

Molecular Testing and Targeted Therapies in NSCLC

Millie Das, MD

Clinical Associate Professor, Stanford University

Chief, Oncology, VA Palo Alto Health Care System

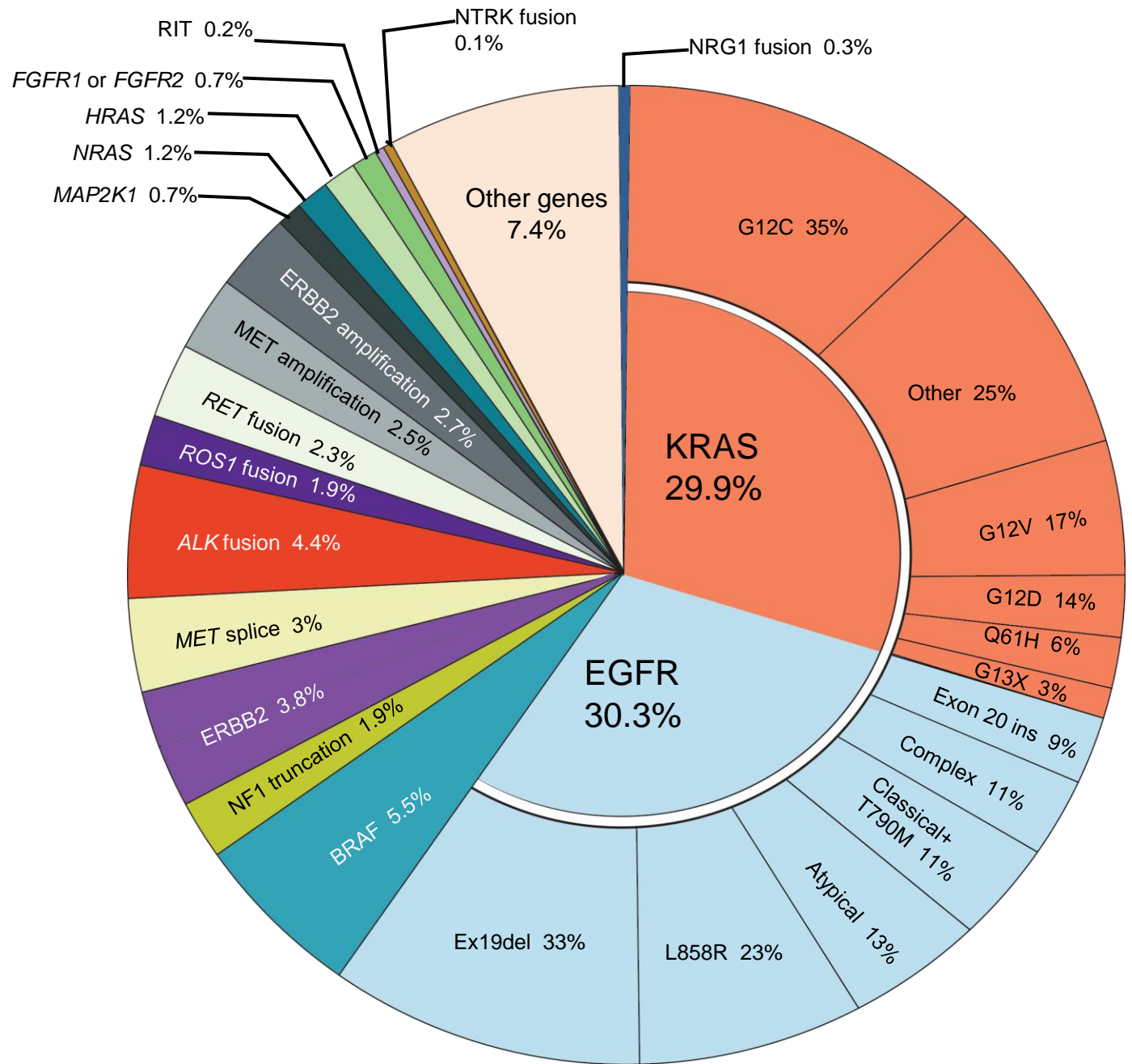
Consultant: Beigene, Astra
Zeneca, Sanofi/Genzyme,
Eurofins, Janssen, Genentech
(uncompensated), Bristol
Myer Squibb
(uncompensated)

Research: Merck, CellSight,
Genentech, Novartis, Abbvie,
United Therapeutics, Varian,
Verily, Celgene

Agenda

- Role of biomarkers in therapy selection for lung cancer
- Molecular testing recommendations in NSCLC
- Updated data for therapy selection
 - EGFR
 - MET
 - NTRK
 - ALK
 - Kras
 - RET
 - ROS1
 - HER2

Identification of driver mutations leads to treatment with targeted therapies in metastatic NSCLC



Treatment Options: Overview

- Targeted therapies in the metastatic setting result in robust responses and prolonged disease control for NSCLC but cannot cure- RESISTANCE IS INEVITABLE
- For patients without a targetable mutation, standard firstline treatment recommendation is chemotherapy + IO, regardless of PDL-1 status
- Immunotherapy alone can be considered for patients with PDL-1 \geq 50%

Treatment considerations

Who should get molecular testing?

- All patients with metastatic non-squamous NSCLC
- Consider also in patients with metastatic squamous NSCLC

Timing of Treatment

- Wait for rapid molecular testing (EGFR, ALK, ROS1, PDL-1) results prior to treatment initiation (usually 1 week)

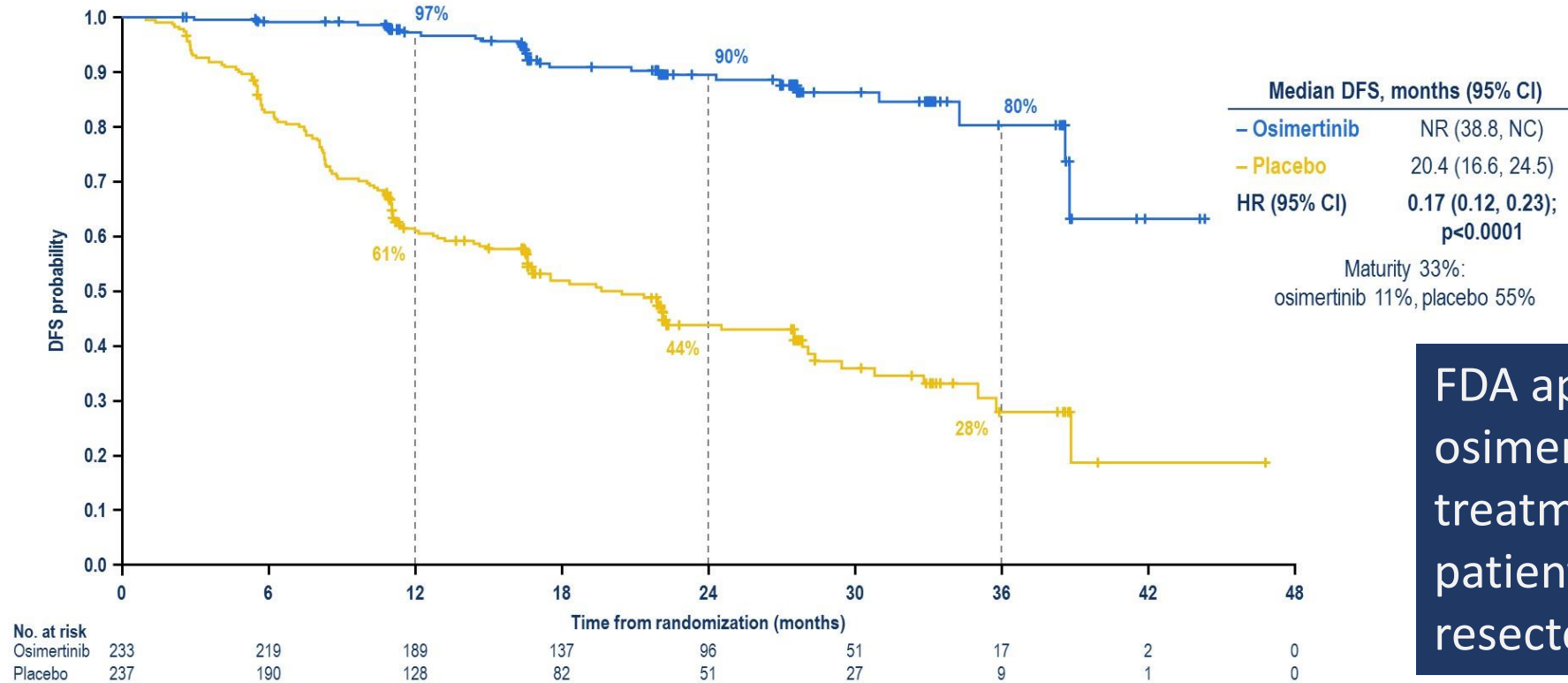
EGFR Mutations

- 15-20% of NSCLC
 - More frequently seen in Asian, never or light smokers
- Most common sensitizing mutations are exon 19 del and L858R
- Firstline treatment with osimertinib in stage IV (FLAURA)
- Brain metastases seen commonly with good CNS penetration of osimertinib
- Exon 20 insertions are generally resistant to classical TKIs with some variant exceptions
- Resistance to EGFR TKIs is common

ADAURA TRIAL:

Adjuvant osimertinib improves DFS in early stage II/IIIA EGFR+ NSCLC

Primary endpoint: DFS in patients with stage II/IIIA disease



FDA approved osimertinib as adjuvant treatment in Dec 2020 in patients with early stage resected EGFR+ NSCLC

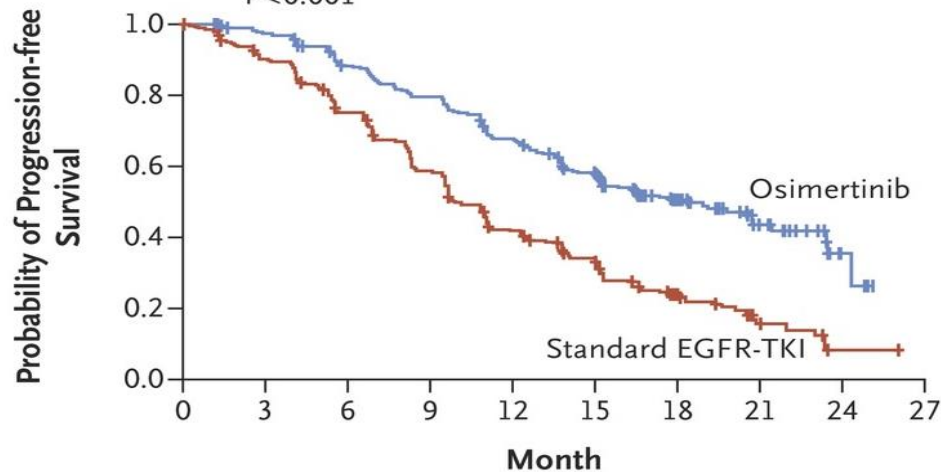
FLAURA TRIAL:

Osimertinib Improves PFS & OS Compared to Older Generation EGFR TKIs in Stage IV EGFR+ NSCLC

PFS

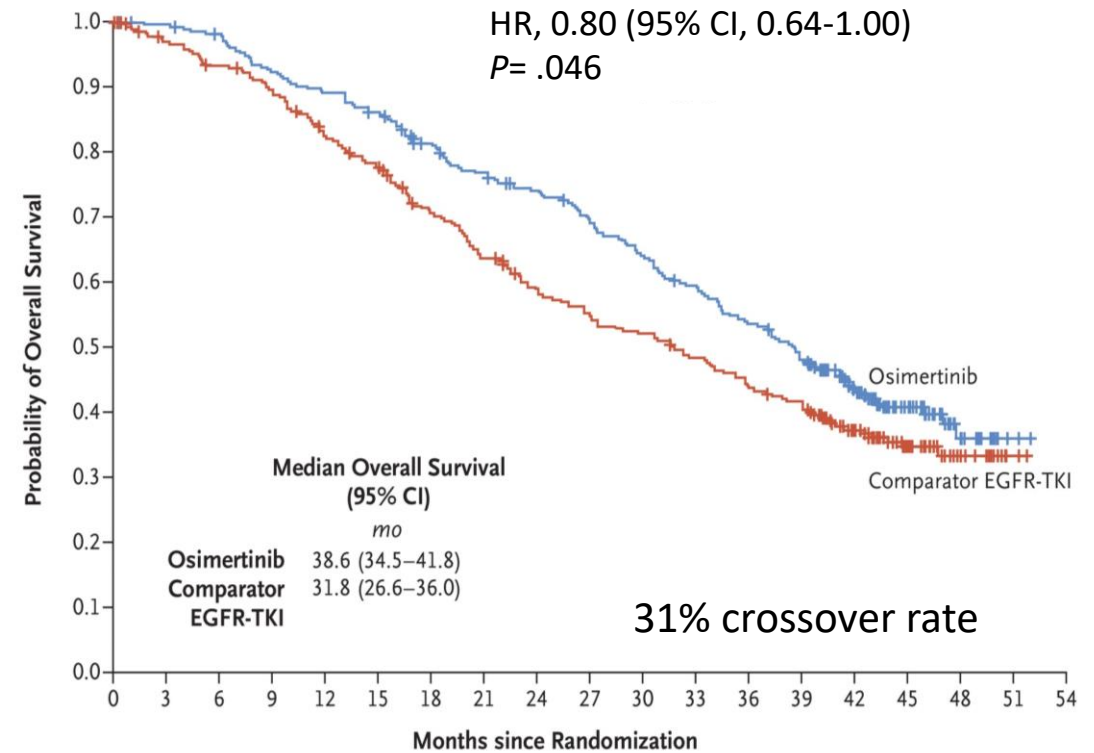
	No. of Patients	Median Progression-free Survival (95% CI) <i>mo</i>
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

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



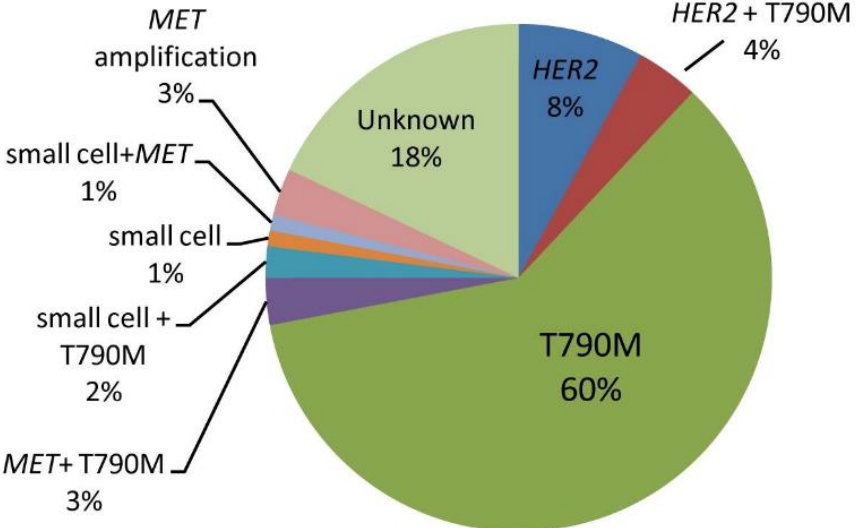
No. at Risk	0	3	6	9	12	15	18	21	24	27
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

OS



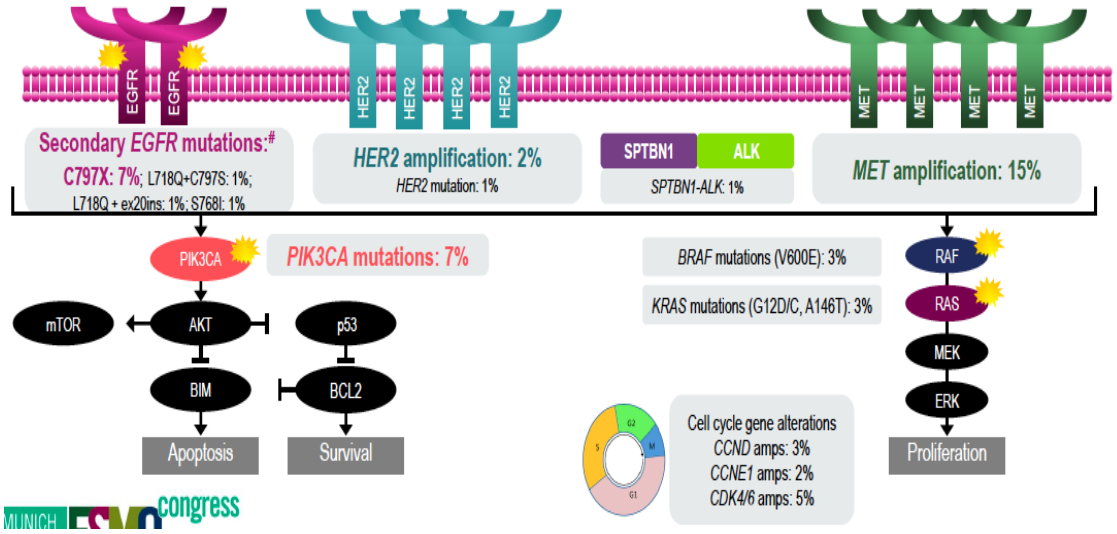
No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Resistance to targeted therapy inevitable & resistance mechanisms more challenging with next generation drugs



Dominant mechanism of resistance for 1st generation EGFR TKIs erlotinib or gefitinib

Yu H et al. Clin Cancer Res. 2013 Apr 15;19(8):2240-7.



Heterogeneous & multiple simultaneous mechanisms of resistance to 3rd generation EGFR TKI osimertinib

Ramalingam SS et al. ESMO 2018, Munich

CHRYSALIS: Amivantamab in Post-platinum NSCLC Patients With *EGFR* Exon20ins Mutations

Fully humanized, bispecific IgG1 antibody targeting EGFR/cMET

Response	Efficacy Population (n = 81)
ORR, % (95% CI)	40 (29-51)
CBR,* % (95% CI)	74 (63-83)
Best response, n (%)	
• CR	3 (4)
• PR	29 (36)
• SD	39 (48)
• PD	8 (10)
• NE	1 (1)
Median DoR, mos (95% CI)	11.1 (6.9-NR)

May 2021: FDA approved amivantamab for patients with NSCLC who harbor EGFR exon 20 insertion mutation and whose disease has progressed on or after platinum-based chemotherapy

Ongoing phase III PAPHILLON trial

- Firstline amivantanab + chemo vs. chemo alone in EGFR exon 20 ins patients

*CBR = CR, PR, of SD at ≥ 2 disease assessments.

†Does not include 9 patients with race not reported and multiple race.

CHRYSALIS: Amivantamab in Post-platinum NSCLC Patients With *EGFR* Exon20ins Mutations

	Safety Population (n = 114), n (%)	Patients Treated at the RP2D (n=258), n (%)
Any AE	113 (99)	257 (100)
Grade ≥ 3 AE	40 (35)	101 (39)
Serious AE	34 (30)	79 (31)
AE leading to death	8 (7)	13 (5)
AE leading to discontinuation	11 (10)	17 (7)
AE leading to dose reduction	15 (13)	26 (10)
AE leading to dose interruption*	40 (35)	88 (34)

- Safety profile consistent with AEs resulting from EGFR and MET pathway inhibition
- Infusion-related reactions primarily occurred during first infusion (94% of cases)
- Should be withheld if patients develop symptoms of interstitial lung disease

*Excludes infusion-related reactions.

Mobocertinib in Post-platinum NSCLC Patients With *EGFR* Exon20ins Mutations

Oral small-molecule TKI that selectively target EGFR ex20ins mutations

Outcome	No. (%)
	PPP cohort (n = 114)
IRC-assessed confirmed objective response^b	
Patients, No. (%) [95% CI]	32 (28) [20-37]
Complete response	0
Partial response	32 (28)
Stable disease ^c	57 (50)
Not evaluable	12 (11)
Confirmed disease control rate, No. (%) [95% CI] ^d	89 (78) [69-85]
Investigator-assessed confirmed objective response^b	
Patients, No. (%) [95% CI]	40 (35) [26-45]
Complete response	1 (<1)
Partial response	39 (34)
Stable disease ^c	49 (43)
Not evaluable	11 (10)
Confirmed disease control rate, No. (%) [95% CI] ^d	89 (78) [69-85]
Duration of response in confirmed responders^e	
IRC-assessed	
No.	32
Median (95% CI), mo	17.5 (7.4-20.3)
Investigator-assessed	
No.	40
Median (95% CI), mo	11.2 (5.6-NR)

Sept 2021: FDA approved mobocertinib for patients with NSCLC who harbor EGFR exon 20 insertion mutation and whose disease has progressed on or after platinum-based chemotherapy

EGFR Targeted Therapy: Summary

- Recent ADAURA trial is practice changing
 - **Test all early stage patients for EGFR!**
- Strategies in development to delay or overcome resistance to osimertinib
- Usually chemotherapy is administered after resistance to osimertinib develops
- Identifying specific resistance mutations in each patient's tumor (i.e., tissue biopsy, liquid biopsy) and tailoring subsequent approach
- Newly approved drugs for EGFR exon 20 ins
 - Amivantanab
 - Mobocertinib

ALK Targeted Therapy

3-5% of NSCLC

- More frequent in males
- More frequent in never or light smokers
- Brain metastases commonly seen

Frontline treatment options

- Alectinib
- Brigatinib (approved May 2020)
- Lorlatinib (approved March 2021)

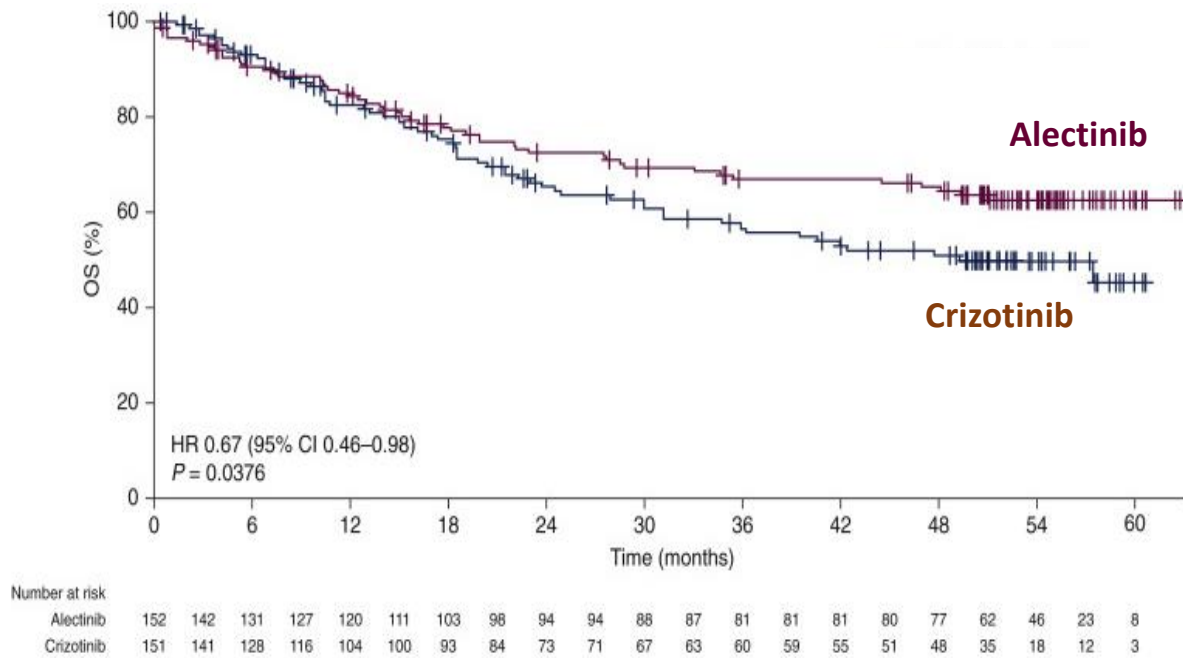
Other ALK inhibitors

- Ceritinib, Crizotinib

ALEX Phase III TRIAL:

Alectinib superior to Crizotinib in Untreated ALK-Positive NSCLC

Overall Survival

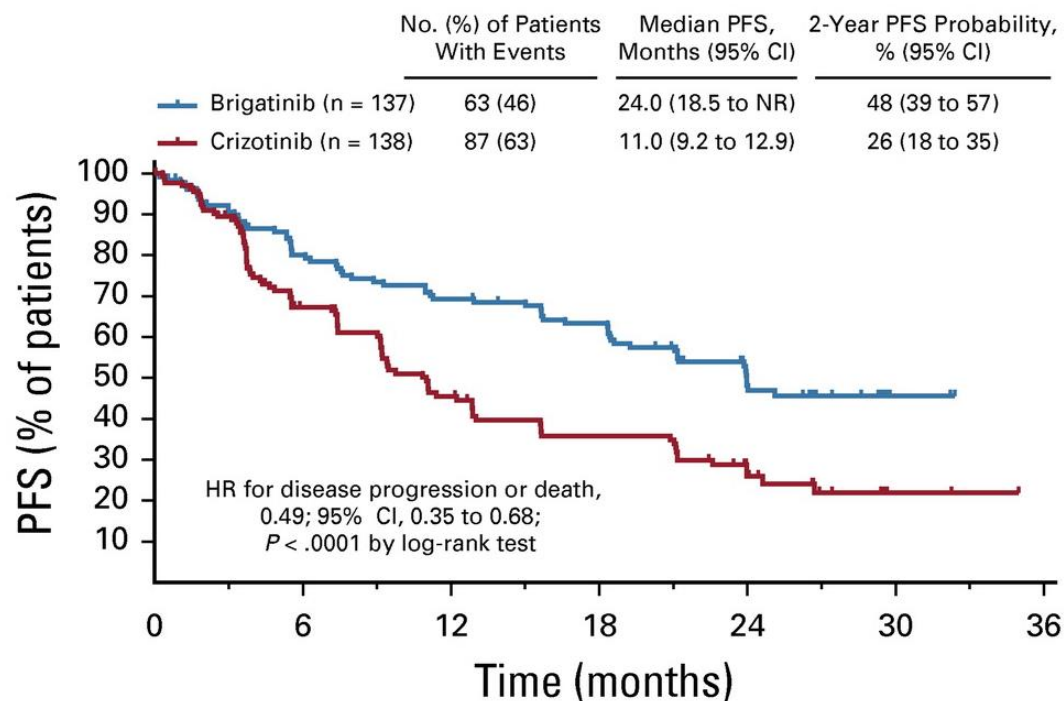


Name	Level	Log-rank	Hazard ratio		Interaction test
		P value	Hazard ratio	95% CI	P value (likelihood ratio)
All	n/a	0.0609	0.70	(0.48–1.02)	
Age group (years)	< 65	0.1481	0.73	(0.48–1.12)	0.6768
	≥ 65	0.2189	0.63	(0.30–1.33)	
Sex	Female	0.3020	0.76	(0.45–1.28)	0.6923
	Male	0.1155	0.66	(0.39–1.11)	
Race	Asian	0.3298	0.74	(0.40–1.36)	0.8575
	Non-Asian	0.1161	0.69	(0.43–1.10)	
Smoking status	n = 17 Active smoker	0.4126	1.97	(0.38–10.20)	0.5471
	Non-smoker	0.1181	0.68	(0.42–1.11)	
	Past smoker	0.1339	0.62	(0.33–1.17)	
ECOG PS	0	0.1266	0.52	(0.22–1.22)	0.4636
	1	0.0960	0.68	(0.44–1.07)	
	n = 20 2	0.6440	1.30	(0.43–3.90)	

FDA approved alectinib in the first line for patients with ALK-positive NSCLC in November 2017

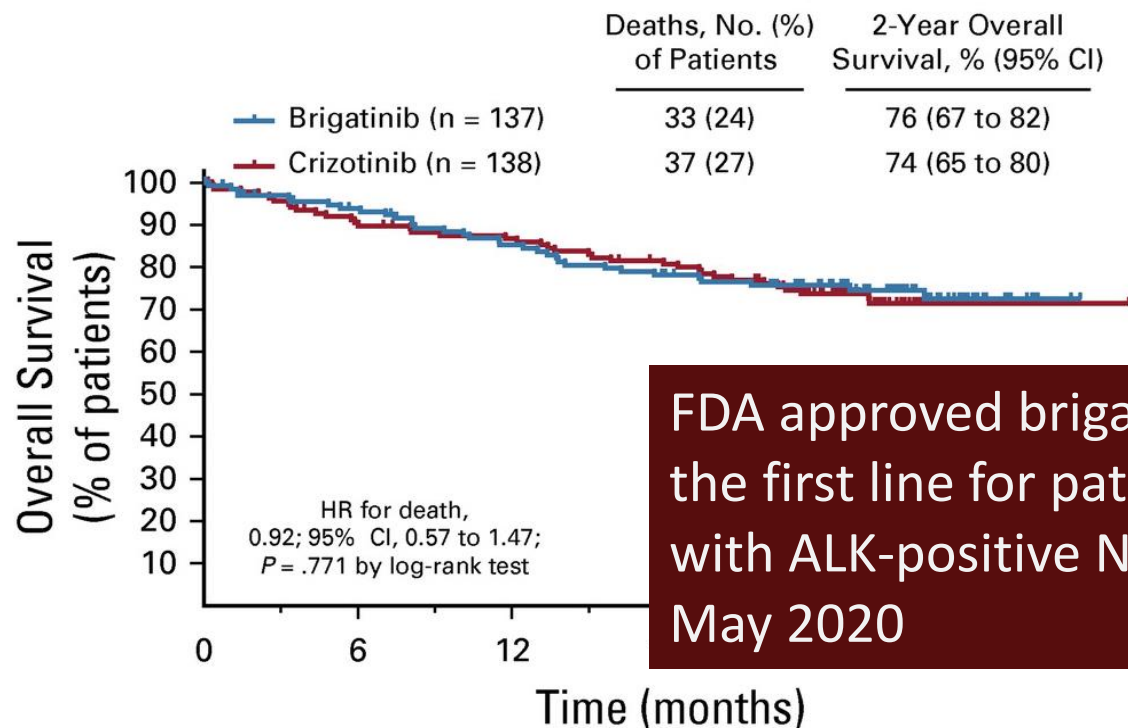
ALTA-1L Phase III TRIAL: Brigatinib superior to Crizotinib in Untreated ALK-Rearranged NSCLC

BIRC-Assessed Systemic PFS: ITT Population



No. at risk:	0	6	12	18	24	30	36
Brigatinib	137	97	84	75	39	3	0
Crizotinib	138	80	49	37	17	2	0

Overall Survival: ITT Population



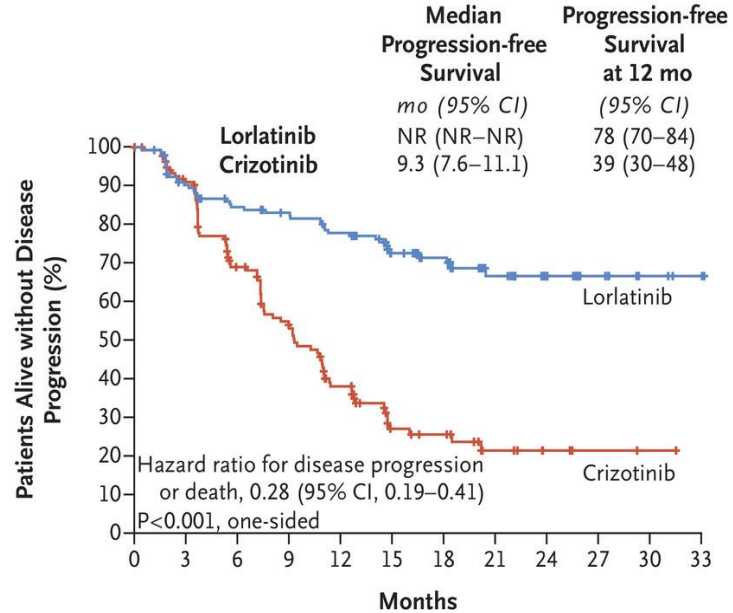
No. at risk:	0	6	12	18	24	30	36
Brigatinib	137	121	108	97	79	16	0
Crizotinib	138	123	116	106	84	19	1

FDA approved brigatinib in the first line for patients with ALK-positive NSCLC in May 2020

CROWN Phase III TRIAL:

Lorlatinib superior to Crizotinib in Advanced *ALK*-Positive NSCLC

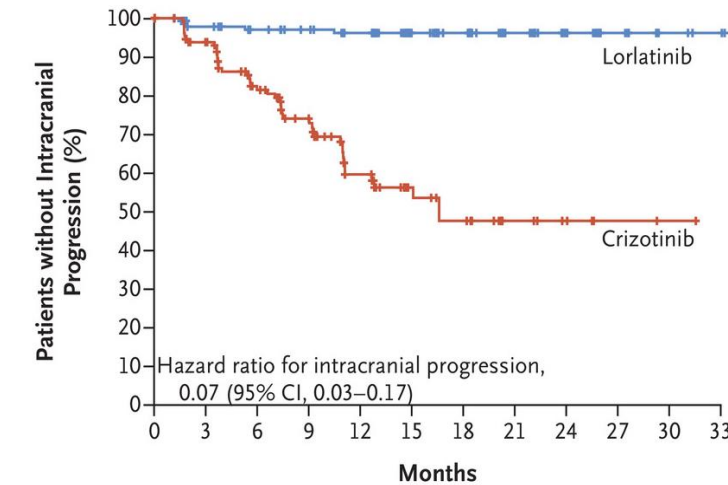
Progression Free Survival



No. at Risk

Lorlatinib	149	129	118	113	105	73	59	33	20	11	4	2
Crizotinib	147	120	84	62	39	19	16	8	4	2	1	0

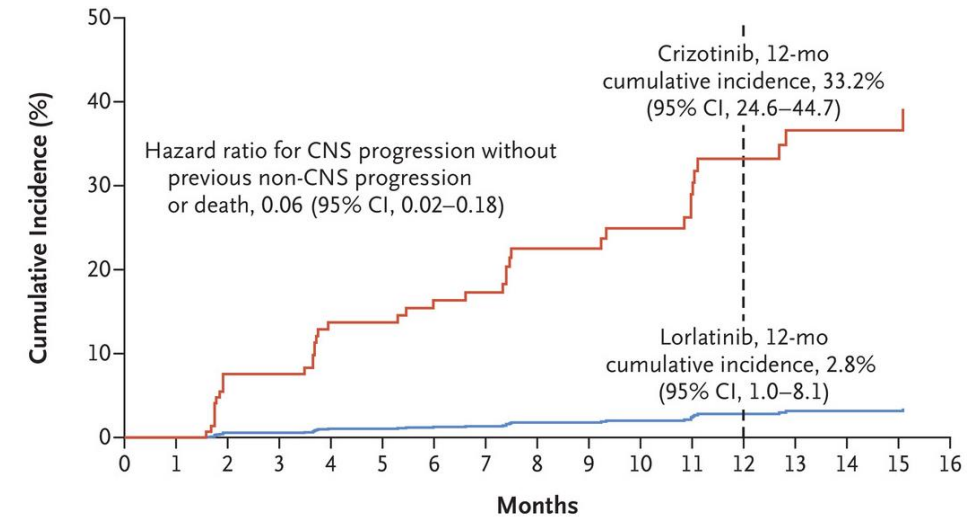
Time to Intracranial Progression



No. at Risk

Lorlatinib	149	131	122	117	110	78	65	39	25	12	4	2
Crizotinib	147	115	84	65	38	21	16	8	5	2	1	0

Cumulative Incidence of CNS Progression as the First Event



FDA approved lorlatinib for patients with NSCLC whose tumors are *ALK*-positive in March 2021

ALK Targeted Therapy: Summary

- Multiple first line FDA approved ALK TKI options
- Alectinib is generally preferred first line given favorable side effect profile and high CNS penetration
- Resistance to ALK TKIs occurs
- Can use other ALK TKIs at the time of disease resistance (brigatinib, lorlatinib)

ROS1 Targeted Therapy

Found in 1% of NSCLC

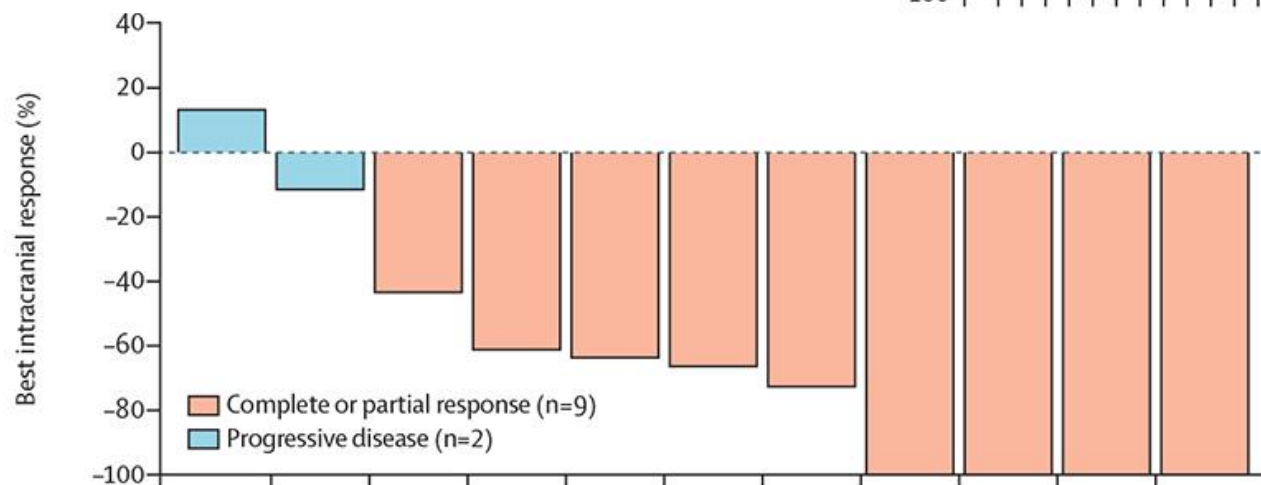
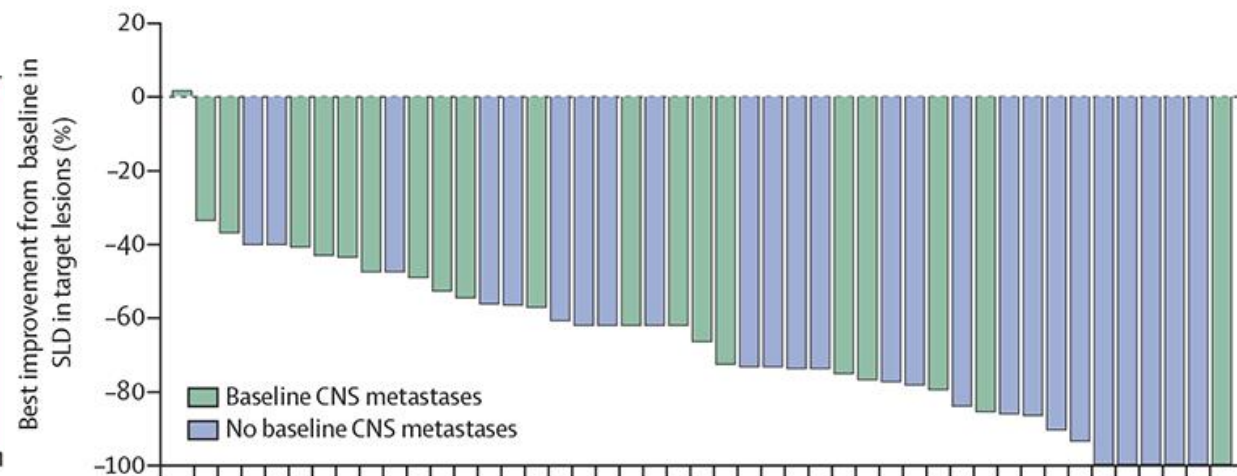
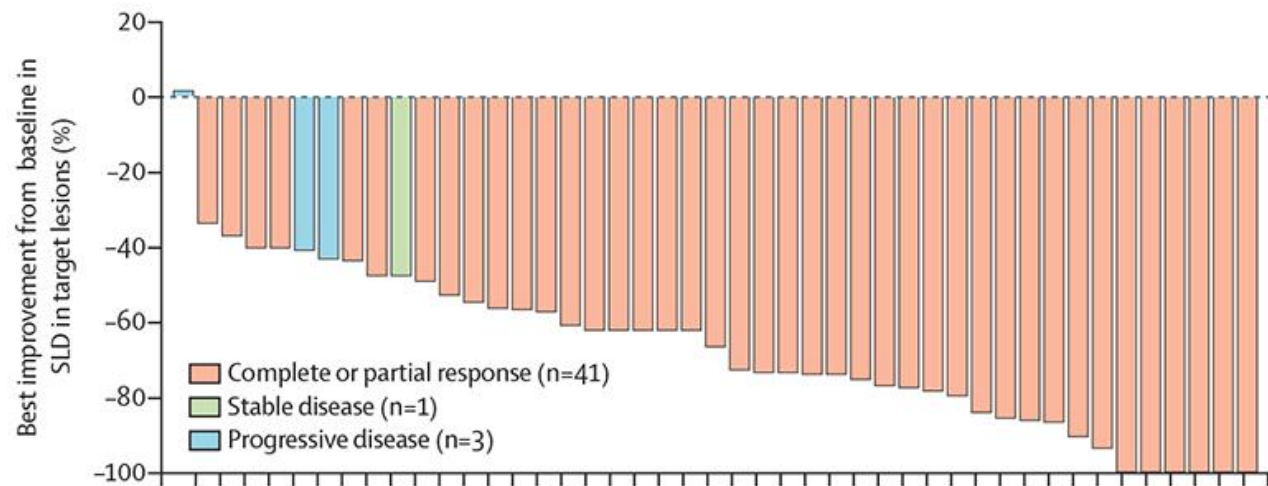
- More common in light or never smokers
- Longer median OS of patients

Targeted therapies

- Crizotinib
- Entrectinib (approved Aug 2019)
- Ceritinib

Entrectinib in *ROS1* Fusion-positive NSCLC

Integrated Analysis of 3 Phase I/II Trials (STARTRK-1, ALKA, STARTRK-2)



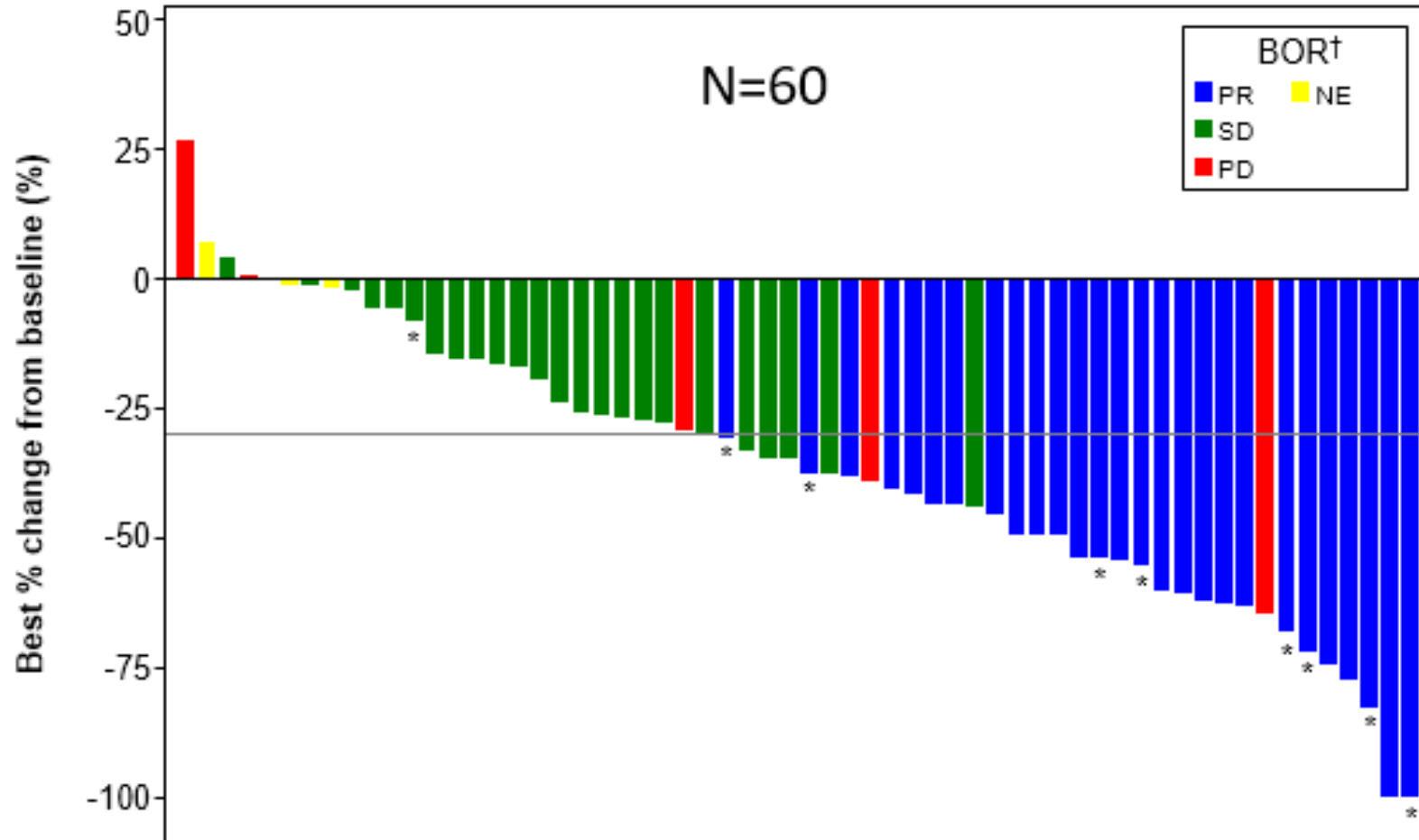
FDA approved entrectinib for patients with *ROS1* fusion-positive NSCLC in August 2019

MET Targeted Therapy

- MET alterations occur in many solid malignancies, including NSCLC (gene amplification and exon 14 skipping mutations)
- MET antibodies and TKIs being investigated
- MET amplification seen in cases of EGFR-TKI resistance
- Capmatinib and tepotinib are FDA approved first line treatment options for patients MET exon 14 skipping mutations

GEOMETRY mono-1 TRIAL:

Subsequent line Capmatinib effective in *MET*ex14—mutated NSCLC



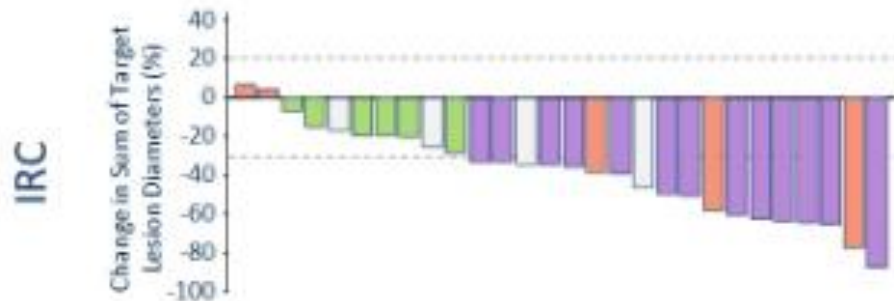
Subsequent line Capmatinib N=69	
ORR	40.6%
mDoR	9.7 mos
mPFS	5.4 mos

May 2020: FDA granted accelerated approval for capmatinib for patients with *MET*ex14—mutated NSCLC
Aug 2022: FDA granted regular approval

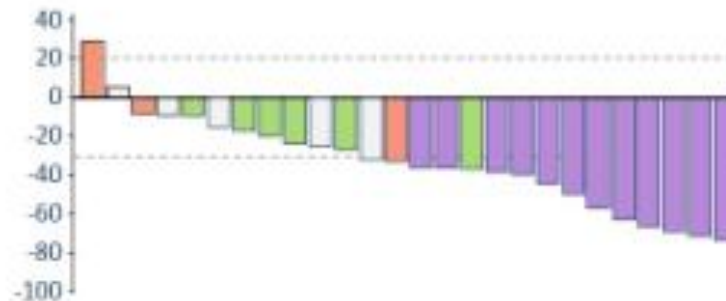
VISION TRIAL: Tepotinib targets MET Exon 14 skipping mutations

First line

Evidence of tumor shrinkage in 92% of patients by both IRC and Investigator read



Second line



≥Third line

Evidence of tumor shrinkage in ≥75% of patients



Best overall response

■ CR ■ PR ■ SD ■ PD ■ NE

	Tepotinib N=87
ORR	45%
mDoR	1.7mos

February 2021: FDA granted accelerated approval for tepotinib in patients with mNSCLC harboring MET exon 14 skipping alterations

MET Targeted Therapy: Summary

- Capmatinib and tepotinib are standard of care 1st line treatment for MET exon 14 skipping mutations
- Other MET targeted drugs are in clinical development

KRAS targeted therapy

- KRAS is the common mutation in lung adenoCA (25%)
- KRAS G12C mutations found in 13% of lung adenoCA
- Up until recently, KRAS mutations were not felt to be targetable in lung cancer

Sotorasib for Patients With Advanced *KRAS*^{G12C}-Mutated Advanced NSCLC Previously Treated With Standard Therapies

Phase II Trial

Tumor Response to Sotorasib Therapy According to Independent Central Review	
Variable	Patients (N = 124)
ORR — % (95% CI) [†]	37.1 (28.6–46.2)
Disease control — % (95% CI) [‡]	80.6 (72.6–87.2)
Best response — no. (%)	
CR	4 (3.2)
PR	42 (33.9)
SD	54 (43.5)
PD	20 (16.1)
Could not be evaluated	2 (1.6)
Missing scan	2 (1.6)
Median duration of objective response (95% CI) — mo [§]	11.1 (6.9–NE)
Kaplan-meier estimate of objective response (95% CI) — %	
At 3 mo	90.5 (76.7–96.3)
At 6 mo	70.8 (54.3–82.2)
At 9 mo	57.3 (40.4–71.0)

May 2021: FDA approved sotorasib for *KRAS* G12C-mutated NSCLC for patients who have received at least one prior systemic therapy

Adagrasib

- Phase I/II study (N=110; n = 79 with NSCLC [51 evaluable])
 - Efficacy in NSCLC
 - CR/PR: 45% of NSCLC
 - Disease control (CR/PR/SD): 96%
 - Safety
 - Most common AEs: nausea, diarrhea, vomiting, fatigue, and increased liver enzymes
 - Grade ≥ 3 AEs: 30%
 - 2 deaths (pneumonitis, cardiac failure)

In June 2021, adagrasib earned a breakthrough therapy designation from the FDA for patients with KRAS G12C–mutant NSCLC

KRAS targeted therapy: Summary

- Sotorasib is a viable second line therapy option with KRAS G12 mutated NSCLC (chemo+IO still firstline)
- No targeted treatment options for other KRAS non-G12C mutations

HER2 (ERBB2) Targeted Therapy

- Currently no standard therapies targeting HER2 pathway in NSCLC
 - Approved therapies in HER2+ gastric and breast cancers
- No clear correlation between HER2 overexpression, amplification, or mutation (not mutually exclusive)
 - HER2 mutations in 2-4% (most exon 20 ins)
 - HER2 amplification in 10-20%
 - HER2 overexpression in 2.4-38%
- HER2 alterations can represent primary driver or mechanism of acquired resistance

DESTINY-Lung01 Trial: Trastuzumab deruxtecan (HER2 Targeted Therapy)

- International, open-label, multicohort phase II trial

- Patients with unresectable/metastatic nonsquamous NSCLC that is HER2 expressing or with a *HER2*-activating mutation
- R/R to standard therapy
- No previous HER2-targeted therapy (pan-HER TKIs allowed)
 - ECOG PS 0-1 (planned N = 170)



Cohort 1: HER2 Expressing (IHC 2+/3+)

T-DXd 6.4 mg/kg Q3W
(n = 42)



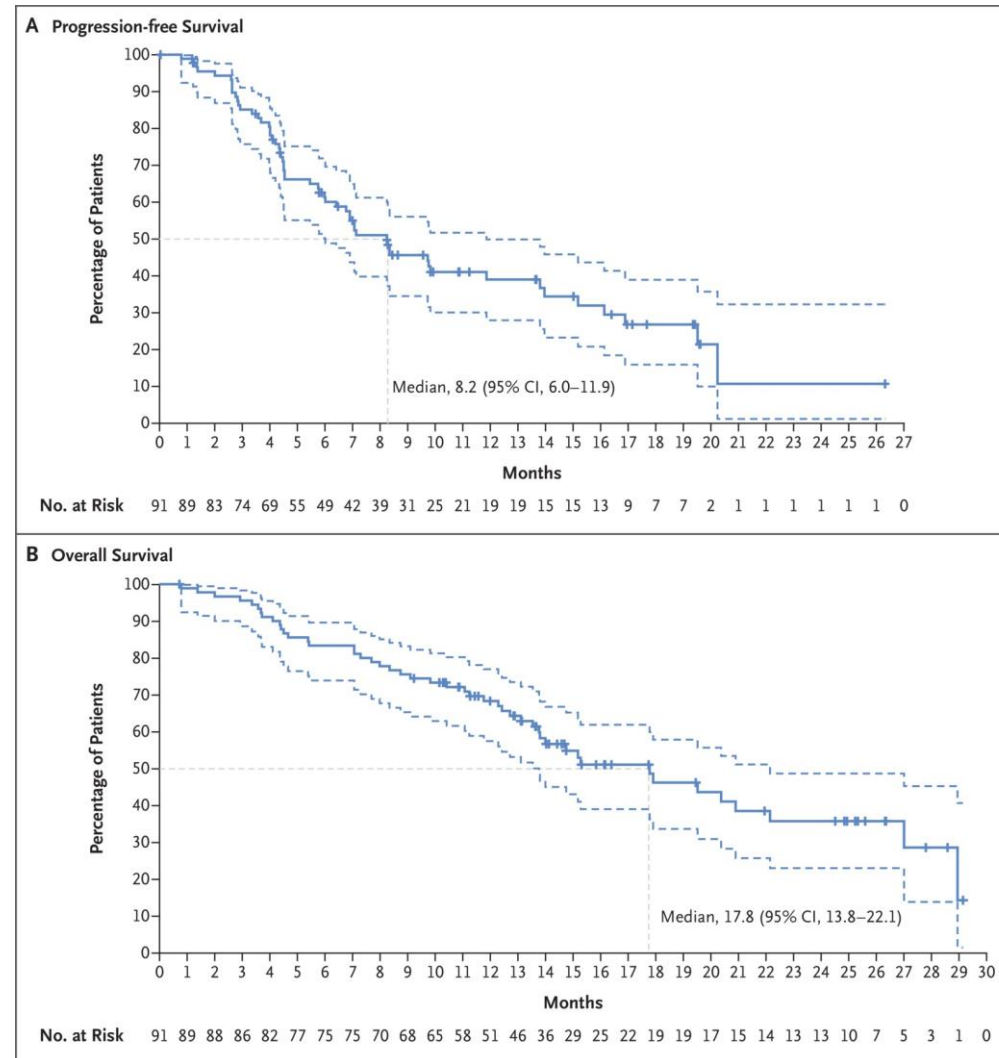
Cohort 2: *HER2* Mutated

T-DXd 6.4 mg/kg Q3W
(n = 42)

Primary endpoint:
confirmed ORR per ICR

Secondary endpoints:
DoR, PFS, OS

DESTINY Lung-01 TRIAL: PFS and OS of Trastuzumab Deruxtecan in HER2-mutant NSCLC



Aug 2022: FDA granted accelerated approval to trastuzumab deruxtecan for unresectable/metastatic NSCLC patients with HER2 mutations who have received a prior systemic therapy

HER2 Targeted Therapy

	First author	Overall response rate <i>HER2</i> mutation	Overall response rate <i>HER2</i> amplification
Dacomitinib	Kris	3/26 (12%)	0/4 (0%)
Neratinib	Hyman	1/26 (4%)	NA
Neratinib	Gandhi	0/17 (0%)	NA
Neratinib + tamsirolimus	Gandhi	8/43 (19%)	NA
Afatinib	Smit	0/13 (0%)	NA
Afatinib	Lai	3/22 (14%)	NA
Trastuzumab	Gatzemeier	NA	NA*

* Negative randomized phase 2 trial cisplatin/gemcitabine ± trastuzumab in HER2 IHC2+/3+ lung cancers.

- TKIs are minimally effective with overall low response rates
- Poziotinib, a more potent inhibitor of EGFR and HER2 exon 20 mutations, being studied in phase II trial

HER2 Targeted Therapy: Poziotinib

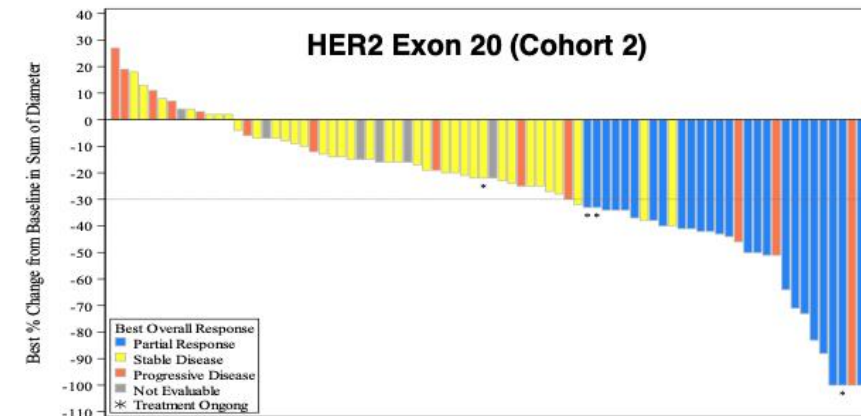
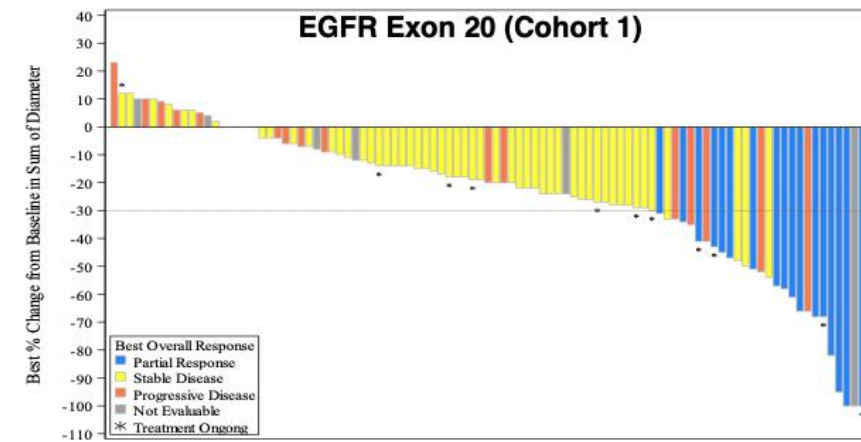


2020 World Conference
on Lung Cancer Singapore

Primary Efficacy and Safety

- Cohort 2 (2L HER2 exon 20) primary endpoint was met
- Median age 61yrs; median prior therapy = 2 (1-9); 66% females; 67% non-smokers; 13% stable brain metastases at entry
- Common Grade 3 TRAEs: Diarrhea (26%), Rash (29%), mucosal inflammation (10%)

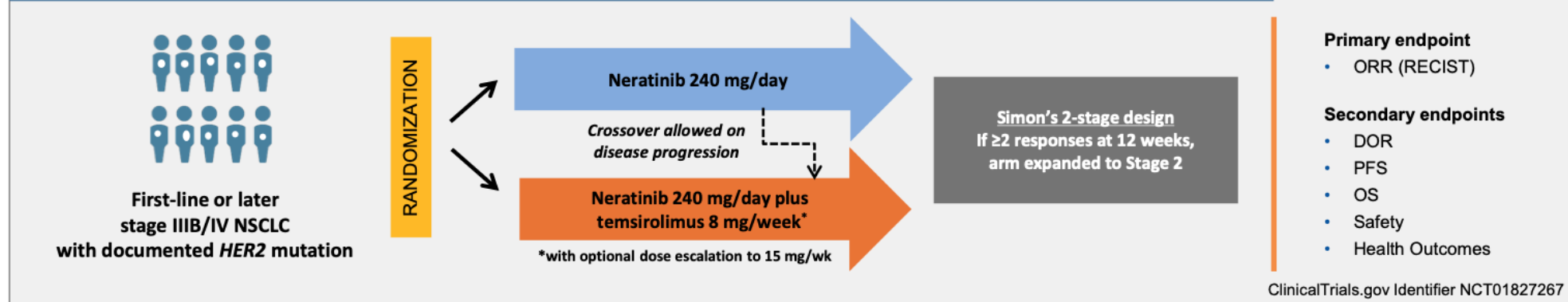
	2L EGFR Exon 20 (N=115)	2L HER2 Exon 20 (N=90)
ORR (n), [95% CI]	14.8% (17) [8.9, 22.6%]	27.8% (25) [18.9, 38.2%]
Unconfirmed ORR (n), [95% CI]	19.1% (22) [12.4, 27.5%]	31.1% (28) [21.8, 41.7%]
DCR (n), [95% CI]	68.7% (79) [59.4, 77.0%]	70.0% (63) [59.4, 79.2%]
DoR, median (months), [95% CI]	7.4 [3.7, 9.7]	5.1 [4.2, 5.5]
PFS, median (months), [95% CI]	4.2 [3.7, 6.6]	5.5 [3.9, 5.8]



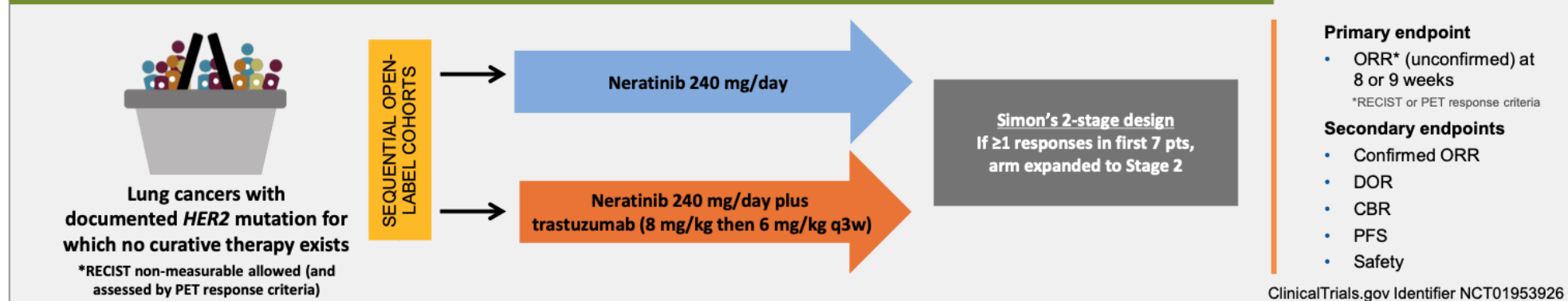
HER2 Targeted Therapy: Neratinib

Study design: Phase 2 trials of neratinib in *HER2*-mutated lung cancers

Study 4201 (PUMA-NER-4201): Randomized phase 2 study in *HER2*-mutant NSCLC



SUMMIT (PUMA-NER-5201): Open-label phase 2 basket study in *HER2*-mutant tumors

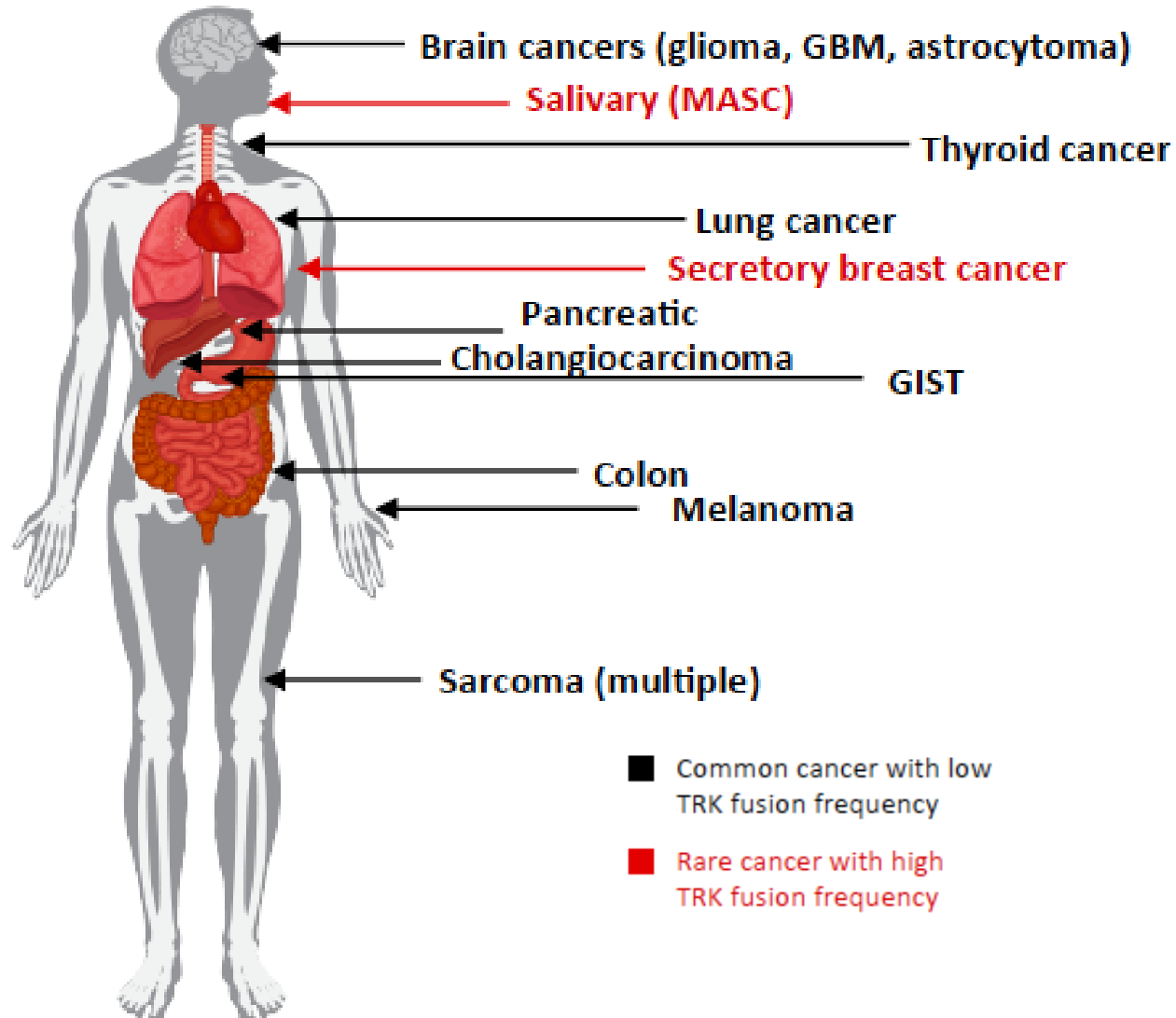


HER2 Targeted Therapy: Summary

- Recent FDA approval of trastuzumab-deruxtecan
- Existing and emerging small molecule TKIs are only modestly active
- Poziotinib demonstrates increased activity against HER2 mutated NSCLC compared to other TKIs

Other less common actionable targets:
NTRK, RET

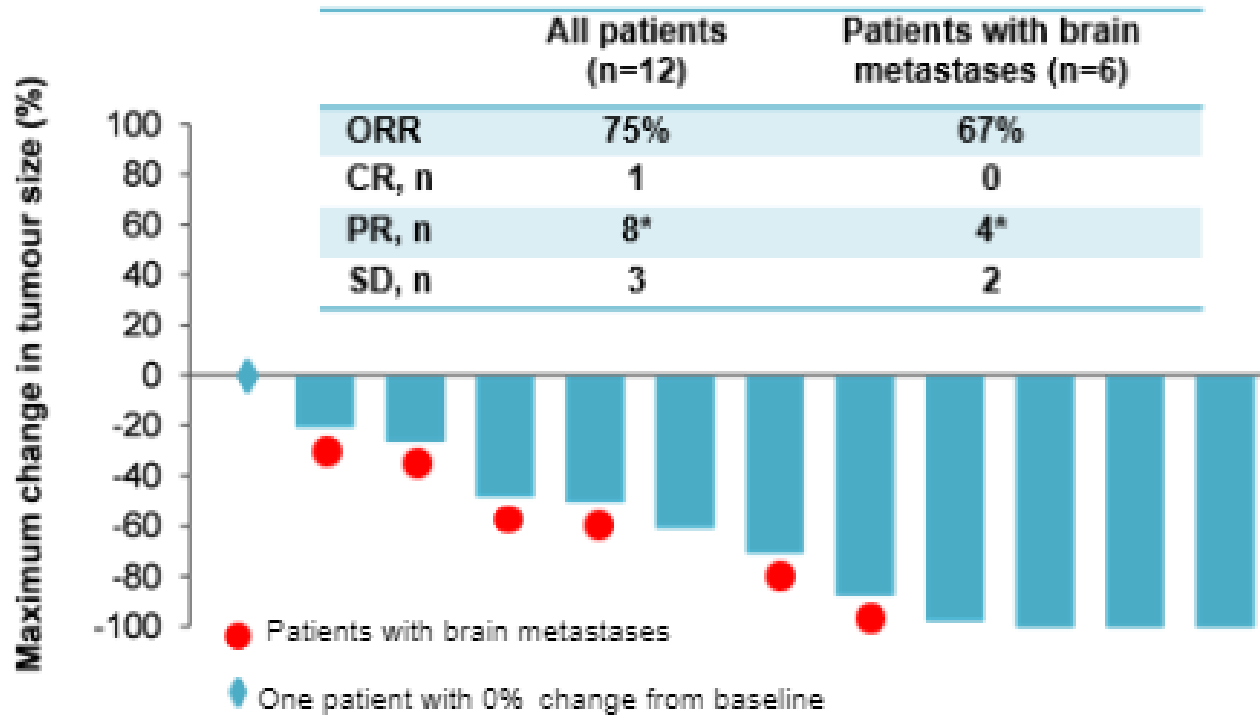
NTRK Targeted Therapy



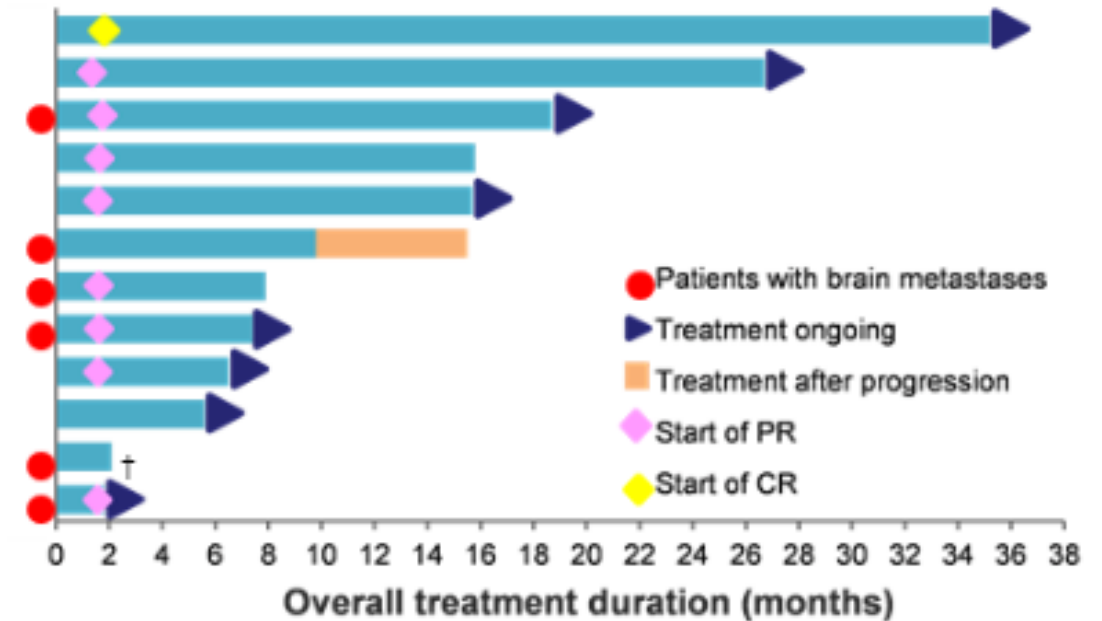
NTRK fusions are found across multiple cancer histologies

1500-5000 patients in United States annually

LOXO-TRK-14001/SCOUT/NAVIGATE TRIALS: Larotrectinib with efficacy in solid tumors with NTRK gene fusion



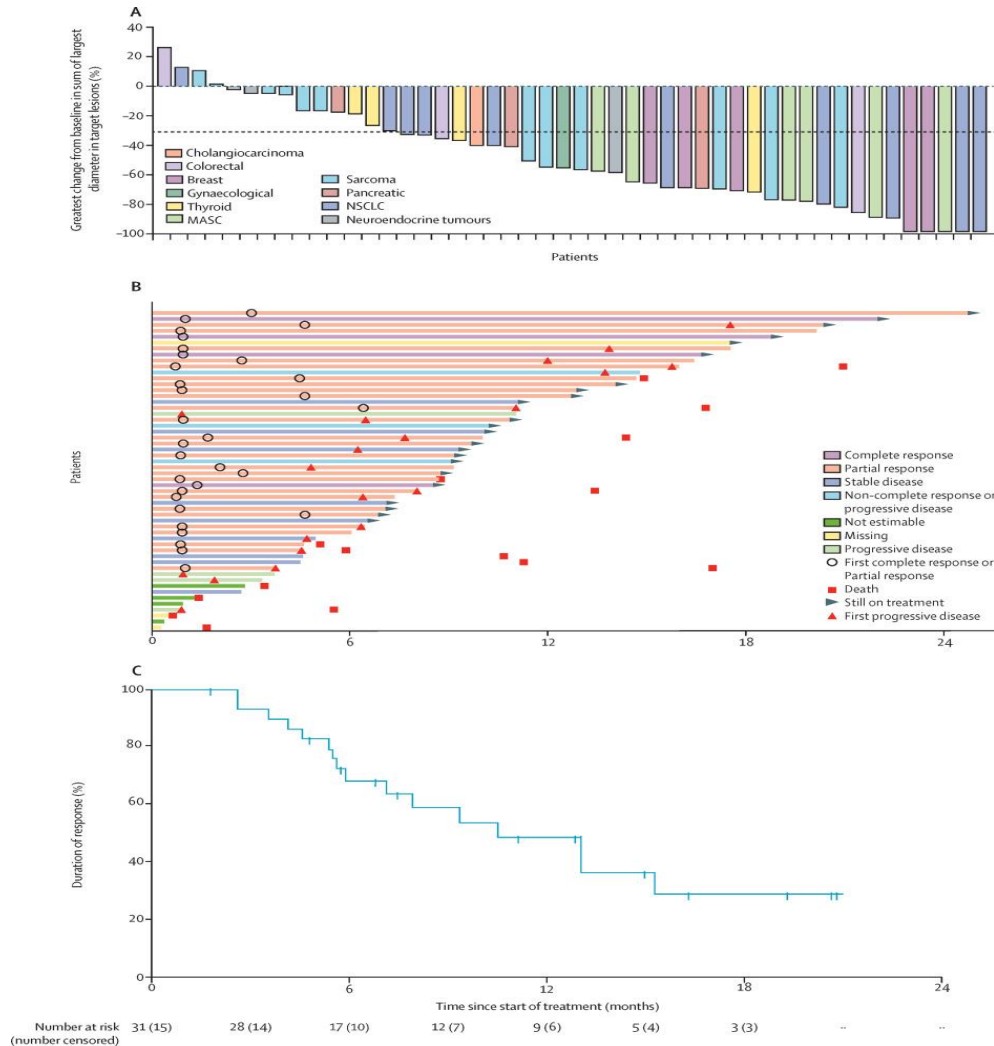
Median duration of response not reached (range 3.9⁺ to 25.9⁺ months)
(median follow-up of 12.8 months)



Duration of treatment: 1.8⁺ to 35.2⁺

November 2018: FDA
approved larotrectinib for
solid tumors harboring NTRK
gene fusion

ALKA-372-001/STARTRK-1/STARTRK-2 TRIALS: Entrectinib with efficacy in solid tumors with NTRK gene fusion



- Pooled analysis of 3 phase I/II trials
- 10 different tumor types
- 31 of 54 patients had objective response
 - 7% CR
 - 50% PR
- Most common AEs
 - Increased weight
 - Anemia
 - Cognitive disorder

August 2019: FDA approved entrectinib for solid tumors harboring NTRK gene fusion

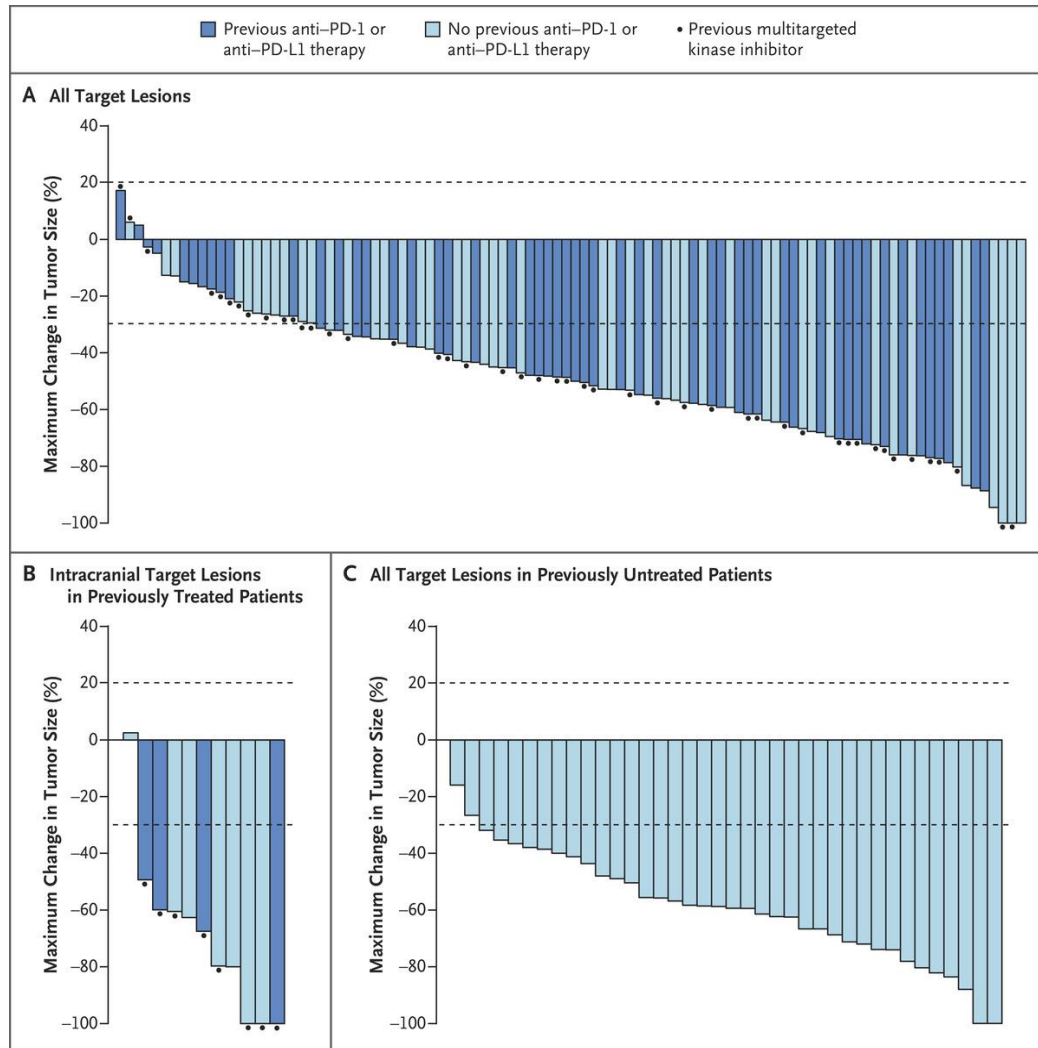
NTRK Targeted Therapies: Summary

- NTRK is an uncommon mutation in NSCLC (<0.5%)
- NTRK inhibitors larotrectinib and entrectinib are FDA approved for NTRK positive solid tumors, including NSCLC
- High response rates (>70%) and generally well tolerated

RET Alterations

- Seen in 1-2% of NSCLC
- Associated with high risk of CNS metastases
- Multi-kinase inhibitors target various kinases and other receptors (including RET)
 - Sunitinib, sorafenib, vandetanib, cabozantinib, regorafenib, lenvatinib, alectinib
 - Limited clinical benefit
 - Dose-limiting off target toxic effects
- Recent FDA approvals of selpercatinib and pralsetinib

LIBRETTO-001 TRIAL: Selpercatinib effective in *RET*-fusion-positive NSCLC



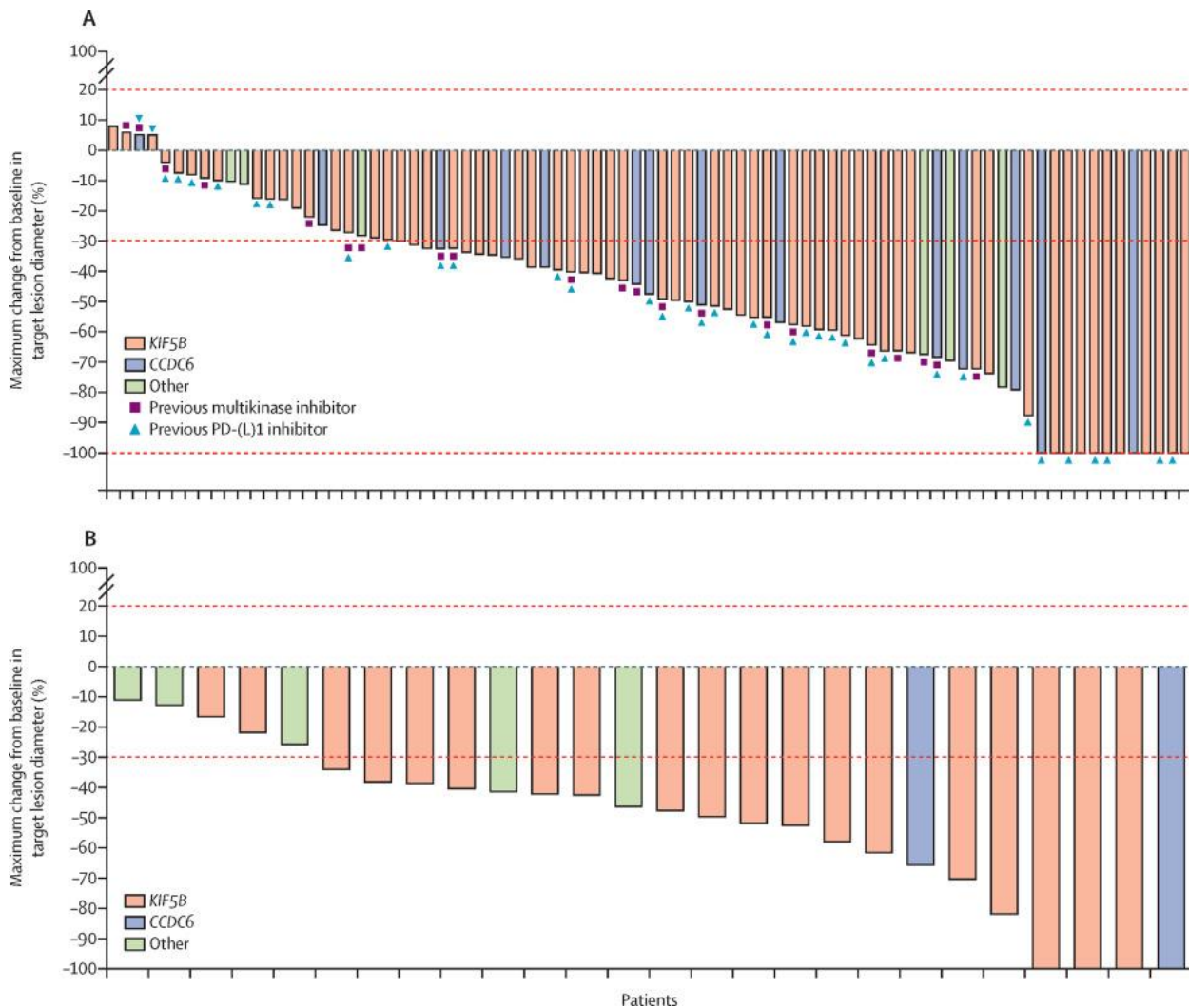
- 105 patients with RET positive NSCLC
- ORR= 64%
- Intracranial response: 91%
 - Noted in 10/11 patients with CNS mets
- Most common AEs
 - HTN
 - Increased AST

May 2020: FDA accelerated approval of selpercatinib for patients for RET+ NSCLC

Sept 2022: FDA approved selpercatinib for patients for advanced or metastatic tumors with RET gene fusion

ARROW TRIAL:

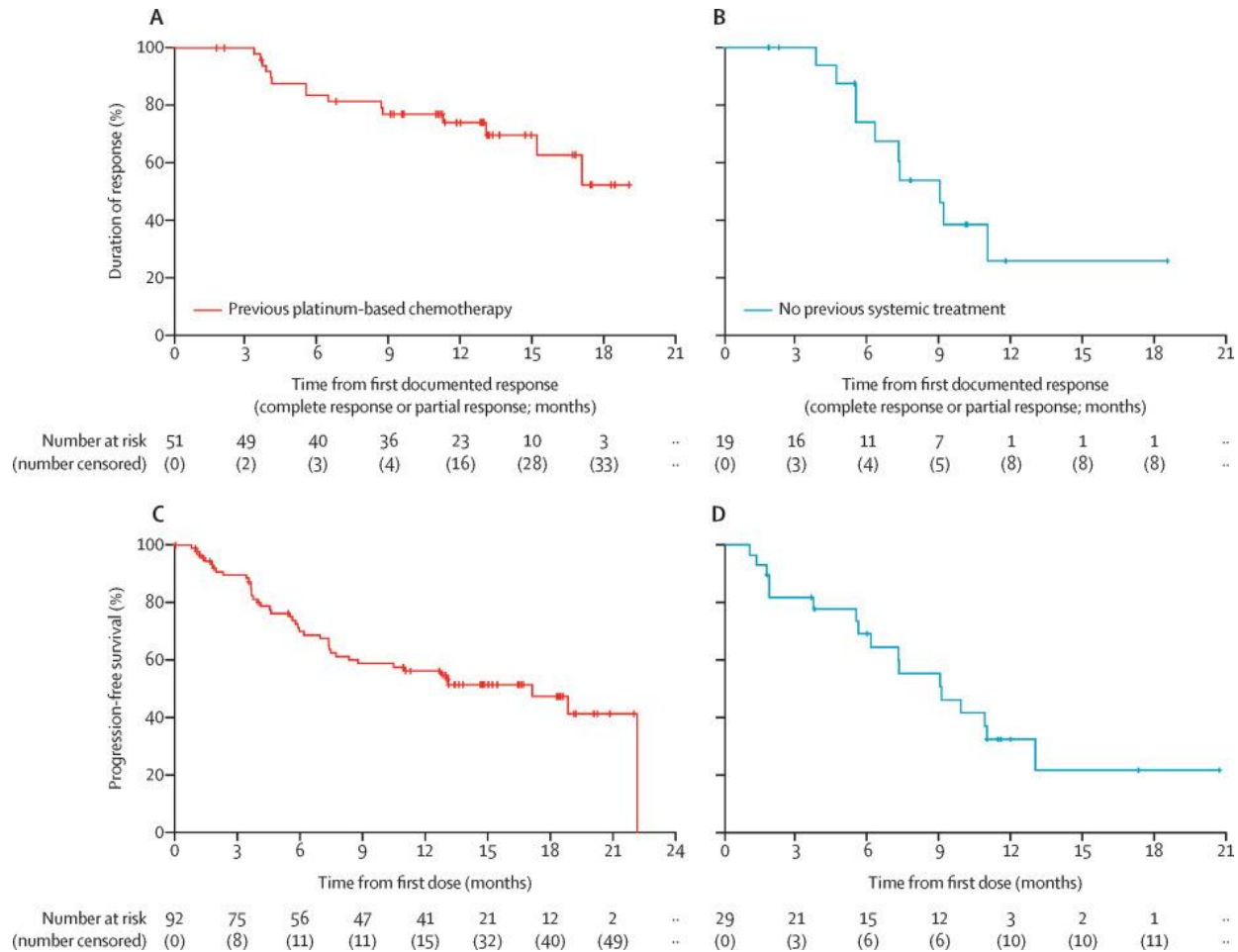
Pralsetinib effective in *RET*-fusion-positive NSCLC



- Phase I/II study
- 233 patients with RET positive NSCLC
 - 92 patients with prior platinum-based chemo (ORR= 61%)
 - 29 patients were treatment naïve (ORR= 70%)
- Most common AEs
 - Neutropenia
 - HTN
 - Anemia

December 2020: FDA accelerated approval for pralsetinib for patients with RET+ NSCLC

Pralsetinib



- Shrinkage of CNS mets noted in all 9 patients with measurable intracranial metastases
 - 5/9 patients had intracranial response (with 3 CRs)

RET Targeted Therapy: Summary

- RET fusions seen in 1-2% of NSCLC
- Associated with high risk of CNS metastases
- Selpercatinib and pralsetinib are newly FDA approved options for RET-rearranged NSCLC

Conclusions

- Obtain sufficient tissue for molecular testing, even in early stage patients
- Driver mutations (even rare subsets) are being identified on NGS panels in NSCLC tumor specimens
- Novel targeted therapeutics offer better outcomes with many recent FDA approvals
- Cancer Moonshot initiative
 - Accelerate research, making more therapies available through precision oncology
 - Bench to bedside