

Non-small cell lung cancer

Non-small Cell Lung Cancer

Eva Szabo, MD

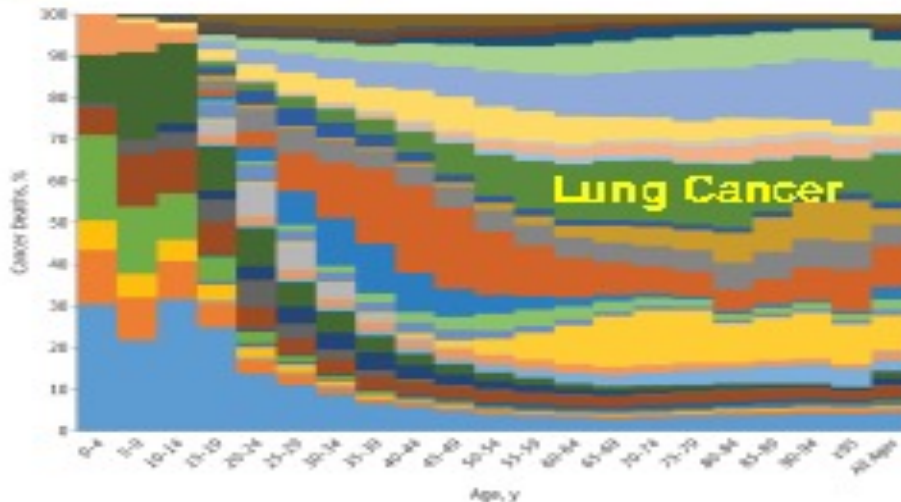
*Chief, Lung and Upper Aerodigestive
Cancer Research Group*

Division of Cancer Prevention, NCI

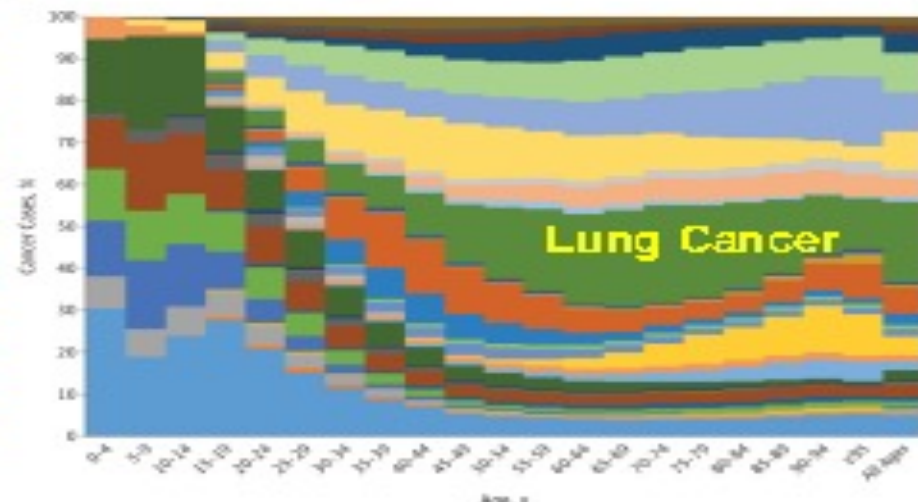
Cancer incidence and mortality

Global Cancer Incidence and Mortality, 1990-2016

Incidence



Mortality



US lung cancer statistics, 2021

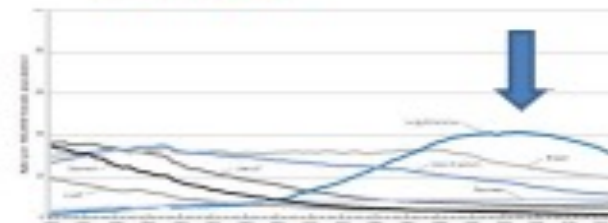
US Lung Cancer Statistics, 2021

- 235,760 estimated new cases (lung and bronchus)
- 131,880 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
- 21% five-year survival
 - 5% in 1950's, 12% in 1970's
- 22% of all male and female cancer deaths

Deaths ♂



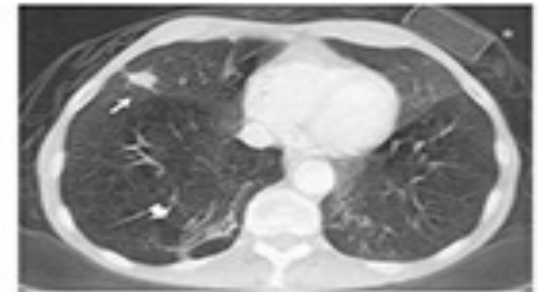
Deaths ♀



Risk factors

Risk Factors

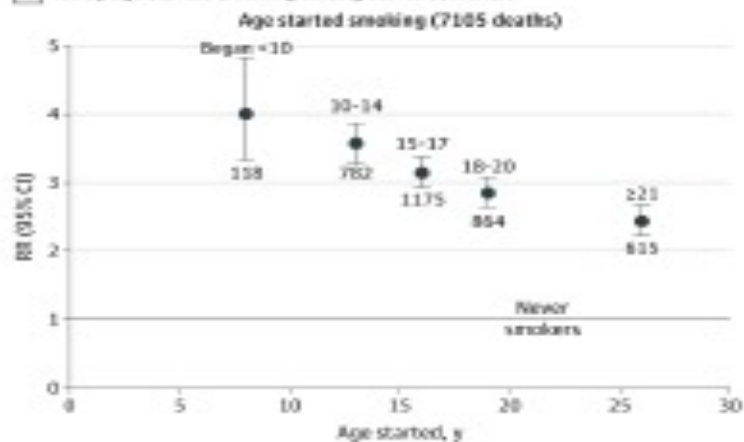
- Tobacco, tobacco, tobacco (85% lung ca.)
 - Including passive smoking
 - Prior aerodigestive malignancy
 - COPD
- Other exposures
 - Asbestos, radon, polycyclic aromatic hydrocarbons, chromium, nickel, inorganic arsenic – mining, ship building, oil refining
- Genetic predisposition
 - Familial lung 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



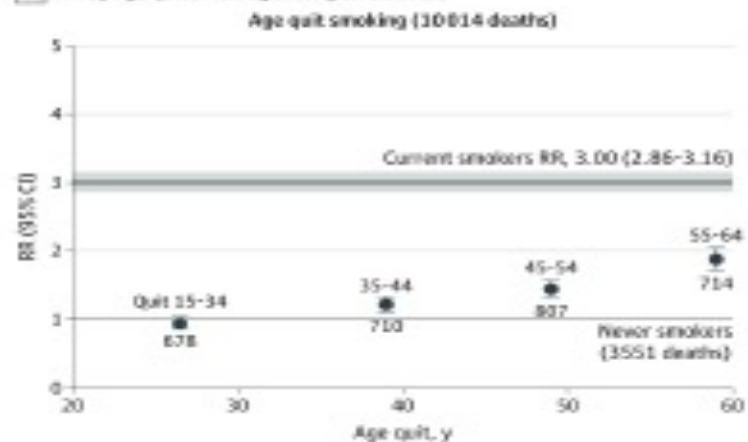
Tobacco and cancer

Association Between Tobacco and All Cancer Death

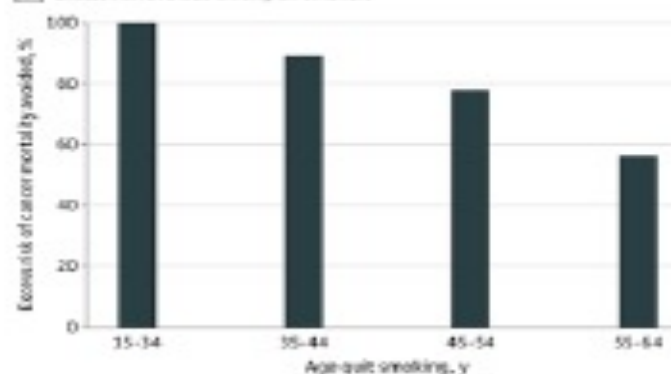
A RR by age started smoking among current smokers



B RR by age quit smoking among ex-smokers

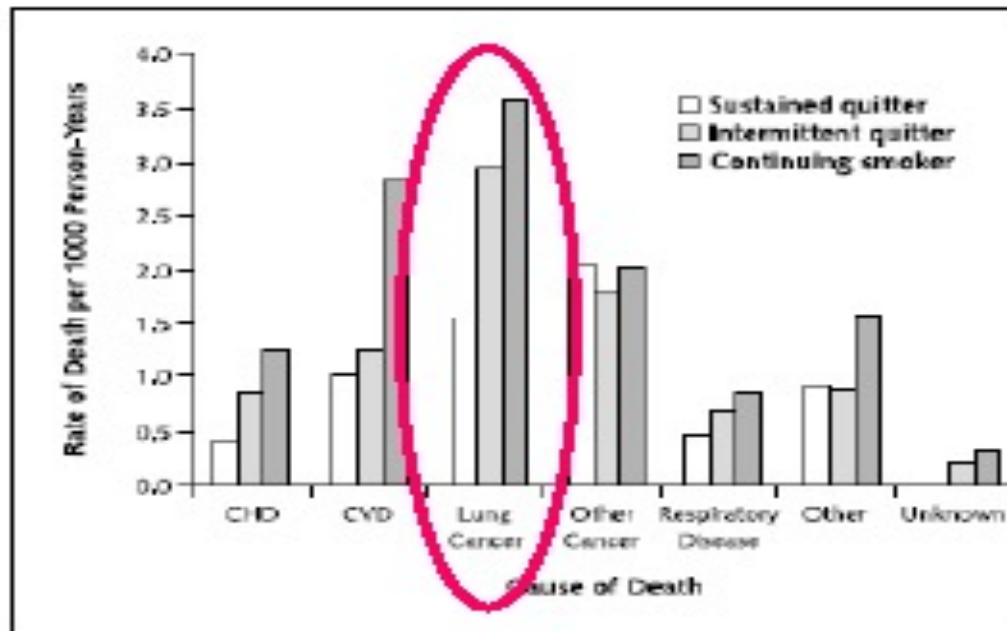


C Excess risk avoided among ex-smokers



Smoking cessation

Effect of Smoking Cessation on Lung Cancer Deaths Lung Health Study, 14.5 yr F/U

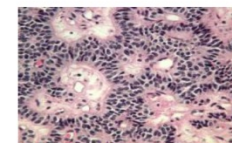
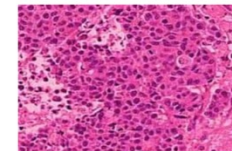
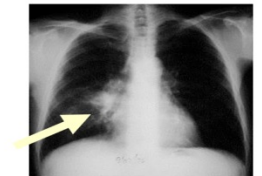
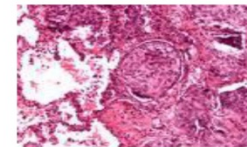
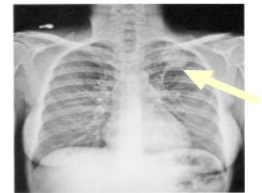
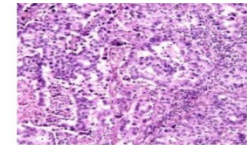


**Lung Health Study,
14.5 yr f/u**
-Anthonisen et al.,
Ann Intern Med
2005;142:233

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

The Continuum of Lung Carcinogenesis Opportunities for Intervention



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

Prevention

Early Detection

Treatment

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)**

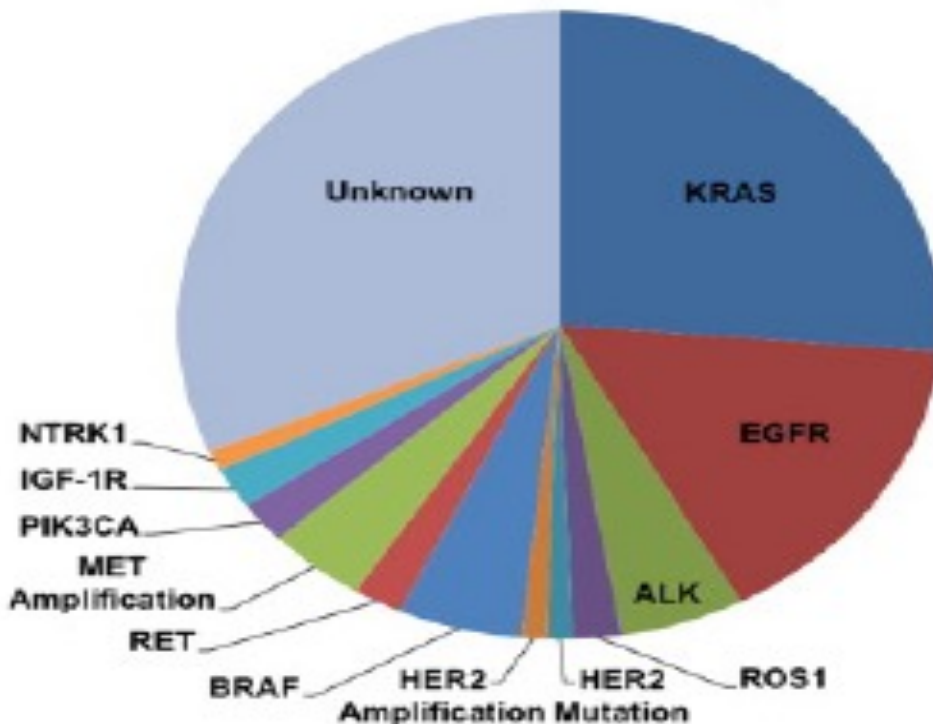
Treatment options

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



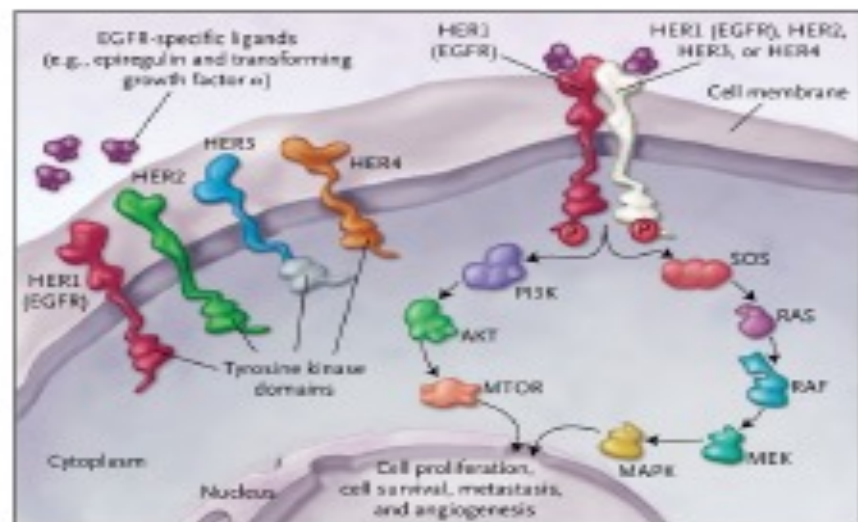
Targetable mutations/gene fusions

- EGFR
 - multiple drugs
- ALK
 - multiple drugs
- ROS1
 - crizotinib
- BRAF-V600E only
 - dabrafenib/trametinib
- RET
 - Experimental drugs (BLU-667)
- NTRK
 - larotrectinib
- MET ex 14 skipping
 - crizotinib
- HER2/Neu – exon 20 mutations
 - HER2 antibodies + chemo

****Response rates 50-80%***

EGFR and NSCLC

EGFR as a Target for NSCLC

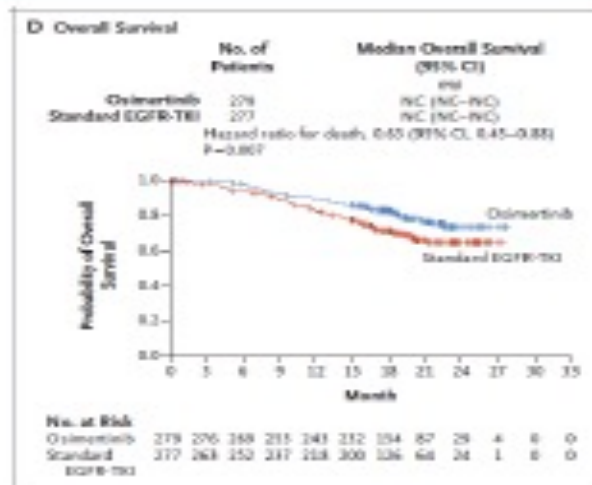
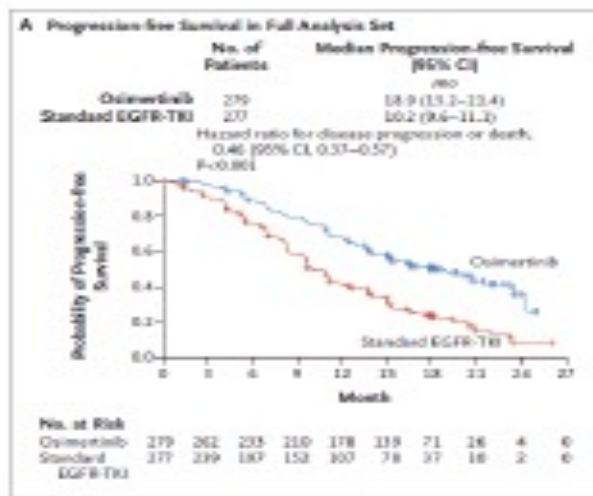


- Epidermal growth factor receptor (EGFR) mutated in ~15% NSCLC
- Oncogenic driver; primarily in non-smokers
- Targeted therapies tyrosine kinase inhibitors (TKIs) highly active
 - 60-80% response rates EGFR-MT disease
 - Progression-free survival 10-14 months (c/w chemo 4-6 months)
 - Median survival 30 vs. 24 months with chemo
 - Maemondo et al *N Engl J Med* 2010;362:2380
- Multiple TKIs approved for frontline use; 3rd generation TKI (osimertinib) superior
- Mechanisms of resistance well understood (T790M; osimertinib)

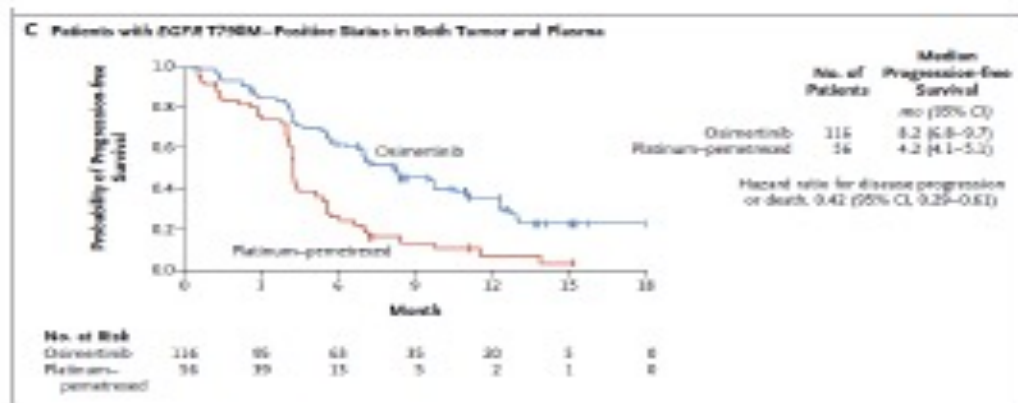
Osimertinib

Osimertinib in Chemotherapy-naïve Patients

No prior Rx



Prior frontline TKI
but no prior chemo

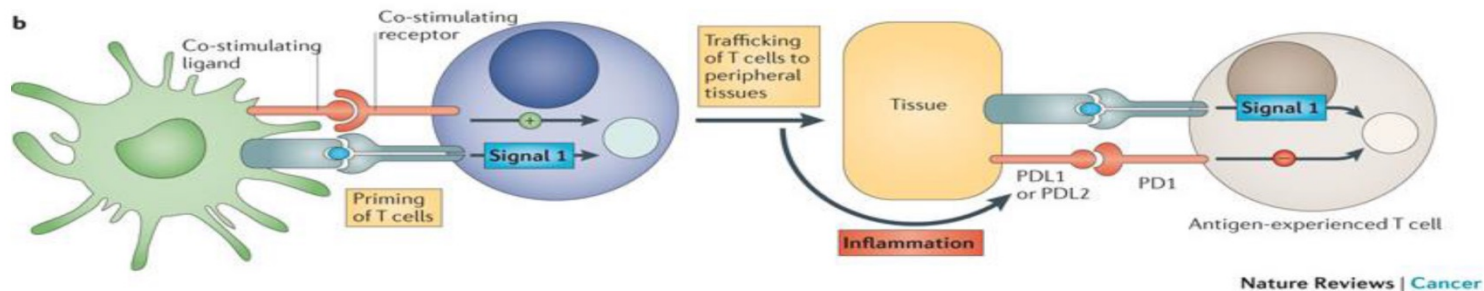


Maik TS et al. *NEJM* 2016
Soria J C et al. *NEJM* 2017

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)



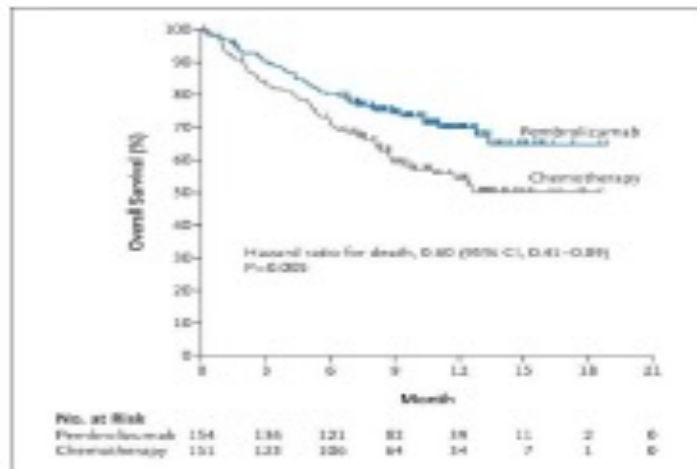
Nature Reviews | Cancer

Immunotherapy

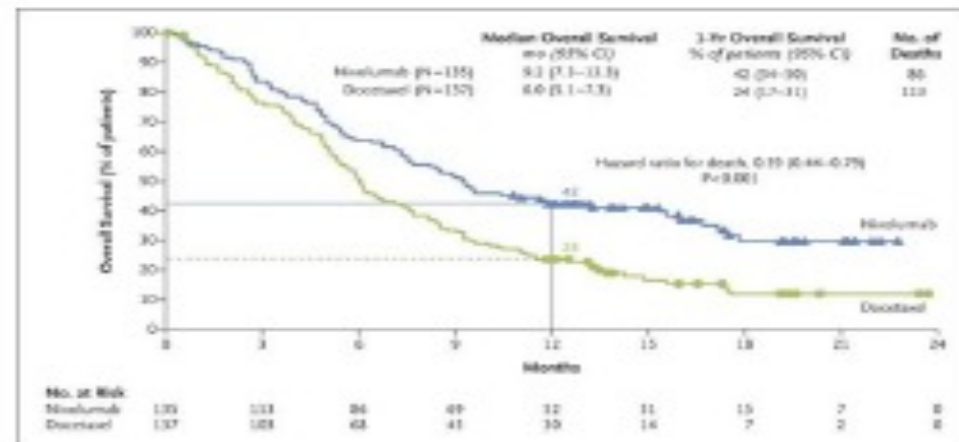
Immunotherapy

- **Anti-PD-1 or PD-L1 antibodies approved for frontline NSCLC, second line Rx, in combination with chemo (frontline), and maintenance post-chemoradiation**
 - Tail of the survival curves suggests long term benefit for minority of patients

Frontline treatment



Second line treatment

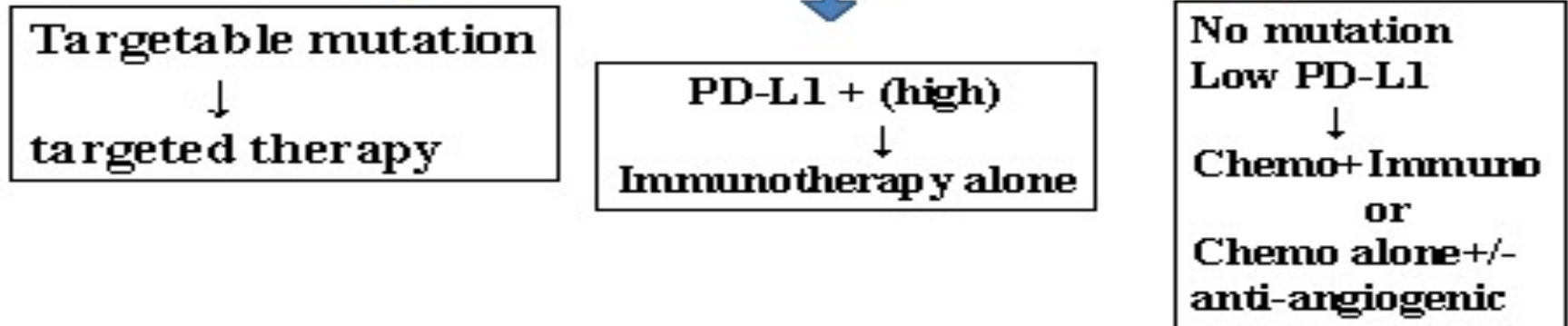


Reck Met et al *NEJM* 2016;375:1823–1833
 Brahmer J et al *NEJM* 2015;373:123–135

Clinical approach

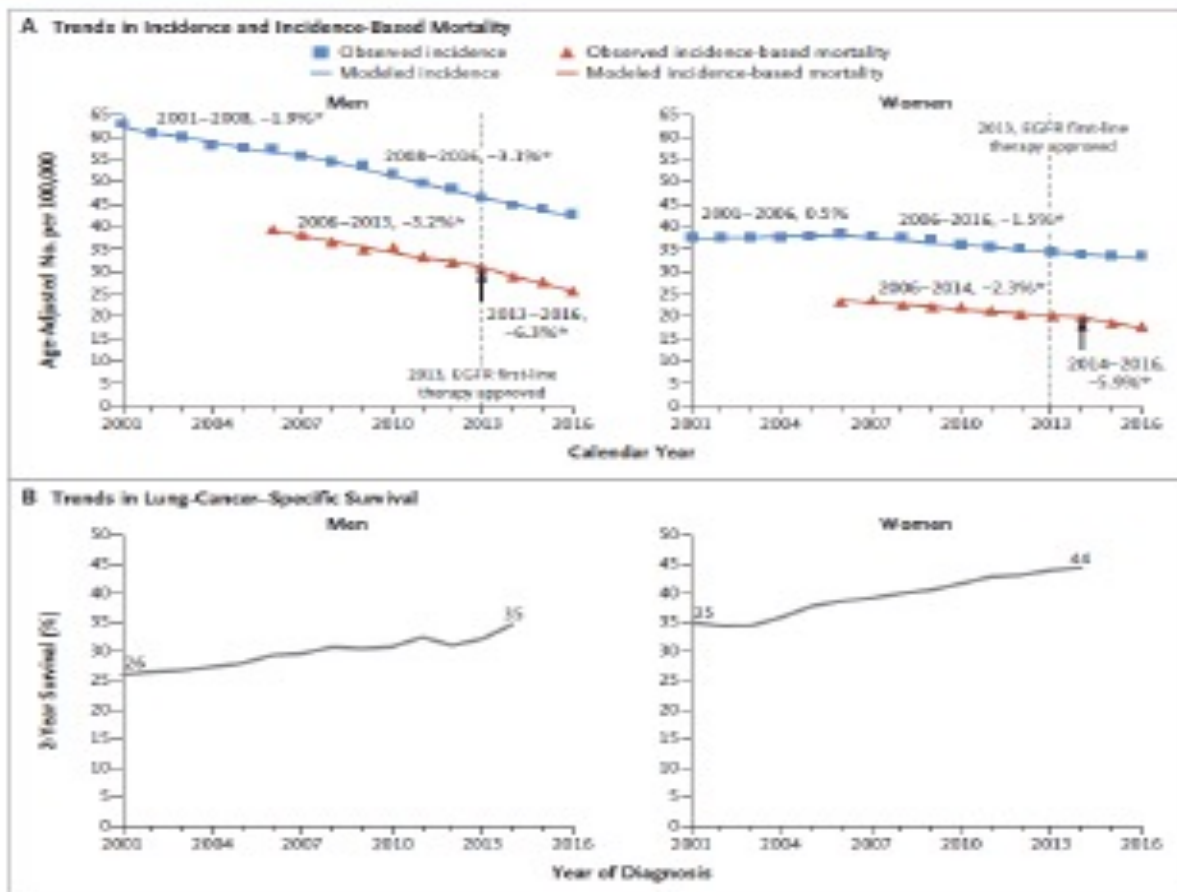
Approach to the Patient with Metastatic NSCLC

Biopsy for molecular analysis



NSCLC mortality

↓ Mortality from NSCLC with Improved Therapy



Mortality decreased faster than incidence

- 2013–2016 -Mortality ↓6.3% annually (men)
- 2008–2016 - Incidence ↓3.1% annually (men)
- Lung cancer specific survival improved from 26% to 35% from 2001 to 2016
- Similar in women, across all races/ethnic groups
- For SCLC, decreased mortality was same as decreased incidence
- **Conclusion: treatment advances (esp. targeted therapies) responsible**

Approaches to reducing cancer morbidity and mortality

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

Lung carcinogenesis

The Continuum of Lung Carcinogenesis Opportunities for Intervention



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

Prevention

Early Detection

Treatment

Cancer Chemoprevention

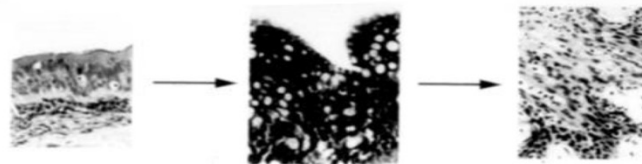
The use of natural or synthetic agents to suppress or reverse carcinogenesis

- 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**



Lung premalignancy

Evolution of Lung Premalignancy

Normal → Hyperplasia/Metaplasia → Dysplasia → Cancer

Mild/Moderate/Severe/CIS

**Squamous
(central)**



**Adenomatous
(peripheral)**



Bronchial dysplasia

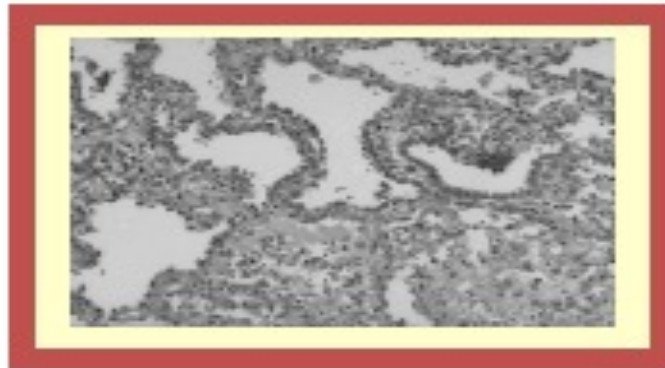
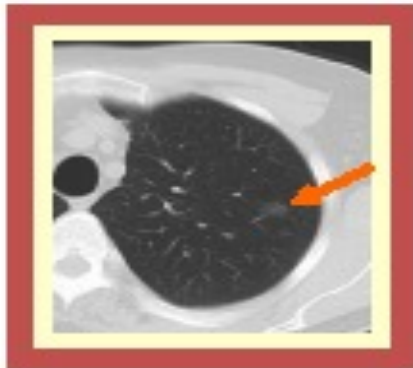
Squamous Cell Carcinoma Precursor: Bronchial Dysplasia



- 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; Vennans 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*

Atypical adenomatous hyperplasia

Adenocarcinoma Precursor: Atypical Adenomatous Hyperplasia (AAH)



- **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, ≤ 3 cm, solid component ≤ 5 mm)
 - f/u 4.3 ± 2.5 years
 - 1046 pure GGN \rightarrow 5.4% became part solid
 - 81 heterogeneous GGN \rightarrow 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*

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

Phase IIb budesonide trial

DCP Phase IIb Trial of Inhaled Budesonide in Bronchial Dysplasia

112 smokers with dysplasia
by bronchoscopy



Helical CT

Screened (sputum): 1040
Cancers detected: 13

Budesonide vs. Placebo x 6mths

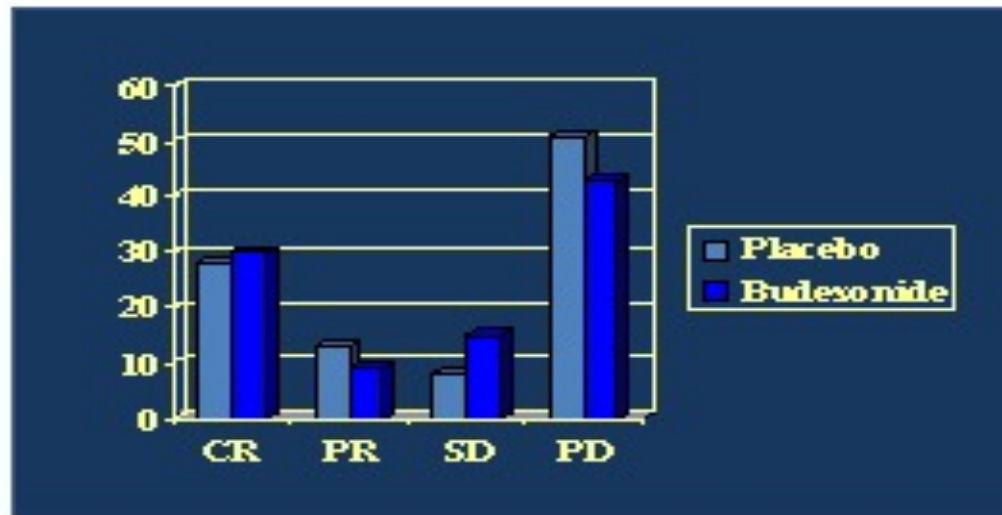


Bronch,
Spiral CT)

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

Bronchial dysplasia

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)**

Chemoprevention trial Phase IIb Trial

Peripheral Lung Carcinogenesis Trial Design Phase IIb Budesonide Chemoprevention Trial

202 participants with persistent LD-CT-detected peripheral nodules



Randomize

inhaled budesonide vs. placebo x 1 year



repeat LD-CT

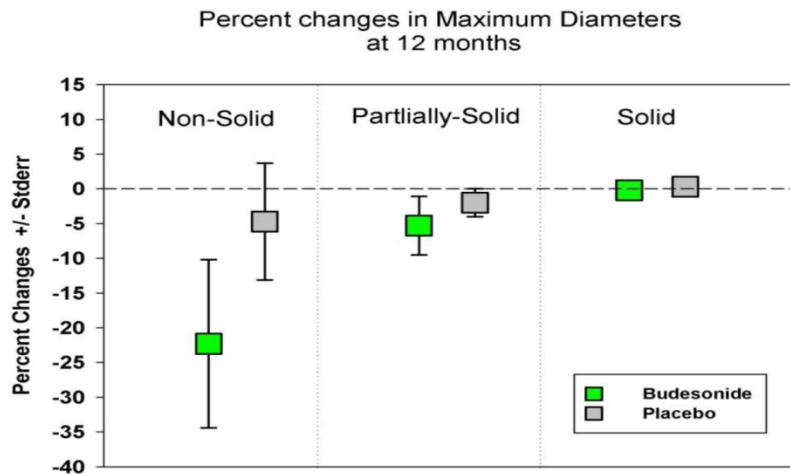
Primary endpoint: shrinkage of lung nodules



Chemoprevention Trial

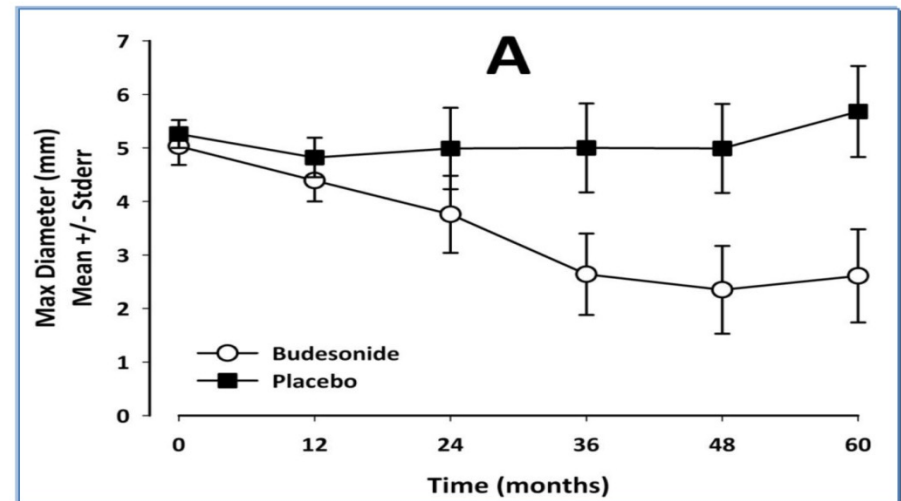
Phase IIb Budesonide Chemoprevention Trial Lesion Specific Analysis

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

Aspirin and Mortality

Effect of Aspirin on Lung Cancer Mortality

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

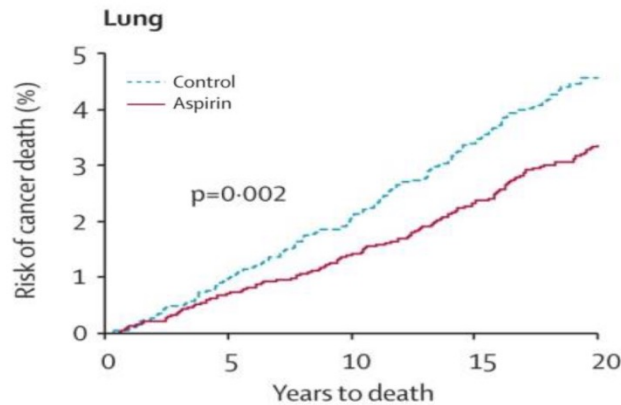
-individual patient data from trials of ASA vs. none

-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

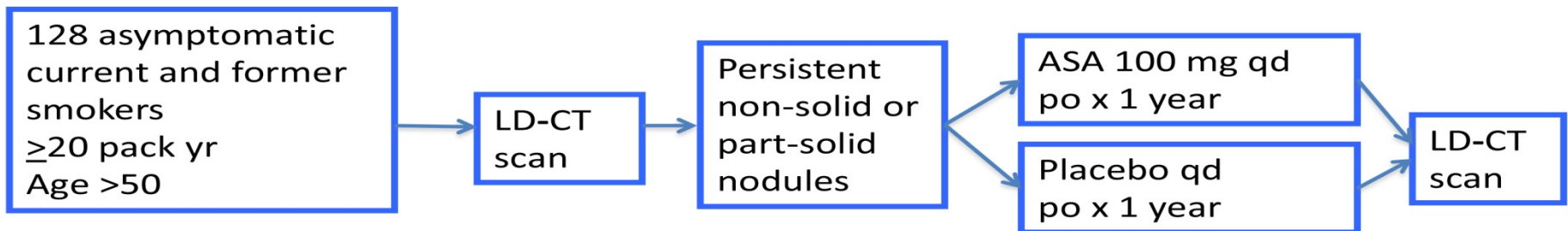
-benefit only after 5 yrs



Number at risk					
Aspirin	6258	5816	5243	4485	2634
Control	4244	3948	3545	3006	1493

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



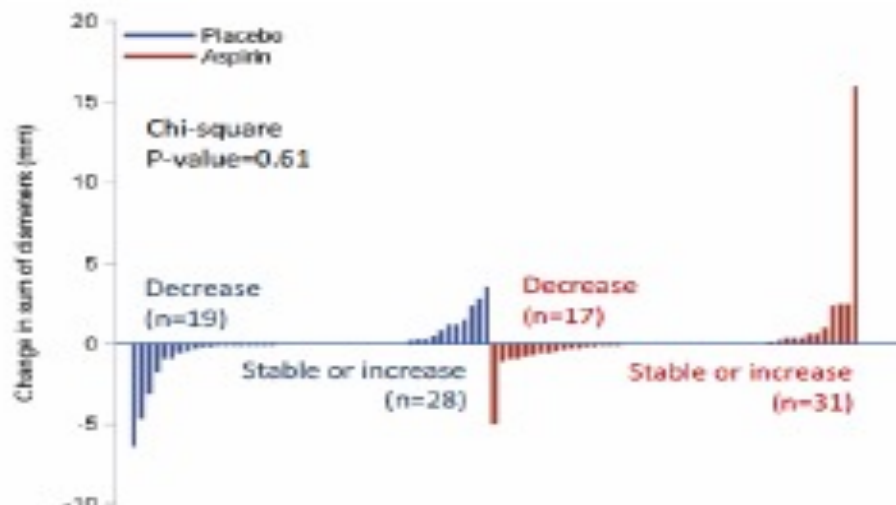
1° Endpoint: #/Size semisolid lung nodules

2° Endpoints: COX/LOX urinary metabolites (hs-CRP, PGEM, LTE4), miRNA signature, nodule-based endpoints

Accrual as of October 15, 2015: 47 participants

Aspirin trial

Phase II Trial of Low Dose Aspirin Trial

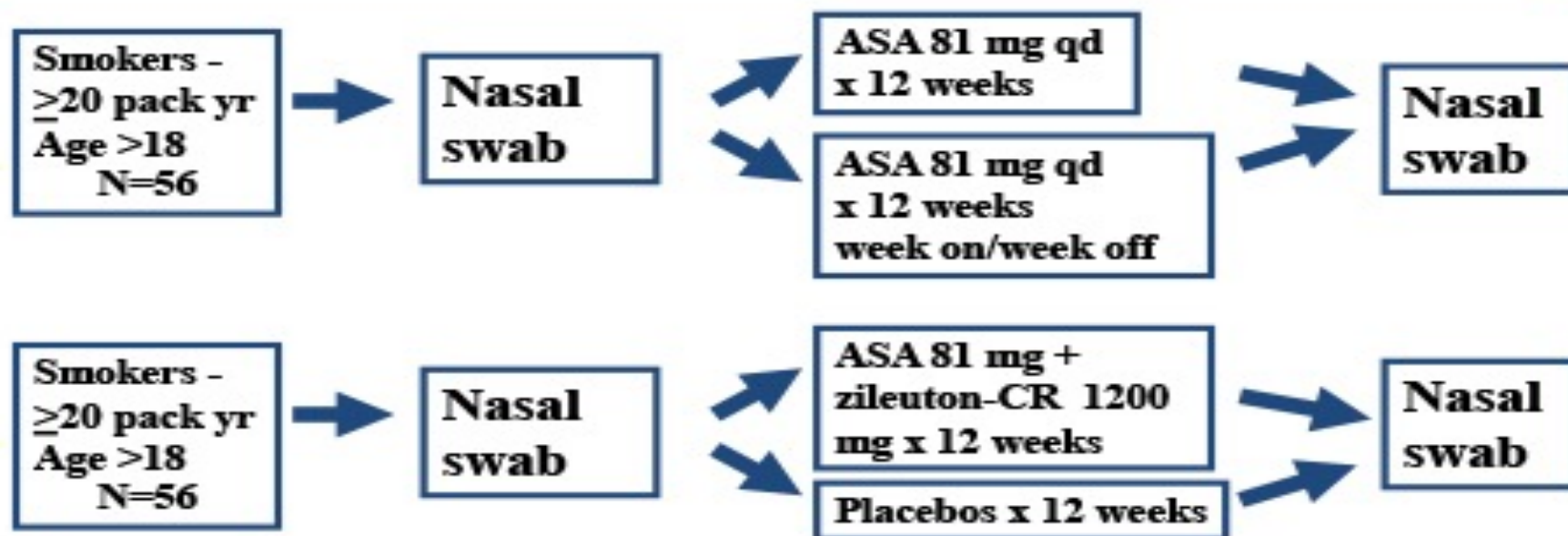


- 98 participants randomized
- no difference in nodule size, new nodules
- no differences by sex, smoking status
- underpowered to detect differences in new cancers

Biomarkers

Biomarker Aspirin Chemoprevention Trials

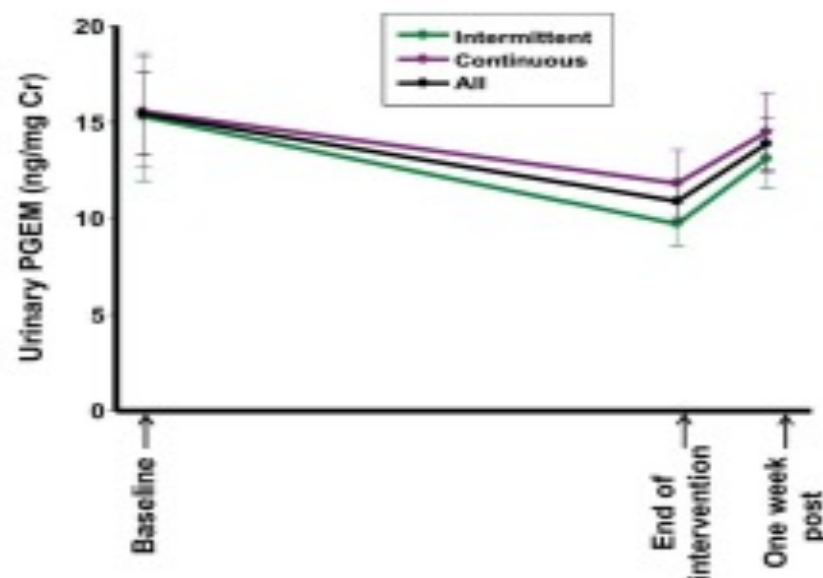
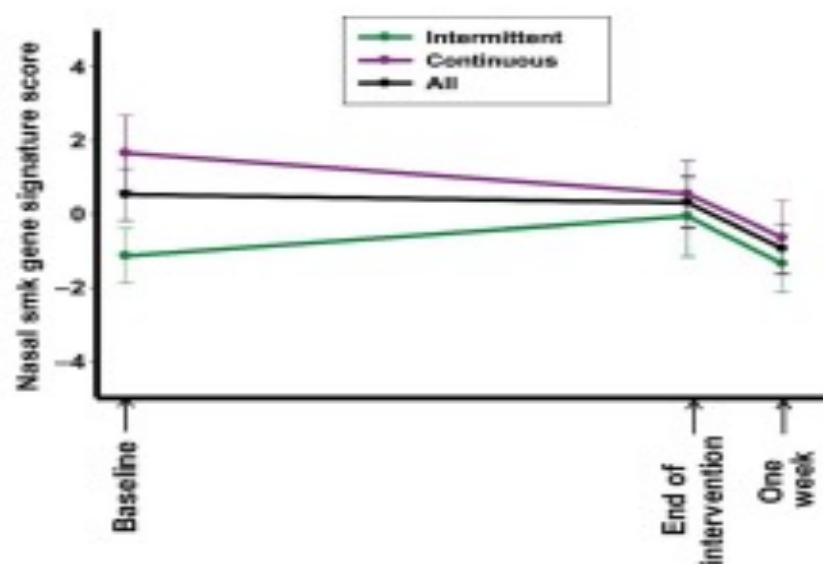
Linda Garland, University of Arizona



1° Endpoint: smoking gene expression signature (nasal epithelium)
2° Endpoint: PI3K gene expression signature, lung cancer gene expression Signature, COX/LOX urinary metabolites (PGEM, LTE4)

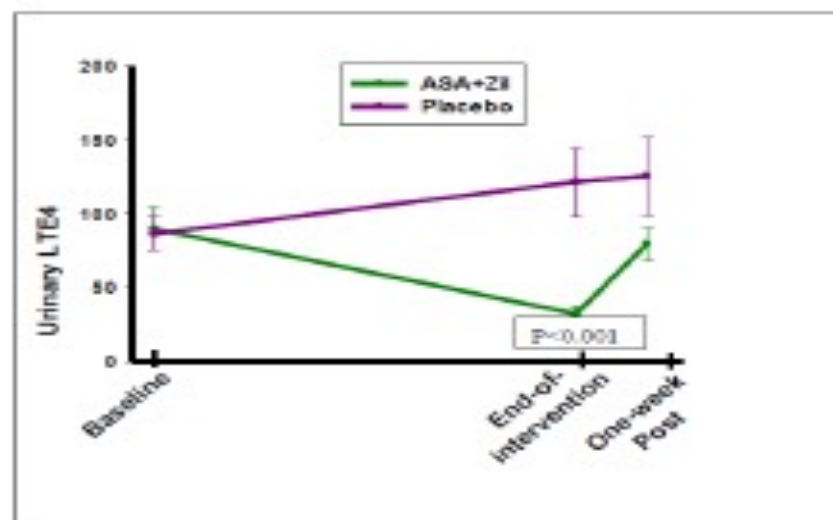
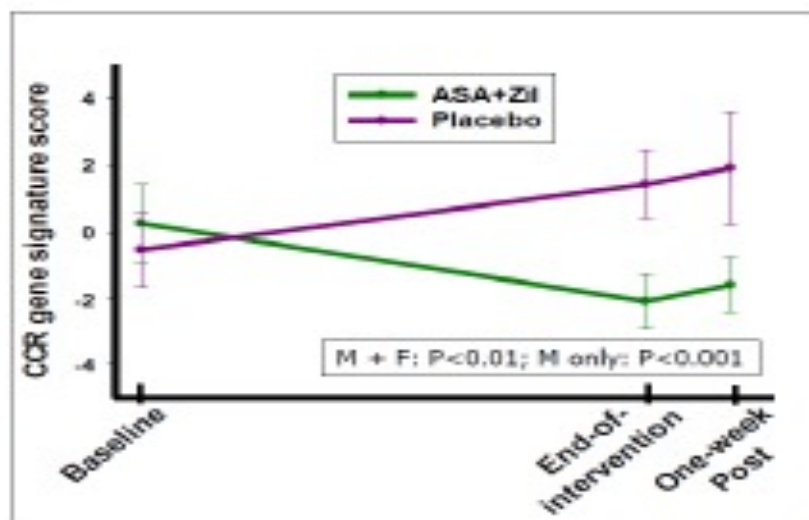
Aspirin

Minimal Effects of Continuous vs. Intermittent Aspirin on Nasal Smoking Gene Signature Score



Aspirin and zileuton

Effect of Aspirin and Zileuton on Nasal Dysplasia Gene Signature Score

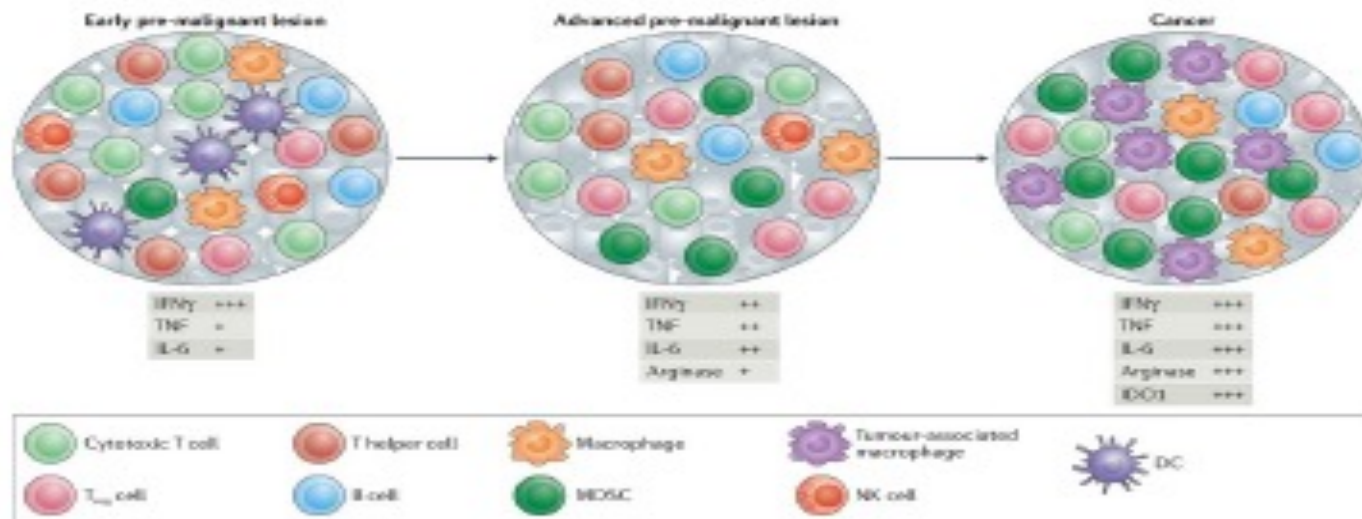


- Significant decrease in dysplasia gene score
- No effect on nasal smoking gene signature score
- Significant effect on lipoxygenase metabolism (LTE4)
- Minimal effect on cyclooxygenase metabolism
 - PGEM borderline suppressed ($p = 0.07$)

-unpublished

Cancer Immunoprevention

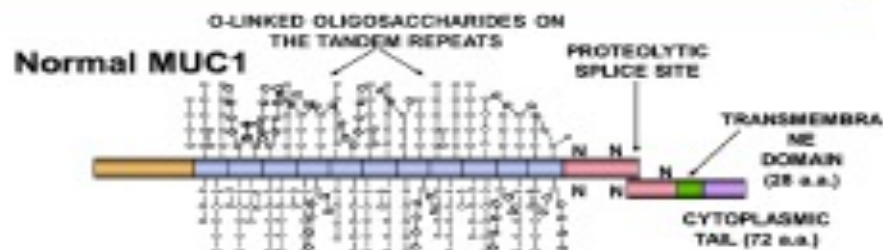
Cancer Immunoprevention: Potential for prevention of multiple cancers



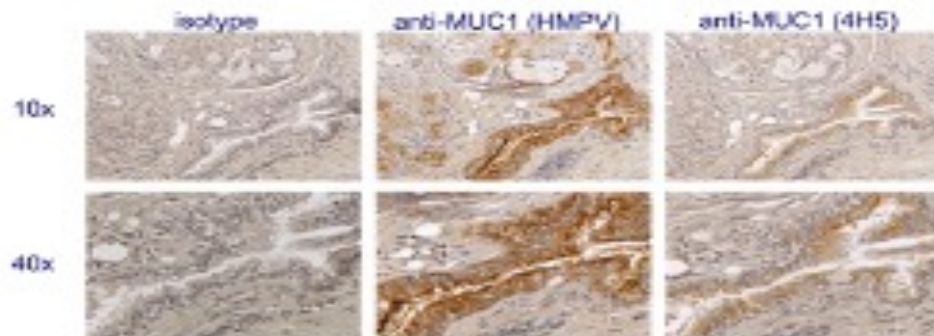
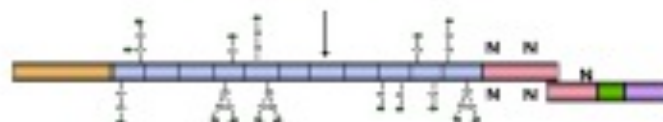
MUC1

MUC1

- Human tumor-associated antigen discovered in 1989
- Expressed on all human adenocarcinomas
- Differentially glycosylated compared to normal cells
 - particularly VNTR region
- Cancer therapy target; may be more immunogenic at preinvasive stage
 - Highly expressed in many premalignancies



Abnormal MUC1 1 repeat = 29 a.a.
HGVTSA PDTRPAPGSTAPPA



Courtesy of Olja Finn and Paul Limburg

MUC1 vaccine

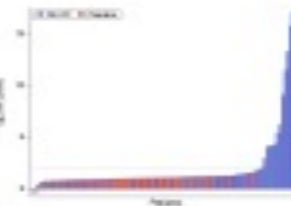
MUC1 Vaccine in Patients with Newly Diagnosed Advanced Colorectal Adenomas (O. Finn Vaccine)

- **Trial overview**

- Age 40-70 years; recent advanced colorectal adenoma
- MUC1 vaccine vs. placebo at weeks 0, 2, 10 (Part I) and 53 (Part II)
- Primary endpoint: Δ MUC1 IgG level at week 12 vs. week 0
- Secondary endpoints: Δ MUC1 IgG level at week 55 vs. week 53; adenoma recurrence at up to week 156

- **Results**

- 102 participants evaluable (MUC1 n=52; placebo n=50)
- 2-fold IgG \uparrow (=response) in 25% MUC1
- Response correlated with low baseline PMN-MDSC levels ($p = .000$)
- Adenoma recurrence \downarrow 38% in responders (not intent-to-treat)



- **Ongoing immunogenicity study in heavy smokers undergoing CT screening**

metformin

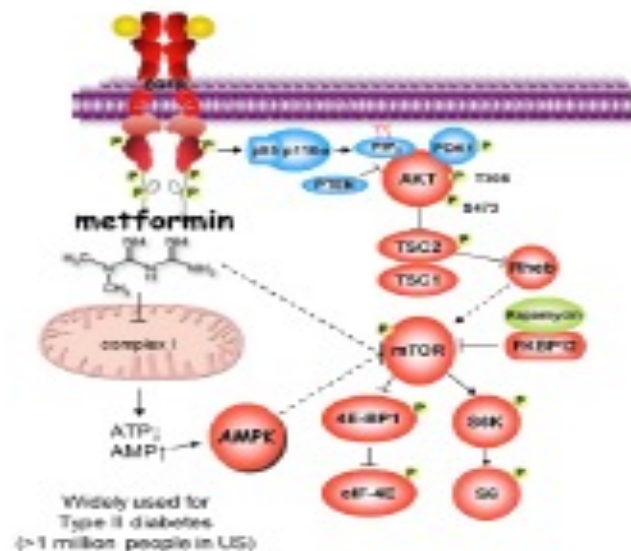
Metformin

- Cancer incidence literature mixed and affected by multiple confounders and time-related biases
- DCP meta-analysis, RR=0.69, 95%CI, 0.52-0.90
 - Correction for BMI or time-related biases reduced RR to 0.82 and 0.90, respectively

Endpoints	Groups	SRR (95%CI)	I ²	n studies*
Cancer incidence	All studies	0.69 (0.52, 0.90)	88	19
	Adjusted for BMI	0.82 (0.70, 0.96)	76	11
	Adjusted for time related bias	0.90 (0.89, 0.91)	56	8
	Prospective studies	0.71 (0.47, 1.07)	89	12
Cancer mortality	Randomized Clinical Trials	0.95 (0.69, 1.30)	5	5
	All studies	0.66 (0.54, 0.81)	21	7
	Adjusted for BMI	0.60 (0.45, 0.80)	0	5
	Adjusted for time related bias	0.45 (0.16, 1.26)	0	3
	Prospective studies	0.48 (0.23, 0.97)	0	4

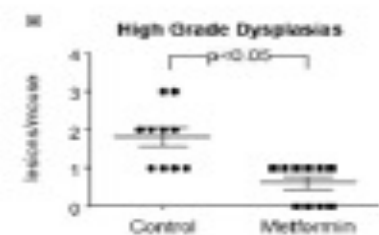
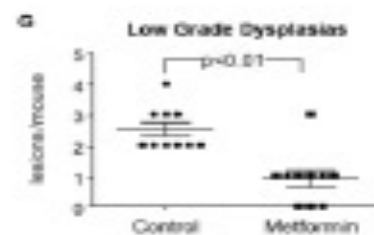
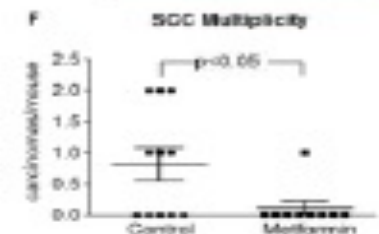
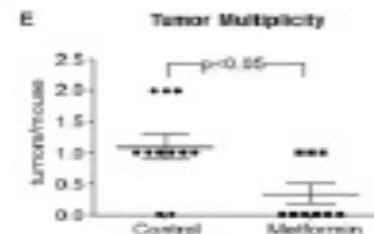
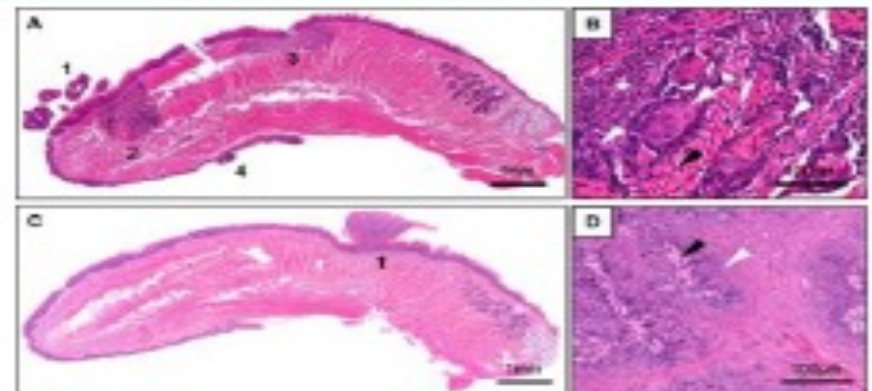
Metformin

Targeting mTOR with Metformin for Oral Cancer Prevention



~90% human HNSCC activation
Activated in oral premalignancy

Vitale-Cross et al., *Cancer Prev Res*, 2012
- slide courtesy of Silvio Gutkind



Metformin Trial

Phase IIa Metformin Trial in Oral Leukoplakia

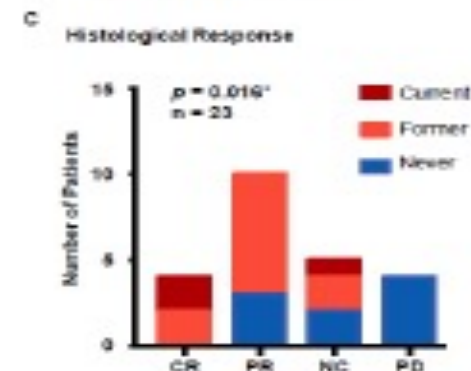
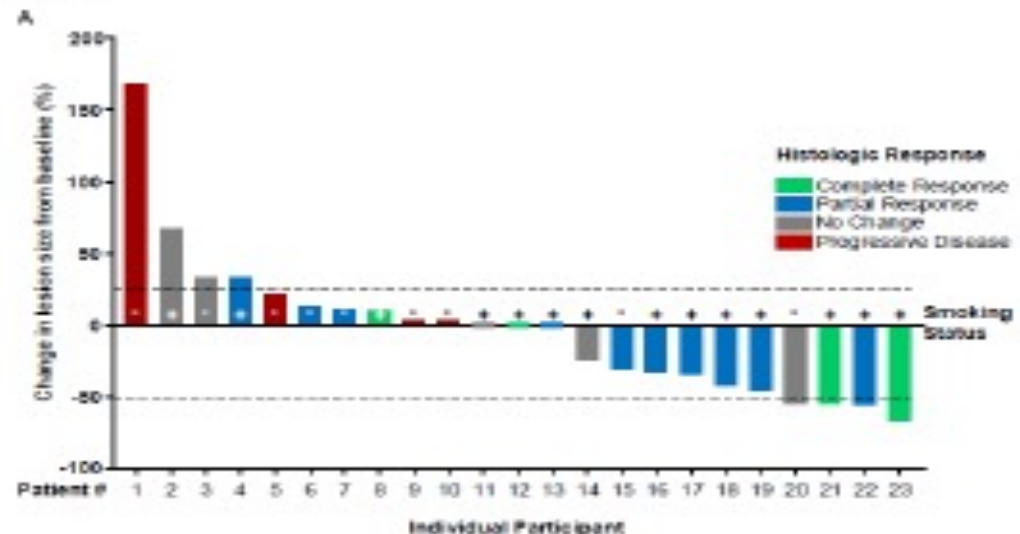
Clinical and Lesion Histologic Responses (n=23)

Post Intervention Clinical Response, n (%)

CR - Complete Response	0 (0.0)
PR - Partial Response	4 (17.4)
NC - No Change	15 (65.2)
PD - Progressive Disease	4 (17.4)

Post Intervention Lesion Histological Response, n (%)

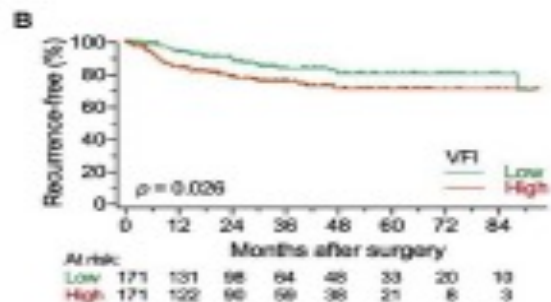
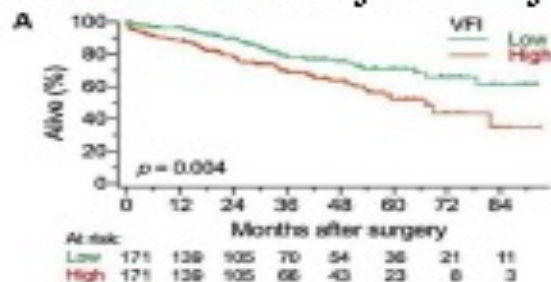
CR - Complete Response	4 (17.4)
PR - Partial Response	10 (43.5)
NC - No Change	5 (21.7)
PD - Progressive Disease	4 (17.4)



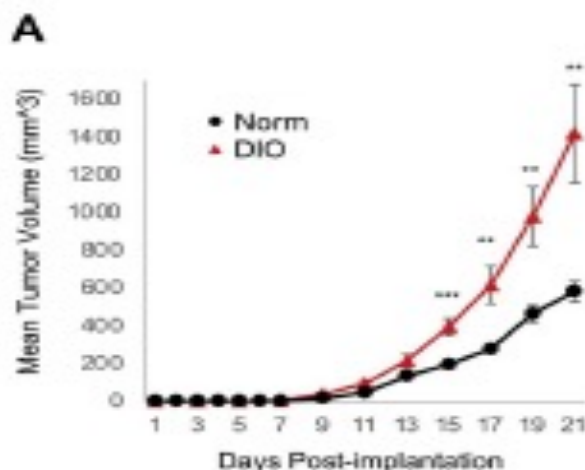
Obesity

Visceral Obesity Promotes Lung Cancer Progression and an Immune Suppressive Tumor Microenvironment

OS and RFS by Obesity



Obesity-induced LLC tumor growth in mice



- Obesity affects TME
 - Effector cell deficits, exhausted phenotypes
 - ↑ Tregs, MDSCs, activated phenotypes
- Metformin assoc with OS in stage I pts. with high BMI
- Metformin reverses obesity effects in mice

Intervention

The Continuum of Lung Carcinogenesis Opportunities for Intervention



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

Prevention

Early Detection

Treatment

Lung Cancer Screening

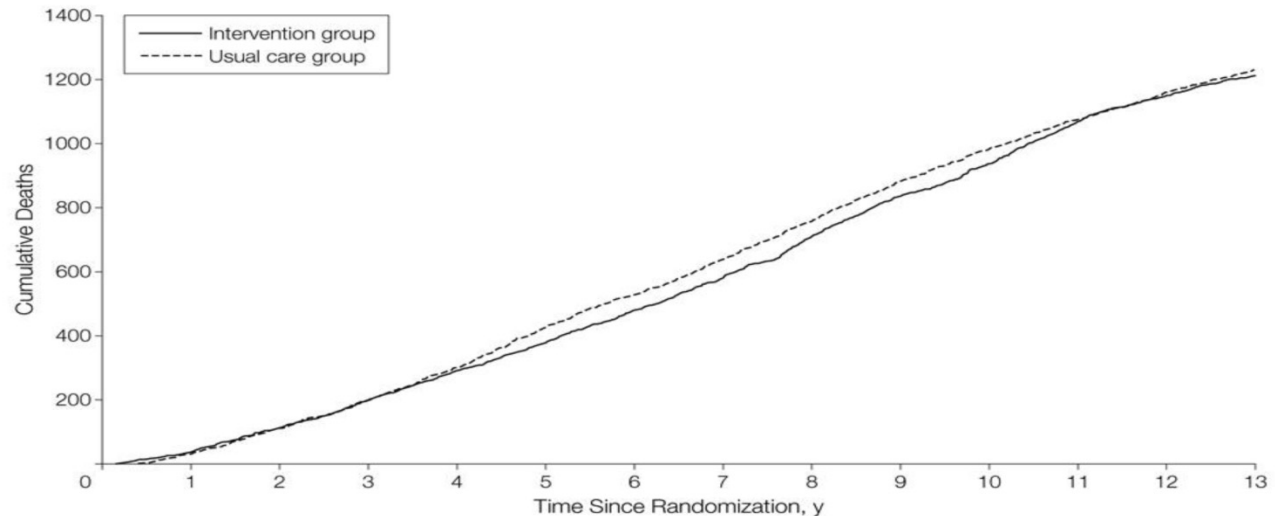
Issues in Lung Cancer Screening

- **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 Trial

PLCO CXR Randomized Trial - Mortality

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



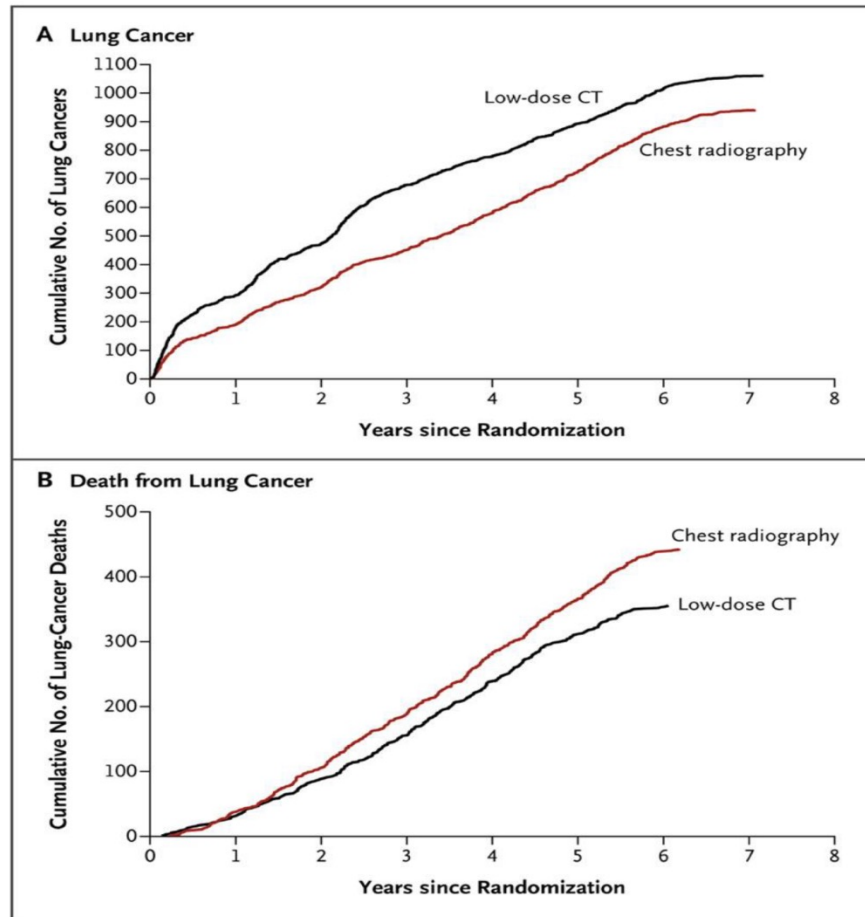
Intervention group													
Cumulative deaths	36	113	196	292	378	480	582	711	838	937	1070	1150	1213
Cumulative person-years	77 268	154 053	230 270	305 833	380 691	454 773	527 937	600 004	670 274	735 098	789 540	832 441	864 227
Usual care group													
Cumulative deaths	30	111	198	301	426	527	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

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

Lung Cancer and Deaths

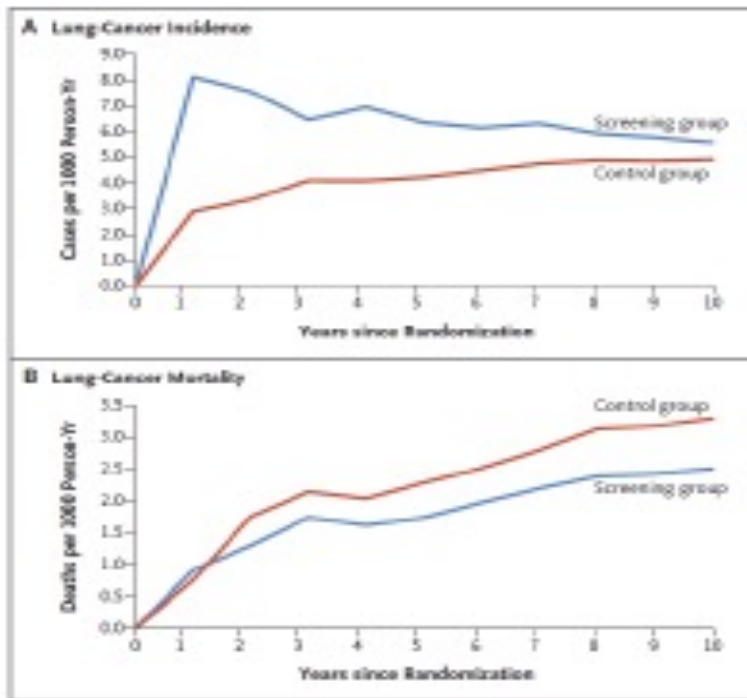
Cumulative Lung Cancers and Deaths from Lung Cancer



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

CT screening

NELSON CT Screening Trial



- **13,195 men and 2594 women**
- **age 50-74**
- **Screening baseline, yr 1, yr 3, yr 5.5**
- **Volumetric analysis**
- **10 yr follow-up**
- **Men: RR=0.76**
- **Women: RR=0.67**

Summary

Summary

- **Tremendous progress has been made in understanding lung carcinogenesis**
 - **Pathologic classification oversimplifies molecular complexity**
 - **Heterogeneity in tumors and premalignant lesions complicates efforts to intervene**
 - **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**
 - **Applications to prevention not yet clear**
 - **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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- **Avrum Spira, Boston University**