Lung Cancer

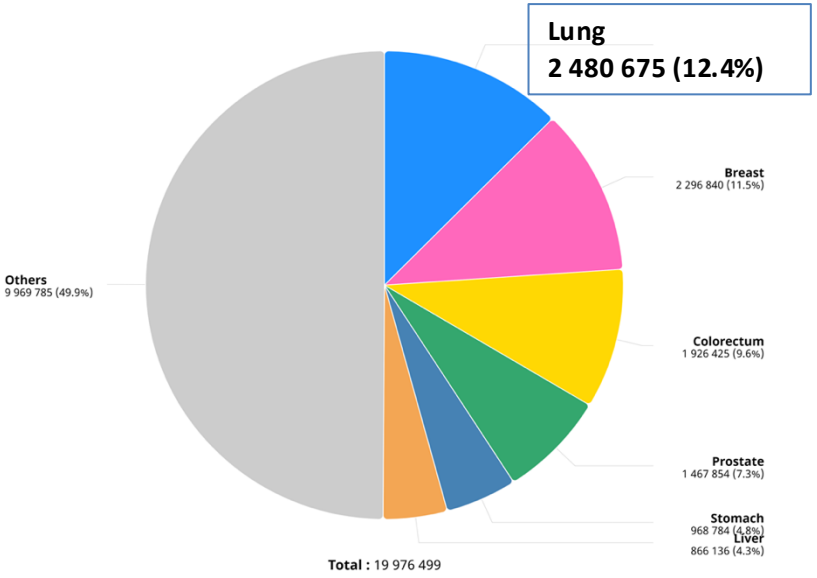
- **Terry Moody, Ph.D.**
  Center for Cancer Training
  National Cancer Institute
  October 19,2026

Global Burden of Cancer 2022

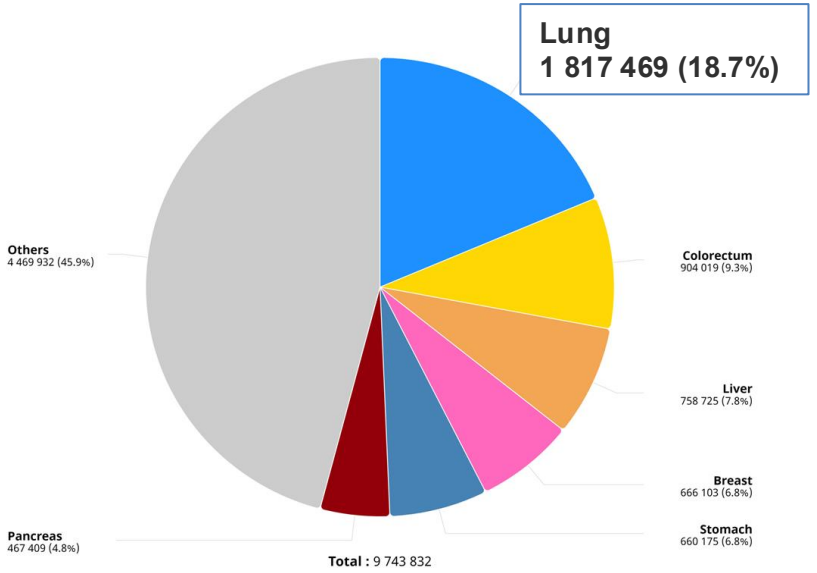
International Agency for Research on Cancer
World Health Organization

Source: Globocan 2022

of new cases in 2022, both sexes, all ages



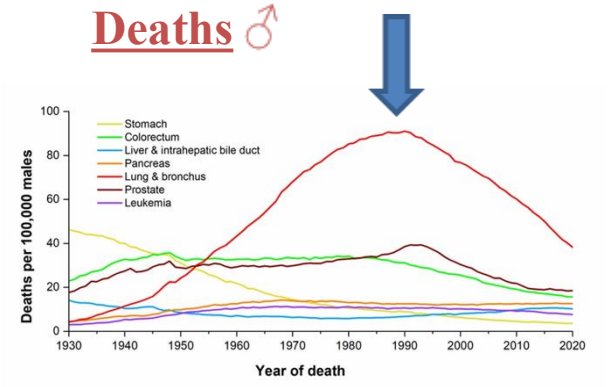
of deaths in 2022, both sexes, all ages

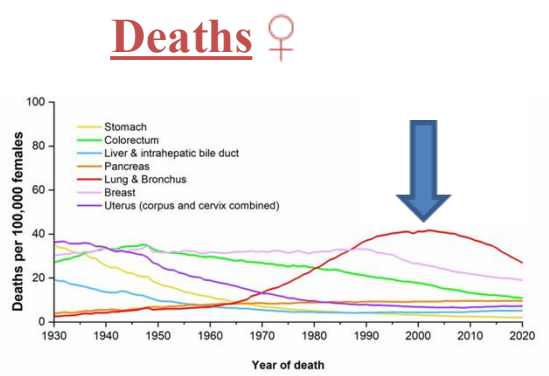


https://gco.iarc.fr/today/en

US Lung Cancer Statistics

- 234,580 estimated new cases (lung and bronchus)
- 125,070 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
- 20-21% of all male and female cancer deaths, respectively

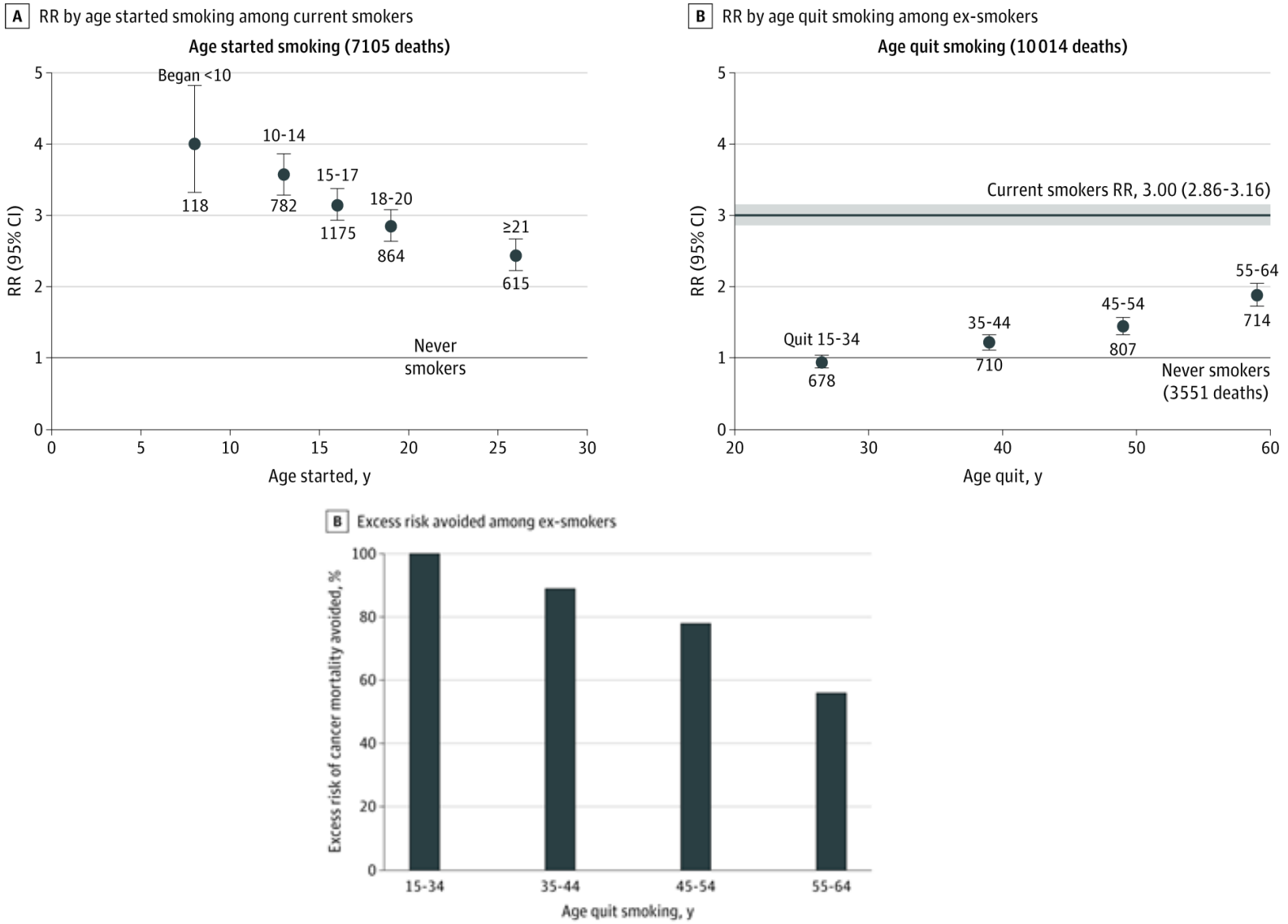


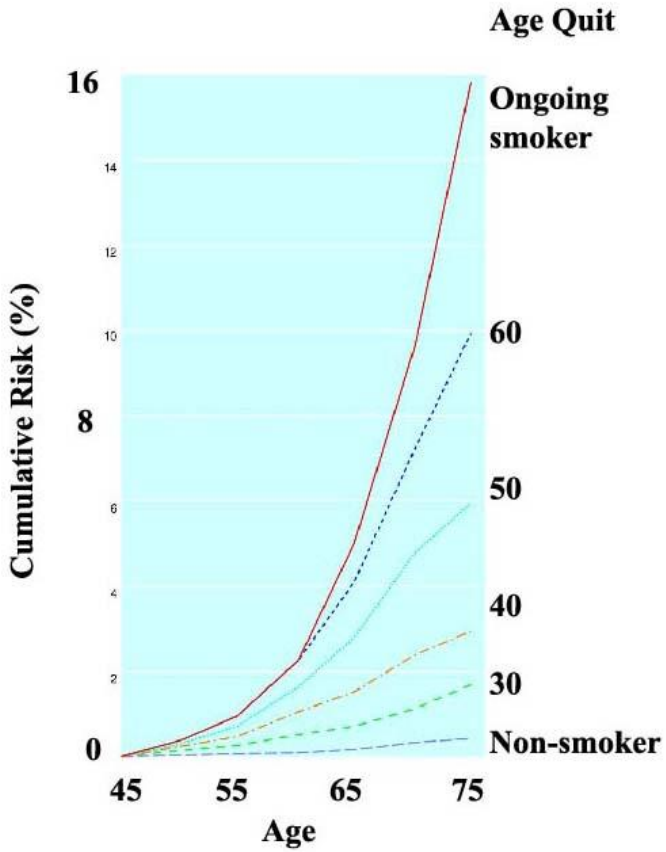


Risk Factors

- **Tobacco, tobacco, tobacco (85% lung ca.)**
  - Including secondhand smoke exposure
  - Prior aerodigestive malignancy
  - COPD
- **Other exposures**
  - Radon (2nd leading cause)
  - Asbestos, polycyclic aromatic hydrocarbons, chromium, cadmium, nickel, inorganic arsenic, radiation, air pollution – mining, ship building, oil refining, rubber manufacturing, etc.
- **Genetic predisposition**
  - Familial lung cancer – Germline mutations - EGFR T790M
    - *Bell et al., Nat Gen 2005;37:1315*

Association Between Tobacco and All Cancer Death

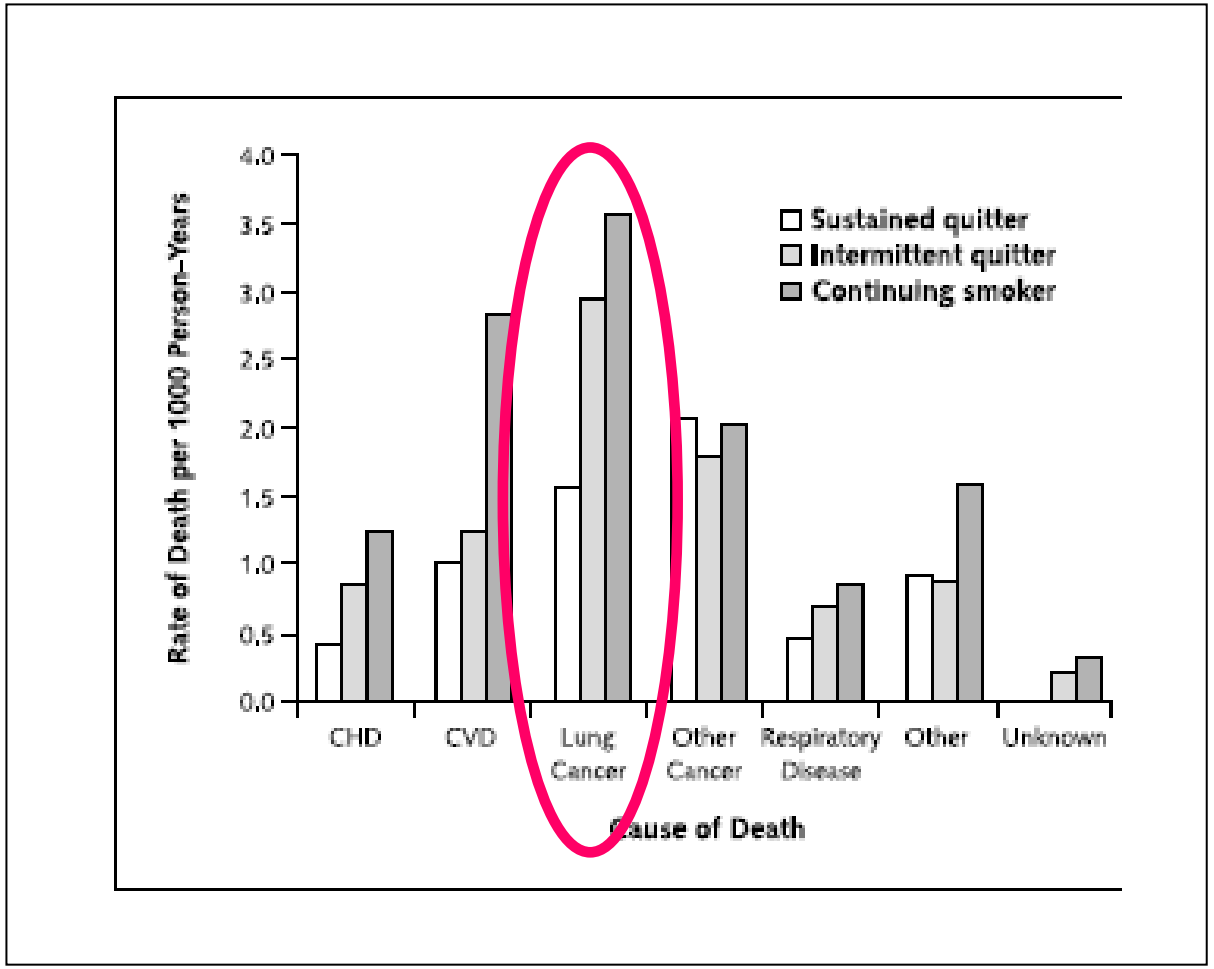




Thompson B et al., JAMA Oncol. Published online October 21, 2021. doi:10.1001/jamaoncol.2021.494

Peto et al., BMJ 321:323, 2000

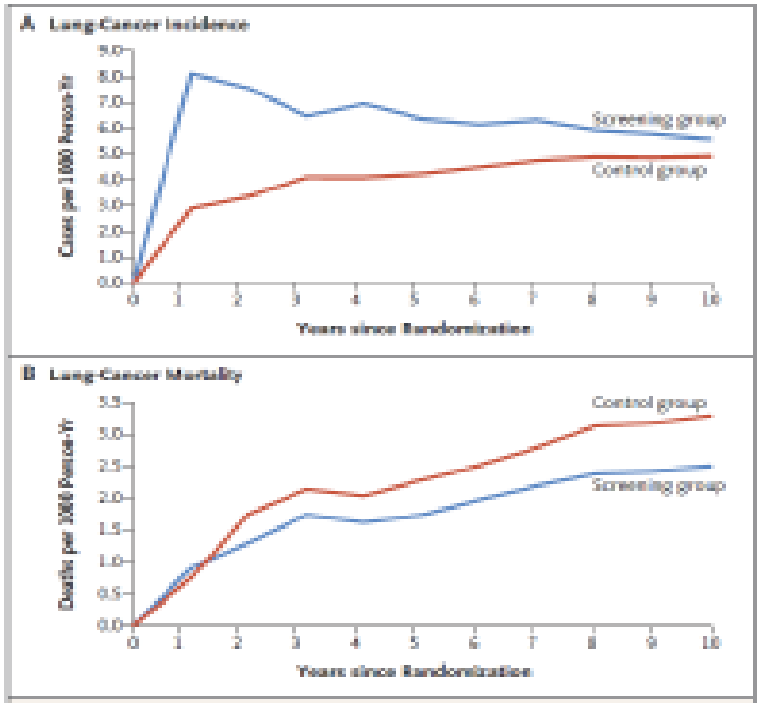
Effect of Smoking Cessation on Lung Cancer Deaths
Lung Health Study, 14.5 yr F/U



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

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

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**

Cancer Prevention

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

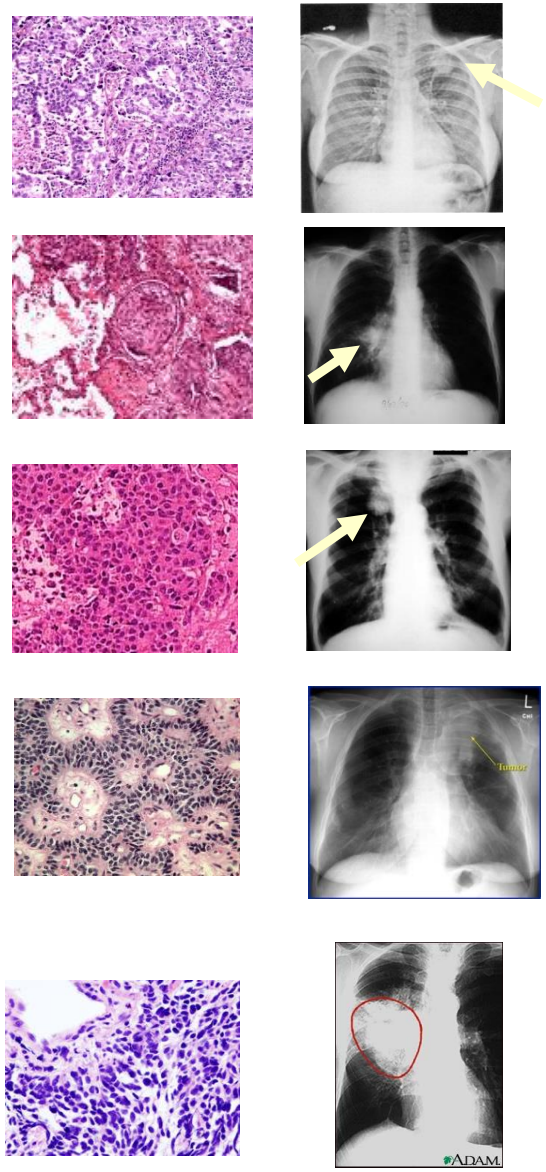
- **Regress existing neoplastic lesions (treat intraepithelial neoplasia)**
- **Prevent development of new neoplastic lesions (preneoplastic and cancer)**
- **Suppress recurrence of neoplastic lesions**

Classically applied to agents (chemoprevention), but also anti-obesity agents such as Ozempic, Wegovy or Zepbound.

Lung Cancer Pathology

Non-small Cell Lung Cancer

- Adenocarcinoma, bronchoalveolar
  – 40%
- Squamous cell carcinoma
  – 20%
- Large cell carcinoma
  – 15%
- Others (carcinoid, mesothelioma)



Small cell lung cancer - 20%

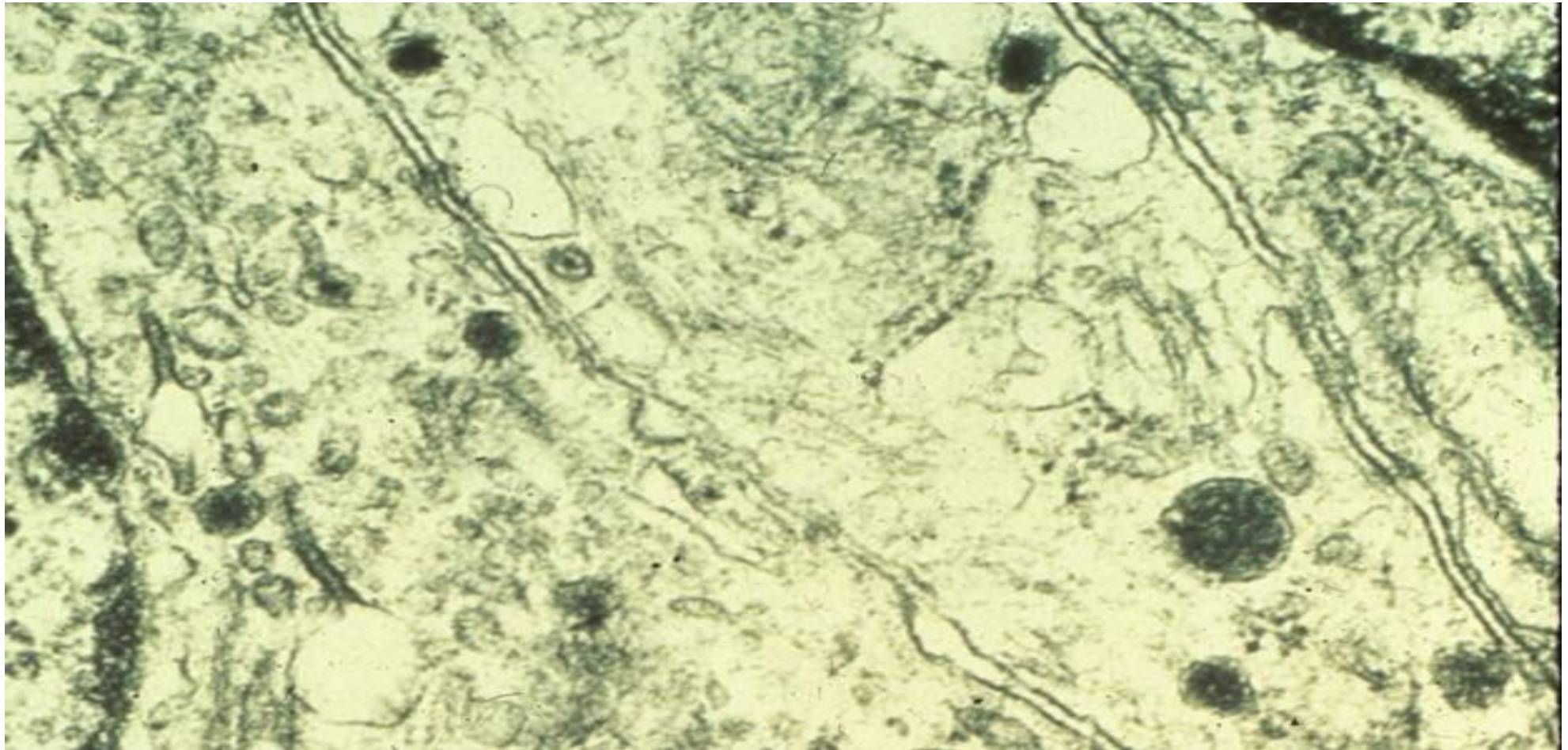
SCLC treatment

- **Small cell lung cancer (SCLC)**
  - **accounts for 20% lung cancer cases.**
  - **limited disease is treated with surgical resection**
  - **Patients with extensive disease are treated with chemo/radiation therapy and immunotherapy.**

SCLC Cancer

- ● The 3 year survival for SCLC patients with limited disease is 56%.
  ● The 3 year survival of patients with extensive disease (stage IV) is 18%
  ● SCLC initially responds to treatment, but relapse occurs
  ● SCLC undergoes metastasis to the brain, bone, liver, lymph nodes and pancreas

SCLC is a neuroendocrine tumor



SCLC has high levels of neuroendocrine peptides such as bombesin (BB)

Cell line	Density (pmol/mg protein
NCI-H209	17.4
NCI-H345	7.8
NCI-H510	5.4
NCI-N417	0.9

- Immunoreactive BB was detected using mAb2A11.

Phase II trial

- **mAb2A11 was tested as a therapeutic agent for SCLC**
  - **2A11 recognized the C-terminal octapeptide of BB or GRP and inhibited the growth of SCLC cell lines**
  - **mAb 2A11 inhibited the growth of SCLC xenografts in nude mice**
  - **mAb 2A11 inhibited tumor growth in 1/13 SCLC patients**
  - ***(Kelly et al., Chest 1997; 112:256)***

Phase II trial

- mAb2A11 inhibited the growth of human
- SCLC cells
- mAb2A11 inhibited the growth of SCLC tumors in nude mice
- mAb 2A11 inhibited the growth of SCLC tumors in 1/13 patients.

p53

- mediates the G1 to S-phase checkpoint of the cell cycle,
- drives programmed cell death or apoptosis after DNA damage,
- is increased along with p21 (cell cycle checkpoint) after DNA damage.
- Phosphorylated p53 induces expression of BAX (apoptosis), GADD45 (DNA repair) and thrombospondin (angiogenesis)

Air pollution

- **Exposure to Los Angeles air pollution increases the risk of p53 mutations.**
  Erhunmwunsee et al. Cancer Epidemiology Biomarkers Prevention, 2021; 30: 1498.

Retinoblastoma (Rb)

- ● Rb-1 is a tumor suppressor gene which is inactivated in SCLC.
  ● RB-1 controls cell cycle growth by regulating cyclin dependent kinase inhibitors (p16).
  ● Normal Rb genes were present in 6% of the SCLC patients analyzed whereas 94% were Rb deficient.
  ● The Rb deficiencies result from genetic truncation (48%), genetic splice variants (28%), and deletions (15%).

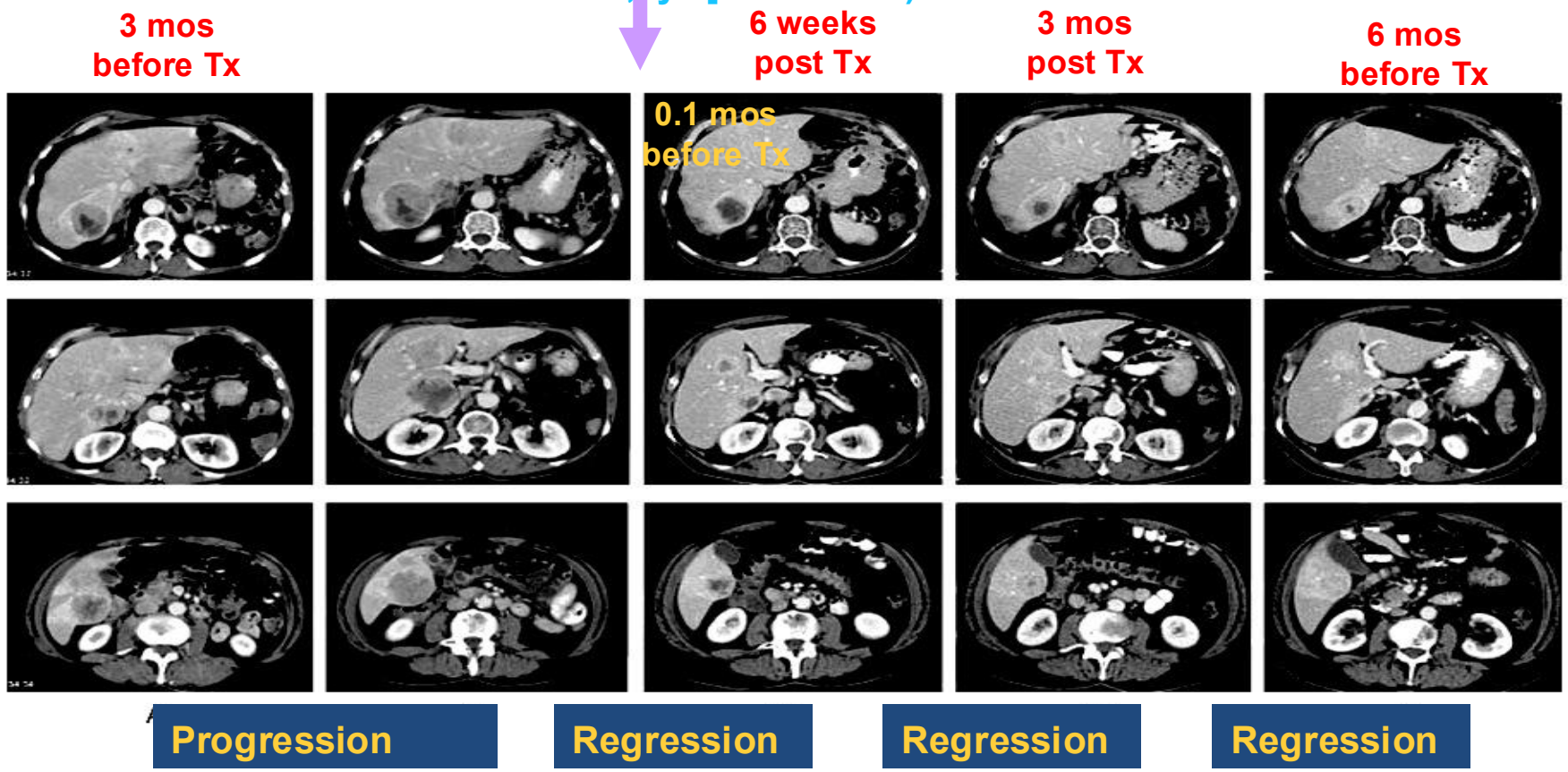
SCLC can be treated with chemotherapy, radiation or immunotherapy

- ● Chemotherapy drugs include cisplatin and/ or etoposide
  ● Radiation can be used for patients with limited – stage SCLC (stage I, II, III)
  ● Immunotherapy can be used for patients with stage IV disease if the tumors are enriched in PDL1.

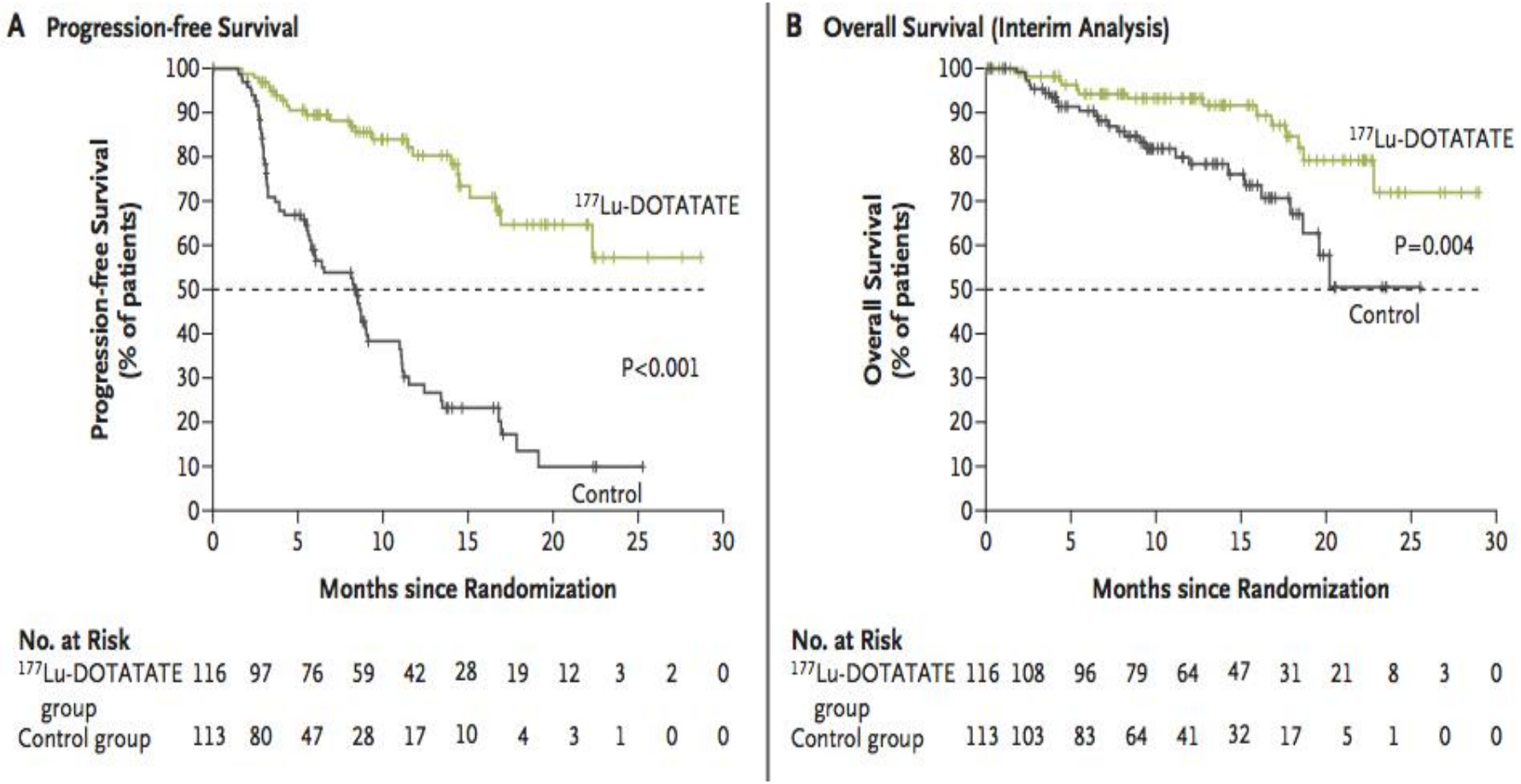
Theranosti,mmm,mcs

Peptide radioreceptor therapy (PRRT) of GI-NETs: An example

(Pt with a metastatic pancreatic neuroendocrine tumor treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate)



177LuDoTATATE increases survival of patients with neuroendocrine tumors (NETs)



SCLC summary

- SCLC is traditionally treated with chemotherapy and radiation therapy, but relapse occurs.
- SCLC undergoes metastasis to the liver, lymph nodes, bone, pancreas and brain
- It remains to be determined if theranostics will be useful to treat patients with SCLC.

Mesothelioma

- Primarily occurs in people exposed to asbestos
- Fibers accumulate on the outside of the lung causing inflammation
- causes 1% of the lung cancer deaths annually
- Mesothelioma can occur on the outside of the lungs, intraperitoneal cavity or heart

Mesothelioma has alterations of the BAP1 tumor suppressor gene

- The BAP1 gene is related to BRCA1
- Loss or mutation of the BAP1 gene increases the risk of mesothelioma
- The C-terminal of BAP1 is a deubiquitinase which prevents degradation of proteins associated metastasis.
- The BAP1 gene is associated with DNA repair
- The BAP1 gene increases immune response

Mesothelioma patients respond to immunotherapy

- is treated with cisplatin chemotherapy responds to immune checkpoint inhibitors such as nivolumab (blocks PD1 on immune cells), pembrolizumab (blocks PD-L1 on cancer cells) and/or ipilmumab (blocks CTLA-4 on T cells).

NSCLC is composed of large cell cancer, squamous cell carcinoma and adenocarcinoma

Symptoms

- Stubborn cough with blood
- Shortness of breath
- Chest pain
- Wheezing
- Recurring bouts of pneumonia or bronchitis

Large cell lung cancer

- accounts for 15% of the lung cancer deaths
- is undifferentiated
- starts in the epithelial cell borders.

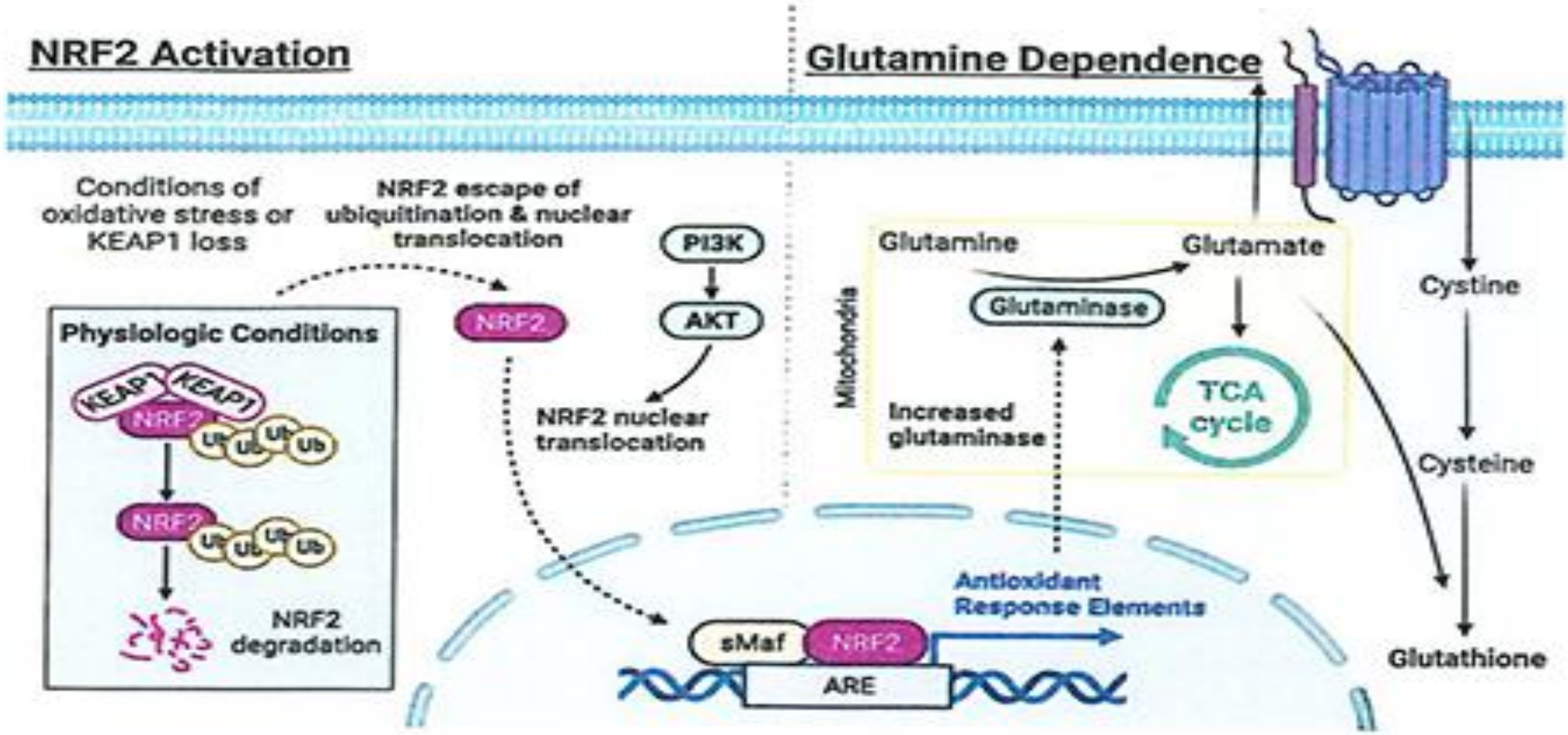
Large Cell Lung Cancer

- is SCLC-like with RB1 and/or TP53 mutations
- is NSCLC-like with KRAS, STK11 and KEAP1 mutations
- Both types of large cell cancer patients are treated with chemotherapy using etoposide plus platinum

Important Large Cell Lung Cancer Proteins

- STK11 is a serine/threonine kinase which phosphorylates AMPK inhibiting growth
- KEAP1 is a ubiquitin ligase which inhibits Nrf2 proteolysis
- K-RAS mutations active the RAF, MEK and ERK pathway leading to increased proliferation

KEAP loss leads to oxidative stress



Large Cell Lung Cancer Patient treatment depends upon the cancer stage

- LC treatment for Stages I to III is surgery, radiation therapy and adjuvant chemotherapy
- LC treatment for Stage IV is chemotherapy and/or immunotherapy

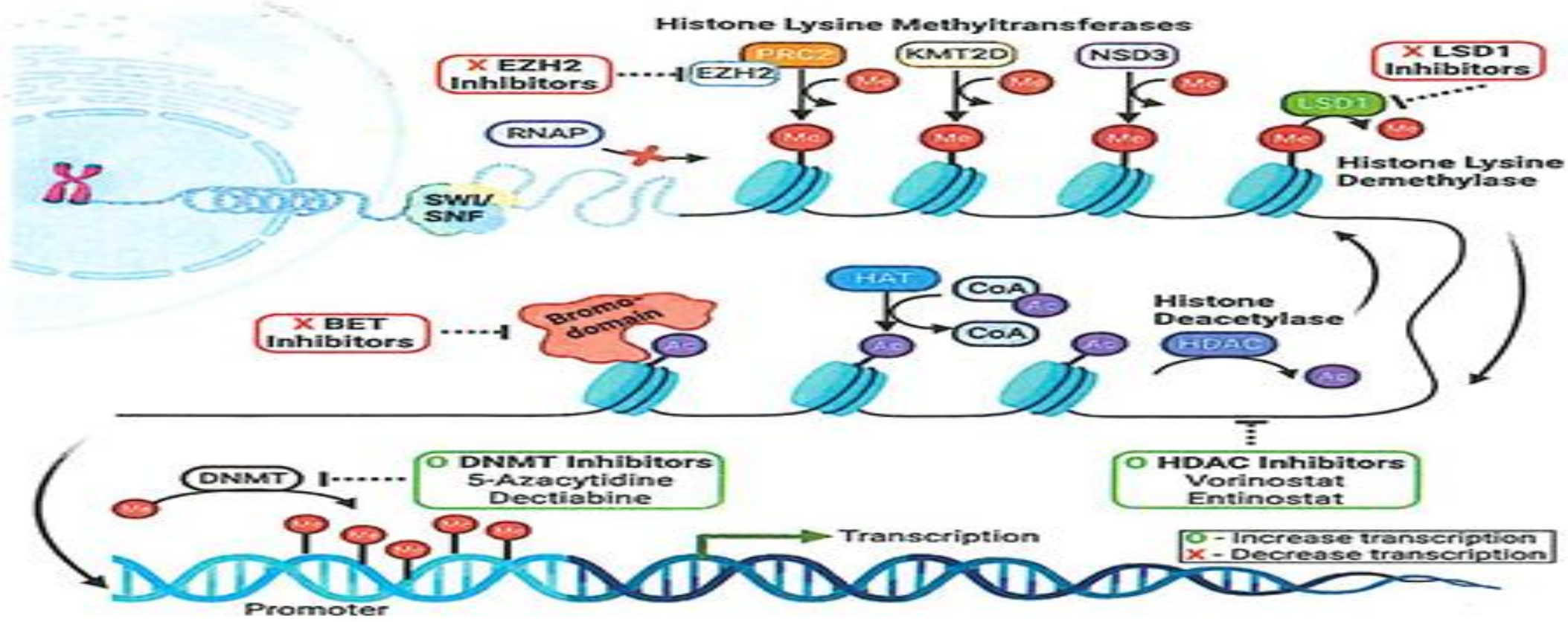
Lung Squamous cell Carcinoma

- Causes 20% of the lung cancer deaths
- Starts as flat, thin cells that line the central airways or bronchi of the lungs
- The primary risk factor is tobacco and cigarette smoking

Squamous cell Lung Cancer

- EGFR is amplified but not mutated
- When FGFR is amplified, nintedinib blocks
- Discoidin domain receptors (DD2Rs) are mutated
- Epigenetic treatment can be used for SOX2 amplification which increases LSD1 which activates Histone Lysine Demethylase
- EZH2 is overexpressed altering expression of tumor suppressor genes

Epigenetics may play an important role



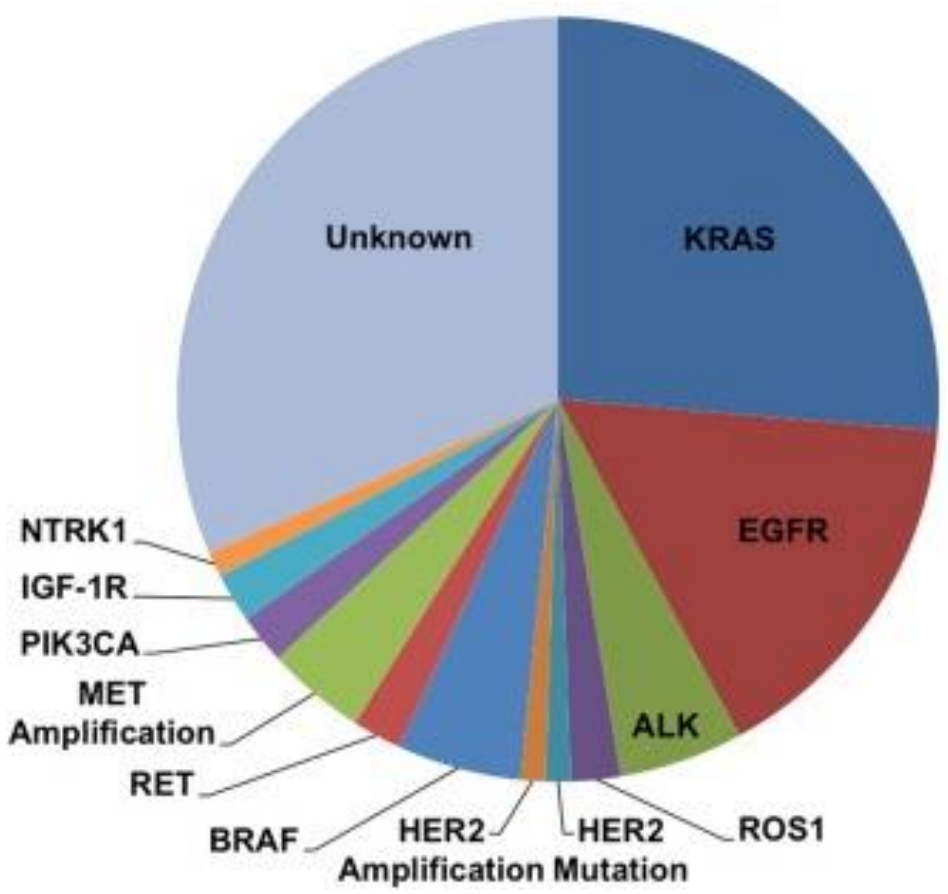
- *Sally et al., Cancer Cell 2022; 40: 1279*

Squamous Cell Lung Cancer Patient treatment depends upon the cancer stage

- Treatment for Stages I to II is surgery and radiation therapy
  Treatment for Stage III is chemotherapy and radiation therapy
- Treatment for Stage IV is chemotherapy and immunotherapy

- accounts for 40% lung cancer cases
- Starts in mucus-secreting glandular cells often within the alveoli.
- Leading type of lung cancer found in non-smokers, women, and adults under the age of 45
- Early stage symptoms include
long lasting cough, bloody mucous and
pain in chest or back

Genetic Abnormalities in Lung Adenocarcinoma



Targetable mutations/gene fusions

- EGFR
  - multiple drugs
- ALK
  - multiple drugs
- ROS1
  - Crizotinib, entrectinib
- BRAF-V600E only
  - dabrafenib/trametinib
- RET
  - Selpercatinib, pralsetinib
- NTRK
  - Larotrectinib, entrectinib
- MET ex 14 skipping
  - Tepotinib, capmatinib
- HER2/Neu – exon 20 mutations
  - HER2 antibodies + chemo
- KRAS G12C
  - Sotorasib, adagrasib (2nd line Tx)

Response rates up to 50-80%

Berge and Doebele Sem Oncol 2014; Hunter et al. Nature 2004; Heinmoller P et al. Clin Cancer Res 2003; Drilon A et al. JCO 2016 suppl; Drilon A NEJM 2018

Alk rearragements

- **ALK rearrangements occur in 5% of the NSCLC patients**
  - **ALK is microtubule associated activated after fusion with the echinoderm protein like 4 (EML4).**
  - **ALK is inhibited by the TKIs crizotinib or brigatinib**

ROS oncogene

The c-ROS oncogene (ROS1) is a RTK driver in 1-2% of the NSCLC patients

- **ROS1 is a protocogene that is activated by gene fusions**
- **Crizotinib and entrectinib are ROS1 inhibitors which are used in certain NSCLC patients.**
- **ROS1 is associated with increased PD-L1 expression.**

K-RAS

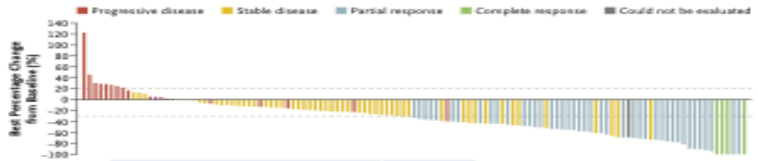
KRAS mutations

- occur in approximately 30% of lung adenocarcinoma patients
- KRAS G12C mutation is most common
- Sororasib is KRAS G12C inhibitor which has efficacy in lung adenocarcinoma patients

Sotorasib therapy is as effective as Docetaxelin lung cancer patients

Efficacy of KRAS G12C inhibitor in lung cancer

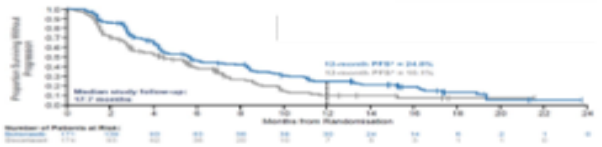
Phase 2 trial: Sotorasib single arm in advanced NSCLC with KRAS G12C mutation (CodeBreaK100)



Partial response	33.9%
Diease control	80.6%

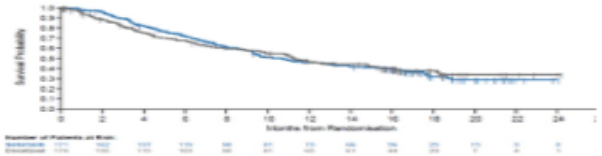
(Skoulidis et al NEJM 2021)

Phase 3 trial: Sotorasib vs. docetaxel in advanced NSCLC with KRAS G12C mutation (CodeBreaK200, cross-over allowed)



Median PFS (p = 0.002)

Sotorasib	5.6 mo
Docetaxel	4.5 mo



Median OS (p = n.s.)

Sotorasib	10.6 mo
Docetaxel	11.3 mo

- **Single agent KRASi has limited efficacy in late stage patients**
  - Move KRASi to a first-line setting
  - Drug combinations with more durable response

References
Skoulidis et al. NEJM 2021
De Langen et al. Lancet 2023

MET

- MET is a receptor tyrosine kinase which binds hepatocyte growth factor and can be amplified in NSCLC
- MET activation increases proliferation thru the ERK pathway and survival through the PI3K pathway
- Capmatinib and repotinib are MET RTK inhibitors
- Splice variants occur in exon 14 of MET leading to resistance in chemotherapy.

Micro RNAs

Micro RNAs are small noncoding RNA moleculaes of 18-25 nucleotides

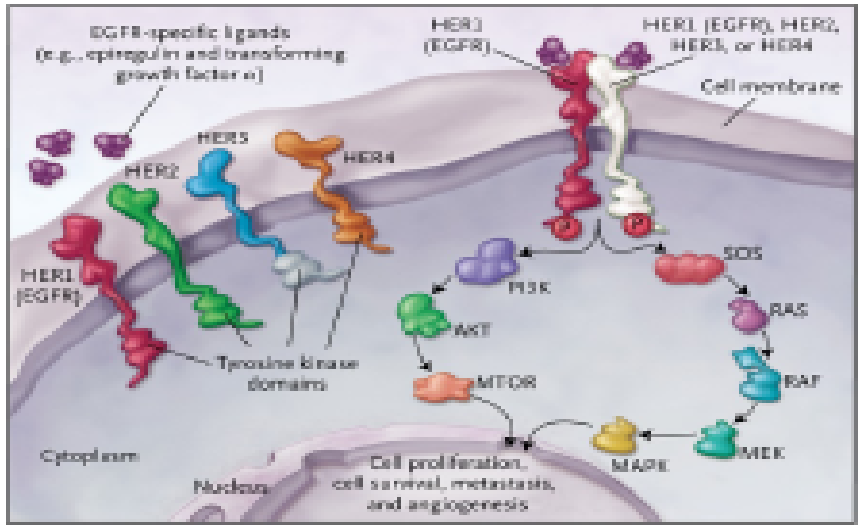
- Micro mRNAs can function as oncogenes or tumor suppressor genes
- In lung adenocarcinoma oncogenic mRNAs include miR-155, miR16, miR19a, miR-20a, miR-26a, miR31, miR93, miR-99a, miR-100, miR-106b, miR135b, miR-200b and miR-200c. Tumor suppressor miRs include miR374a and miR33a.

MIR-21

- ● MIR-21 is often expressed in never smoker lung cancer patients.
‘

EGFR and NSCLC

EGFR as a Target for NSCLC

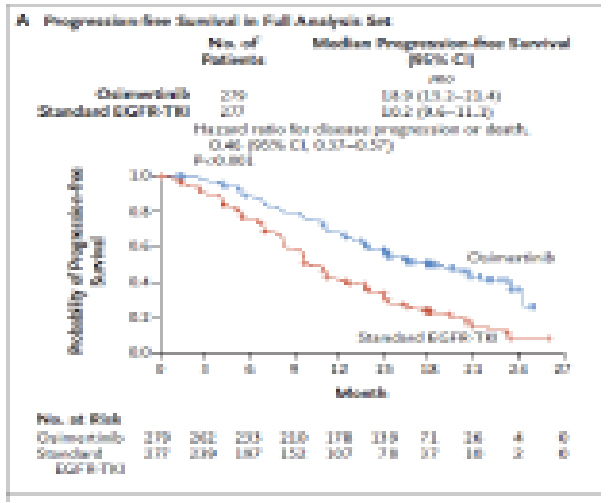


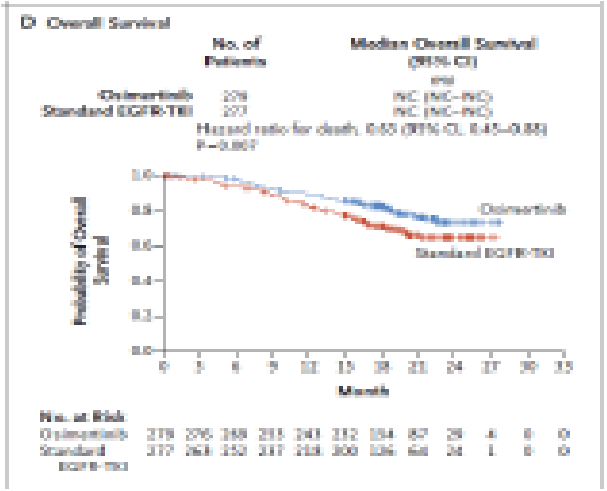
- Epidermal growth factor receptor (EGFR) mutated in ~15% NSCLC
- Oncogenic driver; primarily in non-smokers
- Targeted therapies tyrosine kinase inhibitors (TKIs) highly active
  - 60-80% response rates EGFR-MT disease
  - Progression-free survival 10-14 months (c/w chemo 4-6 months)
  - Median survival 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

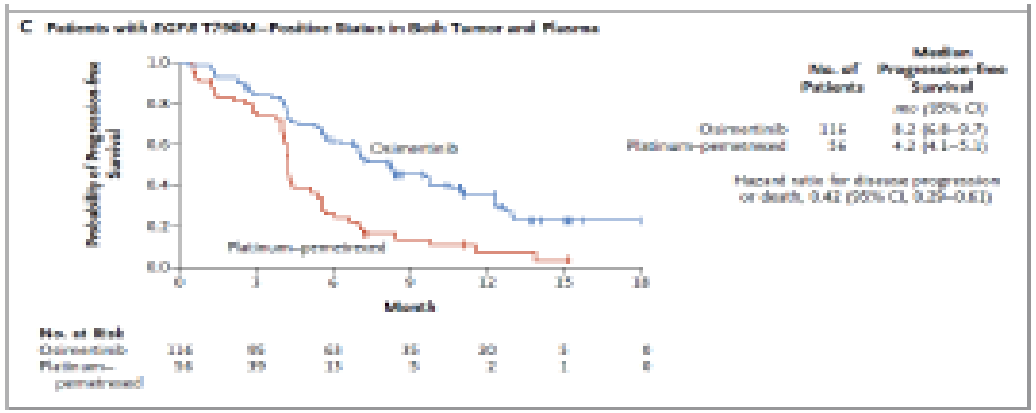
Osimertinib in Chemotherapy-naïve Patients

No prior Rx





Prior frontline TKI but no prior chemo

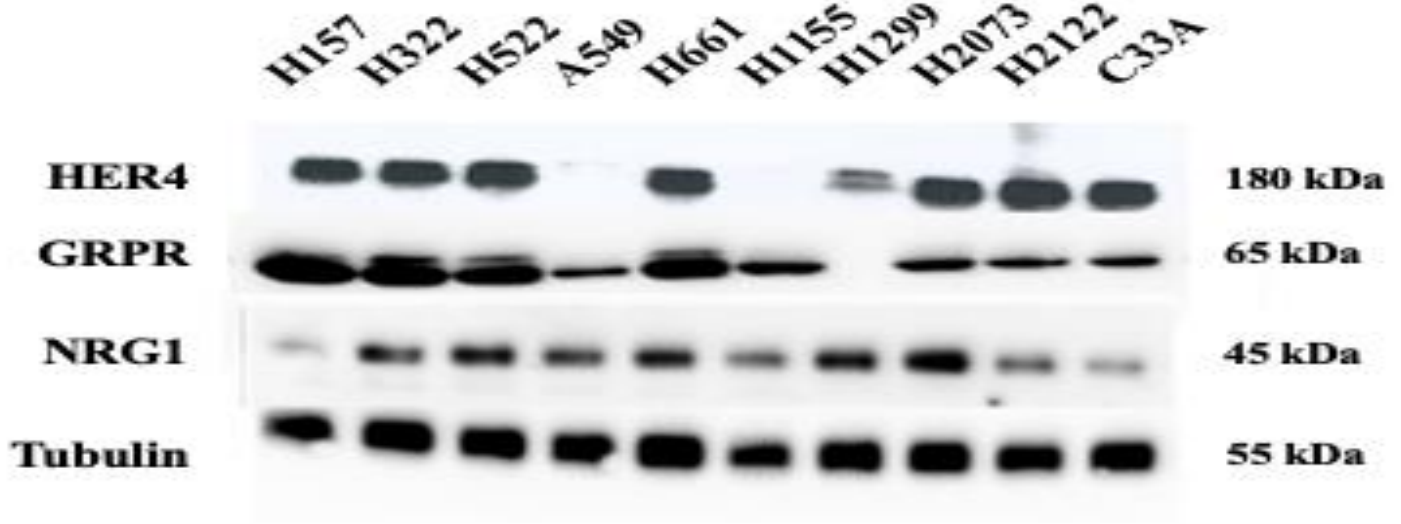


Mok TS et al. NEJM 2016
Soria J-C et al. NEJM 2017

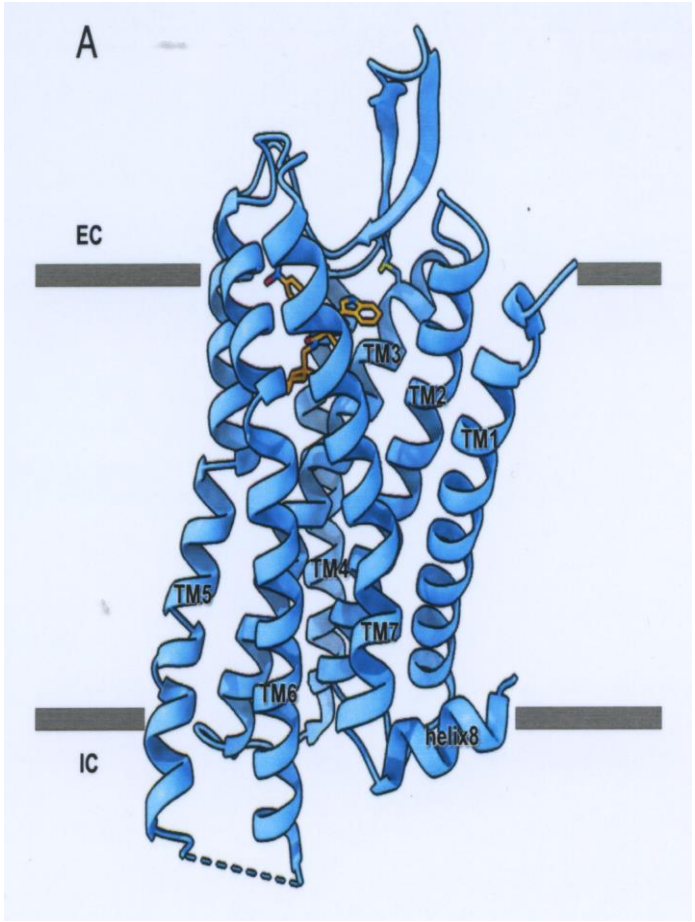
BBRs are present in NSCLC cells

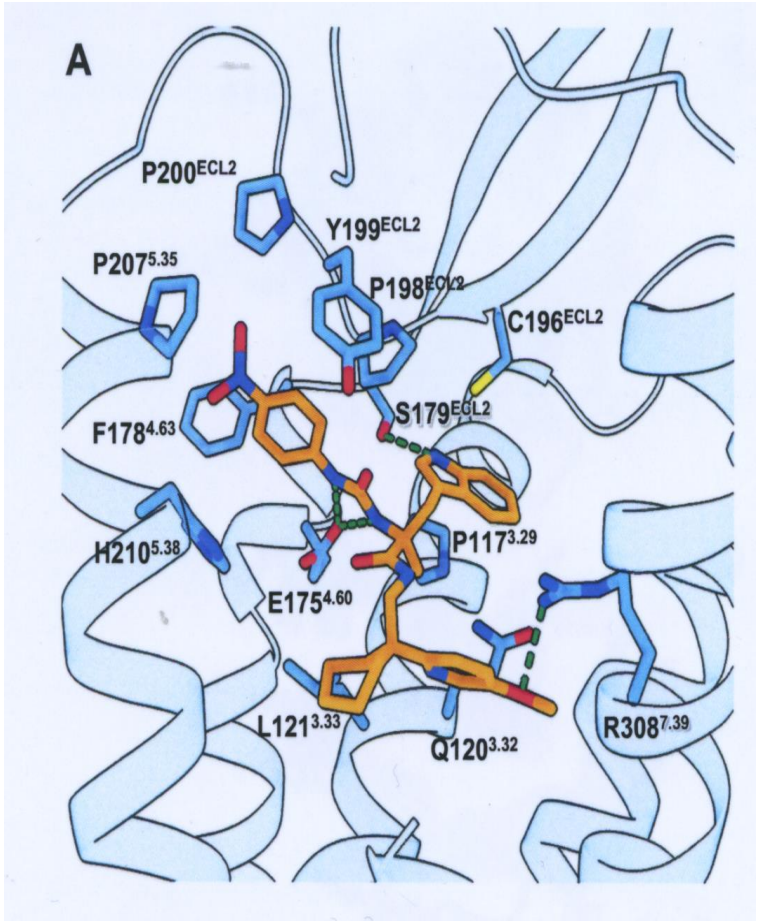
Fig. 2

A

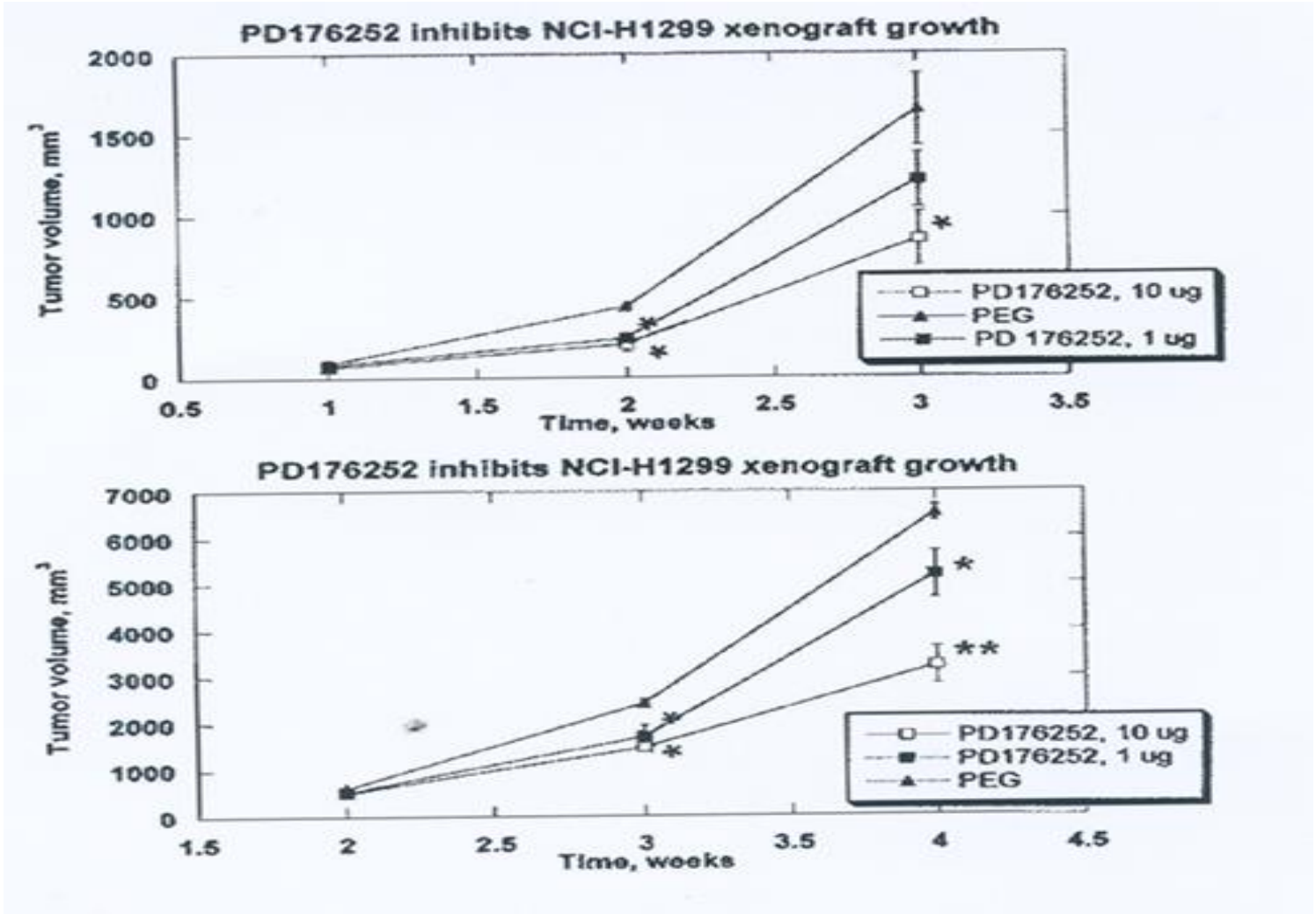


The BBR is a type 1 GPCR *(Peng et al., PNAS, 2023)*

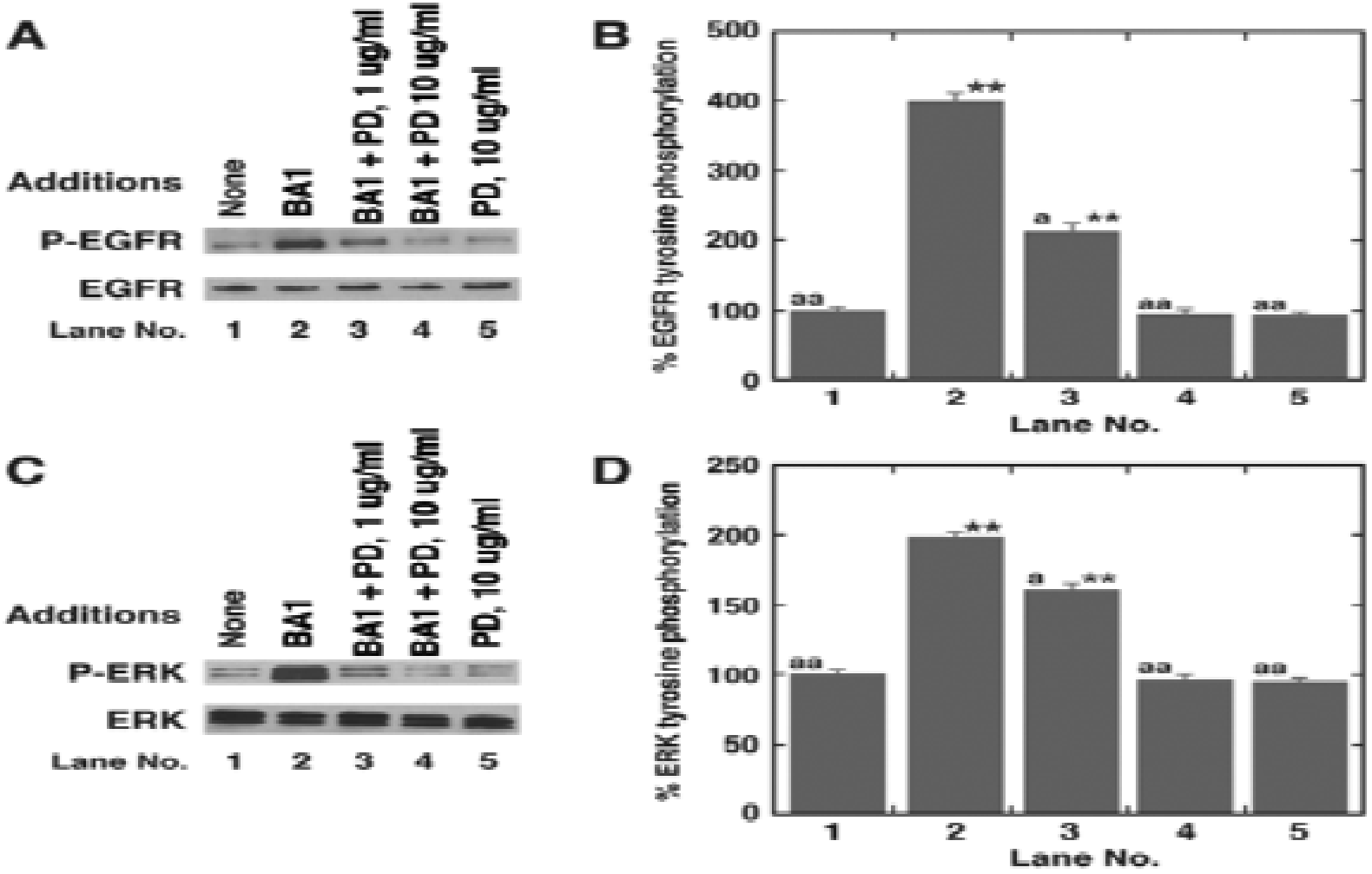




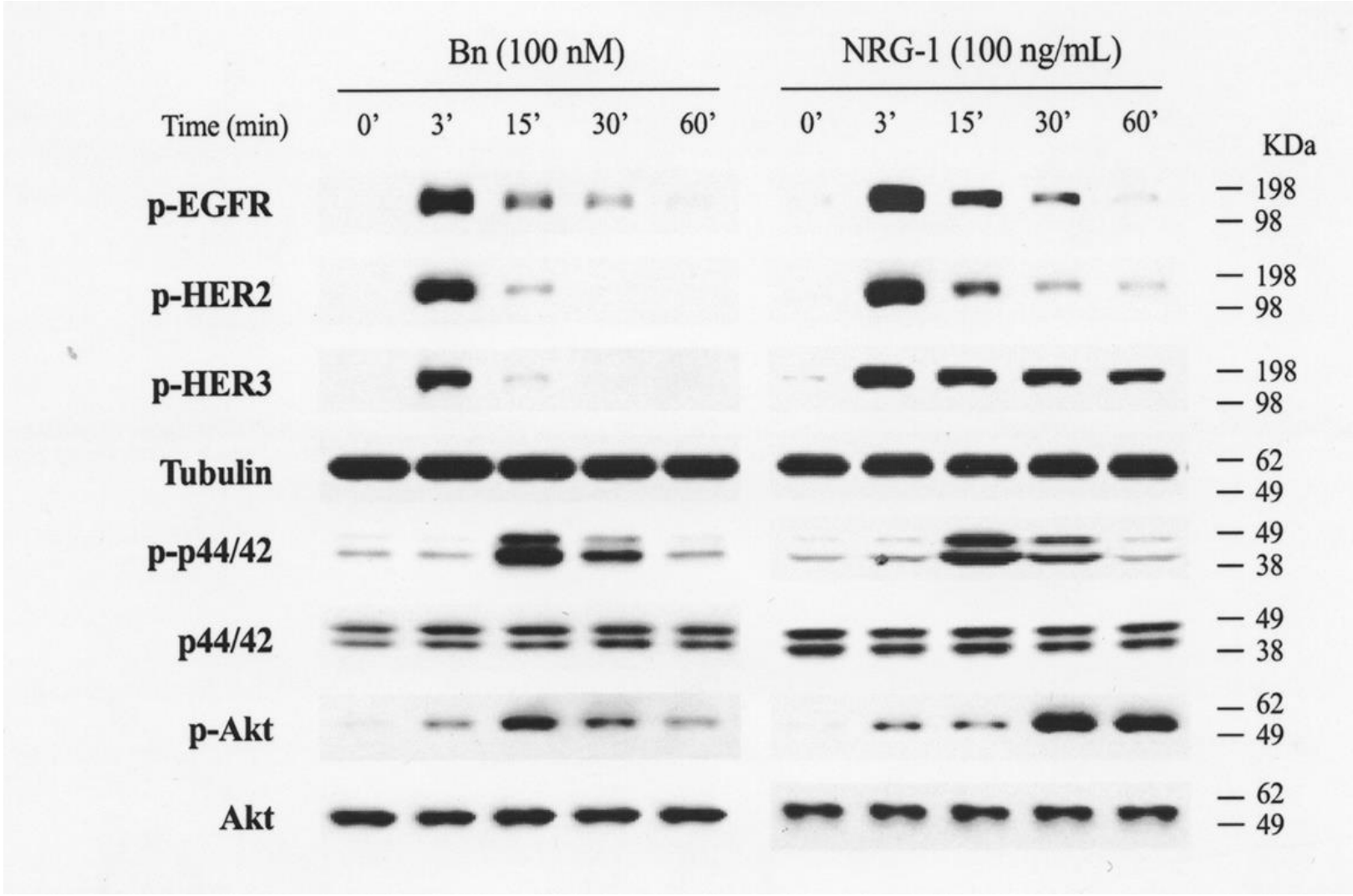
PD176252 inhibits NSCLC growth in vivo



PD176272 impairs the ability of BA1 to cause phosphorylation of the EGFR and ERK

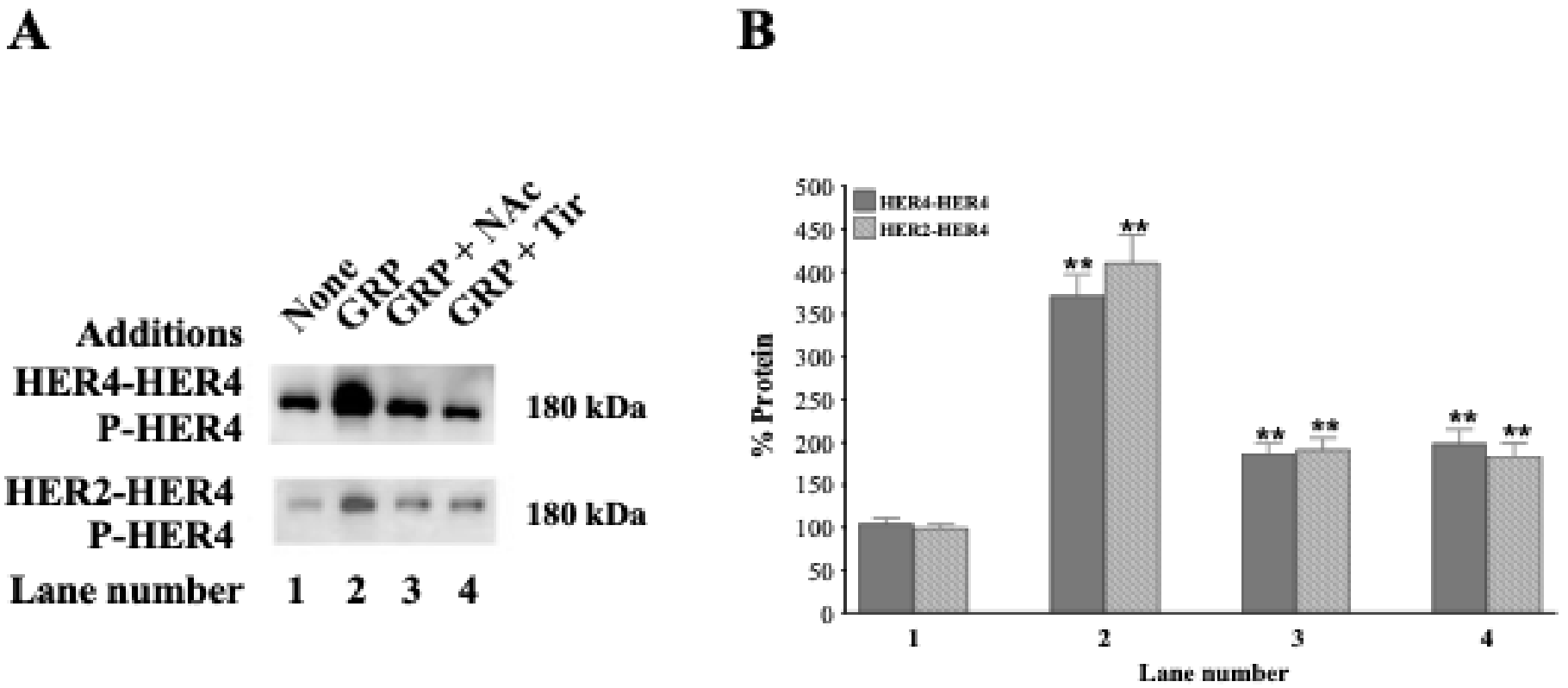


BB or NRG-1 increase P-EGFR, P-HER2, P-HER3, P-ERK and P-AKT. *(Lee et al., BBAMCR, 2020)*

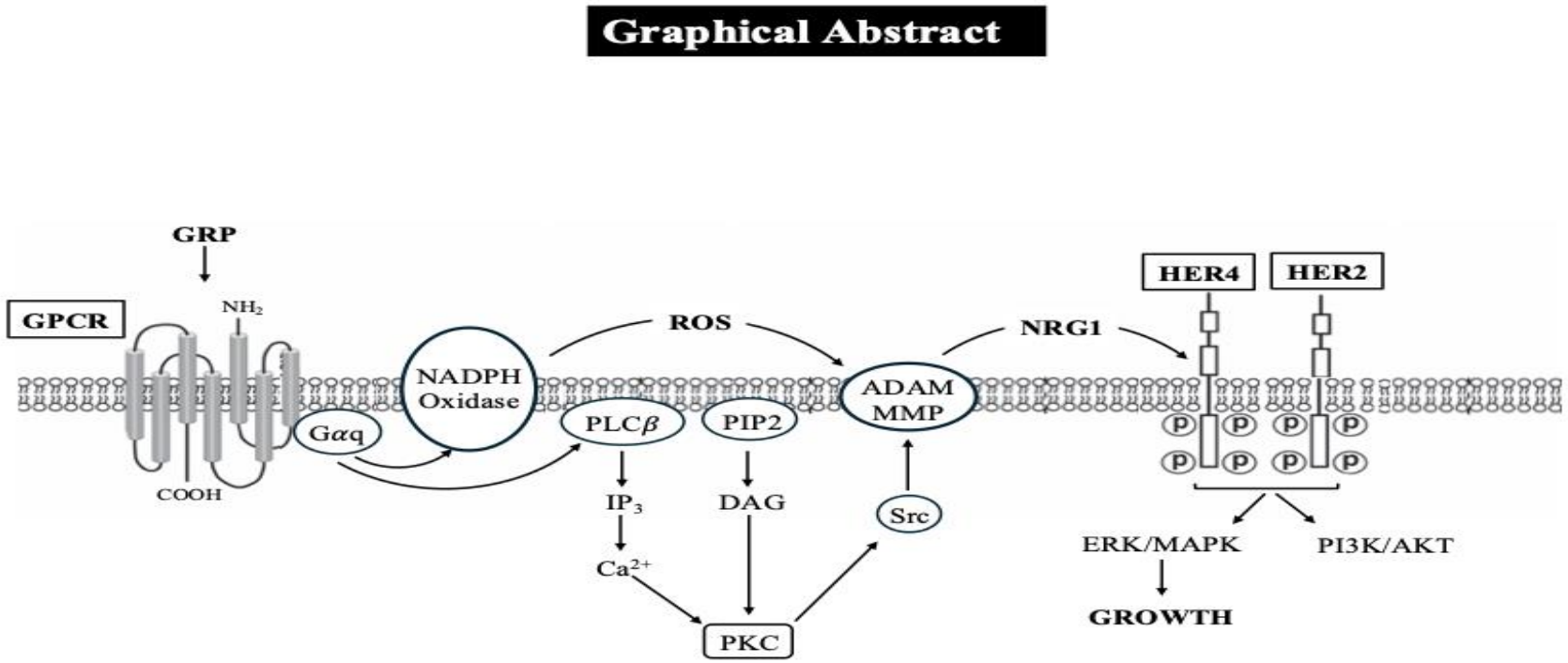


The GRPR regulates RTK phosphorylaion

Fig. 6



Transactivation mechanism



Summary

- SCLC is a neuroendocrine tumor which can be treated with chemotherapy, radiation therapy or immune therapy.
- Mesothelioma is associated with asbestos fibers and can be treated with immune therapy.
- NSCLC is an epithelial cancer which can be treated with chemotherapy and/or immune therapy.
- Progress is being made in lung cancer therapy in that the number of recent deaths in the USA has decreased in the past decade from 150,000 to 125,000 per year

Summary

- NSCLC is traditionally treated with chemotherapy, however the 5 year survival rate is less than 20%.
- For patients with PD1, they can be treated with immune checkpoint inhibitors.
- For patients with EGFR mutations they can be treated with tyrosine kinase inhibitors.
- For patients with K-RAS mutations they can be treated with sotorasib.
- GPCRs antagonists reduce RTK transactivation and can be combined with TKI to inhibit NSCLC growth.

References

- Kim, SY, Park, HS; Chiang, AC. Small cell lung cancer; A review. JAMA 2025; 333: 1906-1917.
- Meyer, ML, Fitzgerald BG, Paz-Ares, L. Cappuzzo, F., Janne PA, Peters S, Hirsch FR. New promises and challenges in the treatment of advanced non-small-cell lung cancer. Lancet 2024; 404: 803-822.