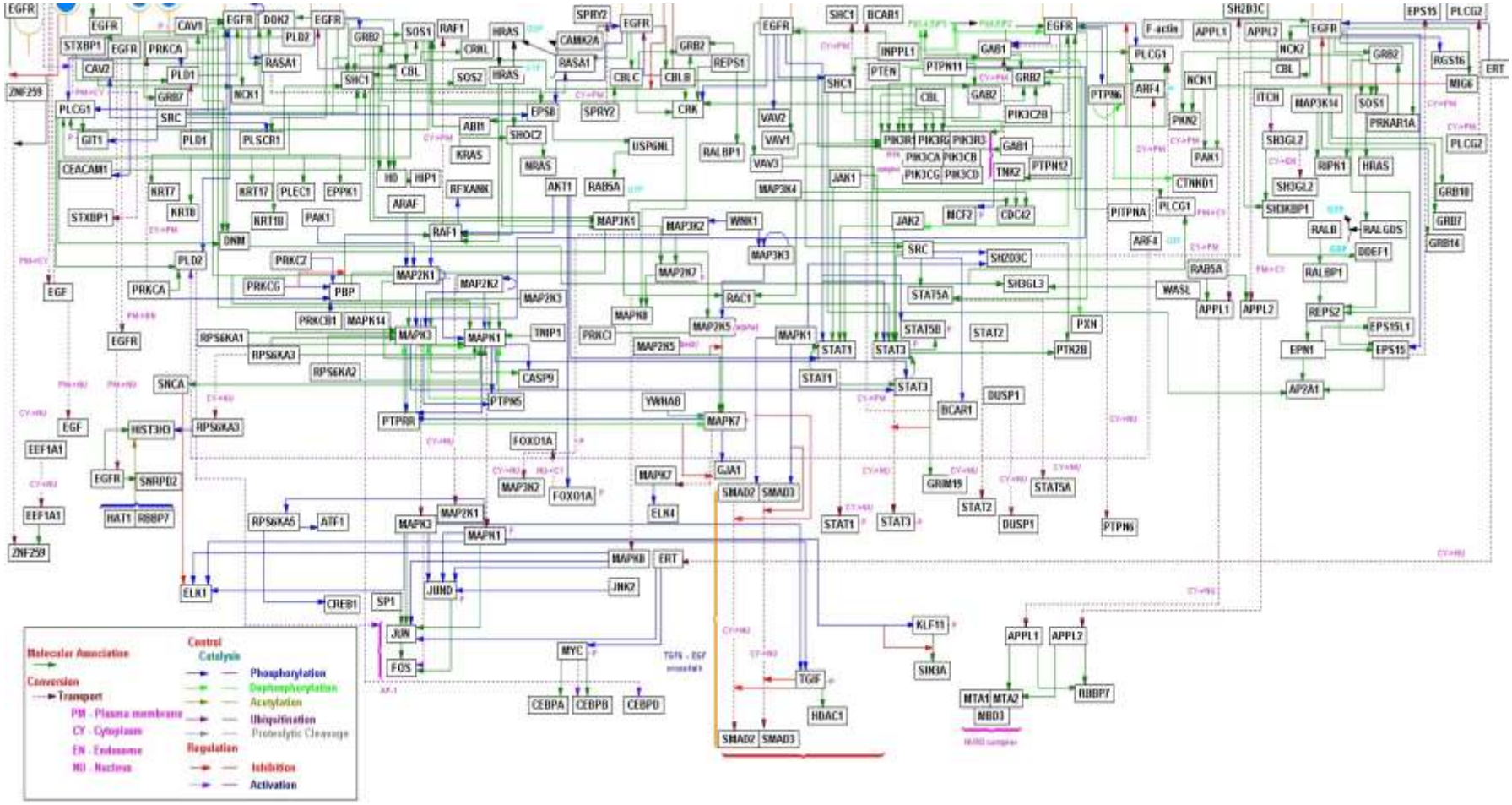
Molecular Pathology

P.Pauwels

Kennis / Ervaring / Zorg

Molecular alterations in solid tumors



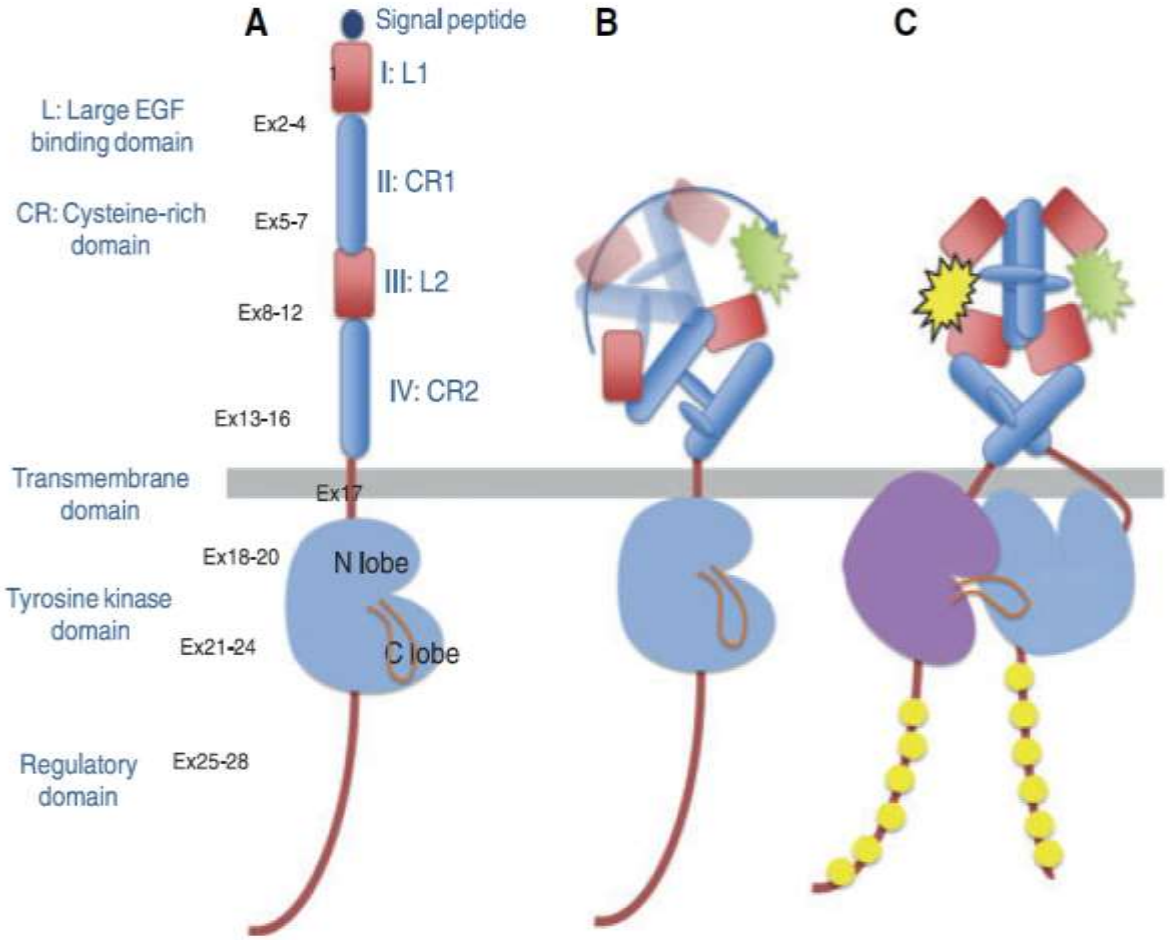
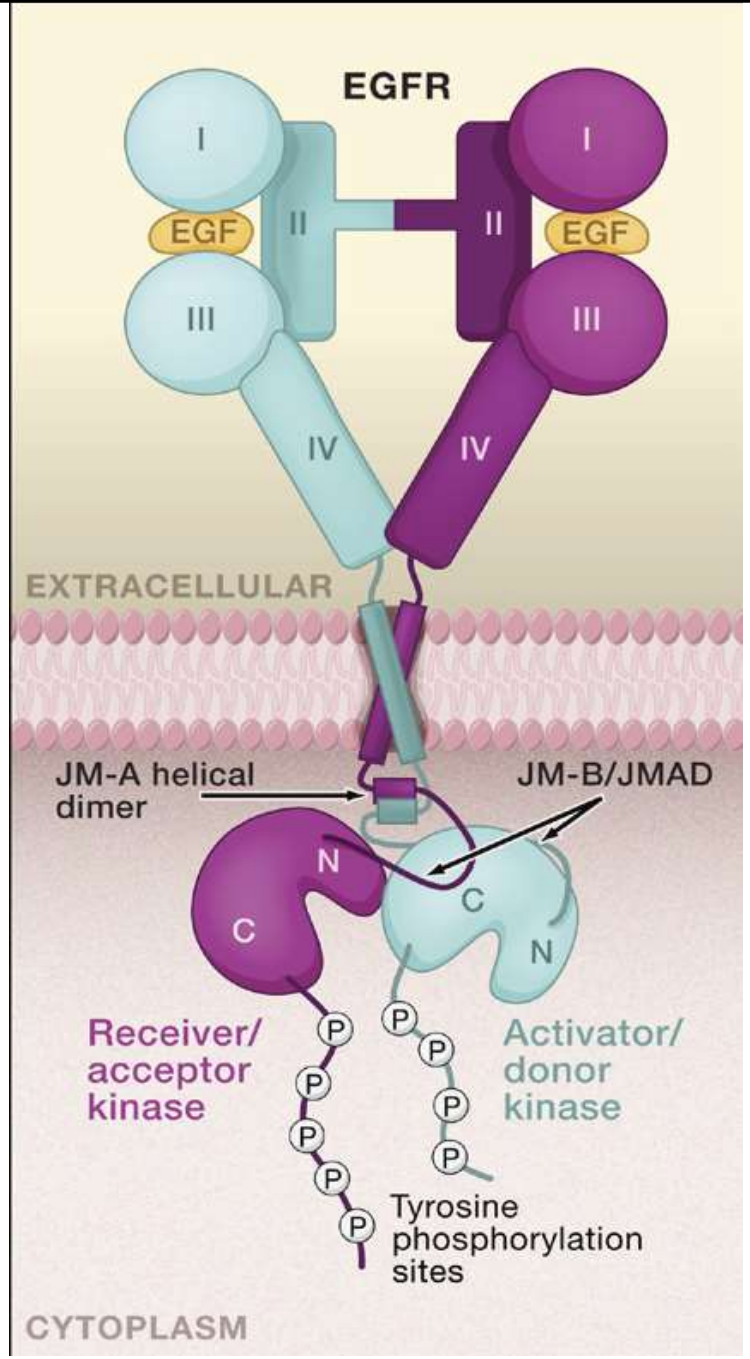


Fig. 1. Structure of the EGFR protein (A), activation (B) and dimerization by ligand binding (C).



Cell

Oncogenic Mutations Counteract Intrinsic Disorder in the EGFR Kinase and Promote Receptor Dimerization

Yibing Shan,[1,*] Michael P. Eastwood,[1] Xuewu Zhang,[2] Eric T. Kim,[1] Anton Arkhipov,[1] Ron O. Dror,[1] John Jumper,[1] John Kuriyan,[3] and David E. Shaw[1,4,*]

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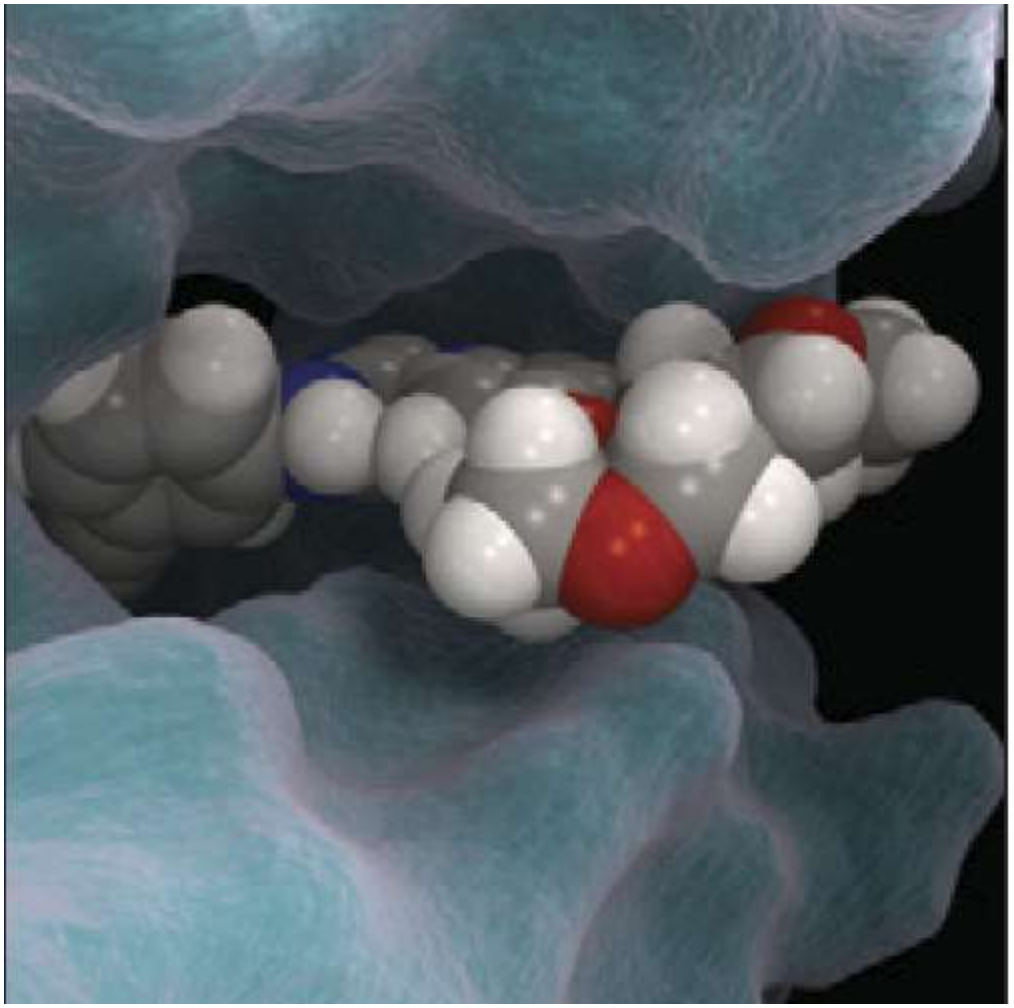
DOI 10.1016/j.cell.2012.02.063

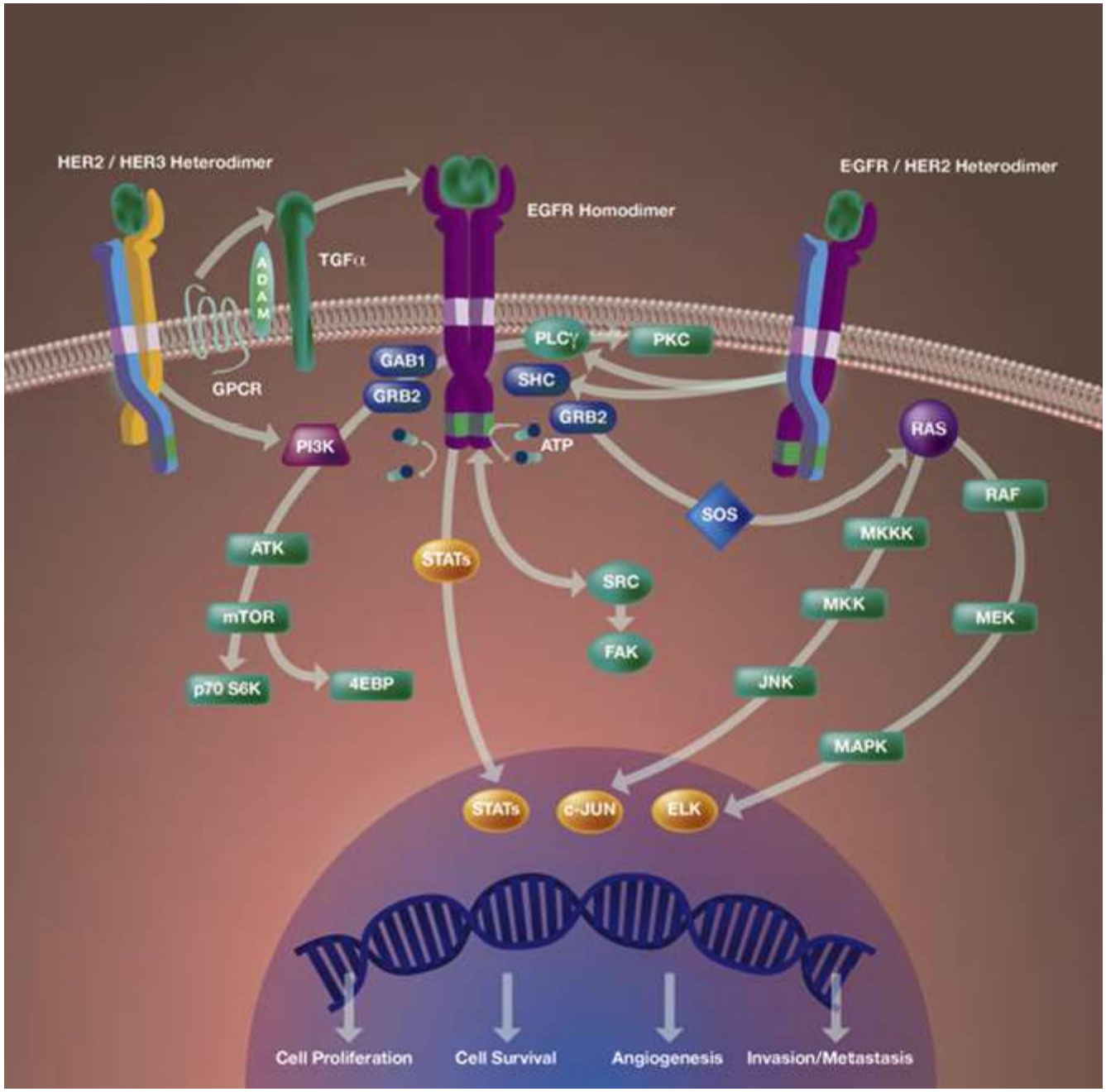


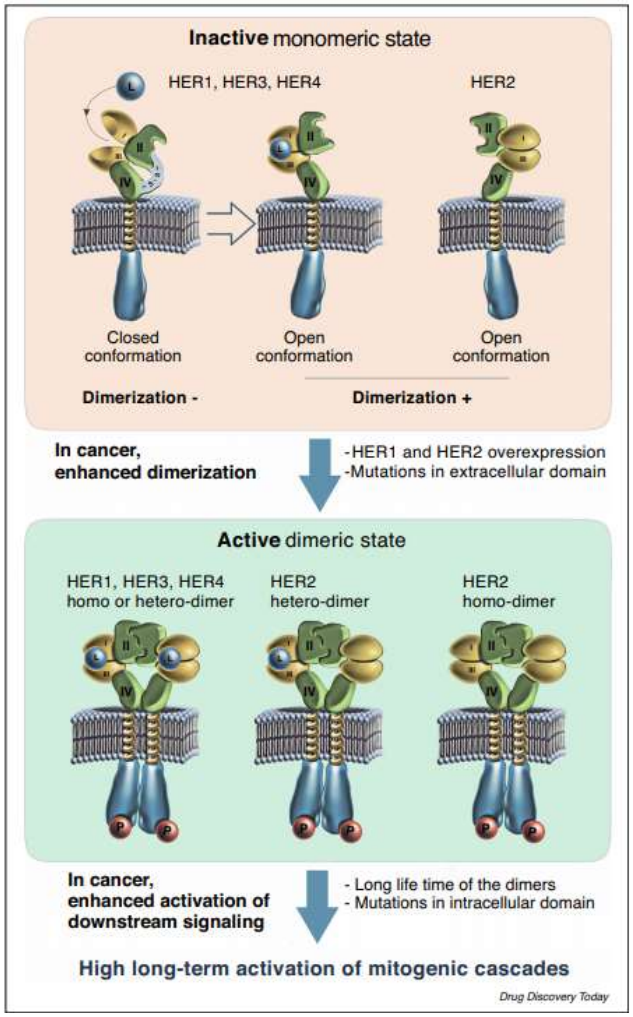
The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP

Cai-Hong Yun*†, Kristen E. Mengwasser†, Angela V. Toms*†, Michele S. Woo‡, Heidi Greulich‡§, Kwok-Kin Wong‡¶, Matthew Meyerson‡§‖, and Michael J. Eck*†**

Departments of *Biological Chemistry and Molecular Pharmacology and ‖Pathology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115; Departments of †Cancer Biology and ‡Medical Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115; ¶Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115; and §The Broad Institute of Harvard and Massachusetts Institute of Technology, 320 Charles Street, Cambridge, MA 02141

Edited by Harold E. Varmus, Memorial Sloan–Kettering Cancer Center, New York, NY, and approved December 13, 2007 (received for review October 11, 2007)


HER2 / HER3 Heterodimer
EGFR Homodimer
EGFR / HER2 Heterodimer
TGFα
ADAM
GPCR
PLCγ
PKC
GAB1
GRB2
SHC
GRB2
ATP
PI3K
RAS
RAF
SOS
MKKK
ATK
STATs
SRC
MKK
MEK
mTOR
FAK
p70 S6K
4EBP
JNK
MAPK
STATs
c-JUN
ELK
Cell Proliferation
Cell Survival
Angiogenesis
Invasion/Metastasis

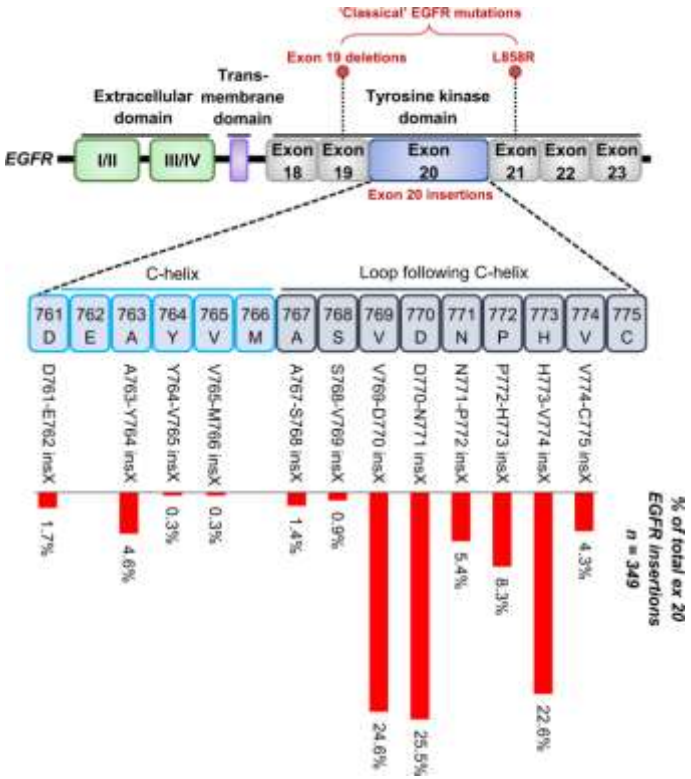

Inactive monomeric state
HER1, HER3, HER4
HER2
Closed conformation
Open conformation
Open conformation
Dimerization -
Dimerization +
In cancer, enhanced dimerization
-HER1 and HER2 overexpression
-Mutations in extracellular domain
Active dimeric state
HER1, HER3, HER4 homo or hetero-dimer
HER2 hetero-dimer
HER2 homo-dimer
In cancer, enhanced activation of downstream signaling
- Long life time of the dimers
- Mutations in intracellular domain
High long-term activation of mitogenic cascades
Drug Discovery Today

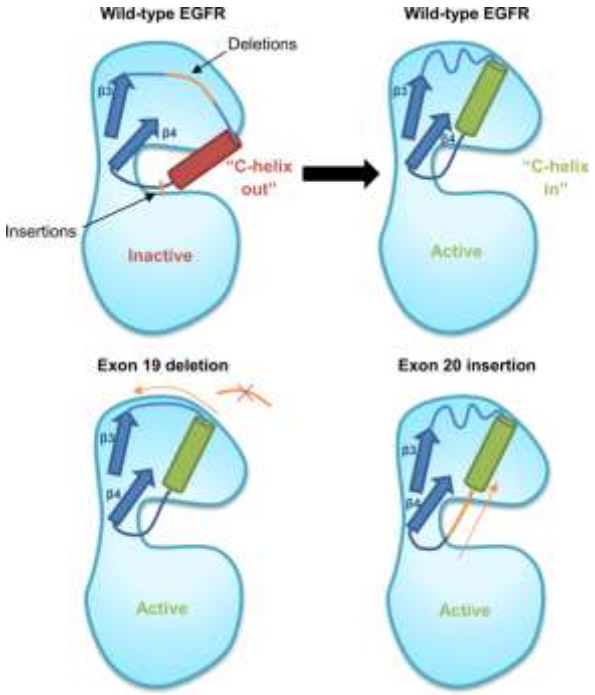
Amivantamab: Treating *EGFR* Exon 20–Mutant Cancers With Bispecific Antibody-Mediated Receptor Degradation

Jens Köhler, MD[1] and Pasi A. Jänne, MD, PhD[1,2,3]

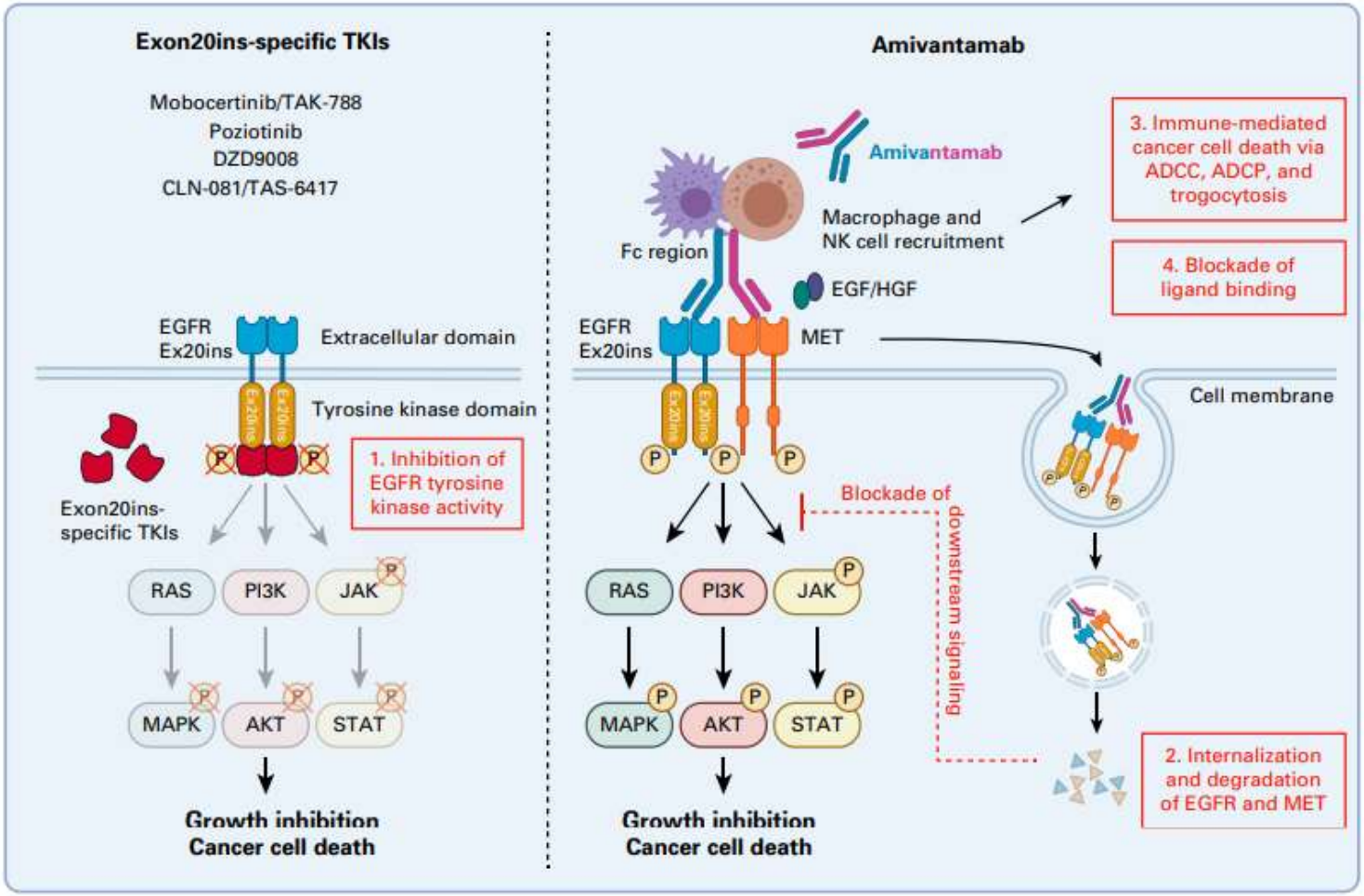
Accepted on July 8, 2021 and published at ascopubs.org/journal/jco on August 2, 2021: DOI https://doi.org/10.1200/JCO.21.01494

EGFR exon 20 mutations

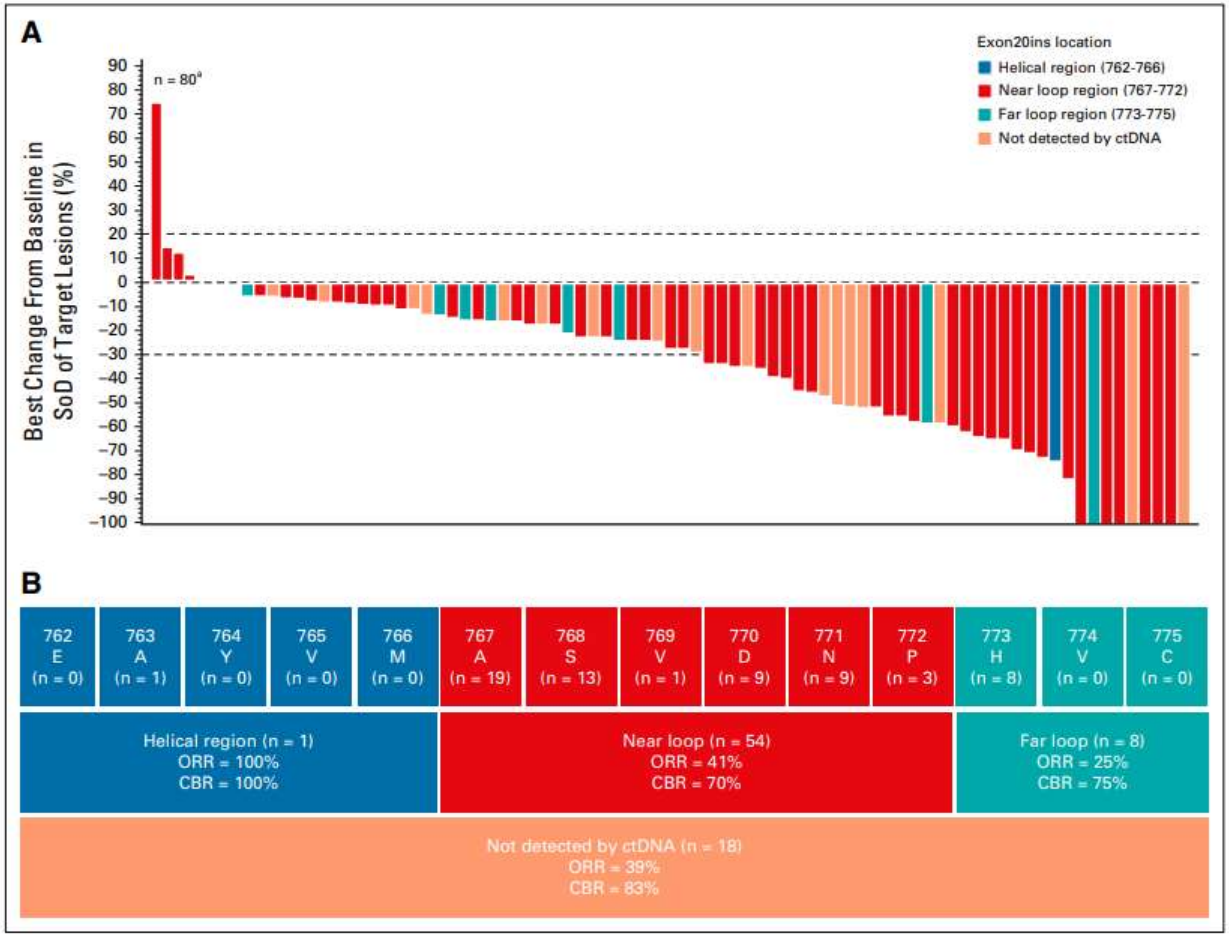




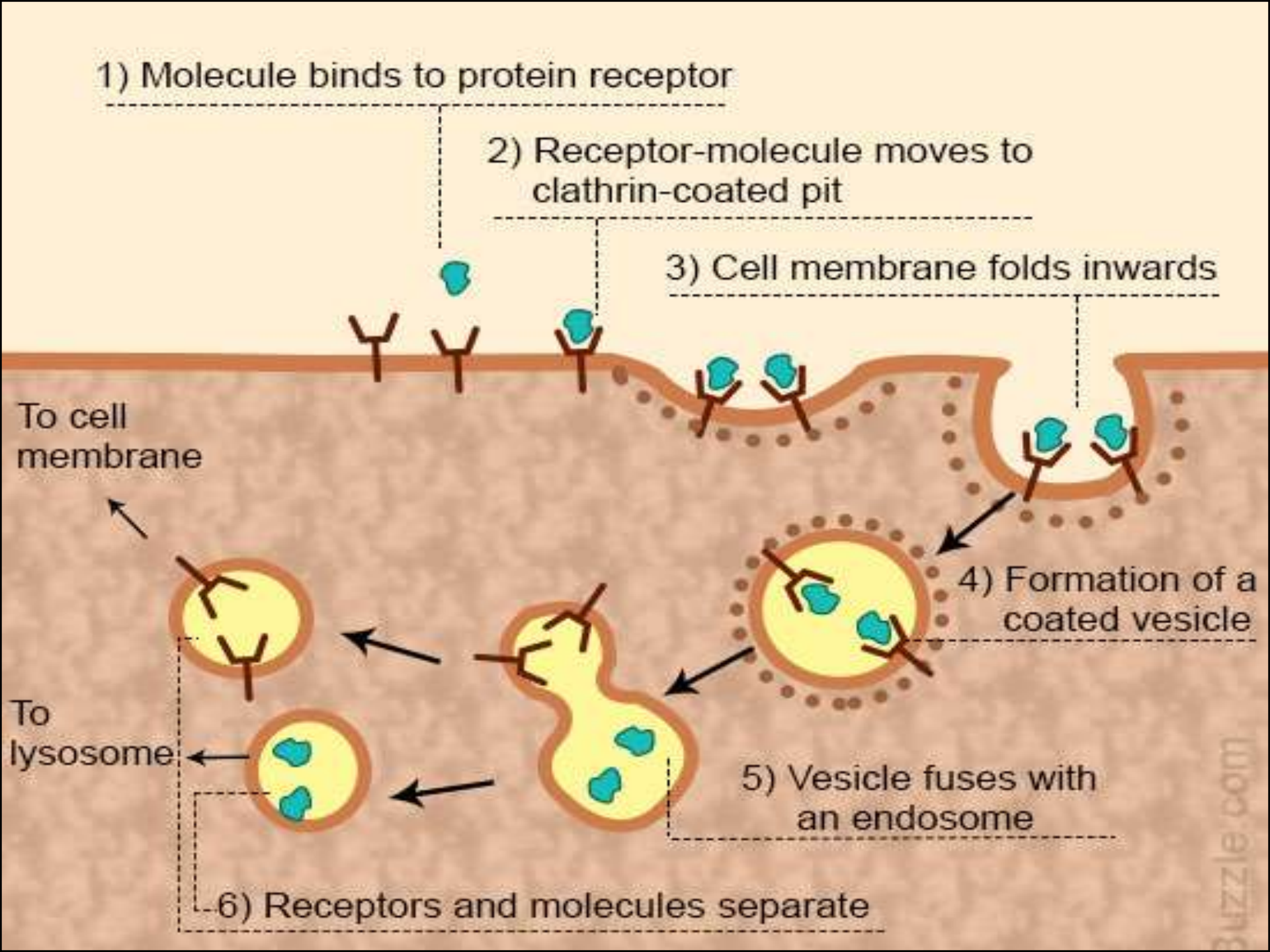
1. Vyse S, Huang PH. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduction and Targeted Therapy [Internet] 2019;4(1). Available from: https://dx.doi.org/10.1038/s41392-019-0038-9



Accepted on July 8, 2021 and published at ascopubs.org/journal/jco on August 2, 2021: DOI https://doi.org/10.1200/JCO.21.01494



J Clin Oncol 39:3391-3402.


1) Molecule binds to protein receptor
2) Receptor-molecule moves to clathrin-coated pit
3) Cell membrane folds inwards
To cell membrane
4) Formation of a coated vesicle
To lysosome
5) Vesicle fuses with an endosome
6) Receptors and molecules separate

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

REVIEW

Targeting HER2 in non-small-cell lung cancer (NSCLC): a glimpse of hope? An updated review on therapeutic strategies in NSCLC harbouring HER2 alterations

M. Riudavets[1], I. Sullivan[2], P. Abdayem[1] & D. Planchard[1*]

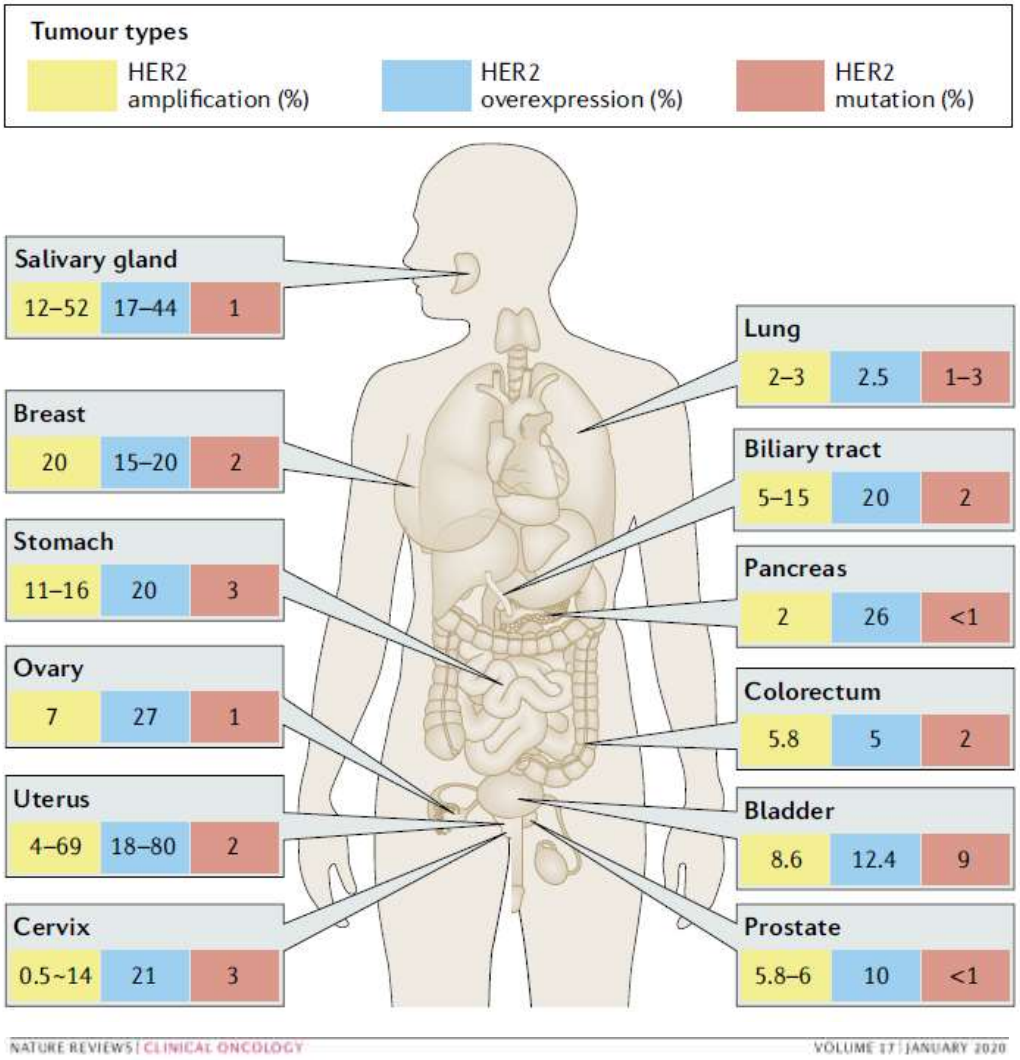
[1]Department of Cancer Medicine, Gustave Roussy Cancer Campus, Villejuif, France; [2]Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

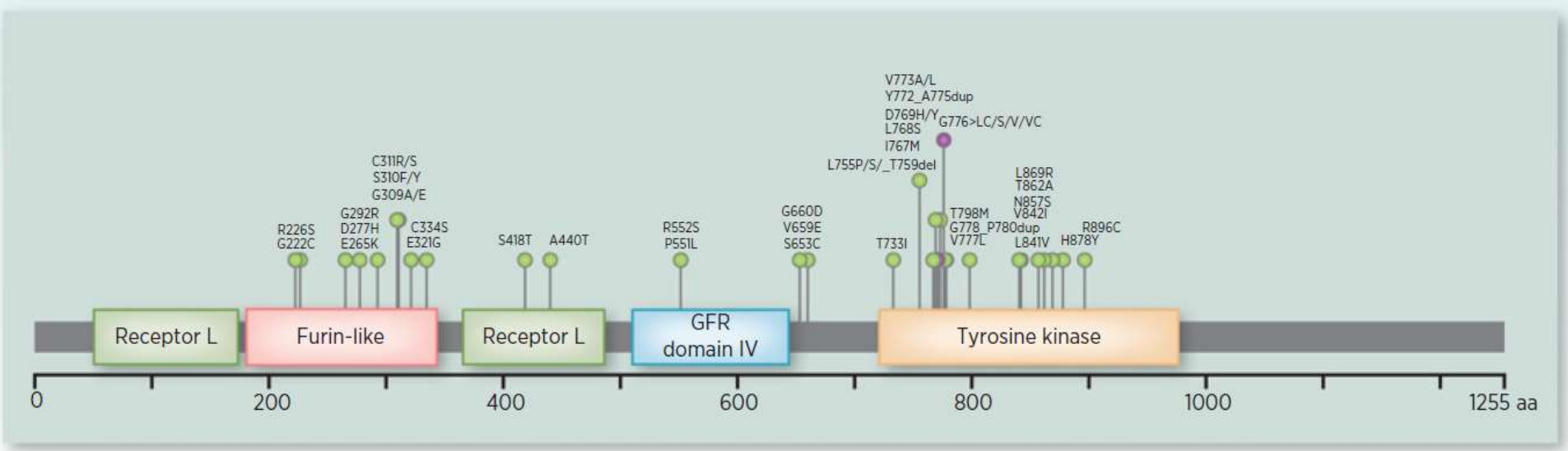
Published OnlineFirst March 25, 2020; DOI: 10.1158/2159-8290.CD-20-0215

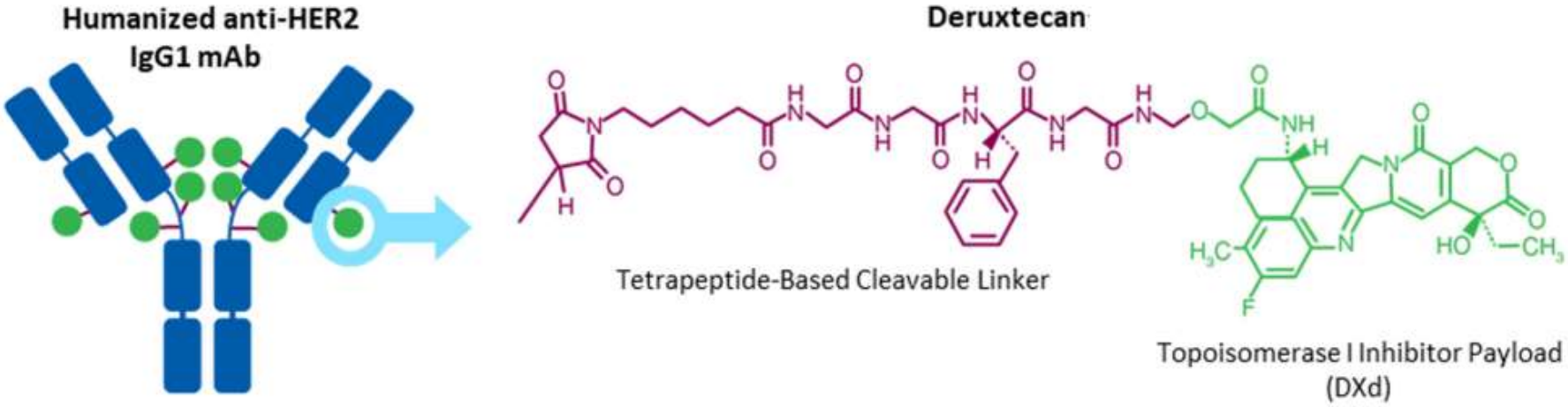
RESEARCH ARTICLE

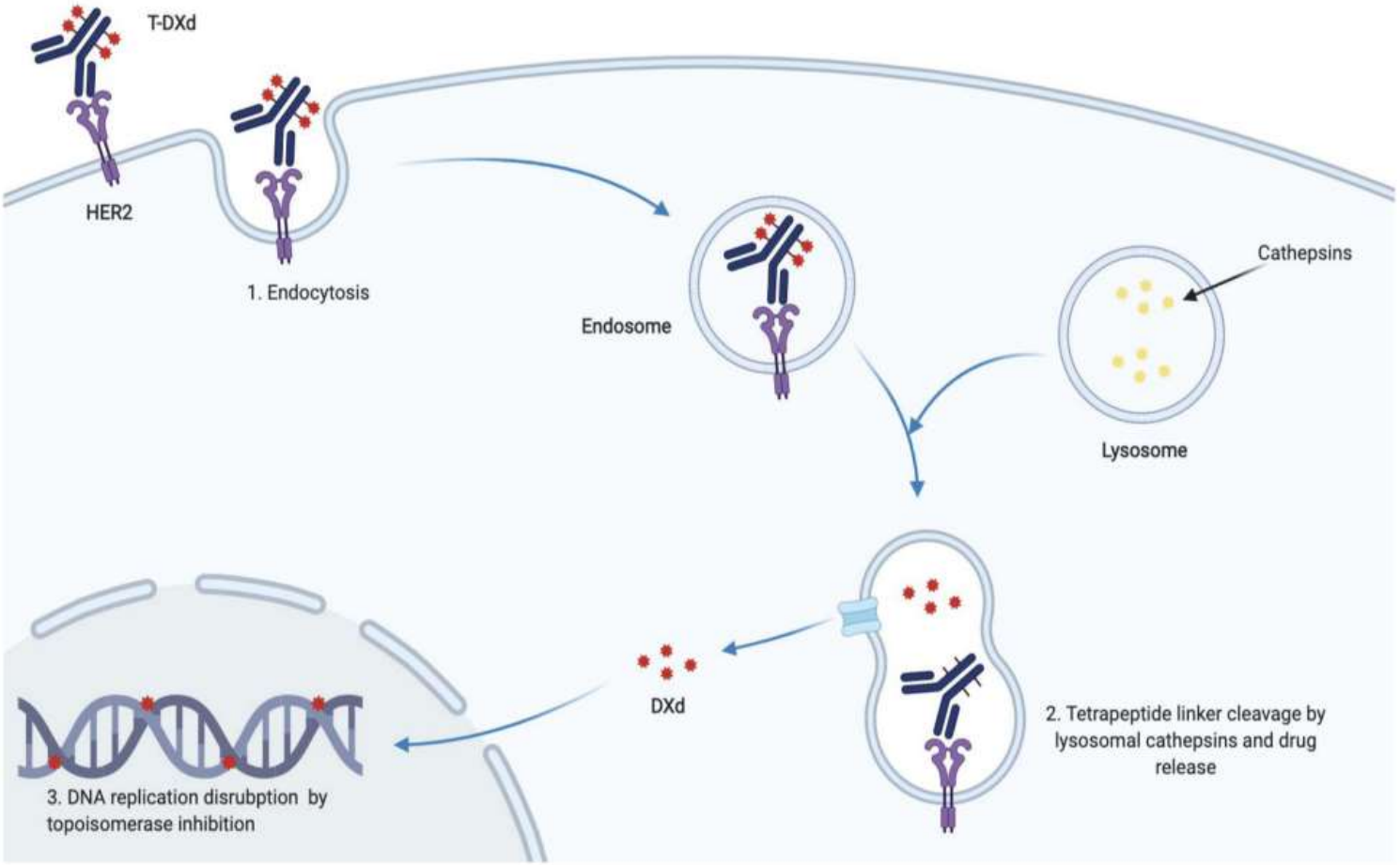
HER2-Mediated Internalization of Cytotoxic Agents in *ERBB2* Amplified or Mutant Lung Cancers

Bob T. Li[1,2], Flavia Michelini[3,4], Sandra Misale[5], Emiliano Cocco[4], Laura Baldino[3,4], Yanyan Cai[3,4], Sophie Shifman[4], Hai-Yan Tu[1,6], Mackenzie L. Myers[1], Chongrui Xu[1,6], Marissa Mattar[5,7], Inna Khodos[5,7], Megan Little[5,7], Besnik Qeriqi[5,7], Gregory Weitsman[8], Clare J. Wilhem[1], Alshad S. Lalani[9], Irmina Diala[9], Rachel A. Freedman[10], Nancy U. Lin[10], David B. Solit[1,2,4,11], Michael F. Berger[3,4,11], Paul R. Barber[8,12], Tony Ng[8,12], Michael Offin[1,2], James M. Isbell[2,13], David R. Jones[2,13], Helena A. Yu[1,2], Sheeno Thyparambil[14], Wei-Li Liao[14], Anuja Bhalkikar[14], Fabiola Cecchi[15], David M. Hyman[1,2], Jason S. Lewis[2,16,17], Darren J. Buonocore[3], Alan L. Ho[1,2], Vicky Makker[1,2], Jorge S. Reis-Filho[3,4], Pedram Razavi[1,2], Maria E. Arcila[3], Mark G. Kris[1,2], John T. Poirier[1,5], Ronglai Shen[18], Junji Tsurutani[19], Gary A. Ulaner[2,5,14], Elisa de Stanchina[5,7], Neal Rosen[5,20], Charles M. Rudin[1,2], and Maurizio Scaltriti[3,4,20]

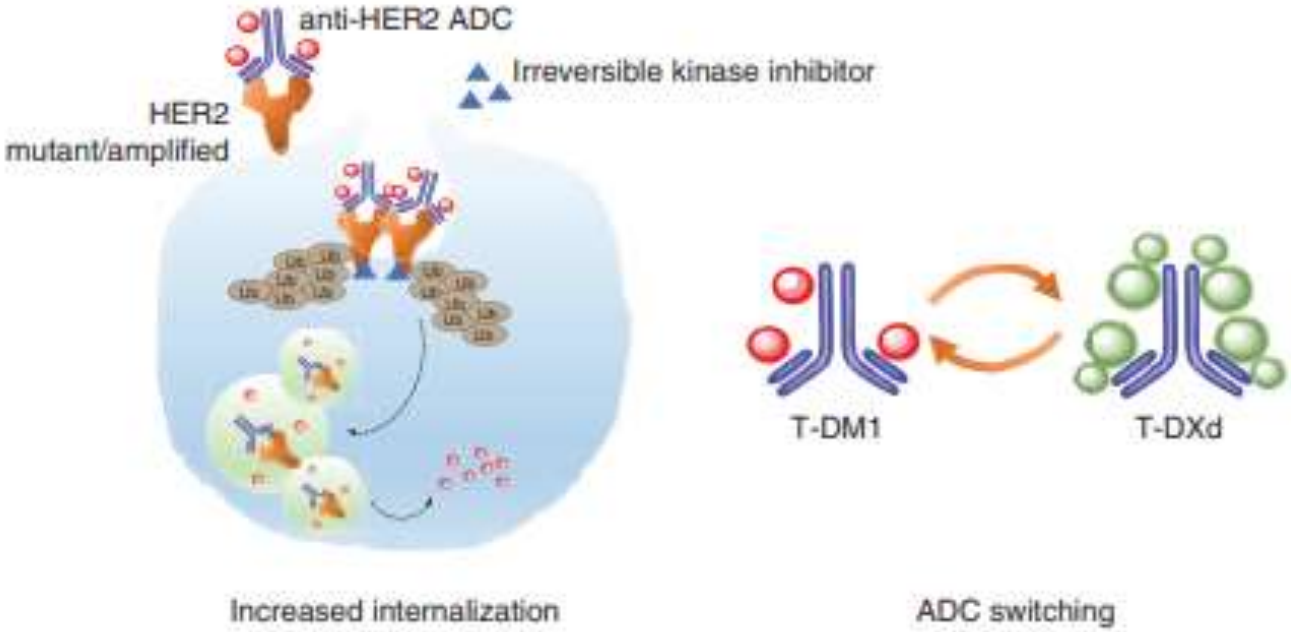

Tumour types
HER2 amplification (%)
HER2 overexpression (%)
HER2 mutation (%)
Salivary gland
12–52
17–44
1
Breast
20
15–20
2
Stomach
11–16
20
3
Ovary
7
27
1
Uterus
4–69
18–80
2
Cervix
0.5~14
21
3
Lung
2–3
2.5
1–3
Biliary tract
5–15
20
2
Pancreas
2
26
<1
Colorectum
5.8
5
2
Bladder
8.6
12.4
9
Prostate
5.8–6
10
<1




Humanized anti-HER2
IgG1 mAb
Deruxtecan
Tetrapeptide-Based Cleavable Linker
Topoisomerase I Inhibitor Payload
(DXd)



Lung Cancer: Targets and Therapy 2021:12


anti-HER2 ADC
Irreversible kinase inhibitor
HER2
mutant/amplified
T-DM1
T-DXd
Increased internalization
ADC switching

REVIEWS

RAS-targeted therapies: is the undruggable drugged?

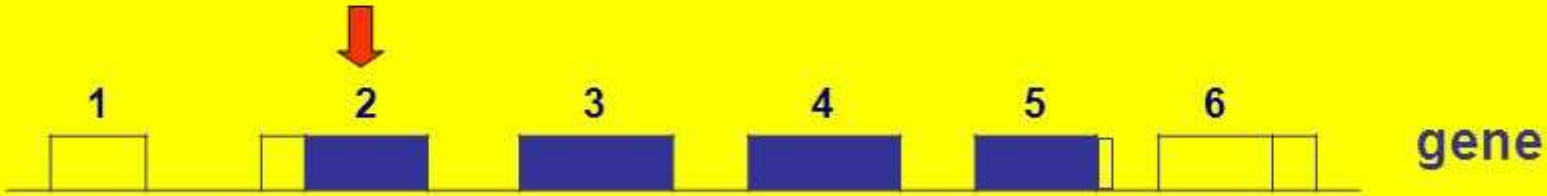
Amanda R. Moore[1], *Scott C. Rosenberg*[1], *Frank McCormick*[2] *and Shiva Malek*[1] ✉

https://doi.org/10.1038/s41573-020-0068-6

KRAS

v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

The KRAS gene is located on the short (p) arm of chromosome 12 at position 12.1. More precisely, the KRAS gene is located from base pair 25,249,446 to base pair 25,295,120 on chromosome 12.



ENSG00000133703

Exons: 6 **Transcript length:** 5,419 bps **Protein length:** 189 residues

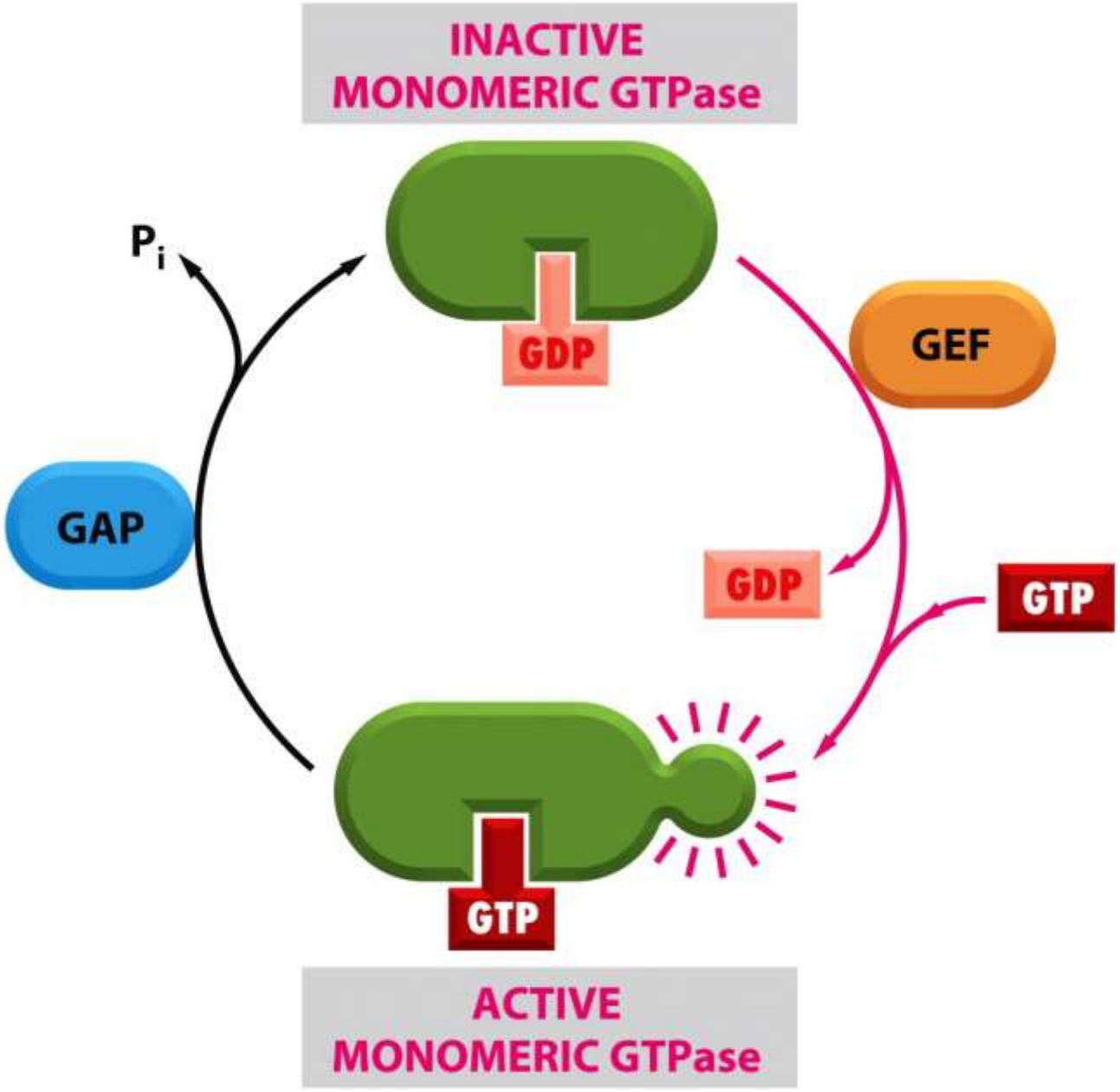
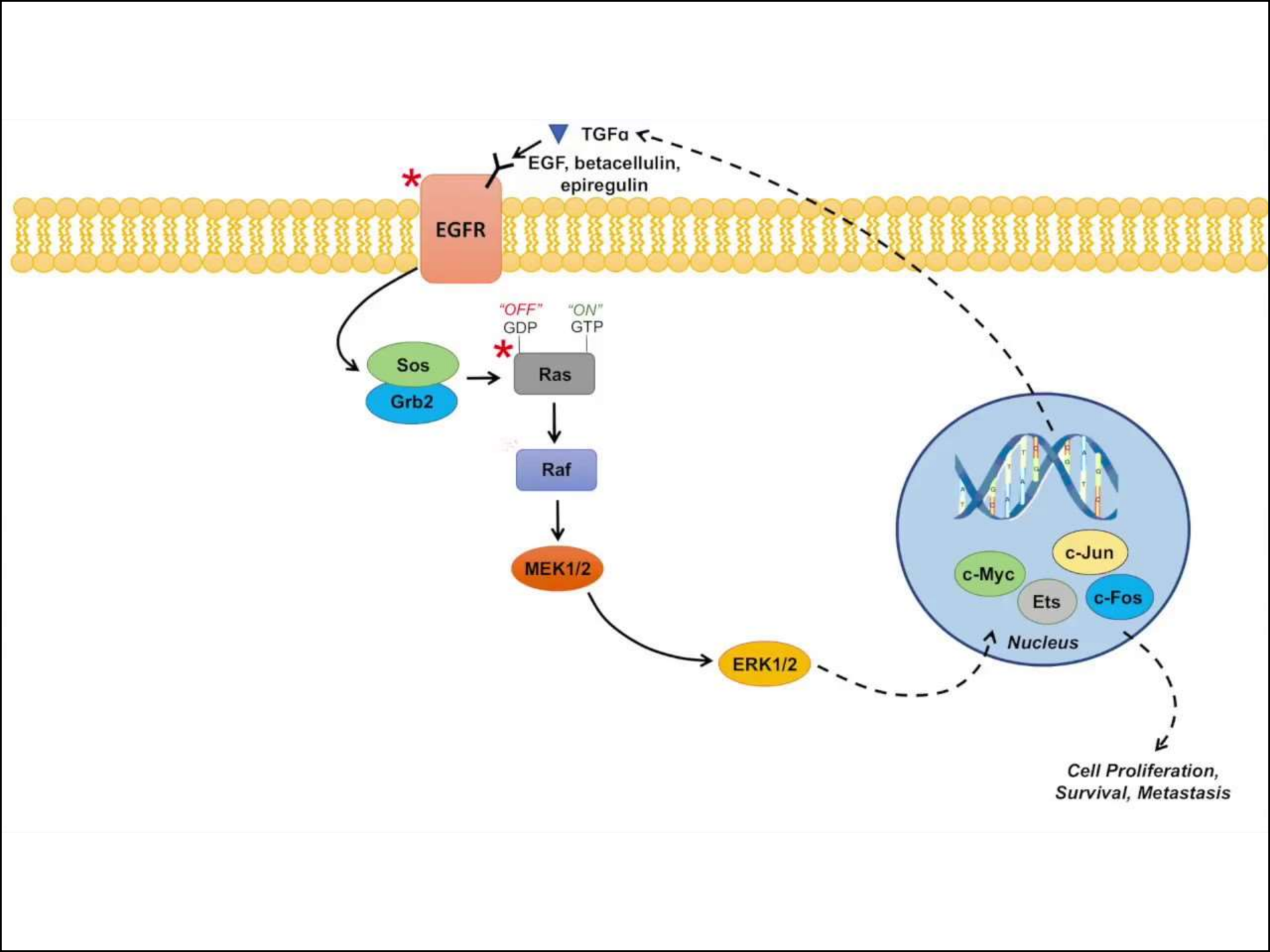
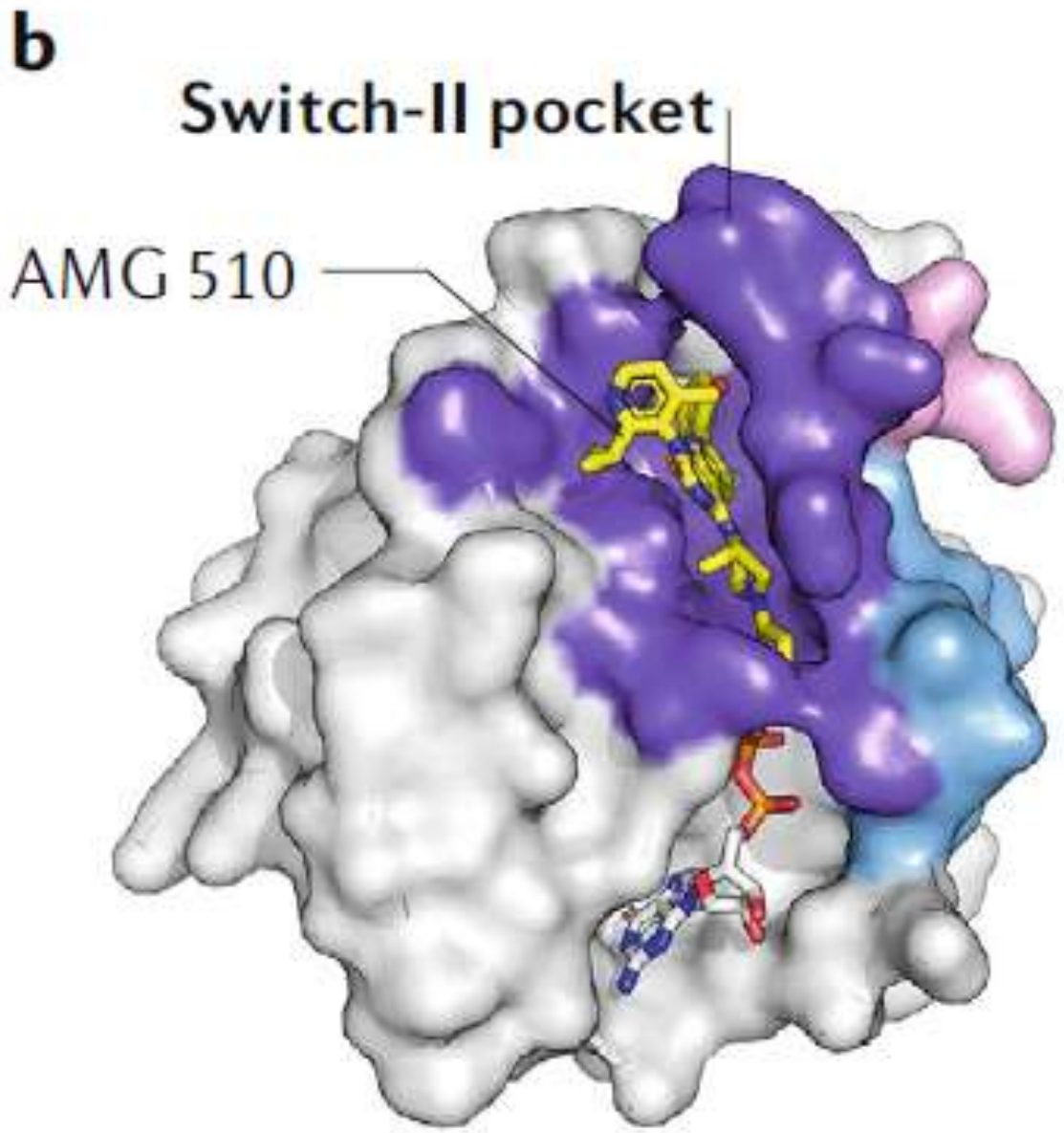
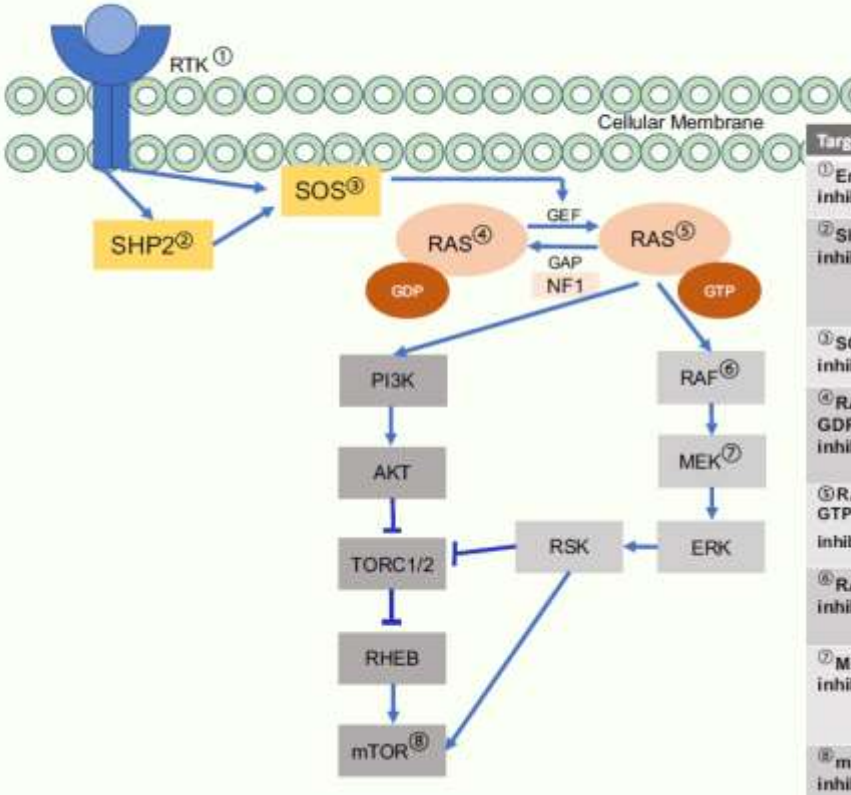


Figure 15-19 Molecular Biology of the Cell 5/e (© Garland Science 2008)


TGFα
EGF, betacellulin, epiregulin
EGFR
"OFF" GDP
"ON" GTP
Sos
Grb2
Ras
Raf
MEK1/2
ERK1/2
c-Jun
c-Myc
Ets
c-Fos
Nucleus
Cell Proliferation, Survival, Metastasis

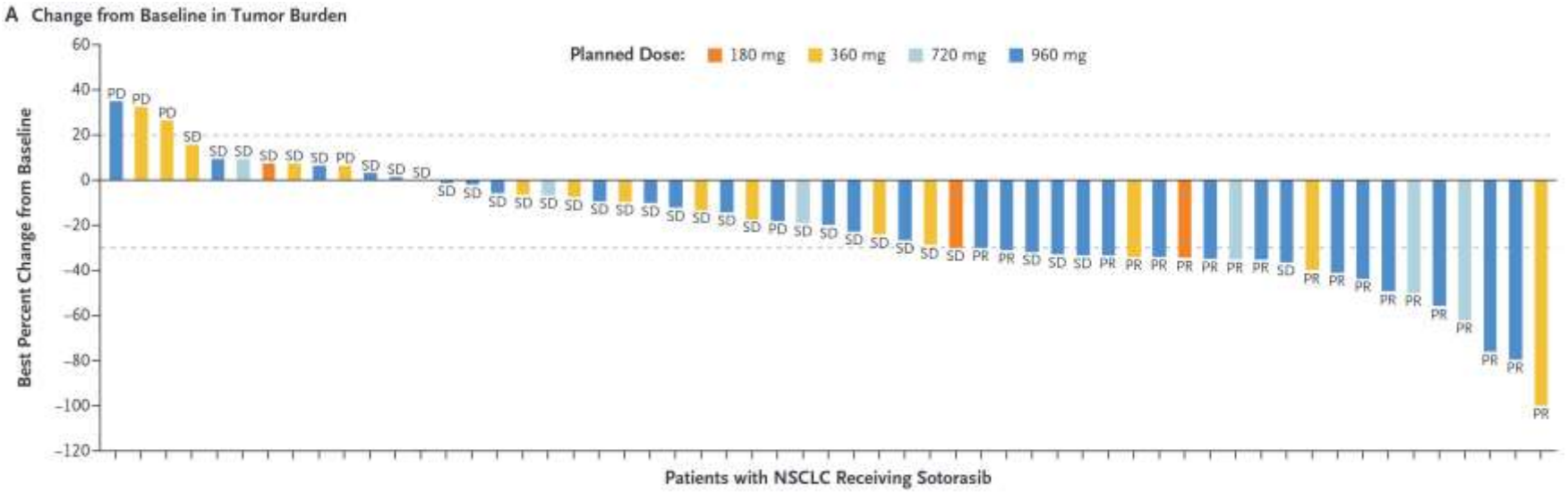


https://doi.org/10.1038/
s41573-020-0068-6



Target	Therapeutics
①ErbB inhibitors	e.g., afatinib, cetuximab
②SHP2 inhibitors	e.g., TNO155, RLY-1971, RMC-4630, JAB-3312, JAB-3068
③SOS1 inhibitors	e.g., BI 1701963, BAY293
④RAS-GDP inhibitors	e.g., sotorasib (AMG510), adagrasib (MRTX849), GDC-6036, D-1553
⑤RAS-GTP inhibitors	e.g., RMC-6291
⑥RAF inhibitors	e.g., sorafenib, dabrafenib, vemurafenib
⑦MEK inhibitors	e.g., selumetinib, trametinib, mirdametinib, binimetinib, cobimetinib
⑧mTOR inhibitors	e.g., vistusertib, ridaforolimus, everolimus

Molecular alterations in lung cancer



1. Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nature Reviews Cancer 2019;19(9):495–509.

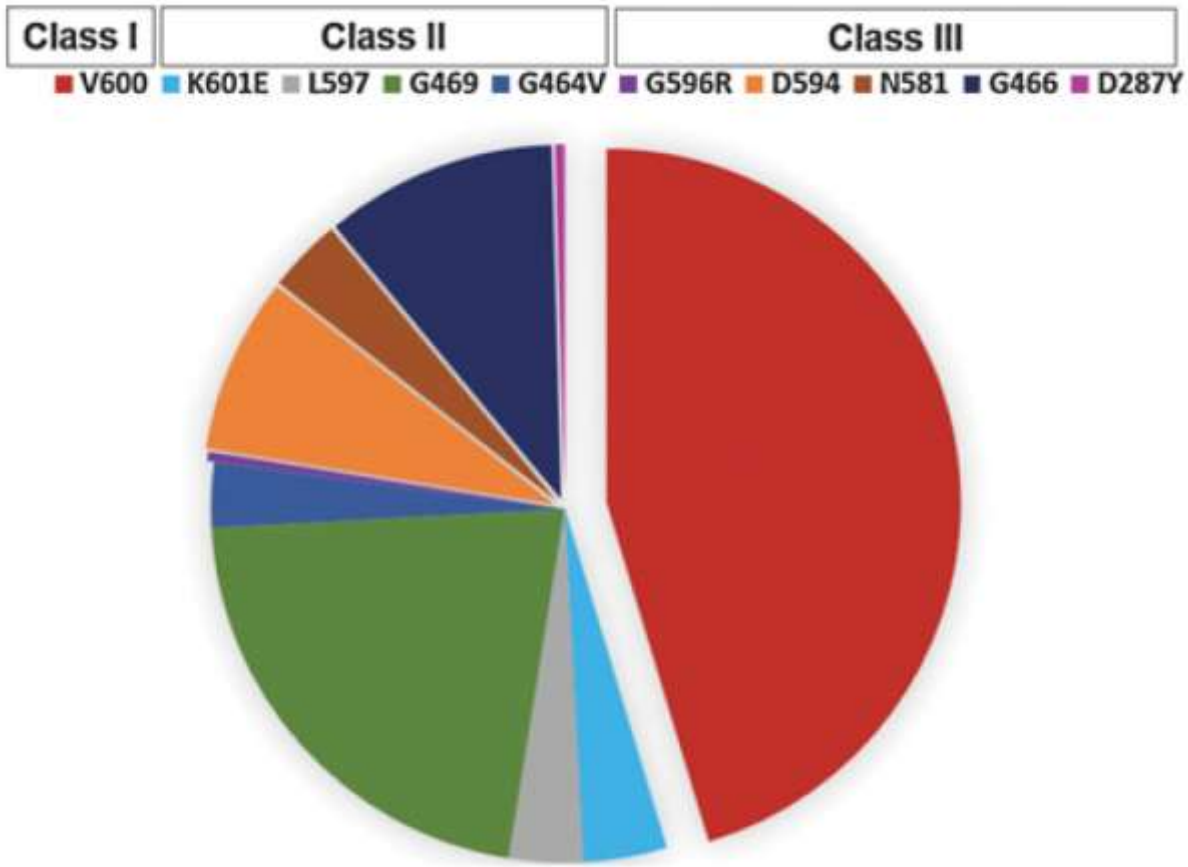
Published OnlineFirst October 4, 2019; DOI: 10.1158/1078-0432.CCR-19-2732

CCR Translations

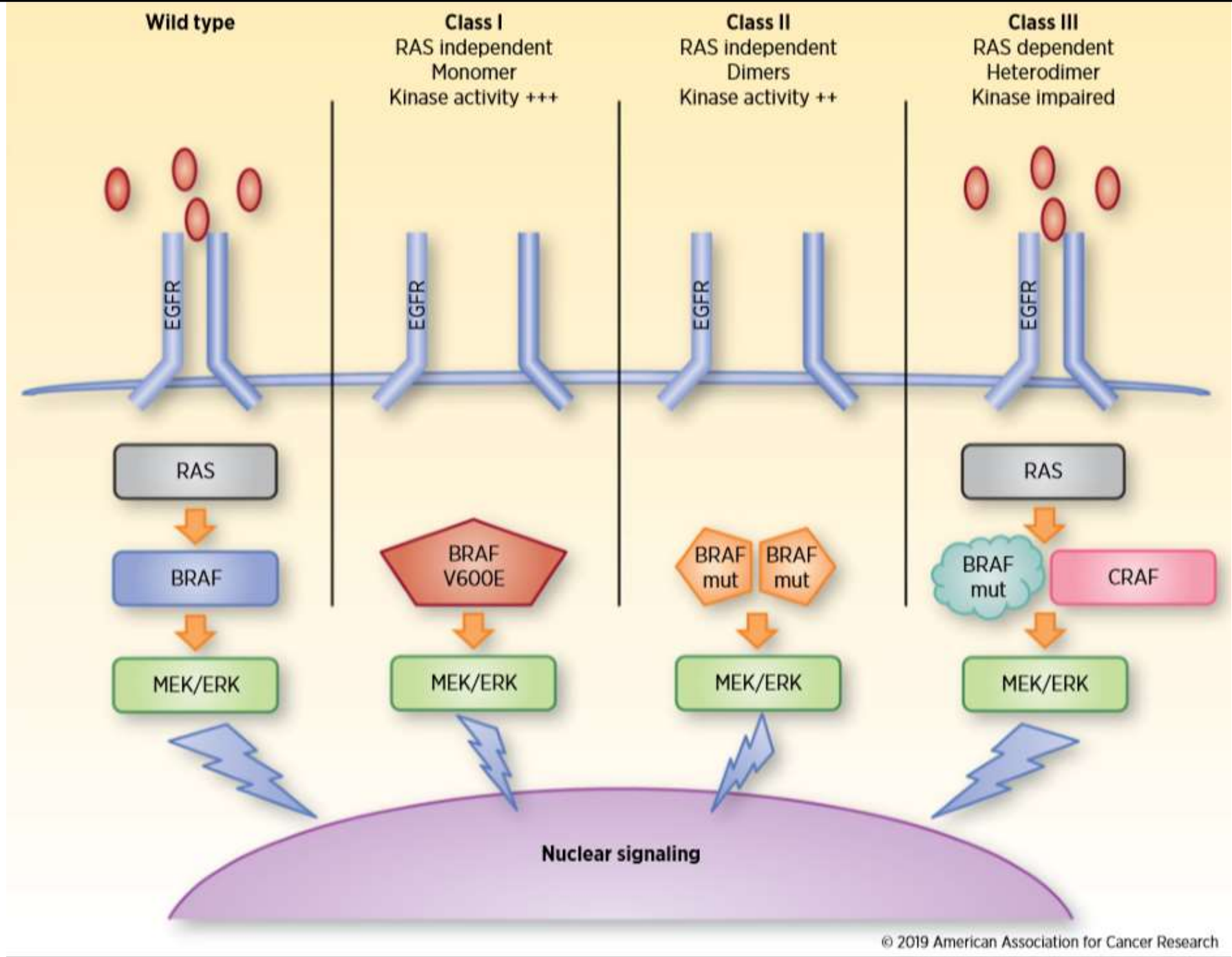
Clinical Cancer Research

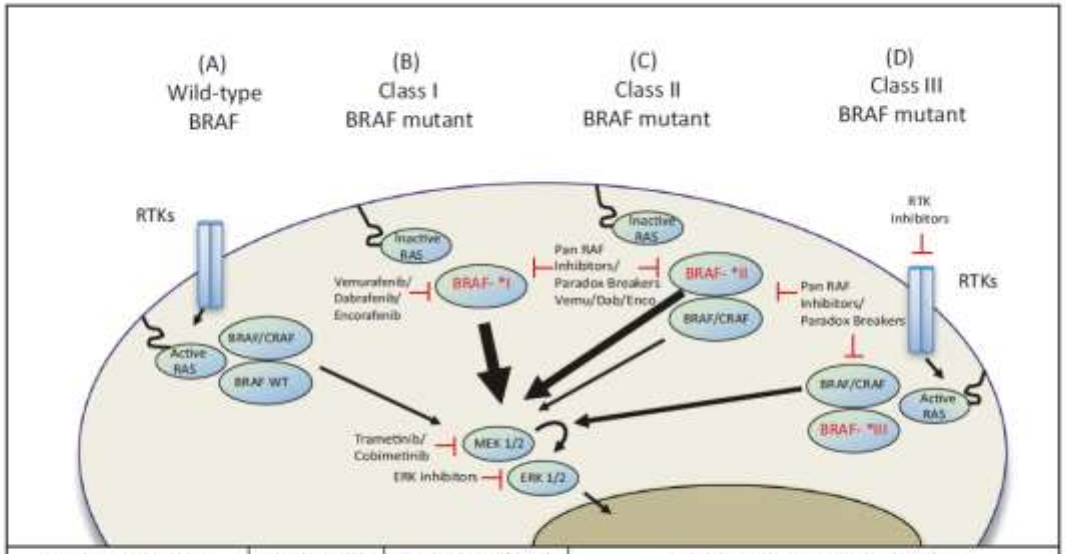
Class(y) Dissection of *BRAF* Heterogeneity: Beyond Non-V600

Elisa Fontana[1] and Nicola Valeri[1,2,3]



Clin Cancer Res; 25(1) January 1, 2019





BRAF Mutant Class	Dimerization	RAS-Dependency	MAPK Targeted Agents Proposed
(A) Wild-Type BRAF	+	+	None
(B) Class I BRAF mutant	-	-	BRAF and MEK inhibitors*
(C) Class II BRAF mutant	+	-	MEK inhibitors (possibly with BRAF inhibitors)
(D) Class III BRAF mutant	+	+	MEK inhibitors + RTK inhibitors if no activated RAS

***CRC is an exception due to frequent upstream activation of RAS by receptor tyrosine kinases that promotes BRAF dimerization. Class I BRAF mutant CRC are refractory to BRAF inhibitors for this reason.**

Oncogene (2018) 37:3183–3199
https://doi.org/10.1038/s41388-018-0171-x

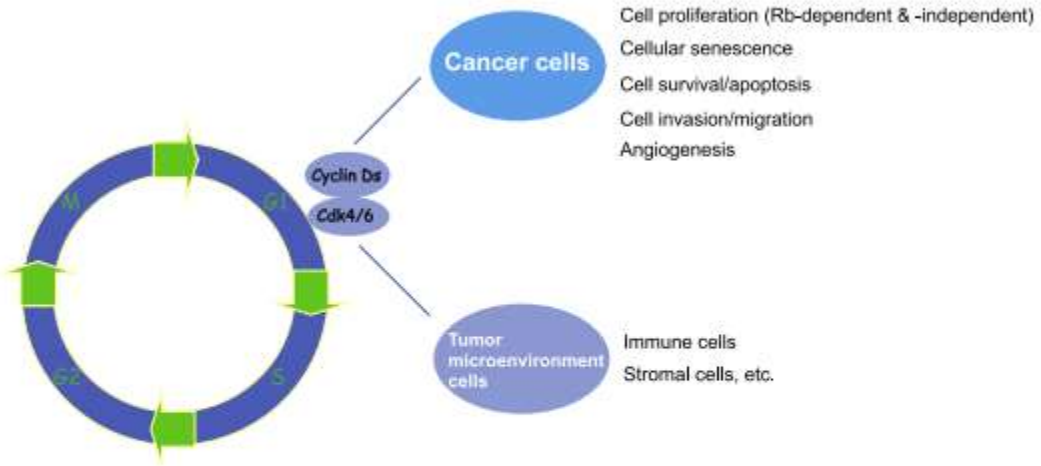
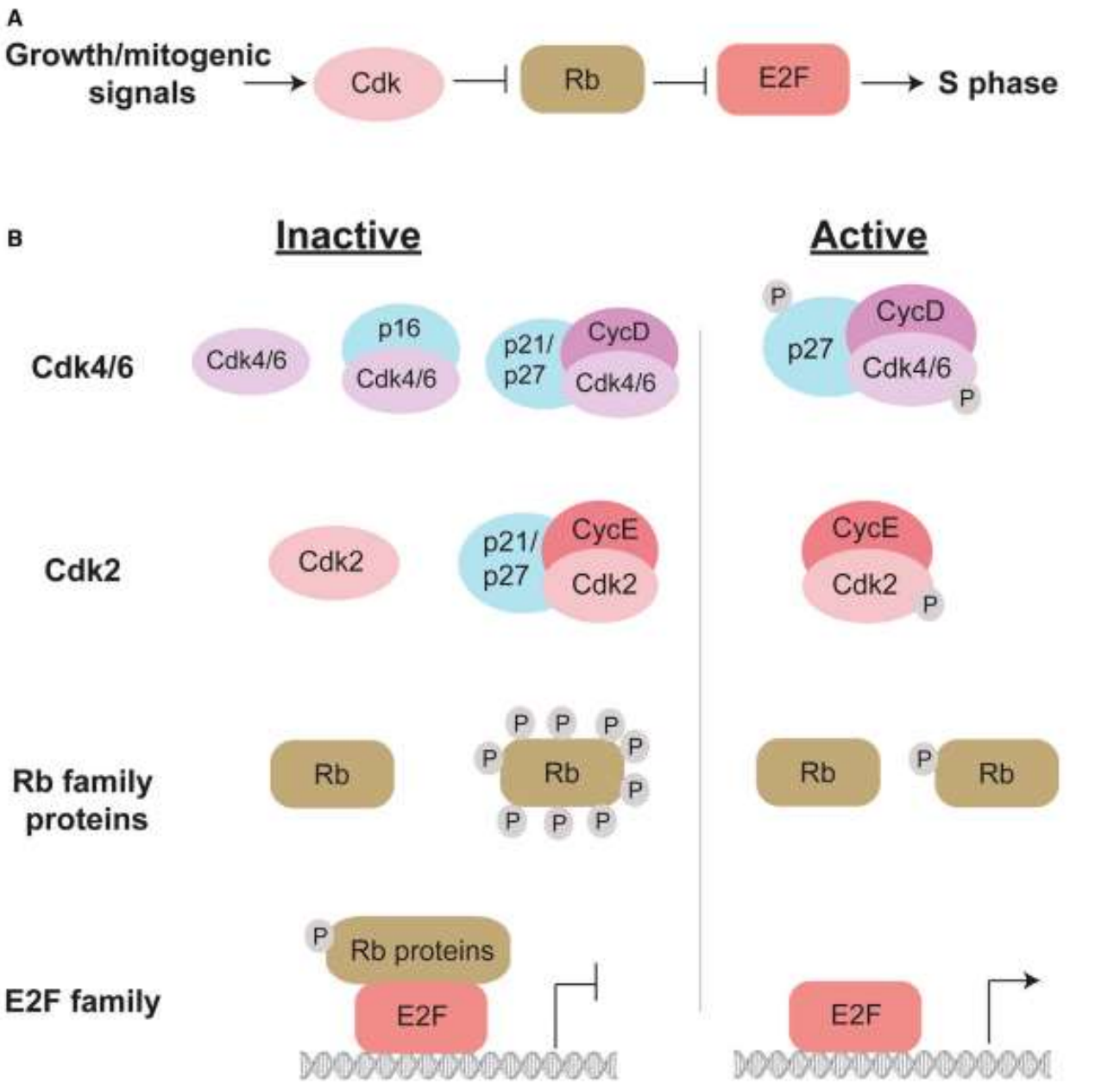
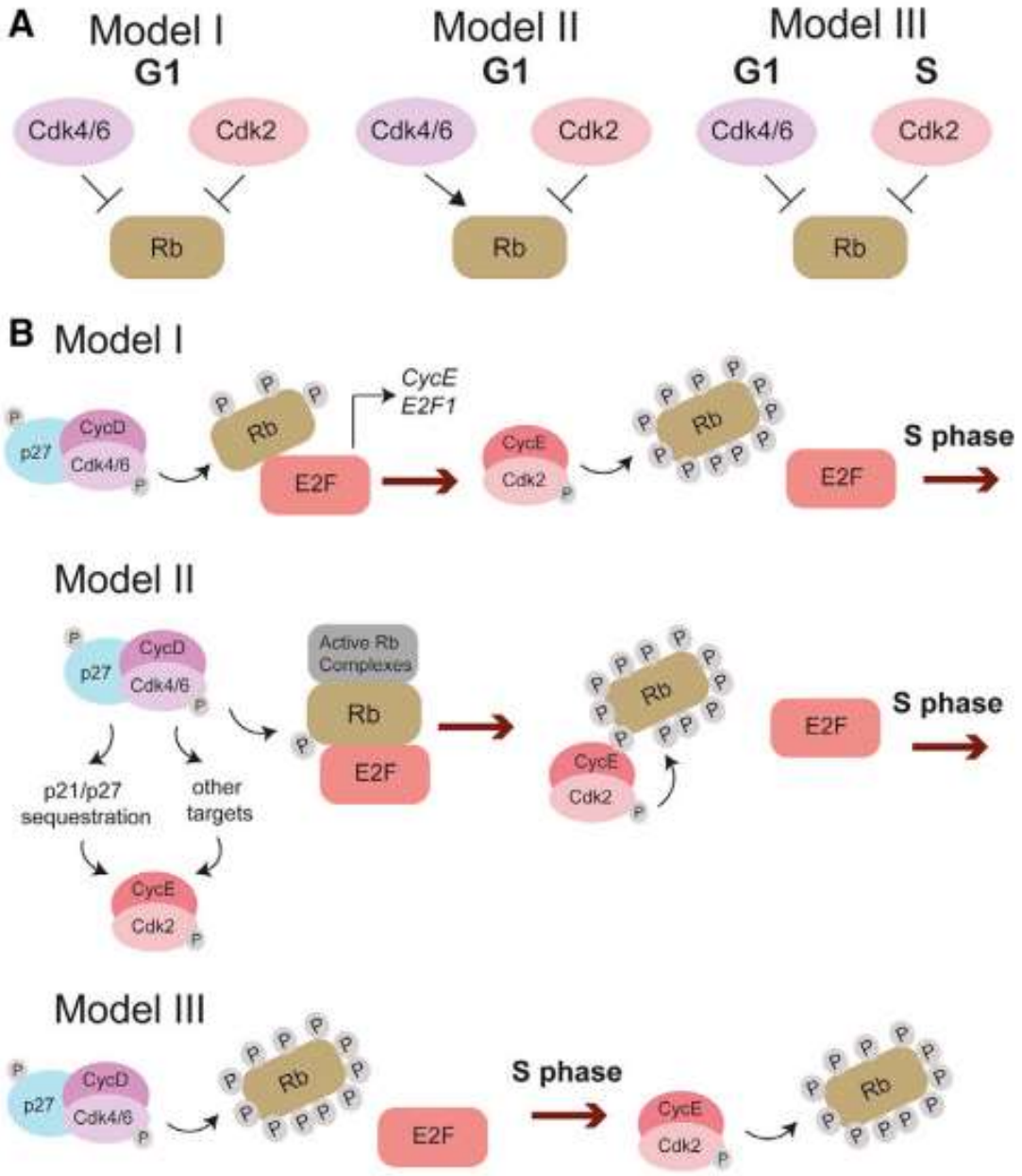


Fig. 1 Four phases of the mitotic cell division cycle: first gap (G1), second gap (G2), mitosis (M), and DNA synthesis (S). Cyclin Ds and their associated cyclin-dependent kinases (CDK4 and CDK6) play critical roles in the transition from G1 to S phase via phosphorylating Rb proteins. Cyclin Ds-CDKs have functions in tumorigenesis, such as proliferation, senescence, migration, apoptosis, and angiogenesis. Cyclin Ds-CDKs also carry out functions in tumor microenvironment cells to facilitate tumorigenesis.


A
Growth/mitogenic signals
Cdk
Rb
E2F
S phase
B
Inactive
Active
Cdk4/6
Cdk4/6
p16
Cdk4/6
p21/
p27
CycD
Cdk4/6
P
p27
CycD
Cdk4/6
P
Cdk2
Cdk2
p21/
p27
CycE
Cdk2
CycE
Cdk2
P
Rb family proteins
Rb
P
Rb
Rb
P
Rb
E2F family
P
Rb proteins
E2F
E2F

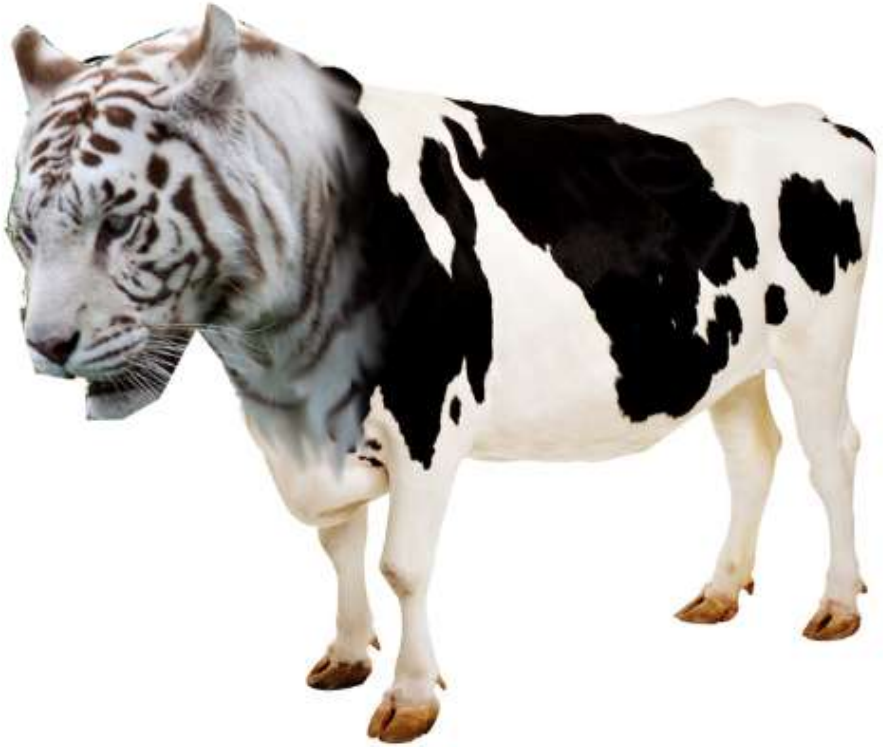

A
Model I
G1
Cdk4/6
Cdk2
Rb
Model II
G1
Cdk4/6
Cdk2
Rb
Model III
G1
S
Cdk4/6
Cdk2
Rb
B
Model I
p27
CycD
Cdk4/6
Rb
E2F
CycE
E2F1
CycE
Cdk2
Rb
E2F
S phase
Model II
p27
CycD
Cdk4/6
Active Rb
Complexes
Rb
E2F
p21/p27
sequestration
other
targets
CycE
Cdk2
Rb
CycE
Cdk2
E2F
S phase
Model III
p27
CycD
Cdk4/6
Rb
E2F
S phase
CycE
Cdk2
Rb

Fusion genes.

P. Pauwels
(UZA, UA)

Kennis / Ervaring / Zorg

UZA



4 *EML4-ALK*融合基因的检测方法

自从该融合基因发现以来，为寻找更简便和更准确的方法，研究人员做了各方面大量的研究。目前最常用的方法是反转录PCR（RT-PCR）。RT-PCR是一种很灵敏的技术，可以检测很低拷贝数的RNA。RT-PCR广泛应用于遗传病的诊断，并且可以用于定量监测某种RNA的含量。利用手术切除标本或其他标本，提取总RNA后进行RT-PCR，对PCR产物进行电泳以确定是否含有*EML4-ALK*融合基因。通过对各种不同亚型进行专门引物的设计，可以分辨出各种不同亚型的*EML4-ALK*融合基因。

荧光原位杂交技术（fluorescent in situ hybridization, FISH）也是常用的方法。FISH是利用荧光标记的特异核酸探针与细胞内相应的靶DNA分子或RNA分子杂交，通过在荧光显微镜或共聚焦激光扫描仪下观察荧光信号，来确定与特异探针杂交后被染色的细胞或细胞器的形态

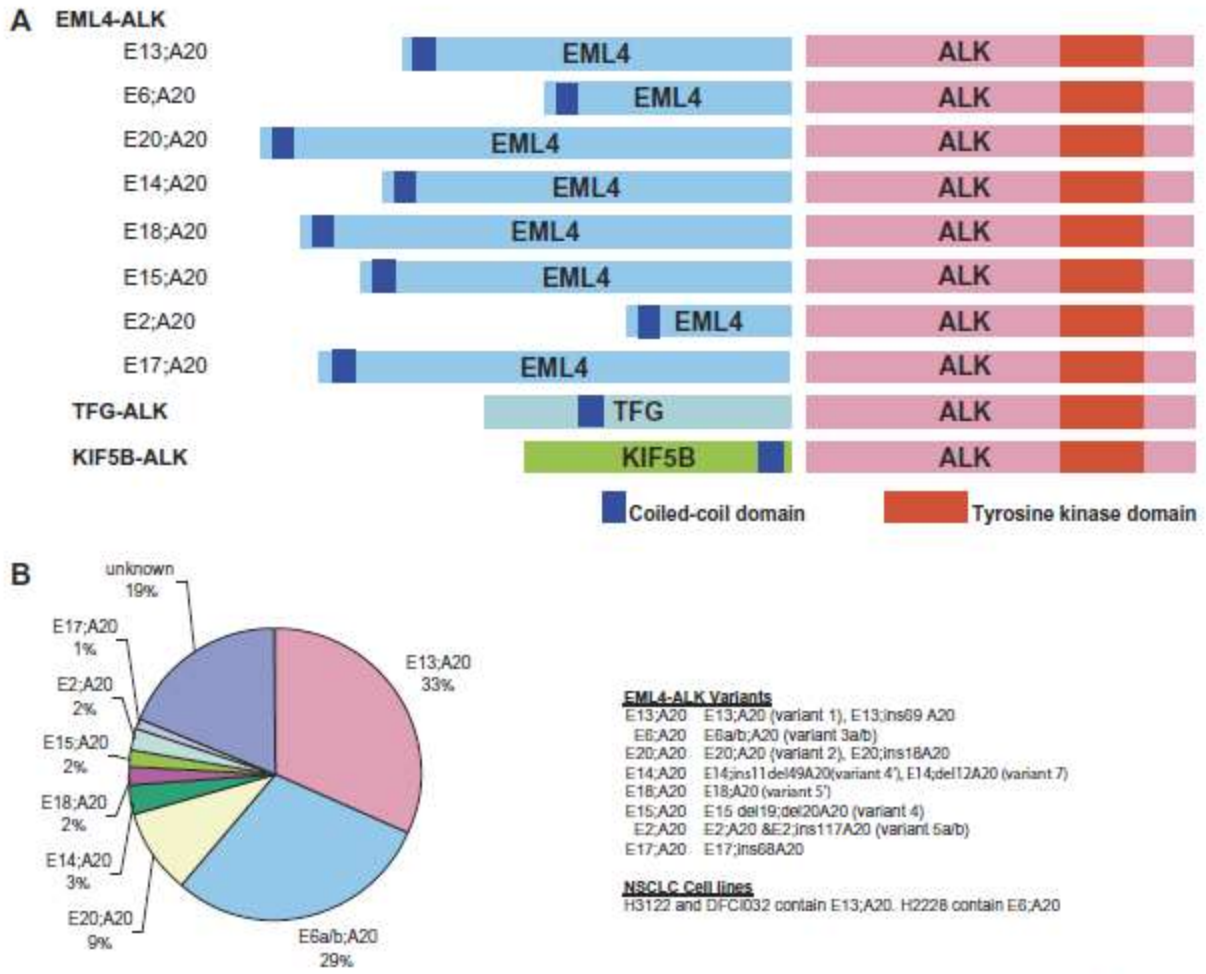
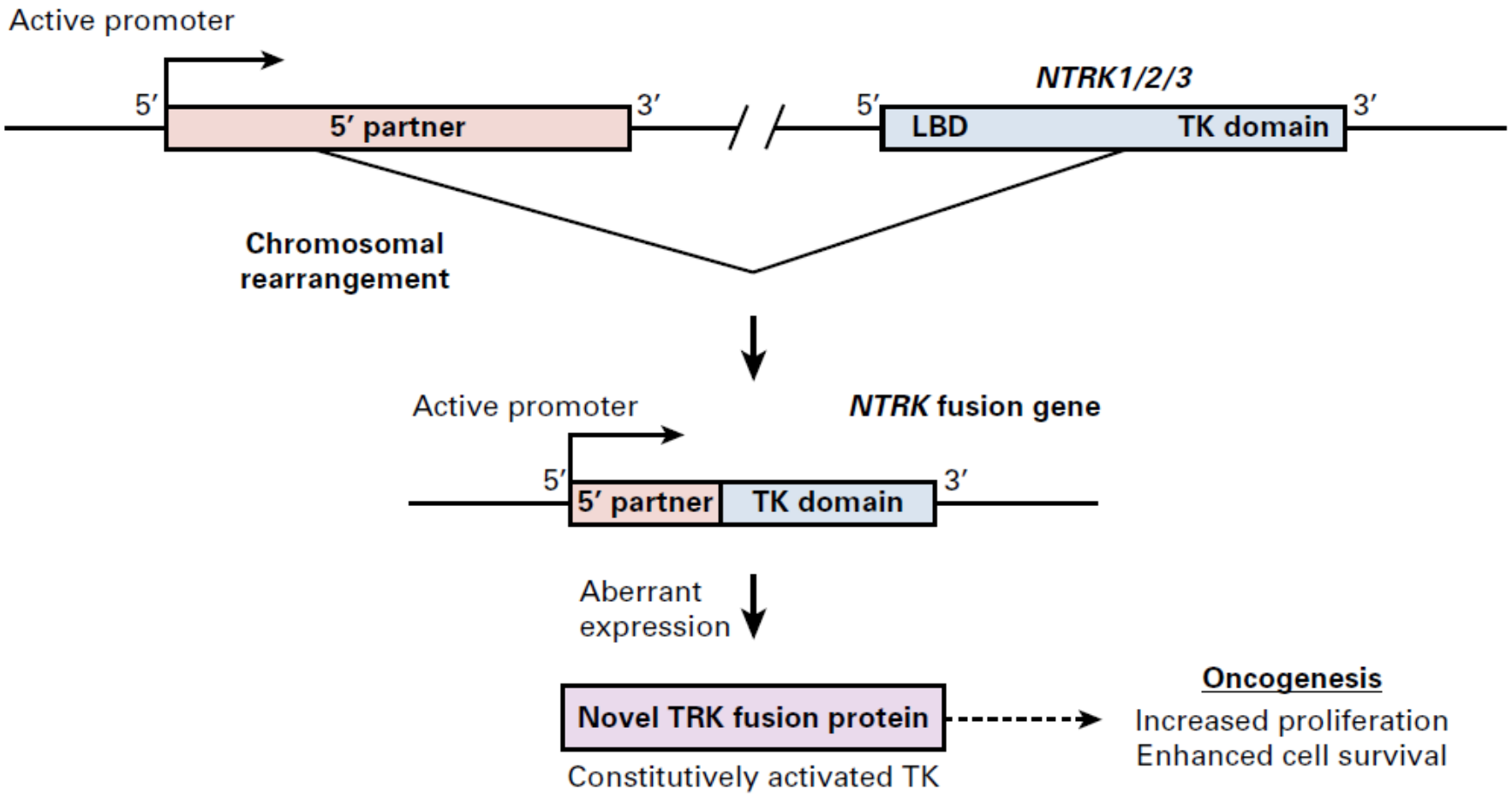
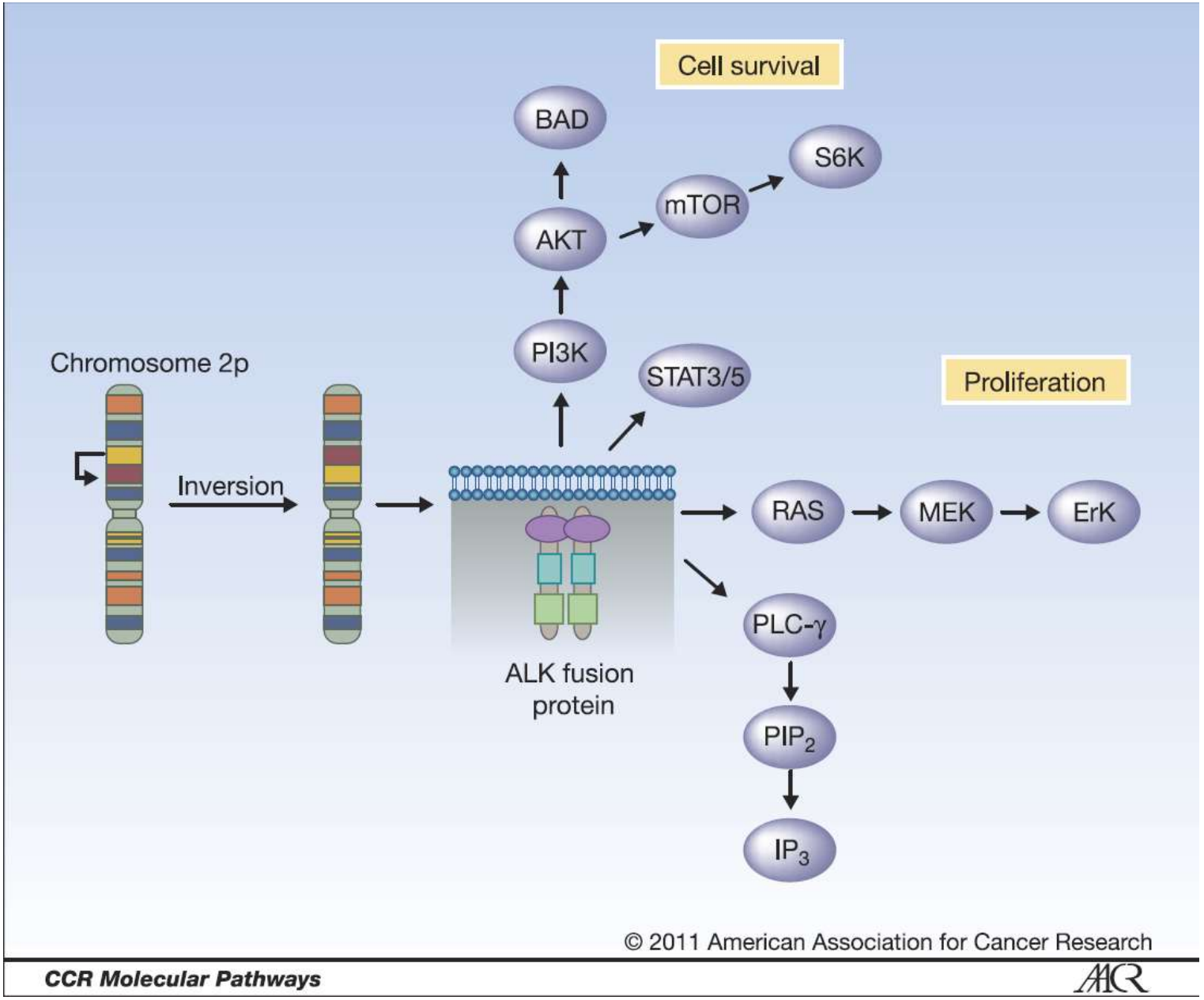


Fig. 3 – Different variants of *EML4-ALK* and non-*EML4* fusion partners. (A) Different variants of *EML4-ALK* are depicted. The nomenclature refers to the exon in *EML4* translocated to the exon in *ALK*. (B) Frequency of different *EML4-ALK* variants. The most common variants are E13;A20 (variant 1) and E6a/b; A20 (variant 3). Data obtained from.[4-11,30,32-36] Of note not all studies list the specific *EML4-ALK* variant.




Cell survival
BAD
S6K
mTOR
AKT
PI3K
STAT3/5
Proliferation
Chromosome 2p
Inversion
RAS
MEK
ErK
PLC-γ
ALK fusion protein
PIP2
IP3
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CCR Molecular Pathways
AACR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Ravi Salgia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

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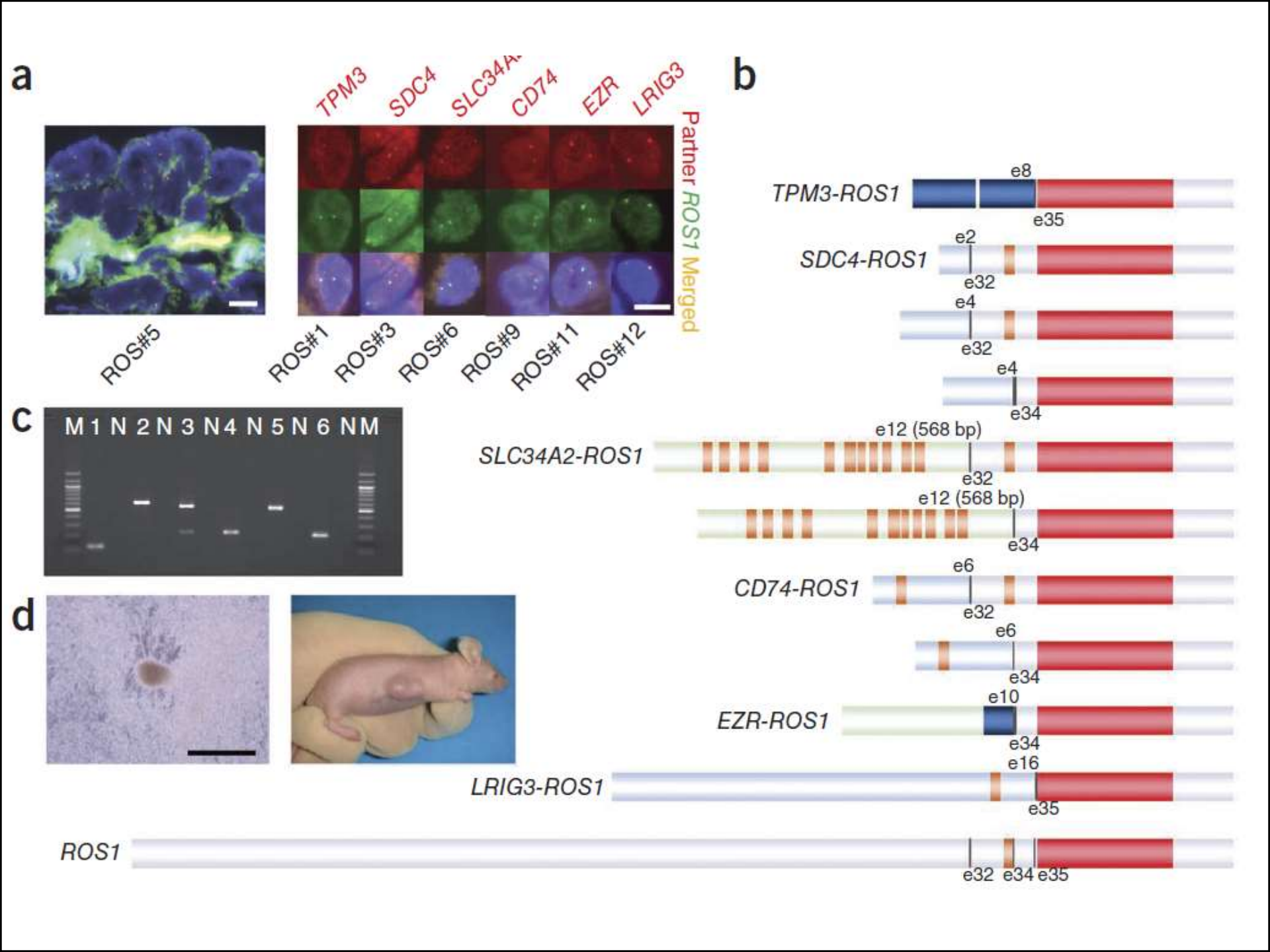
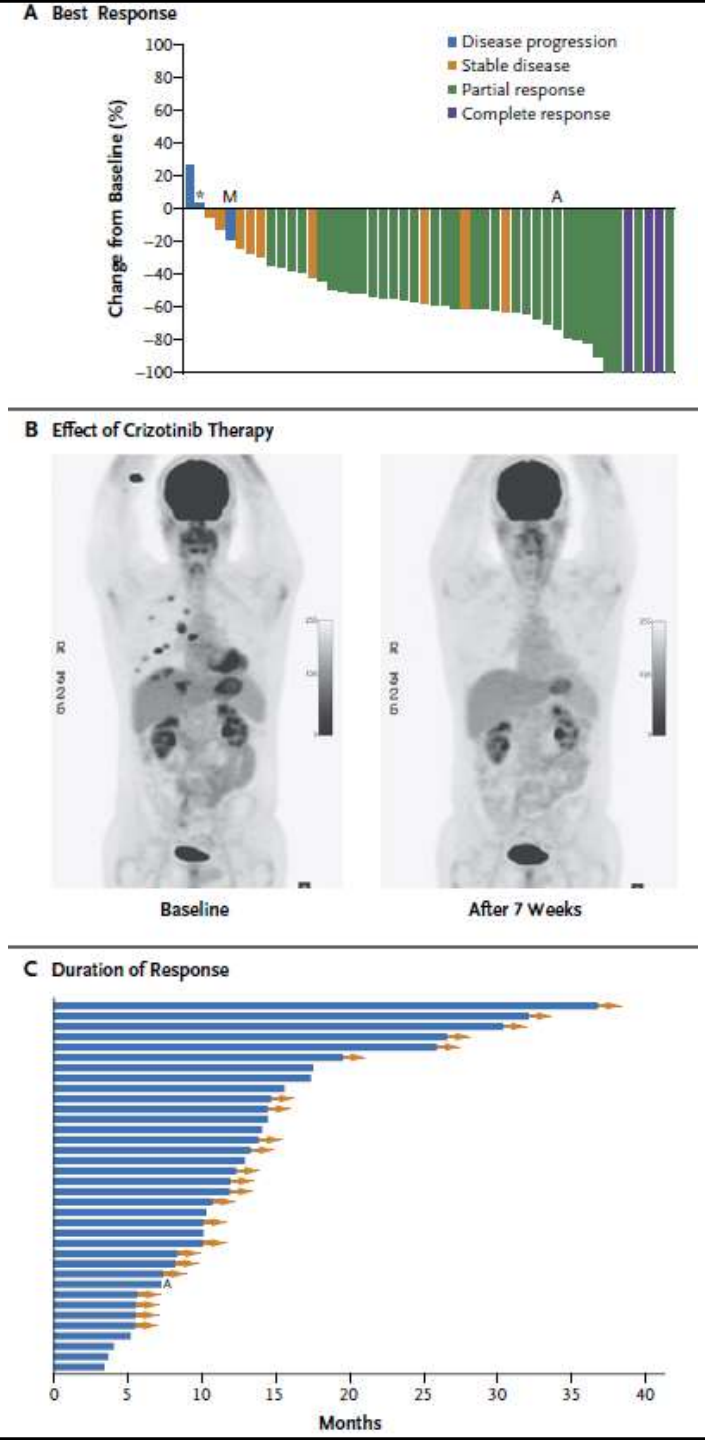
DOI: 10.1056/NEJMoa1406766


a
TPM3
SDC4
SLC34A
CD74
EZR
LRIG3
Partner ROS1 Merged
ROS#5
ROS#1
ROS#3
ROS#6
ROS#9
ROS#11
ROS#12
b
TPM3-ROS1
e8
e35
SDC4-ROS1
e2
e32
e4
e32
e4
e34
SLC34A2-ROS1
e12 (568 bp)
e32
e12 (568 bp)
e34
CD74-ROS1
e6
e32
e6
e34
EZR-ROS1
e10
e34
LRIG3-ROS1
e16
e35
ROS1
e32 e34 e35
c
M 1 N 2 N 3 N 4 N 5 N 6 NM
d


A Best Response
Disease progression
Stable disease
Partial response
Complete response
Change from Baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
*
M
A
B Effect of Crizotinib Therapy
Baseline
After 7 Weeks
C Duration of Response
A
0
5
10
15
20
25
30
35
40
Months

OXFORD

Carcinogenesis, 2020, Vol. 41, No. 2, 123–129

doi:10.1093/carcin/bgz184
Advance Access Publication November 11, 2019
40th Anniversary Review Article

40TH ANNIVERSARY REVIEW ARTICLE

*RET*oma: a cancer subtype with a shared driver oncogene

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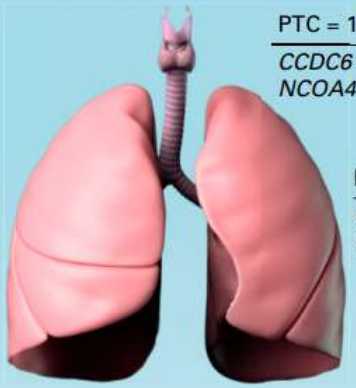


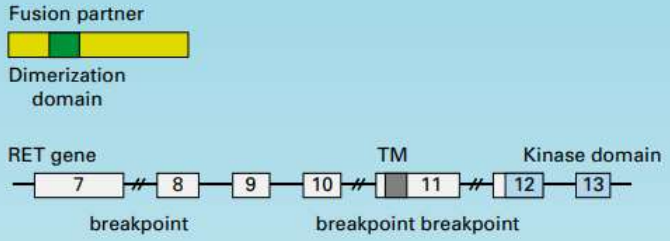
PTC = 10%-20%

CCDC6 = 59%
NCOA4 = 36%

NSCLC = 2%

KIF5B = 83.6%
CCDC6 = 15.1%

Other solid tumors
Colon < 1%
Pancreatic cancer < 1%
Spitzoid < 1%



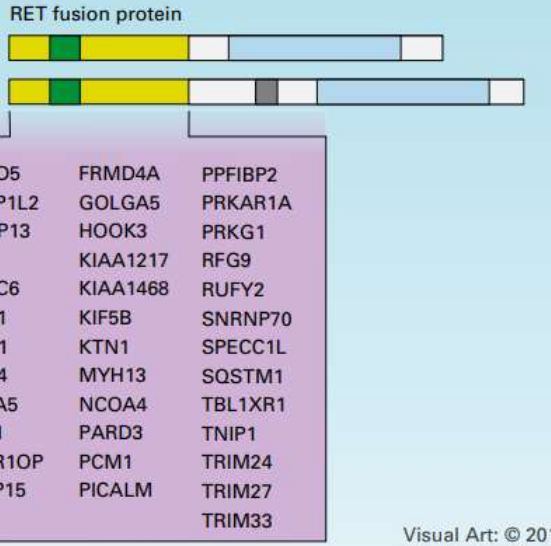


Table 1. Summary of main features, strengths and weaknesses of all available techniques to detect *RET* rearrangements

Method	Sensitivity	Specificity	Detection of partner	Detection of expression	Screening
IHC	Moderate[a]	Moderate[b]	No	Yes	No
FISH	High	High	No/Yes[c]	No	Rare circumstances
RT-PCR	Moderate/high[d]	High	Yes/No[e]	Yes	Rare circumstances
DNA-seq NGS	Moderate[f]	High/moderate[g]	Yes	No	Yes
RNA-seq NGS	High	High	Yes	Yes[h]	Yes

DNA-seq NGS, DNA sequencing by next-generation sequencing; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; RNA-seq NGS, RNA sequencing by next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction.

[a] False positive up to 40%.

[b] False negative up to 40%.

[c] In case of the use of specific fusion partner probe.

[d] In settings with many possible fusion partners, risk of lower sensitivity.

[e] Does not allow the detection of novel partners.

[f] False positive: detected rearrangements by DNA-based assays may not result in fusions, so correlation with RNA-based confirmation of predicted fusion transcript is needed.

[g] False negative: some introns involved in rearrangements may be inadequately covered for technical reasons.

[h] Indication on the in-frame nature of the fusion (functionality).

Published OnlineFirst February 24, 2020; DOI: 10.1158/2159-8290.CD-19-1116

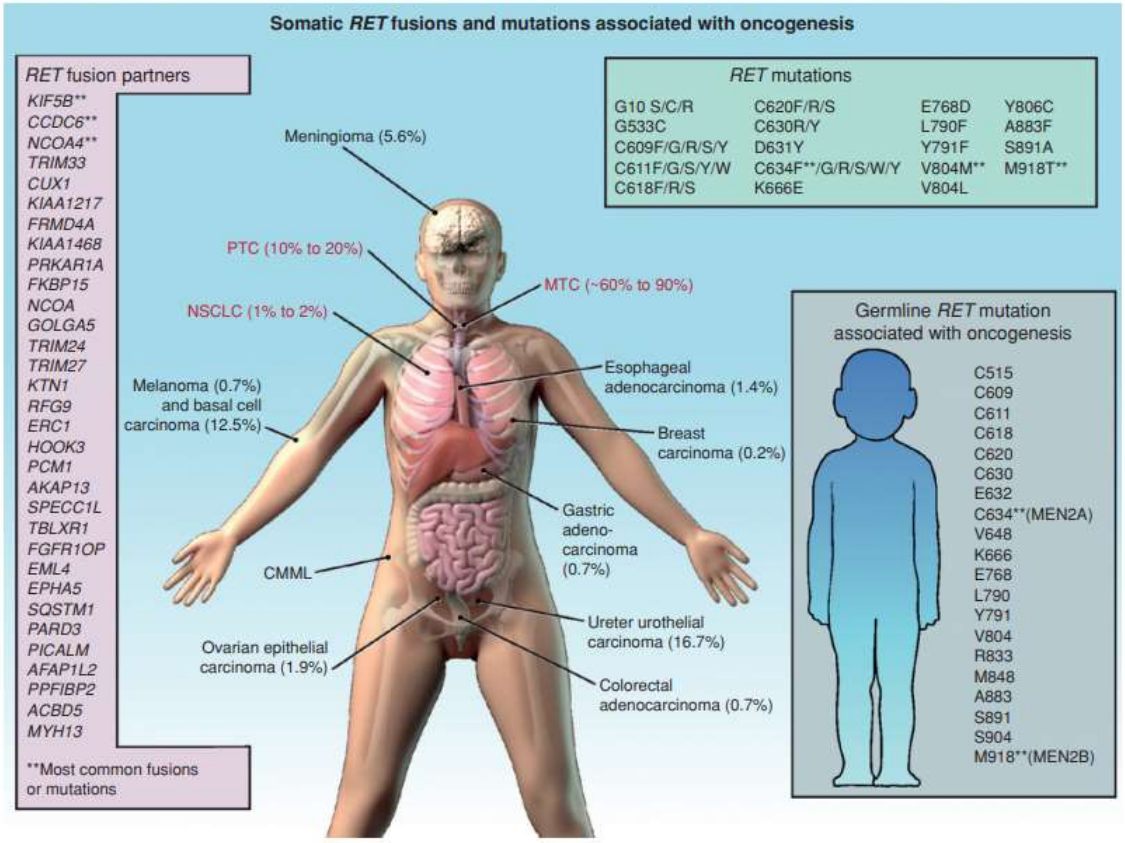
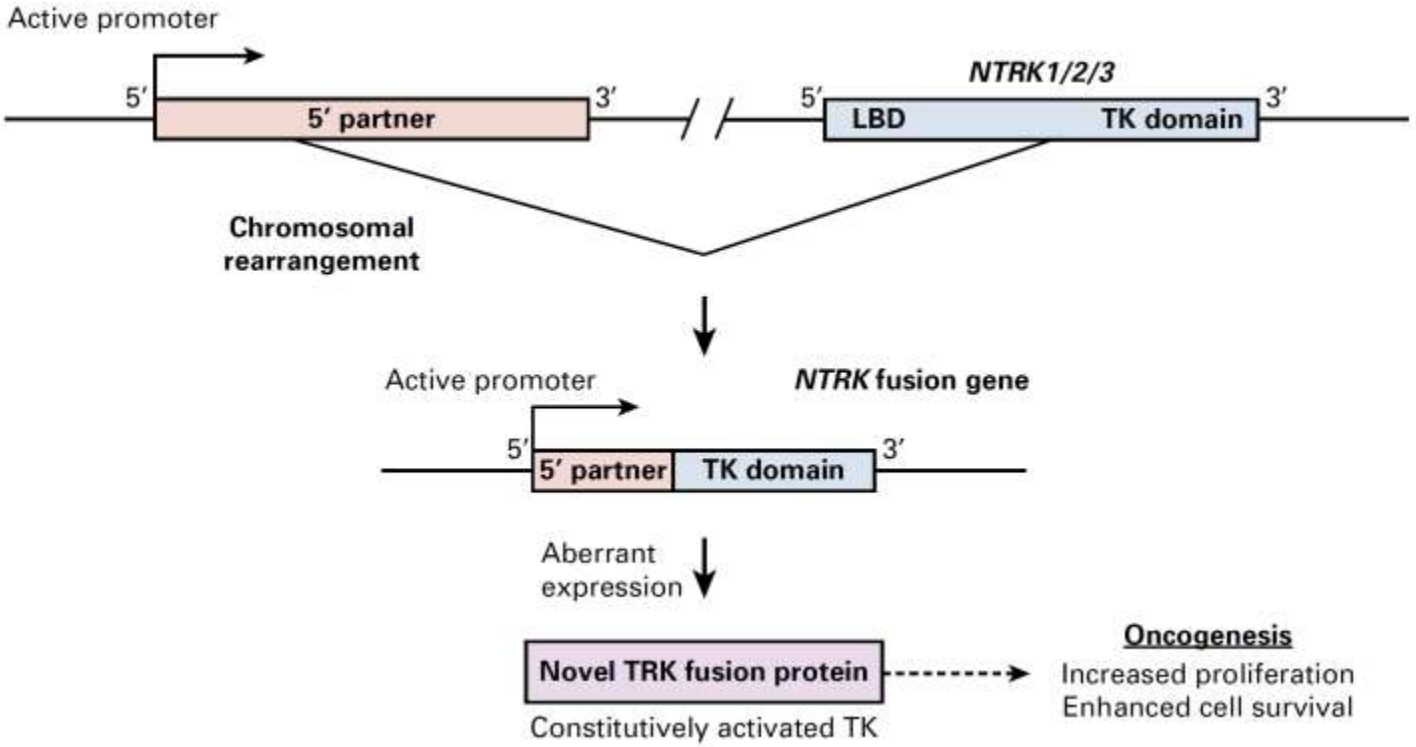


Figure 1. Frequency and distribution of *RET* fusions and *RET* mutations across malignancies. Visual art © 2019 The University of Texas MD Anderson Cancer Center. Red text indicates the most prevalent RET-dependent malignancies. CMML, chronic myelomonocytic leukemia.

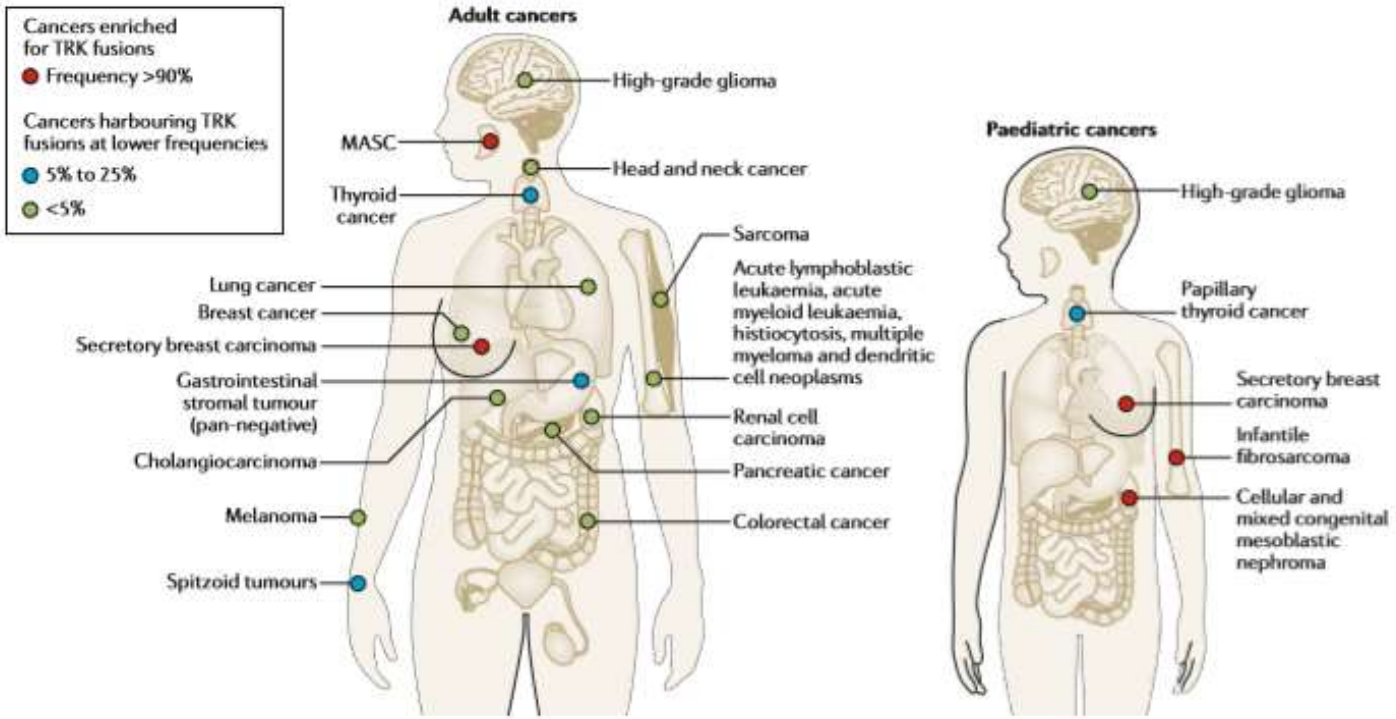
NTRK fusion-positive cancers and TRK inhibitor therapy

*Emiliano Cocco[1], Maurizio Scaltriti[1,2] and Alexander Drilon[3,4]**

NTRK fusions

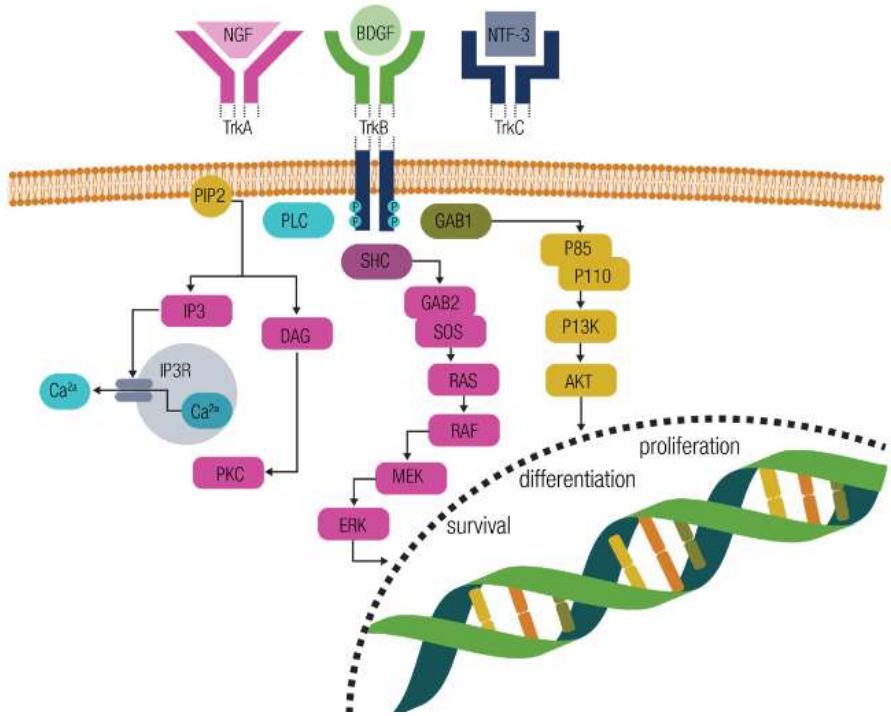


J Clin Oncol 37. © 2018 by American Society of Clinical Oncology

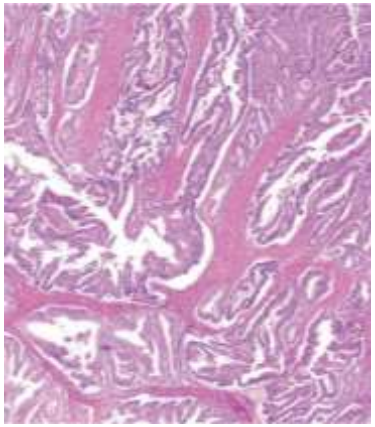
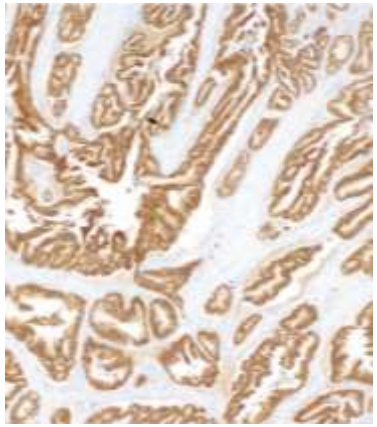
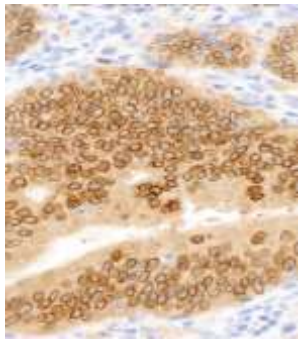
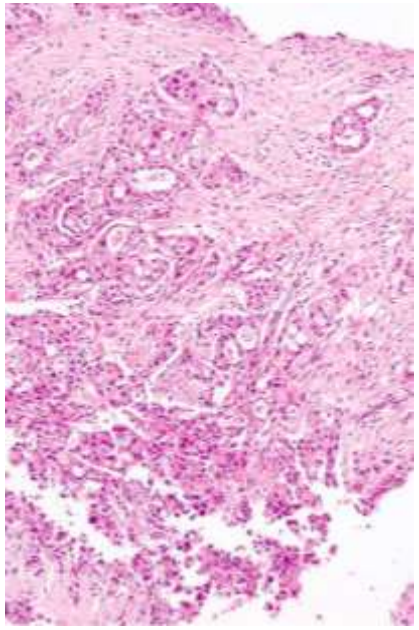
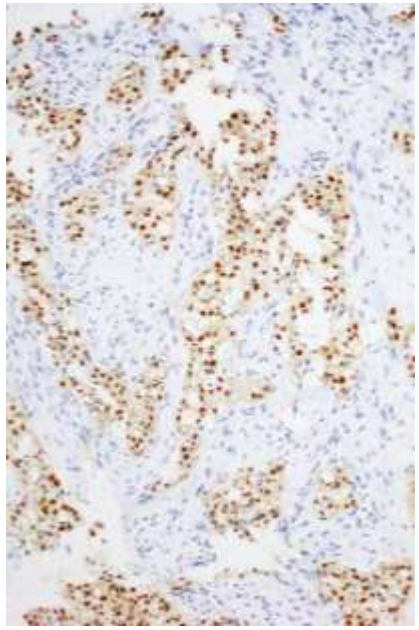

Cancers enriched for TRK fusions
Frequency >90%
Cancers harbouring TRK fusions at lower frequencies
5% to 25%
<5%
Adult cancers
High-grade glioma
MASC
Head and neck cancer
Thyroid cancer
Sarcoma
Lung cancer
Acute lymphoblastic leukaemia, acute myeloid leukaemia, histiocytosis, multiple myeloma and dendritic cell neoplasms
Breast cancer
Secretory breast carcinoma
Gastrointestinal stromal tumour (pan-negative)
Renal cell carcinoma
Cholangiocarcinoma
Pancreatic cancer
Melanoma
Colorectal cancer
Spitzoid tumours
Paediatric cancers
High-grade glioma
Papillary thyroid cancer
Secretory breast carcinoma
Infantile fibrosarcoma
Cellular and mixed congenital mesoblastic nephroma

NTRK fusions

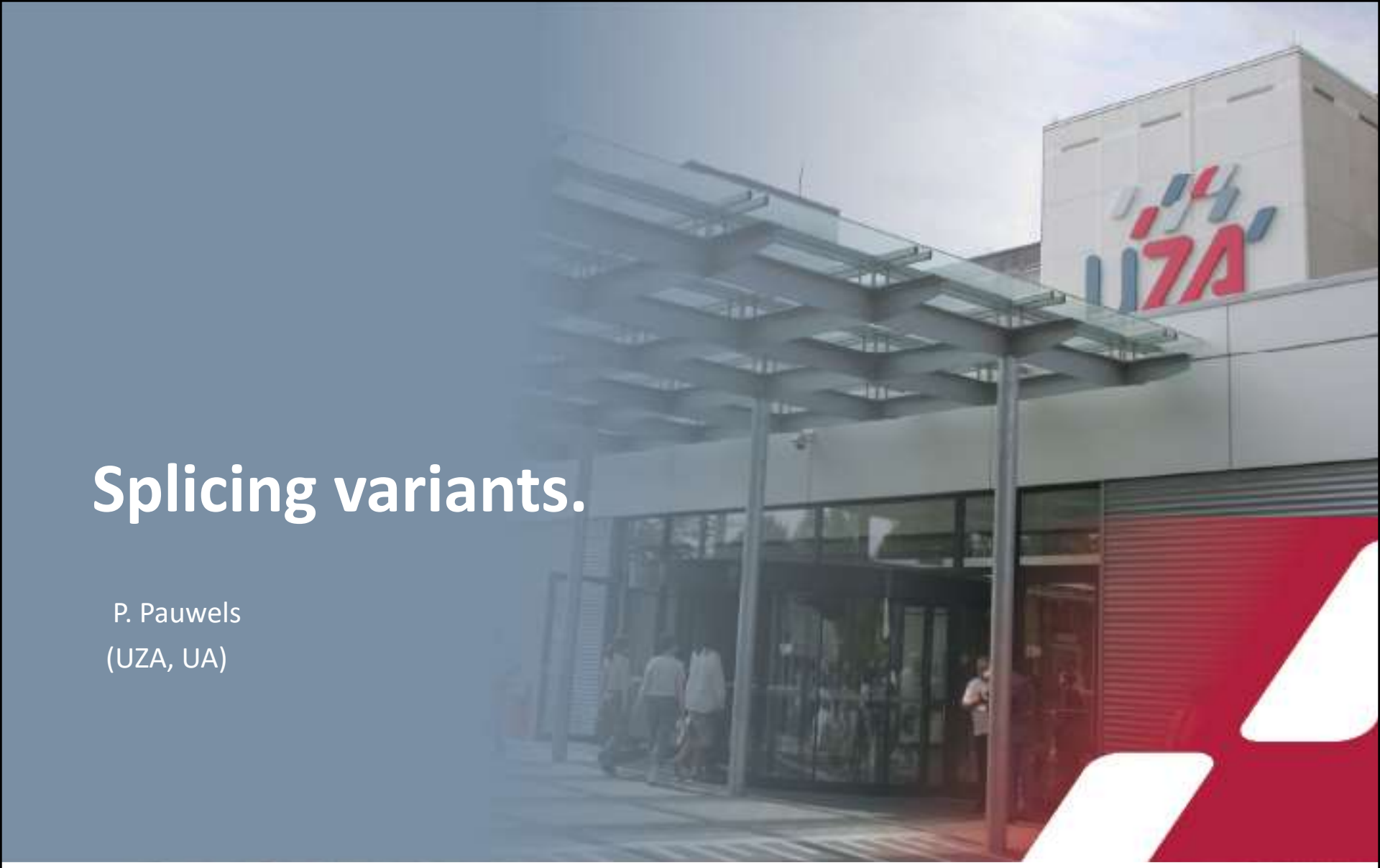
Figure 2: TRK Receptor Signalling



NTRK immunohistochemistry

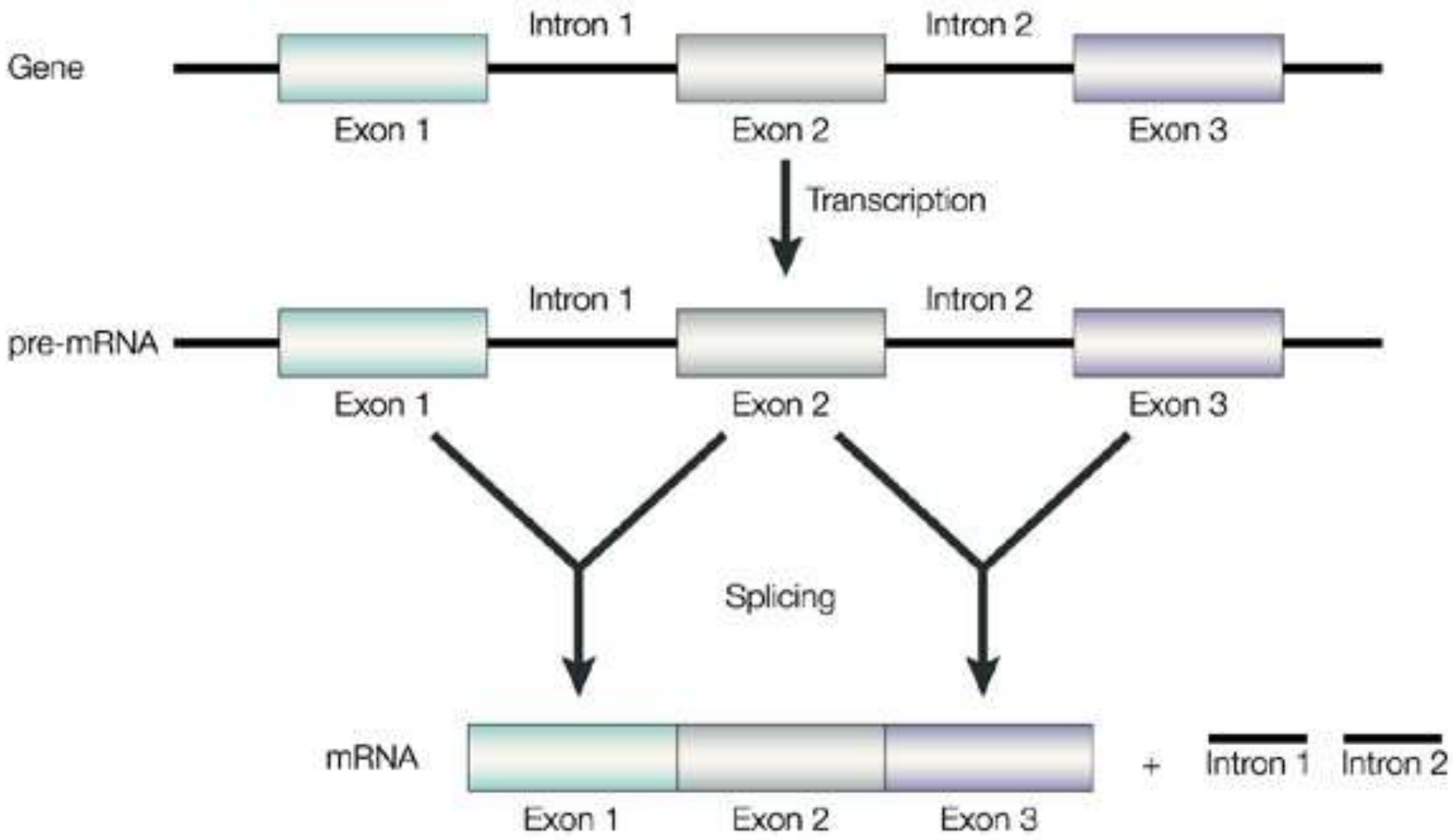
Confirm by FISH or RNA sequencing



Splicing variants.

P. Pauwels
(UZA, UA)

Kennis / Ervaring / Zorg


Gene
Intron 1
Intron 2
Exon 1
Exon 2
Exon 3
Transcription
pre-mRNA
Intron 1
Intron 2
Exon 1
Exon 2
Exon 3
Splicing
mRNA
Exon 1
Exon 2
Exon 3
+
Intron 1
Intron 2

OXFORD

JNCI J Natl Cancer Inst (2017) 109(5): djw262

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First published online February 10, 2017
Review

REVIEW

Exon 14 Deleted MET Receptor as a New Biomarker and Target in Cancers

Alexis B. Cortot, Zoulika Kherrouche, Clotilde Descarpentries, Marie Wislez, Simon Baldacci, Alessandro Furlan, David Tulasne

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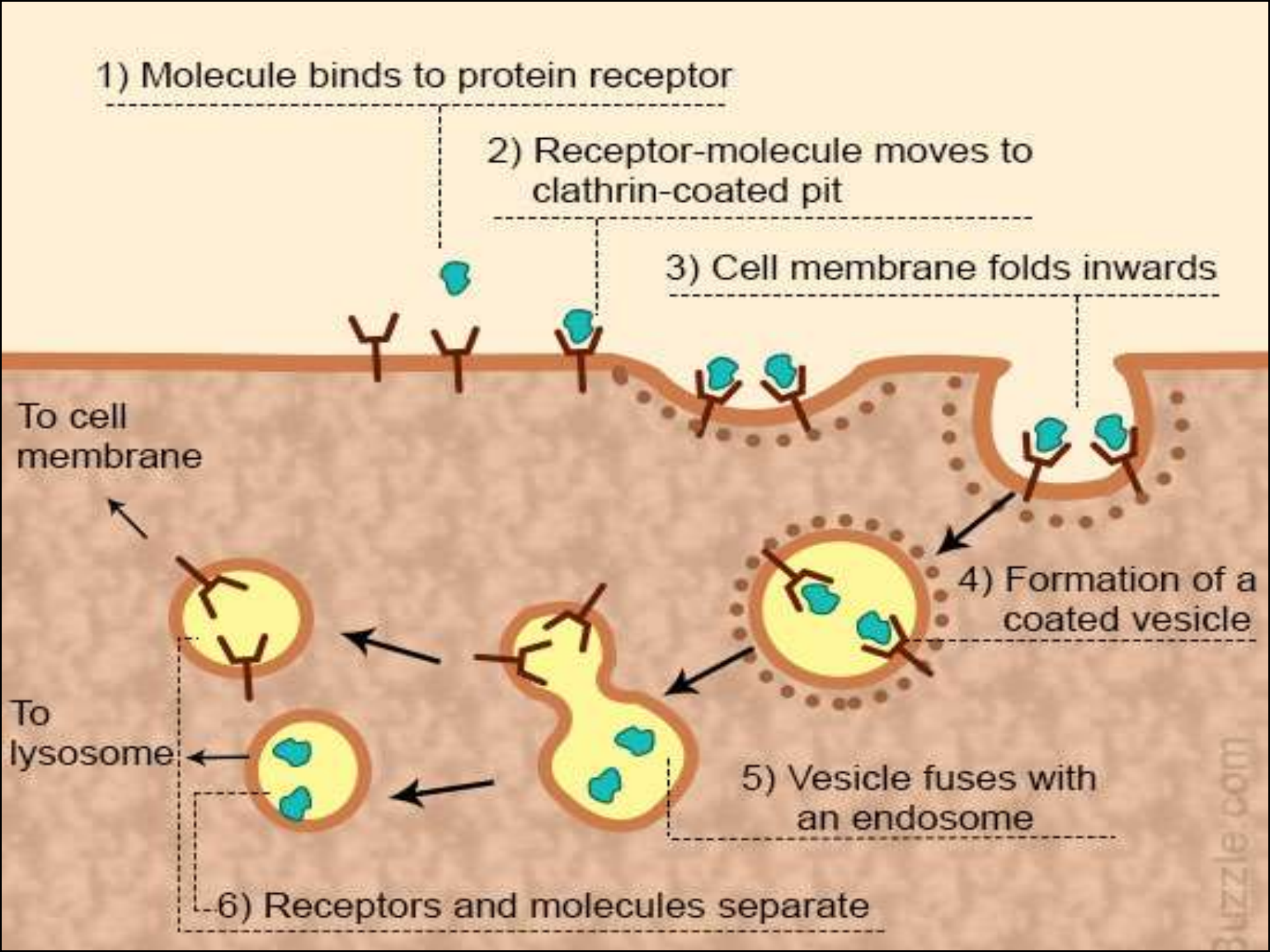
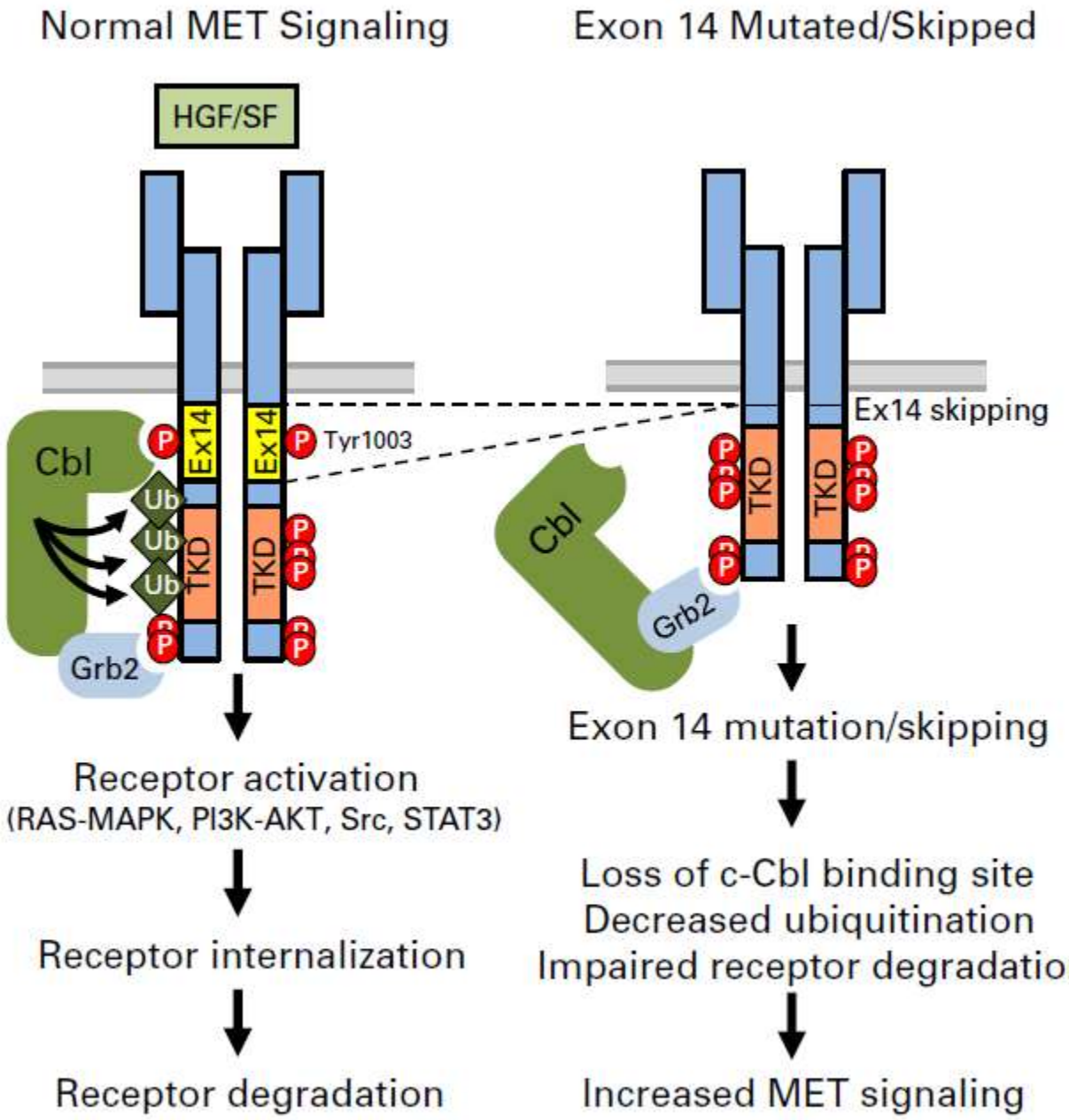
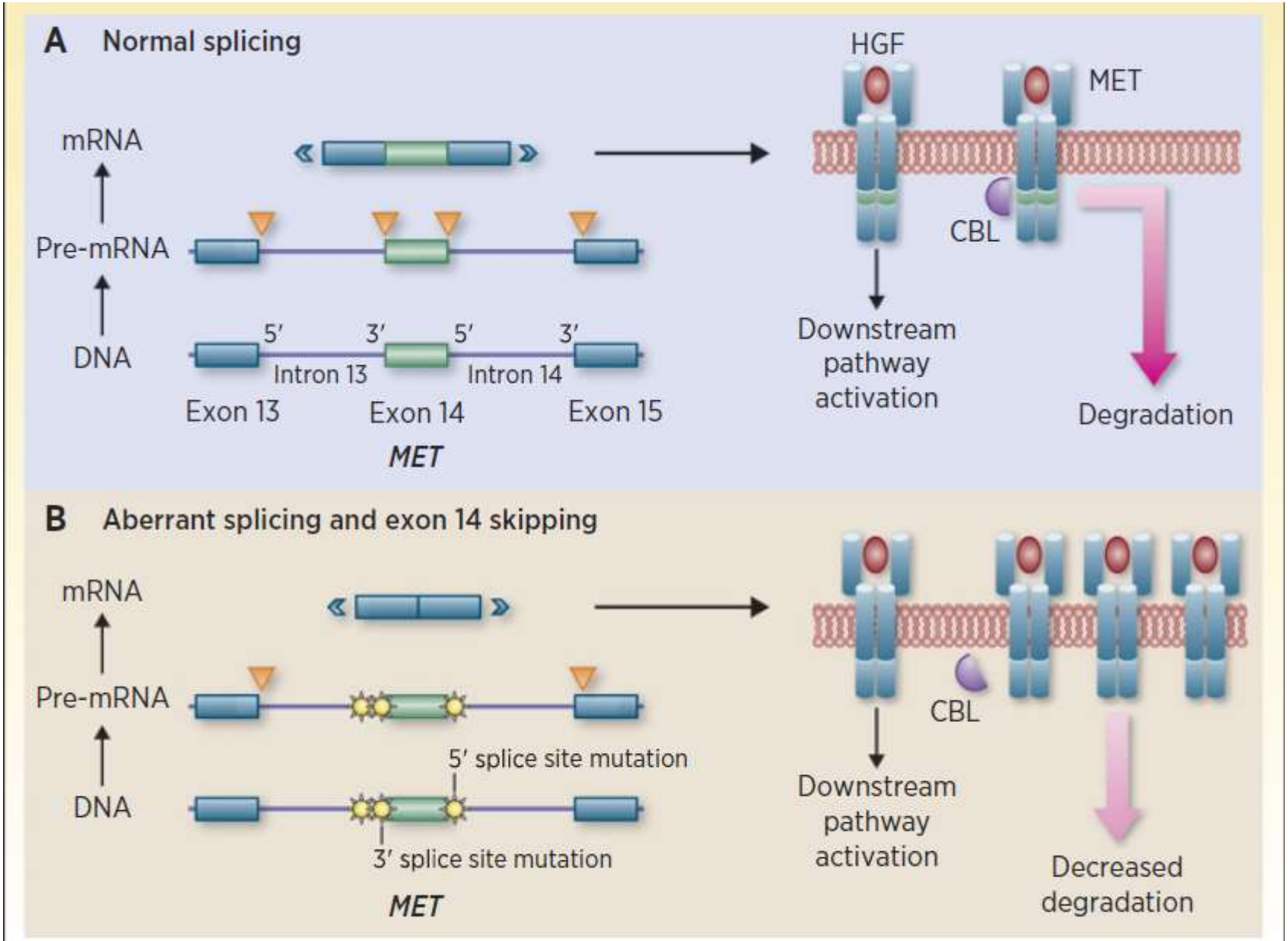
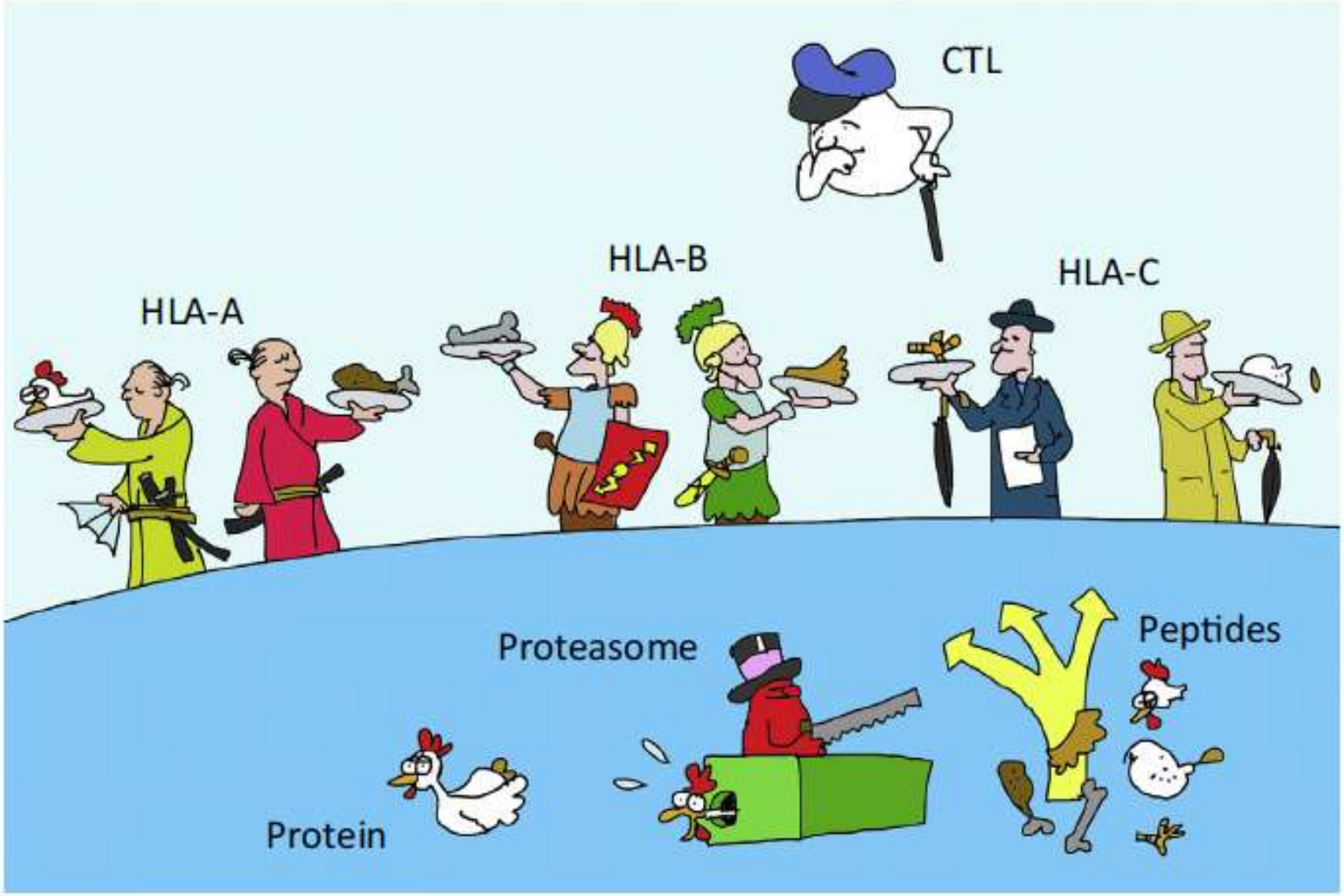

1) Molecule binds to protein receptor
2) Receptor-molecule moves to clathrin-coated pit
3) Cell membrane folds inwards
To cell membrane
4) Formation of a coated vesicle
To lysosome
5) Vesicle fuses with an endosome
6) Receptors and molecules separate

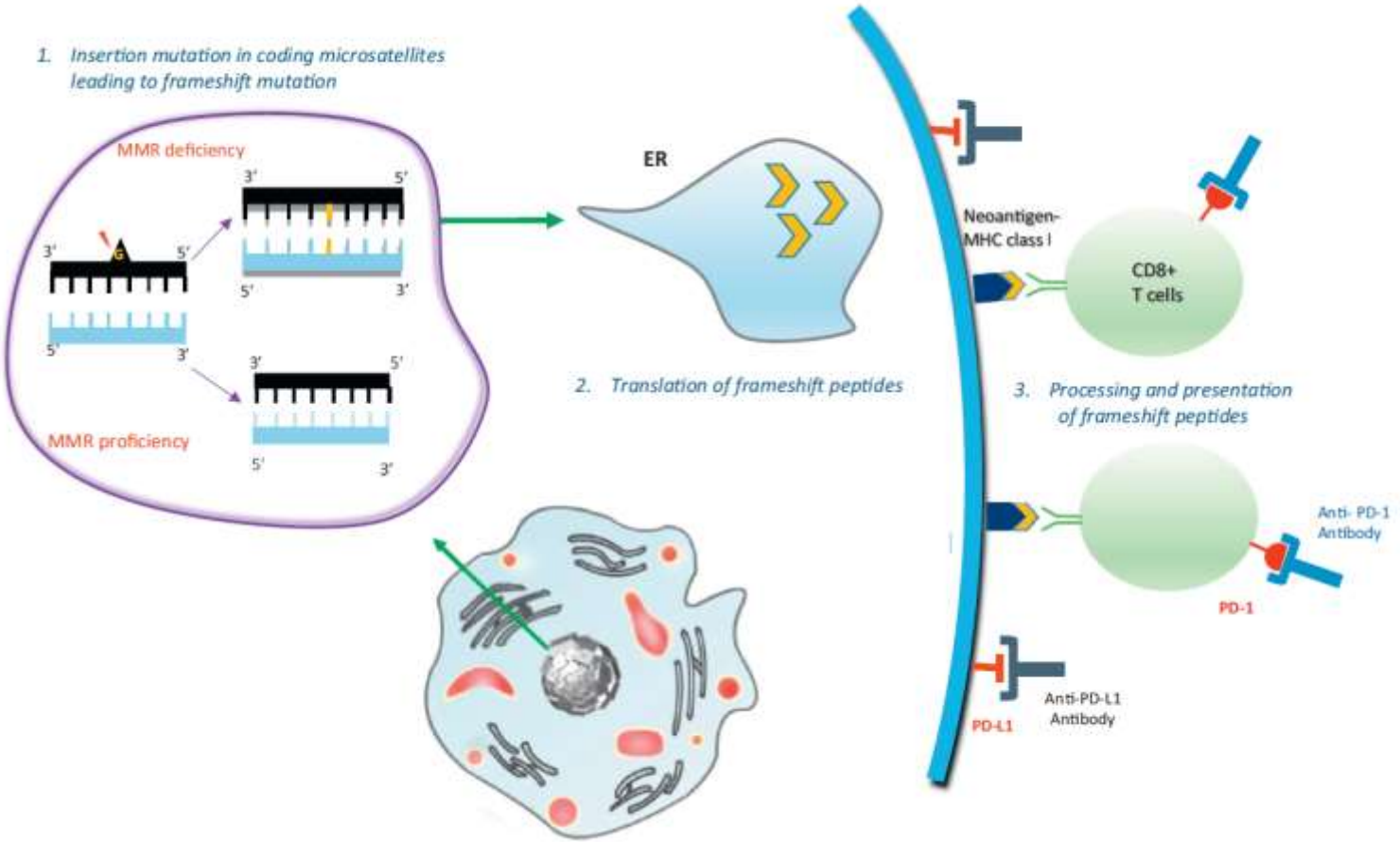


Journal of Clinical Oncology, Vol 34, No 8 (March 10), 2016: pp 879-881

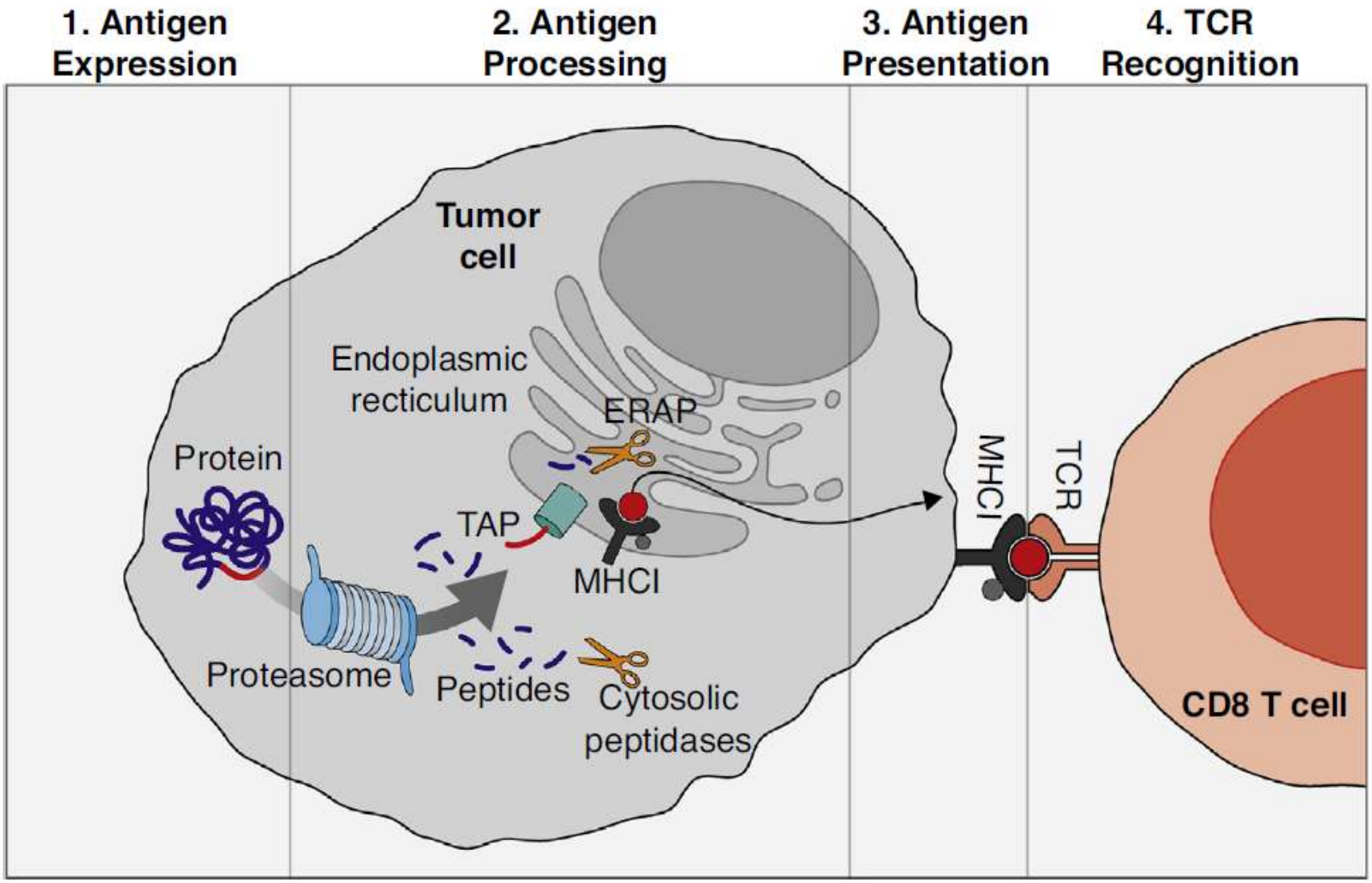




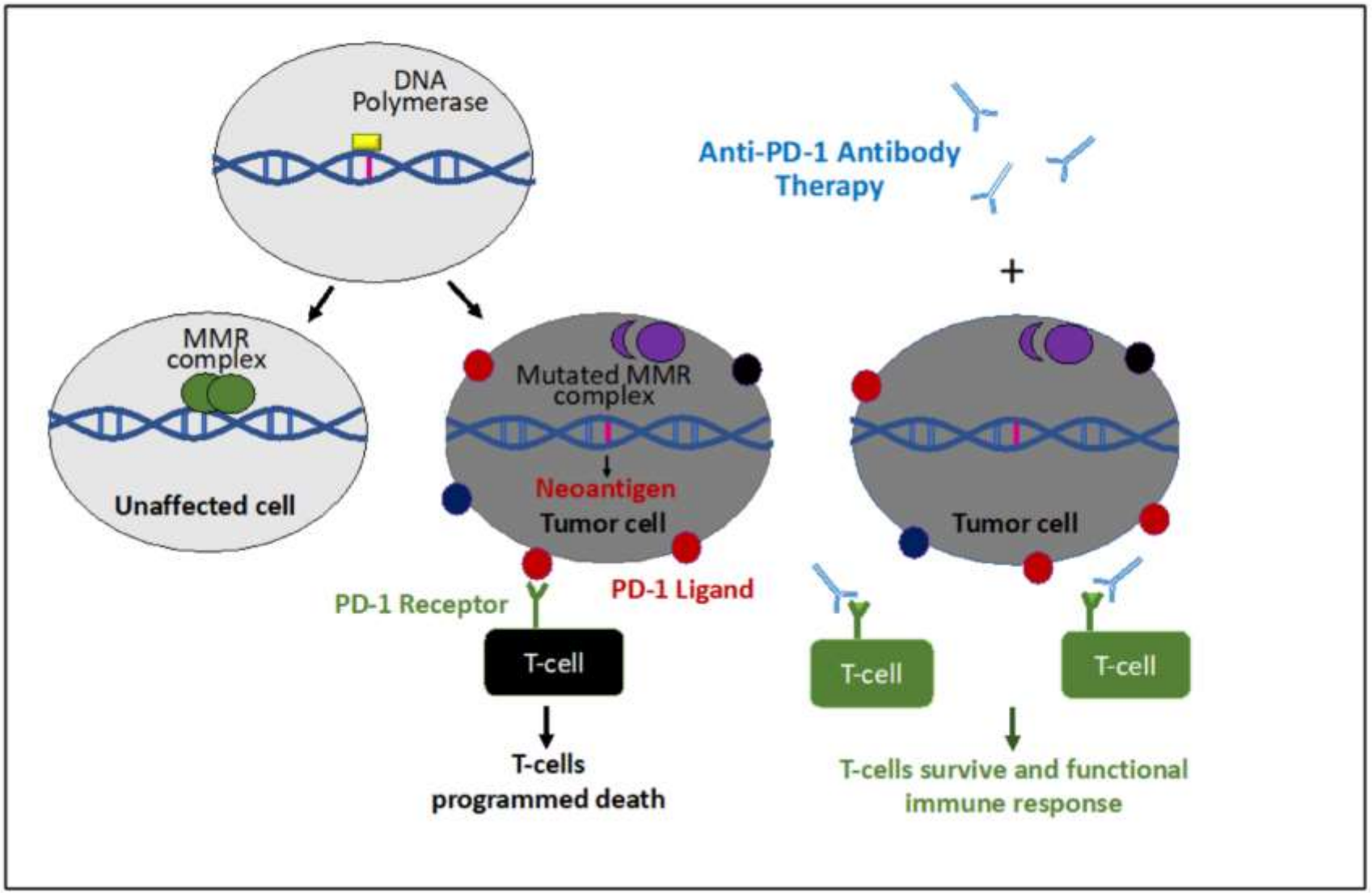
Trends in Immunology



M. Baretti, D.T. Le / Pharmacology & Therapeutics 189 (2018) 45–62



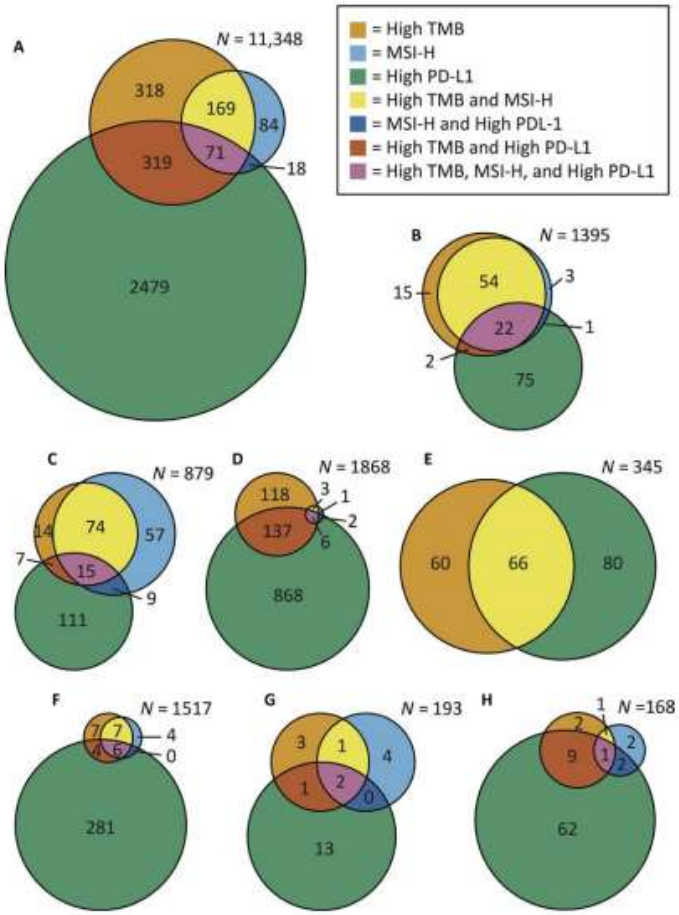
Current Opinion in Immunology


DNA
Polymerase
MMR
complex
Unaffected cell
Mutated MMR
complex
Neoantigen
Tumor cell
PD-1 Receptor
PD-1 Ligand
T-cell
T-cells
programmed death
Anti-PD-1 Antibody
Therapy
+
Tumor cell
T-cell
T-cell
T-cells survive and functional
immune response

Tumor Mutational Burden (TMB) or Tumor Mutation Load (TML)

TMB or TML: total number of somatic/acquired mutations per coding area of a tumor genome (Mut/Mb)

The number of mutations can vary across different tumor types.



doi: 10.1002/cam4.1372