Is there a role for targeted therapy in the adjuvant or neoadjuvant setting?

Nathan Pennell, M.D., Ph.D.

February 11, 2017
44 Year Old Woman, Nonsmoker

- Presented in 2009 with RLL nodule, staging indicated likely stage IA adenocarcinoma
- RLL lobectomy: 2.8cm adeno, level 7 node+ (N2; Stage IIIA), *EGFR* exon 19 deletion mutation
- Completed adjuvant cisplatin/pemetrexed and PORT
- Enrolled on phase 2 trial of 2 years of adjuvant erlotinib, required dose reduction to 100mg
- Completed 2 years of erlotinib in 2011
Case continued

• Recurrence in right pleural space in 2013
• Biopsy showed same exon 19 deletion mutation
• Restarted erlotinib with partial response
• Late 2014 had progression (after 14 months)
• Progressed on chemotherapy and then nivolumab
• Rebiopsy in Dec 2015 showed T790M mutation, started osimertinib, no PD to date
PET/CT 2009
PET/CT 2013
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Overview

- Adjuvant chemotherapy improves survival in early-stage non-small cell lung cancer (NSCLC)
- EGFR and ALK-targeted therapies are more effective than chemotherapy in advanced EGFR/ALK+ NSCLC, but do they improve cure rates in earlier stages?
- Review data on adjuvant targeted therapies
- Review ongoing adjuvant trials
LACE Meta-Analysis of Adjuvant Cisplatin-Based Chemo in NSCLC

5-year absolute benefit of 5.4% from chemotherapy

Phase III Trials of EGFR and ALK TKIs vs. Chemotherapy as First-Line Treatment of Patients with Advanced EGFR/ALK+ NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Response Rate</th>
<th>PFS</th>
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</thead>
<tbody>
<tr>
<td>LUX-Lung 3</td>
<td>56% vs. 22%</td>
<td>13.6 vs. 6.9 months (HR 0.47)</td>
</tr>
<tr>
<td>LUX-Lung 6</td>
<td>67% vs. 28%</td>
<td>11 vs. 5.6 months (HR 0.28)</td>
</tr>
<tr>
<td>EURTAC</td>
<td>58% vs. 14.9%</td>
<td>9.7 vs. 5.2 months (HR 0.37)</td>
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<tr>
<td>OPTIMAL</td>
<td>83% vs. 36%</td>
<td>13.1 vs. 4.6 months (HR 0.16)</td>
</tr>
<tr>
<td>NEJ 002</td>
<td>74% vs. 31%</td>
<td>10.8 vs. 5.4 months (HR 0.30)</td>
</tr>
<tr>
<td>WJTOG 3405</td>
<td>62% vs. 31%</td>
<td>9.2 vs. 6.3 months (HR 0.49)</td>
</tr>
<tr>
<td>Profile 1014 (crizotinib)</td>
<td>74% vs. 45%</td>
<td>10.9 vs. 7 months (HR 0.45)</td>
</tr>
</tbody>
</table>

No differences in overall survival!
If TKIs are more effective than chemotherapy in stage 4 disease, why not try them in the adjuvant setting?

- Adjuvant targeted treatment is proven effective and approved in
  - Breast cancer (hormonal and HER2-directed therapy)
  - GIST (cKIT directed therapy, i.e. imatinib)
  - Melanoma (anti-CTLA4 i.e. ipilimumab)

1. EBCTCG meta-analysis, Lancet Oncol 2012
2. Moja et al., Cochrane Database Syst Rev 2012
3. Joensuu et al., JAMA 2012
4. Eggermont et al., Lancet Oncol 2015
A retrospective cohort study demonstrated an 89% vs. 72% 2-year DFS in EGFR mutant patients prescribed adjuvant erlotinib or gefitinib compared with untreated patients.
Evidence Against? BR.19

- Phase 3 trial of adjuvant gefitinib versus placebo in UNSELECTED early stage NSCLC
- Halted early after <50% accrued (509 pts)
- Possible harm in adjuvant TKI arm (HR 1.24)
- BUT only 15 patients with EGFR mutations identified so too few to draw conclusions of benefit or harm
Prospective Data to Date for Adjuvant TKIs

• For ALK? Nothing to date.

• For EGFR mutant NSCLC, there have been 2 trials completed: RADIANT and SELECT
RADIANT Trial Design

- Stage IB–IIIA NSCLC
- Complete surgical resection
- Tumor samples
  - EGFR IHC+ and/or EGFR FISH+
- Randomization stratified by:
  - histology, stage, prior adjuvant chemo, EGFR FISH status, smoking status, country
- Erlotinib 150mg/day
- Placebo
- (N=973)
- (n=623)
- (n=350)
- 2:1
- 2-yr treatment period
- Up to 4 cycles of platinum-based doublet
- No adjuvant chemotherapy
- ≤90 d
- ≤180 d

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

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

Adopted from Dr. Karen Kelly
ASCO 2014
RADIANT Mutation + Subgroup (n=161): Disease Free Survival and Overall Survival

Median DFS 46.4 mos vs. 28.5 mos with placebo, p=0.0391

Kelly et al., ASCO 2014
SELECT: Study Design

- Single arm Phase II study
- Adjuvant erlotinib following surgery and standard adjuvant therapy

CT surveillance:
- Every 6 mo x 3 years
- Annually years 4 and 5

Erlotinib 150 mg PO daily

Primary Endpoint:
- Disease Free Survival:
  Goal: 2-year >86%

Secondary Endpoints:
- Safety and Tolerability
- Overall Survival

- Stage IA-IIIA NSCLC
- Surgically resected
- EGFR mutation positive
- Completed routine adjuvant chemotherapy and/or XRT

2 years duration

Observation
SELECT Results

- 45% stage 1, 27% stage 2, 28% stage 3
- 2/3 completed full 2 years of treatment
- 2-year DFS was 89% compared to expected 76% in historical control (MSK cohort)
- 29 recurrences, but only 4 on erlotinib
- Most recurrent pts responded to rechallenge with TKI, only 1 T790M+ on recurrence
- DFS consistent with improvements seen in retrospective cohort and RADIANT subgroup!

Pennell et al., ASCO 2014
Ongoing Adjuvant Trials

- NCI Cooperative group ALCHEMIST trials
- Phase 2 trial of 3 yrs vs. 3 months of adjuvant afatinib (NCCN; NCT01746251)
- ADAURA Phase 3 trial of 3 yrs of adjuvant osimertinib versus placebo in stage IB-IIIA EGFR mutant NSCLC (NCT02511106)
- Japanese WJOG 6410L comparing 2 yrs of adjuvant gefitinib vs. chemo for resected stage II to IIIA EGFR mutant NSCLC
- Chinese C-TONG 1104 same design
ALCHEMIST Design

Trials conducted at sites in the NCI Clinical Trials Networks: NCTN & NCORP

Non-squamous NSCLC (n=6,000 to 8,000 pts)
Clinical/Pathologic Stage IB (≥ 4cm), II, IIIA
Post-Op cohort with negative surgical margins

Pre-op cohort
Post-op cohort

Complete resection + standard adj therapy per treating physician

Central EGFR & ALK genotyping

EGFR-mutation:
Phase III trial of erlotinib vs placebo x 2 years (n=410) after any adj tx

ALK-rearranged:
Phase III trial of crizotinib vs placebo x 2 years (n=360) after any adj tx

Without Molecular Alterations: Followed q6 months x 5 years after any adj tx

FFPE tissue & blood specimen

FFPE tissue from biopsy done at recurrence

Conclusions

• Adjuvant EGFR TKIs in early stage EGFR mutant NSCLC may improve DFS based on consistent signal in multiple studies
• However, unclear if this will lead to improved OS or cure rates and so not routinely recommended at this time
• Support ALCHEMIST and other trials
• Longer duration of therapy and more tolerable drugs may be necessary (ADAURA?)
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