Cleveland Clinic
Taussig Cancer Institute

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

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

February 11, 2017

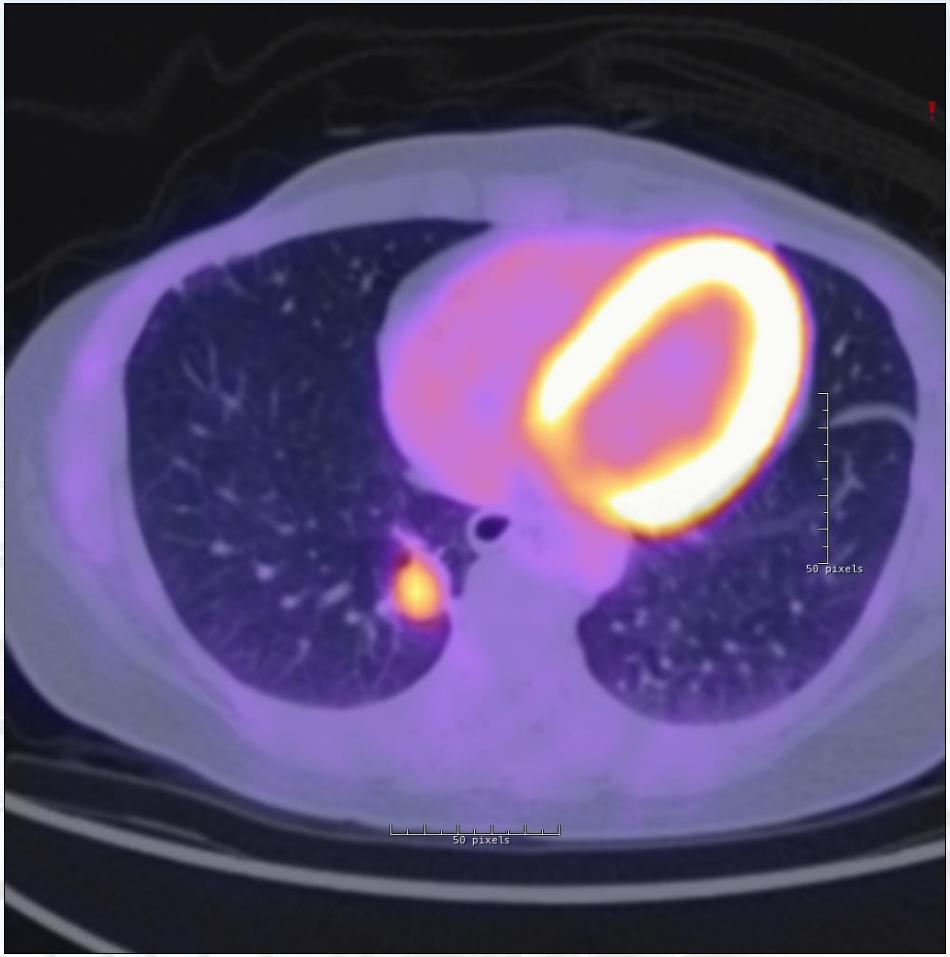
44 Year Old Woman, Nonsmoker

- 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

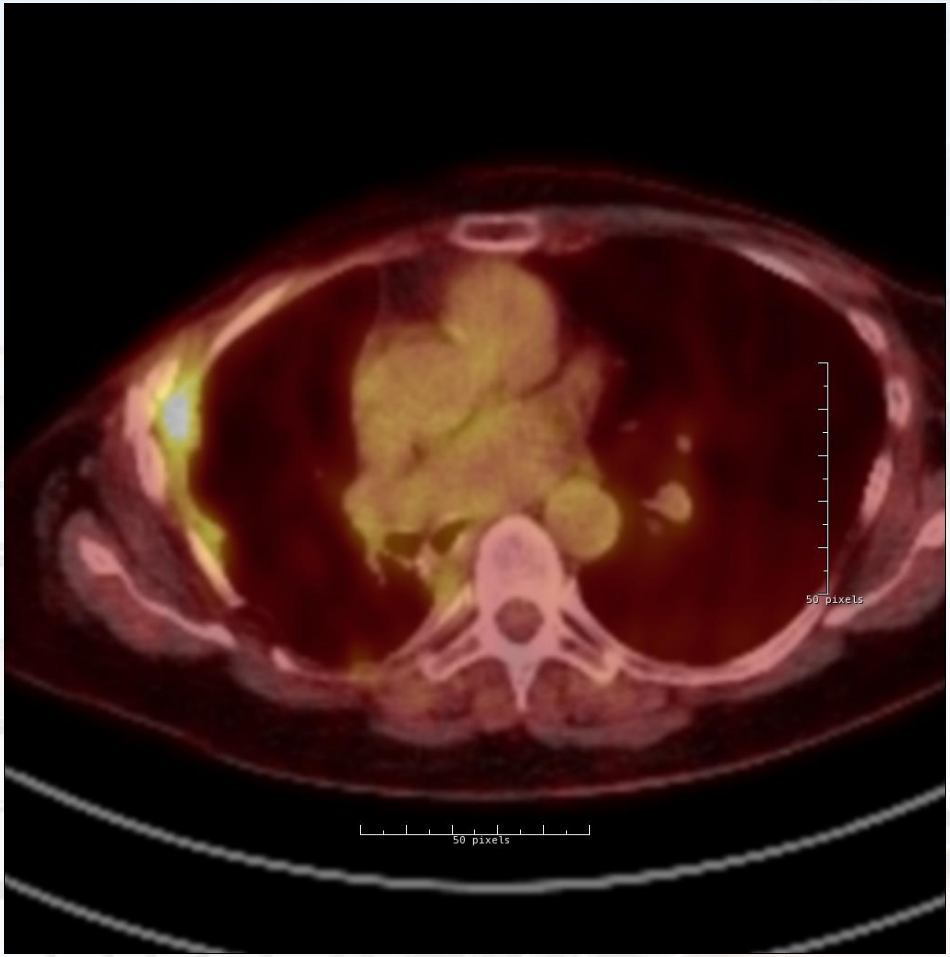
Case continued

- 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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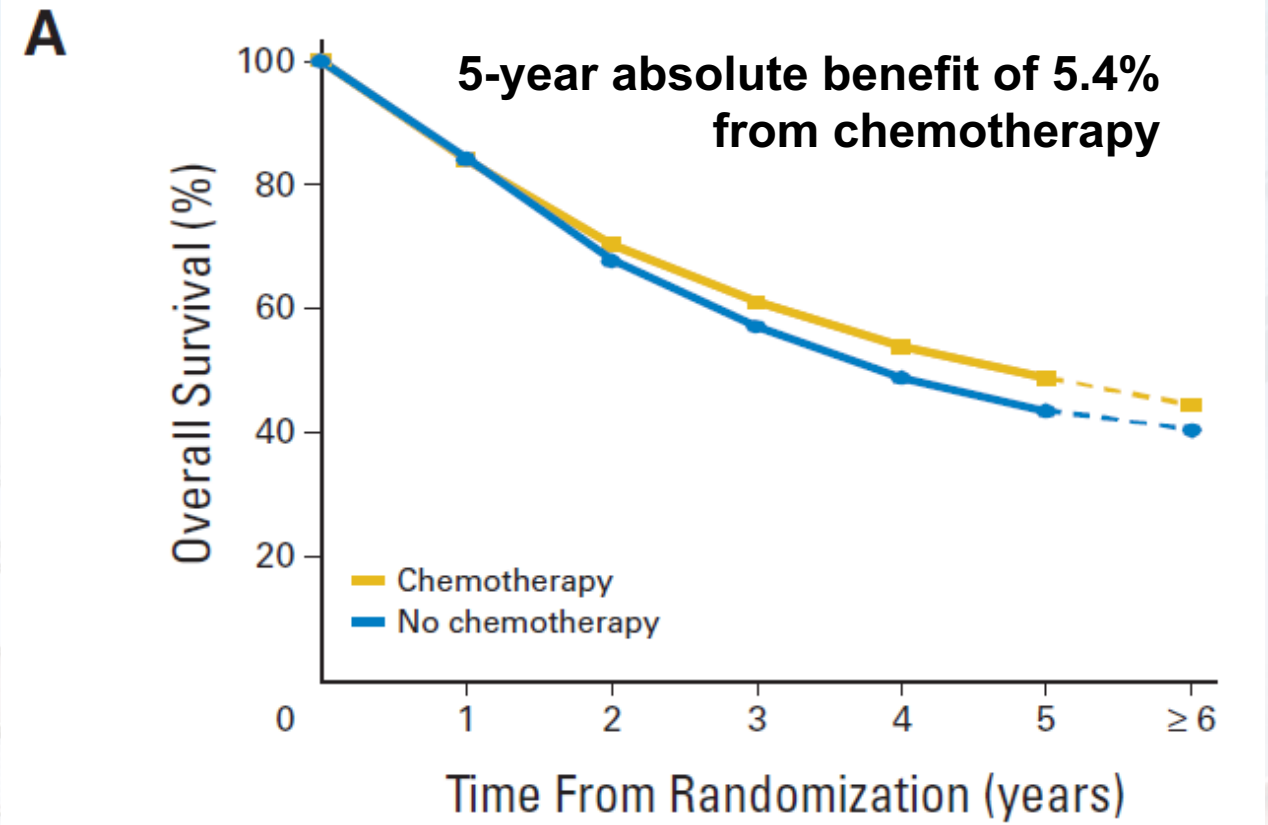
Overview

- 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



Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

Pignon et al., JCO 2008;26(21):3552-9.

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

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

No differences in overall survival!

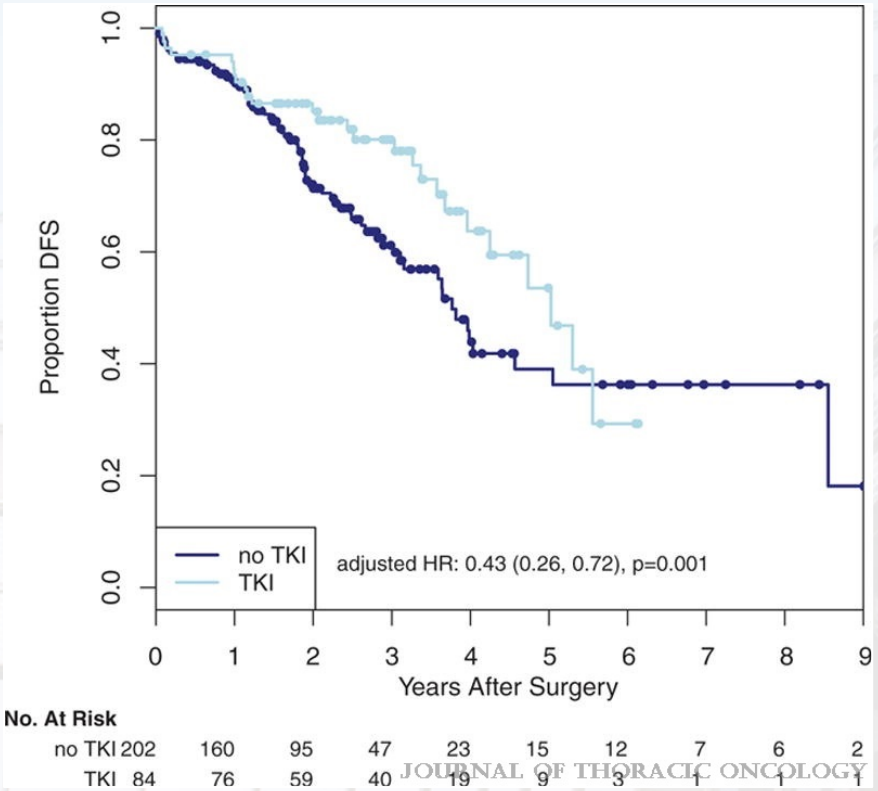
If TKIs are more effective than chemotherapy in stage 4 disease, why not try them in the adjuvant setting?

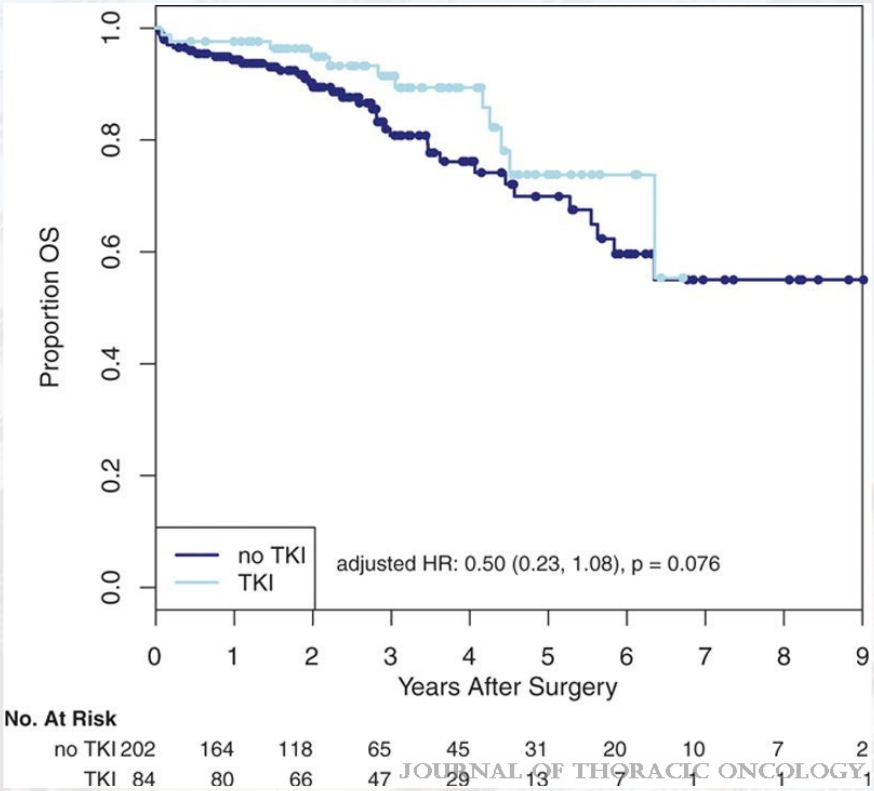
- Adjuvant targeted treatment is proven effective and approved in
  - Breast cancer (hormonal[1] and HER2-directed[2] therapy)
  - GIST (cKIT directed therapy, i.e. imatinib[3])
  - Melanoma (anti-CTLA4 i.e. ipilimumab[4])

[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

Evidence in Favor?
MSK Retrospective Cohort Study

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





Janjigian et al. J Thoracic Oncol. 2011;6:569.
D'Angelo et al., 2012 JTO 7(12); 1815-22.

Evidence Against? BR.19

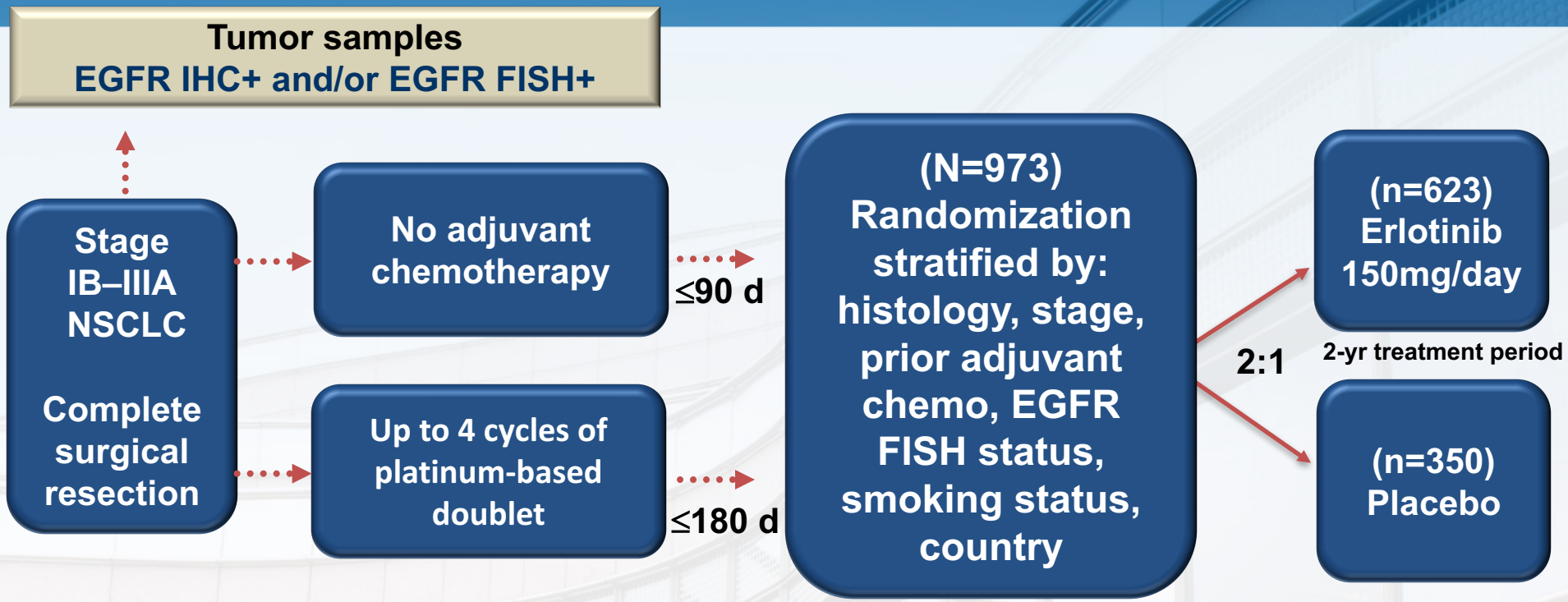
- Phase 3 trial of adjuvant gefitinib versus placebo in UNSELECTED early stage NSCLC
- Halted early after <50% accrued (509 pts)
- Possible harm in adjuvant TKI arm (HR 1.24)
- BUT only 15 patients with *EGFR* mutations identified so too few to draw conclusions of benefit or harm

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

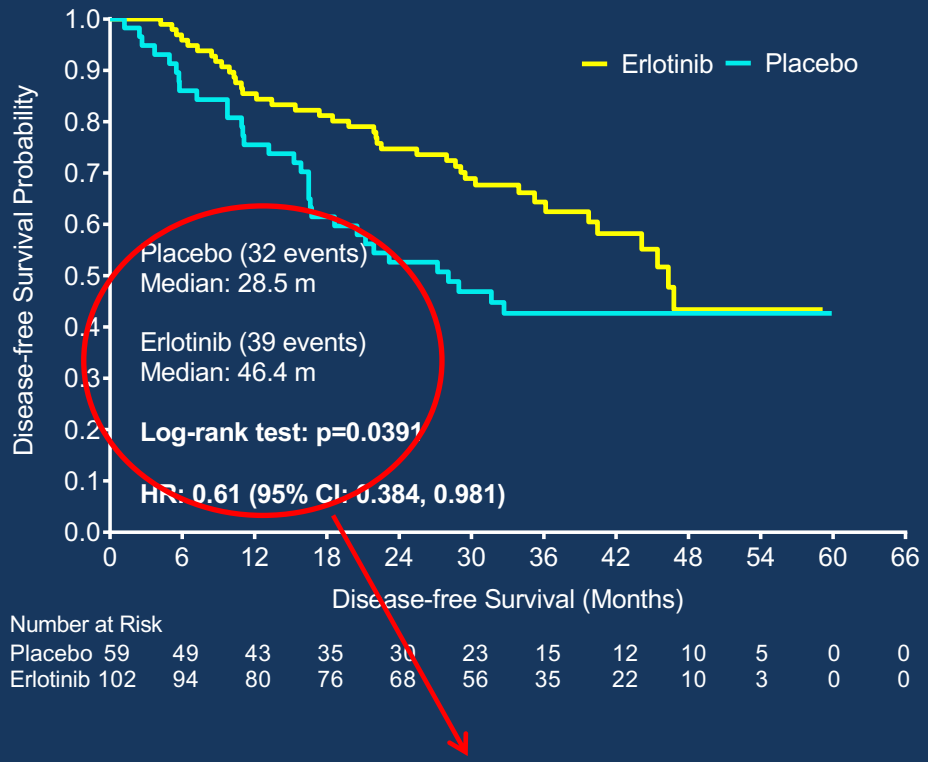


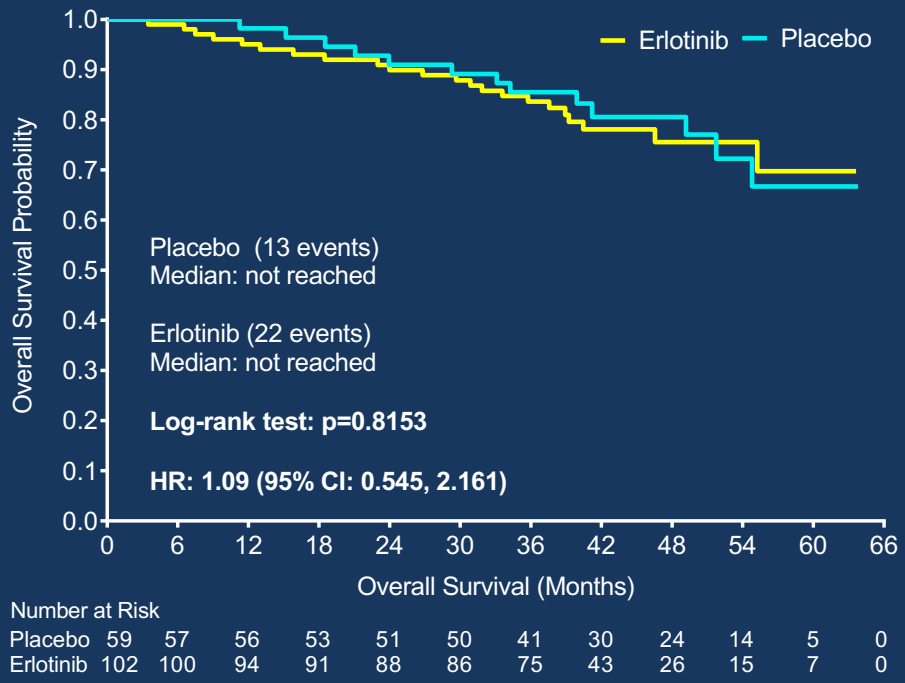
- Radiology assessment: every 3 months on treatment and yearly during long-term follow up

- 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

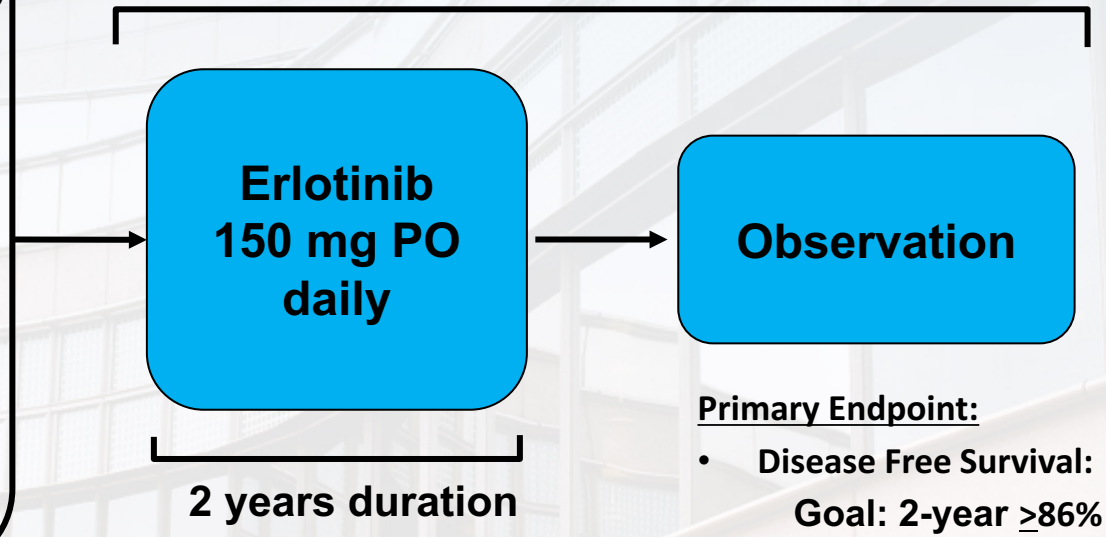
SELECT: Study Design

- 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

- Stage IA-IIIA NSCLC
- Surgically resected
- EGFR mutation positive

- Completed routine adjuvant chemotherapy and/or XRT



Primary Endpoint:

- Disease Free Survival:
  Goal: 2-year ≥86%

Secondary Endpoints:

- Safety and Tolerability
- Overall Survival

SELECT Results

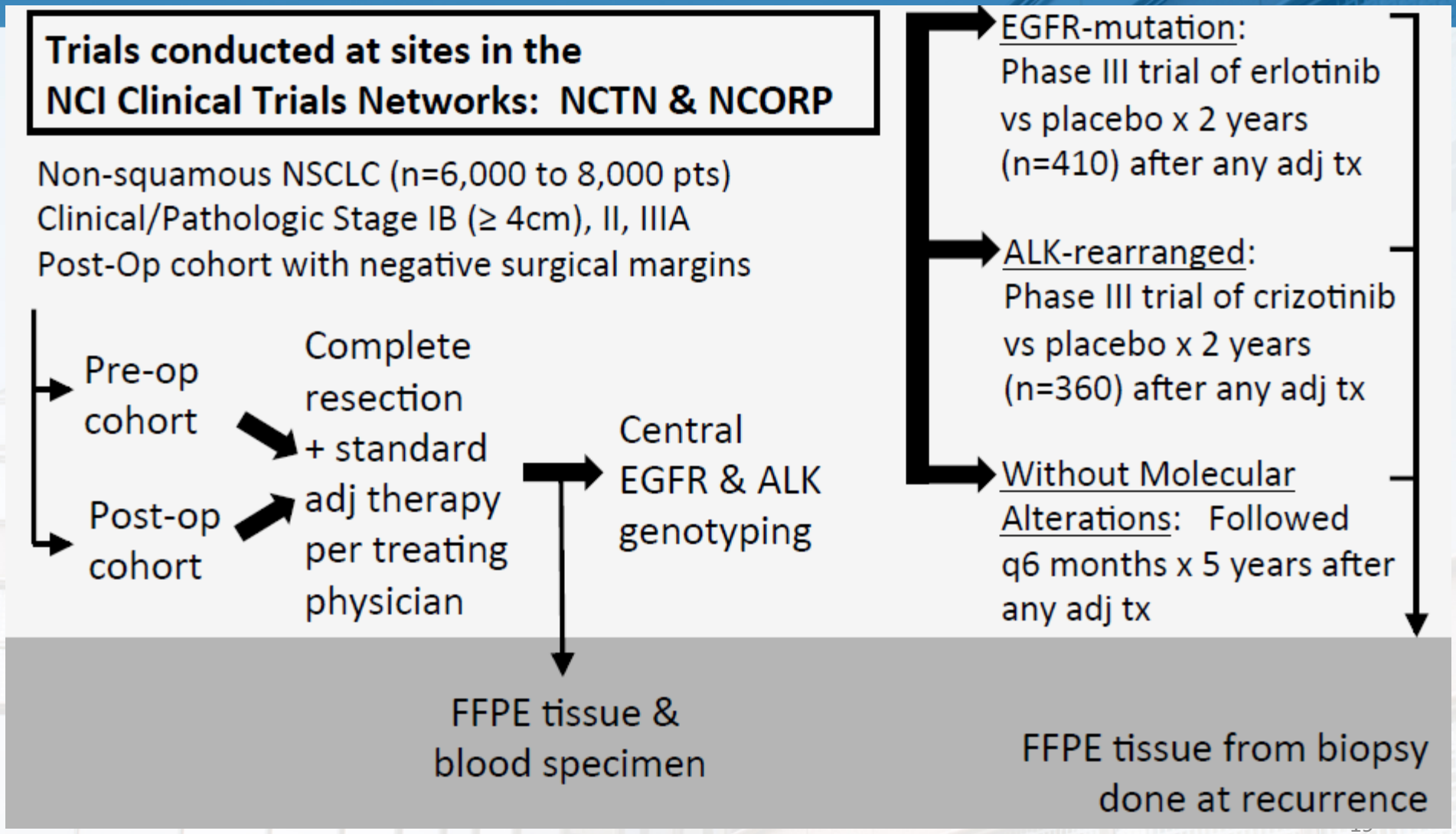
- 45% stage 1, 27% stage 2, 28% stage 3
- 2/3 completed full 2 years of treatment
- 2-year DFS was 89% compared to expected 76% in historical control (MSK cohort)
- 29 recurrences, but only 4 on erlotinib
- Most recurrent pts responded to rechallenge with TKI, only 1 T790M+ on recurrence
- DFS consistent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



https://www.allianceforclinicaltrialsinoncology.org/main/cmsfile?cmsPath=/Public/Alliance-Feature/files/ALCHEMIST-Slide-Deck-08182014.pdf

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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