

Lung Cancer Year in Review

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Tobacco and Environment

Screening

Stereotactic Radiotherapy

Molecular Profiling

Targeted Therapy

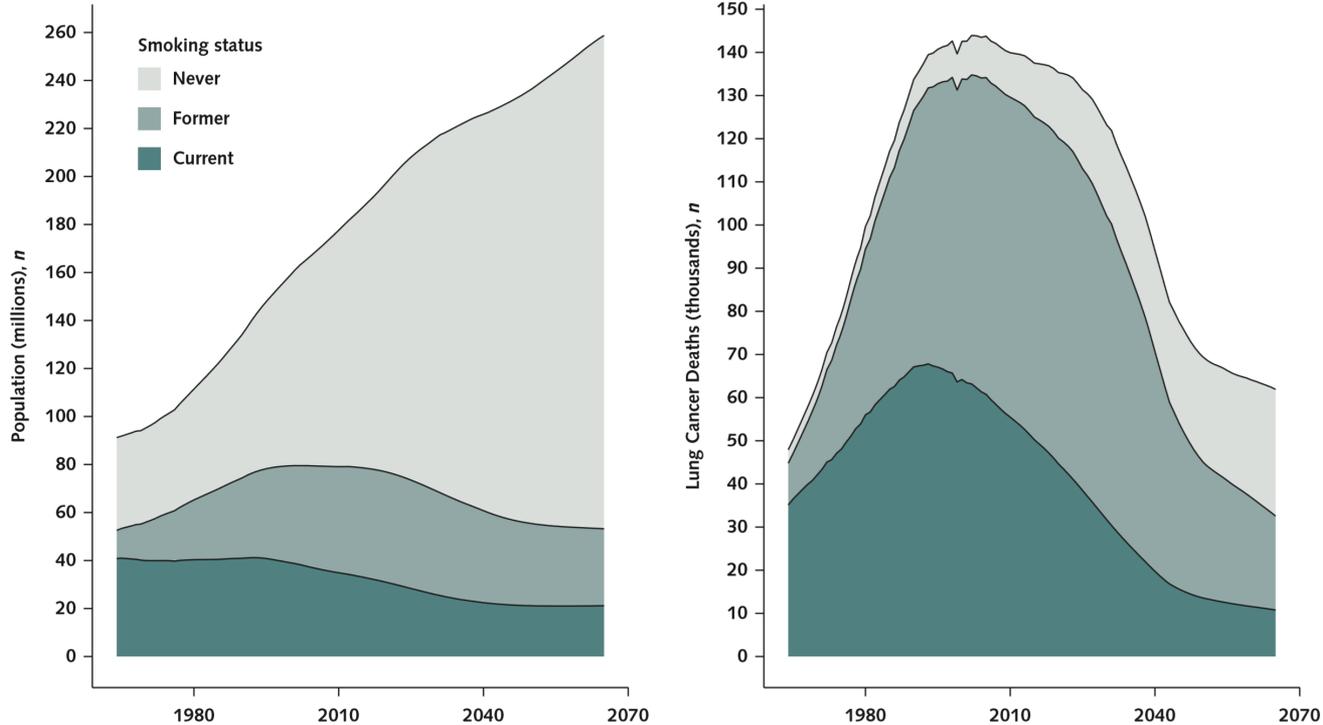
Immune Checkpoint Inhibitors

Tobacco and Environment

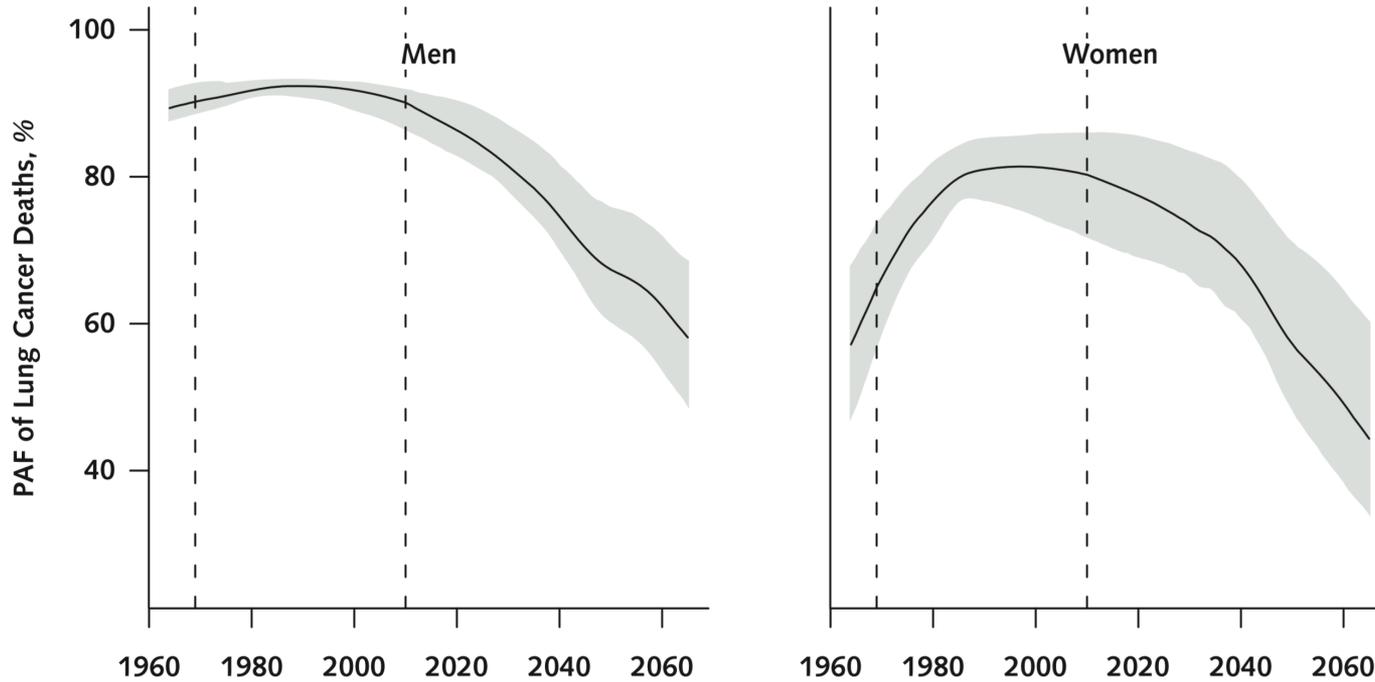
Lung Cancer Phenotype Changes

- **Background:** Tobacco control efforts implemented in the United States since the 1960s have led to considerable reductions in smoking.
- **Study Question:** Given projected reductions in tobacco use, what is the projected reduction in lung cancer mortality from 2015 to 2065.
- **Study Design:** Comparative modeling approach using 4 simulation models that relate temporal smoking patterns to lung cancer rates.

Lung Cancer Phenotype Changes



Lung Cancer Phenotype Changes



Lung Cancer Phenotype Changes

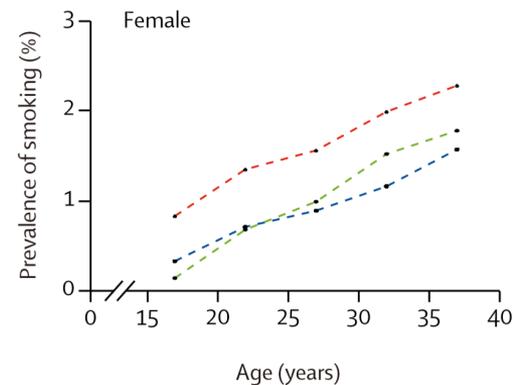
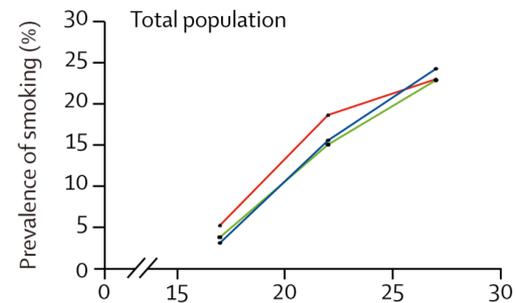
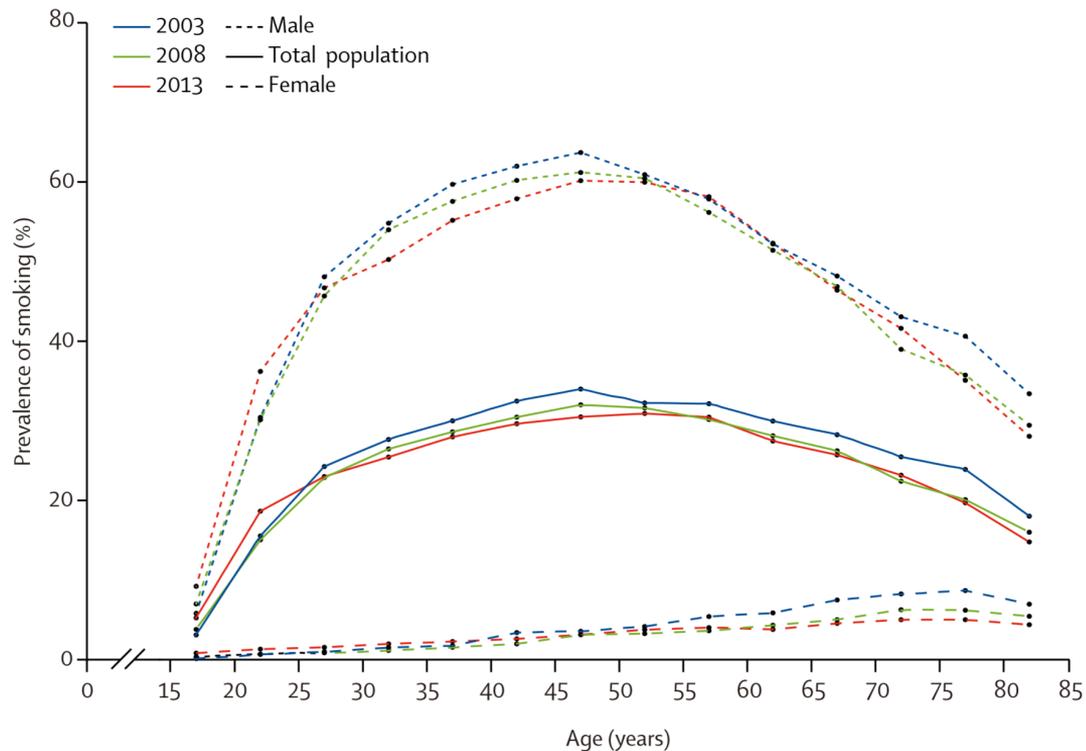
■ Interpretation:

- Tobacco control efforts implemented since the 1960s will continue to reduce lung cancer rates well into the next half-century.
- Additional prevention and cessation efforts will be required to sustain and expand these gains to further reduce the lung cancer burden in the United States.

Smoking Rates in China

- **Background:** China is the world's largest consumer of tobacco and has a large smoking-related chronic disease burden.
- **Study Question:** How has the smoking prevalence changed since the implementation of tobacco control policies in China in 2003?
- **Methods:** Collected data from serial cross-sectional National Health Service Surveys done in China in 2003, 2008, and 2013. Analyzed the variation in smoking prevalence from 2003 to 2013.

Smoking Rates in China



Wang, Lancet Respir Med 2019.

Smoking Rates in China

■ Interpretation:

- The implementation of tobacco control policies in China since the signing of the WHO Framework Convention on Tobacco Control in 2003 has not been effective in reducing smoking prevalence.
- Smoking prevalence among adolescents of both genders has increased substantially and there has been a steady increase among young women.
- Action is needed to prevent the large and growing smoking-related chronic disease burden further increasing as China's population ages.

E-Cigarettes vs. Nicotine Replacement Therapy

- **Background:** E-cigarettes are commonly used in attempts to stop smoking, but evidence is limited regarding their effectiveness as compared with that of approved nicotine products.
- **Study Question:** In adults attending the U.K. National Health Service stop-smoking services is e-cigarette use more effective than nicotine-replacement products in producing smoking abstinence?
- **METHODS:** Subjects were randomized to nicotine-replacement products or an e-cigarette starter pack, with a recommendation to purchase further e-liquids of the flavor and strength of their choice. The primary outcome was sustained abstinence for 1 year.

E-Cigarettes vs. Nicotine Replacement Therapy

Abstinence	E-Cigarettes	Nicotine Replacement	Adjusted RR
At 52 weeks	18.0	9.9	1.75
At 4 weeks	43.8	30.0	1.43
At 26 weeks	35.4	25.1	1.36
26-52 weeks	21.2	11.9	1.82

E-Cigarettes vs. Nicotine Replacement Therapy

At 52 weeks	E-Cigarettes	Nicotine Replacement
Use of Product (%)	39.5	4.3
Use of Product (quit) (%)	79.7	9.1
Cough (%)	30.8	39.8
Phlegm (%)	25.1	36.9

E-Cigarettes vs. Nicotine Replacement Therapy

- **Interpretation:**

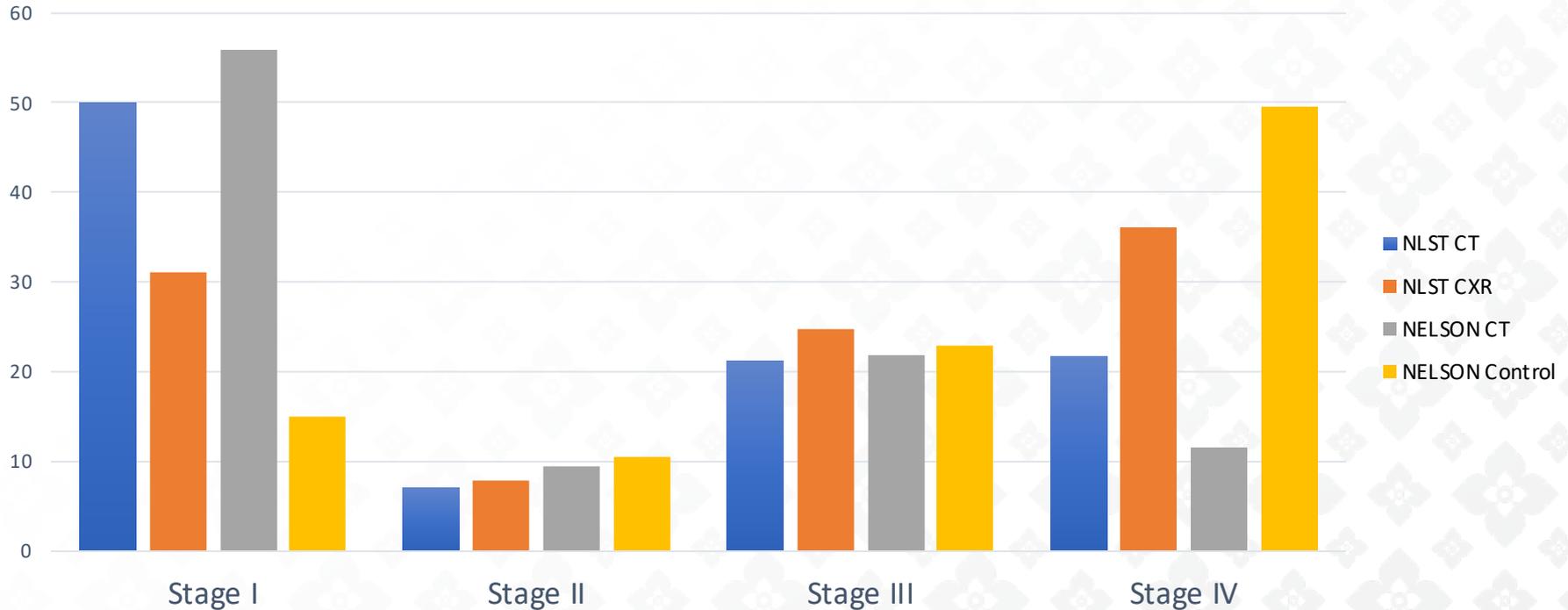
- E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support.

Summary

- Smoking cessation is difficult to achieve.
- Substantial benefits to the reduction of chronic diseases and lung cancer can be seen with successful smoking cessation efforts.
- Disparities exist in the rates of smoking cessation that should be considered in future smoking cessation efforts.
- Evidence of improvement in smoking cessation rates with e-cigarette use is being shown before enough time has passed to understand their harms.

Screening

NELSON and NLST Stage Shift



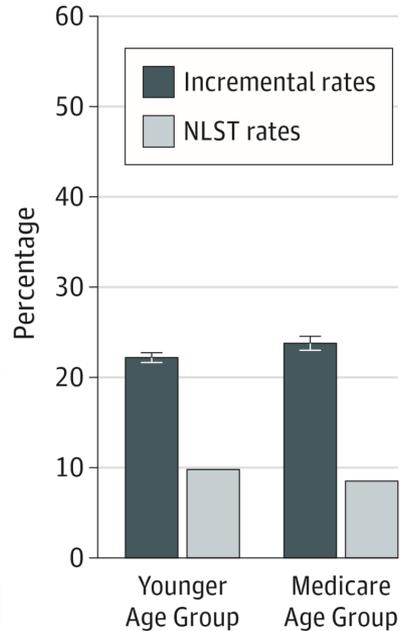
NLST team, NEJM 11. NELSON WCLC 18.

Procedure Complication Rates

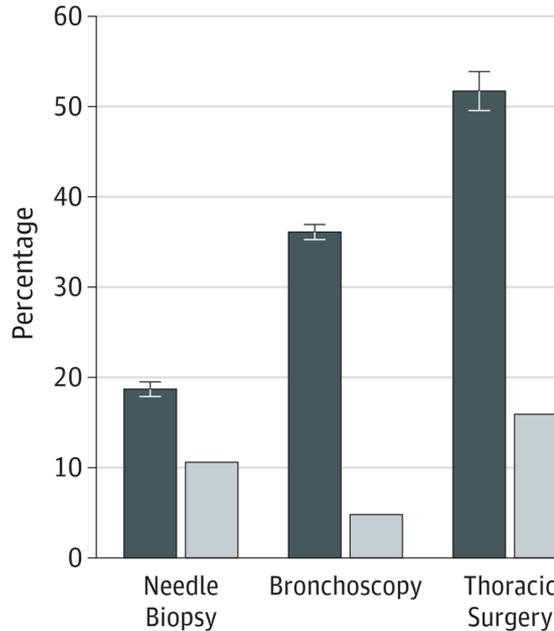
- **Background:** Abnormal findings from thoracic imaging often trigger subsequent invasive diagnostic procedures.
- **Study Question:** What are the complication rates and downstream medical costs associated with invasive diagnostic procedures performed in the community setting.
- **Methods:** A retrospective cohort study of non-protocol-driven community practices was conducted. A nationally representative sample of 344510 patients aged 55 to 77 years who underwent invasive diagnostic procedures between 2008 and 2013 was included.

Procedure Complication Rates

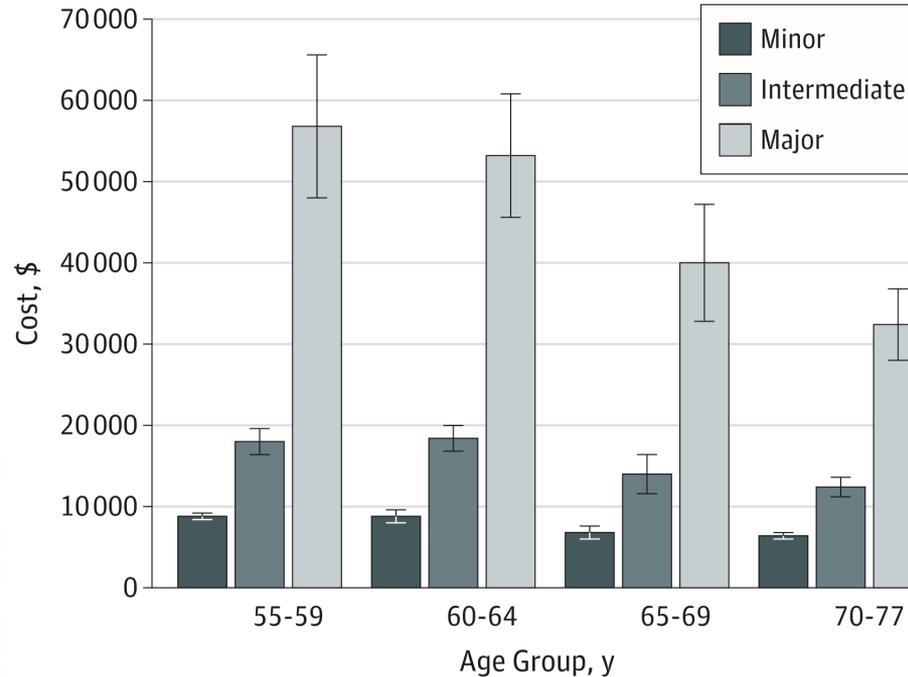
A Incremental complication rates by age



B Incremental complication rates by procedure type



Procedure Complication Rates



Procedure Complication Rates

■ Interpretation:

- The rates of complications after invasive diagnostic procedures were higher than the rates reported in clinical trials. Physicians and patients should be aware of the potential risks of subsequent adverse events and their high downstream costs in the shared decision-making process.

Summary

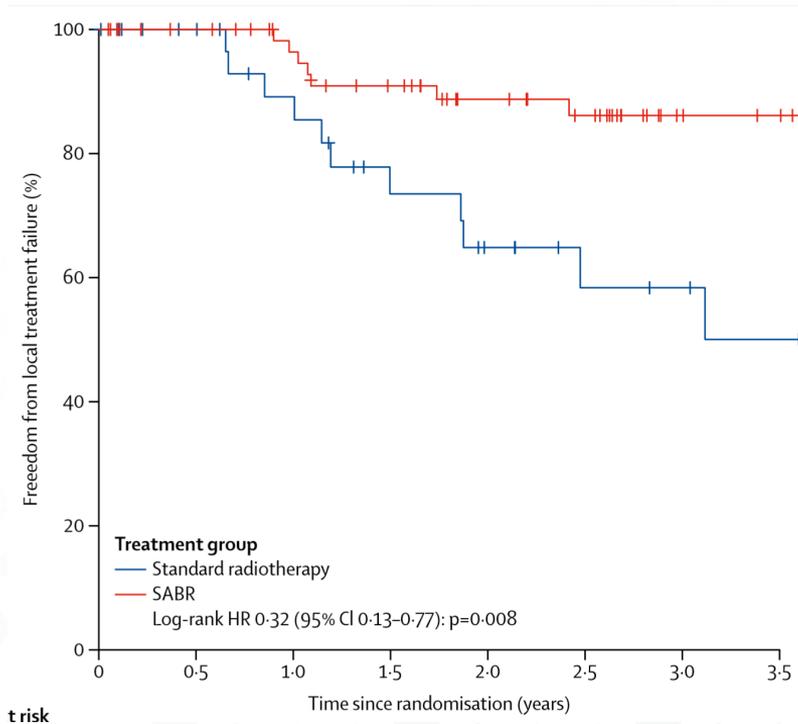
- Exciting time for early lung cancer detection.
- Await details of the NELSON trial to incorporate the findings into current screening policy.
- Must remember that screening means we are testing asymptomatic individuals, healthy enough to benefit from early lung cancer detection.
- Few benefit from screening while all are exposed to potential harms.
- Harms must be minimized.

Stereotactic Radiotherapy

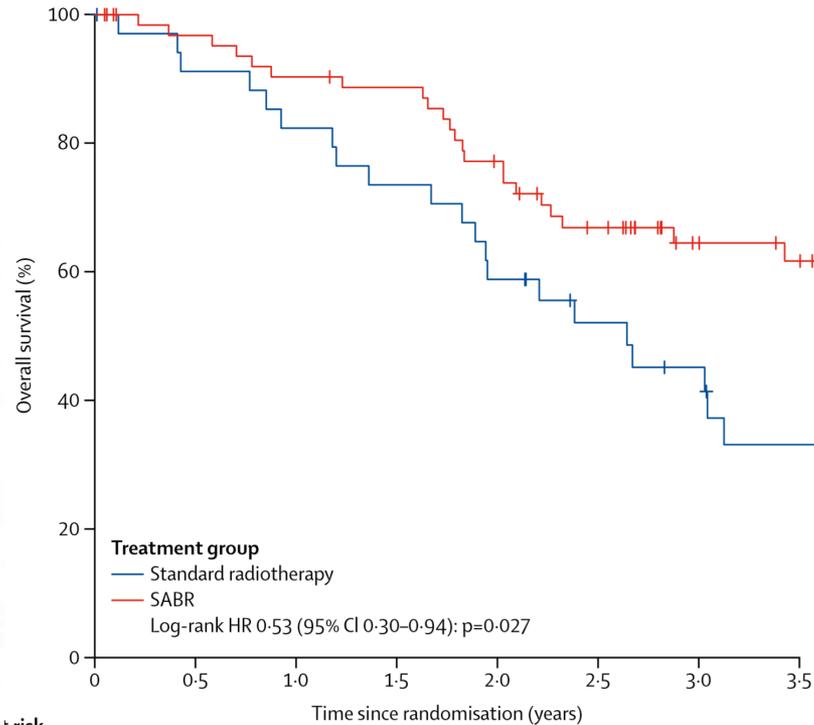
SABR vs. Conventional Radiotherapy

- **Background:** There is an absence of prospective evidence that SABR improves local control or prolongs overall survival compared with standard radiotherapy.
- **Study Question:** Does SABR improve local control and prolong overall survival in patients with stage I NSCLC compared to standard radiotherapy?
- **Methods:** Multicentre, phase 3, randomised, controlled trial in 14 hospitals in Australia and New Zealand. Patients were aged 18 years or older, had stage 1 (T1–T2aN0M0) NSCLC, and were medically inoperable or had refused surgery. The primary endpoint was time to local treatment failure.

SABR vs. Conventional Radiotherapy



SABR vs. Conventional Radiotherapy



SABR vs. Conventional Radiotherapy

■ Interpretation:

- In patients with inoperable peripherally located stage 1 NSCLC, compared with standard radiotherapy, SABR resulted in superior local control of the primary disease without an increase in major toxicity.
- The findings of this trial suggest that SABR should be the treatment of choice for this patient group.

Summary

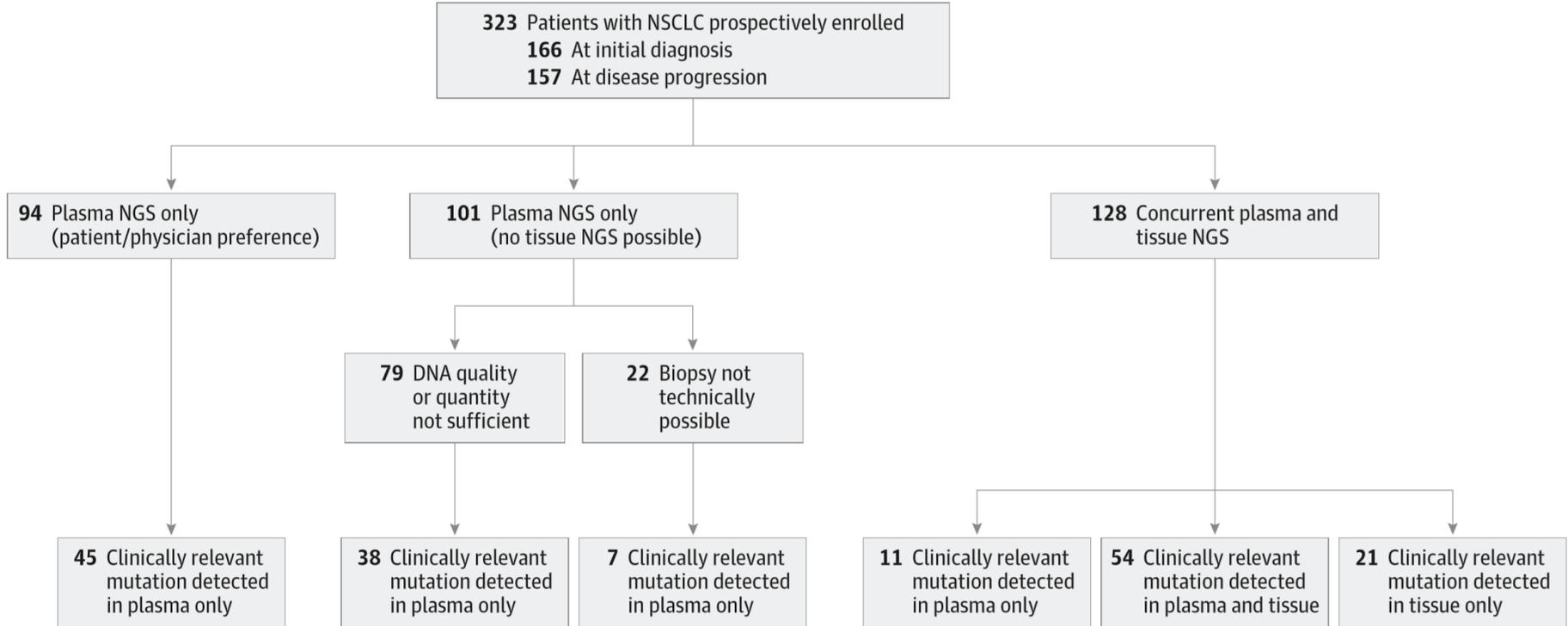
- SABR should be selected over standard radiation where available.
- Expertise required to minimize complications.
- Performance supports comparison with other treatments for stage I lung cancer.
- Helpful to see clinical utility proven.

Molecular Profiling

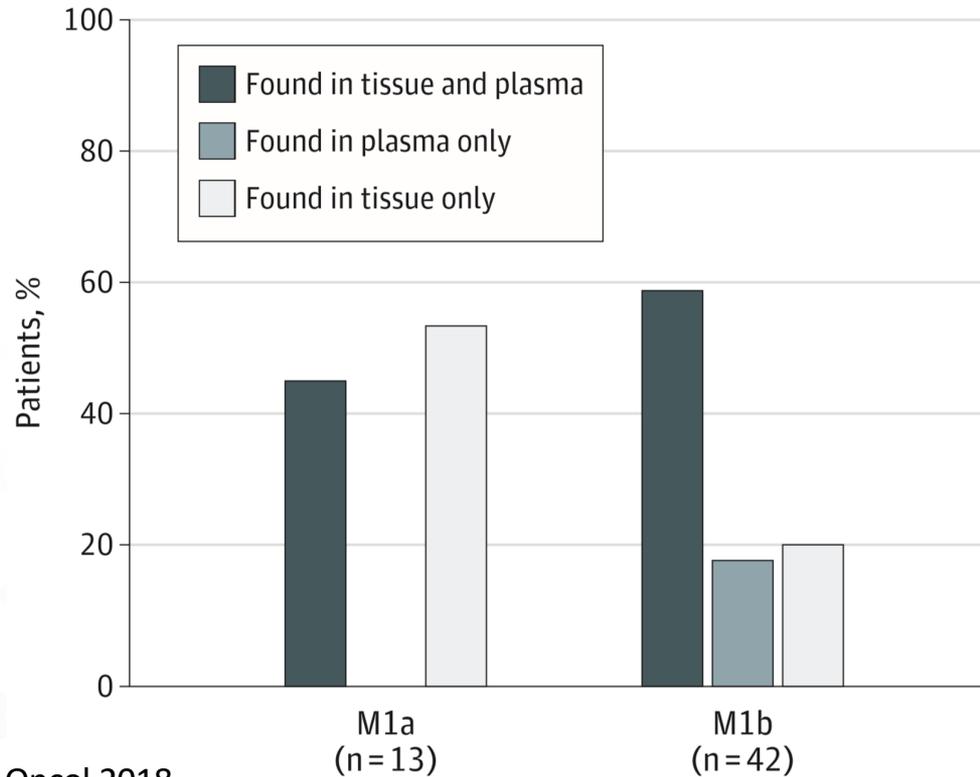
Plasma Genotyping

- **Background:** The clinical implications of adding plasma-based ctDNA NGS to tissue NGS for targetable mutation detection in NSCLC have not been formally assessed.
- **Study Question:** Does plasma NGS testing improve mutation detection and enhance delivery of personalized therapy in a real-world clinical setting?
- **Methods:** Prospective cohort study of 323 patients with metastatic NSCLC who had plasma testing ordered as part of routine clinical management. The number of patients with targetable alterations detected with plasma and tissue NGS was assessed.

Plasma Genotyping



Plasma Genotyping



Plasma Genotyping

■ Interpretation:

- Integration of plasma NGS testing into the routine management of stage IV NSCLC demonstrates a marked increase of the detection of therapeutically targetable mutations and improved delivery of molecularly guided therapy.

Summary

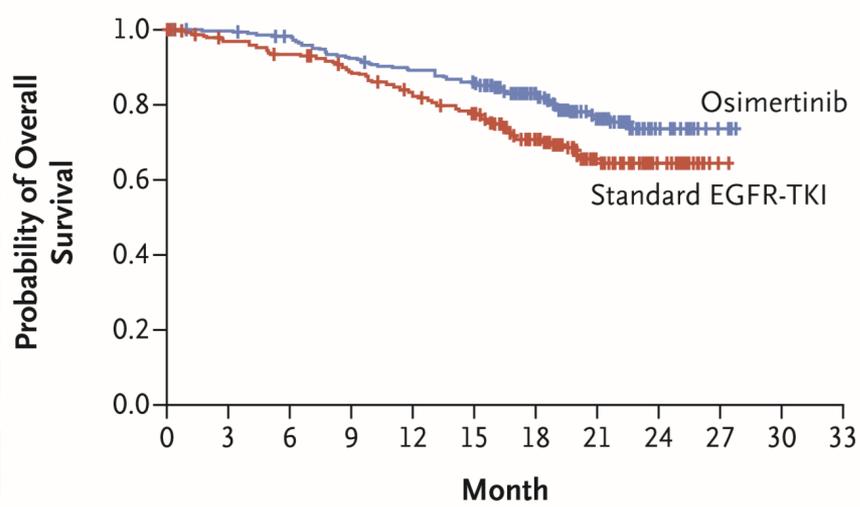
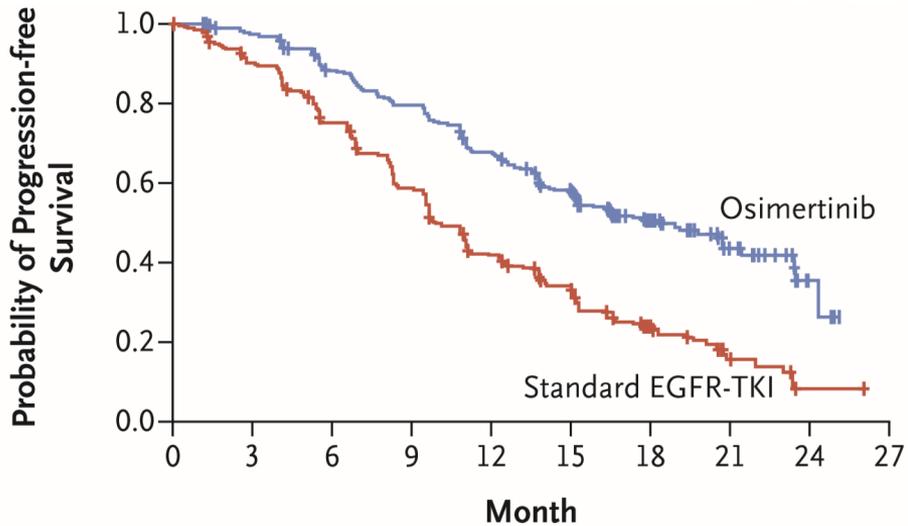
- Current guidelines do not recommend plasma genotyping patients with enough tissue to perform molecular analysis.
- An opportunity to perform a clinical utility study.

Targeted Therapy

EGFR Mutations

- **Background:** Osimertinib is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI–sensitizing and EGFR T790M resistance mutations.
- **Study Question:** Does osimertinib improve progression-free survival compared to standard EGFR-TKIs in patients with previously untreated, EGFR mutation–positive advanced NSCLC?
- **Methods:** Double-blind, phase 3 trial of 556 patients with previously untreated, EGFR mutation–positive advanced NSCLC randomly assigned to receive either osimertinib or a standard EGFR-TKI.

EGFR Mutations



Soria, N Engl J Med 2018.

EGFR Mutations

	Osimertinib	Standard EGFR-TKI
Duration of Response		
Median (months)	17.2	8.5
At 12 months (%)	64	37
Survival at 12 Months (%)	89	82

Soria, N Engl J Med 2018.

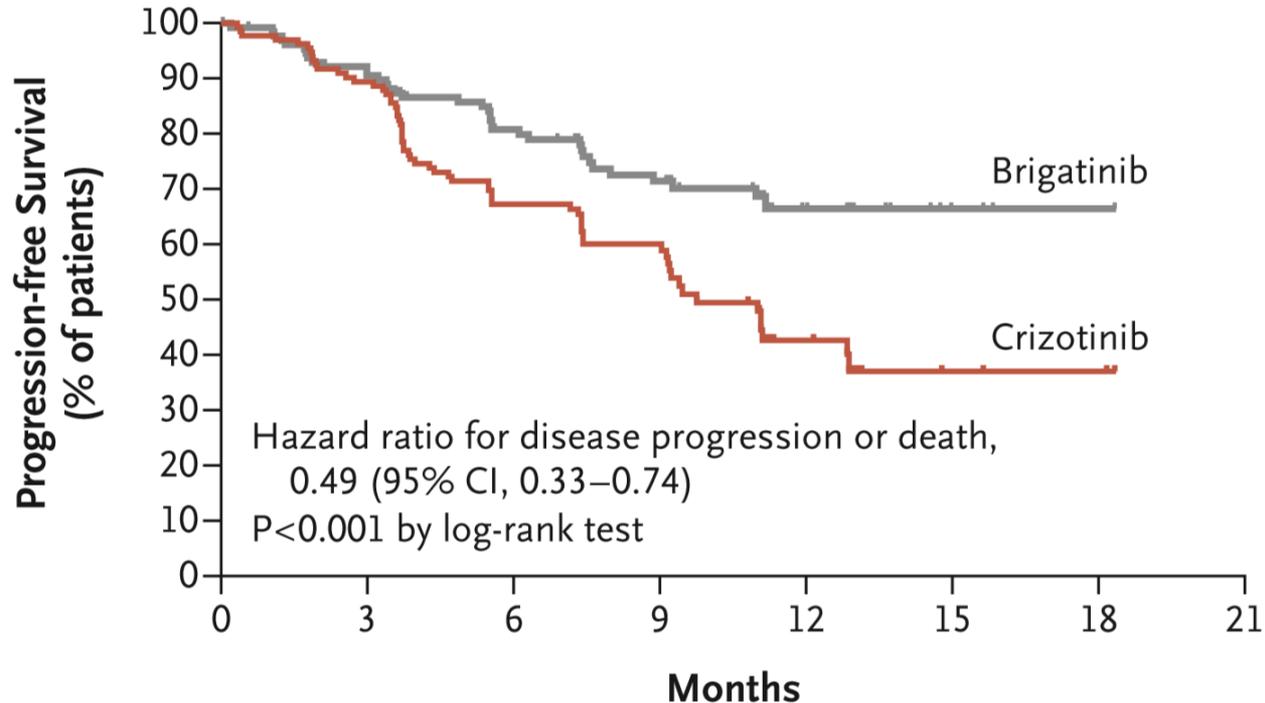
EGFR Mutations

- **Interpretation:**
 - Osimertinib showed efficacy superior to that of standard EGFR-TKIs in the first-line treatment of EGFR mutation–positive advanced NSCLC, with a similar safety profile and lower rates of serious adverse events.

EML4-ALK Translocation

- **Background:** Brigatinib, a next-generation ALK inhibitor, has robust efficacy in patients with ALK-positive NSCLC that is refractory to crizotinib.
- **Study Question:** Does brigatinib improve progression-free survival, as compared with crizotinib, in patients with advanced ALK-positive NSCLC who have not previously received an ALK inhibitor?
- **Methods:** An open-label, phase 3 trial, where patients with advanced ALK-positive NSCLC who had not previously received ALK inhibitors were randomized to receive brigatinib or crizotinib.

EML4-ALK Translocation



EML4-ALK Translocation

	Brigatinib	Crizotinib
Duration of Response		
Median (months)	NR	11.1
At 12 months (%)	75	41
Brain Mets Response (%)	79	23

EML4-ALK Translocation

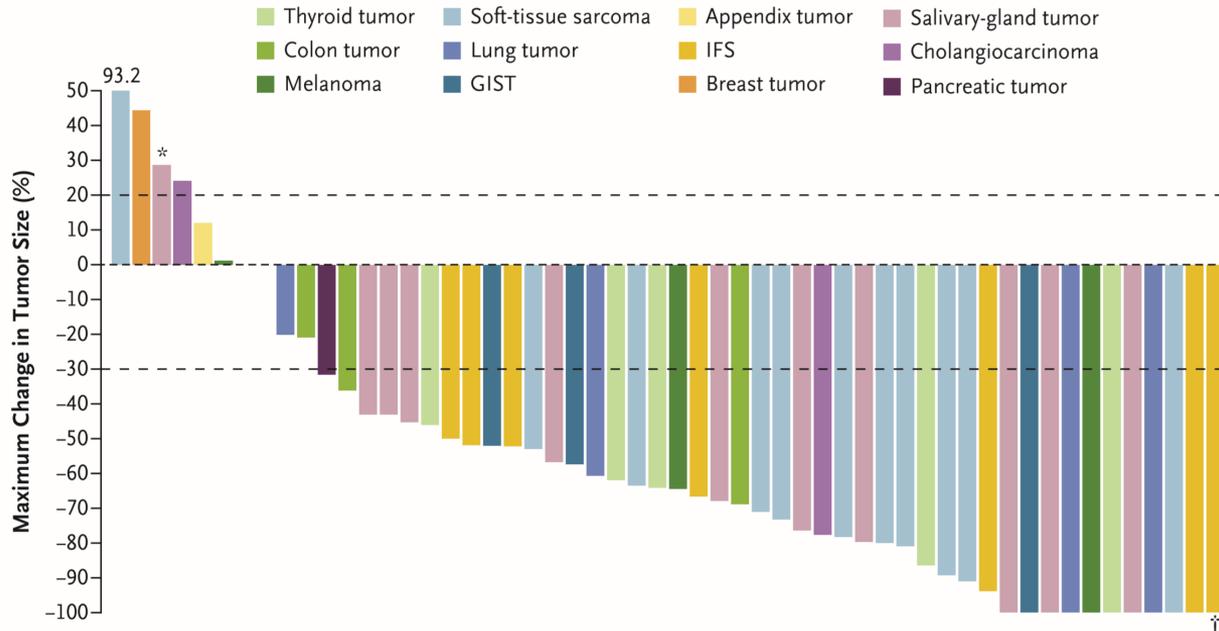
- Interpretation:
 - Among patients with ALK-positive NSCLC who had not previously received an ALK inhibitor, progression-free survival was significantly longer among patients who received brigatinib than among those who received crizotinib.

Cross-Cancer Targets

- **Background:** Fusions involving one of three tropomyosin receptor kinases (TRK) occur in diverse cancers in children and adults.
- **Study Question:** What is the overall response rate and safety of larotrectinib, a highly selective TRK inhibitor, in adults and children who have tumors with these fusions?
- **Methods:** Patients with TRK fusion– positive cancers were enrolled into one of three protocols: a phase 1 study involving adults, a phase 1–2 study involving children, or a phase 2 study involving adolescents and adults.

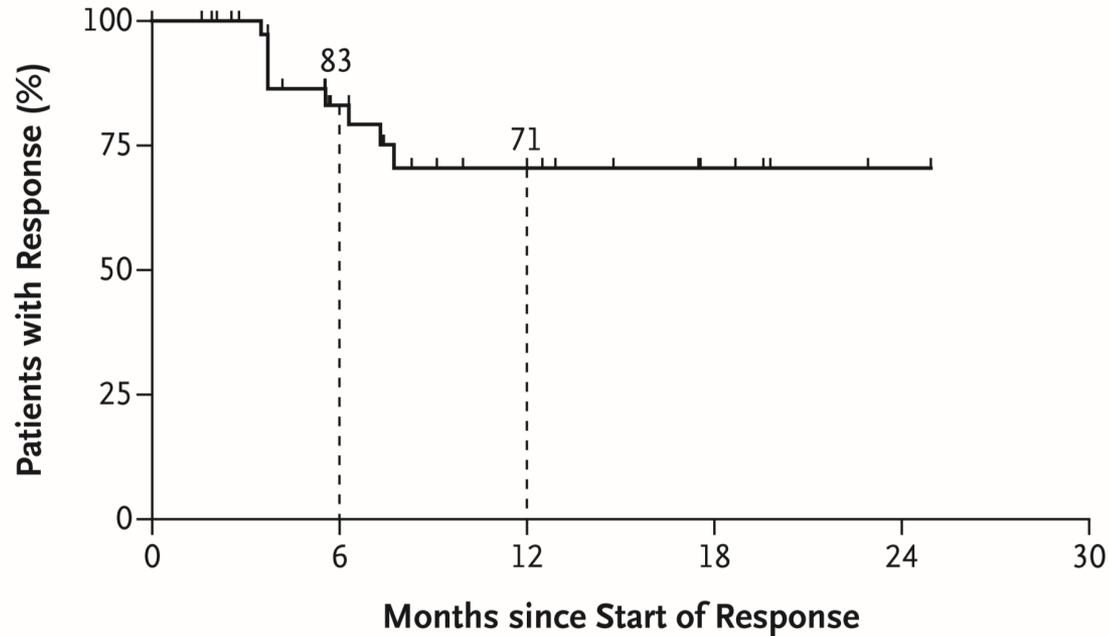
Cross-Cancer Targets

A Maximum Change in Tumor Size, According to Tumor Type



Cross-Cancer Targets

Duration of Response among Patients with Response



Cross-Cancer Targets

- **Interpretation:**

- Larotrectinib had marked and durable antitumor activity in patients with TRK fusion–positive cancer, regardless of the age of the patient or of the tumor type.

Summary

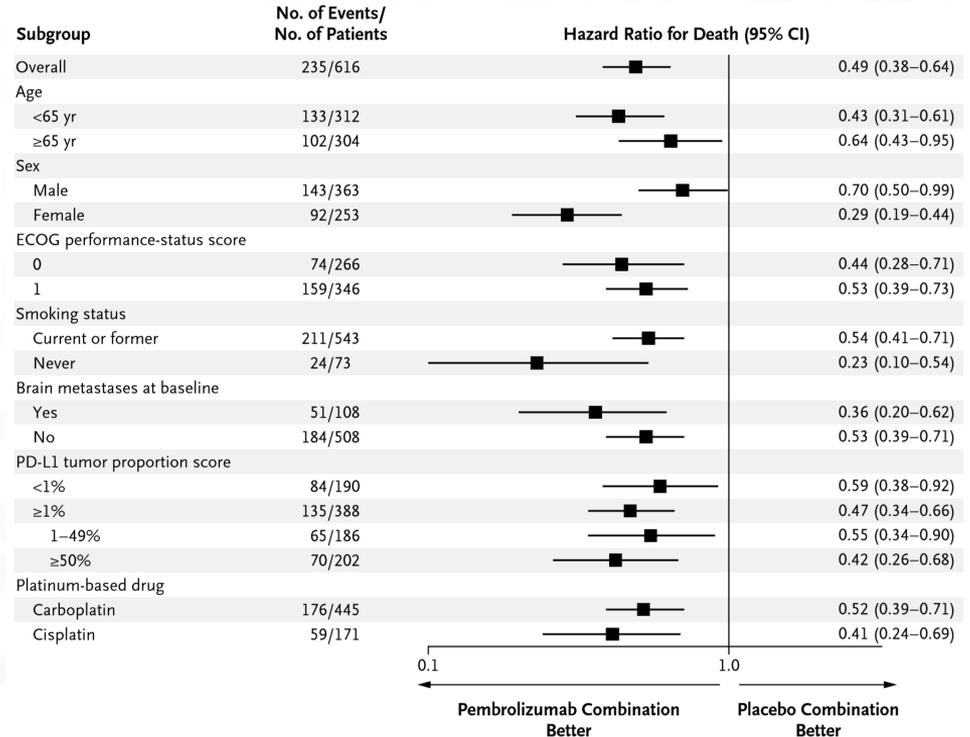
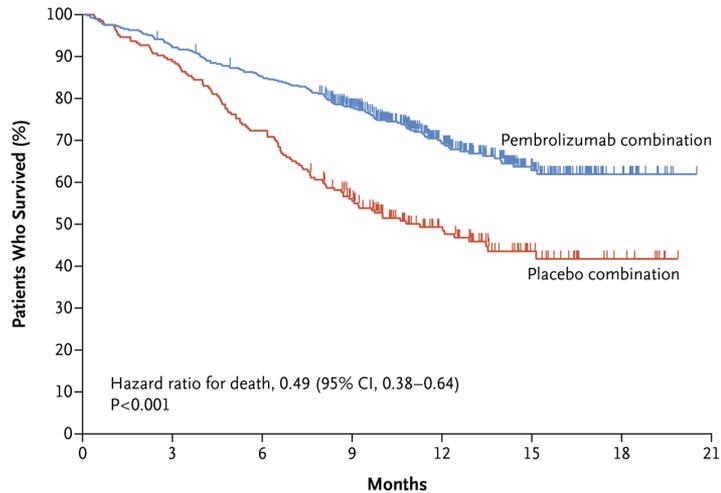
- Increasing number of targetable mutations.
- New options being developed with increased potency and ability to overcome resistance mutations.
- Highlights the importance of molecular testing.
- A new era where the type of cancer is based on molecular testing rather than location of the primary cancer.

Immune Checkpoint Inhibitors

ICI + Chemotherapy

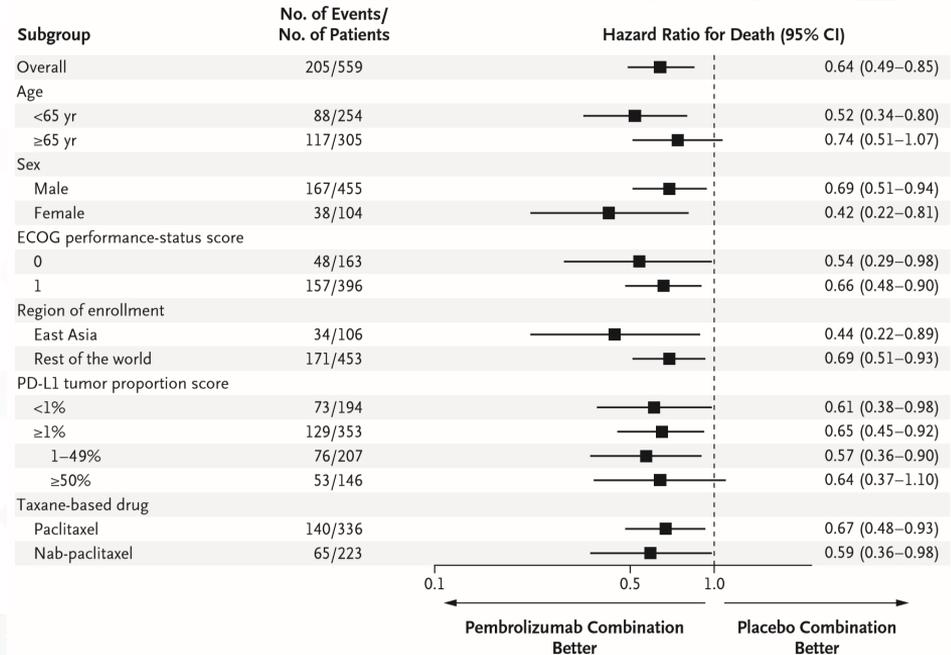
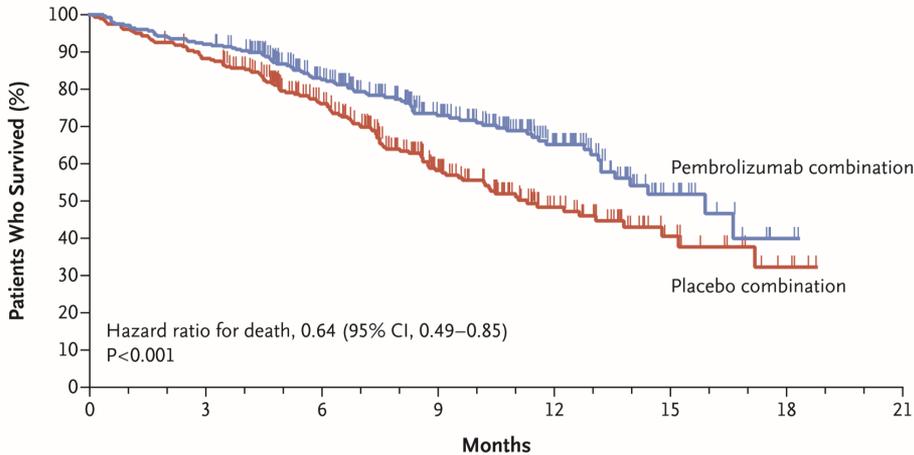
- **Background:** The addition of pembrolizumab to chemotherapy resulted in significantly higher response rates and longer PFS than chemotherapy alone in a phase 2 trial.
- **Study Questions:** Does the addition of pembrolizumab to chemotherapy improve survival as compared to chemotherapy alone in patients with untreated metastatic NSCLC without sensitizing EGFR or ALK mutations?
- **Methods:** Double-blind, phase 3 trials, of patients with metastatic NSCLC who had received no previous treatment for metastatic disease, randomized to receive standard chemotherapy plus either 200 mg of pembrolizumab or placebo.

ICI + Chemotherapy



Gandhi, N Engl J Med 2018.

ICI + Chemotherapy



Paz-Ares, N Engl J Med 2018.

ICI + Chemotherapy

- **Interpretation:**

- In patients with previously untreated metastatic NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy resulted in significantly longer overall survival and progression-free survival than chemotherapy alone.

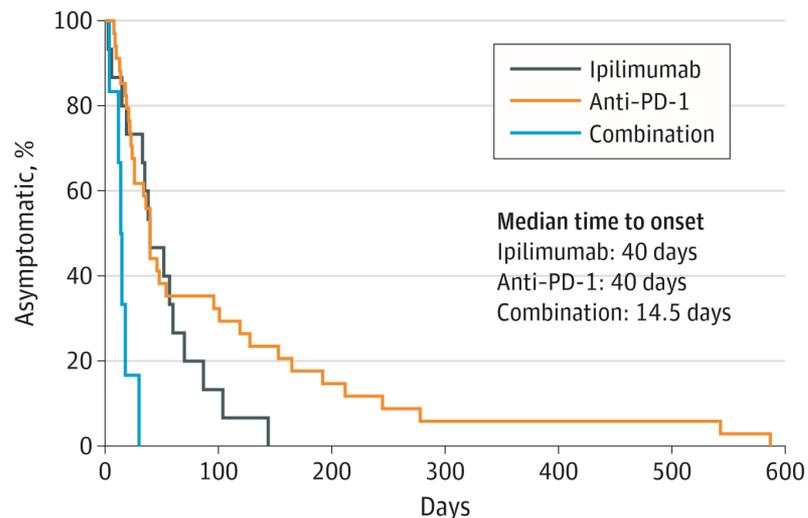
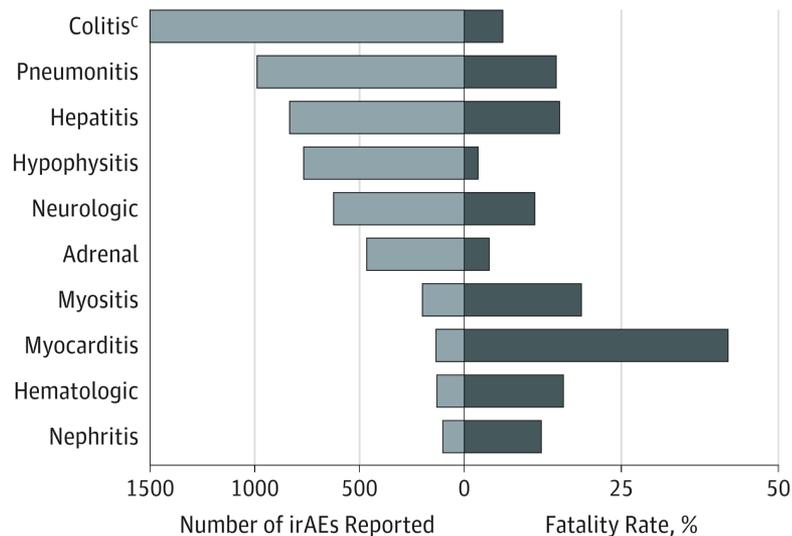
Immune Related Adverse Events

- **Background:** Although rare, fulminant and fatal toxic effects of ICIs may complicate these therapies.
- **Study Question:** What are the spectrum, timing, and clinical features of fatal ICI-associated toxic effects?
- **Methods:** Retrospective review and meta-analysis of published trials of anti-PD-1/PD-L1 and anti-CTLA-4 to evaluate their incidence using data from large academic medical centers, global WHO pharmacovigilance data, and all published ICI clinical trials of patients with cancer treated with ICIs internationally.

Immune Related Adverse Events

	Treatment Related Fatality (%)
Anti-PD-1	0.36
Anti-PD-L1	0.38
Anti-CTLA-4	1.08
Combination	1.23

Immune Related Adverse Events



Immune Related Adverse Events

- **Interpretation:**

- In the largest evaluation of fatal ICI-associated toxic effects published to date to our knowledge, we observed early onset of death with varied causes and frequencies depending on therapeutic regimen. Clinicians across disciplines should be aware of these uncommon lethal complications.

Summary

- ICIs are an exciting treatment advance
 - First line alone if PD-1 > 50%
 - First line in combination with chemotherapy for all comers without targetable mutations
 - Second line alone regardless of PD-1 status
 - Stage III and small cell
- Awareness of toxicities is important