WEBINAR

Longkanker met mutaties

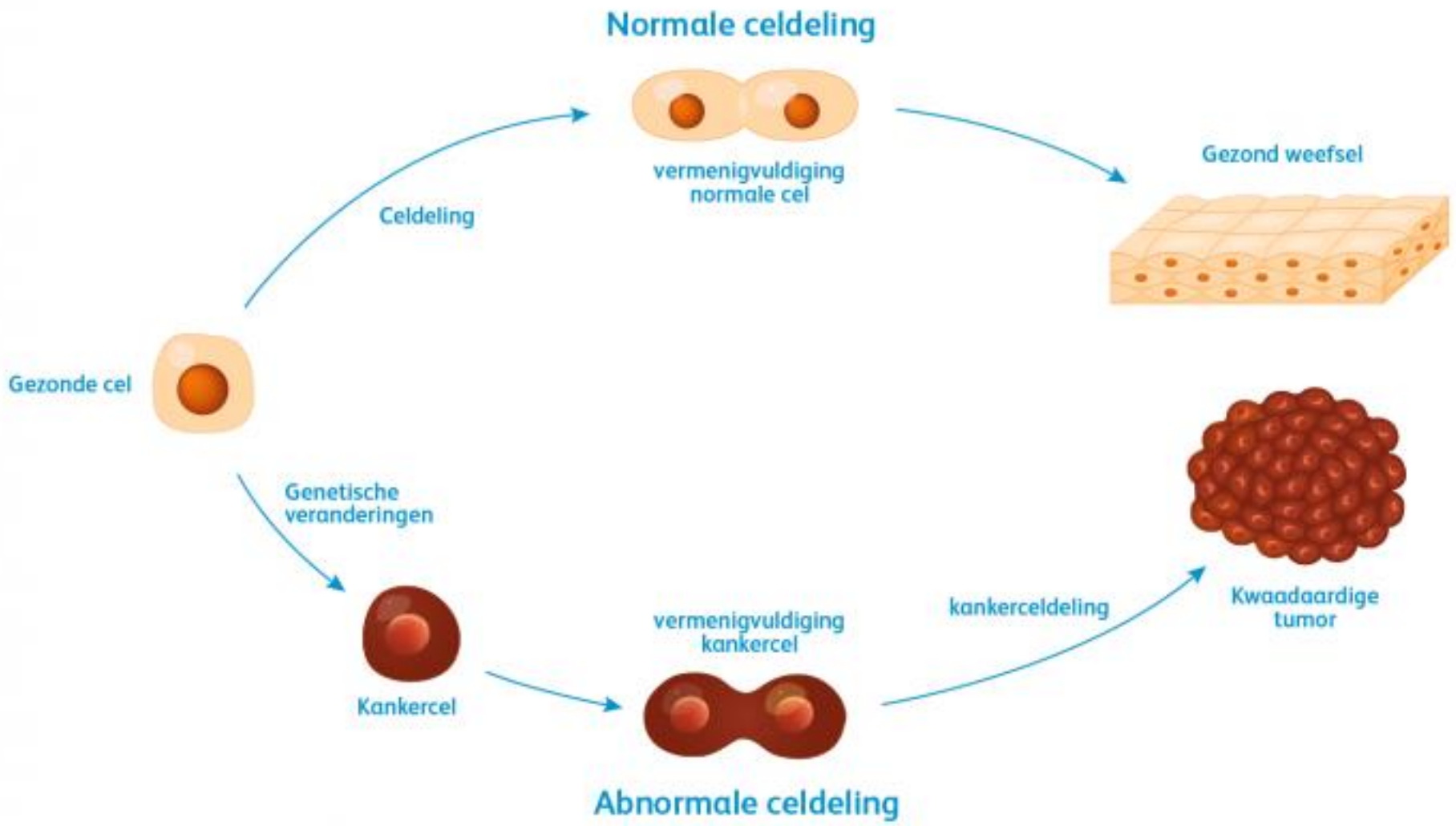
Robin Cornelissen

Erasmus MC
Universitair Medisch Centrum Rotterdam
Kanker Instituut

DISCLOSURES

Commercial Interest	Relationship(s)
Speakers fee	Roche, Pfizer, BMS
Advisory board	MSD, Roche, spectrum, janssen

Ontwikkeling kankercellen



Aantallen

Menselijk lichaam bestaat uit cellen

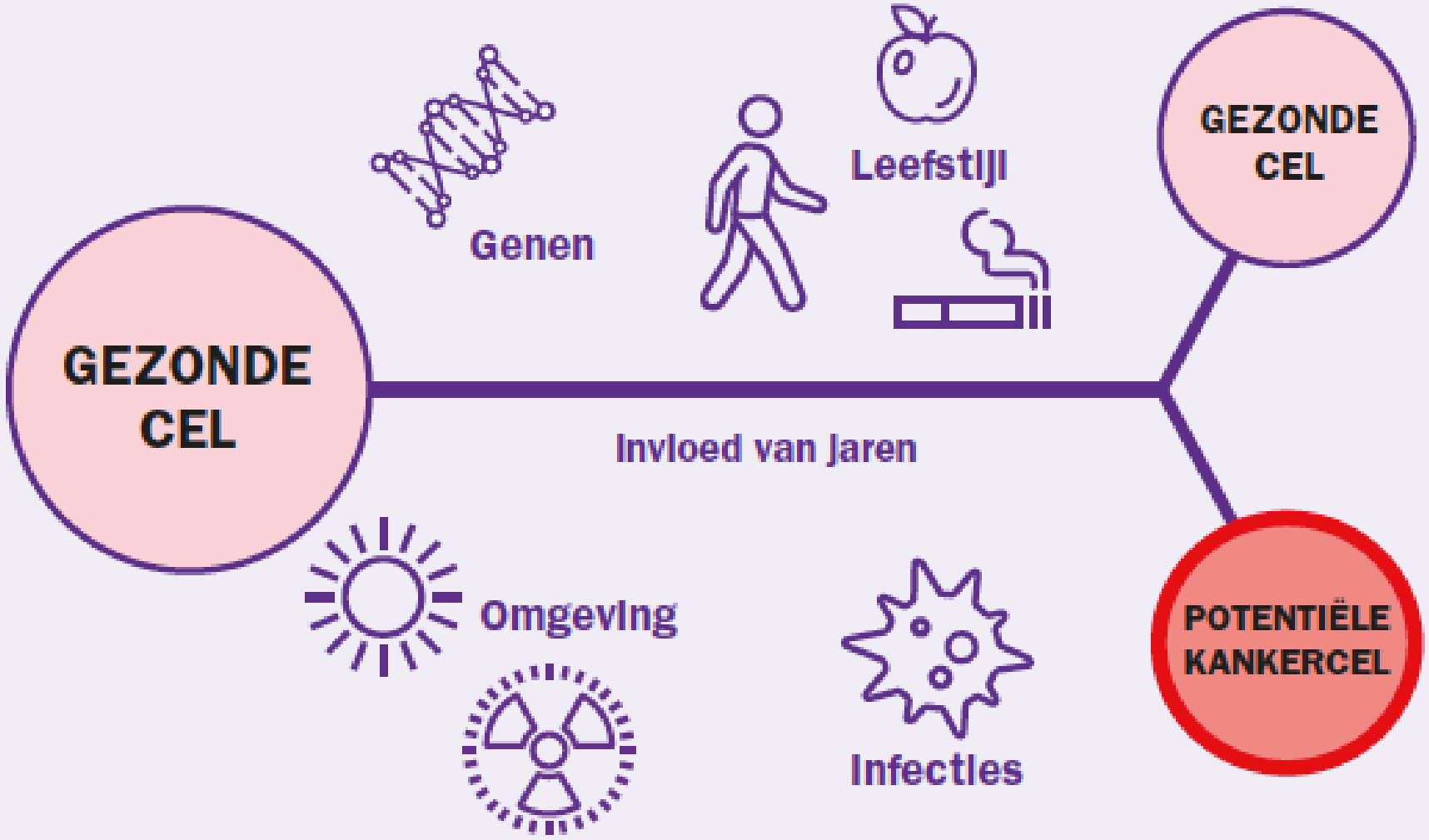
man 36 biljoen cellen (36.000.000.000.000)

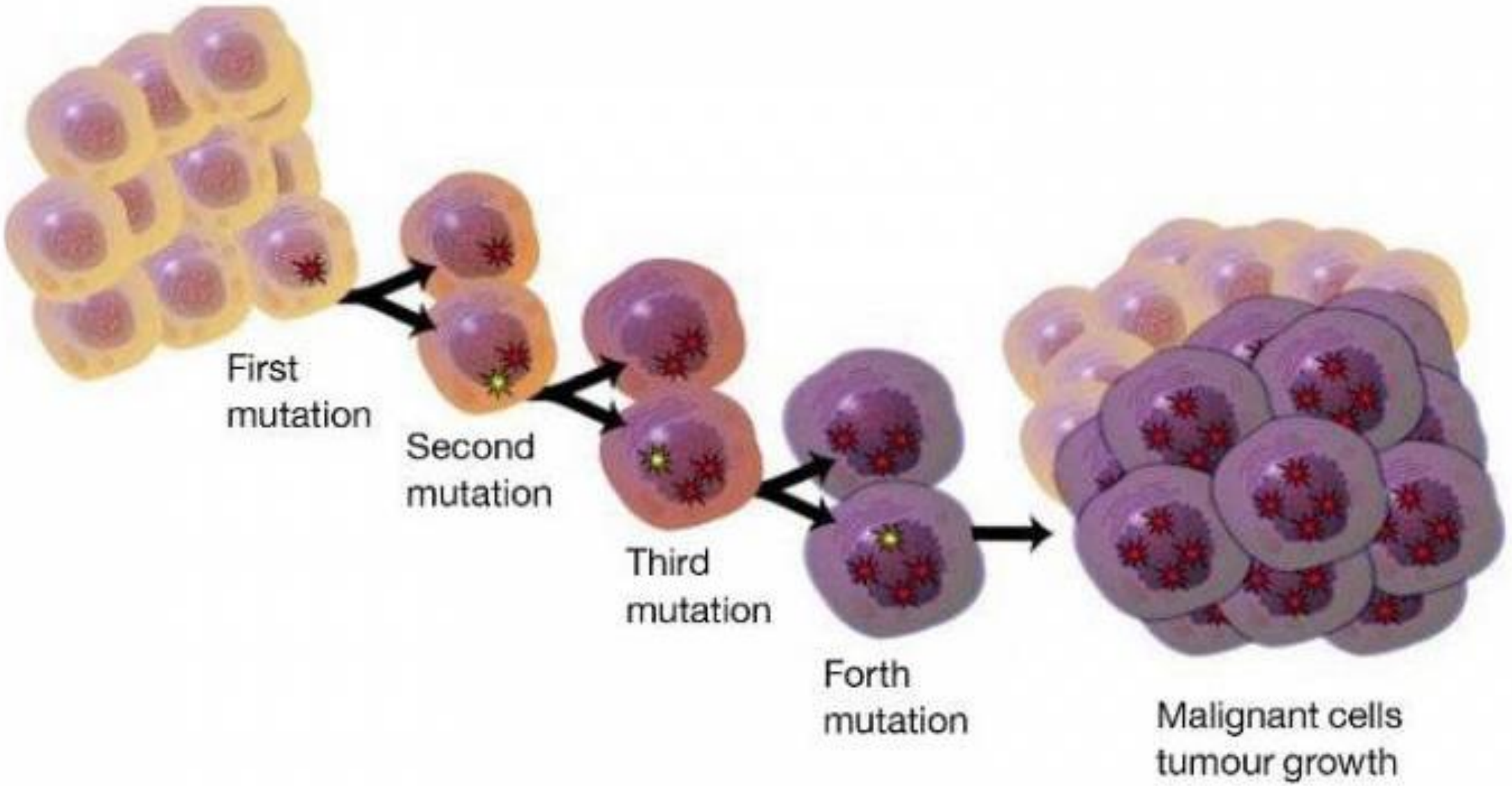
vrouw 28 biljoen cellen (28.000.000.000.000)

Per dag delen 2 biljoen cellen zich (2.000.000.000.000)

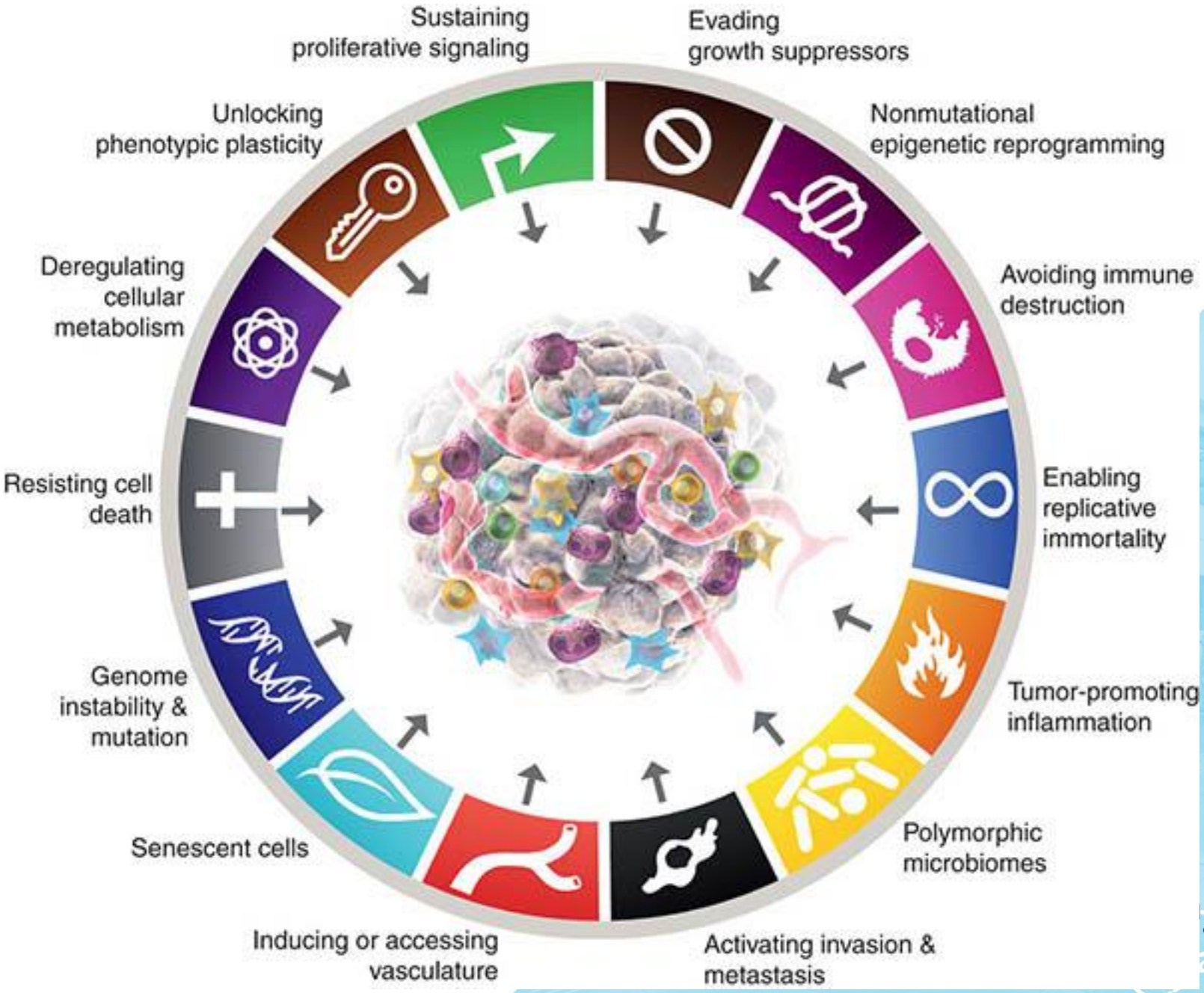
Elke celdeling ongeveer 10 fouten

Factoren die een rol kunnen spelen bij het ontstaan van kanker



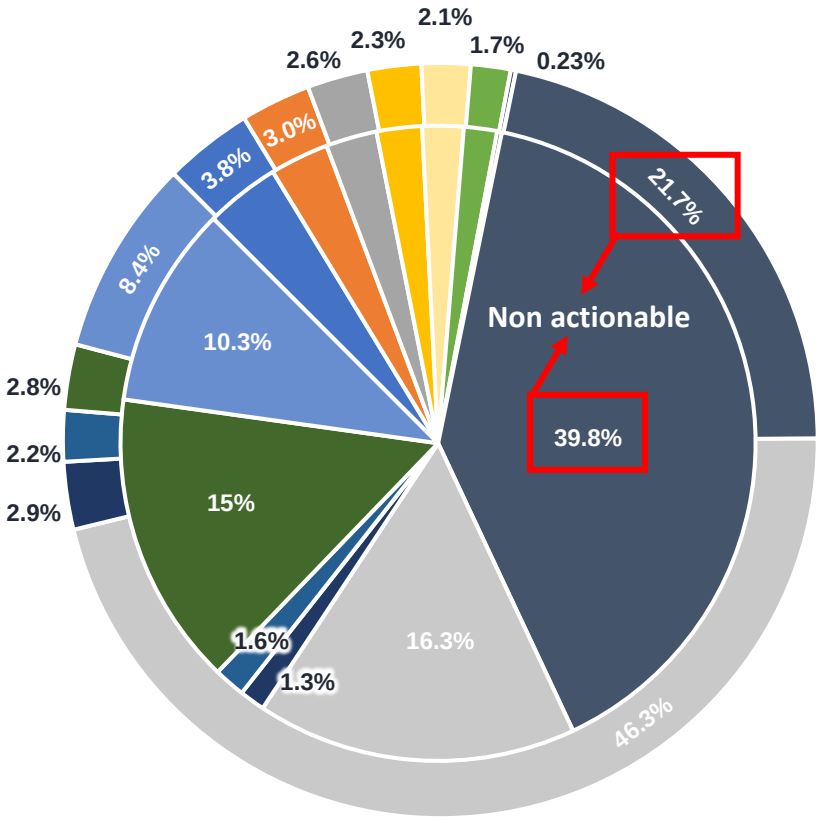

First mutation
Second mutation
Third mutation
Forth mutation
Malignant cells tumour growth


VERNIETIGING DOOR IMMUUNSYSTEEM ONTWIJKEN
GENOOMINSTABILITEIT EN MUTATIE
ENERGIEHUISHOUDING HERPROGRAMMEREN
AANHOUDENDE GROEISIGNALEN
WEEFSELS BINNENDRINGEN EN UITZAAIEN
ONTWIJKEN VAN GROEIONDERDRUKKERS
NIEUWE BLOEDVATEN MAKEN
CELDOOD WEERSTAAN
TUMORSTIMULERENDE ONTSTEKINGSREACTIES
ONEINDIG KUNNEN DELEN



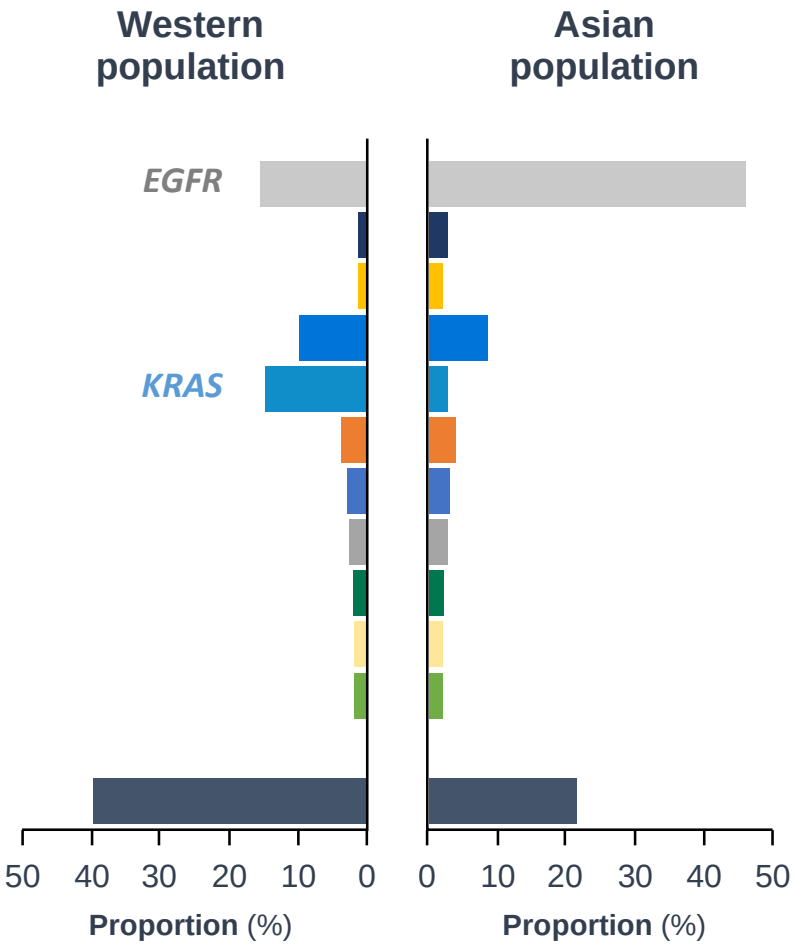
The landscape of genomic alterations in NSCLC

The current big nine: *EGFR, KRAS, ALK, ROS1, MET, HER2, BRAF, RET and NTRK*

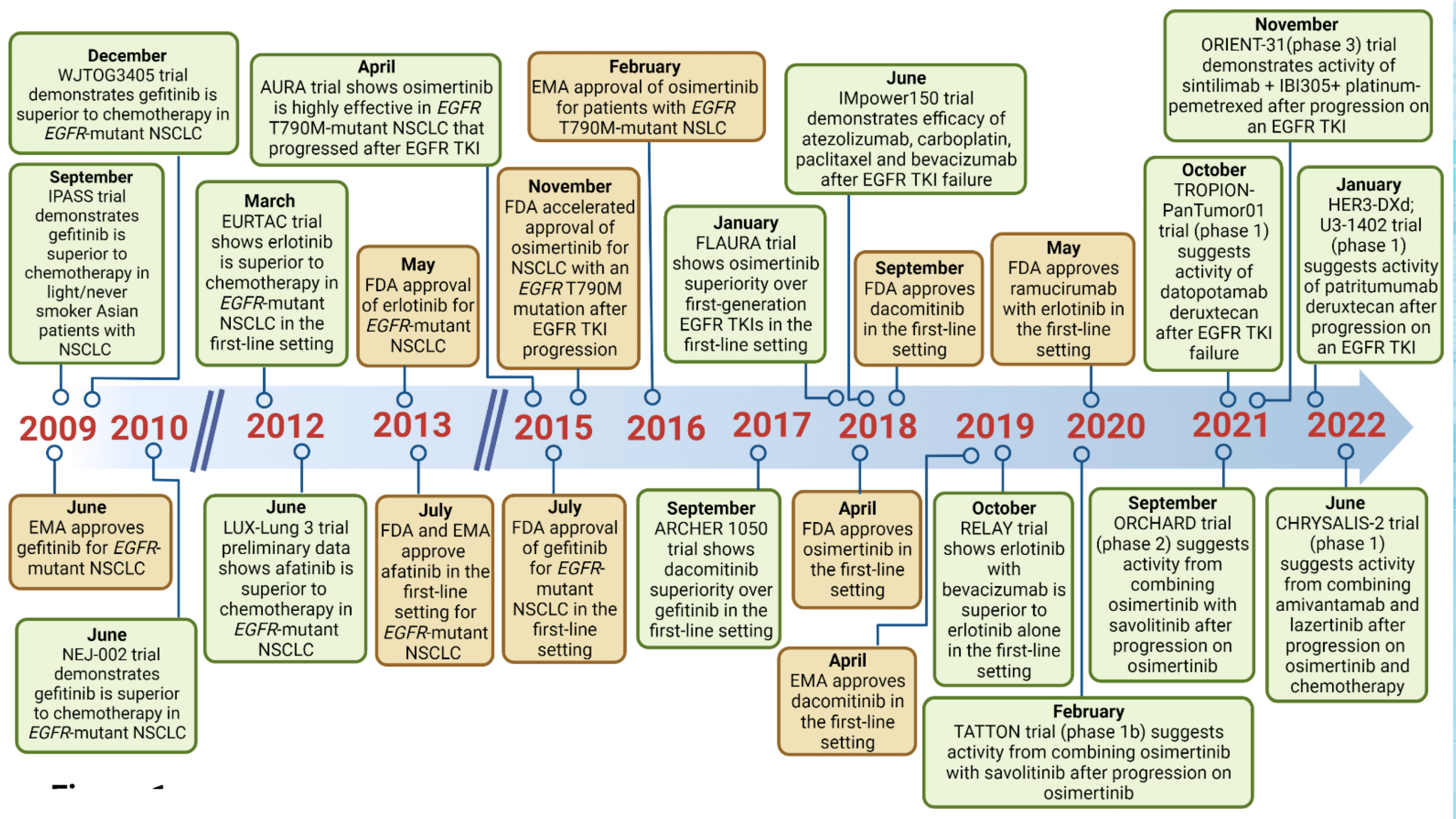


Outer circle: Asian populations
Inner circle: Western populations

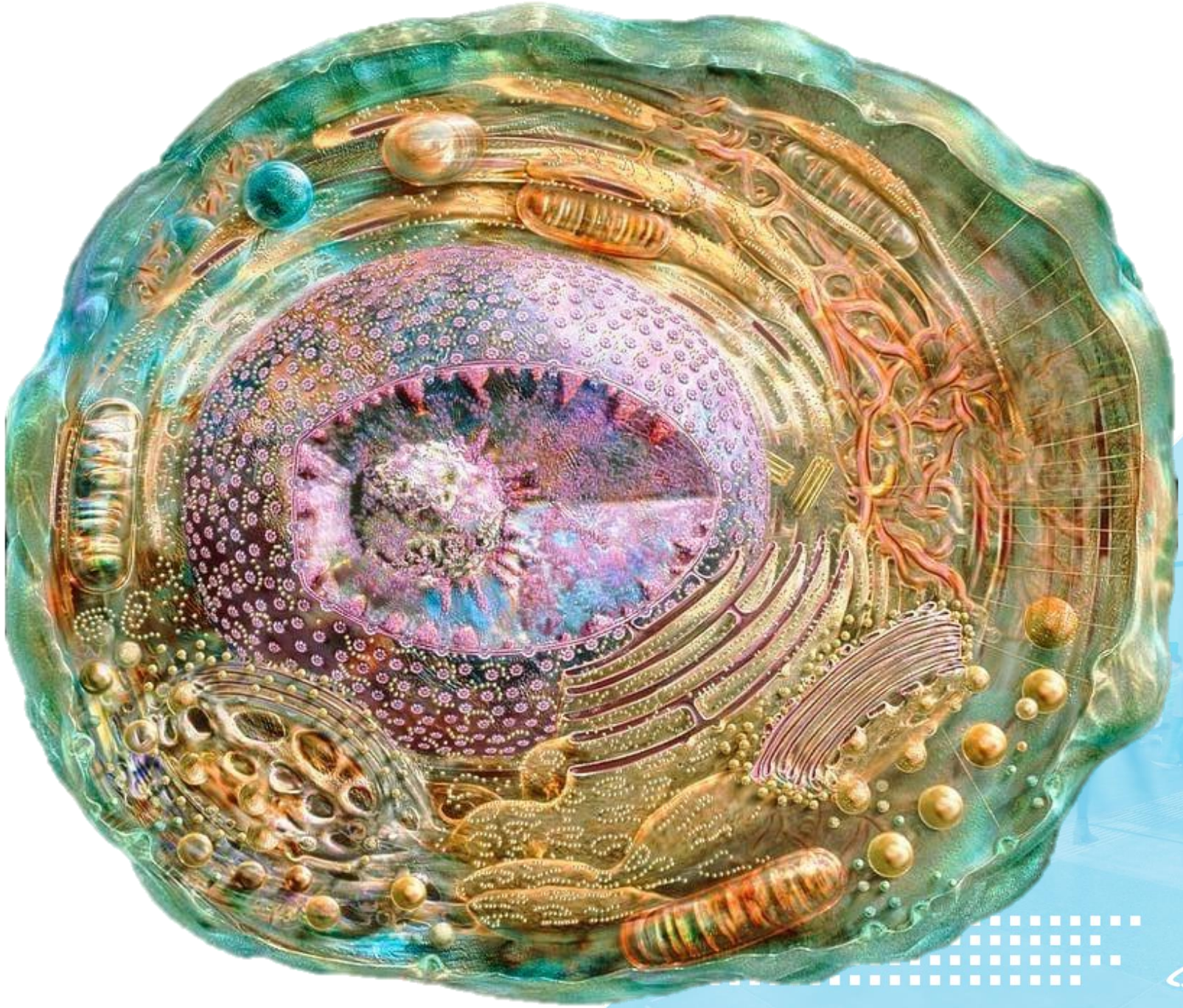
- No actionable alteration
- *EGFR* exon 19 deletion and L858R mutation
- *EGFR* exon 20 insertion mutation
- Other *EGFR* mutation
- *KRAS* G12C mutation
- Other *KRAS* mutation
- *ALK* rearrangement
- *MET* exon 14 mutation
- *ROS1* rearrangement
- *HER2* exon 20 insertion mutation
- *BRAF* V600E mutation
- *RET* rearrangement
- *NTRK* rearrangement



Modified according to Tan AC and Tan DSW. *J Clin Oncol*. 2022;40:611−25.


December
WJTOG3405 trial demonstrates gefitinib is superior to chemotherapy in *EGFR*-mutant NSCLC
April
AURA trial shows osimertinib is highly effective in *EGFR* T790M-mutant NSCLC that progressed after EGFR TKI
February
EMA approval of osimertinib for patients with *EGFR* T790M-mutant NSLC
June
IMpower150 trial demonstrates efficacy of atezolizumab, carboplatin, paclitaxel and bevacizumab after EGFR TKI failure
November
ORIENT-31(phase 3) trial demonstrates activity of sintilimab + IBI305+ platinum-pemetrexed after progression on an EGFR TKI
September
IPASS trial demonstrates gefitinib is superior to chemotherapy in light/never smoker Asian patients with NSCLC
March
EURTAC trial shows erlotinib is superior to chemotherapy in *EGFR*-mutant NSCLC in the first-line setting
May
FDA approval of erlotinib for *EGFR*-mutant NSCLC
November
FDA accelerated approval of osimertinib for NSCLC with an *EGFR* T790M mutation after EGFR TKI progression
January
FLAURA trial shows osimertinib superiority over first-generation EGFR TKIs in the first-line setting
September
FDA approves dacomitinib in the first-line setting
May
FDA approves ramucirumab with erlotinib in the first-line setting
October
TROPION-PanTumor01 trial (phase 1) suggests activity of datopotamab deruxtecan after EGFR TKI failure
January
HER3-DXd; U3-1402 trial (phase 1) suggests activity of patritumumab deruxtecan after progression on an EGFR TKI
2009
2010
2012
2013
2015
2016
2017
2018
2019
2020
2021
2022
June
EMA approves gefitinib for *EGFR*-mutant NSCLC
June
NEJ-002 trial demonstrates gefitinib is superior to chemotherapy in *EGFR*-mutant NSCLC
June
LUX-Lung 3 trial preliminary data shows afatinib is superior to chemotherapy in *EGFR*-mutant NSCLC
July
FDA and EMA approve afatinib in the first-line setting for *EGFR*-mutant NSCLC
July
FDA approval of gefitinib for *EGFR*-mutant NSCLC in the first-line setting
September
ARCHER 1050 trial shows dacomitinib superiority over gefitinib in the first-line setting
April
FDA approves osimertinib in the first-line setting
April
EMA approves dacomitinib in the first-line setting
October
RELAY trial shows erlotinib with bevacizumab is superior to erlotinib alone in the first-line setting
February
TATTON trial (phase 1b) suggests activity from combining osimertinib with savolitinib after progression on osimertinib
September
ORCHARD trial (phase 2) suggests activity from combining osimertinib with savolitinib after progression on osimertinib
June
CHRYSALIS-2 trial (phase 1) suggests activity from combining amivantamab and lazertinib after progression on osimertinib and chemotherapy

EGFR



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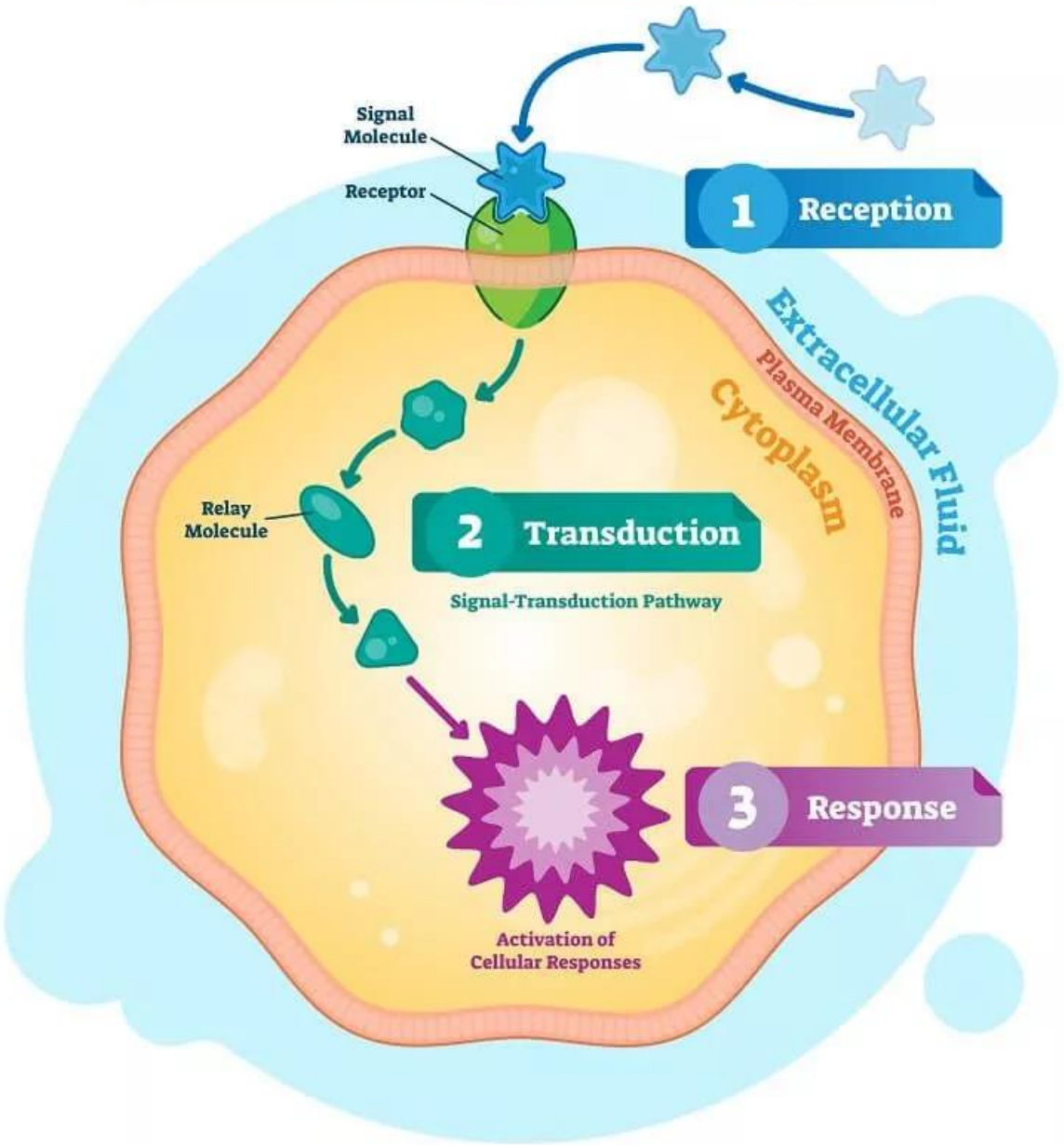
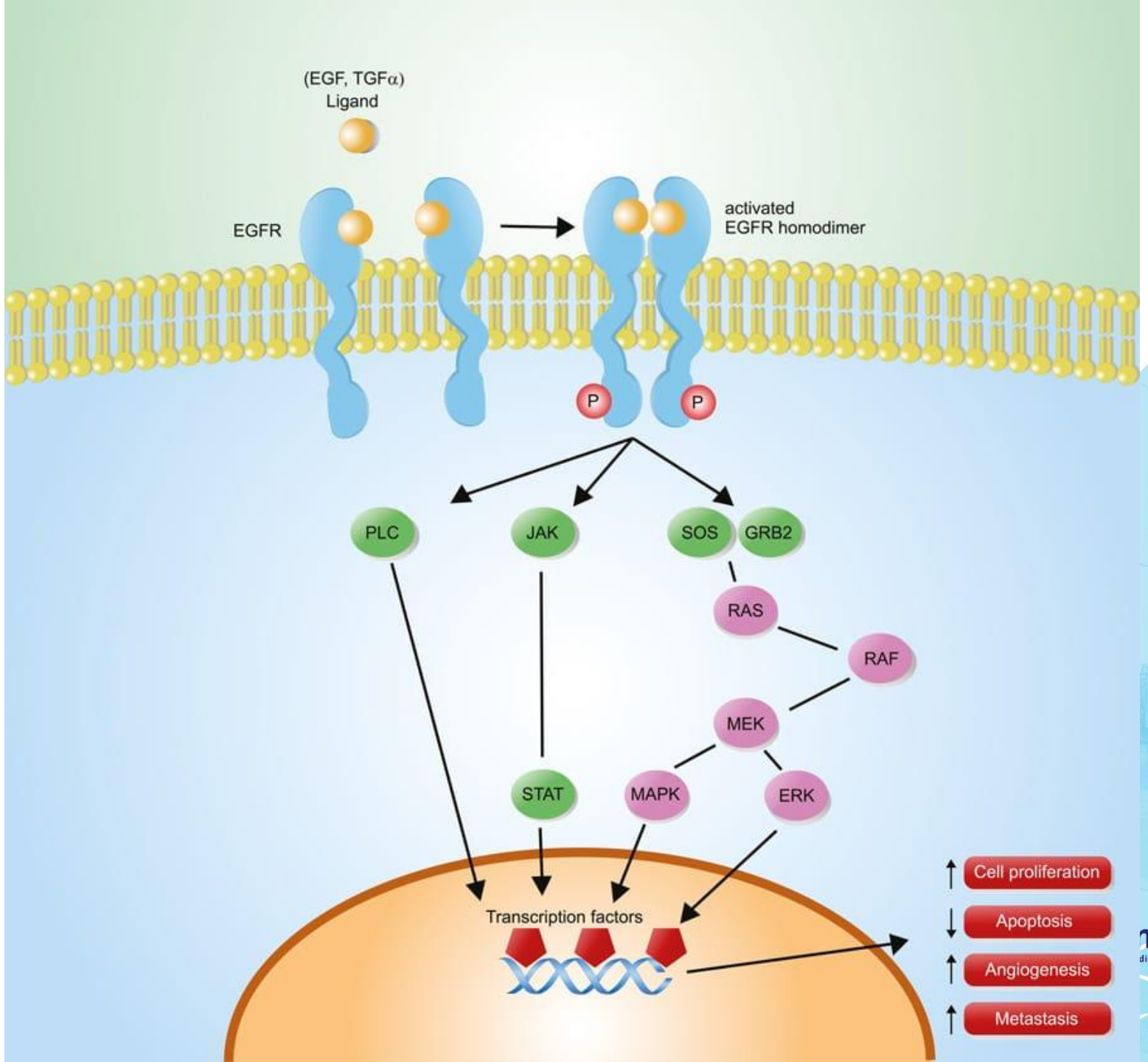
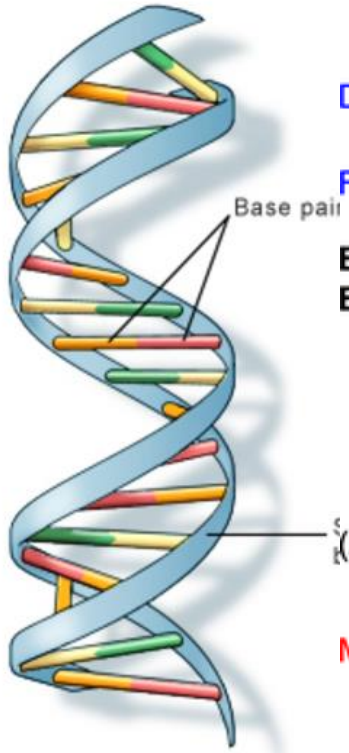
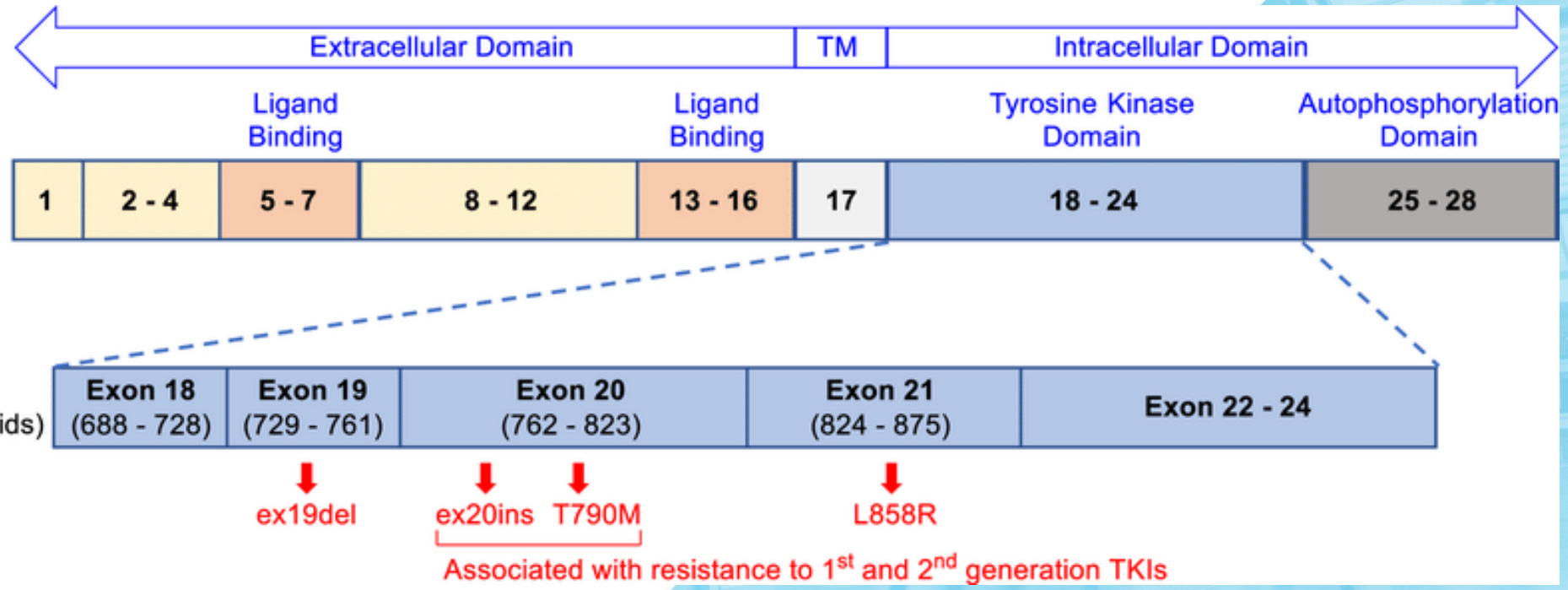
Bio Signaling







U.S. National Library of Medicine



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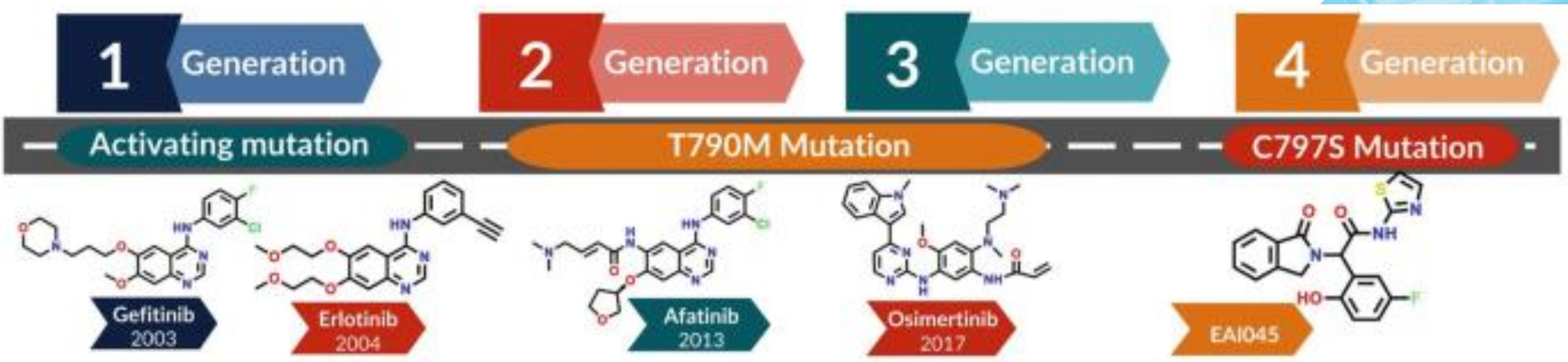
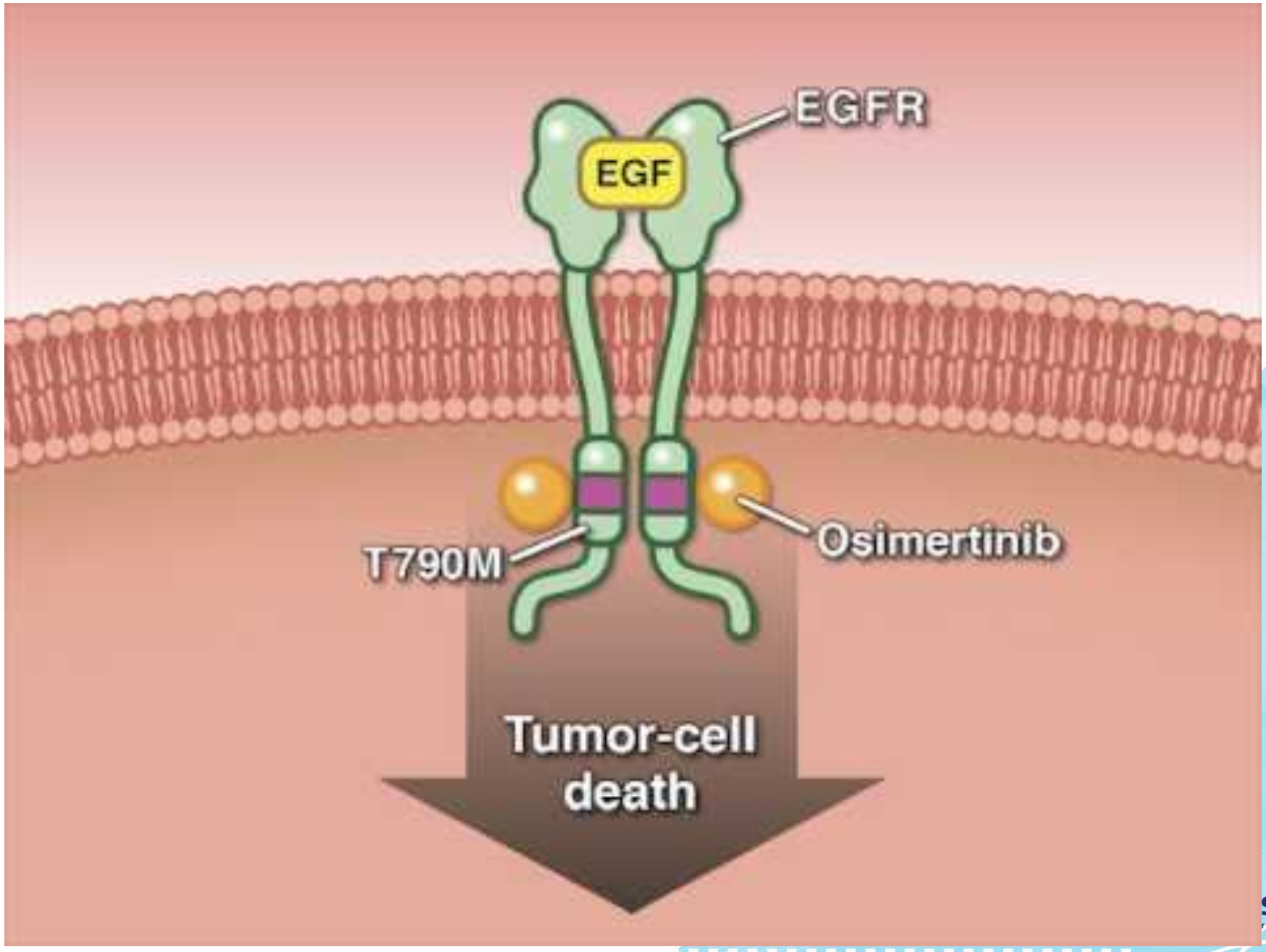

1 Generation
2 Generation
3 Generation
4 Generation
Activating mutation
T790M Mutation
C797S Mutation
Gefitinib
2003
Erlotinib
2004
Afatinib
2013
Osimertinib
2017
EAI045



Osimertinib als eerste lijns behandeling bij klassieke EGFR mutaties (exon 19 del / L858R)

Afname tumor bij 80%

Geen groei van tumor bij 97%

Gemiddeld 18.9 maanden controle op de tumor

Vraag

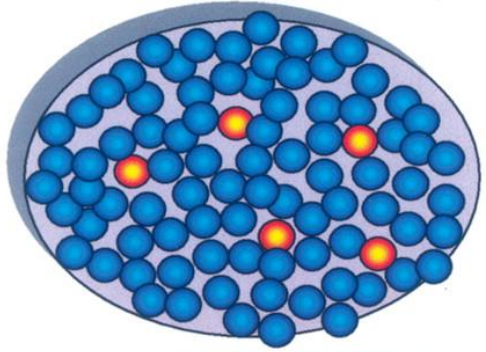
Na 6 jaar Gefitinib te hebben gebruikt neemt sinds anderhalf jaar de werking af en is er sprake van tumorgroei in 3 lymfeklieren in het longgebied.
In maart van dit jaar reeds 18 bestralingen gehad op groeiende tumor op snijvlak van de geopereerde long 9 jaar geleden.

In de zoektocht naar een nieuwe mutatie heeft er onlangs twee keer binnen 14 dagen een EBUSonderzoek plaatsgevonden. Een keer door de luchtpijp en een keer via de slokdarm.
Beide met negatief resultaat vanwege onvoldoende aanwezigheid van kankercellen; Wel is opnieuw EGFR vastgesteld maar T970M is niet gevonden.

Is het aannemelijk om te denken dat er dat de T970M in de toekomst nog aangetoond kan worden bij meer tumorgroei? We hebben nu besloten om het proces te volgen met scans om de twee maanden.
De andere keus zou zijn starten met chemo of chemo/immuno.

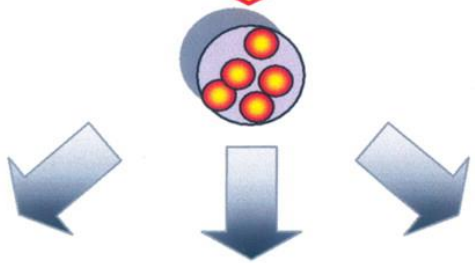
HETEROGENEITY WITHIN AN ONCOGENE ADDICTED TUMOR

- Addicted to oncogene X
- Non-addicted "persisters"



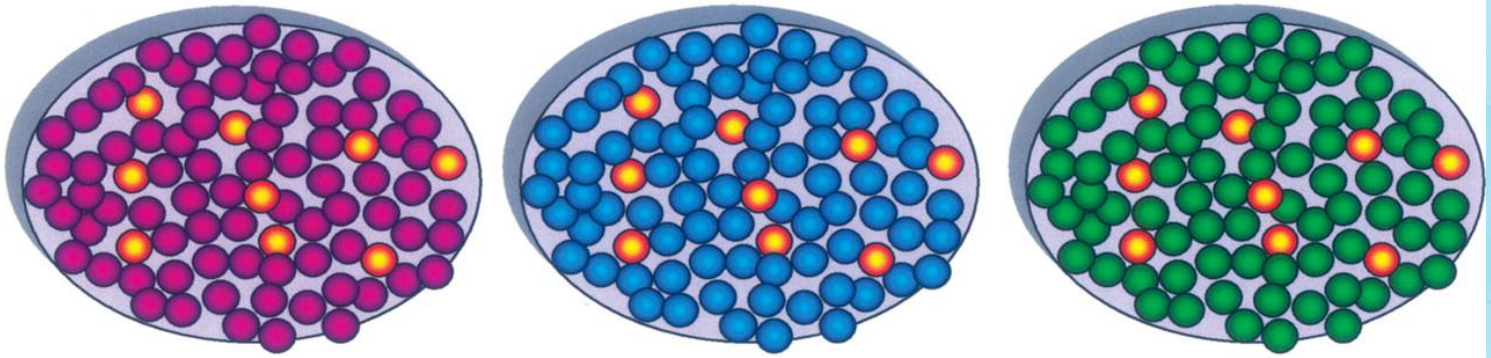
TARGETED THERAPEUTIC

TUMOR SHRINKAGE



SLOW GROWING DRUG-TOLERANT "PERSISTERS"

TUMOR REGROWTH AND REGENERATION OF TUMOR HETEROGENEITY

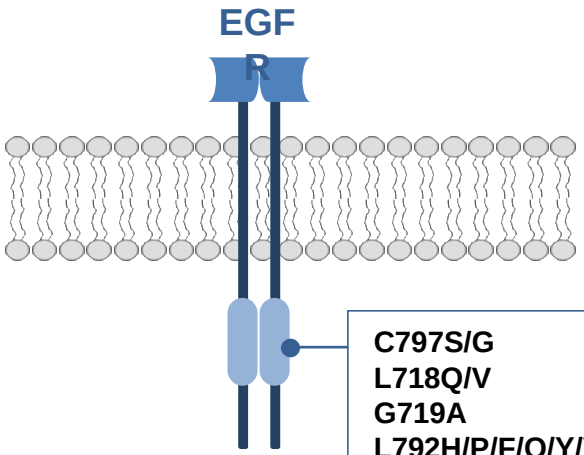


Addicted to oncogenes X+Y Non-addicted "persisters"	Addicted to oncogene X Non-addicted "persisters"	Addicted to oncogene "Y" Non-addicted "persisters"
"CO-ADDICTION"	*"REVERSIBLE RESISTANCE"*	*"ADDICTION SWITCHING"*

Resistance Mechanism to Osimertinib

On-target Resistance

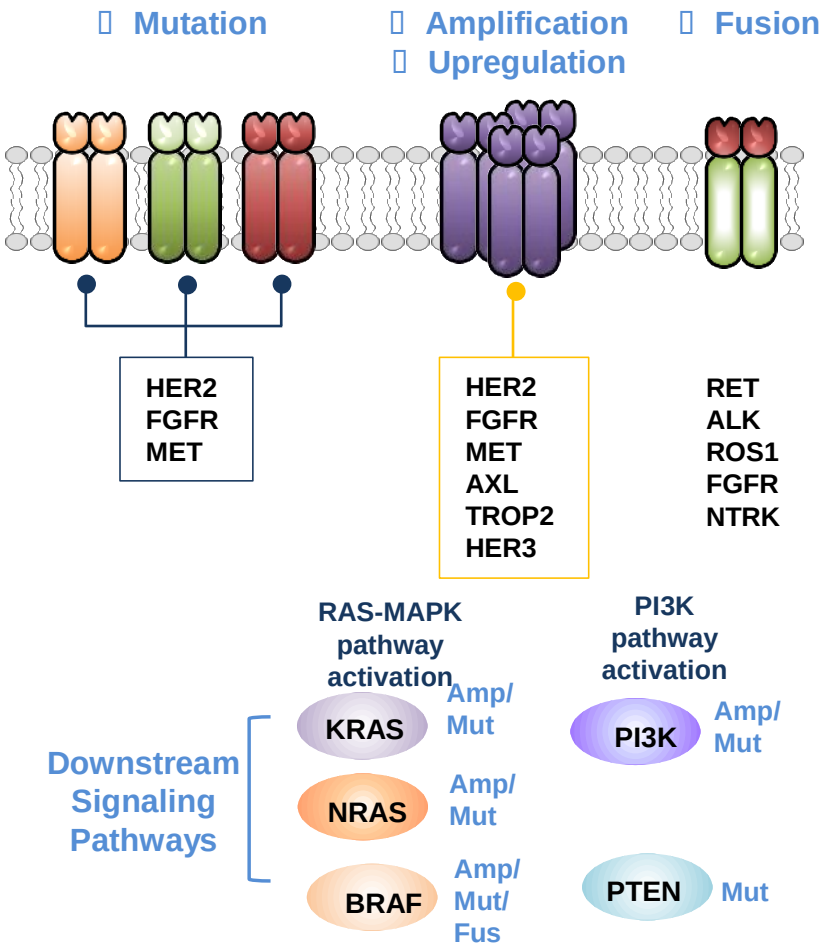
On-target mutations



C797S/G
L718Q/V
G719A
L792H/P/F/Q/Y/V
G796S/D/R/C
G724S
F712L, L798I, T854A, L844V, V843I, L692V, V726M, E709K, G824D, V802I/F, L747P, L834L, S768I, E758D
EGFR Amp

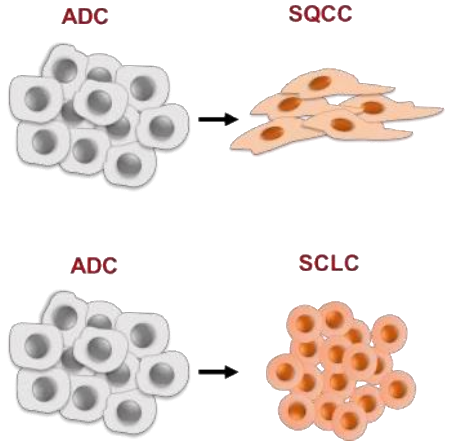
Off-target Resistance

Bypass Pathway Activation



Phenotypic Transformation

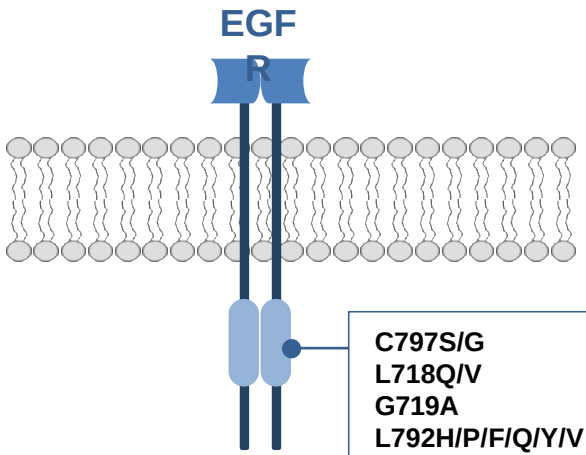
- EMT
- Histologic transformation
  - SQCC
  - SCLC



Int. J. Mol. Sci. 2022
J. Hematology & Oncology. 2022

Treatment Strategies to Overcome Resistance

On-target mutations



C797S/G
L718Q/V
G719A
L792H/P/F/Q/Y/V
G796S/D/R/C
G724S
F712L, L798I, T854A, L844V, V843I, L692V, V726M, E709K, G824D, V802I/F, L747P, L834L, S768I, E758D
EGFR Amp

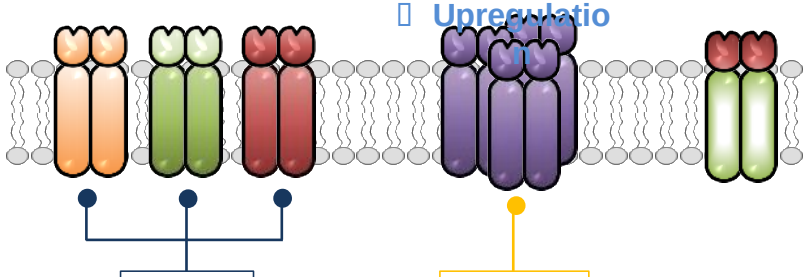
4th G TKIs
Brigatinib
EAI045
JBJ-04-125-02
BLU-945
BLU-701
BDTX-1535

EGFR mAb
Necitumumab

EGFR/MET BsAb
Amivantamab

Bypass Pathway Activation

- Mutation
- Amplification
- Upregulation
- Fusion



HER2
FGFR
MET

MET TKI
Savolitinib
Capmatinib
Tepotinib

HER2
FGFR
MET
AXL
TROP2
HER3

RET
ALK
ROS1
FGFR
NTRK

ALKi
Alectinib

AXLi
Cabozantinib
S49076
MGCD265
MGCD516
ASLAM002
BGB324
TP-0903

RAS-MAPK pathway activation

Downstream Signaling Pathways

KRAS — Amp/Mut
NRAS — Amp/Mut
BRAF — Amp/Mut/Fus

BRAFi
Dabrafenib

PI3K pathway activation

PI3K — Amp/Mut
PTEN — Mut

Phenotypic Transformation

- EMT
- Histologic transformation
  - SQCC
  - SCLC

SoC

ADC

TROP2-ADC
Datopotamab deruxtecan
Sactituzumab govitecan

HER3-ADC
Patritumab deruxtecan

MET-ADC
Telisotuzumab vedotin

Chemo+IO

IMPOWER150
ORIENT 031
ATTLAS

MADRID 2023 ESMO congress

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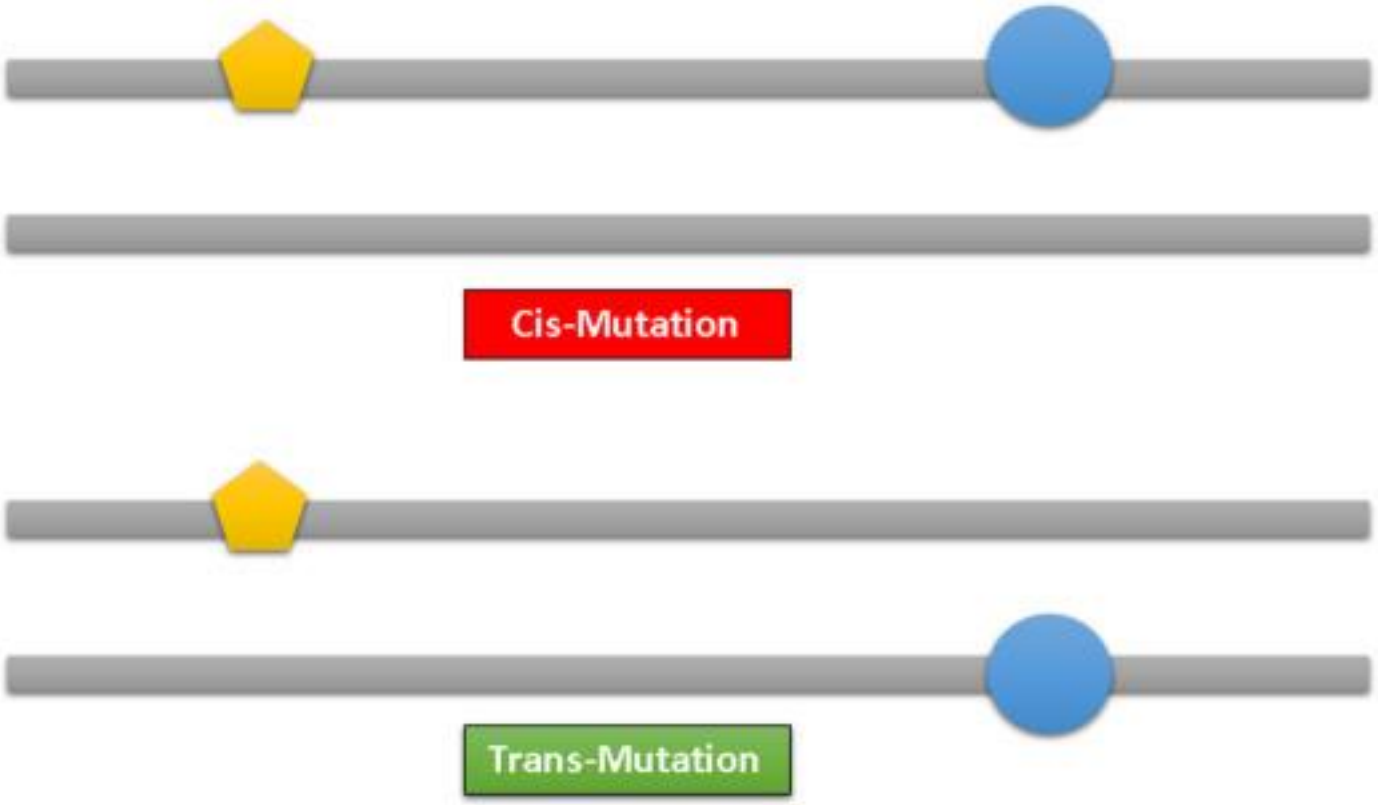
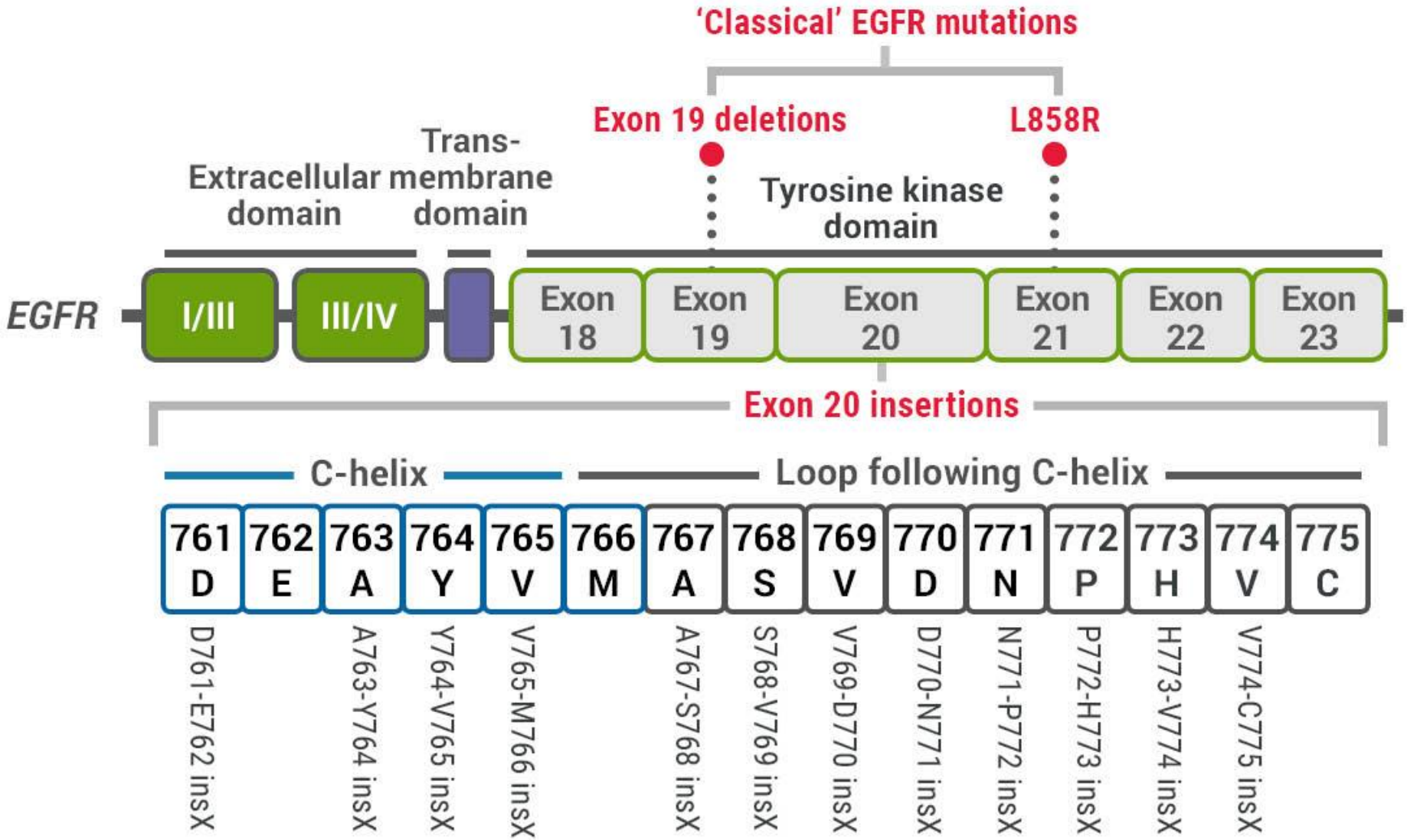

Cis-Mutation
Trans-Mutation


T790M
C797S

EGFR exon 20 mutations in Non-Small Cell Lung Cancer



Healio

Updated Efficacy, Safety and Dosing Management of Poziotinib in Previously Treated EGFR and HER2 Exon 20 NSCLC Patients

R. Cornelissen,[1] M.C. Garassino,[2] X. Le,[3] J. Clarke,[4] N. Tchekmedyian,[5] J. Goldman,[6] F. Lebel,[7] G. Bhat,[8] M. Socinski[9]

[1]Pulmonary Medicine, Erasmus Mc, Rotterdam/NL, [2]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan/IT, [3]Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston/CA/US, [4]Duke Cancer Institute, Durham/NC/US, [5]Pacific Shores Medical Group, Long Beach/CA/US, [6]David Geffen School of Medicine at University of California Los Angeles, Los Angeles/CA/US, [7]Clinical R&D, Spectrum Pharmaceuticals, Irvine/CA/US, [8]Clinical Science, Spectrum Pharmaceuticals, Irvine/CA/US, [9]Adventhealth Cancer Institute, Orlando/AL/US

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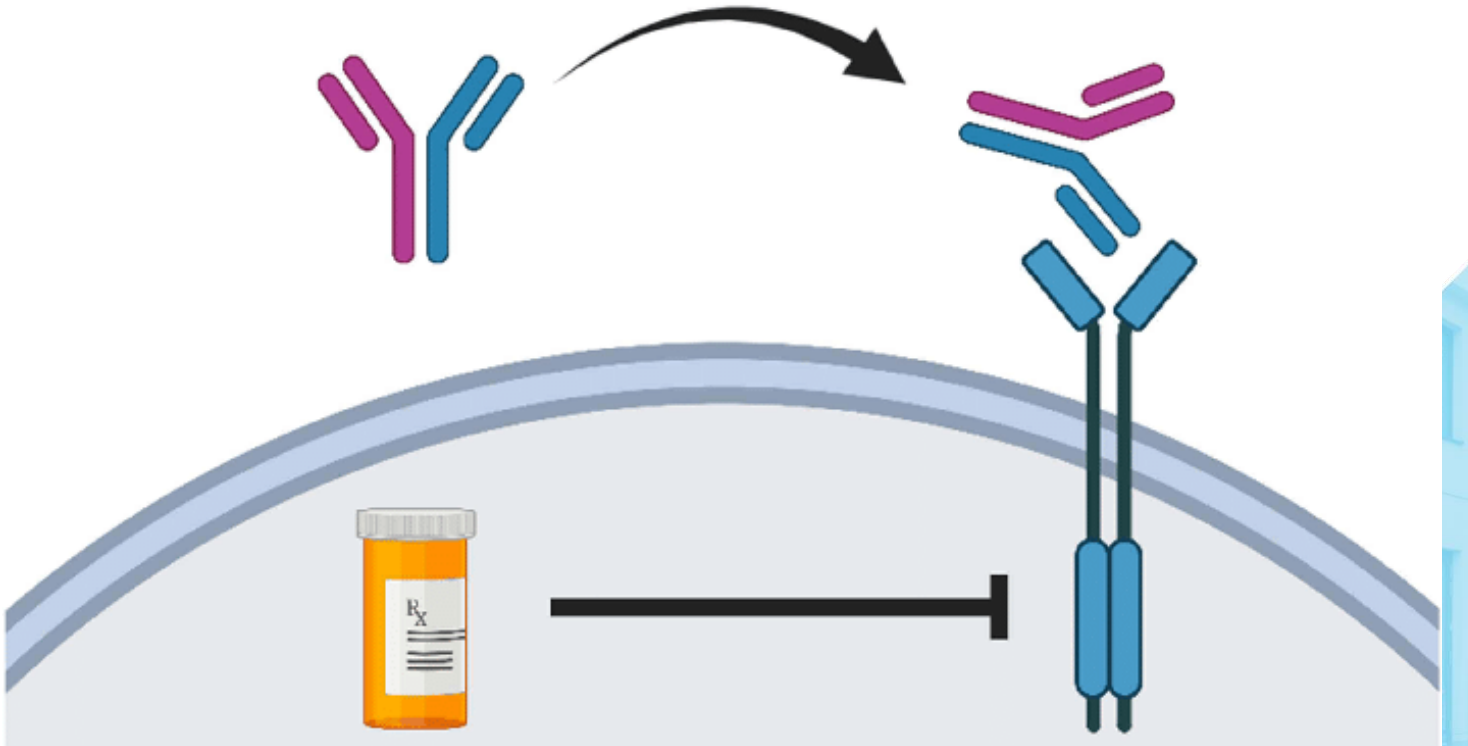
Amivantamab

Binds to the extracellular domain

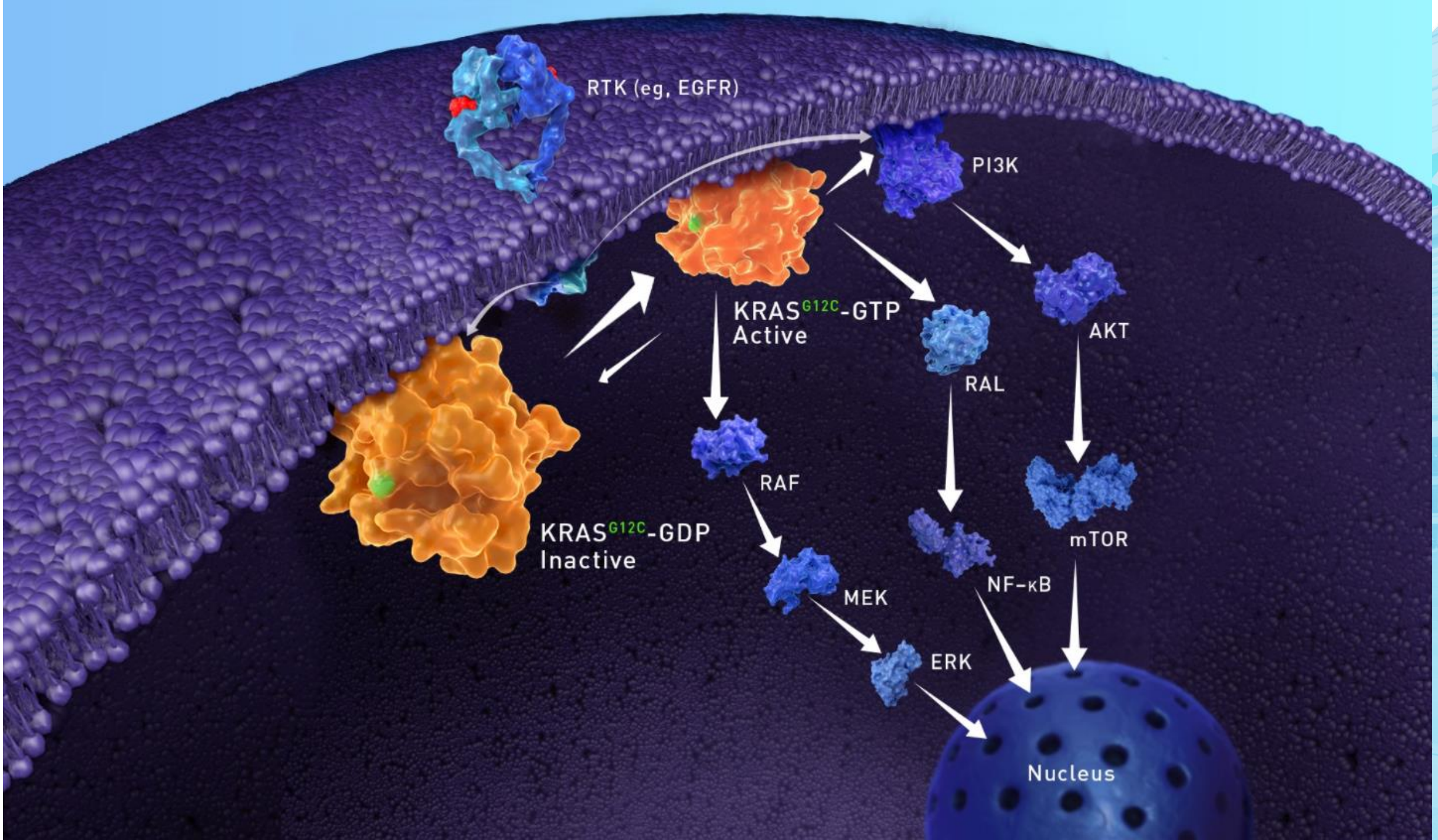


Approved EGFR TKIs

EGFR Exon20ins

Cannot bind to EGFR Exon20ins mutated active site

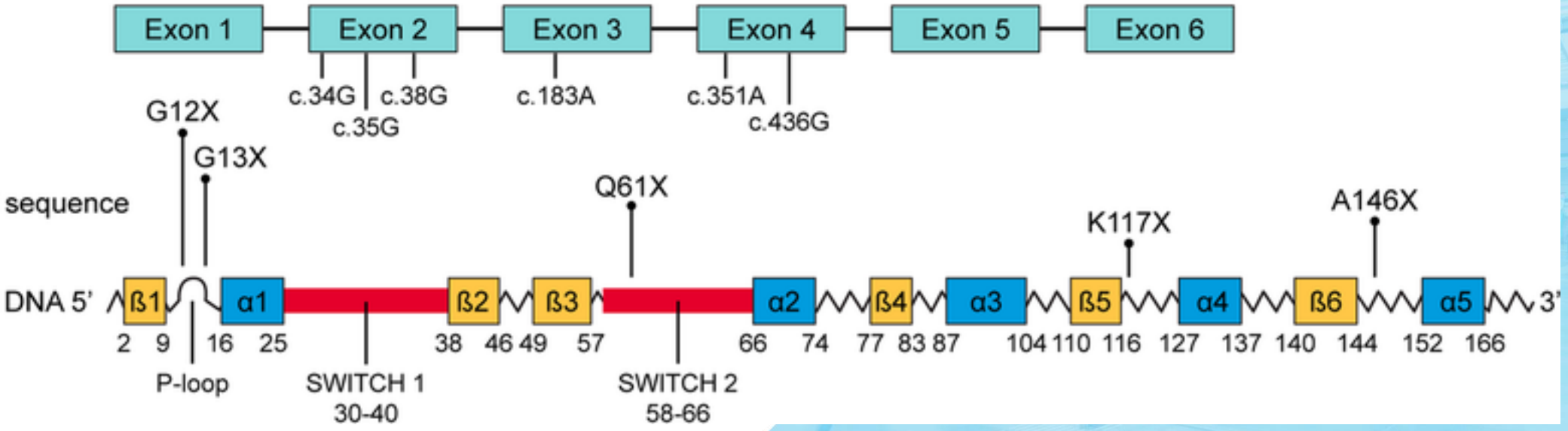
KRAS


RTK (eg, EGFR)
PI3K
KRAS^{G12C}-GTP
Active
AKT
RAL
RAF
KRAS^{G12C}-GDP
Inactive
mTOR
NF-κB
MEK
ERK
Nucleus

KRAS gene structure

KRAS gene location

Gene structure with common mutation hotspots



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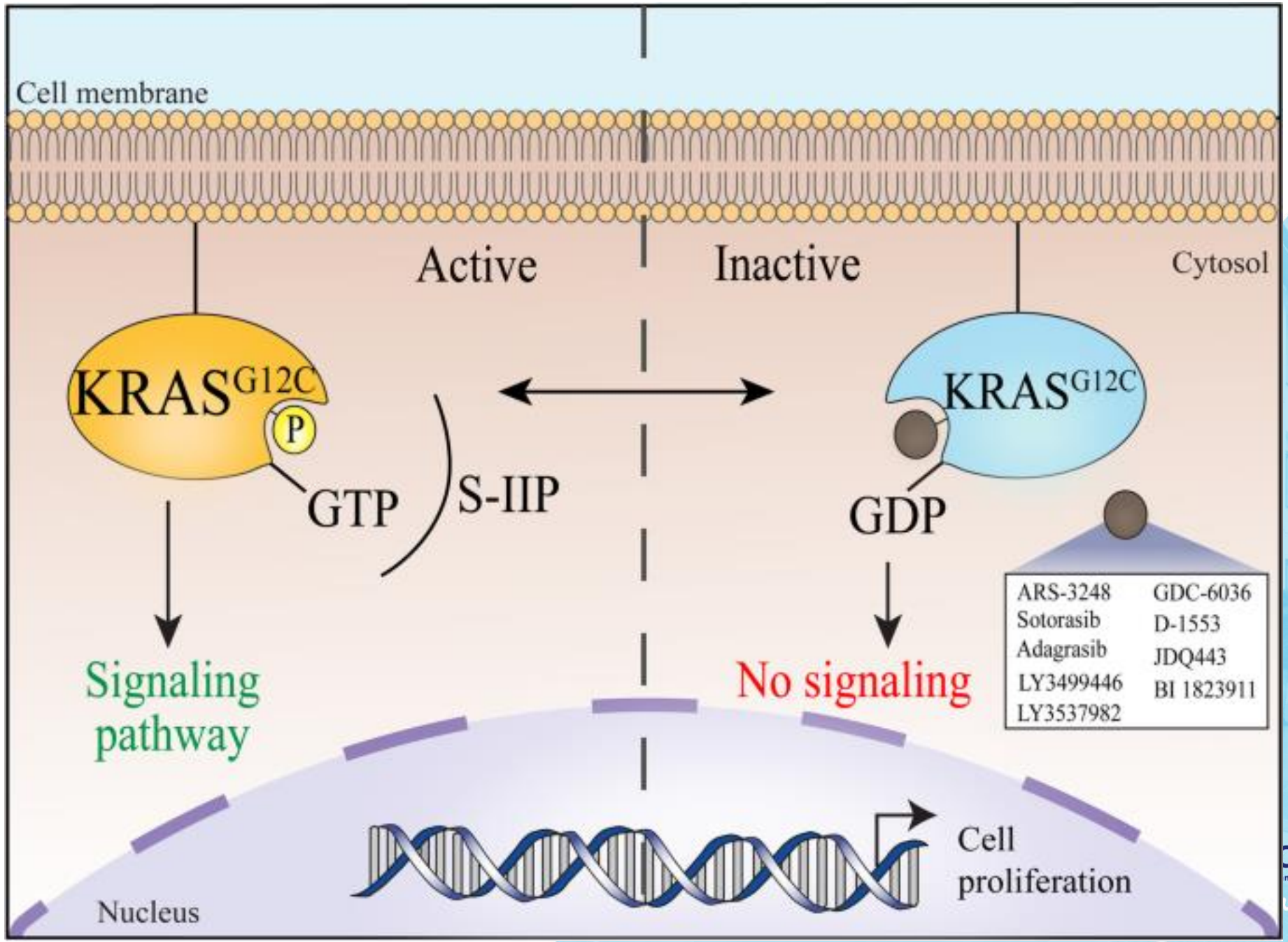

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Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with *KRAS*^{G12C} mutation: a randomised, open-label, phase 3 trial

Adrianus Johannes de Langen, Melissa L Johnson, Julien Mazieres, Anne-Marie C Dingemans, Giannis Mountzios, Miklos Pless, Jürgen Wolf, Martin Schuler, Hervé Lena, Ferdinandos Skoulidis, Yasuto Yoneshima, Sang-We Kim, Helena Linardou, Silvia Novello, Anthonie J van der Wekken, Yuanbin Chen, Solange Peters, Enriqueta Felip, Benjamin J Solomon, Suresh S Ramalingam, Christophe Dooms, Colin R Lindsay, Carlos Gil Ferreira, Normand Blais, Cynthia C Obiozor, Yang Wang, Bhakti Mehta, Tracy Varrieur, Gataree Ngarmchamnanrith, Björn Stollenwerk, David Waterhouse, Luis Paz-Ares*, for the CodeBreaK 200 Investigators†*

Sotorasib bij

Afname tumor bij 28%

Geen groei van tumor bij 83%

Gemiddeld 5.6 maanden controle op de tumor

Hepatotoxicity in patients with *KRAS*^{G12C}-mutated non-small cell lung cancer treated with sotorasib after prior immunotherapy.

FPN 1398P

Sophie M. Ernst[a], Maaike M. Hofman[a,b], Tessa E. van der Horst[a], Marthe S. Paats[a], Frank W.J. Heijboer[a], Joachim G.J.V. Aerts[a], Daphne W. Dumoulin[a], Robin Cornelissen[a], Jan H. von der Thüsen[c], Peter de Bruijn[b], Esther Oomen-de Hoop[b], Ron H.J. Mathijssen[b], Stijn L.W. Koolen[b,d], Anne-Marie C. Dingemans[a].

[a] Department of Respiratory Medicine, Erasmus MC Cancer Institute, Rotterdam, the Netherlands. [b] Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands. [c] Department of Pathology, Erasmus University Medical Center, Rotterdam, the Netherlands. [d] Department of Pharmacy, Erasmus University Medical Center, Rotterdam, the Netherlands.

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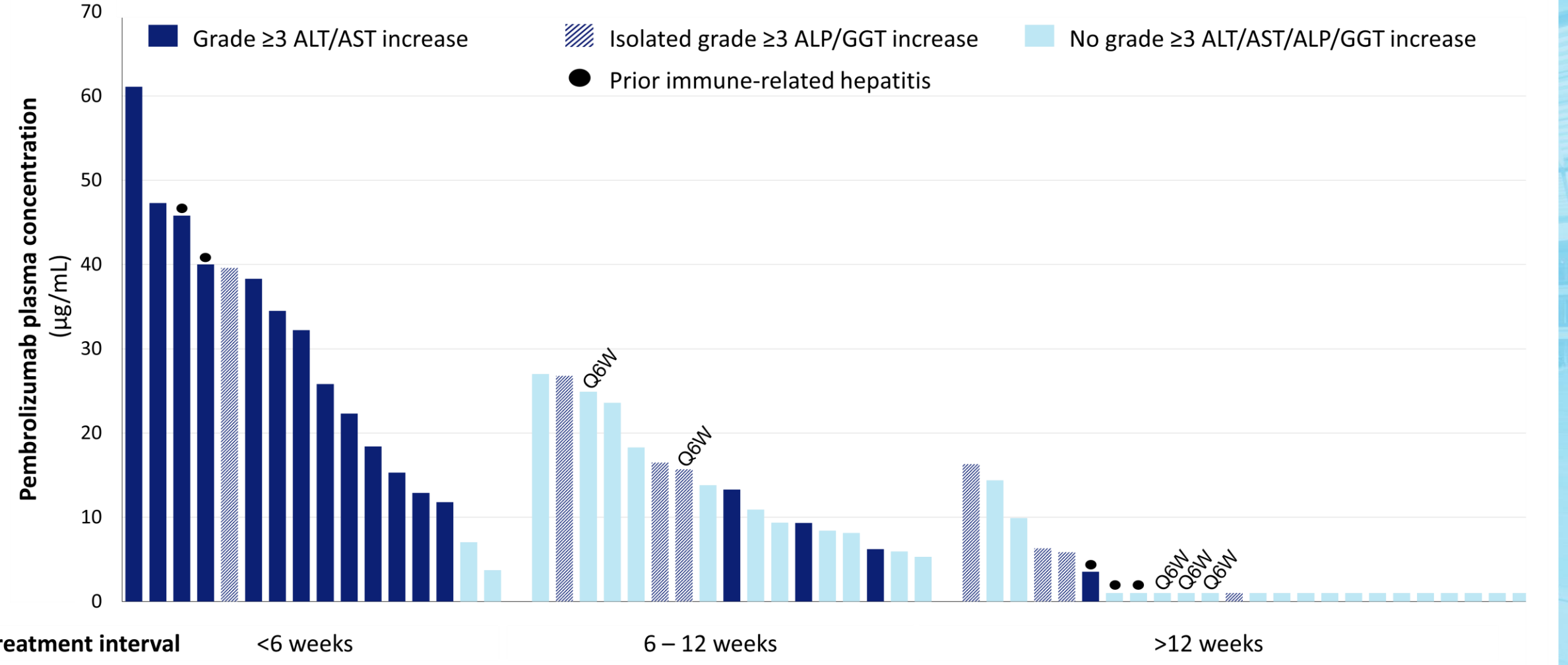

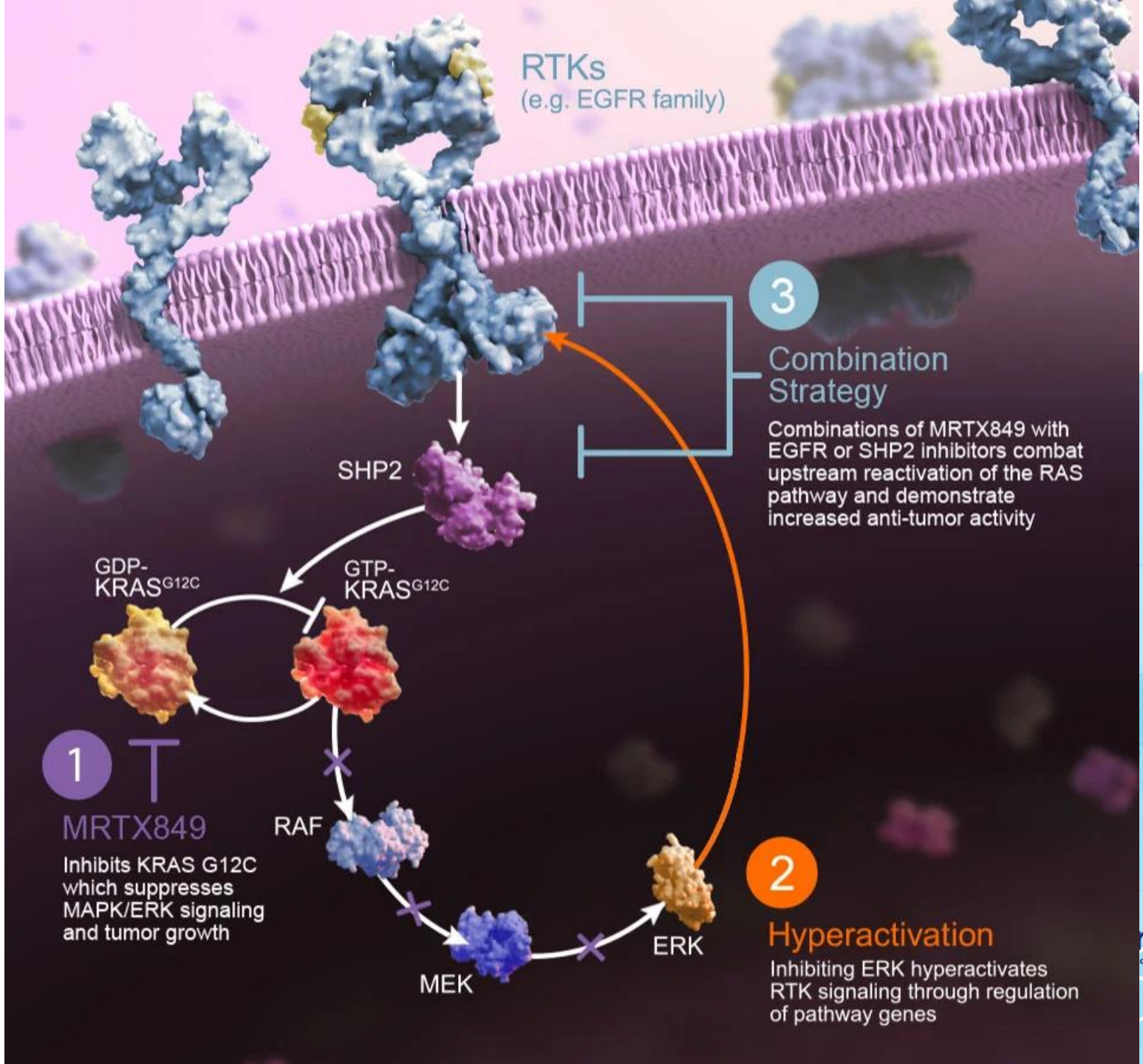

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Vraag

Ik heb nu longkanker met Kras, stadium 4. Sinds juli 2017
Tegen alle verwachting in reageerde ik super op de behandeling met 2 jaar pembroluzimab.
Helaas kwam de kanker na ruim 1 jaar stop/bewaken weer terug maar kon en mocht ik weer opnieuw met evenveel succes aan weer 2 jaar pembro.
Okt 2022 laatste gift en helaas nu weer groei. Waarschijnlijk kan ik nu geholpen worden met bestraling maar als dit niet zou werken kan/ mag ik niet voor een derde keer pembro krijgen zegt mijn (geweldige) behandelend arts. Dat doen ze in Nederland niet zegt hij….
Maar als het voor mijn zo goed werkt, klopt dat dan? Kan ik ergens anders bv AvL dat wél krijgen? Maw hoe nu verder?