Neo-adjuvant and adjuvant systemic treatment of NSCLC

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8TH ESO ARAB AND SOUTHERN EUROPEAN COUNTRIES MASTERCLASS IN CLINICAL ONCOLOGY

23-27 January 2020; Limassol, Cyprus
Disclosure information

The presenter has no conflict of interest to disclose regarding this presentation.
NSCLC stage distribution

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total (N=2609)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>648 (24.9%)</td>
</tr>
<tr>
<td>II</td>
<td>287 (11.0%)</td>
</tr>
<tr>
<td>III</td>
<td>515 (19.8%)</td>
</tr>
<tr>
<td>IV</td>
<td>1153 (44.3%)</td>
</tr>
</tbody>
</table>

Stahel et al., ESMO 2019
Survival of NSCLC patients, stage I-IV

Micro-metastasis is an early event in NSCLC.
Staging and treatment of non-metastatic NSCLC patients

ESMO guidelines; Postmus et al., Ann Oncol 2017
Background: adjuvant vs neoadjuvant Tx

The role of peri-operative chemotherapy is well established

### POTENTIAL ADVANTAGES OF NEO-ADJUVANT VS ADJUVANT THERAPY

<table>
<thead>
<tr>
<th>Advantage</th>
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<tbody>
<tr>
<td>Earlier treatment of micrometastatic disease</td>
</tr>
<tr>
<td>In vivo assessment of treatment response</td>
</tr>
<tr>
<td>Identification of surrogate endpoints for OS or PFS</td>
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<tr>
<td>Shorter time frame to completion of clinical trials</td>
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<tr>
<td>Better tolerability of systemic therapy</td>
</tr>
<tr>
<td>Identification of cohort of patients most likely to benefit from surgical resection</td>
</tr>
</tbody>
</table>

Pignon, J Clin Oncol 2008; Watanabe, J Clin Oncol 2017; Tsao, Ed Book ASCO 2019
5 Randomized trials, > 4,500 pts included.
Overall HR of death was 0.89 (95% CI, 0.82 to 0.96; \( P = 0.005 \));
5-year absolute benefit of 5.4\% from chemotherapy.
Benefit limited to ECOG PS 0-1 & stage II-III pts.

Pignon et al., JCO 2008
1888 pts from 4 trials (IALT, ANITA, BLT, JBR.10); the largest subgroup (41%) in LACE database, and the most homogeneous in terms of drug doses and eligibility.

OS improvement at 5 yrs 8.9% (HR 0.80)

Benefit at 5 years: 14.7% (stage III), 11.6% (stage II), and 1.8% (stage I).

Douillard et al., JTO 2010
Adjuvant chemo with different cisplatin-based regimens

Adjuvant chemotherapy ± bevacizumab in resected NSCLC (E1505): pooled outcomes based on chemotherapy subsets.

Non-squamous NSCLC

Non-randomised
No significant differences

Squamous NSCLC

Non-randomised
No significant differences

Wakelee et al., Lancet Oncol 2017
Adenocarcinoma subtype: benefit from adjuvant chemotherapy (LACE)

575 pts. Benefit in DFS only seen in micropapillary/solid subtype. No difference in OS benefit with adjuvant chemo according to histologic subgroups.

Tsao et al., J Clin Oncol 2015
Adjuvant chemo for elderly pts

2.763 pts ≥ 70 yrs treated with surgery (2001-2006).

Increasing use of adjuvant CT in this population from 3.3% (2001-2003) to 16.2% (2004-6). Signals of increased survival in the more recent cohorts.
The OS benefit was for all categories but not for those who were > 80 yrs old.

Comprehensive geriatric assessment is suggested!
### Summary of recommendations

<table>
<thead>
<tr>
<th>Adjuvant chemotherapy</th>
<th>LoE, GoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should be offered in resected stage II and III patients</td>
<td>I, A</td>
</tr>
<tr>
<td>Should be discussed in resected stage IB patients with primary tumour &gt;4cm</td>
<td>II, B</td>
</tr>
<tr>
<td>Pre-existing comorbidity, time from surgery and postoperative recovery should be evaluated by an MDT</td>
<td>V, A</td>
</tr>
<tr>
<td>A two-drug combination with cisplatin is preferable (cisplatin/vinorelbine is the most frequently studied regimen)</td>
<td>I, A</td>
</tr>
</tbody>
</table>

Postmus et al., Ann Oncol 2017
### Improving adjuvant treatments: strategies

1. **Pharmacogenomic approach**
2. **Targeted therapy (VEGF-R, EGFR)**
3. **Immunotherapy**

<table>
<thead>
<tr>
<th></th>
<th>Stage IB</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Die despite chemo</td>
<td>33</td>
<td>51</td>
<td>61</td>
</tr>
<tr>
<td>Alive due to surgery</td>
<td>64</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>Alive due to chemo</td>
<td>3</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>
Study objective: To compare adjuvant pharmacogenomic-driven (personalised) chemotherapy, based on thymidylate synthase (TS) and excision-repair cross-complementing-1 (ERCC1) gene expression versus standard adjuvant chemotherapy.

Key patient inclusion criteria
- Completely resected NSCLC
- Stage II–IIIA
- ECOG PS 0–1
- Stratification: stage II vs III, smoking status

Primary endpoint
- OS (5-year rate)

Secondary endpoints
- Disease-free interval (DFI), toxicity

N= 761

Profile 1: ERCC1 low, TS low
- Cis/pem
- Control

Profile 2: ERCC1 low, TS high
- Cis/gem
- Control

Profile 3: ERCC1 high, TS low
- Pemetrexed
- Control

Profile 4: ERCC1 high, TS, high
- Taxanes
- Control

Buffoni et al. Curr Treat Opin Oncol 2016
Targeting VEGF: adjuvant bevacizumab (ECOG 1505 trial)

Study objective: To evaluate the addition of bevacizumab to adjuvant chemotherapy in early stage resected NSCLC.

Key patient inclusion criteria

- Resected
- Stage IB (≥4cm)–IIIA
- 6–12 weeks post-op
- No prior chemotherapy
- ECOG PS 0–1

*Chemotherapy regimens q3w
Cisplatin 75 mg/m² D1 combined with any of the following:
- vinorelbine 30 mg/m² D1, 8
- docetaxel 75 mg/m² D1
- gemcitabine 1200 mg/m² D1, 8
- pemetrexed 500 mg/m² D1

N: 1501

Chemotherapy* x 4 cycles (n=749)

Stratification: cisplatin doublet, stage, histology, gender

Chemotherapy* x 4 cycles + bevacizumab 15 mg/kg q3w x 1 yr (n=752)

Primary endpoint: OS
Secondary endpoints: DFS, safety

Wakelee et al., Lancet Oncol 2017
The addition of bevacizumab to adjuvant chemotherapy failed to improve survival for patients with surgically resected early stage NSCLC. Increased toxicity and treatment withdrawals.

**OS**
- OS FR (B:A): 0.99
- 95%CI 0.81, 1.21
- p=0.93

**DFS**
- DFS HR (B:A) 0.98
- 95%CI 0.84, 1.14
- p=0.75

Targeting VEGF: adjuvant bevacizumab (ECOG 1505 trial)

Wakelee et al., ASCO 2016 & Lancet Oncol 2017
Targeting EGFR: adjuvant gefitinib – BR19 and RADIANT trials

NO BIOLOGICAL SELECTION based on EGFRmut; in RADIANT, 161 pts/973 were EGFRmut.
Targeting EGFR: adjuvant gefitinib– ADJUVANT Study

**Key patient inclusion criteria**
- Completely resected stage II–IIIA (N1–N2) NSCLC
- No PET CT required at baseline
- EGFR-activating mutation*
- ECOG PS 0–1
  (n=220)

**Primary endpoint**
- DFS

**Gefitinib 250 mg/day**
- 24 months (n=111)
  - PD/toxicity

**Vinorelbine 25 mg/m² D1, 8**
- cisplatin 75 mg/m² D1 q3w (up to 4 cycles)
  (n=111)
  - PD

**Secondary endpoints**
- OS, safety, HRQoL

* del19 or L858R(21)

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Zhong et al., Lancet Oncol 2018
mDFS 28.7 vs 18.0 mos; 3y-DFS 34% vs 27% (HR 0.60)
AEs G≥3 12.3% vs 48.3%

OS data non mature, but at 36 mos DFS curves collide, with no “non progressor tail”

Zhong et al., Lancet Oncol 2018
Meta-analysis of adjuvant EGFR-TKIs

A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer

Hua Cheng, Xiao-Jian Li, Xiao-Jin Wang, Zuo-Wen Chen, Rui-Qi Wang, Hong-Cheng Zhong, Tian-Chi Wu, Qing-Dong Cao*

Department of Thoracic Surgery, The 4th Affiliated Hospital of Sun Yat-Sen University, China

5 RCTs: 3 vs placebo, 2 vs chemotherapy

**DFS in EGFRmut patients:**
- HR 0.59 (95%CI 0.40-0.88), p=0.009 vs PLACEBO
- HR 0.42 (95%CI 0.19-0.93), p=0.03 vs CHEMOTHERAPY

Treatment was not active in EGFRwt population.

Cheng et al., Lung Cancer 2019
The ALCHEMIST trials (EGFRmut & ALKrearr)

Govindan et al., Clinical Cancer Res 2015
ADAURA study: adjuvant osimertinib

**ADAURA: A Phase III Study of Osimertinib versus Placebo for EGFR Mutation-Positive Stage IB-IIIA NSCLC After Complete Tumor Resection with or without Adjuvant Chemotherapy**

**Eligibility (N = 700)**
- Stage IB-IIIA EGFR mutation-positive NSCLC

**Primary Endpoint:** Disease-free survival
**Key Secondary Endpoints:** Overall survival and quality of life

- **Osimertinib**
  - Until disease recurrence or maximum 3 years

- **Placebo**

**Wu et al., Clin Lung Cancer 2018**
Adjuvant trials with ICIs

ANVIL (primary endpoints: DFS, OS)
- Registered to the ALCHEMIST-SCREEN trial (NCT02194738) prior to randomisation
- Complete surgical resection of stage Ib–IIa NSCLC with negative surgical margins
- Prior adjuvant chemotherapy
- No prior checkpoint inhibitor therapy
- N=714

PEARLS (primary endpoint: DFS)
- Stage Ib–IIa NSCLC
- Complete surgical resection with resection margins microscopically free of disease (R0)
- Adjuvant therapy (maximum of 4 cycles)
- N=1400

IMpower010 (primary endpoint: DFS)
- Resected Stage Ib–IIA NSCLC
- Cisplatin + pemetrexed, docetaxel, or vinorelbine up to 4 cycles
- N=717
- Atezolizumab 1200mg q21d (16 cycles)
- No Crossover
- Best supportive care

BR31 (primary endpoint: DFS in PD-L1+)
- Stage Ib–IIa NSCLC
- Complete surgical resection of primary tumour with negative surgical margins
- Prior adjuvant chemotherapy is allowed
- No neoadjuvant chemotherapy or other anticancer therapy
- N=1100
- Durvalumab (up to 1 year)
- Placebo
Treatment of pathological N2 non-metastatic NSCLC patients

**Single-station N2 disease**
- Resection followed by adjuvant chemotherapy
  - OR
  - Induction chemotherapy followed by surgery
  - OR
  - Induction CRT followed by surgery
  - PORT is an option if induction chemotherapy given alone before surgery

**Multistation N2 or N3 disease**
- Concurrent definitive CRT is preferred
- Experienced MDT is important when determining strategy, including surgical options

ESMO guidelines; Postmus et al., Ann Oncol 2017
Significant benefit of preoperative chemotherapy on survival (hazard ratio [HR] 0.87, 95% CI 0.78–0.96, p=0.007).

Absolute survival improvement of 5% at 5 years, from 40% to 45%.

No clear evidence of a difference in the effect on survival by chemotherapy regimen or scheduling, number of drugs, platinum agent used, or whether postoperative radiotherapy was given.

15 R trials, 2385 pts
Neoadjuvant CRT in stage III resectable NSCLC

Pless et al., Lancet 2015
MAJOR PATHOLOGICAL RESPONSE (Defined as < 10% viable cancer cells)

Pataer et al., J Thor Oncol 2012

Hellmann et al., Lancet Oncol 2014; Pataer et al., J Thor Oncol 2012; Blumenthal et al., J Thor Oncol 2018
Targeting EGFR: neoadjuvant erlotinib (EMERGING/CTONG1103 Study)

Zhong et al., J Clin Oncol 2019

* del19 or L858R(21)
EMERGING/CTONG1103 Study: radiological response

Erlotinib

Chemo (GC)

ORR

OR (95% CI)  P
2.26 [0.87-5.84]  0.092

Enrolled number

54.1% [37.2%-70.9%]

34.3% [17.7%-60.8%]

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib</th>
<th>GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>3 (8.1%)</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (35.1%)</td>
<td>15 (42.9%)</td>
</tr>
<tr>
<td>PR</td>
<td>20 (54.1%)</td>
<td>12 (34.3%)</td>
</tr>
</tbody>
</table>

Zhong et al., J Clin Oncol 2019
**EMERGING/CTONG1103 Study: surgery & pathology**

50 surgical resected specimens were available, No pCR cases in both groups.

**Safety results consistent with prior studies.**

**Table:**

<table>
<thead>
<tr>
<th>Type of resection</th>
<th>Erlotinib group (n=37)</th>
<th>GC group (n=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, n (%)</td>
<td>31 (83.8)</td>
<td>24 (68.6)</td>
<td>0.129</td>
</tr>
<tr>
<td>Complete resection, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>27 (73.0)</td>
<td>22 (62.9)</td>
<td>0.358</td>
</tr>
<tr>
<td>R1</td>
<td>1 (2.7)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>3 (8.1)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Lymph node downstage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2→pN0</td>
<td>3 (8.1)</td>
<td>1 (2.9)</td>
<td>0.185</td>
</tr>
<tr>
<td>N2→pN1</td>
<td>1 (2.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>N2→pN2</td>
<td>27 (73.0)</td>
<td>23 (65.7)</td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**

The major pathological response (MPR)

- Erlotinib: 25
- GC: 22

Zhong et al., J Clin Oncol 2019
EMERGING/CTONG1103 Study: survival outcome

Zhong et al., J Clin Oncol 2019

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LCMC4: Screening patients with suspected early-stage NSCLC for actionable oncogene targets

1000 pts who are candidates for neoadjuvant therapy

Resectable IB-IIIB (8th ed) Enroll with local genotyping or ctDNA

Major and Complete pathologic response rates Correlates in persister cells Adjuvant therapy -investigator’s choice followed by personalized strategies per future research studies

Blumenthal et al., J Thor Oncol 2018
# Neo-adjuvant immunotherapy in NSCLC: preliminary data

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent</th>
<th># Patients</th>
<th>ORR</th>
<th>MPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forde et al. NEJM 2018</td>
<td>Nivolumab 2 cycles</td>
<td>21 IB-IIIA</td>
<td>10% PR 86% SD</td>
<td>45%</td>
</tr>
<tr>
<td>Kwiatkowsky et al. ASCO 2019</td>
<td>Atezolizumab 2 cycles</td>
<td>77 IB-IIIA</td>
<td>NR</td>
<td>19%</td>
</tr>
<tr>
<td>Cascone et al. ESMO 2018</td>
<td>Nivolumab 3 cycles</td>
<td>16 IB-IIIA</td>
<td>31% PR 50% SD</td>
<td>28%</td>
</tr>
<tr>
<td>Cascone et al. ESMO 2018</td>
<td>Nivolumab + Ipilimumab</td>
<td>16 IB-IIIA</td>
<td>12% PR 69% SD</td>
<td>33%</td>
</tr>
</tbody>
</table>

**ORR:** radiological response; **MPR:** major pathological response

**MPR 19-45%**
### Neo-adjuvant chemo/immunotherapy in NSCLC: the NADIM study

#### A phase II multicenter exploratory study—SLCG (46 pts)

**NSCLC IIIA resectable**

- N2 or T4N0/N1

**Neoadjuvant treatment**

- Nivolumab 360mg + Paclitaxel 200mg/m² + Carboplatin AUC 6
  - Q3W
  - 3 cycles

**Surgery**

During Week 3 or 4 from Day 21 cycle 3 of neoadjuvant treatment

**Adjuvant treatment**

- Nivolumab 240mg Q2W for 4 months
- Nivolumab 480mg Q4W for 8 months
  - 1 year

**Follow up**

(3 years)

#### Primary endpoint: PFS at 24 months

**Radiological response rate (N=46)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>3 (6.5%)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>33 (72%)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>8 (17.5%)</td>
</tr>
</tbody>
</table>

**Pathological response rate (N=41)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR</td>
<td>35 (85.36%)</td>
</tr>
<tr>
<td>CPR</td>
<td>25 (71.4%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (14.6%)</td>
</tr>
</tbody>
</table>

*Provencio et al., ASCO 2019*
Neo-adjuvant chemo/immunotherapy in NSCLC: atezolizumab

Target accrual: 30 pts

Pathological response

MPR: 50%
CPR: 21%

Shu et al., ASCO 2018
Neo-adjuvant immunotherapy in NSCLC: randomized trials

IMpower030 (primary endpoint: MPR/EFS)
- Atezolizumab + Pt-chemo
- Placebo + Pt-chemo
- Surgery and pathological response assessment (MPR, pCR)
- Atezolizumab
- BSC
- Survival follow-up

AEGEAN (primary endpoint: MPR)
- Durvalumab + Pt-chemo
- Placebo + Pt-chemo
- Surgery and pathological response assessment
- Durvalumab
- Placebo

CHECKMATE 77T (primary endpoint: EFS)
- Nivolumab + Pt-chemo
- Placebo + Pt-chemo
- Surgery
- Nivolumab

CHECKMATE 816 (primary endpoint: EFS/CPR)
- Nivolumab + Pt-chemo
- Platinum-based chemotherapy
- Surgery and pathological response assessment

KEYNOTE-671 (primary endpoint: EFS/OS)
- Pembrolizumab + Pt-chemo 4 cycles
- Placebo + Pt-chemo 4 cycles
- Surgery and pathological response assessment
- Pembrolizumab 13 cycles
- Placebo 13 cycles

Stahel, 2019
Conclusions - Take home messages

1. Treatment of early stage and locally advanced NSCLC requires a multi-disciplinary team approach. Results of lymph node radiological and pathological evaluation are mandatory in defining which treatment a patient will receive.

2. Adjuvant chemotherapy with cisplatin-based doublets remains the standard of care in fit patient with completely resected stage II-III NSCLC. No established role of pharmaco-genomic approach and targeted therapy. Immunotherapy with ICIs under evaluation.

3. Neoadjuvant chemotherapy improves survival by a similar extent of adjuvant treatment, but with weaker evidence from randomized trials.

4. Neoadjuvant immunotherapy (+/- chemotherapy) can induce high rates of MPR in resectable NSCLC and show potential to improve survival outcomes.

ESMO GUIDELINES: Postmus et al., Ann Oncol 2017