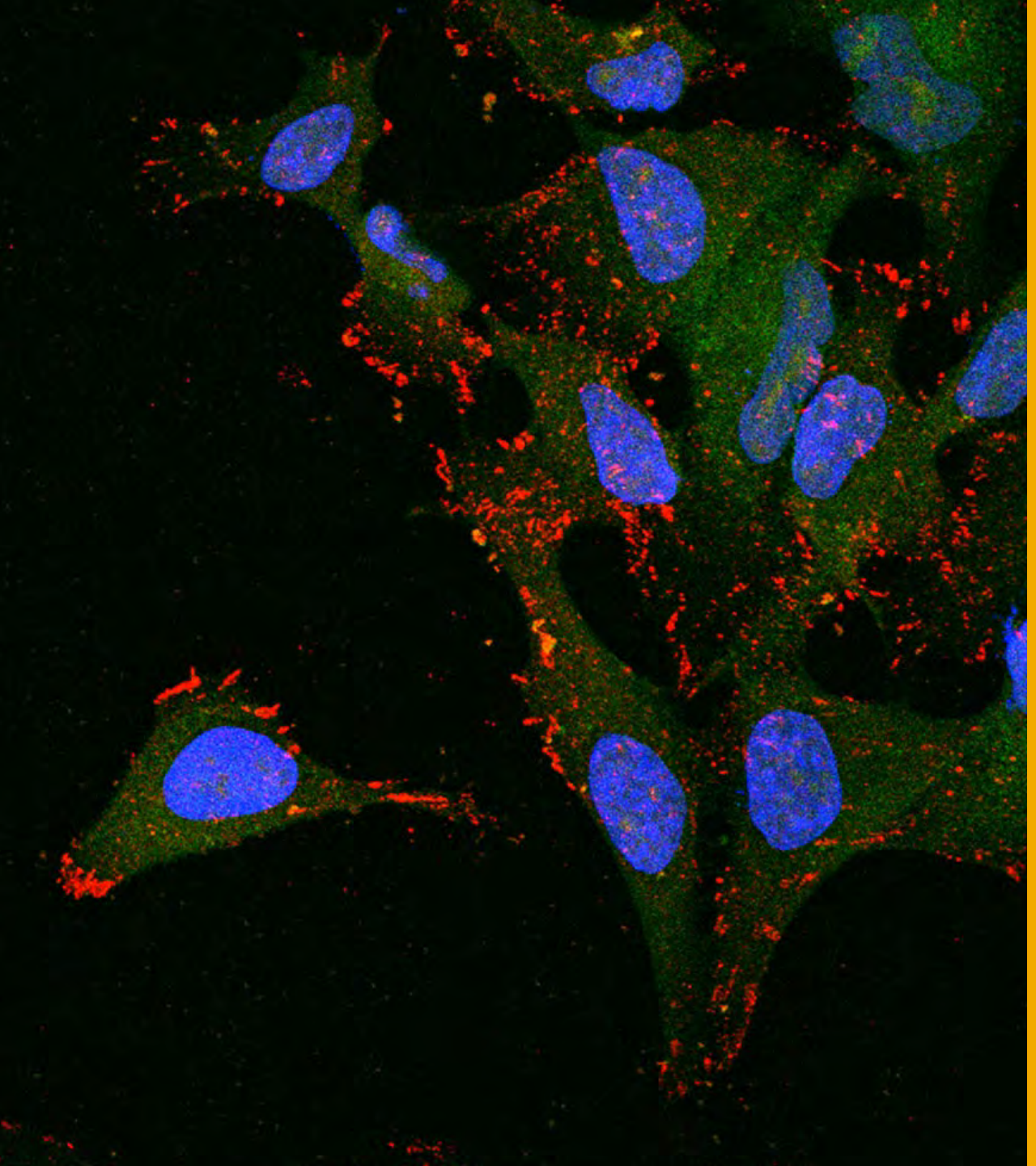

UPDATES IN TARGETED THERAPY FOR ADVANCED NSCLC

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National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

DISCLOSURES

Scientific advisory board/consultant

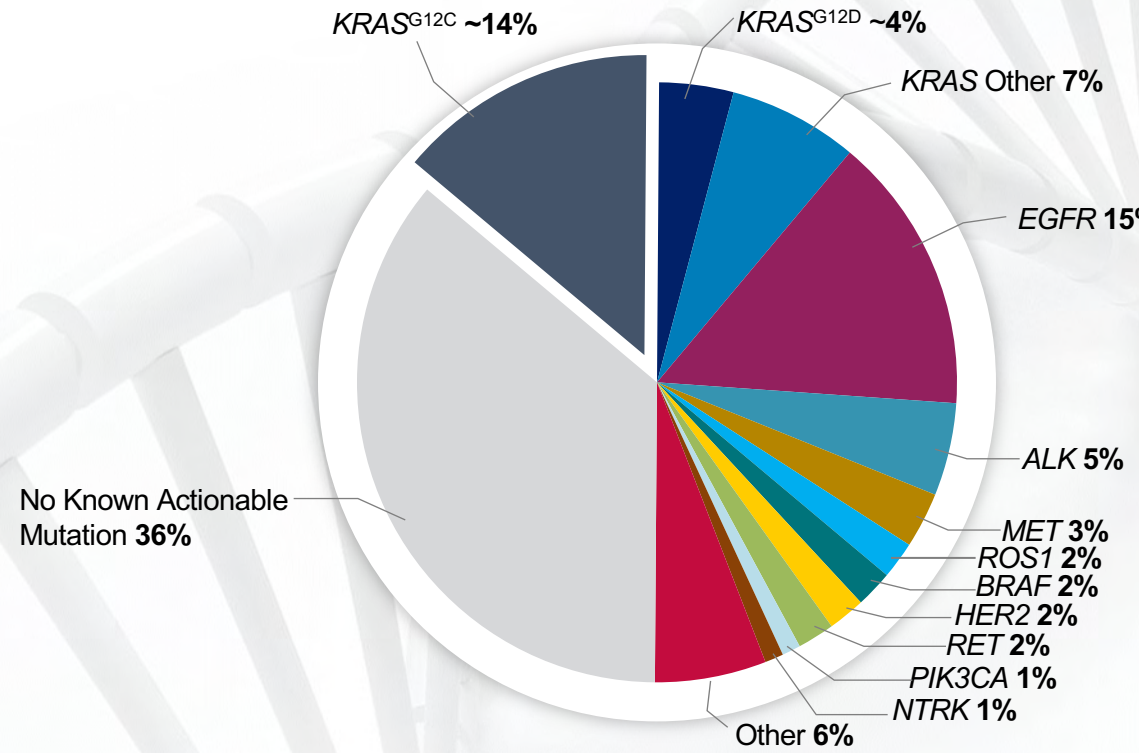
- Amgen, Bristol Myers Squibb, Eisai, Glaxo SmithKline

Research support (to institution)

- Amgen, Advaxis, Astra Zeneca, Bristol Myers Squibb, Merck, Glaxo SmithKline, Takeda, Genmab

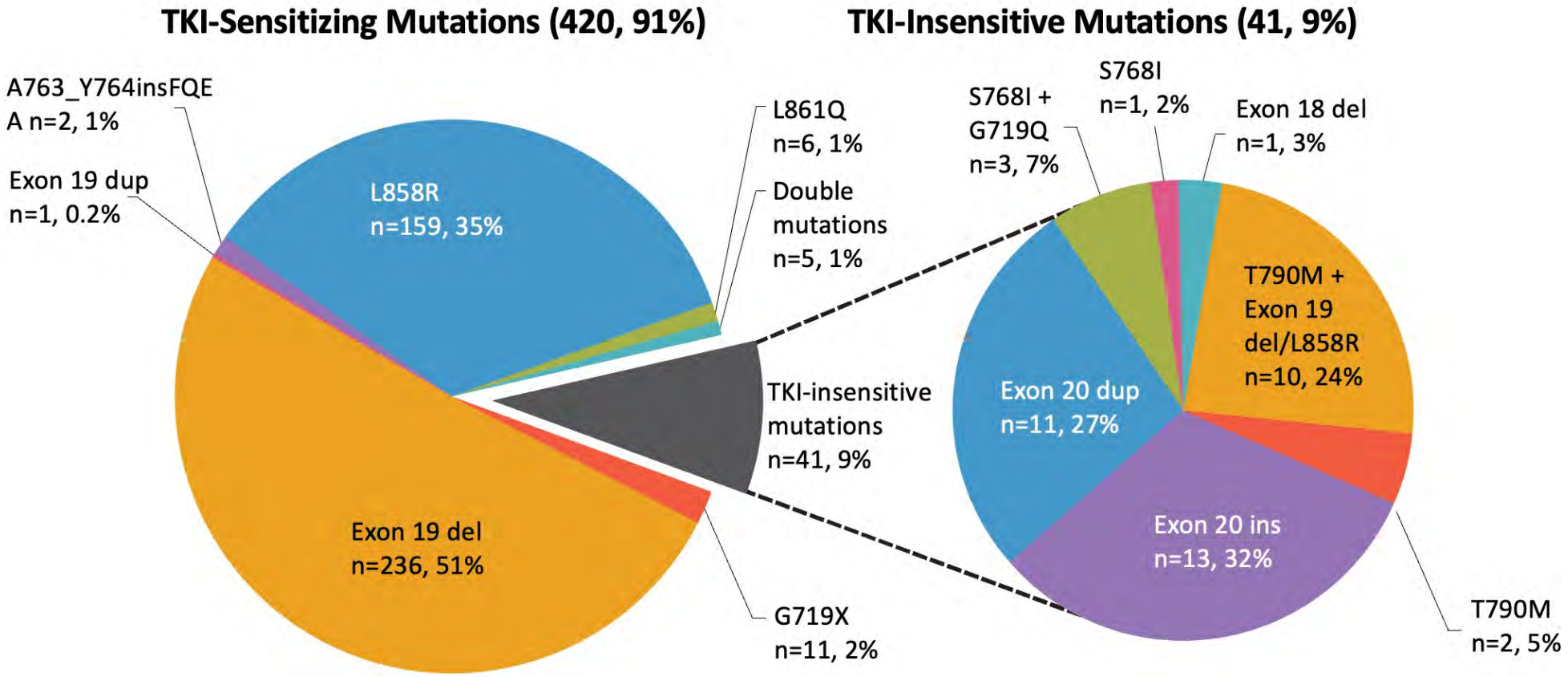
MUTATED ONCOGENES IN NSCLC

Prevalence of Oncogenic Mutations in Lung Adenocarcinoma[1]



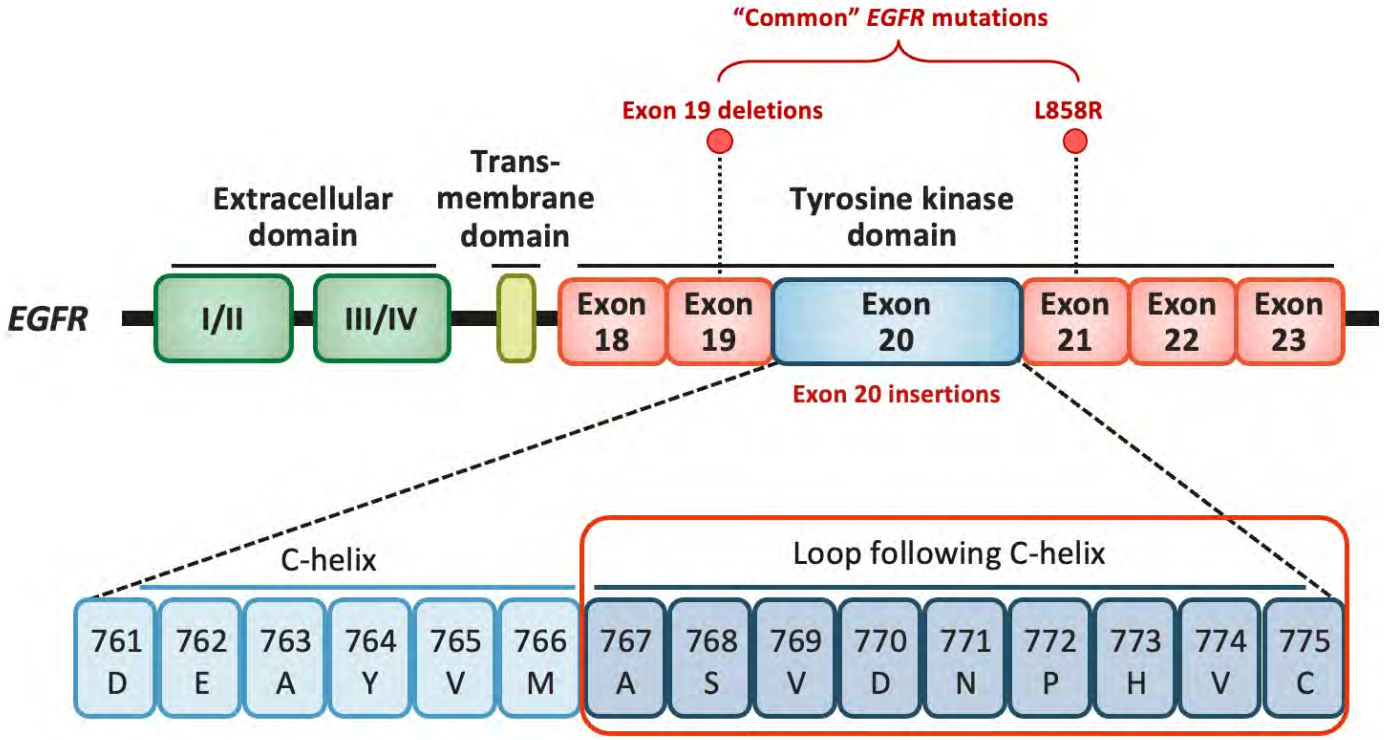
1. Forde PM, et al. *Expert Rev Anticancer Ther*. 2013;13(6):745-758. 2. Pakkala S, et al. *JCI Insight*. 2018;3(15):e120858. 3. Loh Z, et al. *Intern Med J*. 2019;49(12):1541-1545.

EGFR MUTATIONS ARE NOT ONE ENTITY



Retrospective review of 461 EGFR mutation positive, advanced lung adenocarcinoma patients diagnosed at a tertiary Asian cancer center from January 2009 to April 2013.
TKI=tyrosine kinase inhibitor.
Presented with permission from Dreamstime.com.
Jain A, et al. *PLoS ONE.* 2015;10(5):e0123587.

SPECTRUM OF EXON 20 MUTATIONS



EGFR=epidermal growth factor receptor.
Vyse S, Huang PH. *Signal Transduct Target Ther*. 2019;4-5.

COMMON *EGFR* MUTATIONS

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FLAURA: OSIMERTINIB VS. 1ST GEN TKI

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years*
- WHO performance status 0 / 1
- Exon 19 deletion / L858R (enrollment by local† or central‡ EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification by **mutation status** (Exon 19 deletion / L858R) **and race** (Asian / non-Asian)

Randomized 1:1

Osimertinib (80 mg p.o. qd) (n=279)

EGFR-TKI SoC# **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) (n=277)

RECIST 1.1 assessment every 6 weeks¶ until objective progressive disease

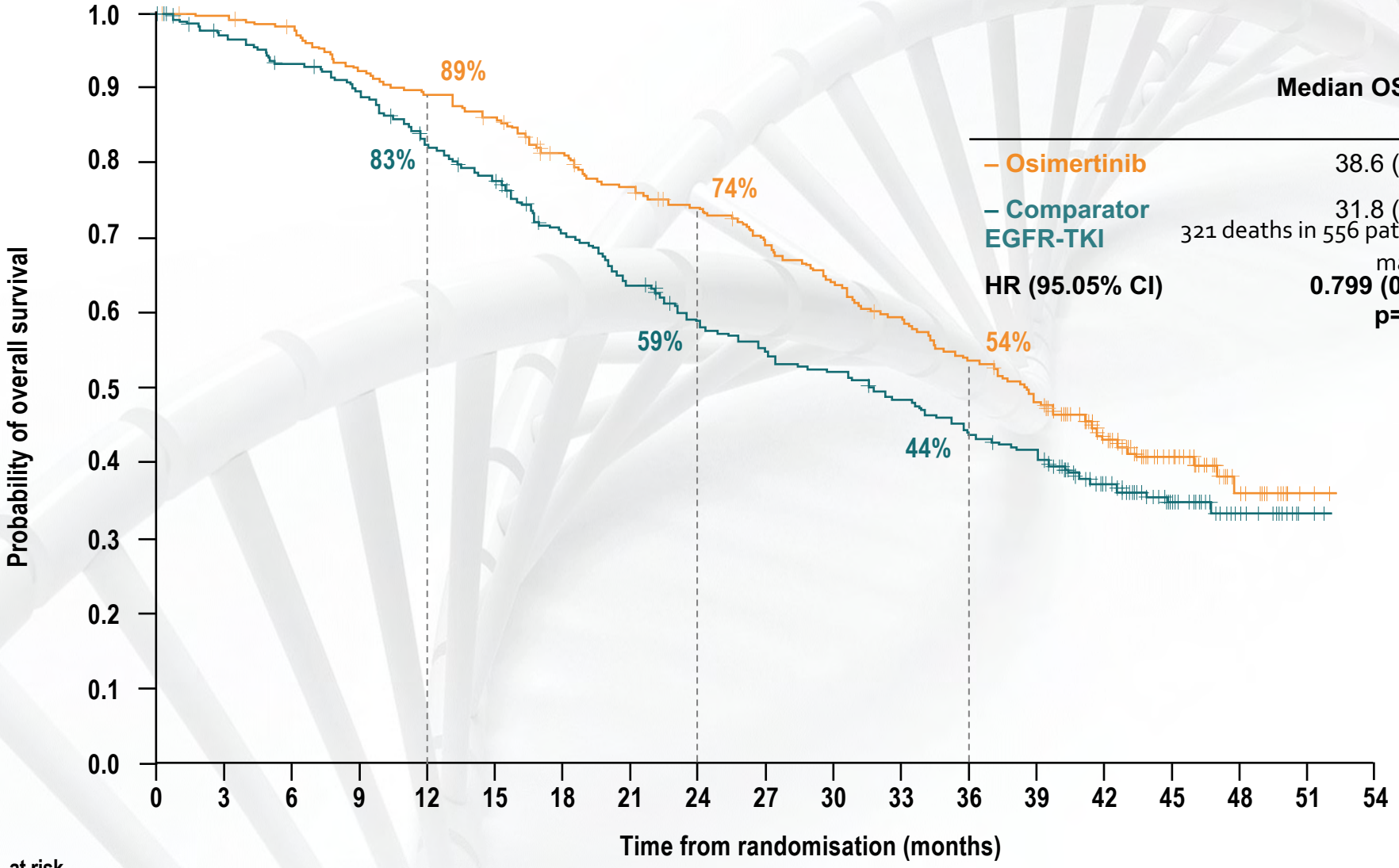
Crossover was allowed for patients in the **SoC** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

Ramalingam et al, N Engl J Med, 2020.

FINAL ANALYSIS: OVERALL SURVIVAL



	Median OS, months (95% CI)
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)

321 deaths in 556 patients at data cut-off: 58% maturity

HR (95.05% CI) **0.799 (0.641, 0.997); p=0.0462**

No. at risk																			
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Ramalingam et al, N Engl J Med, 2020.

COMBINATION APPROACHES: CHEMOTHERAPY + TKI

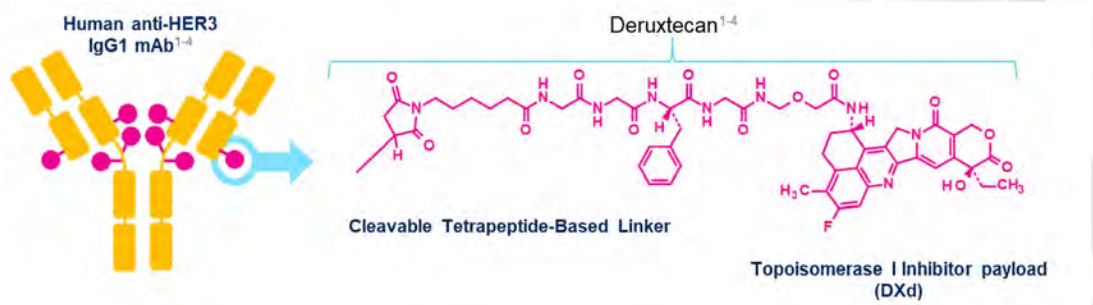
- Two studies conducted in Asia
  - NEJ 009 (Japan)
  - Tata Memorial Trial (India)
- Chemotherapy + Gefitinib Vs. Gefitinib
- Improvement in PFS and OS
  - HR ~0.50- 0.72
- Role of chemotherapy + Osimertinib?
  - FLAURA 2

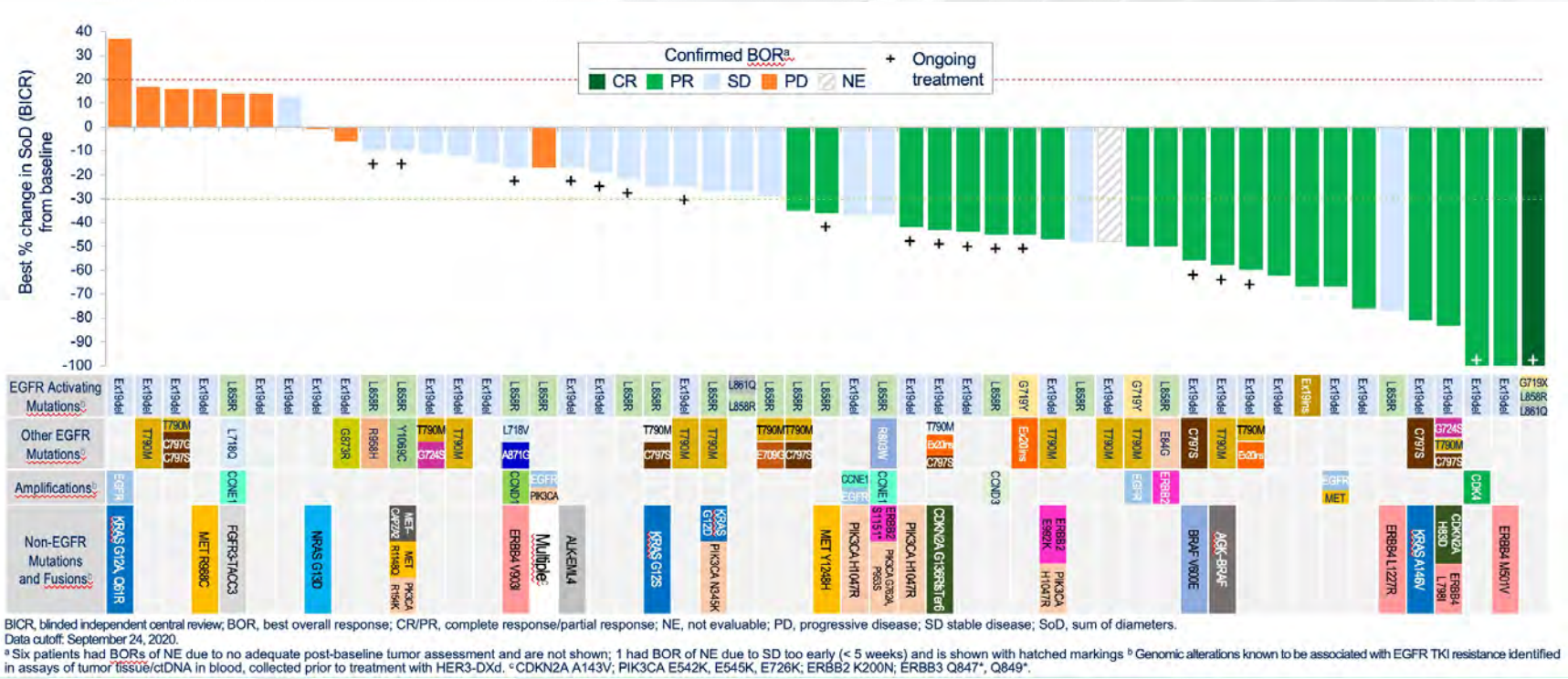
Noronha et al, J Clin Oncol, 2020; Hosomi et al, J Clin Oncol, 2020.

MANAGING ACQUIRED RESISTANCE TO EGFR TKI

- Oligoprogression
  - Role of local therapy
- Conversion to SCLC/Squamous histology
  - 3-5%; consider biopsy based on clinical suspicion
- Systemic therapy
  - Platinum-based chemotherapy
  - Role of immune checkpoint inhibition

PATRITUMAB DERUXTECAN: ADC AGAINST HER3





BICR, blinded independent central review; BOR, best overall response; CR/PR, complete response/partial response; NE, not evaluable; PD, progressive disease; SD stable disease; SoD, sum of diameters.
Data cutoff: September 24, 2020.
[a] Six patients had BORs of NE due to no adequate post-baseline tumor assessment and are not shown; 1 had BOR of NE due to SD too early (< 5 weeks) and is shown with hatched markings [b] Genomic alterations known to be associated with EGFR TKI resistance identified in assays of tumor tissue/ctDNA in blood, collected prior to treatment with HER3-DXd. [c] CDKN2A A143V; PIK3CA E542K, E545K, E726K; ERBB2 K200N; ERBB3 Q847*, Q849*.

Response Rate ~35%
mPFS: ~8 m

Janne P et al, Cancer Discovery, 2021.

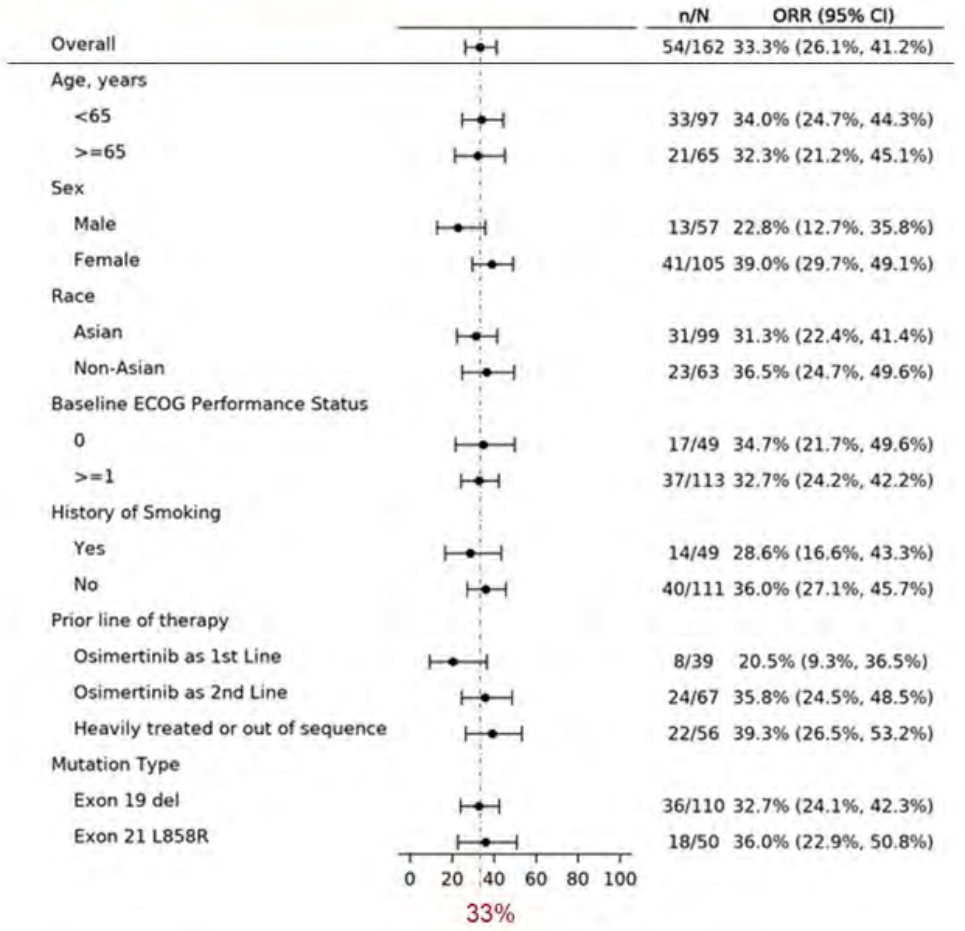
Antitumor Activity of Amivantamab + Lazertinib

BICR-assessed Response	n=162
ORR	33% (95% CI, 26–41)
Median DOR	9.6 mo (95% CI, 7.0–NE)
Best response, n (%)	
Complete response	2 (1)
Partial response	52 (32)
Unconfirmed partial response	1 (0.6)
Stable disease	69 (43)
Progressive disease	28 (17)
NE	10 (6)
Clinical benefit rate[a]	57% (95% CI, 49–65)

Investigator-assessed ORR=28% (95% CI, 22–36)
Investigator-assessed median DOR=8.4 mo (95% CI, 5.6–NE)

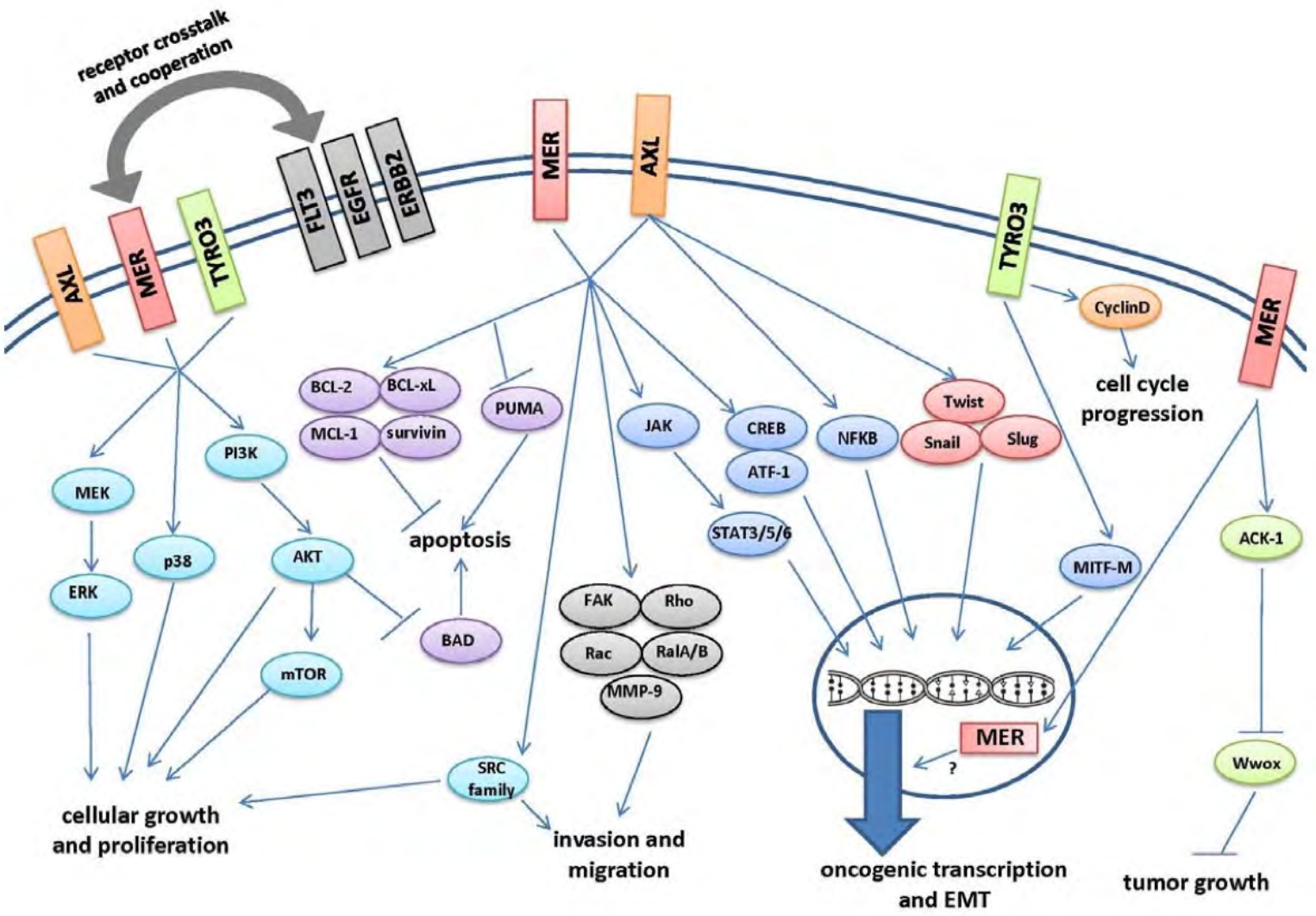
Median follow-up=10.0 mo (range, 0.3–20.2)
Median progression free survival=5.1 mo (95% CI, 4.2–6.9)
Median overall survival=14.8 mo (95% CI, 12.1–NE)

[a]Percentage of patients with confirmed response or durable stable disease (duration of ≥11 weeks).
BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; mo, months; NE, not evaluable; ORR, overall response rate.



Shu et al, ASCO 2022.

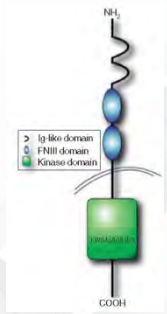
TAM SIGNALING IN CANCER



Graham et al, *Nat Rev Cancer,* 2014

MERTK: A DUAL TARGET IN CANCER

MERTK



MERTK over-expressed in tumor cells e.g., leukemia, lung cancer, melanoma, GBM

→ Survival signal

MERTK Inhibitors
Reverse survival & chemoresistance

Combination w/ chemotherapy and targeted agents

MERTK TKIs could have a dual anti-cancer effect

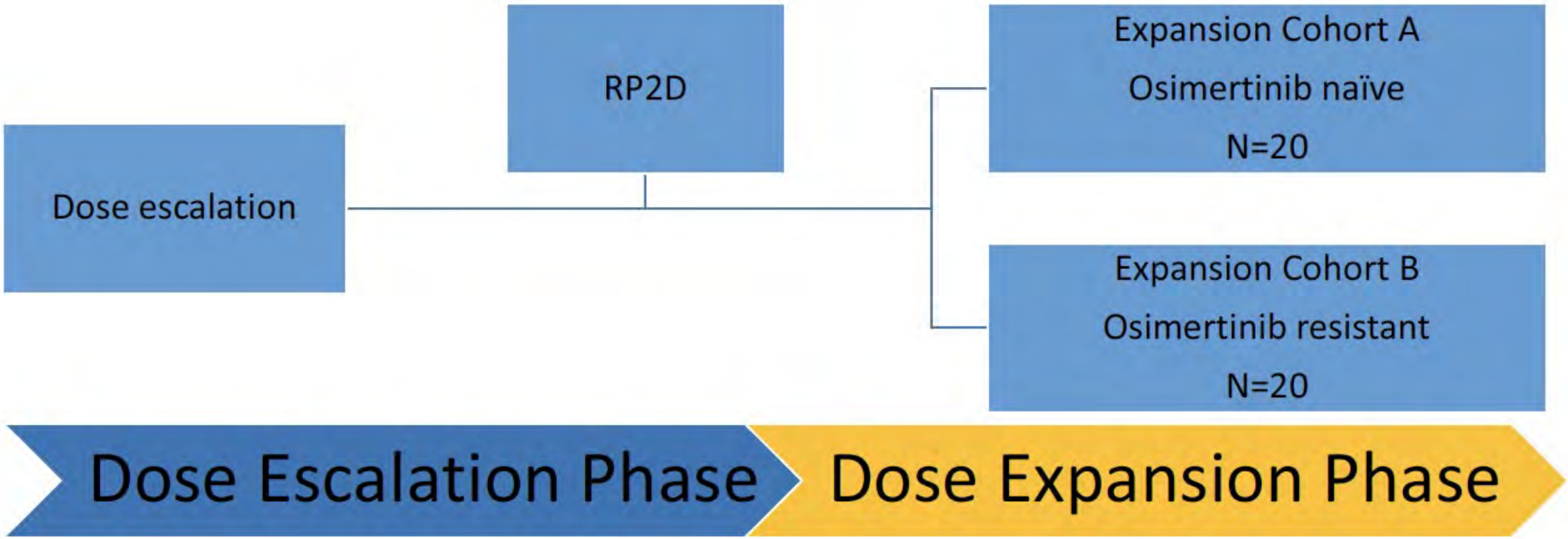
Expressed in tumor macrophages e.g., breast & lung cancer

→ Suppresses tumor immunity

MERTK Inhibitors
Stimulate innate anti-tumor immunity

Combination w/ immunotherapy and targeted agents

COMBINATION OF OSIMERTINIB PLUS MRX 2843
EMORY LUNG SPORE



PI: Conor Steuer

ADJUVANT EGFR TKI THERAPY

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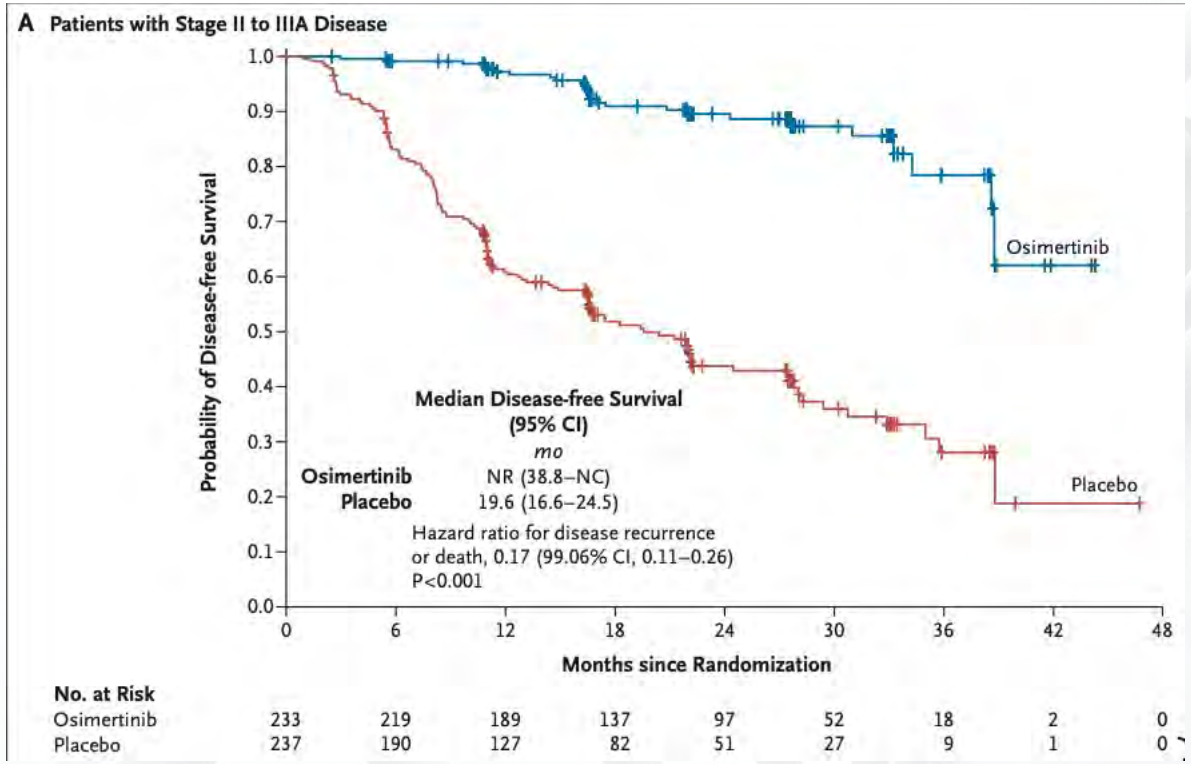
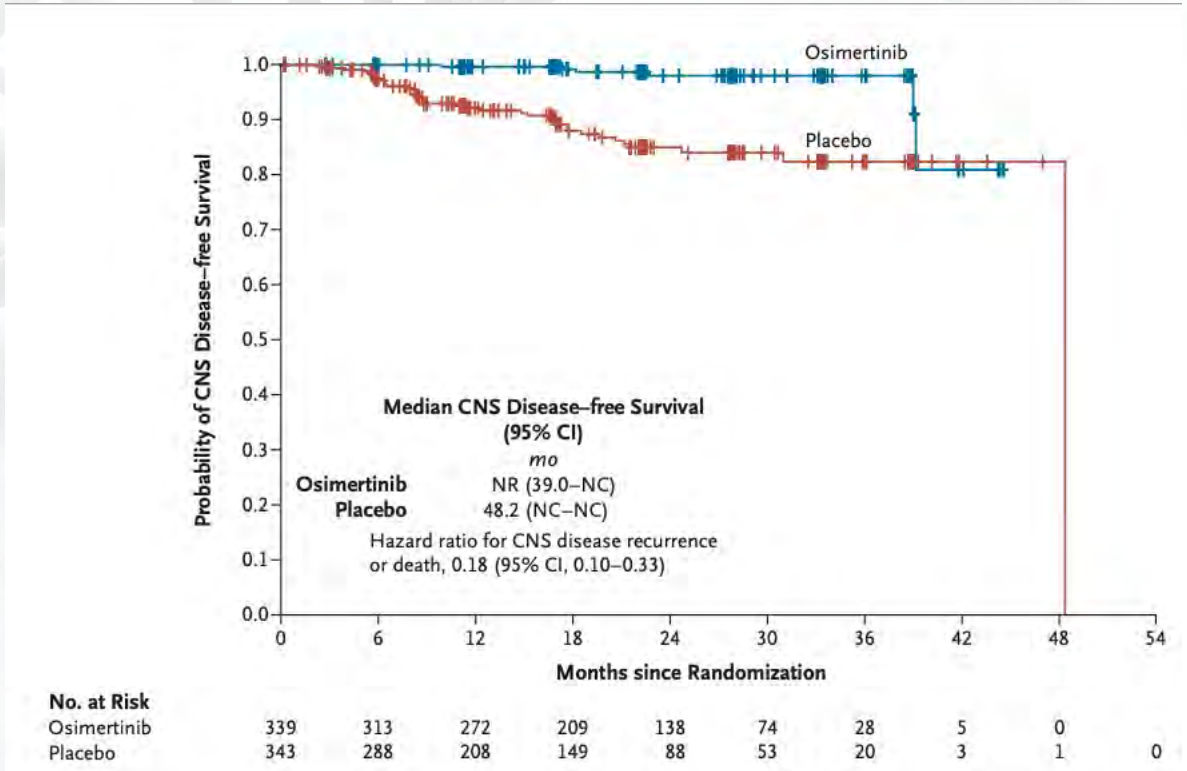
ADJUVANT OSIMERTINIB: ADAURA TRIAL





Wu Y et al, N Engl J Med, 2020.

EGFR EXON 20 INSERTION MUTATION

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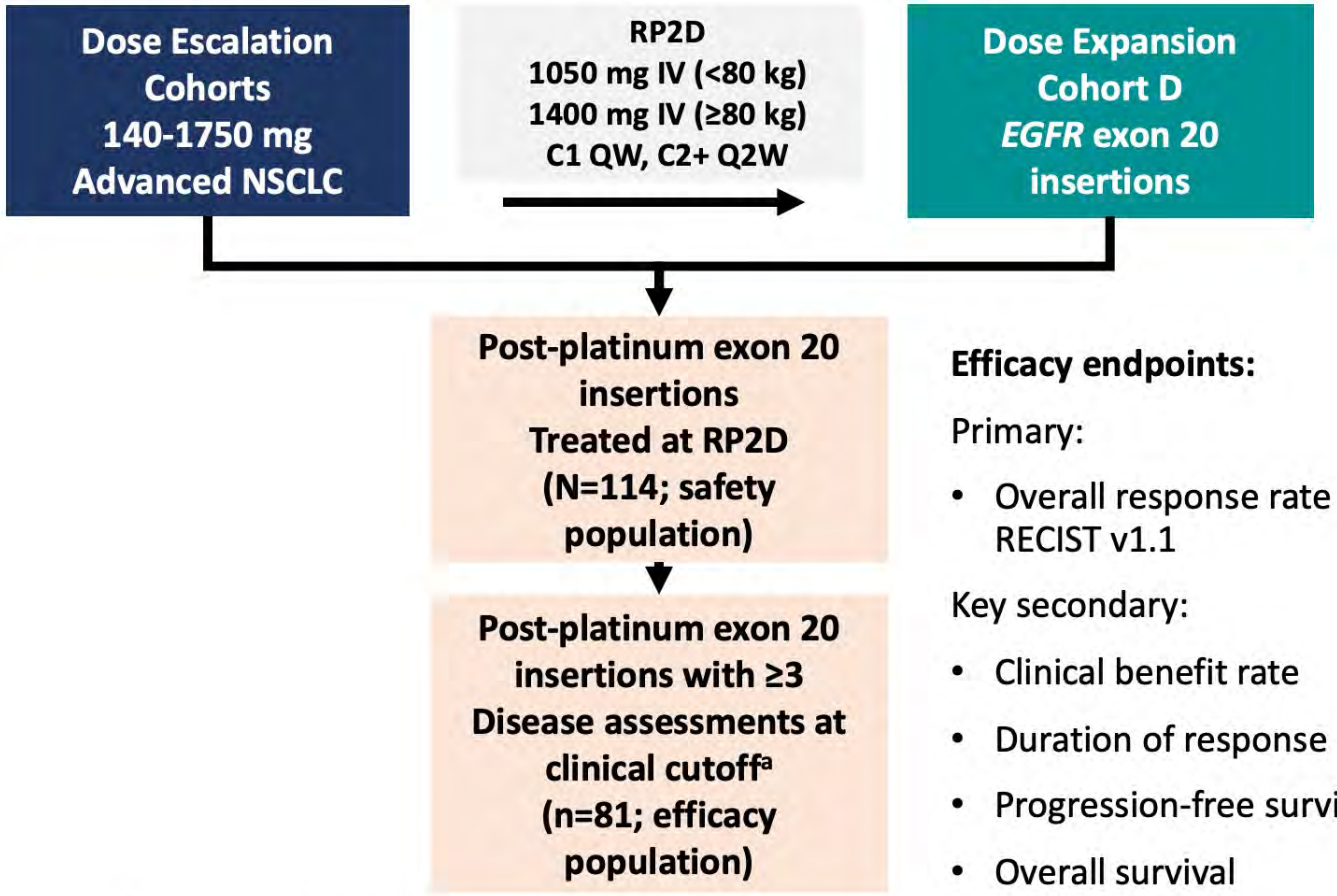
CHRYSALIS TRIAL: AMIVANTAMAB FOR *EGFR* EXON 20 INSERTION

Key eligibility criteria for post-platinum population:

- Metastatic/unresectable NSCLC
- *EGFR* exon 20 insertion mutation
- Progressed on platinum-based chemotherapy

Key objectives:

- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D



Efficacy endpoints:

Primary:

- Overall response rate per RECIST v1.1

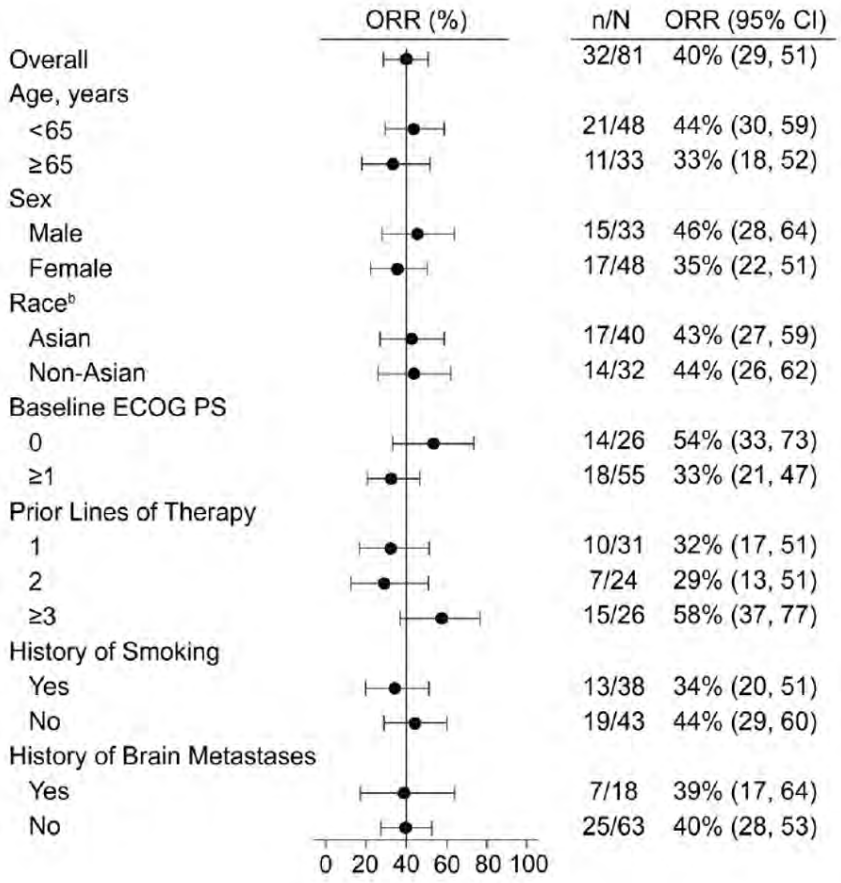
Key secondary:

- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

EGFR=epidermal growth factor receptor; NSCLC=non–small cell lung cancer; RP2D=recommended phase 2 dose.
Amivantamab is currently undergoing clinical evaluation outside of the US.
[a]Post-platinum patients treated at the RP2D and had ≥3 scheduled disease assessments or discontinued, progressed, or died prior to the third postbaseline assessment at the time of clinical cutoff (June 8, 2020). By Oct 8, 2020, all responders in the efficacy population had ≥6 months of follow-up from their first disease assessment.
Park K, et al. *J Clin Oncol.* 2021 Aug 2; JCO2100662. doi: 10.1200/JCO.21.00662. Online ahead of print.

CHRYSALIS: EFFICACY RESULTS

BICR-Assessed Response*	Efficacy Population (n=81)
Overall response rate, % (95% CI)	40 (29-51)
Median duration of response, months (95 % CI)	11.1 (6.9-NR)
Best response, n (%)	
Complete response	3 (4)
Partial response	29 (36)
Stable disease	39 (48)
Progressive disease	8 (10)
Not evaluable	2 (2)
Clinical benefit rate, % (95% CI)[a]	74 (63-83)



Park K et al, J Clin Oncol, 2021.

CHRYSALIS: SAFETY RESULTS

N=129	AEs (≥10% of patients), %	
	All Grades, %	Grades ≥3, %
Skin and subcutaneous tissue disorders		
Rash	84	3.9
Pruritus	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue	33	2.3
Edema	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	37	2.3
Cough	25	0

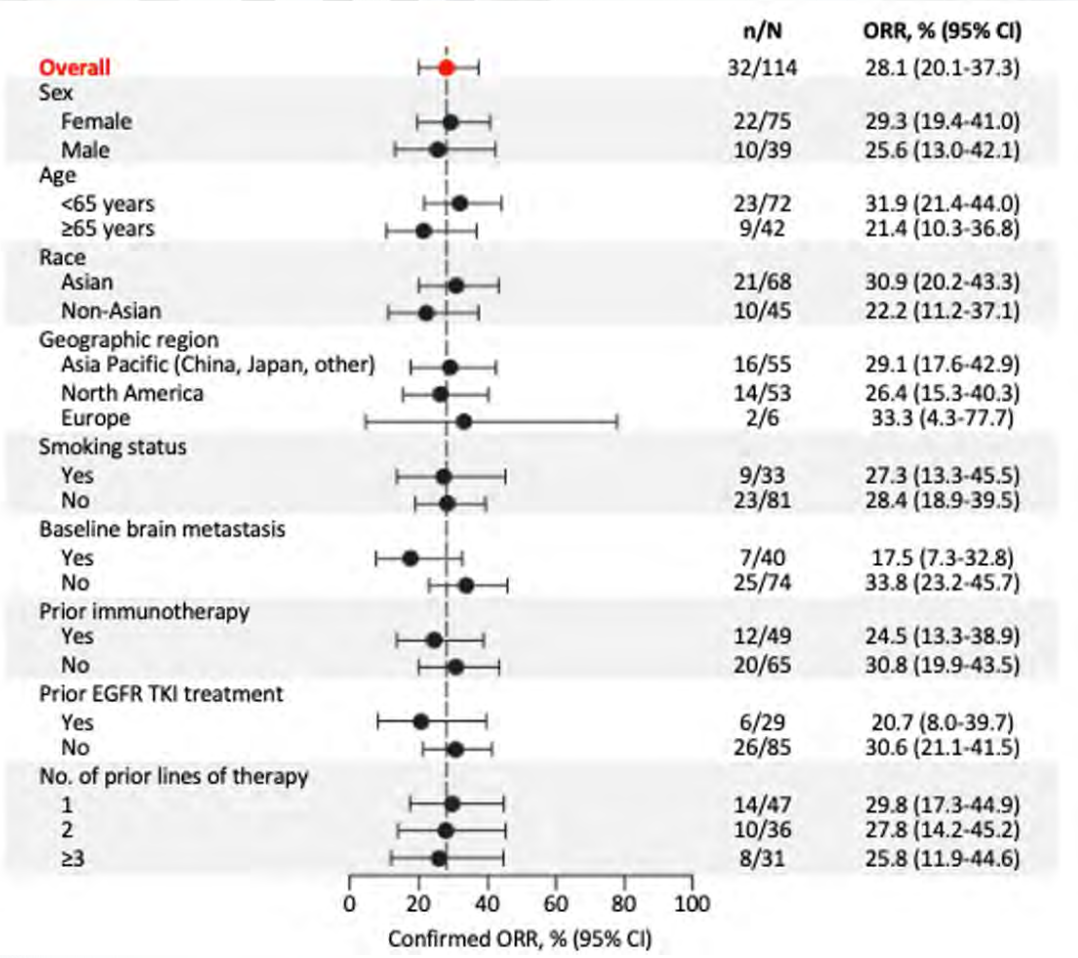
N=129	AEs (≥10% of patients), %	
	All Grades, %	Grades ≥3, %
Gastrointestinal disorders		
Nausea	36	0
Stomatitis	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal pain	11	0.8
Vascular disorders		
Hemorrhage	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy	13	0
Dizziness	12	0.8
Headache	10	0.8

Park K et al, J Clin Oncol, 2021.

MOBOCERTINIB: EFFICACY IN *EGFR* EXON 20 INSERTION

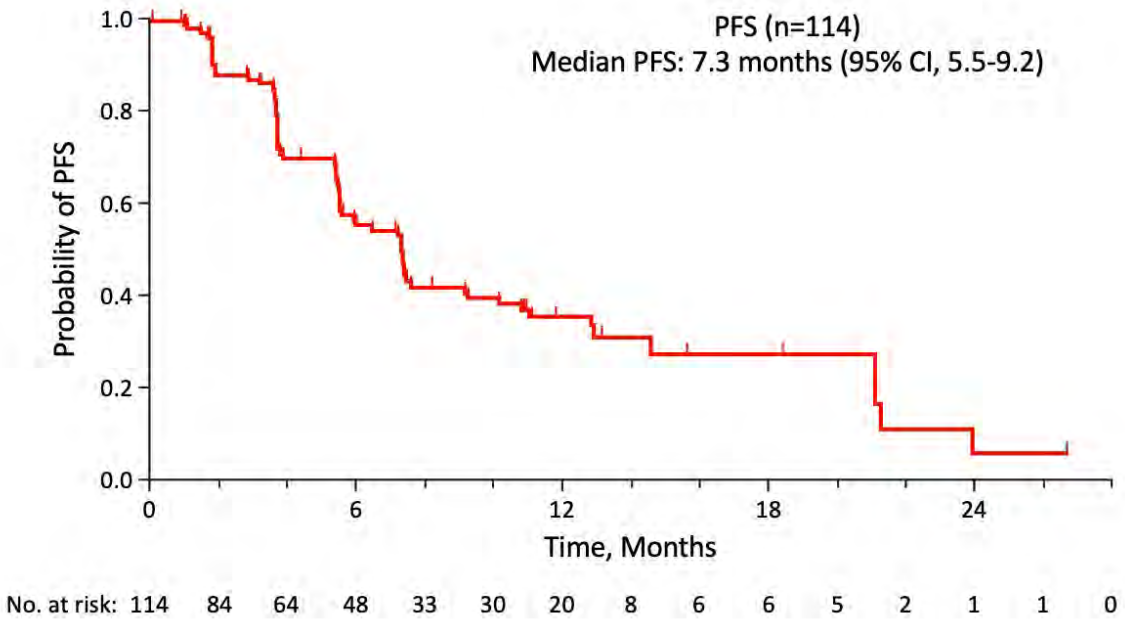
IRC Assessments	PPP Cohort[c] (N=114)
Confirmed ORR, % (95% CI)	28 (20-37)
CR, %	0
PR, %	28
Median DOR, months (95% CI)[a]	17.5 (7.4-20.3)
Confirmed DCR, % (95% CI)[b]	78 (69-85)
Investigator Assessments	
Confirmed ORR, % (95% CI)	35 (26-45)
CR, %	<1
PR, %	34
Median DOR, months (95% CI)[a]	11.2 (5.6-NE)
Confirmed DCR, % (95% CI)[b]	78 (69-85)

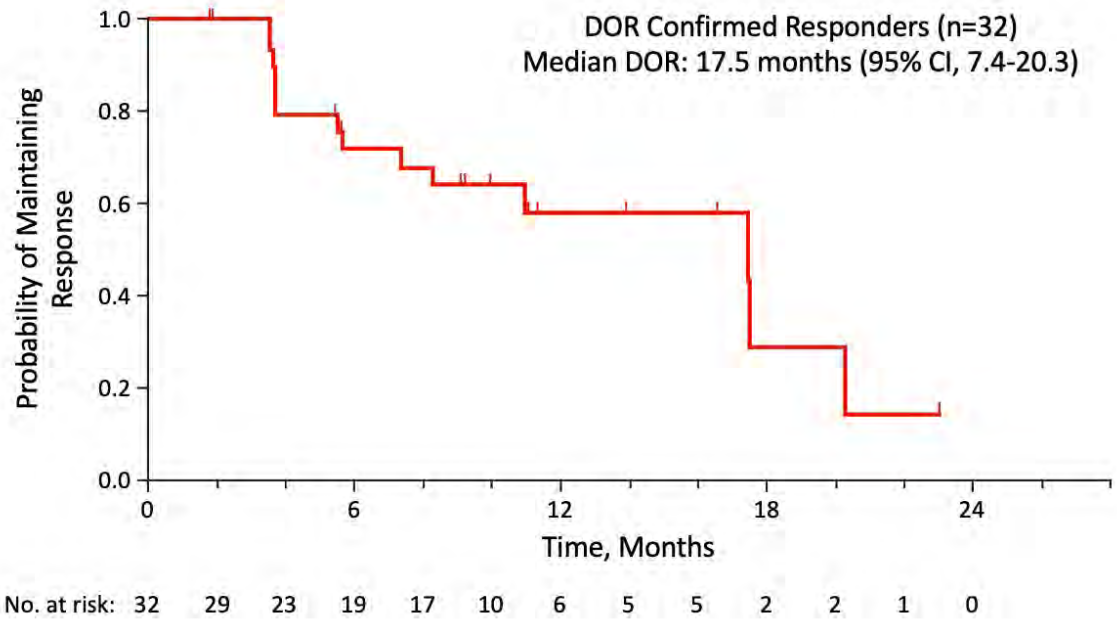
Median follow-up was 14.2 months (range, 0.7-35.8)



Zhou C, et al, JAMA Oncol, 2021.

MOBOCERTINIB: EFFICACY RESULTS





Zhou C, et al, JAMA Oncol, 2021.

MOBOCERTINIB: SALIENT SAFETY RESULTS

	PPP Cohort (N=114)	
	Any Grade, %	Grades ≥3, %
Diarrhea	91	21
Rash	45	0
Paronychia	38	1
Decreased appetite	35	1
Nausea	34	4
Dry skin	31	0
Vomiting	30	3
Increased creatinine	25	2
Stomatitis	24	4
Pruritis	21	1

Zhou C, et al, JAMA Oncol, 2021.

FUSION-POSITIVE NSCLC

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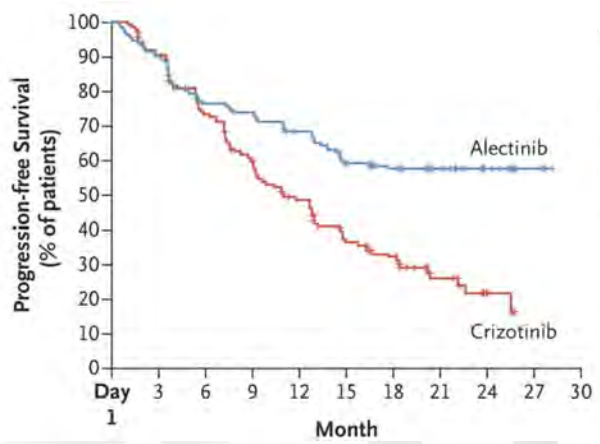
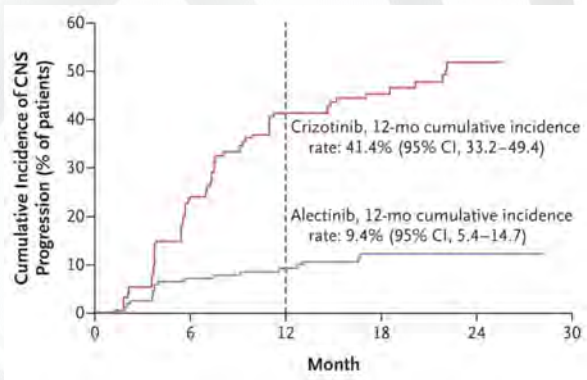
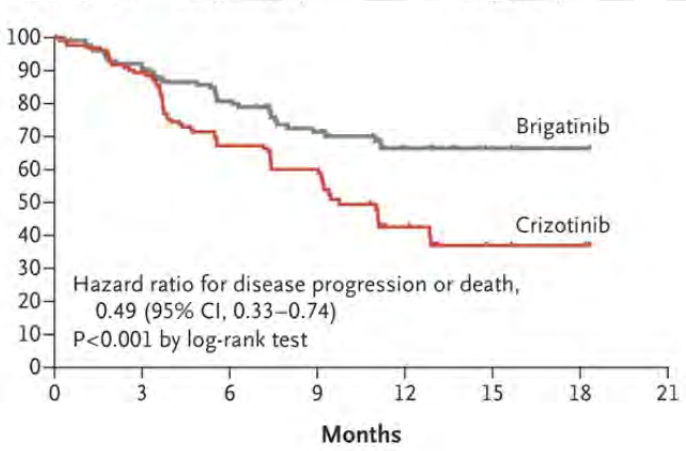
LATER-GENERATION ALK TKIS IMPROVE PFS AND CNS OUTCOMES COMPARED TO EARLY-GENERATION TKI THERAPY

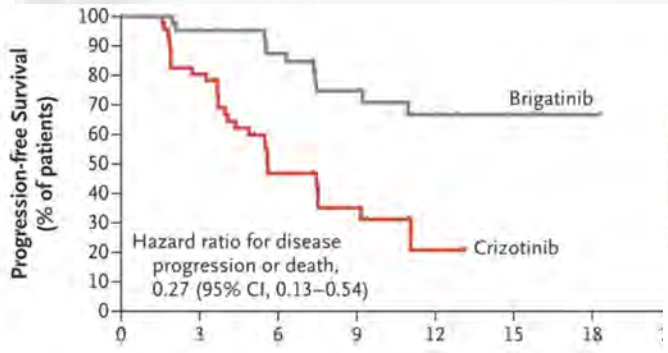
ALECTINIB



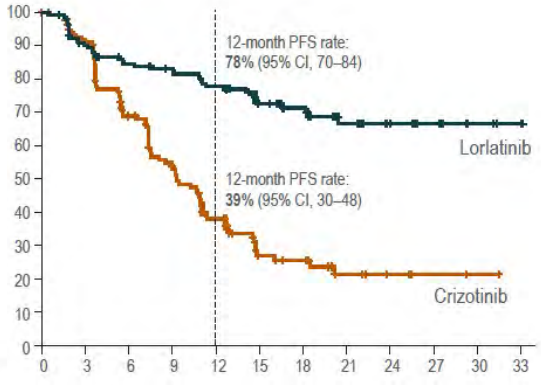


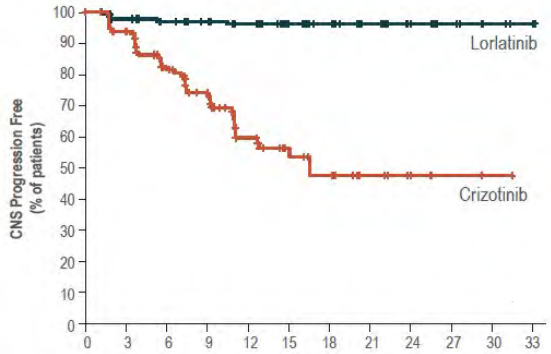
BRIGATINIB





LORLATINIB





Peters et al NEJM 2017, Camidge et al NEJM 2018, Mok et al Ann Oncol 2020

THE DECISION TO USE A LATER-GENERATION TKI: NO LARGE-SCALE RANDOMIZED DATA IS YET AVAILABLE

TKI	ORR	PFS	PFS HR (vs crizotinib)	Dose reduction (AE profile includes)
Alectinib (ALEX, INV) FDA-approved	83%	34.8 months	0.47	19% (transaminitis)
Brigatinib (ALTA1L, INV) FDA-approved	79%	29.4 months	0.45	38% (pulmonary events)
Lorlatinib (CROWN, INV)	76%	Not reached	0.27	22%* (hyperlipidemia, CNS)
Crizotinib (ALEX, INV)	75%	10.9 months	-	20%

Solomon et al ASCO 2022, Peters et al NEJM 2017, Camidge et al NEJM 2018, Mok et al Ann Oncol 2020, *Solomon et al Lancet Oncol 2018

ROS1 FUSION

ROS1 TKI	Study (phase)	Overall outcomes				Intracranial outcomes	
		ORR (*n*)	Median DoR	Median PFS	Median OS	ORR (*n*)	Other
ROS1 TKI-naive setting							
Crizotinib	PROFILE 1001 (REF.[141]) (Ib)	72% (38/53)	24.7 months	19.3 months	51.4 months	–	–
	OxOnc[101] (II)	72% (91/127)	19.7 months	15.9 months	–	–	–
	EUCROSS[212] (II)	70% (21/30)	19.0 months	20.0 months	–	–	–
	AcSe[213] (II)	69% (25/36)	–	5.5 months	17.2 months	–	–
	METROS[167] (II)	65% (17/26)	21.4 months	22.8 months	–	33% (2/6)	–
Entrectinib	Drilon et al.[145] (I/II)	77% (41/53)	24.6 months	19.0 months	–	55% (11/23)	DoR 12.9 months; PFS 7.7 months

No brain mets

18% brain mets

>40% brain mets

20.5 months 15.7 months

Baseline brain mets

DoR 14.9 months

PFS

No brain mets

DoR 34.8 months

PFS 21.1 months

Drilon et al JTO CRR 2022, Drilon et al Nature Rev Clinical Oncol 2020

SELECTIVE RET INHIBITORS ARE ACTIVE IN *RET* FUSION+ NSCLC

	Selpercatinib (LIBRETTO-001)	Pralsetinib (ARROW)
ORR (Naïve)	85% (n=48)	74% (n=43)
mPFS (Naïve)	not reached	10.9 mo
ORR (PreTx)	57% (n=218)	62% (n=126)
mPFS (PreTx)	19.3 mo	16.5 mo
iORR (PreTx)	82% (n=18)	56% (n=9)
miPFS (PreTx)	13.7 mo	-

Drilon et al, NEJM 2020; Gainor et al, ASCO 2020; Besse et al, ASCO 2021, Curigliano et al, ASCO 2021

MET EXON 14 MUTATION

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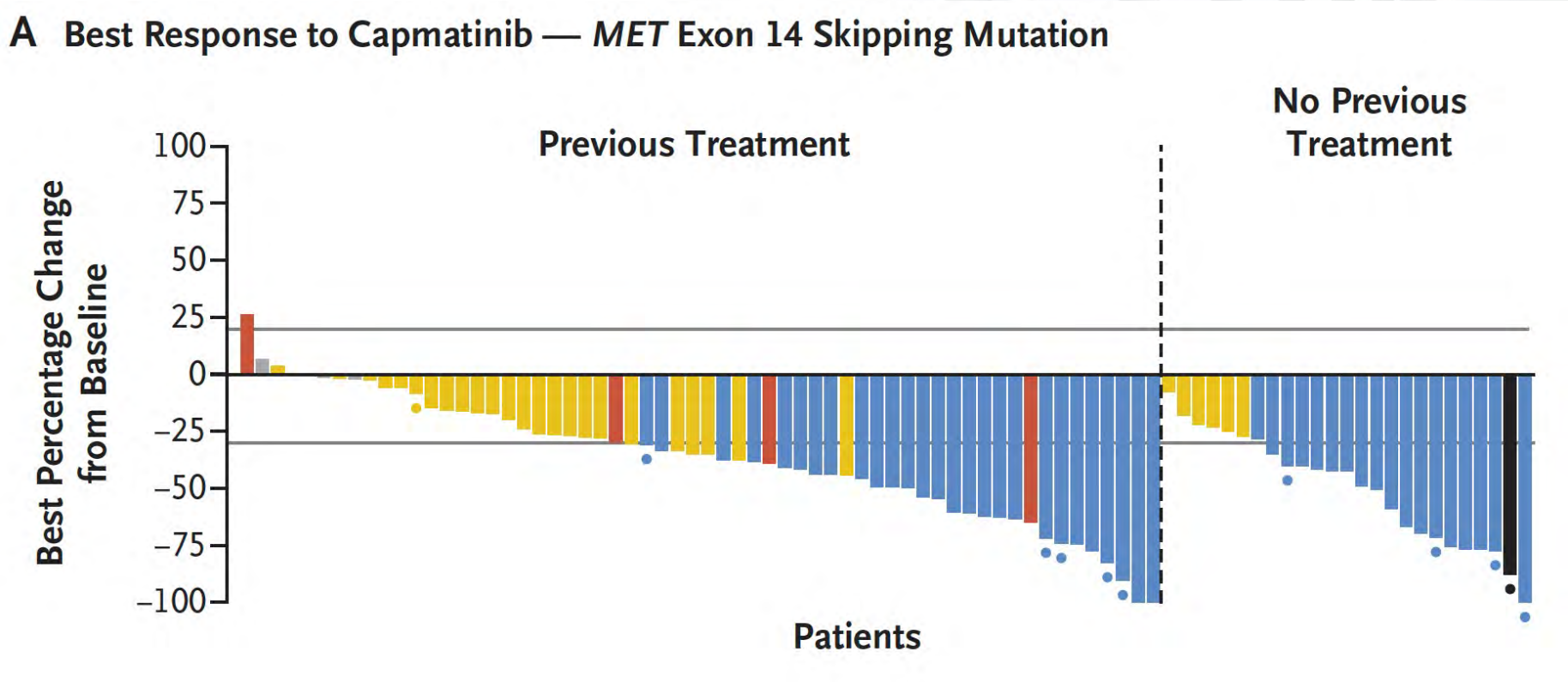
MET EXON14 MUTATION: CAPMATINIB



Response Rate

No Prior Tx : 68%
Prior Tx: 41%

mPFS

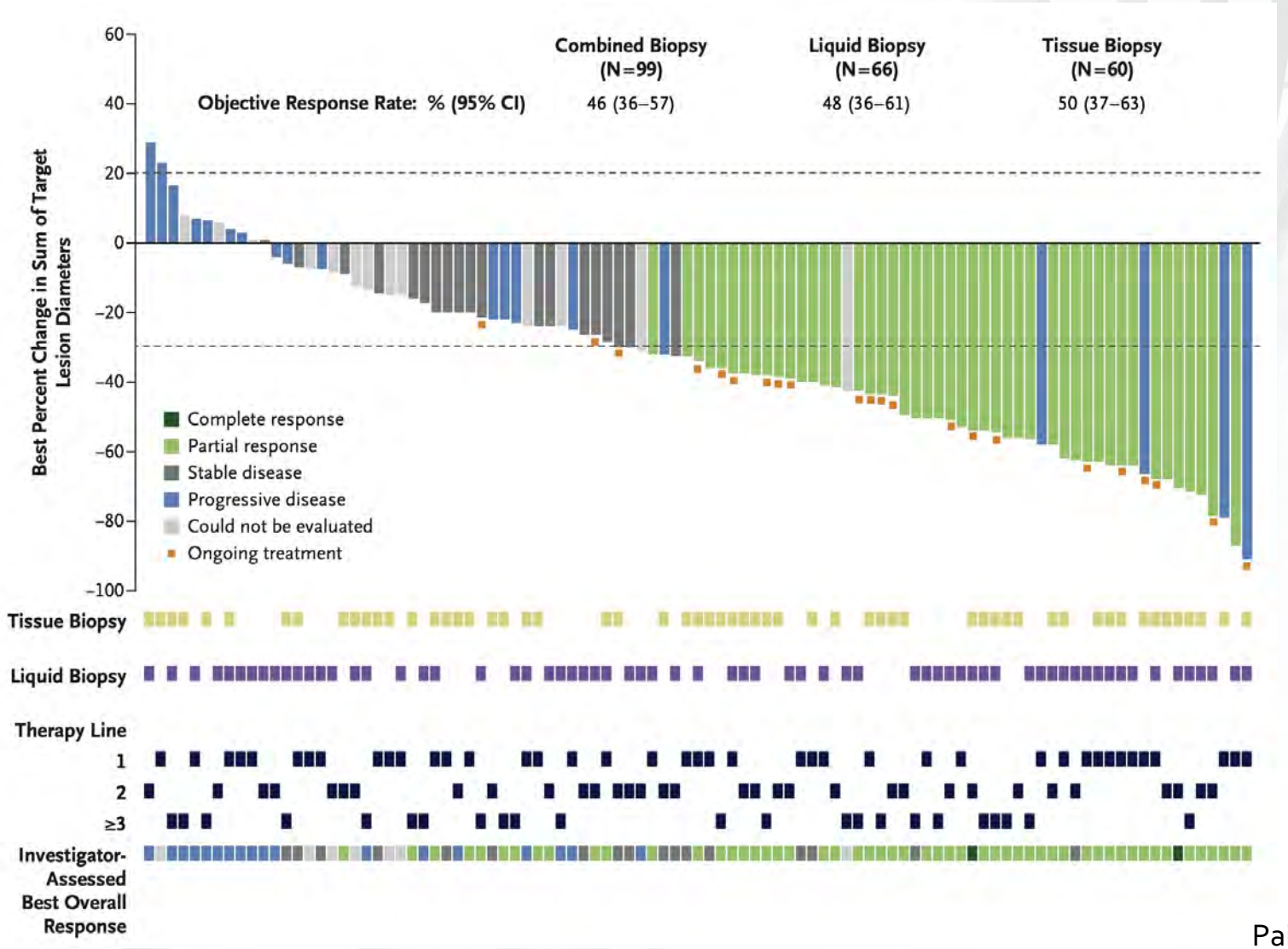
No Prior Tx: 12.4 m
Prior Tx: 5.4 m

Dose

400 mg PO BID

Wolf J et al, N Engl J Med, 2020

MET EXON 14 MUTATION: TEPOTINIB

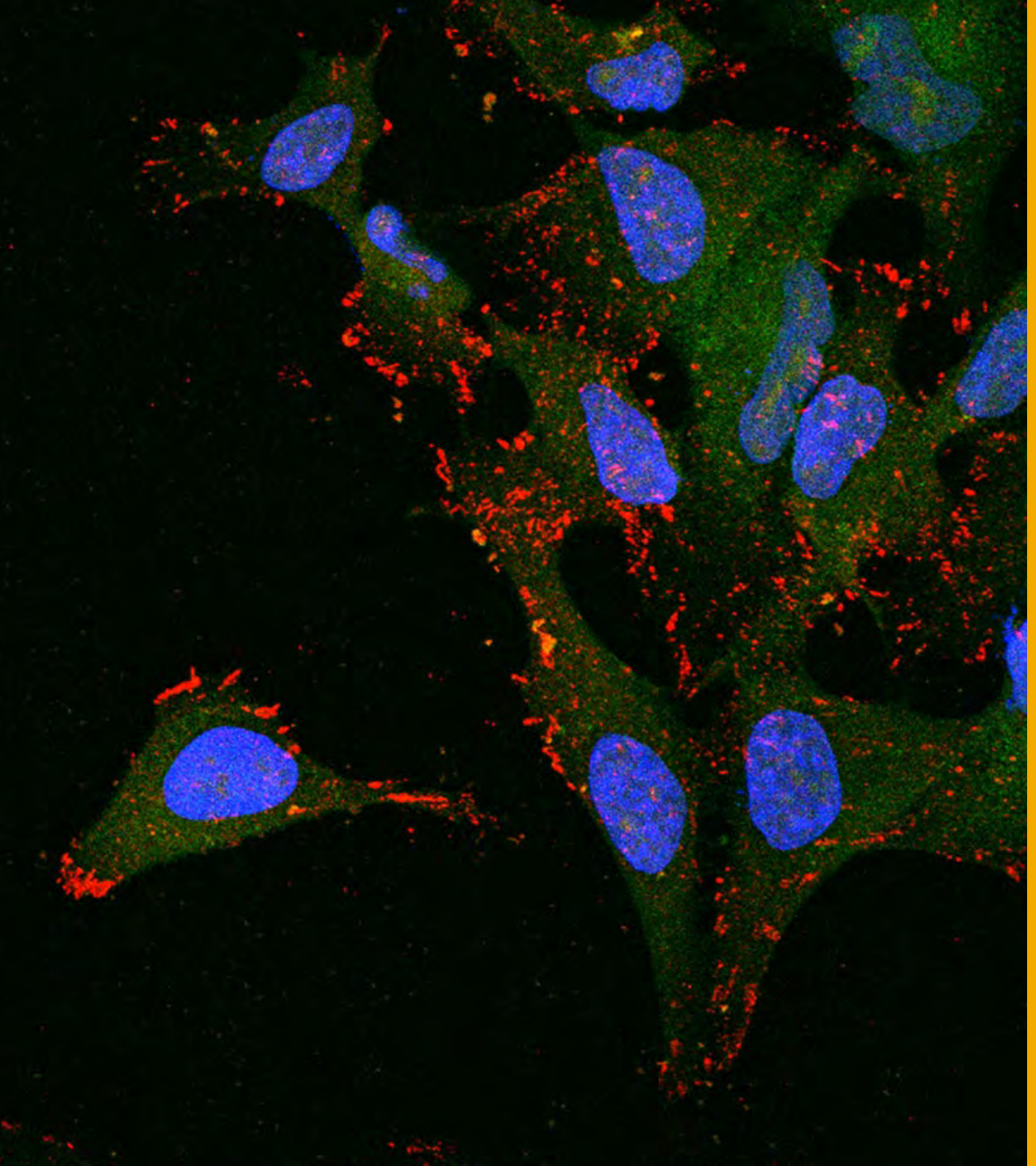


Efficacy

ORR: 46%
mPFS: 8.5 m

Dose: 500 mg PO QD

Paik PK et al, N Engl J Med, 2020

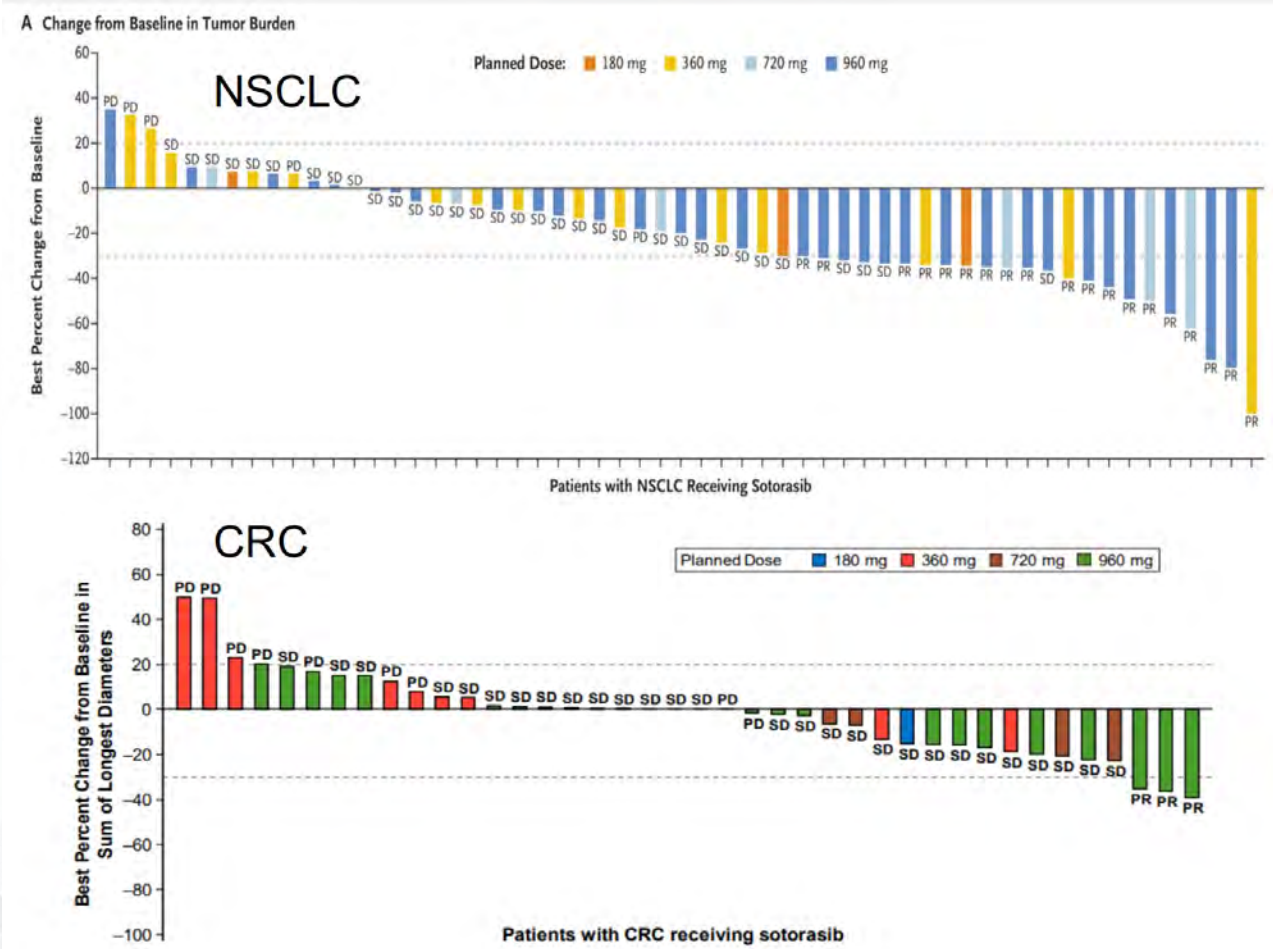


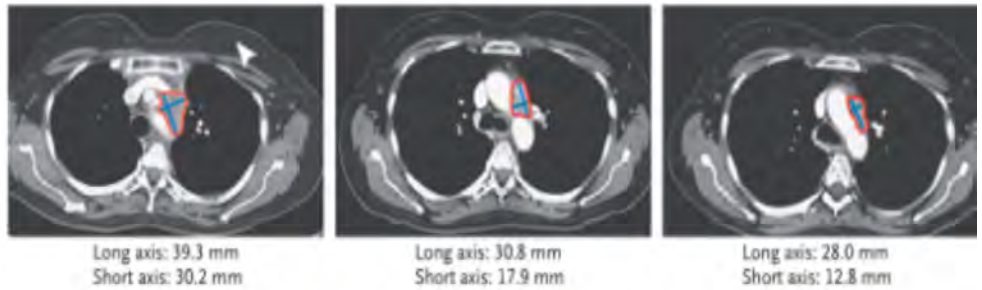
KRAS G12C MUTATION

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center

DIRECT *KRAS G12C* INHIBITION: SOTORASIB





ORR

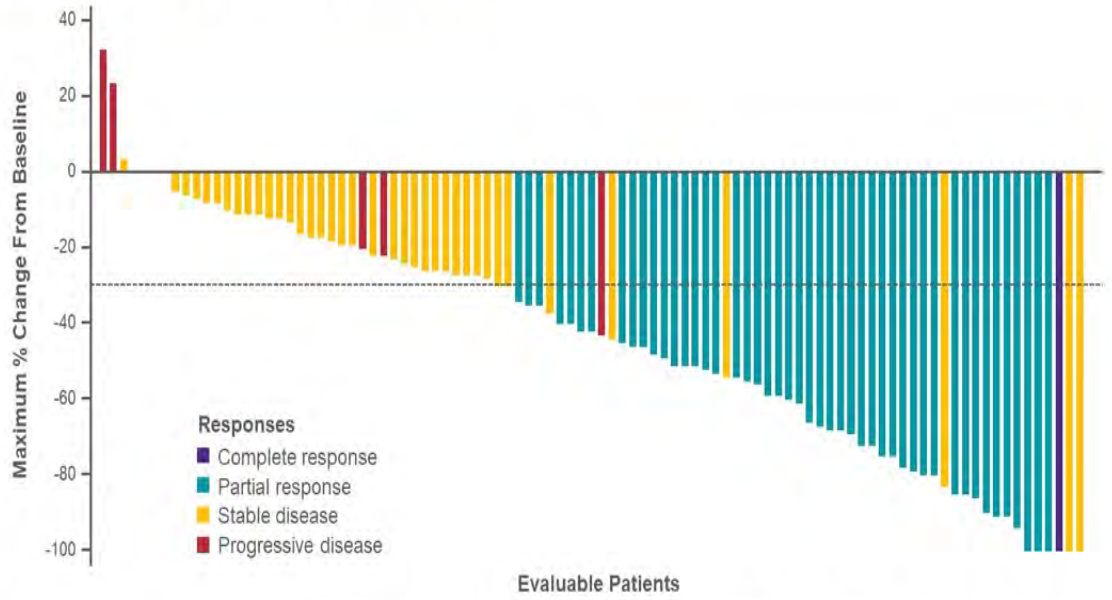
NSCLC (n=59)= 32.2%

CRC (n=42)= 7.1%

NCT03600883 Hong D. et al., N Engl J Med 2020

DIRECT *KRAS G12C* INHIBITION: ADAGRASIB

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Best Tumor Change From Baseline



- Objective responses were observed in 43% (95% CI, 33.5–52.6); DCR was 80% (95% CI, 70.8–86.5)
- Responses were deep with 75% of responders achieving >50% tumor reduction

All results are based on BICR. Responses include target lesion tumor regression, as well as non-target lesion assessment
Data as of October 15, 2021 (median follow-up: 12.9 months)

RR: 42%; DCR: 80%
mPFS: 6.5 m
mOS: 12.6 m

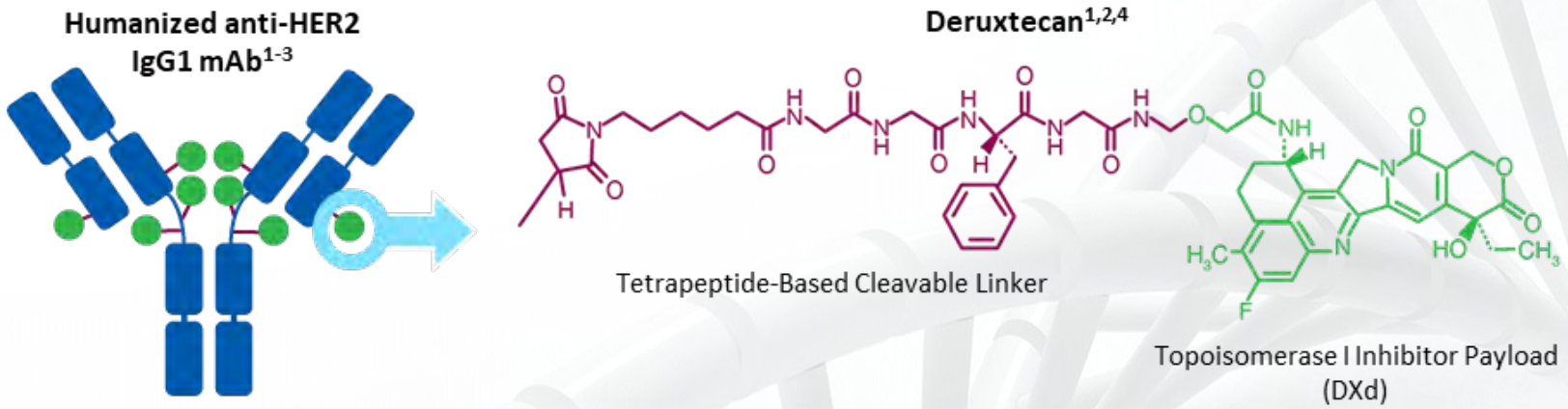
Spira et al, ASCO 2022.

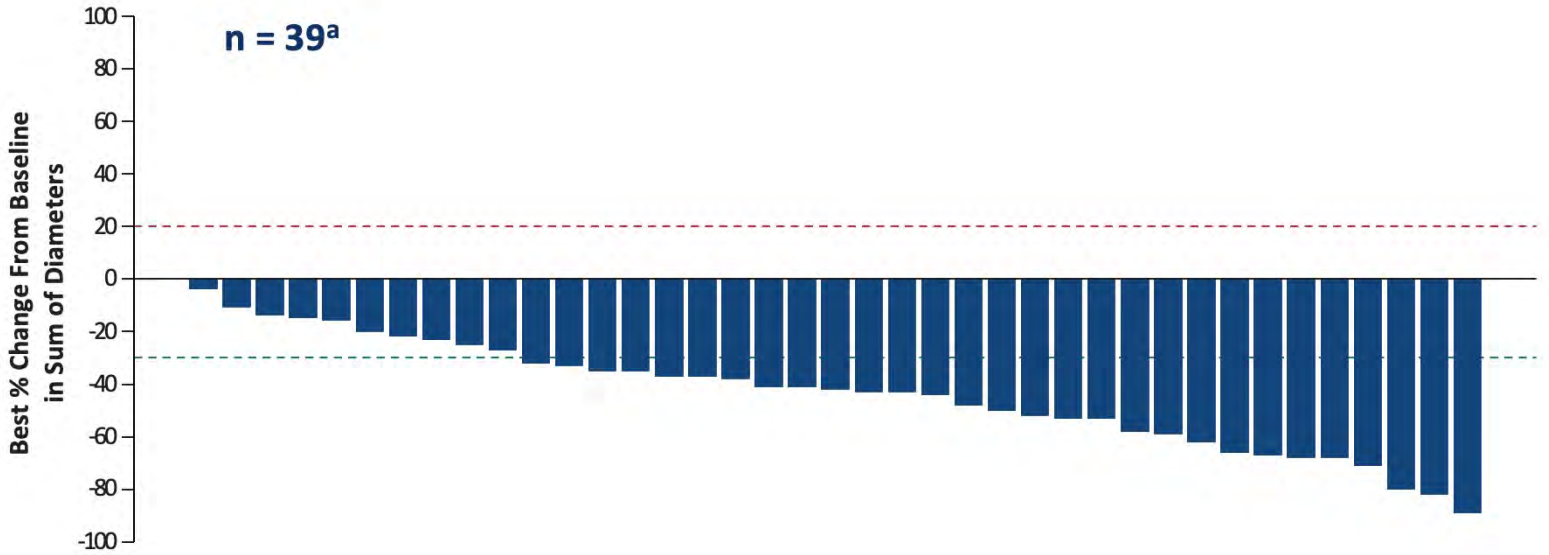
HER2 MUTATION

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center

HER-2 MUTATED NSCLC: TRASTUZUMAB DERUXTECAN





Efficacy

Response rate: 62%
mPFS: 14 m

Dose
6.4 mg/kg iv Q 3 weeks

Smit E et al, ASCO 2020

CONCLUSIONS

- Targeted therapies improve outcomes for advanced NSCLC
- NGS should be performed in all patients with metastatic non-squamous NSCLC prior to starting therapy
- Adjuvant Osimertinib improves DFS
- Promising agents in the horizon to manage acquired resistance