

# MEDIZINISCHE ONKOLOGIE:

## Lungen Krebs

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ESMO Faculty Immunooncology

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ESO Chair Lung Program

# Outline

## Introduction to cancer and lung cancer

## Development of targeted treatments for lung cancer

- Introduction
- Results
- Challenges

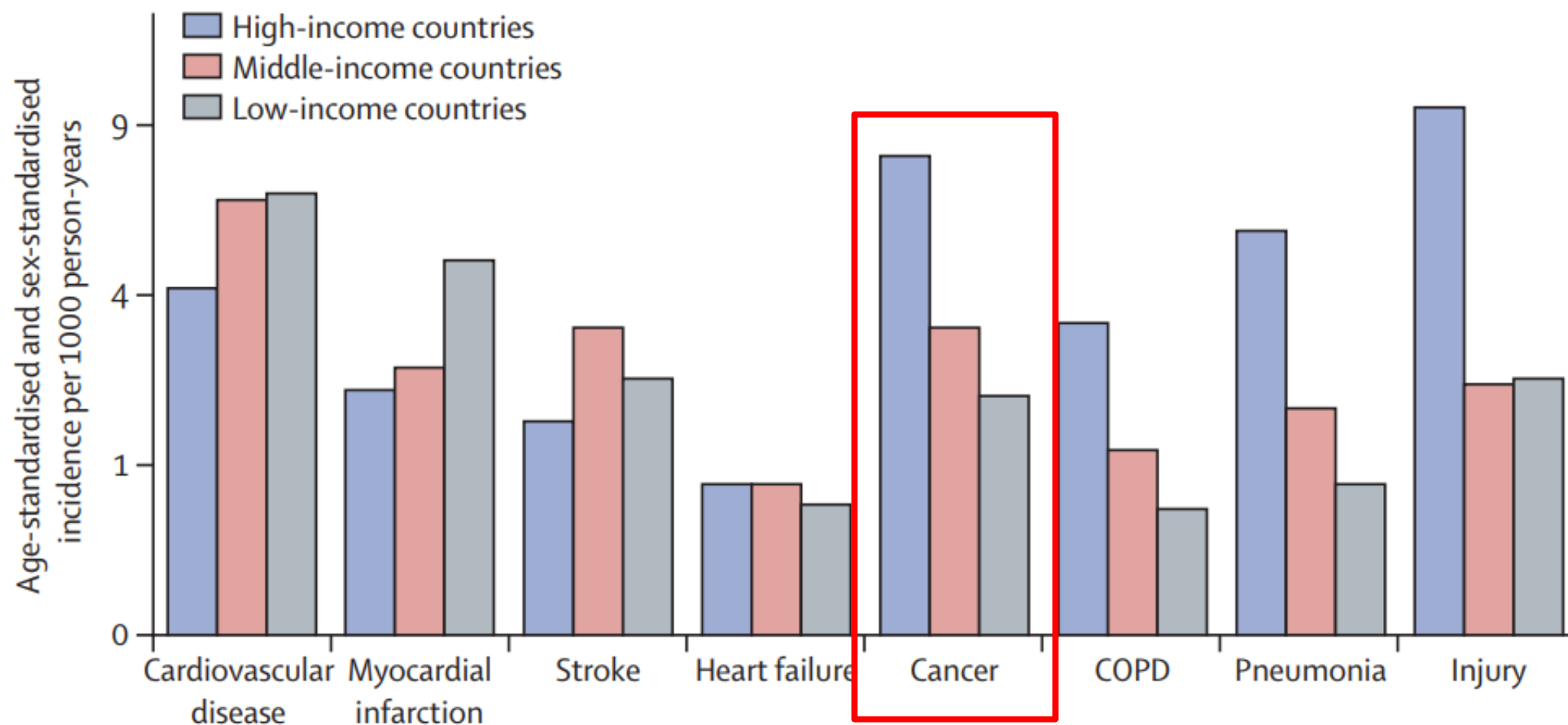
# Outline

## Introduction to cancer and lung cancer

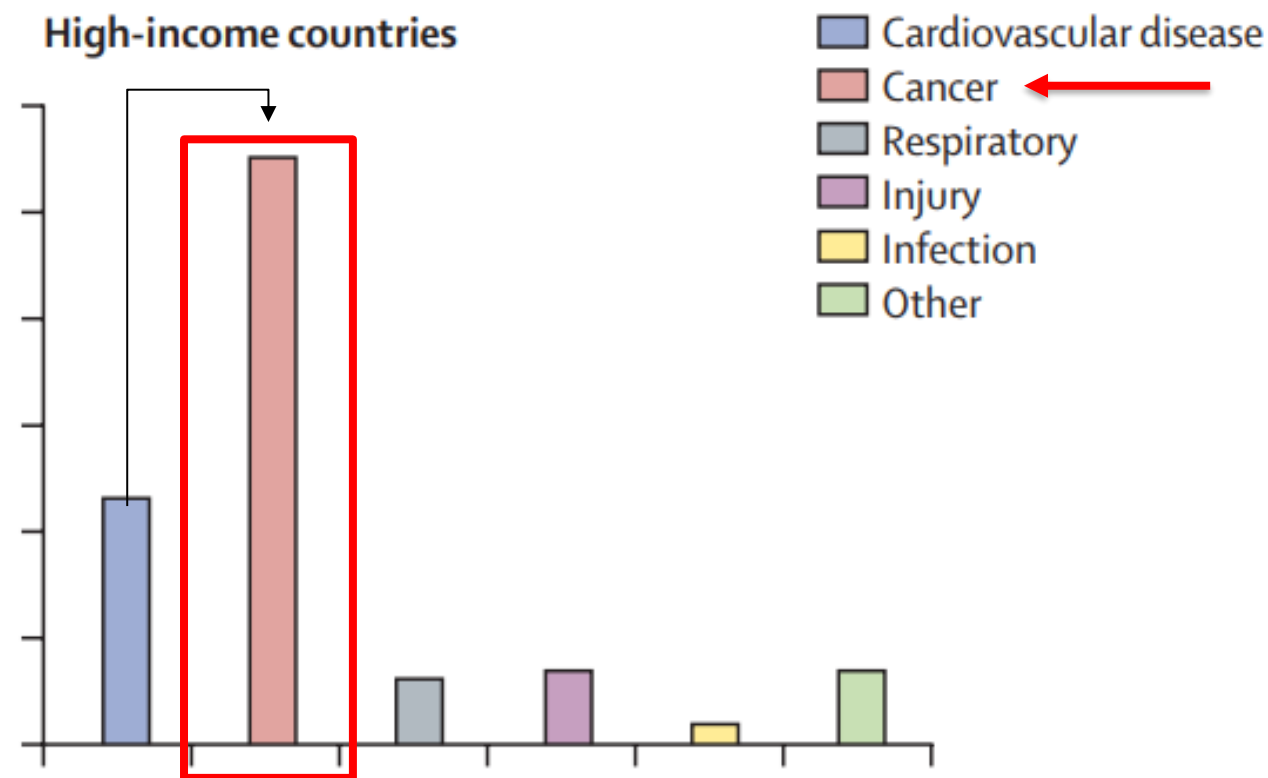
### Development of targeted treatments for lung cancer

- Introduction
- Results
- Challenges

# Cancer **incidence** is higher in high-income countries



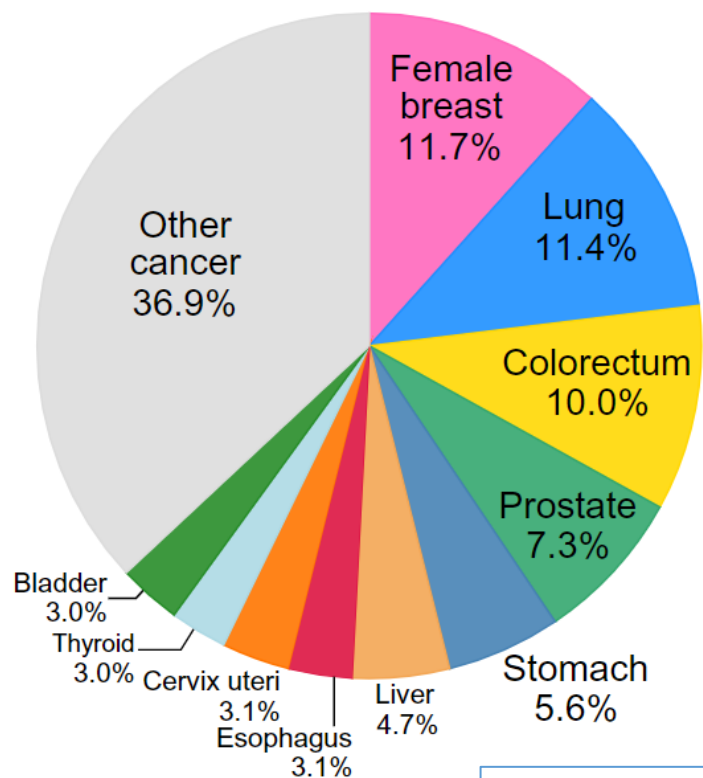
# Cancer causes twice as many **deaths** as cardiovascular disease in high-income countries



G R Degenais The Lancet 2020

**All cancers:**  
19.3 Million  
new cases

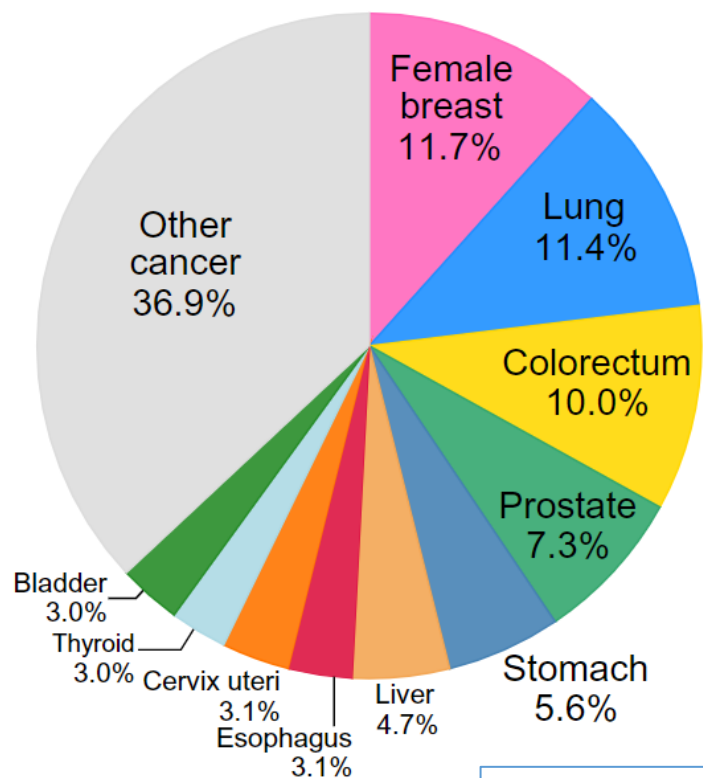
## INCIDENCE



**Lung Cancer, 2020**  
2.1 million new cases/year  
1.8 million deaths/year

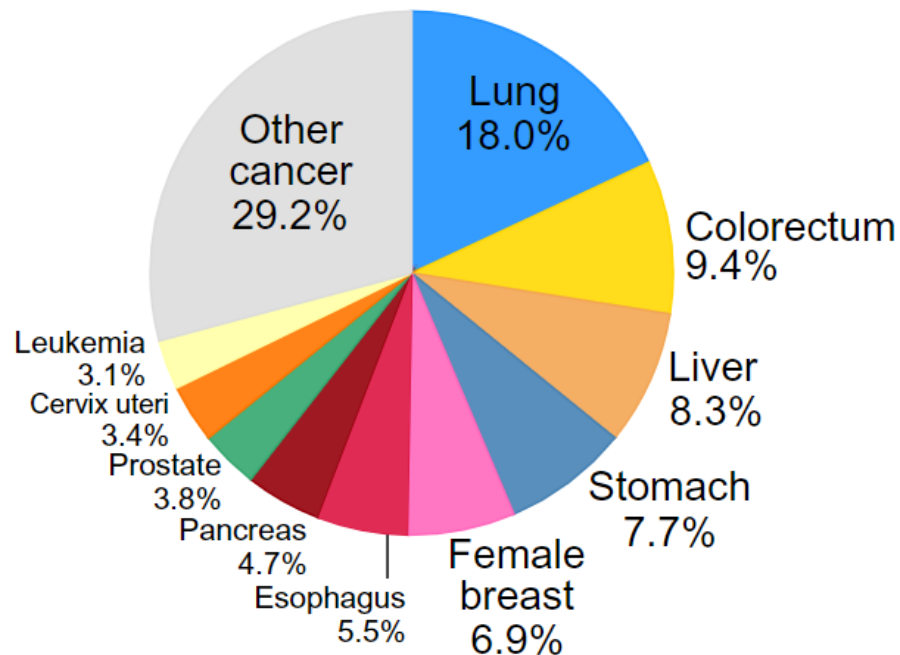
**All cancers:**  
19.3 Million  
new cases

## INCIDENCE



## MORTALITY

**All cancers:**  
9.9 Million  
deaths



**Lung Cancer, 2020**  
2.1 million new cases/year  
1.8 million deaths/year

## All cancers (2022)

Number of new cases

**4 471 422**

Number of deaths

**1 986 093**

Global Cancer Observatory, European Network of Cancer Registries, European Cancer Information System



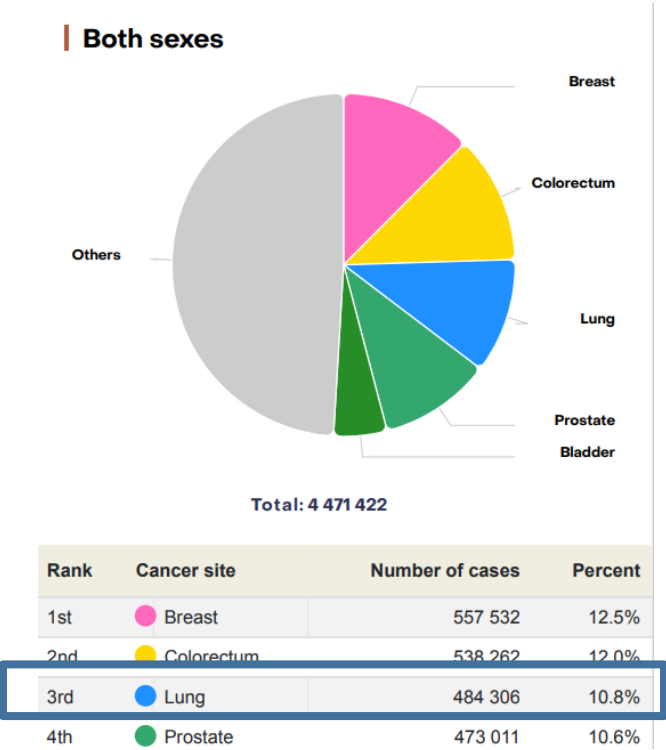
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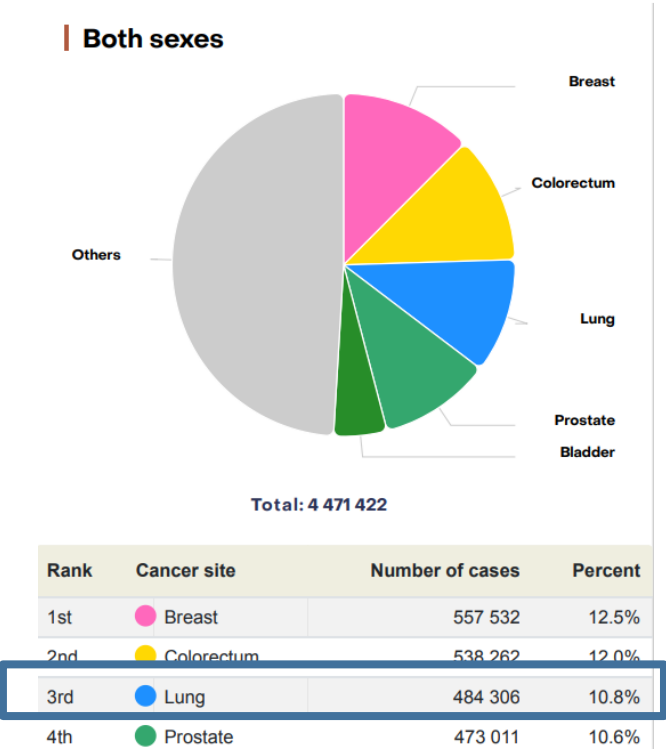
All cancers (2022)

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4 471 422

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Cancer	New cases			Deaths		
	Number	Rank	(%)	Number	Rank	(%)
Breast	557 532	1	12.5	144 439	3	7.3
Colorectum	538 262	2	12.0	247 842	2	12.5
Lung	484 306	3	10.8	375 569	1	18.9

Global Cancer Observatory, European Network of Cancer Registries, European Cancer Information System

All cancers (2022)

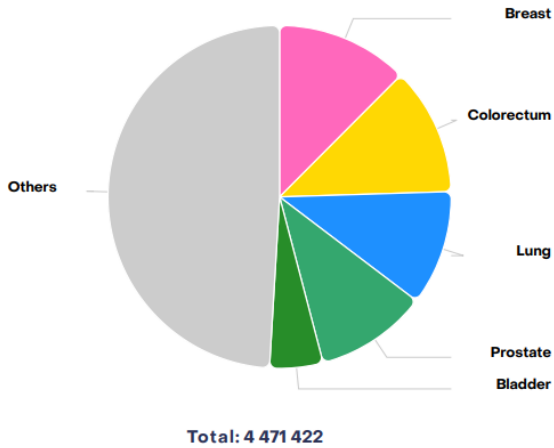
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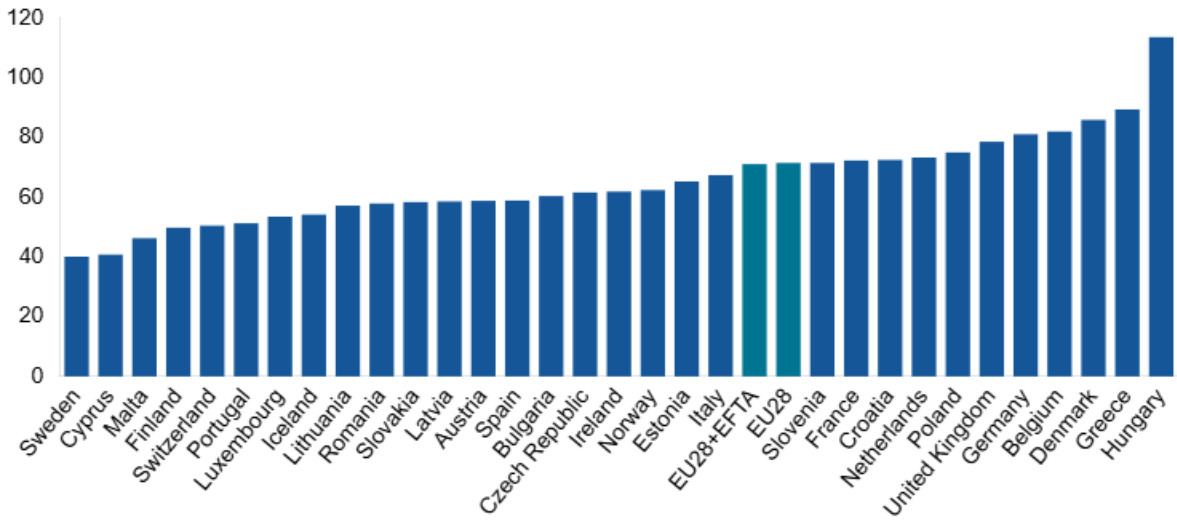
Both sexes



Rank	Cancer site	Number of cases	Percent
1st	Breast	557 532	12.5%
2nd	Colorectum	538 262	12.0%
3rd	Lung	484 306	10.8%
4th	Prostate	473 011	10.6%

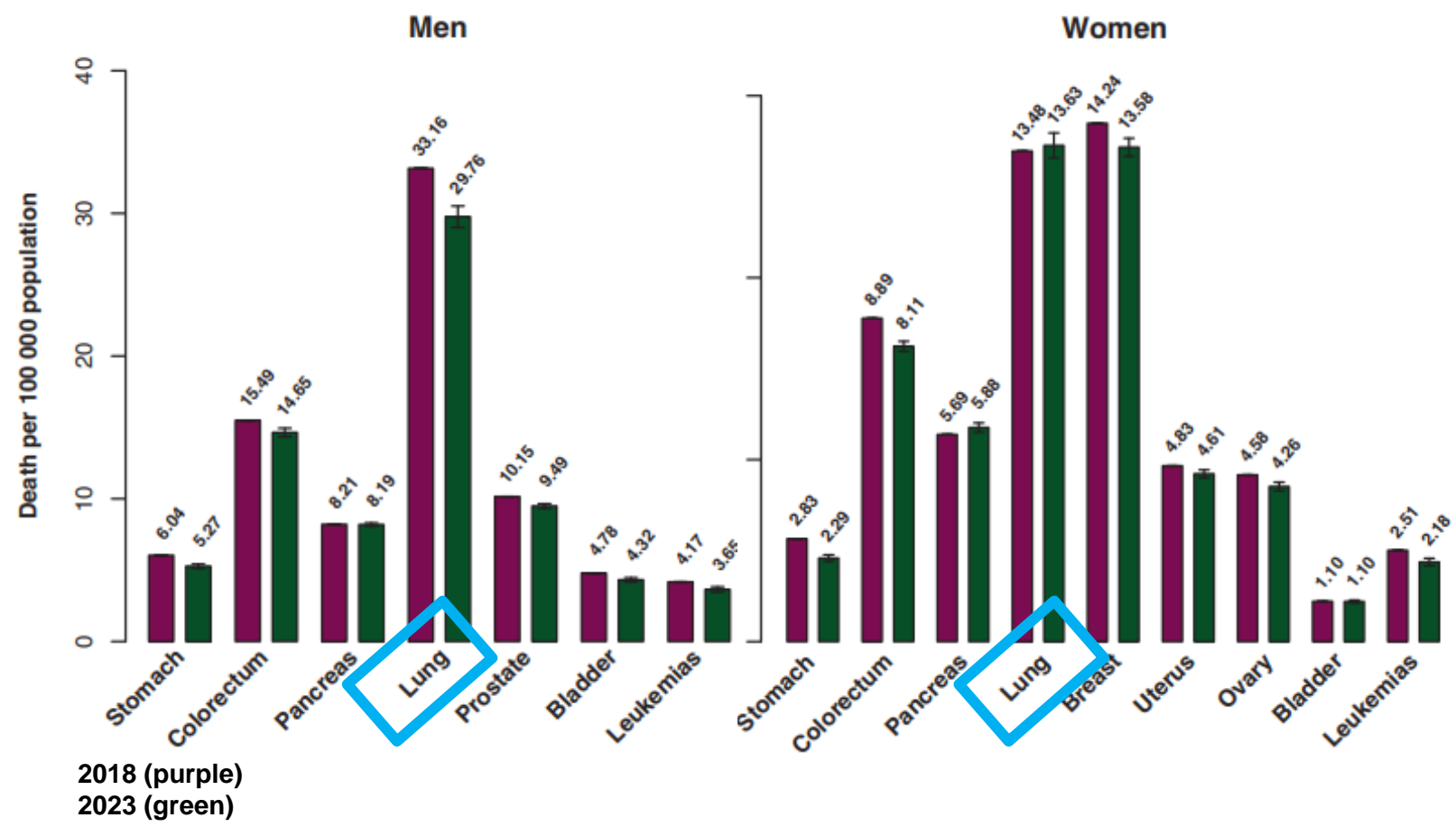
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Lung cancer incidence (crude rate per 100,000) 2018



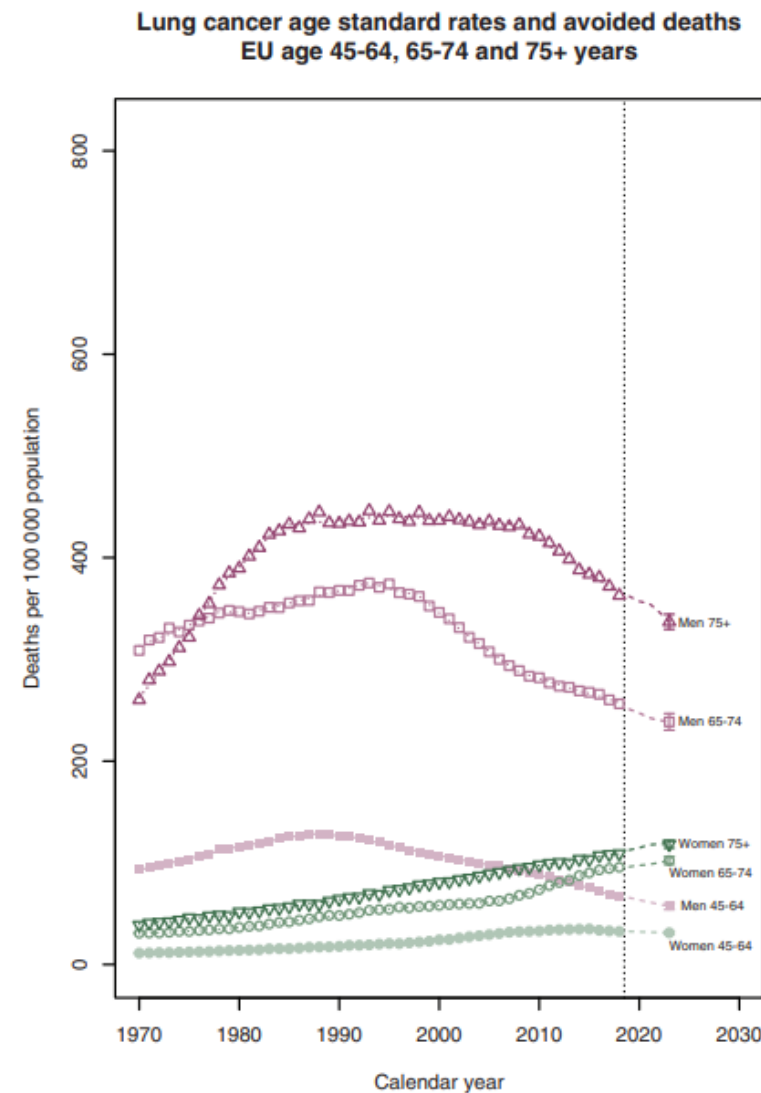
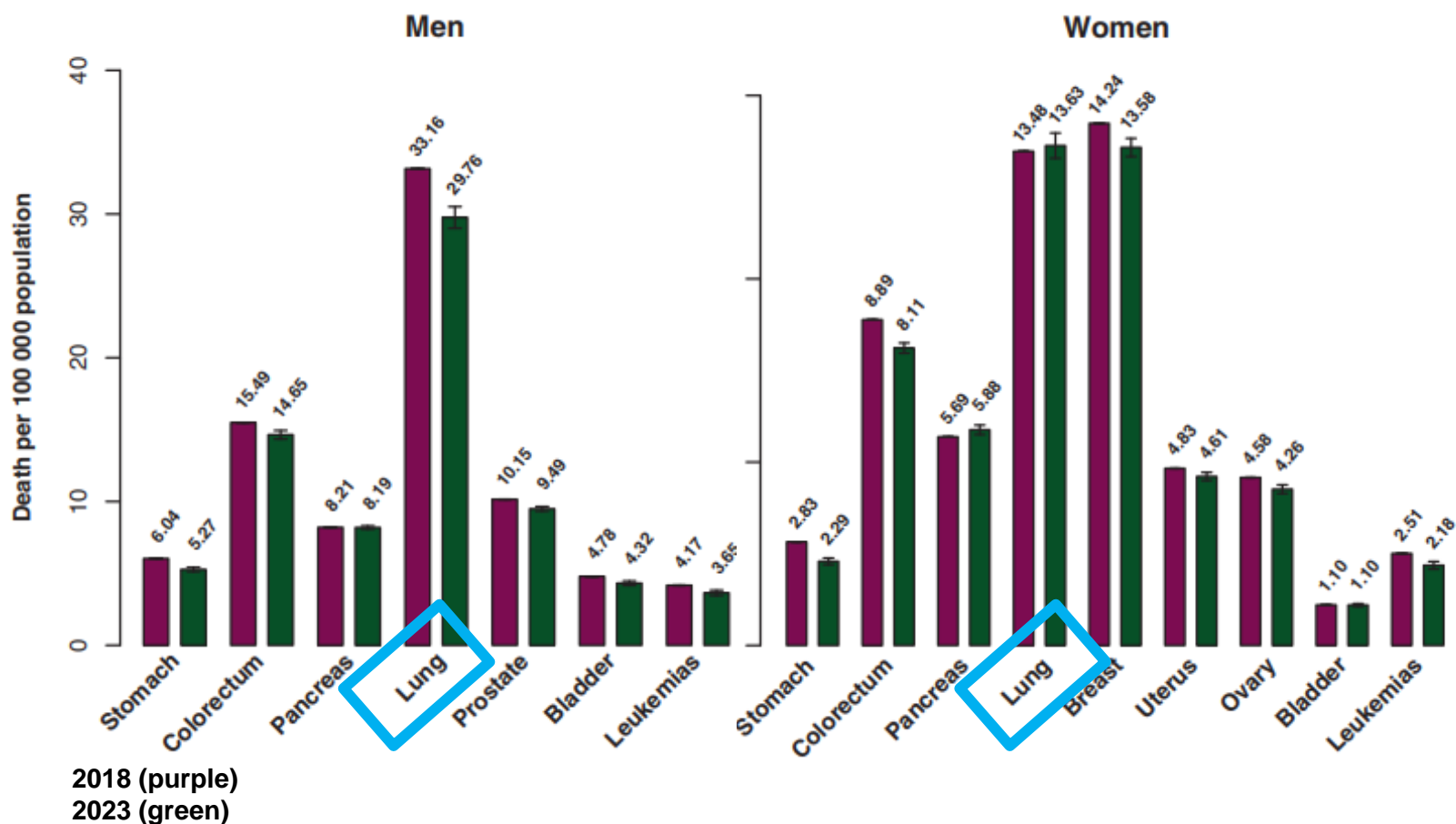
Global Cancer Observatory, European Network of Cancer Registries, European Cancer Information System

# Epidemiology Europe: Lung Cancer Deaths



M. Malvezzi , Annals of Oncology 2023

# Epidemiology Europe: Lung Cancer Deaths

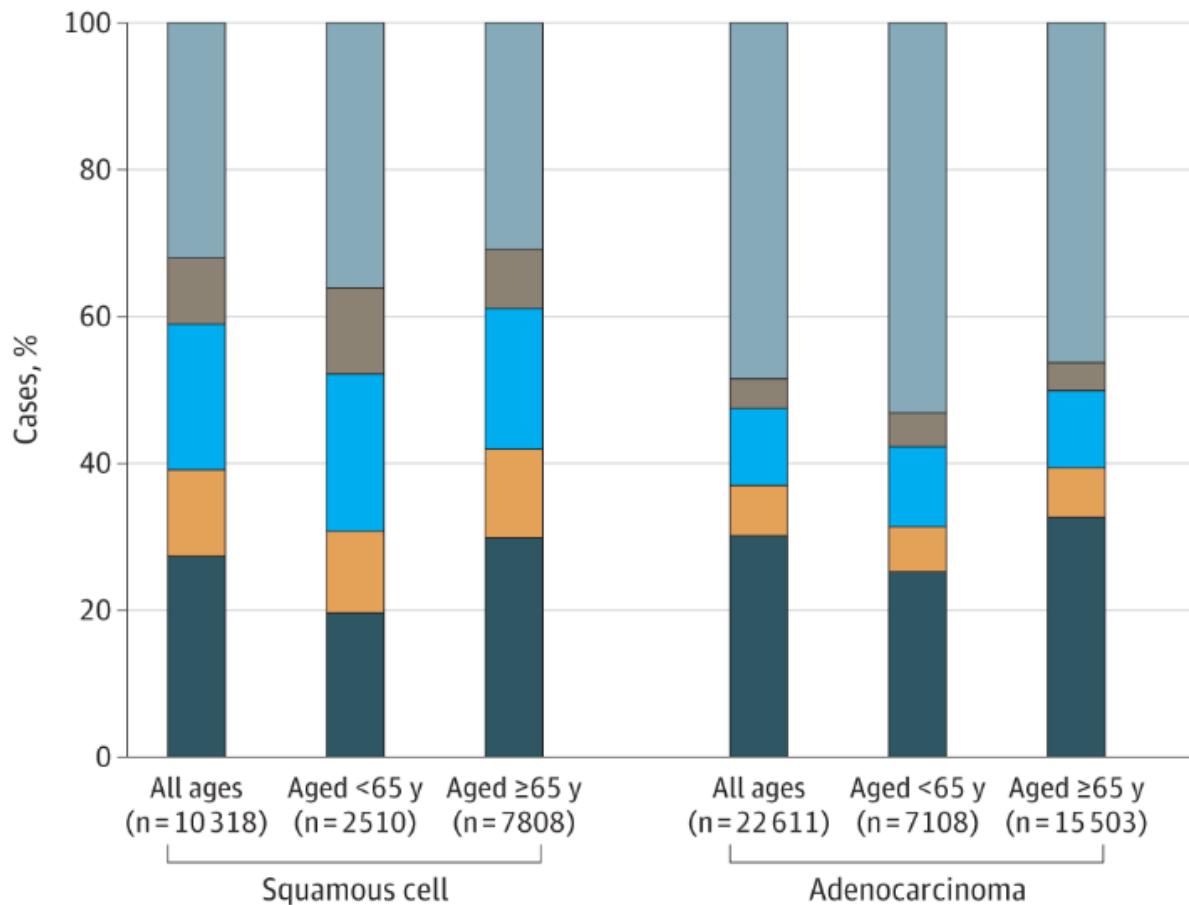


M. Malvezzi , Annals of Oncology 2023

# NSCLC: Stage distribution at diagnosis

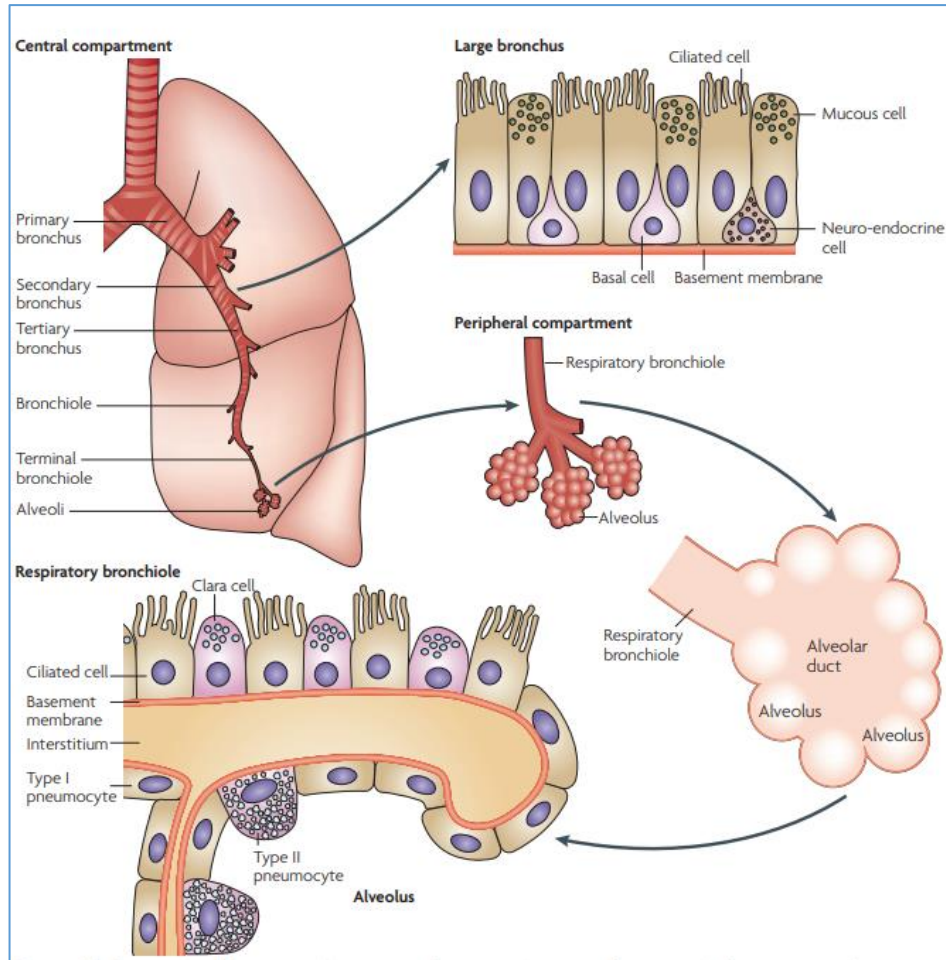


C NSCLC stage by histologic findings, overall and by age (SEER-18, 2017)



A.K. Ganti, JAMA Oncology 2021

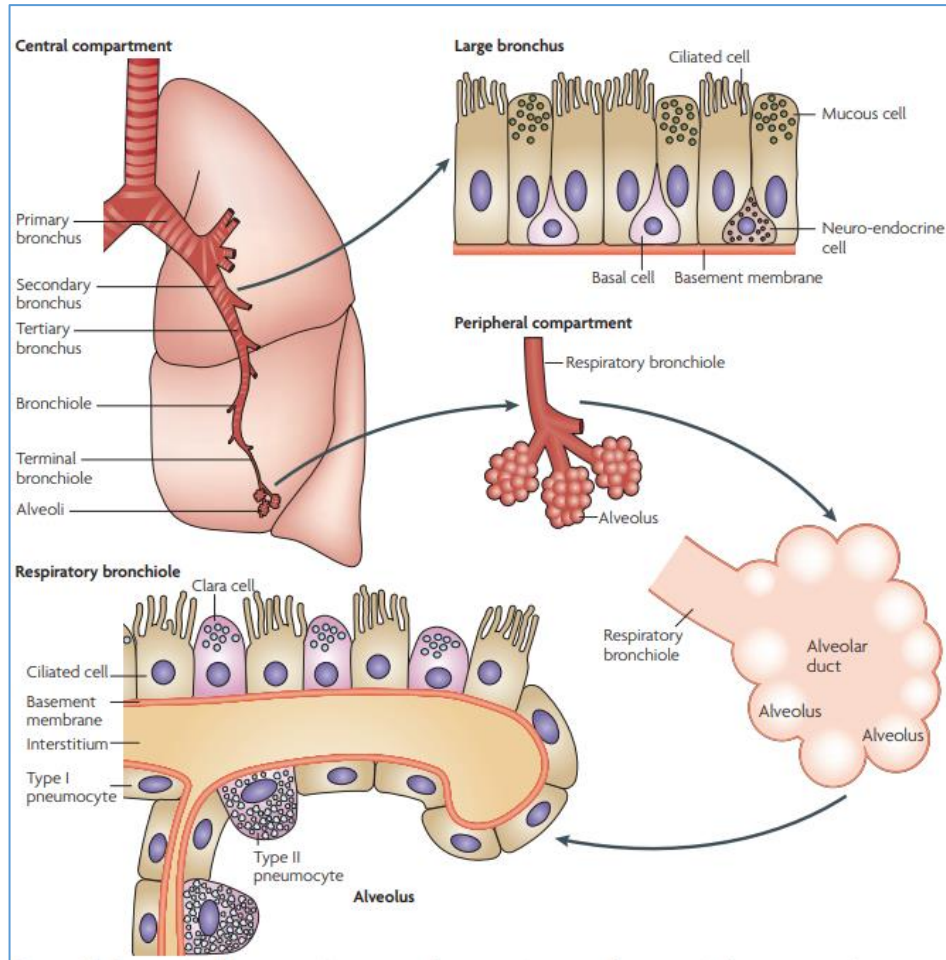
## Lung Cancer: Histological subtypes



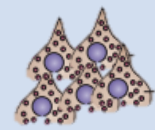
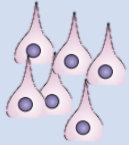
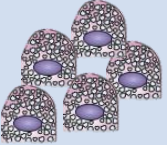
S. Sun Nature Rev 2007



## Lung Cancer: Histological subtypes



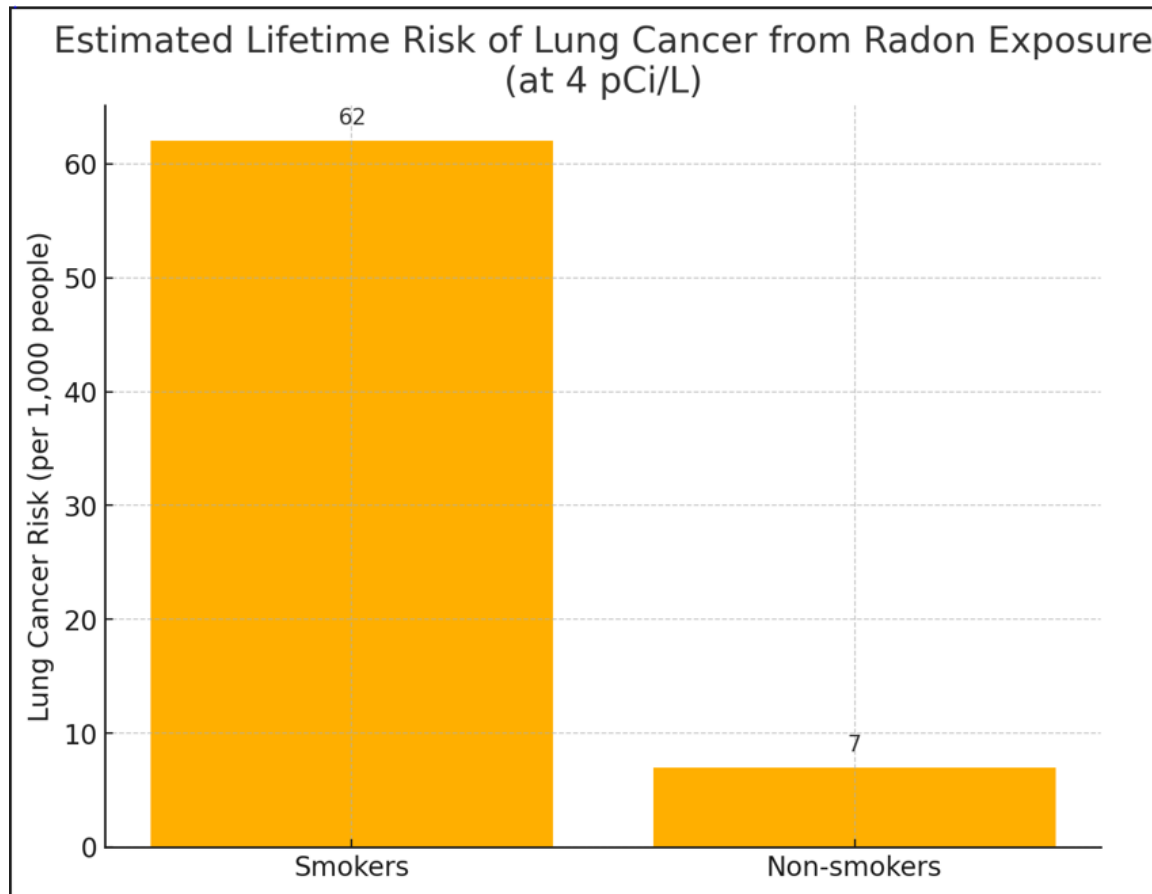
S. Sun Nature Rev 2007

Feature	Small-Cell Lung Cancer	Squamous carcinoma	Adenocarcinoma
Prevalence	15% of all Lung cancers	20% (decreasing) of NSCLC	75% (increasing) of NSCLC
Sex	More prevalent in men	More prevalent in men	The most frequent in women
Location	Central	Central	Peripheral and multifocal
Risk factors	>95% smokers	>90% smokers	25% non- smokers
Cell of Origin	Neuroendocrine cells 	Basal cells 	Alveolar Type 2 cells 

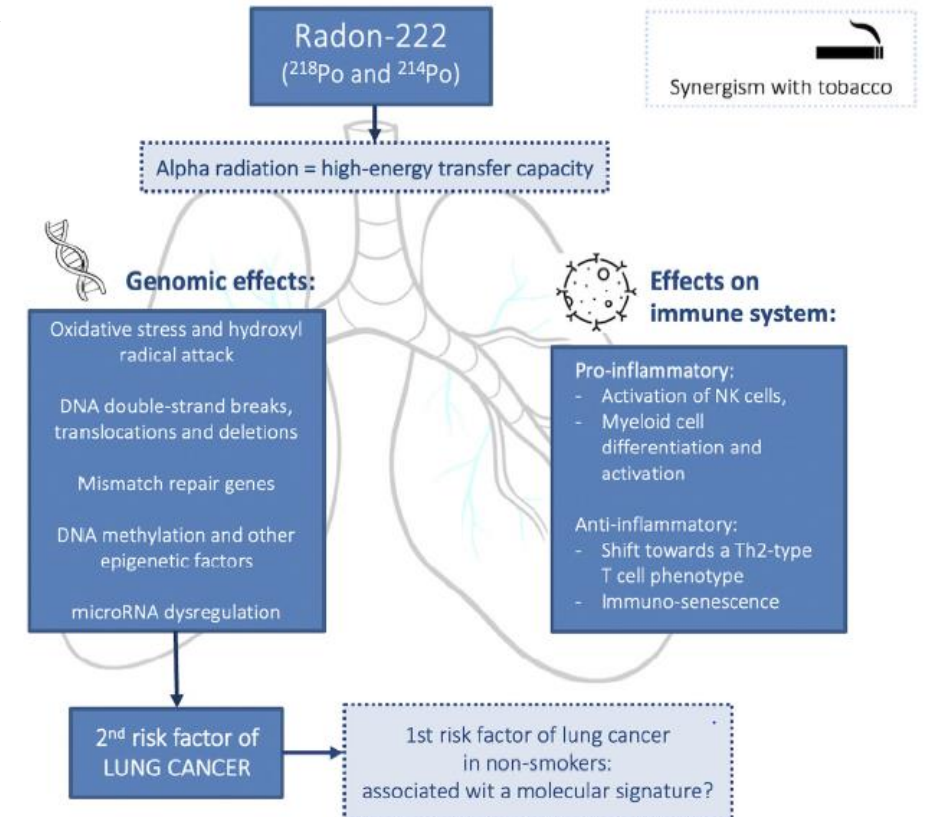


- Relative risk (smokers: non-smokers) = 30:1
- Correlation with smoke (Men 90%, Women 60%)
- Risk based on pack /years: smoked packs of cigarettes/day x duration in years
- Radon is the **second leading cause** of lung cancer after smoking
- Factors related to work-exposure: Asbestos, Cadmium, Chrome, Nickel



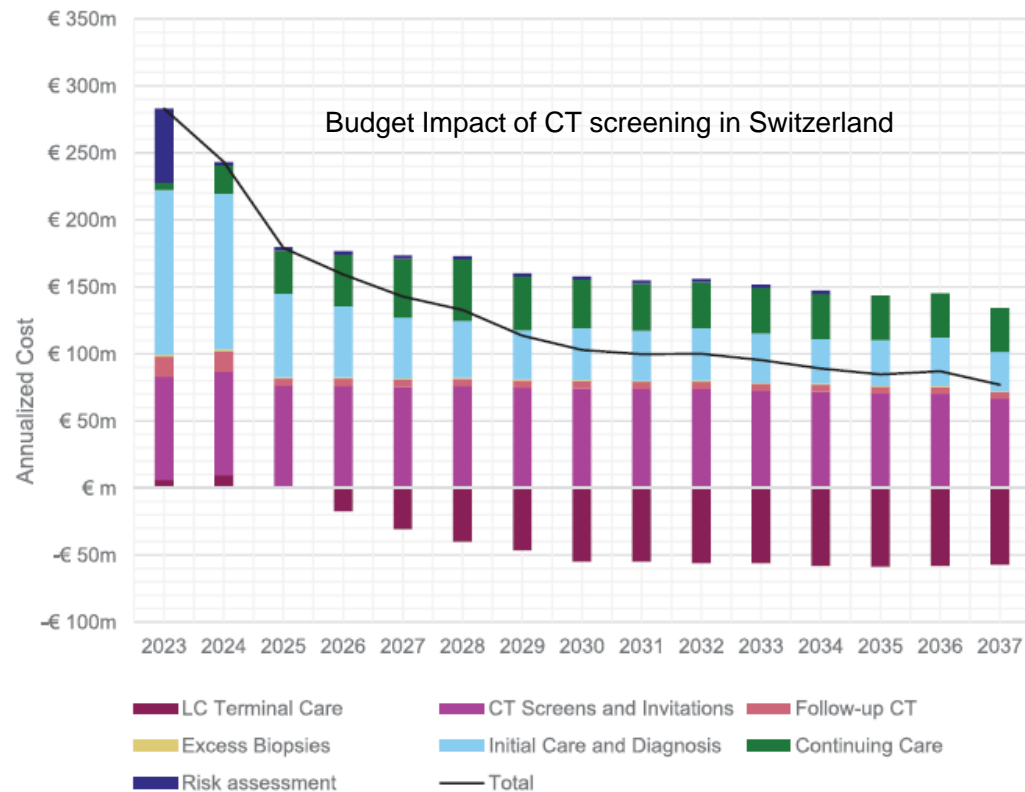


U.S. EPA, World Health Organization (WHO), and Surgeon General's Office



M Riudavets, Cancers 2022

## Lung Cancer Screening



Tomonaga et al IJC 2022



Swiss Cancer Screening Committee -  
Expertengremium Krebsfrüherkennung – Comité d'experts du dépistage du cancer

### Recommendation for Lung Cancer Screening Using Low-dose Computed Tomography (low-dose CT, LDCT)

Background	Lung cancer is the leading cause of cancer-related deaths. Around 3,300 people die from it every year in Switzerland. Tobacco smoking is by far the leading risk factor for lung cancer, accounting for about 80-90% of lung cancer diagnoses. Consequently, several international studies have investigated whether lung cancer screening by means of low-dose computed tomography in high-risk individuals could lead to earlier lung cancer diagnosis and to prevention of deaths. At-risk individuals are current and former tobacco smokers aged 55 and older. The Swiss Cancer Screening Committee appraised the evidence on the ethical issues in lung cancer screening, the clinical effectiveness, cost-effectiveness, as well as the budget impact and has provided a recommendation for Switzerland.
Recommendation	The Cancer Screening Committee suggests offering low-dose computed tomography (LDCT) lung cancer screening to people at risk. (GRADE conditional recommendation)
Justification	The Cancer Screening Committee issued a conditional recommendation in favour of screening because LDCT lung cancer screening probably results in a reduction of lung cancer deaths (43 fewer lung cancer deaths per 10,000 people over 10 years). Furthermore, the evidence implies that screening would result in more lung cancer cases being diagnosed at an earlier stage.
Recommendation's Scope	The scope of this recommendation is centred on the individual perspective of people at risk. The Swiss Cancer Screening Committee thinks that a majority of informed high-risk people would consider screening.
Considerations for Implementation	<p>The Swiss Cancer Screening Committee strongly recommends offering LDCT lung cancer screening within organised programmes. Only an organised programme can ensure a broad, accessible and equitable offer of screening. In a programme, the quality and reproducibility of indicated follow-up testing after a suspicious screening result and a structured and target-group oriented invitation of the at-risk population can also be guaranteed. A programme would also allow exemption from the deductible according to the standard rules of Swiss statutory health insurance, which is another important prerequisite for equity of access.</p> <p>In lung cancer screening, standardized procedures should be used for further diagnostic investigation of abnormal findings and for diagnosis.</p> <p>Reaching the at-risk population is a central concern and a major challenge that requires specific recruitment and implementation strategies.</p> <p>People at risk need to be supported in decision-making by appropriately trained health professionals (shared decision-making) so that each person can make a decision that is in line with his/her values, preferences and individual situation.</p> <p>Participation in screening should be a free choice and non-participation should not have negative consequences, in terms of stigmatisation or exclusion from healthcare services.</p> <p>Smoking cessation support according to the current state of knowledge should always be offered to persons at risk; regardless of their decision to undergo screening or not.</p>
Full Report	<a href="https://cancerscreeningcommittee.ch/en/">https://cancerscreeningcommittee.ch/en/</a>

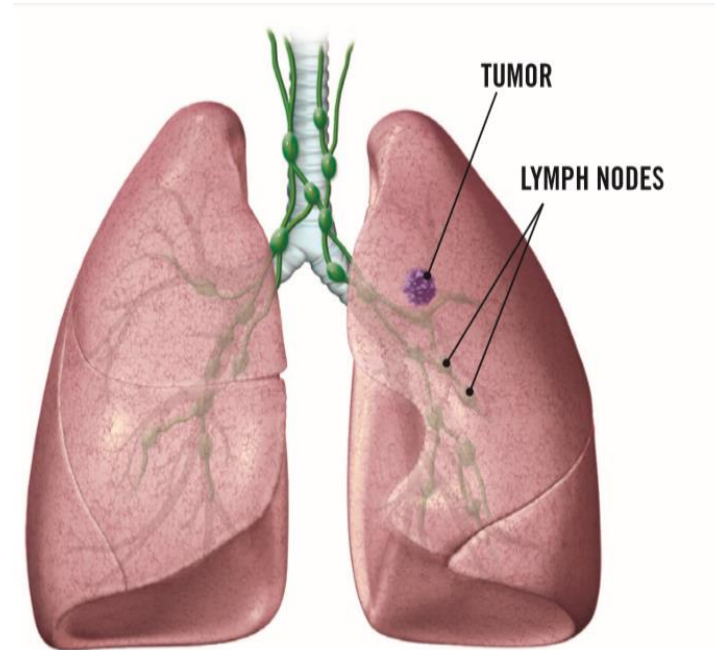
# NSCLC: Approach to treatment

Stage IA

Stage IB



If not-operable



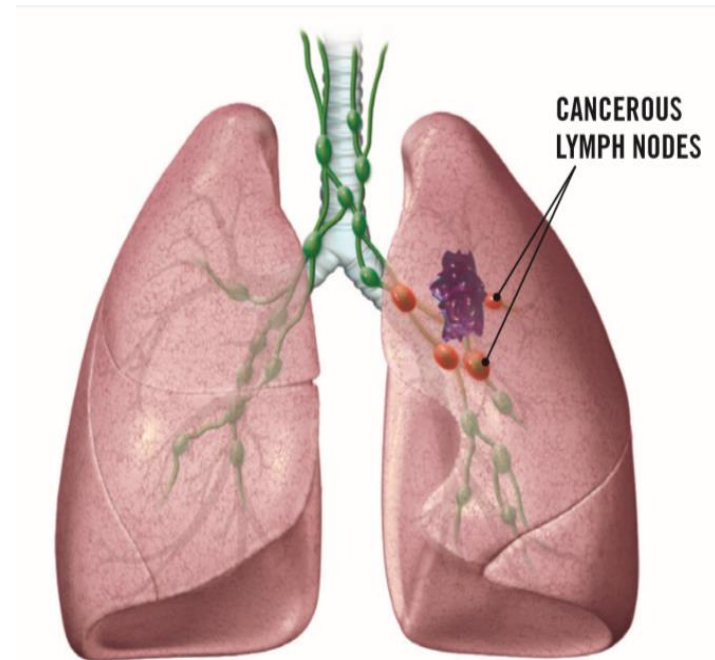
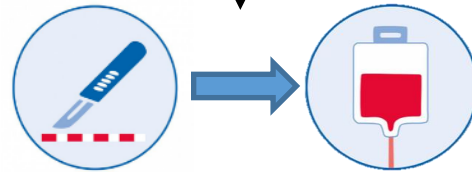


## NSCLC: Approach to treatment

Stage IA

Stage IB

Stage IIA/B



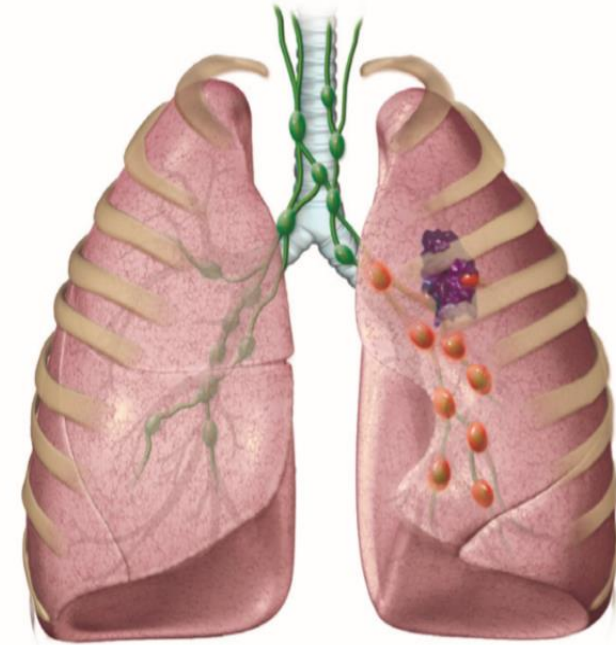
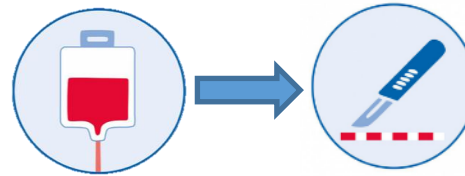
## NSCLC: Approach to treatment

Stage IA

Stage IB

Stage IIA/B

Stage IIIA  
cT3 N1  
T4 N0/1



## NSCLC: Approach to treatment

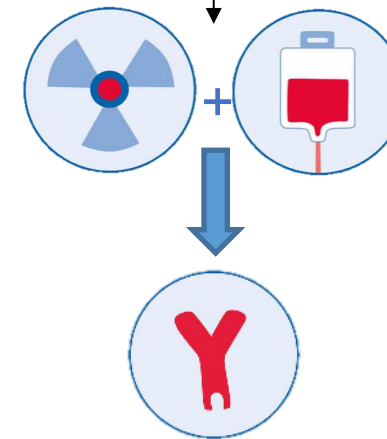
Stage IA

Stage IB

Stage IIA/B

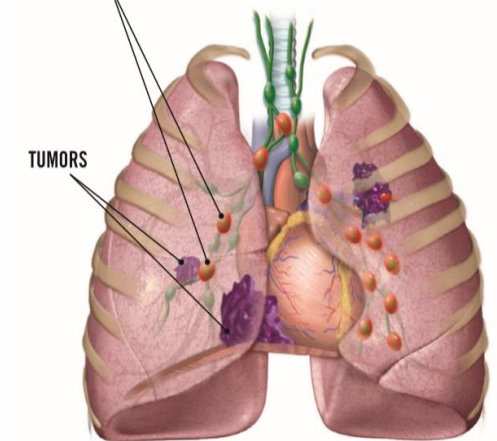
Stage IIIA  
cT3 N1  
T4 N0/1

Stage IIIA/B not  
operable  
Pancoast Tumor



CANCEROUS  
LYMPH NODES

TUMORS



# NSCLC: Approach to treatment

Stage IA

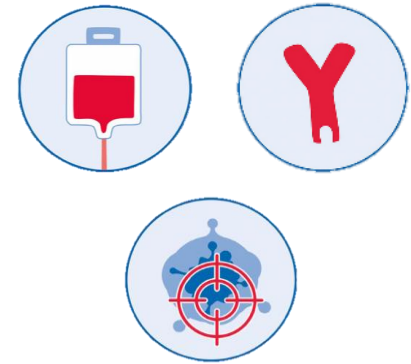
Stage IB

Stage IIA/B

Stage IIIA  
cT3 N1  
T4 N0/1

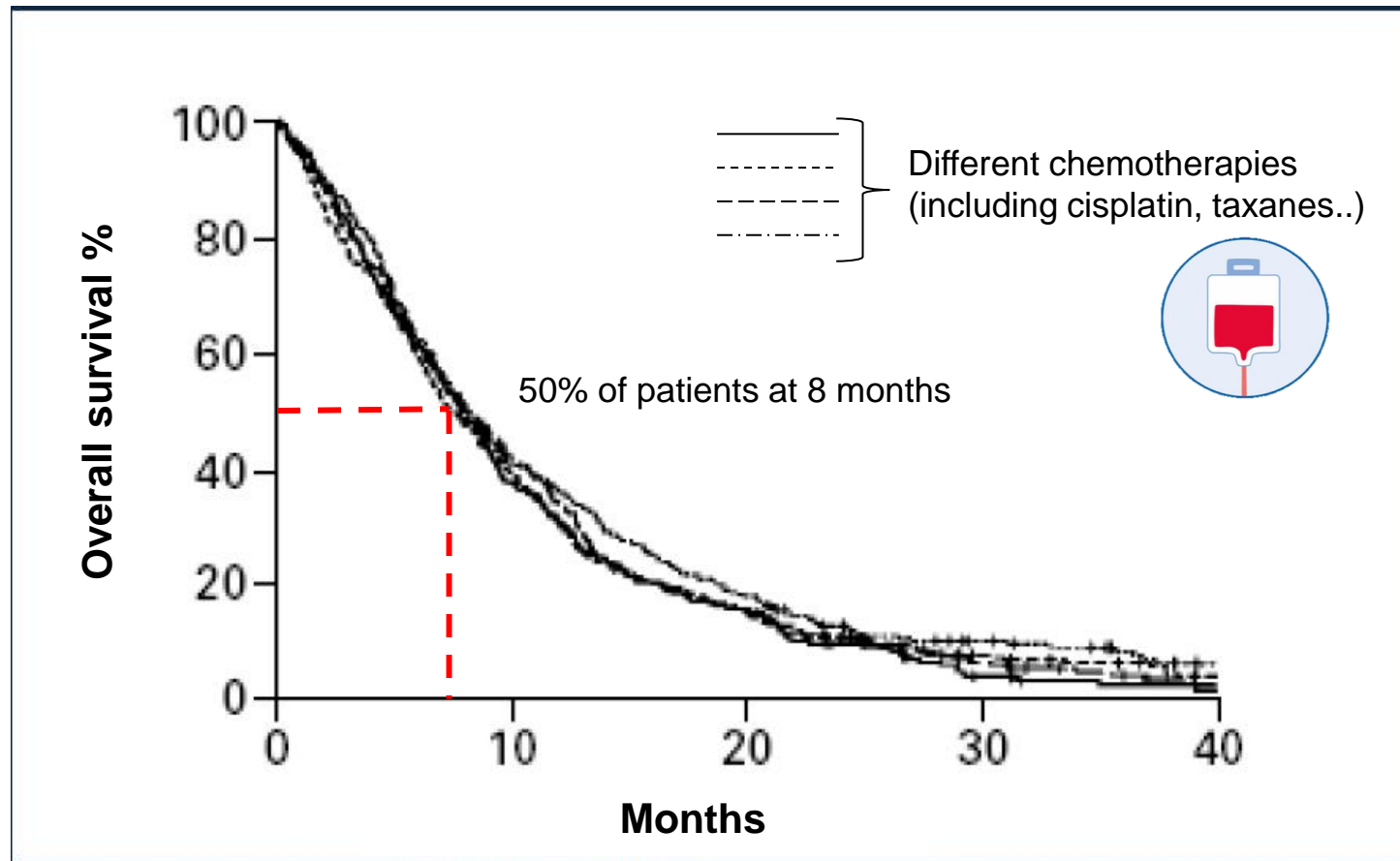
Stage IIIA/B not  
operable  
Pancoast Tumor

Stage IVA/B





## NSCLC: Survival at Stage IV in 2002



Schiller NEJM 2002

# Outline

Introduction to cancer and lung cancer

## Development of targeted treatments for lung cancer

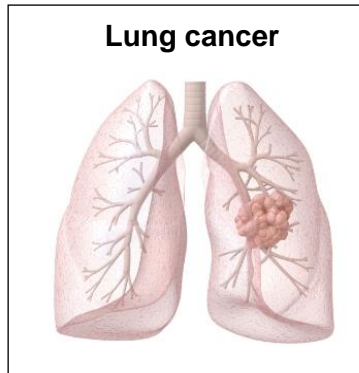
- Introduction
- Results
- Challenges



# Cancer classification: From tumor origin to molecular signatures

**1980s**

Anatomical classification

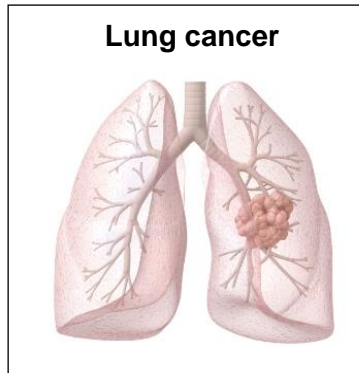


Adapted from: Munoz, Nat Rev Clin Onco 2013; Xing, Oncogene 2012

# Cancer classification: From tumor origin to molecular signatures

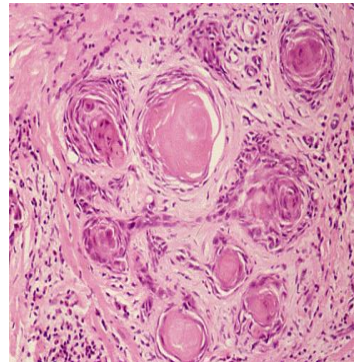
**1980s**

Anatomical classification

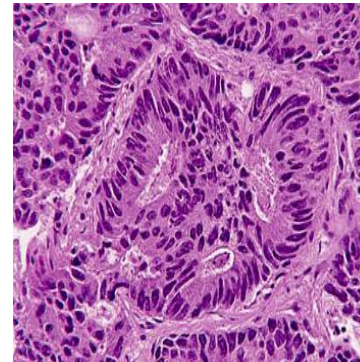


**1990s-2000s**

Histological classification



**Squamous carcinoma**

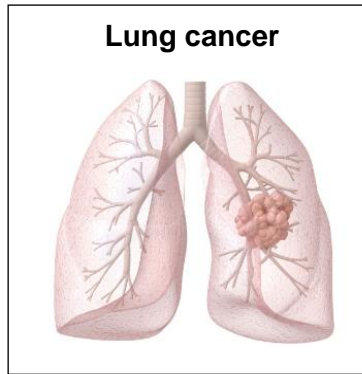


**Adenocarcinoma**

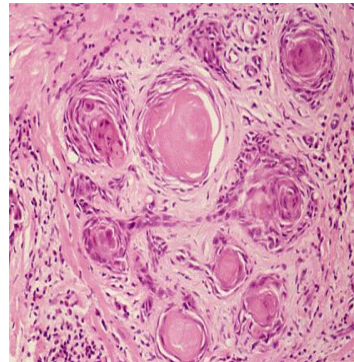
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# Cancer classification: From tumor origin to molecular signatures

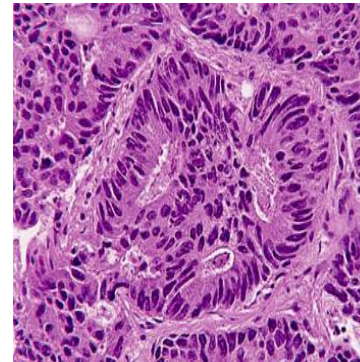
## 1980s Anatomical classification



## 1990s-2000s Histological classification



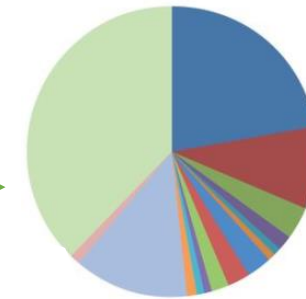
Squamous carcinoma



Adenocarcinoma



## 2010s Molecular classification

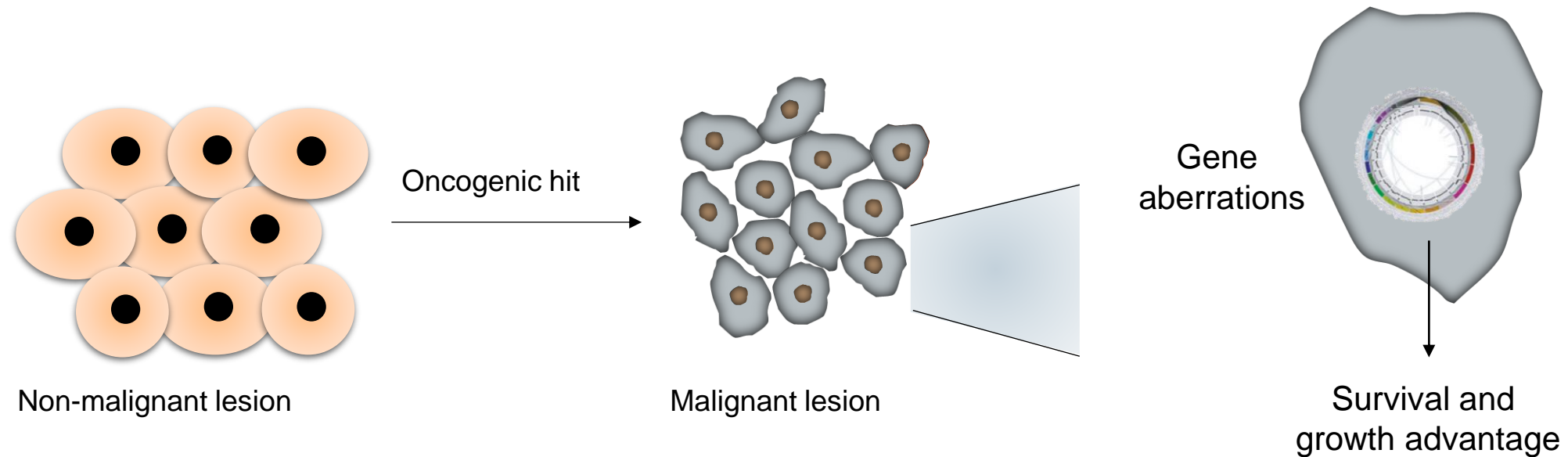


■	KRAS mutation	25%
■	EGFR mutation	10%
■	ALK fusion	4%
■	ROS1 fusion	1.9%
■	RET fusion	0.9%
■	NTRK1 fusion	1%
■	HER2 mutation	3%
■	BRAF mutation	3%
■	PI3KCA mutation	2%
■	HRAS mutation	1%
■	NRAS mutation	1%
■	AKT mutation	1.1%
■	MET exon 14 mutation	3%
■	MAP3K1 mutation	1%
■	Unknown	42%

Adapted from: Munoz, Nat Rev Clin Onco 2013; Xing, Oncogene 2012



# Molecular aberrations may lead to malignant transformation



Adapted from: Munoz, Nat Rev Clin Onco 2013; Xing, Oncogene 2012

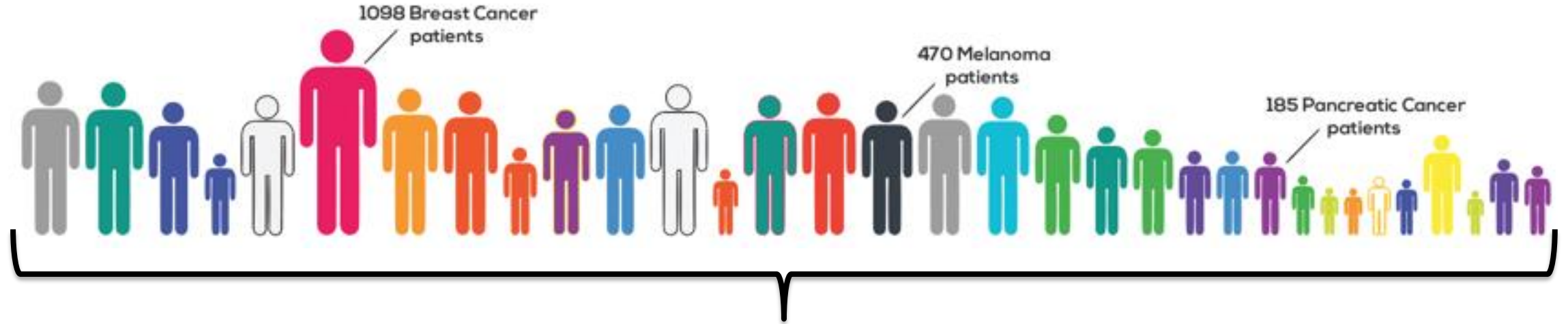
## Discovery of molecular signatures



- TCGA: The Cancer Genome Atlas
- Started in 2005
- Sequencing more than 11,000 patients from 33 cancer types

Adapted from: <https://www.sevenbridges.com>

# Discovery of molecular signatures for clinical application

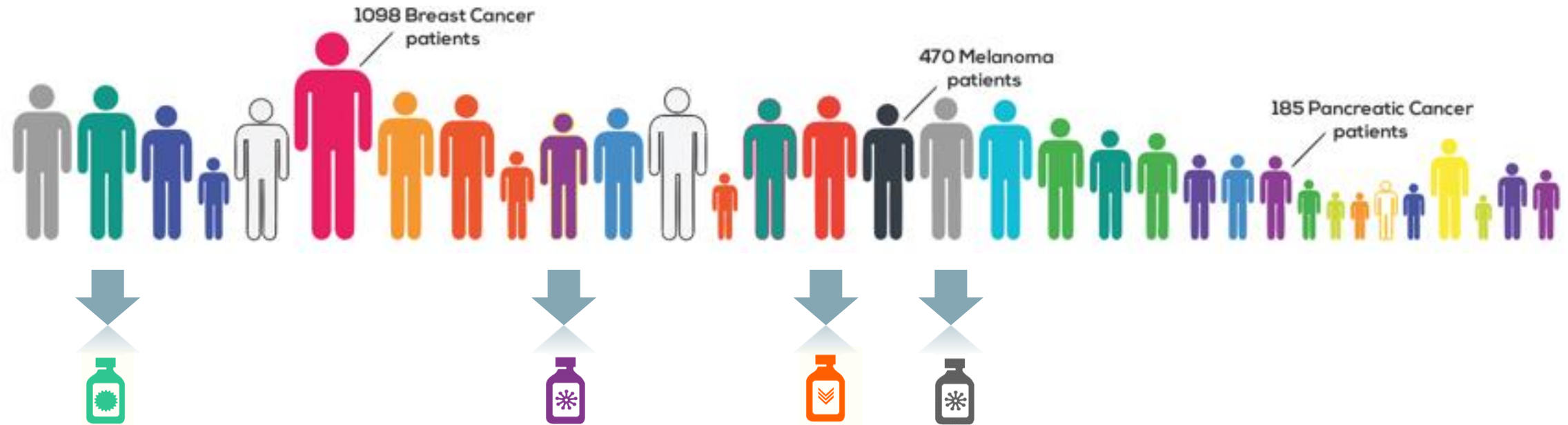


**Chemotherapy:**  
Low specificity &  
High toxicity

Adapted from: <https://www.sevenbridges.com>



# Discovery of molecular signatures for clinical application



**Targeted-therapy:**  
High specificity & Low toxicity

Adapted from: <https://www.sevenbridges.com>

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# The impact of molecular testing on patients with lung cancer

Lung Cancer in Switzerland/year		
Men	Women	Total
2700	1800	4500

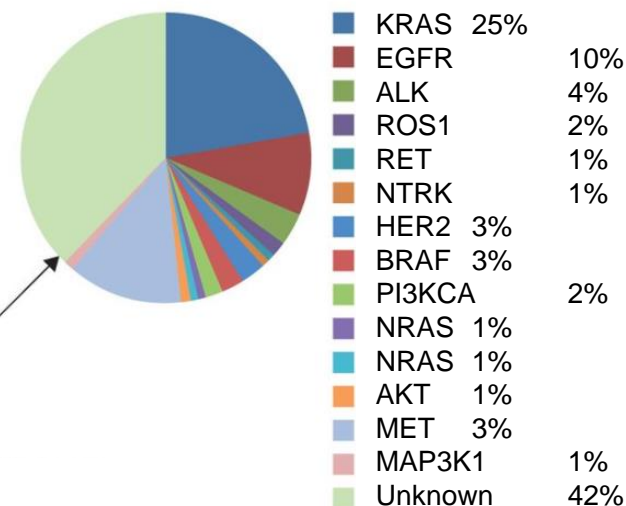
Swiss Cancer League report 2020

# The impact of molecular testing on patients with lung cancer

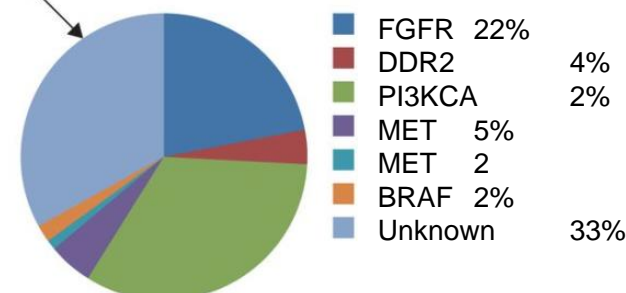
Lung Cancer in Switzerland/year		
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Swiss Cancer League report 2020

## Adenocarcinoma



## Squamouscarcinoma



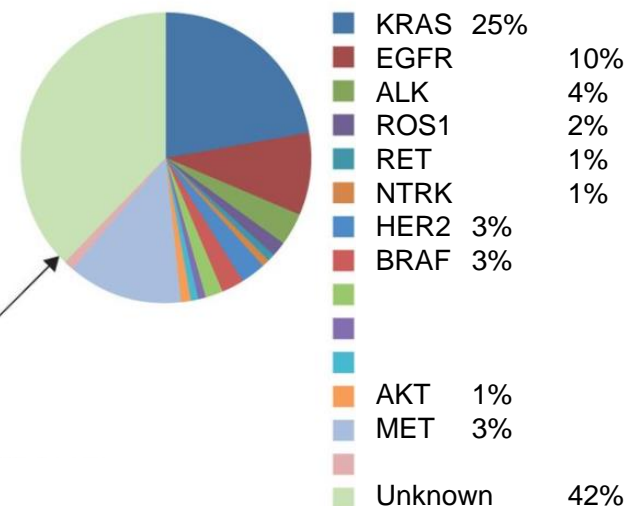
Adapted from Bubendorf, Europ Resp Rev 2017

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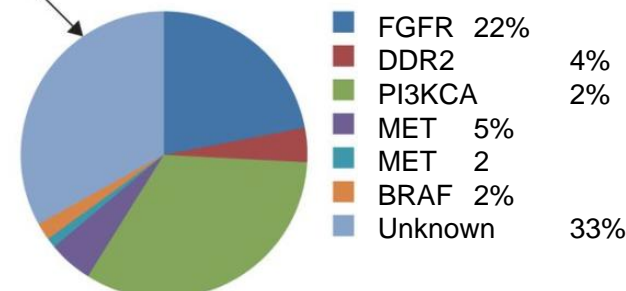
Swiss Cancer League report 2020

## Adenocarcinoma



Targetable alterations  
(40% = 1800 patients)

## Squamouscarcinoma



....Not yet targetable

Adapted from Bubendorf, Europ Resp Rev 2017

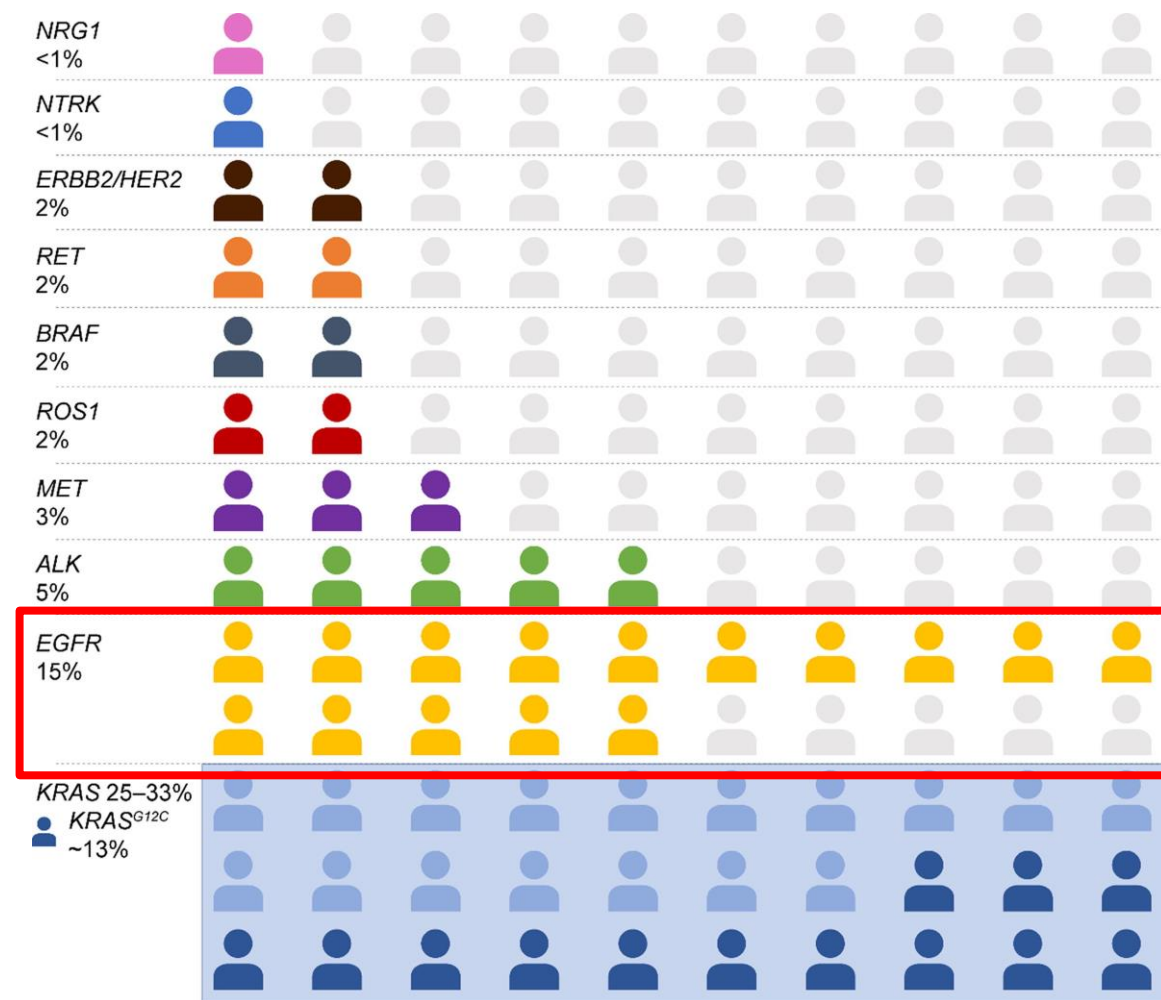
## Indoor radon concentration and molecular alterations in NSCLC patients

Study	n Total of Patients	Type of Study	Molecular Alterations	Place of Radon Measurement	Studied Area	Radon Median Bq/m <sup>3</sup> Exposition	Statistical Significance
Taga et al. [86] Prospective 2012	n = 70	Case control study	EGFRm ex19/21 (n = 24)	Current home	Non radon-prone area (Moussuri, USA)	EGFRm: 46.5 Bq/m <sup>3</sup>	Non sig. p = 0.16
Ruano-Raviña et al. [87] Retrospective 2016	n = 323	Case control study (subanalysis of previous study)	EGFRm * (n = 90) ALKr (n = 12)	Current home	Radon prone area (Galicia, Spain)	EGFRm ex19: 216 Bq/m <sup>3</sup> EGFRm ex21: 118 Bq/m <sup>3</sup> ALKr: 290 Bq/m <sup>3</sup>	Non sig. (p value non-available)
Mezquita et al. [88] Retrospective 2018	n = 116,424	Ecologic study **	EGFRm (n = 13,125) ALKr (n = 2928) BRAFm (n = 2419) HER2m (n = 816) ROS1r (n = 373) KRASm (n = 27,314)	Current home	Non-radon prone, Intermediate and radon-prone area (France)	-	p < 0.0001
Mezquita et al. [38] Prospective 2019	n = 48	Cross-sectional study	EGFR m ^ (n = 36) ALKr (n = 10) BRAFm (n = 2) EGFRm (n = 468)	Current home	Intermediate and radon-prone area (Madrid, Spain)	EGFRm: 96 Bq/m <sup>3</sup> ALKr: 116 Bq/m <sup>3</sup> BRAFm: 125 Bq/m <sup>3</sup>	Non sig. p = 0.238
Mezquita et al. [89] Retrospective 2021	n = 3994	Ecologic study **	EGFRm (n = 468) ALKr (n = 129) BRAFm (n = 89) HER2m (n = 32) KRASm (n = 985)	Childhood home	Non-radon prone, intermediate and radon-prone area (France)	EGFRm: 72.49 Bq/m <sup>3</sup> ALKr: 80.24 Bq/m <sup>3</sup> BRAFm: 73.22 Bq/m <sup>3</sup> HER2m: 72.74 Bq/m <sup>3</sup> KRASm: 71.79 Bq/m <sup>3</sup>	p = 0.0472

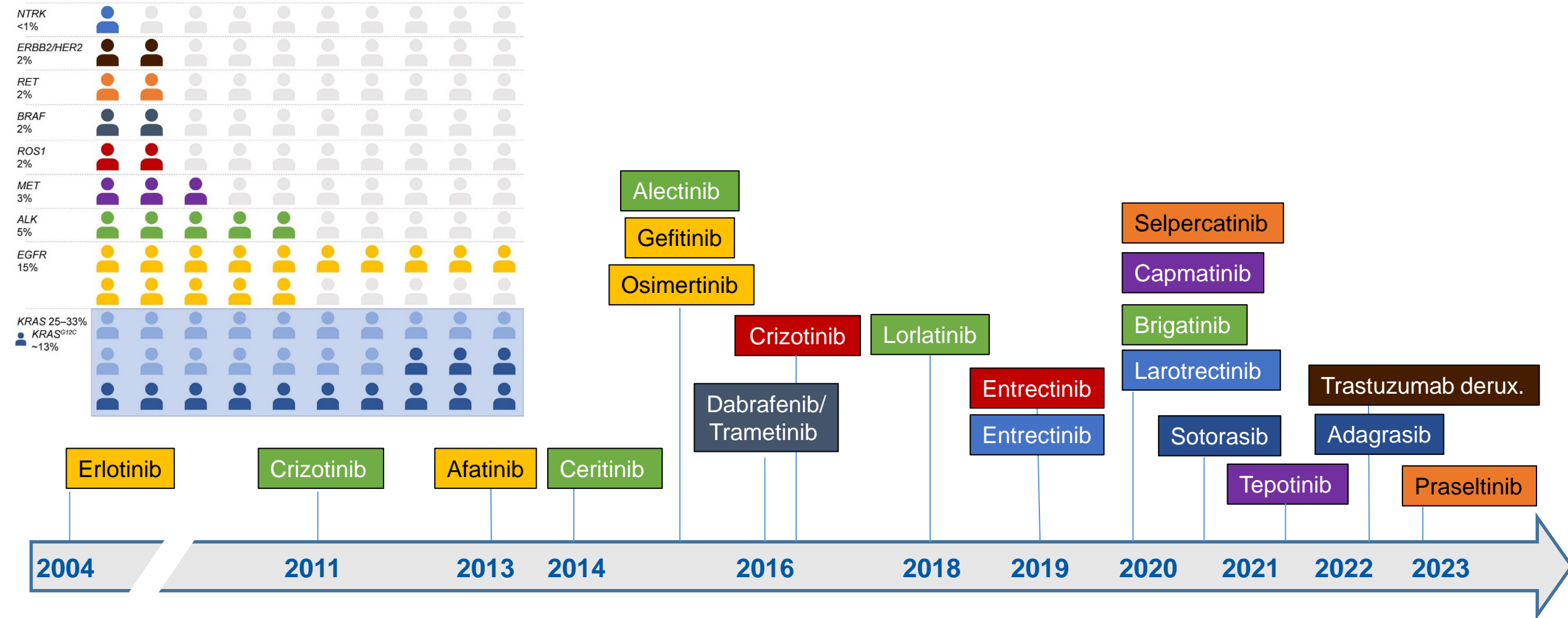
M Riudavets, Cancers 2022



# The impact of molecular testing on patients with lung cancer

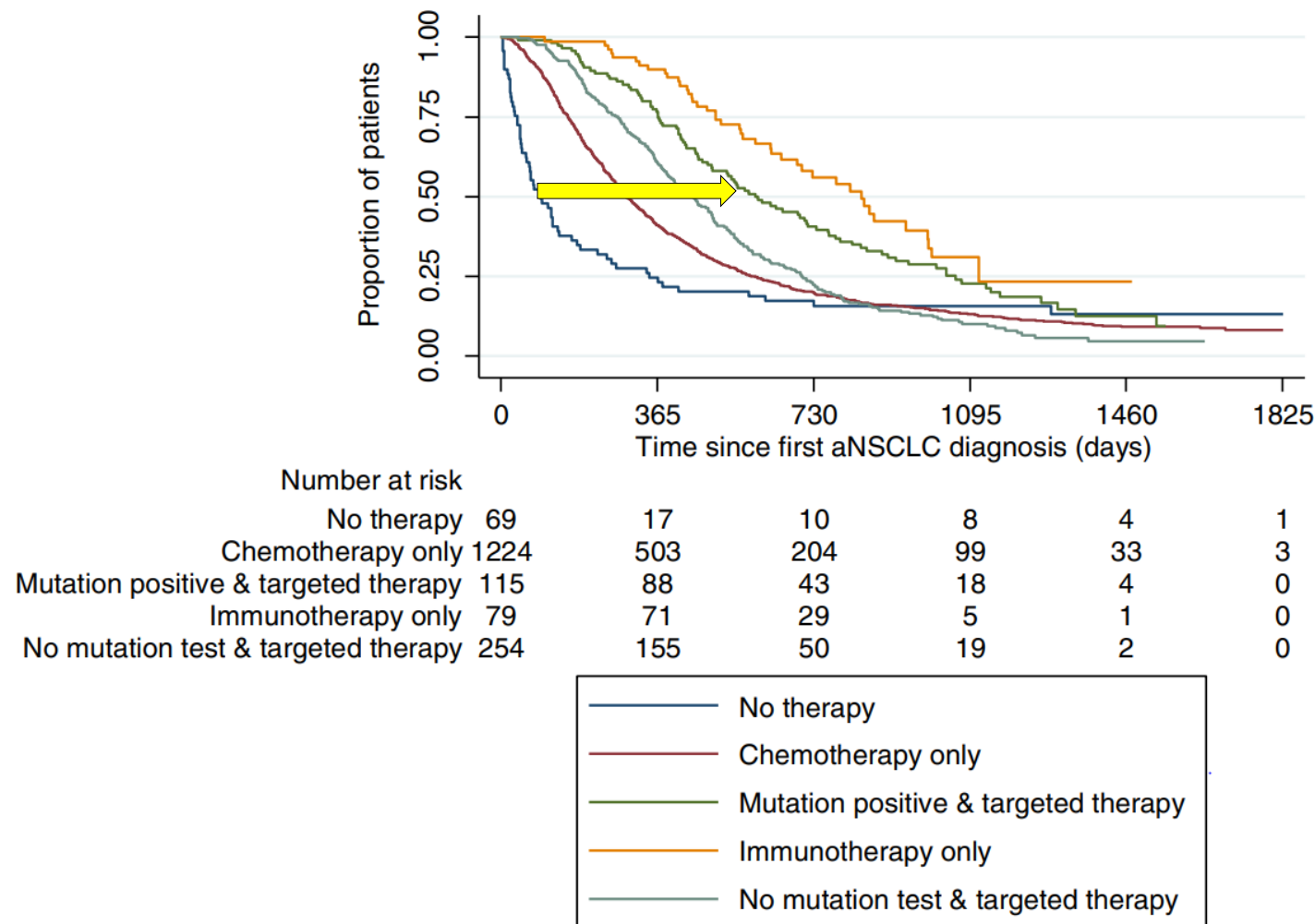


# Current targeted treatments for patients with stage IV NSCLC



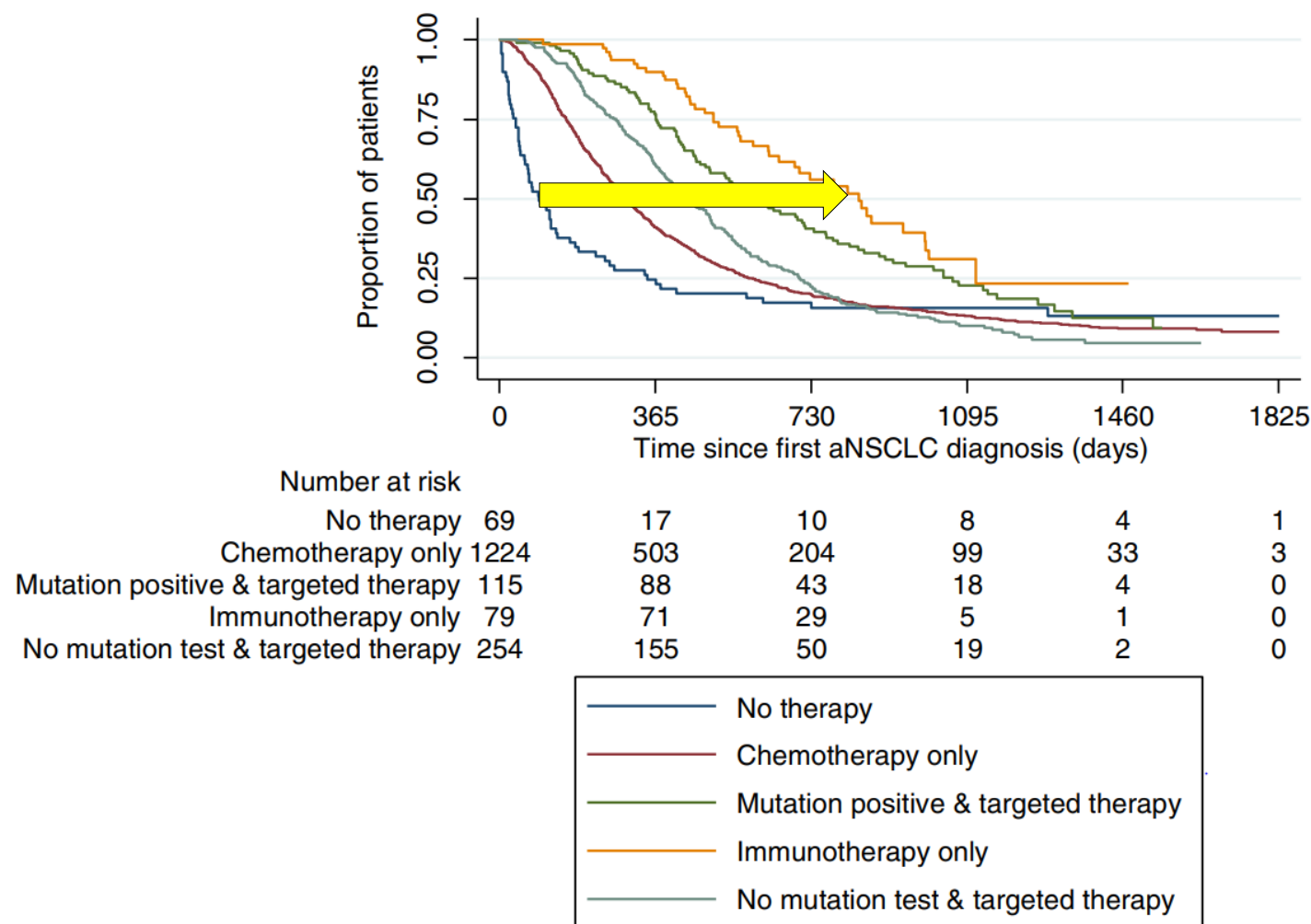


# Current targeted treatments for patients with stage IV NSCLC



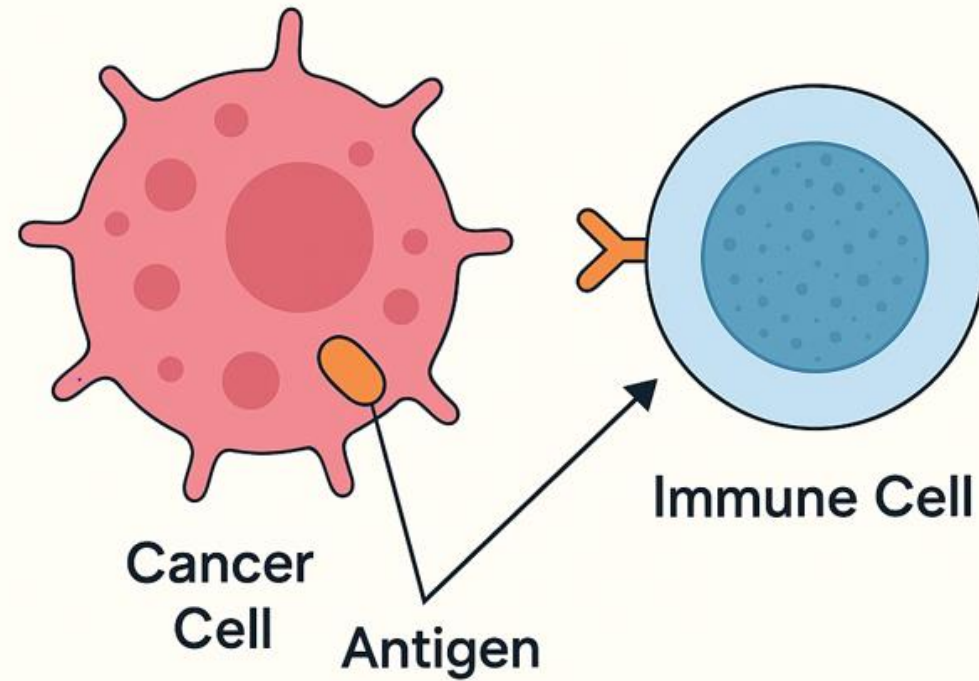
Hardtstock et al. BMC Cancer 2020

# Current targeted treatments for patients with stage IV NSCLC

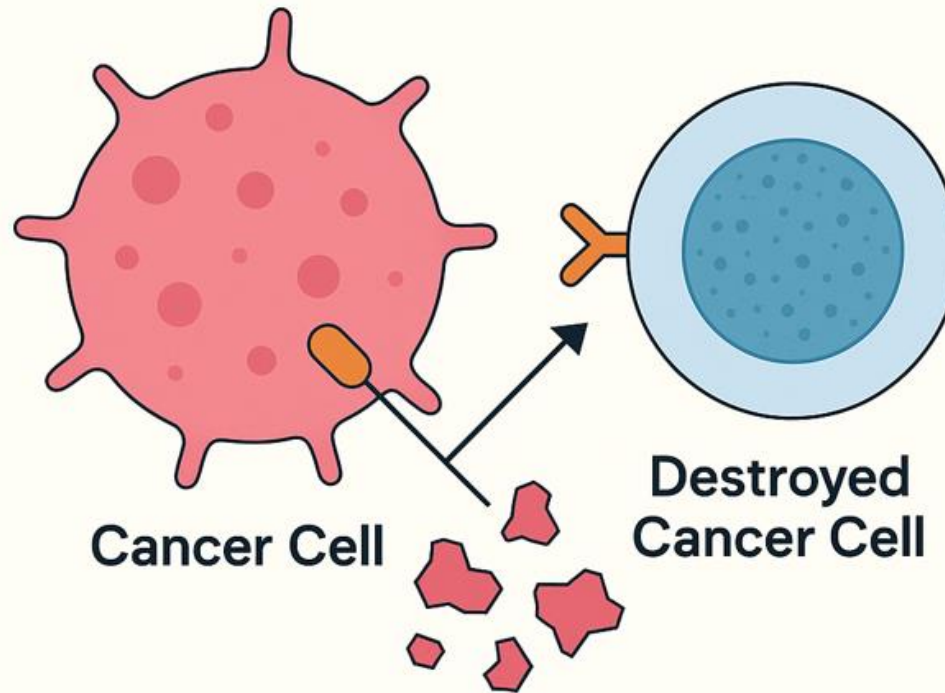


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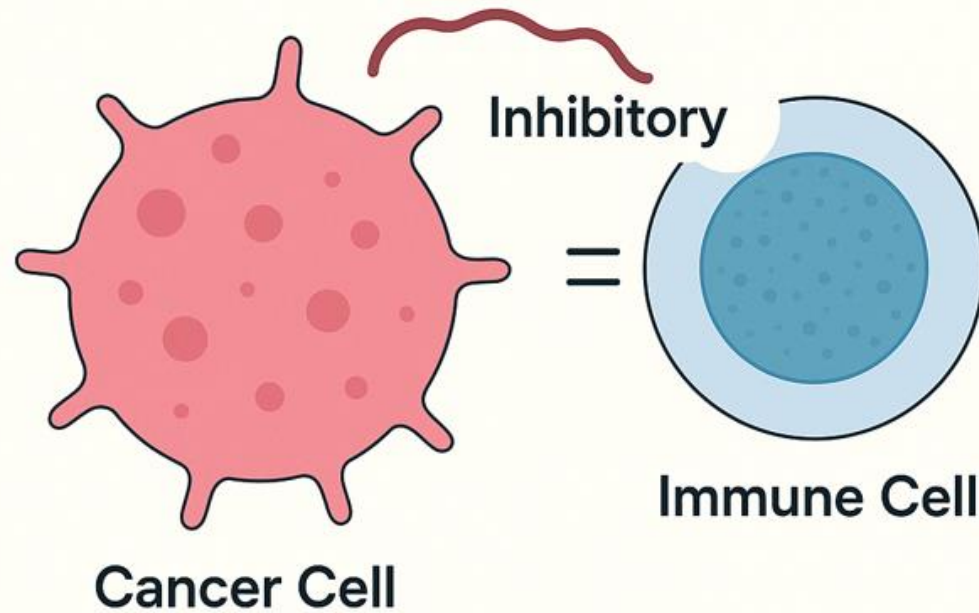
## Recognition of Cancer Cells by the Immune System



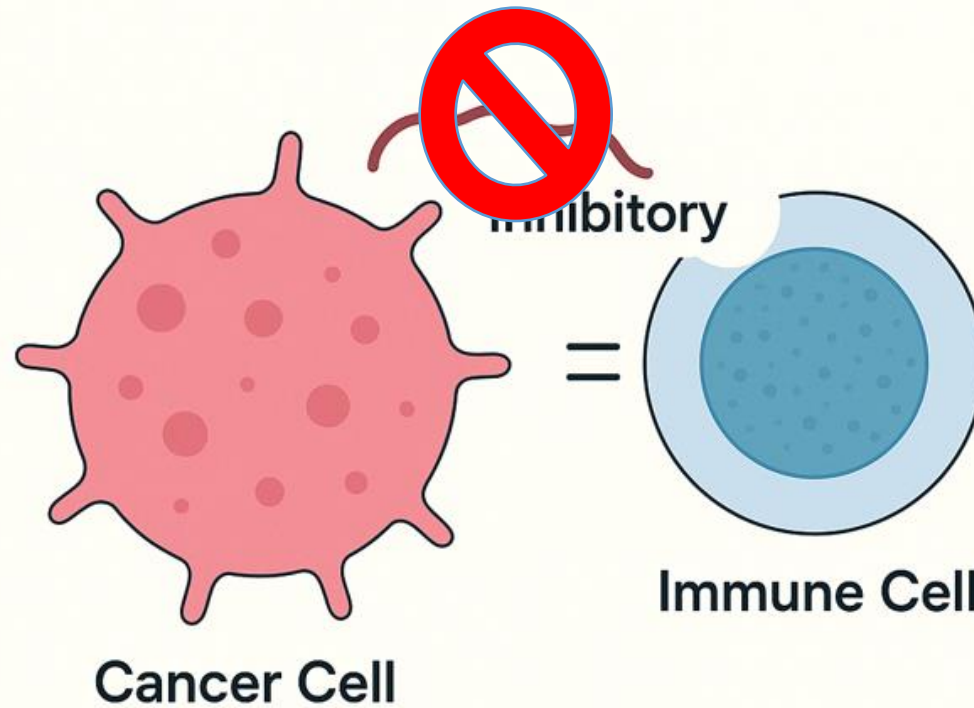
## Killing of Cancer Cells by the Immune System



## Suppression of the Immune System by Cancer Cells

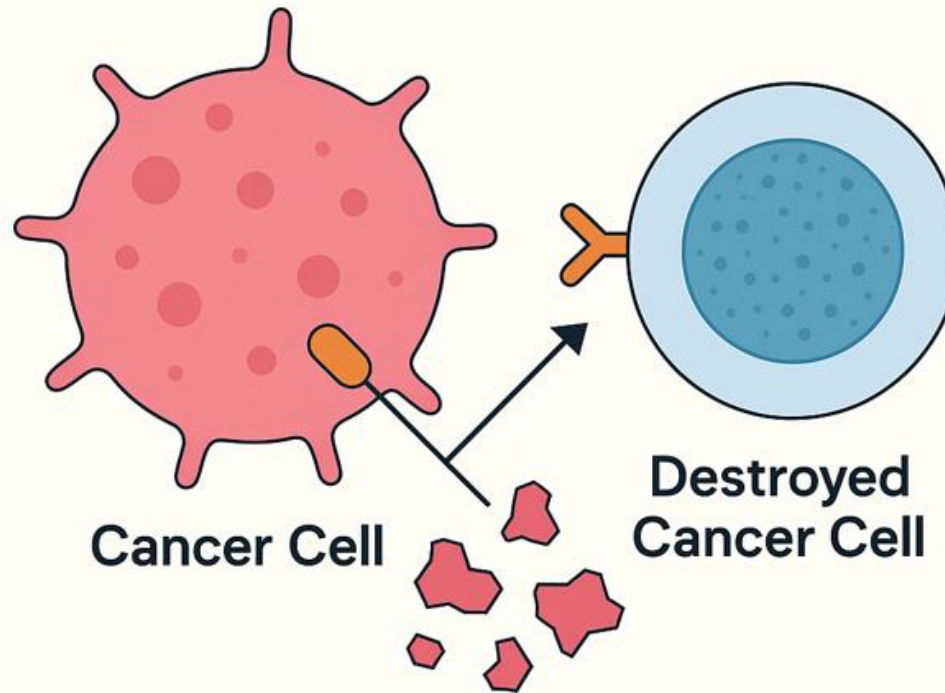


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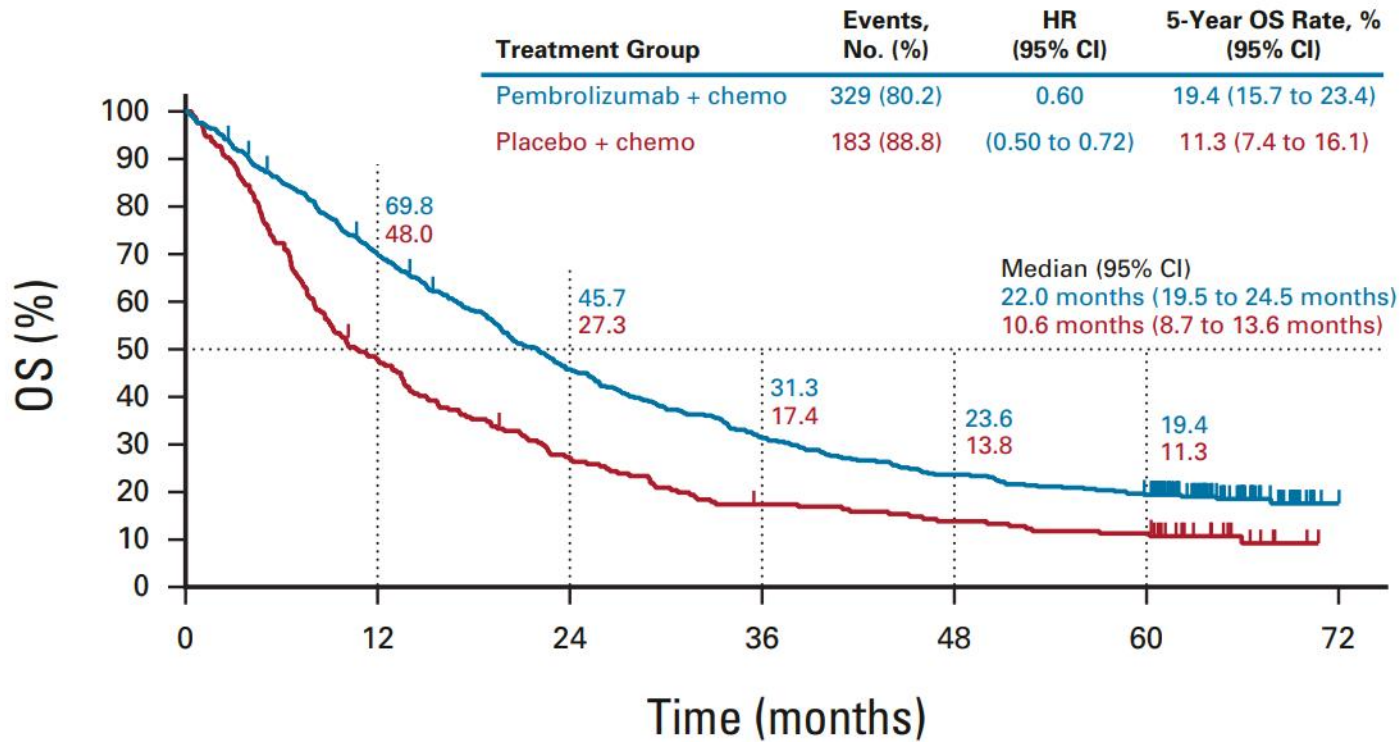




## Killing of Cancer Cells by the Immune System



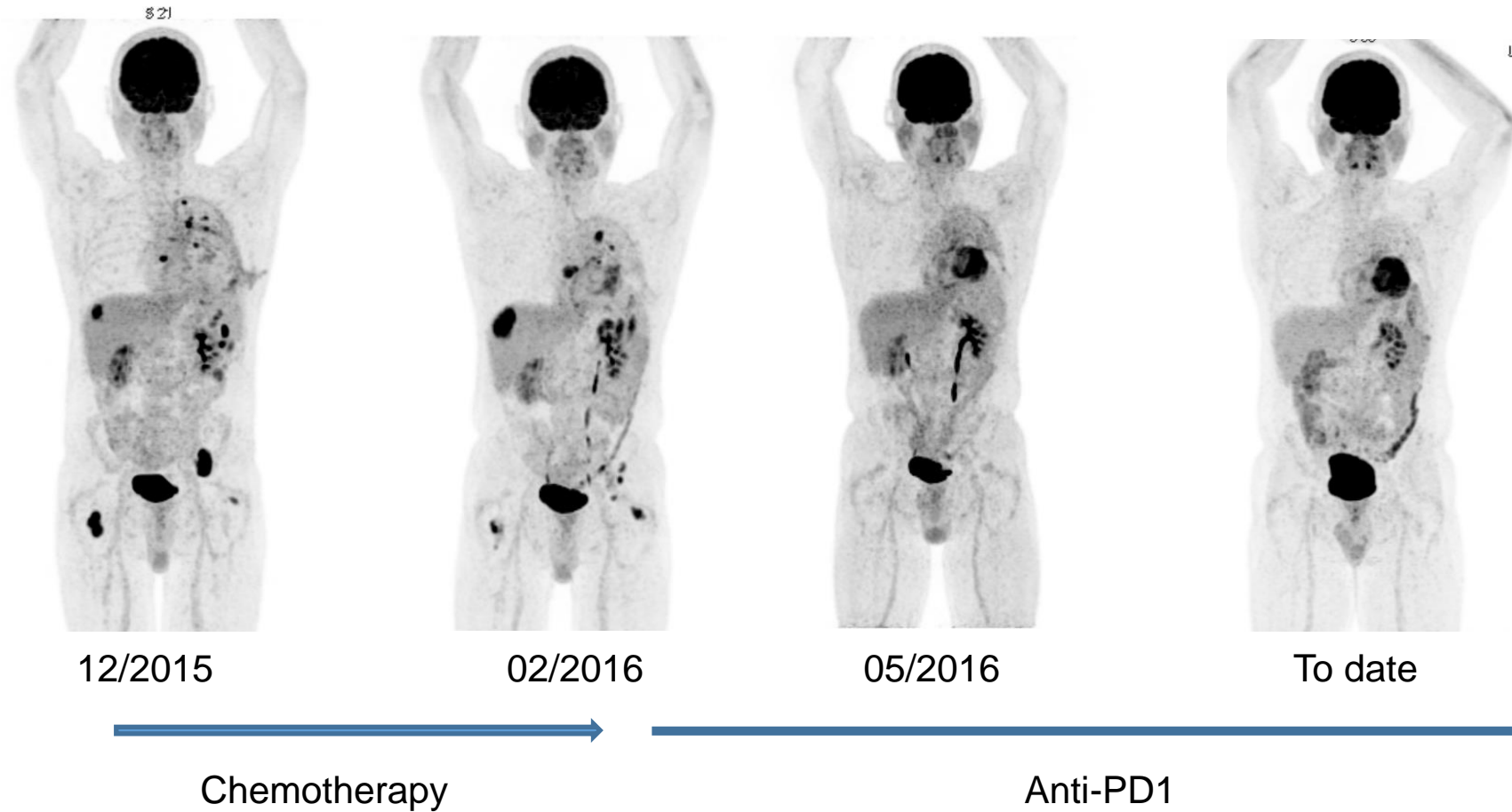
# Long-Term Survival in patients with stage IV, 1<sup>st</sup> line



<u>Chemo + Immuno</u>	No. at risk:							
	Pembrolizumab + chemo	410	283	184	126	95	77	0
Chemo	Placebo + chemo	206	98	55	34	27	22	0

Garassino M JCO 2023

### 59 yo male: Stage IV Adenocarcinoma of the lungs

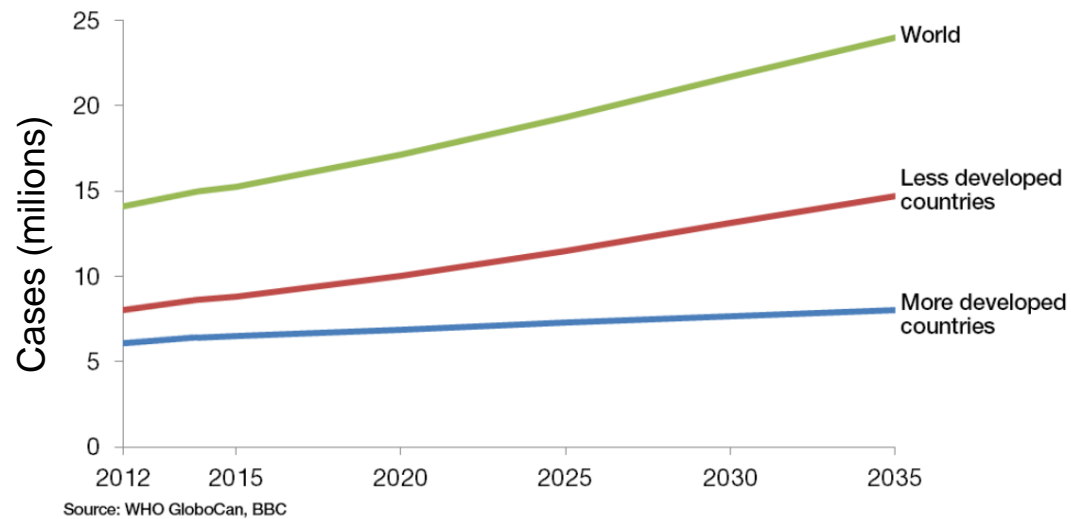


# Thank you





# Socio-economic impact of targeted drugs



**43 Million**  
*Life Years Saved*



**\$4.7 Trillion**  
*New Economic Activity*



Targeted treatments: Better QUANTITY and QUALITY of life

Adapted from, WHO GloboCan, BBC, Centers for Disease Control and Prevention and National Center for Health Statistics, US, 2013