Current Treatment Paradigm for NSCLC (transmembrane Tyrosine kinase receptors EGFR, ALK, ROS, MET, RET, NTRK)

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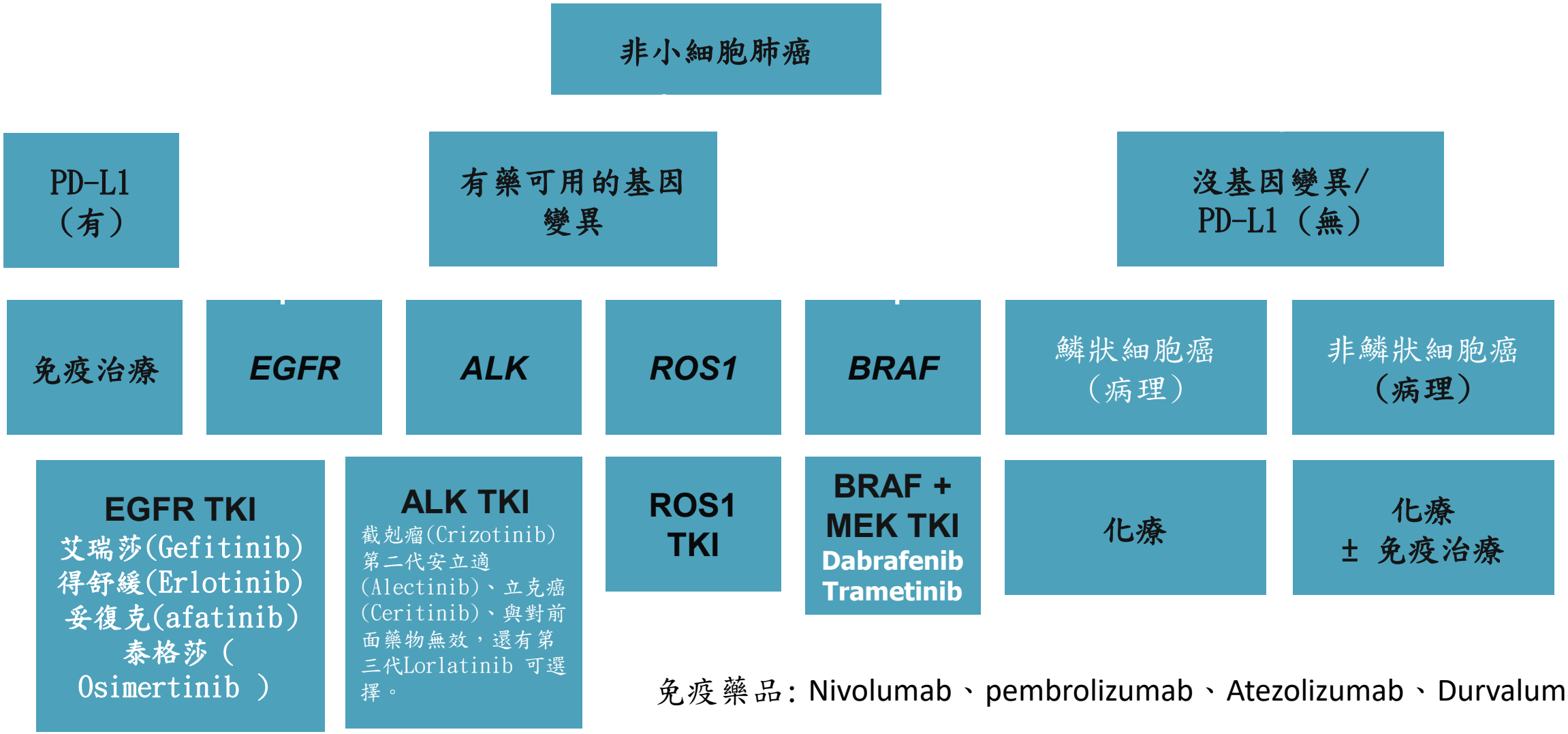
2021/04/09

Outline

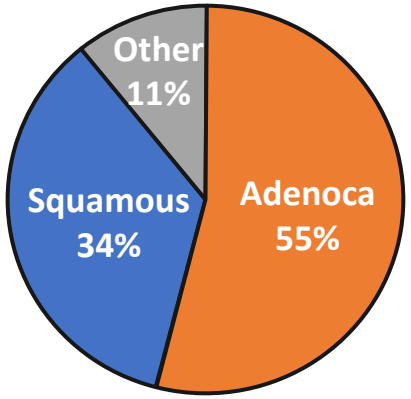
- Transmembrane Tyrosine developmental History
- Role in Cancer treatment (Type of cancer, Driven gene, role of treatment)
- Drug mechanism
- Indication
  - Clinical measurement
  - Lab data
  - Drug studies and comparison (ORR, OS)
  - ADR
- Side effect management
- Education
- Conclusion

晚期非小細胞癌的第一線治療的決定

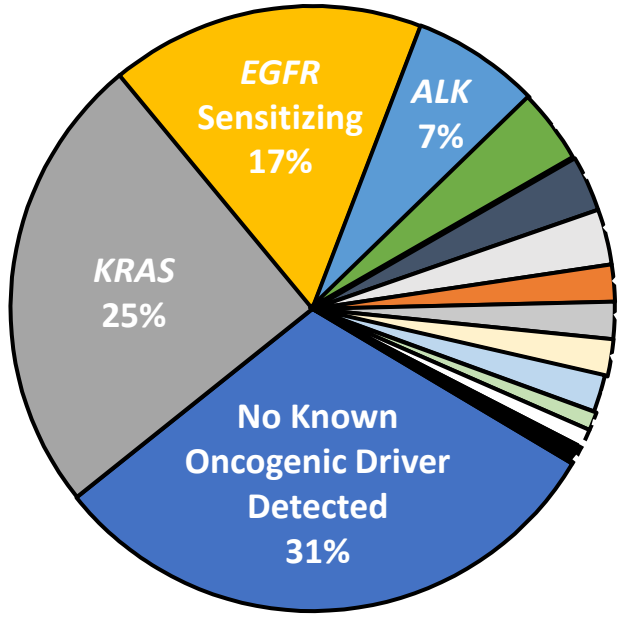


免疫藥品: Nivolumab、pembrolizumab、Atezolizumab、Durvalumab

Non-Small-Cell Lung Cancer: Not One Disease, but Many!



Adenocarcinoma



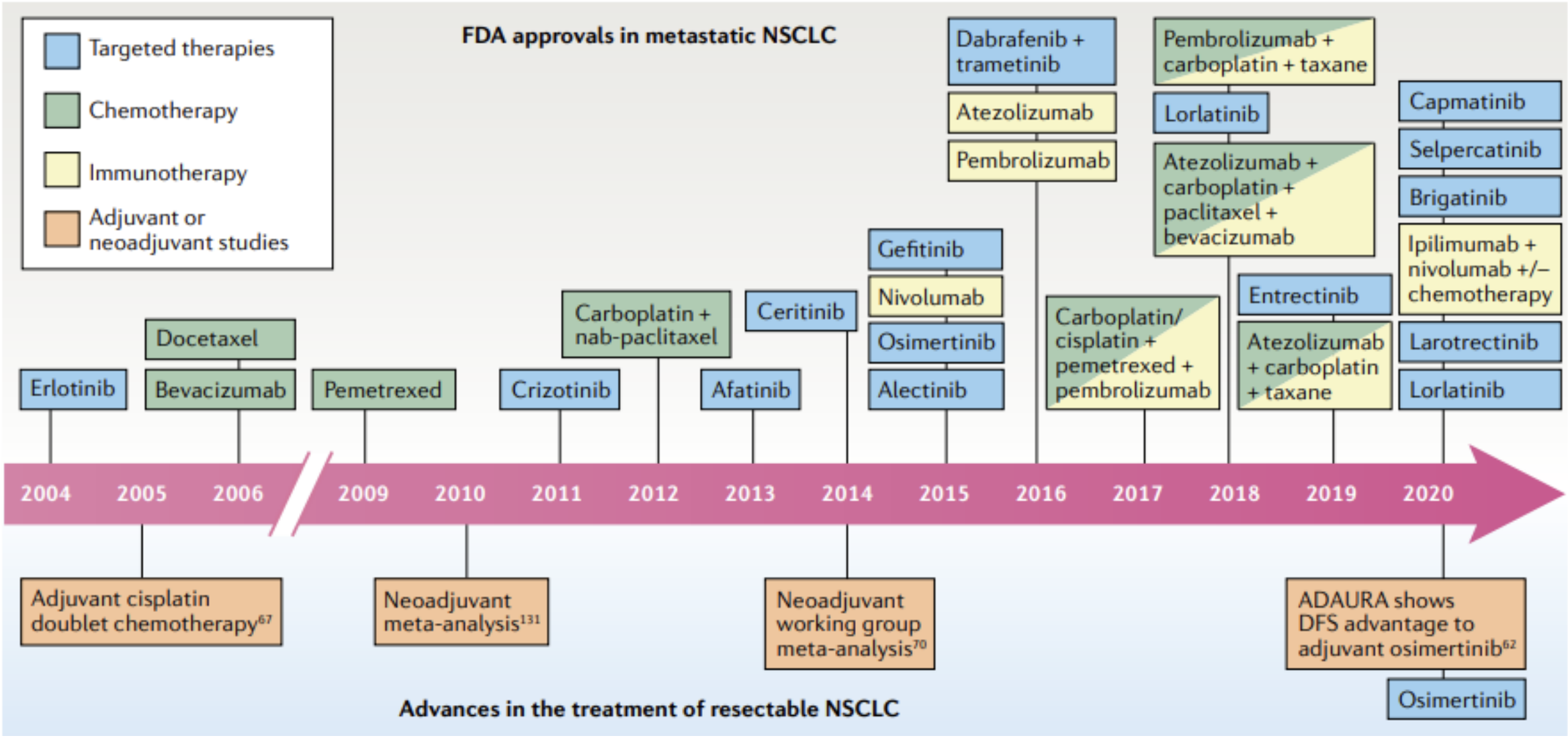
EGFR **Other 4%**
MET **3%**
> 1 Mutation 3%
HER2 **2%**
ROS1 **2%**
BRAF **2%**
RET **2%**
NTRK **< 1%**
PIK3CA **1%**
MEK1 **< 1%**

Then **Histology-Based Subtyping** **Now**

Li. JCO. 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

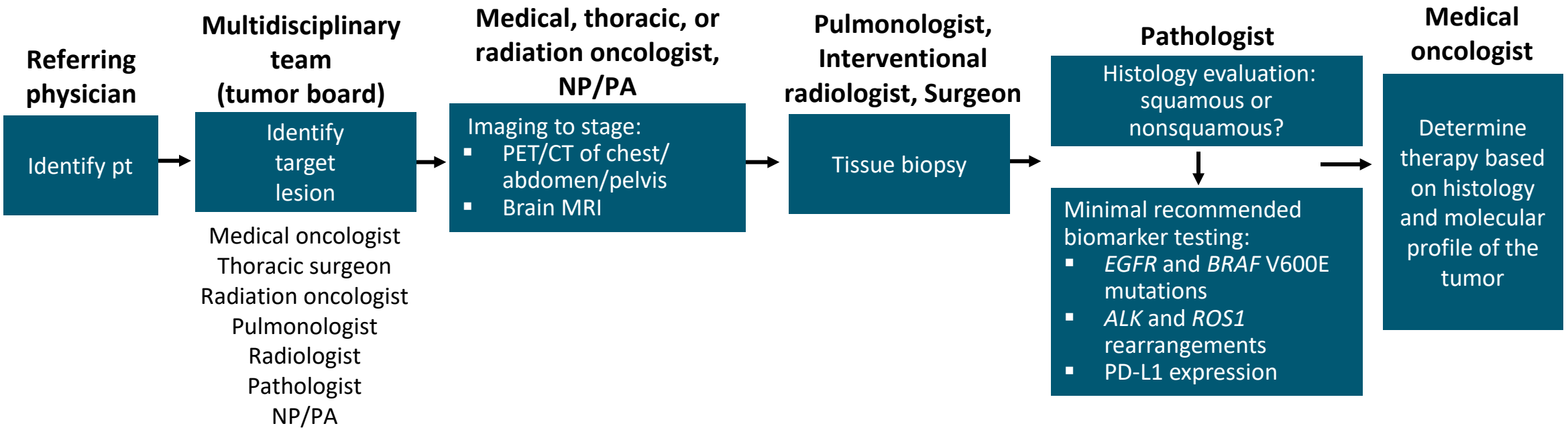
Slide credit: clinicaloptions.com

Treatment of metastatic and non-metastatic NSCLC

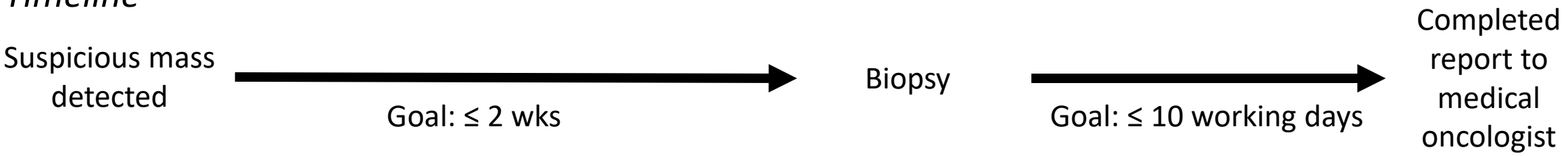


Nat Rev Clin Oncol 18, 547–557 (2021).

Diagnostic Algorithm of Advanced NSCLC

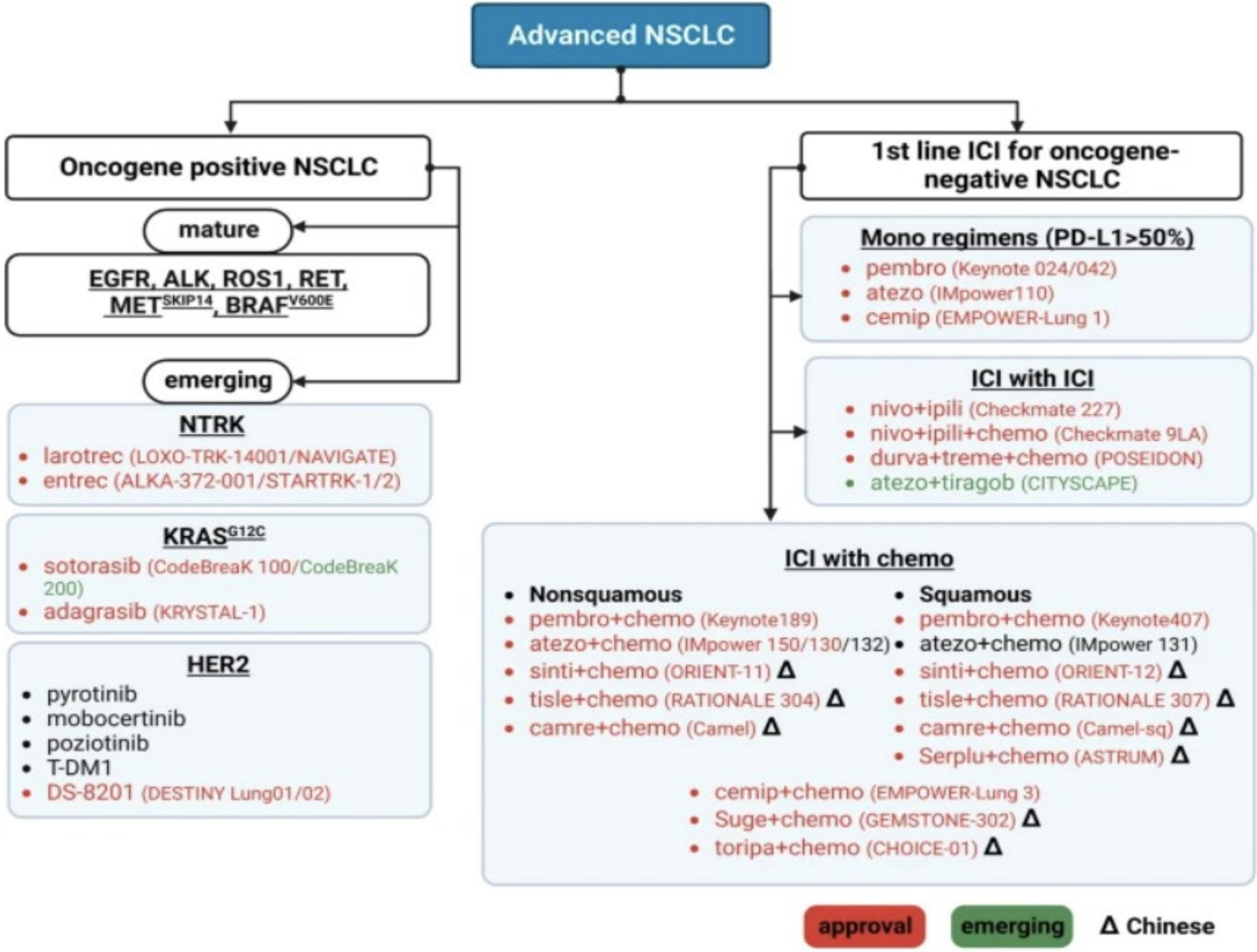


Timeline



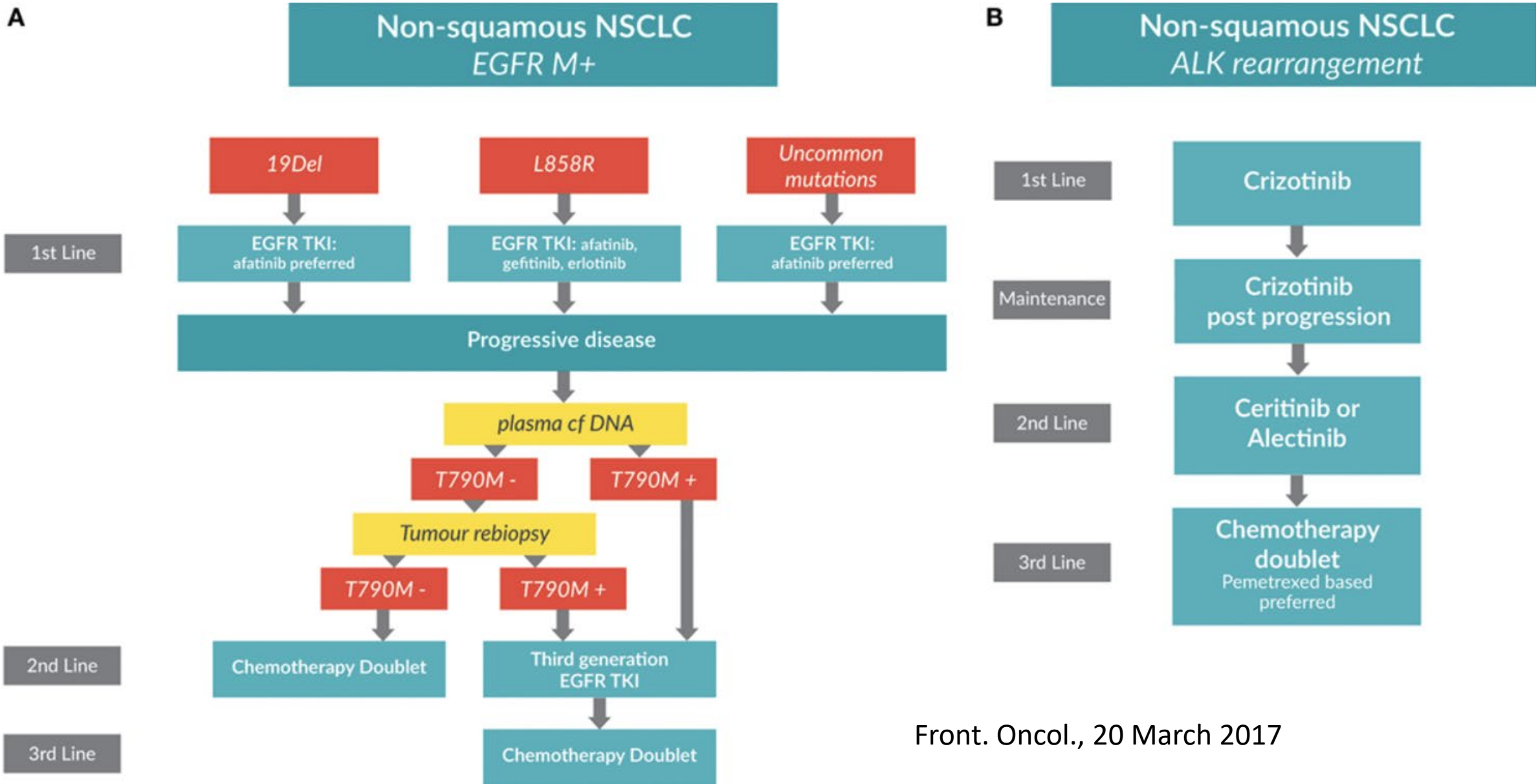
Hirsch. Clin Lung Cancer. 2018;19:331.

Slide credit: clinicaloptions.com



J Hematol Oncol 16, 40 (2023).

Treatment Algorithms for non-small cell lung cancer patients with biomarkers



Front. Oncol., 20 March 2017

First-line Treatment: 2 Agents Are More Effective Than 1

- Meta-analysis: 65 trials (N = 13,601) between 1980-2001
  - Compared efficacy of
    - Doublet vs single-agent regimens
    - Triplet vs doublet regimens

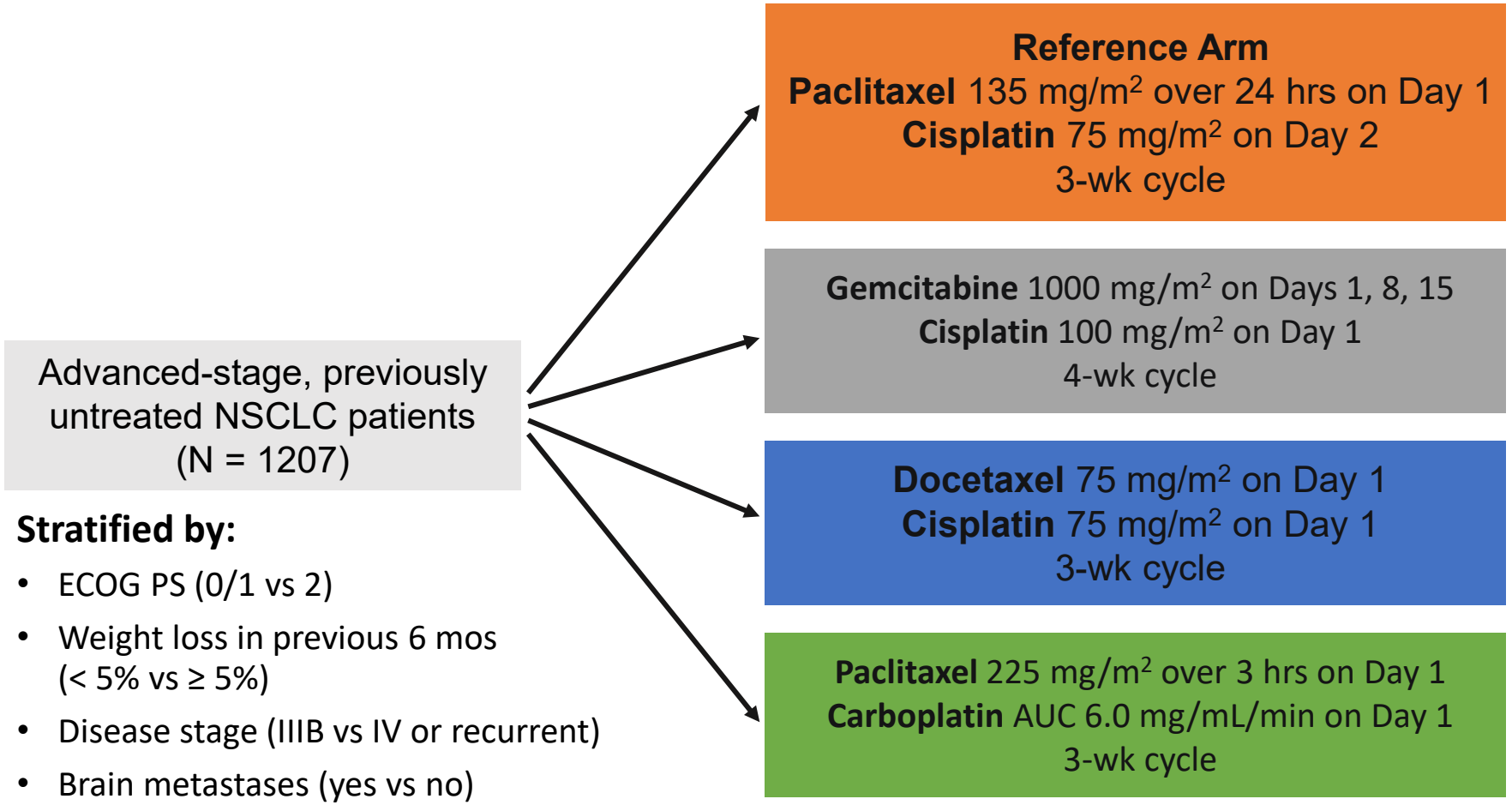
Survival Outcome	Doublet vs Single-Agent Regimens	Triplet vs Doublet Regimens
1-yr OS	Doublet > single-agent ▪ OR: 0.80; 95% CI: 0.70-0.91; *P* < .001 ▪ 5% absolute benefit	Triplet = doublet ▪ OR: 1.01; 95% CI: 0.85-1.21; *P* = .88
Median OS	Doublet > single-agent ▪ MR: 0.83; 95% CI: 0.79-0.89; *P* < .001	Triplet = doublet ▪ MR: 1.00; 95% CI: 0.94-1.06; *P* = .97

Delbaldo C, et al. JAMA. 2004;292:470-484.

To change practice trials

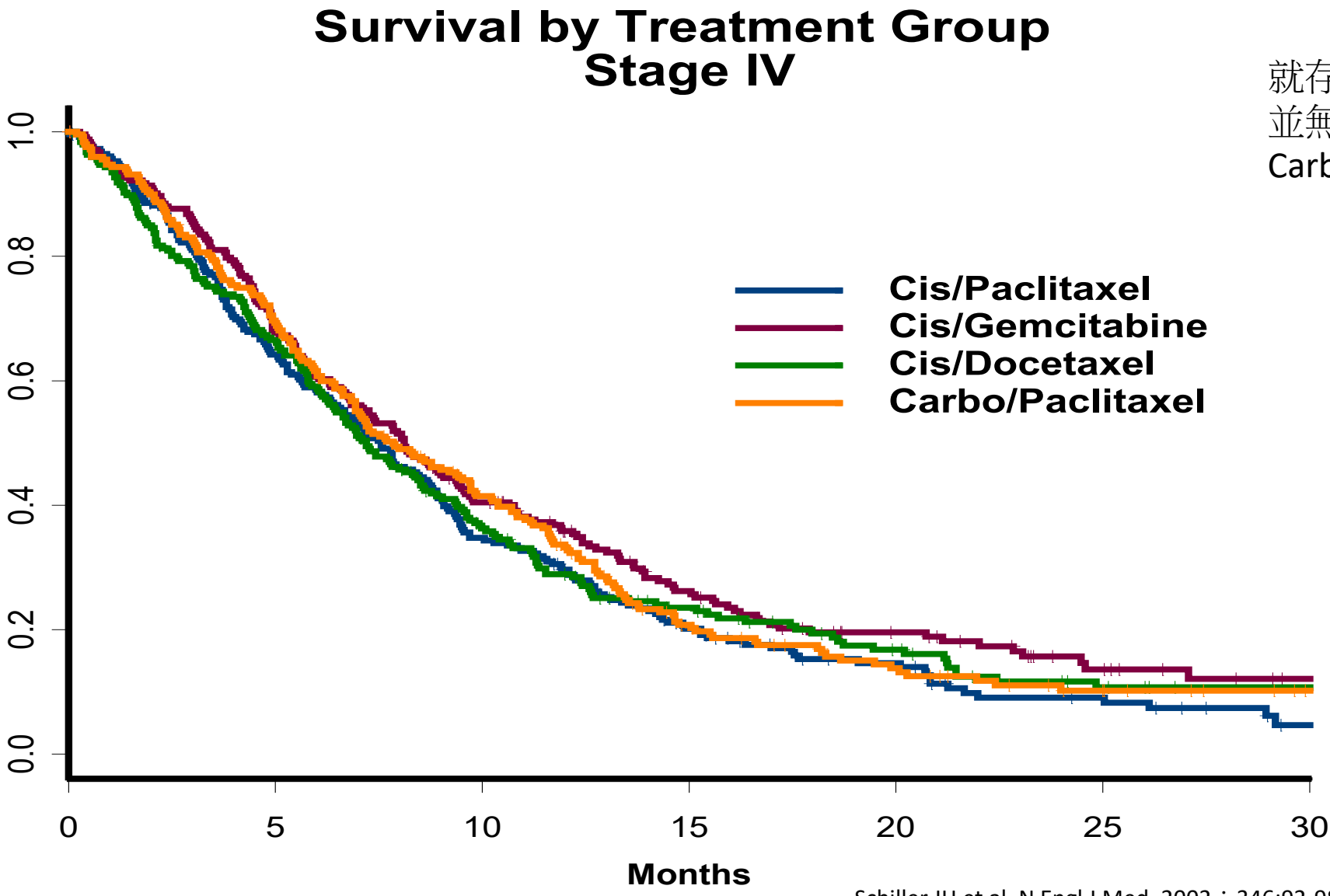
- ECOG 1594: 4組白金類化療組合比較
- ECOG 4599: Carbo/Pac 該不該加Bevacizumab?
- JMDB: Cis + Pemetrexed vs. Cis + Gemcitabine

ECOG 1594: Comparison of 4 First-line Doublet Regimens in Advanced NSCLC



Schiller JH, et al. N Engl J Med. 2002;346:92-98.

ECOG 1594-platinum doublets



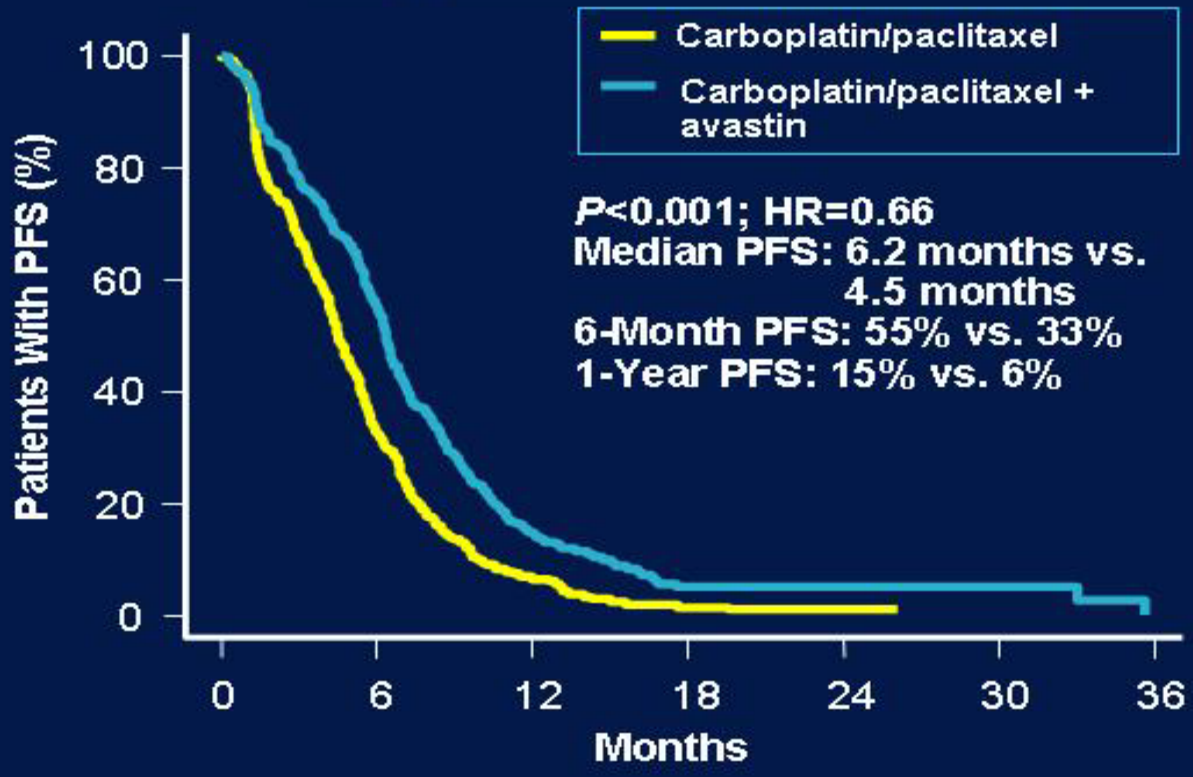
就存活率而言，這4個組合並無差異
Carbo/Pac的毒性最小

Schiller JH et al. N Engl J Med. 2002；346:92-98.

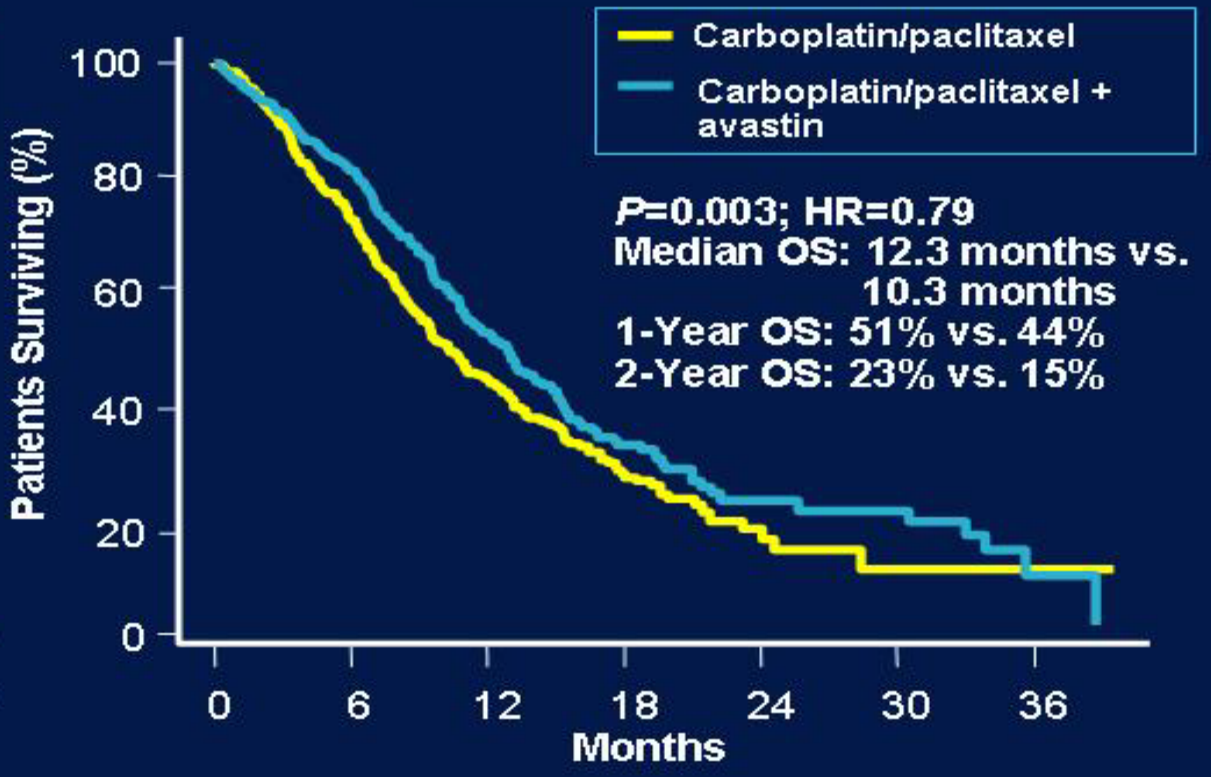
Carboplatin/Paclitaxel +/- Avastin: Key Clinical Outcomes

- Response rate: 15% for carbo/paclitaxel vs. 35% for same chemo + avastin

Progression-Free Survival



Overall Survival

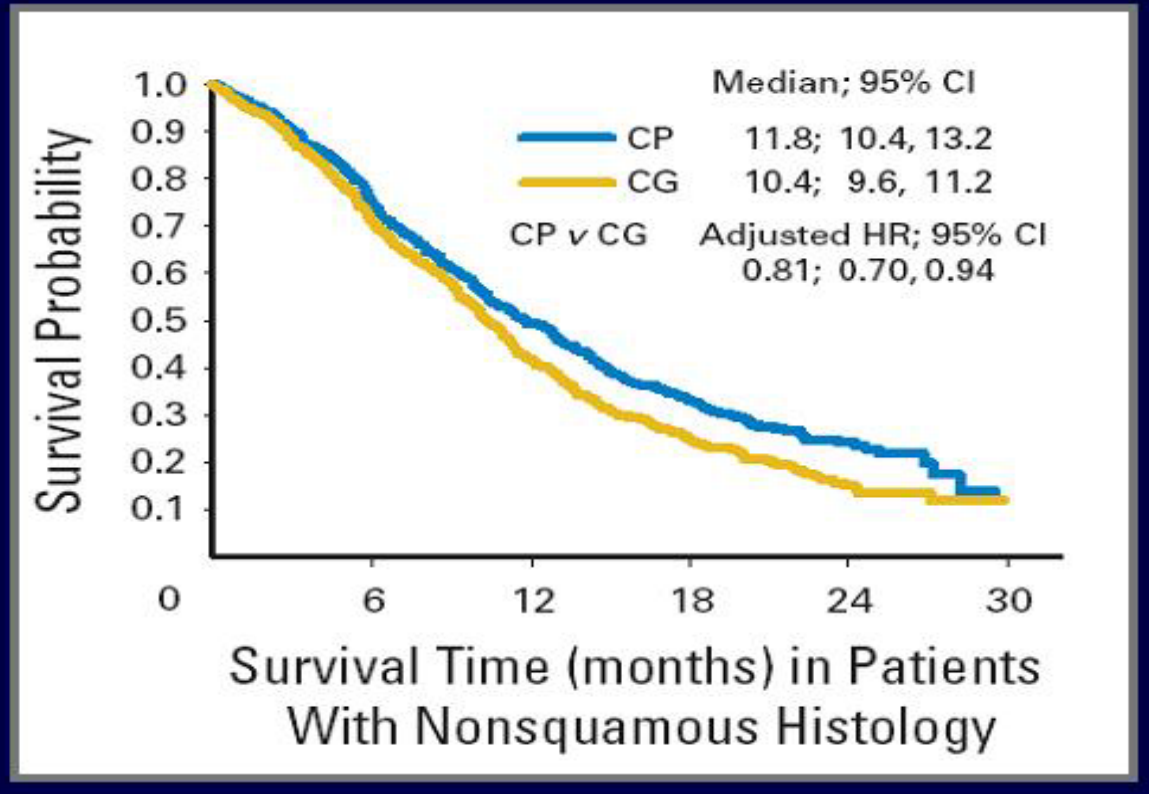


HR=hazard ratio; OS=overall survival; PFS=progression-free survival.

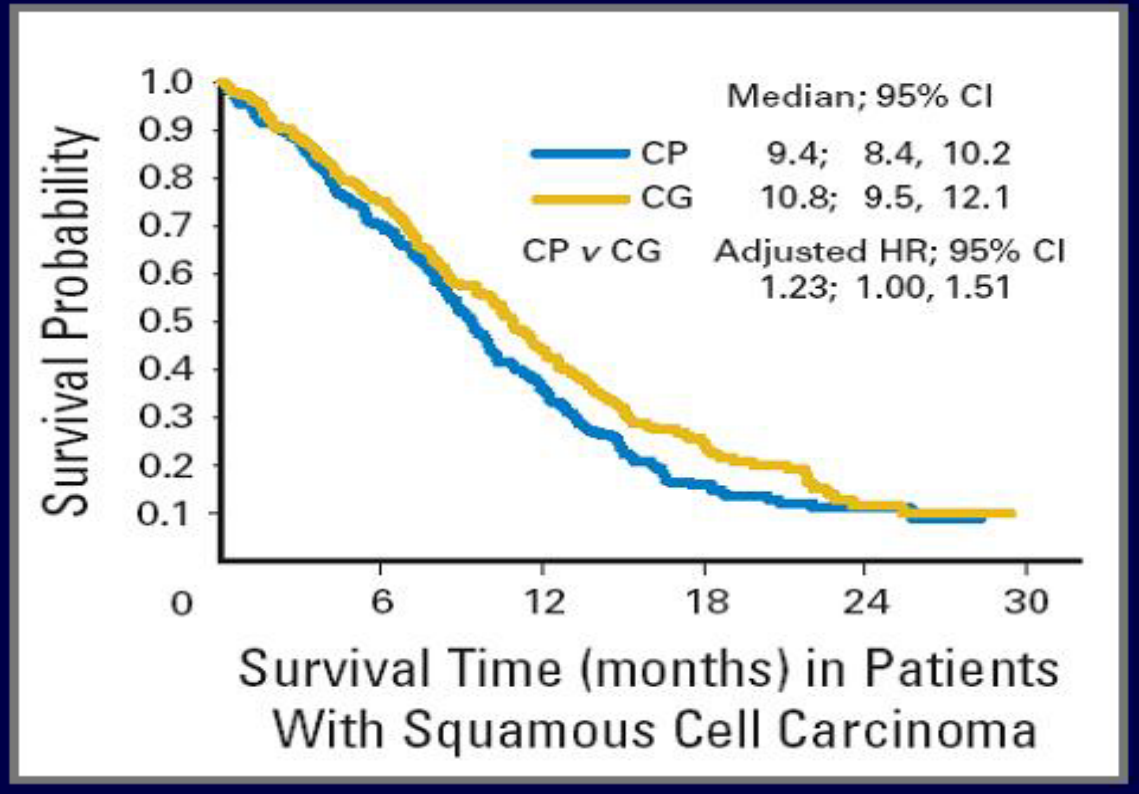
Sandler et al. *N Engl J Med.* 2006;355:2542; Sandler et al. *ASCO.* 2005 (abstr 4).

Outcomes of Different NSCLC Subtypes on Alternate Chemo Regimens

Non-Squamous NSCLC

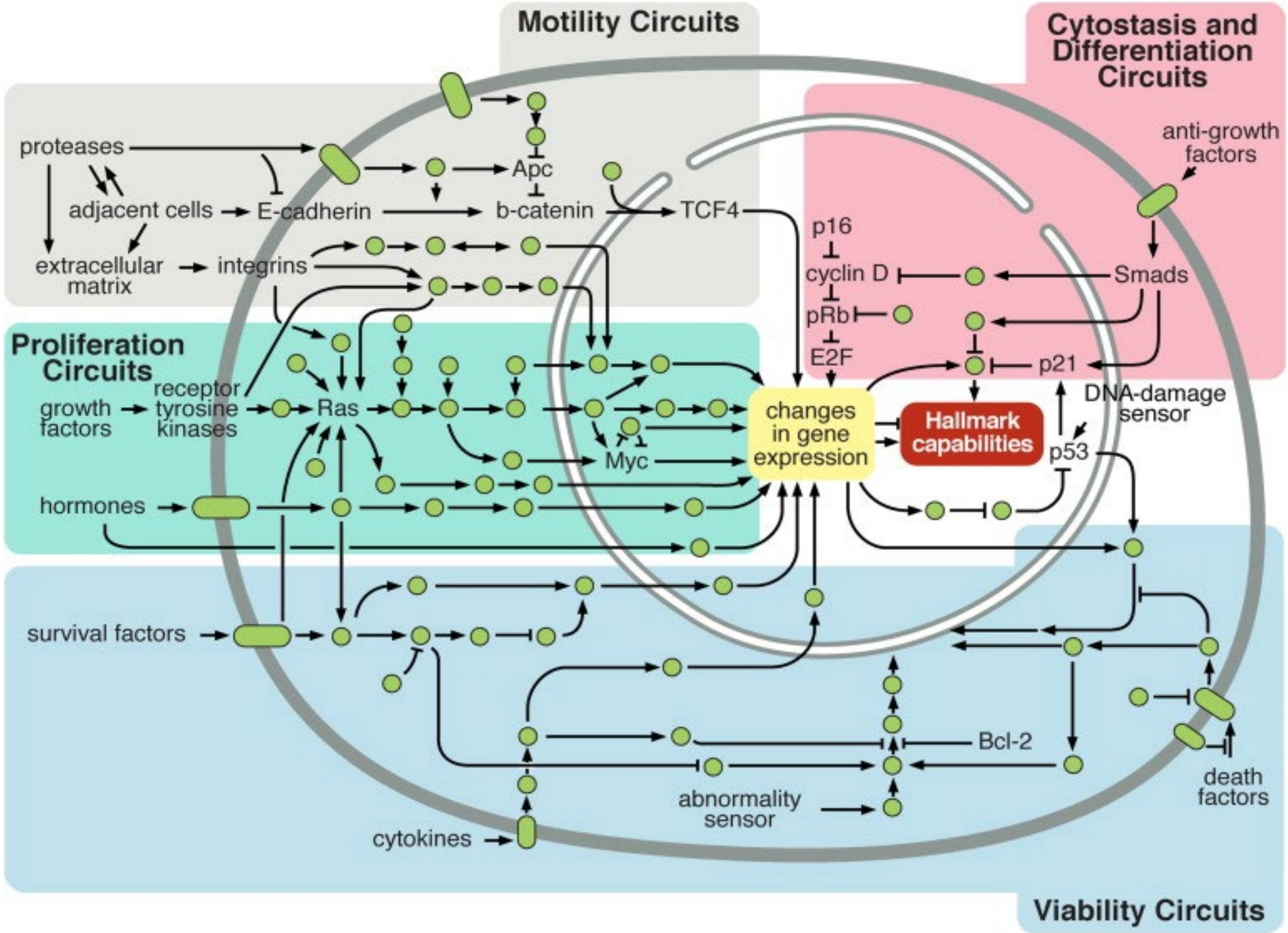


Squamous NSCLC



Scagliotti, J Clin Oncol 2008

Target therapy : EGFR, ALK, ROS1, MET, RET,NTRK)



正常細胞內運行如同精細的集成電路，並經過重新編程以調節癌細胞內的標誌性功能。 單獨的子電路（此處在不同顏色的區域中進行了描述）專用於協調各種功能。 一方面，這種描述是簡單的，因為在這些子電路之間存在相當大的串擾(crosstalk)。 此外，由於每個癌細胞都暴露於來自其微環境的信號的複雜混合物，因此這些子電路中的每一個都與來自腫瘤微環境中其他細胞的信號相連。

Cell 2011 Mar 4;144(5):646-74

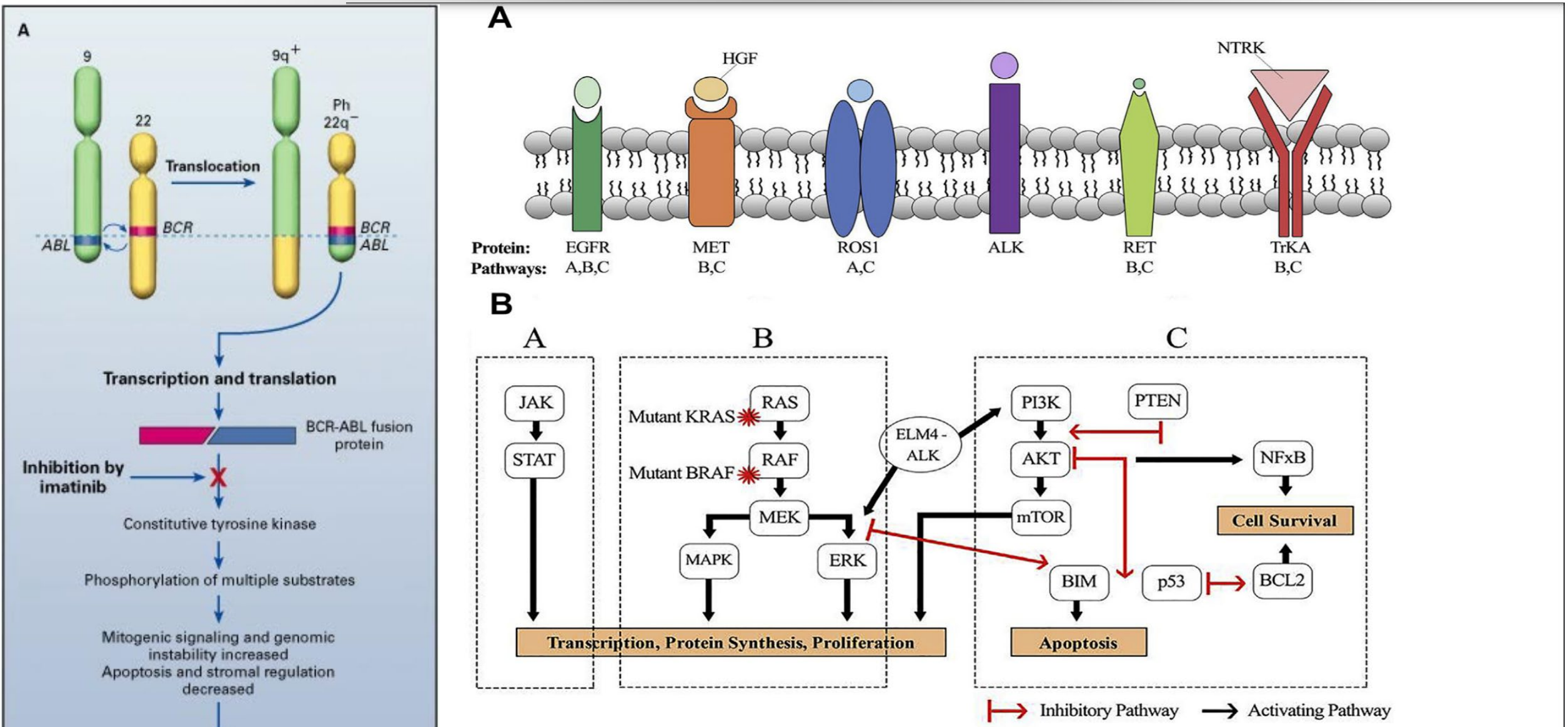


Fig. 1. The EGFR, MET, ROS1, ALK, RET, and NTRK oncogenes and their major signaling networks. (*A*) Presented are the oncogenes EGFR, MET, ROS1, ALK, RET, and NTRK and some of their ligands (ie, HGF for MET and neurotrophins for TRK receptors). (*B*) The signaling networks for each pathway are matched with receptor (ie, EGFR signals through A, B, and C and MET signals through B and C).

Small Molecular agents	
Tinib	Tyrosinkinase inhibitor · **BCR-ABL : CML** – Imatinib (TKI), nilotinib, dasatinib, bosutinib, Ponatinib · **Multikinase Inhibitors : RCC** – sunitinib malate (SM, a c-Kit/PDGFR/VEGFR TKI) , sorafenib, Vandetanib, cabozantinib, Lenvatinib, pazopanib, axitinib, regorafenib · EGFR (NSCLC) – Gefitinib, erlotinib , afatinib, (exon 19 deletions, exon 21 L858R), osimetinib (EGFR T790M) lapatinib (EGFR & HER2) · **Anaplastic Lymphoma Kinase (ALK) inhibitor :** crizotinib, Alectinib, brigatinib, Ceritinib
Brutinib	**Bruton's Tyrosine Kinase (BTK) inhibitor :**Ibrutinib, acalabrutinib (CLL)
Zomib	Proteasome inhibitor (bortezomib, Carfilzomib, Ixazomib)

Ciclib	Cyclin-dependent kinase · **CDK 4/6 inhibitors :** Palbociclib, Ribociclib, abemaciclib (breast)
Toclax	**BCL-2 : venetoclax (Bcl-2 (B-cell lymphoma 2))**
Degib	**Hedgehog pathway inhibitors : Itraconazole, Vismodegib ,sonidegib (basal cell carcinoma)**
Parib	**PARP (poly-ADP-ribose polymerase)inhibitors :** Olaparib, Rucaparib, Niraparib, Talazoparib
Lisib	PI3K/AKT/mTOR pathway : phosphoinositide 3-kinase inhibitor
Metinib	MEK inhibitor
Fenib	**BRAF inhibitor :**vemurafenib, Dabrafenib (melanoma)
Trectinib	NTRK : Larotrectinib, Entrecitinib in 2019
Rasib	KRAS :mutation (NSCLC) Sotorasib in 2020
Gatinib	FGFR2 a fibroblast growth factor receptor 2 (FGFR2) fusion pemigatinib 2020

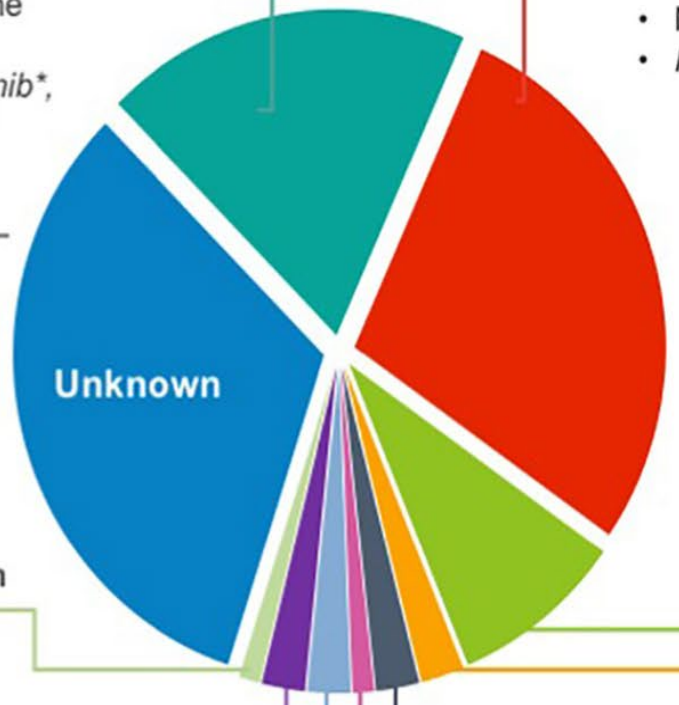
Common Genomic Alterations in Lung Adenocarcinoma

* *PBS reimbursed*

EGFR Mutation — 17%
- Point mutations in tyrosine kinase domain
- *erlotinib*, gefitinib*, afatinib*, dacomitinib, osimertinib**

Tyrosine kinase domain of *EGFR* gene

KRAS Mutation — 25%
- Activation of MAPK pathway
- Negative prognostic marker
- *No therapeutic agents identified*



ALK Rearrangement — 8%
- Fusion between ALK and EML4
- Constitutive ALK kinase activity
- *crizotinib*, ceritinib*, alectinib*, entrectinib, brigatinib, lorlatinib, ropotrectinib*

ALK-EML4 fusion oncogene

RET Rearrangement — 2%
- Fusion between RET tyrosine kinase domain and partner gene
- *vandetanib, cabozantinib, alectinib, lenvatinib, sunitinib, sorafenib, LOXO-292, Blu-667*

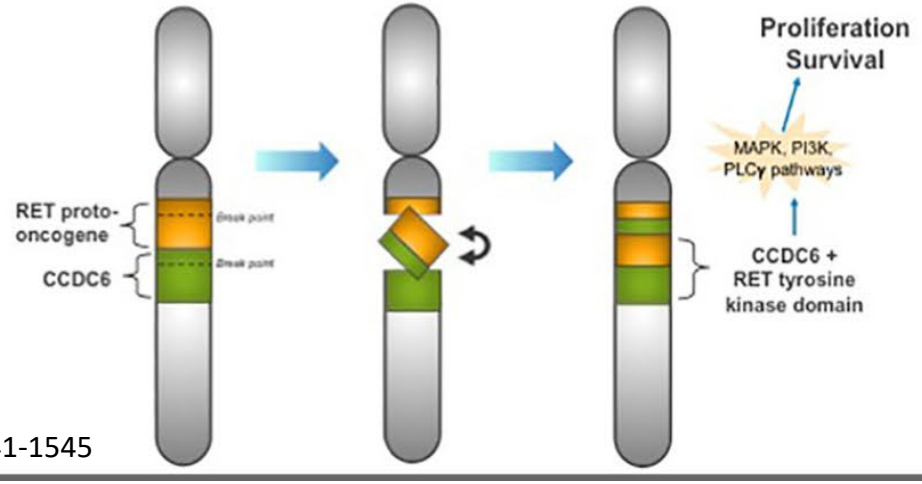
ERBB2(HER2) Mutation — 1%
- *afatinib, TDM-1*

ROS1 Rearrangement — 2%
- *crizotinib*, ceritinib, lorlatinib, entrectinib, ropotrectinib*

MET Mutation/ Amplification — 2%
- *crizotinib*

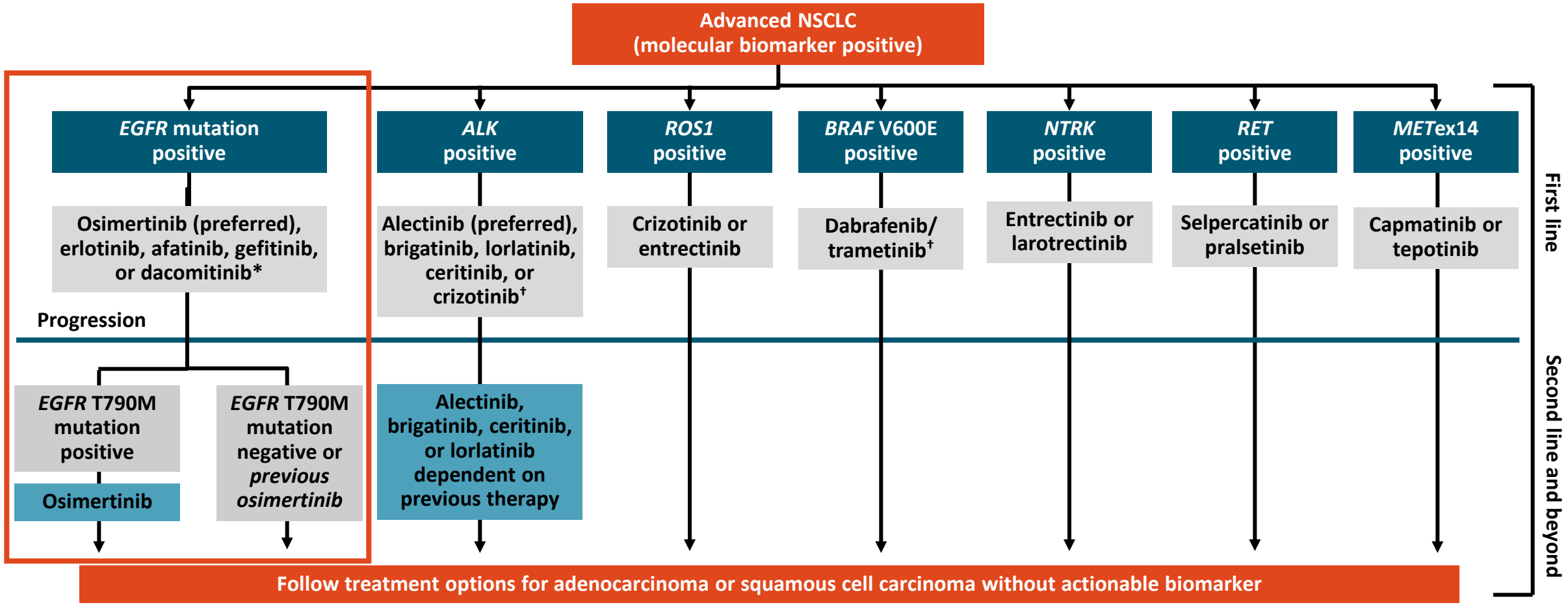
BRAF Mutation — 2%
- *dabrafenib + trametinib, vemurafenib*

NTRK Rearrangement — 1%
- *larotrectinib, entrectinib*



Internal Medicine Journal, Volume: 49, Issue: 12, Pages: 1541-1545

Current Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC



*Afatinib, dacomitinib, erlotinib (alone or in combination with ramucirumab), gefitinib, osimertinib approved for *EGFR* exon 19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q. †Or as second-line after CT.

Afatinib PI. Alectinib PI. Capmatinib PI. Ceritinib PI. Crizotinib PI. Dabrafenib PI. Dacomitinib PI. Entrectinib PI. Erlotinib PI. Gefitinib PI. Lorlatinib PI. Larotrectinib PI. Osimertinib PI. Pralsetinib PI. Selpercatinib PI. Trametinib PI.

Slide credit: clinicaloptions.com

First-line EGFR TKIs vs Chemotherapy in *EGFR* Mutation–Positive NSCLC: A Clear Pattern

Study	N	Treatment	ORR, %	Median PFS, Mo	Median OS, Mo
NEJ002[1]	230	Gefitinib vs carboplatin/paclitaxel	74 vs 31	10.8 vs 5.4 (*P* <.001)	30.5 vs 23.6 (HR: 0.89)
WJTOG 3405[2,3]	172	Gefitinib vs cisplatin/docetaxel	62 vs 32	9.6 vs 6.6 (*P* <.001)	34.8 vs 37.3 (HR: 1.25)
OPTIMAL[4,5]	165	Erlotinib vs carboplatin/gemcitabine	83 vs 36	13.1 vs 4.6 (*P* <.0001)	22.8 vs 27.2 (HR: 1.19)
EURTAC[6,7]	174	Erlotinib vs platinum-based chemotherapy	58 vs 15	9.7 vs 5.2 (*P* <.0001)	22.9 vs 19.5 (HR: 0.93)
LUX-Lung 3[8,9]	345	Afatanib vs cisplatin/pemetrexed	56 vs 23	11.1 vs 6.9 (*P* = .001)	28.2 vs 28.2 (HR: 0.88)
LUX-Lung 6[9,10]	364	Afatinib vs cisplatin/gemcitabine	67 vs 23	11.0 vs 5.6 (*P* <.0001)	23.1 vs 23.5 (HR: 0.93)

1. Maemondo. NEJM. 2010;362:2380. 2. Mitsudomi. Lancet Oncol. 2010;11:121. 3. Yoshioka. ASCO 2014. Abstr 8117. 4. Zhou. Lancet Oncol. 2011;12:735. 5. Zhou. AnnOncol. 2015;26:1877. 6. Rosell. Lancet Oncol. 2012;13:239. 7. Khozin. Oncologist. 2014;19:774. 8. Sequist. JCO. 2013;31:3327. 9. Yang. Lancet Oncol. 2015;16:141. 10. Wu. Lancet Oncol. 2014;15:213.

EGFR TKIs: Properties

Parameter	Erlotinib	Gefitinib	Afatinib	Dacomitinib	Osimertinib
Generation	First	First	Second	Second	Third
EGFR mutations approved for in first-line setting	Ex19del, Ex21 L858R	Ex19del, Ex21 L858R	Ex18 G719X,* Ex19del, Ex20 S768I,* Ex21 L858R, Ex21 L861Q*	Ex19del, Ex21 L858R	Ex19del, Ex21 L858R†
EGFR binding	Reversible	Reversible	Irreversible	Irreversible	Irreversible
Half life, hr	36	48	37	59-85	48
Food effect (take on empty stomach)	Increase F from ~ 60% to ~ 100%	No change	Decrease AUC by 39%	No change	No change
CNS penetration, AUC ratio	0.03X CSF/Plasma	0.01X CSF/Serum	0.02X CSF/Plasma	CNS activity reported	2X brain/plasma

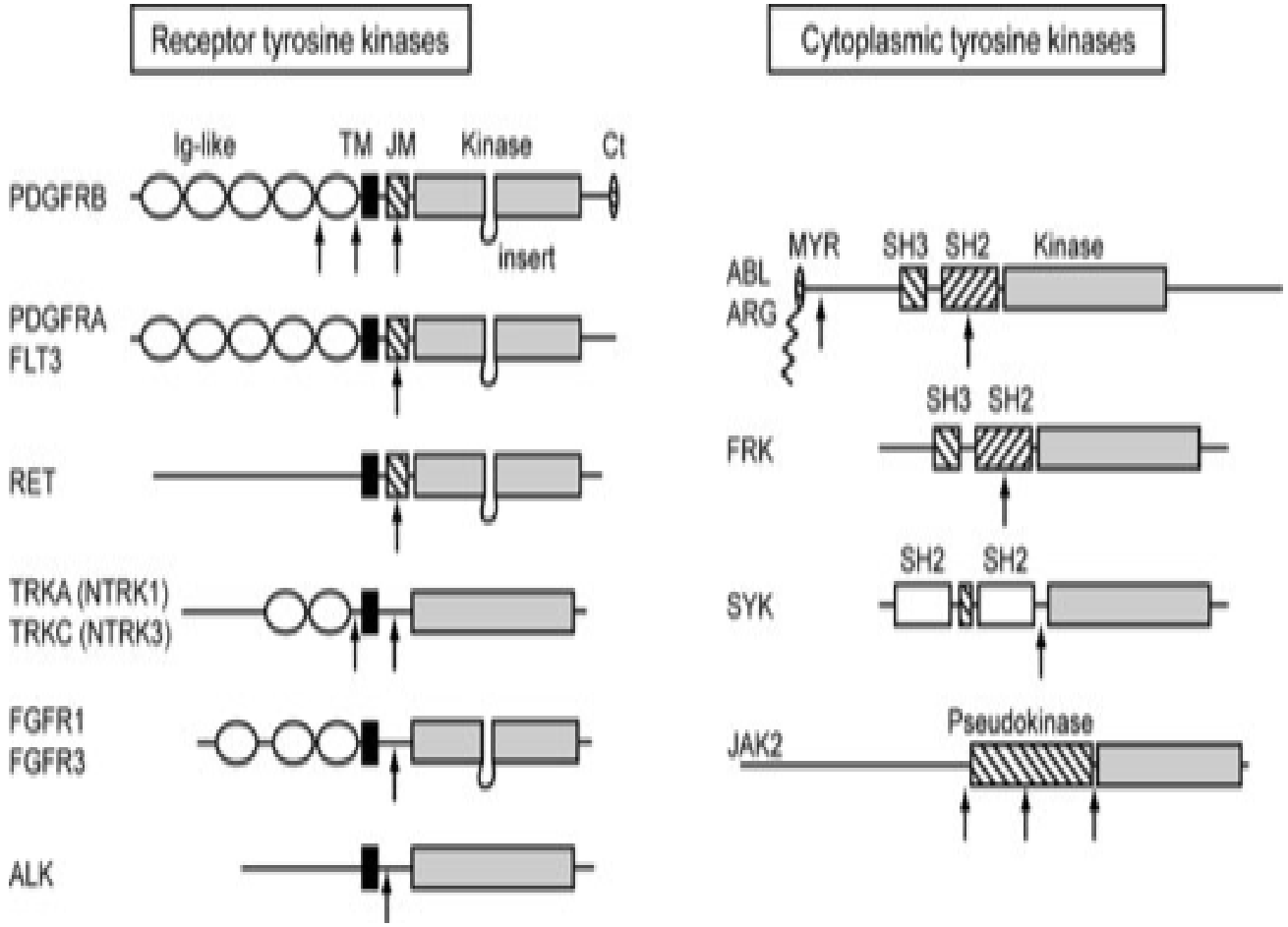
*Uncommon nonresistant *EGFR* mutations. †Also approved for resistant mutation T790M in second-line setting.

Afatinib PI. Dacomitinib PI. Erlotinib PI. Gefitinib PI. Osimertinib PI. Boehrer. Cell Cycle. 2011;10:3168. Togashi. Cancer Chemother Pharmacol. 2012;70:399. Tamiya. ESMO 2016. Abstr 1241P. Engelman. Cancer Res. 2007;67:11924. Gonzalez. Mol Cancer Ther. 2008;7:1880. Jänne. Clin Cancer Res. 2011;17:1131. Ou. Drugs Des Devel Ther. 2015;9:5641. Hochmair. Target Oncol. 2018;13:269. Mizusaki. Thorac Cancer. 2021;12:114. Kudo. Intern Med. 2020;59:1739.

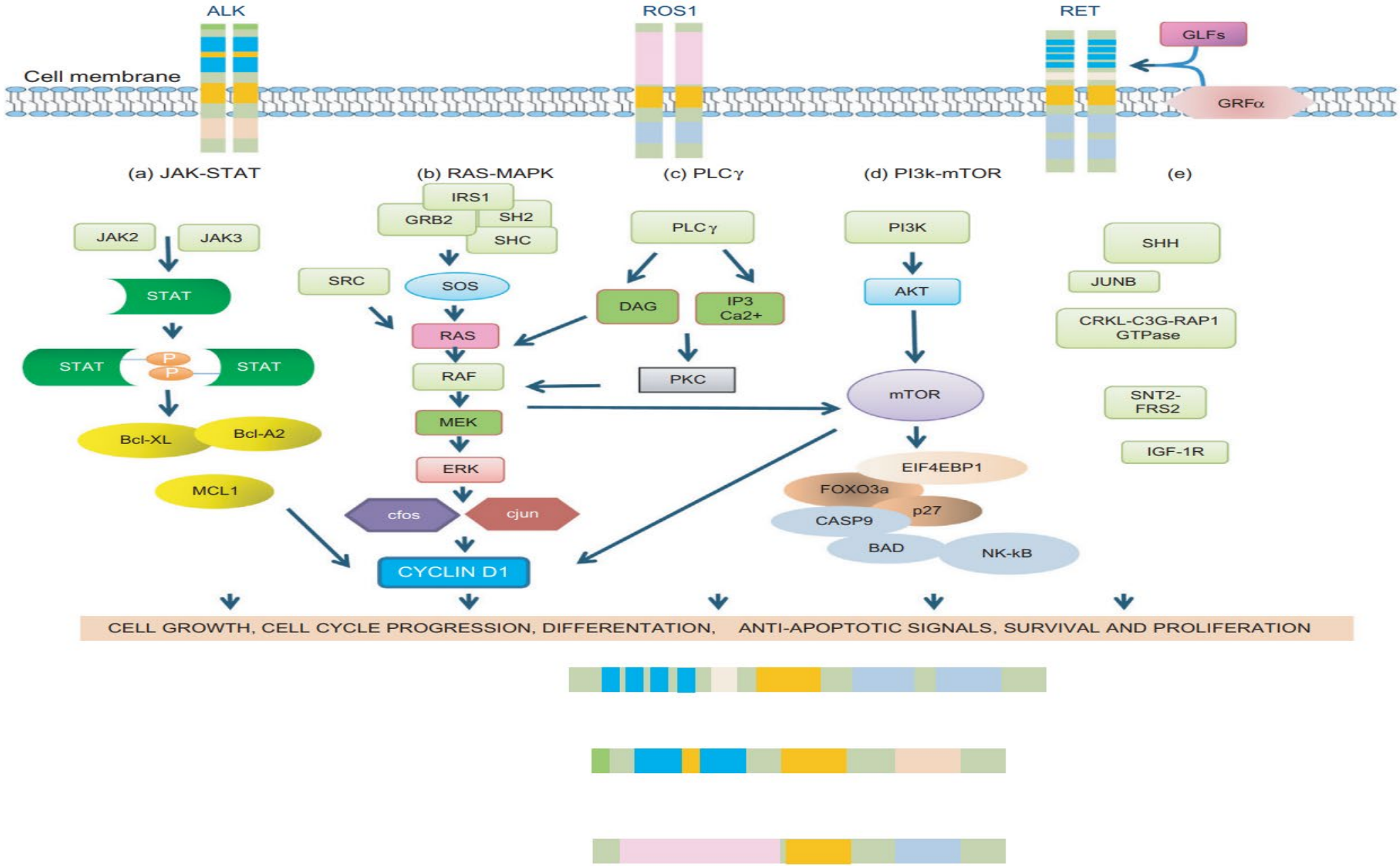
Slide credit: clinicaloptions.com

kinase fusion genes (KFGs)

- 1. EMLA-ALK (echinoderm microtubule associated protein like 4 – anaplastic lymphoma kinase (EML4-ALK))
  2. ROS
  3. NTRK (neurotrophic receptor tyrosine kinase (NTRK))
  4. RET (rearranged during transfection)



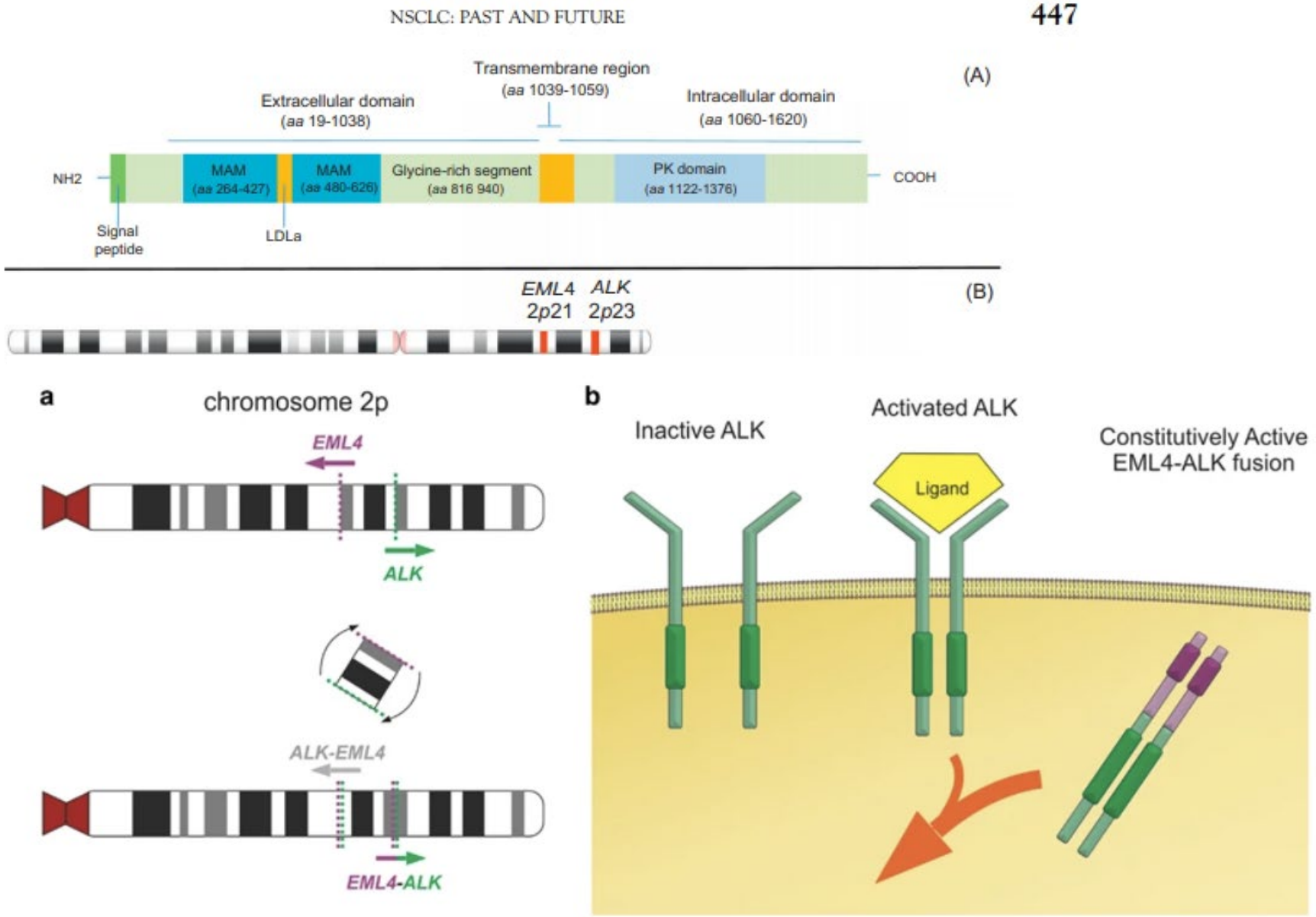
J. Cell. Mol. Med. Vol 16, No 2, 2012 pp. 237-24


ALK
ROS1
RET
GLFs
GRFα
Cell membrane
(a) JAK-STAT
(b) RAS-MAPK
(c) PLCγ
(d) PI3k-mTOR
(e)
JAK2
JAK3
STAT
STAT
P
P
STAT
Bcl-XL
Bcl-A2
MCL1
IRS1
GRB2
SH2
SHC
SRC
SOS
RAS
RAF
MEK
ERK
cfos
cjun
CYCLIN D1
PLCγ
DAG
IP3
Ca2+
PKC
PI3K
AKT
mTOR
EIF4EBP1
FOXO3a
p27
CASP9
BAD
NK-kB
SHH
JUNB
CRKL-C3G-RAP1
GTPase
SNT2-
FRS2
IGF-1R
CELL GROWTH, CELL CYCLE PROGRESSION, DIFFERENTATION,
ANTI-APOPTOTIC SIGNALS, SURVIVAL AND PROLIFERATION

ALK Rearrangement: Context

- Found in ~ 5% of NSCLC patients[1]
- Occurs more frequently in younger patients, light or never-smokers, males, and those with the adenocarcinoma subtype[1,2]
- Predominantly a fusion of *ALK* with partner oncogenes, particularly *EML4*[3]
- Occurs in similar subgroups as patients with *EGFR* mutations, but *EGFR* mutations and *ALK* rearrangements are predominantly mutually exclusive[1-4]

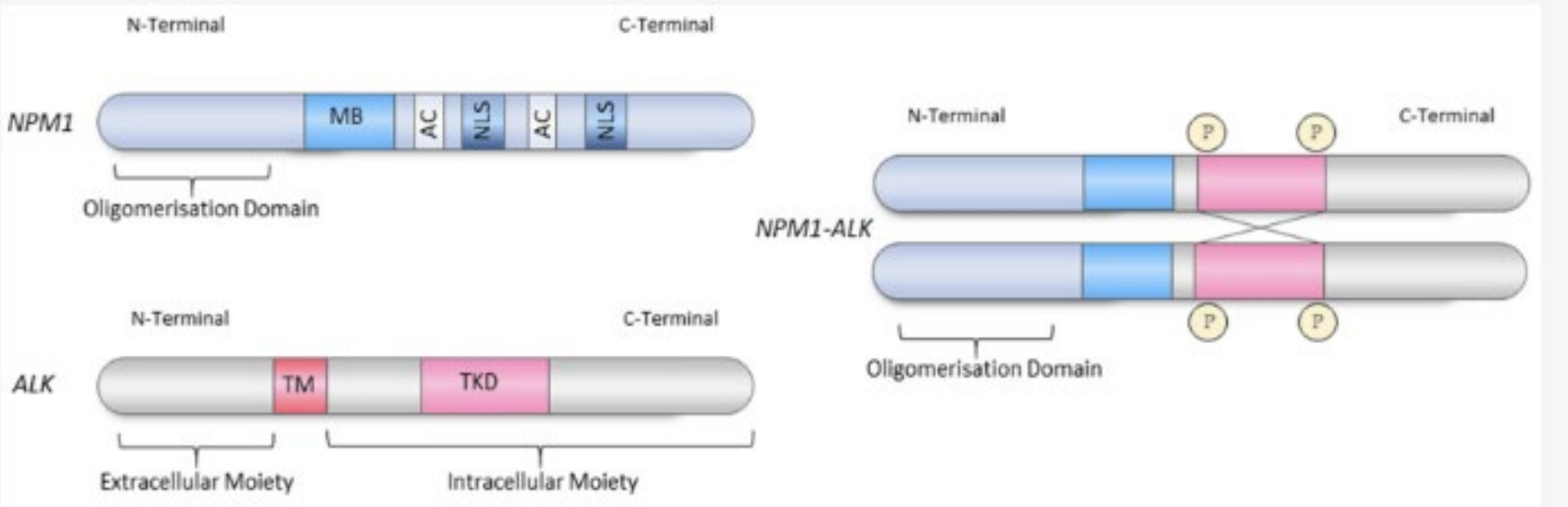
1. American Cancer Society. Targeted therapy drugs for non-small cell lung cancer. 2. Shaw. J Clin Oncol. 2009;27:4247. 3. Hofman. Cancers (Basel). 2017;9:107. 4. Soda. Nature. 2007;448:561.



Inversion of chromosome 2p results in constitutively active EML4-ALK fusion protein

ALK 基因的結構重排會導致多種癌症。 在非小細胞肺癌中，涉及 ALK 基因座的最常見結構重排是 2p 染色體部分的倒位，將 EML4 的 5’ 部分與 ALK 的 3’ 部分並置（a）。 ALK 在成人肺部正常情況下不轉錄，但在 EML4 啟動子的控制下，EML4-ALK 融合基因進行轉錄。 值得注意的是，ALK 5’ 部分與 EML4 3’ 部分並置的相互易位也會發生，但由於它保留了 ALK 啟動子，因此不會被轉錄（以灰色表示）。 野生型 ALK 是一種受體酪胺酸激酶，已知可驅動發育途徑，特別是在神經系統中（深綠色條表示酪胺酸激酶結構域）。 在 ALK 配體存在的情況下，野生型 ALK 蛋白會同二聚化，驅動下游發育過程，例如細胞增殖（b）。 在 EML4 啟動子的轉錄控制下，EML4-ALK 融合蛋白在肺組織中表達，EML4 的二聚化結構域（深紫色條）允許 TK 結構域不受調控的二聚化，組成型活化下游路徑。

(NPM1)-ALK fusion protein



由 t(2;5)(p23;q25) 產生的核磷蛋白 1 (NPM1)-ALK 融合蛋白。 5 號染色體上的 NPM1 基因與 2 號染色體上的 ALK 基因融合導致 NPM1-ALK（組成活化的酪胺酸激酶）的表達。 NPM1 編碼一個寡聚結構域（residues 1-117）、一個金屬結合結構域（MB；residues(殘基) 104-115）、兩個酸性胺基酸簇（AC：D 和E 胺基酸豐富的結構域，用作核仁靶向訊號的受體區域；殘基 120-132 和 161-188）和兩個核定位訊號（NLS；殘基 152-157 和 191-197）。 ALK 編碼Meprin/A5/蛋白質酪胺酸磷酸酶結構域（未顯示）、胞外結構域中的配體結合位點（殘基391-401）、親脂性跨膜區(TM)和包含酪氨酸激酶催化的胞內結構域（TKD, tyrosine-kinase catalytic domain ）。

Cancers 2019, 11(8), 1074;

TABLE 31.1 Chromosomal Translocations Involving *ALK* Gene in Non-Small Cell Lung Cancer

Gene Fusion	Partner Protein	Locus of the Fusion Partner	Chromosomal Rearrangement
EML4-ALK	Echinoderm microtubule-associated protein like-4	2p21	inv(2)(p21p23)
TFG-ALK	TRK-fused gene	3q21	t(2;3)(p23;q21)
KIF5B-ALK	Kinesin family member 5B	10p11	t(2;10)(p23;p11)
KLC1-ALK	Kinesin light-chain 1	14q32	t(2;14)(p23;q32.1)
PTPN3	Protein tyrosine phosphatase, nonreceptor type 3	9q31.3	t(2;9)(p23;q31)
STRN	Striatin, calmodulin-binding protein	2p22.2	—
TPR	Translocated promoter region	1q31.1	t(1;2)(q31.1;p23)
HIP1	Huntingtin-interacting protein 1	7q11.23	—

Palmirotta Raffaele (2019). *Gene Fusion in NSCLC. , (Oncogenomics), 443–464.*

A fusion gene, echinoderm microtubule associated protein like 4 – anaplastic lymphoma kinase (EML4-ALK) 融合基因，約占非小細胞肺癌 3-5%。
ROS1 (ROS proto-oncogene 1 , receptor tyrosine kinase)
此藥一開始的臨床試驗是在非小細胞肺癌。其無進展存活中位數好於傳統化療。

Crizotinib (Xalkori)	ALK, MET, ROS1(第一代) 其 median progression-free survival(7.7 months vs 3 months) 好於傳統化療。	Non-small cell lung cancer (with ALK fusion or ROS1 gene alteration) NEJM 2013; 368:2385-2394
Alectinib (Alecensa)	ALK (第二代)：可進腦血管障壁 (BBB):12-month event-free survival rate, 68.4% (alectinib) vs. 48.7% crizotinib;	Non-small cell lung cancer (with ALK fusion) NE JM 2017;377:829-38.
Ceritinib (Zykadia) 不管對 crizotinib 有無抗藥性，都有 50%以上反應效果。	overall response rate was 58% , resist to crizotinib (the response rate 56%)	Non-small cell lung cancer (with ALK fusion) NEJ M 2014; 370:1189-1197
Brigatinib (Alunbrig)	ALK ALK (第二代)：可進 BBB 用於對 crizotinib 無效或進展的轉移 NSCLC	Non-small cell lung cancer (ALK+) NE JM 2017;377:829-38.
Lorlatinib 具有第二代特色，進入 BBB。對 crizotinib 無效病人，又可使 crizotinib 恢復療效	ALK (第三代) led to a restored sensitivity to crizotinib，	Non-small cell lung cancer (NSCLC) (ALK+) NEJM 2016; 374:54-61 1. Hepatotoxicity during treatment 2. cardiovascular toxicity (AV block) 3. CNS 4. Hyperlipidemia 5. Pulmonary toxicity

First-line Treatment With ALK Inhibitors in *ALK*-Rearranged NSCLC: Phase III Trials

Agent/Study	N	Study Design	ORR, %	Median PFS, Mos
Crizotinib				
▪PROFILE 1014[1]	343	Crizotinib vs pemetrexed + cis or carbo	74 vs 45	10.9 vs 7.0
Ceritinib				
▪ASCEND-4[2]	376	Ceritinib vs pemetrexed + cis or carbo	72.5 vs 26.7	16.6 vs 8.1
Alectinib				
▪J-ALEX[3]	207	Alectinib vs crizotinib	92 vs 79	NR vs 10.2
▪ALEX[4]	303	Alectinib vs crizotinib	82.9 vs 75.5	NR vs 11.1
Brigatinib				
▪ALTA-1L[5]	275	Brigatinib vs crizotinib	71 vs 60	NR vs 9.8

- Alectinib, crizotinib, and ceritinib are FDA approved for newly diagnosed *ALK*+, metastatic NSCLC[6-8]

1. Solomon. NEJM. 2014;371:2167. 2. Soria. Lancet. 2017;389: 917. 3. Hida. Lancet. 2017;390:29.
4. Peters. NEJM. 2017;377:829. 5. Camidge. NEJM. 2018;[Epub]. 6. Crizotinib PI. 7. Ceritinib PI. 7. Alectinib PI.

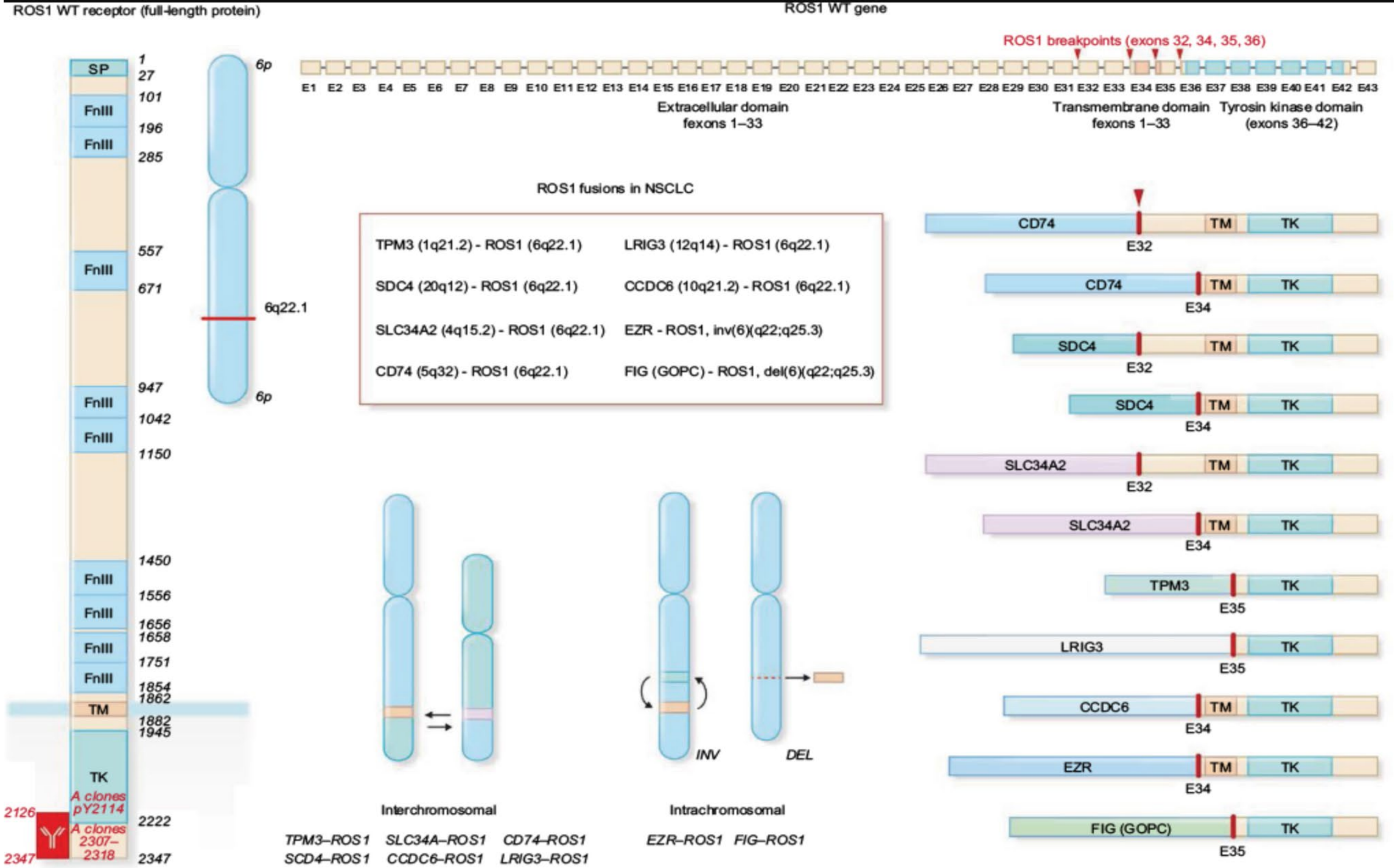
ALK fusion gene NSCLC

- General principles
  - All of the TKI except lorlatinib approved as first line therapy
  - Second generation are active after crizotinib
  - But unclear if active after another 2nd generation TKIs.
  - Lorlatinib active after crizotinib and modestly active 2nd generation of TKI

ROS1 mutations

- Nonsmokers, an earlier onset, high-grade histology, 30% of patients have stage IV disease at clinical diagnosis
- Contrast to ALK-addicted NSCLCs
  - a lower rate of CNS metastasis at diagnosis
  - a lower incidence of brain metastases during tumor progression
- ROS1—ROS1 (OMIM *165020) maps to locus 6q22.1.
- The sequence shares 49% homology with ALK and 77% homology at the ATP-binding site.
- This similarity provides the rationale for using ALK inhibitors to treat ROS1-driven cancers

Journal of Clinical Oncology 35, no. 23 (August 10, 2017) 2613-2618.


ROS1 WT receptor (full-length protein)
SP
FnIII
FnIII
FnIII
FnIII
FnIII
FnIII
FnIII
FnIII
TM
TK
1
27
101
196
285
557
671
947
1042
1150
1450
1556
1656
1658
1751
1854
1862
1882
1945
2126
2222
2347
2347
A clones pY2114
A clones 2307–2318
6p
6q22.1
6p
ROS1 WT gene
ROS1 breakpoints (exons 32, 34, 35, 36)
E1 E2 E3 E4 E5 E6 E7 E8 E9 E10 E11 E12 E13 E14 E15 E16 E17 E18 E19 E20 E21 E22 E23 E24 E25 E26 E27 E28 E29 E30 E31 E32 E33 E34 E35 E36 E37 E38 E39 E40 E41 E42 E43
Extracellular domain fexons 1–33
Transmembrane domain fexons 1–33
Tyrosin kinase domain (exons 36–42)
ROS1 fusions in NSCLC
TPM3 (1q21.2) - ROS1 (6q22.1)
SDC4 (20q12) - ROS1 (6q22.1)
SLC34A2 (4q15.2) - ROS1 (6q22.1)
CD74 (5q32) - ROS1 (6q22.1)
LRIG3 (12q14) - ROS1 (6q22.1)
CCDC6 (10q21.2) - ROS1 (6q22.1)
EZR - ROS1, inv(6)(q22;q25.3)
FIG (GOPC) - ROS1, del(6)(q22;q25.3)
CD74 TM TK
E32
CD74 TM TK
E34
SDC4 TM TK
E32
SDC4 TM TK
E34
SLC34A2 TM TK
E32
SLC34A2 TM TK
E34
TPM3 TK
E35
LRIG3 TK
E35
CCDC6 TM TK
E34
EZR TM TK
E34
FIG (GOPC) TK
E35
INV
DEL
Interchromosomal
TPM3–ROS1 SLC34A–ROS1 CD74–ROS1
SCD4–ROS1 CCDC6–ROS1 LRIG3–ROS1
Intrachromosomal
EZR–ROS1 FIG–ROS1

ROS1 Inhibitors

- **Crizotinib**: Approved for patients with metastatic ***ROS1* rearrangement–positive** or ***ALK* fusion–positive NSCLC**[1]
- **Entrectinib**: Approved for select adult and pediatric patients with locally advanced or metastatic ***NTRK* fusion–positive solid tumors** and for patients with metastatic ***ROS1*+ NSCLC**[2]

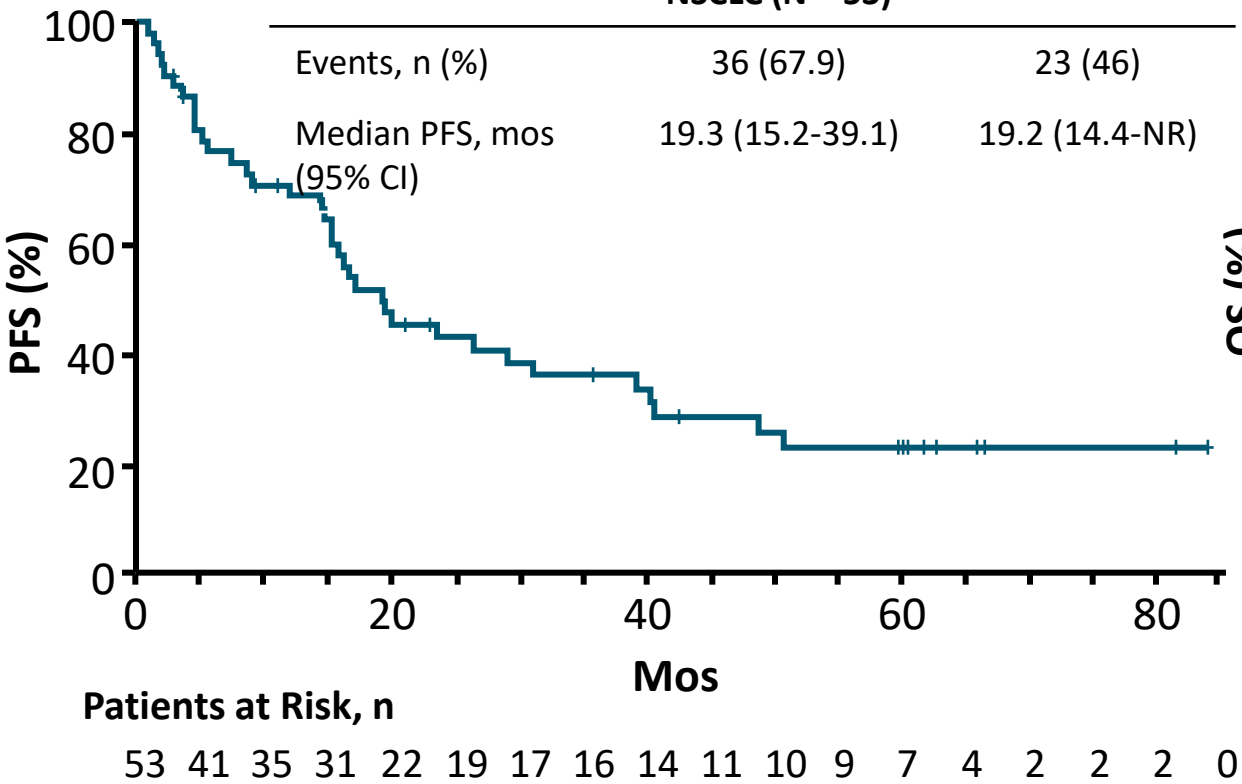
1. Crizotinib PI. 2018. 2. Entrectinib PI. 2019.

Slide credit: clinicaloptions.com

Crizotinib in *ROS1* Rearrangement–Positive NSCLC: Survival

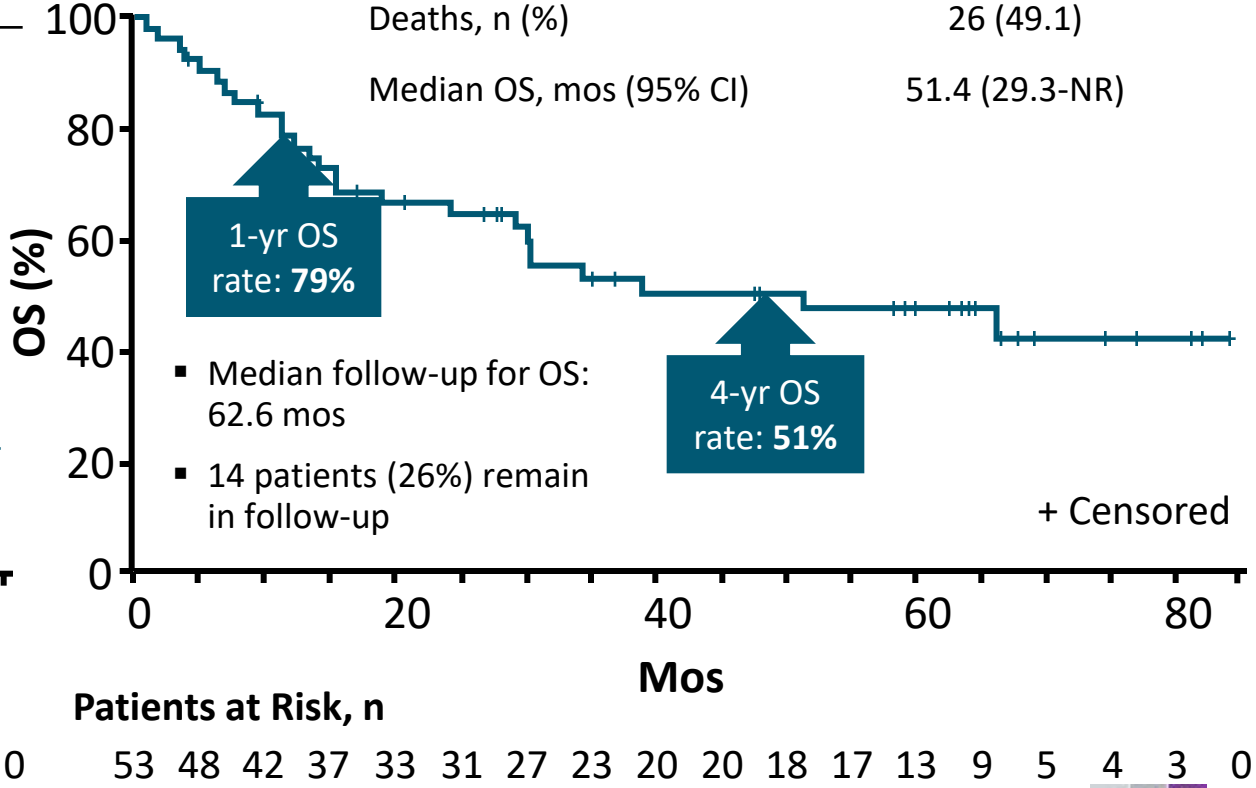
PFS

	ROS1-Rearranged NSCLC (N = 53)	Shaw et al 2014 (N = 50)
Events, n (%)	36 (67.9)	23 (46)
Median PFS, mos (95% CI)	19.3 (15.2-39.1)	19.2 (14.4-NR)



OS

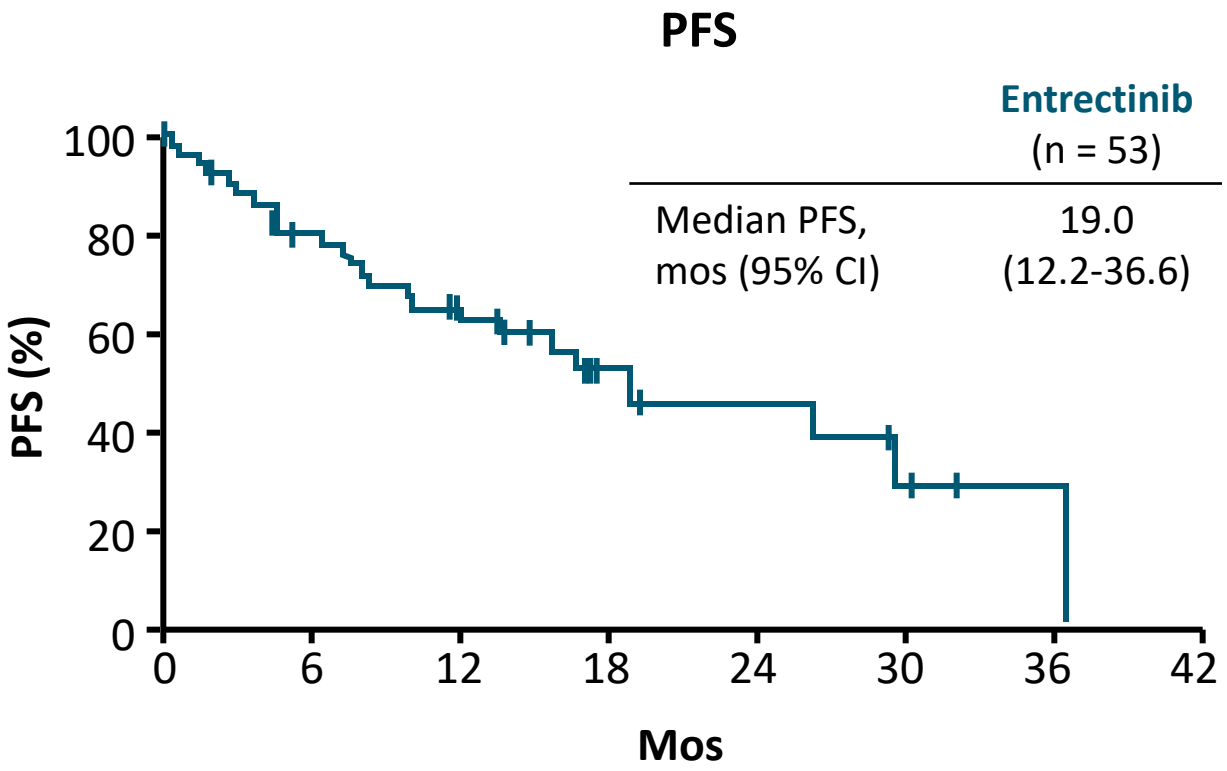
	ROS1-Rearranged NSCLC (N = 53)
Deaths, n (%)	26 (49.1)
Median OS, mos (95% CI)	51.4 (29.3-NR)

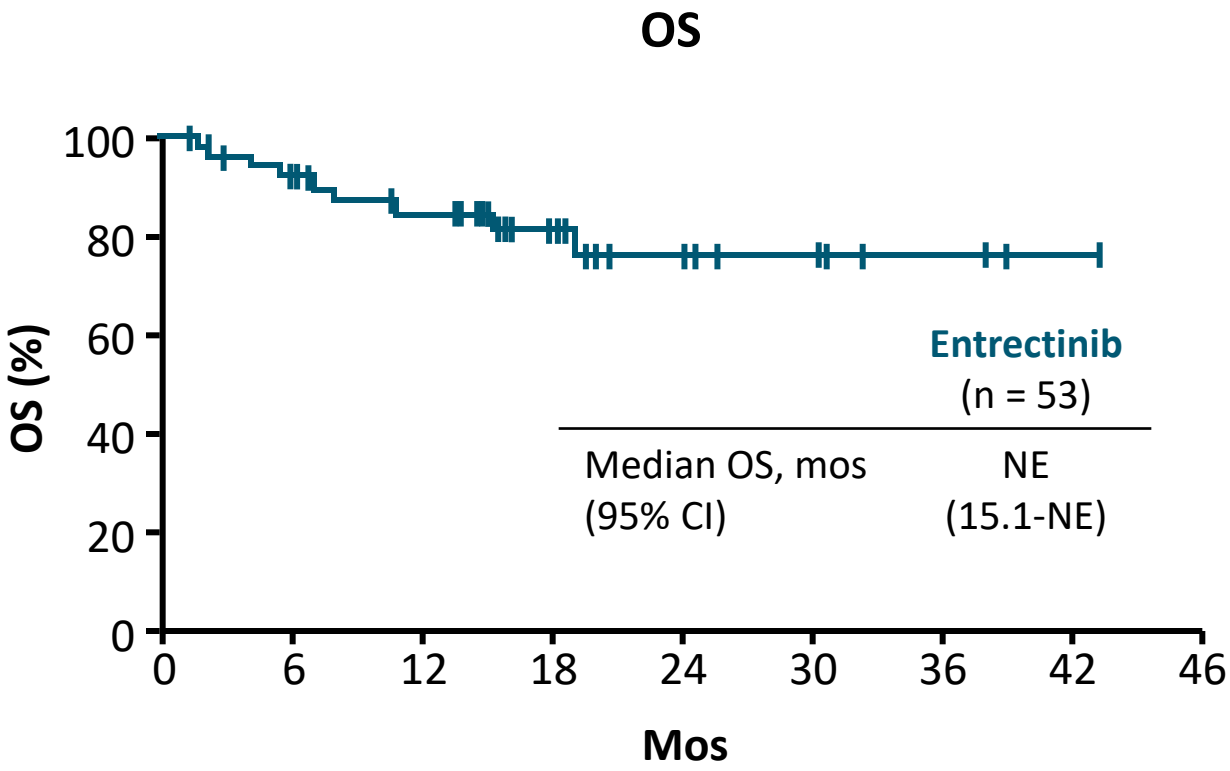


Shaw. Ann Oncol. 2019. [Epub]

Slide credit: clinicaloptions.com

Entrectinib in *ROS1* Rearrangement–Positive NSCLC: Survival





- Median PFS for patients with CNS mets (n = 20) vs those without (n = 30): 13.6 vs 26.3 mos

Drilon. Lancet Oncol. 2020;21:261.

Median follow-up: 15.5 mos.

Slide credit: clinicaloptions.com

Entrectinib in *ROS1*+ NSCLC: Safety Summary

- N = 355 patients in 3 clinical trials
- Most AEs grade 1/2, reversible
- Treatment-related AEs
  - Leading to treatment discontinuation: 3.9%
  - Leading to dose reduction: 27.3%
  - Leading to dose interruption: 25.4%
  - Serious AEs: 8.5%
  - No deaths due to treatment-related AEs

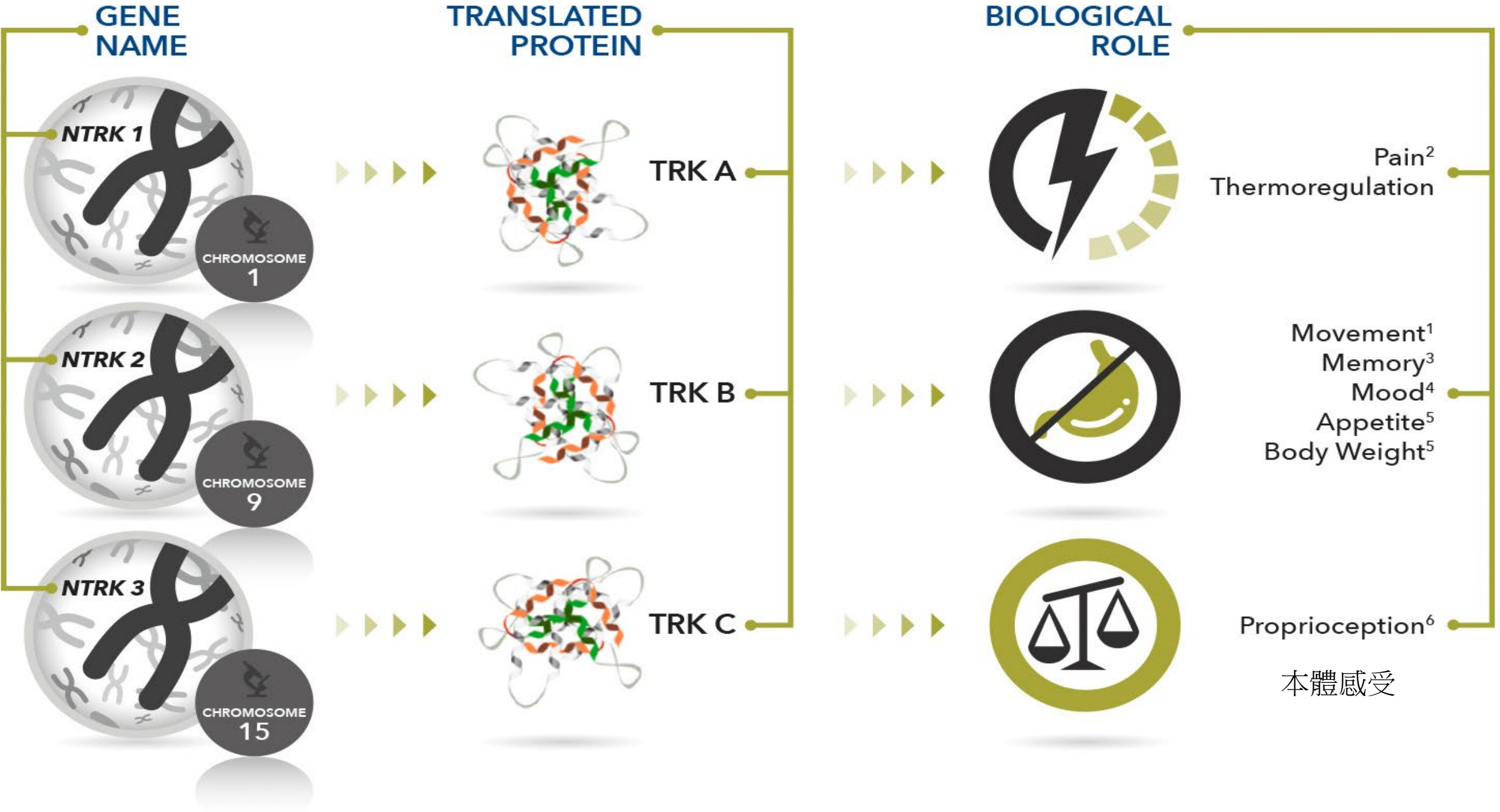
Treatment-Related AE in ≥ 10% of Patients, n (%)	Safety-Evaluable Population (N = 355)	
	All Grades	Grade 3/4
Dysgeusia（味覺障礙）	147 (41.4)	1 (0.3)
Fatigue	99 (27.9)	10 (2.8)
Dizziness	90 (25.4)	2 (0.6)
Constipation	84 (23.7)	1 (0.3)
Nausea	74 (20.8)	0
Diarrhea	81 (22.8)	5 (1.4)
Weight increased	69 (19.4)	18 (5.1)
Paresthesia	67 (18.9)	0
Blood creatinine increased	54 (15.2)	2 (0.6)
Myalgia	54 (15.2)	2 (0.6)
Peripheral edema	50 (14.1)	1 (0.3)
Vomiting	48 (13.5)	0
Anemia	43 (12.1)	16 (4.5)
Arthralgia	44 (12.4)	2 (0.6)
AST increased	39 (11.0)	4 (1.1)

Doebele. WCLC 2018. Abstract OA02.01.

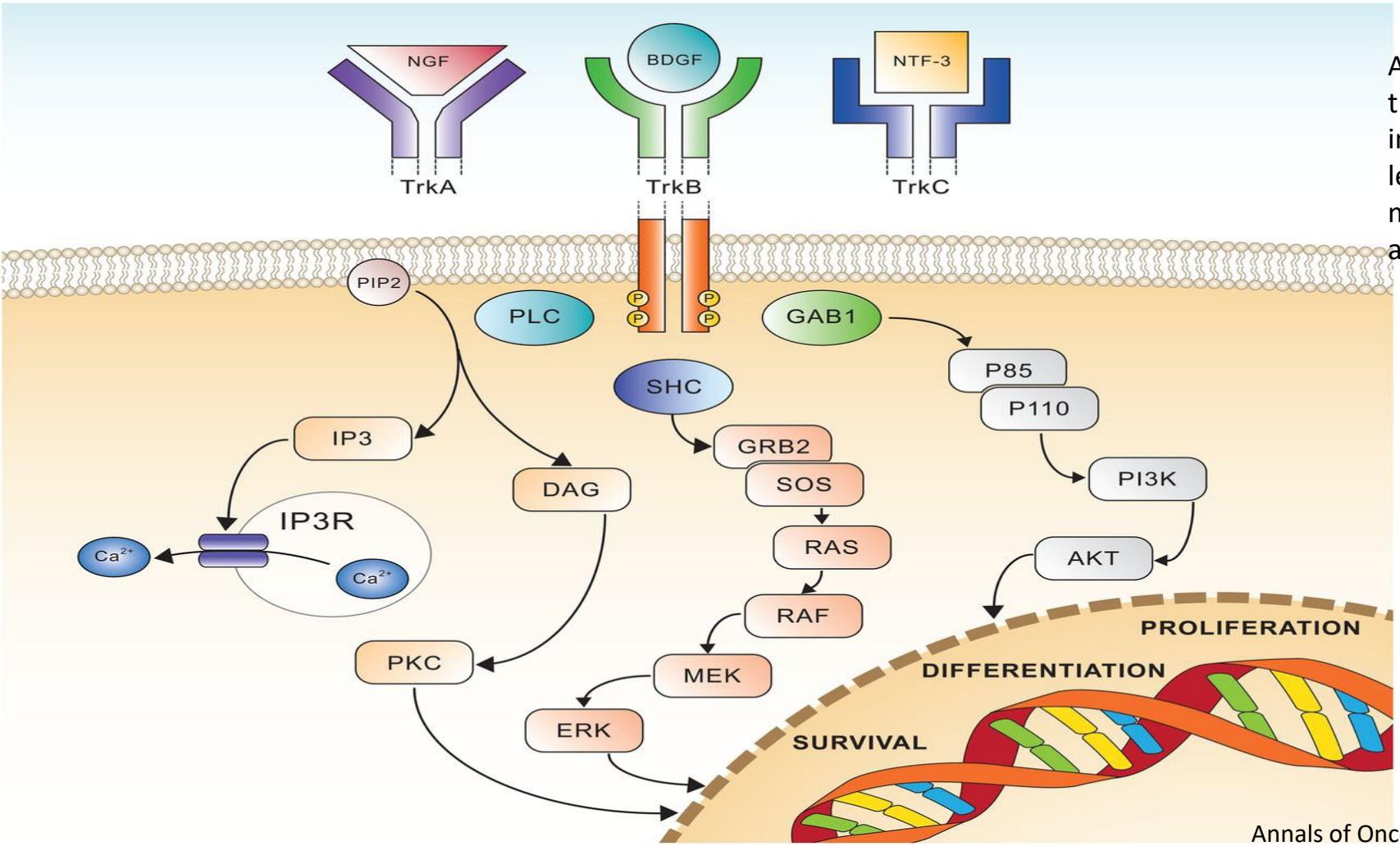
Slide credit: clinicaloptions.com

NTRK (Neurotrophic tropomyosin receptor kinase) Gene Fusion
(神經營養受體酪氨酸激酶基因）
TRK Inhibitors: Tissue-Agnostic Anti-Cancer Drugs

不定腫瘤類型的抗癌藥物
（廣譜標靶藥）

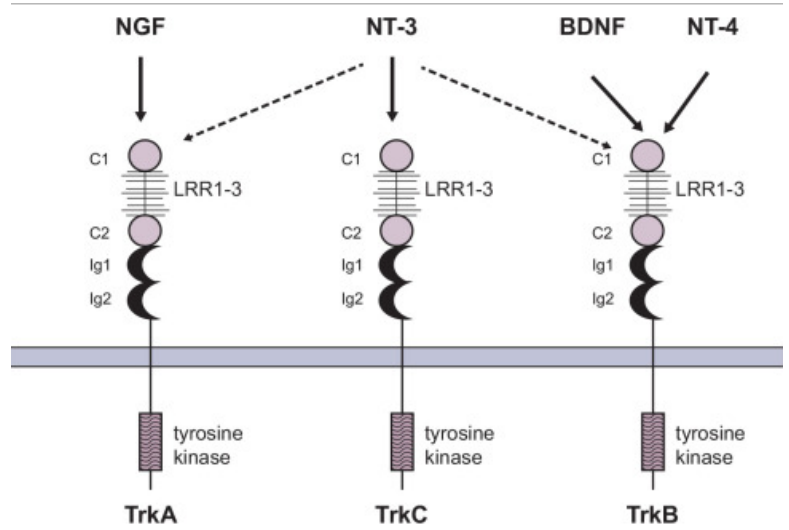

GENE NAME
TRANSLATED PROTEIN
BIOLOGICAL ROLE
NTRK 1
CHROMOSOME 1
NTRK 2
CHROMOSOME 9
NTRK 3
CHROMOSOME 15
TRK A
TRK B
TRK C
Pain[2]
Thermoregulation
Movement[1]
Memory[3]
Mood[4]
Appetite[5]
Body Weight[5]
Proprioception[6]
本體感受

Schematic view of Trk receptors signalling, showing the three major pathways involved in cell differentiation and survival.

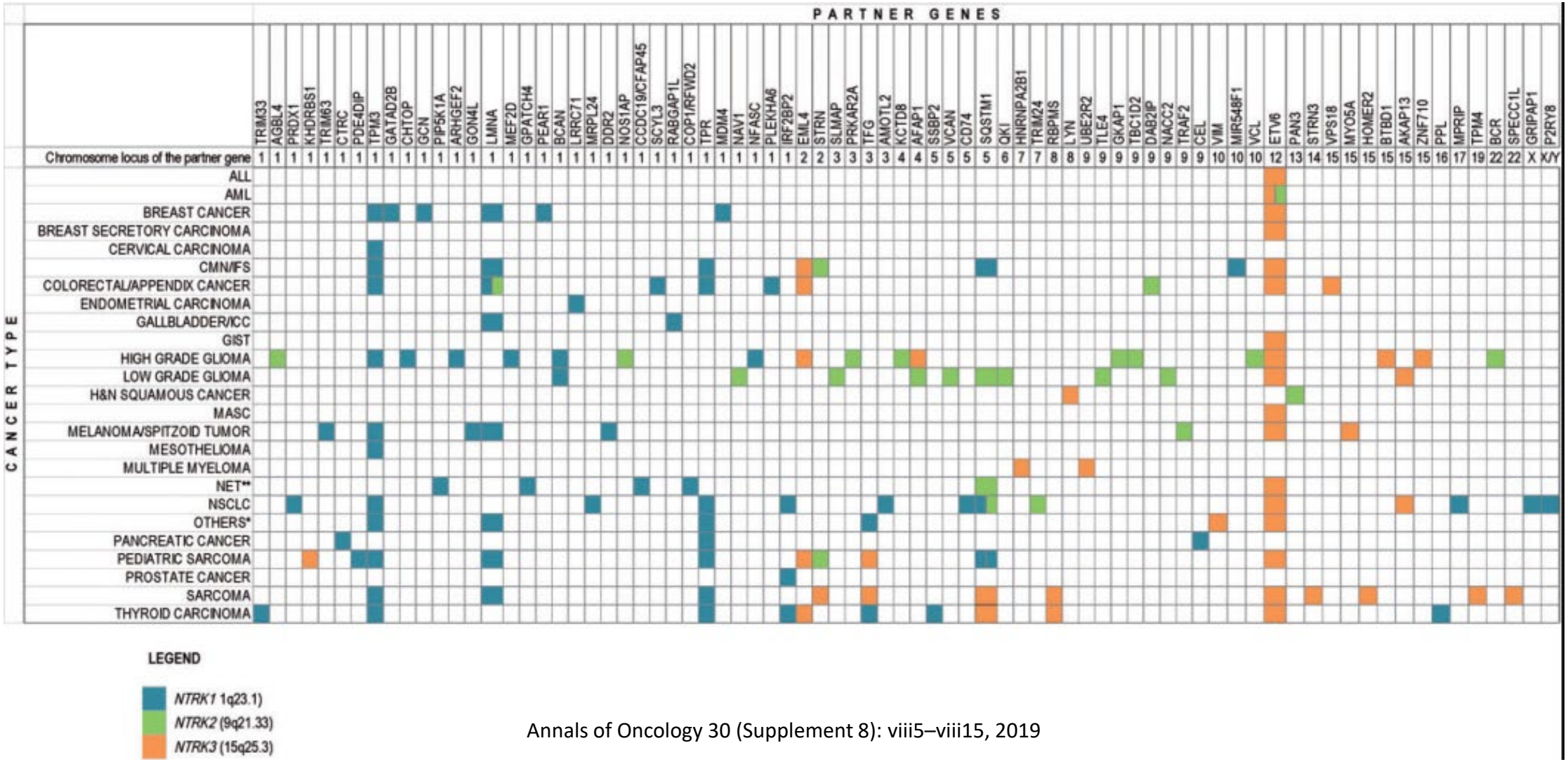


Alessio Amatu et al. ESMO Open 2016;1:e000023

All TRK proteins share similar structural domains in the extracellular region, including two immunoglobulin-like (Ig1 and Ig2) and three leucine-rich 24-residue motifs (LRR1–3). The LRR1–3 motifs, flanked by two cysteine clusters (C1 and C2), are specific to TRK proteins

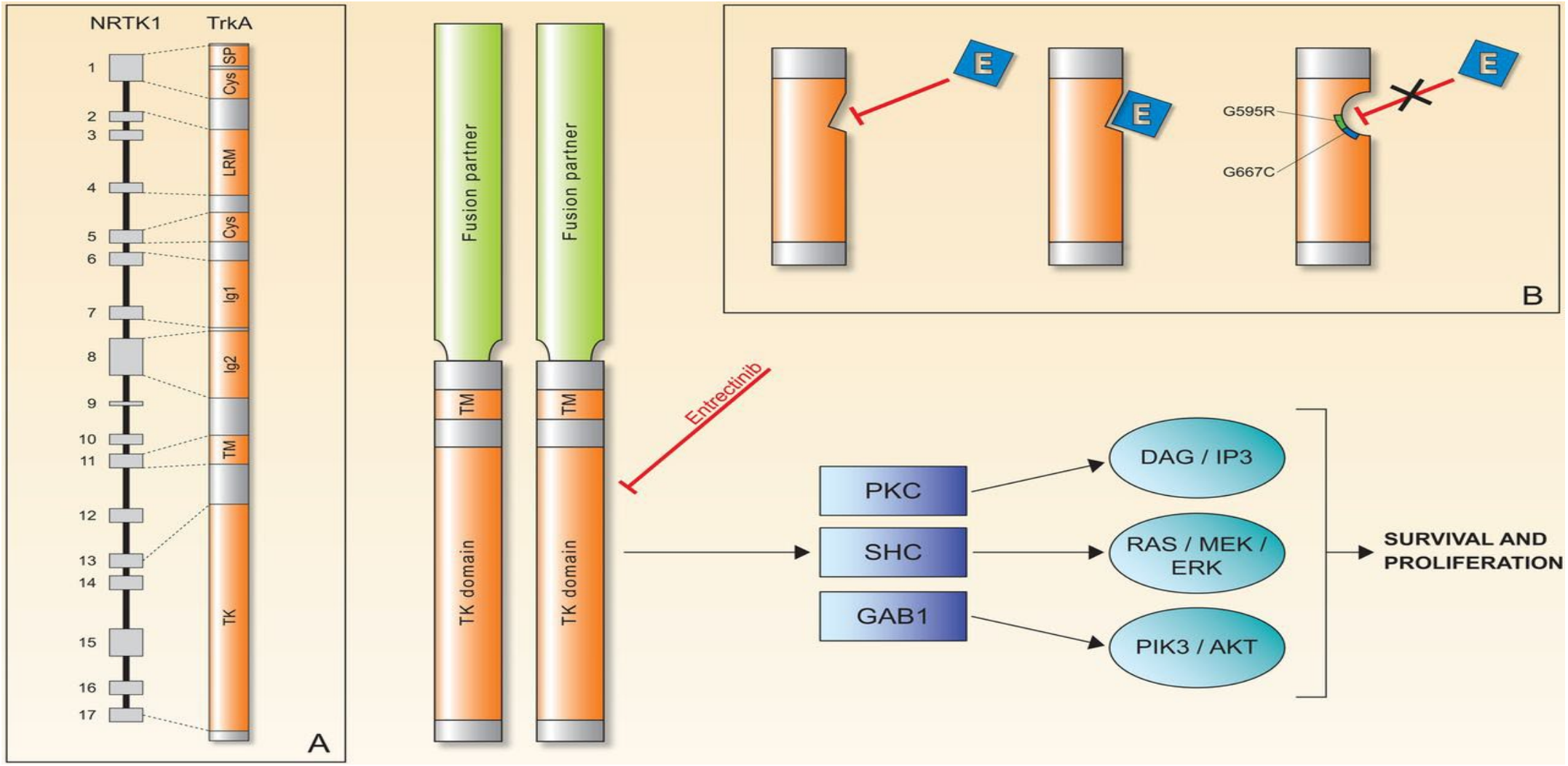


Annals of Oncology 30 (Supplement 8): viii5–viii15, 2019



Annals of Oncology 30 (Supplement 8): viii5–viii15, 2019

The chimeric Trk protein, composed by the TK domain with ATPase activity and a TM loop along with a fusion partner.



Alessio Amatu et al. ESMO Open 2016;1:e000023

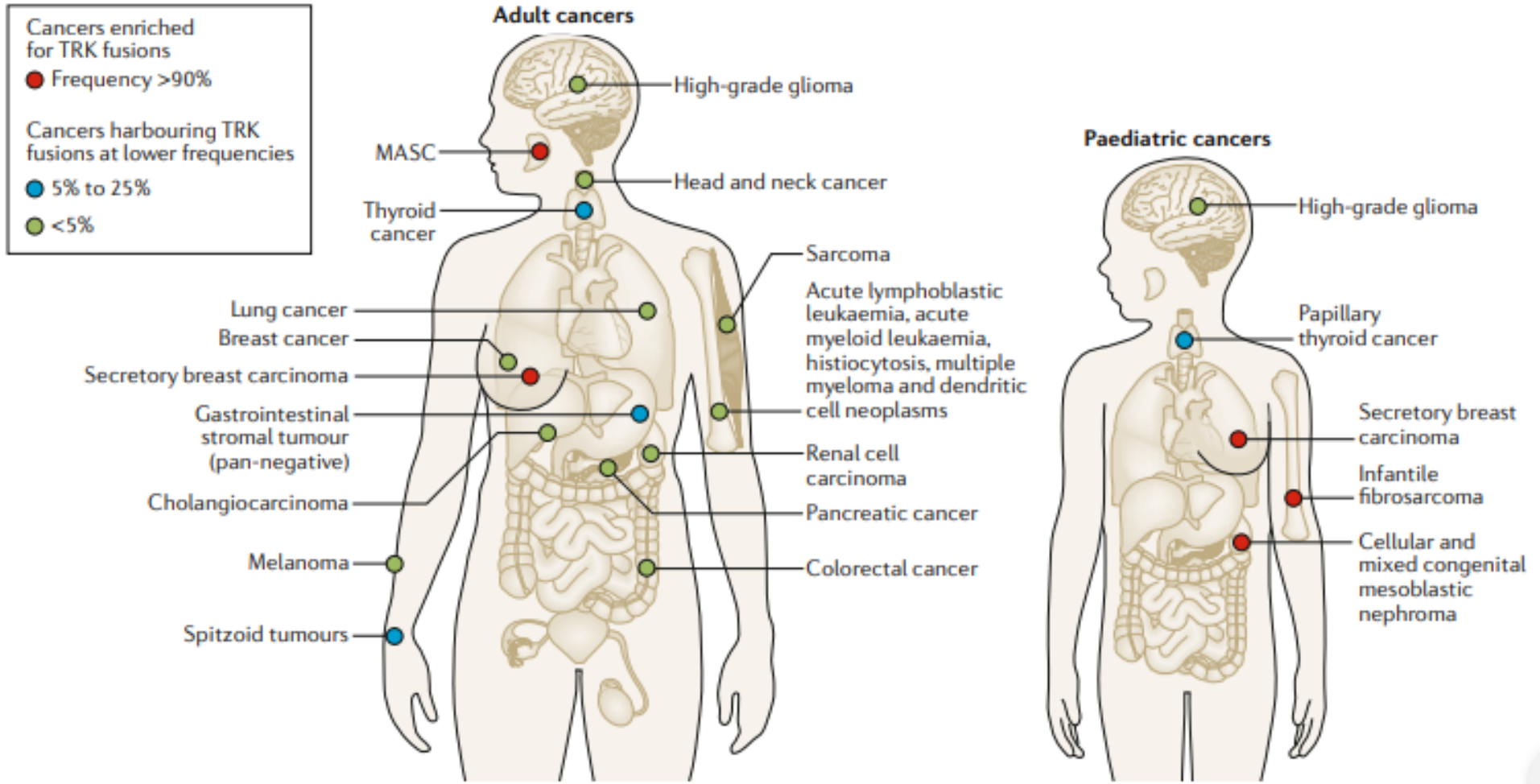


Fig. 4 | **Distribution and frequency of *NTRK* fusions in adult and paediatric tumours.** *NTRK* fusions are identified across multiple paediatric and adult cancer histologies. The frequency of these fusions varies from <1% in cancer types including lung, colorectal, pancreatic and breast cancers, melanoma and other solid or haematological cancers (green circles), up to 25% in tumours including thyroid, spitzoid and gastrointestinal stromal tumours (blue circles), to >90% in rare tumours types, specifically secretory breast carcinoma, mammary analogue secretory carcinoma (MASC), congenital infantile fibrosarcoma and cellular or mixed congenital mesoblastic nephroma (red circles) for which the *NTRK* fusions are considered practically pathognomonic.

Nature Reviews Clinical Oncology 15 (2018): 731-747.

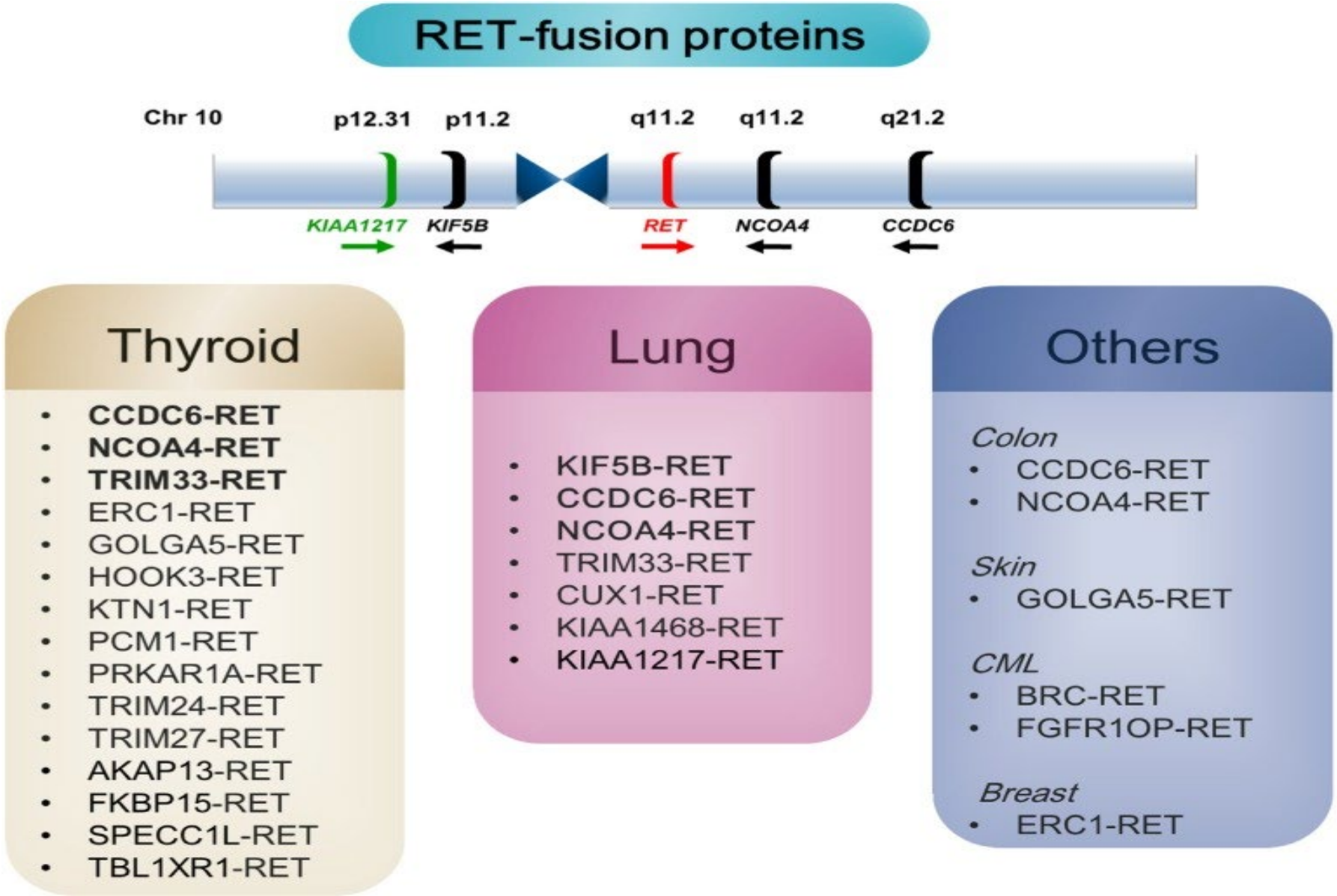
NTRK (Neurotrophic tropomyosin receptor kinase) Gene Fusion

- 神經營養受體酪氨酸 激酶基因NTRK1，NTRK2和NTRK3 編為原肌球蛋白受體激酶 TRK）蛋白質分別為TRKA，TRKB和TRKC。

- 2018年 FDA TRK inhibitor larotrectinib 的上市
  - 是第一個獲得FDA批准的不定腫瘤類型（tumor-agnostic indication）的抗癌藥物。用於有神經營養受體酪氨酸激酶 neurotrophic receptor tyrosine kinase (NTRK)基因融合(gene fusion)的各種癌症。
- 2019年8月15日 FDA 加快批准entrectinib
  - 用於青少年及成人上患有神經營養性酪氨酸受體激酶（NTRK）基因融合但無後天抗藥性突變的轉移性或手術切除可能導致嚴重的併發症，並且在治療後疾病依然持續進展或目前沒有令人滿意的標準療法。另外，FDA還批准entrectinib 用於有轉移性非小細胞肺癌（NSCLC）且其腫瘤呈ROS1陽性的成人。

Larotrectinib	RR 80%	•Solid tumors (with neurotrophic receptor tyrosine kinase [NTRK] gene fusion) NEJ M 2018; 378:731-739
Entrecitinib	The ORR 57%, with 7.4% of CR *ROS1*-positive lung cancer: RR 78%, CR 5.9% , 55% had a response persist for 12 months or longer	**•Solid tumors, neurotrophic tyrosine receptor kinase (NTRK) gene fusion positive:** Children ≥12 years and Adolescents **•Non-small cell lung cancer (metastatic), ROS1-positive**

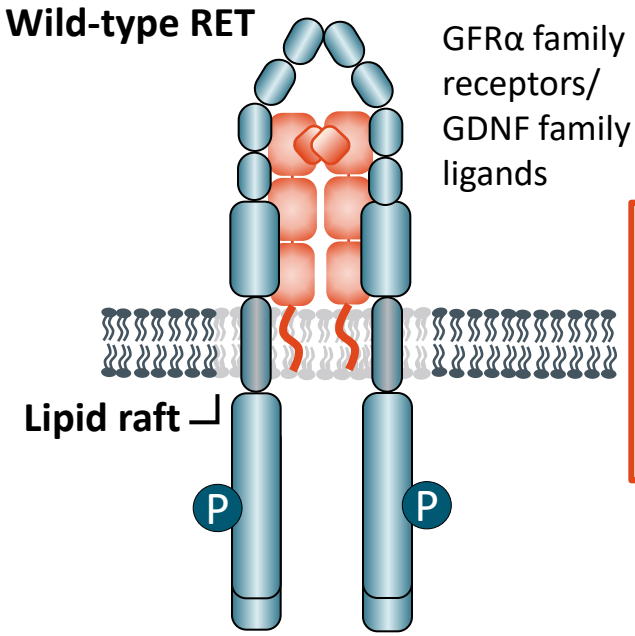
RET (glial cell line-derive neurotrophic factor family, proto-oncogene) : a transmembrane glycoprotein RTK (receptor- tyrosine kinase) is encoded by the proto-oncogene RET (rearranged during transfection) located on chromosome 10



101-36114

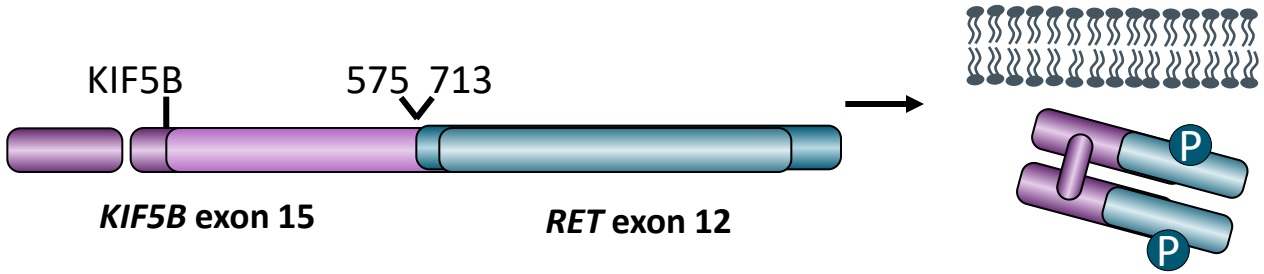
RET Receptor Tyrosine Kinase and *RET* Fusions in NSCLC

- Normal role in neural, genitourinary development
- In cancer, *RET* gene rearrangements give rise to chimeric, cytosolic proteins with constitutively active RET kinase domain
  - 1%-2% of nonsquamous NSCLC
  - 10%-20% of papillary thyroid carcinoma
- Majority of *RET* fusions can be detected by DNA NGS but increased sensitivity with RNA NGS



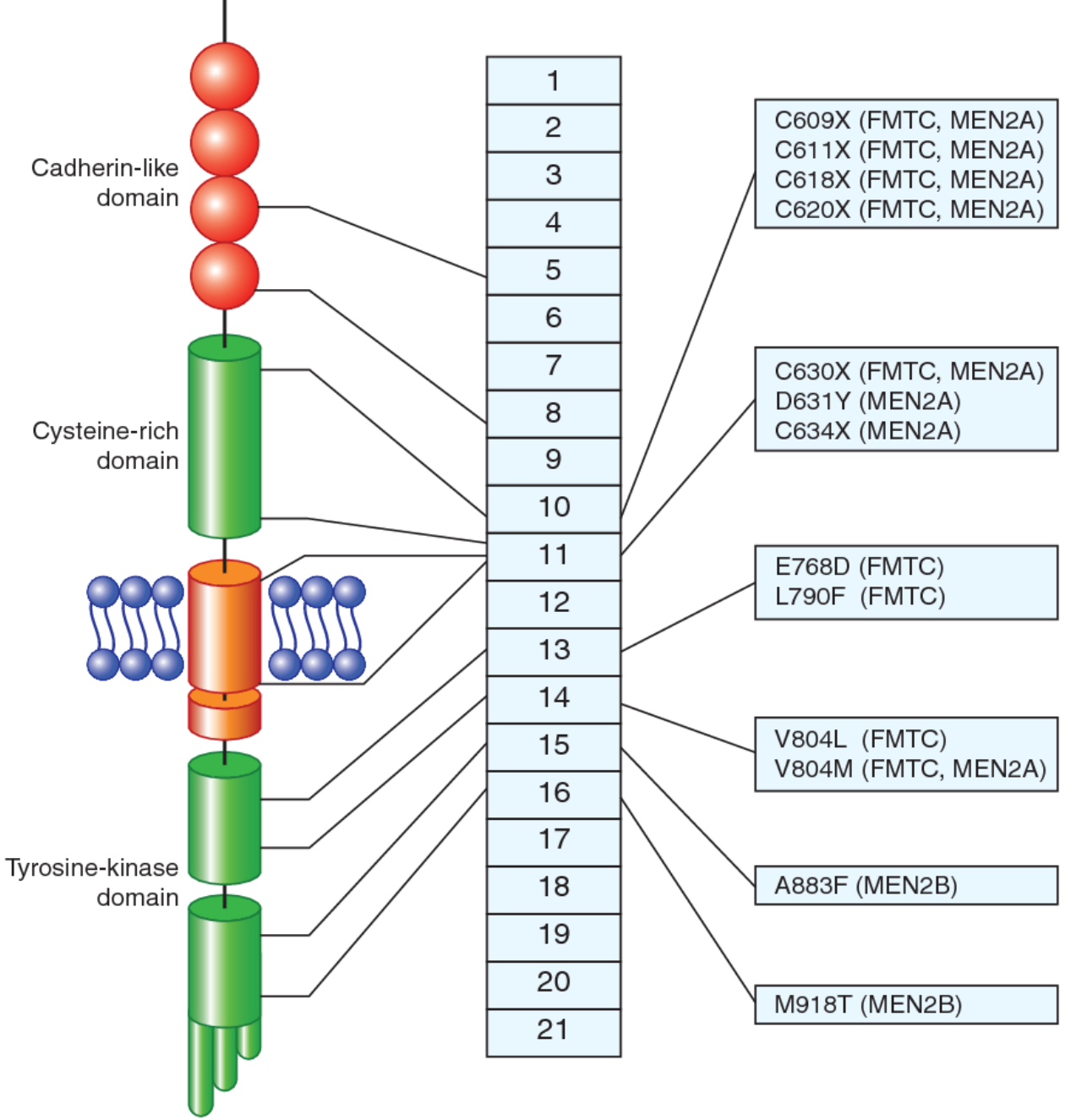
Heterodimerization of ligand–coreceptor complex and RET leads to autophosphorylation and downstream activation

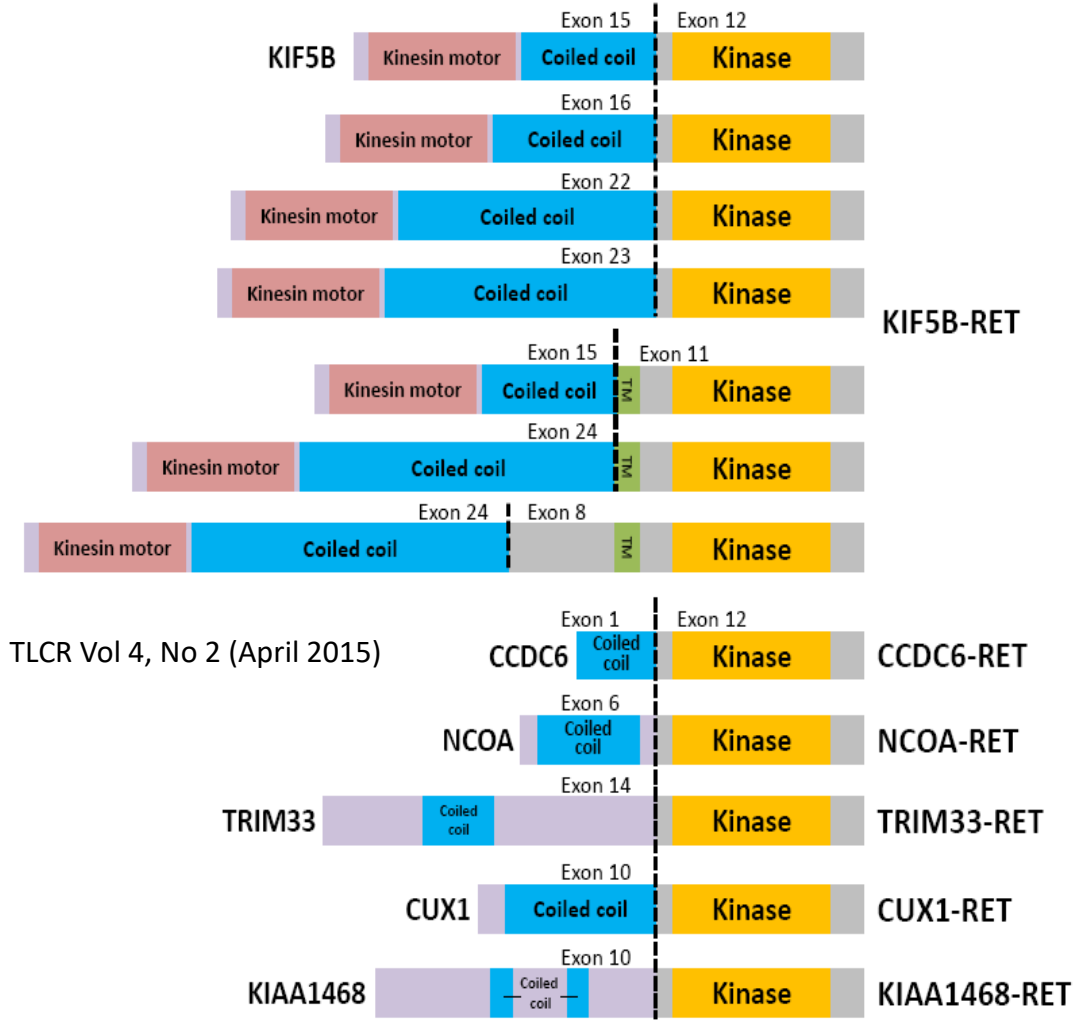
Most Common *RET* Translocation in Lung Adenocarcinoma: KIF5B-RET



Gautschi. JCO. 2017;13:1403. Ferrara. J Thorac Oncol. 2018;13:27. Kato. Clin Cancer Res. 2017;23:1988. Wang . JCO. 2012;30:4352. Airaksinen. Nature Rev Neuroscience. 2002;3:383.

Slide credit: clinicaloptions.com



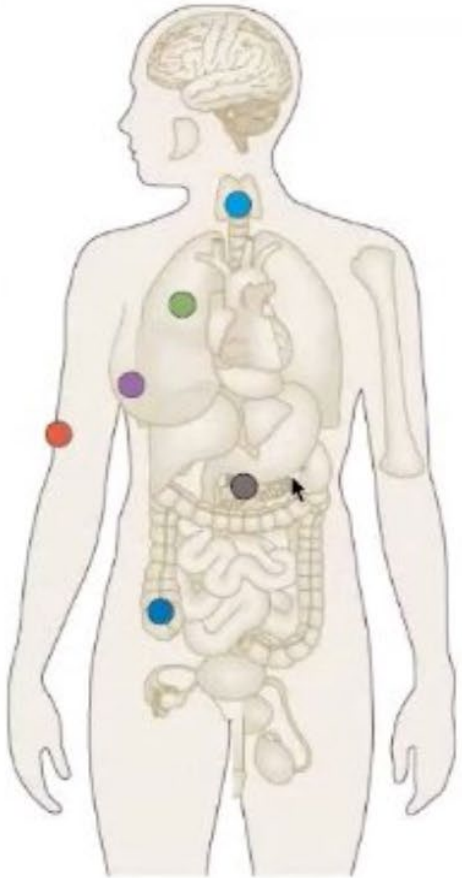


TLCR Vol 4, No 2 (April 2015)

The domains are highlighted in different colors: RET tyrosine kinase domain (orange), RET transmembrane domain (TM; green), and coiled-coil domain (blue) in fusion partners. lung adenocarcinoma. Kinesin motor :驅動蛋白

RET is activated by two major mechanisms in cancer

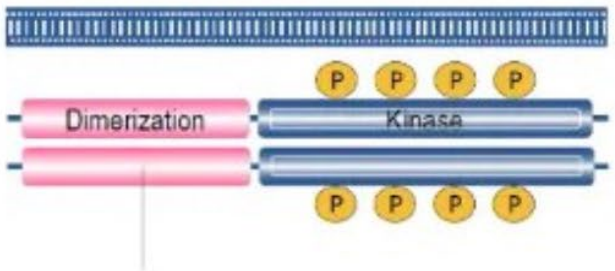
RET fusions



Non-small cell lung cancer (2%)

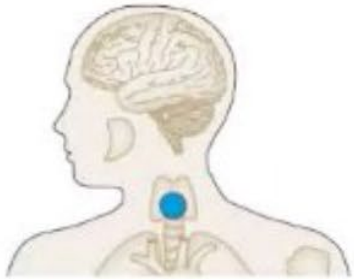
Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



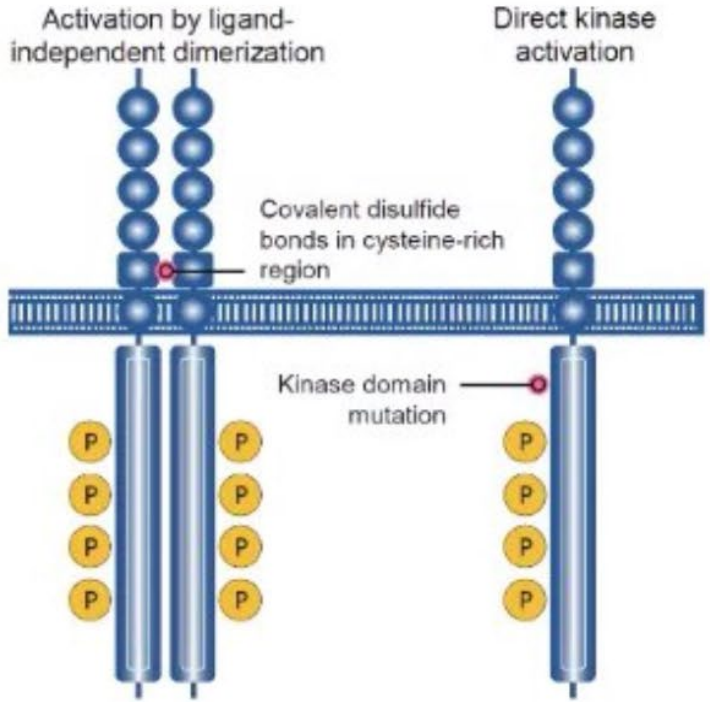
KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

RET mutations



Medullary thyroid cancer

sporadic (>60%)
hereditary (>90%)



Common mutation: ***RET* M918T**

Drilon et al. Nat Rev Clin Oncol 2018;15:151–67; Kato et al. Clin Cancer Res 2017; 23:1988–97; Pietrantonio et al. Ann Oncol 2018;Mar 10; Su et al. PLoS One 2016;11(11)
Li AY (Rolfo C), et al. Cancer Treat Rev 2019

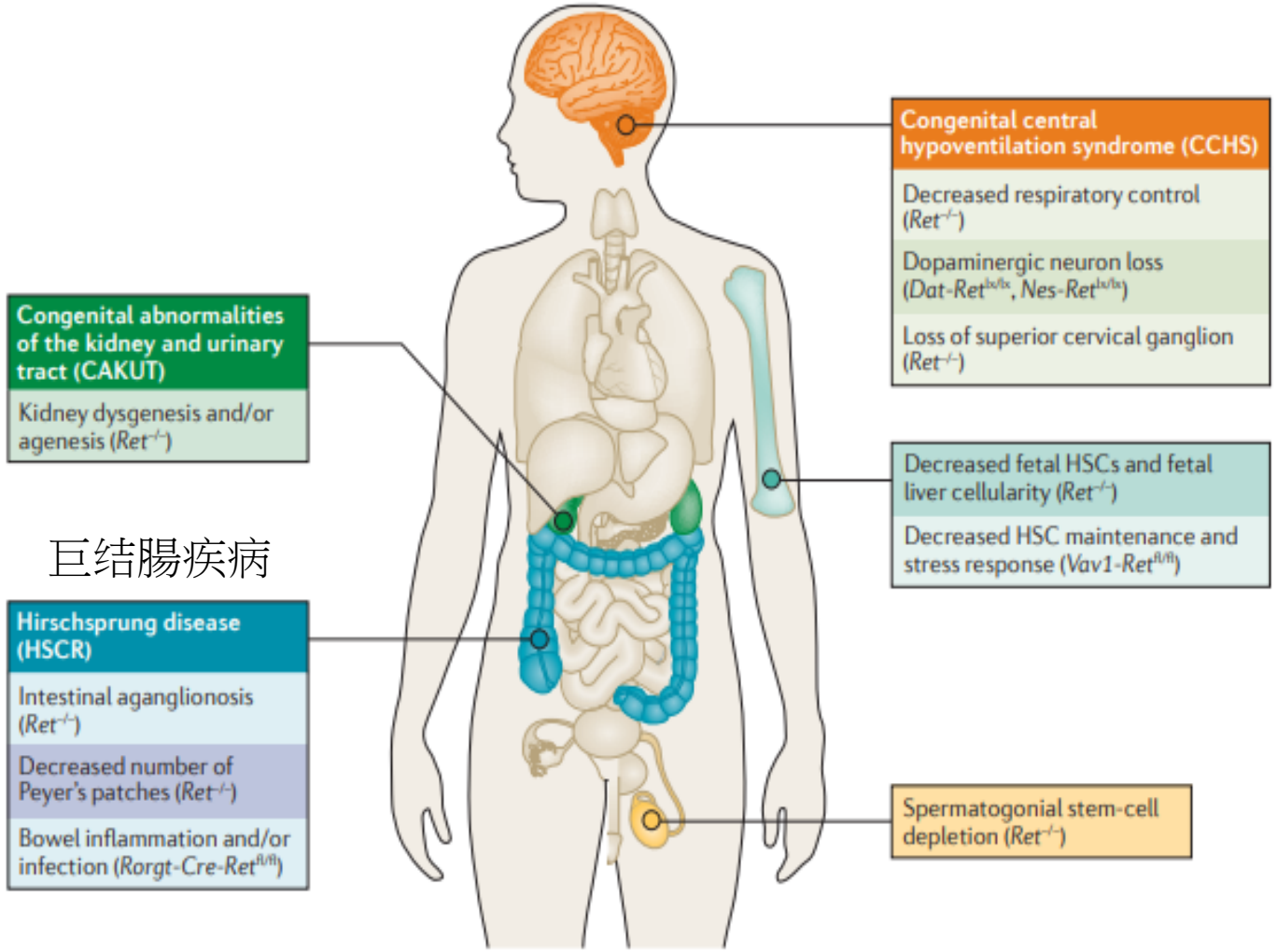
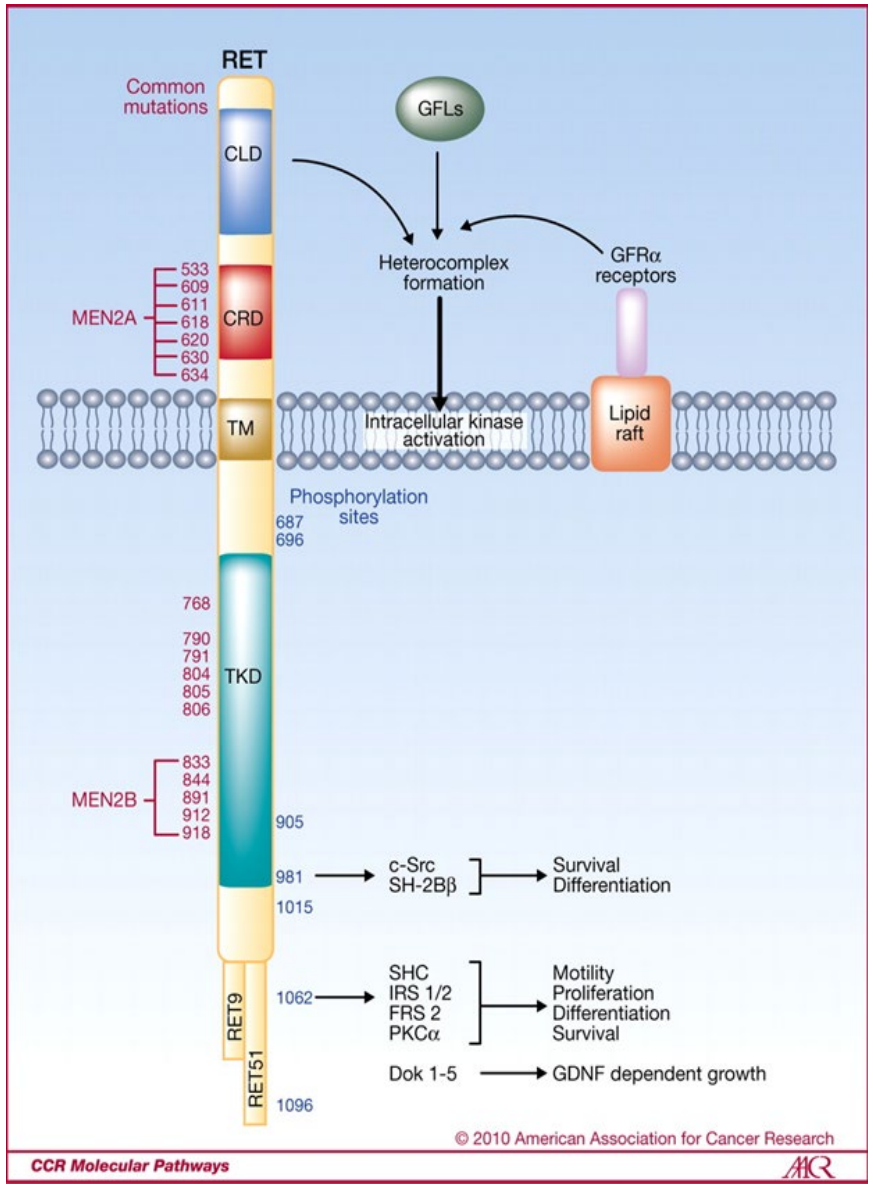


Figure 3 | **Consequences of inactivating *RET* mutations or *Ret* knockout.** The inactivation of RET leads to a variety of consequences that can affect organs including the genitourinary (green and yellow), gastrointestinal (blue), respiratory (orange), and haematopoietic (light blue) systems. Shown here are the human conditions associated with germ-line inactivating *RET* mutations (CAKUT, CCHS, and HSCR), and the pathobiological effects observed in *Ret*-null (*Ret*$^{-/-}$) or tissue-specific *Ret*-knockout (*Ret*$^{fl/fl}$ or *Ret*$^{lx/lx}$) mice. These findings illustrate that the deficiency or absence of RET can have substantial consequences on embryonic development; however, the phenotypic effects of RET deficiency in adult animals are typically mild, with a less-severe symptomatology, indicating that potent and selective RET inhibitors might have a favourable safety profile in older children or adult patients. HSC, haematopoietic stem cell.

Schematic RET protein structure showing common mutation and phosphorylation sites

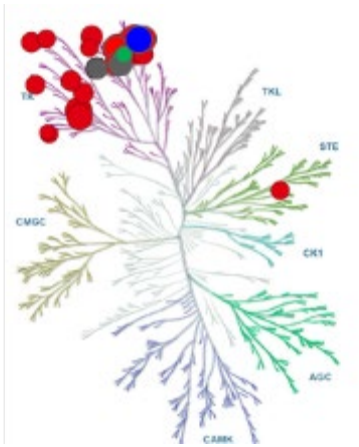


Clin Cancer Res 2010;16:5936-5941

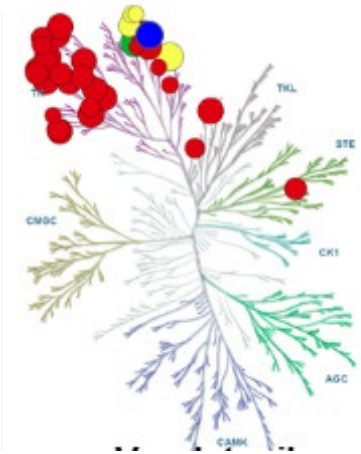
RET Multikinase Inhibitors in *RET*-Rearranged NSCLC

- RET
- KDR/VEGFR2
- FGFR1-3/EGFR
- MET/ALK/ROS
- Other kinases

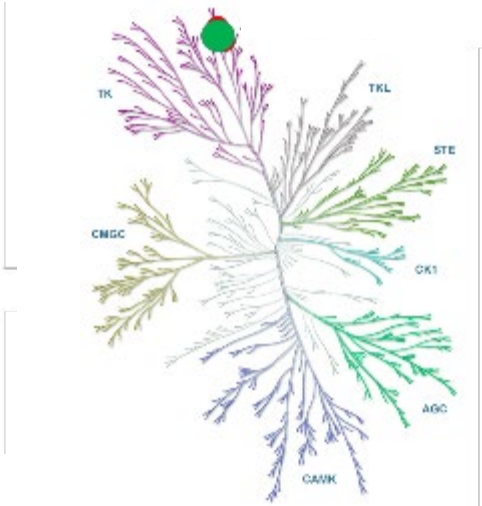
Cabozantinib



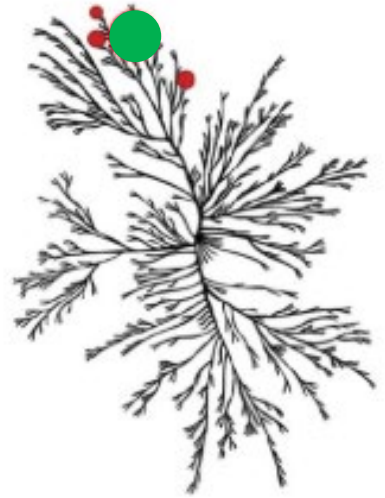
Vandetanib



Selpercatinib (LOXO-292)



Pralsetinib (BLU-667)



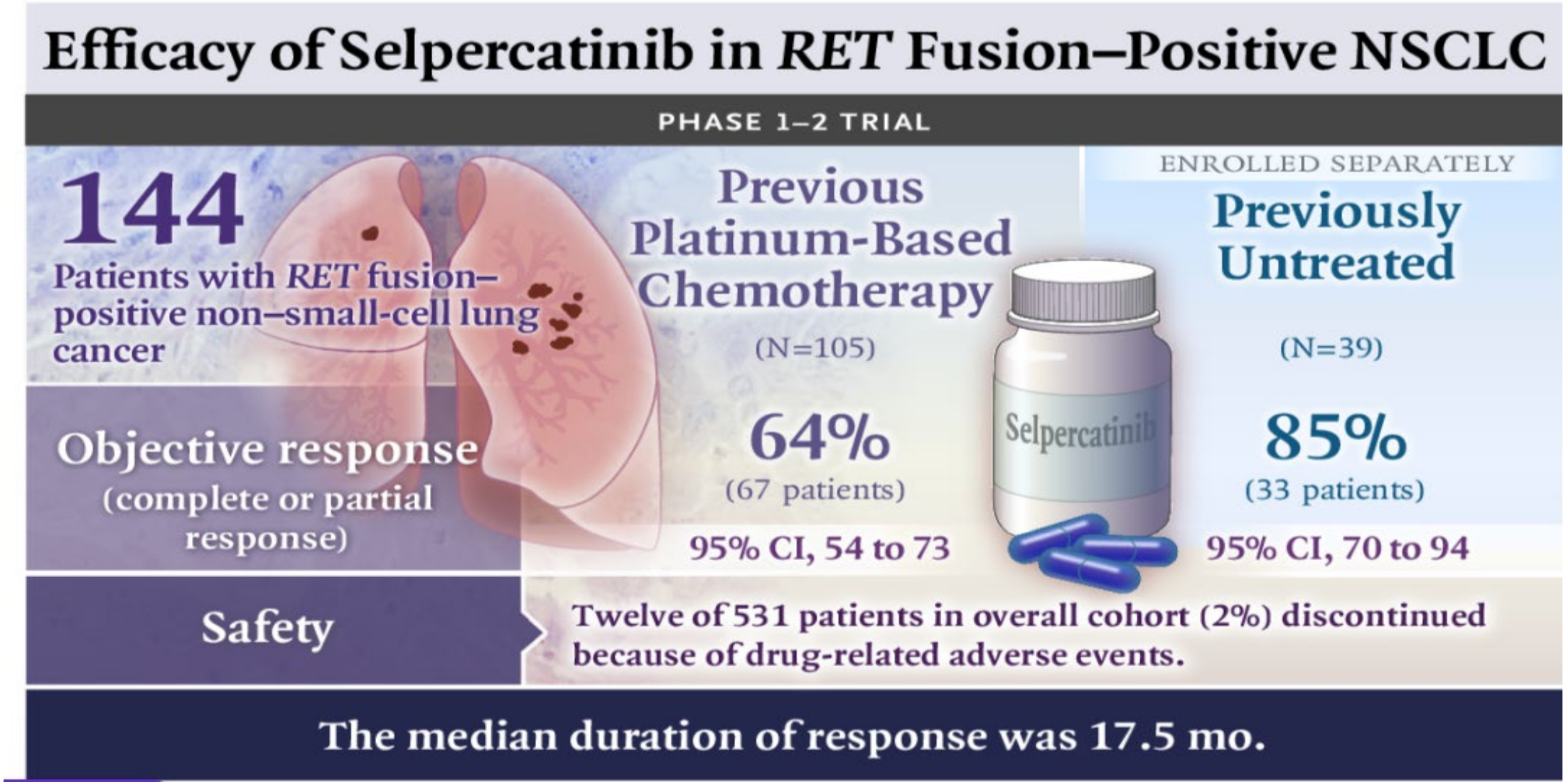
Agent	Cabozantinib	Vandetanib	Selpercatinib (LOXO-292)	Pralsetinib (BLU-667)
IC_{50} RET, nM*	11	4	3	0.4
ORR, %	37	18	68	58
▪ CR	5	0	2	1

*Cell free.

Velcheti. WCLC 2017. Abstr OA 12.07. Gautschi. JCO. 2017;35:1403. Drilon. WCLC 2019. Abstr PL02.08. Gainor. ASCO 2019. Abstr 9008. Rahal. AACR 2017. Abstr B151. Solomon. J Thorac Oncol. 2020;15:541.

Slide credit: clinicaloptions.com

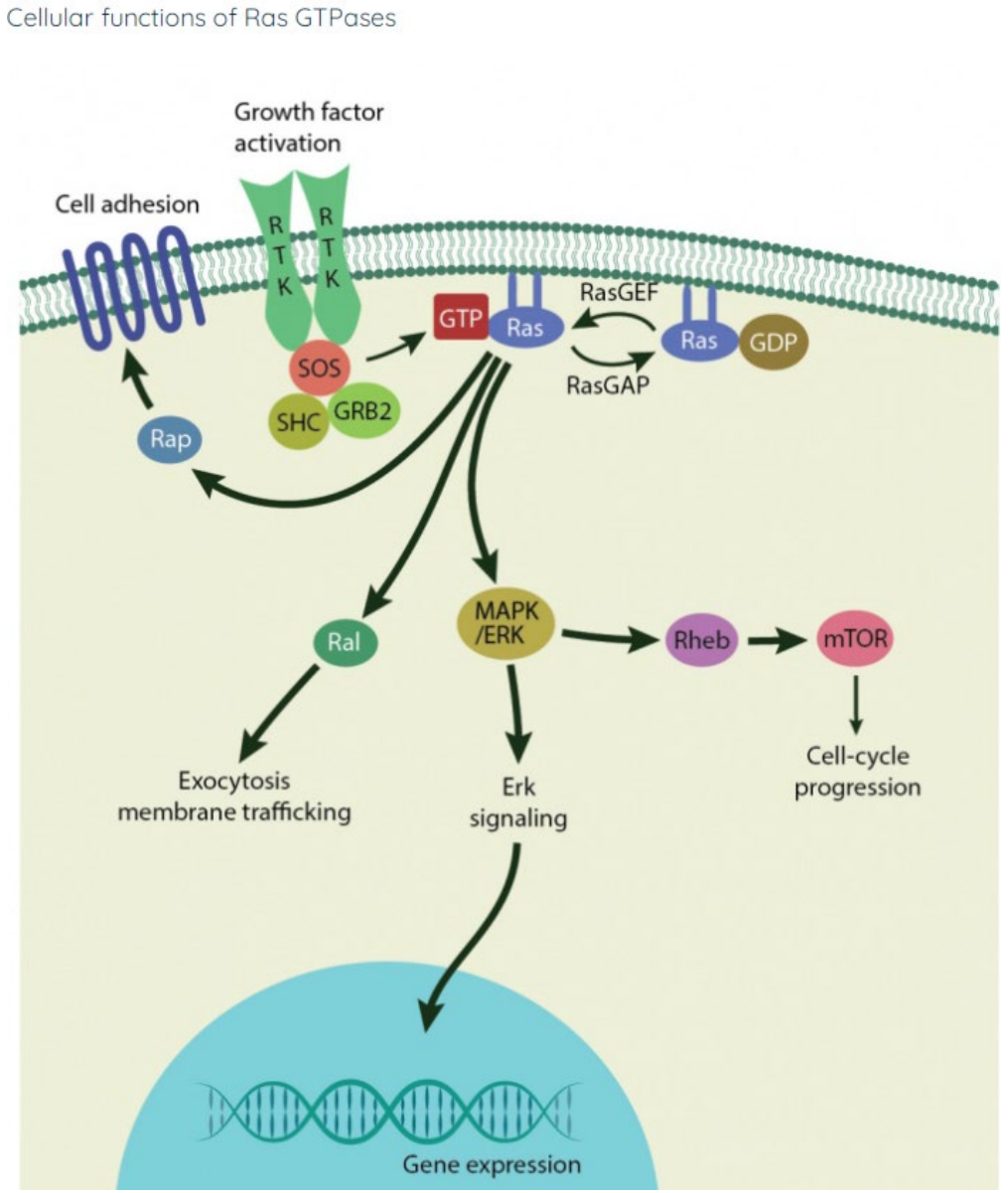
The NEW ENGLAND JOURNAL of MEDICINE



Objective intracranial response was 91% (銳癌寧(selpercatinib) N Engl J Med 2020; 383:813-824
> = grade 3 hypertension (14%), GOT (12%), GPT (10%), hyponatremia (6%), lymphopenia (6%). discontinued selpercatinib because of a drug-related (2%)

RAS (Rat sarcoma virus)

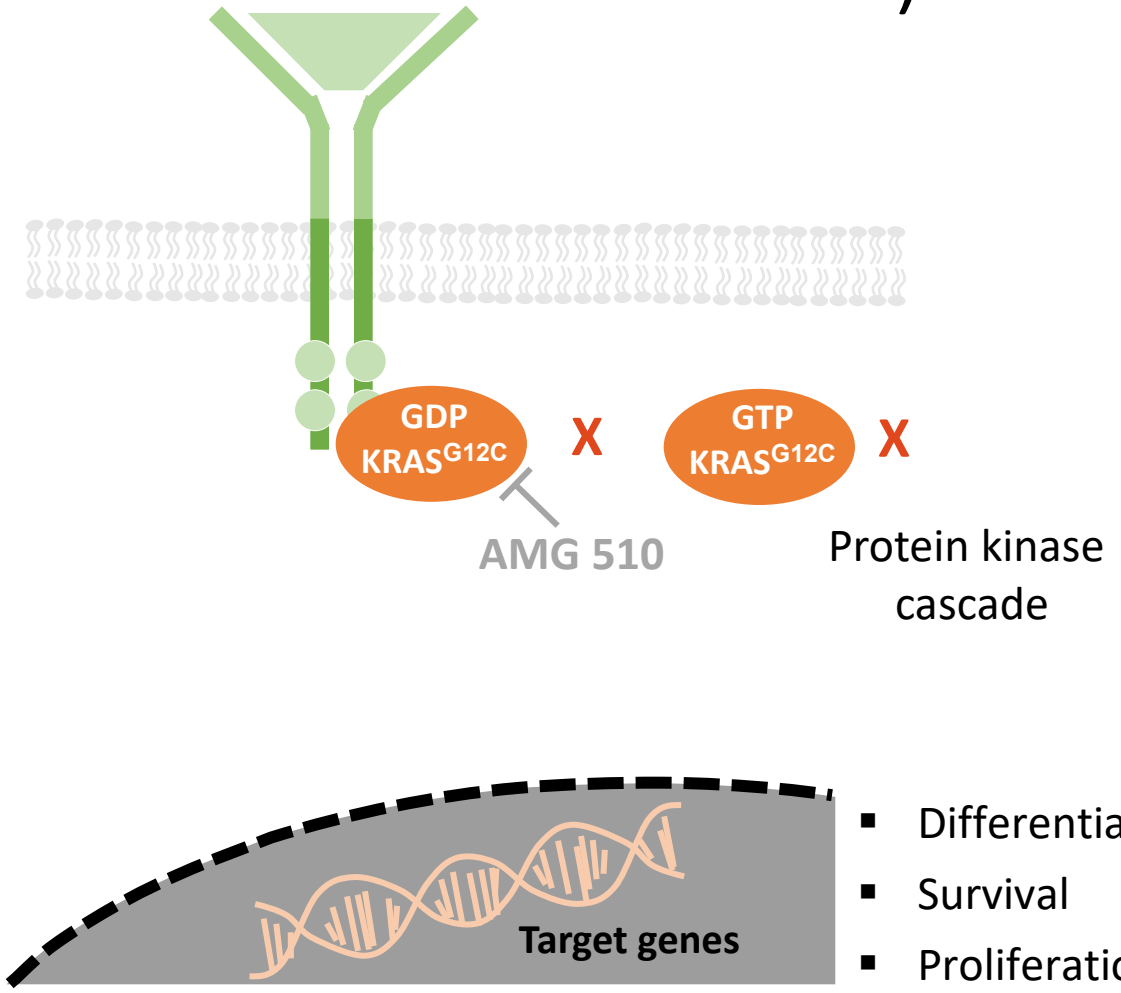
- The Ras family of small GTPases were originally discovered during a search for oncogenic retroviruses.
- Named for their ability to cause rat sarcomas, human *RAS* genes were identified in 1982
- The Ras genes (Hras, Kras, and Nras) encode GTPase proteins that help transduce survival- and growth-promoting signals.



Ras family members are involved in many cellular processes. In terms of mechanobiology, Ras GTPases are involved in cell adhesion, membrane trafficking, and apoptosis.

KRAS : Sotorasib (Small GTPases inhibitor)

- GTP-binding protein connecting receptor tyrosine kinase activation and intracellular signaling
- *KRAS* mutations are most common mutation in NSCLC at 25% to 33%
  - *KRAS*^{G12C} mutations: 13%
- Currently approved therapy targeting *KRAS*^{G12C} mutation
  - Non–small cell lung cancer, locally advanced or metastatic, *KRAS* G12C-mutated: Oral: 960 mg once daily

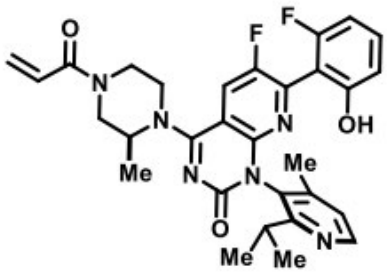


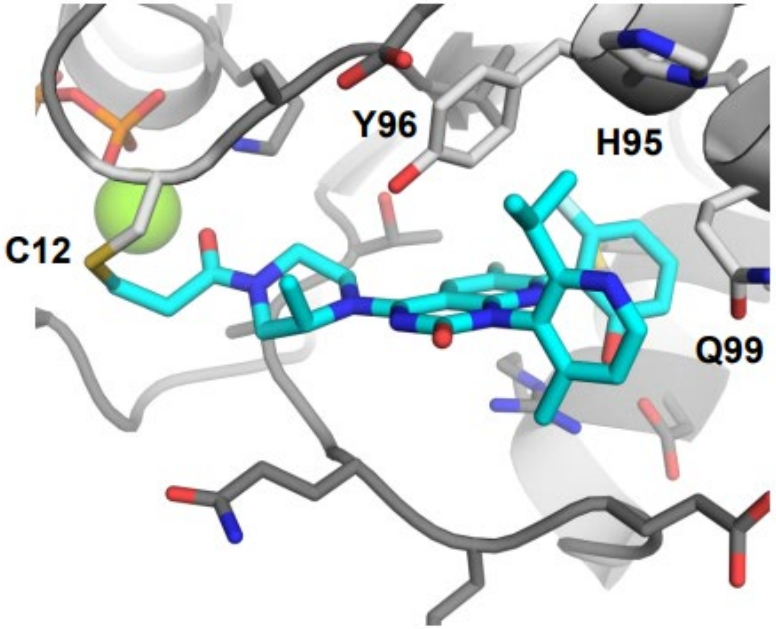
Fakih. ASCO 2019. Abstr 3003. Biernacka. Cancer Genet. 2016;209:195. Tsao. J Thorac Oncol. 2016;11:613. McCormick. J Mol Med (Berl). 2016;94:253. CGARN. Nature. 2014;511:543. Canon. Nature. 2019;575:217.

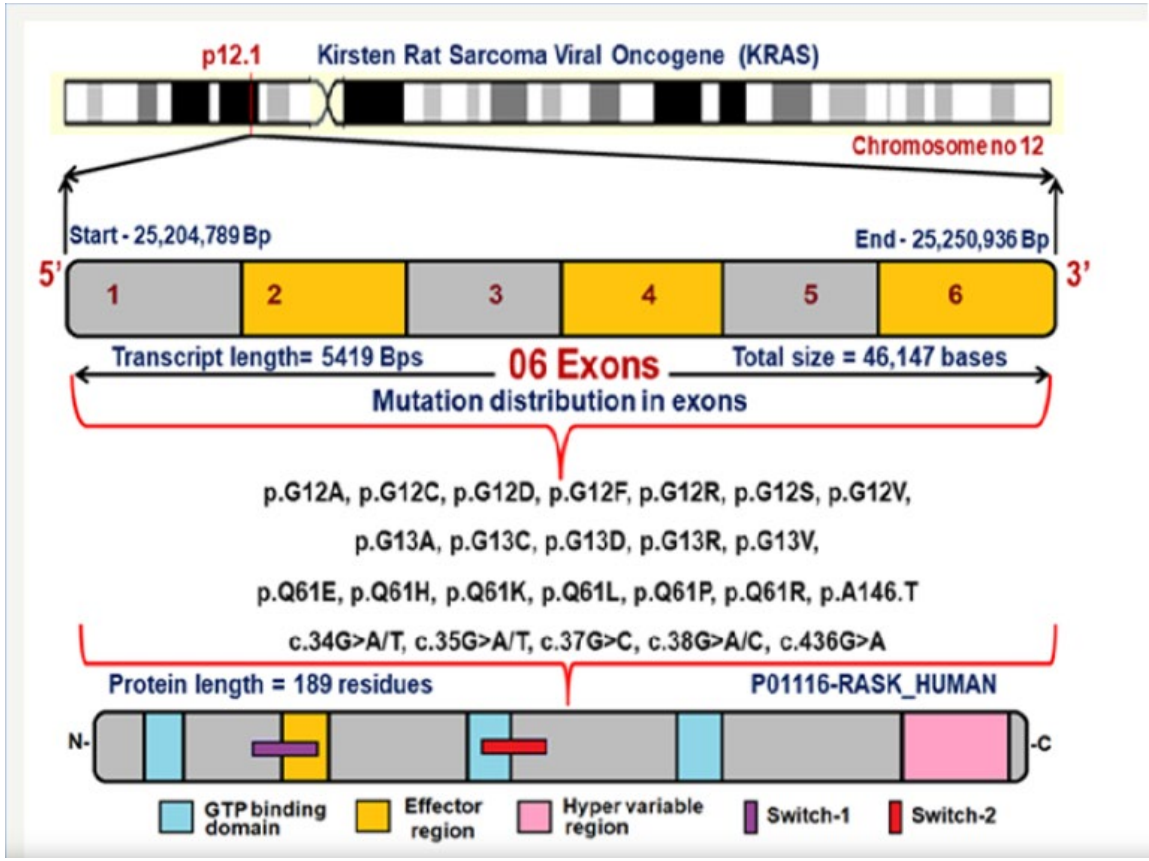
Slide credit: clinicaloptions.com

Sotorasib： Co-crystal Structure of GDP-KRASG12C Bound by Sotorasib Co-crystal structure of sotorasib bound to GDP-KRASG12C

KRAS： *KRAS* p.G12C mutation







Sotorasib

Table 3. Efficacy of Sotorasib in All Tumor Types.

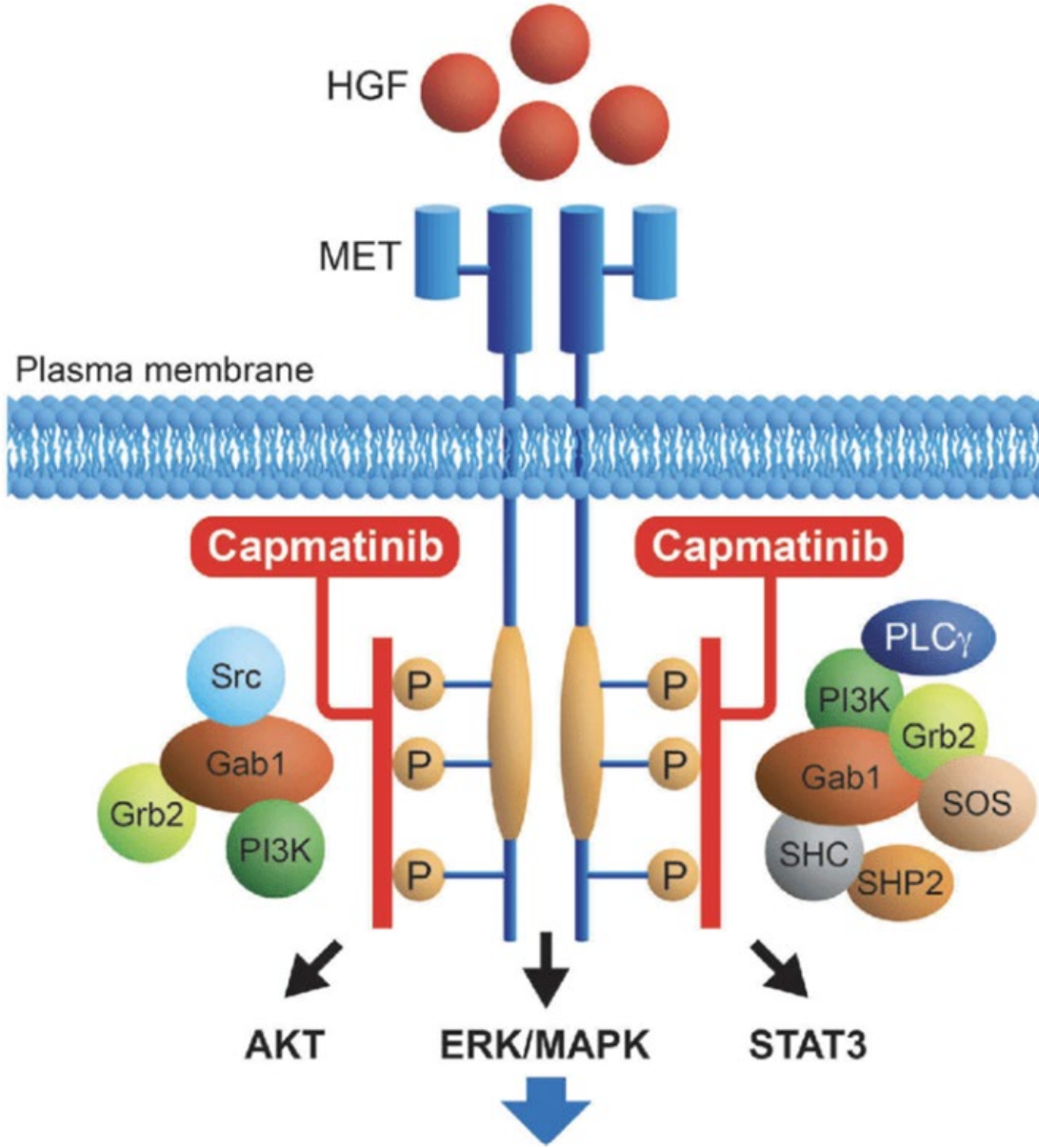
	NSCLC (N=59)	Colorectal Cancer (N=42)	Other (N=28)
Best overall response — no. (%)			
Confirmed complete response	0	0	0
Confirmed partial response	19 (32.2)	3 (7.1)	4 (14.3)
Stable disease	33 (55.9)	28 (66.7)	17 (60.7)
Progressive disease	5 (8.5)	10 (23.8)	4 (14.3)
Could not be evaluated	1 (1.7)	0	1 (3.6)
No assessment*	1 (1.7)	1 (2.4)	2 (7.1)
Objective response — % (95% CI)†	32.2 (20.62–45.64)	7.1 (1.50–19.48)	14.3 (4.03–32.67)
Disease control — % (95% CI)‡	88.1 (77.07–95.09)	73.8 (57.96–86.14)	75.0 (55.13–89.31)

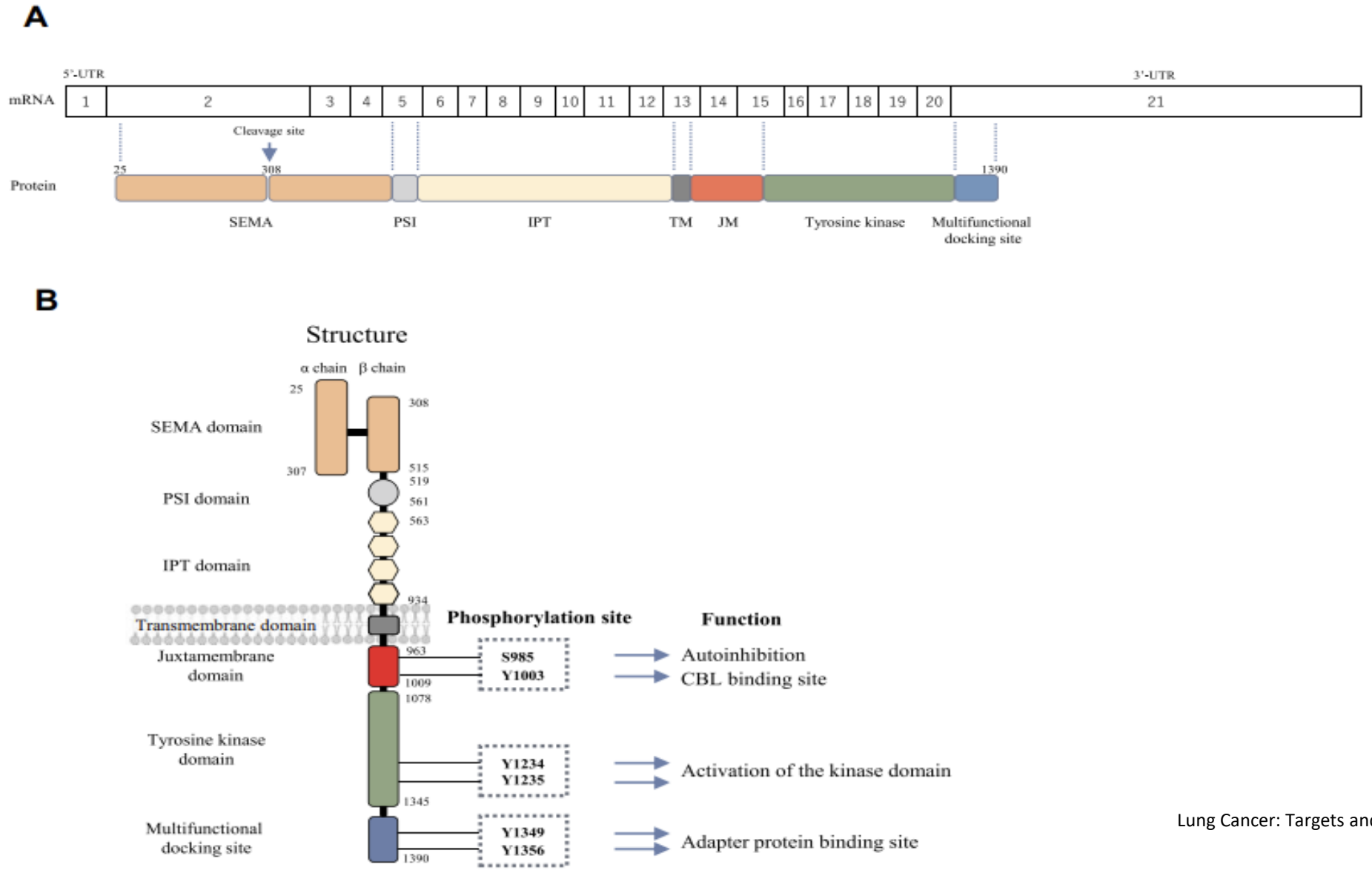
- A total of 73 patients (56.6%) had treatment-related adverse events; 15 patients (11.6%) had grade 3 or 4 events.
- NSCLC
  - the median progression-free survival was 6.3 months (range, 0.0+ to 14.9
- Colorectal cancer
  - the median progression-free survival was 4.0 months (range, 0.0+ to 11.1+).
- Responses were also observed in : pancreatic, endometrial, and appendiceal cancers and melanoma.
- **CONCLUSIONS**
  - Sotorasib showed encouraging anticancer activity in patients with heavily pretreated advanced solid tumors harboring the *KRAS* p.G12C mutation.
  - Grade 3 or 4 treatment-related toxic effects occurred in 11.6% of the patients.

MET inhibitors

間質上皮轉化因子外顯子14 跳讀式突變(**MET exon 14 skipping mutation**)。

- The *MET (*Mesenchymal Epithelial Transition *)* oncogene
  - first identified in the early 1980s in a human osteosarcoma tumor cell line that was exposed to *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine, which produced a chromosomal translocation and a novel fusion protein, between a region called the translocated promoter region (TPR) on chromosome 1 and MET kinase domain on chromosome 7.
- The ligand ：as a mitogenic factor of liver cells called hepatocyte growth factor (HGF)
- Function
  - MET-HGF/SF signaling is essential for embryonic development and regeneration.
  - induces cell proliferation, motility, scattering, angiogenesis, or invasion

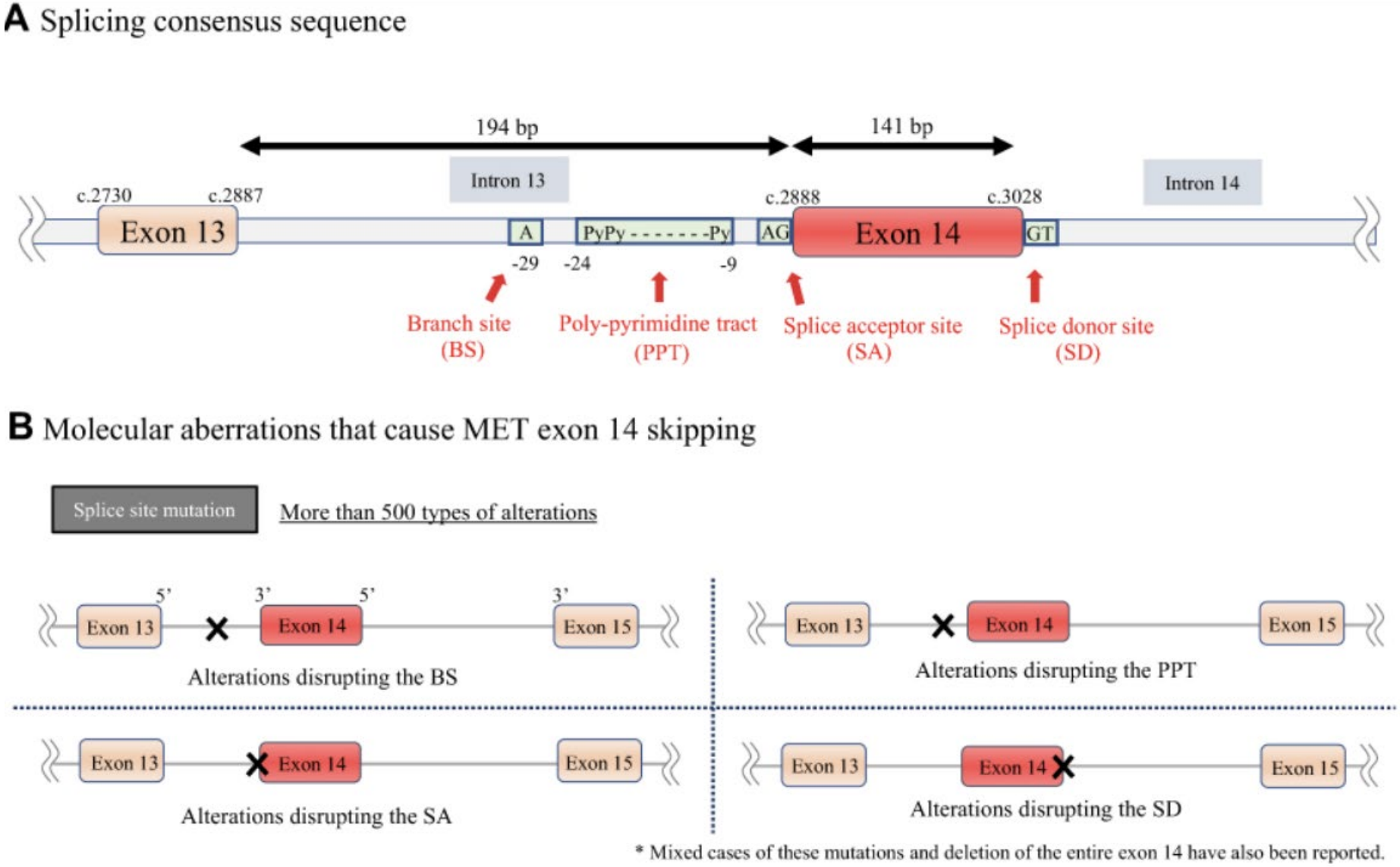




Lung Cancer: Targets and Therapy 2021:12 35–50

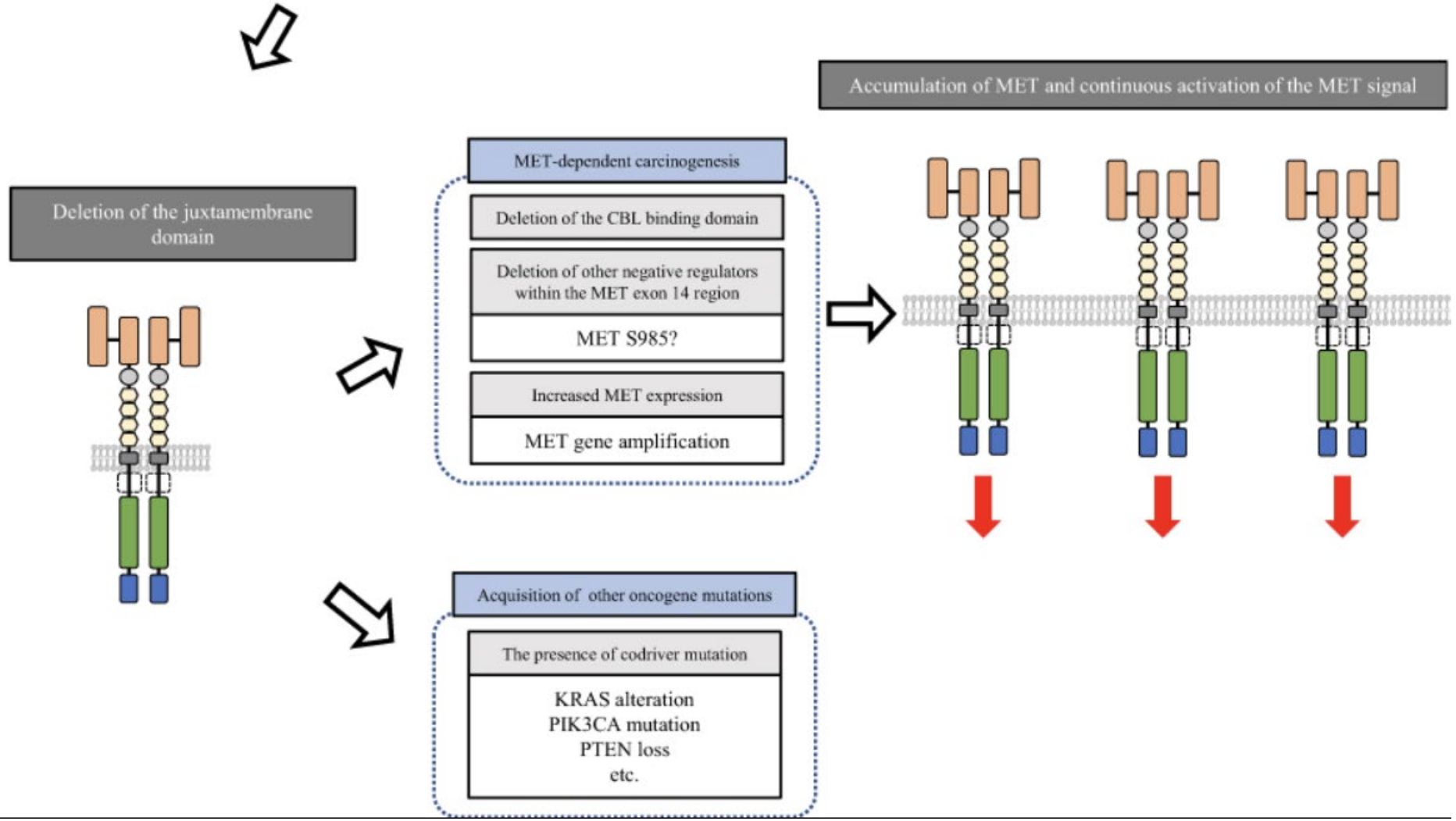
Figure 1 (A) Relationship between the MET protein and mRNA coding region and (B) the structure of normal MET. Mature MET consists of a 50 kDa alpha chain and a 145 kDa beta chain heterodimer through disulfide bonds. The extracellular domain of MET consists of the semaphorin (SEMA), plexin-semaphorin-integrin (PSI), and immunoglobulin-plexin-transcription (IPT) domains; the intracellular domain consists of juxtamembrane, tyrosine kinase and multifunctional docking site domains.

(A) Splicing consensus sequence consisting of a branch site, polypyrimidine tract, splice acceptor site and splice donor site. (B) Activation mechanism by MET exon 14 skipping(外顯子跳讀突變). A large number of alterations, such as point mutations or insertions or deletions in the 3′ or 5′ splice site in MET exon 14, cause the mis-splicing of MET exon 14 by disrupting the splicing consensus.



Lung Cancer: Targets and Therapy 2021:12

An abnormal MET protein lacking a CBL-binding site. This causes the accumulation of shrinked MET receptors followed by increased MET signaling



Lung Cancer:
Targets and Therapy
2021:12

MET Receptor Tyrosine Kinase and *MET* Exon 14 Skipping Mutations in NSCLC

- Normal role in embryogenesis and wound healing
- The hepatocyte growth factor/scatter factor (HGF/SF) activates c-Met, an RTK important for many normal cellular functions.
- In cancer, *MET*ex14 skipping mutations cause in-frame deletion of juxtamembrane domain resulting in increased stability and constitutive kinase activation
  - 3-4% of nonsquamous NSCLC, more commonly in patients who smoked and whose tumors have sarcomatoid features on pathology
  - 20-30% of sarcomatoid cancers
- Majority of *MET*ex14 skipping mutations can be detected with DNA NGS but increased sensitivity with RNA NGS

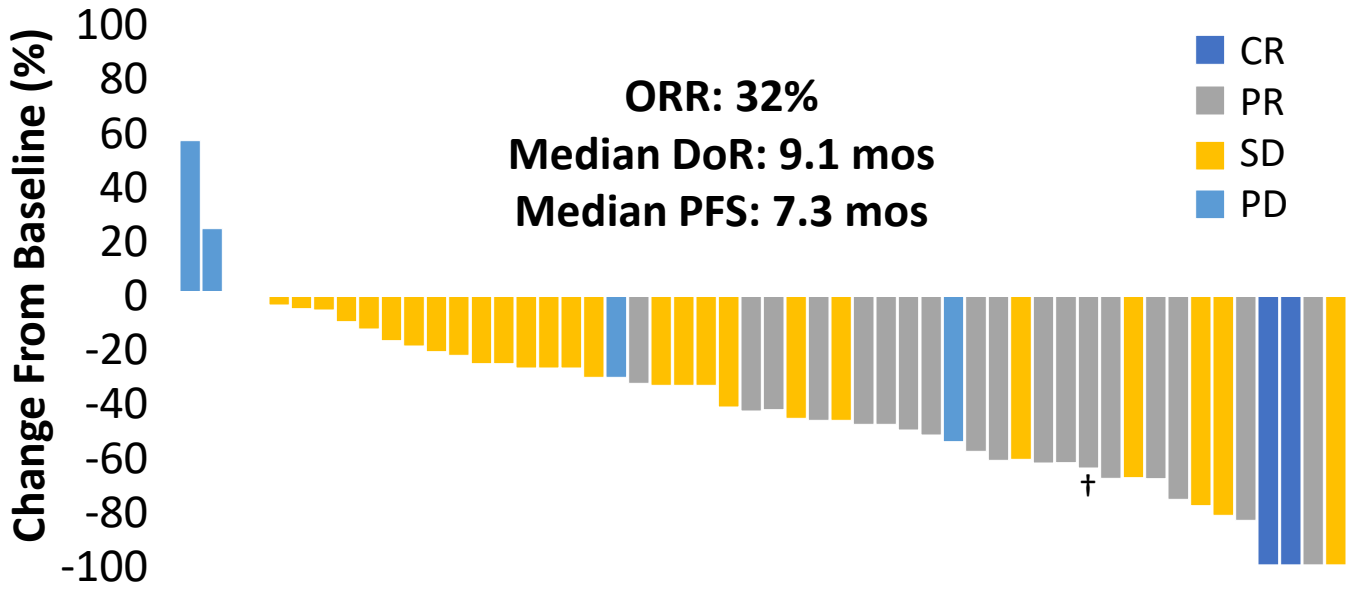
Drilon. Clin Cancer Res. 2016;22:2832. Awad. JCO. 2016;34:721. Tong. Clin Cancer Res 2016;22:3048.

Slide credit: clinicaloptions.com

PROFILE 1001: Crizotinib in *MET* Exon 14–Altered NSCLC

- Crizotinib: multikinase TKI approved for treatment of *ALK*+ and *ROS*+ NSCLC
- Open-label, multicohort phase I study evaluating efficacy, safety of crizotinib in NSCLC, including a *MET*ex14 expansion cohort (n = 69)
- MET inhibition with crizotinib a viable off-label option for patients with *MET* exon 14–altered NSCLC

Best % Change in Target Lesion Size from Baseline (n = 52*)



*Of 65 response-evaluable patients, 13 excluded from waterfall plot.
†*MET*ex14 alteration by local testing; *ROS1*+, WT *MET* by central testing.

MET TKI Potency

	Crizotinib	Cabozantinib	Savolitinib	Tepotinib	Capmatinib
IC_{50}, nM	22.5	7.8	2.1	~1.7-3.0	0.6

Drilon. Nat Med. 2020;26:47. Paik. ASCO 2019. Abstr 9005. Wolf. ASCO 2019. Abstr 9004.

Slide credit: clinicaloptions.com

Emerging MET TKIs in Clinical Trials for Advanced NSCLC With *MET* Exon 14 Skipping Mutations

- **Capmatinib:** highly selective MET inhibitor[1]
- 400mg bid
- Single-arm, multicohort, phase II study (GEOMETRY mono-1)
  - Cohort 4: Pretreated (2L/3L) (n = 69)
  - Cohort 5B: Tx naive (1L) (n = 28)
- Endpoints
  - Primary: ORR by BICR
  - Secondary: DoR by BICR, PFS, OS, safety
- Approved by the FDA in May 2020

- **Tepotinib (**Tepotinib（德邁特/TEPMETKO)健保給付規定自112年7月1日生效）**:** highly selective, ATP-competitive, reversible MET TKI[2]
- 500mg qd
- Single-arm, multicohort, phase II study (VISION)
  - Cohort A: *MET*ex14 skipping mutations as identified by tissue or liquid biopsy (n = 87)
- Endpoints
  - Primary: ORR by IRC
  - Secondary: ORR by investigator, DoR, objective disease control, PFS, OS, safety, HRQoL

1. Wolf. ASCO 2019. Abstract 9004. 2. Paik. ASCO 2019. Abstract 9005.

Slide credit: clinicaloptions.com

Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified NSCLC (GEOMETRY mono-1 ClinicalTrials)

- Pts : 364 with NSCLC with a *MET* exon 14 skipping mutation
  - ORR 41% : 69 pts (> 1 or 2 lines of therapy previously), DOR(duration of response): 9.7 months
  - ORR 68% : 28 pts (Naïve treatment) DOR : 12.6 months
  - Limited efficacy was observed in previously treated patients with *MET* amplification who had a gene copy number of less than 10 (ORR : 7 to 12%).
  - *MET* amplification >10 gene copy number (ORR : 29% of previous treated pts), Naïve : 40%
  - ADR : peripheral edema (in 51%) and nausea (in 45%); these events were mostly of grade 1 or 2.

N Engl J Med 2020; 383:944-957

Phase II VISION: Efficacy With Tepotinib in *MET*ex14 Mutation–Positive NSCLC

Tumor Response by IRC	
Pt group, n	ORR, %
Liquid biopsy, 66	48.5
Tissue biopsy, 60	50.0
Line of therapy	
•First, 43	44.2
•Second, 33	48.5
•Second or later, 56	48.2
•Third or later, 23	47.8

- Durability of response
  - Overall DoR (n = 99): 11.1 mos
- By L biopsy (n = 66): 9.9 mos
    - By T biopsy (n = 60): 15.7 mos
  - PFS:
    - By L biopsy (n = 66): 8.5 mos
    - By T biopsy (n = 60): 11.0 mos
- Both patients with and without CNS mets achieved benefit from treatment

Paik. NEJM 2020. [online ahead of print].

Slide credit: clinicaloptions.com

MET Inhibitor Safety Overview

TRAEs With Capmatinib,* n (%)	All Patients (N = 334)	
	Any Grade	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea†	111 (33.2)	6 (1.8)
Creatinine increased‡	65 (19.5)	0
Vomiting†	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Appetite decreased†	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

*≥ 10% of patients. †Capmatinib administered in fasting conditions at the time, a restriction that has since been removed. ‡Known to inhibit creatinine transporters.

TRAEs With Tepotinib,* n (%)	All Patients (N = 152)	
	Any Grade	Grade 3
Any	135 (89)	41 (27)†
Peripheral edema	96 (63)	11 (7)
Nausea	39 (26)	1 (1)
Diarrhea	33 (22)	1 (1)
Creatinine increased	27 (18)	1 (1)
Asthenia	12 (8)	1 (1)
Amylase increased	17 (11)	4 (3)†
ALT increased	11 (7)	4 (3)†
AST increased	10 (7)	3 (2)†
Hypoalbuminemia	24 (16)	3 (2)

*≥ 5% of patients.
†including grade 4: any (3), increased amylase (1), ALT (1), AST (1)

Paik. NEJM 2020. [online ahead of print]. Wolf. ASCO 2019. Abstr 9004.

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Thank you for listening

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癌症臨床藥物資料庫

本資料庫由癌症臨床藥師方麗華所建立，關注癌症藥物、補充治療資訊、兒童幹細胞移植等領域。
搜尋結果均以本站制定的格式編寫，提供專業人士及一般民眾更易閱讀的藥物資訊！

快速搜尋癌症藥物、用藥相關知識