Non-small Cell Lung Cancer

Non-small Cell Lung Cancer

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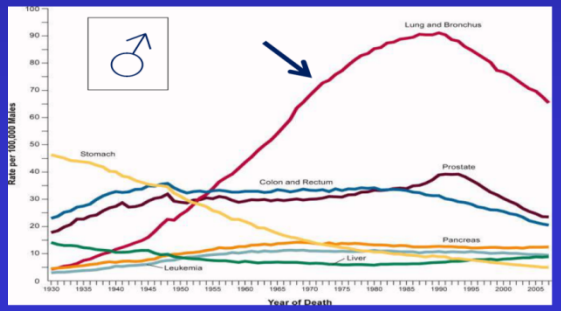
TRACO 12-1-14

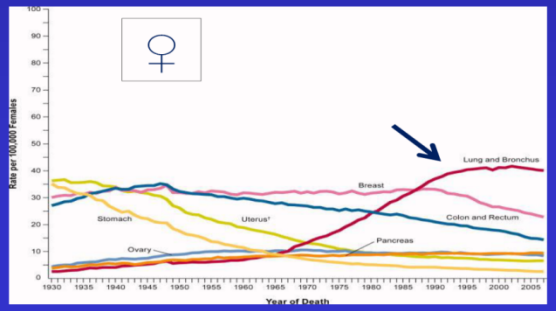
US Lung Cancer Statistics, 2014

US Lung Cancer Statistics, 2014

Siegel R et al., CA Cancer J Clin 2014;64:9

- Estimates: 224,210 new cases, 159,260 deaths
- Leading cause of cancer deaths (> breast+prostate+colon)
  - Death rate per 100,000 decreasing (90.56 in 1990 vs. 67.45 in 2006), incidence finally decreasing in women
- 16% five year survival
  - 5% in 1950's, 13% in 1970's
  - 28% of all male cancer deaths, 26% of all female cancer deaths





Linking Tobacco Use to Lung Cancer

Radiographic Evidence Linking Tobacco Use to Lung Cancer

-McMullen, DM & Cohen GA, NEJM 354:397, 2006

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 – 6q23-25 (Am J Hum Gen, 9/04)
  - 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

Five-year survival

Five-year survival by TNM status in NSCLC (old staging system)

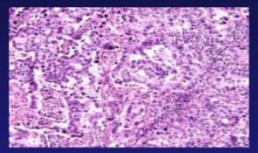
Stage	TNM classification	5-year survival (%)
IA	T1N0M0	61
IB	T2N0M0	38
IIA	T1N1M0	34
IIB	T2N1M0 or T3N0M0	24
IIIA	T1-3N2M0 orT3N1M0	13
IIIB	$T4N_{any}M0$ or $T_{any}N3M0$	5
IV	$T_{any}N_{any}M1$	1

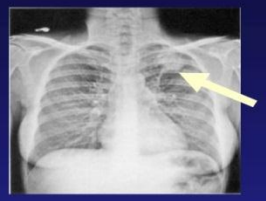
Mountain 1997

Pathology of NSCLC

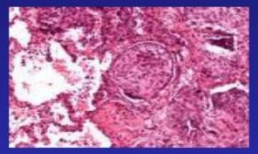
Pathology: Non-small Cell Lung Cancer

- Adenocarcinoma, inc bronchoalveolar
  - 40%

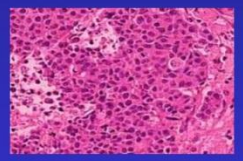




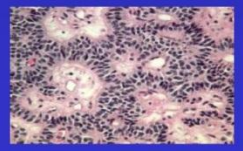
- Squamous cell carcinoma
  - 20%



- Large cell carcinoma
  - 15%



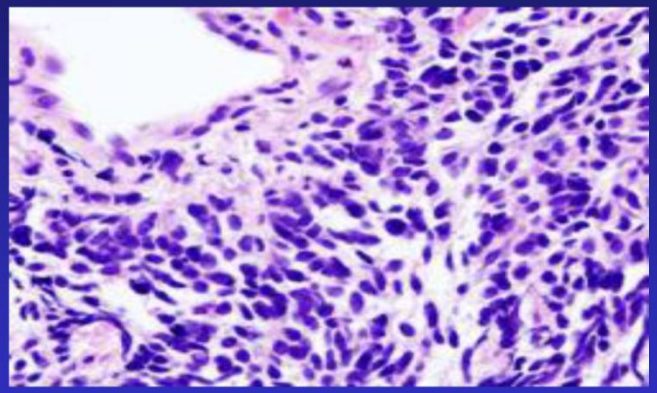
- Others (carcinoid, etc.)



Pathology: SCLC

Pathology: Small Cell Lung Cancer

- Small cell lung cancer - 20%



The Continuum of Lung Carcinognesis

The Continuum of Lung Carcinogenesis

Opportunities for Intervention

Normal → Hyper/Metaplasia → Dysplasia → Early-Late Cancer

Prevention

Early Detection

Treatment

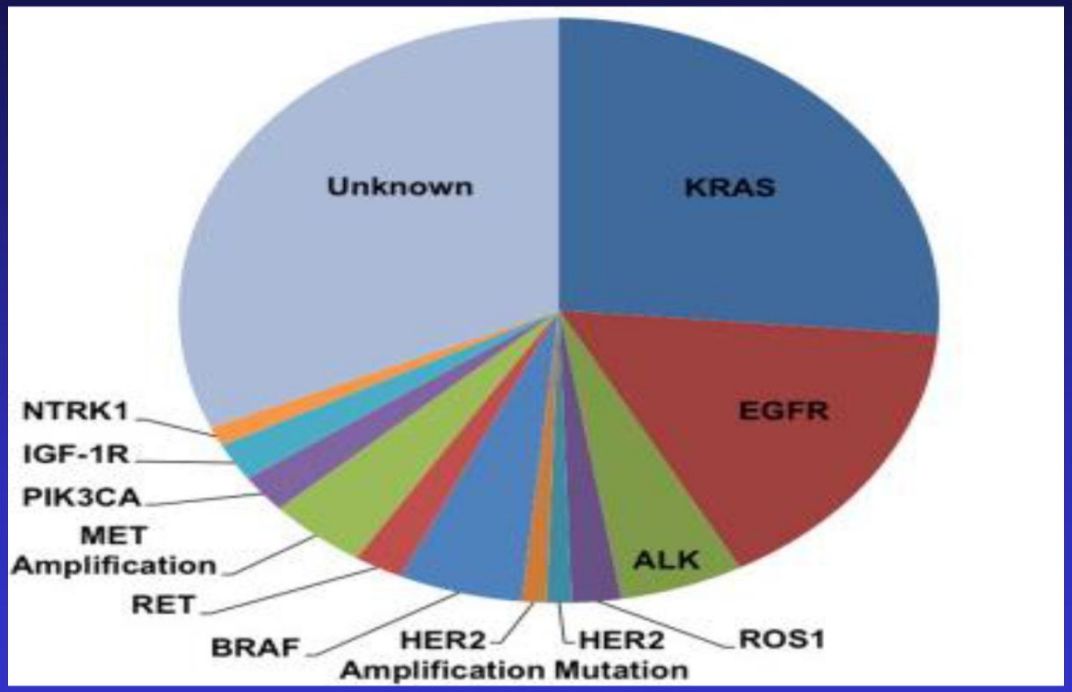
Treatment Strategies

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 mets
- Small cell lung cancer: chemotherapy (+thoracic radiation for limited stage; prophylactic cranial radiation to prevent brain mets)

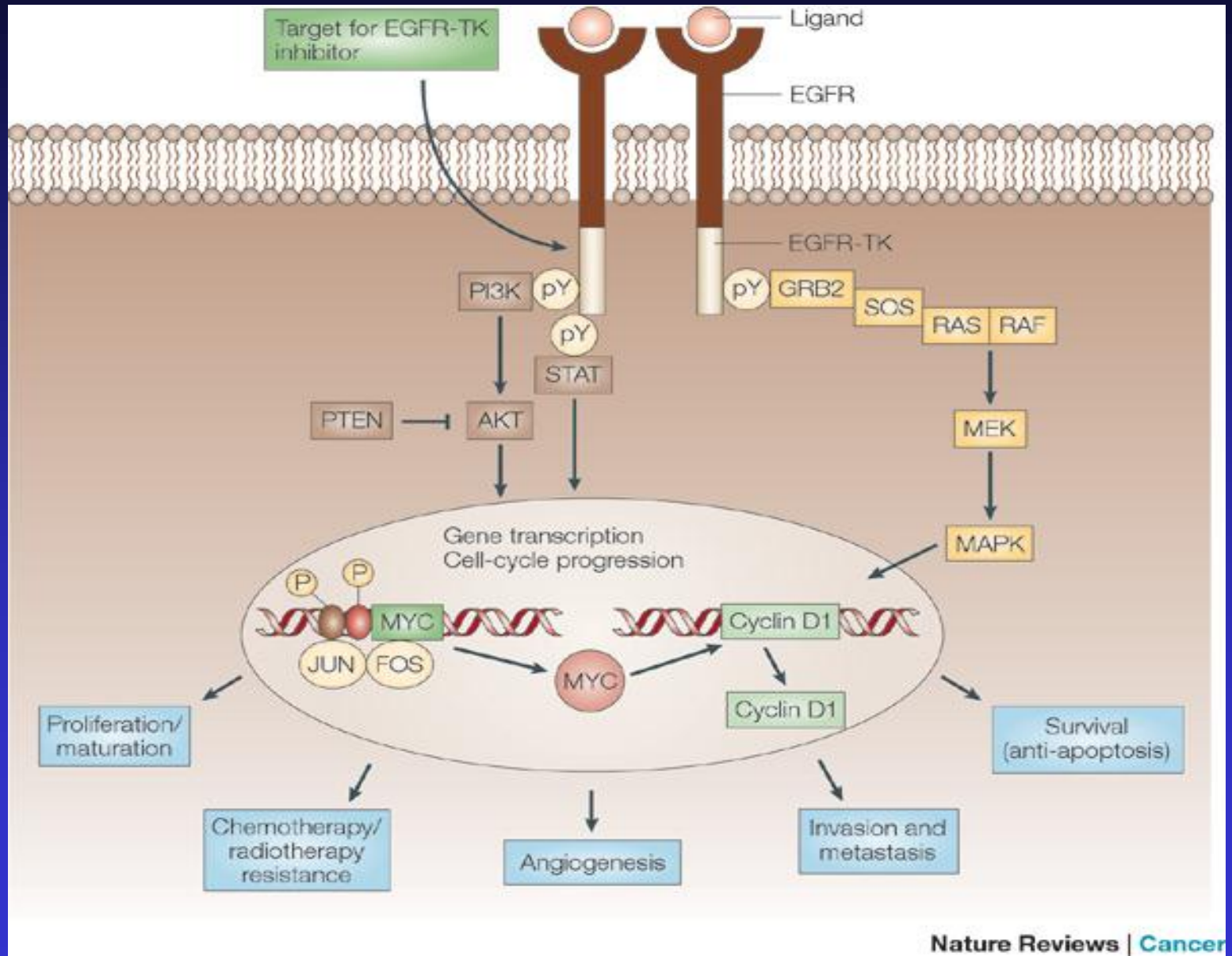
Personalizing Therapy

Personalizing Therapy for NSCLC
Genetic Abnormalities in Lung Adenocarcinoma



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

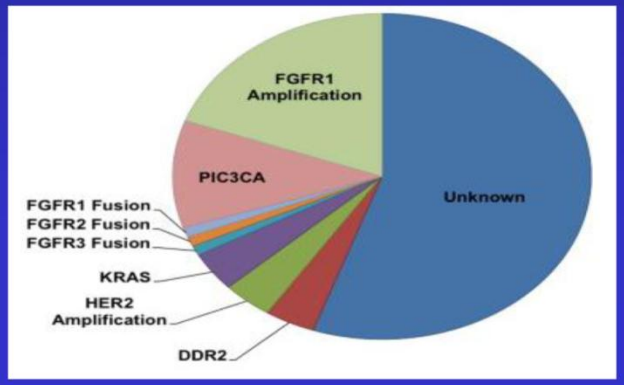
Epidermal Growth Factor (EGFR) Signaling



Personalizing Therapy for NSCLC

Personalizing Therapy for NSCLC
Genetic Abnormalities in Lung Squamous Cell Ca.

- FGFR1 amplification ~22% of squamous cell carcinomas (smokers), not in adenocarcinomas
  - experimental FGFR inhibitors in development
    - Weiss J et al., Sci Transl Med 2010;62:62ra93
- DDR2 (discoidin domain receptor 2 tyrosine kinase) mutations in ~4% squamous cell carcinomas
  - Sensitive in vitro to dasatinib
    - Hammerman PS et al., Cancer Discovery 2011;1:OF77

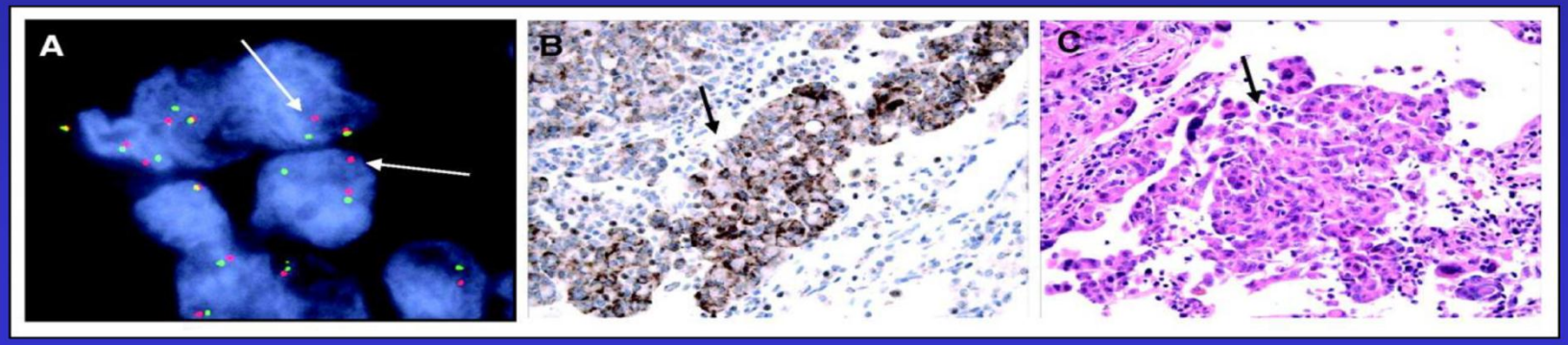


-Berge and Doebele, Sem Oncol 2014;41:110

EML-4ALK Fusion Gene as a Target for NSCLC

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

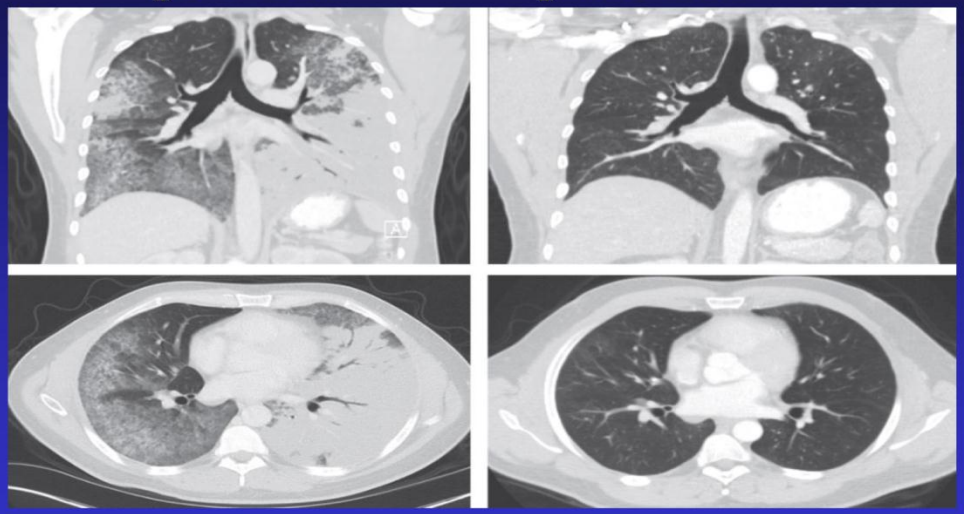


Shaw AT et al., JCO 2009;27:4247

Ros1 Rarrangements as a Target

ROS1 Rearrangements as a Target

pre-Rx post-Rx



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

Other Targetable Mutations in Adenocarcinoma

Other Targetable Mutations in Adenocarcinoma

Berge and Doebele Sem Oncol 2014;41:110

- **HER2/neu**
  - Mutations in kinase domain in 4%, amplification (FISH) in 2-5% NSCLC (Hunter et al., Nature 2004;30:431; Heinmoller P et al. Clin Cancer Res 2003;9:5283)
  - Clinical trials for HER2 overexpression (IHC) negative, but 16 pts. with exon 20 mutation treated with HER2-based Rx (mainly with chemo) RR=50%
- **BRAF**
  - **1-5% NSCLC, V600E mutation→dabrafenib RR=54%**
- **RET**
  - **Gene fusions 1-2% NSCLC, multiple partners, case reports of responses to cabozantinib and vandetanib**

Personalizing therapy

Personalizing Therapy for NSCLC

Genetic Abnormalities in Lung Squamous Cell Ca.

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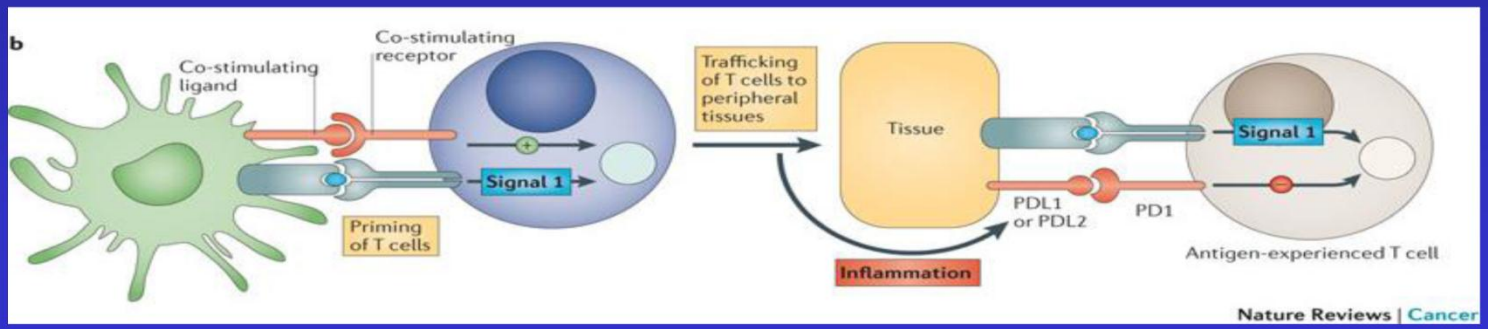
New Approaches-Immunotherapy

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

New Approaches- Immunotherapy

New Approaches - Immunotherapy

- BMS anti-PD-1 and PD-L1 antibodies – 10-18% response rates, some long term, 14% severe toxicities (grade 3-4)
  - Topalian et al. NEJM 2012;366:2443, Brahmer et al NEJM 2012;366:2455
- MK-3475 (anti-PD-1) – 24% response rate; median overall survival 51 wks in 7/9 responders; mainly low level toxicities (grade 1-2)
  - (IASLC World Conference on Lung Cancer, Sydney, AU 10/2013)
- Multiple agents in clinical trials
- Why the excitement – *long term responses in responders,* at times without ongoing treatment

Approaches to reducing cancer morbidity and mortality

Approaches to reducing cancer morbidity and mortality

- Prevention (primary, secondary, tertiary)
- Early detection
- Better therapeutics

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Prevention

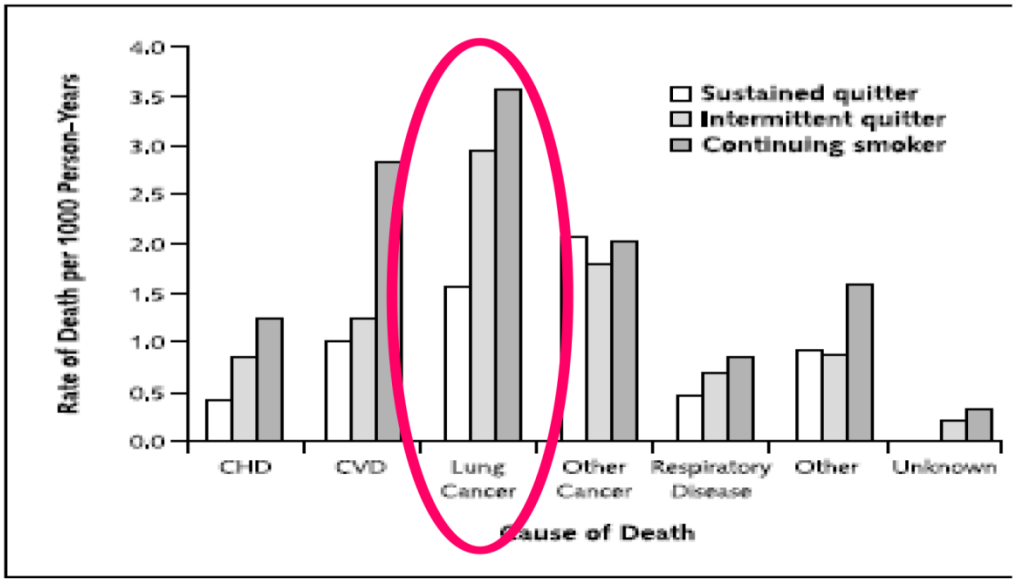
Early Detection

Treatment

Effect of Smoking Cessation on Lung Cancer Deaths

Effect of Smoking Cessation on Lung Cancer Deaths

Lung Health Study, 14.5 yr F/U



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

Cancer Chemoprevention

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

Rationale for 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

When is the best time to intervene during carcinogenesis?

When is the best time to intervene during carcinogenesis?

- Efficacy of intervention
  - Early stage cancer is more curable than late
  - Are precursor lesions more curable than invasive cancer?
  - Can carcinogen-induced DNA damage be prevented?
  - Multiple pathways of carcinogenesis
- Toxicity of intervention
  - High toxicity acceptable short-term, in setting of cancer
- Target population – size and ability to identify
  - Many at risk (smokers), relatively few get cancer/yr
  - Inability to identify non-smokers at risk
- Cost (resources, psychological impact, etc.)

Minimal Requirements for Preventive Strategies

Minimal Requirements for Preventive Strategies

- **Benefit**
  - **Efficacy** in preventing cancer and associated morbidity/mortality
- **Risk**
  - **Lack of adverse side effects** that increase morbidity/mortality from other diseases, short- and long-term (major side effects)
  - **Tolerability** of intervention (minor side effects affecting compliance)

Efficacy: How Do We Identify New Agents?

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

Targetting Inflammation for Lung Cancer Prevention: Rationale

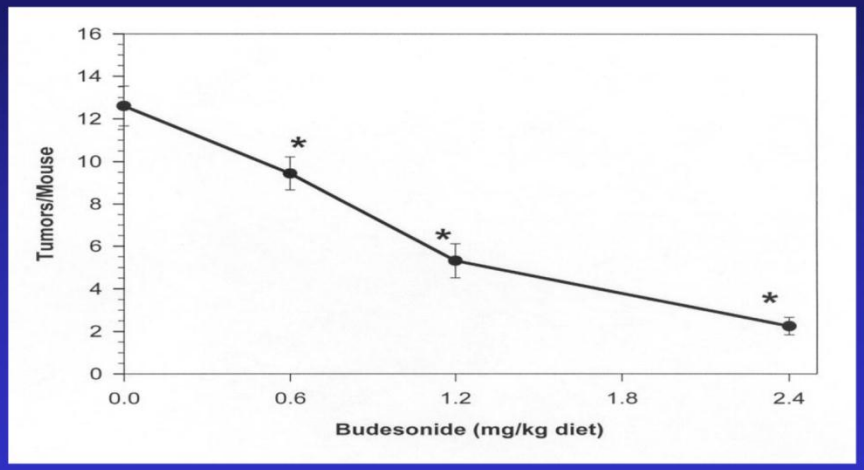
Targeting Inflammation for Lung Cancer Prevention: Rationale

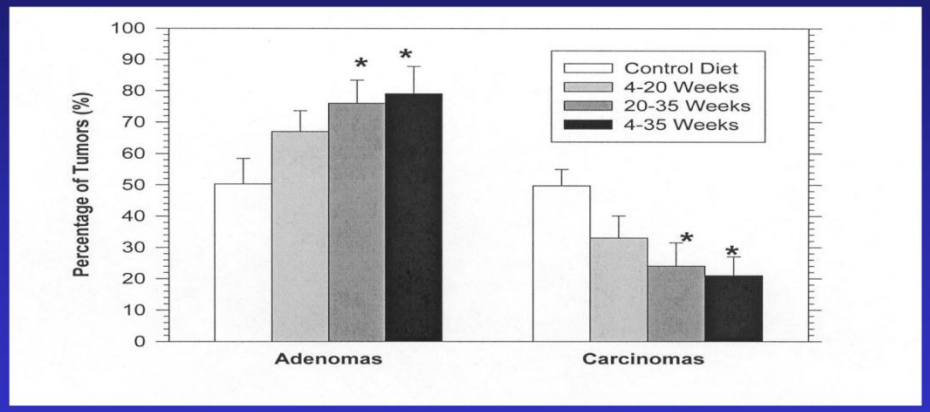
- Animal data showing role for steroids in cancer prevention
  - 1970's – skin
  - Early 1990's – lung (oral steroids)
  - Late 1990's – lung (inhaled steroids)
- Epidemiology/Human data –
  - Mainly negative (but studies of short exposure duration)
  - VA cohort with COPD (n=10,474) – HR 0.39 (95% CI,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

Effect of Budesonide on Mouse Lung Tumorigenesis

Effect of Budesonide on Mouse Lung Tumorigenesis

Pereira et al., Carcinogenesis 2002





-82% decrease in tumors

-Shift from adenoma to carcinoma

DCP Phase IIb Trial of Budesonide

DCP Phase IIb Trial of Budesonide

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

112 smokers with dysplasia (Bronch)

↓ (Spiral CT)

Budesonide vs. Placebo x 6mths

↓ (Bronch, Spiral CT)

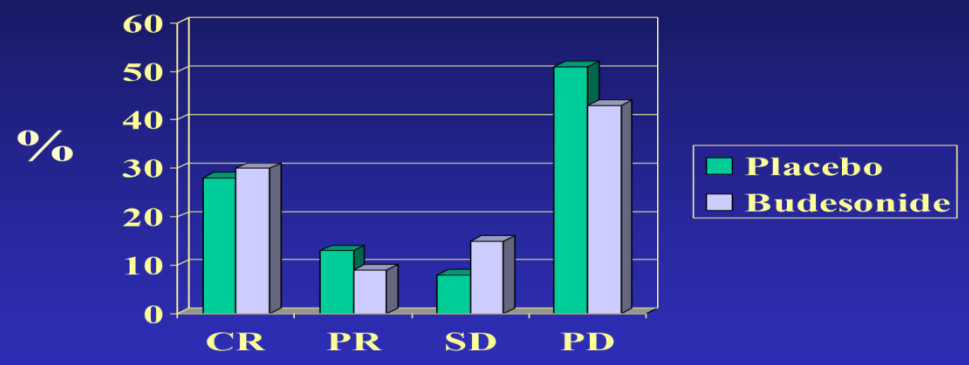
1º Endpoint: bronchial dysplasia (#sites/grade)
2º Endpoints: multiple biomarkers

Screened (sputum): 1040
Cancers detected: 13

Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia

Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia

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



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

Phase IIb Budesonide Chemoprevention Trial

Phase IIb Budesonide Chemoprevention Trial

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

202 participants with persistent spiral CT-detected peripheral nodules

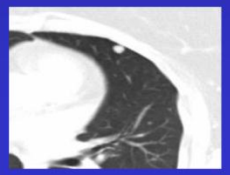
↓ **Randomize**

inhaled budesonide vs. placebo x 1 year

↓

repeat spiral CT

Primary endpoint: shrinkage of lung nodules

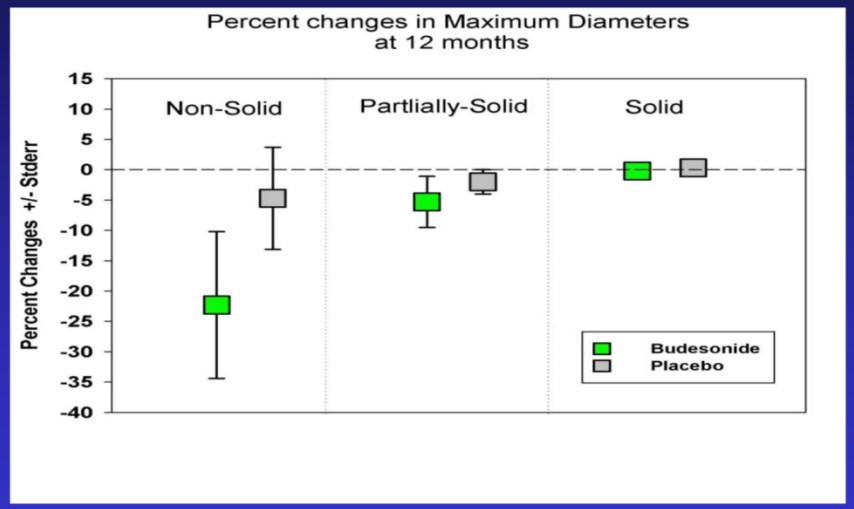


Phase Iib Budesonide Chemoprevention Trial

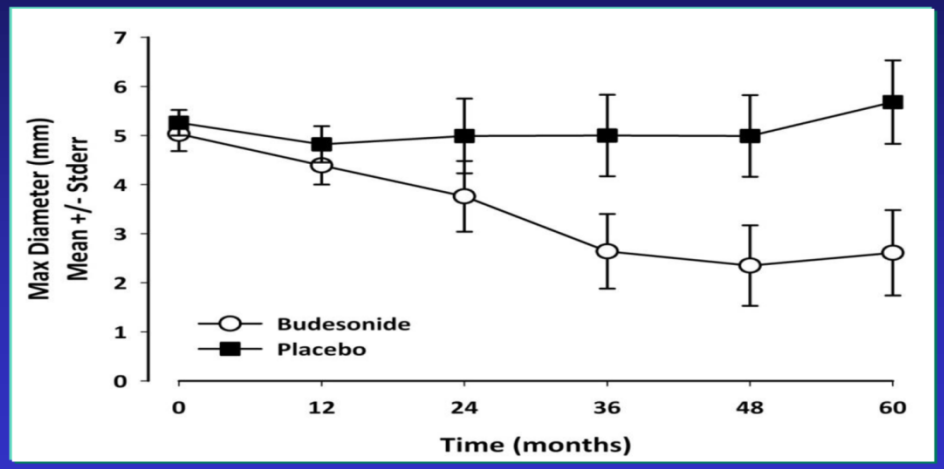
Phase IIb Budesonide Chemoprevention Trial

Lesion Specific Analysis

12 months



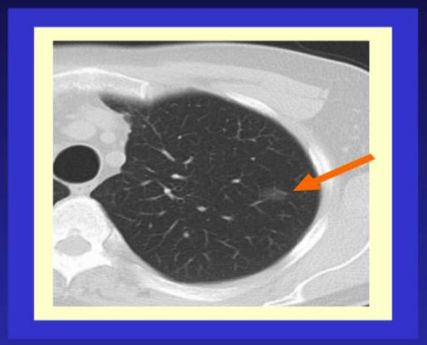
5-yr f/u, non-solid
p=0.029

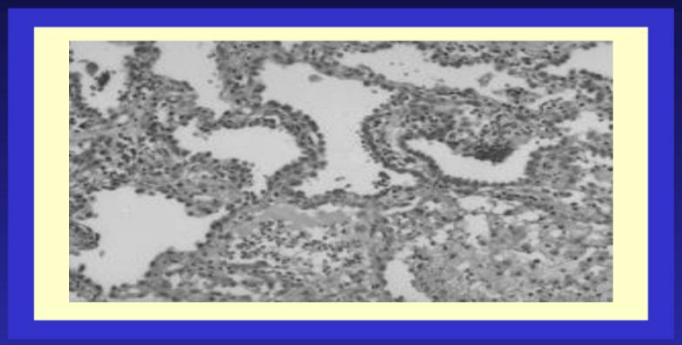


-Overall response negative, but trend toward regression in non-solid lesions (putative precursors of adenocarcinoma)

Adenocarcinoma Precursor: Atypical Adenomatous Hyperplasis

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: Natural History

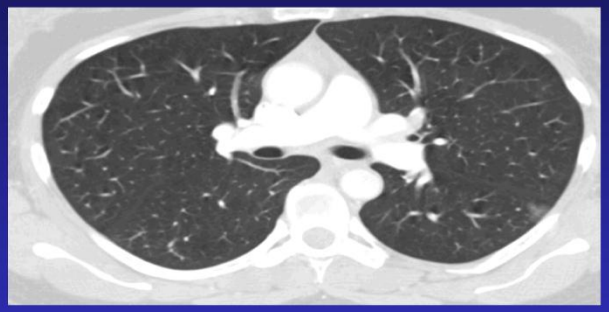
Non-solid nodules – Natural History

- 67 patients with 120 nodules (≤3cm, GGO≥50%)
  - 34 (28%) lesions grew by ≥2mm, median f/u 4.2 yrs
  - OR=6.51 (95%CI 2.08-22.82; p<0.01) for smoking hx
    - Kobayashi Y et al., Lung Cancer 2014;83:61-66

Evolution of CT-detected Lung Nodule

Evolution of CT-detected Lung Nodule

4-1-04



7-14-04

8-19-10

7-25-11

Dx:
Invasive adenocarcinoma (stage I)
Adjacent AAH

Non-solid nodules

Non-solid nodules – Risk of Lung Cancer

Pinsky et al. Cancer Prev Res, *In Press*

- Analysis of NLST data with long term f/u
  - 26,272 participants with LD-CT at baseline and yearly x2
    - f/u: 0-23 mths (short-term, 468 cancers), 24-59 mths (medium-term, 413 cancers), and 60-84 mths (long-term, 190 cancers)

	0-23 Months HR (95% CI)	24-59 Months HR (95% CI)	60-84 Months HR (95% CI)
≥1 10+ mm nodules (vs. 4-9 mm)	12.8 (9.5-17.2)	4.7 (2.9-7.5)	N.S.
≥1 nodule w/ Ground Glass Attenuation (vs. soft tissue)	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

Implications-Molecular Selection Criteria

Implications – Molecular Selection Criteria &/or Endpoints

- Does PI3K activation truly identify smokers at risk for cancer?
  - 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!

Potential for Personalized Chemoprevention

Phase Iib myo-Inositol Chemoprevention Trial

Phase IIb *myo*-Inositol Chemoprevention Trial

PI: Stephen Lam, British Columbia Cancer Agency

30+ pack yr. smokers with dysplasia, age ≥45-79
N=110

↓ (Bronch, Spiral CT)

myo-inositol 9g bid vs. placebo x 6 mths

↓ (Bronch, Spiral CT)

1º Endpoint: bronchial dysplasia (# sites/grade)
2º Endpoints: multiple biomarkers (gene expression)

Clinical sites: BCCA, Mayo Clinic, New Mexico VA

Peroxisome Proliferator-Activated Receptor γ (PPARγ)

Peroxisome Proliferator-Activated Receptor γ (PPAR γ) as a Target for Prevention of Aerodigestive Carcinogenesis

- Pioglitazone – PPARγ agonist approved for type II DM
- Rationale:
  - Cell lines – induces growth arrest, differentiation (NSCLC)
  - Animal carcinogenesis models
    - 4-NQO rat tongue model; incidence and multiplicity ↓ 10-fold
      - Yoshida et al., Cancer Sci 94:365, 2003
  - Epidemiology
    - 33% ↓ lung cancer in diabetics using TZDs (RR=0.67; 95% CI, 0.51-0.87); Nonsignificant decrease in colon and prostate cancer
      - Govindarajan et al. JCO 2007;25:1476-81
    - 41-55%↓ HNSCC in diabetics using TZDs
      - Govindarajan R et al. JCO 2007;25:63s

Pioglitazone in Oral Leukoplakia

Pioglitazone in Oral Leukoplakia

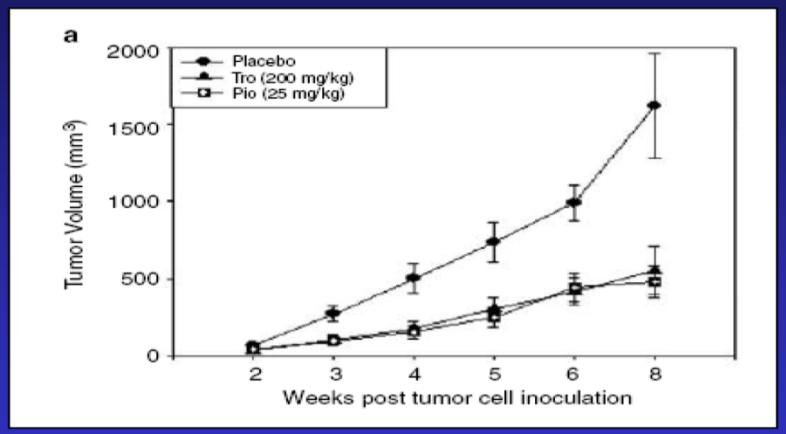
- DCP phase IIa clinical trial - 22 pts., 81% clinical response rate, 79% average ↓size
  - F. Ondrey, U Minn
    - AACR Frontiers Cancer Prev Res, 2007

- New trial – phase IIb, 100 person, 6 mths Rx
  - PIs: J Boyle, MSKCC and F Ondrey, U Minn

Effect of PPARγ Agonists on NSCLC: Animal Models

Effect of PPARγ Agonists on NSCLC: Animal Models

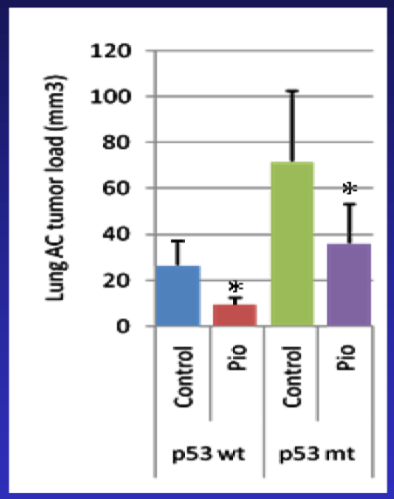
Treatment



-tumor volume ↓ 66.7%
-growth delay 104 days

-Keshamouni et al. Oncogene 2004;23:100-8

Prevention



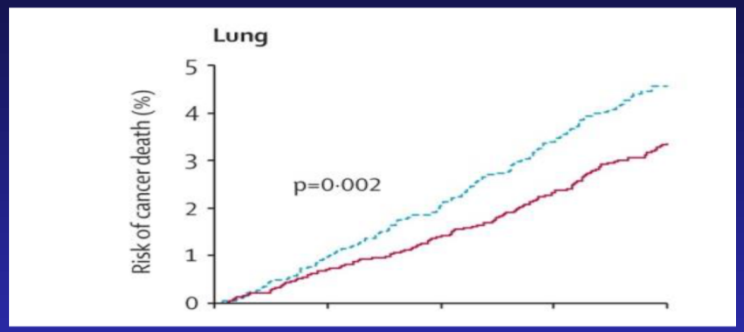
- Vinyl carbamate-treated mice
  - 56-64% ↓ in tumor burden in wildtype and p53 mutant animals
  - Ming You et al. Mol Cancer Ther 2010;9:30742

Current Pioglitazone Clinical Trials (NCI sponsered)

Current Pioglitazone Clinical Trials (NCI sponsored)

- Phase IIb oral leukoplakia
  - Pioglitazone 45 mg qd vs placebo x6 months
  - 100 participants; 11 sites
  - 1° Endpoint: clinical and pathologic response
  - PIs: Jay Boyle, MSKCC and Frank Ondrey, UMinn
- Pilot trial presurgical NSCLC trial
  - Pioglitazone 45 mg qd for 2-6 weeks prior to definitive surgery
  - 20 participants; biomarker endpoints
  - PI: Dennis Wigle, Mayo

Effect of Aspirin on Lung Cancer Mortality



	0	5	10	15	20
			Years to death		
Number at risk					
Aspirin	6258	5816	5243	4485	2634
Control	4244	3948	3545	3006	1493

Effect of Aspirin on Lung Cancer Mortality
-Rothwell et al., Lancet 2011;377:31
-individual patient data from trials of ASA vs. none
-lung:

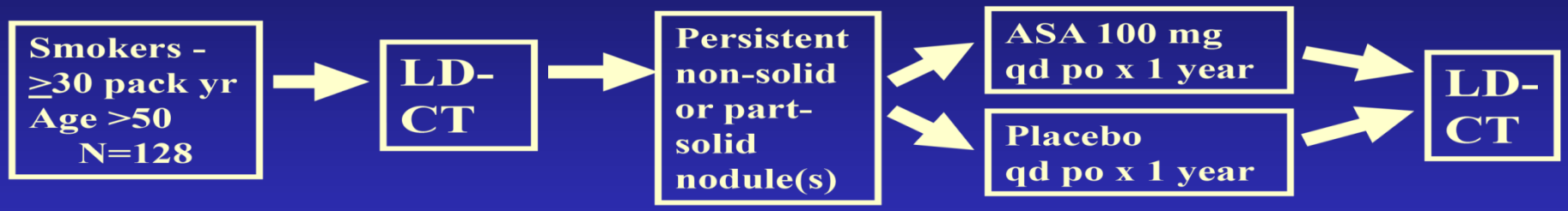
f/u	0-10 yrs	0-20 yrs
HR	0.68 (0.50-0.92, p=0.01)	0.71 (0.58-0.89, p=0.002)

adenocarcinoma only
-benefit only after 5 yrs

The Continuum of Lung Carcinogenesis

Phase IIb Aspirin Chemoprevention Trial

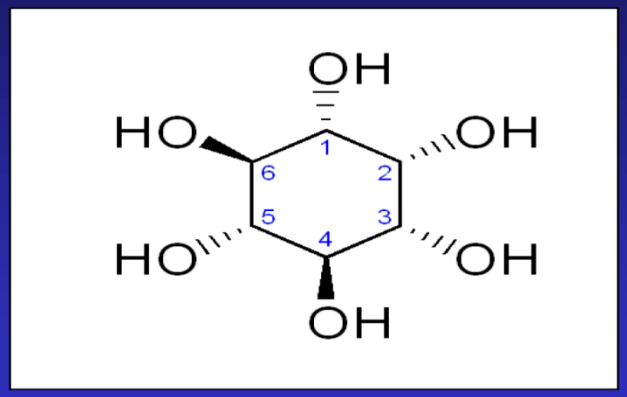
Giulia Veronesi, European Institute of Oncology



1º Endpoint: #/Size non-solid lung nodules
2º Endpoint: COX/LOX urinary metabolites (PGEM, LTE4), miRNA signature , nodule-based endpoints

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

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 in Bronchial Dysplasia

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

-Lam et al., CEBP 2006;15:1526

- Phase I study (26 participants)
  - tolerable 18 g/d
  - 91% vs. 48% regression dysplasia, P=0.014 (10 participants)
  - BP↓ ~14 mm Hg, independent of meds

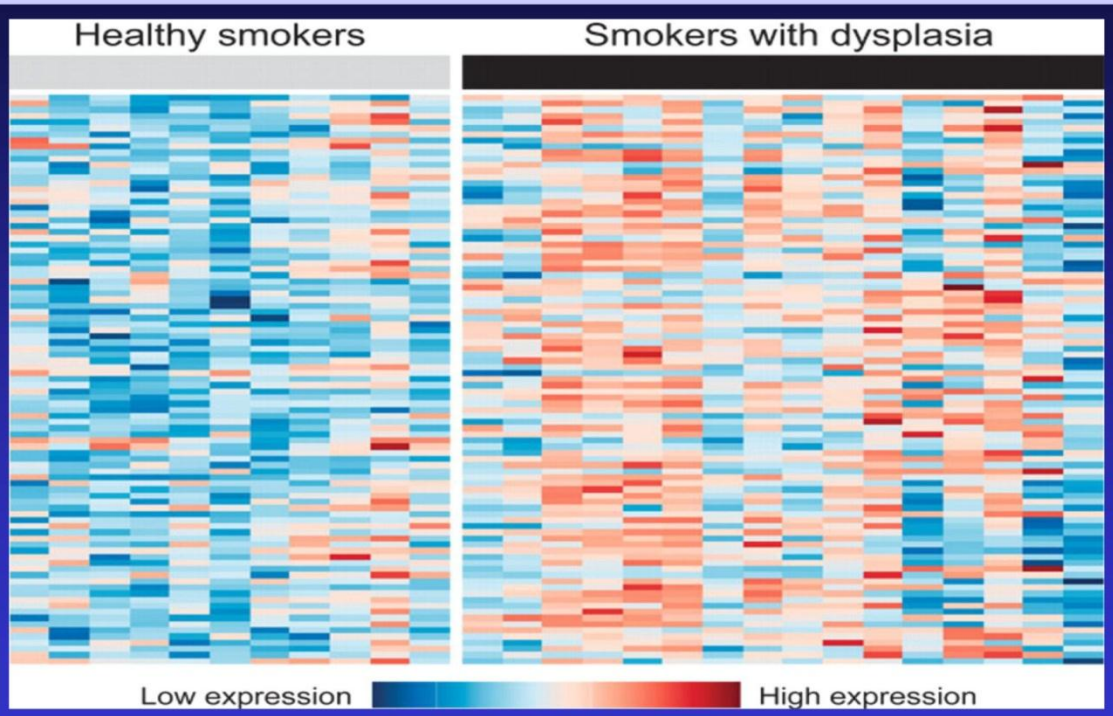
Table 5. Changes in pathologic grades of bronchial biopsy samples at baseline and after 3 months of *myo*-inositol (18 g): Lesion-specific analysis

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

PI3K pathway activation in the airways of smokers with dysplasia

PI3K pathway activation in the airways of smokers with dysplasia

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



-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 ($p=0.04$)

The Continuum of Lung

Carcinogenesis Opportunities for Intervention

The Continuum of Lung Carcinogenesis

Opportunities for Intervention

Normal → Hyper/Metaplasia → Dysplasia → Early-Late Cancer

Prevention

Early Detection

Treatment

Issues in Lung Cancer Screening

Issues in Lung Cancer Screening

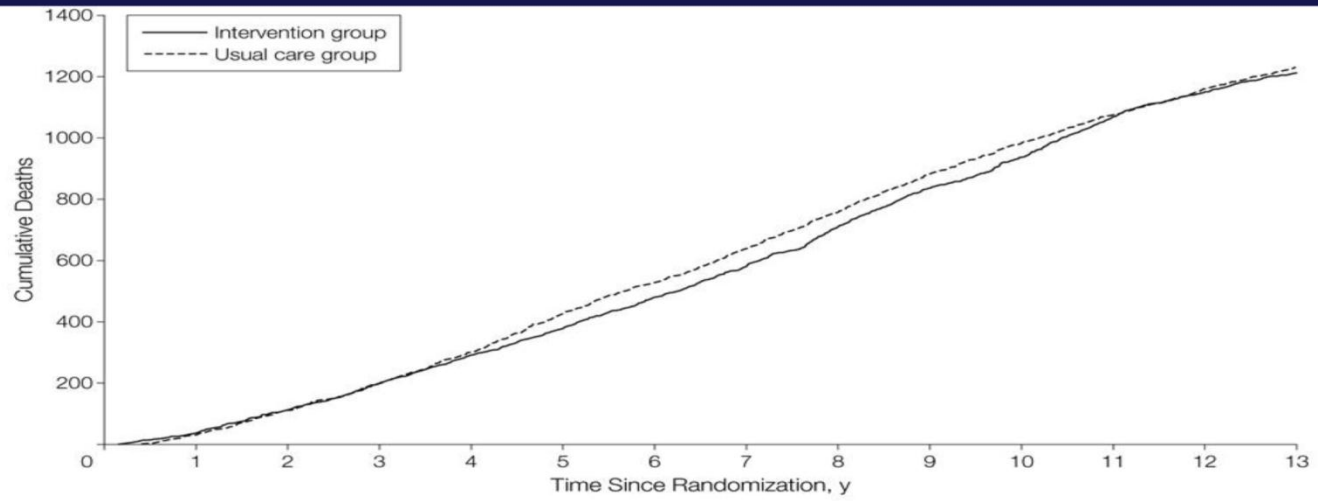
- **Lead-time bias**=earlier diagnosis but no postponement of death (survival appears longer)
- **Length bias**=diagnosis of more indolent disease with longer preclinical phase (better prognosis, better outcome)
- **Overdiagnosis**=identification of clinically unimportant lesions that would not be diagnosed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

- Morbidity/mortality/cost of screening and subsequent work-up

PLCO CXR Randomized Trial-Mortality

PLCO CXR Randomized Trial - Mortality

Oken, M. M. et al. JAMA 2011;306:1865-1873



Intervention group													
Cumulative deaths	36	113	196	292	378	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	198	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

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

NLST (National Lung Screeniing Trial)

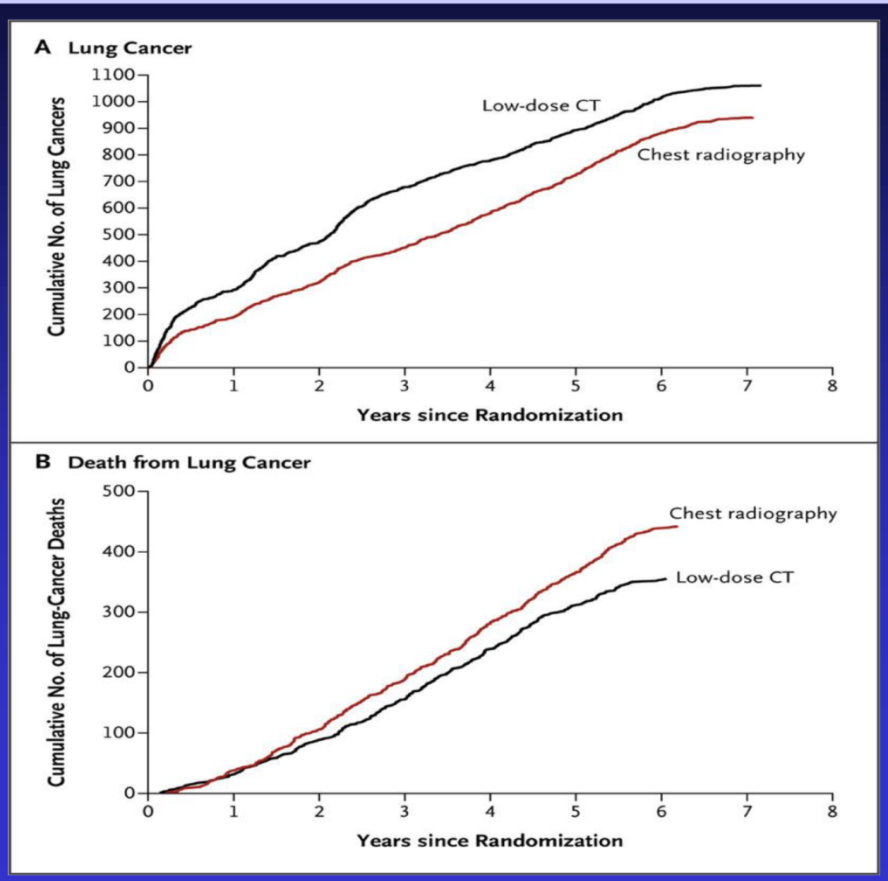
NLST (National Lung Screening Trial)

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

- 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

Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer

Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer



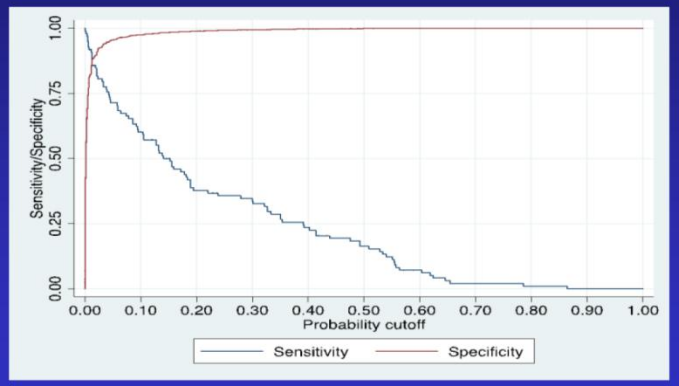
NLST Research Team
N Engl J Med
2011;365:395-409

Lung Cancer Risk Prediction Model

Lung Cancer Risk Prediction Model – 1st Screening CT

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

- 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

Summary

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

"An ounce of prevention
is worth a pound of cure"
-Benjamin Franklin