Lung Cancer – Non-small Cell Local, Regional, Small Cell, Other Thoracic Cancers: “The Question Isn’t Can We, but Should We”

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Abstracts To Be Discussed

- **Abstract 7500**: A multinational phase III randomized trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small cell lung cancer (CCHeIN). *(K. Park)*

- **Abstract 7503**: Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): Results of a Japanese randomized phase III trial. *(T. Seto)*

- **Abstract 7502**: Randomized trial on thoracic radiotherapy (TRT) in extensive-stage small cell lung cancer. *(B. J. Slotman)*

- **Abstract 7501**: A randomized double blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results. *(K. Kelly)*

- **50th Anniversary-Themed Education Session**: 50 Years of Lung Cancer: The Current Status of Therapy for Non-Small Cell Lung Cancer—Adjuvant Therapy, Chemoradiotherapy, and Systemic Treatment
Abstract 7500 (Park)

Study: A Multinational Randomized Phase III Trial with or without Consolidation Chemotherapy Using Docetaxel and Cisplatin after Concurrent Chemoradiation in Inoperable Stage III Non-small Cell Lung Cancer (CCheIN)

Study Purpose:
• Evaluate whether additional chemotherapy beyond concurrent chemoradiation (CCRT) improves survival

Hypothesis:
• Overall survival will improve with:
Cisplatin/Taxotere/XRT → Cisplatin/Taxotere v. Cisplatin/Taxotere/XRT alone
SWOG 9504: Docetaxel After Concurrent Chemoradiation Therapy

Concurrent Chemoradiation
- PE: Cisplatin 50 mg/m² IV d 1, 8, 29, 36
  Etoposide 50 mg/m² IV d 1-5, 29-33
- RT: 45 Gy (1.8 Gy/fraction)
  16 Gy boost (2 Gy/fraction)

Consolidation Docetaxel X 3 cycles

Median Survival Time: 26 months
5 Year Survival: 29%

Consolidation Chemotherapy

Observation

Locally Advanced, Inoperable Stage III NSCLC

Stratified by center, performance

PD → Off Protocol

Consolidation Chemotherapy

Observation

CCheIN Study Design

Randomization

Conc Chemoradiotherapy

4-8 weeks

Consolidation (Weekly DP)

1 2 3 4 5 6 7 8 9

Week

1 2 3 4 5 6 7

Docetaxel

CDDP

TRT

66 Gy/6.5 weeks

Consolidation (Weekly DP)

20mg/m²

35mg/m²

Park et al., ASCO 2014, abstract 7500.
CCheIN Study: Overall Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Events</th>
<th>mPFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT alone</td>
<td>209</td>
<td>180</td>
<td>8.05 (7.56, 8.90)</td>
</tr>
<tr>
<td>CCRT + consolidation</td>
<td>211</td>
<td>169</td>
<td>9.10 (7.92, 10.94)</td>
</tr>
</tbody>
</table>

Hazard ratio = 0.911 (95% CI, 0.720-1.253)  
P = 0.438

Median follow-up: 50.7 months
Overall Survival
Randomized Patients (n=147)

Observation: Median: 24.1 months
3 year survival: 28%
Docetaxel: Median: 21.5 months
3 year survival: 27%
P-value: 0.940

Percent of patients surviving
Months since registration
Hanna et al, PASCO 2007 #7512

BEST OF ASCO
2014 ANNUAL MEETING
Different Regimens: Similar Results

Park et al., ASCO 2014, abstract 7500.

Graph 1: Comparison of Overall Survival between CCRT alone and CCRT + consolidation.

Graph 2: Overall Survival for Randomized Patients (n=147).
CCHeIN Take Home Points

- This second randomized trial showing no benefit to consolidation chemo after CCRT
- No conflicting randomized trials show benefit in this setting
- Additional systemic therapy after CCRT in locally advanced NSCLC is investigational, and should not be routinely offered
Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): Results of a Japanese randomized phase III trial.
Data Shows PCI survival benefit

Overall survival

1 year: 27.1% vs. 13.3%

HR: 0.68 (0.52-0.88)  p=0.003

Months from randomization

Slotman et al, PASCO 2007 #4
PCi for ED-SCLC Study Design

Primary endpoint: Overall Survival

Secondary endpoints: Time to BM (evaluated every 3 months), Progression-Free Survival (PFS), Safety, Mini Mental State Examination (MMSE)

PCI: 25 Gy 10 fractions
No PCI
Follow-up by MR imaging

1st line chemo Platinum-based doublet

Any response
No BM by MRI assessment

< 6 weeks
3-8 weeks

No response

Seto T et al., ASCO 2014, abstract 7503.
Time to Brain Metastasis

Seto T et al., ASCO 2014, abstract 7503.

Gray's test: $P < 0.001$ (2-sided)

Arm A: PCI
n=84

Arm B: no PCI
n=79

BM at 12 months
32.4%
58.0%
Overall Survival

Stratified log-rank test: $P=0.091$ (2-sided)

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of OS Events</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.38 (0.95-2.02)</td>
<td></td>
</tr>
<tr>
<td>Median OS (95%CI), mo</td>
<td>10.1 (8.5-13.2)</td>
<td>15.1 (10.2-18.7)</td>
</tr>
</tbody>
</table>

Seto T et al., ASCO 2014, abstract 7503.
PCI for ED-SCLC Results & Conclusions

- This study was terminated after 1st interim analysis
- PCI did not show survival benefit for ED-SCLC pts with confirmed absence of BM
- MRI was required at baseline
Similar Approach: Different Results

Seto T et al., ASCO 2014, abstract 7503.
Contextualization regarding PCI

• An effective therapy can harm cancer cells, but that doesn’t mean it extends survival
• Confidence interval includes 1, however, “it isn’t definitively harmful” doesn’t generate much enthusiasm
• Japanese data has at times differed from data outside Japan (although usually more positive)
Take Home Point Regarding PCI

• Unless you believe that the study was poorly conducted or analyzed, or that there is something different about how Japanese patients respond to PCI, with modern CNS imaging, the benefits of PCI after a response in ED-SCLC are strongly in doubt.
Abstract 7502 (Slotman)

Study: Randomized trial on thoracic radiotherapy (TRT) in extensive-stage small cell lung cancer (ES-SCLC) (Chest Radiotherapy Extensive Stage Trial)

Study Purpose:
• Evaluate whether local therapy directed at thoracic disease in ES-SCLC can improve survival, as some patients progress initially with thoracic disease

Hypothesis:
• Prophylactic Cranial Irradiation (PCI) + TRT after chemotherapy improves OS
CREST Trial Design

ES-SCLC, WHO 0-2

RANDOMIZE

TRT (30Gy in 10fx)

PCI

PCI

4-6 platinum-based chemotherapy

Any response
CREST Trial Overall Survival

12 mos OS - Thoracic RT: 32.7 (95% CI: 27.2 - 39.3)
12 mos OS - No Thoracic RT: 27.6 (95% CI: 22.5 - 33.9)

ITT, events/n (224 / 248 - 201 / 247)
HR = 0.84 (95% CI: 0.69 - 1.01)
stratified log-rank p-value 0.066

HR = 0.84 (95% CI 0.69-1.01)
p = 0.066

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

Slotman B et al., ASCO 2014, abstract 7502.
CREST Trial Conclusions and Results

Take Home Point

• A survival benefit was not seen with the addition of thoracic radiotherapy using conventional endpoints.

• It is intriguing that a subset appeared to derive significant prolongation of survival.

• It would be helpful to know who were the ones who with extended survival.

• The question will be similar to Slotman’s PCI trial though, in evaluating whether those benefiting may in fact have been incorrectly staged.
Study: A randomized double blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB–IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results

Study Purpose:
• Evaluate whether this molecularly targeted agent can enhance disease control in a molecularly unselected population

Hypothesis:
• Erlotinib prolongs disease-free survival (DFS) in completely resected patients with early stage (IB–IIIA) NSCLC whose tumor expressed EGFR by IHC or FISH
Addition of 1 year of adjuvant trastuzumab significantly improved DFS and OS among women with HER2-positive breast cancer.

RADIANT Trial Design

Tumor samples
EGFR IHC+ and/or EGFR FISH+

Stage IB–IIIA NSCLC
Complete surgical resection

No adjuvant chemotherapy

Up to 4 cycles of platinum-based doublet

≤90 d

≤180 d

(N=973)
Randomization stratified by:
histology, stage, prior adjuvant chemo, EGFR FISH status, smoking status, country

(n=623)
Erlotinib 150mg/day

2:1
2-yr treatment period

(n=350)
Placebo

- Radiology assessment: every 3 months on treatment and yearly during long-term follow up

- Primary endpoint: Disease Free Survival (DFS)
- Secondary endpoints: Overall survival (OS); DFS and OS in patients with del19/L858R (EGFR M+)

Kelly K et al., ASCO 2014, abstract 7501.
RADIANT Patient Population

- 51% had stage IB disease v. 15.5% had stage IIIA disease
- 53% also received adjuvant chemotherapy
- 16.5% had EGFR del19/L858R
RADIANT Disease-free Survival KM Plot

Placebo (156 events)
Median: 48.2 m

Erlotinib (254 events)
Median: 50.5 m

Log-rank test: p=0.3235

HR: 0.90 (95% CI: 0.741, 1.104)

Addition of 1 year of adjuvant trastuzumab significantly improved DFS and OS among women with HER2-positive breast cancer.

**RADIANT: Disease-free Survival: EGFR M+**

- **Placebo (32 events)**
  - Median: 28.5 m

- **Erlotinib (39 events)**
  - Median: 46.4 m

**Log-rank test: p=0.0391** (not statistically significant due to hierarchical testing)

**HR: 0.61 (95% CI: 0.384, 0.981)**

Kelly K et al., ASCO 2014, abstract 7501.
Is DFS the in EGFRM+ pts an appropriate endpoint for analysis?

40% who are surgically cured:

- only difference is that 2/3 took erlotinib

60% who are not surgically cured

- It is unknown if the benefit is changed

--- erlotinib per protocol | year
--- erlotinib after progression
RADIANT Conclusions and Results

• For patients whose tumors had del19 and L858R mutations, DFS favored erlotinib v. placebo.
  – But NOT statistically significant due to hierarchical testing
  – Questions as to its relevance as an endpoint

Take Home Point

• It is still unclear that erlotinib leads to cure in more patients after complete resection, and the effect in EGFRM+ patients is also unclear
50 Years of Lung Cancer

• 50 Years of Lung Cancer: The Current Status of Therapy for Non-Small Cell Lung Cancer—Adjuvant Therapy, Chemoradiotherapy, and Systemic Treatment
Accomplishments

• Adjuvant cisplatin chemotherapy SOC for pts w/resected stage II/IIIA NSCLC
• Over the past 50 years combined modality regimens for inoperable stage III NSCLC have almost tripled the median survival of this disease.
• Still Working On…
  – Biomarkers
  – Targeted Therapies
  – Immunotherapies
When You Return Back to Clinic on Monday…

- Additional chemotherapy beyond concurrent chemoradiation (CCRT) needed: No
- Additional treatment after chemotherapy in ES-SCLC patients: Probably not, but perhaps be a little more vigilant for LS that looks like ES
- Adjuvant erlotinib after complete resection: No, but role in EGFR del19/L858R patients unclear
- Over past 50 years progress being made in lung cancer treatment: Yes, but not enough. Consider clinical trials, ideally in your clinic