Lung Cancer
Diagnosis and therapy of advanced disease

Rolf Stahel
Comprehensive Cancer Center Zürich
Consultant or Advisory Role in the last two years
I have received honoraria as a consultant at advisory boards from Abbvie, AstraZeneca, MSD, Pfizer, Regeneron, Roche, Seattle Genetics and Takeda.

Speaker Honoraria in the last two years
I have received honoraria as a speaker from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD and Roche.

DMC in the last two years
Genentech/Roche and Takeda

Financial Support of ETOP trials (president and scientific chair)
AstraZeneca, BMS, Boehringer Ingelheim, Genentech, MSD, Roche, and Pfizer.
Patient case: 50 year-old women

- October 2018: Nurse in obstetrics returning from a 3 months bicycle trip with partner presents with headache, shortness of breath and cough, as well as pain in left hip.
- November 1: Chest CT suspicion of lung cancer
- November 2: Bronchoscopy with biopsy: Adenocarcinoma, TTF-1 positive
- November 8: PET/CT and brain MRI: Metastases in lymph nodes, bone and brain (6 lesions)
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- November 2: Bronchoscopy with biopsy: Adenocarcinoma, TTF-1 positive
- November 8: PET/CT and brain MRI: Metastases in lymph nodes, bone and brain (6 lesions)
Chemotherapy in addition to supportive care improves survival in advanced NSCLC: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials

Results showed a significant benefit of chemotherapy (HR, 0.77; 95% CI, 0.71 to 0.83; P <= .0001), equivalent to a relative increase in survival of 23% or an absolute improvement in survival of 9% at 12 months, increasing survival from 20% to 29%.

NSCLC Meta-analyses Collaborative Group, JCO 2008
Molecular profiling of metastatic NSCLC: At diagnosis

November 15: Molecular testing demonstrates EGFR exon 19 deletion

FO: Foundation One
OFA: Oncomine Focus Assay
OFA CF: cell free DNA

If material insufficient

OFA (CF assay) Or Re-biopsy
NSCLC with oncogenic driver mutations: current status

Activating mutations
- EGFR
  - Crizotinib
  - Alectinib
  - Ceritinib
  - Lorlatinib
  - Osimertinib
- ALK
- MET
  - Crizotinib
  - Cabozantinib
- HER2
  - Trastuzumab emtansine
  - Afatinib
- BRAF
  - vemurafenib
  - Dabrafenib
- RET
  - Cabozantinib
  - Altabitib
  - Loxo-292
  - BLUE-6678

Gene translocations
- KRAS
- EGFR
- ALK
- MET
- HER2
- ROS1
- BRAF
- RET
- NTRK1
- PIK3CA
- MEK1

Amplifications and/or mutations
- EGFR Sensitizing
- ALK
- HER2
- ROS1
- BRAF
- RET
- NTRK1
- PIK3CA
- MEK1

Unknown Oncogenic Driver Detected
31%

> 1 Mutation
3%

HER2
2%

ROS1
2%

BRAF
2%

RET
2%

NTRK1
1%

PIK3CA
1%

MEK1 <1%

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

MEK1
- Trametinib
- Selumetinib
- Cobimetinib

PIK3CA
- LY3023414
- PQR 309
IPASS study on first line EGFR TKI versus chemotherapy

Overall response rate (%)

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR M+ odds ratio (95% CI)</td>
<td>2.75 (1.65, 4.60), p=0.0001</td>
<td>0.04 (0.01, 0.27), p=0.0013</td>
</tr>
</tbody>
</table>

- Mutation positive patients
  - Gefitinib: 71.2% (n=132)
  - Carboplatin / paclitaxel: 47.3% (n=129)

- Mutation negative patients
  - Gefitinib: 1.1% (n=91)
  - Carboplatin / paclitaxel: 23.5% (n=85)

Mok, ESMO 2008
Mode of Actions of EGFR TKIs

**Erlotinib**
- **Gefitinib**
  - 1st-generation TKI
  - EGFR inhibition
  - Activity range: Reversible binding to wild-type and mutant EGFR; Inactive on T790M mutant

**Afatinib**
- **Dacomitinib**
  - 2nd-generation TKI
  - ErbB Family blockade
  - Activity range: Irreversible covalent binding to EGFR, ErbB2 and ErbB4 to inhibit all ErbB Family signalling; Broader activity to overcome EGFR TKI-resistant mutations

**Osimertinib**
- 3rd-generation TKI
- EGFR mutant-specific inhibitor
  - Activity: Specificity for EGFR T790M mutant; EGFR wild-type sparing; Irreversible covalent binding to mutant EGFR

Liao, Curr Opin Oncol 2015
Randomized controlled trials of 1st-line EGFR TKIs in EGFR-mutated NSCLC: Better RR, better PFS, similar OS

<table>
<thead>
<tr>
<th>Study</th>
<th>TKI</th>
<th>RR (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS</td>
<td>gefitinib</td>
<td>71 vs 47</td>
<td>10 vs 6</td>
<td>22 vs 22</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>gefitinib</td>
<td>62 vs 32</td>
<td>8 vs 5</td>
<td>36 vs 39</td>
</tr>
<tr>
<td>NEJGSG002</td>
<td>gefitinib</td>
<td>74 vs 31</td>
<td>11 vs 5</td>
<td>31 vs 24</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>erlotinib</td>
<td>83 vs 36</td>
<td>13 vs 5</td>
<td>22.8 vs 27.2</td>
</tr>
<tr>
<td>EURTAC</td>
<td>erlotinib</td>
<td>58 vs 15</td>
<td>9.7 vs 5.2</td>
<td>19 vs 19</td>
</tr>
<tr>
<td>LUX-Lung 3</td>
<td>afatinib</td>
<td>61 vs 22</td>
<td>14 vs 7</td>
<td>31 vs 28</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>afatinib</td>
<td>67 vs 23</td>
<td>11 vs 6</td>
<td>24 vs 24</td>
</tr>
</tbody>
</table>
FLAURA: Progression-free survival and preliminary survival

A  Progression-free Survival in Full Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>18.9 (15.2–21.4)</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>277</td>
<td>10.2 (9.6–11.1)</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001

D  Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Median Overall Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td>NC (NC–NC)</td>
</tr>
<tr>
<td>Standard EGFR-TKI</td>
<td>277</td>
<td>NC (NC–NC)</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007

Soria NEJM 2018
Patient case: 50 year-old women

Osimertinib started November 15:

November 8, 2018
November 30, 2018
November 8, 2018
November 30, 2018
Patient case: 50 year-old women

April 12, 2019
Stage IV lung carcinoma with ALK translocation

- Crizotinib [I, A; MCBS 4]
- Alectinib [I, A; MCBS 4]
- Ceritinib [I, B; MCBS 4]
- Brigatinib [I, B]*

Disease progression

Oligoprogression

- Local treatment (surgery or RT) and continue targeted systemic treatment

Systemic progression

Re-biopsy recommended (not mandatory for decision)

Systemic progression

- Alectinib [I, A; MCBS 4]
- Ceritinib [I, A; MCBS 4]

Systemic progression

Platinum-based ChT (see Figure 2)
In selected cases, alternative new generation ALK TKIs if available (lorlatinib, brigatinib) [II, B]*
Carbolatin/paclitaxel/bevacizumab/atezolizumab [II, B]*
Case 1: 62-y/o man

- July 2012: Adenocarcinoma of the lung, stage IIIB with bilateral mediastinal and supraclavicular nodal metastases, EGFR WT
- July – September 2012: Treatment with 3 cycles of carboplatin and pemetrexed: Stable disease
- September 2012: Start of Crizotinib
Case 1: 62-y/o man

Continuing crizotinib

- March 2017: Stereotactic radiotherapy of the 4 cerebellar lesions
- November 2018: Stereotactic radiotherapy of lesion at nucleus olivaris
Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in ALK-mutation-positive NSCLC

Overall survival

OS adjusted for cross-over

Solomon, JCO 2018
First line alectinib versus crizotinib in advanced ALK-positive NSCLC: Progression-free survival

Camidge, ASCO 2018
Frequency of brain metastases in fusion gene lung cancer

**B** Cumulative incidence of brain metastases

- ALK
- RET
- ROS1

Gray's test $p = 0.0039$

<table>
<thead>
<tr>
<th>Year since metastatic diagnosis</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>98</td>
</tr>
<tr>
<td>RET</td>
<td>54</td>
</tr>
<tr>
<td>ROS1</td>
<td>29</td>
</tr>
</tbody>
</table>

Drilon, JTO 2018
Systemic therapy for patients with advanced NSCLC with oncogenic driver mutations such as EGFR mutations and ALK gene rearrangement

- Molecular testing of non-squamous NSCLC for oncogenic driver mutations is part of the routine diagnostic work-up
- For patient with tumors harboring oncogenic driver mutations including EGFR, ALK front line targeted therapy with an tyrosine kinase inhibitors is indicated
- About half of patients with EGFR-mutated tumors progressing under first or second generation TKIs have the resistance mutation T790M which can be successfully treated with the third generation EGFR TKI osimertinib
- Patients with ALK-rearranged tumors progressing under crizotinib can be successfully treated with second or third generation ALK TKIs
- The current tendency is to use later generation TKIs upfront
CTLA-4 and PD1/PD-L1 axis
CTLA-4 and PD-1 pathway inhibition

Nivolumab
Pembrolizumab
Cemiplimab
Tislelizumab
Atezolizumab
Avelumab
Durvalumab

Ipilimumab
Tremelimumab
Biomarkers for therapy with immune checkpoint inhibitors

Tumour microenvironment

Tumour

Tumour-infiltrating immune cells
PD-L1, PD-1, CTLA-4, CD8 and CD45RO expression phenotypes

PD-L1 expression
Tumour-mutational burden

IFNγ mRNA expression
Microsatellite instability

Cell-mediated immune system
T cells, dendritic cells, plasma cells, macrophages, eosinophils, natural killer cells, myeloid cells

Serum/circulating factors
- Cytokines (e.g. IFNγ)
- Lactate dehydrogenase (LDH)
- Absolute/relative cell counts

Nishino, Nat Rev Clin Oncol 2017
Single agent immune checkpoint inhibition in later line of therapy can result in long term survival and potentially cure in patients with advanced NSCLC without oncogenic driver mutation

Nivolumab in second or later line

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N = 128)</td>
<td>9.9 (7.8, 12.4)</td>
</tr>
</tbody>
</table>

Pembrolizumab in second or later line

Atezolizumab in second or later line

Gettinger, JCO 2018; Garon, JCO 2019; Horn, EJC 2018
Systemic therapy of advanced NSCLC without oncogenic driver mutation: Immunotherapy is the new standard second line therapy

The addition of single agent immune checkpoint blockade to platin-based combinations improves the survival of patients with non-squamous NSCLC

**Pembrolizumab**

**KEYNOTE-189**
- Treatment-naive non-squamous NSCLC
- N=580
- Pembrolizumab + platin/pem
- Platin/pem
- Primary endpoints: PFS and OS

**Atezolizumab**

**IMpower 150**
- Stage IV non-squamous NSCLC
- N=1200
- Atezolizumab + bevacizumab + carbo/pacl
- Bevacizumab + carbo/pacl
- Primary endpoint: PFS and OS

**Atezolizumab**

**IMpower 130**
- Stage IV non-squamous NSCLC
- N=578
- Atezolizumab + carbo/nab-pacl
- Carbo/nab-paclitaxel
- Primary endpoint: PFS and OS

**Atezolizumab**

**IMpower 132**
- Stage IV non-squamous NSCLC
- N=68
- Atezolizumab + carbo/pem
- Carbo/pem
- Primary endpoint: PFS and OS

Pos. PFS and OS
- TPS < 50%: Pembro/ Approval by EMA and FDA

Pos. PFS and OS
- Approval by FDA excluding mEGFR and by EMA for mEGFR failing TKIs

Pos. PFS and OS

Pos. PFS, final OS pending
KN-189: Randomized double blind phase 3 study of pembrolizumab or placebo plus pemetrexed and platinum as 1L for metastatic non-squamous NSCLC

**Key Eligibility Criteria**
- Untreated stage IV non-squamous NSCLC
- No sensitizing EGFR or ALK alterations
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No asymptomatic brain metastases
- No pneumonitis requiring systemic steroids

**Stratification Factors**
- PD-L1 expression (TPS >1% vs <1%)
- Platinum [carboplatin vs cisplatin]
- Smoking history (never vs former/current)

**Overall Survival, ITT**

**Events** | **HR (95% CI)** | **P**
---|---|---
Pembro/Pem/Plat | 31.0% | 0.49 (0.38-0.64) | <0.00001
Placebo/Pem/Plat | 52.4% | | |

**Median (95% CI)**
- NR (NE-NE)
- 11.3 mo (8.7-15.1)

**Data cut-off date:** Nov 8, 2017.

Ghandi, AACR 2018 and NEJM 2018
KN-189: Randomized double blind phase 3 study of pembrolizumab or placebo plus pemetrexed and platinum as 1L for metastatic non-squamous NSCLC: OS

<table>
<thead>
<tr>
<th>TPS &lt;1%</th>
<th>TPS 1-49%</th>
<th>TPS ≥50%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pembro/Pem/Plat</strong></td>
<td><strong>Placebo/Pem/Plat</strong></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>HR (95% CI)</td>
<td>Events</td>
</tr>
<tr>
<td>38.6%</td>
<td>0.59 (0.38-0.92)</td>
<td>28.9%</td>
</tr>
<tr>
<td>55.6%</td>
<td>0.0095</td>
<td>48.3%</td>
</tr>
</tbody>
</table>

Median (95% CI):
- TPS <1%: 15.2 mo (12.3-NE)
- TPS 1-49%: 12.0 mo (7.0-NE)
- TPS ≥50%: NR (NE-NE)

No. at Risk:
- TPS <1%:
  - 0: 127, 63
  - 1: 113, 54
  - 2: 104, 45
  - 3: 79, 45
  - 4: 42, 32
  - 5: 20, 21
  - 6: 6, 6
  - 7: 0
- TPS 1-49%:
  - 0: 128, 58
  - 1: 119, 54
  - 2: 108, 47
  - 3: 84, 32
  - 4: 52, 17
  - 5: 21, 17
  - 6: 5, 5
  - 7: 0
- TPS ≥50%:
  - 0: 132, 70
  - 1: 122, 64
  - 2: 114, 50
  - 3: 96, 35
  - 4: 66, 18
  - 5: 25, 12
  - 6: 6, 6
  - 7: 0

Ghandi, AACR 2018
Overall survival in phase 3 studies of first line immune checkpoint inhibitors combined with platin-base chemotherapy for patient with advanced squamous NSCLC

**Pembrolizumab**

*KEYNOTE-407*

- Treatment-naïve squamous NSCLC
- N=560
- Primary endpoint: PFS and OS
- FDA and EMA approved
- Pos. PFS and OS

**Atezolizumab**

*IMpower 131*

- Stage IV squamous NSCLC
- N=1200
- Primary endpoint: PFS and OS
- Pos. PFS, preliminary OS neg
KN-407: Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel with or without pembrolizumab for metastatic squamous NSCLC
Five-year overall survival for patients with advanced NSCLC treated with pembrolizumab: Results from the phase I KEYNOTE-001 study

First line pembrolizumab

<table>
<thead>
<tr>
<th>Events, n/N</th>
<th>TPS ≥ 50%</th>
<th>Median OS, mo (95% CI)</th>
<th>5-Year OS Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS ≥ 50%</td>
<td>17/27</td>
<td>35.4 (20.3 to 63.5)</td>
<td>29.6 (7.7 to 56.1)</td>
</tr>
<tr>
<td>TPS 1–49%</td>
<td>43/52</td>
<td>19.5 (10.7 to 28.3)</td>
<td>15.7 (7.3 to 26.9)</td>
</tr>
</tbody>
</table>

Later line pembrolizumab

<table>
<thead>
<tr>
<th>Events, n/N</th>
<th>TPS ≥ 50%</th>
<th>Median OS, mo (95% CI)</th>
<th>5-Year OS Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS ≥ 50%</td>
<td>104/138</td>
<td>15.4 (10.6 to 18.6)</td>
<td>25.0 (18.0 to 32.5)</td>
</tr>
<tr>
<td>TPS 1–49%</td>
<td>146/168</td>
<td>8.5 (6.0 to 12.6)</td>
<td>12.6 (7.9 to 18.5)</td>
</tr>
<tr>
<td>TPS &lt; 1%</td>
<td>83/90</td>
<td>8.6 (5.5 to 10.6)</td>
<td>3.5 (0.7 to 10.0)</td>
</tr>
</tbody>
</table>

Garon, JCO 2019
With the approval of single agent immune checkpoint inhibition for patients with metastatic NSCLC, should we still consider IO combination with platin-base therapy?

**Pembrolizumab**

**KEYNOTE-026**
- Treatment-naïve NSCLC
- PD-L1-positive NSCLC
- N=495
- Pembrolizumab 3 mg/kg IV Q2W
- Investigators choice chemotherapy
- Primary endpoint: PFS

**Pembrolizumab**

**KEYNOTE-042**
- Treatment-naïve non-squamous NSCLC
- PD-L1-positive NSCLC
- N=1240
- Pembrolizumab 200 mg IV Q3W
- Carbo/pacl or cabo/pem
- Primary endpoint: OS

**Pembrolizumab**

**KEYNOTE-042**
- Treatment-naïve NSCLC
- PD-L1-positive NSCLC
- N=305
- Pembrolizumab 200 mg IV Q3W
- Platin-based chemotherapy
- Primary endpoint: OS

**Durvalumab**

**MYSTIC**
- Advanced NSCLC
- N=675
- Durvalumab
- Durvalumab + tremelimumab
- SOC chemotherapy
- Primary endpoint: PFS and OS

**Nivolumab**

**CHECKMATE 026**
- Treatment-naïve non-squamous NSCLC
- PD-L1-positive NSCLC
- N=495
- Nivolumab 3 mg/kg IV Q2W
- Investigators choice chemotherapy
- Primary endpoint: PFS

**Pembrolizumab**

**KEYNOTE-042**
- Treatment-naïve NSCLC
- PD-L1-positive NSCLC
- N=305
- Pembrolizumab 200 mg IV Q3W
- Platin-based chemotherapy
- Primary endpoint: OS

**TPS ≥ 50%:**
- Pos. OS
- FDA and EMA approved

**PD-L1 ≥ 25%:**
- Neg. OS
- Another future cut-off?

**≥ 5% PD-L1:**
- Neg. OS
- Importance of TMB

**TPS ≥ 1%:**
- Pos OS
- FDA approved
- A controversial option for TPS 1-49%?
Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced NSCLC
Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic NSCLC (KEYNOTE-042)

KEYNOTE-042 Study Design

Key Eligibility Criteria
- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥ 20%
- No untreated EGF or ALK alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Randomize 1:1

Pembrolizumab 200 mg Q3W for up to 35 cycles

Stabilization Factors
- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (adenocarcinoma vs non-adenocarcinoma)
- PD-L1 TPS (50% vs 1%–8%)

End points
- Primary: OS in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%
- OS and PFS in PD-L1 TPS ≥ 100%, ≥ 50%, and ≥ 1%
- Safety in TPS ≥ 1%

Current analysis planned to occur ~65 months after start date.

Mok, Lancet 2019
Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS)

PD-L1 expression

Any expression of PD-L1

PS 0-1

< 70 years and PS 2 or Selected ≥ 70 years and PS 0-2

PS 3-4

PD-L1 ≥ 50%

High TMB ≤ 10 mutations/Mb)

PS 0-1

Pembrolizumab/ pembrolizumab and platinum-based ChT (4 cycles), followed by pembrolizumab/ pembrolizumab [I, A; MCBS 5]

Nivolumab/ ipilimumab [I, A]6

Pembrolizumab/ pembrolizumab and platinum-based ChT (4-6 cycles), followed by pembrolizumab/ pembrolizumab [I, A; MCBS 4]

Atezolizumab/ pembrolizumab with carboplatin and paclitaxel (4-6 cycles), followed by atezolizumab/ bevacizumab [I, A]6

Atezolizumab/ pembrolizumab with carboplatin and paclitaxel (4-6 cycles), followed by atezolizumab/ bevacizumab [I, A]6

4-6 cycles

Platinum-based ChT:
Cisplatin/gemcitabine [I, A]
Cisplatin/docetaxel [I, A]
Cisplatin/paclitaxel [I, A]
Cisplatin/vinorelbine [I, A]
Carboplatin/gemcitabine [I, A]
Carboplatin/docetaxel [I, A]
Carboplatin/paclitaxel [I, A]
Carboplatin/vinorelbine [I, A]
Carboplatin/pemetrexed [I, A]
Carboplatin/pemetrexed [I, B]
Carboplatin/nab-P [I, B]
/+ bevacizumab [I, A with carboplatin/ paclitaxel, otherwise III, B]

Maintenance treatment:
Pemetrexed (continuation) [I, A]
Gemcitabine (continuation) [I, B]
Pemetrexed (switch) [I, B]
/+ bevacizumab (if given before)

< BSC [I, B]

Partial response or stable disease

4-6 cycles

Carboplatin-based ChT:
< 70 years and PS 2 [I, A]
≥ 70 years and PS 0-2 [I, A]
Single-agent ChT:
Gemcitabine, vinorelbine, docetaxel [I, B]
or pemetrexed [III, B]

Planchard, updated ESMO guidelines 2019
The likelihood of response to immunotherapy is correlated with the mutational tumor burden
Systemic therapy for advanced NSCLC without oncogenic driver mutations

• Determination of PD-L1 expression by immunohistology is part of routine diagnostic work-up

• Patients with tumors with ≥ 50% tumors cells expressing PD-1 have a superior survival when treated with pembrolizumab, an anti-PD-1 antibody alone or its combination with chemotherapy as compared to chemotherapy alone.

• Patients with tumors with < 50% tumor cells expressing PD-L1 have a superior survival when treated with combined immune checkpoint inhibition with chemotherapy as compared to chemotherapy alone.

• The role of combined CTLA-4 and PD-1/PD-L1 inhibition is being explored for patients with a high tumor mutation burden.
Case 4: 44-y/o man

- February 2011:
  - Patient complains of cough and pain in the lower back. A general practitioner who performs a chest X-ray and refers the patient to pulmonology at the University Hospital
Case 1: 44-y/o man

- February 2011:
  - Patient complains of cough and pain in the lower back. A general practitioner who performs a chest X-ray and refers the patient to pulmonology at the University Hospital.
  - A PET/CT reveals FDG uptake in the right lower lobe, in a subcarinal lymph node and in lumbar vertebrae.
  - A bronchosopic biopsy of an endobronchial lesion and the subcarinal node reveals adenocarcinoma.
Case 1: 44-y/o man

- February 2011:
  - Molecular pathology: EGFR deletion exon 19, ALK IHC negative, PD-L1 not done
  - Brain MRI: no cerebral metastases
Case 1: 44-y/o man with EGFR-mutated adenocarcinoma of the lung treated with first line gefitinib

- March 2011:
  - Start therapy with gefitinib
  - Start therapy with denosumab
Case 1: 44-y/o man  Case 4: 44-y/o man with EGFR-mutated adenocarcinoma of the lung treated with first line gefitinib

Gefitinib + zoledronic acid

Case 1: 44-y/o man with EGFR-mutated adenocarcinoma of the lung treated with first line gefitinib

- November 2011:
  - Intention to do a thoracoscopic wedge resection of PET positive re-emerging lesion
  - Documentation of multiple pleural lesions
  - Biopsy: Adenocarcinoma
  - Molecular pathology: EGFR deletion exon 19, T790M mutation
Case 1: 44-y/o man with EGFR-mutated adenocarcinoma of the lung with acquired resistance to gefitinib
Case 1: 44-y/o man with EGFR-mutated adenocarcinoma of the lung with acquired resistance to gefitinib

<table>
<thead>
<tr>
<th>Osimertinib</th>
<th>Carbo/Eto + MTX i.t.</th>
</tr>
</thead>
<tbody>
<tr>
<td>08.2014</td>
<td>08.2015</td>
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<tr>
<td>08.2015</td>
<td>12.2015</td>
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<td>01/2016</td>
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Leptomeningeal disease
Progression liver, lung
>> Biopsy of liver lesion: transformation to SCLC
Case 2: 64-y/o man with squamous cell lung carcinoma

- June 2015:
  - Squamous cell carcinoma right upper lobe with lymph node and bone metastases
  - Pathology: strong positivity of PD-L1
Case 2: 64-y/o man squamous cell lung carcinoma

- July – September 2015: Chemotherapy with cisplatin/gemcitabine 3 cycles
Case 2: 64-y/o man squamous cell lung carcinoma

- July – September 2015: Chemotherapy with cisplatin/gemcitabine 3 cycles
- October 2015: Palliative resection of right upper lobe

Severe pain upper and lower back due to progressive bone metastases
Case 2: 64-y/o man squamous cell lung carcinoma

- December 2015: Radiotherapy to thoracic and sacrum, two applications of an immune checkpoint inhibitor
- January 2016: Shortness of breath while walking to doctors office

January 2016:
PiO2 67%
CRP 115 ng/l
WBC 11 G/l

November 2015
Case 2: 64-y/o man squamous cell lung carcinoma

- December 2015: Radiotherapy to thoracic and sacrum, two applications of an immune checkpoint inhibitor
- January 2016: Shortness of breath while walking to doctors office

Hospitalization in intensive care: O2, methylprednisolon 250 mg iv (1d), followed by prednison in slowly decreasing amounts. Piperacillin and bactrim.
Case 2: 64-y/o man squamous cell lung carcinoma
Correlations between the immune-related adverse events Spectrum and efficacy of anti-PD1 immunotherapy in NSCLC patients

A  Progression Free Survival

B  Overall Survival

Number at risk
Group: No 328 40 3 0 0 0 0
Group: Yes 231 67 31 10 1 1 0

Number at risk
Group: No 328 74 14 4 0 0 0
Group: Yes 231 97 50 18 4 3 0

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