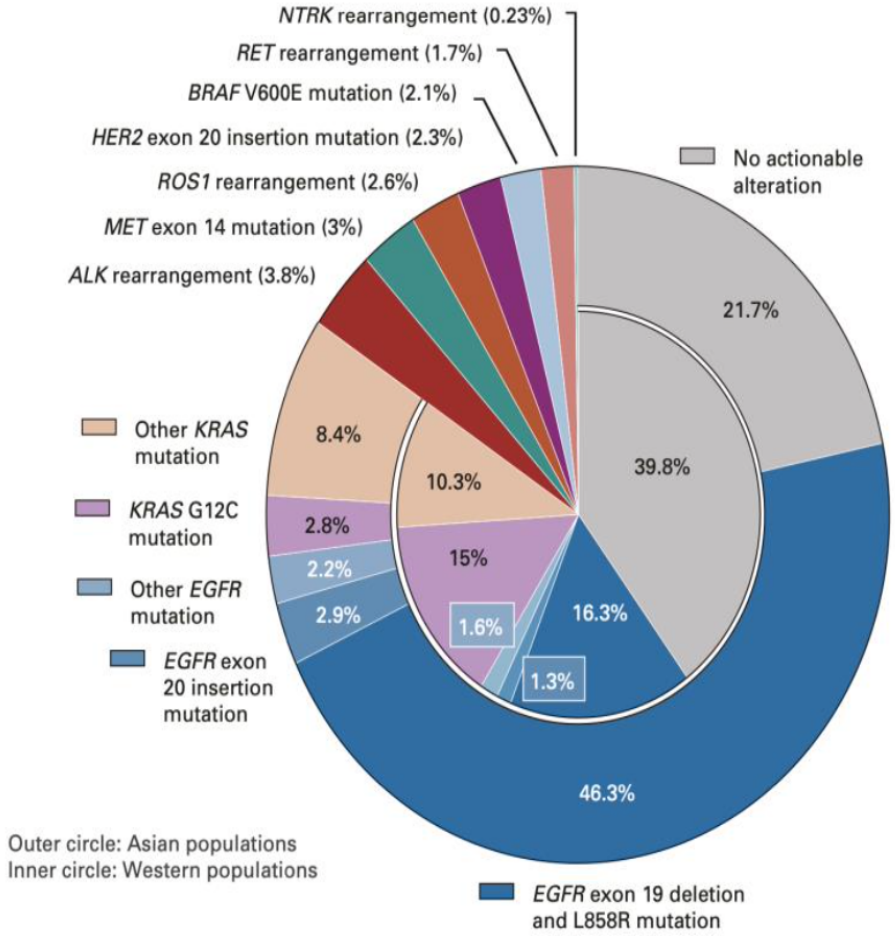
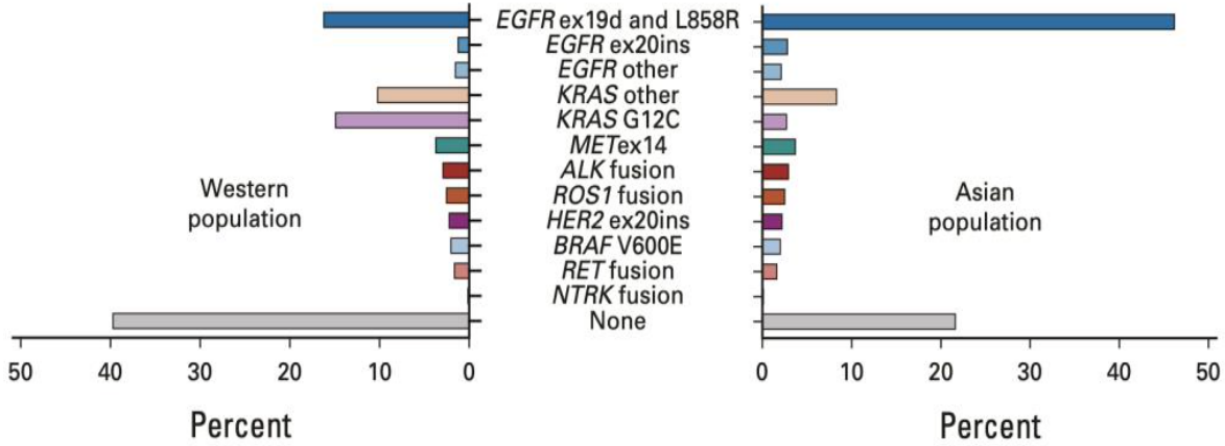
Metastatik KHDAC EGFR Mutant ve ALK + Hastalıklara Güncel Bakış

Dr M Mustafa ATCI

Anladıkça Hedefledikçe Akciğer Aşkımız Biraz Daha Arttı





Tan et al, JCO 2022; 40611-625.

Yöntemlerde Gelişme Klasik → Az Materyal Az Yöntem
Hedef→ Çoklu Sonuç

	Variant Type	Tissue Biopsy Specimens				Liquid Biopsy Specimens	
		IHC	FISH [1]	PCR [2]	NGS [3]	PCR [2]	NGS [3]
Established Targets	*EGFR* mutations (sensitizing and T790M)	—	—	••	••	•• [4]	••
	ALK fusions [5]	••	••	•	••	•	••
	ROS1 fusions	S	••	•	••	•	••
	NTRK fusions	S	••	•	••	—	•
	BRAF mutations	• [6]	—	••	••	••	••
Updated Target Inclusion	*EGFR* exon 20 insertions	—	—	•	••	•	••
	EGFR resistance mutations (excluding T790M)	—	—	••	••	••	••
	MET exon 14 skipping mutations	—	—	••	••	•	•
	KRAS G12C mutation	—	—	••	••	••	••
	HER2 mutations	—	—	••	••	•	••
	RET fusions	—	••	•	••	•	•
	MET amplification	— [7]	••	—	••	—	•
	ALK mutations	—	—	••	••	•	••
	ROS1 mutations	—	—	••	••	•	••
	BRAF fusions	—	••	—	••	—	•
	MET fusions	—	••	—	••	—	•
	NRG1 fusions	— [7]	••	—	••	—	•

1 FISH using break-apart probes is not informative regarding the specific fusion partner. 2 PCR will not detect unknown or novel fusion partners. For *EGFR* exon 20 insertion mutations, PCR only detects a small number of the known insertion mutations. 3 Limitations are capability and sensitivity of NGS assays. 4 ddPCR is a suitable method 5 Oncogenic fusions resulting from gene rearrangements. 6 For V600E variant.7 IHC assays are in development.
•: lower clinical utility. ••: higher clinical utility.

Genel Sağ kalım: Mutasyon Varlığı ve Tedaviye Göre

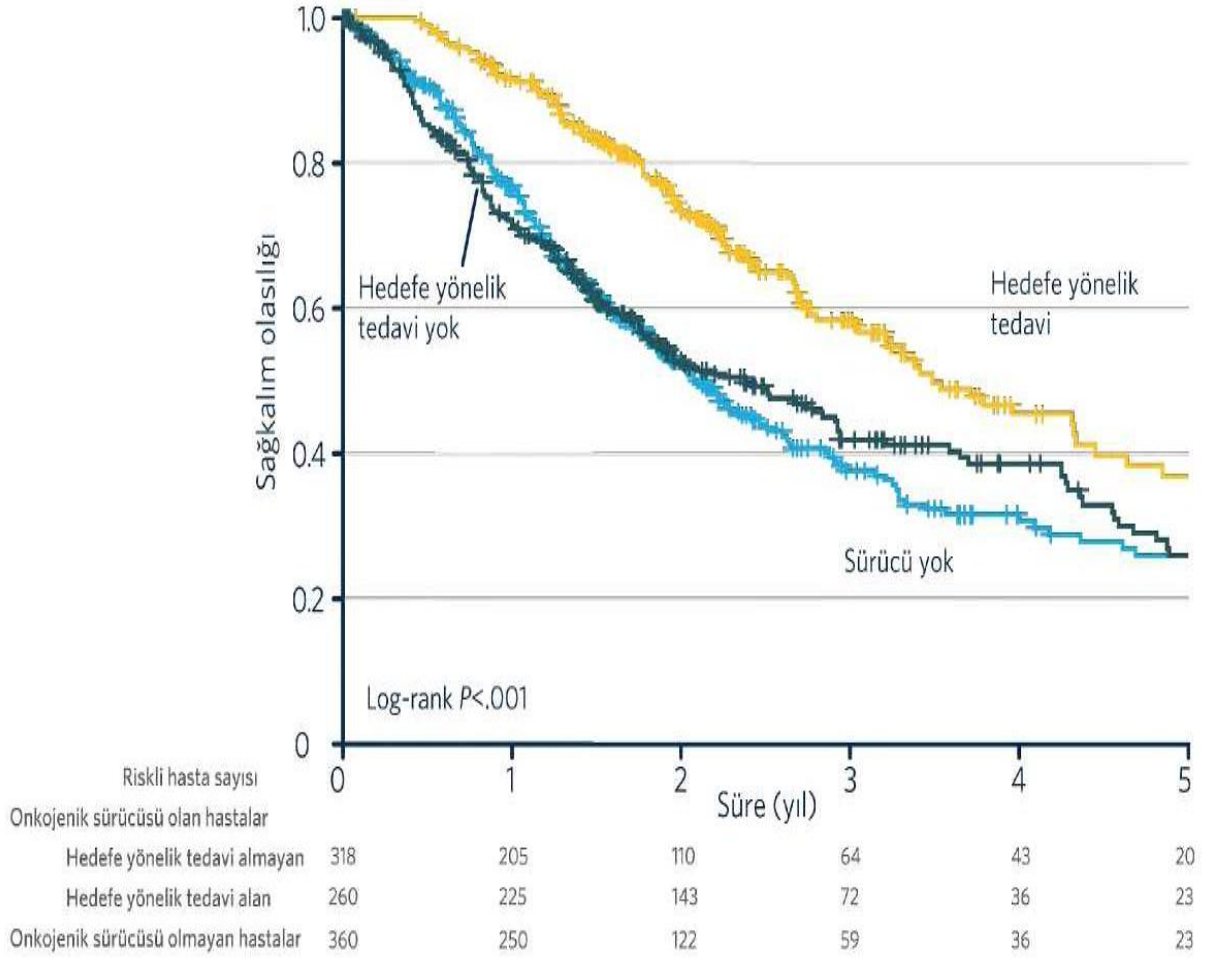
- Driver mutasyonu olan ve hedefli tedavi alan hastalarda OS 3.5 yıl iken almayanlarda 2.4 yıl.
- Driver mutasyonu olmayan hastalarda ise OS 2.1 yıl.
- Median OS süreleri

✓ EGFR+ hastalıkta 30-39 ay (KT kombine 52 ay)

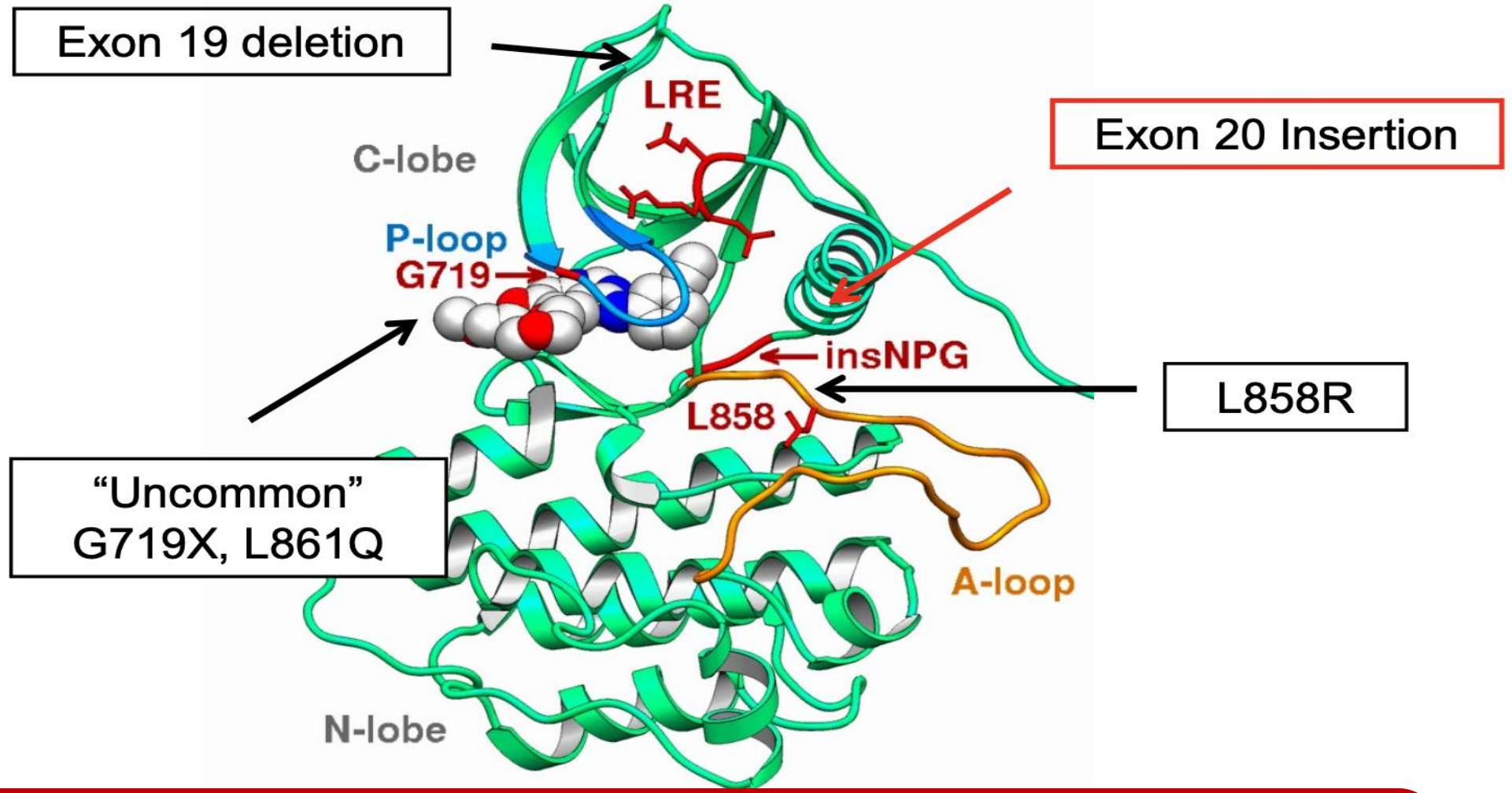
✓ ALK+ hastalıkta 100 ay

✓ ROS1+ hastalıkta 52 ay

✓ BRAF + hastalıkta 25 ay



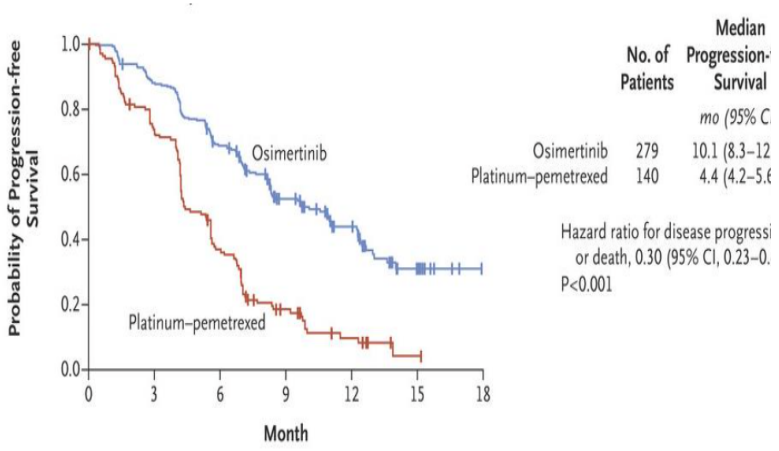
Journal of Clinical Oncology 2013 31:15_suppl, 8019-8019



Exon 19/L858R – 85% -, osimertinib, osi/chemo, Amivantamab/lazertinib
G719X, L861Q, S768I – 8-10% - afatinib, osi (off label)
Exon 20 - 5-7% - Amivantamab/chemo; second line TKIs

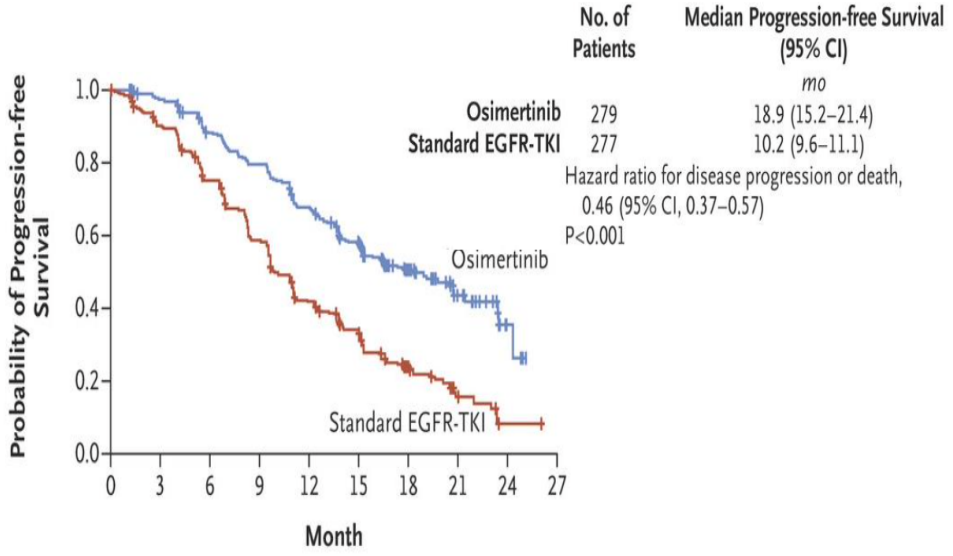
EGFR Mutasyonu Pozitif Hastalarda Osimertinib

EGFR T790M Patients (AURA 3) – at resistance!



RR: 71% vs. 31%; p < 0.001

EGFR TKI Naïve Patients (FLAURA)

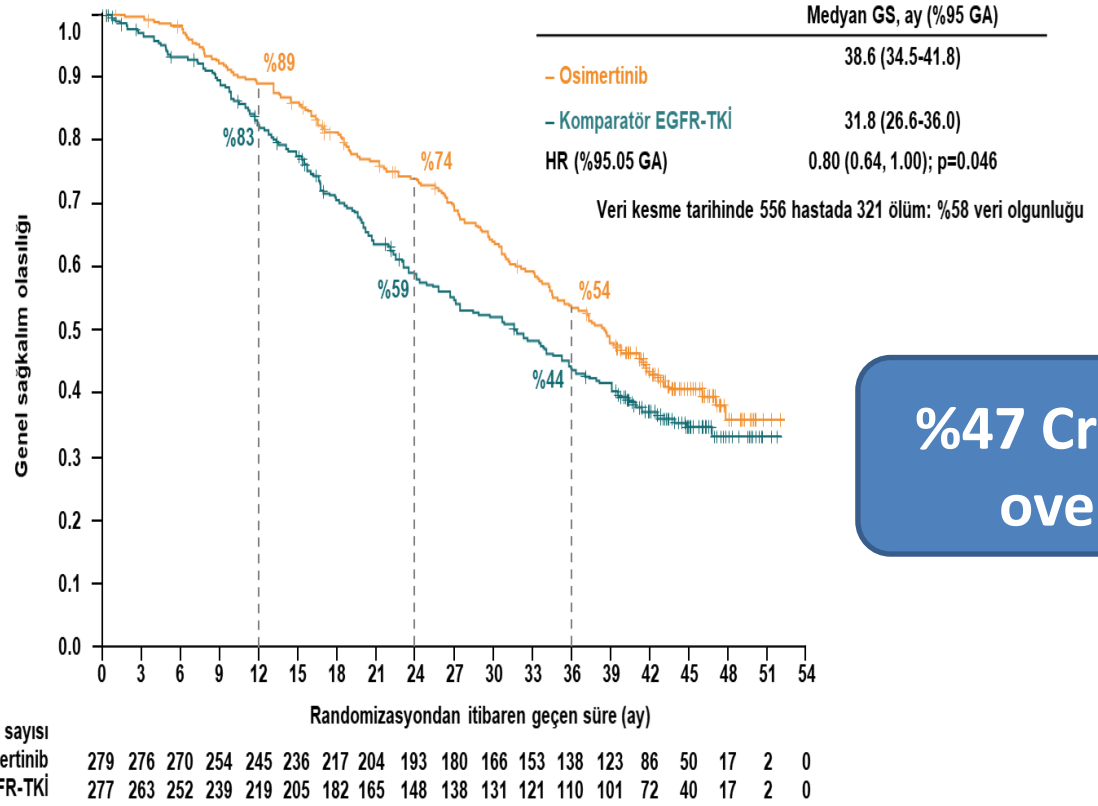


RR: 80% vs. 76%; p = 0.24

High rate of CNS activity including in brain metastases and leptomeningeal carcinomatosis

Mok et al. NEJM 2017; Soria et al. NEJM 2018; Goss et al. Ann Oncol 2018; Yang et al. ASCO 2016

Final Analiz: Genel Sağ Kalım



%47 Cross-over

Table 1. Overall Survival and Continuation of First-Line Trial Drug.*

Variable	Osimertinib (N=279)	Comparator EGFR-TKI (N=277)
Overall survival — % (95% CI)		
At 12 mo	89 (85–92)	83 (77–87)
At 24 mo	74 (69–79)	59 (53–65)
At 36 mo	54 (48–60)	44 (38–50)
Patients continuing to receive first-line trial drug — no. (%)		
At 12 mo	194 (70)	131 (47)
At 24 mo	118 (42)	45 (16)
At 36 mo	78 (28)	26 (9)

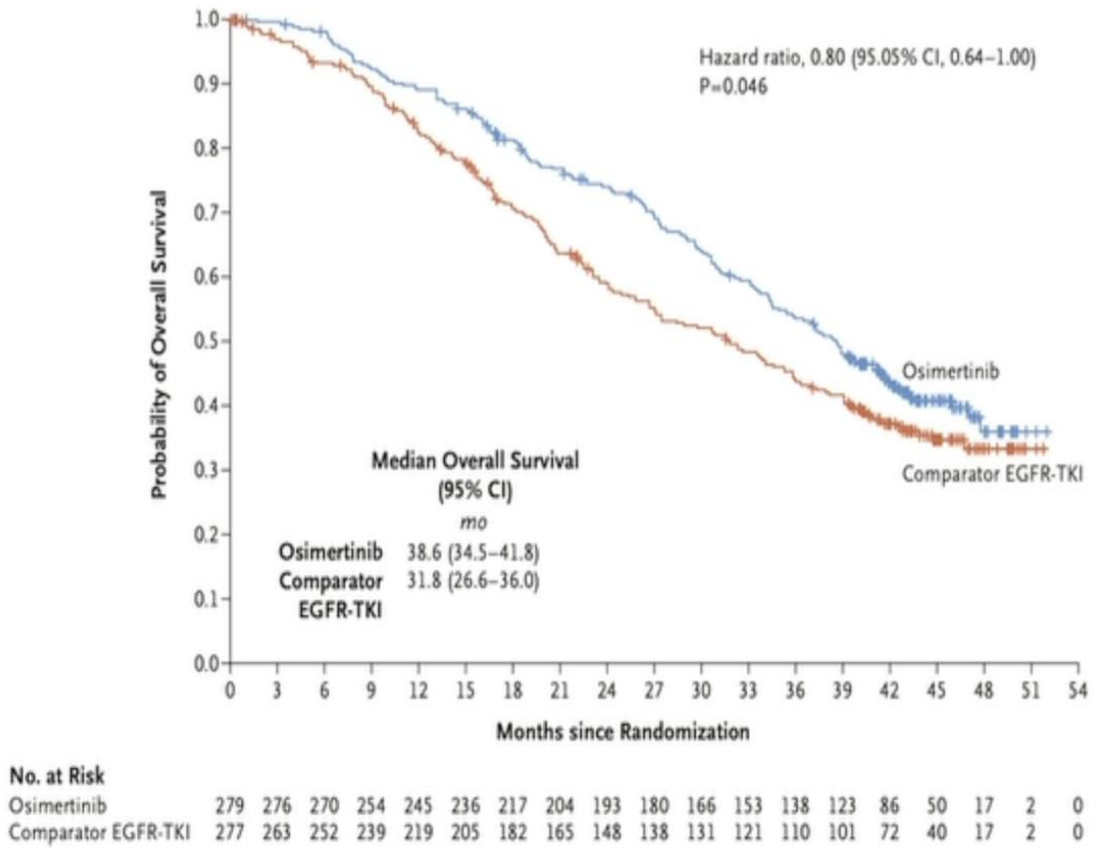
* In the comparator group, patients received one of two tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR-TKI): gefitinib or erlotinib.

FLAURA veri kesme tarihi: 25 Haziran 2019.
İstatistiksel anlamlılık için, O'Brien-Fleming yaklaşımıyla belirlenen 0.0495'ten küçük bir p değerine ihtiyaç duyulmuştur.

GA = güven aralığı; EGFR-TKİ = epidermal büyüme faktörü reseptörü-tirozin kinaz inhibitörü; HR = tehlike oranı; GS = genel sağkalım.

Ramalingam SS et al. *N Engl J Med*. 2020; 382:41-50.

Sonuç Olarak

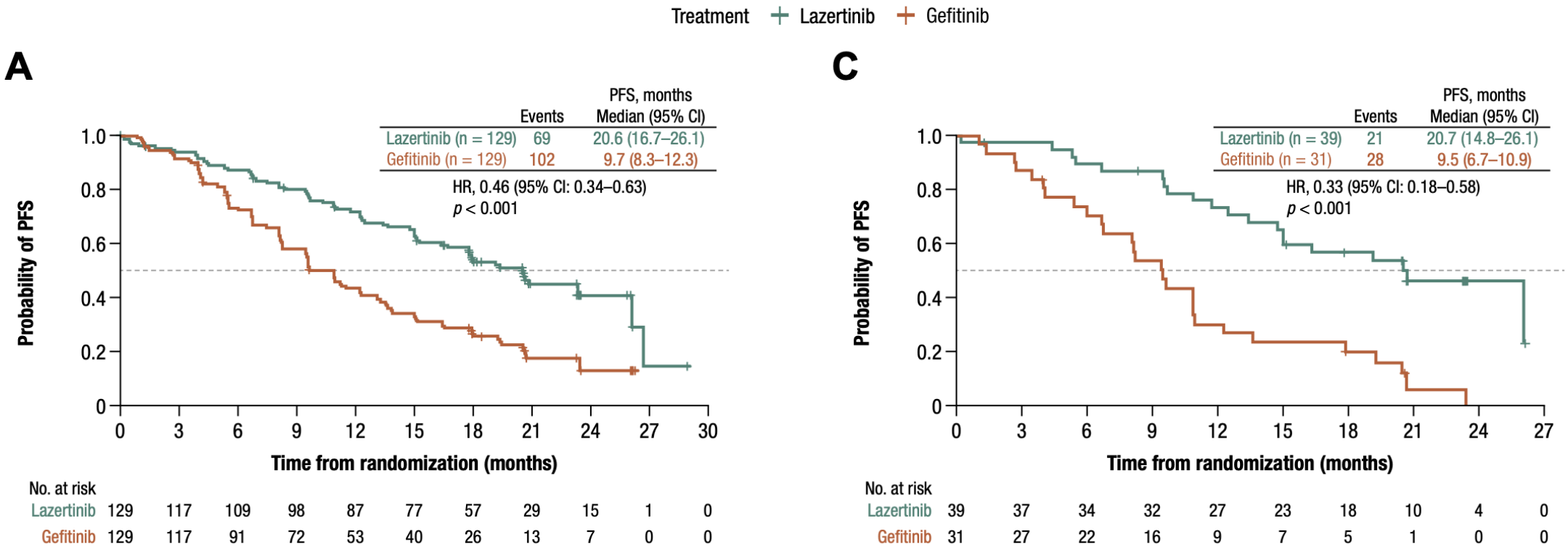


→mPFS 18,9 ay mOS 38,9 ay

Toksisiteler →Döküntü, Diyare, Paronişi,Qtc uzaması, ILD (nadir) GO iyi tolere edilir

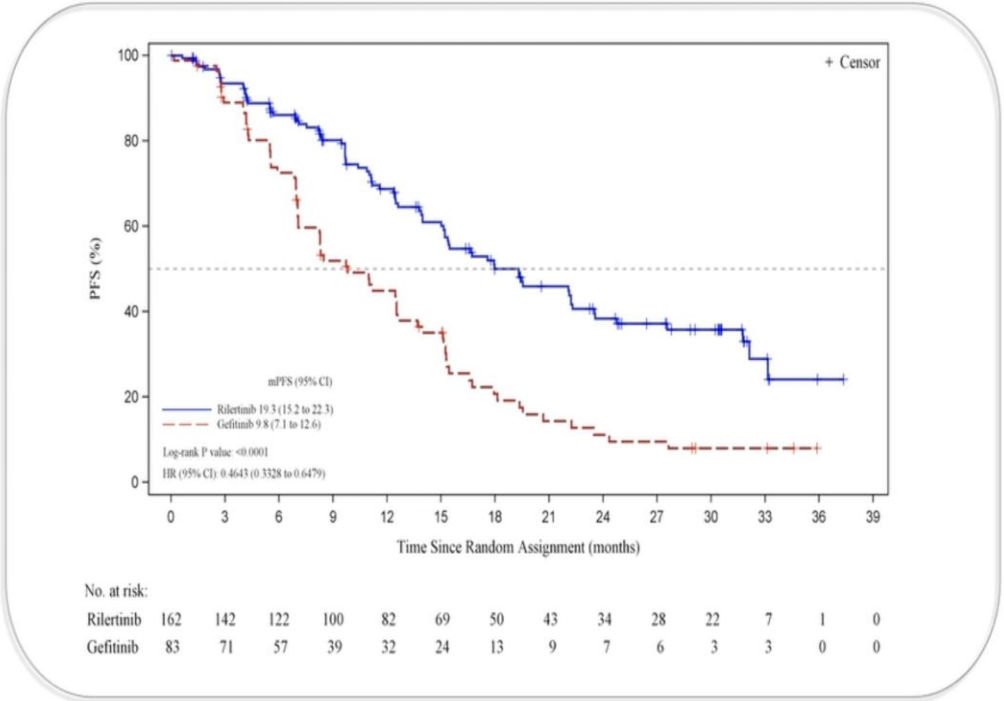
→İntrakranial penetrasyon iyi Oral kullanım, Çoğu hastam 2 ayda 1 geliyor

Lazertinib

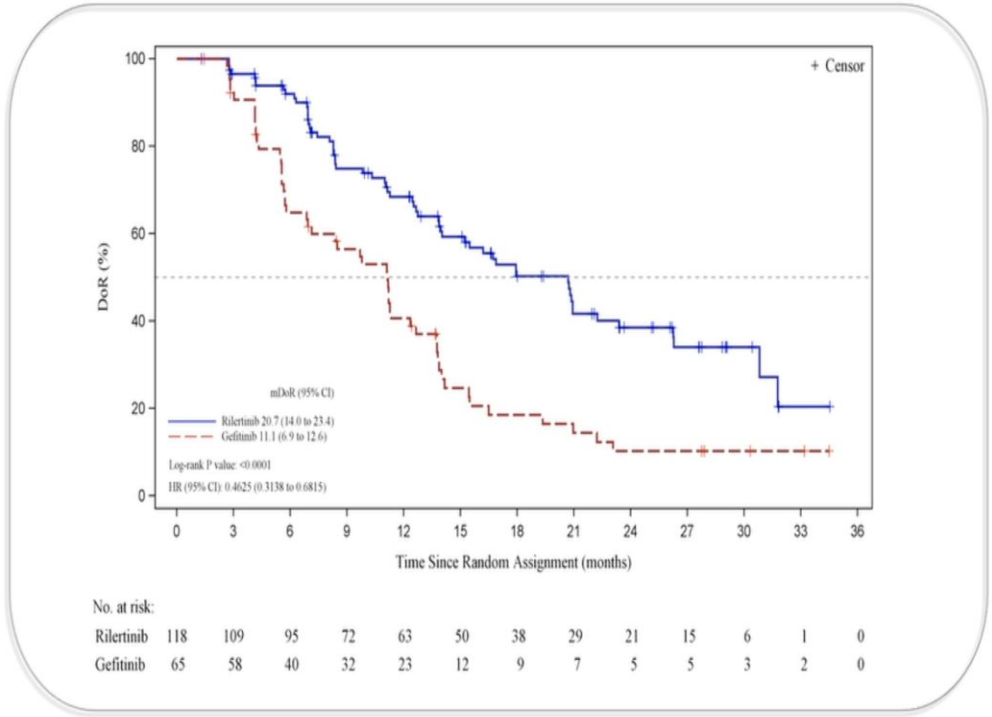

Treatment
Lazertinib
Gefitinib
A
Events
PFS, months
Median (95% CI)
Lazertinib (n = 129) 69 20.6 (16.7–26.1)
Gefitinib (n = 129) 102 9.7 (8.3–12.3)
HR, 0.46 (95% CI: 0.34–0.63)
p < 0.001
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0
0 3 6 9 12 15 18 21 24 27 30
Time from randomization (months)
No. at risk
Lazertinib 129 117 109 98 87 77 57 29 15 1 0
Gefitinib 129 117 91 72 53 40 26 13 7 0 0
C
Events
PFS, months
Median (95% CI)
Lazertinib (n = 39) 21 20.7 (14.8–26.1)
Gefitinib (n = 31) 28 9.5 (6.7–10.9)
HR, 0.33 (95% CI: 0.18–0.58)
p < 0.001
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0
0 3 6 9 12 15 18 21 24 27
Time from randomization (months)
No. at risk
Lazertinib 39 37 34 32 27 23 18 10 4 0
Gefitinib 31 27 22 16 9 7 5 1 0 0

Rilertinib

IRC-assessed median PFS was significantly longer in the rilertinib group than the gefitinib group, with values of 19.3 months (15.2–22.3) versus 9.8 months (7.1–12.6), respectively (HR, 0.46; 95% CI, 0.33–0.65; P < 0.0001)



IRC-assessed median DoR was significantly longer in the rilertinib group than the gefitinib group, with values of 20.7 months (14.0–23.4) versus 11.1 months (6.9–12.6), respectively (HR, 0.46; 95% CI, 0.31–0.68; P < 0.0001)



- Bütün TKİ lar Benzer mi?

Lazertinib vs Osimertinib in 1L *EGFR*-mutant Advanced NSCLC: A Randomized, Double-blind, Exploratory Analysis From MARIPOSA

Se-Hoon Lee[1], Byoung Chul Cho[2], Hidetoshi Hayashi[3], Enriqueta Felip[4], Alexander I Spira[5], Nicolas Girard[6], Yu Jung Kim[7], Yuriy Ostapenko[8], Pongwut Danchaivijitr[9], Baogang Liu[10], Adlinda Alip[11], Ernesto Korbenfeld[12], Josiane Mourão Dias[13], Ki Hyeong Lee[14], Hailin Xiong[15], Soon Hin How[16], Ying Cheng[17], Gee-Chen Chang[18], James Chih-Hsin Yang[19], Benjamin Besse[20], Michael Thomas[21], Joshua C Curtin[22], Jiarui Zhang[22], John Xie[23], Tao Sun[23], Melissa Martinez[23], Seema Sethi[22], Roland E Knoblauch[22], Elizabeth Fennema[24], Mahesh Daksh[23], Mariah Ennis[22], Joshua M Bauml[22], Shun Lu[25]

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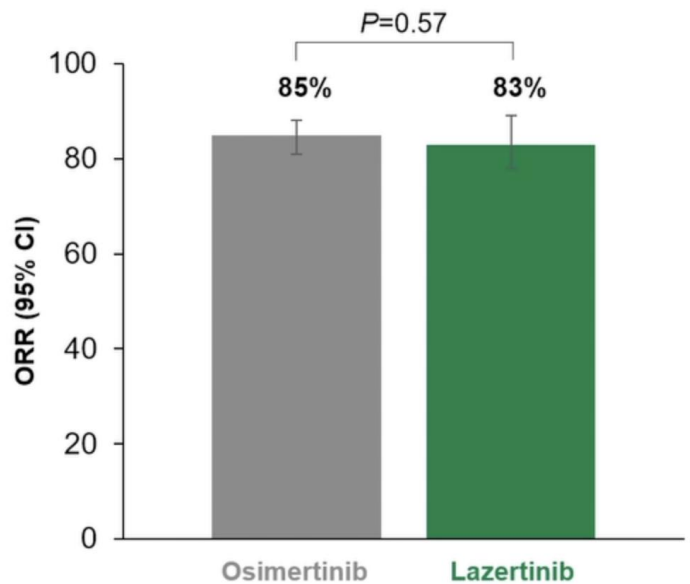
ORR and DoR by BICR

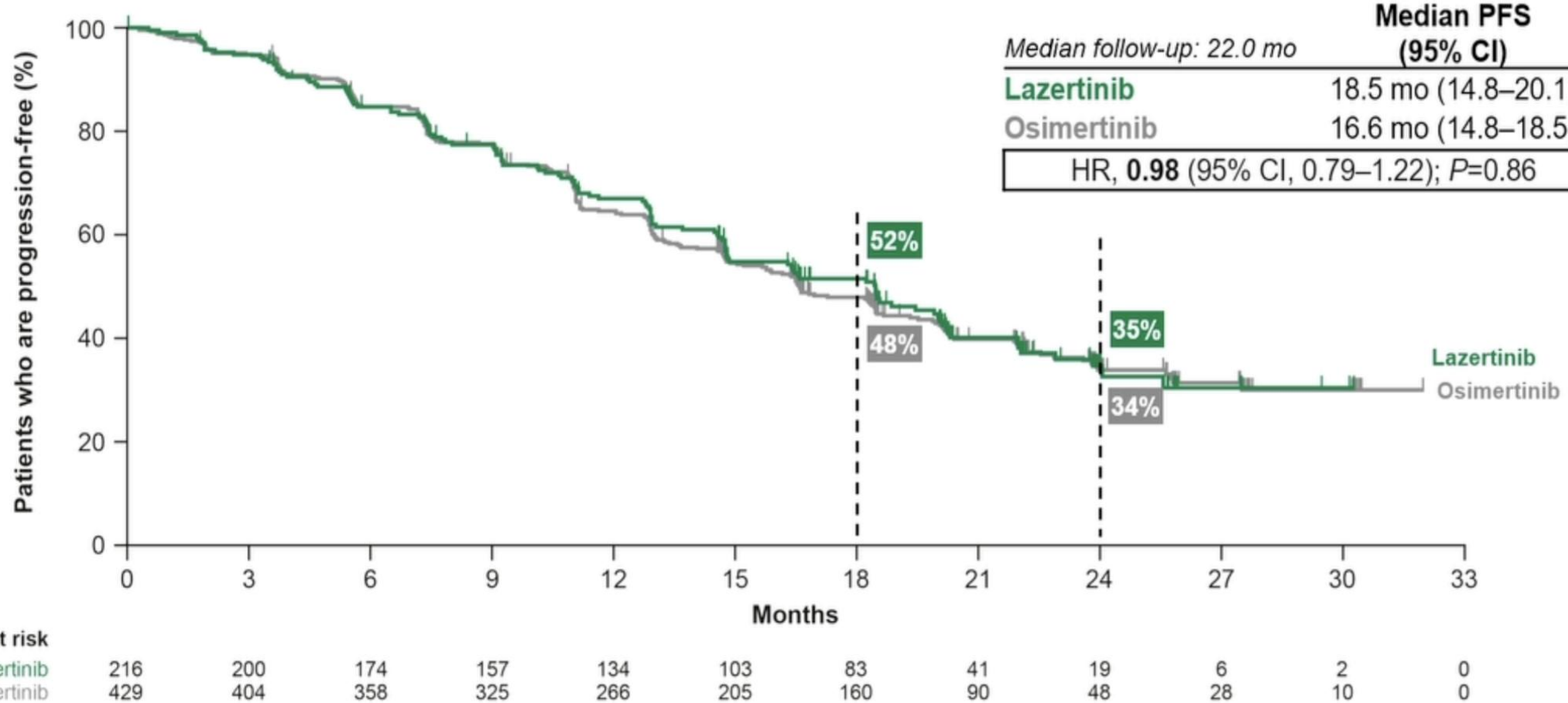
ORR and median DoR were comparable between lazertinib and osimertinib



BICR-assessed response, n (%)[a]	Osimertinib (n=429)	Lazertinib (n=216)
ORR		
All responders	85% (95% CI, 81–88)	83% (95% CI, 77–88)
Confirmed responders	76% (95% CI, 71–80)	75% (95% CI, 68–80)
Best response[b]		
CR	15 (4)	9 (4)
PR	335 (81)	168 (79)
SD	42 (10)	23 (11)
PD	11 (3)	9 (4)
NE	11 (3)	5 (2)
Median DoR[c]	16.8 mo (95% CI, 14.8–18.5)	16.6 mo (95% CI, 14.8–20.2)
Ongoing responses	151 of 314 (48)	77 of 160 (48)

PFS by BICR

PFS was comparable between the lazertinib and osimertinib arms



- PFS was comparable between lazertinib and osimertinib among prespecified subgroups including Asian race[a] and *EGFR* mutation subtype[b]

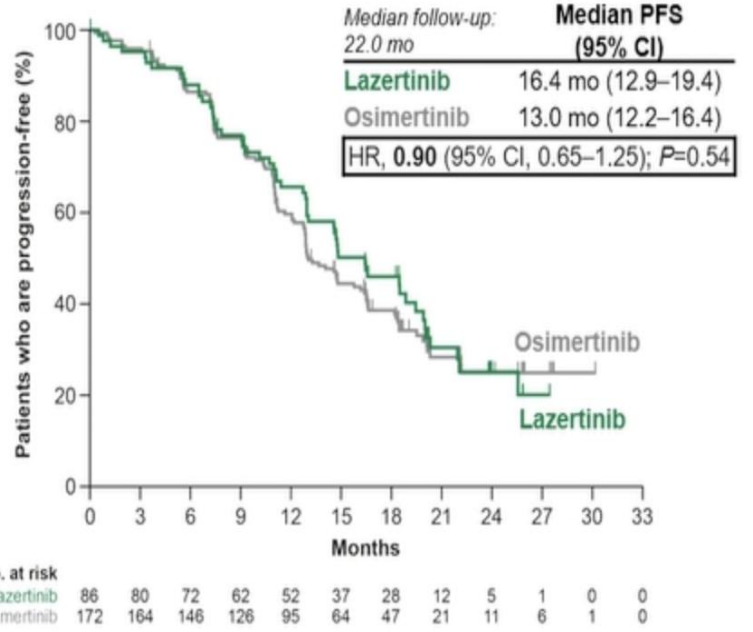
[a]HR, 1.02 (95% CI, 0.77–1.35). [b]Exon 19 deletion: HR, 1.03 (95% CI, 0.78–1.37); L858R: HR, 0.91 (95% CI, 0.65–1.28).

PFS by High-risk Subgroups

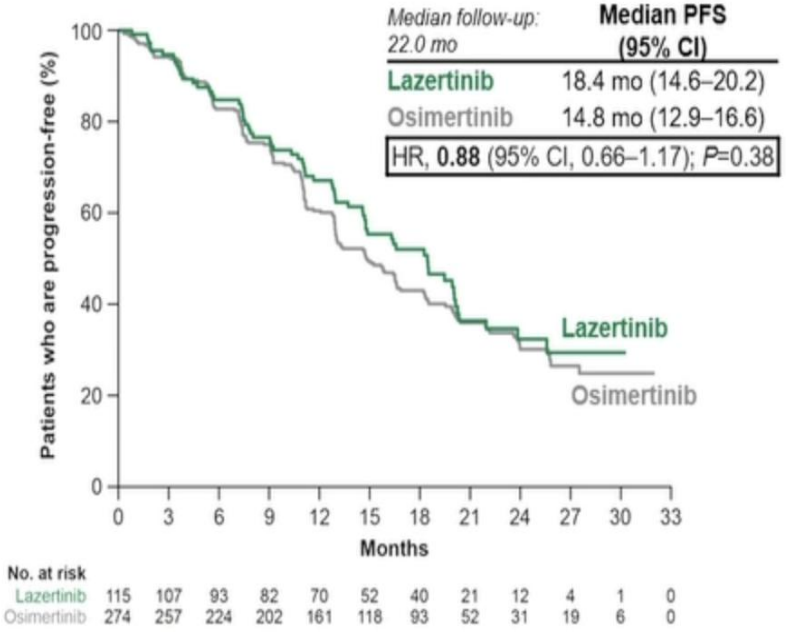
MARIPOSA
1L *EGFR*+ NSCLC

High-risk features, such as brain metastases, ctDNA shedding, and baseline TP53 co-mutations are common in patients with EGFR-mutated NSCLC.[1–4] PFS results in these groups were comparable across arms

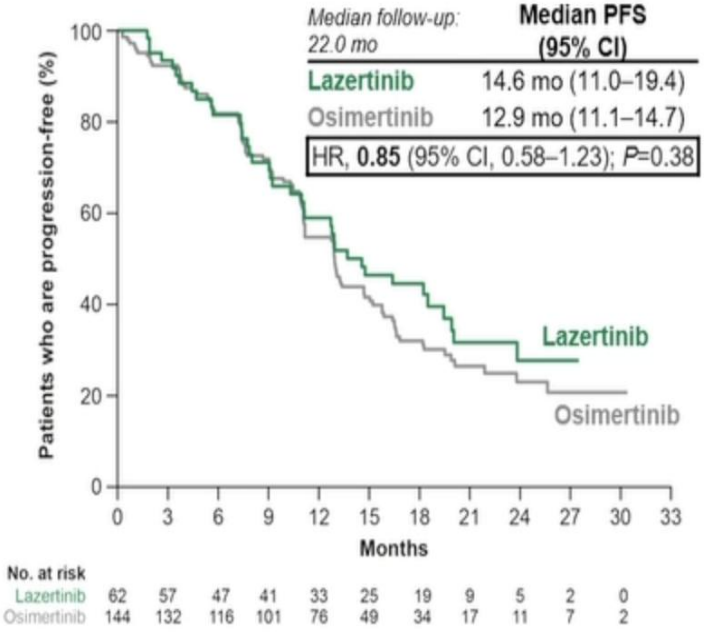
With brain metastases[a]



With detectable ctDNA at baseline[a,b]



With TP53 co-mutations[a,b]



[a]PFS was comparable for patients without a history of brain metastases (lazertinib: n=130, osimertinib: n=257; HR, 1.01 [95% CI, 0.75–1.35]), without detectable ctDNA at baseline (lazertinib: n=31, osimertinib: n=42; HR, 1.32 [95% CI, 0.99–1.75]), and for patients with wild-type *TP53* (lazertinib: n=84, osimertinib: n=172; HR, 0.95 [95% CI, 0.71–1.26]). [b]Pathogenic alterations were detected with the Guardant Health G360® panel.

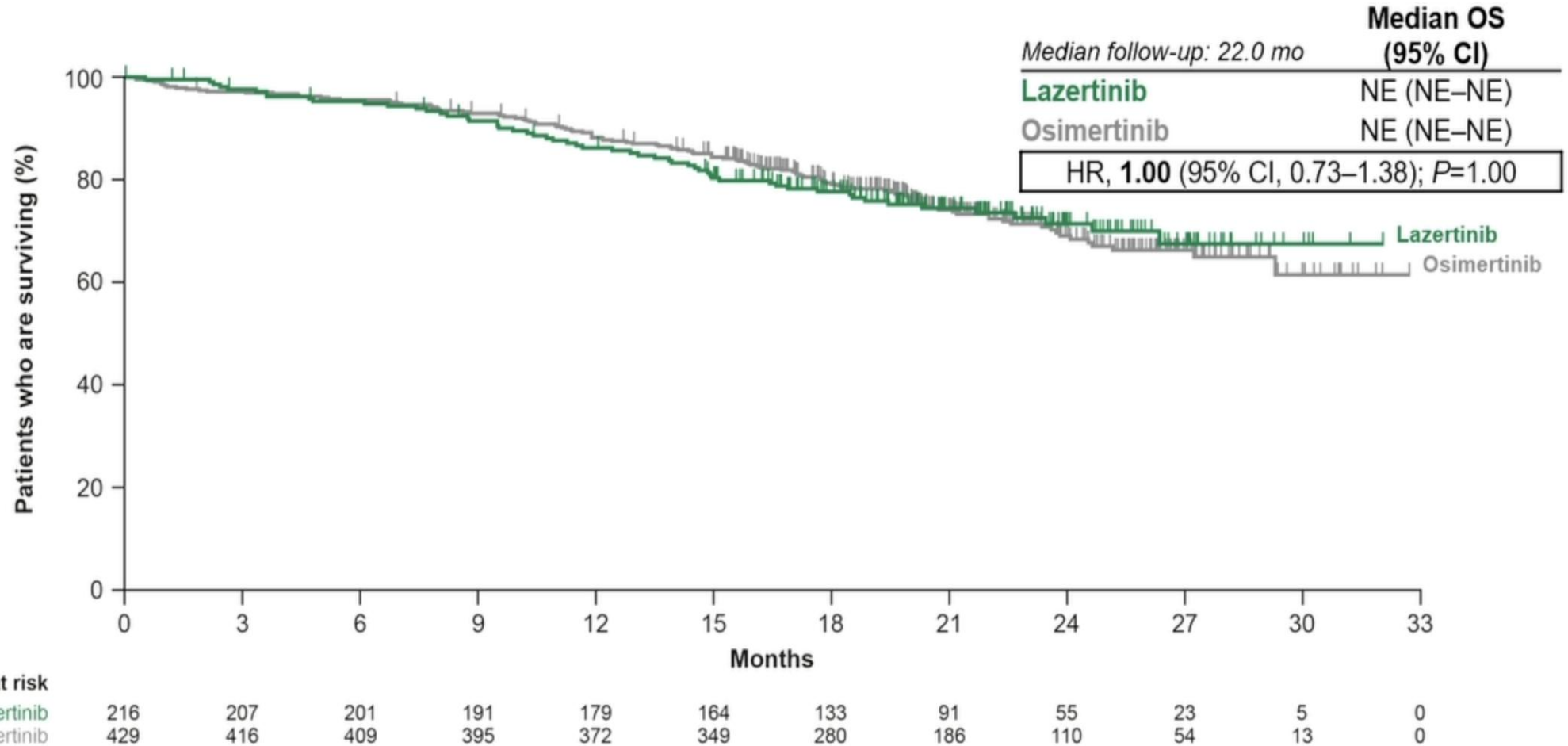
CI, confidence interval; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; NSCLC, non-small cell lung cancer.

1. Gray JE, et al. *Clin Cancer Res*. 2023;29(17):3340–3351. 2. Ma S, et al. *Transl Lung Cancer Res*. 2021;10(1):326–339. 3. Takeyasu Y, et al. *JTO Clin Res Rep*. 2024;5(2):100636. 4. Soria JC, et al. *N Engl J Med*. 2018;378(2):113–125.

Interim OS

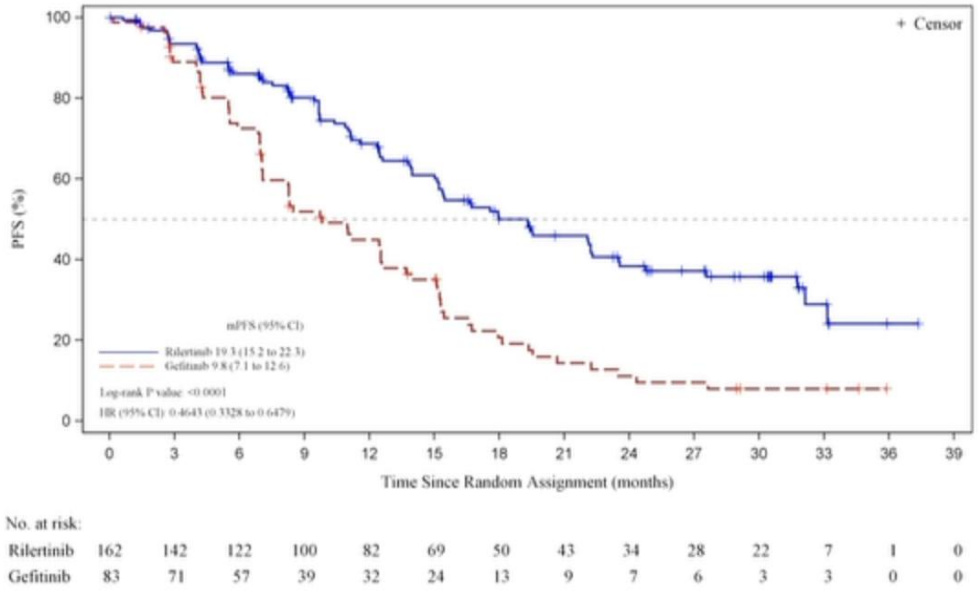
MARIPOS
1L *EGFR*+ NS

Early data demonstrated comparable survival outcomes between lazertinib and osimertinib



CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

Rilertinib vs Osimertinib



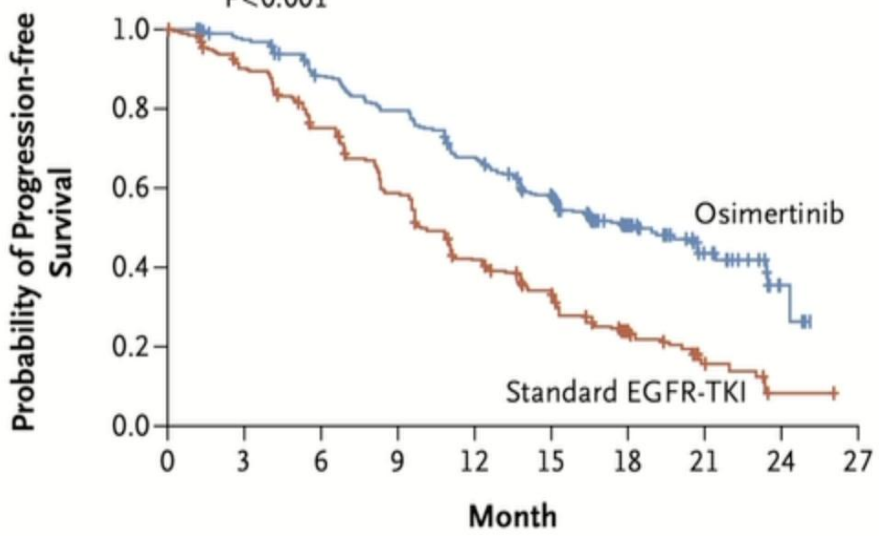
No. at risk:

Rilertinib	162	142	122	100	82	69	50	43	34	28	22	7	1	0
Gefitinib	83	71	57	39	32	24	13	9	7	6	3	3	0	0

Anwen Xiong, WCLC 2024

Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

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



No. at Risk

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

Flaura Soria JC Nejm 2018

- Kombinasyonda yeni neler var?

OSIRAM-1 (TORG1833): PFS (Primary Endopoint)

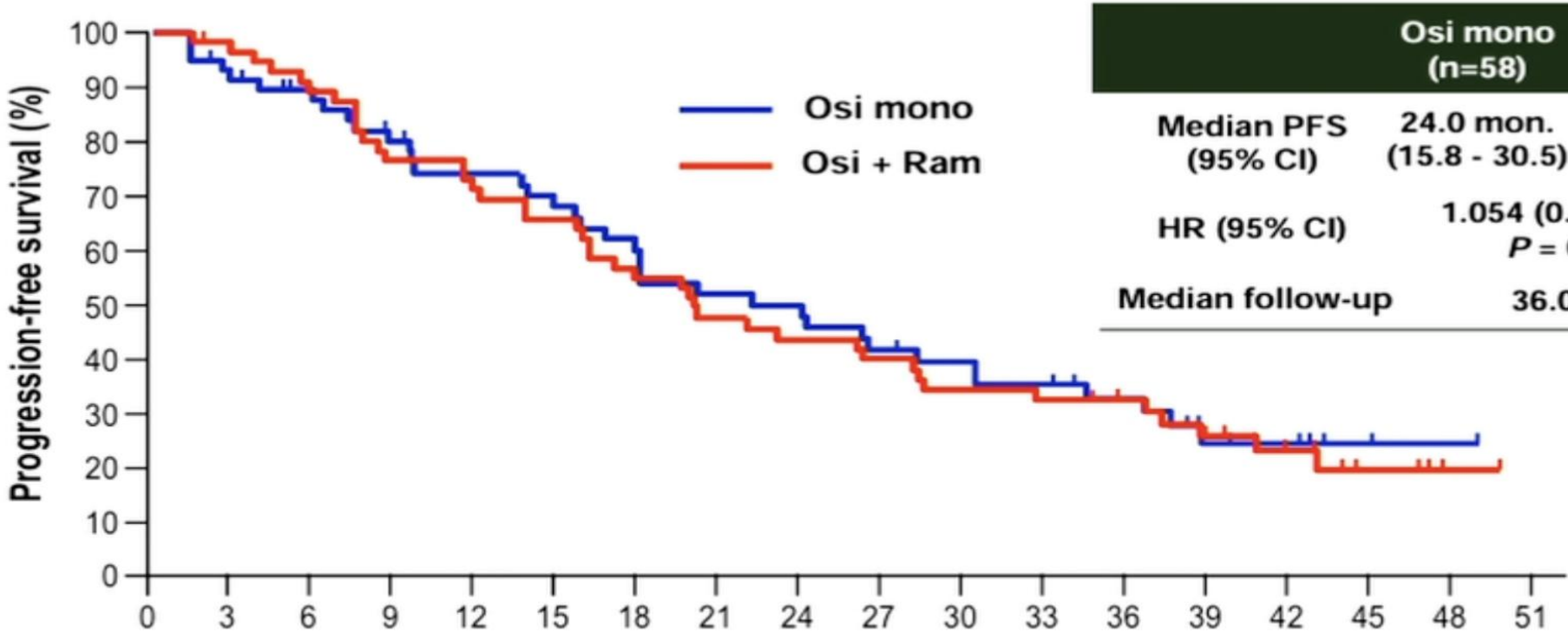
Key patient inclusion criteria

- Untreated advanced non-Sq NSCLC harboring EGFR activating mutations
- ECOG PS 0, 1
- At least 1 measurable target lesion
- Absence of symptomatic brain metastases

N=122 → R 1:1

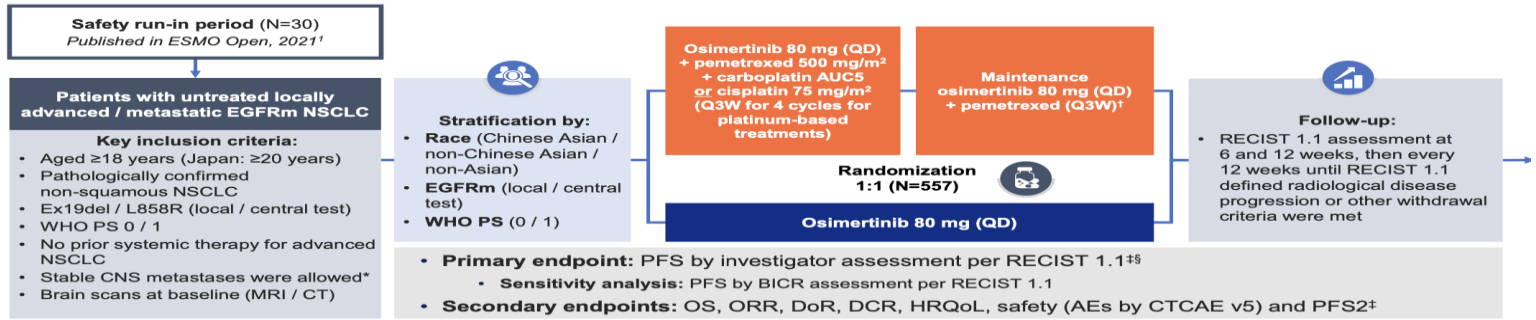
- Osimertinib monotherapy (80mg, daily)
- Osimertinib (80mg, daily) + Ramucirumab (10mg/kg, q2w)

→ Treatment until PD or unacceptable toxicity

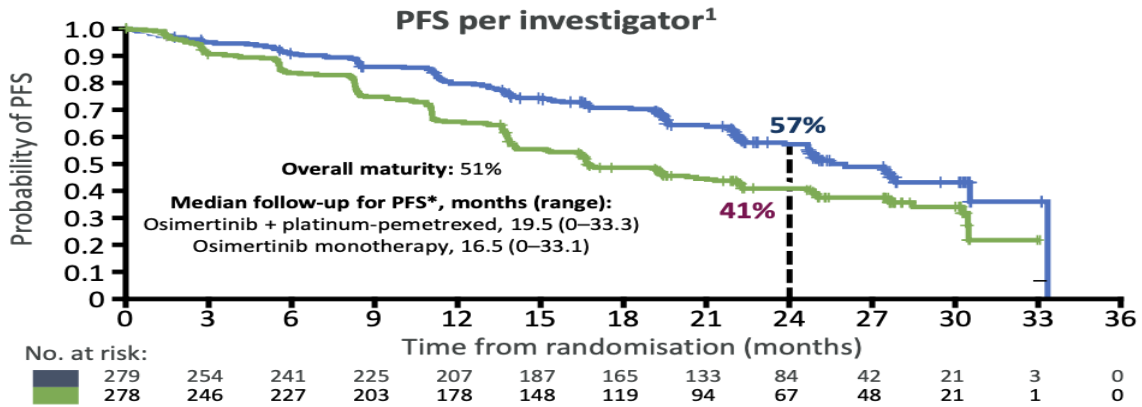


	Osi mono (n=58)	Osi + Ram (n=57)
Median PFS (95% CI)	24.0 mon. (15.8 - 30.5)	20.0 mon. (15.9 - 28.3)
HR (95% CI)	1.054 (0.674-1.648) *P* = 0.4621	
Median follow-up	36.0 mon.	

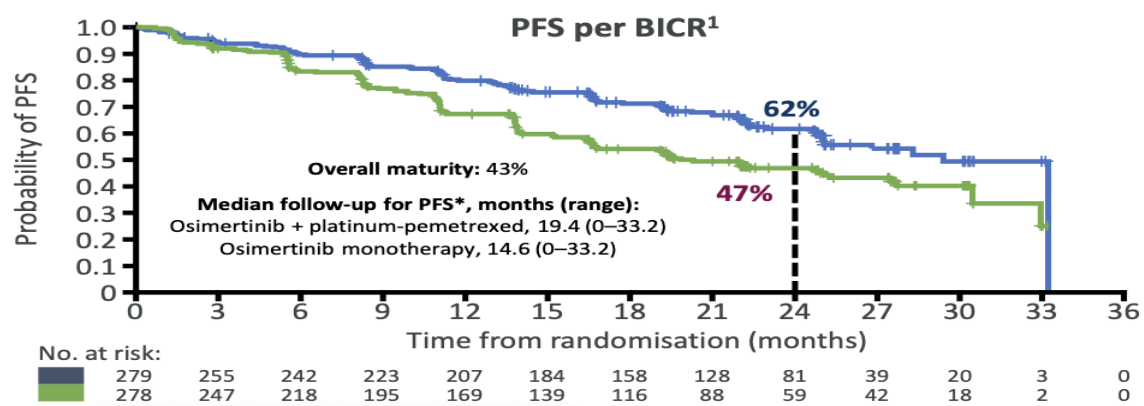
FLAURA2 Phase III study design



FLAURA2: 1L osimertinib plus chemotherapy was associated with statistically significant improvement in PFS vs. osimertinib monotherapy



Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	25.5 (24.7, NC)
Osimertinib monotherapy	16.7 (14.1, 21.3)
HR (95% CI)	0.62 (0.49, 0.79); p<0.0001

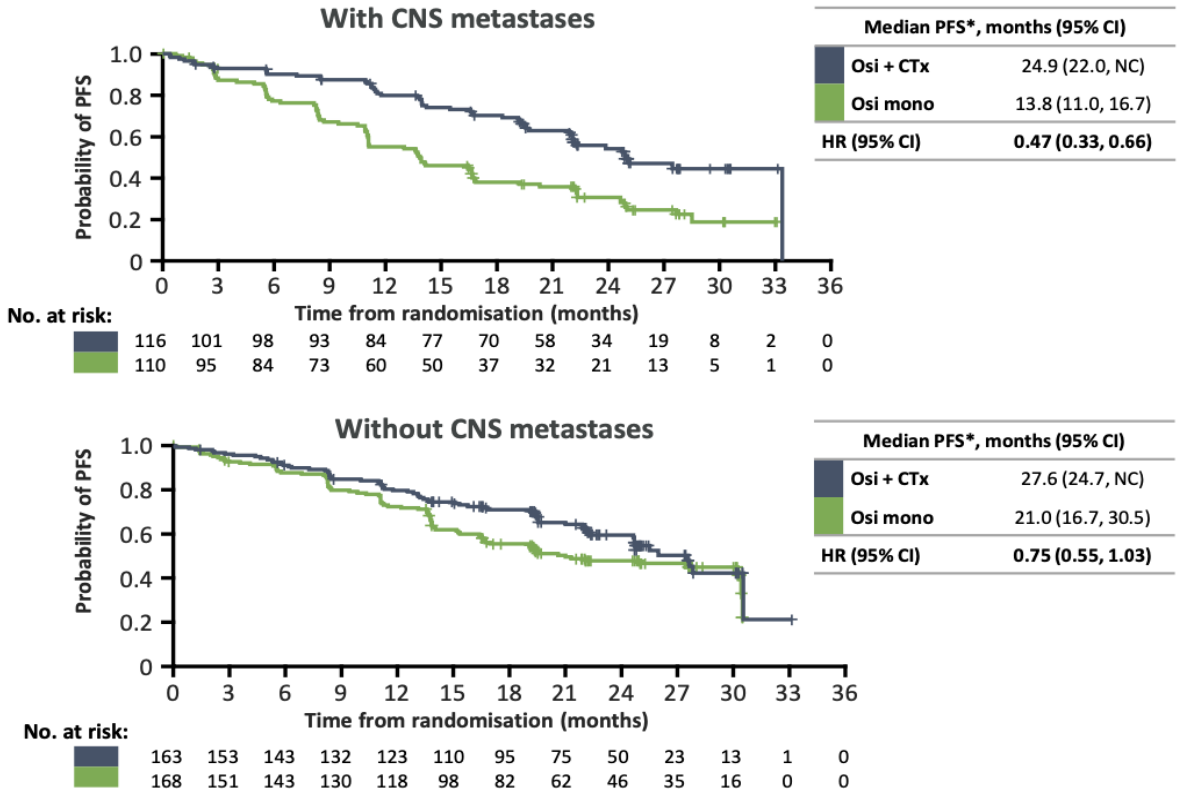


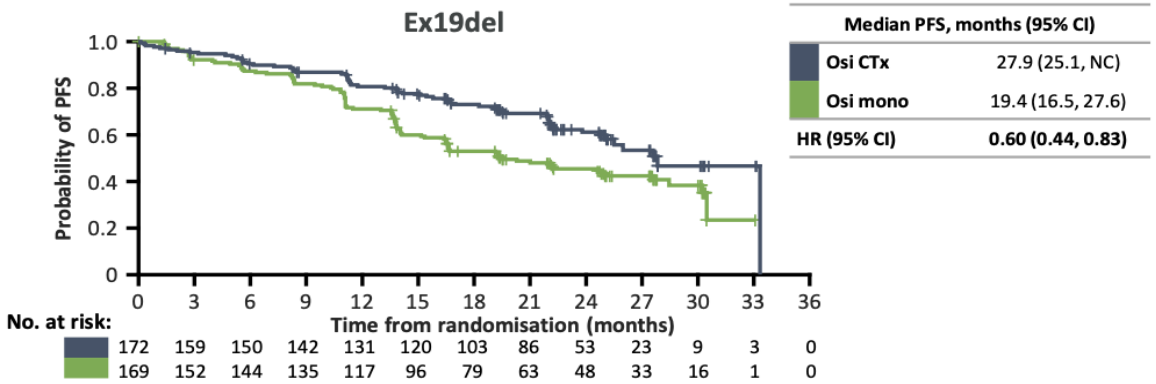
tel:279%20254%20241%203%200

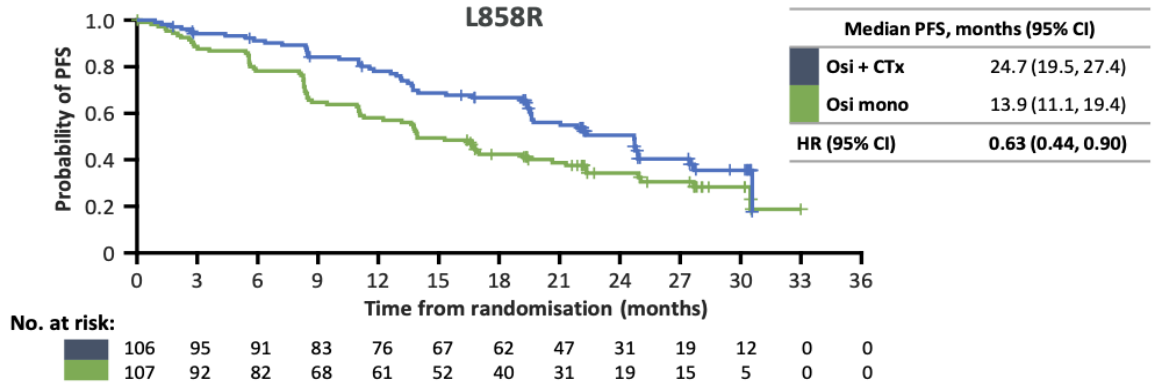
months (95% CI)	
Osimertinib + platinum-pemetrexed	29.4 (25.1, NC)
Osimertinib monotherapy	19.9 (16.6, 25.3)
HR (95% CI)	0.62 (0.48, 0.80); p=0.0002

Median PFS associated with osimertinib monotherapy was **consistent** across **FLAURA2** (16.7 months [95% CI 14.1, 21.3]) and **FLAURA** (18.9 months [95% CI 15.2, 21.4])[1,2]

SSS Metastazı ve EGFR Mutasyon Durumu



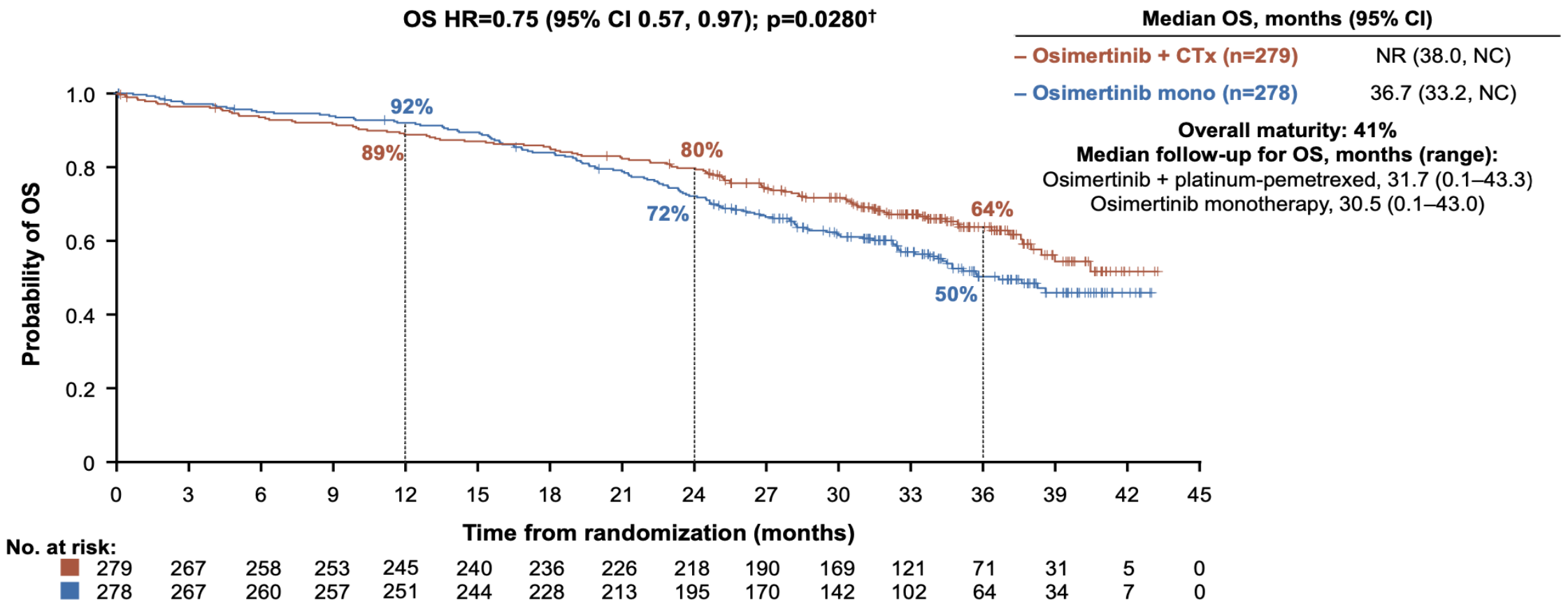




Planchard, Jänne et al., NEJM 2023

FDA approved in the US Feb 15th, 2024 !

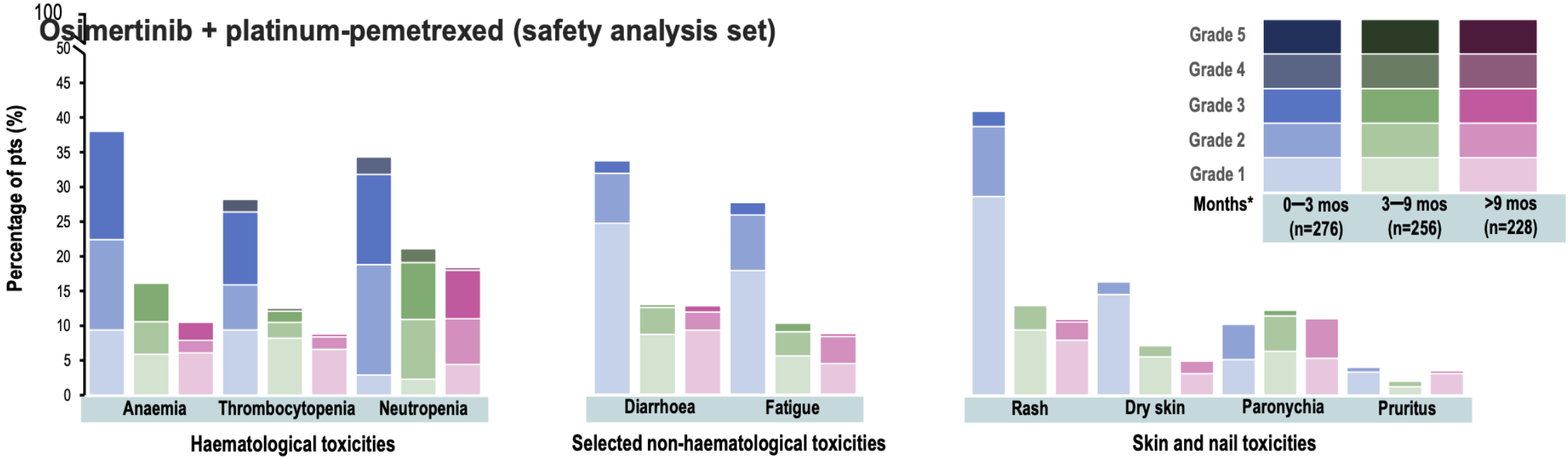
Bu Grafikten Genel Sağ Kalım Çıkar ☺

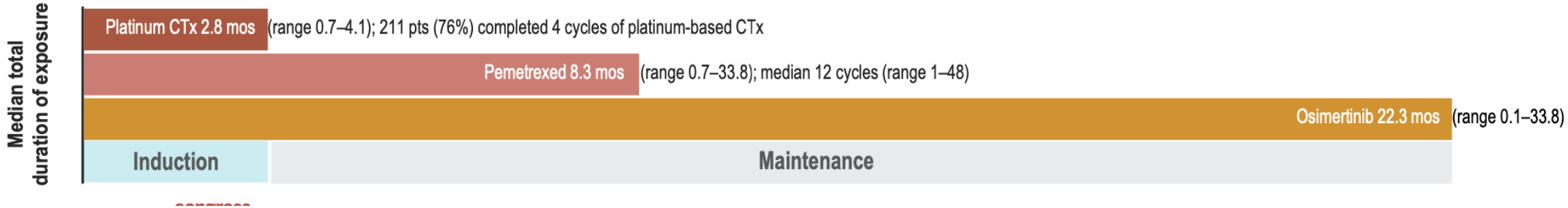


Data cut-off: 08 January 2024. HR was calculated by a stratified log-rank test. Figure from Valdiviezo N, et al. Presented at: ELCC 2024 (4O)
†A p-value of ≤0.000001 was required for statistical significance at this second interim analysis
Valdiviezo N, et al. ESMO Open 2024;9:102583
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; NC, not calculable; NR, not reached; OS, overall survival

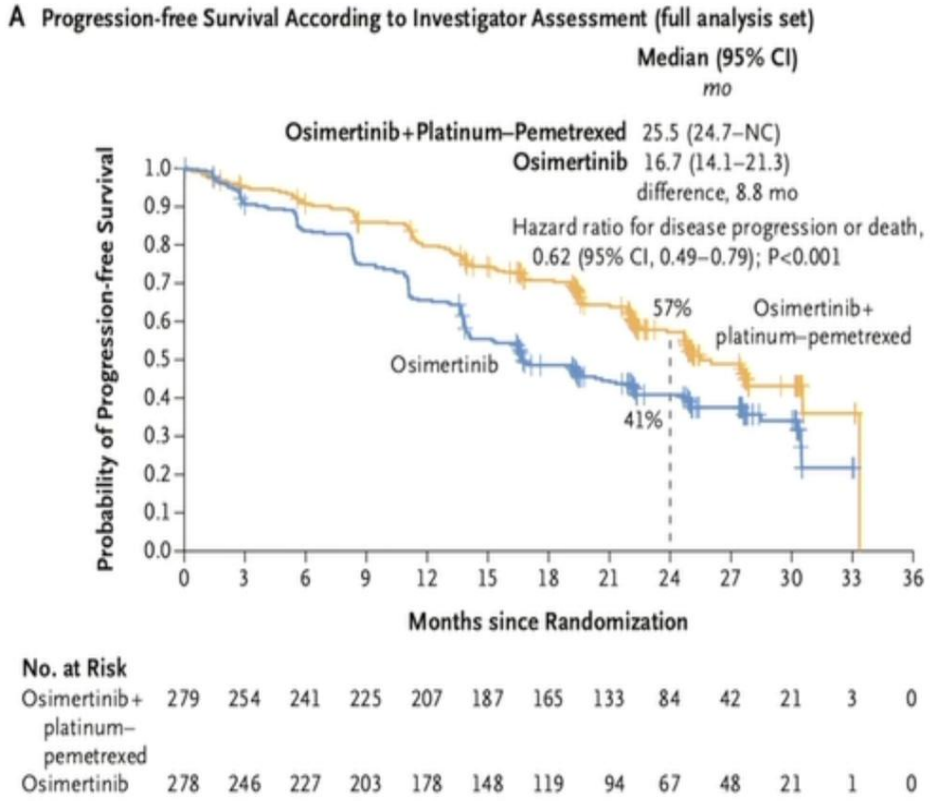
Yan etkiler erken dönemde çok olsa da zamanla azalma eğiliminde

- In the osi + CTx arm, the onset of ≥Grade 3 AEs reduced by ~50% between 0–3 mos (n=135; 49%) and 3–9 mos (n=62; 24%)





Flaura 2: Sonuç



FLAURA2

Platinum-Pemetrexed/Osimertinib vs. Osi mono

- **mPFS 25.5 months (HR vs. Osi, 0.62)**[1]
- **mOS** (*2nd interim analysis*)[3]: NR vs 36.7 mos, HR 0.75 95% confidence interval 0.57–0.97; p=0.0280*)
  **Did not reach prespecified level of statistical significance*

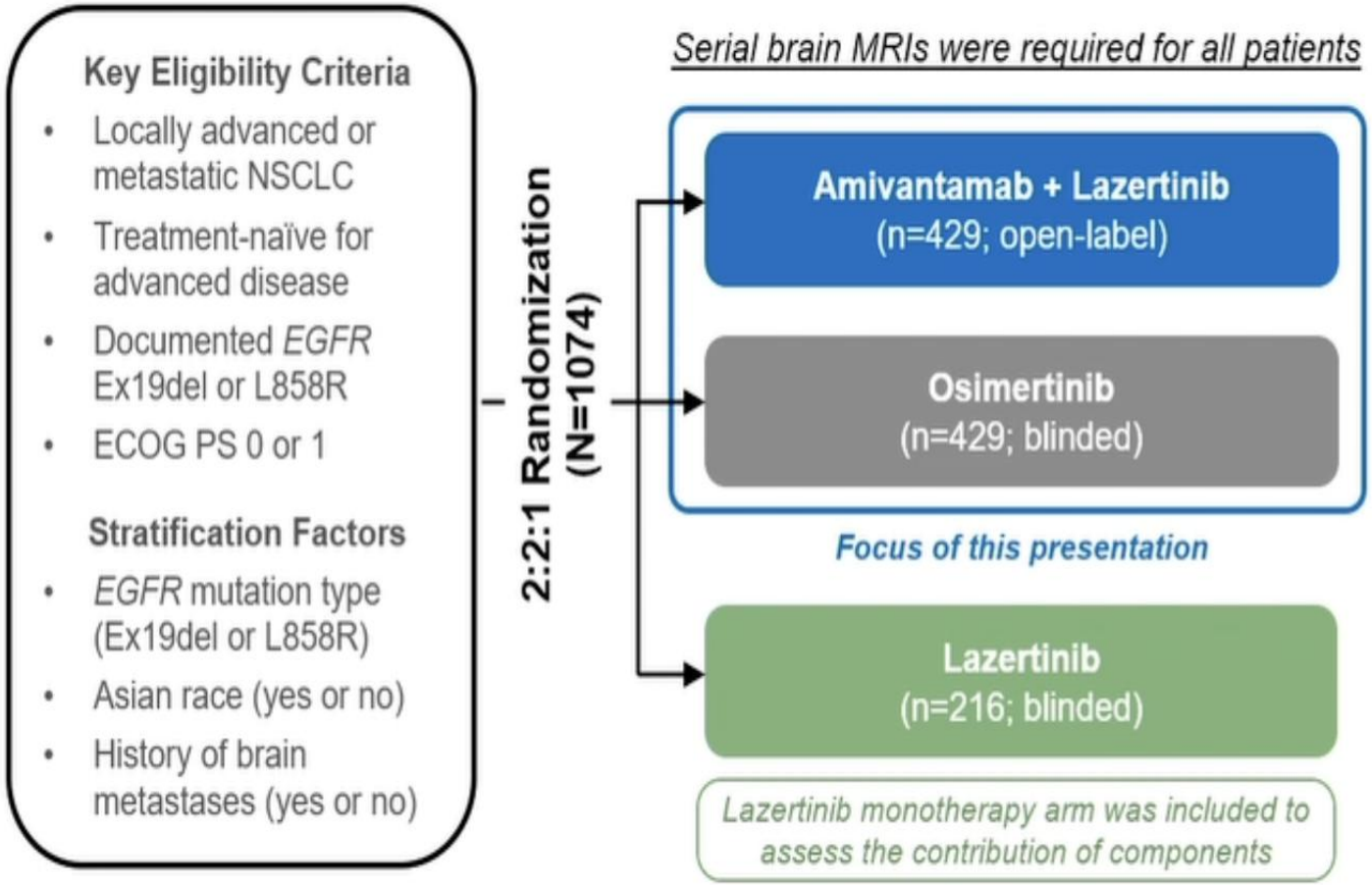
Toxicities: Myelosuppression, diarrhea, nausea, anorexia, rash

Key Factors:

- Requires IV administration q21 days
- Median pemetrexed exposure was **8.3 months**[2]
- More intracranial CRs and lower risk of intracranial progression with Osi/chemo suggest potential benefit in patients with CNS disease[2].

1. Planchard D, et al, NEJM 2023
2. Planchard D, et al, ESMO 2023
3. Valdiviezo Lama NI, ELCC 2024

Mariposa Çalışması



Primary endpoint of progression-free survival (PFS) by BICR per RECIST v1.1:

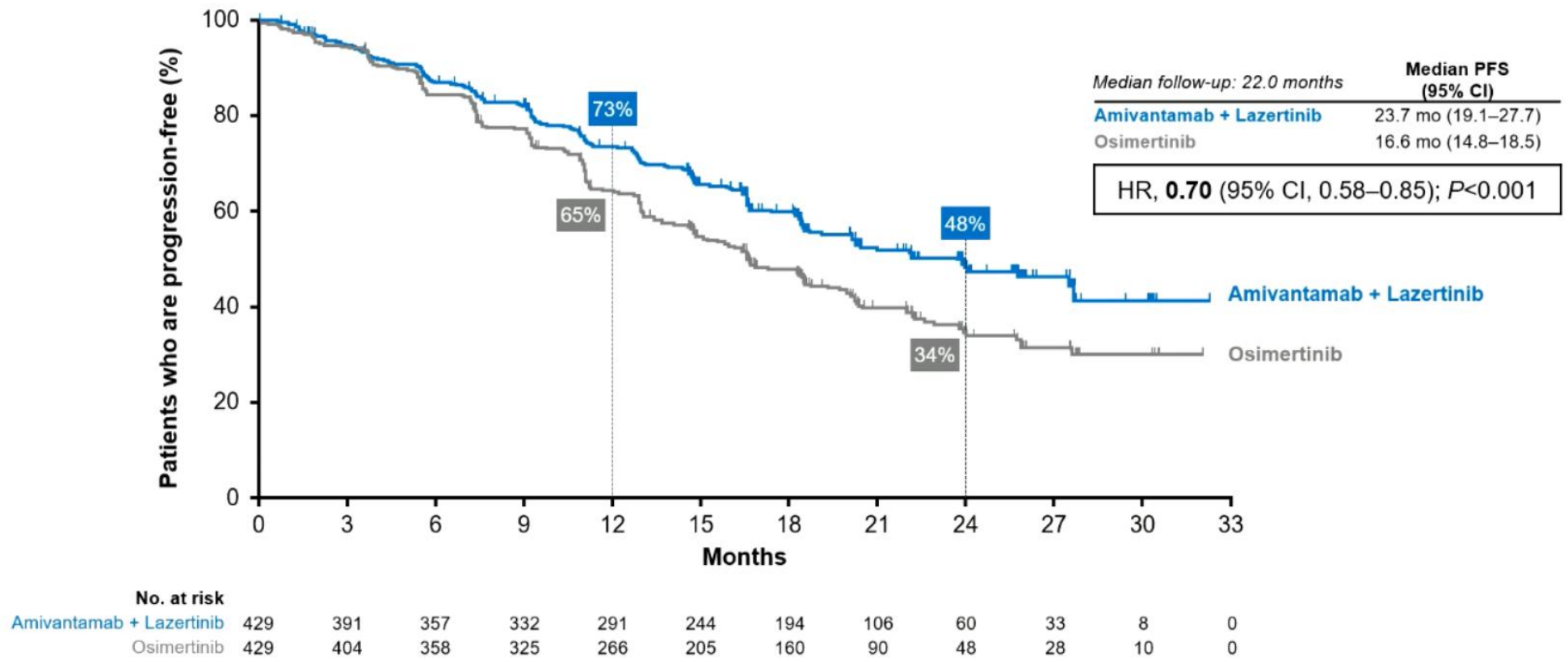
- **Amivantamab + lazertinib** vs osimertinib

Endpoints reported in this presentation[a]:

- Intracranial PFS (icPFS)
- Intracranial DoR (icDoR)
- Intracranial ORR (icORR)
- Time to treatment discontinuation (TTD)
- Time to subsequent therapy (TTST)
- PFS after first subsequent therapy (PFS2)
- Overall survival

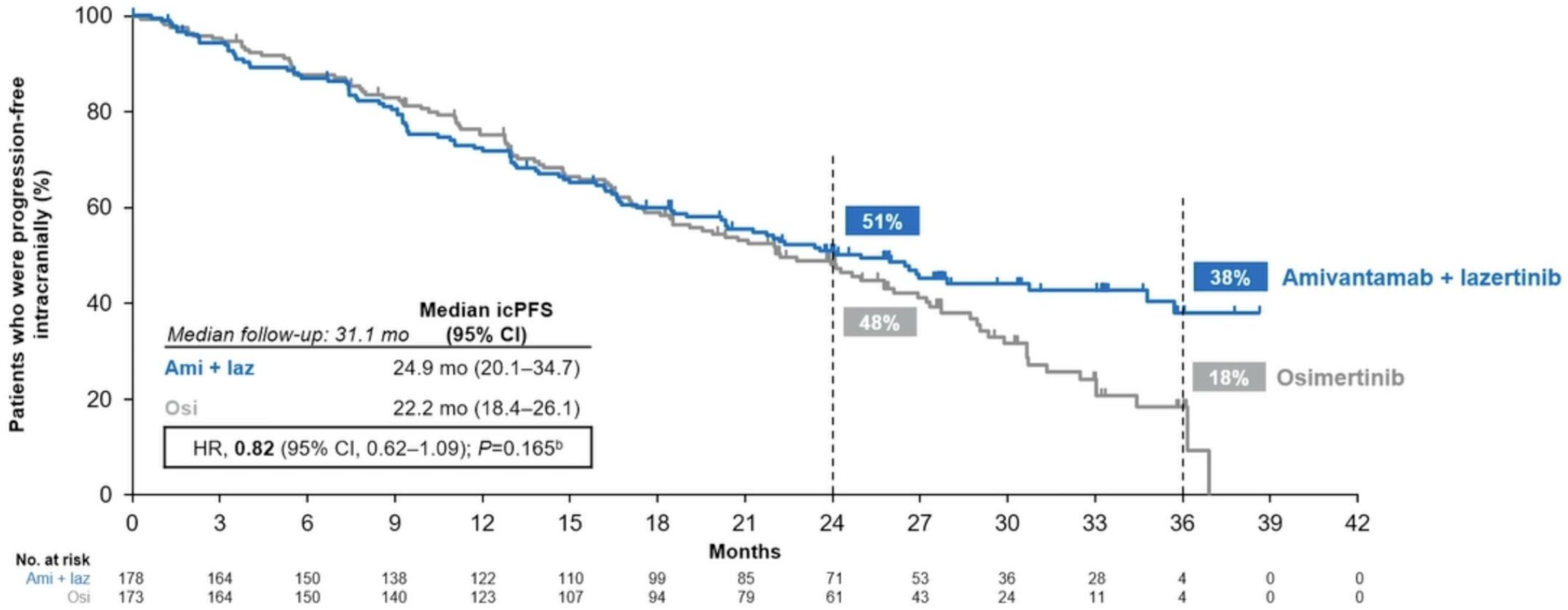
[a]Endpoints not part of formal statistical testing; all *P*-values in this presentation are nominal

Progresyonsuz Sağ Kalım



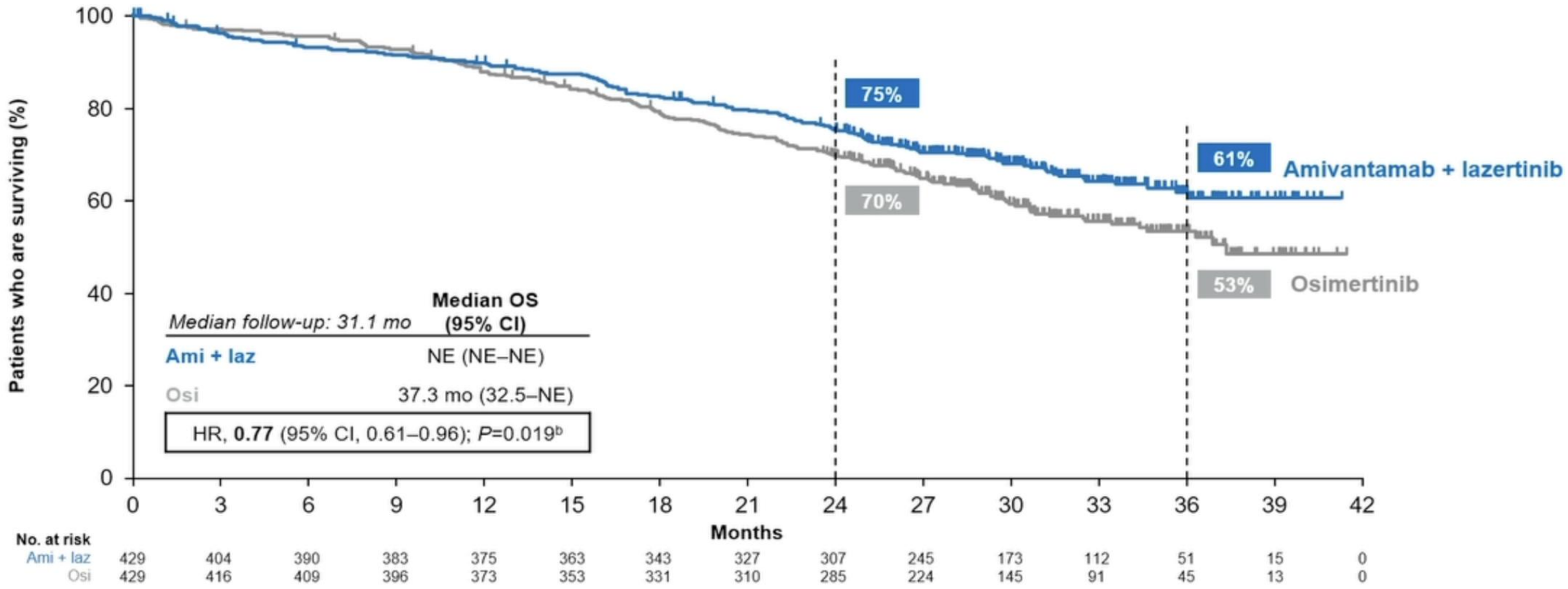
Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months

İntrakranial PFS



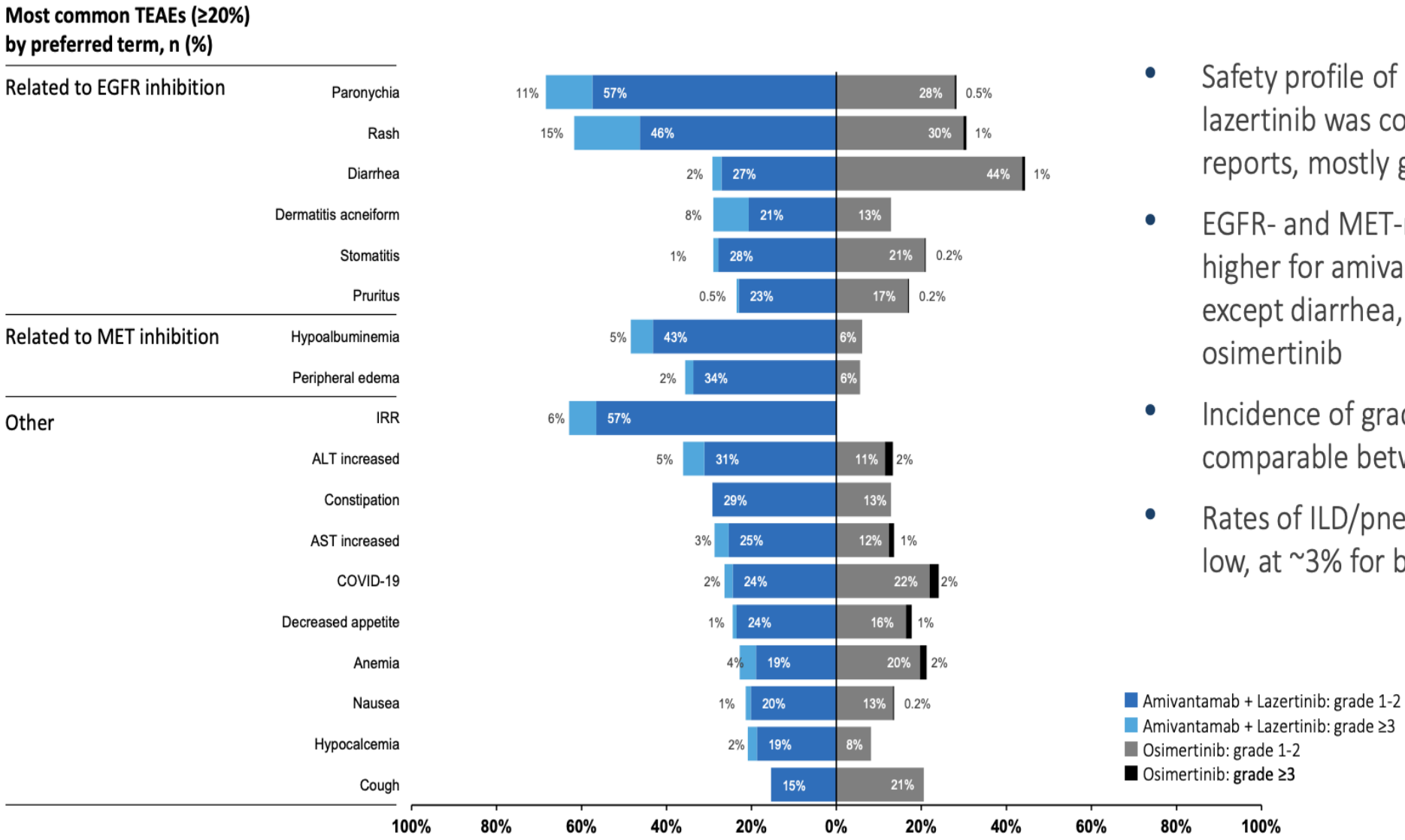
3-year landmark icPFS was double for amivantamab + lazertinib vs osimertinib (38% vs 18%)

Bu Grafikten de Genel Sağ Kalım Çıkar ☺



OS curves separate early and widen over time favoring amivantamab + lazertinib, with 61% of patients alive at 3 years vs 53% with osimertinib

Yan Etki



- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis remained low, at ~3% for both arms

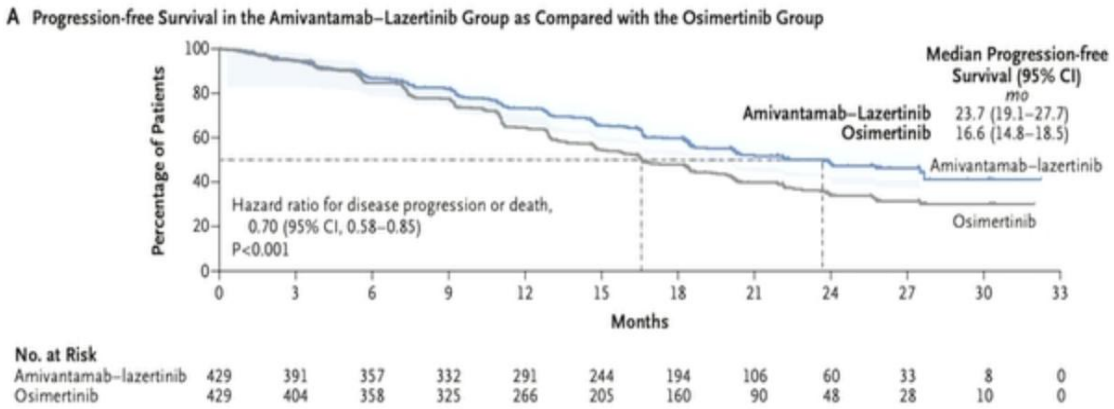
Yan Etki Özet

- Median treatment duration was 18.5 mo for amivantamab + lazertinib and 18.0 mo for osimertinib

TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)
Discontinuations of any agent	147 (35)	58 (14)

Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% with osimertinib

Mariposa: Sonuç



MARIPOSA[1]

Lazertinib + Amivantamab vs. Osimertinib

mPFS 23.7 months (HR vs. Osi, 0.70)[1]

mOS (*interim analysis, WCLC 2024*): HR 0.77 (95% CI, 0.61-0.96, p=0.019)[3]

Did not reach prespecified level of statistical significance

Toxicities: Paronychia, IRR*, rash, VTE

Key Factors:

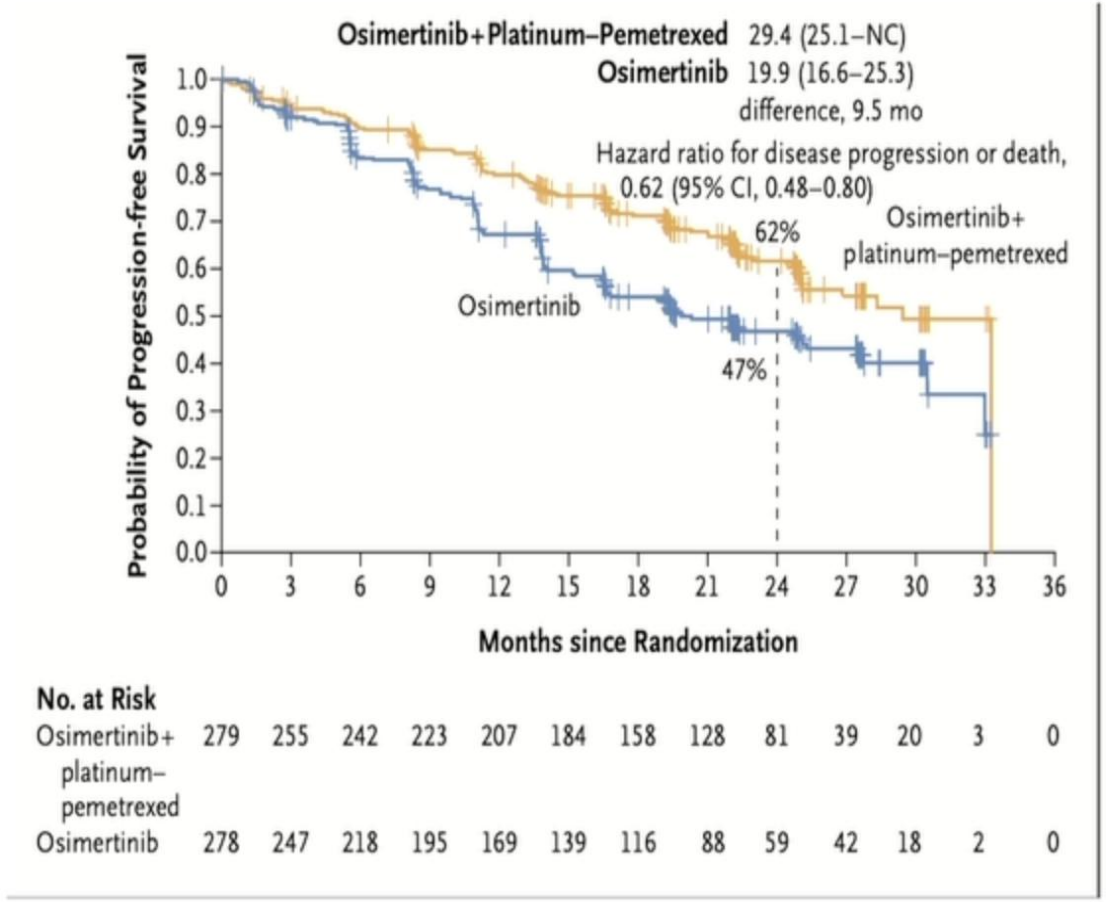
- IV administration with frequent initial visits*
- Significant dermatologic toxicities (rash, scalp irritation, paronychia)
- Benefit observed across high risk subgroups[2]
  - Detectable baseline ctDNA, HR 0.68
  - TP53 co-mutations, HR 0.65
  - Brain metastases, HR 0.69

**IRR less frequent with subcutaneous formulation*

1. Cho BC, NEJM 2024
2. Felip E, et al. ASCO 2024
3. Gadgeel S, et al, WCLC 2024

Benzer PFS Avantajı

Flaura 2



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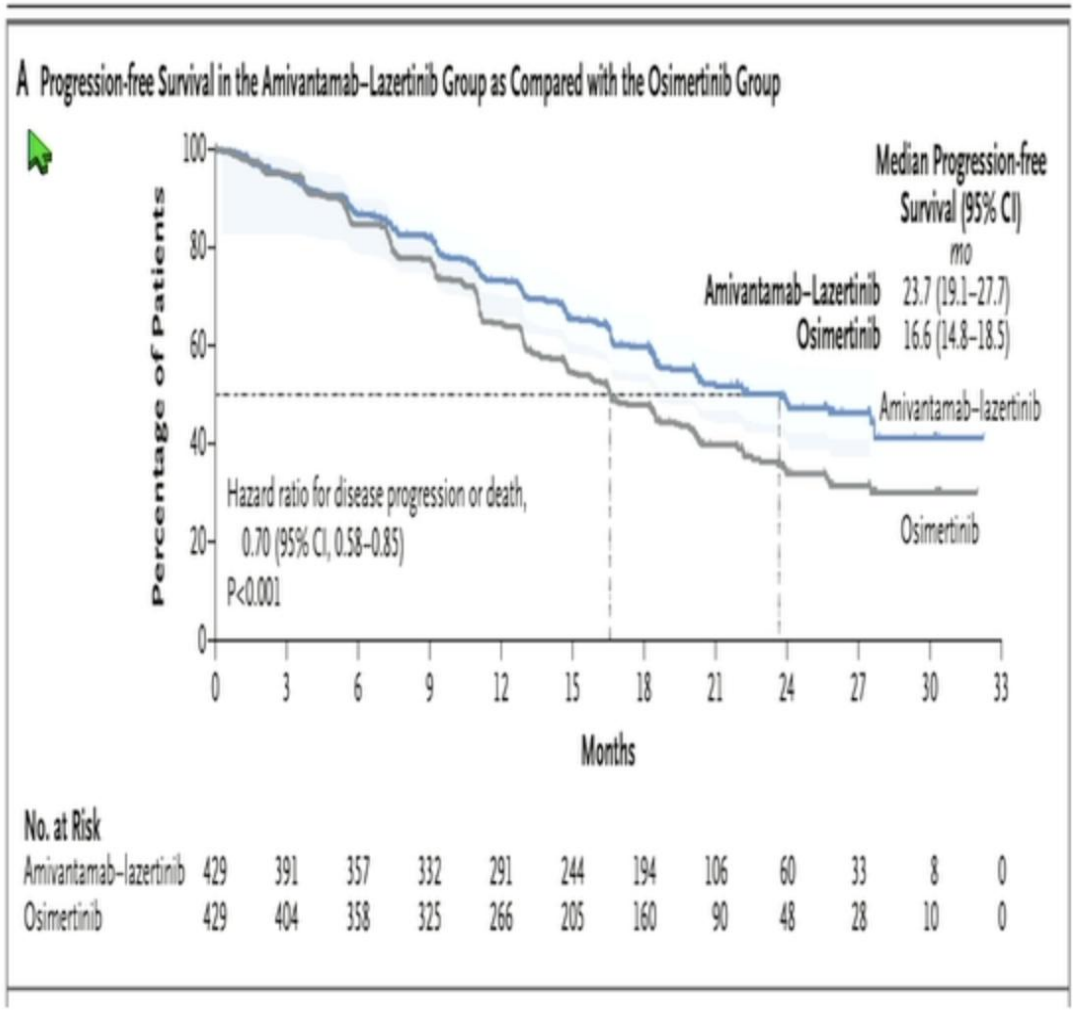
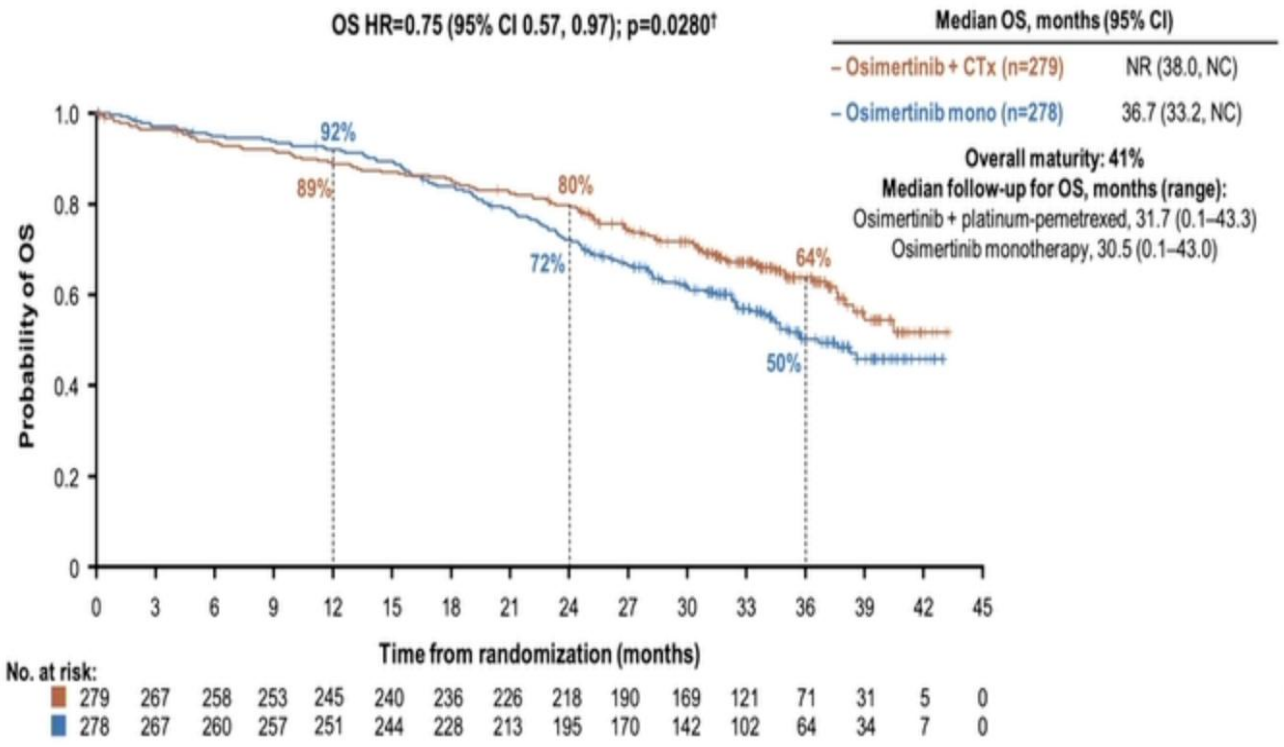


Benzer OS

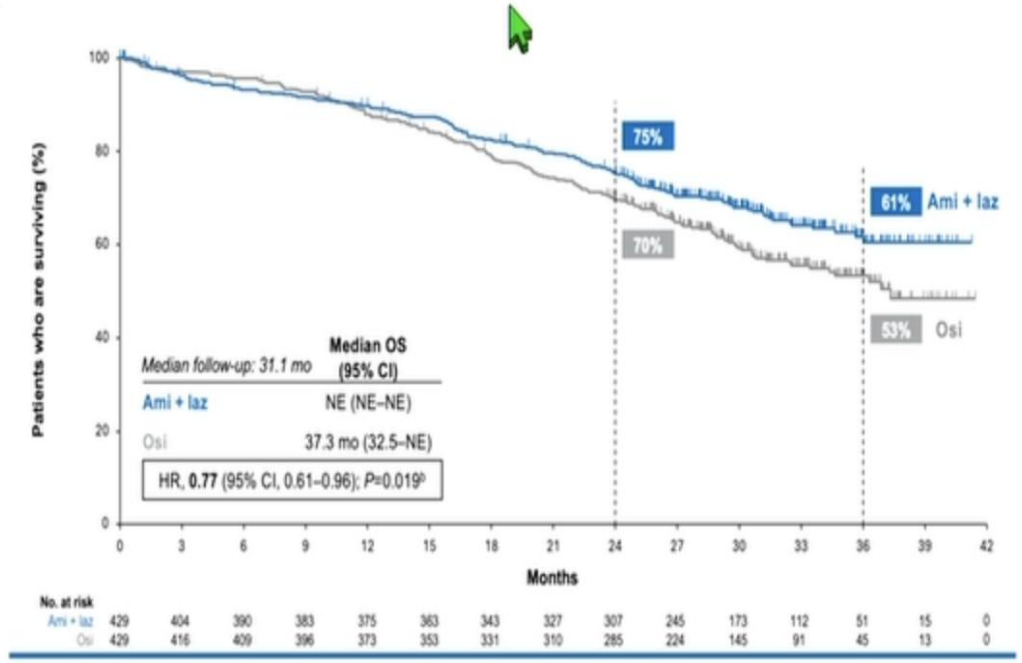
Flaura 2

HR 0.75



Mariposa

HR 0.77



Regimen	FDA Approved?	National guidelines?
Osimertinib monotherapy	Yes (April 2018)	Yes
Osimertinib + Platinum-Pemetrexed	Yes (February 2024)	Yes
Lazertinib + Amivantamab	Yes (August 2024)	No

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

***EGFR* EXON 19 DELETION OR EXON 21 L858R MUTATIONS[nn]**

FIRST-LINE THERAPY[rr]

***EGFR* exon 19 deletion or exon 21 L858R mutations**

***EGFR* mutation discovered prior to first-line systemic therapy**

Preferred
Osimertinib[ss] (category 1) → Progression → Subsequent Therapy (NSCL-22)

Other Recommended
Amivantamab-vmjw + lazertinib (category 1)[tt] → Progression → Subsequent Therapy (NSCL-22)
or
Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) (category 1) → Progression → Systemic Therapy, Subsequent (NSCL-K 4 of 5)

Useful in Certain Circumstances
Afatinib[ss] (category 1)
or Dacomitinib[ss] (category 1)
or Erlotinib[ss] (category 1)
or Erlotinib + bevacizumab[uu,vv]
or Erlotinib + ramucirumab
or Gefitinib[ss] (category 1)
→ Progression → Subsequent Therapy (NSCL-23)

***EGFR* mutation discovered during first-line systemic therapy**

Add osimertinib to pemetrexed + (cisplatin or carboplatin) (nonsquamous) → Progression → Systemic Therapy, Subsequent (NSCL-K 4 of 5)
or
Interrupt current therapy[ww,xx] and start Osimertinib or Amivantamab-vmjw + lazertinib[tt] → Progression → Subsequent Therapy (NSCL-22)
or
Afatinib or Dacomitinib or Erlotinib or Erlotinib + bevacizumab[uu,vv] or Erlotinib + ramucirumab or Gefitinib → Progression → Subsequent Therapy (NSCL-23)

- Yaşlı, Performans düşük, tm yükü düşük, SSS met yok veya sınırlı, toksisite korkutuyorsa → OSİMERTİNİB

- Tam tersi → OSİMERTİNİB + KT

- Amivantanab + Lazertinib data güzel ama Uygulama ?? Maliyet?? Toksisite ??

- PEKİ 3. JENERASYON KULLANDIK
- SONRA????

MARIPOSA 2

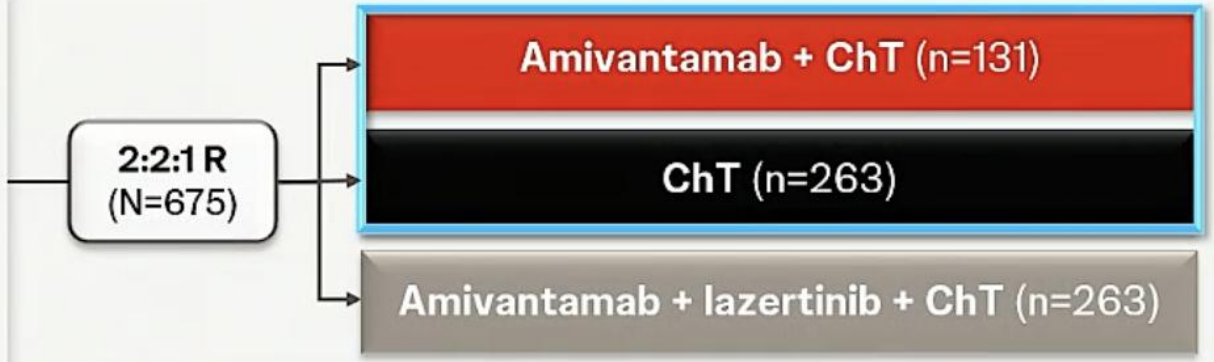
Amivantamab + ChT ± lazertinib vs ChT in *EGFR*-mutant advanced NSCLC, post-osimertinib*

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Documented *EGFR* exon19del or L858R
- Progressed on or after osimertinib monotherapy (as most recent line)
- ECOG PS 0 or 1
- Stable brain metastases were allowed; radiation/definitive therapy was not required (untreated)

Stratification factors

- Osimertinib line of therapy (1L or 2L)
- Asian race (yes or no)
- History of brain metastases (yes or no)



Serial brain MRIs were required for all patients†

Dosing (in 21-day cycles):

Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Cycle 3 (Week 7)

Lazertinib: 240 mg daily starting after completion of carboplatin‡

ChT administered at the beginning of every cycle:

- Carboplatin: AUC5 for the first 4 cycles
- Pemetrexed: 500 mg/m^2 until PD

Dual primary endpoint of PFS§ by BICR per RECIST v1.1

- Amivantamab + lazertinib + ChT vs ChT
- Amivantamab + ChT vs ChT

Secondary endpoints

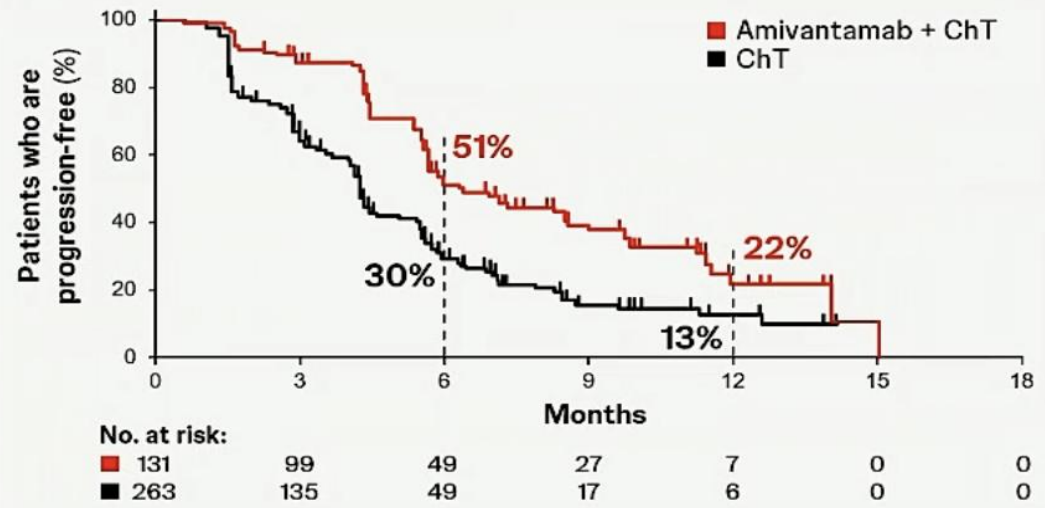
- ORR§
- DoR
- OS§
- Intracranial PFS
- TTST
- PFS2
- Symptomatic PFS
- Safety

*Data cut-off: 10 July 2023; †Patients who could not have an MRI were allowed to have CT scans; ‡All patients randomised before 7 November 2022 initiated lazertinib on the first day of Cycle 1; §Key statistical assumptions: 600 patients with 350 events across all 3 arms would provide approximately 83% and 93% power for amivantamab + ChT and amivantamab + lazertinib + ChT, respectively, vs ChT to detect a HR of 0.65 using a log-rank test, with an overall 2-sided alpha of 0.05 (mPFS of 8.5 months for amivantamab-containing arms vs 5.5 months for ChT). Statistical hypothesis testing included PFS, ORR, and then OS. 1/2L, first/second-line; AUC, area under the curve; BICR, blinded independent central review; ChT, chemotherapy; CT, computed tomography; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; exon19del, exon 19 deletion; HR, hazard ratio; mPFS, median PFS; MRI, magnetic resonance imaging; ORR, overall response rate; PD, progressive disease; PFS2, PFS after first subsequent therapy; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; TTST, time to first subsequent therapy.

1. Passaro A, et al. *Ann Oncol*. 2024:35;77–90;
2. Passaro A, et al. Presented at ESMO 2023: LBA15.

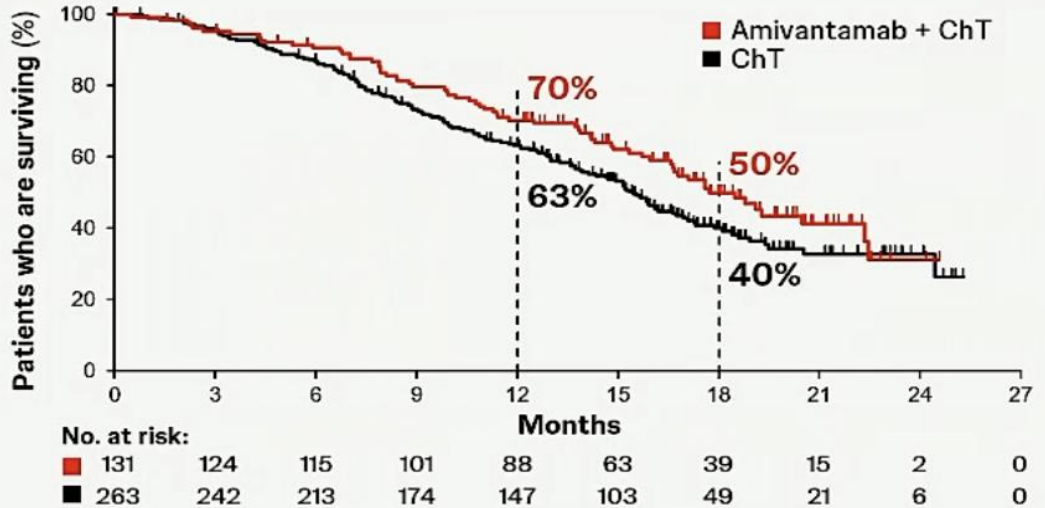
MARIPOSA 2

PFS*[1,2]



mPFS, months (95% CI)		
Amivantamab + ChT	**6.3** (5.6–8.4)	**HR, 0.48** (95% CI, 0.36–0.64); **p<0.001**
ChT	**4.2** (4.0–4.4)	

Second interim OS†[3]



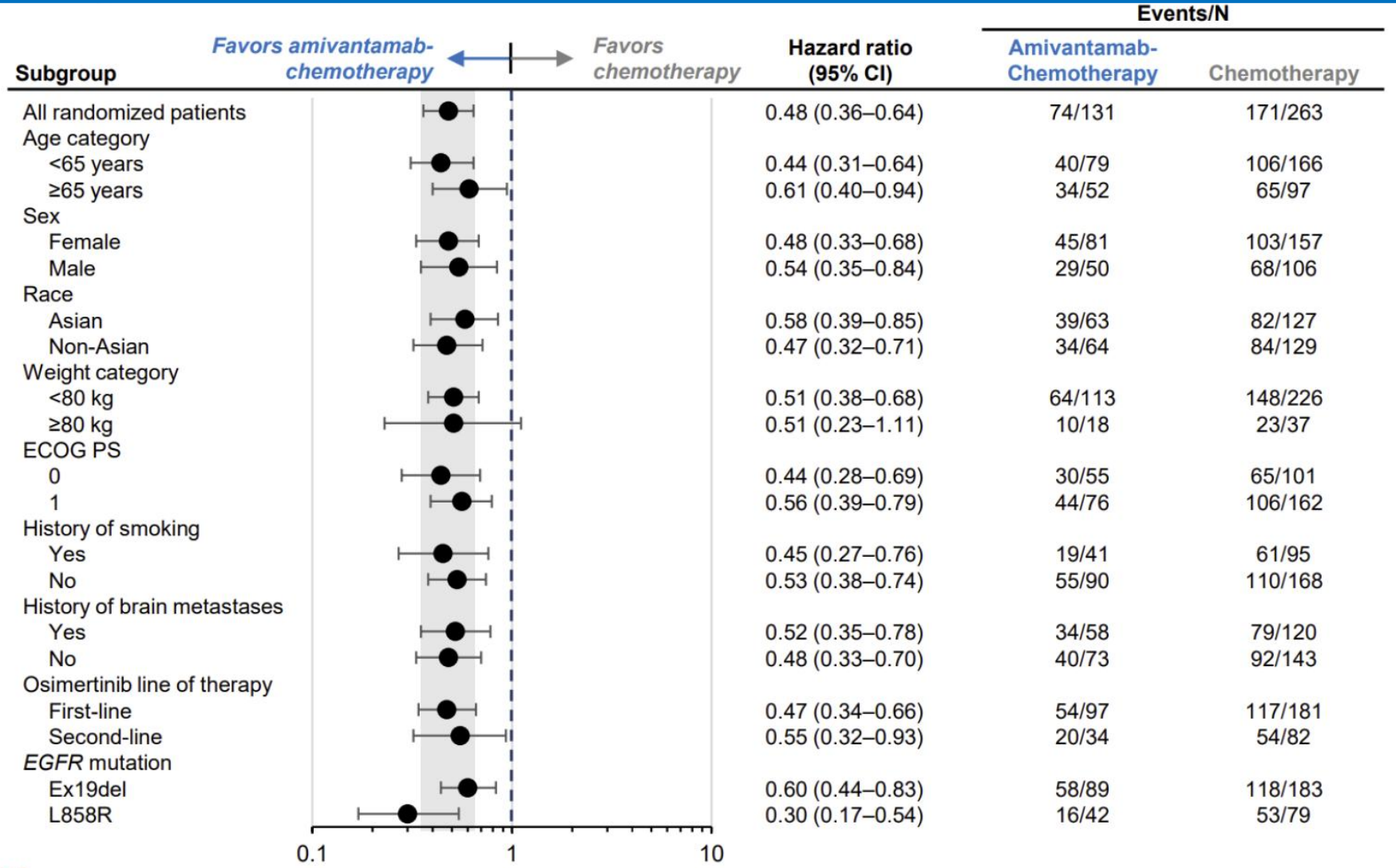
mOS, months (95% CI)		
Amivantamab + ChT	**17.7** (16.0–22.4)	**HR, 0.73** (95% CI, 0.54–0.99); **p=0.039‡**
ChT	**15.3** (13.7–16.8)	

Amivantamab + ChT reduced the risk of progression or death by 52% and demonstrated a favourable trend in OS in patients with *EGFR*-mutant NSCLC, post-osimertinib[1–3]

1. Passaro A, et al. *Ann Oncol*. 2024:35;77–90; 2. Gentzler RD, et al. Presented at ELCC 2024: 3MO; 3. Popat S, et al. Presented at ESMO 2024: LBA54.

*PFS by BICR assessment; †Median follow-up of 18.1 months; ‡P-value is from a log-rank test stratified by osimertinib line of therapy (1L or 2L), history of brain metastases (yes or no), and Asian race (yes or no). OS was evaluated at a 2-sided alpha of 0.0142.
1/2L, first/second-line; BICR, blinded independent central review; ChT, chemotherapy; HR, hazard ratio; mOS, median OS; mPFS, median PFS.

MARIPOSA 2



Subgroup	Hazard ratio (95% CI)	Events/N: Amivantamab-Chemotherapy	Events/N: Chemotherapy
All randomized patients	0.48 (0.36–0.64)	74/131	171/263
Age category			
<65 years	0.44 (0.31–0.64)	40/79	106/166
≥65 years	0.61 (0.40–0.94)	34/52	65/97
Sex			
Female	0.48 (0.33–0.68)	45/81	103/157
Male	0.54 (0.35–0.84)	29/50	68/106
Race			
Asian	0.58 (0.39–0.85)	39/63	82/127
Non-Asian	0.47 (0.32–0.71)	34/64	84/129
Weight category			
<80 kg	0.51 (0.38–0.68)	64/113	148/226
≥80 kg	0.51 (0.23–1.11)	10/18	23/37
ECOG PS			
0	0.44 (0.28–0.69)	30/55	65/101
1	0.56 (0.39–0.79)	44/76	106/162
History of smoking			
Yes	0.45 (0.27–0.76)	19/41	61/95
No	0.53 (0.38–0.74)	55/90	110/168
History of brain metastases			
Yes	0.52 (0.35–0.78)	34/58	79/120
No	0.48 (0.33–0.70)	40/73	92/143
Osimertinib line of therapy			
First-line	0.47 (0.34–0.66)	54/97	117/181
Second-line	0.55 (0.32–0.93)	20/34	54/82
EGFR mutation			
Ex19del	0.60 (0.44–0.83)	58/89	118/183
L858R	0.30 (0.17–0.54)	16/42	53/79

MARIPOSA 2 Güvenlik

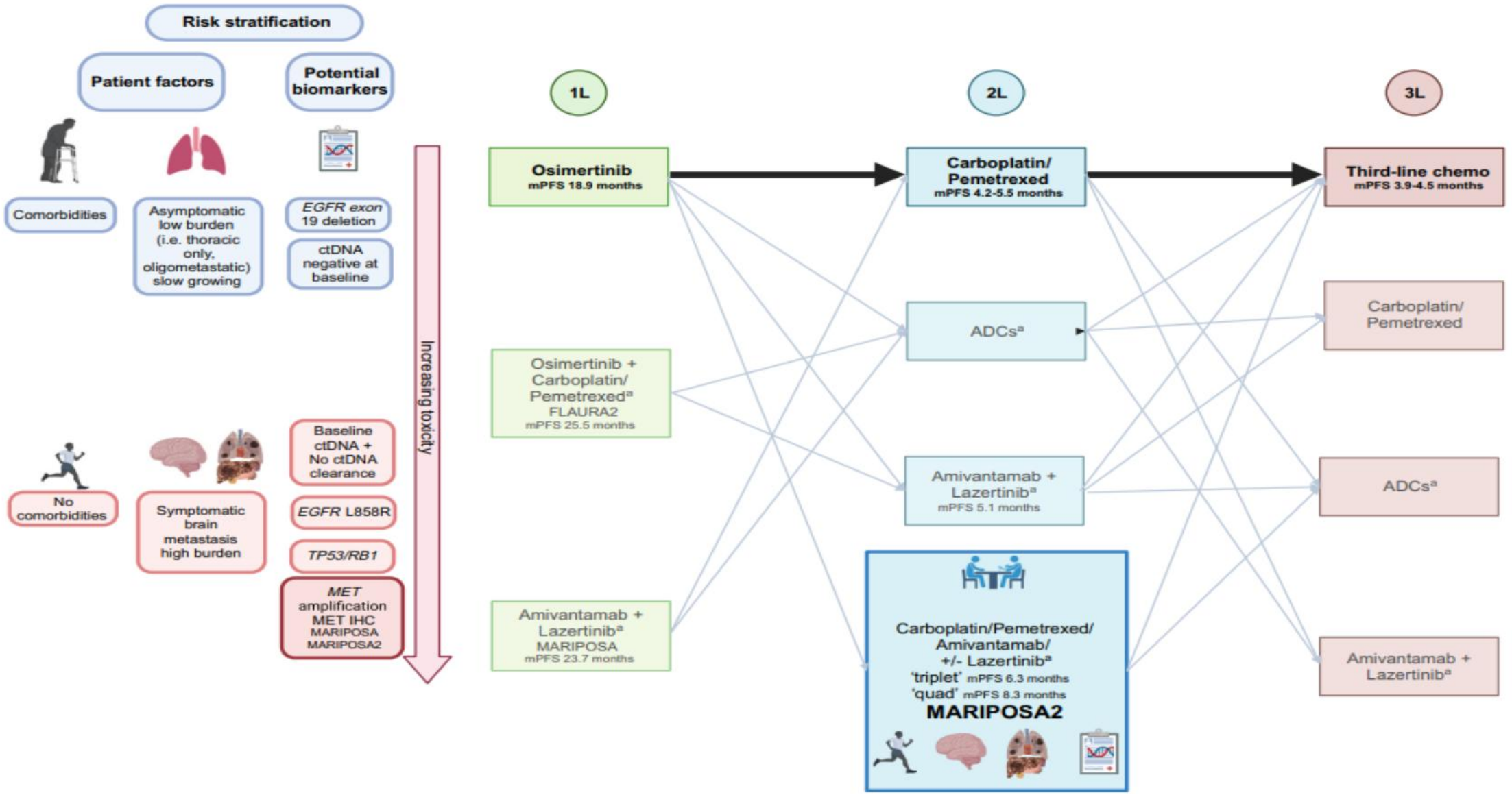
Most common TEAEs (≥25%) by preferred term, n (%)[1,2]		Amivantamab + ChT (n=130)		ChT (n=243)	
		All Grades	Grade ≥3	All Grades	Grade ≥3
Associated with EGFR inhibition	Paronychia	48 (37)	3 (2)	1 (0.4)	0
	Rash	56 (43)	8 (6)	12 (5)	0
	Stomatitis	41 (32)	1 (1)	21 (9)	0
	Diarrhoea	18 (14)	1 (1)	16 (7)	1 (0.4)
Associated with MET inhibition	Hypoalbuminaemia	29 (22)	3 (2)	21 (9)	1 (0.4)
	Peripheral oedema	42 (32)	2 (2)	15 (6)	0
Associated with ChT	Neutropenia	74 (57)	59 (45)	101 (42)	52 (21)
	Thrombocytopenia	57 (44)	19 (15)	72 (30)	22 (9)
	Anaemia	51 (39)	15 (12)	97 (40)	23 (9)
	Leukopenia	37 (28)	26 (20)	68 (28)	23 (9)
Other	IRR	76 (58)	7 (5)	1 (0.4)	0
	Nausea	58 (45)	1 (1)	90 (37)	2 (1)
	Constipation	50 (38)	1 (1)	72 (30)	0
	Decreased appetite	40 (31)	0	51 (21)	3 (1)
	Vomiting	32 (25)	1 (1)	42 (17)	1 (0.4)
	Fatigue	36 (28)	4 (3)	47 (19)	4 (2)
	Asthenia	34 (26)	1 (1)	40 (16)	5 (2)
	ALT increase	26 (20)	7 (5)	67 (28)	10 (4)
AESIs by grouped term	Rash*	92 (71)	13 (10)	30 (12)	0
	VTE†	13 (10)	3 (2)	11 (5)	7 (3)
	ILD	2 (2)	1 (1)	0	0

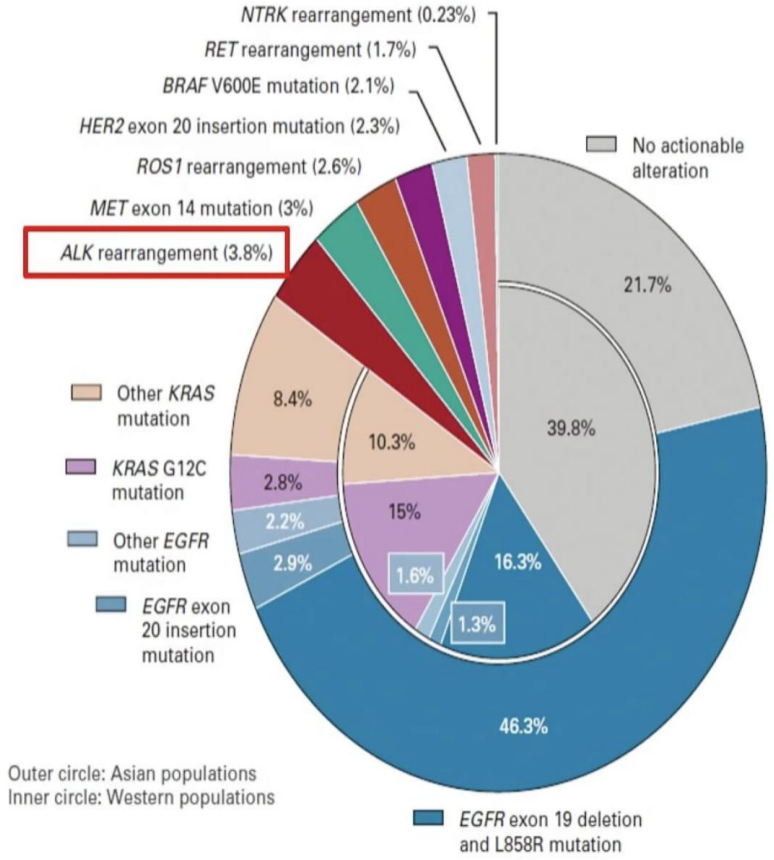
- Amivantamab + ChT demonstrated higher rates of EGFR- and MET-related AEs[1,2]
- Haematologic AE onset and severity were highest in Cycle 1 and decreased over time[3]
- Incidence of ILD was low[2]

*Grouping includes the following preferred terms: Rash, dermatitis acneiform, rash maculo-papular, erythema, acne, rash pruritic, rash erythematous, rash macular, drug eruption, folliculitis, dermatitis, skin lesion, rash pustular, papule, rash follicular, exfoliative rash, pustule, rash papular, skin exfoliation; †Grouping includes the following preferred terms: Pulmonary embolism, deep vein thrombosis, embolism, renal vein thrombosis, venous thrombosis limb, venous thrombosis, embolism venous, jugular vein thrombosis, superficial vein thrombosis, thrombophlebitis, thrombosis.
AE, adverse event; AESI, AE of special interest; ALT, alanine aminotransferase; ChT, chemotherapy; ILD, interstitial lung disease; IRR, infusion-related reaction; TEAE, treatment-emergent AE; VTE, venous thromboembolism.

1. Passaro A, et al. *Ann Oncol*. 2024:35;77–90; 2. Passaro A, et al. Presented at ESMO 2023: LBA15; 3. Gentzler RD, et al. Presented at ELCC 2024: 3MO.

Sonuç Olarak



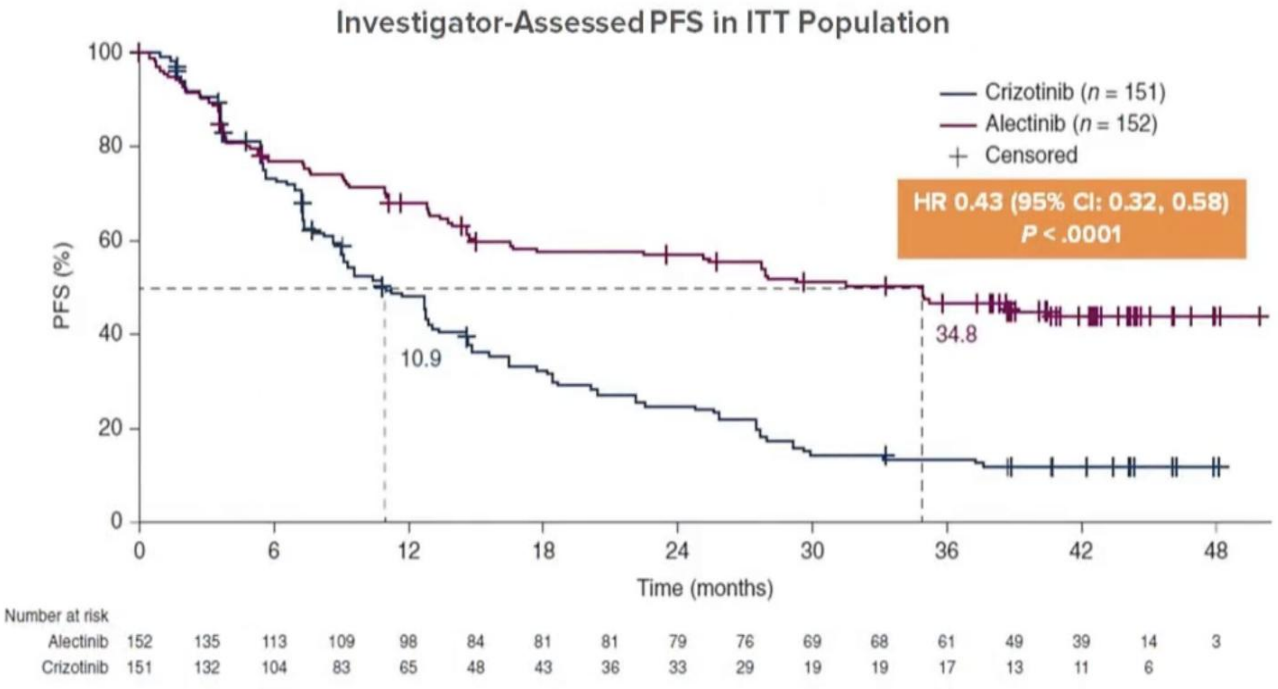


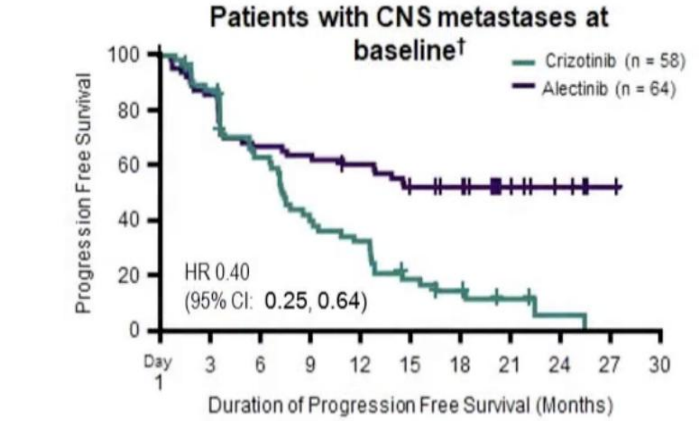
Tsao A, Tan D, JCO 2022

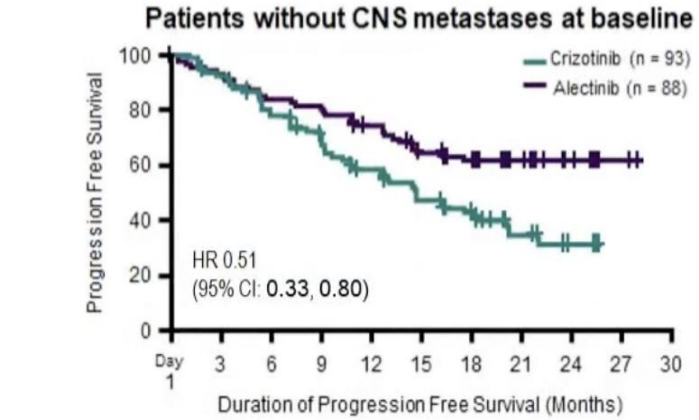
- Tüm KHDAK’ de yaklaşık %3-8 oranında
- Tüm adenokarsinomlar, sigara içmemiş %22
- Tüm adenokarsinomlar, sigara içmemiş ve EGFR (-) %33 görülmektedir.

- Adenokarsinom (asiner veya taşlı yüzük hücre morfolojisi)
- Perikardiyal Plevral effüzyon ile birliktelik sık
- Daha genç Medyan yaş: 52 (vs. 66)
- Tanı anında beyin metastazı sıklığı %30 Takipte %70

ALECTİNİB PFS





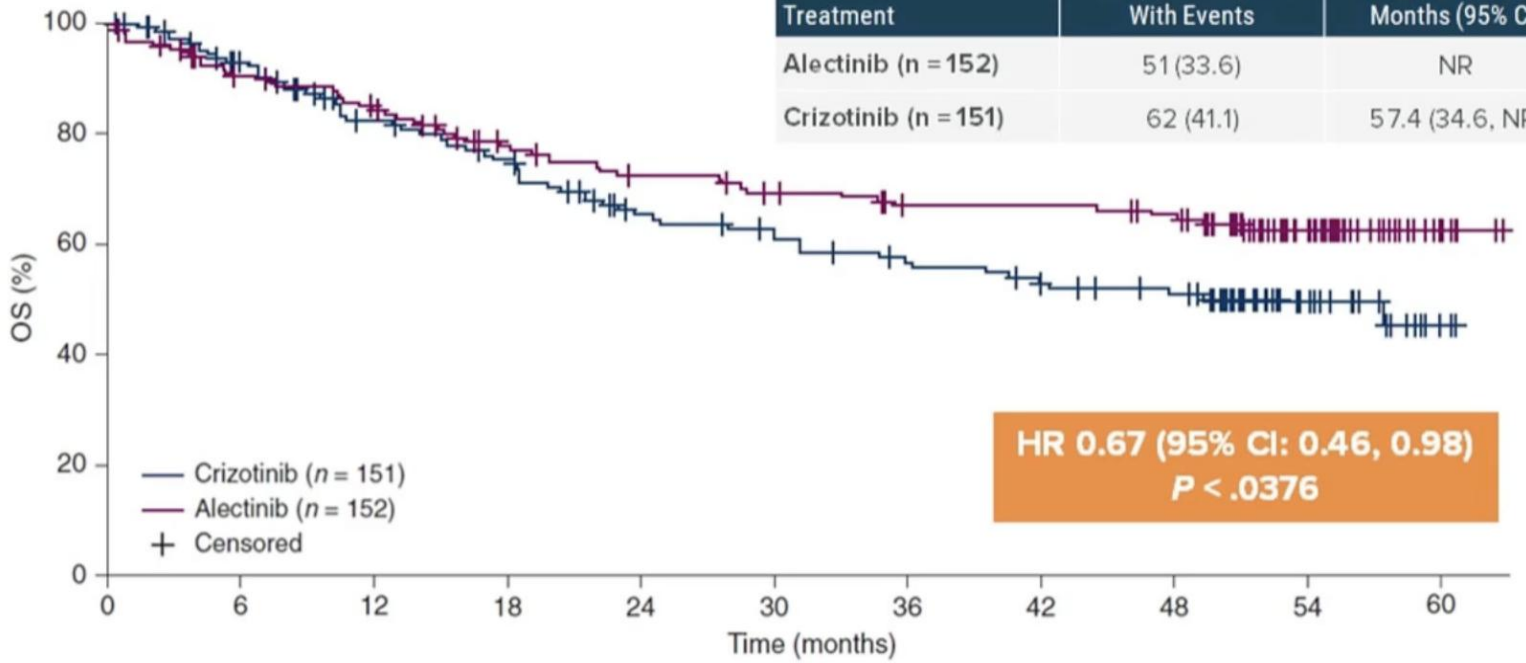


Mok T, et al. Ann Oncol. 2020;31:1056-1064; Gadgeel, Ann Oncol 2018;29:2214-2222

ALECTİNİB OS

Investigator-Assessed OS in ITT Population

Treatment	No. (%) of Patients With Events	Median OS Months (95% CI)	5-Year OS, % (95% CI)
Alectinib (n = 152)	51 (33.6)	NR	62.5 (54.3, 70.8)
Crizotinib (n = 151)	62 (41.1)	57.4 (34.6, NR)	45.5 (33.6, 57.4)



Number at risk

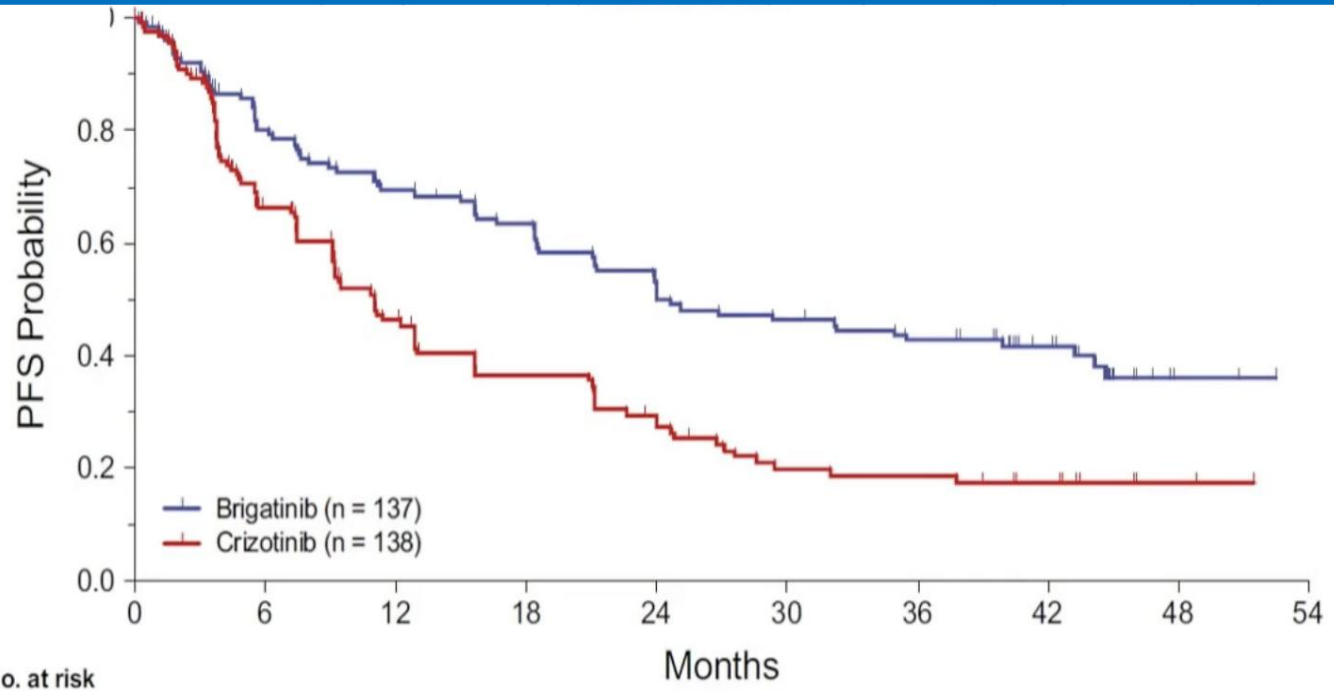
Alectinib	152	142	131	127	120	111	103	98	94	94	88	87	81	81	81	80	77	62	46	23	8
Crizotinib	151	141	128	116	104	100	93	84	73	71	67	63	60	59	55	51	48	35	18	12	3

Cross over to

Alectinib : 21.1%
Ceritinib: 21.1%
Brigatinib: 9.6%
Lorlatinib: 8.8%

Mok T, et al. Ann Oncol. 2020;31:1056-1064.

BRİGATİNİB PFS



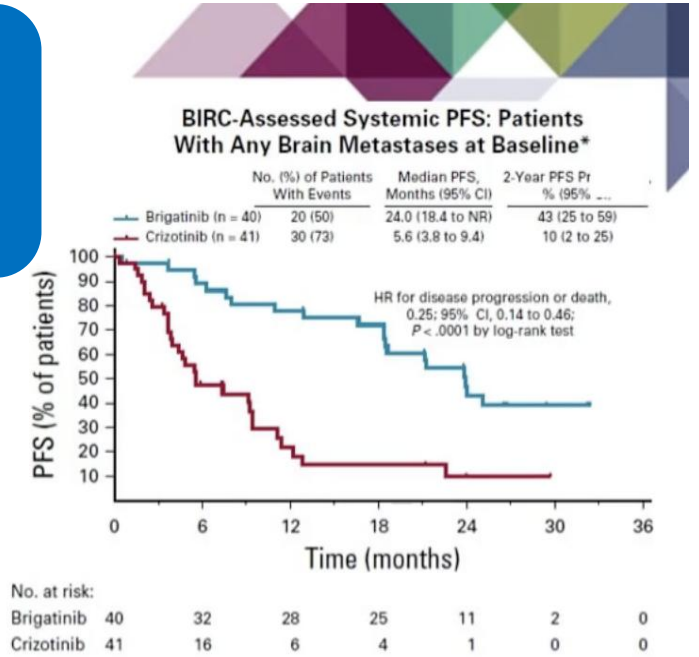
No. at risk

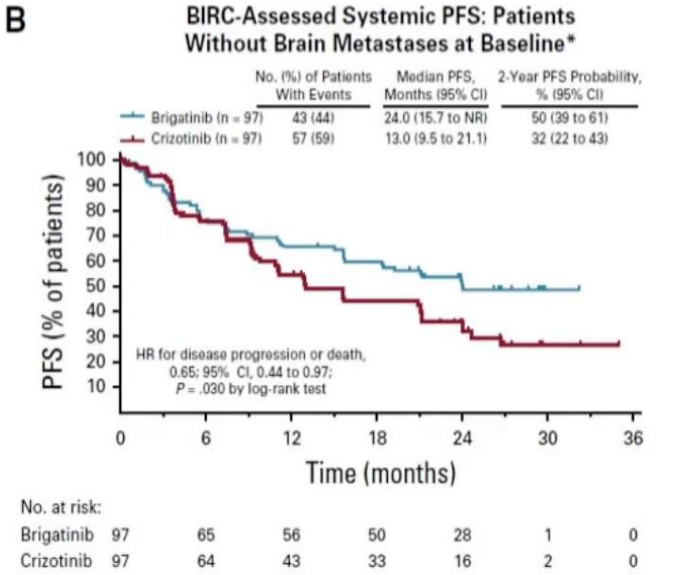
Brigatinib	137	97	84	75	59	53	47	30	2
Crizotinib	138	79	49	37	26	18	17	8	2

Treatment	No. (%) of Patients With Events	Median PFS Months (95% CI)	3-Year PFS, % (95% CI)	4-Year PFS, % (95% CI)
Brigatinib	73 (53)	24.0 (18.5, 43.2)	43 (34, 51)	36 (26, 46)
Crizotinib	93 (67)	11.1 (9.1, 13.0)	19 (12, 27)	18 (11, 26)

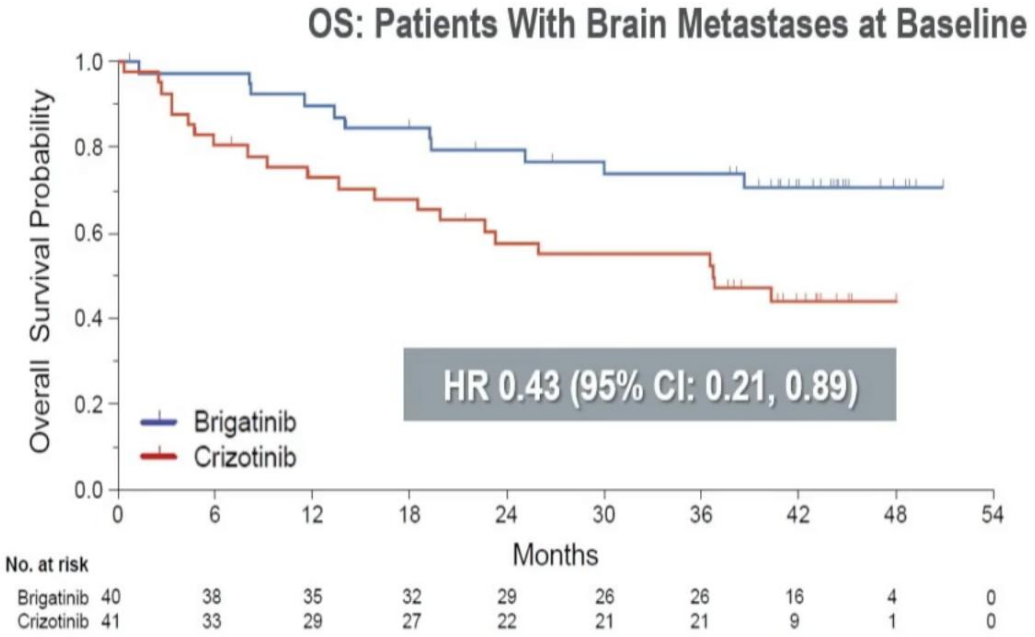
HR 0.48 (95% CI: 0.35, 0.66) *P* < .0001

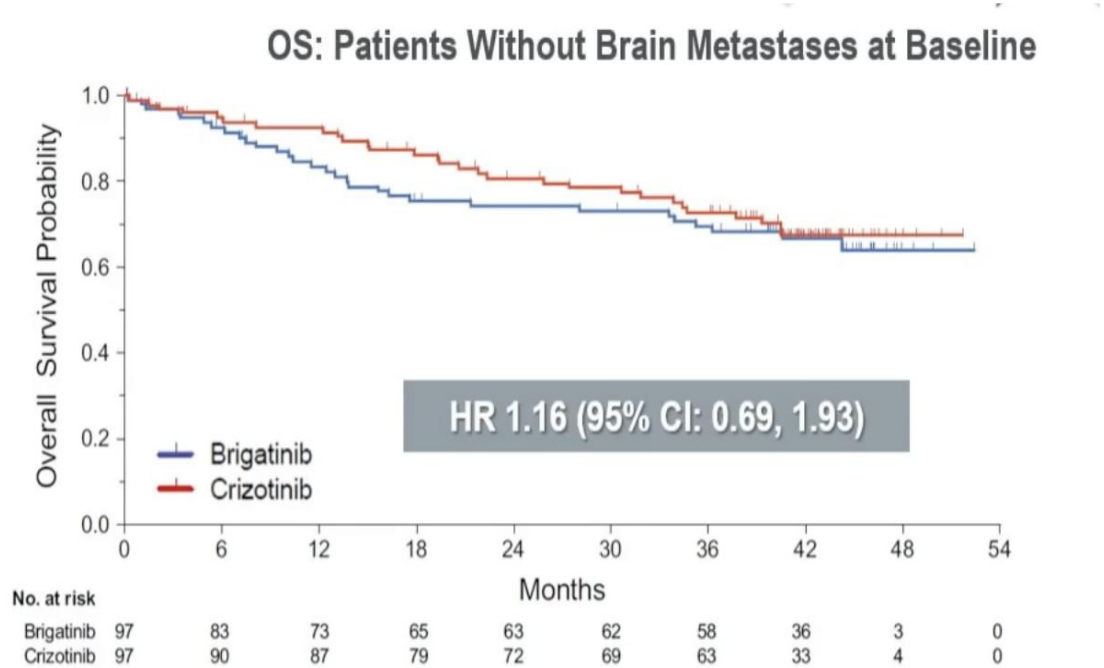
Camidge DR, et al. J Thorac Oncol. 2021; Camidge R, JCO 2020.





BRİGATİNİB OS





Treatment	Deaths, No. (%) Patients	3-Year Survival % (95% CI)	4-Year Survival % (95% CI)
Brigatinib (n = 40)	11 (28)	74 (57, 85)	71 (53, 83)
Crizotinib (n = 41)	22 (54)	55 (38, 69)	44 (28, 59)

Treatment	Deaths, No. (%) Patients	3-Year Survival % (95% CI)	4-Year Survival % (95% CI)
Brigatinib (n = 97)	30 (31)	70 (59, 78)	64 (52, 74)
Crizotinib (n = 97)	29 (30)	55 (62, 81)	67 (56, 76)

Camidge DR, et al. J Thorac Oncol. 2021;16:2091-2108.

Subsequent treatments in crizotinib arm: brigatinib (66%) and alectinib (23%)

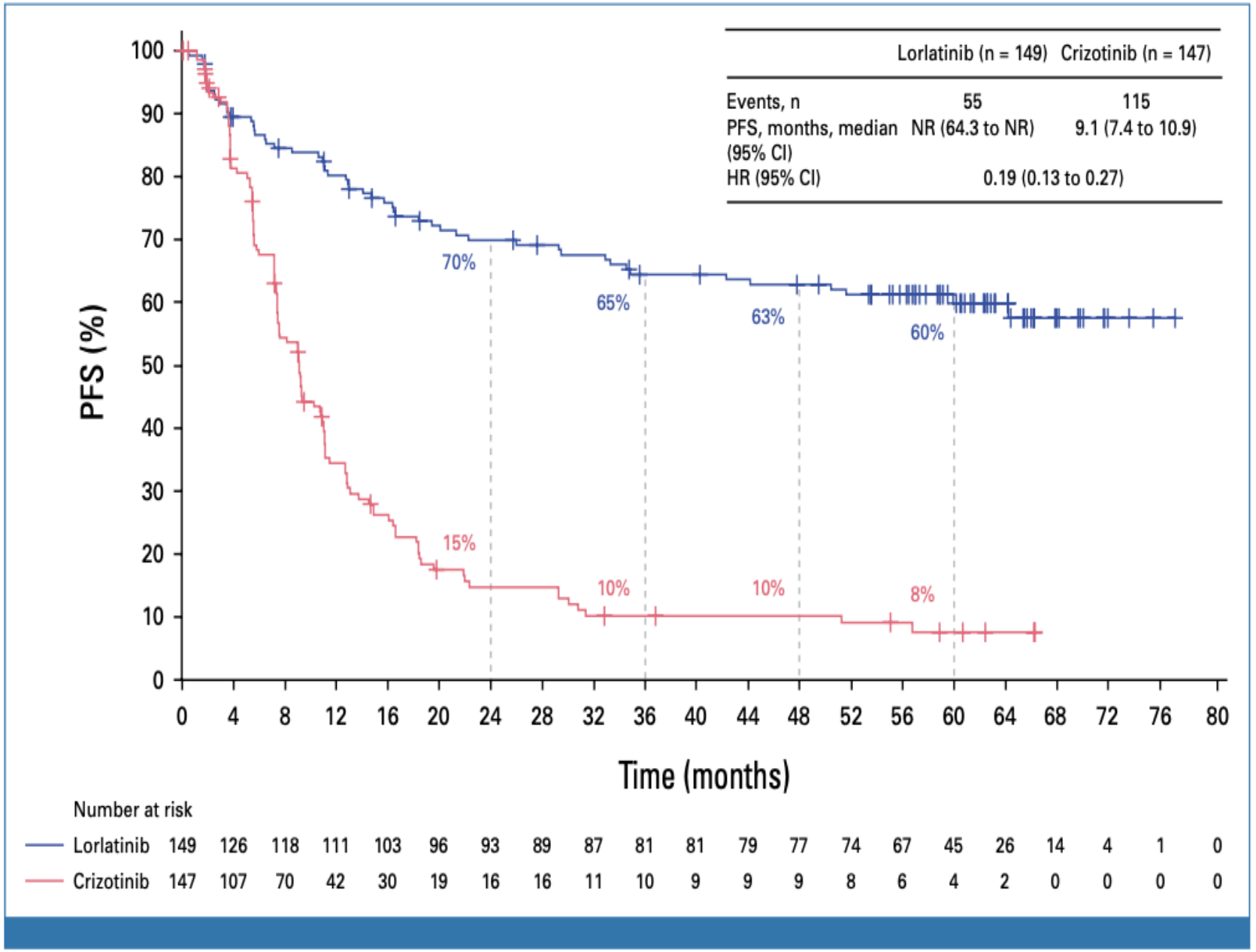
Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study

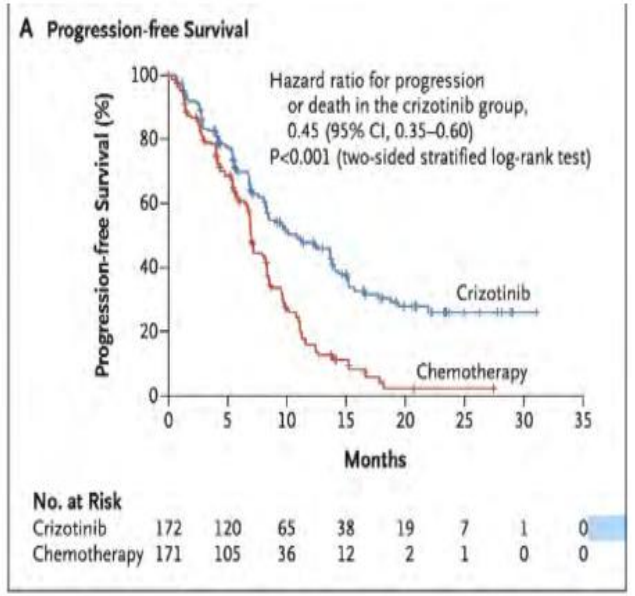
Benjamin J. Solomon, MBBS, PhD[1]; Geoffrey Liu, MD[2]; Enriqueta Felip, MD[3]; Tony S.K. Mok, MD[4]; Ross A. Soo, MBBS, PhD[5]; Julien Mazieres, MD[6]; Alice T. Shaw, MD, PhD[7]; Filippo de Marinis, MD[8]; Yasushi Goto, MD[9]; Yi-Long Wu, MD[10]; Dong-Wan Kim, MD, PhD[11]; Jean-François Martini, PhD[12]; Rossella Messina, PhD[13]; Jolanda Paolini, BS[13]; Anna Polli, BS[13]; Despina Thomaidou, MS[13]; Francesca Toffalorio, MD, PhD[13]; and Todd M. Bauer, MD[14]

CONCLUSION After 5 years of follow-up, median PFS has yet to be reached in the lorlatinib group, corresponding to the longest PFS ever reported with any single-agent molecular targeted treatment in advanced NSCLC and across all metastatic solid tumors. These results coupled with prolonged intracranial efficacy and absence of new safety signals represent an unprecedented outcome for patients with advanced *ALK*-positive NSCLC and set a new benchmark for targeted therapies in cancer.

PROFILE 1014

Solomon et al. NEJM 2014

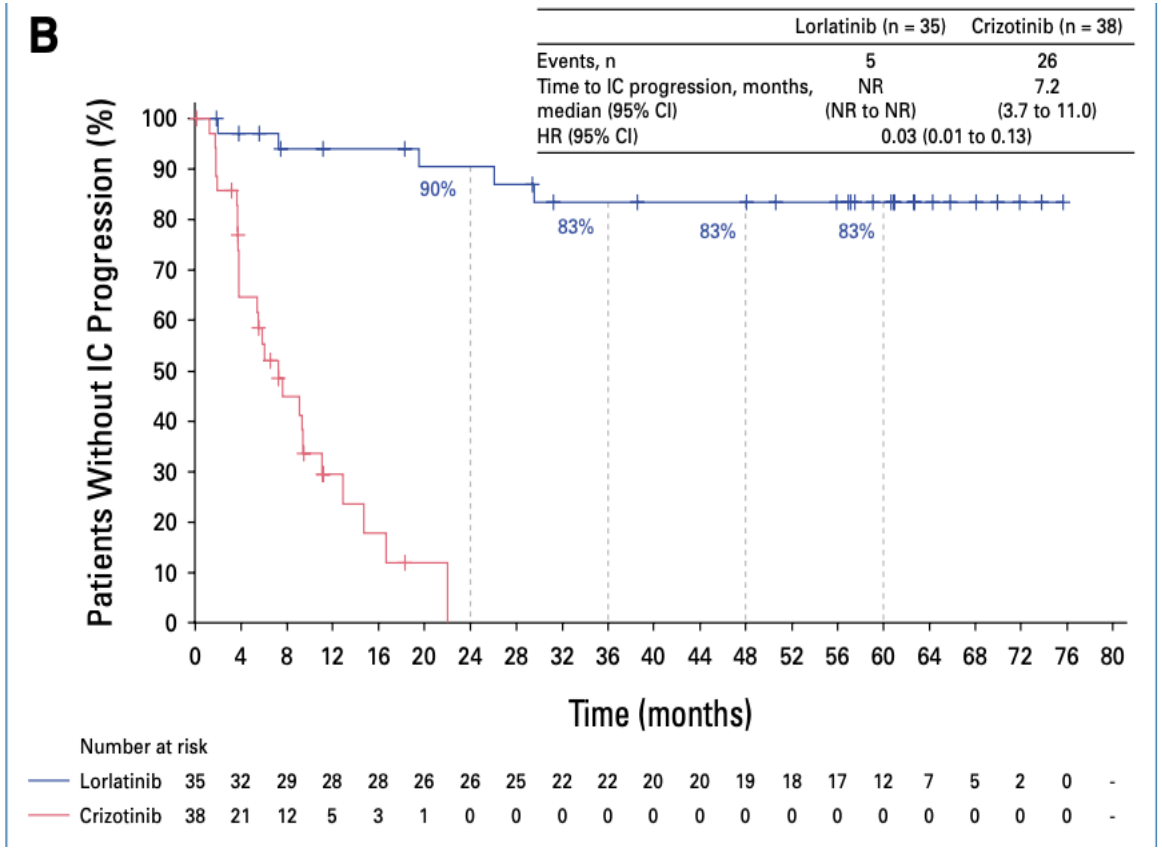


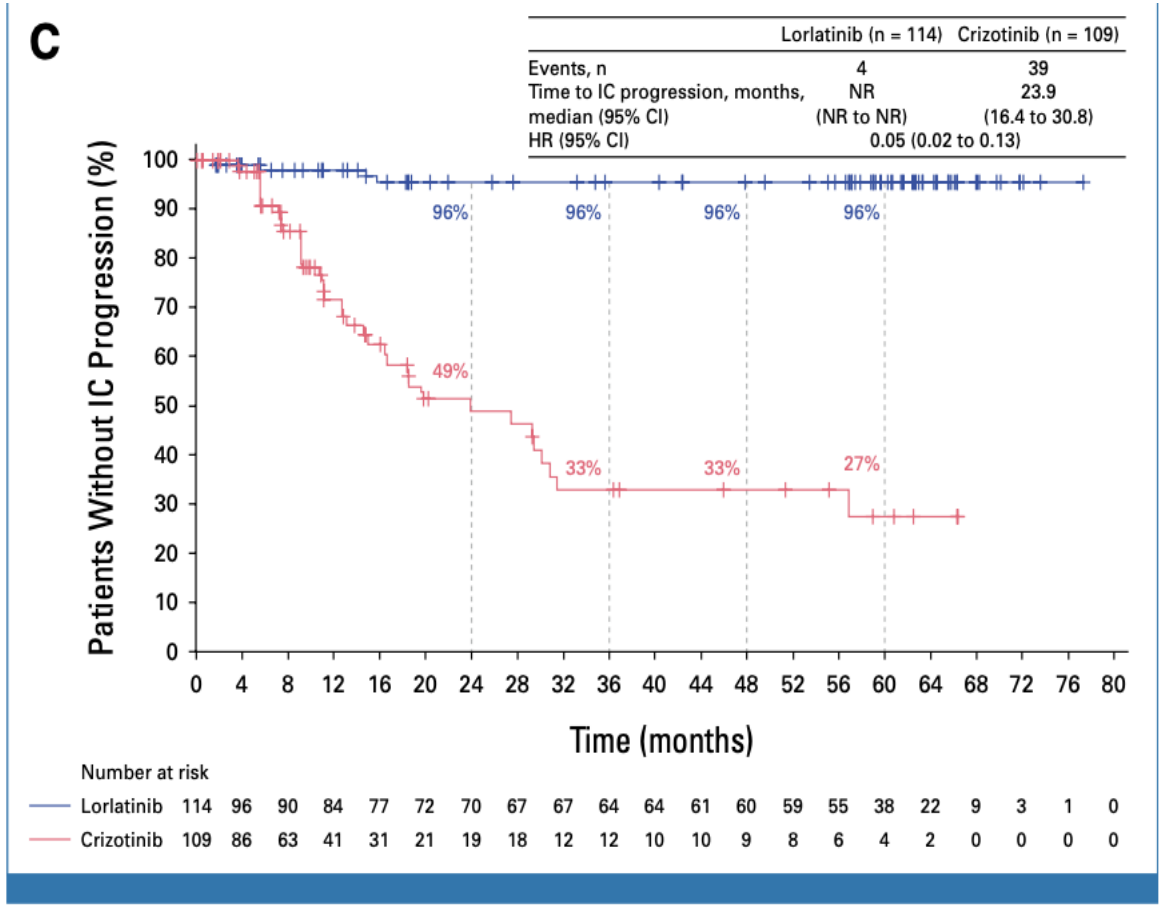


1014	PFS	HR	ORR
crizotinib	10.9	0.45	74 %
chemoT	7.0		45%

1st Line

CNS Met + ve CNS Met -





Sonuç→Yanıtlar

	Alectinib - ALEX	Brigatinib - ALTA-1L	Lorlatinib - CROWN
Brain metastases, % in the whole trial	40%	29%	26%
Prior radiotherapy to brain, % of patients with brain metastases	38%	13%	6%
Previous chemotherapy, %	0	27%	0
HR for PFS, BIRC (95% CI)	**0.50** (0.36 to 0.70)	**0.48** (0.35 to 0.66)	**0.27** (0.18 to 0.39)
HR for PFS, investigators (95% CI)	**0.43** (0.32 to 0.58)	**0.43** (0.31 to 0.58)	**0.19** (0.13 to 0.27)
3-year PFS, %	**46.4** (Inv.)	**43** (BIRC)	**63.5** (BIRC)
HR for PFS, patients with brain metastases at baseline	**0.37** (0.23 to 0.58) (Inv.)	**0.25** (0.14 to 0.46) (BIRC)	**0.21** (0.10 to 0.44) (BIRC)
HR for PFS, patients without brain metastases at baseline	**0.46** (0.31 to 0.68) (Inv.)	**0.65** (0.44 to 0.97) (BIRC)	**0.29** (0.19 to 0.44) (BIRC)

Peters S, et al. N Engl J Med. 2017;377:829-838; Gadgeel S, et al. Ann Oncol. 2018;29:2214-2222; Camidge DR, et al. N Engl J Med. 2018;379:2027-2039; Camidge DR, et al. J Thorac Oncol. 2021;16:2091-2108;. Shaw AT, et al. N Engl J Med. 2020;383:2018-2029; Solomon B et al., AACR 2022; Pérol M, Swalduz A, JCO 2022

Sonuç→Güvenlik ve Tolerabilite

	ALEX[b]		ALTA-1L[a]		CROWN[c]	
	Alectinib	Crizotinib	Brigatinib	Crizotinib	Lorlatinib	Crizotinib
TRAEs leading to dose reduction, %	**20.4**	19.9	**44**	25	**21**	15
TRAEs leading to treatment discontinuation, %	**14.5**	14.6	**13**	9	**7**	9
Most common grade ≥ 3 AEs *vs.* crizotinib	Anemia (5.9%), aspartate transaminase (5.3%), alanine aminotransferase (4.6%), pneumonia (4.6%)		Blood creatine phosphokinase (26%), lipase (15%), hypertension (14%), amylase (6%), pneumonia (5%)		**Hypercholesterolemia (16%), Hypertriglyceridemia (20%)** edema (4%), **weight gain (17%),** peripheral neuropathy (2%), cognitive effects (2%)	

Camidge DR, et al. J Thorac Oncol. 2021;16:2091-2108; b. Mok T, et al. Ann Oncol. 2020;31:1056-1064; c. Shaw AT, et al. N Engl J Med. 2020;383:2018-2029.

Sonuç

- ALK pozitif hastalık artık kronik hastalık
- Yan etkiler yönetebilir
- Uygulanabilir en etkin tedavi en önce olmalı B planı herzaman uygulamaya koyulamayabilir
- Yeni jenerasyon TKİ lar geliştirilmeye devam ediyor → Aşil effekti
- Kombinasyon yönetilemez toksisite
- TKİ sonrası Bispesifik İO VEGF vs kombinasyonları ?
- TKİ sonrası KT ve ADC ler gelebilir

→Hedeflenebilir mutasyonu olanda yoldan şaşma sonuna kadar mutasyon için uğraş

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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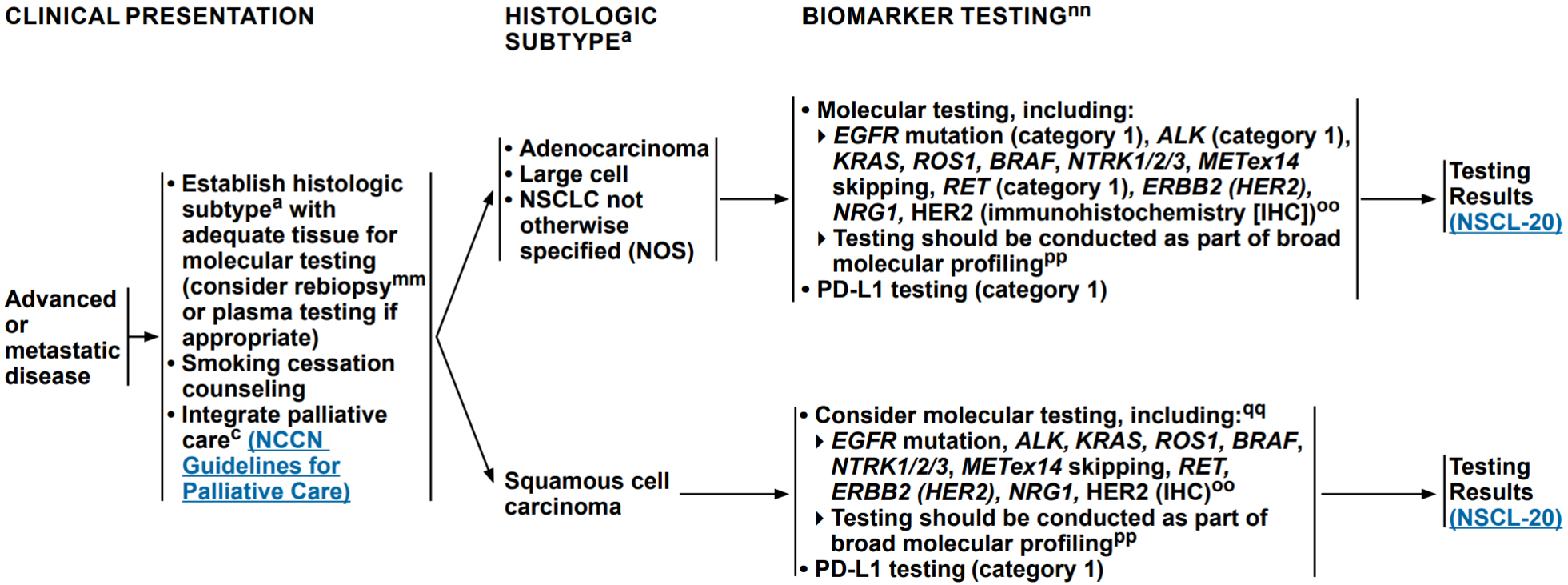
Discussion



TESTING RESULTS[mm,nn]

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
NRG1 **gene fusion positive**	NSCL-37
PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-38
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-39

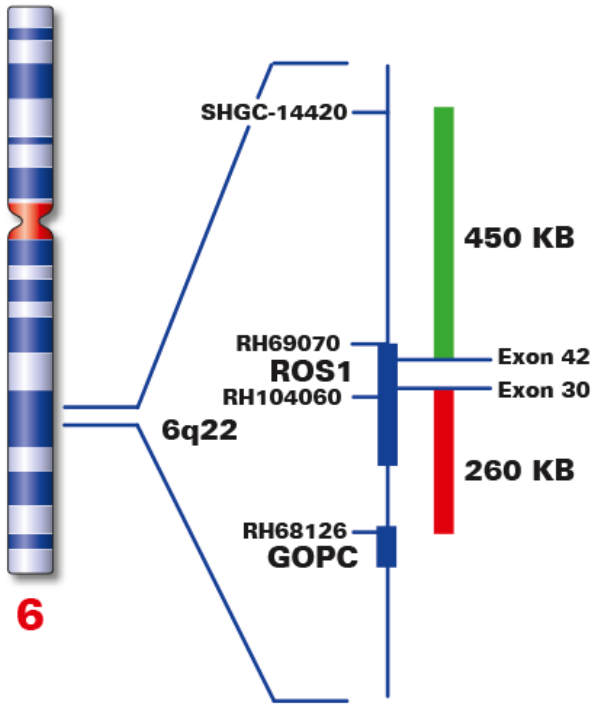
TEŞEKKÜRLER

EGFR, ALK Dışı Mutasyonlar Varlığında Güncel Yaklaşım

Metastatik KHDAK'de Nadir Driver Mutasyonlar

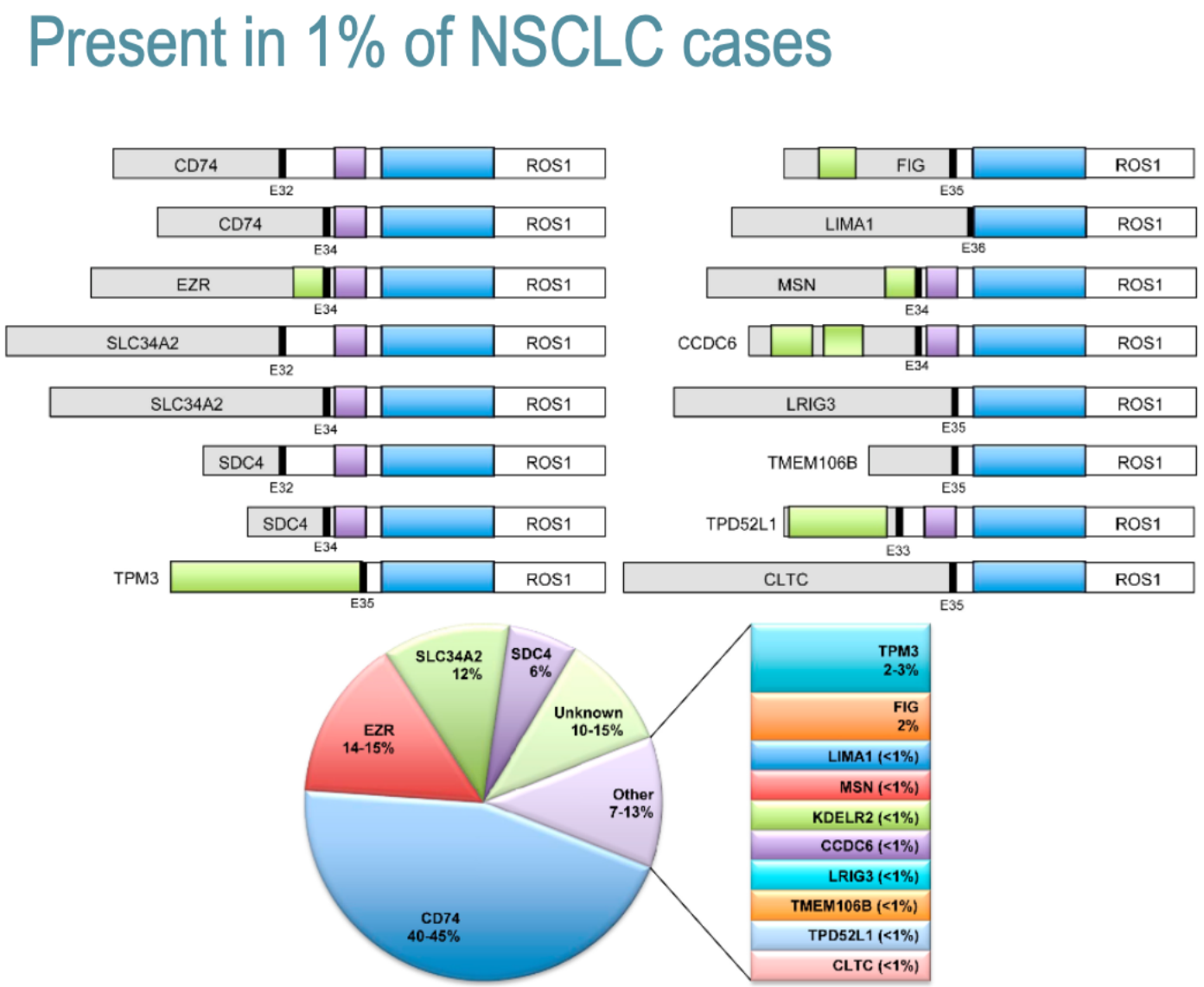
- ROS Füzyonu
- BRAF Mutasyonu
- Met exon 14 Mutasyonu
- RET Füzyonu
- NTRK Füzyonu
- Kras G12C Mutasyon
- Her2/EGFR 20 Mutasyonu

ROS -1 MUTANT KHDAK



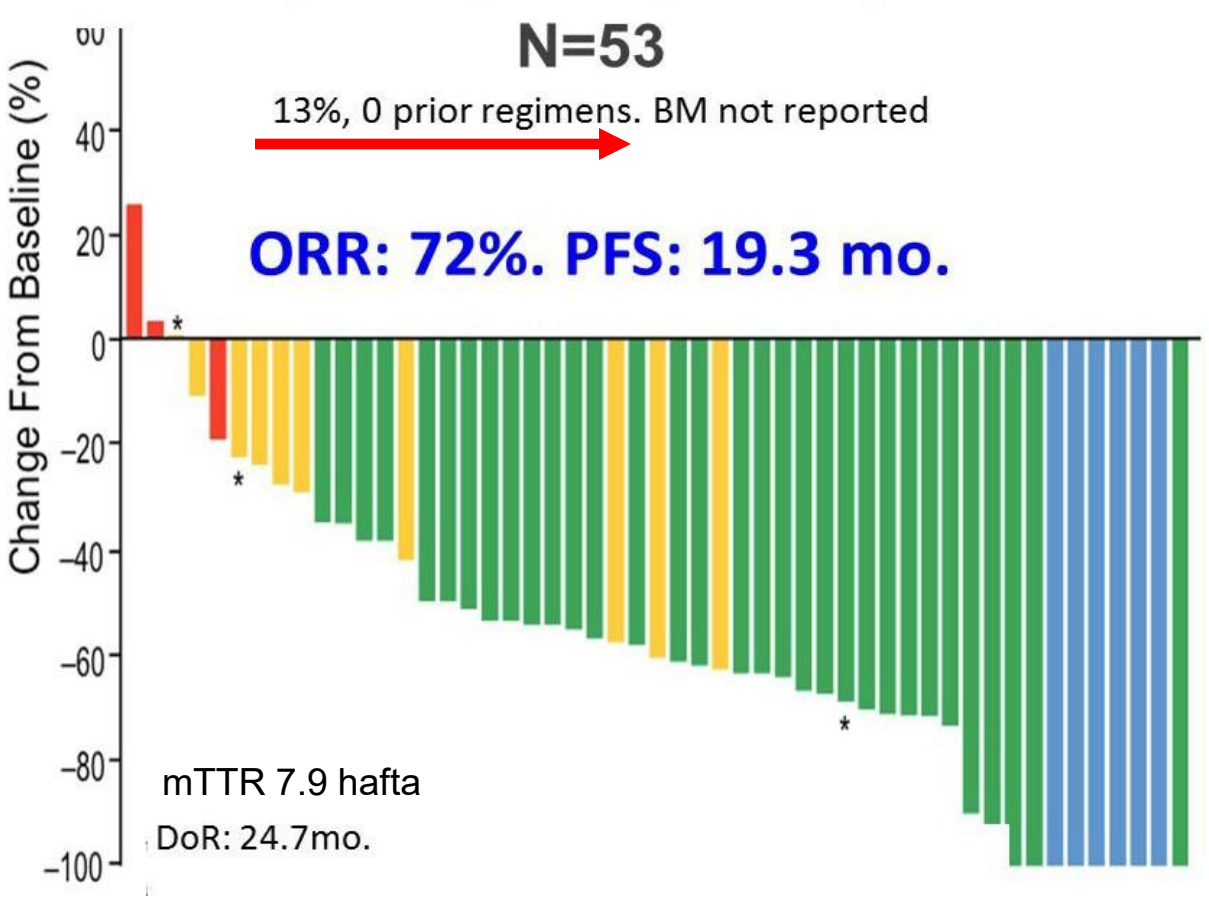
ROS1 KHDAK

- ✓ Tirozin kinaz reseptöründen farklı olarak bir proto-onkogen
- ✓ ALK gibi insülin reseptör ailesinden 6. kromozomun uzun kolu 22. lokusda
- ✓ ROS rearranjmanı ile füzyon geni oluşur.
- ✓ KHDAK %1-2'si
- ✓ Daha genç
- ✓ Sigara içmemiş, kadınlarda sık
- ✓ EGFR-ALK-ROS birlikteliği yok
- ✓ **Tanı anında %30-40 SSS metastazı**

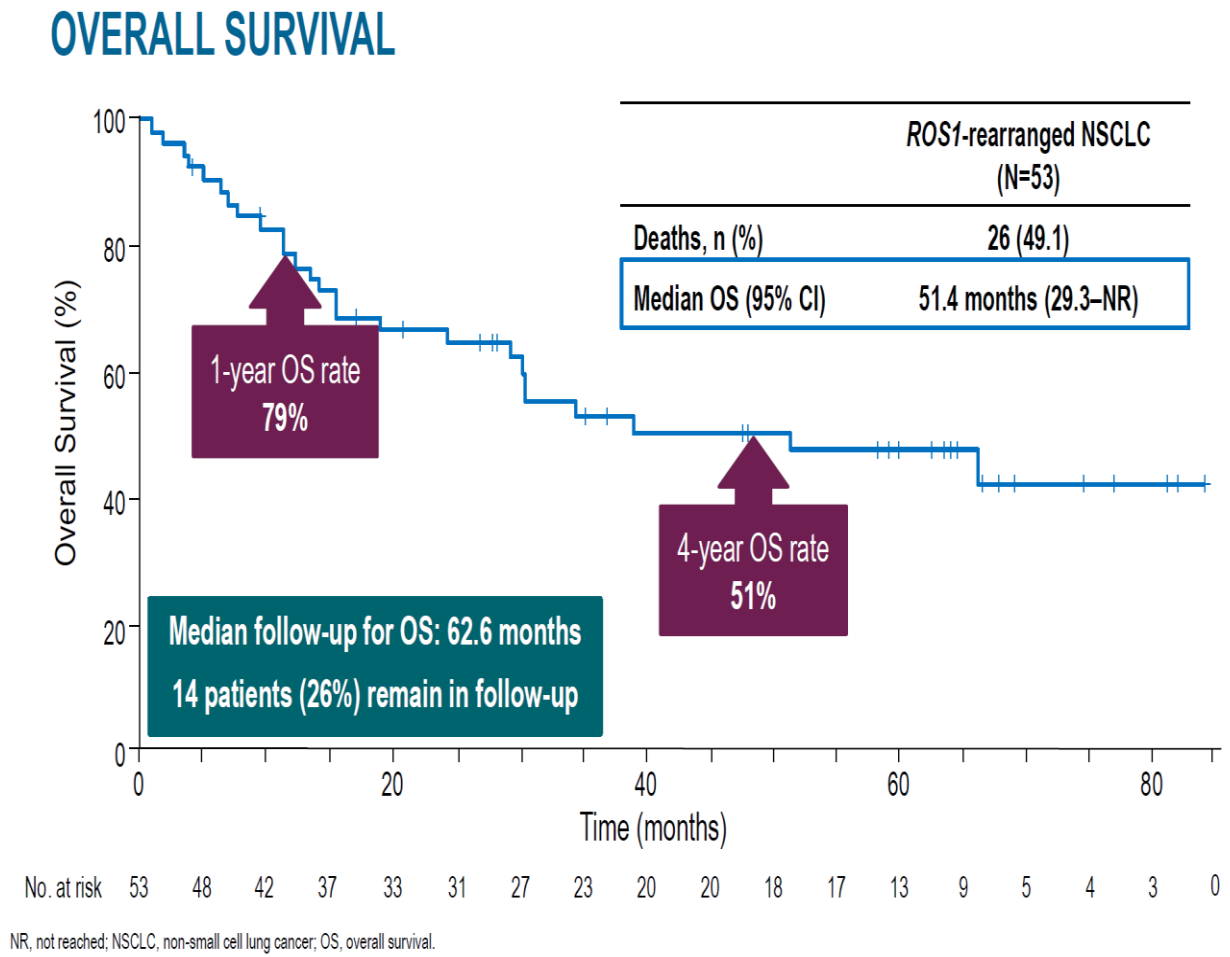


Rossi, Giulio, et al. *Lung Cancer: Targets and Therapy* 8 (2017): 45.

ROS1-Rearranged KHDAK: Crizotinib-PROFİLE 1001 ROS1 Kohortu



Shaw, NEJM 2014



Shaw et al.Annals of Oncology 2019

ROS1-Rearranged KHDAK: Crizotinib

Trial	N	Region	ORR	PFS (mo.)	mOS / 1-year OS
PROFILE 1001, ph I	53	World	72%	19.3	51.4 mo. / 79%
OxOnc, ph II	127	East Asia	72%	15.9	32.5 mo. / 83.1%
EUROS, pooled	32	Europe	80%	9.1	NR
AcSé, basket trial	37	France	54%	5.5	17.2 mo. / NR
EUCROSS, ph II	34	Spain/Germany	73%	20.0	NR / 83%
METROS, ph II	26	Italy	62%	17.2	Not reached

Crizotinib approved by FDA (11 March 2016) and EMA (21 July 2016)

Courtesy of J.Remon

Shaw NEJM 2014, Shaw ESMO 2016 (1206PD), Wu JCO 2018, Mazières JCO 2015
Moro-Sibilot WCLC 2018, Vassal ASCO 2018, Michels JTO 2019, Landi JTO 2017

ROS1 Rearranged KHDAK Hastalarında Ceritinib Faz II Çalışması (N=32)

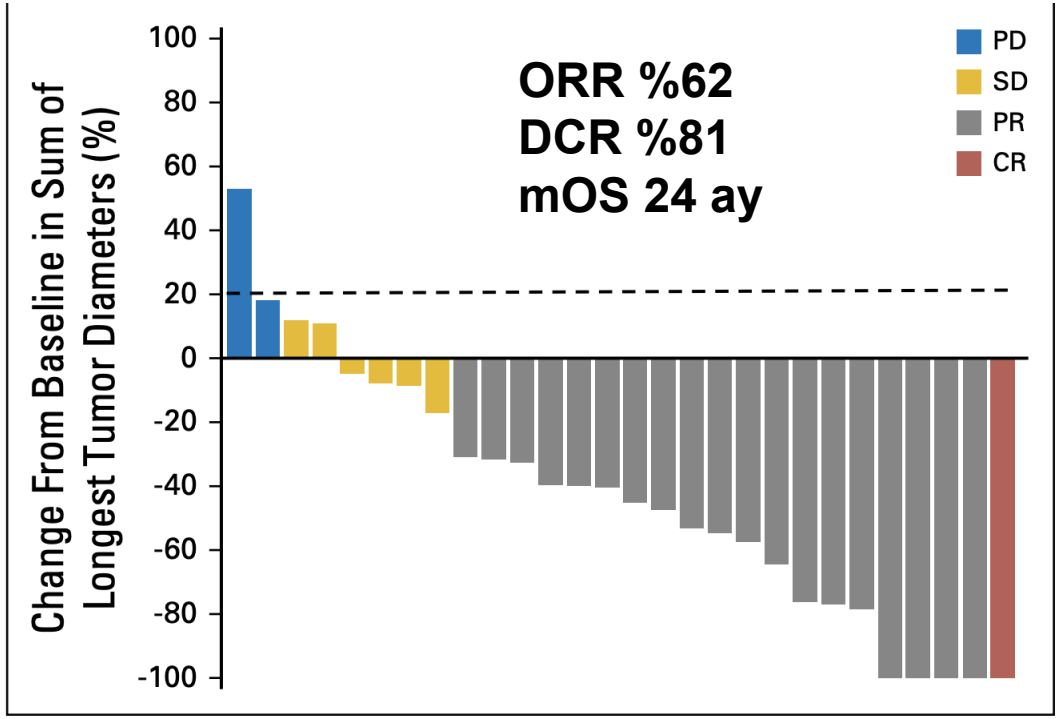


Fig 1. Best percentage change from baseline in tumor volume in patients with at least one postbaseline measurement. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

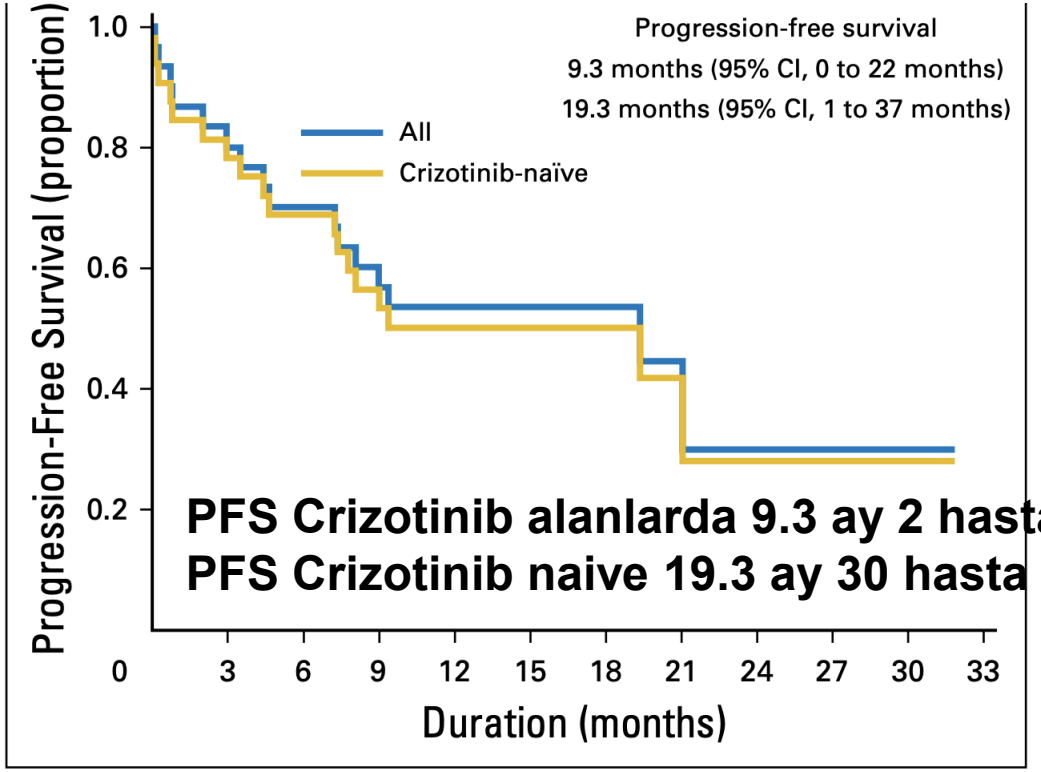
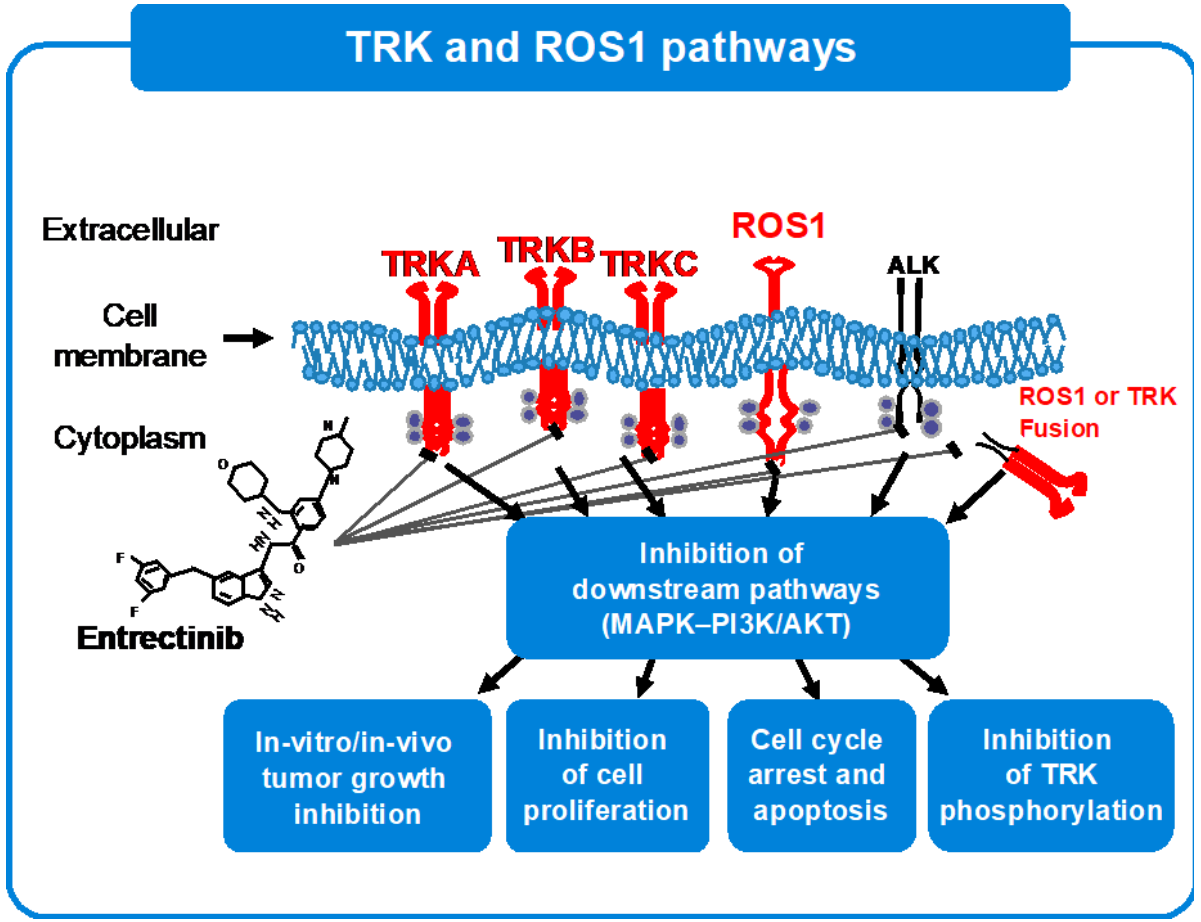


Fig 2. Kaplan-Meier curve of progression-free survival in all patients and crizotinib-naïve patients.

İntrakranial hastalık kontrolü 5/8 hasta: %63

Lim, Sun Min, et al. *Journal of clinical oncology* 35.23 (2017): 2613-2618.

ROS1 Füzyon KHDAK-Entrectinib: ROS1 ve TRK İnhibitörü



Target	ROS1	TRKA	TRKB	TRKC
IC_{50} (nM)	0.2	1.7	0.1	0.1

Entrectinib SSS geçişi olan oral, güçlü ve selektif **ROS1/NTRK/ALK tirozin kinaz inhibitörü**

- Krizotinibden daha güçlü ve SSS geçisi daha iyi olan ROS-1 inhibitörü
- Primer beyin tümörlerinde ve sekonder SSS metastazlarında görülen klinik aktivite ile kan-beyin bariyerini geçmek ve SSS içinde kalmak için tasarlanmıştır.
- Potent pan-TRK inhibisyonu

ROS1 Rearranged KHDAK Hastalarında Entrektinib'in Faz I (ALKA-372-001, STARTRK-1) ve Faz II (STARTRK-2) Çalışmalarının Kombine Analizi (N=161)

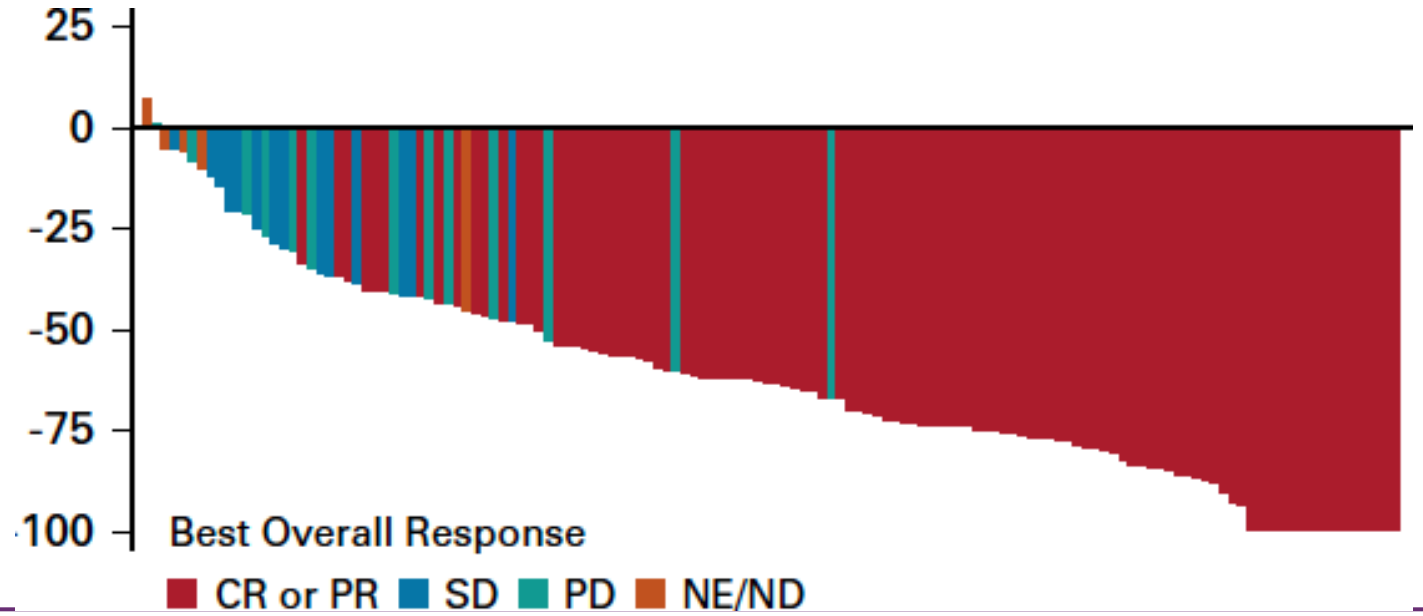
Primer Sonlanım:ORR, DoR
Sekonder Sonlanım:PFS, OS, IC ORR ve DoR, Güvenlik

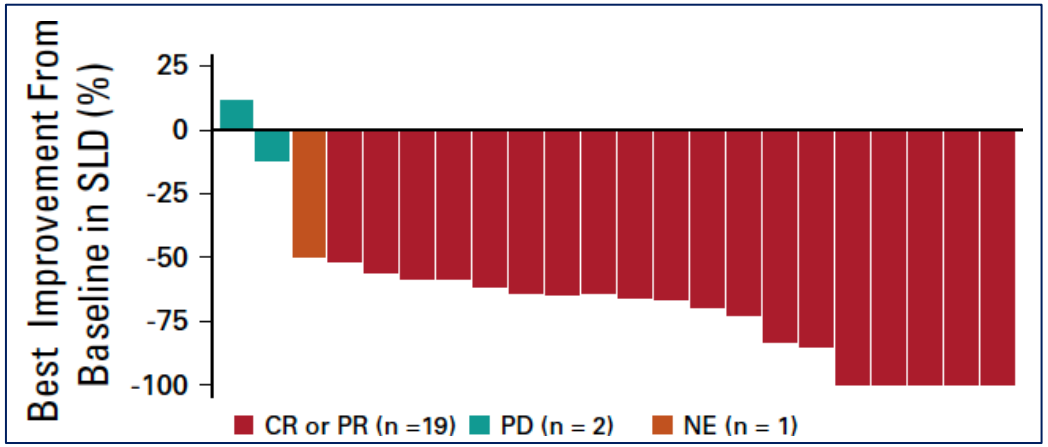
60 hasta (%37.3) tedavi naive

Overall response ITT
ORR %67.1 (CR %9)
mDOR 15.7 ay
mPFS 15.7 ay

Outcome	Total (N = 161)	CNS Disease at Baseline (n = 56)	No CNS Disease at Baseline (n = 105)
ORR, n (%) (95% CI)	108 (67.1) (59.3-74.3)	35 (62.5) (48.6-75.1)	73 (69.5) (59.8-78.1)
Median PFS, mo (95% CI)	15.7 (11.0-21.1)	11.8 (6.4-15.7)	19.0 (12.0-29.6)

İntrakranial aktivite: 24 hasta
İC ORR %79.2
İC PFS 12 ay
OS 28.3 ay



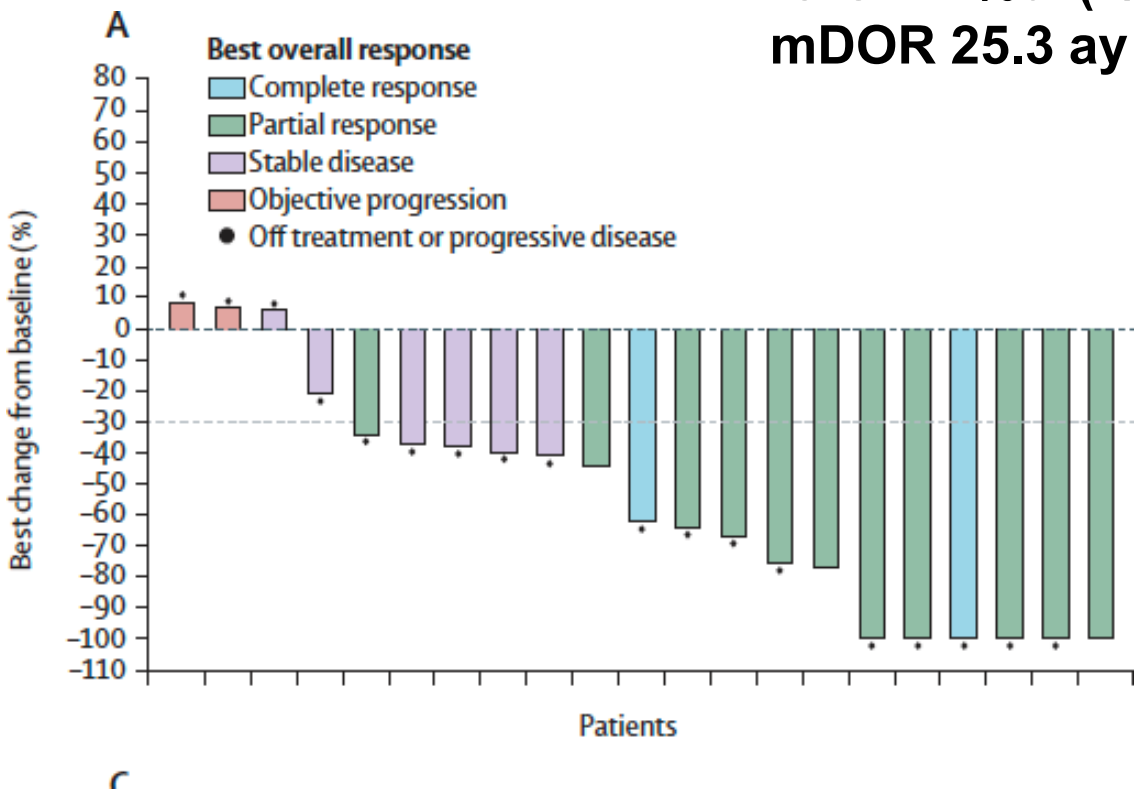


Dziadziuszko et al, JCO 2021

ROS1 Rearranged KHDAK Hastalarında Lorlatinib Faz I-II Çalışması (N=69)

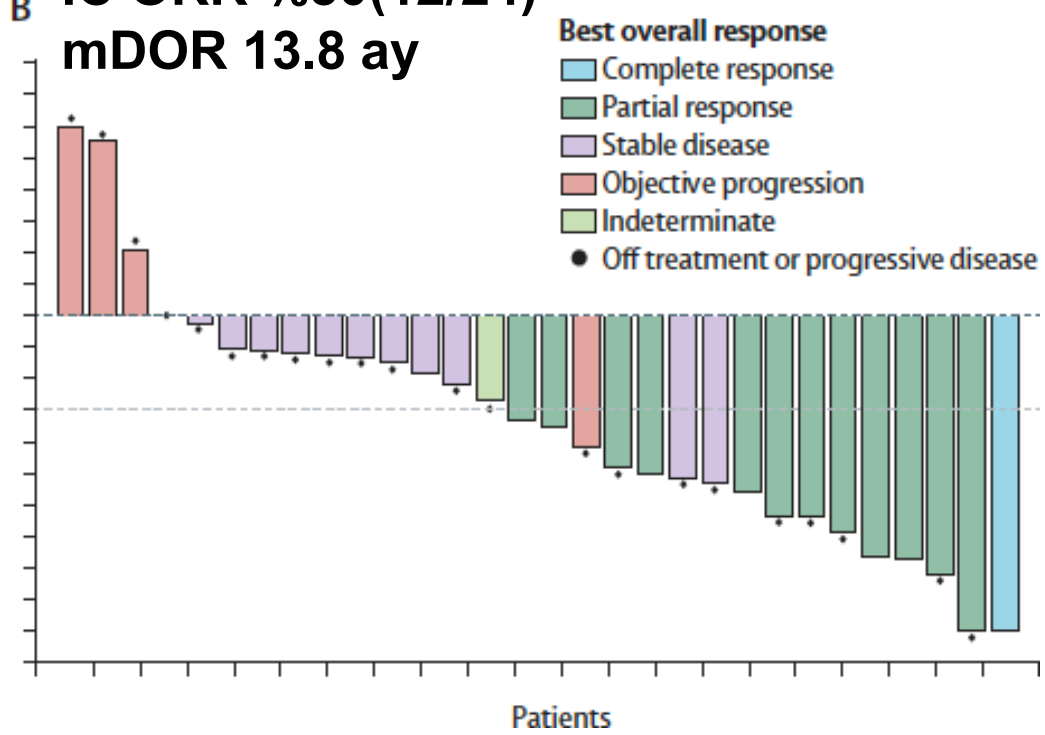
TKİ Naive 21/69 (%30)

ORR %62
mPFS: 21 ay
İC ORR %64(7/11)
mDOR 25.3 ay



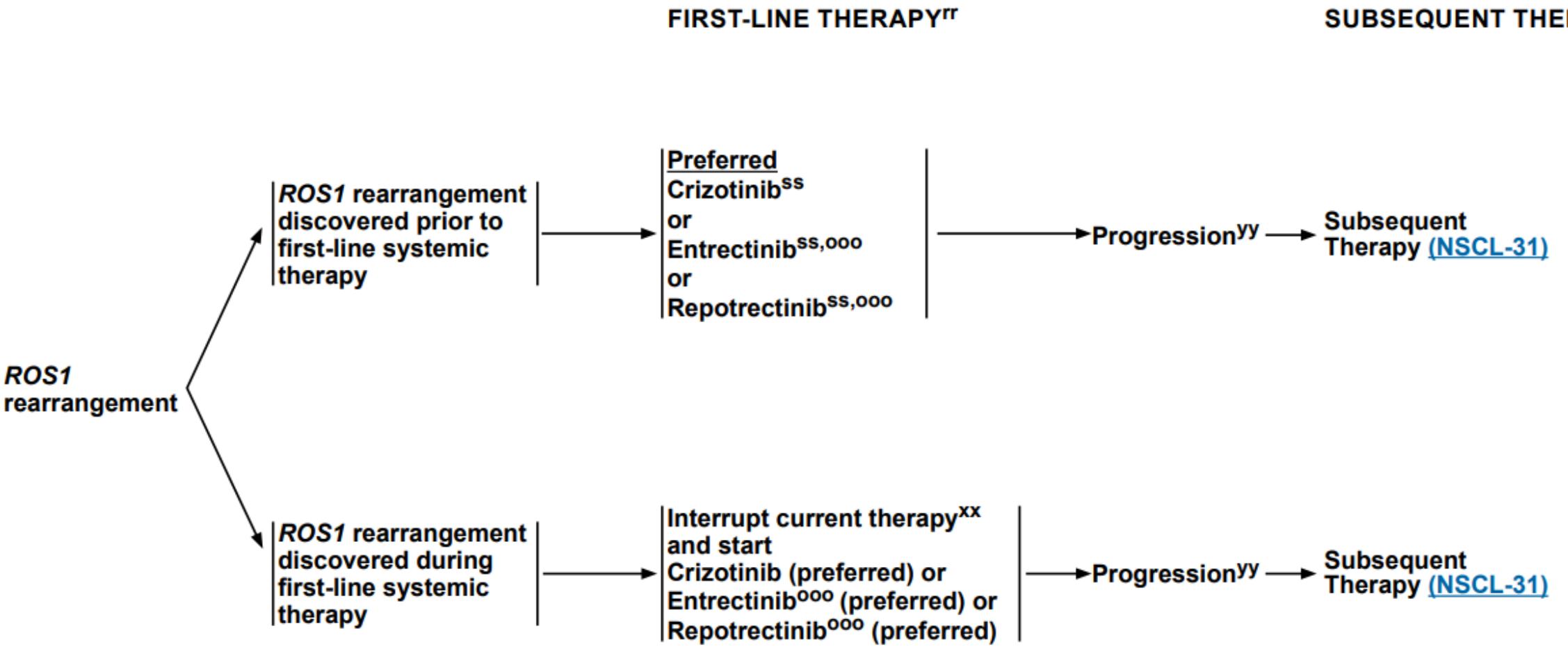
Crizotinib alan 40/69 (%58)

ORR %35
mPFS: 8.5 ay
İC ORR %50(12/24)
mDOR 13.8 ay

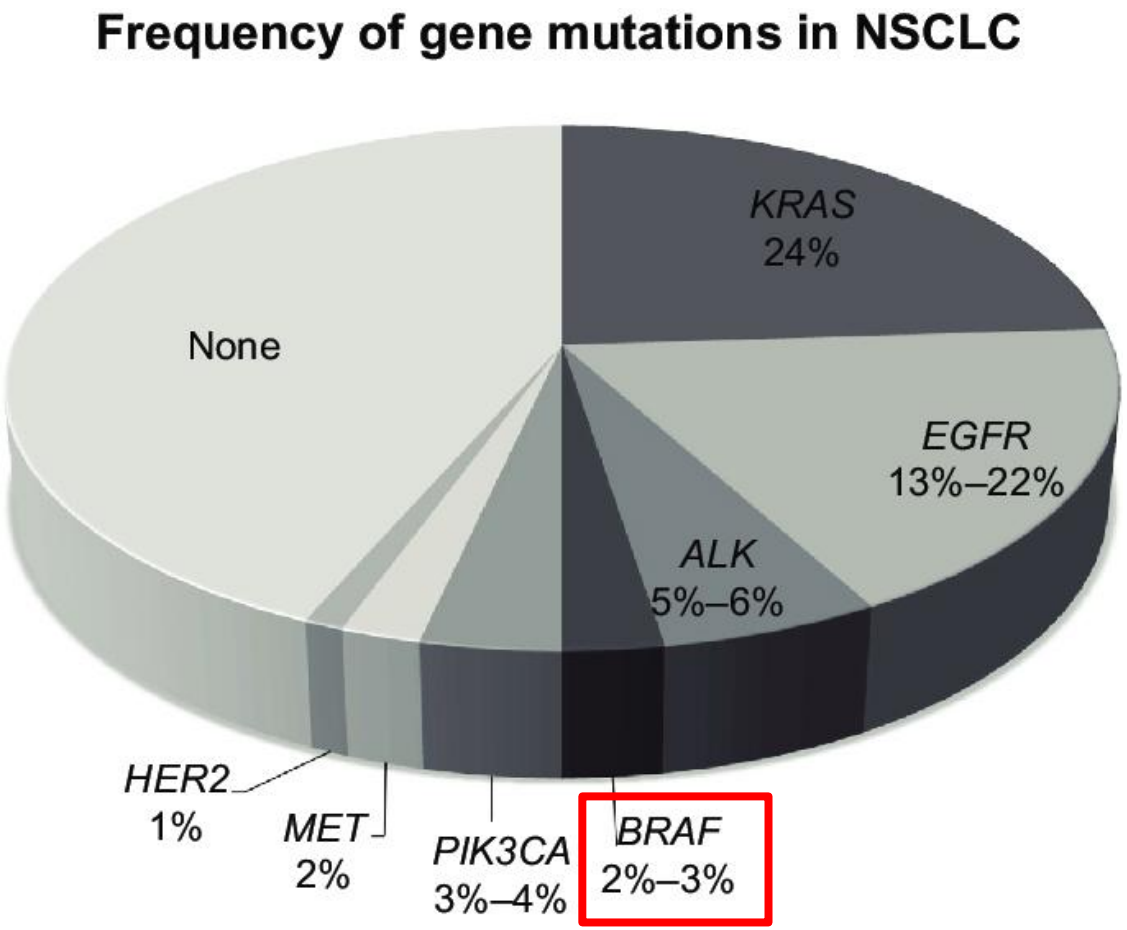


Shaw, Alice T., et al. *The Lancet Oncology* 20.12 (2019): 1691-1701.

ROS1 REARRANGEMENT[nn]

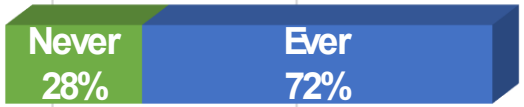


BRAF V600E MUTASYONU



KHDAK'de BRAF V600E Mutasyonu: %1-2

Smoking status



Clas I>Klas II-III

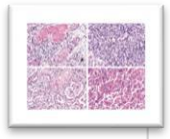
Median Age

67

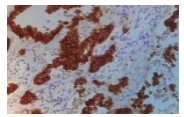
Sex Ratio

Non-V600

Non-Squamous



PD-L1 ≥1%

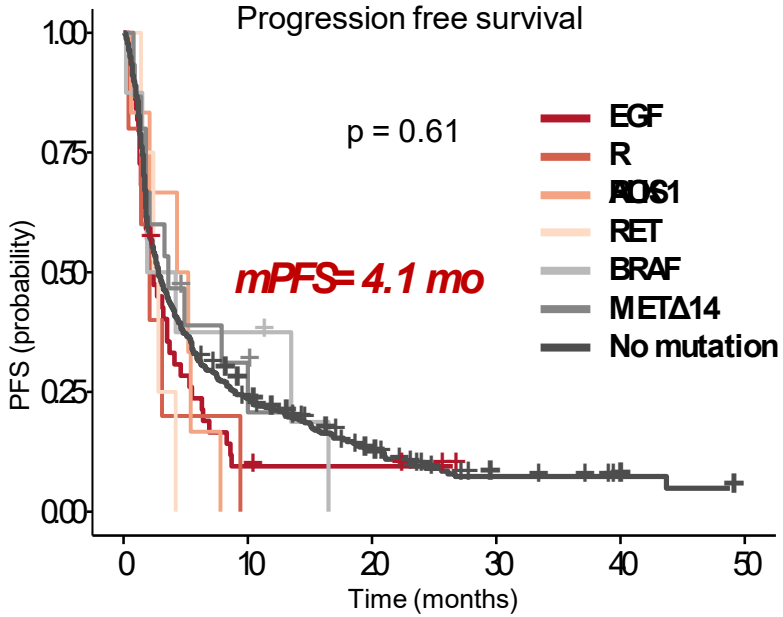


75%

Median TMB

5.4%

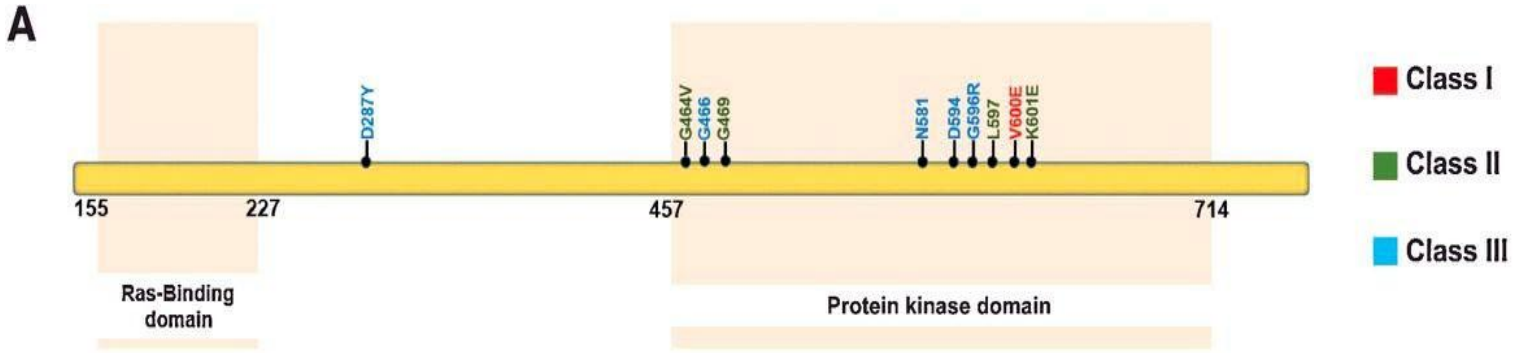
Prognostic value

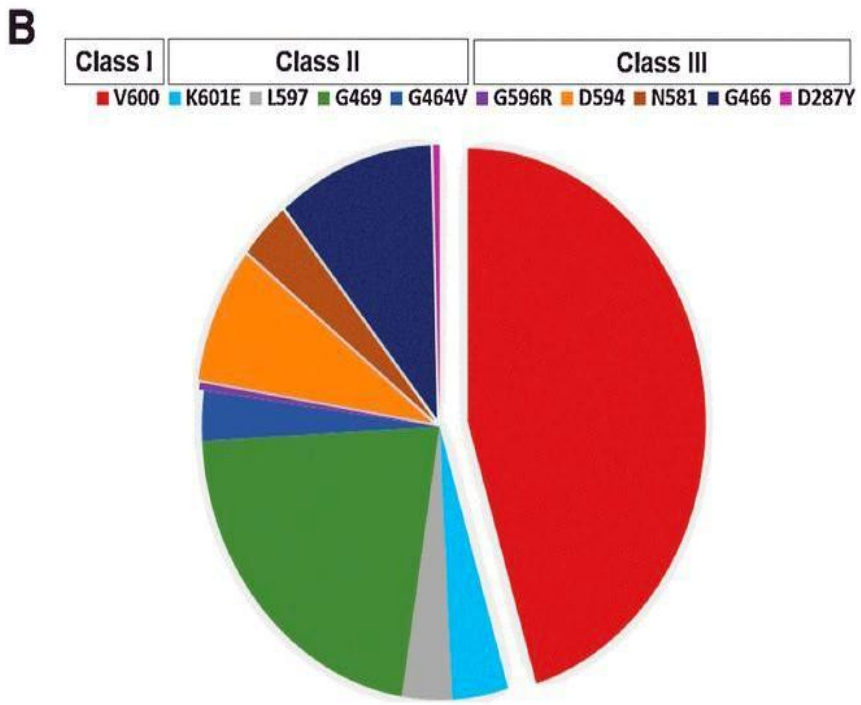


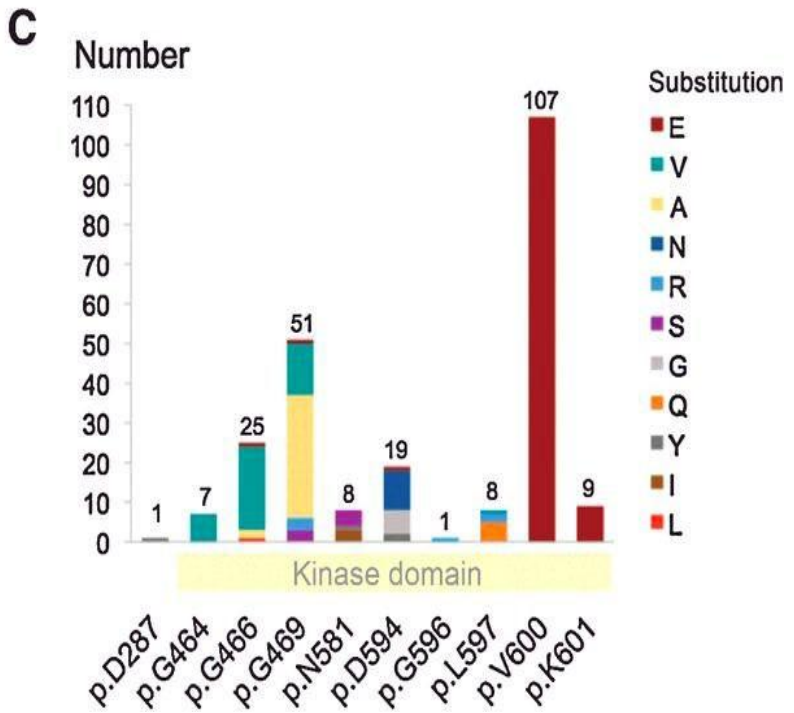
Low rate brain Mets at diagnosis

BRAF (V600) Varyantları

%50 BRAF V600E ya da class 1 BRAF mutasyonu







Klas I 107 hasta (%45)
Klas II 75 hasta (%32)
Klas III 54 hasta (%23)

Beyin metastazı
Klass II-III>Klas I

BRAF mutasyonu	
V600	107 (%45)
G469	51 (%22)
D466	25 (%11)
D594	19 (%8)

%86

Clin Cancer Res. 2019;25(1):158-165. doi:10.1158/1078-0432.CCR-18-2062

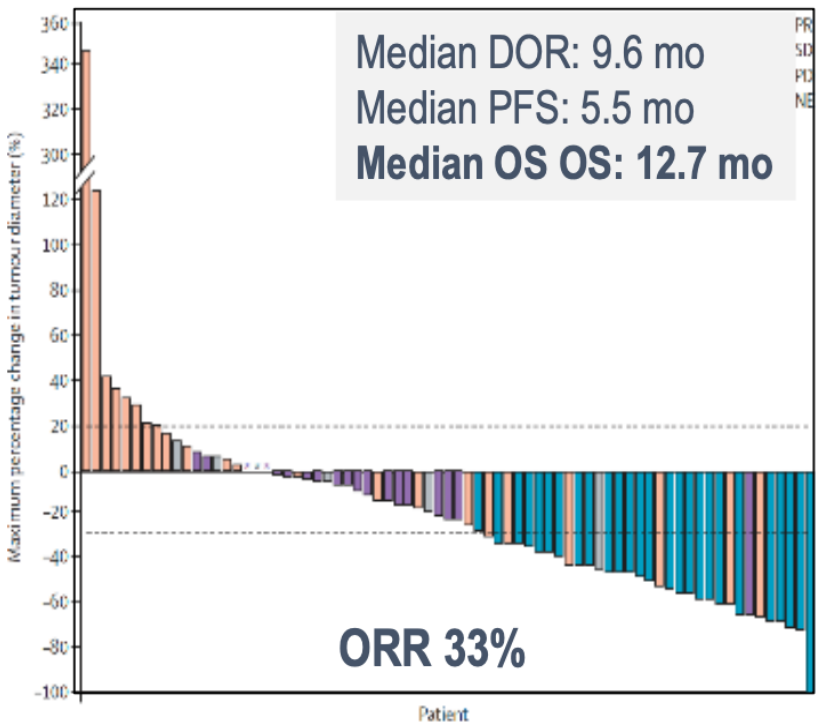
THERAPEUTIC TARGETING OF CLASS I BRAF MUTATIONS (V600E)

Strategy 1: SINGLE BRAF INHIBITION

Dabrafenib 150 mg BID

BRF 113928[1]

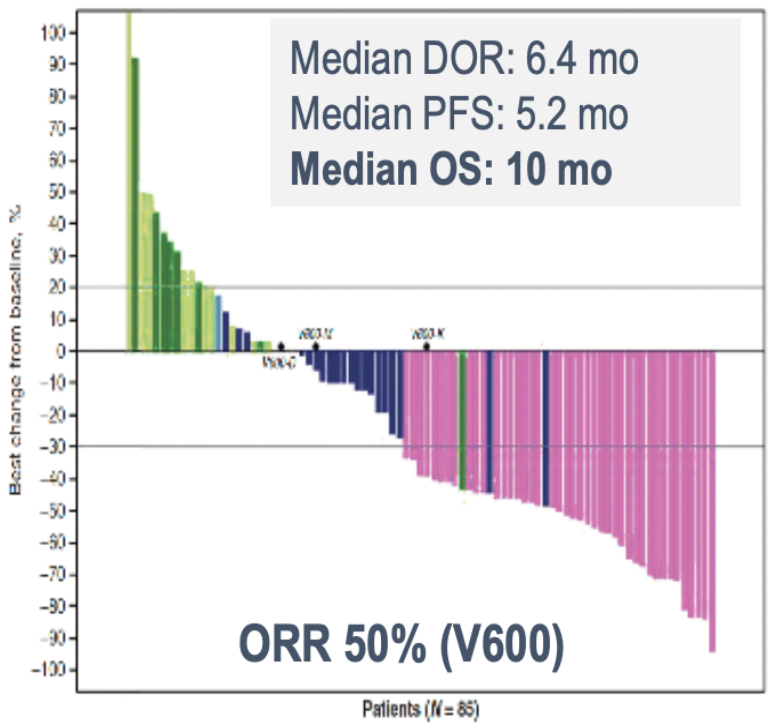
Pretreated V600 (N= 78)



Vemurafenib 960 mg BID

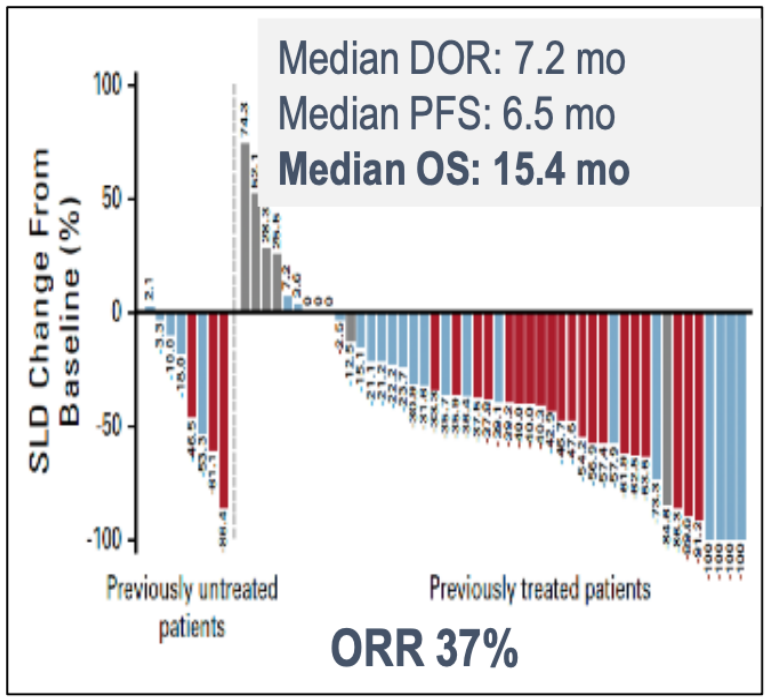
AcSé[2]

Pretreated V600 (N= 101)



VE-BASKET[3]

Pretreated/Naïve V600 (N= 62)



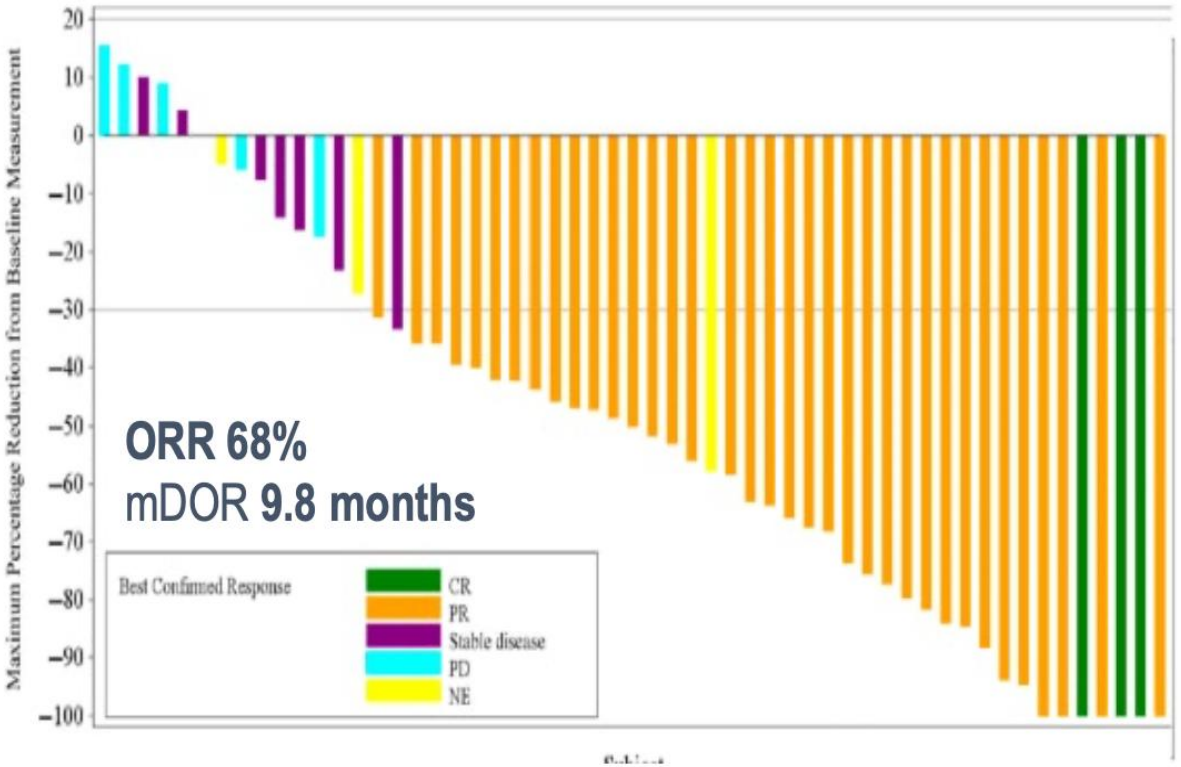
1.- Planchard D., et al, Lancet Oncol 2016; 2.- Mazieres J. et. al., Annals of Oncology 2020; 3.-Subbiah V et al., JCOPO 2019

THERAPEUTIC TARGETING OF CLASS I BRAF MUTATIONS (V600E)

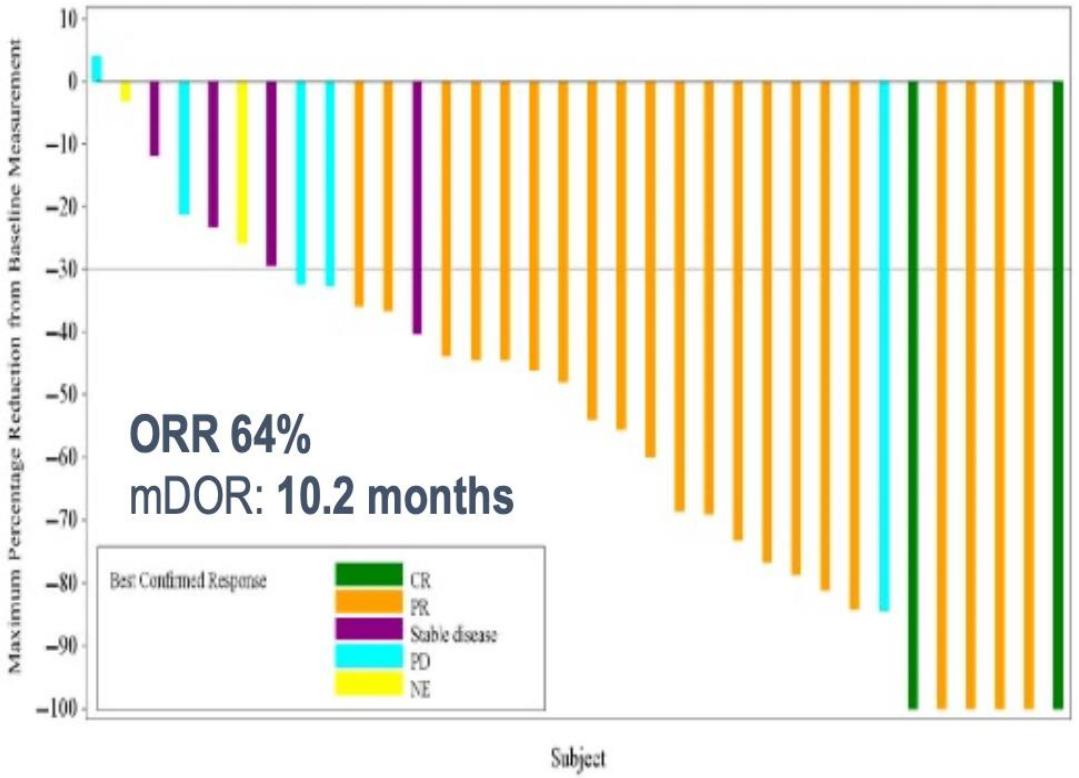
Strategy 2: Double MAPK Blockade — Dabrafenib + Trametinib (BRF 113928, Phase 2 Trial)

Dabrafenib 150 mg BID + Trametinib 2 mg QD

COHORT B: Pretreated V600 (N=57)



COHORT C: Treatment-naïve V600 (N=36)



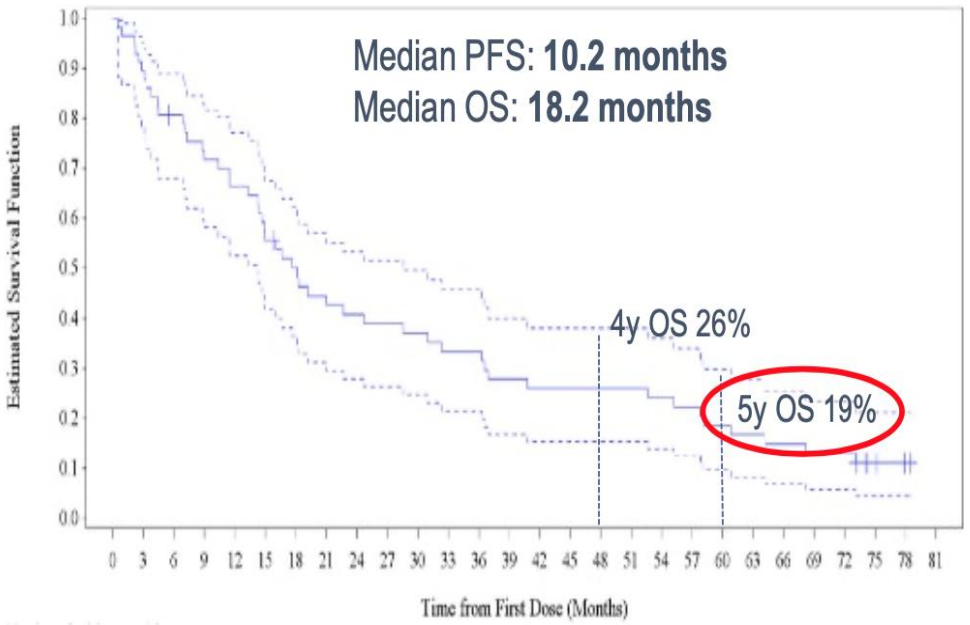
1.- Planchard D., et al, JTO 2022

THERAPEUTIC TARGETING OF CLASS I BRAF MUTATIONS (V600E)

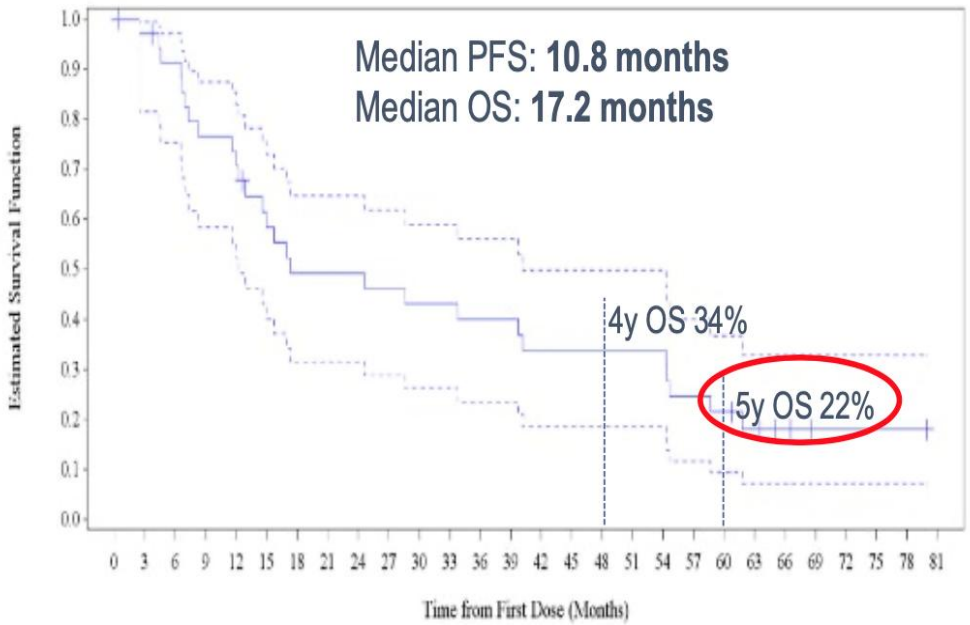
Strategy 2: Double BRAF/MEK Blockade — Dabrafenib + Trametinib (BRF 113928, Phase 2 Trial)

5-year update

COHORT B: Pretreated V600 (N=57)[1]



COHORT C: Treatment-naïve V600 (N=36)[2]



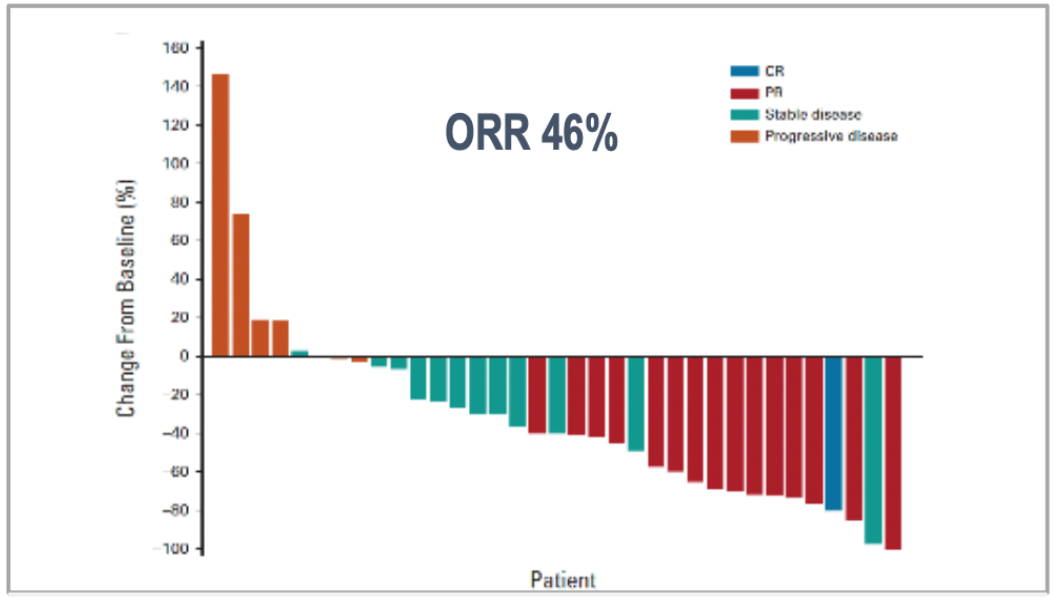
1.- Planchard D., et al, JTO 2022

THERAPEUTIC TARGETING OF CLASS I BRAF MUTATIONS (V600E)

NEW COMBOS — Encorafenib + Binimetinib (PHAROS Trial)

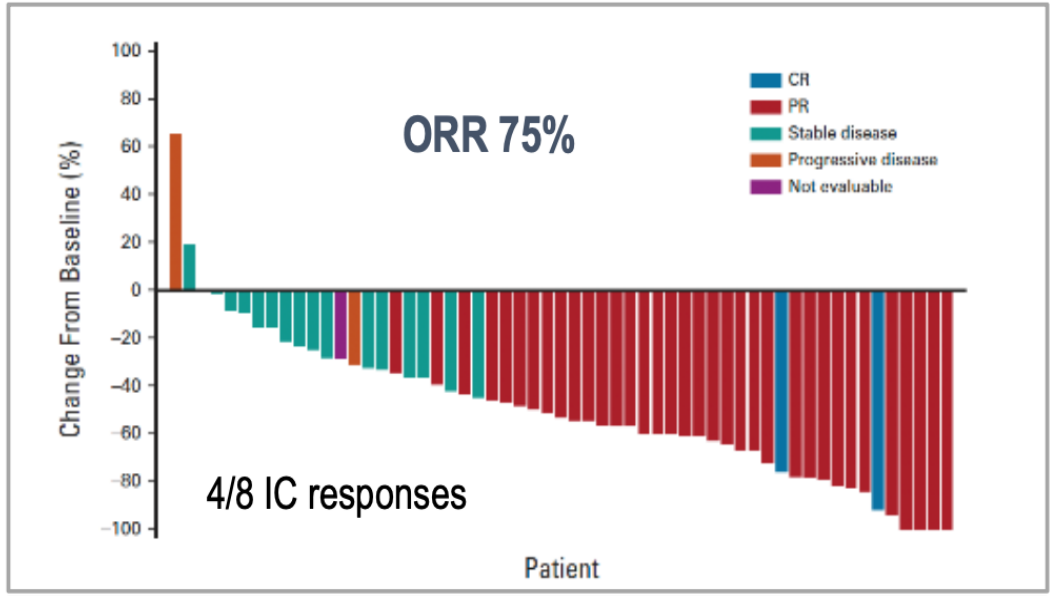
Encorafenib 450 mg QD + Binimetinib 45 mg BID

Pretreated V600 (N=39)



Median DOR: 9.0 months
Median PFS: 9.3 months
Median OS: NE

Treatment-naïve V600 (N=59)



Median DOR: 10.4 months
Median PFS: NE
Median OS: NE

1.- Riely GJ et al ASCO 2023; 2.- Riely GJ et al JCO 2023

BRAF nonV600 Mutasyonları (Vemurafenib)- Klas II ve III-Faz II

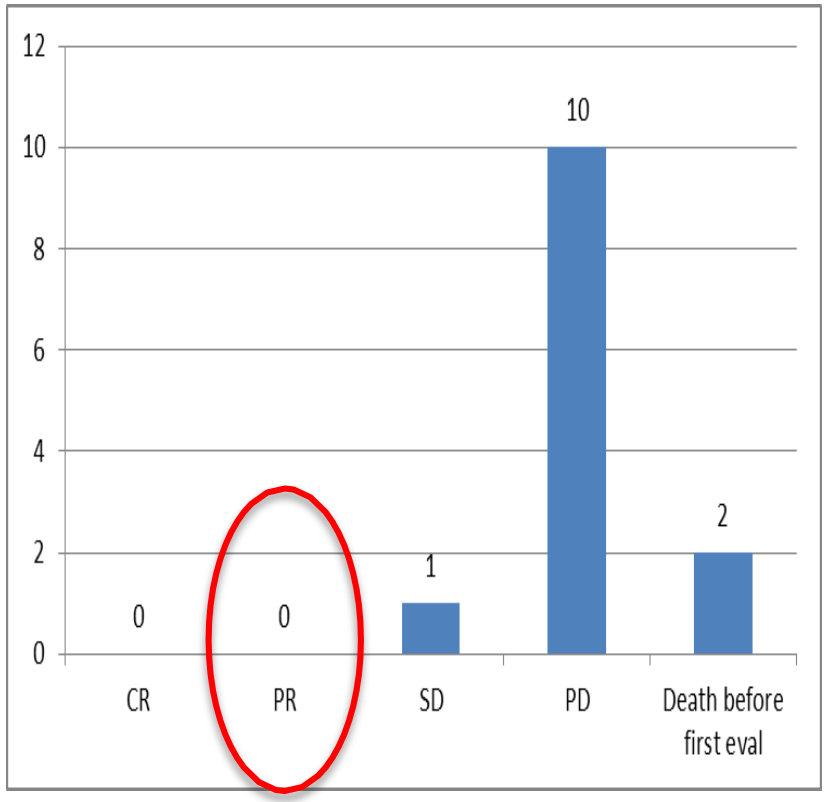
- Mean Bayesian Estimated Success rate : **5.9%** ; credibility 95%CI : [0.2%; 20.6%]
- Prob ORR < futility bound (10%): 81.5% - **study stopped**

Non V600 mutations

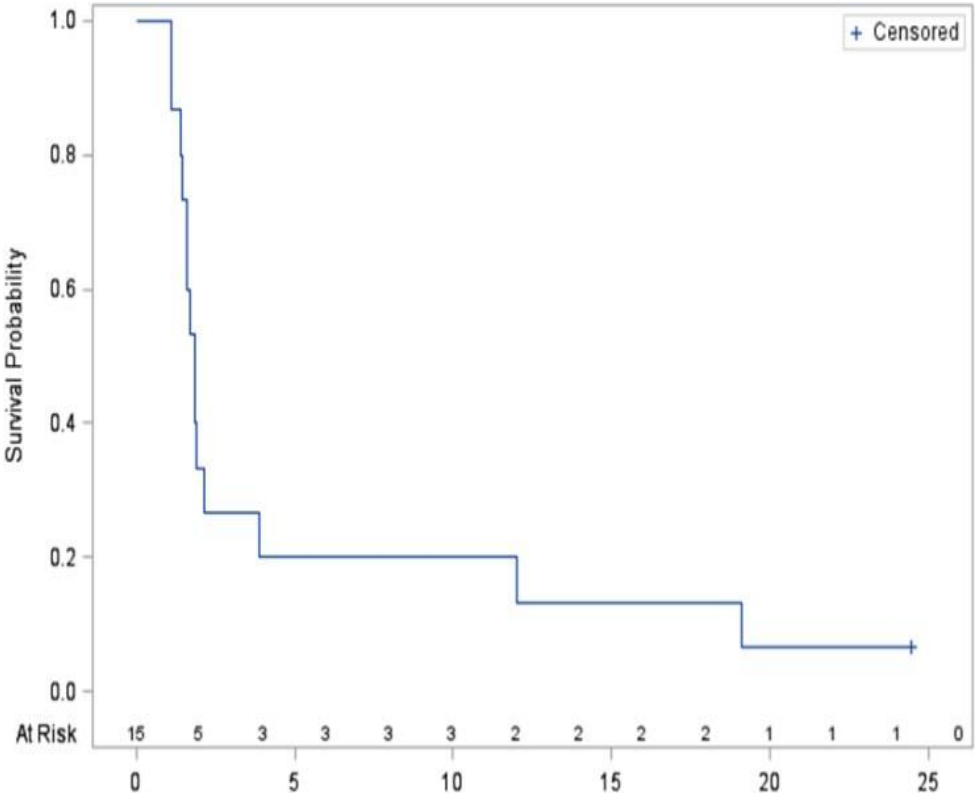
n = 17

G466A : n=1
G466V : n=3
G469A : n=3
G469V : n=1
N581S : n=3
G596R : n=1
K601E : n=3
K601N : n=2

Response rate: 0%

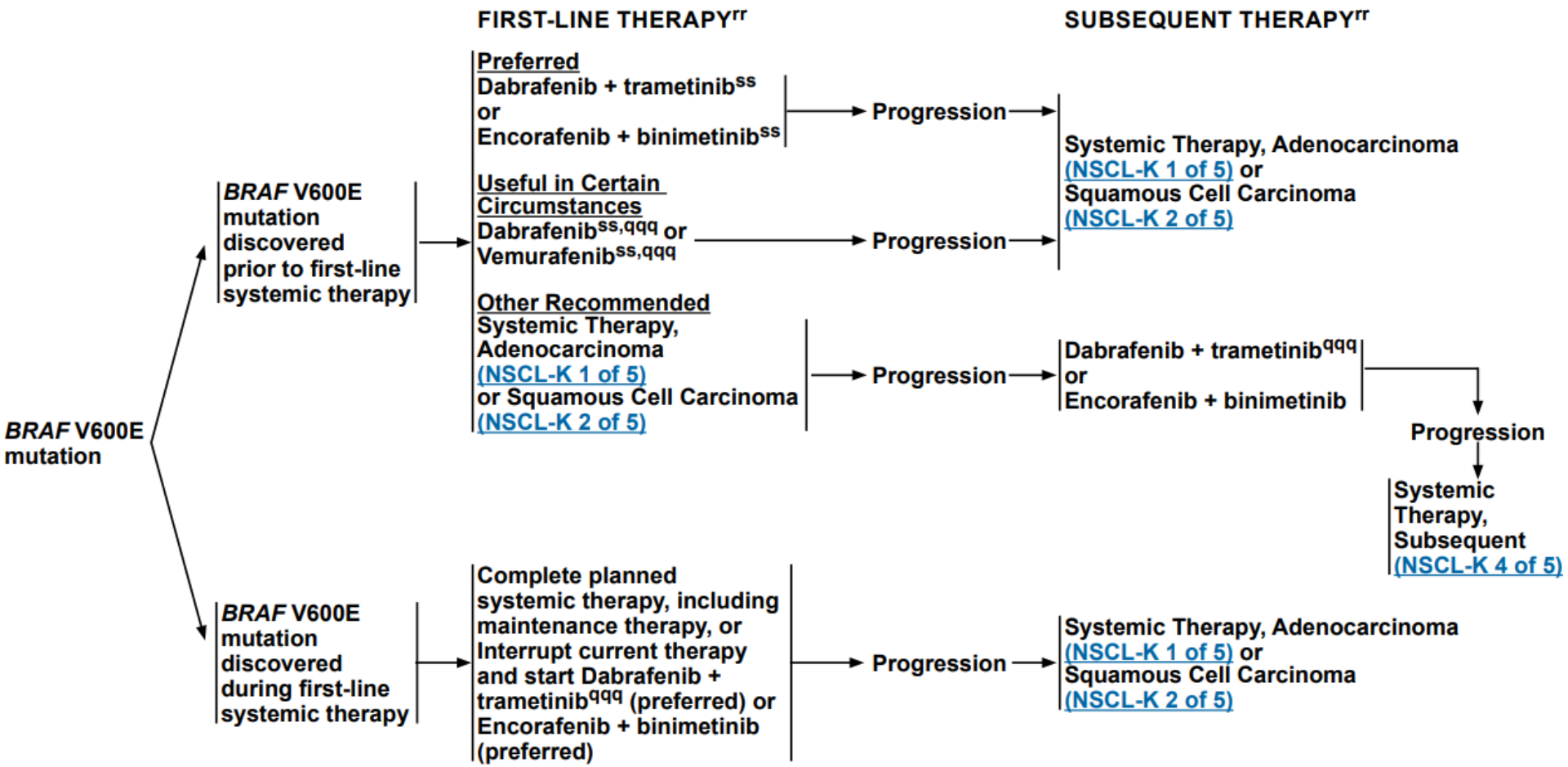


PFS: 1.8 m. [1.4;2.1]



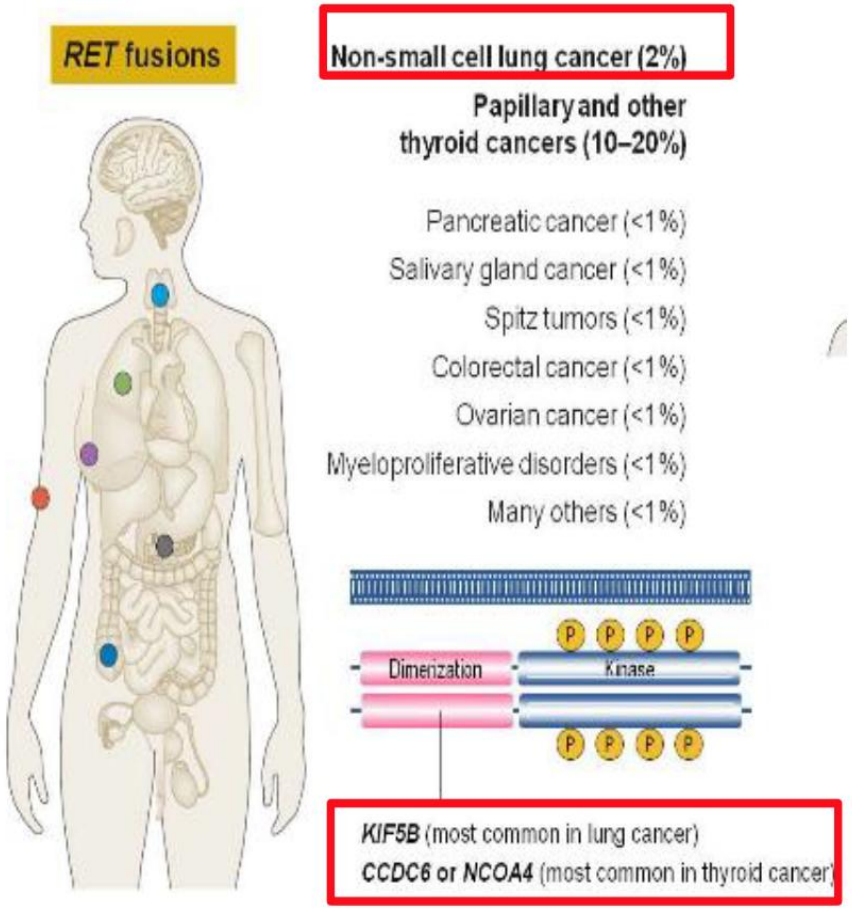
J.Mazieres et al, WCLC 2018

BRAF V600E MUTATION[nn]



RET FUSIONS IN SOLID TUMORS

A very rare disease



RET fusions are reported in about 1-2% of patients with NSCLC

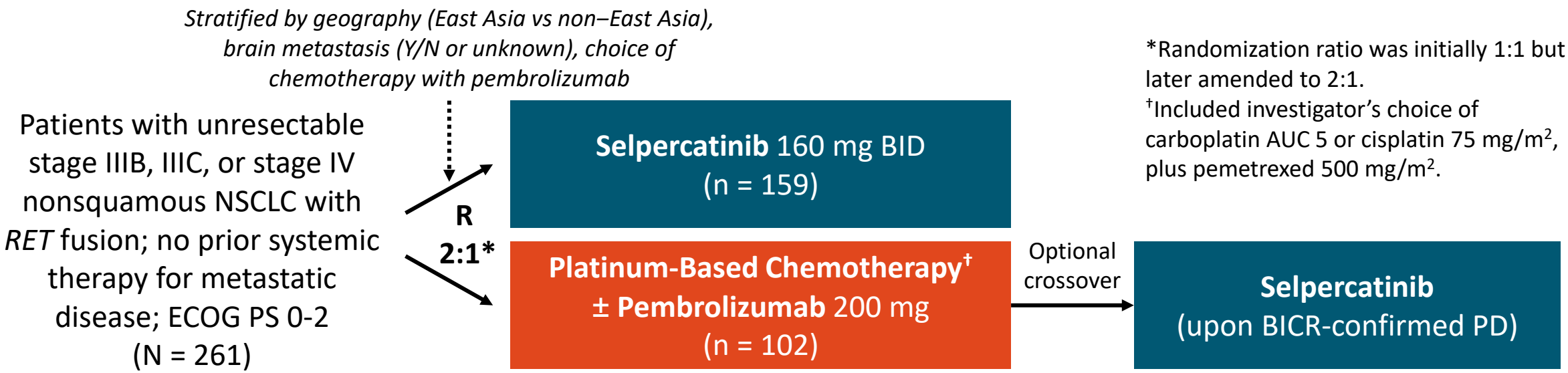
AGE				
YOUNG < 60 y	EQUAL DISTRIBUTION	NEVER SMOKERS	Poorly differentiated Mostly adenocarcinoma Signet-ring cells	LOW TMB

Distinct clinical profile: YOUNG, NON-SMOKERS

1.- Alexander Drilon at 2018 ASCO Annual Meeting

LIBRETTO-431: Study Design

- International, randomized, open-label phase III trial

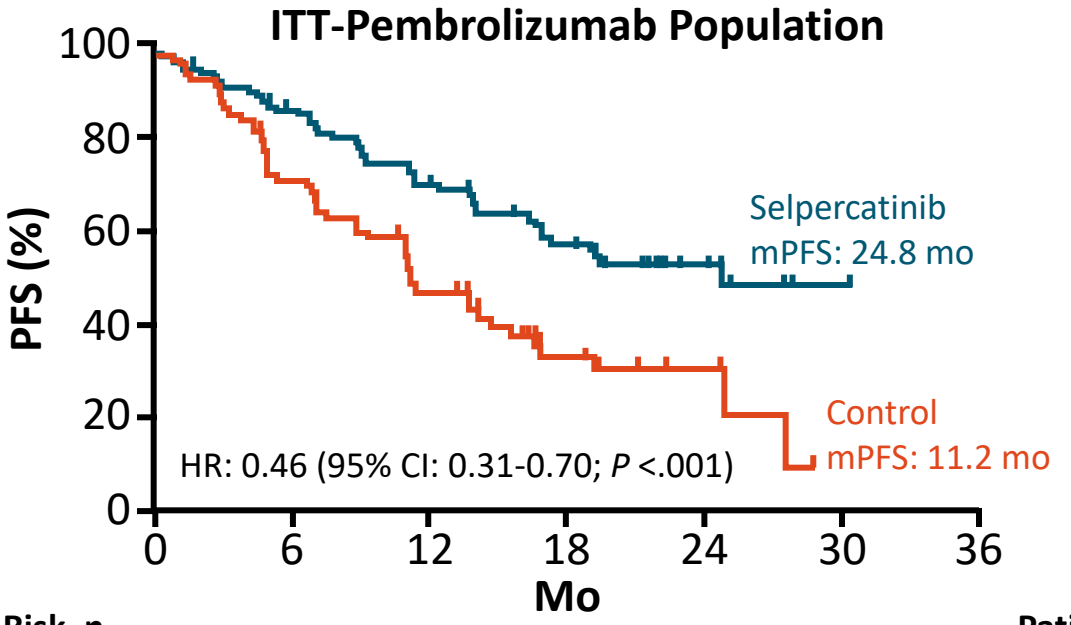


- **Gated primary endpoints:** PFS by BICR in ITT-pembrolizumab and ITT populations
  - ITT-pembrolizumab = patients stratified by investigator intent to receive pembrolizumab with chemotherapy; had to comprise ≥80% of ITT population per protocol (n = 212 randomized)
- **Secondary endpoints:** OS, ORR, DoR, CNS ORR, CNS DoR, CNS TTP, safety, PROs

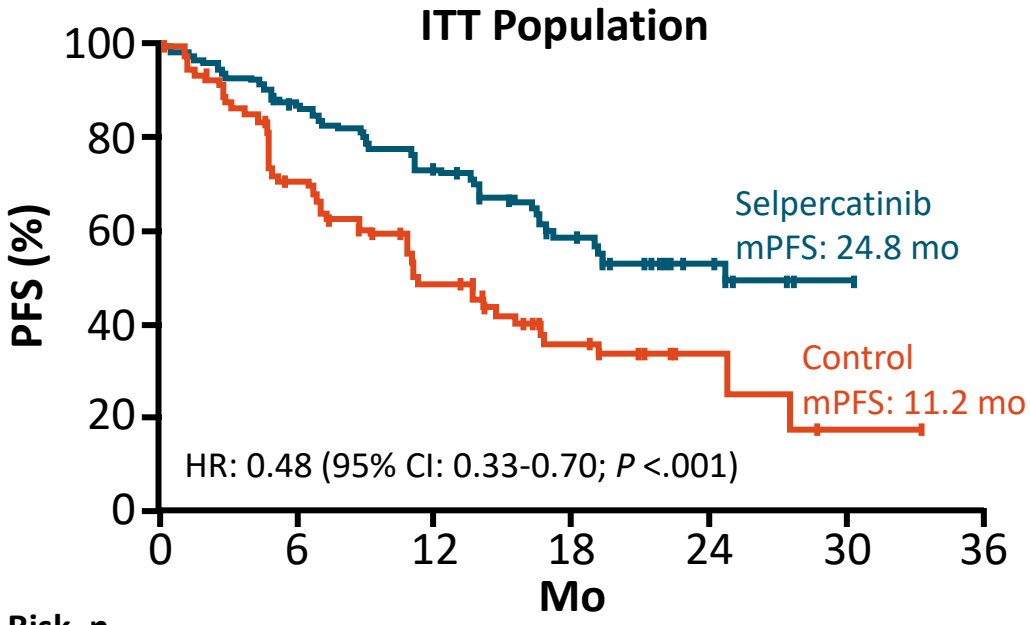
Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

LIBRETTO-431: PFS by BICR (Primary Endpoint)

- Selpercatinib yielded statistically significant improvement in PFS vs control arm in both ITT-pembrolizumab and ITT populations, meeting both primary endpoints



Patients at Risk, n							
Selpercatinib	129	105	72	44	16	2	0
Control	83	51	29	15	6	1	0

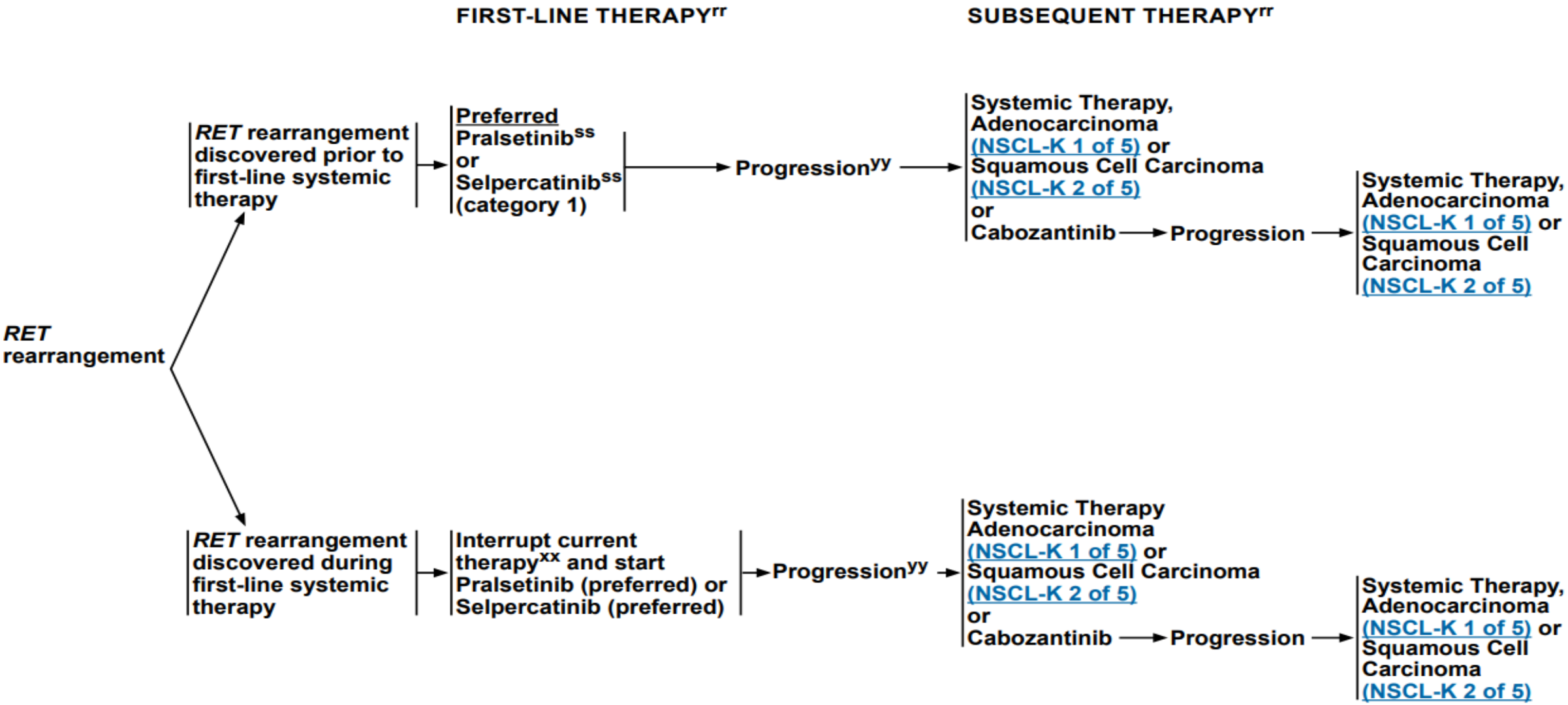


Patients at Risk, n							
Selpercatinib	159	130	90	52	18	3	0
Control	102	64	36	16	7	1	0

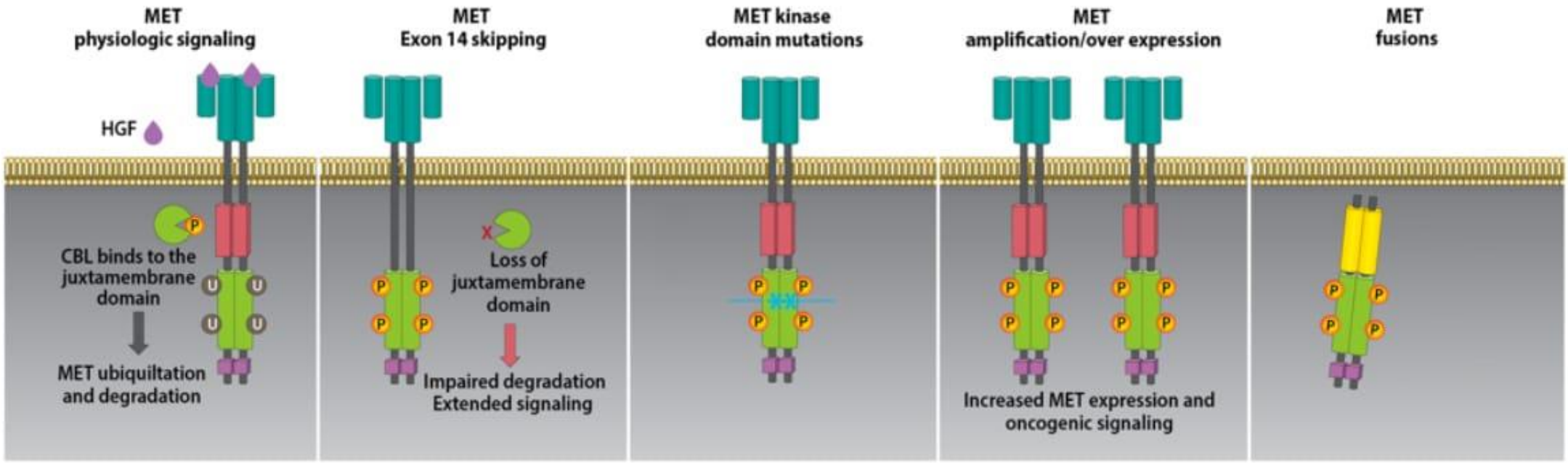
tinib also yielded PFS benefit vs cont preplanned subgroups

Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

RET REARRANGEMENT[nn]



MET Mutasyonu



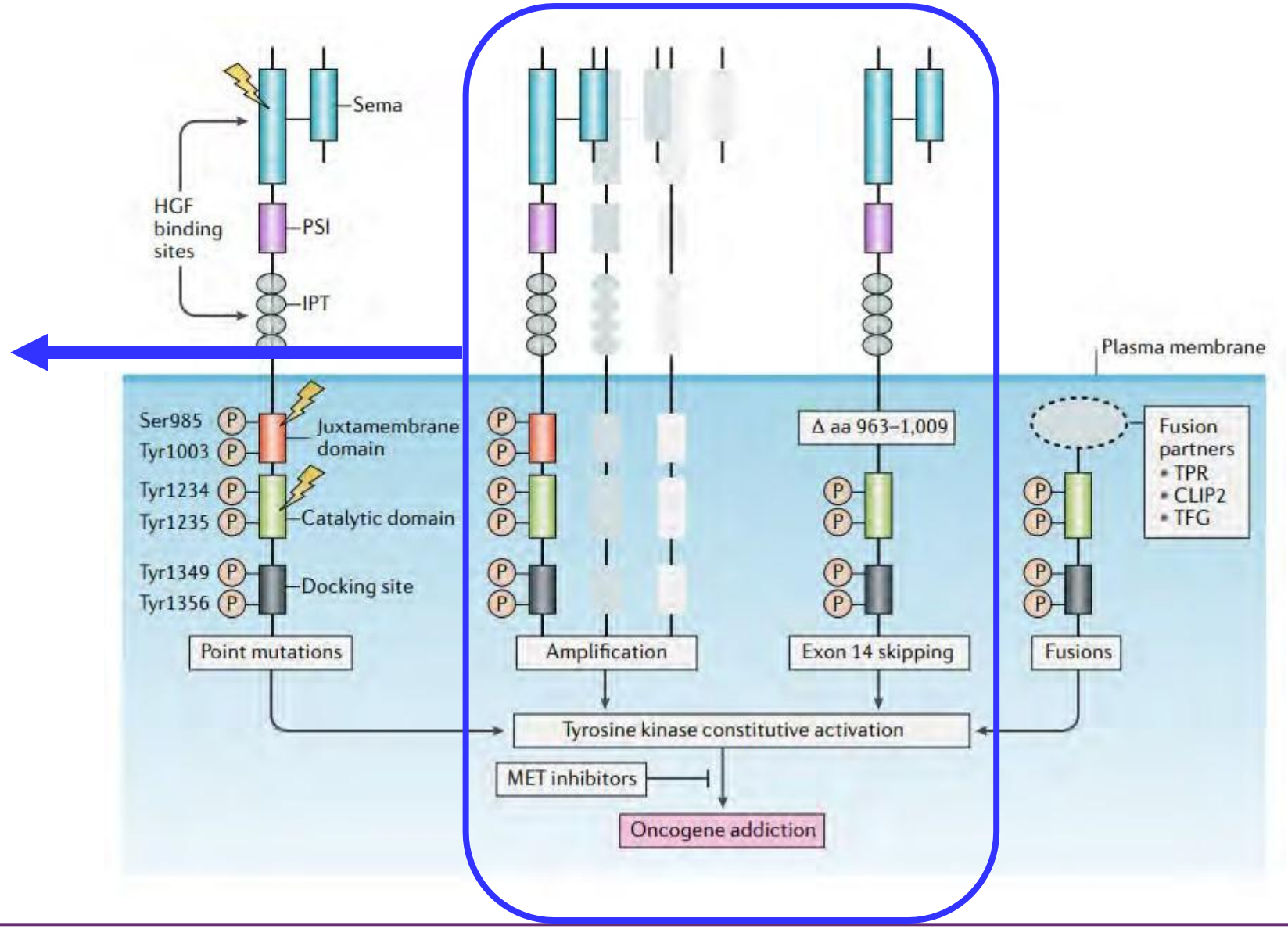
KHDAK'de MET-Mesenchymal Epithelial Transition Factor Yolağı

- **Primer sürücü mutasyonu olarak KHDAK'de**

- **Amplifikasyon (%2-5)**
- **Exon 14 skipping mutasyonu (%3-4)**

- **MET sekonder driver/co-driver olarak EGFR TKI direnci**

- **Amplifikasyon (%6-19)**



KHDAK'de MET-Mesenchymal Epithelial Transition Factor Receptor

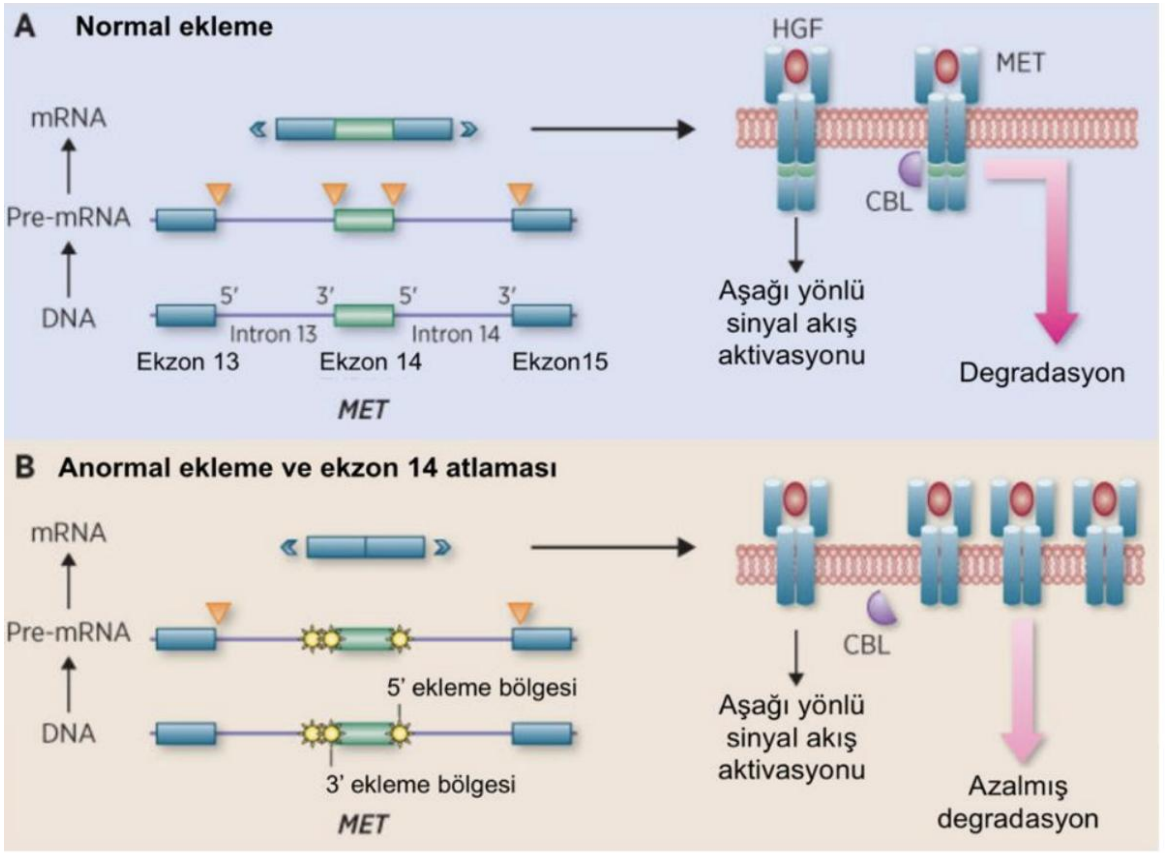
- Normal rolü embriyogenezis, yara iyileşmesi ve karaciğer rejenerasyonu

- METex14 MET'in degradasyonundan sorumlu reseptörün juxtamembran bölgesini kodlar. Nokta mutasyonları, juxtamembran alanın çerçeve içi silinmesine neden olarak, artan stabilite ve yapısal kinaz aktivasyonu ile sonuçlanır.

- İnsidans
- **Non-skuamöz KHDAK %3-4**
- **Sarkomatoid akciğer kanseri %8-30**

- **Klinikopatolojik özellikleri**
- Daha ileri yaş
- K>E
- Hiç sigara içmeyen hasta oranı daha az
- Diğer driver mutasyonlar ile mutually exclusive

- **<u>DNA bazlı NGS ile karşılaştırıldığında RNA bazlı NGS ile daha fazla saptanma oranına sahip</u>**



8. Anormal ekleme ile MET ekzon 14 atlaması ve sonuçları (Copyright © An

Drilon et al. J Thorac Oncol . 2017 January ; 12(1): 15–26.

MET Kinaz Hedefli Tedaviler

Tyrosine kinase Inhibitors

Crizotinib ●
Nonselektif

Capmatinib ●

Cabozantinib ●
Nonselektif

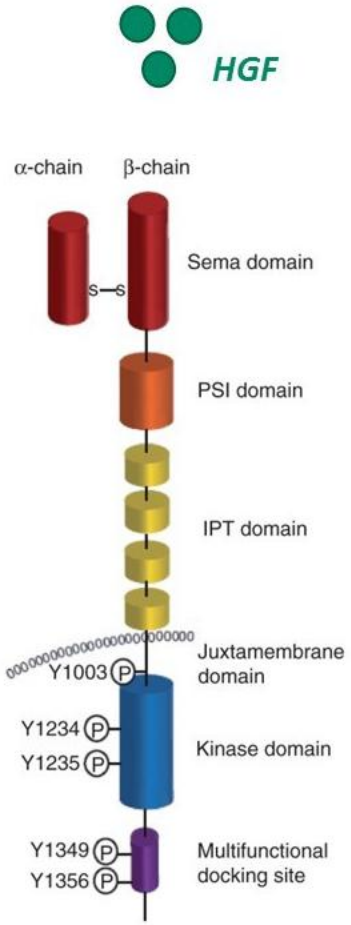
Savolitinib ●

Tepotinib ●

Glesatinib ●

Merestinib ●

Multikinase
Selective



Monoclonal Antibodies

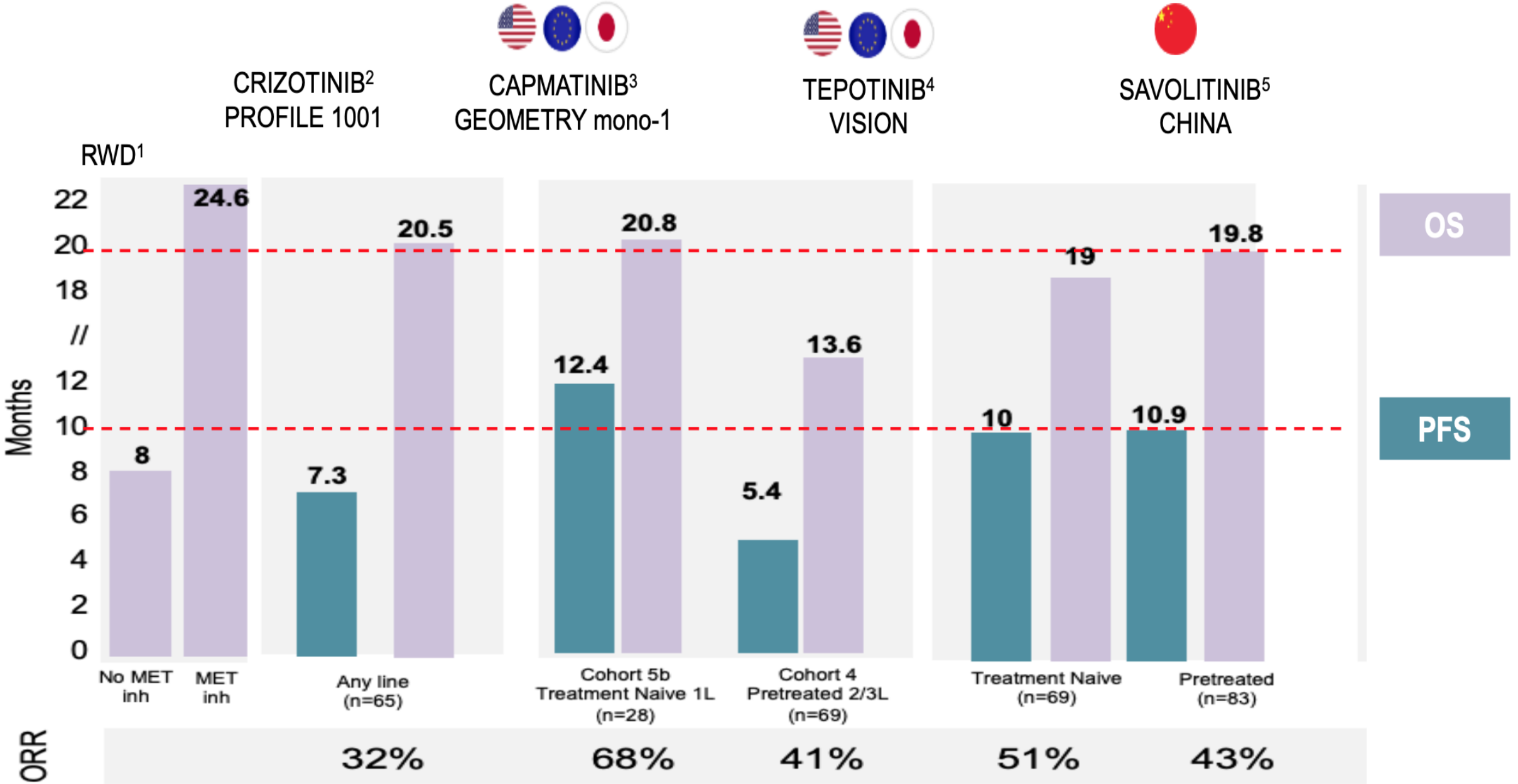
Specific HCF

Specific-MET

Bispecific Antibody

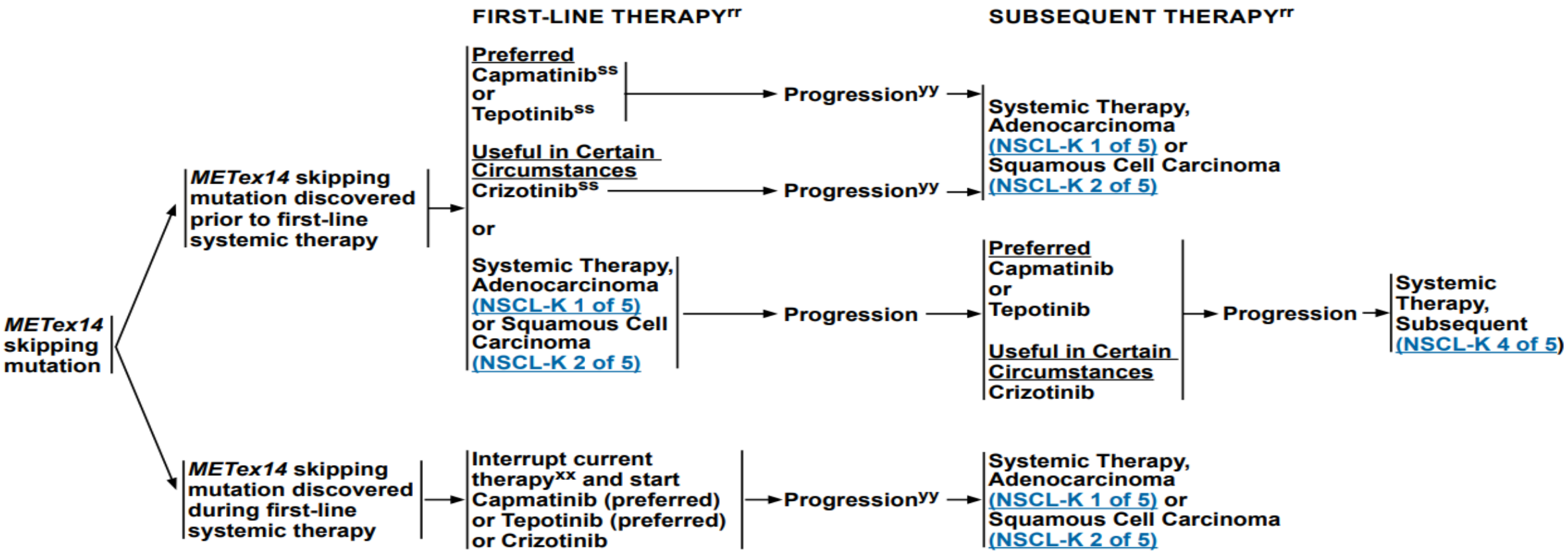
MET-MET
MET-EGFR
MET-others

Antibody-drug conjugate



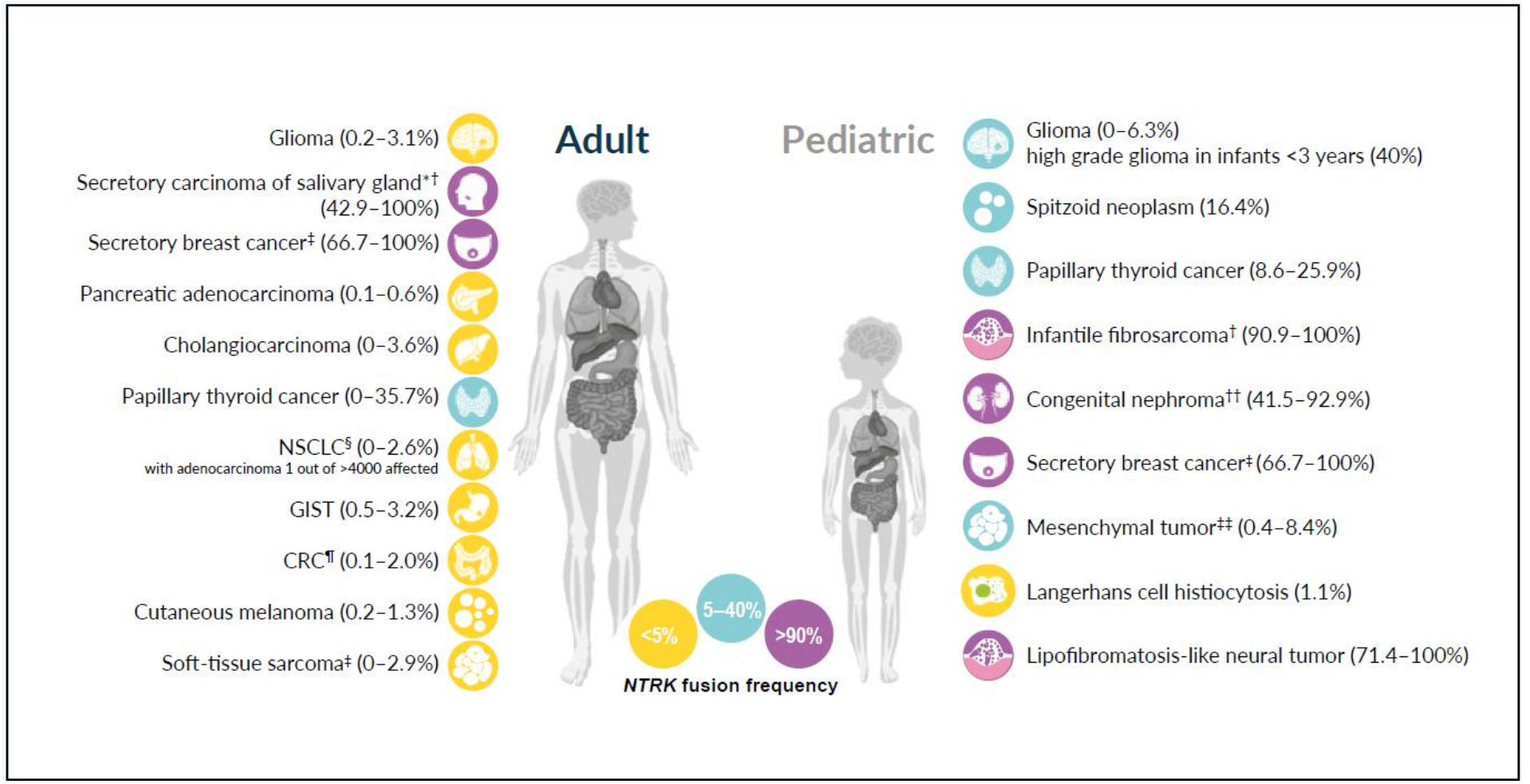
1.- Awad MM et al, Lung Cancer 2019; 2.- Drilon A et al, Nature Medicine 2020; 3.- Wolf, J et al, ASCO 2021; 4.- Thomas M et al, WCLC 2022; 5.- Shun Lu et al, ELCC 2022

METex14 SKIPPING MUTATION[nn]

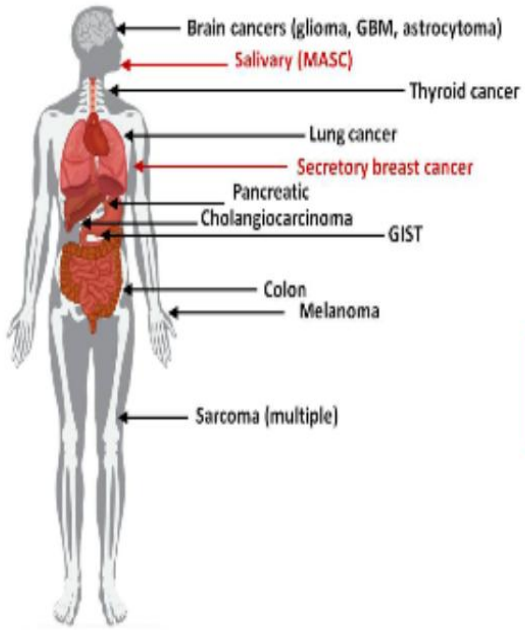


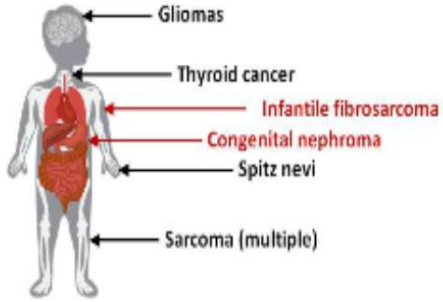
[nn] Principles of Molecular and Biomarker Analysis (NSCL-H)

NTRK FUZYONU



Low prevalence (< 1%) across tumors…but up to 90% in rare cancers





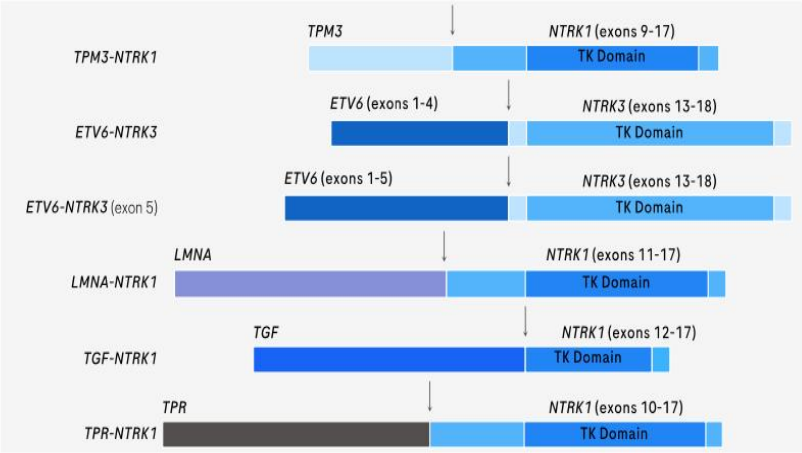
LUNG CANCER

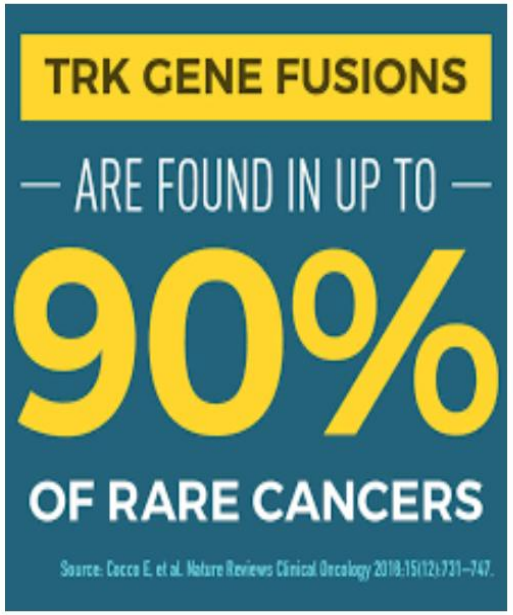
<1%

- Common cancer with low TRK fusion frequency (<1%)
- Rare cancer with high TRK fusion frequency (>80%)

Lung cancer most common *NTRK1*

>80 fusion partners identified to date[1-3]





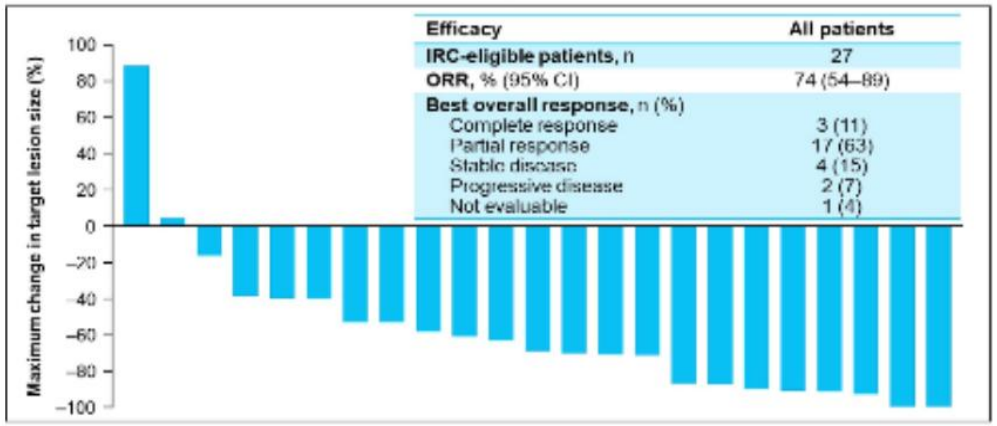
1.- Figure adapted from Planchard, ESMO Oncology_PRO 2019; .- 2.-Amatu, et al. Ann Oncol 2019; 3.- Wu, et al. Nat Genet 2014; 4.- Joshi, et al. Leukemia 2019; 5.- Rosen, et al. Clin Cancer Res 2020; 6.-Solomon, et al. Ann Oncol 2019

CONSISTENT RESULTS IN NSCLC HARBORING *NTRK* FUSIONS

Updated data in NSCLC

Larotrectinib[1]

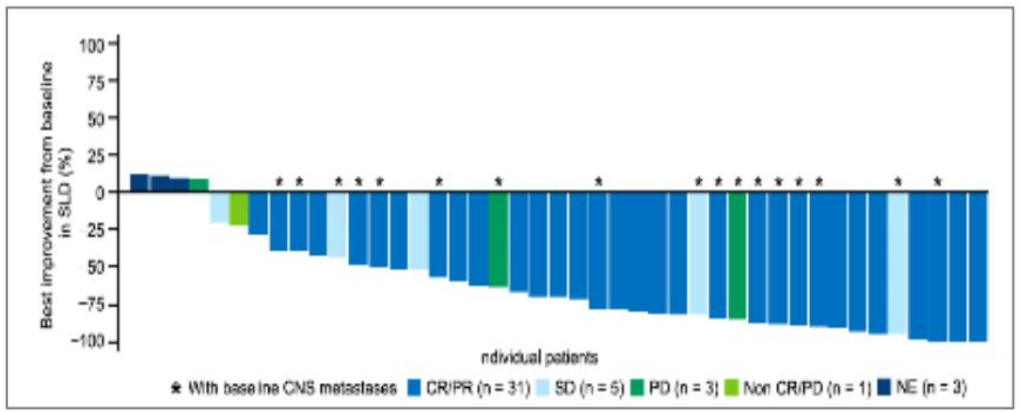
***NTRK*+ NSCLC (all n=30, BM n=12)**



ORR	74%
Intracranial ORR	80%
PFS median	33 months
OS median	39 months

Entrectinib[2]

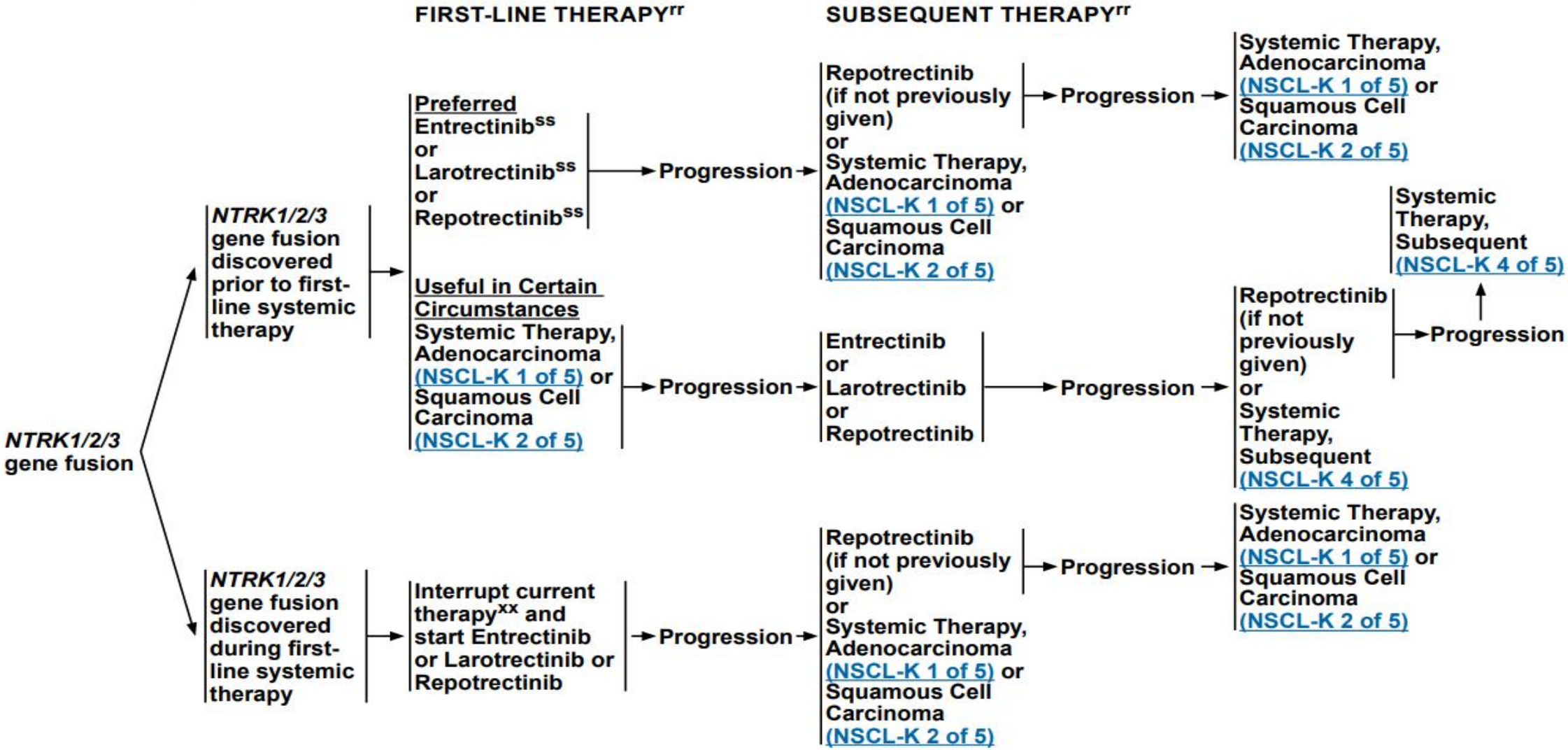
***NTRK*+ NSCLC (all n=51, BM n=20)**



ORR	63%
Intracranial ORR	67%
PFS median	28 months
OS median	41.5 months

1.- Lin J et al. ASCO 2023; 2.- Cho et al. Lung Cancer 2024

NTRK GENE FUSION[nn]



KRAS (+) KHDAK

- Mutasyon ya da amplifikasyon olabilir.
- KHDAK %20-30, **$KRAS^{G12C}$ %13**
- Sigara ile ilişkili
- Kötü prognoz

$KRAS^{G12C}$ Mutant KHDAK'de 2. Sıra ve sonrasında Tedavi

KRYSTAL-1 Study Design

Screening/ Enrollment	Phase 2: Monotherapy Treatment

Key Eligibility Criteria

- Solid tumor with $KRAS^{G12C}$ mutation[a]
- Unresectable or metastatic disease
- Prior treatment with a PD-1/L1 inhibitor in combination or following chemotherapy (NSCLC)[b]
- Treated and/or stable brain metastases[c]

Endpoints

Primary: ORR(RECIST1.1) by independent central review

Key Secondary: DOR, PFS, OS, safety, MTD, PK, RP2D

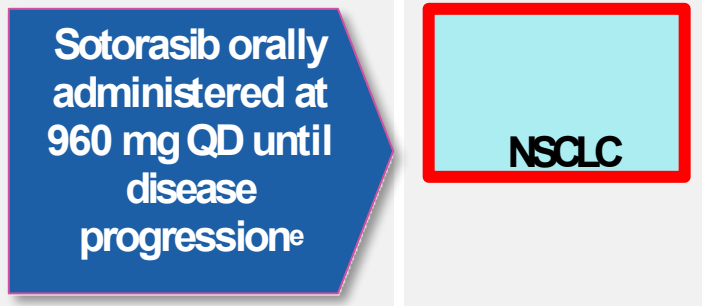
Exploratory: Evaluation of biomarkers

CodeBreaK100 Study Design

Screening/ Enrollment	Phase 2: Monotherapy Treatment	Safety and Long-Term Follow-Up[f]

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- $KRAS^{G12C}$ mutation as assessed by central testing of tumor biopsies
- Progressed on standard therapies[d]
- Stable brain metastases were allowed



Endpoints

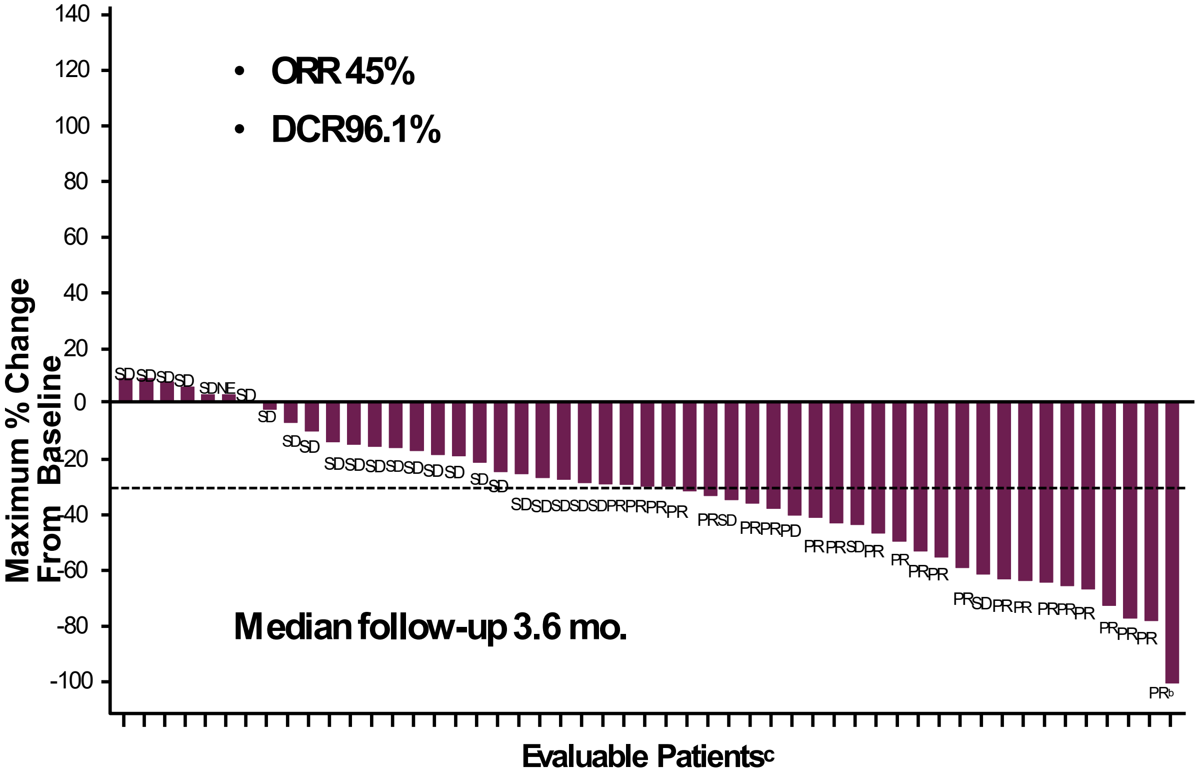
Primary: ORR(RECIST1.1) by independent central review

Key Secondary: DOR, DCR, TTR, PFS, OS, safety

Exploratory: Evaluation of biomarkers

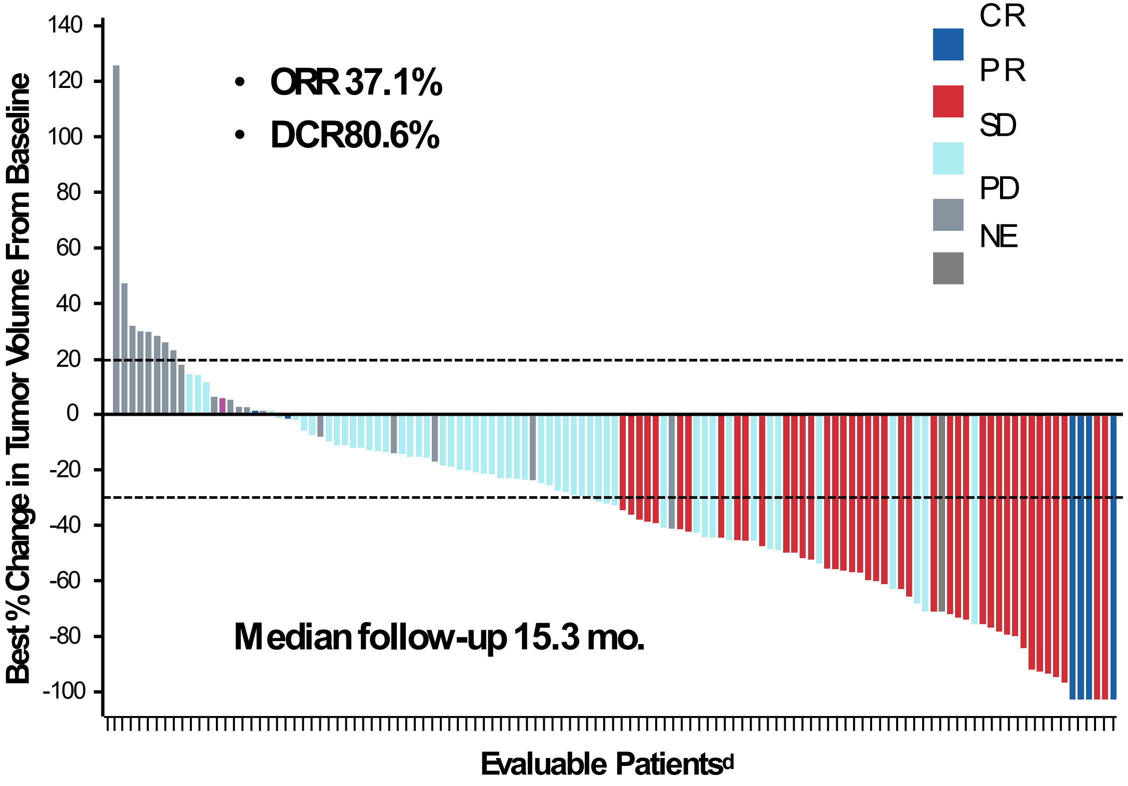
KRAS^{G12C} Mutant KHDAK'de 2. Sıra ve sonrasında Adagrasib ve Sotorasib

Adagrasib Response in KRAS^{G12C}-Mutated NSCLC



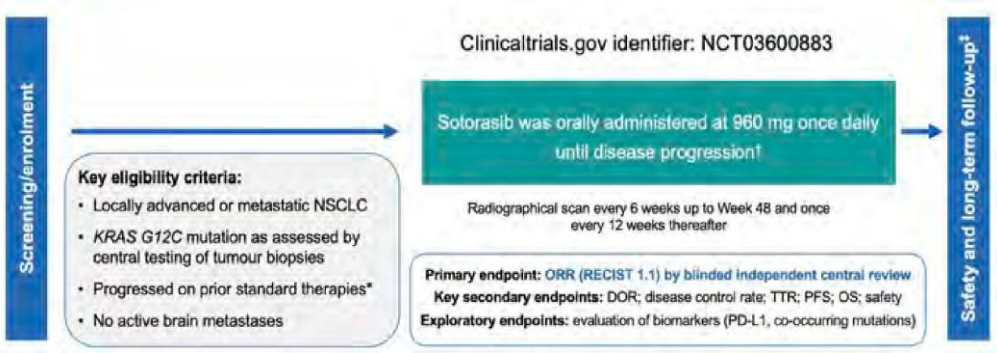
Janne, AACR-NCI-EORTC meeting 2020
Ou, JCO 2022

Sotorasib Response in KRAS^{G12C}-Mutated NSCLC

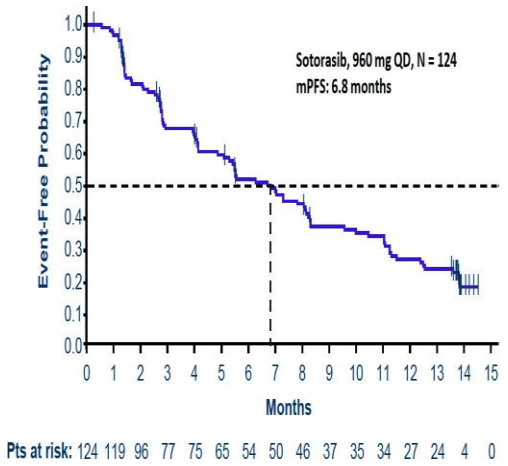


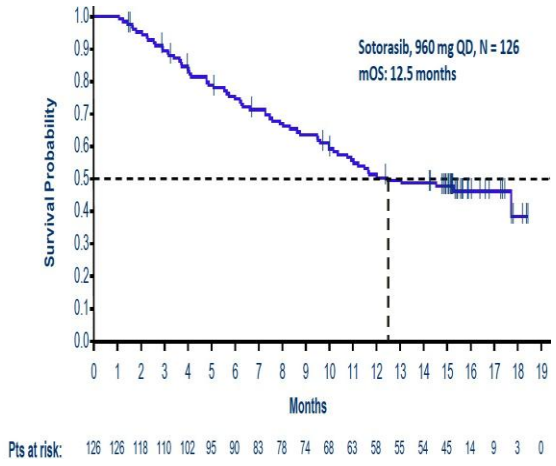
Skoulidis, NEJM 2021

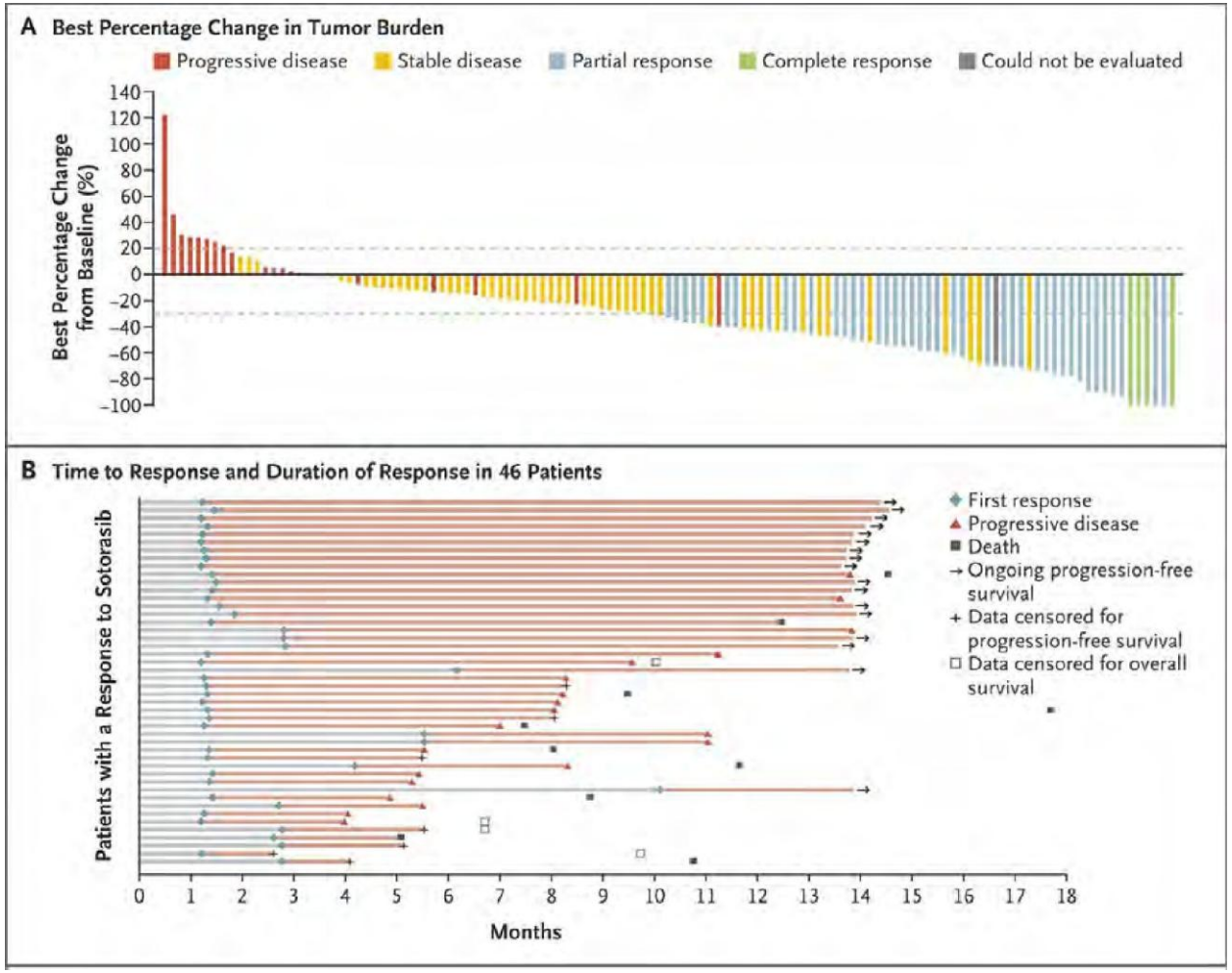
Faz II CodeBreak 100 Sotorasib: KRAS^{G12C} Mutant KHDAK Kohortu



- 126 hasta, %81 Platin bazlı KT ve Ḋ
- mPFS 6.8 ay
- mOS 12.5 ay







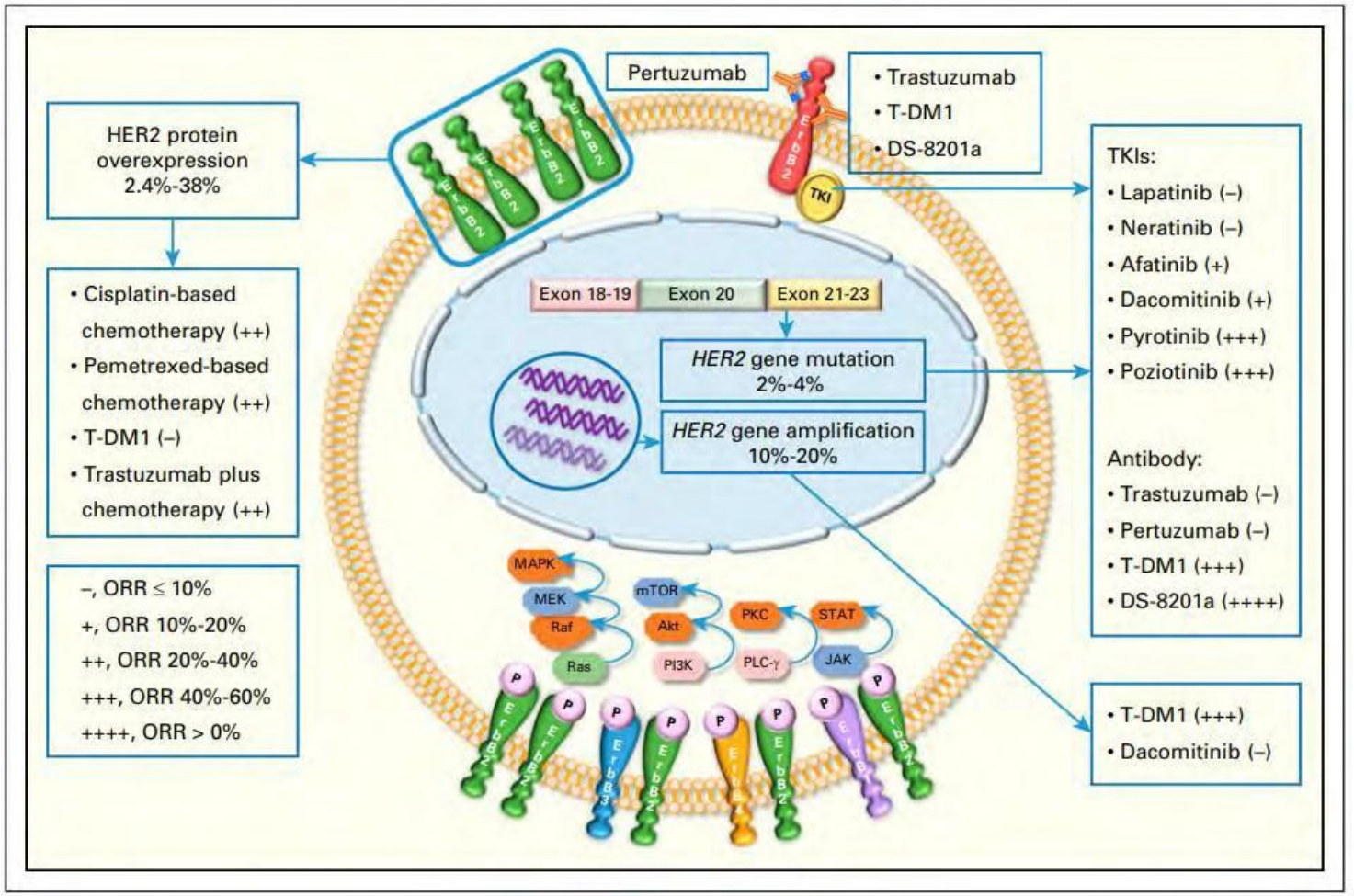
Skoulidis, NEJM 2021

Her2+ mKHDAK

- ➢ **HER2 mutasyonu**
- ✓ **KHDAK %2-4**
- ✓ **HER-2 Ekzon 20 in-frame insersiyonu en sık**
- ✓ **Kinaz domain Her2 mutasyonu devamlı yapısal aktiviteye sebep olur.**
- ✓ **NGS**

- ➢ **HER2 Gen Amplifikasyonu**
- ✓ **HER2 gen kopya sayısında artış**
- ✓ **EGFR TKİ Naive hastaların %3**
- ✓ **EGFR TKI rezistan %10**
- ✓ **FISH yada NGS**

- ➢ **HER2 protein overekspresyonu**
- ✓ **İHK +++) %3-6**



Pillai Cancer. 2017;123(21):4099-105. Li J Thorac Oncol. 2016;11(3):414-9. Zhao JCO Precision Oncology 2020 :4, 411-425.

Her2+ mKHDAK'li Hastalarda Hedefli Tedaviler

Agent	Phase of Study	Sample Size	*HER2* Mutation	ORR, %	PFS	Dose Reduction Rate, %
Kinase inhibitors						
Afatinib[16]	II	13	Exon 20	7.7	15.9 weeks	NA
Afatinib[17]	II	7	All	0	17.0 weeks	44
Dacomitinib[18]	II	26	Exon 20	11.5	3 months	17
Neratinib[19]	II	26	All	3.8	5.5 months	NA
Neratinib plus temsirolimus[20]	I	7	All	33.3	NA	30
Pyrotinib[21]	II	60	All	30	6.9 months	NA[a]
Poziotinib[22]	II	30	Exon 20	27	5.5 months	73
Poziotinib[23]	II	90	Exon 20 insertion	27.8	5.5 months	77
Monoclonal antibodies						
Trastuzumab plus pertuzumab plus docetaxel[24]	II	45	Exon 20	29	6.8 months	NA
Trastuzumab plus pertuzumab[25]	II	14	Activating[b]	21	NA	NA
ADCs						
TDM-1[26]	II	18	All	44	5 months	0
TDM-1[27]	II	7	Exon 20 insertion	14.3	NA	27
T-DXd[28]	II	91	Activating[c]	55	8.2 months	34

Abbreviations: ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; NA, not applicable; ORR, objective response rate; PFS, progression-free survival; TDM-1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]Dose reduction rate reported only for diarrhea (5%).

[b]Includes exon 20 insertions, deletions around amino acids 755-759, and several nonsynonymous amino acid substitutions.

[c]Includes extracellular, transmembrane, and kinase domain mutations.

DESTINY-Lung01: Her2 Overekspresyon Metastatik KHDAK Trastuzumab deruxtecan, Multicenter, Faz II Çalışma

Key eligibility criteria

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]

Cohort 1: HER2-overexpressing[c] (IHC 3+ or IHC 2+) T-DXd 6.4 mg/kg q3w N = 49

Cohort 1a: HER2-overexpressing[c] (IHC 3+ or IHC 2+) T-DXd 5.4 mg/kg q3w N = 41

Cohort 2: *HER2*-mutated T-DXd 6.4 mg/kg q3w N = 42

Cohort 2 expansion: *HER2*-mutated T-DXd 6.4 mg/kg q3w N = 49

Primary end point

- Confirmed ORR by ICR[d]

Secondary end points

- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point

- Biomarkers of response

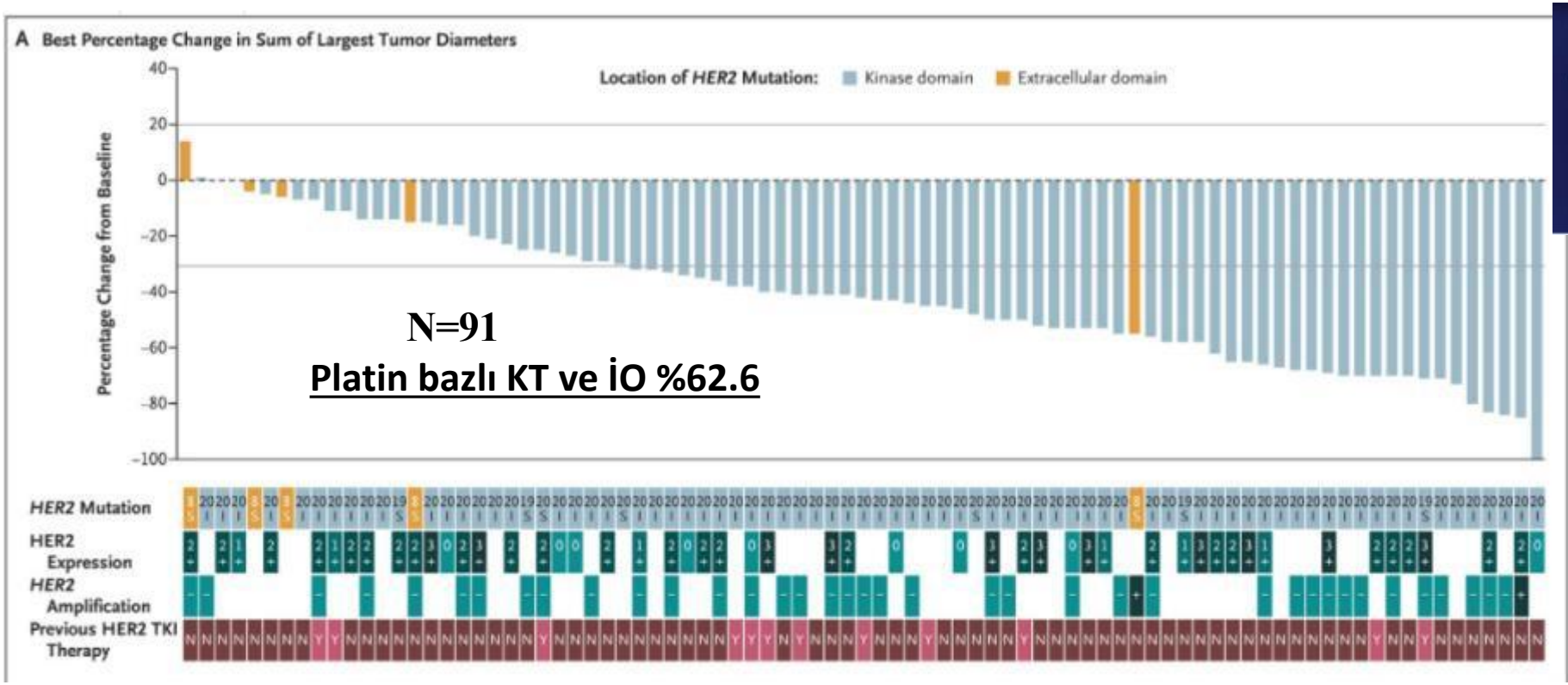
Data cutoff: May 3, 2021

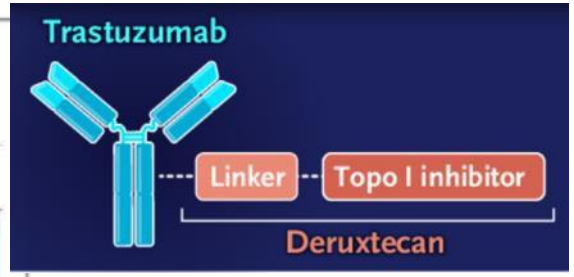
- 91 patients with *HER2*m NSCLC were enrolled and treated with T-DXd
- 15 patients (16.5%) remain on treatment to date
- 76 patients (83.5%) discontinued, primarily for progressive disease (37.4%) and adverse events (29.7%)

[a]Patients with asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll [b]*HER2* mutation documented solely from a liquid biopsy could not be used for enrolment [c]HER2 overexpression without known *HER2* mutation was assessed by local assessment of archival tissue and centrally confirmed [d]Per RECIST v1.1

DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

DESTINY-Lung01: Her2 Mutant Metastatik KHDAK T-DXd





ORR: 55%
mPFS: 8.2 mo
mOS: 17.8 mo (18.6 mo update ESMO 2022)
Safety: common AEs gastrointestinal and hematologic events, decreased appetite, and alopecia
26% drug-related interstitial lung disease

DESTINY-Lung02 trial: ORR 42.9% (6.4 mg/kg)
53.8% (5.4 mg/kg)
(Goto et al. ESMO 2022)

FDA approval Aug 2022

Li et al. N Engl J Med 2022; 386:241-251

TEŞEKKÜRLER