Targeted Therapies in Lung Cancer

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City of Hope

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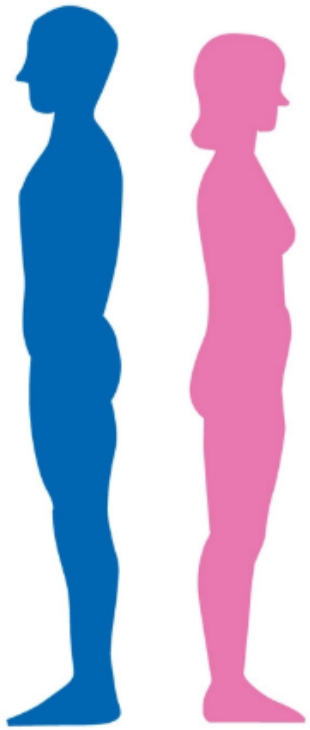
Objectives

- **Lung Cancer**
  - General Overview
- **Targeted Therapies**
- **EGFR**
  - Management
  - Resistance
- **ALK**
  - Management
  - Resistance
- **Immunotherapy**

Lung Cancer Incidence

Estimated New Cases

Males			Females		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	8%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All Sites	**870,970**	**100%**	**All Sites**	**891,480**	**100%**

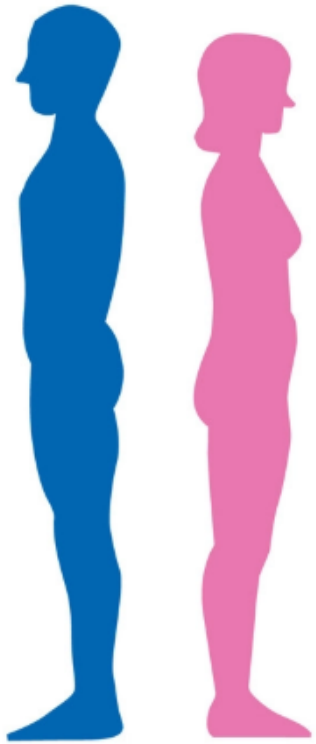


Siegel et. al. Cancer Statistics, 2019

Lung Cancer Mortality

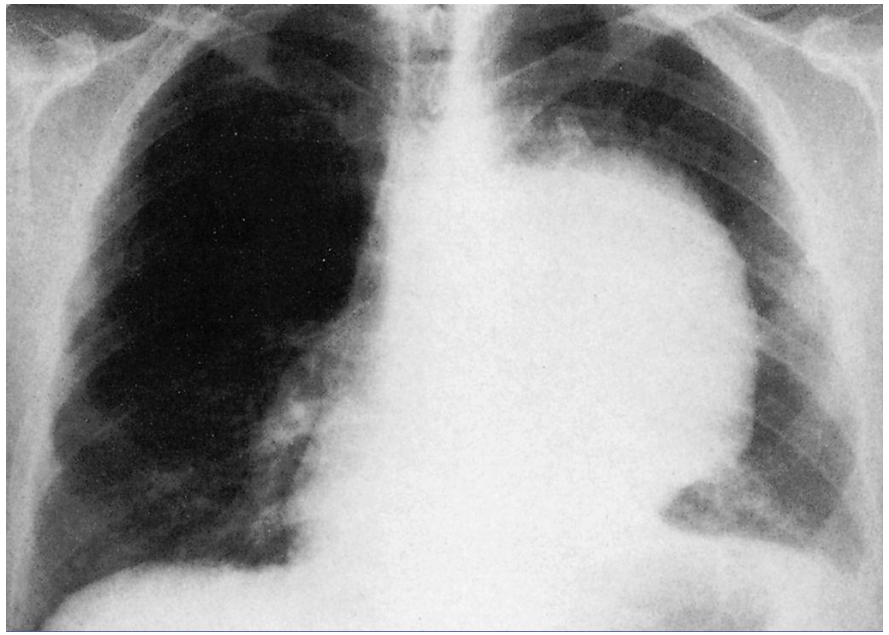
Estimated Deaths

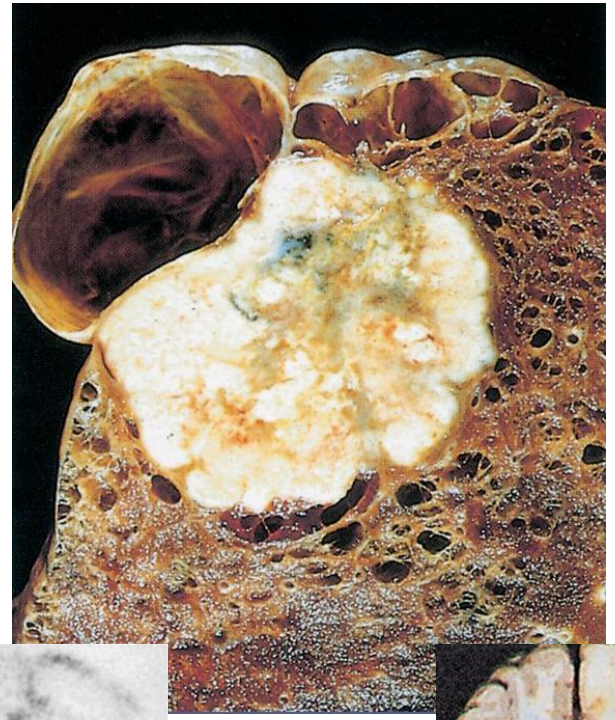
Males			Females		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All Sites	**321,670**	**100%**	**All Sites**	**285,210**	**100%**

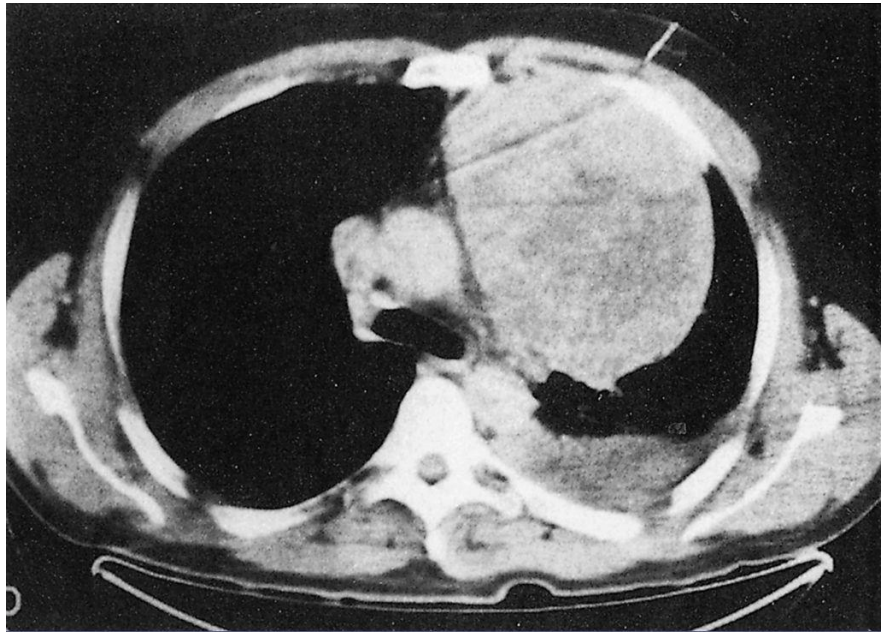


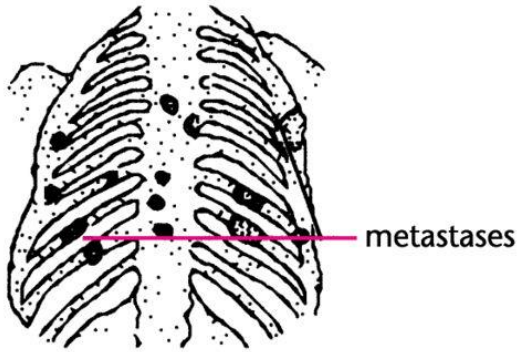
Siegel et. al. Cancer Statistics, 2019

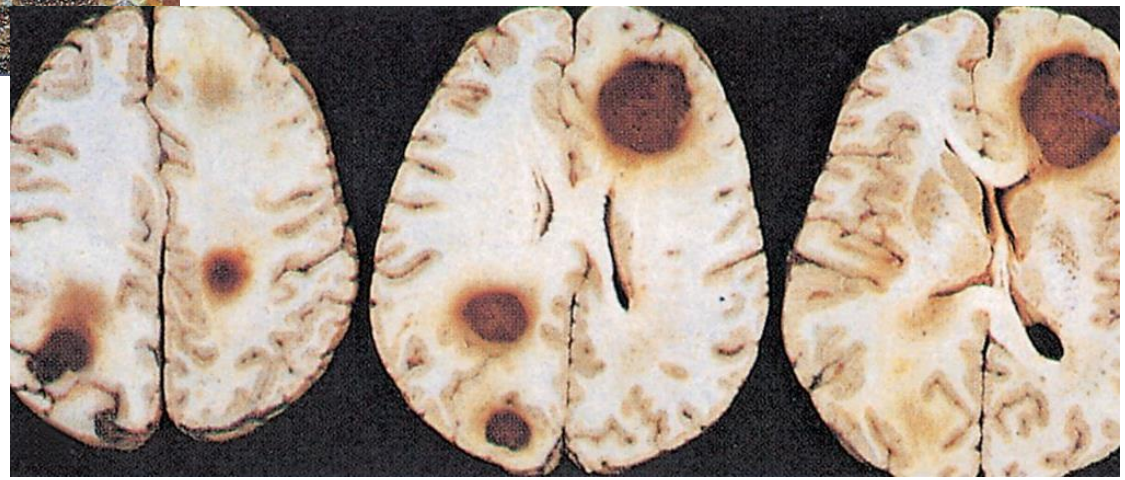
Lung Cancer









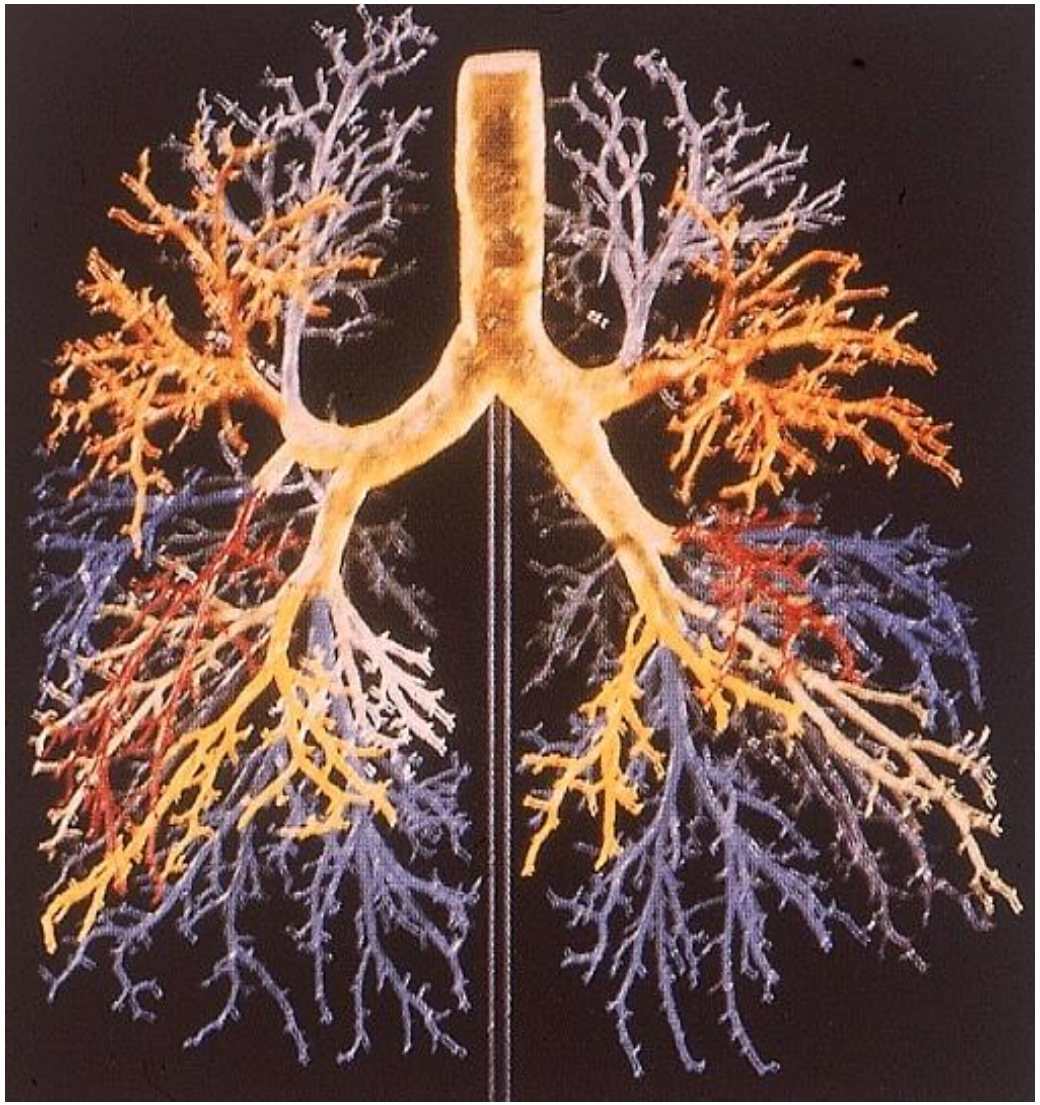


Salgia, et al, 2010

Lung Cancer Location

CENTRAL/HILAR
Squamous Cell Carcinoma
Small Cell Carcinoma

Peripheral
Adenocarcinoma



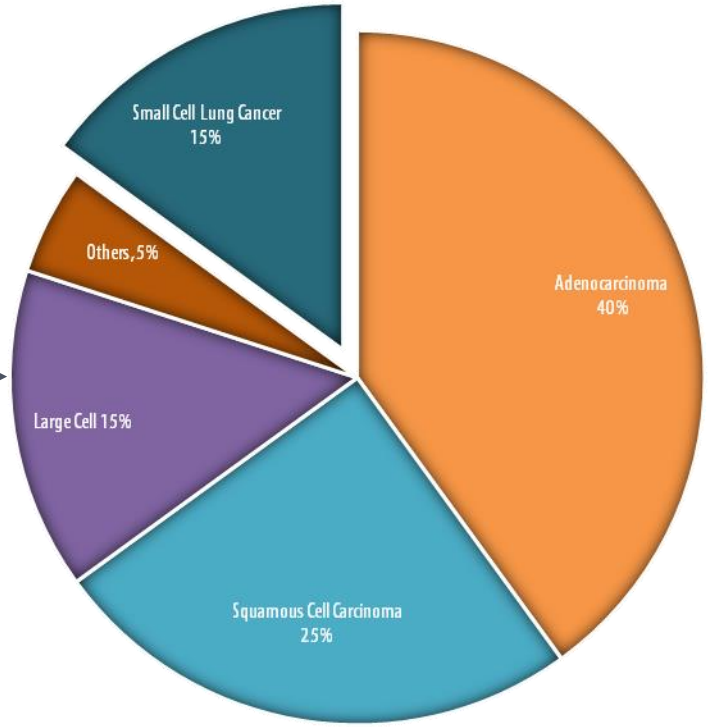
Salgia, et al, 2010

Lung Cancer Classification Timeline

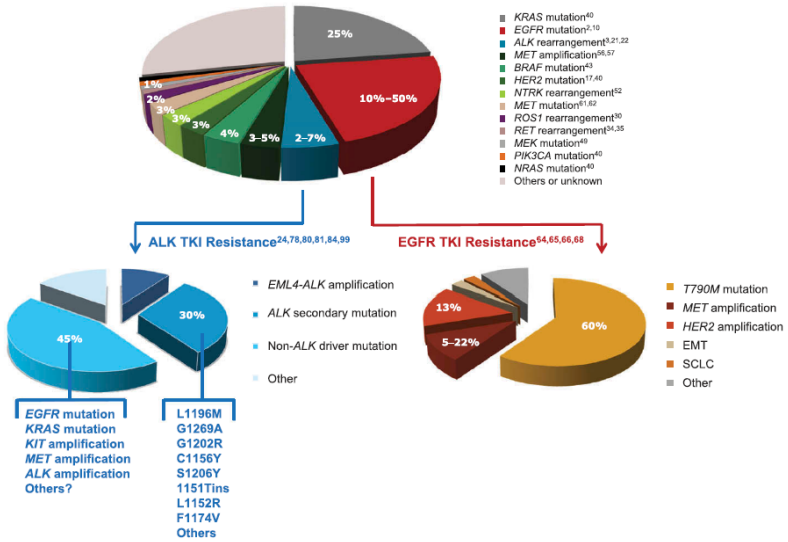
Historical

Lung Cancer as one disease

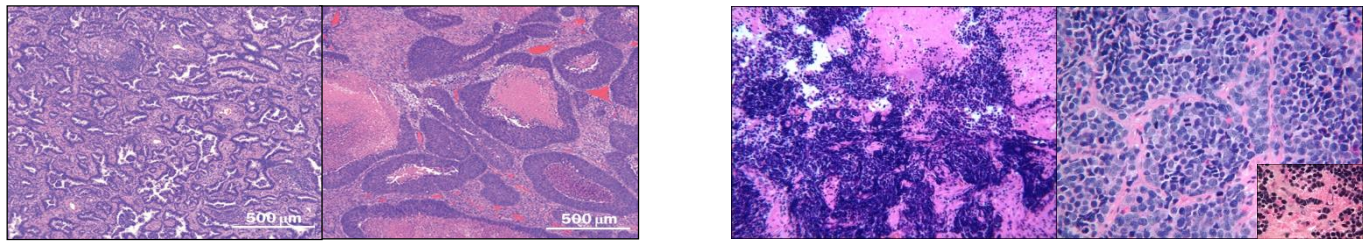
NSCLC and SCLC subtypes



Genomic subtypes



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



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NSCLC

85% of all cases of lung cancer

- Adenocarcinoma ~40%
- Squamous cell carcinoma ~25-30%
- Large cell carcinoma ~10-15%

5-year relative survival rates

- Stage I: ~66-82%
- Stage II: ~47-52%
- Stage III: ~19-36%
- Stage IV: ~6%

Markers of NSCLC subtypes

- TTF-1
- Napsin A
- CK7
- p63
- CK5/6

Grows more slowly

Surgery possible in 35% of patients

<40% chemotherapy response rate

Chemotherapy indicated in Select Patients

Targeted and immunotherapy available

MORE AND MORE THERAPEUTIC OPTIONS TO BECOME AVAILABLE

SCLC

15% of all cases of lung cancer

- Small cell carcinoma >90%
- Combined small cell carcinoma <10%
- Variant <5%

5-year relative survival rates

- Stage I: **~31%**
- Stage II: **~19%**
- Stage III: **~8%**
- Stage IV: **~2%**

Markers of Neuroendocrine Differentiation

- Chromogrannin A
- Synaptophysin
- Leu-7
- Bombesin or Gastrin Releasing Peptide

Fast growing and aggresive

Surgery possible in <10% of patients

>80% chemotherapy response rate

Chemotherapy indicated in All Patients

Treatment limited to Platinum chemo and radiation

MORE WORK NEEDS TO BE DONE IN TERMS OF BIOLOGY AND THERAPEUTICS

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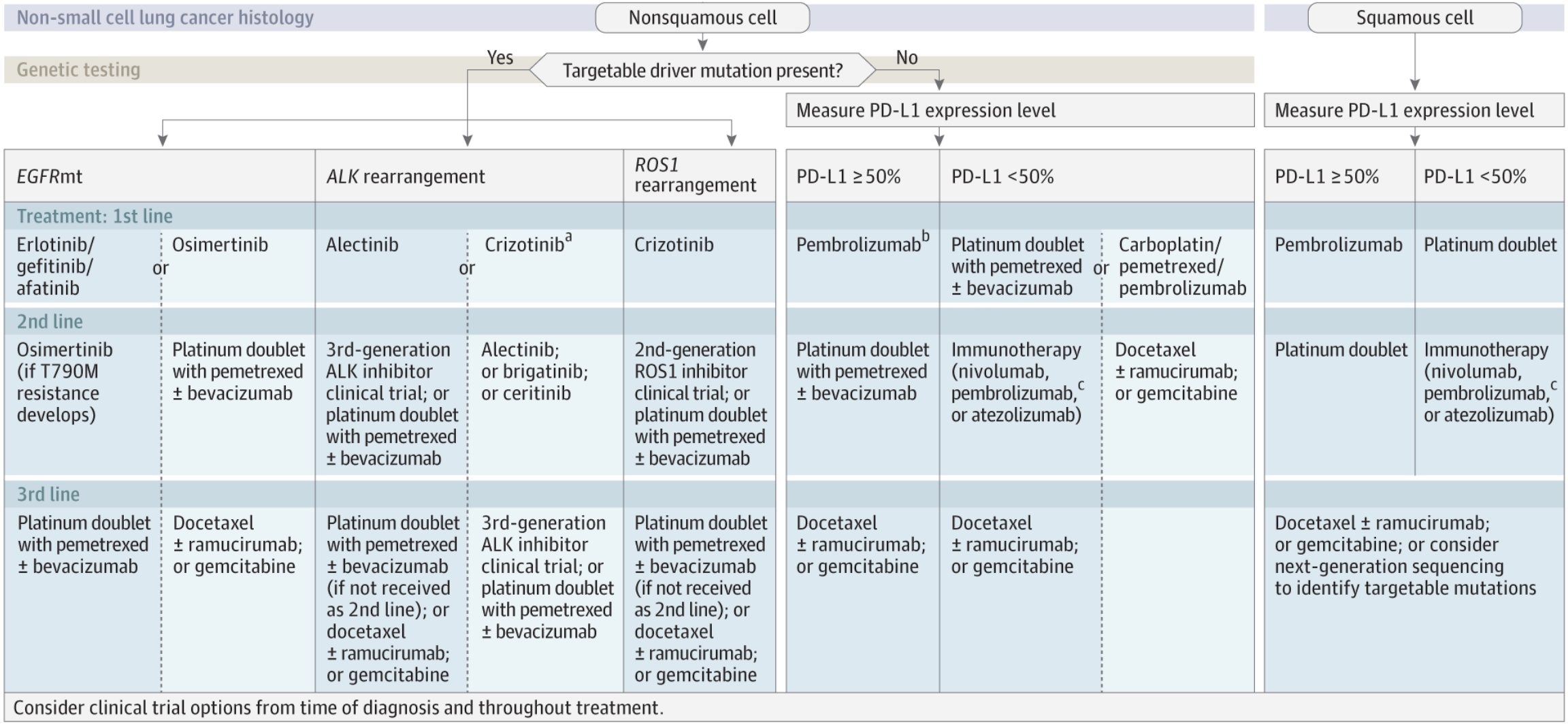
NSCLC management



Abbreviations: PD-L1, programmed cell death 1 ligand 1; *EGFR*mt, *EGFR* mutated.

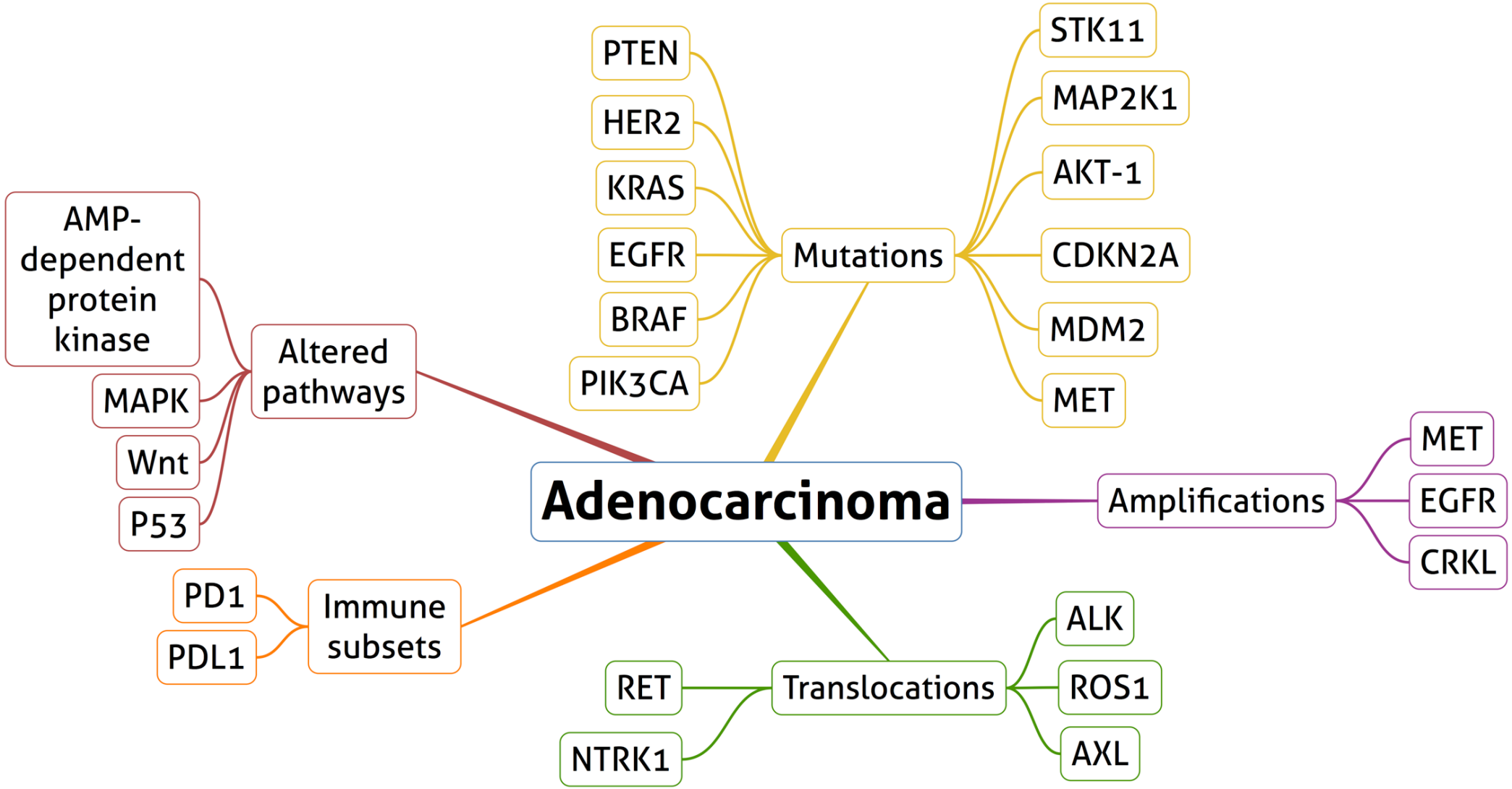
[a]If crizotinib treatment was started prior to FDA approval of alectinib for 1st-line treatment.

[b]Carboplatin/pemetrexed/pembrolizumab is also FDA approved in this setting.

[c]Pembrolizumab use requires PD-L1 >1%.

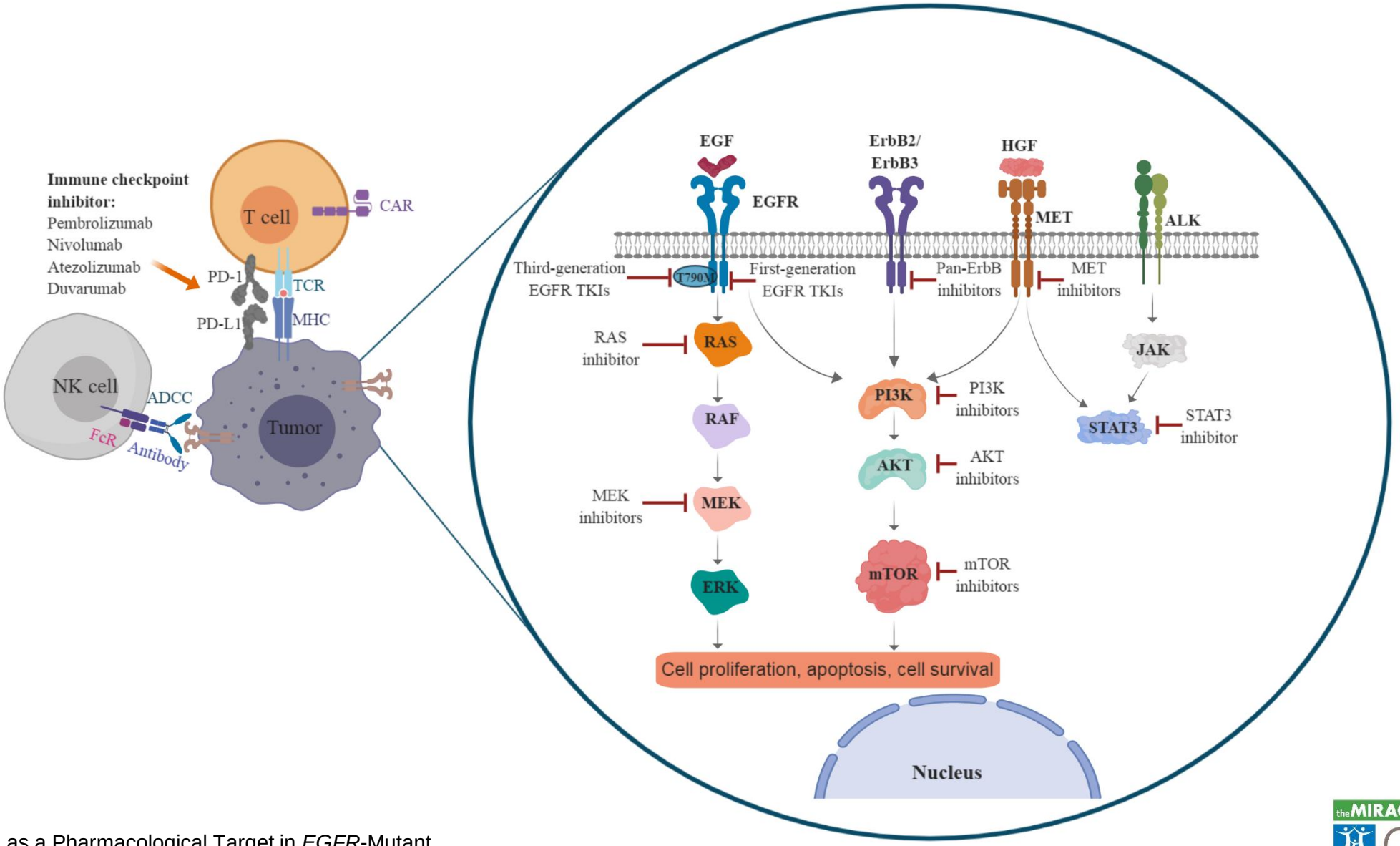
Doroshow et al. JAMA Oncology 2018

Genomics



Hensing, Mambetsariev, Salgia; 2017; in Pass et al. IASLC Thoracic Oncology 2nd Ed.

EGFR Mechanism of Action



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

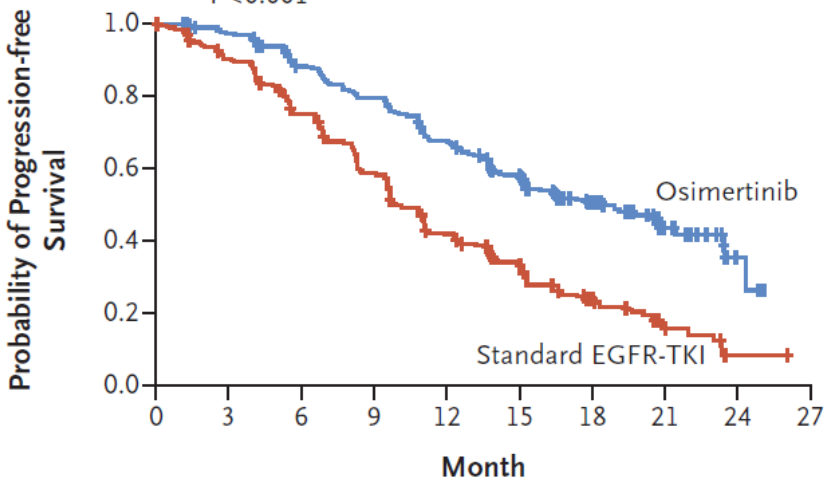
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

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

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



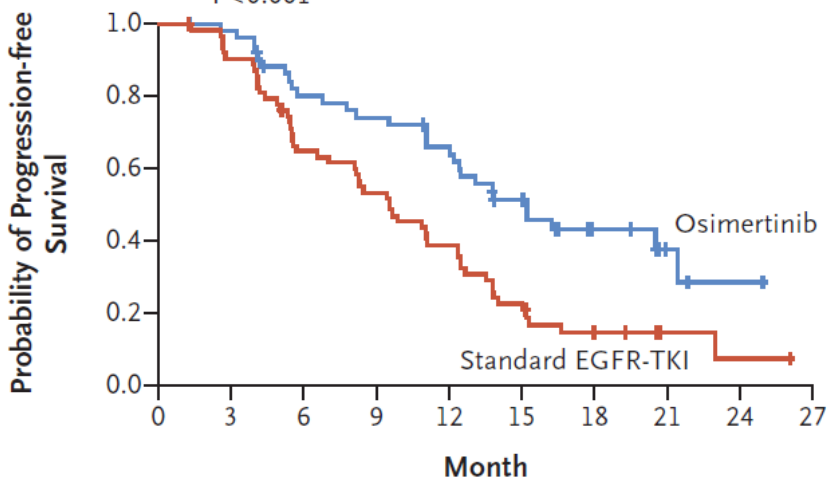
No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

B Progression-free Survival in Patients with CNS Metastases

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	53	15.2 (12.1–21.4)
Standard EGFR-TKI	63	9.6 (7.0–12.4)

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)
P<0.001



No. at Risk

Osimertinib	53	51	40	37	32	22	9	4	1	0
Standard EGFR-TKI	63	57	40	33	24	13	6	2	1	0

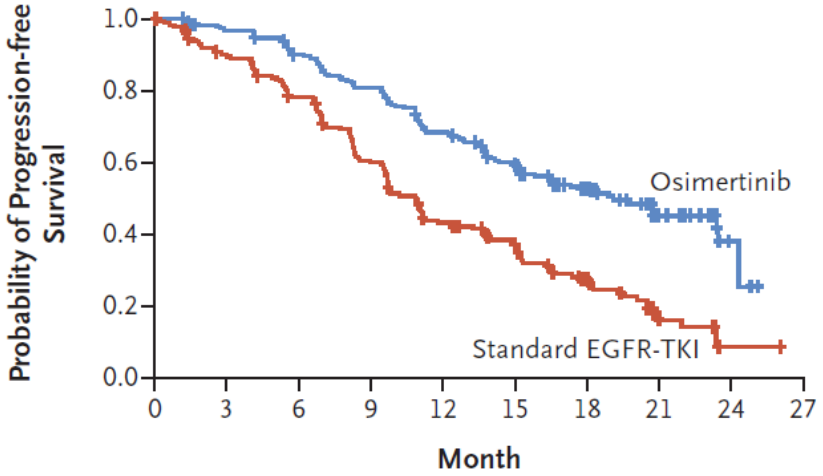
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

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

C Progression-free Survival in Patients without CNS Metastases

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	226	19.1 (15.2–23.5)
Standard EGFR-TKI	214	10.9 (9.6–12.3)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.36–0.59)
P<0.001

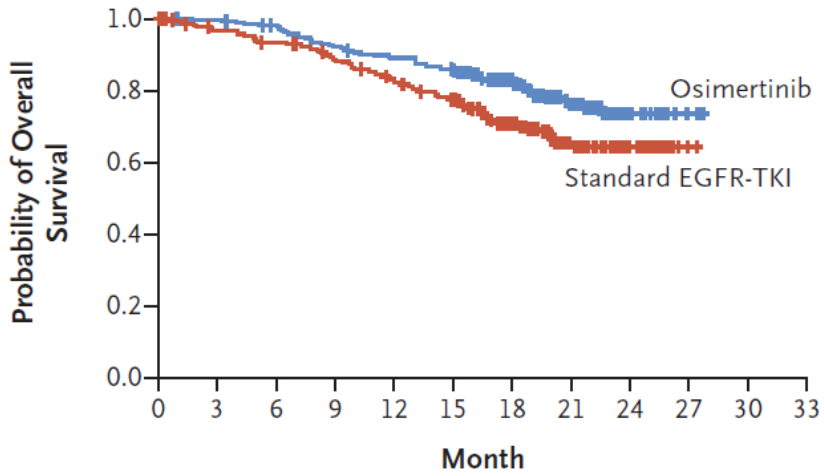


No. at Risk										
Osimertinib	226	211	193	173	146	117	62	22	3	0
Standard EGFR-TKI	214	182	157	119	83	65	31	8	1	0

D Overall Survival

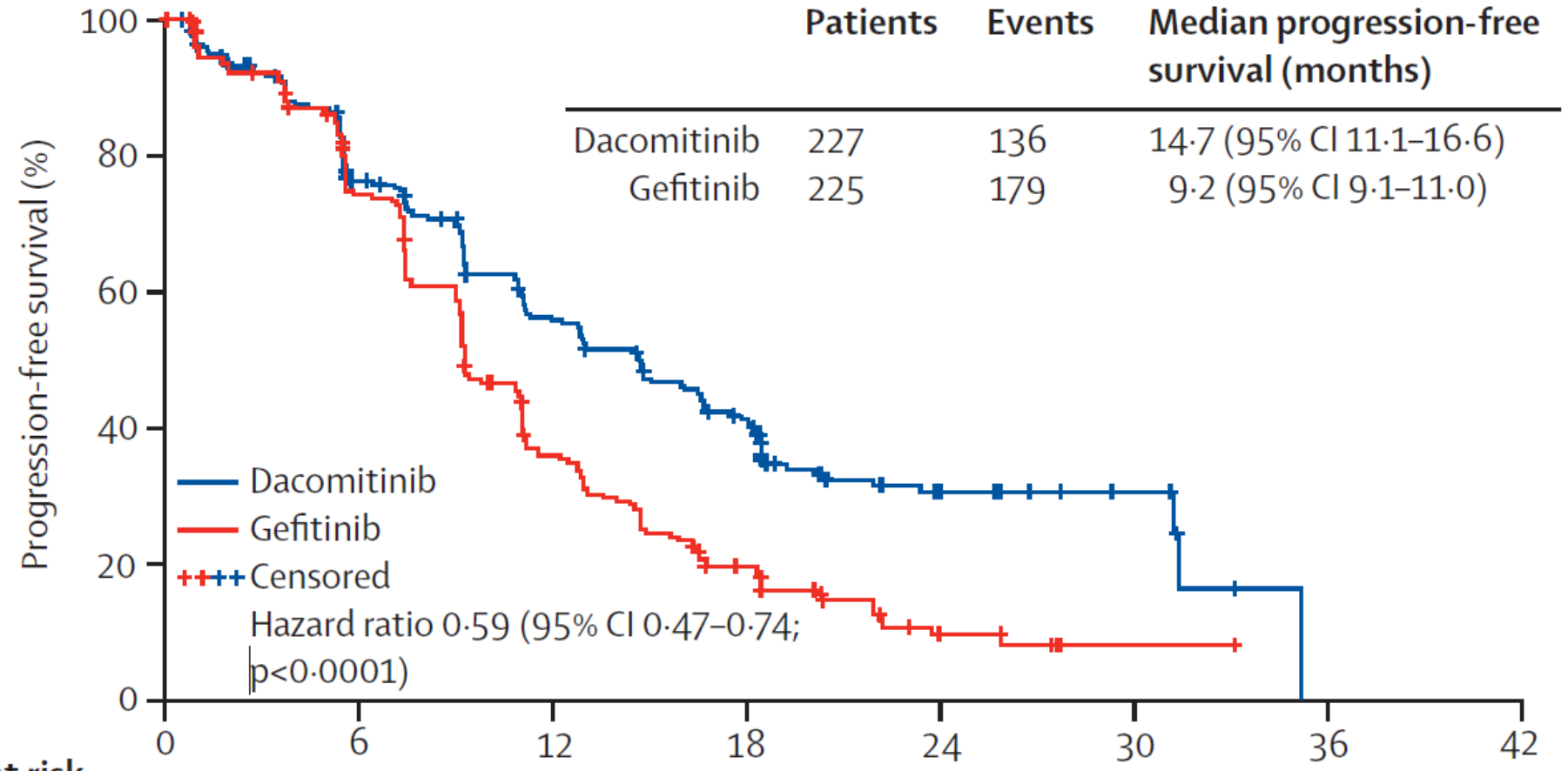
	No. of Patients	Median Overall Survival (95% CI)
		mo
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007



No. at Risk												
Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

Dacomitinib vs Gefitinib PFS (ARCHER-1050)

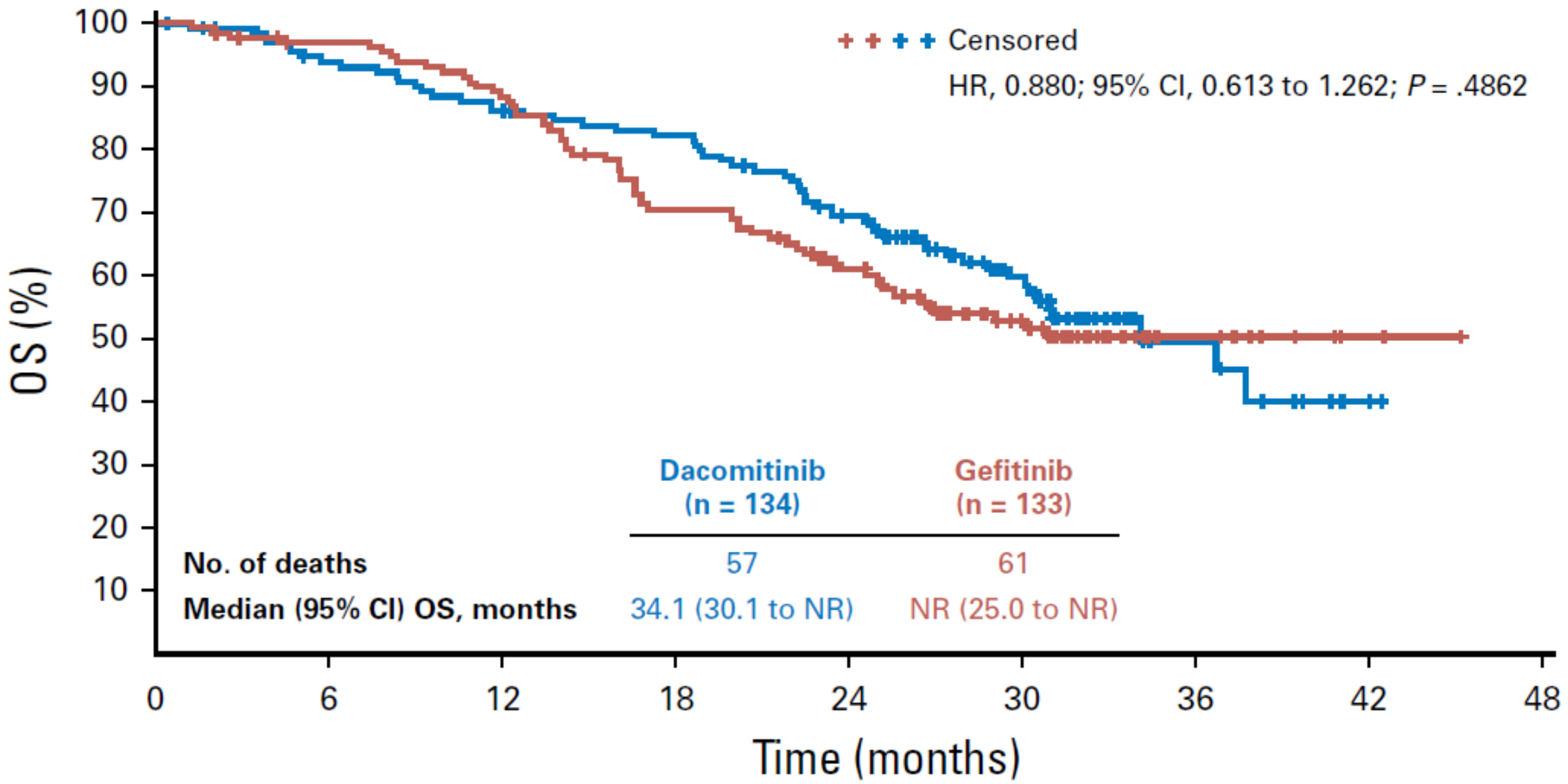


	Patients	Events	Median progression-free survival (months)
Dacomitinib	227	136	14·7 (95% CI 11·1–16·6)
Gefitinib	225	179	9·2 (95% CI 9·1–11·0)

Number at risk (number censored)								
Dacomitinib	227 (0)	154 (23)	106 (31)	73 (36)	20 (74)	6 (88)	0 (91)	0 (91)
Gefitinib	225 (0)	155 (15)	69 (23)	34 (27)	7 (40)	1 (45)	0 (46)	0 (46)

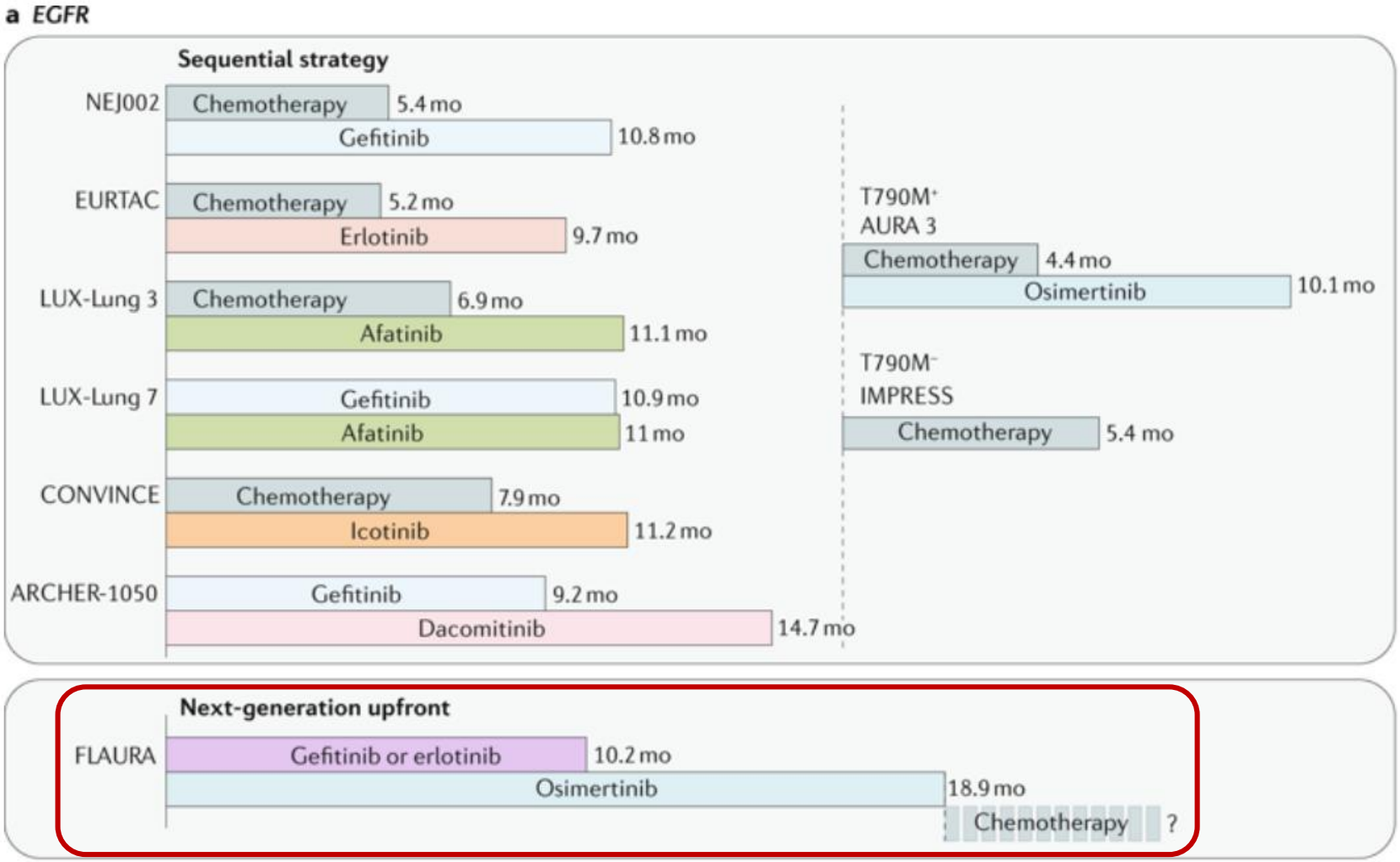
Wu et al., Lancet 2018

Dacomitinib vs Gefitinib OS (ARCHER-1050)



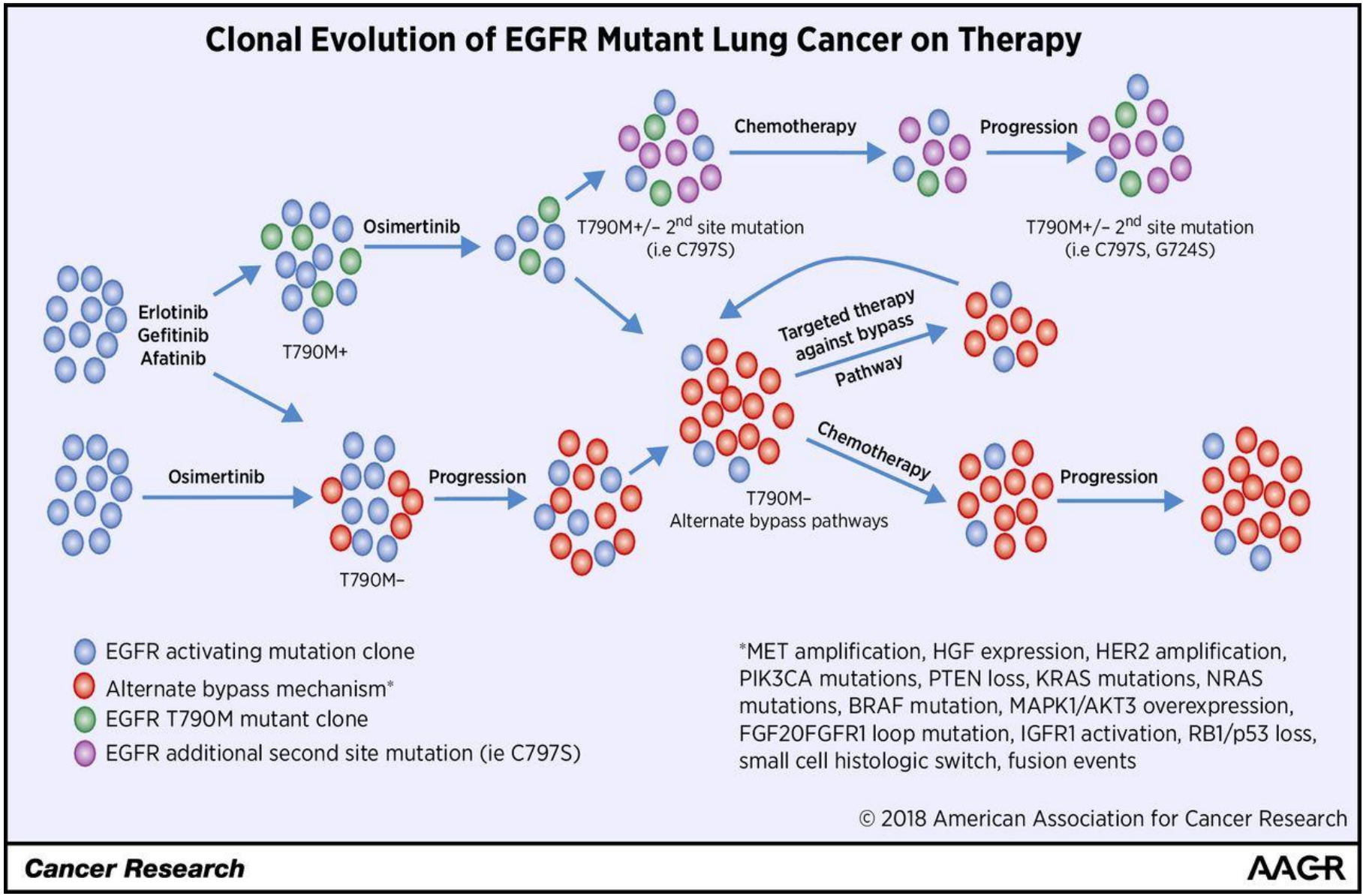
Mok et al., JCO 2018

Frontline EGFR Treatment PFS



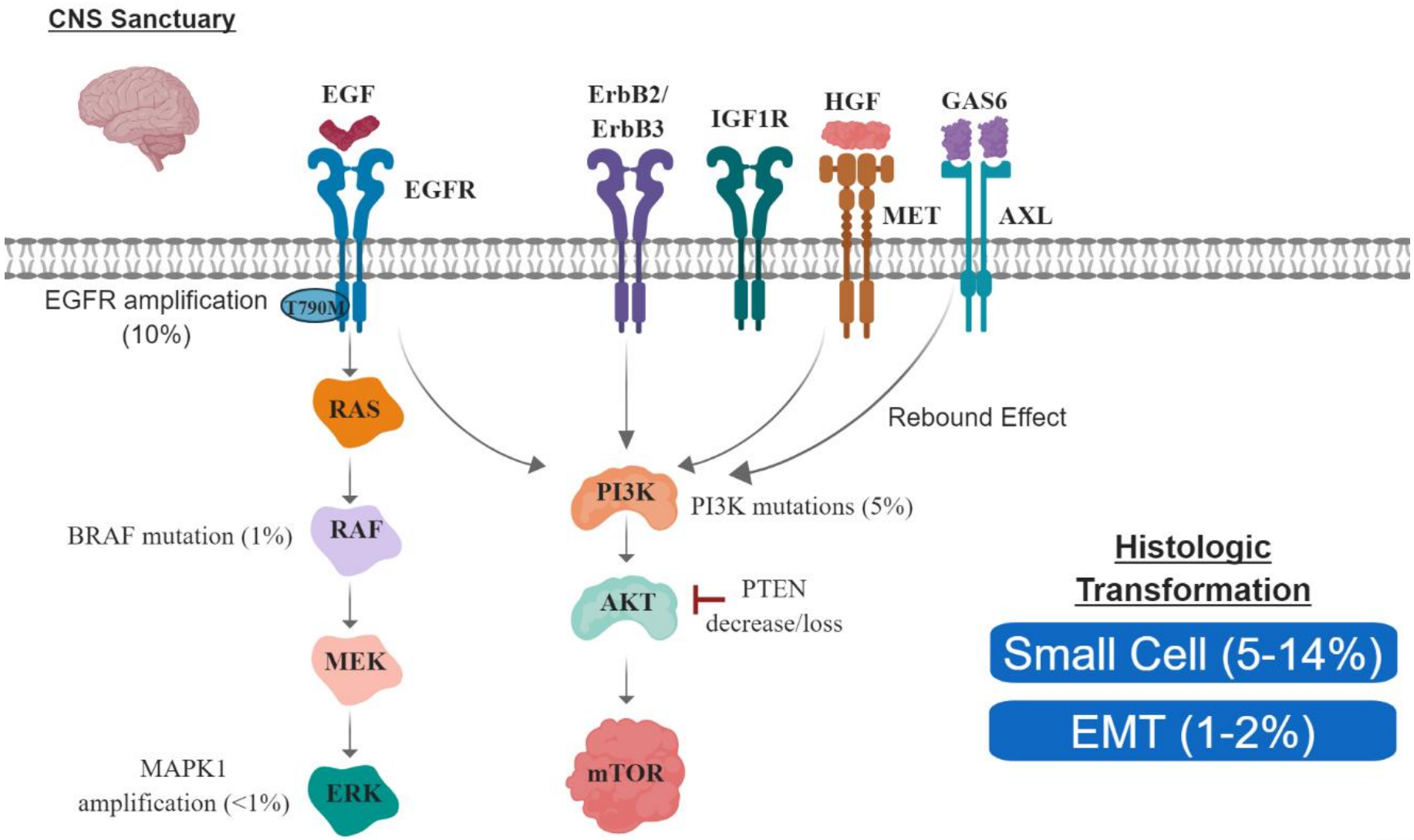
Recondo G et al. Making the first move in EGFR-driven or ALK-driven NSCLC: first-generation or next-generation TKI? Nat Rev Clin Oncol. 2018 Aug 14.

EGFR Clonal Evolution



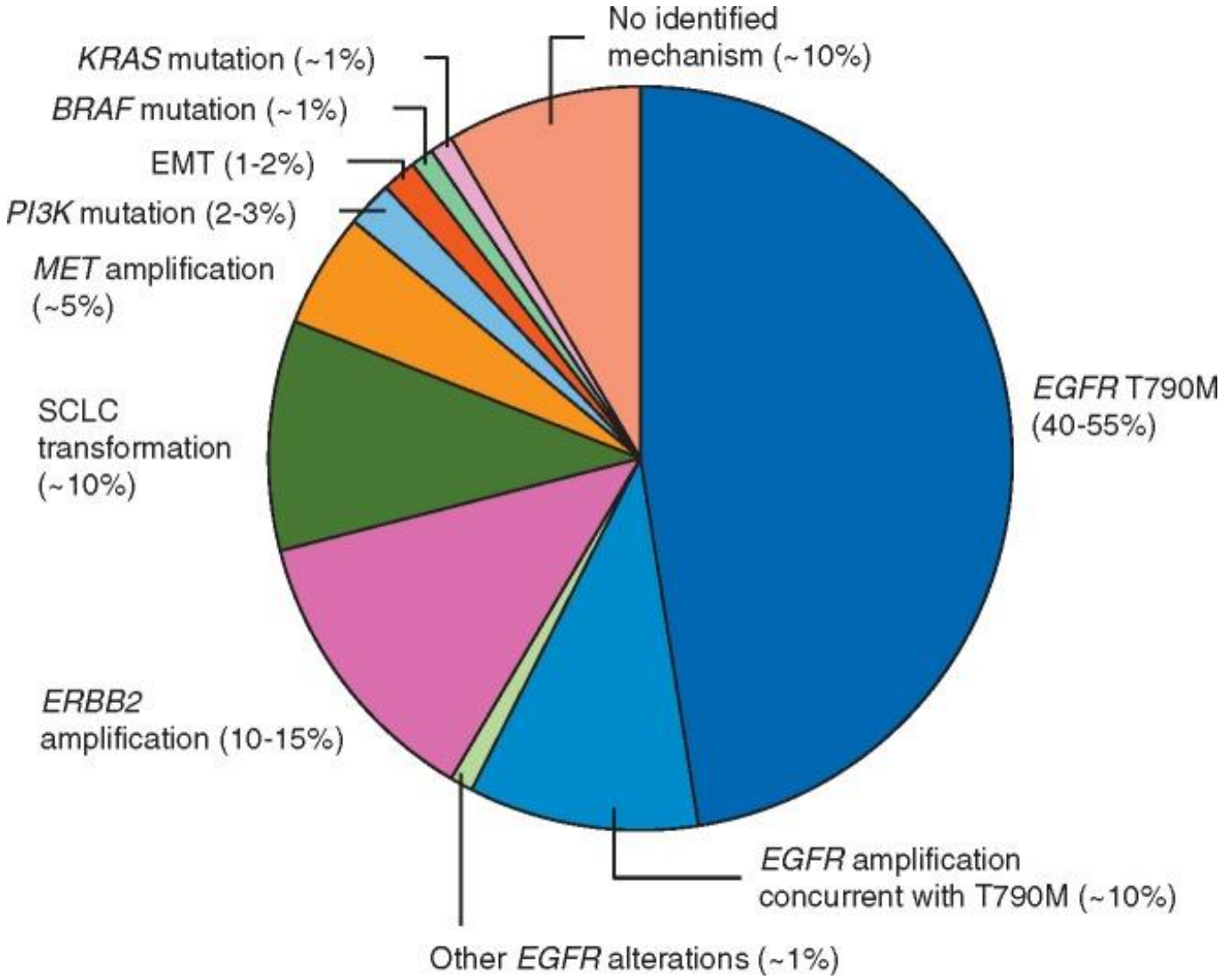
Murtuza et al. Cancer Research 2019

EGFR Mechanisms of Resistance



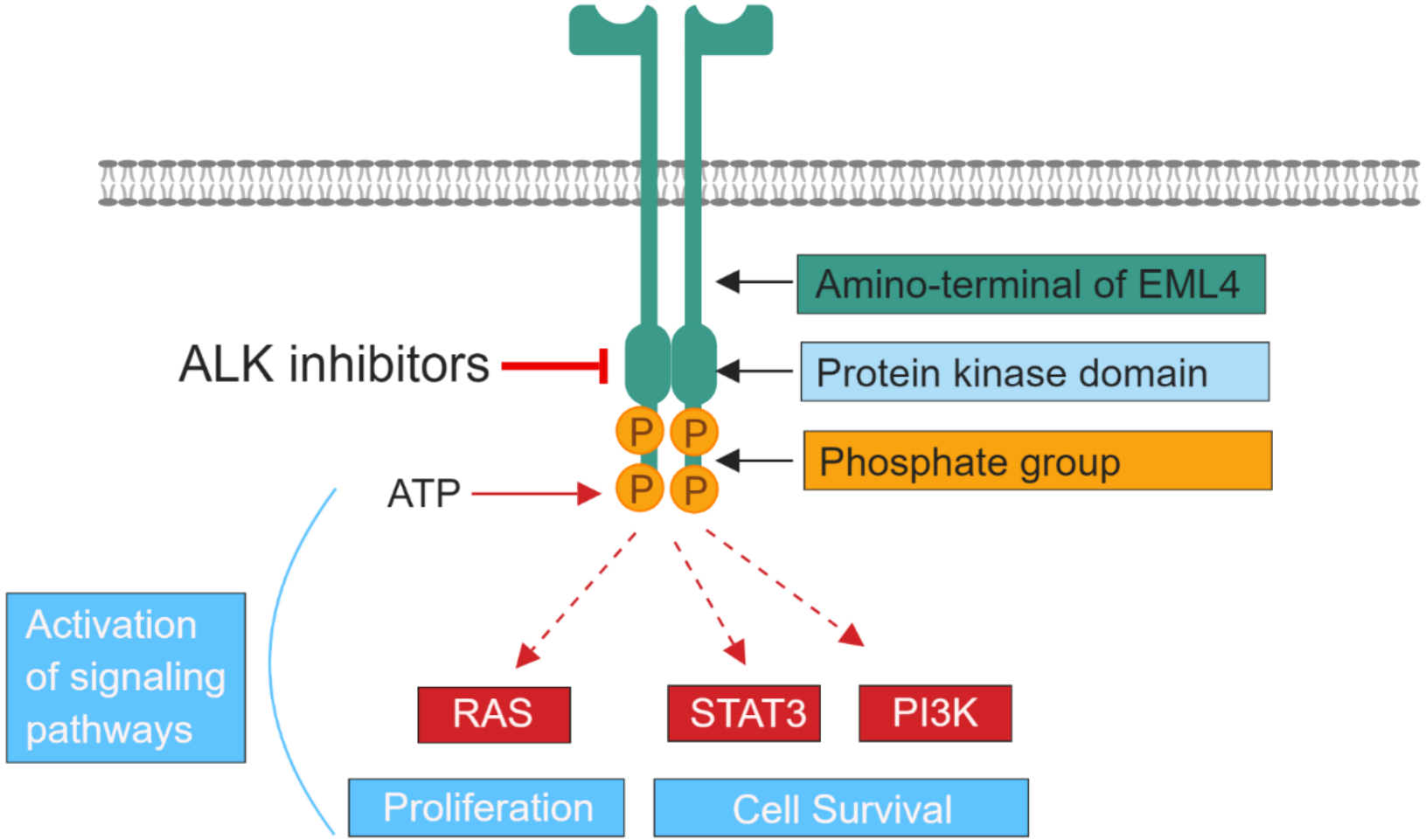
Adapted from: Management of EGFR-mutated non-small-cell lung cancer: practical implications from a clinical and pathology perspective. M. Cabanero et al. Current Oncology. 2017

EGFR TKI Resistance Frequencies



Westover et al. Ann. Oncol., 2018

ALK Mechanism of Action

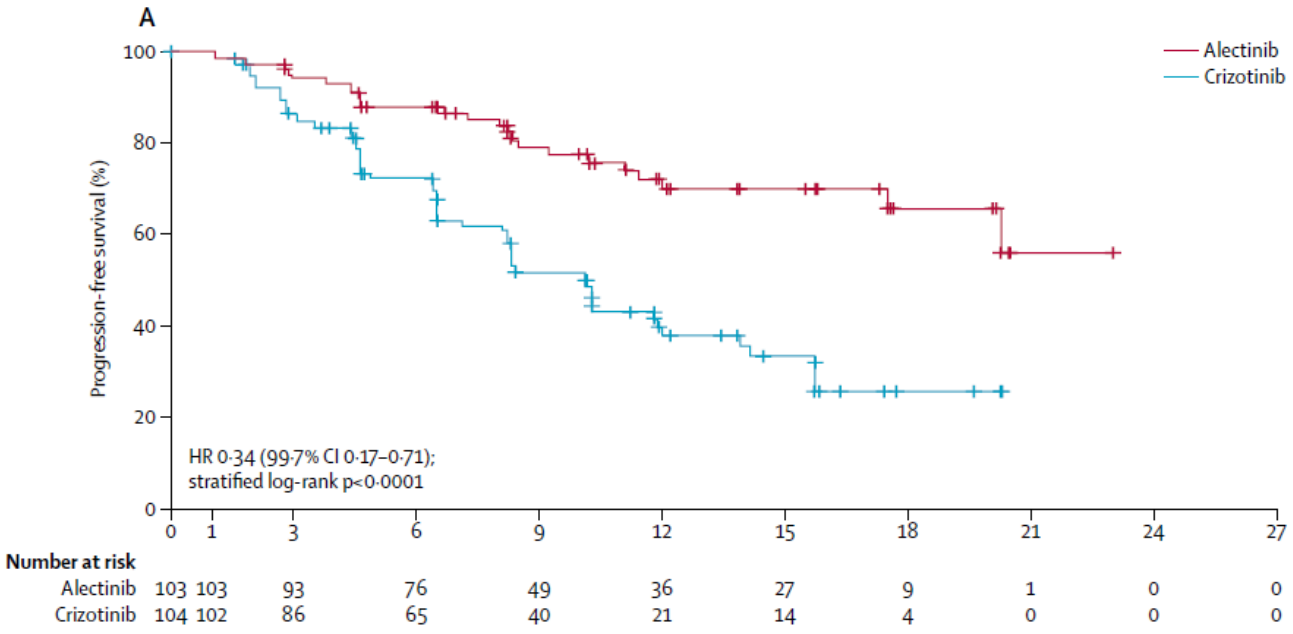


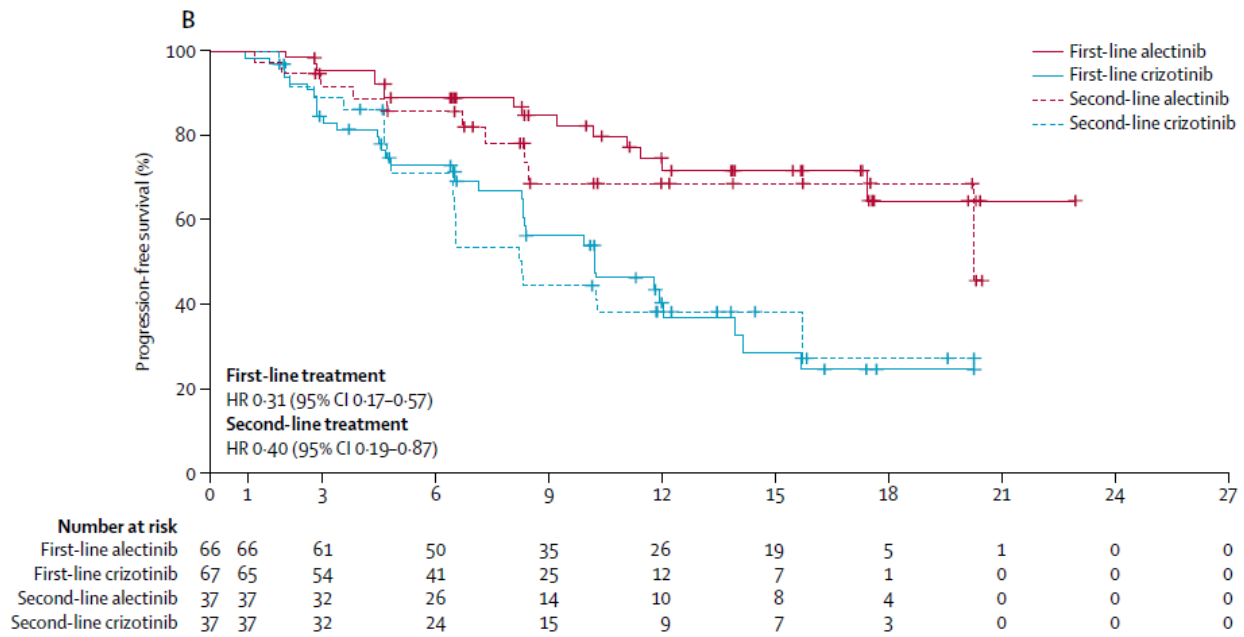
Adapted from: http://www.personalizedmedonc.com/article/alectinib-an-anaplastic-lymphoma-kinase-alk-inhibitor/

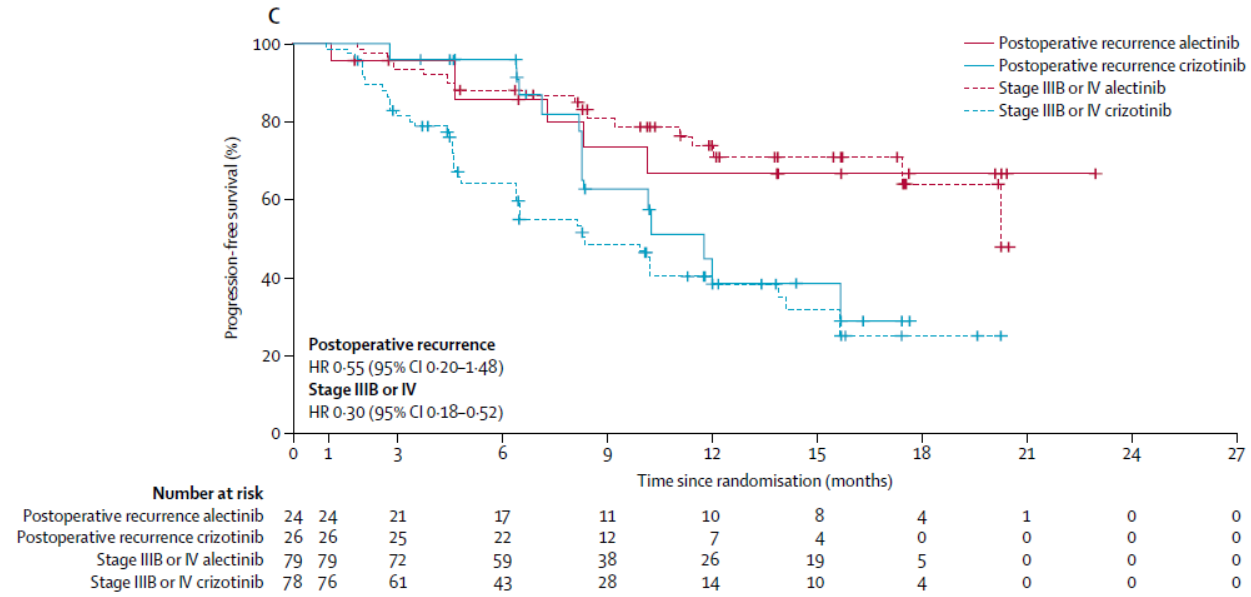
ALK rearranged NSCLC

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 versus Crizotinib (J-ALEX)

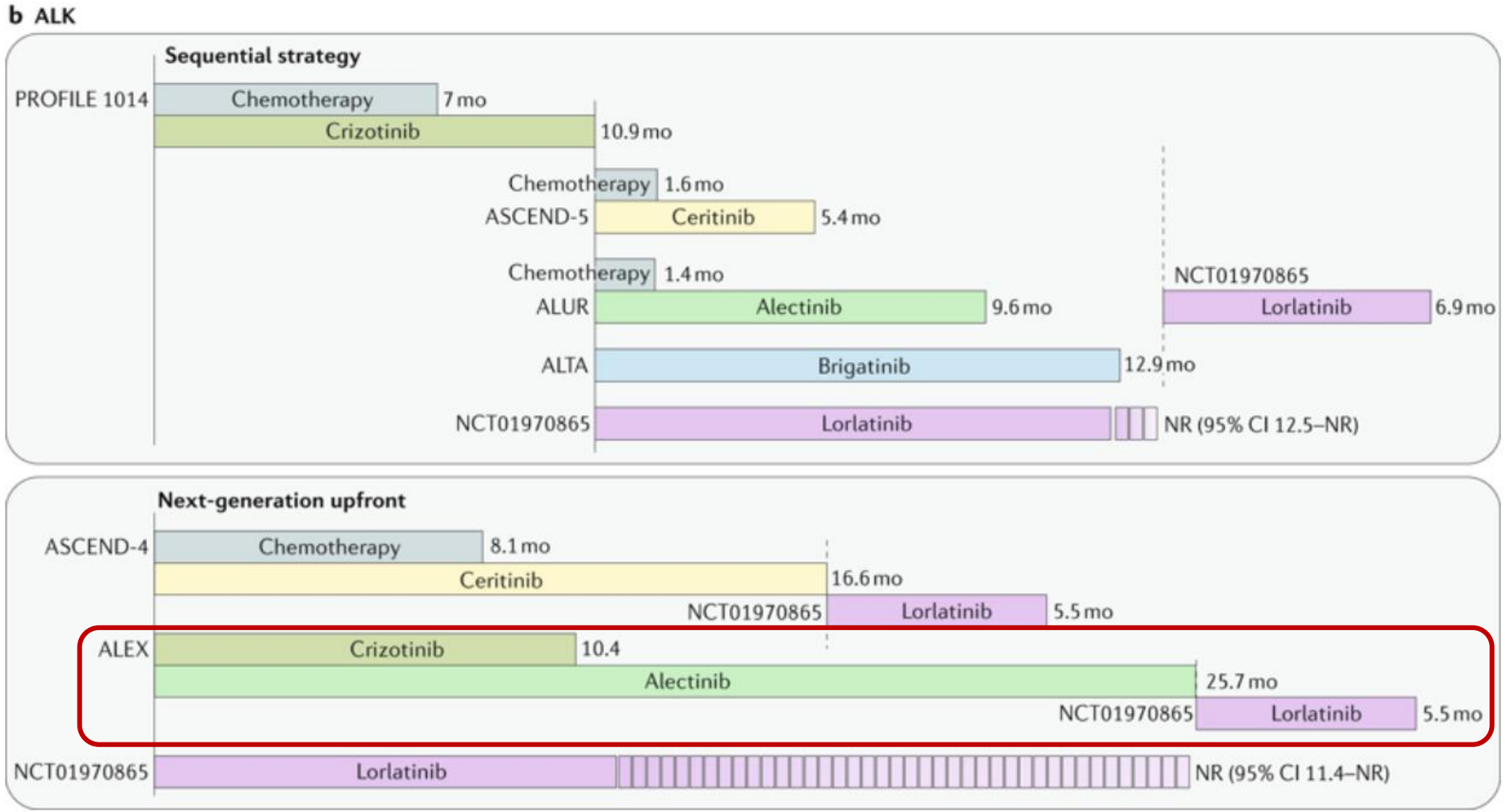






Hida et al., Lancet, 2017

Front-line ALK Treatment PFS



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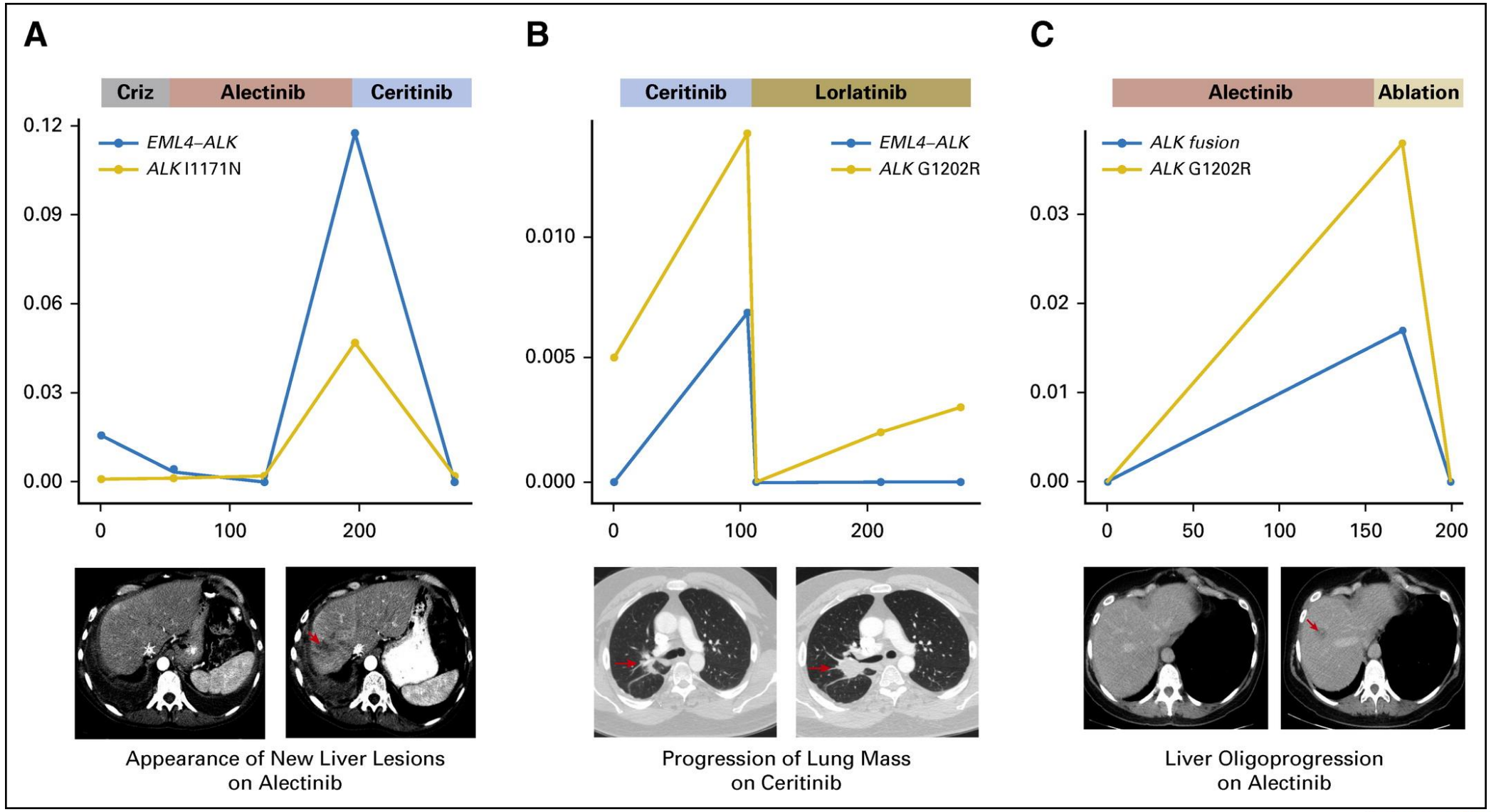
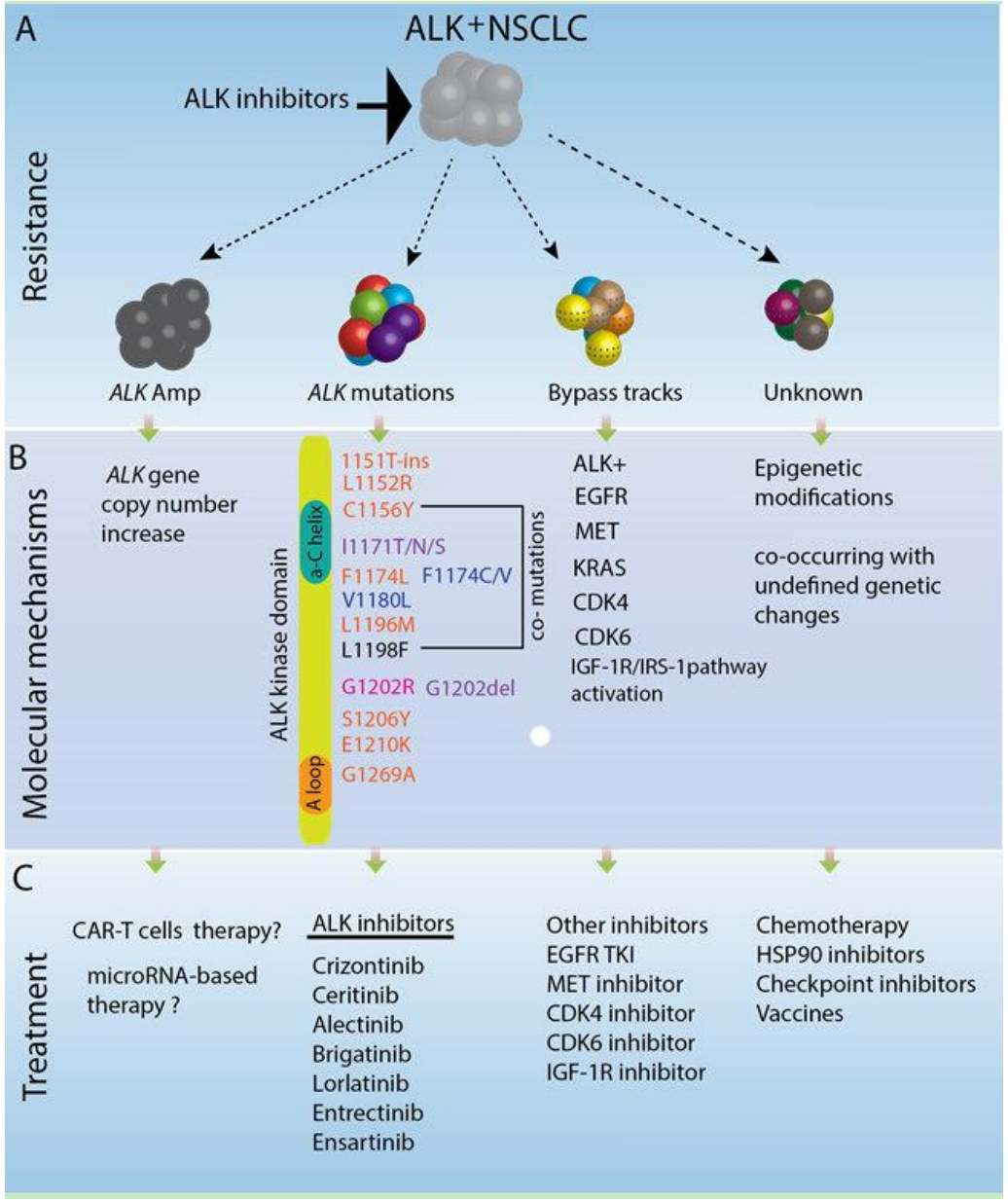
ALK Clonal Evolution



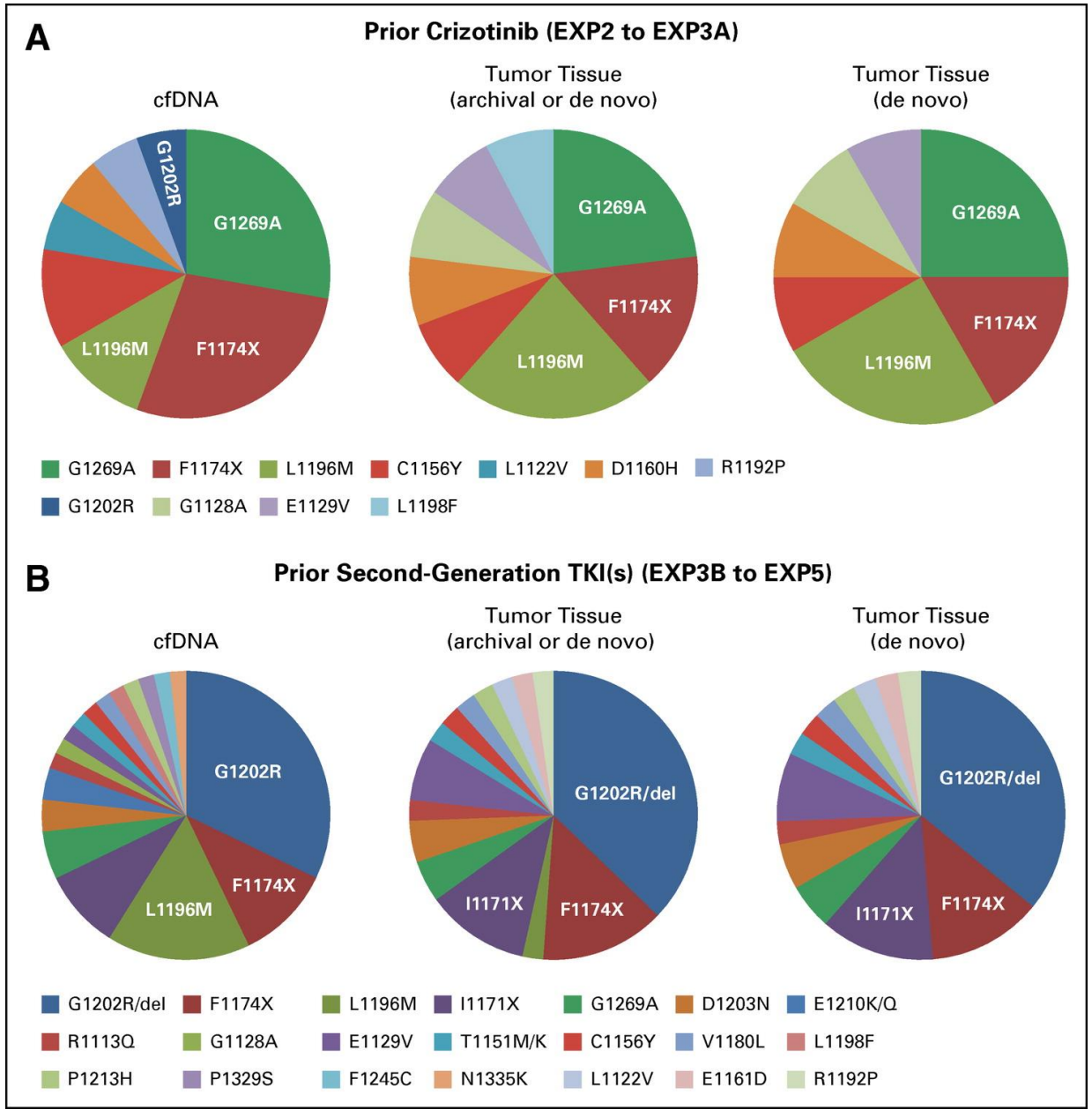
Dagogo-Jack et al. JCO PO, 2018

ALK Mechanism of Resistance



Wu et al. Cancers 2017

ALK TKI Resistance frequencies



Shaw et al. JCO 2019

ALK TKI Sensitivity

IC_{50} ≤50 nM | IC_{50} >50–<200 nM | IC_{50} ≥200 nM

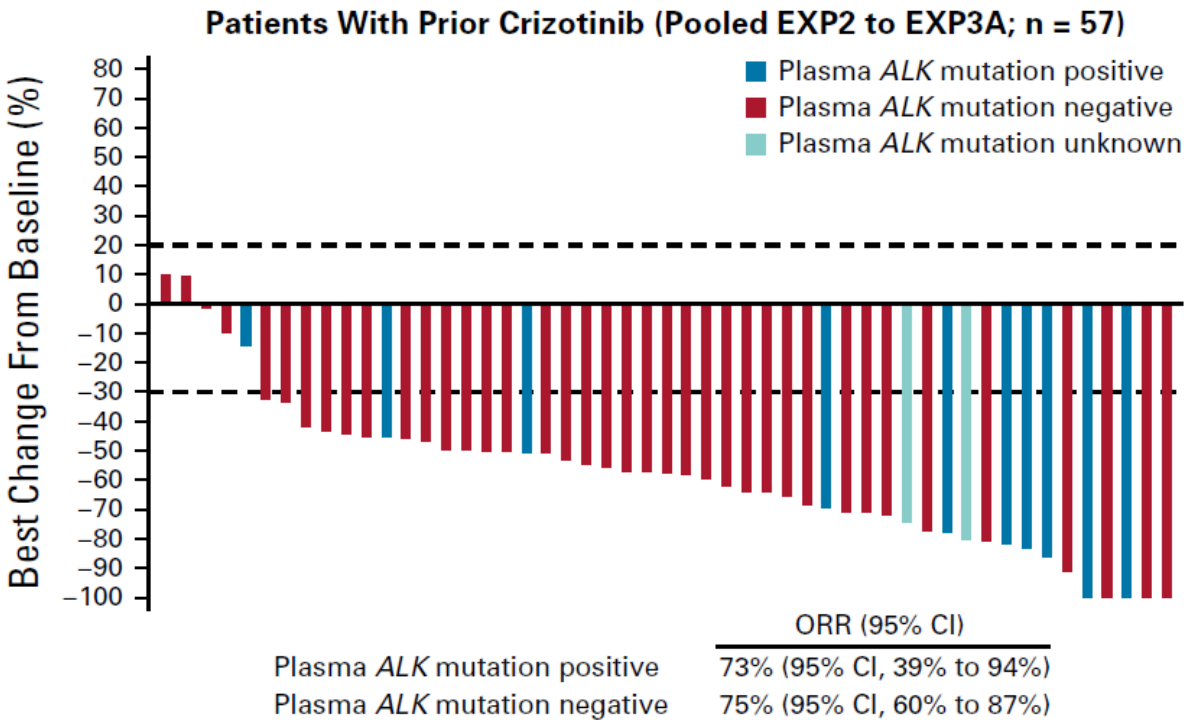
Cellular ALK Phosphorylation Mean IC_{50} (nM)

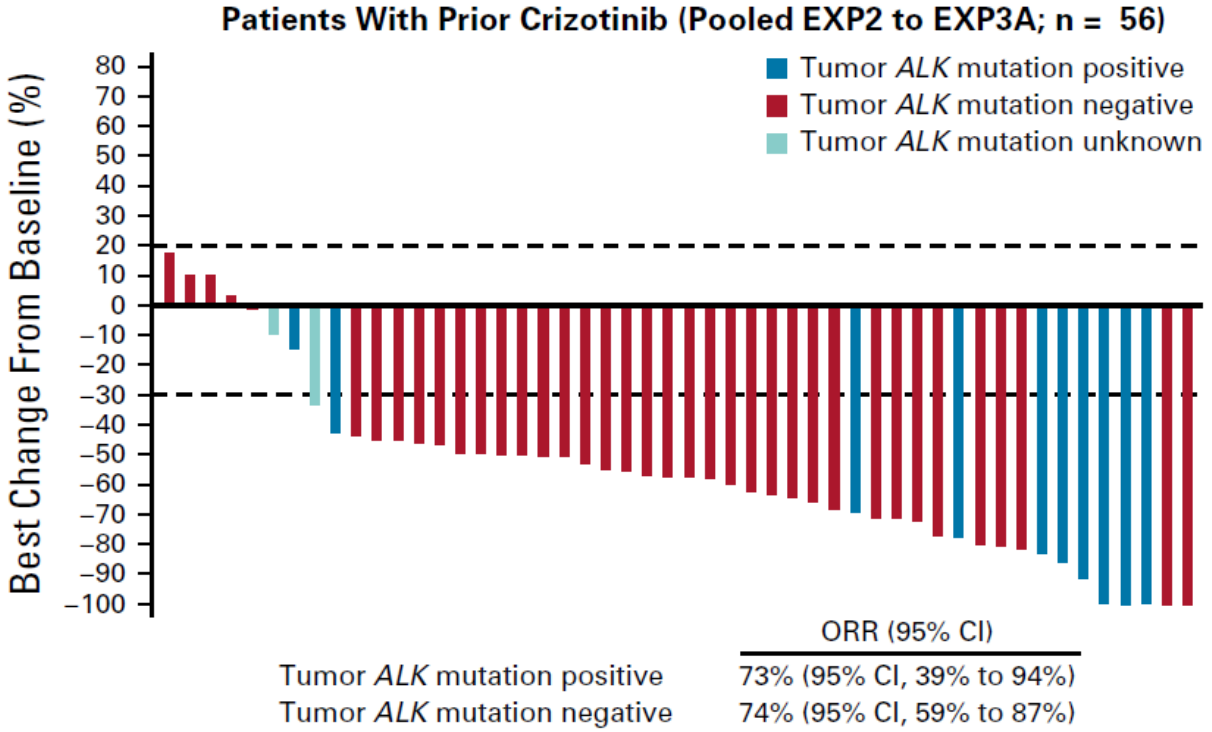
Mutation Status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental BA/F3	763.9	885.7	890.1	2774.0	11293.8
V1	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0

Adapted from Gainor JF, et al. *Cancer Discov*. 2016;6:1118–1133.

Shaw et al ASCO 2017 #9006

Lorlatinib in Crizotinib resistant patients





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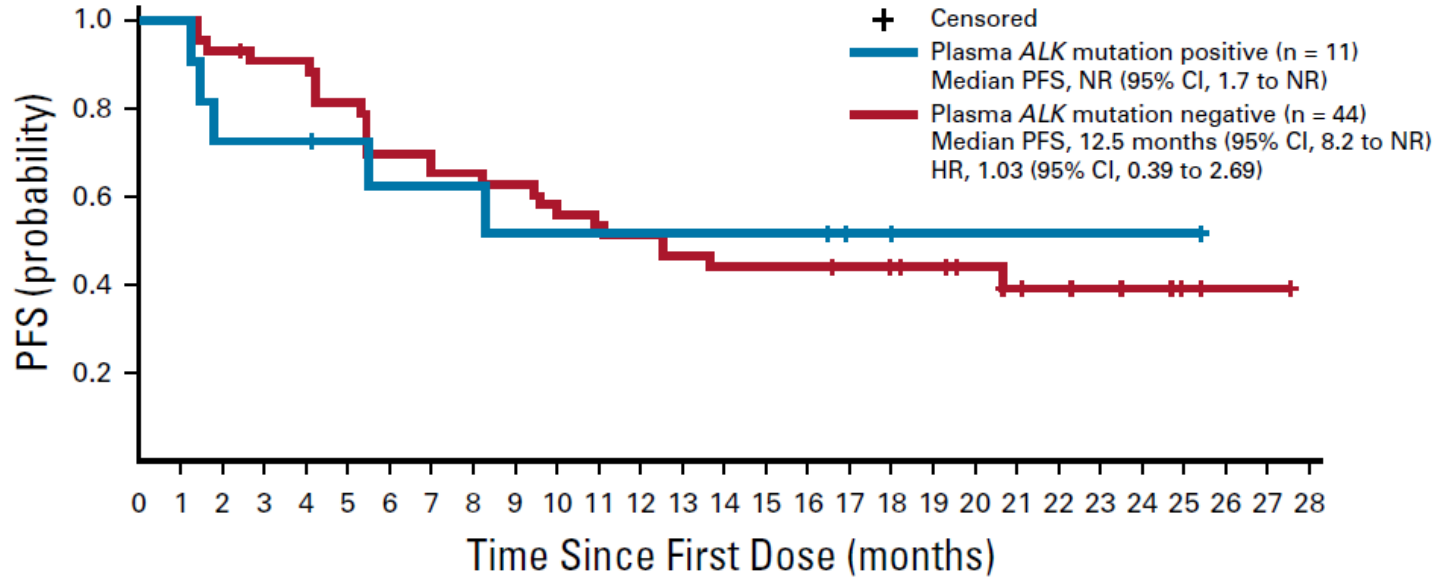
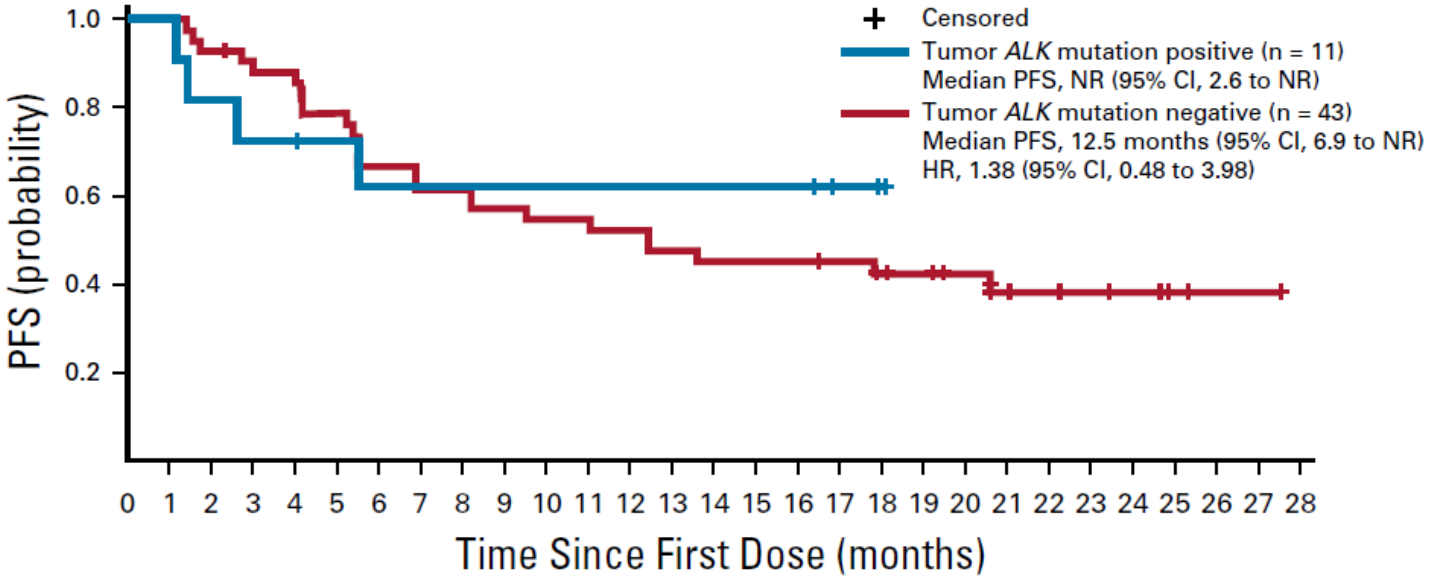
Lorlatinib in Crizotinib resistant patients





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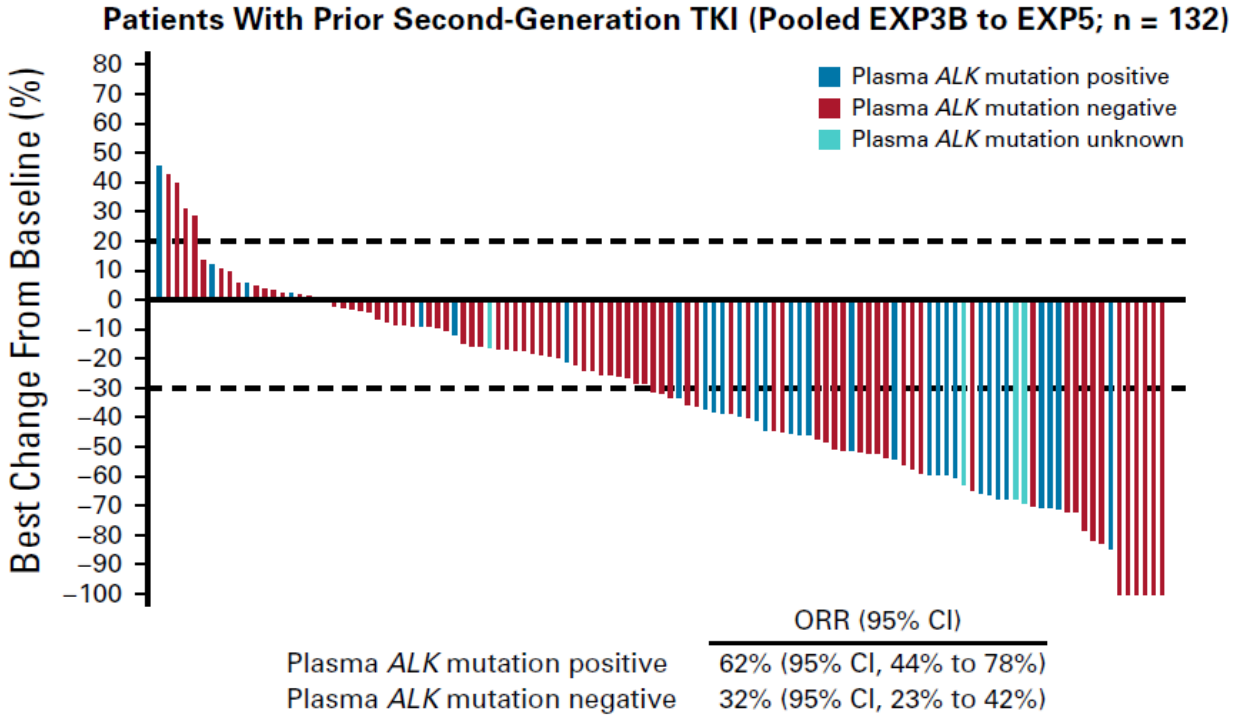
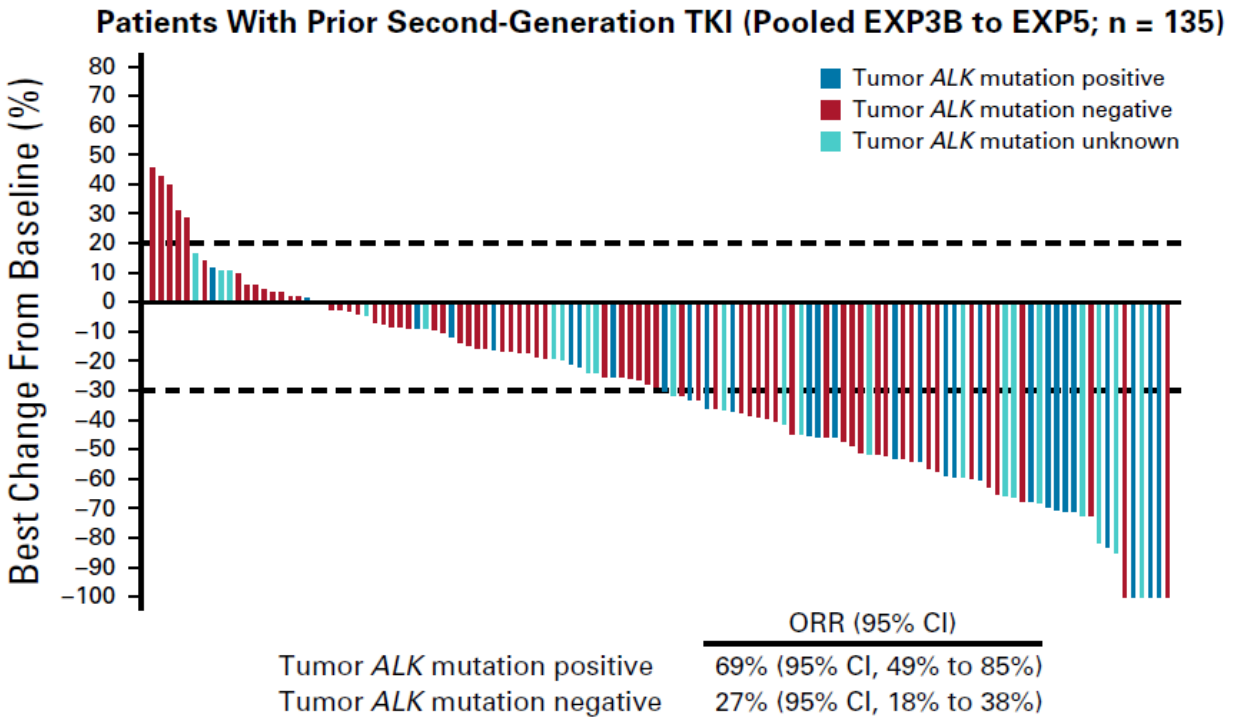
Lorlatinib in Second-gen ALK resistant patients





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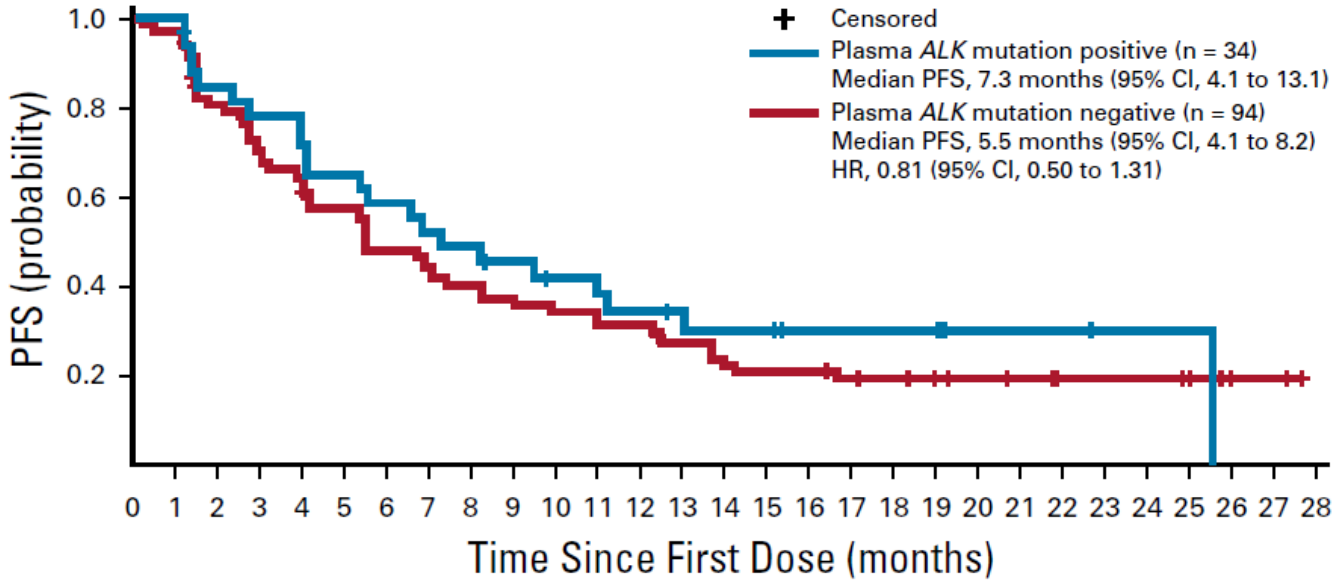
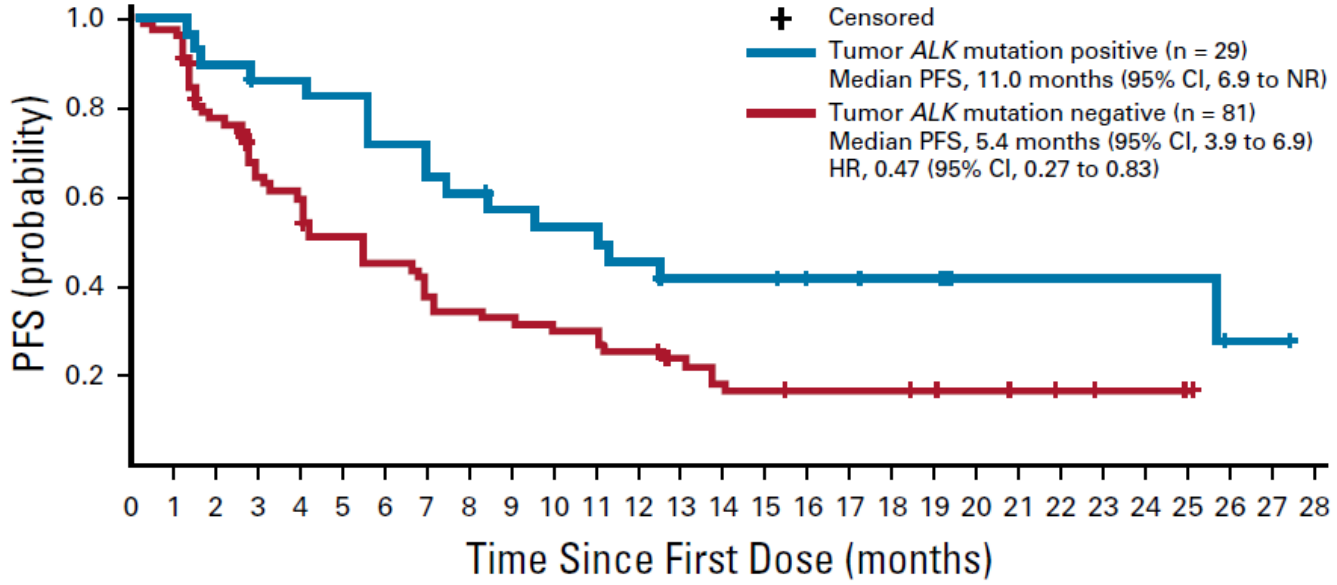
Lorlatinib in Second-gen ALK resistant patients





Shaw et al. JCO 2019

Lung Cancer Genetic Heterogeneity and Treatment

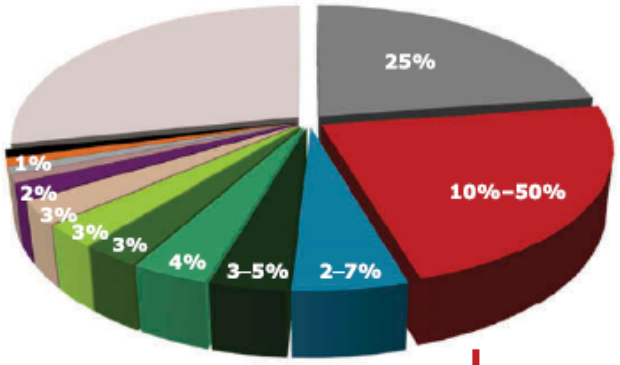
ROS1
- Crizotinib
- Cabozantinib
- Ceritinib
- Lorlatinib
- DS-6051b

ALK
- Crizotinib
- Alectinib
- Ceritinib
- Lorlatinib
- Brigatinib

BRAF
- Vemurafenib
- Dabrafenib

MET
- Crizotinib
- Cabozantinib

MEK1
- Trametinib
- Selumetinib
- Cobimetinib



- *KRAS* mutation[40]
- *EGFR* mutation[2,10]
- *ALK* rearrangement[3,21,22]
- *MET* amplification[56,57]
- *BRAF* mutation[43]
- *HER2* mutation[17,40]
- *NTRK* rearrangement[52]
- *MET* mutation[61,62]
- *ROS1* rearrangement[30]
- *RET* rearrangement[34,35]
- *MEK* mutation[49]
- *PIK3CA* mutation[40]
- *NRAS* mutation[40]
- Others or unknown

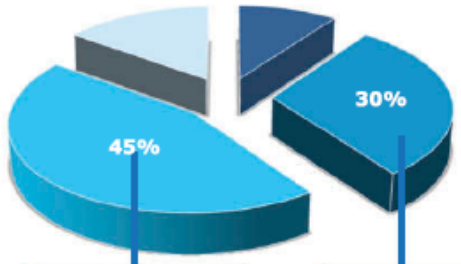
EGFR Sensitizing
- Gefitinib
- Erlotinib
- Afatinib
- Osimertinib
- Necitumumab
- Rociletinib

RET
- Cabozantinib
- Alectinib
- Apatinib
- Vandetanib
- Ponatinib
- Lenvatinib

HER2
- Trastuzumab emtansine
- Afatinib
- Dacomitinib

PIK3CA
- LY3023414
- PQR 309

ALK TKI Resistance[24,78,80,81,84,99]

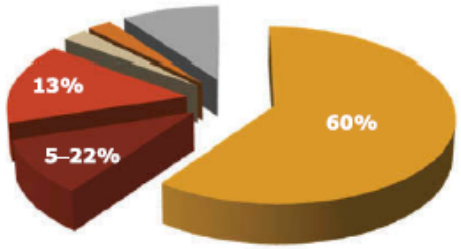


- *EML4-ALK* amplification
- *ALK* secondary mutation
- Non-*ALK* driver mutation
- Other

EGFR mutation
KRAS mutation
KIT amplification
MET amplification
ALK amplification
Others?

L1196M
G1269A
G1202R
C1156Y
S1206Y
1151Tins
L1152R
F1174V
Others

EGFR TKI Resistance[64,65,66,68]



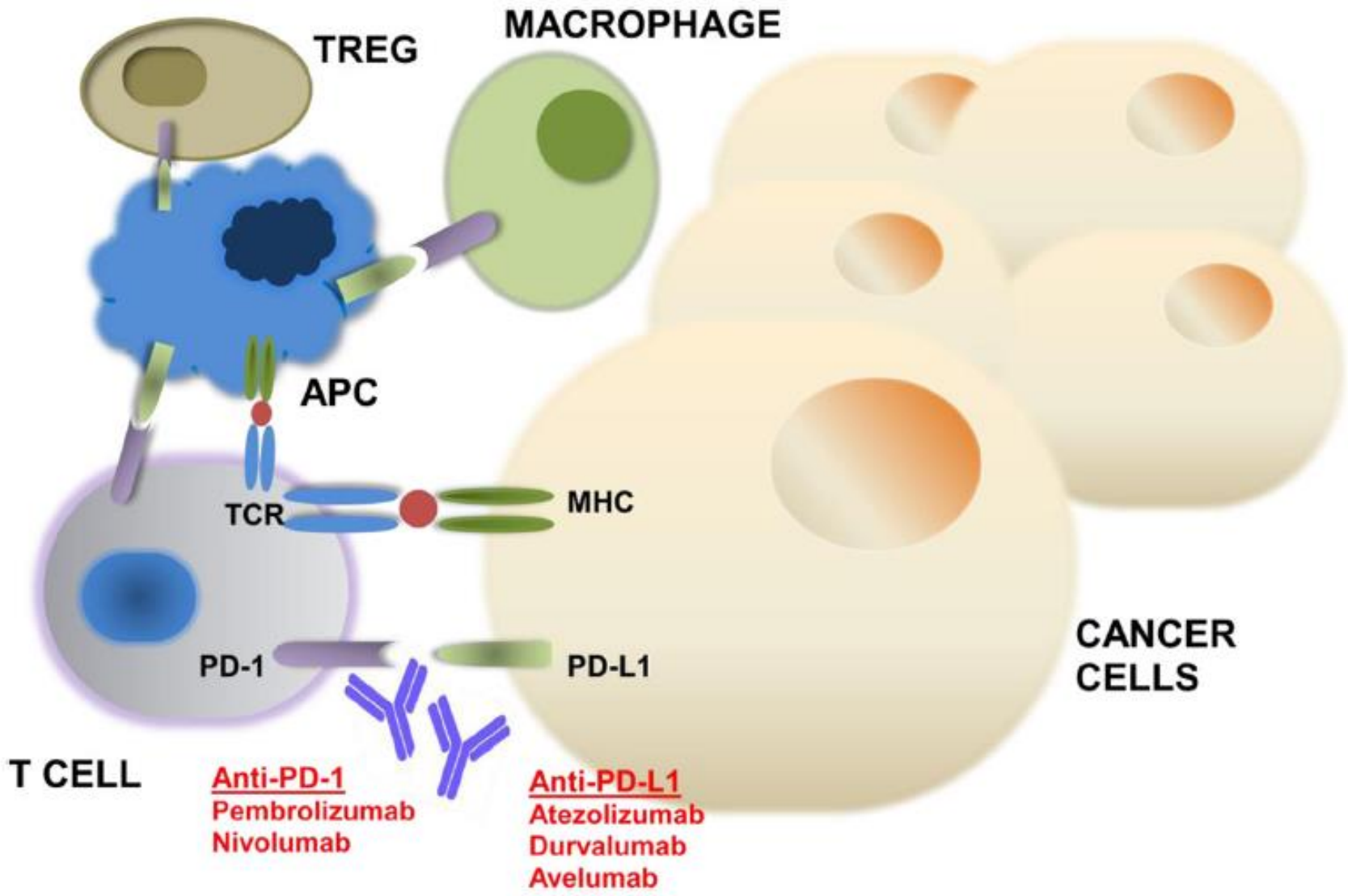
- *T790M* mutation
- *MET* amplification
- *HER2* amplification
- EMT
- SCLC
- Other

NTRK1
- Entrectinib
- LOXO-101
- Cabozantinib
- DS-6051b

Salgia Expert Rev Mol Diagn. 2016

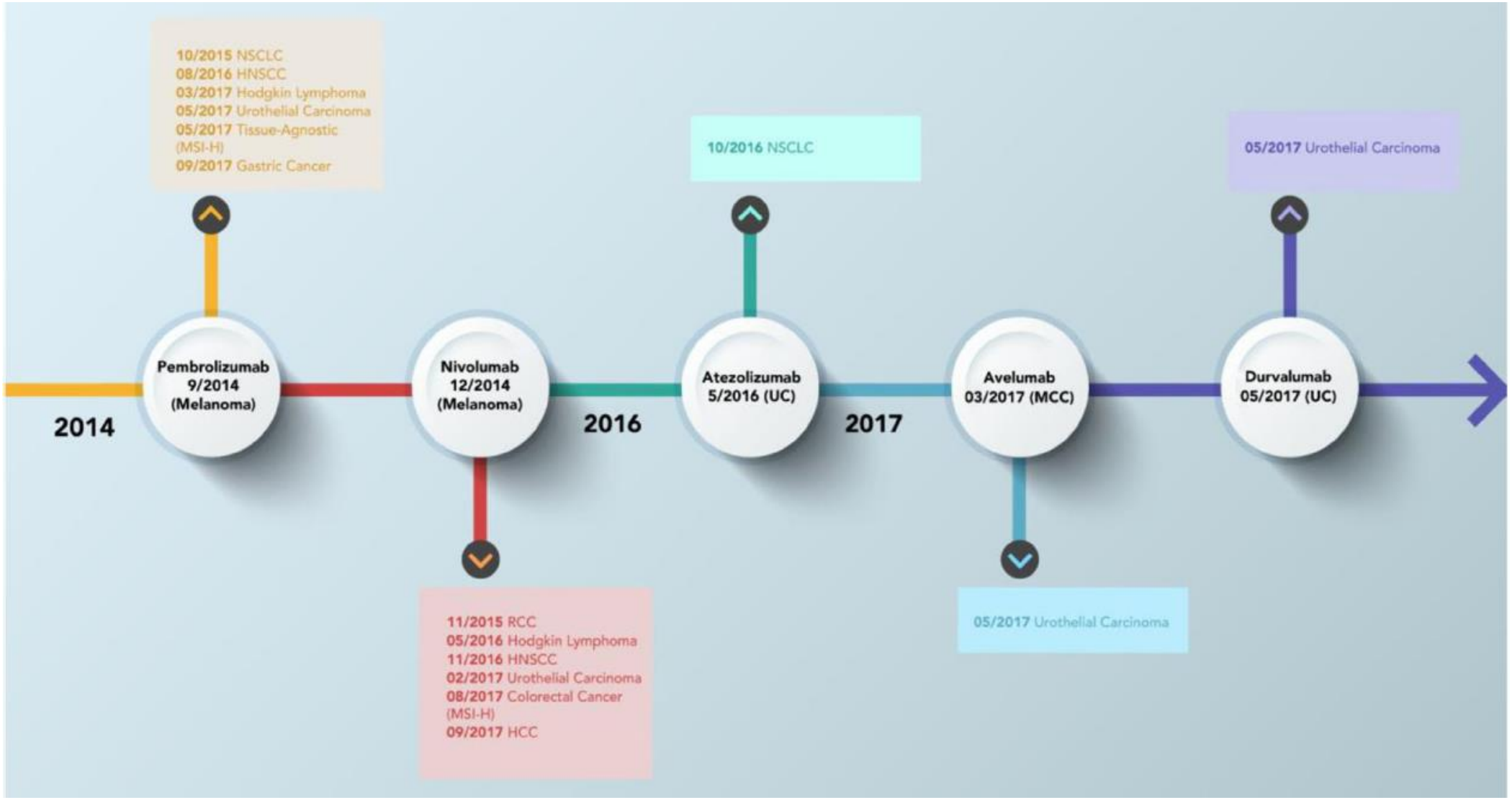
Tsao AS, et al. JTO, 2016

Mechanism of action of PD-1 and PD-L1 inhibitors



Jun Gong, Chehrazi-Raffle, Reddi and Salgia; Journal of ImmunoTherapy of Cancer 2018

Timeline of FDA approvals for PD-1 and PD-L1 inhibitors

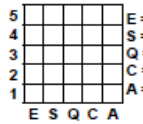


Jun Gong, Chehrazi-Raffle, Reddi and Salgia; Journal of ImmunoTherapy of Cancer 2018

NCCN Guideline Chemotherapy + Immunotherapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2018
Non-Small Cell Lung Cancer
NCCN Evidence Blocks™



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

NCCN Guidelines Index
Table of Contents
Discussion

EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC ADENOCARCINOMA

First-line Systemic Therapy

	PS 0-1	PS 2
Bevacizumab/carboplatin/paclitaxel	■	—
Bevacizumab/carboplatin/pemetrexed	■	—
Bevacizumab/cisplatin/pemetrexed	■	—
Carboplatin/albumin-bound paclitaxel	■	■
Carboplatin/docetaxel	■	■
Carboplatin/etoposide	■	■
Carboplatin/gemcitabine	■	■
Carboplatin/paclitaxel	■	■
Carboplatin/pemetrexed	■	■
Cisplatin/docetaxel	■	—
Cisplatin/etoposide	■	—
Cisplatin/gemcitabine	■	—

	PS 0-1	PS 2
Cisplatin/paclitaxel	■	—
Cisplatin/pemetrexed	■	—
Gemcitabine/docetaxel	■	■
Gemcitabine/vinorelbine	■	■
Pembrolizumab/carboplatin/pemetrexed	■	—
Pembrolizumab/cisplatin/pemetrexed	■	—
Atezolizumab/carboplatin/paclitaxel/ bevacizumab	■	—
Albumin-bound paclitaxel	—	■
Docetaxel	—	■
Gemcitabine	—	■
Paclitaxel	—	■
Pemetrexed	—	■

Maintenance Therapy

Atezolizumab*	■	Bevacizumab/pemetrexed	■
Atezolizumab/bevacizumab*	■	Gemcitabine	■
Bevacizumab	■	Pemetrexed	■
Bevacizumab*	■	Pembrolizumab/pemetrexed†	■

*If atezolizumab/ carboplatin/paclitaxel/ bevacizumab given.
†If pembrolizumab/ carboplatin/pemetrexed or pembrolizumab/ cisplatin/pemetrexed given.

Jun Gong, Chehrazi-Raffle, Reddi and Salgia; Journal of ImmunoTherapy of Cancer 2018

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Long-term OS for ICIs in NSCLC

Study (sample)	Immune checkpoint inhibitor	OS (time of assessment)
CA209-003 (*N* = 129)	Nivolumab	16% (at 5 years)
Checkmate 017 (*N* = 222)	Nivolumab	16% (at 3 years)
Checkmate 057 (*N* = 240)	Nivolumab	18% (at 3 years)
Keynote 001 (*N* = 550)	Pembrolizumab	26.4% (at 3 years) 19% (at 3 years)
Keynote 010 (*N* = 47)	Pembrolizumab (2 mg/kg) Pembrolizumab (10 mg/kg)	30.1% (at 2 years) 37.5% (at 2 years)
POPLAR (*N* = 144)	Atezolizumab	19% (at 3 years)
OAK (*N* = 425)	Atezolizumab	28% (at 2 years)
ATLANTIC (*N* = 265)	Durvalumab	22% (at 2 years)

Nadal et al.; Cancer Immunology, 2019

Immunotherapy Response and AEs

Study	Drug	ORR (%)	Grade ≥3 AEs (%)
Monotherapy			
KEYNOTE-024	Pembrolizumab	44.8	31.2
KEYNOTE-042	Pembrolizumab	27.3	17.8
CHECKMATE-026	Nivolumab	26	18
BIRCH	Atezolizumab	22	41
Combination			
KEYNOTE-021	Pembro+CarboPem	55	39
KEYNOTE-189	Pembro+CarboPem	47.6	67.2
KEYNOTE-407	Pembro+CarboTaxol	58.4	69.8
CHECKMATE-227	Nivo+Ipi	45.3	31.2
IMpower-150	AtezoCarboTaxolBev	63.5	58.5

Bylicki et al.; BioDrugs, 2019

City of Hope NSCLC Immunotherapy Clinical Trials

IRB	Immune checkpoint inhibitor	PI
17150	Atezolizumab	M. Fakih
16208	Atezolizumab	K. Reckamp
19059	Durvalumab	M. Koczywas
17056	Nivolumab	M. Koczywas
18465	Durvalumab	M. Koczywas
18545	Pembrolizumab and canakinumab	M. Koczywas
17143	APX005M and Nivolumab	R. Salgia
17414	Nivolumab	E. Massarelli
17468	Atezolizumab	E. Massarelli
15346	Screening protocol	K. Reckamp
15303	MAGE-A10c796T	K. Reckamp
18389	TCRs alone or in combination with pembrolizumab	K. Reckamp
16195	AZD9291 and Necitumumab	M. Koczywas

Summary

- Lung cancer is a heterogenous group of cancers
- Early stage is treated with surgery and potentially adjuvant chemotherapy
- Localized unresectable disease is treated with chemotherapy/radiation therapy followed by durvalumab
- Metastatic NSCLC treatment has come a long way
  - Chemotherapy/Immunotherapy
  - Targeted Therapy
    - EGFR
    - ALK
    - Others—ROS1, BRAF, MET, RET