Current standard of care of NSCLC

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DISCLOSURE OF INTEREST

Consultant or Advisory Role in the last two years
I have received honoraria as a consultant at advisory boards from Abbvie, AstraZeneca, Boehringer Ingelheim, MSD, Pfizer, Roche and Takeda.

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

DMC in the last two years
Roche and Takeda
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
Molecular diagnosis

- EGFR mutation status should be systematically analysed in advanced non-squamous NSCLC [I, A]. Test methodology should have adequate coverage of mutations in exons 18–21, including those associated with specific drug resistance. At a minimum, when resources or material are limited, the most common activating mutations (exon 19 deletion and exon 21 L858R point mutation, including exon 20 T790M) should be determined [I, A]

- Testing for ALK rearrangement should be systematically carried out in advanced NSCC [II, A]. Detection of the ALK translocation by FISH remains the standard, but IHC with high-performance ALK antibodies may be considered for screening

Molecular testing in non-squamous cell NSCLC at University Hospital Zürich

- **EGFR-Mutation**
- **KRAS-Mutation**
- **Sanger Sequencing**

Diagnoses of advanced disease:
- (TTF1)
- PD-L1
- ALK
- ROS1
- cMET

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

Failure of first line treatment
- Diagnoses of advanced disease

Progression under target therapy
- t
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 combined chemotherapy or combined immunotherapy approaches
Systemic therapy of advanced NSCLC: How many cycles of therapy?

- Neither a large individual trial nor a meta-analysis found an overall survival (OS) benefit of six versus fewer cycles of first-line platinum-based doublets, although a longer PFS coupled with significantly higher toxicity was reported in patients receiving six cycles.

- Four cycles of platinum-based doublets followed by less toxic maintenance monotherapy, or four up to a maximum of six cycles in patients not suitable for maintenance monotherapy, are currently recommended [I, A].
Six versus fewer planned cycles of first-line platinum-based chemotherapy for NSCLC: a systematic review and meta-analysis of individual patient data

Rossi, Lancet 2014
First line chemotherapy in squamous NSCLC

- Platinum-based doublets with a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients [I, A]
- Necitumumab plus gemcitabine and cisplatin represents a treatment option for advanced SCC expressing EGFR by IHC [I, B; ESMO-MCBS v1.0 score: 1]
- Immune checkpoint inhibition with pembrolizumab has become an option for patients with tumors with strong PD-L1 expression
Gemcitabine and cisplatin with or without necitumumab in squamous cell lung cancer

Thatcher, Lancet Oncol 2015
ESMO clinical practice guidelines in metastatic non-squamous cell carcinoma: 1st line

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

- <70 years and PS 0-1
  - 4-6 cycles:
    - Cisplatin – gemcitabine [I, A]
    - 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-based doublets [II, B]
    - Single-agent chemotherapy
      - (gemcitabine, vinorelbine or docetaxel) [I, A]

- PS 0-1
  - Partial response or stable disease
    - Maintenance treatment:
      - Paclitaxel (switch) [I, B]
      - Paclitaxel (continuation) [I, A]
      - Erlotinib (EGFR-activating mutation) [I, B]
      - +/- bevacizumab (II given below)

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

First line therapy of non-squamous NSCLC

• Any platinum-based doublets with a third-generation agent including gemcitabine, vinorelbine or taxanes can be used in non-squamous NSCLC.
• The incorporation of pemetrexed and bevacizumab into individual treatment schedules should be considered based on the following:
• Pemetrexed-based combination chemotherapy represents a therapeutic option, based on the results of a recent meta-analysis that showed a slight but significant survival benefit compared with gemcitabine- or docetaxel-based combinations and of a pre-planned subgroup analysis of a large randomized phase III trial [II, A]
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)

Scagliotti, JCO 2008
First line therapy of non-squamous NSCLC

- Findings of two randomized clinical trials revealed that bevacizumab improves OS when combined with paclitaxel/carboplatin regimens in patients with NSCC and PS 0-1, and, therefore, may be offered in the absence of contraindications in eligible patients with advanced NSCC [I, A]
Bevacizumab added to chemotherapy: Phase III trials in combination with carboplatin and paclitaxel

E4599 overall patient population

OS estimate

Time (months)

0 6 12 18 24 30 36 42

E4599 overall patient population

HR (95% CI) 0.79 (0.67–0.92)

p value 0.003

Median OS (months) 10.3 12.3

Overall Survival (proportion)

Time of Study (month)

No. at risk

PI + CP 138 122 89 64 50 9 0

B + CP 138 128 102 83 64 18 0

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

Sandler, NEJM 2006; Zhou, JCO 2015
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]
Maintenance therapy in non-squamous NSCLC

- Continuing pemetrexed following completion of four cycles of first-line cisplatin/pemetrexed chemotherapy is recommended in patients with non-squamous NSCLC, in the absence of progression after first-line chemotherapy and upon recovery from toxicities from the previous treatment [I, A]
PARAMOUNT: Overall survival

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

**Induction Therapy**
- 4 cycles, q21d

**Continuation Maintenance Therapy**
- q21d until PD

CR/PR/SD per RECIST

- Pemetrexed + Cisplatin
- Placebo + BSC

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

**A**
- Pemetrexed: median = 13.9 mos (12.8 to 16.6 mos)
- Placebo: median = 11.0 mos (10.6 to 12.5 mos)
- Log-rank P = .0195
- Unadjusted HR: 0.76 (0.64 to 0.90)

**B**
- Pemetrexed: median = 16.9 mos (15.8 to 19.6 mos)
- Placebo: median = 14.0 mos (12.8 to 15.3 mos)
- Log-rank P = .0191
- Unadjusted HR: 0.76 (0.64 to 0.90)

Paz-Ares, JCO 2013
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

**Platinum-Doublet Chemotherapy**
- 200 mg IV Q3W (4-6 cycles)

**Pembrolizumab**
- 200 mg IV Q3W (2 years)

**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>

OBJECTIVE RESPONSE

Δ17%  

P = 0.0011

CR  

45%  
n = 6  
n = 63

PR  

28%  
n = 1  
n = 41

Reck, ESMO 2016 and NEJM 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>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS (Mok TS, et al. <em>N Engl J Med</em>. 2009;361:947-957)</td>
<td>1217</td>
<td>Gefitinib</td>
<td>Carboplatin/placinixel</td>
<td>IIIB/IV</td>
<td>5.7 vs 5.8 mo <em>(EGFR-mutated patients HR = 0.48; nonmutated patients HR = 2.84)</em></td>
<td>18.6 vs 17.3 mo <em>(P = NS)</em></td>
<td>First-line</td>
</tr>
</tbody>
</table>
ASPIRATION: 1st line erlotinib until and beyond progression in Asian patients with EGFR mutated NSCLC

Median PFS 1: 11.0 months
Median PFS 2: 14.1 months

Park, JAMA Oncol 2016
**Patients**
- Age ≥18 years (≥20 years in Japan)
- WHO PS 0-1
- Histologically confirmed stage IIIb/IV EGFR mutation-positive advanced NSCLC
- Chemotherapy-naïve
- Achieved CR/PR ≥4 months or SD >6 months with first-line gefitinib
- Disease progression (RECIST) <4 weeks prior to study randomisation

**Endpoints**

**Primary**
- Progression-free survival

**Secondary**
- Overall survival
- Objective response rate
- Disease control rate
- Safety and tolerability
- Health-related quality of life

**Exploratory**
- Biomarkers

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**ORR and DCR (ITT population)**

<table>
<thead>
<tr>
<th>gefitinib</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>DCR (%)</td>
</tr>
<tr>
<td>31.5</td>
<td>34.1</td>
</tr>
<tr>
<td>(n=133)</td>
<td>(n=132)</td>
</tr>
</tbody>
</table>

Odds ratio (95% CI) for ORR:
- gefitinib vs placebo: 0.92 (0.85, 1.00), p=0.780
- gefitinib vs placebo: 8.42 (7.43, 2.82), p=0.306

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*Mock, ESMO 2014; Soria, Lancet Oncol 2015*
Patients with EGFR-mutated NSCLC

- Evidence from retrospective series and case reports suggests that, in patients where there is evidence of radiological progression in a single site, but with ongoing dependence on the driver oncogene addiction and without rapid systemic progression, the combination of continuing the EGFR TKI with local treatment (radiotherapy or surgery) may represent a reasonable option and could be considered on an individualised basis [III, B]

- Patients who progress after an EGFR TKI should undergo a rebiopsy to perform molecular analysis specifically looking for EGFR T790M mutation

- In patients with clinically relevant progression after previous treatment with an EGFR TKI and confirmed T790M mutation, treatment with osimertinib should be considered [III, A]
Local therapy of oligoprogressive disease prolongs disease control in EGFR and ALK driven tumors

- Retrospective analysis of 38 pts treated with crizotinib and 27 pts treated with erlotinib at UCCC

<table>
<thead>
<tr>
<th>Site of First Progression</th>
<th>No. of Patients</th>
<th>PFS1 (mo) (CI)</th>
<th>PFS2 (mo) (CI)</th>
<th>Site of Second Progression</th>
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</thead>
<tbody>
<tr>
<td>CNS</td>
<td>10</td>
<td>10.9</td>
<td>7.1</td>
<td>2 (20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.3–18.3</td>
<td>1.7–11.3</td>
<td>No prog</td>
</tr>
<tr>
<td>eCNS</td>
<td>15</td>
<td>9.0</td>
<td>4.0</td>
<td>4 (27%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.5–13.8</td>
<td>2.7–7.4</td>
<td>No prog</td>
</tr>
<tr>
<td>All patients</td>
<td>25</td>
<td>9.8</td>
<td>6.2</td>
<td>6 (24%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.8–13.8</td>
<td>3.7–8.0</td>
<td>No prog</td>
</tr>
</tbody>
</table>

*a* Includes three patients who progressed eCNS and CNS at PFS1.

CI, confidence interval; CNS, central nervous system as site of disease; eCNS, extra-CNS sites of disease; PFS1, median progression-free survival.

Weickhardt, JTO 2013
Osimertinib or platinum-pemetrexed in EGFR TKI pretreated EGFR T790M–positive NSCLC

A Patients in Intention-to-Treat Population

- Osimertinib
- Platinum–pemetrexed

B Patients with CNS Metastases

- Osimertinib
- Platinum–pemetrexed

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Month</th>
<th>Kaplan-Meier Survival Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>279</td>
<td></td>
</tr>
<tr>
<td>Platinum–pemetrexed</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Month</th>
<th>Kaplan-Meier Survival Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Platinum–pemetrexed</td>
<td>51</td>
<td></td>
</tr>
</tbody>
</table>

**Median Progression-Free Survival**

- Osimertinib: 10.1 (95% CI, 8.3–12.3) mo
- Platinum–pemetrexed: 4.4 (4.2–5.6) mo

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

- Osimertinib: 8.5 (6.8–12.3) mo
- Platinum–pemetrexed: 4.2 (4.1–5.4) mo

Hazard ratio for disease progression or death: 0.32 (95% CI, 0.21–0.49)
First TKIs in EGFR mutated NSCLC: Current status

**EURTAC:**
Erlotinib median PFS 9.7 months

- Erlotinib (n=86)
- Chemotherapy (n=87)
- HR 0.37 (95% CI 0.25-0.54); log-rank p<0.0001

**FLAURA:**
Osimertinib median PFS 18.9 months

- No. at Risk
  - Osimertinib: 279, 262, 233, 210, 178, 139, 71, 26, 4, 0
  - Standard: 277, 239, 197, 152, 107, 78, 37, 10, 2, 0

*Rosell, Lancet Oncol 2012*
*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
Patients with ALK-rearranged NSCLC

• First-line treatment with crizotinib is the preferred treatment of patients with ALK-rearranged NSCLC [I, A]

• Several alternative ALK inhibitors are currently in clinical development, with broader activity against a number of mutated ALK genes and mainly characterised by higher brain activity

• In patients who progress after an ALK TKI, second-generation ALK inhibitors such as ceritinib are recommended [III, A]
Crizotinib in first line: PRORILFE 1014

Salomon, NEJM 2014
Optimal first line therapy?

**First line**
- **Alectinib** (11 months)
- **Ceritinib** (16.6 months (single PFS))
- **Crizotinib**

**Second line**
- **Next-gen ALK TKI** (18–20 months (combined PFS))
- **Other ALK TKI**
- **Chemotherapy Immunotherapy?**

**Other ALK TKI**
- **Chemotherapy Immunotherapy?**

** brigatinib/lorlatinib?** (25.7 months (single PFS))
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 nitendatib to docetaxel in non-squamous NSCLC and the addition of ramicirumab 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
• The observation of durable remissions in patients with metastatic NSCLC progressing after chemotherapy suggests a small proportion of patients might be cured by single agent immune checkpoint inhibition
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
Docetaxel plus nintedanib (LUME-Lung 1) or docetaxel plus ramucirumab (REVEL) versus docetaxel plus placebo for 2nd 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
Systemic therapy of advanced NSCLC without oncogenic driver mutation: Immunotherapy as preferred second line therapy

Nivolumab

Pembrolizumab

Atezolizumab


Horn, JCO 2017

Rittmeyer, Lancet 2017


Horn, JCO 2017

Rittmeyer, Lancet 2017


Horn, JCO 2017

Rittmeyer, Lancet 2017
Less toxicity with immune checkpoint inhibitors in second line comparative studies

<table>
<thead>
<tr>
<th>Toxicity Gade</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Check-mate 17</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>All</td>
<td>59</td>
</tr>
<tr>
<td>3-5</td>
<td>8</td>
</tr>
</tbody>
</table>
Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced NSCLC: Overall survival

54% pretreated with 3-5 therapies, 17% confirmed responses
Of the 16 pts surviving 5 years, 12 had a PR, 3 SD and 1 PD as best response

Brahmer, AACR 2017
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Medicine</th>
<th>ESMO-MCBS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC 2L</td>
<td>Nivolumab</td>
<td>5</td>
</tr>
<tr>
<td>NSCLC 2L</td>
<td>Pembrolizumab</td>
<td><strong>5 in PD-1 &gt; 50%</strong></td>
</tr>
<tr>
<td>NSCLC 2L</td>
<td>Pembrolizumab</td>
<td><strong>3 in PD-L1 &gt; 1%</strong></td>
</tr>
<tr>
<td>NSCLC (EGFR mutated together with erlotinib)</td>
<td>Bevacizumab</td>
<td>2</td>
</tr>
<tr>
<td>NSCLC 2L Squamous</td>
<td>Afatinib</td>
<td>1</td>
</tr>
<tr>
<td>NSCLC 1L Squamous</td>
<td>Necitumumab</td>
<td>1</td>
</tr>
<tr>
<td>NSCLC change to existing indication (2L non-mutated)</td>
<td>Erlotinib</td>
<td>1</td>
</tr>
<tr>
<td>NSCLC 2L</td>
<td>Ramucirumab</td>
<td>2</td>
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