PERIOPERATIVE TREATMENT OF NON SMALL CELL LUNG CANCER

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Besançon, France
LEARNING OBJECTIVES

1. To understand the potential of perioperative treatments
2. To identify patients who should receive perioperative treatment for NSCLC
3. To choose the most appropriate perioperative treatment
4. 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 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

HR 0.86
(95% CI 0.81, 0.92; p<0.00011)

1. This article was published in The Lancet 375, NSCLC Meta-analysis Collaborative Group, Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data, 1267-77, Copyright Elsevier 2010; 2. Burdett S, et al., Cochrane Database of Systematic Reviews 2015;2(3):CD011430. Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
THE CISPLATIN-BASED ADJUVANT CHEMOTHERAPY META-ANALYSIS

Overall Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Events / No. of Patients</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>569 / 1,088</td>
<td>0.95</td>
<td>0.81 to 1.12</td>
</tr>
<tr>
<td>ANITA</td>
<td>458 / 840</td>
<td>0.82</td>
<td>0.68 to 0.98</td>
</tr>
<tr>
<td>BLT</td>
<td>186 / 307</td>
<td>0.95</td>
<td>0.71 to 1.27</td>
</tr>
<tr>
<td>IALT</td>
<td>980 / 1,867</td>
<td>0.91</td>
<td>0.81 to 1.04</td>
</tr>
<tr>
<td>JBR10</td>
<td>197 / 482</td>
<td>0.71</td>
<td>0.54 to 0.94</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,390 / 4,584</strong></td>
<td><strong>0.89</strong></td>
<td><strong>0.82 to 0.96</strong></td>
</tr>
</tbody>
</table>

Chemotherapy effect: Logrank statistic = 8.5, P = .005
Test for heterogeneity: \(\chi^2 = 4.25, P = .37, I^2 = 6\%\)

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ADJUVANT CHEMOTHERAPY: WHICH STAGES?

Overall survival

Curves by stage for the cisplatin-vinorelbine vs. the observation (no chemotherapy) groups

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Events / No. Patients</th>
<th>Hazard Ratio</th>
<th>Probability of interaction/trend* test</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>104 / 347</td>
<td></td>
<td>.06</td>
</tr>
<tr>
<td>Stage IB</td>
<td>515 / 1,371</td>
<td></td>
<td>.04*</td>
</tr>
<tr>
<td>Stage II</td>
<td>893 / 1,616</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>878 / 1,247</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE OF SURGERY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>783 / 1,346</td>
<td></td>
<td>.39</td>
</tr>
<tr>
<td>Other type of surgery</td>
<td>1,420 / 2,926</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chemotherapy Better | Control Better

ADJUVANT CHEMOTHERAPY IN STAGE IB NSCLC

Interaction p=0.02

ADJUVANT CHEMOTHERAPY: WHICH DRUGS? WHICH DOSES?

### Overall Survival

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Events / No. Patients</th>
<th>Hazard Ratio</th>
<th>Probability of interaction/trend* test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSOCIATED DRUGS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin + vinorelbine</td>
<td>935</td>
<td>1,888</td>
<td>.11</td>
</tr>
<tr>
<td>Cisplatin + 1 other drug</td>
<td>742</td>
<td>1,373</td>
<td></td>
</tr>
<tr>
<td>Cisplatin + 2 other drugs</td>
<td>713</td>
<td>1,323</td>
<td></td>
</tr>
</tbody>
</table>

### Disease-Free Survival

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Events / No. Patients</th>
<th>Hazard Ratio</th>
<th>Probability of interaction/trend* test</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLANNED DOSE OF CISPLATIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 300 mg/m²</td>
<td>186</td>
<td>307</td>
<td>.26</td>
</tr>
<tr>
<td>300 mg/m²</td>
<td>985</td>
<td>1,903</td>
<td>.13*</td>
</tr>
<tr>
<td>&gt; 300 mg/m²</td>
<td>1,219</td>
<td>2,374</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at the 0.05 level.
TIMING OF ADJUVANT CHEMOTHERAPY

- 12,473 pts
- US National cancer database

Cox proportional hazards model of patients who underwent adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Covariate</th>
<th>No.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy timing</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>

- 3,976 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></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>
</tr>
<tr>
<td>MD Anderson 1994</td>
<td>19/28</td>
<td>27/32</td>
<td>-6.40</td>
<td>11.19</td>
<td></td>
</tr>
<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>137/179</td>
<td>146/176</td>
<td>-12.99</td>
<td>70.22</td>
<td></td>
</tr>
<tr>
<td>SWOG S9015</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>-0.50</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>151/258</td>
<td>158/261</td>
<td>-2.92</td>
<td>77.01</td>
<td></td>
</tr>
<tr>
<td>SWOG S9900</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>
<td></td>
</tr>
<tr>
<td>NATCH</td>
<td>99/201</td>
<td>109/212</td>
<td>-4.11</td>
<td>51.95</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>682/1178</strong></td>
<td><strong>745/1207</strong></td>
<td><strong>-50.62</strong></td>
<td><strong>351.78</strong></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, $I^2=25\%$

[Graph showing HR (95% CI) and p value with data points and error bars for preoperative chemotherapy better and non-preoperative chemotherapy better.]

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?

Age group (<60, 60–64, 65–69, ≥70)
14 trials, 2359 patients
Greater treatment effect in older patients

Age
14 trials, 2359 patients
Greater treatment effect in older patients

Performance status (0, 1, 2+)
11 trials, 2198 patients
Greater treatment effect with worse performance status

Clinical stage (I, II, III)
9 trials, 2171 patients
Greater treatment effect with higher clinical stage

Clinical stage (IA, IB, II, III)
9 trials, 2171 patients
Greater treatment effect with higher clinical stage

Sex (male, female)
11 trials, 2288 patients
Greater treatment effect for females

Histology (squamous or adenocarcinoma)
14 trials, 2359 patients
Greater treatment effect with squamous histology

Overall survival

Interaction HR
(95% CI), p value

Greater treatment effect in younger patients
1.00 (0.91–1.10), p = 0.97, heterogeneity p = 0.63

Greater treatment effect in younger patients
1.01 (0.89–1.15), p = 0.83, heterogeneity p = 0.45

Greater treatment effect with better performance status
0.84 (0.67–1.06), p = 0.14, heterogeneity p = 0.62

Greater treatment effect with lower clinical stage
0.98 (0.83–1.16), p = 0.83, heterogeneity p = 0.13

Greater treatment effect with lower clinical stage
0.96 (0.83–1.12), p = 0.64, heterogeneity p = 0.22

Greater treatment effect for males
1.08 (0.81–1.44), p = 0.62, heterogeneity p = 0.04

Greater treatment effect with adenocarcinoma
0.83 (0.64–1.07), p = 0.16, heterogeneity p = 0.09
**ADJUVANT VS. NEOADJUVANT**

- Multi-centre phase 3 trial
- Mar. 2006 ~ May 2011
- Stratification:
  - Gender, centre, stage (IB vs. II vs. IIIA), pathology (adenocarcinoma vs. non-adenocarcinoma)
- Objectives:
  - Primary endpoint: 3-yr DFS
  - Secondary endpoints: safety, 5-yr OS

---

Eligible Stage IB-IIIA NSCLC (n=214)

Randomly assigned (n=198)

Neo-adjuvant arm (n=97)
  - Chemotherapy (n=97)
  - Surgery (n=82)

Adjuvant arm (n=101)
  - Surgery (n=101)
  - Chemotherapy (n=86)

Stop for slow accrual

### DFS

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Median (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>101</td>
<td>52</td>
<td>5.2 (1.3–9.0)</td>
<td>0.057</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>97</td>
<td>67</td>
<td>2.3 (1.6–3.0)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI) = 0.70 (0.49–1.01)

### OS

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Median (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>101</td>
<td>45</td>
<td>7.3</td>
<td>0.087</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>97</td>
<td>59</td>
<td>4.2 (3.2–5.2)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI) = 0.71 (0.48–1.05)

ADJUVANT OR NEOADJUVANT CHEMOTHERAPY VS. SURGERY
A meta-analysis

ADJUVANT OR NEOADJUVANT?

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

Paclitaxel 200 mg/m² + carboplatin AUC 6 q3wk
Main objective: PFS at 5 yr 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>
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<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>
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RESPECTIVE ADVANTAGES OF (NEO)ADJUVANT CHEMOTHERAPY

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Staging</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Earlier delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Evaluation of tumour response</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Research purposes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue availability</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
- Perioperative immunotherapy
- Postoperative mediastinal radiotherapy

In EGFR mutated NSCLC
PREOPERATIVE CHEMORADIATION FOR STAGE IIIA N2

- Multicentre phase III
- 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 chemotherapy
- Preoperative chemoradiation
- Perioperative targeted treatments
- Perioperative immunotherapy
- Postoperative mediastinal radiotherapy

In EGFR mutated NSCLC
ADJUVANT GEFITINIB IN ALL-COMERS (BR19)

Stage IB, II, IIIA completely resected
Trial prematurely closed
Gefitinib x 2 yr

ADJUVANT ERLOTINIB IN ALL-COMERS

- Primary endpoint: DFS
- Phase III trial
- Adjuvant erlotinib (2 yr) vs. placebo
- pStage IB-IIIA
- OS: HR=1.09 (95%CI=0.545-2.161) p=.815

Investigator Choice of 4 chemotherapy regimens
21-day cycles all with Cisplatin given at 75 mg/m² on day 1
Cisplatin / Vinorelbine: 30 mg/m² day 1, 8
Cisplatin / Docetaxel: 75 mg/m² day 1
Cisplatin / Gemcitabine: 1200 mg/m² day 1, 8
Cisplatin / Pemetrexed: 500 mg/m² day 1 (2009 amendment)

Bevacizumab 15 mg/kg IV q 3 weeks for up to 1 year

Primary endpoint: Overall survival
ADJUVANT BEVACIZUMAB

OS hazard ratio (B:A): 0.99
95% CI: 0.81–1.21
p=0.93

DFS hazard ratio (B:A): 0.98
95% CI: 0.84–1.14
p=0.75

Wakelee H, et al., Presented at WCLC 2015: Plen 04-03. With permission from Professor Heather Wakelee.
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
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

MAGE A-3 VACCINE IN MAGE A-3+ NSCLC: OVERALL SURVIVAL

NEOADJUVANT NIVOLUMAB

- 18 pts with resectable stage I–IIIA NSCLC
- Nivolumab 3 mg/kg D-28&14, prior to surgery
- Responses:
  - 7 major pathologic response (<10% residual tumour)
  - 1 complete pathologic response
  - 13 stable disease
- 1 Grade 3–4 adverse event
- No delay in surgery in any patient
- Increased T cell infiltrate in responders

Forde P, ESMO 2016: Abstract LBA41_PR
### ONGOING PHASE III 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/ANVL – 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>Atezolizumab (Impower 010)</td>
<td>placebo</td>
<td>IB (4 cm) – IIIA, after adjuvant chemo</td>
<td>all</td>
<td>DFS</td>
</tr>
<tr>
<td>MEDI 4736 (international)</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

In EGFR wild-type NSCLC

- Perioperative chemotherapy
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- Perioperative immunotherapy
- Postoperative mediastinal radiotherapy

In EGFR mutated NSCLC
POSTOPERATIVE RADIOTHERAPY: THE UPDATED META-ANALYSIS

- IPD meta-analysis
- 11 trials / 2343 pts
- HR=1.18
- 18% relative increase in risk of death
- Absolute detriment: 5% at 2 yr (95% CI=2-9%)
- Reducing survival from 58 to 53%
POSTOPERATIVE RADIOTHERAPY FOR STAGE III? FOR N2?

LUNG ART IFCT05-03

Eligible:
Pre and/or postoperative chemotherapy accepted

Primary endpoint:
Disease-free survival
433/500 pts included

Complete resection
Pathological N2

R

1:1

Arm A: Control

Arm B: Conformational radiotherapy (54 Gy)
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
ERLOTINIB IN EGFR-MUT IN RADIANT

B

Disease-Free Survival (probability)

Placebo
Median: 28.5 months

Erlotinib
Median: 46.4 months

HR: 0.61 (95% CI, 0.38 to 0.98)

No. at risk
Placebo 59 49 43 35 30 23 15 12 10 5 0 0 0
Erlotinib 102 94 80 76 68 56 35 22 10 3 0 0 0

Time (months)

NS due to hierarchical testing
OS immature

### Ongoing EGFR TKI Adjuvant Trials in EGFR-Mut Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country</th>
<th>EGFR TKI</th>
<th>Control</th>
<th>EGFR TKI duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCHEMIST</td>
<td>USA</td>
<td>Erlotinib</td>
<td>Placebo</td>
<td>2 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crizotinib (for ALK+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPACT WJOG 6401L</td>
<td>Japan</td>
<td>gefitinib</td>
<td>Cisplatin vinorelbine x4</td>
<td>2 yr</td>
</tr>
<tr>
<td>C-TONG 1104</td>
<td>China</td>
<td>gefitinib</td>
<td>Cisplatin vinorelbine x4</td>
<td>2 yr</td>
</tr>
<tr>
<td>NCT02125240 without adjuvant chemo</td>
<td>China</td>
<td>Icotinib</td>
<td>Placebo</td>
<td>6-12 months</td>
</tr>
<tr>
<td>NCT01996098 (after 4 cycles of adjuvant platinum-based chemo)</td>
<td>China</td>
<td>Icotinib</td>
<td>observation</td>
<td>6-12 months</td>
</tr>
</tbody>
</table>
CONCLUSIONS: PERIOPERATIVE CHEMOTHERAPY

- 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
CONCLUSIONS: PERIOPERATIVE RADIOTHERAPY

- Preoperative radiotherapy does not add to preoperative chemotherapy in stage IIIA N2
- Postoperative radiotherapy can be delivered in pN2 disease
CONCLUSIONS: NEW TREATMENTS

- No indication for targeted therapies in wild-type EGFR
- Activity of EGFR and ALK TKIs to be demonstrated in EGFRmut/ALK+ NSCLC
- Activity of immune checkpoint inhibitors to be demonstrated
THANK YOU!