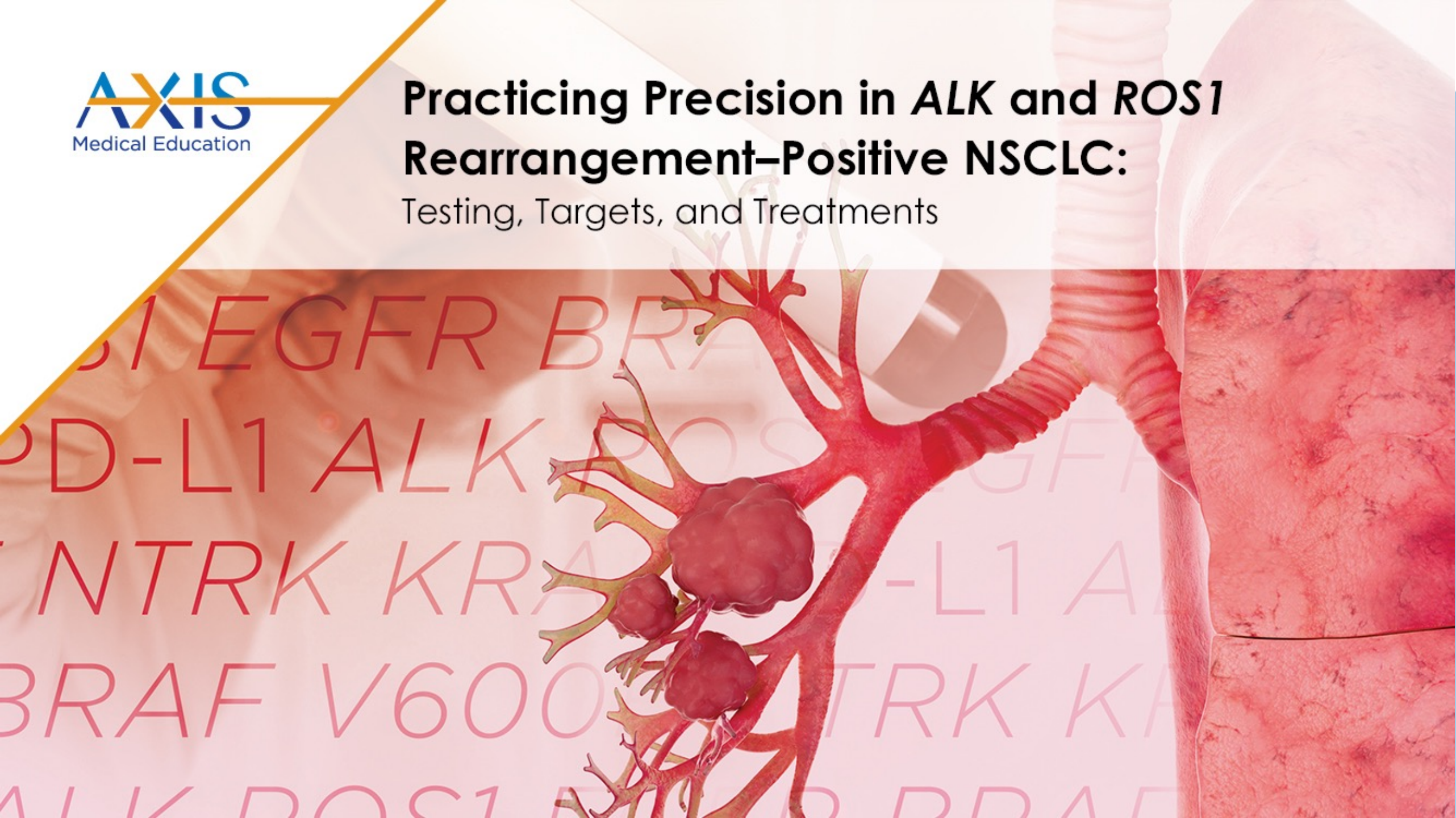
AXIS Medical Education

Practicing Precision in *ALK* and *ROS1* Rearrangement–Positive NSCLC:

Testing, Targets, and Treatments



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Disclosure of Conflicts of Interest

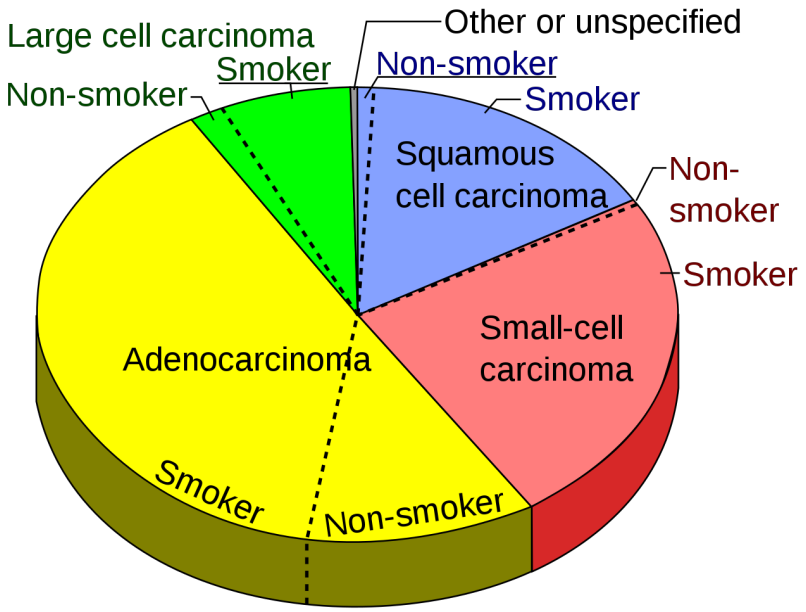
- **Maria E. Arcila, MD**, reported a financial interest/relationship or affiliation in the form of *Consultant*: Bristol-Myers Squibb Co, AstraZeneca Pharmaceuticals LP, and Janssen Oncology. *Serve(d) as a speaker or a member of a speakers bureau for:* Biocartis and Invivoscribe.

- **Alexander Drilon, MD**, reported a financial interest/relationship or affiliation in the form of *Advisory board*: Roche/Genentech/Ignyta; Loxo/Bayer/Lilly; Takeda Oncology/Ariad/Millenium; Turning Point Therapeutics, Inc; AstraZeneca Pharmaceuticals LP; Pfizer, Inc; Blueprint Medicines; Helsinn Therapeutics (US) Inc; BeiGene LTD; BerGenBio; Hengrui Therapeutics, Inc; Exelixis, Inc; Tyra Biosciences; Verastem Inc; MORE Health; and AbbVie. *Research grant*: Foundation Medicine. *Research support to Memorial Sloan Kettering Cancer Center*: Pfizer, Inc; Exelixis, Inc; GlaxoSmithKline; Teva Pharmaceuticals; Taiho Pharmaceutical Co, Ltd; and Pharma Mar, S.A. *Royalty*: Wolters Kluwer. *Other, Food and Beverage*: Merck & Co, Inc and PUMA Biotechnology.

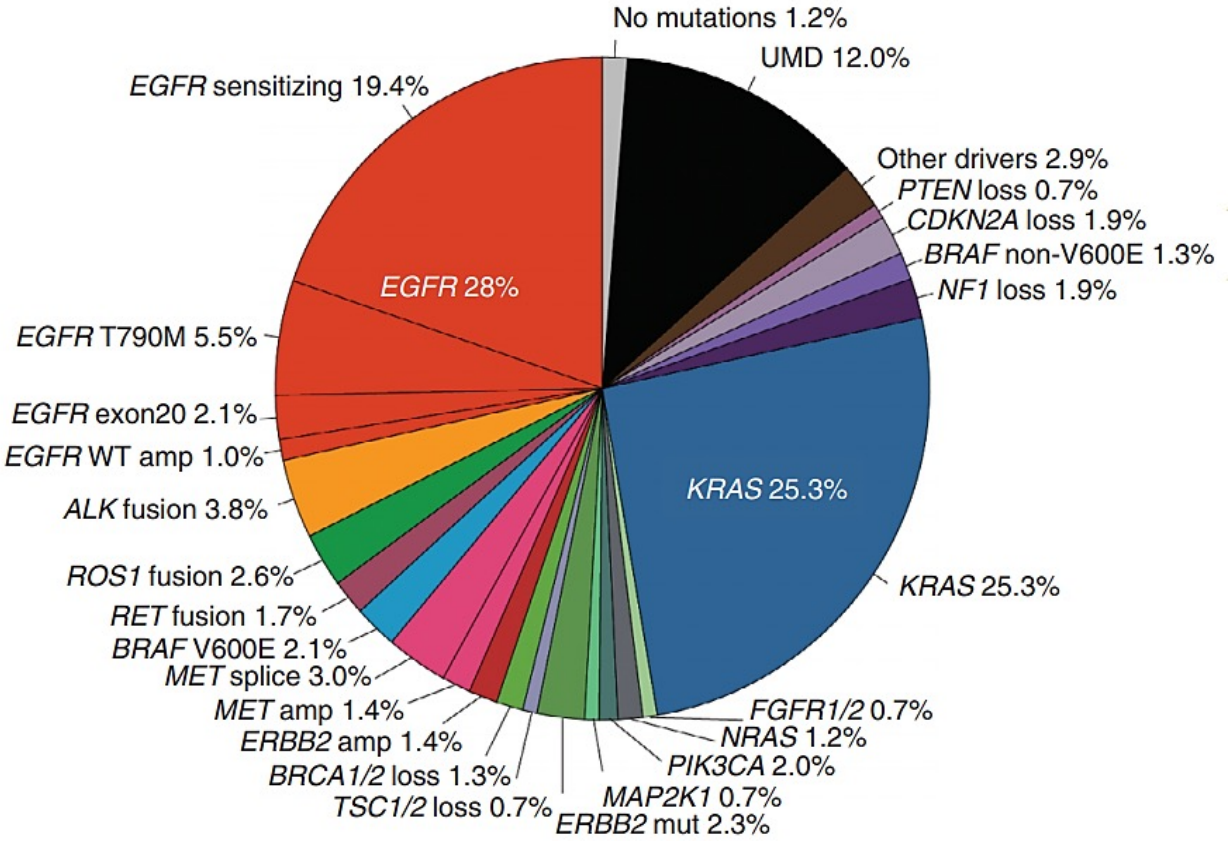
The Impact of Precision Medicine in NSCLC and Overview of Unique Subtypes of NSCLC

Lung Cancer: Molecular Heterogeneity

NSCLC is Heterogenous



Biomarker Distribution in Adenocarcinoma



Häggström M. 2014. https://upload.wikimedia.org/wikiversity/en/7/7b/Medical_gallery_of_Mikael_H%C3%A4ggstr%C3%B6m_2014.pdf; Jordan et al. *Cancer Discov*. 2017;7(6):596-609.

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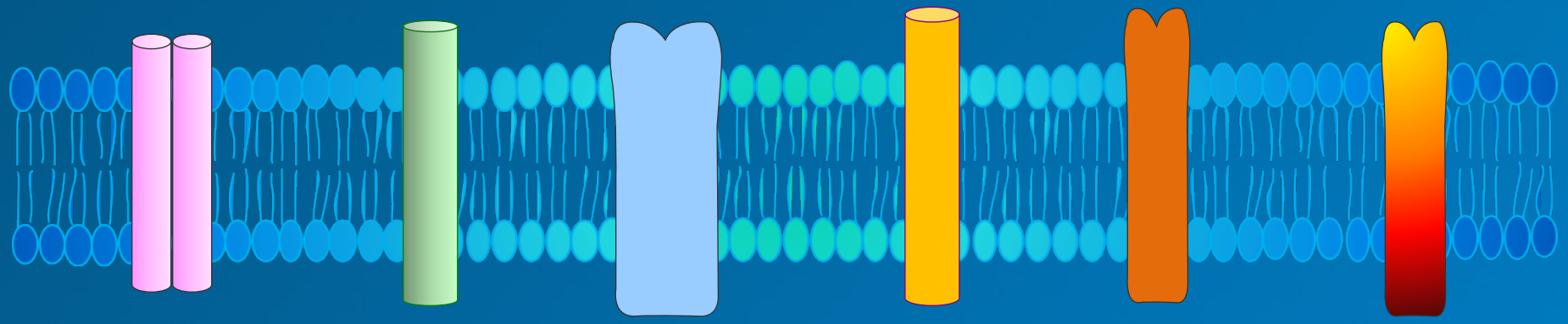
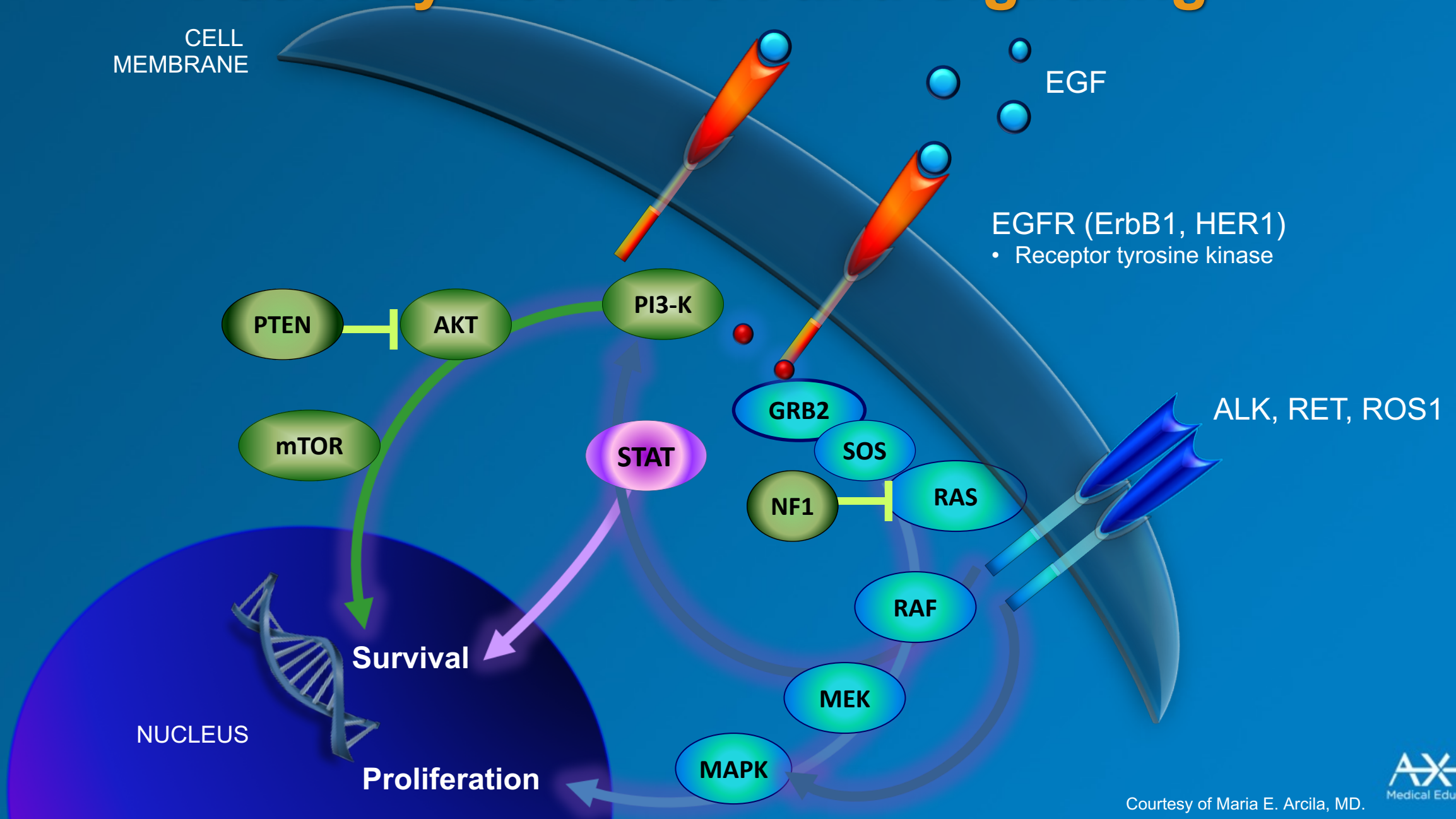
High Number of Receptor Tyrosine Kinases or Effectors in Common Downstream Pathways



EGFR, HER2	MET	ROS1	ALK	RET	TRK
Pathways (JAK-STAT, RAS/MAPK PI3K)	Pathways (RAS/MAPK PI3K)	Pathways (JAK-STAT, PI3K)	Pathways (JAK-STAT, PI3K)	Pathways (JAK-STAT, PI3K)	Pathways (JAK-STAT, PI3K)

Courtesy of Maria E. Arcila, MD.

Pathway Activation and Signaling



Courtesy of Maria E. Arcila, MD.

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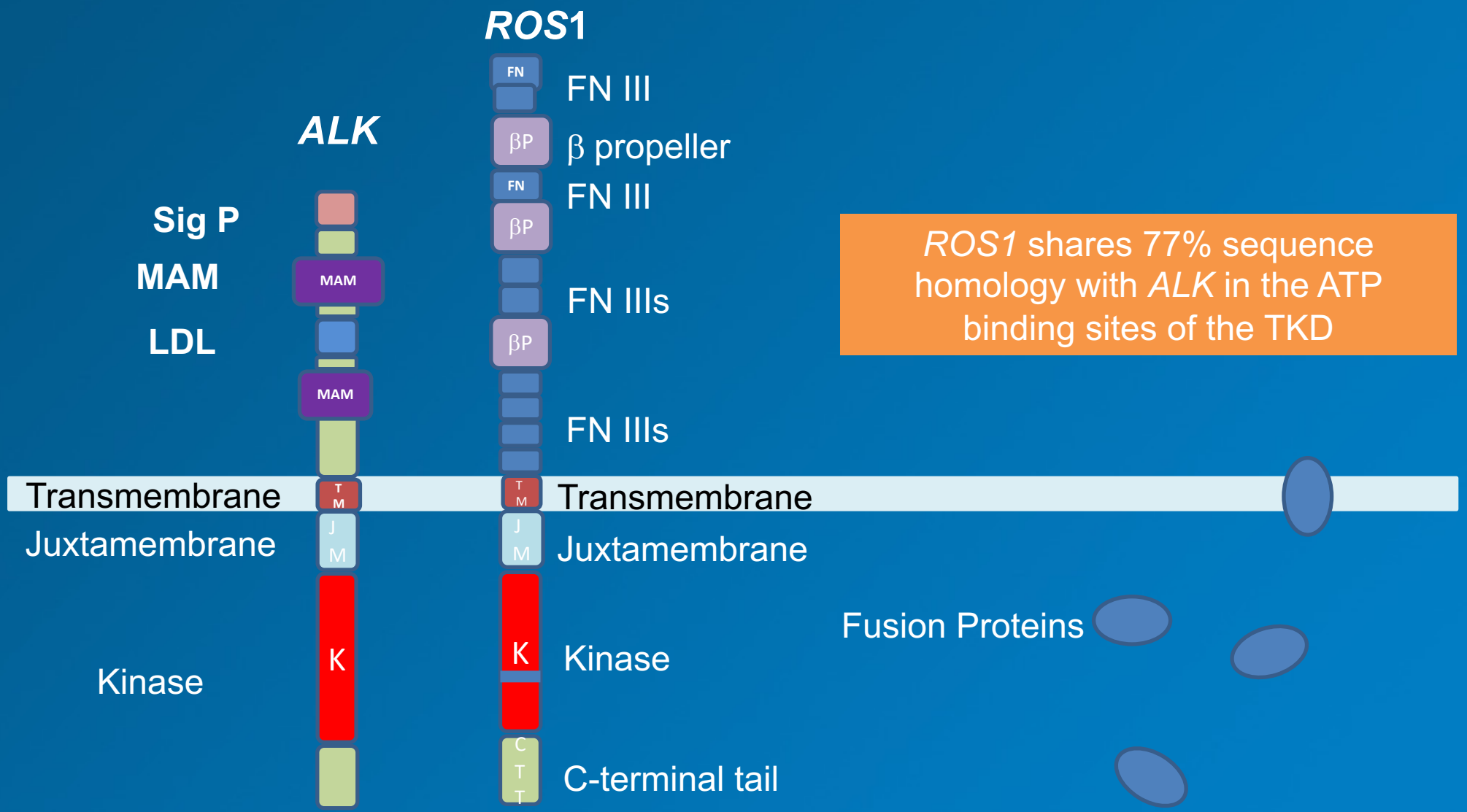
ALK and ROS1



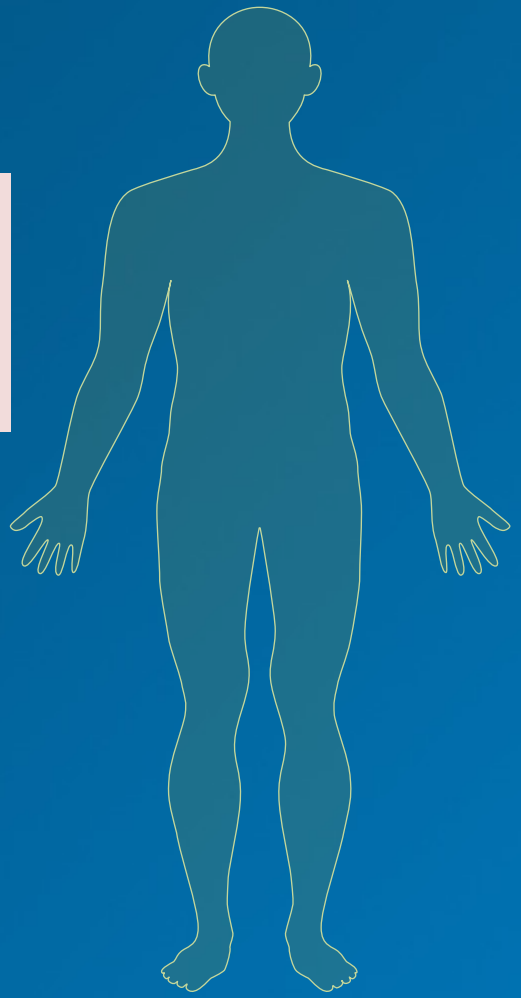
ROS1 shares 77% sequence homology with *ALK* in the ATP binding sites of the TKD

FN III, fibronectin III–like domain; LDL, low-density lipoprotein; MAM, meprin, A-5 protein, RTK phosphatase mu; Sig P, signal peptide; TKD, tyrosine kinase domain.

ALK Fusions

ALCL (~55%)
NPM1 (5q35.1)
TPM3 (1q21.3)
ATIC (2q35)
TFG (3q12.2)
TRAF1 (9q33.2)
CLTC (17q23.1)
RNF213 (17q25.3)
TPM4 (19p13.1)
MYH9 (22q12.3)
MSN (Xq12)
Additional rare rearrangements

DLBCL (<1%)
RANBP2 (2q13)
EML4 (2p21)
SEC31A (4q21.22)
SQSTM1 (5q35)
NPM1 (5q35.1)



Other Cancers

Breast Cancer
EML4 (2p21)

Colorectal Cancer (<1%)
EML4 (2p21)
WDCP (2p23.3)

Esophageal Cancer (ND)
TPM4 (19p13.1)

Ovarian cancer (ND)
FN1 (2q35)

Renal Cell Carcinoma (<1%)
VCL (10q22.2)
TPM3 (1q21.2)
EML4 (2p21)
STRN (2p22.2)

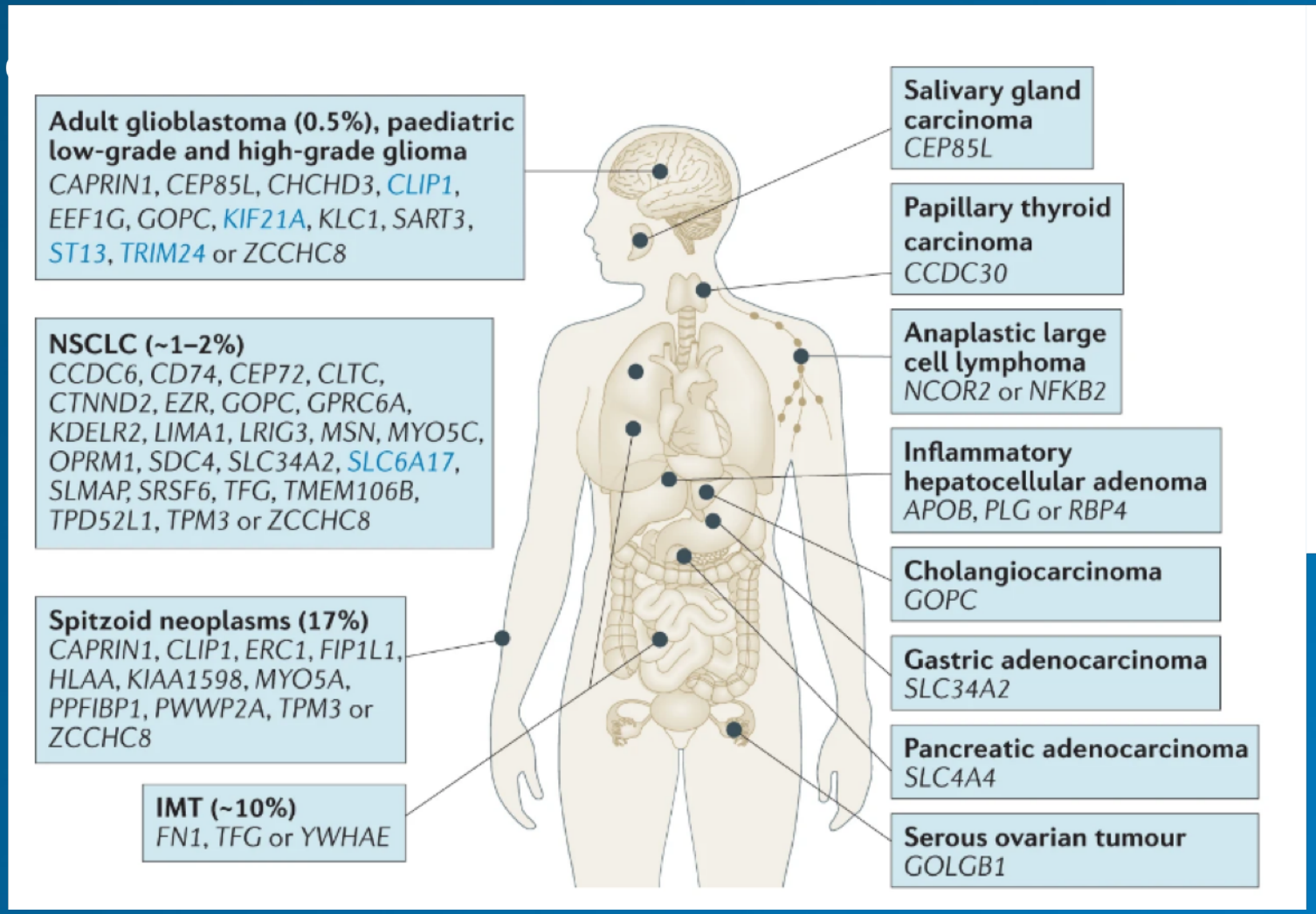
Renal Medullary Carcinoma (ND)
VCL (10q22.2)

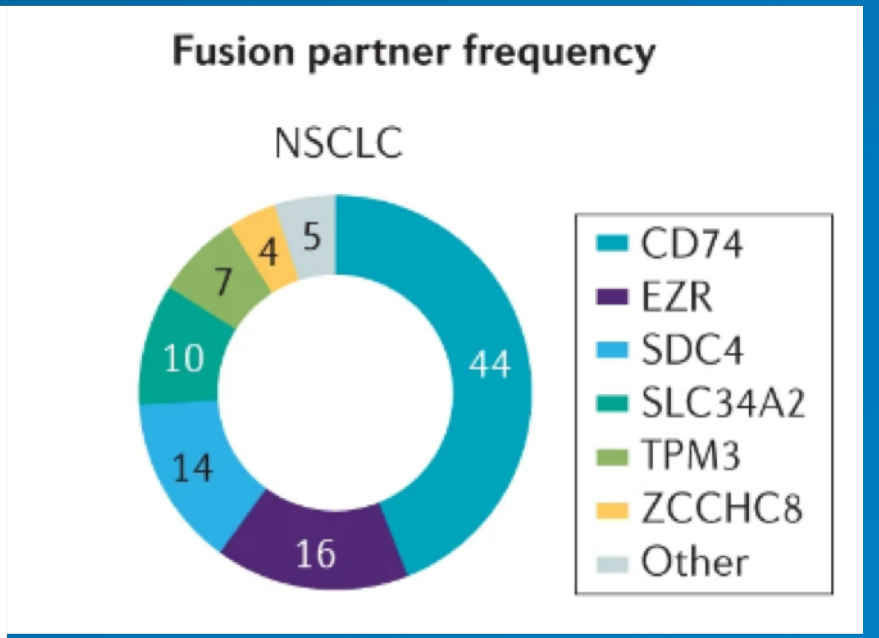
NSCLC (3-7%)
EML4 (2p21)
TPR (1q31.1)
CRIM1 (2p22.2)
STRN (2p22.1)
TFG (3q12.2)
HIP1 (7q11.23)
PTPN3 (9q31)
KIF5B (10p11.22)
KLC1 (14q32.3)
CLTC (17q23.1)

IMT (~50%)
TPM3 (1q21.3)
RANBP2 (2q13)
ATIC (2q35)
SEC31A (4q21.22)
CARS (11p15.4)
PPFIBP1 (12p11)
CLTC (17q23.1)
TPM4 (19p13.1)

ALK, anaplastic lymphoma kinase; ALCL, anaplastic large-cell lymphoma; ATIC, 5-Aminoimidazole-4-Carboxamide Ribonucleotide Formyltransferase/IMP Cyclohydrolase; CARS, cysteinyl-tRNA synthetase; CLTC, clatherin heavy chain; CRIM1, cysteine rich transmembrane BMP regulator 1; DLBCL, diffuse large B-cell lymphoma; EML4, echinoderm microtubule-associated protein-like 4; FN1, fibronectin 1; HIP1, huntingtin interacting protein 1; IMT, inflammatory myofibroblastic tumor; KIF5B, kinesin family member 5B; KLC1, kinesin light chain 1; MSN, moesin; MYH9, myosin heavy chain 9; N.D., not described; NPM1, nucleophosmin; NSCLC, non-small-cell lung cancer; PPFIBP1, PPFIA binding protein 1; PTPN3, protein tyrosine phosphatase, non-receptor type 3; RANBP2, RAN binding protein 2; RCC, renal cell carcinoma; RMC, renal medullary carcinoma; RNF213, ring finger protein 213; SEC31A, SEC31 Homolog A; SQSTM1, sequestosome 1; STRN, Striatin; TFG, TRK-fused gene; TPM3, tropomyosin 3; TPM4, tropomyosin 4; TPR, translocated promoter region, nuclear basket protein; TRAF1, TNF receptor associated factor 1; VCL, vinculin; WDCP, WD repeat and coiled coil containing.

ROS1 Fusions





From Drilon et al. *Nat Rev Clin Oncol*. 2020;18:35-55.

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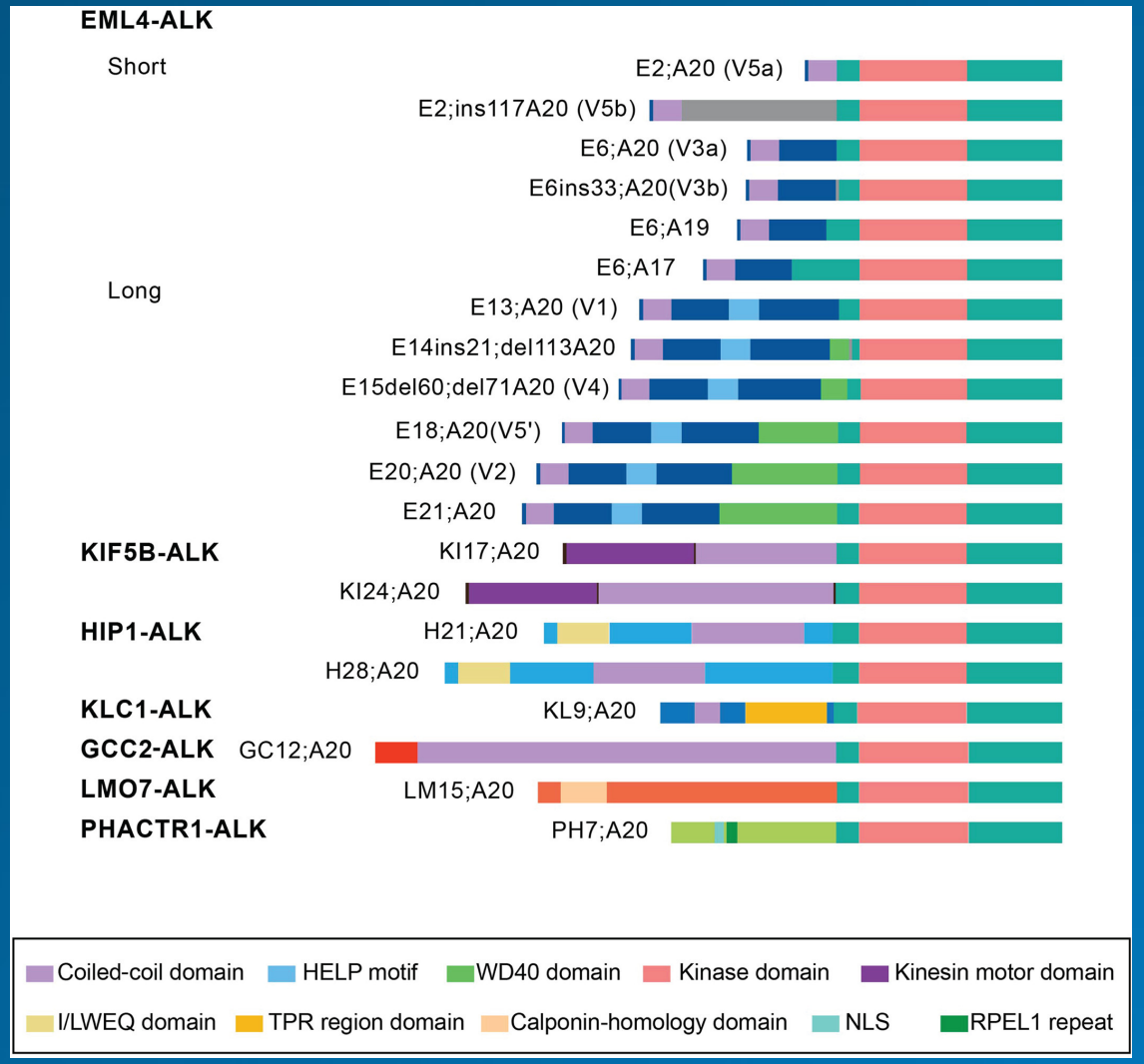
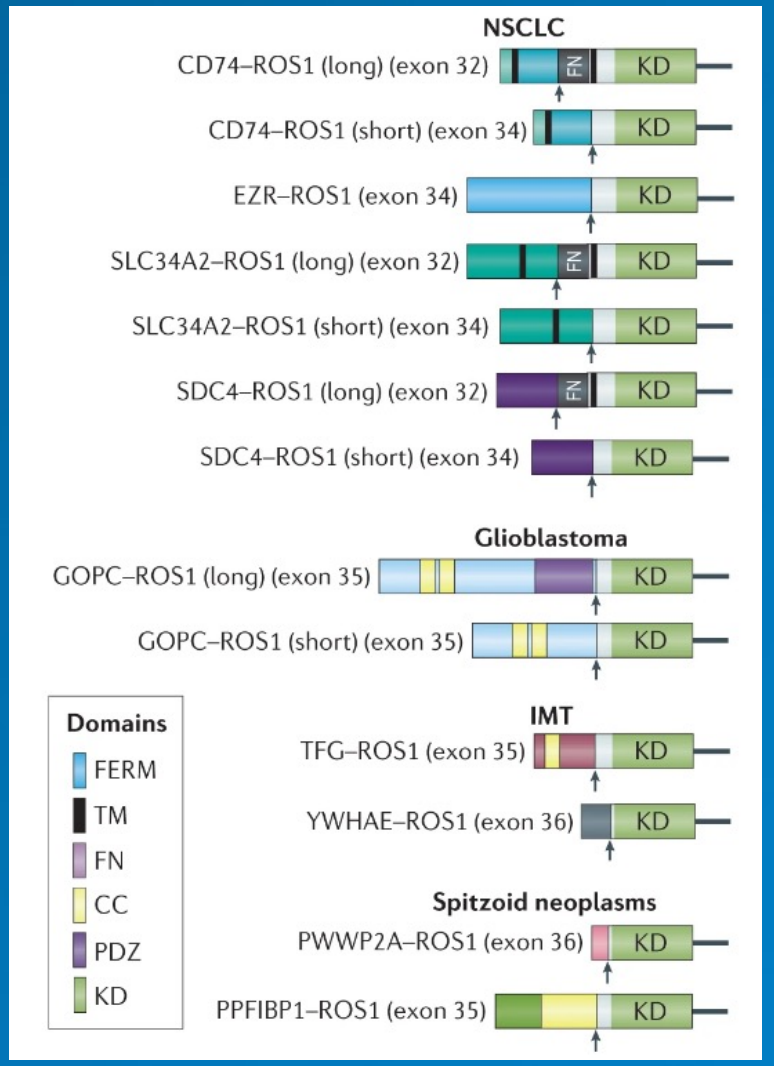
High Heterogeneity

Different Break Points, Different Partners

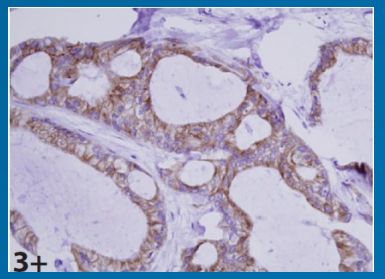




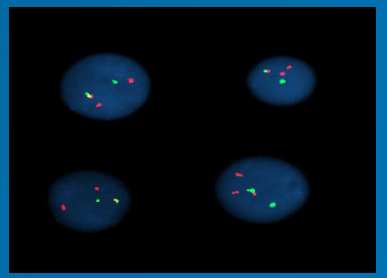
Noh K-W et al. *J Pathol*. 2017;243(3):307-319. Drilon et al. *Nat Rev Clin Oncol*. 202018;35-55.

Methods of Detection

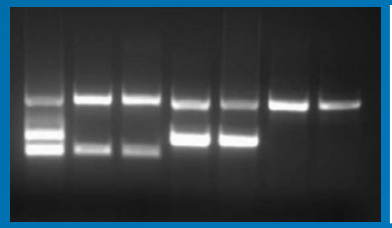
IHC
- Detects Protein expression - surrogate for fusion
  - No information on the breakpoint region or the partner

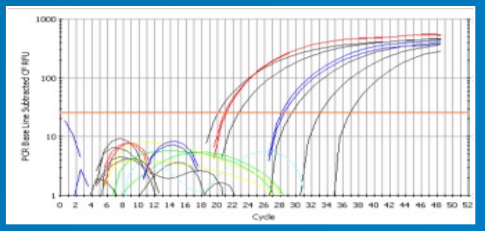


FISH
- Detects gene break – low throughput
  - Use fluorescent probes detect and localize specific DNA sequences - Generally 1-2 gene targets
- No information of breakpoint region or partner

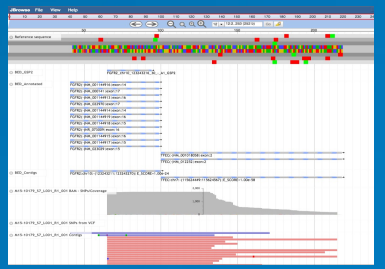


RT-PCR
- Low throughput fusion product detection
  - Detects few specific fusions depending on design





NGS
- High throughput detection
  - Comprehensive detection but depends on assay type and design

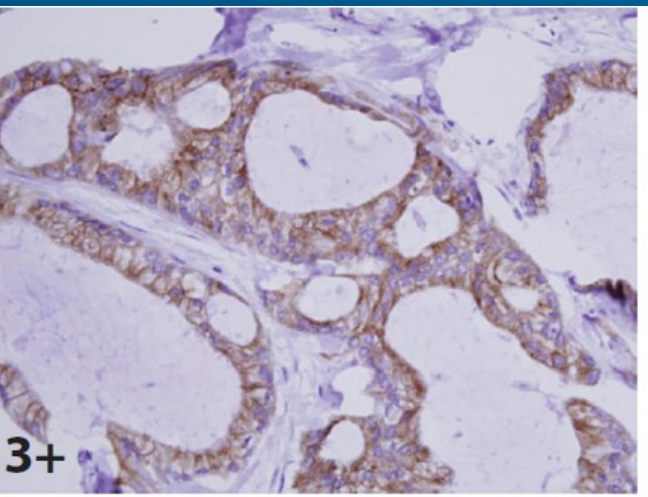


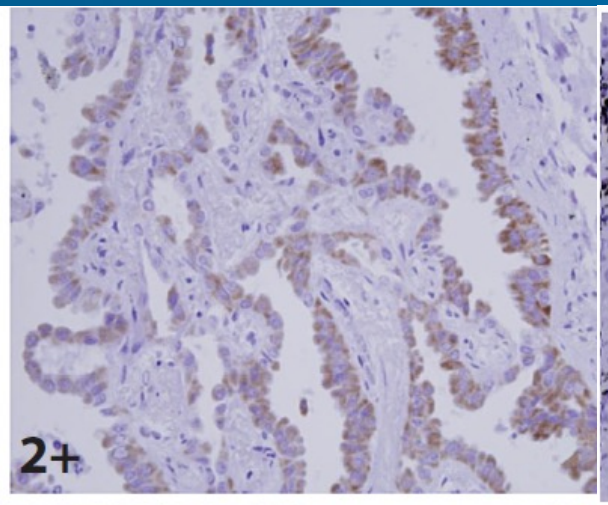
FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; RT-PCR, reverse transcriptase polymerase chain reaction.
Courtesy of Maria E. Arcila, MD.

Either IHC, FISH or NGS Can be Performed for *ALK* Testing

ALK IHC: Usually clearly positive or negative (95%), but occasionally equivocal (ALK D5F3 FDA approved)

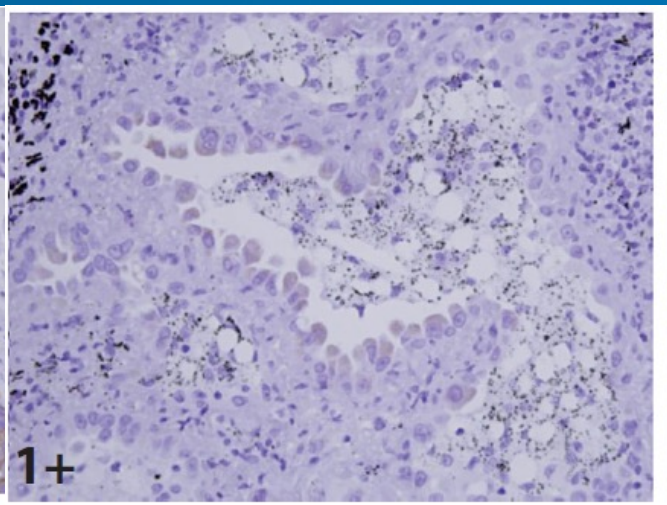
POSITIVE:
Strong-moderate cytoplasmic staining with membranous accentuation





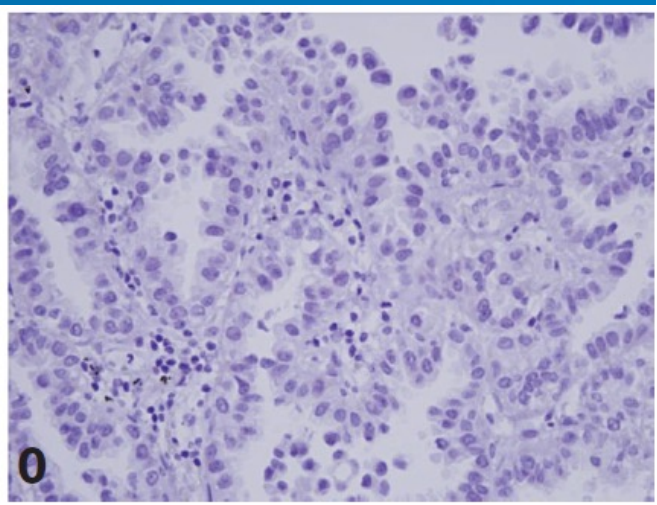
Sufficient to qualify for ALK inhibitors

Rare Cases -
equivocal 1+ staining



2018 Guideline:
Any weak equivocal staining must be confirmed with FISH/molecular

NEGATIVE



No further testing

FDA, US Food & drug Administration; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing.

Thunnissen et al. ALK testing with IHC. In: Tsao MS, Hirsch FR, Yatabe Y, eds. *International Association for the Study of Lung Cancer (IASLC) Atlas of ALK and ROS1 Testing in Lung Cancer*. 2nd ed. North Fort Myers, FL: Editorial Rx Press; 2016:26-33.

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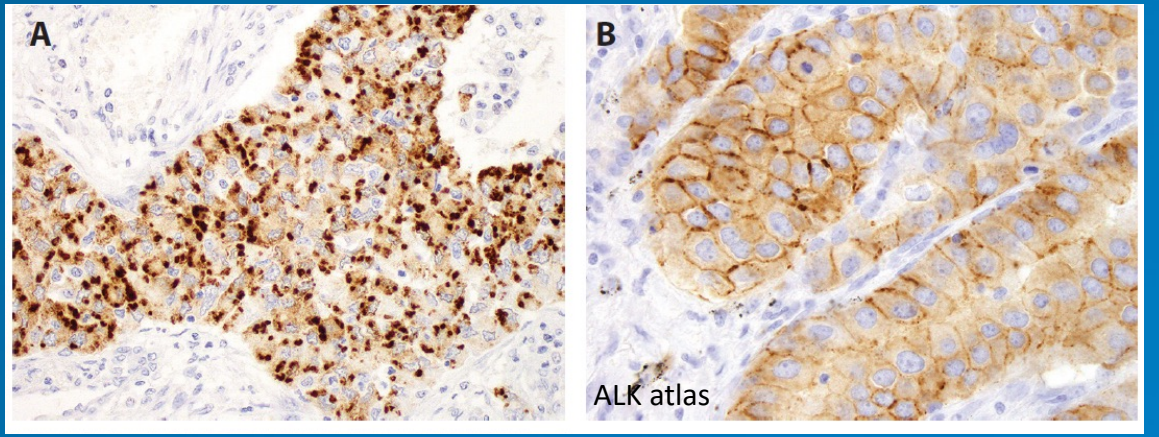
Testing for *ROS1* Fusions

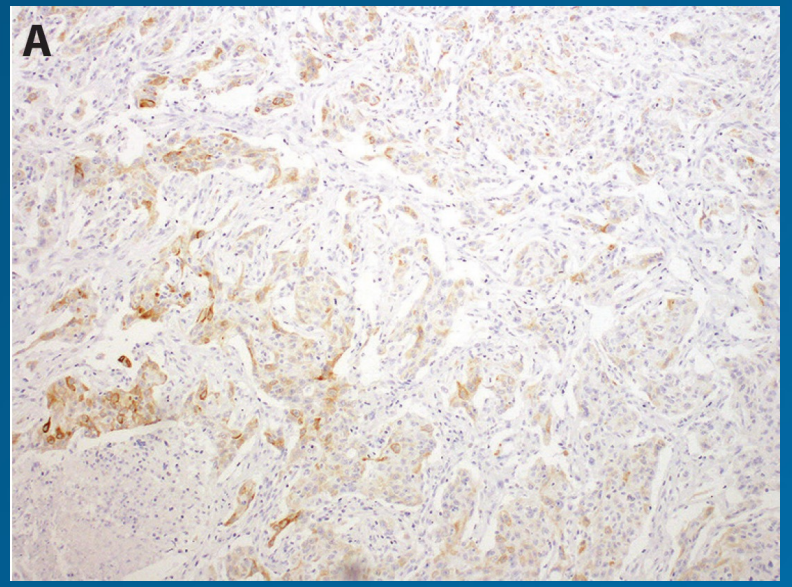
- Highly-sensitive antibody for *ROS1* – D4D6 is commercially available
- Fusion+ cases usually have diffuse/strong staining
- Unlike *ALK* – it has imperfect specificity (false-positive staining in fusion-negative cases)



Patterns vary with *ROS1* fusion partners
(Cytoplasmic +/- membranous accentuation, some globular staining)
Strong/diffuse

Courtesy of Maria E. Arcila, MD.

ROS1: Nonspecific Staining in Fusion-Negative Cases



- Nonspecific staining is typically patchy and weak
- Rate of nonspecific staining reported as 5%-10% (higher if focal staining is included)

IASLC Guidelines	
ROS1 testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics	Strong recommendation
ROS1 IHC may be used as a screening test in lung adenocarcinoma patients; however, positive ROS1 IHC results should be confirmed by a molecular or cytogenetic method.	Expert consensus opinion

IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry.

Tsao et al eds. *International Association for the Study of Lung Cancer (IASLC) Atlas of ALK and ROS1 Testing in Lung Cancer*. 2nd ed. North Fort Myers, FL: Editorial Rx Press; 2016:26-33.

Practicing Precision in *ALK*+ NSCLC: Overview of ALK Targeted Agents for NSCLC

First-Line TKI Therapy: Study Design of Regulatory Data Sets

ALK Inhibitors: Trial Design

KEY ELIGIBILITY

- Advanced or metastatic *ALK*+ NSCLC
- *ALK*+ by central IHC testing
- ALK inhibitor-naïve
- ECOG PS 0–2
- Measurable disease
- Asymptomatic brain metastases allowed

Alectinib
ALEX 600mg BID, n=152
J-ALEX 300mg BID, n=103

Brigatinib
ALTA-1L 180 mg QD, n = 137

Lorlatinib
CROWN 100 mg QD, n = 149

Ensartinib
eXalt3 225 mg QD, n = 143

Crizotinib
250 mg BID

ENDPOINTS

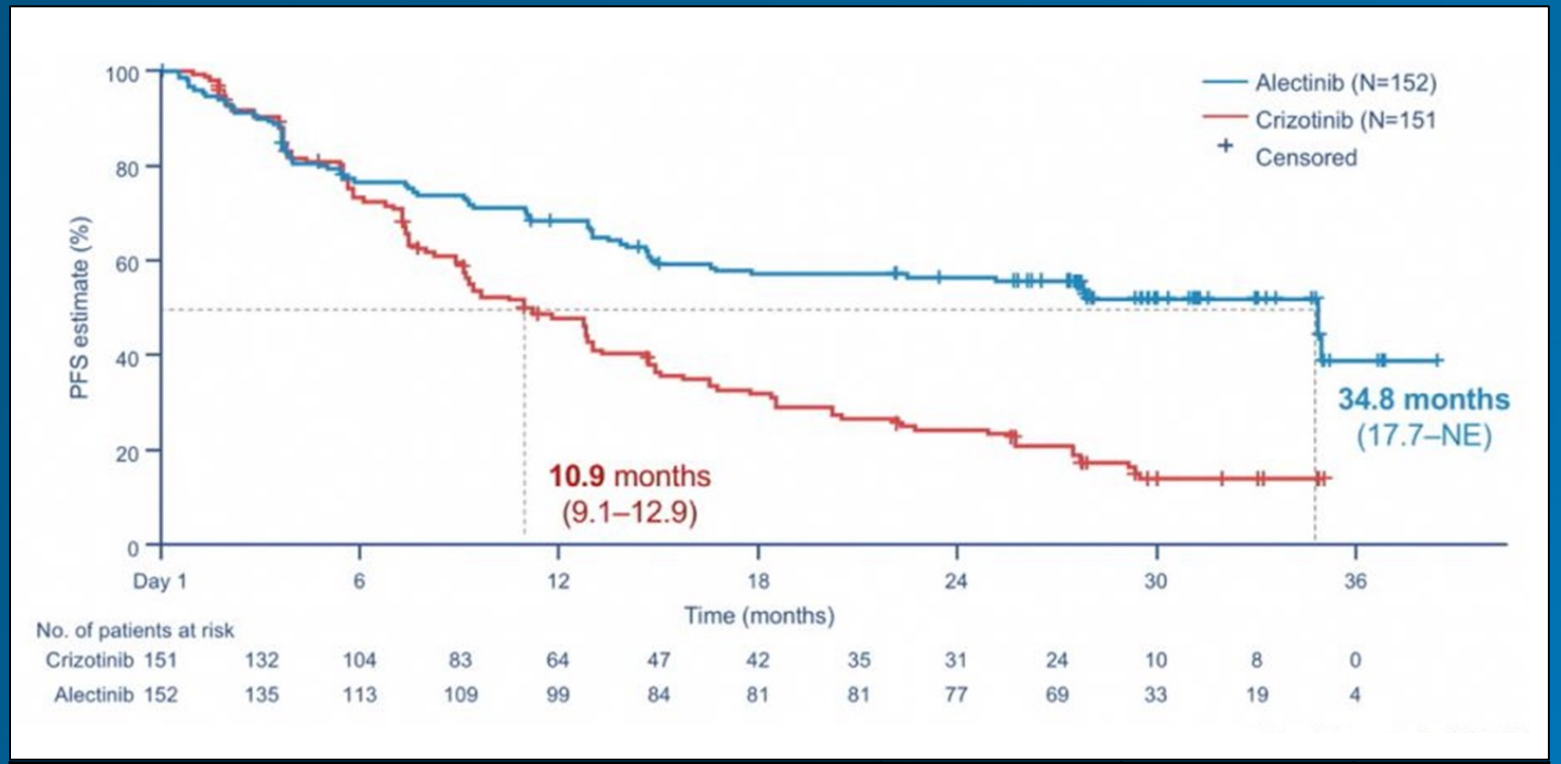
- Primary:
  - PFS
- Secondary:
  - ORR
  - OS
  - CNS outcomes
  - Safety and tolerability
  - Patient-reported outcomes

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily.

Peters et al. *N Engl J Med*. 2017;377:829-838; Hida et al. *Lancet*. 2017;390(10089):29-39; Camidge et al. *N Engl J Med*. 2018;379:2027-2039; Shaw et al. *N Engl J Med*. 2020;383:2018-2029; Horn et al. 2020 WCLC, abstract 2.

ALEX: Alectinib Superior to Crizotinib in First-Line Setting

Progression-Free Survival



Median PFS, mo	Crizotinib	Alectinib	HR
Final median PFS, investigator-assessed	10.9	34.8	0.43
Patients **with** baseline CNS metastases	7.4	25.4	0.37
Patients **without** baseline CNS metastases	14.8	38.6	0.46

Overall Survival*

Result	Crizotinib	Alectinib	HR
Median OS	57.4 mo	NR	0.67
5-year OS	45.5%	62.5%	

*OS data immature

CNS, central nervous system; NR, not reached; OS, overall survival; PFS, progression-free survival.

Camidge et al. *J Thorac Oncol*. 2019;14(7):1233-1243; Mok et al. *Ann Oncol*. 2020;31(8):1056-1064. Peters et al. *N Engl J Med*. 2017;377:829-838.

J-ALEX: Progression-Free Survival

PFS (IRF-assessed)	Crizotinib	Alectinib
Median PFS, mo	10.2	Not reached
HR	0.34	
P	<.0001	
Final median PFS, mo	10.2	34.1
HR	0.37	

IRF, independent review facility; PFS, progression-free survival.

Hida et al. *Lancet* 2017;390(10089):29-39; Nakagawa et al. *Lung Cancer* 2020;139:195-199.

ALTA-1L: Progression-Free Survival
Brigatinib Superior to Crizotinib in First-Line Setting

PFS	Crizotinib	Brigatinib
First prespecified interim analysis BIRC-assessed estimated 12-month PFS, %	43%	67%
HR	0.49	
P	<.001	
Second interim analysis BIRC-assessed median PFS, mo	11.0	24.0
HR	0.49	
P	<.0001	
Second interim analysis investigator-assessed median PFS, mo	9.2	29.4
HR	0.43	

BIRC, blinded independent review committee; PFS, progression-free survival.

Camidge et al. *N Engl J Med*. 2018;379:2027-2039; *J Clin Oncol*. 2020;38:3592-3603.

CROWN: Progression-Free Survival

PFS	Crizotinib	Lorlatinib
BIRC-assessed median PFS, mo	9.3	NR
HR	0.28	
P	<.001	
12-month PFS, %	39%	78%
HR	0.28	
P	<.001	
Investigator-assessed 12-month PFS, %	35%	80%
HR	0.21	

BIRC, blinded independent review committee; NR, not reached; PFS, progression-free survival.
Shaw et al. *N Engl J Med*. 2020;383:2018-2029.

ALK+ NSCLC: First-Line ALK Inhibitor Summary

	Alectinib		Brigatinib	Lorlatinib	Ceritinib	Crizotinib
Trial	ALEX	J-ALEX	ALTA-1	CROWN	ASCEND-4	PROFILE 1014
Comparator	crizotinib		crizotinib	crizotinib	chemotherapy	chemotherapy
Median PFS, months	34.8 (HR 0.43)	34.1 (HR 0.37)	24.0 (HR 0.49)	NR (HR 0.28)	16.6 (HR 0.55)	10.9 (HR 0.45)

Mok et al. *Ann Oncol*. 2020;31:P1056-1064; Nakagawa et al. *Lung Cancer* 2020;139:195-199; Camidge et al. *J Clin Oncol*. 2020;38:3592-3603; Shaw et al. *N Engl J Med*. 2020;383:2018-2029; Soria et al. *Lancet* 2017;389:917-929; Solomon et al. *N Engl J Med*. 2014;371:2167-2177.

eXalt3: Progression-Free Survival

PFS	Crizotinib	Ensartinib
ITT population BIRC-assessed median PFS, mo	12.7	25.8
HR	0.51	
P	<.0001	
Modified ITT population BIRC-assessed median PFS, mo	12.7	NR
HR	0.51	
P	.001	

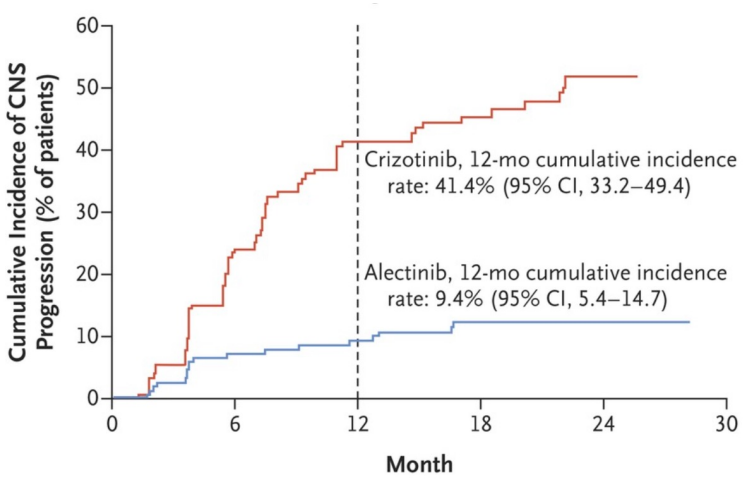
- ITT population: patients with locally tested ALK+ NSCLC
- Modified ITT population: all centrally ALK+ patients by Abbott FISH test

BIRC, blinded independent review committee; ITT, intention to treat; PFS, progression-free survival; NR, not reached.
Horn et al. 2020 World Conference on Lung Cancer. Presidential Symposium. Abstract 2.

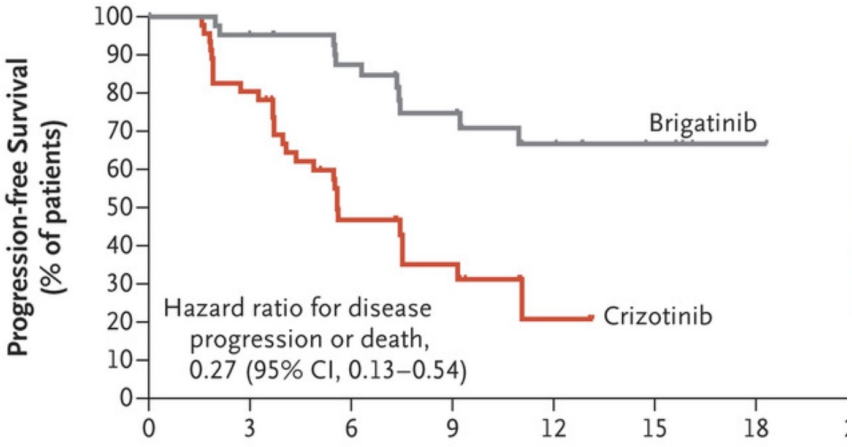
CNS Activity of Next-Generation ALK Inhibitors

ALK TKI CNS Outcomes

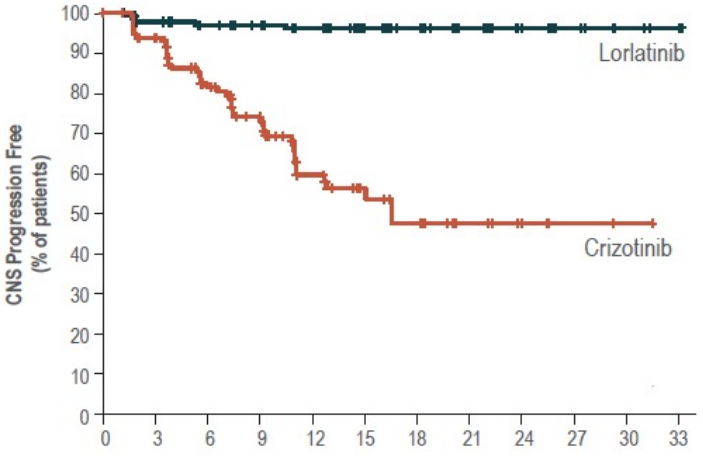
Alectinib



Brigatinib



Lorlatinib



Camidge et al. *J Thorac Oncol*. 2019;14(7):1233-1243; Mok et al. *Ann Oncol*. 2020;31(8):1056-1064. Peters et al. *N Engl J Med*. 2017;377:829-838.

ALK TKI Therapy versus Chemotherapy

PROFILE 1014: Study Design

KEY ELIGIBILITY

- *ALK* positive with central FISH testing*
- Locally advanced, recurrent, or metastatic non-squamous NSCLC
- No prior systemic treatment for advanced disease
- ECOG PS 0–2
- Measurable disease
- Stable treated brain metastases allowed

R
1:1

Crizotinib
250 mg BID PO,
continuous dosing
(n = 172)

Pemetrexed 500 mg/m^2
+
cisplatin 75 mg/m^2
or
carboplatin AUC 5-6 q3w
for ≤6 cycles
(n = 171)

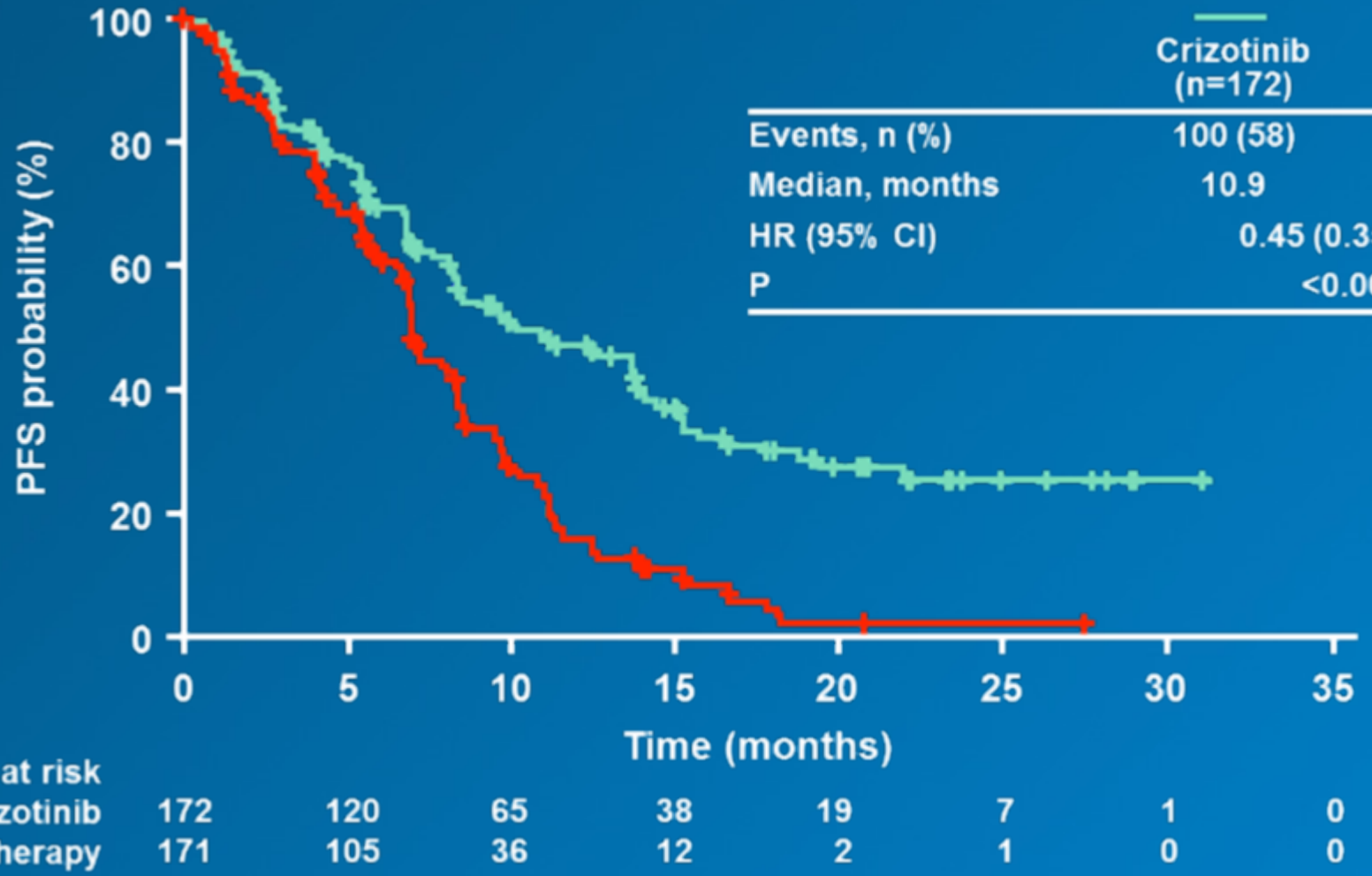
CROSSOVER TO CRIZOTINIB
PERMITTED AFTER PROGRESSION¶

ENDPOINTS

- Primary:
  - PFS (RECIST 1.1, IRR)
- Secondary:
  - ORR
  - OS
  - Safety
  - Patient-reported outcomes (EORTC QLQ-C30, LC13, EQ-5D)

**ALK* status determined using standard *ALK* break-apart FISH assay.
‡Stratification factors: ECOG PS (0/1 vs. 2), Asian vs. non-Asian race, and brain metastases (present vs. absent).
¶Assessed by IRR.
AUC, area under the curve; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IRR, independent radiologic review; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; q3w, every 3 weeks.
Solomon et al. *N Engl J Med*. 2014;371:2167-2177.

PROFILE 1014: Progression-Free Survival



	Crizotinib (n=172)	Chemotherapy (n=171)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35–0.60)	
P	<0.0001	

PFS, progression-free survival.
Adapted from Solomon et al. *N Engl J Med*. 2014;371:2167-2177.

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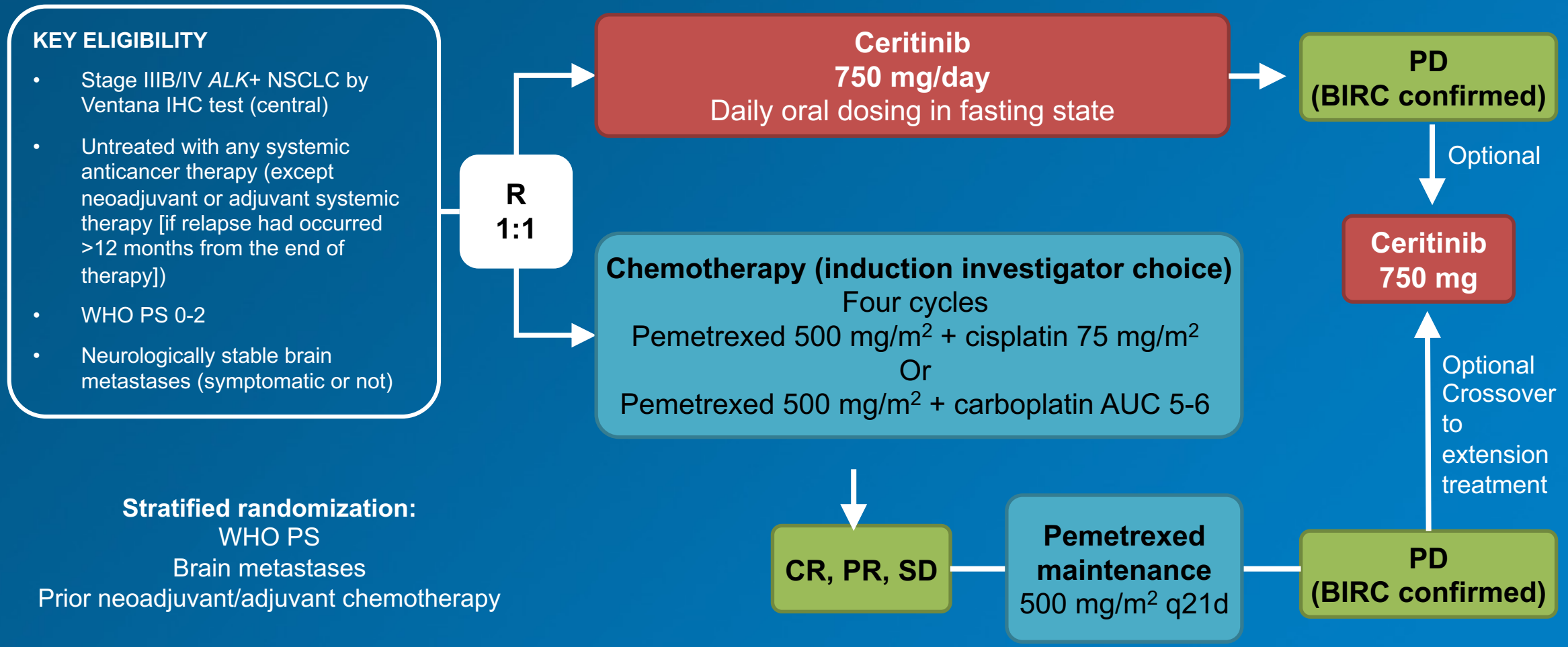
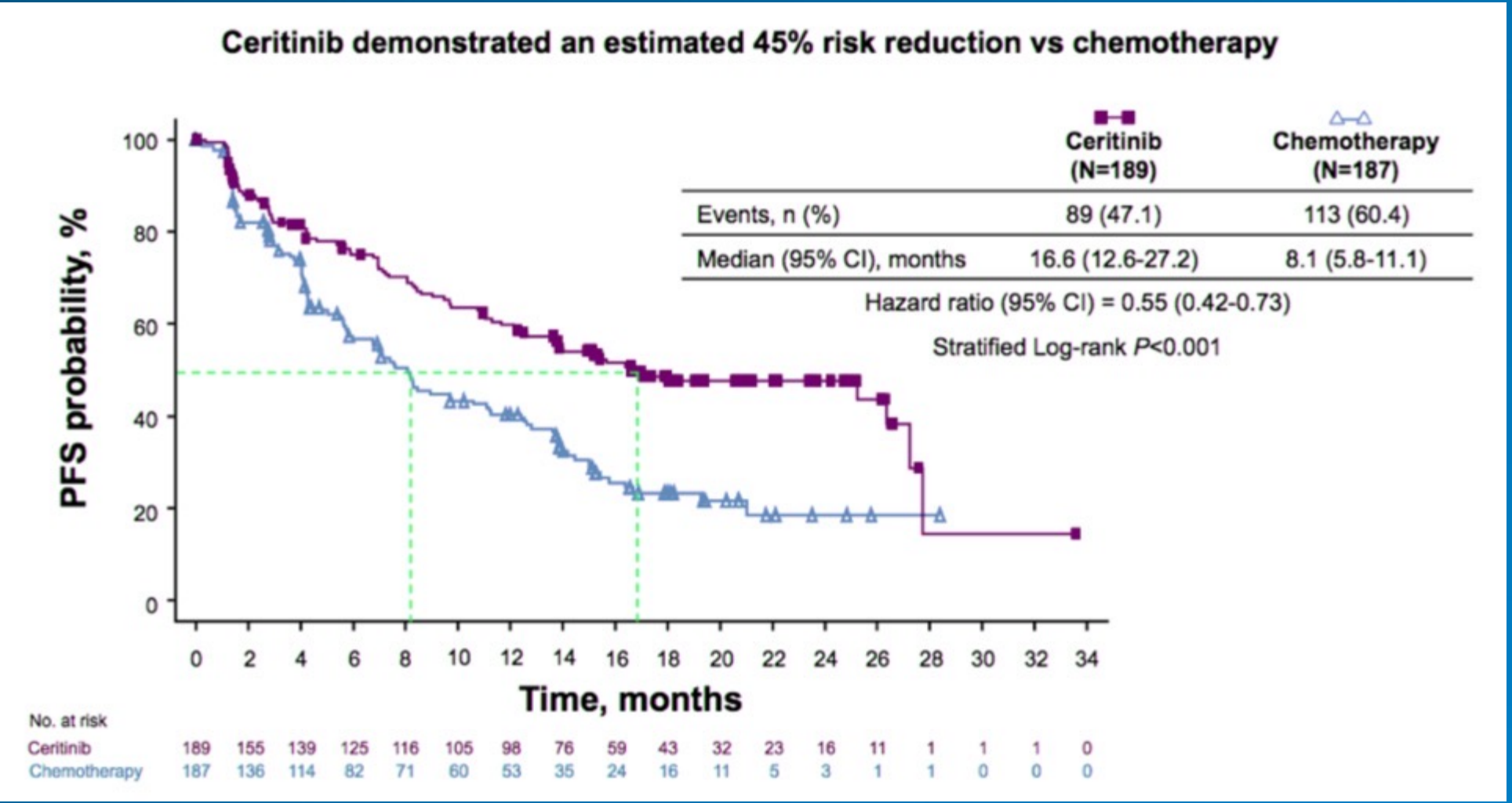
ASCEND-4: Study Design



AUC, area under the curve; BIRC, blinded independent review committee; CR, complete response; IHC, immunohistochemistry; NSCLC, non–small cell lung cancer; PD, progressive disease; PR, partial response; PS, performance status; q21d, every 21 days; R, randomized; SD, stable disease; WHO, World Health Organization.

Soria et al. *Lancet* 2017;389:917-929.

ASCEND-4: Progression-Free Survival



PFS, progression-free survival.
Adapted from Soria et al. *Lancet* 2017;389:917-929.

Sequential TKI Therapy

ALK Rearrangement–Positive Advanced/Metastatic NSCLC: Subsequent Therapy Options

ALK Inhibitor	Trial(s)	Reference(s)
Alectinib	NP28673 Phase 2	Ou et al. *J Clin Oncol*. 2016;34:661-668. Shaw et al. *Lancet Oncol*. 2016;17:234-242.
Brigatinib	Phase 2 ALTA	Kim et al. *J Clin Oncol*. 2017;35:2490-2498.
Ceritinib	ASCEND-5	Shaw et al. *Lancet Oncol*. 2017;18:874-886.
Lorlatinib	Phase 2	Solomon et al. *Lancet Oncol*. 2018;19:1654-1667.

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 5.2021.

Adverse Effects of ALK TKIs

	Alectinib	Brigatinib	Lorlatinib	Ceritinib
Dose reduction	20%	38%	22%	20%
AE profile includes	Transaminitis	Pneumonitis	Hyperlipidemia, Cognitive changes	Gastrointestinal side-effects

AE, adverse event; TKIs, tyrosine kinase inhibitors.

Mok et al. *Annals of Oncology*. 2020;31:P1056-1064; Camidge et al. N Eng J Med. 2018;379:2027-2039; Shaw et al. *N Engl J Med*. 2020;383:2018-2029; Solomon et al. *N Engl J Med*. 2014;371:2167-2177.

Virtual Tumor Board 1

ALK+ Case Study

- 32-year-old woman never smoker who has a 3-cm lung mass, multiple intrathoracic enlarged lymph nodes, liver and bone metastases
- A biopsy specimen of a liver metastasis shows adenocarcinoma consistent with a lung primary
- PD-L1 expression is 95%
- Outside testing shows no *EGFR* mutations and *KRAS* was not mutated
- Plasma ctDNA testing returns negative

From a diagnostic perspective, what is the next step?

ALK+ Case Study

- Tumor sample sent for next-generation sequencing using DNA-based assay
- Comprehensive evaluation including multiple fusions, mutations and copy number changes in 450 genes was unremarkable for an oncogenic driver

From a diagnostic perspective, what is the next step?

ALK+ Case Study

- Leftover tumor is sent for RNA-based targeted sequencing
- An *EML4-ALK* fusion is identified
- An MRI of the brain shows a few subcentimeter lesions
- The patient is asymptomatic except for a mild cough

What is your preferred treatment?

ALK+ Case Study

- The patient was treated with brigatinib and had 2 years of disease control with therapy
- Thereafter, a solitary bone metastasis with a substantial soft tissue component begins to grow

What is the next diagnostic step?

ALK+ Case Study

- Biopsy of the metastatic lesion confirms lung adenocarcinoma
- Molecular profiling shows persistence of the *ALK* fusion, now with an acquired *ALK* G1202R mutation

What is the next therapeutic step?

Practicing Precision in *ROS1*+ NSCLC: Overview of ROS1-Targeted Agents for NSCLC

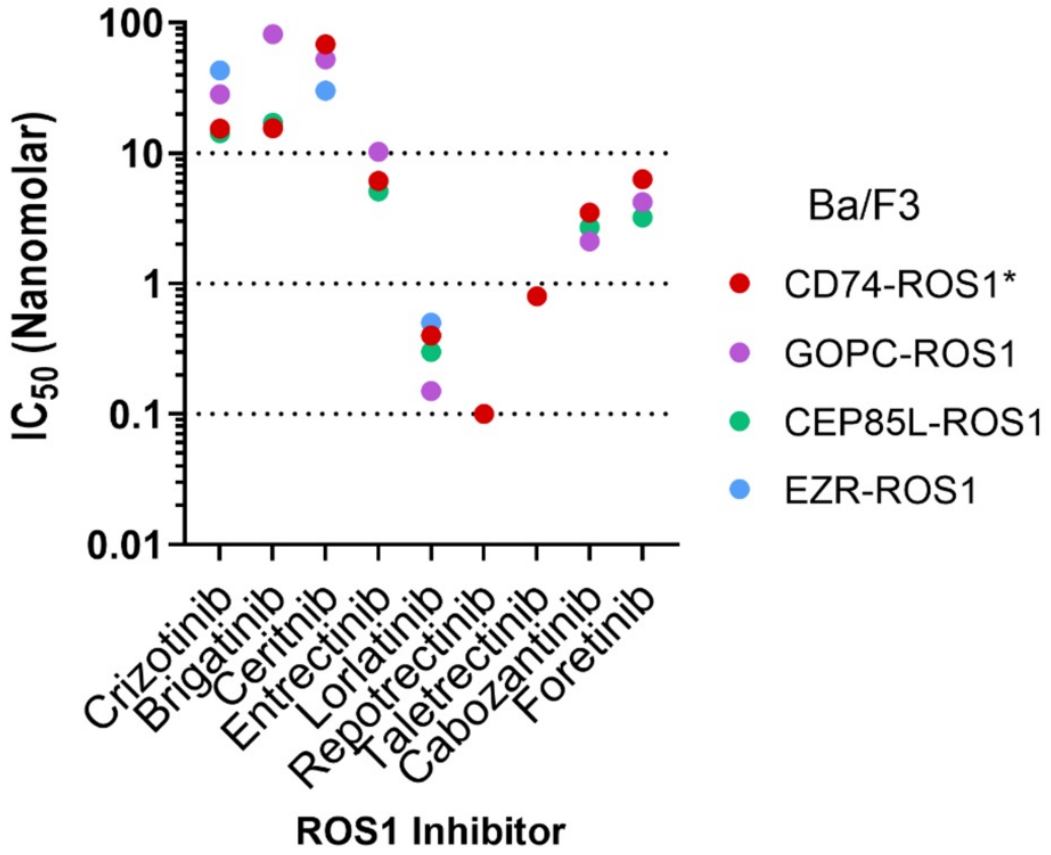
ROS1 Rearrangement–Positive Advanced/Metastatic NSCLC

NCCN® Recommendation	Drug	Trial(s)	Reference(s)
First-Line Therapy			
Preferred	Entrectinib*	ALKA-372-001 STARTRK-1 STARTRK-2	Drilon et al. *Lancet Oncol*. 2020;21:261-270.
	Crizotinib	PROFILE 1001	Shaw et al. *N Engl J Med*. 2014;371:1963-1971.
Other recommended	Ceritinib	Phase 2	Lim et al. *J Clin Oncol*. 2017;35:2613-2618.
Subsequent Therapy			
	Lorlatinib	Phase 2	Solomon et al. *Lancet Oncology*. 2018;19:1654-1667. Shaw et al. *J Clin Oncol*. 2019;37:1370-1379.
	Entrectinib (CNS PD)**	ALKA-372-001 STARTRK-1 STARTRK-2	Drilon et al. *Lancet Oncol*. 2020;21:261-270.

*Entrectinib may be better for patients with brain metastases.
**Entrectinib is primarily for patient with CNS progression after crizotinib.
Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 5.2021.

Early- and Next-Generation ROS1 TKIs have Varying Potencies

Inhibitory activity of ROS1 TKIs against different *ROS1* fusions in Ba/F3 cell assays



Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

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Early-Generation ROS1 TKIs Are Active in TKI-Naïve Patients

ROS1 TKI	Study (phase)	ORR	Median DoR, mo	Median PFS, mo	Median OS, mo
Crizotinib	PROFILE 1001 (1b)	72%	24.7	19.3	51.4
	OxOnc (2)	72%	19.7	15.9	-
	EUCROSS (2)	70%	19.0	20.0	-
	AcSe (2)	69%	-	5.5	17.2
	METROS (2)	65%	21.4	22.8	-
Entrectinib	Drilon et al. (1/2)	77%	24.6	19.0	-
Ceritinib	Lim et al. (2)	67%	21.0	19.3	24.0
Brigatinib	Gettinger et al. (1)	100%	-	-	-

DoR, duration of response; ORR, overall response rate; OS, overall survival; TKI, tyrosine kinase inhibitor.
Adapted from Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

Early-Generation ROS1 TKIs Achieve Improved Outcomes Compared to Chemotherapy

Study (n)	Efficacy Measure	Crizotinib	Platinum-based chemotherapy	*P*
Shen et al (77)	ORR	86.7%	44.7%	<.001
	Median PFS	18.4 mo	8.6 mo	<.001
Xu et al (102)	ORR	83.9%	56.5%	.002
	Median PFS	14.9 mo	8.5 mo	.001
Zhang et al (51)	ORR	80.0%	40.8%	<.05
	Median PFS	9.4 mo	3.5 mo	<.05

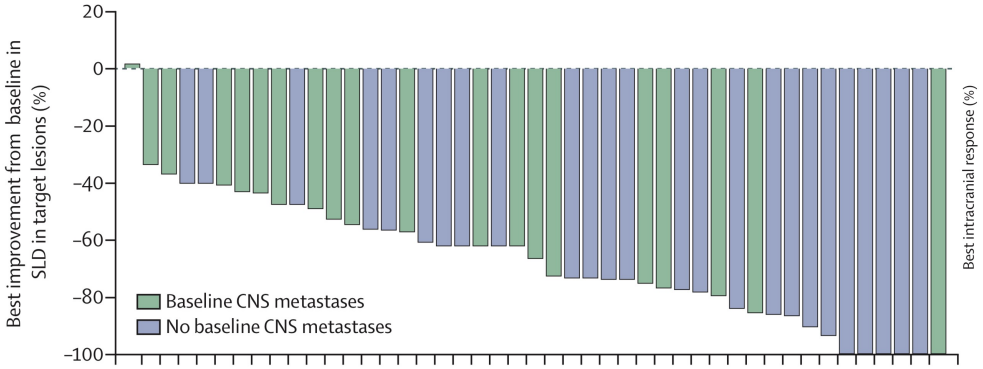
Series	Chemotherapy	ORR	Median PFS
Xu et al	Platinum-based, first-line (n = 46) Non-platinum agents were: pemetrexed (n = 35), paclitaxel (n = 5), docetaxel (n = 2) or gemcitabine (n = 4)	–	8.5 mo (95% CI 6.8-10.3)
	Platinum-pemetrexed (n = 35; subset analysis of the above)	–	8.8 mo (95% CI 6.8-10.8)
Shen et al	Platinum-pemetrexed, first-line (n = 47)	44.7% (95% CI 29.8–57.4)	8.6 mo (95% CI 6.9-10.3)
	With bevacizumab	–	9.0 mo
	Without bevacizumab	–	8.1 mo
Park et al	Pemetrexed-based (n = 90)	53.3%	8.0 mo (95% CI 6.4-11.7)
Drilon et al	Pemetrexed-based (n = 10) Alone or combination with a platinum agent ± bevacizumab	–	23 mo
Mazieres et al (EUROS1)	Pemetrexed-based chemotherapy (n = 31) Pemetrexed alone or in combination with a platinum agent	57.5%	7.2 mo (95% CI 4.8-9.6)

ORR, overall response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Adapted from Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

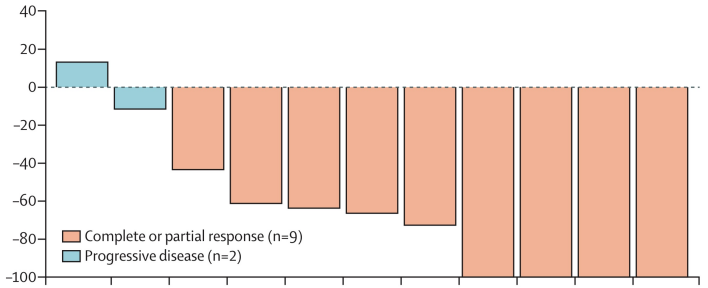
Entrectinib Trial Enriched for Patients With Baseline Brain Metastases

All patients in integrated analysis (n=53)	
CNS disease present at baseline‡	23 (43%)
Measurable	5 (9%)
Not measurable	18 (34%)

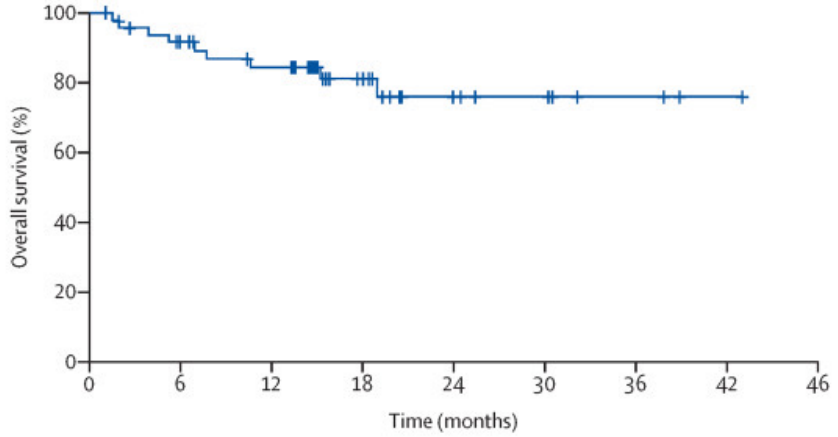
Overall Response



Intracranial Response

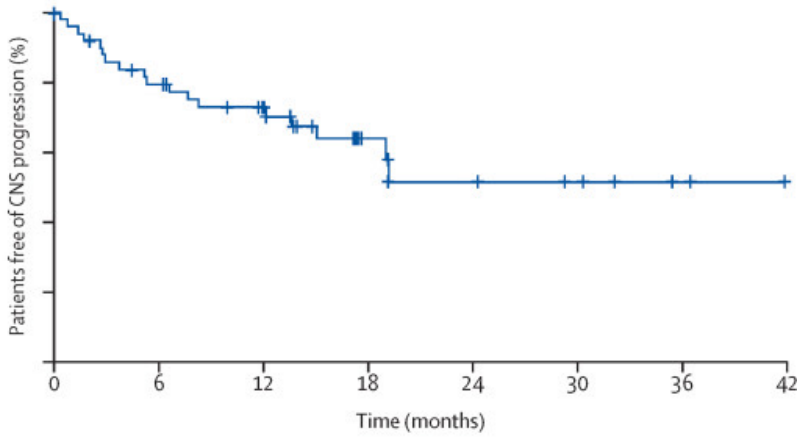


Overall Survival



Number at risk (number censored)															
	53 (44)	46 (39)	42 (37)	38 (35)	36 (34)	27 (25)	18 (17)	9 (9)	8 (8)	6 (6)	6 (6)	3 (3)	3 (3)	1 (1)	1 (1)

Time to CNS Progression



53 (35)	42 (31)	38 (30)	33 (28)	30 (25)	18 (15)	11 (9)	7 (7)	7 (7)	6 (6)	5 (5)	3 (3)	2 (2)	1 (1)	

Drilon et al. *Lancet Oncol*. 2020;21:261-270.

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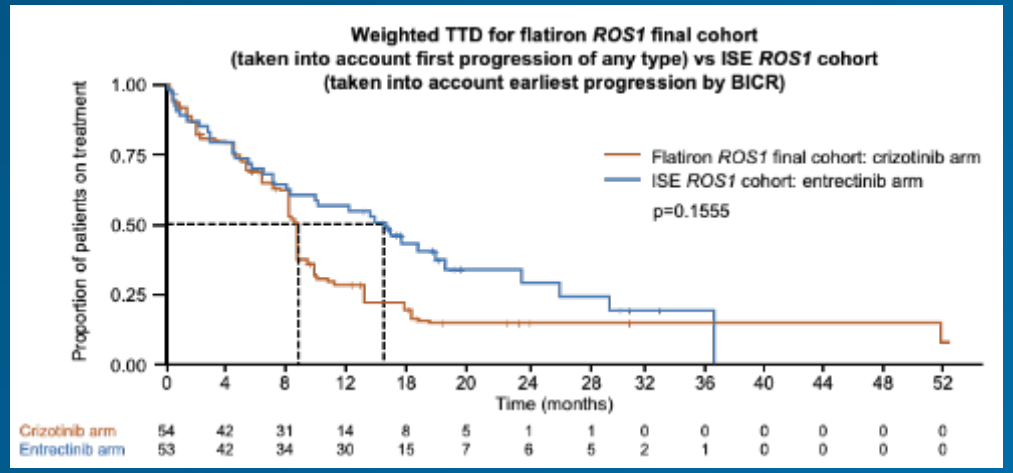
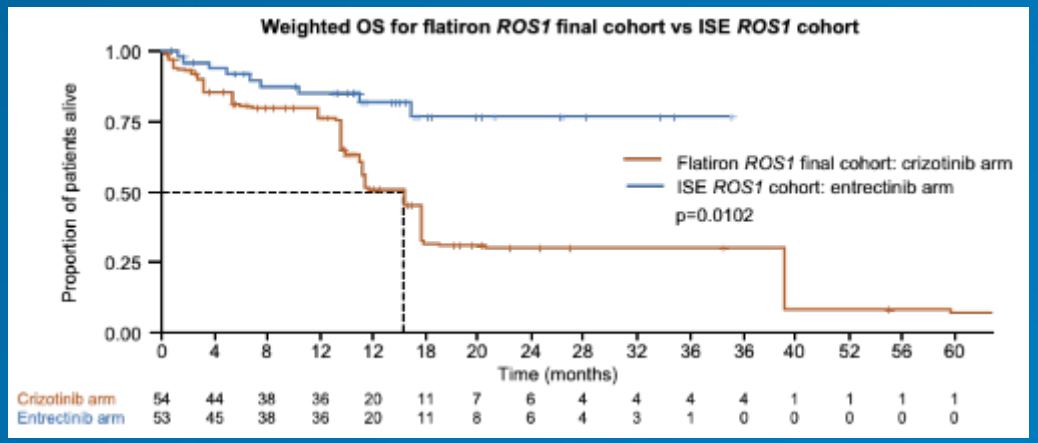
Early-Generation ROS1 TKIs Active in *ROS1*-rearranged Lung Cancers

Time to Treatment Discontinuation



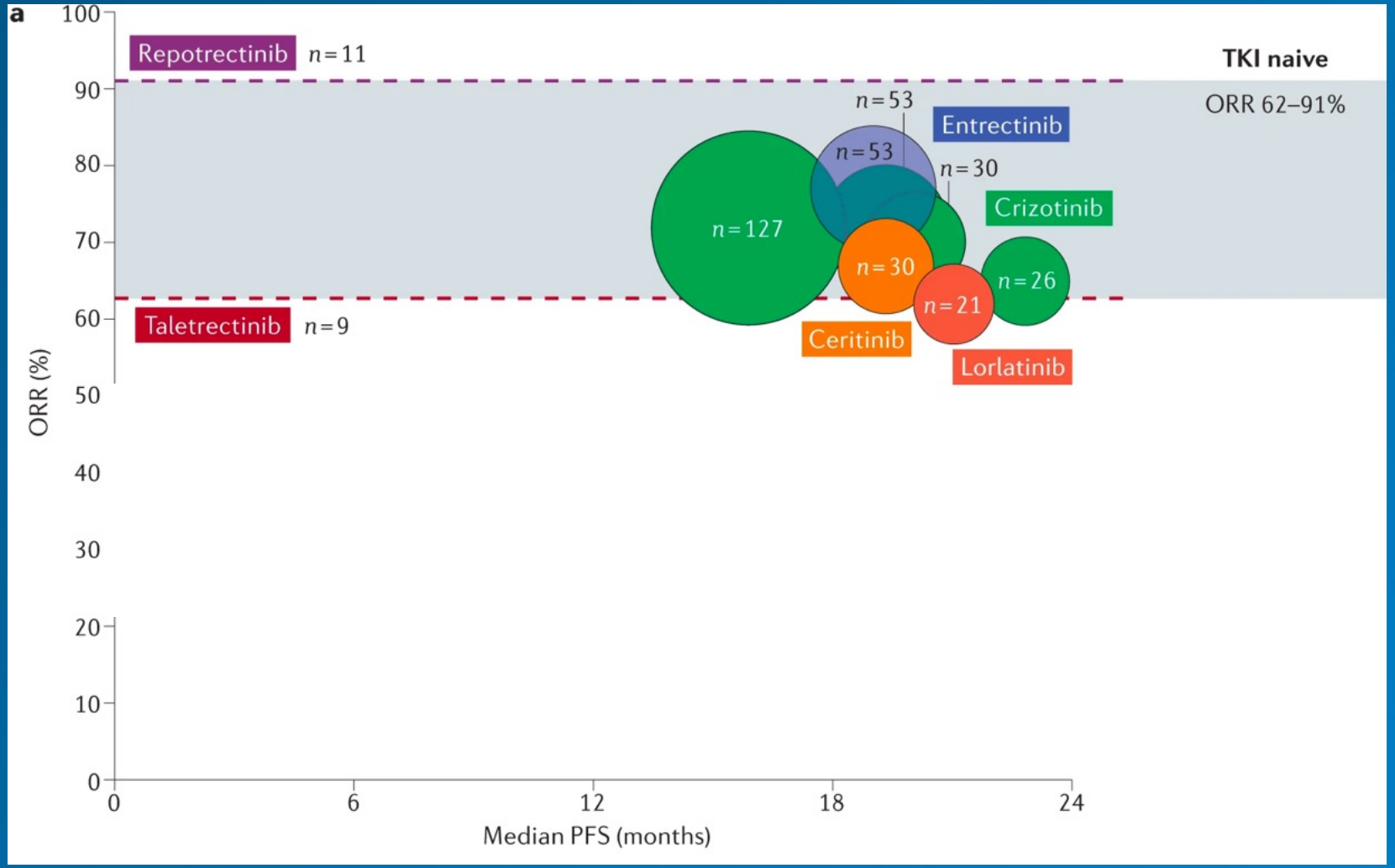
Overall Survival



	Crizotinib	Entrectenib
TTD	8.8 months	14.6 months
OS	~20 months	Not reached

Doebele et al. *J Clin Oncol*. 2019;15:9070.

Next-Generation ROS1 TKIs Yet to Achieve Much Longer PFS Compared to Early-Generation TKIs



PFS, progression-free survival; TKIs, tyrosine kinase inhibitors.
Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

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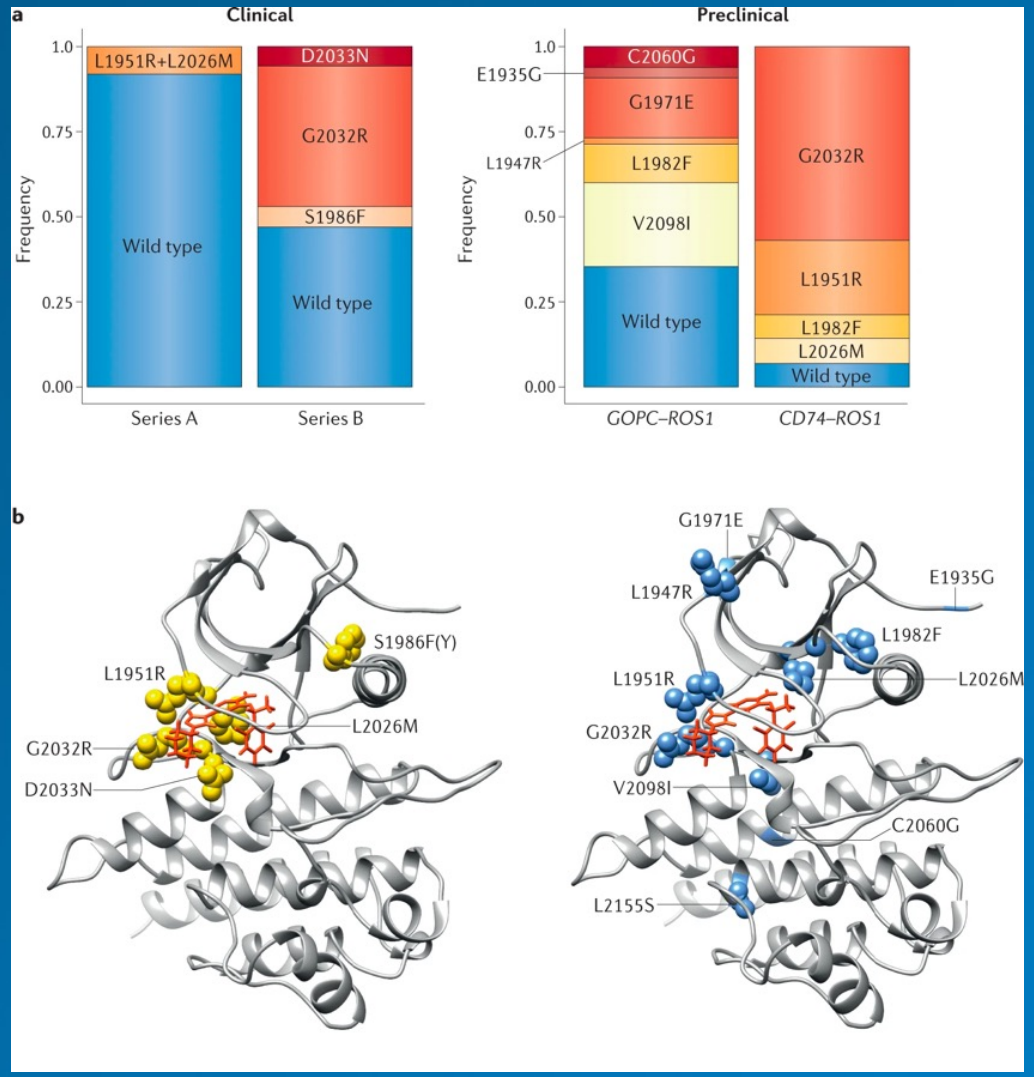
On-Target Resistance to ROS1 TKI Therapy Occurs in Form of Acquired *ROS1* Kinase Domain Mutations



TKI, tyrosine kinase inhibitors.
Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

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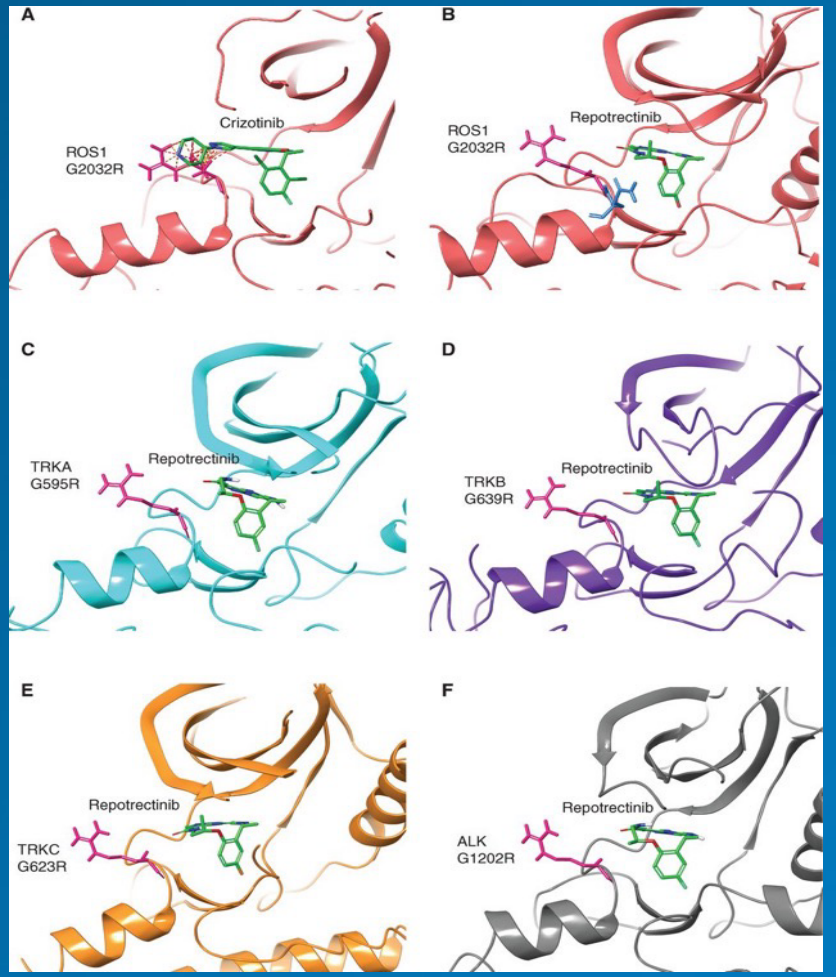
Common Design Parameter of Next-Generation ROS1 TKIs: Smaller Compared to First-Generation Drugs and Macrocyclics



TKIs, tyrosine kinase inhibitors.
Drilon et al. *Cancer Discov*. 2018;8:1227-1236.

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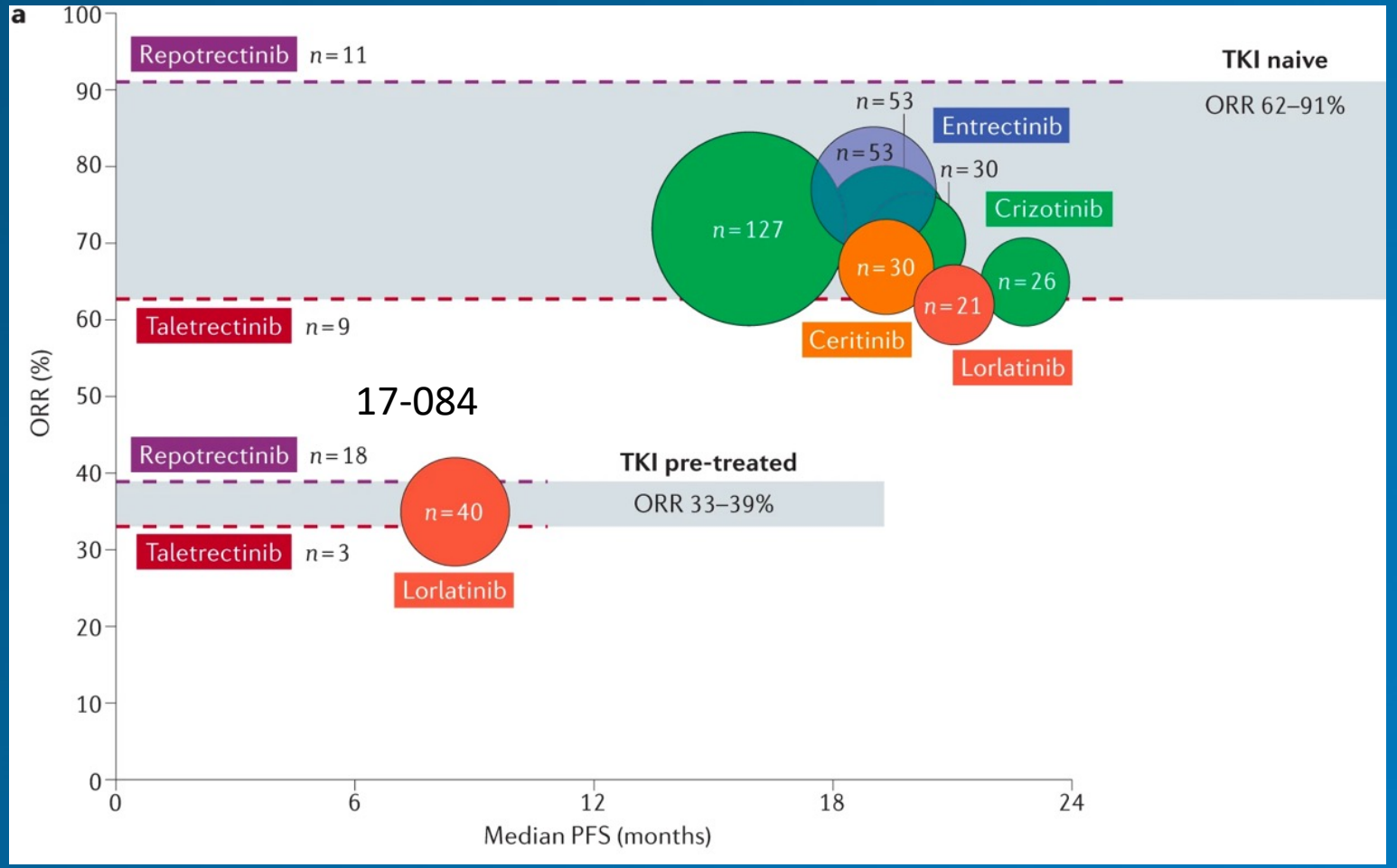
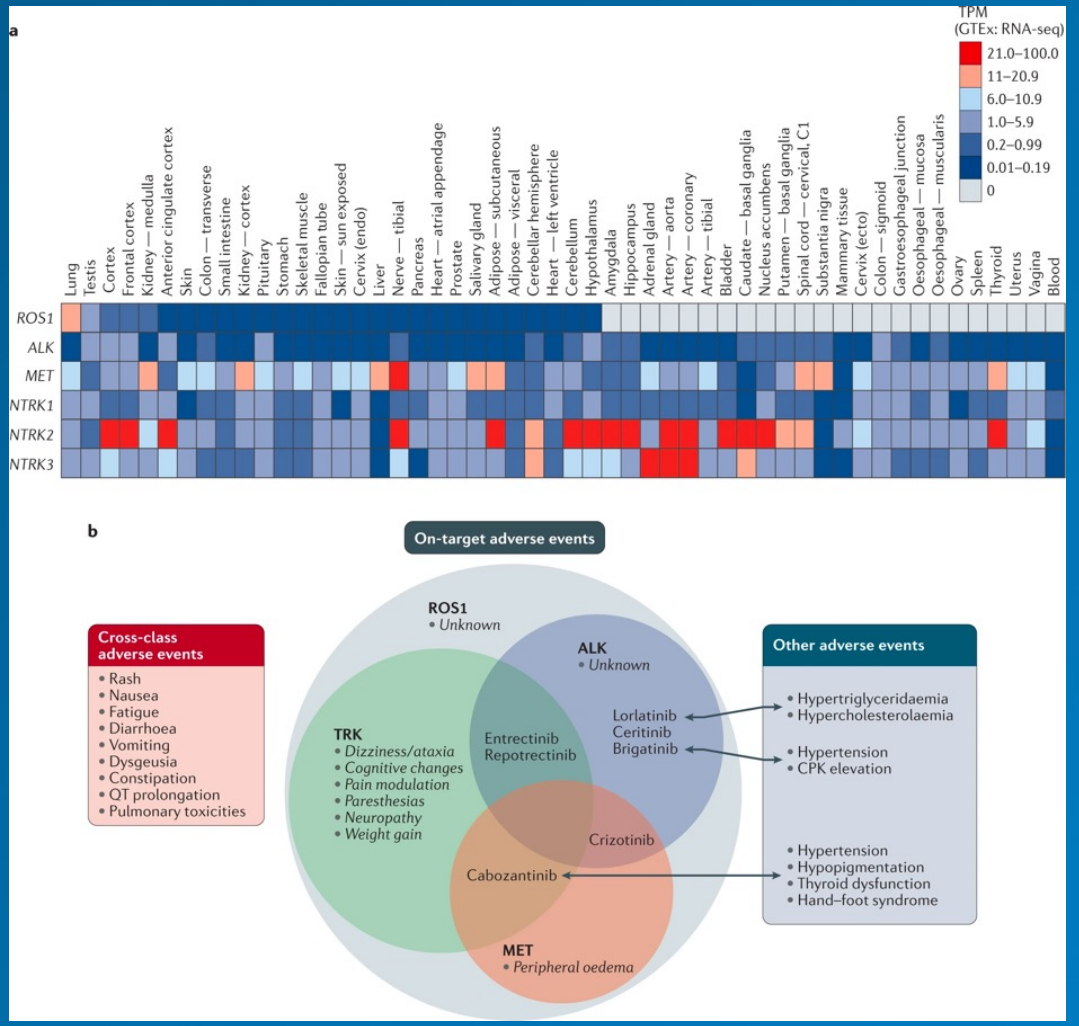
Response to Next-Generation ROS1 TKIs in ROS1 TKI Pretreated NSCLCs Occurs in a Subset of Patients



- **Repotrectinib**
  - FDA fast-track designation 8/2020 (prior chemo and 1-2 prior ROS1 TKIs)

ORR, overall response rate; TKIs, tyrosine kinase inhibitors.
Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

Consequences of ROS1 Inhibition in Non-Neoplastic Cells Remain Unclear: AEs Defined by Concurrent Kinase Inhibition



AEs, adverse events.

Drilon et al. *Nat Rev Clin Oncol*. 2021;18:35-55.

Virtual Tumor Board 2

ROS1+ Case Study

- 65-year-old male, former smoker with 50 pack-year history, presents with multiple bilateral pulmonary nodules and brain metastases
- Biopsy of one of the lung nodules positive for adenocarcinoma consistent with a lung primary
- A contralateral biopsy specimen is morphologically similar
- DNA-based next-generation sequencing finds no actionable drivers except a complex *ROS1* rearrangement of unknown significance

What is the next diagnostic step?

ROS1+ Case Study

- FISH testing confirms *ROS1* probe break apart and RNA-based targeted sequencing finds an *EZR-ROS1* fusion
- While testing was being performed, a local oncologist began carboplatin, pemetrexed, and pembrolizumab with a notable response after 2 cycles

What is the next therapeutic step?

ROS1+ Case Study

- Chemoimmunotherapy was continued for 1 year after which widespread progression was noted
- A new liver lesion was biopsied but was inadequate and a second biopsy was not deemed feasible
- Plasma ctDNA identified a *ROS1* G2032R mutation; however, a *ROS1* fusion was not detected

Does the absence of a *ROS1* fusion preclude any further ROS1-directed therapy?

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Practicing Precision in *ALK* and *ROS1* Rearrangement–Positive NSCLC:

Testing, Targets, and Treatments