



A Teaching Affiliate  
of Harvard Medical School

# Lung Cancer 2022

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# Disclosures

Consulting/Honoraria: Creative Education Concepts, OncLive, ASCO Post, DAVA Oncology, Medscape, Total Health, and American Lung Association, consulting fees from AstraZeneca, Bayer, BostonGene, Catalyst, Genentech, Janssen, Novocure, Pfizer, Regeneron, Sanofi/Genzyme, Syros, and Xcovery

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# Learning Objectives

1. Review updated guidelines for lung cancer screening
2. Discuss management strategies for early-stage (stage I-III) lung cancer
3. Review the evolving paradigm for management of metastatic lung cancer





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# Lung Cancer by the Numbers

- 236,640 new cases of lung cancer in 2022
- 130,180 deaths in the U.S in 2022
- Leading cause of cancer-related mortality
- 10-15% of NSCLCs occur in never/minimal smokers

## Estimated New Cases

			Males	Females			
Prostate	268,490	27%			Breast	287,850	31%
Lung & bronchus	117,910	12%			Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%			Colon & rectum	70,340	8%
Urinary bladder	61,700	6%			Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%			Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%			Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%			Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%			Pancreas	29,240	3%
Leukemia	35,810	4%			Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%			Leukemia	24,840	3%
<b>All Sites</b>	<b>983,160</b>	<b>100%</b>			<b>All Sites</b>	<b>934,870</b>	<b>100%</b>

## Estimated Deaths

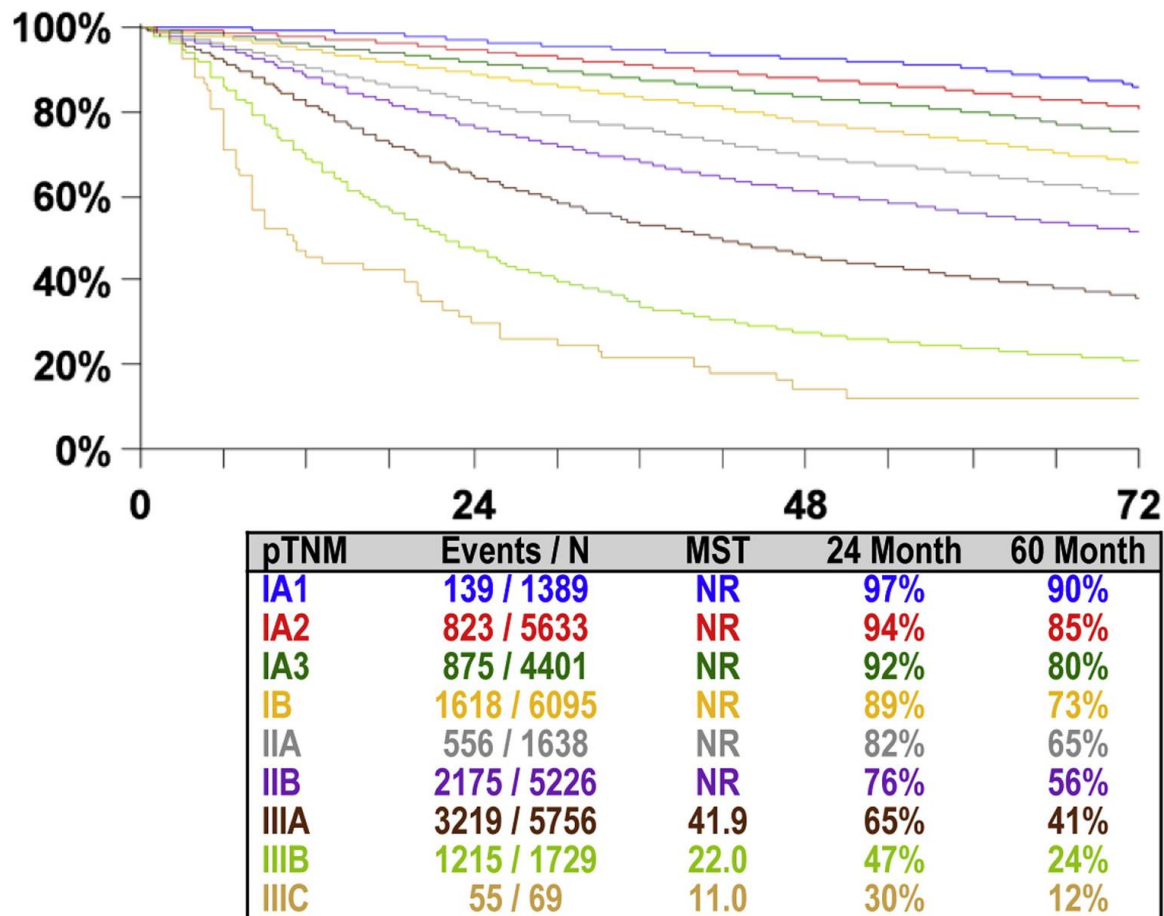
			Males	Females			
Lung & bronchus	68,820	21%			Lung & bronchus	61,360	21%
Prostate	34,500	11%			Breast	43,250	15%
Colon & rectum	28,400	9%			Colon & rectum	24,180	8%
Pancreas	25,970	8%			Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%			Ovary	12,810	4%
Leukemia	14,020	4%			Uterine corpus	12,550	4%
Esophagus	13,250	4%			Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%			Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%			Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%			Brain & other nervous system	7,570	3%
<b>All Sites</b>	<b>322,090</b>	<b>100%</b>			<b>All Sites</b>	<b>287,270</b>	<b>100%</b>



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# Overall Survival By Pathologic Stage



Fewer than 5% of patients with stage IV NSCLC survive  $\geq 5$  years

# Lung Cancer Screening



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

# Question

Which of the following patients would not be eligible for lung cancer screening with a LDCT per the revised CMS coverage criteria (February 2022)?

- A) 75-year-old, current smoker
- B) 60-year-old, former smoker (25 pack year, quit 2000)
- C) 51-year-old, former smoker (20 pack year, quit 2010)
- D) 78-year-old, current smoker, with prior lung cancer
- E) B & D



# Low-Dose CT Screening

Trial Name	Study Design	Number Recruited	Characteristics of Participants				Year Started	Report Date	LC Baseline Rate (LDCT)	Stage I Cancer at Baseline/Mortality Reduction
			Age	Sex	Smoker (Pack yrs)	Ex-Smoker (yrs)				
 NLST	LDCT vs. CXR	53,454	55-74	M/F	≥30	<15	2002	2011	1%	63% / 20%
 NELSON	LDCT vs. UC	15,822	50-75	M/F	≥15	<10	2003	2016	0.9%	63.9%
 MILD	LDCT vs. UC	4,099	≥49	M/F	>20	<10	2005	2011	0.6%	63%
 DANTE	LDCT vs. UC	2,811	60-74	M	≥20	<10	2001	2007	2.2%	57%
 DEPISCAN	LDCT vs. CXR	765	50-75	M/F	≥15	<15	2002	2006	2.4%	0.9%
 ITALUNG	LDCT vs. UC	3,206	55-69	M/F	≥20	<10	2004	N/A	1.5%	47.6%
 DLCST	LDCT vs. UC	4,104	50-70	M/F	≥20	<10	2004	2016	0.8%	58.8%
 LUSI	LDCT vs. CXR	4,052	50-69	M/F	>15	<10	2007	2012	1.1%	78.2%
 UKLS	LDCT vs. UC	32,000 planned	50-75	M/F	N/A	N/A	2012	N/A	N/A	N/A

LDCT = Low-Dose Computed Tomography; CXR = Chest Radiograph; LC = Lung Cancer; UC = Usual Care

- Multiple randomized trials have compared the impact of LDCT screening vs. usual care on lung cancer-specific and overall mortality
  - 5 trials: usual care arm was no screening
  - 3 trials: usual care arm was CXR (including NLST trial)
- NELSON (2020 Update):
  - ~13,000 men and 3,000 women
  - Randomized to no screening vs CT at baseline, Y1, Y3, Y5.5
  - At 10 years: 24% and 33% reduction in lung cancer related mortality in men and women, respectively



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Reduced Lung-Cancer Mortality with Low-Dose Computed  
Tomographic Screening

The National Lung Screening Trial Research Team\*



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# Criteria for Participation in National Lung Screening Trial (NLST)

- Eligibility criteria:
  - 55-74 years old, no signs or symptoms of lung cancer
  - Active or former smoker with a 30-pack year history
  - If a former smoker, must have quit within 15 years
- Exclusions:
  - Prior history of lung cancer, hemoptysis
- Compared low-dose (LDCT) yearly (baseline, 1 year, 2 years) to CXR

# CT screening of smokers and former smokers saves lives and is cost-effective

- 20% reduction in lung cancer specific mortality
- 7% reduction in all cause mortality
- One study estimates \$4.4 billion in US healthcare costs added by LDCT screening for a population of 18 million individuals age 50-64 years and a minimum smoking history of at least 30 pack-years.<sup>1</sup>
- Despite being costly, LDCT could save 18,000 lives annually, at an average cost of \$170,500 per life saved (2012 US dollars).<sup>1</sup>
- Cost effectiveness analysis based on the NLST population estimates \$81K per QALY gained and \$52K per life-year gained. (Both less than \$100K)<sup>2</sup>

<sup>1</sup> Pyenson, 2012, <sup>2</sup>Black, 2014



## CMS Decision (Dates Back to 2015)

- CMS will cover lung screening CTs
- Age 55-77
- Asymptomatic
- At least 30 pack-year history
- Current smoker or quit within 15 years
- First screen must have a lung screening/shared decision-making visit prior to order
- Shared decision-making, including decision-aid
- Counseling on importance of abstinence from smoking or smoking cessation
- Counseling on importance of adherence to screening

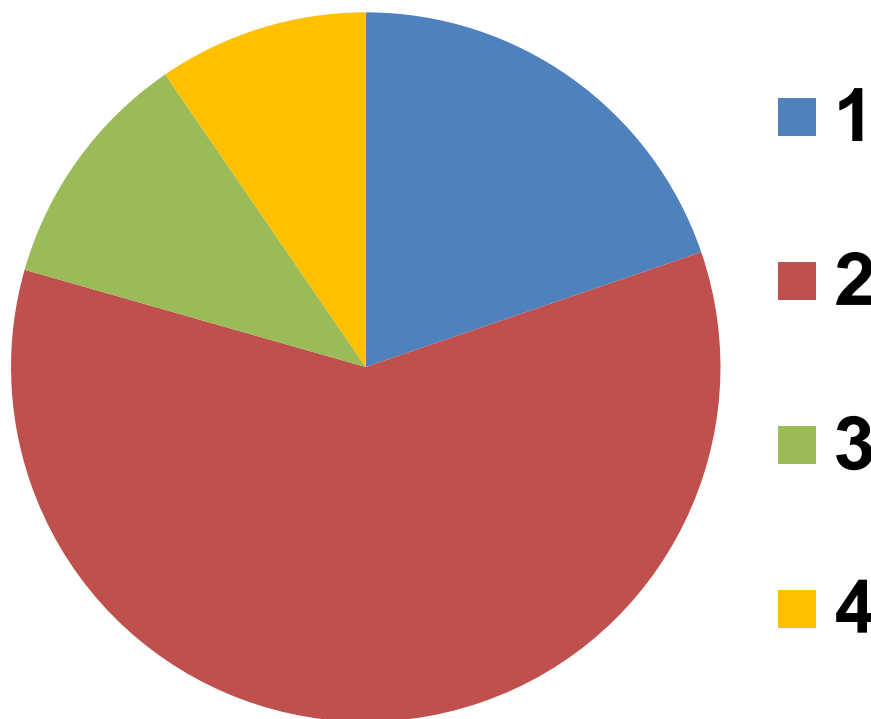
# CMS Decision (Updated February 2022)

- CMS will cover lung screening CTs
- Age 50-77
- Asymptomatic
- At least 20 pack-year history
- Current smoker or quit within 15 years
- First screen must have a lung screening/shared decision-making visit prior to order
- Shared decision-making aid must be used
- Counseling on importance of abstinence from smoking or smoking cessation
- Counseling on importance of adherence to screening

# Lung-RADS

LungRADS Category	Abbreviated Nodule Description	Recommended Follow-Up Scan Interval	Prevalence Among Screened Population	Likelihood of Being Lung Cancer
1	Normal CT scan, no nodules	1 year	90%	< 1%
2	Nodule < 6mm or unchanged over time; benign-appearing	1 year		
3	Nodule $\geq 6$ mm	6 months	5%	1-2%
4A	$\geq 8$ mm or growing over time	3 months	2%	5-15%
4B	$\geq 15$ mm or $\geq 8$ mm and growing	Immediate work-up	2%	>15%

**MGH**



# MGH Lung Screening/Pulmonary Nodule Clinic Workflow

## Pre-Visit

- RN or Navigator collects focused history, gathers images, and communicates with referring MD
- Multidisciplinary team reviews images, decides which MDs will see patient at first appointment

## Initial Appointment

- Designated MDs see patient
- Images reviewed with patient
- Tobacco cessation offered
- Recommended studies and procedures planned

## Follow-up

- Navigator ensures scan follow-up & scheduling of procedures
- Patients are scheduled at PNLCSO for follow-up visits
- Patients with no procedures planned are seen by clinic NP

## Discharge

- Criteria: No further scans required, >2 years of stability, appropriate procedure(s) planned
- Discharge is documented in medical record & letters are sent to referring MD

Referrals come from PCPs, pulmonology, specialists, radiology, patient self-referral



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# Early Stage (Localized) Lung Cancer



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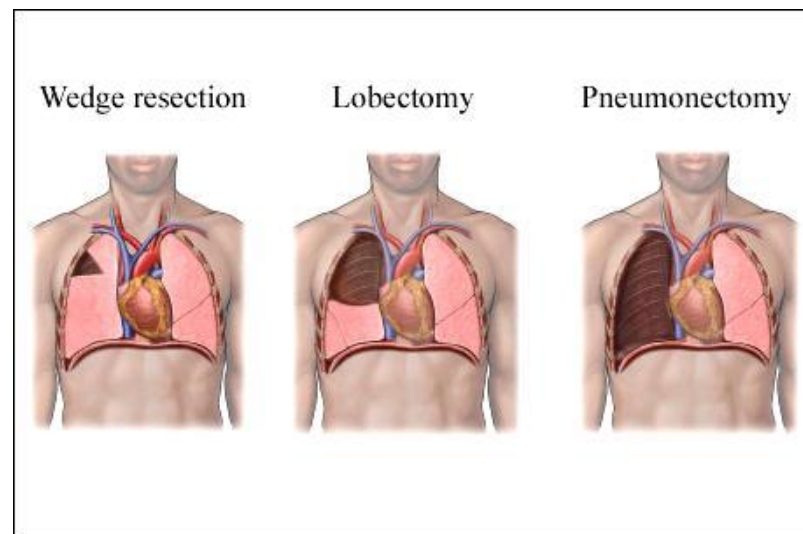
# Case Presentation

- 60-year-old male, current smoking history (35 pack year) presents to his primary care doctor for annual visit.
- He is asymptomatic.
- It is recommended that he undergo a low-dose chest CT for lung cancer screening.
- A nodule is detected.
- No other imaging abnormality
- Biopsy: lung adenocarcinoma

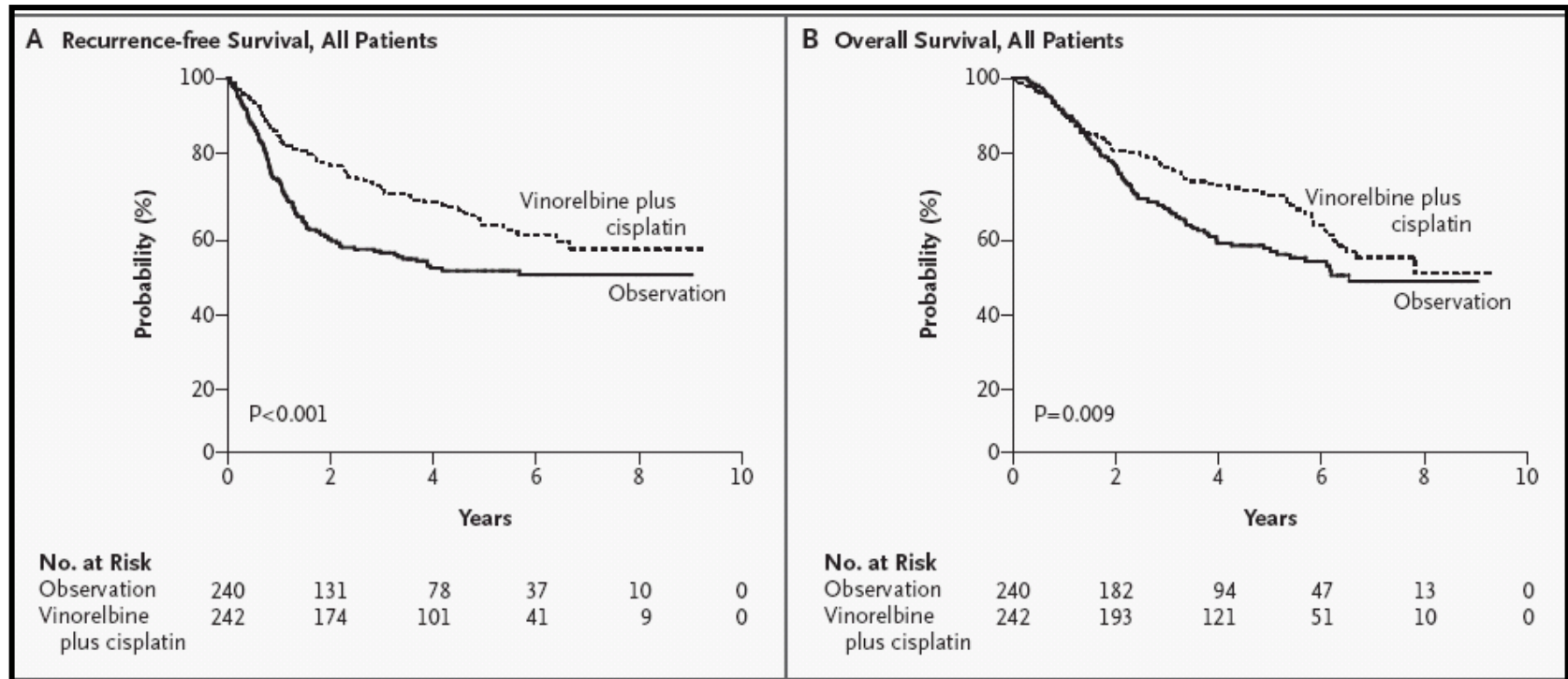


# Surgical Management of Localized Lung Cancer

- Surgery - backbone of therapy for localized NSCLC
- Type of Resections
  - Anatomic Resections: Pneumonectomy, Segmentectomy, and Lobectomy
  - Non-anatomic Resections: Wedge Resection
- **The gold standard for operable patients is an anatomic resection, ideally lobectomy or segmentectomy**



# Adjuvant Therapy: How it Started (Chemo)



NEJM 2005; 352: 2589-97

5% improvement in survival at 5 years

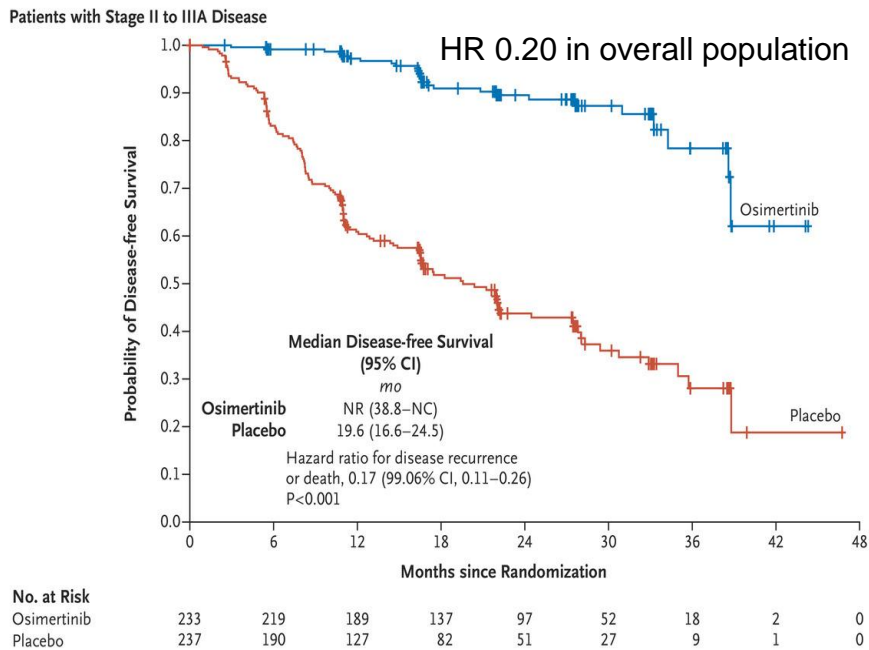


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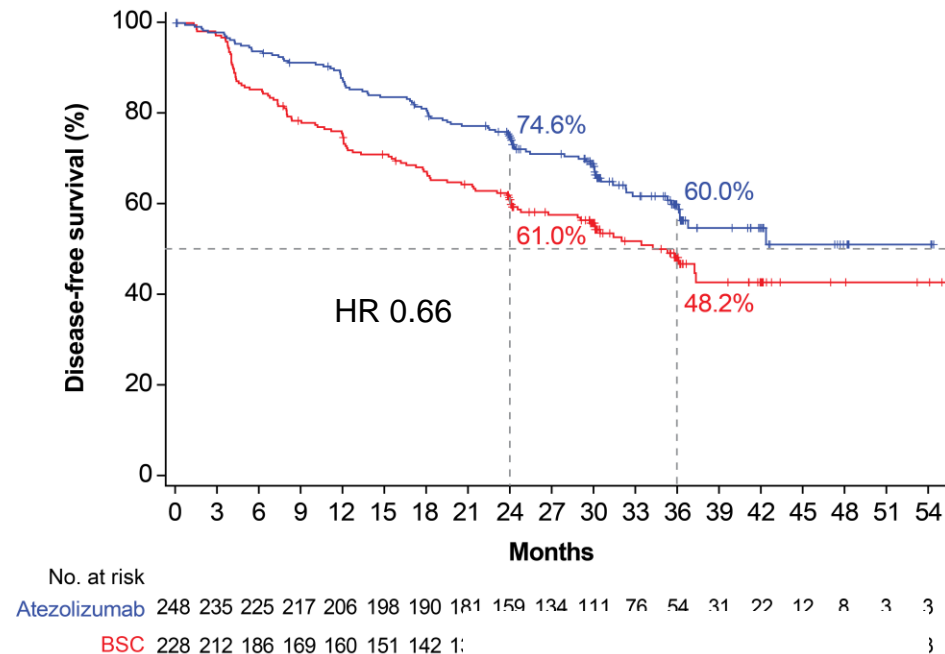
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# Adjuvant Therapy: How It's Going (2022)

Markedly improved disease-free survival with targeted therapy + chemo for EGFR+ NSCLC



Improved disease-free survival with immunotherapy + chemo for PD-L1+ stage II-III NSCLC



# Case Presentation

- 70-year-old with active smoking history, coronary artery disease, congestive heart failure, and severe COPD. She has a baseline 2-3L supplemental O2 requirement.
- A screening CT scan demonstrates a 1.5 cm LUL nodule. The nodule persists on short interval follow-up imaging. The nodule is FDG avid on PET scan. Biopsy is not possible due to risk.



# Question

**Which of the following is the most appropriate approach to management of this patient?**

- A) Referral to hospice
- B) Referral to thoracic surgery for resection
- C) Repeat CT scan in 6 months
- D) Referral to radiation oncology for radiation therapy



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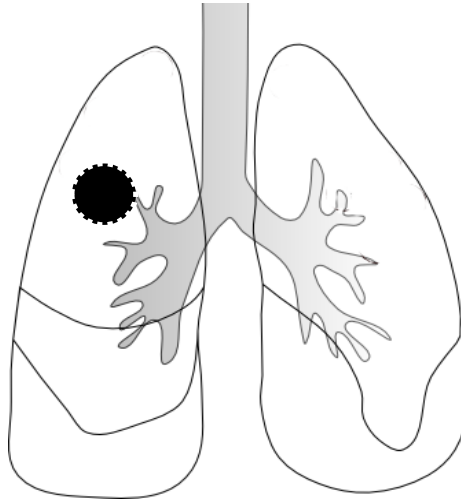
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# Role of radiation therapy in the management of early-stage NSCLC

- 20-25% of NSCLC patients have stage I disease
- 20-30% of patients are medically inoperable

## Operable

- **Anatomical resection**
  - lobectomy
  - segmentectomy
  - pneumonectomy



## Medically inoperable

- **Radiation**
- **IR ablative options**  
(e.g., cryotherapy)

## High-risk operable

- **Wedge resection**
- **Radiation**
- **IR ablative options**



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# Stereotactic Body Radiation Therapy (SBRT)

- SBRT has emerged as the **standard treatment for medically inoperable patients** with early-stage NSCLC up to ~ 5 cm in size
- Treatment consists typically of **3-5 fractions delivering a total dose of 45-60 Gy** with various techniques available
- **Local tumor control is 90-95% at 5 years**, and nodal failures are in the range of 5-15% depending on tumor size and other factors
- **Toxicity is uncommon**, even for central and chest wall-based tumors, with typically no or mild, self-limited acute side effects and a generally <10% risk of serious late toxicity
- **Areas of investigation/controversy:** SBRT without biopsy, role in high-risk operable patients
- SBRT for **operable patients remains investigational**



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# Locally-Advanced (Stage III), Inoperable Lung Cancer



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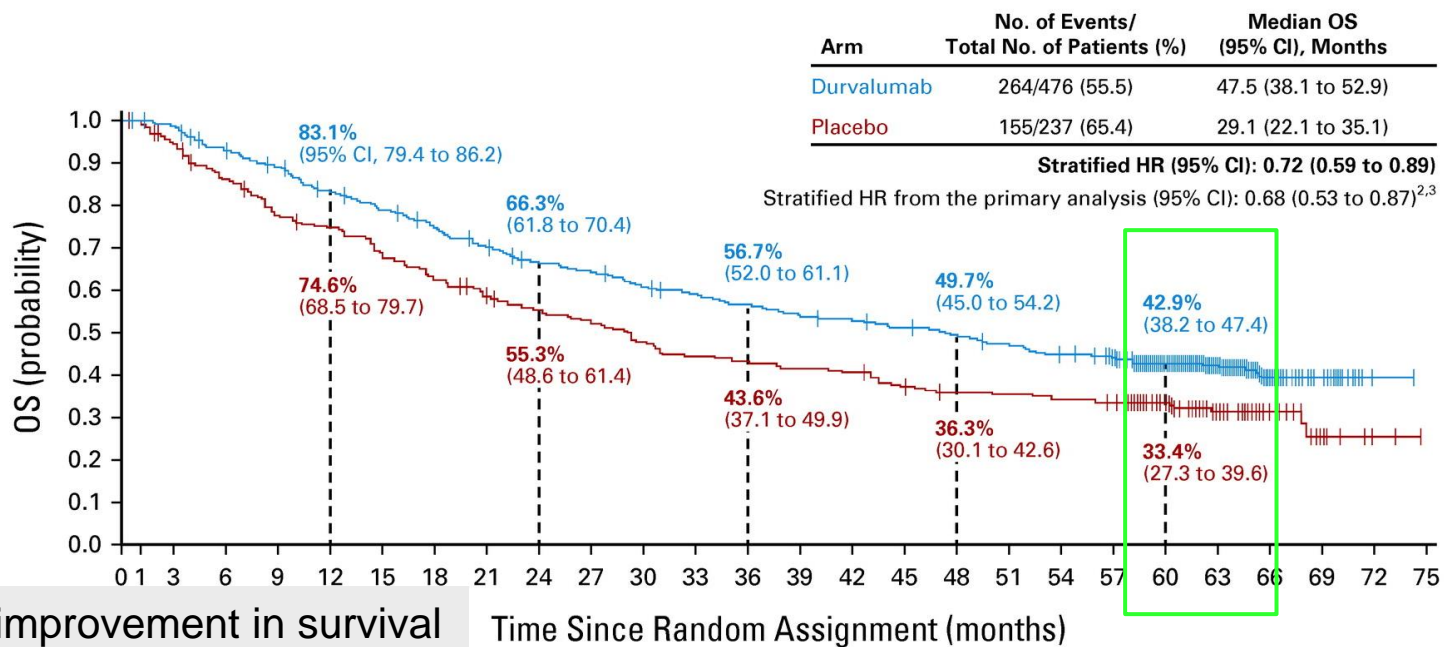
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# Case Presentation

- 74-year-old who quit smoking 5 years ago presents with persistent cough and 10 lbs unintentional weight loss.
- CT scan demonstrates a 4 cm mass in the right lung, as well as enlarged lymph nodes involving the bilateral hilar and mediastinal stations.
- PET scan reveals uptake in the lung mass and multiple lymph node stations. No extrathoracic FDG uptake. Brain MRI is unrevealing.
- Bronchoscopy with biopsy of lymph nodes confirms lung adenocarcinoma involving lymph nodes from both sides of the chest (**stage IIIc**).

# Management of Inoperable Stage III NSCLC

- Multimodality treatment is ideal.
- Treatment involves 6 weeks of chemo delivered with daily radiation
- Then, patients receive 1 year of immunotherapy (durvalumab).



No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

# Metastatic Lung Cancer



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# Question

**Which of the following is not a standard component of first-line treatment of metastatic lung cancer?**

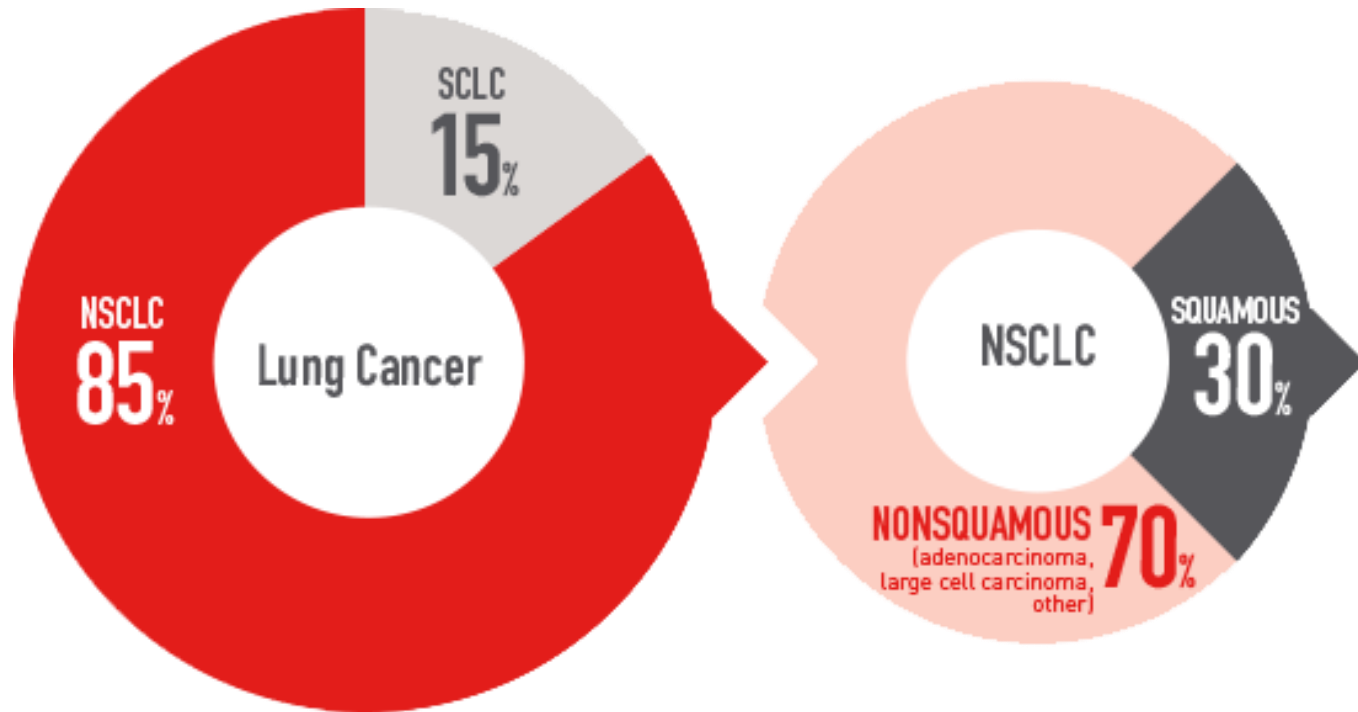
- A) Palliative radiation
- B) Surgical Resection
- C) Chemotherapy
- D) Immunotherapy
- E) Targeted Therapy



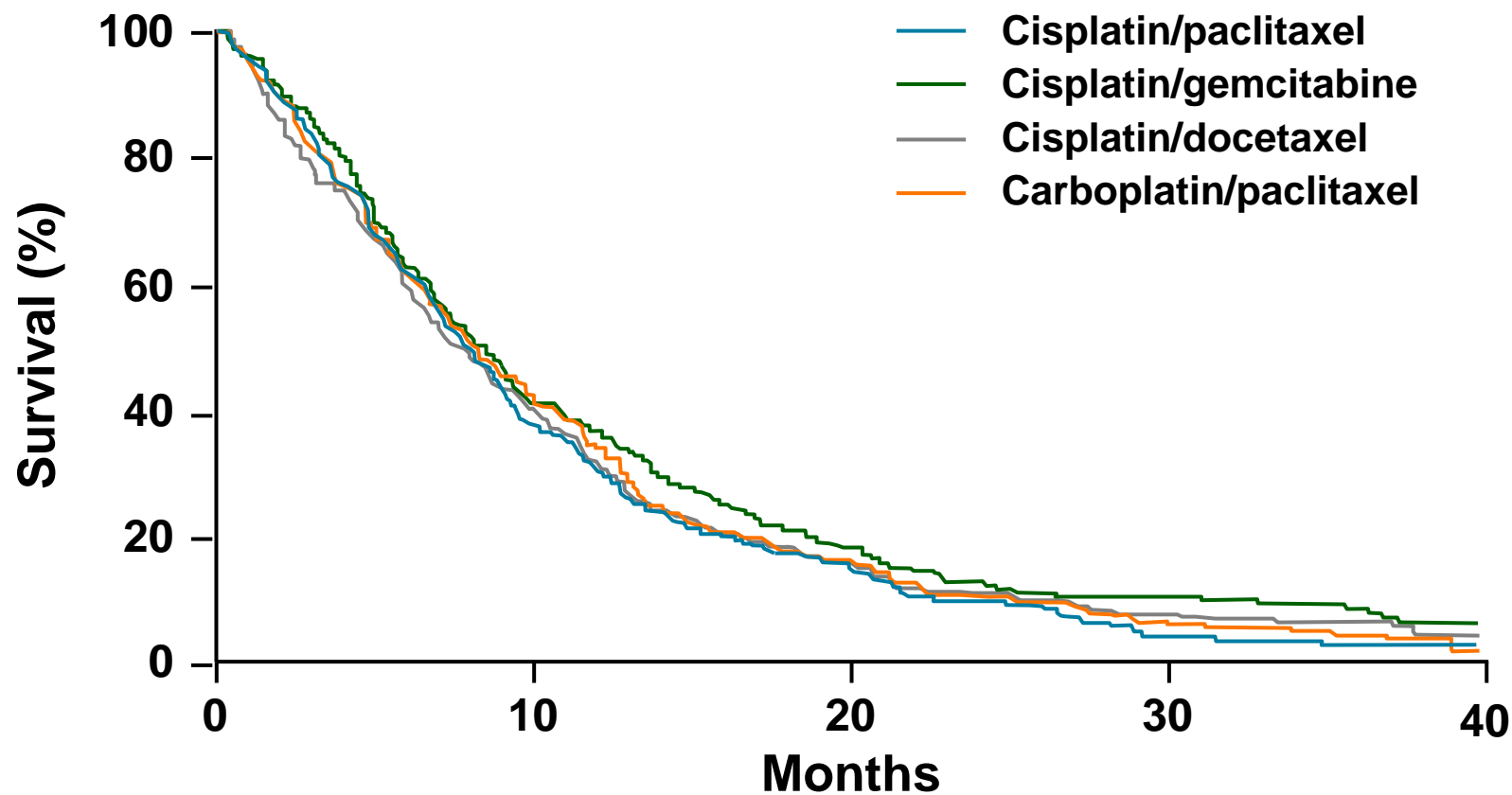
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# Breakdown by Histology

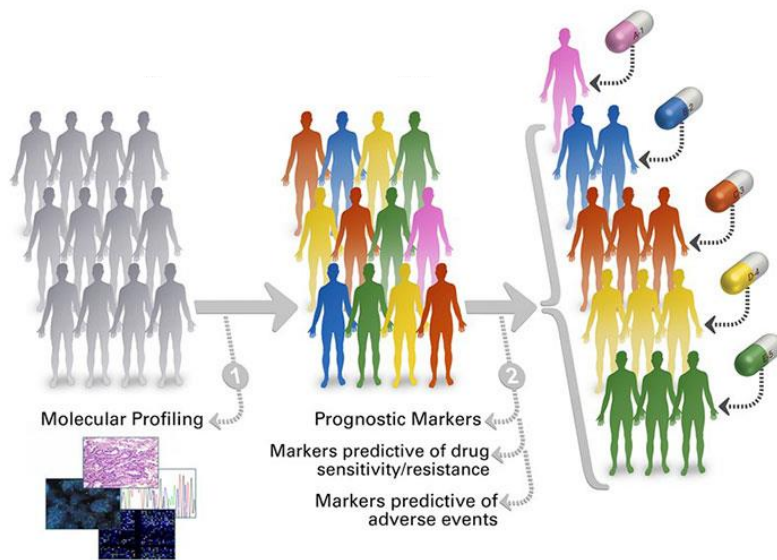


# Historical Paradigm: Platinum Doublet Chemo



# Care of Metastatic Lung Cancer Has Been Revolutionized by Two Types of Therapy in Recent Years

## Targeted Therapy



## Immunotherapy



Most patients who are eligible for approved first-line targeted therapies have minimal tobacco exposure.

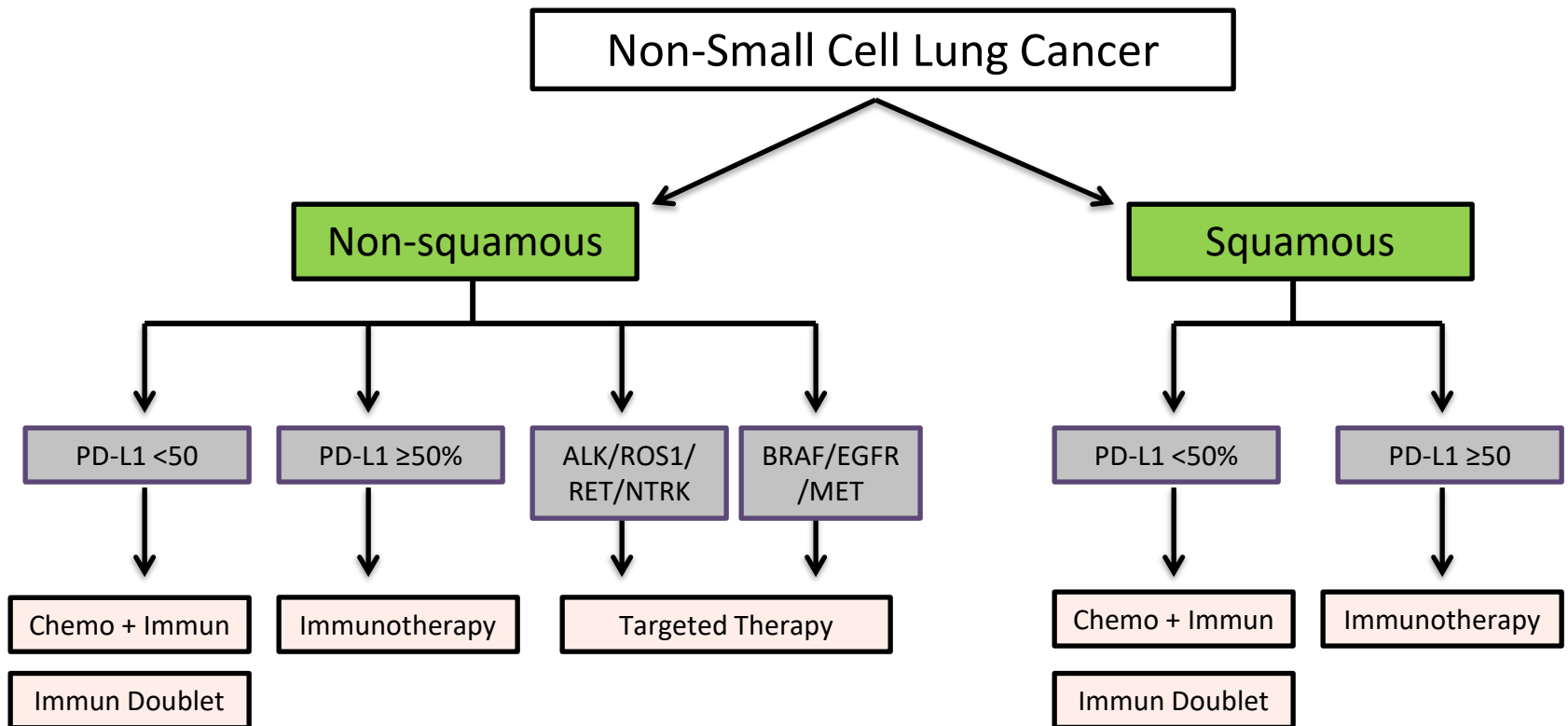


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# Shifting Paradigm for First-Line Treatment of NSCLC



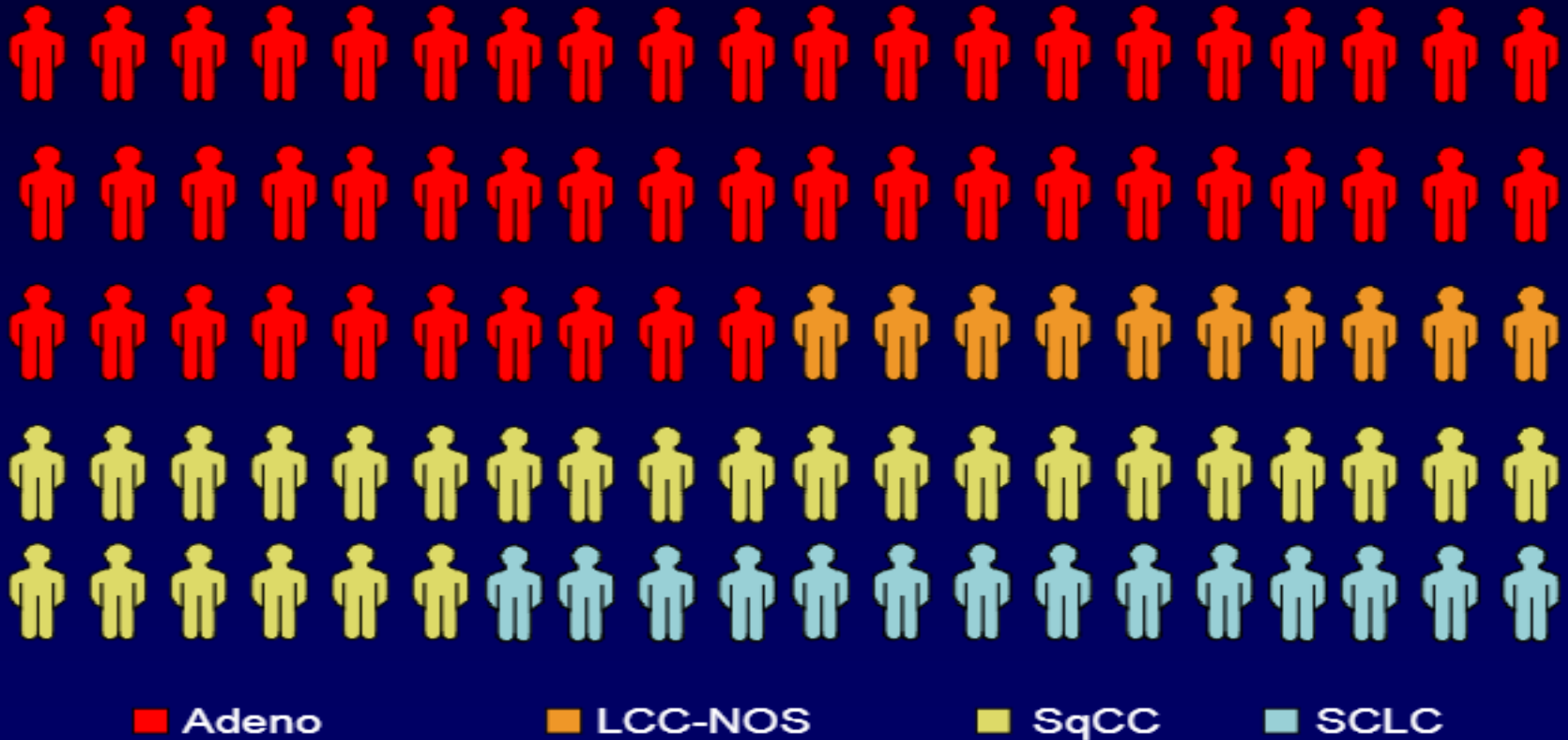
Immun= immunotherapy



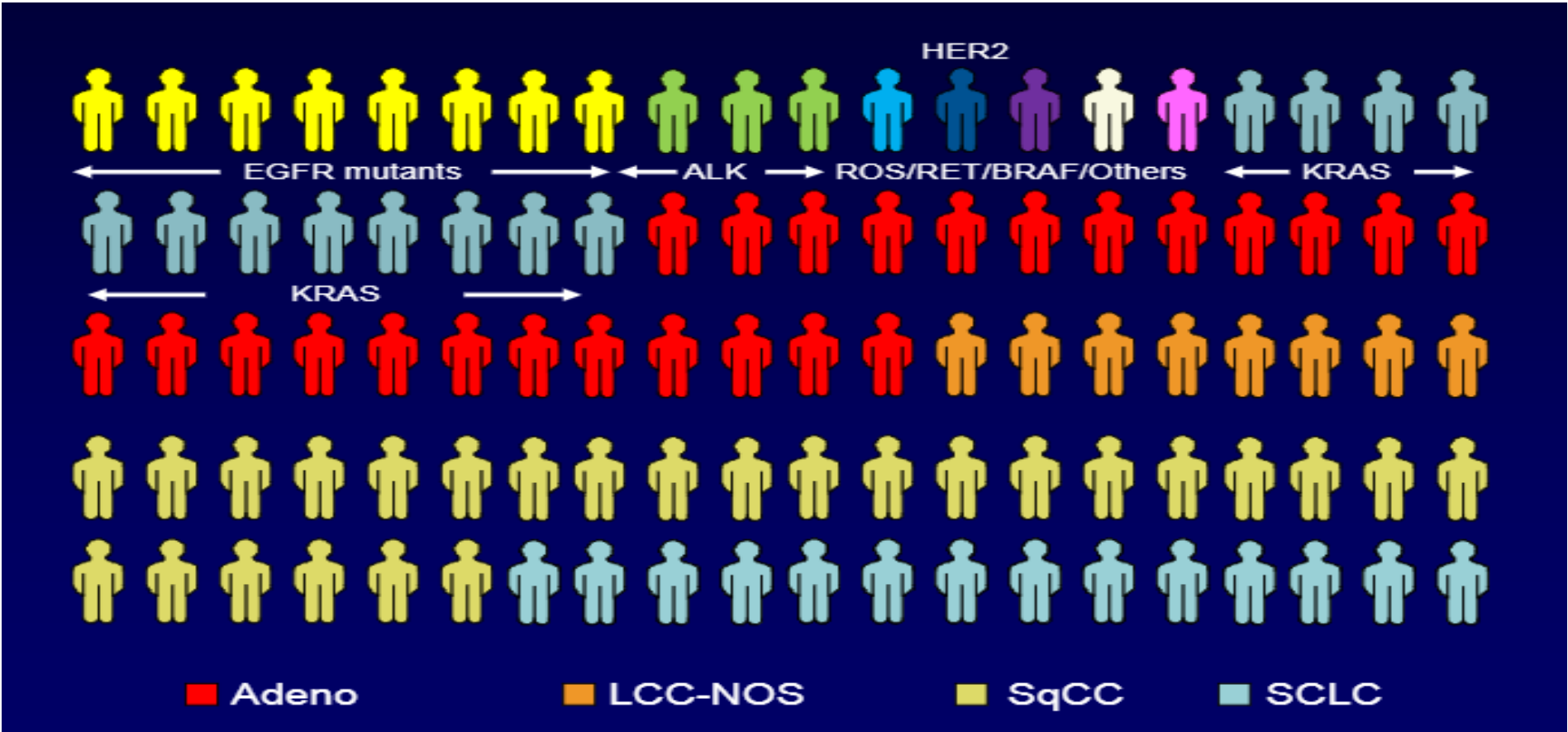
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# Improved Understanding of the Biology of Lung Cancer



# Improved Understanding of the Biology of Lung Cancer



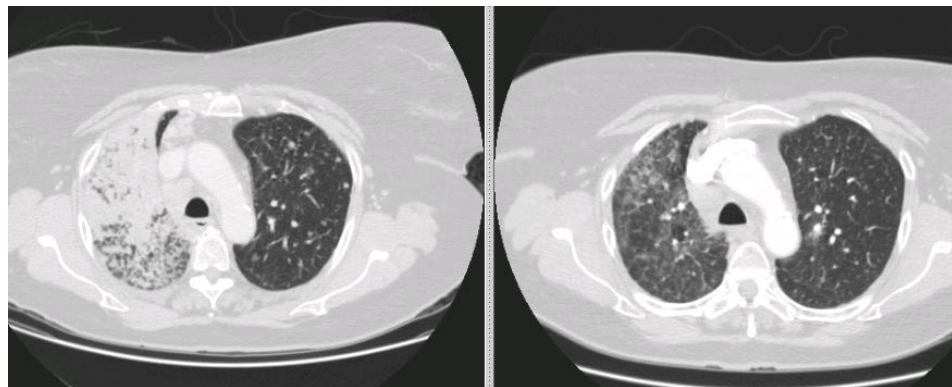
# FDA-Approved Targeted Therapies for Stage IV Lung Cancer

EGFR mutation	Erlotinib, Gefitinib, Afatinib, Dacomitinib, Osimertinib, Amivantamab (exon 20 insertion)
ALK rearrangement	Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib
ROS1 Fusion	Crizotinib, Entrectinib
BRAF V600E	Dabrafenib + Trametinib
MET exon 14 skipping	Capmatinib, Tepotinib
RET rearrangement	Selpercatinib, Pralsetinib

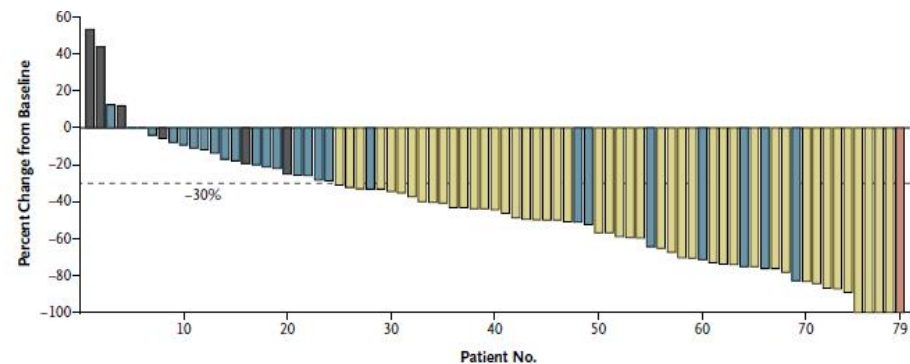
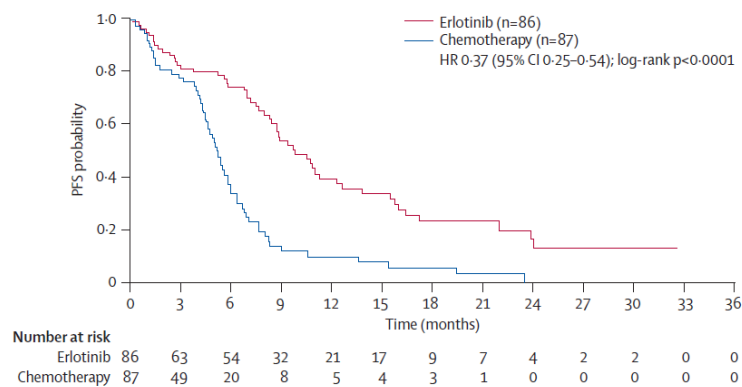
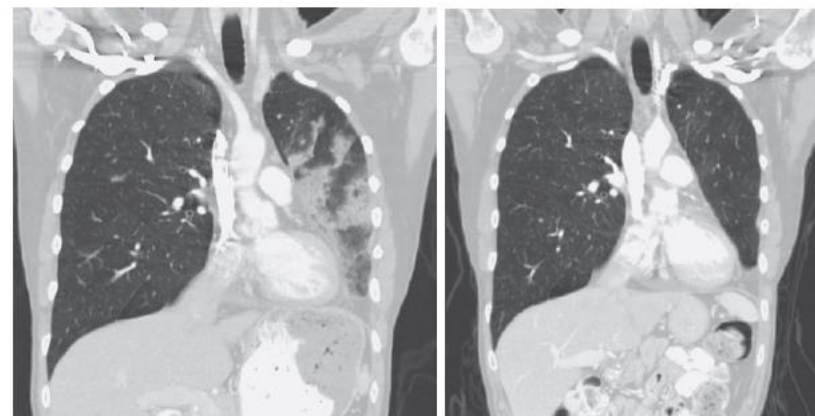


# Impact of Targeted Therapies in NSCLC

## EGFR-Mutant NSCLC



## ALK-Positive NSCLC

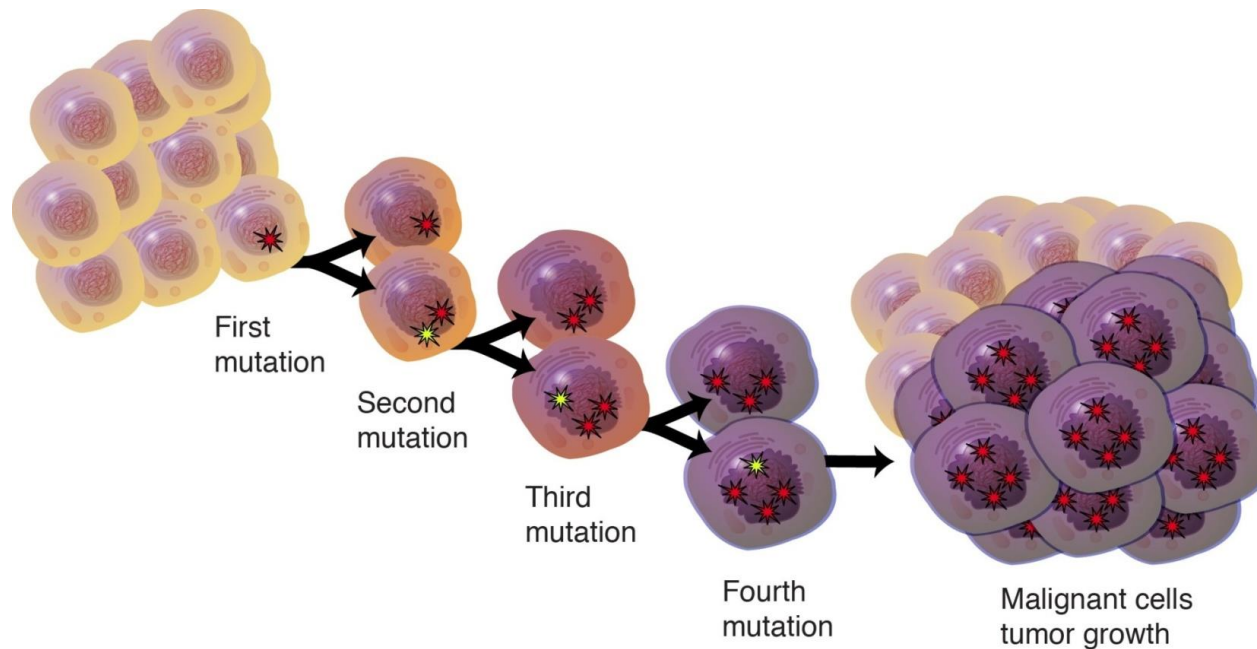


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# Central Premise of Immunotherapy

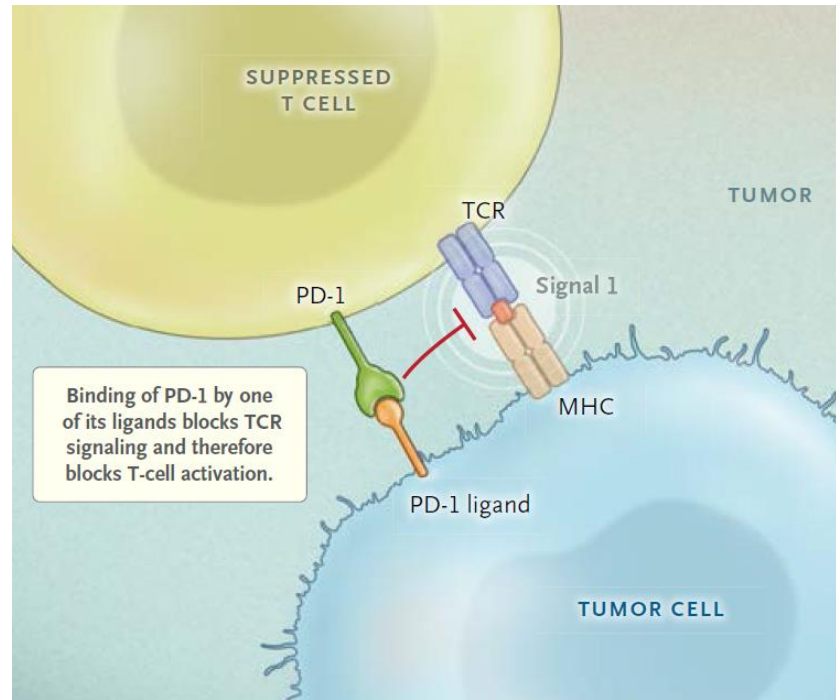
***Cancer cells possess genetic alterations that may generate neoantigens, which may be recognized by the immune system.***



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# Immune Checkpoints

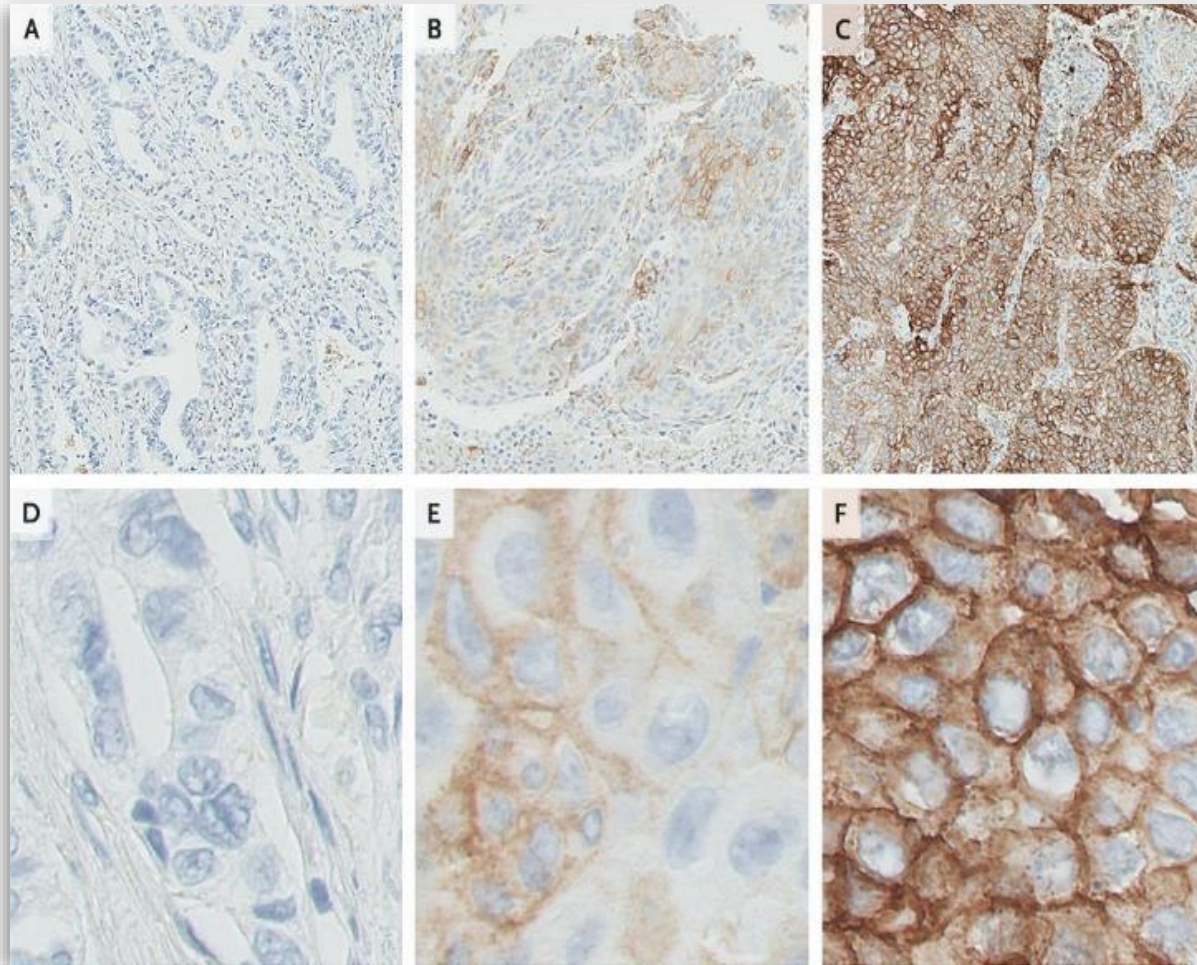


# PD-L1 Testing is Mandatory for all Metastatic NSCLCs

Proportion score < 1%

1 - 49%

> 50%



PD-L1 immunohistochemistry is an important component of management of stage 4 NSCLC



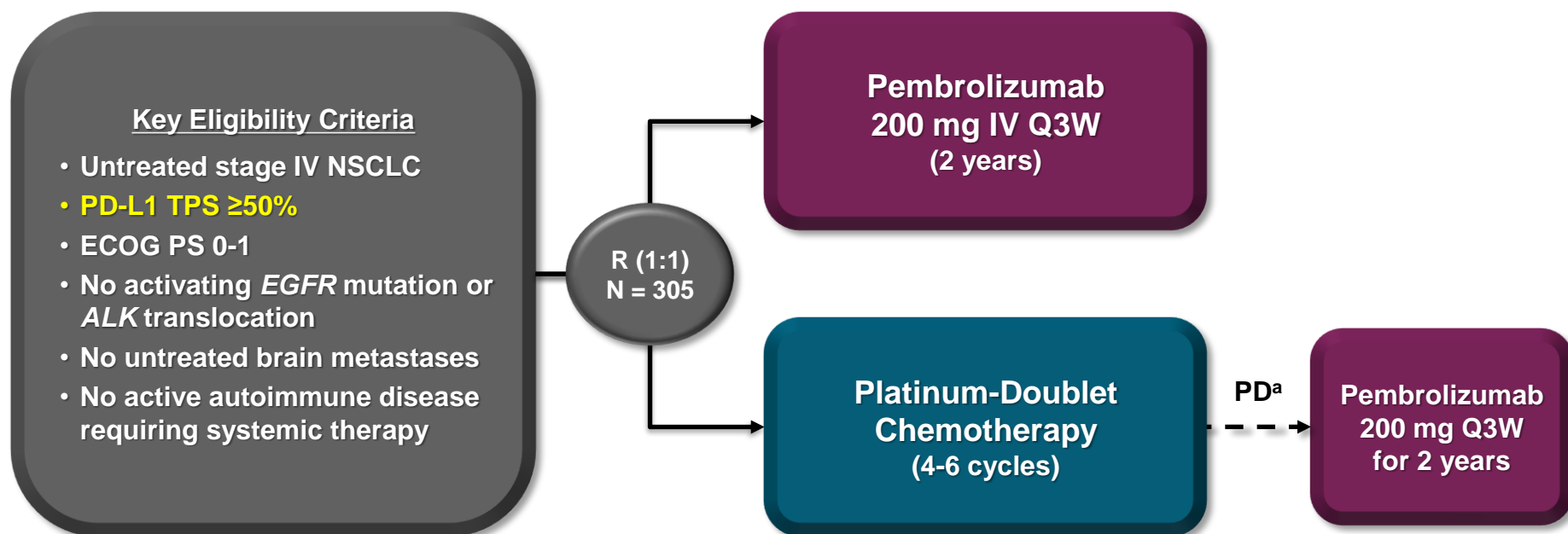
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# Immunotherapy in the First-Line Setting

## KEYNOTE-024 Study Design (NCT02142738)



### Key End Points

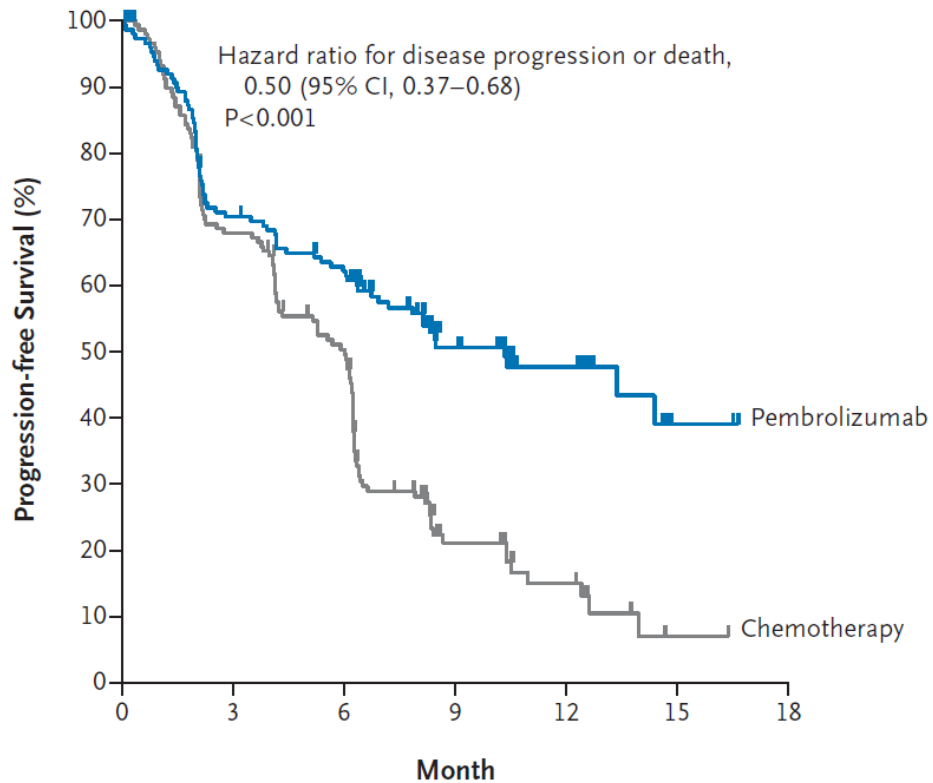
Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

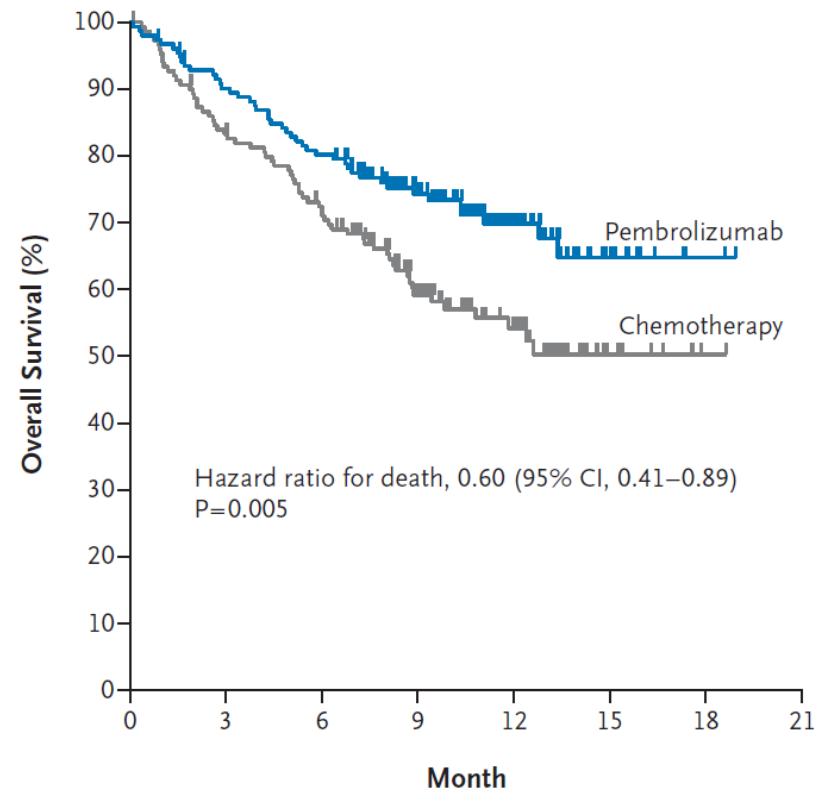
Exploratory: DOR

# Immunotherapy Alone in the First-Line Setting: PD-L1 High

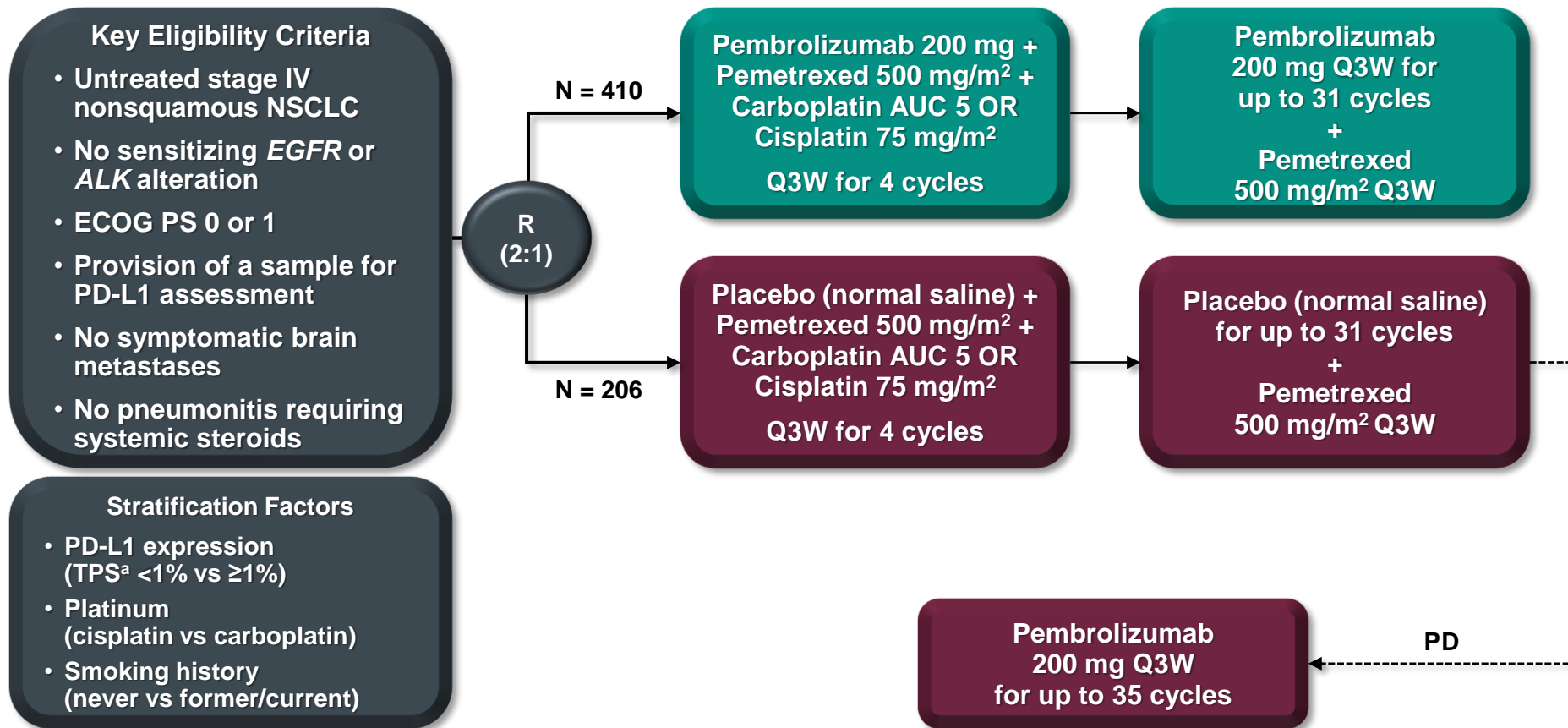
## Progression-Free Survival



## Overall Survival



# Immunotherapy + Chemo in the First-Line Setting: All-Comers

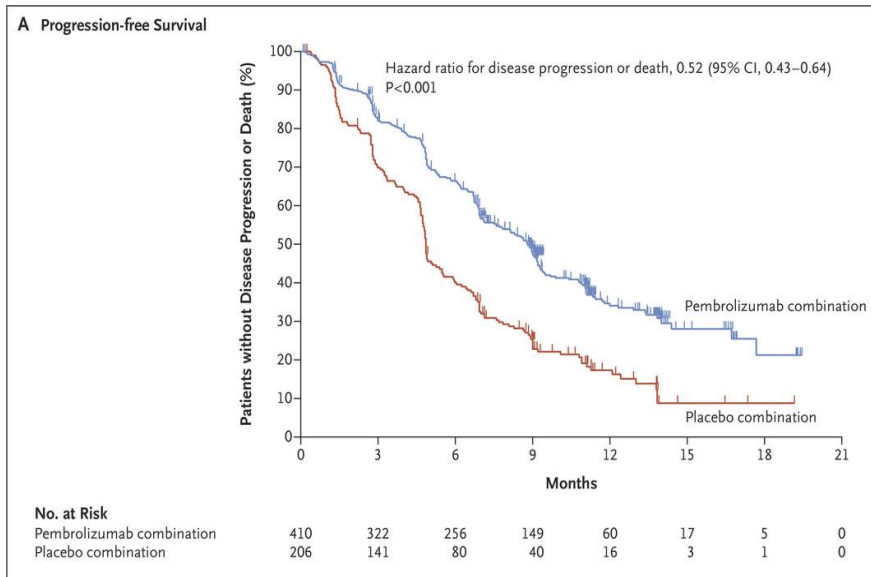


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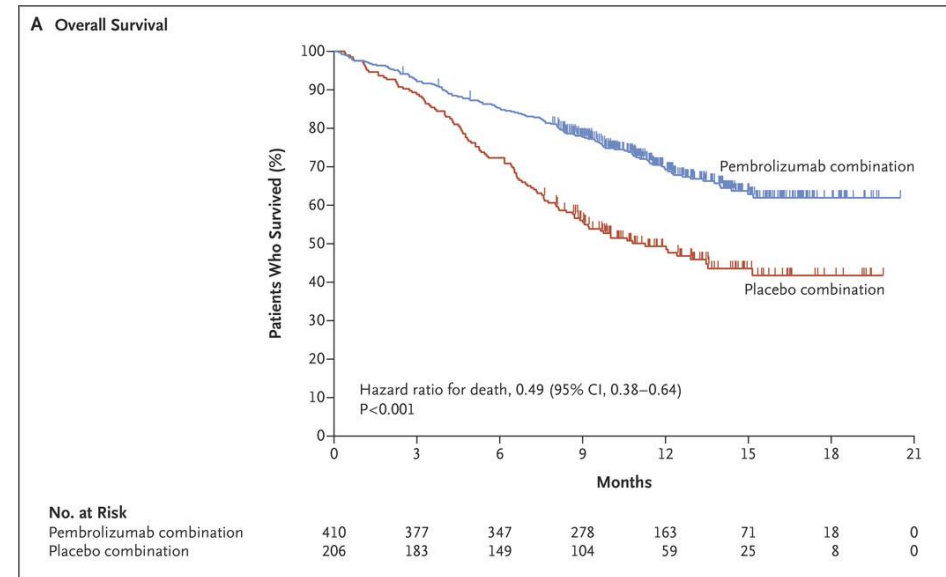
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# Chemotherapy + Immunotherapy in the First-Line Setting

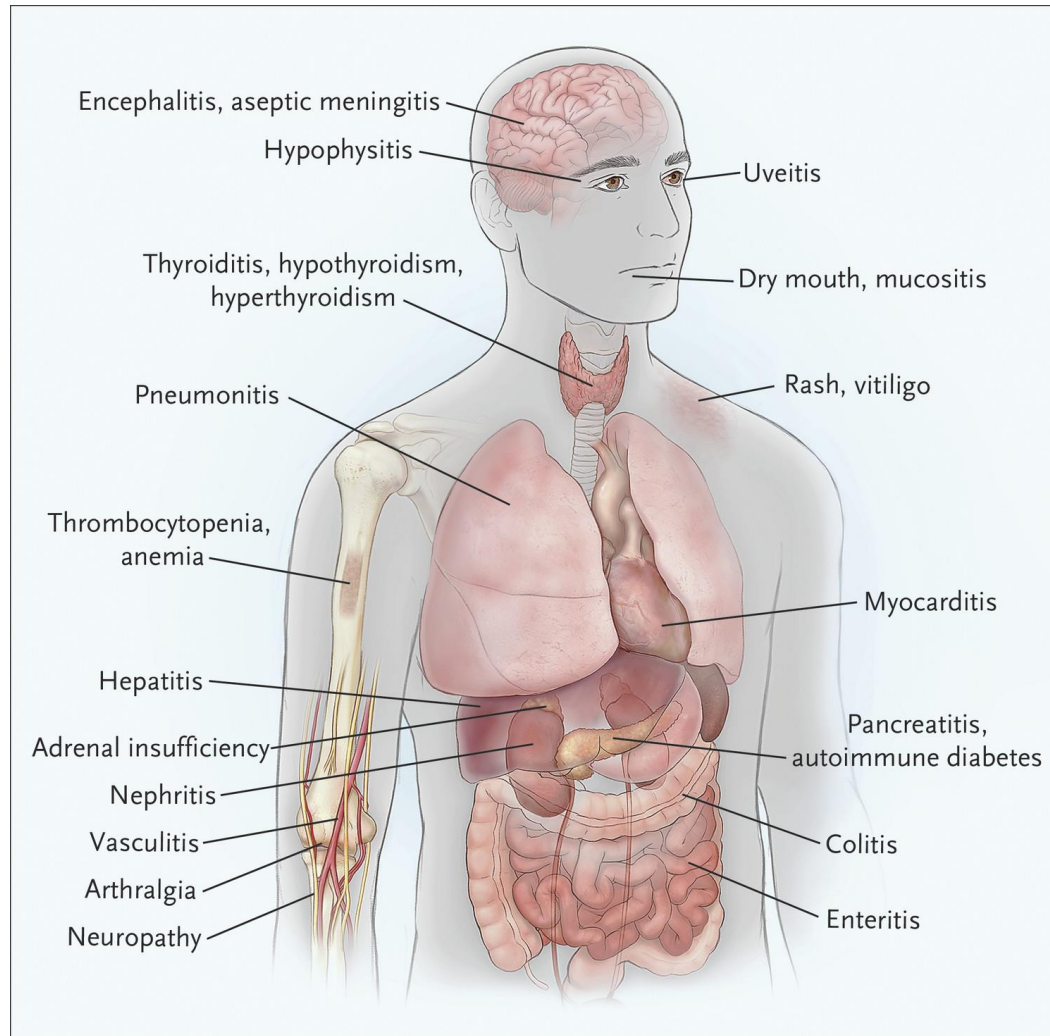
## Progression-Free Survival



## Overall Survival



# Immune-Mediated Toxicities



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# Metastatic NSCLC Prognosis

	No Chemo	Platinum Doublet	<b>EGFR-</b> Mutant on TKI	<b>ALK-</b> rearranged on TKI	<b>PDL1-high</b> 1 <sup>st</sup> line pembrolizumab
Median Survival (months)	6 mo	~1 year	>3 years	> 5 years	26 months 32% alive at 5 yrs
1-year (%)	10%	40%	80 + %	80 + %	70%
ORR	0%	25-30%	70+%	70+%	>45%

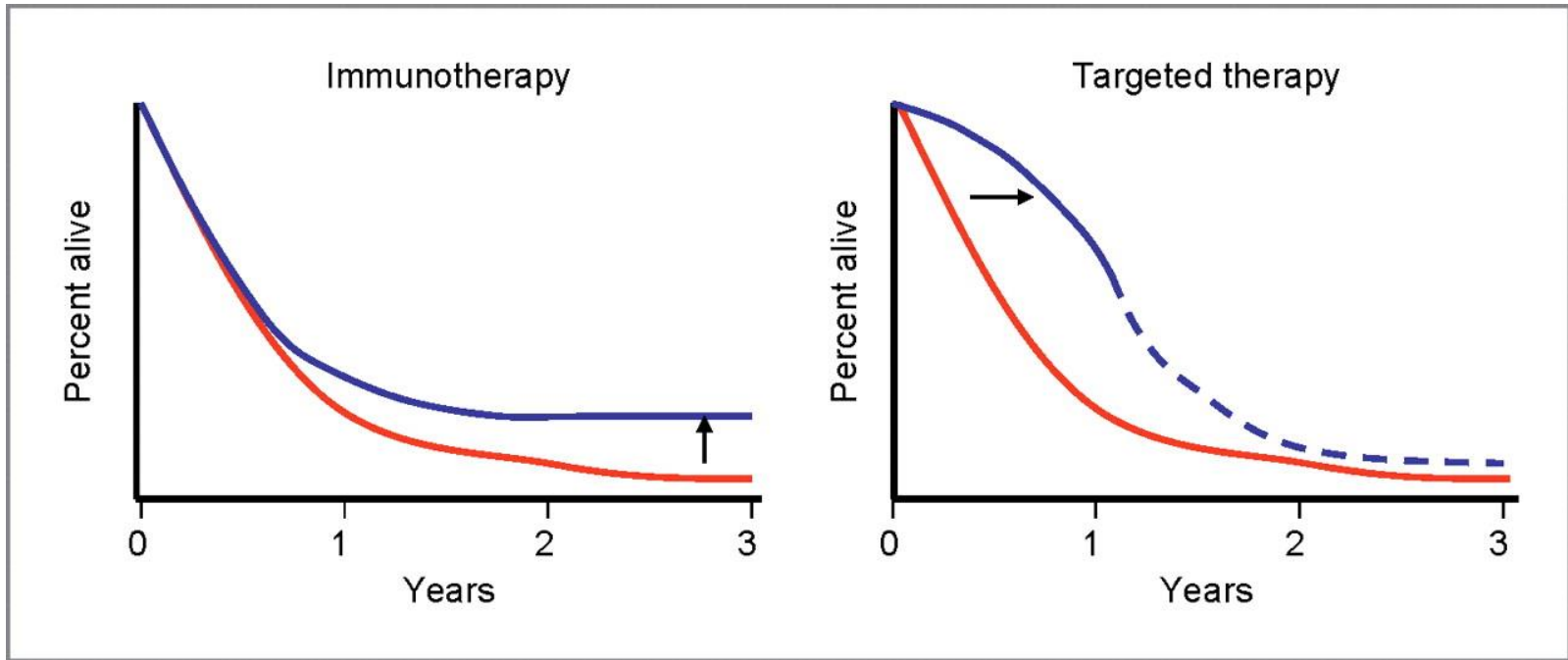
NSCLC Meta-Analyses. *JCO*. 2008;26:4617-4625; Scagliotti GV. *JCO*. 2008;26:3543-3551; Mok TS et al. *NEJM*. 2009;361:947-957; Mok TS et al. *NEJM*. 2017;376(7):629-640; Shaw AT. *Lancet Onc*. 2012;12:1004-1012; Shaw AT. *Lancet Onc*. 2016 Feb; 17(2): 234–242; Reck M. *JCO*.2021.



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# NSCLC Prognosis: The Tail of the Curve



# Paul, a 60-something year old with metastatic NSCLC

- Diagnosed with metastatic NSCLC with brain metastases and pericardial tamponade in 2014
- 2014: Received his first targeted therapy
- 2015: Received his second targeted therapy
- 2016: Started his third targeted therapy
- 2022: He continues to respond to his third targeted therapy
- Since I've known him, he has welcomed three grandchildren.



# Peggy, a 70 something year old with metastatic NSCLC

- Peggy has been on dialysis for several years
- 2017: Diagnosed with NSCLC metastatic to the brain
- She underwent resection of the brain metastasis and subsequently received radiation
- 2017: She started treatment with pembrolizumab
- 2019: She had a complete response to treatment. Pembrolizumab discontinued after 2 years. She is now on surveillance without evidence of recurrence.
- It is possible that Peggy may not need more treatment for her metastatic NSCLC

# Summary

- Lung cancer is a prevalent and often fatal disease.
- Lung screening is essential for reducing mortality from lung cancer.
- There are alternatives to surgery for patients with localized lung cancer who have extensive comorbidities.
- Most patients receive 3-36 months of additional therapy after surgery (e.g., chemo, targeted therapy, immuno).
- Novel targeted therapies are improving the survival of patients with metastatic NSCLC, but these therapies are not available for all.
- Immunotherapies have transformed the management of NSCLC and are now the backbone of first-line therapy.



Questions?