biomarker established in the randomized phase II study
- C-MET and EGFR mutation known in most patients
Negative factors

- C-MET may not be a driver oncogene
- Met-positive by IHC is semi-quantitative subjective biomarker
- Limited sample size (n=66) of met-positive patient in the randomized phase II study
- Role of erlotinib in EGFR mutation wild type is debatable
Media Release

Basel, 3 March 2014

Roche provides update on phase III study of onartuzumab in people with specific type of lung cancer

Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that an independent data monitoring committee has recommended that the phase III METLung study be stopped due to a lack of clinically meaningful efficacy.
Can we do real time monitoring?

Haber et al Cell 2011
FASTACT-2 study design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Study treatment</th>
<th>Maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated stage IIIB/IV NSCLC, PS 0/1 (n=451)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib 150mg/day</td>
<td></td>
<td>PD</td>
</tr>
<tr>
<td>Gemcitabine 1,250mg/m² (d1, 8) + carboplatin AUC=5 or cisplatin 75mg/m² (d1) + erlotinib 150mg/day (d15–28); q4wks x 6 cycles GC-erlotinib (n=226)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>PD</td>
</tr>
<tr>
<td>Gemcitabine 1,250mg/m² (d1, 8) + carboplatin AUC=5 or cisplatin 75mg/m² (d1) + placebo (d15–28); q4wks x 6 cycles GC-placebo (n=225)</td>
<td></td>
<td>Erlotinib 150mg/day</td>
</tr>
</tbody>
</table>

IRC = independent review committee

Wu YL et al Lancet Oncology 2013
Serial plasma sample at baseline, C3 and PD

Baseline Tissue Samples

397 (88%) patients consented

268 (59.4%) samples available

241 (53.4%) samples analyzable

Plasma Samples

451 (100%) patients consented

447 (99.1%) baseline samples available

447 (99.1%) baseline samples analyzable

362 (80.3%) cycle 3 samples available

362 (80.3%) cycle 3 samples analyzable

376 (83.4%) PD samples available

376 (83.4%) PD samples analyzable

238 (52.8%) patients with matched tumor and plasma results

305 (67.6%) Patients with all three time points plasma results
Semi-quantitation change in plasma EGFR mutation DNA during treatment

<table>
<thead>
<tr>
<th>Median EGFR mutant DNA (copy/mL plasma)</th>
<th>C</th>
<th>C+T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>83</td>
<td>6</td>
</tr>
</tbody>
</table>
Dynamic change in plasma EGFR status during therapy

Patients treated with GC+
Placebo

Mutant DNA copy/mL of plasma

Patients treated with GC+
Erlotinib

Mutant DNA copy/mL of plasma

Baseline  C3  PD

Baseline  C3  PD

Not detectable

Mok et al WCLC 2013
What happened to patients with persistent EGFR mutation at cycle 3?
Positive versus negative pEGFR mut status at C3 (both treatment arms combined)

pEGFR mut+ at baseline (n=122)

pEGFR mut+ at C3 (n=42)

ORR = 33% (14/42)

OR = 3.93 (95% CI: 1.78–8.66); p=0.0007

pEGFR mut– at C3 (n=80)

ORR = 66% (53/80)

ORR = objective response rate; OR = odds ratio
Association between pEGFR mut+ at C3 and PFS/OS (both treatment arms combined)

Positive pEGFR at baseline followed by negative pEGFR at C3 is associated with improved outcomes; patients positive at baseline and still positive at C3 experienced worse outcomes.
**pEGFR mut+ at C3 predicts PFS and OS (GC+E arm only)**

**PFS**
- C3 mut+
  - Median=7.8 months (95% CI: 7.2–14.6)
- C3 mut–
  - Median=16.6 months (95% CI: 12.8–20.0)

HR=0.45 (95% CI: 0.18–1.13); p=0.0831

**OS**
- C3 mut+
  - Median=17.7 months (95% CI: 11.8–undefined)
- C3 mut–
  - Median=32.4 months (95% CI: 23.5–undefined)

HR=0.45 (95% CI: 0.18–1.13); p=0.0831

Positive pEGFR at baseline followed by negative pEGFR at C3 is associated with improved outcomes; patients positive at baseline and still positive at C3 experienced worse outcomes
Conclusion

• The traditional phase I-IV study design may not be directly applicable to biomarker-based molecular targeted therapy
• Biomarker driven design is the trend
• Understanding the epidemiology of driver oncogene is essential to clinical study design
• It is best to have a known biomarker before engaging in late drug study (retrospective analysis could be risky)
• Avoid chemotherapy +/- targeted as much as you can
• Plasma DNA (or CTC) may provide real time monitoring of treatment outcomes