Assessing the Evidence for NSCLC Treatment Today

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Conflict of interest (COI)

I have no of conflicts of interest to disclose.
Content

• Metastatic NSCLC: non-oncogene & oncogene-addicted
• Unresectable stage III NSCLC: how to build on the PACIFIC standard?
• Resectable NSCLC: novel perioperative therapies in the clinic
• Metastatic NSCLC
Dual world: non-oncogene & oncogene-addicted
Dual world of metastatic NSCLC clinical & pathological reiew

**TARGETED THERAPY**
Hit the target, not the patient
- Mostly adenocarcinoma
- Never/few smokers
- More females
- Good general conditions
- Cold tumor microenvolvement (e.g. EGFR and ALK driven tumors)

**IMMUNOTHERAPY**
Power of the immune system
- All NSCLC histologies
- Heavy smokers
- More males
- Important comorbidity
- Hot tumor microenvolvement (especially squamous cell carcinoma)

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Image courtesy: Prof. B. Weyand

Pleural biopsy **EGFRmut+ adenocarcinoma**

Bronchial biopsy **squamous cell carcinoma**
Dual world of metastatic NSCLC pathological

Special Articles:

Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

Hendriks et al,
Ann Oncol 34:358-376, 2023
Ann Oncol 34:339-357, 2023
Dual world of metastatic NSCLC non-oncogene addicted

Stage IV NSq/NSSC, molecular tests negative (EGFR/ALK/ROS1/BRAI/RET/MET/EGFR ex20ins/KRAS G12C/NTRK/HER2)* without contraindication for immunotherapy

Oligometastatic

Systemic therapy & LRT [II, B]

ECOG PS and PD-L1 expression level

PS 0-2 and PD-L1 >50%

Pembrolizumab
[I, A, MCBS 5]
Atezolizumab
(also for ICS ≥10%)
[I, A, MCBS 5]
Cemiplimab
[I, A, MCBS 4]
(for PS 2 for all drugs [III, B])

Disease progression?

PS 0-2*

PS 3-4

If 4 cycles of gemcitabine–cisplatin, gemcitabine continuation maintenance [I, C]
Platinum-doublet CHT [I, A] (permetrexed preferred) [II, I, A, MCBS 4]

PS 2 and PD-L1 ≤50%

Disease progression?

PS 0-2*

PS 3-4

Pemetrexed [I, B]
Docetaxel [I, B]
Ninilodipine–docetaxel [I, B]
Ramucirumab–docetaxel [I, B, MCBS 1]*
Re-challenge ICI [III, B]*

PS 0-2*

BSC alone [III, A]

Single-agent CHT [permetrexed] II, B; gemcitabine, vinorelbine or docetaxel [I, B]

PS 0-2* regardless of PD-L1

Nivolumab–ipilimumab (only for PD-L1 ≥1% [I, A, MCBS 4]*

PS 3-4

Dual world of metastatic NSCLC oncogene addicted

Treatment algorithm for stage IV mNSCLC after positive findings on molecular tests

European guidelines initial 4 oncogenes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>30.3%</td>
</tr>
<tr>
<td>ALK</td>
<td>4.4%</td>
</tr>
<tr>
<td>ROS1</td>
<td>1.9%</td>
</tr>
<tr>
<td>BRAF</td>
<td>5.5%</td>
</tr>
<tr>
<td>MET</td>
<td>2.3%</td>
</tr>
<tr>
<td>NTRK</td>
<td>0.5%</td>
</tr>
<tr>
<td>KRAS</td>
<td>2.5%</td>
</tr>
<tr>
<td>KIT</td>
<td>29.9%</td>
</tr>
</tbody>
</table>

EMA approved

Refer to ESMO CPG on non-oncogene-addicted mNSCLC® [II, A]
• Unresectable stage III NSCLC

_How to build on the PACIFIC standard?_
Unresectable stage III NSCLC
the PACIFIC progress

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced NSCLC


Unresectable stage III NSCLC
PACIFIC after 5 years

Unresectable stage III NSCLC lessons from PACIFIC after 5 years

Unresectable stage III NSCLC: how to build on the PACIFIC standard?

<table>
<thead>
<tr>
<th>PACIFIC</th>
<th>Doublet chemotherapy</th>
<th>Radiotherapy 60 – 66 Gy</th>
<th>Durvalumab 1 year</th>
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</thead>
<tbody>
<tr>
<td>CONCURRENT ICI</td>
<td>Doublet chemotherapy</td>
<td>Radiotherapy 60 – 66 Gy</td>
<td>Immunotherapy 1 year</td>
</tr>
<tr>
<td>NEOADJUVANT ICI</td>
<td>Immunotherapy</td>
<td>Doublet chemotherapy</td>
<td>Radiotherapy 60 – 66 Gy</td>
</tr>
<tr>
<td>Combined ICI</td>
<td>Doublet chemotherapy</td>
<td>Radiotherapy 60 – 66 Gy</td>
<td>Immunotherapy 1 year</td>
</tr>
<tr>
<td>De-escalation</td>
<td>Less/No chemotherapy</td>
<td>Radiotherapy lower dose</td>
<td>Immunotherapy shorter duration</td>
</tr>
</tbody>
</table>

• Resectable NSCLC

*Novel perioperative therapies in the clinic*
Resectable NSCLC
the next wave of progress: (neo)adjuvant therapies

Immuno and target therapy in surgical NSCLC

Immuno and target therapy in advanced NSCLC
Resectable NSCLC perioperative therapy

Optimal aim of (neo)adjuvant therapy

- Eliminate (distant) minimal residual disease
- To improve cure rates (~5 Y OS)
- Along with acceptable safety profile

Resectable NSCLC
state of the art

Early and locally advanced NSCLC:
ESMO clinical practice guidelines for
diagnosis, treatment and follow up

Surgery
± ChT

Anatomical resection
(Sleeve) lobectomy, pneumonectomy
Recent RCTs on sublobular resections

Adjuvant platinum doublet ChT
Indicated for stage IIB and IIIA
Can be considered for stage IIB (T>4cm)

Stage according to TNM 8

Resectable NSCLC
RCTs on novel perioperative therapies

IMpower-10 vs. observation
Keynote-091 placebo controlled
ADAURA placebo controlled

Surgery ± ChT

Chemo th
- Atezo for 1 year
- Pembro for 1 year
- Osimertinib up to 3 y

adjuvant
Resectable NSCLC

RCTs on adjuvant Atezolizumab

Stage II – IIIA
HR 0.79 (0.64-0.96) – p=0.02

2022 — EMA approved atezolizumab as adjuvant treatment, following complete resection and platinum-based chemotherapy, for NSCLC with PD-L1 ≥50%

Resectable NSCLC
RCTs on adjuvant Atezolizumab: 5 y OS* report

*follow-up 45 mo [25% maturity]

Felip et al, WCLC 2022
Resectable NSCLC
RCTs on adjuvant Pembrolizumab

All patients
HR 0.76 [0.63-0.91] – P = 0.0014

PD-L1≥50%
HR 0.82 [0.57-1.18] – P = 0.14

*follow-up 36 mo

Resectable NSCLC
RCTs on adjuvant Osimertinib in EGFRmut+ resected NSCLC

2022 — EMA approved osimertinib as an adjuvant treatment after complete resection with stage IB-IIIA NSCLC with EGFR exon 19 deletion or exon 21 (L858R) mutation

Resectable NSCLC
RCTs on adjuvant Osimertinib: OS analysis

Herbst et al, ASCO 2023, abstr LBA3
Resectable NSCLC
RCTs on adjuvant Osimertinib: OS analysis

Herbst et al, ASCO 2023, abstr LBA3
Early stage NSCLC RCTs on novel perioperative therapies

- Checkmate-816 vs. ChT only
- AEGEAN placebo controlled
- KEYNOTE-671 placebo controlled

**neoadjuvant**

**Surgery ± ChT**

- Durva for 12 months
- Pembro for 12 months
Resectable NSCLC
RCTs on neoadjuvant ChT + Nivolumab

HR 0.63 [0.43-0.91]
$P = 0.0052$

Resectable NSCLC
RCTs on neoadjuvant ChT + Nivolumab

Resectable NSCLC
RCTs on neoadjuvant ChT + Nivolumab

May 26, 2023 – CHMP positive advice for Nivolumab in combination with platinum-based chemotherapy for neoadjuvant treatment of resectable NSCLC at high risk of recurrence and with PD-L1 ≥ 1%

Forde et al, ELCC 2023, abstr 840
Resectable NSCLC
RCTs on perioperative ChT + Durvalumab

Heymach et al, AACR 2023, abstr CT005

EFS HR = 0.68 [0.53-0.88] – P=0.0039
Median EFS = NR vs. 25.9 mo

median FU 11.7 mo
Resectable NSCLC
RCTs on perioperative ChT + Pembrolizumab

Wakelee et al, ASCO 2023, abstr LBA100
Take-Home Message No 1

• In unresectable stage III NSCLC treated with CRT, consolidation immunotherapy with Durvalumab was proven to improve cure rates,

• In resectable stage II-IIIA NSCLC with complete resection + adjuvant ChT
  - Adjuvant immunotherapy improved DFS (Atezolizumab EMA approved in PD-L1 ≥50%)

• In resectable stage II-IIIA NSCLC with complete resection + adjuvant ChT
  - Adjuvant osimertinib improved OS in EGFR mutated NSCLC (EMA approved)
  - First trial showing clear OS benefit with targeted therapy in resected NSCLC

• In resectable stage II-IIIB(N2) NSCLC
  - Neoadjuvant chemo-immunotherapy improved EFS compared to ChT alone (Nivolumab now has CHMP recommendation)
  - Similar results are for perioperative chemo-immunotherapy with Durvalumab and Pembrolizumab
Take-Home Message No 2

• Three types of medically fit patients
  – Resectable: most patients with stage I (N0) and stage II (N1)
    • Preferred strategy: direct resection. For N1: adjuvant ChT. Adjuvant ICI if PD-L1 ≥50% *
    * adjuvant therapy may be considered in case of N0 and T >4 cm
  – Potentially resectable: some patients with stage II (N1), some with stage IIIA-B (N2)
    • Preferred strategy: neoadjuvant chemo-immuno therapy → surgery → consolidation ICI to be considered
  – Unresectable: many patients with stage IIIA-B and all with stage IIIC (N3)
    • Preferred strategy: chemoradiotherapy → Durvalumab 1 year

• This judgment REMAINS the unique privilege of your multidisciplinary tumor board
  – Patients considered for neo-adjuvant chemo+ICI should be considered operable upfront by the MDTB
Thank you