Chemotherapy and targeted therapy of non-small cell lung cancer

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University Hospital of Zürich
Chemotherapy can prolong survival in patients with advanced NSCLC – report of a Canadian multicenter randomized trial
Chemotherapy of NSCLC: a meta-analysis using updated data on individual patients from 52 randomized trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No of patients entered</th>
<th>No of events/No of patients entered</th>
<th>Variance</th>
<th>Observed - expected deaths</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Supportive care</td>
<td>Supportive care plus chemotherapy</td>
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<tr>
<td>Long term alkylating agents:</td>
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<td>Oxford</td>
<td>120/121</td>
<td>62/67</td>
<td>16.40</td>
<td>43.80</td>
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<td>Quebec</td>
<td>20/20</td>
<td>18/18</td>
<td>-4.38</td>
<td>7.99</td>
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<td>140/141</td>
<td>80/85</td>
<td>12.02</td>
<td>51.79</td>
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<td>Vinca alkaloids/etoposide:</td>
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<tr>
<td>Gwent 2</td>
<td>96/111</td>
<td>67/75</td>
<td>-5.15</td>
<td>38.00</td>
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<td>Subtotal</td>
<td>96/111</td>
<td>67/75</td>
<td>-5.15</td>
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<td>Cisplatin based:</td>
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<tr>
<td>RLW 8351</td>
<td>84/86</td>
<td>80/81</td>
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<td>NCIC CTG</td>
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<td>51/53</td>
<td>-11.28</td>
<td>28.24</td>
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<td>Southampton</td>
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<td>1.16</td>
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<td>30/31</td>
<td>-4.83</td>
<td>14.53</td>
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<td>Ancona 1</td>
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<td>50/50</td>
<td>-14.98</td>
<td>18.77</td>
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<td>CEP-85</td>
<td>23/25</td>
<td>21/24</td>
<td>-10.52</td>
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<td>352/362</td>
<td>-51.31</td>
<td>165.31</td>
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<td>645/668</td>
<td>499/522</td>
<td>-44.44</td>
<td>255.09</td>
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</table>
Systemic therapy of NSCLC: A plateau had been reached.
2nd line NSCLC phase III: Docetaxel vs BSC

MST 7.5 vs 4.7 months

OS 7.5 vs 6.4 ms

Shepherd, JCO 2000
Histological classification is necessary for decision making in advanced NSCLC

• A diagnosis of “non-small cell lung cancer” is no longer acceptable as sufficient basis for treatment decisions:
  • Cisplatin superior to carboplatin in adenocarcinoma
    Ardizzoni, JNCI 2007
  • Benefit of bevacizumab added to first line chemotherapy in non-squamous cell carcinoma
    Sandler, JCO 2006; Reck; JCO 2009; Zhou, JCO 2015
  • Differential effect of pemetrexed in non-squamous vs squamous cell carcinoma and pemetrexed maintenance
    Scagliotti, JCO 2008; Paz-Ares, JCO 2013
  • Histology will help guide decision about further molecular analysis
Pathological diagnosis

- Pathological diagnosis of all sample types should be made according to the 2015 WHO classification
- Immunohistochemistry (IHC) should be used to increase the specificity of diagnosis in the small sample setting and reduce the NSCLC-NOS (not otherwise specified) rate to fewer than 10% of cases diagnosed [IV, A]
- Minimal IHC should be used. Two markers only, p40 or p63 to predict squamous cell carcinoma and TTF1 to predict adenocarcinoma, are generally all that is required
- EGFR mutation status should be systematically analysed in advanced NSCC [I, A]
- Testing for ALK rearrangement should be systematically carried out in advanced NSCC [II, A]
Molecular testing in non-squamous cell NSCLC at University Hospital Zürich

Diagnoses of advanced disease

Failure of first line treatment

Progression under target therapy

If positive: FISH confirmation

If all negative or MET IHC positiv:
NGS (OFA panel):
BRAF Mutationen
HER2 Mutationen
HER2 Amplifikation
MET Exon 14
RET Translokationen

Re-biopsie und/oder liquid biopsy
NGS (OFA panel):
Resistenzmechanismen

stainings

EGFR-Mutation
KRAS-Mutation
Sanger Sequencing

(TTF1)
PD-L1
ALK
ROS1
cMET
What can we conclude for the first line therapy of advanced NSCLC without oncogenic driver mutation

- There is no single platinum-based doublet standard chemotherapy, however pemetrexed combinations are favoured in non-squamous cell NSCLC
- If platinum-based chemotherapy is indicated, a combination with bevacizumab is a treatment option in eligible patients with non-squamous NSCLC. In this case, carboplatin/paclitaxel is the preferred combination
- Pemetrexed maintenance therapy is an option for patients with non-squamous NSCLC without progression after first line therapy
- Immune checkpoint inhibition with pembrolizumab is becoming an option for patients with tumors with strong PD-L1 expression
- Current developments in first line immunotherapy are moving into chemotherapy71O or IO71O combinations
ESMO clinical practice guidelines in metastatic non-squamous cell carcinoma: 1st line

ESMO clinical practice guidelines in metastatic non-squamous cell carcinoma: 1

- <70 years and PS 0-1
  - 4-6 cycles:
    - Cisplatin – pemetrexed (II, A)
    - Cisplatin – gemcitabine (I, B)
    - Cisplatin – docetaxel (I, B)
    - Carboplatin – pachlita (I, B)
    - Carboplatin – nab-paclitaxel (I, B)
    +/- bevacizumab

- <70 years and PS 2 or >70 years and PS 0-2
  - 4-6 cycles:
    - Carboplatin-based doublets (II, B)
    - Single-agent chemotherapy
      - Gemcitabine (I, B)
      - Paclitaxel (I, B)
      - Paclitaxel (I, A)

- PS 0-1
  - Partial response or stable disease

- Maintenance treatment:
  - Pemetrexed (switch) (II, B)
  - Pemetrexed (continuation) (I, A)
  - Erlotinib (EGFR-activating mutation) (I, B)
  +/- bevacizumab (II given below)

- PS 3-4
  - BSC [II, B]

Bevacizumab added to chemotherapy: Initial Phase III trials

**E4599**

1. **Previously untreated, stage IIIb, IV or recurrent non-equamous NSCLC (n=878)**
2. **Primary endpoint: OS**
   - CP x 6 (n=444)
   - Bevacizumab (15mg/kg) every 3 weeks + CP x 6 (n=534)
   - Bev
   - CP

**AVAIL**

1. **Previously untreated, stage IIIb, IV or recurrent non-equamous NSCLC (n=1,343)**
2. **Primary endpoint: PFS**
   - Placebo (15mg/kg) + CG x 6 (n=351)
   - Bevacizumab (7.5mg/kg) + CG x 6 (n=351)
   - Placebo
   - Bev

**E4599 overall patient population**

- **HR**: 0.79 (95% CI: 0.67-0.92)
- **p value**: 0.003
- **Median OS**:
  - CP (n=444): 12.3 months
  - Bevacizumab 7.5mg/kg + CP (n=454): 10.3 months

**Graphs**

- **A**: Progression-Free Survival (probabilty)
- **B**: Progression-Free Survival (probability)

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Sandler, NEJM 2006; Reck, JCO 2009
BEYOND: A randomized, double-Blind, placebo-controlled, multicenter, phase III study of 1\textsuperscript{st} line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with NSCLC

Randomly assigned treatment
- Pi + CP
- B + CP

Median PFS 6.5 vs 9.2 months
HR, 0.40; 95\% CI, 0.29 to 0.54
P < .001

Randomly assigned treatment
- Pi + CP
- B + CP

Median OS 17.7 vs 24.3 months
HR, 0.68; 95\% CI, 0.50 to 0.93
P = .0154

No. at risk
Pi + CP 138
B + CP 138

Time of Study (month)

Overall Survival (proportion)
Cisplatin-pemetrexed vs cisplatin-gemcitabine in advanced NSCLC

Overall no difference in PFS or survival between study arms

Cis/pem better than in non-squamous cell carcinoma
(HR 0.81, p=0.005)

Cis/pem inferior than cis/gem in squamous cell carcinoma
(HR 1.23, p=0.05)
PARAMOUNT: Overall survival

Induction Therapy
4 cycles, q21d

Continuation Maintenance Therapy
q21d until PD

- Previously untreated
- PS 0/1
- Stage IIIB-IV NS-NSCLC

CR/PR/SD per RECIST

2:1

Pemetrexed + Cisplatin

Pemetrexed + BSC

Placebo + BSC

Stratified for:
- PS (0 vs 1)
- Disease stage (IIIB vs IV) prior to induction
- Response to induction (CR/PR vs SD)

A

Survival Probability (%)

Time From Random Assignment (months)

Pemetrexed: median = 13.3 mos (12.8 to 16.0 mos)
Placebo: median = 11.6 mos (10.6 to 12.5 mos)
Log-rank P = .0195
Unadjusted HR: 0.78 (0.64 to 0.96)

B

Survival Probability (%)

Time From Induction (months)

Pemetrexed: median = 16.9 mos (15.9 to 19.0 mos)
Placebo: median = 14.6 mos (12.9 to 15.5 mos)
Log-rank P = .0191
Unadjusted HR: 0.78 (0.64 to 0.96)

CR/PR
HR = 0.81

SD
HR = 0.76

No. at risk
Pemetrexed + BSC
Placebo + BSC

Paz-Ares, JCO 2013
First line systemic therapy in the elderly and frail

- In patients with PS 2, chemotherapy compared with BSC prolongs survival and improves QoL [I, B]
- Carboplatin-based combination chemotherapy should be considered in eligible PS 2 patients [II, A]
- Single-agent chemotherapy with gemcitabine, vinorelbine and docetaxel is an alternative treatment option [I, B]
- Poor PS (3–4) patients should be treated with BSC only [II, B]
ESMO clinical practice guidelines in metastatic squamous cell carcinoma: 1st line

Stage IV SCC

- Never or former light smoker (<15 packs/year)
- Molecular test (ALK/EGFR)
- Molecular test negative
- Molecular test positive
- Targeted therapy

- Age
- PS

- <70 years and PS 0-1
- 4-6 cycles:
  - Cisplatin – gemcitabine ([I, A])
  - Cisplatin – docetaxel ([I, A])
  - Cisplatin – vinorelbine ([I, A])
  - Carboplatin – paclitaxel ([I, A])
  - Carboplatin – nab-paclitaxel ([II, B])
  - Cisplatin – gemcitabine – nectarhumab (II EGFR: expression by IHC) ([I, B, MCBRS I])

- <70 years and PS 2 or >70 years and PS 0-2
- 4-6 cycles:
  - Carboplatin-based doublets ([II, B])
  - Single-agent chemotherapy (gemcitabine, vinorelbine or docetaxel) ([I, A])

- PS 3-4
- BSC ([II, B])

Gemcitabine and cisplatin with or without necitumumab in squamous cell lung cancer
Second and further line therapy for patients with NSCLC without oncogenic driver mutation – the shift to immunotherapy

- Docetaxel, or pemetrexed if not used in first line, used to be the standard of care
- The addition of nintedanib to docetaxel in non-squamous NSCLC and the addition of ramucirumab to docetaxel in all histologies of NSCLC is associated with small, but significant survival improvement over docetaxel alone
- Second line therapy with single agent immune checkpoint inhibitors (nivolumab, pembrolizumab or atezolizumab) provides a survival advantage over chemotherapy and is associated with fewer side effects and better quality of life
Second line chemotherapy and antiangiogenic agent in advanced NSCLC

LUME-Lung 1: Nintedanib in adenocarcinoma

Reck, Lancet Oncol 2014

OS 12.6 vs 10.3 months

REVEL: Ramucirumab in all histologies

Garon, Lancet Oncol 2014

OS 10.5 vs 9.1 months
NSCLC with oncogenic driver mutations: current status

EMA approval in NSCLC

Available otherwise

Key
1 - Phase I
2 - Phase II
3 - Phase III
4 - Approved

MEK1
- Trametinib
- Selumetinib
- Cobimetinib

PIK3CA
- LY3023414
- PQR 309

NTRK1
- Entrectinib
- LOXO-101
- Cabozantinib

BRAF
- Dasatinib
- Trametinib

ROS1
- Crizotinib
- Cabozantinib

MET
- Crizotinib
- Cabozantinib

HER2
- Trastuzumab emtansine
- Afatinib
- Dacomitinib

ALK
- Crizotinib
- Alectinib
- Ceritinib
- Lorlatinib
- Brigatinib

NTRK1
- Entrectinib
- LOXO-101
- Cabozantinib

EGFR Sensitizing
- Gefitinib
- Erlotinib
- Afatinib
- Osimertinib
- Runitritinib

Unknown Oncogenic Driver Detected
31%

Shaw, NEJM 2014
Planchard, Lancet Oncol 2016

Tsao, JTO 2016
Where do we stand with targeted therapy in first line for patients with NSCLC with activating EGFR mutations?

- There is no clear preference between the three EGFR TKIs approved by the EMA.
- The combination of erlotinib and bevacizumab has been approved by EMA based on a Japanese study and supported by the BELIEF trial.
- Osimertinib has been approved for patients with acquired T790M mutation based on superior PFS as compared to platin-based combination therapy. Osimertinib had excellent activity in patients with CNS metastases.
- The FLAURA randomized phase III trial has documented a superiority of osimertinib over first generation TKIs in terms of progression-free survival for patients with activating EGFR mutations.
First TKI versus chemotherapy in EGFR mutated NSCLC

Mok, NEJM 2009

Rosell, Lancet Oncol 2012
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment Arm</th>
<th>Control Arm</th>
<th>Stage</th>
<th>mPFS</th>
<th>Median OS</th>
<th>Indication</th>
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<tbody>
<tr>
<td>IPASS</td>
<td>1217</td>
<td>Gefitinib</td>
<td>Carboplatin/placinaxel</td>
<td>IIIB/IV</td>
<td>5.7 vs 5.8 mo (EGFR-mutated patients HR = 0.48; nonmutated patients HR = 2.84)</td>
<td>18.6 vs 17.3 mo (P = NS)</td>
<td>First-line</td>
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<tr>
<td>WJTOG3405</td>
<td>177</td>
<td>Gefitinib</td>
<td>Cisplatin, docetaxel</td>
<td>IIIB/IV</td>
<td>9.2 vs 6.3 mo (P &lt; .001)</td>
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<td>First-line</td>
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<tr>
<td>OPTIMAL</td>
<td>165</td>
<td>Erlotinib</td>
<td>Carboplatin/gemcitabine</td>
<td>IIIB/IV</td>
<td>13.6 vs 4.6 mo (HR = 0.16, P &lt; .0001)</td>
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<td>First-line</td>
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<tr>
<td>EURTAC</td>
<td>153</td>
<td>Erlotinib</td>
<td>Platinum-based chemotherapy</td>
<td>IIIB/IV</td>
<td>9.4 vs 5.2 mo (HR = 0.42, P &lt; .0001)</td>
<td>22.9 vs 18.8 mo (P = .42)</td>
<td>First-line</td>
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</table>
LUX-Lung 7: Comparison of afatinib versus gefitinib in first line treatment of EGFR-mutated NSCLC

- Stage IIIIB/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

Controlled ZNS metastases included

PFS

<table>
<thead>
<tr>
<th>Median, mo</th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
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<tbody>
<tr>
<td></td>
<td>11.0</td>
<td>10.9</td>
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</table>

HR (95% CI) 0.74 (0.57–0.95)
p-value 0.0178

**LUX-Lung 7: Comparison of afatinib versus gefitinib in first line treatment of EGFR-mutated NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
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<tbody>
<tr>
<td></td>
<td>Grades 1-2</td>
<td>Grade 3</td>
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<tr>
<td>Total</td>
<td>106 (66%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>124 (78%)</td>
<td>1 (1%)</td>
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<tr>
<td>Rash or acne*</td>
<td>127 (79%)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis†</td>
<td>96 (60%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>86 (54%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>52 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>37 (23%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue‡</td>
<td>24 (15%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 (16%)</td>
<td>1 (1%)</td>
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</table>
LUX-Lung 7: Comparison of afatinib versus gefitinib in first line treatment of EGFR-mutated NSCLC

Estimated PFS probability

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<th>Afatinib (n=160)</th>
<th>Gefitinib (n=159)</th>
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<tr>
<td>Median, months</td>
<td>27.9</td>
<td>24.5</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.86 (0.66–1.12)</td>
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<tr>
<td>p-value</td>
<td>0.2580</td>
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</table>

No. at risk:
- Afatinib: 160
- Gefitinib: 159

Time (months)

<table>
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<th>Del19</th>
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<td>Afatinib N=93</td>
<td>Gefitinib N=93</td>
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<tr>
<td>Median, mo</td>
<td>30.7</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.83 (0.58–1.17)</td>
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<tr>
<td>p-value</td>
<td>0.2641</td>
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No. at risk:
- Afatinib: 93
- Gefitinib: 93

Time (months)

<table>
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<tr>
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<th>L858R</th>
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<tr>
<td>Afatinib N=67</td>
<td>Gefitinib N=66</td>
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<tr>
<td>Median, mo</td>
<td>25.0</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.91 (0.62–1.36)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.6085</td>
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</table>

No. at risk:
- Afatinib: 67
- Gefitinib: 66

Pas-Ares, ESMO 2016
Afatinib in uncommon EGFR mutations: Specific mutations of relative frequency

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Objective response</th>
<th>Progression-free survival (months)</th>
<th>Overall survival (months)</th>
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</thead>
<tbody>
<tr>
<td>Gly719Xaa (n=18)</td>
<td>Gly719Xaa (n=8)</td>
<td>14 (77.8%, 52.4–93.6)</td>
<td>13.8 (6.8–NE)</td>
</tr>
<tr>
<td>Gly719Xaa+Thr790Met (n=1)</td>
<td>Gly719Xaa+Ser768Ile (n=5)</td>
<td>Gly719Xaa+Leu861Gln (n=3)</td>
<td>Gly719Xaa+Thr790Met+Leu858Arg (n=1)</td>
</tr>
<tr>
<td>Leu861Gln (n=16)</td>
<td>Leu861Gln (n=12)</td>
<td>9 (56.3%, 29.9–80.2)</td>
<td>8.2 (4.5–16.6)</td>
</tr>
<tr>
<td>Leu861Gln+Gly719Xaa (n=3)</td>
<td>Leu861Gln+Del19 (n=1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser768Ile (n=8)</td>
<td>Ser768Ile (n=1)</td>
<td>8 (100.0%, 63.1–100.0)</td>
<td>14.7 (2.6–NE)</td>
</tr>
<tr>
<td>Ser768Ile+Gly719Xaa (n=5)</td>
<td>Ser768Ile+Leu858Arg (n=2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%; 95% CI) or median (95% CI). NE=not estimable. Uncommon mutation categories overlap for those with compound mutations, so individual patients might appear in more than one category.

Yang, Lancet Oncology 2015
**Gefitinib plus chemotherapy versus chemotherapy in EGFR mutation-positive NSCLC resistant to first-line gefitinib (IMPRESS)**

**PFS**

- **HR 0.86 (95% CI 0.65-1.13); p=0.27**

**OS**

- **Probability of Overall Survival**
  - Gefitinib plus CT
  - Placebo plus CT

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**Patients**
- Age 18-80 years (≥ 30 years in Japan)
- WHO PS 0-1
- Histologically confirmed stage IIIb or stage IV NSCLC with EGFR mutation-positive advanced NSCLC
- Chemotherapy-naive
- Achieved CR, PR, or stable disease for ≥ 6 months or ≥ 16 months with time-to-progression
- Disease progression (RECIST™ ≤ weeks prior to study randomisation)

**Endpoints**
- **Primary**
  - Progression-free survival
- **Secondary**
  - Overall survival
  - Objective response
  - Disease control rate
  - Safety
  - Health-related quality of life
  - Biosimilarity

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**Soria, Lancet Oncol 2015; Mok, JCO 2017**
EGFR-mutated advanced NSCLC: Erlotinib with bevacizumab in first-line

- **JO25567**: Ph2, randomized, Japanese multicenter, open-label[a]

**BELIEF**: Ph2, multicenter, single-arm study, stratified by pretreatment T790M status[b]

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**PFS**

**Seto, Lancet Oncol 2014; Rosell, Lancet Respir Med. 2017**
Multiple reasons for acquired resistance to TKIs

**Pharmacological**

- Non-compliance/dose reduction or interruption
- Acquired reduction in drug concentration
- Reduced permeability of BBB: decreased CNS penetration

**Altered drug target**

- Resistance mutations in same drug target
- Gene copy number gain of drug target
- Coincident in same cell (second drivers)
- Emergence of distinct clone (separate driver)

T790M mutation causes drug resistance in over 50% of patients by increased the affinity for ATP as compared to TKIs

**Not shown:**
- Phenotypic change
- Manipulation of downstream signalling pathways

Camidge Nat Rev Clin Oncol 2014
EGFR TKIs

First generation EGFR TKIs
- gefitinib
- erlotinib

Second generation EGFR TKIs
- afatinib

Third generation EGFR TKIs
- AZD9291
- rociletinib

Inhibitory concentration of EGFR TKI

Higher
- del + T790M
- L858R + T790M
- del/L858R + T790M
- C797S

Lower
- exon19 deletion(del)
- L858R
- del + T790M
- L858R + T790M
AURA3: Osimertinib or platinum-pemetrexed in EGFR TKI pretreated EGFR T790M–positive NSCLC

Patients
Chemotherapy naive
Activating EGFR mutation
Centrally confirmed T790M
PD on first-/second-generation EGFR TKI

Osimertinib (80 mg daily) n=279

Platinum / pemetrexed n=140

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib 80 mg n=30</th>
<th>Chemotherapy n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS ORR (95% CI)</td>
<td>70% (51, 85)</td>
<td>31% (11, 59)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>5.13 (1.44, 20.64), P = .015</td>
<td></td>
</tr>
<tr>
<td>Median time to response, weeks</td>
<td>6.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Median Duration of Response, months (95% CI)</td>
<td>8.9 (4.3, NC)</td>
<td>5.7 (NC, NC)</td>
</tr>
<tr>
<td>DCR (95% CI)</td>
<td>93% (78, 99)</td>
<td>63% (35, 85)</td>
</tr>
</tbody>
</table>

Mok, NEJM 2017
AURA3: Osimertinib or platinum-pemetrexed in EGFR TKI pretreated EGFR T790M-positive NSCLC

A Patients in Intention-to-Treat Population

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)  
P<0.001

No. at Risk
Osimertinib 279 240 162 88 50 13 0
Platinum–pemetrexed 140 93 44 17 7 1 0

Median Progression-free Survival
mo (95% CI)
Osimertinib 279 10.1 (8.3–12.3)
Platinum–pemetrexed 140 4.4 (4.2–5.6)

Mok, NEJM 2017
Mechanisms of resistance to third generation EGFR TKIs

- MET amplification [osimertinib]
  - MET amplification [osimertinib]
  - HER2 amplification [osimertinib]
  - EGFR amplification [osimertinib]
  - Tertiary EGFR mutations L718Q, L844V, C797S [WZ4002, osimertinib]
  - C797S [osimertinib]
  - EGFR amplification [rociletinib]

- P13K E545K mutation [osimertinib]
  - RAS mutation [osimertinib]
  - NRAS E63K mutation [osimertinib]
  - Gain in copy number of WT NRAS /KRAS [osimertinib]
  - BRAF V600E mutation [osimertinib]

- Others:
  1) Small cell [rociletinib]
  2) Loss of T790M [osimertinib, rociletinib]

- EMT [rociletinib]

Cell proliferation + survival
Osimertinib as first-line treatment: Biomarker at progression

- 38/42 with plasma for NGS at RECIST-defined progression:
  - 19 detectable DNA
  - 9 identified with putative resistance mechanisms

<table>
<thead>
<tr>
<th>Baseline EGFR mutation</th>
<th>Post-dose plasma EGFR mutation (allelic fraction %)</th>
<th>Post-dose plasma resistance identified (allelic fraction %, copies)</th>
<th>Other post-dose plasma mutations identified (allelic fraction %)</th>
<th>Total time receiving osimertinib (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex19del*</td>
<td>None detected</td>
<td>JAK2 V617F (1.5%)</td>
<td>None detected</td>
<td>29.9+</td>
</tr>
<tr>
<td>Ex19del</td>
<td>Ex19del (5.2%)</td>
<td>EGFR C797S (3.0%)</td>
<td>P53 R273H (6.6%), CTNNB1 G34V (6.5%)</td>
<td>27.8+</td>
</tr>
<tr>
<td>L858R</td>
<td>L858R (16.7%)</td>
<td>PIK3CA E545K (1.6%)</td>
<td>P53 H179R (13.3%), PTEN Q171* (8.1%), NOTCH G2299G (4.6%)</td>
<td>26.3</td>
</tr>
<tr>
<td>Ex19del</td>
<td>Ex19del (34.6%)</td>
<td>MET CNV (3.0 copies)</td>
<td>RB1 R255* (64.1%), P53 pHis179fs (62.9%)</td>
<td>26.3</td>
</tr>
<tr>
<td>Ex19del</td>
<td>None detected</td>
<td>KRAS G12D (8.6%)</td>
<td>CTNNB1 S37F (3.6%)</td>
<td>24.9</td>
</tr>
<tr>
<td>L858R and T790M</td>
<td>L858R (4%) + T790M (5%)</td>
<td>EGFR C797S (1%)</td>
<td>NF2 T352M (1.5%)</td>
<td>14.5</td>
</tr>
<tr>
<td>Ex19del</td>
<td>Ex19del (7.5%)</td>
<td>KRAS CNV (3.7 copies), EGFR CNV (3.0 copies)</td>
<td>P53 H175M (15.9%), RB1 pLys427fs (9.9%)</td>
<td>14.3</td>
</tr>
<tr>
<td>G719S and S768I</td>
<td>G719S (6.9%) + S768I (5.7%)</td>
<td>MEK1 (MAP2K1) G128V (3.2%)</td>
<td>SMAD4 G358E (4.6%), PDGFR A S961C (1.1%)</td>
<td>5.6</td>
</tr>
<tr>
<td>L858R</td>
<td>None detected</td>
<td>HER2 ex20 ins (12.3%), HER2 E1247K (4.2%)</td>
<td>P53 R213* (6.3%), IDH2 R140Q (2.5%)</td>
<td>1.2</td>
</tr>
</tbody>
</table>

CNV, copy number variant; Ex19del, Exon 19 deletion; ND, none detected

*Mutation identified by local testing
+ indicates that the patient remained on osimertinib at the time of data cutoff
Osimertinib resistance mediated by loss of \textit{EGFR} T790M is associated with early resistance and competing resistance mechanisms.

37 | Oxnard, WCLC 2017

[Diagram showing T790M loss vs. T790M maintained resistance with various genotypes and outcomes.]
FLAURA: First or third generation TKI inhibitors as first line therapy for patients with EGFR mutated NSCLC

Endpoints
- Primary endpoint: PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- Secondary endpoints: objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Osimertinib (n=279)</th>
<th>SoC* (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male / female</td>
<td>36 / 64</td>
<td>38 / 62</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>64 (26–85)</td>
<td>64 (35–93)</td>
</tr>
<tr>
<td>Race: White / Asian / other*</td>
<td>36 / 62 / 1</td>
<td>36 / 62 / 1</td>
</tr>
<tr>
<td>Smoking status: never / ever</td>
<td>65 / 35</td>
<td>63 / 37</td>
</tr>
<tr>
<td>CNS metastases at study entry*</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>WHO performance status*: 0 / 1</td>
<td>40 / 60</td>
<td>42 / 58</td>
</tr>
<tr>
<td>Overall disease classification*: metastatic / advanced</td>
<td>95 / 5</td>
<td>95 / 5</td>
</tr>
<tr>
<td>Histology: adenocarcinoma / other</td>
<td>99 / 1</td>
<td>98 / 2</td>
</tr>
<tr>
<td>EGFR mutation at randomisation*: Exon 19 deletion / L858R</td>
<td>63 / 37</td>
<td>63 / 37</td>
</tr>
</tbody>
</table>

* Crossover was allowed for patients in the SoC arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity.
FLAURA: Primary endpoint progression-free survival

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)

Median PFS, months (95% CI)
- Osimertinib: 18.9 (15.2, 21.4)
- SoC: 10.2 (9.6, 11.1)

HR 0.46
(95% CI 0.37, 0.57)

p<0.0001
141 deaths in 556 patients at DCO: 25% maturity; osimertinib: 58 deaths (21%), SoC: 83 deaths (30%)

Median overall survival

HR 0.63
(95% CI 0.45, 0.88)
p=0.0068†

†A p-value of <0.0015 was required for statistical significance at current maturity
Table S4. Reason for CNS progression, by investigator assessment (full analysis set)

<table>
<thead>
<tr>
<th>Reason for progression</th>
<th>Known/treated CNS metastases at trial entry</th>
<th>No known/treated CNS metastases at trial entry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Osimertinib (n=53)</td>
<td>Osimertinib (n=226)</td>
</tr>
<tr>
<td></td>
<td>Standard EGFR-TKI (n=63)</td>
<td>Standard EGFR-TKI (n=214)</td>
</tr>
<tr>
<td></td>
<td>Number (percent)</td>
<td>Number (percent)</td>
</tr>
<tr>
<td>Total number of progression events</td>
<td>29 (55)</td>
<td>107 (47)</td>
</tr>
<tr>
<td></td>
<td>53 (84)</td>
<td>153 (71)</td>
</tr>
<tr>
<td>Number of patients with progression due to</td>
<td>4 (8)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>death*</td>
<td>4 (6)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Number of patients with CNS progression*</td>
<td>10 (19)</td>
<td>7 (3)</td>
</tr>
<tr>
<td></td>
<td>27 (43)</td>
<td>15 (7)</td>
</tr>
</tbody>
</table>

Soria, NEJM 2018
Where do we stand with targeted therapy in first line in patients with NSCLC with other oncogenic driver mutations

- Crizotinib is approved for the first line treatment of patients with ALK translocated and ROS1 translocated NSCLC
- Ceritinib, alectinib and brigatinib are approved for patients ALK translocated NSCLC progressing under crizotinib. Also there is limited access to lorlatinib in clinical studies or as compassionate use.
- The results of the J-ALEX and ALEX trial suggest alectinib to become the preferred first line therapy in ALK translocated NSCLC
- The combination of dabrafenib + trametinib has been approved by EMA for the treatment of BRAF V600 mutated NSCLC
- Other targets are under investigation
Crizotinib in first line: PRORILFE 1014

Salomon, NEJM 2014

Crizotinib (N = 172) vs. Chemotherapy (N = 171)

- Events, n (%):
  - Crizotinib: 100 (58)
  - Chemotherapy: 137 (80)
- Median, months:
  - Crizotinib: 10.9
  - Chemotherapy: 7.0
- HR (95% CI):
  - Crizotinib: 0.45 (0.35-0.60)
  - P < .0001

ALK+ disease according to FISH:
- Locally advanced or metastatic NSCLC
- No prior platinum-based chemotherapy regimen
- ECOG PS 0-2

Crizotinib 250mg BID

Pemetrexed/cisplatin or pemetrexed/carboplatin i.v.q3w

(n=343)
First-line ceritinib versus platinum-based chemotherapy in advanced \textit{ALK}-rearranged NSCLC (ASCEND-4):

\textbf{ASCEND-4:} randomised, multicentre, phase III, open-label study of 1L ceritinib vs chemo in ALK+ NSCLC²

- Newly diagnosed stage IIIB/IV or relapsed locally advanced or metastatic non-squamous NSCLC
- ALK+ disease according to IHC
- No previous treatment
- ≥1 measurable lesion as defined by RECIST 1.1

\textbf{Key Points:}
- Ceritinib 750mg/day
- Pemetrexed/cisplatin or pemetrexed/carboplatin i.v. q3w
- Maintenance therapy

\textbf{Median duration of follow-up:} 19.7 months
Alectinib vs crizotinib in treatment-naïve advanced ALK+ NSCLC: primary results of the global phase III ALEX study

ALEX: randomised, multicentre, phase III, open-label study of alectinib versus crizotinib in treatment-naïve ALK+ NSCLC

Stage IIIb/IV NSCLC
ALK+ disease
Treatment naïve
ECOG PD 0-2

(n=303)

Shaw, ASCO 2017; Peters, NEJM 2017
Alectinib vs crizotinib in treatment-naïve advanced ALK+ NSCLC: primary results of the global phase III ALEX study: CNS activity

- Competing risk of CNS progression, non-CNS progression, and death based on first event was analyzed

<table>
<thead>
<tr>
<th>CNS Progression, no Previous Systemic PD</th>
<th>Alectinib (n = 152)</th>
<th>Crizotinib (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with event, n (%)</td>
<td>18 (12)</td>
<td>68 (45)</td>
</tr>
<tr>
<td>Cause-specific HR (95% CI)</td>
<td>0.16 (0.10–0.28)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Cumulative Incidence of CNS Progression

- Alectinib, 12-mo cumulative incidence rate: 9.4% (95% CI; 5.4–14.7)
- Crizotinib, 12-mo cumulative incidence rate: 41.4% (95% CI; 33.2–49.4)

Shaw, ASCO 2017; Peters, NEJM 2017
# ALK inhibitors after crizotinib failure

<table>
<thead>
<tr>
<th></th>
<th>Alectinib NP28673 (IRC)</th>
<th>Alectinib NB28761 (IRC)</th>
<th>Brigatinib* (180mg qd) (IRC)</th>
<th>Ceritinib ASCEND-1 (prior ALKi)</th>
<th>Ceritinib ASCEND-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>n=122</td>
<td>n=69</td>
<td>n=110</td>
<td>N=163</td>
<td>N=140</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>50</td>
<td>51</td>
<td>55</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td><strong>DCR, %</strong></td>
<td>79</td>
<td>80</td>
<td>86</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td><strong>mDoR, mos</strong></td>
<td>11.2</td>
<td>13.5</td>
<td>13.8</td>
<td>8.3</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>mPFS, mos</strong></td>
<td>8.9</td>
<td>8.1</td>
<td>15.6</td>
<td>6.9</td>
<td>5.7</td>
</tr>
<tr>
<td><strong>Toxicity issues</strong></td>
<td>Very few</td>
<td>Dyspnea (low grade with lead-in 90mg 7days)</td>
<td>GI (impacting QoL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Perol, ELCC 2016

Pérol, ESMO 2016; Ahn, WCLC1017
## ALK inhibitors after crizotinib failure: CNS activity

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (n=60)</th>
<th>Brigatinib (180mg qd) (n=18)</th>
<th>Ceritinib ASCEND-2 (n=20)</th>
<th>Ceritinib ASCEND-1 (n=75)</th>
<th>Ceritinib ASCEND-1 (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS ORR, %</strong></td>
<td>64</td>
<td>67</td>
<td>45</td>
<td>19</td>
<td>36</td>
</tr>
<tr>
<td><strong>CR, %</strong></td>
<td>22</td>
<td>0</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td><strong>CNS DCR, %</strong></td>
<td>80</td>
<td>83</td>
<td>80</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td><strong>CNS mDoR, months</strong></td>
<td>10.8</td>
<td>(7.4-NR)</td>
<td>-</td>
<td>6.9</td>
<td>11.1</td>
</tr>
</tbody>
</table>

- **CNS ORR, %** represents the percentage of patients achieving a Complete Response (CR) or a Partial Response (PR) in the central nervous system (CNS) compartment.
- **CR, %** represents the percentage of patients achieving a Complete Response (CR) in the CNS compartment.
- **CNS DCR, %** represents the percentage of patients achieving a Complete Response (CR) or a Partial Response (PR) in the CNS compartment.
- **CNS mDoR** represents the median duration of response in the CNS compartment.

*Kim, ASCO 2016 and Pérol ELCC 2016*