Non-small cell lung cancer

Non-small Cell Lung Cancer

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NIH NATIONAL CANCER INSTITUTE

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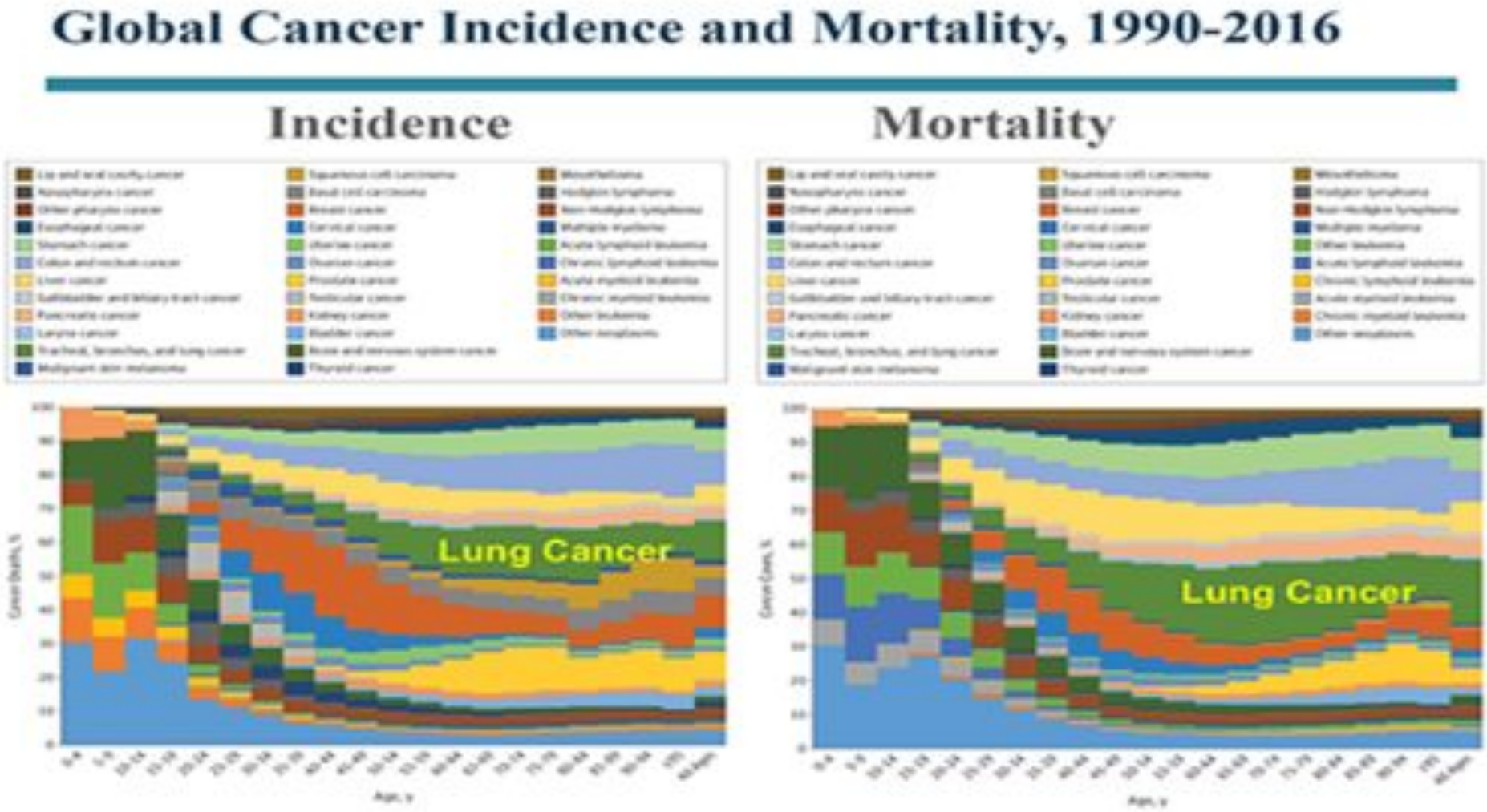
Global incidence and mortality



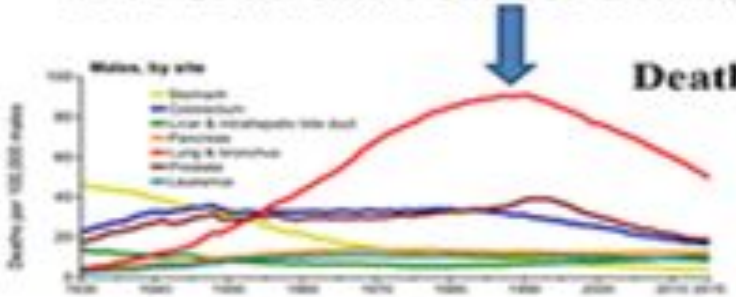
Fitzmaurice C et al., JAMA Oncol 2018 epub

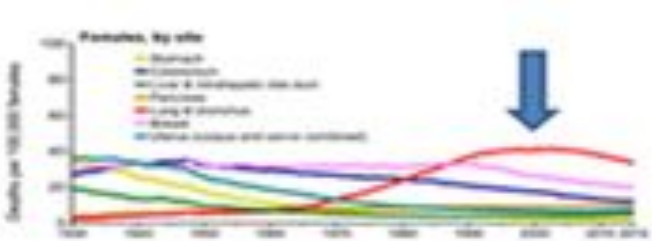
Cancer Statistics, 2018

US Lung Cancer Statistics, 2018

- 234,030 estimated new cases (lung and bronchus)
- 154,050 estimated deaths
- leading cause of cancer deaths
  - greater than breast+prostate+colon
  - death rate per 100,000 decreasing (90.56 in 1990; 67.45 in 2006)
    - Incidence declining in men since mid-1980's, women since mid-2000's
- 18% five year survival
  - 5% in 1950's, 13% in 1970's

26% of all male cancer deaths, 25% of all female cancer deaths

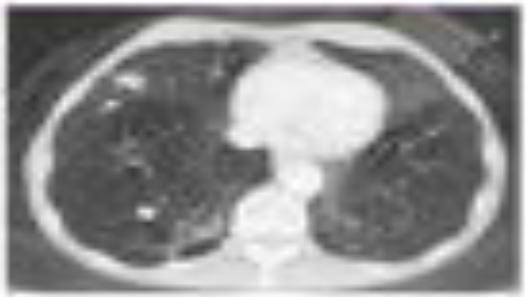




https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf

Risk factors

Risk Factors

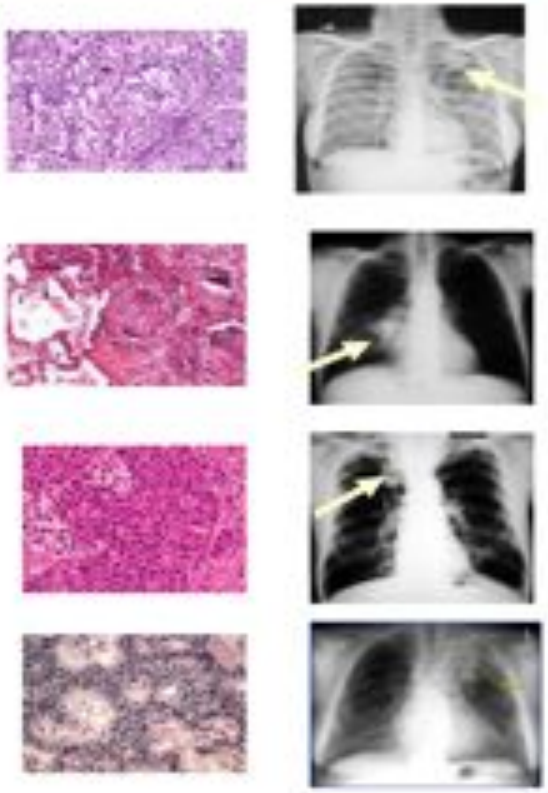


- Tobacco, tobacco, tobacco (85% lung ca.)
  - Including passive smoking
  - Prior aerodigestive malignancy
  - COPD
- Other exposures
  - Asbestos, radon, polycyclic aromatic hydrocarbons, chromium, nickel, inorganic arsenic – mining, ship building, oil refining
- Genetic predisposition
  - Familial lung cancer – Germline mutations - EGFR T790M
    - Bell et al., Nat Gen 2005;37:1315
  - 15q24-25.1 – nicotinic acetylcholine receptor subunits CHRNA3 and CHRNA5, OR=1.3, attributable risk ~14%
    - Amos et al., Nat Gen 2008;40:616, Hung et al. Nature 2008;452:633, Thorgeirsson et al. Nature 2008;452:638
  - CH3NA3/5 is also susceptibility locus for COPD
    - Pillai et al. PLoS Genet 2009;5:1

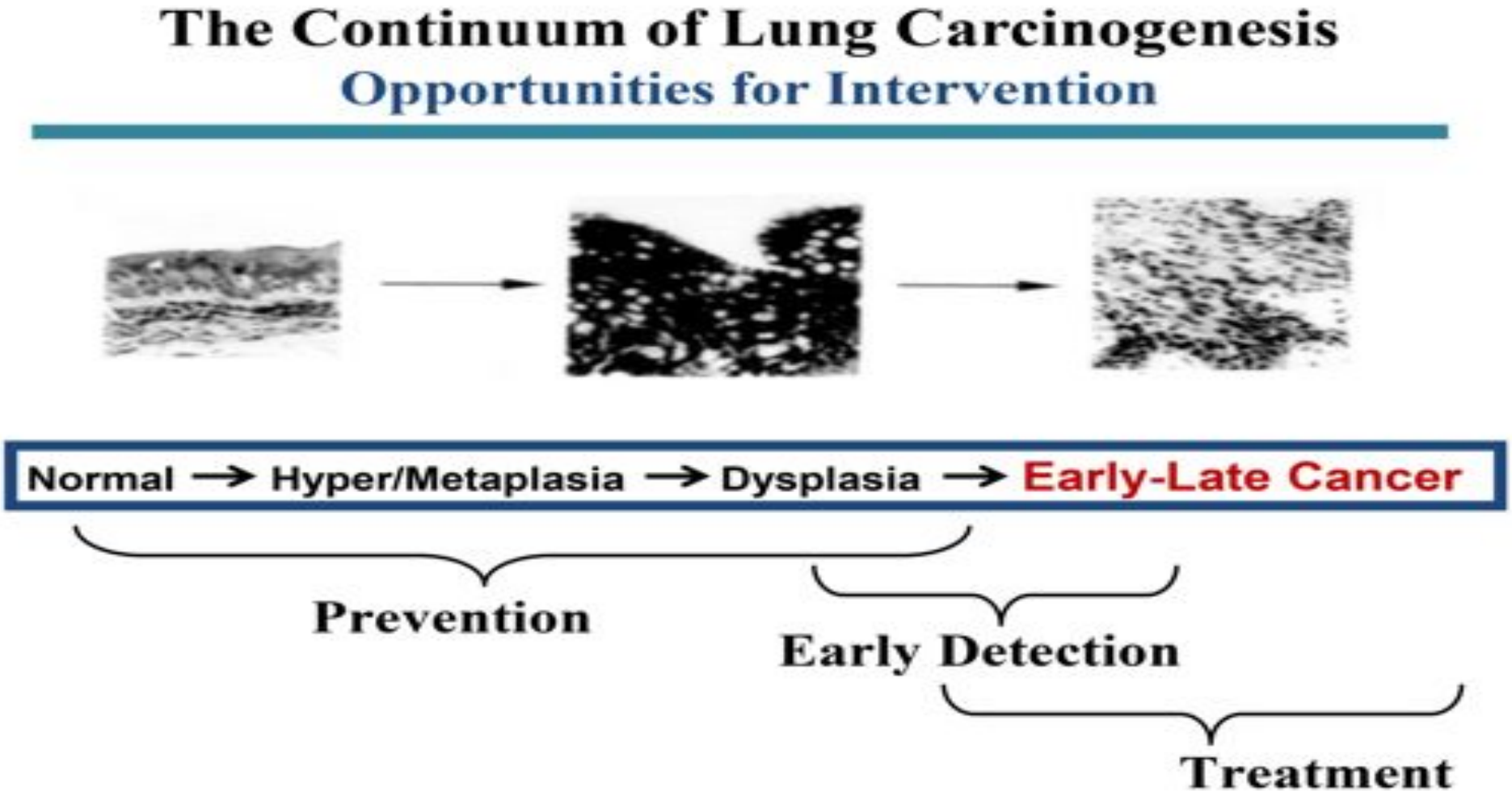
Pathology: NSCLC

Pathology: Non-small Cell Lung Cancer

- **Adenocarcinoma, inc bronchoalveolar**
  - **40%**
- **Squamous cell carcinoma**
  - **20%**
- **Large cell carcinoma**
  - **15%**
- **Others (carcinoid, etc.)**



Lung carcinogenesis



Treatment Strategies for Lung Cancer

- **Treatment based on stage:**
  - **Early stage (Stage I) – surgery**
  - **Early stage (Stage II, IIIA resected)-surgery + adjuvant chemo**
  - **Regional spread (IIIA/IIIB) – combined modality (chemoradiation; +/- surgery for IIIA)**
  - **Metastatic (IIIB "wet"/IV)– chemotherapy, radiation as needed for local control, occasional resection of isolated metastases**
- **Small cell lung cancer: chemotherapy (+thoracic radiation for limited stage; prophylactic cranial radiation to prevent brain mets)**

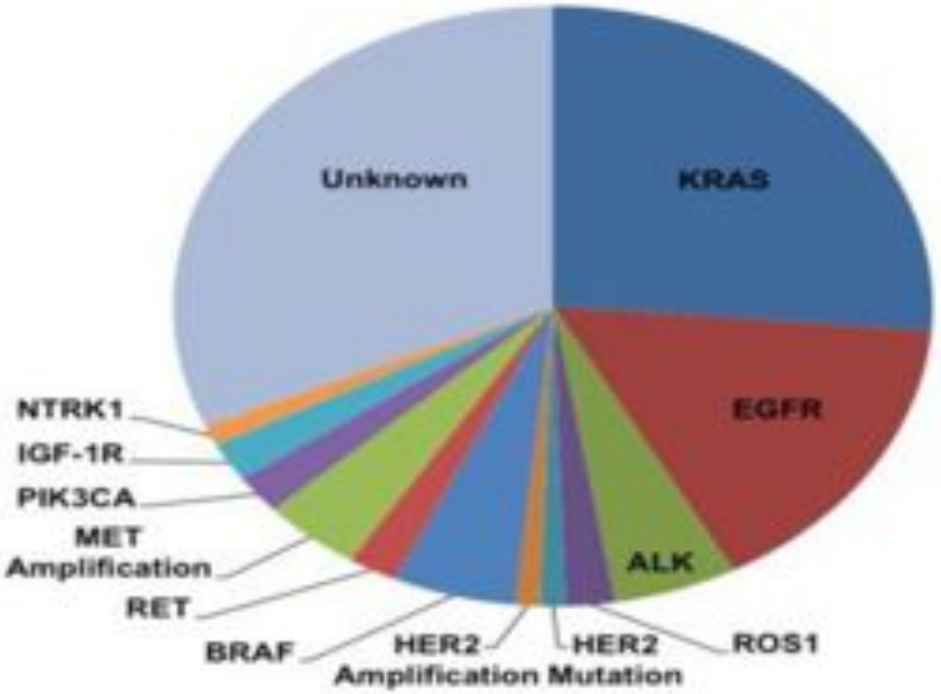
Treatment options

Treatment Options for Metastatic NSCLC

- **Chemotherapy**
  - Platinum doublets, iv
  - Adjuvant, metastatic disease
  - Still a mainstay of treatment
- **Targeted therapy**
  - For minority of patients with targetable mutations
  - Oral therapies, better tolerance
  - Extended survival
- **Immunotherapy**
  - Now a definitive role, frontline and second line

Personalizing Therapy for NSCLC

Personalizing Therapy for NSCLC
Genetic Abnormalities in Lung Adenocarcinoma



-Berge and Doebele, Sem Oncol 2014;41:110

EGFR as a Target for NSCLC

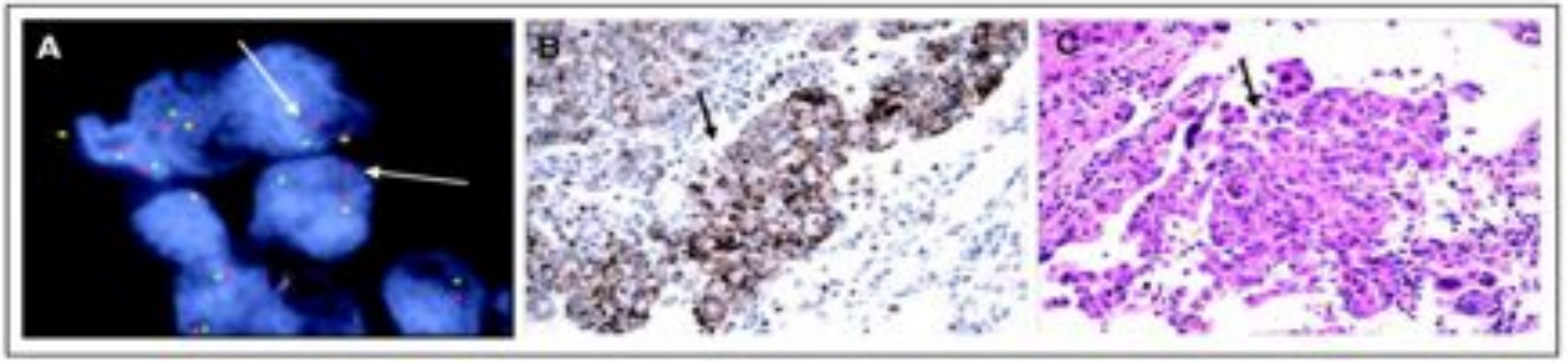
Standard of Care in 2015

- Epidermal growth factor receptor (EGFR) inhibition in advanced NSCLC
  - 10% response rate in advanced disease, 30% prolonged stabilization
  - Survival advantage (erlotinib)
    - Shepherd, F. A. et al. N Engl J Med 2005;353:123-132
  - Mutually exclusive with K-ras
  - Most benefit for non-smoking related NSCLC, with EGFR mutations (females, adenocarcinomas, Asian)
    - Lynch et al., NEJM 350:2129, 2004; Paez et al., Science 304:1497, 2004; Pao et al., PNAS 101:13306, 2004
  - Mechanisms of secondary resistance to EGFR inhibitors being identified (T790M mutation-50%, Met amplification-10-20%, others), new drugs
    - Pao et al., PLoS Med 2:e17, 2005; Engelman et al., Science 316:1039, 2007
- Erlotinib approved as single agent for 1st, 2nd and 3rd line treatment of NSCLC
  - Also for maintenance after 1st line non-progression after chemo
  - Afatinib, gefitinib also approved

EML4-ALK

EML4-ALK Fusion Gene as a Target for NSCLC

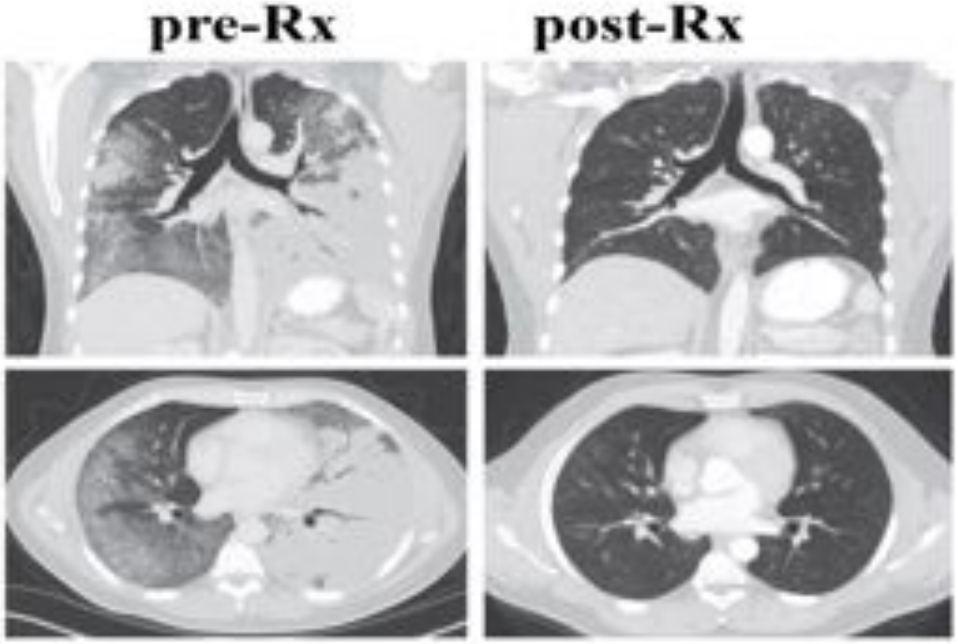
- Identified in 2007
- ~5% NSCLC, mainly never smokers
- Striking response to inhibitor – crizotinib- 57% RR, 33% stable disease (FDA approved)
  - Kwak EL et al. NEJM 2010;363:1693
- 2nd line agent approved (ceritinib), 56% RR
  - Shaw AT, et al. NEJM 2014;370:1189
- Multiple mechanisms of resistance



Shaw AT et al., JCO 2009;27:4247

ROS1 Rearrangements

ROS1 Rearrangements as a Target

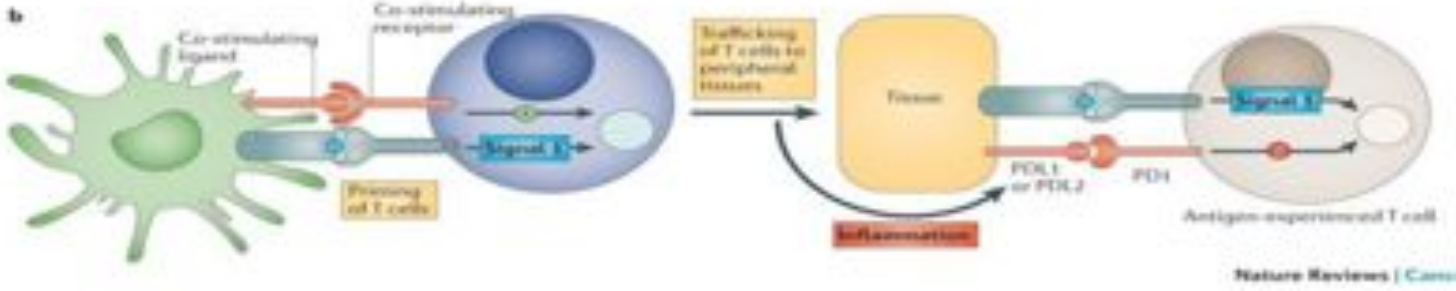


- Tyrosine kinase (insulin receptor family)
- 1.7% of NSLC have rearrangements
- Multiple different partners
- crizotinib – RR=72%, median duration 17.6 mths
  - Shaw AT et al., NEJM 2014;371:1963

New Approaches-Immunotherapy

New Approaches - Immunotherapy

- PD-1
  - T-cell co-inhibitory receptor, regulates T-cell activation
  - Main role: to limit activity of T cells in peripheral tissues during inflammatory response to infection and to limit autoimmunity
  - ligands PD-L1 (frequently expressed on tumors) and PD-L2
  - Blockade of PD-L1/PD-1 interaction potentiates immune response (to tumor)

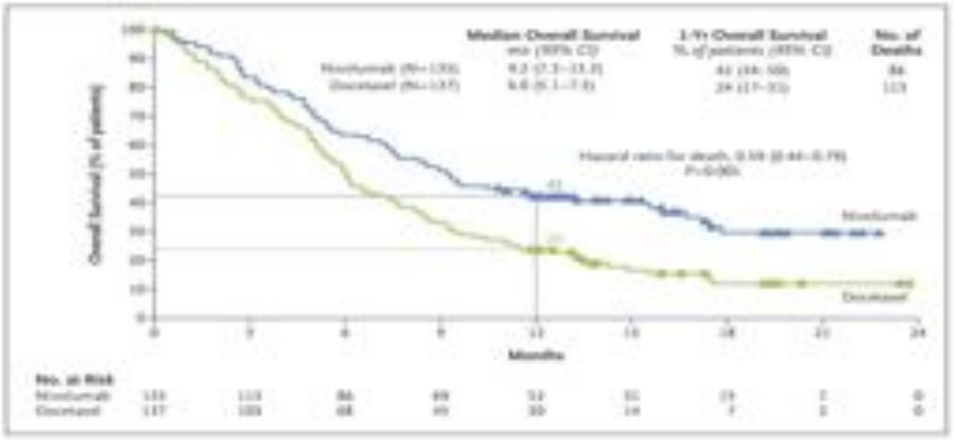


Pardoll D Nat Rev Cancer 2012;12:252

Immunotherapy

New Approaches - Immunotherapy

- **Anti-PD-1 antibodies approved for 2nd line NSCLC; nivolumab and pembrolizumab (PD-L1+)**
  - **~20% response rate (vs. 10% docetaxel)**
  - **~3 month improved overall survival nivolumab c/w docetaxel**
  - **Long term responses (median duration 12.5 mths with pembro)**



Squamous, nivolumab: -Brahmer J et al. N Engl J Med 2015;373:123-135.

Non-squamous, nivolumab: Borghaei H et al. N Engl J Med 2015;373:1627-1639
Any NSCLC, pembrolizumab: Garon EB et al. N Engl J Med 2015;372:2018-2028

Second line immunotherapy

Second line immunotherapy treatment

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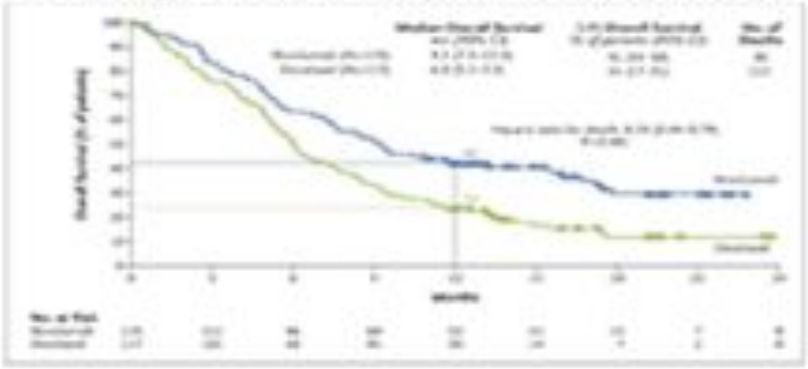


Squamous, nivolumab:
-Brahmer J et al. N Engl J Med 2015;373:123-135.

- **Anti-PD-L1 antibody: atezolizumab- similar efficacy**

Non-squamous, nivolumab: Borghaei H et al. N Engl J Med 2015;373:1627
Any NSCLC, pembrolizumab: Garon EB et al. N Engl J Med 2015;372:2018
Any NSCLC, atezolizumab: Rittmayer A et al. Lancet 2017;389:255

Approaches to reducing cancer morbidity and mortality

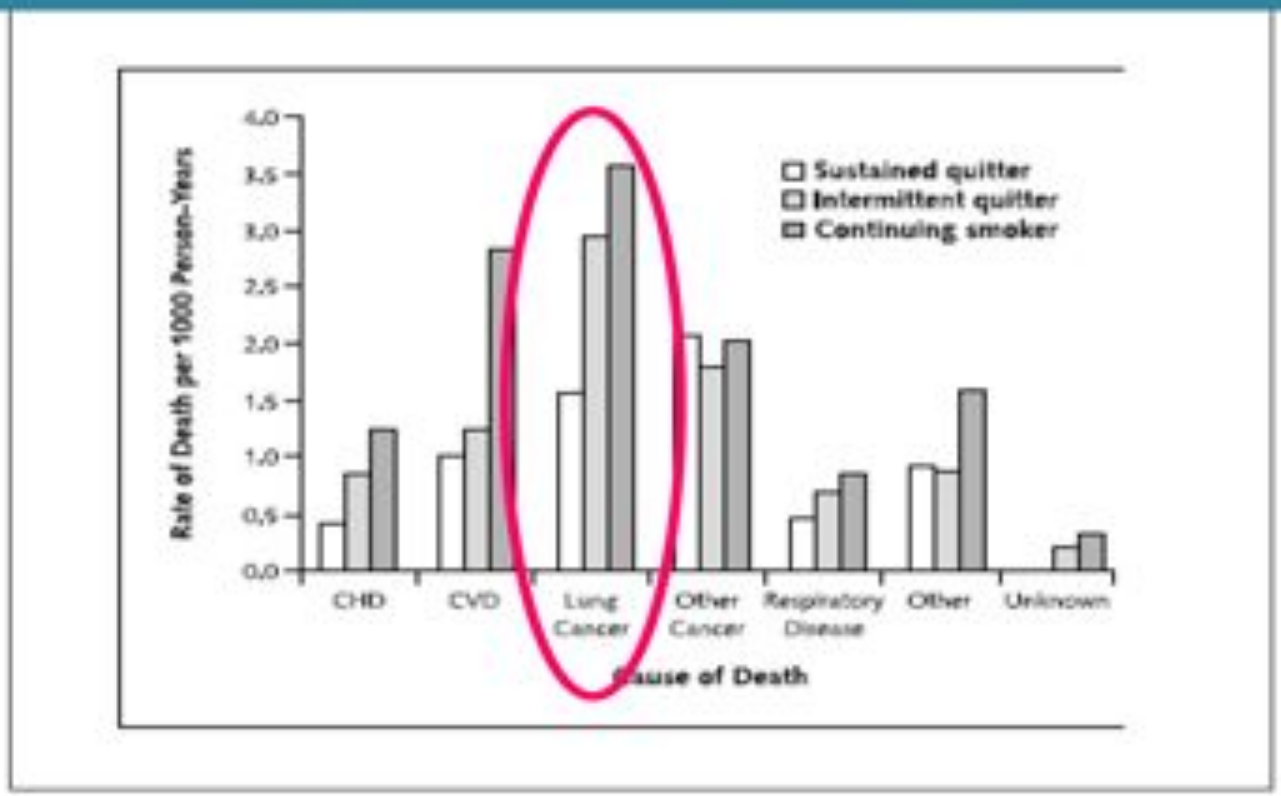
- **Prevention (primary, secondary, tertiary)**
- **Early detection**

- **Better therapeutics**

Smoking Cessation and Lung Cancer

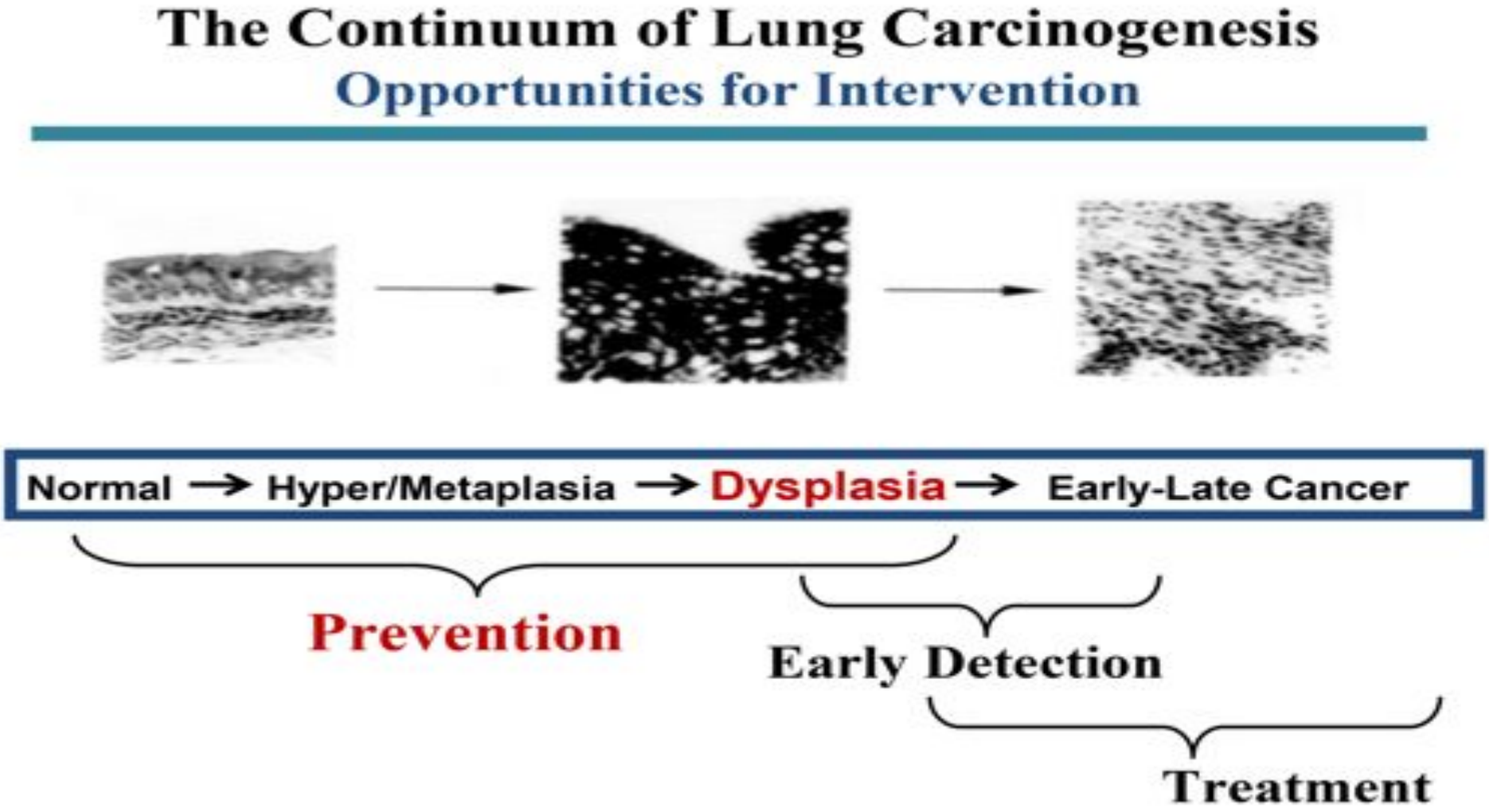
Effect of Smoking Cessation on Lung Cancer Death

Lung Health Study, 14.5 yr F/U



Anthonisen et al., Ann Intern Med 142:233, 2005

Lung carcinogenesis



Cancer Chemoprevention

The use of natural or synthetic agents to suppress or reverse carcinogenesis

- **Regress existing neoplastic lesions (treat intraepithelial neoplasia)**
- **Prevent development of new neoplastic lesions (preneoplastic and cancer)**
- **Suppress recurrence of neoplastic lesions**

Lung Cancer Prevention

Rationale for Lung Cancer Prevention

- **Metastatic cancer is rarely curable**
  - **US lung cancer 5 yr survival is ~15% (5% 1950's, 13% 1970's)**
- **Cancer is preventable**
  - **P1, STAR breast cancer prevention trials with tamoxifen and raloxifene**
    - *Fisher B et al., JNCI 1998;190:1371; Vogel, VG et al., JAMA 2006;295:2727*
  - **Multiple animal studies with multiple agents**
- **Long preclinical phase with increasing histologic and molecular abnormalities, identifiable populations at risk**

Efficacy: How Do We Identify New Agents?

- **Knowledge of mechanism**
  - **Example: HPV vaccine and cervical cancer**
  - **Need: understanding molecular pathogenesis**
- **Preclinical (in vitro and animal models)**
  - **Example: NSAID treated carcinogenesis and transgenic models**
  - **Need: models reflective of complexity of human disease**
- **Observational epidemiology (cohort and case-control studies)**
  - **Example: NSAIDs and colon cancer incidence/mortality**
- **Secondary endpoints from clinical trials (including other diseases)**
  - **Example: Tamoxifen/raloxifene and breast cancer**

Clinical agents

Clinical Agent Development – What are the major issues?

- **Targets/agent selection – correctly match target/agent to right process/person (Precision Medicine)**
  - Different pathogenesis/progenitor cell lineages→different intervention?
  - Temporal considerations – accumulating molecular abnormalities over time may require different strategies to be delivered at different time points
- **Cohort selection**
  - Squamous (central) cancers – bronchial dysplasia?
  - Adenocarcinoma (peripheral) cancers – lung nodules?
  - Other histologies - ???
- **Risk-benefit balance**
  - Efficacy vs. tolerability or major adverse side effects
- **Endpoints – cancer for phase III, intermediate endpoints (preliminary efficacy) for phase II**
- **Clinical trial designs**

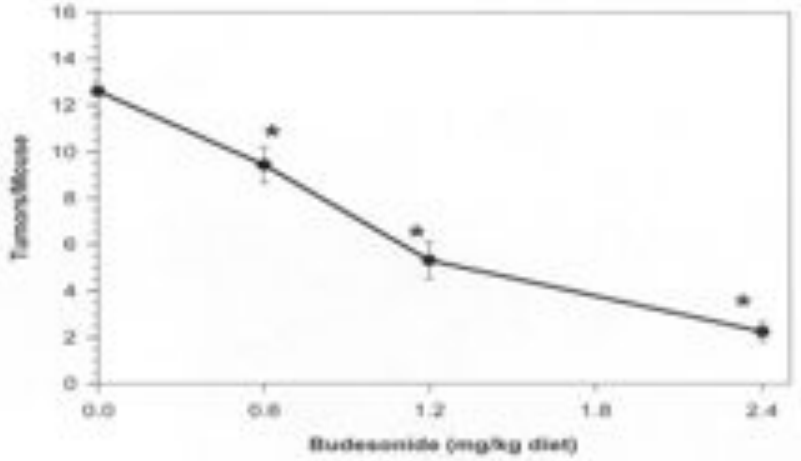
Targeting inflammation

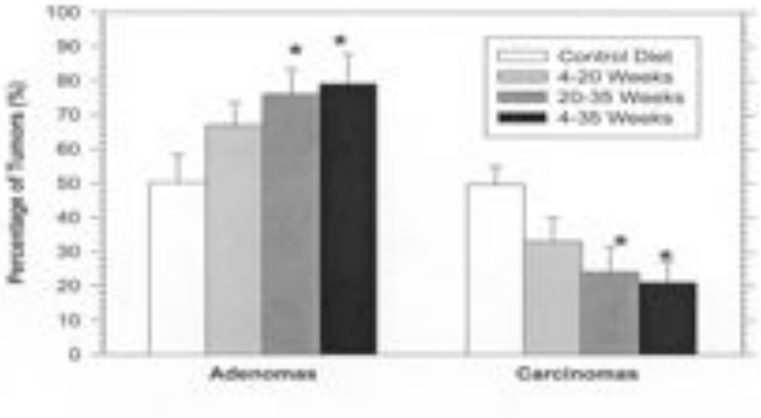
Targeting Inflammation for Lung Cancer Prevention: Rationale

- **Animal data showing role for steroids in cancer prevention**
  - **1970's – skin**
  - **Early 1990's – lung (oral steroids)**
  - **Late 1990's – lung (inhaled steroids)**
- **Epidemiology/Human data –**
  - **Mainly negative (but studies of short exposure duration)**
  - **VA cohort with COPD (n=10,474) – HR 0.39 (95% CI, 0.16-0.96)**
    - **Parimon T et al., AJRCCM 175:712, 2007**

Budesonide and Lung Tumorigenesis

Effect of Budesonide on Mouse Lung Tumorigenesis



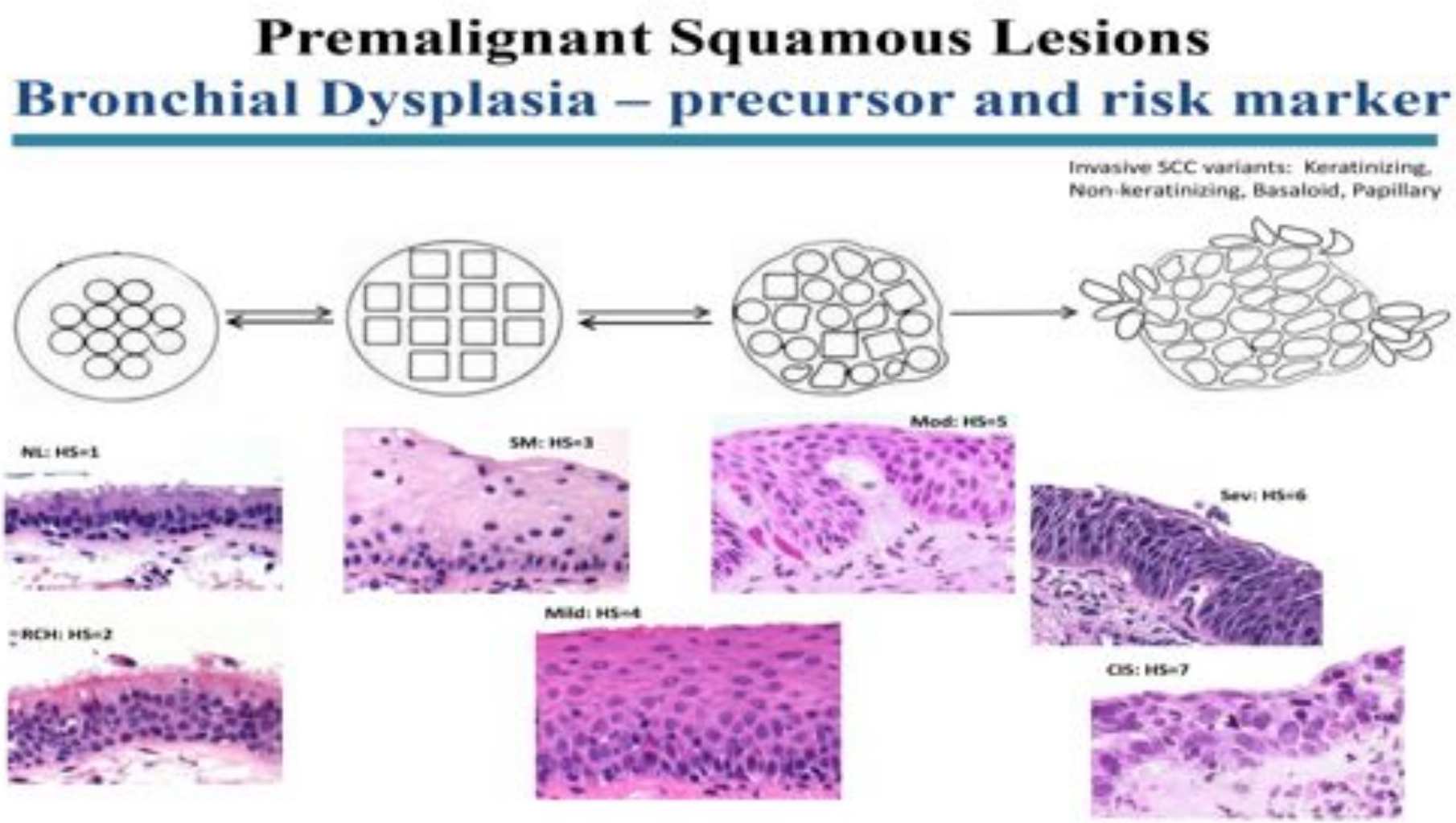


-82% decrease in tumors

-Shift from adenoma to carcinoma

Pereira et al., Carcinogenesis 2002

Bronchial Dysplasia



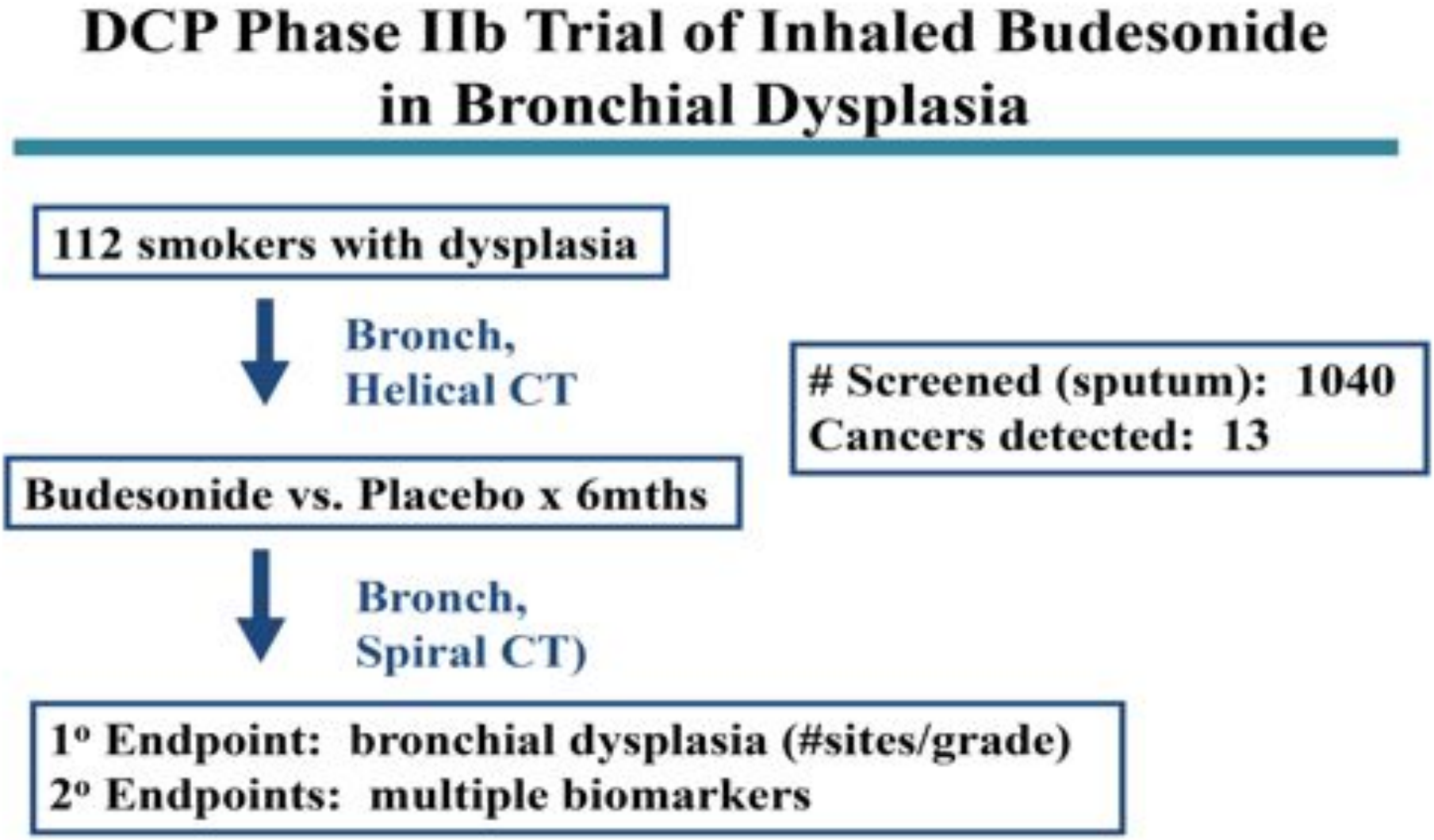
Squamous cell carcinoma precursor

Squamous Cell Carcinoma Precursor: Bronchial Dysplasia

- **Progression to cancer based on bronchoscopic dx, median 2-3 yr f/u** *(Bota et al., Am J Respir Crit Care Med 2001:164;1688; Venmans et al., Chest 2000:117;1572; Breuer et al. Clin Cancer Res 2005:11;537)*
  - **Metaplasia: 37-42% regress, 2-9% CIS/cancer (at 4-59 mths)**
  - **Mild/moderate dysplasia: 37-64% regress, 9% CIS/cancer (at 7-57 mths)**
  - **Severe dysplasia: 41-52% regress, 32% CIS/cancer (1-32 mths)**
  - **Carcinoma in situ: 56% progress at site (44% also had severe dysplasia or CIS elsewhere)**
- **164 pts. with low or high-grade lesions** (Van Boerdonk et al., Am J Respir Crit Care Med 2015;192:1483)
  - **33.5% developed invasive cancer, median 16.5 mths**
  - **41% cancers developed from abnormal site, 59% from other sites (central or peripheral)**
  - **High grade lesions assoc with cancer; COPD and prior hx lung ca assoc with OS**

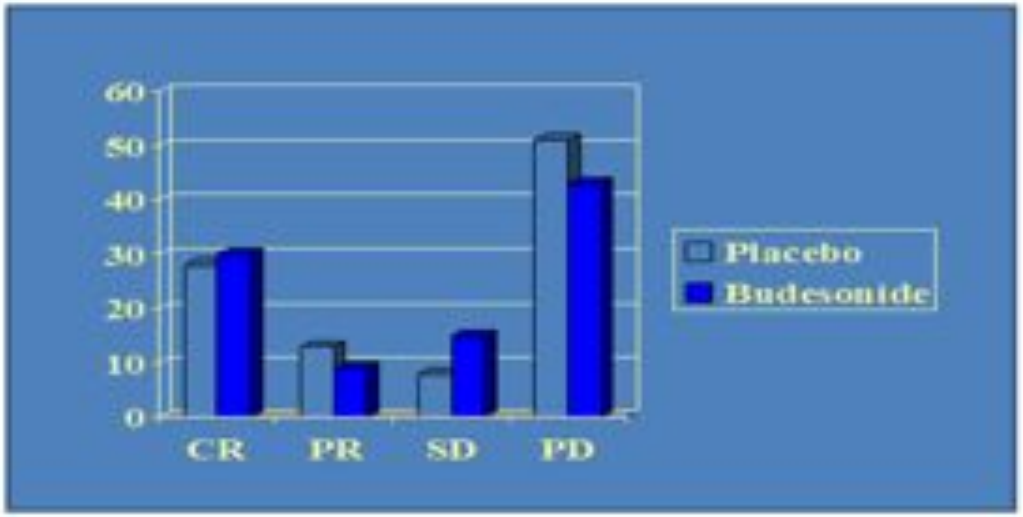
- **Bronchial dysplasia both precursor and risk marker for abnormal field**

Phase IIb Trial



Inhaled Budesonide

Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia



- **Bronchial dysplasia – no effect of 6 mth Rx**
- **CT-detected lung nodules - 27% vs. 12% resolved (p=0.024)**

Lam et al., Clin Cancer Res 2004;10:6502

Budesonide Trial

Phase IIb Budesonide Trial in CT-Detected Lung Nodules

202 participants with persistent LD-CT-detected peripheral nodules

↓ Randomize

inhaled budesonide vs. placebo x 1 year

↓

repeat LD-CT

Primary endpoint: shrinkage of lung nodules

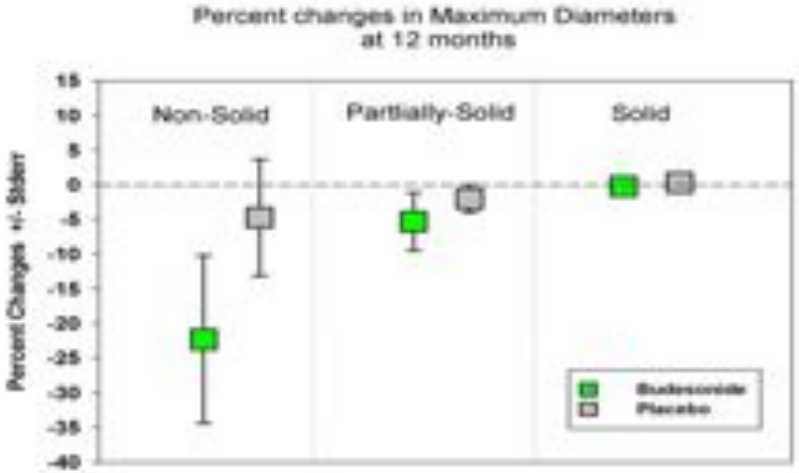
Veronesi et al., Cancer Prev Res 2011;4:34-42

Chemoprevention Trial

Phase IIb Budesonide Chemoprevention Trial

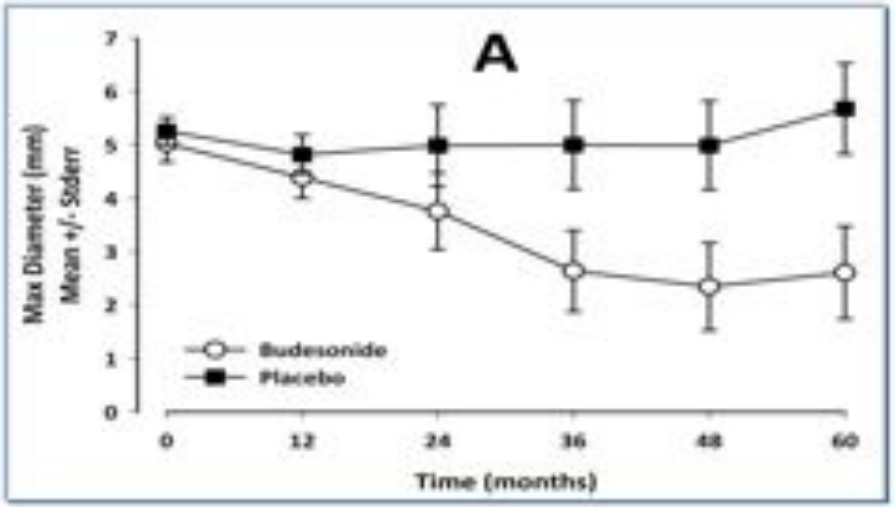
Lesion Specific Analysis

12 months



5-yr f/u, non-solid

p=.029

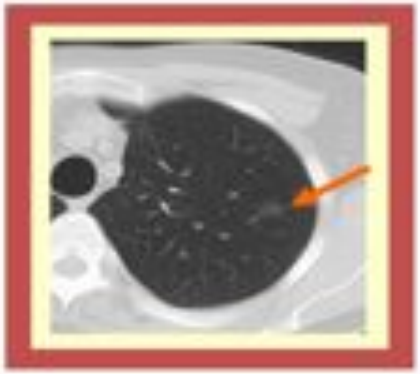


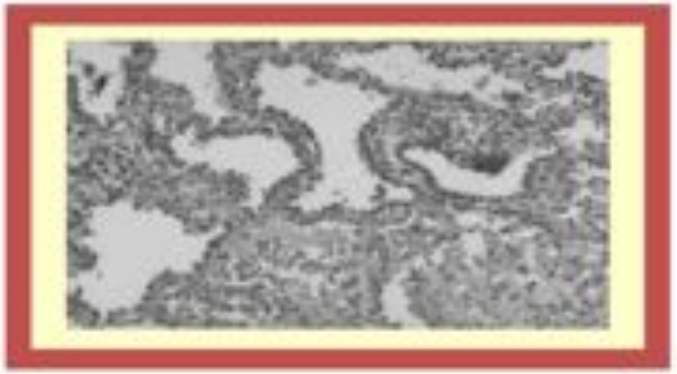
-Overall response negative, but trend toward regression in non-solid lesions (putative precursors of adenocarcinoma)

Veronesi et al., Cancer Prev Res 2011;4:34-42
Veronesi et al., Ann Oncol 2015;26:1025-30

Atypical Adenomatous Hyperplasia

Adenocarcinoma Precursor: Atypical Adenomatous Hyperplasia





- Natural history not well understood
- Localized ground glass opacities on CT:
  - AAH 25%; bronchoalveolar ca 50%; invasive adenoca 10%; fibrosis 15% (Nakajima et al., J Comput Assist Tomogr 2002;26:323)
  - AAH 63%; bronchoalveolar ca 34%; scar 3% (Ohtsuka et al., Eur J Cardio-Thor Surg 2006;30:160)

Non-solid nodules

Non-solid nodules – Natural History

- Prospective trial, 795 patients with 1229 subsolid nodules (GGNs, ≤3cm, solid component ≤5 mm)
  - f/u 4.3±2.5 years
  - 1046 pure GGN → 5.4% became part solid
  - 81 heterogeneous GGN → 19.8% became part solid
  - Resected nodules (in 80 patients)
    - 35/997 pure GGNs (9 MIA, 21 AIS, 5 AAH)
    - 7/78 heterogeneous GGNs (5 MIA, 2 AIS)
    - 49/174 part solid GGNs (12 invasive, 26 MIA, 10 AIS, 1 AAH)

  - *1% of all nodules became invasive cancer (all were part solid)*
  - *3.3% became MIA, 2.7% AIS, 0.5% AAH*

Kakinuma et al., J Thor Oncol 2016;11:1012

CT-detected Lung Nodule

Evolution of CT-detected Lung Nodule

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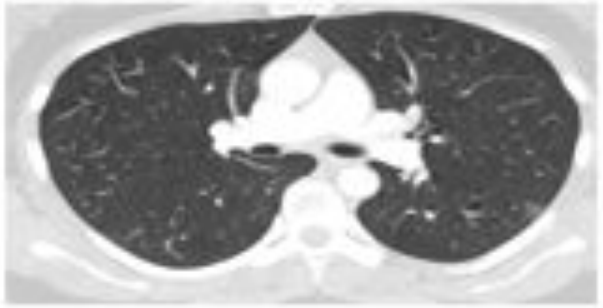

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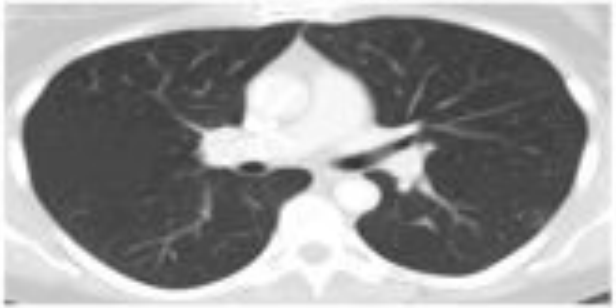

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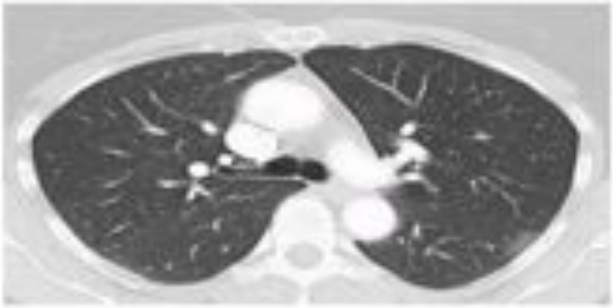
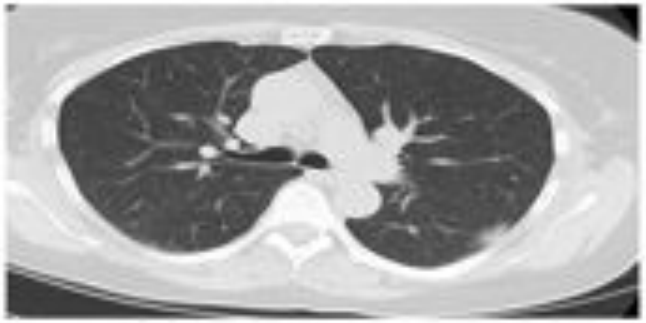


7-25-11



Dx:
Invasive adenocarcinoma (stage I)
Adjacent AAH

Non-calcified nodules

Non-calcified nodules (NCN) Risk of Lung Cancer in the NLST

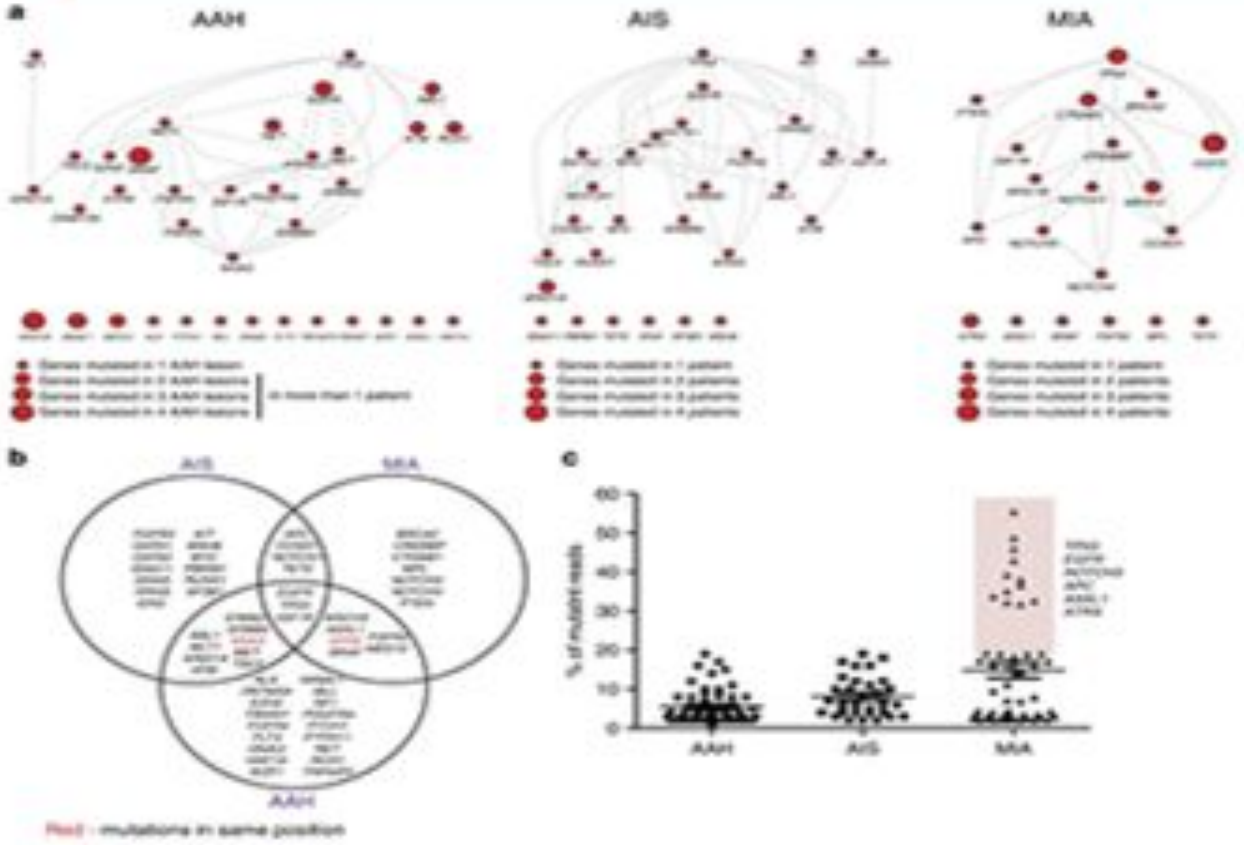
	0-23 Months HR (95% CI)	24-59 Months HR (95% CI)	60-84 Months HR (95% CI)
≥1 10+ mm NCN (vs. only 4-9 mm NCNs)	12.8 (9.5-17.2)	4.7 (2.9-7.5)	N.S.
≥1 NCN w/ Spiculated or Poorly Defined Margins (vs. only NCNs with smooth margins)	4.1 (3.0-5.5)	2.3 (1.5-3.5)	N.S.
≥1 Persistent NCN (vs. non-persistent NCNs)	N/A	4.8 (2.8-8.3)	N.S.
≥1 NCN w/ Ground Glass Attenuation (vs. soft tissue attenuation)	0.3 (0.2-0.4)	N.S.	3.1 (1.4-6.6)

Interpretation:
Increased long-term risk of ground glass nodules suggests *some* are lung cancer precursors

Pinsky et al. Cancer Prev Res 2014

Mutational spectrum

Mutational Spectrum of Adenocarcinoma Precursors



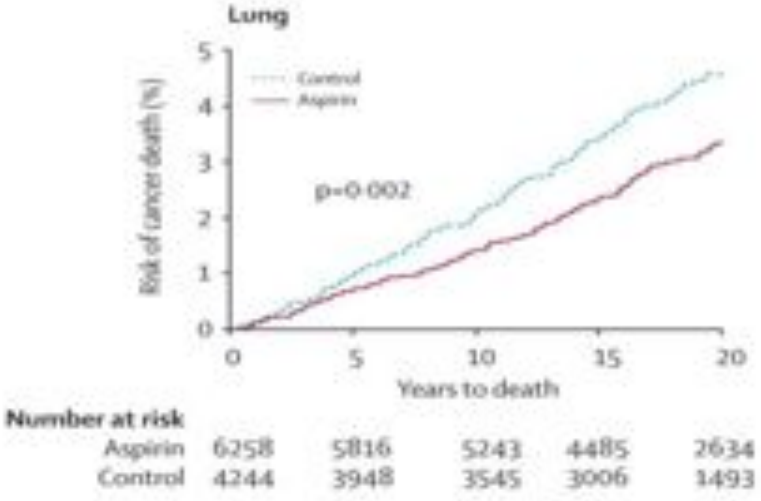
- Targeted next-generation sequencing
- 6 patients with AAH (5 smoking history), 5 AIS, 5 MIA
- Spectrum differs
- AAH – only p53 and EGFR (1 pt.) or Kras (1 pt) shared with tumor
- AAH: 4/6 BRAF
- DNA repair abn in most
- **Heterogeneity in preinvasive lesions**

Izumchenko E et al., Nature Com 2015

Aspirin and Mortality

Effect of Aspirin on Lung Cancer Mortality

-Rothwell et al., Lancet 2011;377:31



-individual patient data from trials of ASA vs. none

-lung:

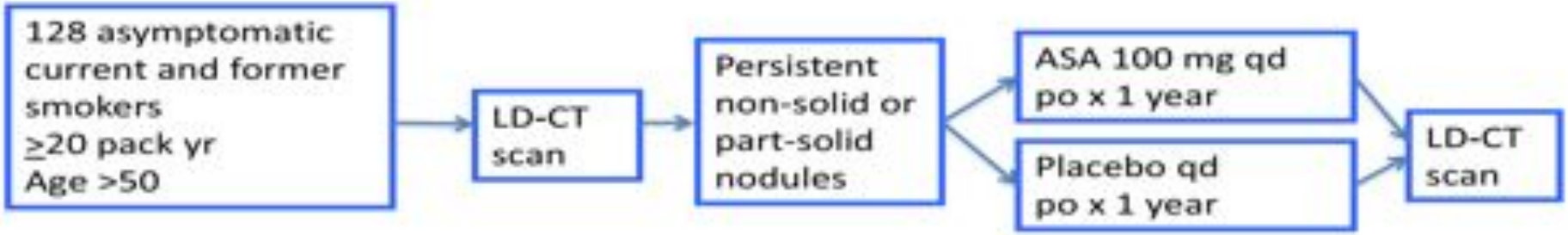
f/u	0-10 yrs	0-20 yrs
HR	0.68	0.71
	(0.50-0.92, p=0.01)	(0.58-0.89, p=0.002)

-adenocarcinoma only

-benefit only after 5 yrs

Phase II Trial

A Randomized Phase II Trial of Low Dose Aspirin versus Placebo in High-Risk Individuals with CT Screen Detected Subsolid Lung Nodules
PIs: Giulia Veronesi, MD and Bernardo Bonanni, MD; IEO

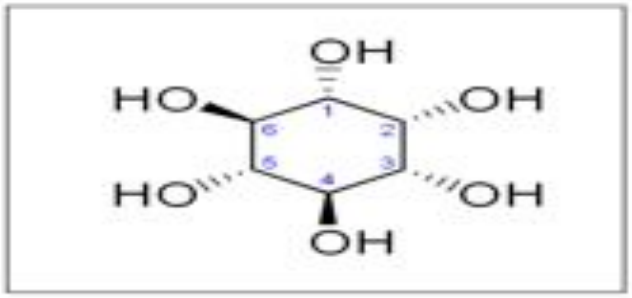


1° Endpoint: #/Size semisolid lung nodules
2° Endpoints: COX/LOX urinary metabolites (hs-CRP, PGEM, LTE4), miRNA signature, nodule-based endpoints

Accrual as of October 15, 2015: 47 participants

Myo-Inositol

myo-Inositol



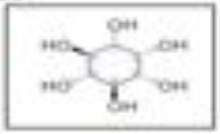
- Glucose isomer
- Source of several second messengers & signaling molecules
- Dietary sources (grains, beans, fruits, rice)
- Studied in psychiatric conditions (+/-), diabetic neuropathy(+/-), polycystic ovary syndrome (+)

Rationale for *myo*-Inositol in Lung Cancer Prevention

- **Efficacy**
  - **Multiple animal studies show inhibition of carcinogen induced tumors in mice (40-50%)**
    - **Estensen and Wattenberg, Carcinogenesis 1993;14:1975**
    - **Hecht et al., Carcinogenesis 2002;23:1455**
  - **Inhibits carcinogenesis in mainstream/sidestream smoke-exposed A/J mice by 53%**
    - **Witschi H et al., Carcinogenesis 1999;20:1375**
  - **Combination with budesonide ↑↑ efficacy up to 80%**
    - **Estensen and Wattenberg, Carcinogenesis 1993;14:1975**
    - **Witschi et al. Carcinogenesis 1999;20:1375**
    - **Wattenberg et al. Carcinogenesis 2000;21:179**
- **Safety**
  - **Used in multiple short term trials for psychiatric and diabetic neuropathy indications – no toxicity reported**
  - **Generally Regarded as Safe (GRAS) by US FDA terminology**

Phase I Study of myo-Inositol

Phase I Study of *myo*-Inositol in Bronchial Dysplasia



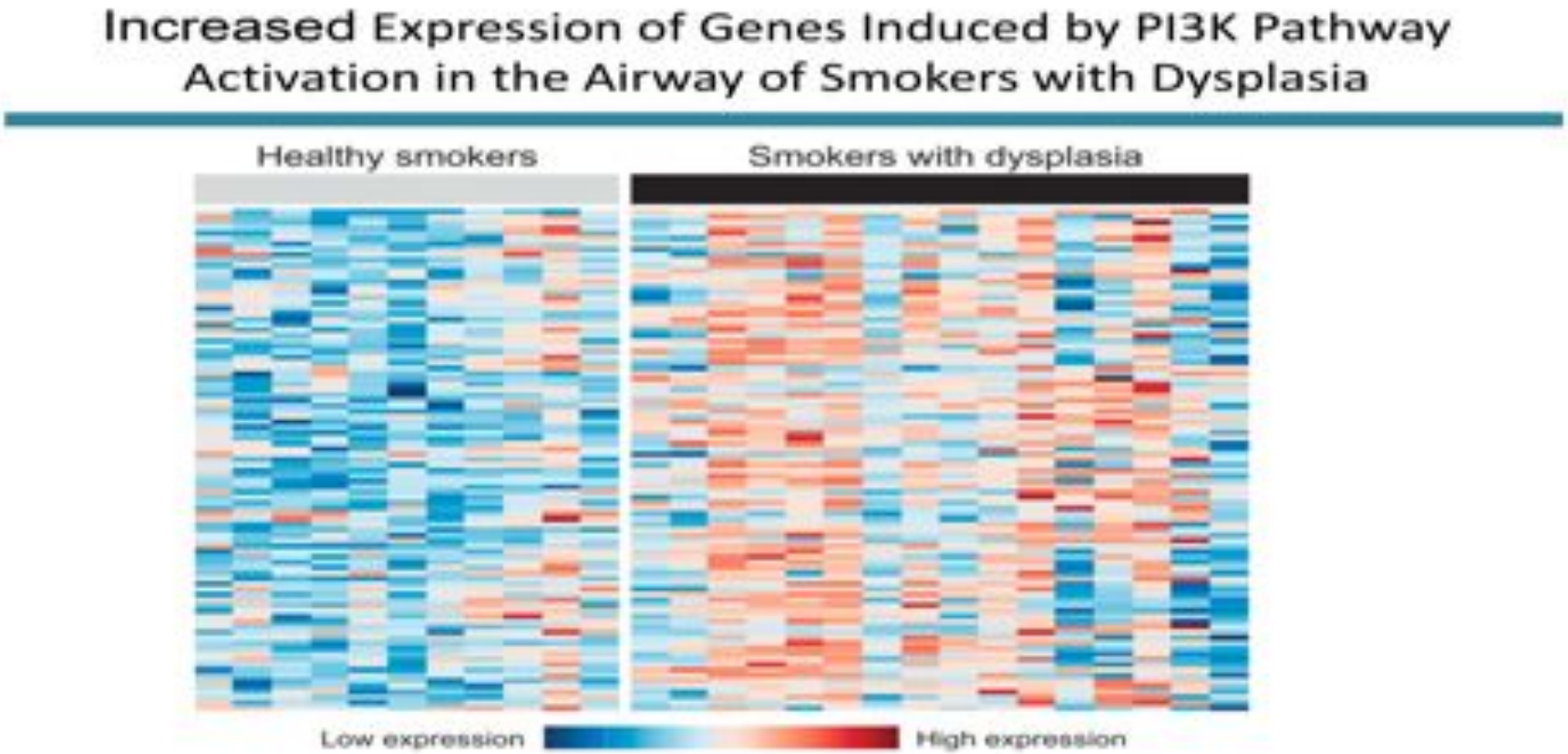
- **Inhibits B[a]P carcinogenesis in mice (53%); combination with budesonide ↑↑**
- **Phase I study (26 participants)**
  - **tolerable 18 g/d**
  - **91% vs. 48% regression dysplasia, P=0.014 (10 participants)**

Table 5. Changes in pathologic grades of bronchial biopsy samples at baseline and after 3 months of *myo*-inositol (18 g): Lesion-specific analysis

Pathologic grades of bronchial biopsies at baseline	Status after 3 months of treatment			
	N	Stable	Regression*	Progression†
Placebo group (from ref. 18)				
Normal/hyperplasia/metaplasia	256	219	0	37
Mild dysplasia	134	72	62	0
Moderate/severe dysplasia	13	5	8	0
myo-Inositol group				
Normal/hyperplasia/metaplasia	38	36	0	2
Mild dysplasia	10	1	9	0
Moderate/severe dysplasia	1	0	1	0

Lam et al., CEBP 2006;15:1526

PI3K pathway genes



-PI3K pathway is activated in smokers with dysplasia in airway p<0.001

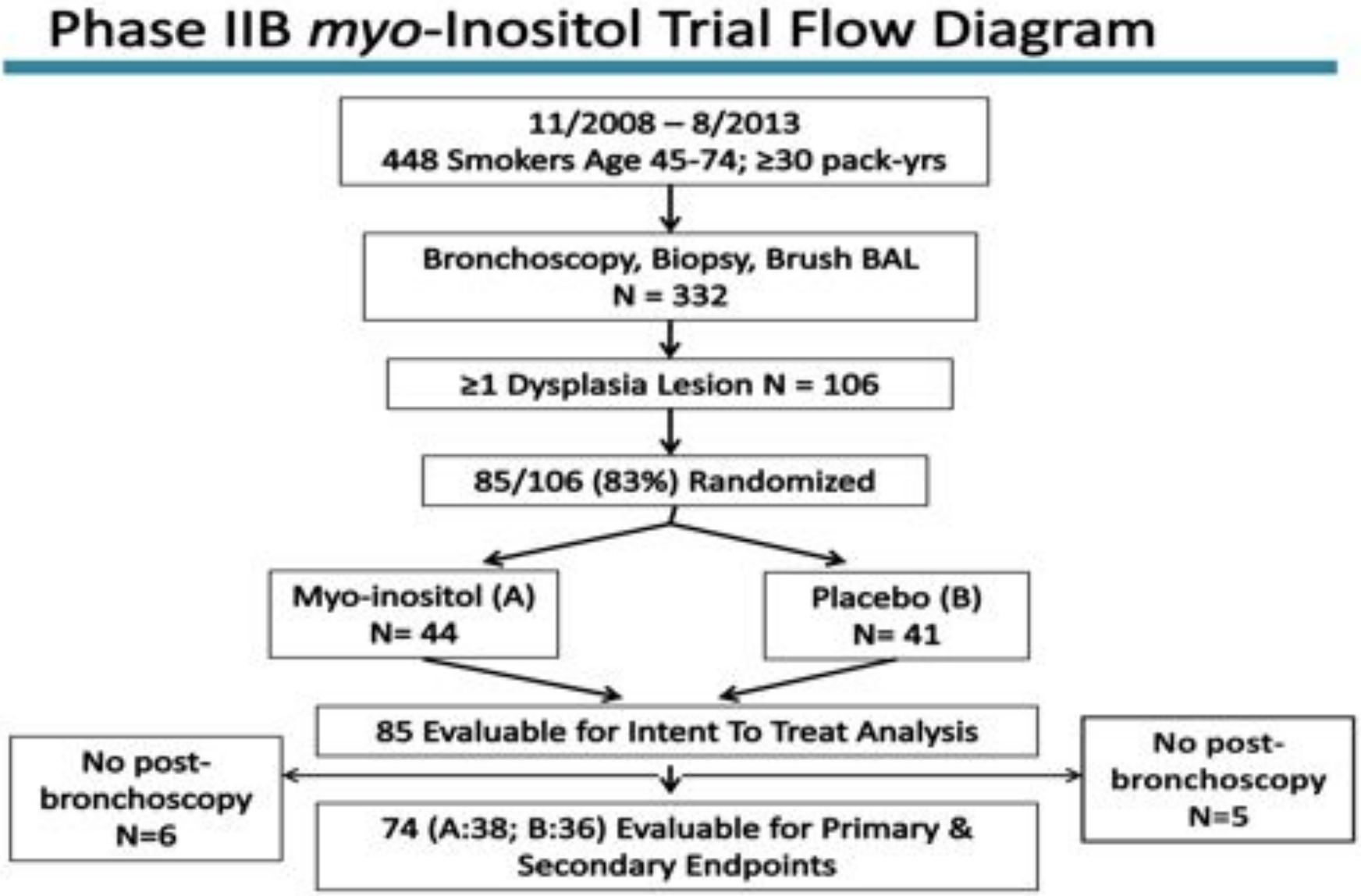
-Myo-inositol inhibited PI3K activation in normal bronchial airways in smokers with regression of dysplasia (p=0.04)

Gustafson et al., *Sci Transl Med* 2010

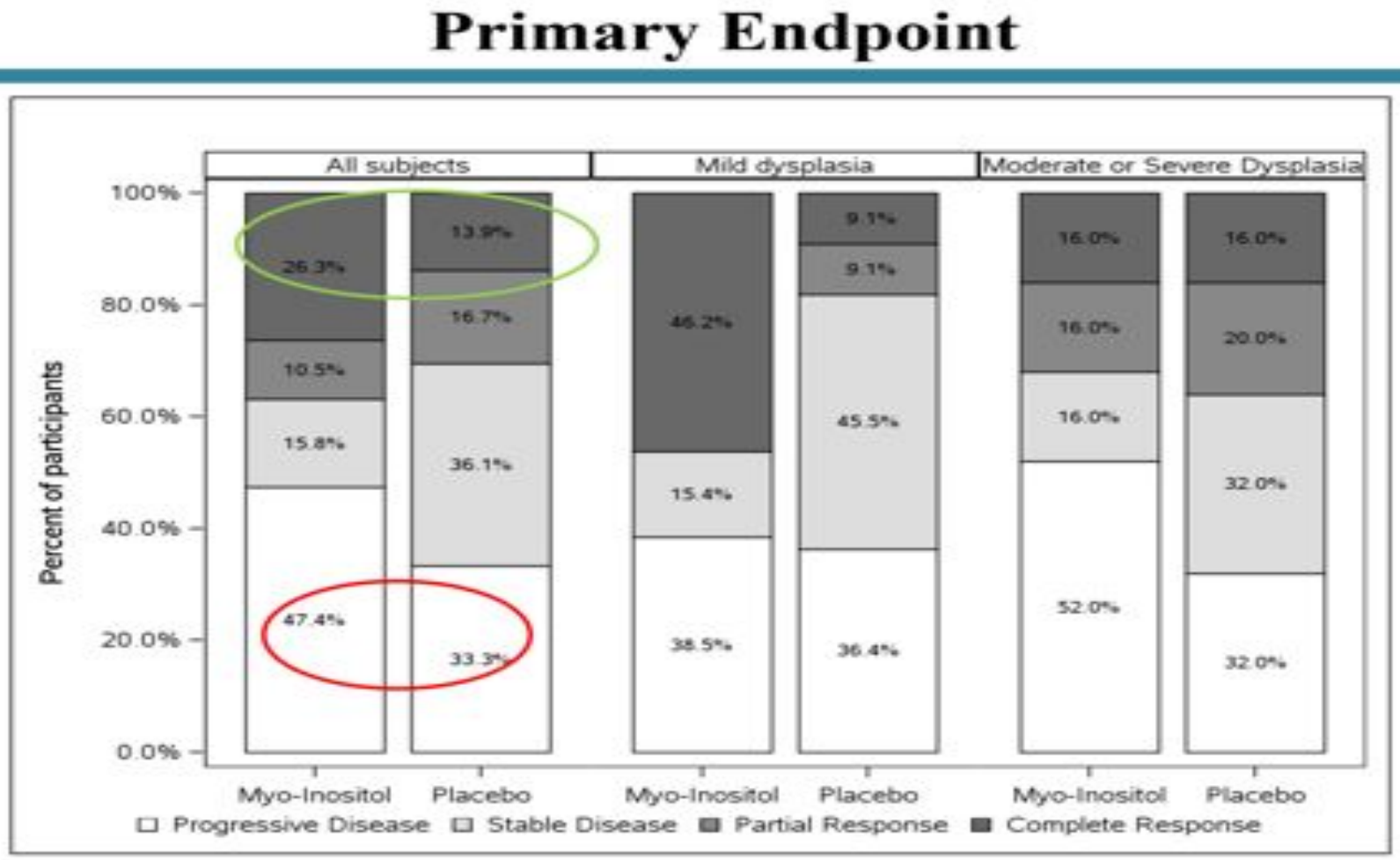
Implications – Molecular Selection Criteria &/or Endpoints

- **Does PI3K activation truly identify smokers at risk for cancer?P**
  - **Easier to get normal brushings than to identify dysplasia (sampling bias); do not remove biomarker with procedure**
  - **Potential to identify "the right" cohort**
- **New potential clinical trial model – pathway analysis pre- and post-treatment, smaller # participants, shorter interventions**
  - **Identify mechanisms of interventions**
  - **Needs validation!**

Phase IIB myo-Inositol Trial

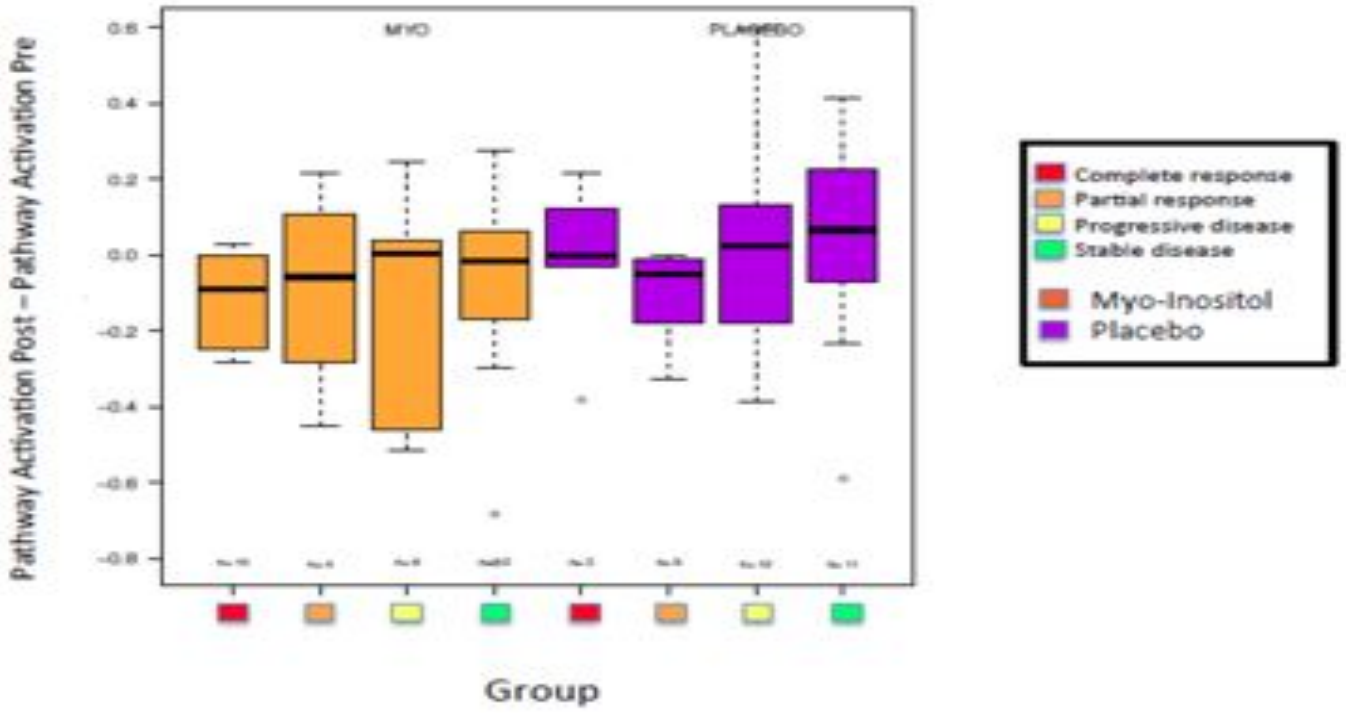


Primary endpoint



Akt activation

AKT Pathway Activation is decreased in Myo-inositol Complete Responders

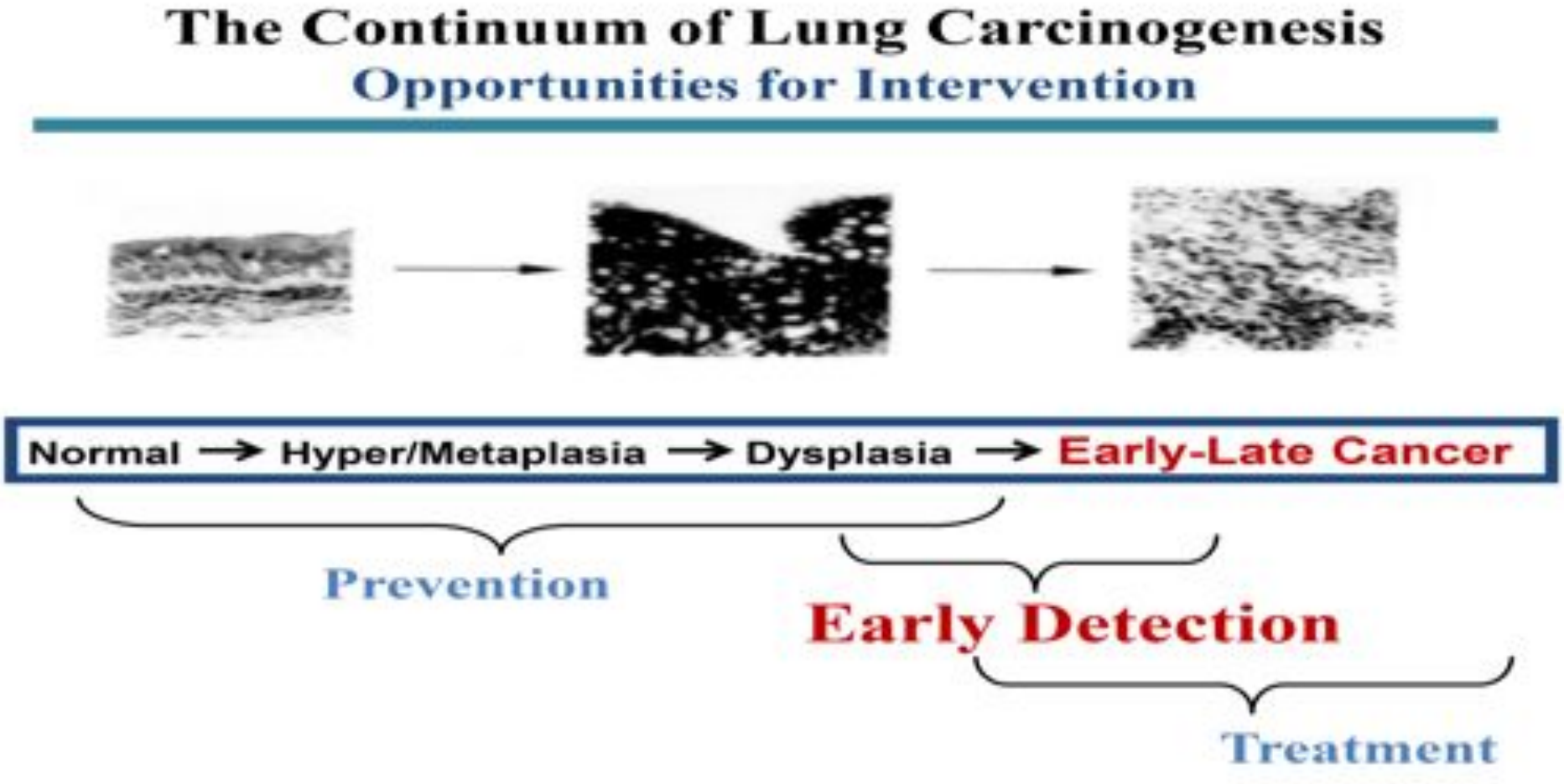


Summary

Summary

- **Compared with placebo, *myo*-inositol 9 g BD x 6 m:**
  - significant reduction of IL-6 and borderline significant reduction of myeloperoxidase levels in BAL
  - significant reduction of AKT pathway activation in complete responders
- **Heterogeneous response in regression and progression of dysplasia**
- **Results suggested a targeted therapy approach based on molecular alterations is needed in future clinical trials**

Lung Carcinogenesis



Issues in Lung Cancer Screening

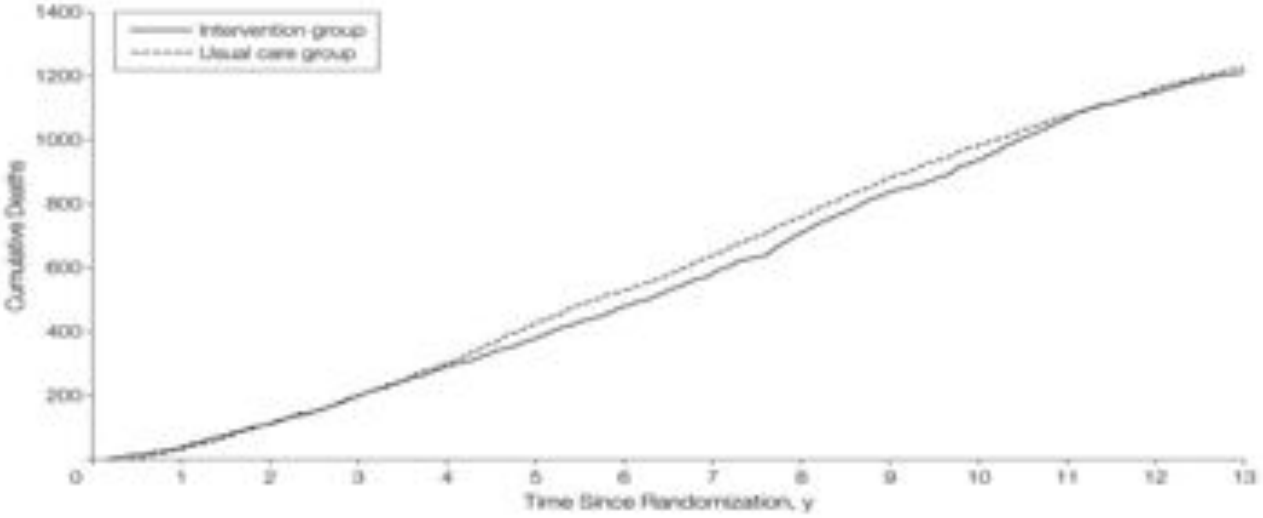
- **Lead-time bias=earlier diagnosis but no postponement of death (survival appears longer)**
- **Length bias=diagnosis of more indolent disease with longer preclinical phase (better prognosis, better outcome)**
- **Overdiagnosis=identification of clinically unimportant lesions that would not be diagnosed otherwise**

- **Morbidity/mortality/cost of screening and subsequent**

PLCO Trial

PLCO CXR Randomized Trial - Mortality

154,901 participants, PA CXR vs. usual care x 4 screens, 13 yr f/u



Intervention group													
Cumulative deaths	36	113	196	292	379	480	582	711	838	937	1070	1150	1213
Cumulative person-years	77 268	154 053	230 270	305 833	380 691	454 773	527 937	600 004	670 274	735 098	789 540	832 441	864 227
Usual care group													
Cumulative deaths	30	111	196	301	426	527	639	761	884	987	1076	1162	1230
Cumulative person-years	77 286	154 116	230 348	305 902	380 725	454 719	527 804	599 790	669 955	734 523	788 854	831 678	863 330

Oken, MM et al. JAMA 2011;306:1865-73

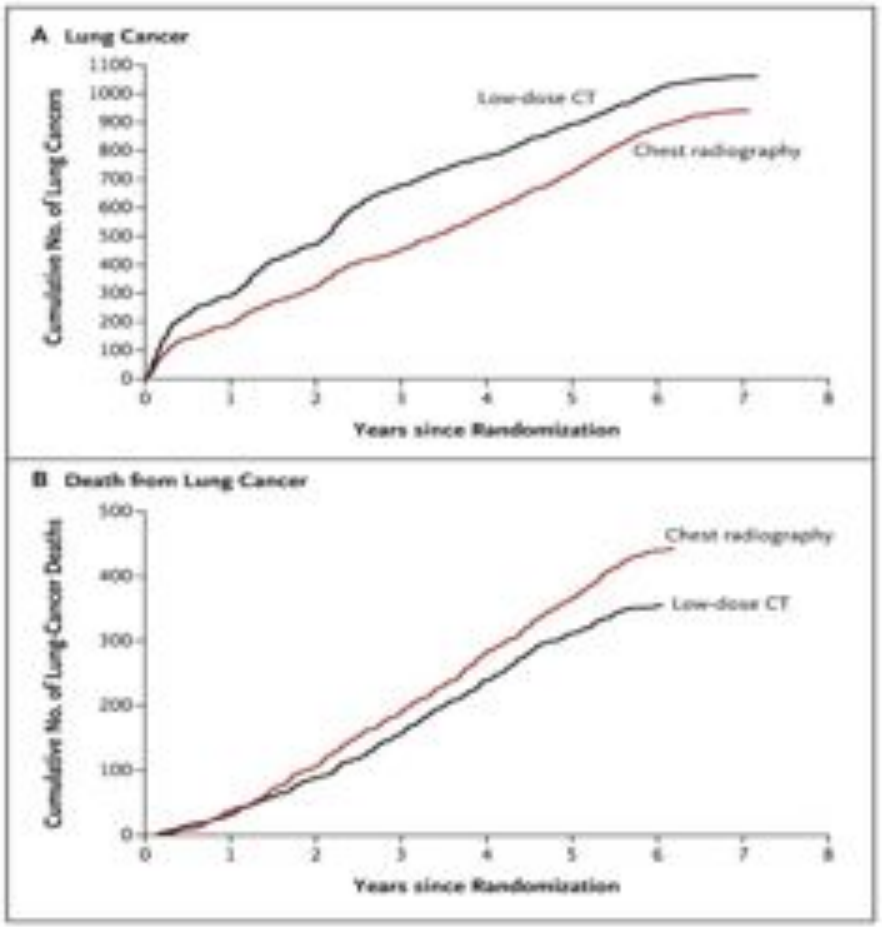
NLST (National Lung Screening Trial)

- **NLST design**
  - **53,454 smokers (current and former)**
  - **30 pack-yr smoking hx; quit ≤15 yrs ago**
  - **Age 55-74**
  - **Helical CT vs. chest X-ray (prevalence, then x2)**
- **NLST results**
  - **CT - 24.2% 'positive' tests, 354 lung cancer deaths**
  - **CXR – 6.9% 'positive' tests, 442 lung cancer deaths**
  - **20.0% reduction in lung cancer mortality**
  - **6.7% reduction in all cause mortality**

NLST Research Team. N Engl J Med 2011;365:395-409

Lung Cancer and Deaths

Cumulative Lung Cancers and Deaths from Lung Cancer

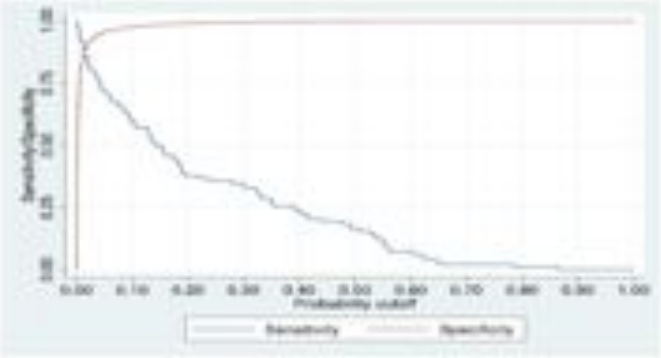


NLST Research Team N Engl J Med 2011;365:395-409

Lung Cancer Risk

Lung Cancer Risk Prediction Model – 1st Screening CT

- **Risk of lung cancer in nodules from baseline screening CT**
  - **Age, sex, family history, emphysema**
  - **Nodule size, type, location, count**
  - **AUC >0.90**
- **Ability to identify highest risk:**
  - **For subsequent screening**
  - **Chemoprevention (ph III)**



- www.brocku.ca/cancerpredictionresearch

McWilliams et al. N Eng J Med 2013;369:910-9

Moving forward

How do we move forward?

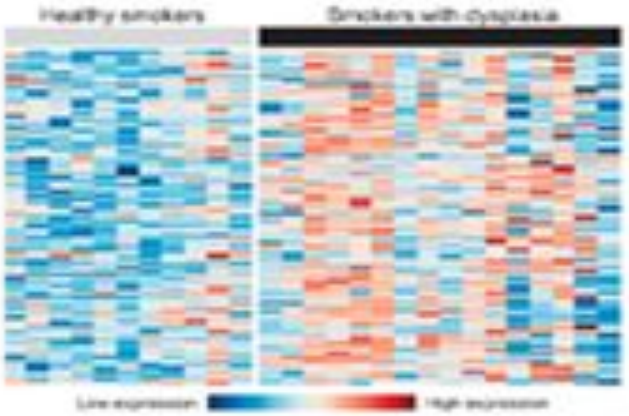
- **Understand the genesis and natural history of carcinogenesis**
  - **Understanding molecular mechanisms of carcinogenesis, TCGA of premalignancy (PCA)**
    - **Molecularly targeted agents**
    - **Repurposed 'old' drugs**
    - **Target deregulated processes driving carcinogenesis**
    - **Harness the immune response**
  - **Persistent versus regressive premalignant lesions - who is likely to progress and why?**

Innovation trial designs

How do we move forward ?

Innovative Trial Designs

- **Sample the field using 'omic' technologies**
  - **To detect drug effects on deregulated pathways in a short time frame**



- **Focus on at-risk (molecularly?) homogeneous cohorts**
- **Multiple trial designs to build a "body of evidence"**

-Gustafson et al. Sci Transl Med 2010;2:26ra25

Summary

Tremendous progress has been made in understanding lung carcinogenesis

- **Precision medicine applicable to significant (but small) subset of advanced stage patients, increased survival**
- **Early days of immunotherapy – prolonged survival in small subset of patients**
- **Early detection with helical CT –decreased lung cancer mortality**
- **New targets and tools available for chemoprevention research**

“An ounce of prevention is worth a pound of cure”

-Benjamin Franklin

Acknowledgments

Acknowledgments

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