

Epidemiologi, etiologi, patologi og molekylær patologi (EGFR, ALK, ROS, PD-L1) ved lungecancer samt kort om lungecancerscreening

Odd Terje Brustugun, dr med

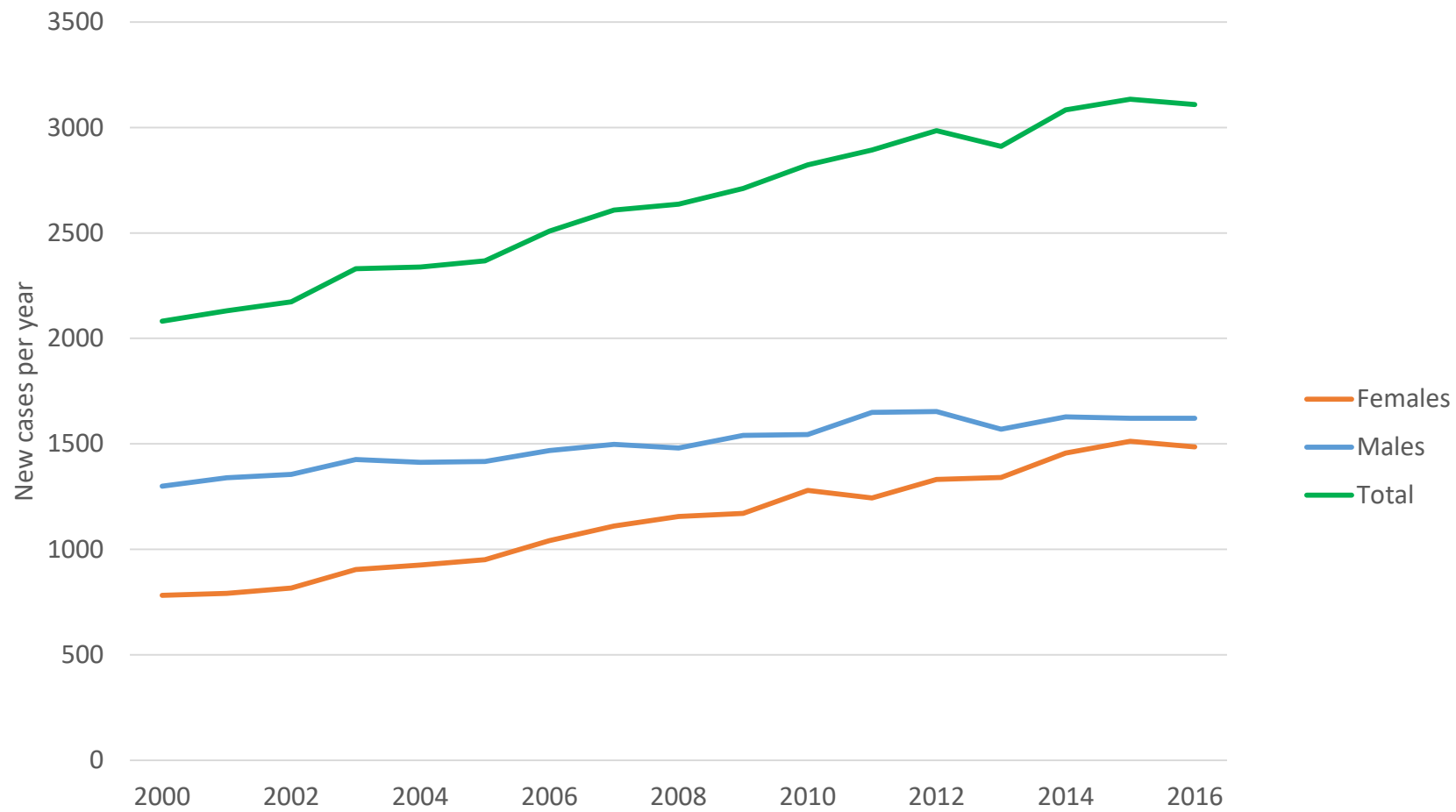
Egentlig onkolog

Men later nå som jeg er epidemiolog, patolog og molekylærbiolog
samt spåmann

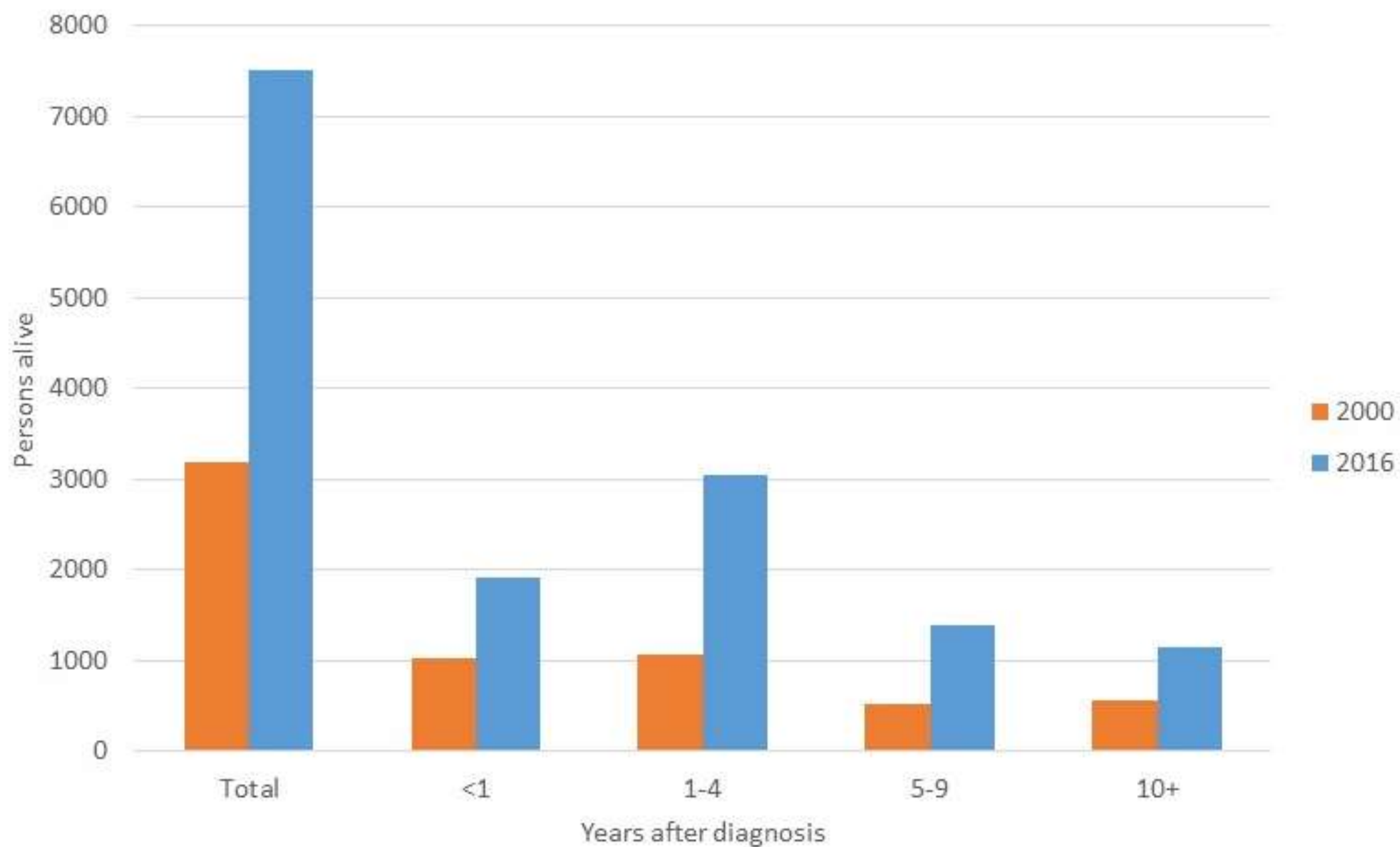
Onkologisk seksjon, Drammen sykehus

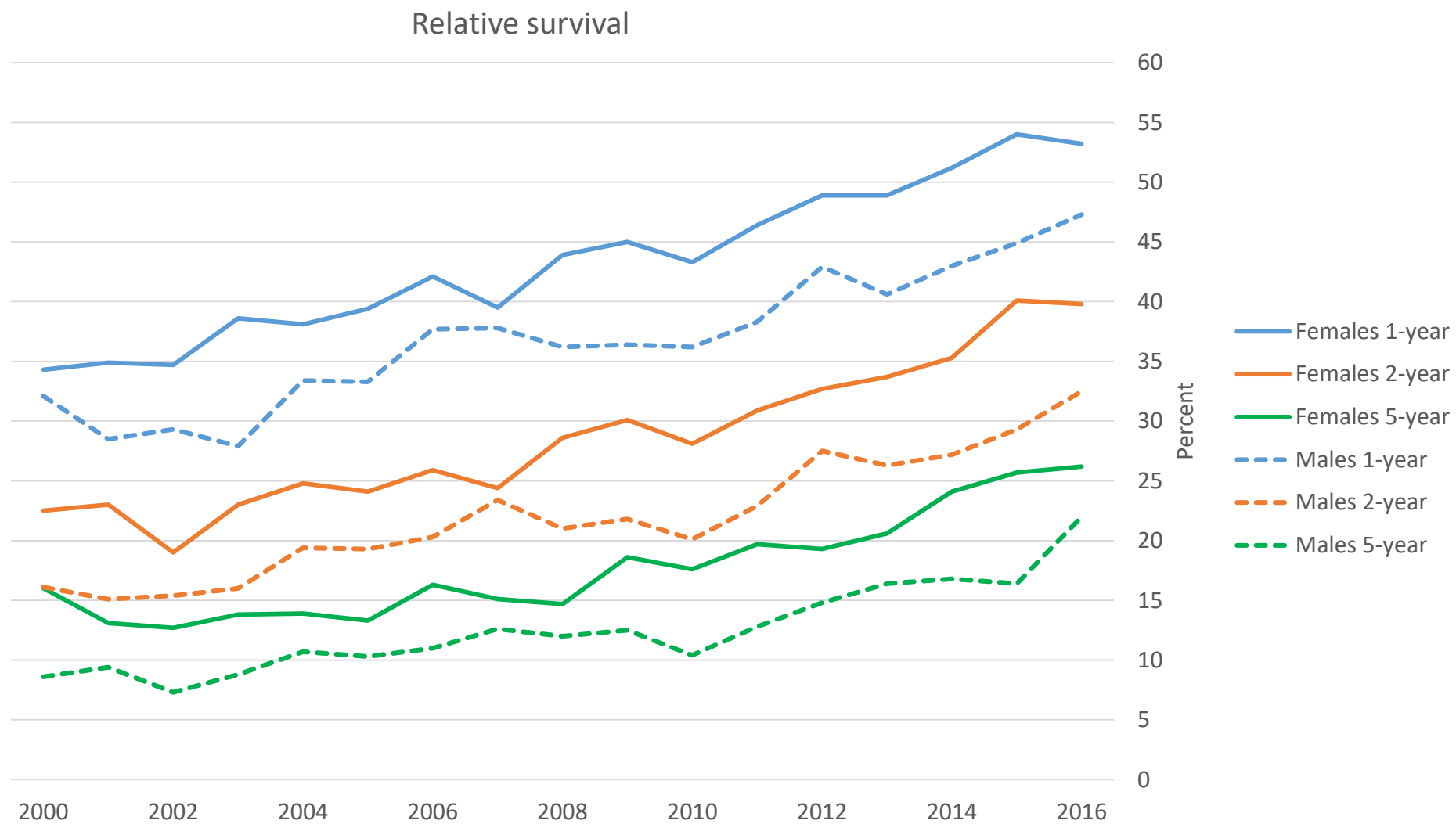
Epidemiologi

Incidence, lung cancer

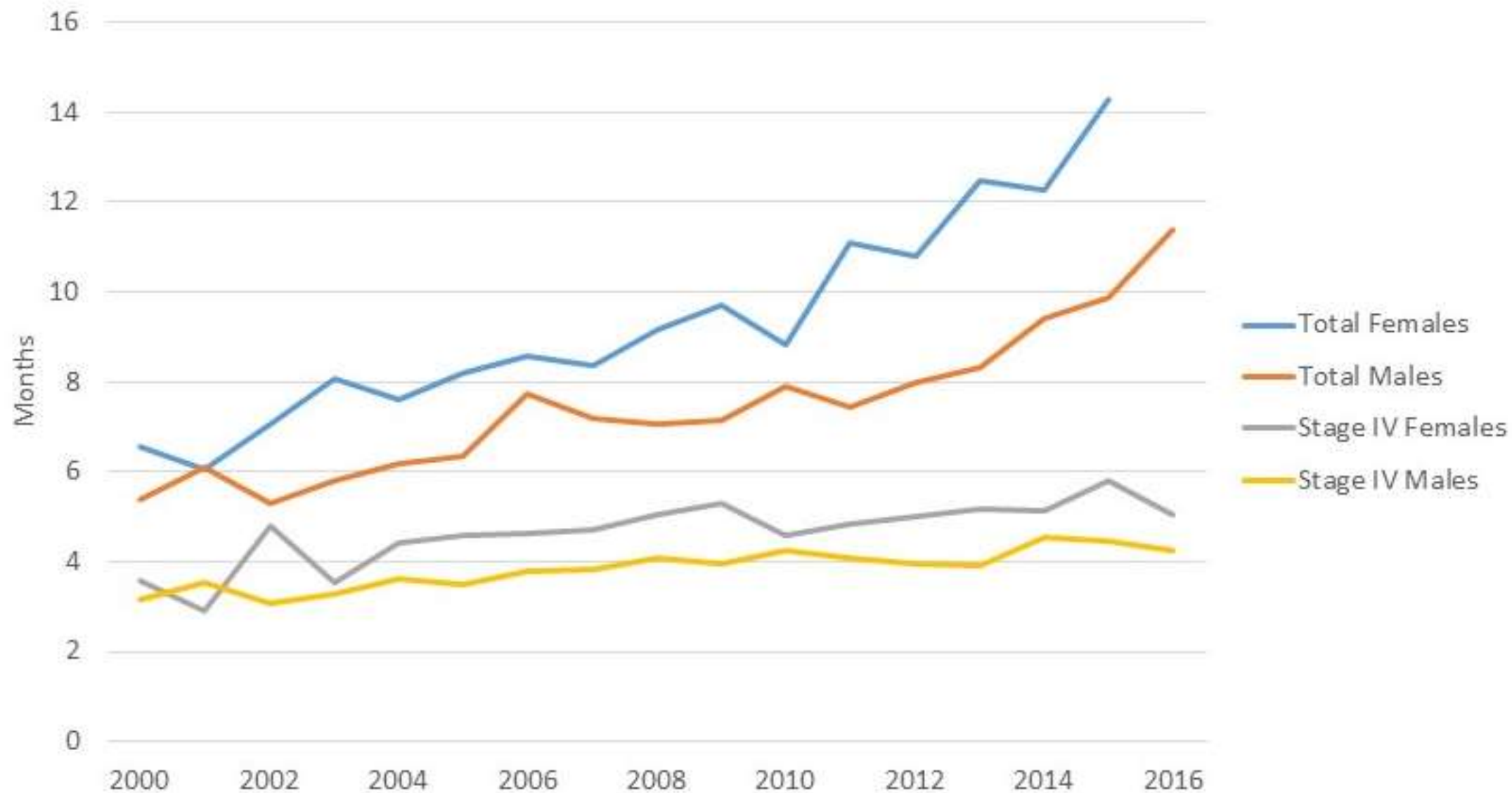


Prevalence of lung cancer

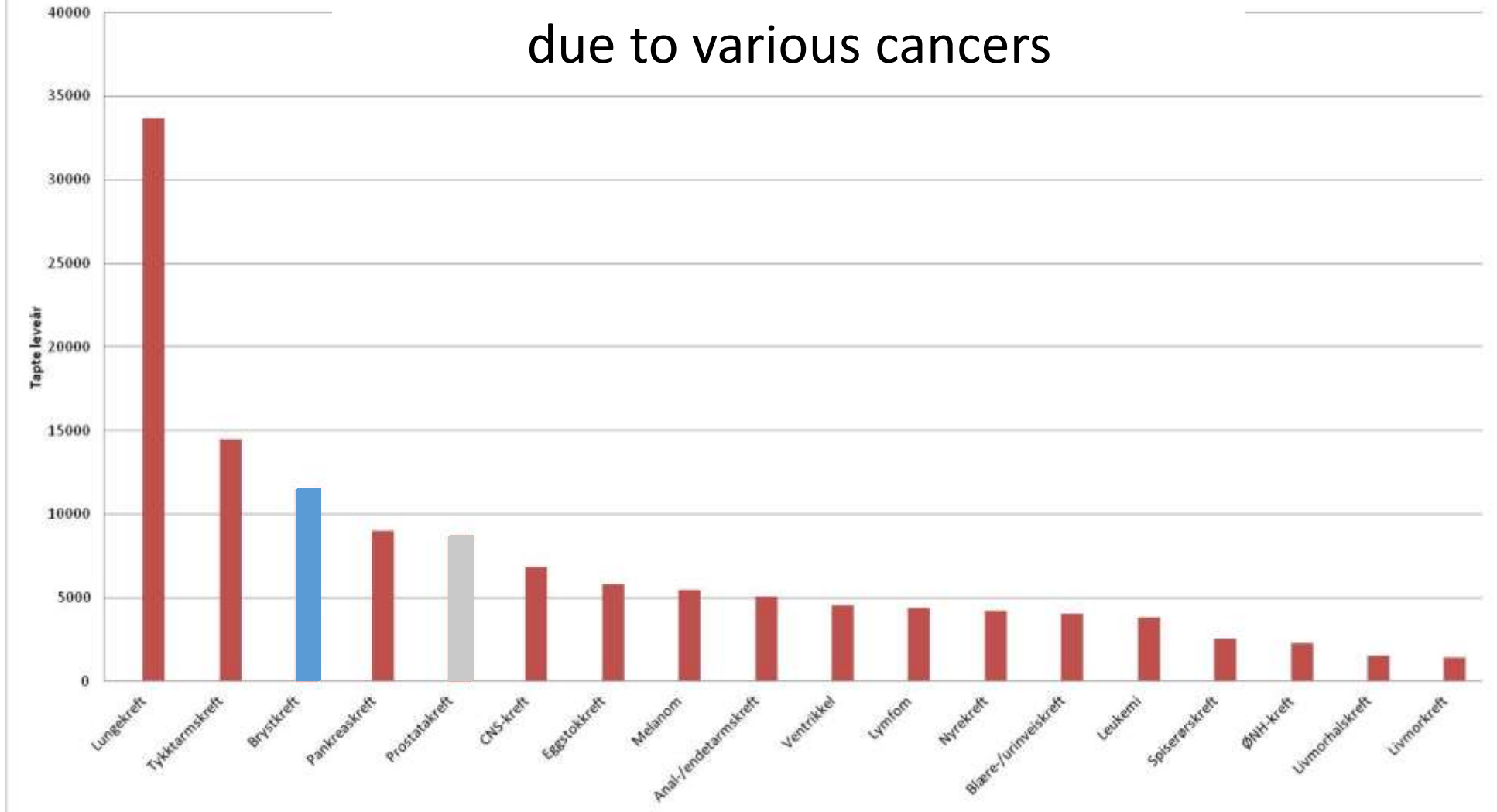




Median survival



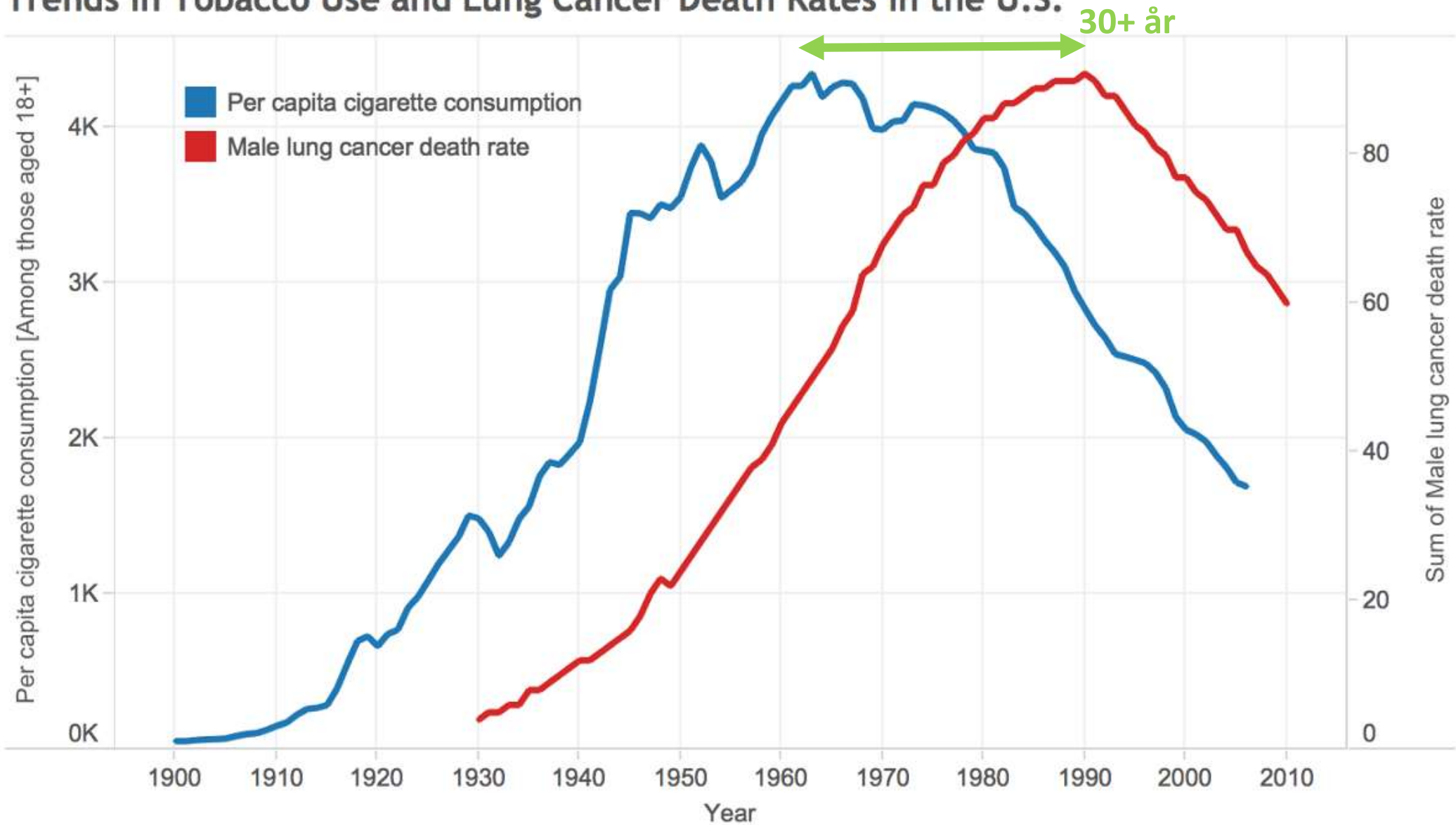
Years of life lost due to various cancers



Etiologi



Trends in Tobacco Use and Lung Cancer Death Rates in the U.S.



Death rates source: US Mortality Data, 1960-2010, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

Cigarette consumption source: US Department of Agriculture, 1900-2007.

Not only smoking



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MiniReview

Triggering Mechanisms and Inflammatory Effects of Combustion Exhaust Particles with Implication for Carcinogenesis

Johan Øvrevik , Magne Refsnes, Marit Låg, Bendik C. Brinckmann, Per E. Schwarze, Jørn A. Holme

First published: 15 March 2017 [Full publication history](#)

DOI: 10.1111/bcpt.12746 [View/save citation](#)

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[Funding information](#)

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Special Issue:
MiniReviews and original
articles from the Focused
Nordic Conference: The
European Environmental
Mutagenesis and
Genomics
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Abstract

A number of biological responses may contribute to the carcinogenic effects of combustion-derived particulate matter (CPM). Here, we focus on mechanisms that trigger CPM-induced pro-inflammatory responses. Inflammation has both genotoxic and non-genotoxic implications and is considered to play a central role in development of various health outcome associated with CPM exposure, including cancer. Chronic, low-grade inflammation may cause DNA damage through a persistent increased level of reactive oxygen species (ROS) produced and released by activated immune cells. Moreover, a number of pro-inflammatory cytokines and chemokines display mitogenic, motogenic, morphogenic and/or angiogenic properties and may therefore contribute to tumour growth and metastasis. The key triggering events involved in activation of pro-inflammatory responses by CPM and soluble CPM components can be categorized into (i) formation of ROS and oxidative stress, (ii) interaction with the lipid layer of cellular membranes, (iii) activation of receptors, ion channels and transporters on the cell surface and (iv) interactions with intracellular molecular targets including receptors such as the aryl hydrocarbon receptor (AhR). In particular, we will elucidate the effects of diesel exhaust particles (DEP) using human lung epithelial cells as a model system.

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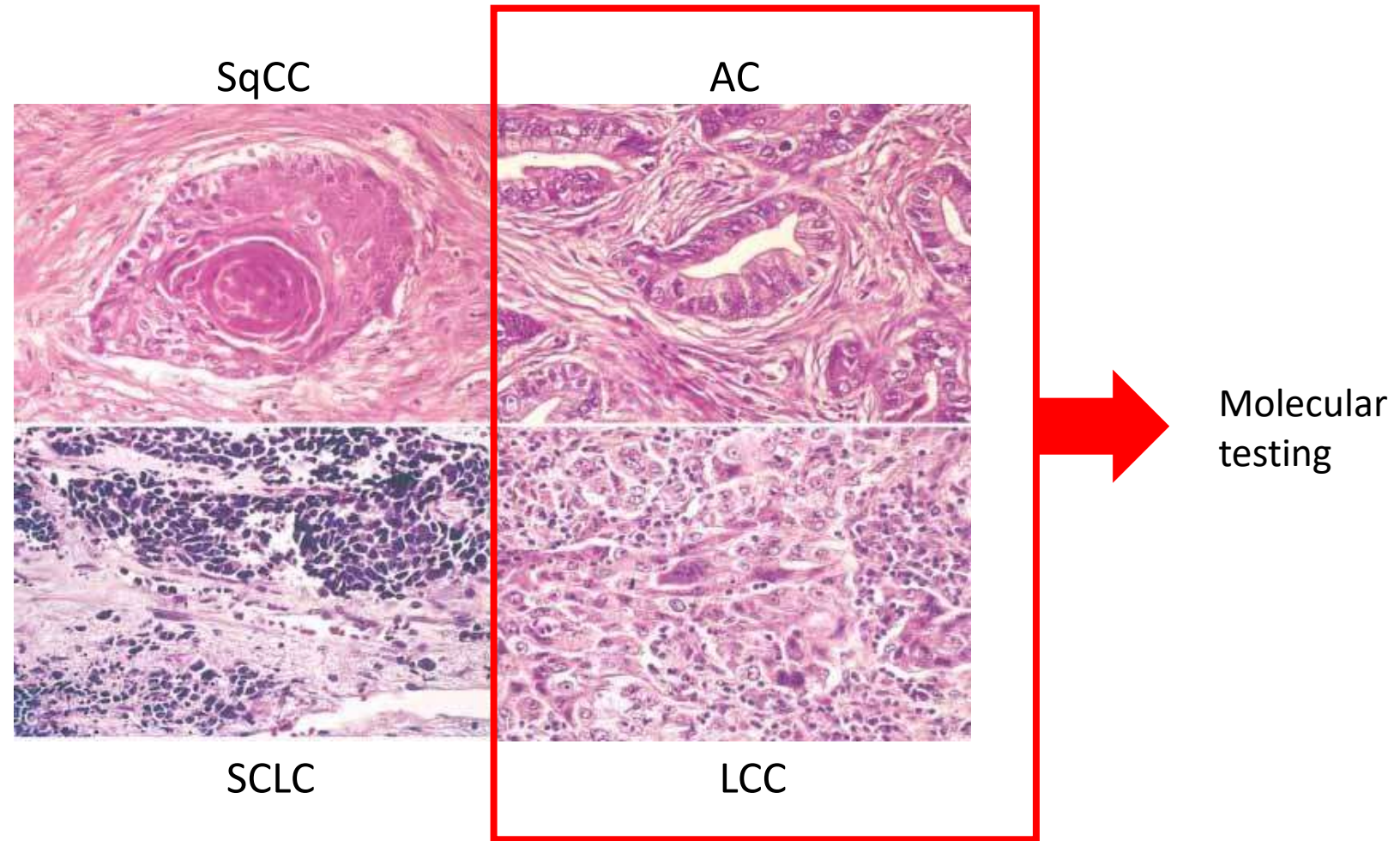
Har aldri røykt – fikk lungekreft

Av: Shazia Sarwar , Sigrid Helene Svendsen , Jan Petter Lynau (foto)

Liv Marie Schou (57) mosjonerer, har aldri tatt en røyk og lever sunt. Likevel fikk hun lungekreft – i likhet med én av ti norske kvinner som får denne kreftformen hvert år, men som aldri har røykt.

Patologi, molekylærpatologi

Starting points



Prediktive analyser i rutine

Alle NSCLC:

- **PD-L1**-ekspresjonsanalyse (IHC)

Alle non-platteepitelkarsinom (NSCLC)

- **EGFR**-mutasjonsanalyse (DNA)
- **ALK**-translokasjonsanalyse (FISH eller IHC)
- **ROS1** hjå utvalde
- **BRAF** hjå utvalde

Molekyære prediktive analyser i rutine

Alle NSCLC:

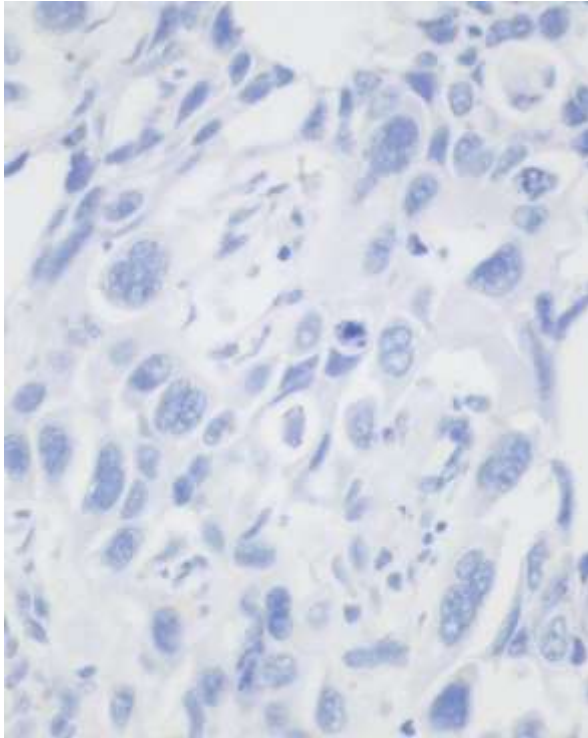
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Alle non-platteepitelkarsinom (NSCLC)

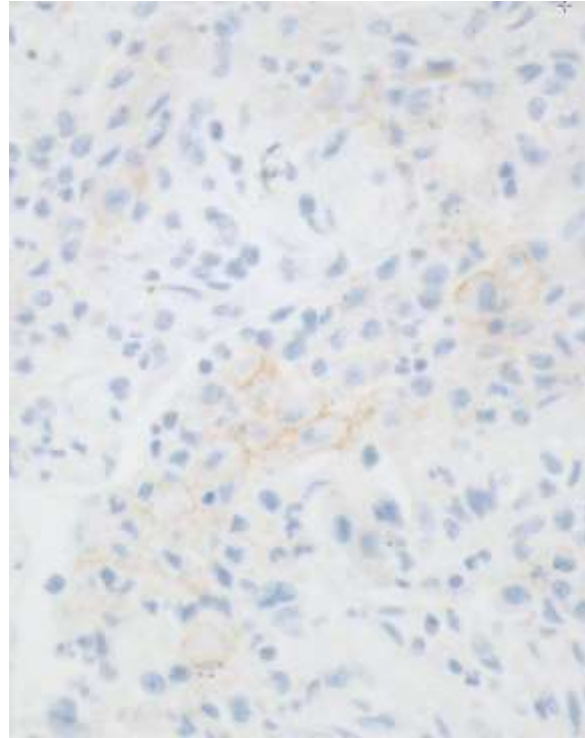
- **EGFR**-mutasjonsanalyse (DNA)
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- **ROS1** hjå utvalde
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Immunotherapy acts best when PD-L1 is highly expressed

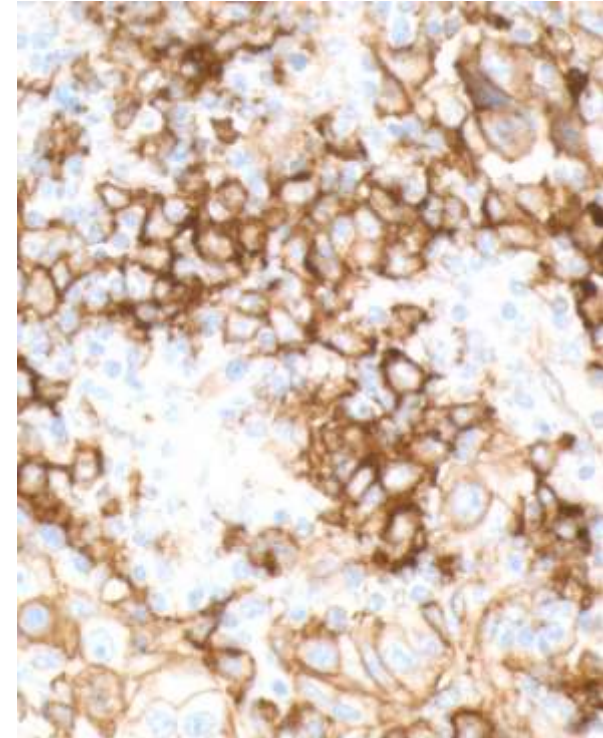
PD-L1 <1%



PD-L1 1-49%

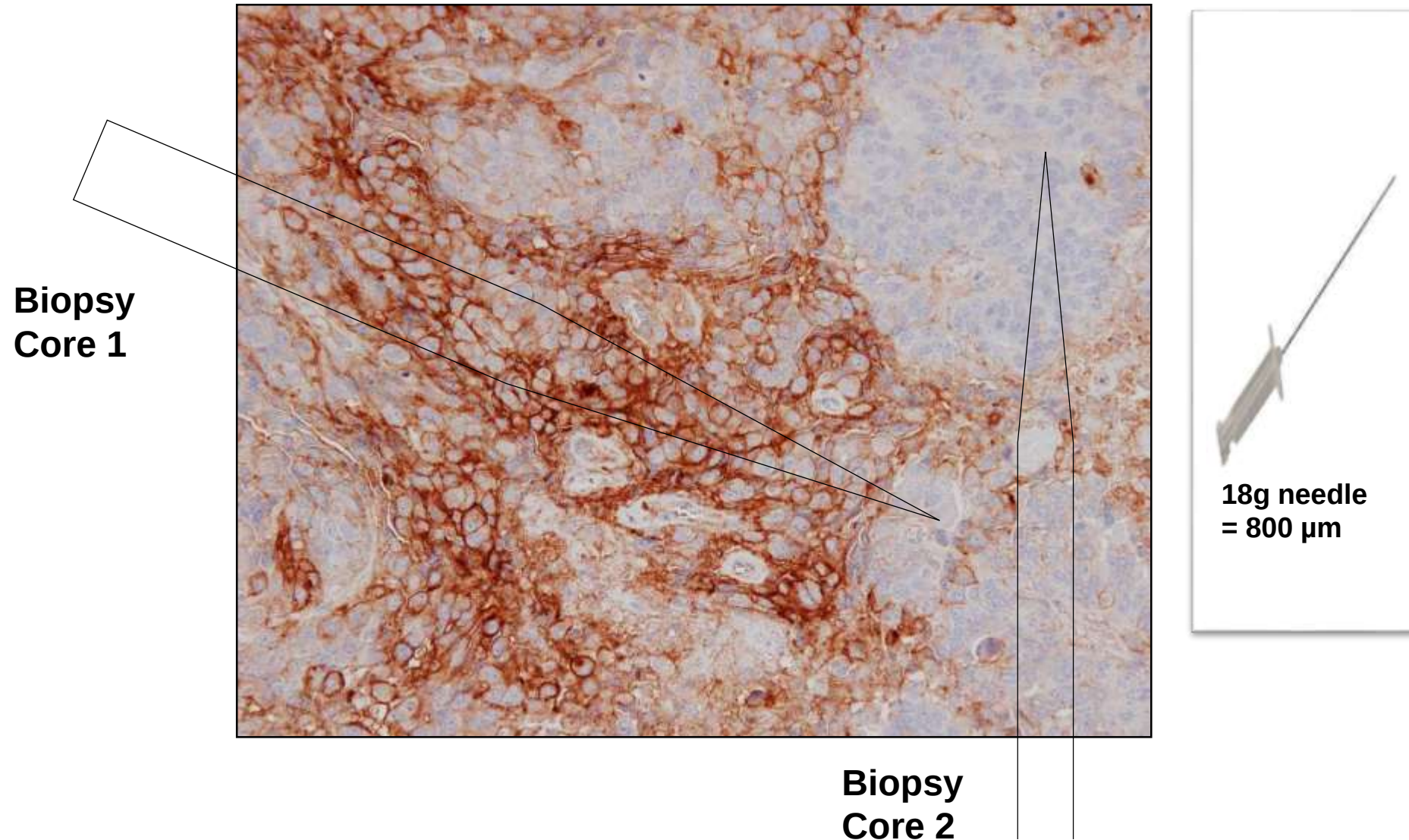


PD-L1 >50%

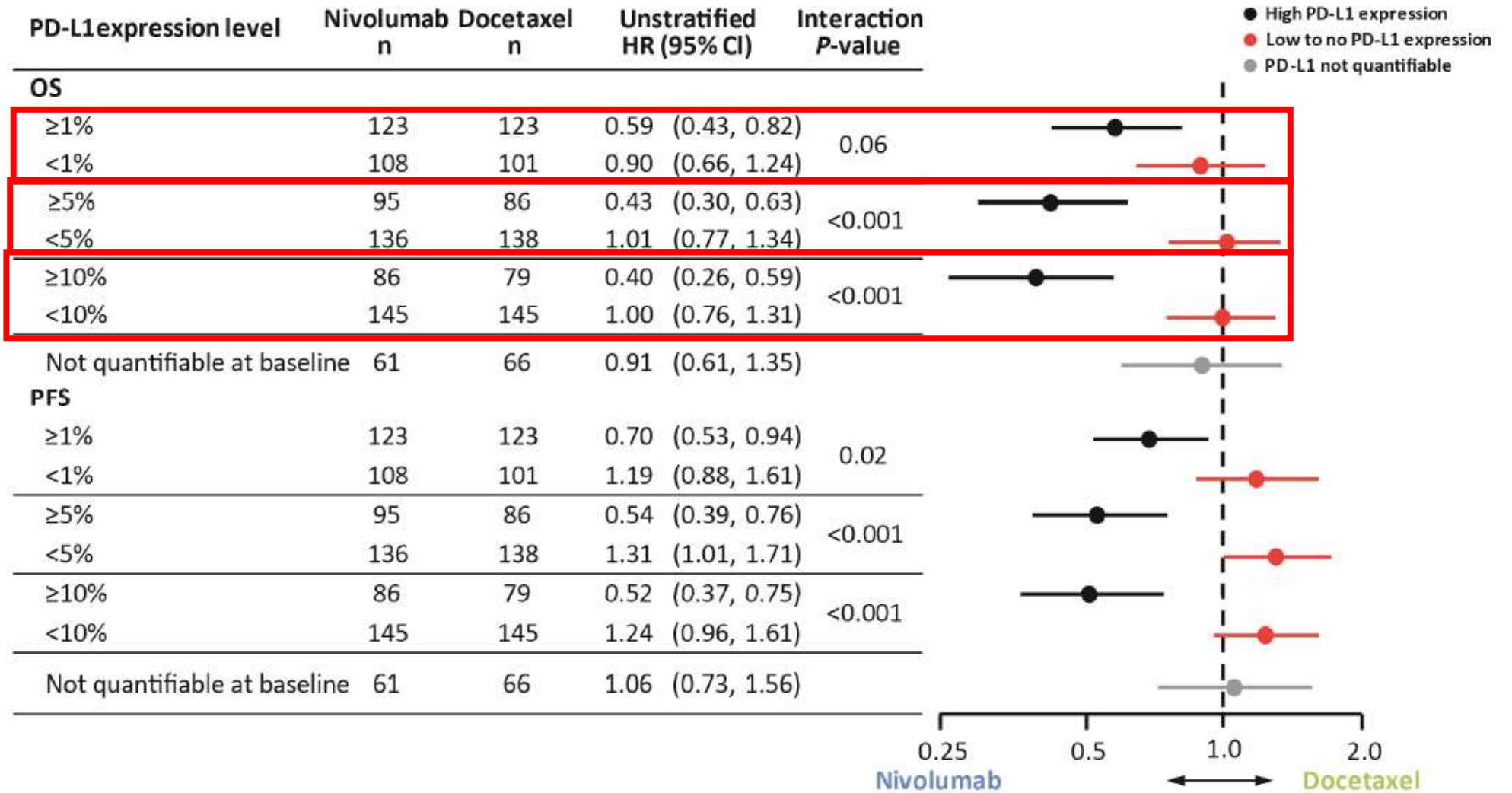


How to make a “cold” tumour “hot”?

PD-L1 Immunohistochemistry: Expression Heterogeneity and Potential for Sampling Error



Nivo 2nd line, adenocarcinoma



Pembro 2nd line NSCLC

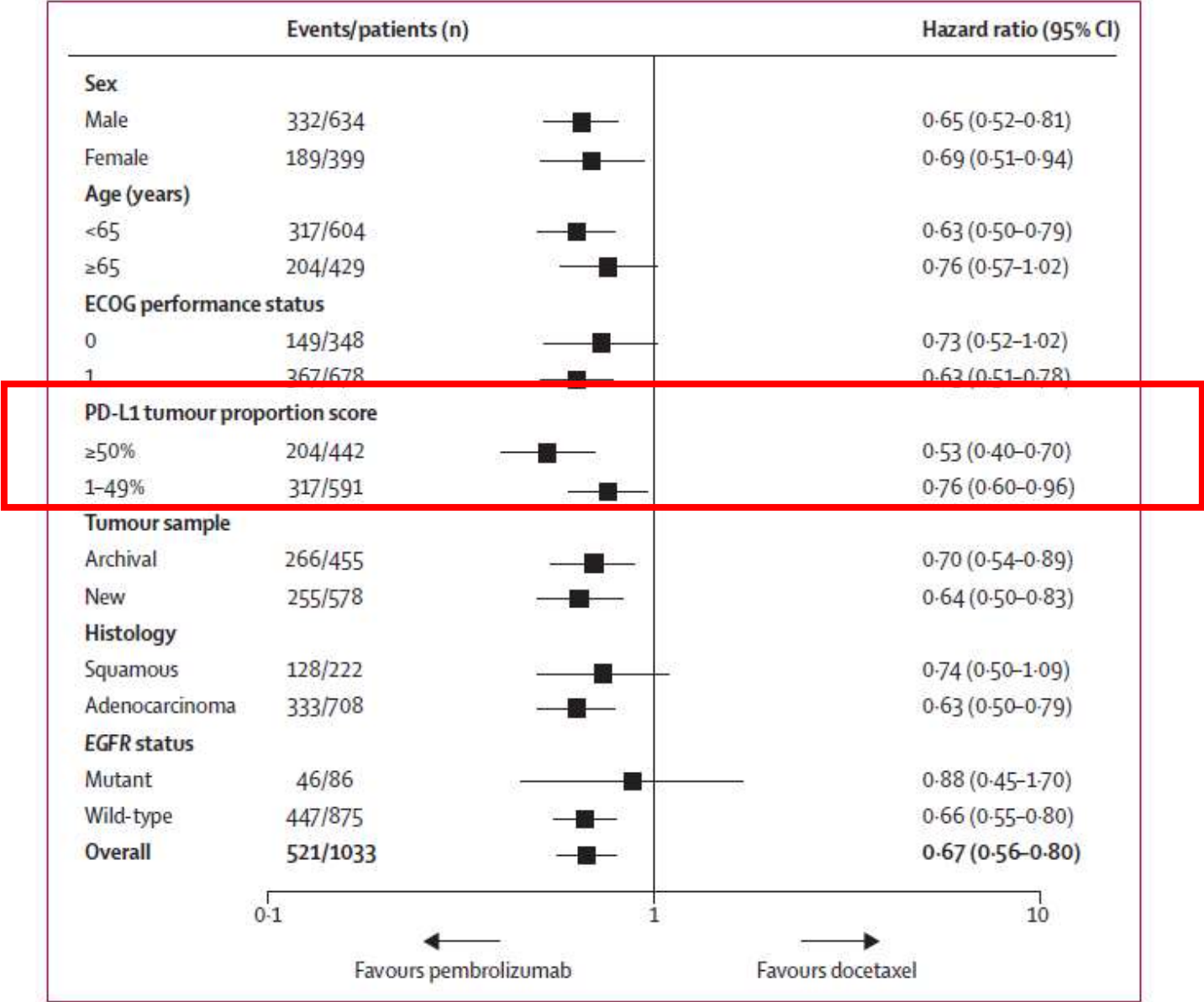
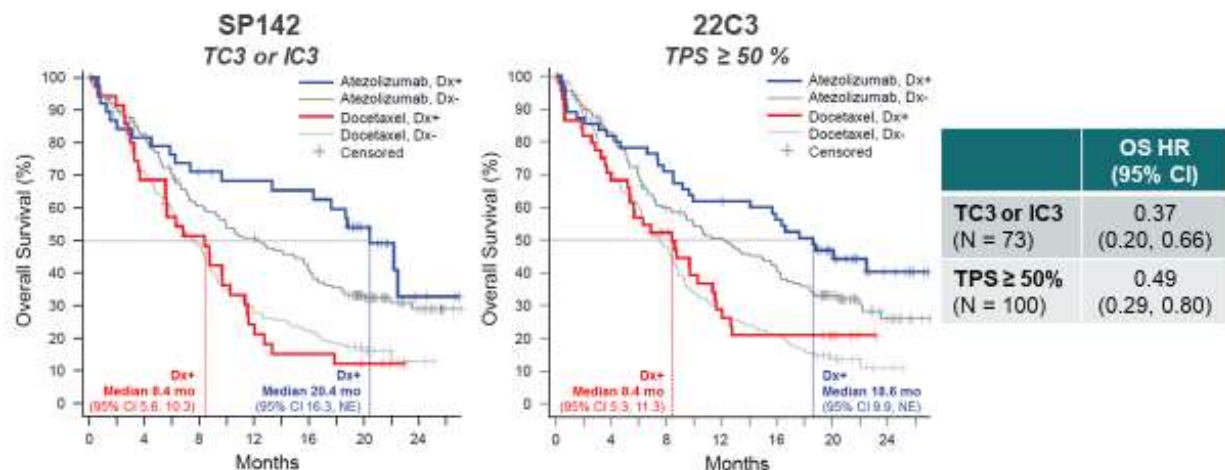


Figure 3: Subgroup analysis of overall survival
Shows the comparison of the pooled pembrolizumab doses versus docetaxel. ECOG=Eastern Cooperative Oncology Group.

ATEZOLIZUMAB: Overall Survival in PD-L1 High Subgroups

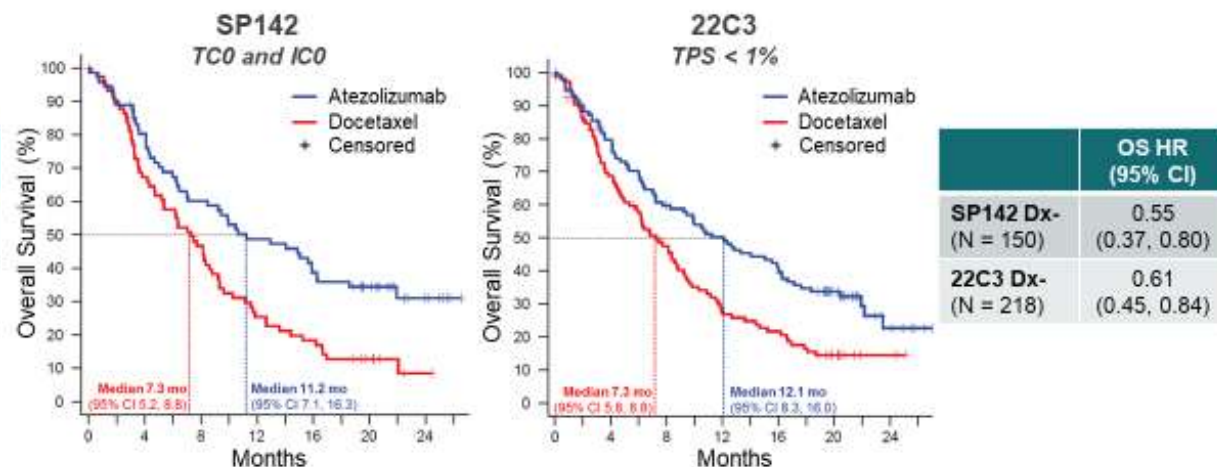


- High PD-L1 expression, as defined by either IHC assay, enriches for improved survival benefit

Dx+, TC3 or IC3 (SP142) or TPS ≥ 50% (22C3); Dx-, not TC3 or IC3 (SP142) or TPS < 50% (22C3); IC, tumor infiltrating immune cell; OS, overall survival; TC, tumor cell; TPS, tumor proportion score.

Gadgeel S, et al. 22C3 vs SP142 in OAK

ATEZOLIZUMAB; Overall Survival in PD-L1 Negative Subgroups in OAK BEP

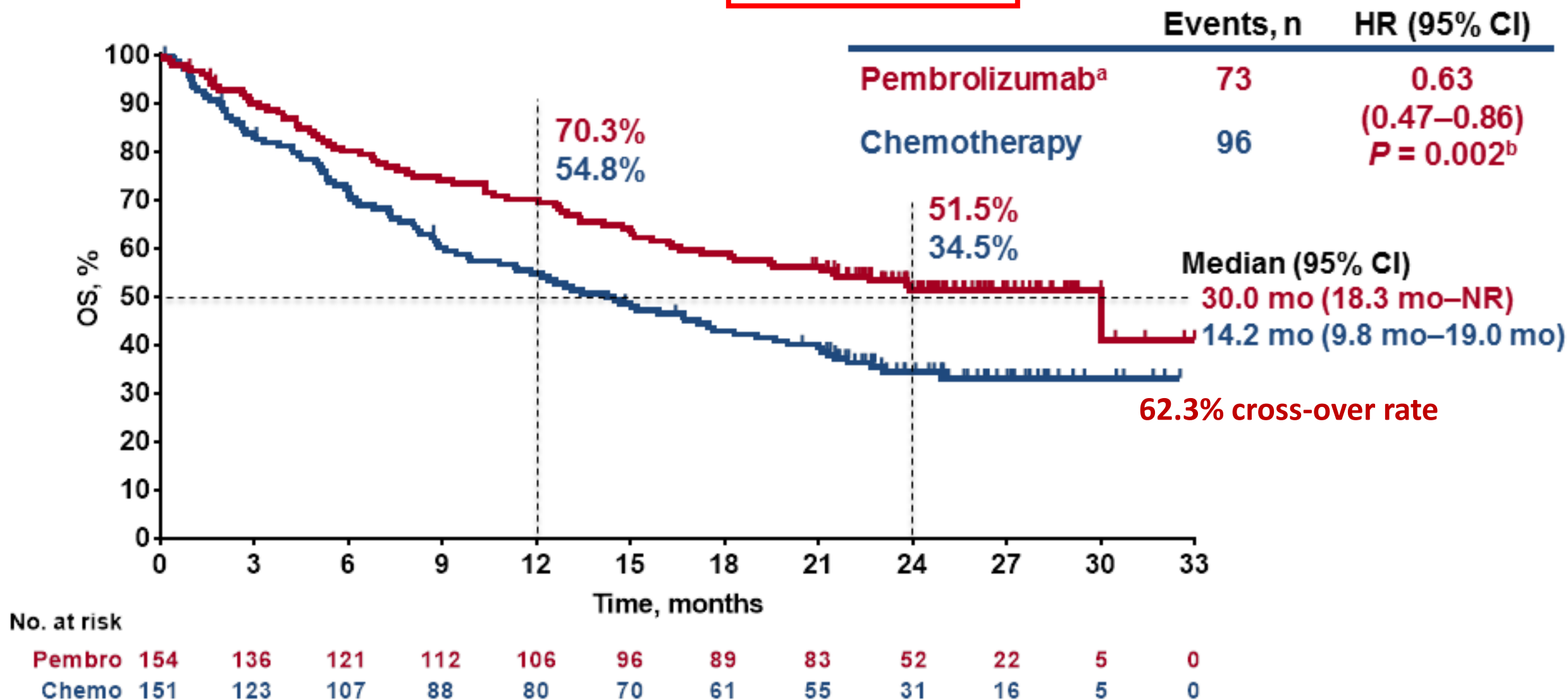


- OS benefit observed in PD-L1 negative populations as defined by either assay

SP142 assay: TC0 and IC0, PD-L1 expression on <1% TC and IC.
22C3 assay: TPS <1%, PD-L1 expression on <1% TC.
Dx-, no or low PD-L1 expression; OS, overall survival; PD-L1, programmed death-ligand 1.

Gadgeel S, et al. 22C3 vs SP142 in OAK

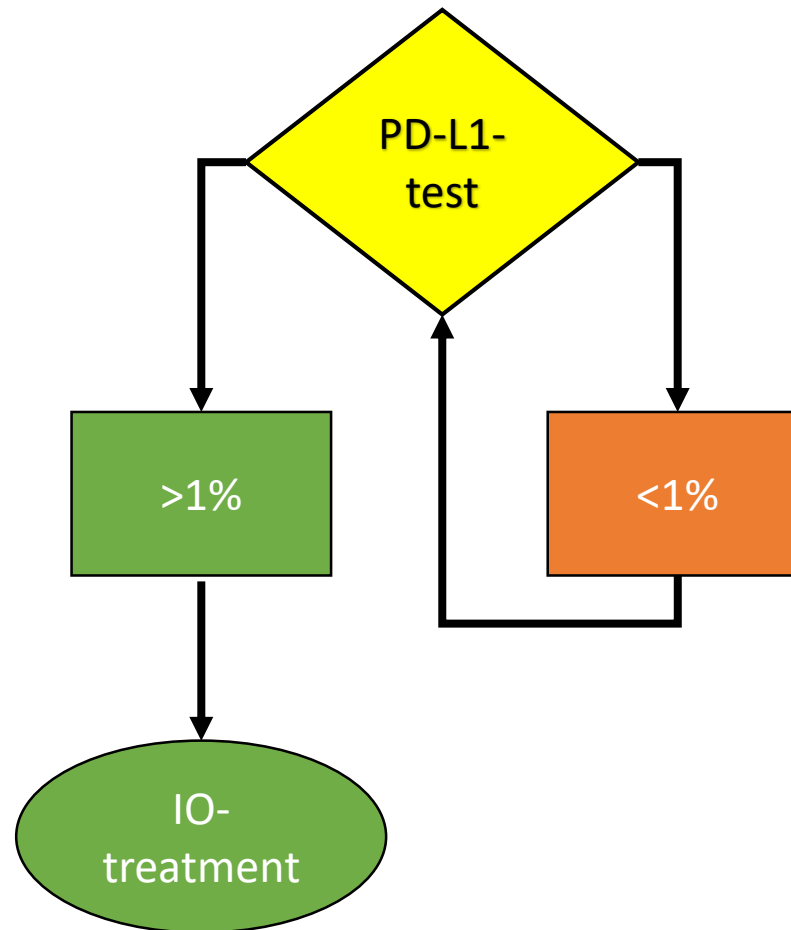
Pembrolizumab 1st line NSCLC (PD-L1>50%)



PD-L1-svar fra patolog:

“Andel tumorceller med PD-L1-uttrykk skal angis med minimum følgende kategorier: <1%, 1-49%, ≥50%”

PD-L1 test algorithm...



Mange legemidler skal vurderes i dette møtet i Beslutningsforum. I tillegg er det et par saker om prinsipper og retningslinjer. Se sakslista.

2. Radisson Blu Airport Hotel,
FEBRUAR Gardermoen.

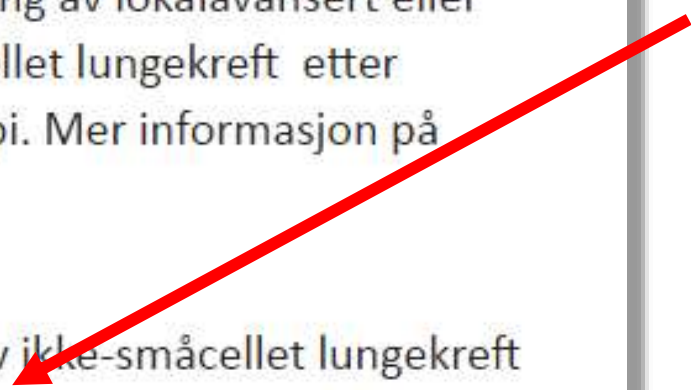
kl. 09.30–11.00

Sak 5-2018

Atezolizumab (Tecentriq) til behandling av lokalavansert eller metastatisk PD-L1 positiv ikke-småcellet lungekreft etter tidligere behandling med kjemoterapi. Mer informasjon på [metodesiden](#) (link)

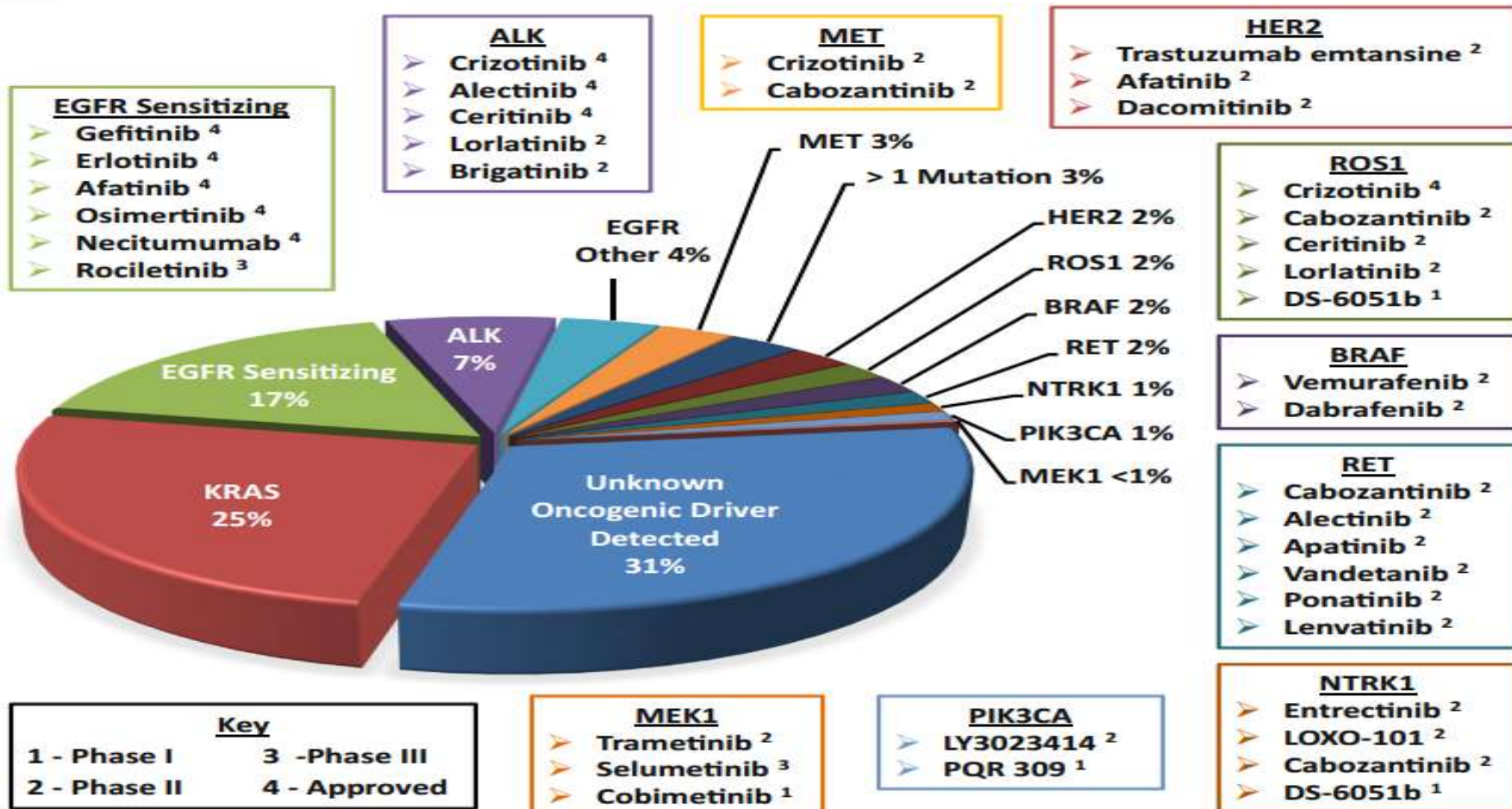
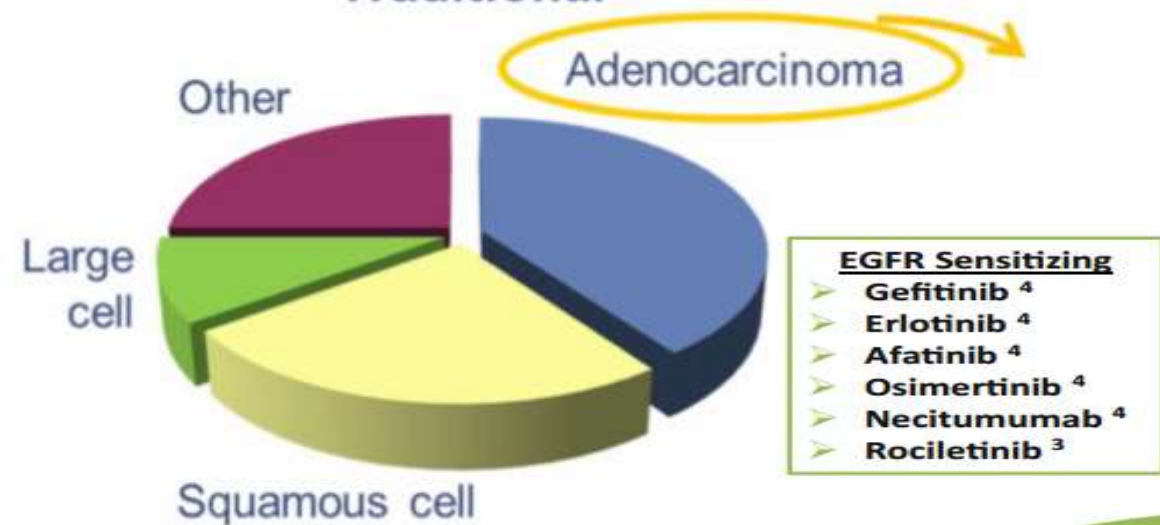
Sak 6-2018

Nivolumab (Opdivo) til behandling av ikke-småcellet lungekreft av typen plateepitelkarsinom som ikke uttrykker PD-L1, ny vurdering.

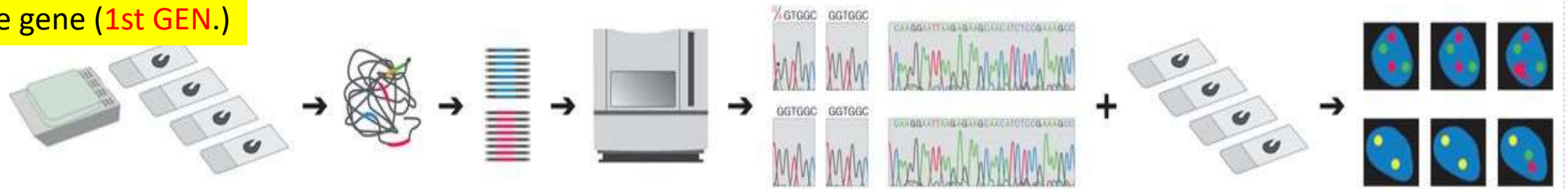


Molekylær diagnostikk

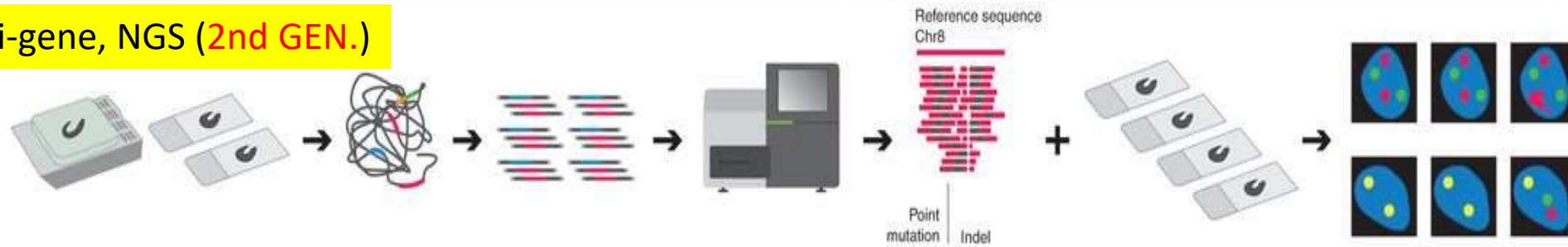
Traditional



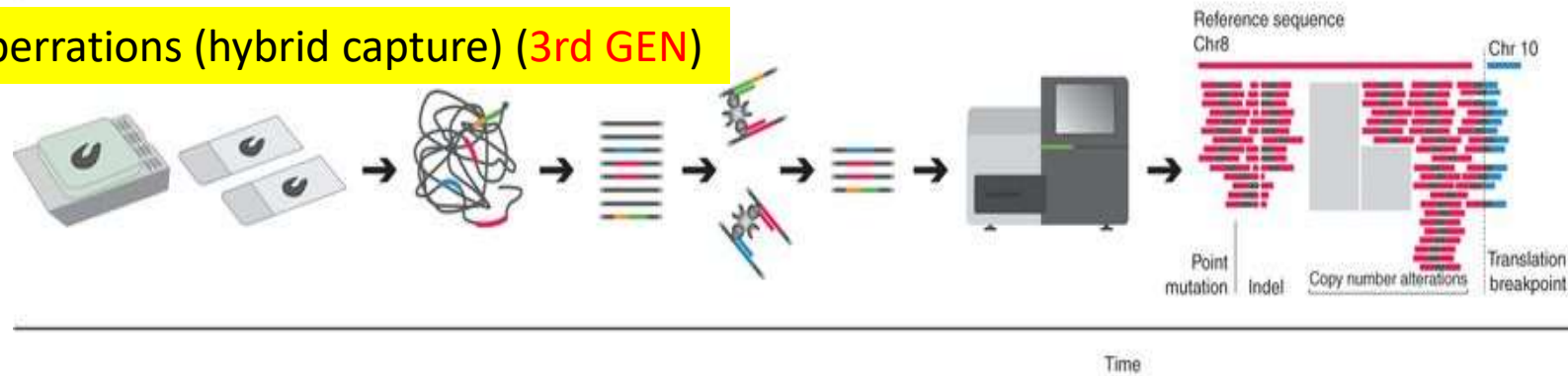
Single gene (1st GEN.)



Multi-gene, NGS (2nd GEN.)

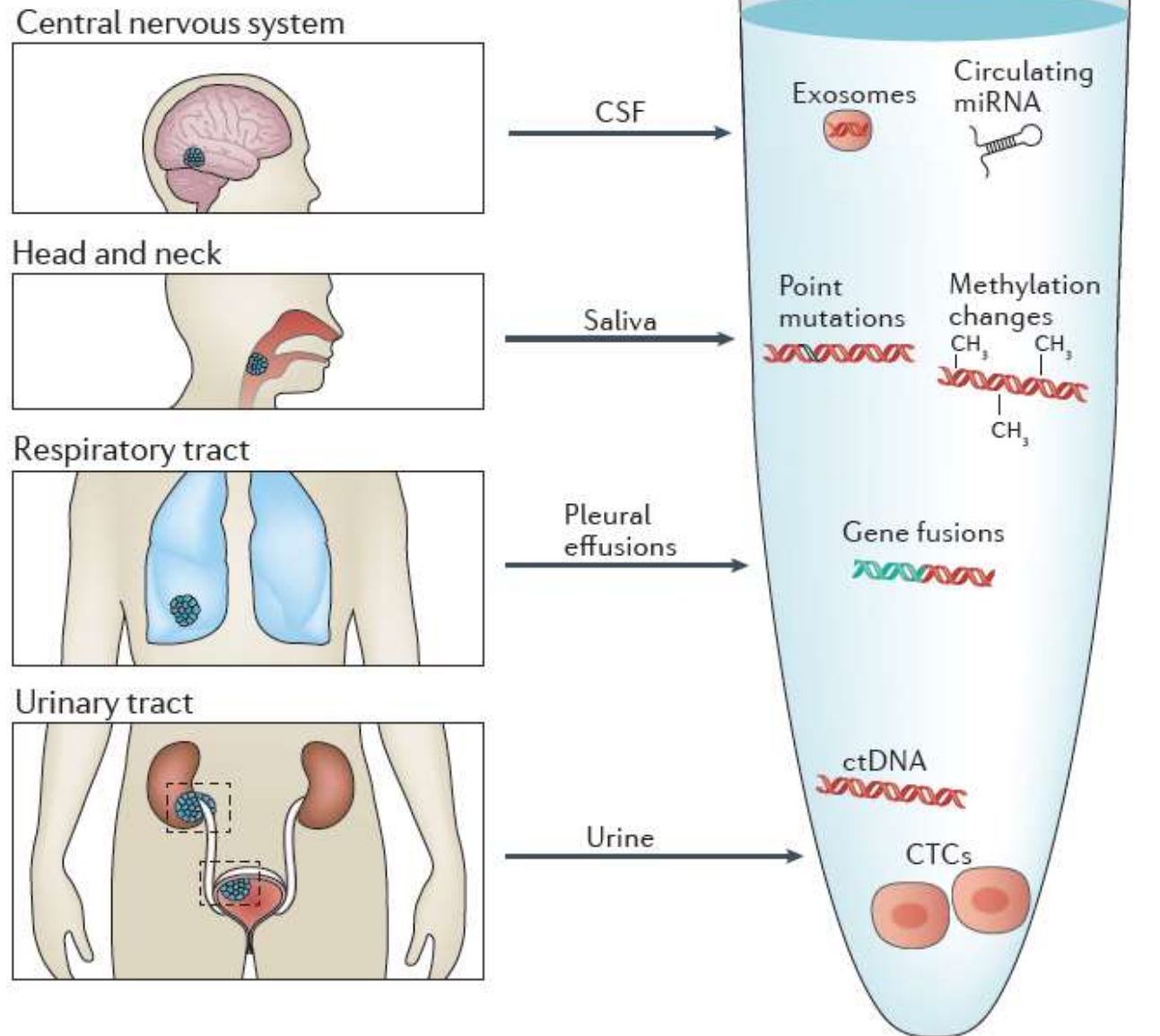


All aberrations (hybrid capture) (3rd GEN.)



«One sample. All answers.»

Liquid biopsies





Idylla™ ctBRAF Mutation Assay (RUO)

A revolution in liquid biopsy cancer research

The Idylla™ ctBRAF Mutation Assay is the first and only fully automated liquid biopsy assay.

Discover the benefits of Idylla™ ctBRAF Assay - the easiest solution to implement liquid biopsy testing in research.

- **Directly from 1 ml plasma sample into the cartridge**
- **Less than 1 minute hands-on time**
- **Total turnaround time of around 100 minutes**

news

4 April 2017, 7:00 AM

PRESS RELEASE: Biocartis establishes US subsidiary and appoints US General Manager

30 March 2017, 7:00 AM

PRESS RELEASE: Biocartis announces publication of 2016 Annual Report

events

Apr 20th - 22nd, 2017

Encontros de Primavera en Oncologie
Évora, Portugal

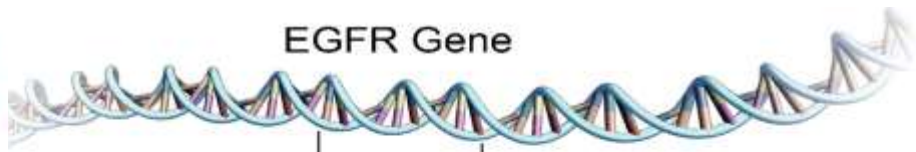
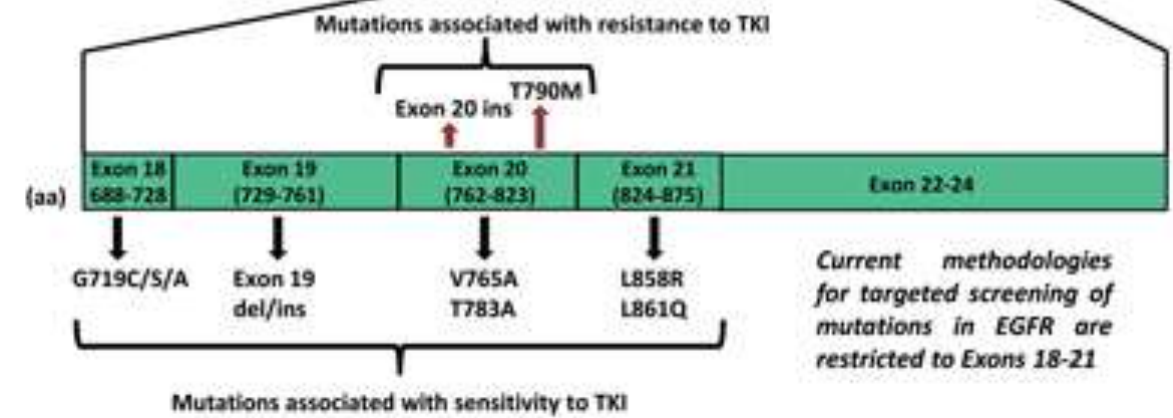
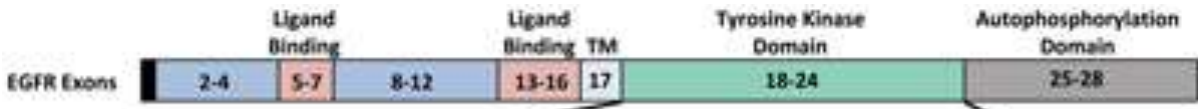
Molekyære prediktive analyser i rutine

Alle NSCLC:

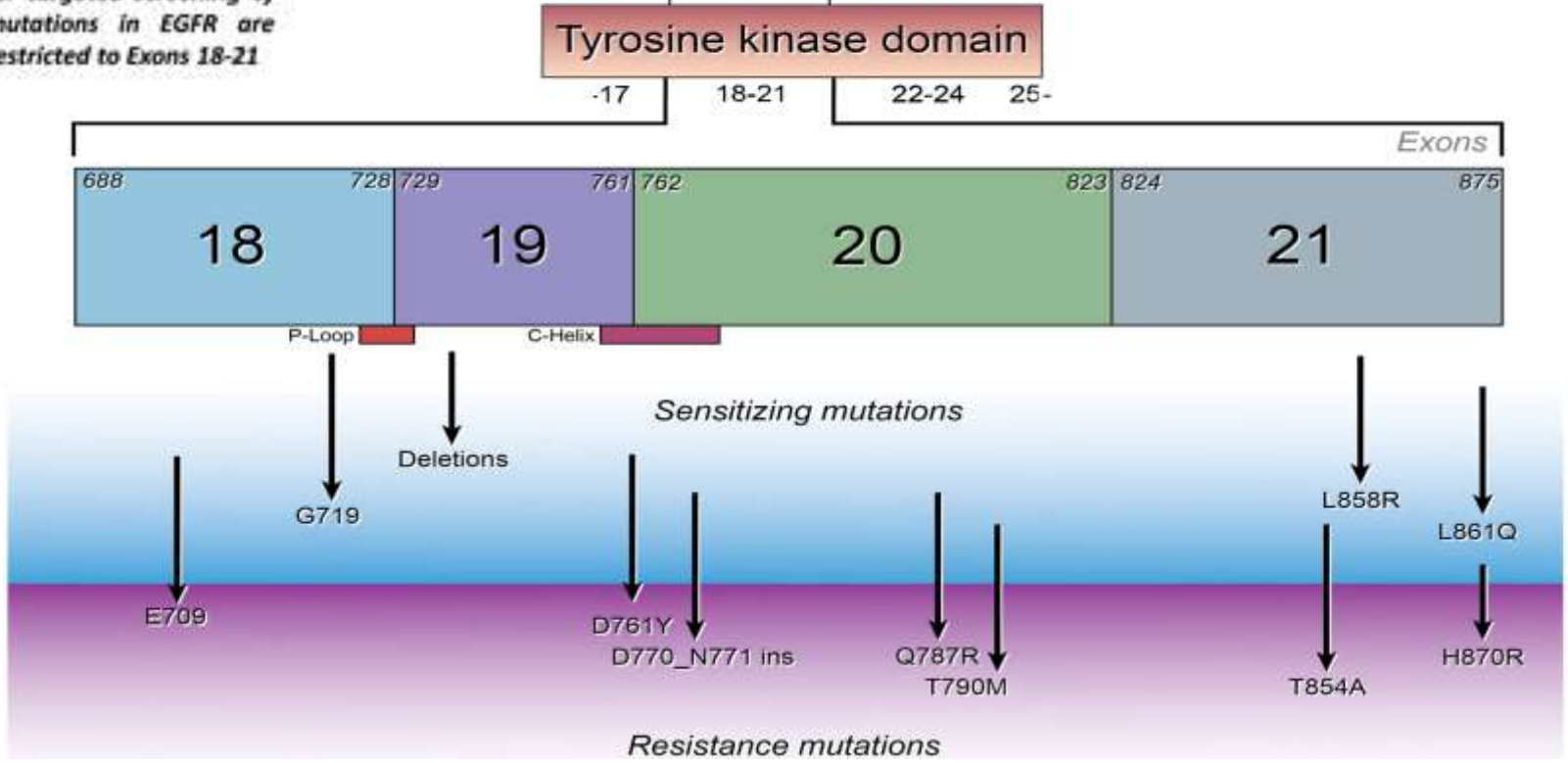
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Alle non-platteepitelkarsinom (NSCLC)

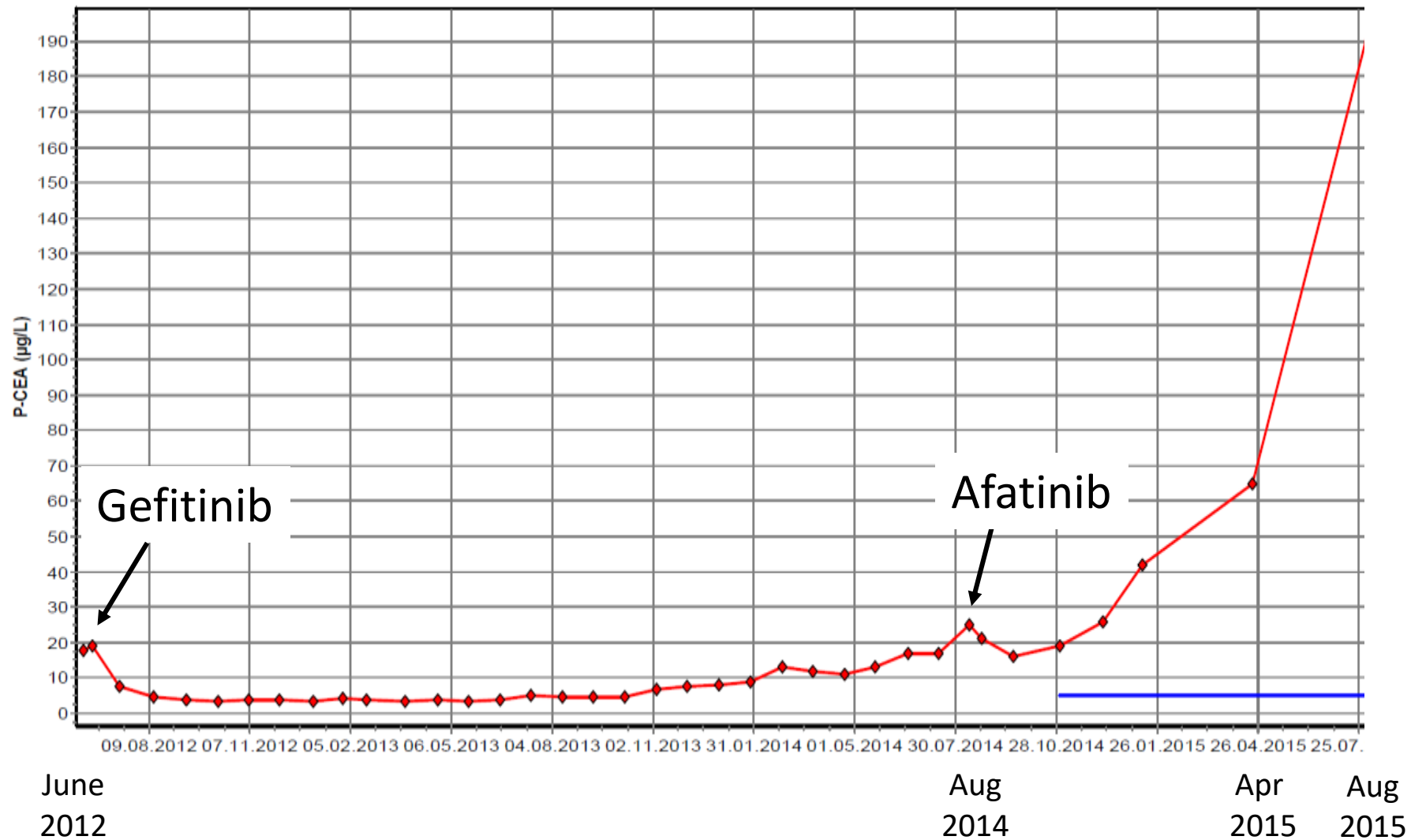
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- **ROS1** hjå utvalde
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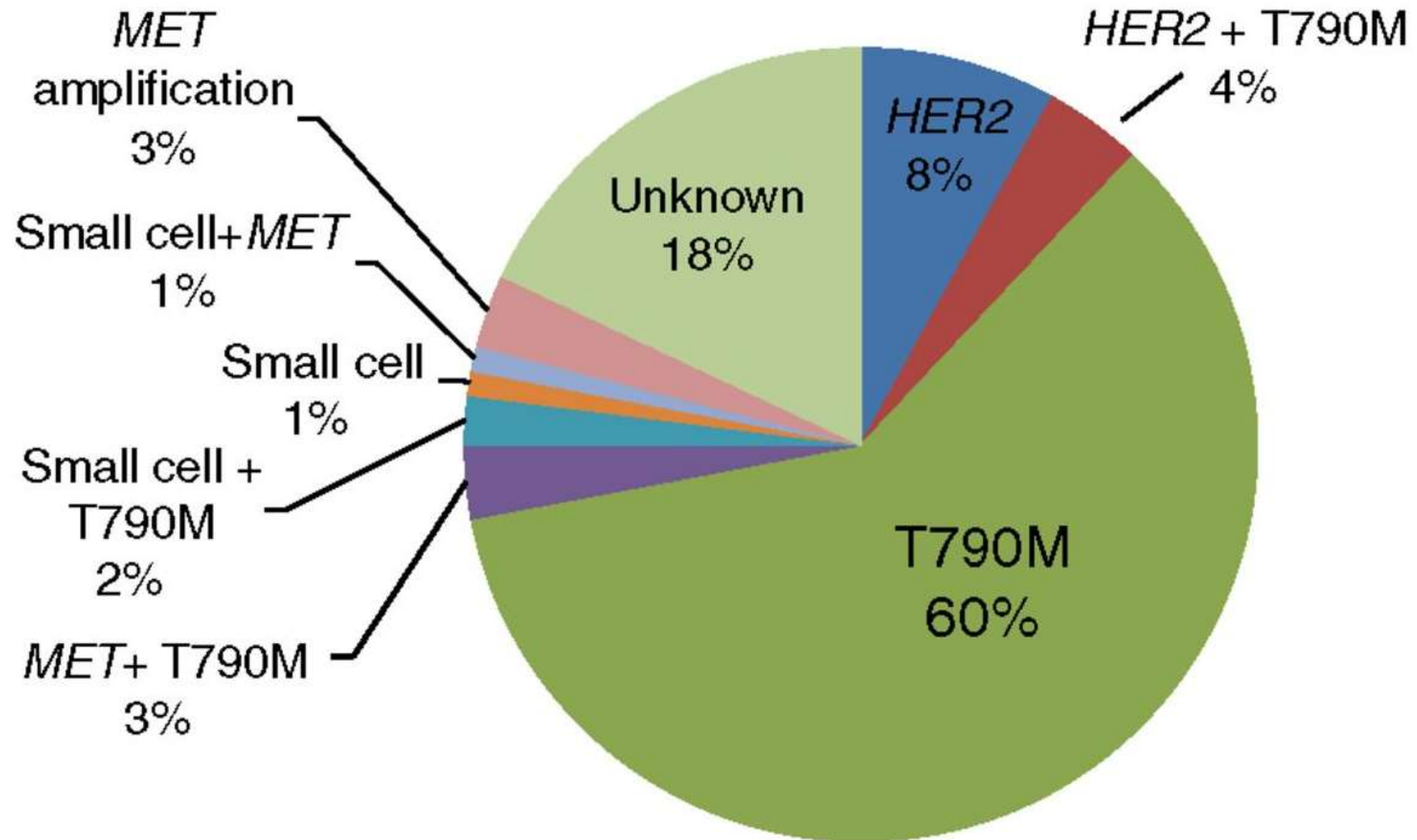
Current methodologies for targeted screening of mutations in EGFR are restricted to Exons 18-21



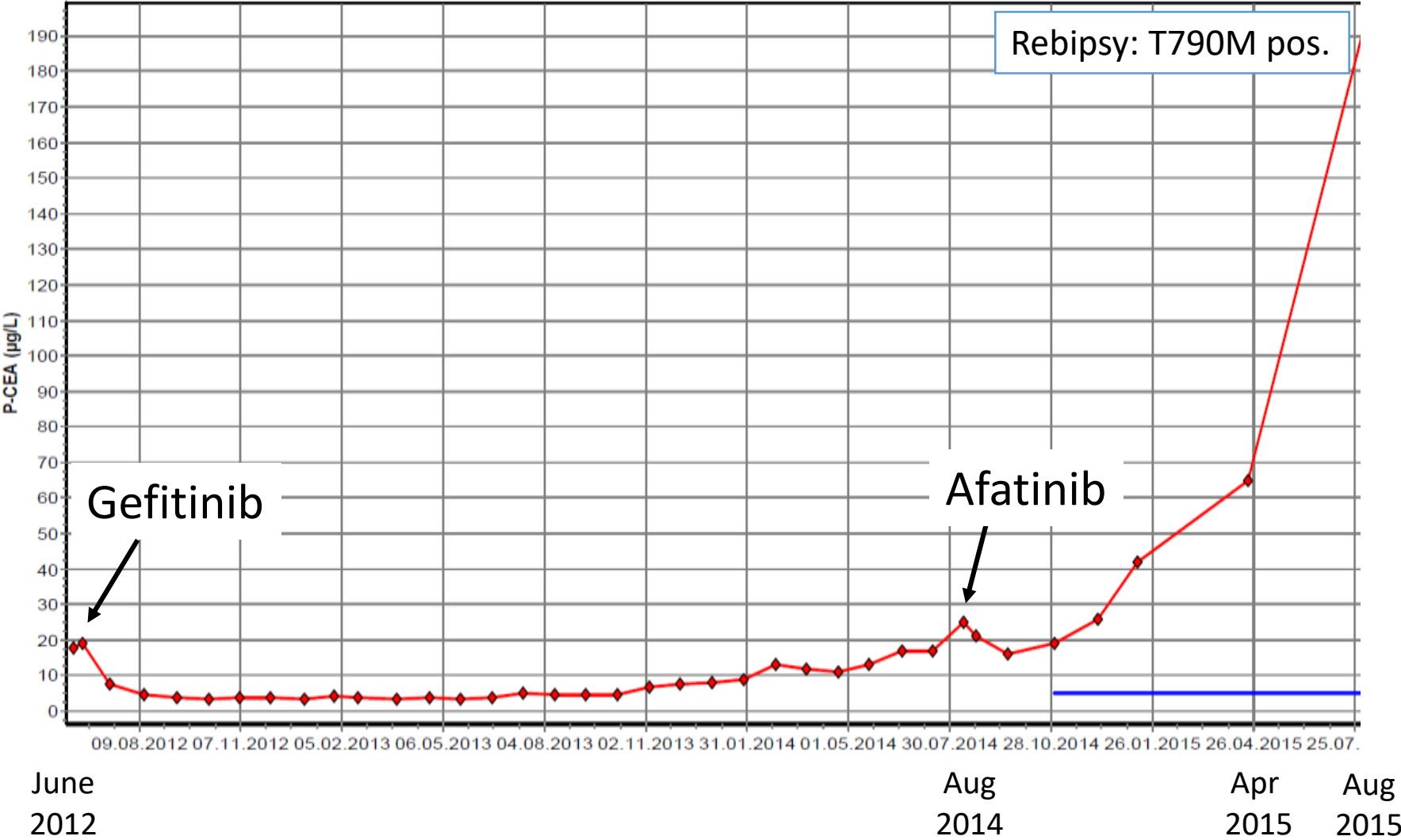
How it can be

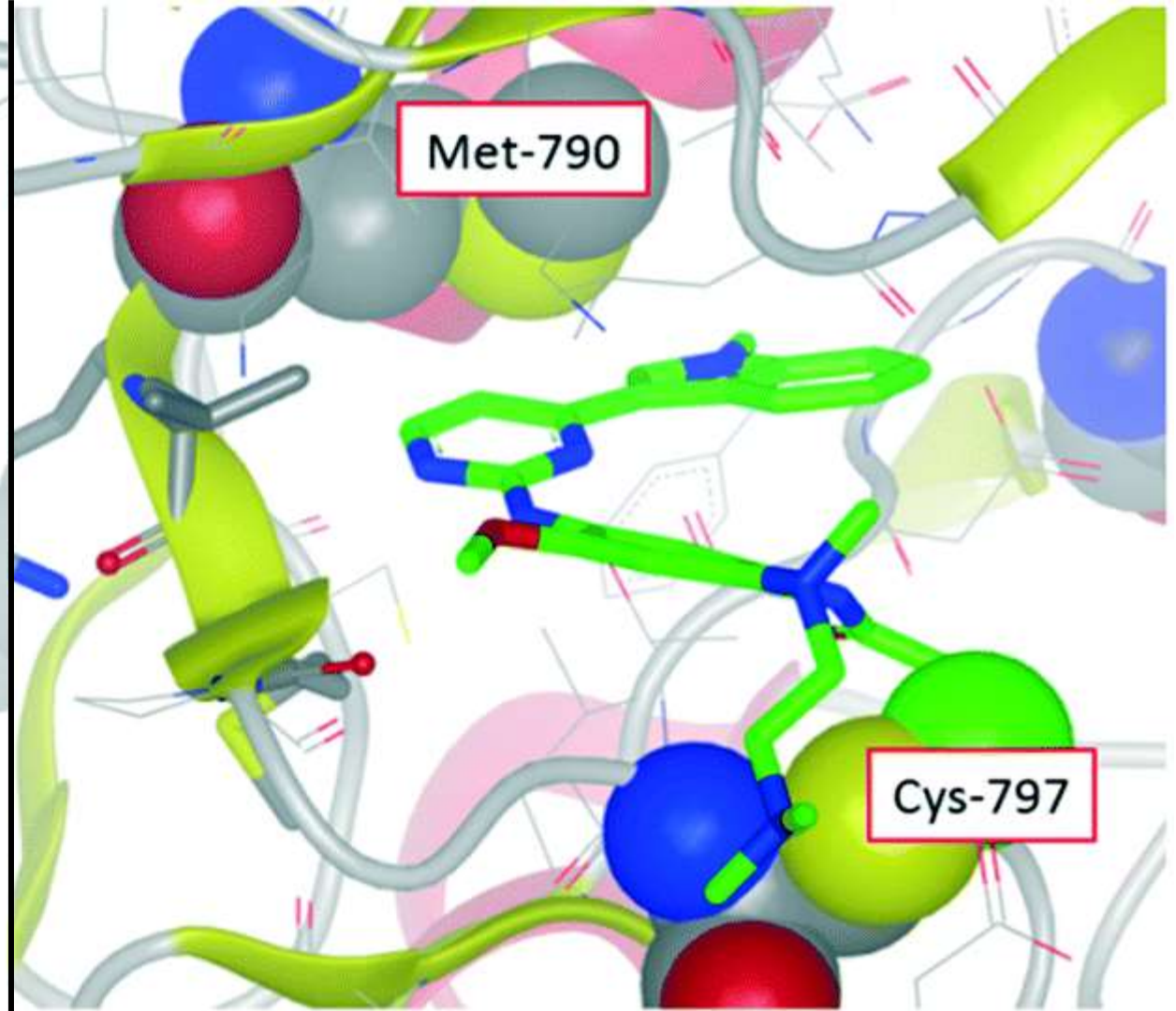
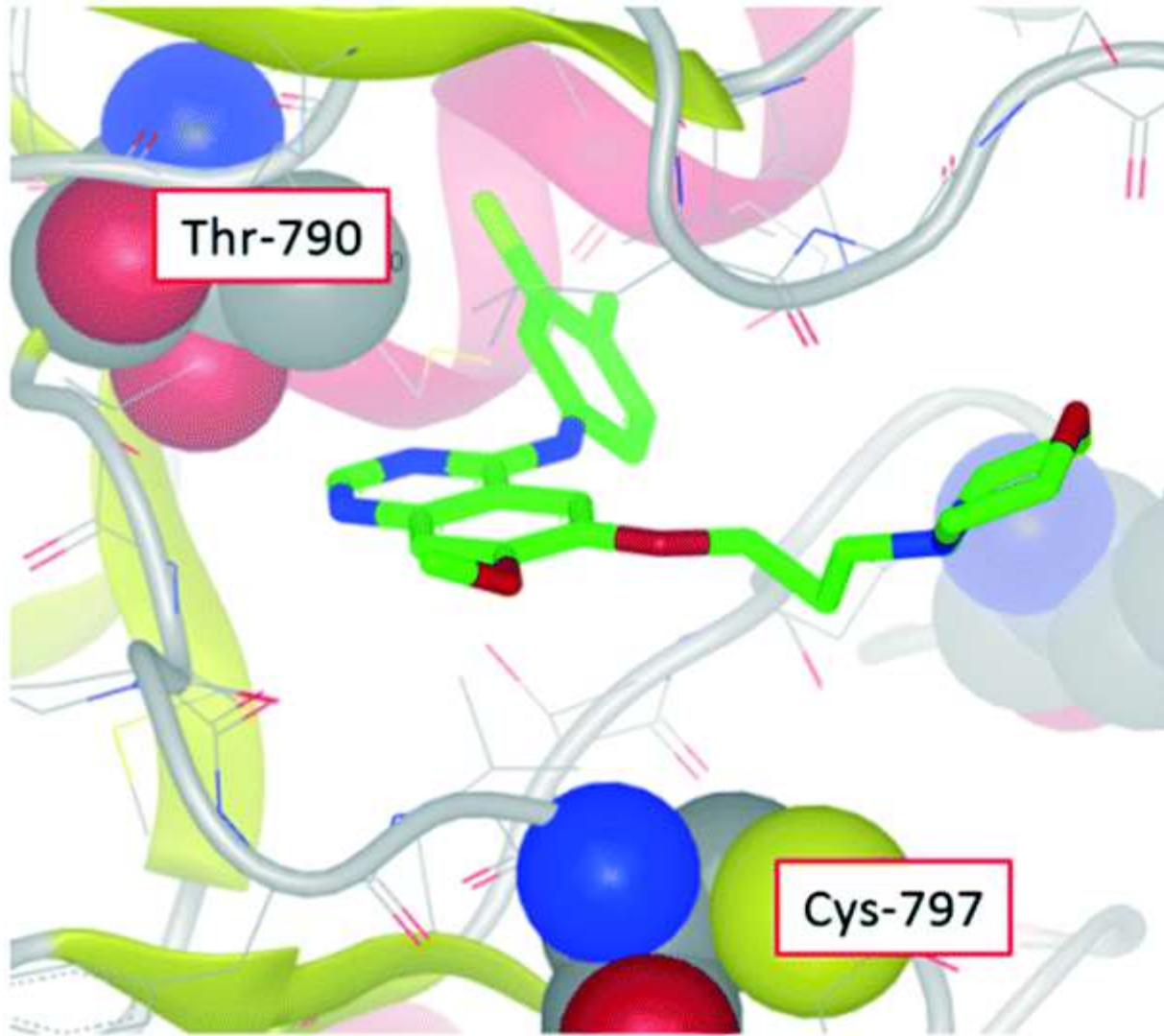


Mechanisms of EGFR-resistance



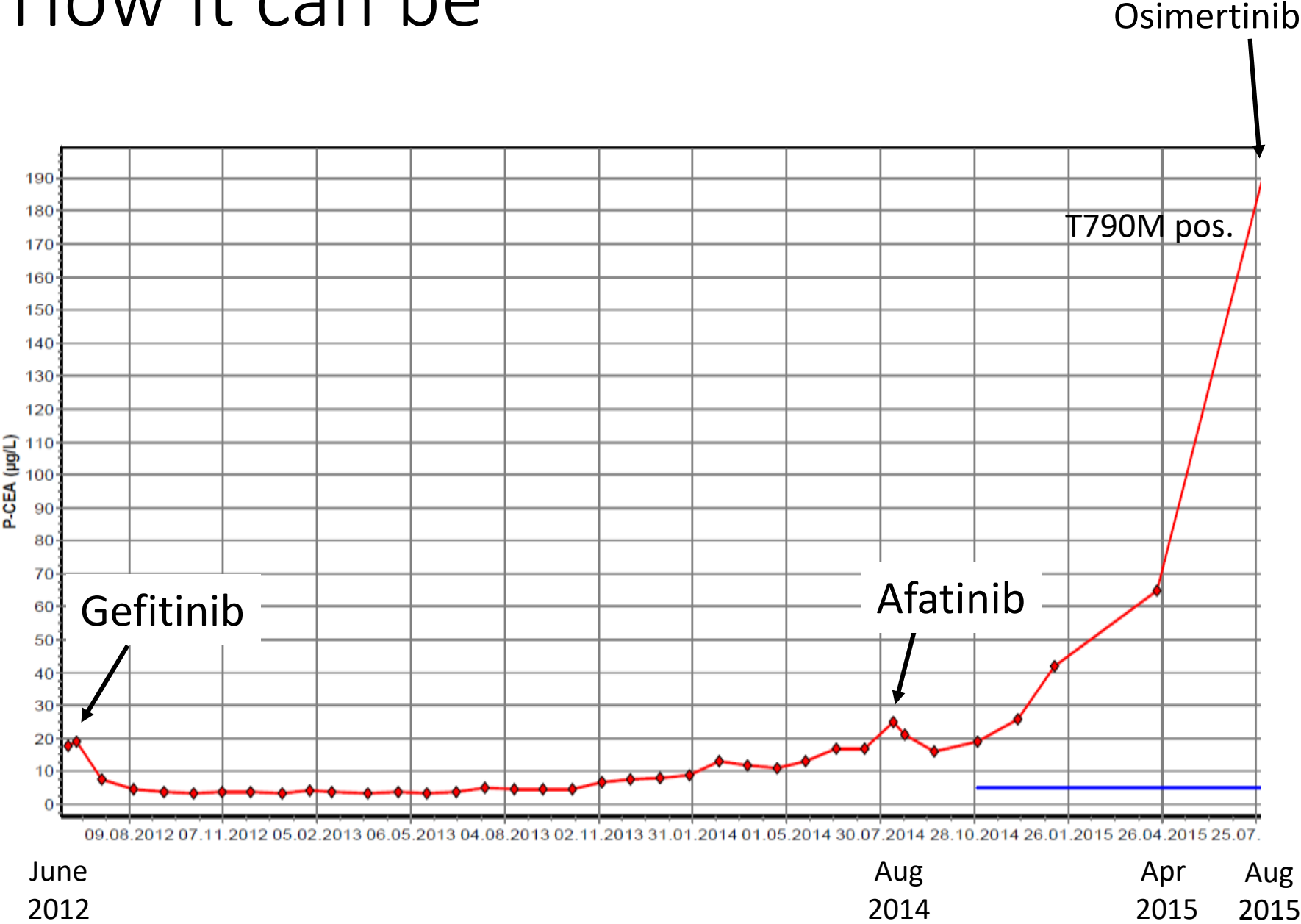
How it can be





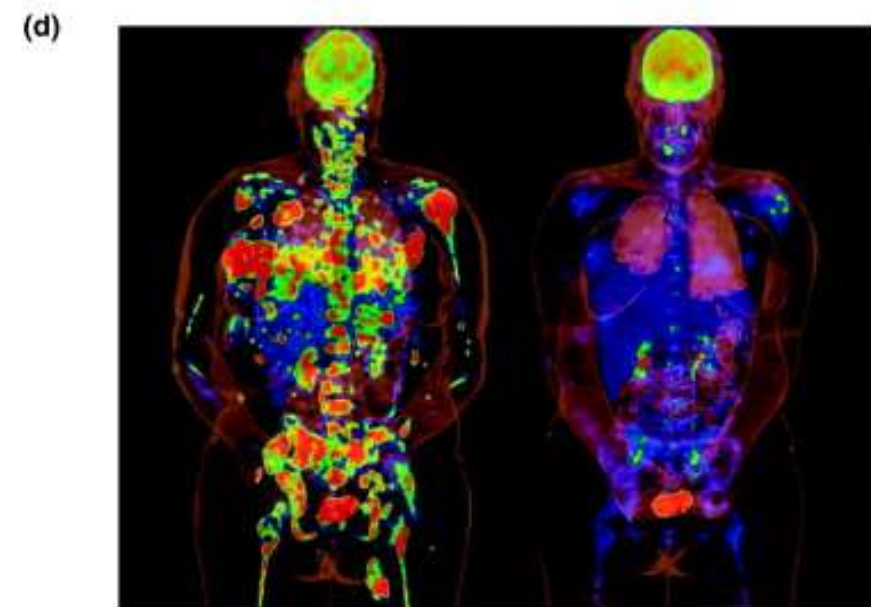
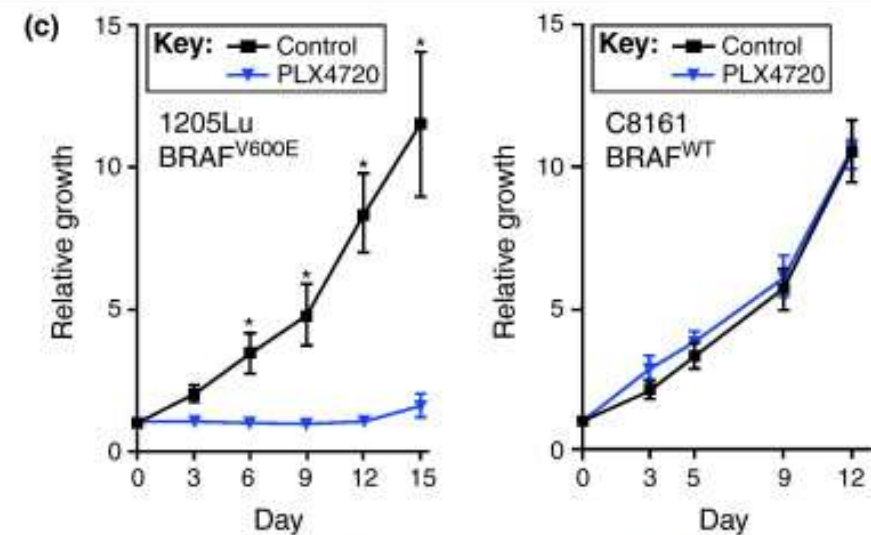
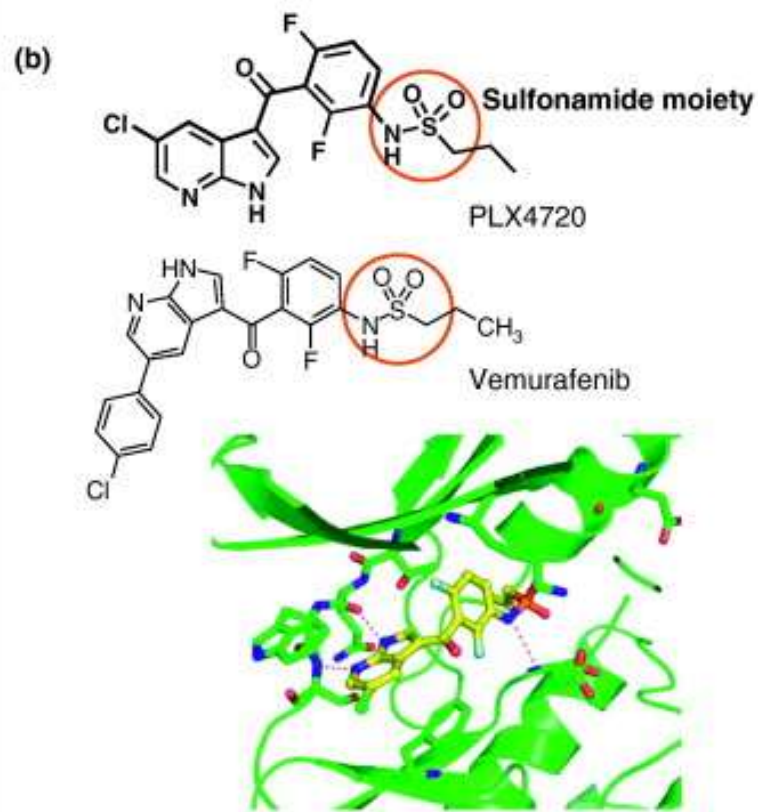
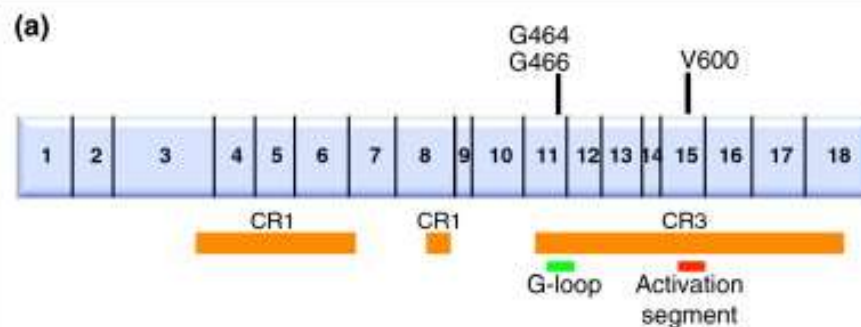
X-ray crystal structure of gefitinib in wild-type EGFR showing close proximity of the compound with the threonine gatekeeper (left). Modelled structure of osimertinib in T790M mutant of EGFR showing close proximity with the methionine gatekeeper residue and also covalent bond to Cys-797 (right).

How it can be



BRAF

- Kun V600E/K



Molekyære prediktive analyser i rutine

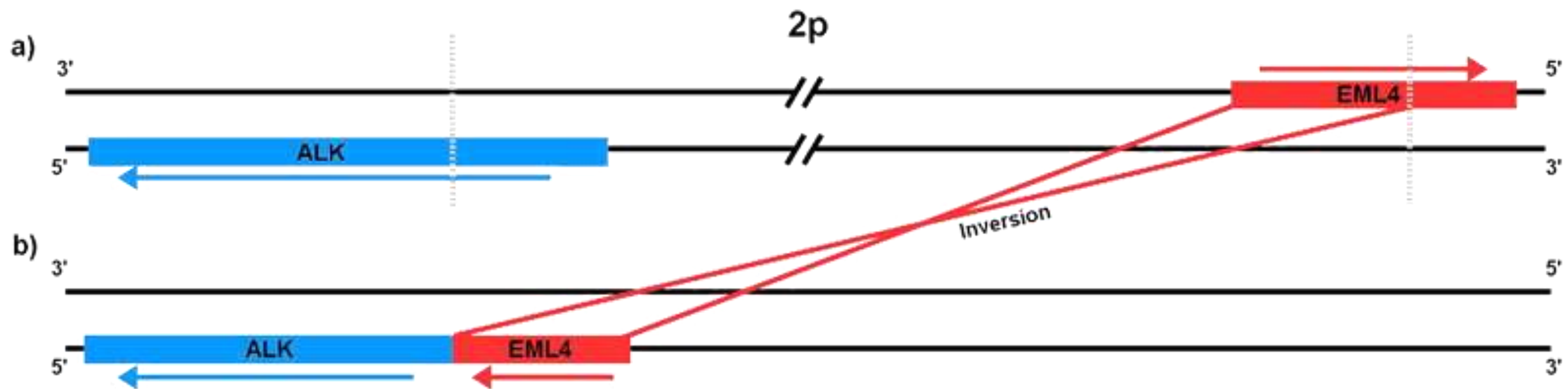
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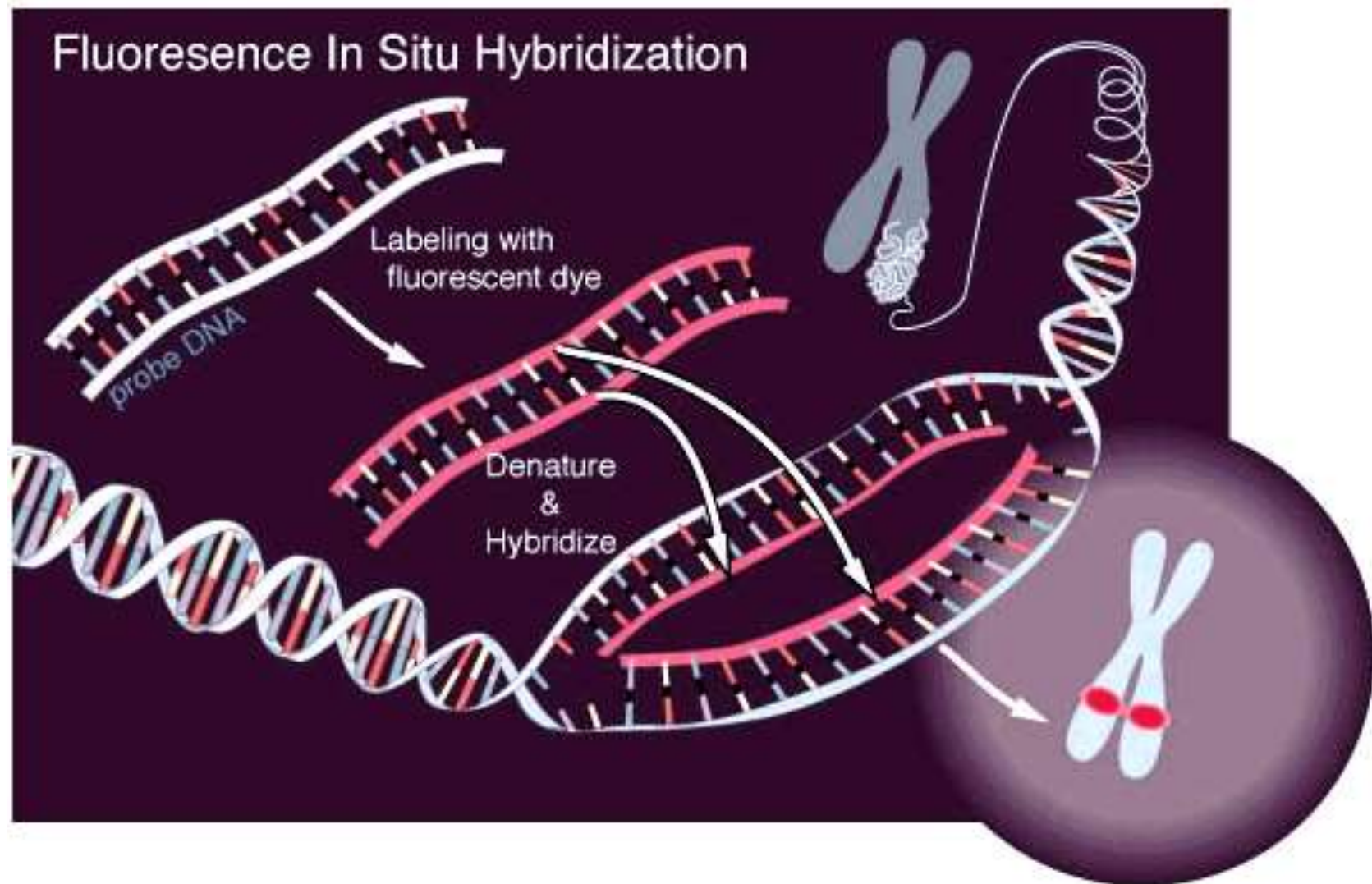
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- **EGFR**-mutasjonsanalyse (DNA)
- **ALK**-translokasjonsanalyse (FISH eller IHC)
- **ROS1** hjå utvalde
- **BRAF** hjå utvalde

EML4-ALK fusion



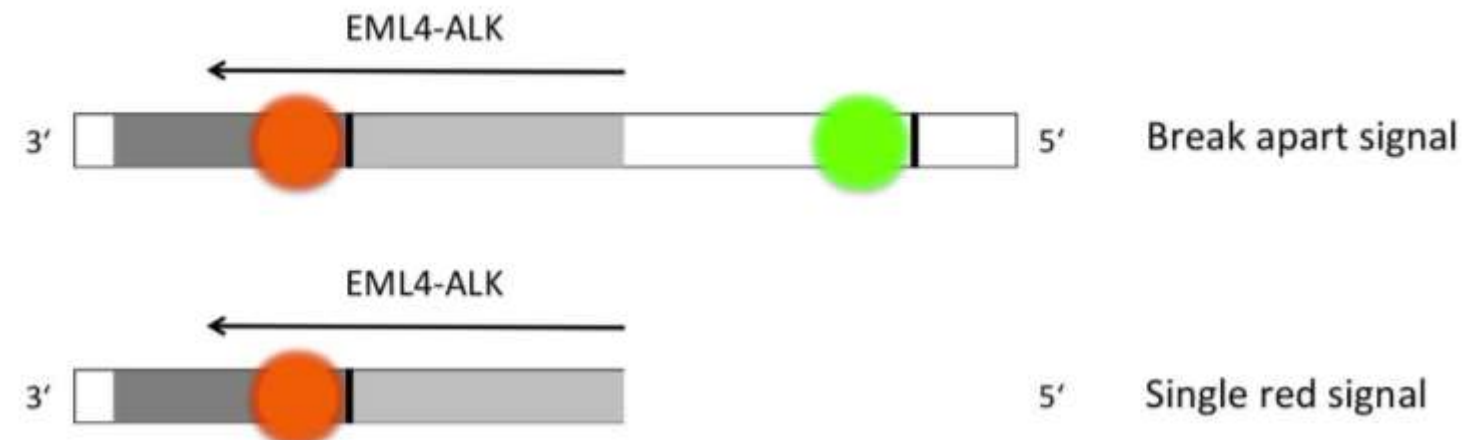
FISH



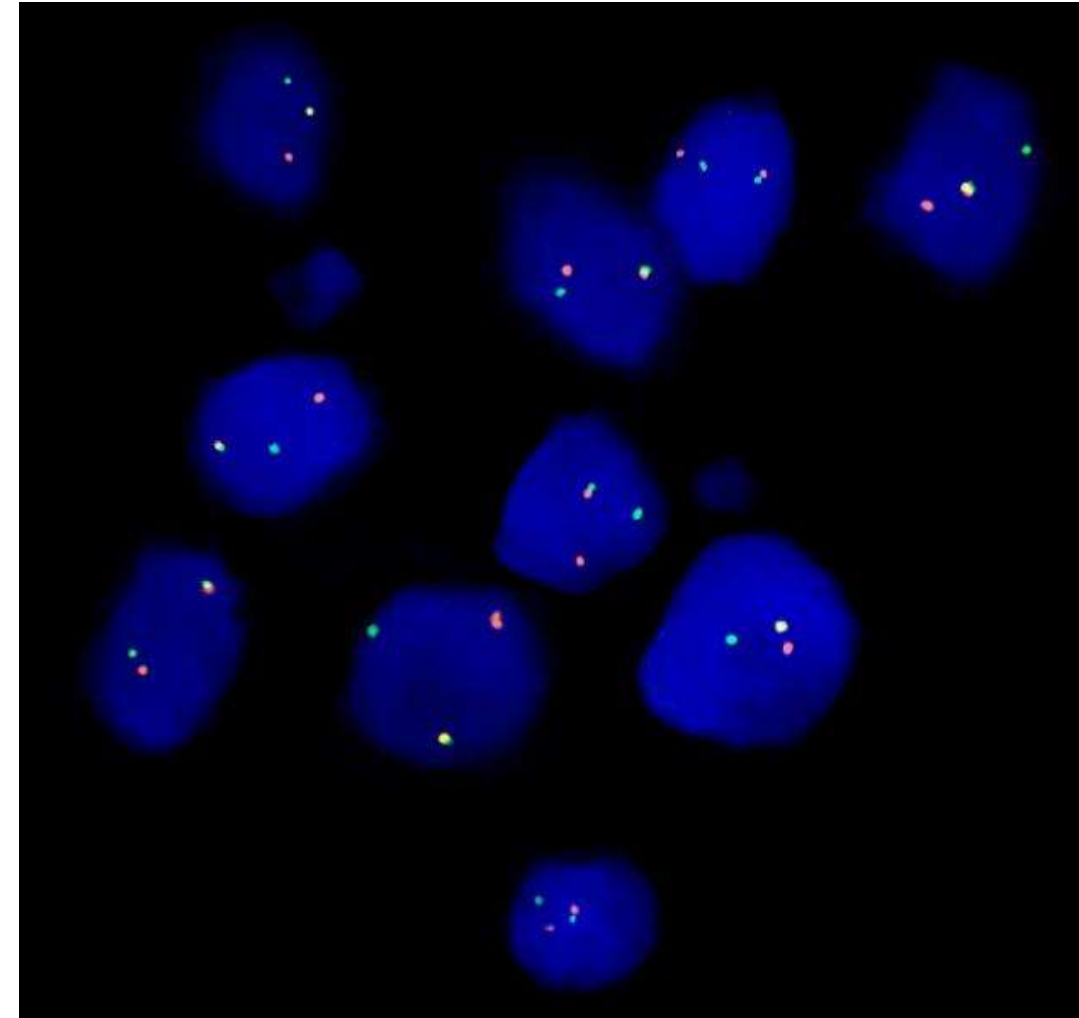
No ALK Rearrangement



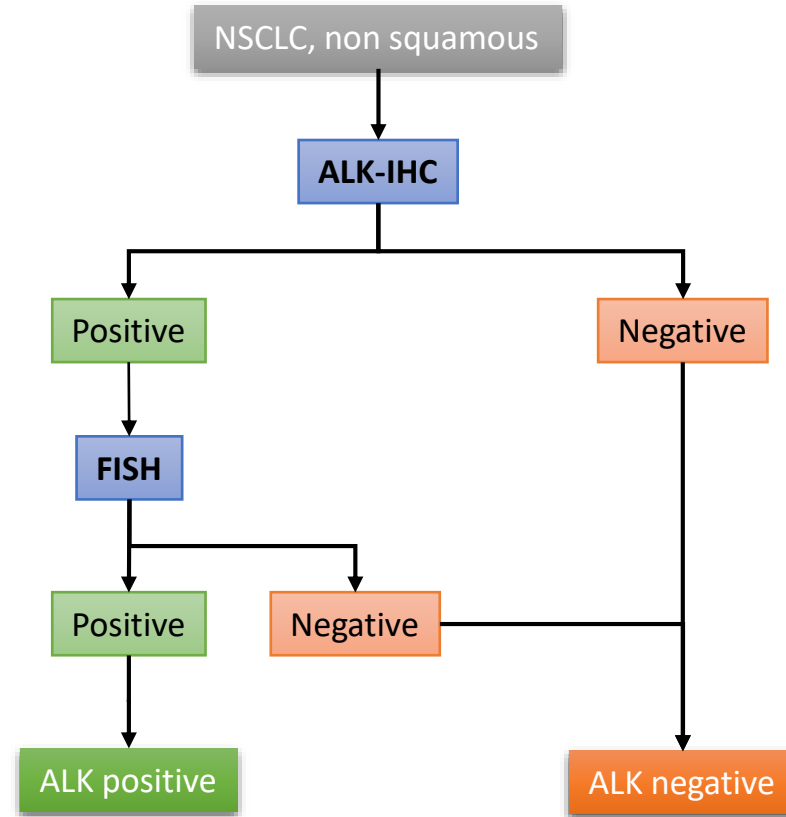
EML4-ALK Fusion



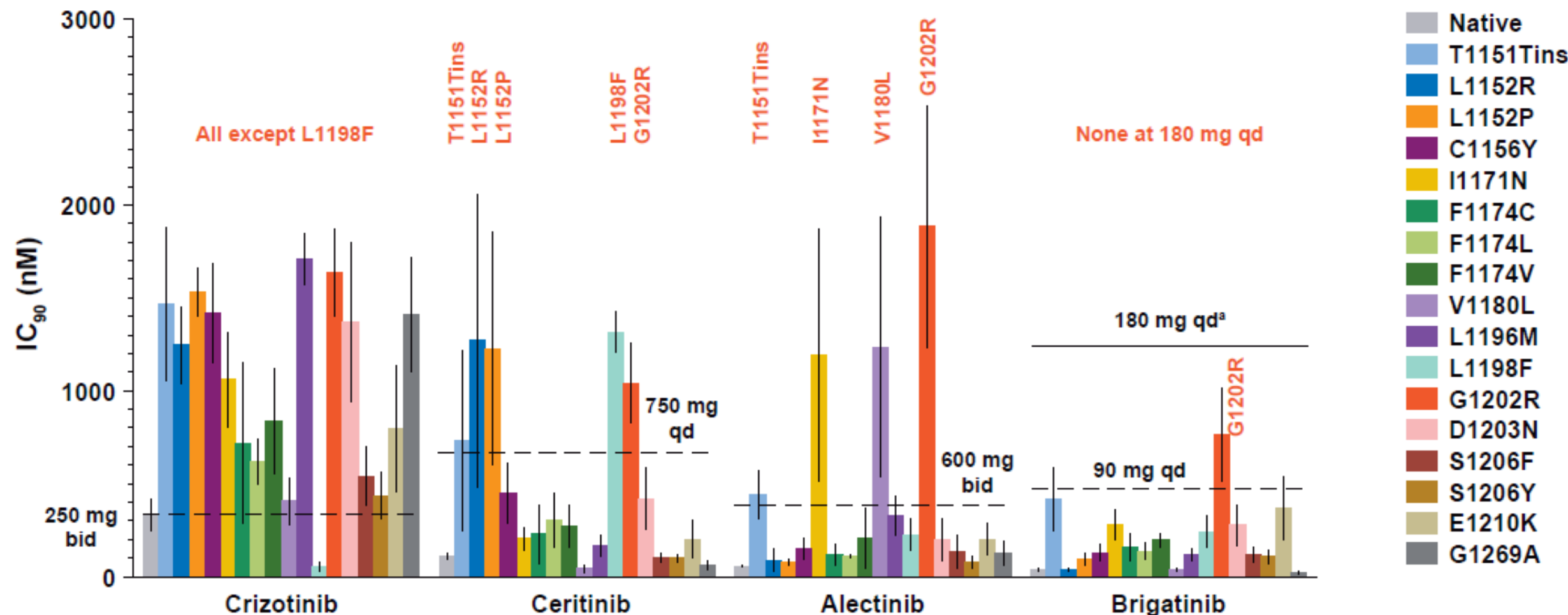
ALK “break apart”-FISH



Algorithm for ALK-testing

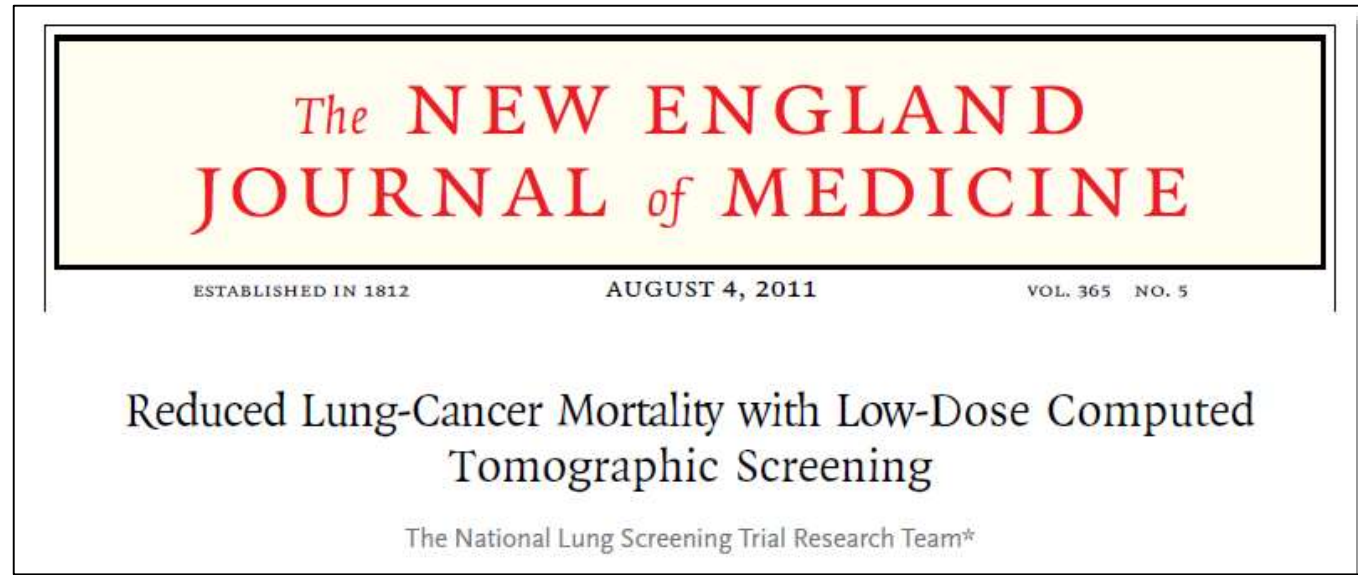


A variety of resistance mutations within the EML4-ALK fusion gene



Rebiopsy and re-analysis is important

Lungekreftscreening



representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; $P=0.004$). The rate of death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 13.6; $P=0.02$).

Europa: venter fortsatt på Nelson-studien

Konklusjon

- Økt insidens x bedret prognose = sterkt økt prevalens
- Stor behov for lungeonkologer!
- Og mye spennende molekylært
- En sykdom som kan gå fra ukers til års leveutsikter basert på et molekylærpatologisvar