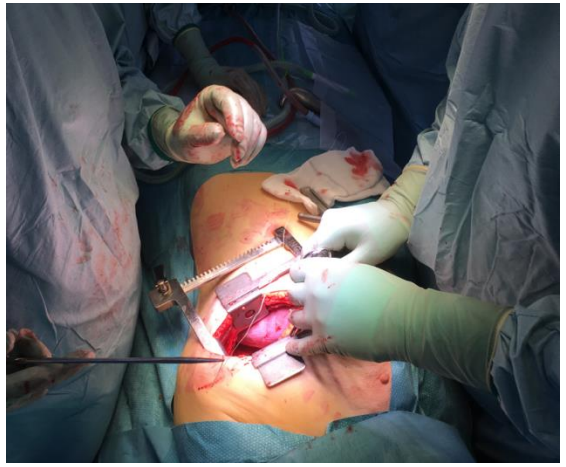
Lungcancerkurs i Lund, SLMF 241008

Målriktad behandling

MARIA PLANCK, DOCENT I ONKOLOGI, ÖVERLÄKARE
LUNDS UNIVERSITET OCH SKÅNES UNIVERSITETSSJUKHUS

Lokal behandling



Kirurgi

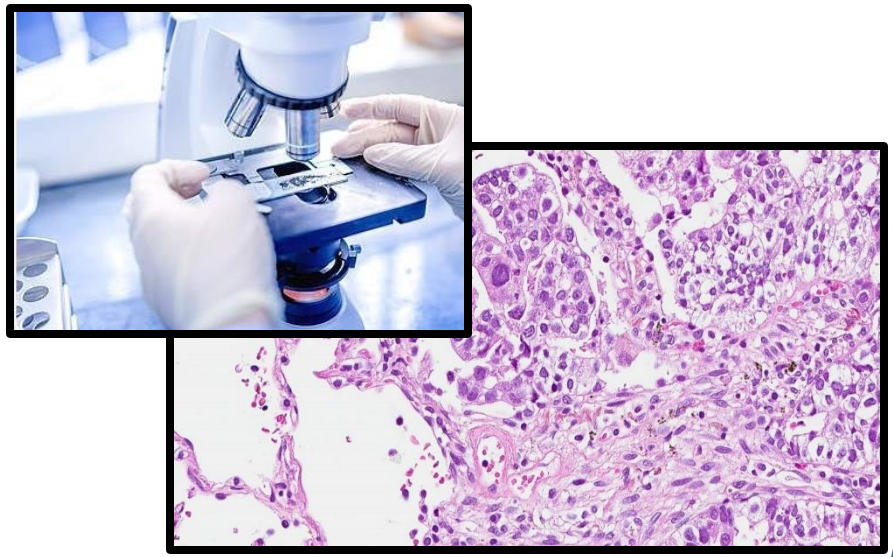
Radioterapi

Systemisk behandling

Kemoterapi
Immunterapi

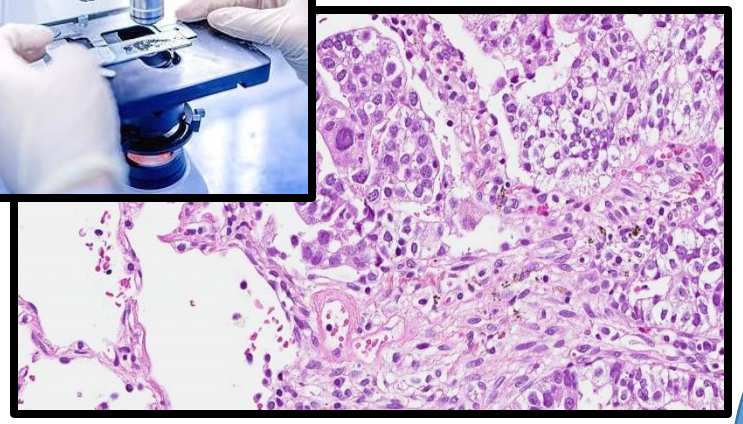
Målriktad behandling


Kirurgi?
Immuno+kemoterapi?
Kirurgi + radioterapi?
Immunterapi?
Kirurgi + målriktad beh?
Radioterapi?
Kemoterapi?
Endast Best Supportive Care?
Kirurgi + kemoterapi?
Hur ska vi behandla? (MDK)
Radioterapi + kemoterapi?
Radioterapi + kemoterapi+ målriktad beh?
Immunterapi + kemoterapi + kirurgi?
Radioterapi + immunterapi?
Målriktad behandling?



Diagnosis
+ subtype
differentiation
proliferation
etc.

?



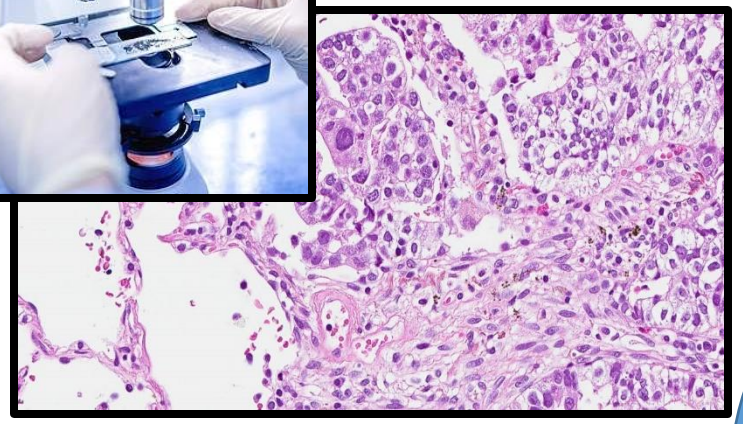
?

Disease stage

Tumor size (T)

Lymph node involvement (N)

Metastatic sites (M)

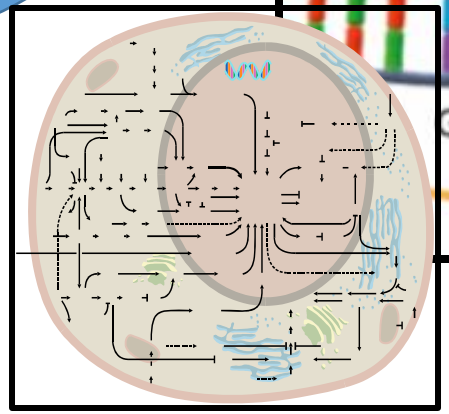


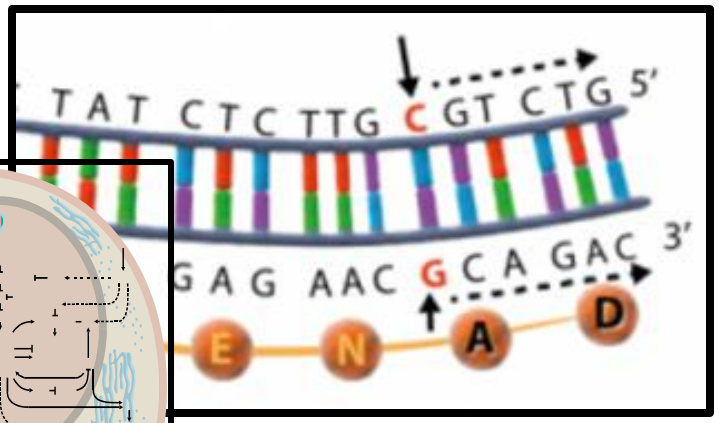
?

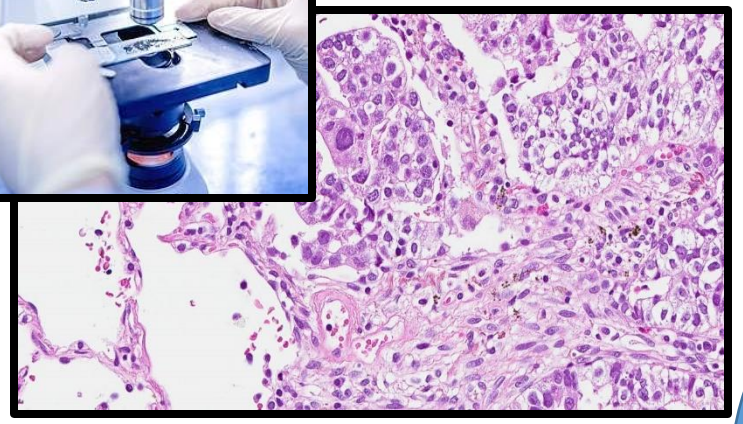
Molecular factors

Mutations / gene fusions

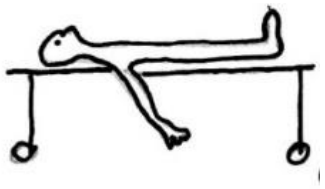
IHC expression



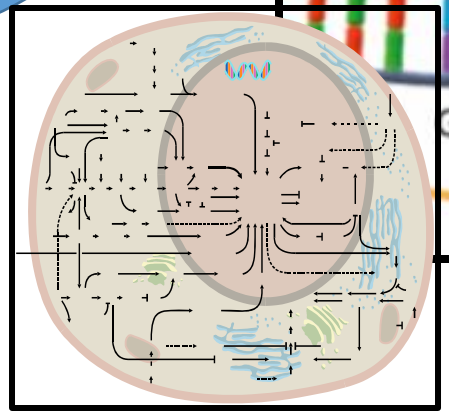


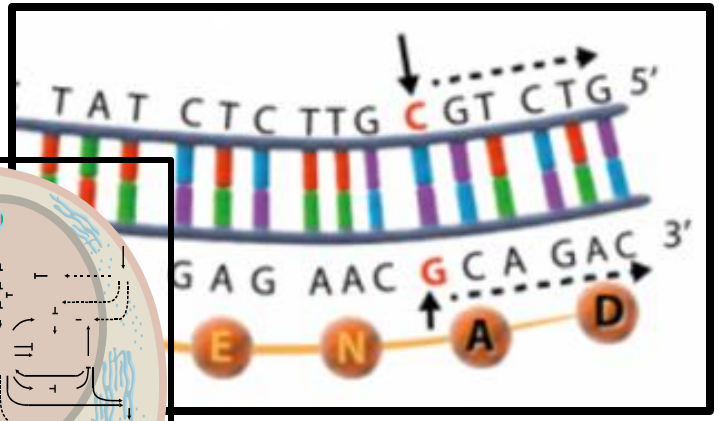


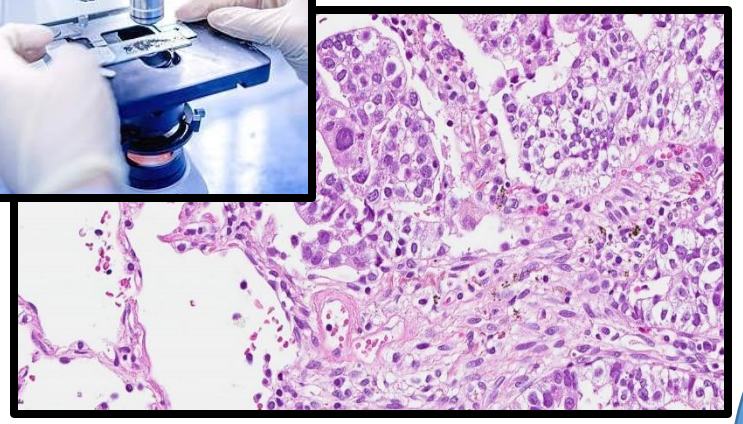
?



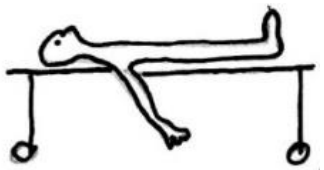
Patient Performance Status (WHO 1-4)

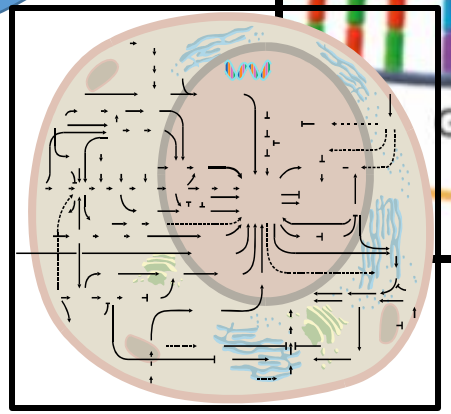


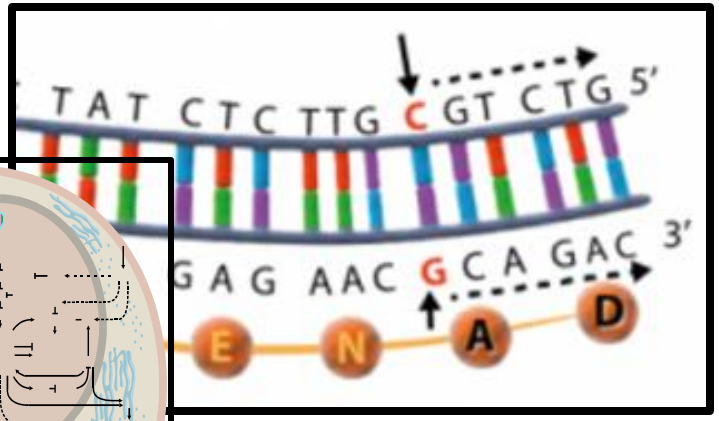




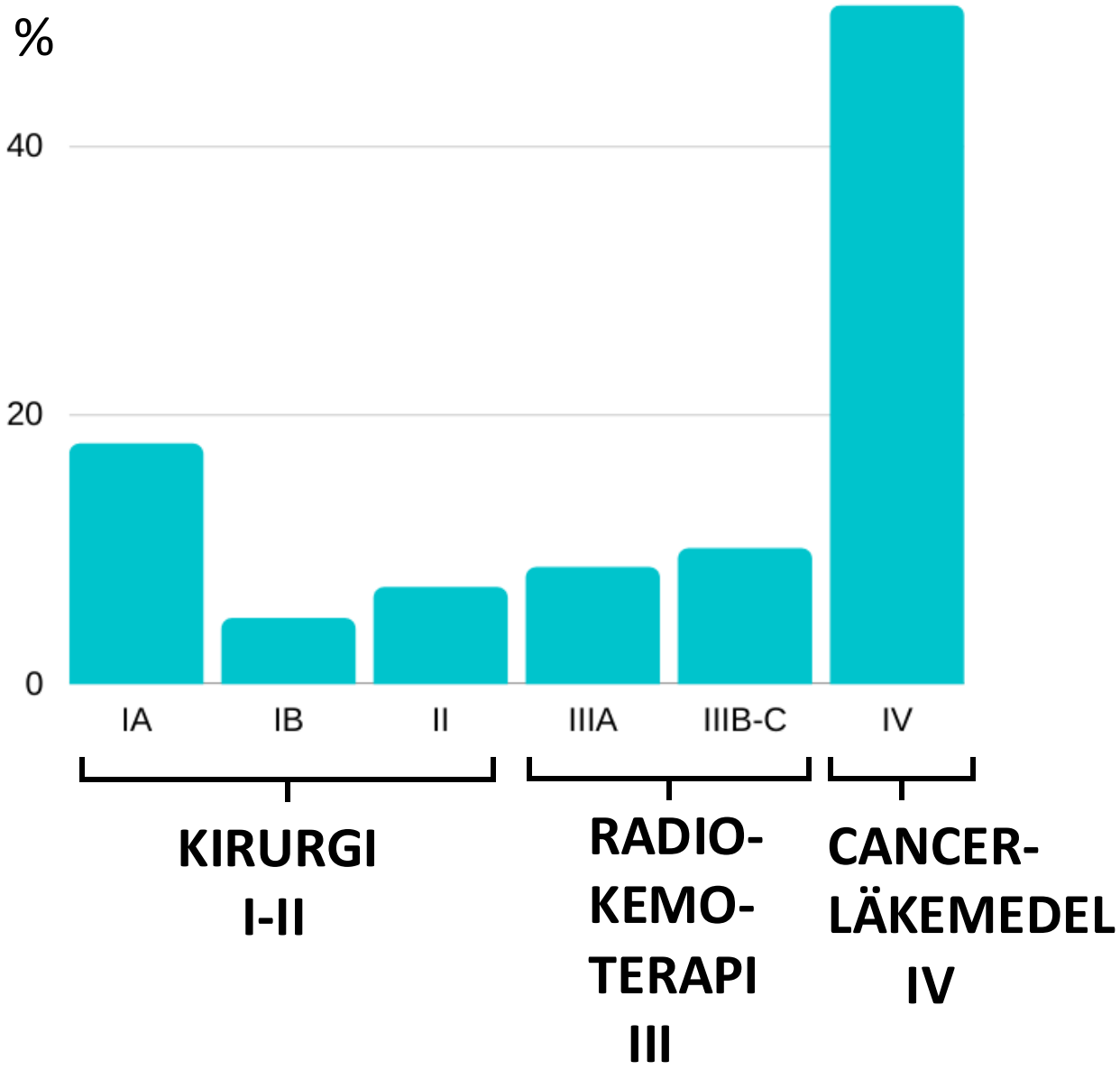
Behandlings-plan



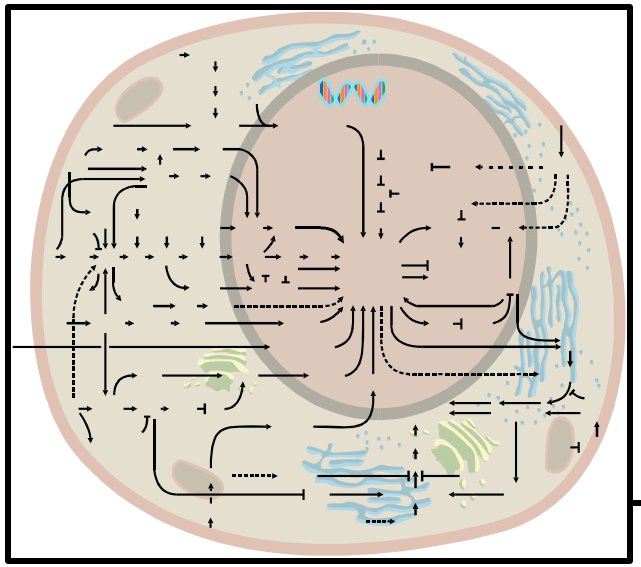


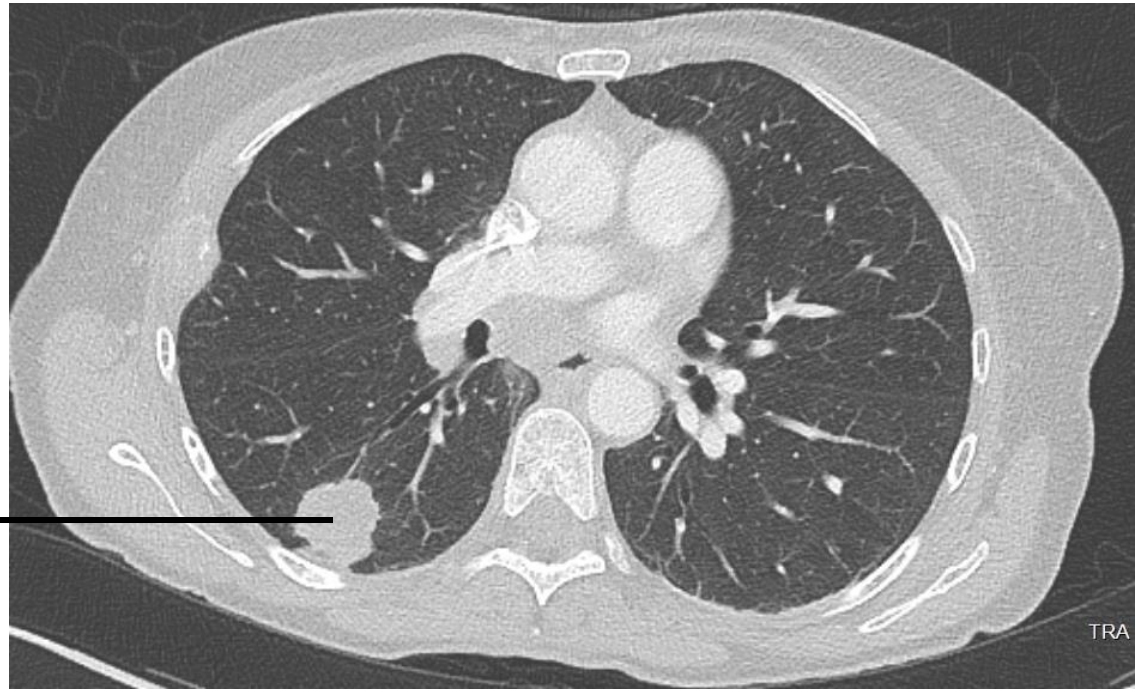


Stadiefördelning, NSCLC



Målriktade behandlingar i lungcancer



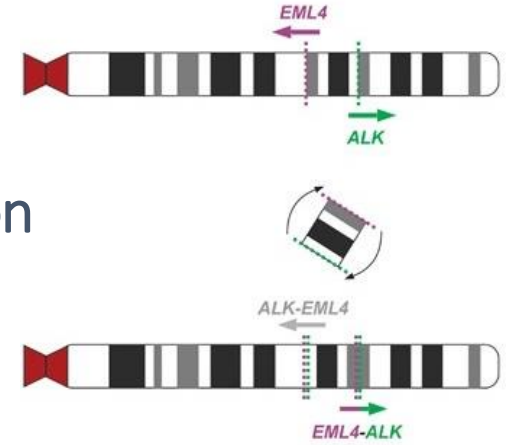


- Växande patientgrupp
- Längre antitumoral behandlingseffekt
- Färre biverkningar

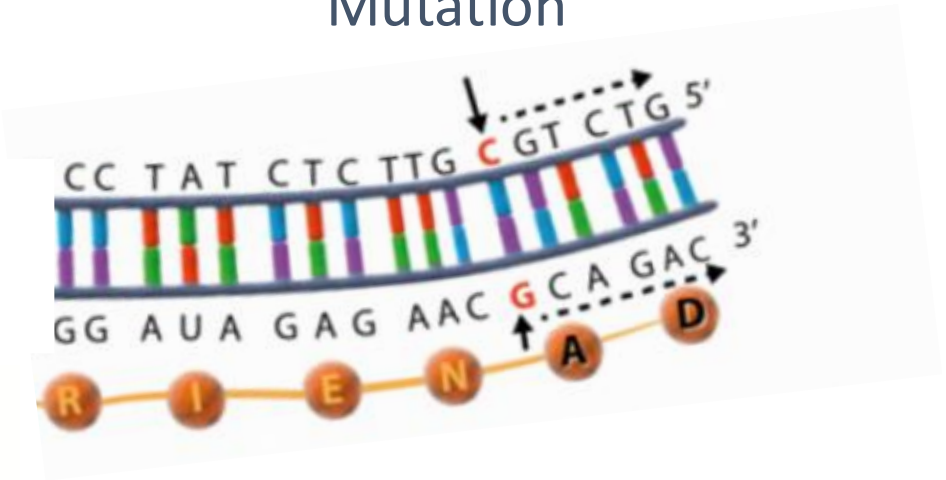
} ALLTID MOLEKYLÄR DIAGNOSTIK !

Förvärvade genetiska förändringar i cancerceller

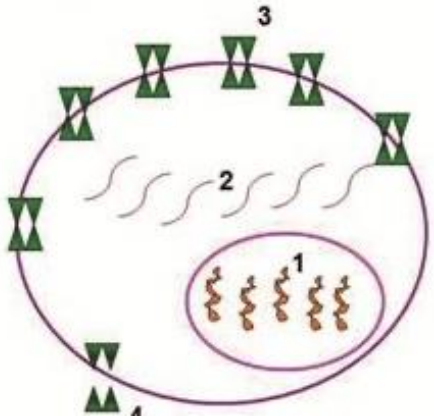
Translokation

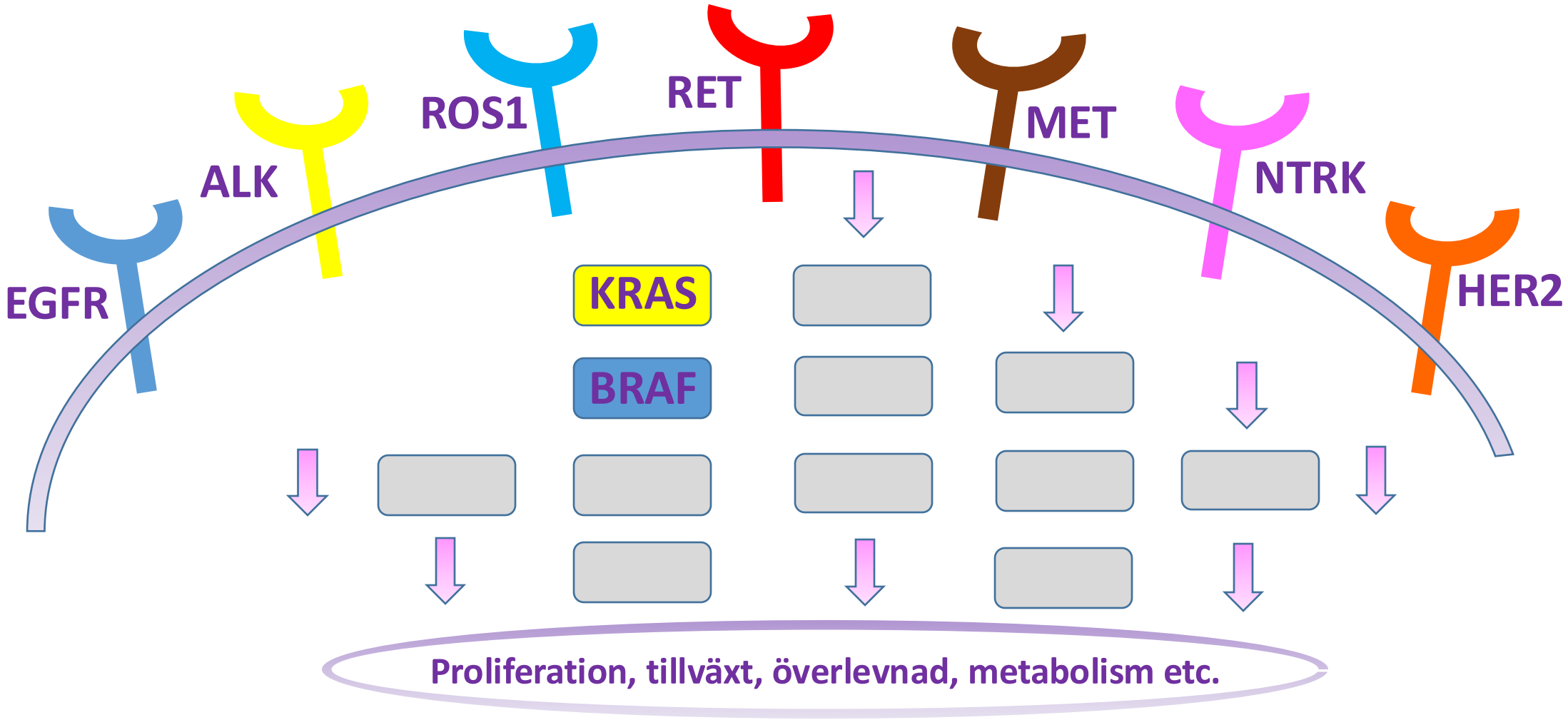


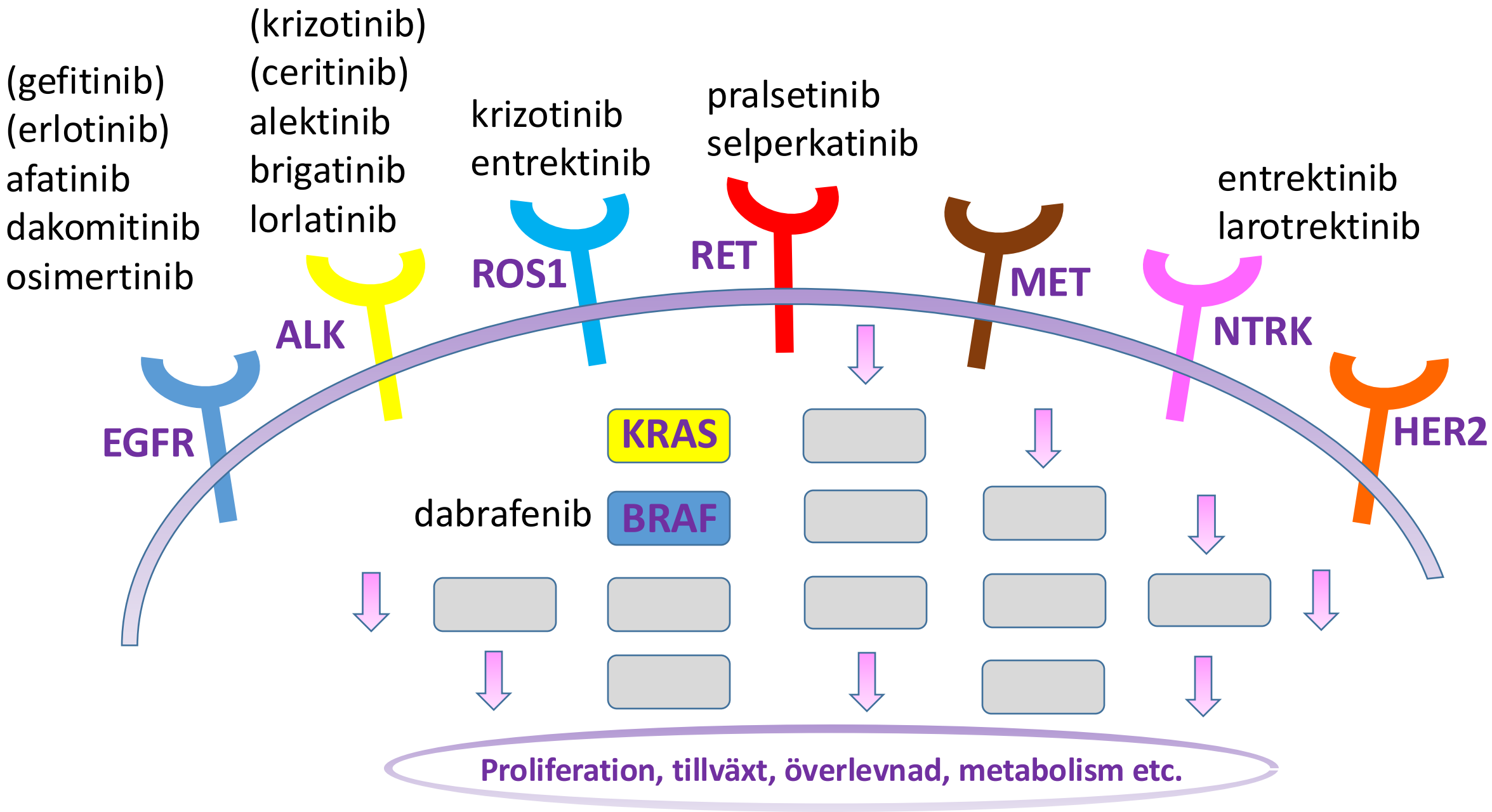
Mutation

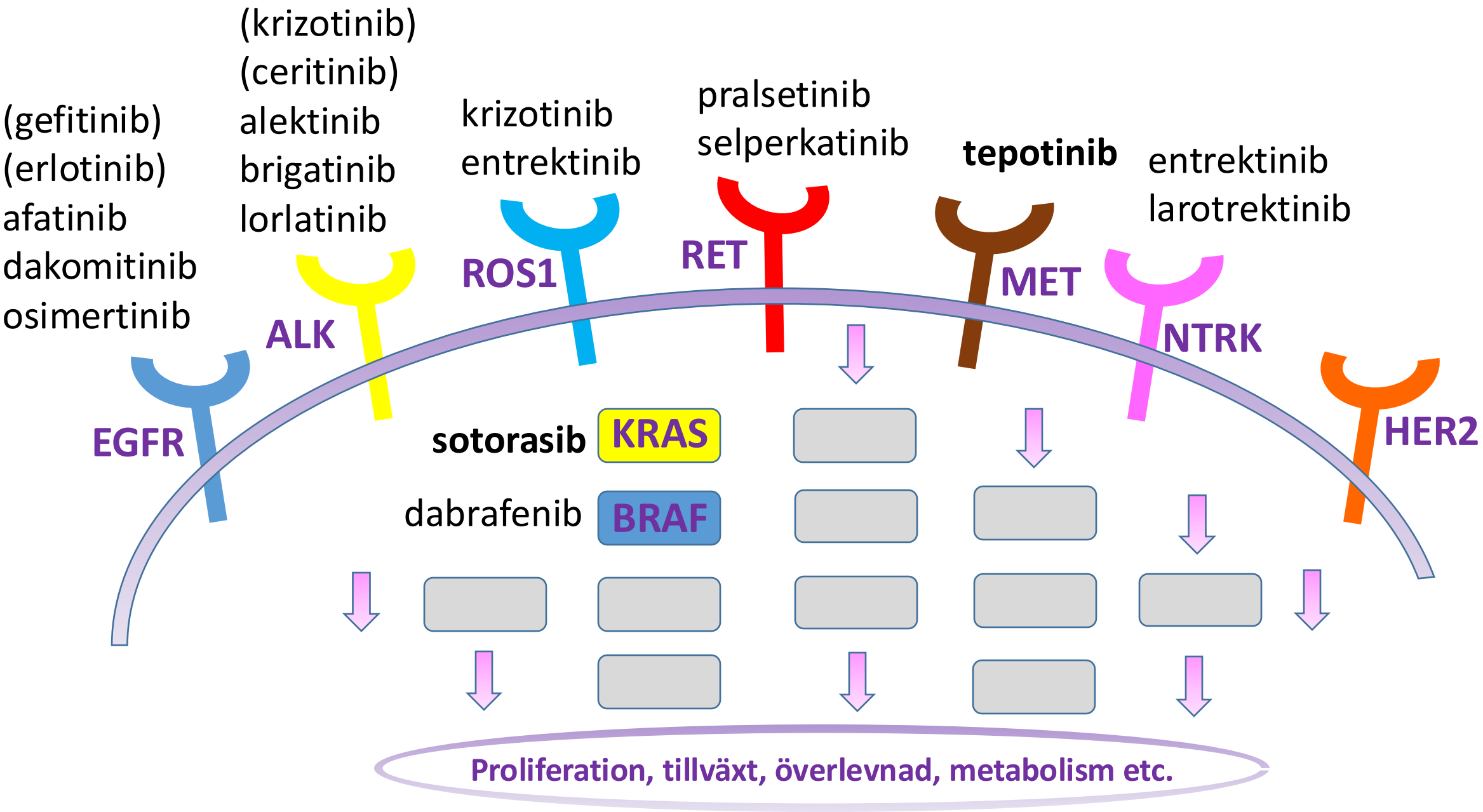


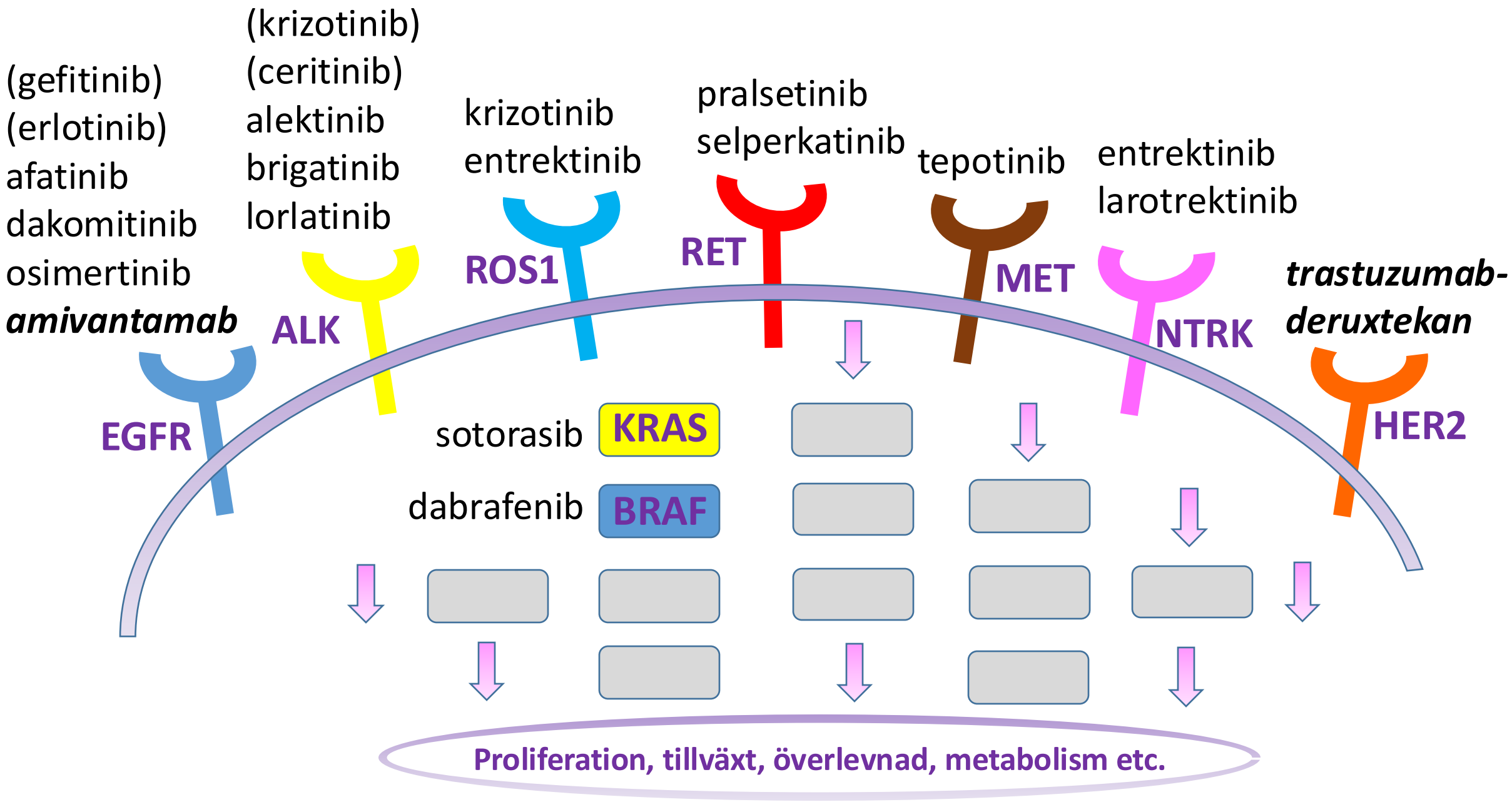
Amplifiering



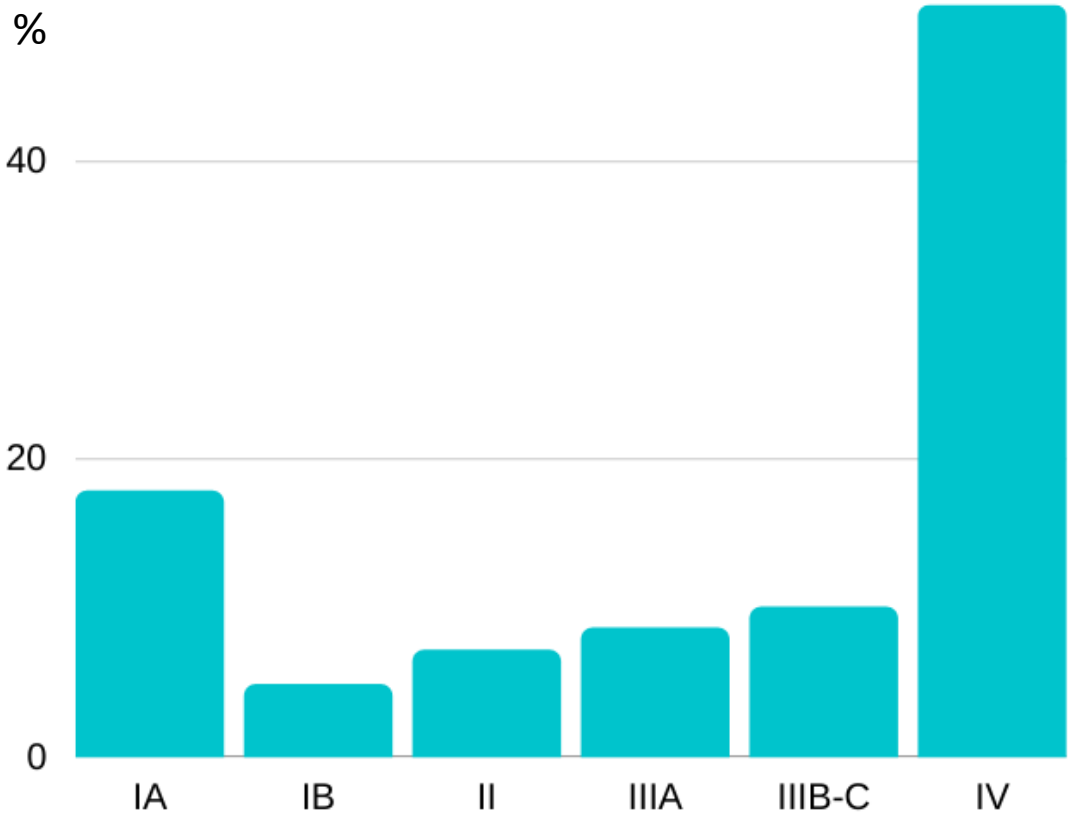

EGFR
ALK
ROS1
RET
MET
NTRK
HER2
KRAS
BRAF
Proliferation, tillväxt, överlevnad, metabolism etc.


(gefitinib)
(erlotinib)
afatinib
dakomitinib
osimertinib
(krizotinib)
(ceritinib)
alektinib
brigatinib
lorlatinib
krizotinib
entrektinib
pralsetinib
selperkatinib
entrektinib
larotrektinib
EGFR
ALK
ROS1
RET
MET
NTRK
HER2
KRAS
dabrafenib
BRAF
Proliferation, tillväxt, överlevnad, metabolism etc.


(gefitinib)
(erlotinib)
afatinib
dakomitinib
osimertinib
(krizotinib)
(ceritinib)
alektinib
brigatinib
lorlatinib
krizotinib
entrektinib
pralsetinib
selperkatinib
tepotinib
entrektinib
larotrektinib
EGFR
ALK
ROS1
RET
MET
NTRK
HER2
sotorasib
KRAS
dabrafenib
BRAF
Proliferation, tillväxt, överlevnad, metabolism etc.

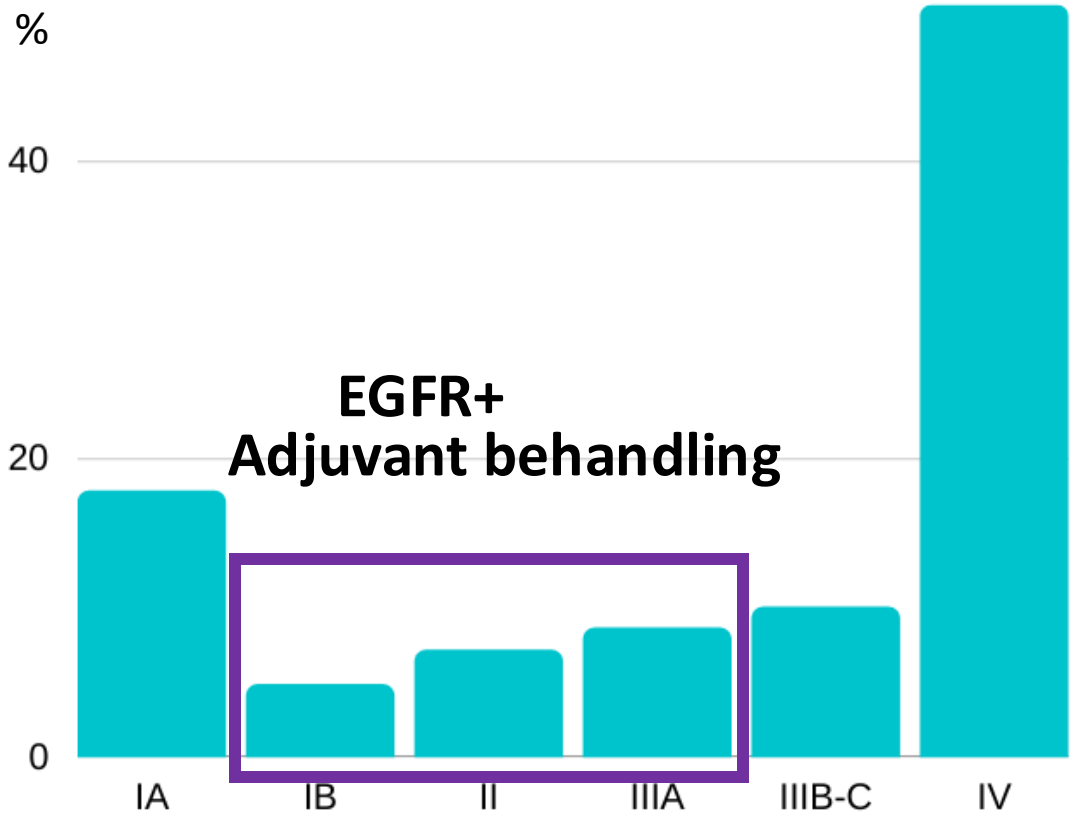

(gefitinib)
(erlotinib)
afatinib
dakomitinib
osimertinib
amivantamab
(krizotinib)
(ceritinib)
alektinib
brigatinib
lorlatinib
krizotinib
entrektinib
pralsetinib
selperkatinib
tepotinib
entrektinib
larotrektinib
trastuzumab-deruxtekan
EGFR
ALK
ROS1
RET
MET
NTRK
HER2
sotorasib
KRAS
dabrafenib
BRAF
Proliferation, tillväxt, överlevnad, metabolism etc.

Målriktad behandling, NSCLC

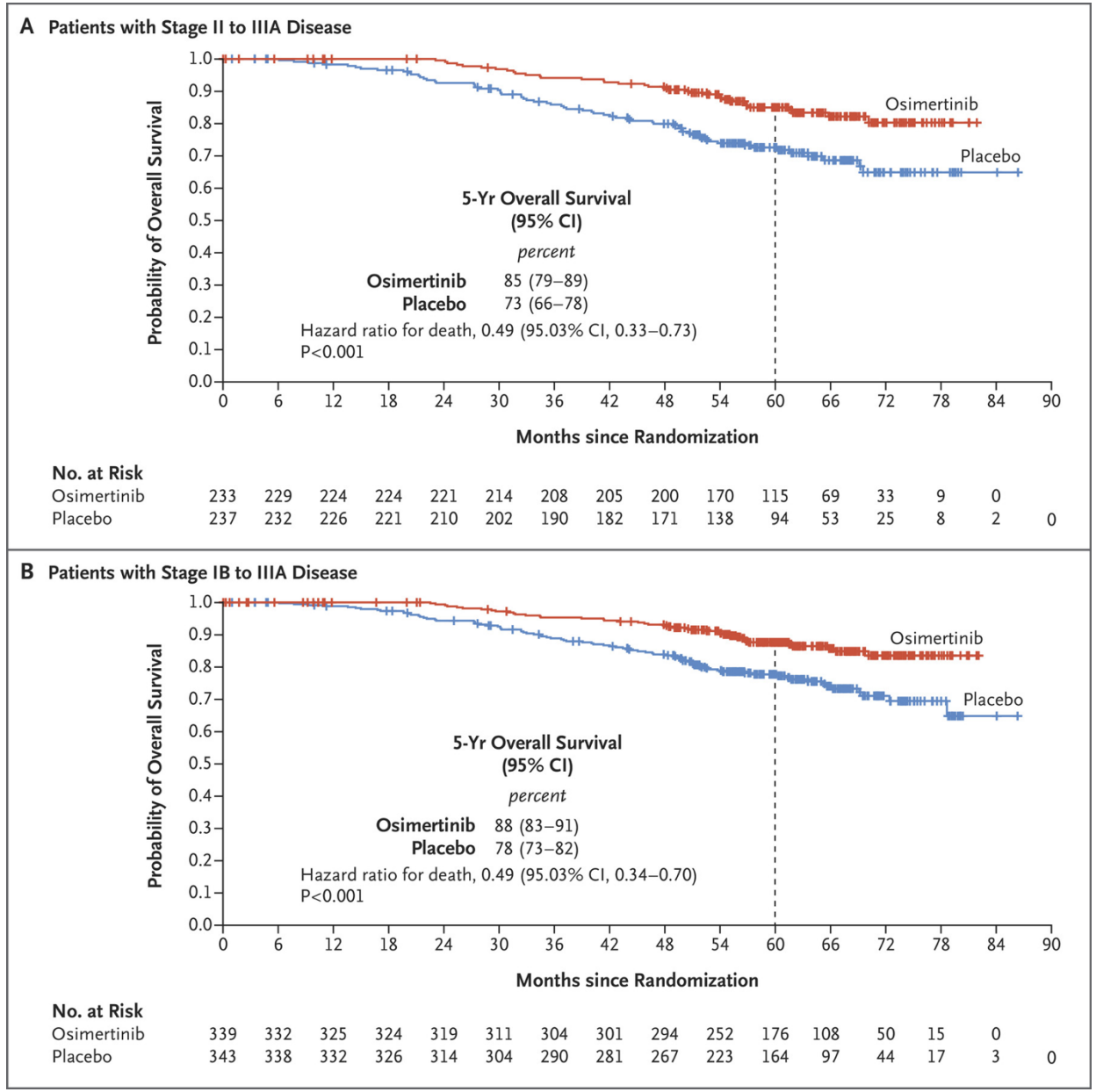


Stadium

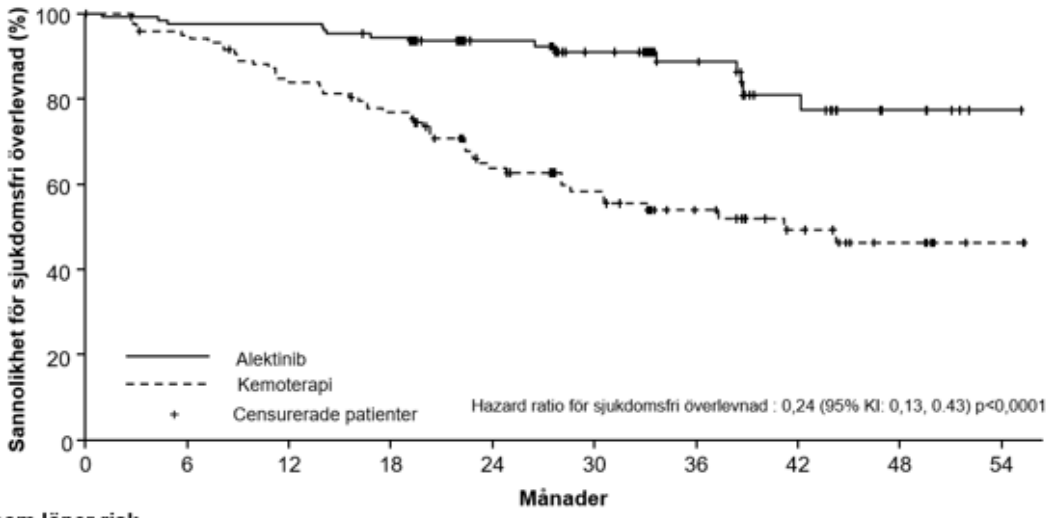
Målriktad behandling, NSCLC



ADAURA

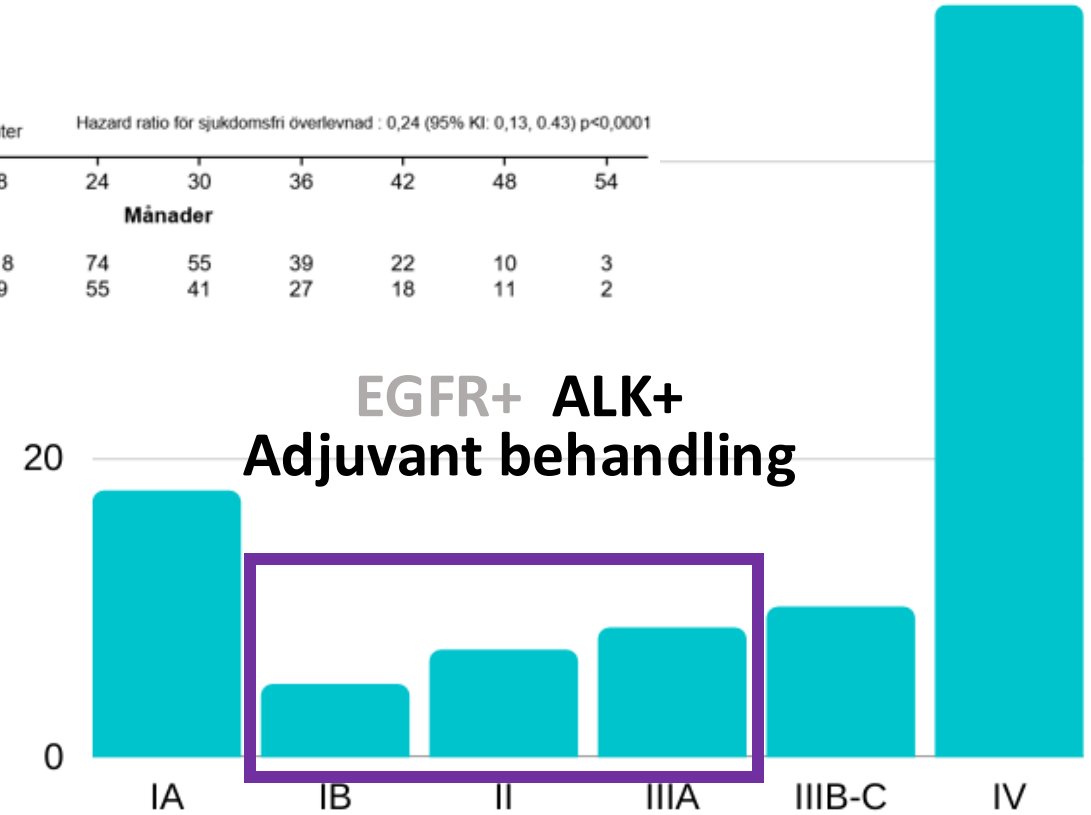

A Patients with Stage II to IIIA Disease
Probability of Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Osimertinib
Placebo
5-Yr Overall Survival
(95% CI)
percent
Osimertinib 85 (79–89)
Placebo 73 (66–78)
Hazard ratio for death, 0.49 (95.03% CI, 0.33–0.73)
P<0.001
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90
Months since Randomization
No. at Risk
Osimertinib 233 229 224 224 221 214 208 205 200 170 115 69 33 9 0
Placebo 237 232 226 221 210 202 190 182 171 138 94 53 25 8 2 0
B Patients with Stage IB to IIIA Disease
Probability of Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Osimertinib
Placebo
5-Yr Overall Survival
(95% CI)
percent
Osimertinib 88 (83–91)
Placebo 78 (73–82)
Hazard ratio for death, 0.49 (95.03% CI, 0.34–0.70)
P<0.001
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90
Months since Randomization
No. at Risk
Osimertinib 339 332 325 324 319 311 304 301 294 252 176 108 50 15 0
Placebo 343 338 332 326 314 304 290 281 267 223 164 97 44 17 3 0

ALINA (N Engl J Med 2024;390:1265-1276)

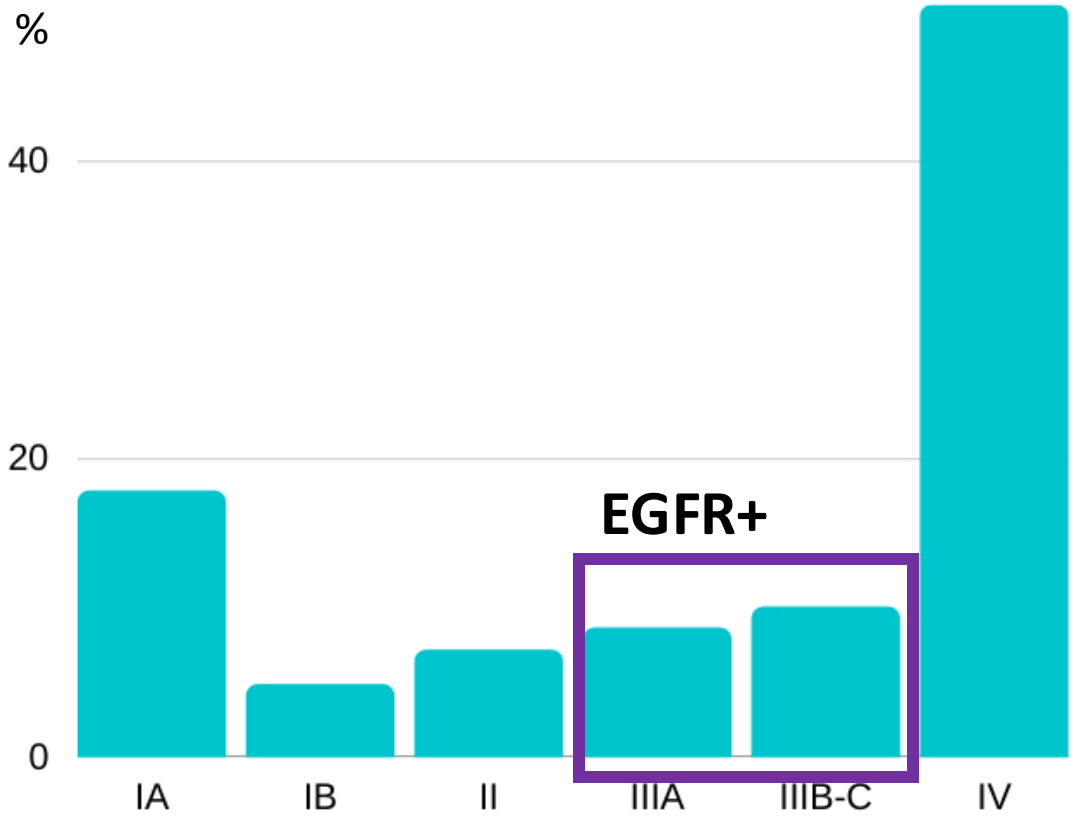


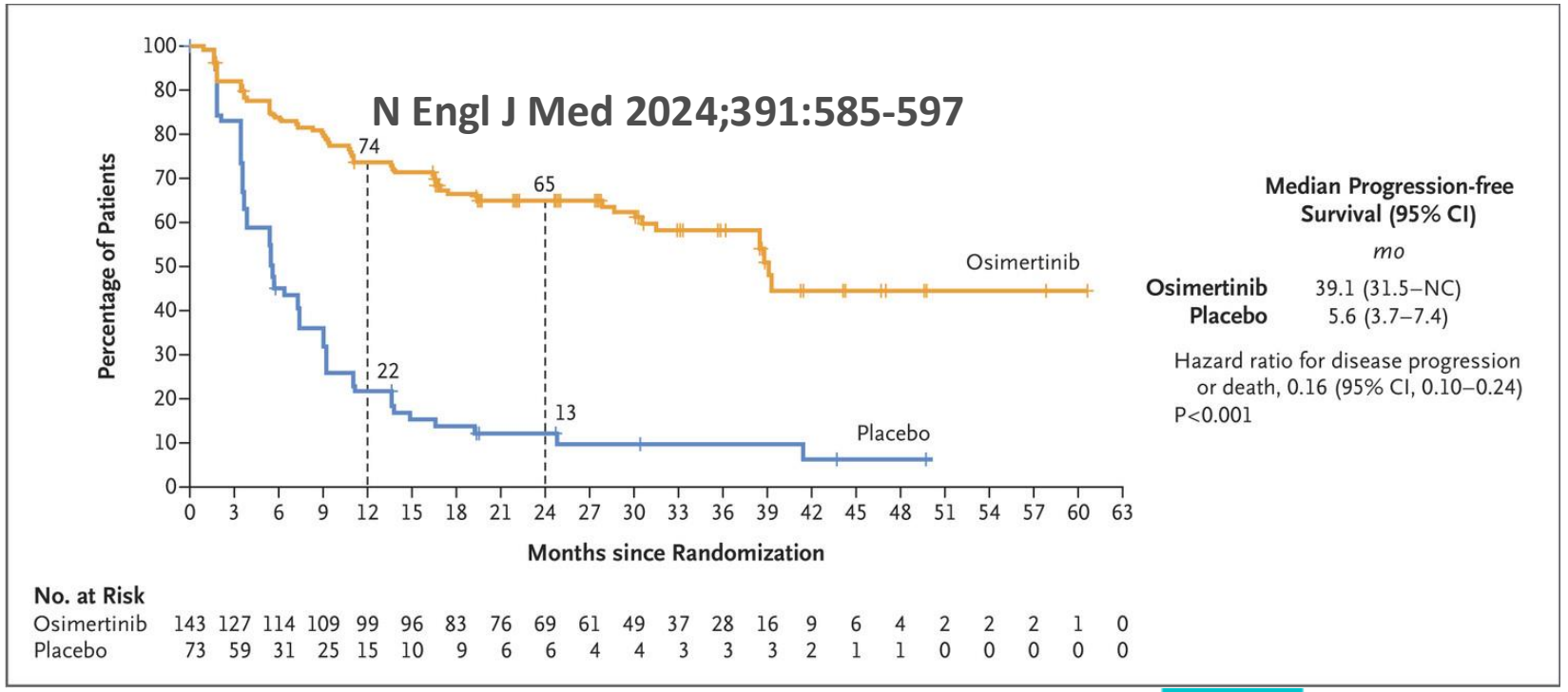
Patienter som löper risk

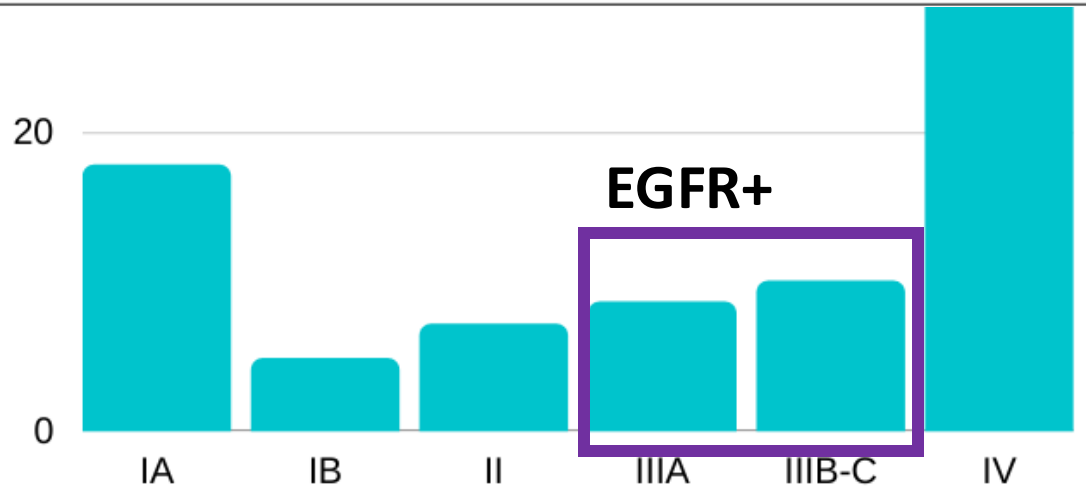
Alektinib	130	123	123	118	74	55	39	22	10	3
Kemoterapi	127	112	98	89	55	41	27	18	11	2



Målriktad behandling, NSCLC



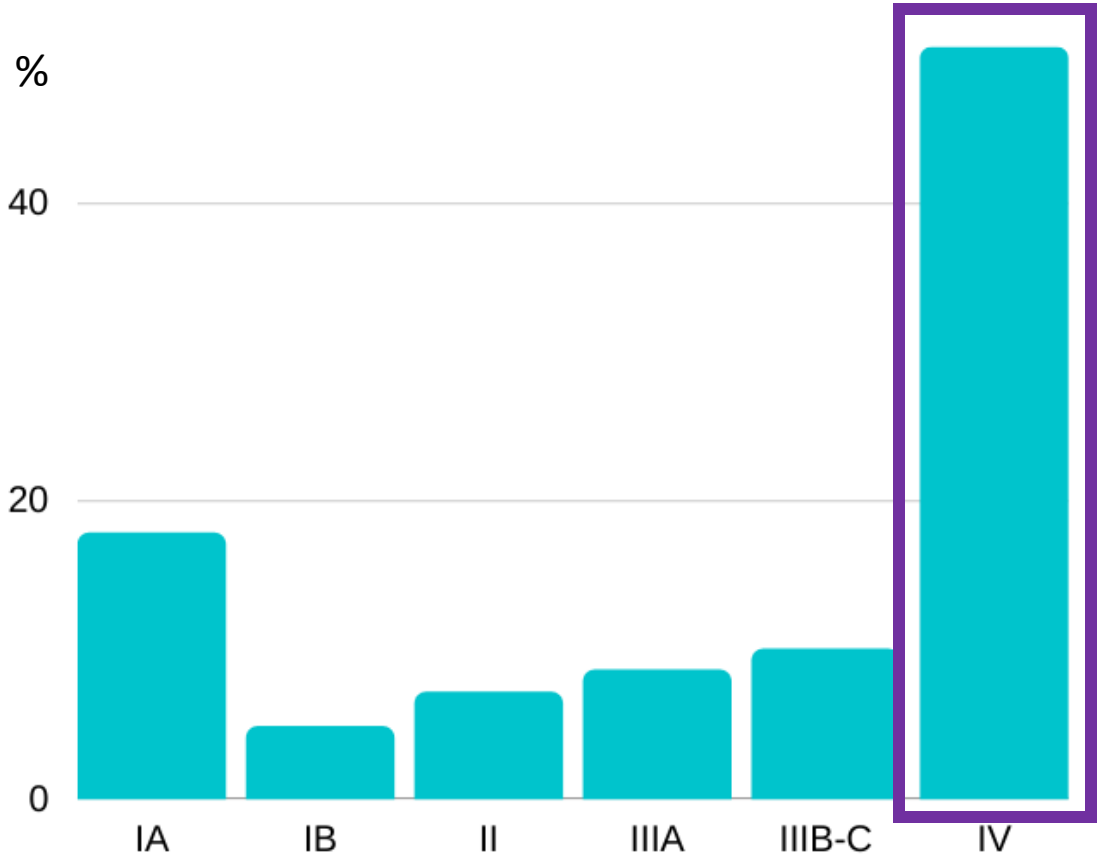

N Engl J Med 2024;391:585-597
Percentage of Patients
Months since Randomization
Osimertinib
Placebo
74
65
22
13
Median Progression-free Survival (95% CI)
mo
Osimertinib 39.1 (31.5–NC)
Placebo 5.6 (3.7–7.4)
Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001
No. at Risk
Osimertinib 143 127 114 109 99 96 83 76 69 61 49 37 28 16 9 6 4 2 2 2 1 0
Placebo 73 59 31 25 15 10 9 6 6 4 4 3 3 3 2 1 1 0 0 0 0 0


20
0
EGFR+
IA
IB
II
IIIA
IIIB-C
IV

Stadium

Målriktad behandling, NSCLC

Palliativ behandling, 9 olika gener



Stadium

Vilken/vilka behandlingslinje(r)?

I första linjen: ***EGFR, BRAFV600, ALK, ROS1, RET, NTRK***

Senare linje: ***KRASG12C, MET exon 14 skipping, (EGFR exon 20 ins, HER2)***

Flera linjer på varandra: ***EGFR, ALK, ROS1***

Vilken/vilka behandlingslinje(r)?

I första linjen: ***EGFR, BRAFV600, ALK, ROS1, RET, NTRK***

Senare linje: ***KRASG12C, MET exon 14 skipping, (EGFR exon 20 ins, HER2)***

Flera linjer på varandra: ***EGFR, ALK, ROS1***

1:a generationens EGFR-TKI:

Gefitinib (PFS 10 m. Ej CNS penetration.)

Erlotinib (PFS 10 m. Ej CNS penetration.)

2:a generationen:

Afatinib (PFS 11.1 m)

Dacomitinib (PFS 14.7 m)

3:e generationen:

Osimertinib (PFS 18.9 m, 1:a linjen)

Osimertinib (PFS 10-12 m, 2:a linjen)

Lancet Oncol 2016; 17: 577–89

Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial

Keunchil Park, Eng-Huat Tan, Ken O'Byrne, Li Zhang, Michael Boyer, Tony Mok, Vera Hirsh, James Chih-Hsin Yang, Ki Hyeong Lee, Shun Lu, Yuankai Shi, Sang-We Kim, Janessa Laskin, Dong-Wan Kim, Catherine Dubos Arvis, Karl Kölbeck, Scott A Laurie, Chun-Ming Tsai, Mehdi Shahidi, Miyoung Kim, Dan Massey, Victoria Zazulina, Luis Paz-Ares

Lancet Oncol 2017; 18: 1454–66

Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial

Yi-Long Wu, Ying Cheng, Xiangdong Zhou, Ki Hyeong Lee, Kazuhiko Nakagawa, Seiji Niho, Fumito Tsuji, Rolf Linke, Rafael Rosell, Jesus Corral, Maria Rita Migliorino, Adam Pluzanski, Eric I Sbar, Tao Wang, Jane Liang White, Sashi Nadanaciva, Rickard Sandin, Tony S Mok

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

1:a generationens EGFR-TKI:

Gefitinib (PFS 10 m. Ej CNS penetration.)

Erlotinib (PFS 10 m. Ej CNS penetration.)

2:a generationen:

Afatinib (PFS 11.1 m)

Dacomitinib (PFS 14.7 m)

3:e generationen:

Osimertinib (PFS 18.9 m, 1:a linjen)

Osimertinib (PFS 10-12 m, 2:a linjen)

Lancet Oncol 2016; 17: 577–89

Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial

Keunchil Park, Eng-Huat Tan, Ken O'Byrne, Li Zhang, Michael Boyer, Tony Mok, Vera Hirsh, James Chih-Hsin Yang, Ki Hyeong Lee, Shun Lu, Yuankai Shi, Sang-We Kim, Janessa Laskin, Dong-Wan Kim, Catherine Dubos Arvis, Karl Kölbeck, Scott A Laurie, Chun-Ming Tsai, Mehdi Shahidi, Miyoung Kim, Dan Massey, Victoria Zazulina, Luis Paz-Ares

Lancet Oncol 2017; 18: 1454–66

Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial

Yi-Long Wu, Ying Cheng, Xiangdong Zhou, Ki Hyeong Lee, Kazuhiko Nakagawa, Seiji Niho, Fumito Tsuji, Rolf Linke, Rafael Rosell, Jesus Corral, Maria Rita Migliorino, Adam Pluzanski, Eric I Sbar, Tao Wang, Jane Liang White, Sashi Nadanaciva, Rickard Sandin, Tony S Mok

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

1:a generationens EGFR-TKI:

Gefitinib (PFS 10 m. Ej CNS penetration.)

Erlotinib (PFS 10 m. Ej CNS penetration.)

2:a generationen:

Afatinib (PFS 11.1 m)

Dacomitinib (PFS 14.7 m)

3:e generationen:

Osimertinib (PFS 18.9 m, 1:a linjen)

Osimertinib (PFS 10-12 m, 2:a linjen)

Lancet Oncol 2016; 17: 577–89

Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial

Keunchil Park, Eng-Huat Tan, Ken O'Byrne, Li Zhang, Michael Boyer, Tony Mok, Vera Hirsh, James Chih-Hsin Yang, Ki Hyeong Lee, Shun Lu, Yuankai Shi, Sang-We Kim, Janessa Laskin, Dong-Wan Kim, Catherine Dubos Arvis, Karl Kölbeck, Scott A Laurie, Chun-Ming Tsai, Mehdi Shahidi, Miyoung Kim, Dan Massey, Victoria Zazulina, Luis Paz-Ares

Lancet Oncol 2017; 18: 1454–66

Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial

Yi-Long Wu, Ying Cheng, Xiangdong Zhou, Ki Hyeong Lee, Kazuhiko Nakagawa, Seiji Niho, Fumito Tsuji, Rolf Linke, Rafael Rosell, Jesus Corral, Maria Rita Migliorino, Adam Pluzanski, Eric I Sbar, Tao Wang, Jane Liang White, Sashi Nadanaciva, Rickard Sandin, Tony S Mok

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

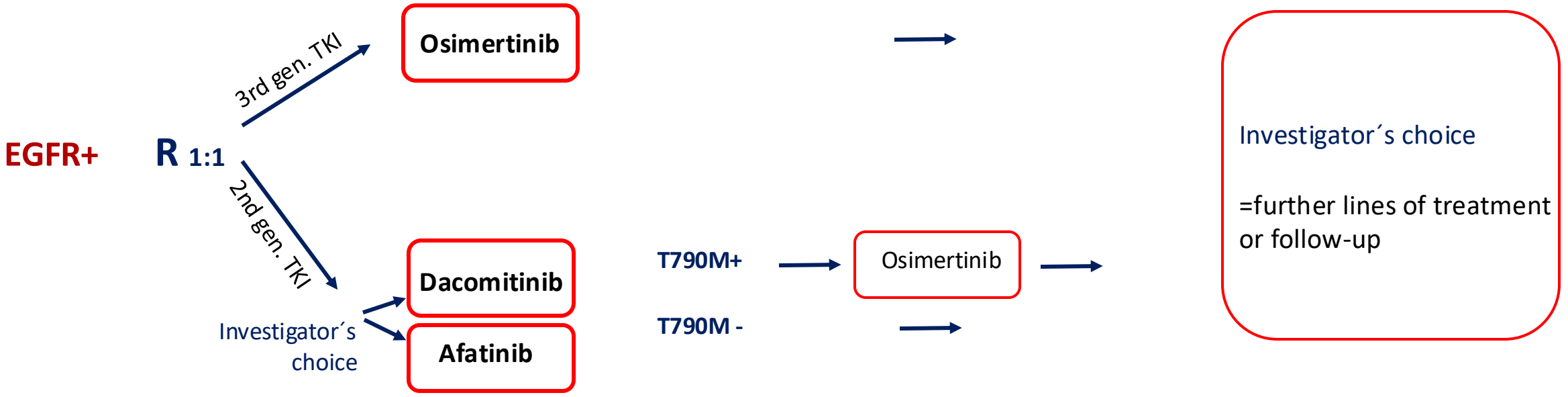
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

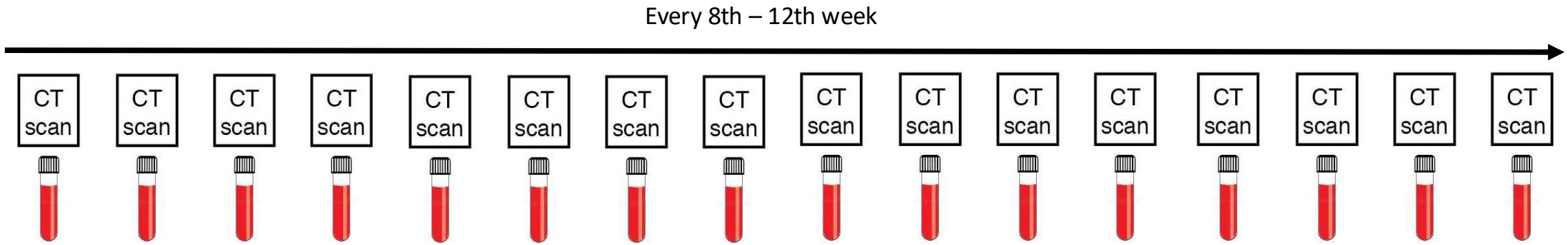
J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

EudraCT no. 2021-003755-41

ERIS (ongoing randomized phase III trial)

Study period 2023-2028 (n=200)





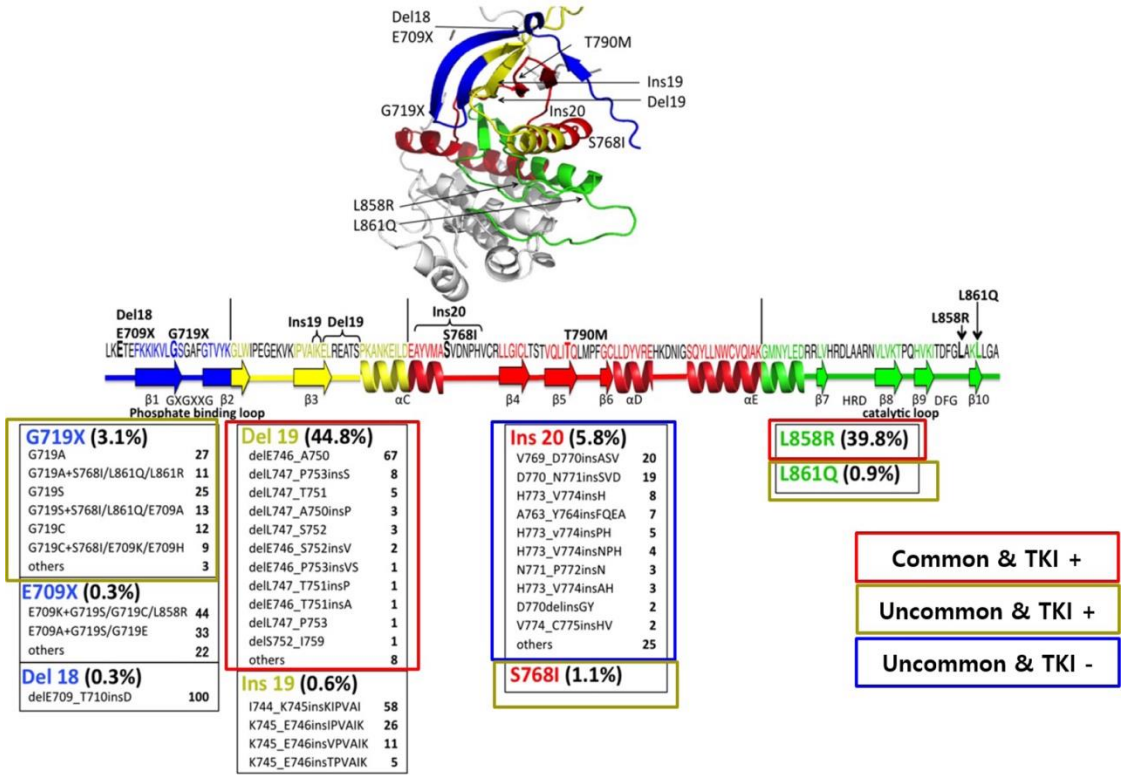
Randomiserade patienter i ERIS

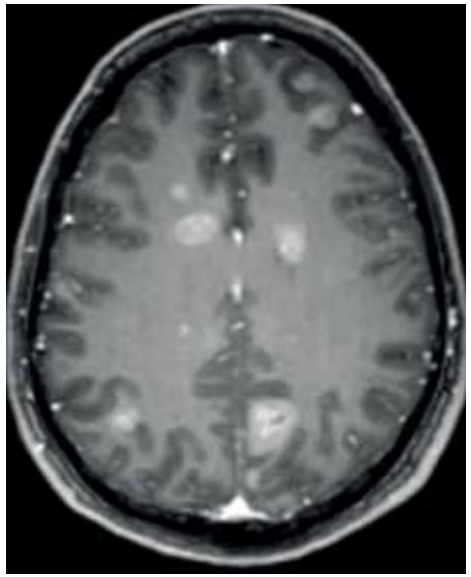
Norr	Umeå	0
Mellansverige	Uppsala	1
	Falun	2
	Örebro	3
	Gävle	0
Väst	Göteborg	6
Sthlm-Gotland	Stockholm	19
Sydost	Linköping	0
Syd	Lund (Halmstad)	18 (3)
	Kristianstad	4
TOTALT		**53** av 200 planerade pat

ERIS, forts

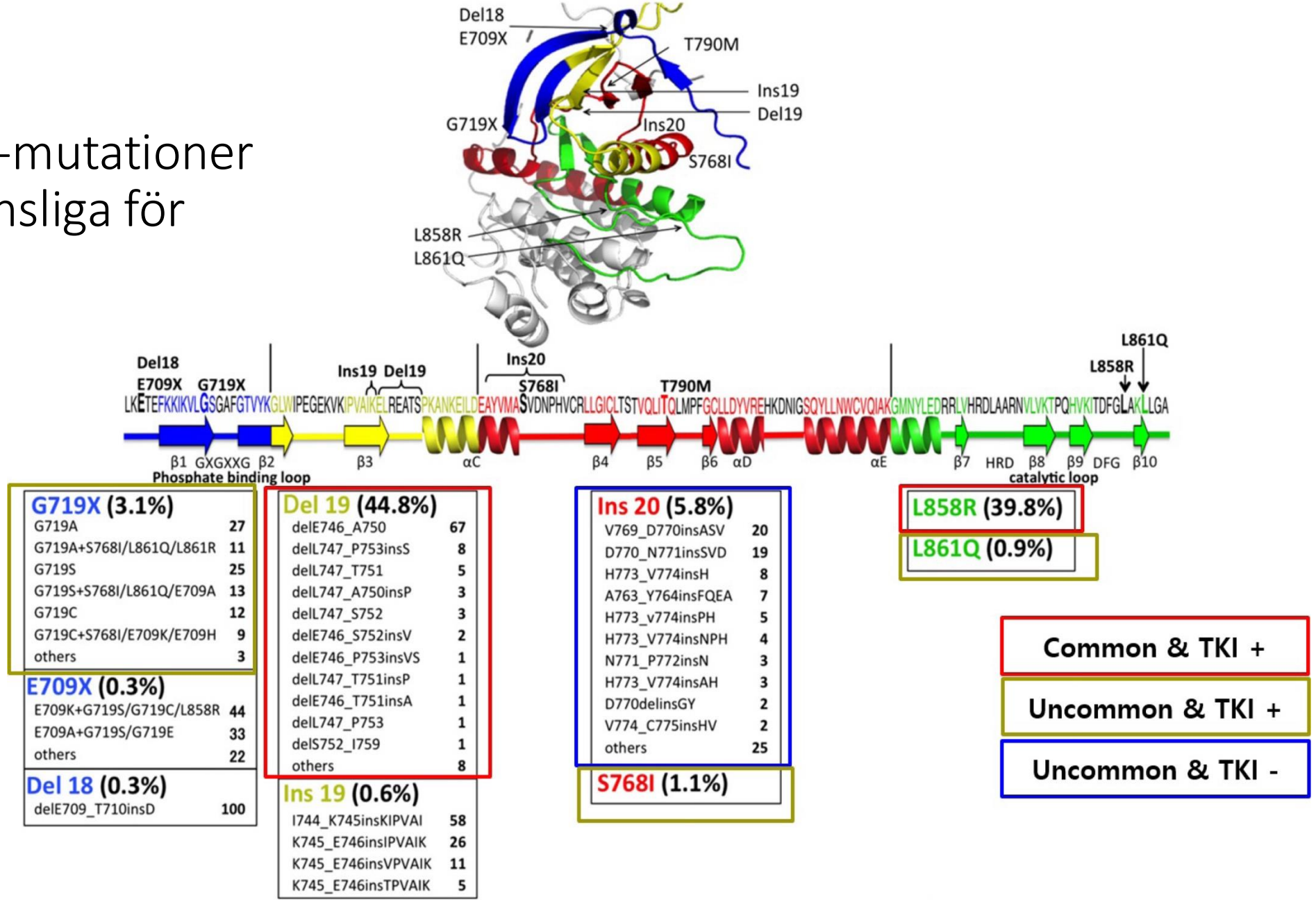
- Mutationstyp
  - Exon 19 deletion
  - L858R
  - Ovanlig mutation eller >1 mutation

- CNS-metastas(er) vid baseline
  - Ja
  - Nej





Alla *EGFR*-mutationer är inte känsliga för EGFR-TKI



G719X (3.1%)	
G719A	27
G719A+S768I/L861Q/L861R	11
G719S	25
G719S+S768I/L861Q/E709A	13
G719C	12
G719C+S768I/E709K/E709H	9
others	3

E709X (0.3%)	
E709K+G719S/G719C/L858R	44
E709A+G719S/G719E	33
others	22

Del 18 (0.3%)	
delE709_T710insD	100

Del 19 (44.8%)	
delE746_A750	67
delL747_P753insS	8
delL747_T751	5
delL747_A750insP	3
delL747_S752	3
delE746_S752insV	2
delE746_P753insVS	1
delL747_T751insP	1
delE746_T751insA	1
delL747_P753	1
delS752_I759	1
others	8

Ins 19 (0.6%)	
I744_K745insKIPVAI	58
K745_E746insIPVAIK	26
K745_E746insVPVAIK	11
K745_E746insTPVAIK	5

Ins 20 (5.8%)	
V769_D770insASV	20
D770_N771insSVD	19
H773_V774insH	8
A763_Y764insFQEA	7
H773_v774insPH	5
H773_V774insNPH	4
N771_P772insN	3
H773_V774insAH	3
D770delinsGY	2
V774_C775insHV	2
others	25

S768I (1.1%)

L858R (39.8%)

L861Q (0.9%)

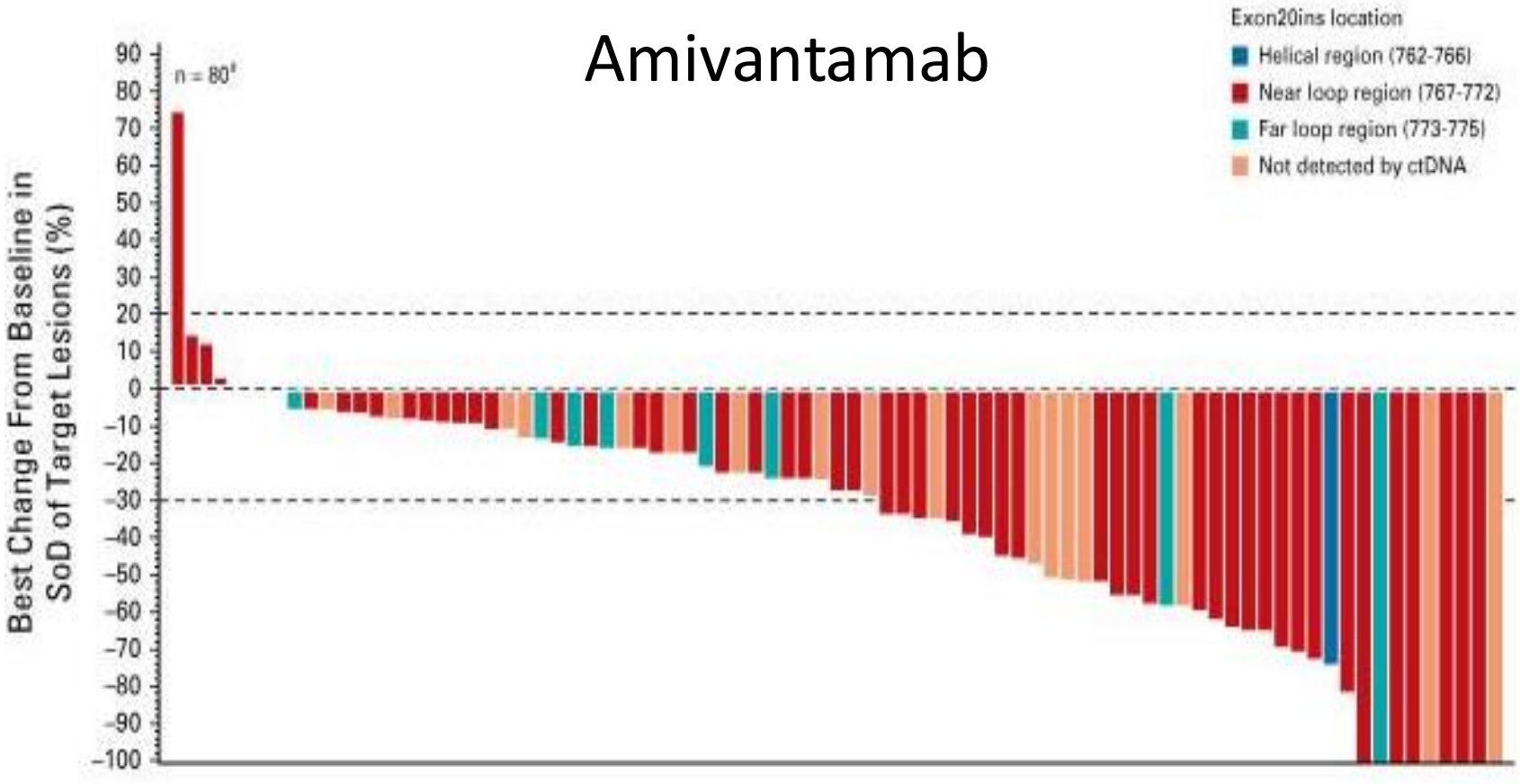
Common & TKI +

Uncommon & TKI +

Uncommon & TKI -

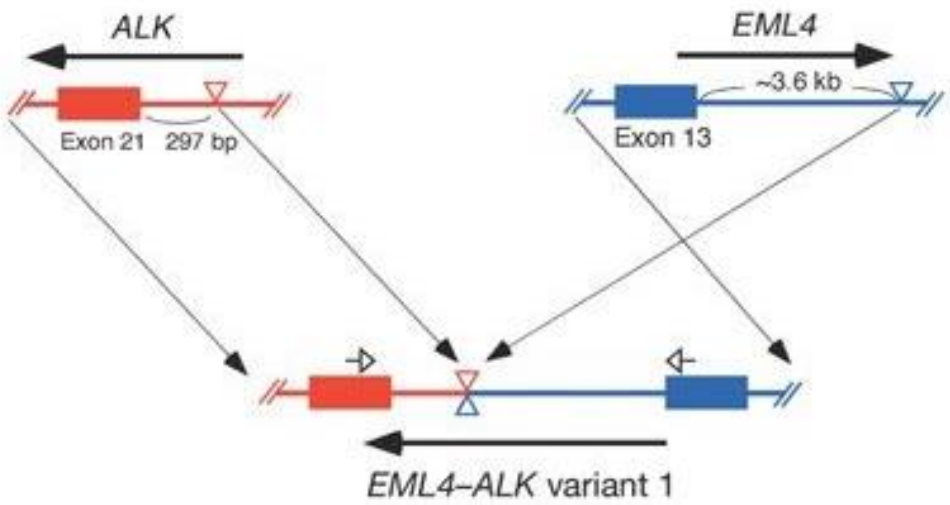
EGFR
Insertion exon 20

Amivantamab

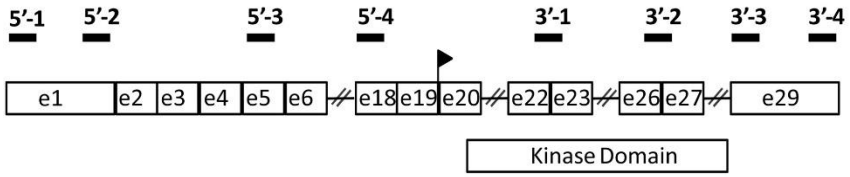


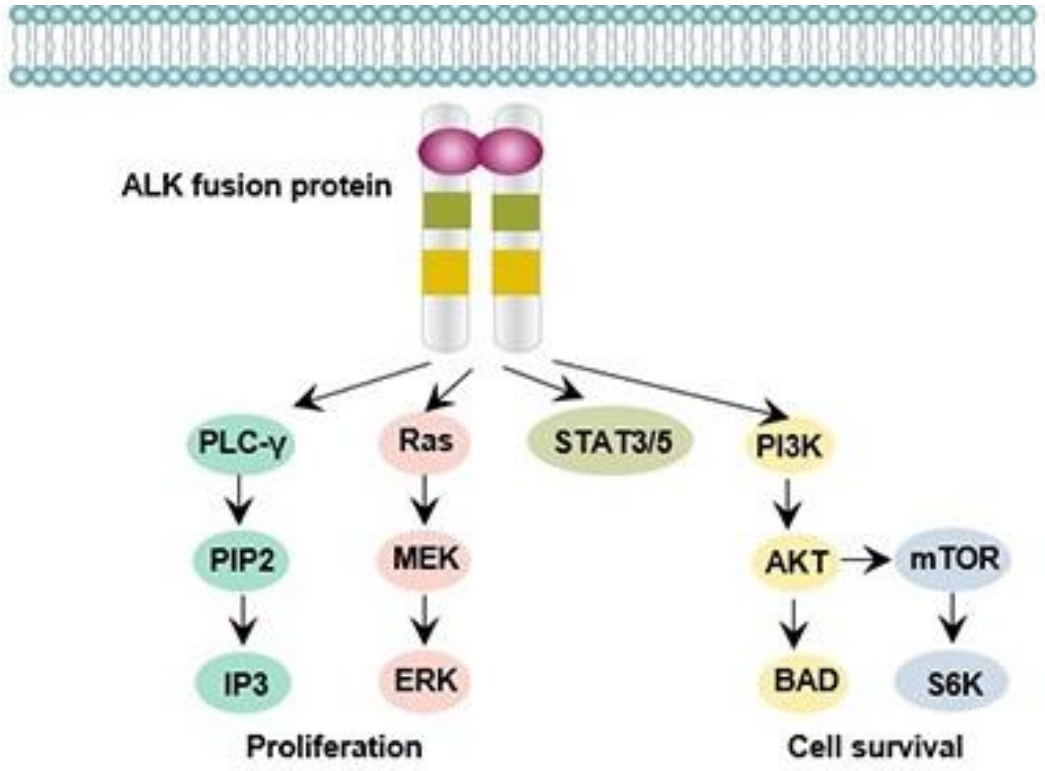
J Clin Oncol. 2021 Oct 20;39(30):3391-3402.

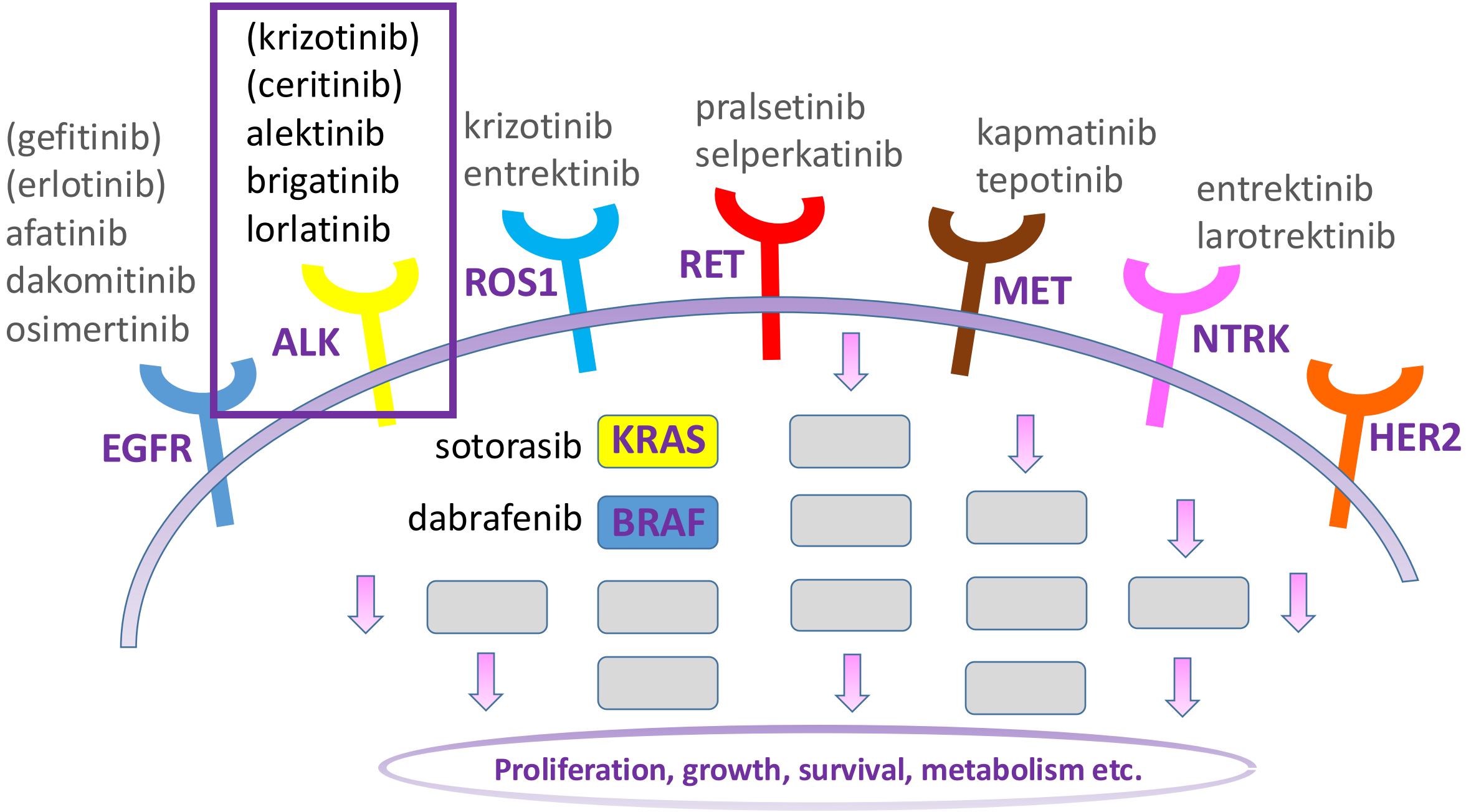
ALK-fusion (5% av NSCLC)



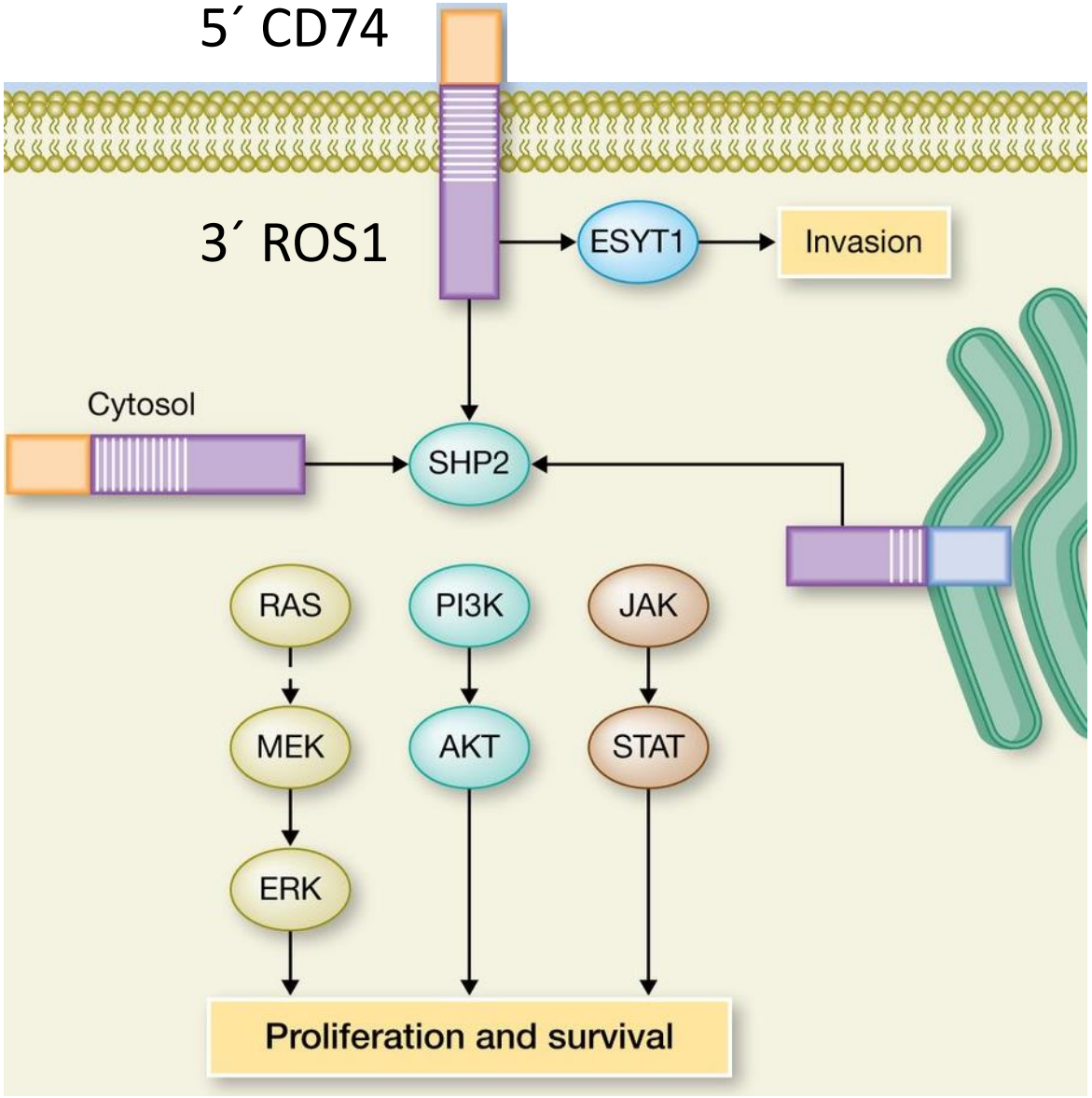
3’ : High expression

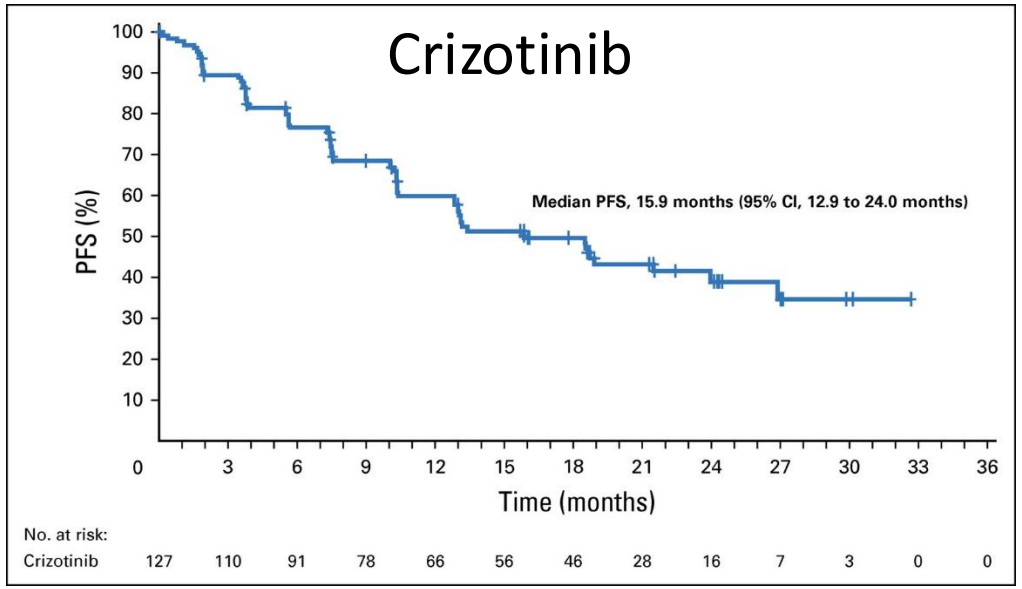


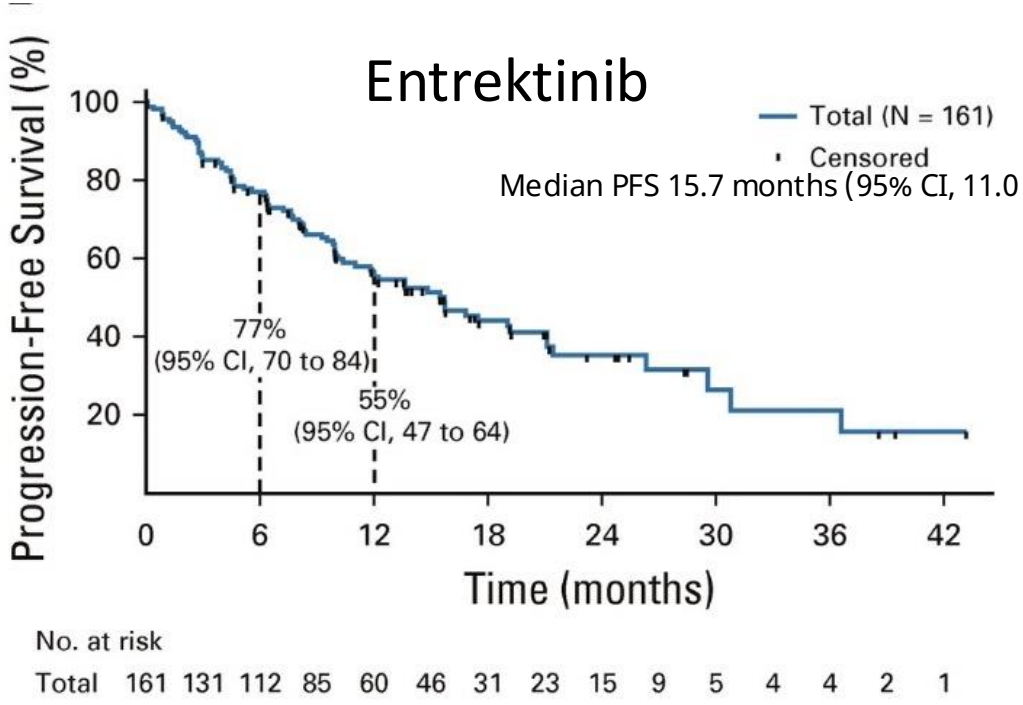



(krizotinib)
(ceritinib)
alektinib
brigatinib
lorlatinib
(gefitinib)
(erlotinib)
afatinib
dakomitinib
osimertinib
krizotinib
entrektinib
pralsetinib
selperkatinib
kapmatinib
tepotinib
entrektinib
larotrektinib
ALK
ROS1
RET
MET
NTRK
EGFR
HER2
sotorasib
KRAS
dabrafenib
BRAF
Proliferation, growth, survival, metabolism etc.

ROS1 fusion (2%)

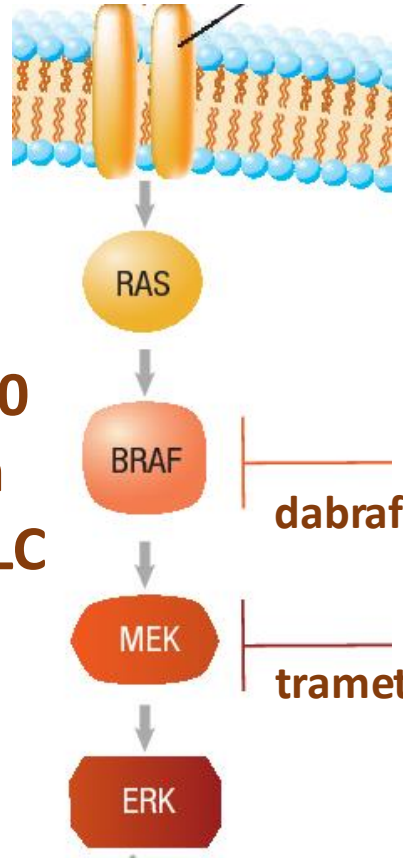






Median PFS 15.7 months (95% CI, 11.0 to 21.1).

BRAF V600 mutation (2%)



***BRAF*V600 Mutation ~2% NSCLC**

dabrafenib

trametinib

Proliferation

Dabrafenib plus Trametinib

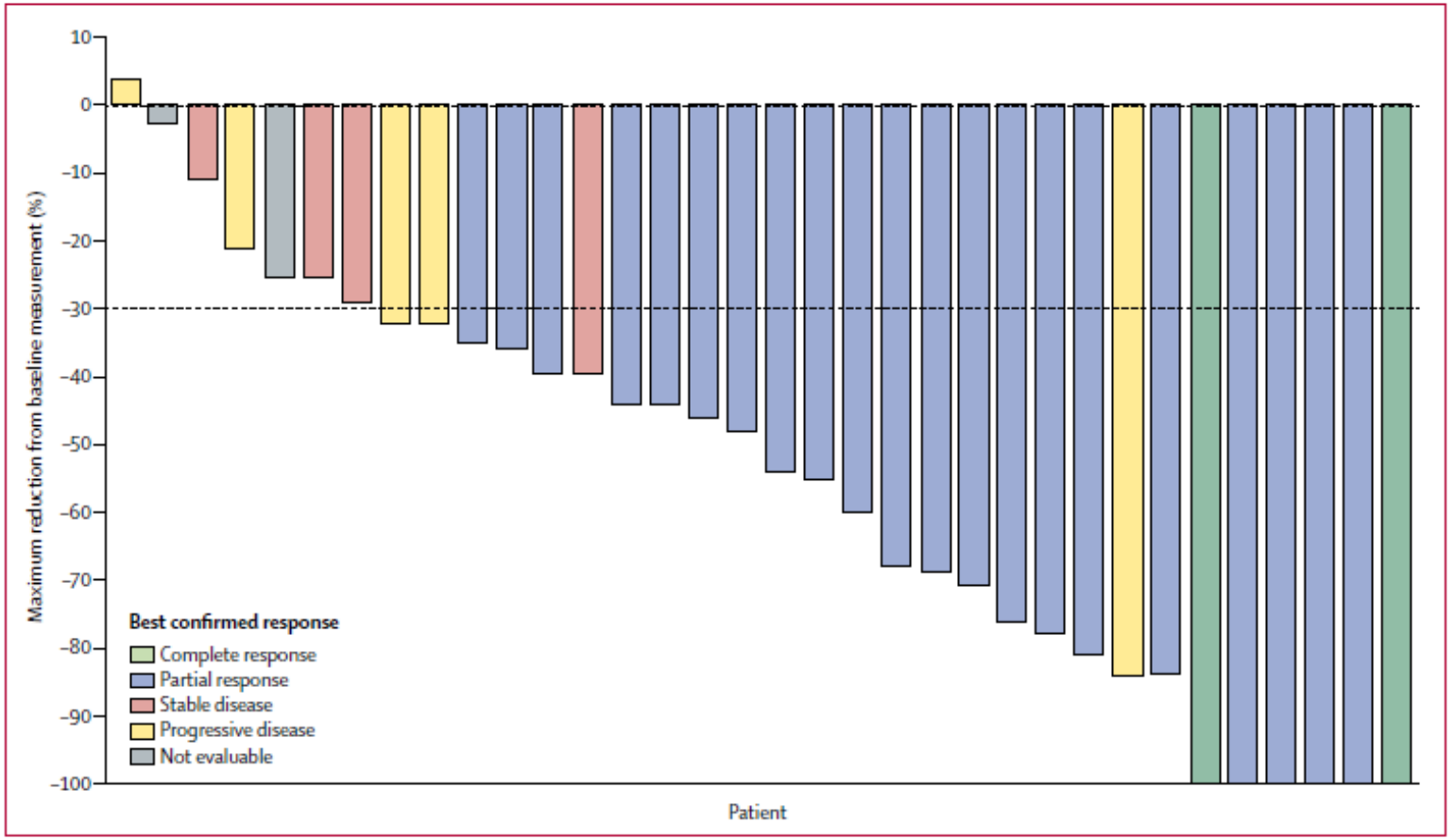


***Figure 2*: Confirmed maximum reduction in target lesions according to investigator assessment**
Dashed line at –30% represents the threshold for partial response, according to Response Evaluation Criteria In Solid Tumors version 1.1. Bars show maximum reduction from baseline sum of diameters by best confirmed response. Two patients were not included because they did not have a post-baseline assessment of target lesions.

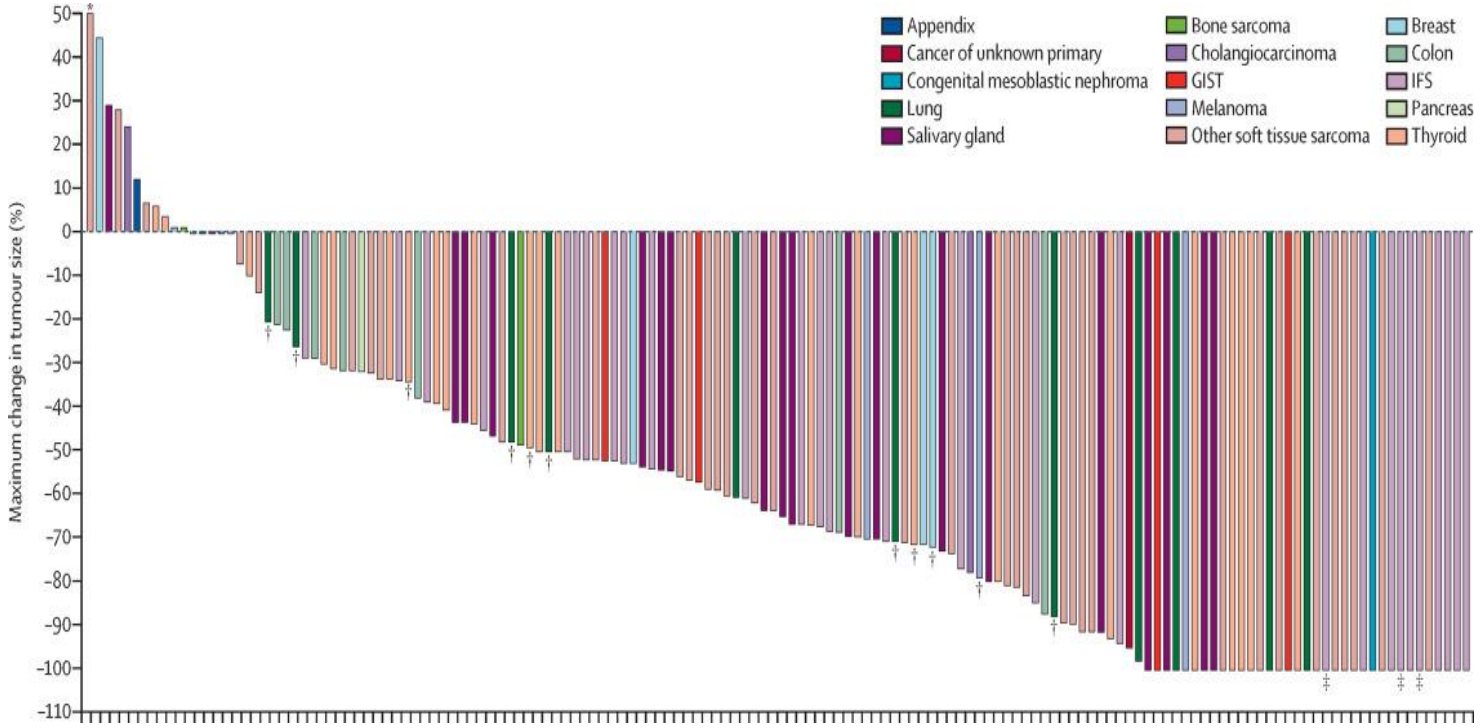
Planchard *et al.* Lancet Oncol 2017

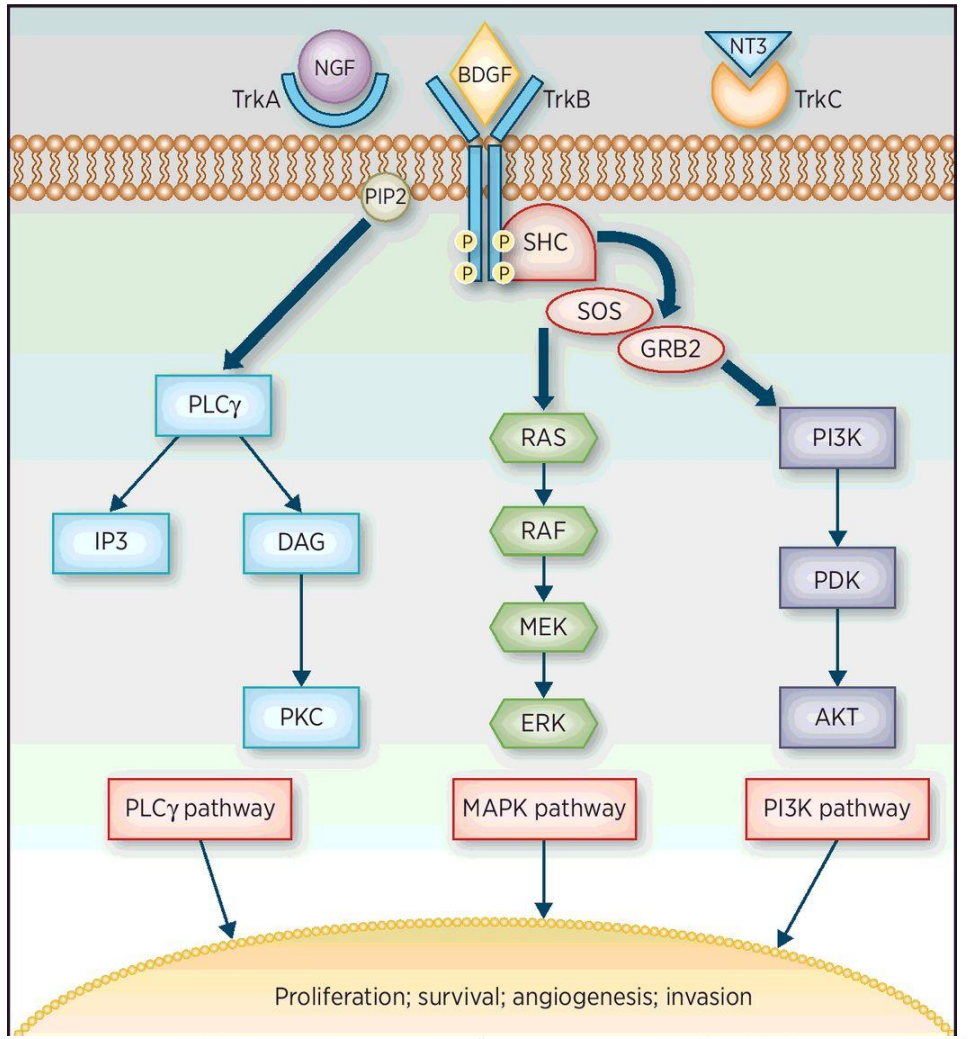
NTRK-fusion

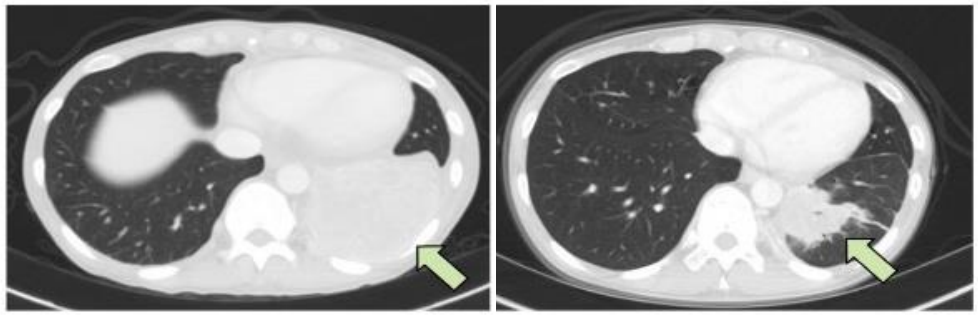
<0.5% av NSCLC

=Låg frekvens men i <u>>20 tumörtyper</u>

Entrektinib (*NTRK*- och *ROS1*-fusioner)

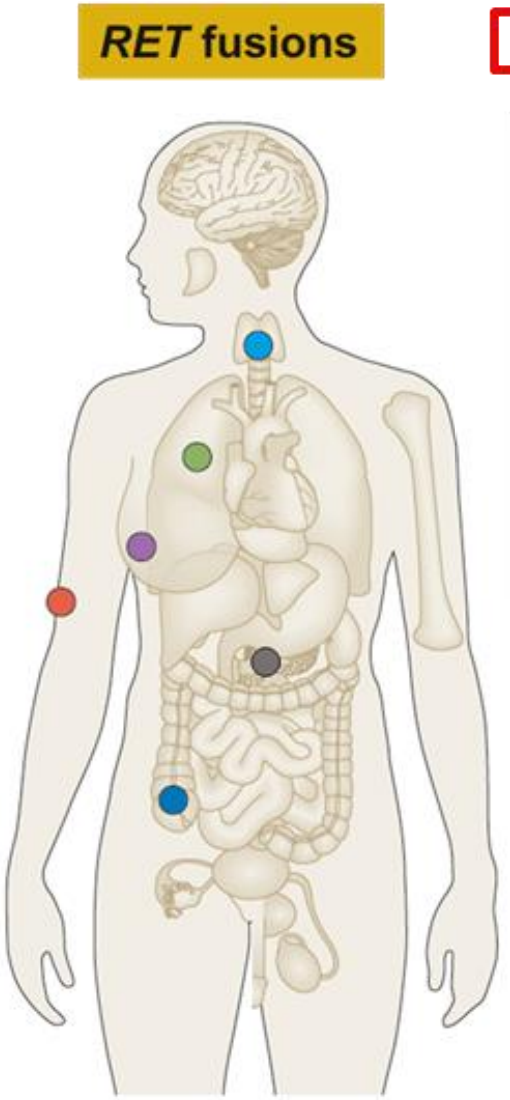






Baseline 4 mån

RET-fusion, 2-3% av NSCLC



Non-small cell lung cancer (2%)

Thyroid cancers (10–20%)

Pancreatic cancer (<1%)

Salivary gland cancer (<1%)

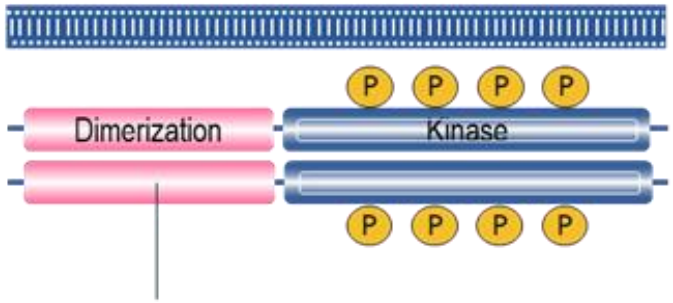
Spitz tumors (<1%)

Colorectal cancer (<1%)

Ovarian cancer (<1%)

Myeloproliferative disorders (<1%)

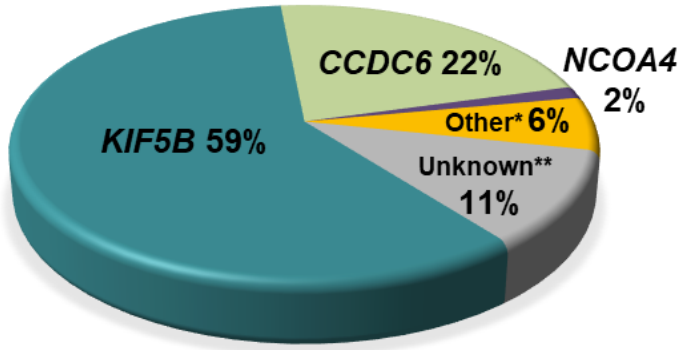
Many others (<1%)



KIF5B (most common in lung cancer)

CCDC6* or *NCOA4 (most common in thyroid cancer)

***RET* fusion partner (n=144)**



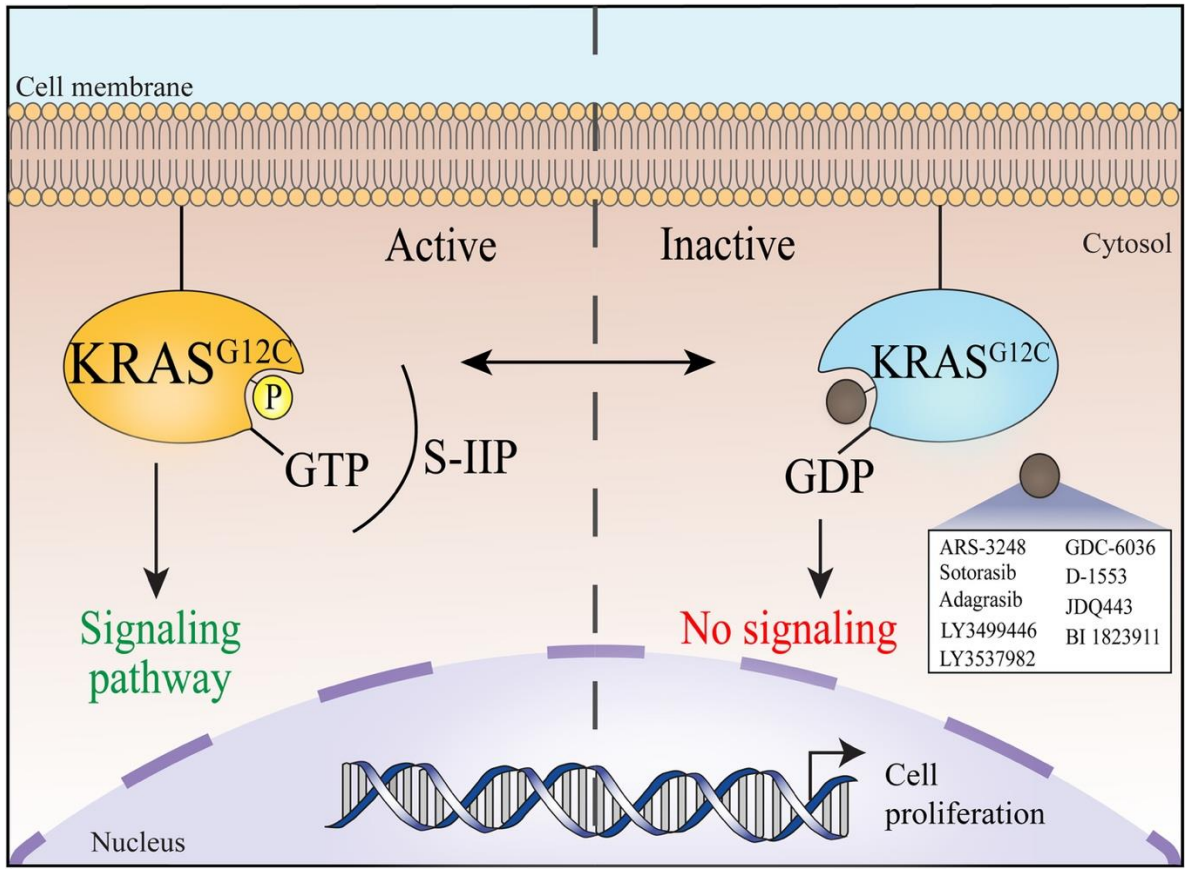
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

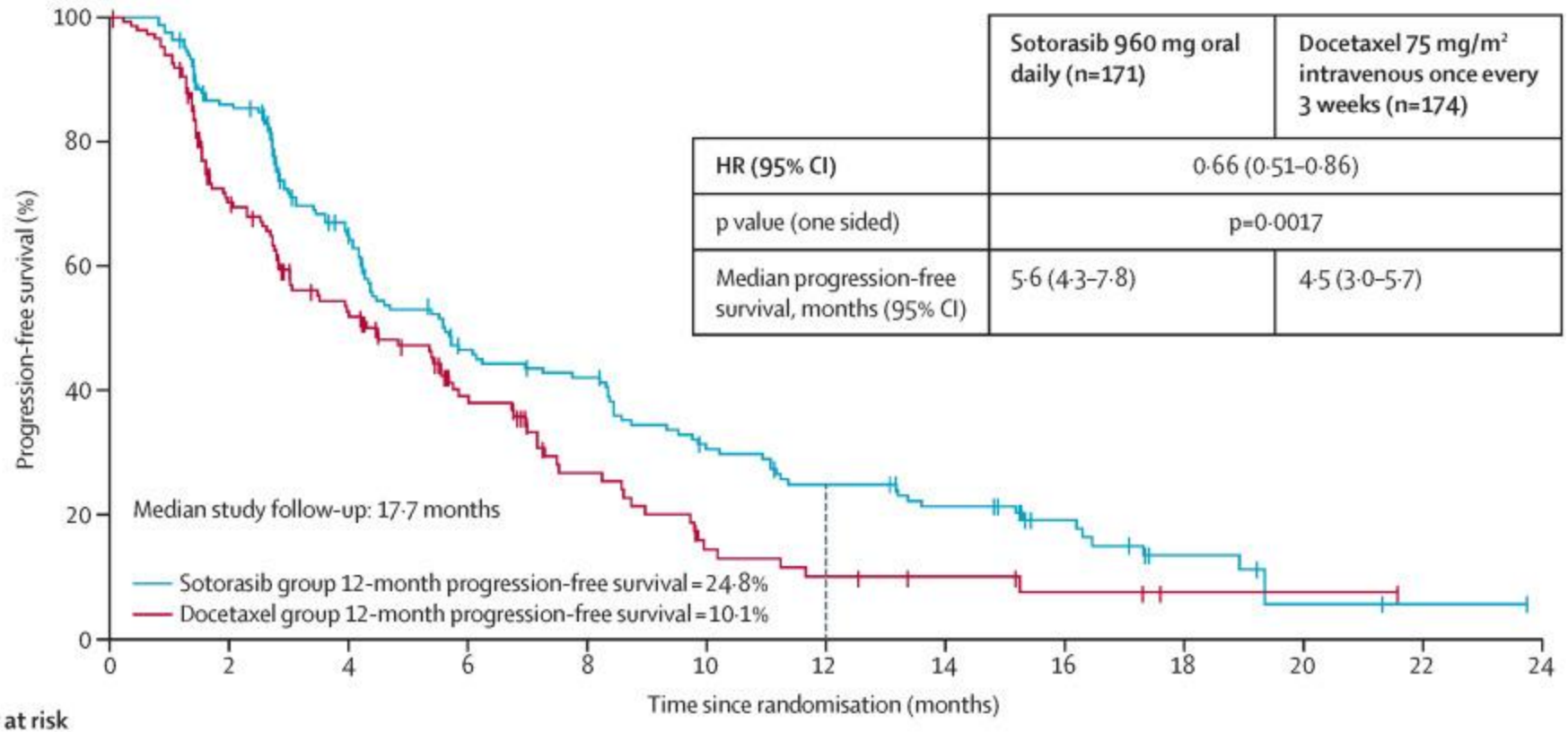
A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C.E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.-J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P.A. Cassier, L. Bazhenova, F. De Braud, E. Garralda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.M. Rothenberg, K. Goto, and V. Subbiah

Sotorasib: en selektiv *KRAS* G12C-hämmare



CodeBreak200

A



	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
HR (95% CI)	0·66 (0·51–0·86)	
p value (one sided)	p=0·0017	
Median progression-free survival, months (95% CI)	5·6 (4·3–7·8)	4·5 (3·0–5·7)

Number at risk (number censored)

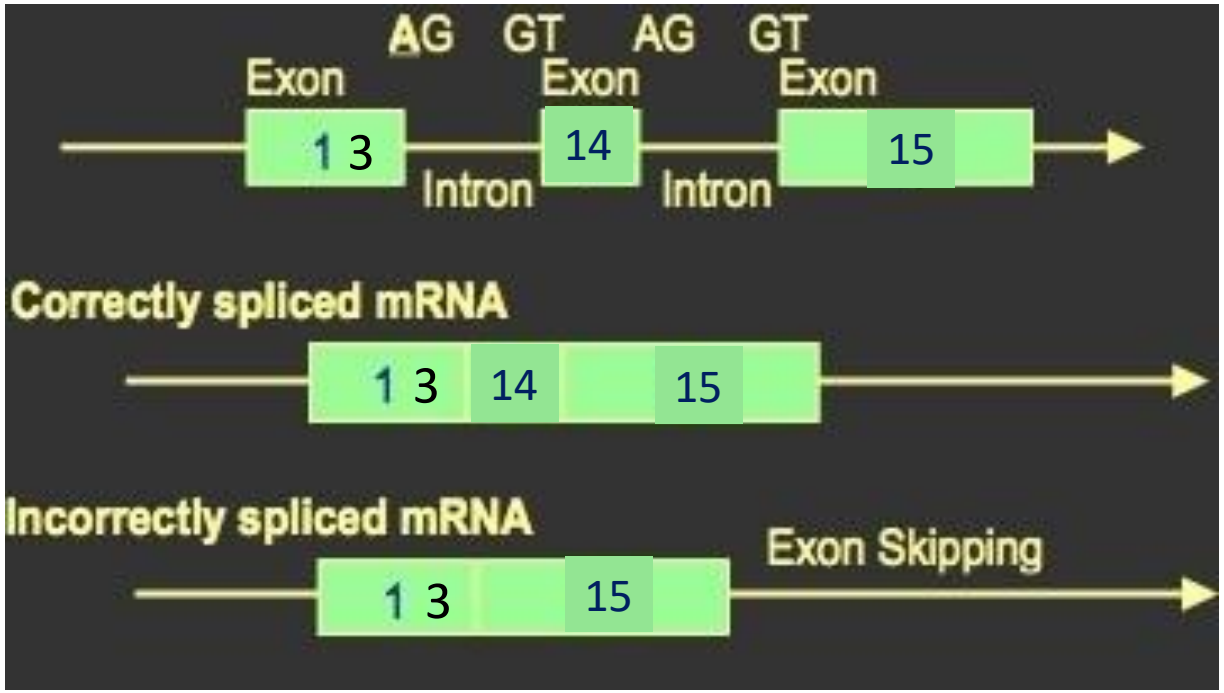
Sotorasib group	171 (0)	139 (9)	93 (14)	63 (4)	56 (1)	38 (3)	30 (1)	24 (2)	14 (8)	6 (4)	2 (1)	1 (1)	0 (1)
Docetaxel group	174 (0)	93 (39)	62 (9)	36 (12)	20 (6)	10 (1)	7 (0)	5 (2)	3 (1)	1 (2)	1 (0)	0 (1)	..

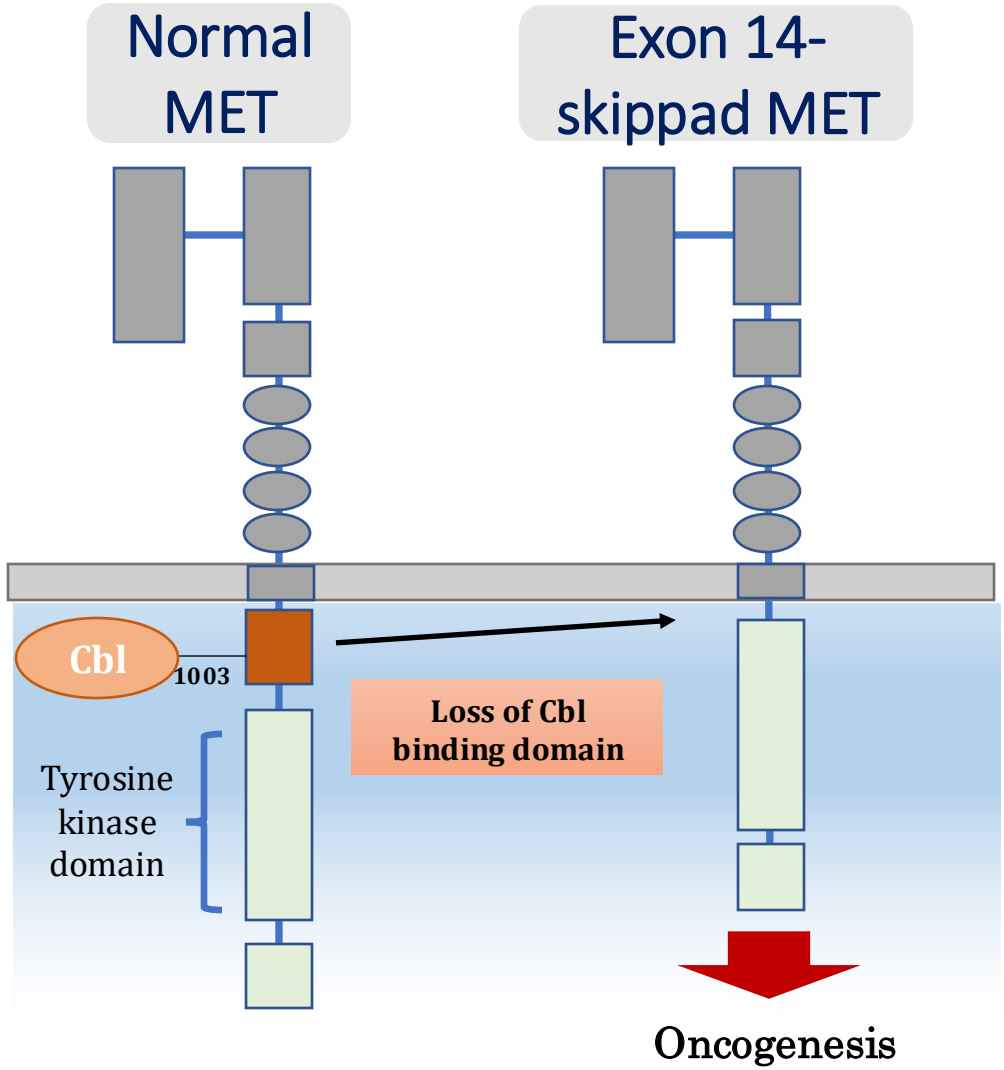
MET exon 14 skipping

3% av NSCLC

(12% hos svenska aldrig-rökande LC-pat!)

SPLICE SITE MUTATION





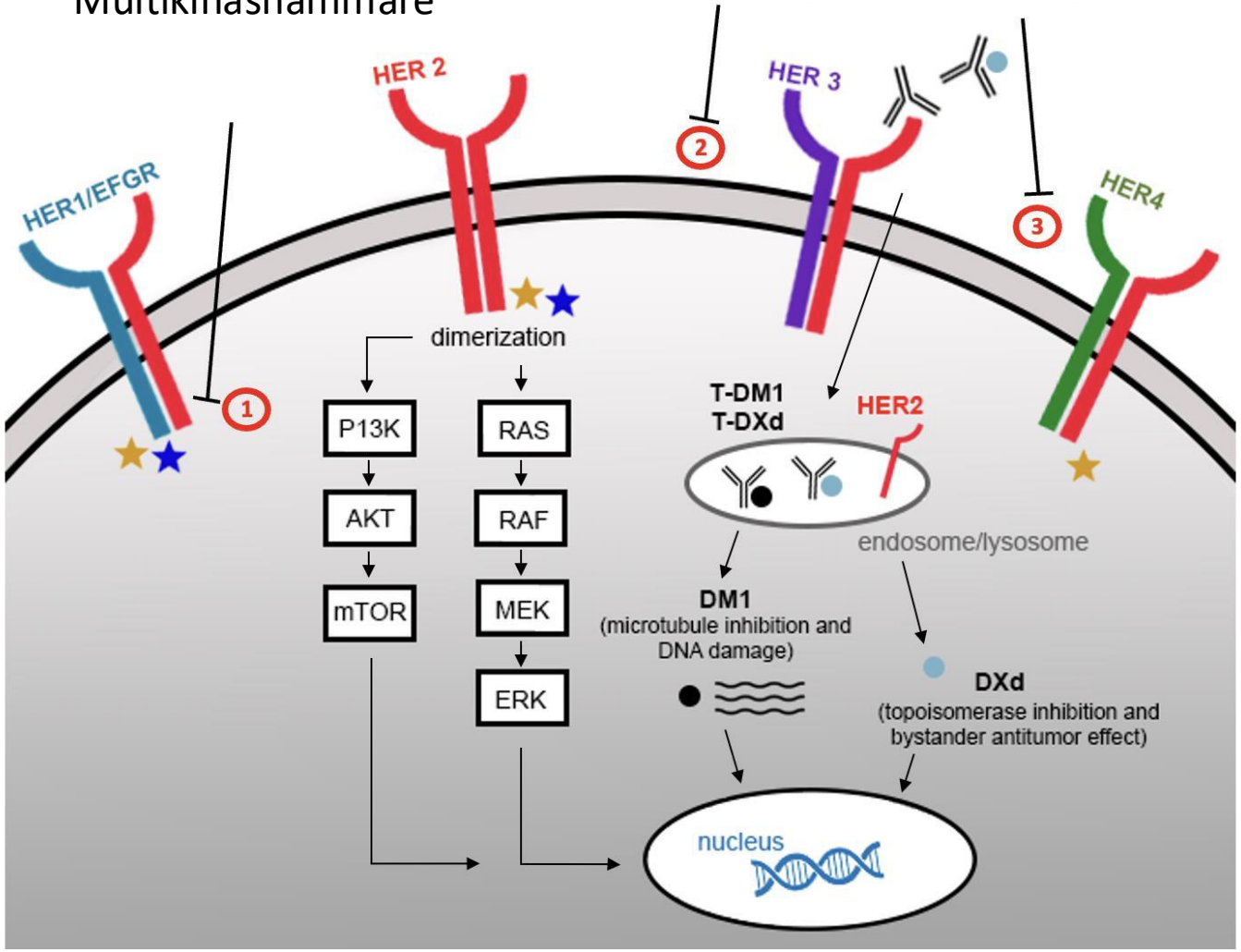
HER2-mutationer

2% av NSCLC

HER2-antikropp
(trastuzumab)

Antikropps-cytostatika-konjugat
(trastuzumab-deruxtekan)

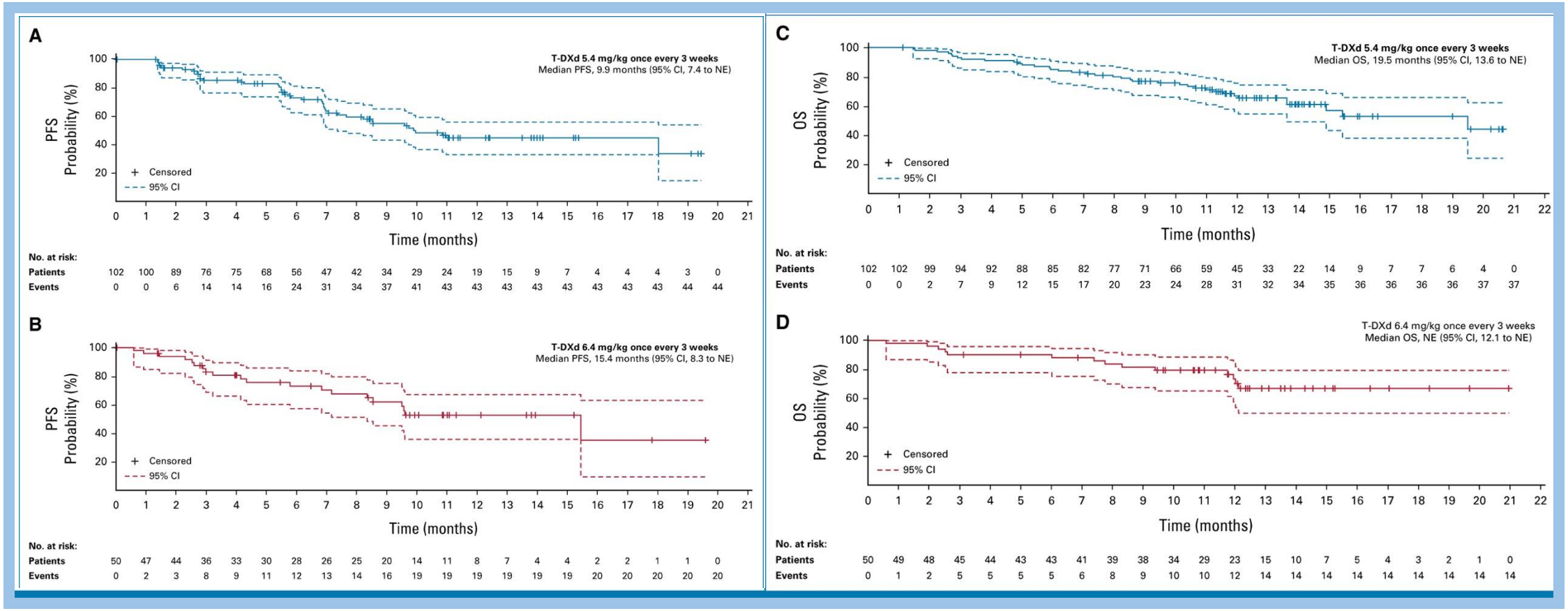
Multikinashämmare



Uy NF et al. HER2 in Non-Small Cell Lung Cancer: A Review of Emerging Therapies. **Cancers**, 2022. DOI 10.3390/cancers14174155.

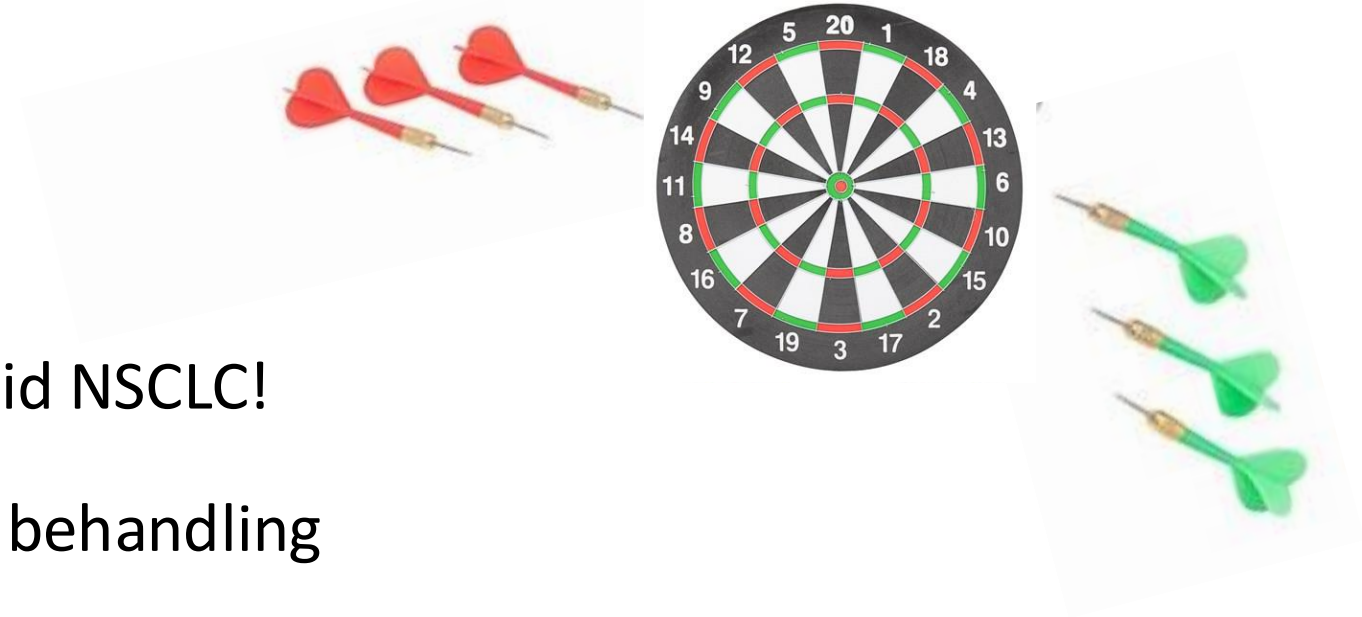
DESTINY Lung02: Trastuzumab-deruxtekan

Goto K, et al. JCO 2023; 41(31):4852-63



SAMMANFATTNING

Målriktad behandling



- Alltid molekylär diagnostik vid NSCLC!
- 1, snart 2, targets i adjuvant behandling
- 6 targets i första linjens och 2, snart 4, targets i senare linjers palliativa behandling.
- Rebiopsera, om möjligt, vid progress (särskilt EGFR och ALK)! (Men förr eller senare behövs kemoterapi…)
- 15% av lungcancerpatienterna i Sverige har aldrig rökt och av dessa har >70% en fusion/mutation som redan nu eller i en nära framtid är behandlingsbar

maria.planck@med.lu.se