Nouvelles stratégies
Prise en charge en cas d’altération oncogénique

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Thoracic Unit
Gustave Roussy – Villejuif (France)
Consultancy fees from

- AstraZeneca, BMS, Boehringer Ingelheim, GSK, Lilly, MSD, Pfizer, Roche, Sanofi, Pierre Fabre, Merck, Novartis
Frequency of genetic alterations

- Full WT 15%
- EGFR 11%
- KRAS 29%
- Unknown 35%
- BRAF 2%
- HER2 1%
- PIK3CA 2%
- ALK 5%

F.Barlesi et al, Lancet 2016
# EGFR-TKI as standard for 1<sup>st</sup> ligne treatment for EGFR mut patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>N (EGFRmut)</th>
<th>RR</th>
<th>Median PFS(months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURTAC&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Erlotinib vs cddp/doc</td>
<td>173</td>
<td>58.1% vs 14.9%</td>
</tr>
<tr>
<td>OPTIMAL&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Erlotinib vs carbo/gem</td>
<td>154</td>
<td>83% vs 36%</td>
</tr>
<tr>
<td>IPASS&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Gefitinib vs carbo/pacl</td>
<td>261</td>
<td>71.2% vs 47.3%</td>
</tr>
<tr>
<td>NEJ002&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Gefitinib vs carbo/pacl</td>
<td>224</td>
<td>73.7% vs 30.7%</td>
</tr>
<tr>
<td>WJTOG3405&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Gefitinib vs cddp/doc</td>
<td>172</td>
<td>62.1% vs 32.2%</td>
</tr>
<tr>
<td>LL3&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Afatinib vs cddp/pem</td>
<td>345</td>
<td>56% vs 23%</td>
</tr>
<tr>
<td>LL6&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Afatinib vs cddp/gem</td>
<td>364</td>
<td>66.9% vs 23%</td>
</tr>
</tbody>
</table>

Selecting treatment in patients in 2016

Advanced NSCLC
Non-squamous histology

EGFR mut+

Strength of recommendation: A
Level of evidence: I

EGFR mut+

EML4-ALK- / EGFR WT or unknown

Diagnosis

Good PS (PS 0–1)

Platinum-based combination therapy
- Cis + gem/taxanes (I,B)
- Pem + cis (II,B)
- Bev + platinum-based regimen (I,A)

Poor PS (PS ≥2)

Single agent chemotherapy
- Gemcitabine, vinorelbine, + taxanes

Platinum-based combinations
- Carboplatin + paclitaxel or pemetrexed

BSC (absence of activating EGFR mutations)

EGFR TKI (erlotinib)
EGFR TKI (afatinib)
EGFR TKI (gefitinib)

Adapted from NSCLC ESMO Guidelines
Meta-Analysis of afatinib, erlotinib or gefitinib in *EGFR* Mut+ NSCLC

PFS with first-line afatinib, erlotinib or gefitinib in *EGFR* Mut+ NSCLC

Eight phase III studies

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib</th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 95% CI</td>
<td>0.25 (0.15–0.42)</td>
<td>0.44 (0.26–0.75)</td>
<td>0.43 (0.31–0.63)</td>
</tr>
</tbody>
</table>

Favours EGFR TKI

Favours chemotherapy

Lopes & Haaland. WCLC 2013, JTO 2014
Combined OS analysis (Lux-lung 3 and 6): Mutation categories (Del19 vs L858R)

No of patients
Afatinib 236 230 223 217 202 192 173 160 145 131 117 90 50 38 22 6 1 0
Chemo 119 113 103 95 87 72 63 55 51 43 38 27 14 9 1 1 0 0

No of patients
Afatinib 183 181 167 154 141 128 111 91 80 70 64 51 27 20 11 3 0 0
Chemo 93 86 82 78 75 69 61 55 50 40 32 25 20 14 9 4 1 0

OS: 31.7 vs 20.7

Median, months
Del19 Afatinib L858R Afatinib
Median, months
31.7 20.7 22.1 26.9

HR (95%CI), p-value
Del19 Afatinib Chemo
0.59 (0.45–0.77), p=0.0001

L858R Afatinib Chemo
1.25 (0.92–1.71), p=0.1600

James Chih-Hsin Yang et al, lancet onco 2015
Study design: LUX-Lung 7

• Stage IIIB/IV adenocarcinoma of the lung
• *EGFR* mutation (Del19 and/or L858R) in the tumor tissue*
• No prior treatment for advanced/metastatic disease
• ECOG PS 0/1

Primary endpoints:
• PFS (independent)
• TTF
• OS

Secondary endpoints:
• ORR
• Time to response
• Duration of response
• Duration of disease control
• Tumor shrinkage
• HRQoL
• Safety

Stratified by:
• Mutation type (Del19/L858R)
• Brain metastases (present/absent)

Afatinib 40 mg once daily†

Gefitinib 250 mg once daily

1:1

• Treatment beyond progression allowed if deemed beneficial by investigator
• RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter

*Central or local test
†Dose modification to 50, 30, 20 mg permitted in line with prescribing information

ECOG PS, Eastern Oncology Cooperative Group performance status; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTF, time to treatment failure

Keunchil Park et al, ESMO Asia 2015
Objective response and duration of response (independent review)

Afatinib
n=112/160

Gefitinib
n=89/159

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=112)</th>
<th>Gefitinib (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DoR (months)</td>
<td>10.1</td>
<td>8.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>(7.8–11.1)</td>
<td>(7.4–10.9)</td>
</tr>
</tbody>
</table>

DoR, duration of response

Keunchil Park et al, ESMO Asia 2015
PFS by independent review

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>160 142 112 94 67 47 34 27 21 13 6 3 1 0 0</td>
<td>Gefitinib</td>
</tr>
</tbody>
</table>

Estimated PFS probability

Time (months)

- **Afatinib**: Median PFS (months) = 11.0
- **Gefitinib**: Median PFS (months) = 10.9
- HR (95% CI): 0.73 (0.57–0.95)
- p value: 0.0165

Keunchil Park et al, ESMO Asia 2015
Efficacy in patients with Del19 mutation

<table>
<thead>
<tr>
<th></th>
<th>Afatinib</th>
<th>Gefitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>12.7</td>
<td>11.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.55–1.06)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.1071</td>
<td></td>
</tr>
</tbody>
</table>

No. of patients
Afatinib | 93 | 83 | 67 | 58 | 43 | 31 | 22 | 18 | 14 | 9 | 4 | 2 | 1 | 0 | 0
Gefitinib | 93 | 76 | 64 | 53 | 32 | 17 | 11 | 7 | 6 | 4 | 3 | 3 | 1 | 1 | 0

Afatinib (n=93)  Gefitinib (n=93)

ORR 73%  66%

Keunchil Park et al, ESMO Asia 2015
Efficacy in patients with L858R mutation

Keunchil Park et al, ESMO Asia 2015
Almost all patients with an initial response to EGFR TKI therapy develop ‘acquired resistance’

After a median of 9–14 months

- **Continue beyond RECIST PD**
  - Pts often asymptomatic and disease growth is slow
- **Switch (or add) chemotherapy**
  - IMPRESS
- **Figure out resistance mechanism and treat with novel agent or combination of agents**

D. Ross Camidge et al, Nat rev clin oncol 2014
IMPRESS results do not support the continuation of gefitinib after disease progression (by RECIST criteria)

Patients at risk:
Gefitinib 133   Placebo 132

<table>
<thead>
<tr>
<th>Time of randomisation (months)</th>
<th>Gefitinib (n=133)</th>
<th>Placebo (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>17</td>
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<tr>
<td>8</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median PFS, months
Gefitinib 5.4
Placebo 5.4

Number of events, n (%)
Gefitinib 98 (73.7)
Placebo 107 (81.1)

HR^a (95% CI) = 0.86 (0.65, 1.13); p=0.273

^a Primary cox analysis with covariates
A HR <1 implies a lower risk of progression with gefitinib

T.Mock et al, ESMO 2014
In EGFR Mut+ NSCLC various mechanisms of Resistance for EGFR TKI

- **MET amplification**: 3%
- **Small cell + MET**: 1%
- **Small cell**: 1%
- **Small cell + T790M**: 2%
- **MET + T790M**: 3%
- **HER2**: 8%
- **HER2 + T790M**: 4%
- **Unknown**: 18%
- **T790M**: 60%
AZD9291 (Tagrisso): Response rate in T790M positive cohorts (central test)

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

T790M positive (central test) 80 mg cohort – progression-free survival

Investigator assessed

• Median progression-free survival, 10.9 months (95% CI 8.3, not calculable; 40% maturity, 25/63 events)

Independent review#

• Median progression-free survival, 13.5 months (95% CI 8.3, not calculable; 38% maturity, 24/63 events)

Dots indicate censored observations, shaded area represents 95% CIs. Progression based on RECIST 1.1; progression events that do not occur within 14 weeks of the last evaluable assessment (or first dose) are censored.

Population: 80 mg centrally confirmed T790M positive patients (n=63)

#One patient did not have measurable disease; one patient’s scan was not sent for independent review

Data cut-off 2 Dec 2014

3\textsuperscript{rd} Generation TKI-EGFR

- **Rociletinib**
  - Table:
    - N: 48, 114, 77, 4, 243
    - ORR (%): 60, 54, 46, 75, 53
    - DCR (%): 90, 84, 82, 100, 85

- **ASP8273**
  - Graph: 
    - Negative
    - Positive
    - Unknown
  - Legend: n/N(%) = 40/53 (75.5%)

- **EGF816**
  - Graph: 
    - Best percent change from baseline
    - Treatment groups: 75 mg, 150 mg, 225 mg, 300 mg, 400 mg

- **BI 1482694 (HM61713)**
  - Graph: 
    - Tumor volume change (%)
    - PR, partial response
  - Legend: PR (n=43), Confirmed PR (n=32), SD (n=20), NE (n=3), PD (n=3)
What happen beyond EGFR-TKI 3\textsuperscript{rd} (Tagrisso) ?

Mechanism of resistance...

15 AZD9291-treated subjects (T790M)
- 6 cases acquired the C797S mutation,
- 5 cases maintained the T790M but did not acquire the C797S mutation
- 4 cases lost the T790M

Kenneth S Thress et al., Nature med 2015
Allelic Context of C797S Mutation Acquired Impacts Sensitivity to Subsequent Treatment Strategies

Matthew J. Niederst et al, CCR 2015
What is the Best Sequence?

Today

EGFR mut → 1st generation TKI → Progression T790m- → Chemotherapy → Death

EGFR mut → 1st generation TKI → Progression T790M+ → Third generation TKI → Chemotherapy → Death

Tomorrow

EGFR mut → Third generation TKI → ? → Progression → Chemotherapy

OS
DoR and PFS in AZD9291 first-line cohorts (investigator assessed)

**Duration of response**

<table>
<thead>
<tr>
<th></th>
<th>80 mg N=20</th>
<th>160 mg N=25</th>
<th>Total N=45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median DoR,* months (95% CI)</td>
<td>13.6 (11.1, NC) Maturity: 35%</td>
<td>NC (9.7, NC) Maturity: 28%</td>
<td>NC (12.3, NC) Maturity: 31%</td>
</tr>
<tr>
<td>Maximum DoR, months</td>
<td>18.0+</td>
<td>12.6+</td>
<td>18.0+</td>
</tr>
</tbody>
</table>

**Remaining in response,† % (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>89 (64, 97) 76 (46, 90)</td>
<td>78 (56, 90) 69 (45, 84)</td>
</tr>
<tr>
<td>160 mg</td>
<td>83 (68, 92) 71 (53, 83)</td>
<td></td>
</tr>
</tbody>
</table>

**Progression-free survival**

<table>
<thead>
<tr>
<th></th>
<th>80 mg N=30</th>
<th>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) Maturity: 40%</td>
<td>NC (11.1, NC) Maturity: 30%</td>
<td>NC (13.7, NC) Maturity: 35%</td>
</tr>
<tr>
<td>Maximum PFS, months</td>
<td>19.2+</td>
<td>13.8+</td>
<td>19.2+</td>
</tr>
</tbody>
</table>

**Remaining alive and progression-free,† % (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>83 (64, 93) 75 (55, 87)</td>
<td>80 (60, 90) 69 (48, 82)</td>
</tr>
<tr>
<td>160 mg</td>
<td>81 (69, 89) 72 (58, 82)</td>
<td></td>
</tr>
</tbody>
</table>

Population: all dosed patients, data cut-off August 1, 2015
Progression events that do not occur within 14 weeks of the last evaluable assessment (of first dose) are censored
*Duration of response is the time from first documentation of response until date of progression or death or last evaluable RECIST assessment for patients who do not progress;
†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
DoR, duration of response; NC, not calculable; PFS, progression-free survival

Suresh S. Ramalingam et al, IASLC 2015
FLAURA Study Design

Enrollment by local* or central# EGFR mutation testing of biopsy sample

Stratified by:

Asian / non-Asian

Ex19del / L858R

Randomize patients 1:1

AZD9291 (80 mg p.o. qd)

EGFR-TKI standard of care##: gefitinib or erlotinib

RECIST 1.1 assessment every 6 weeks until objective progressive disease

Patients randomized to standard of care may receive AZD9291 after progression§

Primary objective: efficacy by PFS

*With central laboratory assessment performed for sensitivity
#cobas™ EGFR Mutation Test (Roche Molecular Systems)
##Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation
§Patients randomized to the standard of care treatment arm may receive open-label treatment with AZD9291 on central confirmation of both objective disease progression and T790M positive tumor

OS, overall survival; PFS2, second progression-free survival (time from randomization to second progression); p.o., orally

Genetic alterations of ALK

**Point mutation (in neuroblastoma)**
- ALK
  - N-lobe
  - C-lobe
  - F1174
  - F1245
  - R1275

**ALK fusion gene**
- Oligomerization domain
- Tyrosine kinase
  - NPM–ALK
  - EML4–ALK
  - KIF5B–ALK

**Identified mutation in ALK (neuroblastoma)**
- R1060H (germline)
- T1151M
- M1166R
- I1170N/S
- I1171N
- F1174C/I/L/S/V
- I1183T (germline)
- L1196M
- A1200V
- L1204F (germline)
- L1240V
- F1245C/I/L/V
- D1270G (inactivating mutant)
- R1275L/Q (germline)
- Y1278S
- G1286R
- T1343I

**Identified ALK fusion gene**
- NPM–ALK
- EML4–ALK
- ATIC–ALK
- C2orf44–ALK
- CARS–ALK
- CLTC–ALK
- CLTC1–ALK
- FNI–ALK
- HIP1–ALK
- KIF5B–ALK
- KLIC1–ALK
- LMNA–ALK
- MSN–ALK
- PPFIBP1–ALK
- PRKAR1A–ALK
- RANBP2–ALK
- SEC31A–ALK
- SQSTM1–ALK
- STRN–ALK
- TFG–ALK
- TPM3–ALK
- TPM4–ALK
- VCL–ALK

Ryohei Katayama et al, CCR 2015
Response rates to ALKi crizotinib in ALK+ NSCLC patients (phase I&II)

Study 1001 - n=116
Median time to response: 8 wk

Study 1005 - n=133

ORR 61%

ORR 60%

Eunice L. Kwak et al, NEJM 2010
Efficacy of crizotinib according to the line of treatment

<table>
<thead>
<tr>
<th></th>
<th>Profile 1001</th>
<th>Profile 1005</th>
<th>Profile 1007</th>
<th>Profile 1014</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>143</td>
<td>259</td>
<td>172</td>
<td>172</td>
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<tr>
<td><strong>Phase</strong></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>61%</td>
<td>60%</td>
<td>65%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>9.7</td>
<td>8.1</td>
<td>7.7</td>
<td>10.9</td>
</tr>
</tbody>
</table>
Selecting treatment in patients in 2016

Advanced NSCLC
Non-squamous histology

Diagnosis

EML4-ALK/EGFR mut+

EML4-ALK+  
Crizotinib

EGFR TKI (erlotinib)

EGFR TKI (afatinib)

EGFR TKI (gefitinib)

EML4-ALK- / EGFR WT or unknown

Good PS (PS 0–1)

Platinum-based combination therapy

Cis + gem/ taxanes (I,B)

Pem + cis (II,B)

Bev + platinum-based regimen (I,A)

Single agent chemotherapy

Gemcitabine, vinorelbine, + taxanes

Poor PS (PS ≥2)

Platinum-based combinations

Carboplatin + paclitaxel or pemetrexed

BSC (absence of activating EGFR mutations)

EGFR TKI 3rd G (Tagrisso)

Adapted from NSCLC ESMO Guidelines
Most patients develop resistance to crizotinib usually within 1–2 years

- **ALK+**
- **Crizotinib**
- **Progression**
- **Chimio / ALK-TKI…**

### Resistance Mechanisms

- **No identification AR mechanism** ~25%
- **KIT amplification** ~10%
- **Change in driver mutations** ~5%
- **Increased EGFR signalling** ~30–35%
- **ALK mutations** ~22–33%
  - L1196M
  - G1202R
  - S1206Y
  - G1269A
  - 1151Tins
  - Others
- **ALK amplification** ~6–16%

D. Ross Camidge et al, nature reviews 2014
## ALK inhibitors in the crizotinib-failure setting
### Systemic efficacy

<table>
<thead>
<tr>
<th></th>
<th>Alectinib NP28673 (n=138)*</th>
<th>Alectinib NP28761 (n=87)*</th>
<th>Brigatinib (n=71)*</th>
<th>Ceritinib ASCEND-1 (prior ALKi) (n=163)**</th>
<th>Ceritinib ASCEND-2* (n=140)**</th>
<th>Lorlatinib (n=41) All pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>n=122</td>
<td>n=67</td>
<td>n=70</td>
<td>n=163</td>
<td>n=140</td>
<td>n=130</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>50.8</td>
<td>52.2</td>
<td>71</td>
<td>55</td>
<td>39</td>
<td>47</td>
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<tr>
<td><strong>DCR</strong></td>
<td>78.7</td>
<td>79.1</td>
<td>87</td>
<td>74</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td><strong>mDoR, mos</strong></td>
<td>14.1</td>
<td>13.5</td>
<td>9.9</td>
<td>8.3</td>
<td>9.7</td>
<td>–</td>
</tr>
<tr>
<td><strong>mPFS, mos</strong></td>
<td>8.9</td>
<td>8.1</td>
<td>13.4</td>
<td>6.9</td>
<td>5.7</td>
<td>–</td>
</tr>
</tbody>
</table>

*By IRC; **By investigator; † Termination before scan

Barlesi, et al. ECC 2015; Shaw, et al. WCLC; Gettinger, et al. WCLC
<table>
<thead>
<tr>
<th>ALK IC$_{50}$ (µM)</th>
<th>Crizotinib</th>
<th>Céritinib</th>
<th>Alectinib</th>
<th>AP26113</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1196M</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C1156Y</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>L1152R</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>F1174L</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>F1174V, C</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>S1206Y</td>
<td>-</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1202R</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G1269A</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1151Tins</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1180L*</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>I1171T*</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

*Cell lines exposed to alectinib*
Sequential ALK inhibitor therapy in ALK+ NSCLC

1L
- Crizotinib

2L
- Alectinib
- Ceritinib

3L
- Ceritinib
- Alectinib

I1171T
- G1202R
- F1174V

Crizotinib
- Ceritinib, Alectinib, Brigatinib...
- Lolartinib

Crizotinib
- Ceritinib
- Alectinib
Resensitization to Crizotinib by the Lorlatinib ALK Resistance Mutation L1198F

Alice T. Shaw et al NEJM 2016
## ALK inhibitors: CNS activity

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (n=50)</th>
<th>Alectinib (n=136)</th>
<th>Brigatinib* (n=15)</th>
<th>Non-measurable (n=31)</th>
<th>Ceritinib (n=20)</th>
<th>Measurable and non-measurable (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS ORR, %</strong></td>
<td>64.0</td>
<td>42.6</td>
<td>53</td>
<td>35</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>CR</td>
<td>22.0</td>
<td>27.2</td>
<td>7</td>
<td>35</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>PR</td>
<td>42.0</td>
<td>15.4</td>
<td>47</td>
<td>NA</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>SD</td>
<td>26.0</td>
<td>42.6</td>
<td>20</td>
<td>48</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>PD</td>
<td>6.0</td>
<td>8.8</td>
<td>13</td>
<td>6</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td><strong>CNS DCR, %</strong></td>
<td>90.0</td>
<td>85.3</td>
<td>87</td>
<td>94</td>
<td>85</td>
<td>65</td>
</tr>
<tr>
<td>CNS mPFS, months</td>
<td>–</td>
<td>–</td>
<td>(n=46)</td>
<td>15.6</td>
<td>–</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*8% patients with CNS mets at baseline were crizotinib-naïve

---

Mehra, et al. SNO 2014; Mok, et al. ASCO 2015

Slide from M.Perol
Optimal 1st line therapy for ALK+ NSCLC

1L
ALK+
Crizotinib

2L
Nex generation TKI
11 months
18 months
Combined PFS

18 months
(single PFS)
## Efficacy of ALK-TKI in Crizotinib naïf patients

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib Profile 1014</th>
<th>Ceritinib Ascend 1</th>
<th>Alectinib AF-001 JP</th>
<th>Brigatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>III</td>
<td>I</td>
<td>I/II</td>
<td>I</td>
</tr>
<tr>
<td><strong>Nb patients</strong></td>
<td>172</td>
<td>83</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>74%</td>
<td>72%</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>10.9</td>
<td>18.4</td>
<td>27.7</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Global</td>
<td>Global</td>
<td>Japon</td>
<td>USA/Espagne</td>
</tr>
<tr>
<td><strong>Diagnostic</strong></td>
<td>FISH central</td>
<td>FISH local</td>
<td>IHC + FISH central</td>
<td>FISH local</td>
</tr>
</tbody>
</table>

---

Solomon, NEJM 2014; Felip, ESMO 2014; Tamura, CMSTO 2014; Gettinger, WCLC 2015; d'après A. Shaw, ECC 2015
ALEX Phase III Trial

**Primary Endpoints**
- Progression free survival by investigator

**Secondary Endpoints**
- PFS by independent review
- Time to CNS progression
- ORR, DoR
- OS
- PROs
- Safety

**Stage IV NSCLC**
- ALK+ by IHC central testing
- Treatment-naive
- PS 0-2
- Measurable disease
- Stable untreated brain metastases allowed

**Crizotinib**
- 250 mg BID
- N=143

**Alectinib**
- 600 mg BID
- N=143

**No crossover**

Accrual completed
Management of ALK+ NSCLC in 2016

1L
- ALK+
- Crizotinib
- Progression
- Chemotherapy
- Death

2L
- Which ALK inhibitor?
  - CNS efficacy
  - Resistance mechanism
  - Tolerability
- Second generation TKI
- Chemotherapy
- Death

Today
- ALK+
- Crizotinib
- Second generation TKI
- Chemotherapy
- Death
ROS1 rearrangements in NSCLC

- Present in ~1% of NSCLC cases (also found in some GBMs and cholangiocarcinomas)
- Enriched in younger never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers

Crizotinib ROS1
Best Response

- 3 patients (6%) complete response
- 33 patients (66%) partial response
- 9 patients (18%) stable disease

Overall response rate: 72%

Alice T. Shaw et al, NEJM 2014
Progression-free survival

mPFS: 19.2 months (95% CI, 14.4 to NR)

Alice T. Shaw et al, NEJM 2014
**ROS inhibitors**

- **ALK/ROS1 inhibitors**
  - Crizotinib
  - Ceritinib
  - Brigatinib (AP26113)
  - Entrectinib (RXDX-101)
  - Lorlatinib

- **Non-ALK inhibitor**
  - DS6051b (inhibitor of the tyrosine kinases ROS1 and NTRKs)
Tumor shrinkage seen in intermediate and high MET cohorts

Best percent change from baseline in target tumor lesions\(^a\) by patient

Low MET
\(n=2\)

Intermediate MET
\(n=6\)

High MET
\(n=6\)

ORR: 0 (0–84)

ORR: 17 (0–64)

ORR: 67 (22–96)

\(^a\)Confirmed objective responses.

\(^b\)Based on investigator assessment.

\(^c\)Two patients in the intermediate MET group had an unconfirmed PR that was not confirmed in a second assessment.

DR Camidge, et al ASCO 2014
Partial response in a patient with high MET amplification

Duration of response: 31+ months

8/16/2011

12/9/2011

3/27/2014

MET/CEP7 ratio: >5

Images: G. Shapiro DFCI
MET exon 14 splicing

4% of patients with adenocarcinoma

Cabozantinib

Crizotinib

Crizotinib

Patient 2

Baseline

1 month follow-up cabozantinib

Patient 4

Baseline

1 month follow-up crizotinib

Patient 5

Baseline

6 week follow-up crizotinib
MET 14 skipping in pulmonary sarcoma

- Eight (22%) of 36 patients with pulmonary sarcoma.
- One with a concurrent PIK3CA mutation

<table>
<thead>
<tr>
<th>Smoking status, % (n = 38)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>28</td>
</tr>
<tr>
<td>Former</td>
<td>64</td>
</tr>
<tr>
<td>Never</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pack-years, % (n = 34)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.8</td>
</tr>
<tr>
<td>0.1-20 (light)</td>
<td>41.2</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>50</td>
</tr>
</tbody>
</table>

Liu et al. JCO. 2015.
Rearranged during transfection (RET) gene fusion

• Frequency: 1%
• Fusions partners: CCDC6-RET, KIF5B-RET
• ADC, never smokers
• Mutually exclusive with other drivers
• Inhibitors: vandetanib, sorafenib, sunitinib, cabozantinib, levantinib

Response to Cabozantinib in patients with *RET*-rearranged lung adenocarcinomas

<table>
<thead>
<tr>
<th>Best Response</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>44% (7/16)</td>
</tr>
<tr>
<td>confirmed</td>
<td>38% (6/16)</td>
</tr>
<tr>
<td>unconfirmed</td>
<td>6% (1/16)</td>
</tr>
<tr>
<td>SD</td>
<td>56% (9/16)</td>
</tr>
</tbody>
</table>

**ORR 38% (95% CI 15%-65%)**

**ORR$_{12\text{wks}}$ 36% (95% CI 13%-65%)**

(5 PRs of 14 evaluable at 12 wks)

*Drilon et al* ASCO 2015. Abstract 8007

PR - partial response, SD - stable disease

ORR – overall response rate, CI - confidence interval

Imaging performed at baseline, 4 weeks, and every 8 weeks thereafter.

Response evaluable patients: received ≥ 1 cycle of therapy.
BRAF V600E and Vemurafenib or Dabrafenib
BASKET Trial: Vemurafenib in Multiple Non-melanoma cancers with BRAF V600 Mutations

mPFS: 7.3 months (95% CI, 3.5 to 10.8)

<table>
<thead>
<tr>
<th>Variable</th>
<th>NSCLC (N=20)</th>
<th>Colorectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vemurafenib (N=10)</td>
<td>Vemurafenib + Cetuximab (N=27)</td>
</tr>
<tr>
<td>Patients with ≥1 postbaseline assessment — no.</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>8 (42)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease — no. (%)</td>
<td>8 (42)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>2 (11)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Missing data — no. (%)†</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Overall response — no. (%) [95% CI]</td>
<td>8 (42) [20–67]</td>
<td>0</td>
</tr>
</tbody>
</table>

David M. Hyman et al, NEJM 2015
**Phase II BRAF+ NSCLC trial design**

**Statistical Assumptions:**

- **2L Cohort A:** Primary, Original (n=40) 92.6% power to detect 30% ORR. Per FDA guidance expanded to 60 pts, ORR of 30% @95% CI(18.9%, 43.2%). To achieve 60 evaluable, enrolled 78 2L+ pts. Included 6 1L pts.
  - Secondary PFS, OS, safety and tolerability, pop PK

- **2L Cohort B:** Primary, 92.2% power to detect 55% ORR. To achieve 40 evaluable, enrolled 59. Included 1 1L.
  - Secondary PFS, OS, safety and tolerability, pop PK

- **1L Cohort C:** Primary, 92.2% power to detect 60% ORR
  - Secondary PFS, OS, safety and tolerability, pop PK

**Stage IV NSCLC**
- **BRAF V600E**
- **ECOG 0-2**
- **Prior Tx**

- **Non-randomized**

**Cohort A:**
- dabrafenib: 150 mg BID
  - (n = 84)
- ORR: 1° endpoint

**Cohort B:**
- dabrafenib: 150 mg BID + trametinib: 2 mg QD
  - (n = 59)
- ORR: 1° endpoint

**Cohort C:**
- dabrafenib: 150 mg BID + trametinib: 2 mg QD
  - (planned sample size n=25)
- ORR: 1° endpoint

**Stage IV NSCLC**
- **BRAF V600E**
- **ECOG 0-2**
- **No Prior Tx**

- **Non-randomized**

**Enrollment completed N=84**
- (78 2L+, 6 1L)

**Enrollment completed N=59**
- (58 2L+, 1 1L)

**Enrollment on-going**
- Target: 25 evaluable
Cohort B: Phase II BRAF+ NSCLC D+T combination interim results

- In Phase II Study BRF113928, D+T demonstrated clinically meaningful activity in BRAF V600E NSCLC (Cohort B)
- Efficacy of D+T (Cohort B) at interim analysis was numerically superior to dabrafenib monotherapy (Cohort A) when indirectly compared across cohorts
- Similar benefit observed in BRAF V600 metastatic melanoma; D+T demonstrated significantly superior anti-tumor activity vs. BRAF inhibitor monotherapy*

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>D+T Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D#</td>
<td>D+T&amp;</td>
</tr>
<tr>
<td>(primary analysis; N=78)</td>
<td>32%</td>
<td>63%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(21.9%, 43.6%)</td>
<td>(40.6%, 81.2%)</td>
</tr>
<tr>
<td>IRC Assessed ORR</td>
<td>23%</td>
<td>68%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(14.3%, 34.0%)</td>
<td>(45.1%, 86.1%); N=22¹</td>
</tr>
</tbody>
</table>

¹ Excludes two subjects who did not have scans available for IRC review

D+T, Dabrafenib + Trametinib; D, Dabrafenib
ORR, Overall Response Rate; IRC, Independent Review Committee

*Flaherty, NEJM 2012; Long, NEJM 2014; Robert, NEJM 2014; # Planchard ESMO 2014; & Planchard ASCO 2015
Maximum Reduction of Sum of Lesion Diameters By Best Confirmed Response in $\geq 2$nd Line (N = 24$^a$)

- The median duration of response was not reached

$^a$1 patient discontinued at day 23 and did not have any post-baseline scans for efficacy.

D.Planchard et al, ASCO 2015
US FDA has supported pathway to registration based on the Phase II study

July 2015: Based on interim findings from the ongoing clinical trial, the FDA granted dabrafenib + trametinib Breakthrough Therapy Designation for metastatic BRAF V600E NSCLC.

FDA Guidance on D+T Trial Design & Submission

- **Study Design:** Single-arm study with a 50% ORR (lower bound of the CI ~35%) and ≥6 months follow-up on all patients could support a sNDA filing for a line agnostic BRAF V600E NSCLC indication.

- **Line Agnostic Filing:** Agreed it may be infeasible to conduct a randomized trial in 1st line; not in a position to comment on ability of the 1st line cohort (Cohort C) to support an indication.

Expected Patient Enrollment at Time of Submission

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Monotherapy)</td>
<td>84</td>
</tr>
<tr>
<td>B (D+T Combo 2nd Line)</td>
<td>59</td>
</tr>
<tr>
<td>C (D+T Combo 1st Line)</td>
<td>~14</td>
</tr>
</tbody>
</table>

**Note:** 70 NSCLC trial sites have been open globally for over 3 years with only ~150 patients enrolled.
59 Year Old Male Pt (Former Smoker) with V600E BRAF Mutation Treated With Dabrafenib + Trametinib

Baseline (March 2014)

+12 months (March 2015)

Images courtesy of D.Planchard et al, Gustave Roussy - Villejuif
## Other targetable mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Histology</th>
<th>Frequency</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>Mutation, fusion</td>
<td>ADC</td>
<td>1-3%</td>
<td>Vemurafenib, dabrafenib, trametinib</td>
</tr>
<tr>
<td>MET</td>
<td>Amplification, and exon14 splicing</td>
<td>ADC</td>
<td>2-4%</td>
<td>Tivantinib, cabozantinib, INC280, onartuzumab</td>
</tr>
<tr>
<td>RET</td>
<td>Fusion</td>
<td>ADC</td>
<td>1%</td>
<td>Carbozatinib , sunitinib, sorafenib, lenvatinib, vandetanib</td>
</tr>
<tr>
<td>HER2</td>
<td>Mutation</td>
<td>ADC</td>
<td>2-4%</td>
<td>Neratinib, afatinib, lapatinib, dacomitinib</td>
</tr>
<tr>
<td>NTRK</td>
<td>Fusion</td>
<td>ADC</td>
<td>&lt;1%</td>
<td>Entrectinib</td>
</tr>
<tr>
<td>KRAS</td>
<td>mutation</td>
<td>ADC</td>
<td>15-25%</td>
<td>SML-8-73-1, (Selumetinib, trametinib)</td>
</tr>
<tr>
<td>FGFR1</td>
<td>amplification</td>
<td>SCC</td>
<td>19%</td>
<td>Lucitanib, Nintedanib, dovitinib, AZD4547</td>
</tr>
<tr>
<td>FGFR2-3</td>
<td>Mutation</td>
<td>SCC</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>FGFR1-3</td>
<td>Fusion</td>
<td>SCC</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>SCC</td>
<td>4%</td>
<td>Dasatinib</td>
</tr>
</tbody>
</table>
Summary

- **EGFR mutation**
  - EGFR mutation is well established biomarker for clinical use of first line EGFR TKI
  - Rebiopsy for T790M is mandatory for Tagrisso

- **ALK+**
  - Crizotinib: first choice for patients with ALK translocation
  - several other compounds already available for crizotinib-resistant NSCLC

- **Other uncommon oncogene**
  - Treatment is potentially available for uncommon mutations such as ROS1, BRAF, RET and MET

- **Clinical application of blood based genomics**
  - EGFR mutation from cfDNA is feasible with moderate sensitivity and high specificity
Acknowledgments

Jean-Charles SORIA
Benjamin BESSE
Thierry Le Chevalier

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