

Ontwikkelingen op het gebied van oncogene drivers van longkanker: Alk, RET, ROS1, cMET, HER2

Egbert Smit, longarts

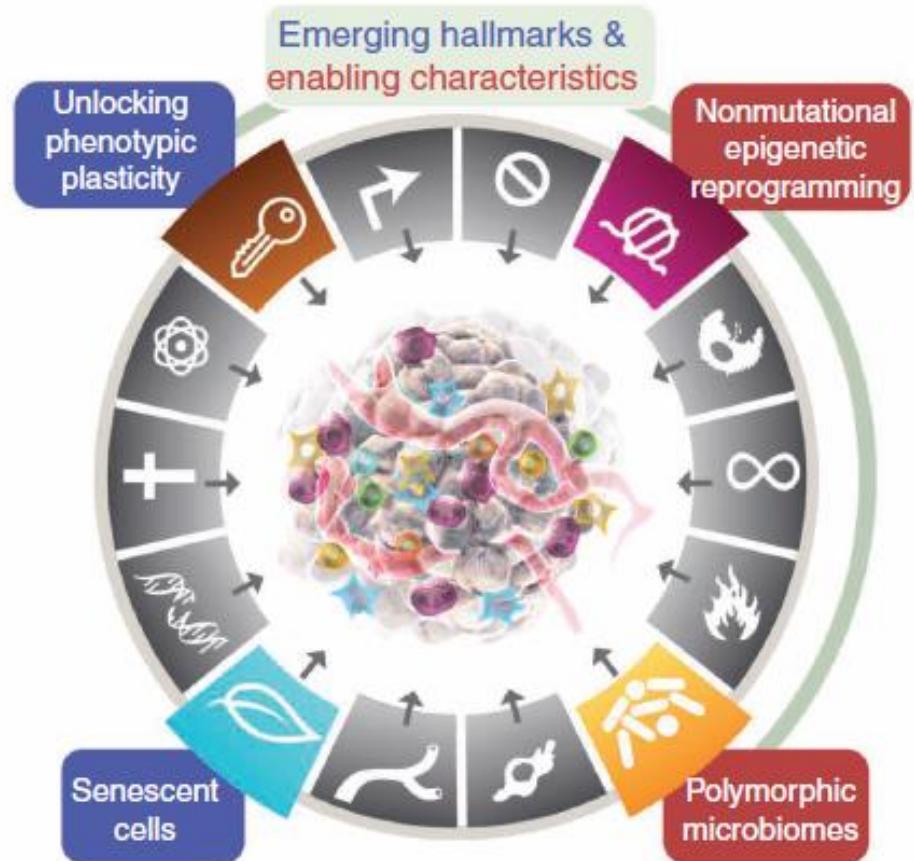
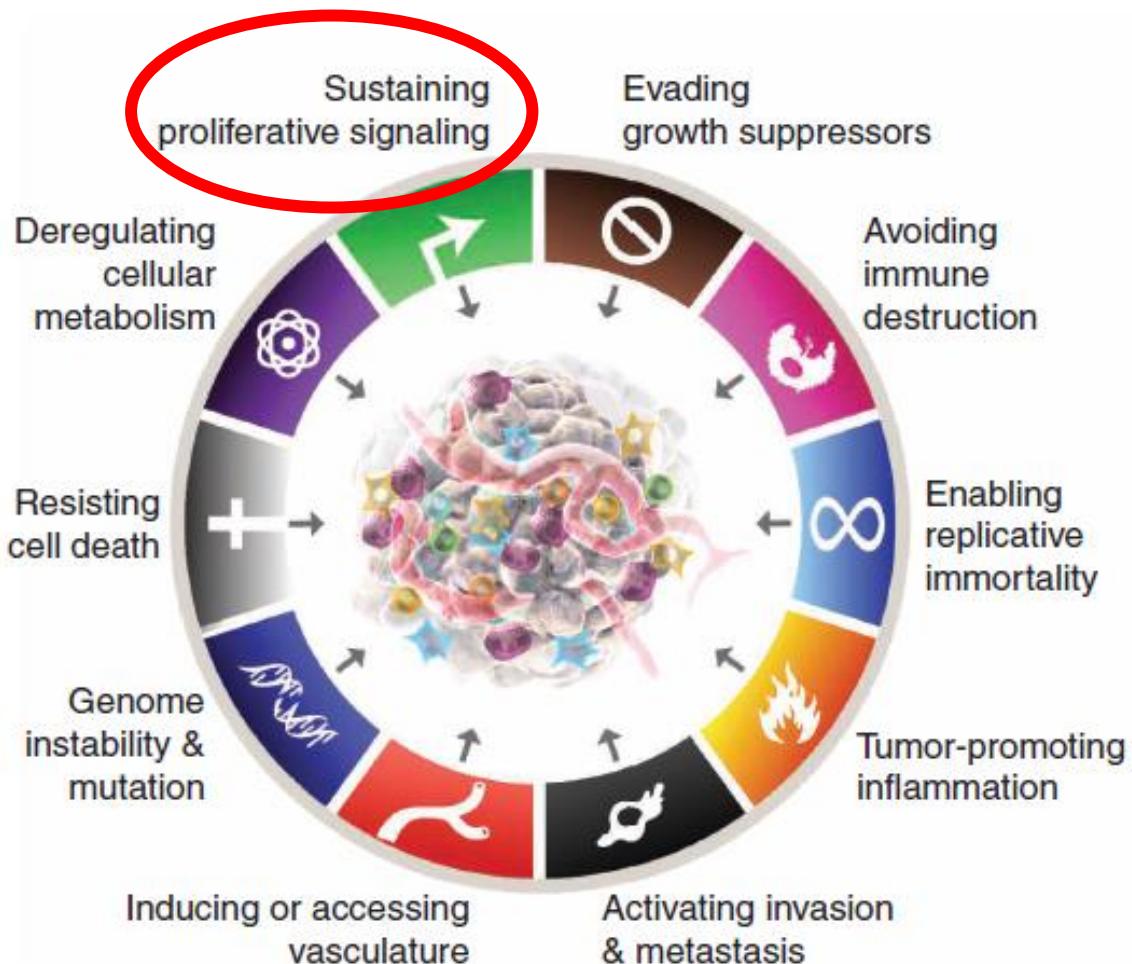
LUMC

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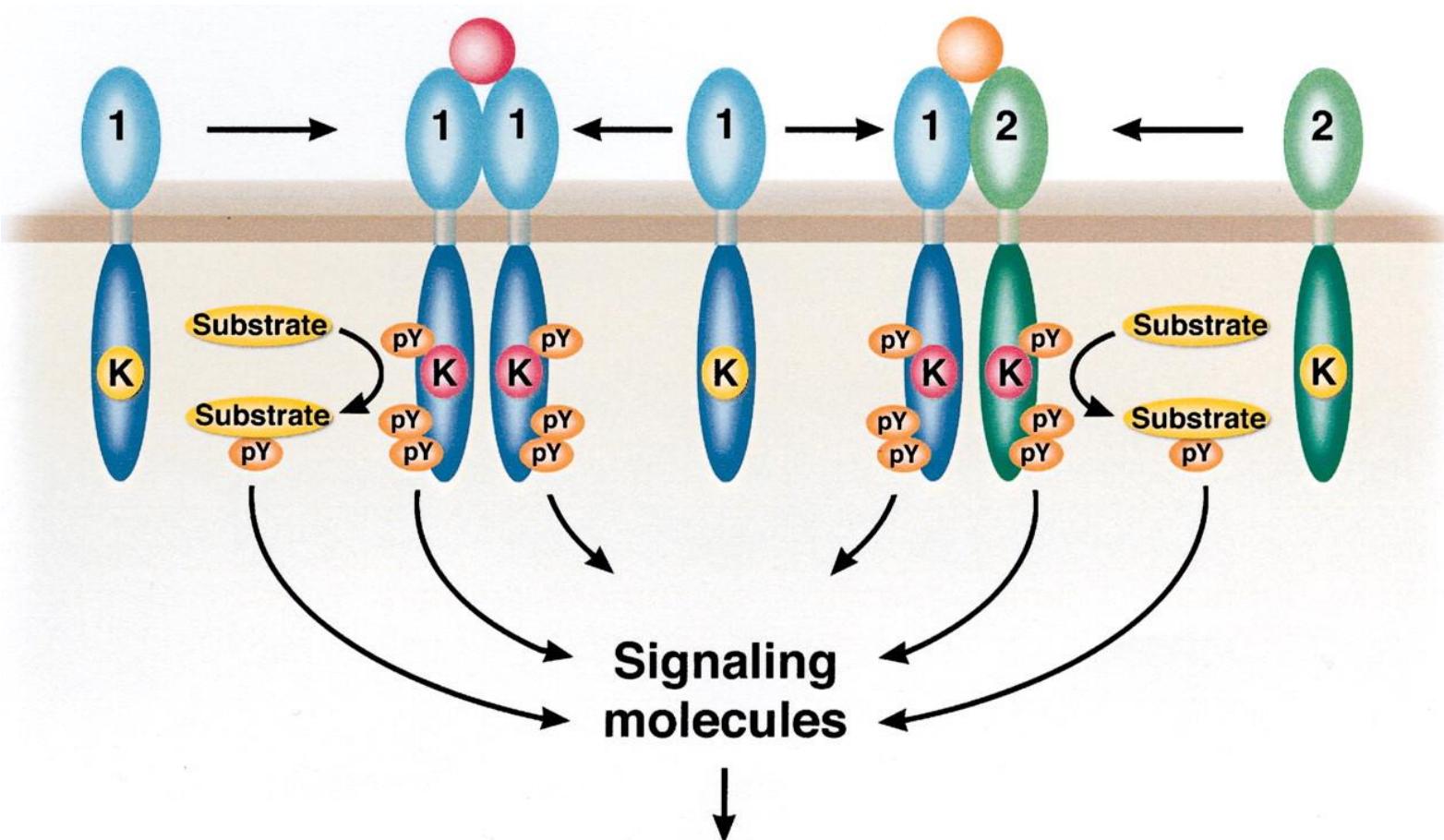
Agenda

- Beetje biologie
 - Waarom werkt die doelgerichte behandeling?
 - Waarom werkt het soms niet?
- Wat heeft doelgerichte behandeling gebracht?
- Waar gaat het naar toe?
- **Val mij gerust in de rede met vragen/opmerkingen**

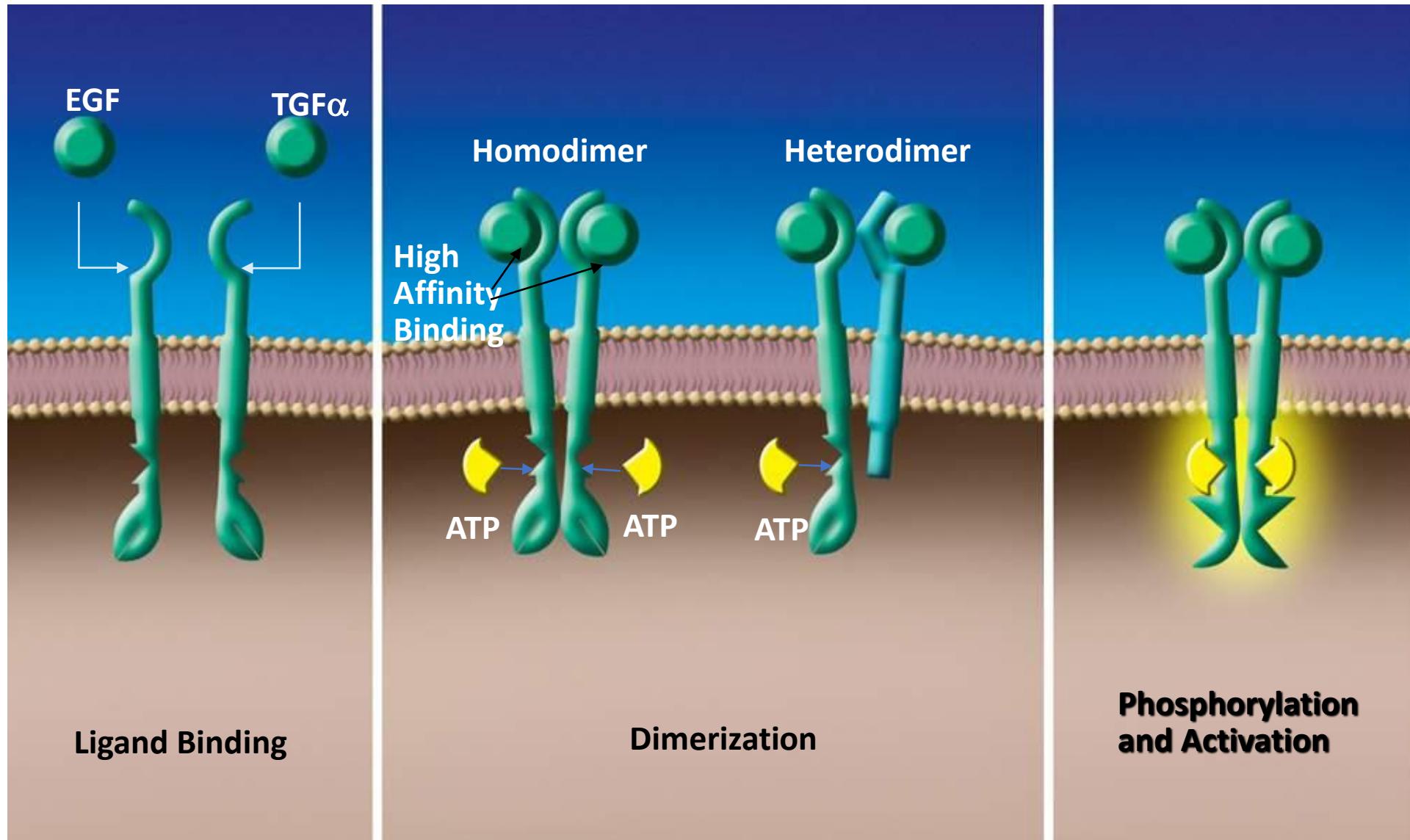
Hallmarks of Cancer



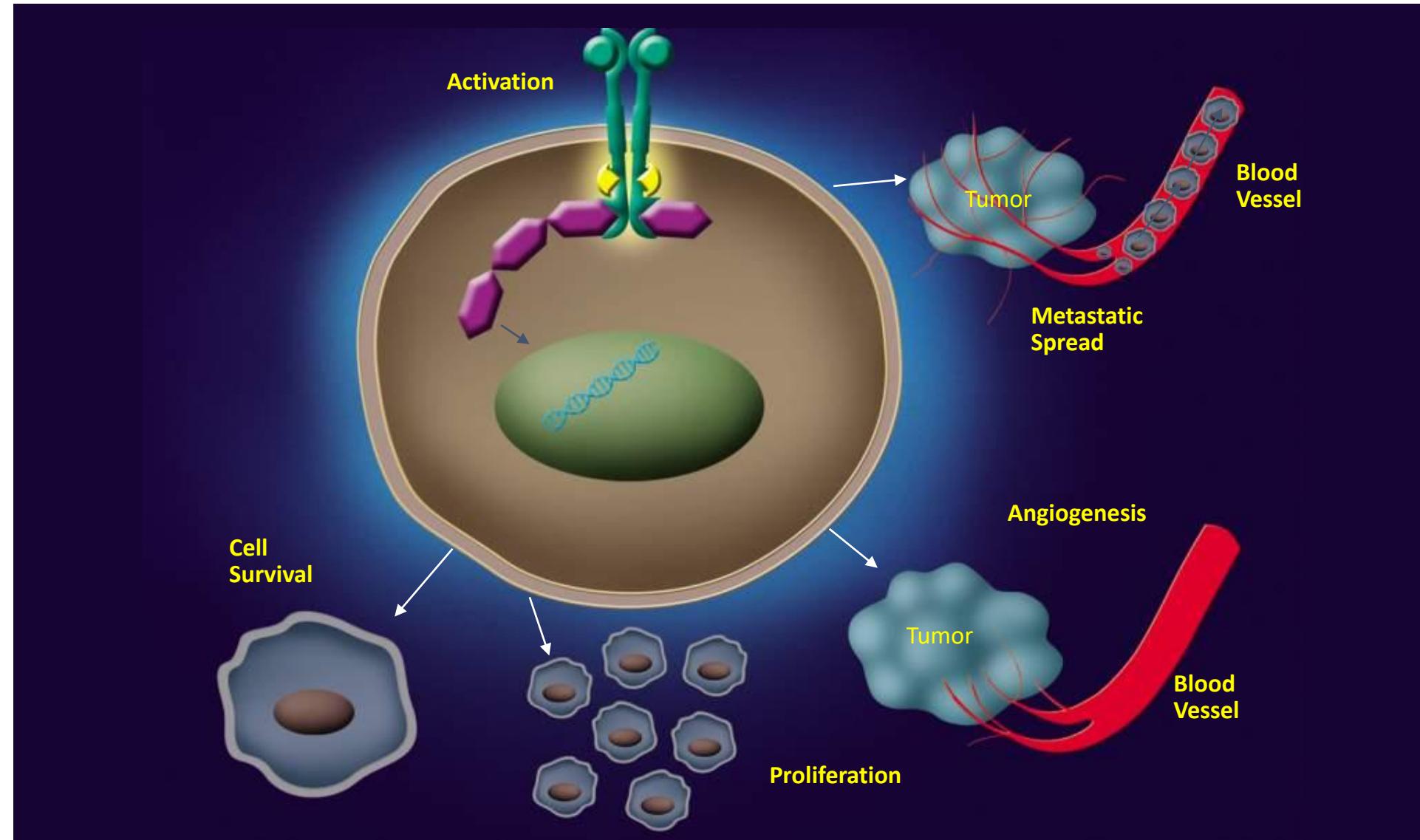
Functie Tyrosine Kinase Receptor



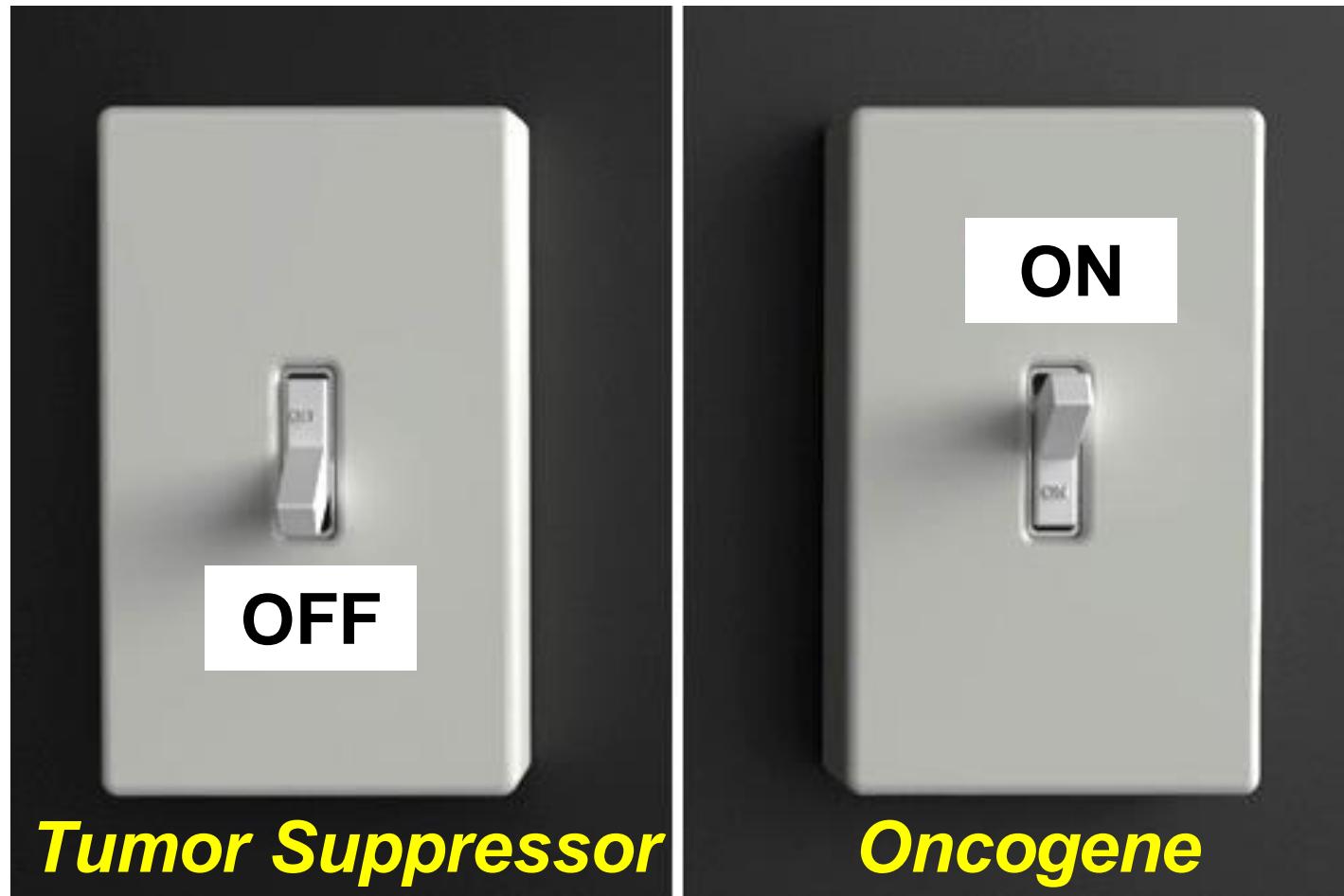
Ligand binding and dimerization: TK Activation



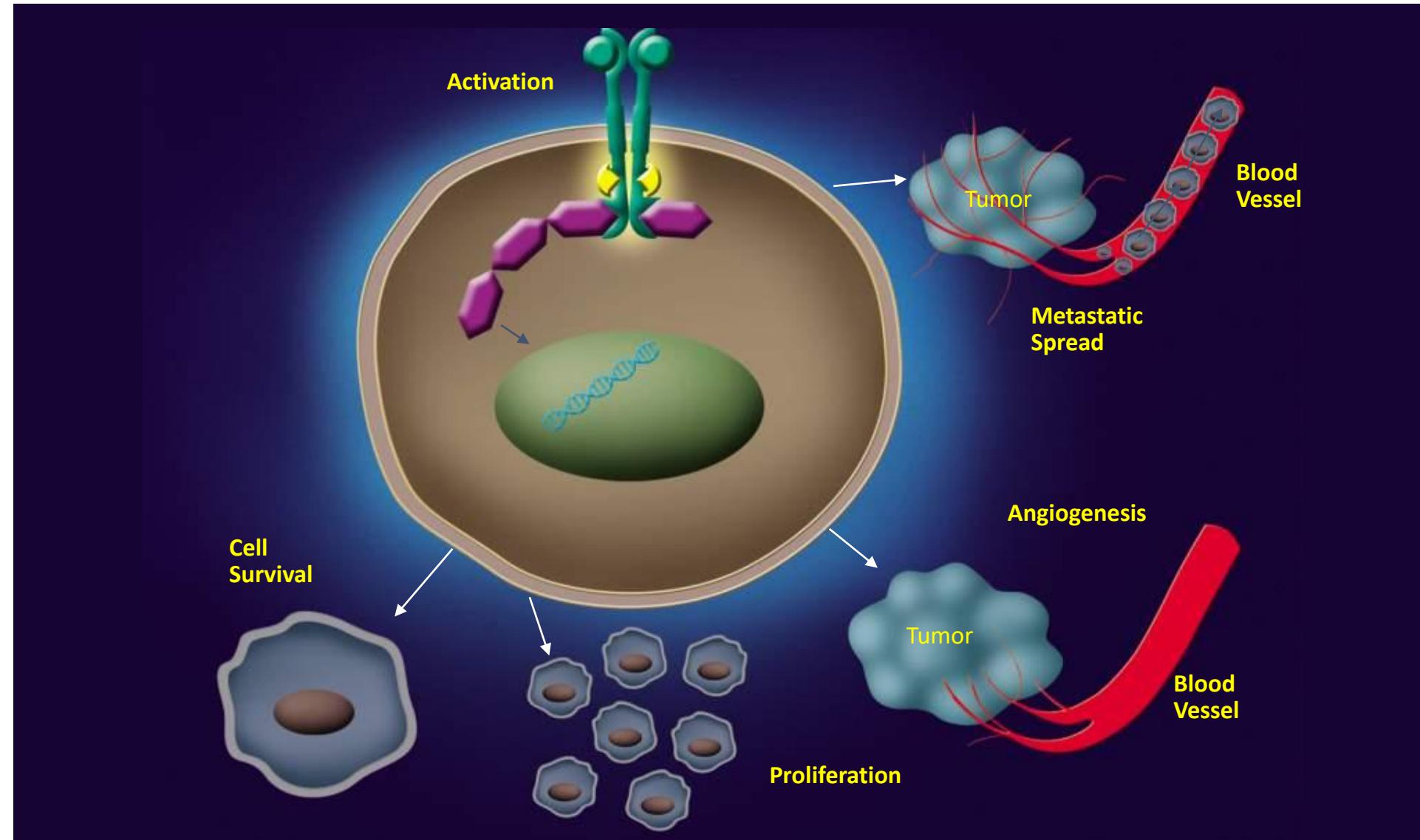
Activation Enhances Pathways Important for Tumor Cell Growth



Fundamental Issues in Biology

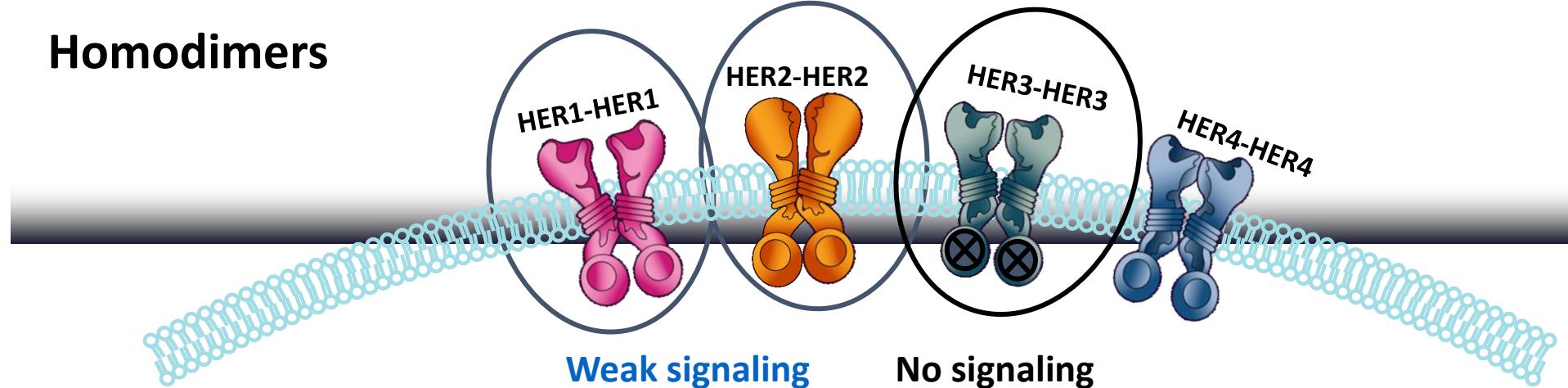


Activation Enhances Pathways Important for Tumor Cell Growth

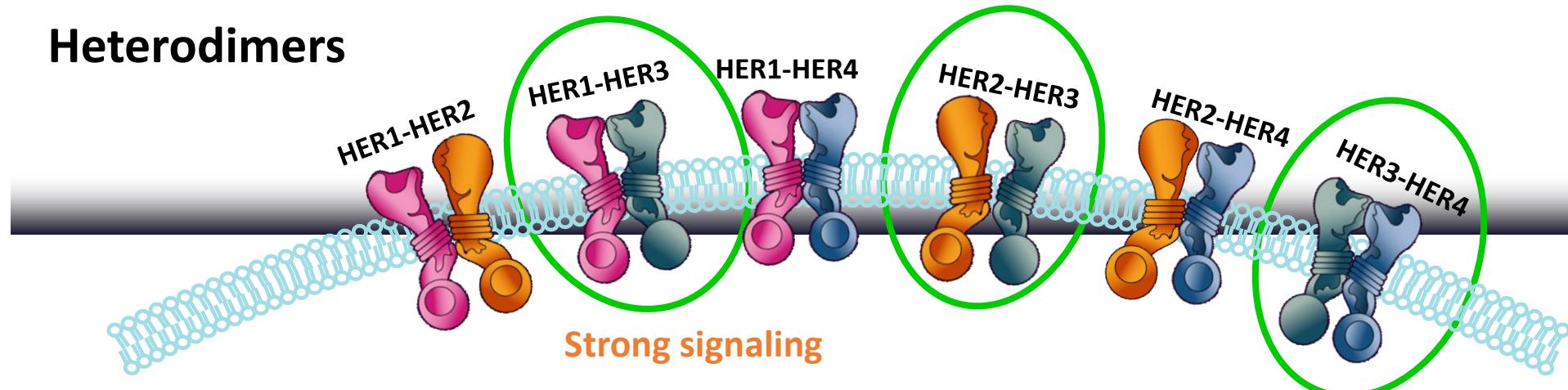


HER Family of Surface Tyrosine Kinases

Homodimers

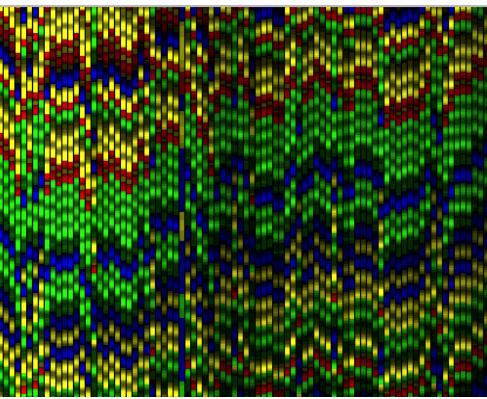
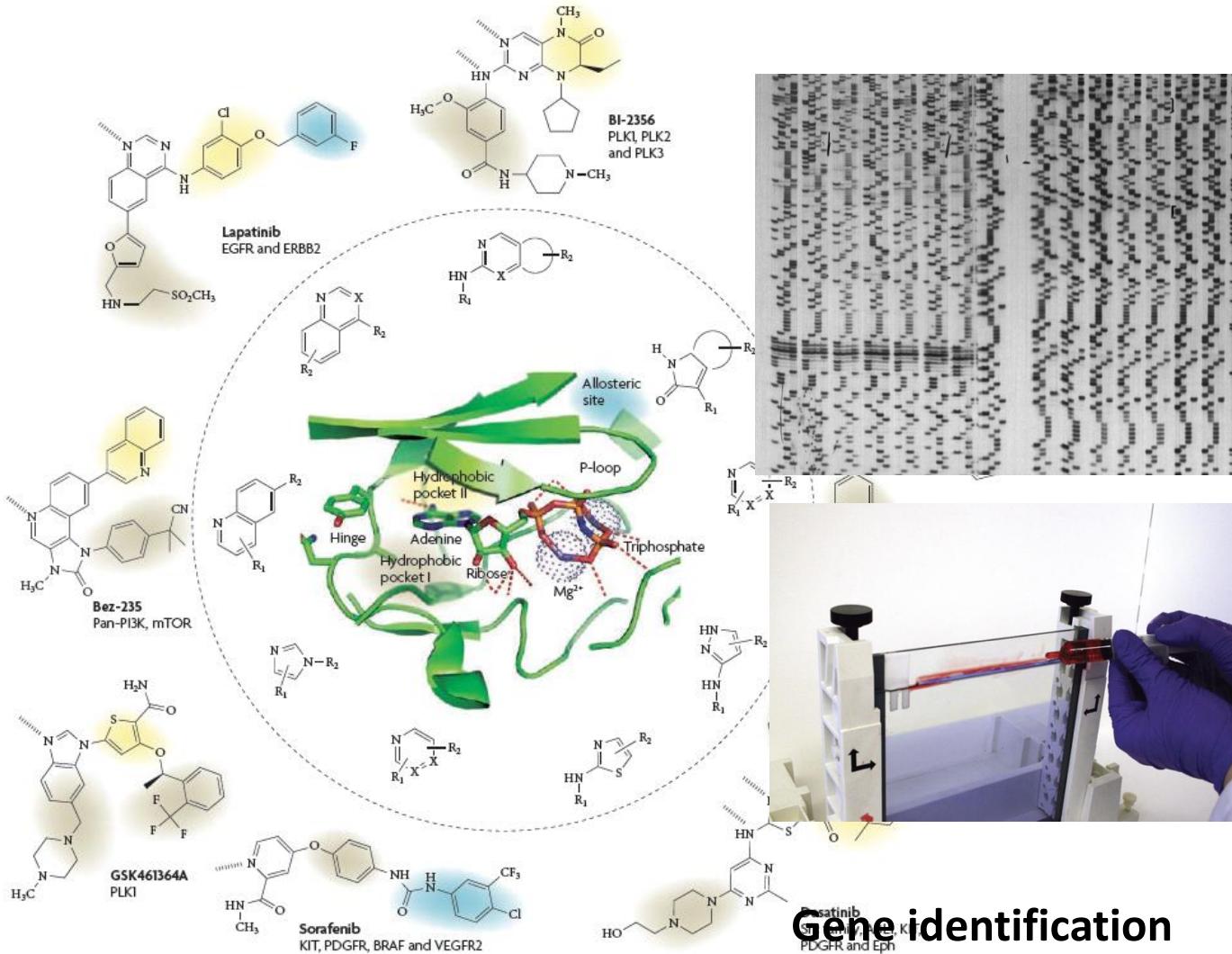


Heterodimers



Rowinsky. *Annu Rev Med.* 2004;55:433; Roskoski. *Biochem Biophys Res Commun.* 2004;319:1;
Herbst. *Int J Radiat Oncol Biol Phys.* 2004;59(suppl):21.

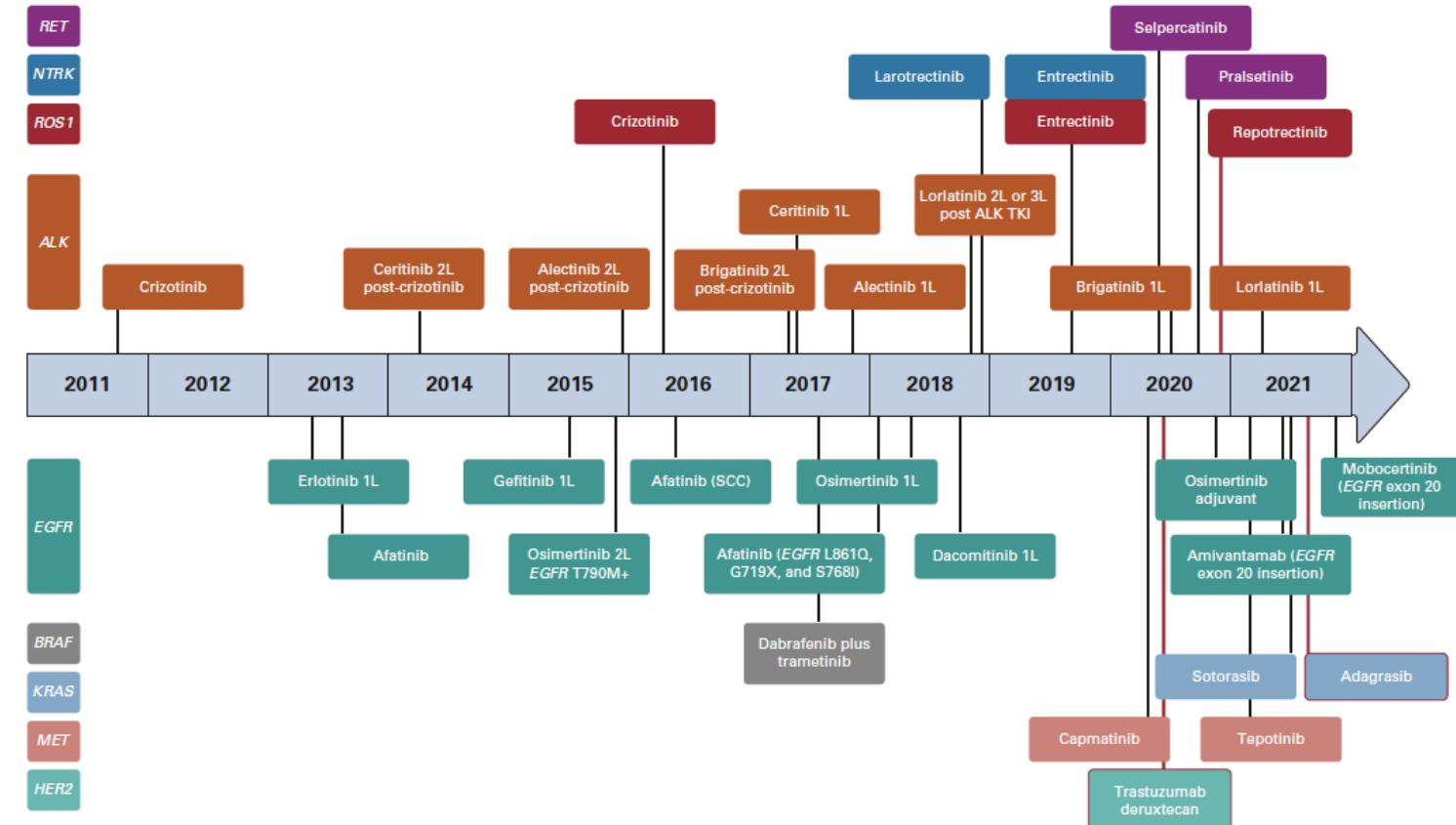
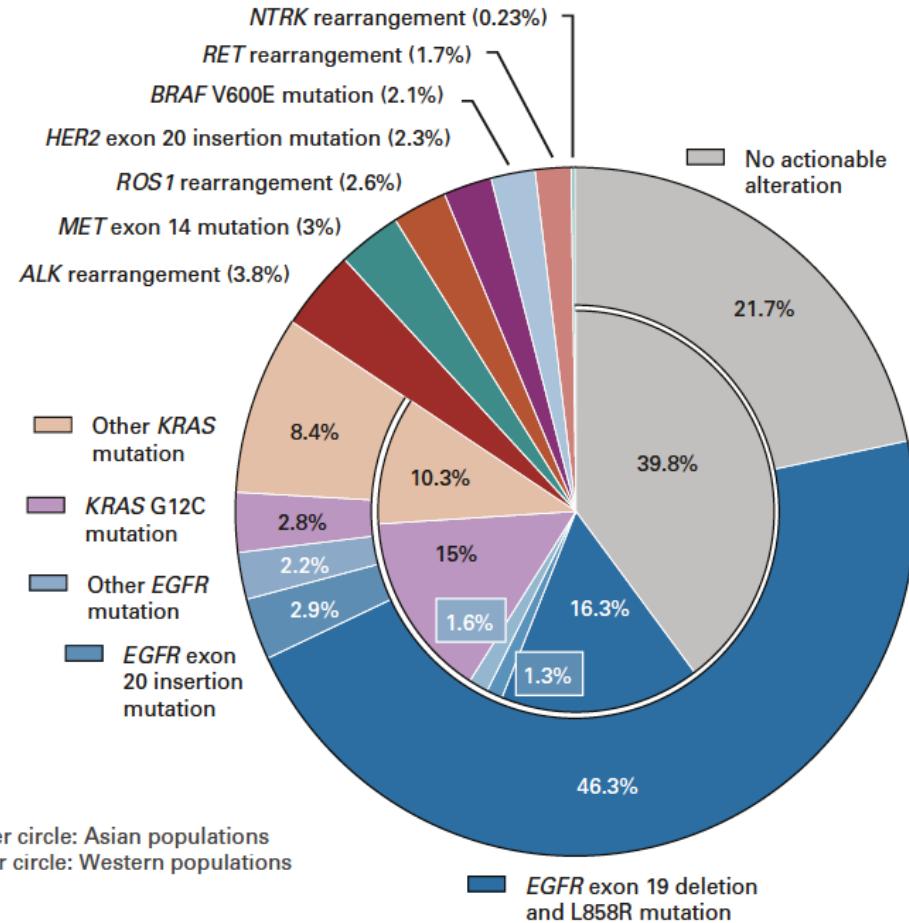
Two developments that fuelled targeted therapies



Reference genome

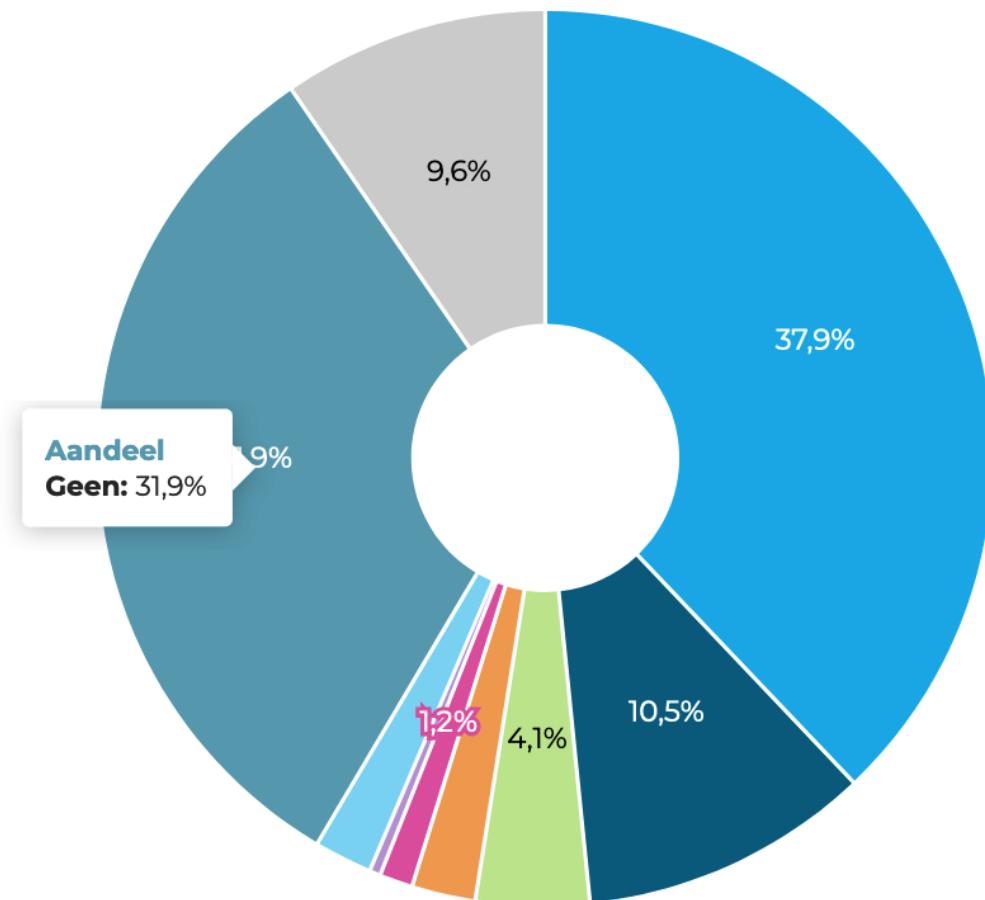
Personalizing treatment in NSCLC

Recent developments stage IV non-squamous NSCLC

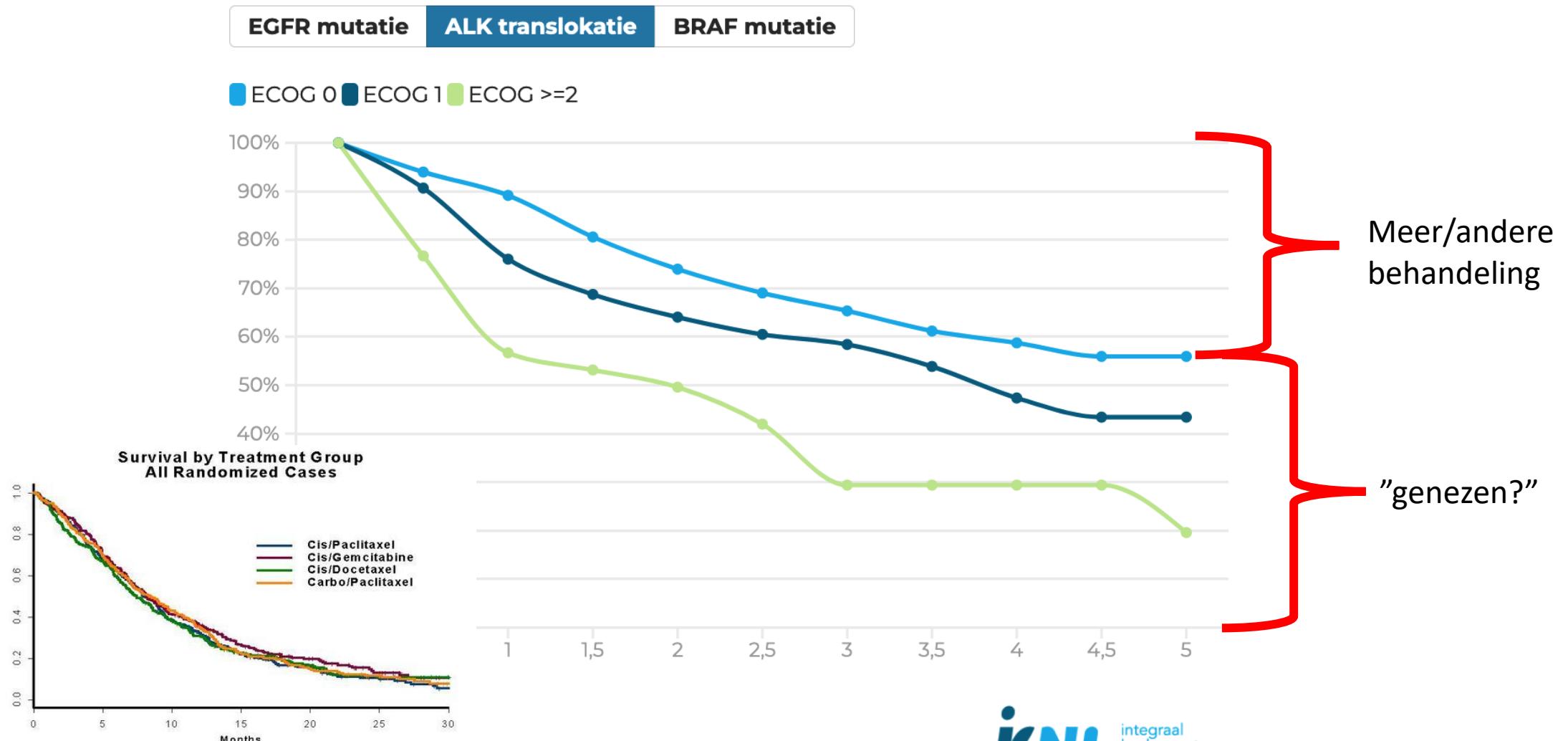


Moleculaire alteraties longkanker stadium IV niet-kleincellig, adenocarcinoom (2021)

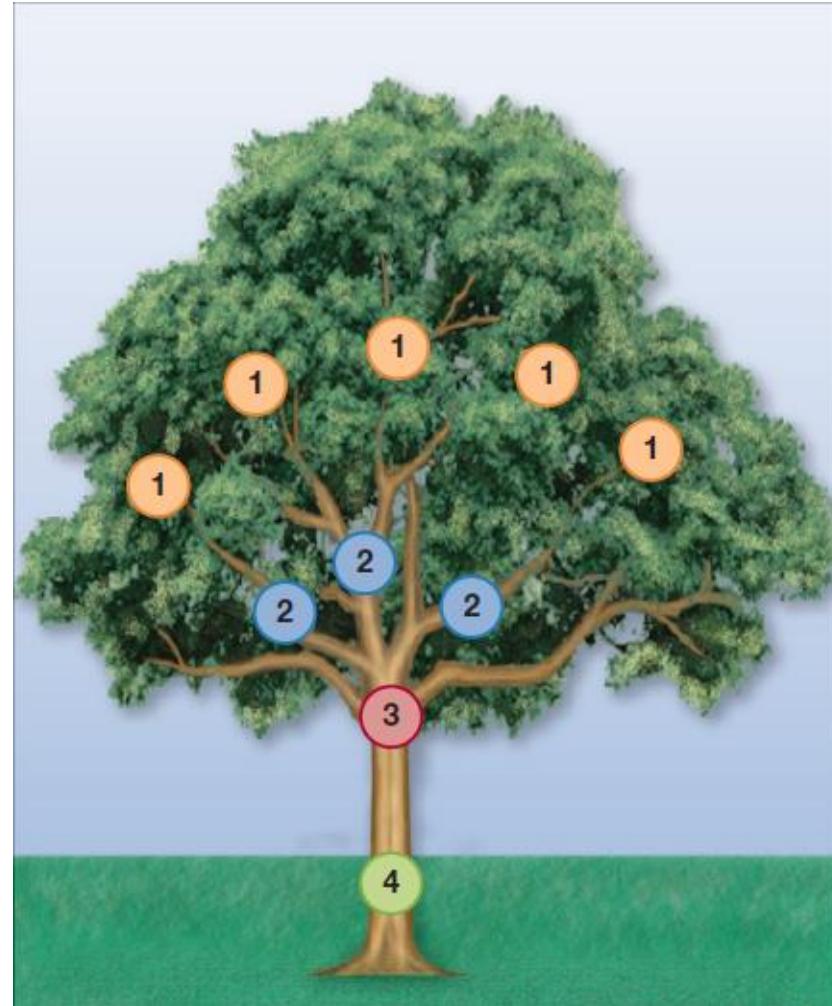
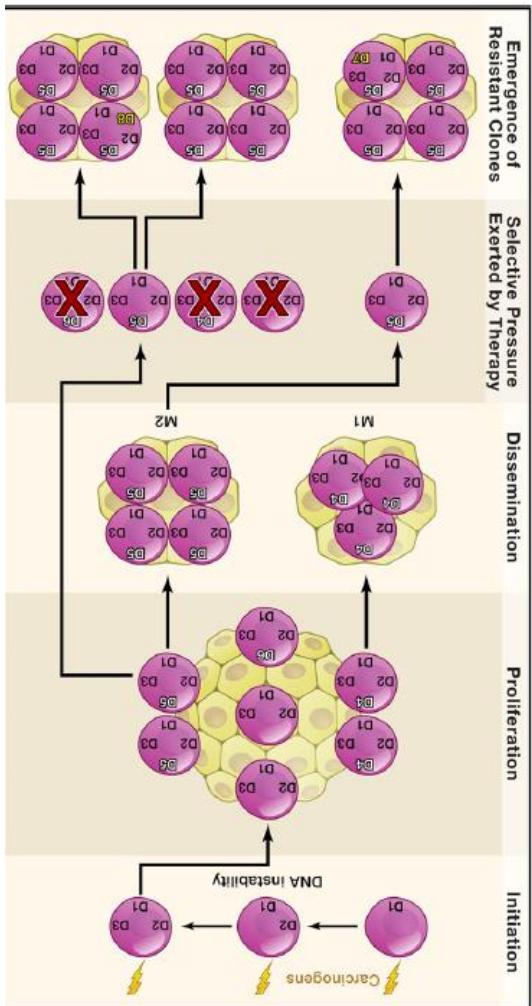
KRAS EGFR BRAF MET ALK ROS1 Overig Geen Niet getest



Overleving bij NSCLC stadium IV met mutaties (2017-2021) eerste lijn doelgerichte medicatie, naar mutatie en ECOG-score

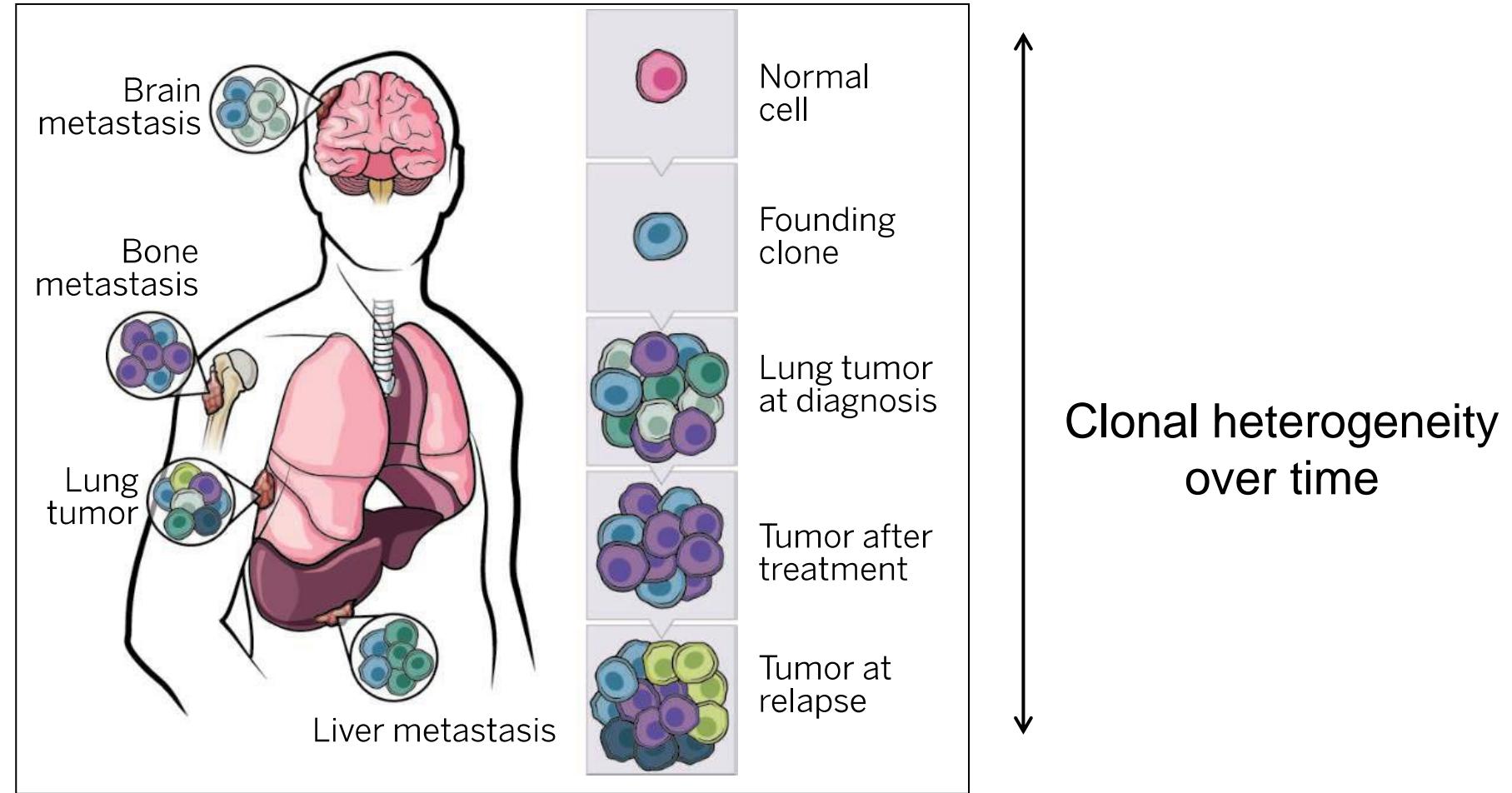


Tumor heterogeneity

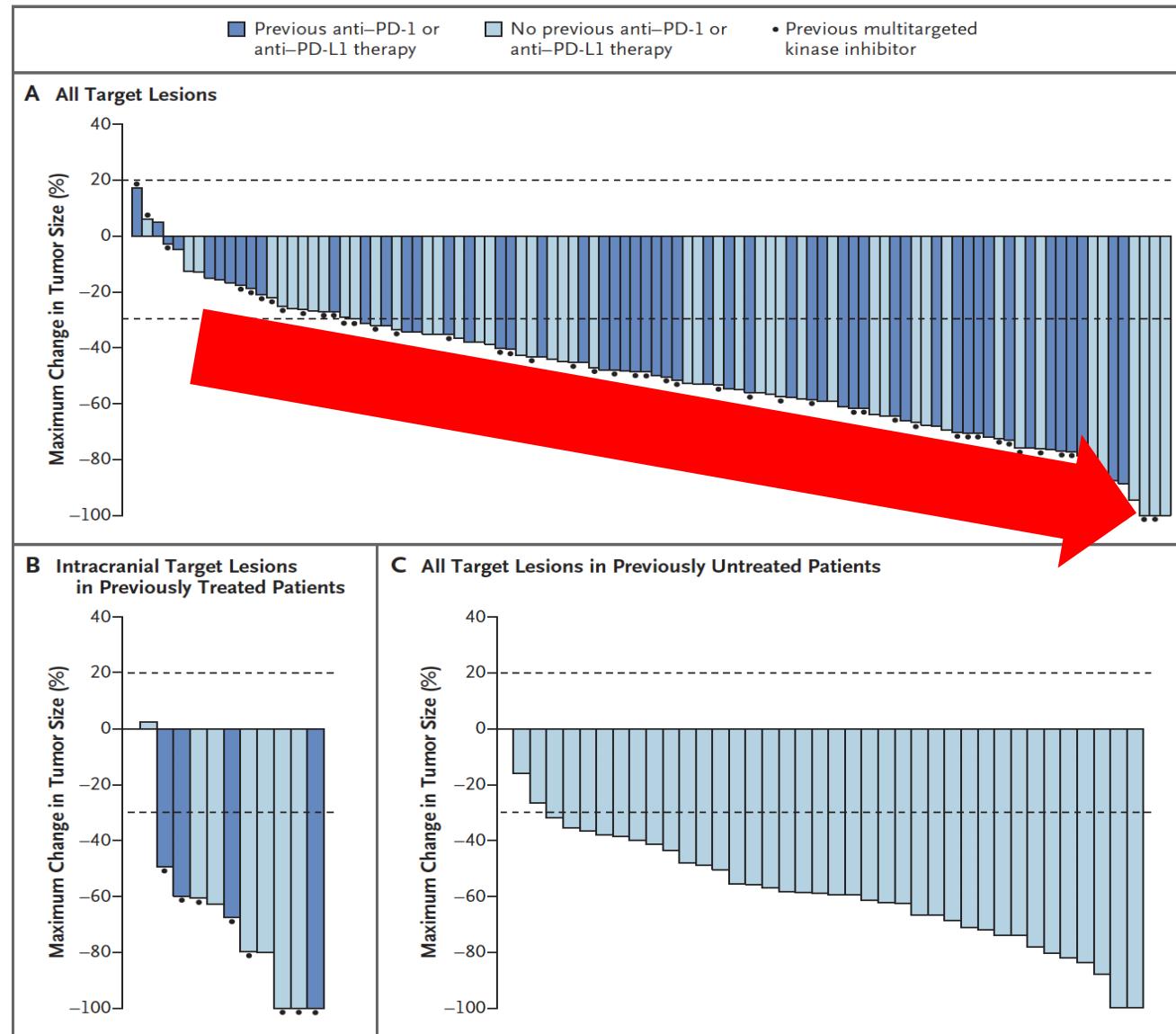


Dencey et al. Cell 2012 (left), Swanton. Cancer Res. 2012 (right)

Major limitation of molecularly guided sequential therapy: tumor heterogeneity



LIBRETTO-001: tumor shrinkage



High CNS ORR (10/11)
Duration of CNS-response:
10.1 months

Drilon et al, NEJM 2020

Where are we now?

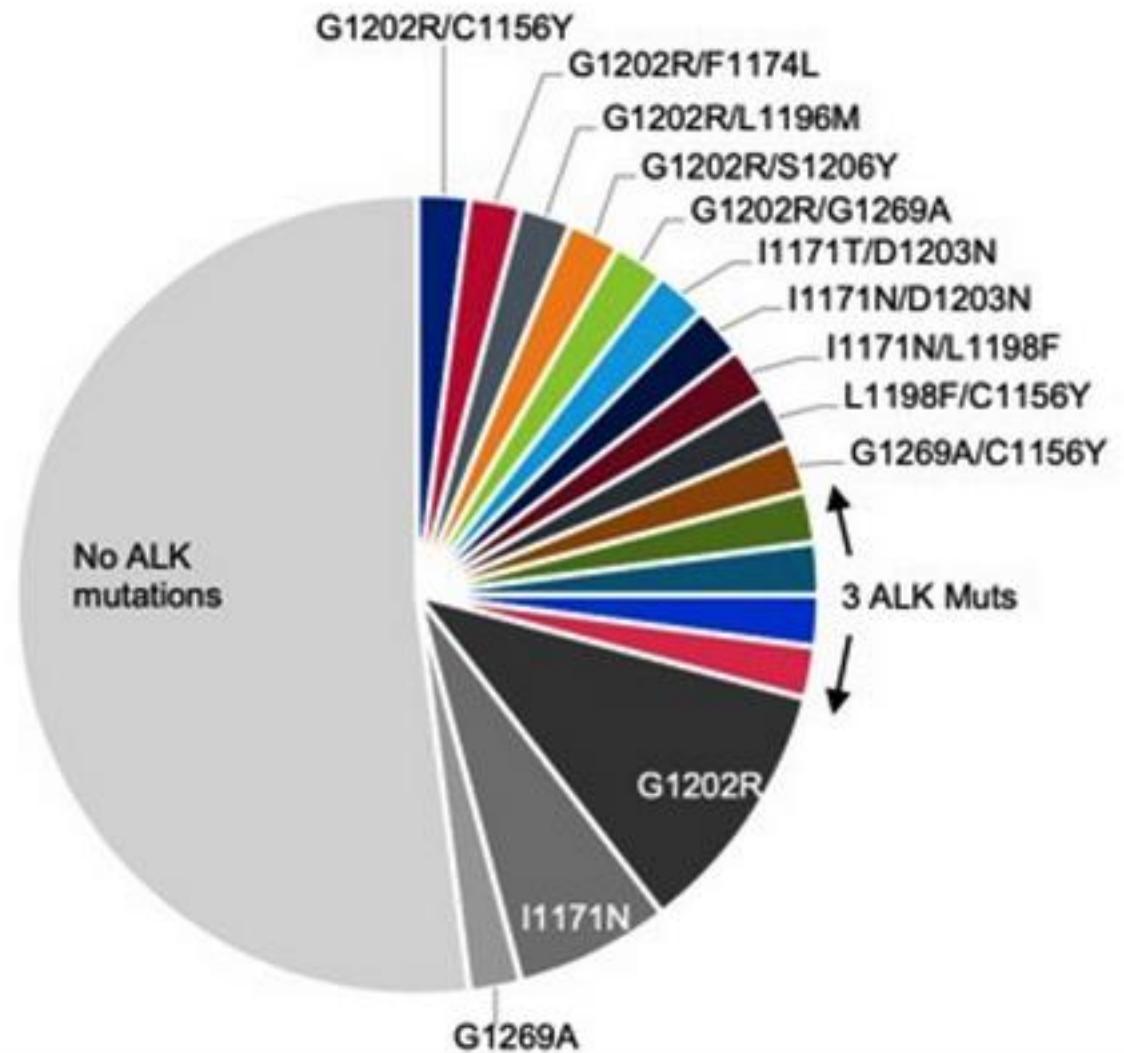
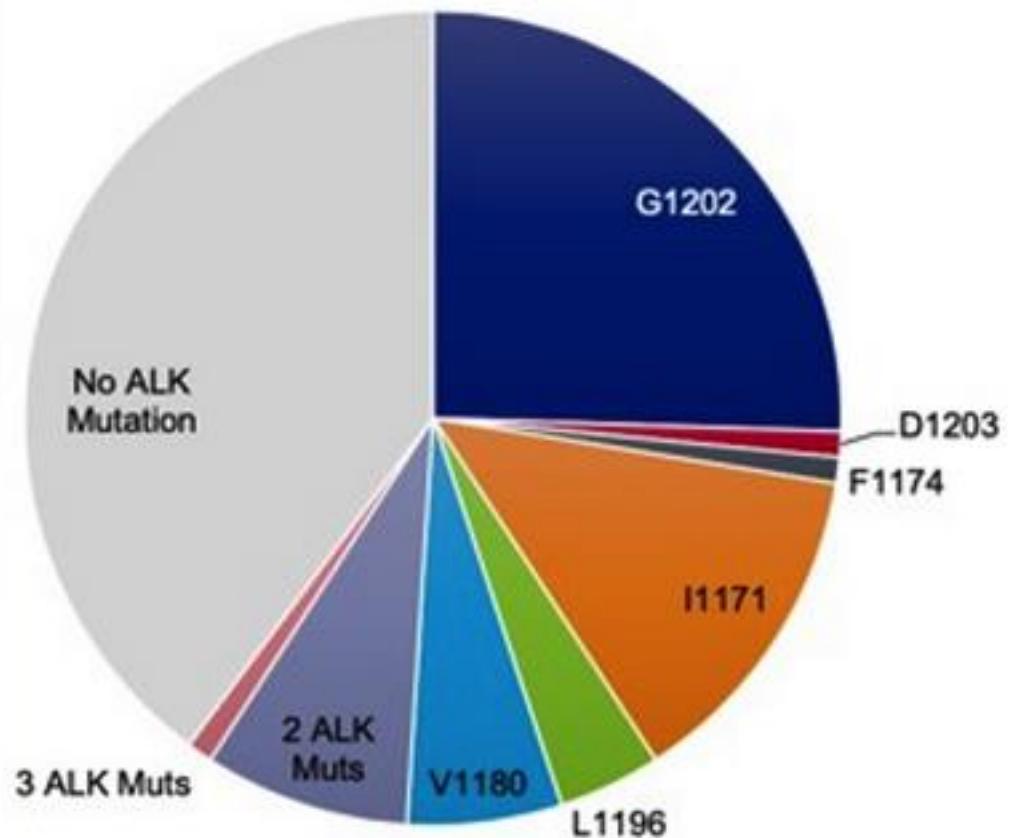


So where are we now?

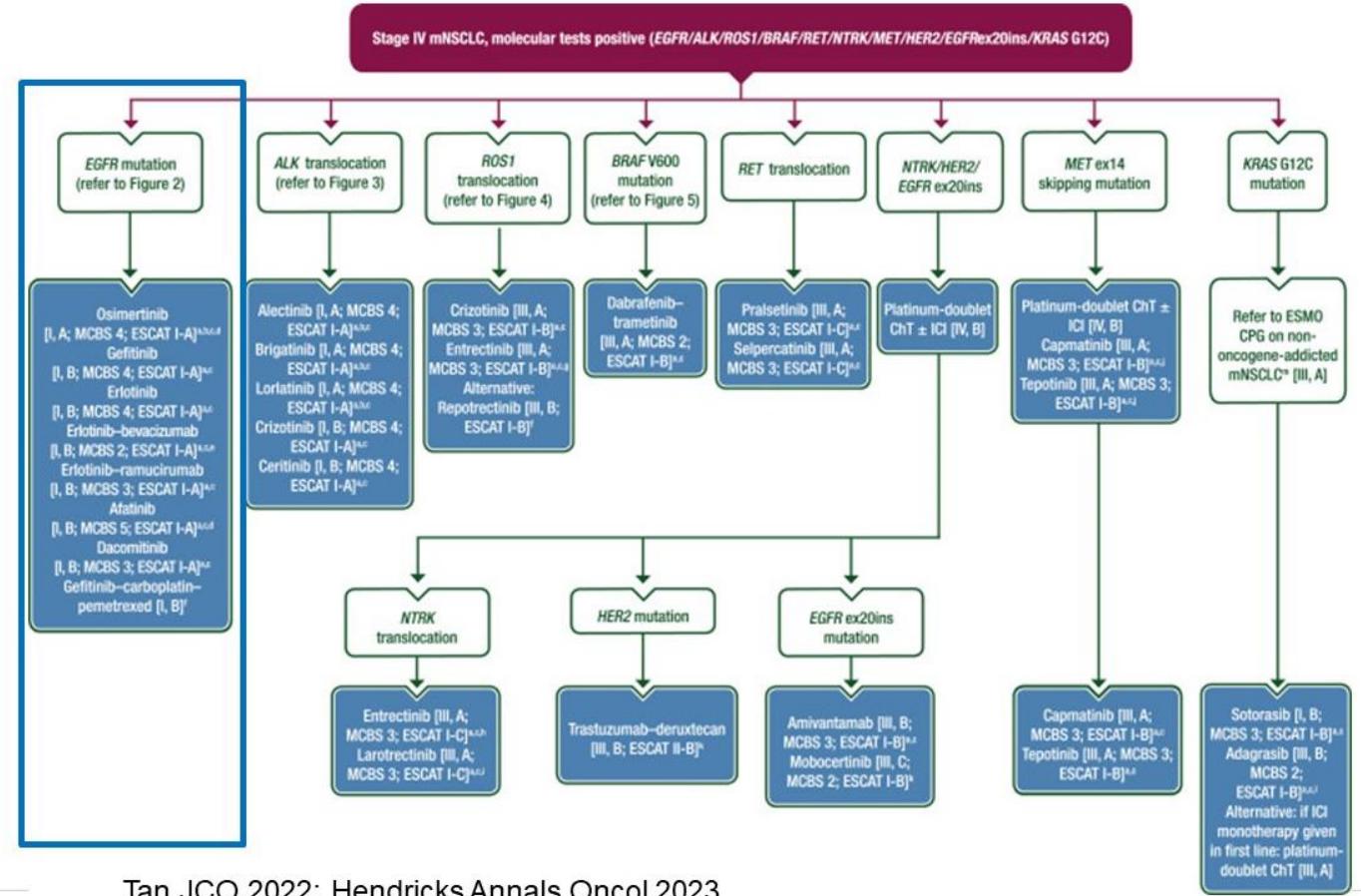
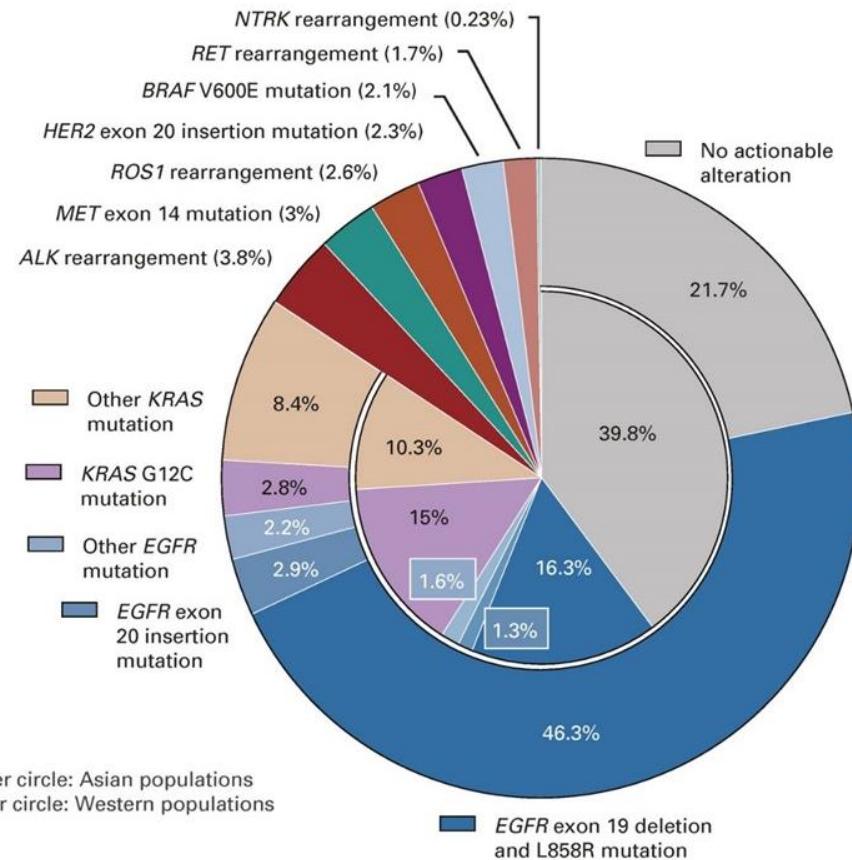
- Growing list of molecular targets and small molecule TKI's
- Increasing OS over the last years, no cure
- Hitting the target harder invariably leads to
 - Further "hard to treat" mutations
 - Off target resistance

2nd-Gen TKI

Lorlatinib



Welke doelgerichte behandelingen zijn beschikbaar?



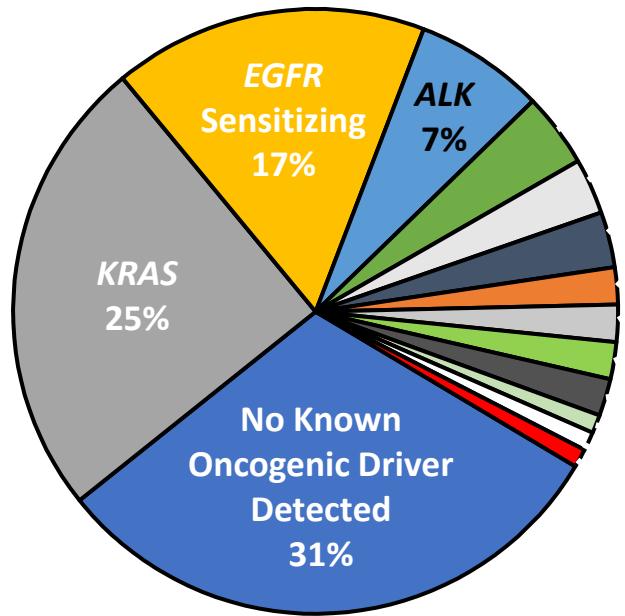
Tan JCO 2022; Hendricks Annals Oncol 2023

Welke zijn beschikbaar en vergoed in Nederland?

- Alk: crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
- cMET: tepotinib (DAP studie)
- B-RAF: dabrafenib-trametinib
- ROS1: crizotinib, lorlatinib
- RET: selpercatinib (DAP)
- NTrk: entrectinib, larotrectinib (DAP)

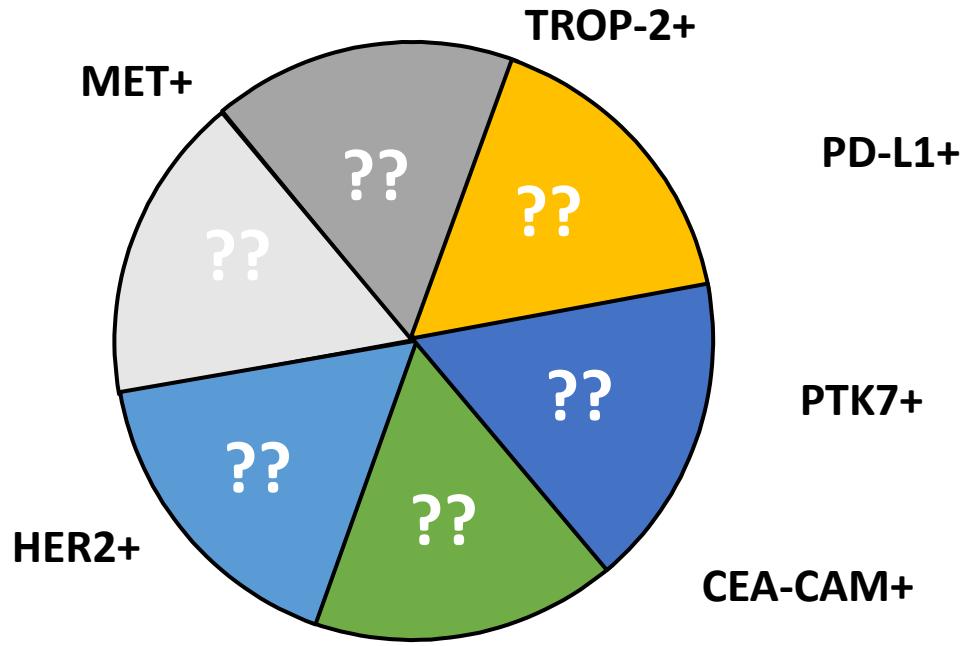
Nieuwe klasse geneesmiddelen: ADC's

Adenocarcinoma



AND

All NSCLC



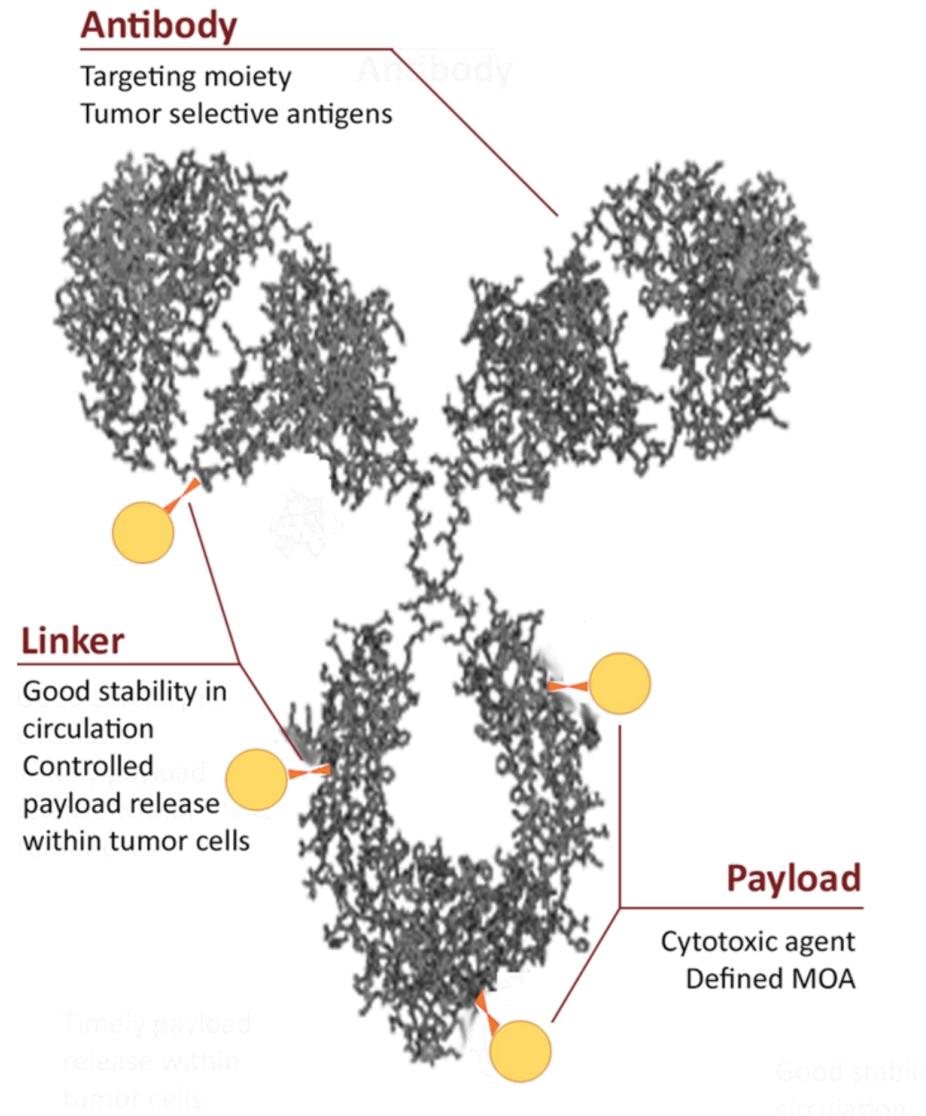
Histology-Based Subtyping

+

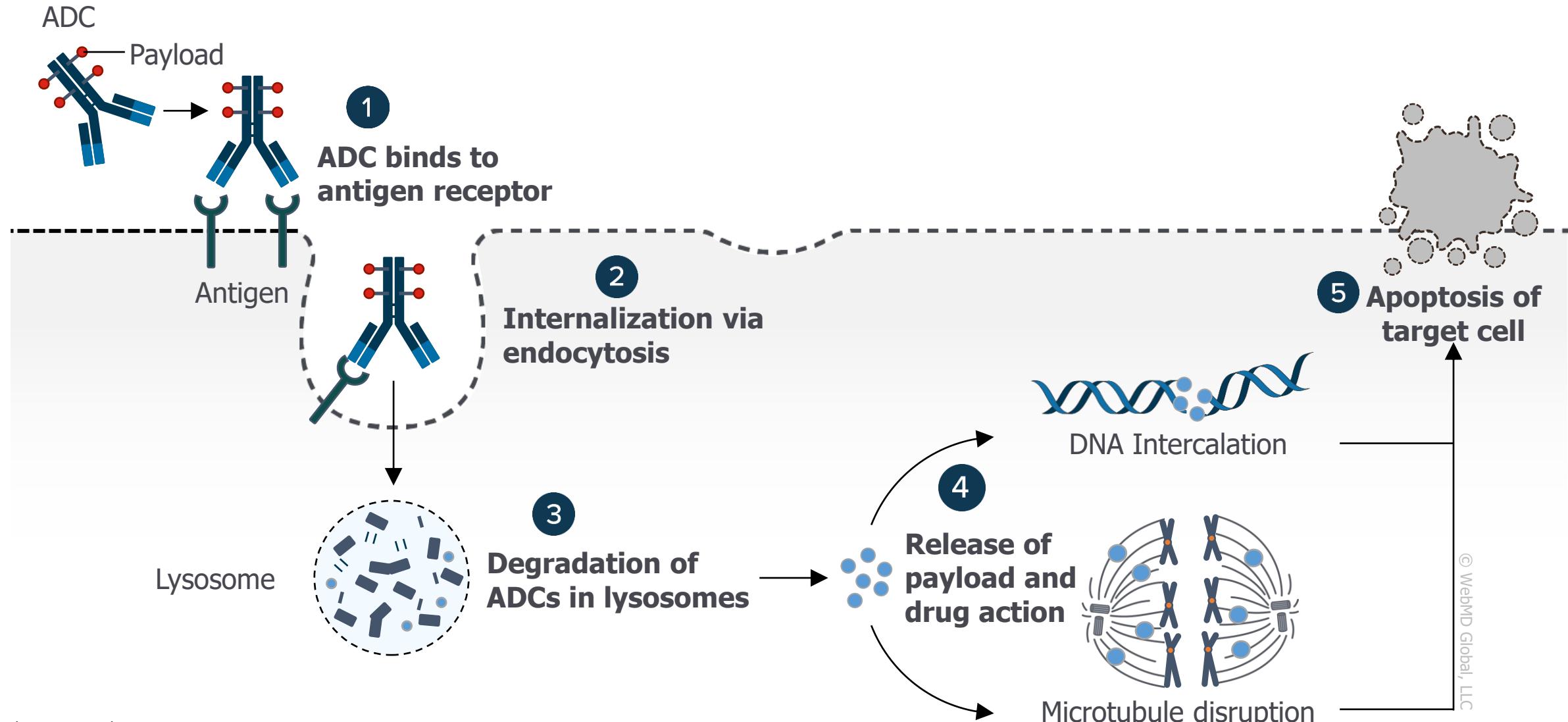
Protein Subtyping

Antibody Drug Conjugates (ADC): True Targeted Therapy

- ADC represent targeted delivery system, potentially shifting efficacy: toxicity ratio of attached drug.



Antibody-Drug Conjugates Key Steps of Action



HER2 in lung cancer

- Protein overexpression (IHC 2+ or 3+) in 12%–20% of cases
- Activating mutations in ~2%–3% of cases
- Amplification in ~ 3% of cases, around 10% of cases in EGFR TKI resistance
 - ✓ HER2 amplification and mutations do not usually occur together

Li JTO 16, Nakamura Int J Cancer 03, Yoshizawa Lung Cancer 14

HER2 mutations in lung ADC

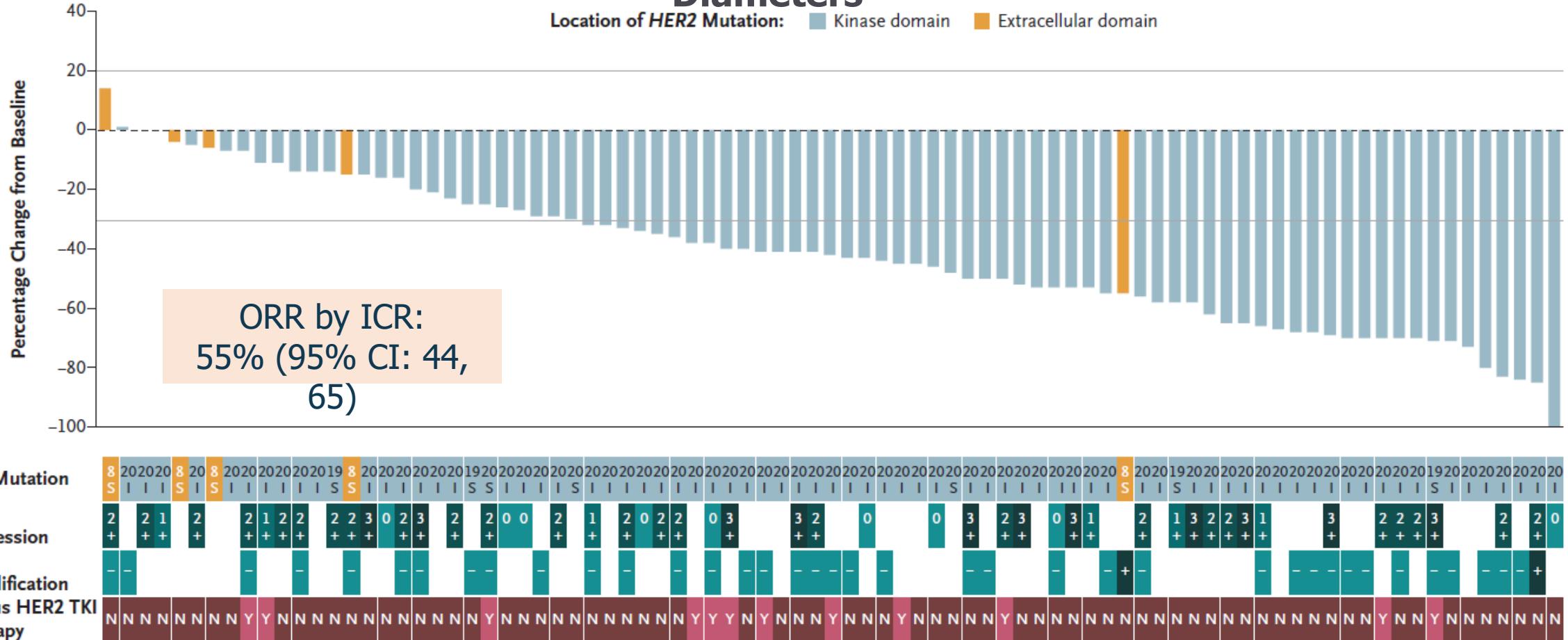
Querying 5413 patients/5697 NSCLC samples
ERBB2 Somatic Mutation Frequency: 2.5%



- More common in women, never smokers
- HER2 kinase domain-mutations in exon 20, the most common the YVMA insertion at codon 775

DESTINY-Lung01: T-DXd in *HER2*-Mutated Cohort *Response*

Best Percentage Change in Sum of Tumor Diameters



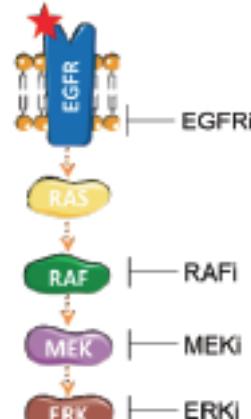
- Li BT, et al. N Engl J Med. 2022;386:241-251.

Waar gaat het naar toe?

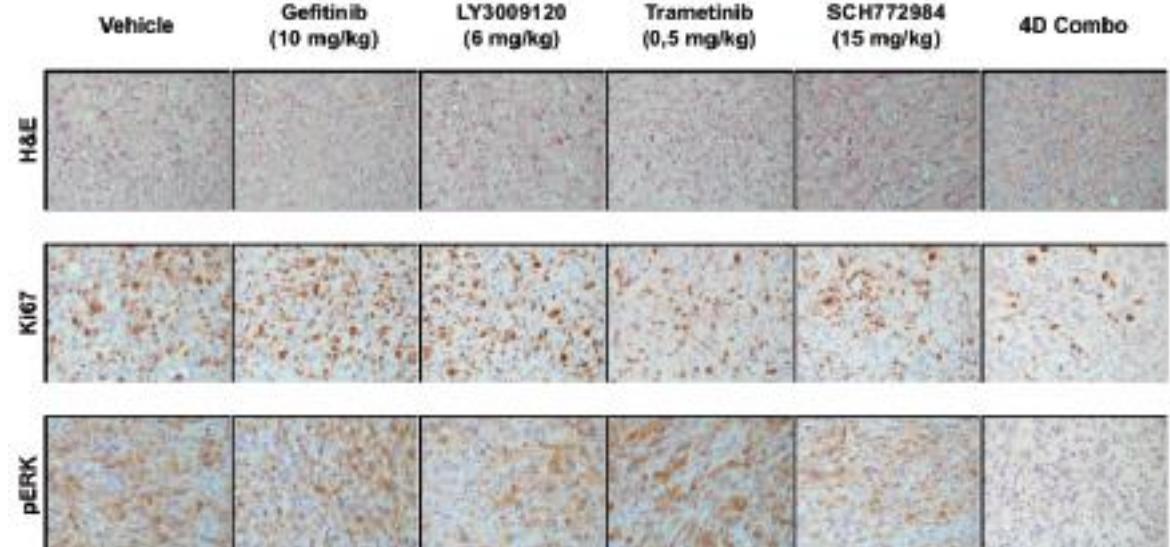
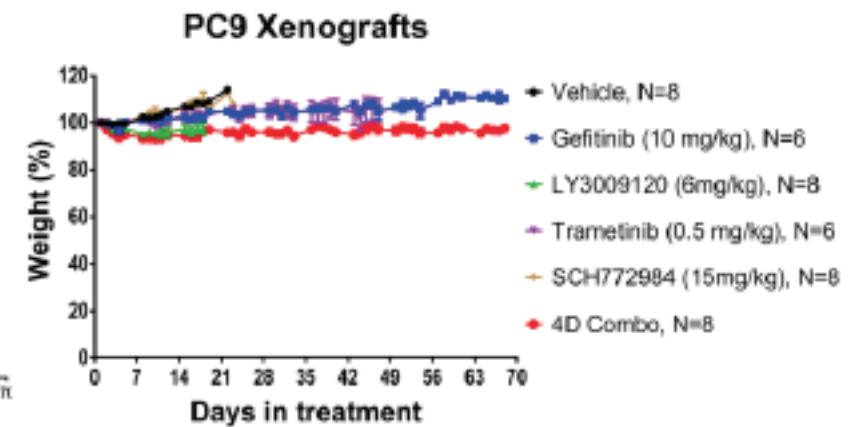
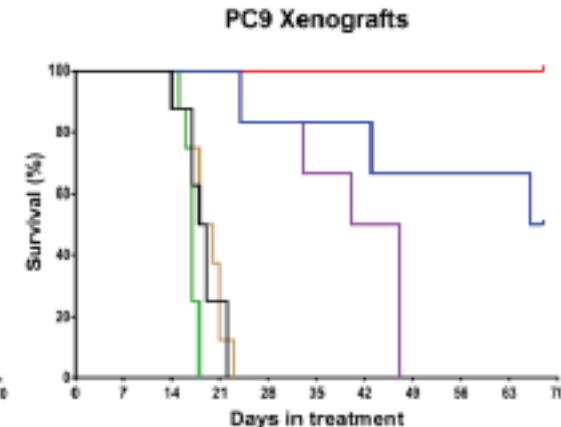
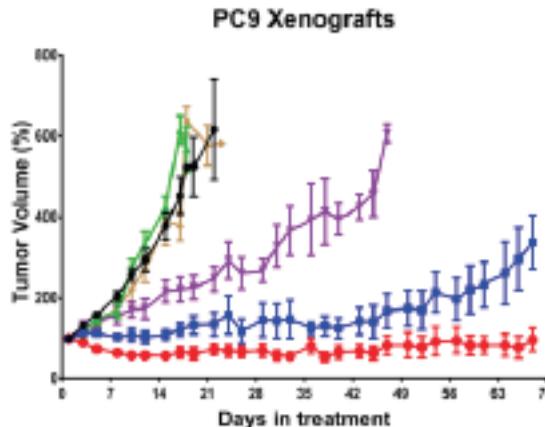


Novel strategies are needed for cure

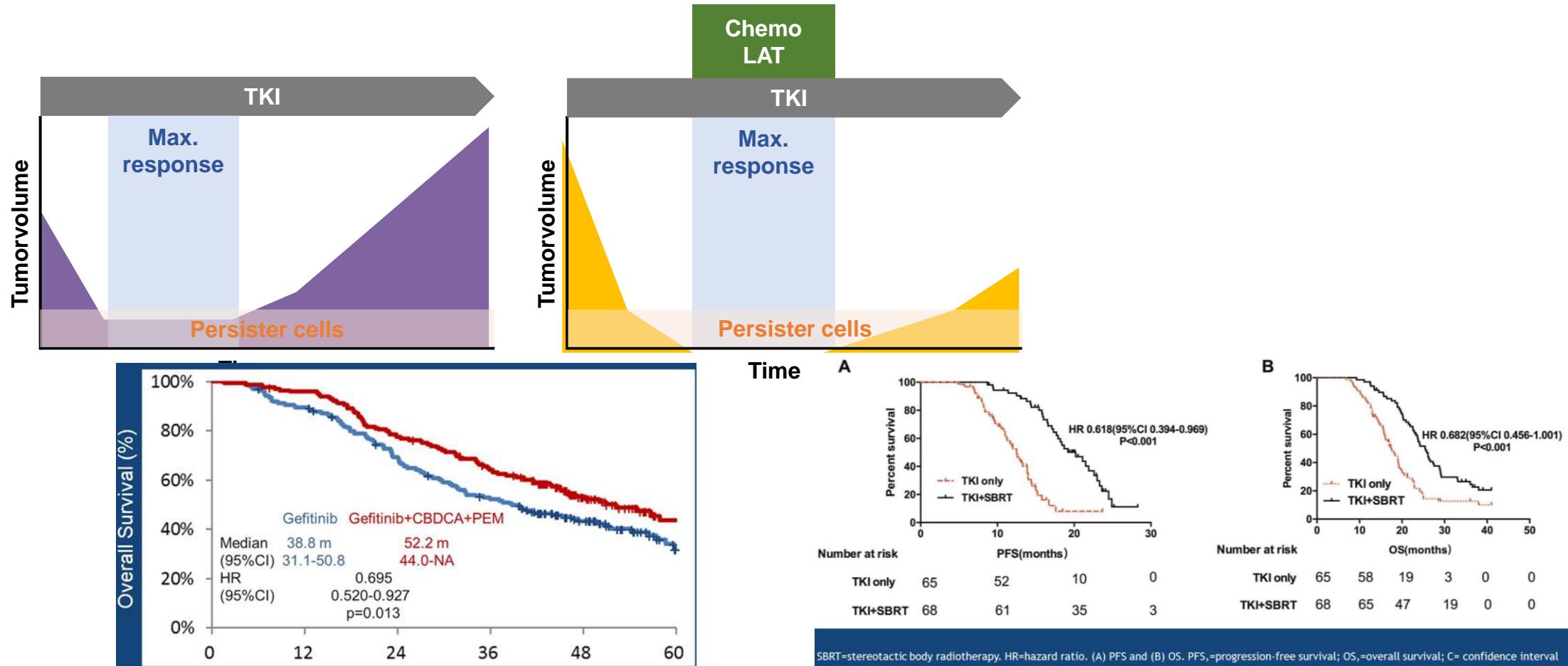
Low dose vertical targeting strategy



- Sustained pathway inhibition
- Apoptosis
- Resistance prevention



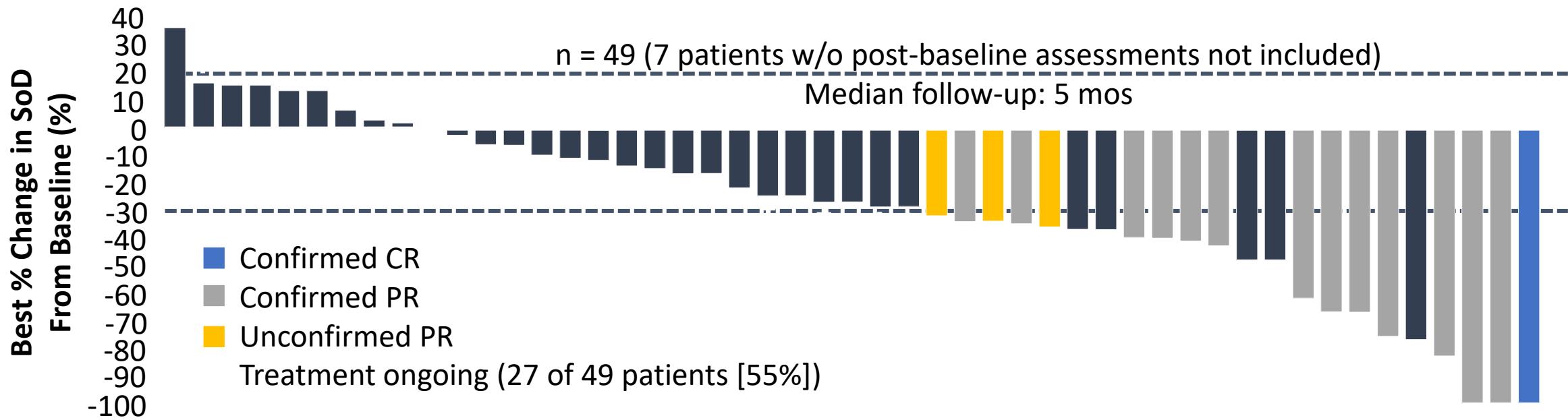
Combinations of targeted and untargeted treatment



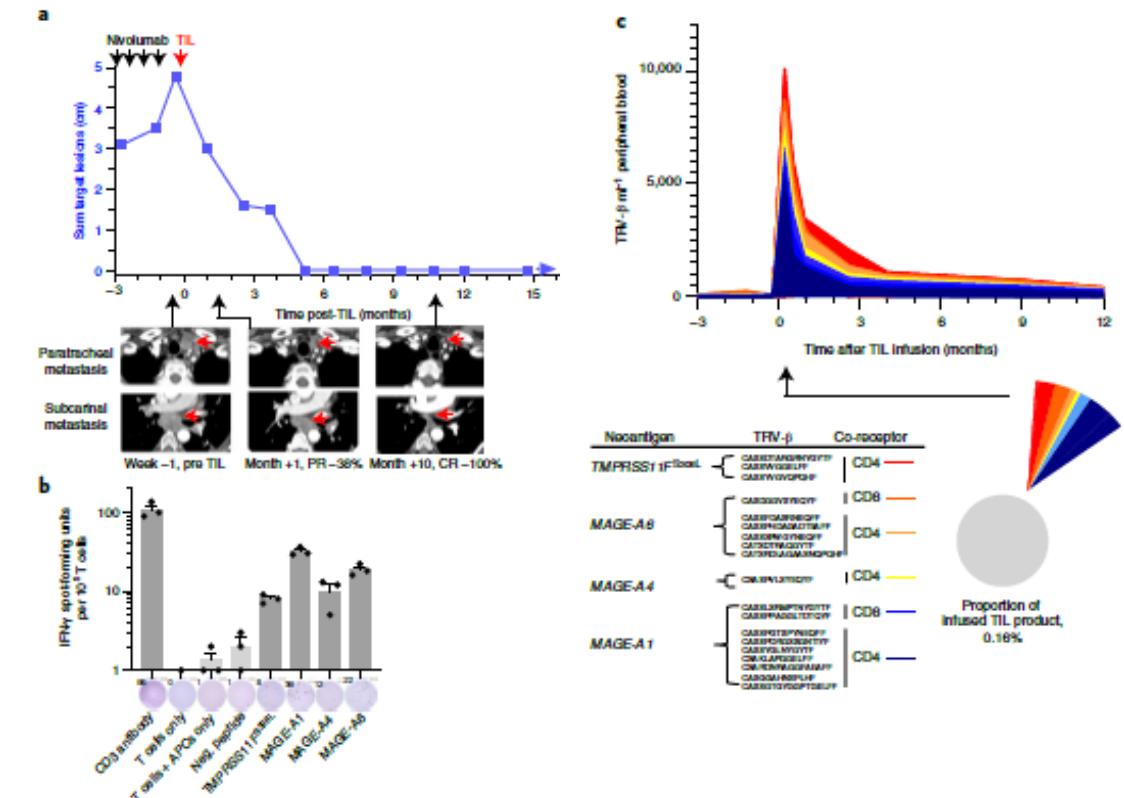
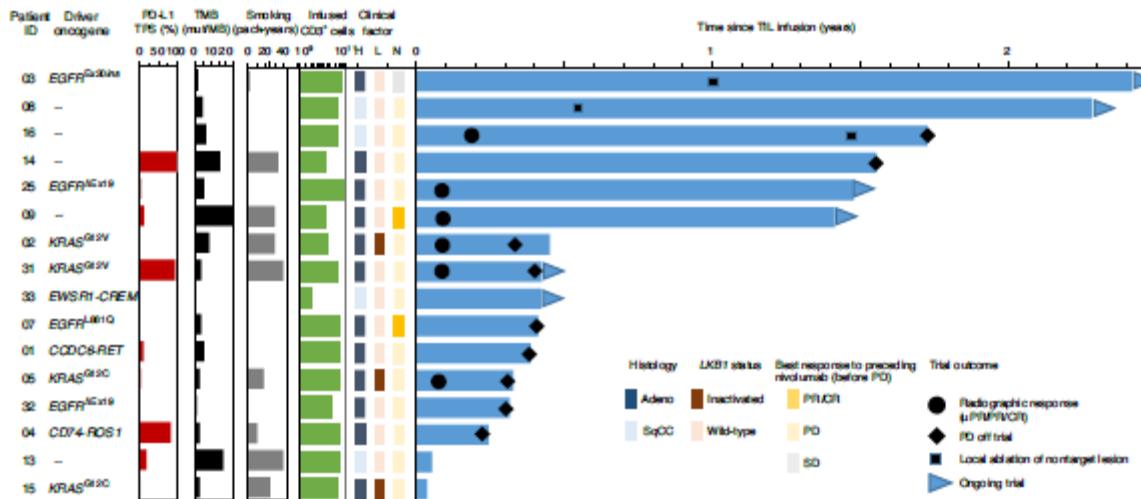
Nakamura et al. ASCO 2018

Wang et al. ASCO 2020

Patritumab Deruxtecan in *EGFR*+ NSCLC with Resistance to Prior TKI Therapy: Phase I Results



Untargeted treatment: TIL for NSCLC after PD-1 failure





Dank voor uw aandacht
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