Current Standard of Care in Thoracic Malignancies

Rolf Stahel
University Hospital of 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 AstraZeneca, 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.
Molecular profiling of metastatic NSCLC: At diagnosis

- Tissue processing
  - H&E staining
  - IHC
- Diagnostic
  - NSCLC
    - Adenocarcinoma / large-cell carcinoma
      - Idylla: EGFR, KRAS, BRAF
      - IHC ALK, ROS1, PD-L1
      - FO
    - Squamous cell carcinoma
      - IHC PD-L1
  - SCLC
- If material insufficient
  - OFA (CF assay)
  - Or
  - Re-biopsy

FO: Foundation One
OFA: Oncomine Focus Assay
OFA CF: cell free DNA
Biomarker development for immune checkpoint inhibition in NSCLC

- PD-L1 expression
- T effector signature
- Tumor mutation burden

Dolled-Filhart, Arch Path Lab Med 2016
Fehrenbacher, Lancet Oncol 2016
Peters, AACR 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

Pembrolizumab in second or later line

Atezolizumab in second or later line
Immune checkpoint inhibition for 2nd line therapy in advanced NSCLC without oncogenic driver mutation. Patient case: 55 y/o woman

November 2015:
• MRI: Two brain metastases
• Neurosurgical resection: Adenocarcinoma TTF-positive
• PET/CT: Tumor in left lower lobe and left adrenal metastases

Dezember 2016:
• SBRT of resection bed and of additional brain metastases
Immune checkpoint inhibition for 2nd line therapy in advanced NSCLC without oncogenic driver mutation. Patient case: 55 y/o woman.
Immune checkpoint inhibition for 2nd line therapy in advanced NSCLC without oncogenic driver mutation. Patient case: 55 y/o woman

SBRT of salivary gland and bone metastases

February 2019

NIvolumab

Mai 2016

Lepidic adenocarcinoma, 1.9 cm, TTF-1 positive, PD-L1 negative
Long-term follow-up of KEYNOTE-010

79 patients completed 2 years of treatment
- 25 (95%) had a CR or PR as best response
- 72 (91%) remained alive
- 48 (64%) had an ongoing response
- 25 (31%) had disease progression
Immune checkpoint inhibition for 2nd line therapy in advanced NSCLC without oncogenic driver mutation: Pts with poor performance status?

Efficacy and safety of nivolumab in patients with advanced NSCLC and PS

The frequency of severe pneumonitis in the poor PS group was significantly higher than that in the good PS group (25% vs. 2%, p=0.010)

Katsura, J Cancer 2019

Pembrolizumab for advanced NSCLC: Efficacy and safety in everyday clinical practice

Ksienski, Lung Cancer 2019
Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or NSCLC treated with nivolumab.
Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or NSCLC treated with nivolumab

Association between depth of response and survival

Association between treatment related AEs and irAE and survival

Topalian, JAMA Oncol 2019
Five-year overall survival for patients with advanced NSCLC treated with pembrolizumab: Results from the phase I KEYNOTE-001 study
Stage IV NSCLC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)

PD-L1 expression

Any expression of PD-L1

PS 0-2

PS 3-4

PD-L1 ≥ 50%

PS 0-1

Pembrolizumab

[1, A; MCBS 5]

High TMB

≥ 10 mutations/Mb

Pembrolizumab/ pemetrexed and platinum-based ChT (4 cycles), followed by pembrolizumab/ pemetrexed [1, A; MCBS 4]

Nivolumab/ ipilimumab

[1, A]

Partial response or stable disease

Maintenance treatment:

Pemetrexed (continuation) [1, A]

Gemcitabine (continuation) [1, A]

Pemetrexed (switch) [1, B]

+/− bevacizumab (if given before)

4-6 cycles

Platinum-based ChT:

Cisplatin/gemcitabine [1, A]

Cisplatin/docetaxel [1, A]

Cisplatin/paclitaxel [1, A]

Cisplatin/vinorelbine [1, A]

Carboplatin/gemcitabine [1, A]

Carboplatin/docetaxel [1, A]

Carboplatin/paclitaxel [1, A]

Carboplatin/vinorelbine [1, A]

Cisplatin/pemetrexed [1, A]

Carboplatin/nab-P [1, B]

+/− bevacizumab [1, A with carboplatin/ paclitaxel, otherwise III, B]

Disease progression

Disease progression

Planchard, updated ESMO guidelines 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
  - ≥ 5% PD-L1: Neg. OS, importance of TMB?

**Atezolizumab**
- **Impower110**
  - Treatment-naïve NSCLC
  - TCGCA
  - N=572
  - Atezolizumab 1200 mg IV Q3W
  - Platin-based chemotherapy
  - Primary endpoint: OS
  - TPS ≥ 50%:
    - Pos. OS, FDA and EMA approved

**Durvalumab**
- **MYSTIC**
  - Advanced NSCLC
  - N=675
  - Durvalumab
  - Durvalumab + tremelimumab
  - SOC chemotherapy
  - Primary endpoint: PFS and OS
  - PD-L1 ≥ 25%:
    - Neg. OS, a new future cut-off?

**Nivolumab**
- **CHECKMATE 026**
  - Treatment-naïve non-squamous NSCLC
  - PD-L1-positive NSCLC
  - N=495
  - Nivolumab 3 mg/kg IV Q2W
  - Platin-based chemotherapy
  - Primary endpoint: PFS
  - ≥ 5% PD-L1:
    - Neg. OS, importance of TMB?

**Pembrolizumab**
- **KEYNOTE-042**
  - Treatment-naïve non-squamous NSCLC
  - PD-L1-positive NSCLC
  - N=1240
  - Pembrolizumab 200 mg IV Q3W
  - Carbo/pacl or cabom/pem
  - Primary endpoint: OS
  - TPS ≥ 1%:
    - Pos OS, FDA approved, but controversial for PD-L1 1-49%
KN-024: 3-year update

Overall Survival: Updated Analysis

Reck, WCLC 2019 and JCO 2019
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-naïve non-squamous NSCLC
  - N=580
  - Pembrolizumab + platin/pem
  - Primary endpoints: PFS and OS
  - Pos. PFS and OS
  - Approval by EMA and FDA

**Atezolizumab**
- **IMpower 150**
  - Stage IV non-squamous NSCLC
  - N=1200
  - Atezolizumab + carbo/pacl
  - Bevacizumab + carbo/pacl
  - Primary endpoint: PFS and OS
  - Pos. PFS and OS
  - Approval by EMA and FDA

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

**Atezolizumab**
- **IMpower 132**
  - Stage IV non-squamous NSCLC
  - N=68
  - Atezolizumab + carbo/pem
  - Carbo/pem
  - Primary endpoint: 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.
KN-189: Updated OS by PD-L1 expression

<table>
<thead>
<tr>
<th>TPS ≥50%</th>
<th>TPS 1-49%</th>
<th>TPS &lt;1%</th>
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</thead>
<tbody>
<tr>
<td>Events</td>
<td>HR (95% CI)</td>
<td>Events</td>
</tr>
<tr>
<td>Pembro/Pem/Plat</td>
<td>43.9%</td>
<td>0.59</td>
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<tr>
<td>Placebo/Pem/Plat</td>
<td>60.0%</td>
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OS, %

Median (95% CI)
NR (20.4 mo–NR)
10.1 mo (7.5–NR)

Median (95% CI)
21.8 mo (17.7–25.9)
12.1 mo (8.7–19.4)

Median (95% CI)
17.2 (13.8–22.8)
10.2 mo (7.0–13.5)

Gadgeel, ASCO 2019
First line therapy with immune checkpoint inhibitors alone for patients with advanced NSCLC without oncogenic driver mutations

- Pembrolizumab single agent has become standard or care for patients with TPS \( \geq 50\% \). Combination with platin-based chemotherapy is an alternative and with lack of randomized data must be chosen based on individual assessment.
- The use of single agent pembrolizumab for patients with TPS \( \geq 1\% \) remains controversial.
- Retrospective subgroup analyses suggest a potential role for high TMB and or KRAS mutation as an additional selection factor, however this will require prospective testing before entering clinical practice.
Precision oncology in non-squamous non-small cell lung cancer: There are many targets.

**Targets with approved agents**

**Targets with agents under development**
Stage IV lung carcinoma with EGFR-activating mutation

PS 0-2 (I, A)
PS 3-4 for all following options (III, A)

Osimertinib (I, A; MCBS 4)\textsuperscript{a}
Gefitinib (I, A)
Erlotinib (I, A)
+/- bevacizumab (II, B; MCBS 3)\textsuperscript{c}
+/- ramucirumab (II, B)\textsuperscript{f}
Atarafib (I, A)
Dacomitinib (I, B; MCBS 3)\textsuperscript{e}
Gefitinib/carboplatin/pemetrexed (I, B)\textsuperscript{e}

Disease progression

Oligoprogession

Local treatment (surgery or RT) and continue targeted systemic treatment (IV, C)

Systemic progression

Exon 20 T790M mutation testing:
Re-biopsy or cfDNA plasma testing, with re-biopsy if plasma test is negative (II, A)

Exon 20 T790M mutation positive

Osimertinib (I, A; MCBS 4)\textsuperscript{e}

Exon 20 T790M mutation negative
Or re-biopsy indicated but not feasible

Platinum-based ChT (I, A) (see Figure 2)
Carboplatin/paclitaxel/bevacizumab/atezolizumab (III, A)\textsuperscript{f}
First or second generation TKIs as single agent for patients with EGFR-mutated NSCLC: OS

**LUX-Lung 7:** Comparison of afatinib versus gefitinib in 1L

**ARCHER:** Comparison of dacomitinib versus gefitinib in 1L*

* The hierarchical statistical testing order was PFS followed by ORR and then OS. No formal testing of OS was conducted since the formal comparison of ORR was not statistically significant. However, a descriptive analysis was conducted.
First or third generation TKIs as single agent for patients with EGFR-mutated NSCLC: PFS and OS

**FLAURA:** Comparison of osimertinib versus gefitinib in 1L: PFS

**FLAURA:** Comparison of osimertinib versus gefitinib in 1L: OS

*Soria, NEJM 2018*  
*Ramalingam, ESMO 2019*
CNS response to osimertinib versus standard EGFR tyrosine Kinase inhibitors in patients with untreated EGFR-mutated advanced NSCLC

CNS progression-free survival

Cumulative incidence of CNS progression

Reungwetawattana, JCO 2018
TKIs combined with anti-angiogenic agents for patients with EGFR-mutated NSCLC: PFS

**NEJ026**: Erlotinib and bevacizumab randomized phase III

**Relay**: Erlotinib and ramucirumab randomised phase III

*Saito, Lancet Oncol 2019; Nakagawa, Lancet Oncol 2019*
TKIs combined with platin-based chemotherapy for patients with EGFR-mutated NSCLC: PFS

**NEJ009:** Gefinitiv vs gefitinib, carboplatin and pemetrexed in 1 L

Gefinitiv vs gefitinib, carboplatin, and pemetrexed in 1 L

Hosomi, JCO 2020; Noronha JCO 2019
Systemic therapy for patients with NSCLC with activating EGFR mutations

• First or second generation EGFR inhibitors still represent one standard of care. Osimertinib is indicated in patients with disease progression and documented resistance mutation T790M-

• First line osimertinib provides a superior PFS, better CNS efficacy, and superior survival as compared to first generation EGFR TKIs

• Combinations of first-generation EGFR inhibitors and anti-angiogenic antibodies are associated with longer PFS, however a survival advantage has not yet been demonstrated

• Combinations of first-generation EGFR inhibitors with platin-based chemotherapy are reported to have a superior PFS and OS, however, at least in part this might have been driven by reduced accessibility of later line therapy
Stage IV lung carcinoma with ALK translocation

Alectinib [I, A; MCBS 4]^a
Crizotinib [I, A; MCBS 4]^a
Ceritinib [I, B; MCBS 4]^a
Brigatinib [I, B]^a

Disease progression

Oligoprogression

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

Systemic progression

Systemic progression

Re-biopsy recommended (not mandatory for decision)

After crizotinib:
Alectinib [I, A; MCBS 4]^a
Ceritinib [I, A; MCBS 4]^a
Brigatinib [III, A; MCBS 3]^a

Systemic progression

Systemic progression

Platinum-based ChT (see Figure 2)
Carboplatin/paclitaxel/bevacizumab/atezolizumab [III, B]^a

After at least 1 ALK TKI, other than crizotinib:
Lorlatinib [III, A; MCBS 3]^a
Patients case 2: 62-y/o man

- July 2012: Adenocarcinoma of the lung, stage IIIB with bilateral mediastinal and supraclavicular nodal metastases, EGFR WT, ALK positive
- July – September 2012: Treatment with 3 cycles of carboplatin and pemetrexed
- September 2012: Start of Crizotinib

FISH in initial biopsy: ALK gene rearrangement present

July 2012  November 2012  March 2017
Patient 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
Frequency of brain metastases in fusion gene lung cancer

B

Cumulative incidence of brain metastases

Gray's test p = 0.0039

<table>
<thead>
<tr>
<th>ALK</th>
<th>RET</th>
<th>ROS1</th>
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<tr>
<td>98</td>
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<td>29</td>
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Drilon, JTO 2018
Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in ALK-mutation-positive NSCLC

Overall survival

OS adjusted for post-study treatment
Updated efficacy and safety data from the global phase III ALEX study of alectinib versus crizotinib in untreated advanced ALK+ NSCLC
Systemic therapy for patients with metastatic NSCLC with ALK gene rearrangements

- Crizotinib, certitininib and alectinib are approved by the European Medicines Agency for the first line treatment of patients with ALK translocated NSCLC.
- Ceritinib, alectinib and brigatinib are approved for patients progressing under crizotinib
- Lorlatinib is approved for patients progressing under second generation ALK inhibitos
- The median survival of patients with ALK-positive NSCLC treated with targeted agents exceeds 5 years when patient have access to more than one line of targeted therapy
- Over time, brain metastases will occur in the majority of patients
- Optimal patient management includes stereotactic radiotherapy in case of oligoprogession
SCLC: H&E and immunohistochemistry for neuroendocrine proteins

Fig. 2  (A) Surgical sample of SCLC (HES stain; original magnification ×200). (B) Synaptophysin expression by tumor cells (immunoperoxidase; original magnification ×200). (C) CD56 expression by tumor cells with a typical membraner staining (immunoperoxidase; original magnification ×200). (D) Chromogranin A expression by tumor cells (immunoperoxidase; original magnification ×200).
COCIS IPD meta-analysis: carboplatin vs. cisplatin-based chemotherapy in poor prognosis and/or ED-SCLC

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<tr>
<th></th>
<th>Pts</th>
<th>Events</th>
<th>Median OS (months)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>328</td>
<td>293</td>
<td>9.64</td>
<td>8.72 to 10.7</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>335</td>
<td>296</td>
<td>9.41</td>
<td>8.75 to 10.7</td>
</tr>
</tbody>
</table>

Rossi, JCO 2012
Prophylactic cranial irradiation in ED SCLC

Selection:
- Any type of response
- No evident CNS or leptomeningeal disease

Radiotherapy:
- 20 Gy in 5 or 8 fractions, 24 Gy in 12 fractions
- 25 Gy in 10 fractions
- 30 Gy in 10 or 12 fractions

HR 0.27
HR 0.68

Slotman, NEJM 2007
Prophylactic cranial irradiation versus observation in patients with extensive-disease SCLC: a multicentre, randomised, open-label, phase 3 trial

Selection:
- absence of brain metastases confirmed by within 4 weeks before enrolment
- absence of tumour regrowth confirmed by thoracoabdominal CT within 4 weeks before enrolment

Radiotherapy:
25 Gy in 10 fractions

Takahasi, Lancet Oncol 2017
Thoracic radiotherapy for extensive SCLC: the CREST study

24 months (95% CI)
Thoracic RT: 13 (8.8 - 18.7)
No Thoracic RT: 3 (1.5 - 7.6)
p=0.004

Survival difference @
18 Months: p=0.03
24 Months: p=0.004

Median follow up 24 months
12 months (95% CI)
Thoracic RT: 33% (27–39)
No Thoracic RT: 28% (22–34)
HR = 0.84 (95%CI 0.89–1.01)
p=0.066

Grade 3+ toxicity<5%

Slotman, Lancet 2014
Phase 3 studies of immune checkpoint inhibitors as first line therapy of extensive disease SCLC

Atecolizumab IMpower-133
- SCLC ED N=500
- Atecolizumab + EP
- Primary endpoints: PFS and OS

Pembrolizumab KEYNOTE-604
- SCLC ED N=430
- Pembrolizumab + EP
- Primary endpoints: PFS and OS

Durvalumab CASPIAN
- SCLC ED N=984
- Durvalumab/Tremelimumab
- Durvalumab + EP
- Primary endpoint: PFS and OS

OS positive
- FDA and EMA approved

*OS negative

* Press release January 2020
Systemic therapy for patients extensive disease SCLC

- Carboplatin or cisplatin combined with etoposide remain the backbone of systemic chemotherapy
- PCI for patients with extensive disease remains controversial
- The addition of anti-PD-L1 checkpoint inhibitors atezolizumab or durvalumab combined with chemotherapy and continued as maintenance therapy leads to a small, but significantly improvement in survival
- An open questions regards safety concerns of integrating consolidating thoracic radiotherapy in this situation