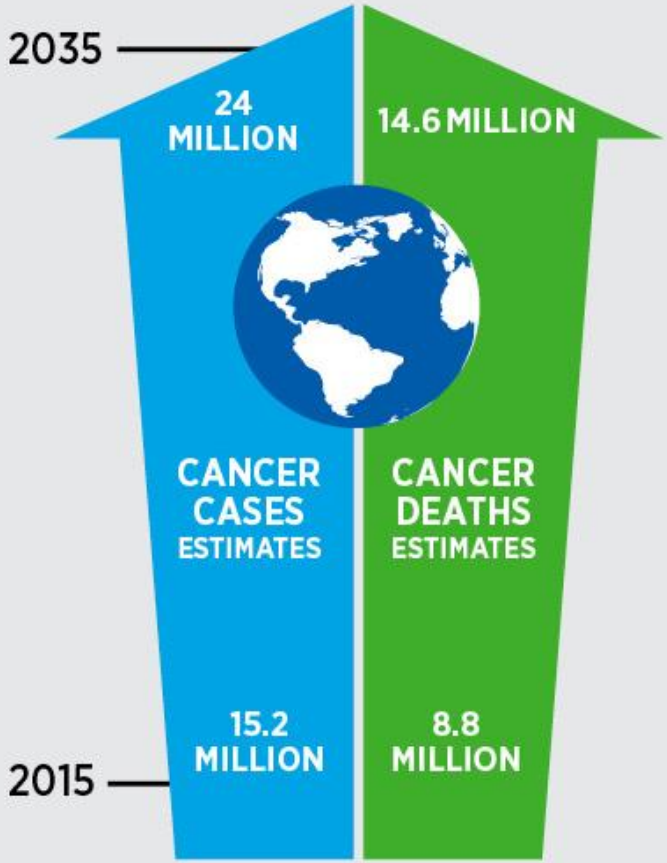
KHDAK de hedefe yönelik tedaviler ve immünoterapi

Dr. Evren FİDAN

Cancer: A Global Challenge

The number of global deaths from cancer is rising, as is the proportion of deaths that cancer accounts for (6).



In 2005, cancer accounted for 7.5 million of the 53.6 million deaths worldwide, meaning it accounted for **1 in 7 deaths.**

In 2015, cancer accounted for 8.8 million of the 55.8 million deaths worldwide, meaning it accounted for almost **1 in 6 deaths.**

The devastating impact of cancer will grow significantly in the coming decades if new and more effective approaches to cancer prevention, early detection, and treatment are not developed and effectively implemented.

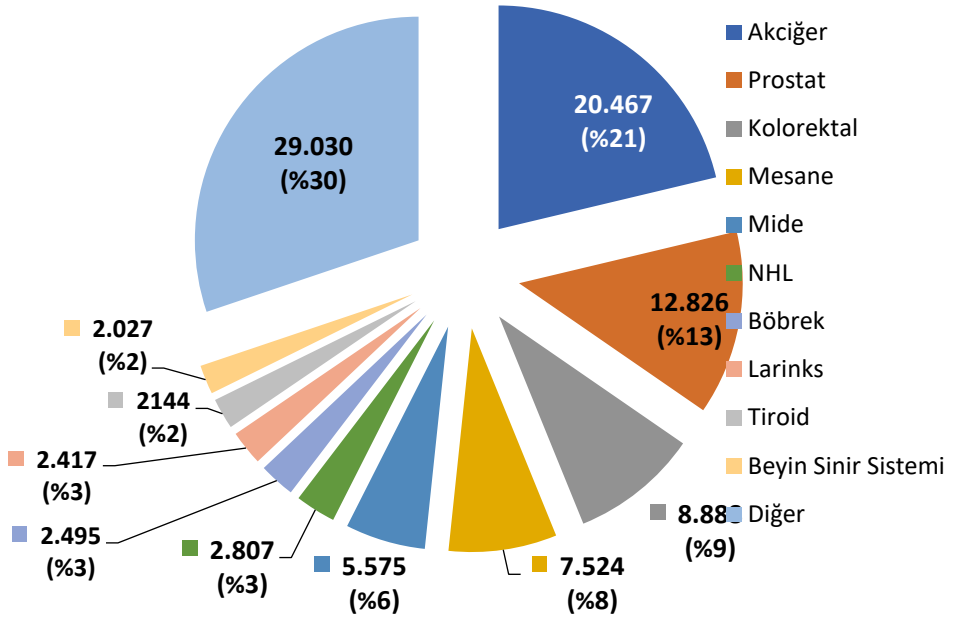
American Association for Cancer Research (AACR) Cancer Progress Report 2017

- En sık görülen kanserler (2018)
- Akciğer (2.09 milyon)
- Meme (2.09 milyon)
- Kolorektal (1.80 milyon)
- Prostat (1.28 milyon)
- Cilt (melanom dışı) (1.04 milyon)
- Mide (1.03 milyon)

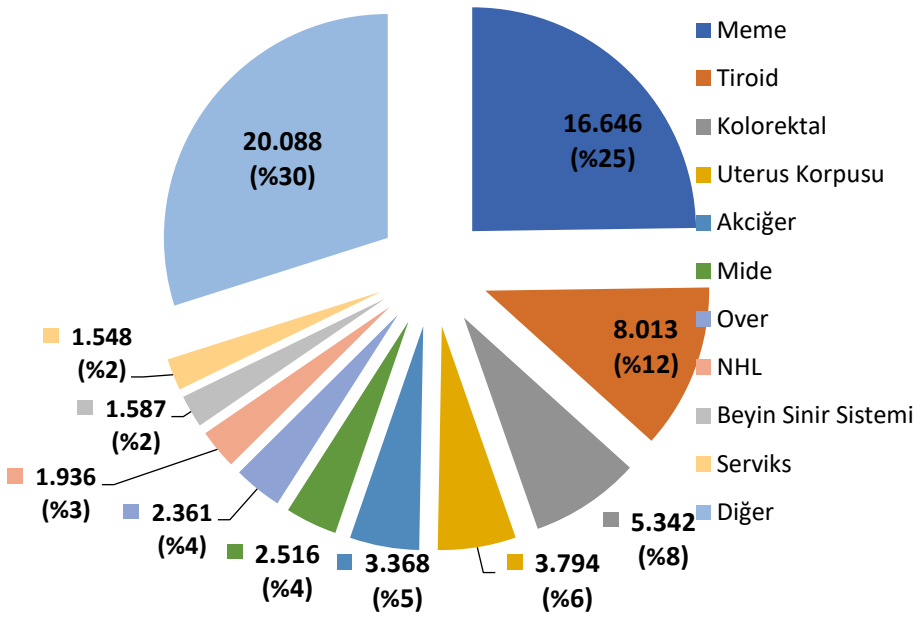
- Kansere bağlı ölümler (2018)
- Akciğer (1.76 milyon)
- Kolorektal (862 000)
- Mide (783 000)
- Karaciğer (782 000)
- Meme (627 000)

- ***WHO's International Agency for Research on Cancer***

Erkeklerde En Sık Görülen Kanserlerin Toplam Sayısı ve Yüzde Dağılımları

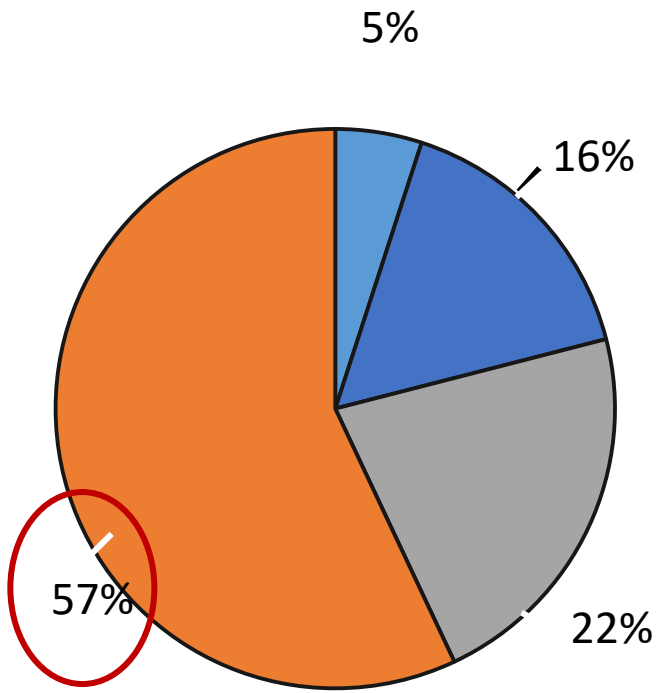


Kadınlarda En Sık Görülen Kanserlerin Toplam Sayısı ve Yüzde Dağılımları



Lung Cancer: US Incidence and 5-Yr Relative Survival (2008-2014)

Percent of Cases by Stage



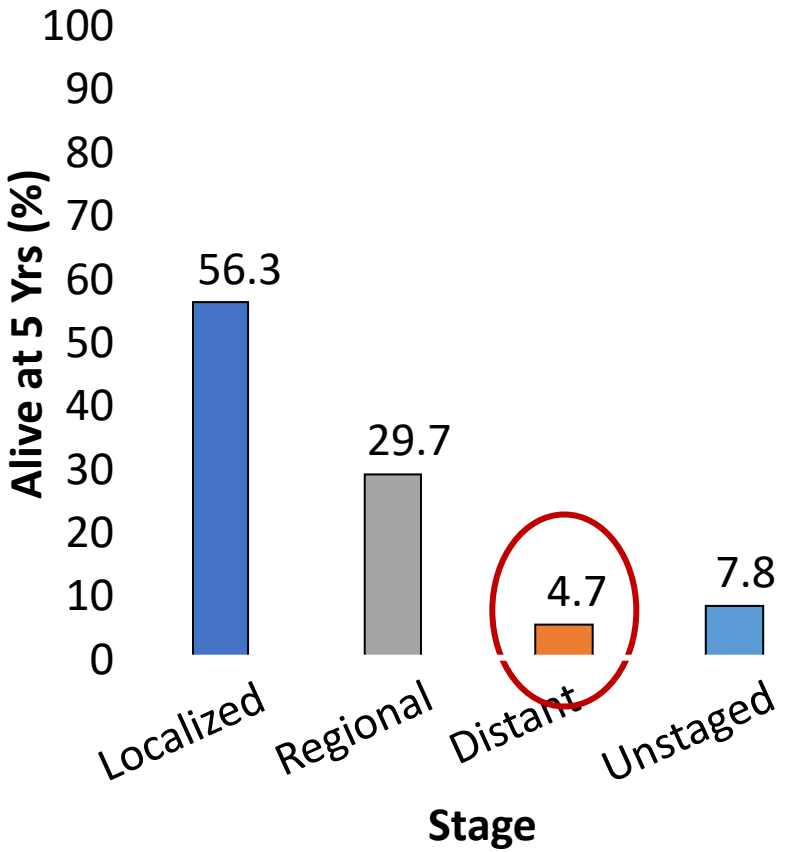
Localized: confined to primary site

Regional: spread to regional lymph nodes

Distant: cancer has metastasized

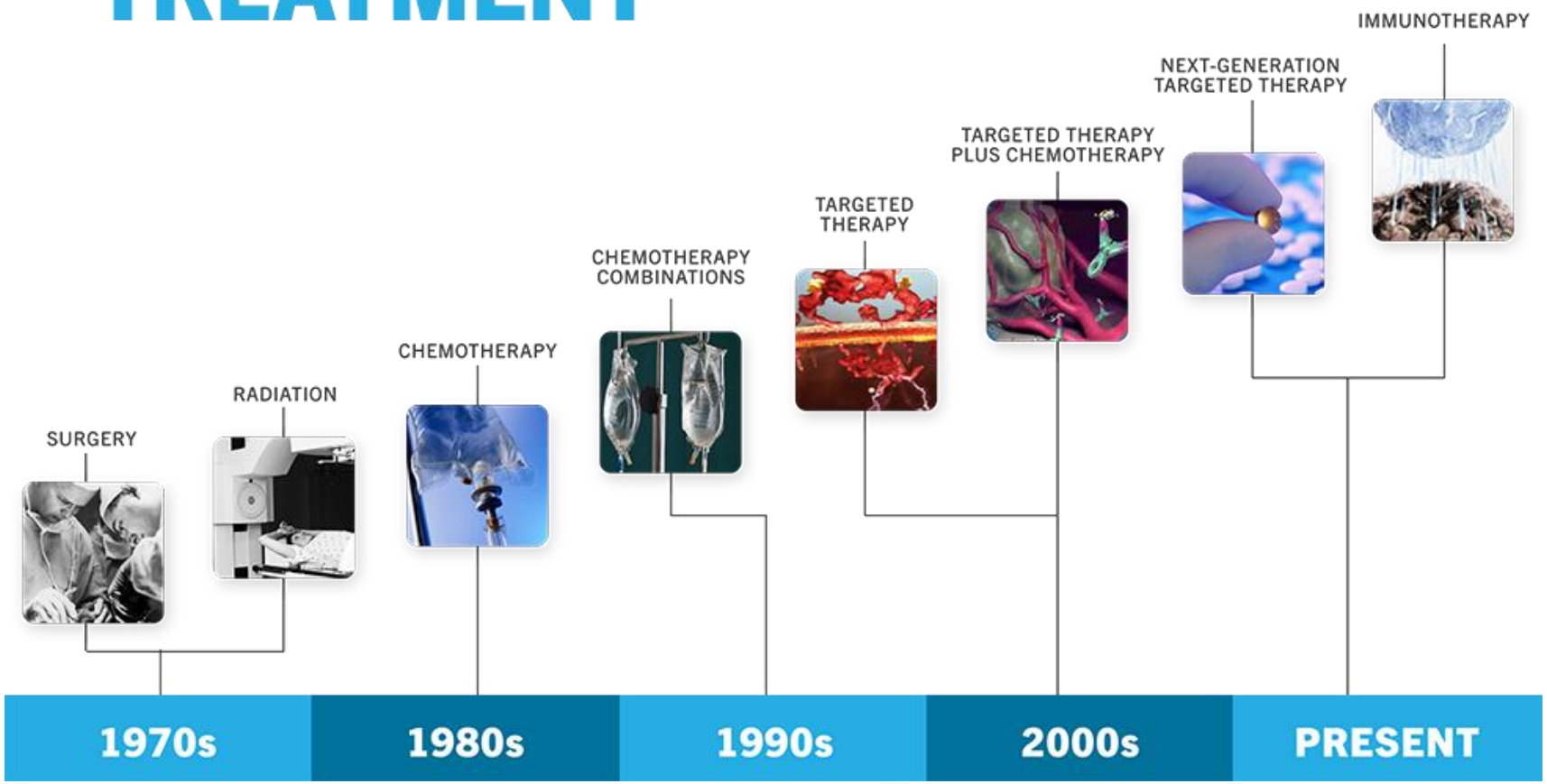
Unknown: unstaged

5-Yr Relative Survival by Stage

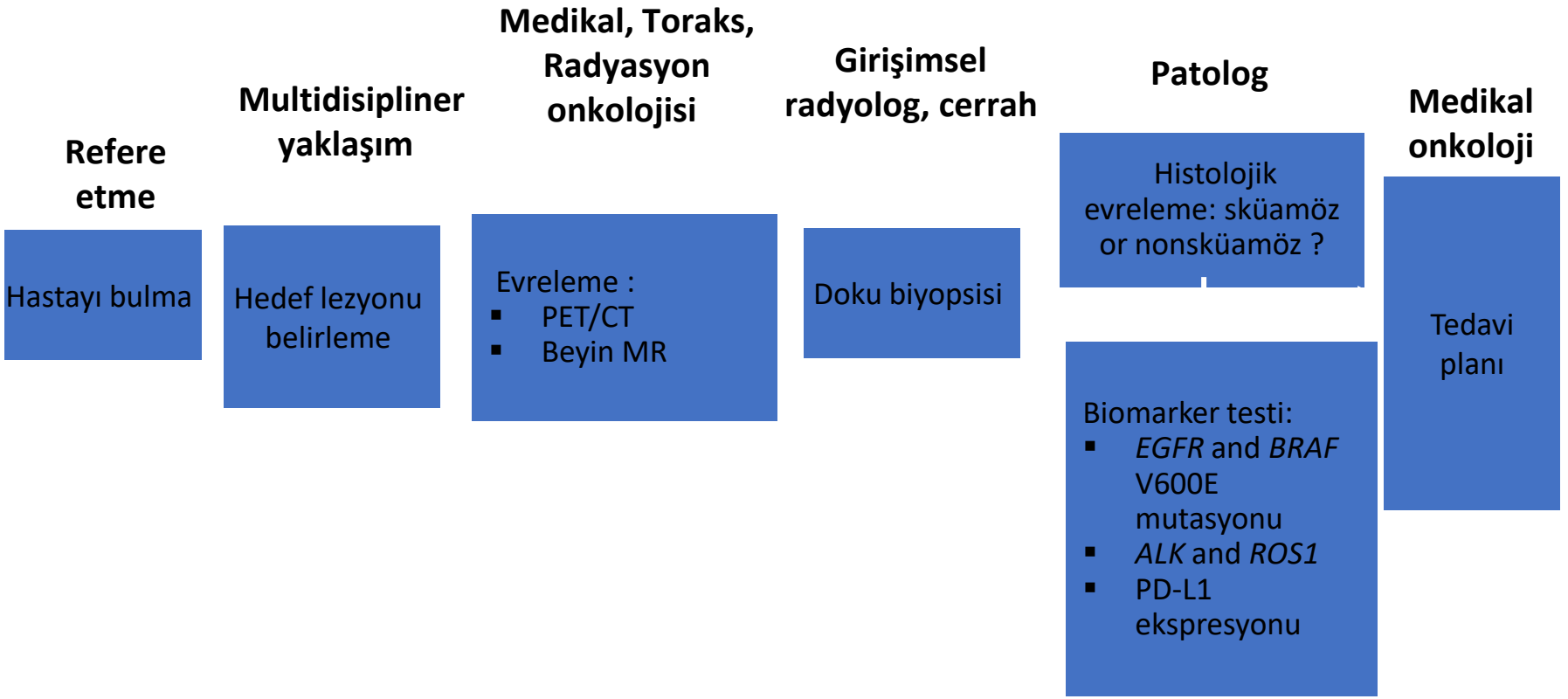


SEER 18 Cancer Statistics Review, 2008-2014.
https://seer.cancer.gov/statfacts/html/lungb.html

PROGRESS IN **LUNG CANCER TREATMENT**



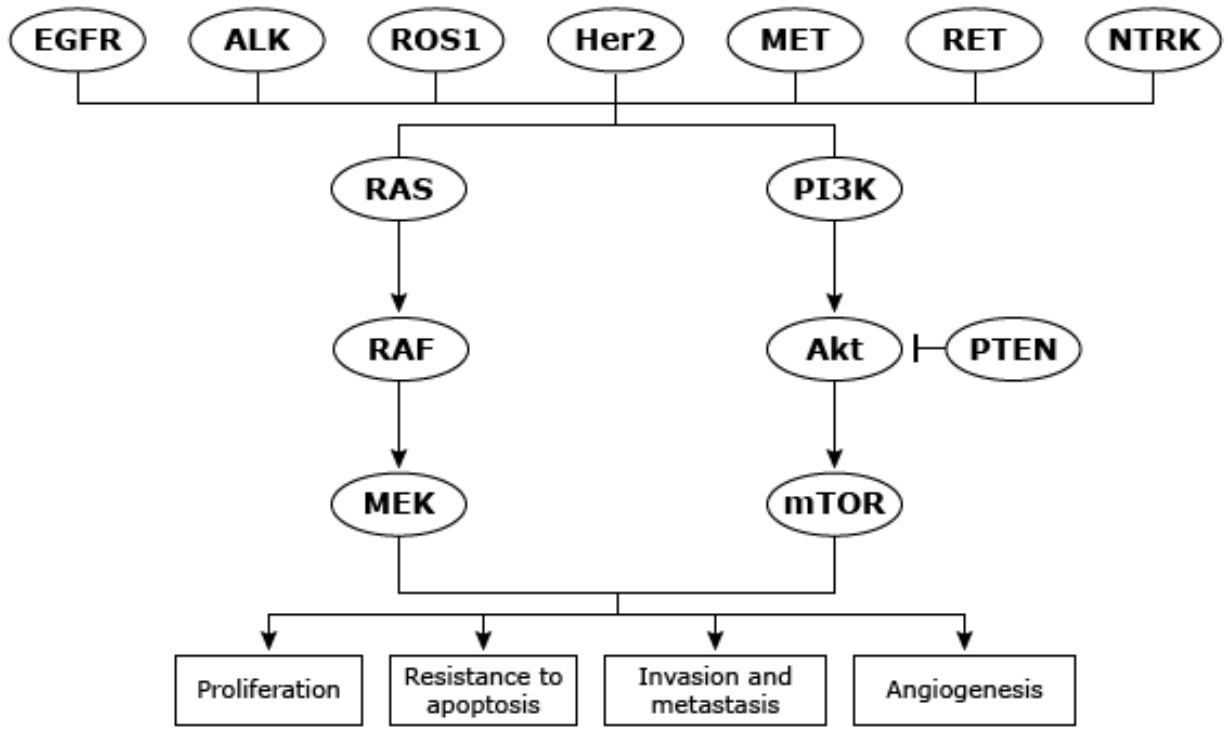
Tanı algoritması



Şüpheli kitle → İdeal Süre ≤ 2 hf → Biopsi → ideal: ≤ 10 iş günü → medikal onkolog

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

Molecular targets in non-small cell lung cancer



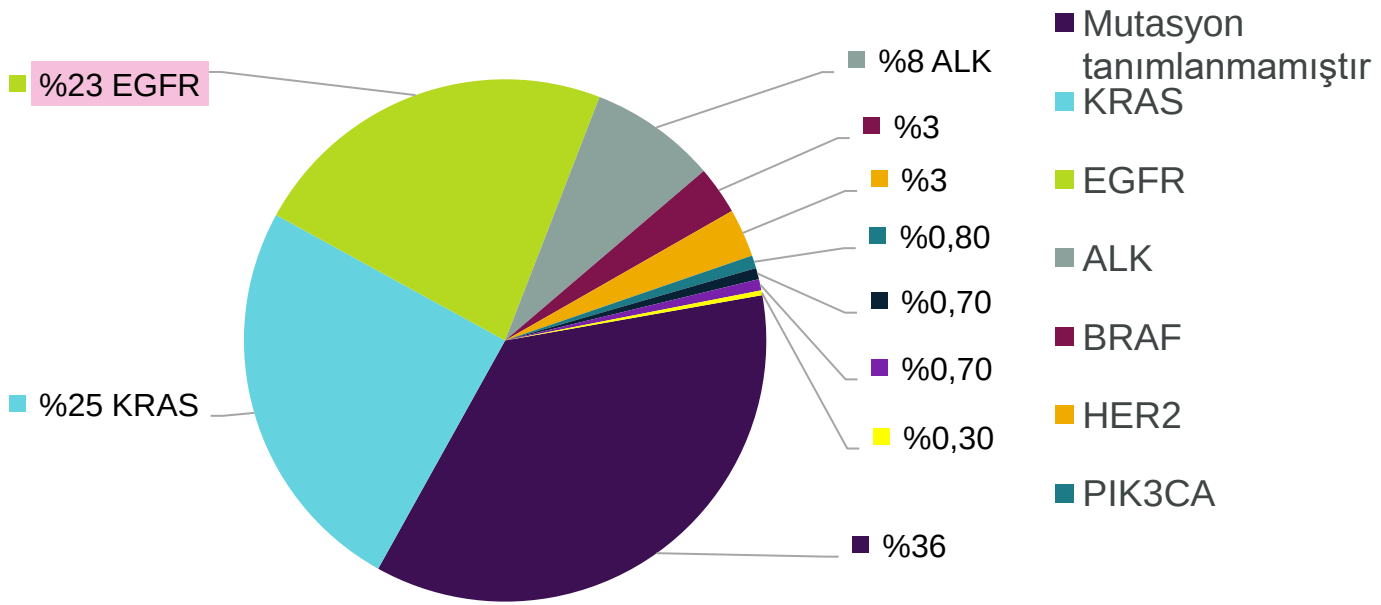
Pathways for molecularly targeted therapy in non-small cell lung cancer.

Original, courtesy of Dr. Joel Neal.

Primer KHDAK adenokarsinomları olan hastaların büyük kısmında tanımlanabilir sürücü mutasyonlar bulunmaktadır.

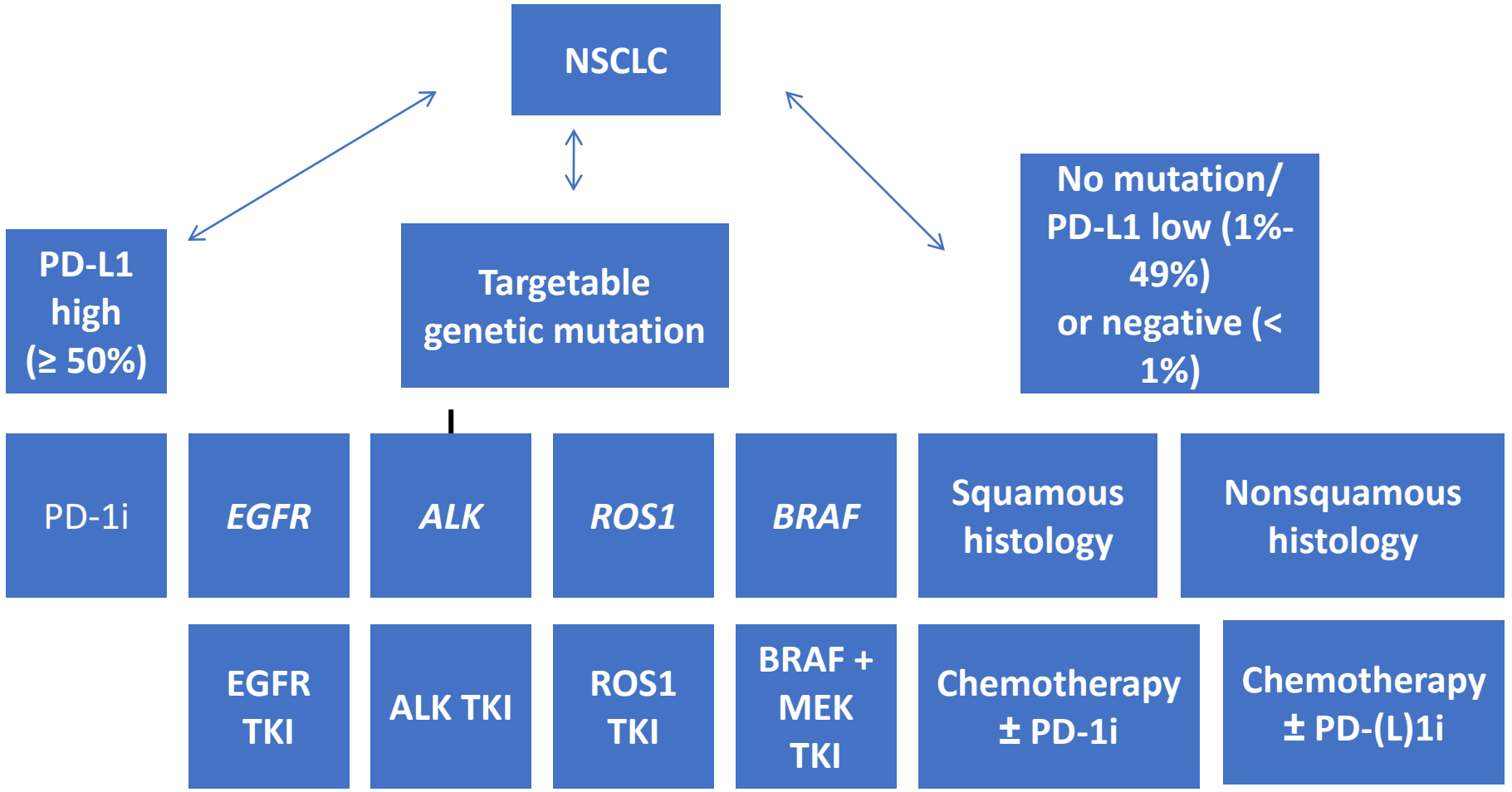
- Akciğer Kanseri Mutasyon Konsorsiyumunun (Lung Cancer Mutation Consortium-LCMC) katılımcı kurumları, klinisyenlerin hedefli tedavileri seçmesine ve klinik araştırmalara hasta almasına yardımcı olmak için 10 geni onkojenik sürücü mutasyonlar açısından analiz etmiştir[1]
- Moleküler analize göre KHDAK adenokarsinomunda en yaygın üç onkojenik sürücü mutasyon[1]:
  - KRAS mutasyonları
  - EGFR mutasyonları
  - ALK yeniden düzenlenmeleri

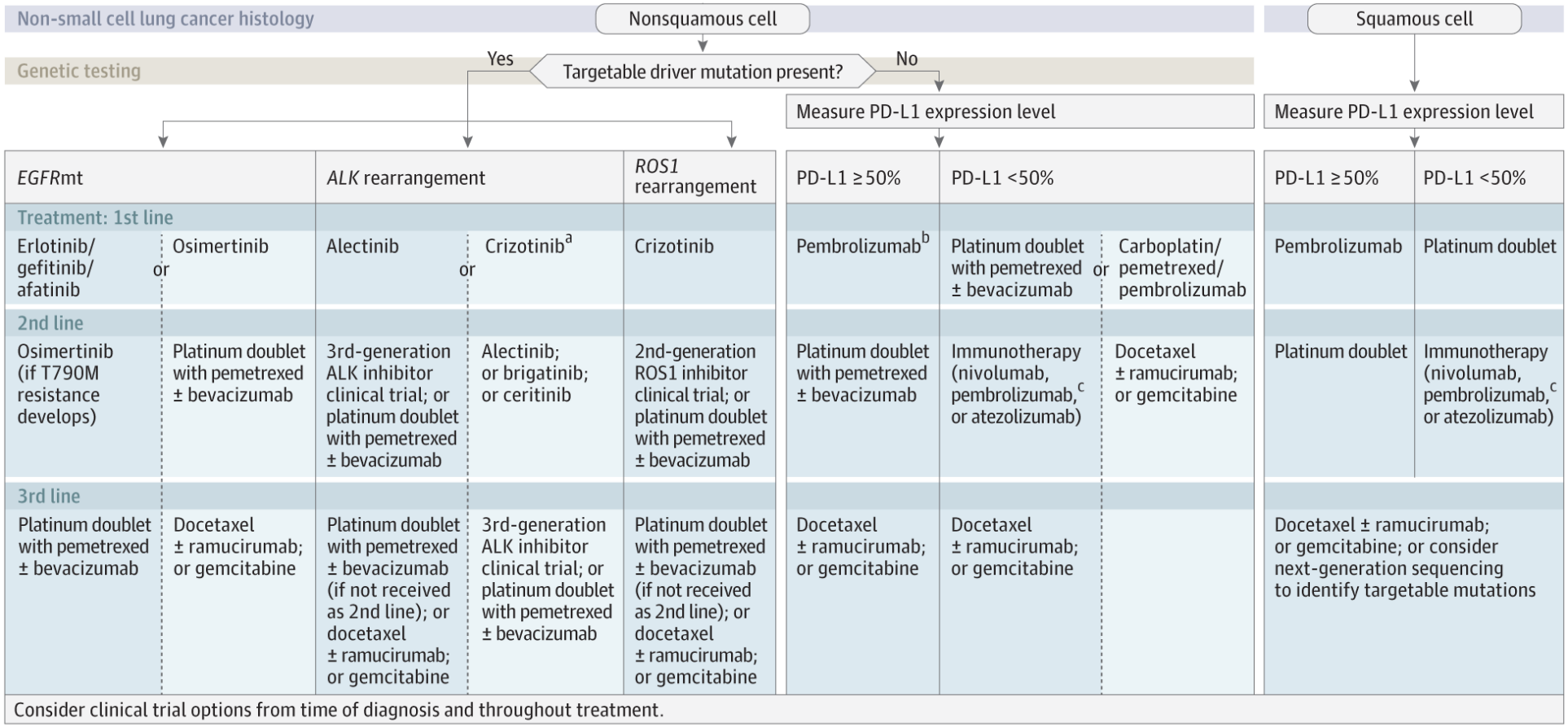
  Proliferasyon ve apoptoz dahil hücre fonksiyonlarını düzenleyen sinyal iletim yolaklarında rol oynar[2]



ALK, anaplastik lenfoma kinaz; BRAF, V-raf mürin sarkomu viral onkogen homoloğu B1; EGFR, epidermal büyüme faktörü reseptörü; HER2, insan epidermal büyüme faktörü reseptörü 2; KRAS, Kirsten sıçan sarkomu viral onkogeni; MAP/ERK kinaz 1, mitojenle aktive edilen protein kinaz/ekstraselüler sinyalle düzenlenen kinaz 1; MEK1, MAPK/ERK kinaz 1; MET, mezenkim-epitel geçişi; NRAS nöroblastom sıçan sarkomu viral onkogen homoloğu; KHDAK, küçük hücreli dışı akciğer kanseri; PIK3CA, fosfatidilinositol-3-kinaz katalitik α polipeptit.

1. Sholl LM, et al. *J Thorac Oncol*. 2015;10(5):768-777. 2. Gerber D, et al. *Am Soc Clin Oncol Educ Book*. 2014:e353-365.


NSCLC
PD-L1 high (≥ 50%)
Targetable genetic mutation
No mutation/ PD-L1 low (1%-49%) or negative (< 1%)
PD-1i
EGFR
ALK
ROS1
BRAF
Squamous histology
Nonsquamous histology
EGFR TKI
ALK TKI
ROS1 TKI
BRAF + MEK TKI
Chemotherapy ± PD-1i
Chemotherapy ± PD-(L)1i



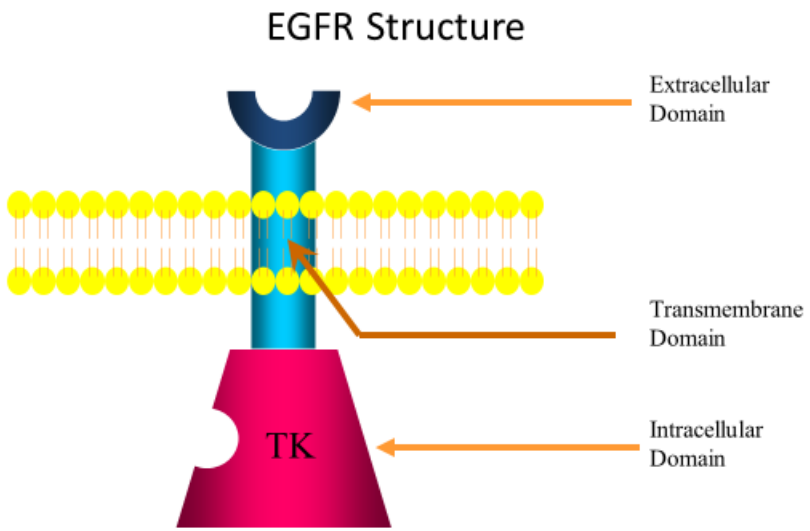
Abbreviations: PD-L1, programmed cell death 1 ligand 1; *EGFR*mt, *EGFR* mutated.

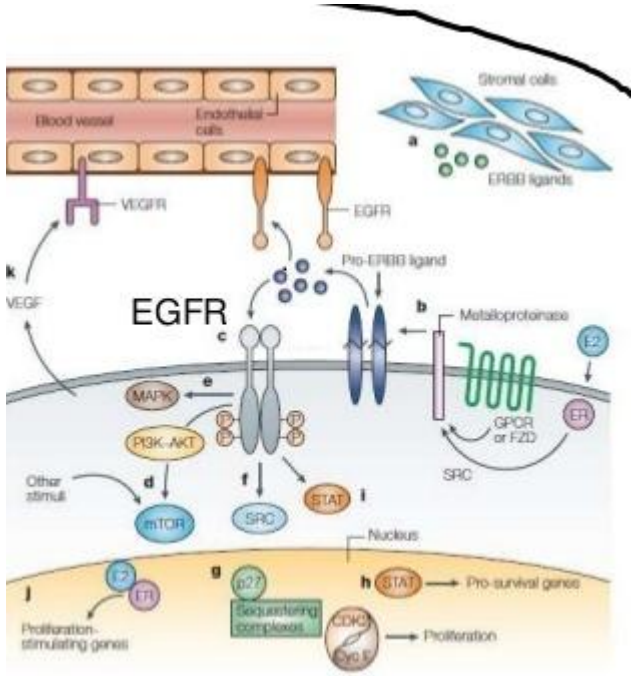
[a]If crizotinib treatment was started prior to FDA approval of alectinib for 1st-line treatment.

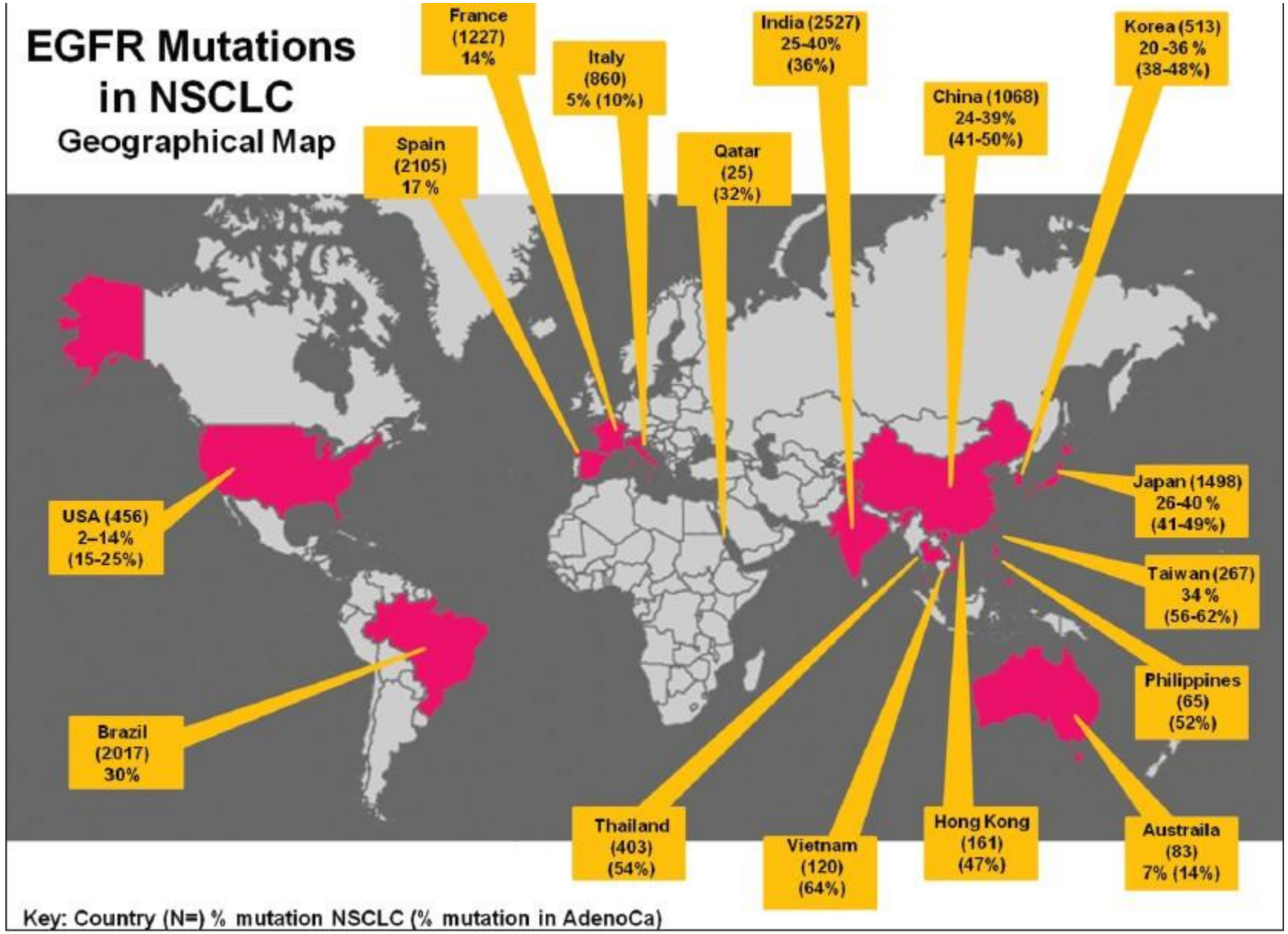
[b]Carboplatin/pemetrexed/pembrolizumab is also FDA approved in this setting.

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

EGFR ailesi

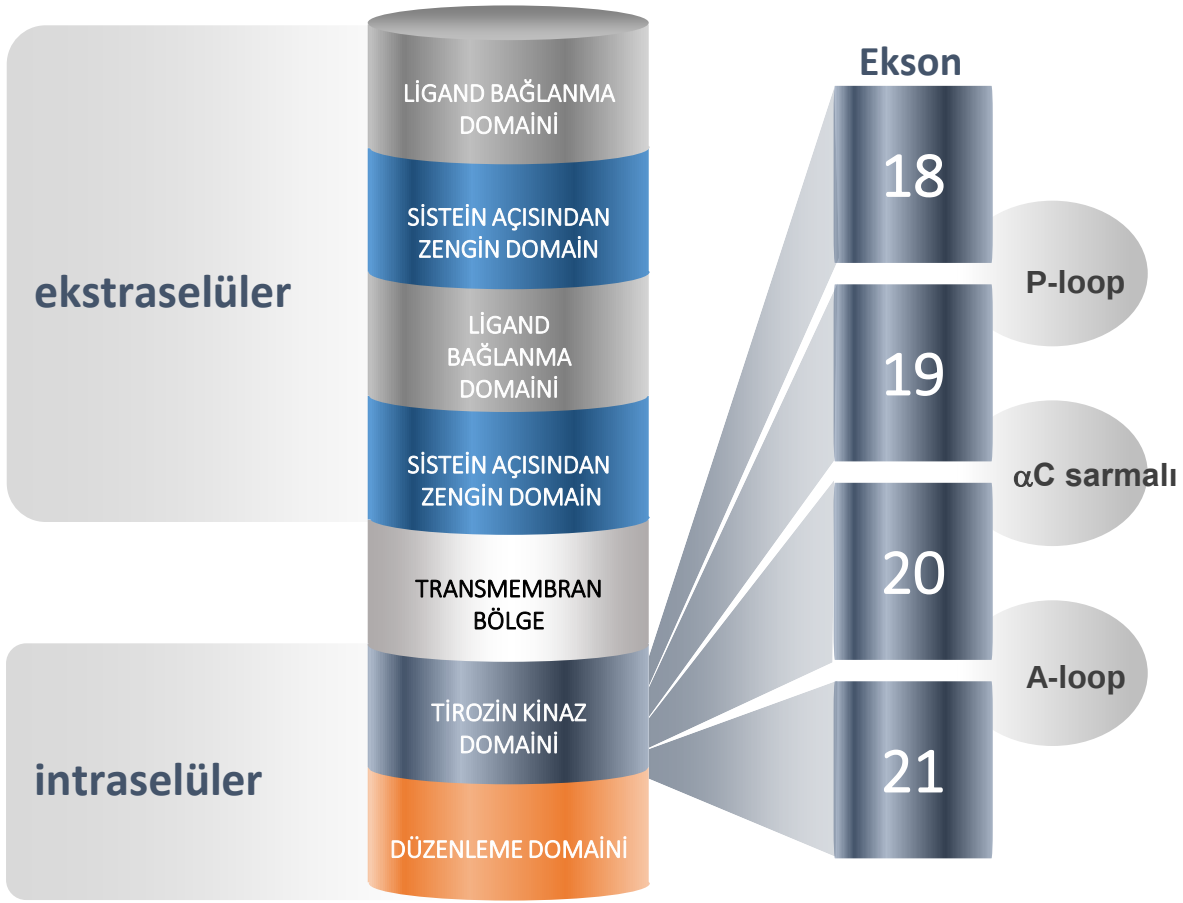

EGFR Structure
Extracellular Domain
Transmembrane Domain
Intracellular Domain
TK


Stromal cells
Blood vessel
Endothelial cells
ERBB ligands
VEGFR
EGFR
Pro-ERBB ligand
VEGF
EGFR
Metalloproteinase
MAPK
PI3K-AKT
GPCR or FZD
ER
SRC
Other stimuli
mTOR
SRC
STAT
Nucleus
E2
ER
p27
Sequestering complexes
STAT
Pro-survival genes
CDK2
Cyc E
Proliferation
Proliferation-stimulating genes


EGFR Mutations in NSCLC
Geographical Map
France (1227) 14%
Italy (860) 5% (10%)
India (2527) 25-40% (36%)
Korea (513) 20 -36 % (38-48%)
Spain (2105) 17 %
Qatar (25) (32%)
China (1068) 24-39% (41-50%)
Japan (1498) 26-40 % (41-49%)
USA (456) 2–14% (15-25%)
Taiwan (267) 34 % (56-62%)
Philippines (65) (52%)
Brazil (2017) 30%
Thailand (403) (54%)
Vietnam (120) (64%)
Hong Kong (161) (47%)
Austraila (83) 7% (14%)
Key: Country (N=) % mutation NSCLC (% mutation in AdenoCa)

EGFR'yi aktive eden mutasyonlar, KHDAK'de ekson 18 ile 21 arasında kümelenme eğilimindedir.

EGFR geni[1-4]



Mutasyon tiplerinin dağılımı[4,*]

Mutasyon tipi	Yüzde
Ekson 18 G719A/C	%1,03
Ekson 19 delesyonu[†]	%46
Ekson 20 T790M de novo Diğer ekson 20 mutasyonları	%4,1 %2,3
Ekson 21 nokta mutasyon L858R[†]	%37,5
L861Q	%1,12

*COSMIC (Catalogue Of Somatic Mutations In Cancer-Kanserde Somatik Mutasyonlar Katalogu) veritabanında bildirilen literatür derlemesi; çalışma ve popülasyon faktörlerine bağlı olarak değişiklik gösterebilir. [†]Birinci ve ikinci nesil TKİ'lere karşı duyarlılık sağlayan duyarlılaştırıcı mutasyonlar

EGFR, epidermal büyüme faktörü reseptörü; KHDAK, küçük hücreli dışı akciğer kanseri; TKİ, tirozin kinaz inhibitörü.

1. Shigematsu H, et al. *J Natl Cancer Inst.* 2005;97(5):339-346. 2. Lynch TJ, et al. *N Engl J Med*. 2004;350(21):2129-2139. 3. Paez JG, et al. *Science*. 2004;304(5676):1497-1500. 4. Siegelin MD, et al. *Lab Invest.* 2014;94(2):129-137.

Erlotinib (Tarceva, Ertinob)

- First generation
- FDA approved: 2011

Afatinib (Giotrif)

- Second generation
- FDA approved: 2013

Osimertinib (Tagrisso)

- Third generation
- FDA approved: 2015

Gefitinib (İressa)

- First generation
- FDA approved: 2015

Dacomitinib (Vizimpro)

- Second generation
- FDA approved: 2018

EGFR TKIs: EGFR mutasyonu hedefli tedaviler

FDA-onaylı EGFR TKI	*EGFR* Mutasyon lokalizasyonu			
	Exon 18	Exon 19	Exon 20	Exon 21
Erlotinib Gefitinib Afatinib	--	Delesyon	--	L858R
Osimertinib	--	Delesyon	T790M	L858R
(on/off label) erlotinib, gefitinib, afatinib	G719X*	İnsersiyon	A763_Y764insFQE A S768I*	L861Q*
EGFR TKI insensitivitesine neden olan mutasyonlar	--	--	İnsersiyon C797S T790M	--

*Afatinib tek ya da kombinasyon şeklinde

Afatinib [package insert]. 2018. Erlotinib [package insert]. 2016. Gefitinib [package insert]. 2015. Osimertinib [package insert]. 2015. Lin YT, et al. Clin Lung Cancer. 2017;18:324-332. Morgillo F, et al. ESMO Open. 2016;1:e000060.

EGFR TKIs: özellikler

Parametre	Erlotinib	Gefitinib	Afatinib	Osimertinib	Dacomitinib
Reseptör bağlanma	EGFR/HER1,* SRC, ABL?	EGFR/HER1, * IGF, PDGF	EGFR/HER1, * HER2, HER4	EGFR/HER1,* HER2, HER3, HER4, BLK, ACK1	EGFR/HER1,* HER2, HER4
EGFR bağlanma	Reversible	Reversible	Irreversible	Irreversible	Irreversible
Yarı öm , hrs	36	48	37	48	59-85
Gıda etkisi (boş mide ile alma)	Artar ~ 60% to ~ 100%	Değişmez	Azalır AUC 39%	Değişmez	Değişmez
SSS penetrasyonu, AUC oranı	0.03X CSF/Plazma	0.01X CSF/Serum	0.02X CSF/Plazma	2X Beyin /Plazma	Veri yok

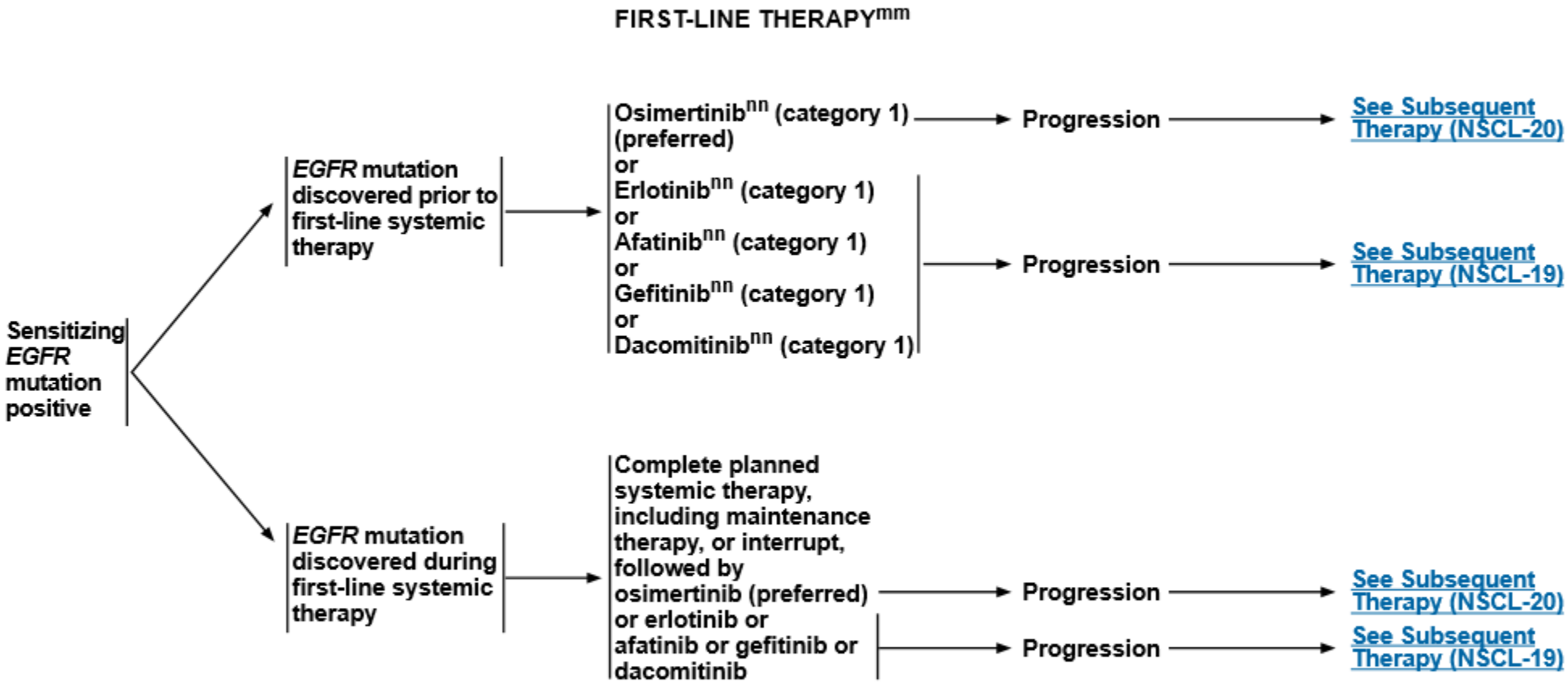
*All inhibit exon 19 deletion and L858R

First-line EGFR TKI vs Kemoterapi
EGFR Mutant KHDAK

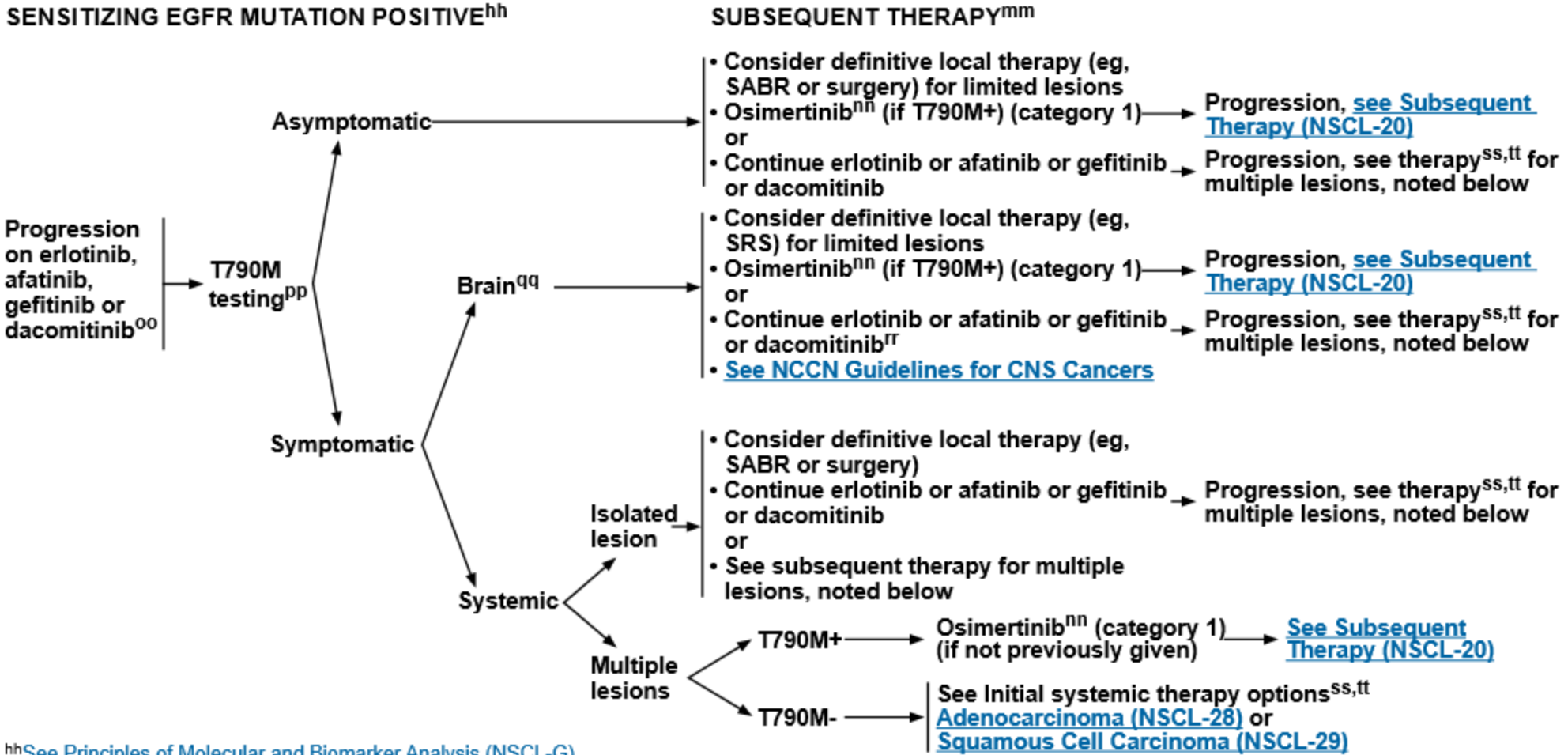
Study	N	Treatment	ORR, %	Median PFS, Mos	Median OS, Mos
NEJ002[1]	230	Gefitinib vs carboplatin/paclitaxel	74 vs 31	10.8 vs 5.4 (*P* < .001)	30.5 vs 23.6 (HR: 0.89)
WJTOG 3405[2,3]	172	Gefitinib vs cisplatin/docetaxel	62 vs 32	9.6 vs 6.6 (*P* < .001)	34.8 vs 37.3 (HR: 1.25)
OPTIMAL[4,5]	165	Erlotinib 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)

References in slidenotes.

SENSITIZING EGFR MUTATION POSITIVE[hh]



[hh] See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn] For performance status 0-4.



[hh] See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn] For performance status 0-4.
[oo] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

ALK pozitif hasta

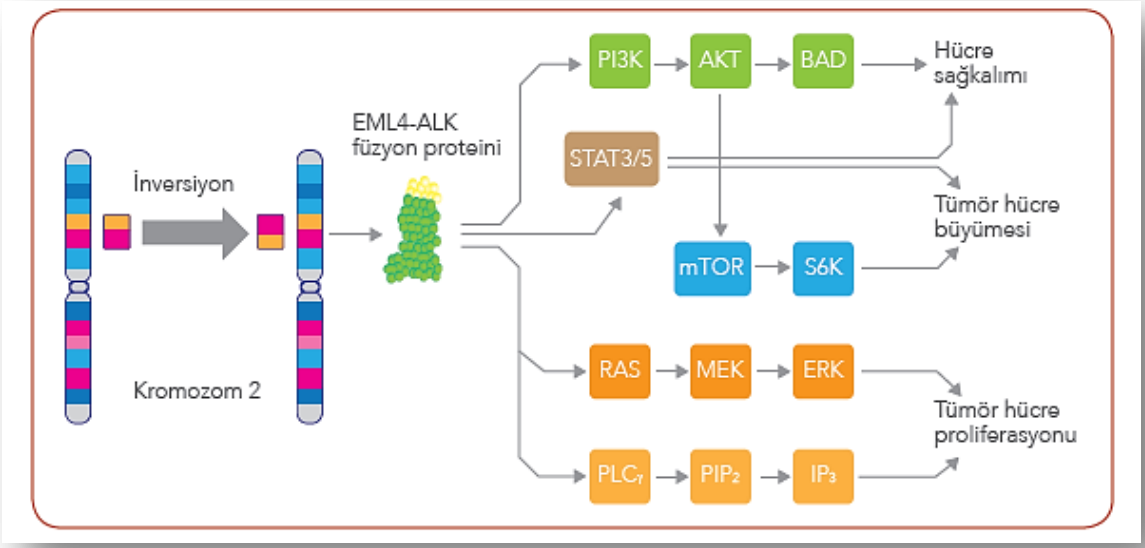
ALK+'liği;

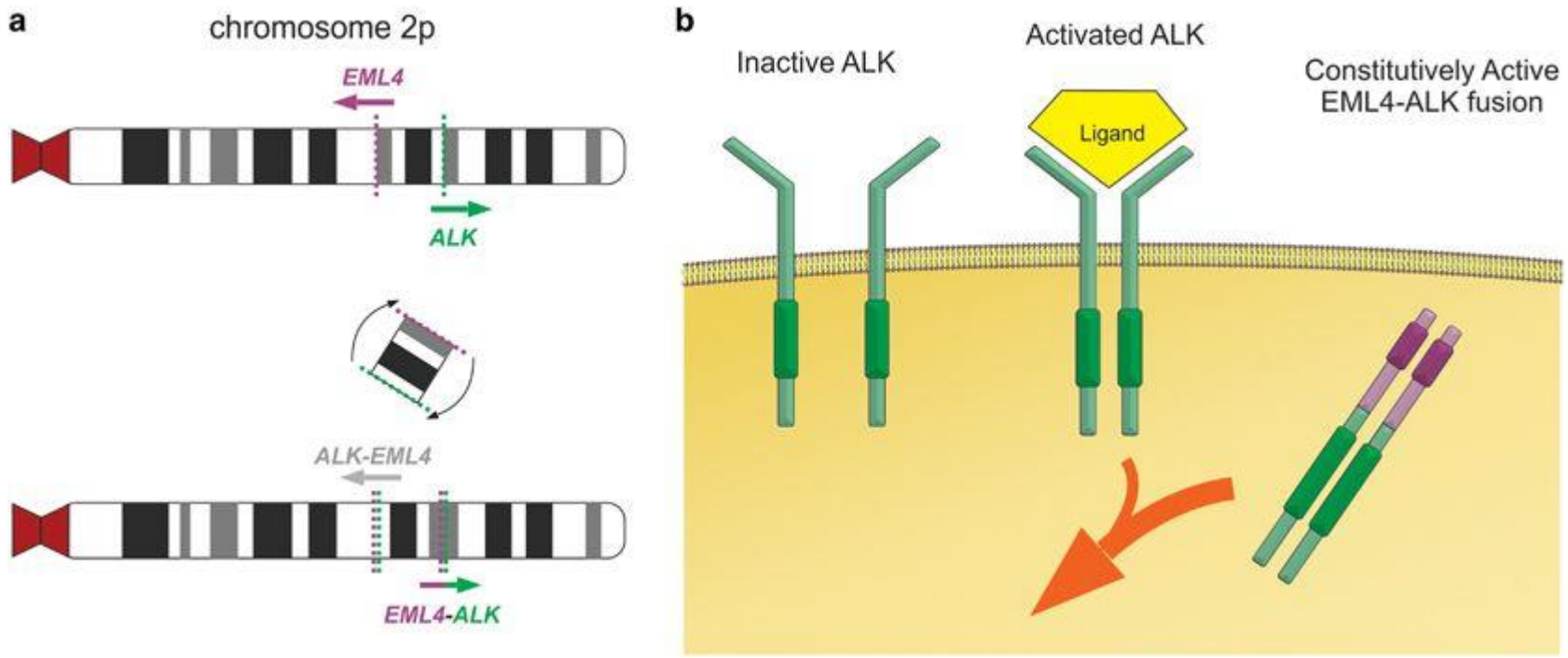
- Tüm **KHDAK**' de yaklaşık **% 3-8 oranında**
- Tüm adenokarsinomlar, **sigara içmemiş % 22**
- Tüm adenokarsinomlar, **sigara içmemiş ve EGFR (-) % 33** görülmektedir.

ALK+ KHDAK bazı subgruplarda daha sık görülmektedir;

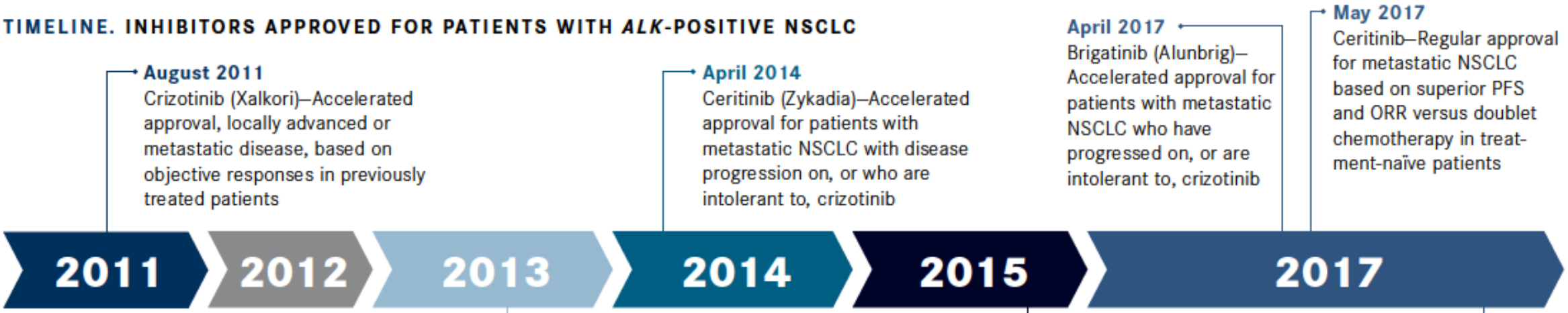
- Non-skuamöz histoloji
- Sigara içmeyen hastalar
- Genç hastalar
- Kadın cinsiyet
- EGFR veya KRAS WT hastalar

- ALK **geni 2. kromozomda** yer alır
- En sık görülen ALK yeniden düzenlenmesi **ALK ile EML4 arasındadır**
- EML4 - ALK füzyon proteininin transmembran domaini yoktur ve yapısal olarak aktiftir




a
chromosome 2p
EML4
ALK
ALK-EML4
EML4-ALK
b
Inactive ALK
Activated ALK
Ligand
Constitutively Active
EML4-ALK fusion

TIMELINE. INHIBITORS APPROVED FOR PATIENTS WITH *ALK*-POSITIVE NSCLC



August 2011
Crizotinib (Xalkori)—Accelerated approval, locally advanced or metastatic disease, based on objective responses in previously treated patients

November 2013
Crizotinib—Regular approval based on superior PFS and ORR versus chemotherapy, based on findings in patients with disease progression after platinum-based doublet chemotherapy

April 2014
Ceritinib (Zykadia)—Accelerated approval for patients with metastatic NSCLC with disease progression on, or who are intolerant to, crizotinib

December 2015
Alectinib (Alecensa)—Accelerated approval for patients with metastatic NSCLC who have progressed on, or are intolerant to, crizotinib

April 2017
Brigatinib (Alunbrig)—Accelerated approval for patients with metastatic NSCLC who have progressed on, or are intolerant to, crizotinib

May 2017
Ceritinib—Regular approval for metastatic NSCLC based on superior PFS and ORR versus doublet chemotherapy in treatment-naïve patients

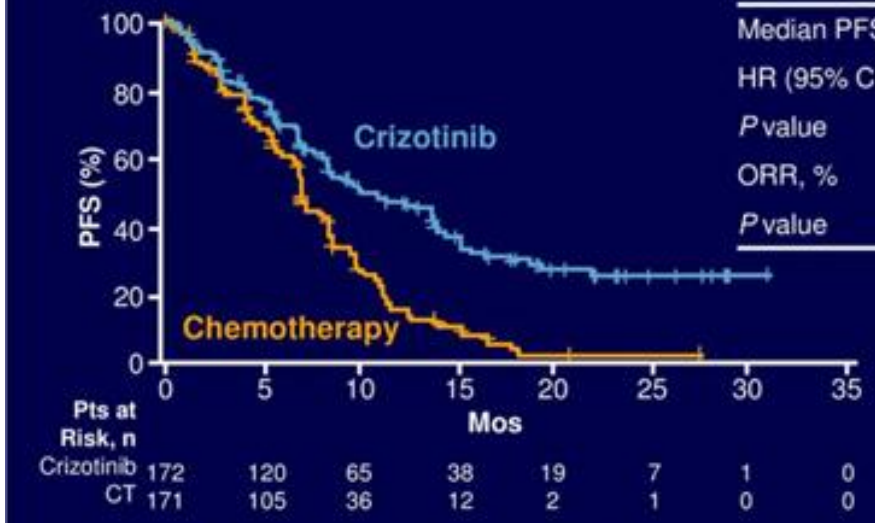
November 2017
Alectinib—Regular approval for metastatic NSCLC based on superior PFS and ORR versus crizotinib in patients who had not received prior systemic therapy for metastatic disease

ALK indicates anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival.

Crizotinib

PROFILE 1014: First-line Crizotinib vs Pemetrexed/Platinum* in Advanced NSCLC

- Phase III trial (N = 343) ALK-positive pts with nonsquamous NSCLC and no prior systemic treatment for advanced disease



	Crizotinib (n = 172)	Chemotherapy (n = 171)
Median PFS, mos	10.9	7.0
HR (95% CI)	0.45 (0.35-0.60)	
P value	< .001	
ORR, %	74	45
P value	< .001	

*Carboplatin or cisplatin.

Solomon BJ, et al. N Engl J Med. 2014;371:2167-2177.

Slide credit: clinicaloptions.com

Ceritinib

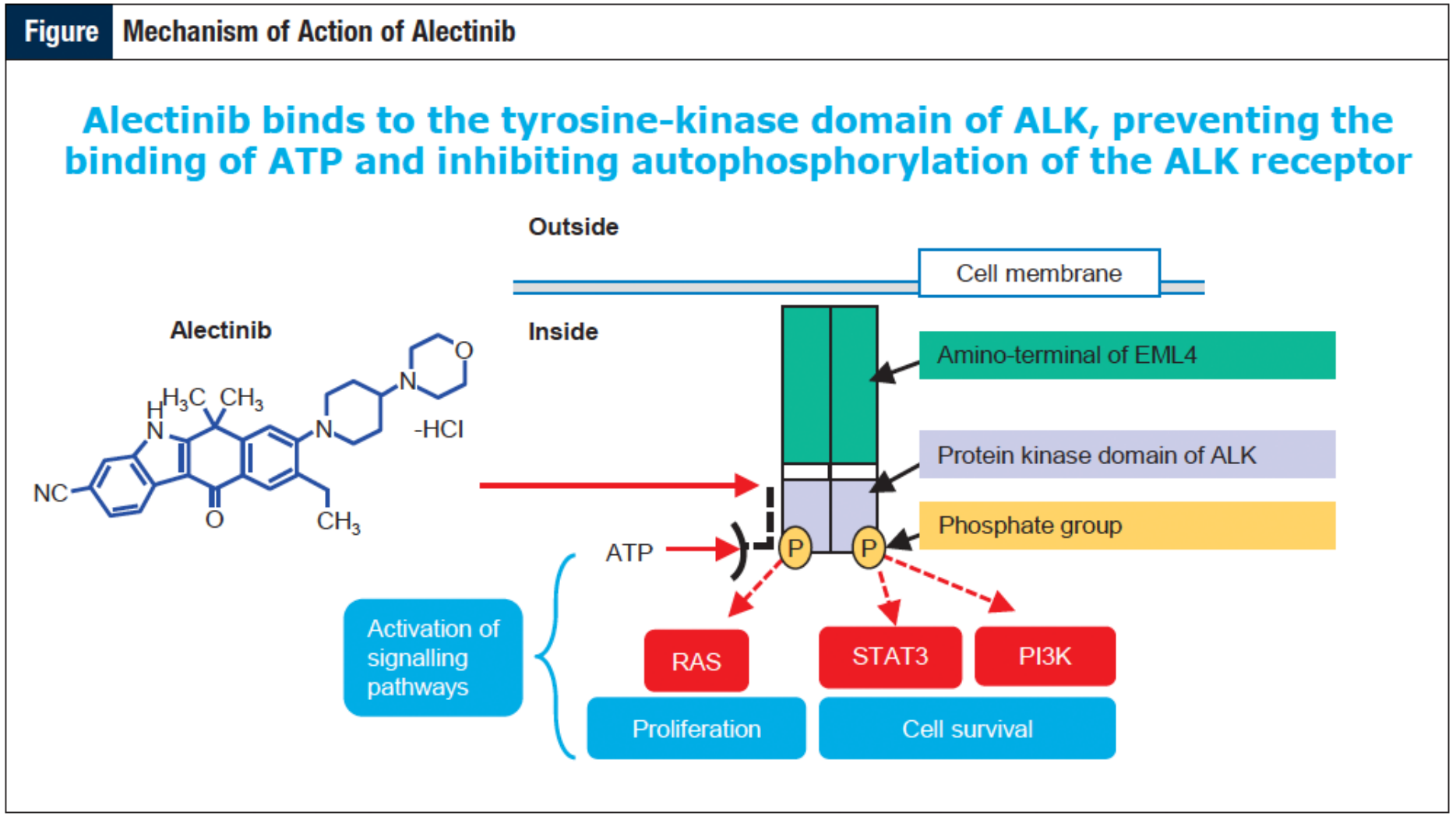
ASCEND-4: First-line Ceritinib Vs Chemotherapy for ALK-Positive NSCLC

- Randomized, global, open-label phase III study
- Primary endpoint: PFS

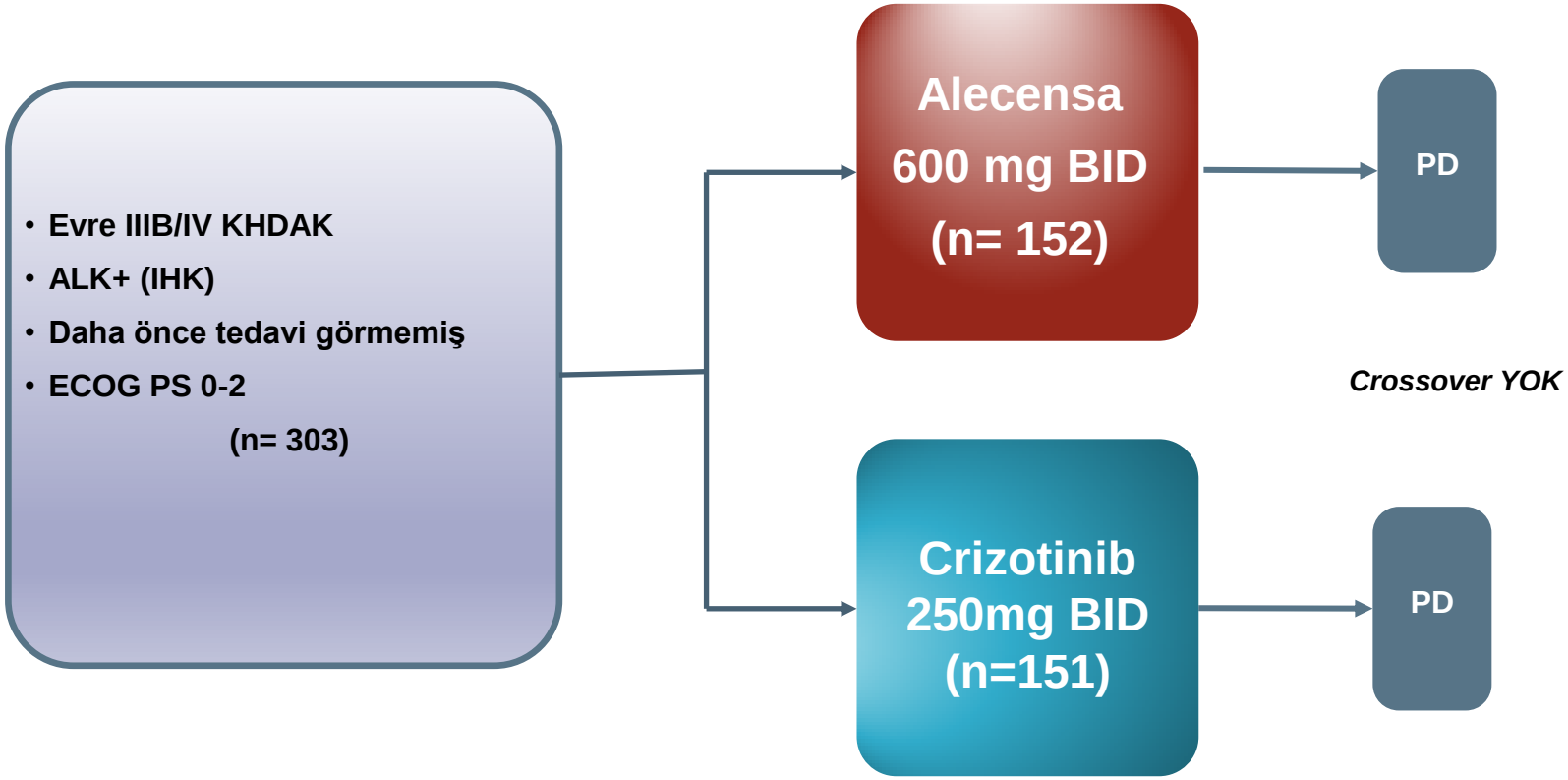
Efficacy outcome	Ceritinib (n = 189)	Chemotherapy (n = 187)	HR	*P* Value
Median PFS, mos	16.6	8.1	0.55	< .001
ORR, %	72.5	26.7	--	--
OIRR, %	72.7 (n = 22)	27.3 (n = 22)	--	--

Alectinib

- **Figure** Mechanism of Action of Alectinib



Alex Çalışma Tasarımı



Primer sonlanım noktası

- **PFS (Araştırmacı değerlendirmesine göre)**

Sekonder sonlanım noktası

PFS (Bağımsız değerlendirmeciye göre), OS, ORR, DOR, MSS TTP, MSS ORR, MSS DoR, Güvenlilik

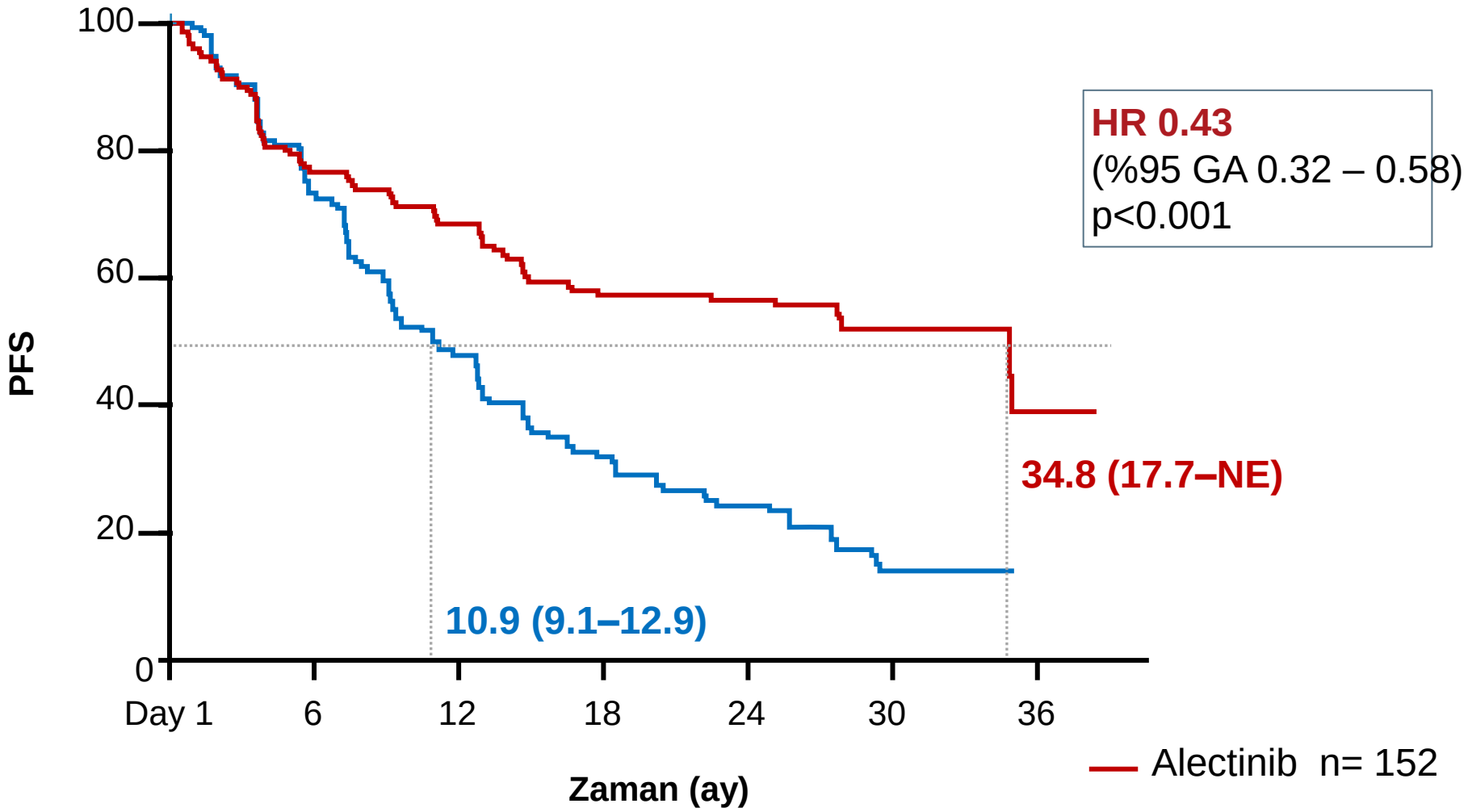
Stratifikasyon faktörleri

- **ECOG PS**
- **Irk**
- **MSS metastaz varlığı**

Peters, et al. NEJM 2017

Alectinib ile progresyon riskinde % 57 azalma

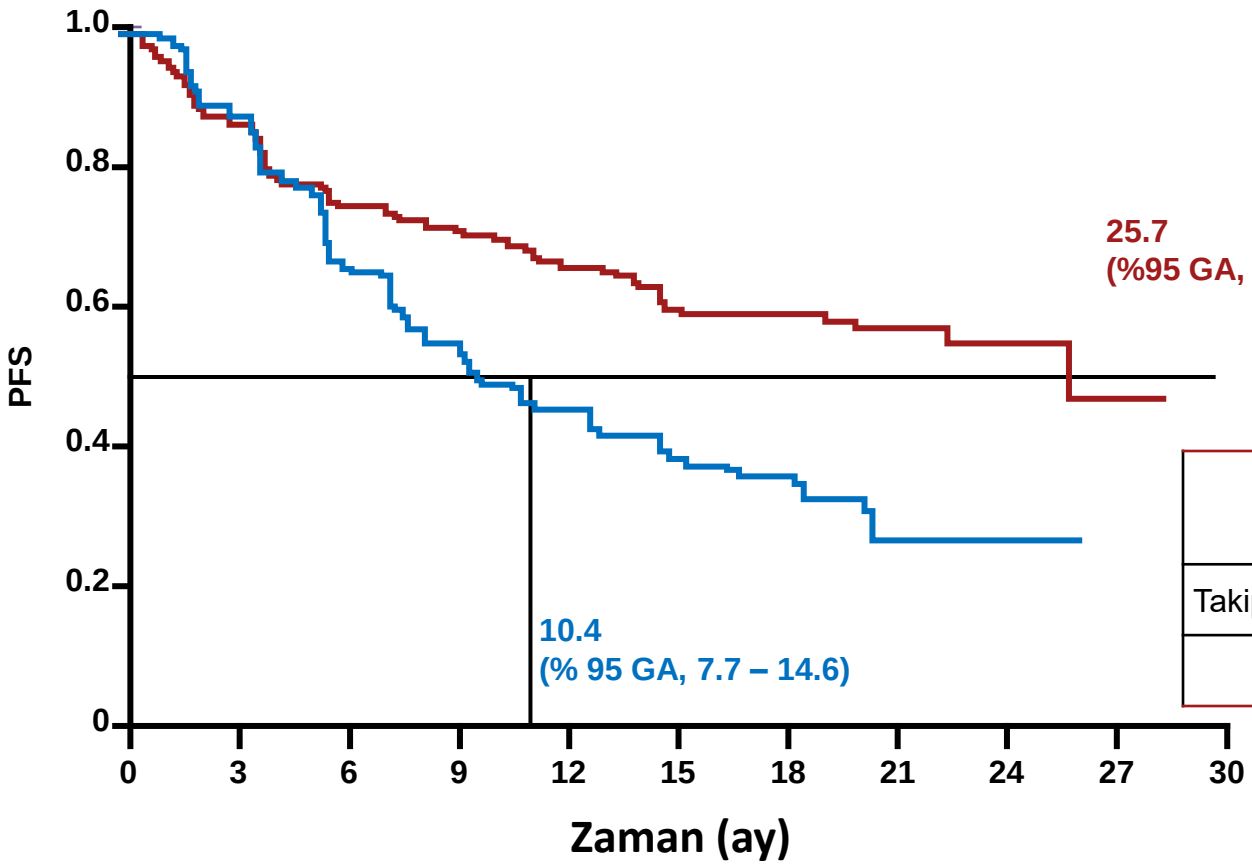
Alectinib ile PFS yararı (Araştırmacı değerlendirmesine göre)



Camidge, et al. ASCO 2018

Alectinib ile progresyonsuz sağkalımda 15.3 aylık yarar

Alectinib ile PFS yararı (Bağımsız değerlendirmeciye göre)



HR 0.50
(%95 GA 0.36 – 0.70)
p<0.001

	Crizotinib (N=151)	Alectinib (N=152)
Takip süresi, ay		
Medyan	22.8	27.8

Alectinib n= 152

Krizotinib n=151

Peters, et al. NEJM 2017

Camidge, et al. ASCO 2018

Alectinib , MSS tutulumundan bağımsız olarak PFS yararı sağlar

Tanı anında MSS tutulumu olan hastalar

	Alectinib (n = 64)	Crizotinib (n = 58)
Median PFS (95% CI)	27.7 (9.2–NE)	7.4 (6.6–9.6)
HR[SEP](95% CI)	0.35 (0.22–0.56)	

Tanı anında MSS tutulumu olmayan hastalar

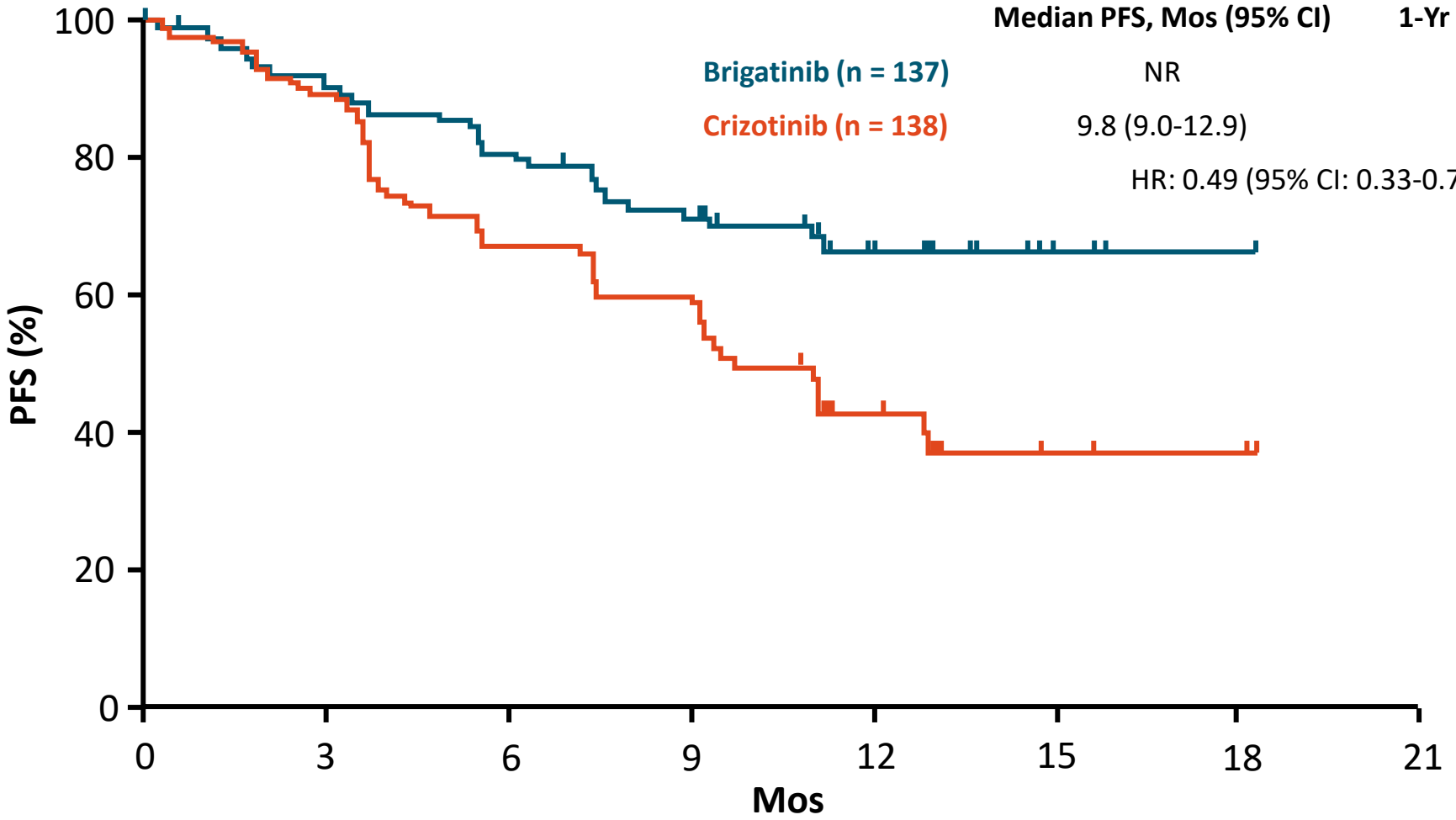
	Alectinib (n = 88)	Crizotinib (n = 93)
Median PFS (95% CI)	34.8 (22.4–NE)	14.7 (10.8–20.3)
HR[SEP](95% CI)	0.47 (0.32–0.71)	

Peters, et al. NEJM 2017

Brigatinib vs Crizotinib in ALKi-Naive Patients With Advanced *ALK*-Positive NSCLC (ALTA-1L): Background

- Brigatinib: next-generation ALK/ROS1 inhibitor
  - ALK inh rezistans mutasyonlar ve EGFR mutasyonlarında etkisini göstredi
  - Faz ı/ıı çalışmalarda crizotinib sonrası brigatinib yüksek cevap oranları ve 16 aya varan PFS
  - ALTA1 çalışması 1. basamak çalışma

ALTA-1L: BIRC-Assessed PFS (Primary Endpoint)



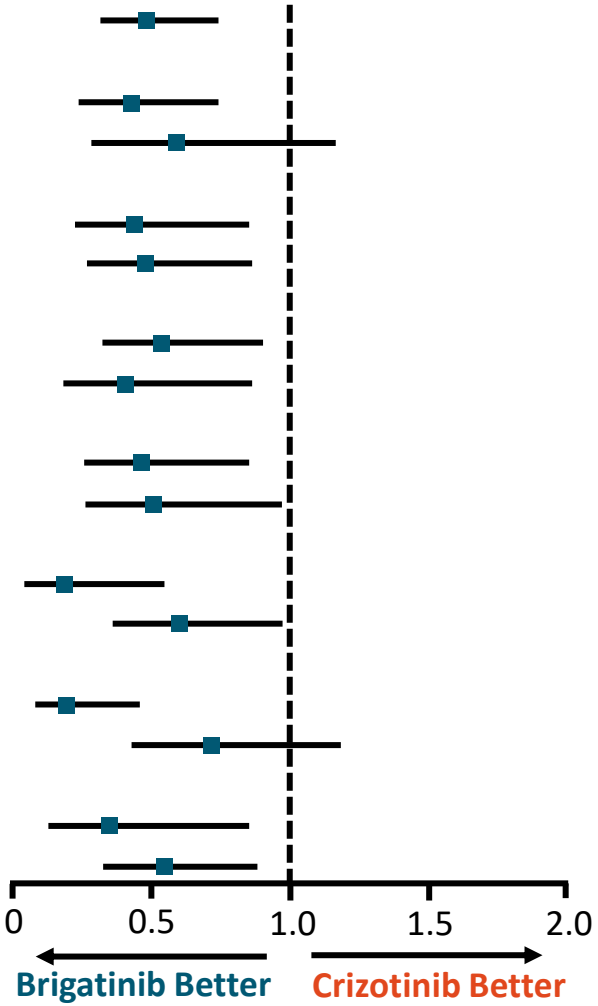
	Median PFS, Mos (95% CI)	1-Yr PFS Rate, % (95% CI)
Brigatinib (n = 137)	NR	67 (56-75)
Crizotinib (n = 138)	9.8 (9.0-12.9)	43 (32-53)

HR: 0.49 (95% CI: 0.33-0.74); *P* < .001

Camidge DR, et al. WCLC 2018. Abstract PL02.03. Camidge DR, et al. N Engl J Med. 2018;[Epub ahead of print].

ALTA-1L: BIRC-Assessed PFS by Prespecified Subgroup

Subgroup	No. of Patients		HR for Disease Progression or Death (95% CI)
	Brigatinib	Crizotinib	
Overall	137	138	0.49 (0.33-0.74)
Age			
18-64 yrs	93	95	0.44 (0.26-0.74)
≥ 65 yrs	44	43	0.59 (0.30-1.18)
Sex			
Female	69	81	0.44 (0.24-0.84)
Male	68	57	0.49 (0.28-0.85)
Race			
Non-Asian	78	89	0.54 (0.33-0.90)
Asian	59	49	0.41 (0.20-0.86)
History of tobacco use			
Never smoked	84	75	0.47 (0.27-0.84)
Former smoker	49	56	0.51 (0.27-0.97)
ECOG PS			
0	58	60	0.19 (0.06-0.55)
1	73	72	0.60 (0.37-0.98)
Brain metastases at baseline			
Yes	40	41	0.20 (0.09-0.46)
No	97	97	0.72 (0.44-1.18)
Previous chemotherapy			
Yes	36	37	0.35 (0.14-0.85)
No	101	101	0.55 (0.34-0.88)



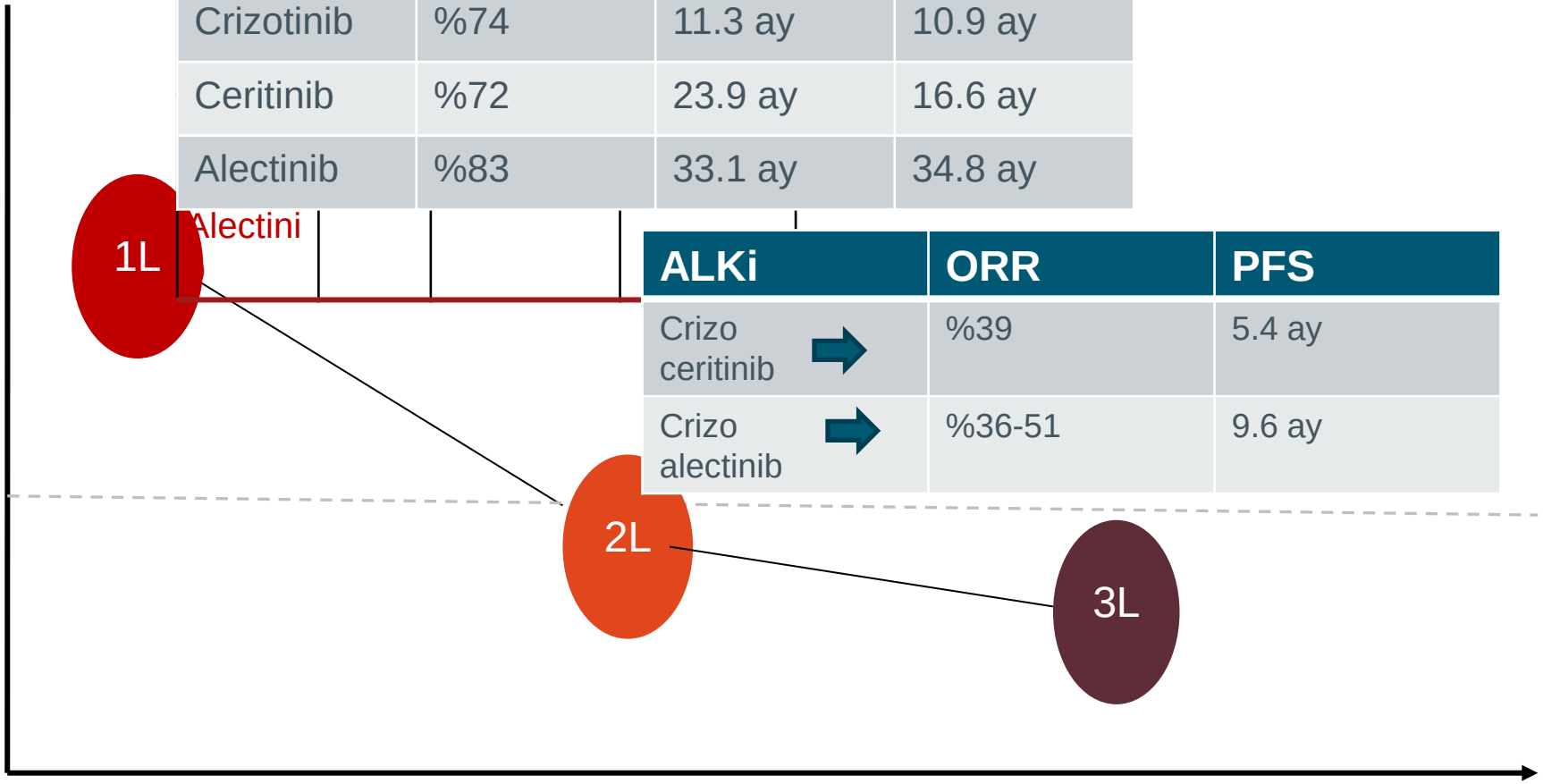
Camidge DR, et al. WCLC 2018. Abstract PL02.03. Camidge DR, et al. N Engl J Med. 2018;[Epub ahead of print].

ALK+ KHDAK 2. Basamak Faz 2/3 Çalışmaları

	ASCEND-5		ALUR	
	Seritinib	Kemoterapi	Alektinib	Kemoterapi
N	115	116	72	35
ORR (%)	39	7	37.5	2.9
PFS (ay)	5.4	1.6	9.6	1.4
HR	0.49		0.15	

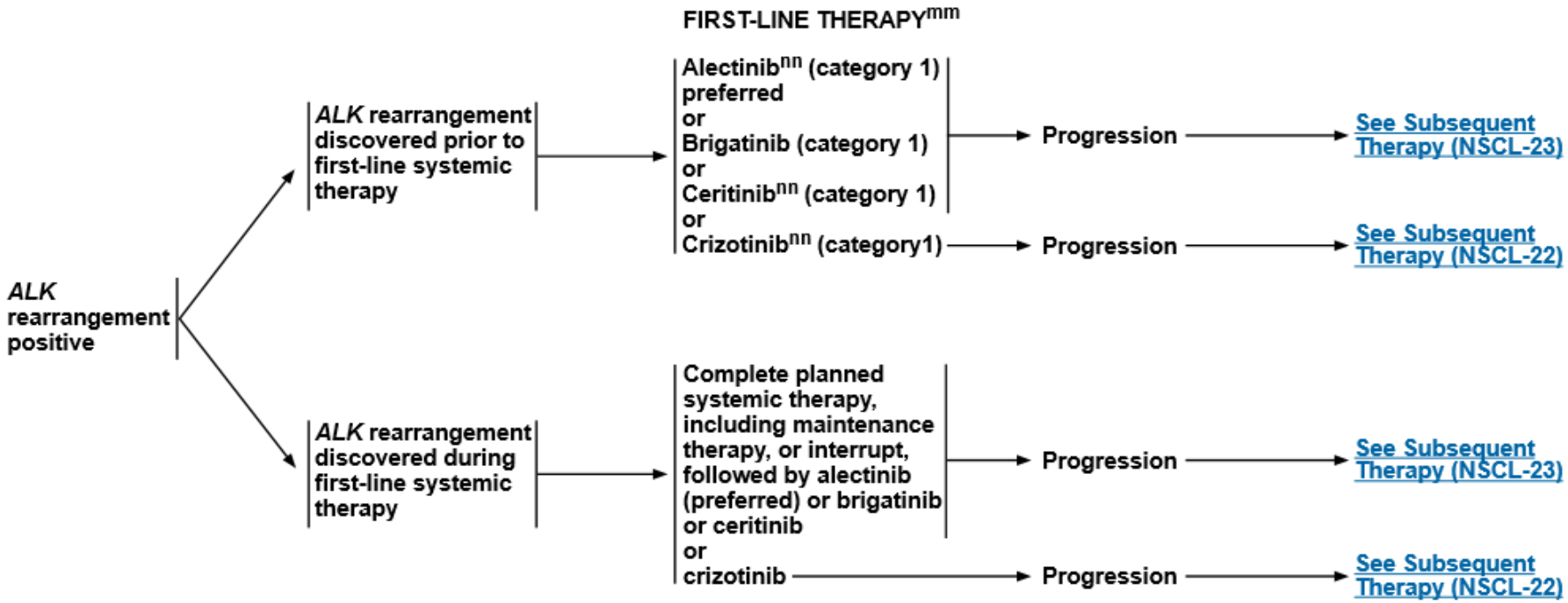
ALK İnhibitörlerinin 1, 2 ve 3. Basamaklarda Kullanımı ve Yanıt Oranları

ALKi	ORR	DoR	PFS
Crizotinib	%74	11.3 ay	10.9 ay
Ceritinib	%72	23.9 ay	16.6 ay
Alectinib	%83	33.1 ay	34.8 ay

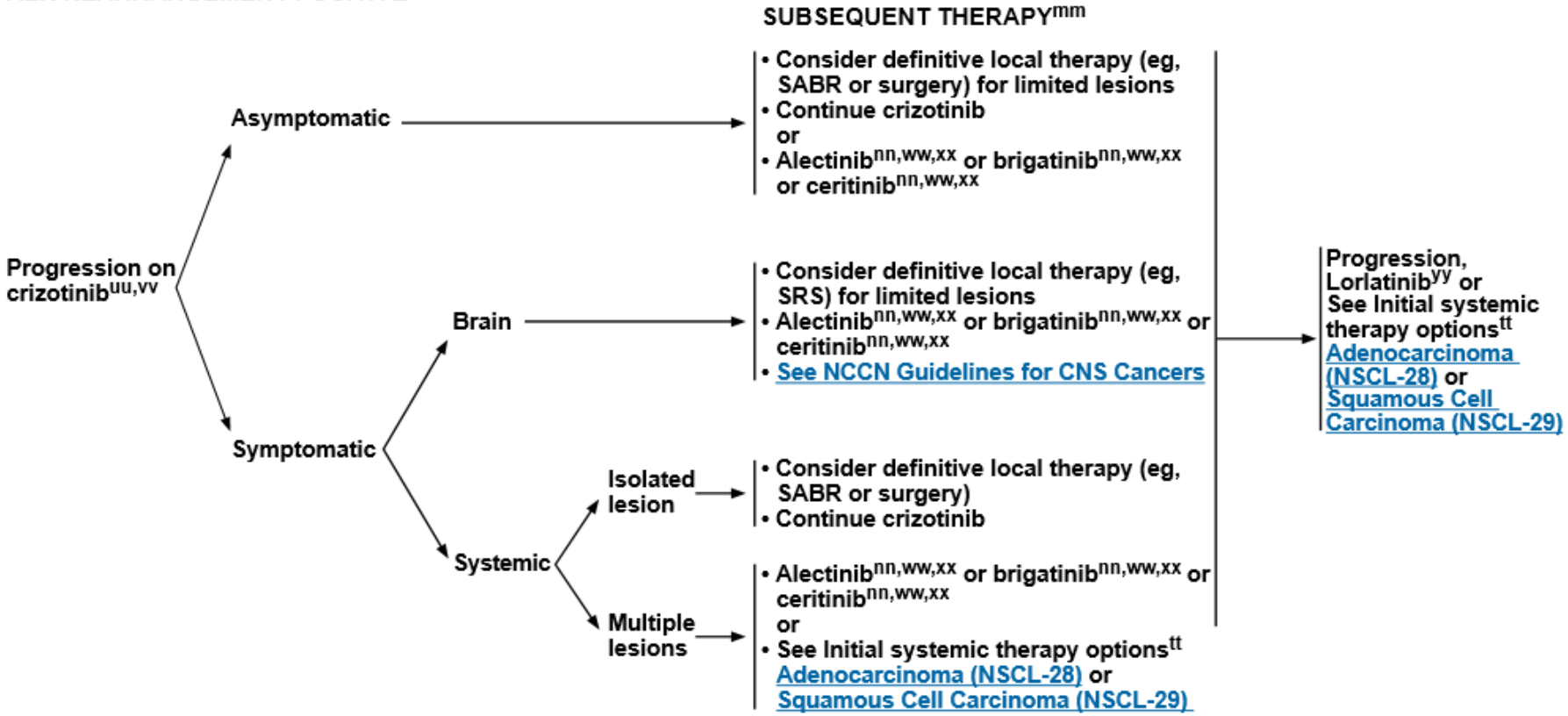


ALKi	ORR	PFS
Crizo ceritinib	%39	5.4 ay
Crizo alectinib	%36-51	9.6 ay

ALK REARRANGEMENT POSITIVE[hh]



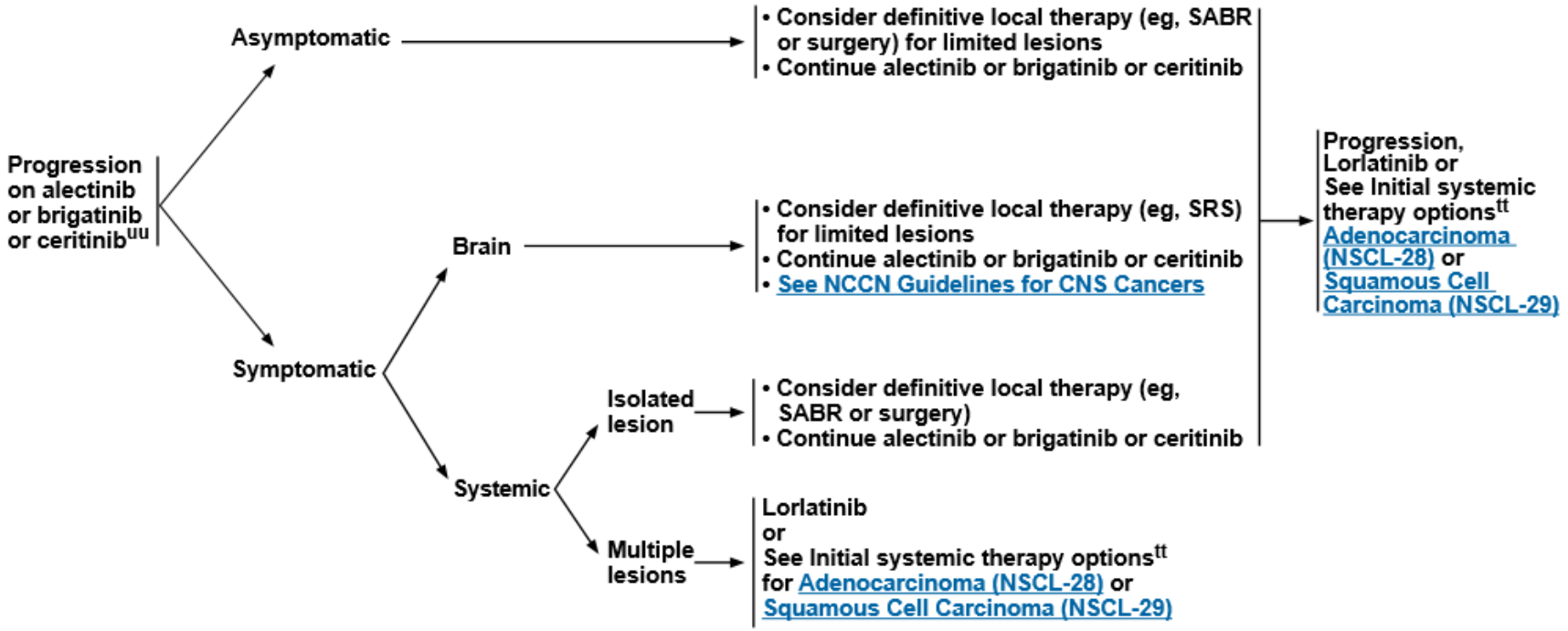
ALK REARRANGEMENT POSITIVE[hh]



[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn]For performance status 0-4.
[tt]The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in EGFR+/ALK+
[vv]Patients who are intolerant to crizotinib may be switched to ceritinib, alectinib, or brigatinib.
[ww]If not previously given.
[xx]Ceritinib, alectinib, or brigatinib are treatment options for patients with ALK-positive metastatic NSCLC that has progressed on crizotinib.

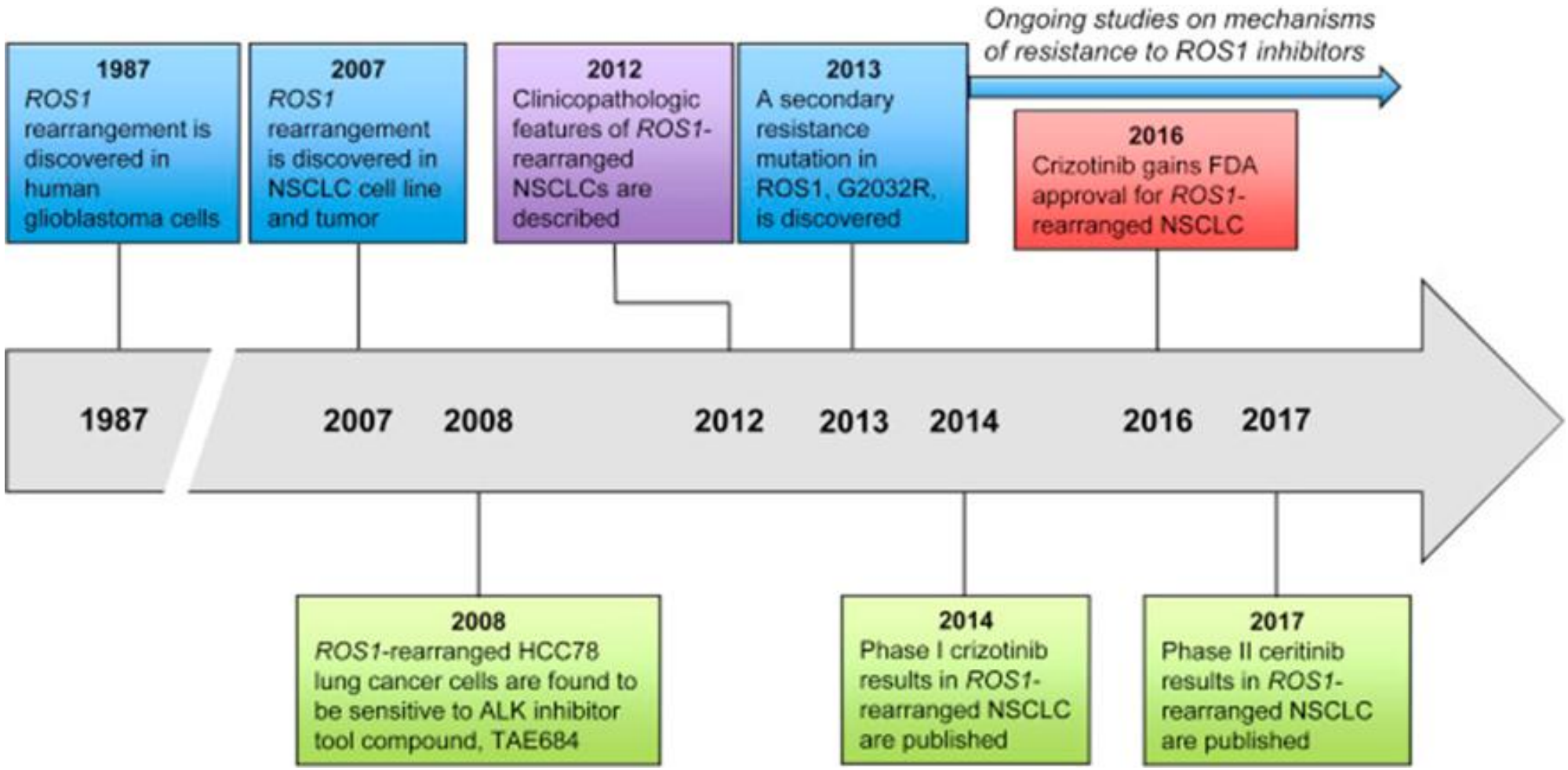
ALK REARRANGEMENT POSITIVE[hh]

SUBSEQUENT THERAPY[mm]



[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).

ROS-1


Ongoing studies on mechanisms of resistance to ROS1 inhibitors
1987
ROS1 rearrangement is discovered in human glioblastoma cells
2007
ROS1 rearrangement is discovered in NSCLC cell line and tumor
2012
Clinicopathologic features of ROS1-rearranged NSCLCs are described
2013
A secondary resistance mutation in ROS1, G2032R, is discovered
2016
Crizotinib gains FDA approval for ROS1-rearranged NSCLC
1987
2007
2008
2012
2013
2014
2016
2017
2008
ROS1-rearranged HCC78 lung cancer cells are found to be sensitive to ALK inhibitor tool compound, TAE684
2014
Phase I crizotinib results in ROS1-rearranged NSCLC are published
2017
Phase II ceritinib results in ROS1-rearranged NSCLC are published

- ROS-1 pozitifliği % 1-2
- Adenokarsinom
- Genç
- Sigara içmemiş

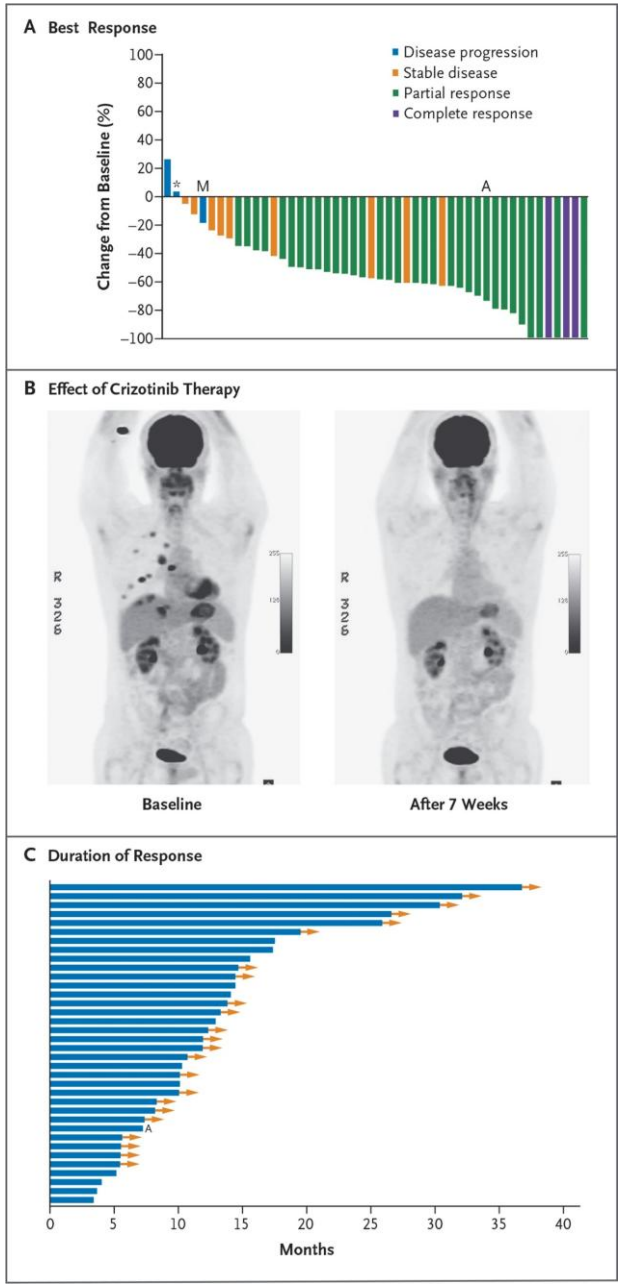
Published in final edited form as:
N Engl J Med. 2014 November 20; 371(21): 1963–1971. doi:10.1056/NEJMoa1406766.

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

Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Ravi Salgia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.
Massachusetts General Hospital Cancer Center (A.T.S., L.P.L., Z.Z., J.W.C., A.J.I.), Dana–Farber Cancer Institute (G.I.S.), and Beth Israel Deaconess Medical Center (D.B.C.) — all in Boston; University of California at Irvine, Irvine (S.-H.I.O.), and Pfizer Oncology, La Jolla (W.T., S.M.S., L.M.T., J.G.C., K.D.W.) — both in California; Seoul National University Hospital, Seoul, South Korea (Y.-J.B.); University of Colorado, Aurora (D.R.C., M.V.-G., R.C.D.); Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (B.J.S.); University of Chicago, Chicago (R.S.); Memorial Sloan Kettering Cancer Center, New York (G.J.R.); Karolinska Institutet, Stockholm (Z.Z.); and Rho, Chapel Hill, NC (P.S.)

Abstract

BACKGROUND—Chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase (*ROS1*) define a distinct molecular subgroup of non–small-cell lung cancers (NSCLCs) that may be susceptible to therapeutic ROS1 kinase inhibition. Crizotinib is a small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), ROS1, and another proto-oncogene receptor tyrosine kinase, MET.



- Objektif cevap oranı % 72
- 3 komplet cevap ve 33 parsiyel cevap
- Ortalama cevap süresi 17.6 ay
- PFS 19.2 ay

J Clin Oncol. 2018 May 10;36(14):1405-1411. doi: 10.1200/JCO.2017.75.5587. Epub 2018 Mar 29.

Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer.

Wu YL[1], Yang JC[1], Kim DW[1], Lu S[1], Zhou J[1], Seto T[1], Yang JJ[1], Yamamoto N[1], Ahn MJ[1], Takahashi T[1], Yamanaka T[1], Kemner A[1], Roychowdhury D[1], Paolini J[1], Usari T[1], Wilner KD[1], Goto K[1].

Author information

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Abstract

Purpose Approximately 1% to 2% of non-small-cell lung cancers (NSCLCs) harbor a c-ros oncogene 1 (ROS1) rearrangement. Crizotinib, an inhibitor of anaplastic lymphoma kinase (ALK), ROS1, and MET, has shown marked antitumor activity in a small expansion cohort of patients with ROS1-positive advanced NSCLC from an ongoing phase I study. We assessed the efficacy and safety of crizotinib in the largest cohort of patients with ROS1-positive advanced NSCLC. Patients and Methods This phase II, open-label, single-arm trial enrolled East Asian patients with ROS1-positive (assessed through validated AmoyDx assay [Amoy Diagnostics, Xiamen, China] at three regional laboratories) advanced NSCLC who had received three or fewer lines of prior systemic therapies. Patients were to receive oral crizotinib at a starting dose of 250 mg twice daily and continued treatment until Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1-defined progression (by independent radiology review [IRR]), unacceptable toxicity, or withdrawal of consent. The primary end point was objective response rate (ORR) by IRR. Results In the efficacy and safety analyses, 127 patients were included, with 49.6% still receiving treatment at data cutoff. ORR by IRR was 71.7% (95% CI, 63.0% to 79.3%), with 17 complete responses and 74 partial responses. ORRs were similar irrespective of the number of prior lines of therapy, and responses were durable (median duration of response, 19.7 months; 95% CI, 14.1 months to not reached). Median progression-free survival by IRR was 15.9 months (95% CI, 12.9 to 24.0 months). No new safety signals associated with crizotinib were reported. Conclusion This study demonstrated clinically meaningful benefit and durable responses with crizotinib in East Asian patients with ROS1-positive advanced NSCLC. Crizotinib was generally well tolerated, with a safety profile consistent with previous reports.

- 127 hastalık Asya çalışmasında PFS 15. 9 ay

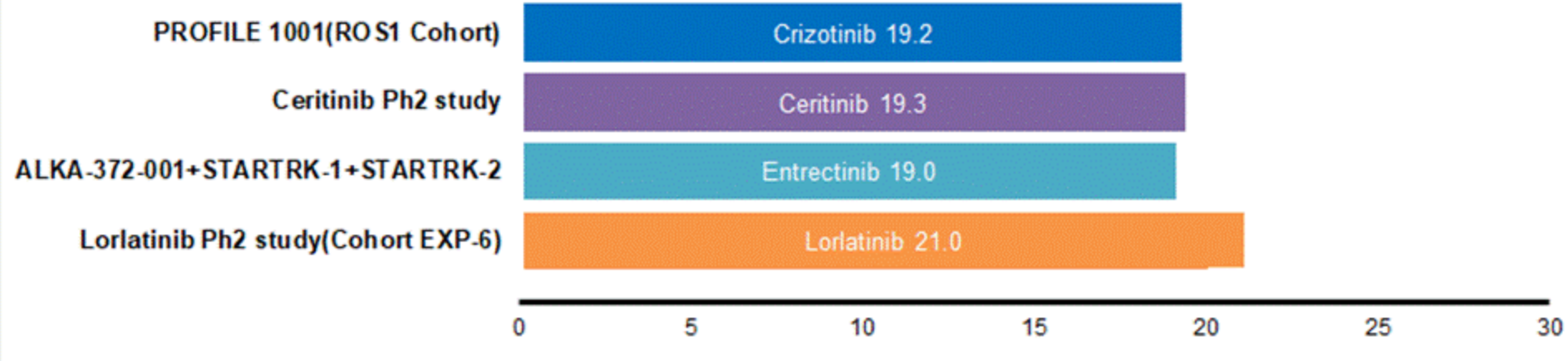
- Ceritinib (ZYKADIA)
- Alectinib (ALECENZA)
- Brigatinib
- Lorlatinib
- Entrectinib

ALK İnhibitörlerinin 1, 2 ve 3. Basamaklarda Kullanımı ve Yanıt Oranları

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG #WCLC2018

First line therapeutic strategies for ROS1-rearranged NSCLC



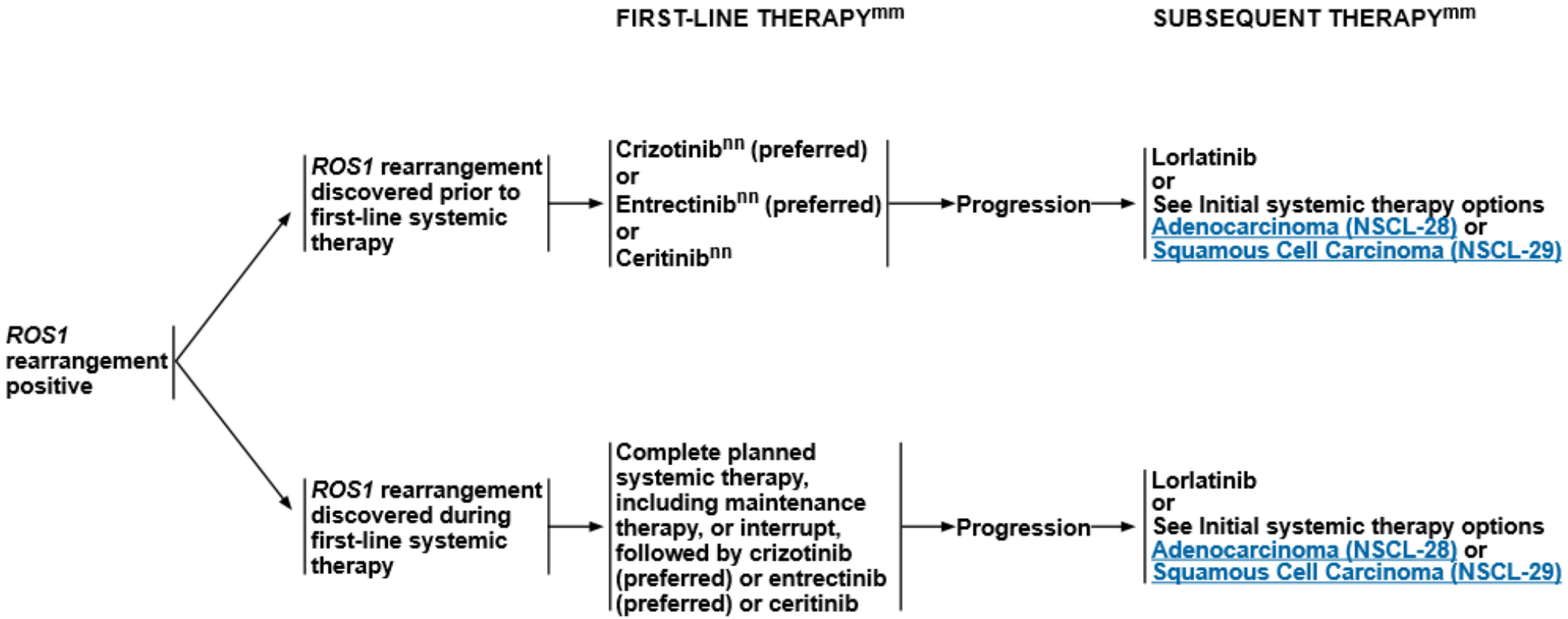
Cabozantinib(phase 2;NCT01639508), **DS-6051b** (phase 1;NCT02279433,NCT02675491), **repotrectinib** (phase 1;NCT03093116): **ongoing**
There are currently no open clinical trials of **brigatinib** in ROS1-rearranged NSCLC.

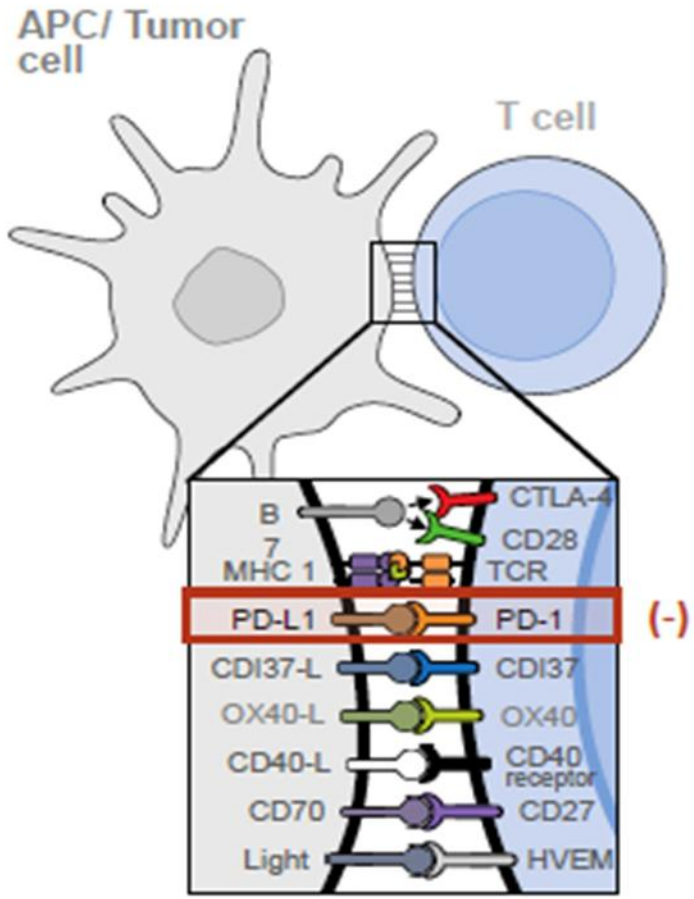
1. Shaw AT et al N Engl J Med 2014 Nov 20;371(21):1963-71. **2**. Lim SM et al. J Clin Oncol 2017;35:2613-18.
3. Doebele RC et al. 2018 WCLC OA02.01.**4**. Ou SI et al. 2018 WCLC OA02.03.

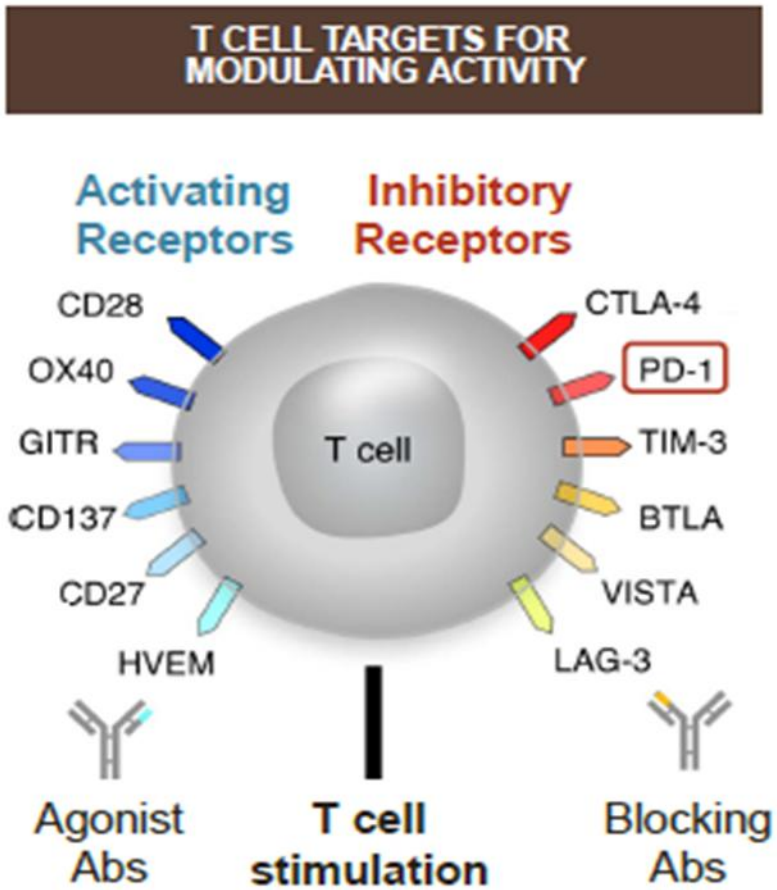
WCLC 2018

1. Solomon, et al. N Engl J Med 2014; 2. Soria, et al. Lancet Oncol 2017; 3. Camidge, et al. ASCO 2018, 4. Shaw, et al. Lancet Oncol 2017; 5. Novello, et al. Ann Oncol 2018
6. Yang, et al. J Thorac Oncol 2017; 7. Ahn, et al. WCLC 2017; 8. Solomon, et al. WCLC 2017

ROS1 REARRANGEMENT POSITIVE[hh]





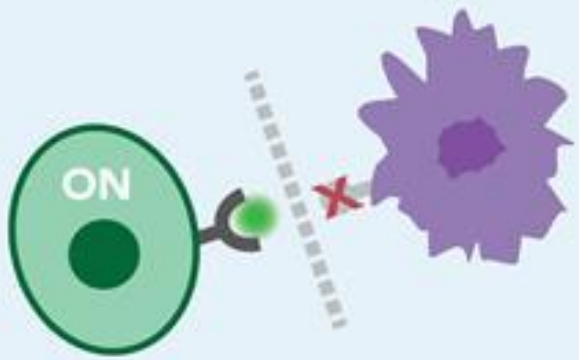


How Does Immunotherapy Work?

Tumor cells bind to T-cells
to deactivate them

T-cell Tumor

Immunotherapy drugs can block
tumor cells from deactivating T-cells



T-cell Drug Tumor

Columbia University
Medical Center

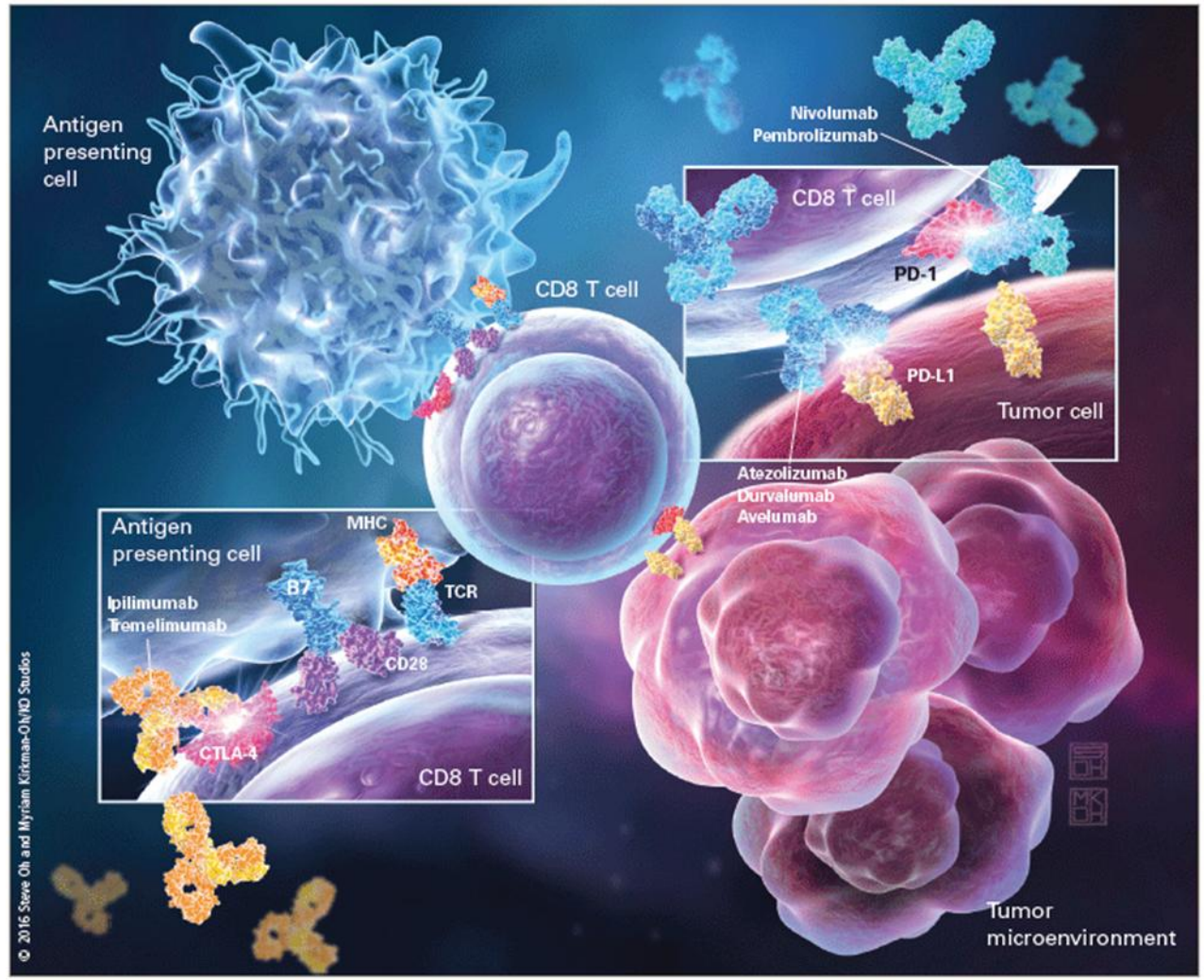
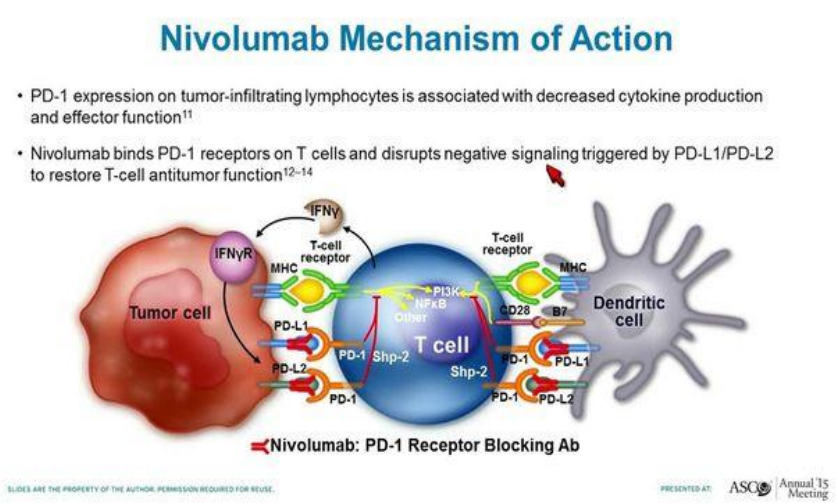


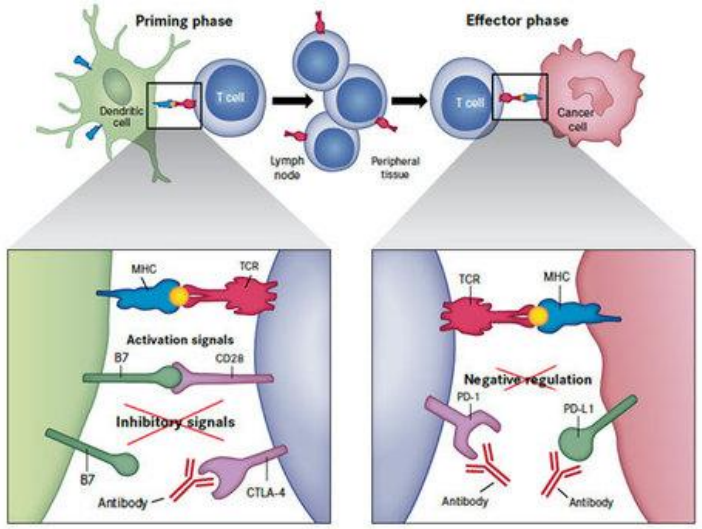
Figure. Immune Checkpoint Inhibition Mechanisms of Action Relevant to Lung Cancer Immunotherapy—T cells express CTLA-4 antigens on their cell surfaces, which downregulate T-cell function. Anti–CTLA-4 antibodies can bind to CTLA-4 on T cells and reverse this T-cell activation downregulation. PD-1 proteins on T cells bind to PD-L1 and PD-L2 ligands on cancer cell and antigen presenting cell surfaces, preventing T-cell activation and cell-mediated antitumor immune responses. Anti–PD-1 antibodies bind to PD-1, preventing interaction with its ligands; anti–PD-L1 antibodies bind to PD-L1 and/or PD-L2, preventing interaction with PD-1. CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4; MHC = major histocompatibility complex; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; TCR = T-cell receptor.

PD-1 inhibitörleri

- Nivolumab:

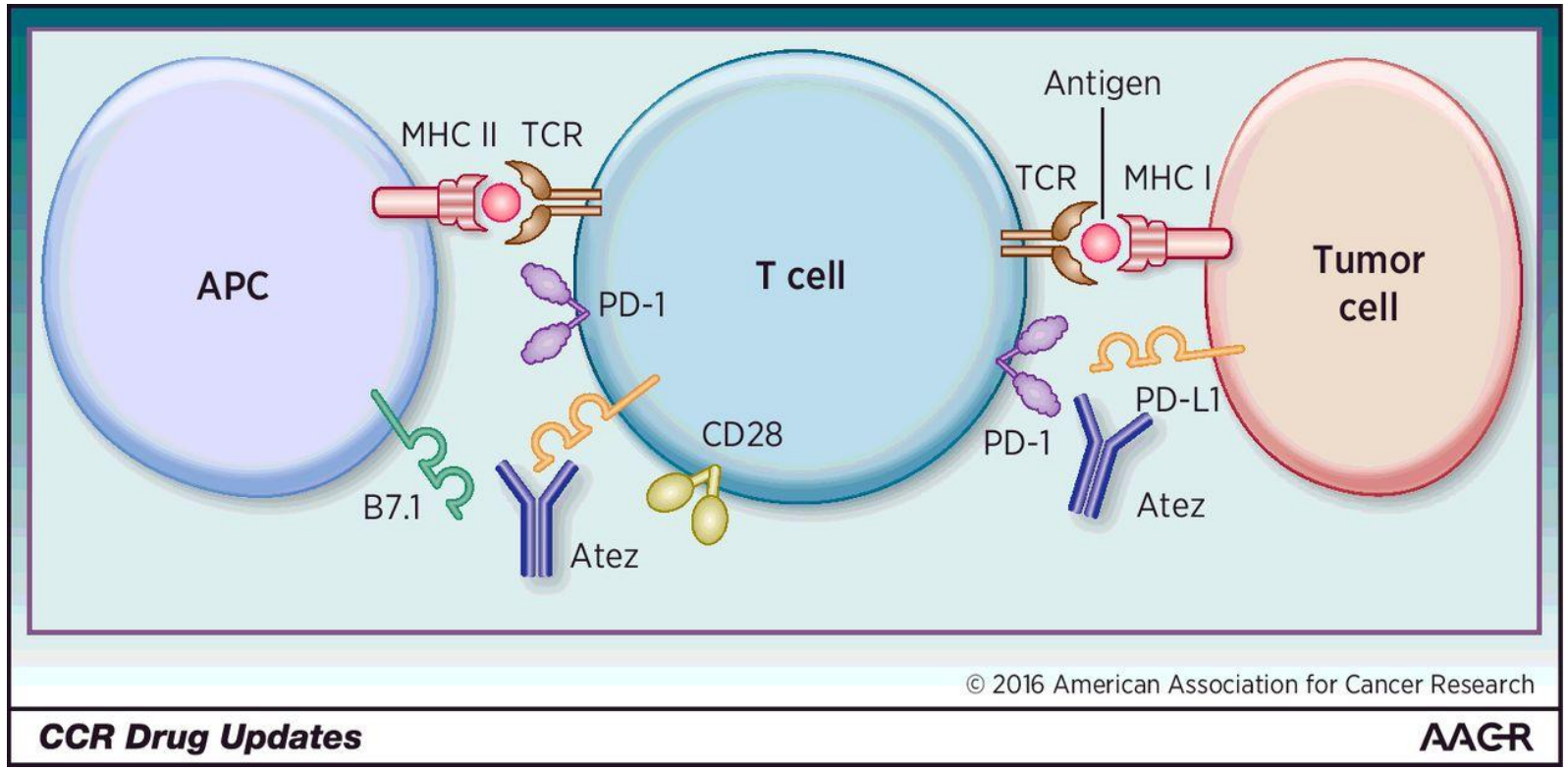


- Pembrolizumab



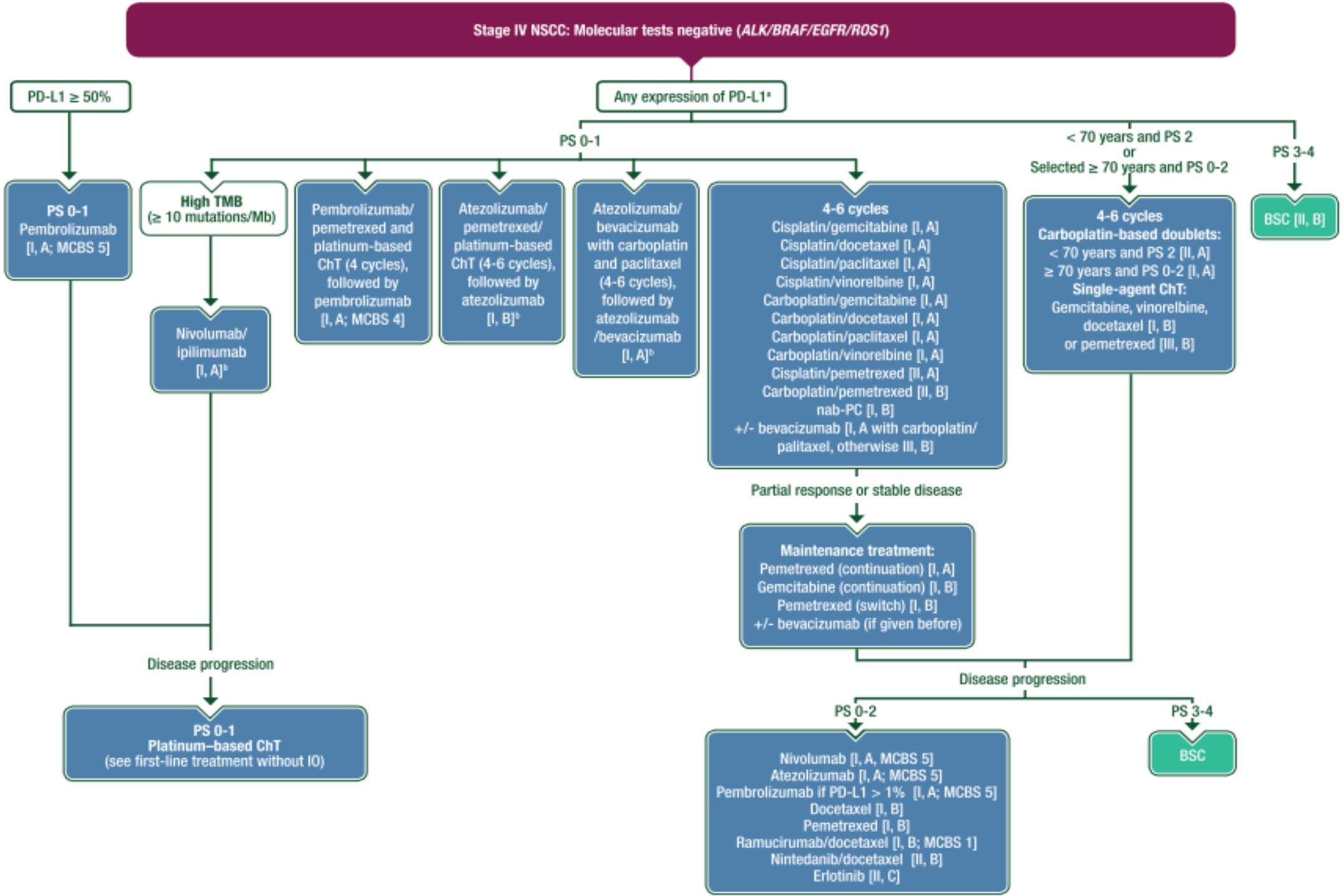
PDL-1 inhibitörleri

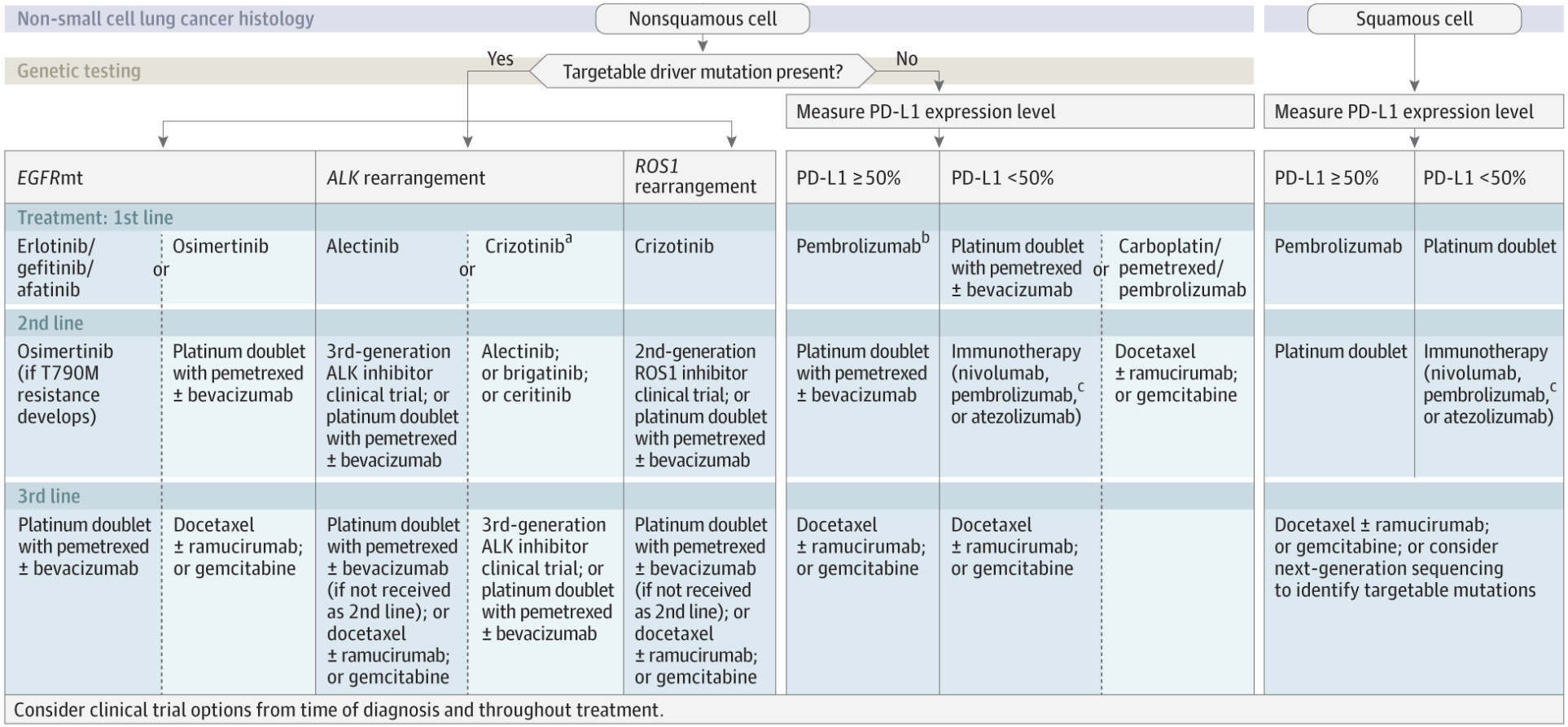
- Atezolizumab



CTLA-4 inhibitörleri

- CTLA-4 t hücrelerinin aktivasyonunu CD80 (B7-1) ve CD86 (B7-2) ve CD28 üzerinden inhibe eder
- İpilumumab ilk CTLA-4 inhibitörü


Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)
PD-L1 ≥ 50%
Any expression of PD-L1[a]
PS 0-1
< 70 years and PS 2 or Selected ≥ 70 years and PS 0-2
PS 3-4
PS 0-1 Pembrolizumab [I, A; MCBS 5]
High TMB (≥ 10 mutations/Mb)
Pembrolizumab/ pemetrexed and platinum-based ChT (4 cycles), followed by pembrolizumab [I, A; MCBS 4]
Atezolizumab/ pemetrexed/ platinum-based ChT (4-6 cycles), followed by atezolizumab [I, B][b]
Atezolizumab/ bevacizumab with carboplatin and paclitaxel (4-6 cycles), followed by atezolizumab /bevacizumab [I, A][b]
4-6 cycles
Cisplatin/gemcitabine [I, A]
Cisplatin/docetaxel [I, A]
Cisplatin/paclitaxel [I, A]
Cisplatin/vinorelbine [I, A]
Carboplatin/gemcitabine [I, A]
Carboplatin/docetaxel [I, A]
Carboplatin/paclitaxel [I, A]
Carboplatin/vinorelbine [I, A]
Cisplatin/pemetrexed [II, A]
Carboplatin/pemetrexed [II, B]
nab-PC [I, B]
+/- bevacizumab [I, A with carboplatin/ palitaxel, otherwise III, B]
4-6 cycles
Carboplatin-based doublets:
< 70 years and PS 2 [II, A]
≥ 70 years and PS 0-2 [I, A]
Single-agent ChT:
Gemcitabine, vinorelbine, docetaxel [I, B]
or pemetrexed [III, B]
BSC [II, B]
Nivolumab/ ipilimumab [I, A][b]
Partial response or stable disease
Maintenance treatment:
Pemetrexed (continuation) [I, A]
Gemcitabine (continuation) [I, B]
Pemetrexed (switch) [I, B]
+/- bevacizumab (if given before)
Disease progression
Disease progression
PS 0-1
Platinum–based ChT
(see first-line treatment without IO)
PS 0-2
PS 3-4
Nivolumab [I, A, MCBS 5]
Atezolizumab [I, A; MCBS 5]
Pembrolizumab if PD-L1 > 1% [I, A; MCBS 5]
Docetaxel [I, B]
Pemetrexed [I, B]
Ramucirumab/docetaxel [I, B; MCBS 1]
Nintedanib/docetaxel [II, B]
Erlotinib [II, C]
BSC



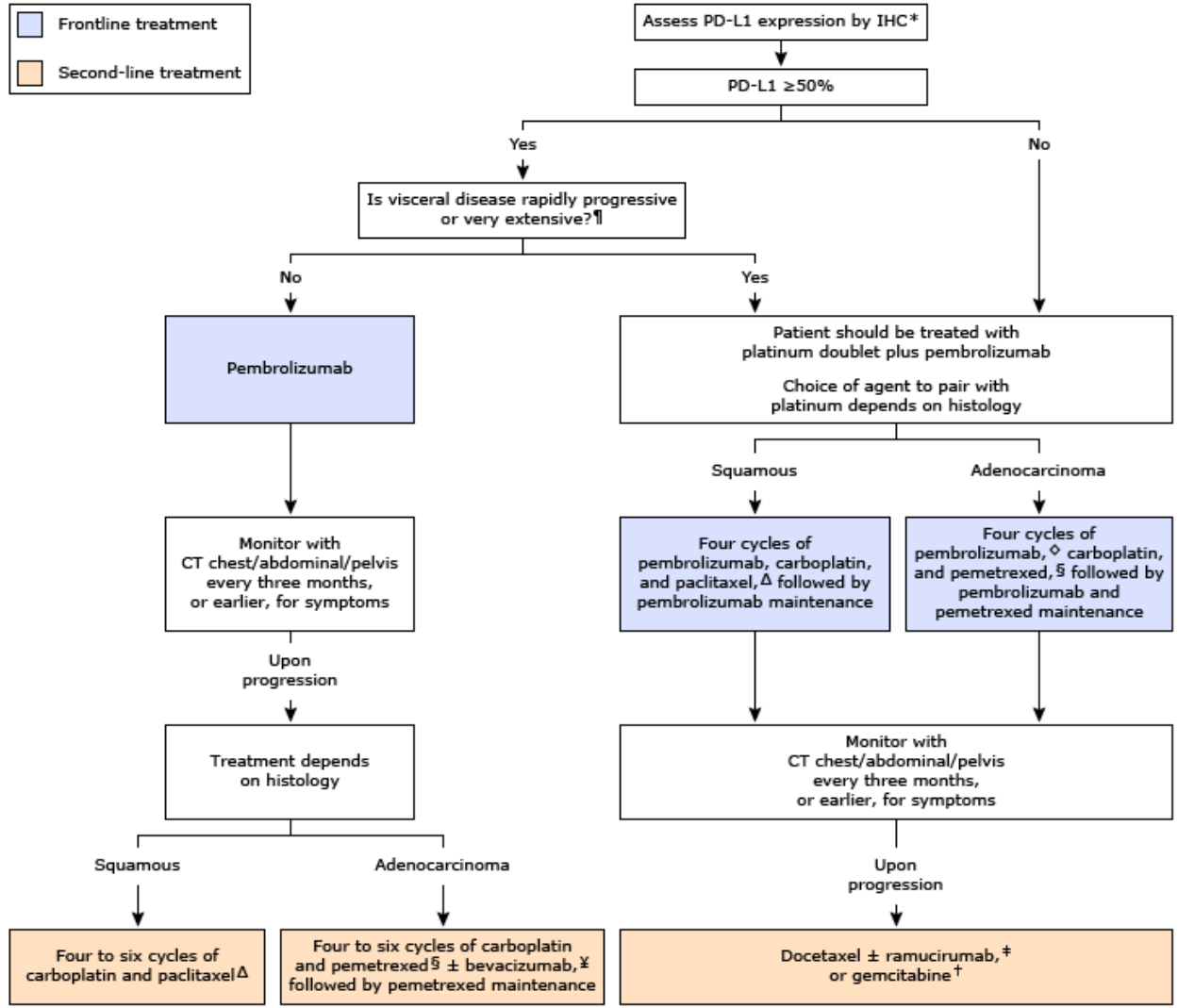
Abbreviations: PD-L1, programmed cell death 1 ligand 1; *EGFR*mt, *EGFR* mutated.

[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%.

Management of advanced non-small cell lung cancer without a targetable driver mutation



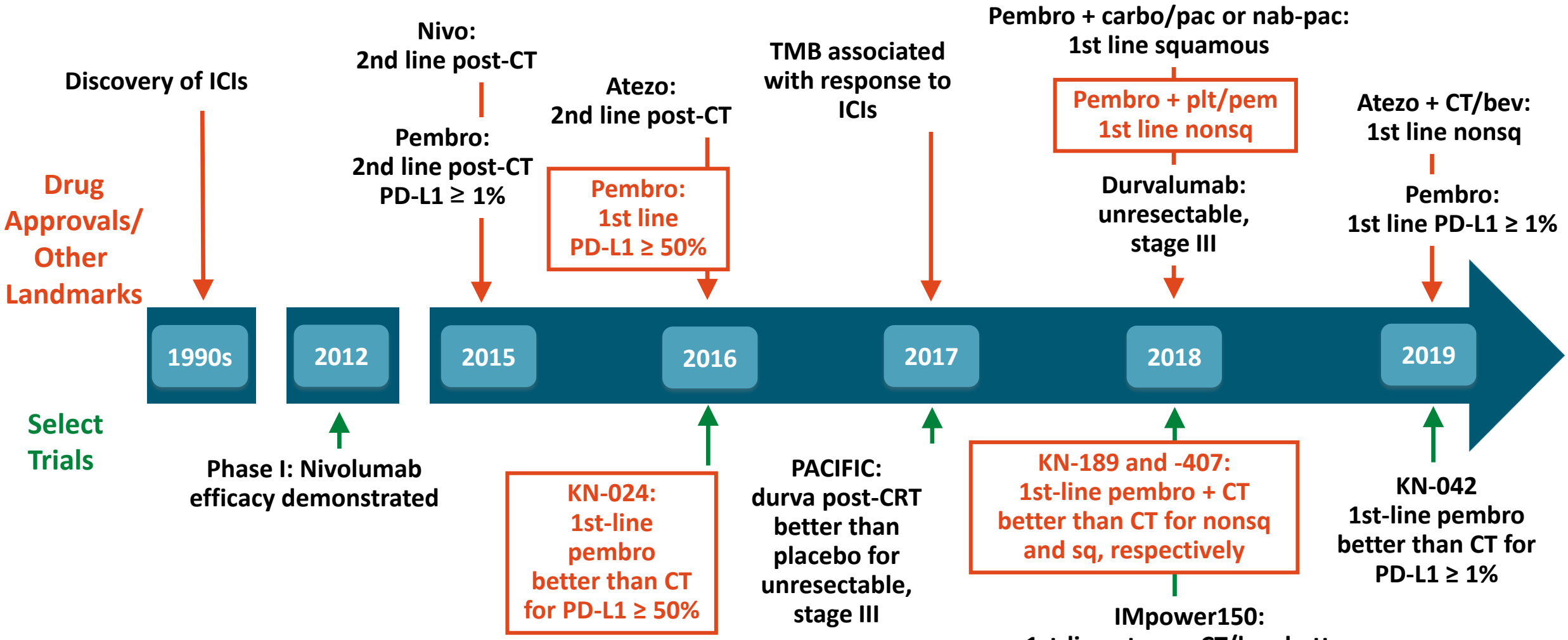
Supportive care and palliation are appropriate management at any point for patients with ECOG PS of 3 or higher or depending on patient preference. Refer to UpToDate content on functional assessment in cancer patients for further details.

PD-L1: programmed death-ligand 1; IHC: immunohistochemistry; CT: computed tomography; ECOG: Eastern Cooperative Group; PS: performance status; NSCLC: non-small cell lung cancer.

* This is typically done at the time of diagnosis, along with next-generation sequencing for actionable driver mutations, including *EGFR*, *ALK*, *ROS1*, and *BRAF*. Those with actionable genetic driver alterations are managed with initial targeted therapy. Refer to UpToDate content on personalized, genotype-directed therapy in NSCLC for further details.

¶ Examples include bulky disease causing end-organ failure or unmanageable symptoms.

İmmunoterapi



Herbst. Nature. 2018;553:446. Ishida. EMBO J. 1992;11:3887. Nishimura. Immunity. 1999;11:141. Freeman. J Exp Med. 2000;192:1027. Antonia. NEJM. 2017;377:1919. Paz-Ares. NEJM. 2018;379:2040. Gandhi. NEJM. 2018;378:2078. Socinski. NEJM. 2018;378:2288. Gettinger. J Clin Oncol. 2015;33:2004. Reck. NEJM. 2016;375:1823. Mok. Lancet. 2019;393:1819.

Pozitif First-line Çalışmalar

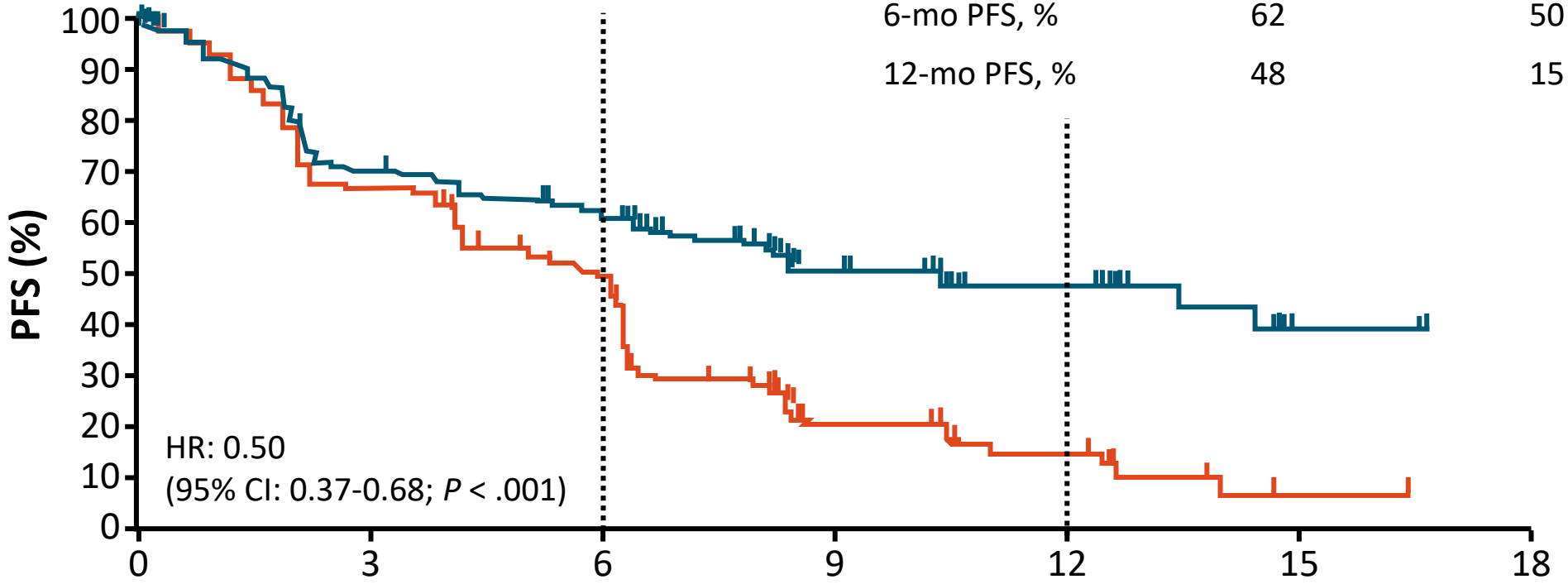
Trial	Comparison	Selection	ORR, %	PFS HR	OS HR
KEYNOTE-024[1,2]	Pembrolizumab vs platinum-doublet CT	PD-L1 ≥ 50%	44.8 vs 27.8	0.50*	0.63*
KEYNOTE-042[3]	Pembrolizumab vs platinum-doublet CT	PD-L1 ≥ 1%	32 vs 39	0.81†	0.69*
KEYNOTE-189[4]	Pembrolizumab or placebo + carboplatin/pemetrexed	PD-L1 unselected; nonsquamous	47.6 vs 18.9*	0.52*	0.49*
IMpower150[5]	Atezolizumab + carboplatin/paclitaxel + bevacizumab vs CT alone	PD-L1 unselected; nonsquamous	64 vs 48	0.62*	Positive‡
KEYNOTE-407[6]	Pembrolizumab or placebo + carboplatin/paclitaxel or nab-paclitaxel	PD-L1 unselected; squamous	57.9 vs 38.4*	0.56*	0.64*
CheckMate 227[7]	Nivolumab + ipilimumab vs platinum-doublet CT	TMB high (≥ 10 mut/Mb)	45.3 vs 26.9	0.58*	Immature

*$P < .01$. †Not significant. ‡Interim analysis.

1. Reck. NEJM. 2016;375:1823. 2. Reck. J Clin Oncol. 2019;37:537. 3. Mok. Lancet. 2019;393:1819. 4. Gandhi. NEJM. 2018;378:2078.
5. Socinski. NEJM. 2018;378:2288. 6. Paz-Ares. NEJM. 2018;379:2040. 7. Hellmann. NEJM. 2018;378:2093.

KEYNOTE-024: PFS

	Pembrolizumab (n = 154)	Chemotherapy (n = 151)
Median PFS, mos (95% CI)	10.3 (6.7-NR)	6.0 (4.2-6.2)
6-mo PFS, %	62	50
12-mo PFS, %	48	15

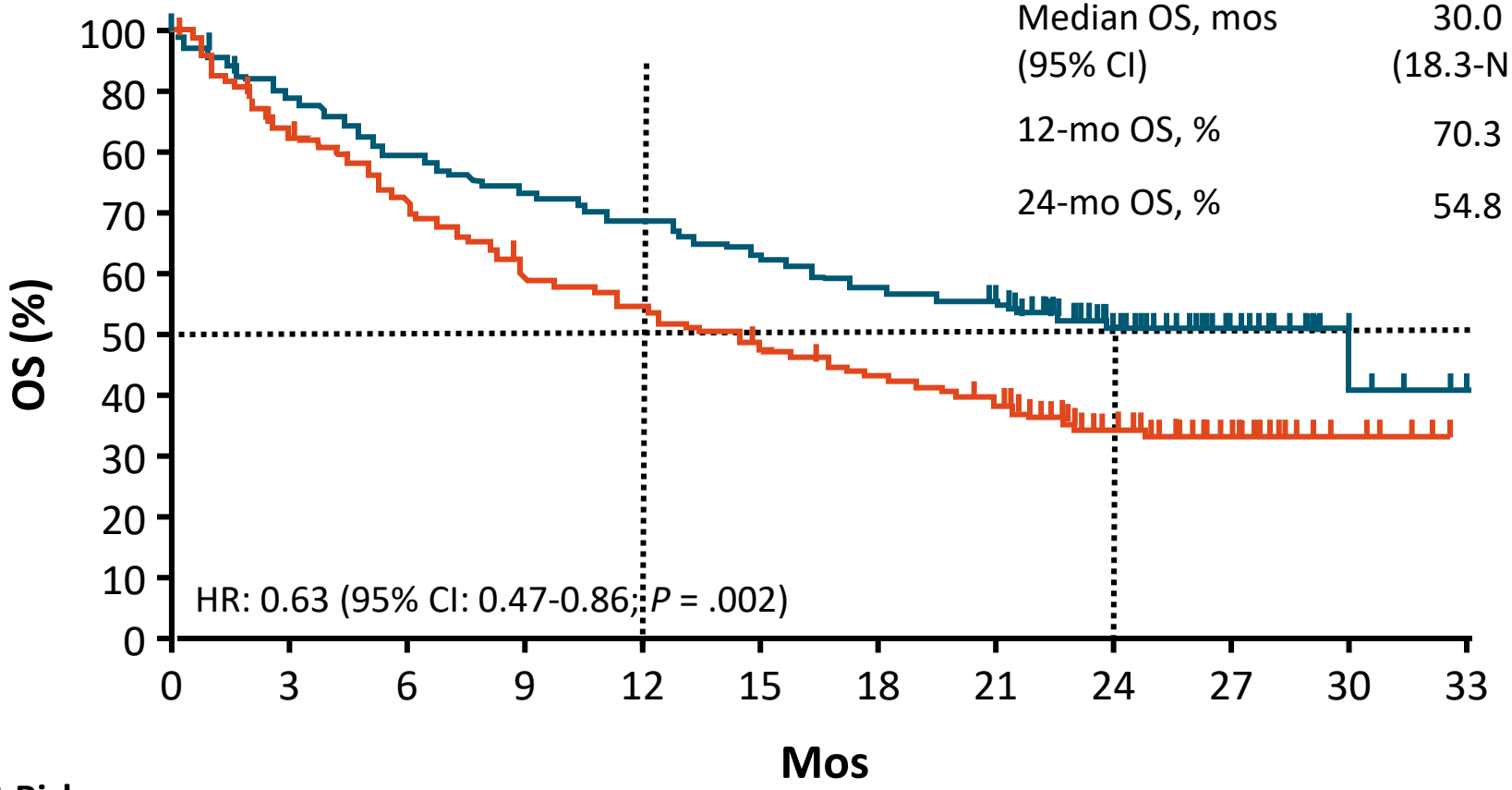


Patients at Risk, n							
Pembrolizumab	154	104	89	44	22	3	1
CT	151	99	70	18	9	1	0

Reck. ESMO 2016. Abstr LBA8_PR. Reck. NEJM. 2016;375:1823.

KEYNOTE-024: OS (Updated)

	Pembrolizumab (n = 154)	Chemotherapy (n = 151)
Median OS, mos (95% CI)	30.0 (18.3-NR)	14.2 (9.8-19.0)
12-mo OS, %	70.3	51.5
24-mo OS, %	54.8	34.5

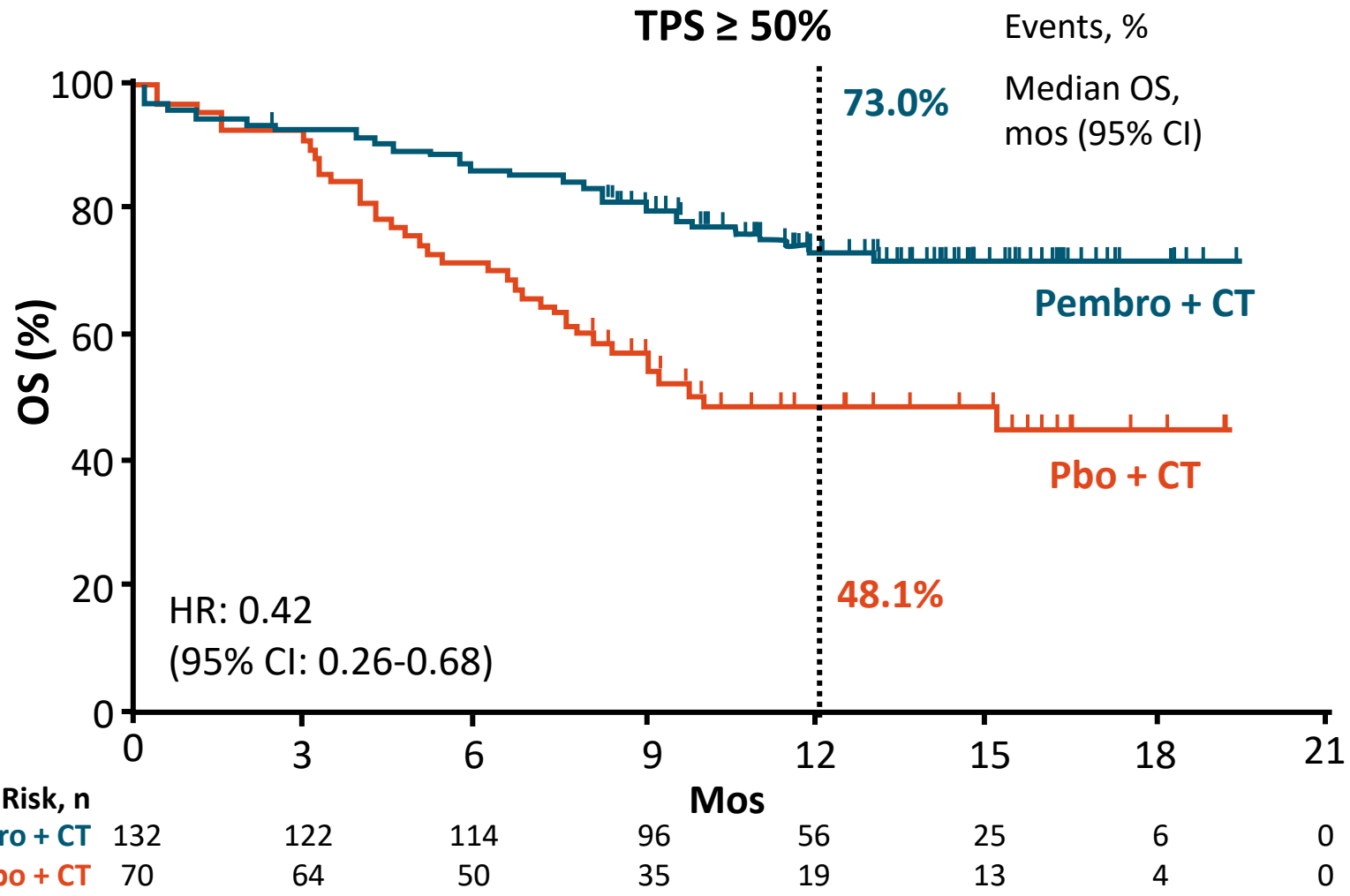


Patients at Risk, n

Pembrolizumab	154	136	121	112	106	96	89	83	52	22	5	0
CT	151	123	107	88	80	70	61	55	31	16	5	0

Reck. J Clin Oncol. 2019;37:537.

KEYNOTE-189: OS in Patients With PD-L1 Tumor Proportion Score ≥ 50%



	Pembrolizumab + CT (n = 127)	Placebo + CT (n = 63)
Events, %	25.8	51.4
Median OS, mos (95% CI)	NR (NE-NE)	10.0 (7.5-NE)

Patients at Risk, n								
Pembro + CT	132	122	114	96	56	25	6	0
Pbo + CT	70	64	50	35	19	13	4	0

Gandhi. NEJM. 2018;378:2078.

Sonuç: yüksek PDL-1 ve non- sküamöz

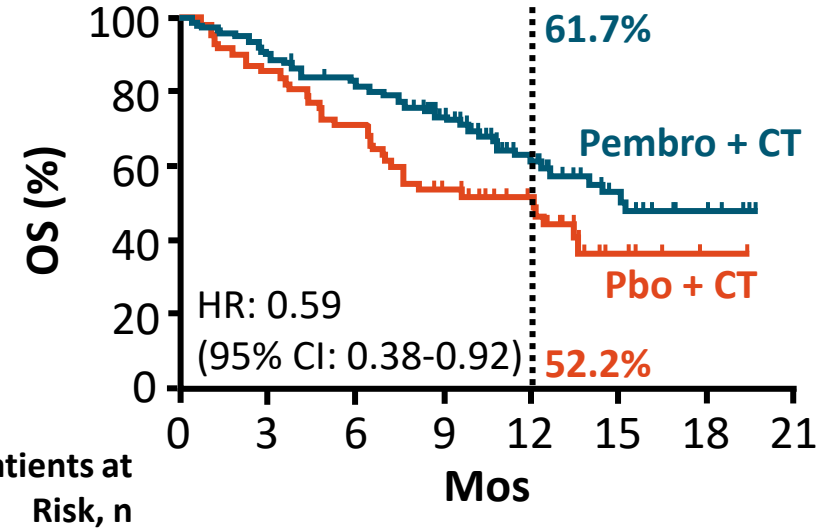
- Pembrolizumab tercih edilmeli

- Yüksek riskli ve semptomatik hastalarda pembro+ KT

KEYNOTE-189: Survival by PD-L1 Tumor Proportion Score

TPS < 1%

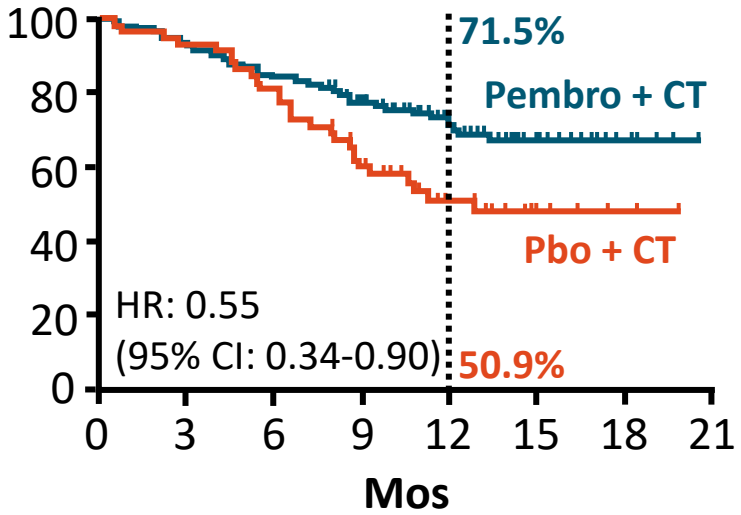
	Pembro + CT	Placebo + CT
Events, %	38.6	55.6
mOS, mos (95% CI)	15.2 (12.3-NE)	12.0 (7.0-NE)



Patients at Risk, n								
Pembro + CT	127	113	104	79	42	20	6	0
Pbo + CT	63	54	45	32	21	6	1	0

TPS 1% to 49%

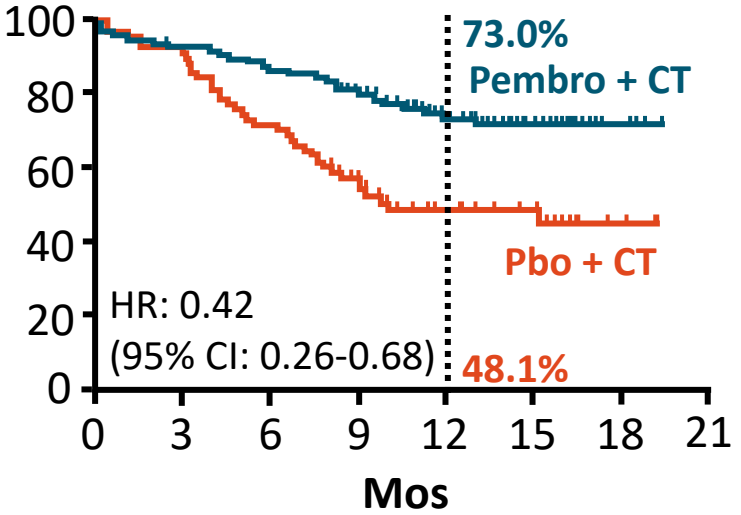
	Pembro + CT	Placebo + CT
Events, %	28.9	48.3
mOS, mos (95% CI)	NR (NE-NE)	12.9 (8.7-NE)



Pembro + CT	128	119	107	84	52	21	5	0
Pbo + CT	58	54	47	32	17	5	2	0

TPS ≥ 50%

	Pembro + CT	Placebo + CT
Events, %	25.8	51.4
mOS, mos (95% CI)	NR (NE-NE)	10.0 (7.5-NE)

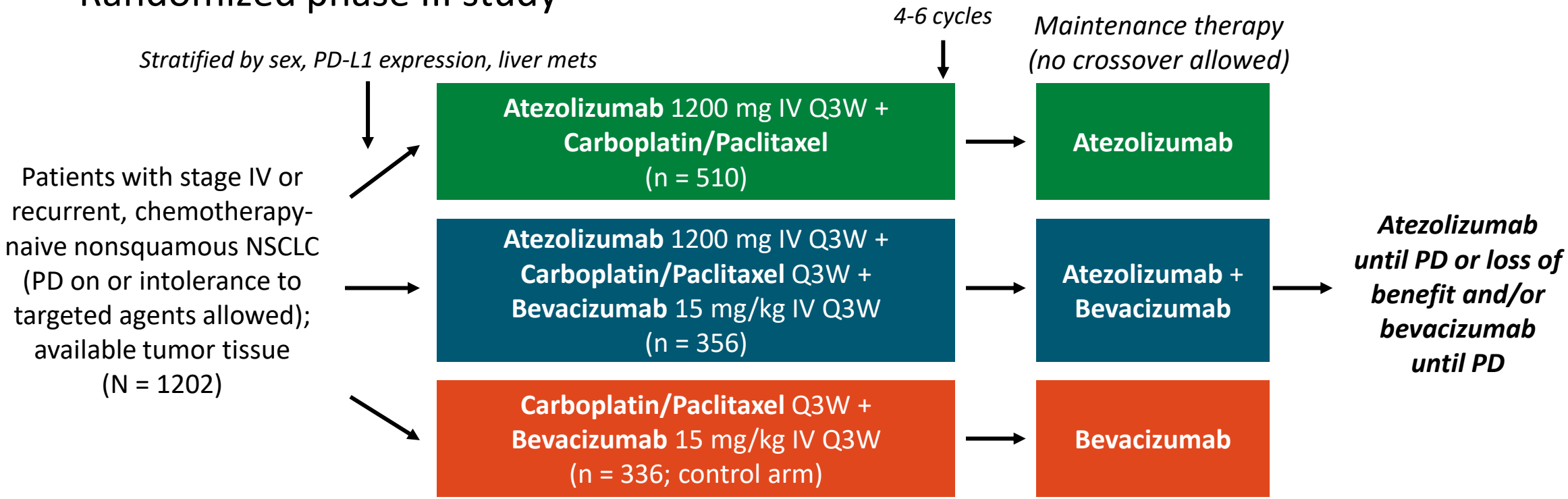


Pembro + CT	132	122	114	96	56	25	6	0
Pbo + CT	70	64	50	35	19	13	4	0

Gandhi. NEJM. 2018;378:2078.

IMpower150: Addition of Atezolizumab to Carbo/Pac + Bevacizumab in Advanced NSCLC

- Randomized phase III study



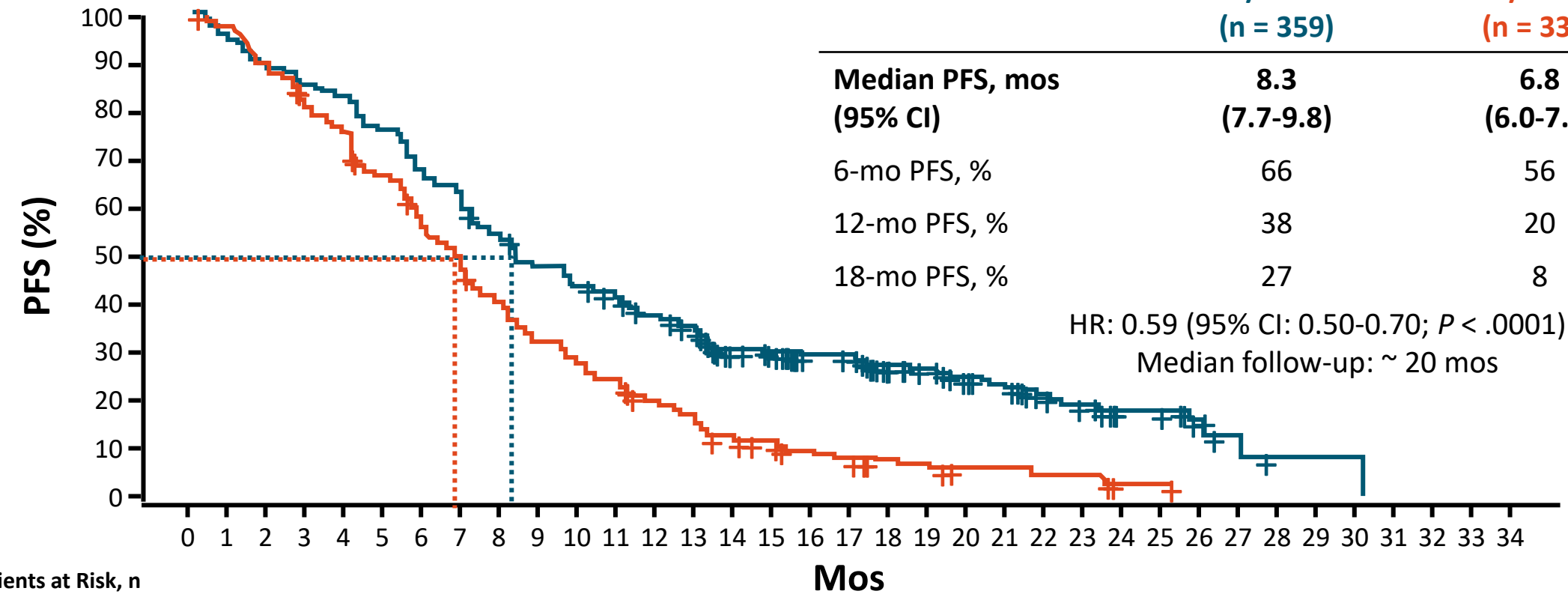
- Primary endpoints: PFS, OS
- Secondary endpoints: PFS (IRF), ORR, OS at Yrs 1 and 2, QoL, safety, PK

Reck. ESMO I-O Congress 2017. Abstr LBA1_PR. Kowanetz. AACR 2018. Abstr CT076. Socinski. NEJM. 2018;378:2288.

IMpower150: Updated PFS in ITT WT Population* (Coprimary Endpoint)

	Atezolizumab + Carbo/Pac + Bev (n = 359)	Carbo/Pac + Bev (n = 337)
Median PFS, mos (95% CI)	**8.3 (7.7-9.8)**	**6.8 (6.0-7.1)**
6-mo PFS, %	66	56
12-mo PFS, %	38	20
18-mo PFS, %	27	8

HR: 0.59 (95% CI: 0.50-0.70; *P* < .0001)
Median follow-up: ~ 20 mos



Patients at Risk, n

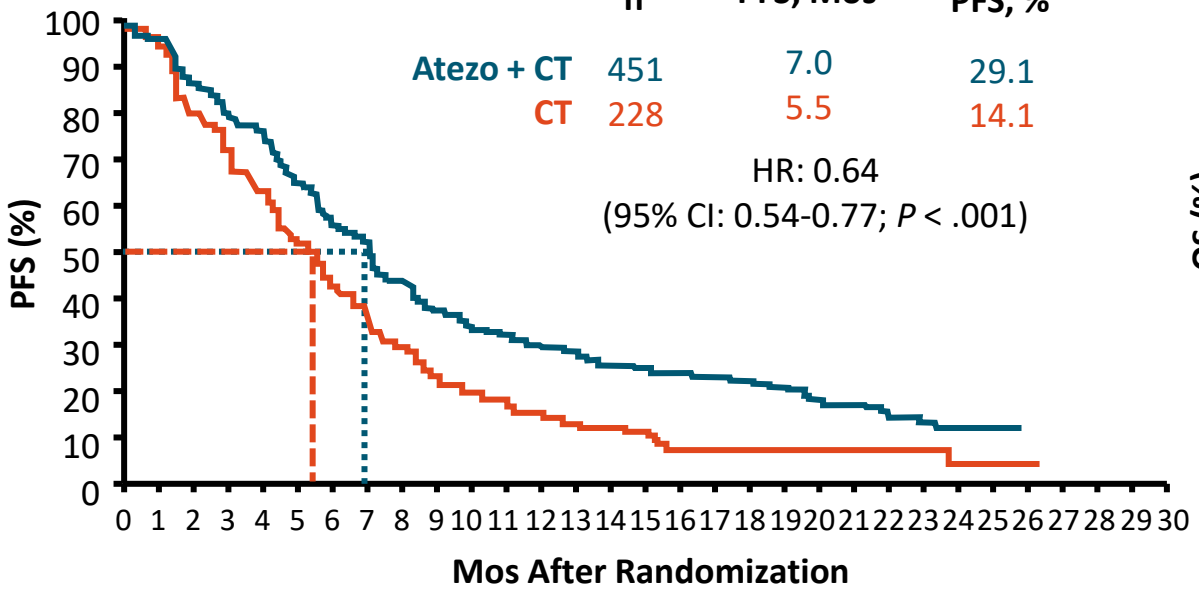
Atezolizumab + Carbo/Pac + Bev	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Carbo/Pac + Bev	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

Data cutoff: January 22, 2018. *ITT WT: patients without *EGFR* or *ALK* alterations; 87% of randomized patients.

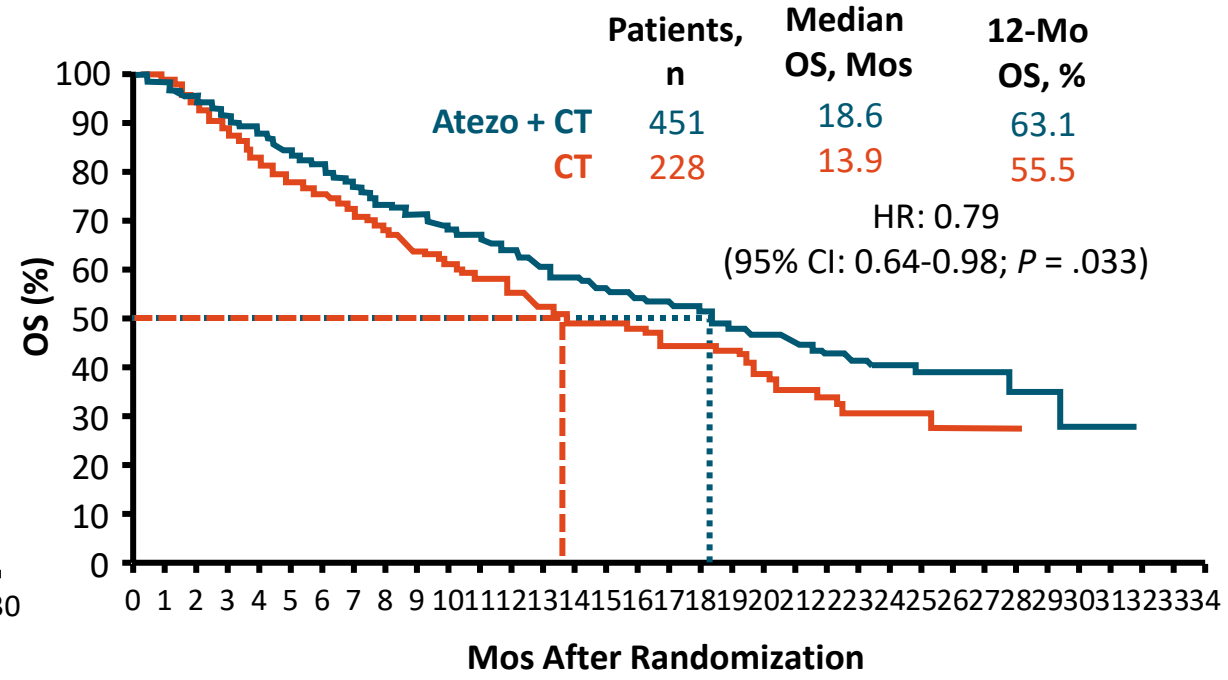
Phase III IMpower130: First-line Atezolizumab + CT in Stage IV Nonsquamous NSCLC

- First-line atezolizumab + carbo/nab-pac followed by maintenance atezolizumab vs CT alone in nonsquamous NSCLC; pretreated *EGFR*/ALK+ allowed (N = 723; ITT-WT n = 679)

PFS



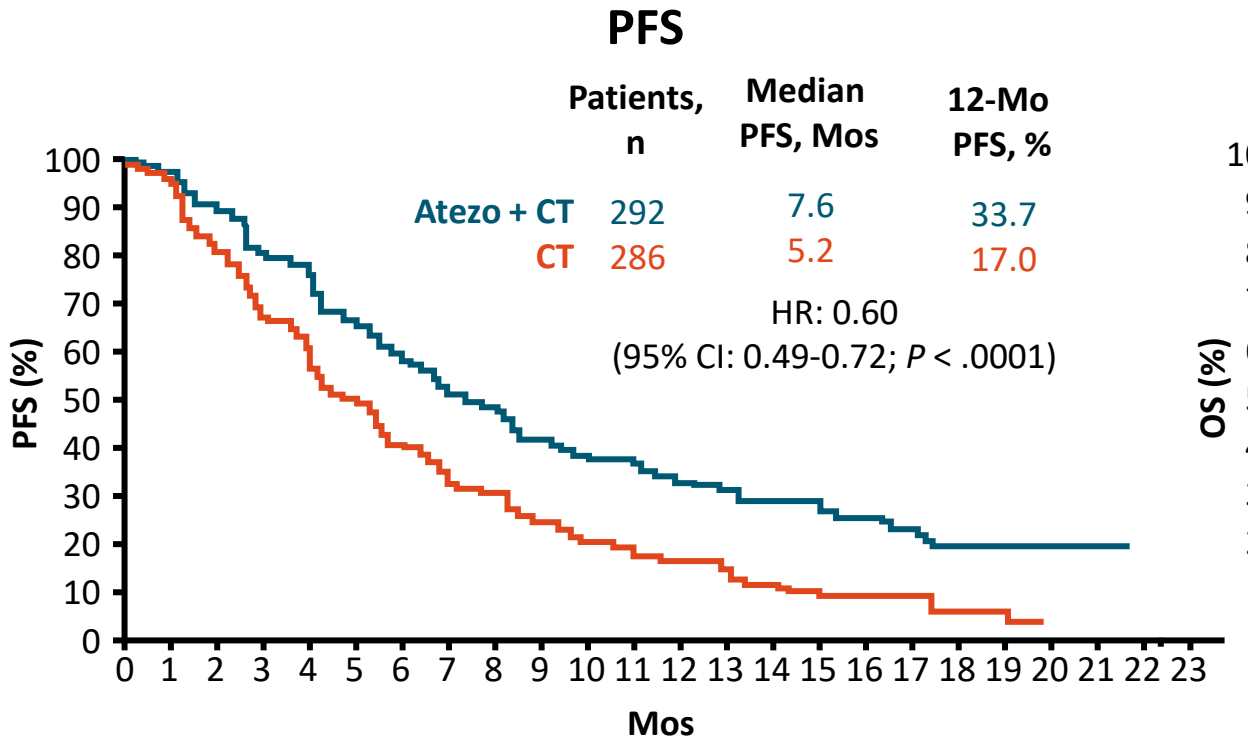
OS

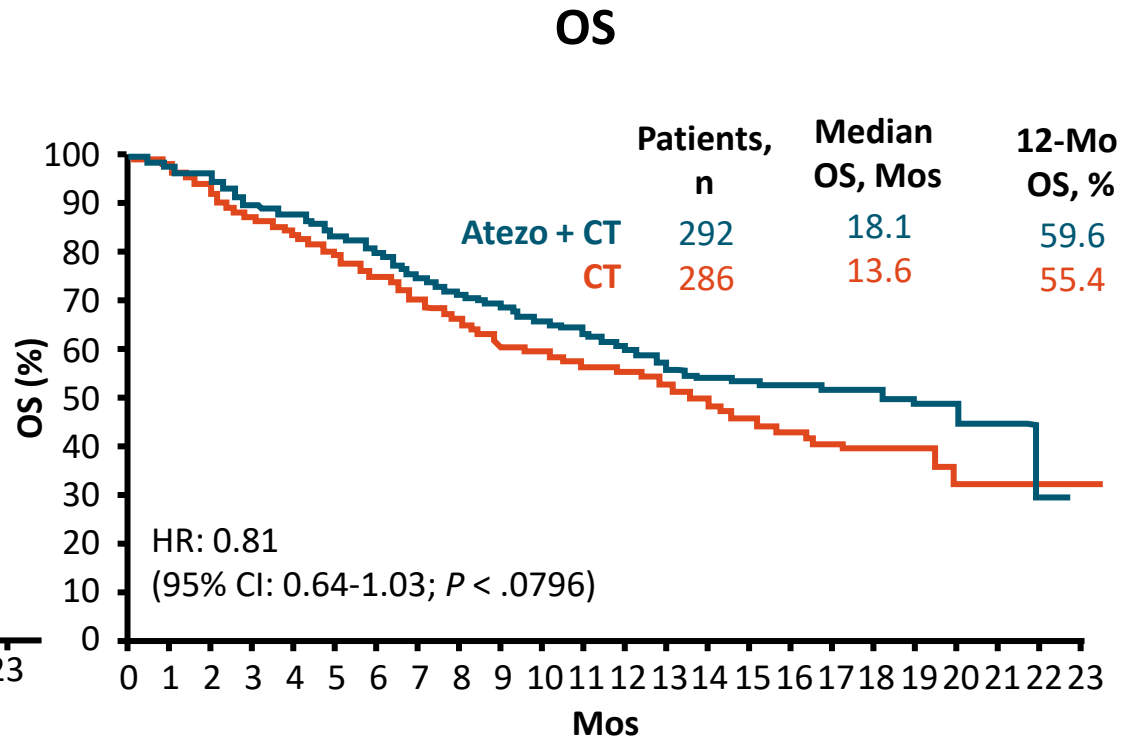


Papadimitrakopoulou. WCLC 2018. Abstr OA05.07.

Phase III IMpower132: First-line Atezolizumab + CT in Stage IV Nonsquamous NSCLC

- First-line atezolizumab + plt/pem followed by maintenance atezolizumab + pem vs CT alone in nonsquamous NSCLC without *EGFR* or *ALK* alterations (N = 578)





Cappuzzo. ESMO 2018. Abstr LBA53.

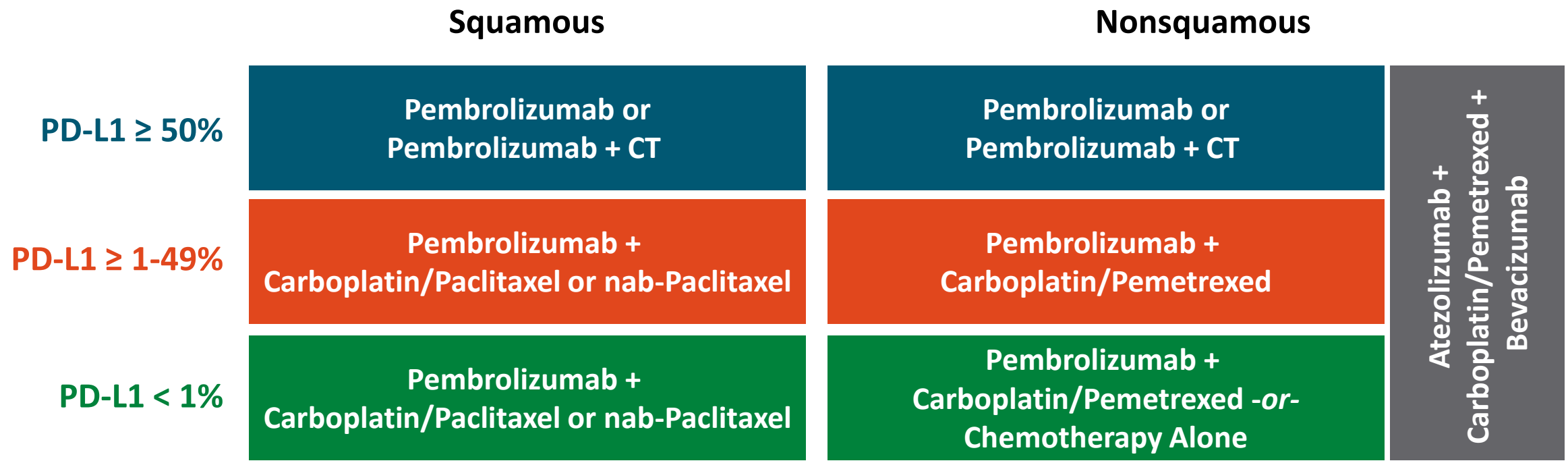
Sonuç: Nonsquamous NSCLC ve PD-L1 yok yada düşük

- Pembro+KT
- IMpower150 rejimi post TKI
- İmmünoterapiye bağlı yan etkiler

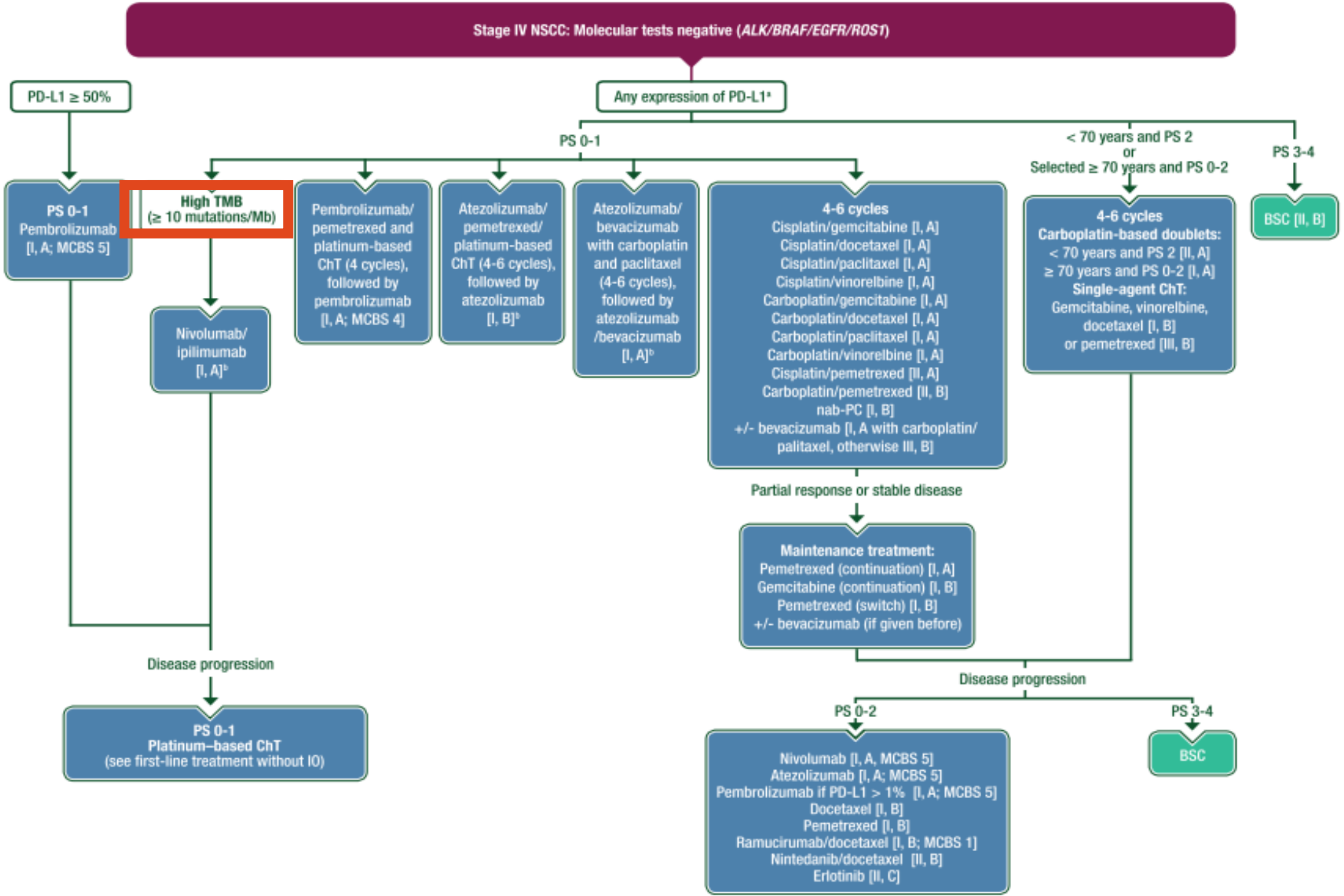
Sonuç : Sküamöz hücreli karsinom ve düşük PDL-1 ekspresyonu

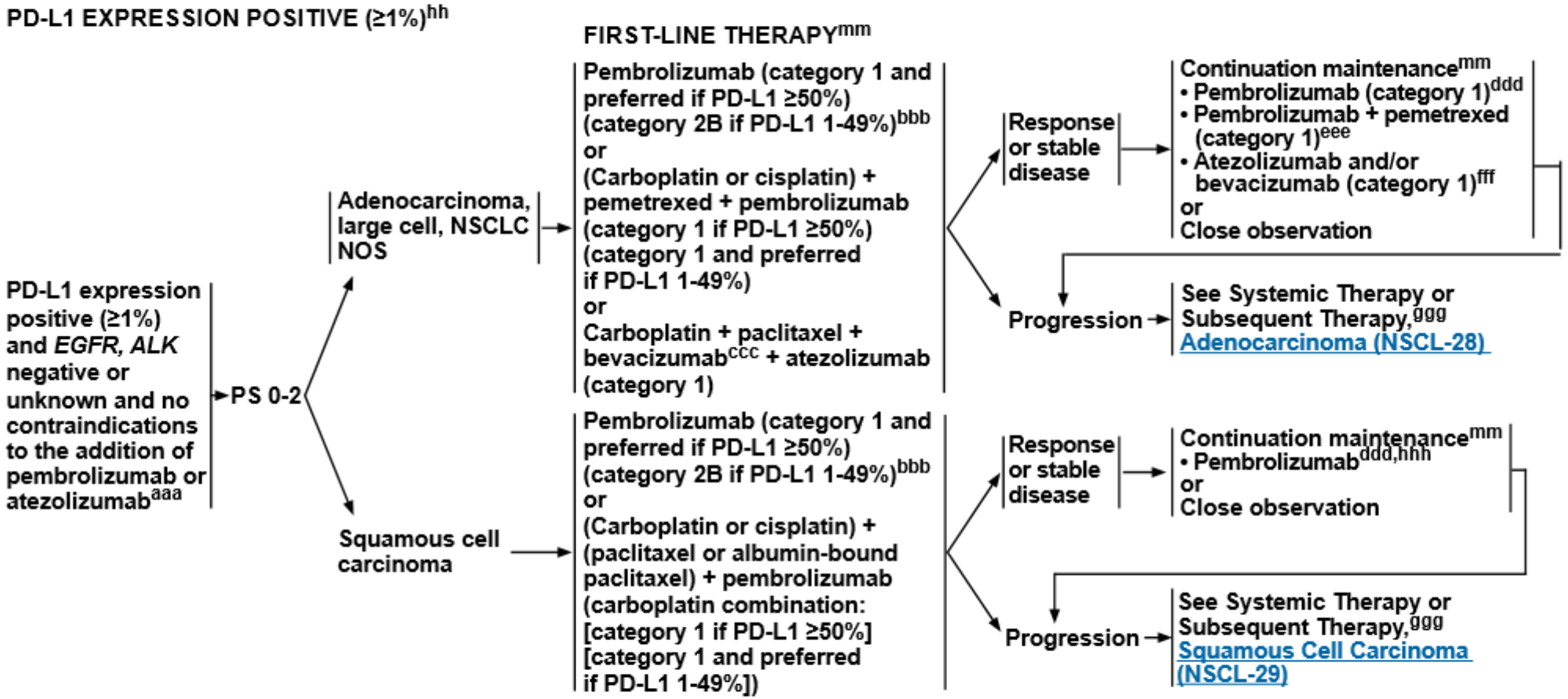
- Optimal yaklaşım: pembrolizumab + carbo/pac veya nab-pac
- Pembro monoterapisi de FDA tarafından onaylandı
- KT + İmmünoterapi
  - KEYNOTE-407:
  - IMpower131:

İmmünoterapi algoritması



- TMB ??

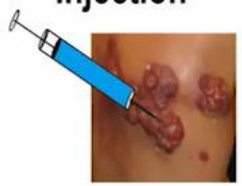

Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)
PD-L1 ≥ 50%
Any expression of PD-L1[a]
PS 0-1
< 70 years and PS 2 or Selected ≥ 70 years and PS 0-2
PS 3-4
PS 0-1 Pembrolizumab [I, A; MCBS 5]
High TMB (≥ 10 mutations/Mb)
Nivolumab/ipilimumab [I, A][b]
Pembrolizumab/pemetrexed and platinum-based ChT (4 cycles), followed by pembrolizumab [I, A; MCBS 4]
Atezolizumab/pemetrexed/platinum-based ChT (4-6 cycles), followed by atezolizumab [I, B][b]
Atezolizumab/bevacizumab with carboplatin and paclitaxel (4-6 cycles), followed by atezolizumab /bevacizumab [I, A][b]
4-6 cycles
Cisplatin/gemcitabine [I, A]
Cisplatin/docetaxel [I, A]
Cisplatin/paclitaxel [I, A]
Cisplatin/vinorelbine [I, A]
Carboplatin/gemcitabine [I, A]
Carboplatin/docetaxel [I, A]
Carboplatin/paclitaxel [I, A]
Carboplatin/vinorelbine [I, A]
Cisplatin/pemetrexed [II, A]
Carboplatin/pemetrexed [II, B]
nab-PC [I, B]
+/- bevacizumab [I, A with carboplatin/palitaxel, otherwise III, B]
4-6 cycles
Carboplatin-based doublets:
< 70 years and PS 2 [II, A]
≥ 70 years and PS 0-2 [I, A]
Single-agent ChT:
Gemcitabine, vinorelbine, docetaxel [I, B]
or pemetrexed [III, B]
BSC [II, B]
Partial response or stable disease
Maintenance treatment:
Pemetrexed (continuation) [I, A]
Gemcitabine (continuation) [I, B]
Pemetrexed (switch) [I, B]
+/- bevacizumab (if given before)
Disease progression
Disease progression
PS 0-2
PS 3-4
PS 0-1
Platinum–based ChT
(see first-line treatment without IO)
Nivolumab [I, A, MCBS 5]
Atezolizumab [I, A; MCBS 5]
Pembrolizumab if PD-L1 > 1% [I, A; MCBS 5]
Docetaxel [I, B]
Pemetrexed [I, B]
Ramucirumab/docetaxel [I, B; MCBS 1]
Nintedanib/docetaxel [II, B]
Erlotinib [II, C]
BSC



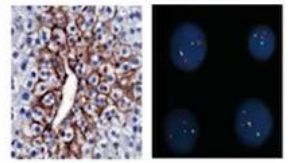
hhSee Principles of Molecular and Biomarker Analysis (NSCL-G).
mmSee Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
aaaContraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents or presence of an oncogene, which would predict lack of benefit. If there are

dddIf pembrolizumab monotherapy given.
eeeIf pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed given.
fffIf atezolizumab/carboplatin/paclitaxel/bevacizumab given.
gggIf patient has not received platinum-doublet chemotherapy, refer to "systemic

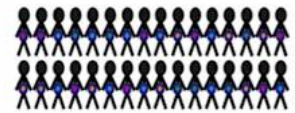
Intratumoral Injection



Predictive Biomarkers

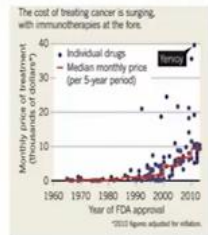


All Patients in Clinical Trial?

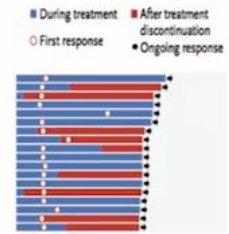


Toxicity

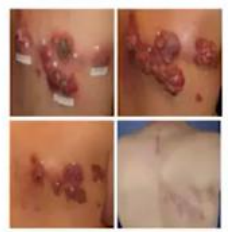
Financial Toxicity



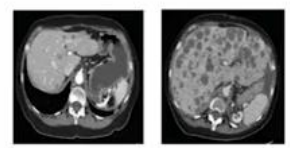
Treatment Duration



Pseudoprogression



Hyperprogression



Parallel vs Sequential