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NETHERLANDS CANCER INSTITUTE
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Outline

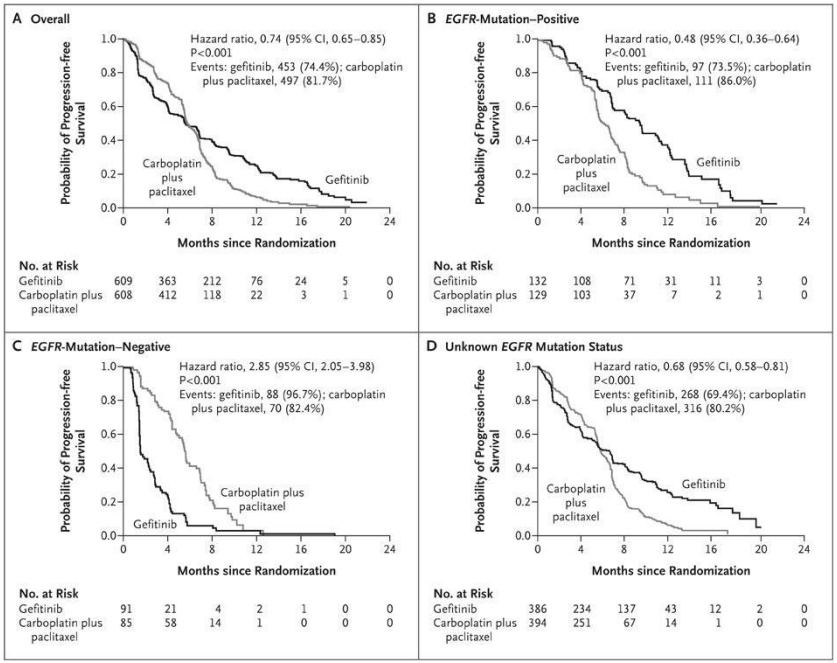
- Geschiedenis biomarkers in longkanker
- Richtlijnen
- Uitvoering
- Vergoeding

What happened in lung cancer?

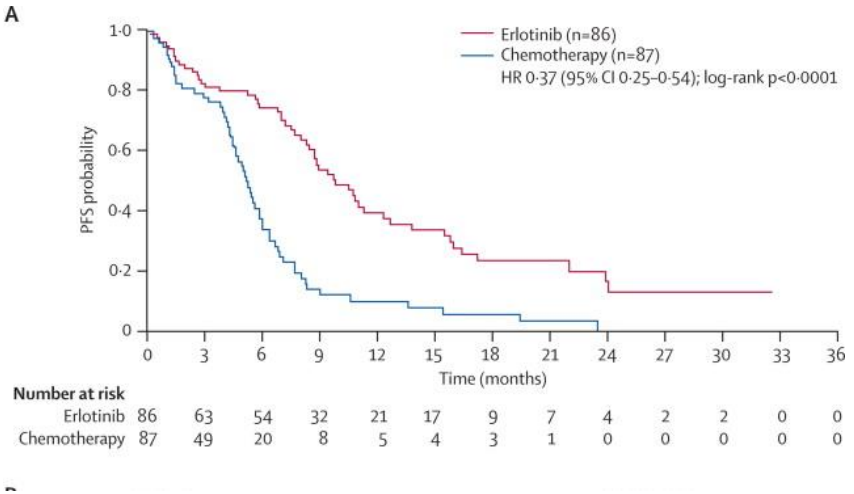
- First description activating EGFR mutation in a biopsy 2004

- First randomized phase III clinical trial showing benefit EGFR TKI vs SoC chemotherapy 2009

First TKI versus chemotherapy in EGFR mutated NSCLC



Mok, NEJM 2009



Rosell, Lancet Oncol 2012

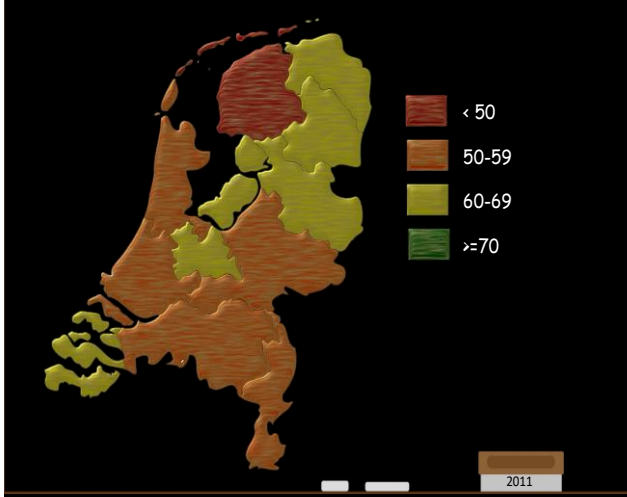
What happened in lung cancer?

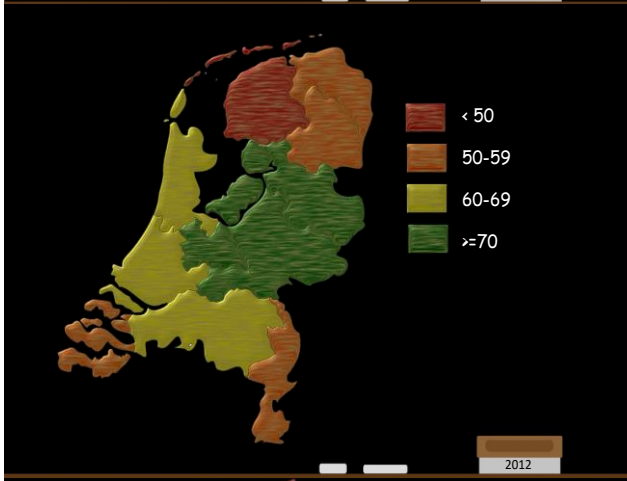
- First description activating EGFR mutation in a biopsy 2004
- First randomized phase III clinical trial showing benefit EGFR TKI vs SoC chemotherapy 2009
- EGFR “testing” mandatory Dutch guideline 2011
- Reimbursement through “complex molecular testing” in DBC

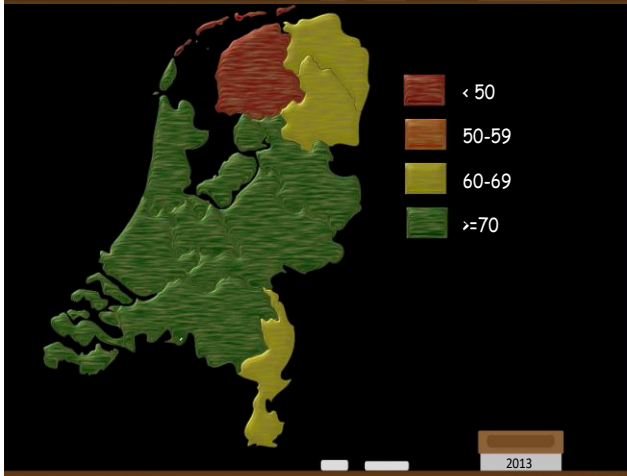
Implementation in clinical practice

Screening for EGFR mutations in the Netherlands

- 2004 0%
- 2011 58%
- 2013 73%





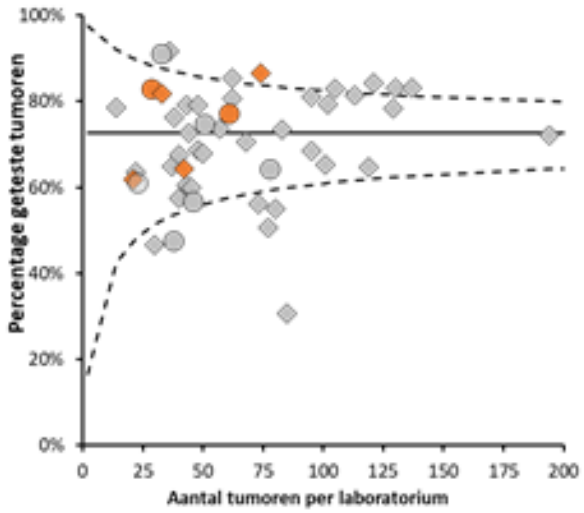


Courtesy of R. Damhuis and R. Willems; A. Eniu

Percentage EGFR-KRAS testen + labvariatie

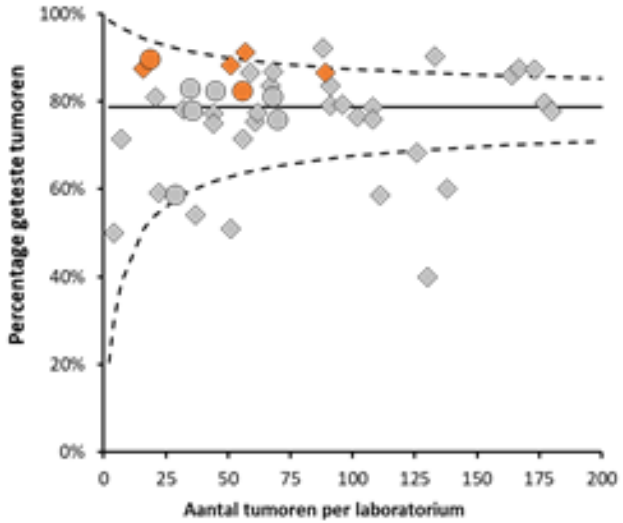
2013

73,1%



2015

78,9%

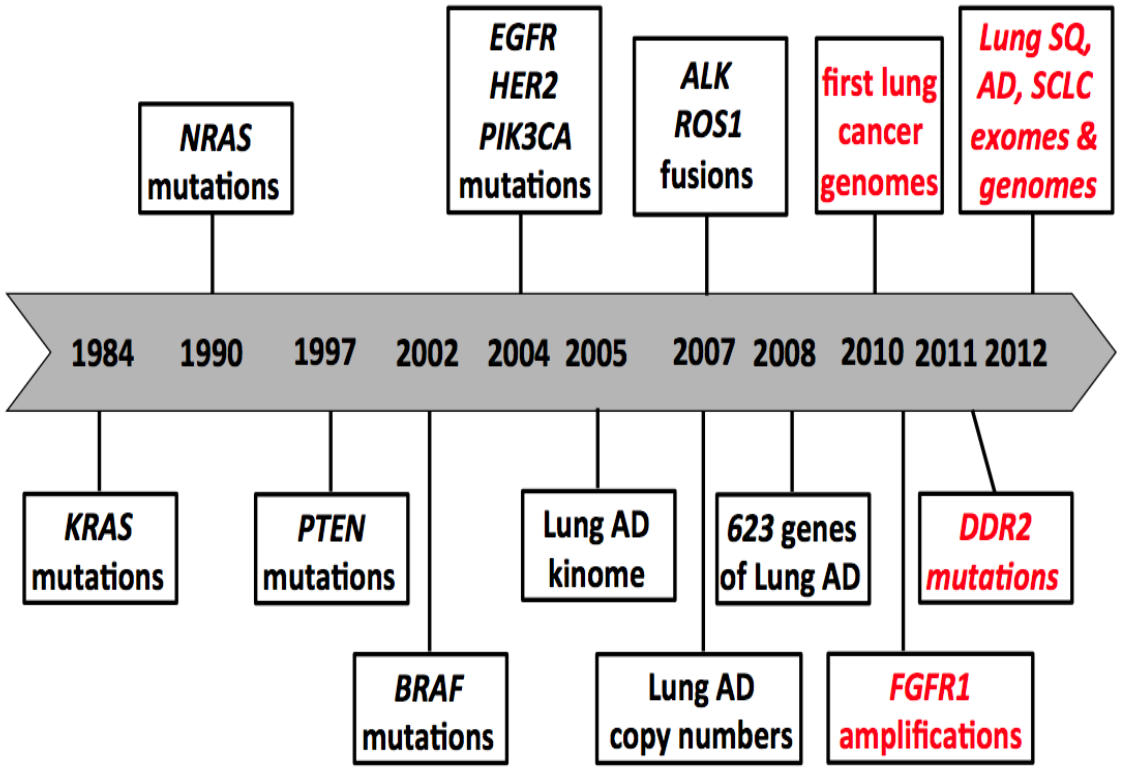


Cirkel = academisch, ruit = niet-academisch.

Stefan Willems
Patholoog UMCU

In the meantime….

Timeline for the discovery of relevant alterations in lung cancer

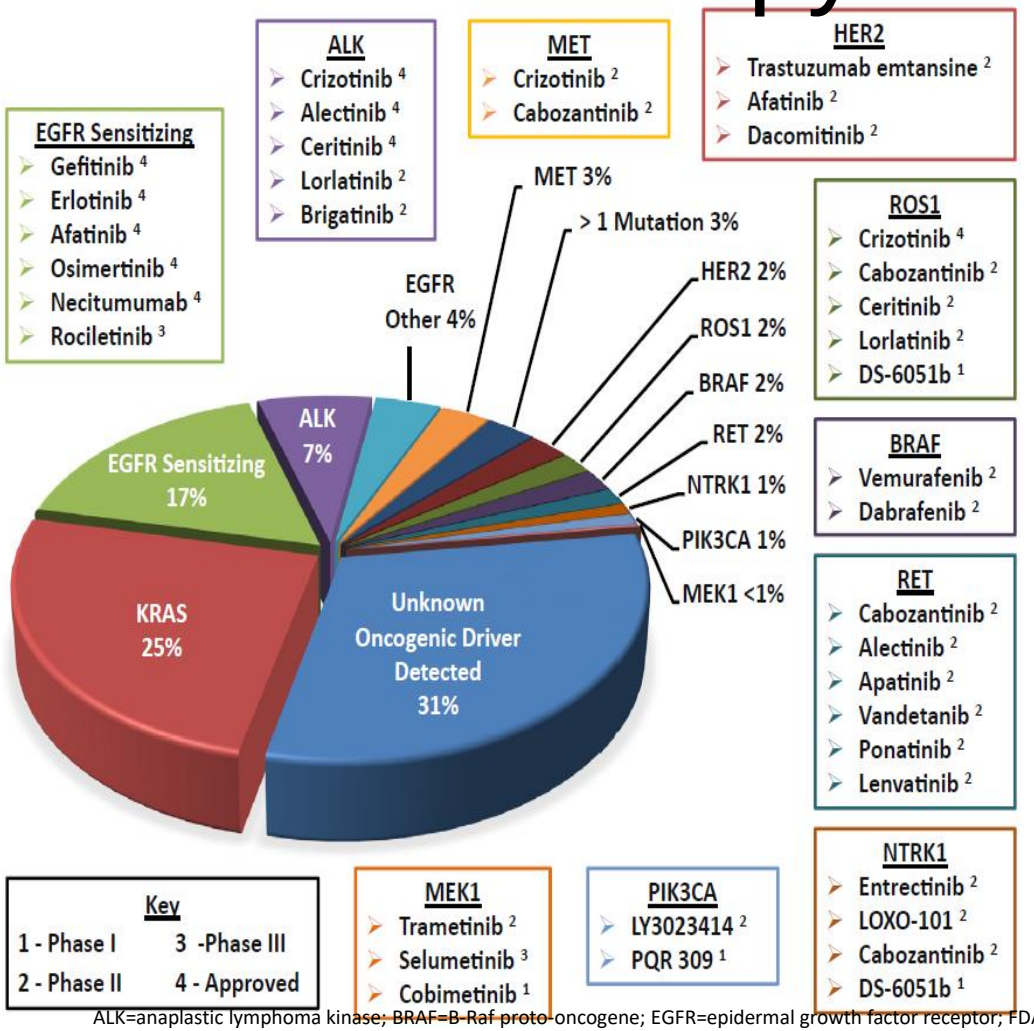


before NGS — NGS era

difficulty: picking the right gene — finding the relevant genes

adapted from: Levy M, Lovly C, Pao W. *Genome Research* 22 (2012)

Adenocarcinomas, Targets and Therapy



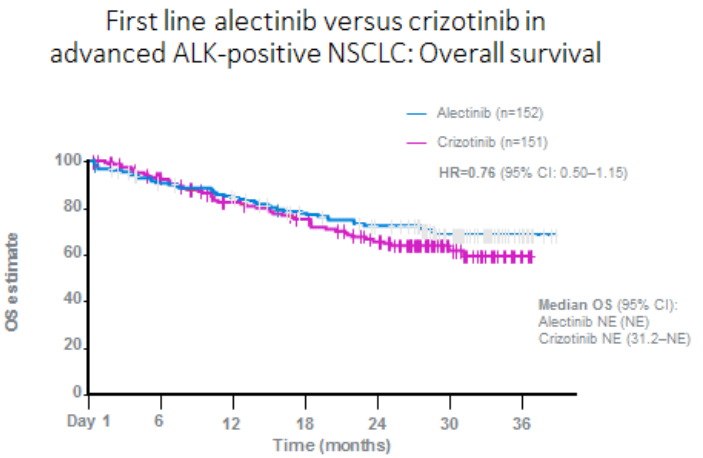
12 of these agents are approved by EMA

Tsao AS et al. *J Thorac Oncol* 2016;11:613-38

ALK=anaplastic lymphoma kinase; BRAF=B-Raf proto-oncogene; EGFR=epidermal growth factor receptor; FDA=US Food and Drug Administration; HER2=human epidermal growth factor receptor 2; KRAS=Kirsten rat sarcoma viral oncogene homologue; MEK1=mitogen-activated protein kinase kinase 1; MET=MET proto-oncogene; NTRK1=neurotrophic tyrosine kinase receptor 1; PIK3CA=phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; RET=rearranged during transfection; ROS1=ROS1 proto-oncogene receptor tyrosine kinase

And it works!

Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%



Camidge, ASCO 2018

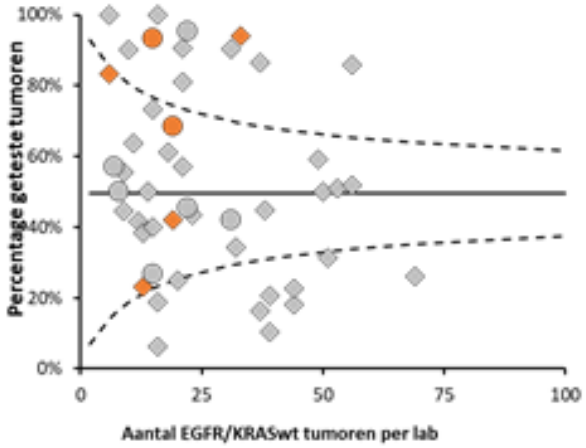
Outcomes of treatment without molecular selection:
2 yr survival 10%

Outcomes of treatment with molecular selection (Alk fusion):
2 yr survival 65%

Percentage ALK testen + labvariatie

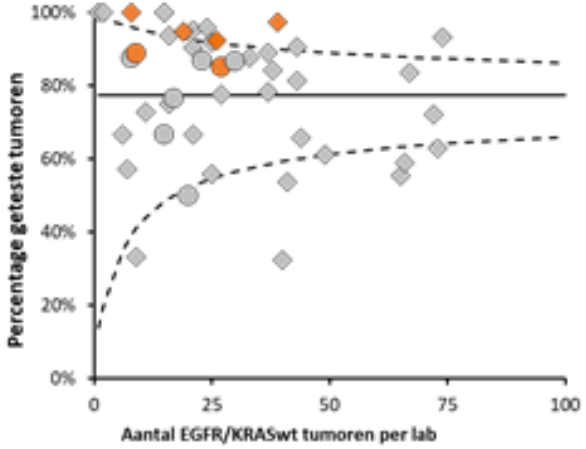
2013

49,5%



2015

77,4%

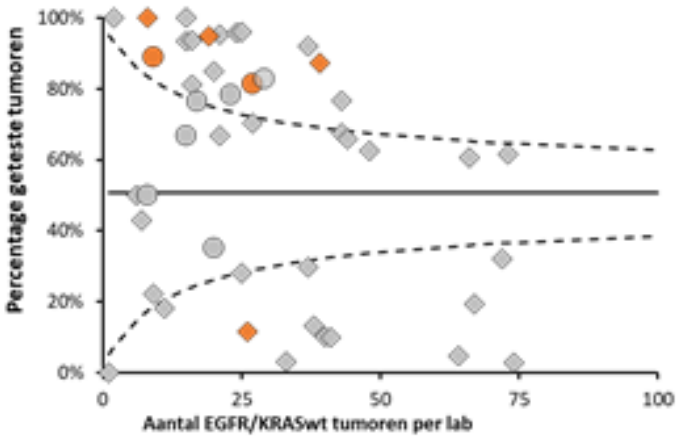


Cirkel = academisch, ruit = niet-academisch.

Percentage ROS testen + labvariatie

2015

50,9%



Oranje = academisch, blauw = niet-academisch.

Wat leren we van deze data?

- Er is een **saturatie rond 80%**
  - Van de overige 20% is meestal (80%)‘**te weinig weefsel**’ de reden van uitval

- **Lag-time** voor het implementeren van een nieuwe test is **2-3 jaar**

- Er is **heterogeniteit** tussen ziekenhuizen

Wie bepaalt eigenlijk wat we moeten testen?

Richtlijnen?

Geneesmiddelen

ASCO® ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

nvmo **cieBOM**

Longartsen

Diagnostische testen

NEDERLANDSE VERENIGING VOOR PATHOLOGIE

Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose

oncoline
richtlijnen oncologische zorg

?

Laboratoria

?

Longartsen

Validatie fase

1-2 jaar

Oncoline NSCLC richtlijn

oncoline
richtlijnen oncologische zorg

Long > Niet kleincellig longcarcinoom

Laatst gewijzigd : 2015-12-18, Versie: 2.3, Verantwoording: Landelijke Werkgroep Longtumoren, Type: Landelijke richtlijn

Aanbevelingen | Literatuurbespreking | Conclusies | Overwegingen

PATHOLOGIEDIAGNOSTIEK

Richtlijn	Methodiek	Laatst gewijzigd
Kleincellig longcarcinoom (1.0)	Evidence based	10-05-2011
Niet kleincellig longcarcinoom (2.3)	Evidence based	18-12-2015

Richtlijn	Methodiek	Laatst gewijzigd
Maligne pleura exsudaat (1.1)	Consensus based	25-10-2005
Pleuritis carcinomatosa (1.2)	Consensus based	28-10-2007
Thymomen (2.0)	Consensus based	01-07-2007


CITRIX
ASTON MARTIN
TAGHeuer
RedBull
Mobil 1
PIRELLI
P ZERO
AT&T
ESSO
3

SPECIAL ARTICLE

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Accepted 29 November 2017

- Conclusions:
  - **EGFR**
  - **ALK**
  - **ROS1**
  - **ERBB2**
  - **MET**
  - **BRAF**
  - **RET**
  - **Immunohistochemistry** as an alternative to fluorescence in situ hybridization for **ALK** and **ROS1**
  - **5% sensitivity assays for EGFR T790M** mutations
  - **cell-free DNA** to “rule in” targetable mutations when tissue is limited or hard to obtain.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 4): iv192–iv237, 2018
doi:10.1093/annonc/mdy275

CLINICAL PRACTICE GUIDELINES

2018

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*

Table 1. A personalised medicine synopsis table for metastatic NSCLC

Biomarker	Method	Use	LoE, GoR
EGFR mutation	Any appropriate, validated method, subject to external quality assurance	To select those patients with *EGFR*-sensitising mutations most likely to respond to EGFR TKI therapy	I, A
ALK rearrangement	Any appropriate, validated method, subject to external quality assurance. FISH is the historical standard but IHC is now becoming the primary therapy-determining test, provided the method is validated against FISH or some other orthogonal test approach. NGS is an emerging technology	To select those patients with *ALK* gene rearrangements most likely to respond to ALK TKI therapy	I, A
ROS1 rearrangement	FISH is the trial-validated standard. IHC may be used to select patients for confirmatory FISH testing but currently lacks specificity. NGS is an emerging technology. External quality assurance is essential	To select those patients with *ROS1* gene rearrangements most likely to respond to ROS1 TKI therapy	II, A
BRAF mutation	Any appropriate, validated method, subject to external quality assurance	To select those patients with *BRAF V600*-sensitising mutations most likely to respond to BRAF inhibitor, with or without MEK inhibitor therapy	II, A
PD-L1 expression	IHC to identify PD-L1 expression at the appropriate level and on the appropriate cell population(s) as determined by the intended drug and line of therapy. Only specific trial assays are validated. Internal and external quality assurance are essential	To enrich for those patients more likely to benefit from anti-PD-1 or anti-PD-L1 therapy. For pembrolizumab, testing is a companion diagnostic for nivolumab and atezolizumab, testing is complementary	I, A

Snellere updates richtlijnen

EMA
Internationale richtlijnen

<u>Jaarlijkse</u> update nederlandse richtlijnen of advies

Publicatie via:
Communicatieplan

Alle patienten

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NCCN National Comprehensive Cancer Network®

COLLEGE of AMERICAN PATHOLOGISTS

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NEDERLANDSE VERENIGING VOOR PATHOLOGIE

Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose

nvmo

De uitvoering:

Lessons learned van predictieve diagnostiek longkanker

Goede diagnostiek is afhankelijk van:

- **Behandelend arts** moet goed op de hoogte zijn
- Heldere aanvraag in **diagnostische pakketten:**
  - predictieve analyse long adenocarcinoom
  - resistentie EGFR na 3de generatie TKI
  - resistentie ALK na TKI
- **Goed materiaal**: aantal biopten/ cytologie
- **Verwerking biopten**: apart inbedden/ efficient aansnijden
- **Subspecialisatie** van patholoog
- **Rapportage** volgens standaard verslaglegging.
  - Ook de reden waarom er **niet wordt getest**

Gestandadiseerde rapportage:

Lung (transthoracic biopsy): TTF-1 positive NSCLC, adenocarcinoma

- Result of NGS mutation analysis using TSACP v2.0 tumour panel (tumour cell proportion 90%)
  - **EGFR**: no mutation
  - **KRAS**: no mutation
  - **BRAF**: no mutation
  - **HER2**: no mutation
  - Other results: **TP53**: p.Q192_H193del (20%), significance: unknown
- **ROS1**: immunohistochemistry (clone D4D6): **1+, score 1 (0–3). FISH follows.**
- **ALK**: immunohistochemistry (clone 5A4): negative, score 0 (0–3)
- **Pan-TRK**: immunohistochemistry (clone A7H6R): negative, score 0 (0–3)
- **RET**: FISH: none detected
- **MET** amplification: none detected in NGS
- **MET** (exon 14 skipping mutation): RT-PCR: **not possible, RNA insufficient quality**
- **PD-L1** (clone 22C3 LDT, Ventana): moderately positive (TPS 1–50%)
  - in this material positive in 30% of tumour cells

Vergoeding

- Het zit niet in de DBC?
- NZA: betaaltitels/ zorgactiviteiten
  - Simpel en complex, 1 x aan te vinken in DOT
  - Worden nu aangepast: meer gedifferentieerd en vaker dan 1 x
- Maar: hoofdlijnen akkoord:
  - maximale groei budget >> broekzak vestzak
- Discussie is grotendeels binnen het ziekenhuis

Nederlandse Zorgautoriteit

Rijksoverheid

Take home messages

- Implementeren van een nieuwe test kost tijd
- Er moet een snellere richtlijn komen met **jaarlijkse updates**
  - Goede **communicatie** van deze updates naar behandelend artsen en pathologen
- Goede diagnostiek is een keten: maak **afspraken** met elkaar:
  - behandelaar, radioloog, patholoog
- **Reimbursement** is grotendeels afhankelijk van discussie binnen het ziekenhuis