PERIOPERATIVE TREATMENT OF NON-SMALL CELL LUNG CANCER
An update

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LEARNING OBJECTIVES

To understand the potential of perioperative treatments

To identify patients who should receive perioperative treatment for NSCLC

To choose the most appropriate perioperative treatment

To know the modalities of delivery for perioperative treatments
PERIOPERATIVE TREATMENTS IN NSCLC

In EGFR wild-type NSCLC
- Perioperative chemotherapy
- Preoperative chemoradiation
- Perioperative targeted treatments
- Perioperative immunotherapy
- Postoperative mediastinal radiotherapy

In EGFR mutated NSCLC
- Adjuvant EGFR TKI vs. chemotherapy
- Adjuvant EGFR TKI after chemotherapy
ADJUVANT CHEMOTHERAPY: SURVIVAL RESULTS 1
(Individual patient data meta-analysis)

Simple non-stratified Kaplan-Meier curves for trials of surgery (S) and chemotherapy (CT) vs. surgery alone and for trials of surgery and chemotherapy and radiotherapy (RT) versus surgery and radiotherapy

THE CISPLATIN-BASED ADJUVANT CHEMOTHERAPY META-ANALYSIS

By stage for cisplatin-vinorelbine vs. observation (no chemotherapy) groups

• Significant interaction between chemotherapy effect and stage (test for trend, p=0.04 for OS. No longer significant if small group of patients with stage IA [n=104] excluded [p=0.35 for OS])

ADJUVANT CHEMOTHERAPY IN STAGE IB NSCLC


ADJUVANT CHEMOTHERAPY: WHICH DRUGS? WHICH DOSES?


*Test for trend
TIMING OF ADJUVANT CHEMOTHERAPY

12,473 patients
US National cancer database

Cox proportional hazards model of patients who underwent adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Covariate</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjuvant chemotherapy timing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference interval (39–56 d)</td>
<td>5137</td>
<td>[Reference]</td>
<td></td>
</tr>
<tr>
<td>Earlier (&lt;39 d)</td>
<td>3359</td>
<td>1.009 (0.944-1.080)</td>
<td>0.79</td>
</tr>
<tr>
<td>Later (&gt;56 d)</td>
<td>3977</td>
<td>1.037 (0.972-1.105)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

3976 propensity-match pairs:
- HR=0.664 (95% CI: 0.623, 0.707; p<0.001)
- >56 days vs. no chemotherapy

NEOADJUVANT CHEMOTHERAPY: SURVIVAL RESULTS 1
(Individual patient data meta-analysis)

<table>
<thead>
<tr>
<th>Country</th>
<th>Preoperative chemotherapy*</th>
<th>Control*</th>
<th>O-E</th>
<th>Variance</th>
<th>HR (95% CI): p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>France 1990</td>
<td>8/13</td>
<td>8/13</td>
<td>0.32</td>
<td>3.97</td>
<td></td>
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<tr>
<td>MD Anderson 1994</td>
<td>19/28</td>
<td>27/32</td>
<td>-6.40</td>
<td>11.19</td>
<td></td>
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<tr>
<td>Spain 1994</td>
<td>19/29</td>
<td>27/30</td>
<td>-8.88</td>
<td>9.65</td>
<td></td>
</tr>
<tr>
<td>MIP-91</td>
<td>13/17/9</td>
<td>14/16/26</td>
<td>-12.99</td>
<td>70.22</td>
<td></td>
</tr>
<tr>
<td>SWOG 59015</td>
<td>3/5</td>
<td>12/16</td>
<td>-1.04</td>
<td>2.94</td>
<td></td>
</tr>
<tr>
<td>JCOG 9209</td>
<td>28/31</td>
<td>25/31</td>
<td>2.25</td>
<td>12.97</td>
<td></td>
</tr>
<tr>
<td>Finland 2003</td>
<td>19/30</td>
<td>19/32</td>
<td>-0.59</td>
<td>9.48</td>
<td></td>
</tr>
<tr>
<td>MRC BLT</td>
<td>4/5</td>
<td>3/5</td>
<td>1.26</td>
<td>1.60</td>
<td></td>
</tr>
<tr>
<td>MRC LU22</td>
<td>15/25/8</td>
<td>15/8/26</td>
<td>-2.92</td>
<td>77.01</td>
<td></td>
</tr>
<tr>
<td>SWOG 59900</td>
<td>93/180</td>
<td>103/174</td>
<td>-9.31</td>
<td>48.84</td>
<td></td>
</tr>
<tr>
<td>China 2002</td>
<td>26/32</td>
<td>18/23</td>
<td>1.42</td>
<td>10.78</td>
<td></td>
</tr>
<tr>
<td>China 2005</td>
<td>8/19</td>
<td>14/21</td>
<td>-3.31</td>
<td>5.44</td>
<td></td>
</tr>
<tr>
<td>CHEST</td>
<td>45/129</td>
<td>61/141</td>
<td>-10.27</td>
<td>26.39</td>
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</tr>
<tr>
<td>NATCH</td>
<td>99/201</td>
<td>109/212</td>
<td>-4.11</td>
<td>50.78</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>682/1178</td>
<td>749/1207</td>
<td>-50.62</td>
<td>351.78</td>
<td></td>
</tr>
</tbody>
</table>

Overall HR
0.87 (0.78-0.96), p=0.007 (fixed effect)
0.86 (0.75-0.98), p=0.03 (random effects)
Heterogeneity: $\chi^2=18.75$, df=14, p=0.18, I²=25%

0.87 (0.78-0.96); p=0.007
NEOADJUVANT CHEMOTHERAPY: SURVIVAL RESULTS 2

Kaplan-Meier curves (non-stratified) of the effect of preoperative chemotherapy on time to survival

13% reduction in the relative risk of death
+ 5% at 5 years
WHO SHOULD RECEIVE NEOADJUVANT CHEMOTHERAPY?

<table>
<thead>
<tr>
<th>Interaction HR (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

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ADJUVANT OR NEOADJUVANT CHEMOTHERAPY VS. SURGERY

A meta-analysis

ADJUVANT OR NEOADJUVANT?

Phase 3
- 624 patients
- IA (>2 cm)
- IB, II, T3N1

Paclitaxel 200 mg/m² + carboplatin AUC 6 q3w
Main objective: PFS at 5-year chemotherapy vs. surgery

## ADJUVANT OR NEOADJUVANT?

### COMPLIANCE

<table>
<thead>
<tr>
<th>Trials</th>
<th>At least 1 cycle</th>
<th>2 cycles</th>
<th>3 cycles</th>
<th>4 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>90%</td>
<td>ND</td>
<td>69%</td>
<td>NA</td>
</tr>
<tr>
<td>IALT</td>
<td>92%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>ANITA</td>
<td>90%</td>
<td>72%</td>
<td>61%</td>
<td>50%</td>
</tr>
<tr>
<td>JBR10</td>
<td>95.5%</td>
<td>64%</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>NATCH adj</td>
<td>66%</td>
<td>ND</td>
<td>61%</td>
<td>NA</td>
</tr>
<tr>
<td>Depierre</td>
<td>98%</td>
<td>90%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NATCH neoadj</td>
<td>97%</td>
<td>ND</td>
<td>90%</td>
<td>NA</td>
</tr>
<tr>
<td>Gilligan</td>
<td>96%</td>
<td>89%</td>
<td>96%</td>
<td>NA</td>
</tr>
<tr>
<td>SWOG 9900</td>
<td>ND</td>
<td>ND</td>
<td>79%</td>
<td>NA</td>
</tr>
</tbody>
</table>
### RESPECTIVE ADVANTAGES OF (NEO)ADJUVANT CHEMOTHERAPY

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of evidence</strong></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Staging</strong></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Earlier delivery</strong></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Evaluation of tumour response</strong></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Research purposes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tissue availability</strong></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>
PERIOPERATIVE TREATMENTS IN NSCLC

In EGFR wild-type NSCLC
- Perioperative chemotherapy
- **Preoperative chemoradiation**
- Perioperative targeted treatments
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PREOPERATIVE CHEMORADIATION FOR STAGE IIIA N2

Multicentre Phase 3
Pathologically proven stage IIIAN2
1:1 randomisation
Cisplatin docetaxel
+/- sequential RT
(44 Gy / 22 F / 3 wk)
Primary endpoint:
event-free survival

HR=1.1 (95% CI: 0.8, 1.4); p=0.67

PREOPERATIVE CHEMORADIATION FOR STAGE IIIA N2:
OVERALL SURVIVAL

HR=1 (95% CI: 0.7, 1.4)

PERIOPERATIVE TREATMENTS IN NSCLC

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  - Perioperative immunotherapy
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- Adjuvant EGFR TKI after chemotherapy
ADJUVANT GEFITINIB IN ALL-COMERS (BR19)


Stage IB, II, IIIA completely resected
Trial prematurely closed
Gefitinib x 2 year
ADJUVANT ERLOTINIB IN ALL-COMERS

Primary endpoint: DFS

Phase 3 trial

Adjuvant erlotinib (2 year) vs. placebo

pStage IB-IIIA

OS: HR=1.09 (95% CI: 0.545, 2.161; p=0.815)

**ADJUVANT BEVACIZUMAB**

*Investigator choice of 4 chemotherapy regimens*

21-day cycles all with cisplatin given at 75 mg/m$^2$ on Day 1
- Cisplatin / Vinorelbine: 30 mg/m$^2$ Day 1, 8
- Cisplatin / Docetaxel: 75 mg/m$^2$ Day 1
- Cisplatin / Gemcitabine: 1200 mg/m$^2$ Day 1, 8
- Cisplatin / Pemetrexed: 500 mg/m$^2$ Day 1 (2009 amendment)

**Bevacizumab** 15 mg/kg IV q3w for up to 1 year

**Primary endpoint:** Overall survival

ADJUVANT BEVACIZUMAB

PERIOPERATIVE TREATMENTS IN NSCLC

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MAGE A-3 VACCINE IN MAGE A-3+ NSCLC: DFS

Resected stage I, II, IIIA NSCLC - 13 intramuscular injections in 27 months - Primary endpoint: DFS

# NeoAdjuvant Monotherapy IO in Phase 2 Studies of Resectable NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02259621 N=22</th>
<th>IONESCO N=50</th>
<th>NEOSTAR N=23/21</th>
<th>LCMC3 N=181</th>
<th>PRINCEPS N=29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Nivolumab 3 mg/kg D-28&amp;14</td>
<td>Durvalumab 750 mg D1, 15, 29</td>
<td>Nivolumab 3 mg/kg q2w x3 or Nivo-Ipilimumab (1 mg/kg)</td>
<td>Atezolizumab 1200 mg q3w x2</td>
<td>Atezolizumab 1200 mg 1cycle</td>
</tr>
<tr>
<td>Stages</td>
<td>I-IIIA</td>
<td>IB (4 cm) – IIIA (non N2)</td>
<td>I-IIIA</td>
<td>IB - IIIB</td>
<td>IB-IIIA</td>
</tr>
<tr>
<td>MPR (≤10 viable cells)</td>
<td>45%</td>
<td>18.6%</td>
<td>N : 22% / NI: 38%</td>
<td>21% (/144pts)</td>
<td>14%</td>
</tr>
<tr>
<td>pCR</td>
<td>15%</td>
<td>7%</td>
<td>N: 9% / NI: 29%</td>
<td>7%</td>
<td>0</td>
</tr>
<tr>
<td>OS</td>
<td>1-yr: 89.1</td>
<td>1-yr: St I-II 92% St III 95%</td>
<td>13% / NI: 10%</td>
<td>Preop:6% Postop:14%</td>
<td>0</td>
</tr>
<tr>
<td>TRAE ≥G3</td>
<td>4.5%</td>
<td>0</td>
<td>13% / NI: 10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHECKMATE 816: NEOADJUVANT CHEMOTHERAPY + IMMUNOTHERAPY

ELIGIBLE:
Resectable
Stage IB-IIIA NSCLC
ECOG ≤1
Available tissue of lung tumour

Primary outcomes
pCR, EFS

Secondary outcomes
OS
MPR
Time to death or distant metastases
Safety

Nivolumab + Ipilimumab (exploratory)

Nivolumab 360 mg + histology-based platinum doublet q3w up to 3 doses

Surgery within 6 weeks

Optional adjuvant chemotherapy +/- radiotherapy

Histology-based platinum doublet q3w up to 3 doses

CHECKMATE 816, PRIMARY ENDPOINT: pCR, ITT RESULTS


pCR rate in the exploratory nivolumab + ipilimumab arm (ITT): 20.4% (95% CI: 13.4, 29.0)
G5 in 2 patients in the NIVO + chemo arm (unrelated to study drug):
1 pulmonary embolism, 1 aortic rupture

## Ongoing Phase 3 Trials of Neoadjuvant Immune Checkpoint Inhibitors (IO) and Chemotherapy and Adjuvant IO

<table>
<thead>
<tr>
<th>Drug (trial)</th>
<th>Control</th>
<th>Stages</th>
<th>PD-L1</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo-Pembrolizumab and adjuvant Pembrolizumab (Keynote 671)</td>
<td>Chemo-placebo and placebo</td>
<td>II, IIIA, IIIB N2</td>
<td>all</td>
<td>EFS/OS</td>
</tr>
<tr>
<td>Chemo-Durvalumab and adjuvant Durvalumab (AEGEAN)</td>
<td>Chemo-placebo and placebo</td>
<td>IIA to select IIIB (N2)</td>
<td>all</td>
<td>pCR*/EFS</td>
</tr>
<tr>
<td>Chemo-Atezolizumab and adjuvant Atezolizumab (IMpower030)</td>
<td>Chemo-placebo and placebo</td>
<td>II, IIIA, select IIIB (T3N2 only)</td>
<td>all</td>
<td>Independent Review Facility-assessed EFS</td>
</tr>
</tbody>
</table>

EFS, Event-Free Survival; pCR, pathological Complete Response
IMPOWER 010:
ADJUVANT IMMUNOTHERAPY

**Press release (March 22, 2021):** Impower 010 met its primary endpoint of PFS in stage II-IIIA at the interim analysis. The magnitude of the effect was particularly pronounced in the PD-L1 positive population. No new safety signal.


**ELIGIBLE:**
- Completely resected
- Stage IB (≥4 cm)-IIIA NSCLC (TNM 7)
- ECOG ≤1
- Tumour tissue available for PD-L1 analysis

**Primary outcomes** (hierarchical testing)
- Inv-assessed DFS:
  - Stage II-IIIA PDL1 ≥1%
  - All stage II-IIIA
  - ITT all st IB-IIIA

**Atezolizumab**
1200 mg q3w up to 16 cycles

**Cisplatin-based chemotherapy**
x4 cycles

**N=1005**
1:1

**BSC**
Reprinted from The Lancet, 398, Felip E, et al., Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial, 1344-1357, Copyright 2021, with permission from Elsevier.
<table>
<thead>
<tr>
<th>n (%)</th>
<th>Atezolizumab (n=495)</th>
<th>BSC (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-cause AE</td>
<td>459 (92.7)</td>
<td>350 (70.7)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>335 (67.7)</td>
<td>-</td>
</tr>
<tr>
<td>Grade 3-4 AE</td>
<td>108 (21.8)</td>
<td>57 (11.5)</td>
</tr>
<tr>
<td>Treatment-related grade 3-4 AE</td>
<td>53 (10.7)</td>
<td>-</td>
</tr>
<tr>
<td>Serious AE</td>
<td>87 (17.6)</td>
<td>42 (8.5)</td>
</tr>
<tr>
<td>Treatment-related serious AE</td>
<td>37 (7.5)</td>
<td>-</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>8 (1.6)(b)</td>
<td>3 (0.6)(c)</td>
</tr>
<tr>
<td>Treatment-related grade 5 AE</td>
<td>4 (0.8)</td>
<td>-</td>
</tr>
<tr>
<td>AE leading to dose interruption of atezolizumab</td>
<td>142 (28.7)</td>
<td>-</td>
</tr>
<tr>
<td>AE leading to atezolizumab discontinuation</td>
<td>90 (18.2)</td>
<td>-</td>
</tr>
<tr>
<td>Immune-mediated AEs</td>
<td>256 (51.7)</td>
<td>47 (9.5)</td>
</tr>
<tr>
<td>Grade 3-4 immune-mediated AEs</td>
<td>39 (7.9)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Immune-mediated AEs requiring the use of systemic corticosteroids</td>
<td>60 (12.1)</td>
<td>4 (0.8)</td>
</tr>
</tbody>
</table>
## Ongoing Phase 3 Trials of Adjuvant Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Drug (trial)</th>
<th>Control</th>
<th>Stages</th>
<th>PD-L1</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (ALCHEMIST/ANVIL – US NCI)</td>
<td>Observation</td>
<td>IB (4 cm) – IIIA, after adjuvant chemo and/or radiotherapy</td>
<td>All</td>
<td>OS/DFS</td>
</tr>
<tr>
<td>MEDI 4736 (international/CCTG BR31)</td>
<td>Placebo</td>
<td>IB (4 cm) – IIIA, after adjuvant chemo</td>
<td>All</td>
<td>DFS</td>
</tr>
<tr>
<td>Pembrolizumab (Keynote 091 – EORTC/ETOP)</td>
<td>Placebo</td>
<td>IB (4 cm) – IIIA, after adjuvant chemo</td>
<td>All</td>
<td>DFS</td>
</tr>
</tbody>
</table>
PERIOPERATIVE TREATMENTS IN NSCLC

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- **Postoperative mediastinal radiotherapy**

In EGFR mutated NSCLC

- Adjuvant EGFR TKI vs. chemotherapy
- Adjuvant EGFR TKI after chemotherapy
POSTOPERATIVE RADIOTHERAPY: THE UPDATED META-ANALYSIS

IPD meta-analysis
11 trials / 2343 patients
HR=1.18
18% relative increase in risk of death
Absolute detriment: 5% at 2 year (95% CI: 2, 9%)
Reducing survival from 58 to 53%

LS2 postoperative radiotherapy for non-small cell lung cancer
Postoperative radiotherapy may be detrimental in earlier stages
POSTOPERATIVE RADIOThERAPY

In the Adjuvant Navelbine International Trialist Association (ANITA) trial

Overall survival according to treatment received in the pN1 patients

Overall survival according to treatment received in the pN2 patients

Lung ART IFCT05-03

Eligible:
Pre and/or postoperative chemotherapy accepted

Primary endpoint:
Disease-free survival

Complete resection
Pathological N2

R
1:1

Conformational radiotherapy
(54 Gy/5.5 weeks)

Control

Lung ART IFCT05-03: DFS RESULTS

95% CI, 95% bilateral Confidence Interval.
Lung ART IFCT05-03: OS RESULTS

Overall survival (secondary endpoint; ITT)

<table>
<thead>
<tr>
<th>Control arm (n=249)</th>
<th>PORT arm (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td></td>
</tr>
<tr>
<td>102 (41.5%)</td>
<td>99 (39.6%)</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
</tr>
<tr>
<td>Progression or recurrence</td>
<td>87 (86.1%)</td>
</tr>
<tr>
<td>Cardio-pulmonary</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>Second primary</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>RT or CT related toxicity</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Overall survival rates at 3 years
Control arm: 67% (95% CI: 59, 73)
PORT arm: 66% (95% CI: 61, 75)

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PHASE 3 TRIALS OF ADJUVANT TKI VS. CHEMOTHERAPY

Inclusion criteria:
Completely resected stage II-III NSCLC, common EGFR activating mutations (exon 19 del, L858R), ECOG PS 0-1, <75 years

CTONG 1104¹

- Gefitinib 250 mg/day for 24 months or until disease progression or unacceptable toxicity
- Vinorelbine (25 mg/m² Days 1 and 8) plus cisplatin (75 mg/m² Day 1) every 3 weeks, for 4 cycles
- Primary endpoint: DFS
- Secondary endpoints: 3-year DFS rate, 5-year DFS rate, OS, 5-year OS rate, safety, HRQoL (FACT-L, LCSS, TOI), exploratory biomarker analyses

IMPACT WJOG6410L²

- Gefitinib 250 mg/day for 24 months or until disease progression or unacceptable toxicity
- Cisplatin 80 mg/m² Day 1 plus vinorelbine 25 mg/m² Days 1 and 8 every 3 weeks, for 4 cycles
- Primary endpoint: DFS by BICRC
- Secondary endpoints: Overall survival, Safety and tolerability, Relapse pattern


PERIOPERATIVE TREATMENTS IN NSCLC

In EGFR wild-type NSCLC
- Perioperative chemotherapy
- Preoperative chemoradiation
- Perioperative targeted treatments
- Perioperative immunotherapy
- Postoperative mediastinal radiotherapy

In EGFR mutated NSCLC
- Adjuvant EGFR TKI vs. chemotherapy
- Adjuvant EGFR TKI after chemotherapy
ADAURA: ADJUVANT OSIMERTINIB
Phase 3 double-blind study design

Patients with completely resected stage\(^a\) IB, II, IIA NSCLC, with or without adjuvant chemotherapy\(^b\)

**Key inclusion criteria:**
- \(\geq 18\) years (Japan/Taiwan: \(\geq 20\))
- WHO performance status 0/1
- Confirmed primary non-squamous NSCLC
- Ex19del / L858R\(^c\)
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins\(^d\)
- Max. interval between surgery and randomisation:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
- Stage (IB vs II vs. IIA)
- EGFRm (EX19del vs. L858R)
- Race (Asian vs. non-Asian)

Planned treatment duration: 3 years

**Osimertinib 80 mg, once daily**

\(R = 1:1\) (N=682)

**Placebo, once daily**

Endpoints

**Primary:** DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70

**Secondary:** DFS in the overall population\(^a\), DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis
- At the time of unblinding, the study had completed enrolment and all patients were followed up for at least 1 year

\(^a\)AJCC 7\(^{th}\) Edition; \(^b\)Prior, post, or planned radiotherapy was not allowed; \(^c\)Centrally confirmed in tissue; \(^d\)Patients received a CT scan after resection and withing 28 days prior to treatment; \(^e\)Stage 1B/II/IIIA. Wu Y, et al. NEJM 2020;383:1711–23.
ADAURA: ADJUVANT OSIMERTINIB
DFS RESULTS

Patients with Stage II to IIIA disease

Patients with Stage IB to IIIA disease

ADAURA: DFS RESULTS ACCORDING TO ADJUVANT CHEMOTHERAPY

60% of patients received adjuvant chemotherapy in both arms

With adjuvant chemotherapy

Without adjuvant chemotherapy

Tick marks indicate censored data. NC, not calculable; NR, not reached.

CONCLUSIONS

Perioperative chemotherapy and radiotherapy

Neoadjuvant and adjuvant chemotherapy increase survival in resectable NSCLC:
- Comparable effectiveness of +5% at 5 years

Adjuvant chemotherapy:
- Stage II-III, IB ≥4 cm
- Best evidence for cisplatin-vinorelbine
- Cisplatin ≥300 mg/m²

There is currently no indication for perioperative radiotherapy
CONCLUSIONS

New treatments

Targeted therapies:
- No indication for targeted therapies in wild-type EGFR
- DFS benefit, no OS benefit of adjuvant EGFR TKIs vs. chemotherapy in EGFRmut NSCLC
- OS benefit remains to be demonstrated (with 3rd generation TKI? In addition to chemotherapy? )

Checkpoint inhibitors:
- Benefit in pCR after neoadjuvant chemotherapy-IO
- DFS benefit of adjuvant atezolizumab, confirmatory and OS results awaited
- Best scheduling (neo/adjuvant, chemotherapy-IO combination) to be defined
THANK YOU!