

Akciğer Kanserinde Hedefe Yönelik Tedavi Seçenekleri

Dr. Deniz Tural

Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi

Tıbbi Onkoloji

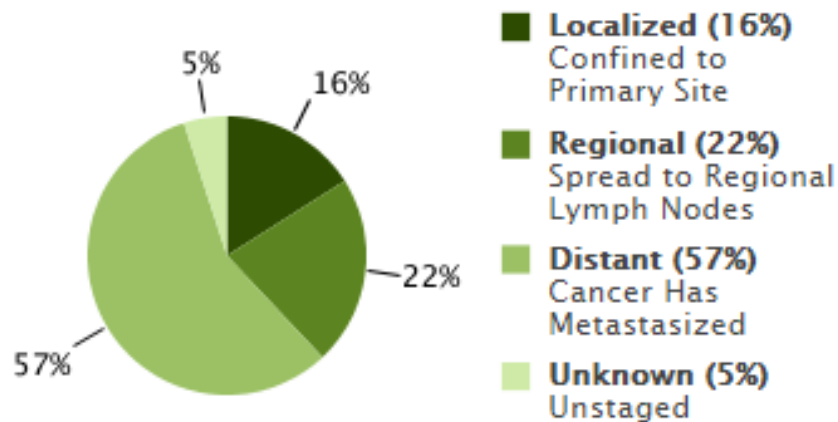
Ders Plan

- ☐ Akciğer kanserin İHK sınıflandırma
- ☐ Moleküler sınıflandırma
- ☐ Tedavi Tarihçesi
- ☐ EGFR ekzon 19, 21 mutasyonunda seçenekler
- ☐ ALK alterasyonunda tedavi seçenekleri
- ☐ ROS1 alterasyonunda tedavi seçenekleri
- ☐ RET alterasyonunda tedavi seçenekleri
- ☐ KRAS G12C mutasyonunda seçenekler
- ☐ Diğer mutasyonlar ve seçenekler

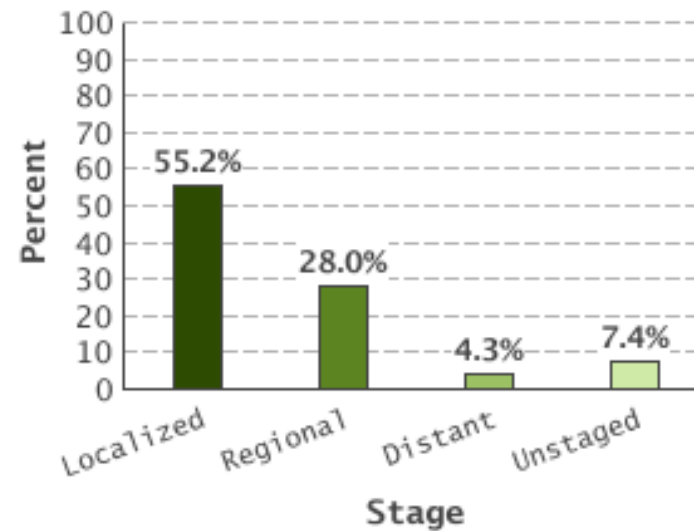
Akciğer Kanserinde İnsidans ve Mortalite

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Lung and Bronchus Cancer

Percent of Cases by Stage



5-Year Relative Survival



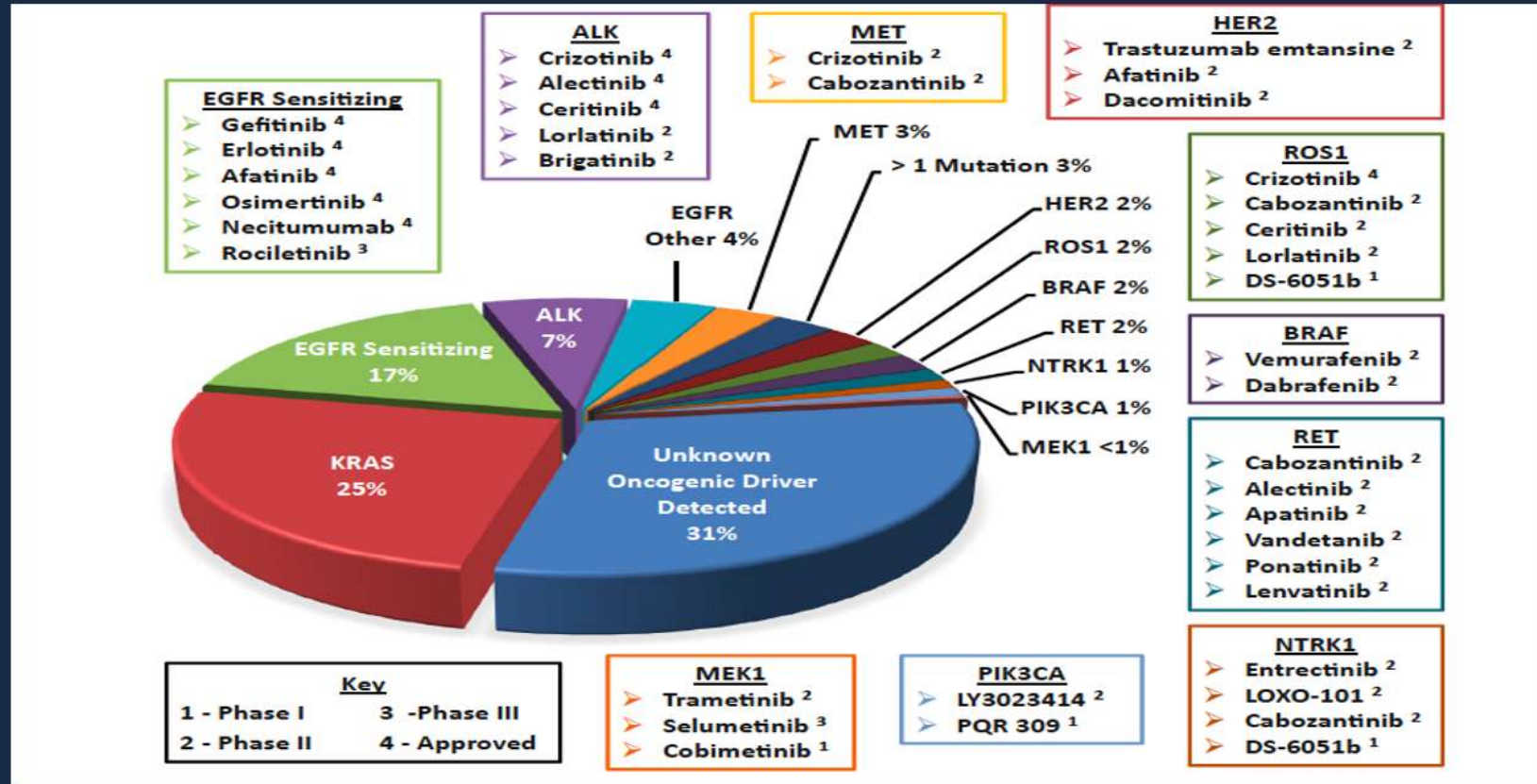
SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

KHDAK Patolojik Sınıflandırma

- Adenocarcinoma of lung
 - TTF-1 (+), Cytokeratin 7/20 (+/-)
- Adenocarcinoma of GI tract
 - CDX 2 (+), Cytokeratin 7/20 (-/+)
- Squamous of lung
 - p63 and p40 (+)
- Mesothelioma
 - WT-1 (+), Calretinin (+), Cytokeratin 5/6 (+)

Metastatik KHDAAK Hedefe Yönelik Tedaviler

Targeted Therapy for Adenocarcinoma



Metastatik KHDAA Hedefe Yönelik Tedaviler

Target	IHC	Translocation	Amplification	Mutation
EGFR	No	No	No	YES
HER-2	No	No	No	YES
ALK	YES	YES	No	No
ROS-1	No	YES	No	No
KRAS	No	No	No	YES
BRAF	No	No	No	YES
RET	No	YES	No	YES
MET	No	No	No	YES
PDL-1	YES	No	No	No

Moleküler patolojiler hangi testle değerlendirilme

Oncogenic Targets and Testing Methodologies

Target	Testing Methodologies
<i>EGFR</i> mutations*	PCR, NGS
<i>BRAF</i> mutations	PCR, NGS, IHC (extensive validation)
<i>KRAS</i> mutations	PCR, NGS
<i>ALK</i> rearrangements [†]	FISH, [‡] NGS, IHC (screening)
<i>ROS1</i> rearrangements [†]	FISH, [‡] NGS, IHC (screening)
<i>RET</i> rearrangements [†]	FISH, [‡] NGS
<i>MET</i> ex14 skipping mutations	NGS
<i>NTRK</i> rearrangements [†]	FISH, [‡] NGS, IHC
<i>MET</i> amplifications	FISH, NGS
<i>HER</i> mutations	PCR, NGS
Tumor mutational burden	NGS

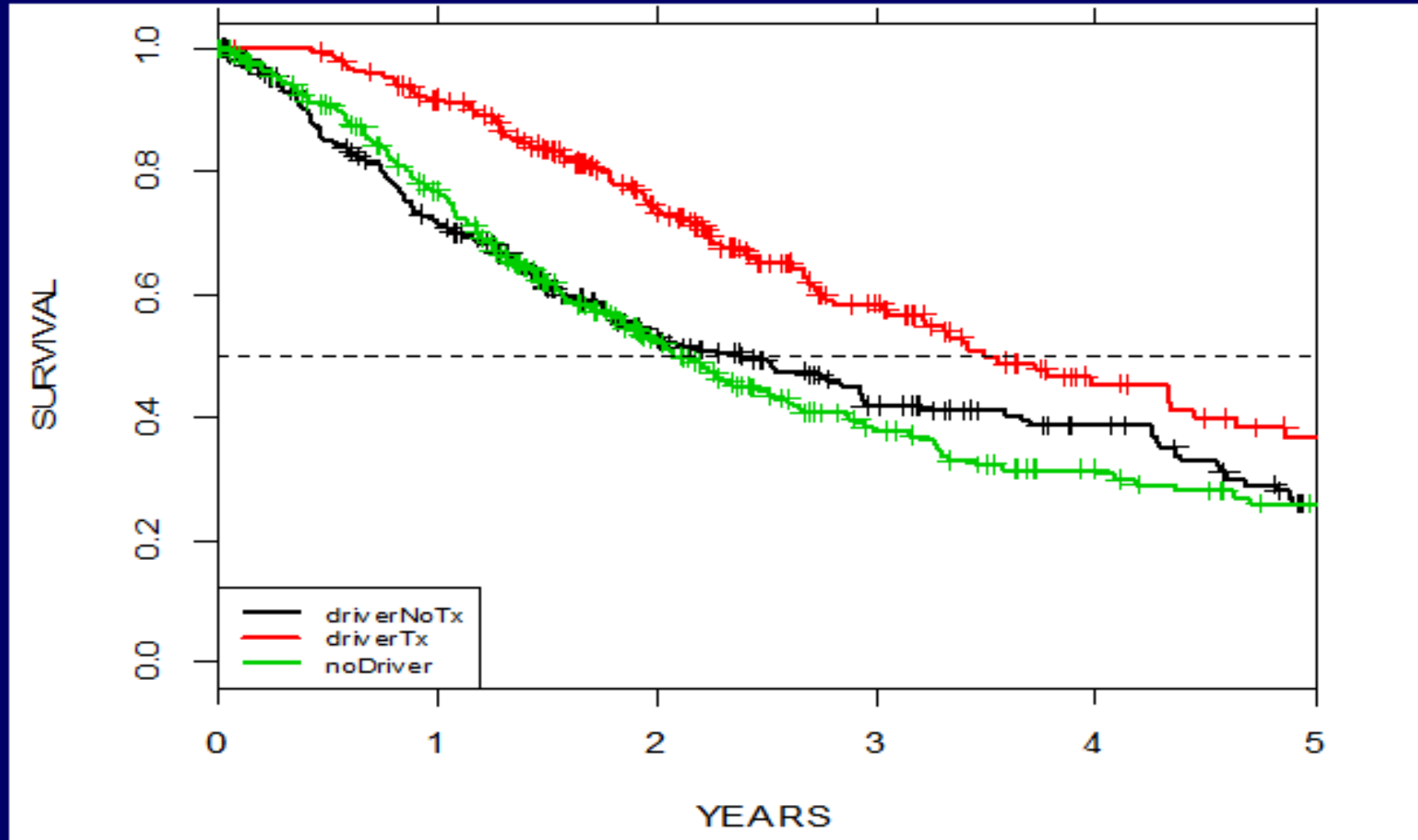
*Majority are L858R or ex19del; ~ 10% are uncommon variants.

[†]Real-time qPCR will miss novel fusion partners.

[‡]Using break-apart probes designed to detect rearrangements.

- Clinical guidelines strongly recommend broad molecular profiling to identify rare driver mutations for which effective drugs may be available, or to appropriately counsel patients about available clinical trials
- Broad molecular profiling is a key component of the improvement of care of patients with NSCLC

Metastatik KHDAAK Hedefe Yönelik Tedaviler



Kris M, et al. *JAMA*. 2014 May 21; 311(19): 1998–2006

Histoloji ve Genomik Özelliklere Göre Tedavi



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

CLINICAL PRESENTATION

HISTOLOGIC SUBTYPE^a

BIOMARKER TESTING^{mm}

Advanced
or
metastatic
disease

- Establish histologic subtype^a with adequate tissue for molecular testing (consider rebiopsy^{ll} or plasma testing if appropriate)
- Smoking cessation counseling
- Integrate palliative care^c ([NCCN Guidelines for Palliative Care](#))

- Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

- Molecular testing, including:
 - *EGFR* mutation (category 1), *ALK* (category 1), *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*ex14 skipping, *RET*, *ERBB2* (*HER2*)
 - Testing should be conducted as part of broad molecular profilingⁿⁿ
- Programmed death ligand 1 (PD-L1) testing (category 1)

[Testing
Results
\(NSCL-20\)](#)

Squamous cell
carcinoma

- Consider molecular testing, including:^{oo}
 - *EGFR* mutation, *ALK*, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*ex14 skipping, *RET*, *ERBB2* (*HER2*)
 - Testing should be conducted as part of broad molecular profilingⁿⁿ
- PD-L1 testing (category 1)

[Testing
Results
\(NSCL-20\)](#)

Histoloji ve Genomik Özelliklere Göre Tedavi



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

TESTING RESULTS^{11,mm}

<i>EGFR</i> exon 19 deletion or exon 21 L858R mutation positive	NSCL-21
<i>EGFR</i> S768I, L861Q, and/or G719X mutation positive	NSCL-24
<i>EGFR</i> exon 20 insertion mutation positive	NSCL-25
<i>KRAS</i> G12C mutation positive	NSCL-26
<i>ALK</i> rearrangement positive	NSCL-27
<i>ROS1</i> rearrangement positive	NSCL-30
<i>BRAF</i> V600E mutation positive	NSCL-32
<i>NTRK1/2/3</i> gene fusion positive	NSCL-33
<i>MET</i>ex14 skipping mutation positive	NSCL-34
<i>RET</i> rearrangement positive	NSCL-35
<i>ERBB2</i> (<i>HER2</i>) mutation positive	NSCL-36
PD-L1 $\geq 1\%$ and negative for actionable molecular biomarkers above	NSCL-37
PD-L1 $< 1\%$ and negative for actionable molecular biomarkers above	NSCL-38

KHDAK'de Sistemik Tedavilerin Tarihsel Yolculuğu

PLATİN BAZLI KEMOTERAPİK AJANLARIN

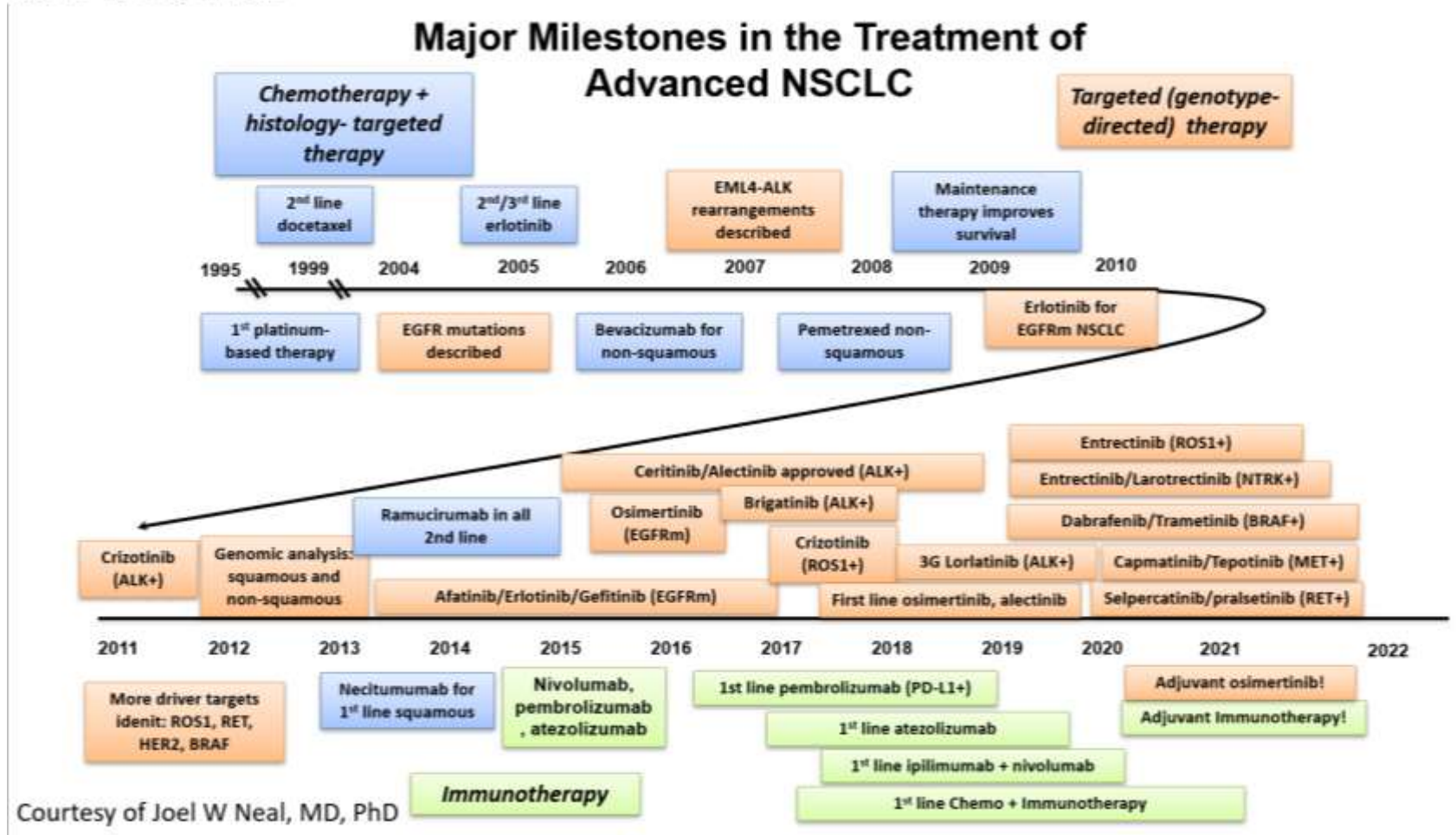
☐ Cevap oranları: %30–40

☐ Medyan sağkalım: 8–10 ay

☐ 1-yıllık sağkalım: %30–40

Metastatik KHDAAK Tedavi Süreci

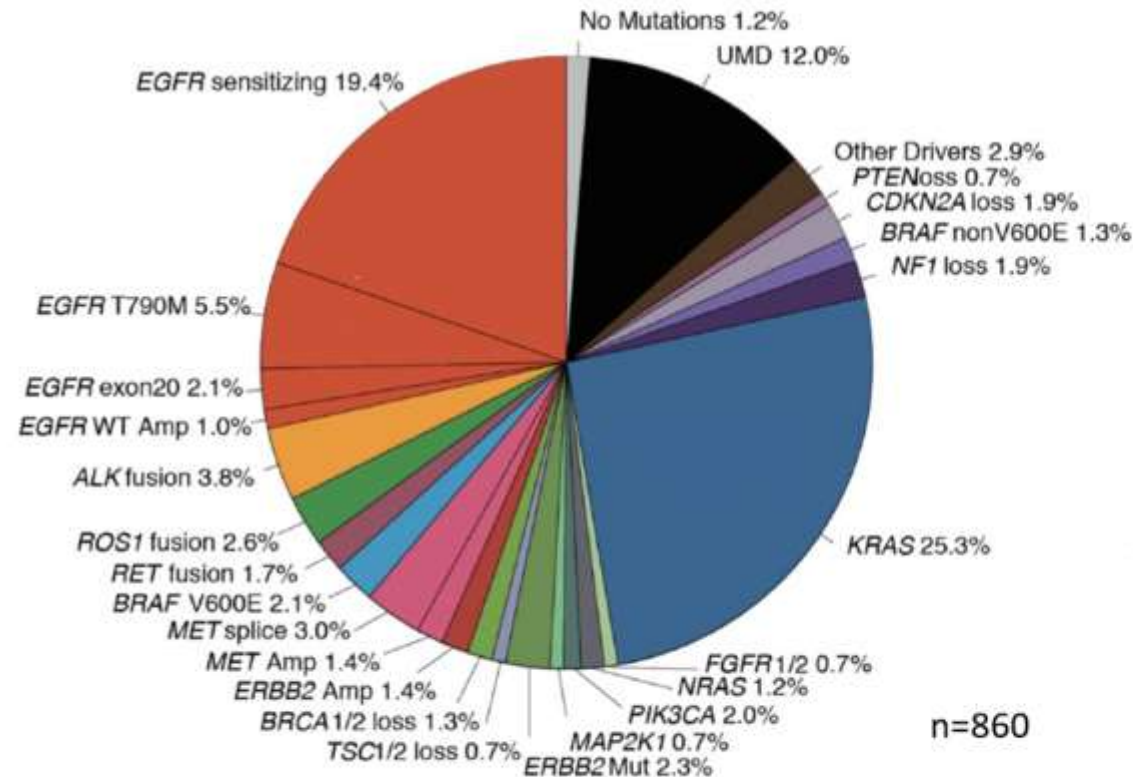
Slayt Gösterisi - MTElung21_Part1 - PowerPoint



Metastatik KHDAK Hedefe Yönelik Tedaviler

Large panel NGS finds targets
of FDA-approved targeted drugs – *circa 2021*

MSK-IMPACT data, MSKCC



EGFR sensitizing 19.4%
EGFR T790M 5.5%
EGFR exon20 2.1%
EGFR WT Amp 1.0%

Metastatik KHDAK Hedefe Yönelik Tedaviler

Printed by deniz tural on 5/24/2022 1:00:10 PM. For personal use only. Not approved for distribution. Copyright © 2022 National Comprehensive Cancer Network, Inc., All Rights Reserved.



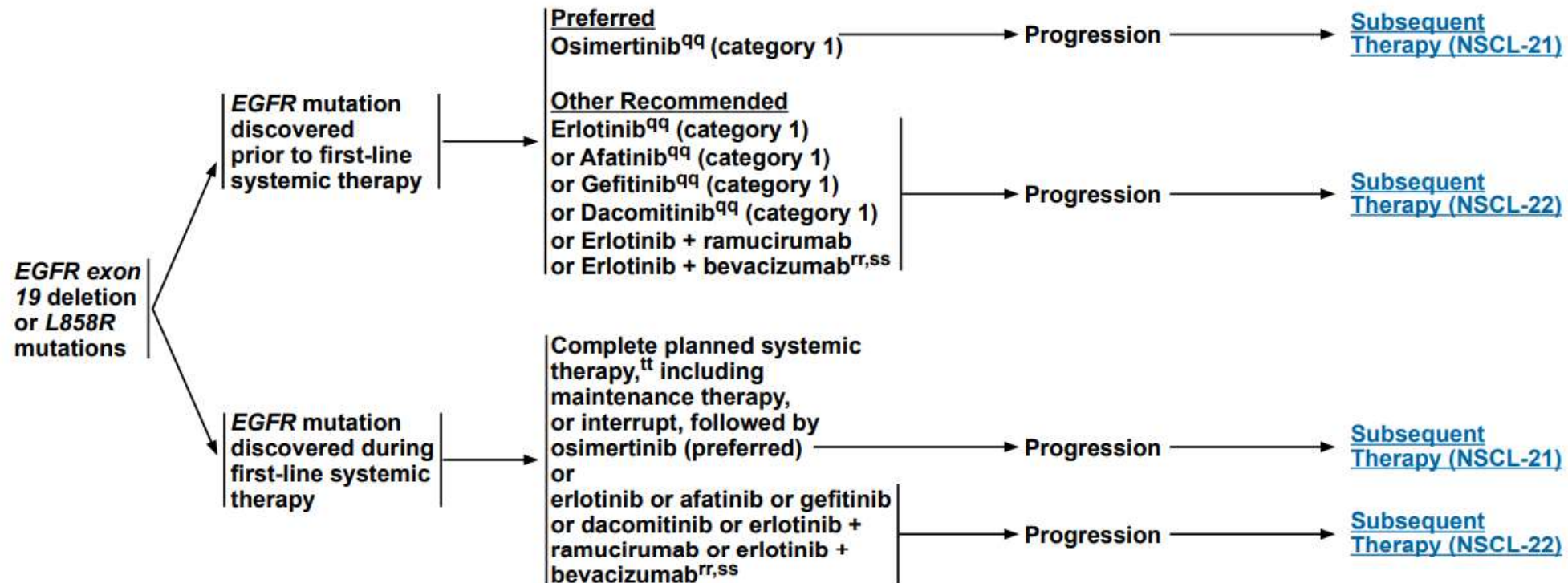
National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 3.2022 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

EGFR EXON 19 DELETION OR L858R MUTATIONS^{mm}

FIRST-LINE THERAPY^{pp}



Metastatik KHDAA Hedefe Yönelik Tedaviler

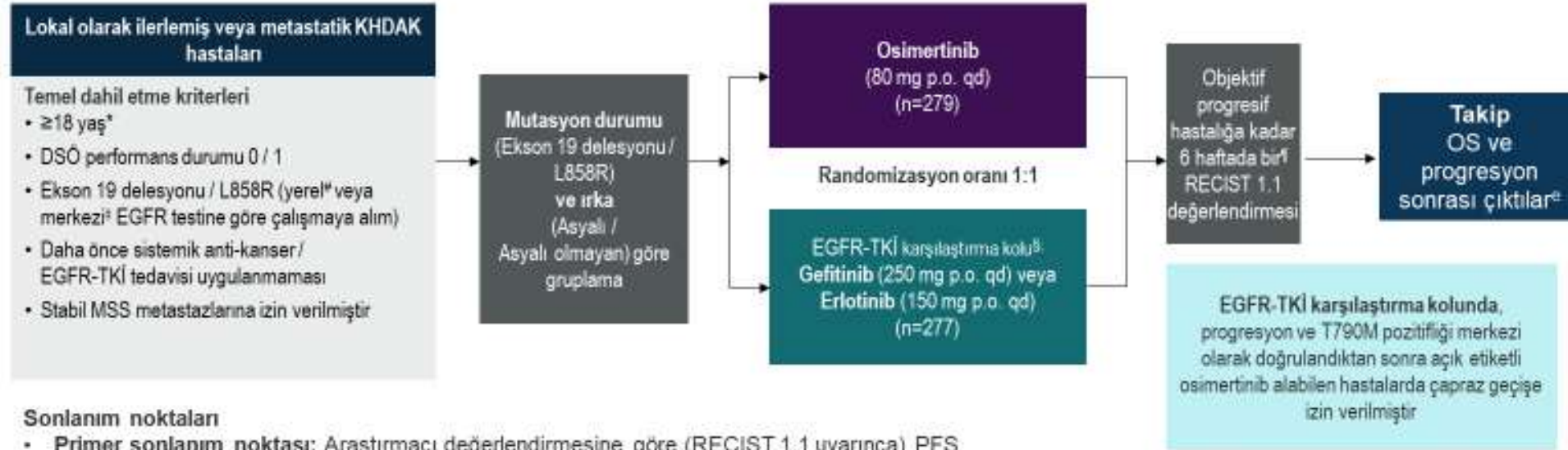
Front-line EGFR mutant NSCLC

Trial	TKI	Chemo	Mutation	mPFS (TKI vs Chemo), p	PFS HR (95%CI)	ORR% (TKI vs Chemo)	≥G3 TKI tox (%)
IPASS	Gefitinib	Carbo-Taxol	All	9.5 vs 6.3; p<0.001	0.48 (0.36-0.64)	71 vs 47	33
NEJ002	Gefitinib	Carbo-Taxol	L858R, Del19	10.8 vs 5.4; p<0.001	0.30 (0.22-0.41)	74 vs 31	41
WJTOG 3405	Gefitinib	Cis-Doce	L858R, Del19	9.2 vs 6.3; p<0.001	0.49 (0.34-0.71)	62 vs 32	NR
OPTIMAL	Erlotinib	Carbo-Gem	L858R, Del19	13.1 vs 4.6; p<0.001	0.16 (0.10-0.26)	83 vs 36	17
EURTAC	Erlotinib	Cis/Carbo- Doce/Gem	L858R, Del19	9.7 vs 5.2; p<0.001	0.37 (0.25-0.54)	58 vs 15	46
LUX-3	Afatinib	Cis-Pem	L858R, Del19	13.6 vs 6.9; p<0.0001	0.47 (0.34-0.65)	56 vs 23	49
LUX-6	Afatinib	Cis-Gem	L858R, Del19	11.0 vs 5.6; p<0.0001	0.28 (0.20-0.39)	67 vs 23	36

Mok NEJM (2009), Mitsudomi Lancet Oncol (2010); Maemondo NEJM (2010); Zhou Lancet Oncol (2011); Rossell Lancet Oncol (2012); Sequist JCO (2013); Wu Lancet Oncol (2014); NR, not reported

Metastatik KHDAK EGFR Mutasyonunda Tedavi

FLAURA çift kör çalışma tasarımı ^{1,2,3}



Sonlanım noktaları

- **Primer sonlanım noktası:** Araştırmacı değerlendirmesine göre (RECIST 1.1 uyarınca) PFS
 - Çalışmanın, %5 iki yönlü alfa düzeyinde 0,71 değerindeki tehlike oranını (10. aydan 14,1. aya kadar medyan PFS'de %29 iyileşmeyi temsil eder) saptama gücü %90'dır
- **Sekonder sonlanım noktaları:** Objektif yanıt oranı, yanıt süresi, hastalık kontrol oranı, yanıt derinliği, genel sağkalım, hasta tarafından bildirilen sonuçlar, güvenlik, Progresyon sonrası etkililik

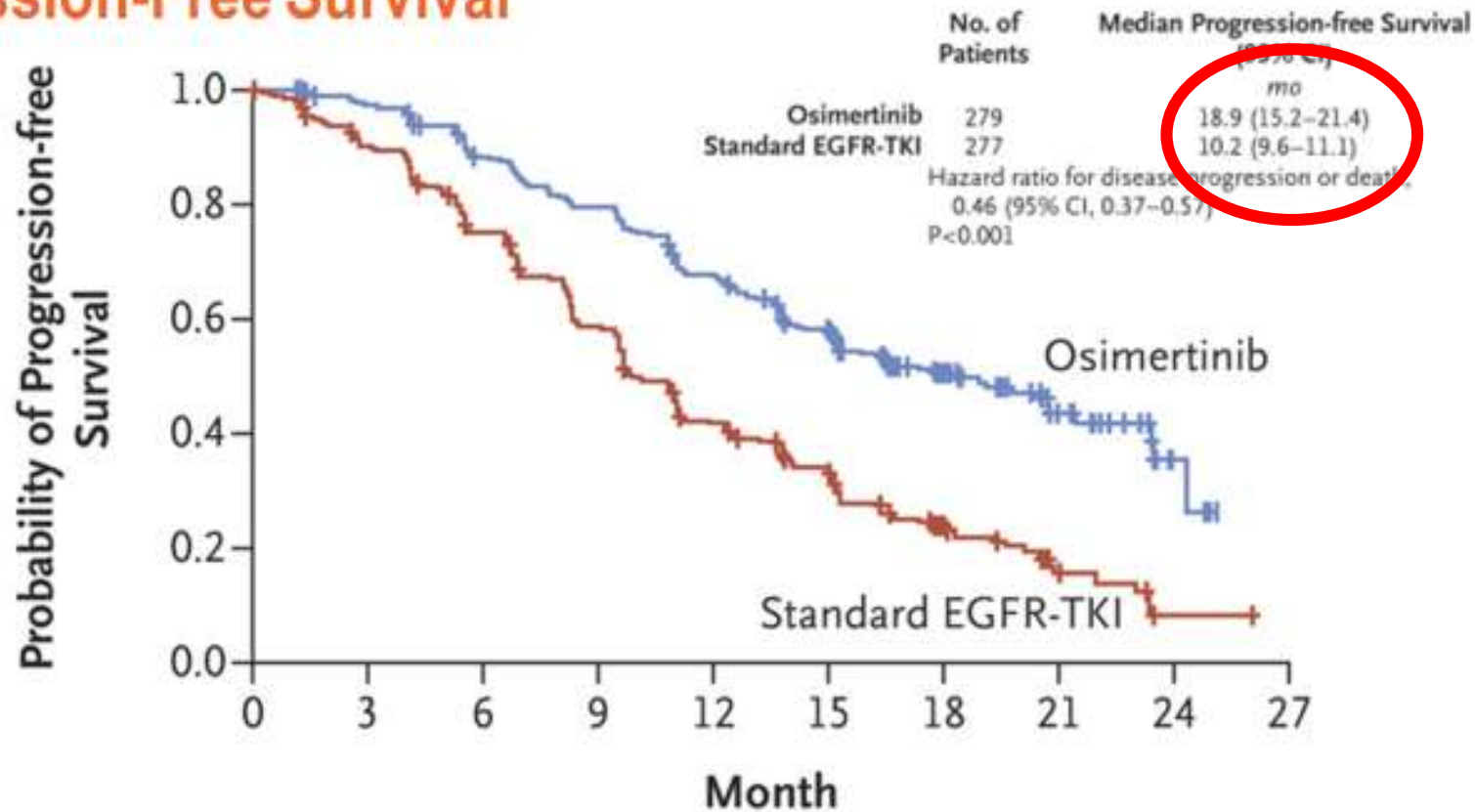
FLAURA verisi tarihi: 12 Haziran 2017, NCT02206125

*Japonyada ≥ 20 yaş, ^aDuyarlık için gerçekleştirilen merkezi laboratuvar değerlendirmesine göre; ^bEkson EGFR Mutasyon Testi (Roche Molecular Systems); ^cMerkezi olarak değerlendirilmeden önce merkezi tek komparatör olarak gefitinib veya erlotinib seçilmiştir. ^d18 aydan sonra 12 haftada bir MSS, merkezi sinir sistemi, EGFR, epidermal büyüme faktörü reseptörü; KHDAK, küçük hücreli dışı akciğer kanseri; PFS, progresyonsuz sağkalım; p.o., oral yoldan; RECIST 1.1, Solid Tümörlerde Yanıt Değerlendirme Kriterleri versiyon 1.1; qd, günde bir doz; SoC, standart tedavi; TKI, tirozin kinaz inhibitörü; DÖ, Dünya Sağlık Örgütü

1. Soria J-C et al. Article and supplementary appendix. *N Engl J Med*. 2016;375:113-125. 2. Planchard D et al. Presented at: European Lung Cancer Congress, 11-14 April 2016; Geneva, Switzerland. 3. Oha Y et al. Presented at: European Society for Medical Oncology Asia Congress; 17-19 November 2017; Singapore

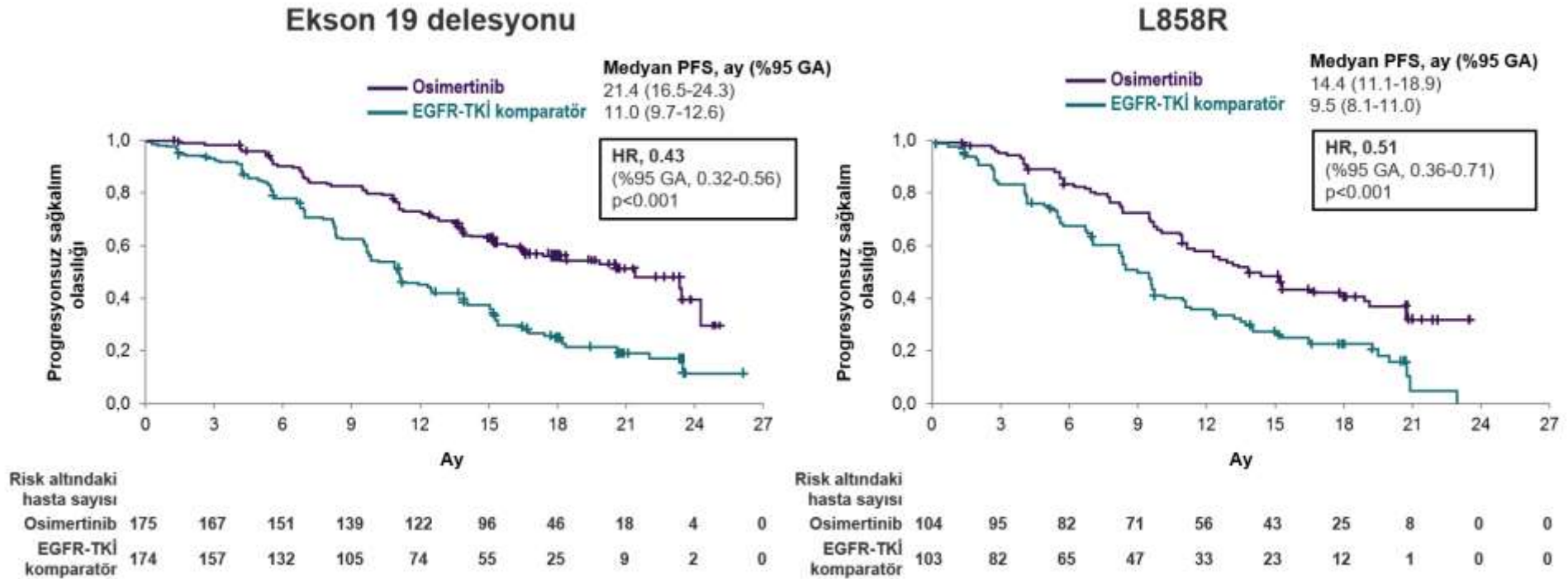
Metastatik KHDAK EGFR Mutasyonunda Tedavi

Osimertinib vs Gefitinib/Erlotinib as first treatment for NSCLC Progression-Free Survival



Metastatik KHDAK EGFR Mutasyonunda Tedavi

FLAURA: TAK'de EGFR mutasyon durumuna göre PFS



FLAURA veri kesme noktası: 12 Haziran 2017.

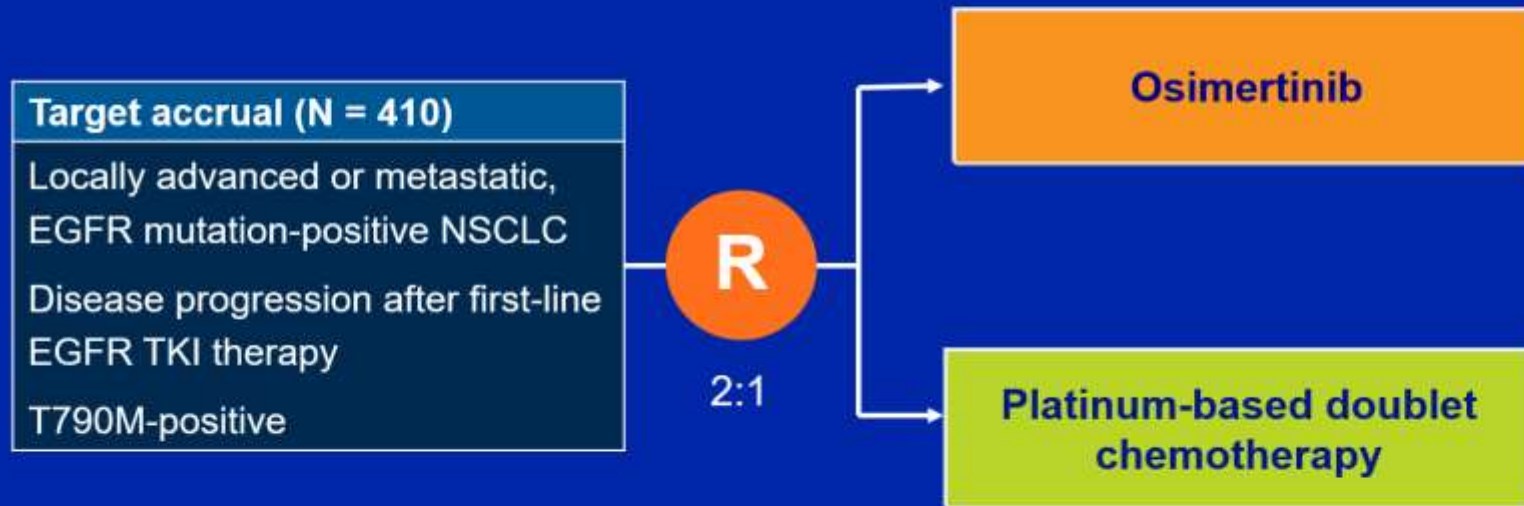
Çentik işaretleri sansürlenmiş verileri göstermektedir.

EGFR = epidermal büyüme faktörü reseptörü; TAK = tam analiz kümesi; HR, tehlike oranı; PFS, progresyonsuz sağkalım; TKİ, tirozin kinaz inhibitörü.

1. Soria J-C et al. Article and supplementary appendix. N Engl J Med. 2018;378:113-125.

Metastatik KHDAAK EGFR Mutasyonunda Tedavi

AURA3: A Phase III Study of Osimertinib versus Platinum-Based Doublet Chemotherapy for Locally Advanced or Metastatic NSCLC

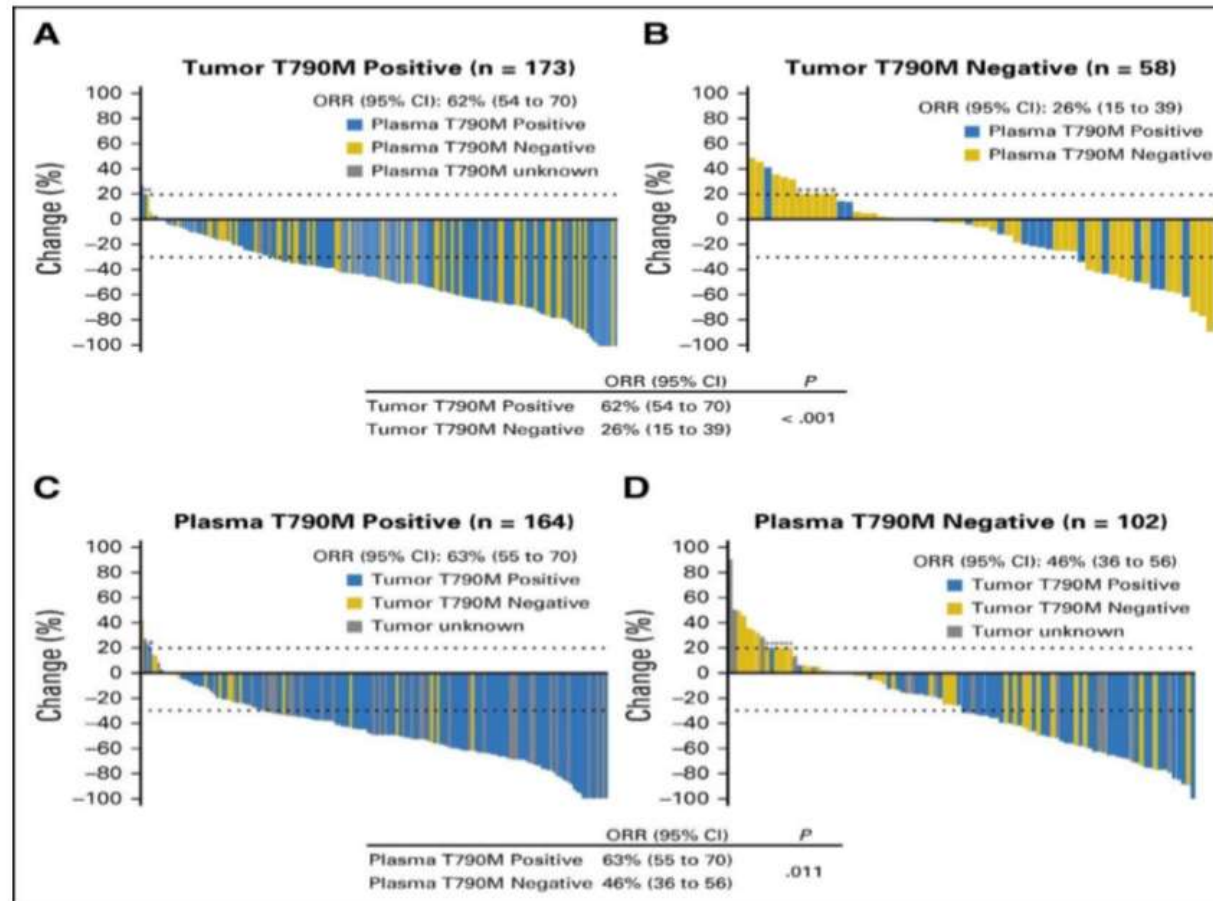


Primary Endpoint: Progression-free survival

Key Secondary Endpoints: Objective response rate, overall survival and safety

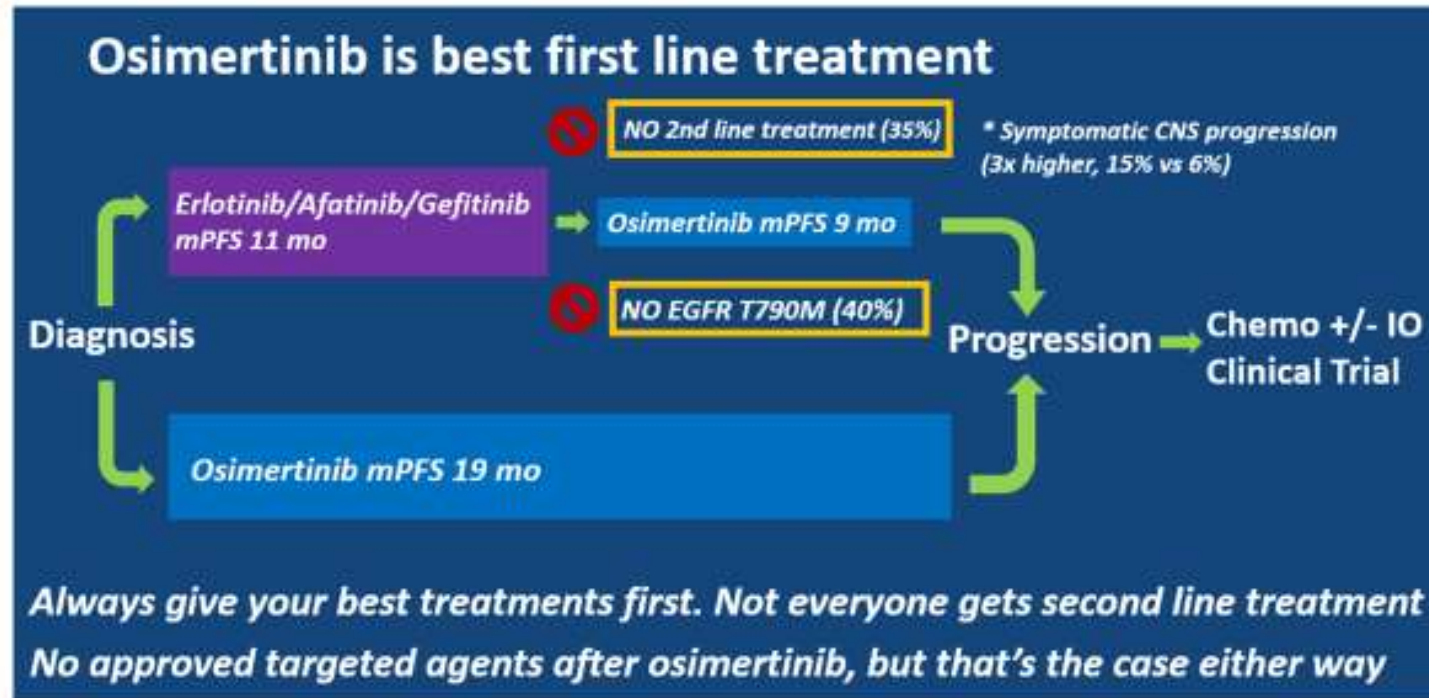
Metastatik KHDAK EGFR Mutasyonunda Tedavi

Response to osimertinib based on plasma/tissue T790M detection



Metastatik KHDAK EGFR Mutasyonunda Tedavi

Osimertinib as best in class EGFR TKI



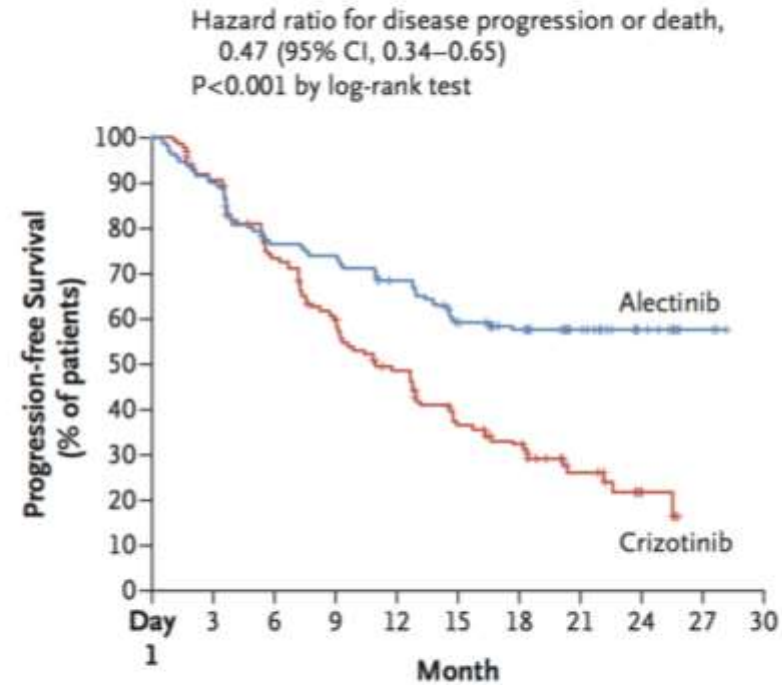
Metastatik KHDAK ALK Alterasyonunda Tedavi

ALEX trial: alectinib frontline against crizotinib

ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D.,
Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D.,
Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D.,
Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zealter, M.D.,
Emmanuel Mitry, M.D., Ph.D., Sophie Golding, M.Sc., Bogdana Balas, M.D.,
Johannes Noe, Ph.D., Peter N. Morcos, Pharm.D., and Tony Mok, M.D.,
for the ALEX Trial Investigators*

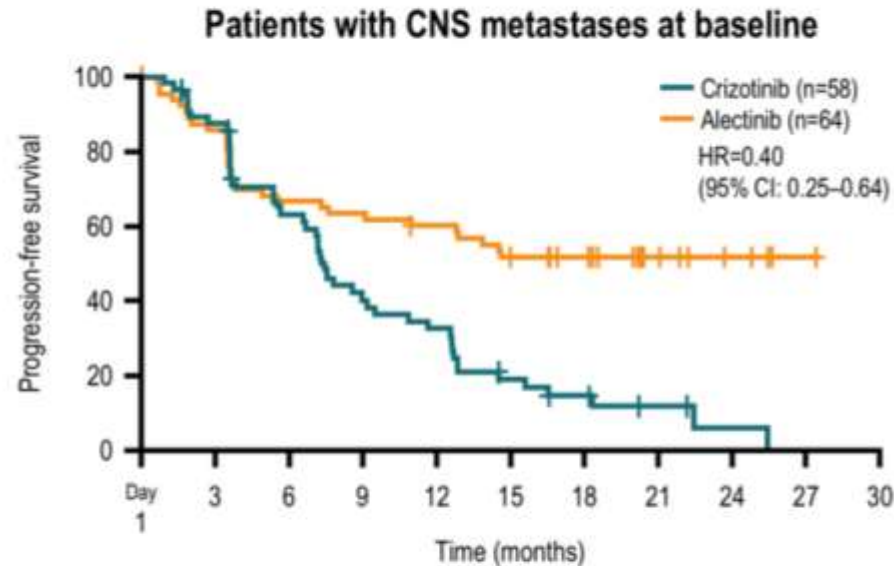


No. at Risk

Alectinib	152	135	113	109	97	81	67	35	15	3
Crizotinib	151	132	104	84	65	46	35	16	5	

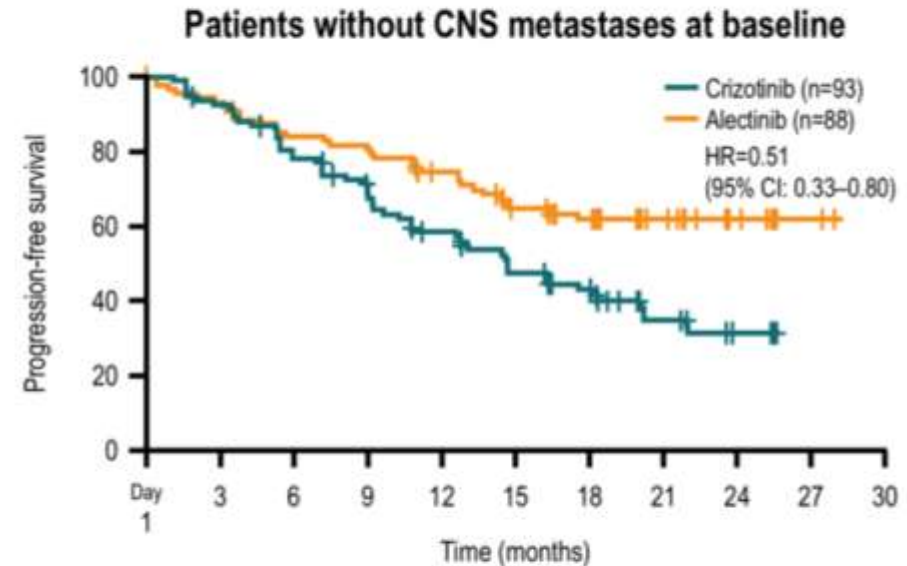
Metastatik KHDAAK ALK Alterasyonunda Tedavi

ALEX: CNS Activity



Patients at risk

Crizotinib	58	48	66	22	17	9	6	3	1
Alectinib	64	54	41	39	36	31	24	10	4



Patients at risk

Crizotinib	93	84	71	62	48	37	29	13	4
Alectinib	88	81	72	70	61	50	43	25	11

Metastatik KHDAAK ALK Alterasyonunda Tedavi

ALTA-1L trial: PFS by independent review

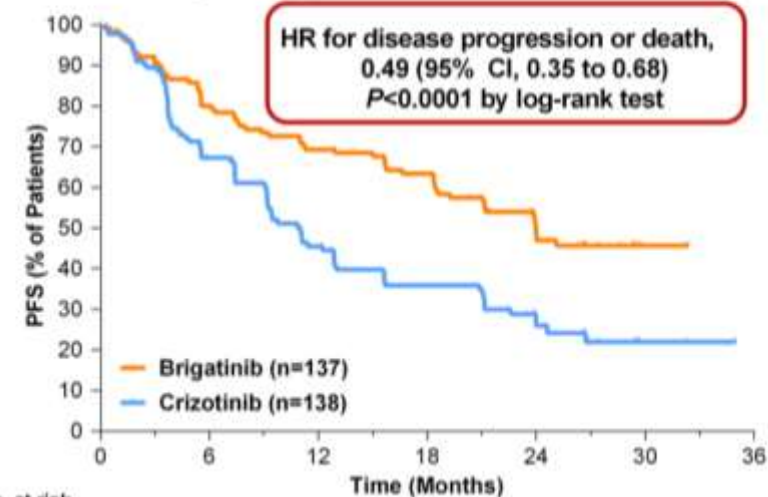
ORIGINAL ARTICLE

Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer

D.R. Camidge, H.-R. Kim, M.-J. Ahn, J.C.-H. Yang, J.-Y. Han, J.-S. Lee, M.J. Hochmair, J.Y.-C. Li, G.-C. Chang, K.H. Lee, C. Gridelli, A. Delmonte, M.R.G. Campelo, D.-W. Kim, A. Bearz, F. Griesinger, A. Morabito, E. Felip, R. Califano, S. Ghosh, A. Spira, S.N. Gettinger, M. Tiseo, N. Gupta, J. Haney, D. Kerstein, and S. Popat

- Same benefit in patients with or without prior chemotherapy
- Independent radiological review
- Interim analysis

Primary Endpoint: BIRC-Assessed PFS



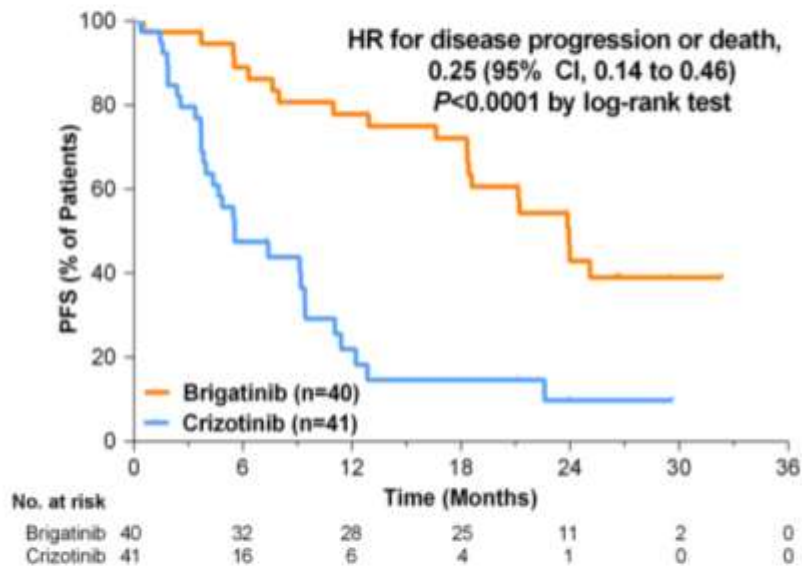
No. at risk		Time (months)					
Brigatinib	137	97	84	75	39	3	0
Crizotinib	138	80	49	37	17	2	0

Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=137)	63 (46)	24.0 mo (18.5–NR)	48 (39–57)
Crizotinib (n=138)	87 (63)	11.0 mo (9.2–12.9)	26 (18–35)

Metastatik KHDAK ALK Alterasyonunda Tedavi

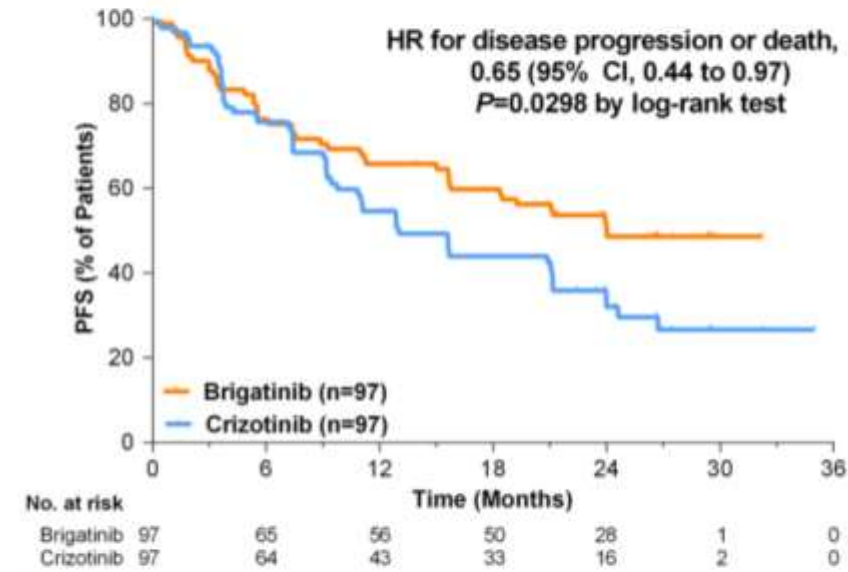
ALTA-1L: PFS with/without brain metastasis

Patients With Any Brain Metastases at Baseline



Treatment	No. (%) Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=40) ^a	20 (50)	24.0 mo (18.4–NR)	43 (25–59)
Crizotinib (n=41) ^a	30 (73)	5.6 mo (3.8–9.4)	10 (2–25)

Patients Without Brain Metastases at Baseline



Treatment	No. (%) Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=97) ^a	43 (44)	24.0 mo (15.7–NR)	50 (39–61)
Crizotinib (n=97) ^a	57 (59)	13.0 mo (9.5–21.1)	32 (22–43)

^a Per investigator assessment

Metastatik KHDAK ALK Alterasyonunda Tedavi

ALKi TOXICITIES

CERITINIB

NAUSEA
DIARRHEA
VOMITING
ALT, AST, GAMMA-GT
ALP

ALECTINIB

ALT, AST, GAMMA-GT
OEDEMA
FATIGUE
MYALGIA
LUNG TOXICITY
(LATE ONSET)

BRIGATINIB

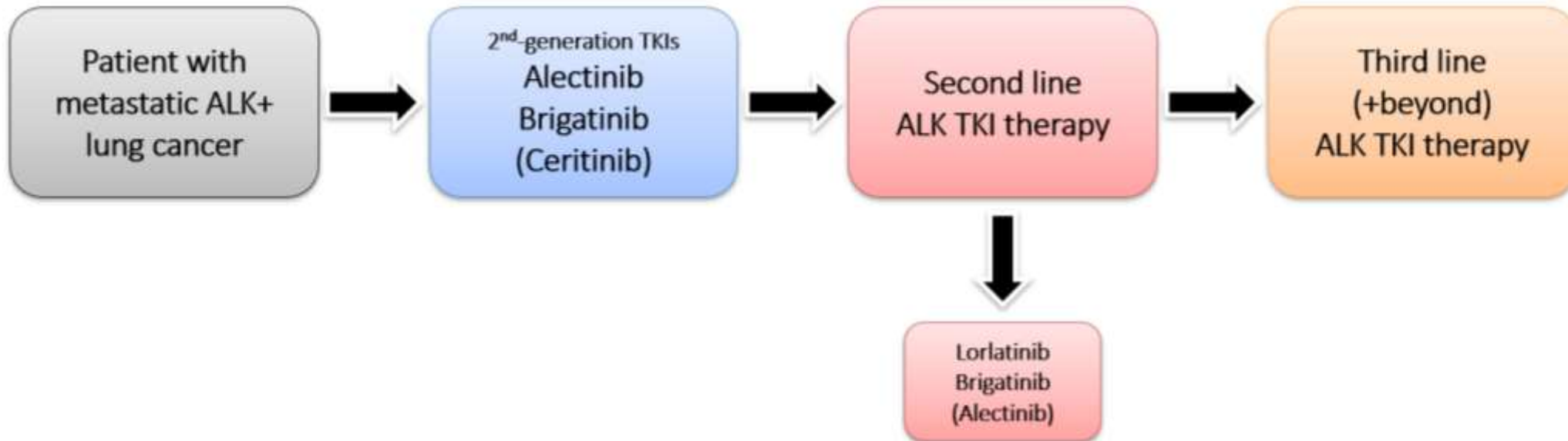
CPK
HYPERTENSION
LIPASE
AMYLASE
DIARRHEA

LUNG TOXICITY
(EARLY ONSET)

Metastatik KHDAAK ALK Alterasyonunda Tedavi

Second line therapy for ALK+ lung cancer, after a 2nd-generation ALK TKI

Much less data in this scenario...



Can we bring resistance biomarker selection into the sequence of ALK TKIs in lung cancer?

Metastatik KHDAK ALK Alterasyonunda Tedavi

CNS Activity of ALK Inhibitors in Advanced NSCLC with ALK Rearrangements

ALK inhibitor	Study	No. of patients	CNS ORR
Crizotinib	ALTA-1L	21	29%
	ALEX	11	50%
Ceritinib	ASCEND-4	54	46%
Alectinib	ALEX	17	81%
Brigatinib	ALTA-1L	18	78%

Lorlatinib first-line Phase III study versus crizotinib (CROWN, NCT03052608) is ongoing with estimated primary completion December 31, 2020

Peters S et al. *NEJM* 2017;377(9):829-38; Camidge DR et al. *NEJM* 2018;379:2027-39.
Soria JC et al. *Lancet* 2017;389(10072):917-29; www.clinicaltrials.gov. Accessed October 2019.

Metastatik KHDAAK ALK Alterasyonunda Tedavi

Mutation Coverage for ALK Inhibitors

Mutations	Crizotinib	Alectinib	Ceritinib	Brigatinib	Lorlatinib
EML4-ALK	S	S	S	S	S
L1196M	R	S	S	S	S
L1152P/R	R	S	R	S	S
G1123S	R	S	R	NA	NA
T1151Tins	R	S	R	NA	S
C1156Y	R	S	R	S	S
F1174V/C/L	R	S	R	S	S
I1171T/N/S	R	R	S	NA	NA
V1180L	R	R	S	NA	NA
G1202R	R	R	R	S	S
G1269A/S	R	S	S	S	S
F1245C	R	NA	S	NA	NA
S1206C/Y/F	R	S	S	R	S
E1210K	R	S	S	S	S
L1198F	S	R	R	S	R
D1203N	R	S	S	S	S
CMET amp	S	R	R	R	R

The letter "S" denotes mutations that are "sensitive" (clinical and/or preclinical data) to a given compound, and "R" denotes resistance. NA = data not available

Tran PN, Klempner SJ. *Front Med* 2016;3:65.

Metastatik KHDAK ALK Alterasyonunda Tedavi

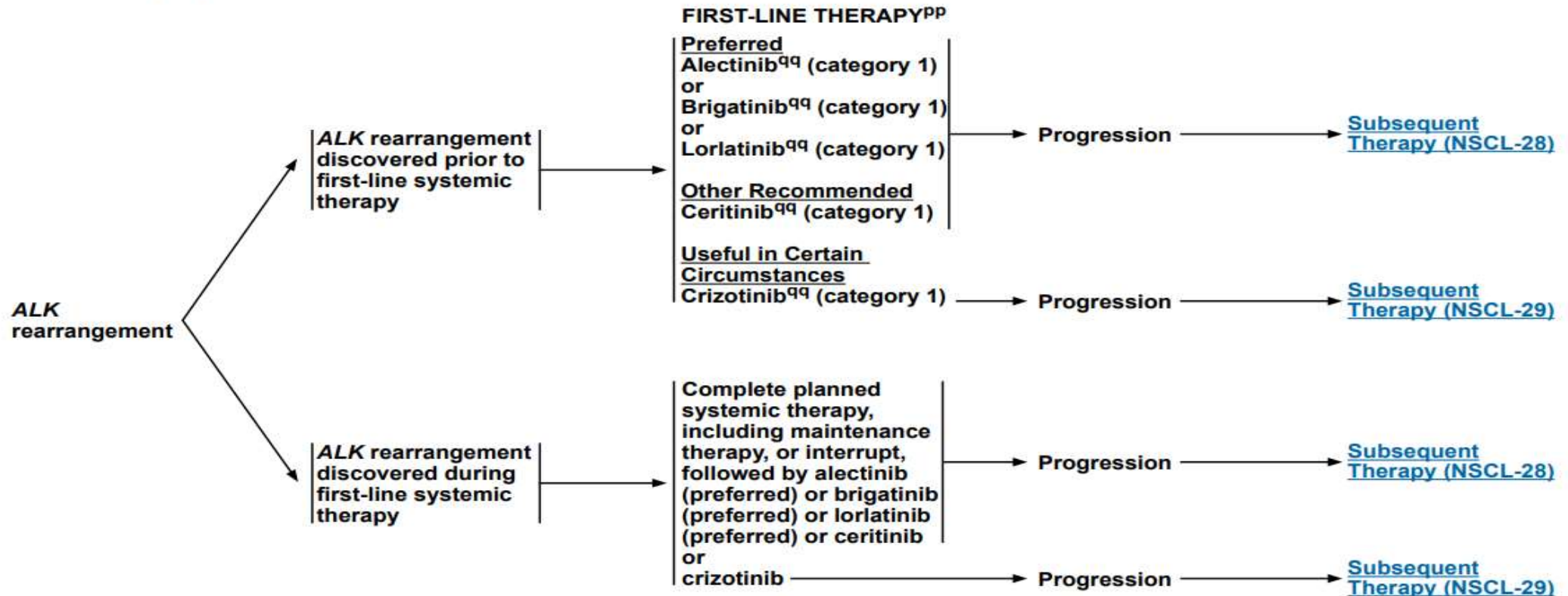


National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

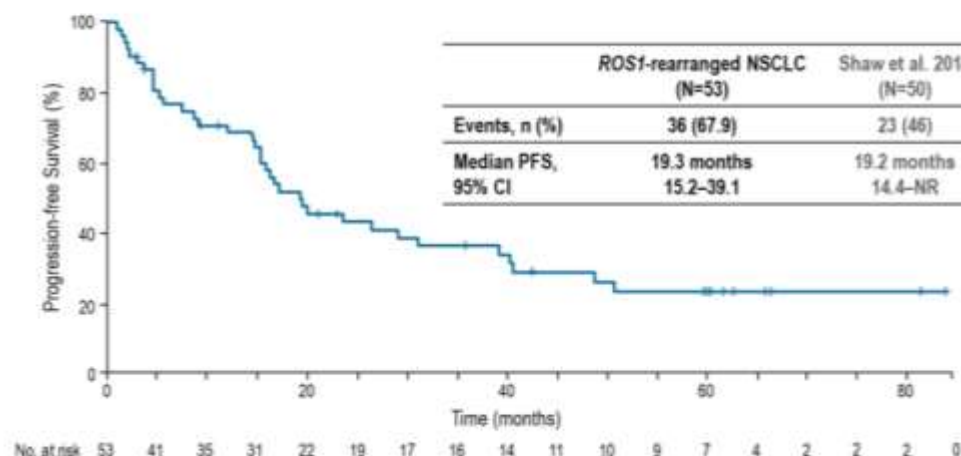
ALK REARRANGEMENT^{mm}



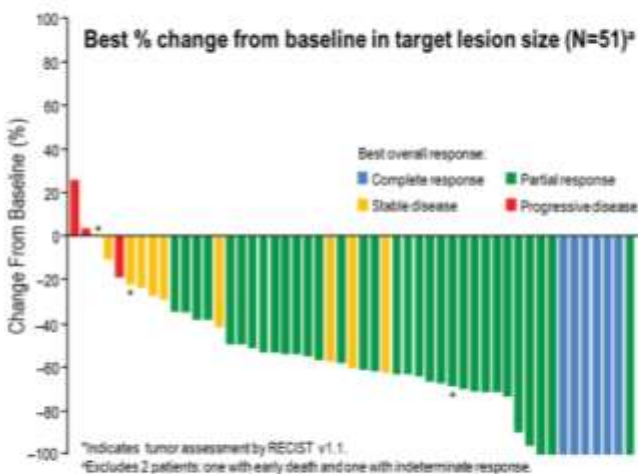
Metastatik KHDAK ROS1 Alterasyonunda Tedavi

Focusing on ROS-1: Crizotinib

UPDATED PROGRESSION-FREE SURVIVAL



UPDATED ANTITUMOR ACTIVITY



	ROS1-rearranged NSCLC (N=53)	Shaw et al. 2014 (N=50)
BOR, n (%)		
CR	6 (11.3)	3 (6)
PR	32 (60.4)	33 (66)
SD	10 (18.9)	9 (18)
PD	3 (5.7)	3 (6)
NE*	2 (3.8)	2 (4)
ORR, %		
95% CI	57.7–83.2	58–84
Median TTR, wks		
Range	4.3–103.6	4.3–32.9
Median DOR ^b , mos		
95% CI	15.2–45.3	14.5–NR

^aResponses could not be evaluated in 2 patients because of early death or indeterminate response.
^bEstimated using the Kaplan-Meier method.

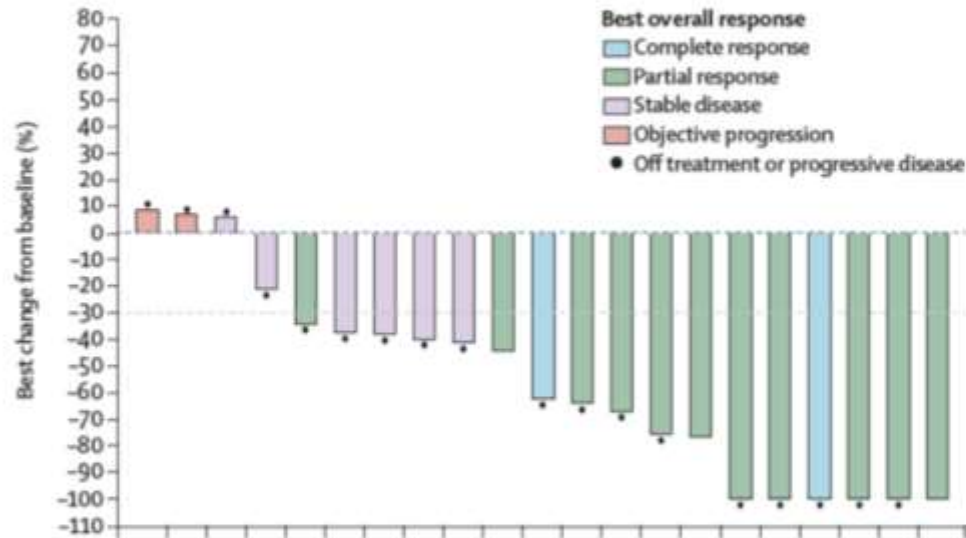
Courtesy of Solange Peters, MD, PhD

Shaw et al 2019 Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001 N Engl J Med. 2014 Nov 20;371(21):1963-71

Metastatik KHDAK ROS1 Alterasyonunda Tedavi

Lorlatinib multicenter, open-label, single-arm, phase 1–2 trial

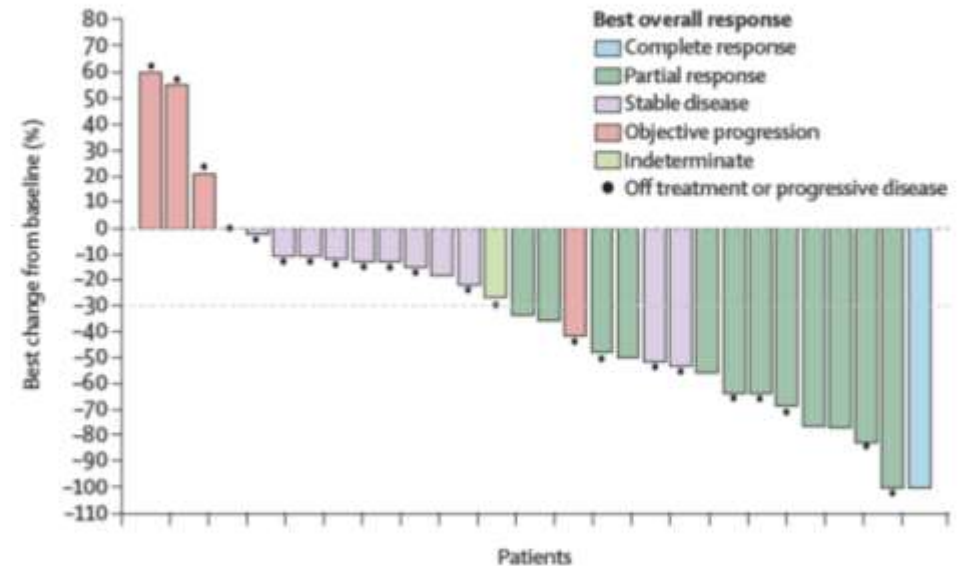
ROS1-TKI naïve pts (n=21)



ORR, %: 62 (38–82)

mDoR, month: 25.3 (7.5–31.9)

Crizotinib pretreated pts (n=40)



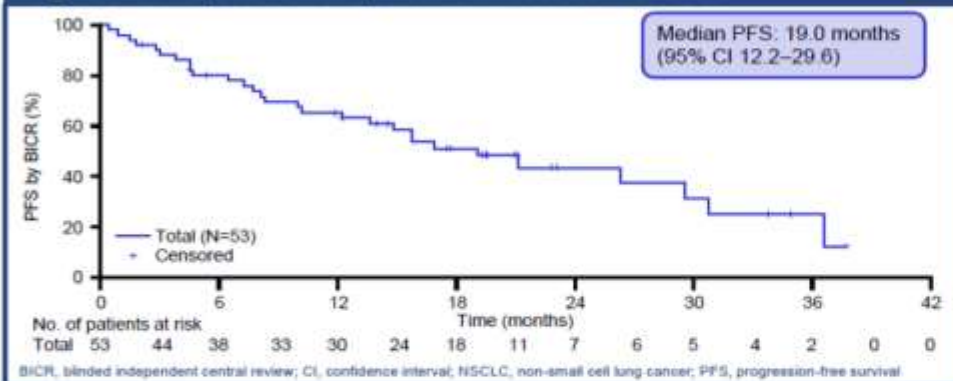
ORR: 35% (21-52)

mDoR, month: 13.8 (9.7–NR)

Metastatik KHDAK ROS1 Alterasyonunda Tedavi

Integrated analysis of STARTRK-2, STARTRK-1 and ALKA-372-001: Entrectinib in ROS1-fusion positive NSCLC (TKI-naïve)

Figure 2. PFS per BICR in patients with ROS1+ NSCLC



Responders, n (%)	ROS1+ NSCLC (n=53)
ORR, % (95% CI)	79.2 (65.9–89.2)
Complete response	5 (9.4)
Partial response	37 (69.8)
Stable disease	1 (1.9)
Progressive disease	4 (7.5)
Non complete/partial response	2 (3.8)
Missing/unevaluable	4 (7.5)

Figure 3. OS in patients with ROS1+ NSCLC

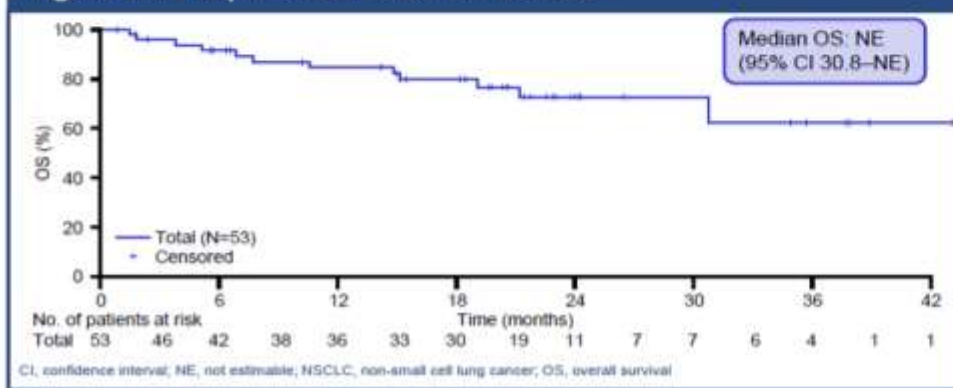


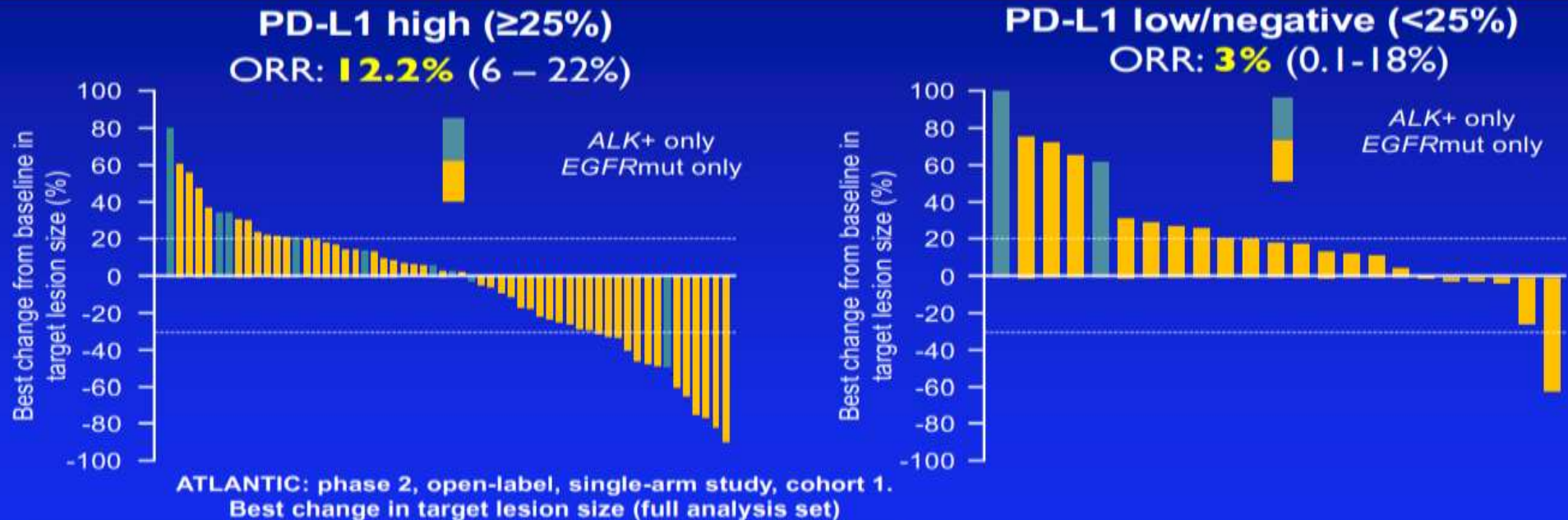
Table 3. IC ORR per BICR in ROS1+ NSCLC with baseline CNS disease

Responders, n (%)	ROS1+ NSCLC with baseline CNS disease (n=20)
ORR, % (95% CI)	55.0 (31.5–76.9)
Complete response	4 (20.0)
Partial response	7 (35.0)
Stable disease	0
Progressive disease	3 (15.0)
Non complete/partial response	4 (20.0)
Missing/unevaluable	2 (10.0)

CNS (disease status determined by BICR)
BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; NSCLC, non-small cell lung cancer
ORR, objective response rate

Driver mutasyonu olanlarda immüne Checkpoint inhibitörlerine yanıt iyi değil

Caution with Single Agent PD-(L)1 in EGFR and Others PD-L1 selection for EGFRm for PD-(L)1 monotherapy

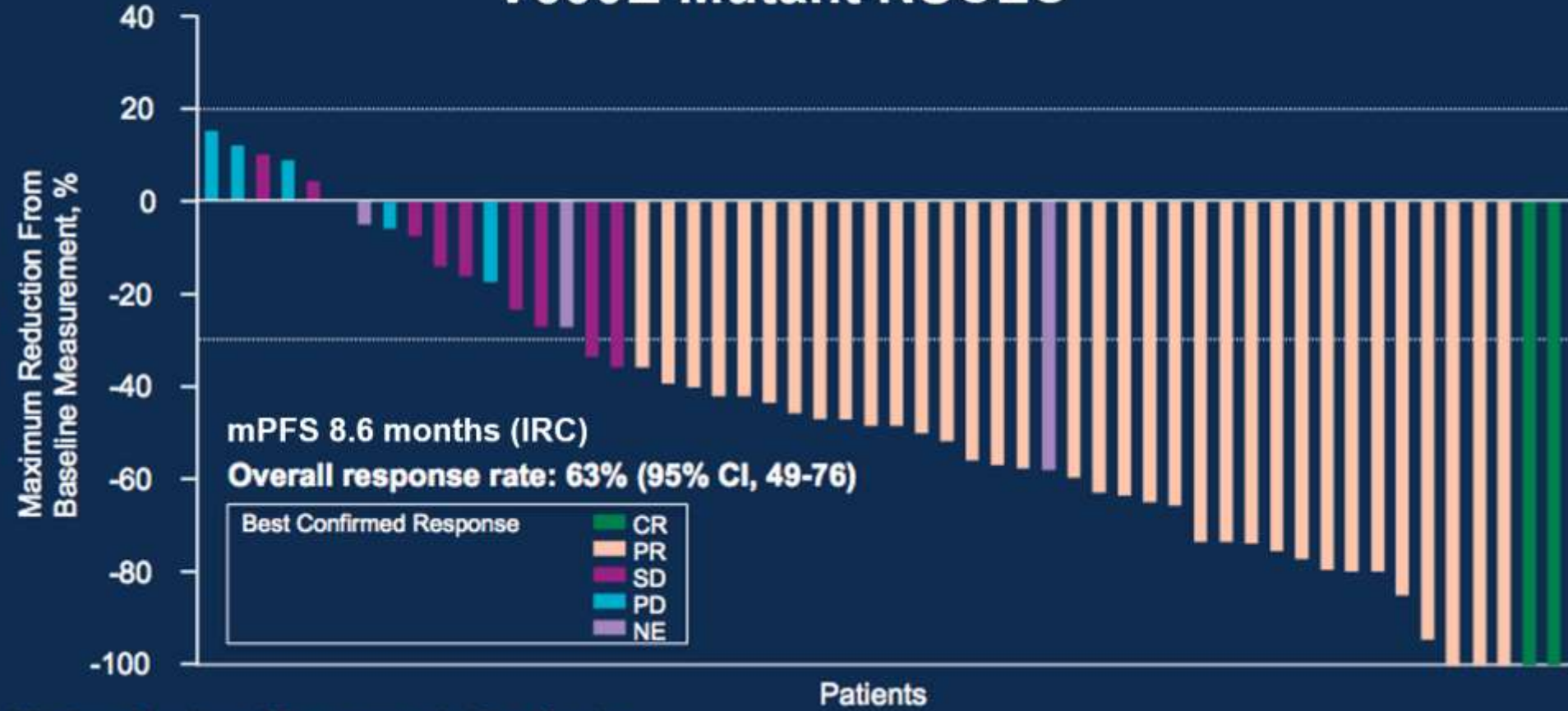


In KN010, CM057 and OAK, the ONLY subgroup that did NOT show superior survival with the PD-(L)1 inhibitor vs docetaxel was the patients with EGFR mutations

Garassino MC *et al.* Ann Onc 2017 28:S2
Lancet Oncol 2018

Metastatik KHDAAK BRAF Mutasyonunda Tedavi

Efficacy of Dabrafenib and Trametinib in Advanced BRAF V600E Mutant NSCLC



NE patients did not have a follow-up scan required for confirmation.

Planchard et al., ASCO 2016

Metastatik KHDAK BRAF Mutasyonunda Tedavi

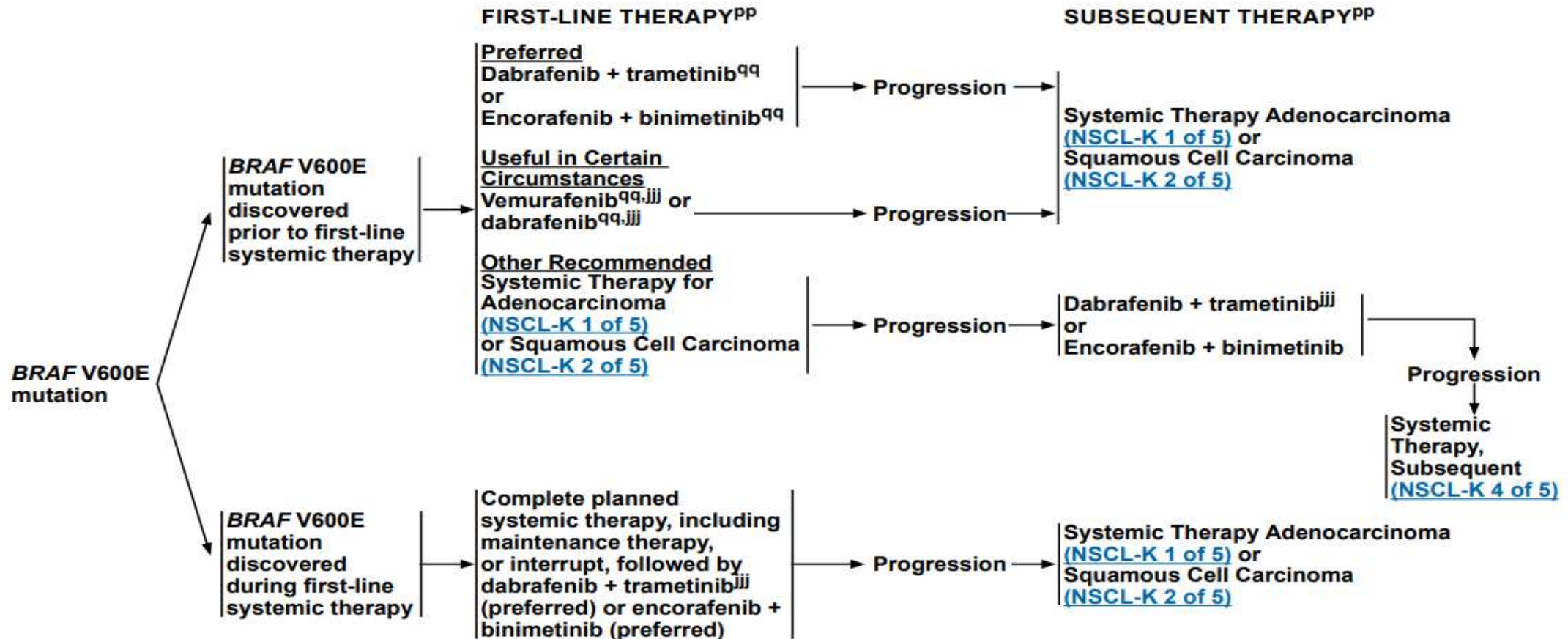


National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024 Non-Small Cell Lung Cancer

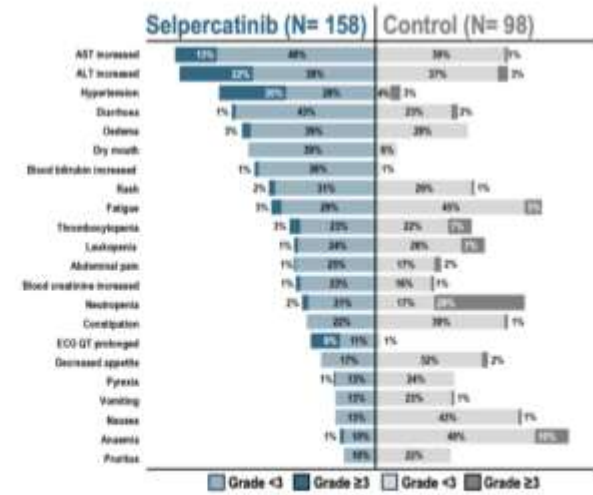
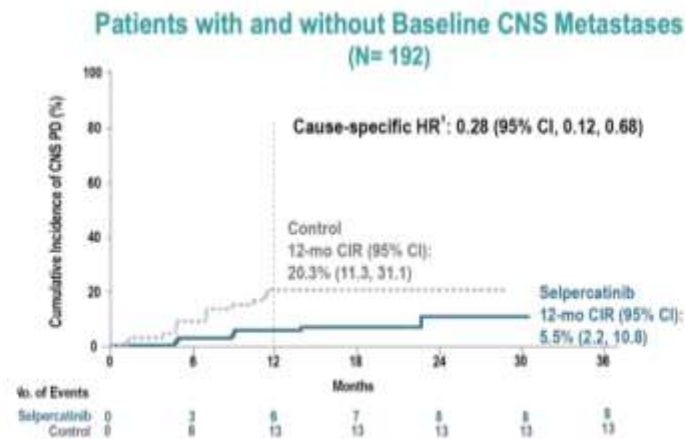
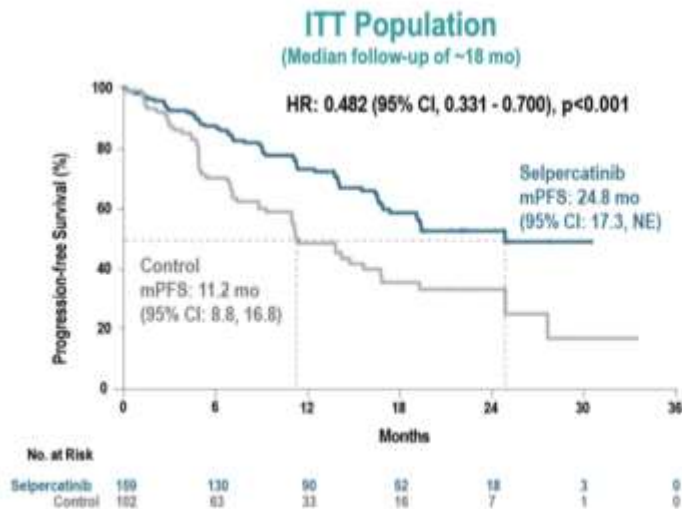
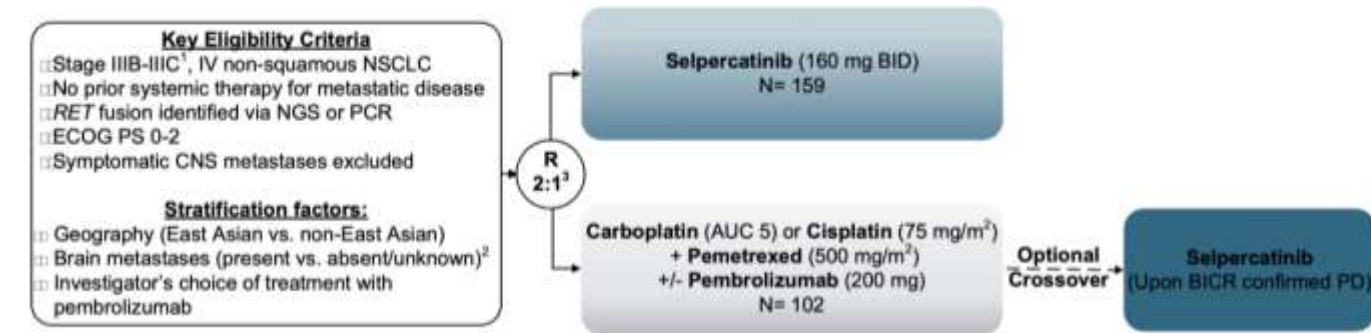
[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

BRAF V600E MUTATION^{mm}



Metastatik KHDAK RET Alterasyonunda Tedavi

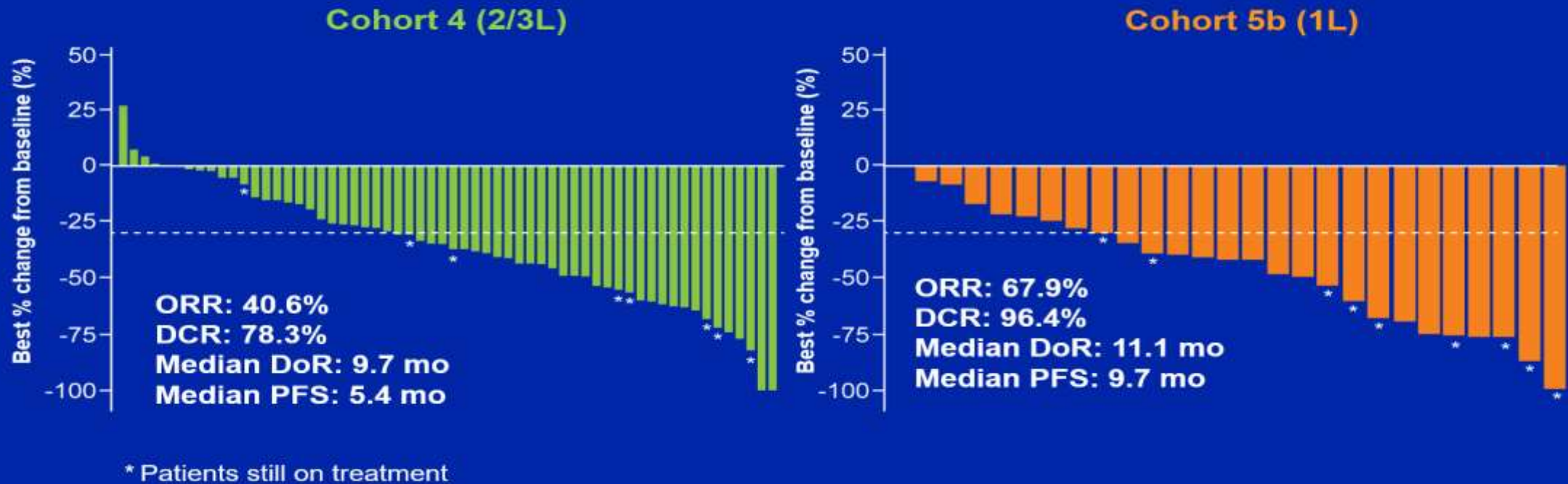
LIBRETTO-431



Any grade treatment-emergent adverse events (TEAEs) occurring in ≥28% of patients in either study arm

Metastatik KHDAK MET ekzon 14 skipping mutasyonunda Tedavi

GEOMETRY mono-1: Efficacy by BIRC of Capmatinib in Advanced NSCLC Harboring MET Exon 14 Skipping Mutation



Metastatik KHDAK RET Mutasyonunda Tedavi



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2024 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level <i>MET</i> amplification ^{a,b}	Capmatinib ¹ Tepotinib ² Crizotinib ^{3,4}

^a The definition of high-level *MET* amplification is evolving and may differ according to the assay used for testing. For NGS-based results, a copy number greater than 10 is consistent with high-level *MET* amplification.

^b In patients with *EGFR*-mutant NSCLC who develop high-level *MET* amplifications, administration of these agents with continuation of osimertinib is acceptable.

¹ Wolf J, Seto T, Han JY, et al; GEOMETRY mono-1 Investigators. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med* 2020;383:944-957.

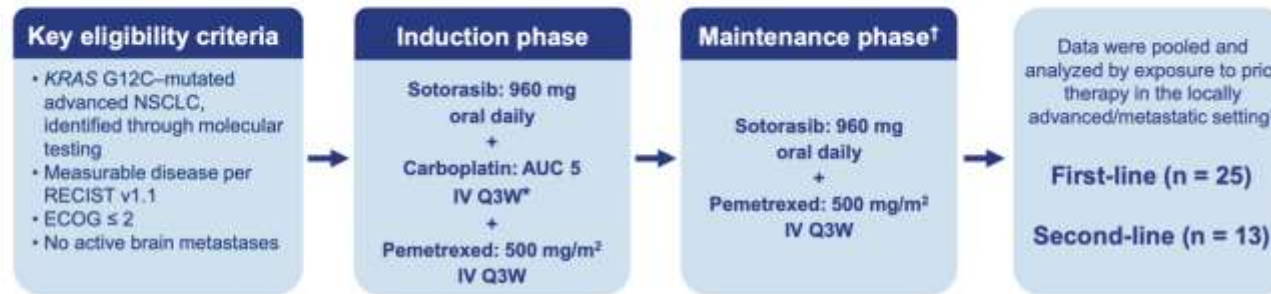
² Le X, Paz-Ares LG, Van Meerbeeck J, et al. Tepotinib in patients with advanced non-small cell lung cancer (NSCLC) with *MET* amplification (*METamp*) [abstract]. *J Clin Oncol* 2021;39(Suppl):Abstract 9021.

³ Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. *J Thorac Oncol* 2011;6:942-946.

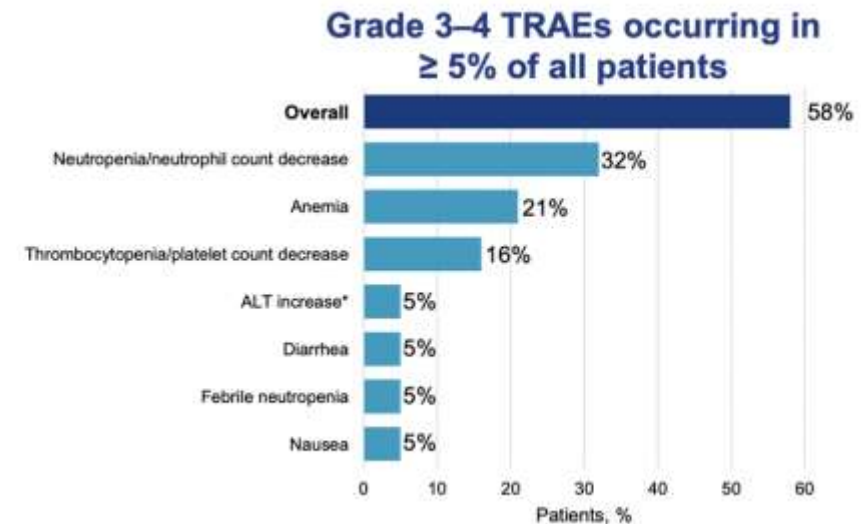
⁴ Camidge DR, Otterson GA, Clark JW, et al. Crizotinib in patients with MET-amplified NSCLC. *J Thorac Oncol* 2021;16:1017-1029.

Metastatik KHDAK KRAS G12C Mutasyonunda Tedavi

KRAS G12C – CodeBreak 101



Response by Investigator Assessments*	Sotorasib + Carboplatin + Pemetrexed	
	First-line (n = 20)	Second-line (n = 13)
ORR, n (%)	13 (65)†	7 (54)
Best overall response, n (%)		
Complete response	0	1 (8)
Partial response	13 (65)	6 (46)
Stable disease	7 (35)	4 (31)
Progressive disease	0	1 (8)
Not evaluable / not done	0	1 (8)
DCR (95% CI)	20 (100) (83.2, 100)	11 (85) (54.6, 98.1)



Metastatik KHDAK KRAS G12C Mutasyonunda Tedavi

KRAS G12C – KRYSTAL-7

KRYSTAL-7 is evaluating Adagrasib + Pembrolizumab in previously untreated KRAS G12C+ NSCLC in 2 cohorts (Cohort 1, PDL1 < 1% and Cohort 2a, PDL1 $\geq$ 1%)

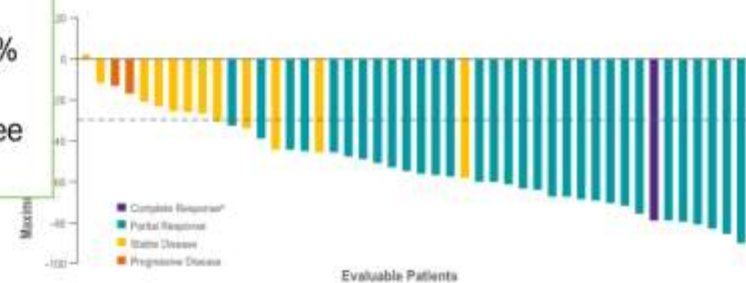
Most Frequent TRAEs ^a , %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51	28	20	3	0
Diarrhea	44	33	7	3	0
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Vomiting	29	17	11	1	0
Fatigue	26	12	10	4	0
Decreased appetite	24	14	9	1	0
Lipase increased	24	3	9	10	1

Most Frequent Liver TRAEs, %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Hepatitis	4	0	2	2	0
Hepatotoxicity ^a	1	0	1	1	0
Liver injury	1	0	1	0	0
Drug-induced liver injury	1	1	0	0	0
Hepatic failure	1	0	0	1	0
Acute hepatitis	1	0	1	0	0
Immune-mediated hepatitis	1	0	0	1	0

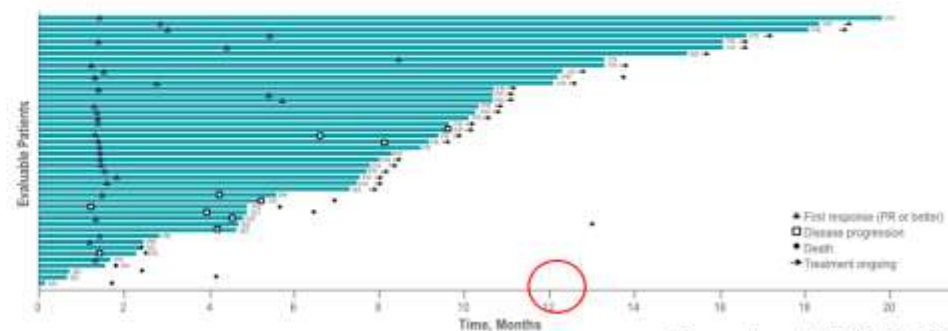
Combining adagrasib + pembrolizumab appeared to be overall fairly well-tolerated, with low rates of high-grade hepatotoxicity.

In PDL1 $\geq$ 50%:

- ORR 63%
- mPFS NR (60% remained progression-free at 12 months)



- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity^a, ORR was 70% (14/20; 95% CI, 46–88)



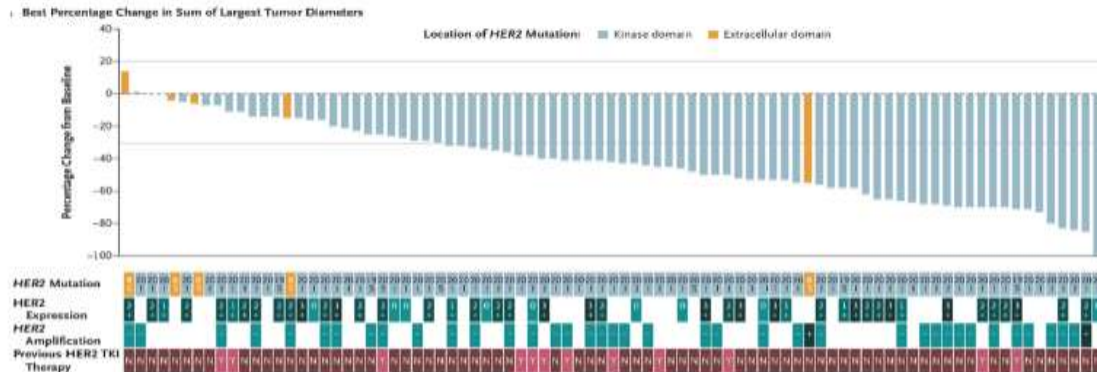
Garassino M, ESMO 2023

Metastatik KHDAAK HER2 Mutasyonunda Tedavi

HER2-mutant NSCLC

DESTINY-Lung 01

- HER2-mutated cohort (N=91):
 - ORR 55% (95% CI, 44–65%)
 - mPFS 8.2 mo (95% CI, 6.0–11.9 mo)
 - mOS 17.8 mo (95% CI, 13.8–22.1 mo)
- Adjudicated drug-related ILD occurred in 26% pts, with 2/91 deaths.



Li B, et al, NEJM 2022

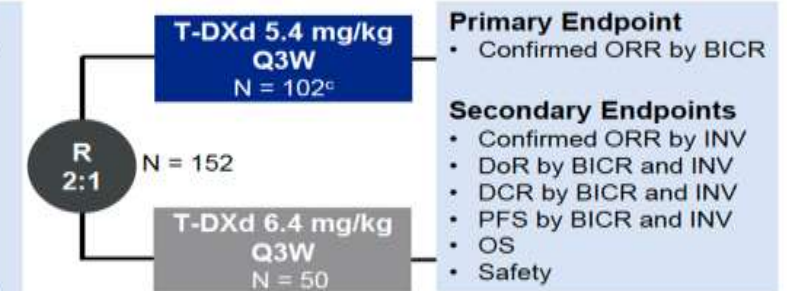
DESTINY-Lung02: Study Design

Key Eligibility Criteria^a

- Metastatic *HER2*^m NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:

- Prior anti-PD-(L)1 treatment



Patients and investigators were blinded to the dose level

Primary analysis data cutoff:
23 December 2022

Janne P, WCLC 2023, Abstract MA13.20

Metastatik KHDAAK HER2 Mutasyonunda Tedavi

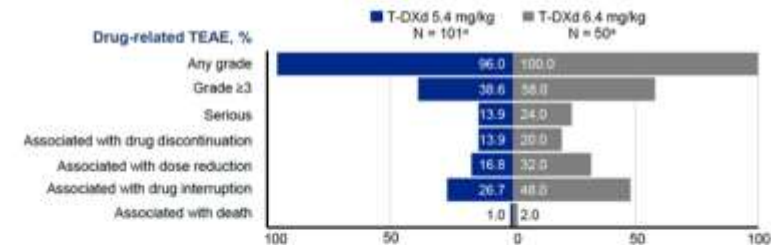
DESTINY-Lung02

Janne P, WCLC 2023, Abstract MA13.20

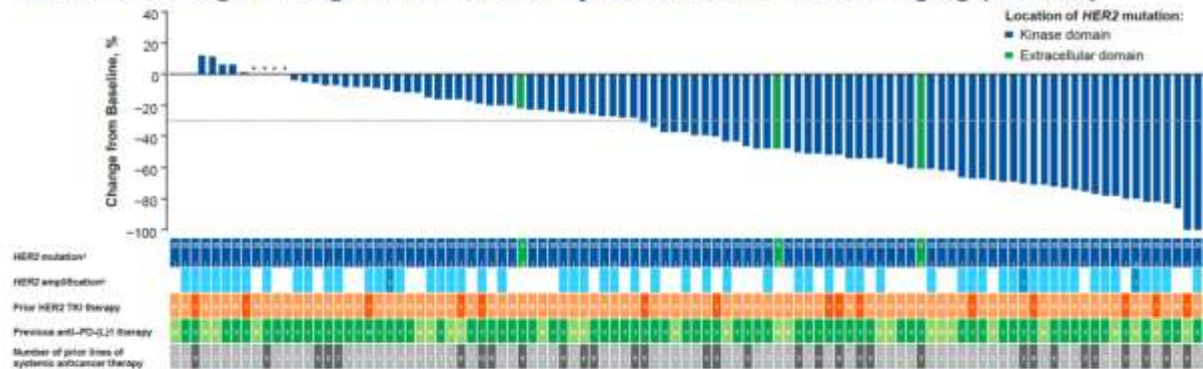
	5.4mg/kg N=102	6.4mg/kg N=50
Conf ORR	49% (39-59.1)	56% (41.3-70)
mDOR	16.8 mo (6.4-NE)	NE (8.3-NE)
Median PFS	9.9 mo (7.4-NE)	15.4 mo (8.3-NE)
Median F/U	11.5 mo	11.8mo



Safety in DL-02



Best Percentage Change in Tumor Size by BICR With T-DXd 5.4 mg/kg (N = 102)



Responses were observed regardless of HER2 mutation type, HER2 amplification status, and number or type of prior therapies

Adjudicated Drug-Related ILD

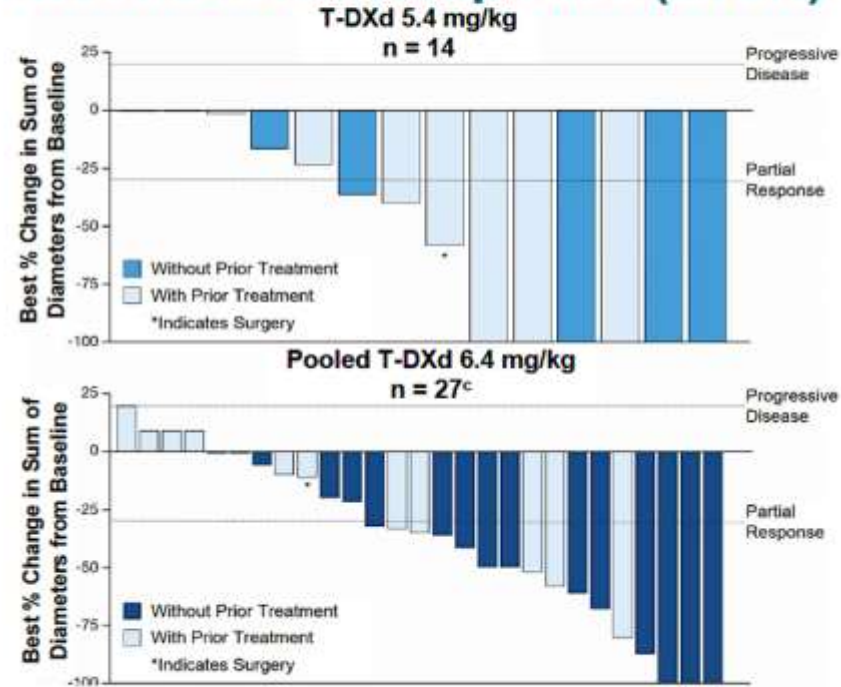
Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101 ^a	T-DXd 6.4 mg/kg N = 50 ^a
Any grade, n (%)	13 (12.9)	14 (28.0)
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

8/11/22: US FDA granted accelerated approval to T-DXd for NSCLC with activating HER2 mutations, who have received a prior systemic therapy. The recommended dose is 5.4mg/kg IV q3 weeks.

Metastatik KHDAAK HER2 Mutasyonunda Tedavi

CNS Outcomes with Trastuzumab Deruxtecan

Best Overall Response (BICR)



Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM n = 14	Pooled T-DXd 6.4 mg/kg DL-01 HER2m/DL-02 BM n = 30
IC-cORR, n (%) ^a	7 (50.0)	9 (30.0)
95% CI ^b	23.0-77.0	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30.0)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE ^c	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%) ^a	13 (92.9)	22 (73.3)
95% CI ^b	66.1-99.8	54.1-87.7
IC-DoR, months ^d		
Median, (95% CI) ^e	9.5 (3.6-NE)	4.4 (2.9-10.2)

	5.4mg/kg (DL02) No prior Rx N=6	Pooled 6.4mg/kg (DL-01/DL-02) No prior Rx N=16
IC -cORR	3/6 (50%)	6/16 (37.5%)
IC- DoR, median	9.5 mo	5.6 mo



MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE^{a,b}

EGFR Exon 19 Deletion or Exon 21 L858R

- First-line therapy
 - Afatinib¹
 - Erlotinib²
 - Dacomitinib³
 - Gefitinib^{4,5}
 - Osimertinib⁶
 - Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous)⁷
 - Erlotinib + ramucirumab⁸
 - Erlotinib + bevacizumab^c (nonsquamous)⁹
- Subsequent therapy
 - Osimertinib¹⁰
 - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)¹¹

EGFR S768I, L861Q, and/or G719X

- First-line therapy
 - Afatinib^{1,12}
 - Erlotinib²
 - Dacomitinib³
 - Gefitinib^{4,5}
 - Osimertinib^{6,13}
- Subsequent therapy
 - Osimertinib¹⁰
 - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)¹¹

EGFR Exon 20 Insertion Mutation

- First-line therapy
 - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)¹⁴
- Subsequent therapy
 - Amivantamab-vmjw¹⁵

KRAS G12C Mutation^d

- Subsequent therapy
 - Sotorasib¹⁶
 - Adagrasib¹⁷

ALK Rearrangement

- First-line therapy
 - Alectinib^{18,19}
 - Brigatinib²⁰
 - Ceritinib²¹
 - Crizotinib^{18,22}
 - Lorlatinib²³
- Subsequent therapy
 - Alectinib^{24,25}
 - Brigatinib²⁶
 - Ceritinib²⁷
 - Lorlatinib²⁸

ROS1 Rearrangement

- First-line therapy
 - Ceritinib²⁹
 - Crizotinib³⁰
 - Entrectinib³¹
 - Repotrectinib³²
- Subsequent therapy
 - Lorlatinib³³
 - Entrectinib³¹
 - Repotrectinib³²

BRAF V600E Mutation

- First-line therapy
 - Dabrafenib/trametinib³⁴
 - Encorafenib/binimetinib³⁵
 - Dabrafenib³⁶
 - Vemurafenib
- Subsequent therapy
 - Dabrafenib/trametinib^{36,37}
 - Encorafenib/binimetinib³⁵

NTRK1/2/3 Gene Fusion

- First-line/Subsequent therapy
 - Larotrectinib³⁸
 - Entrectinib³⁹

MET Exon 14 Skipping Mutation^d

- First-line therapy/Subsequent therapy
 - Capmatinib⁴⁰
 - Crizotinib⁴¹
 - Tepotinib⁴²

RET Rearrangement^d

- First-line therapy/Subsequent therapy
 - Selpercatinib⁴³
 - Pralsetinib⁴⁴
 - Cabozantinib^{45,46}

ERBB2 (HER2) Mutation^d

- Subsequent therapy
 - Fam-trastuzumab deruxtecan-nxki⁴⁷
 - Ado-trastuzumab emtansine⁴⁸

[PD-L1 ≥50% First-line Therapy](#)

[PD-L1 ≥1%–49% First-line Therapy](#)

Sonuç

- ❑ Küçük Hücreli Dışı Akciğer kanseri tedavisine başlamadan önce bakılması gereken mutasyonlar
- ❑ EGFR, ALK, KRAS, ROS1
- ❑ BRAF, NTRK1/2/3, METex14skipping
- ❑ RET alterasyonu, ERBB2 (HER2) mutasyonu
- ❑ PD-L1 düzeyi
- ❑ Driver mutasyonu olanlar genel olarak immüne checkpoint inhibitörlerine iyi yanıt vermezler