



Prof. Dr. Veerle Surmont
Thoracale Oncologie – Longziekten UZ Gent

Thomas Malfait
Endoscopische Eenheid - Longziekten UZ Gent
 thomas.malfait@uzgent.be

127e Reeks Avondcolloquia voor de Practicus - herfst 2019

**(R)evolutie in longkanker :
Epidemiologie, diagnostiek en therapeutische strategieën**

Epidemiologie

Diagnostiek

Therapie

Epidemiologie

Diagnostiek

Therapie

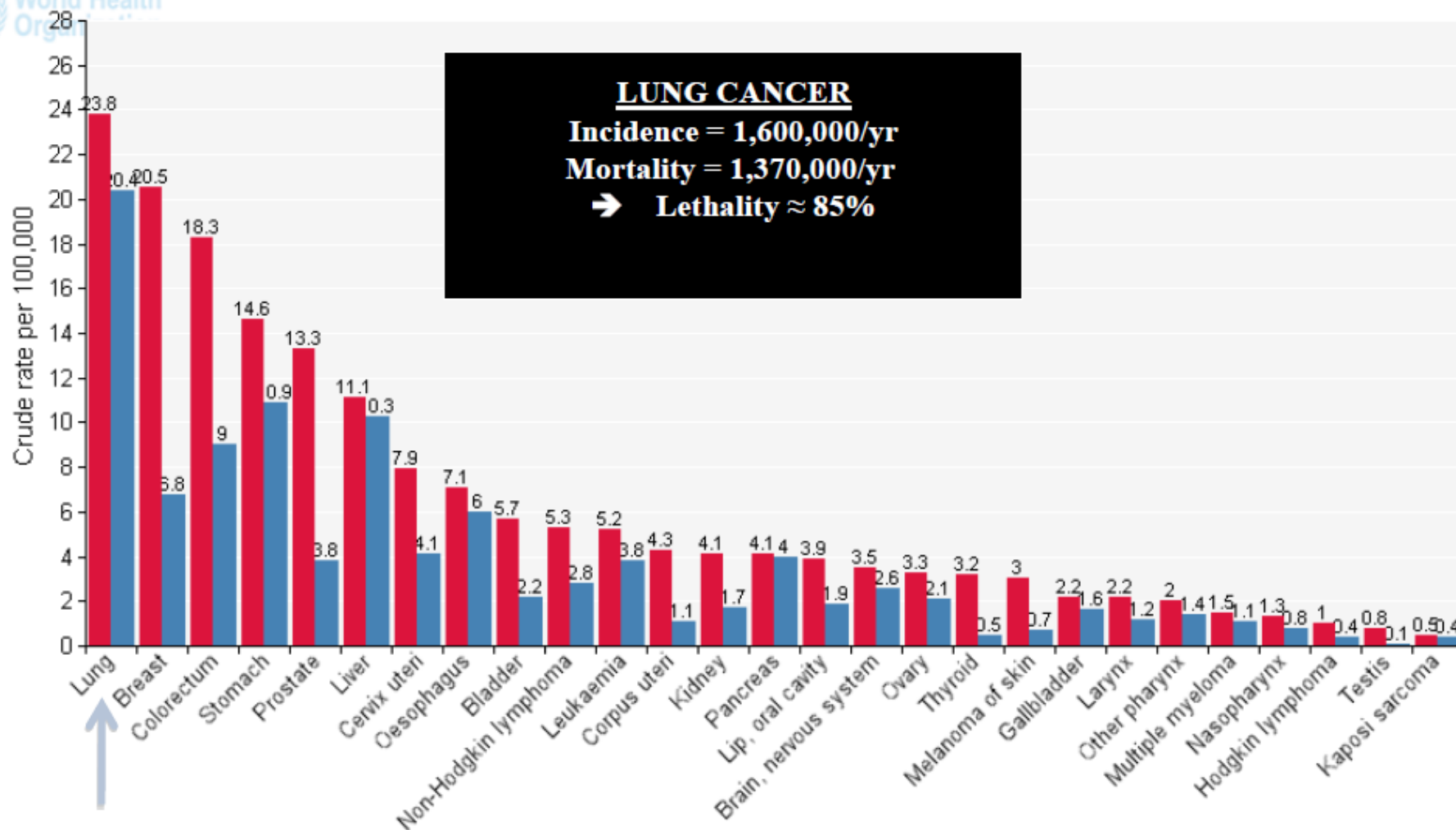
Cancer Incidence and Mortality

International Agency for Research on Cancer

World: Both sexes, all ages



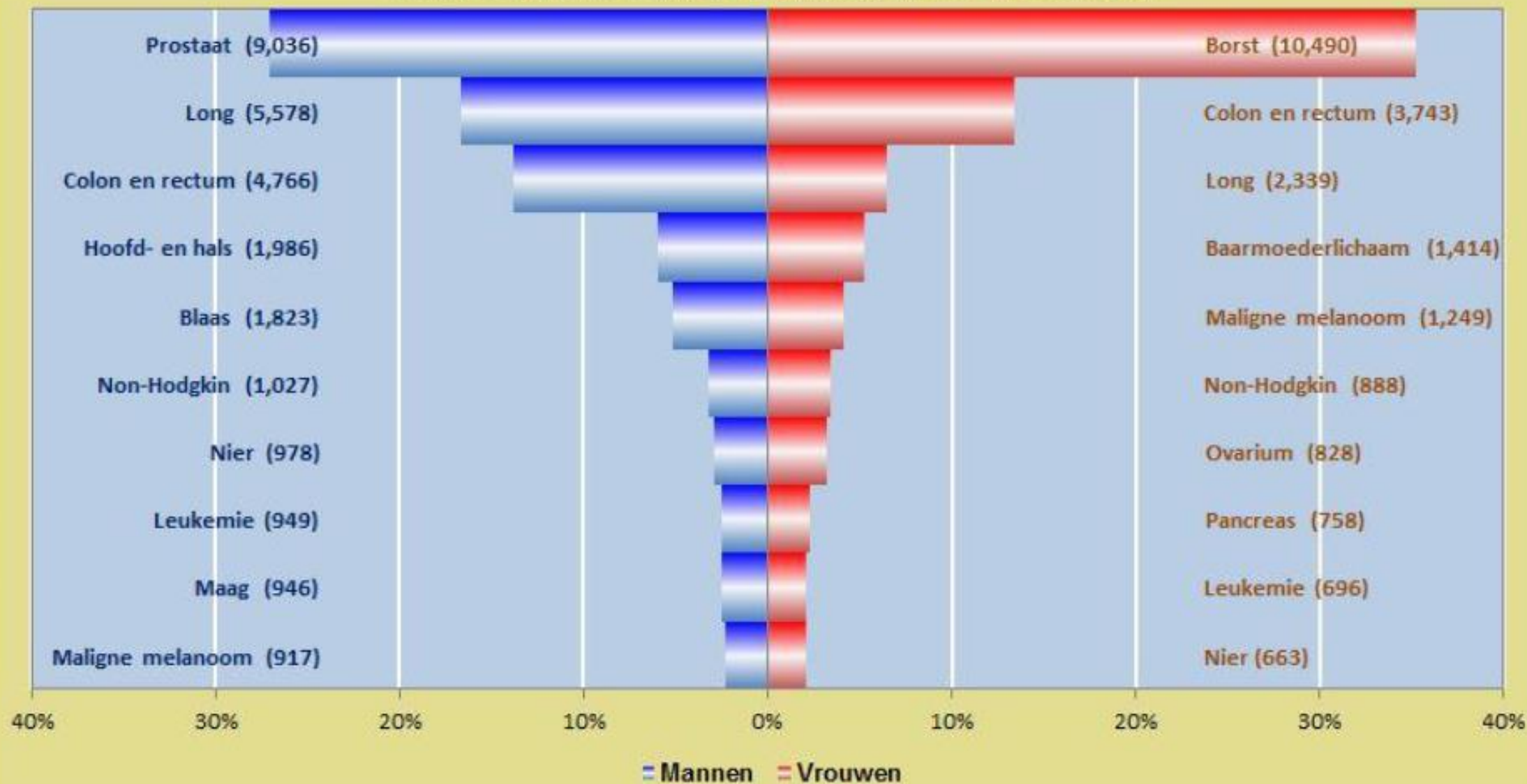
World Health Organization



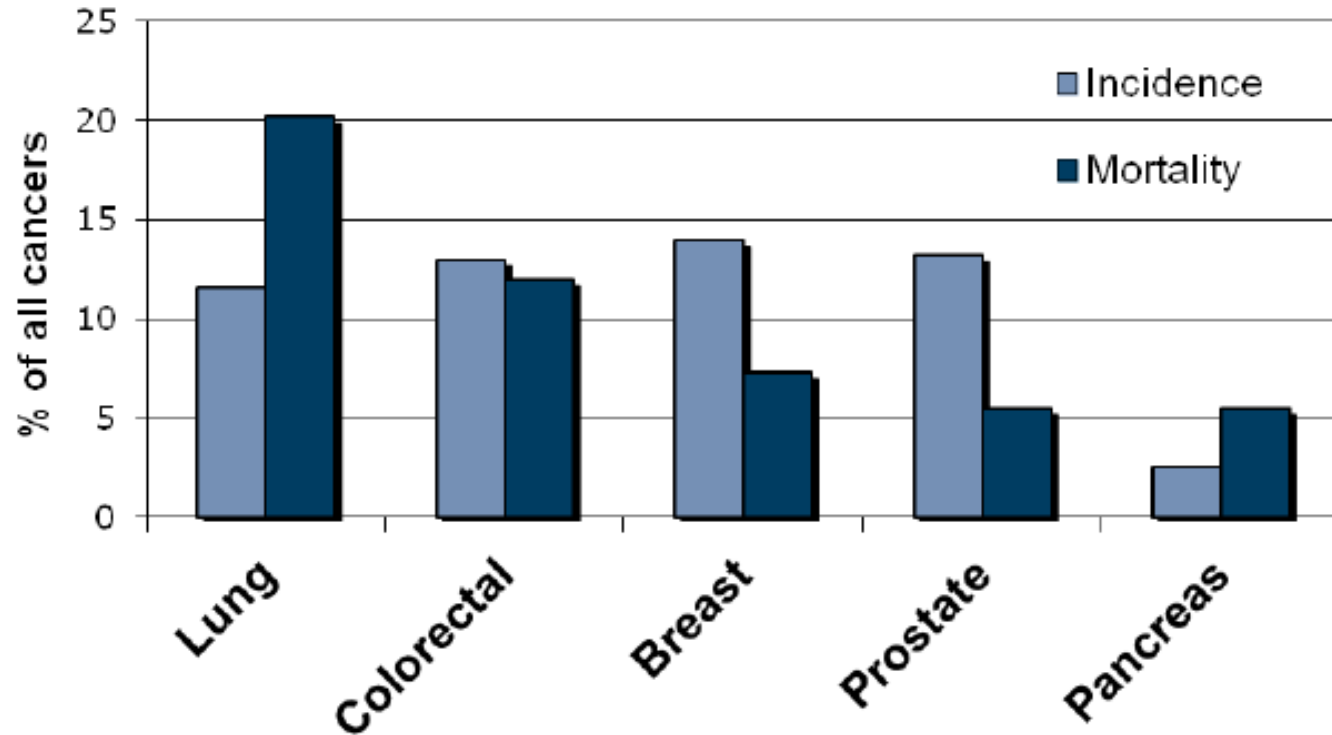
■ Incidence
■ Mortality

De tien meest frequente tumoren per geslacht, België 2011

Bron: Stichting Kankerregister (www.kankerregister.org/statistieken)



Estimates of cancer incidence and mortality in Europe (2006)



Europe	Lung cancer
Incidence	265'000 /y
Mortality	236'000 /y

Cancer mortality in Europe: lung > colorectal + breast

Longkanker: Risicofactoren

De 10 belangrijkste risicofactoren

1. Roken	6. Roken
2. Roken	7. Roken
3. Roken	8. Roken
4. Roken	9. Radon
5. Roken	10. Asbest, ...

~85% van longkankers komen voor bij (ex-) rokers

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG PRELIMINARY REPORT

BY

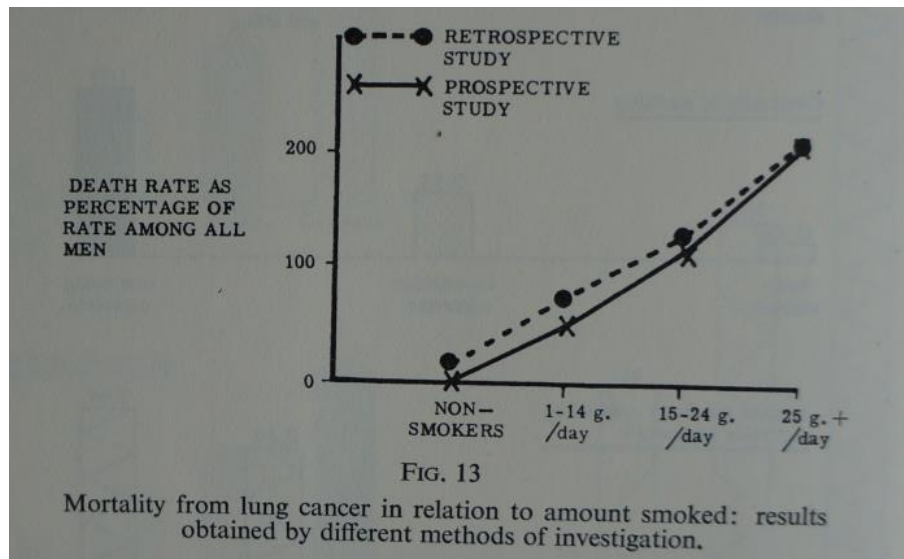
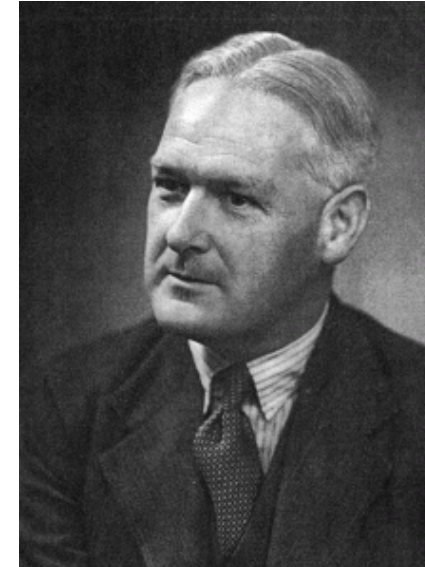
RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, Ph.D., D.Sc.

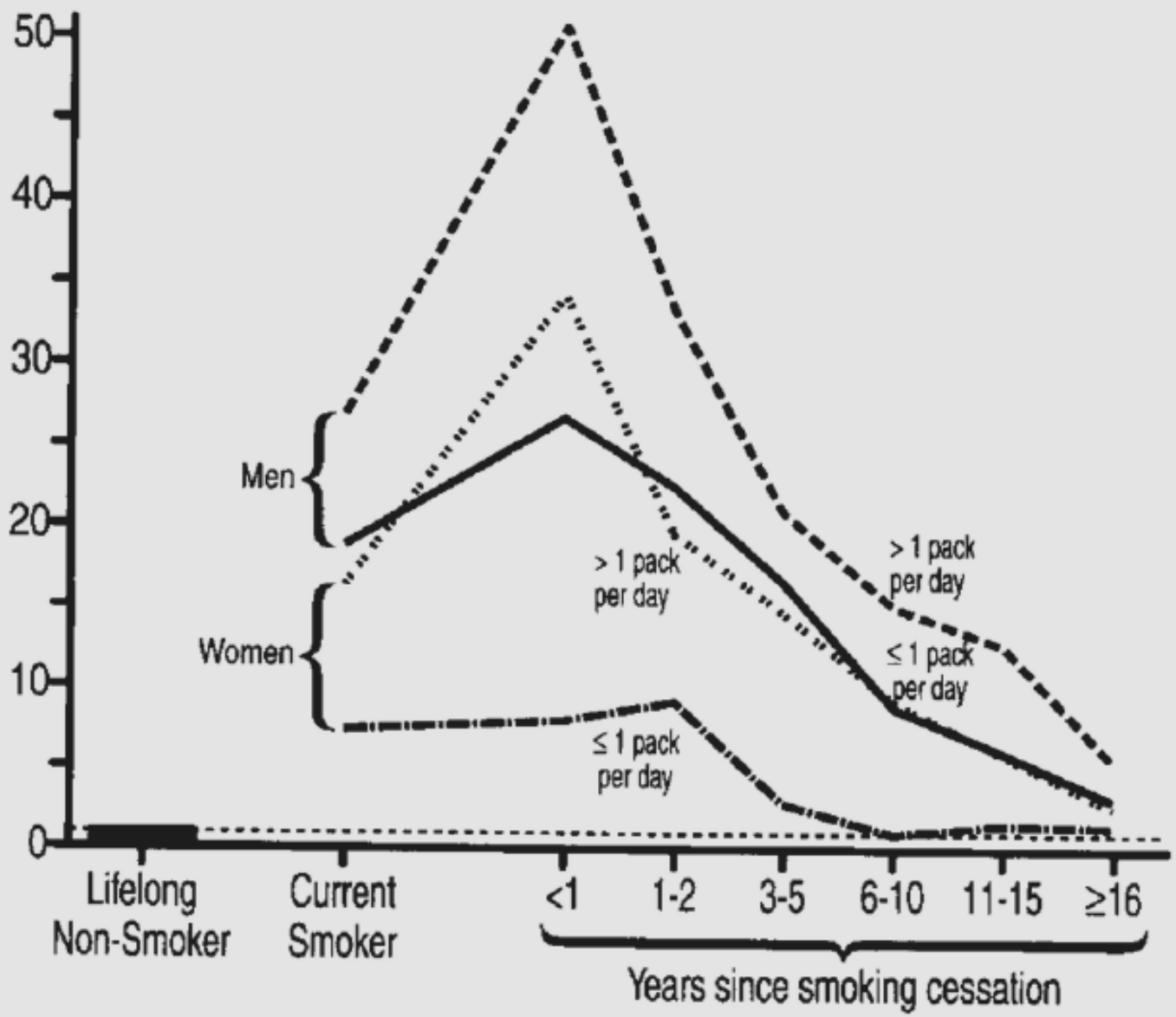
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council



Roken en longkanker

- ▶ Sigarettenrook is een complex aerosol
 - ▶ **“mainstream” rook**: ingeademd tijdens het roken
 - ▶ **“sidestream” rook**: ontstaan bij spontane verbranding (cfr. Passief roken)
- ▶ Sigarettenrook bevat irritantia, vrije radicalen en meer dan 40 carcinogenen, waaronder :
 - ▶ N-nitrosamines
 - ▶ Polycyclische aromatische koolwaterstoffen
- ▶ Carcinogeen effect door vorming van DNA adducts

Age-Adjusted Relative Risk



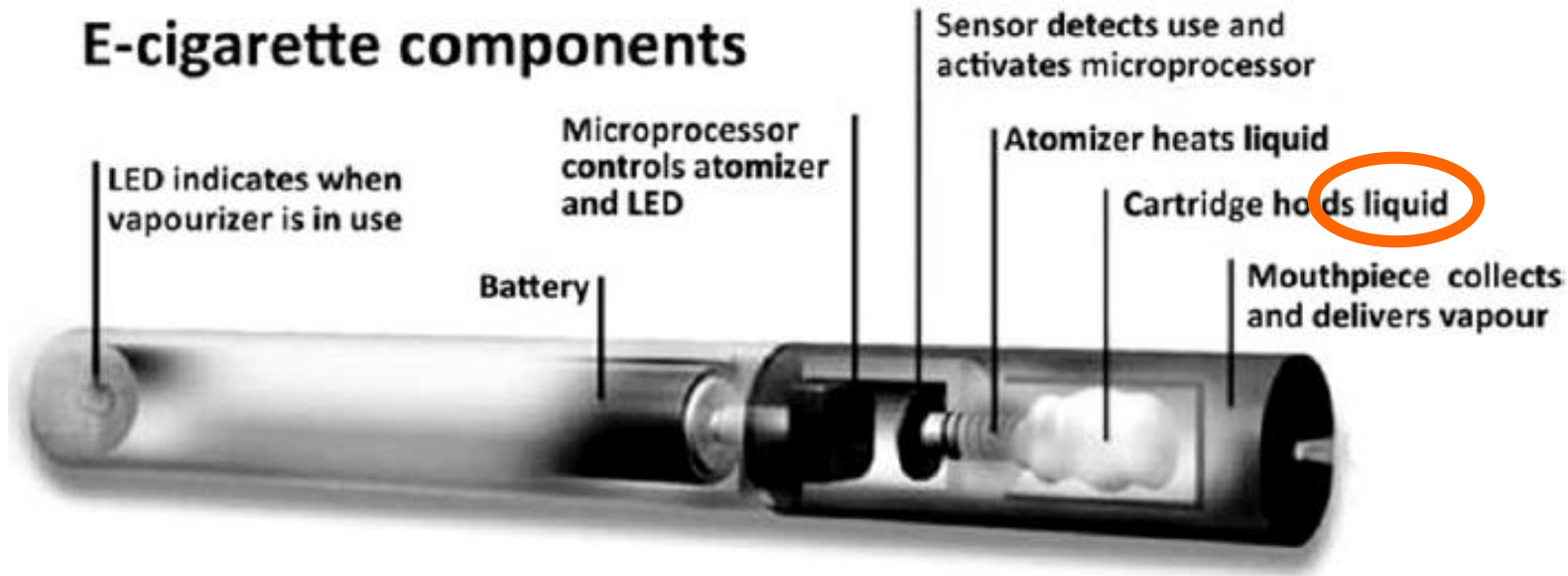
A

E- Cigarettes?

- ▶ Non-combustible tobacco products
 - ▶ Generate inhalable aerosol containing nicotine, flavors, propylene glycol, and vegetable glycerin
 - ▶ Reached the market without either extensive preclinical toxicology testing or long term safety trials

E- Cigarettes?

E-cigarette components



€ 13,80 Ewaks NL Van Google	€ 10,99 DOL.COM Orde verzend Van bestel.nl	€ 10,99 DOL.COM Orde verzend Van bestel.nl	€ 9,90 Majour Van Bigshopper	€ 10,94 Farmaline Van Google	€ 18,89 Newpharma.be Van Google	€ 19,94 DOL.COM Orde verzend Van bestel.nl	€ 28,32 Logimasters Orde verzend Van Google	€ 11,95 Dee Music Van Buy Now	€ 1,88 Vriendship.nl Van Bigshopper	€ 27,80 DOL.COM Orde verzend Van bestel.nl

E- Cigarettes?



- Main page
- Contents
- Featured content
- Current events
- Random article
- Donate to Wikipedia
- Wikipedia store

- Interaction
- Help
- About Wikipedia
- Community portal
- Recent changes
- Contact page

- Tools
- What links here
- Related changes
- Upload file
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View source

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Juul

From Wikipedia, the free encyclopedia

This article is about the vaping device. For other uses, see [Juul \(disambiguation\)](#).

Juul Labs, Inc. (/ˈdʒuːl/, stylized as **JUUL Labs**) is an American **electronic cigarette** company which spun off from Pax Labs in 2017.^[6] It makes the Juul e-cigarette, which packages nicotine salts from leaf tobacco into one-time use cartridges.^[7]

Juul Labs was co-founded by [Adam Bowen](#) and [James Monsees](#).^[8] It headquarters is in [San Francisco](#).^[1] Altria Group (formerly Philip Morris Companies^[9]), acquired a 35% stake in Juul Labs for \$12.8 billion on December 20, 2018.^[10] Juul received a \$2 billion bonus to distribute among its 1,500 employees.^[5]

The Juul became the most popular e-cigarette in the [United States](#) at the end of 2017 and has a market share of 72% as of September 2018.^{[11][12][13]} Its widespread use by youth has triggered concern from the public health community and multiple investigations by the [U.S. Food and Drug Administration](#).^{[1][14]} Given the high nicotine concentrations in Juul, the nicotine-related health consequences of its use by young people could be more severe than those from their use of other e-cigarette products.^[15]

Contents [hide]

- History
 - 1.1 Founders
 - 1.2 Executive Team
 - 1.3 VMR Products
- Investors
- Design
- Usage
 - 4.1 Prevalence among adolescents
 - 4.2 Quitting
- Health concerns
 - 5.1 Nicotine content
- Market share
 - 6.1 United States
 - 6.2 International
- Marketing

Juul Labs, Inc.



Juul vaping device with pods

Type	Private
Predecessor	Pax Labs
Founded	May 22, 2015; 4 years ago

E- Cigarettes? Controversies

- ▶ Effectiveness as a smoking cessation intervention?
 - ▶ Eg : Halpern et al (NEJM 2018;378:2302-10)
- ▶ Impact at a population level?
- ▶ Less harmful than combustible tobacco products?
 - ▶ Measurable adverse biologic effects on organ and cellular health in humans, in animals, and in vitro.
 - ▶ The effects of e-cigarettes have similarities to and important differences from those of cigarettes.
 - ▶ Decades of chronic smoking are needed for development of lung diseases such as lung cancer or chronic obstructive pulmonary disease
 - Population effects of e-cigarette use may not be apparent until the middle of this century

McAfee E-mail Scan

Bestand | Bericht

Negeren | Ongewenste e-mail | Verwijderen | Beantwoorden | Allen beantwoorden | Doorsturen | Meer | Vergadering

Verwijderen | Reageren

Snelle stappen: VAN WESEMAE... | Aan manager | E-mail aan team | Gereed | Antwoorden en... | Nieuwe maken

Verplaatsen | Verplaatsen | OneNote | Acties

Markeren als ongelezen | Coderen | Coderen | Opvolgen

Bewerken: Zoeken | Verwant | Selecteren

Zoomen: In-/uitzoomen



vr 6/09/2019 19:13

NEJM <nejmtoc@nejm.org>

[BULK] September 6, 2019 — Recently Published on NEJM.org

Aan Malfait Thomas

U hebt dit bericht doorgestuurd op 7/09/2019 8:44.

Recently Published, September 6, 2019

Because of the public health implications, the following articles were published on NEJM.org

ORIGINAL ARTICLE

Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report

J.E. Layden and Others

EDITORIAL

Vaping-Induced Lung Injury

D.C. Christiani

CORRESPONDENCE

Imaging of Vaping-Associated Lung Disease

T.S. Henry, J.P. Kanne, and S.J. Kilgerman

CORRESPONDENCE

Pulmonary Lipid-Laden Macrophages and Vaping

S.D. Maddock and Others

FOLLOW US



This email was sent to thomas.malfait@uzgent.be.



11:26
22/10/2019

Longkanker: Risicofactoren

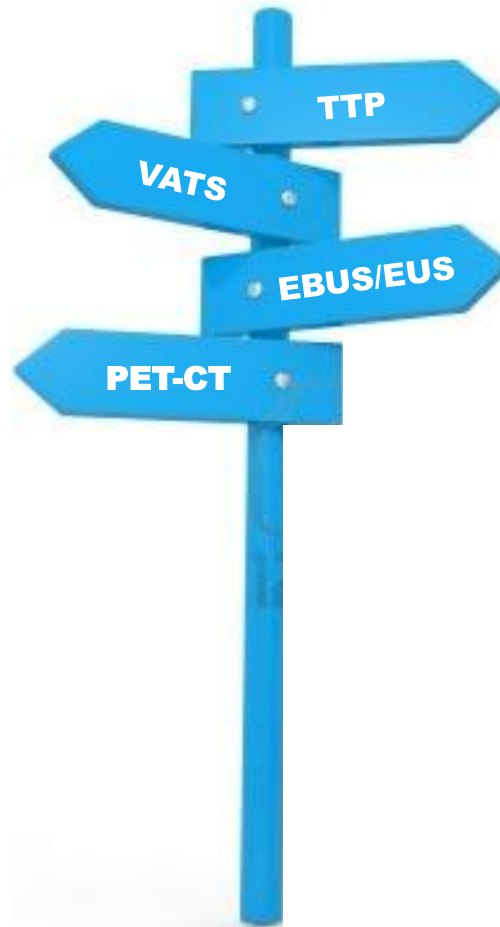
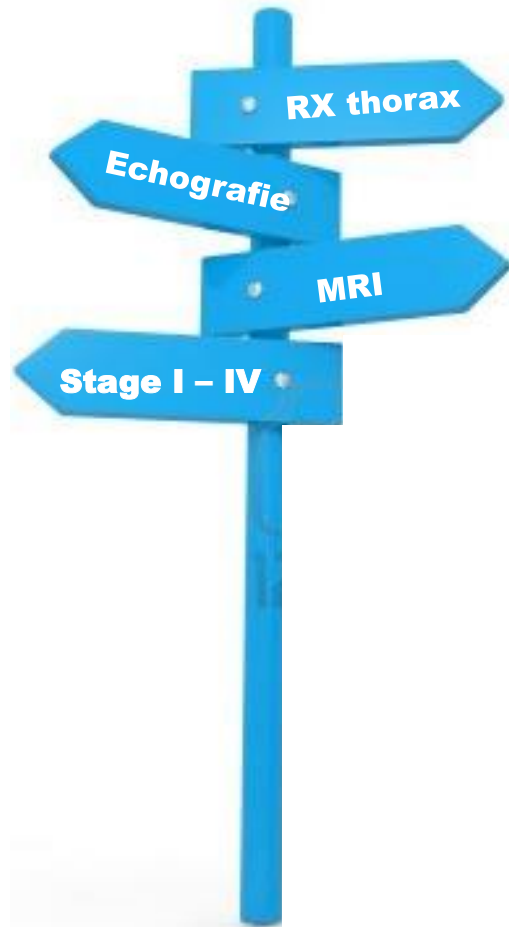
Genetische predispositie

<u>Roken</u>	<u>Fam. An.</u>	<u>Odds ratio</u>
-	+	5.7
+	-	15.1
+	+	30.0

Epidemiologie

Diagnostiek

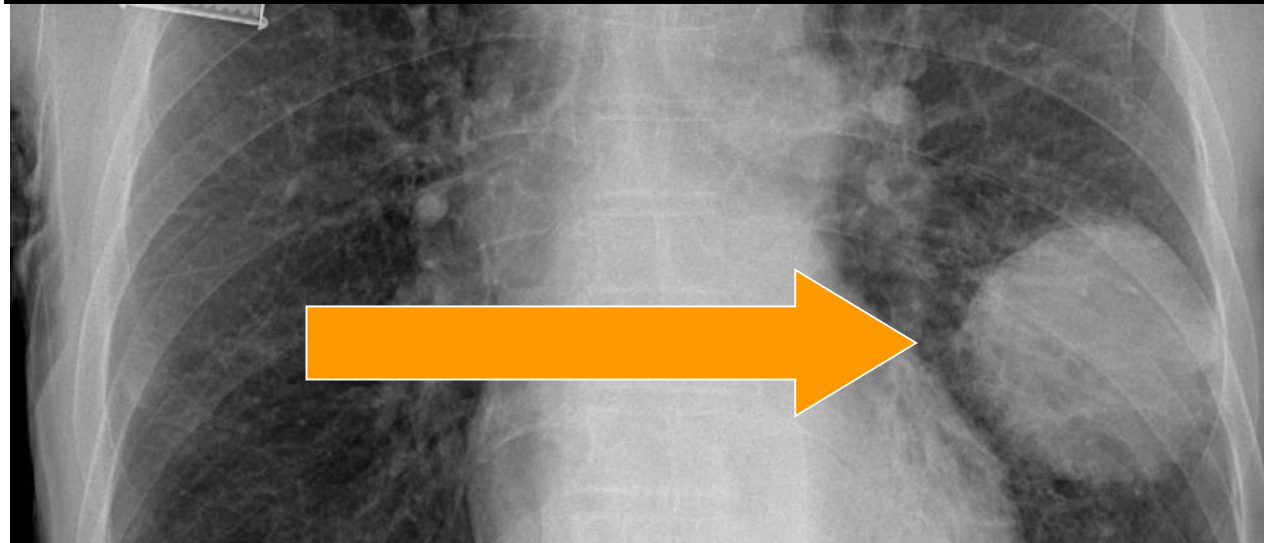
Therapie



- ▶ Concept diagnostiek
- ▶ Concept staging
- ▶ Diagnostisch traject
- ▶ Diagnostische technieken
- ▶ Take home messages



Wat is het ?



Waar zit het ?



- ▶ **Concept diagnostiek**
- ▶ **Concept staging**
- ▶ Diagnostisch traject
- ▶ Diagnostische technieken
- ▶ Take home messages

Diagnostiek = wat is het ?

- ▶ “Tissue is the issue”
 - ▶ Weefseldiagnose is essentieel vooraleer behandeling kan gestart worden
- ▶ Verschillende technieken :
 - ▶ Bronchoscopie, echo-endoscopie, transthoracale punctie, biopt van metastase, pleurapunctie, thoracoscopie, mediastinoscopie...
- ▶ Histologie (biopten) > cytologie (uitstrijkjes)
- ▶ Afweging maken tussen ‘invasiviteit’ (= risico’s) en ‘opbrengst’
- ▶ Pogen om ‘diagnostiek’ en ‘staging’ op elkaar af te stemmen

Stagering = waar zit het ?

- ▶ Kanker opdelen in verschillende groepen op basis van verschillende stadia (stages → stagering) :
 - ▶ Overleving is hoger bij patiënten waar de ziekte nog lokaal is tov patiënten waar de ziekte reeds buiten het primaire orgaan te vinden is.

- ▶ Doel
 1. Clinicus helpen om een **behandelingsplan** op te stellen
 2. Een idee geven omtrent **prognose**
 3. Effect van behandeling beter **evalueren**.
 4. **Informatie-overdracht** vergemakkelijken

FIGURE 70 - LUNG CANCER: RELATIVE SURVIVAL BY STAGE IN MALES (BELGIUM, 2004-2008)

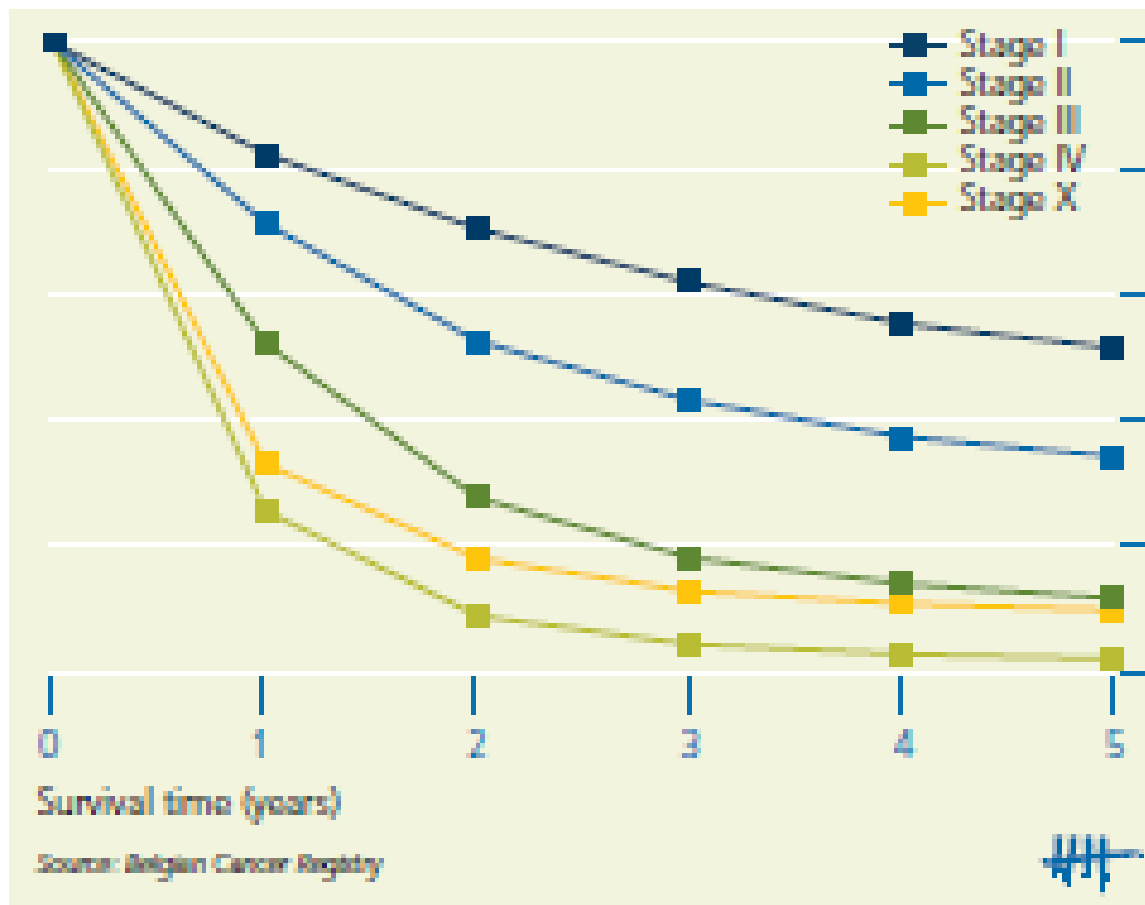
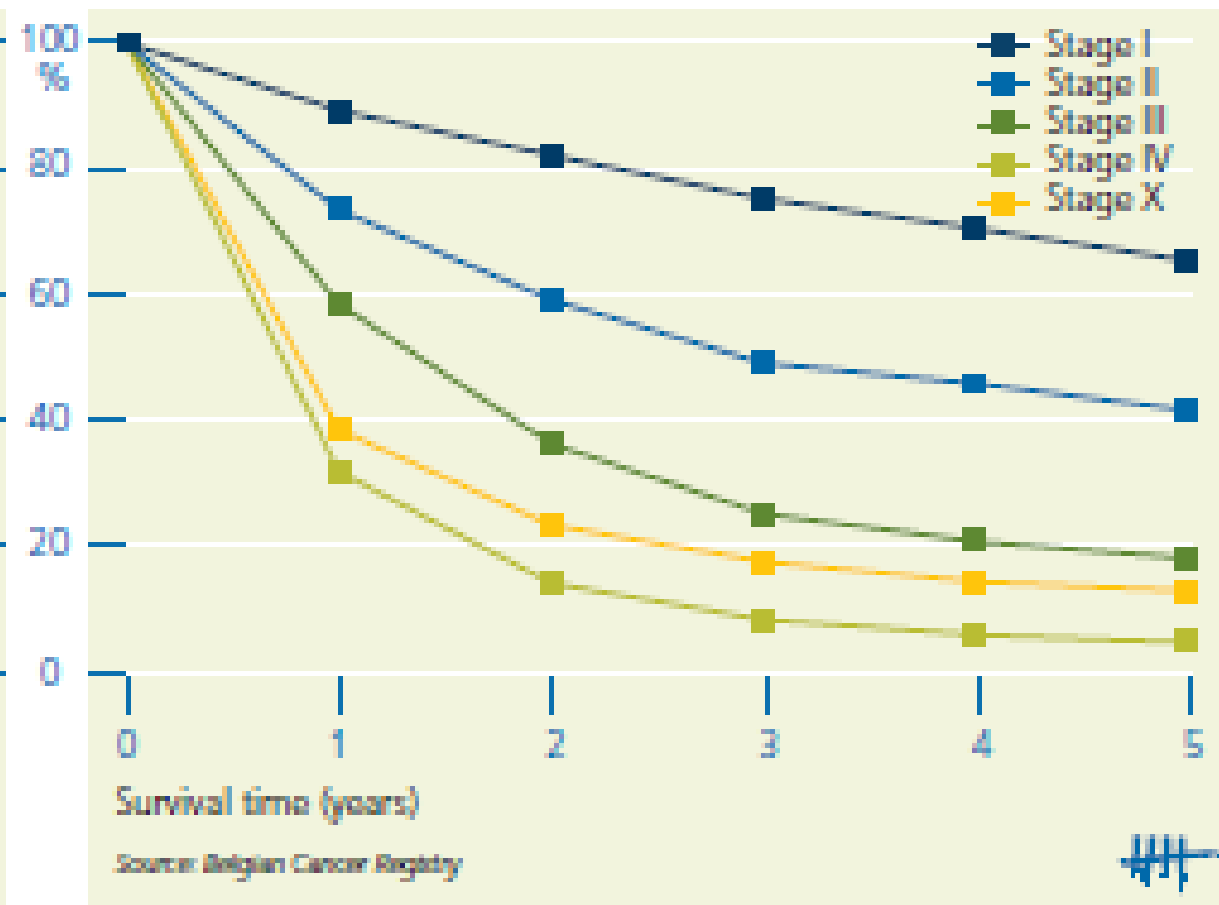


FIGURE 71 - LUNG CANCER: RELATIVE SURVIVAL BY STAGE IN FEMALES (BELGIUM, 2004-2008)

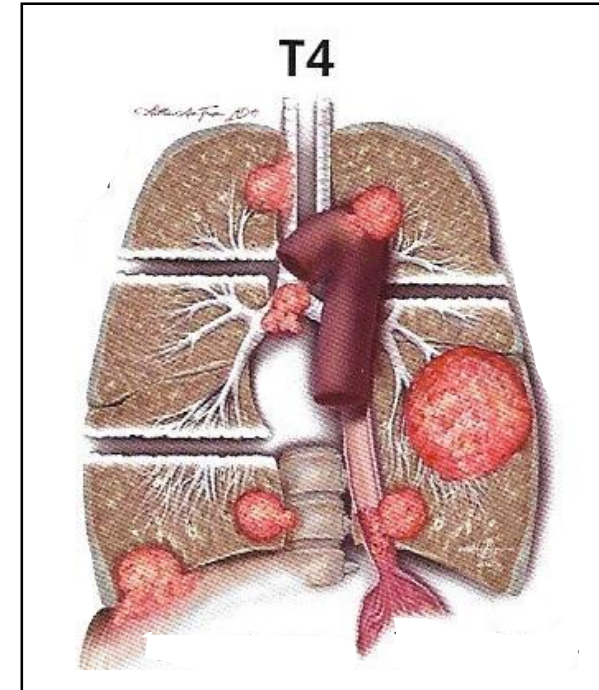
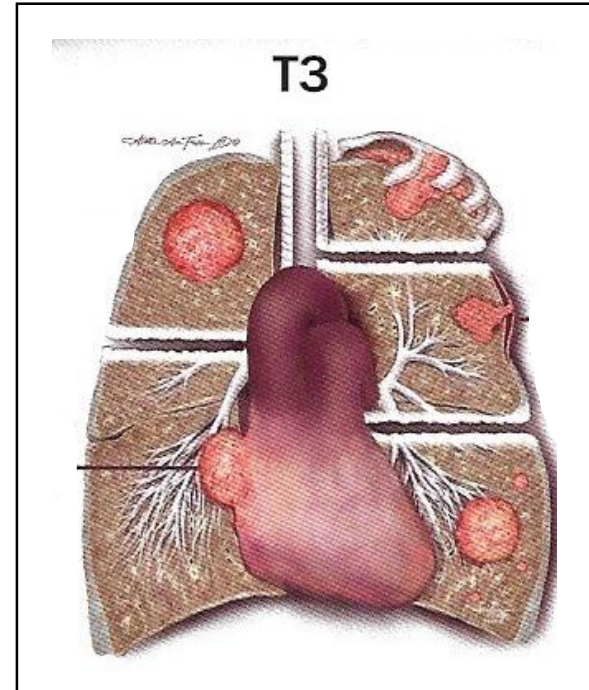
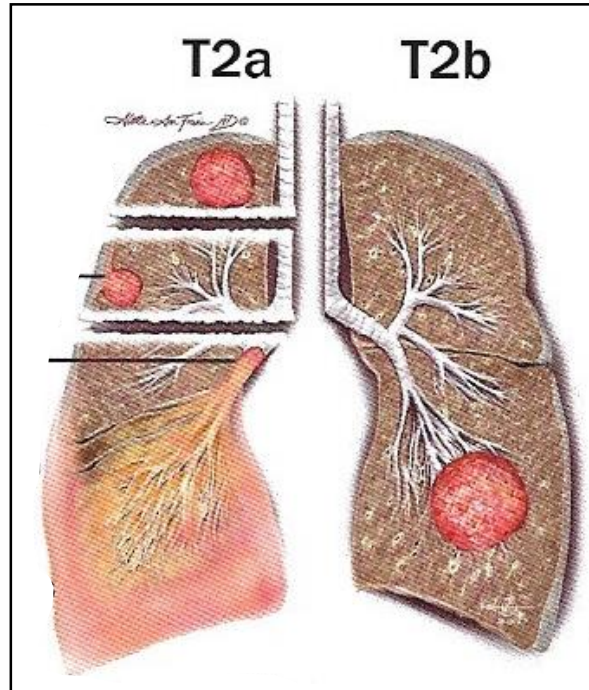
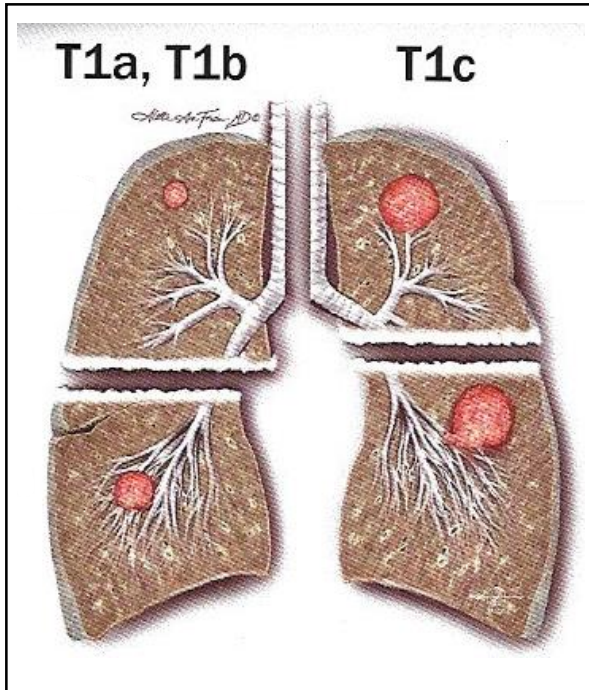


Stagering thoracale maligniteit : overzicht

STAGE	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0

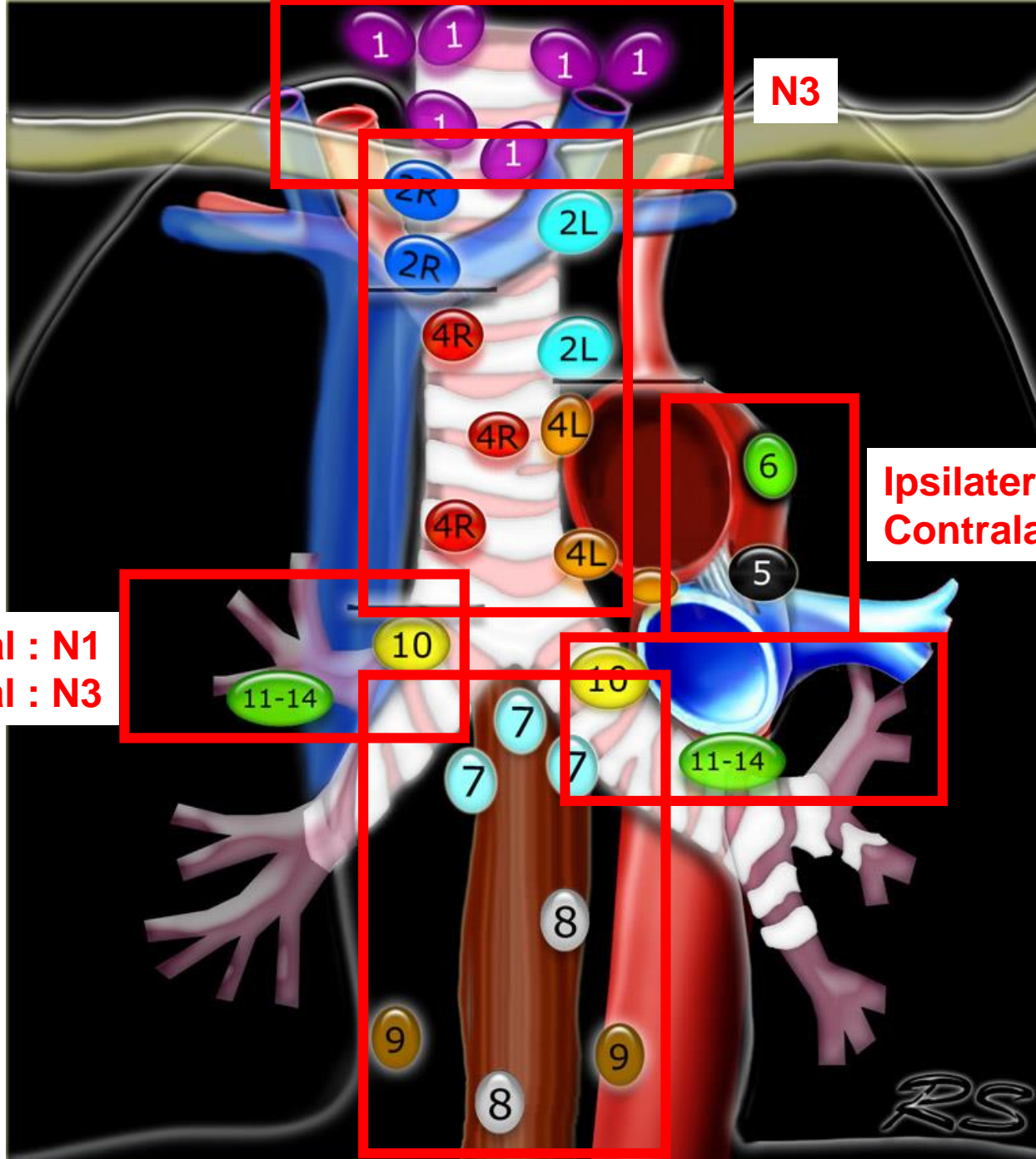
STAGE	T	N	M
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

Stagering : T - status



Stagering : N status

- ▶ N1 Ipsilateraal peribronchiaal, ipsilateraal hilair
- ▶ N2 Subcarinaal, ipsilateraal mediastinaal
- ▶ N3 Contralateraal mediastinaal of hilair, scalenus of supraclaviculair
- ▶ Verschillende klierstations rondom de luchtpijp met elk specifieke lokalisatie en nummering
 - ▶ Supraclaviculair = N3 = **1**
 - ▶ Mediastinale klieren = N2 – N3 = **2 – 9**
 - ▶ Peribronchiaal - Hilaire klieren = N1 = **10 – 14**



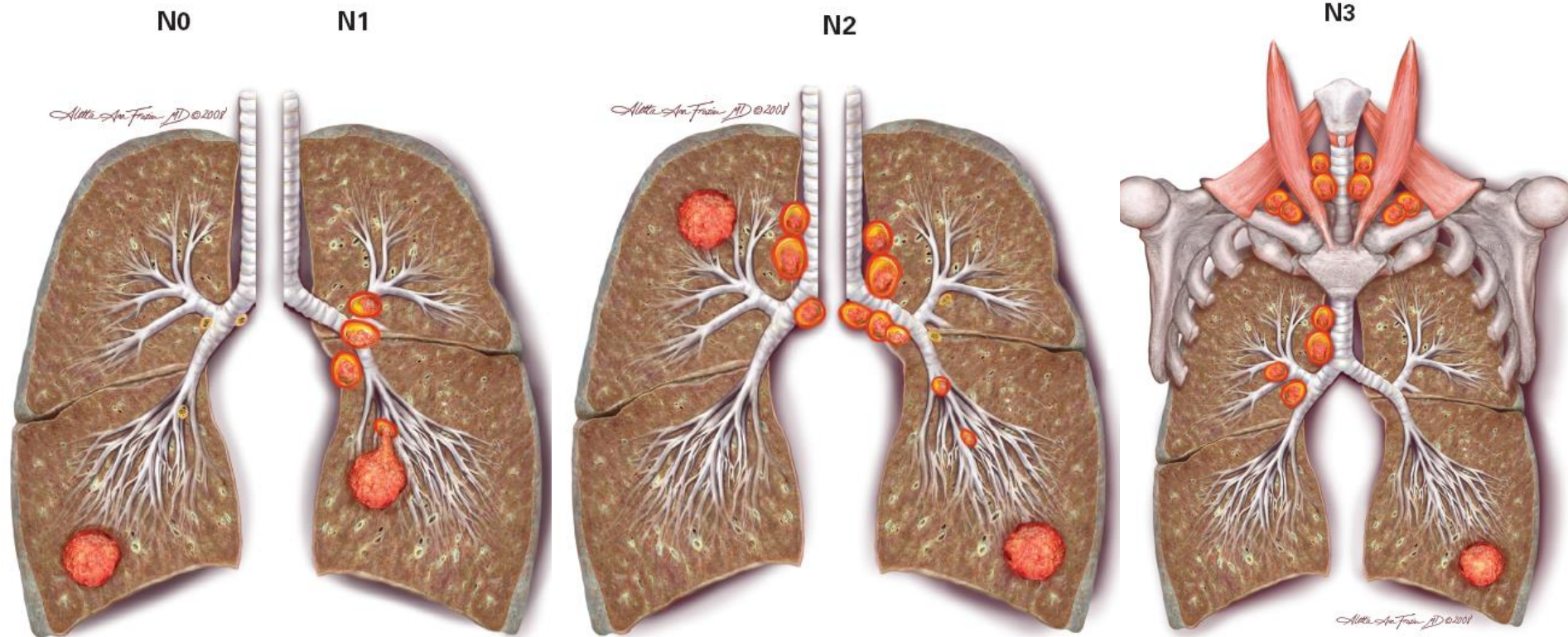
N3

**Ipsilateraal : N2
Contralateraal : N3**

**Ipsilateraal : N1
Contralateraal : N3**

RS

Stagering : N status

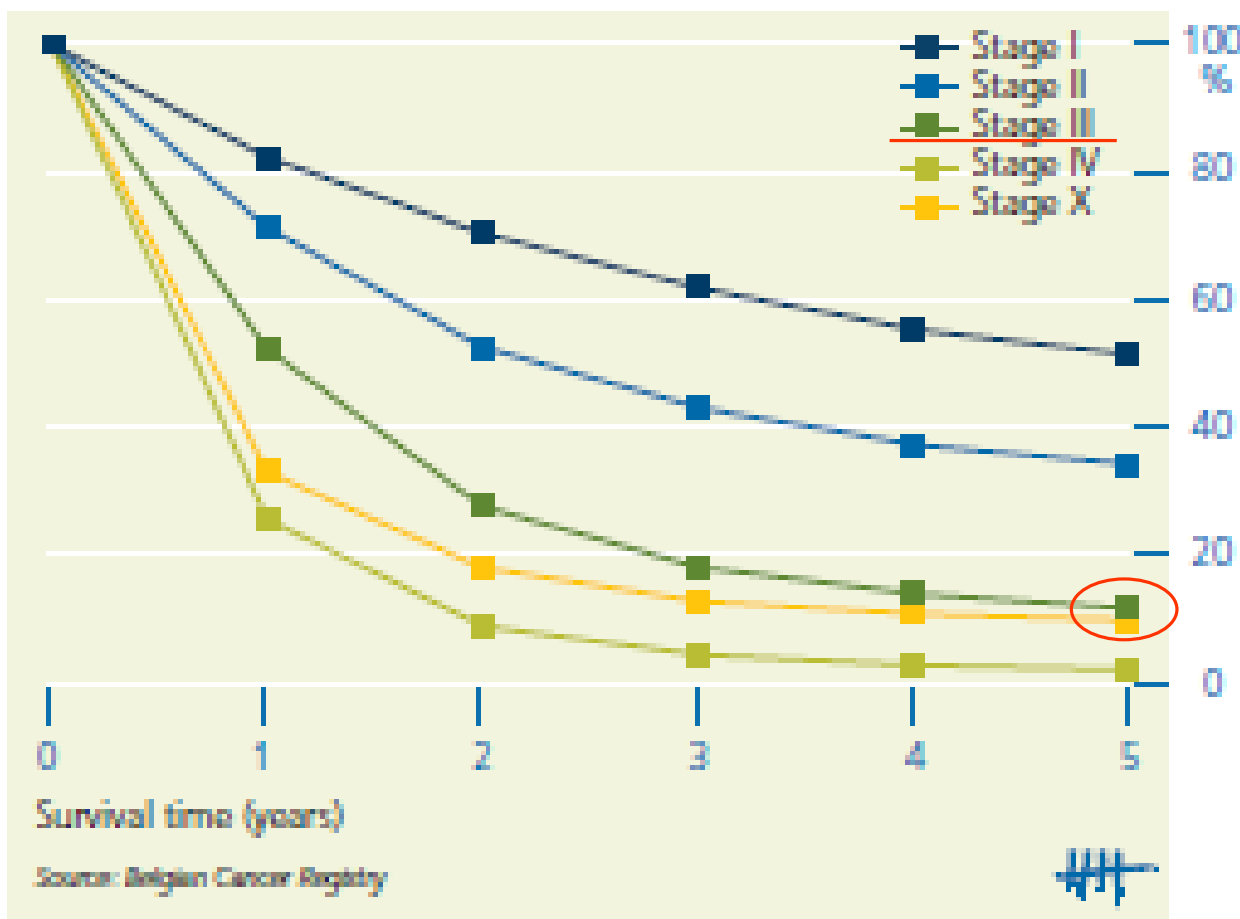


Stagering : N status

- ▶ N1 Ipsilateraal peribronchiaal, ipsilateraal hilair
 - ▶ N2 Subcarinaal, ipsilateraal mediastinaal
 - ▶ N3 Contralateraal mediastinaal of hilair, scalenus of supraclaviculair
-
- **Aanwezigheid van N2 of N3 ziekte heeft belangrijke impact**
 - prognostisch
 - therapeutisch

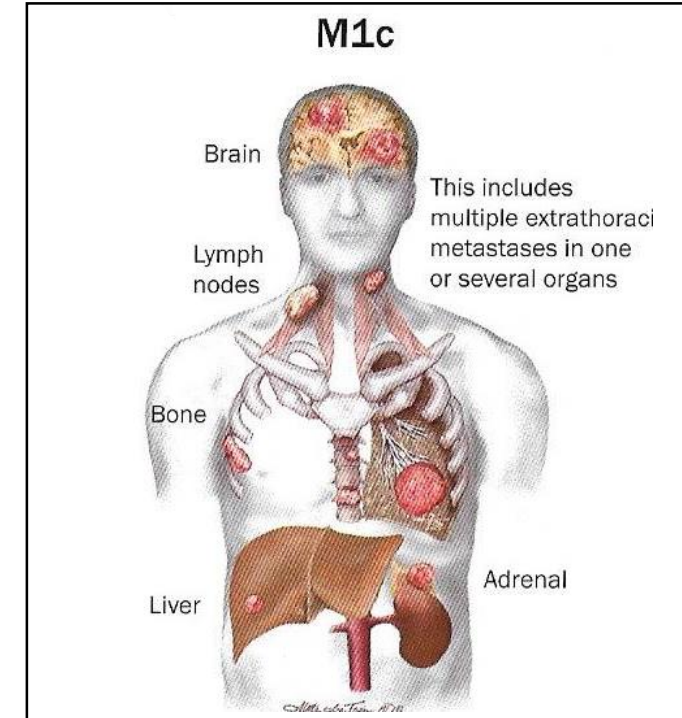
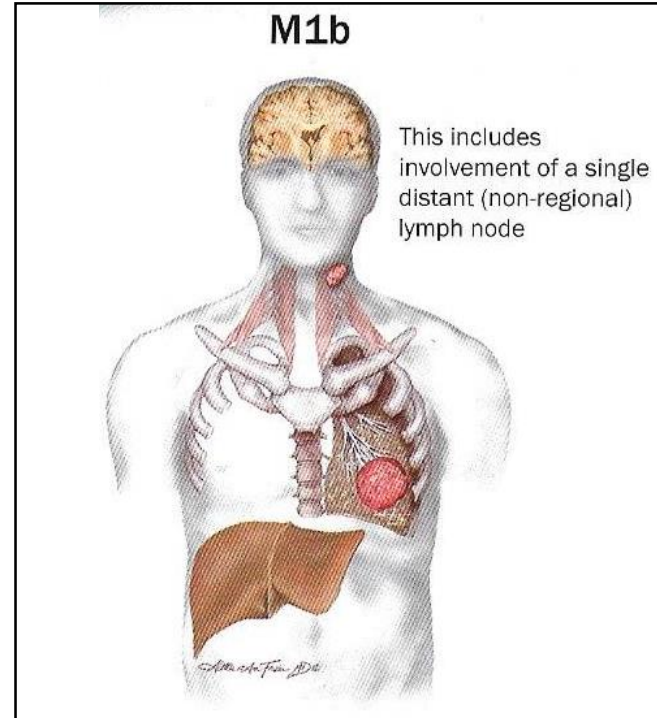
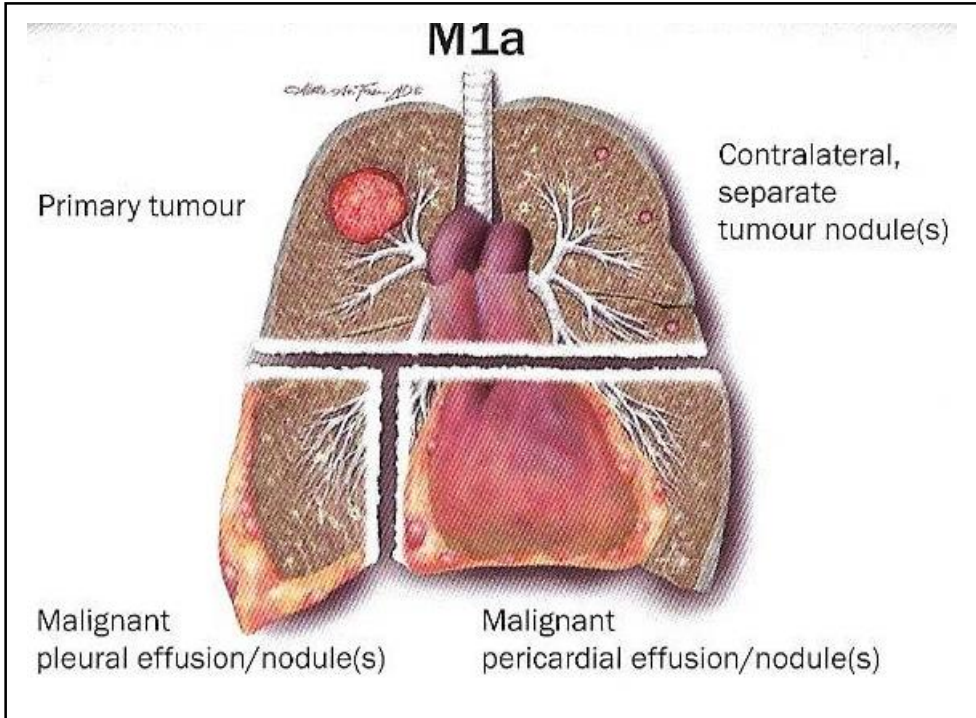
Stagering thoracale maligniteit : Belang van N-status

FIGURE 70 - LUNG CANCER: RELATIVE SURVIVAL BY STAGE IN MALES (BELGIUM, 2004-2008)

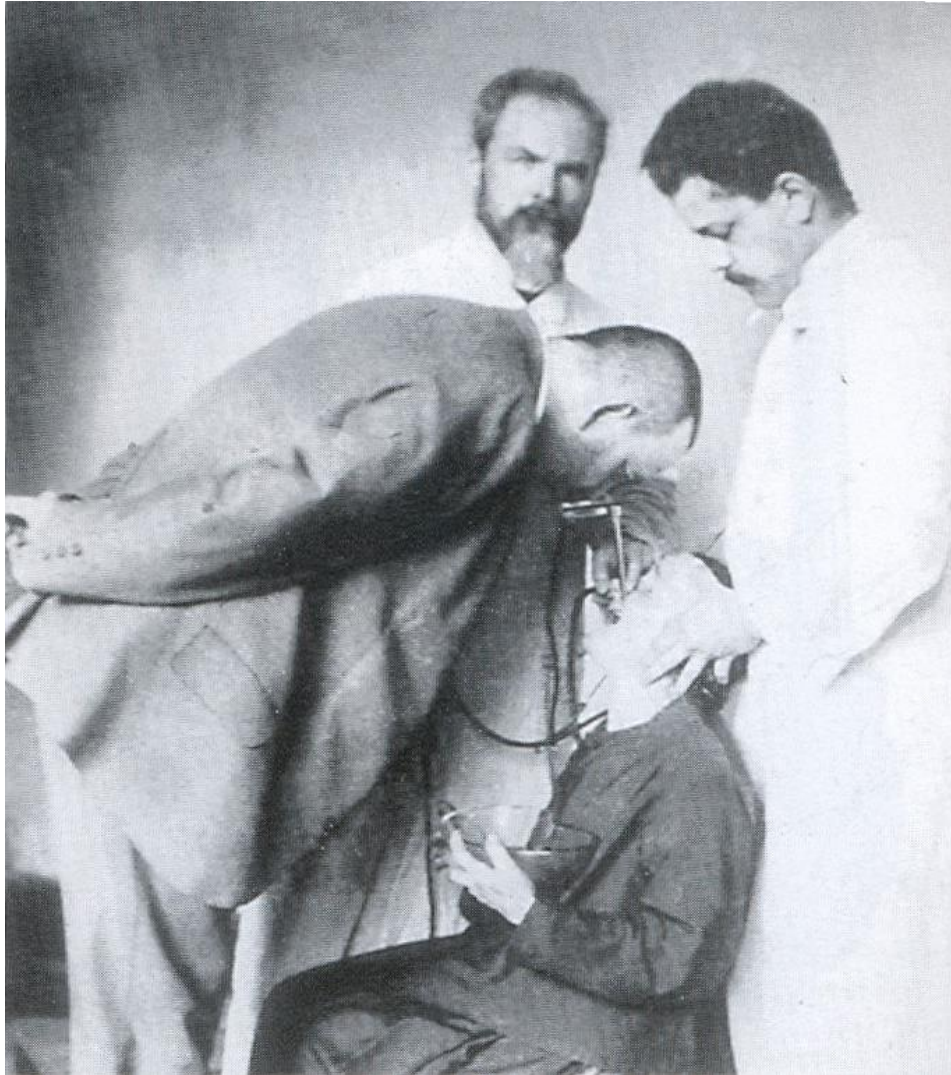


N2	N3
IIIa	IIIb
IIIa	IIIb
IIIa	IIIb
IIIa	IIIb
IIIa	IIIb
IIIa	IIIb
IIIa	IIIb
IIIb	IIIb
IIIb	IIIb
IV	IV
IV	IV
IV	IV

Stagering : M status

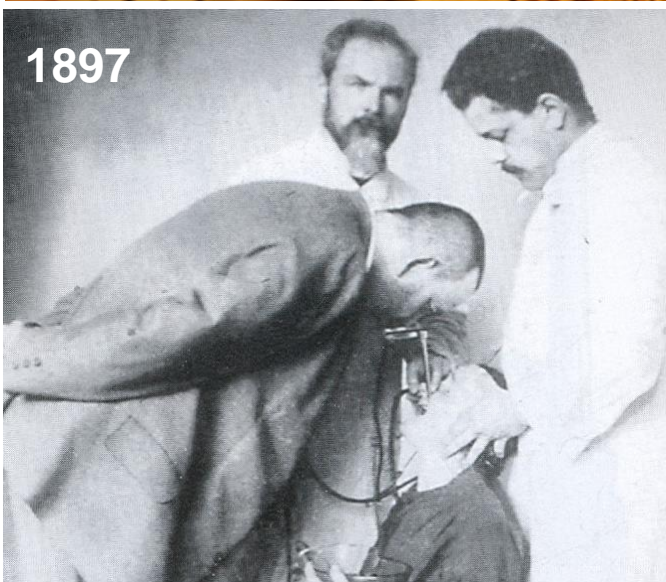


- ▶ Concept diagnostiek
- ▶ Concept staging
- ▶ **Diagnostisch traject**
- ▶ **Diagnostische technieken**
- ▶ Take home messages



Historical Perspective

The first reported TFB extraction was by **Killian** in 1897 [2]. A farmer from the Black Forest in Germany was referred to Dr. **Killian** after swallowing a **pork bone** with symptoms of severe cough, dyspnea, and hemoptysis. Using a Kirstein laryngoscope, **Killian** was able to identify a solid object in the right main stem bronchus. His initial reaction was to perform a tracheostomy; however, not being a surgeon, he was not permitted to do the operation. After consultation with a laryngologist, **Killian** removed the foreign body (**pork bone**) using a Mikulicz–Rosenheim esophagoscope under local cocaine anesthesia.



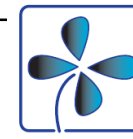


Niet invasief	Minimaal invasief	Invasief
RX	TTNA (Transthoracale punctie – naald aspiraats) (echo geleid – CT geleid)	VATS / Open longbiopsie
CT scan	Bronchoscopie Brushing – biopsien (perifeer – centraal) – lavage – blinde TBNA	Mediastinoscopie
PET – CT	rEBUS - Biopsien	Rigide / starre scopie
MRI	EBUS – TBNA	
Echografie	EUS – TBNA	
	Pleurapunctie	

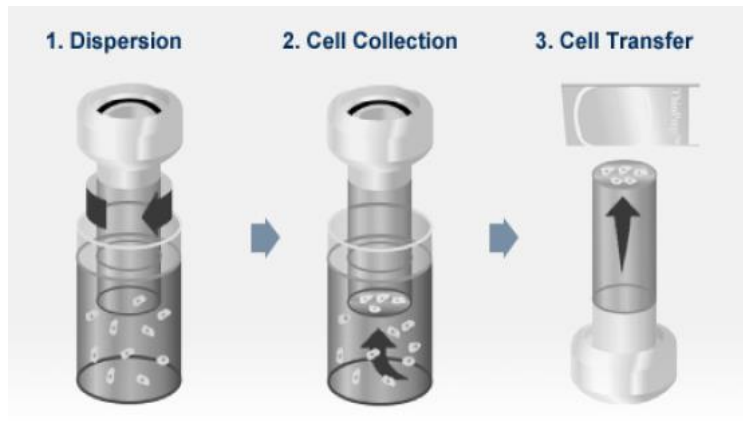
Dr Desender



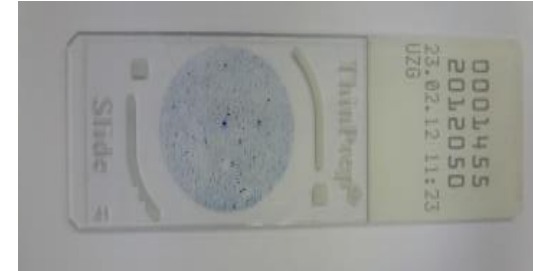
Cytologie	Histologie	
Losliggende cellen zonder weefselverband op een uitstrijkje of in suspensie	Vaste weefselstukken met cellen in duidelijk verband Grotere hoeveelheid materiaal	
	Biopten	Resectiestukken
Bronchoscopie Brushing – lavage – blinde TBNA TTNA (Transthoracale punctie – naald aspiraats) EBUS – TBNA EUS – TBNA Pleurapunctie	Bronchoscopie biopten (perifeer – centraal) rEBUS - Biopten	VATS / Open longbiopt Mediastinoscopie Rigide / starre scopie
Celblok		



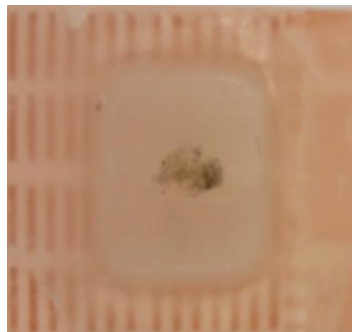
Cell Blocks



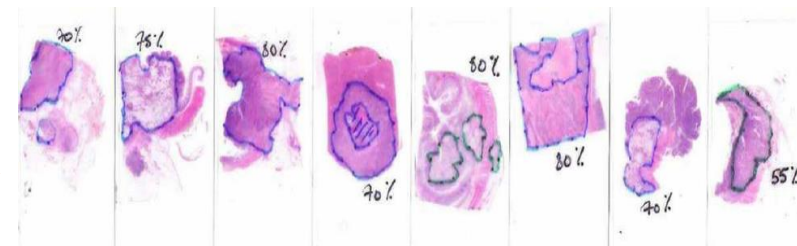
http://www.thinprep.com/hcp/lab_professionals/imaging_system/thinprep_2000.html



Monolayer used for primary diagnosis



Cell block used for further differentiation and mutation testing.



DNA enrichment by manual macrodissection for preparing Therascreen testing.

Pt met vermoeden van
longcarcinoom

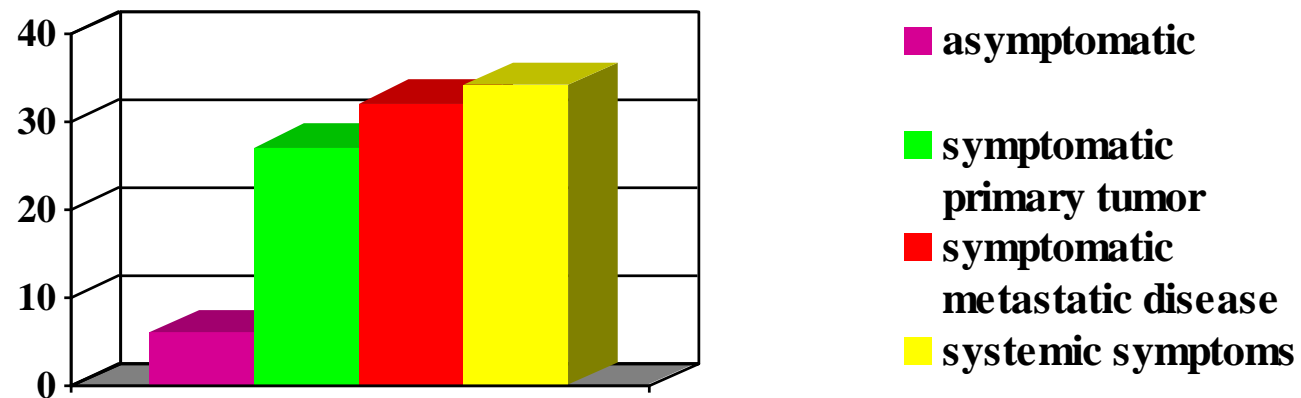
Intake : voorgeschiedenis, rookgedrag, medicatie, klinisch onderzoek, performance status, oude beeldvorming, ...

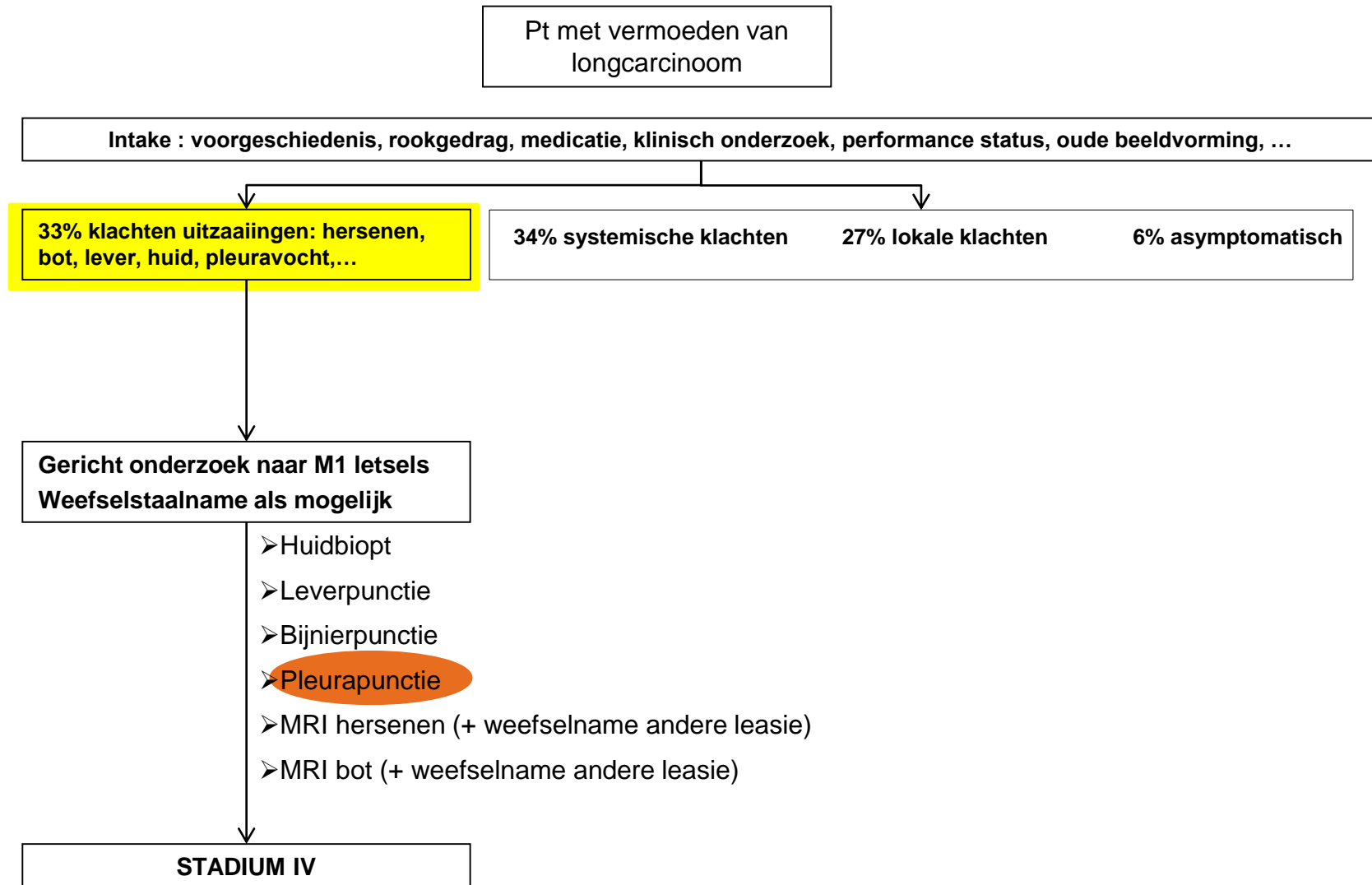
6% asymptomatisch: toeval RX

27% lokaal: hoest, haemoptoe, hees, dyspnoe, slikklachten

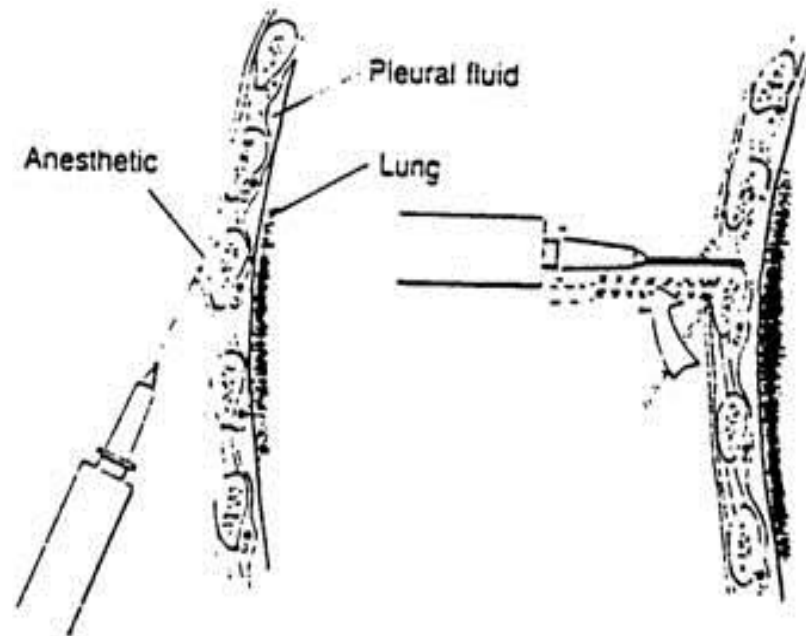
33% klachten tgv uitzaaiingen: hersenen, bot, lever

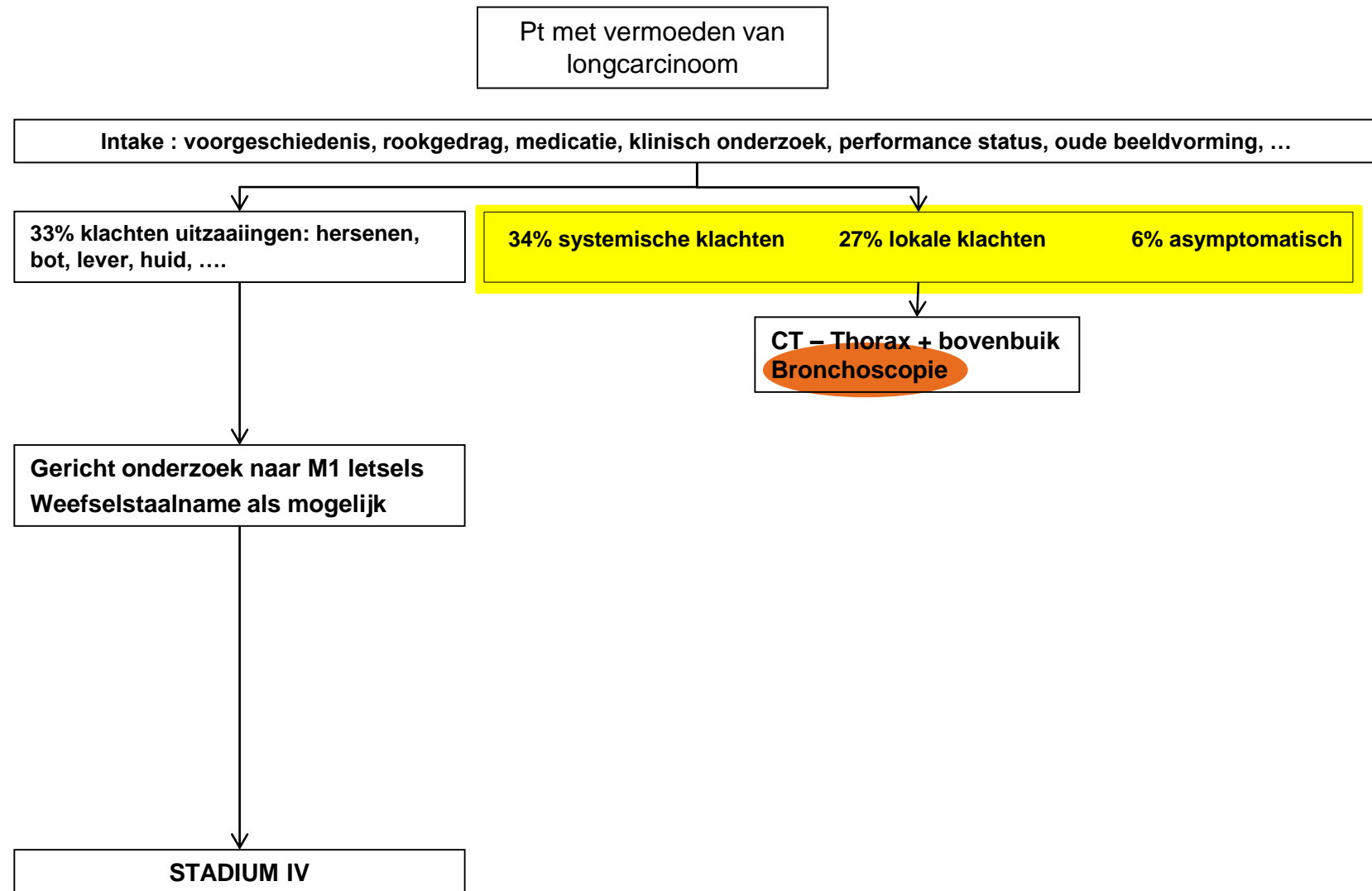
34% systemische klachten: moe, lusteloos, vermagering, koorts





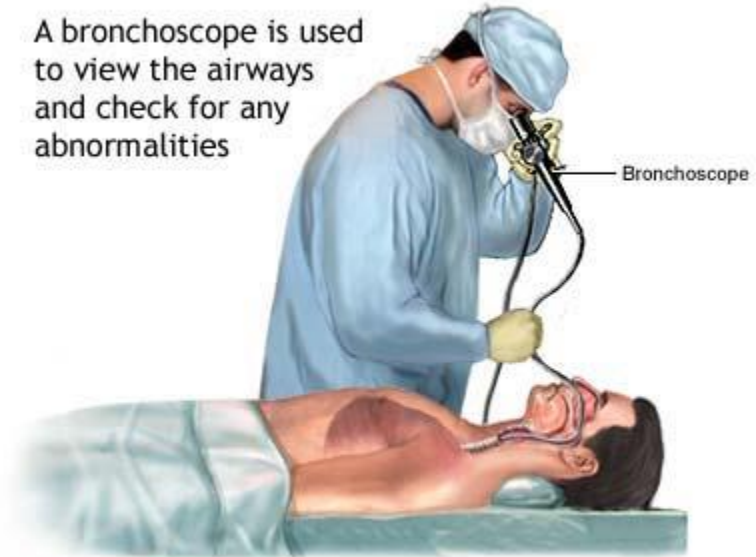
Pleuravocht : thoracocentese techniek



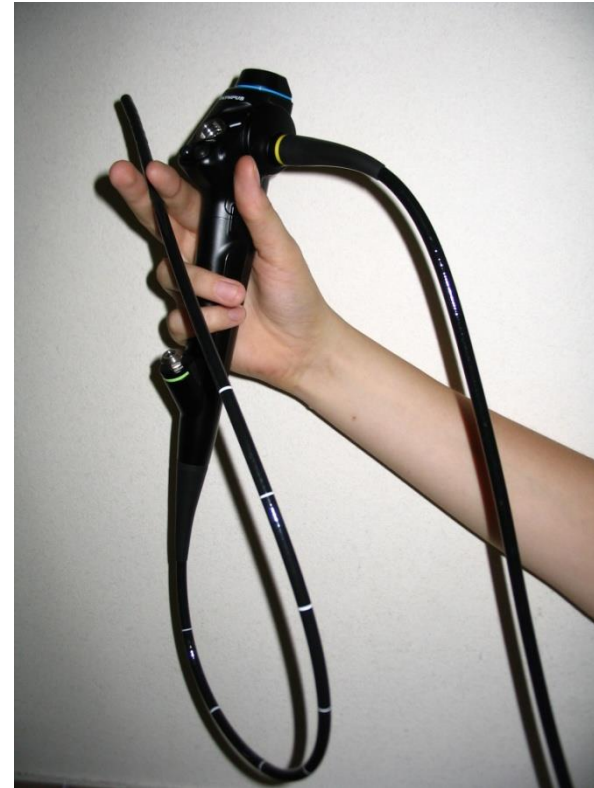


Flexible bronchoscopie

A bronchoscope is used to view the airways and check for any abnormalities

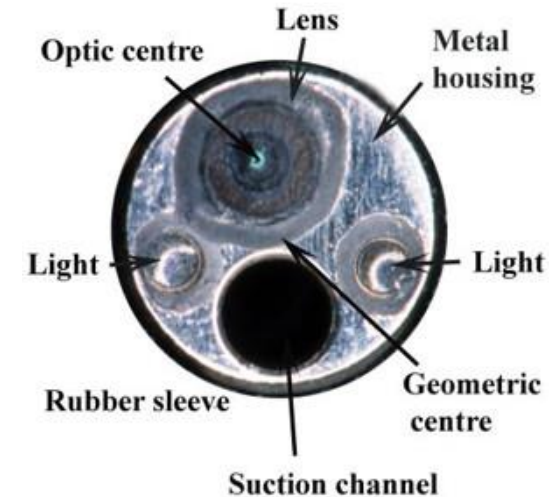


ADAM.

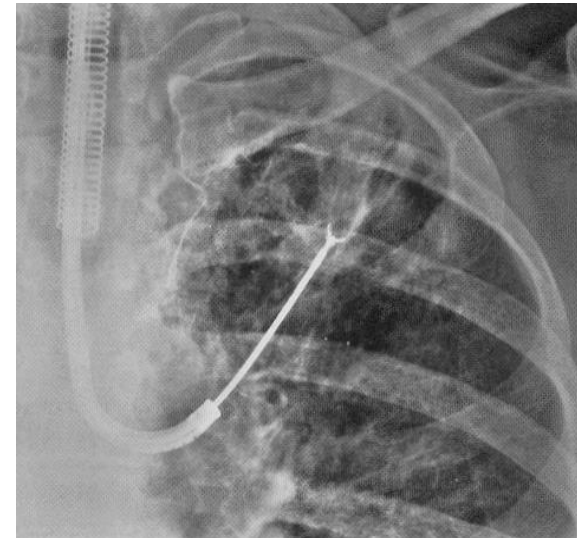
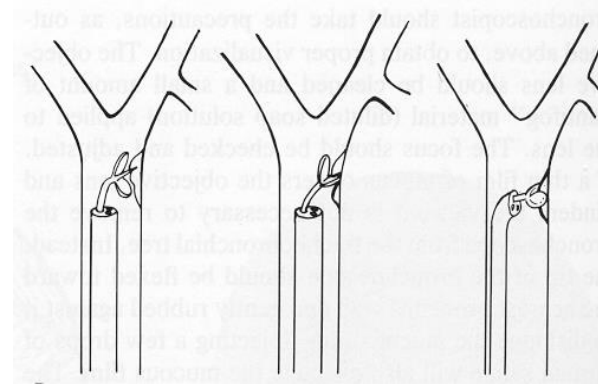
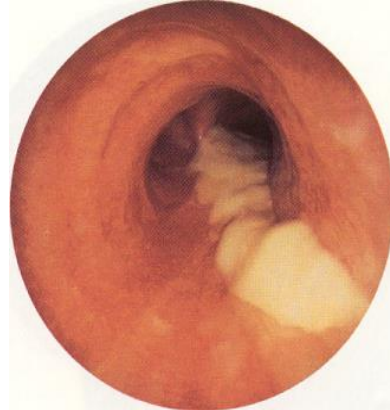
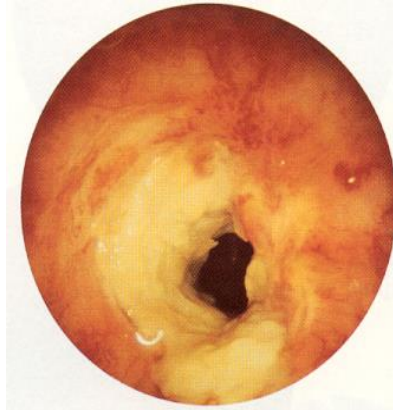


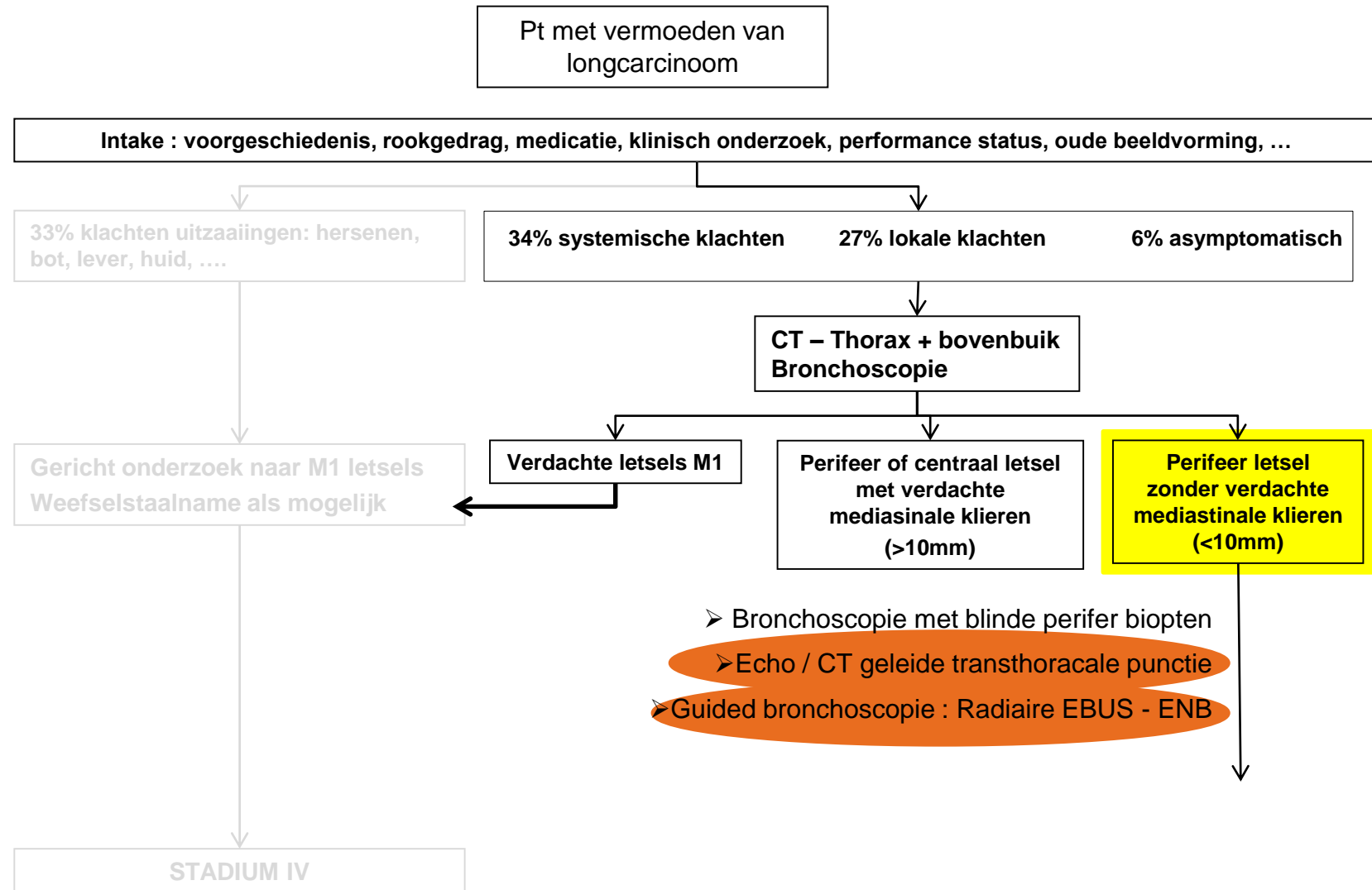
Flexible bronchoscopie

- ▶ Flexible scoop – diameter +/- 6 mm
 - ▶ Camera in de top + 2 lichtjes
 - ▶ Werkkanaal (+/- 2.8mm)
- ▶ Pt zittend of liggend
- ▶ Lokale verdoving van de keel
 - ▶ Sedatie (UZ Gent tot 80%) – Narcose (complexe procedures)
 - ▶ De patiënt blijft gewoon ademen tijdens onderzoek
- ▶ Wat extra zuurstof tijdens onderzoek
- ▶ Voorbereiding : +/- 10 minuten
- ▶ Procedure : +/- 10 minuten
- ▶ Observatie : tot patiënt zich goed voelt (medicatie uitgewerkt is en de bloeddruk/pols/zuurstofmeting in orde is)



Flexible bronchoscope



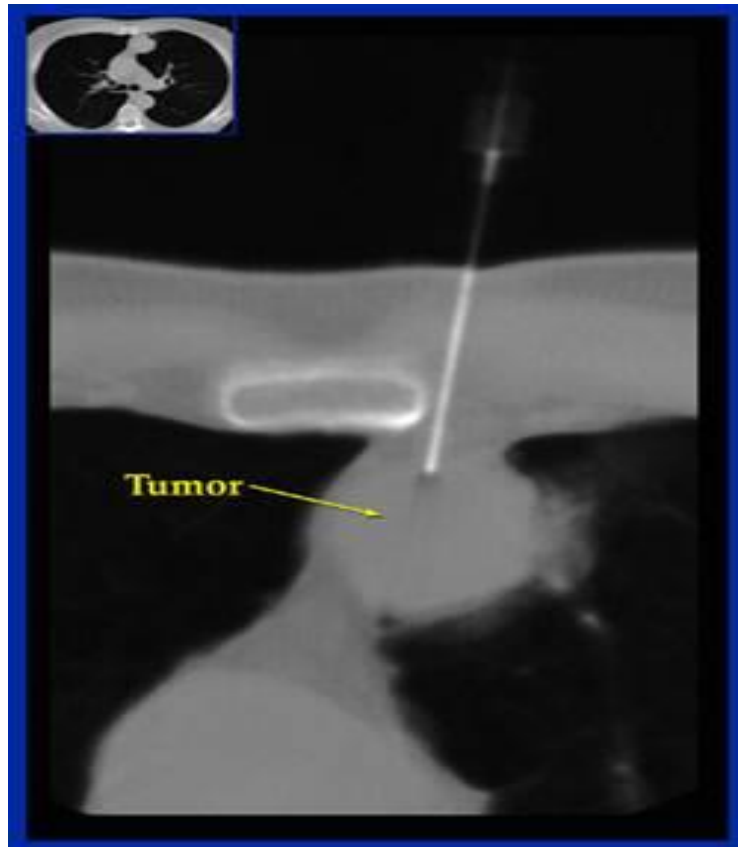


Transthoracale punctie

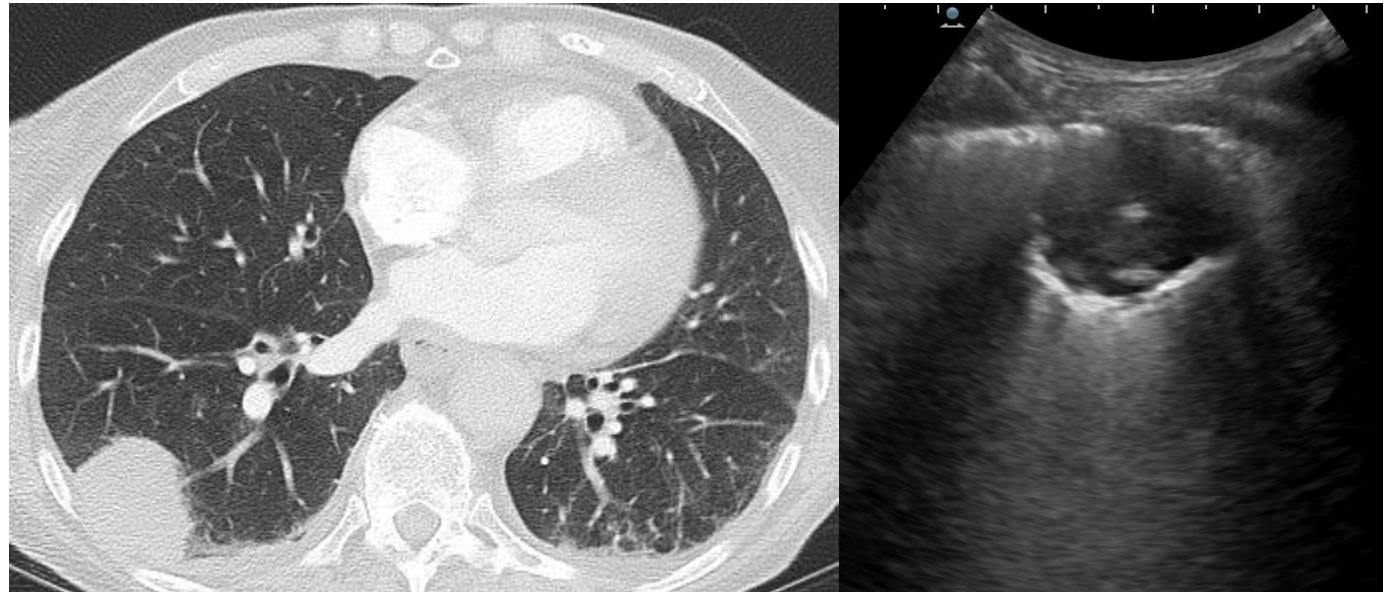
- ▶ Perifere Tumoren
 - ▶ Pleuraal contact : echogeleid
 - ▶ Geen pleuraal contact : CT geleid
- ▶ Cytologie (fijne naaldaspiraats [FNA])
- ▶ Histologie (true cutt biopsie)
- ▶ Gevoelige techniek in ervaren handen
- ▶ 7-35% pneumothorax, zelden drainage nodig
- ▶ CI : respiratoire insufficiëntie, unieke long, pulmonale hypertensie, stollingsstoornissen.

Transthoracale punctie

CT Geleid



Echo Geleid





CHEST

Original Research

PULMONARY PROCEDURES

Meta-analysis of Guided Bronchoscopy for the Evaluation of the Pulmonary Nodule

Jessica S. Wang Memoli, MD; Paul J. Nietert, PhD; and Gerard A. Silvestri, MD, FCCP

	Blind TBB	CT guided	Guided bronchoscopy
Yield	34% [14%-64%]	76%-90%	70% [46%-86%]
Complications			
Pneumothorax		25% [Up to 40%]	1.5% [0%-7.5%]
Drain		15%	0.6%

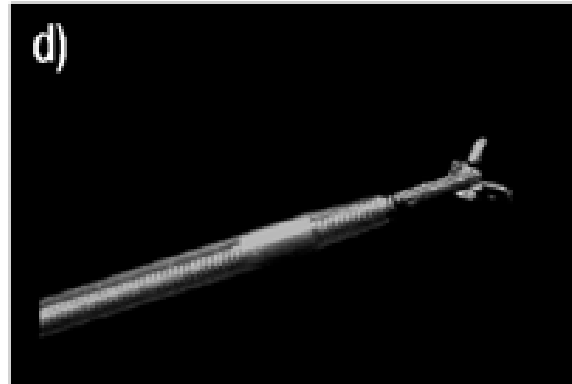
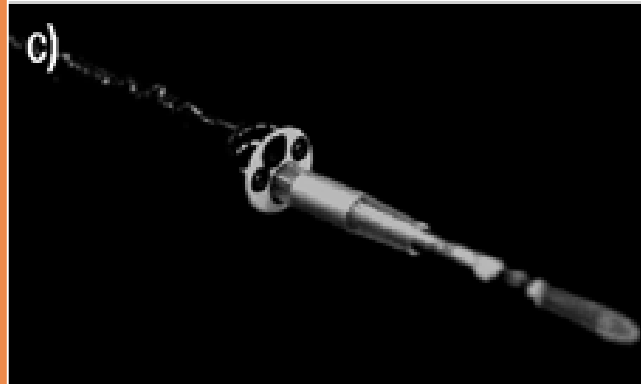
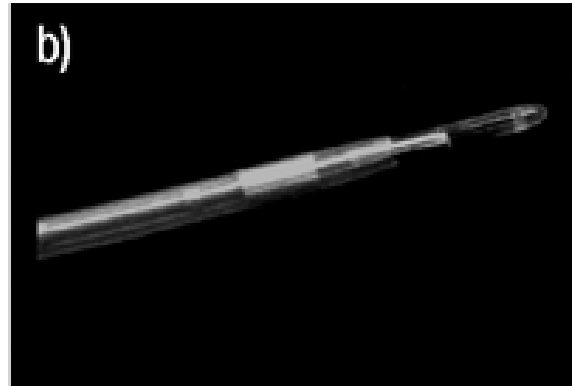
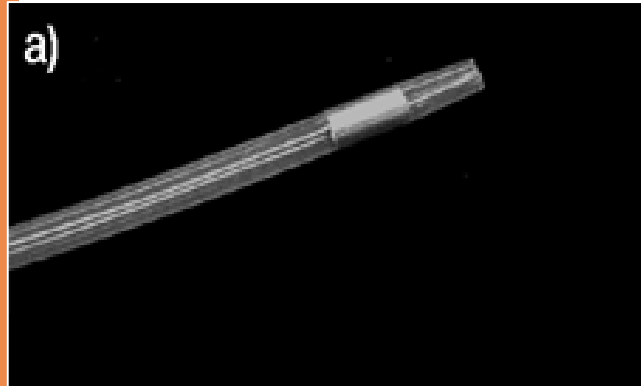
- Nodule size > or < 2cm, bronchus sign, distance to hilum
- 2012 => technological evolution anno 2016?

Guided bronchoscopy

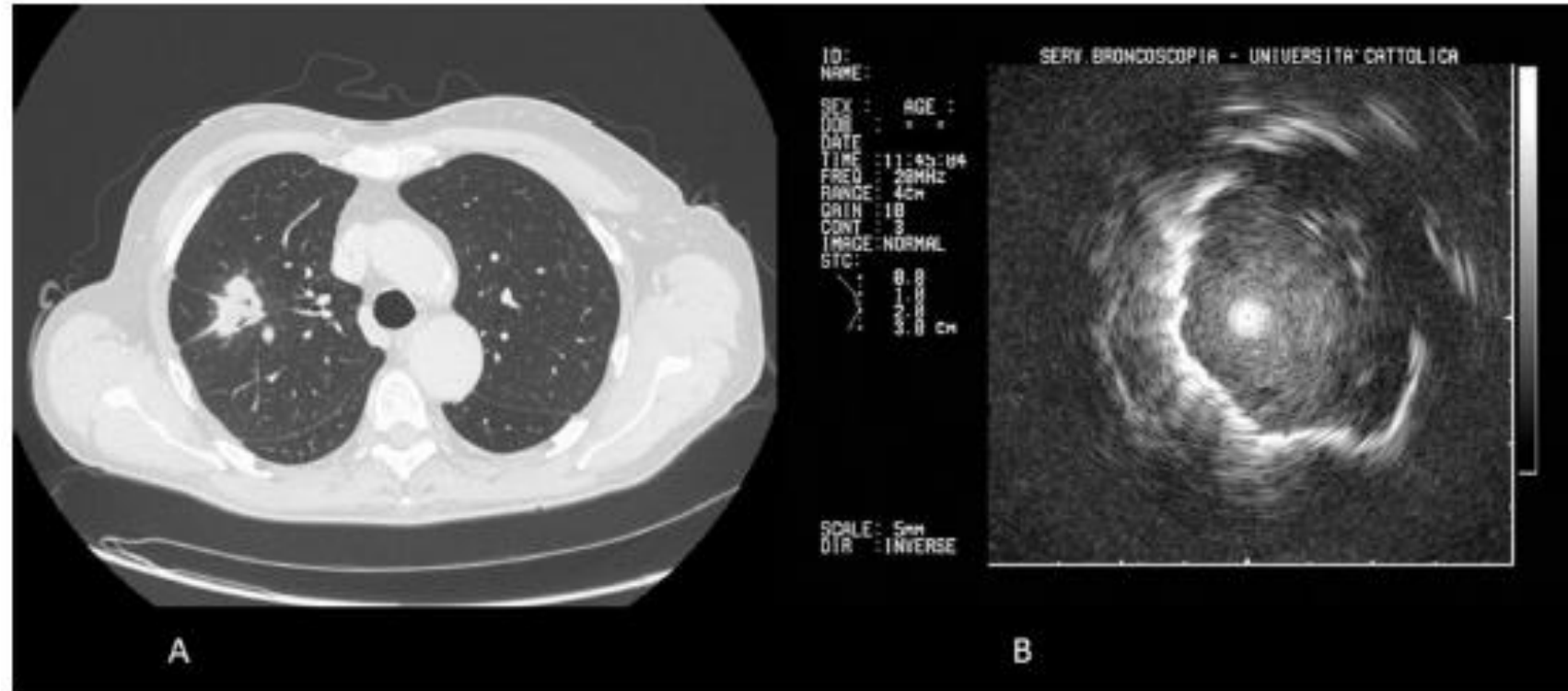
1. **X-ray / Fluoroscopic**
2. **Radial EBUS – Mini Probe**
3. **Ultrathin bronchoscopy**
4. **VBN - Virtual Bronchoscopic Navigation**
5. **ENB – Electromagnetic Navigation Bronchoscopy**

Radiaire echo-endoscopie= radiaire EBUS = miniprobe





E. Kikuchi et al. Endobronchial ultrasonography with guide-sheath for peripheral pulmonary lesions *Eur Respir J* 2004 24:533



Please cite this article in press as: Fuso L, et al. Role of ultrasound-guided transbronchial biopsy in the diagnosis of peripheral pulmonary lesions. Lung Cancer (2013), <http://dx.doi.org/10.1016/j.lungcan.2013.04.004>

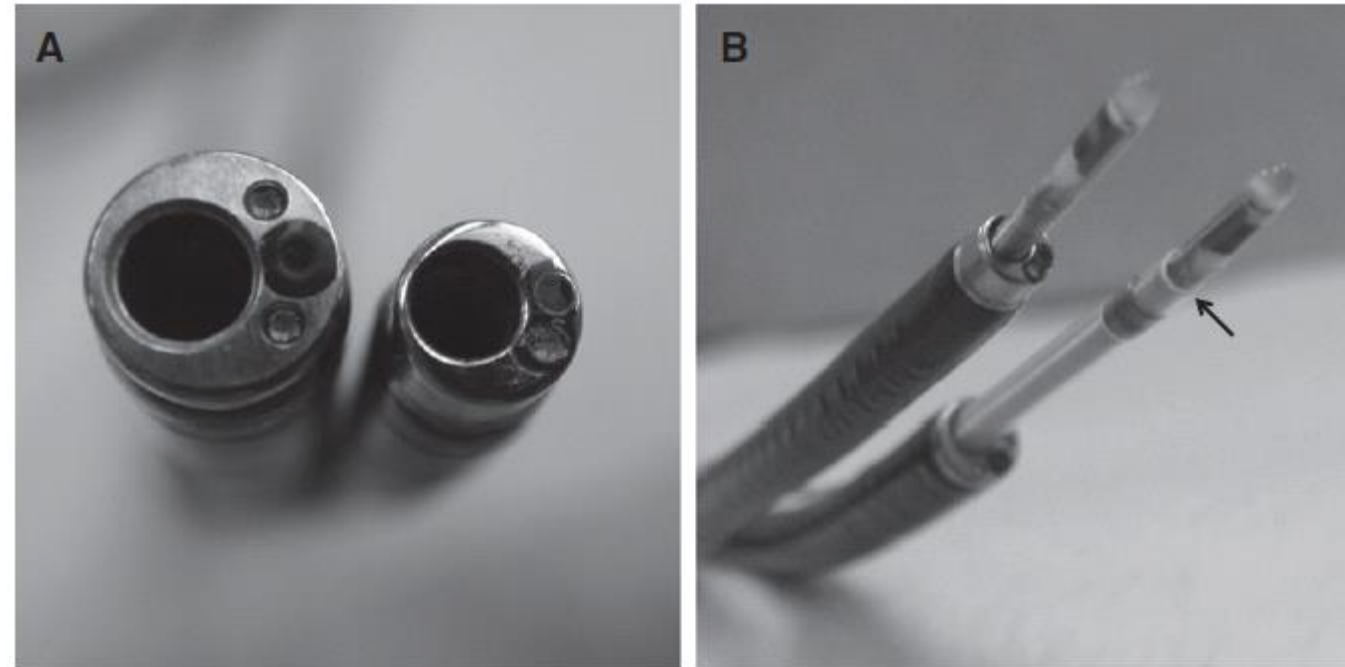


Figure 3. A comparison of bronchoscopes. (A) The 4.0-mm thin bronchoscope with a 2.0-mm working channel (*left*), and the 3.0-mm ultrathin bronchoscope with a 1.7-mm working channel (*right*). (B) A 3.0-mm ultrathin bronchoscope with a 1.4-mm ultrasonic probe (*left*), and a 4.0-mm bronchoscope with a 1.95-mm guide sheath (*arrow*) and a 1.4-mm ultrasonic probe (*right*).

Okí, Saka, Ando, *et al.*: Navigational Endosonographic Ultrathin Bronchoscopy
American Journal of Respiratory and Critical Care Medicine Volume 192 Number 4 | August 15 2015

VBN - Virtual Bronchoscopic Navigation

VIRTUAL BRONCHOSCOPIC NAVIGATION (VBN) SYSTEM

Image Guidance for Bronchoscopy

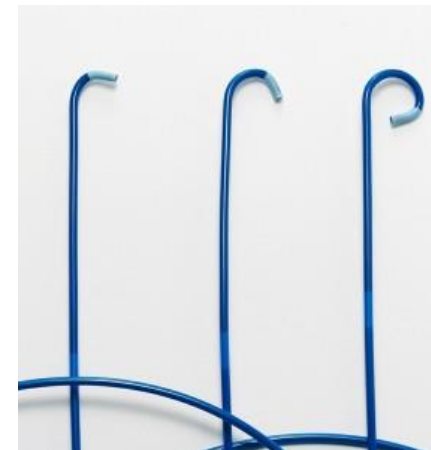
- Provides real-time path navigation within the lungs for lung biopsy and other Dx/Tx procedures
- Side-by-side navigation pairs real time and virtual images throughout procedure
- Navigation guides user to target with 3mm accuracy
- System operation does not require specialized, disposable instruments

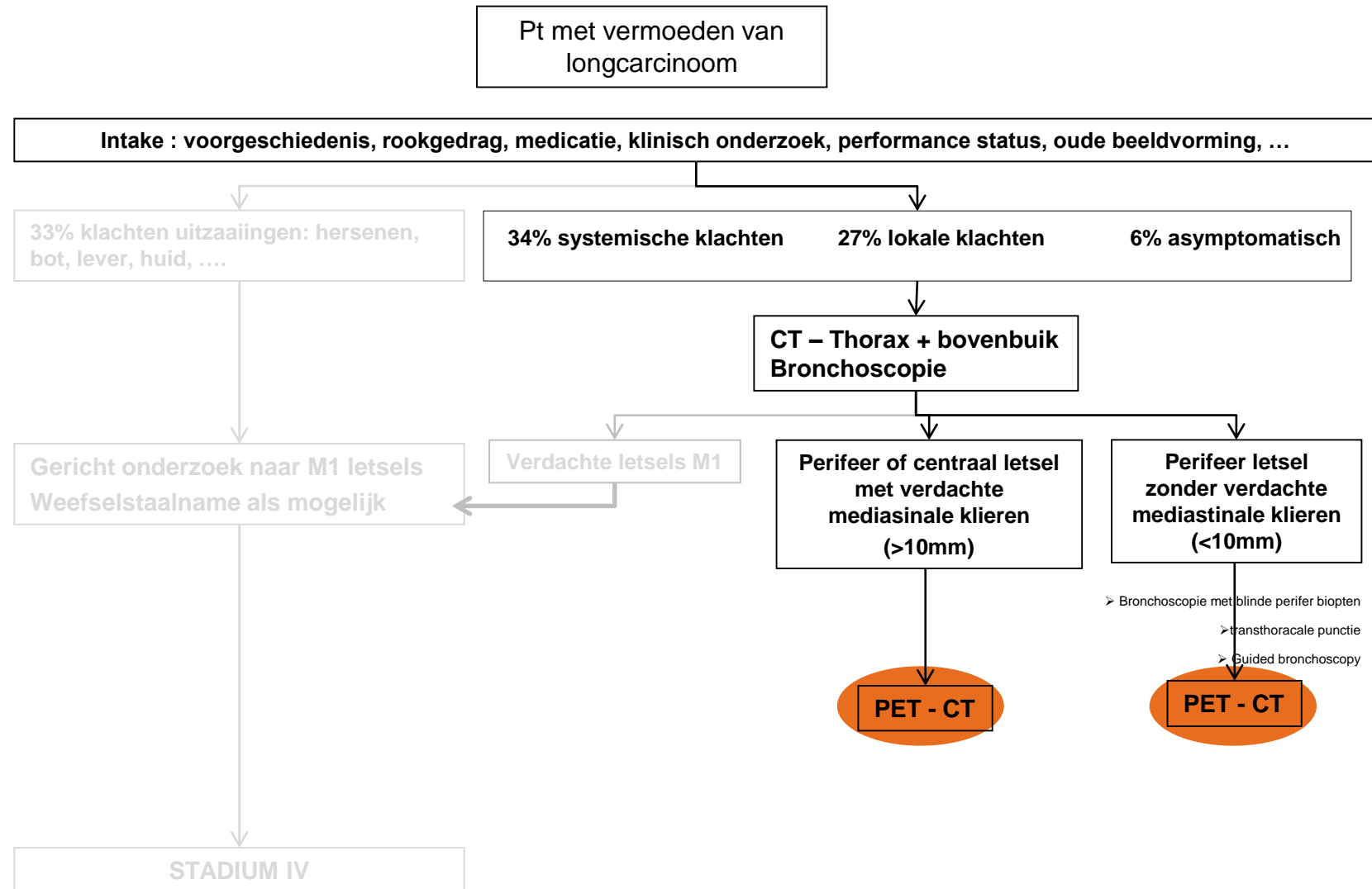


Real-time guidance with LungPoint® Virtual Bronchoscopic Navigation simultaneously shows the live and virtual views and the path to follow—with navigation accuracy of 3 mm



ENB – Electromagnetic Navigation Bronchoscopy [SuperDimension]





WB PET – CT scan

PET scan

- ▶ Suiker moleculen = FDG
 - ▶ 2fluoro 18,2 deoxy D glucose
 - ▶ Positron Emissie
- ▶ Whole Body (WB)
 - ▶ Niet voor CZS
- ▶ Onverwachte M1
 - ▶ 10%
- ▶ Detectiedrempel 1cm

CT scan

- ▶ Iod contraststof
- ▶ Röntgenstralen
- ▶ Helical WB CT
- ▶ Duidelijke structuren

CT Scan

Organs and bones



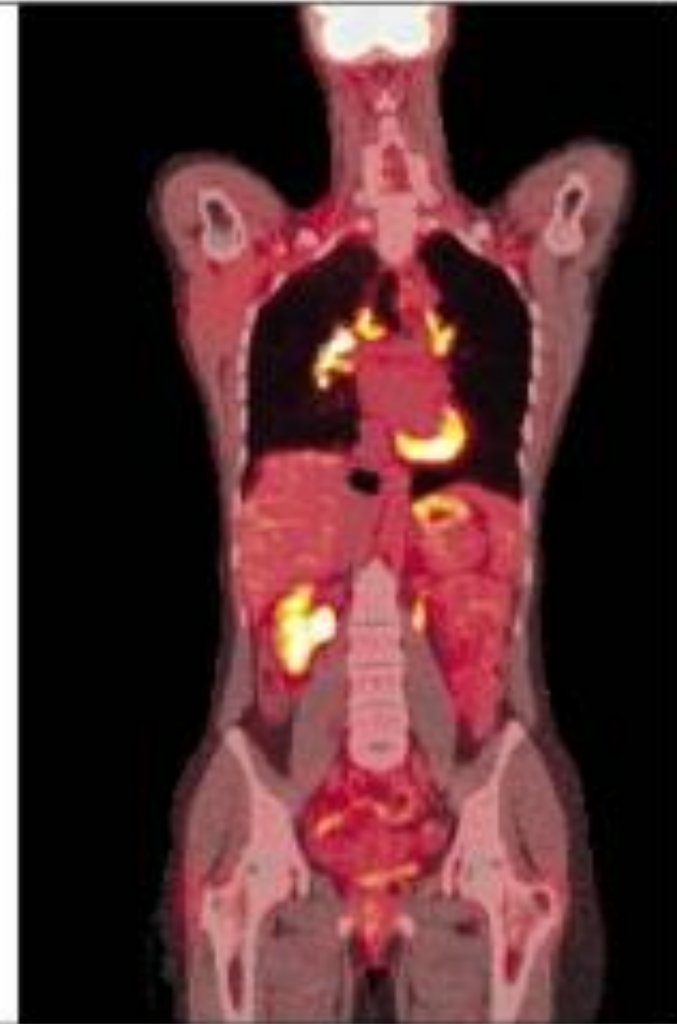
PET Scan

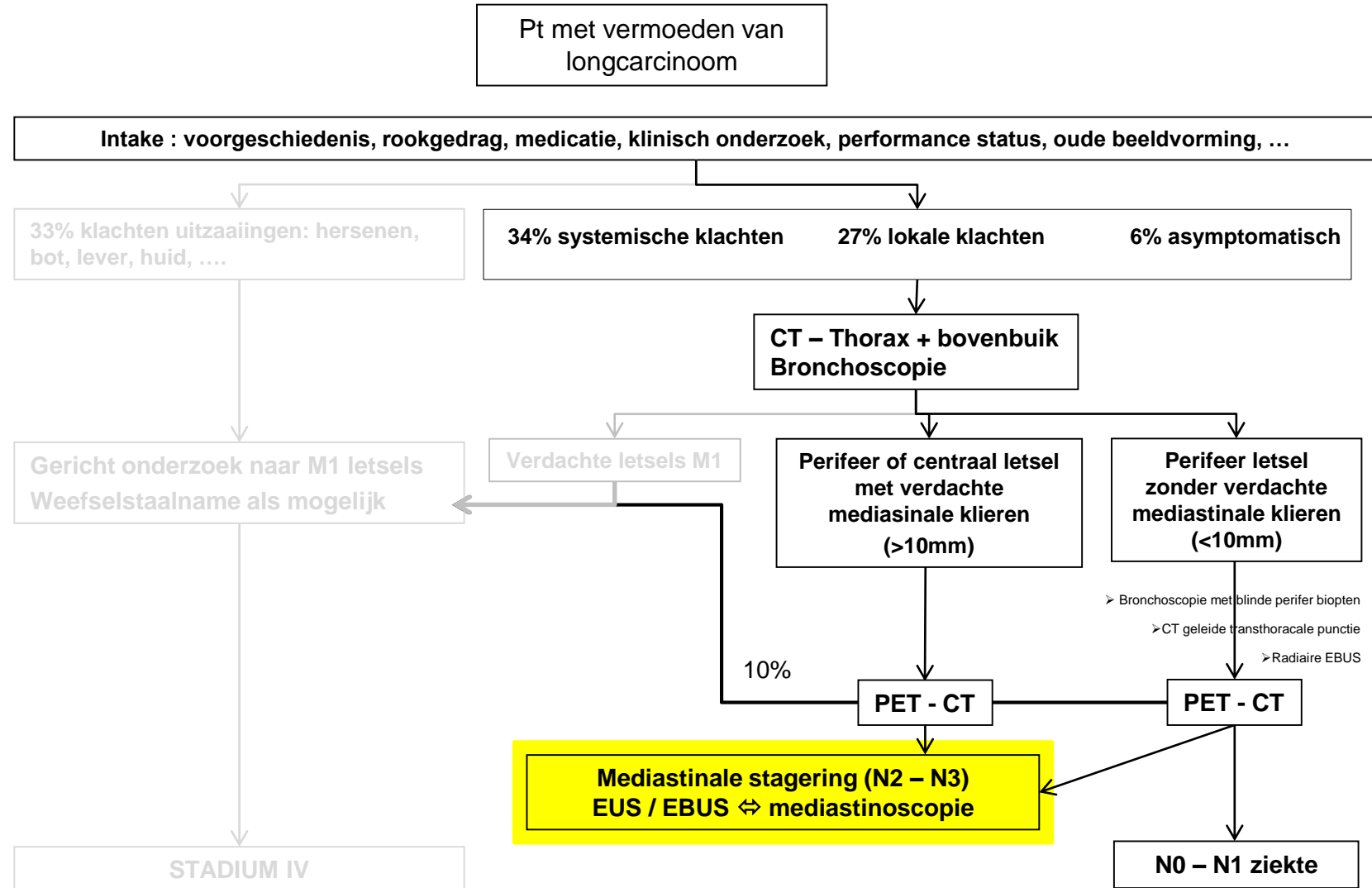
Cell activity



PET/CT Scan*

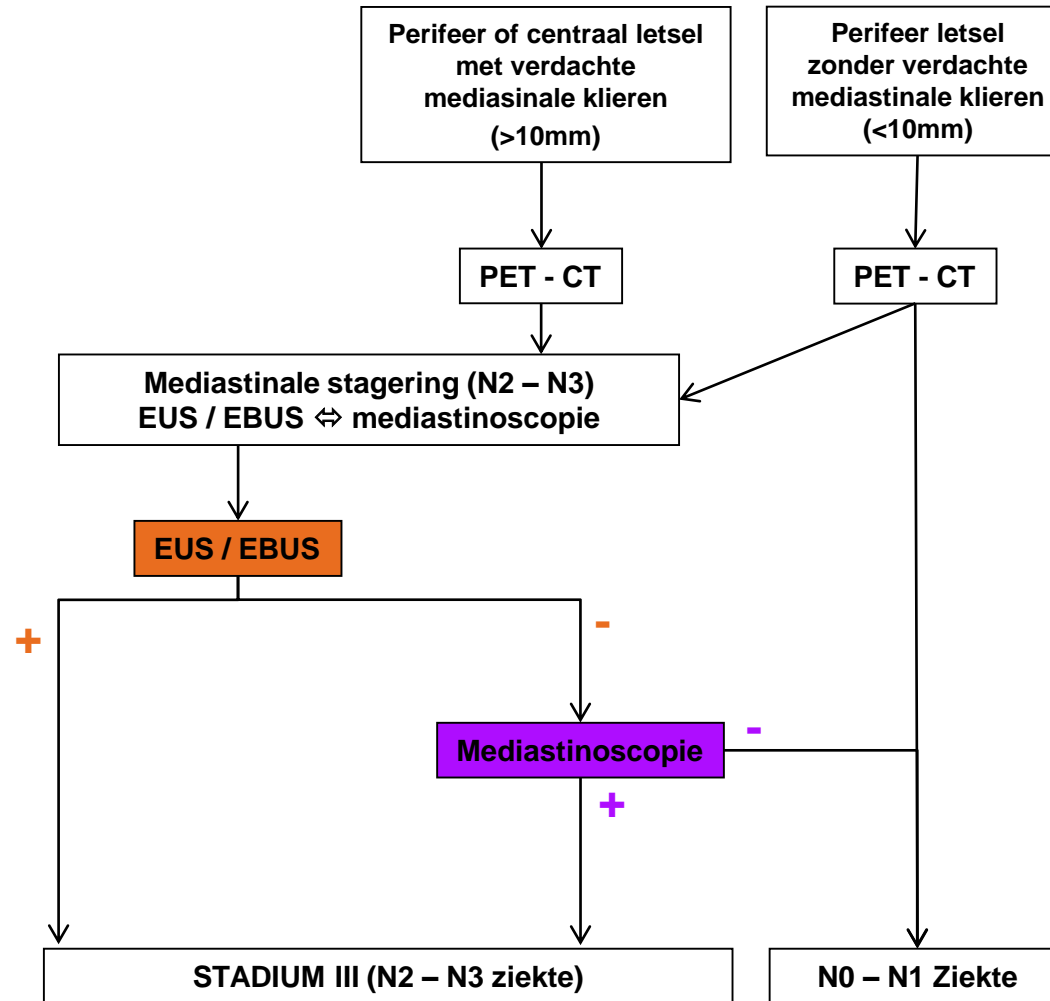
Exact location of high cell activity





Mediastinale stagering (N2 – N3)

- ▶ Bewijzen van maligniteit in N2 en N3 klieren.
- ▶ Minimaal invasief via EUS / EBUS
- ▶ Chirurgisch invasief via mediastinoscopie.
- ▶ Negatief resultaat EUS / EBUS moet steeds gevolgd worden door klassieke mediastinoscopie.



EUS – EBUS : Principe

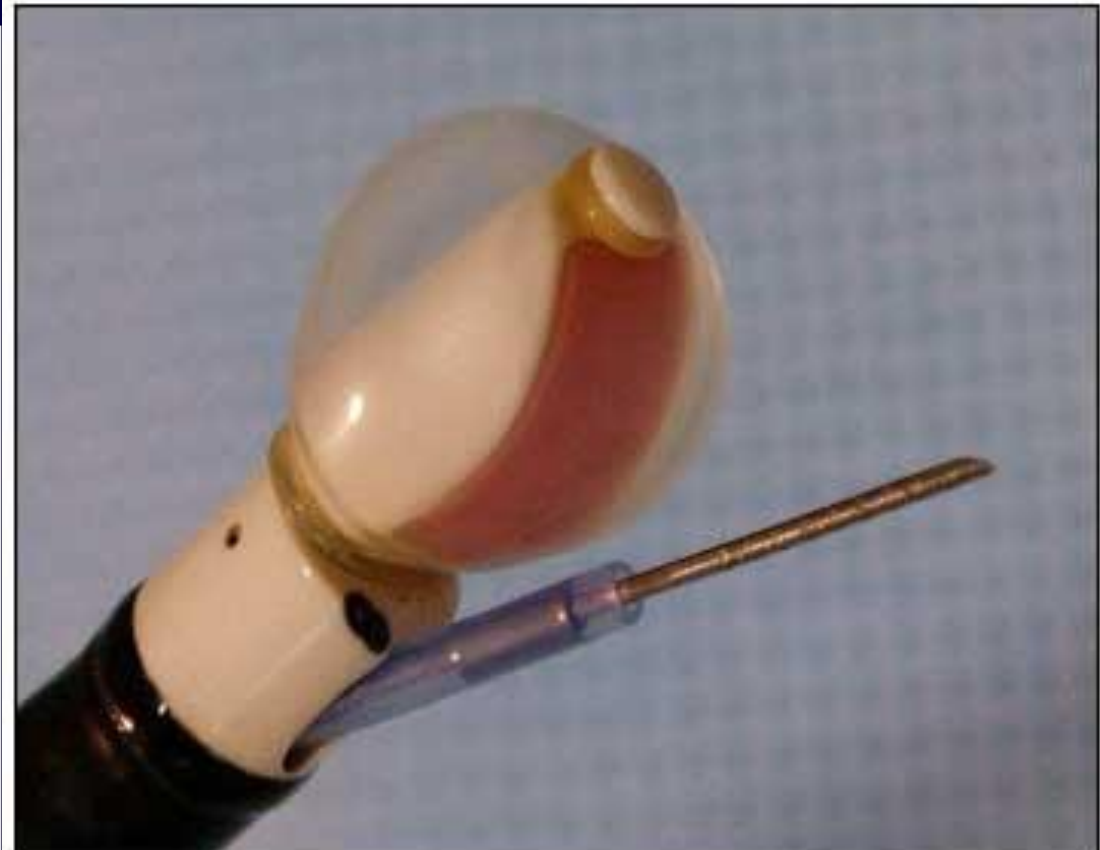
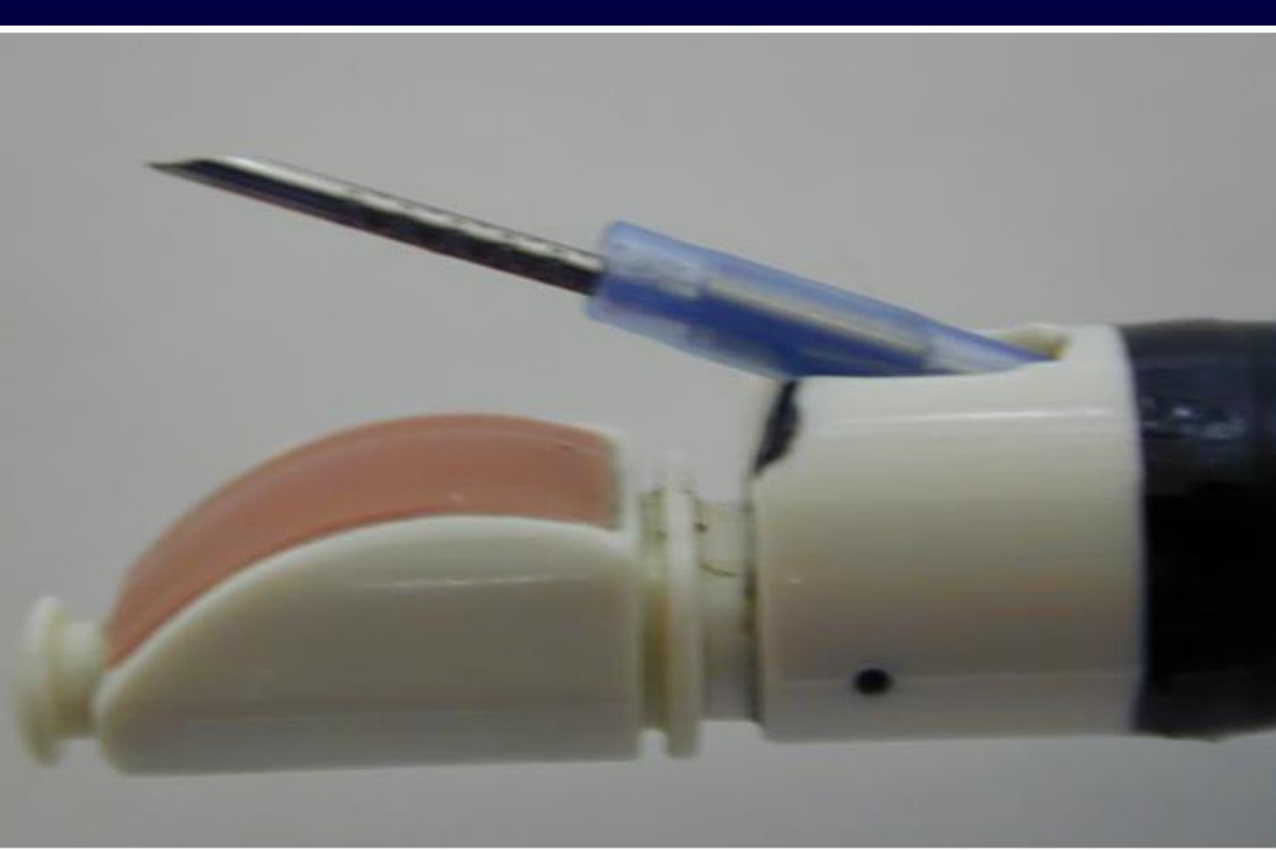
- ▶ Op minimaal invasieve wijze weefsel bekomen van mediastinale en hilaire klieren.
 - ▶ NSCLC, SCLC
 - ▶ Sarcoïdose
 - ▶ Evt lymfoom
- ▶ Obv beeldvorming (CT – PET) bepalen van te stageren klieren.
- ▶ Middels endo-echografie opzoeken van de klierstations.
- ▶ ‘real time’ echografisch aanprikken van vergrote klieren.



EUS – EBUS : Principe

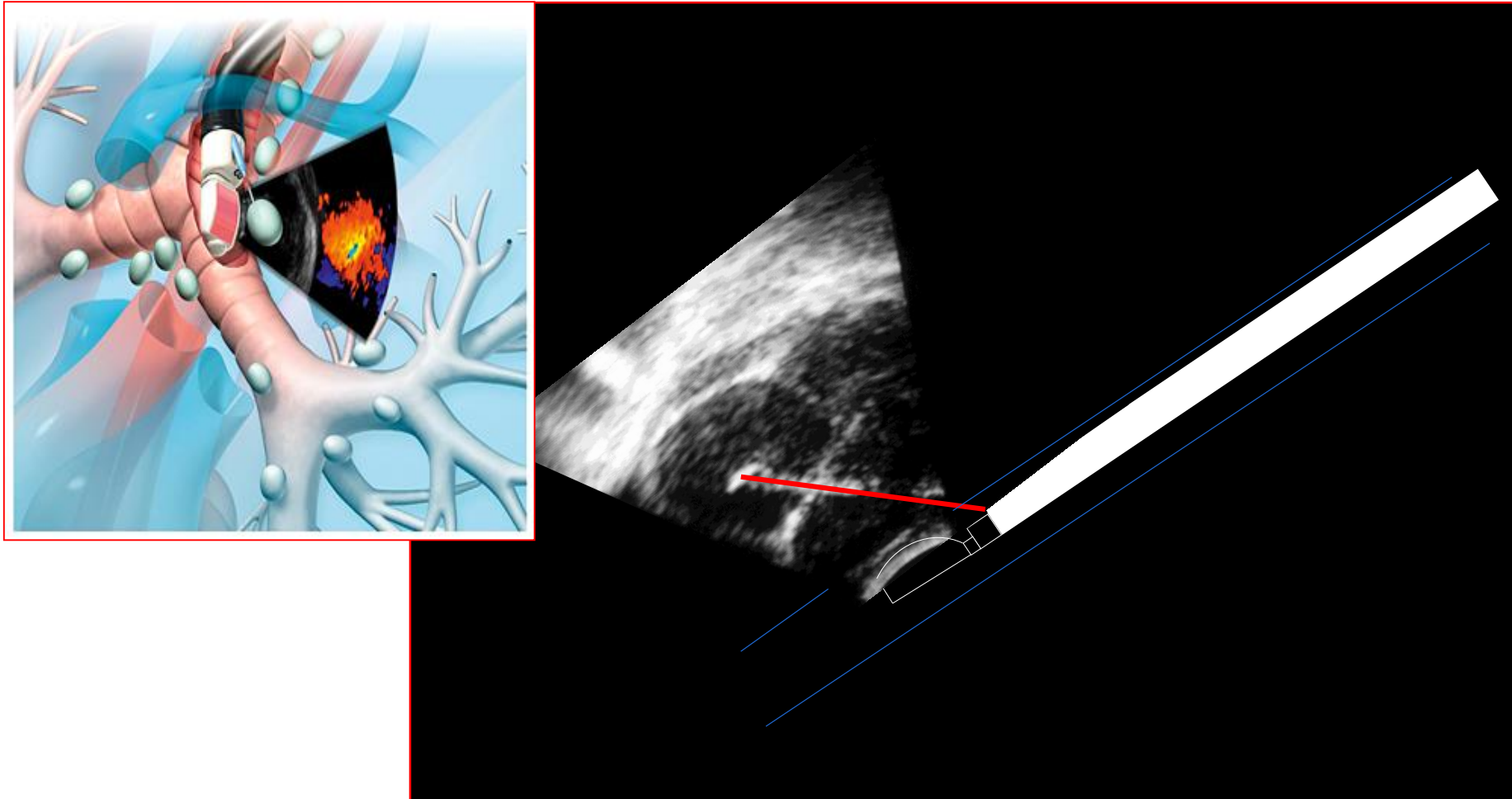


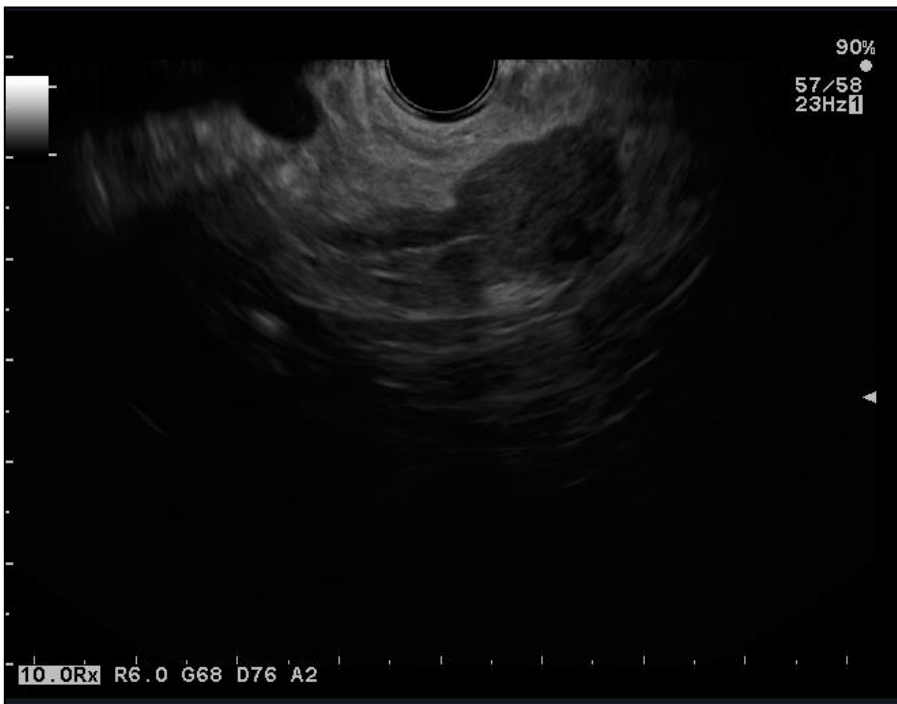
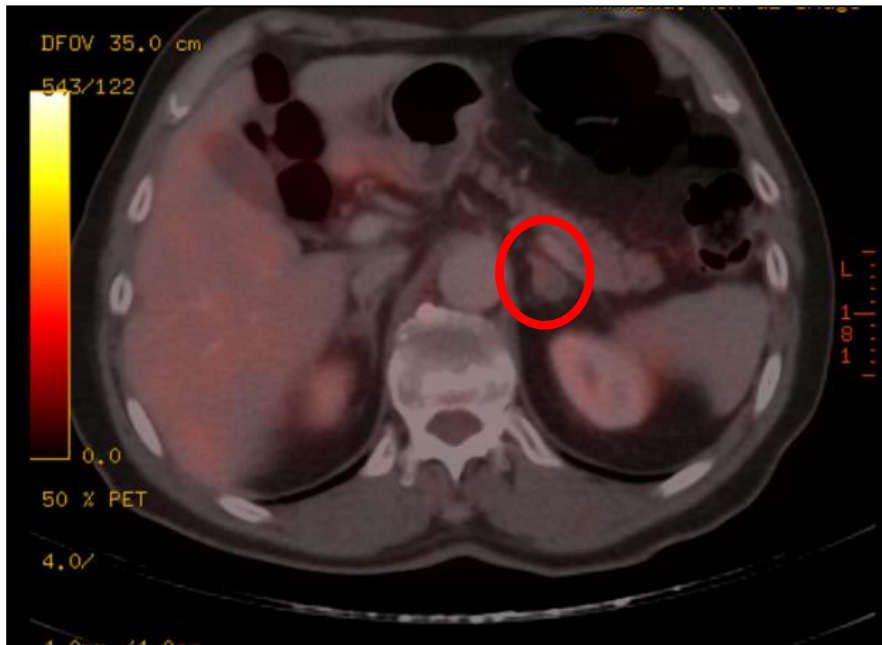
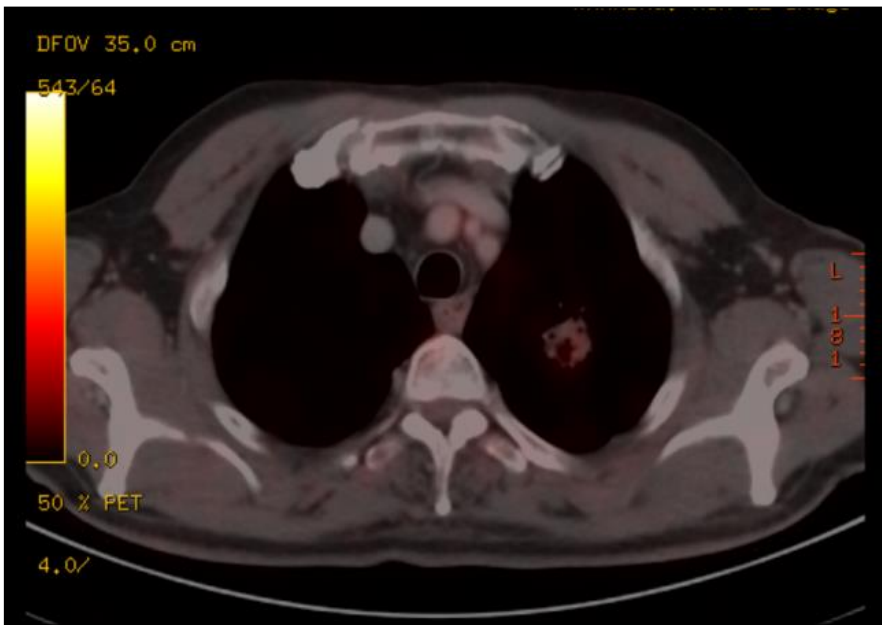
EUS – EBUS : Principe

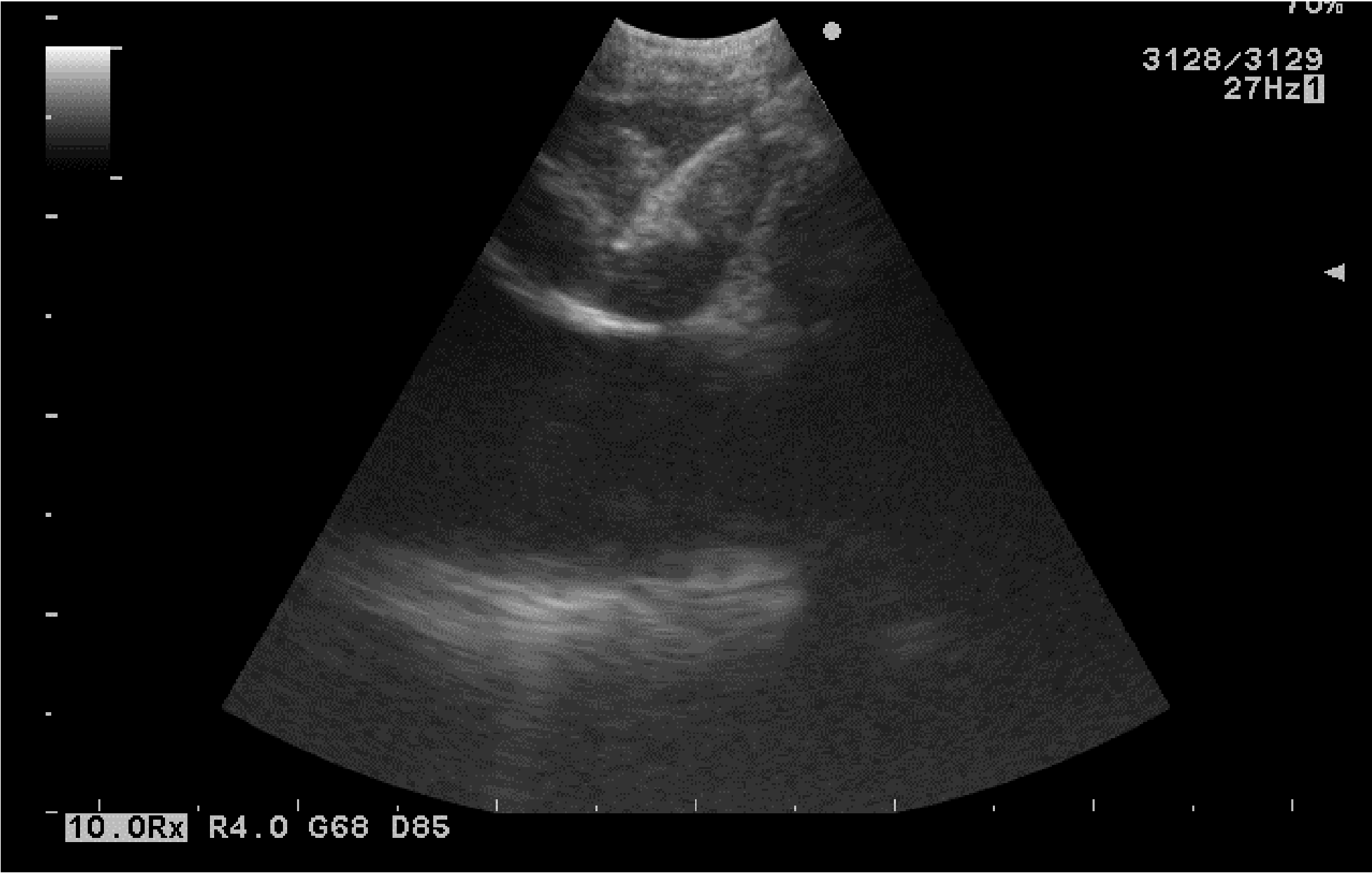


<http://www.gastrohep.com/ebooks/thumbnails.asp?book=1405120819&id=2>

EUS – EBUS : Principe



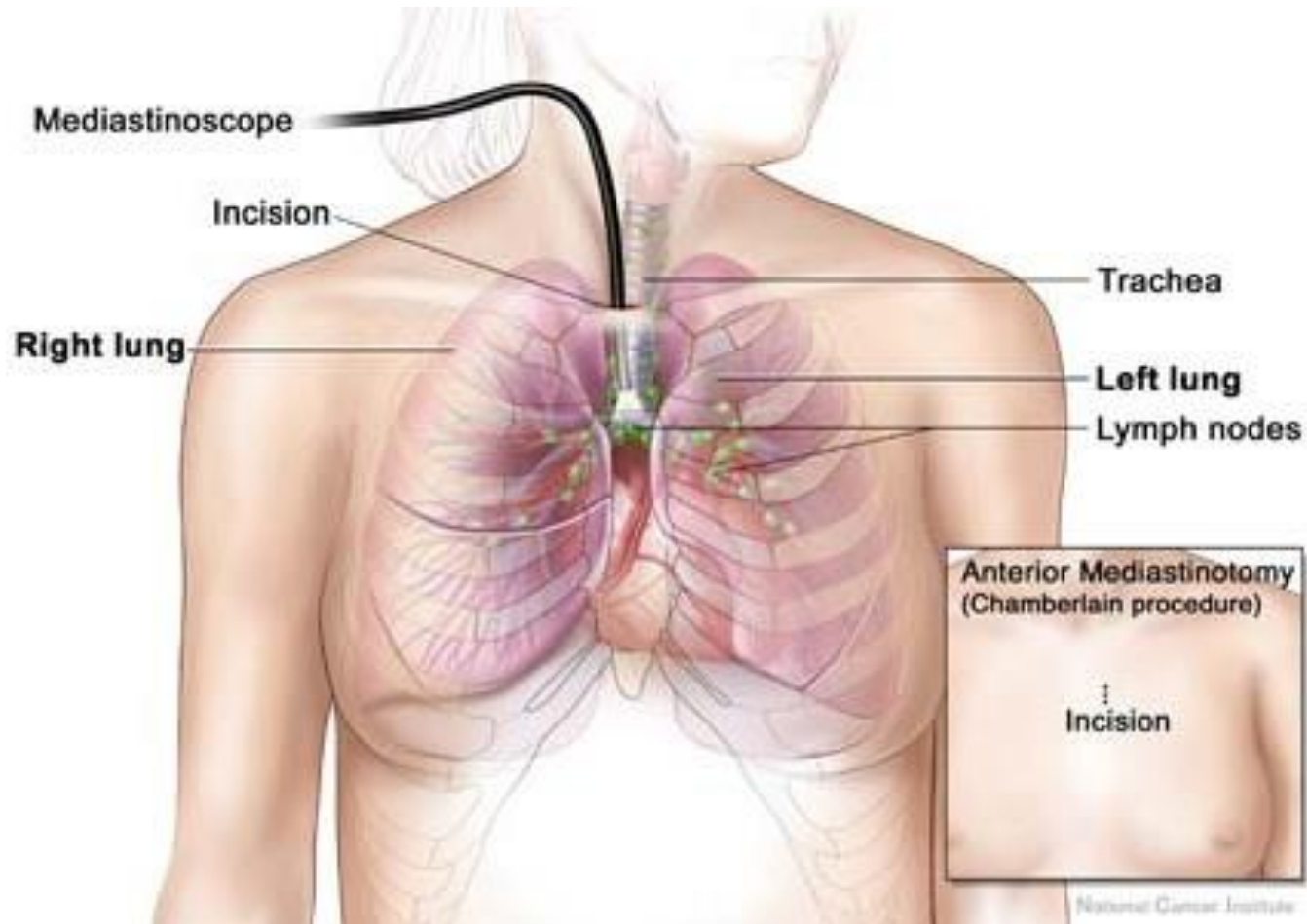




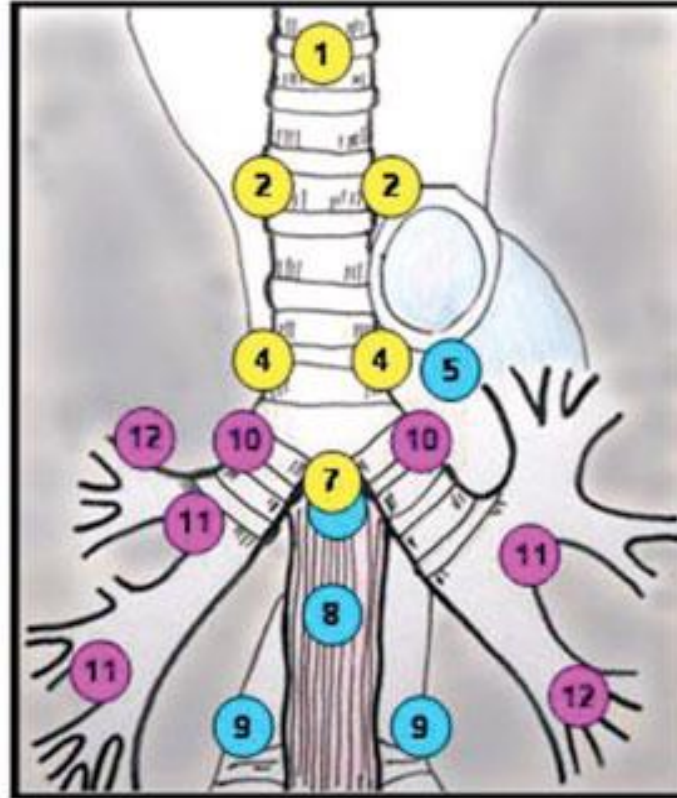
EUS – EBUS : Praktisch UZ Gent




- ▶ Ambulante procedure
 - ▶ Lokale anesthesie van de keel met xylocaïne spray
 - ▶ Sedatie (≠ algemene anesthesie) :
 - Fentanyl
 - Midazolam (Dormicum®)
- ▶ Onderzoek gebeurt liggend :
 - ▶ Ruglig : EBUS
 - ▶ Zijlig : EUS (heup? , schouder?)
- ▶ Continue monitoring saturatie en pols
- ▶ Uitgevoerd door arts en verpleegkundige
- ▶ 2L O₂ / min via neusbril

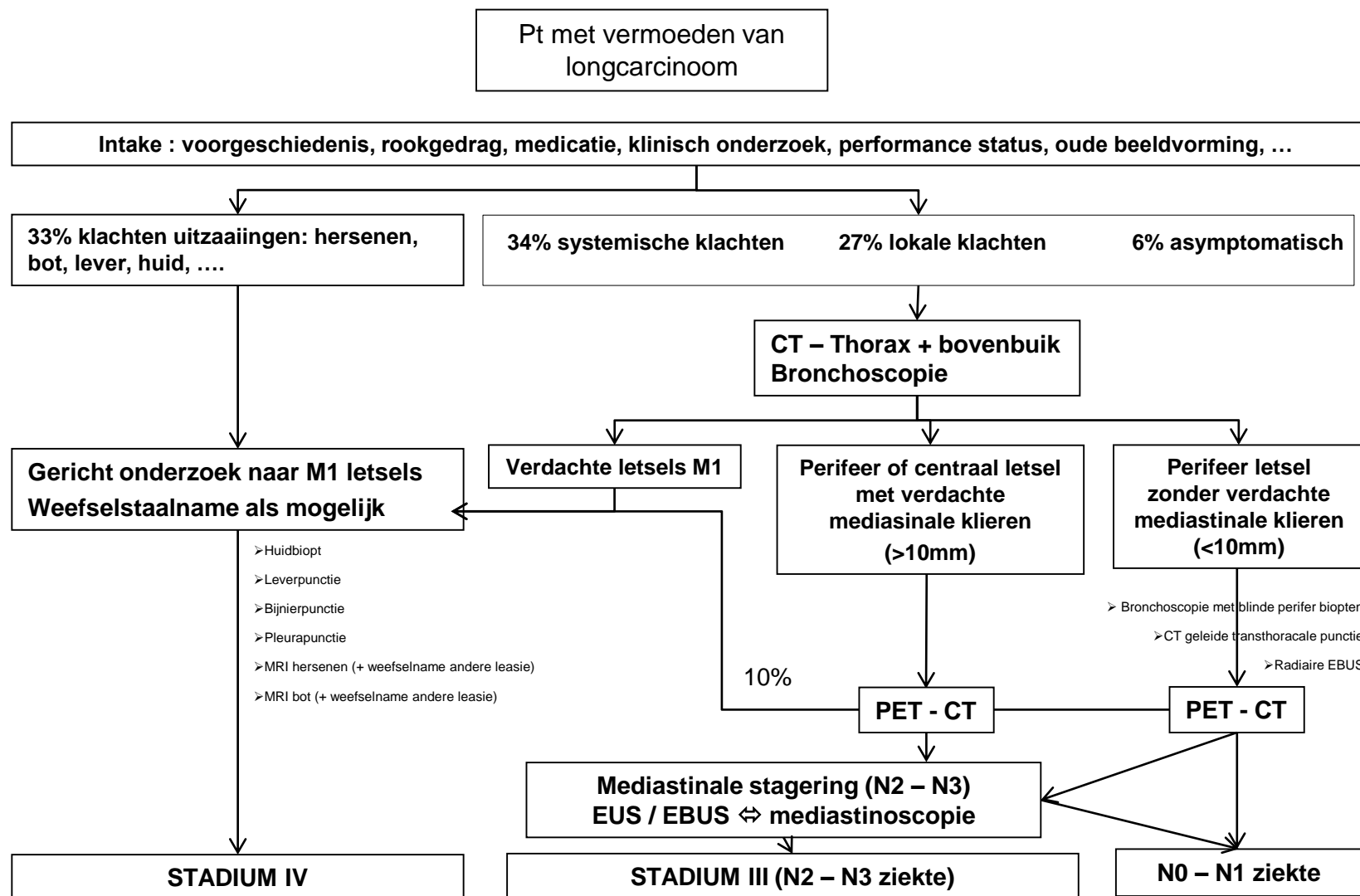
Mediastinoscopie



EUS – EBUS - Mediastinoscopie : Indicaties / Mogelijkheden



-  EBUS-TBNA and Mediastinoscopy
-  EBUS-TBNA
-  EUS-FNA





Take Home Message Diagnostiek / Staging

- ▶ Stagering van longcarcinoom :
 - ▶ Steeds hoogst mogelijke stadium proberen aan te tonen
 - ▶ Geen kookboek – geen recept
 - ▶ Algoritme is houvast – geen dogma
 - ▶ Multidisciplinair overleg
 - ▶ Adequate medische beslissingen

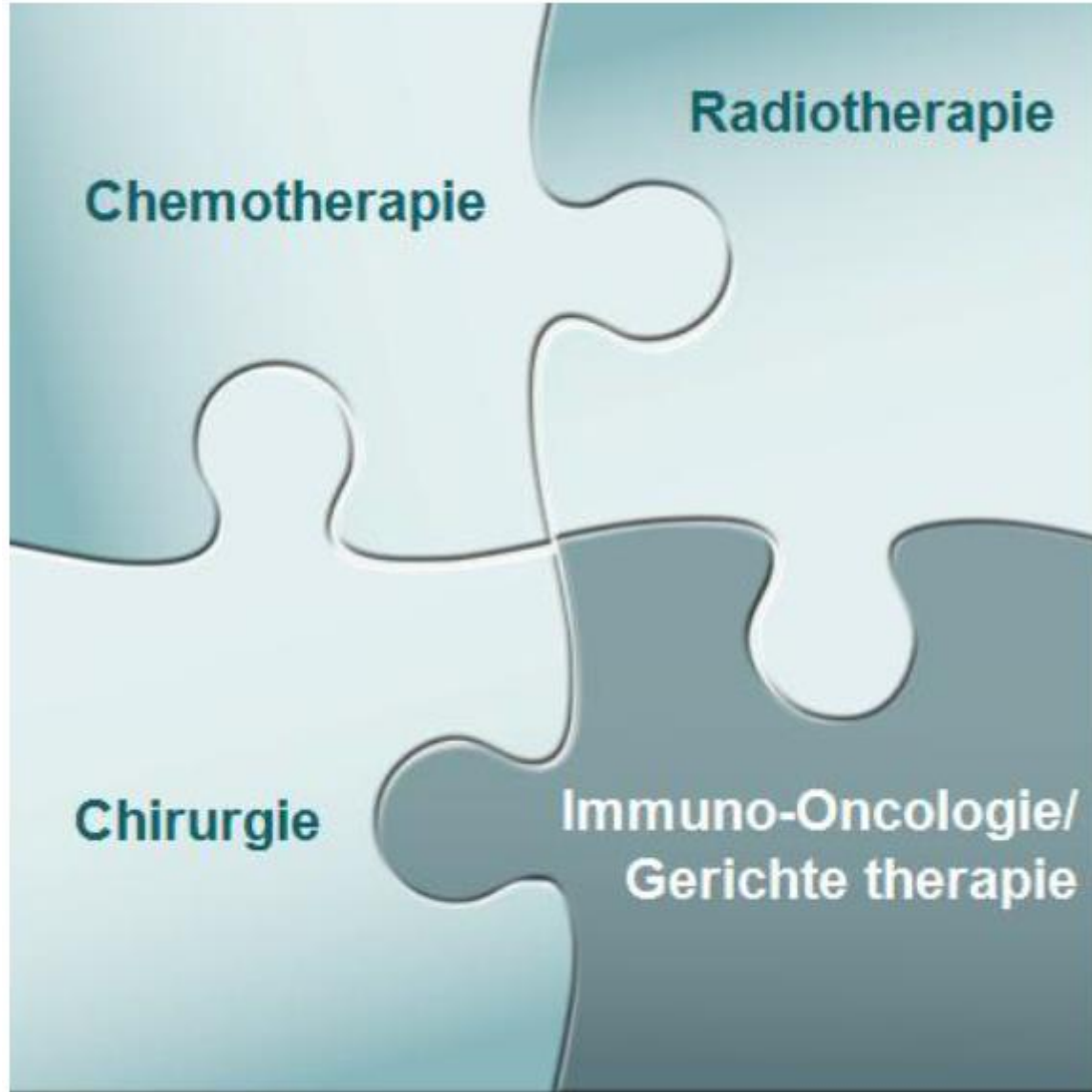
- ▶ Belang van de patiënt :
 - ▶ Met minimum aan belasting voor de patiënt een maximum aan informatie bekomen
 - ▶ Bij twijfel of discussie wordt een lagere groep toegekend aan de patiënt (gunstigere groep).

Epidemiologie

Diagnostiek

Therapie



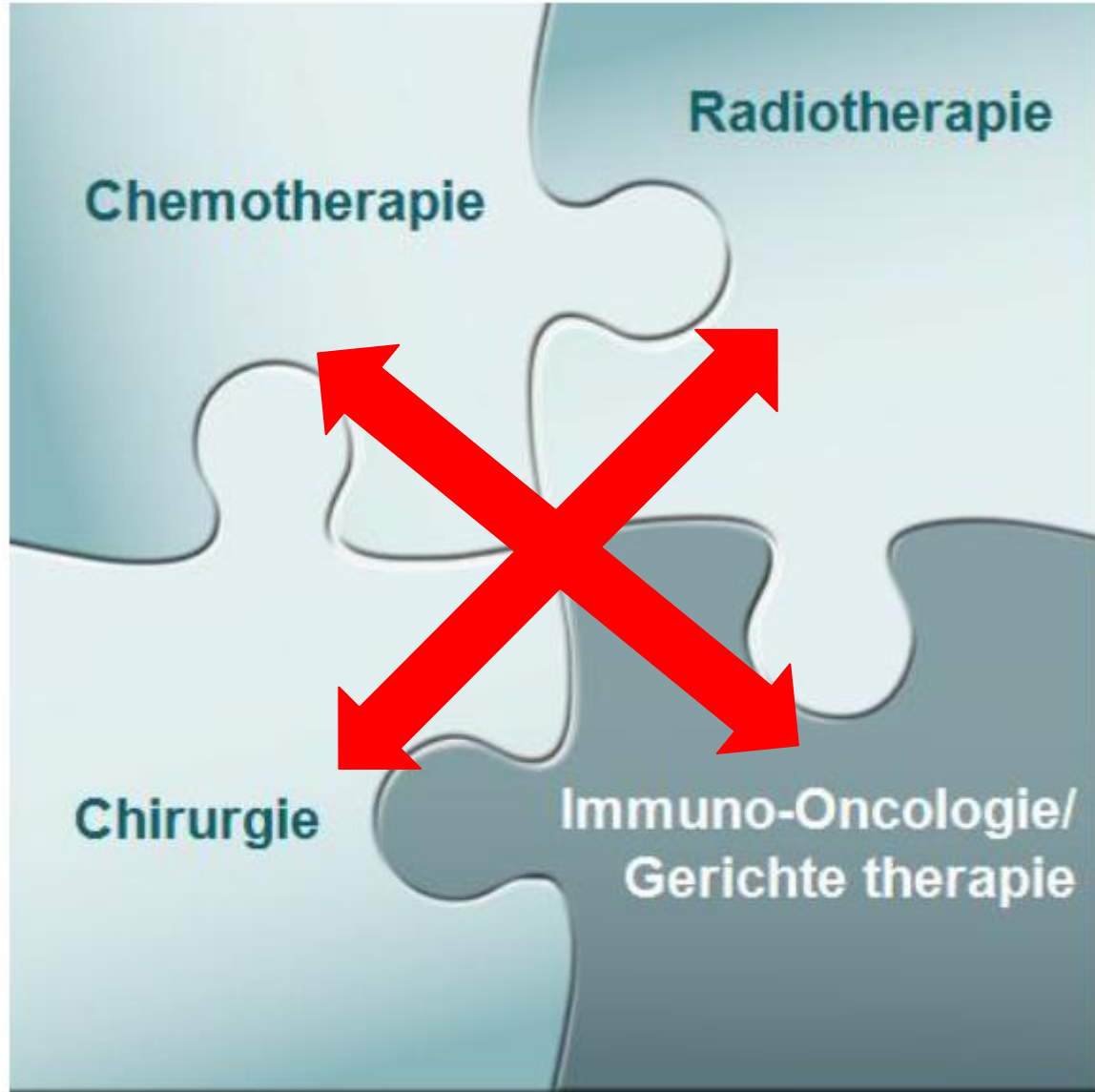


Chemotherapie

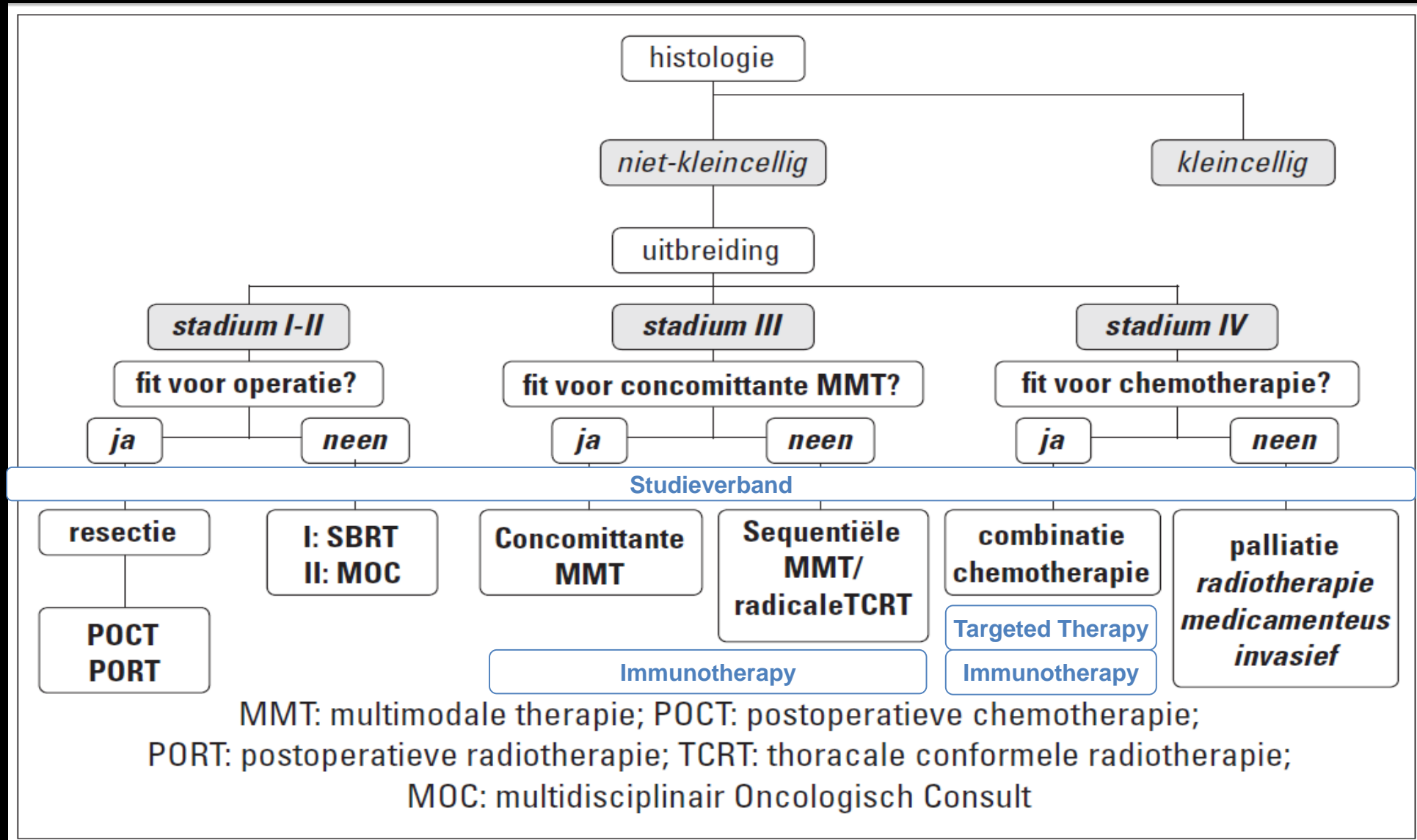
Radiotherapie

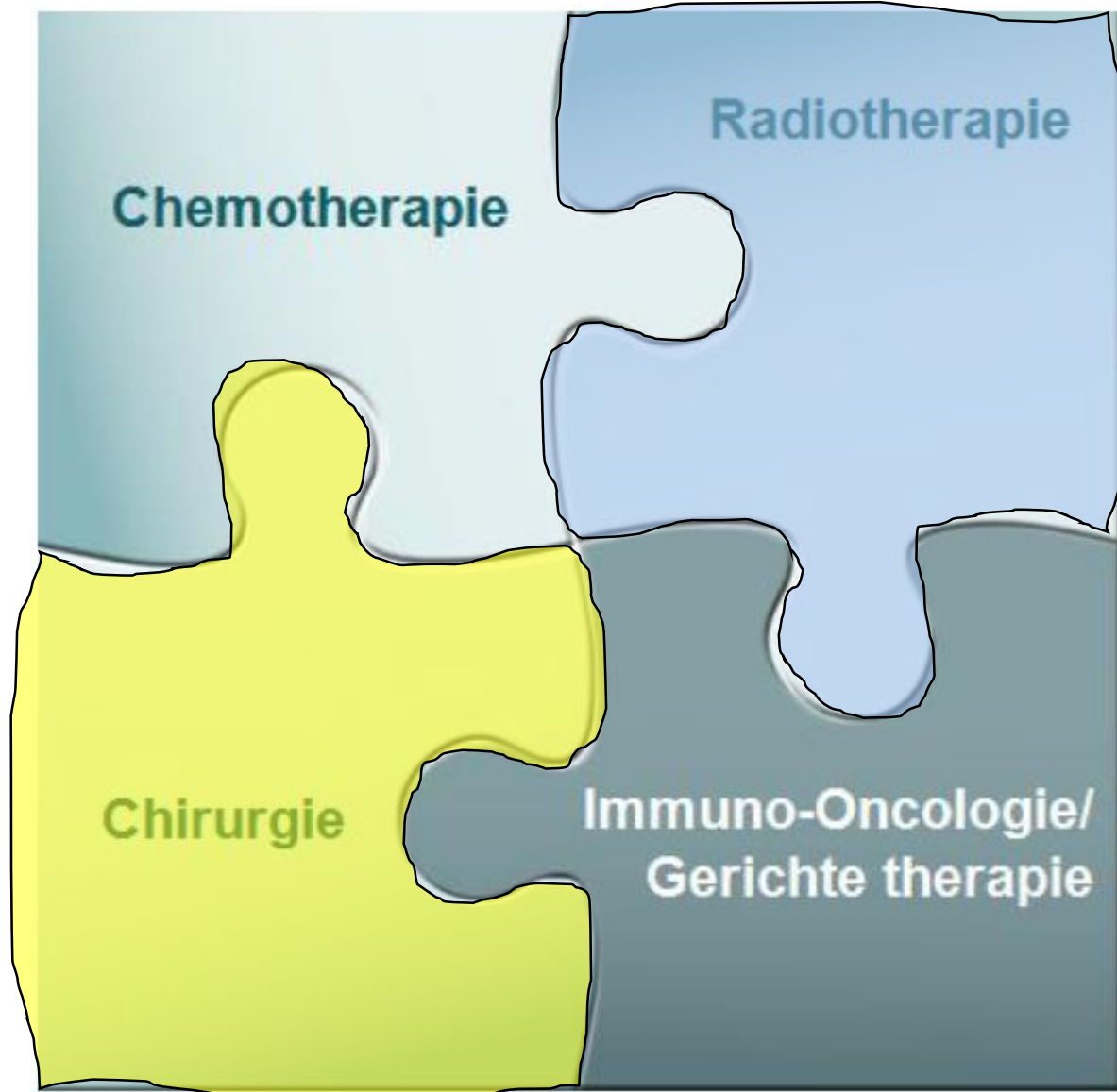
Chirurgie

**Immuno-Oncologie/
Gerichte therapie**



Behandeling van longcarcinoom - NSCLC

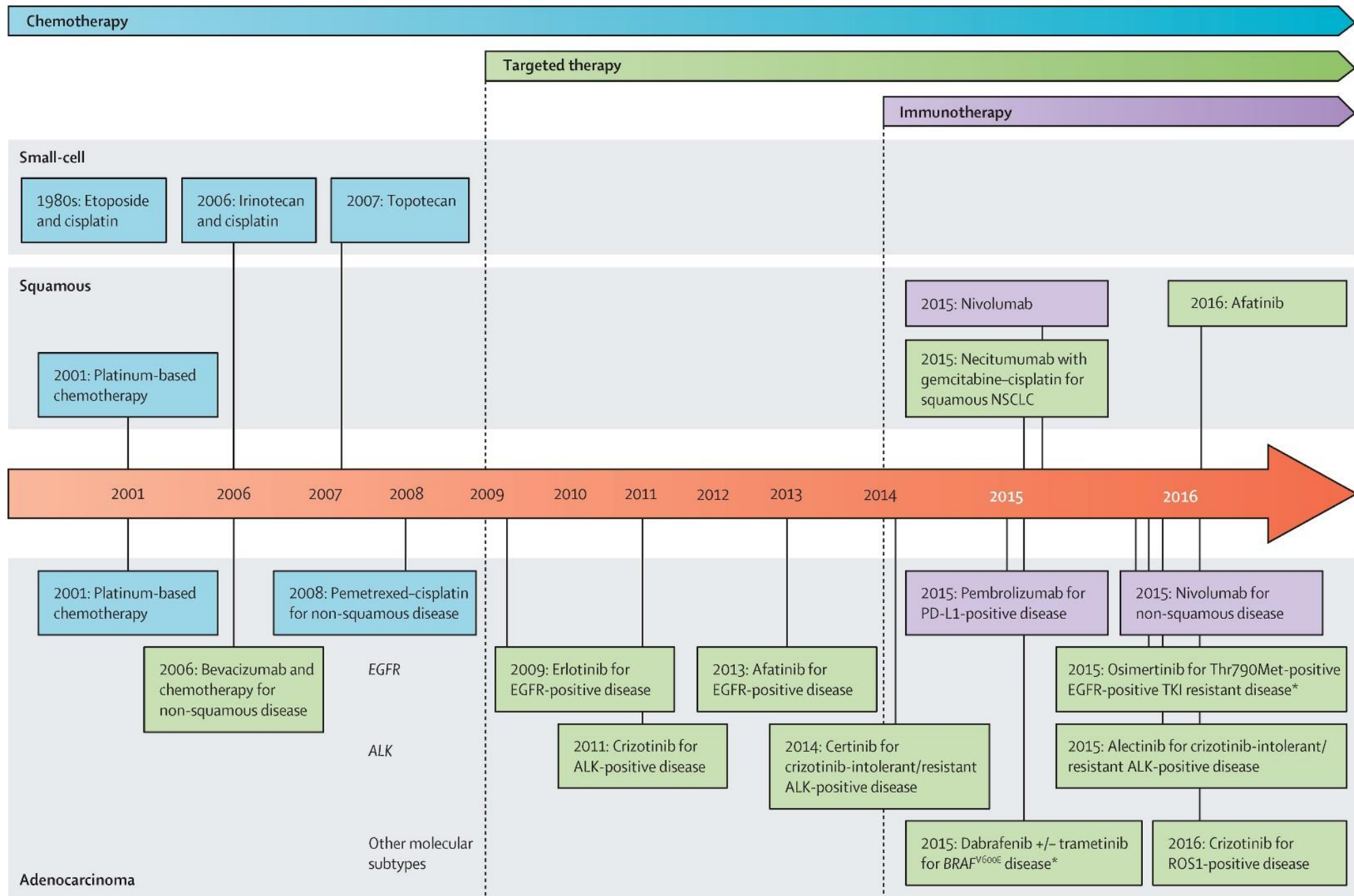




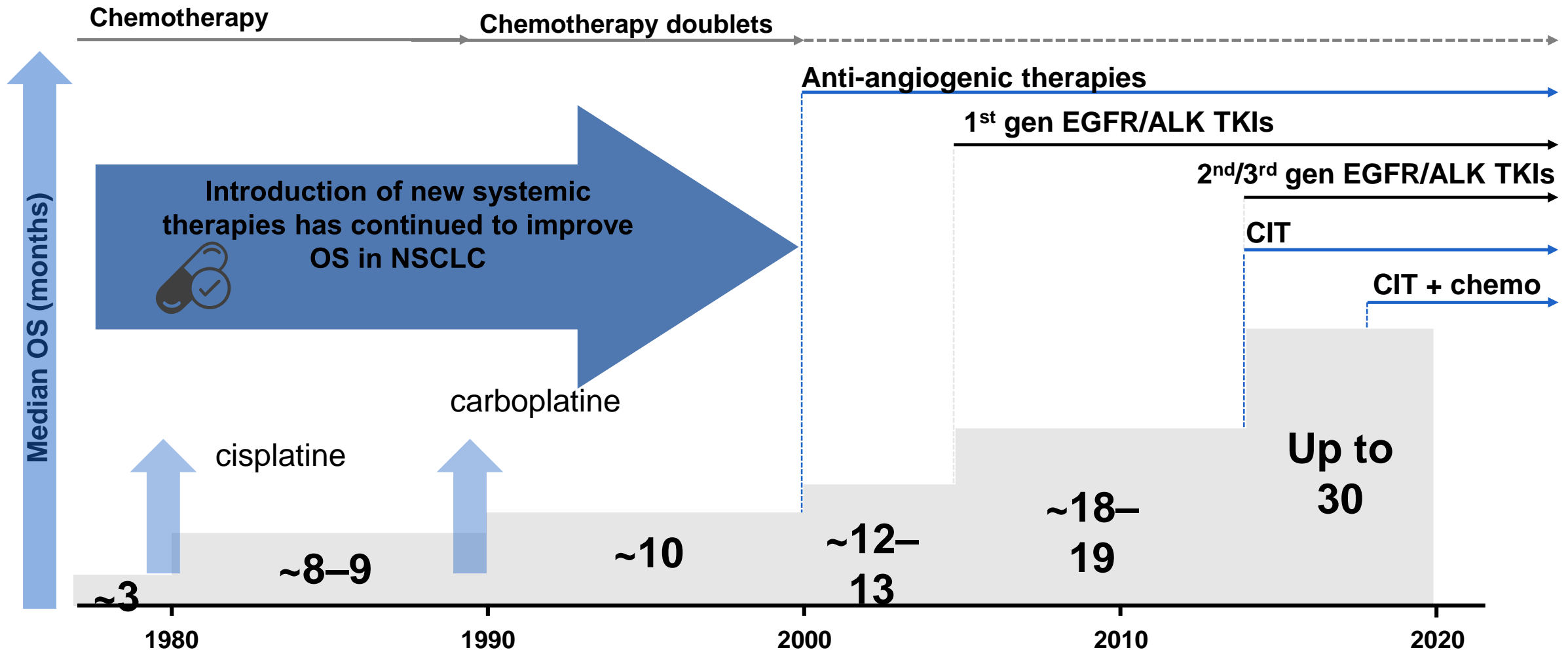
Dr Desender

Prof. Dr. Van Eijkeren



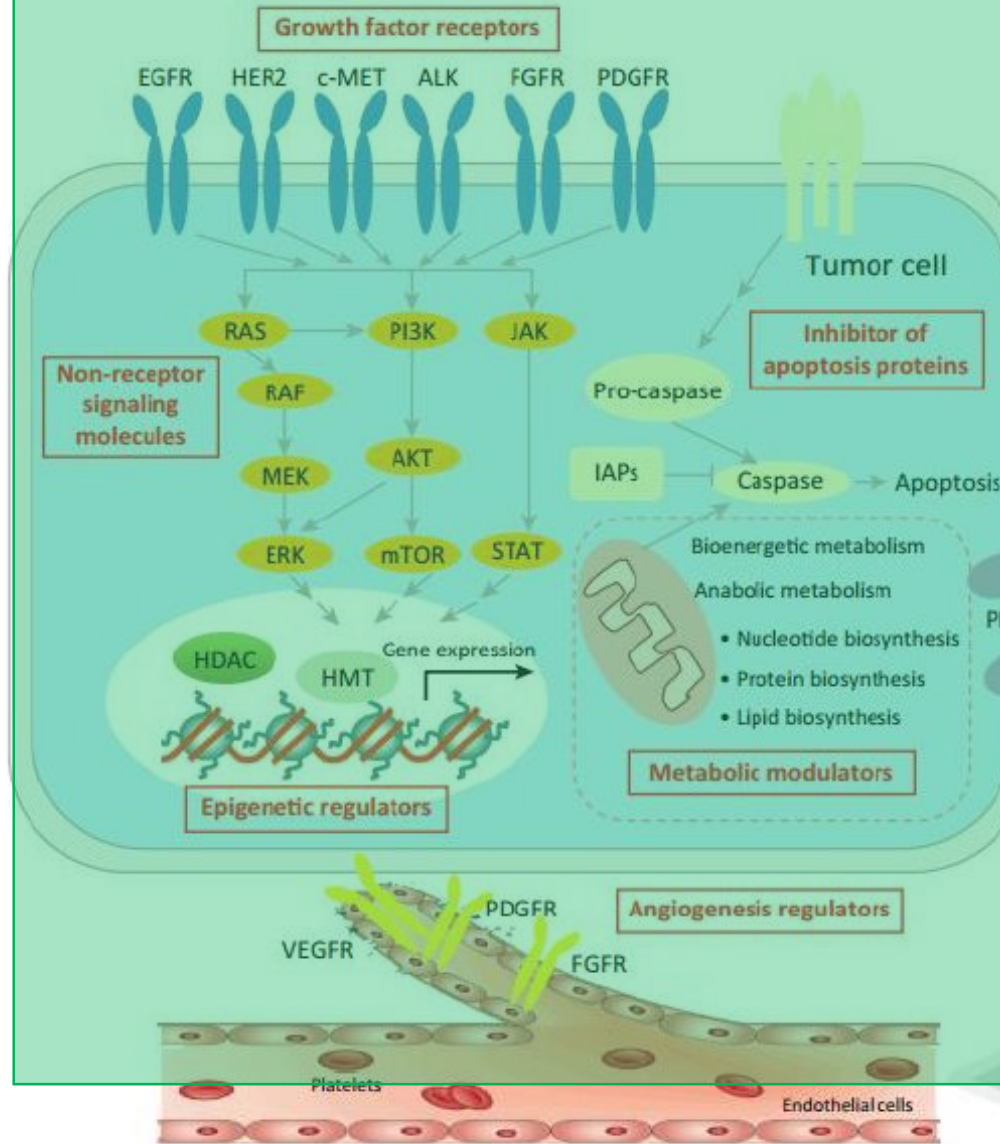


Targeted therapies and cancer immunotherapies (CIT) are revolutionising the treatment of NSCLC (stage IV)

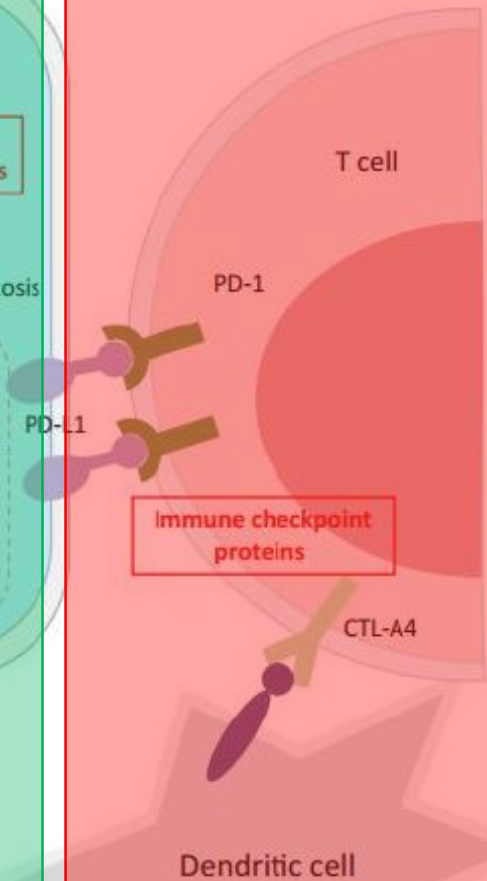


Ganz, et al. Cancer 1989; Bunn, et al. Clin Cancer Res 1998; Delbaldo, et al. JAMA 2004; Scagliotti, et al. J Clin Oncol 2002
 Johnson, et al. J Clin Oncol 2004; Sandler, et al. N Engl J Med 2006; Garon, et al. Lancet 2014; Shepherd, et al. N Engl J Med 2005
 Mok, et al. N Engl J Med 2009; Rossell, et al. Lancet Oncol 2012; Brahmer, et al. WCLC 2017 (Abs OA 17.06)

Targeted therapy



Immuno-oncology



Huang et al, 2014

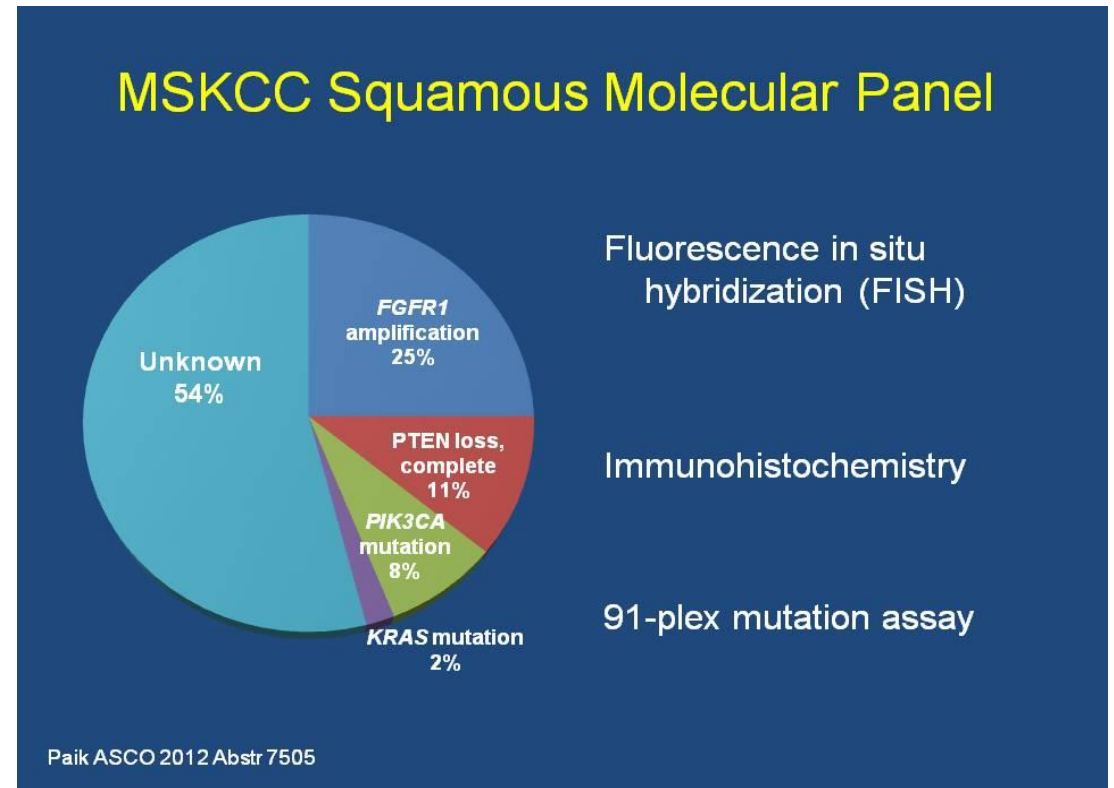
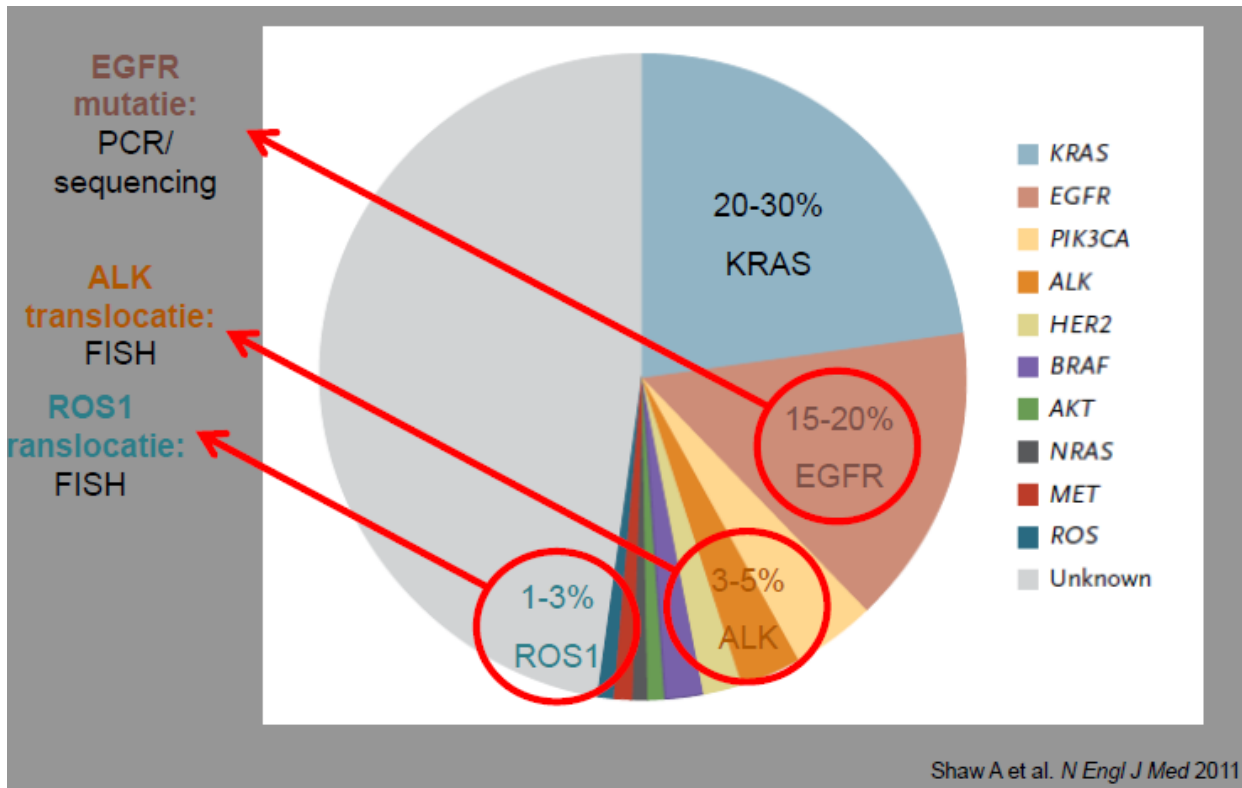
Gemetastaseerd NSCLC met oncogene drivers

EGFR

ALK

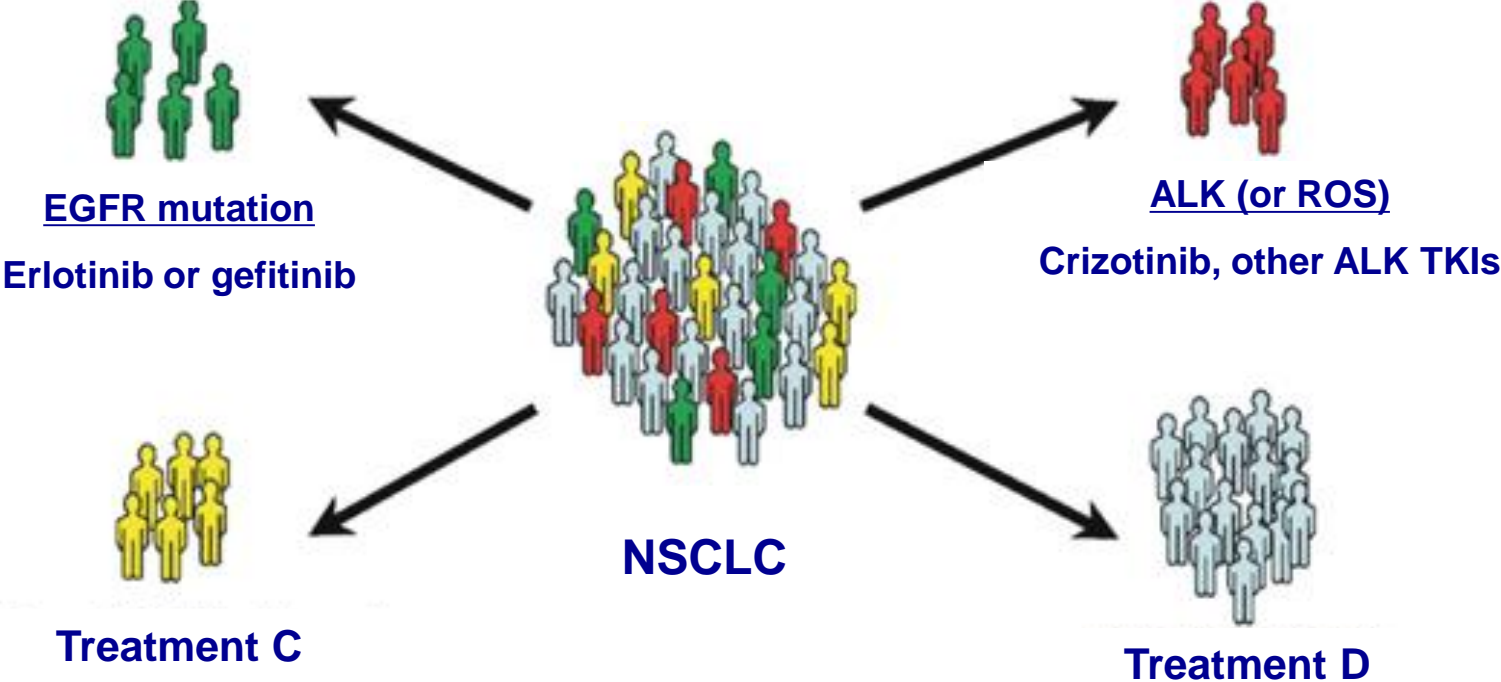
Zeldzame mutaties

Molecular changes drive lung cancer

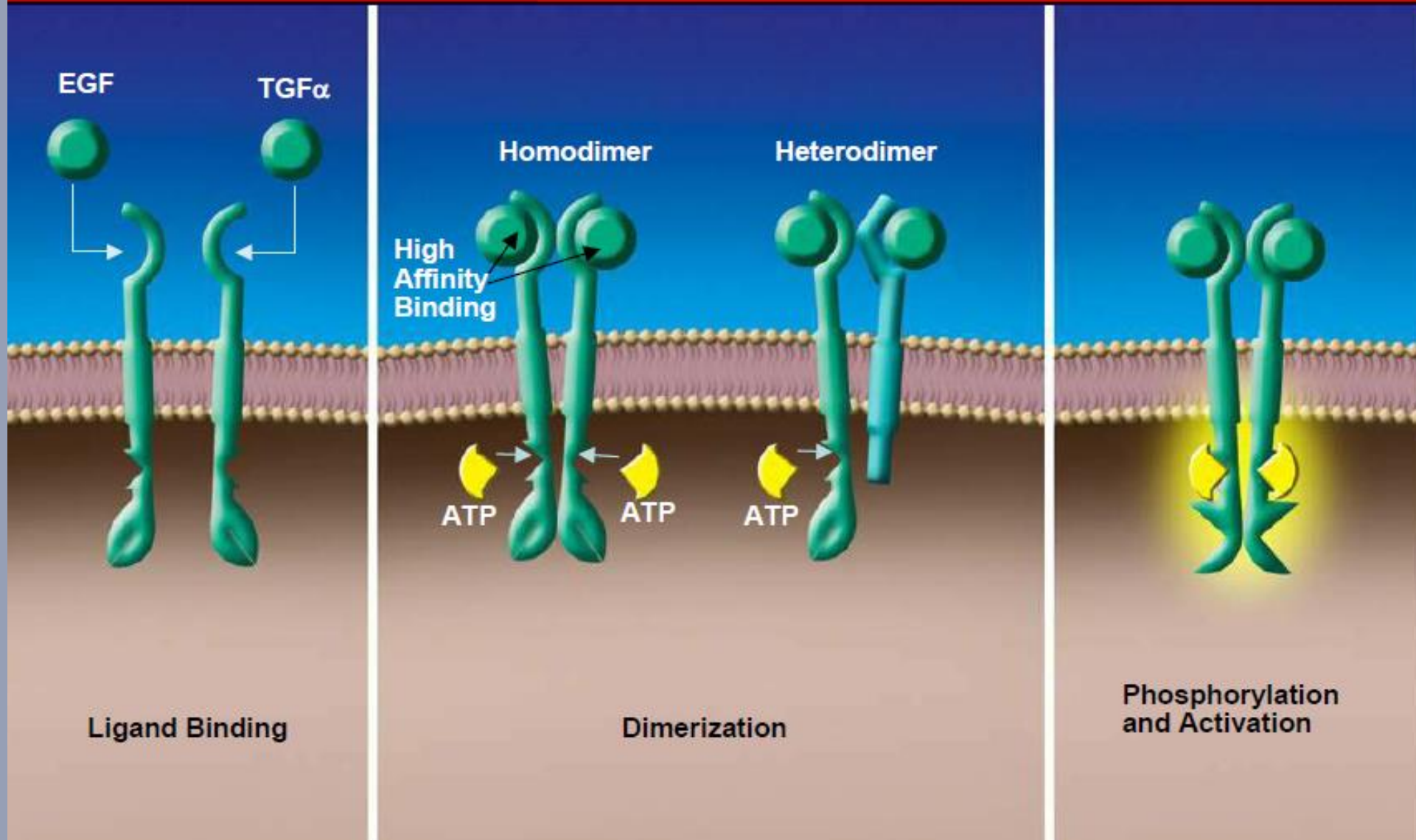


- ▶ young
- ▶ female
- ▶ never smokers

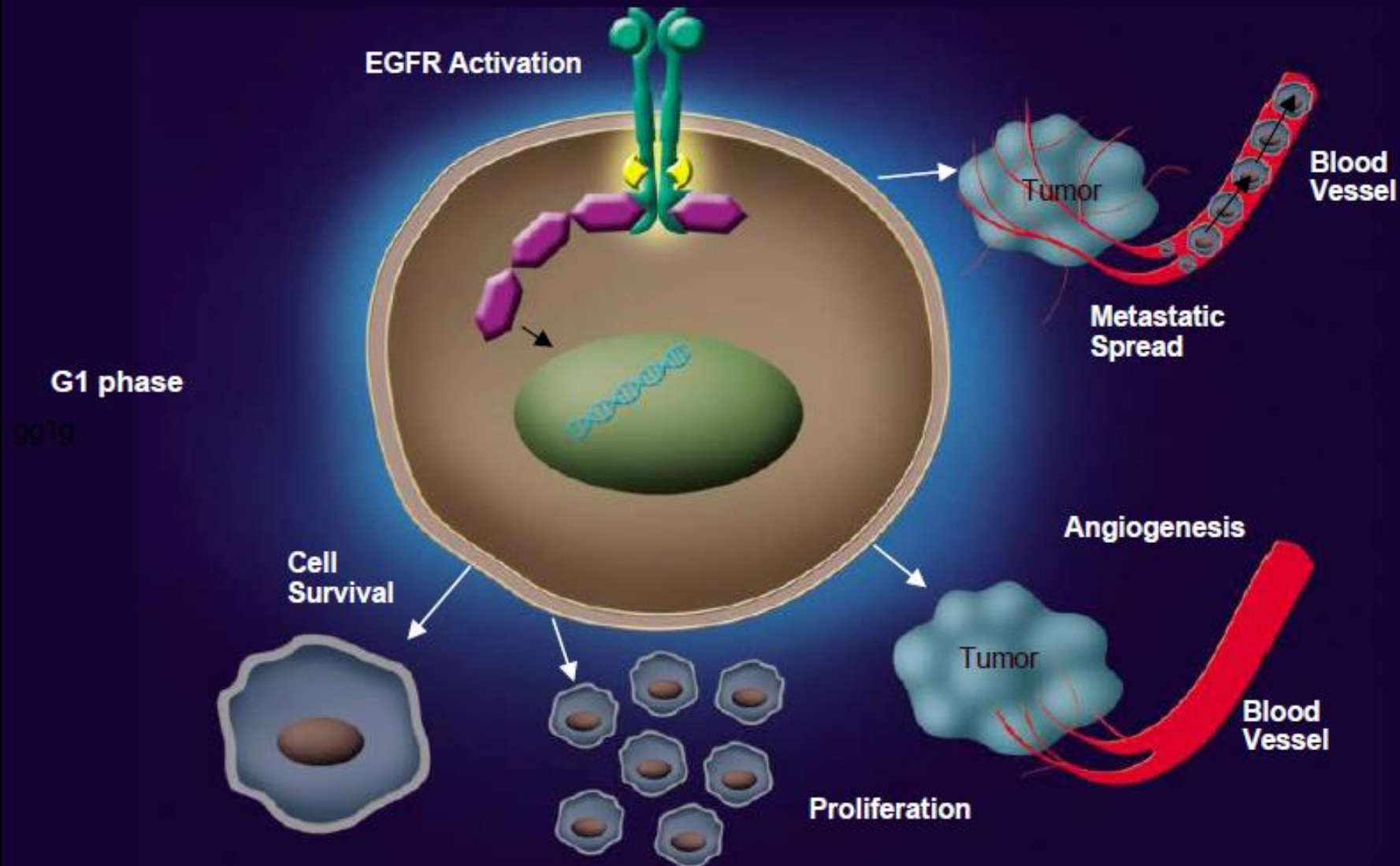
The promise of genotype directed therapy

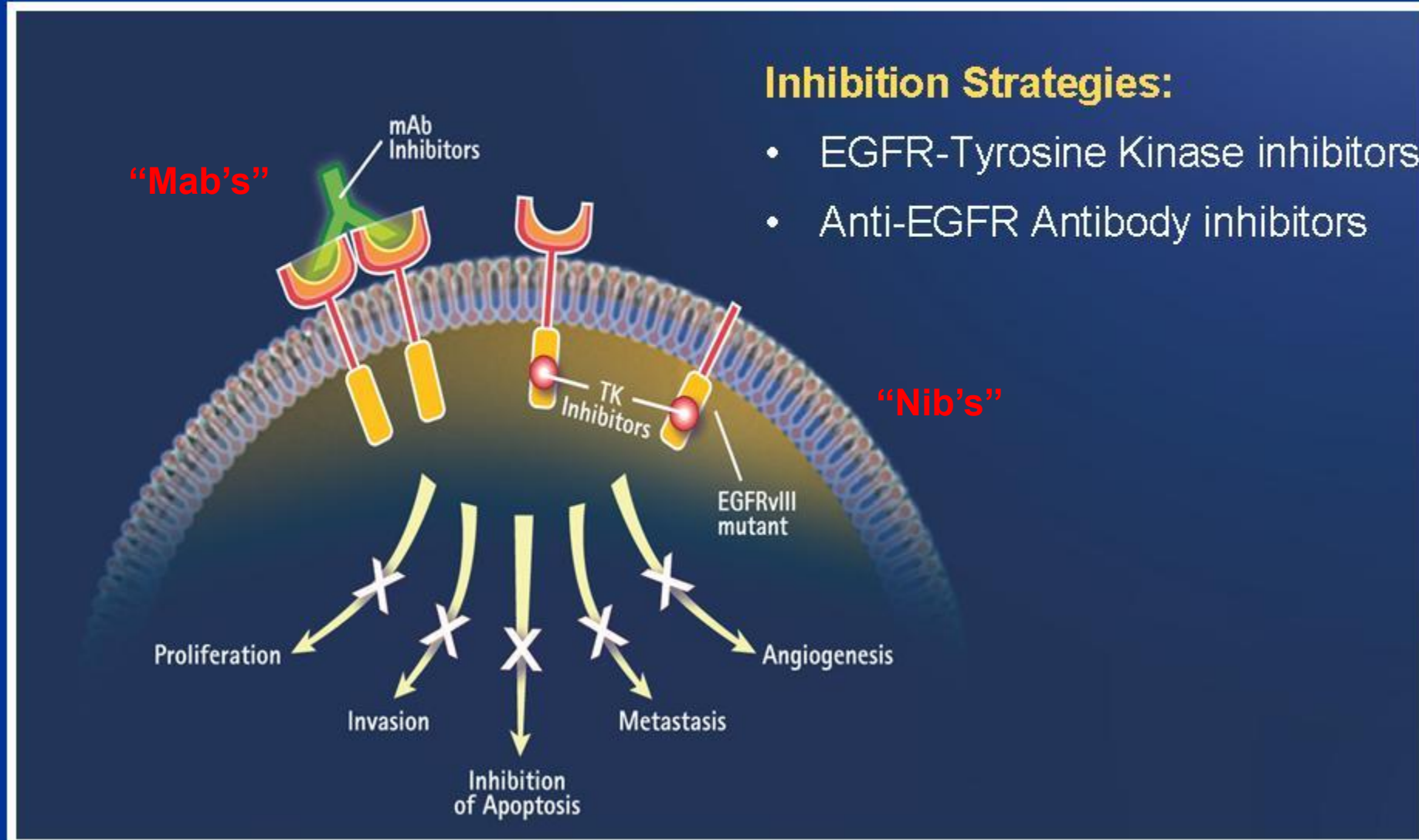


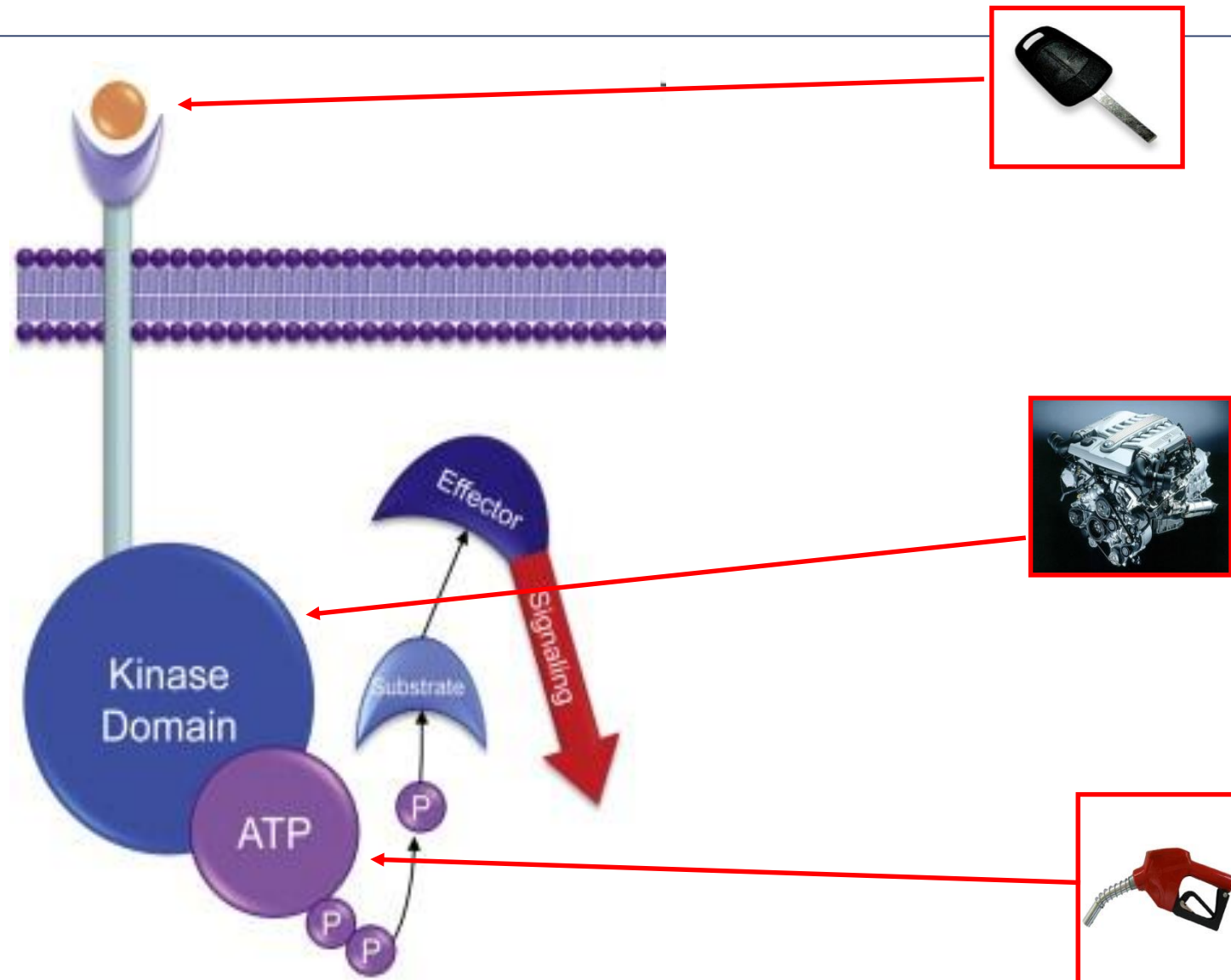
Ligand Binding and Dimerization Result in TK Activation



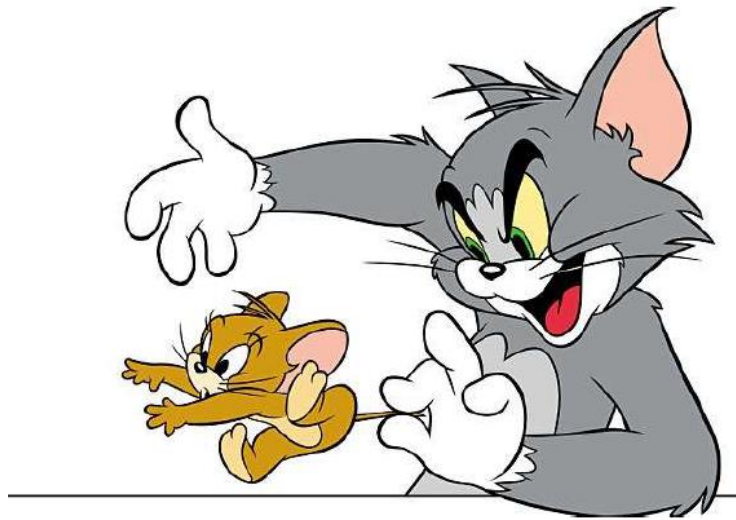
EGFR Activation Enhances Pathways Important for Tumor Cell Growth







The problem of genotype directed therapy

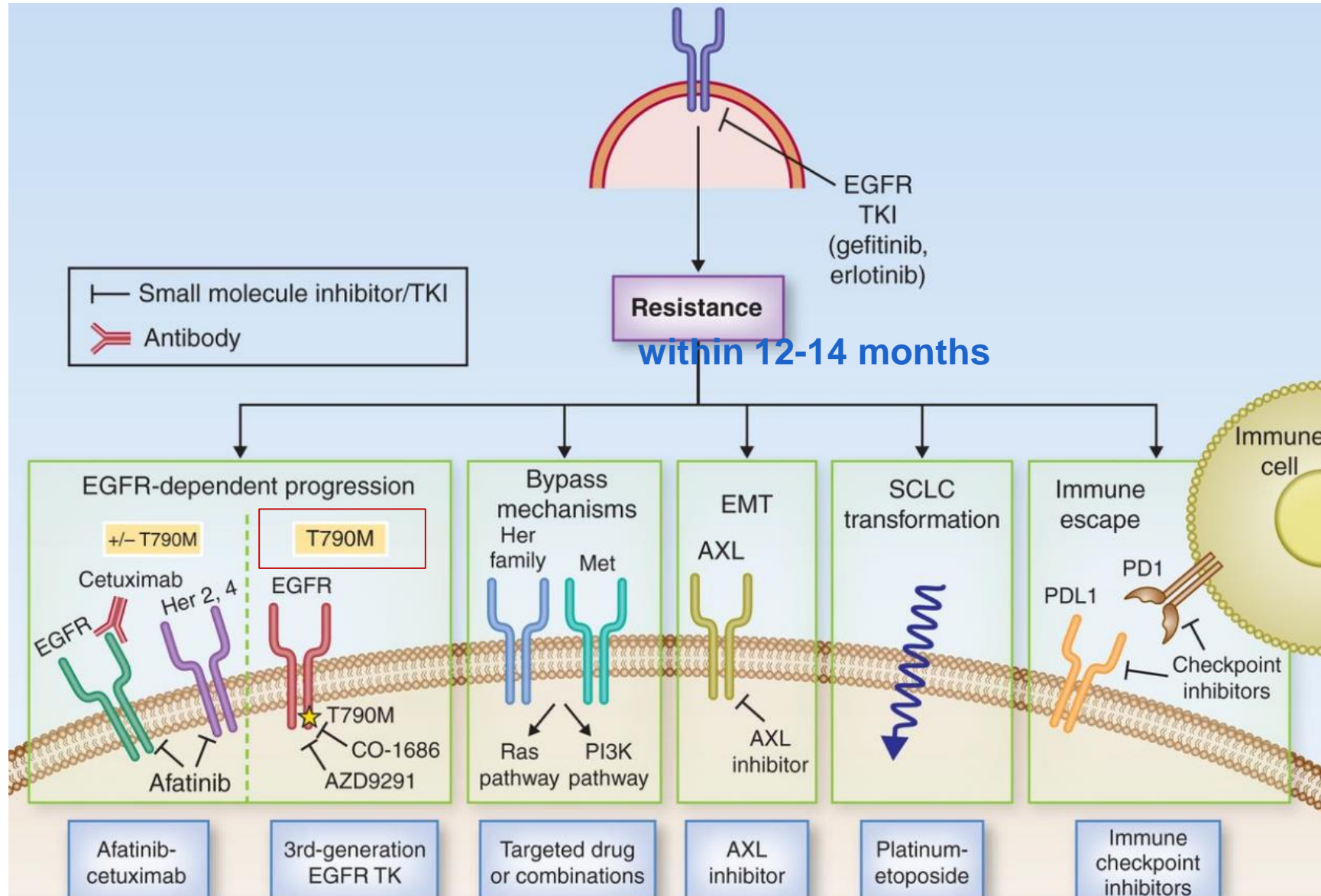


Succes



Failure-resistance

EGFR pathway and resistance mechanisms

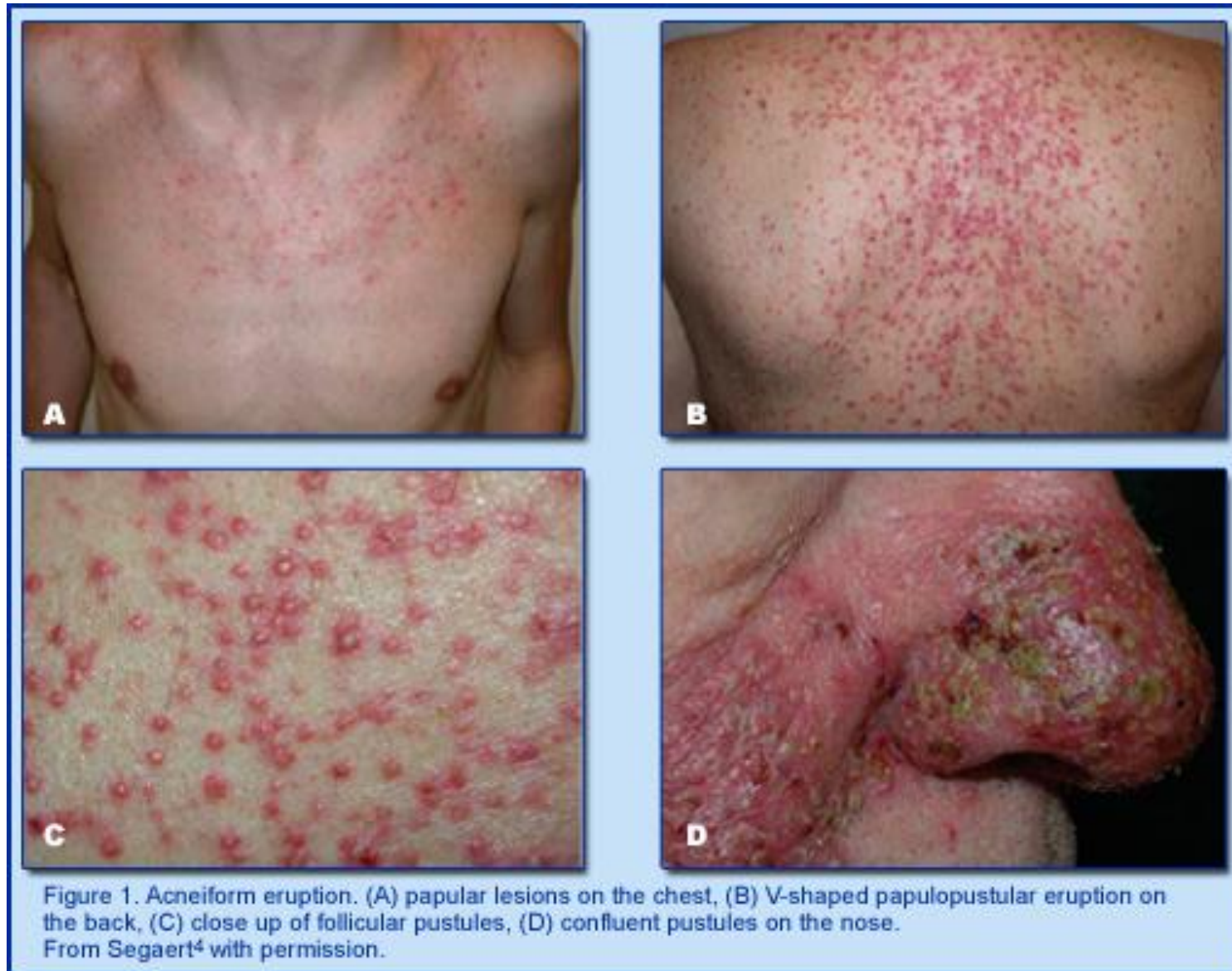


EGFR TKI

EGFR mutation: +/- 15% of NSCLCs	1 st gen.	2 nd gen.	3 rd gen.
Drugs	<ul style="list-style-type: none"> Gefitinib (Iressa[®]) Erlotinib (Tarceva[®]) 	Afatinib (Giotrif [®])	Osimertinib (Tagrisso [®])
Targets	<ul style="list-style-type: none"> Mutated & WT EGFR Not T790M (acquired resistance mutation) 	<ul style="list-style-type: none"> Mutated & WT EGFR Possibly T790M But also HER2/3/4 	<ul style="list-style-type: none"> Mutated EGFR Specifically T790M Not WT EGFR
EGFR binding	Reversible	Irreversible	Irreversible
Current reimbursement	1L	1L	<ul style="list-style-type: none"> 2L if T790M 1L in future?



Skin toxicity

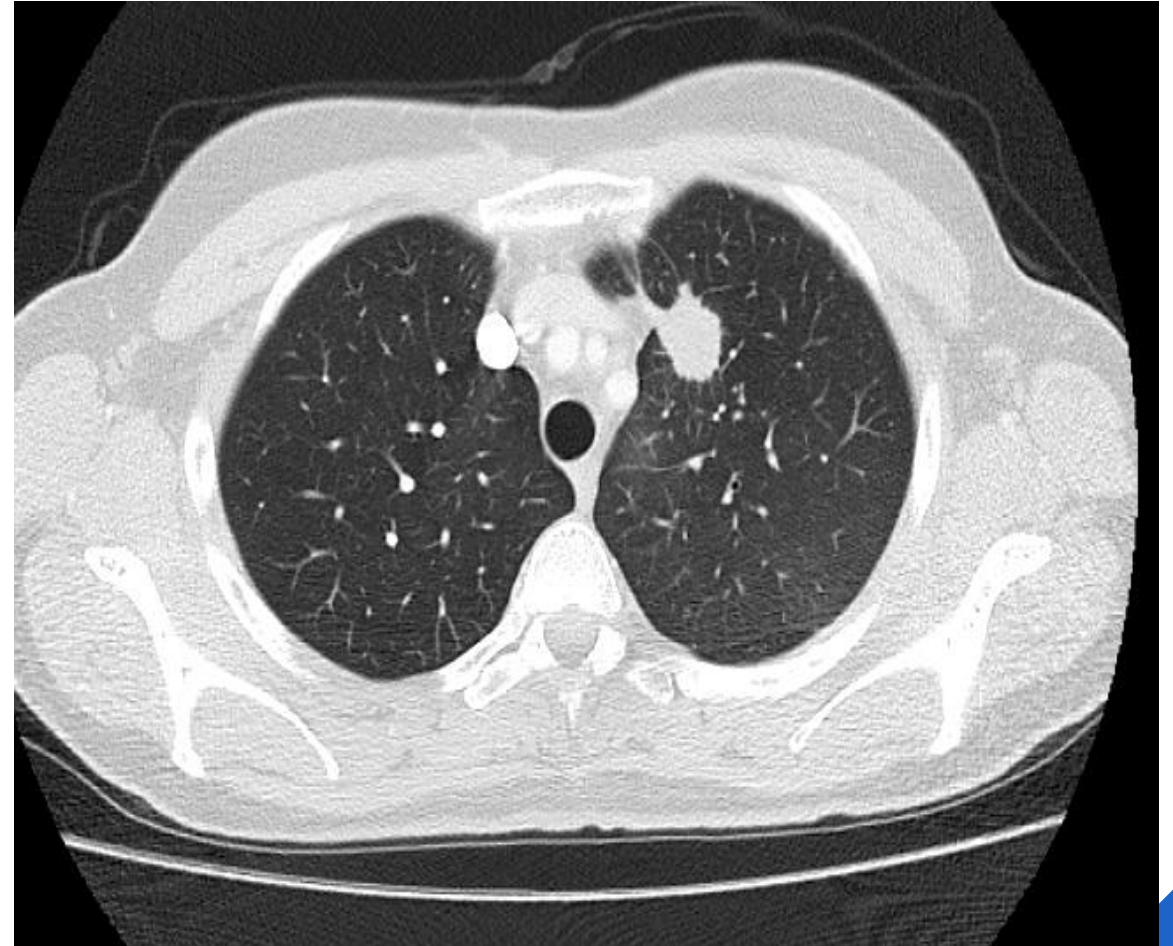
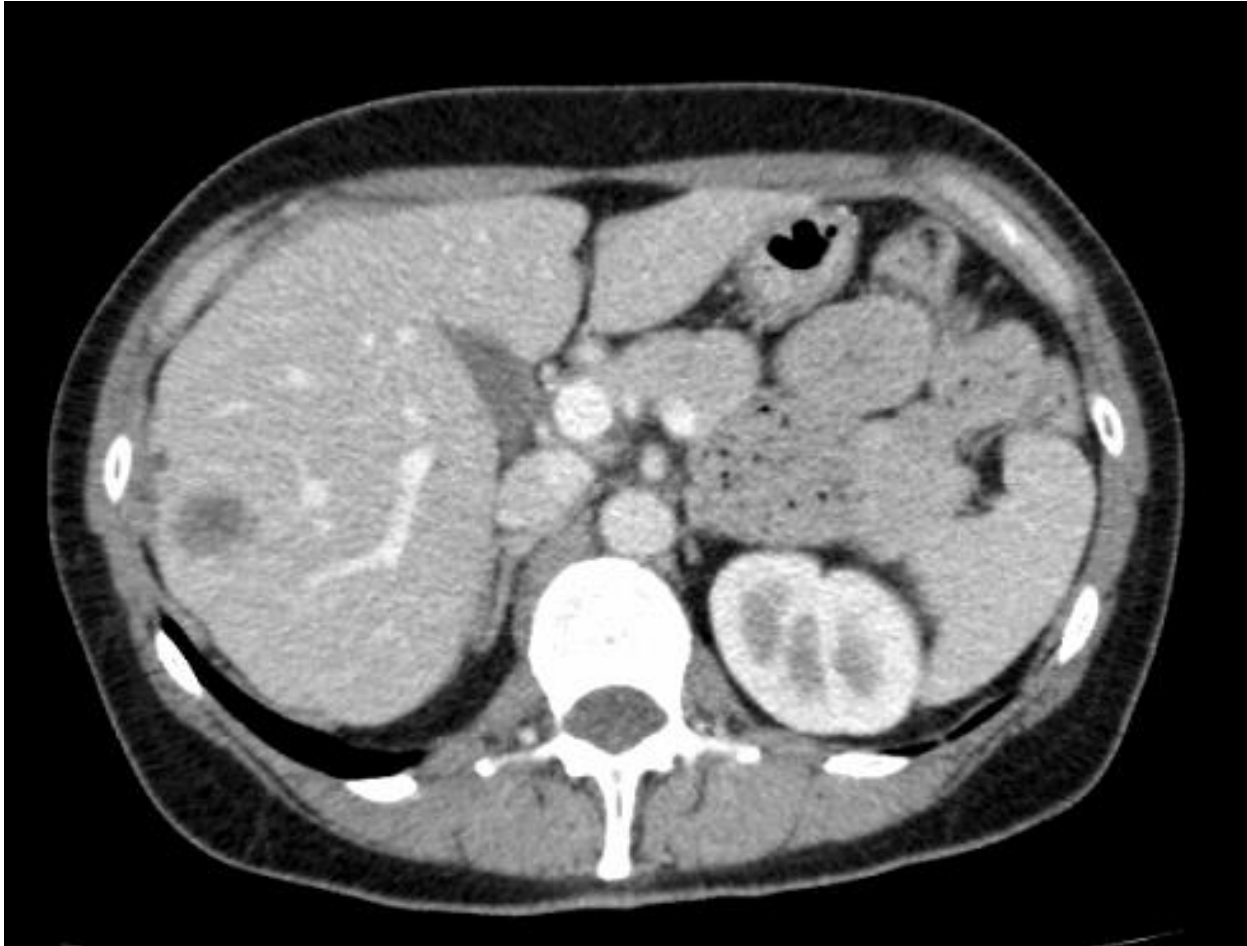


Case presentation

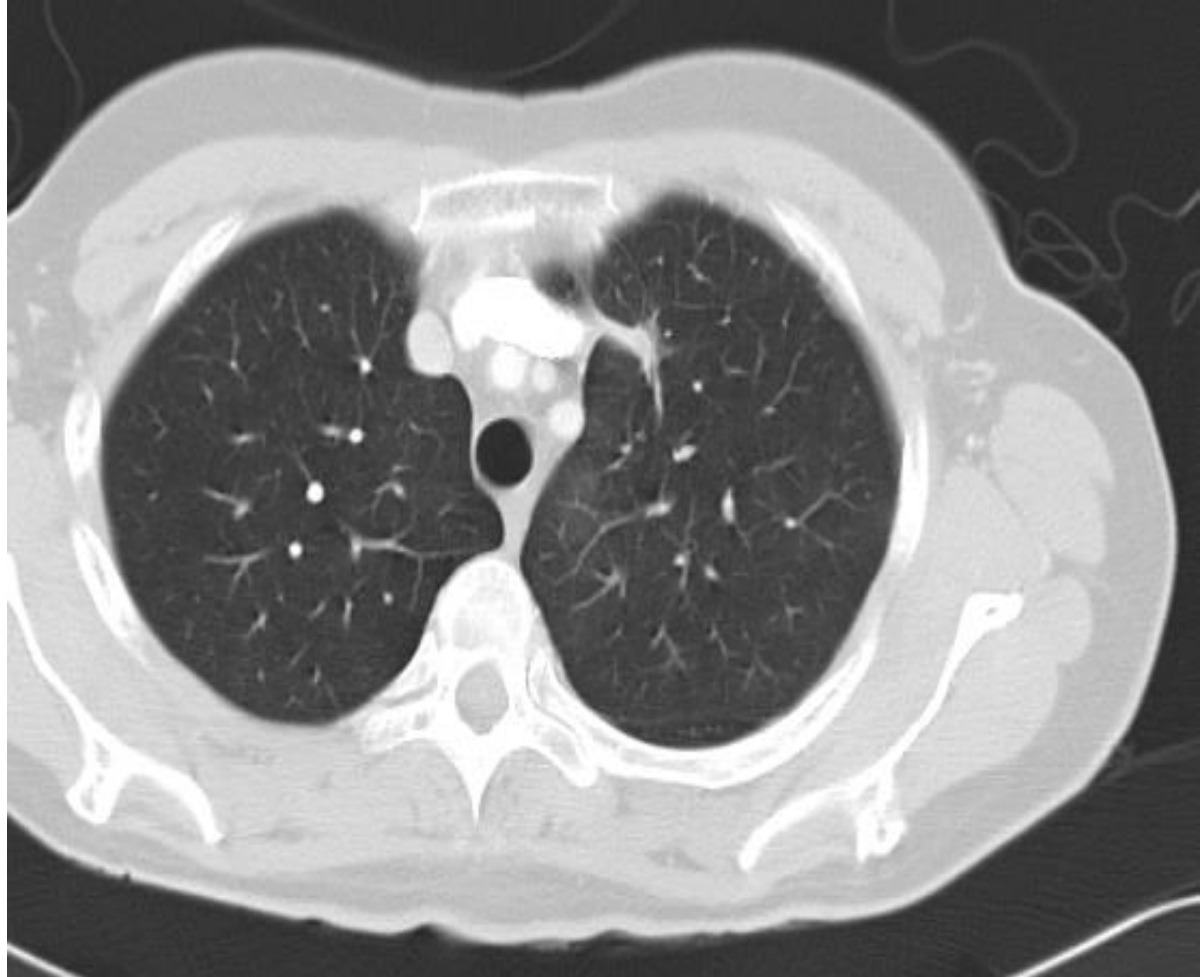
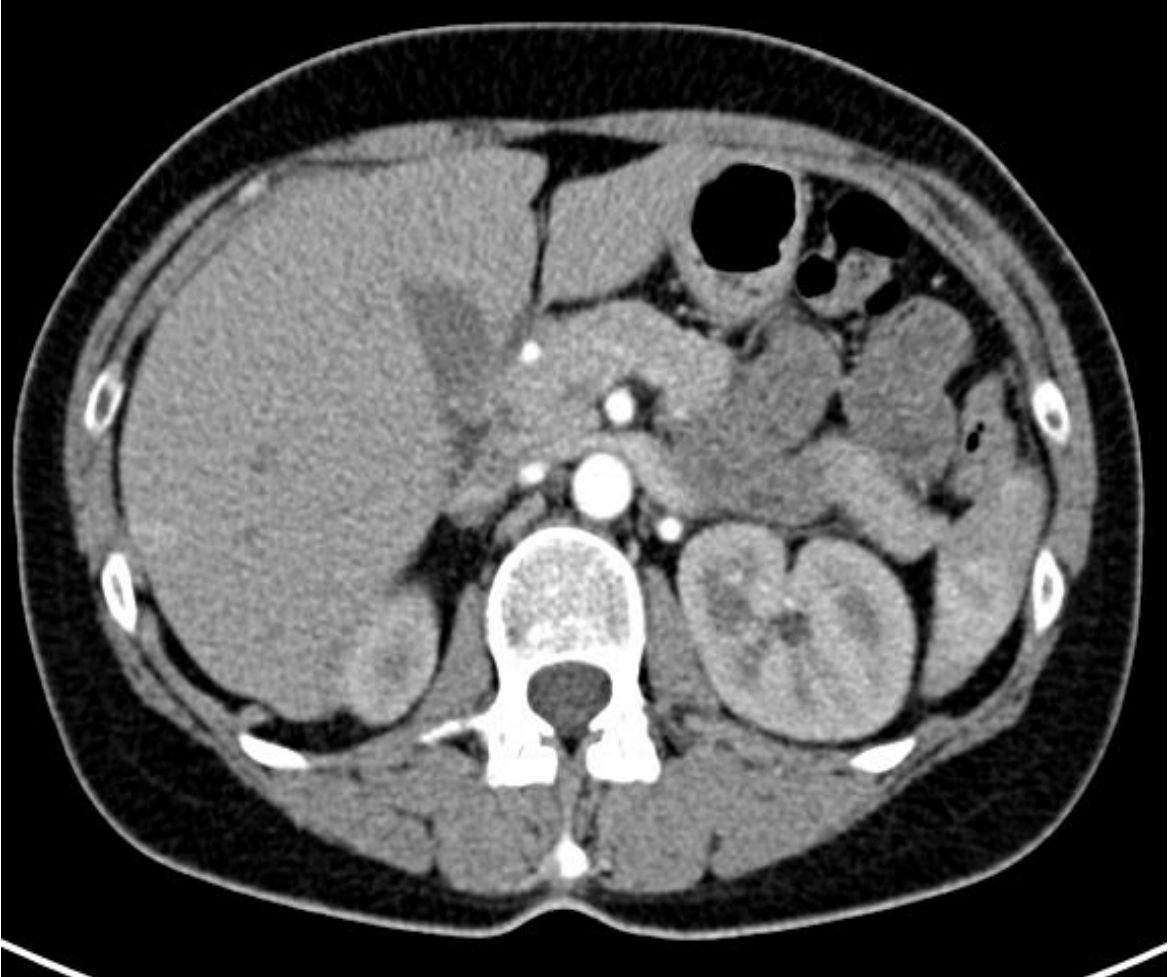
- ▶ Women
- ▶ 57 years
- ▶ Never smoker
- ▶ Weight loss, malaise

- ▶ January 2009: diagnosis of stage IV adenocarcinoma left upper lobe with liver and bone metastases

Mutation in exon 19 (liver biopsy)



After 6 weeks Tarceva



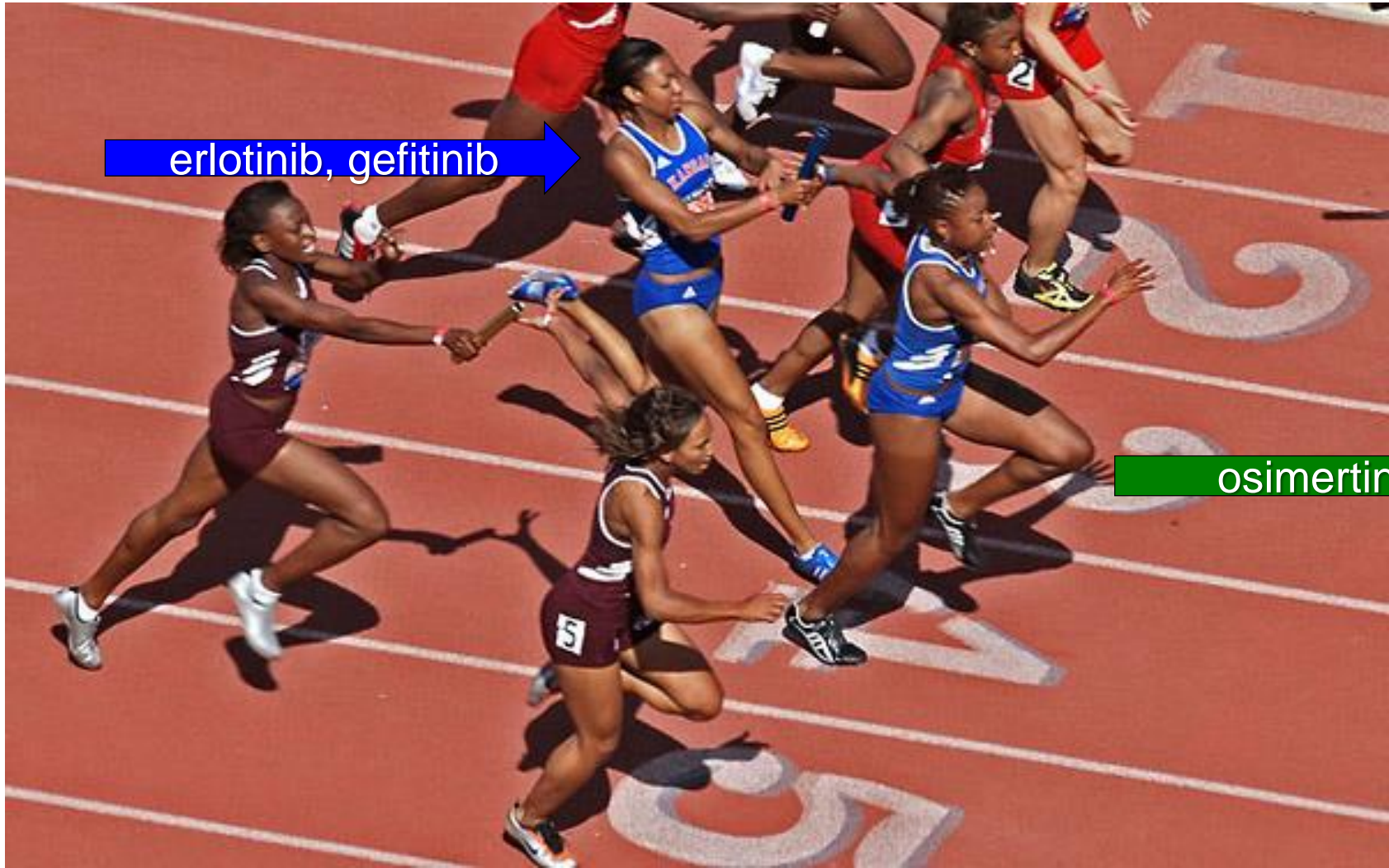
Dramatic Response to Gefitinib



February 6, 2002



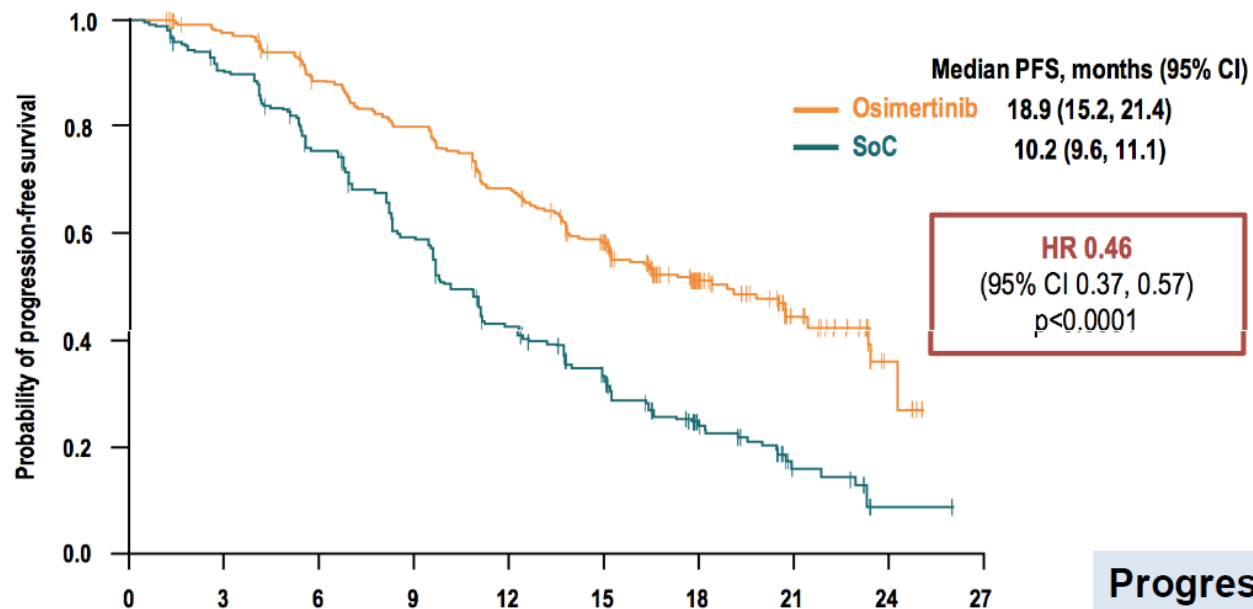
February 11, 2002



erlotinib, gefitinib

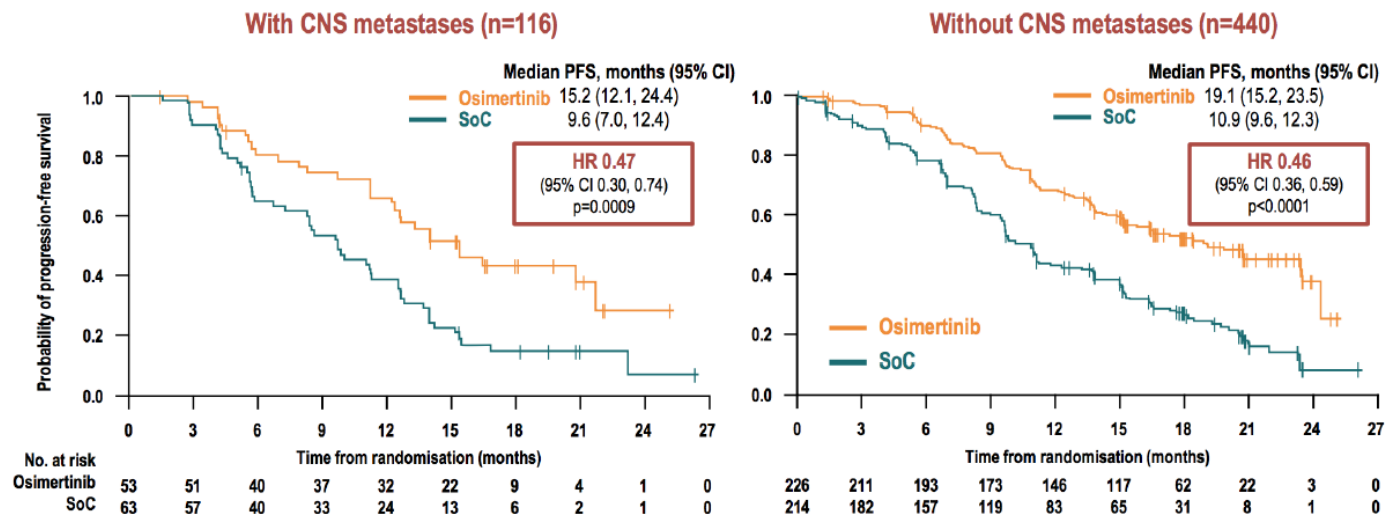
osimertinib

Progression-free survival



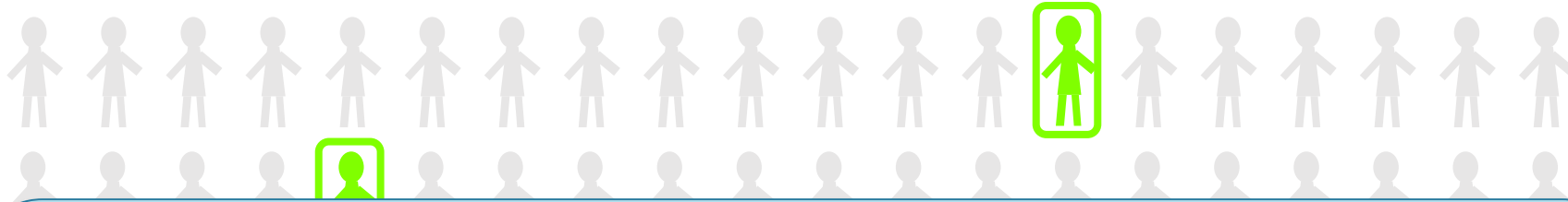
		Time from randomisation (months)									
No. at risk		0	3	6	9	12	15	18	21	24	27
Osimertinib	279	262	233	210	178	139	71	26	4	0	
SoC	277	239	197	152	107	78	37	10	2	0	

Progression-free survival



CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

ALK positive NSCLC

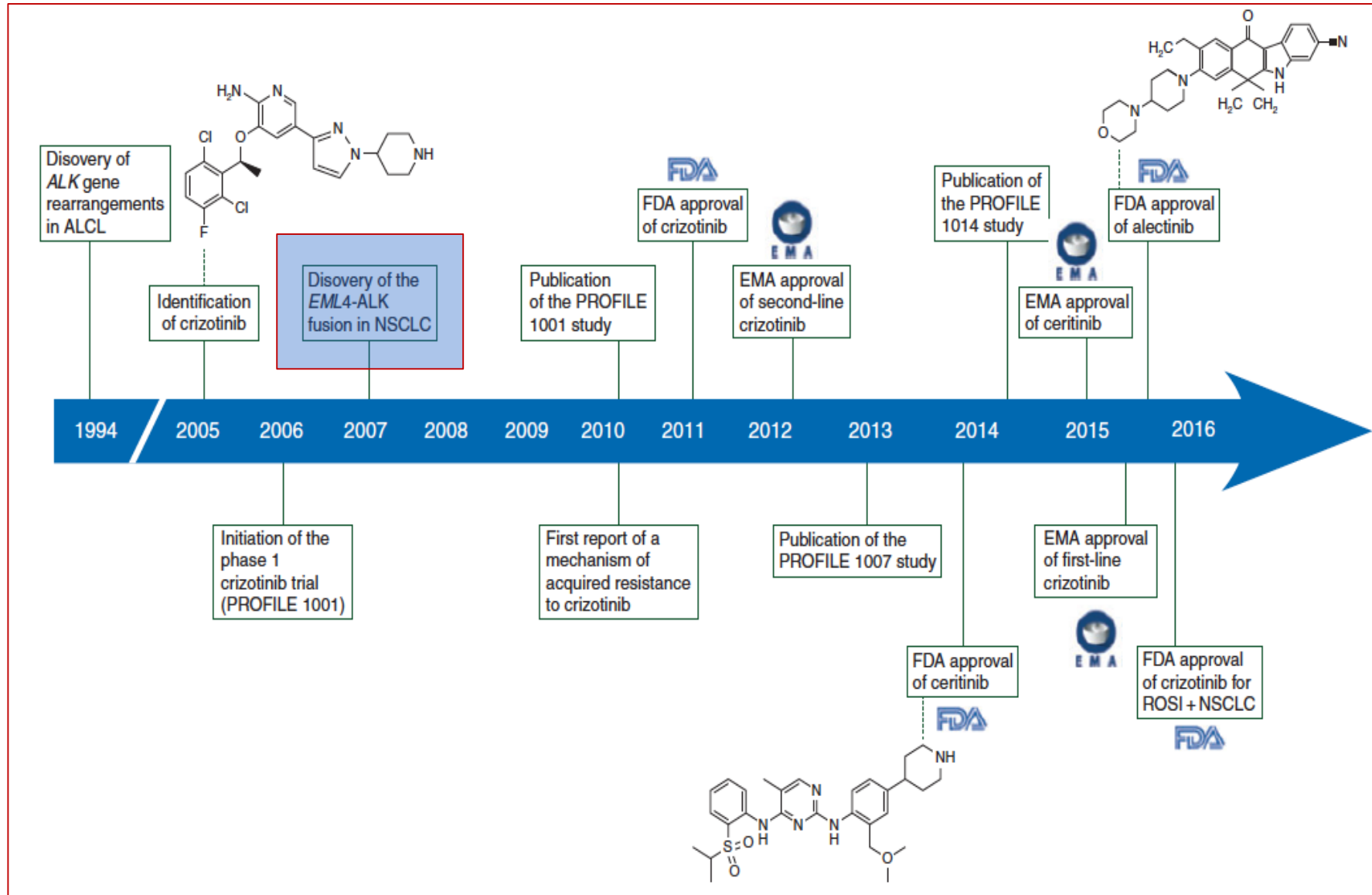


Guidelines recommend testing for *ALK* gene rearrangements in all patients with adenocarcinoma or in whom adenocarcinoma cannot be excluded.

**ALK
Rearrangements**

- 3-5% of NSCLC
- adenocarcinoma
- younger patients
- never smokers

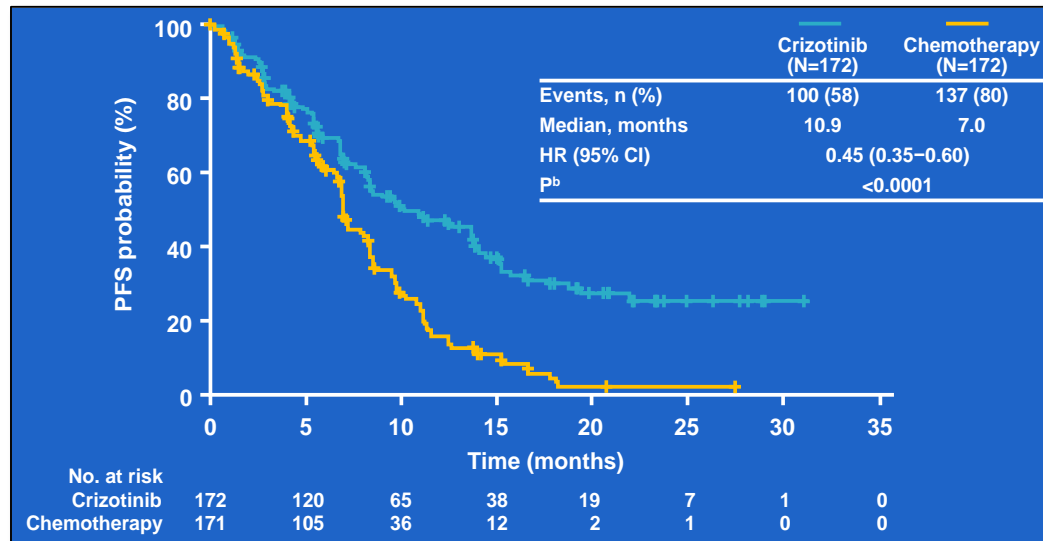
Rapid clinical development and success in a short time



Crizotinib superior to standard chemotherapy

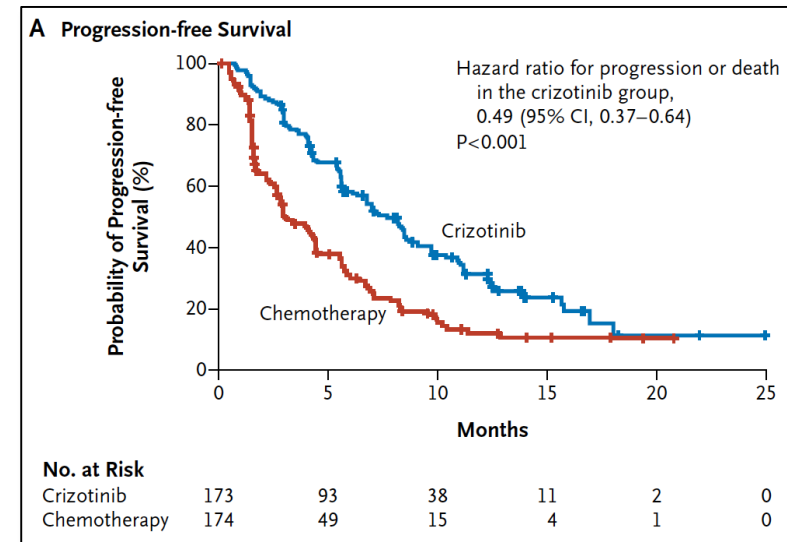
1st Line therapy

Pfizer 1014: Crizotinib vs. Platinum/Pemetrexed

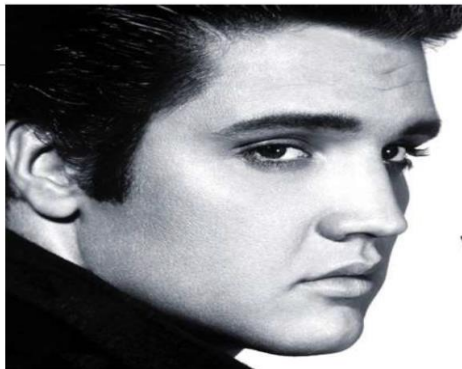


2nd Line therapy

Pfizer 1007: Crizotinib vs. Chemotherapy

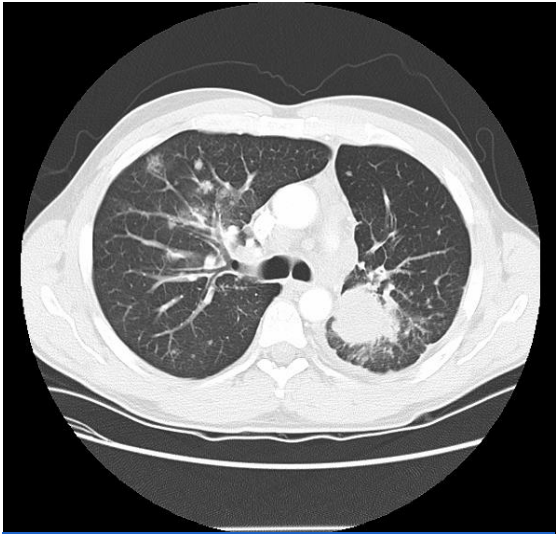


ORR: Crizotinib 65% vs. Chemo 20%

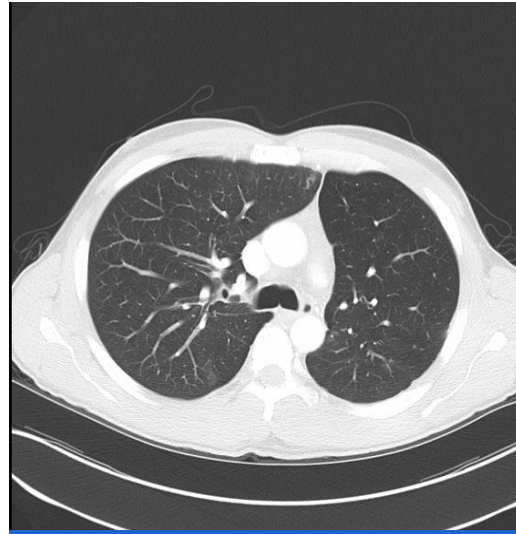


The King of Rock n Roll

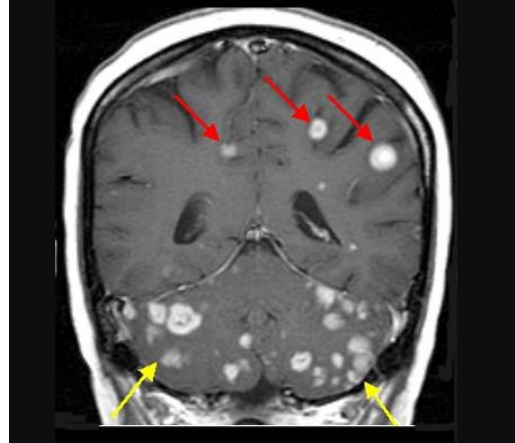
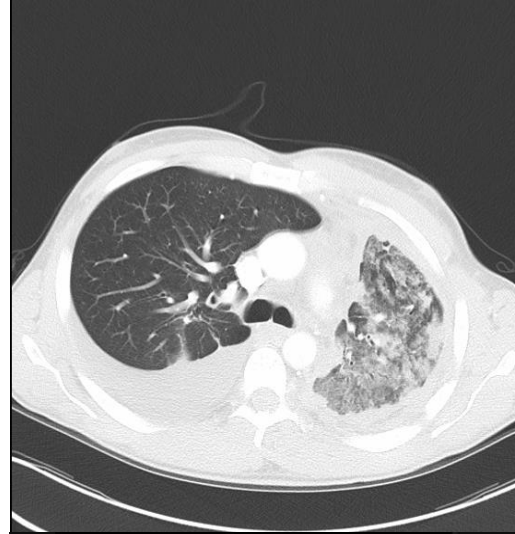
But ... acquired resistance to ALK inhibitors



April 2009



September 2010



September 2011

Crizotinib

???

Next generation ALK inhibitors

Ceritinib

Alectinib

Brigatinib

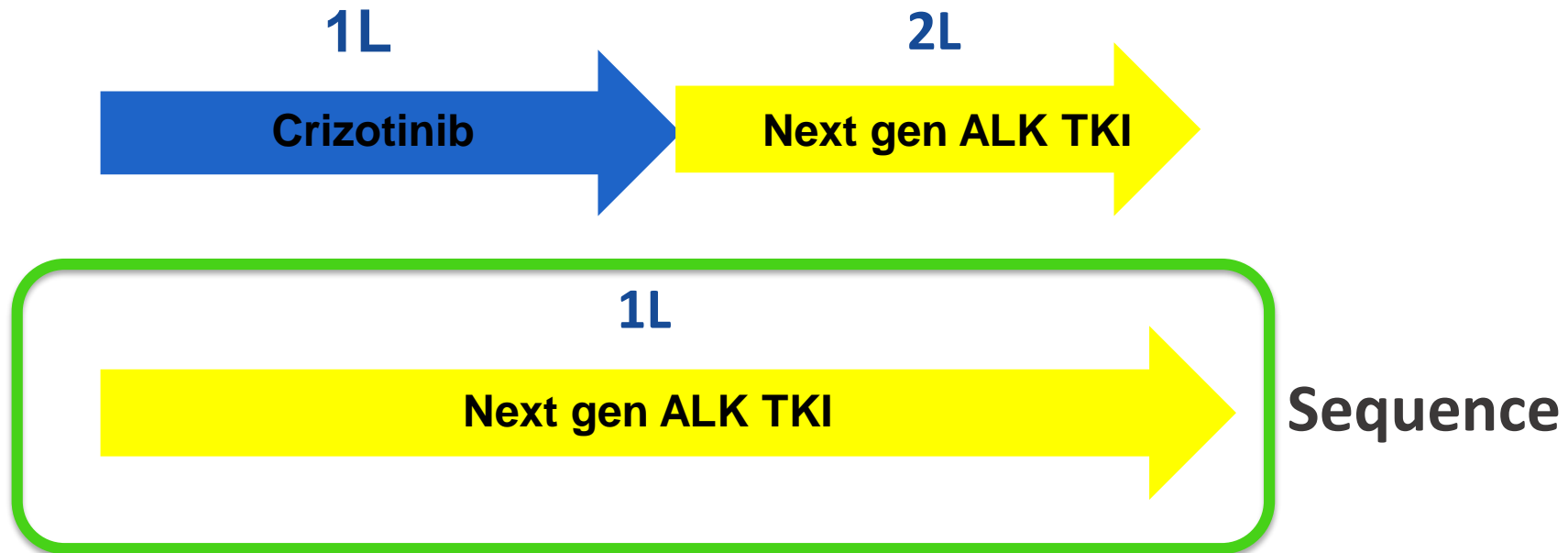
Lorlatinib



Activity against resistance mutations

Better activity in the CNS

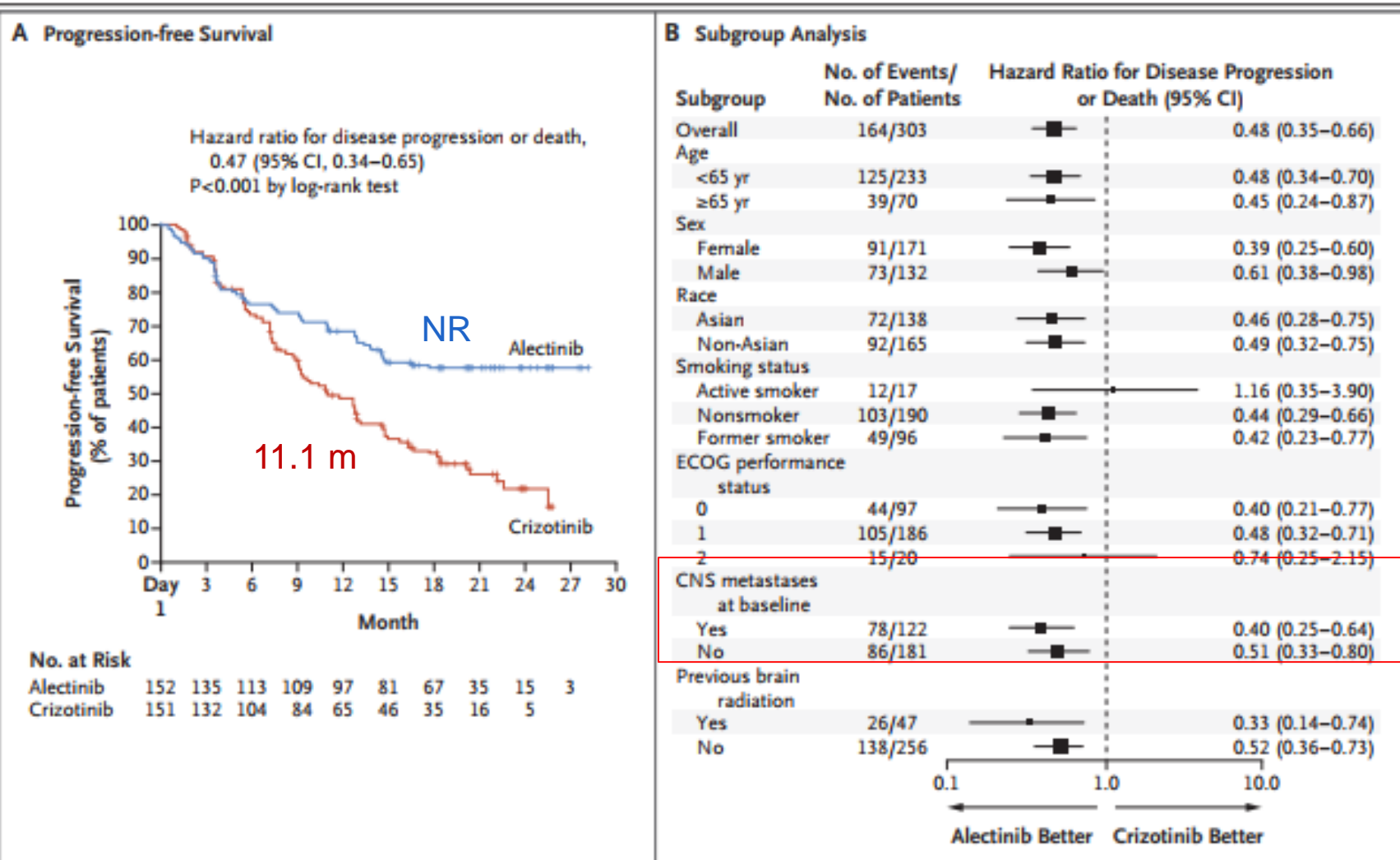
What is the optimal first-line treatment?



- ▶ (J-)ALEX: alectinib vs crizotinib
- ▶ ALTA-1L: brigatinib vs. crizotinib
- ▶ eXalt3: ensartinib vs. crizotinib (recruiting)
- ▶ CROWN: lorlatinib vs. crizotinib (recruiting)

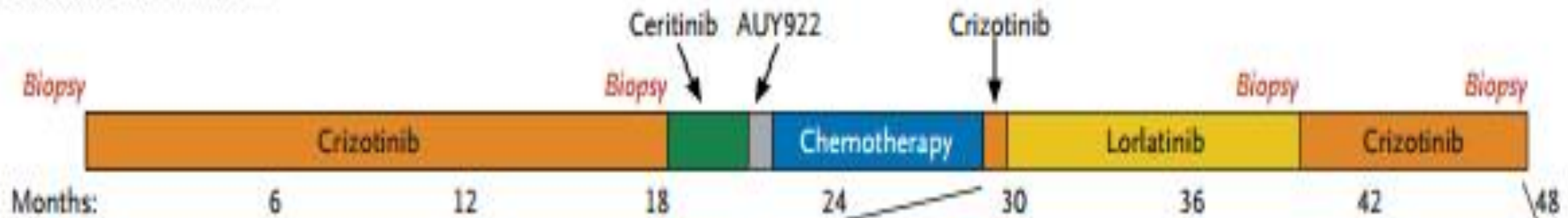
ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer



Sequence is associated with prolonged survival

A Timeline of Treatment

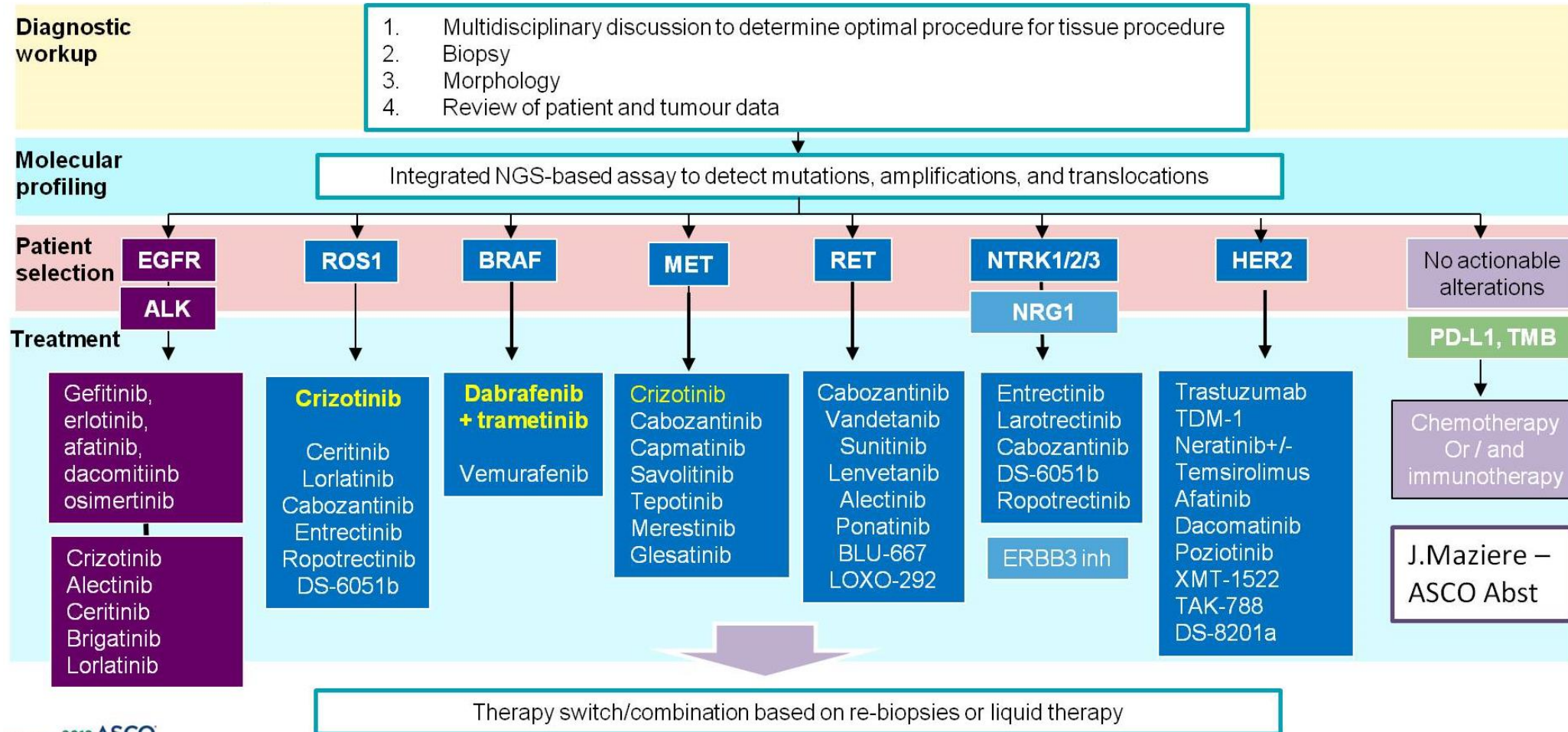


B Effect of Therapy



Promising new drugs for new targets

Presented By David Planchard at 2018 ASCO Annual Meeting



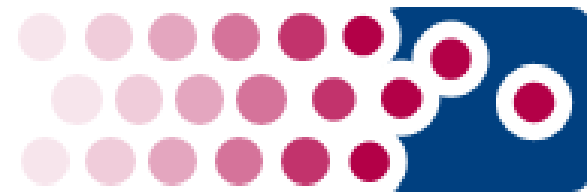
PRESENTED AT: 2018 ASCO ANNUAL MEETING

NGS is important - Refer these patients for trials

Gemetastaseerd NSCLC zonder oncogene drivers

Immunotherapie

Wat verstaat men onder immunotherapie van kanker?



1. vaccinatie

- het lichaam stimuleren om meer tumor-gerichte killer lymfocyten aan te maken

2. Immuun checkpoint blokkade

- verlamde lymfocyten in en rond de tumor ontremmen
vb. anti-CTLA4, anti-PD1 antibodies

3. adoptieve T-cell therapie / T-cell transfusie

- lymfocyten van de patiënt in proefbuis tumor-specifiek maken en terug toedienen
vb. CAR-T cells

Past NSCLC trials : Olympic Marathon



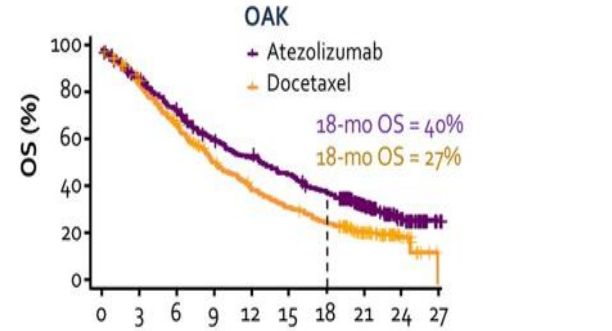
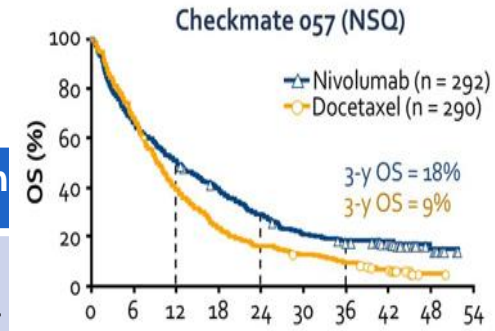
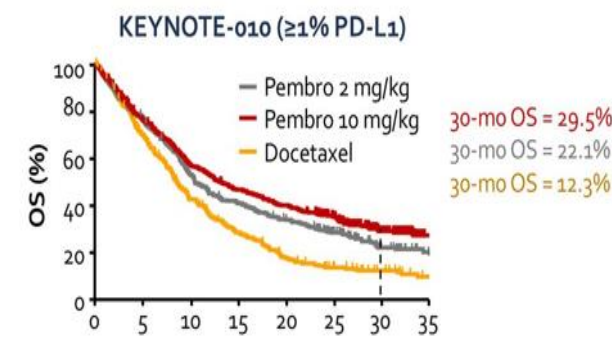
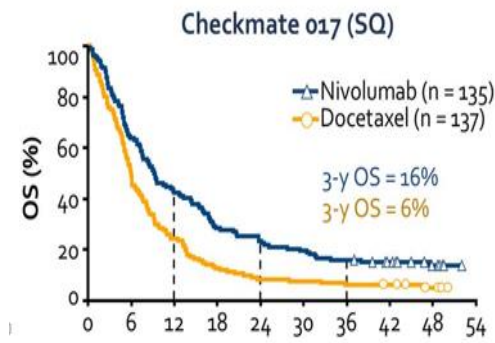
ANTWERP, BELGIUM - AUGUST 22: Runners including Shiso Kanaguri (C) of Japan line up before start of the Marathon during the Antwerp Summer Olympic Games on August 22, 1920 in Antwerp, Belgium. (Photo by The Asahi Shimbun via Getty Images)

Current NSCLC trials: 100 meter dash



What has changed over the past years?

Phase III second line trials



Felip, ESMO 2017; Herbst, ASCO 2017; Rittmeyer, Lancet 2017

Agent	Tumor type	Line	Biomarker	Phase	Referen
pembrolizumab	NSCLC	2	> 1% TPS	3	Herbst Lancet
atezolizumab	NSCLC	2	unselected	3	Rittmeyer et al Lancet 2017
nivolumab	NSCLC	2	unselected	3	Borghaei et al NEJM 2015
nivolumab	squamous	2	unselected	3	Brahmer et al NEJM 2015

Reimbursement of 3 agents in second line

Agent	Tumor type	Line	Biomarker	Phase	RR	PFS	OS	Reference
Pembrolizumab vs platinum doublet (KN-024)	NSCLC	1	≥ 50% TPS	3	44.8 vs 27.8%	HR 0.5 P<0.01	0.63 P<0.01	Reck et al 2016
Pembro vs platinum doublet (KN-042)	NSCLC	1	PD-L1 > 1%	3	27.3 vs 26.5%	HR 1.07 NS	0.81 P<0.01	Late breaking abstract 4
platinum-pem+ pembro vs platinum-pem + placebo (KN-189)	Non-squamous	1	unselected	3	46.6 vs 18.9% P< 0.01	HR 0.52 P<0.01	0.49 P<0.01	Gandhi et al NEJM 2018 HRQoL abstract 9021
Atezo, carbo-paclitaxel, beva vs carbo-paclitacel-beva (IMpower150)	Non-squamous	1	unselected	3	64 vs.48%	HR0.62 p<0.01	Positive HR 0.78	Reck et al ESMO IO 2017 Abstract 9002 Socinski et al AACR 2018
Atezo+ platinum- pem (IMpower132)	Non-squamous	1	unselected	3	47 vs. 32%	HR 0.6 P<0.0001	0.81 NS	WCLC 2018
Nivo+ ipi vs doublet (checkMate227)	NSCLC	1	TMB ≥ 10 mut/MB	3	45.3 vs 26.9%	HR 0.58 P<0.01	0.79 NS	Hellmann et al NEJM 2018
Nivo+ chemo vs. Chemo (checkMate227)	NSCLC	1	PD-L1 < 1%	3	36.7 vs 23.1%	5.6 vs 4.7 HR 0.74	-	Abstract 9001

Agent	Tumor type	Line	Biomarker	Phase	Response Rate	PFS	OS	Reference
Carbo-paclitaxel ± pembro (KN-407)	Squamous	1	unselected	3	58.4 vs 35% P< 0,01	HR 0.56 P<0.01	0.64 P<0.01	Abstract 105
Carbo-Nab paclitaxel ± Atezo (Impower-131)	Squamous	1	unselected	3	49 vs 41%	HR 0.71 P<0.0001	Interim HR 0.91 P=0.69	Late breaking abstract 9000

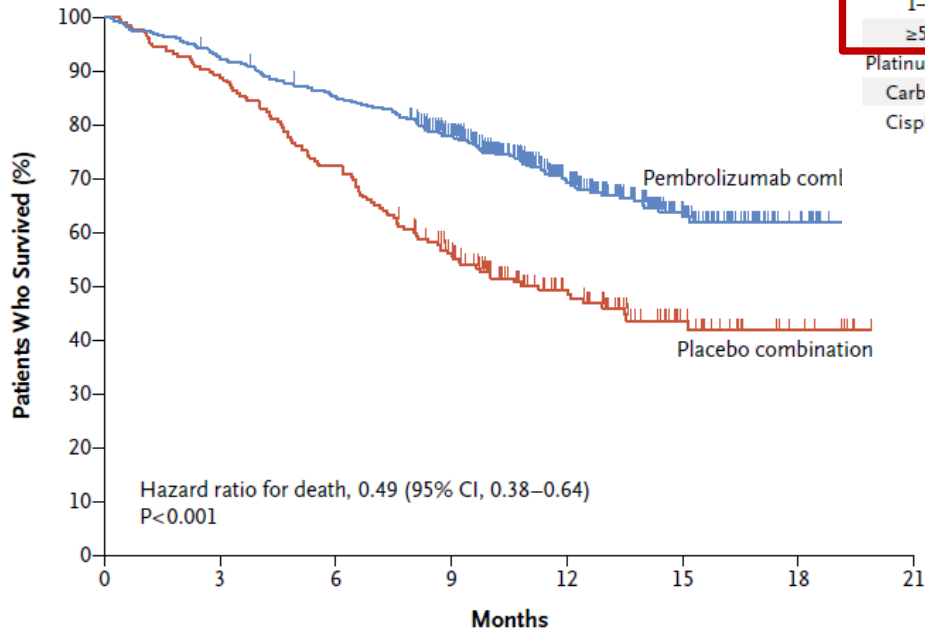


ORIGINAL ARTICLE

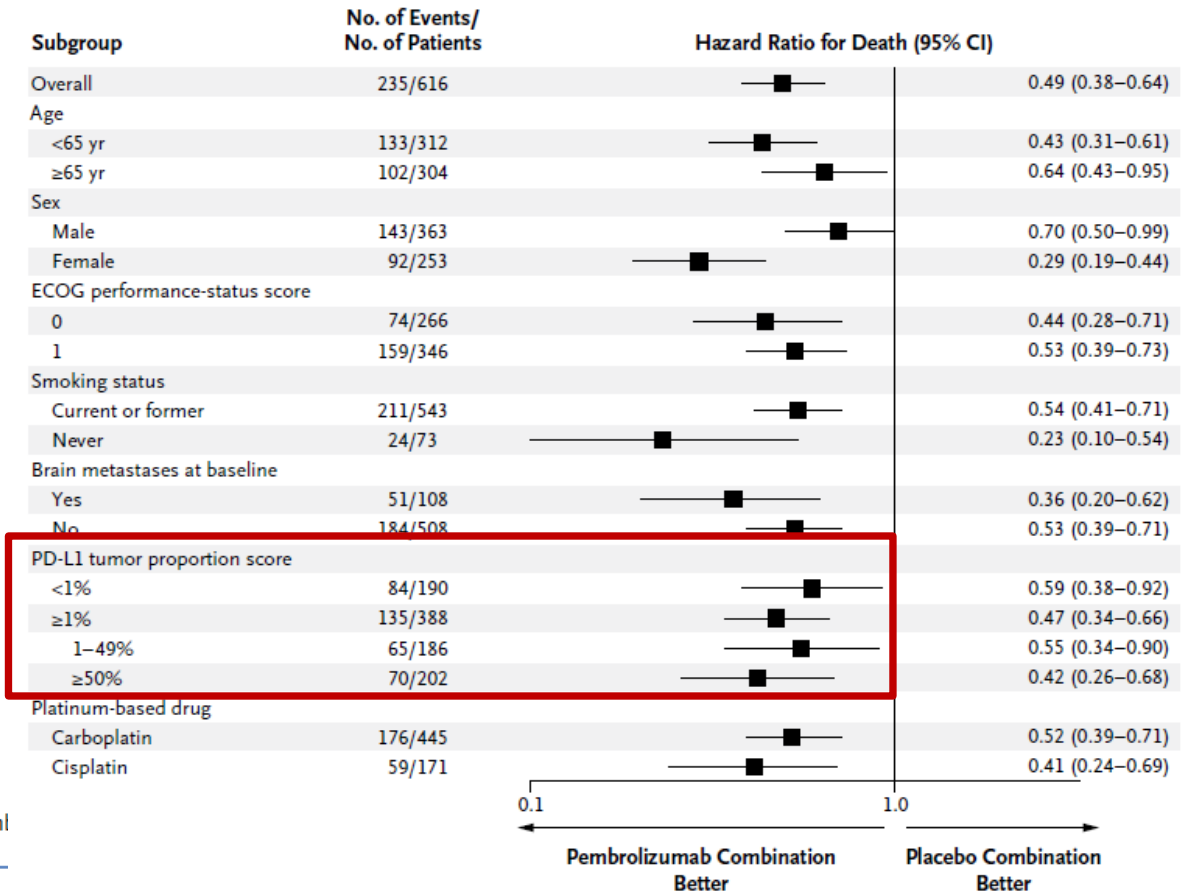
Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

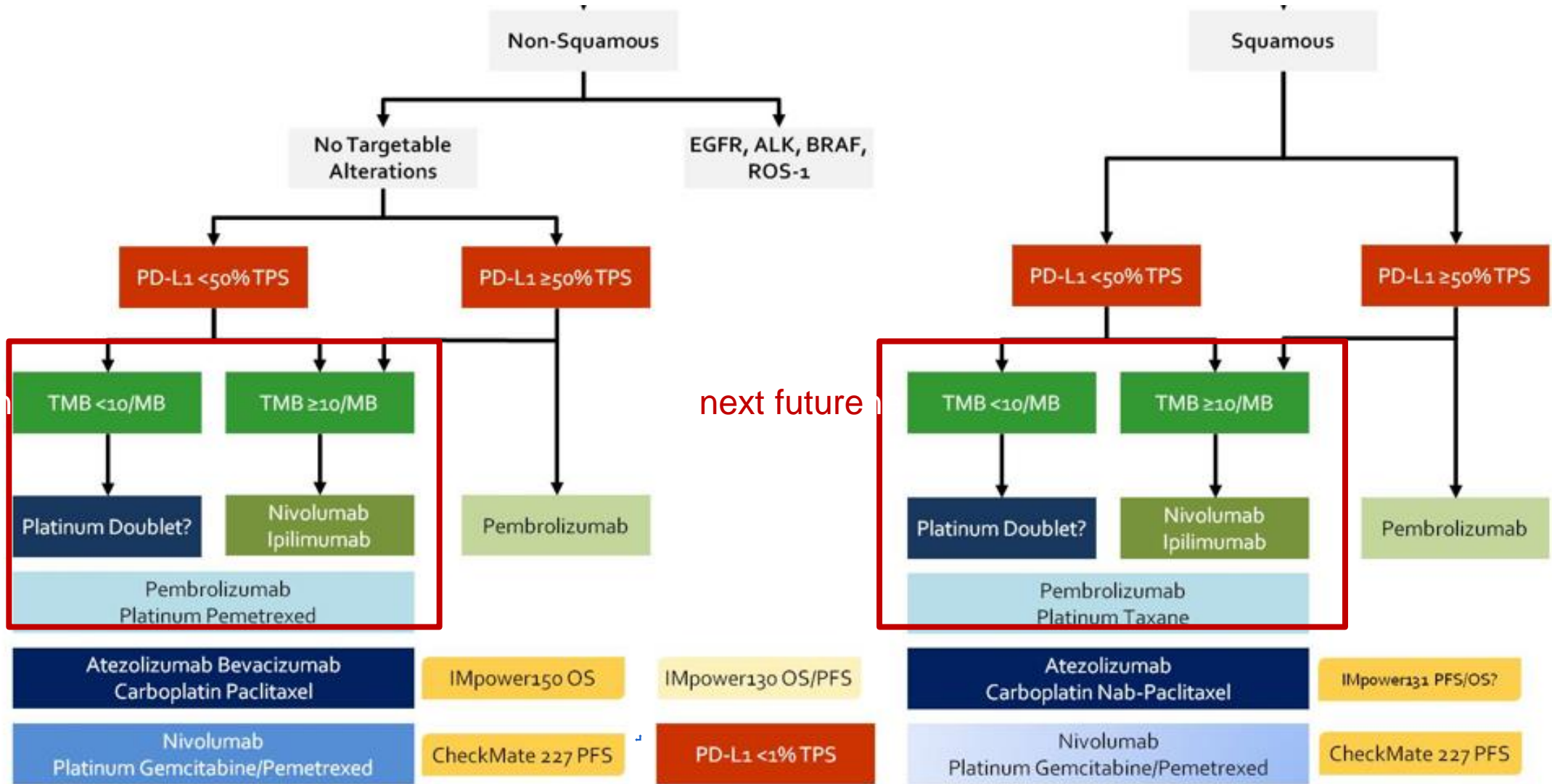
A Overall Survival



No. at Risk	0	3	6	9	12	15	18	21
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0



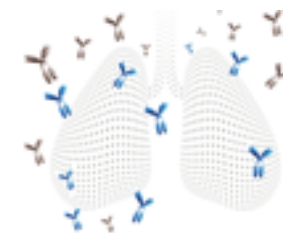
HRQoL was maintained or improved



next future

next future

Considerations for treatment decision-making in first-line NSCLC



Disease & patient characteristics



Performance status / Age

Comorbidities

Location of metastases

Overall tumour burden

- Symptoms
- Lung function
- Number of metastases

Biomarker analysis



Histology

Driver mutations

- *ALK*
- *EGFR*
- *ROS1*
- *BRAF*
- Others

PD-L1

TMB?

Other factors



Patient goals and preferences

Physicians' preferences

Social support network

Wat verstaat men onder immunotherapie van kanker?



1. **vaccinatie**

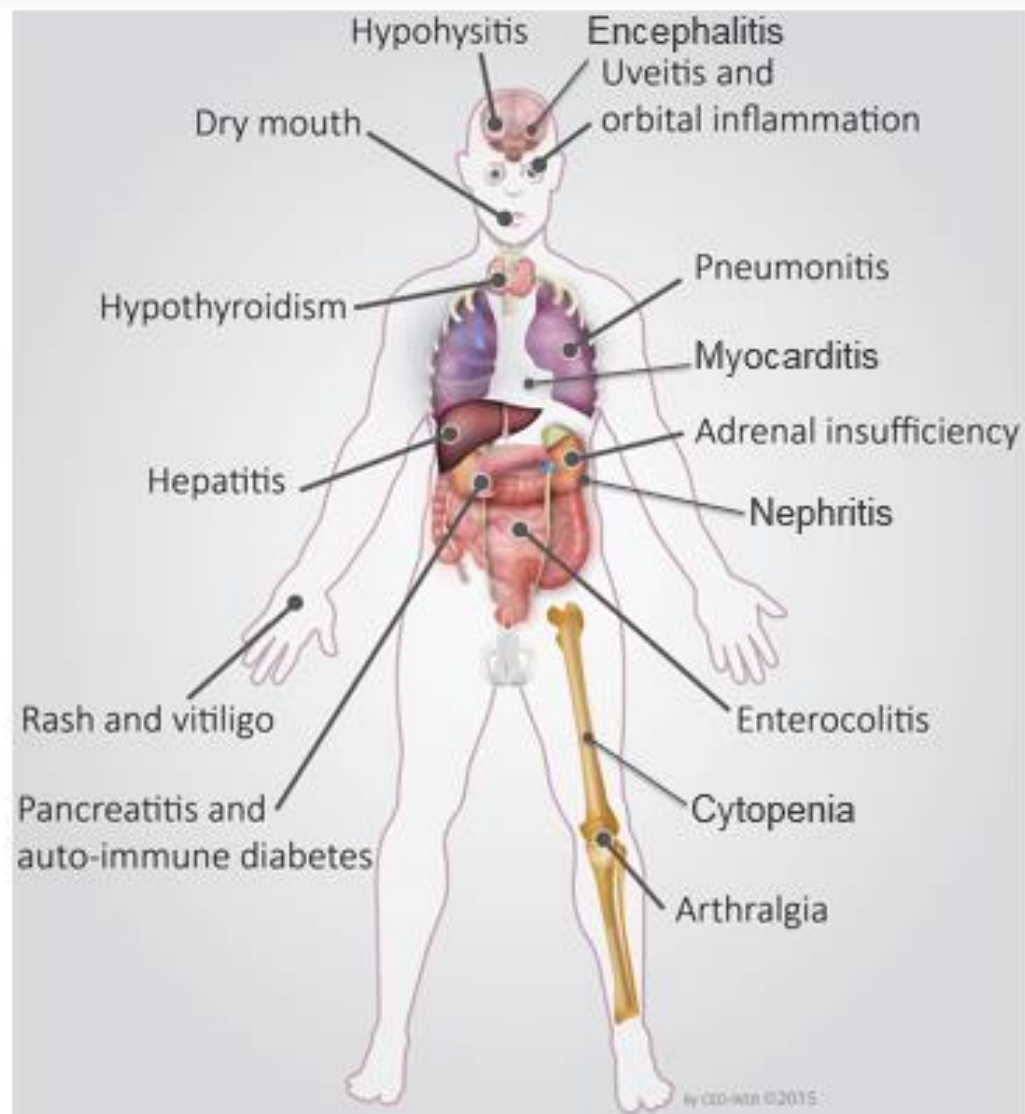
- het lichaam stimuleren om meer tumor-gerichte killer lymfocyten aan te maken

Dezelfde factoren beschermen ons tegen auto-immuniteit

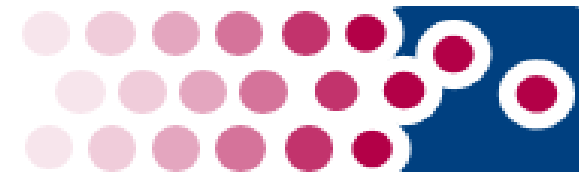
3. **adoptieve T-cell therapie / T-cell transfusie**

- lymfocyten van de patiënt in proefbuis tumor-specifiek maken en terug toedienen
vb. CAR-T cells

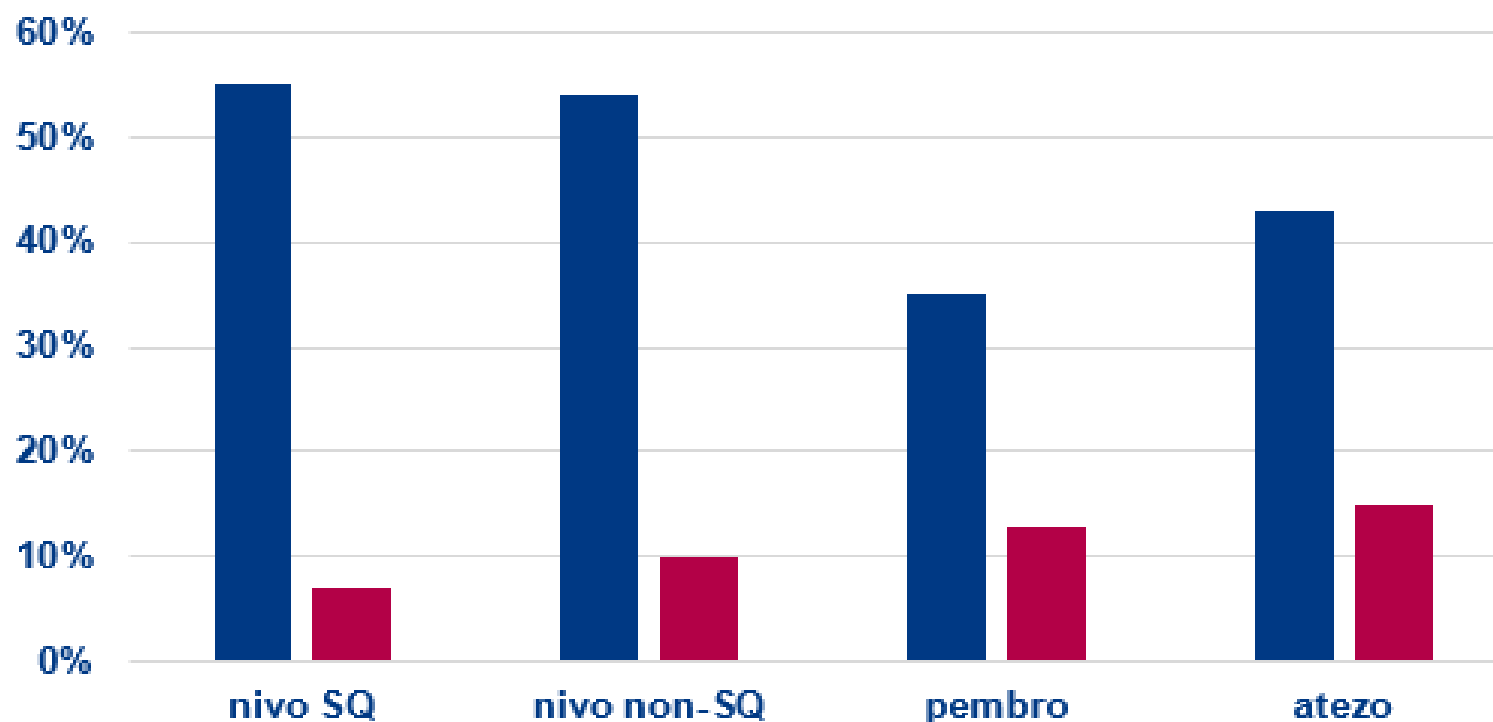
Toxicity of immune checkpoint blockade organ systems at risk



Toxicity of immune checkpoint blockade data from phase 3 anti-PD1 trials



grade 3-4-5 toxicity



J. Brahmer et al, NEJM July 2015

H. Borghaei et al, NEJM October 2015

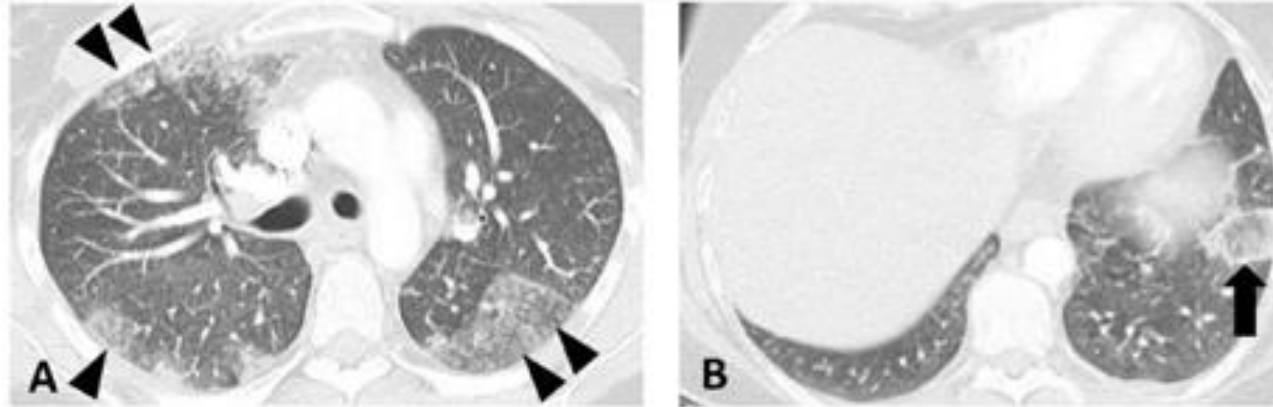
R. Herbst et al, The Lancet December 2015

A. Rittmeyer et al, The Lancet January 2017

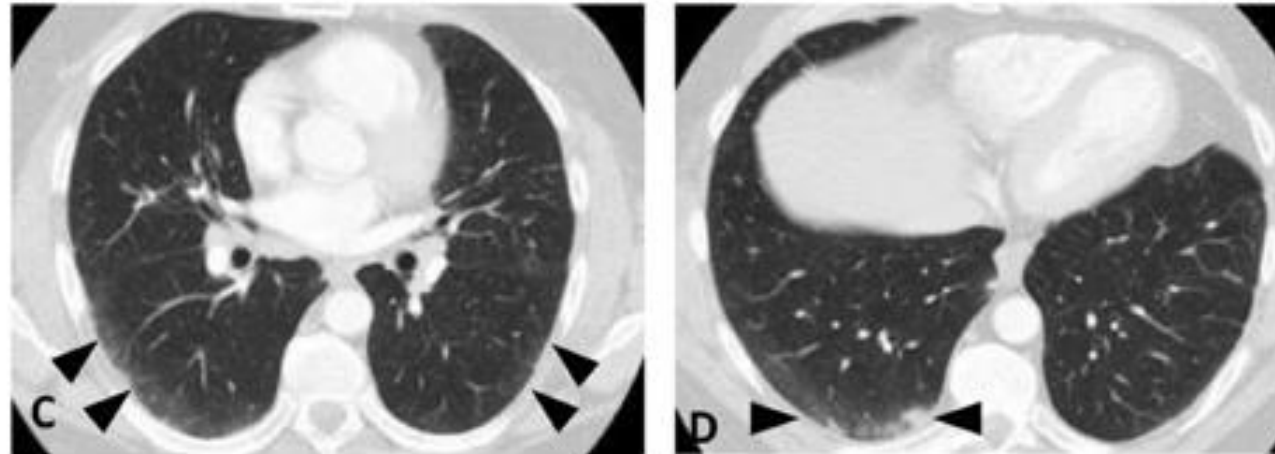
Pneumonitis under PD-1/PD-L1 blockade

radiological patterns

M. Nishino et al, ASCO 2016

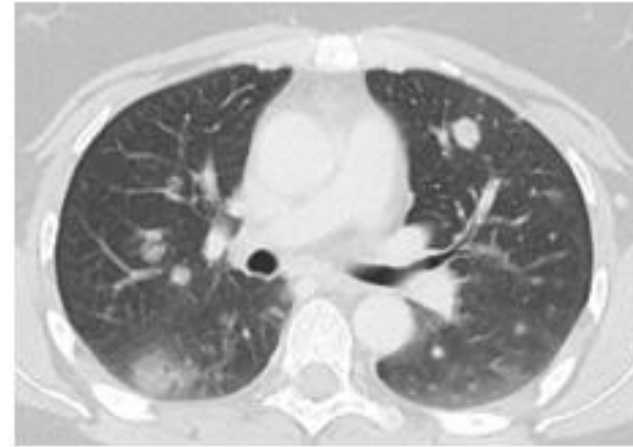
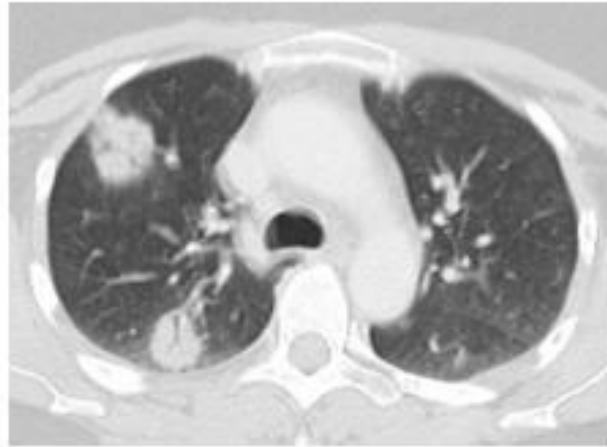


A, B. Pneumonitis with a cryptogenic organizing pneumonia (COP) pattern

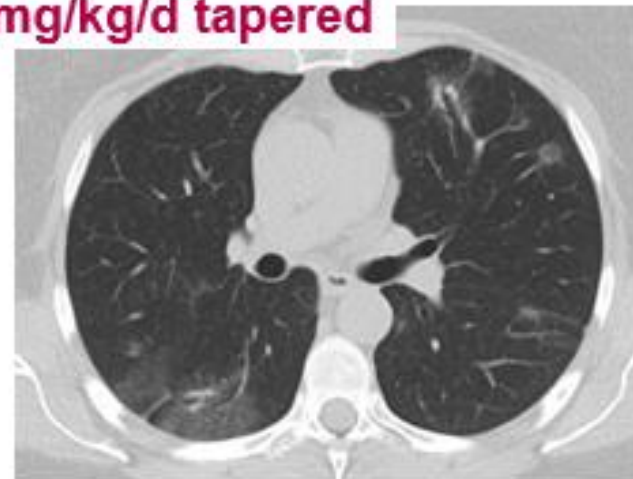


C, D. Pneumonitis with a non-specific interstitial pneumonia (NSIP) pattern

Pneumonitis under PD-1/PD-L1 blockade radiological patterns

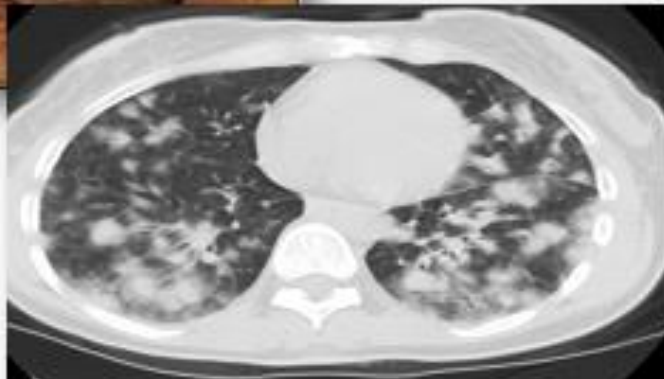
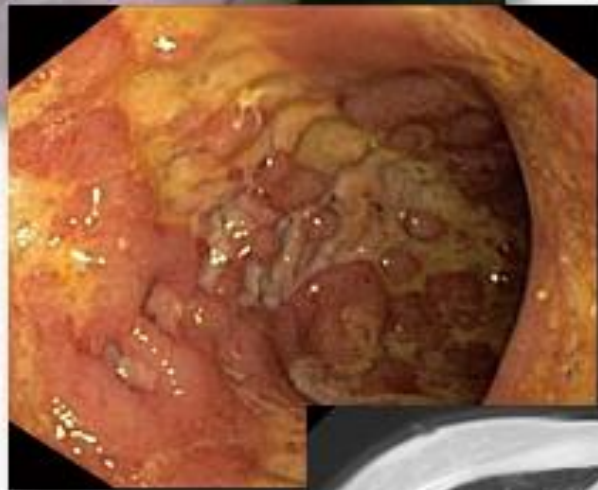


14d steroids 2 mg/kg/d tapered



Immunotherapy for NSCLC

toxicities take home messages



Immune-related toxicities

- occur frequently (all organs/all grades taken together)
 - severe grades are rare
 - can occur at any time
 - can flare up after treatment stop
-
- Corticosteroid use for irAE does not seem to jeopardize long-term anti-tumoral efficacy of checkpoint inhibitors
 - irAEs such as pneumonitis may be associated with higher response rates

Take Home :

Gemetastaseerd NSCLC met oncogene drivers

- ▶ EGFR mutatie:
 - ▶ eerste, tweede en derde generatie; optimale sequens?
 - ▶ personalised sequens
 - ▶ lange overlevingen, betere QoL
- ▶ ALK translocatie:
 - ▶ eerste generatie, next generation
 - ▶ alectinib is een mogelijke eerste lijns optie
 - ▶ optimale sequens? personalised sequens
- ▶ zeldzame mutaties:
 - ▶ NGS is belangrijk
 - ▶ verwijst patiënten voor klinische studies

Take Home : Gemetastaseerd NSCLC zonder oncogene drivers

- ▶ chemo + checkpoint inhibition is de standard of care (pembro+platinum-pem)
- ▶ uitdagingen voor gepersonaliseerde behandelingen
- ▶ immuun related bijwerkingen: frequent, goed te behandelen
- ▶ PD-L1 is een driver voor benefit op immuno
- ▶ mogelijke rol for TMB als biomarker voor patient selectie
 - uitdagingen: harmonisatie, validatie van platforms, cut-off
- ▶ IO in stage III NSCLC, beloftevol in early stage (neoadjuvante setting), SCLC