14th Annual Winter Lung Cancer Conference

Friday-Sunday, February 10-12, 2017, Miami, Florida

Adjuvant And Neoadjuvant Therapy

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Case Presentation

A 77 YO WF who presented to the ER in Nov 2012 with chest pain and mild dyspnea on exertion. A cardiac work up was negative. She underwent a CT scan of the chest which revealed a RUL mass.

Past Medical History:

- Hepatitis C (blood transfusion in 1980)
- Hypertension
- Carotid Stenosis
- Diverticulosis
- Osteoporosis
- Depression

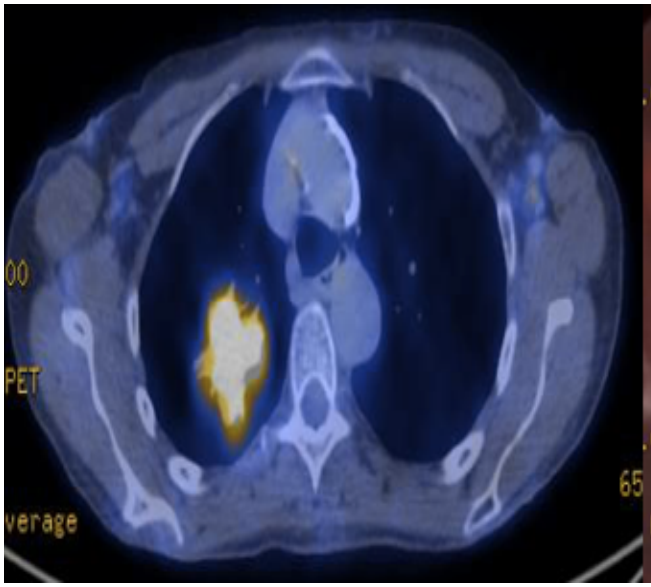
Family History: No history of cancer

Social History: Current smoker, half a pack/day x 60 years

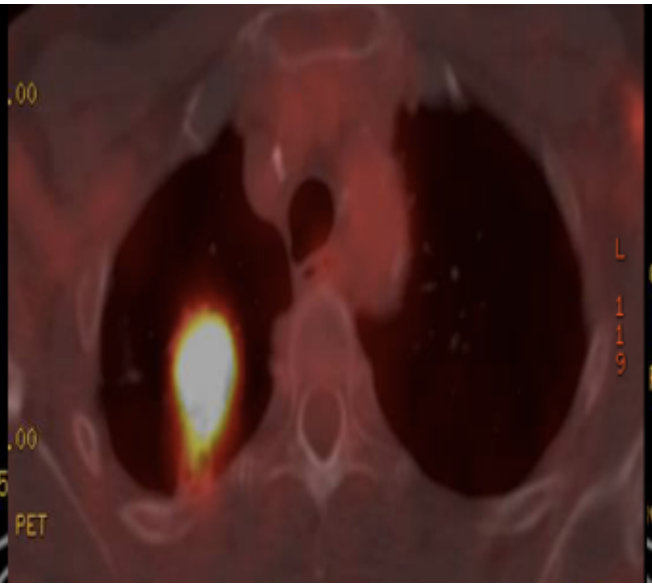
ROS: Wears hearing aides; poor appetite

Physical Exam: Pleasant elderly lady in NAD, PS=0
HEENT: No adenopathy
Lungs: Clear

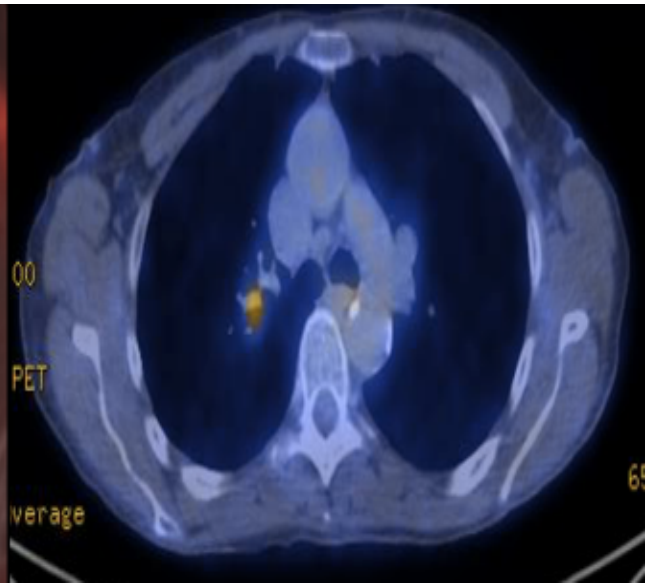
Case Presentation: Imaging



Multilobulated, spiculated RUL mass



Invasion into the posterior pleura



R hilar node

- Brain MRI was negative
- Clinical stage - Stage IIA (T2aN1M0)

Case Presentation: Treatment

Surgical Resection: The patient underwent mediastinal lymph node staging and lobectomy

Pathology: Lung, Right Upper Lobe (Lobectomy)

- Adenocarcinoma
- Moderately To Poorly Differentiated
- 5.5 X 5.2 X 3.0 cm, Extending To Pleural Surface
- Surgical Margins Negative For Tumor

0/15 Lymph nodes Were Positive For Tumor

STAGE pT2bN0M0 adenocarcinoma

Adjuvant treatment: Vinorelbine and Cisplatin x 3 cycles (patient refused the 4th cycle)

NED as of Dec 2016

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Disclosures

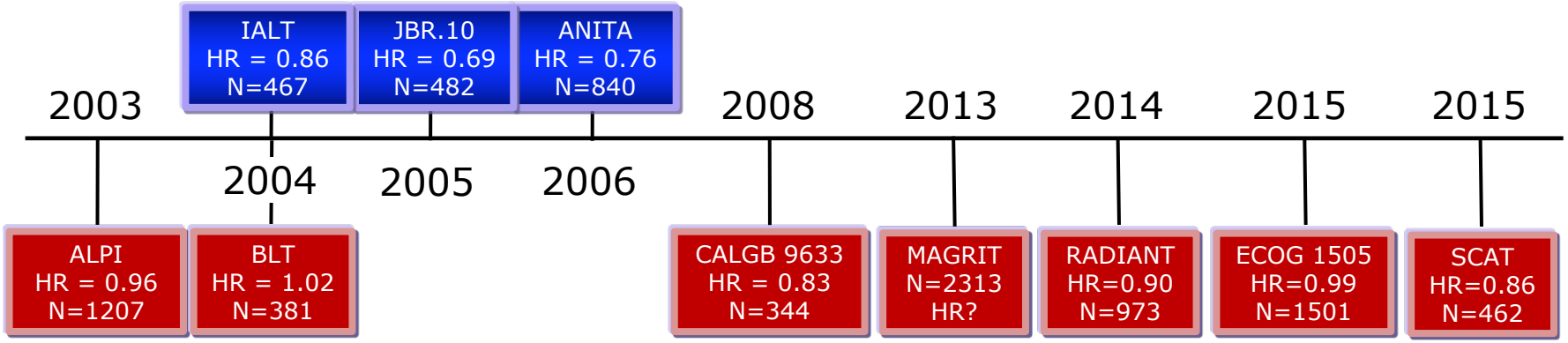
Royalty: UpToDate Author

Advisor: Ariad, AstraZeneca, BMS, Boehringer Ingelheim, Genentech, G1 Therapeutics, Lilly

Research: AbbVie, Celgene, EMD Serono, Five Prime, Genentech, Gilead, Lilly, Millennium, Novartis, Transgene

Adjuvant Therapy Timeline

Phase III Trials

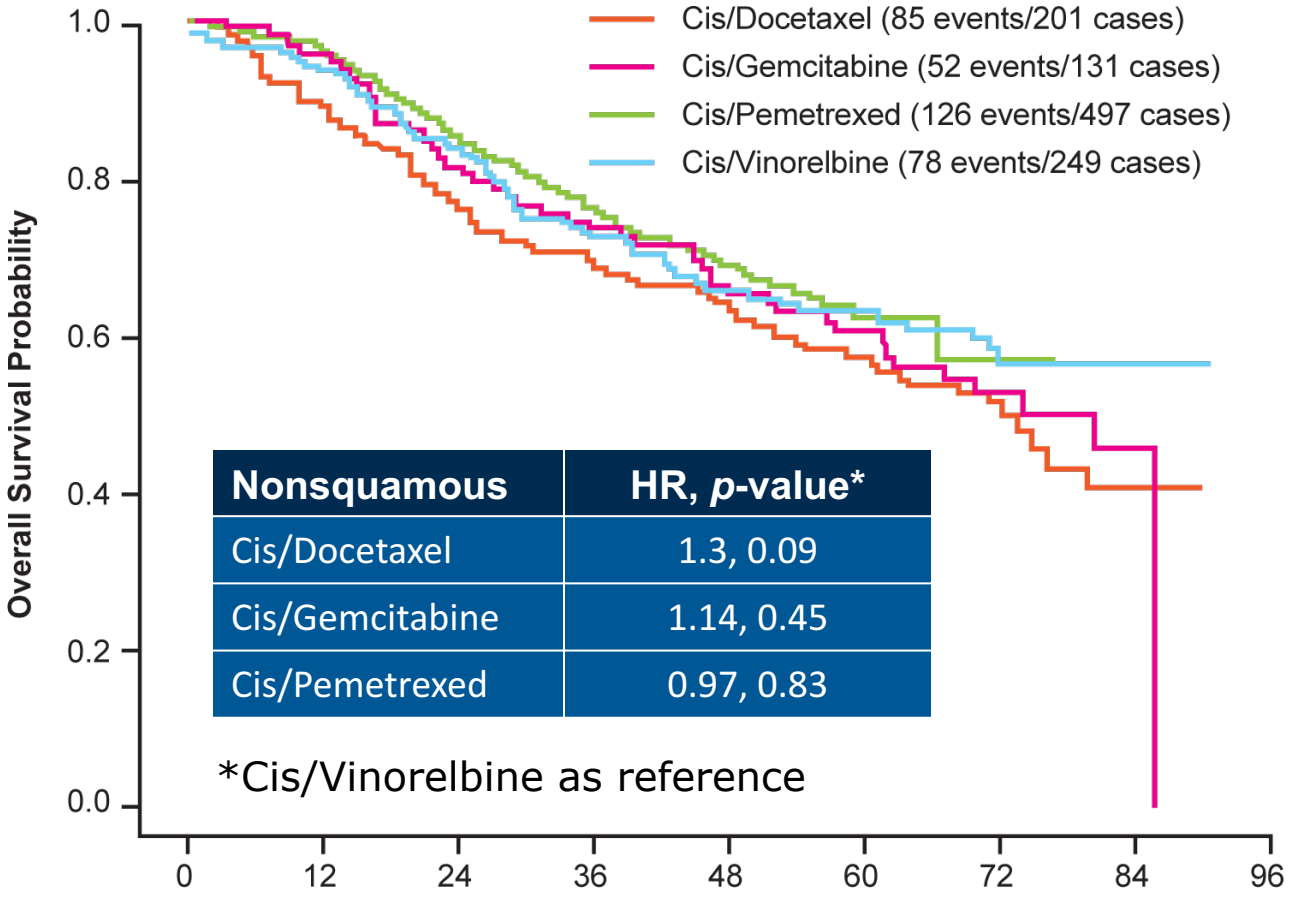


- Adjuvant chemotherapy produces a 4-5% absolute survival benefit at 5 years
- This benefit is greatest in patients with Stage II and IIIA disease
- Patients with stage IB (≥4 cm may also receive adjuvant chemotherapy)
- Novel systemic regimens have not produced an additional survival advantage

ALPI Scagliotti et al. *J Natl Cancer Inst* 95: 1453-61, 2003; BLT Waller et al. *Eur J Cardiothorac Surg* 26:173-182, 2004; IALT Arriagada et al. *N Engl J Med* 350: 350-61, 2004; JBR.10 Winton et al. *N Engl J Med* 352:2589-97, 2005; ANITA Douilland et al. *Lancet Oncol* 7: 719-27, 2006; CALGB 9633 Strauss et al. *J Clin Oncol* 26: 5043-51, 2008; MAGRIT GSK press release Mar 2014; RADIANT Kelly et al. *J Clin Oncol* 32 (abstr 7501), 2014; ECOG 1505 Wakelee et al. WCLC 2015 PLEN04.03; SCAT Massuti et al. *J Clin Oncol* 33 (abstr 7507).

ECOG 1505: Overall Survival by Chemotherapy Group

Nonsquamous



Nonsquamous	HR, *p*-value*
Cis/Docetaxel	1.3, 0.09
Cis/Gemcitabine	1.14, 0.45
Cis/Pemetrexed	0.97, 0.83

*Cis/Vinorelbine as reference

No differences in overall survival were observed between chemotherapy regimens in the squamous cell population

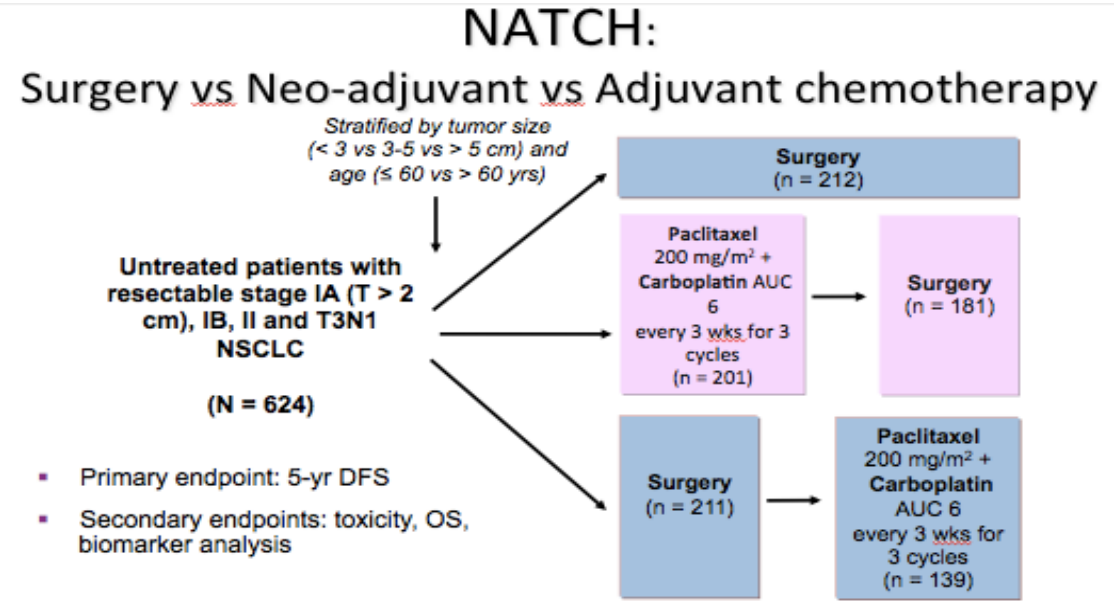
Wakelee HA et al. *Proc ASCO* 2016;Abstract 8507.

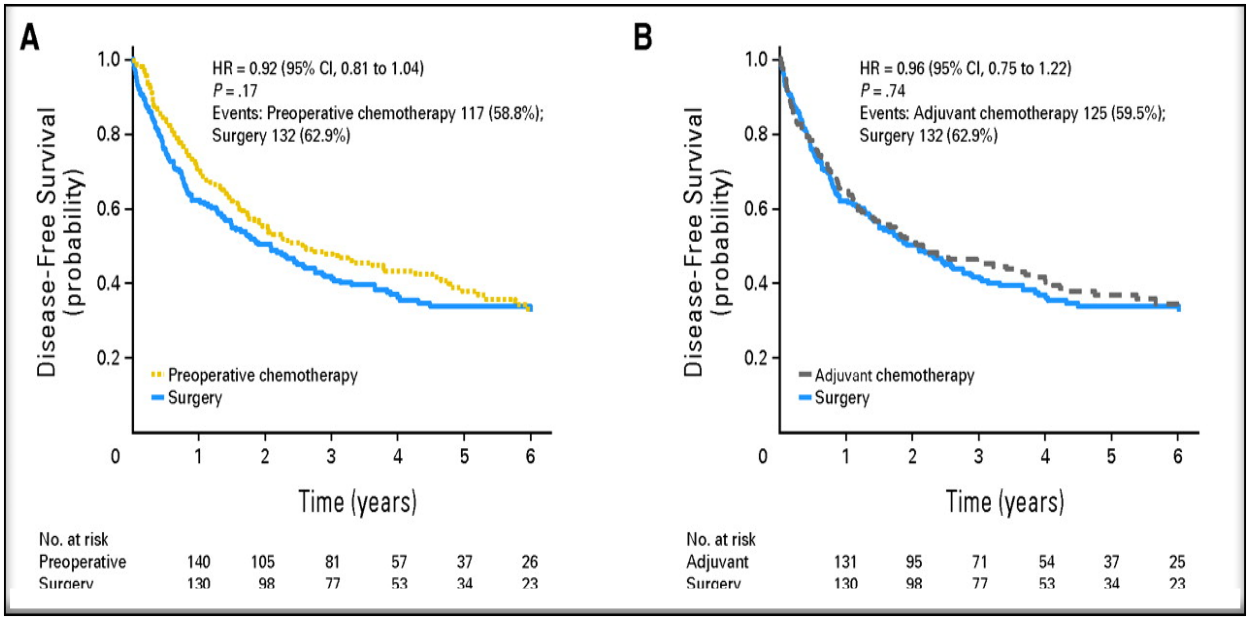
Adjuvant Therapy

- Excess non-cancer deaths (1.4%) on pooled chemotherapy arm after 5 years (*LACE meta-analysis Pignon 2008*)
- Elderly patients (≥70 year) may achieve a similar OS benefit as compared to their younger counterparts without a significant increase in toxicity *(LACE pooled analysis, Fruh 2008; JBR10, Pepe 2007, Ontario Cancer Registry, Cuffe 2012)*
- Carboplatin is an acceptable alternative to cisplatin in the elderly patients *(SEER database; Gu 2011)*
- Completion of all 4 cycles of chemotherapy is associated with better survival *(SCAT trial, Massuti, 2015)*
- There is no optimal cisplatin doublet *(ECOG 1505, Wakelee 2016)*

NeoAdjuvant Therapy

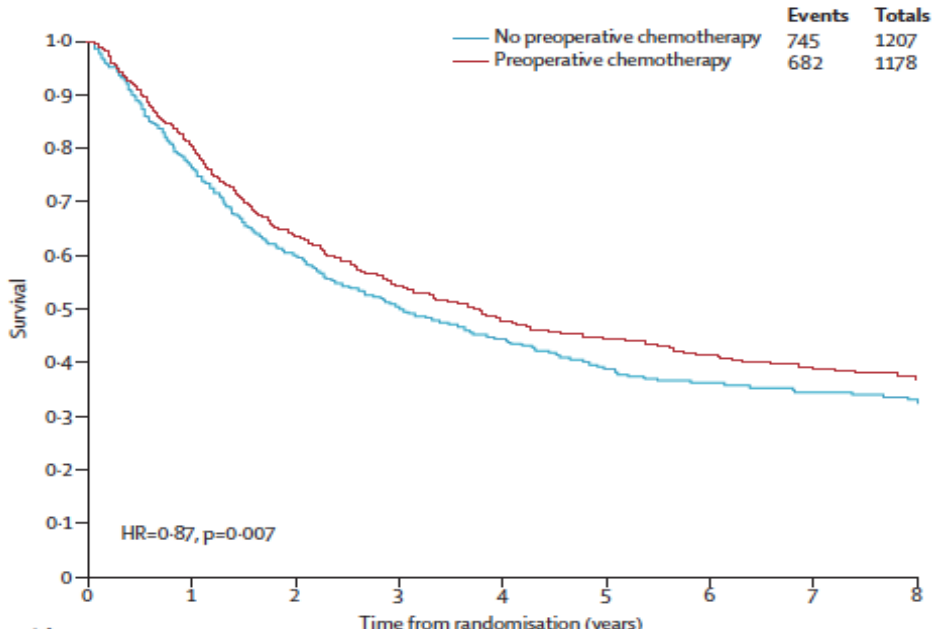
- No significant OS difference
- Non-significant trend toward improved DFS with preoperative chemotherapy
  - 4.2% improvement in 5-yr DFS
- More patients in preoperative chemotherapy arm received treatment
- Similar resectability rates, surgical procedures and postoperative mortality

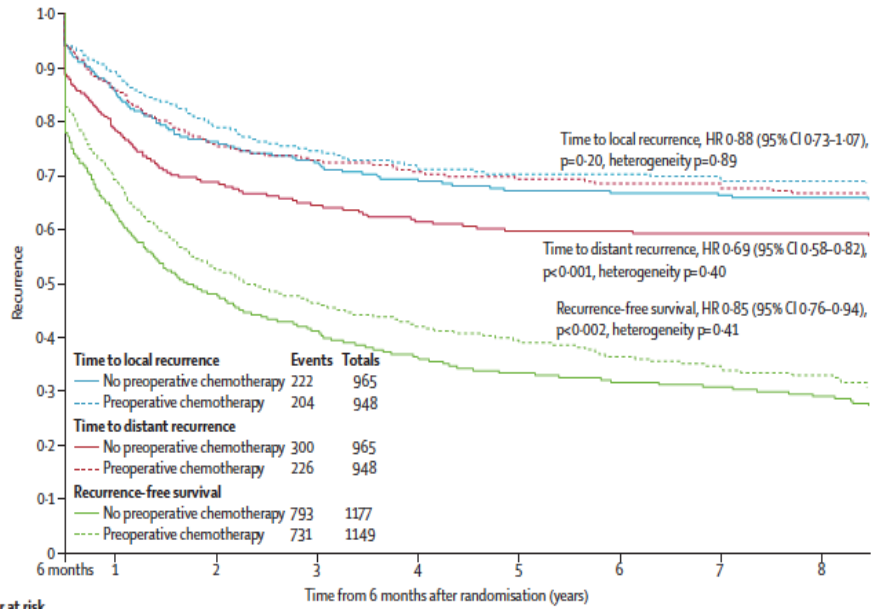




Felip E et al. *JCO* 2010.

Neoadjuvant Therapy: Meta-Analysis





France 1990	8/13	MRC BLT	4/5
MD Anderson 1994	19/28	MRC LU22	151/258
Spain 1994	19/29	SWOG S9900	93/180
MIP-91	137/179	China 2002	26/32
SWOG S9015	3/5	China 2005	8/19
JCOG 9209	28/31	ChEST	45/129
Netherlands 2000	23/39	NATCH	99/201
Finland 2003	19/30	**Total**	**682/1178**

NSCLC Meta-analysis collaborative Group. *Lancet* 2014.
NSCLC Meta-analysis Collaborative Group. *Lancet* 2010.

Neoadjuvant vs. Adjuvant

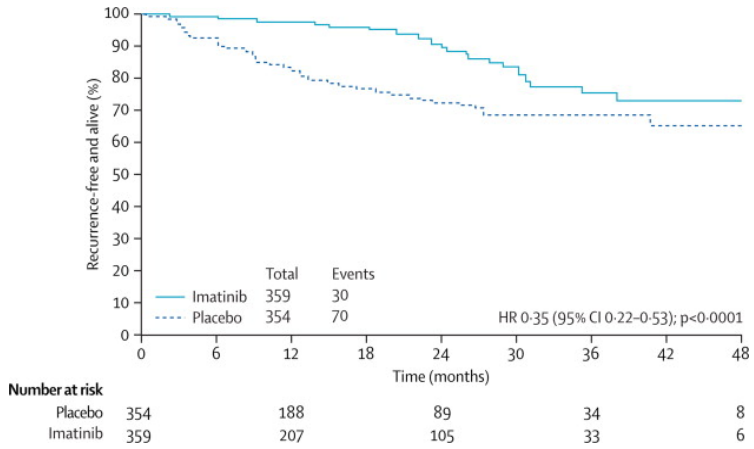
Meta Analysis

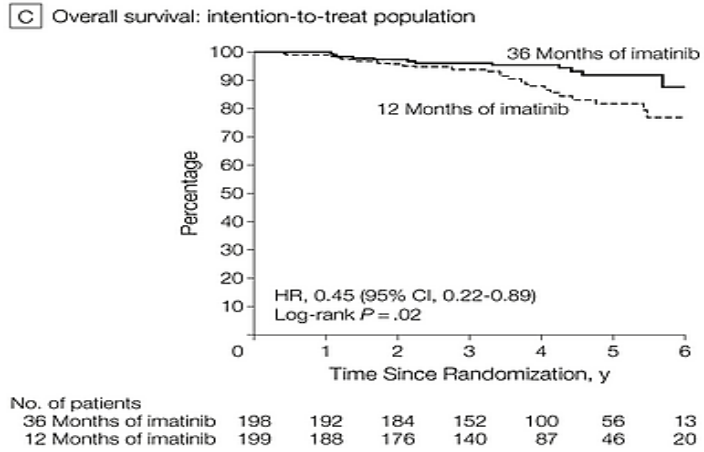
	N	HR	P value
Neoadjuvant Trials	2385	0.87 (95% CI 0.78-0.96)	0.007
Adjuvant Trials	8447	0.86 (95% CI 0.81-0.92)	<0.0001

NSCLC Meta-analysis collaborative Group. *Lancet* 2014.
NSCLC Meta-analysis Collaborative Group. *Lancet* 2010.

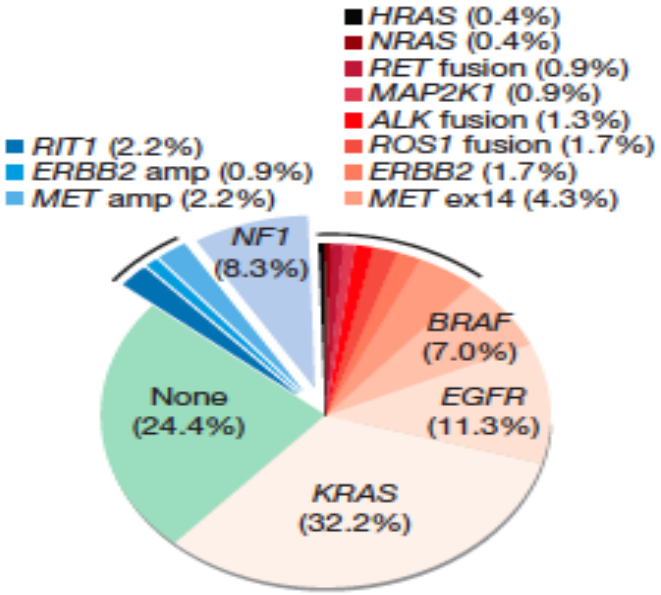
Molecularly Targeted Therapy

Adjuvant Imatinib in KIT+ GIST

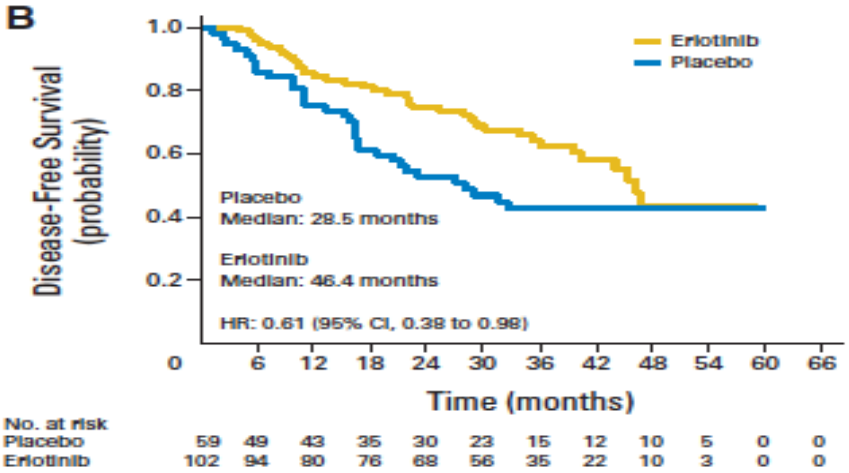




Joensuu H et al. *JAMA* 307:1265-72, 2012.

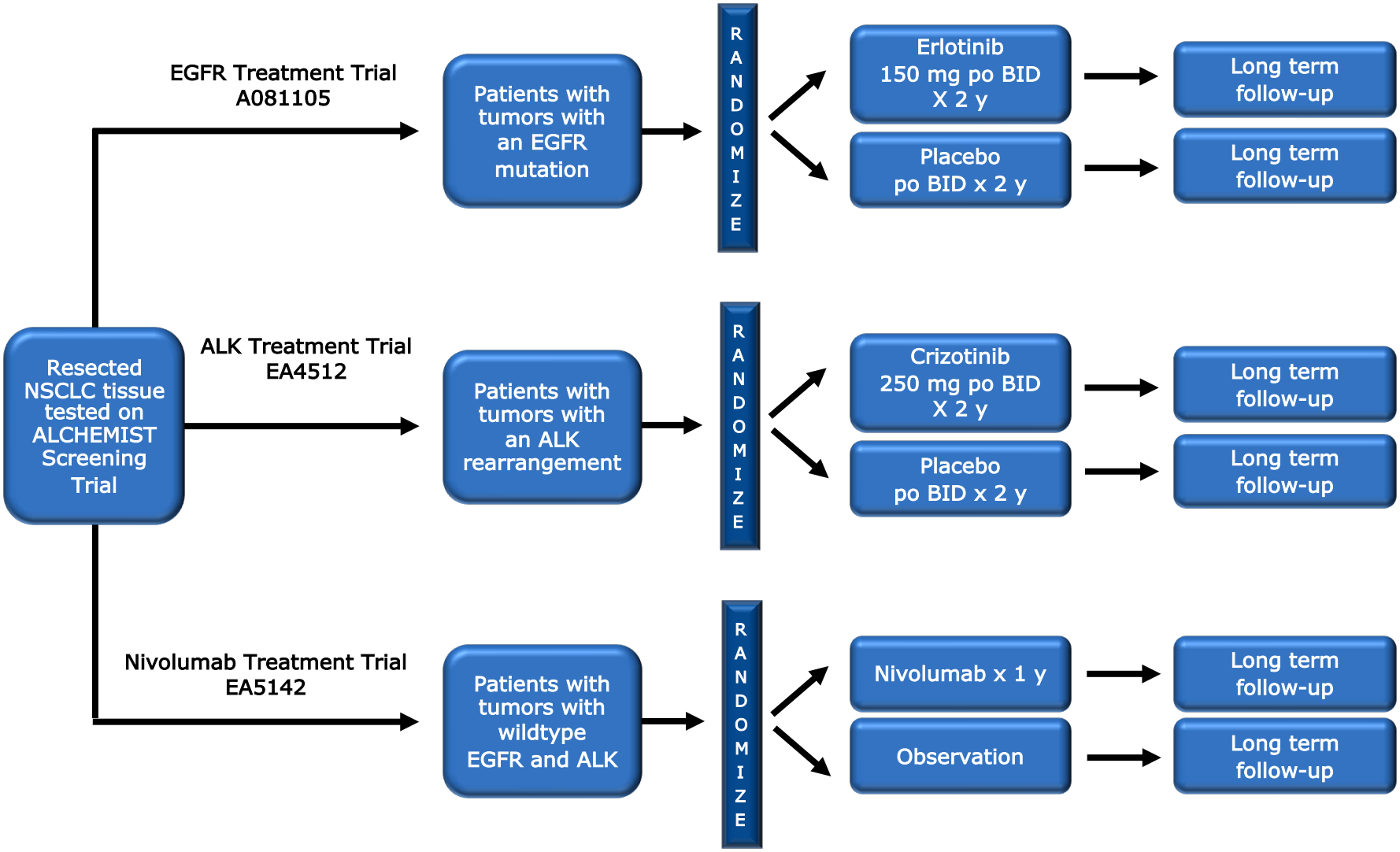


RADIANT: Disease-free Survival: *EGFR* M+ population



Kelly K et al. *J Clin Oncol 2015; 33:4007-14*

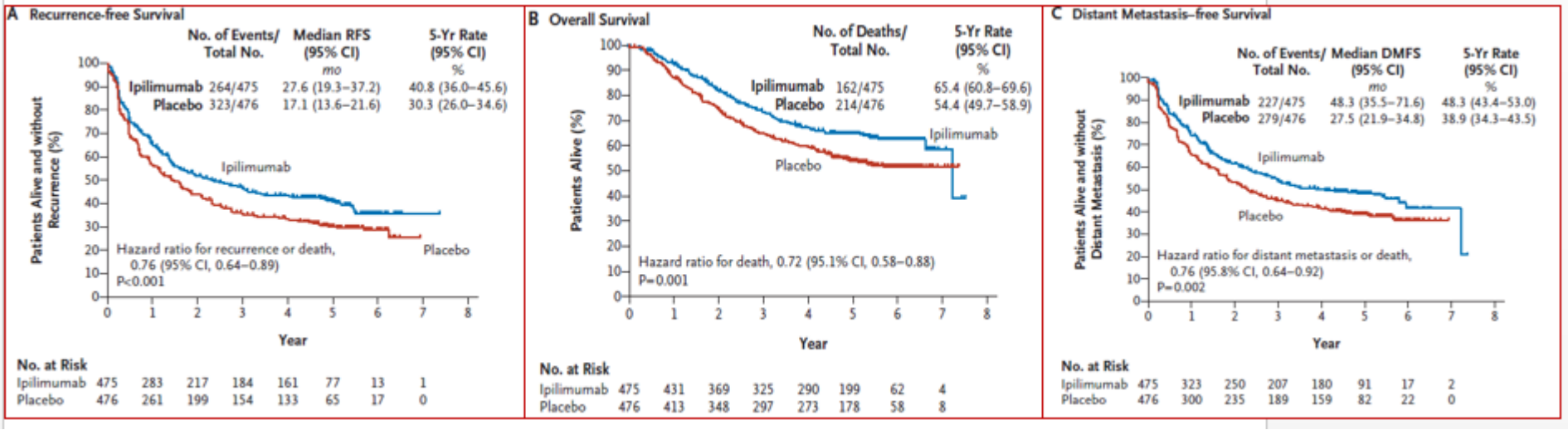
ALCHEMIST


Resected NSCLC tissue tested on ALCHEMIST Screening Trial
EGFR Treatment Trial A081105
Patients with tumors with an EGFR mutation
RANDOMIZE
Erlotinib 150 mg po BID X 2 y
Placebo po BID x 2 y
Long term follow-up
Long term follow-up
ALK Treatment Trial EA4512
Patients with tumors with an ALK rearrangement
RANDOMIZE
Crizotinib 250 mg po BID X 2 y
Placebo po BID x 2 y
Long term follow-up
Long term follow-up
Nivolumab Treatment Trial EA5142
Patients with tumors with wildtype EGFR and ALK
RANDOMIZE
Nivolumab x 1 y
Observation
Long term follow-up
Long term follow-up

Adjuvant Therapy: Phase III Trials in Patients with EGFR+ Tumors

	N	Design	Primary Endpoint
ALCHEMIST	410 pts Stage IB (>4cm-IIIA)	Erlotinib versus placebo x 2 yrs (after chemotherapy)	Overall Survival
ADAURA	700 pts Stage IB-IIIA	Osimertinib (AZD9291) versus placebo x 3 yrs (after chemotherapy)	Disease Free survival
Japan WJOG6401L	230 pts Stage II-IIIA	Gefitinib x 2 years CDDP/VNR 4 cycles	Disease free survival at 5 years
China CTONG1104	220 pts Stage II-IIIA	Gefitinib x 2 years CDDP/VNR 4 cycles	Disease free survival
China ICTAN	477 pts Stage II-IIIA	Chemotherapy Chemotherapy followed by 6 or 12 months of icotinib	Disease free survival
China	300 pts Stage II-IIIA	Icotinib versus placebo x 2 years (after chemotherapy)	Disease free survival
Dana Farber MGH	92 pts Stage I-III	Afatinib 3 months versus 2 years (after chemotherapy)	Disease free survival

Adjuvant Ipilimumab in Melanoma



Median FU 5.3 years

Median # of doses: 4
29% received ~ 1 year of tx
49% discontinued tx due to AE

Eggermont AMM et al. *NEJM* Oct 2016.

Ongoing PD-1/PD-L1 Adjuvant Trials

Drug/Trial	Description	Stages Entered		Primary Endpoint
Nivolumab ALCHEMIST/ANVIL	US NCI, observation as control	IB (4 cm) – IIIA After adjuvant chemotherapy and/or radiation	Phase 3 Allows PD-L1+ and PD-L1-	OS/DFS
Atezolizumab Impower010	Global, placebo controlled	IB (4 cm) – IIIA After adjuvant chemotherapy	Phase 3 Restricted to PD-L1+	DFS
MEDI4736	Global, placebo controlled	IB (4 cm) – IIIA After adjuvant chemotherapy	Phase 3 Allows PD-L1+ and PD-L1-	DFS
Pembrolizumab Keynote-091	ETOP/EORTC, placebo controlled	IB (4 cm) – IIIA After adjuvant chemotherapy	Phase 3 Allows PD-L1+ and PD-L1	DFS

Abbreviations: ETOP/EORTC, European Thoracic Oncology Platform/European Organization for the Research and Treatment of Cancer; US NCI, United States National Cancer Institute

Chuang et al. *Hem Onc Clinics* 2016.

Chemotherapy Predictive Markers

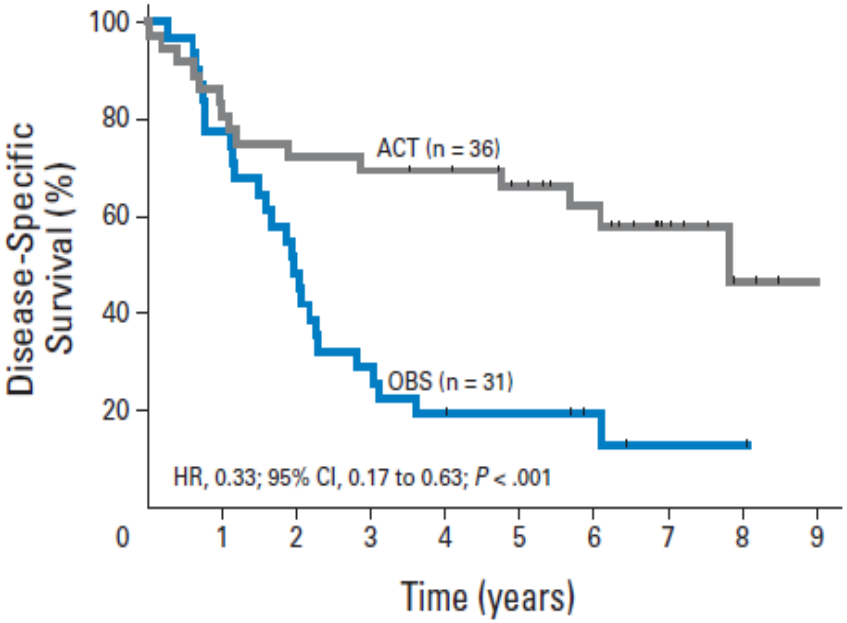
Prospective Phase III Trials

	Marker	Primary Endpoint
TASTE	ERCC1	Did not proceed to Phase III due to the methodology issues
SCAT	BRCA1 RAP80	Did not meet its primary OS endpoint
ITACA	ERCC1 TS	Awaiting results

Who Should Receive Adjuvant Chemotherapy?

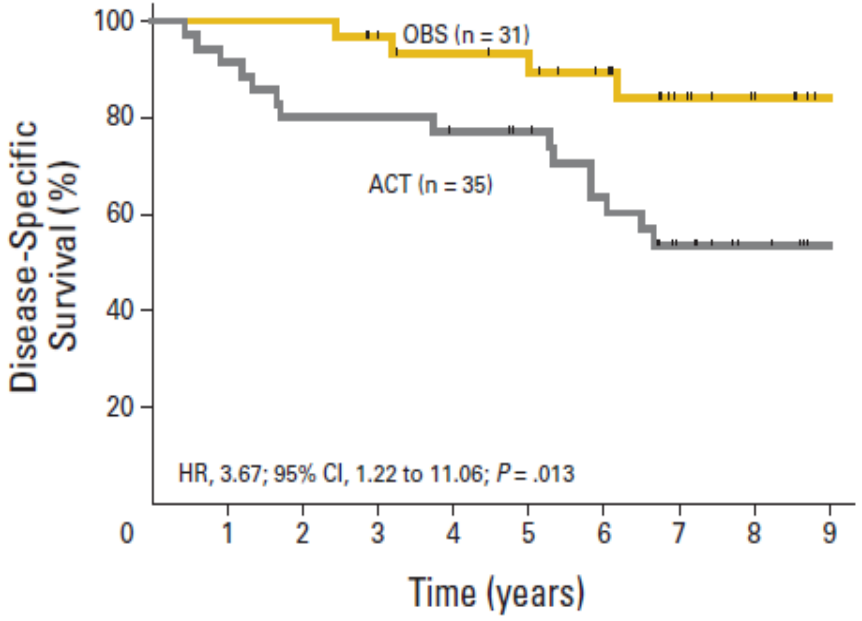
GeneFx® Lung 15 Gene Signature

JBR.10, High Risk (n = 67)



Observ	31	9	3	0
Chemo	36	25	15	1

JBR.10, Low Risk (n = 66)



Observ	31	28	20	1
Chemo	35	28	19	3

Interaction p = 0.0001

Zhu C-Q et al. *J Clin Oncol* 2010, 28: 4417-24.

Summary

- Four cycles of a platinum-based doublet is the standard of care for patients with resected stage IIB-IIIA and is reasonable in patients with resected stage IB ≥4 cm.
- The strongest evidence favors adjuvant administration of chemotherapy but neoadjuvant administration is likely to produce a similar survival benefit.
- There is strong biological and clinical rationale for the evaluation of molecularly targeted therapy and immune checkpoint inhibitors.