Akciğer Kanserinde Hedefe Yönelik Tedavi Seçenekleri

Dr. Deniz Tural

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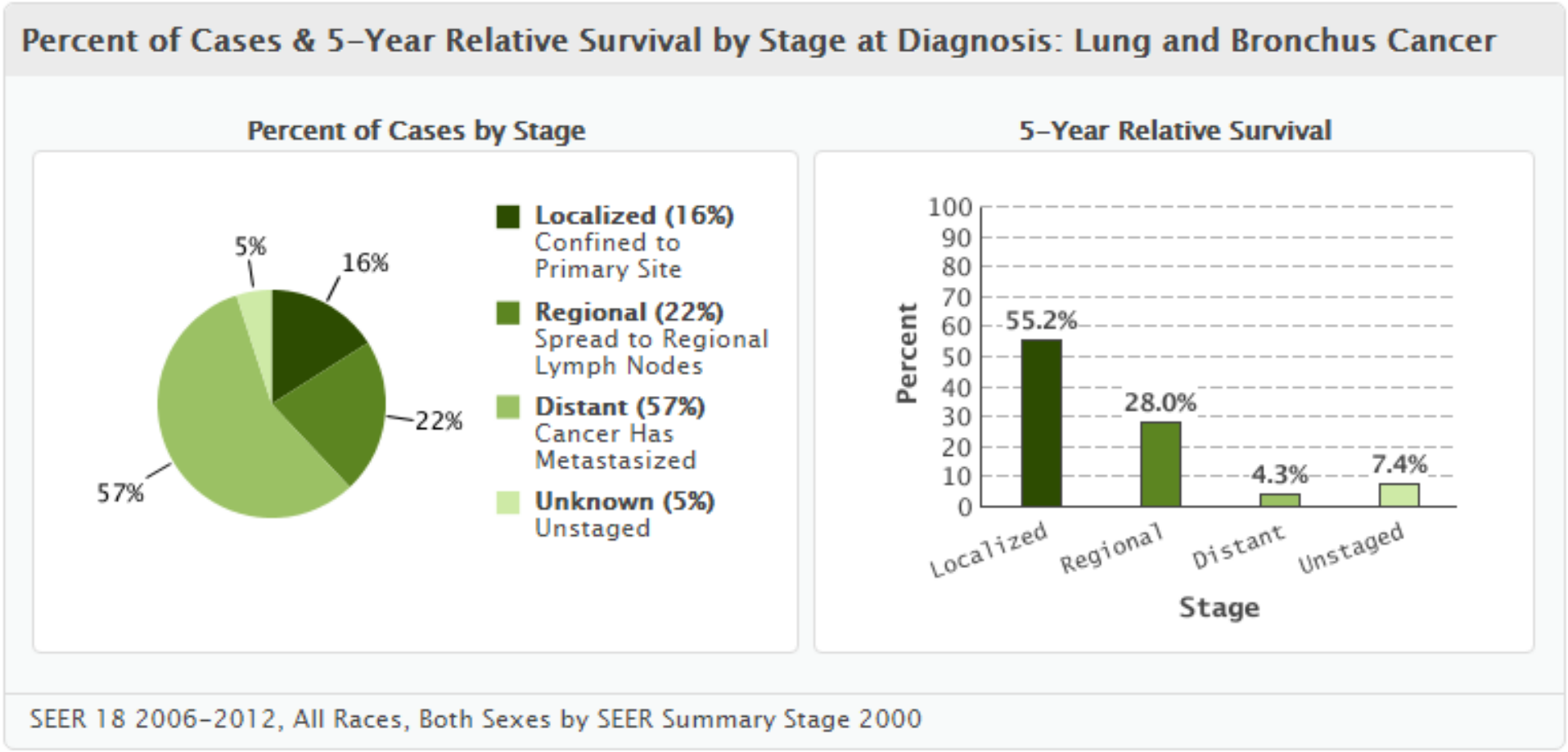
Tıbbi Onkoloji

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**

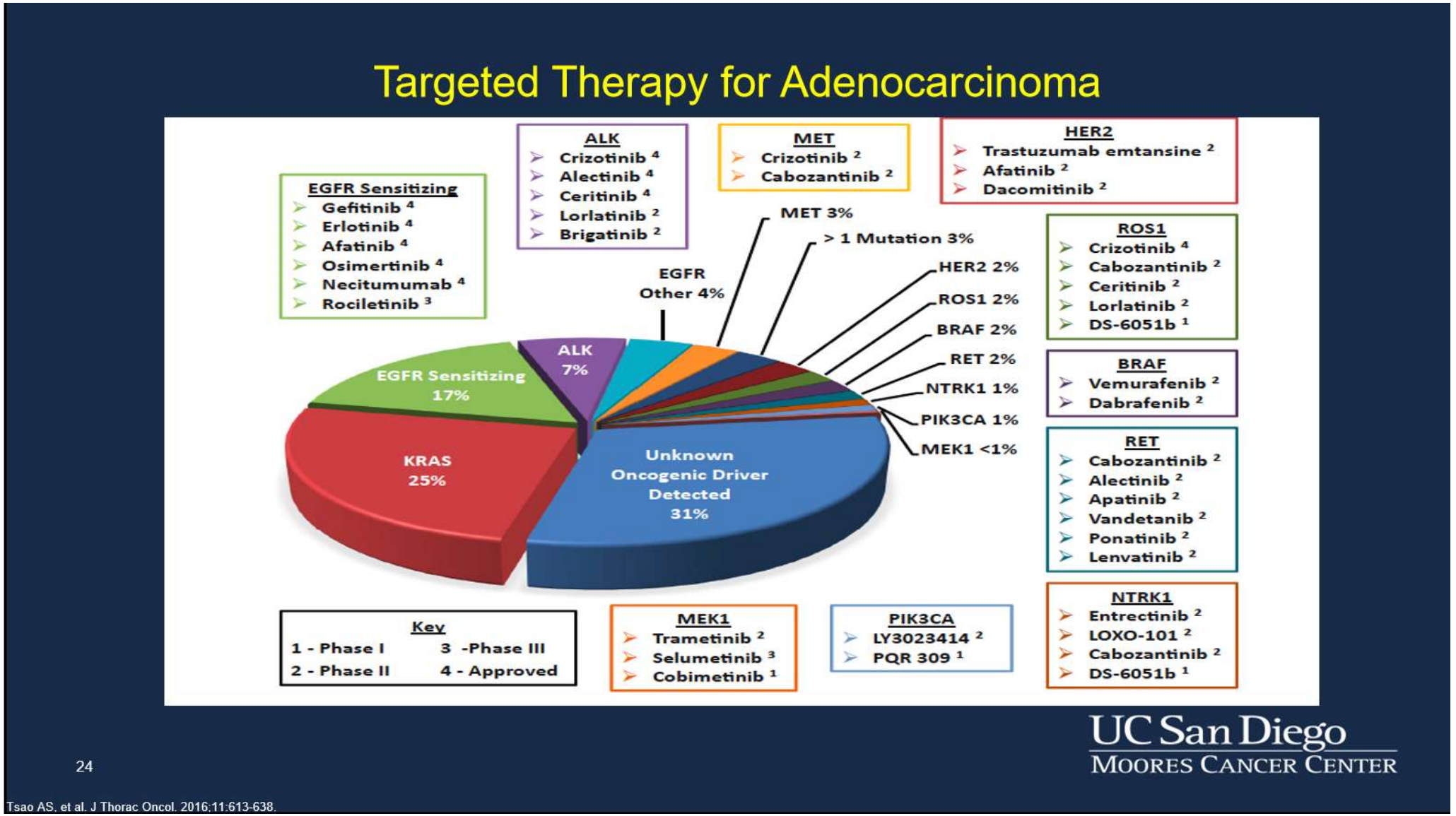
Akciğer Kanserinde İnsidans ve Mortalite



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 KHDAK Hedefe Yönelik Tedaviler



UC San Diego
MOORES CANCER CENTER

Tsao AS, et al. J Thorac Oncol. 2016;11:613-638.

Metastatik KHDAK 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

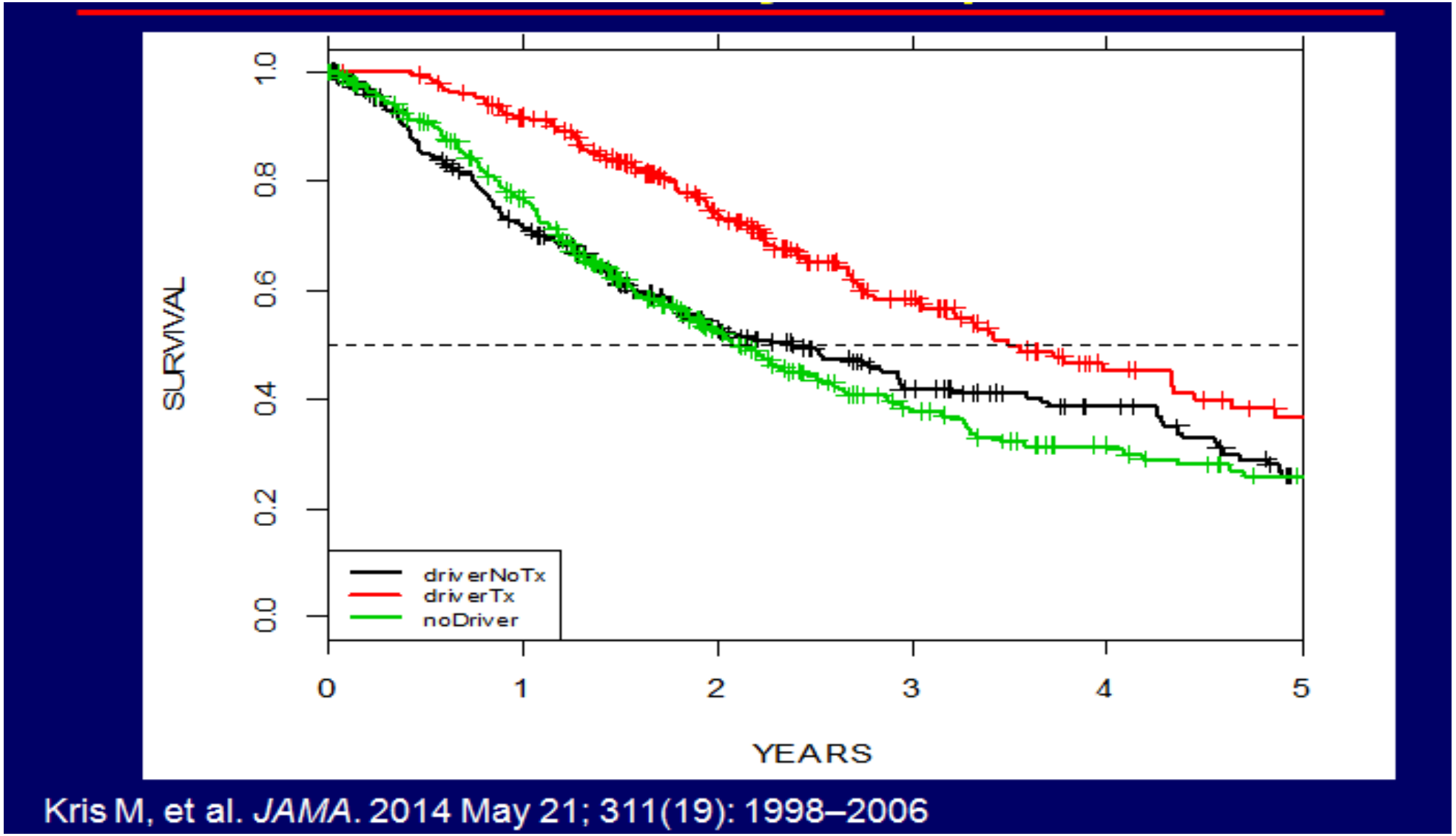
Oncogenic Targets and Testing Methodologies

Target	Testing Methodologies
EGFR mutations*	PCR, NGS
BRAF mutations	PCR, NGS, IHC (extensive validation)
KRAS mutations	PCR, NGS
ALK rearrangements†	FISH,‡ NGS, IHC (screening)
ROS1 rearrangements†	FISH,‡ NGS, IHC (screening)
RET rearrangements†	FISH,‡ NGS
*MET*ex14 skipping mutations	NGS
NTRK rearrangements†	FISH,‡ NGS, IHC
MET amplifications	FISH, NGS
HER 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.

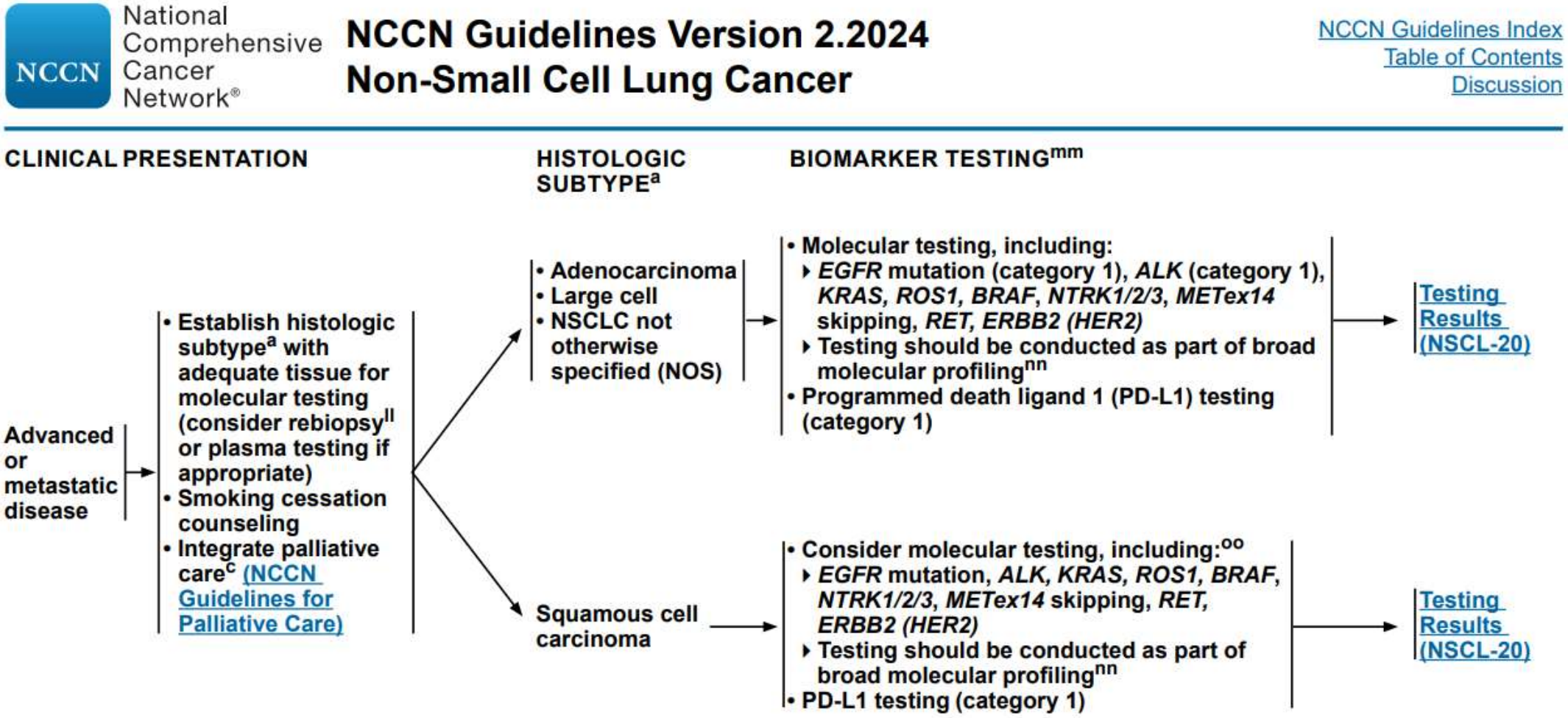
- Clinical guidelines strongly recommend broad molecular profiling to identify rare driver mutations for which effective drugs may be available, or to appropriately counsel patients about available clinical trials
- Broad molecular profiling is a key component of the improvement of care of patients with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

Metastatik KHDAK Hedefe Yönelik Tedaviler



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

Histoloji ve Genomik Özeliklere Göre Tedavi



Histoloji ve Genomik Özeliklere Göre Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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TESTING RESULTS[ll,mm]

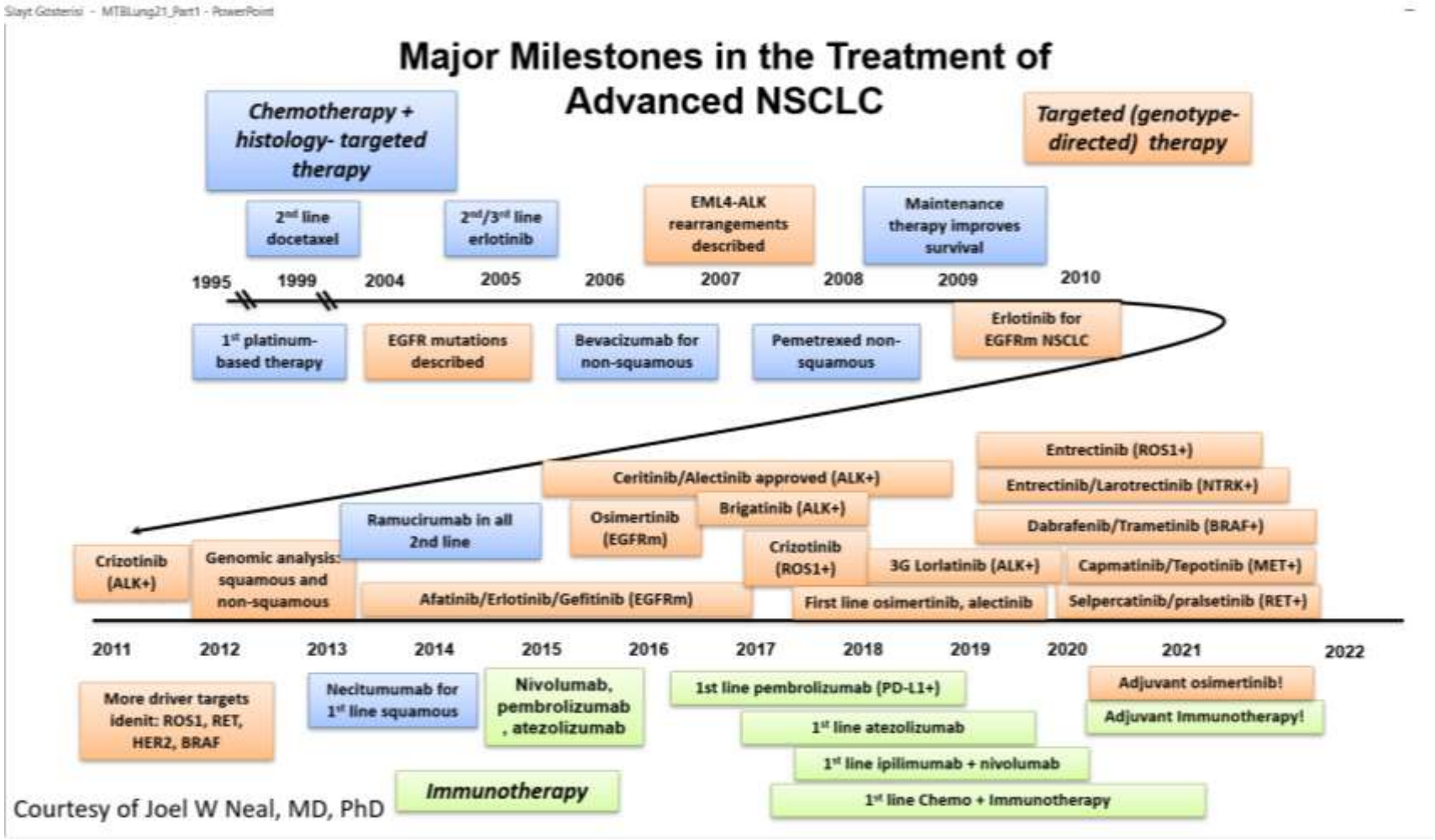
EGFR **exon 19 deletion or exon 21 L858R mutation positive**	NSCL-21
EGFR **S768I, L861Q, and/or G719X mutation positive**	NSCL-24
EGFR **exon 20 insertion mutation positive**	NSCL-25
KRAS **G12C mutation positive**	NSCL-26
ALK **rearrangement positive**	NSCL-27
ROS1 **rearrangement positive**	NSCL-30
BRAF **V600E mutation positive**	NSCL-32
NTRK1/2/3 **gene fusion positive**	NSCL-33
METex14 **skipping mutation positive**	NSCL-34
RET **rearrangement positive**	NSCL-35
ERBB2 (HER2) **mutation positive**	NSCL-36
PD-L1 ≥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

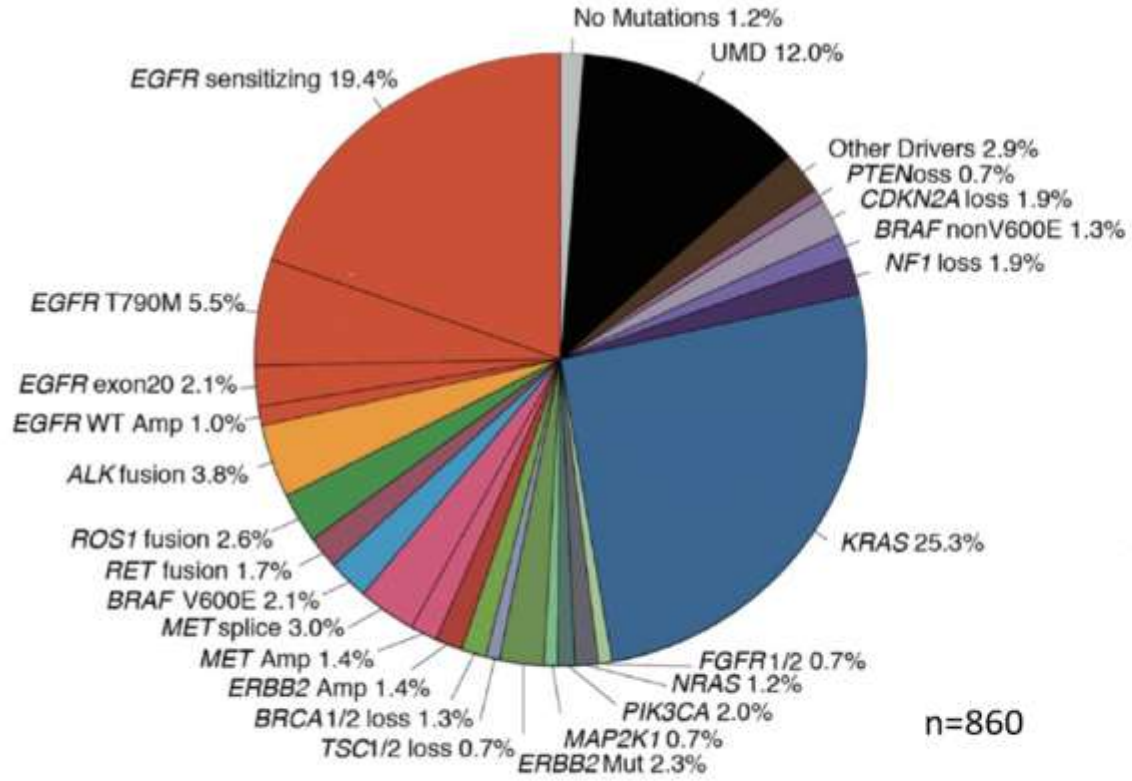
Metastatik KHDAK Tedavi Süreci



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%

Courtesy of Marc Ladanyi, MD

Jordan EJ et al. *Cancer Discovery* 2017

Metastatik KHDAK Hedefe Yönelik Tedaviler

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

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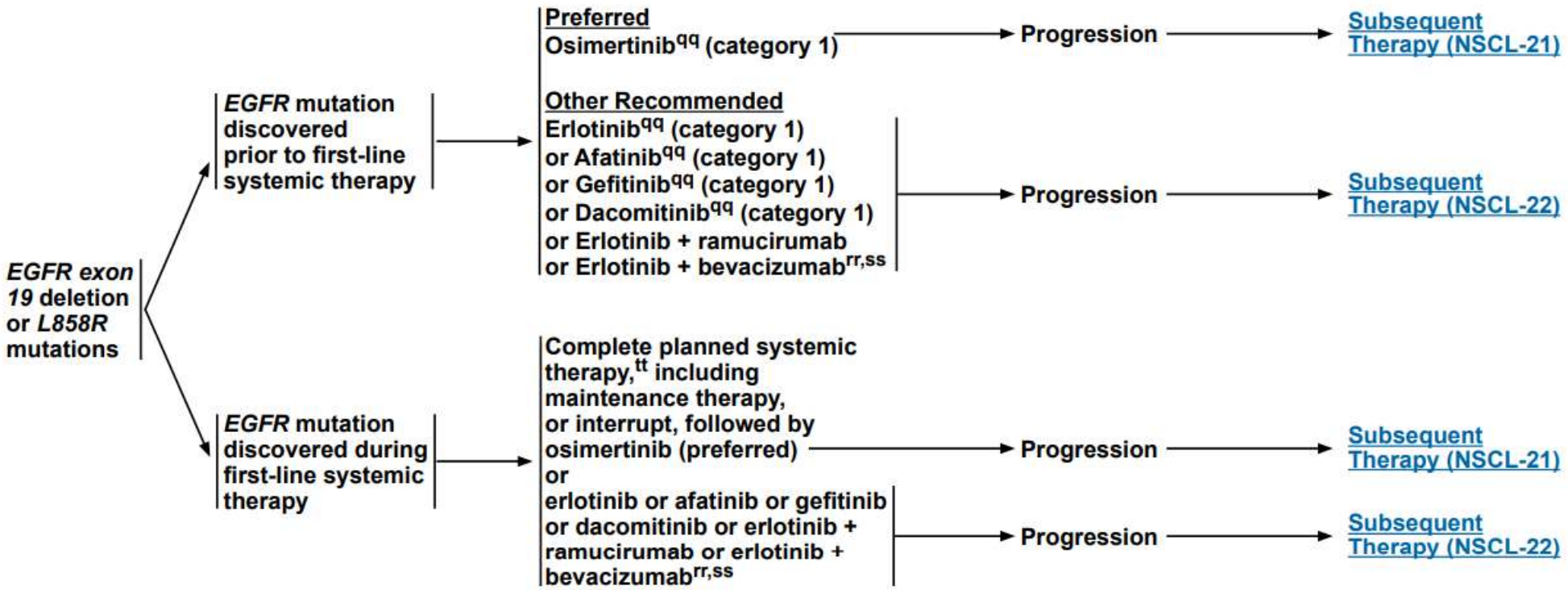
***EGFR EXON 19* DELETION OR *L858R* MUTATIONS[mm]**

FIRST-LINE THERAPY[pp]



Metastatik KHDAK Hedefe Yönelik Tedaviler

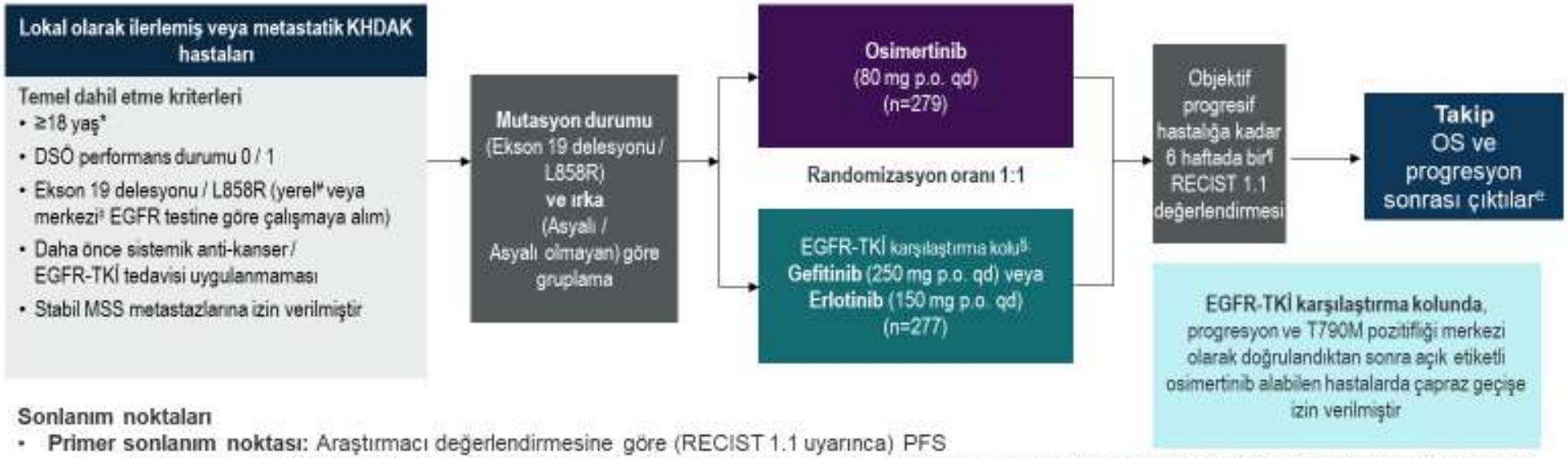
Front-line EGFR mutant NSCLC

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

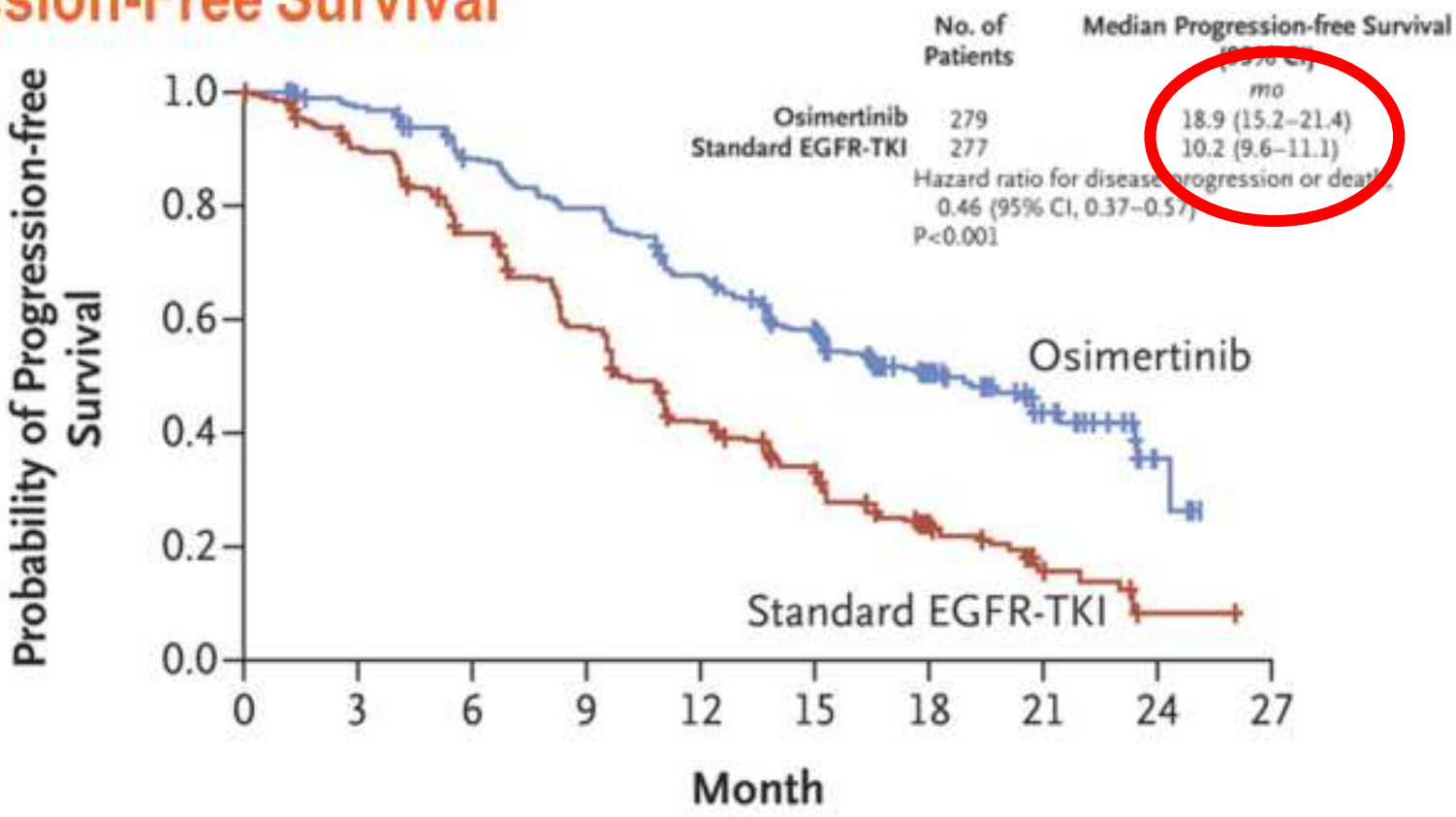
- **Primer sonlanım noktası:** Araştırmacı değerlendirmesine göre (RECIST 1.1 uyarınca) PFS
  - Çalışmanın, %5 iki yönlü alfa düzeyinde 0,71 değerindeki tehlike oranını (10. aydan 14,1. aya kadar medyan PFS'de %29 iyileşmeyi temsil eder) saptama gücü %90'dır
- **Sekonder sonlanım noktaları:** Objektif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

FLAURA veri kesme tarihi: 12 Haziran 2017; NCT02296125
*Japonya'da ≥20 yaş. ¶Duyarlılık için gerçekleştirilen merkezi laboratuvar değerlendirmesine göre; †cobas EGFR Mutasyon Testi (Roche Molecular Systems); §Merkezde çalışma başlamadan önce merkezler tek komparatör olarak gefitinib veya erlotinibi seçmiştir; ¶18 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; TKİ, tirozin kinaz inhibitörü; DSÖ, Dünya Sağlık Örgütü

1. Soria J-C et al. Article and supplementary appendix. *N Engl J Med* 2018;378:113-125. 2. Planchard D et al. Presented at: European Lung Cancer Congress; 11-14 April 2018; 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

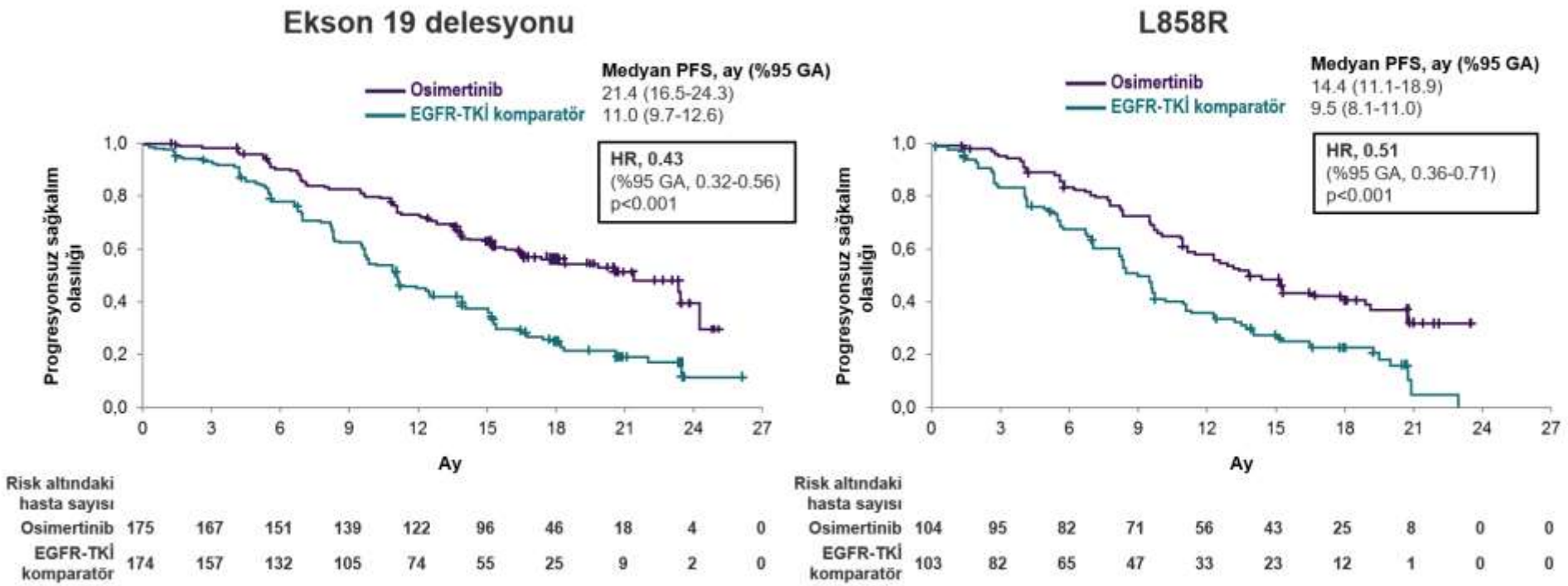
Osimertinib vs Gefitinib/Erlotinib as first treatment for NSCLC
Progression-Free Survival



Soria et al, NEJM 2017

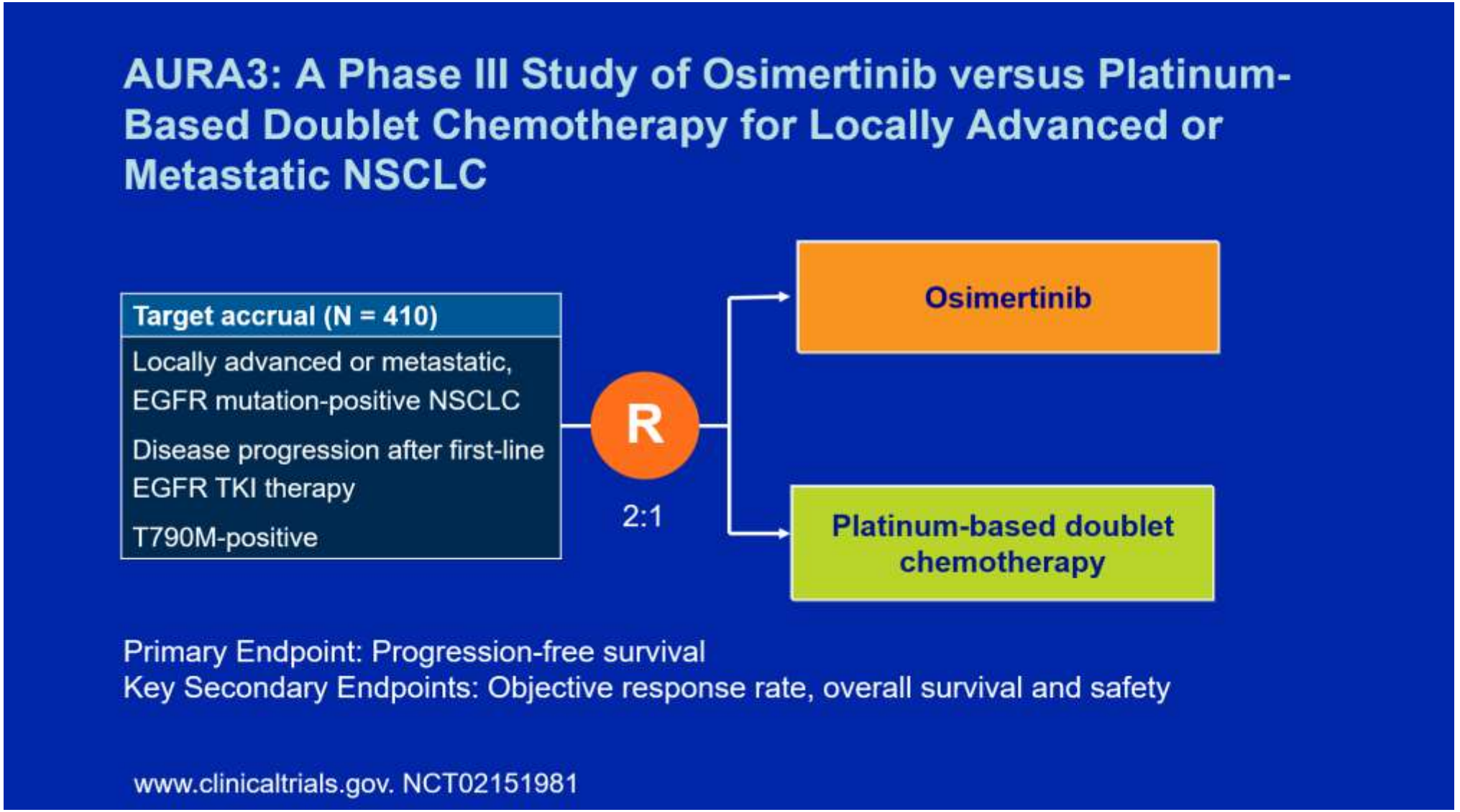
Metastatik KHDAK EGFR Mutasyonunda Tedavi

FLAURA: TAK'de EGFR mutasyon durumuna göre PFS



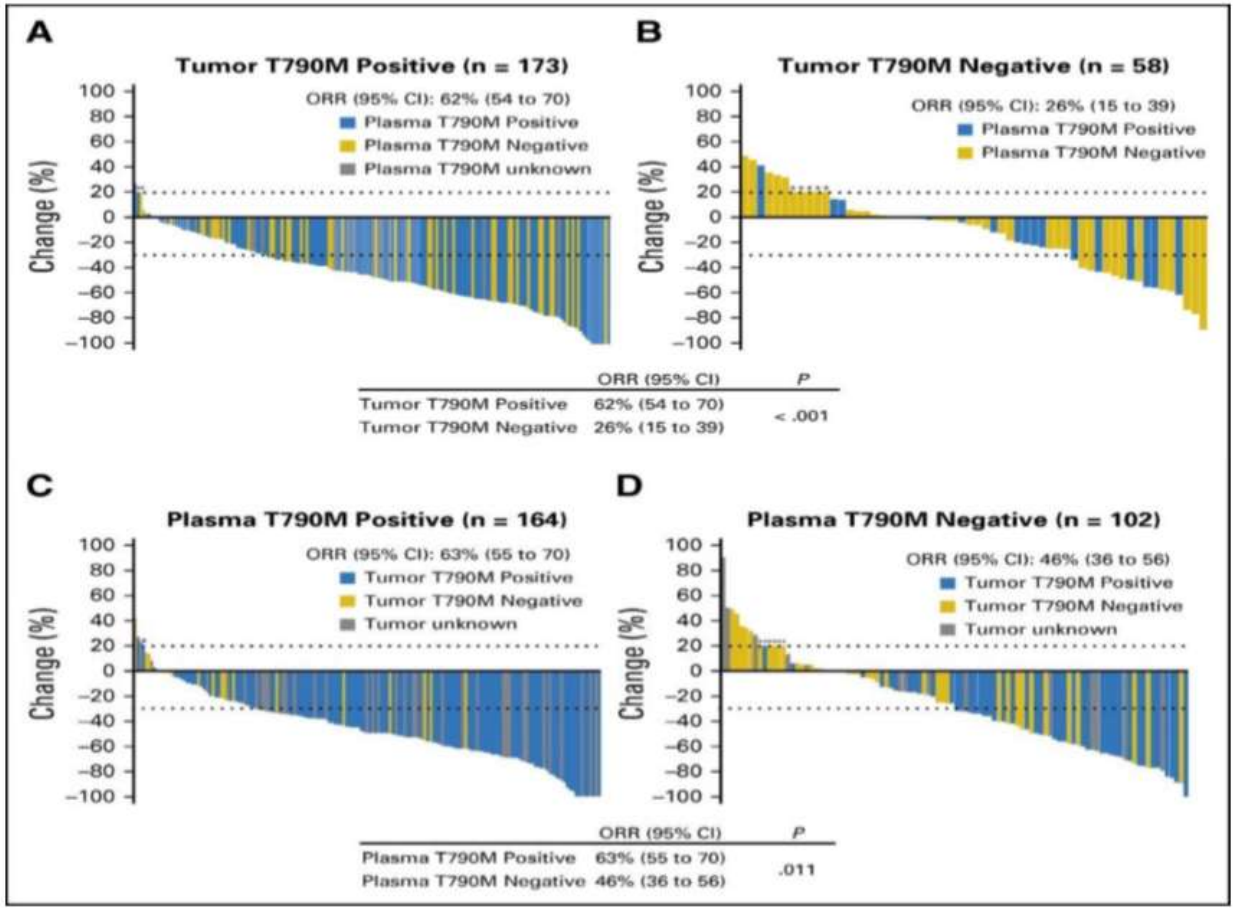
FLAURA veri kesme noktası: 12 Haziran 2017.
Çentik işaretleri sansürlenmiş verileri göstermektedir.
EGFR = epidermal büyüme faktörü reseptörü; TAK = tam analiz kümesi; HR, tehlike oranı; PFS, progresyonsuz sağkalım; TKİ, tirozin kinaz inhibitörü.
1. Soria J-C et al. Article and supplementary appendix. N Engl J Med. 2018;378:113-125.

Metastatik KHDAK EGFR Mutasyonunda Tedavi



Metastatik KHDAK EGFR Mutasyonunda Tedavi

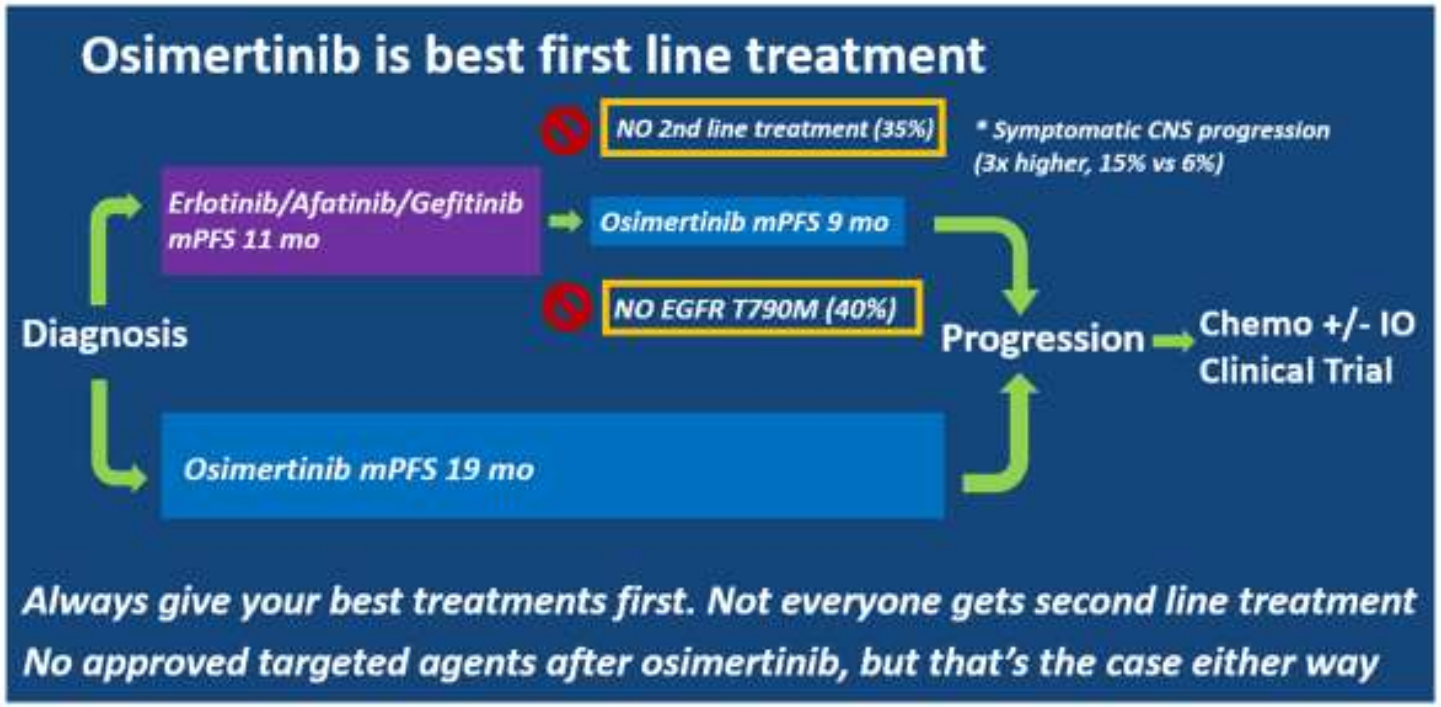
Response to osimertinib based on plasma/tissue T790M detection



Oxnard GR et al. J Clin Oncol 2016

Metastatik KHDAK EGFR Mutasyonunda Tedavi

Osimertinib as best in class EGFR TKI



Memorial Sloan Kettering Cancer Center

Courtesy of Helena Yu, MD

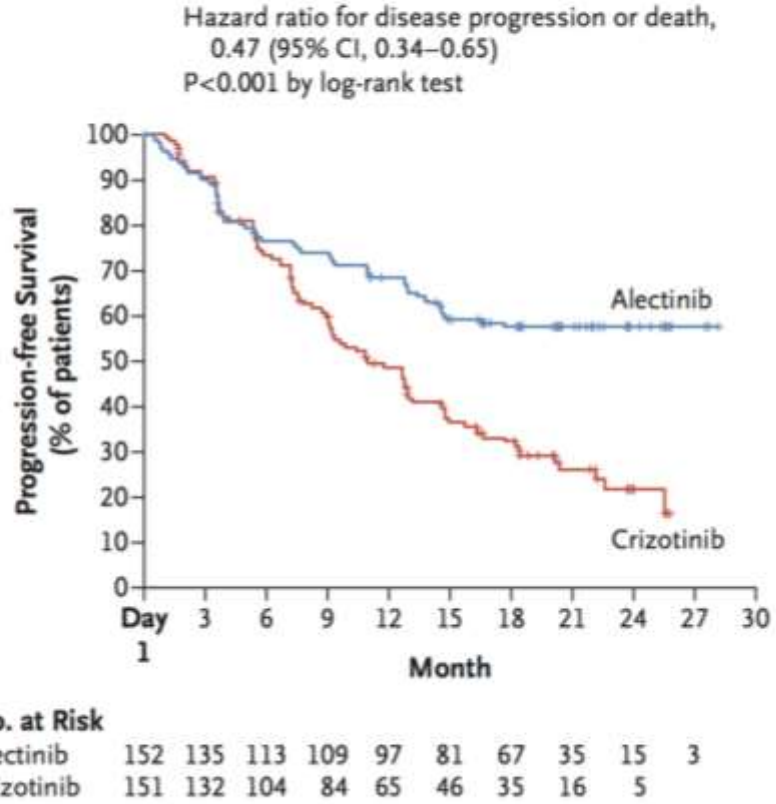
Metastatik KHDAK ALK Alterasyonunda Tedavi

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 Zeaiter, 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*

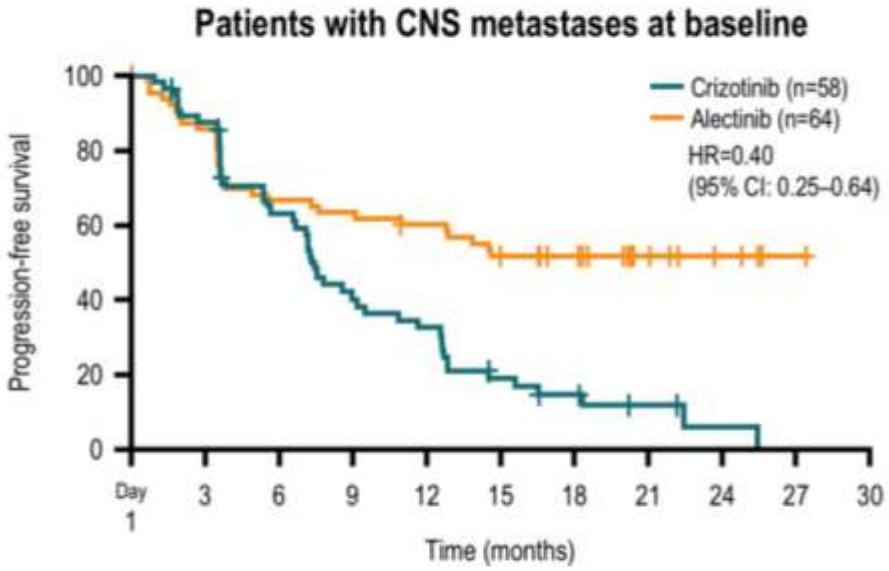


Courtesy of Solange Peters, MD, PhD

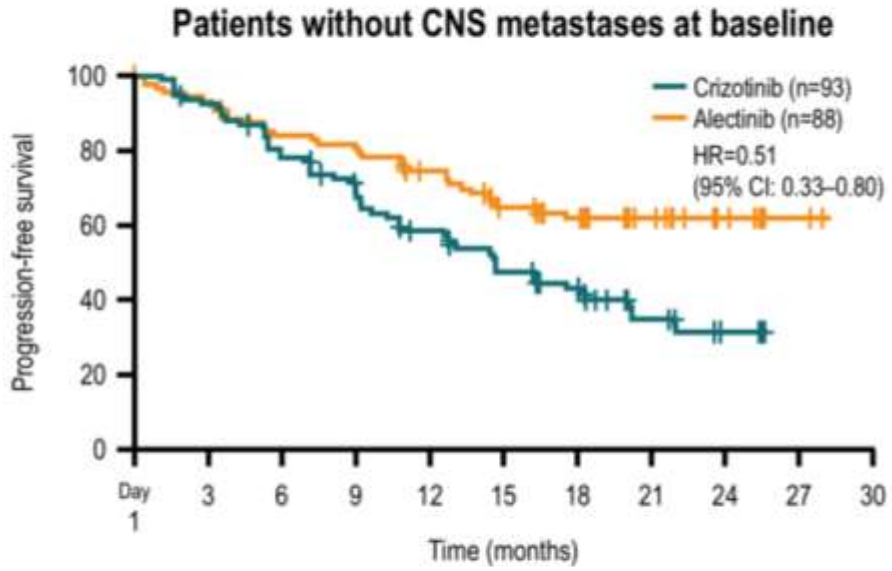
Peters S, et al. *N Engl J Med* 2017;377:829-38.

Metastatik KHDAK 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	1



Patients at risk										
Crizotinib	93	84	71	62	48	37	29	13	4	
Alectinib	88	81	72	70	61	50	43	25	11	2

Courtesy of Solange Peters, MD, PhD

Peters S, et al. *N Engl J Med* 2017;377:829-38.

Metastatik KHDAK ALK Alterasyonunda Tedavi

ALTA-1L trial: PFS by independent review

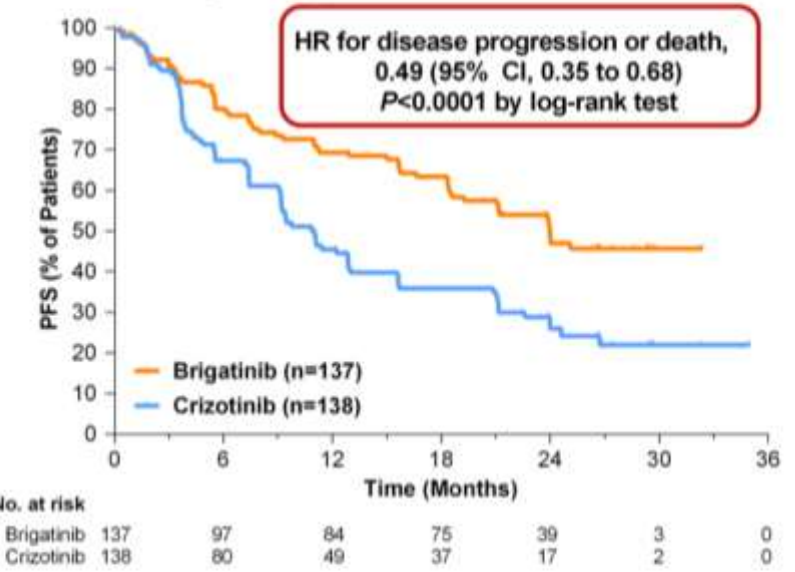
ORIGINAL ARTICLE

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 our without prior chemotherapy
- Independent radiological review
- Interim analysis

Primary Endpoint: BIRC-Assessed PFS



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)

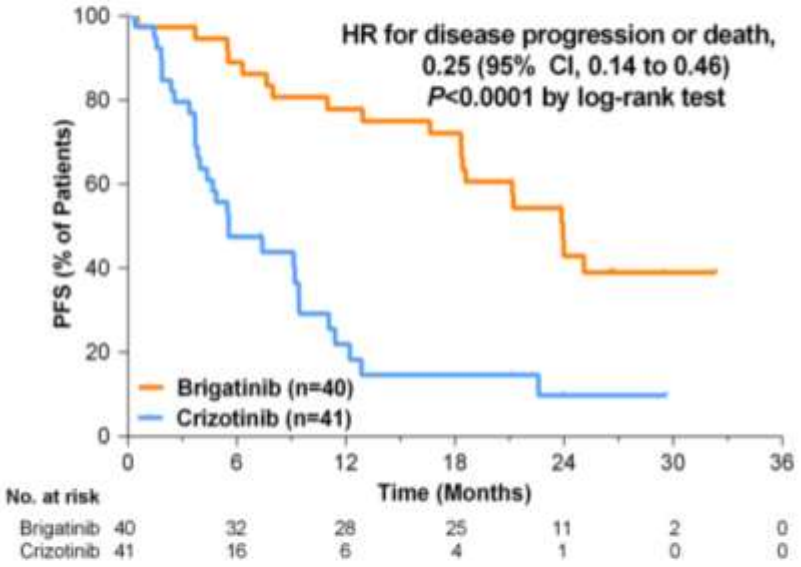
Courtesy of Solange Peters, MD, PhD

Camidge, NEJM 2018; ESMO Asia 2019

Metastatik KHDAK ALK Alterasyonunda Tedavi

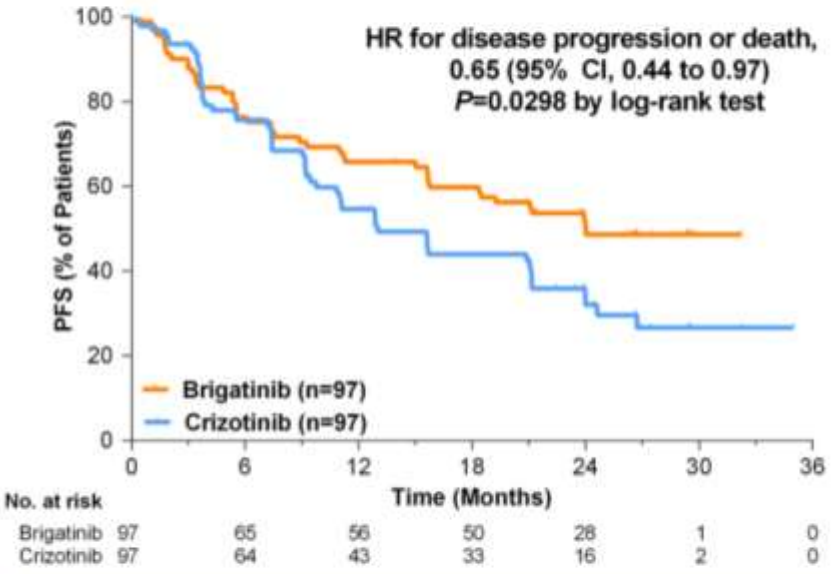
ALTA-1L: PFS with/without brain metastasis

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



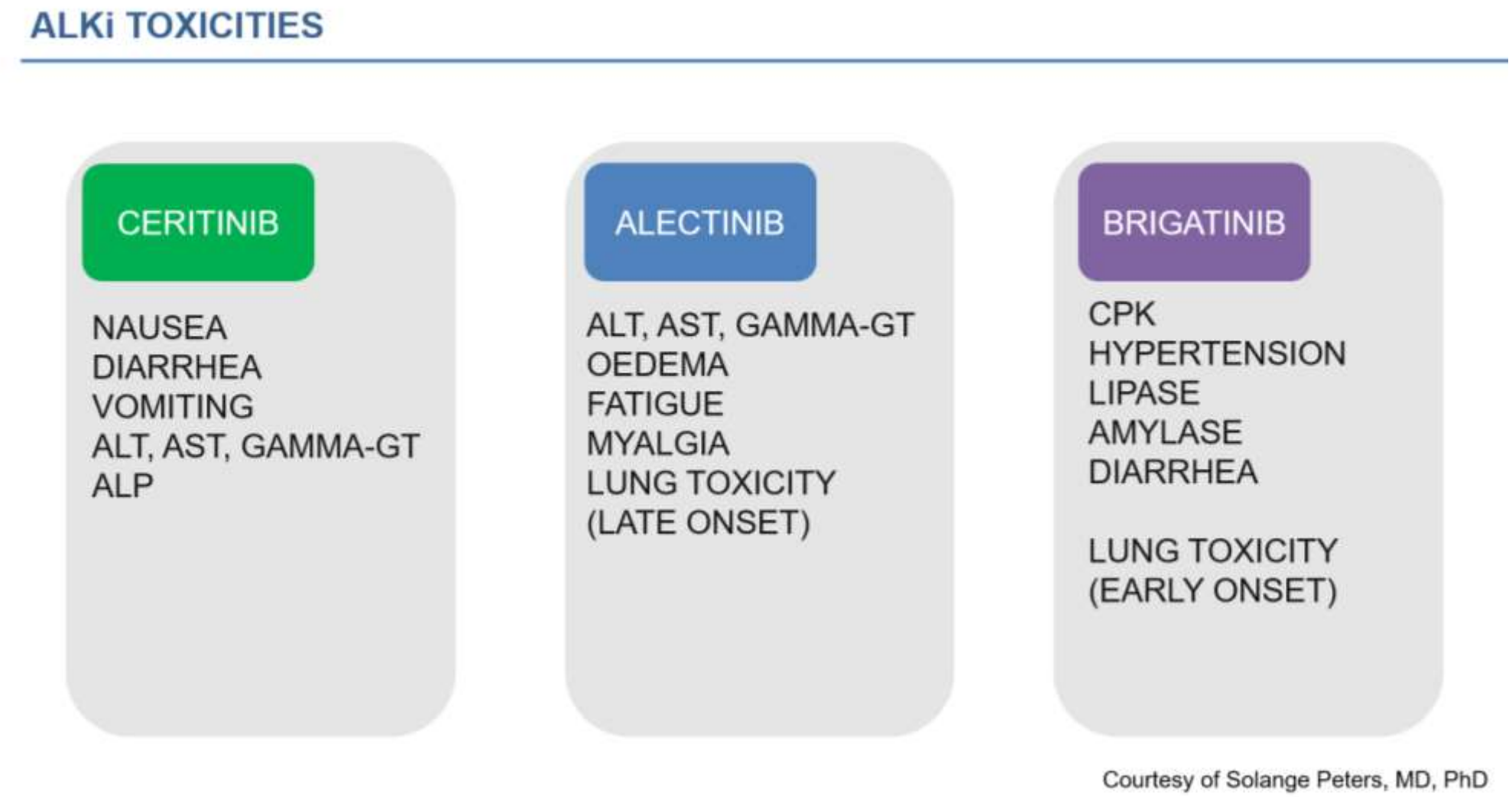
Treatment	No. (%) Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=97)[a]	43 (44)	24.0 mo (15.7–NR)	50 (39–61)
Crizotinib (n=97)[a]	57 (59)	13.0 mo (9.5–21.1)	32 (22–43)

[a] Per investigator assessment

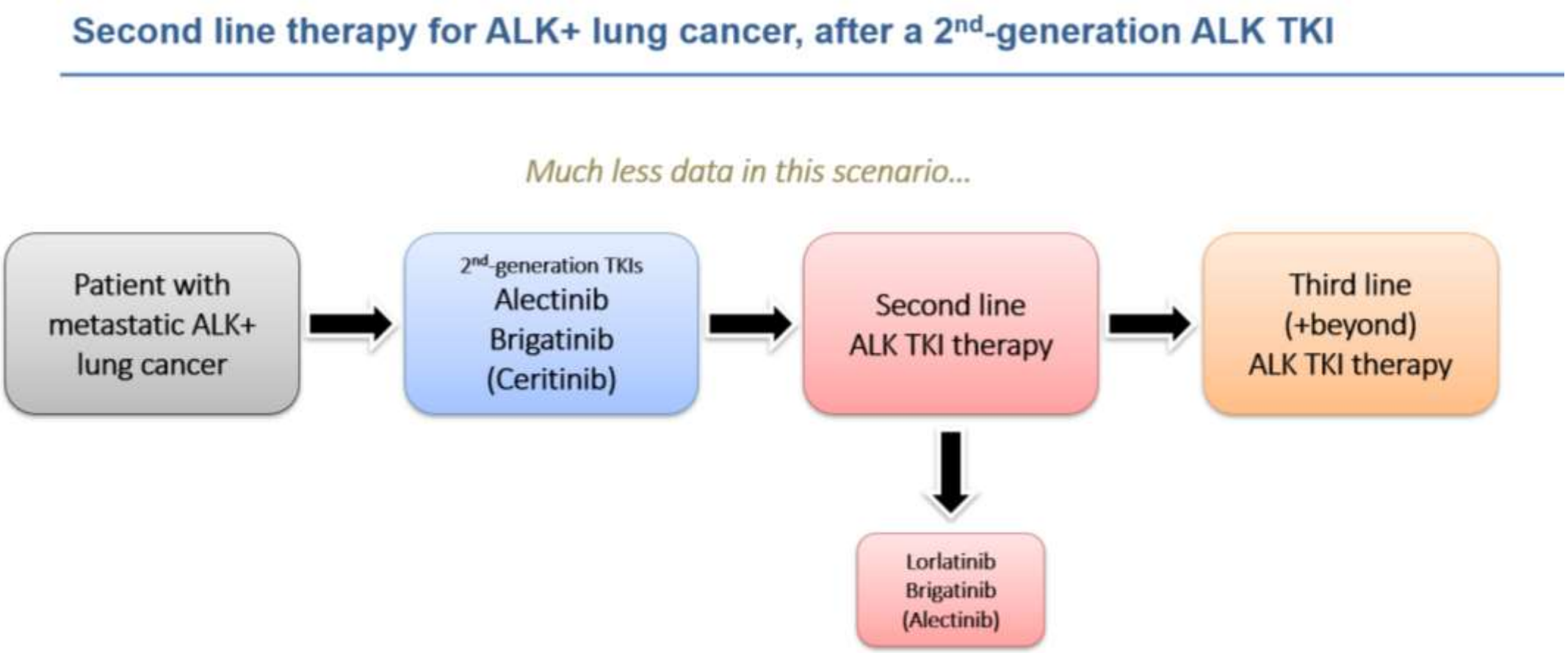
Courtesy of Solange Peters, MD, PhD

Camidge, ESMO Asia 2019.

Metastatik KHDAK ALK Alterasyonunda Tedavi



Metastatik KHDAK ALK Alterasyonunda Tedavi



Modified from Lovly, AACR 2018

Courtesy of Solange Peters, MD, PhD

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 KHDAK ALK Alterasyonunda Tedavi

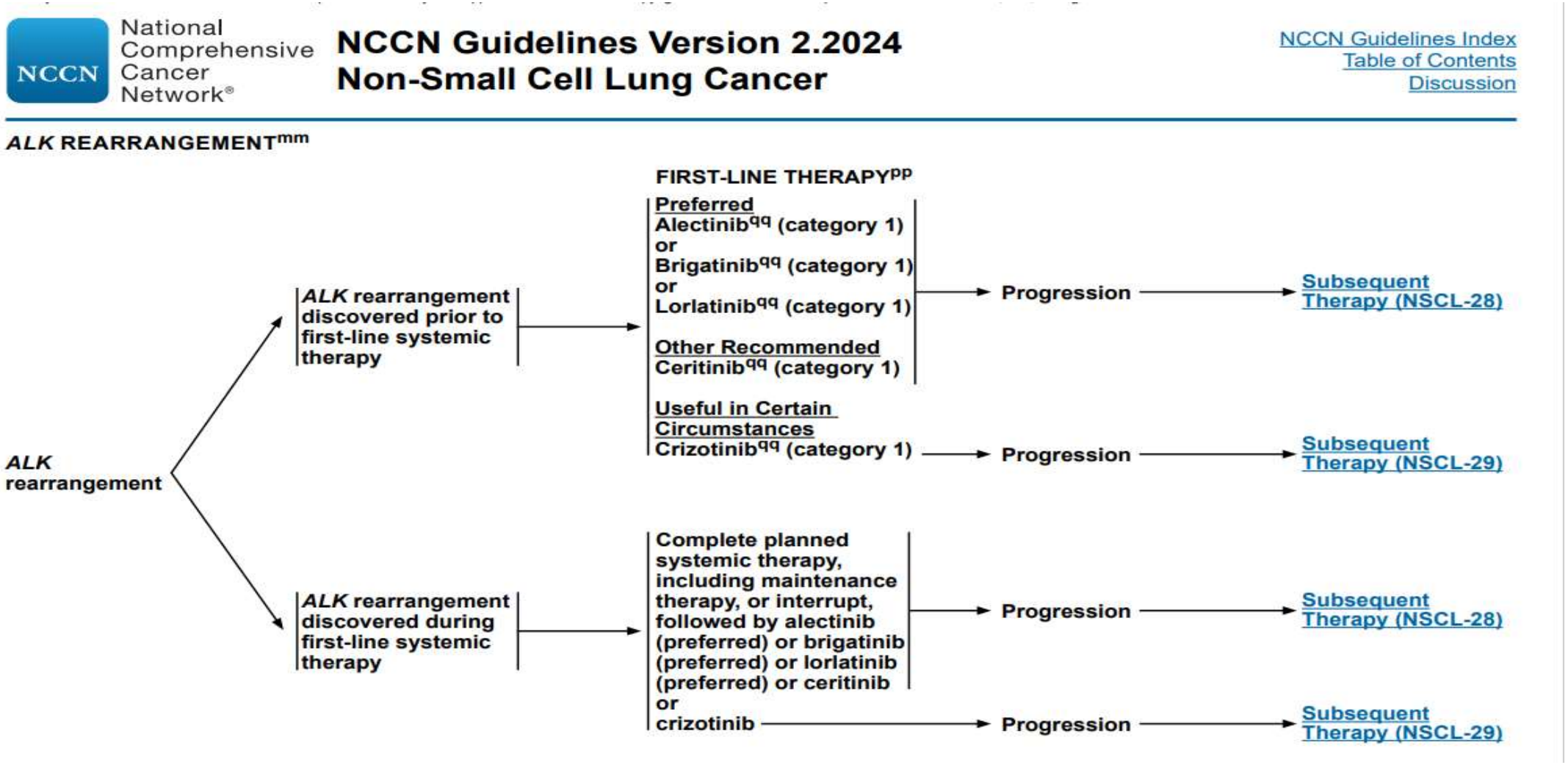
Mutation Coverage for ALK Inhibitors

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
1151Tins	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.

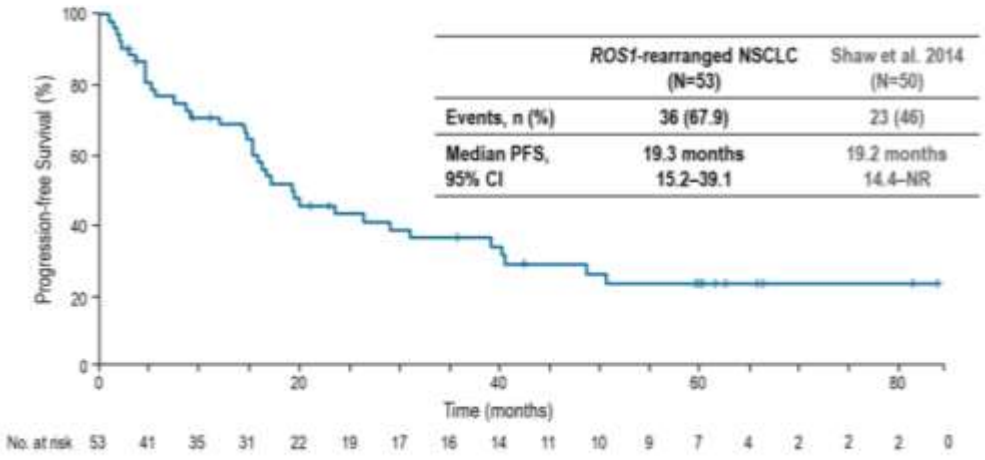
Metastatik KHDAK ALK Alterasyonunda Tedavi



Metastatik KHDAK ROS1 Alterasyonunda Tedavi

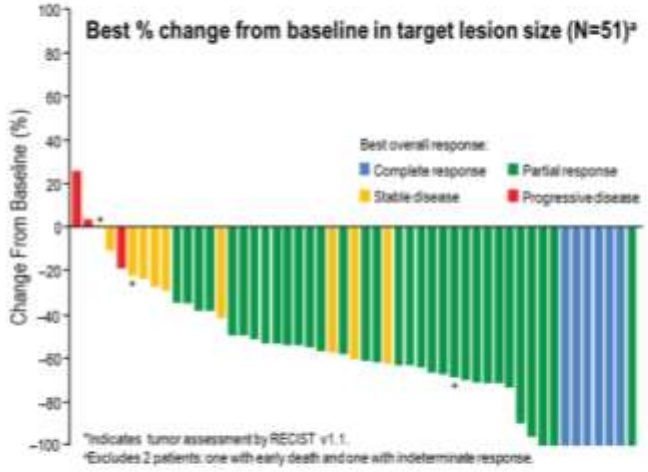
Focusing on ROS-1: Crizotinib

UPDATED PROGRESSION-FREE SURVIVAL



	ROS1-rearranged NSCLC (N=53)	Shaw et al. 2014 (N=50)
Events, n (%)	36 (67.9)	23 (46)
Median PFS, 95% CI	19.3 months 15.2–39.1	19.2 months 14.4–NR

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[a]	2 (3.8)	2 (4)
ORR, %	71.7	72
95% CI	57.7–83.2	58–84
Median TTR, wks	7.9	7.9
Range	4.3–103.6	4.3–32.0
Median DOR[b], mos	24.7	17.6
95% CI	15.2–45.3	14.5–NR

[a]Responses could not be evaluated in 2 patients because of early death or indeterminate response.
[b]Estimated using the Kaplan-Meier method.

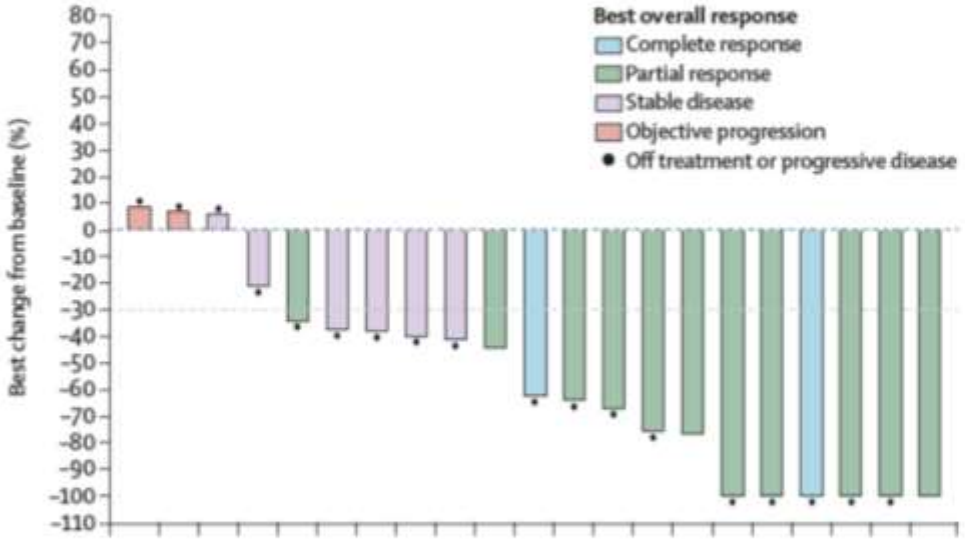
Courtesy of Solange Peters, MD, PhD

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

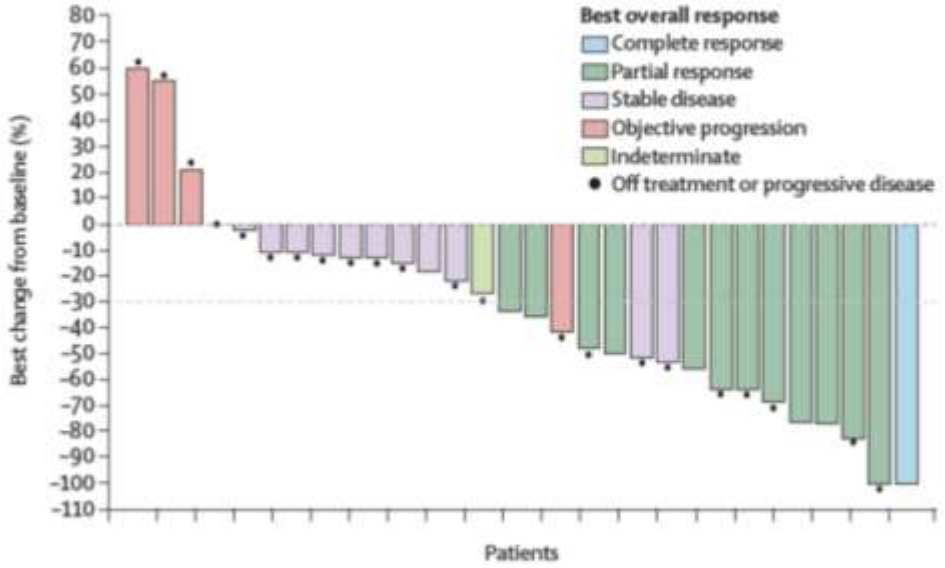
ROS1-TKI naïve pts (n=21)



ORR, %: 62 (38–82)

mDoR, month: 25.3 (7.5–31.9)

Crizotinib pretreated pts (n=40)



ORR: 35% (21-52)

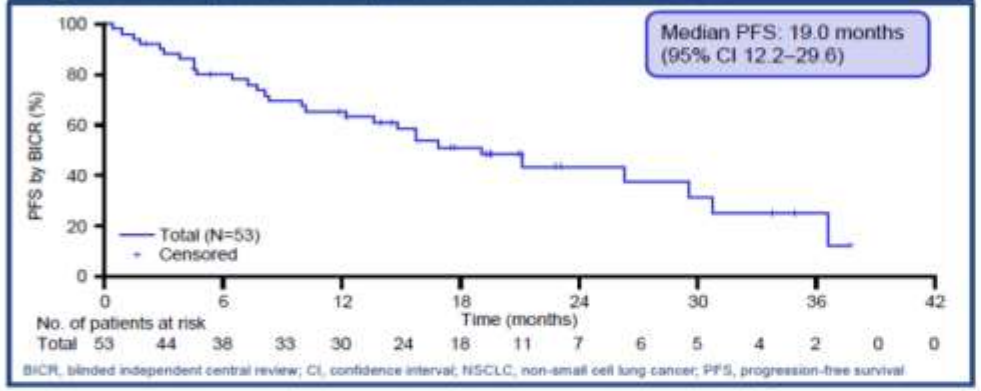
mDoR, month: 13.8 (9.7–NR)

Shaw et al 2020 Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1–2 trial Lancet Oncol. 2019 Dec;20(12):1691-1701. doi: 10.1016/S1470-2045(19)30655-2. Epub 2019 Oct 25.

Metastatik KHDAK ROS1 Alterasyonunda Tedavi

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

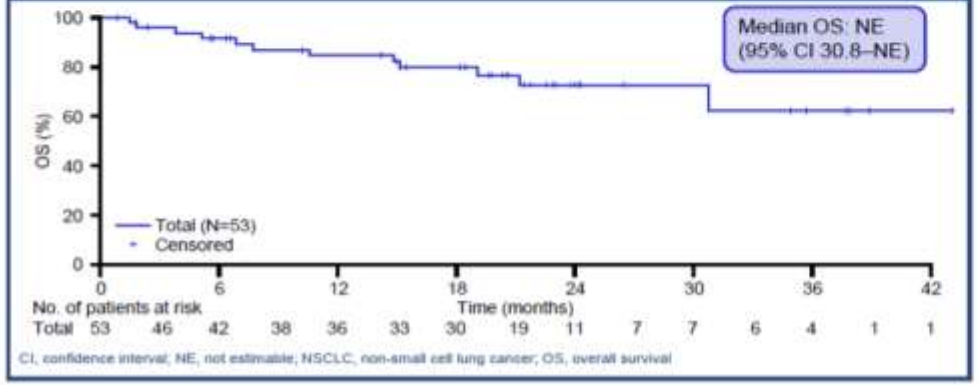
Figure 2. PFS per BICR in patients with *ROS1+* NSCLC



BICR, blinded independent central review; CI, confidence interval; NSCLC, non-small cell lung cancer; PFS, progression-free survival

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



CI, confidence interval; NE, not estimable; NSCLC, non-small cell lung cancer; OS, overall survival

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

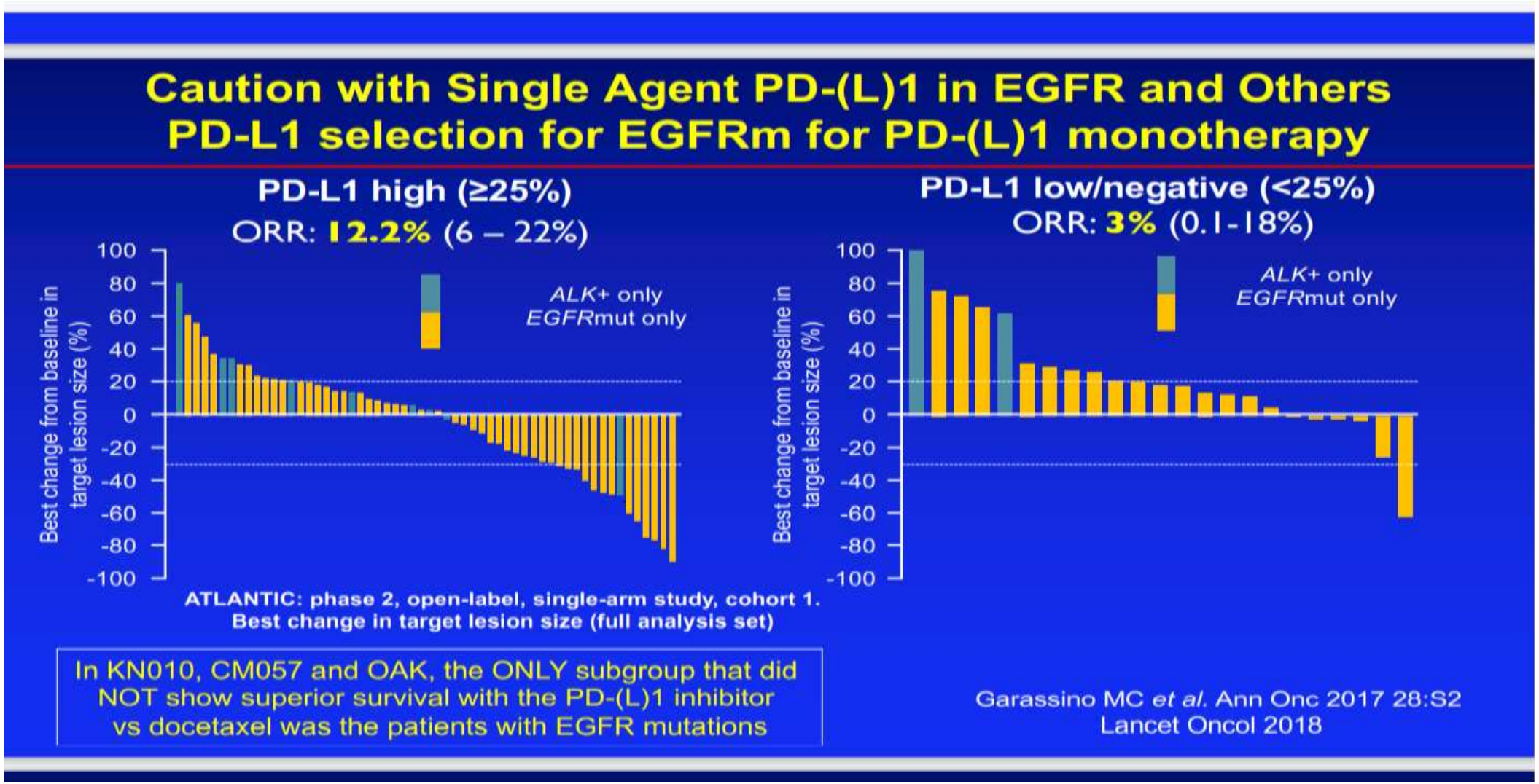
Responders, n (%)	*ROS1+* NSCLC with baseline CNS disease (n=20)
ORR, % (95% CI)	55.0 (31.5–76.9)
Complete response	4 (20.0)
Partial response	7 (35.0)
Stable disease	0
Progressive disease	3 (15.0)
Non complete/partial response	4 (20.0)
Missing/unevaluable	2 (10.0)

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

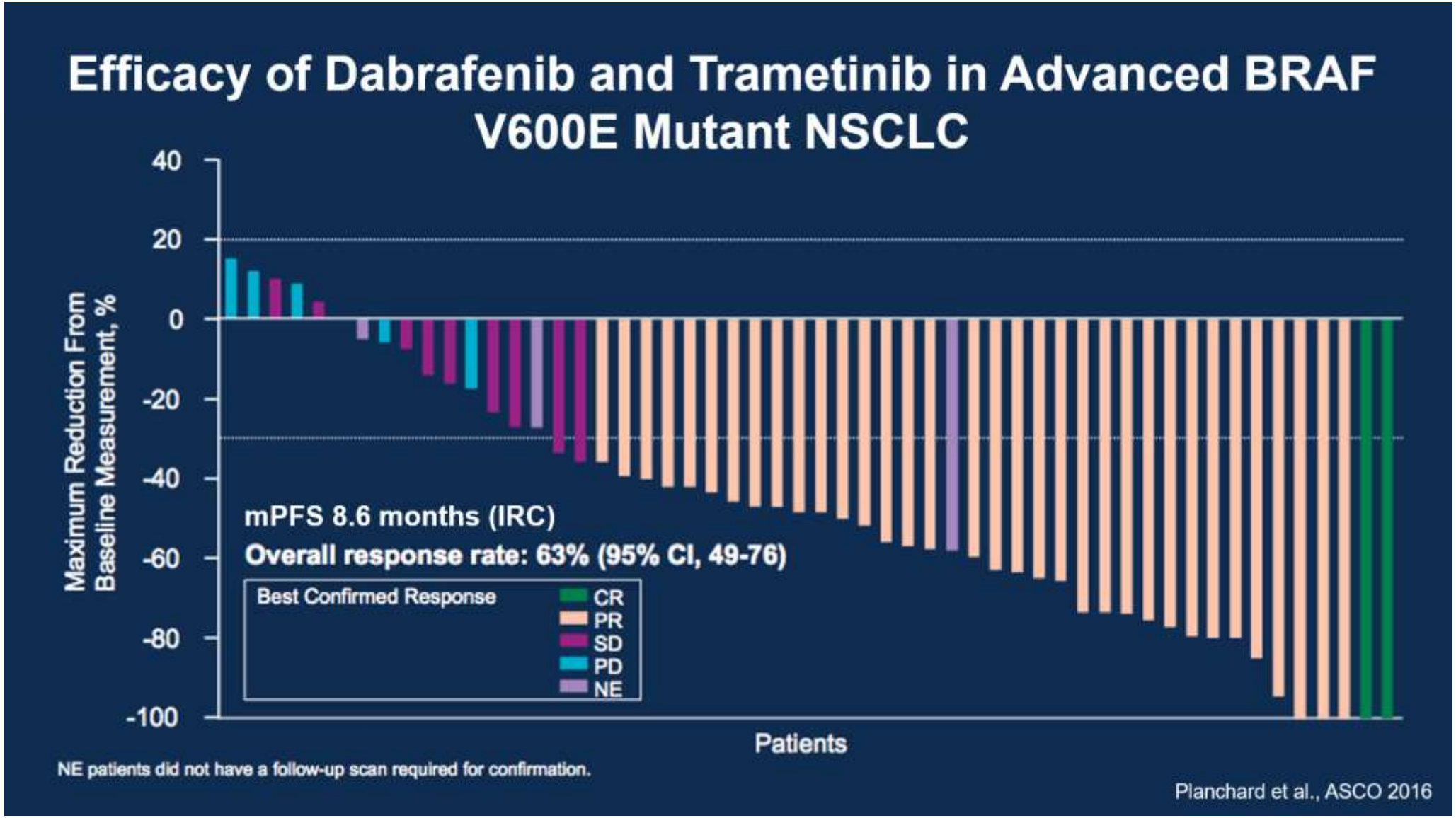
De Braud, ESMO 2019;Abstract 4178.

Courtesy of Solange Peters, MD, PhD

Driver mutasyonu olanlarda immüne Checkpoint inhibitörlerine yanıt iyi değil



Metastatik KHDAK BRAF Mutasyonunda Tedavi



Metastatik KHDAK BRAF Mutasyonunda Tedavi

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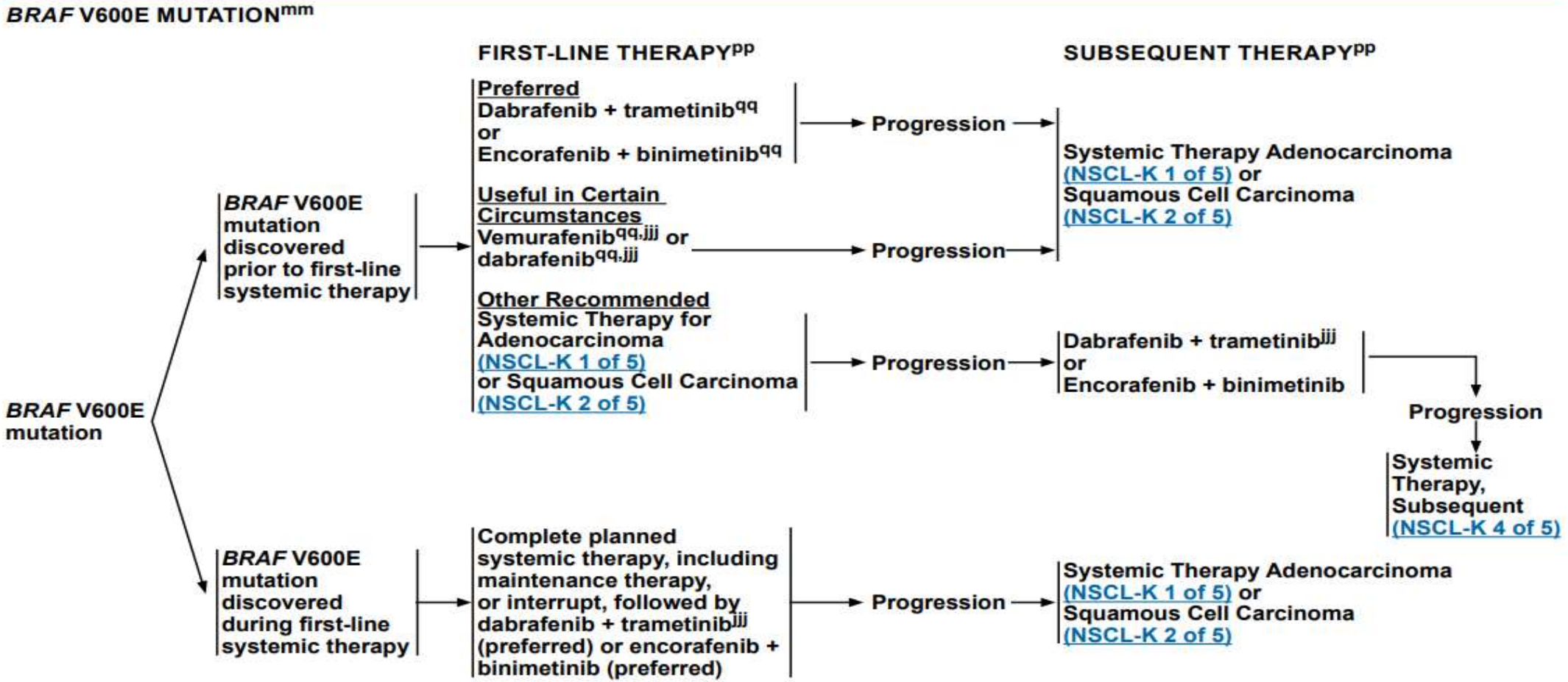


Metastatik KHDAK RET Alterasyonunda Tedavi

LIBRETTO-431

Key Eligibility Criteria
- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

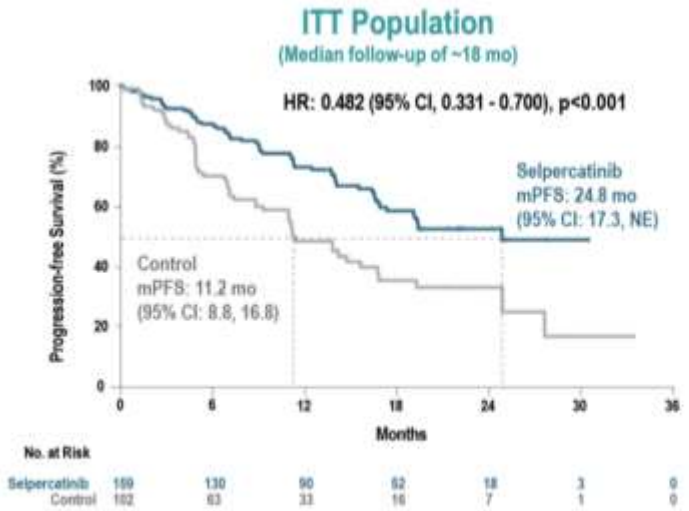
Stratification factors:
- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

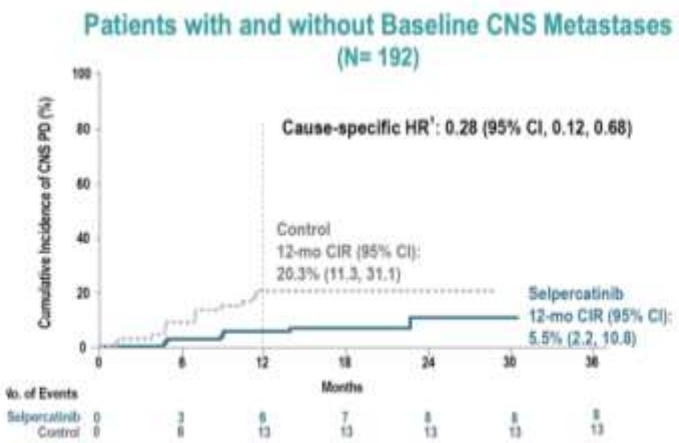
R 2:1[3]

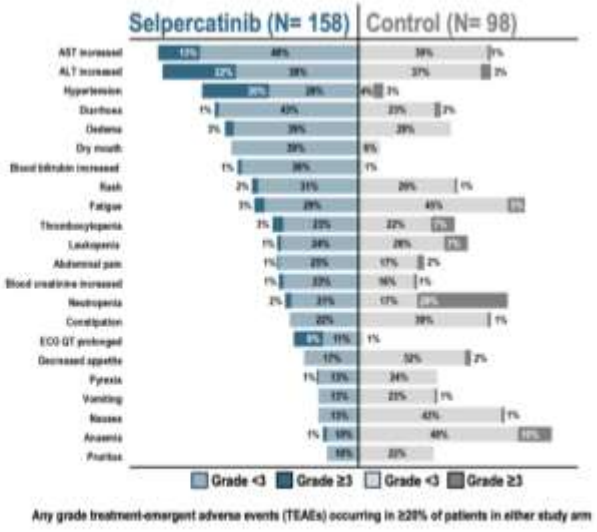
Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Optional Crossover → **Selpercatinib** (Upon BICR confirmed PD)



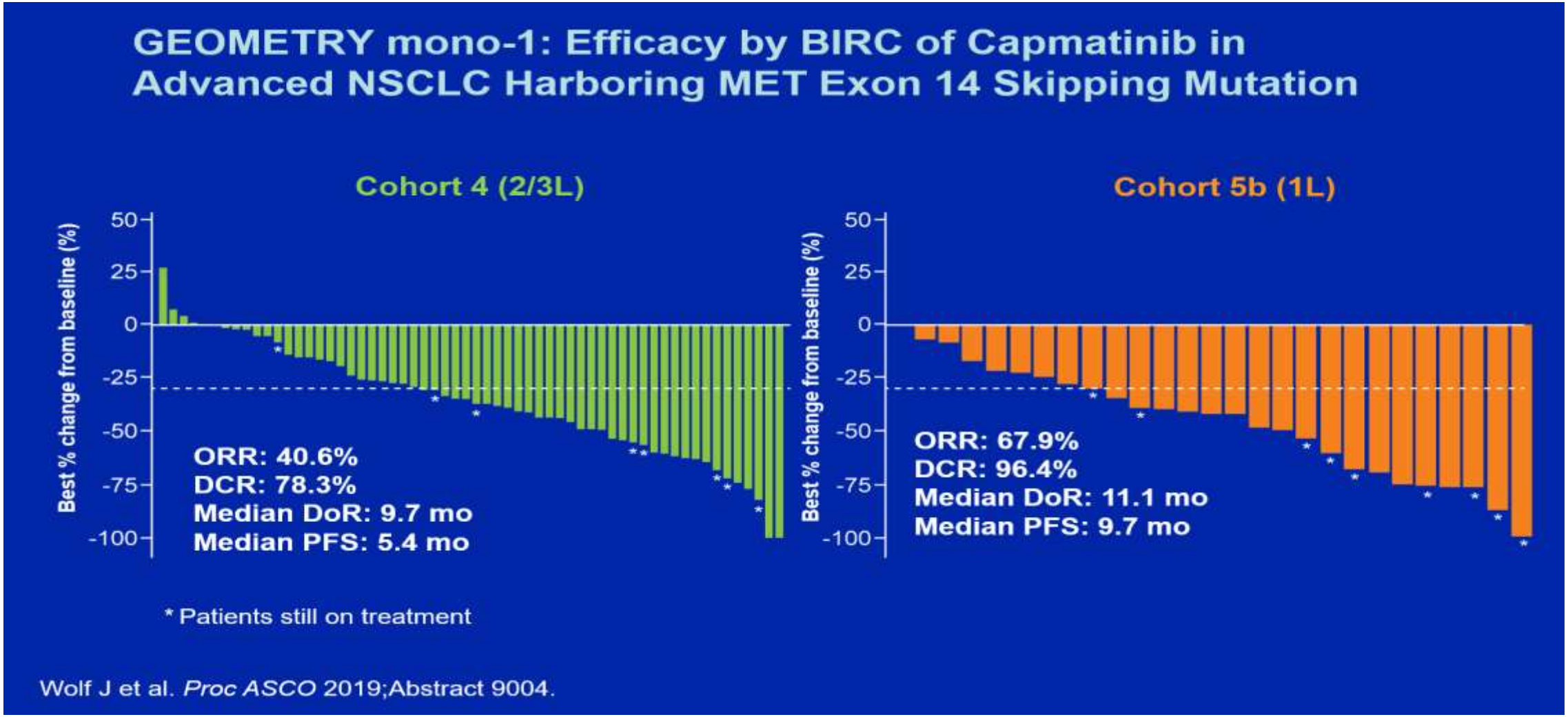




Any grade treatment-emergent adverse events (TEAEs) occurring in ≥20% of patients in either study arm

Loong H, ESMO 2023

Metastatik KHDAK MET ekzon 14 skipping mutasyonunda Tedavi



Metastatik KHDAK RET Mutasyonunda Tedavi

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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 *MET* 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 (*MET*amp) [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

Key eligibility criteria

- *KRAS* G12C–mutated advanced NSCLC, identified through molecular testing
- Measurable disease per RECIST v1.1
- ECOG ≤ 2
- No active brain metastases

→

Induction phase

Sotorasib: 960 mg oral daily
+
Carboplatin: AUC 5 IV Q3W*
+
Pemetrexed: 500 mg/m² IV Q3W

→

Maintenance phase†

Sotorasib: 960 mg oral daily
+
Pemetrexed: 500 mg/m² IV Q3W

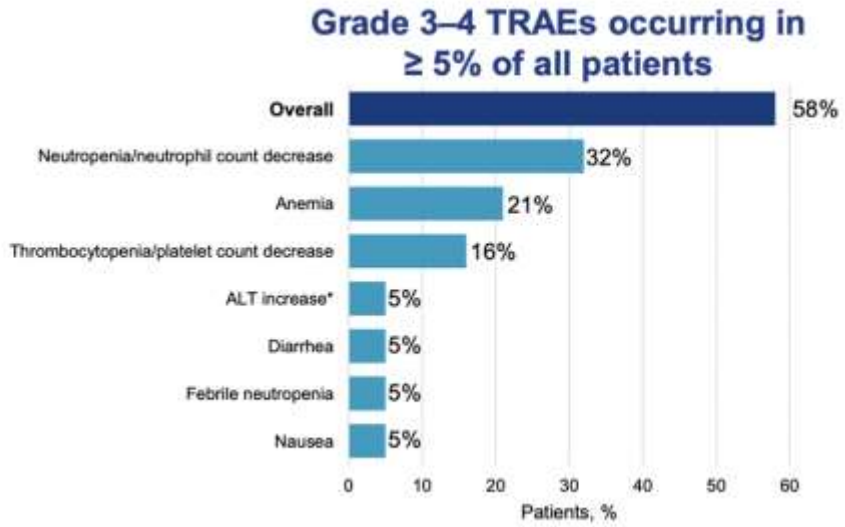
→

Data were pooled and analyzed by exposure to prior therapy in the locally advanced/metastatic setting‡

First-line (n = 25)

Second-line (n = 13)

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)



Clarke JM, WCLC 2023, Abstract MA 06-05

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 ≥ 1%)

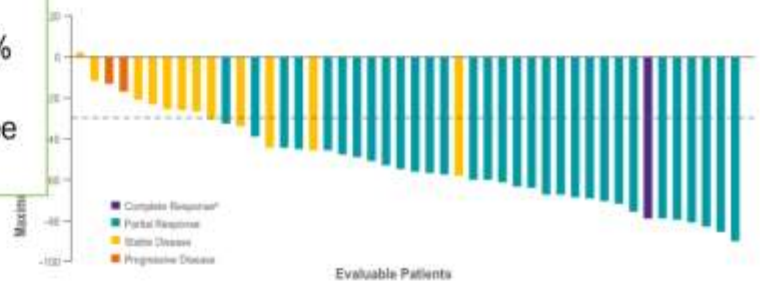
Most Frequent TRAEs[a], %	Concurrent 400 mg BID Adagrasib + Pembrolizumab (N=148)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51	28	20	3	0
Diarrhea	44	33	7	3	0
ALT increase	38	15	13	9	1
AST increase	32	10	8	13	1
Vomiting	29	17	11	1	0
Fatigue	26	12	10	4	0
Decreased appetite	24	14	9	1	0
Lipase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

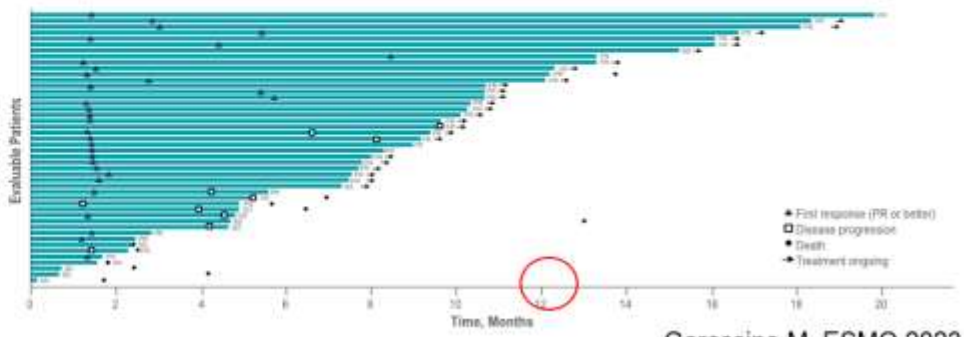
Combining adagrasib + pembrolizumab appeared to be overall fairly well-tolerated, with low rates of high-grade hepatotoxicity.

In PDL1 ≥ 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)



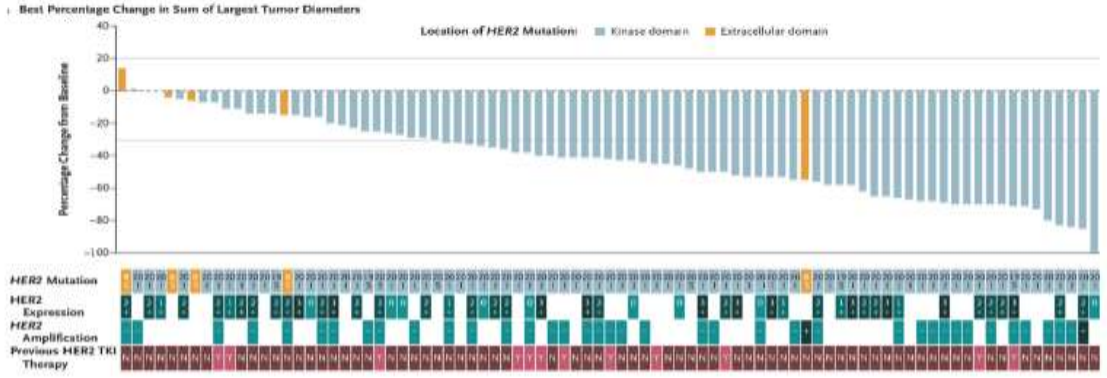
Garassino M, ESMO 2023

Metastatik KHDAK 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[b] 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

R 2:1

N = 152

T-DXd 5.4 mg/kg Q3W N = 102[c]

T-DXd 6.4 mg/kg Q3W N = 50

Primary Endpoint
- Confirmed ORR by BICR

Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

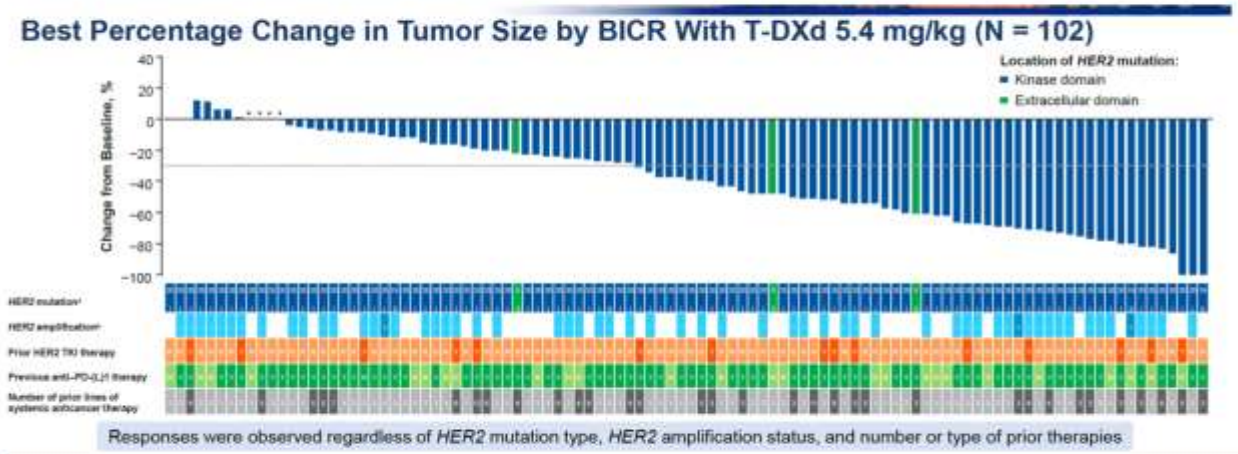
Janne P, WCLC 2023, Abstract MA13.20

Metastatik KHDAK HER2 Mutasyonunda Tedavi

DESTINY-Lung02

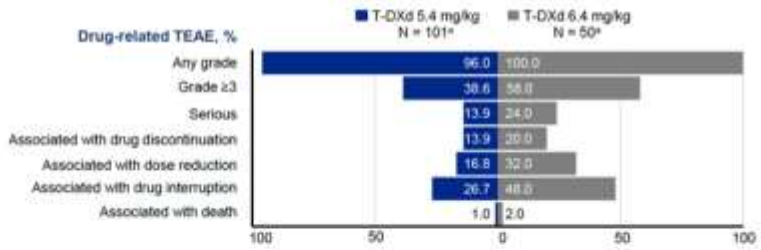
Janne P, WCLC 2023, Abstract MA13.20

	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



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

Safety in DL-02



Adjudicated Drug-Related ILD

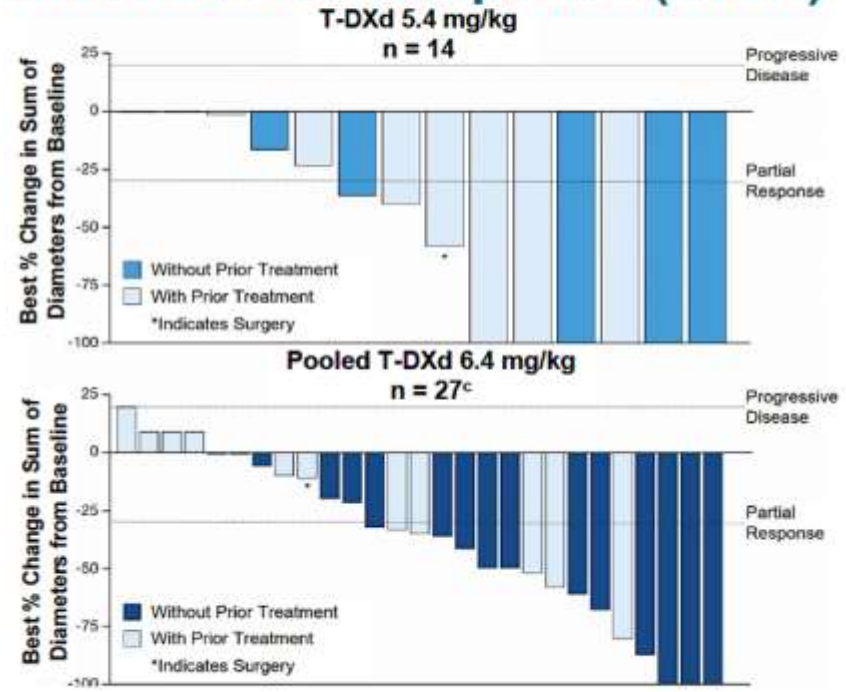
Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

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 KHDAK 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

Planchard D, ESMO 2023

Sonuç

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MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

***EGFR* Exon 19 Deletion or Exon 21 L858R**
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous)[7]
  - Erlotinib + ramucirumab[8]
  - Erlotinib + bevacizumab[c] (nonsquamous)[9]
- Subsequent therapy
  - Osimertinib[10]
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[11]

***EGFR* S768I, L861Q, and/or G719X**
- First-line therapy
  - Afatinib[1,12]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,13]
- Subsequent therapy
  - Osimertinib[10]
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[11]

***EGFR* Exon 20 Insertion Mutation**
- First-line therapy
  - Amivantamab-vmjw + carboplatin + pemetrexed (nonsquamous)[14]
- Subsequent therapy
  - Amivantamab-vmjw[15]

***KRAS* G12C Mutation[d]**
- Subsequent therapy
  - Sotorasib[16]
  - Adagrasib[17]

***ALK* Rearrangement**
- First-line therapy
  - Alectinib[18,19]
  - Brigatinib[20]
  - Ceritinib[21]
  - Crizotinib[18,22]
  - Lorlatinib[23]
- Subsequent therapy
  - Alectinib[24,25]
  - Brigatinib[26]
  - Ceritinib[27]
  - Lorlatinib[28]

***ROS1* Rearrangement**
- First-line therapy
  - Ceritinib[29]
  - Crizotinib[30]
  - Entrectinib[31]
  - Repotrectinib[32]
- Subsequent therapy
  - Lorlatinib[33]
  - Entrectinib[31]
  - Repotrectinib[32]

***BRAF* V600E Mutation**
- First-line therapy
  - Dabrafenib/trametinib[34]
  - Encorafenib/binimetinib[35]
  - Dabrafenib[36]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[36,37]
  - Encorafenib/binimetinib[35]

***NTRK1/2/3* Gene Fusion**
- First-line/Subsequent therapy
  - Larotrectinib[38]
  - Entrectinib[39]

***MET* Exon 14 Skipping Mutation[d]**
- First-line therapy/Subsequent therapy
  - Capmatinib[40]
  - Crizotinib[41]
  - Tepotinib[42]

***RET* Rearrangement[d]**
- First-line therapy/Subsequent therapy
  - Selpercatinib[43]
  - Pralsetinib[44]
  - Cabozantinib[45,46]

***ERBB2 (HER2)* Mutation[d]**
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[47]
  - Ado-trastuzumab emtansine[48]

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