NON-SMALL CELL LUNG CANCER (NSCLC)
OPTIMAL SEQUENCE FOR TARGETED THERAPIES

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Disclosures

- Consultant for AstraZeneca.
- On the Speakers Bureau for AstraZeneca, Merck, and Sanofi.
- Grants from NIH/NCI.

Objectives

- Lung Cancer
- EGFR
- ALK
- KRAS

Lung Cancer- Severity and Impact

Estimated New Cases

Males			Females		
Prostate	248,530	26%	Breast	281,550	30%
Lung & bronchus	119,100	12%	Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%	Colon & rectum	69,980	8%
Urinary bladder	64,280	7%	Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%	Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%	Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%	Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%	Pancreas	28,480	3%
Leukemia	35,530	4%	Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%	Leukemia	25,560	3%
All Sites	**970,250**	**100%**	**All Sites**	**927,910**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	69,410	22%	Lung & bronchus	62,470	22%
Prostate	34,130	11%	Breast	43,600	15%
Colon & rectum	28,520	9%	Colon & rectum	24,460	8%
Pancreas	25,270	8%	Pancreas	22,950	8%
Liver & intrahepatic bile duct	20,300	6%	Ovary	22,950	5%
Leukemia	13,900	4%	Uterine corpus	12,940	4%
Esophagus	12,410	4%	Liver & intrahepatic bile duct	9,930	3%
Urinary bladder	12,260	4%	Leukemia	9,760	3%
Non-Hodgkin lymphoma	12,170	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,500	3%	Brain & other nervous system	8,100	3%
All Sites	**319,420**	**100%**	**All Sites**	**289,150**	**100%**

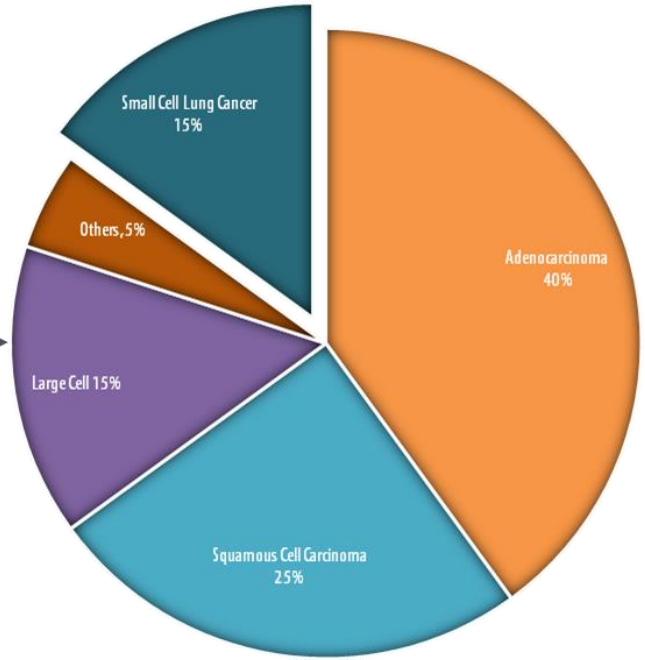
Siegel et. al. Cancer Statistics, 2021

Lung Cancer- The New Frontier

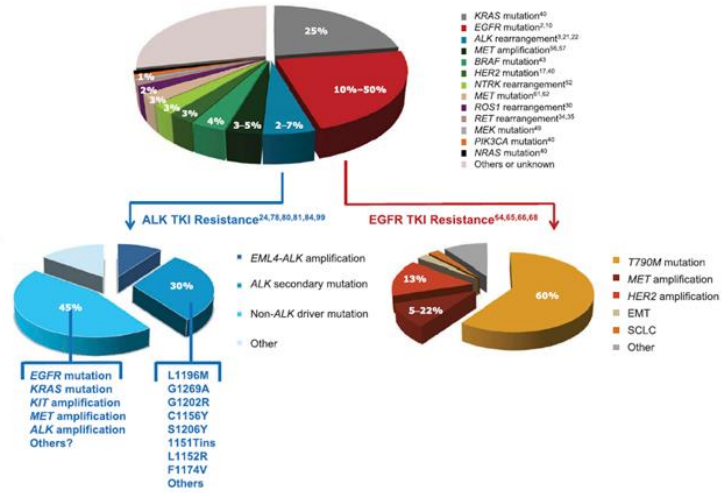
Historical

Lung Cancer as one disease

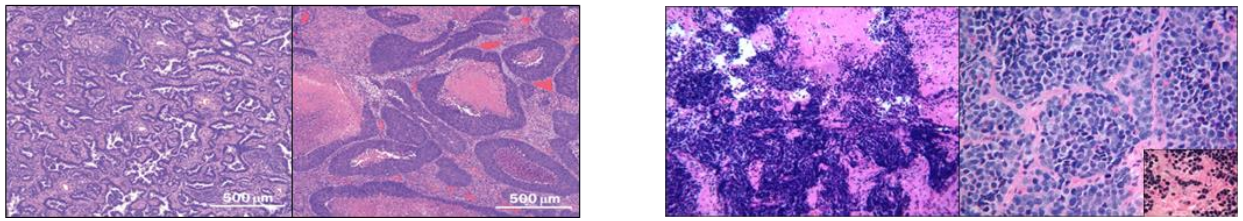
NSCLC and SCLC subtypes



Genomic subtypes



Non-Small Cell Carcinoma Histology **VS** **Small Cell Carcinoma Histology**



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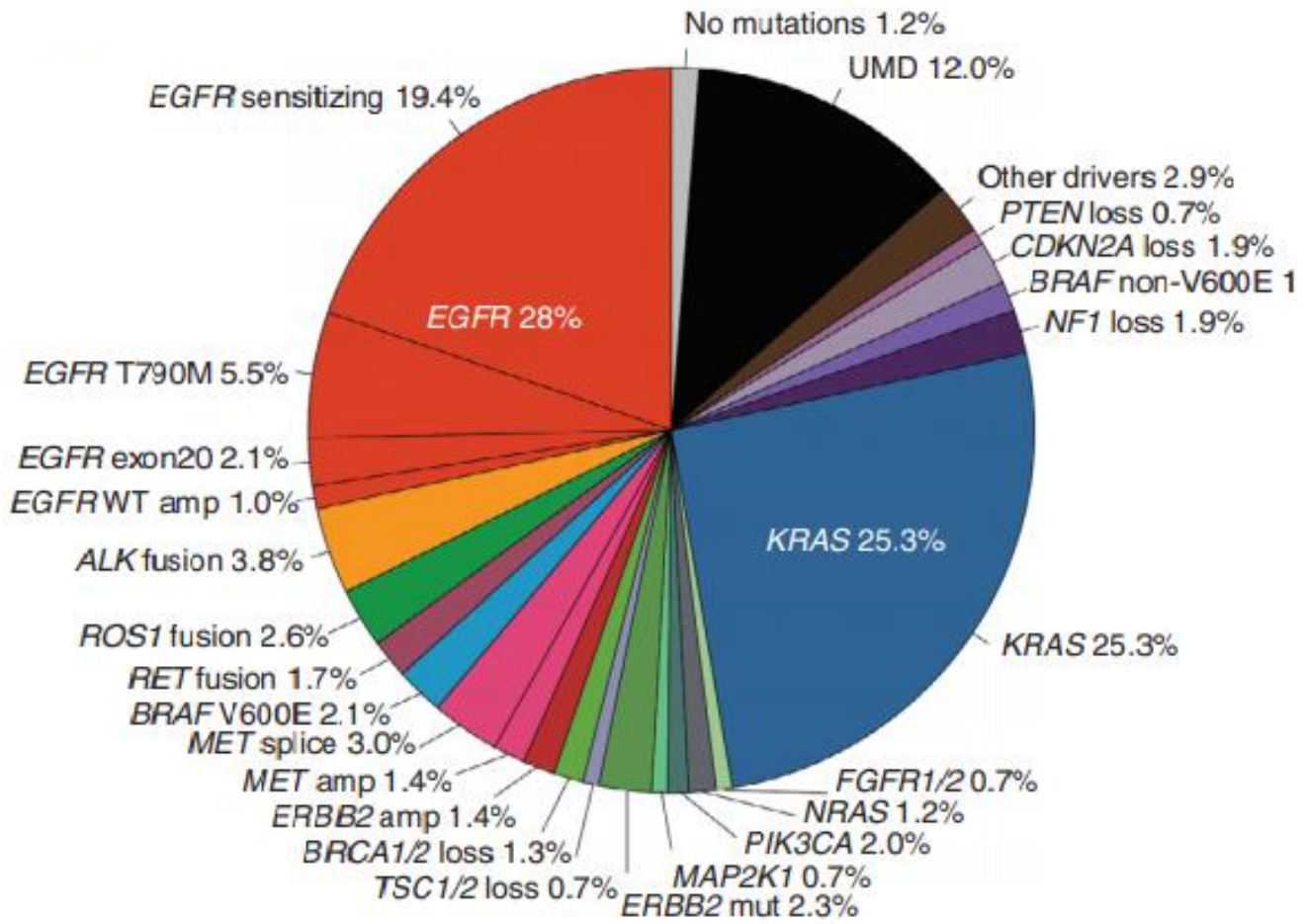
Mutational Profiling in Lung Adenocarcinoma



Jordan et al., Cancer Discovery, 2017

Tumor Heterogeneity in Lung Cancer

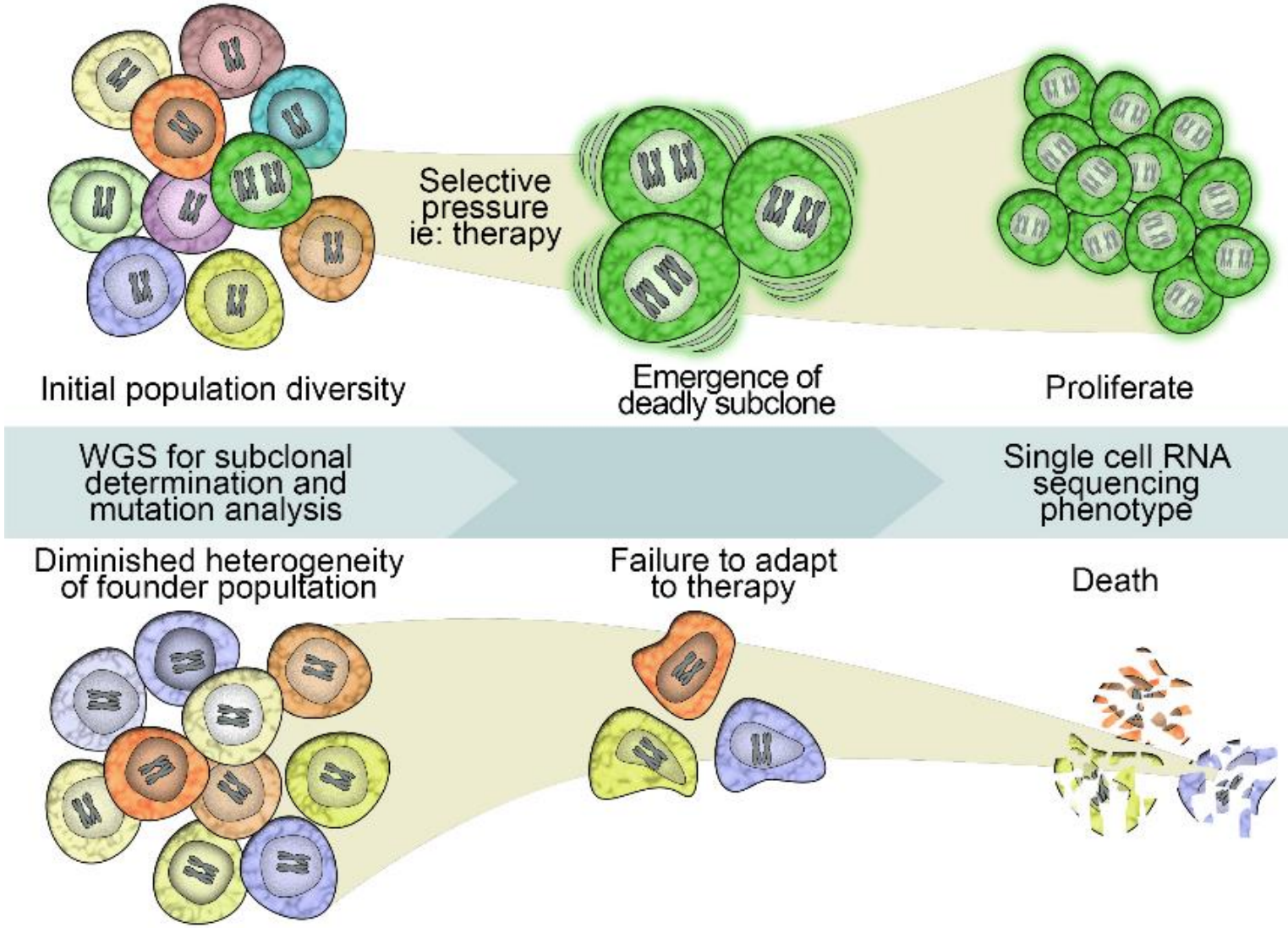
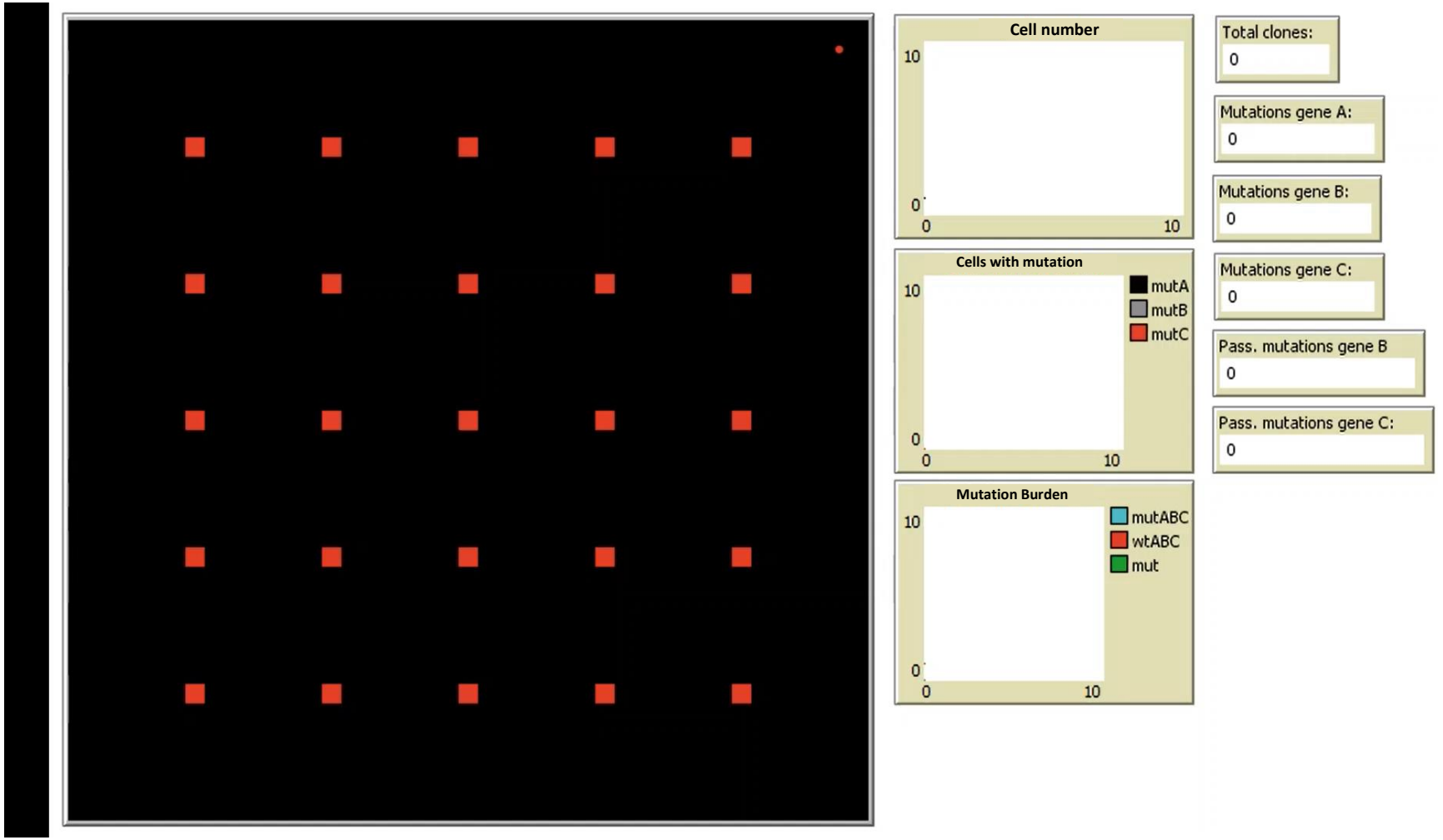


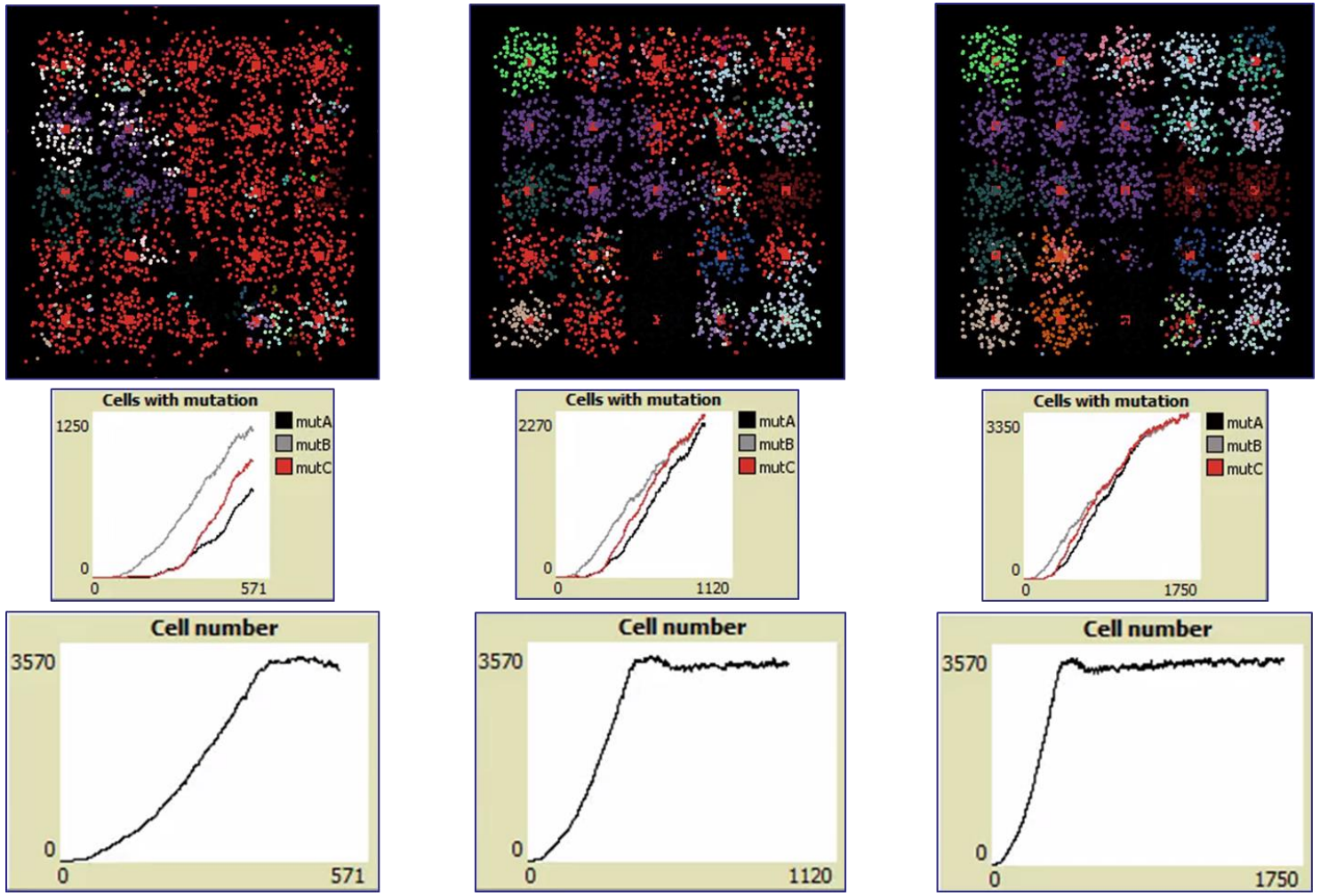
Bild et int. Salgia, 2019

Spatial Tumor Heterogeneity



Salgia et int. Sattler, Oncotarget, 2018

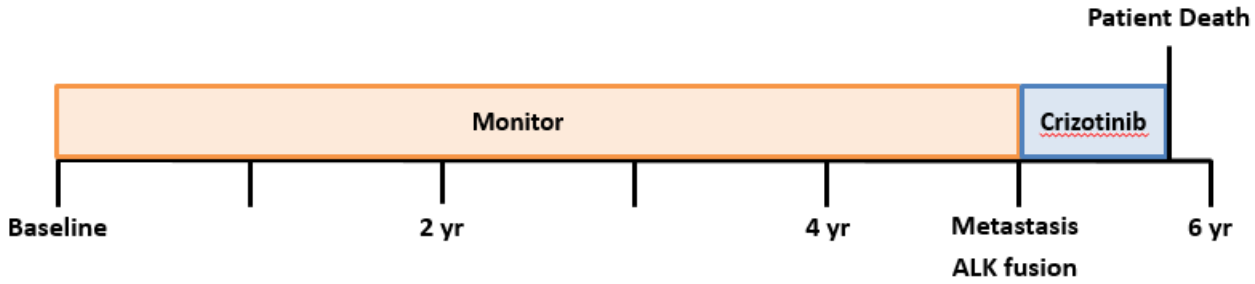
Original Oncogenic Clones Evolve to Develop Resistance and Heterogeneity



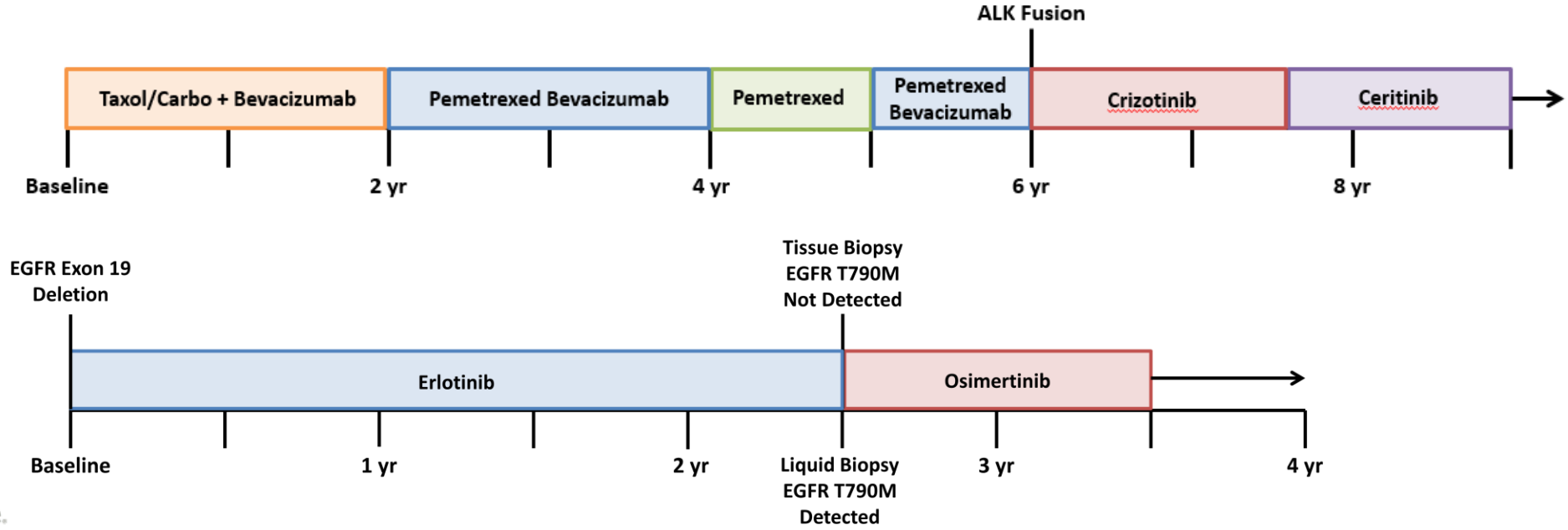
Salgia et int. Sattler, Oncotarget, 2018

Temporal Heterogeneity in Lung Cancer

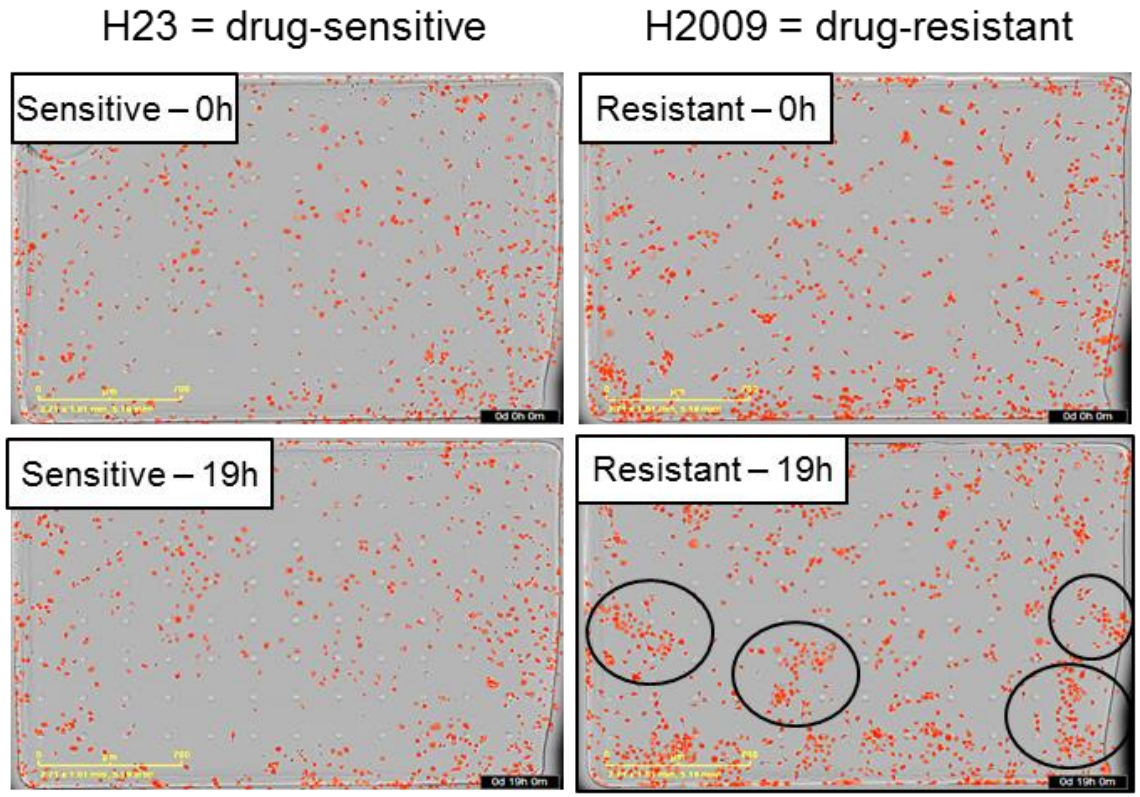
Straightforward Case



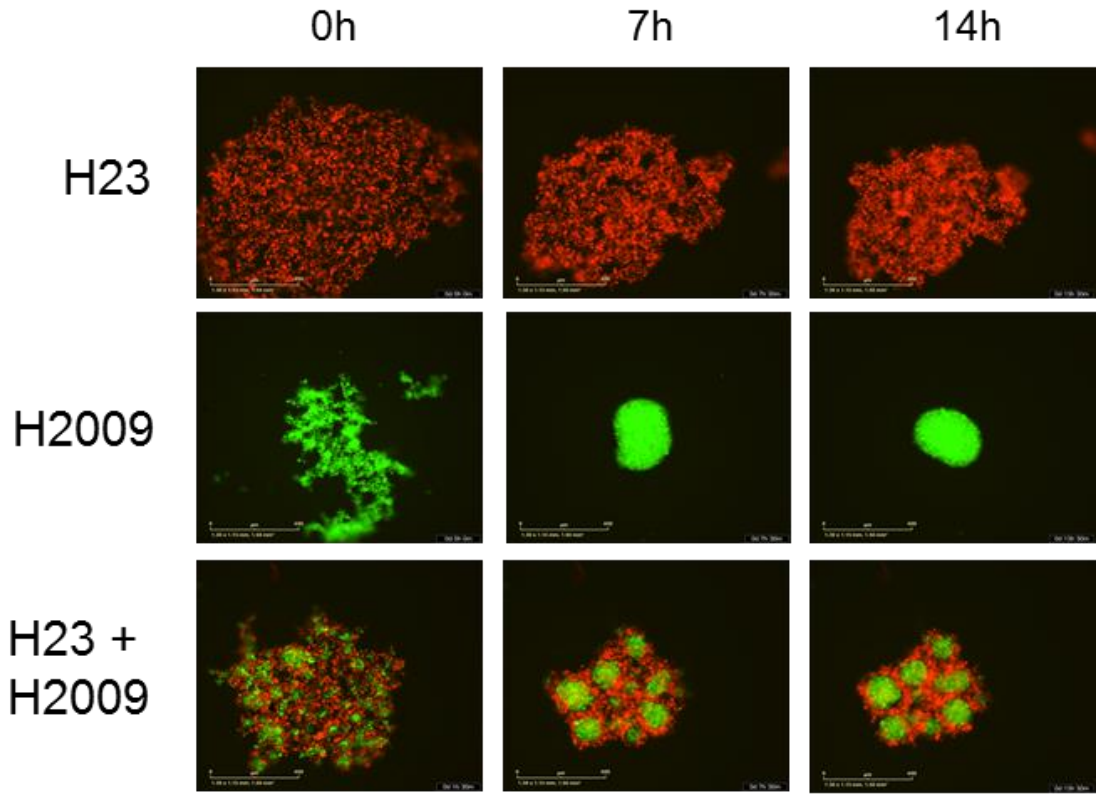
Complex Case



Drug-resistant cells exhibit ‘Group Behavior’



With drug treatment

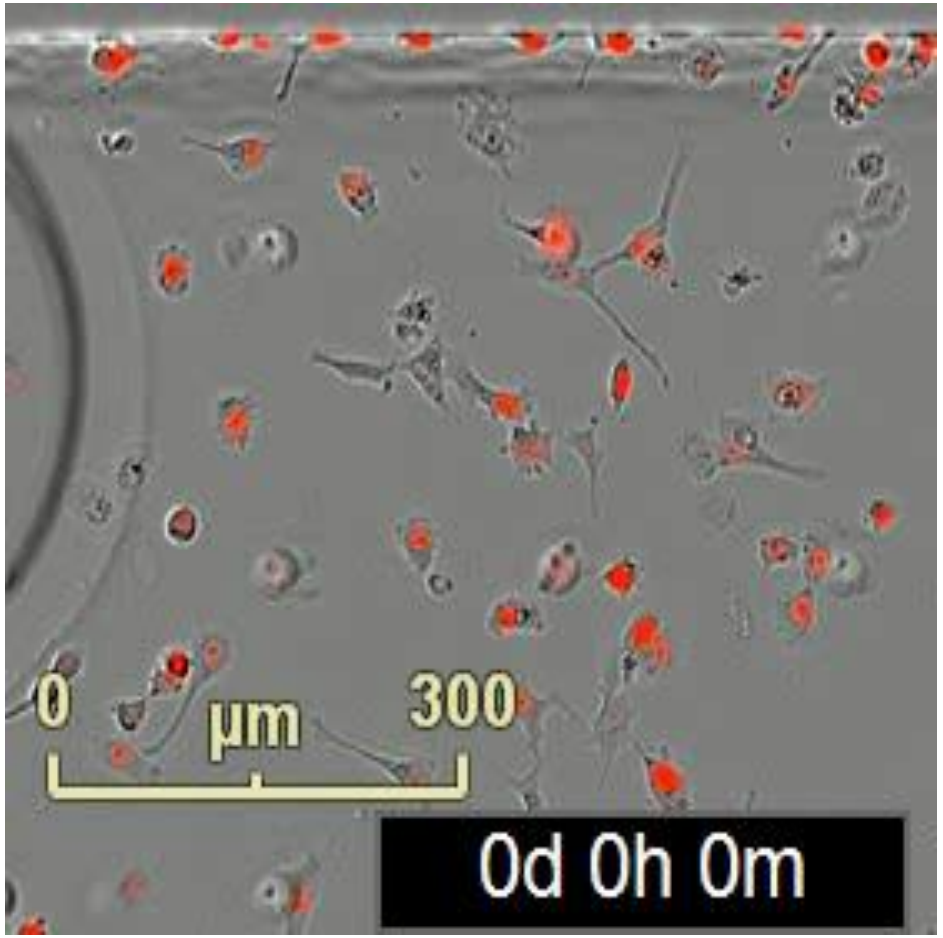


In 3D culture

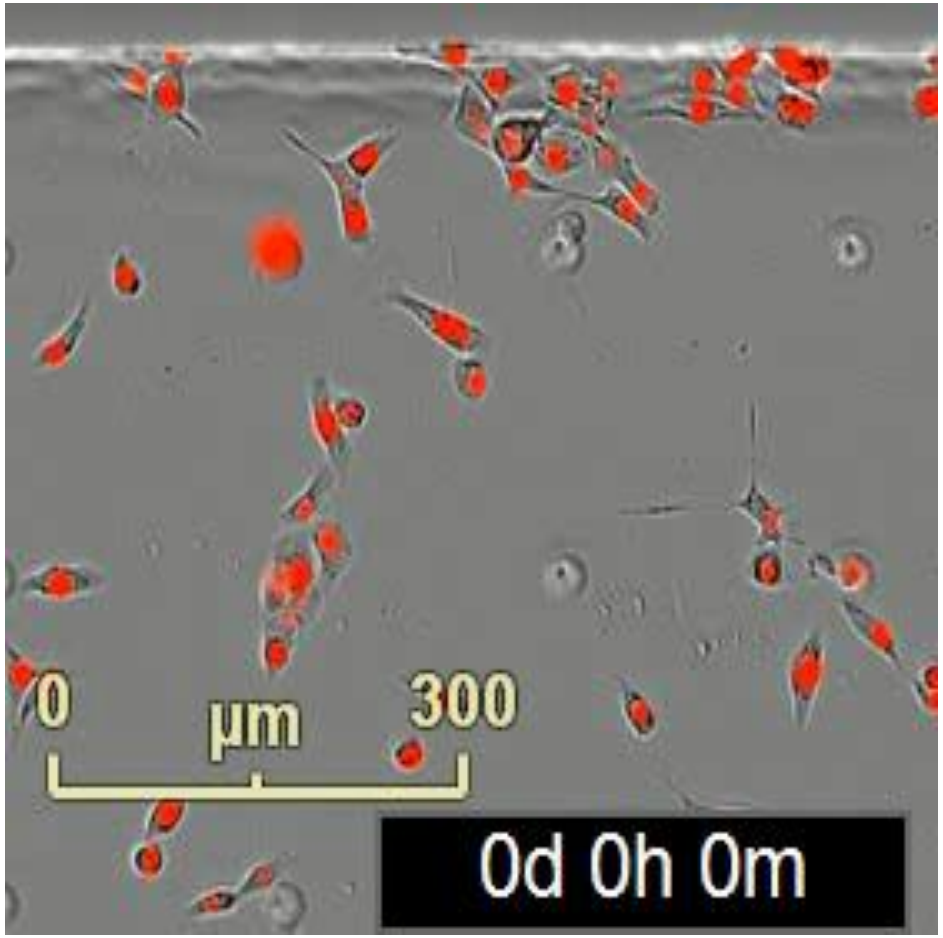
Nam et int. Salgia, 2019

Cells' immediate response to drug

Sensitive

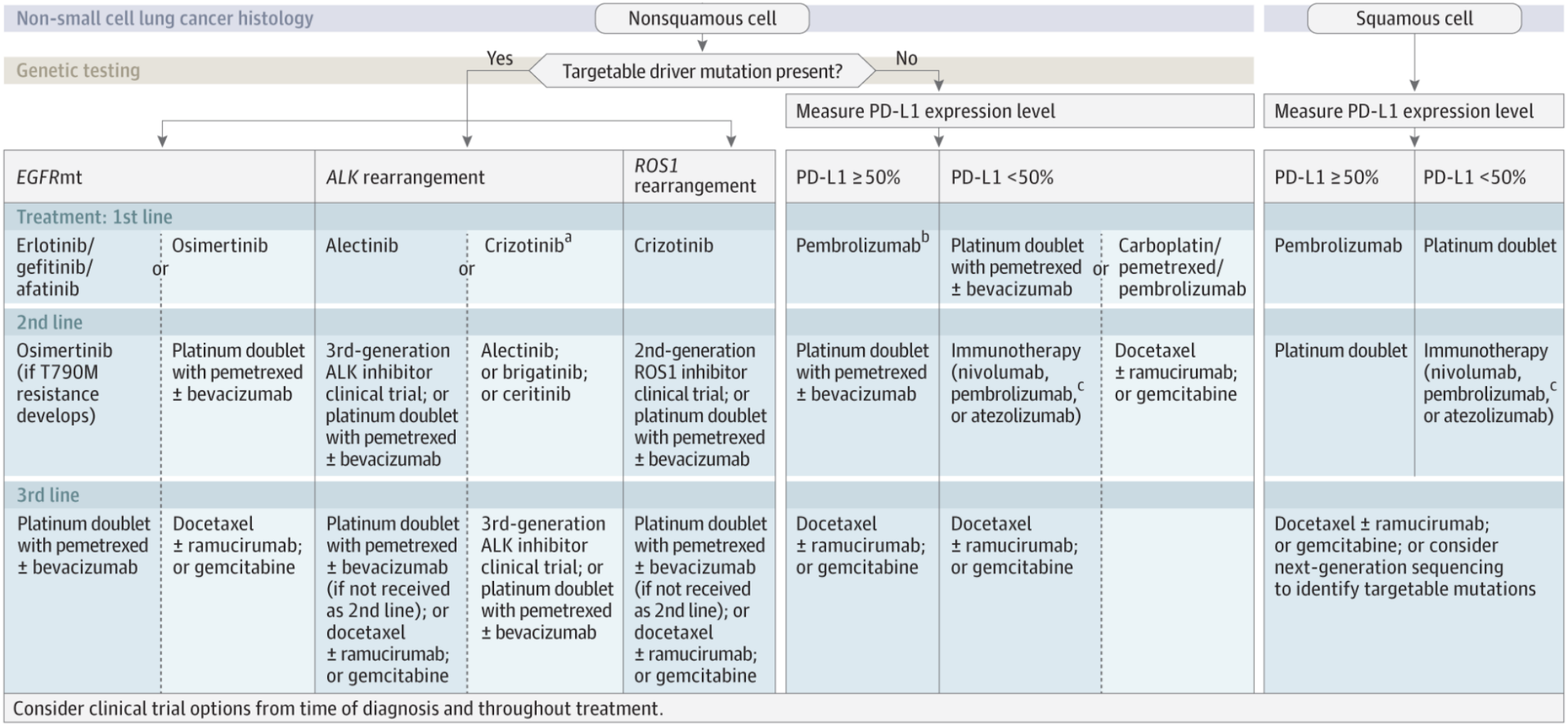


Resistant



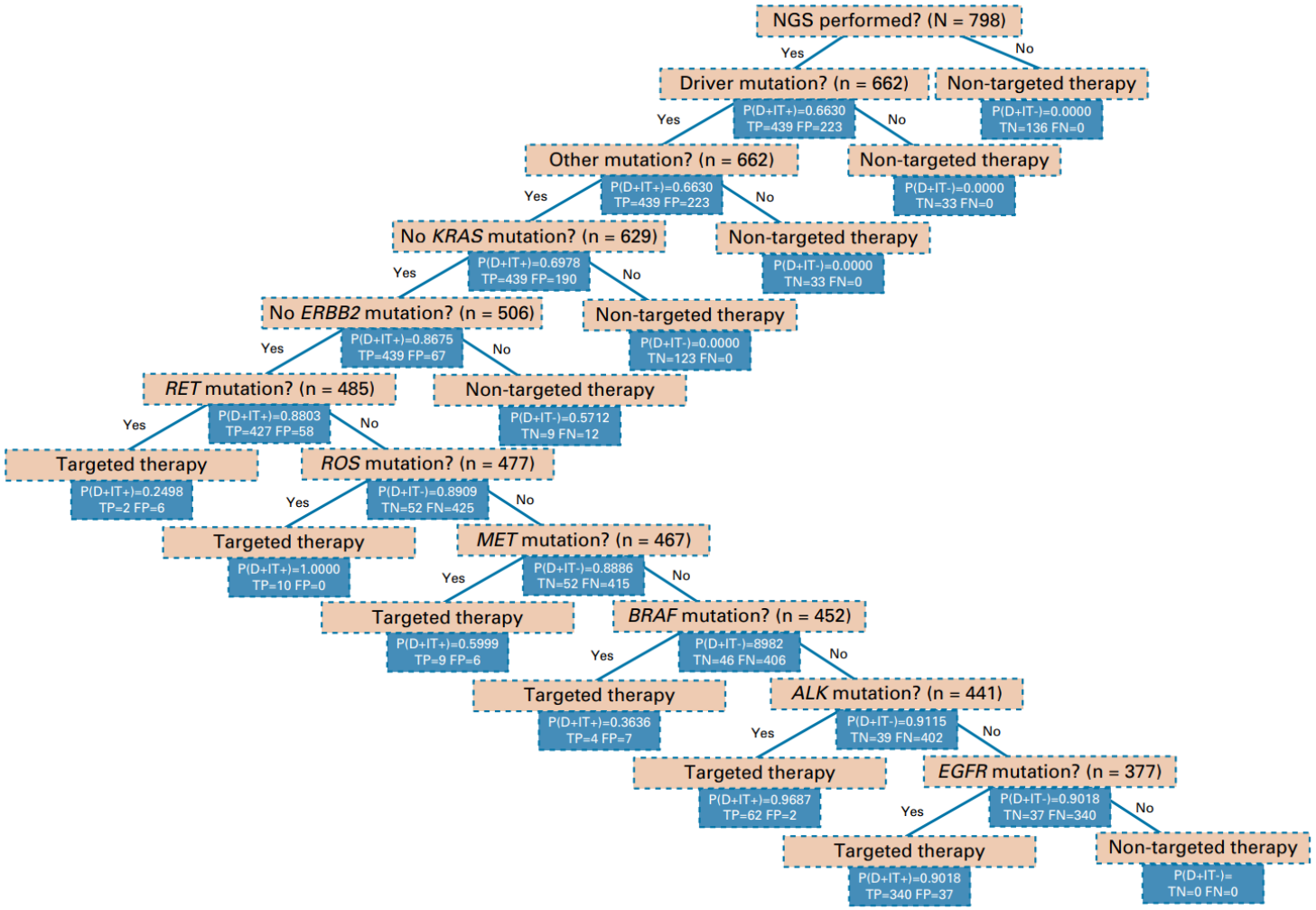
Nam et int. Salgia, 2019

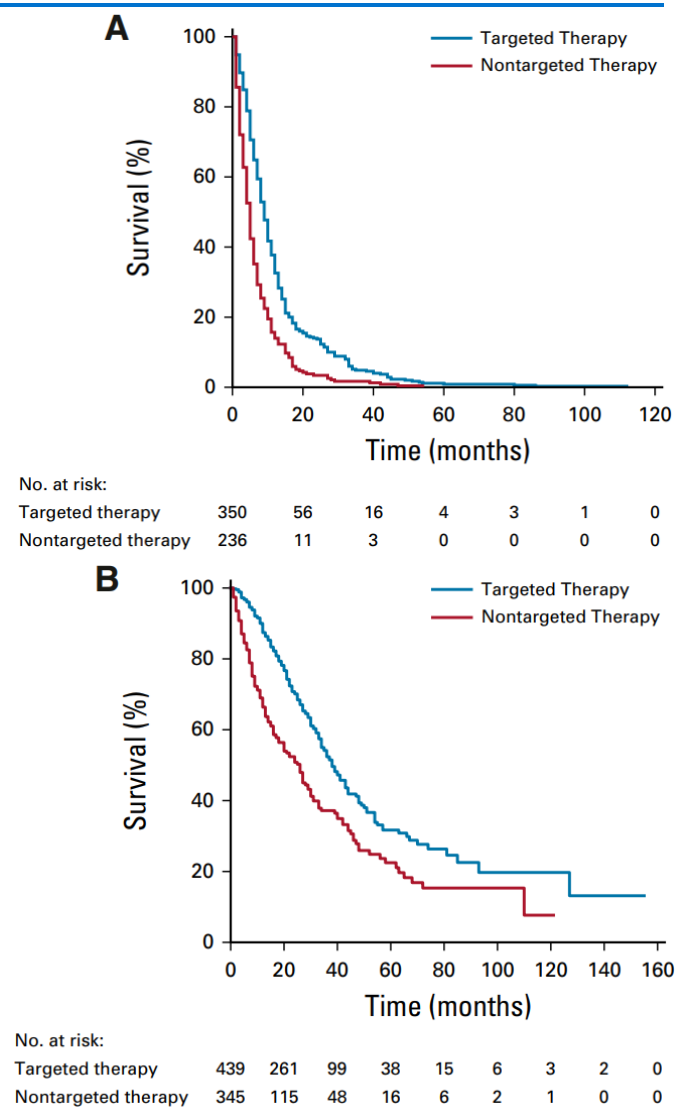
Management of Advanced NSCLC



Doroshow and Herbst, JAMA Network Insights 2018

Decision Trees for Improved Outcomes

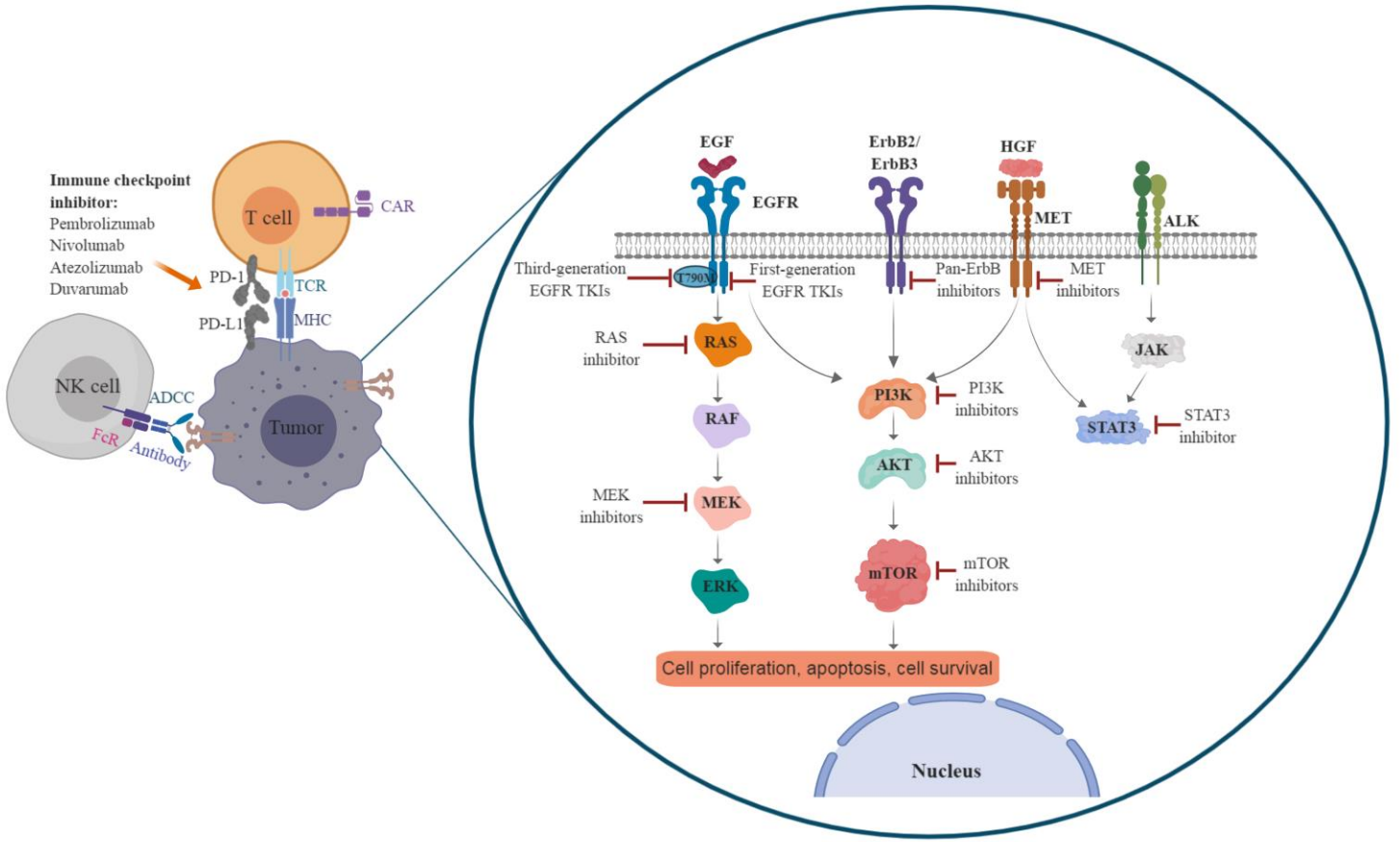




Salgia et al., JCO OP 2021

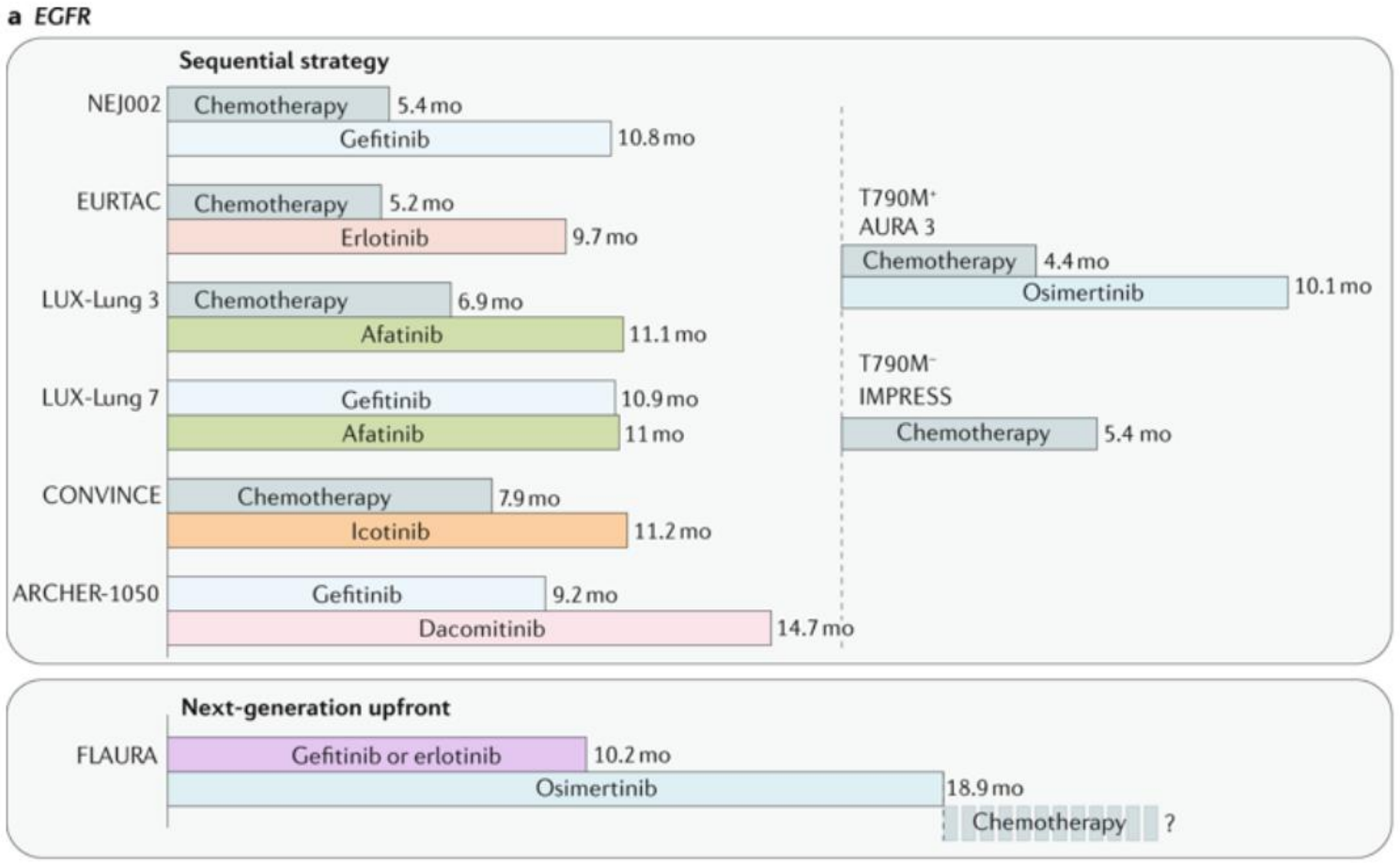
EGFR

Molecular Oncology: EGFR Mechanism of Action



Adapted from EGFR as a Pharmacological Target in *EGFR*-Mutant Non-Small-Cell Lung Cancer: Where Do We Stand Now?

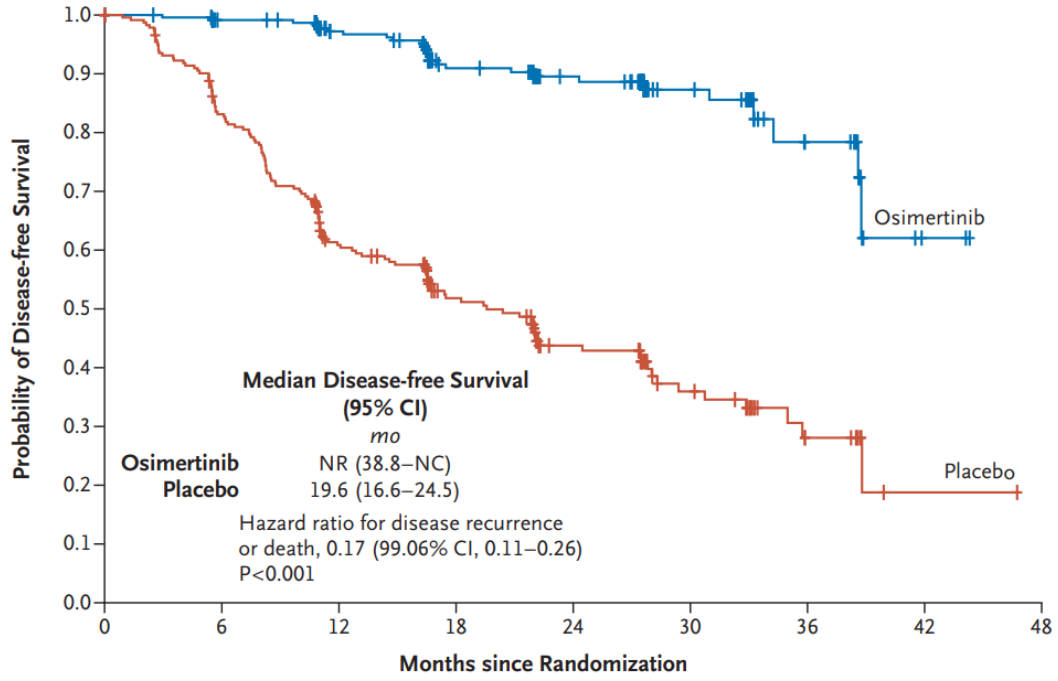
EGFR: Front-line Treatments for NSCLC



Recondo G et al., Nat Rev Clin Oncol. 2018.

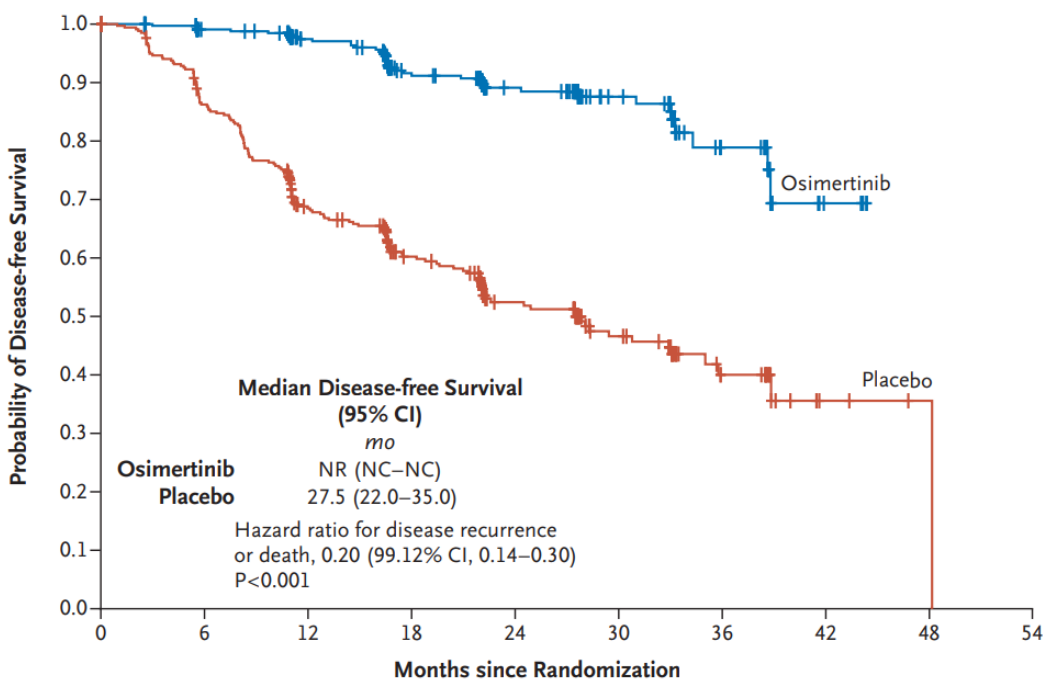
EGFR: ADAURA in Stage IB-IIIA NSCLC

A Patients with Stage II to IIIA Disease



No. at Risk									
Osimertinib	233	219	189	137	97	52	18	2	0
Placebo	237	190	127	82	51	27	9	1	0

B Patients with Stage IB to IIIA Disease



No. at Risk										
Osimertinib	339	313	272	208	138	74	27	5	0	
Placebo	343	287	207	148	88	53	20	3	1	0

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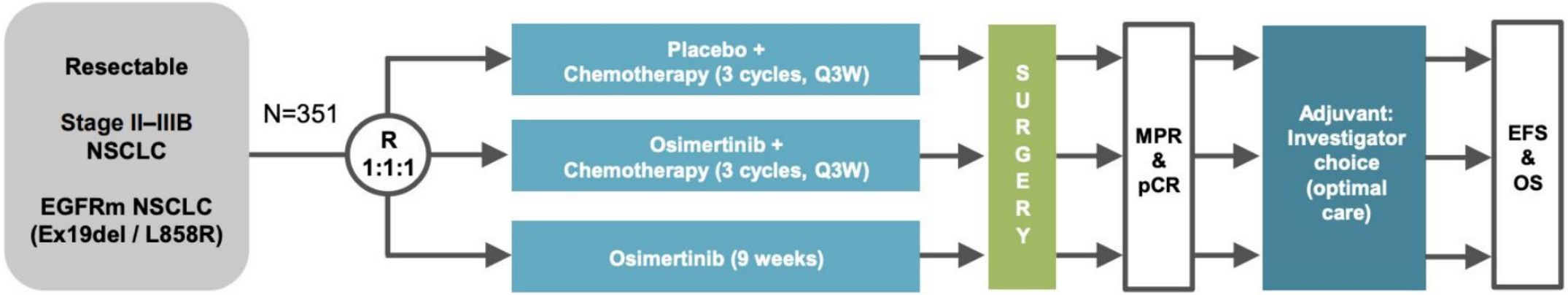
Yi-Long Wu et al., NEJM, 2020

EGFR: NeoADAURA in Resectable NSCLC Ongoing

NeoADAURA (NCT04351555): Phase III, Randomized, Controlled, Multicenter Study of Neoadjuvant Osimertinib in EGFRm Resectable NSCLC



Stratification:

- Stage II/III
- Non-Asian/Chinese/ other Asian
- Ex19del/L858R

Double-blind treatment arms:

1. Placebo QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2
2. Osimertinib 80 mg QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2

Open-label (sponsor-blind) treatment arm:

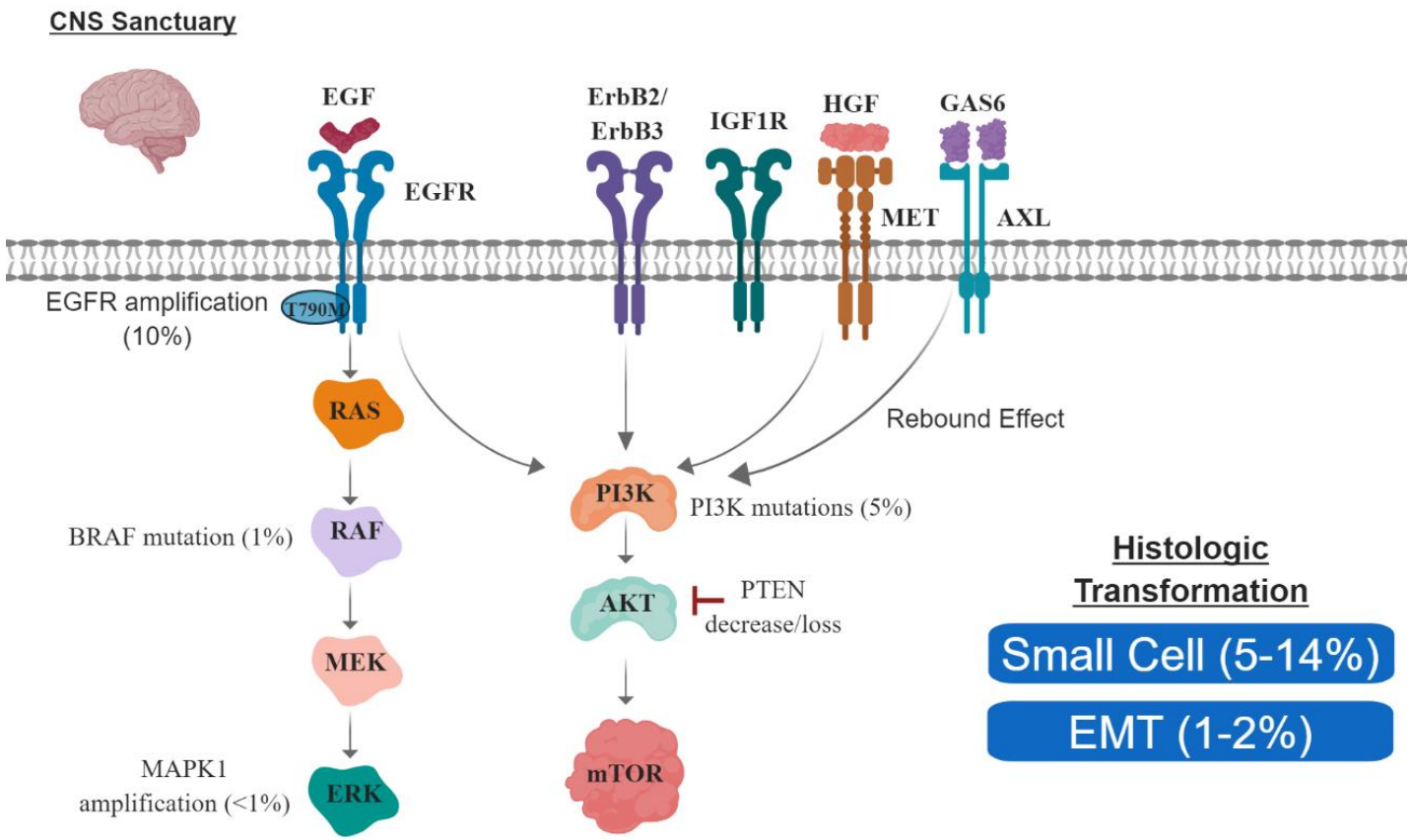
3. Osimertinib 80 mg QD

Adjuvant therapy and follow-up:

- Patients will be followed up for OS until 5 years from surgery, with evaluation at 12 and 24 weeks post-surgery, then every 24 weeks, until disease recurrence or withdrawal of consent
- Osimertinib will be offered to all patients who complete surgery (+/- post-surgical chemotherapy) for up to 3 years or until disease recurrence

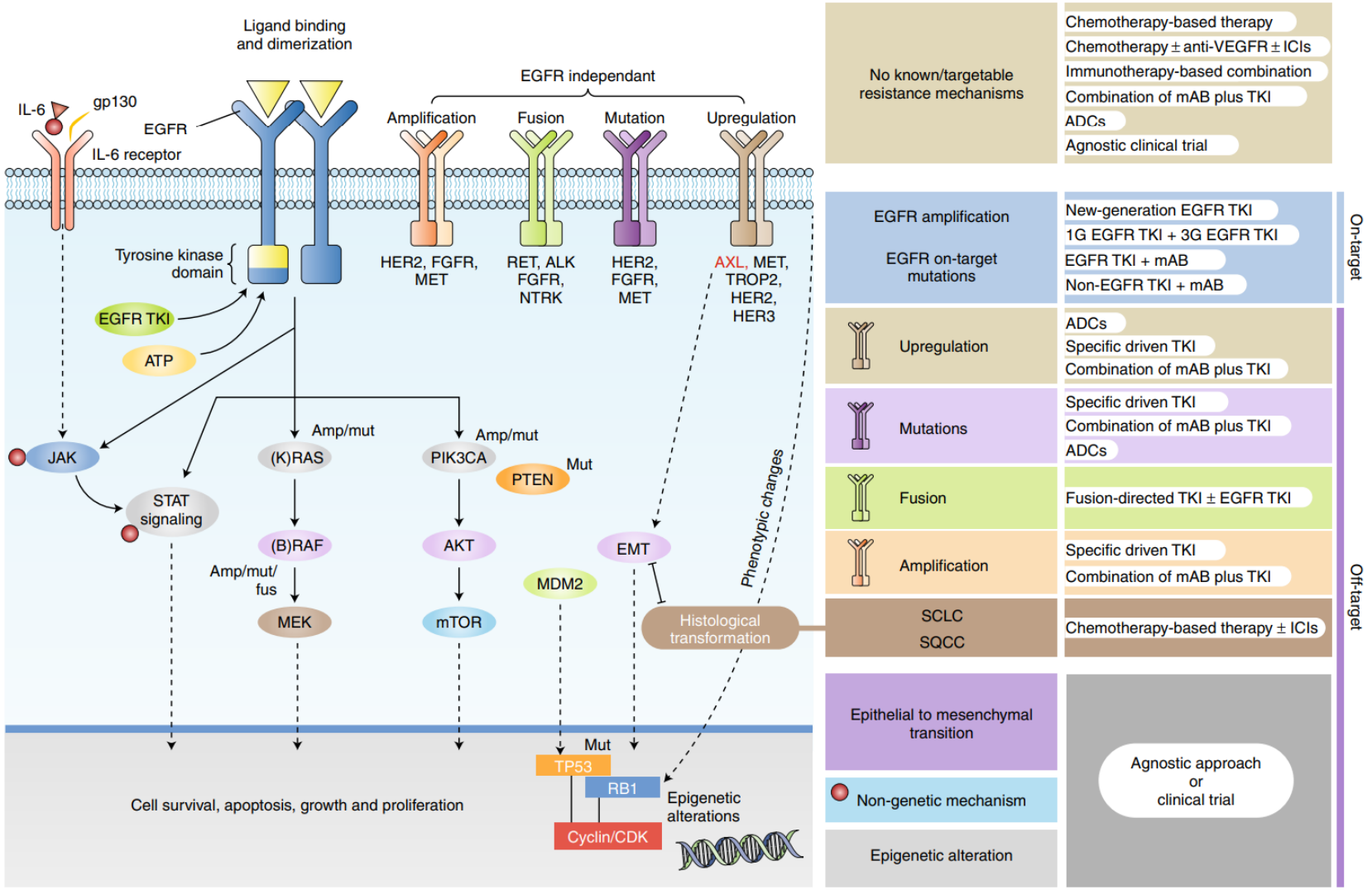
Yi-Long Wu et al., 2021

Primary and acquired resistance to EGFR-TKIs



Adapted from: Management of EGFR-mutated non-small-cell lung cancer: practical implications from a clinical and pathology perspective. M. Cabanero et al. Current Oncology. 2017

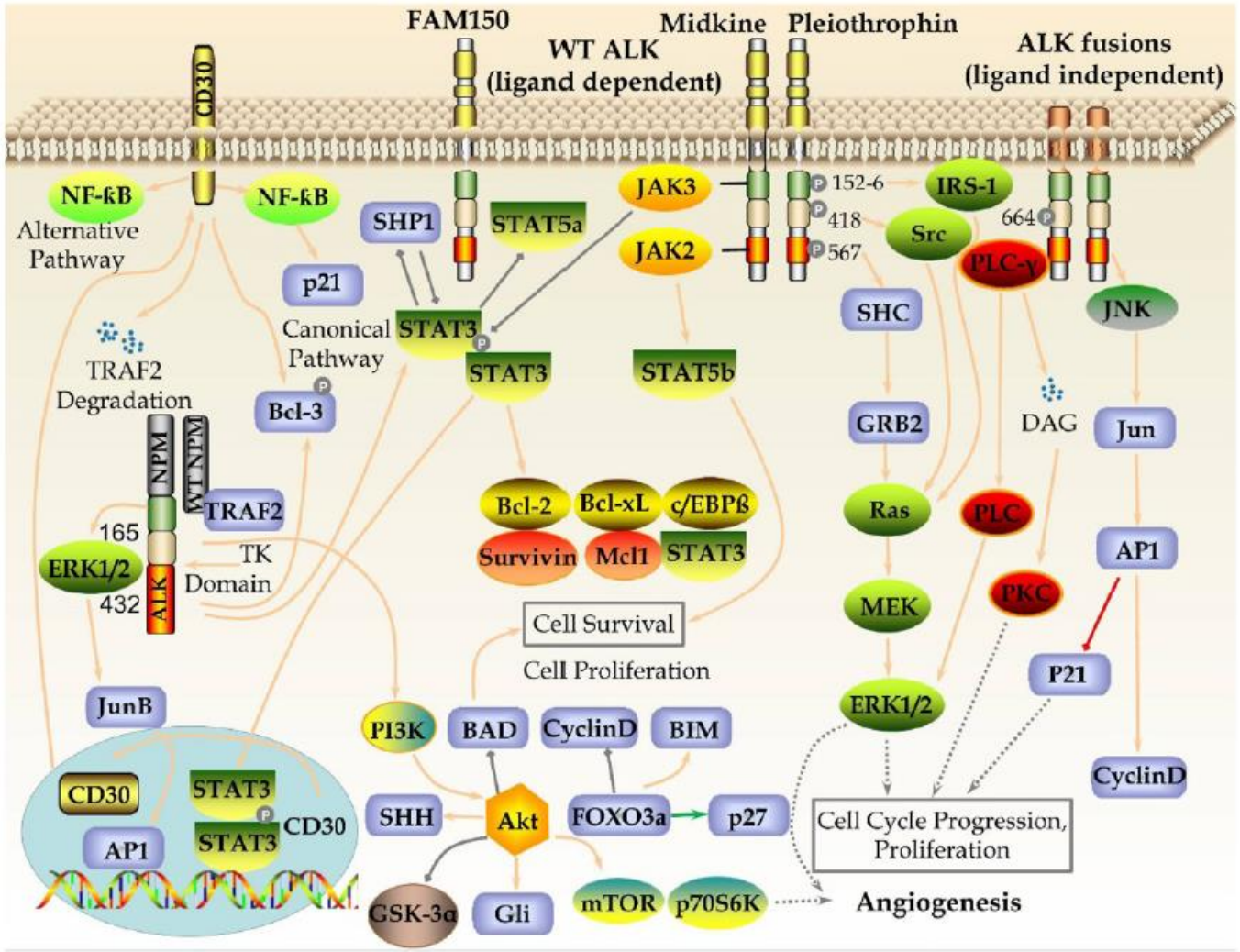
EGFR: Landscape



Passaro et al. Nature Cancer, 2021

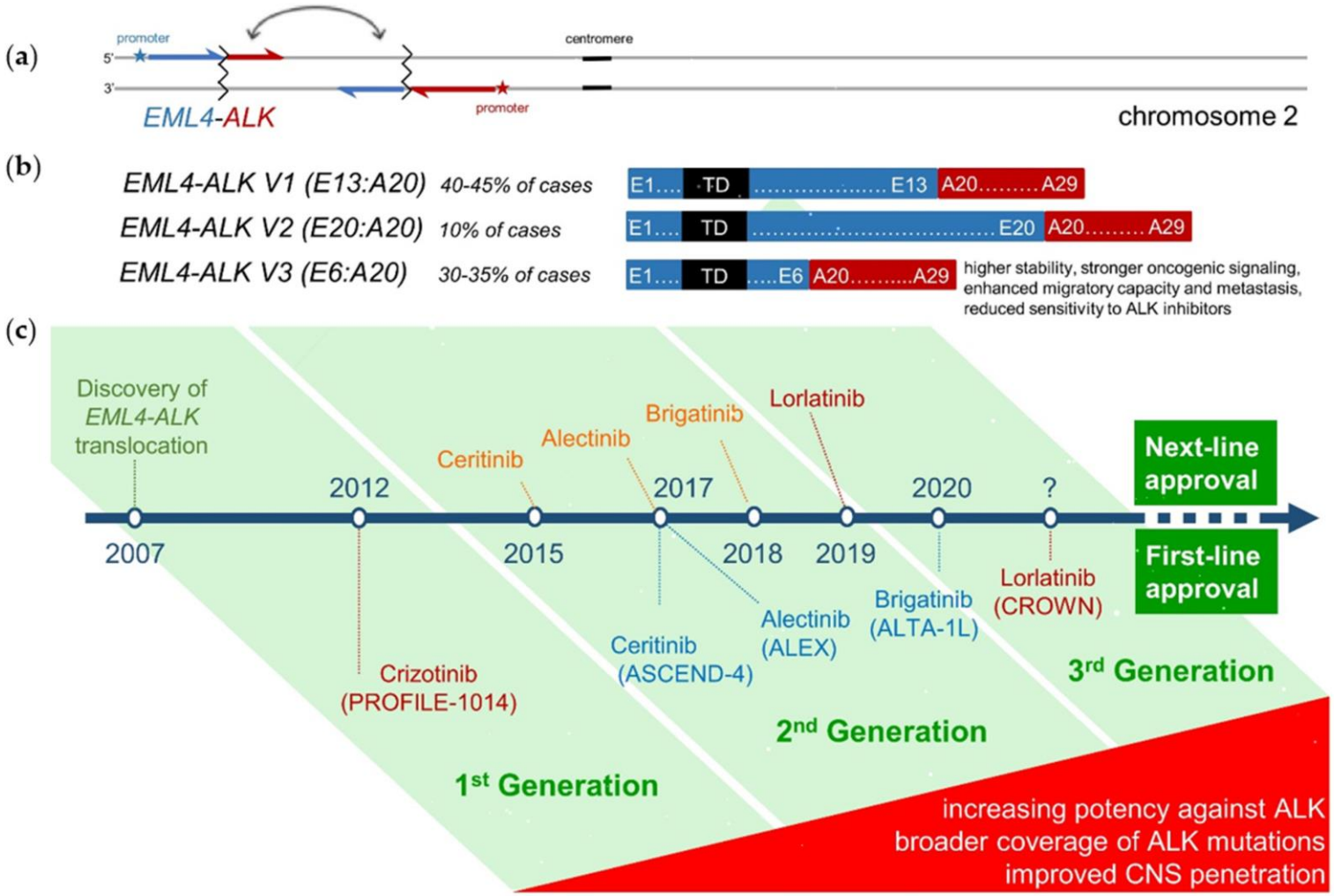
ALK

ALK: Mechanism of Action



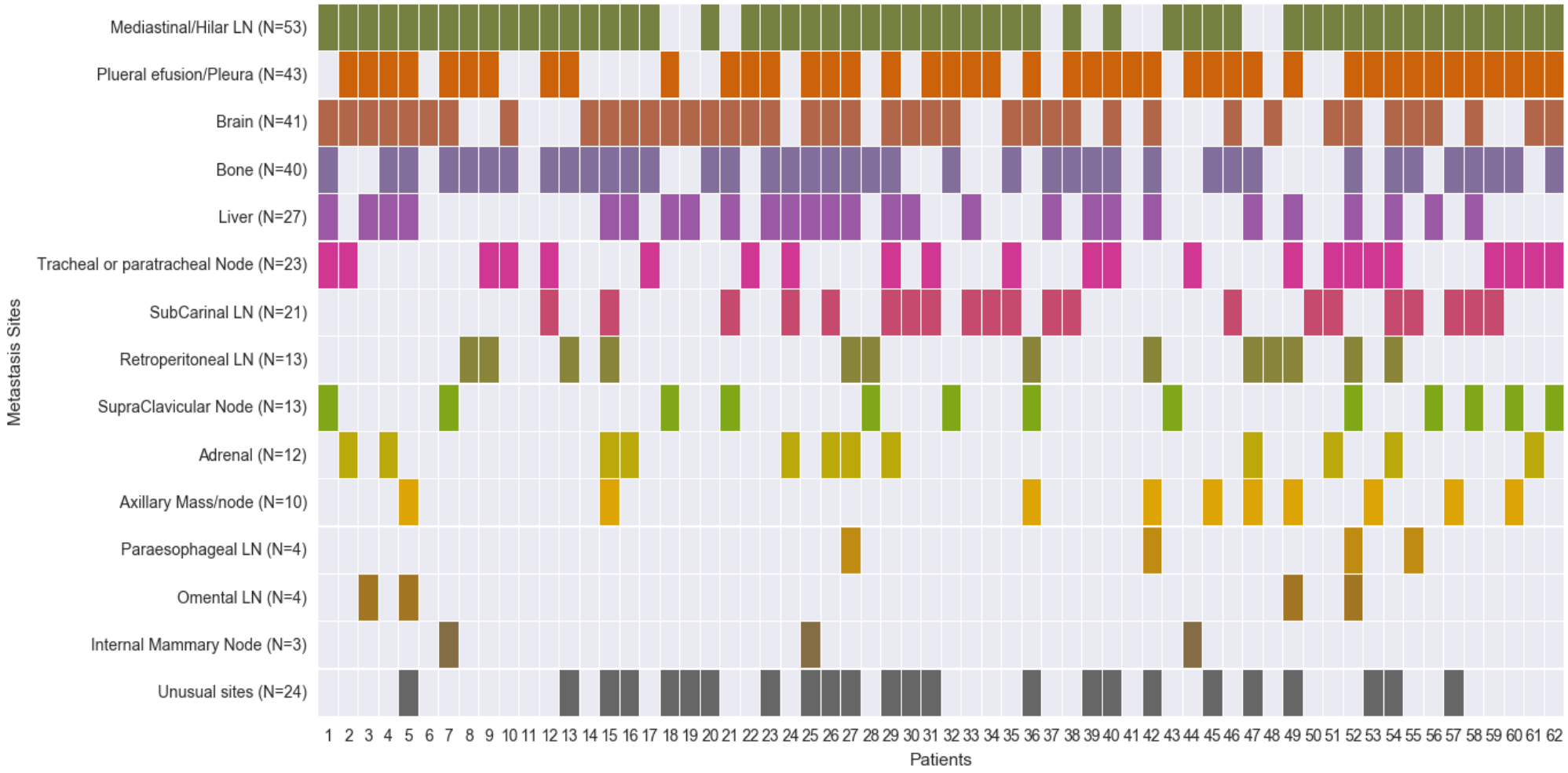
Kong et al., Journal of Medicinal Chemistry 2019

ALK: Timeline of Approval



Elsayed et al, Pharmaceuticals, 2021

Sites of Metastases in ALK patients



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Gupta et int. Salgia, American Journal of Clinical Oncology, 2019

Case #2: Alectinib moves to First-line

Setting	Drug	Generation	FDA approval	EMA approval	Key trials
First line	Alectinib	Second	✓	awaited	J-ALEX/ALEX
First line	Crizotinib	First	✓	✓	PROFILE 1014
First line	Ceritinib	Second	✓	awaited	ASCEND 1,3,4
Post crizotinib	Ceritinib	Second	✓	✓	ASCEND 1,2,5
Post crizotinib	Brigatinib	Second	✓	awaited	ALTA
Post crizotinib	Alectinib	Second	✓	awaited	Phase 2 NA, Intl
Post chemo	Crizotinib	First	✓	✓	PROFILE 1005,1007

Alectinib moves to First-line

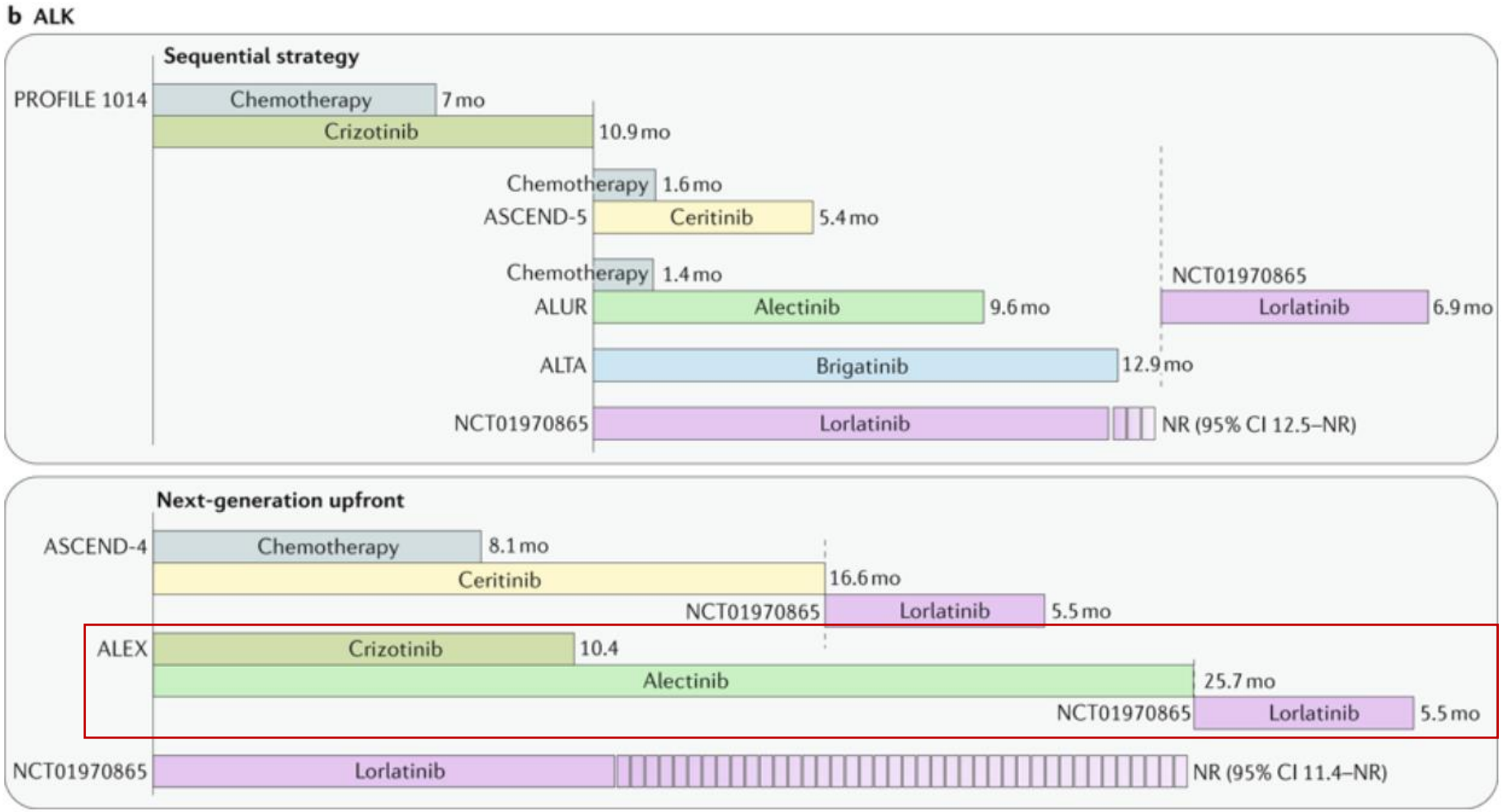
- ALEX places alectinib as the optimal 1st line ALK TKI choice
  - With CNS metastases—enhanced efficacy
  - Without CNS metastases—neuroprotective
  - Questions the role of radiotherapy for CNS disease at presentation

- OS is immature but no current signal of superiority with alectinib
  - PD on crizotinib is salvageable
  - BUT close attention to CNS for failure required (41% at 1yr)

1st-line Phase 3 Trials Ongoing

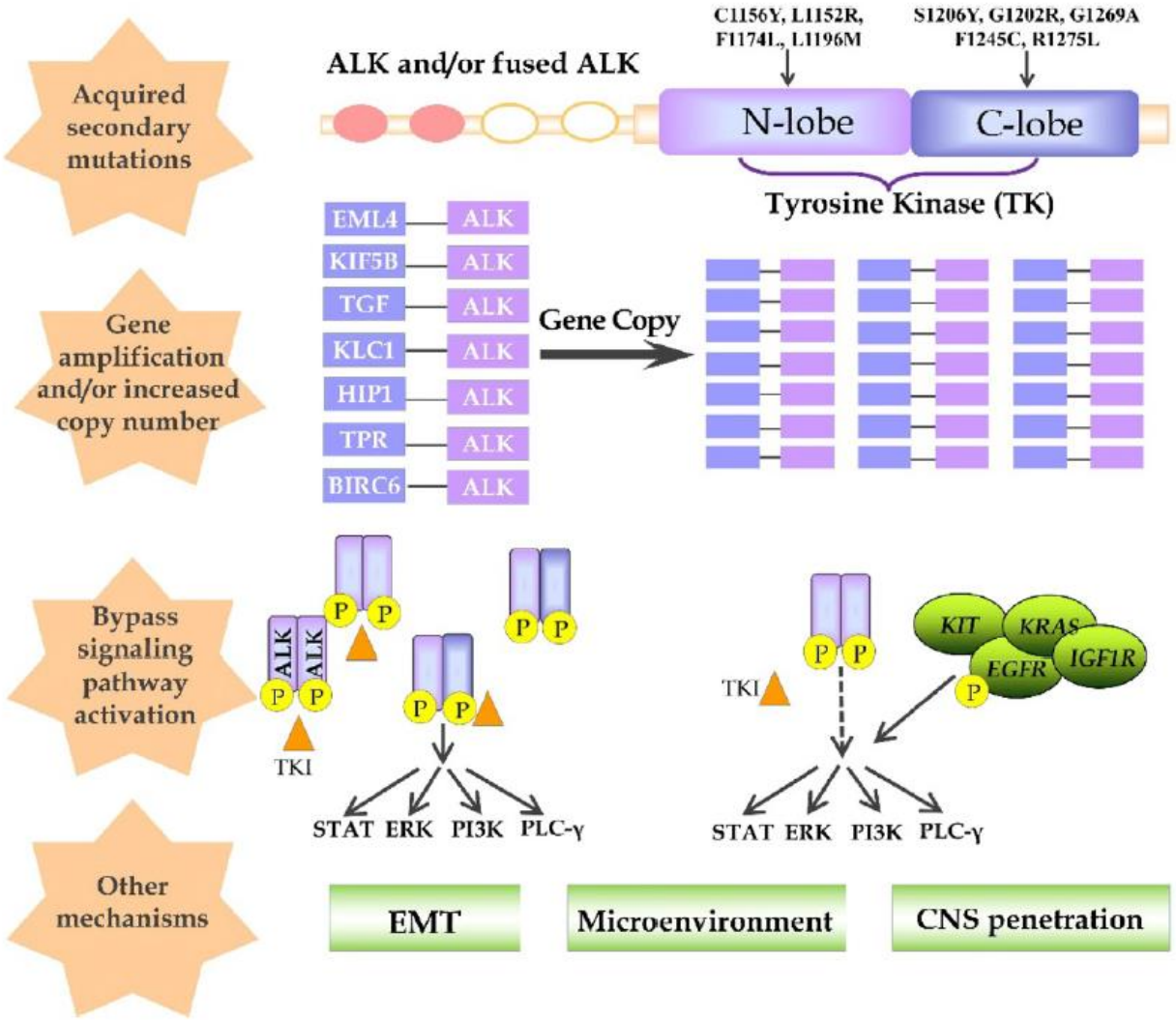
Sponsor	Trial	Drug	Comparator	Target	Reporting date	Trial ID
Takeda	ALTA-1L	brigatinib	crizotinib	270	April 2019	NCT02737501
Pfizer	CROWN	lorlatinib	crizotinib	280	Dec 2019	NCT03052608
Xcovery	eXalt3	ensartinib	crizotinib	402	April 2020	NCT02767804

Overall Sequential Strategy for ALK



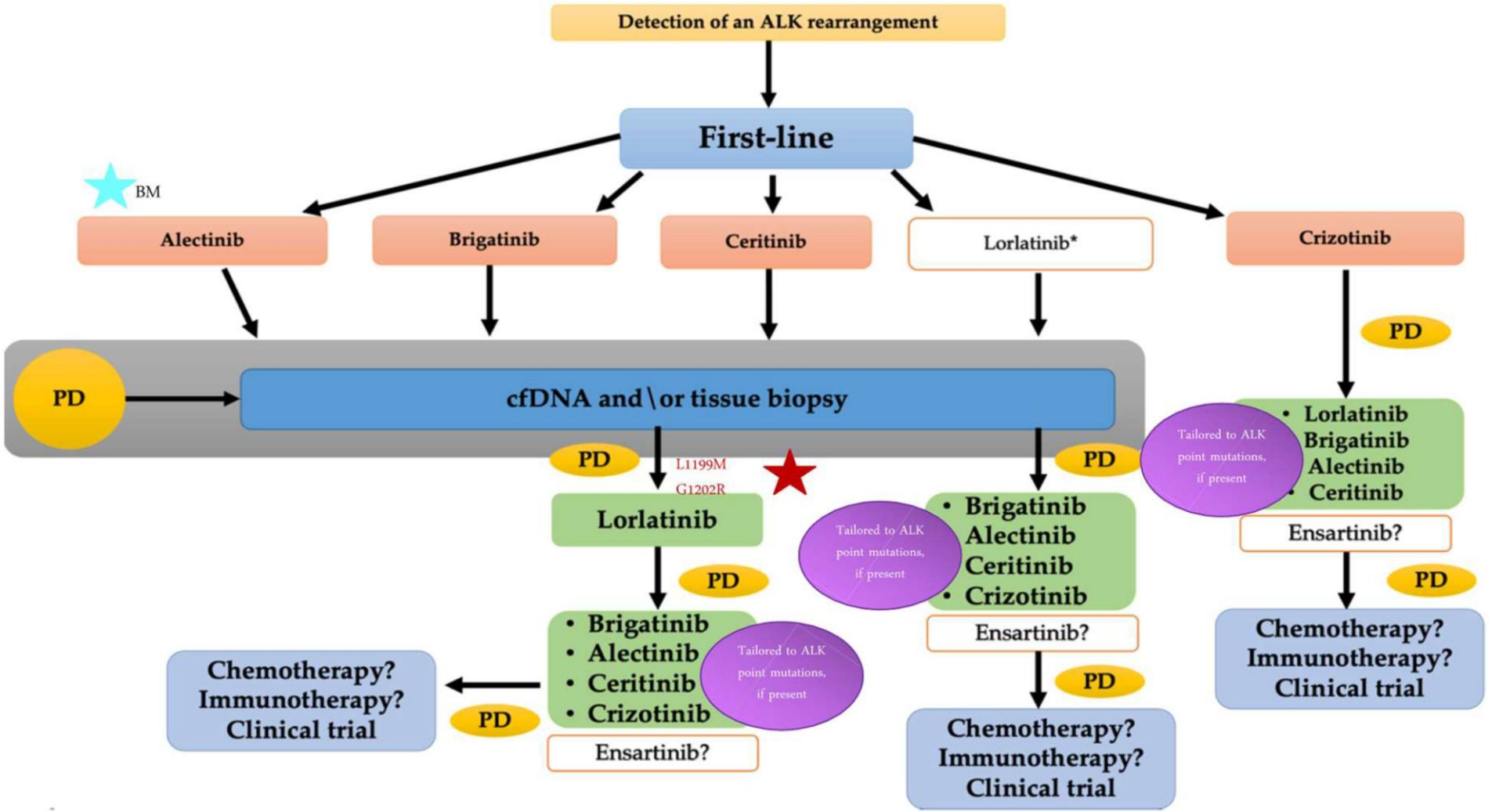
Recondo G et al., Nat Rev Clin Oncol. 2018.

ALK: Mechanisms of Acquired Resistance



Kong et al., Journal of Medicinal Chemistry 2019

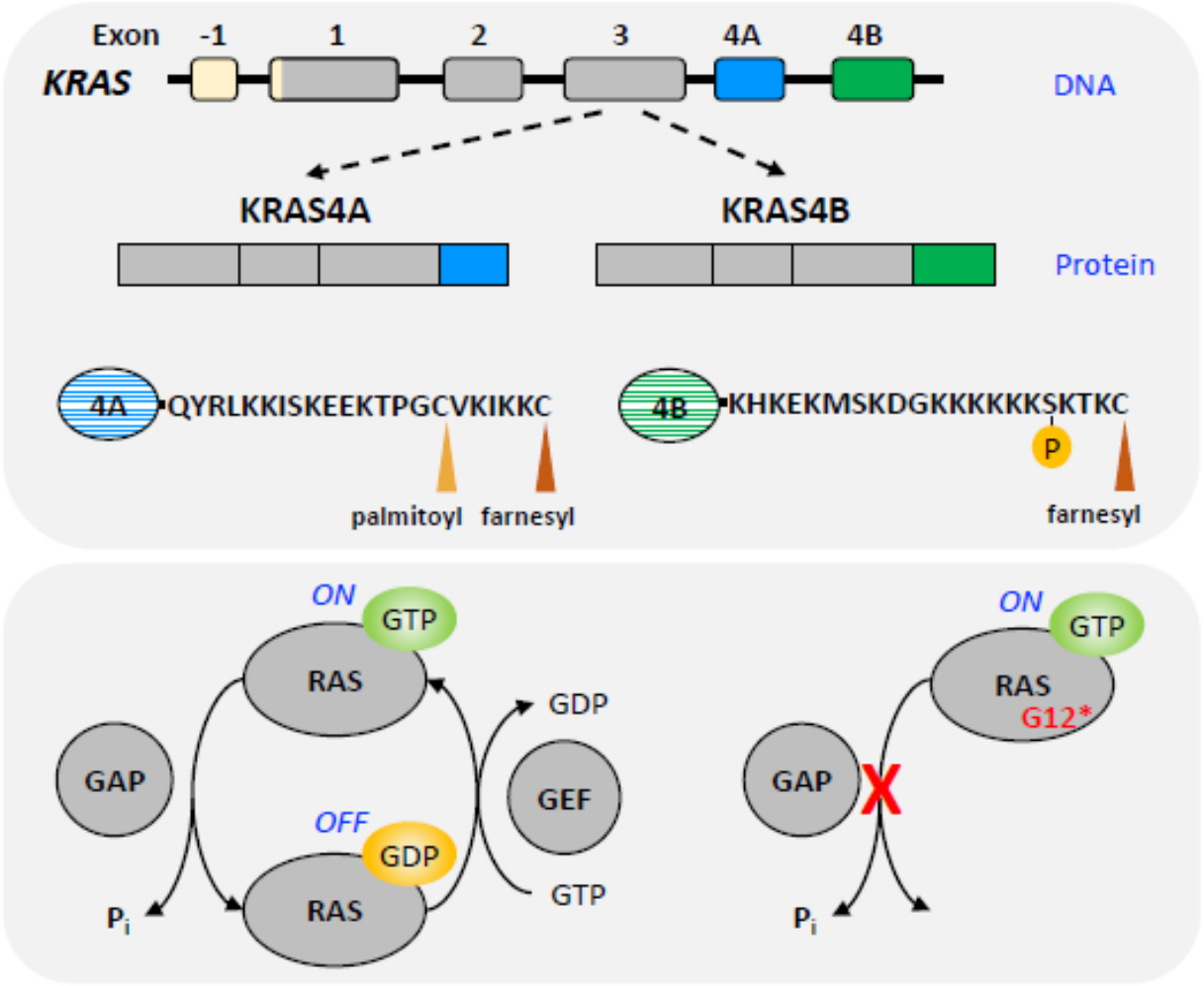
ALK: Current Treatment Strategies



Gristina et al., Pharmaceuticals 2020

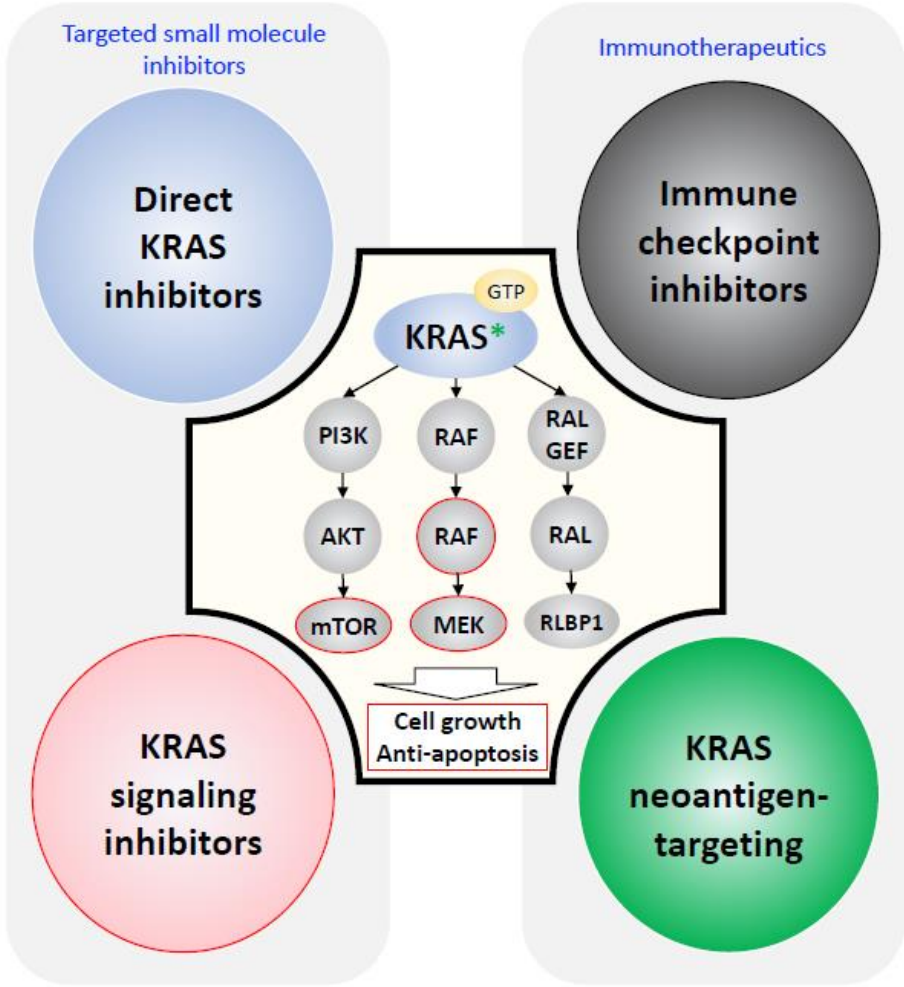
KRAS

KRAS Structure and Function



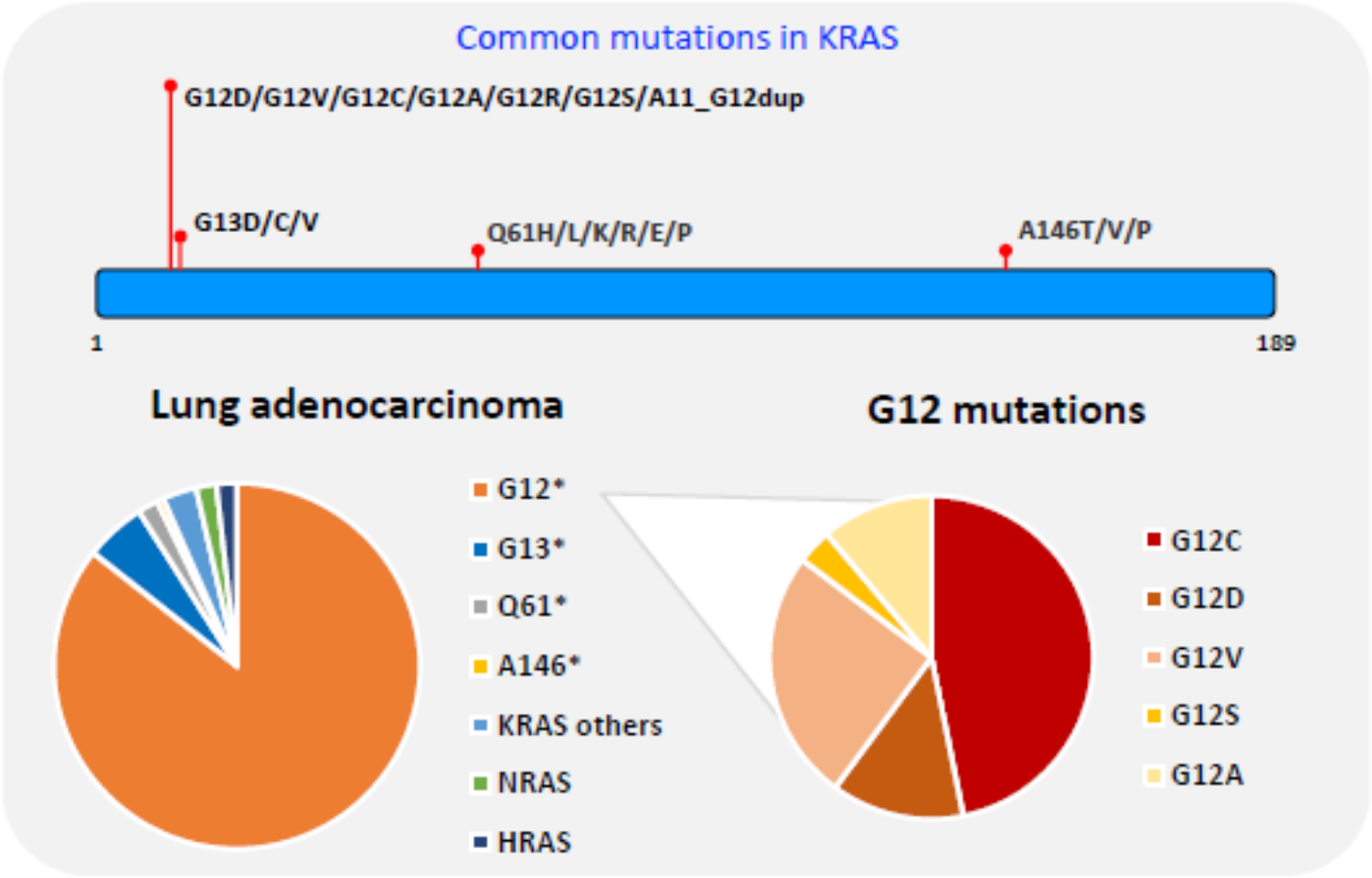
Salgia et int. Sattler, Cell Rep Med, 2021

Therapeutic Approaches in Mutant KRAS Positive Tumors



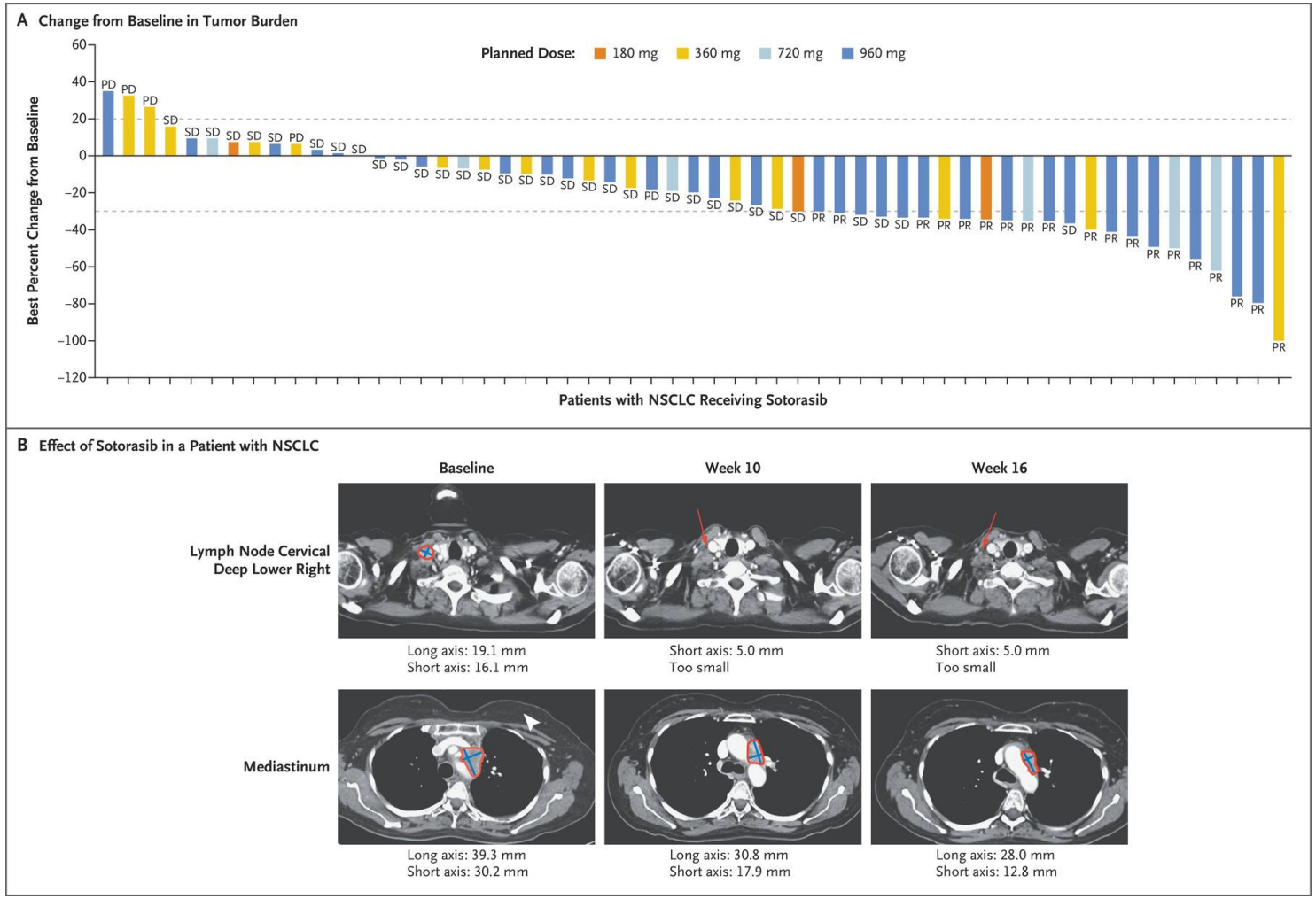
Salgia et int. Sattler, Cell Rep Med, 2021

Common KRAS Mutations in Lung Adenocarcinoma



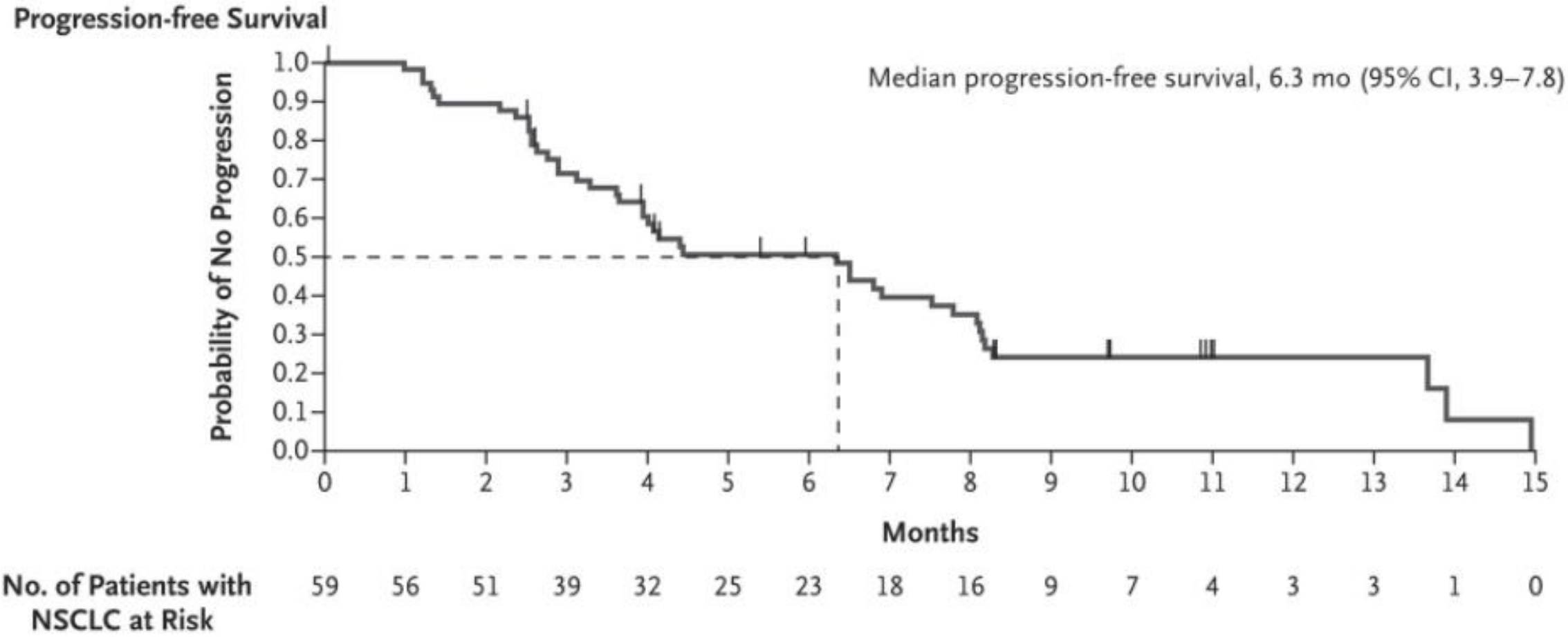
Salgia et int. Sattler, Cell Rep Med, 2021

Phase I Trial KRAS G12C Inhibition with Sotorasib



Hong, Fakih, et al., N. Engl. J. Med., 2020

Phase I Trial KRAS G12C Inhibition with Sotorasib



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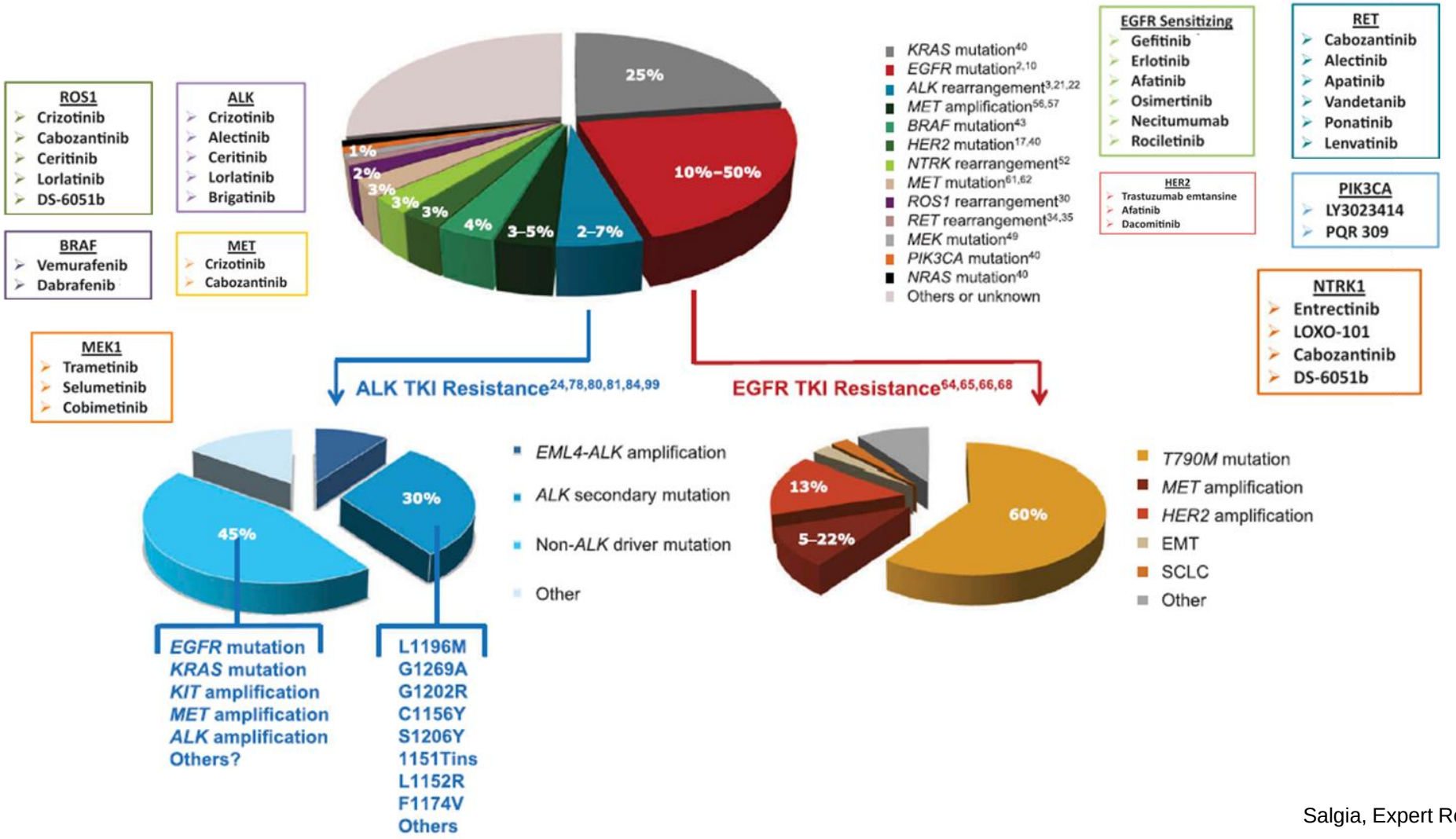
Hong, Fakih, et al., N. Engl. J. Med., 2020

Promising KRAS-Positive Clinical Trials

Therapeutic Drug	Target	Trial	Primary Objective(s)
AMG 510	KRAS G12C	NCT03600883: A Phase 1/2, Study Evaluating the Safety, Tolerability, PK, and Efficacy of AMG 510 in Subjects With Solid Tumors With a Specific KRAS Mutation (CodeBreak 100)	Evaluate the safety and tolerability of AMG 510. Estimate the maximum tolerated dose (MTD) and/or a recommended phase 2 dose. Objective response rate assessed by RECIST 1.1 criteria of AMG 510 as monotherapy.
MRTX849	KRAS G12C	NCT03785249: Phase 1/2 Study of MRTX849 in Patients With Cancer Having a KRAS G12C Mutation KRYSTAL-1	Characterize the safety of MRTX849 and evaluate the pharmacokinetics of the drug. Objective response rate assessed by RECIST 1.1 criteria of MRTX849 as monotherapy.
JNJ-74699157/ ARS-3248	KRAS G12C	NCT04006301: First-in-Human Study of JNJ-74699157 in Participants With Tumors Harboring the KRAS G12C Mutation	Determine the MTD and RP2D of JNJ-74699157. Determine the safety and preliminary antitumor activity of JNJ-74699157.
BI 1701963	Pan-KRAS	NCT04111458: A Phase I Open-label Dose Escalation Trial of BI 1701963 as Monotherapy and in Combination With Trametinib in Patients With KRAS Mutated Advanced or Metastatic Solid Tumors	Determine the MTD and RP2D of BI 1701963 as monotherapy and in combination with trametinib.
mRNA-5671 (cancer vaccine)	KRAS G12C/ G12D/ G13D/ G12V	NCT03948763: A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma	Determine the safety and tolerability and establish a preliminary RP2D of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab infusion.
KRAS-Targeted Long Peptide Vaccine	KRAS	NCT04117087: A Phase 1 Clinical Trial to Access Pooled Mutant KRAS-Targeted Long Peptide Vaccine Combined With Nivolumab and Ipilimumab for Patients With Resected MMR-p Colorectal and Pancreatic Cancer	Evaluate the safety and tolerability of the KRAS-based peptide vaccine. Determine the drug-related toxicities. Determine the fold change in interferon-producing mutant-KRAS-specific CD8 and CD4 T cells at 16 weeks.

NSCLC Targets and Therapies



Salgia, Expert Rev Mol Diagn. 2016

Tsao AS, et al. JTO, 2016

Conclusion

- Lung Cancer is a heterogenous disease
- There are a large number of molecular alterations that can occur
- The specific therapies are dependent on the potential molecular alterations
- There can be genetic and non-genetic mechanisms of resistance that can develop with various TKIs
- It is important to “personalize” the individual therapy
- As more actionable pathways are identified in lung cancer, we need to emphasize further validated targeted therapies