Non-Small Cell Lung Cancer
State of the Art

Rolf Stahel
University Hospital of Zürich
ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of non-small-cell lung cancer (NSCLC)

Treatment of stage III disease

- Preoperative chemotherapy is standard for resectable stage IIIA. In randomised trials the survival of stage IIIA patients was significantly better with induction chemotherapy plus surgical resection than with resection alone [I, A].
- Platinum-based chemotherapy and thoracic radiotherapy is the standard treatment for locally advanced, unresectable Stage IIIB NSCLC or medically inoperable stage IIIA NSCLC [I, A].
Individual patient data meta-analysis: sequential vs concurrent chemo-radiotherapy

A

HR = 0.84 (95%CI, 0.74 to 0.95)

\[ P = .004 \]

Deaths/Person-Years by Period

<table>
<thead>
<tr>
<th></th>
<th>0y–1y</th>
<th>1y–2y</th>
<th>2y–3y</th>
<th>3y–4y</th>
<th>&gt; 4y</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + conc CT</td>
<td>240/498</td>
<td>147/276</td>
<td>67/171</td>
<td>30/116</td>
<td>37/186</td>
</tr>
<tr>
<td>RT + seq CT</td>
<td>253/491</td>
<td>171/242</td>
<td>70/129</td>
<td>30/83</td>
<td>23/126</td>
</tr>
</tbody>
</table>

Aupérin, JCO 2010
Chemoradiotherapy: No evidence for advantage with induction or consolidation chemotherapy in stage III

Carboplatin-paclitaxel induction followed by chemoradiotherapy

Concurrent PE chemoradiotherapy followed by docetaxel consolidation

Vokes, JCO 2007

Hanna, JCO 2008
Special article

ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of non-small-cell lung cancer (NSCLC)

Treatment of stage IV disease

- Platinum-based combination chemotherapy prolongs survival, improves quality of life, and controls symptoms in stage IV disease [1, A].

Second-line chemotherapy

- Second-line chemotherapy improves disease-related symptoms and may improve survival in selected patients [III, C].
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
ESMO clinical practice guidelines in metastatic squamous cell carcinoma: 1\textsuperscript{st} line

Stage IV SCC

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

- Age
  - PS

- <70 years and PS 0-1
- <70 years and PS 2
- >70 years and PS 0-2

- 4-6 cycles:
  - Cetuximab – gemcitabine [I, A]
  - Cetuximab – docetaxel [I, A]
  - Cetuximab – vinorelbine [I, A]
  - Carboplatin – paclitaxel [I, A]
  - Carboplatin – nab-paclitaxel [II, B]
  - Cetuximab – gemcitabine – nustinumab (if EGFR expression by IHC) [II, B; MSOS I]

- 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

Thatcher, Lancet Oncol 2015
Magnitude of Clinical Benefit Scale: Form 2a (primary endpoint OS, OS < 1 year, non-curative)

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>Mark with X if relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR ≤ 0.65 AND Gain ≥ 3 months</td>
<td></td>
</tr>
<tr>
<td>Increase in 2 year survival alone ≥ 10%</td>
<td></td>
</tr>
</tbody>
</table>

| Grade 3 |
|---------|--------------------------|
| HR ≤ 0.65 AND Gain 2.5-2.9 months |
| Increase in 2 year survival alone 5 - <10% |

| Grade 2 |
|---------|--------------------------|
| HR > 0.65-0.70 AND Gain 1.5-2.4 months |
| Increase in 2 year survival alone 3 - <5% |

| Grade 1 |
|---------|--------------------------|
| HR > 0.70 OR Gain <1.5 months |
| Increase in 2 year survival alone <3% |

Curative

A

B

C

Non-curative

5

4

3

2

1

Quality of Life assessment / grade 3-4 toxicities assessment*

- Severe and/or chronic impact on daily well-being
- Her chronic nausea, diarrhoea, fatigue, etc.

≥ 3-4 toxicities impacting daily well-being are shown

of clinical benefit grade

| 2 | 1 |

Cherny et al, Ann Oncol 2015
### Magnitude of Clinical Benefit Scale: Second line squamous cell carcinoma

<table>
<thead>
<tr>
<th>Necitumumab, a second-generation, recombinant, human IgG1 EGFR antibody in combination with gemcitabine and cisplatin</th>
<th>Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous NSCLC (SQUIRE): an open-label, randomised, controlled phase 3 trial.</th>
<th>Gemcitabine and cisplatin as first-line therapy in patients with stage IV SCC. Control OS 9.6 months</th>
<th>OS gain: 1.6 months</th>
<th>OS: HR for death 0.84 (0.74–0.96)</th>
<th>Deteriorated toxicity profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced</td>
<td>[52] Phase III NCT00981058</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ESMO clinical practice guidelines in metastatic squamous cell carcinoma: 2\textsuperscript{nd} line

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

ESMO clinical practice guidelines in metastatic non-squamous cell carcinoma: 1\textsuperscript{st} line

<70 years and PS 0-1

4-6 cycles:
- Cisplatin – panitumumab [I, A]
- Cisplatin – gemcitabine [I, B]
- Cisplatin – docetaxel [I, B]
- Carboplatin – paclitaxel [I, B]
- Carboplatin – nab-paclitaxel [I, B]
+/- bevacizumab

<70 years and PS 2 or >70 years and PS 0-2

4-6 cycles:
- Carboplatin-cisplatin doublets [II, B]
- Single-agent chemotherapy (gemcitabine, vinorelbine or docetaxel) [I, A]

PS 0-1
Partial response or stable disease

Maintenance treatment:
- Panitumumab (switch) [I, B]
- Panitumumab (continuation) [I, A]
- Erlichinib (EGFR-activating mutation) [I, B]
+/- bevacizumab (II given below)

PS 3-4

BSC [II, B]
Bevacizumab in adenocarcinoma

OS for E4599 all patients and adenocarcinoma only

BEYOND: Randomized phase III study from China

- Bevacizumab-based therapy (n=602)
  - extends OS to 14.2 months
  - 31% reduction in the risk of death (HR=0.69)

Sandler, JTO 2008

Zhou JCO 2015
PARAMOUNT: Overall survival

Induction Therapy
4 cycles, q21d

Continuation Maintenance Therapy
q21d until PD

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

Pemetrexed + Cisplatin

CR/PR/SD per RECIST

R 2:1

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

Time From Random Assignment (months)

Survival Probability (%)

Pemetrexed: median = 13.9 mos (12.8 to 16.0 mos)
Placebo: median = 11.0 mos (10.0 to 12.5 mos)
Log-rank P = .0195
Unadjusted HR: 0.76 (0.64 to 0.96)

B

Time From Induction (months)

Survival Probability (%)

Pemetrexed: median = 16.9 mos (15.8 to 19.0 mos)
Placebo: median = 14.0 mos (12.9 to 15.5 mos)
Log-rank P = .0191
Unadjusted HR: 0.78 (0.64 to 0.96)
ESMO clinical practice guidelines in metastatic non-squamous cell carcinoma: 2nd line

- Disease progression
  - PS 0-2
    - Pemetrexed (I, B)
    - Docetaxel (I, B)
    - Nivolumab (I, B, MGBS 5)
    - Pembrolizumab if PD-L1 >1%
  - PS 3-4
    - BSC

2nd line NSCLC phase III: Docetaxel vs BSC

MST 7.5 vs 4.7 months

OS 7.5 vs 6.4 months

Shepherd, JCO 2000
Docetaxel plus nintedanib (LUME-Lung 1) or docetaxel plus ramucirumab (REVEL) versus docetaxel plus placebo for 2\textsuperscript{nd} line treatment of stage IV NSCLC

LUME-Lung 1: Adenocarcinoma
OS 12.6 vs 10.3 months

REVEL: all histologies
OS 10.5 vs 9.1 months

Reck, Lancet Oncol 2014
Garon, Lancet Oncol 2014
<table>
<thead>
<tr>
<th>Magnitude of Clinical Benefit Scale: Second line non-squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab</strong>, a fully human IgG4 PD-1 immune-checkpoint–inhibitor antibody</td>
</tr>
<tr>
<td>Advanced Nivolumab versus docetaxel in advanced non-squamous NSCLC [104]</td>
</tr>
<tr>
<td>Phase III  NCT01673867</td>
</tr>
<tr>
<td>Docetaxel in patients with NSCC that had progressed during or after platinum-based doublet chemotherapy. Control OS 9.4 months</td>
</tr>
<tr>
<td>OS gain: 2.8 months. 2-year survival gain 16%</td>
</tr>
<tr>
<td>Improved toxicity profile</td>
</tr>
<tr>
<td><strong>Ramucirumab</strong>, a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR2, in combination with docetaxel</td>
</tr>
<tr>
<td>Advanced Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV NSCLC after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial [94]</td>
</tr>
<tr>
<td>Phase III  NCT01168973</td>
</tr>
<tr>
<td>Placebo plus docetaxel in patients with SCC or NSCC who had progressed during or after a first-line platinum-based chemotherapy regimen. Control OS 9.1 months</td>
</tr>
<tr>
<td>OS gain: 1.4 months</td>
</tr>
<tr>
<td>OS: HR for death 0.86</td>
</tr>
<tr>
<td>Deteriorated toxicity profile</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong>, an anti-PD-1 monoclonal antibody</td>
</tr>
<tr>
<td>Advanced Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small cell lung cancer (KEYNOTE-010): a randomised controlled trial [96]</td>
</tr>
<tr>
<td>Phase III  NCT01905657</td>
</tr>
<tr>
<td>Docetaxel in patients with previously treated, PD-L1-positive advanced NSCLC. Control OS 8.5 months</td>
</tr>
<tr>
<td>In PD-L1 &gt;1%; OS gain: 1.9 months</td>
</tr>
<tr>
<td>In PD-L1 &gt;50%; OS gain: 6.7 months</td>
</tr>
<tr>
<td>In PD-L1 &gt;1%; OS: HR for death 0.71, (0.58–0.88)</td>
</tr>
<tr>
<td>Improved toxicity profile</td>
</tr>
<tr>
<td>In PD-L1 &gt;50%; OS: HR for death 0.54, (0.38–0.77)</td>
</tr>
<tr>
<td><strong>In PD-L1</strong></td>
</tr>
<tr>
<td>&gt;1%; 3 (Form 2a)</td>
</tr>
<tr>
<td>&gt;50%; 5 (Form 2a)</td>
</tr>
<tr>
<td>Diagnostic Status</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Ab Clone</td>
</tr>
<tr>
<td>Diagnostic Partner</td>
</tr>
<tr>
<td>Scoring Method†</td>
</tr>
<tr>
<td>Approved IVD</td>
</tr>
</tbody>
</table>
| PD-L1 Thresholds | ≥1% (pos), ≥5% (strong), or ≥10% Validated | ≥1% (pos) ≥50% (strong) Validated | TC / IC 3(+) | TC / IC 1(+) | TC PD-L1(+) ≥ 25%
| PD-L1 Thresholds | TBC, TC between all >1% and 25% with moderate or high intensity | | | | |
Analytical evaluation results: Mean TPS per case based on 3 readers: Tumor cells

- Analytical comparison of TPS by case for each assay
- Data points represent the mean score from 3 pathologists for each assay on each case
- No clinical diagnostic cutoff applied
- Conclusion: 3 of 4 assays are analytically similar for tumor cell staining

Hirsch, AACR 2016
Example of PD-L1 tumor expression

Not only technical validation, also clinical validation required
Not all animals are created equal

Hirsch, AACR 2016
Checkmate 017 and 057: 2-years update of OAS (no biomarker selection),

* No biomarker selection
Checkmate 057: OS by PD-L1 Expression

### OS by tumour PD-L1 expression

<table>
<thead>
<tr>
<th>Number of events (number of patients)</th>
<th>Unstratified Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt;1%</strong></td>
<td>0.90 (0.66, 1.24)</td>
</tr>
<tr>
<td><strong>≥1%</strong></td>
<td>0.59 (0.43, 0.82)</td>
</tr>
<tr>
<td><strong>≥1% to &lt;10%</strong></td>
<td>1.33 (0.79, 2.24)</td>
</tr>
<tr>
<td><strong>≥10% to &lt;50%</strong></td>
<td>0.61 (0.30, 1.23)</td>
</tr>
<tr>
<td><strong>≥50%</strong></td>
<td>0.32 (0.20, 0.53)</td>
</tr>
</tbody>
</table>

*a* Post-hoc analysis; results should be interpreted with caution as the subgroup samples sizes are small and, at the time of the analysis, the PD-L1 IHC 28-8 pharmDx assay was not analytically validated at the 10% or 50% expression levels.
KEYNOTE 10: Pembrolizumab versus doxetaxel in 2nd line NSCLC (≥1% of tumor cells PD-L1 positive)

OS, PD-L1 TPS ≥1% (Total Population)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 1 y</th>
<th>HR$^*$ (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>10.4 (9.4-11.9)</td>
<td>43.2%</td>
<td>0.71 (0.58-0.88)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>12.7 (10.0-17.3)</td>
<td>52.3%</td>
<td>0.61 (0.49-0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.5 (7.5-9.8)</td>
<td>34.6%</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

2 vs 10 mg/kg:  
HR 1.17, 95% CI 0.94-1.45

OS, PD-L1 TPS ≥50% Stratum

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>HR$^*$ (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>14.9 (10.4-NR)</td>
<td>0.54 (0.38-0.77)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>17.3 (11.8-NR)</td>
<td>0.50 (0.36-0.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.2 (6.4-10.7)</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

2 vs 10 mg/kg:  
HR 1.12, 95% CI 0.77-1.62

Herbst, ESMO Asia 2015, Lancet 2016
Relationship between level of PD-L1 expression and outcomes in the KEYNOTE-010 trial

P values are nominal only given the post-hoc nature of the analyses.
Horizontal dotted lines represent the ORR for pembrolizumab and docetaxel in the TPS ≥1% population.
Less toxicity with immune checkpoint inhibitors in second line comparative studies

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Check-mate 17</td>
</tr>
<tr>
<td>All</td>
<td>59 87 69 88 63 66 35</td>
</tr>
<tr>
<td>3-5</td>
<td>8 60 10 54</td>
</tr>
</tbody>
</table>
Case study, R.M. 1952

- 06/15 Diagnosis: Pleomorphic carcinoma RUL, clinical state stage T₃N₁M₁ (bone)
- 07/15 – 08/15 3 cycles of cisplatin and gemcitabine
- 28.08.2015 Re-Staging: progression in bone
Case study, R.M. 1952

- 29.09.2015  Right upper lobe resection ypT3 ypN1 (1/8)
- 06.11.2015  Re-Staging: progression bone, LN

Nov 2015  RT Sacrum, paravertebral, Os
Case study, R.M. 1952

Emergency hospitalisation 05.01.2016

- PiO₂ 67%; no fever, ECOG 3-4
- CRP 115, LDH 680; Leucocytes 11 G/l

- Methylprednisolon 250mg iv (1d)
- Prednison 200mg (2d), 100mg (2d), 50mg (3d), 25mg (3d), 20mg (3d), 10mg (2d), 5mg (2d)
- Tazobac + Bactrim
Case study, R.M. 1952

11/2015

Treatment effect on overall survival in Checkmate 57 and KEYNOTE 10

<table>
<thead>
<tr>
<th>EGFR Mutation Status</th>
<th>N</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>82</td>
<td>1.18 (0.69, 2.00)</td>
</tr>
<tr>
<td>Not Detected</td>
<td>340</td>
<td>0.66 (0.51, 0.86)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>160</td>
<td>0.74 (0.51, 1.06)</td>
</tr>
<tr>
<td>ALK Translocation Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Detected</td>
<td>243</td>
<td>0.71 (0.52, 0.96)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>318</td>
<td>0.80 (0.62, 1.04)</td>
</tr>
<tr>
<td>KRAS Mutation Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>62</td>
<td>0.52 (0.29, 0.95)</td>
</tr>
<tr>
<td>Not Detected</td>
<td>123</td>
<td>0.98 (0.66, 1.48)</td>
</tr>
<tr>
<td>Not Reported</td>
<td>397</td>
<td>0.74 (0.58, 0.94)</td>
</tr>
</tbody>
</table>

Borghaei. NEJM 2015; Herbst Lancet 2015
First line immunotherapy: Duration of therapy after response?

A case of a 70-year old man with stage IV adenocarcinoma of the lung treated with two doses of atezolizumab.
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS ≥50%

**KEYNOTE-024 Study Design** (NCT02142738)

- **Key Eligibility Criteria**
  - Untreated stage IV NSCLC
  - PD-L1 TPS ≥50%
  - ECOG PS 0-1
  - No activating EGFR mutation or ALK translocation
  - No untreated brain metastases
  - No active autoimmune disease requiring systemic therapy

- **Randomization (1:1)**
  - N = 305

- **Treatment Arm A**
  - Pembrolizumab 200 mg IV Q3W (2 years)

- **Treatment Arm B**
  - Platinum-Douplet Chemotherapy (4-6 cycles)

- **PD-L1 Screening**
  - 1934 patients entered screening
  - 1729 submitted samples for PD-L1 assessment
  - 1653 samples evaluable for PD-L1
  - 500 TPS ≥50% (30%)
  - 1153 TPS <50%

**Key End Points**
- Primary: PFS (RECIST v1.1 per blinded, independent central review)
- Secondary: OS, ORR, safety
- Exploratory: DOR

Reck, ESMO 2016
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS ≥50%

**Progression-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>73</td>
<td>10.3</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td>(0.37-0.68)</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>NR</td>
<td>0.60</td>
<td>0.005</td>
</tr>
<tr>
<td>Chemo</td>
<td>64</td>
<td>NR</td>
<td>(0.41-0.89)</td>
<td></td>
</tr>
</tbody>
</table>

Reck, ESMO 2016
KEYNOTE-024: Treatment related side effects with incidence >10%

Data cut-off: May 9, 2016.
KEYNOTE-024: Immune-mediated adverse events

Overall incidence
- 29.2% any grade
- 9.7% grade 3-4
- No grade 5 events
Targeted therapy in non-squamous NSCLC lung cancer: First line TKIs: Superior progression-free survival as compared to chemotherapy

- Crizotinib
- Gefitinib
- Erlotinib
- Afatinib

- NTRK fusion
- HRAS (0.4%)
- NRAS (0.4%)
- RET fusion (0.9%)
- MAP2K1 (0.9%)
- ALK fusion (1.3%)
- ROS1 fusion (1.7%)
- ERBB2 (1.7%)
- MET ex14 (4.3%)

- None (24.4%)
- KRAS (20.0%)
- EGFR (11.3%)
- BRAF (7.0%)
- NF1 (8.3%)
First TKI versus chemotherapy in oncogenic driver NSCLC

Aktivating EGFR mutation

ALK rearrangement

Rosell, Lancet Oncol 2012

Mok, NEJM 2014
Targeted therapy in non-squamous NSCLC lung cancer: Second line TKIs: Superior progression-free survival as compared with chemotherapy

NTRK fusion
- HRAS (0.4%)
- NRAS (0.4%)
- RET fusion (0.9%)
- MAP2K1 (0.9%)
- ALK fusion (1.3%)
- ROS1 fusion (1.7%)
- ERBB2 (1.7%)
- MET ex14 (4.3%)

None (24.4%)
EGFR (11.3%)
KRAS (22.3%)
BRAF (7.0%)

RIT1 (2.2%)
ERBB2 amp (0.9%)
MET amp (2.2%)
NF1 (8.3%)

Crizotinib
Ceritinib / Alectinib
Gefitinib
Erlotinib
Afatinib
T790M: Osimertinib
Major mechanisms of resistance to EGFR TKIs

- EMT (~1–2%)
- HER2 amplification (~8–13%)
- BRAF (~1%)
- MET amplification (~5%)
- PIK3CA (~1–2%)
- SCLC alone
- SCLC with PIK3CA

Other EGFR point mutations 1–2%

T790M with EGFR amplification ~10%

No identification AR mechanism ~15–20%

- EGFR target alteration ~60%
- Bypass tracks ~20%

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

Yu, Clin Cancer Res 2013
Osimertinib or platinum-pemetrexed in EGFR T790M–positive NSCLC

Mok, NEJM 2016
Crizotinib-resistant ALK-positive NSCLC

Alectinib phase 2 trial

- RR 48%
- Median PFS 8.1 months

Ceritinib vs chemotherapy (ASCEND-5)

- RR 45% vs 8%

Shaw, Lancet Oncol 2016
Scagliotti, ESMO 2016
Targeted therapy in non-squamous NSCLC lung cancer: TKIs in later line beyond mutated EGFR, ALK or ROS rearrangement

- Trastuzumab
- Crizotinib
- Gefitinib
- Erlotinib
- Afatinib
- Osimertinib
- Dabrafenib/Trametinib
- Vermurafenib
- Entrectinib
- Vandetanib/Levatinib/Alectinib
- Crizotinib
- Ceritinib/Alectinib
- Alectinib
- Crizotinib
- Crizotinib