Dealing with EGFRex19del & L858R, ALK, and K-Ras^{G12C} Genetic Aberrations

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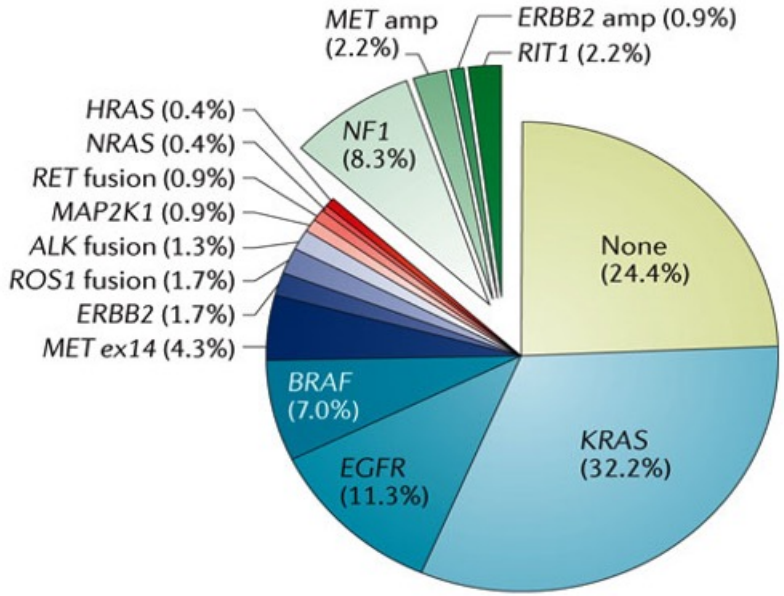
Targeted Therapy in NSCLC: FDA approvals

Lung Cancer is COMPLEX !

Tremendous progress has been made in personalized therapy



EGFR	ALK	ROS1	BRAF	MET	RET	TRK	KRAS G12C
Erlotinib	Crizotinib	Crizotinib	Dabrafenib	Crizotinib	Vandetanib	Larotrectinib	Sotorasib
Gefitinib	Ceritinib	Entrectinib	Vemurafenib	Tepotinib	Cabozantinib	Entrectinib	
Afatinib	Brigatinib		Trametinib	Capmatinib	Selpercatinib		
Osimertinib	Alectinib				Pralsetinib		
Dacomitinib	Lorlatinib						
Ramu + Erl							
Amivantamab							
Mobocertinib							

9 Druggable Pathways in NSCLC→

- EGFR
  - [1]Exon19/Exon 21
  - [2]EGFRex20ins
- [3]ALK
- [4]ROS1
- [5]BRAF
- [6]RET
- [7]MET
- [8]NTRK
- [9]KRAS^{G12C}
- [?]HER2
- [?]NRG1

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

EGFR S768I, L861Q,* and/or *G719X
First-line therapy
- Afatinib[1,10]
- Erlotinib[2]
- Dacomitinib[3]
- Gefitinib[4,5]
- Osimertinib[6,11]

Subsequent therapy
- Osimertinib[9]

***EGFR Exon 20* Insertion Mutation Positive**
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

***KRAS G12C* Mutation Positive**
- Subsequent therapy
  - Sotorasib[14]

***ALK* Rearrangement Positive**
- First-line therapy
  - Alectinib[15,16]
  - Brigatinib[17]
  - Ceritinib[18]
  - Crizotinib[15,19]
  - Lorlatinib[20]
- Subsequent therapy
  - Alectinib[21,22]
  - Brigatinib[23]
  - Ceritinib[24]
  - Lorlatinib[25]

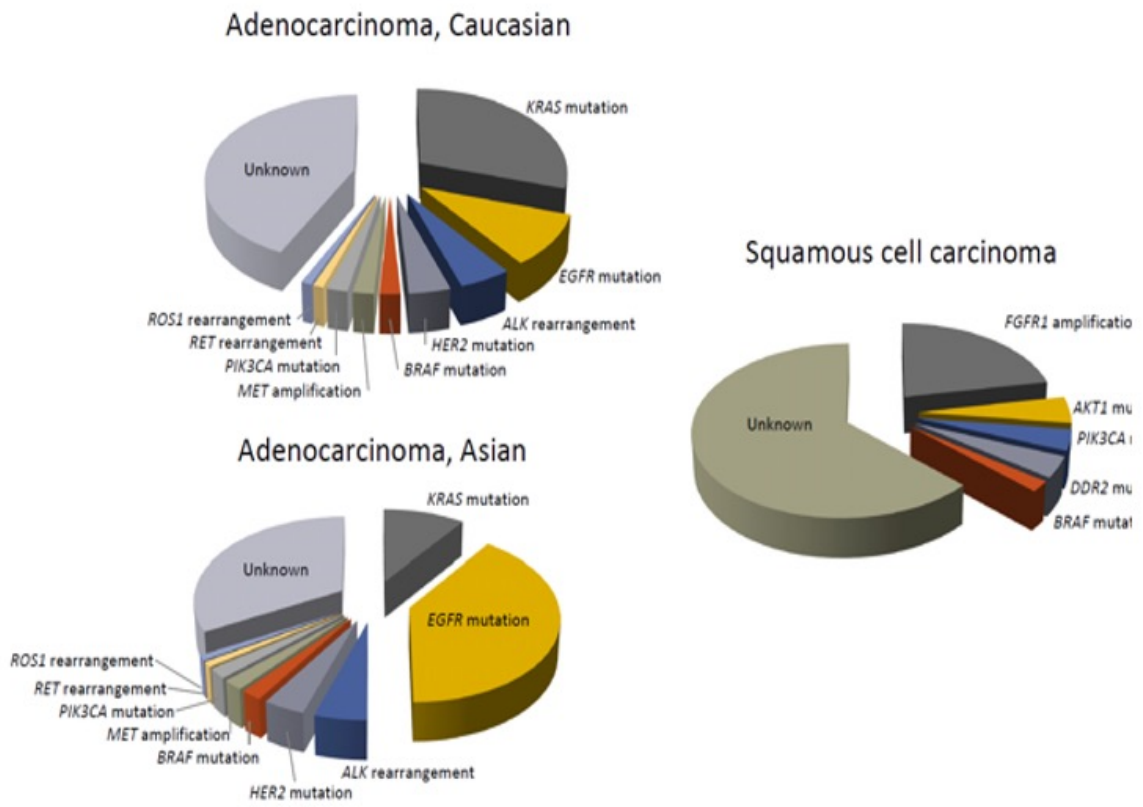
***ROS1* Rearrangement Positive**
- First-line therapy
  - Ceritinib[24]
  - Crizotinib[27]
  - Entrectinib[28]
- Subsequent therapy
  - Lorlatinib[29]
  - Entrectinib[28]

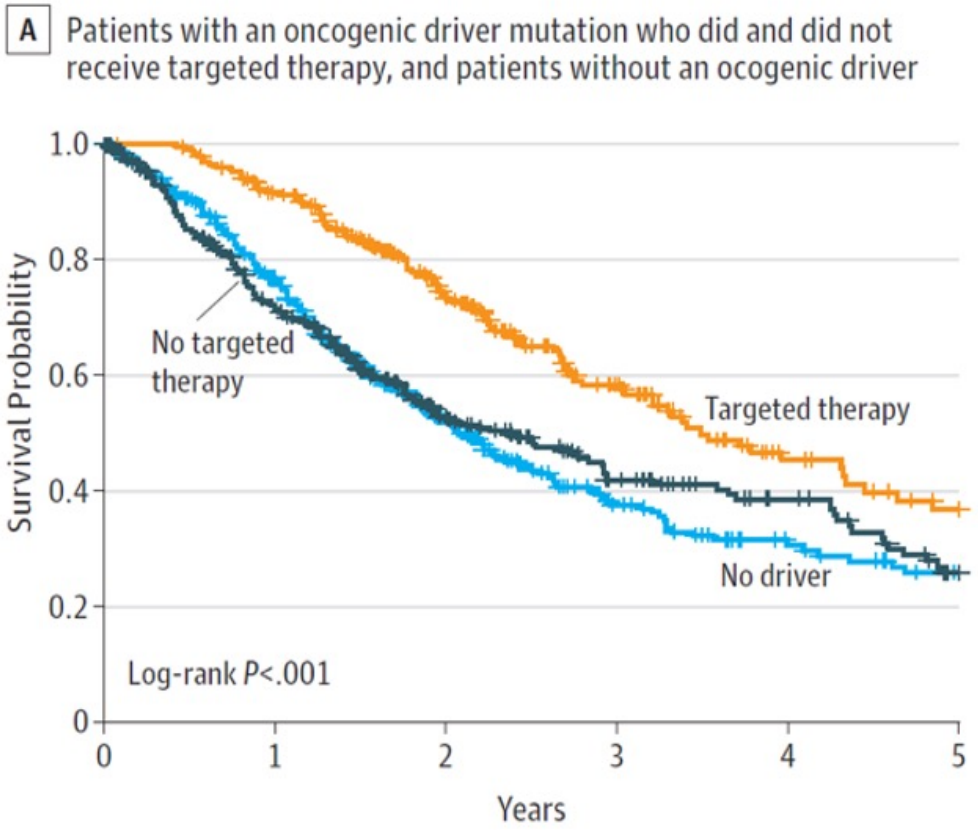
***BRAF* V600E Mutation Positive**
- First-line therapy
  - Dabrafenib/trametinib[30]
  - Dabrafenib[30]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[31,32]

***NTRK1/2/3* Gene Fusion Positive**
- First-line/Subsequent therapy
  - Larotrectinib[33]
  - Entrectinib[34]

NCCN version 3.2022, 3/16/2022

Target Directed Therapy Improves OS





- Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs.
- Kris MG[1], Johnson BE[2], Berry LD[3], Kwiatkowski DJ[4], Iafrate AJ[5], Wistuba II[6], Varella-Garcia M[7], Franklin WA[7], Aronson SL[8], Su PF[3], Shyr Y[3], Camidge DR[7], Sequist LV[5], Glisson BS[6], Khuri FR[9], Garon EB[10], Pao W[3], Rudin C[11], Schiller J[12], Haura EB[13], Socinski M[14], Shirai K[15], Chen H[3], Giaccone G[16], Ladanyi M[1], Kugler K[7], Minna JD[12], Bunn PA[7].
- JAMA. 2014 May 21;311(19):1998-2006. doi: 10.1001/jama.2014.3741.

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EGFR Pathway

→Exon 19 del/Exon 21(L858R)

Front Line

BEVERLY Study

Study design

NSCLC
Untreated
Non-squamous
Activating EGFR mutation
Stage IIIB o IV
PS 0-2

→ **R**

1:1

Control arm
- **Erlotinib** 150 mg orally once daily

Experimental arm
- **Erlotinib** 150 mg orally once daily
- **Bevacizumab** 15 mg/kg iv every 21 days

Strata:
PS (0-1 vs 2)
Type of mutation (exon19 del vs 21 L858R mut vs others)
Centre

Treatment in both arms will be given until disease progression or unacceptable toxicity or patient's or physician's motivated decision to stop

Background...

EGFR TKI + Anti-VEGF

Trial	Phase	n	EGFR TKI	Anti-VEGF	PFS	OS
JO25567[1,2]	Phase 2	154	Erlotinib	Bevacizumab	16 vs 9.7 (HR: 0.54; p =0.005)	47 vs 37.4 (HR: 0.[illegible], p=0.32)
NEJ026[3]	Phase 3	228	Erlotinib	Bevacizumab	16.9 vs 13.3 (HR: 0.605; p=0.015)	50.[illegible] vs 46.2 (HR: [illegible].00)
ALLIANCE[4]	Phase 2	88	Erlotinib	Bevacizumab	17.9 vs 13.5 (HR: 0.81, p= 0.39)	32 vs 30.6 (HR : 1.[illegible], p = 0.33)
RELAY[5]	Phase 3		Erlotinib	Ramucirumab	19.4 vs 12.4 (HR: 0.591; p<0.0001)	Immature

EGFR TKI +Chemotherapy

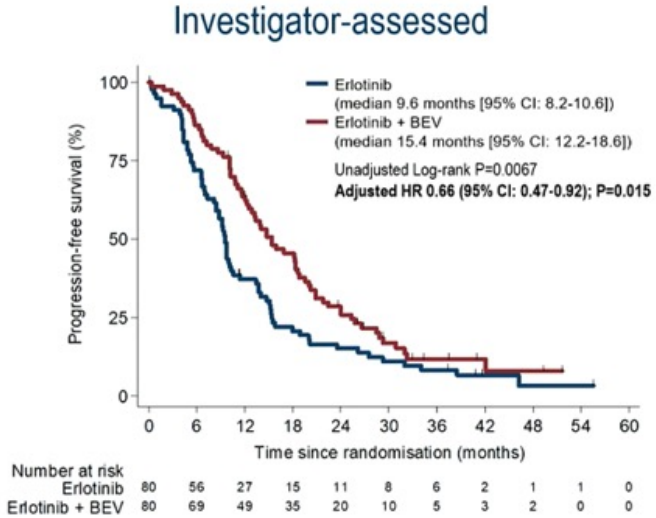
Trial	Phase	n	EGFR TKI	Chemotherapy	PFS	OS
NEJ009[6] G vs GCP	Phase 3	345	Gefitinib	Carboplatin + Pemetrexed	20 vs 11.2 (HR: 0.494; p =0.001)	52 vs 38.8 (HR: 0.65, p=0.013)
Noronha[7] G vs GCP	Phase 3	350	Gefitinib	Carboplatin + Pemetrexed	16 vs 8 (HR: 0.51; p=0.001)	NR vs 17 (HR 0.45; p=0.001)?

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: (1) Seto T, Lancet Oncology 2014 (2) Yamamoto N ASCO 2020 (3) Saito H et al Lancet Oncology 2019 (OS update at ASCO 2020) (4) Stinchcombe T Jama Oncology 2019 (5) Nakagawa Lancet Oncology 2019 (6) Nakamura A ASCO 2018 (7) Noronha V et al. JCO 2019

BEVERLY Trial

Progression-free survival

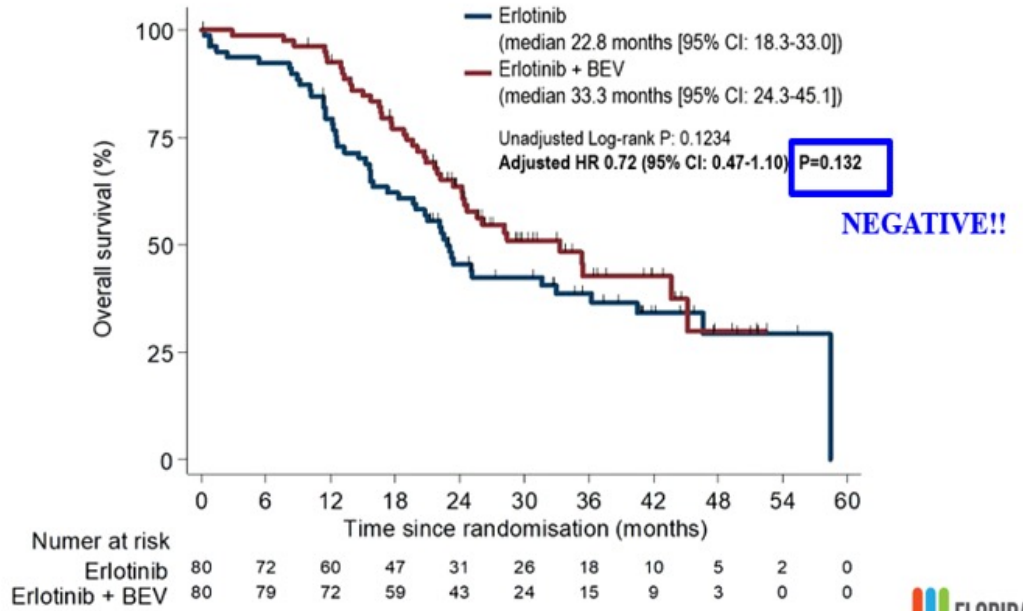


Multivariable Cox model adjusted by:

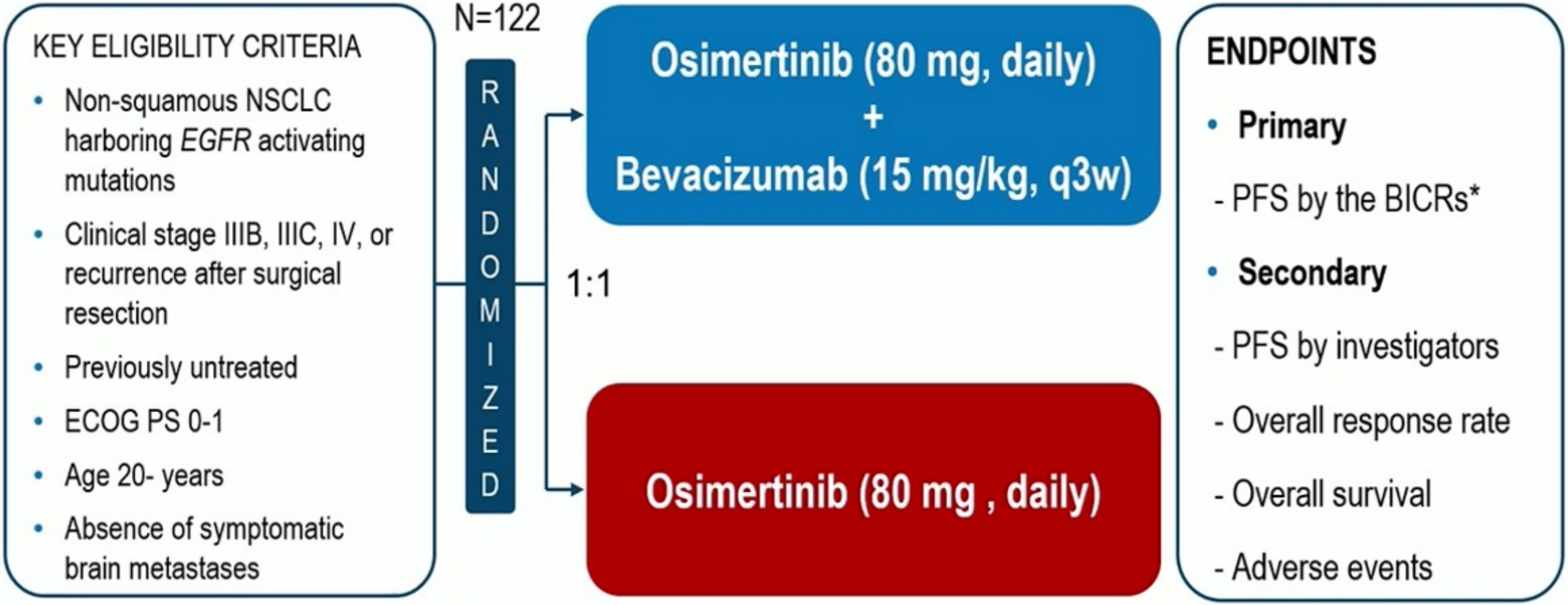
- Age
- Gender
- ECOG Performance status
- Smoking history
- Type of mutation
- Centre size

BEVERLY Trial

Overall survival



WJOG9717L: Study Design

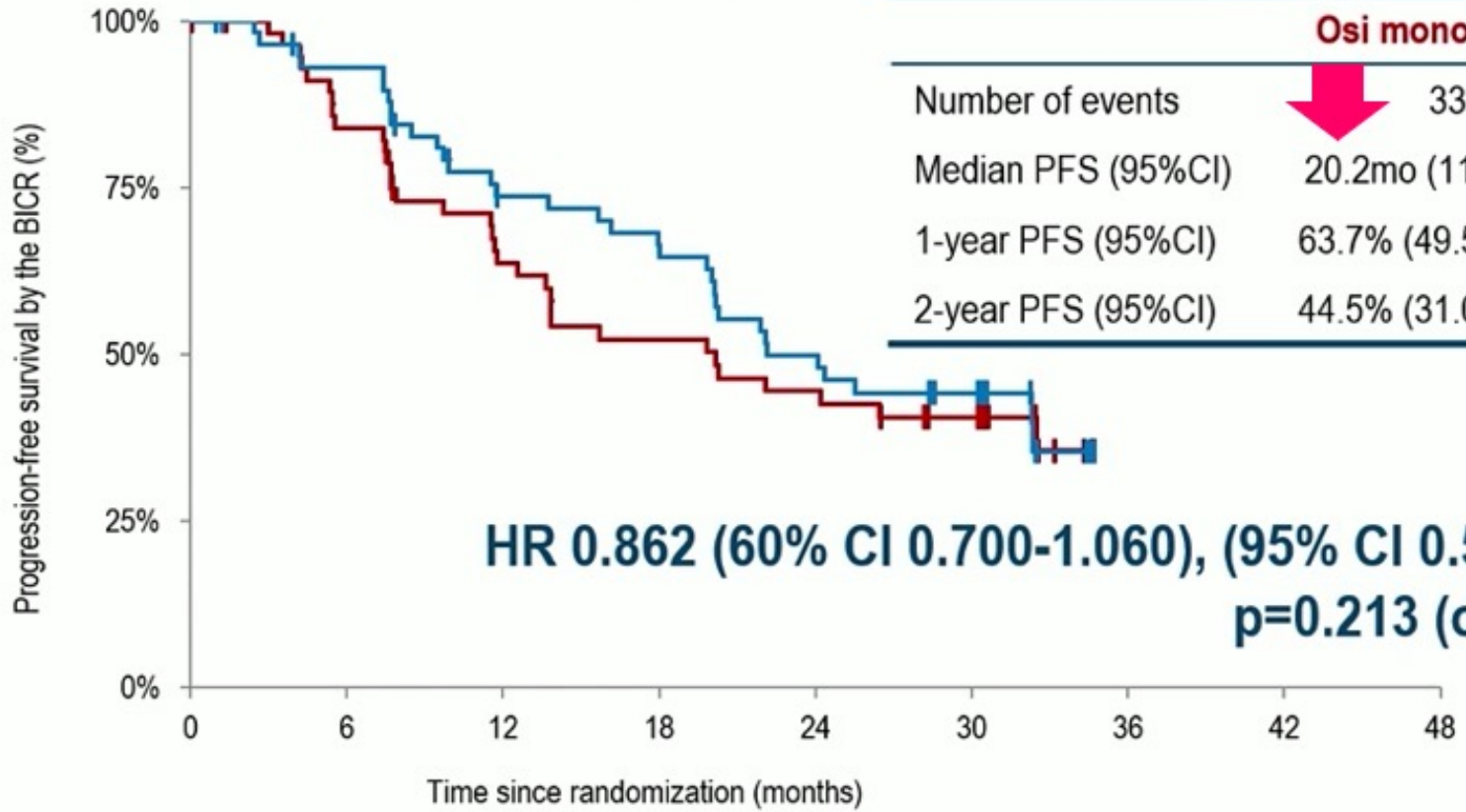


Stratification factors: Sex (female vs. male), Clinical stage (IIIB-IV vs. recurrence)
EGFR mutation (Del19 deletion vs. L858R)

Presented by: Hirotsugu Kenmotsu

WJOG9717L Study

Primary Endpoint: PFS (ITT), assessed by BICRs



	Osi mono (n=61)	Osi+Bev (n=61)
Number of events	33	33
Median PFS (95%CI)	20.2mo (11.79-NE)	22.1mo (19.81-NE)
1-year PFS (95%CI)	63.7% (49.5-74.9%)	73.8% (60.4-83.3%)
2-year PFS (95%CI)	44.5% (31.0-57.2%)	49.8% (36.1-62.1%)

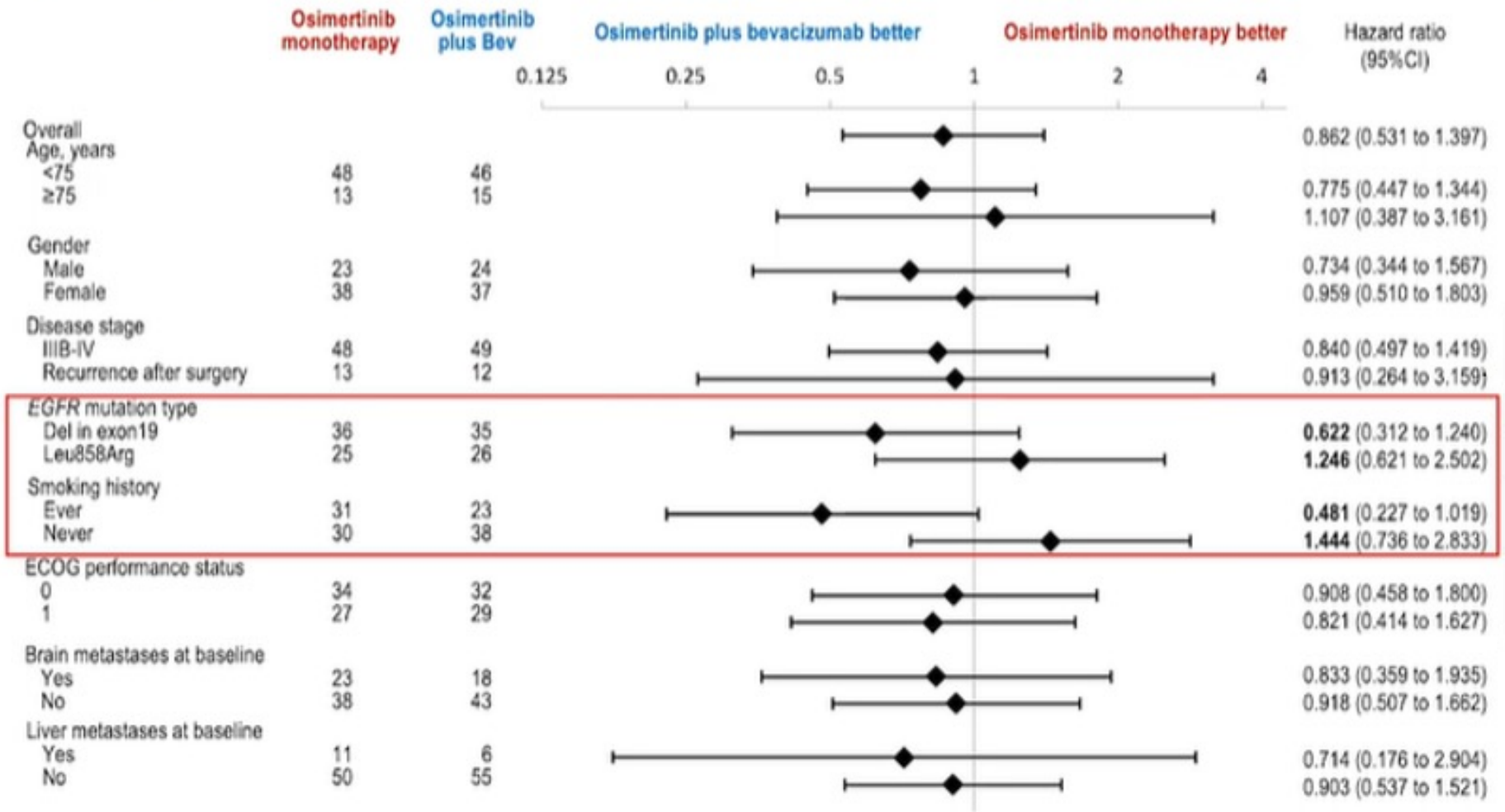
Median follow up; 30.4 mo

HR 0.862 (60% CI 0.700-1.060), (95% CI 0.531-1.397)
p=0.213 (one-sided)

Number at risk (number censored)							
Osimertinib monotherapy	61 (0)	47 (5)	34 (7)	27 (8)	23 (8)	17 (12)	0 (28)
Osimertinib plus bevacizumab	61 (0)	54 (3)	40 (6)	36 (6)	27 (6)	20 (10)	0 (28)

WJOG9717L Study

Subgroup analysis of PFS (ITT), assessed by BICR



Median PFS (m)	Osi	Osi+ Bev
Del 19	20.3	NE
L858R	15.7	20.0
Ever smoker	**13.6**	32.4
Never smoker	32.5	20.3

Is it smoking? Or could it be *TP53* mutation status?

18th Annual MIAMI CANCER MEETING
Breakthrough to Excellence in Cancer Care: Digging More Into Personalized Medicine
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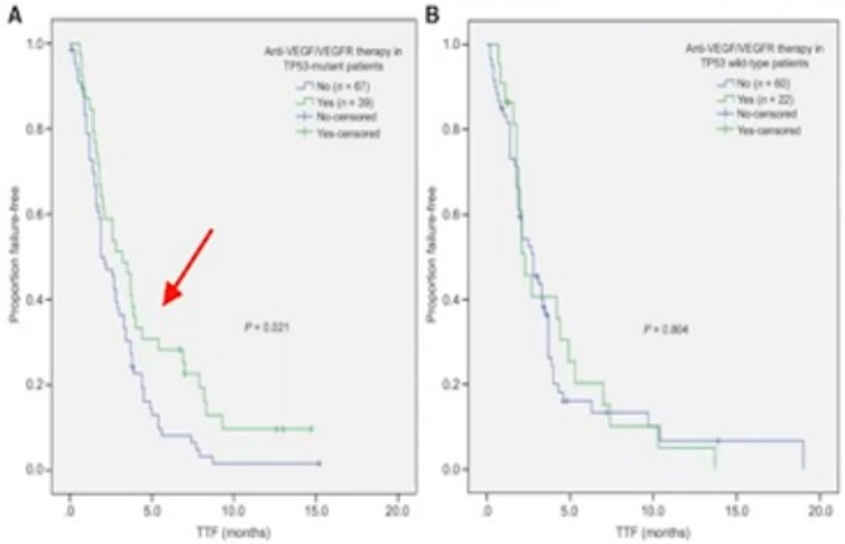
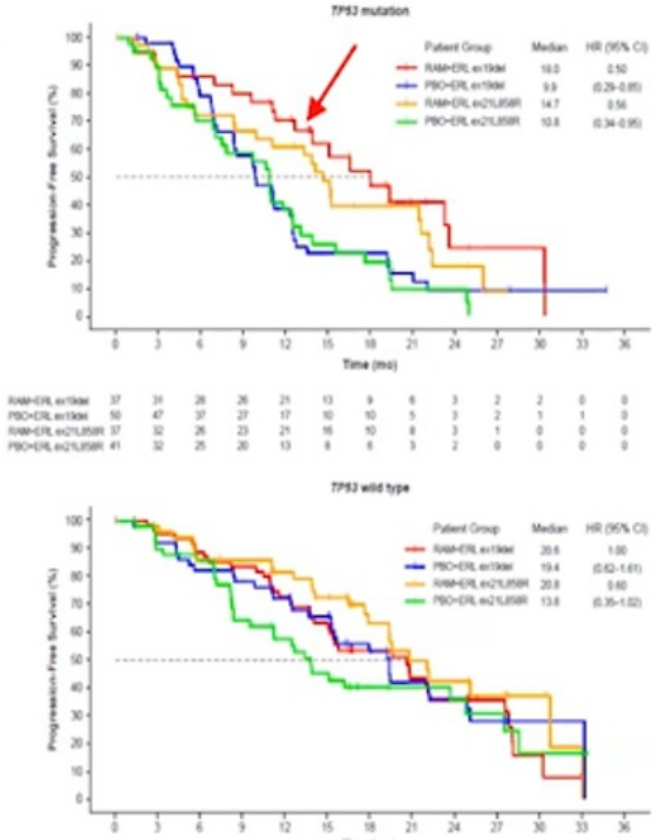
APRIL 1-3, 2022

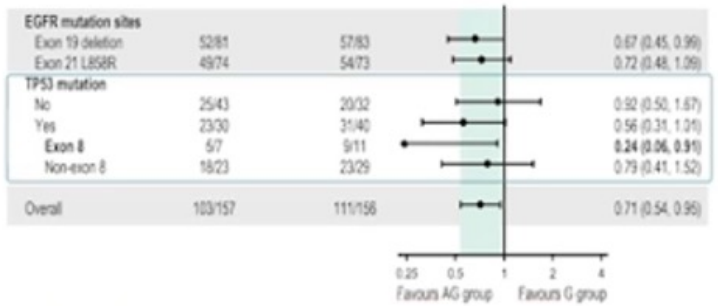
MDACC: Better outcomes with angiogenesis Inhibitors in patients with TP53 mutant tumours



RELAY: Better outcomes with ramucirumab + erlotinib in patients with TP53 mutant tumours



ACTIVE: Better outcomes with apatinib + gefitinib in patients with TP53 mutant tumours (exon 8)



Adapted from LV Sequist ESMO 2020; Wheler et al. Mol Cancer Ther 2016; Nakagawa et al. Clin Cancer Res 2021 Jul 22; Zhao et al. J Thorac Oncol. 2021; 16(9): 1533-46.

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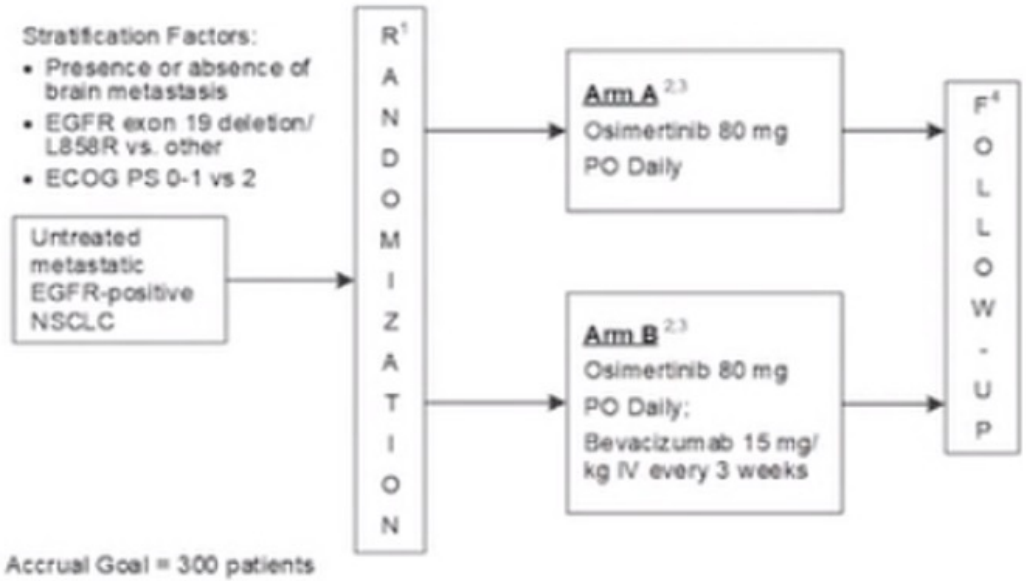
Open Questions Around First-Line Treatment for EGFR Mutant Lung Cancer Patients

Osimertinib and VEGF combination therapy

EA5182



- Randomized first-line study of osimertinib vs osimertinib/bevacizumab is ongoing, EA5182
- Co-primary endpoints of progression-free survival and overall survival as well as CNS endpoints
- Similar study of osimertinib and ramucirumab being done in the Hoosier Oncology network (PI: Le)

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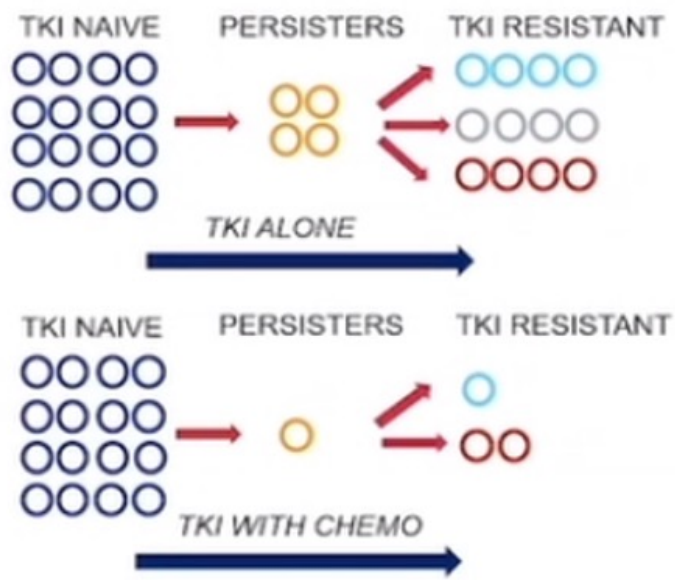
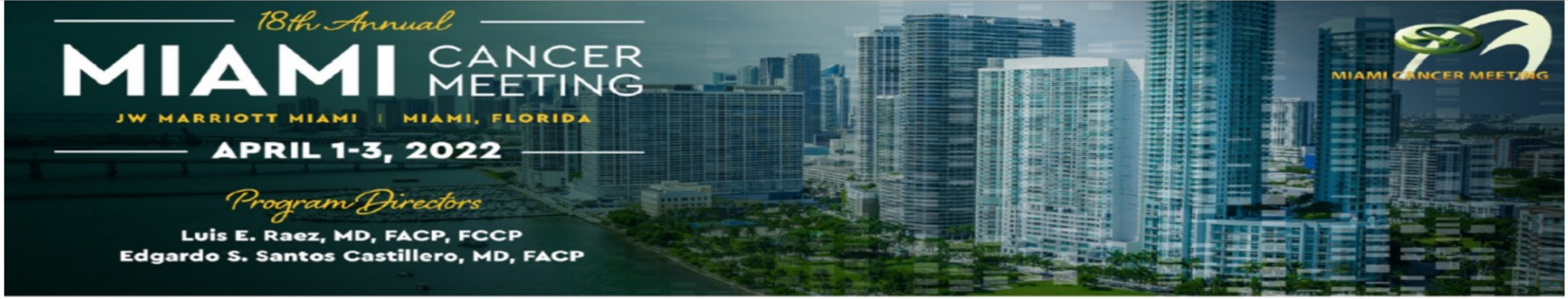
Open Questions Around First-Line Treatment for EGFR Mutant Lung Cancer Patients

EGFR TKI and chemotherapy



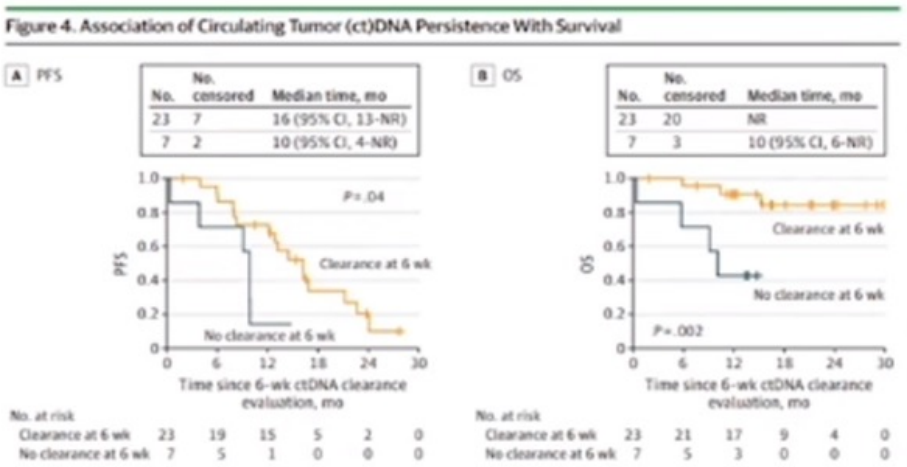
- To combine two active therapies, there needs to be improvement in PFS greater than the sum of sequencing AND/OR improvement in overall survival.
- EGFR TKI and chemotherapy combination therapy may further eradicate subclones that survive EGFR TKI monotherapy (PERSISTERS)
- Early studies demonstrate improvement in OS with the combination suggesting that further eradication of persister subclones changes natural history- longer time on treatment but also improved control throughout the disease course

Yu, H. 2022 Targeted Therapies in Lung Cancer Meeting, IASLC, February 22-26, 2022.



Biomarker-driven treatment escalation

- Identification of a biomarker to select patients for escalation of therapy is important
- Clearance of ctDNA is a biomarker that can be obtained at 3 or 6 weeks after treatment initiation.
- EGFR ctDNA is detected in >75% of pts prior to treatment. ~25% have detectable EGFR ctDNA after starting osimertinib
- In patients with persistent EGFR ctDNA, time on treatment is shorter and overall survival shorter



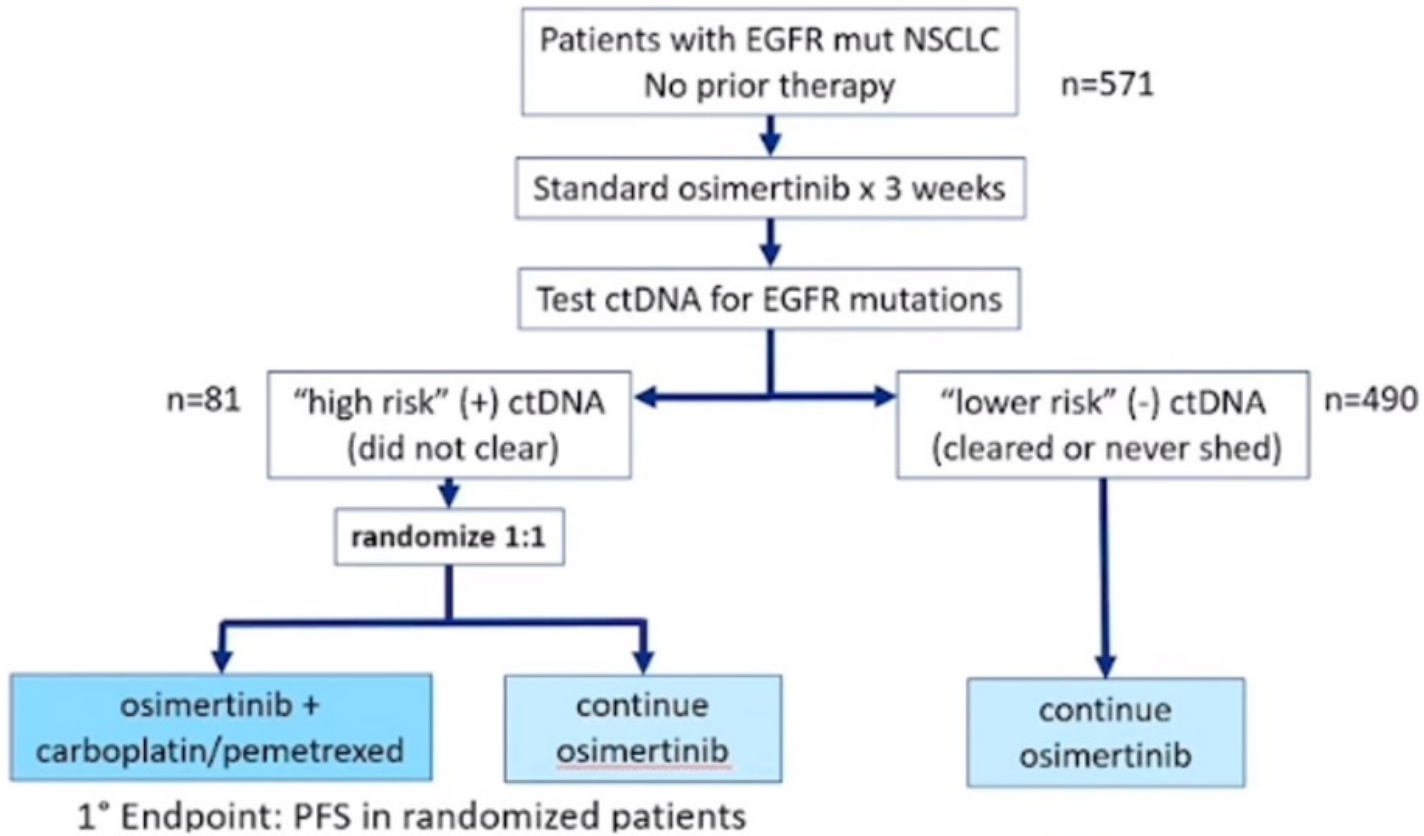
FLAURA	Detectable ctDNA @3w	Non-detectable ctDNA @ 3w
PFS	11.3mo	19.8mo
ORR	78%	86%

Yu JAMA Onc 2020, Zhou PASCO 2020

Biomarker-driven (EGFR ctDNA clearance) treatment escalation

NCT04410796, PI: Yu

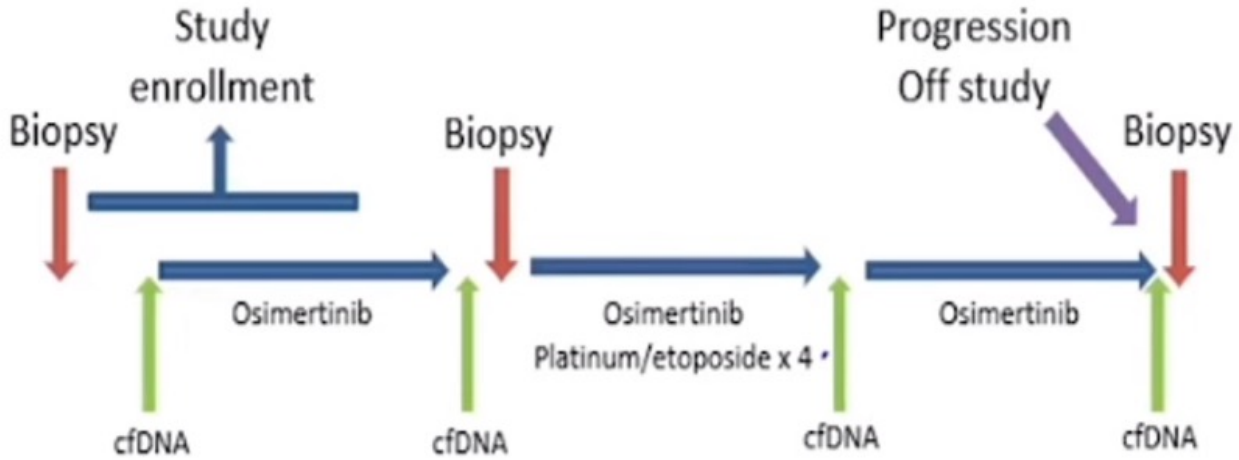
-Patients begin on standard osimertinib monotherapy
- EGFR ctDNA clearance assessed at 3 weeks to risk-stratify
-Persistent EGFR ctDNA identifies patients with limited response to EGFR TKI monotherapy
-Randomize high-risk patients to osimertinib vs osimertinib/chemo
-FLAURA2 for high-risk patients only

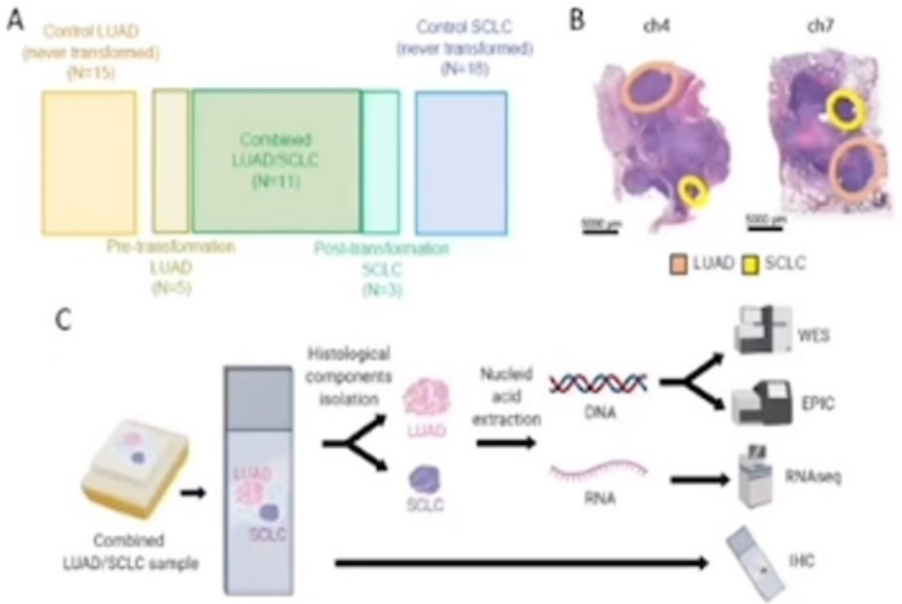


Helena Yu, MD. IASLC 2022 Targeted Therapies in Lung Cancer Meeting, Feb 22-26, 2022.

Open Questions Around First-Line Treatment for EGFR Mutant Lung Cancer Patients

Genomic-based treatment personalization





-Clinical trial that selects patients at risk (EGFR/RB1/TP53 genotype) for small cell transformation and adds in small-cell directed chemotherapy prior to transformation to try to eradicate small-cell subclone

-Comprehensive molecular analyses at different timepoints to identify changes in subclones over treatment and time.

Helena Yu, MD. IASLC 2022 Targeted Therapies in Lung Cancer Meeting, Feb 22-26, 2022.

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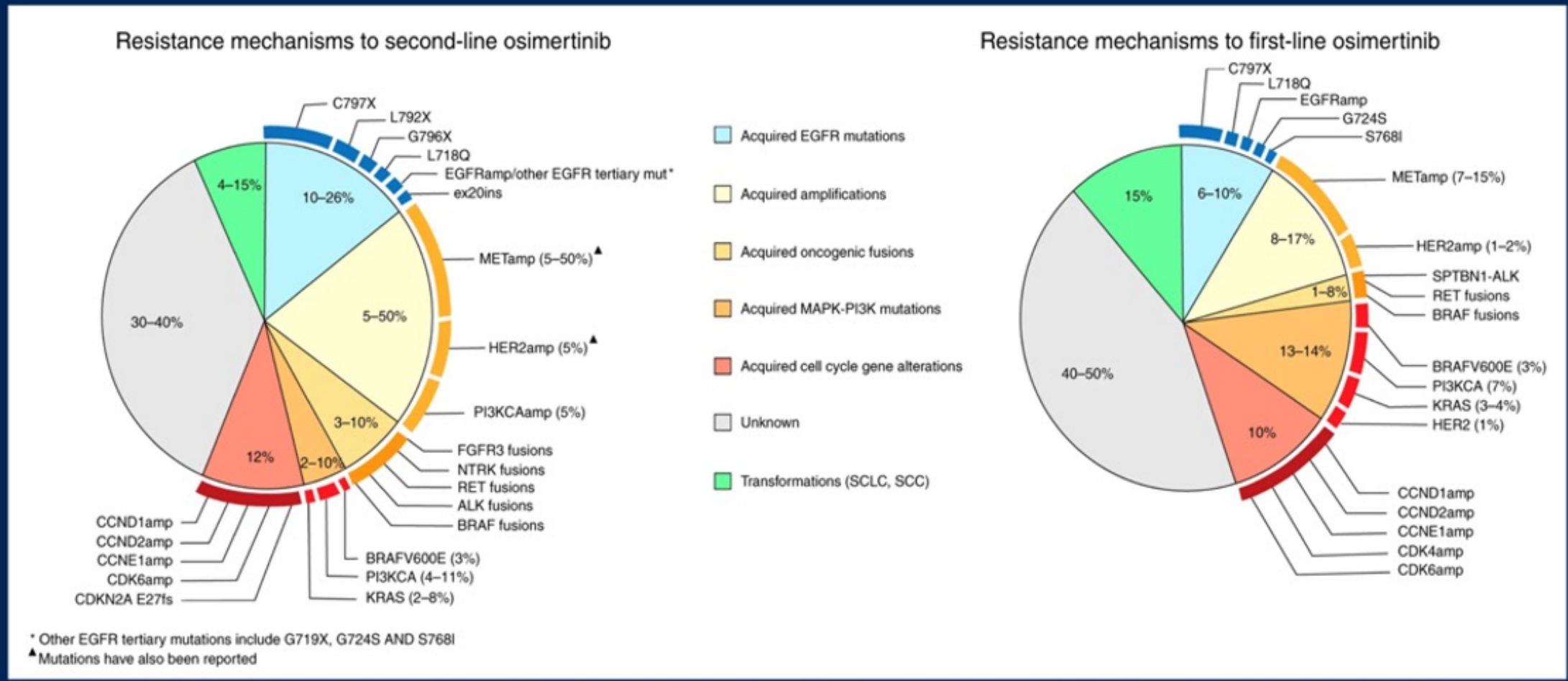
EGFR Pathway

→ To Salvage Osimertinib

HETEROGENEOUS MECHANISMS OF RESISTANCE TO OSIMERTINIB



Leonetti A Br J Cancer, 2019 Oct;121(9):725-737

MC Garassino. 2021 ASCO

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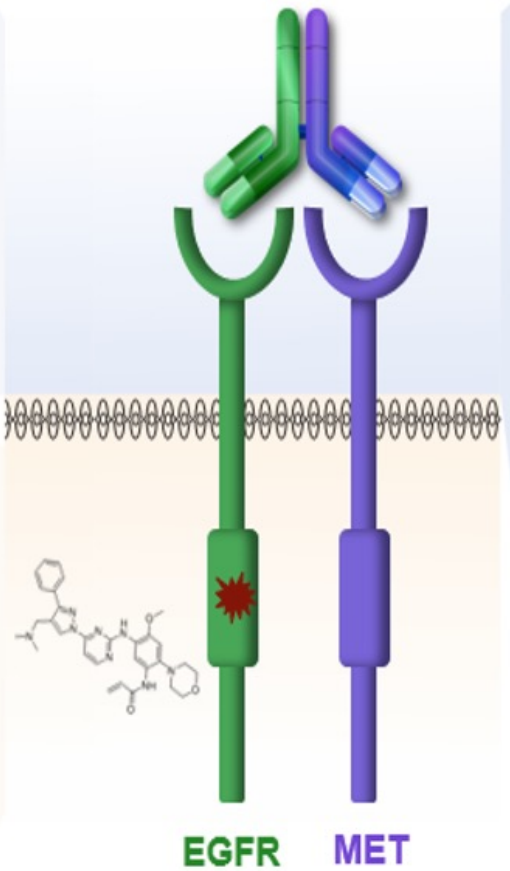
Amivantamab and Lazertinib

Amivantamab (am-e-van-tuh-mab)

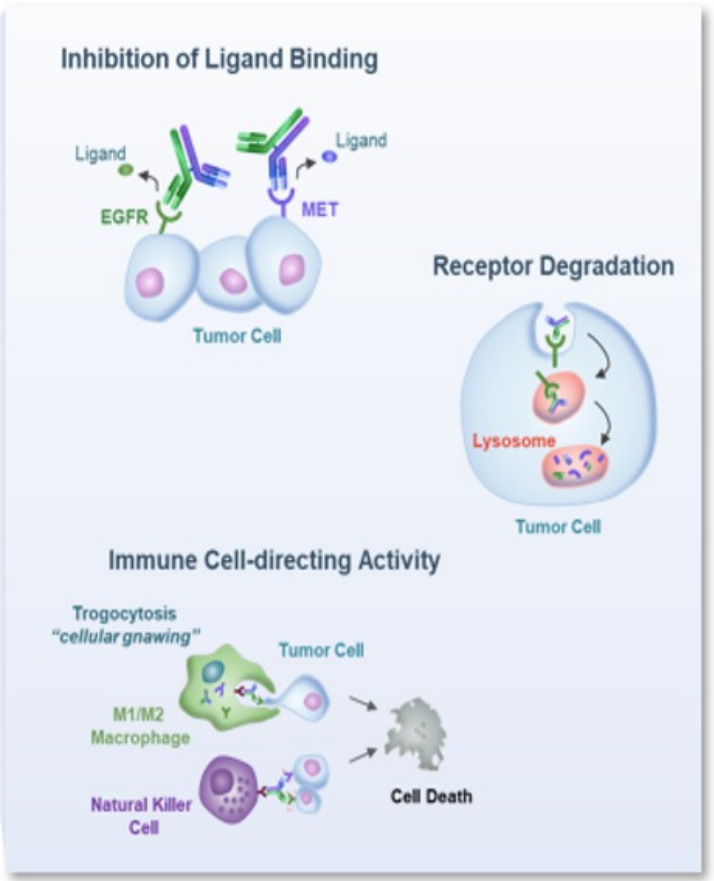
- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

Lazertinib (la-zer-tin-ib)

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[5-6]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low cardiovascular safety risk[7]
- Safety profile that supports combination with other anti-EGFR molecules



Amivantamab MOA



BC Cho. 2021 ASCO

CHRYSALIS Phase 1 Study Design: Combination Cohort
(NCT02609776)

Key Objectives

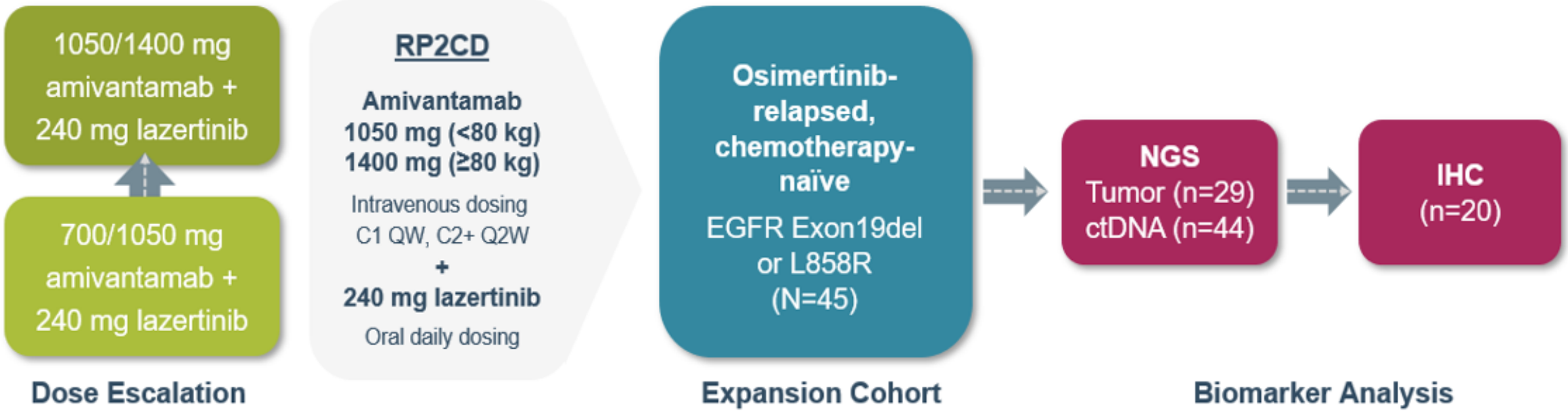
- Establish RP2CD
- Safety and efficacy at RP2CD

Key Eligibility Criteria

- Metastatic/unresectable NSCLC
- Measurable disease (expansion cohort)
- EGFR Exon19del or L858R mutation

Biomarker Analysis[a]

- NGS of pretreatment tumor biopsy and ctDNA collected prospectively
- IHC for EGFR/MET expression



This presentation provides updated results with longer follow-up from the ESMO 2020 oral presentation (Cho *Ann Oncol* 31:S813 Oral #1258O). [a]≥1 alteration detected in 42/44 ctDNA and 29/45 tumor NGS analyses.
C, cycle; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; QW, weekly; Q2W, every 2 weeks; RP2CD, recommended phase 2 combination dose

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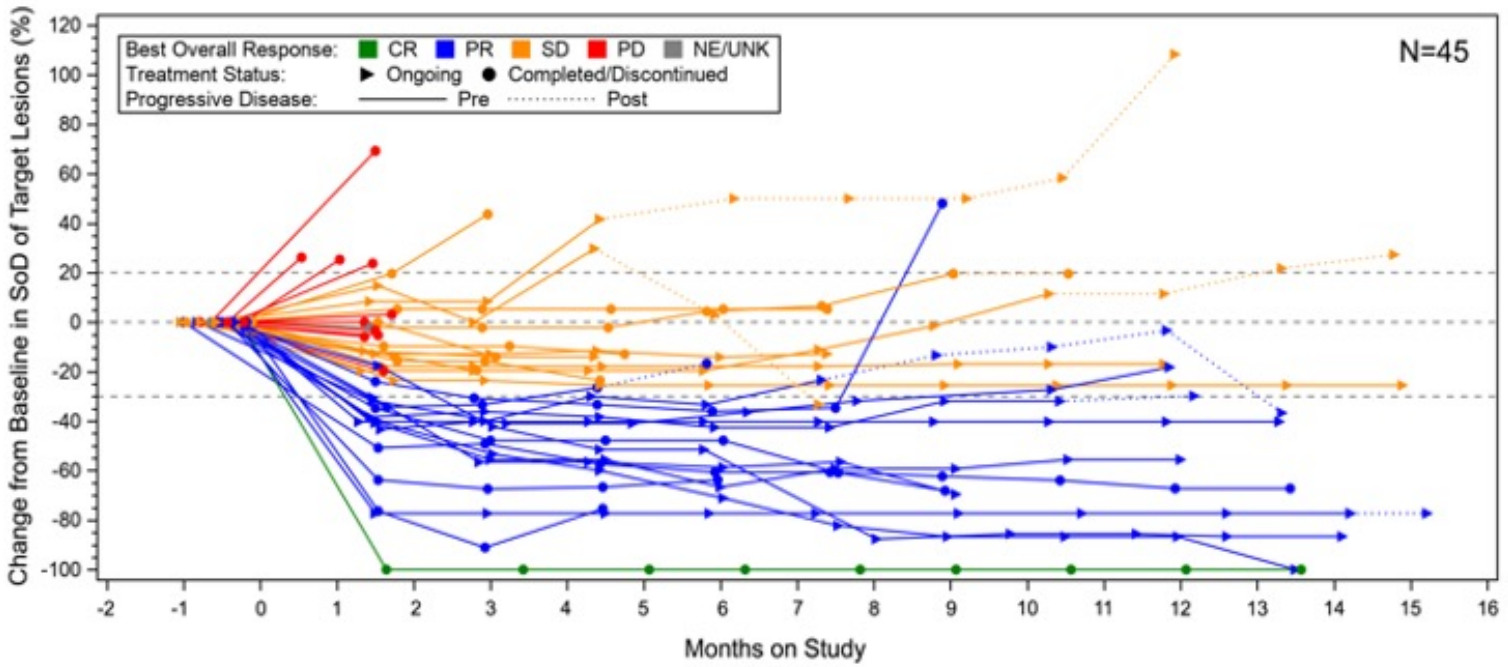
Durable Responses Observed with Amivantamab + Lazertinib with Manageable Safety



Investigator-assessed Response (N=45)
mF/U: 11.0 months (range, 1.0–15.0)
mDOT: 5.6 months (range, 0.5–14.8)

ORR	36% (95% CI, 22–51)
mDOR, months	9.6 (95% CI, 5.3–NR)
DOR ≥6 months	69%
CBR	64% (95% CI, 49–78)
mPFS, months	4.9 (95% CI, 3.7–9.5)

- Safety profile consistent with previous experience with amivantamab + lazertinib[1]
- Most common AEs were IRR (78%), rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%)
  - Majority were grade 1–2
- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

19 Apr 2021 clinical cutoff. Four patients did not have postbaseline disease assessments and are not included in the plot. [1]Cho *Ann Oncol* 31:S813 Oral #1258O.
AE, adverse event; CBR, clinical benefit rate (CR, PR, or SD ≥11 weeks); CR, complete response; IRR, infusion-related reaction; mDOR, median duration of response; mDOT, median duration of treatment; mF/U, median follow-up; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of target lesion diameters; UNK, unknown

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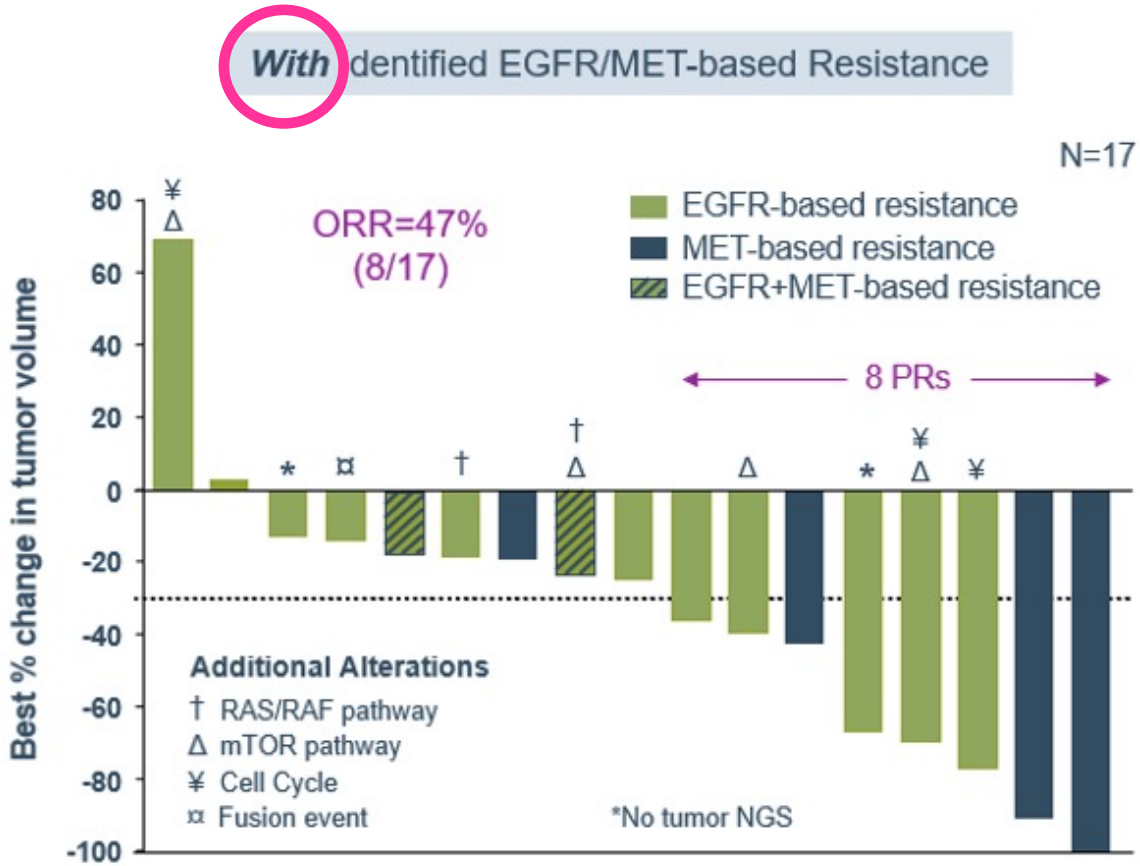
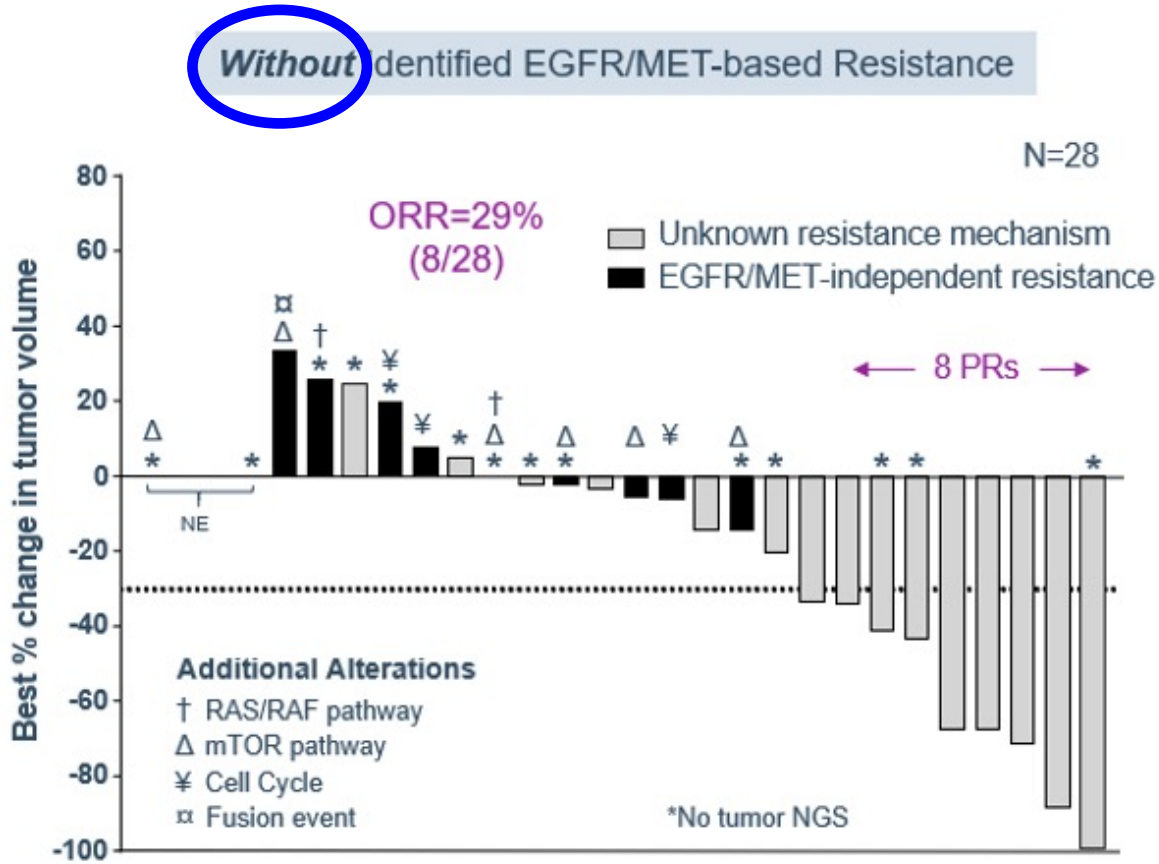
Equal Number of Responders Among Patients with and without Identified EGFR/MET-based Resistance





Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS. NE, not evaluable (no postbaseline assessment for 4 patients).

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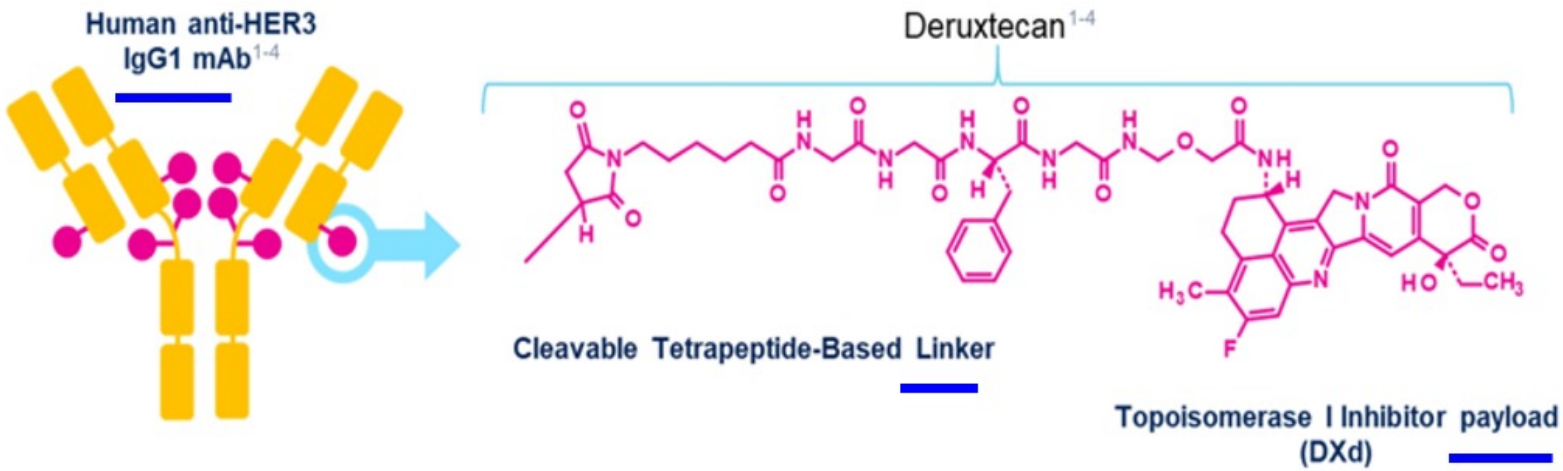
Patritumab Deruxtecan (HER3-DXd)—Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

- HER3-DXd is an ADC with 3 components:[1-6]
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to:
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker
- HER3-DXd is in clinical evaluation for NSCLC, metastatic breast cancer, and colorectal cancer

HER3 is expressed in ! 83% of NSCLC tumors[7,a]

HER3 alterations are not known to be a mechanism of resistance to EGFR TKI in *EGFR*m NSCLC

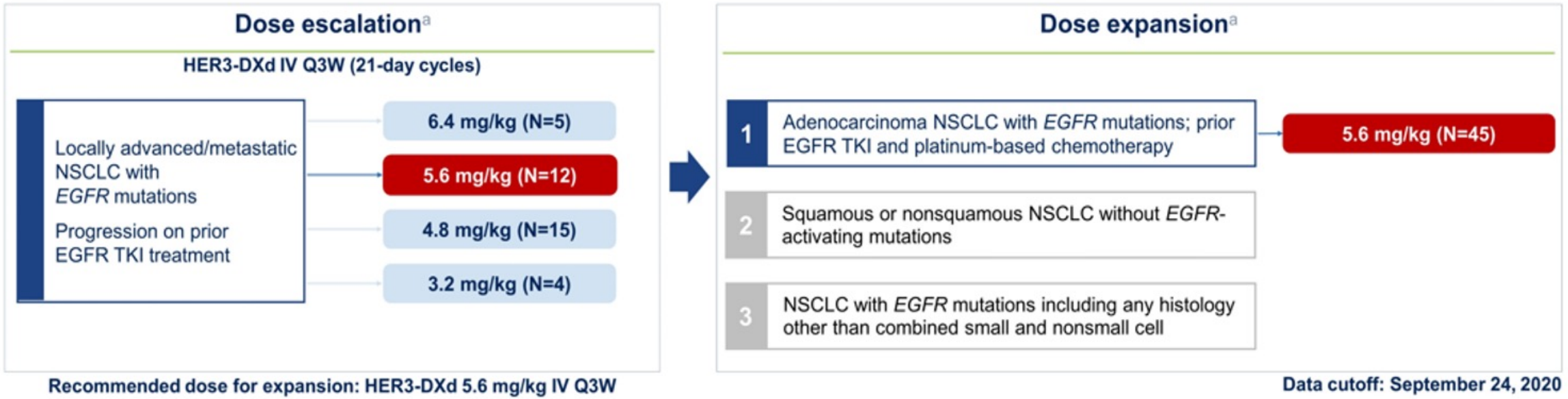


[a] HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC.

1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046. 7. Scharpenseel H et al, *Sci Rep* 2019;9(1):7406.

PA Janne. 2021 ASCO

U31402-A-U102 is a Phase 1 Dose Escalation and Dose Expansion Study in Patients With NSCLC



57 patients with EGFR TKI–resistant, *EGFR*m NSCLC were treated with HER3-DXd 5.6 mg/kg in dose escalation (N=12) and dose expansion Cohort 1 (N=45)

- **Efficacy** evaluation in pooled patients with *EGFR*m NSCLC treated with HER3-DXd 5.6 mg/kg (**N=57**)
  (Median Follow Up: 10.2 mo; range, 5.2-19.9 mo)
- **Safety** evaluation in all patients in dose escalation and dose expansion Cohort 1 (**N=81**)

Clinicaltrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868.
[a] Patients with stable brain metastases were permitted to enroll; A tumor biopsy was required prior to study entry but patients were not selected for inclusion based on measurement of HER3.

PA Janne. 2021 ASCO

Patritumab Deruxtecan
U31402-A-U102

HER3-DXd Demonstrated Durable Antitumor Activity After Failure of EGFR TKI and Platinum-based Chemotherapy (PBC)

Outcomes (BICR per RECIST 1.1) Median Follow Up: 10.2 (range, 5.2-19.9) mo[a]	HER3-DXd 5.6 mg/kg Prior TKI, ± PBC (N=57)	HER3-DXd 5.6 mg/kg Prior OSI, PBC (N=44)
Confirmed ORR, % (95% CI)	39 (26-52)	39 (24-55)
Best overall response, n (%)		
CR	1 (2)	1 (2)
PR	**21 (37)**	**16 (36)**
SD, Non-CR/Non-PD	19 (33)	13 (30)
PD	9 (16)	8 (18)
Not evaluable	7 (12)	6 (14)
Disease control rate, % (95% CI)	72 (59-83)	68 (52-81)
Time to response, median (range), mo	2.6 (1.2-5.4)	2.7 (1.2-5.4)
Duration of response, median (95% CI), mo	6.9 (3.1-NE)	7.0 (3.1-NE)
PFS, median (95% CI), mo	8.2 (4.4-8.3)	8.2 (4.0-NE)

The subgroup of patients treated with prior **osimertinib (OSI)** and **platinum-based chemotherapy** demonstrated similar efficacy to the overall efficacy population

BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Data cutoff: September 24, 2020.
[a] For patients treated with the recommended dose for expansion of HER3-DXd (N=57)

MC Garassino. 2021 ASCO

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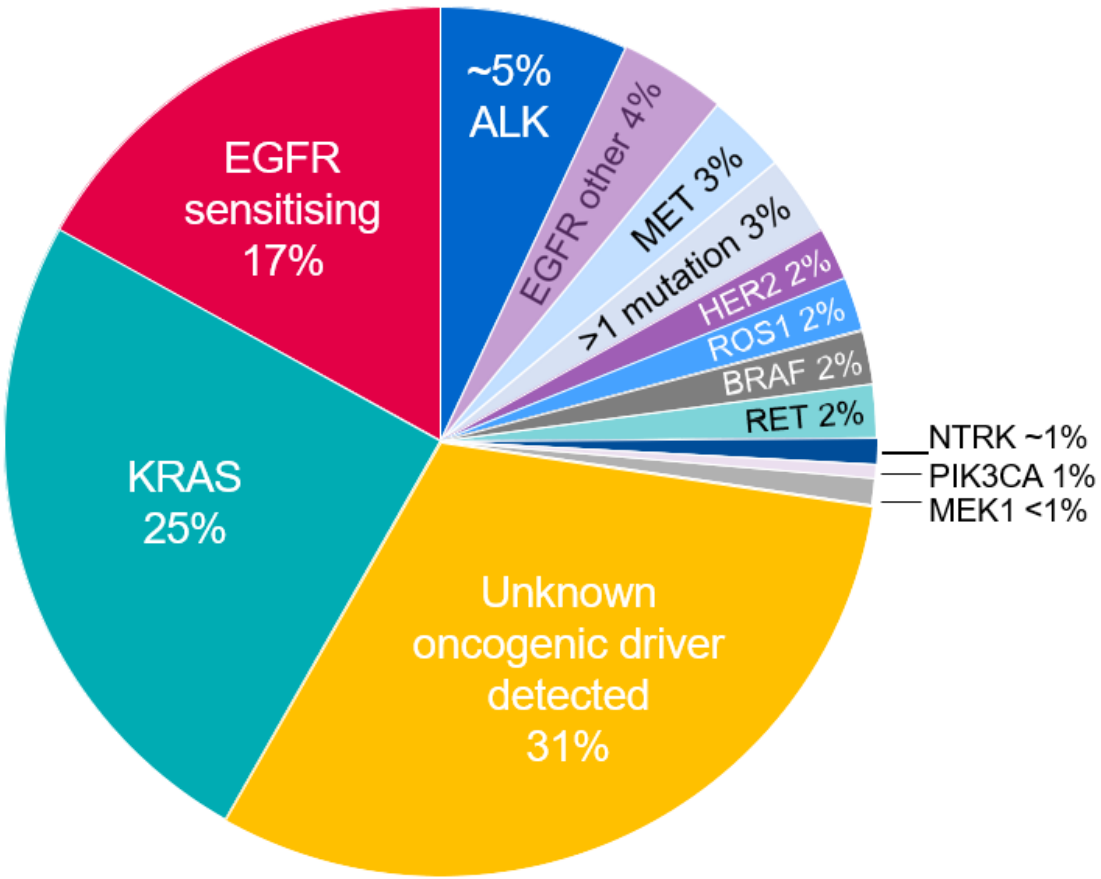
ALK Pathway

ALK is an oncogenic driver mutation for a distinct subset of NSCLC

Driver mutations in lung cancer[1]



Patients tend to be…

Younger[2–4]

Median age ~52 years versus ~70 years for other types of NSCLC

Never or light smokers[3,5,6]

~70% patients with *ALK*+ NSCLC have never smoked

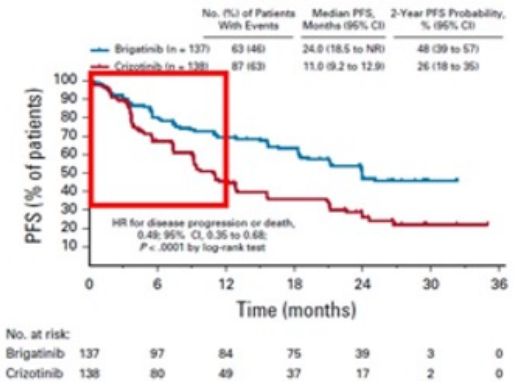
Advanced disease at presentation[7–9]

- Pleural/pericardial effusion
- Multiple lesions/sites
- Symptomatic
- CNS metastases

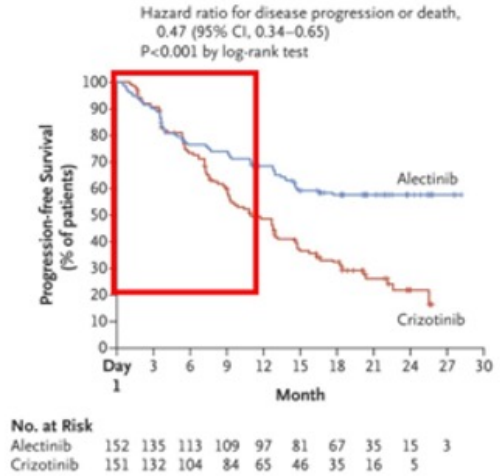
1. Tsao, et al. J Thorac Oncol 2016; 2. Chia, et al. Clin Epidemiol 2014; 3. Camidge, et al. Lancet 2012; 4. SEER Cancer Stat Fact Sheets Lung and Bronchus Cancer
5. Tao, et al. Thorac Cancer 2017; 6. Kayaniyil, et al. Curr Oncol 2016; 7. Solomon, et al. N Engl J Med 2014; 8. Soria, et al. Lancet 2017; 9. Peters, et al. N Engl J Med 2017

Managing ALK+ NSCLC

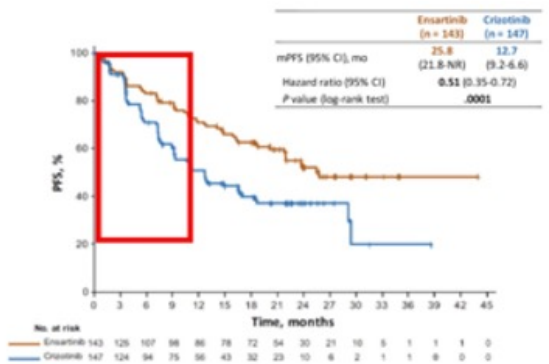
Brigatinib: ALTA-1L
HR 0.49



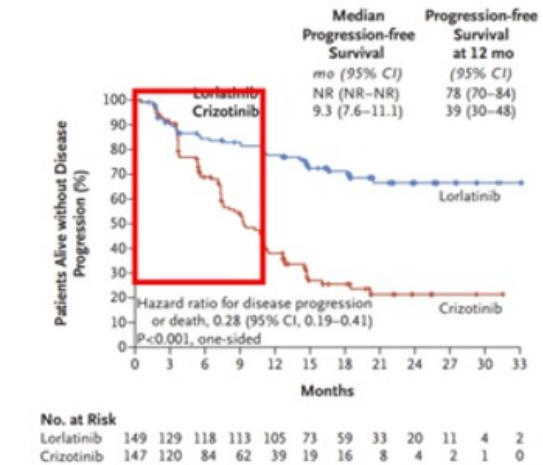
Alectinib: ALEX
HR 0.47



Ensartinib: eXalt3
HR 0.51



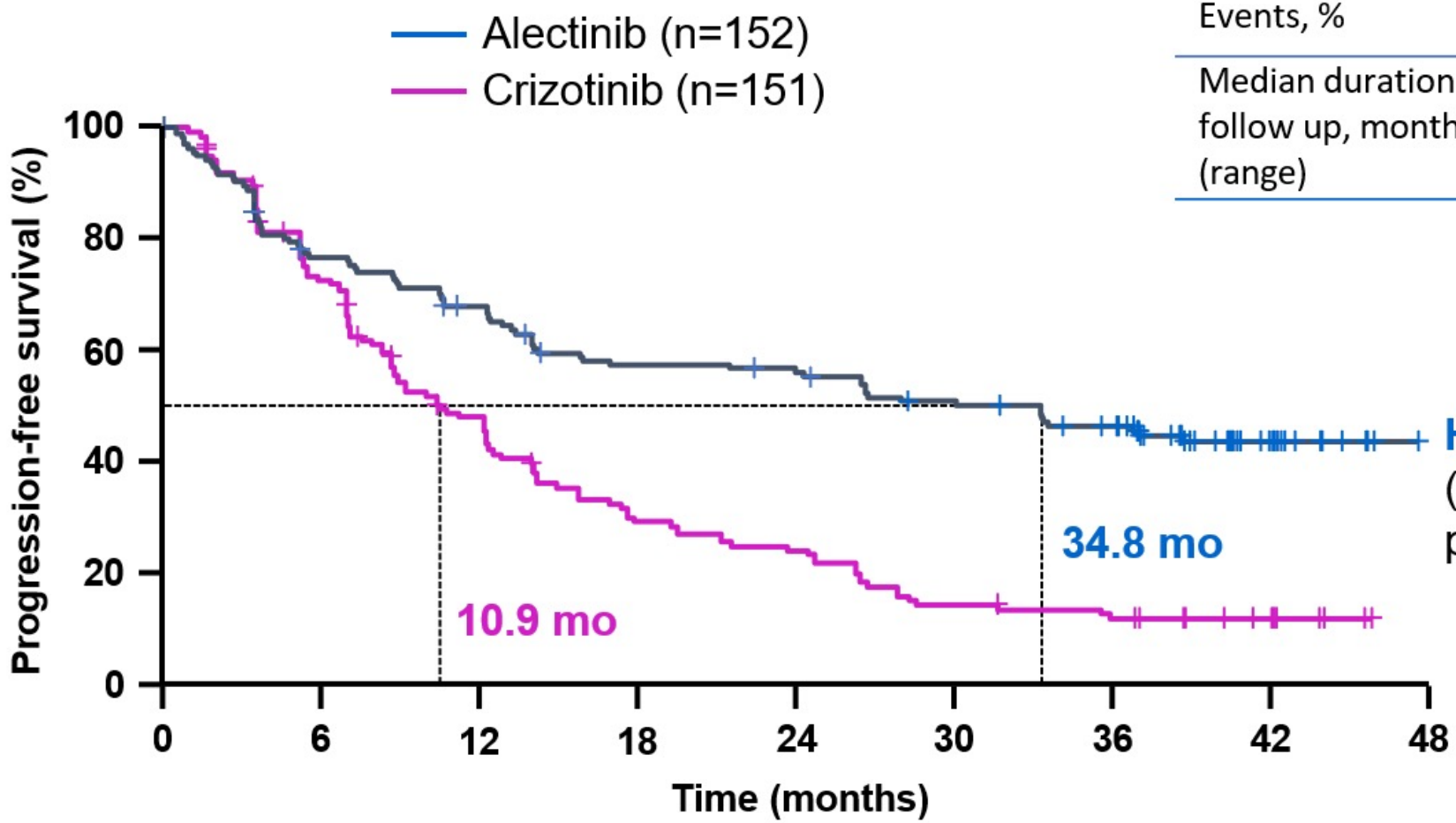
Lorlatinib: CROWN
HR 0.28



Camidge DR, et al, *J Clin Oncol*. 2020 Nov 1;38(31):3592-3603., Horn L, et al, WCLC Presentation, Aug 8, 2020. Peters S, et al, *N Engl J Med*. 2017 Aug 31;377(9):829-838. Shaw AT, et al, *N Engl J Med*. 2020 Nov 19;383(21):2018-2029.

ALEX: Updated PFS

	Alectinib	Crizotinib
Events, %	53	81
Median duration of follow up, months (range)	37.8 (0.5–50.7)	23.0 (0.3–49.8)



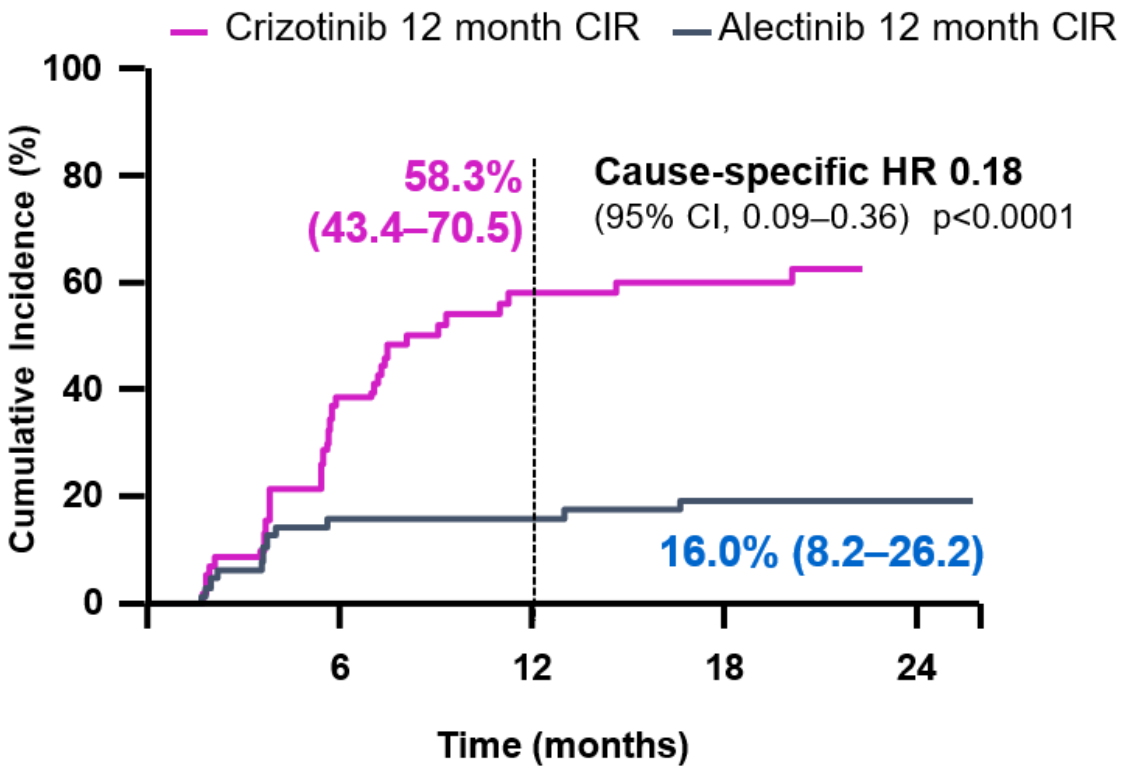
HR=0.43
(95% CI: 0.32–0.58)
p-value (log-rank) <0.0001

Data cut-off: 30 November 2018

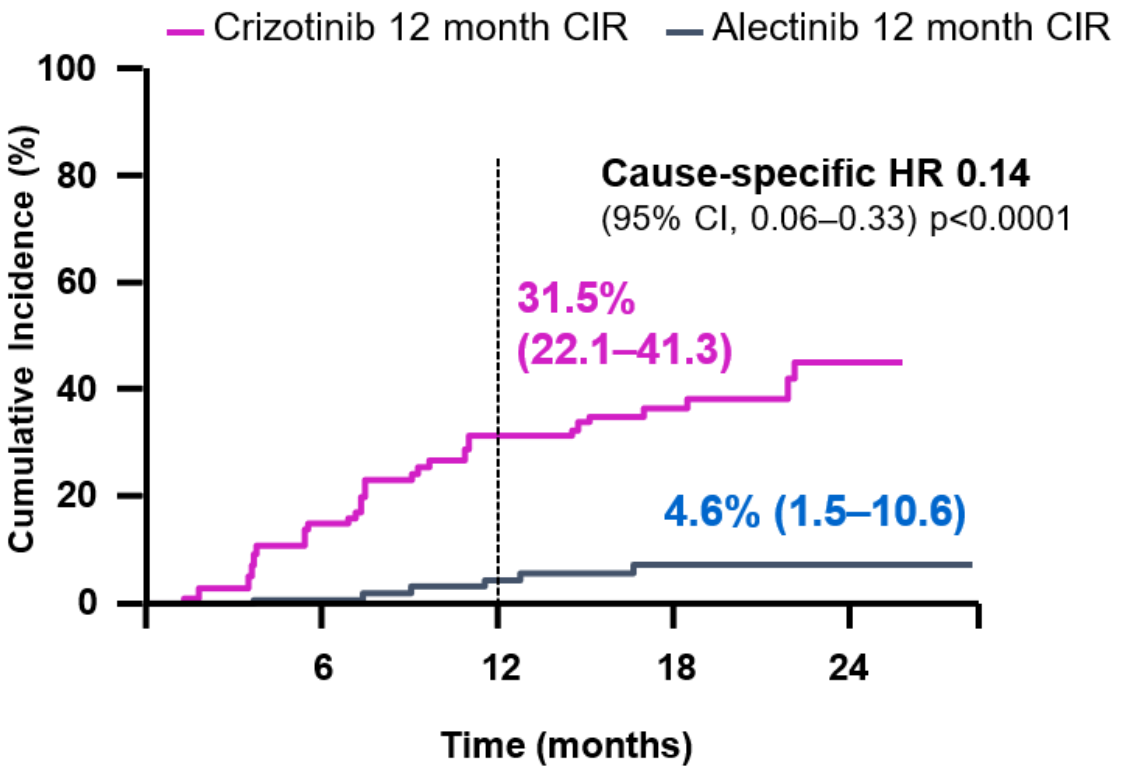
Mok, et al. ESMO 2019

ALEX: CNS progression was lower with alectinib in patients with and without CNS metastases at baseline.

With CNS metastases at baseline

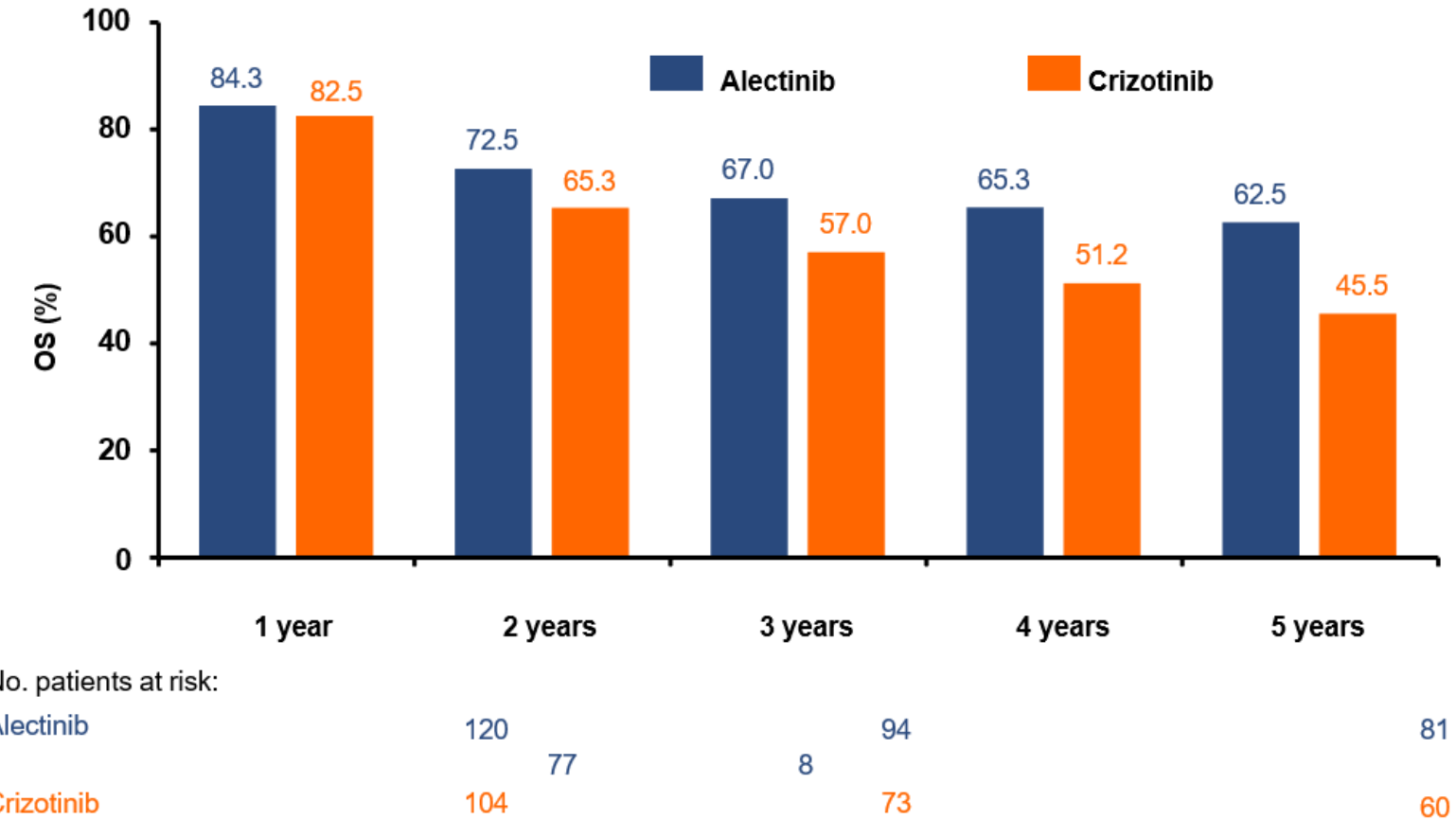


Without CNS metastases at baseline



Gadgeel, et al. Ann Oncol 2018.

ALEX- Overall Survival Event Free Rate



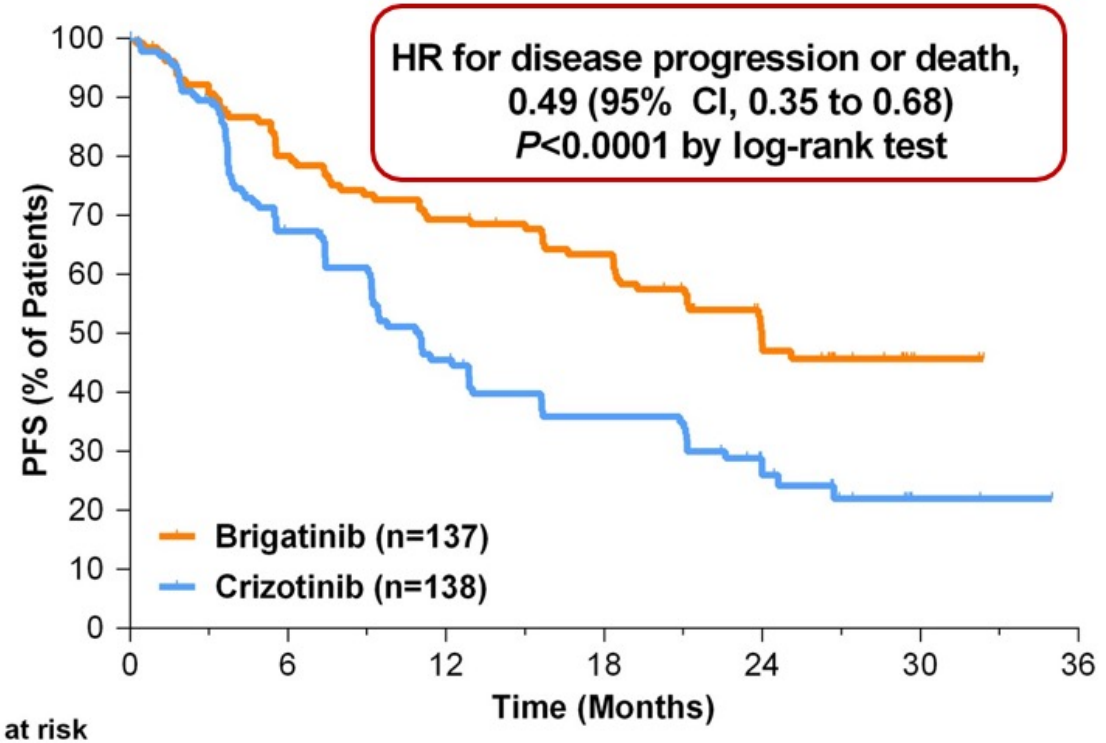
Median OS- NR-alectinib; 57.4 months- crizotinib, HR- 0.67

4 year survival PROFILE 1014- 56.6 %

Peters S, ASCO 2020

Updated PFS ALTA 1L Brigatinib

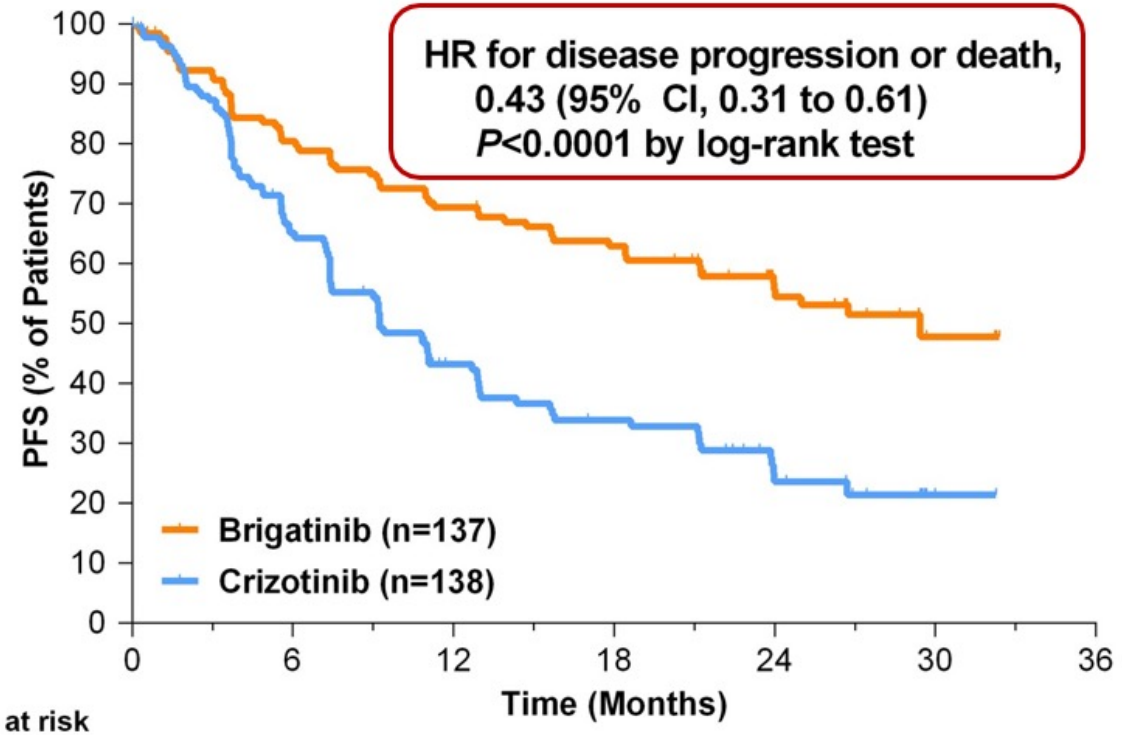
Primary Endpoint: BIRC-Assessed PFS



No. at risk

Brigatinib	137	97	84	75	39	3	0
Crizotinib	138	80	49	37	17	2	0

Investigator-Assessed PFS



No. at risk

Brigatinib	137	102	88	78	46	4	0
Crizotinib	138	82	46	35	14	1	0

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

Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=137)	59 (43)	29.4 mo (21.2–NR)	56 (46–64)
Crizotinib (n=138)	92 (67)	9.2 mo (7.4–12.9)	24 (16–32)

The CROWN study: Randomized Phase 3 Study Comparing Lorlatinib vs. Crizotinib as First-line treatment in *ALK*-positive NSCLC

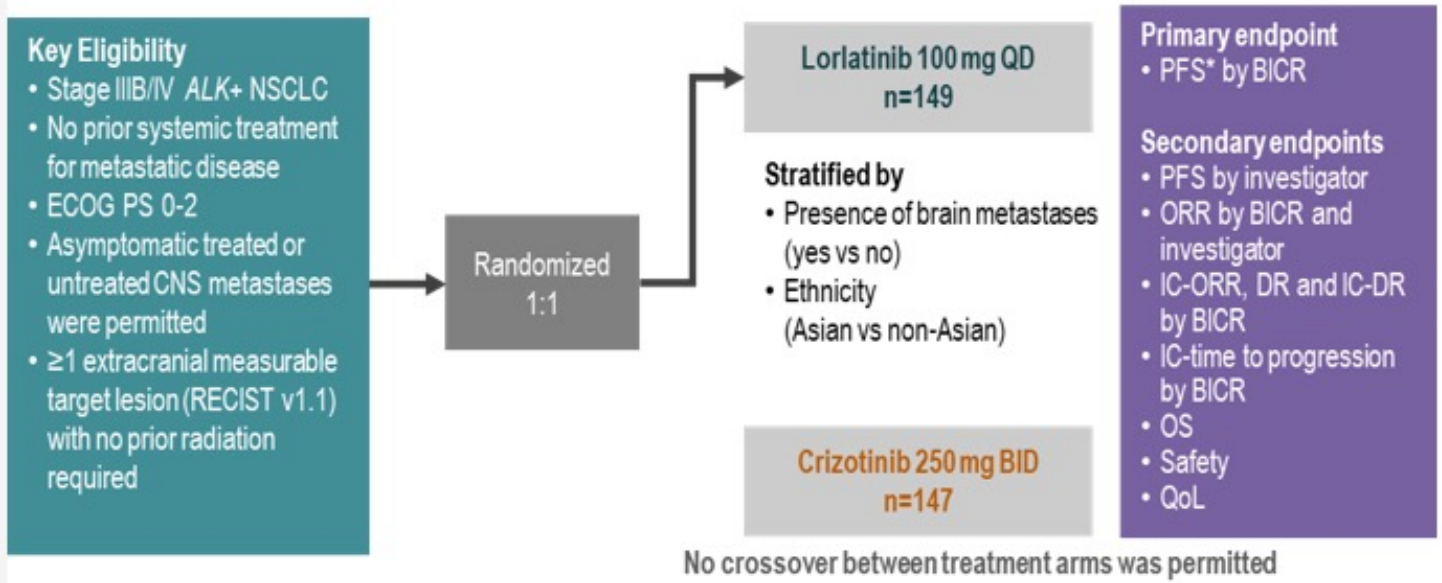
Results from a planned interim analysis

Lorlatinib (a 3rd generation ALK TKI) was designed to be:

- highly potent and selective
- efficacious against ALK kinase domain mutations found in patients who develop resistance to 1st and 2nd generation ALK TKIs
- Highly CNS penetrant

Reference: Zou et. al. *Cancer Cell* 2015

CROWN Study Design



*Defined as the time from randomization to RECIST-defined progression or death due to any cause.

BICR, blinded independent central review; DR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.
ClinicalTrials.gov number, NCT03052608

2020 ESMO Congress. Christine M. Lovly, MD, PhD.

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Summary of CROWN Efficacy Results

Drug (dose)	Clinical Trial	# of patients	CNS Mets at Baseline
Lorlatinib 100mg po qd	CROWN NCT03052608	296	Lorlatinib: 26% Crizotinib: 27%

ORR (%) (95% CI)	PFS (months, by BICR) (95% CI)	Intracranial Response Rate
Lorlatinib: 76% (68-83)	Lorlatinib: NE	Lorlatinib: 82% (57-96)
Crizotinib: 58% (49-66)	Crizotinib: 9.3 (7.6-11.1)	Crizotinib: 23% (5-54)
Odds ratio: 2.25 (1.35-3.89)	**HR: 0.28** (0.19 – 0.41)	* Patients with measurable brain metastases at baseline

2020 ESMO Congress. Christine M. Lovly, MD, PhD.

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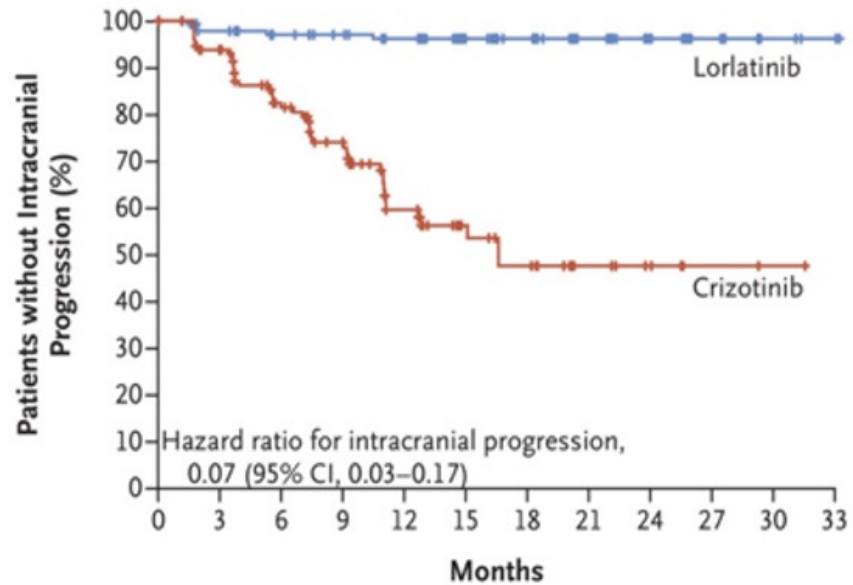
Managing ALK+ NSCLC

CROWN

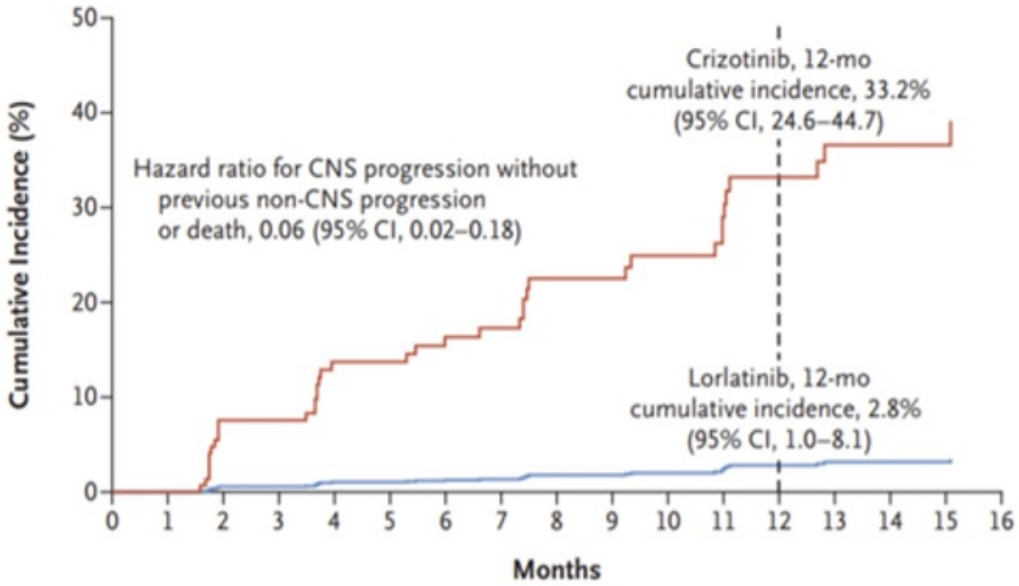
B Survival without CNS Progression



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

C Cumulative Incidence of CNS Progression as First Event



Shaw AT et al. N Engl J Med 2020; 383(21):2018-29.

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The Oncologist®

Lung Cancer

Clinical Management of Adverse Events Associated with Lorlatinib

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[a]Sarah Cannon Cancer Research Institute/Tennessee Oncology, PLLC, Nashville, Tennessee, USA; [b]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [c]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [d]Pfizer Oncology, La Jolla, California, USA; [e]Pfizer Oncology, Groton, Connecticut, USA; [f]Pfizer Oncology, New York, New York, USA; [g]Massachusetts General Hospital, Boston, Massachusetts, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Oncologist 2019

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Categorizing side effects of Lorlatinib

Hyperlipidemia

Hyper-cholesterolemia

Onset:

-4 weeks after starting lorlatinib

Treatment:

-Artorvastatin
-Rosuvastatin
-Pitavastatin

Hyper-triglyceridemia

Onset:
`4 weeks after starting lorlatinib

Treatment:

-Omega-3 fatty acid
-Ezetimibe
-Phenofibrate

Cognitive effect

Hallucinations (Auditory, Visual Olfactory)/ sleep terrors (vivid dreams)

Points:

-Self awareness and with partner/ caregiver

-Culture appropriate hallucinations

-vivid dreams (dreams of being chased, moved legs and arms while dreaming

-early onset (days of starting lorlatinib)
-transient

-if persistent, dose hold, rarely needs dose reduction

Impulse control problem

Points:

-self-awareness
-increase chance if there is CNS radiation
-avoid high stress work and personal relationship situations
-permanent dose reduction if stressful situation not avoidable

Slow speech

Points:

-self-awareness

-usually no social sequalae

-if slow speech affects "activity of daily living" (i.e. profession actor) then dose reduce

Personality changes/ forgetfulness

Points:

-Increase risk with age and/or previous brain radiation

-self-awareness

-care-giver should also aware of this possibility

-need permanent dose reduction

Mood effect

Depression/ suicidal ideation

Points:

-be aware of possibility

-discuss with patient prior to starting lorlatinib

-very very rare occurrence

-no documentation of any successful suicide attempt post-marketing

Euphoria

Points:

-be aware of possibility

-increase appetite

-can lead to weight gain

-usually does not require dose modifications

Physical symptoms

Edema/ weight gain

Points:

-be aware of possibility

-onset usually months after starting lorlatinib

-can again over 20% of baseline weight

-Furosemide does not alleviate edema

-thigh-high compression stocking
-dose interruption for up to 14 days or dose reduction

Peripheral neuropathy

Points:

-not classical chemo-induced peripheral neuropathy

-wrists, joints predominance

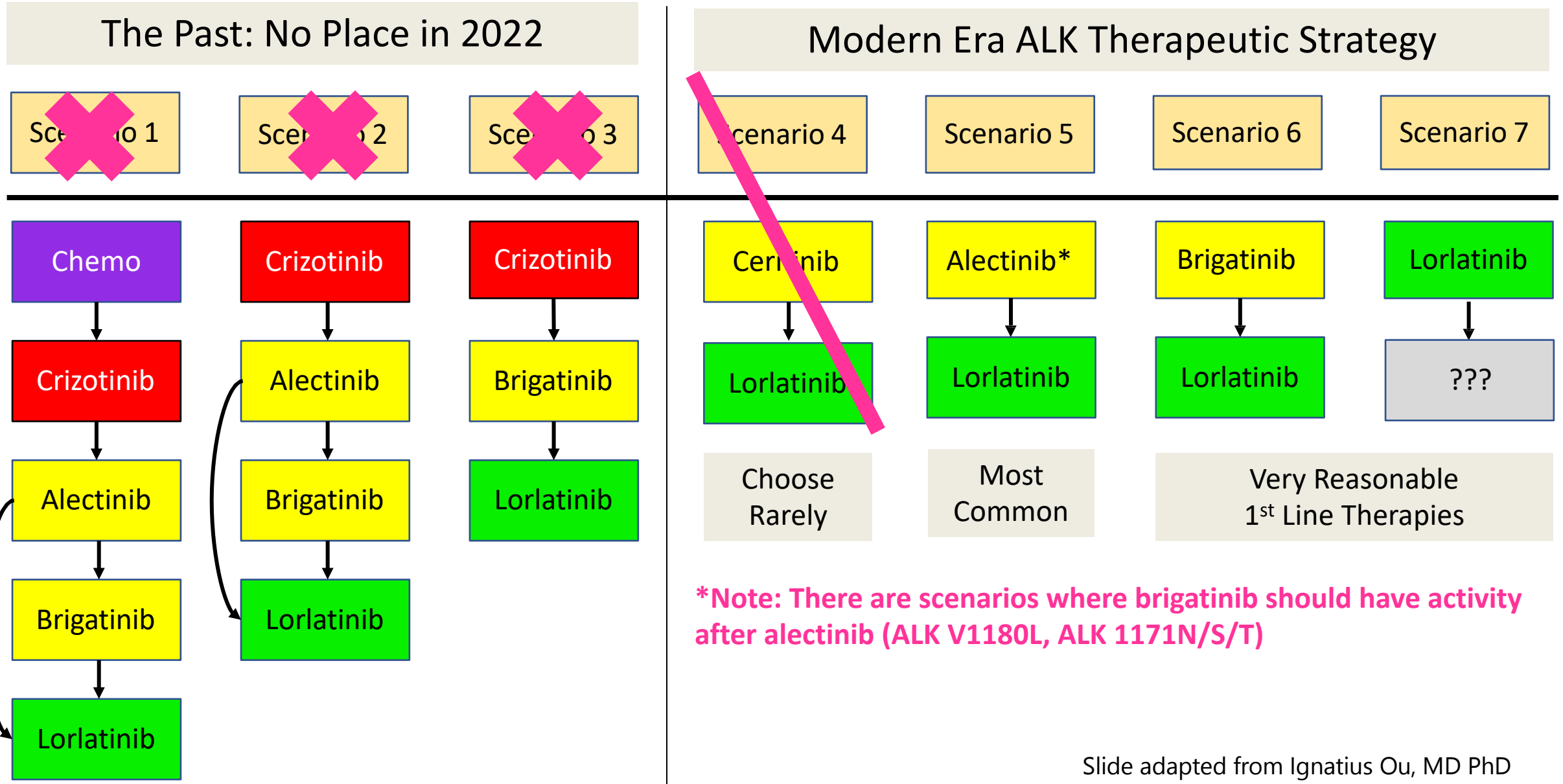
-be aware of possibility and difference

-onset usually weeks or months after starting lorlatinib

-? related to peripheral edema

-dose interruption for up to 14 days

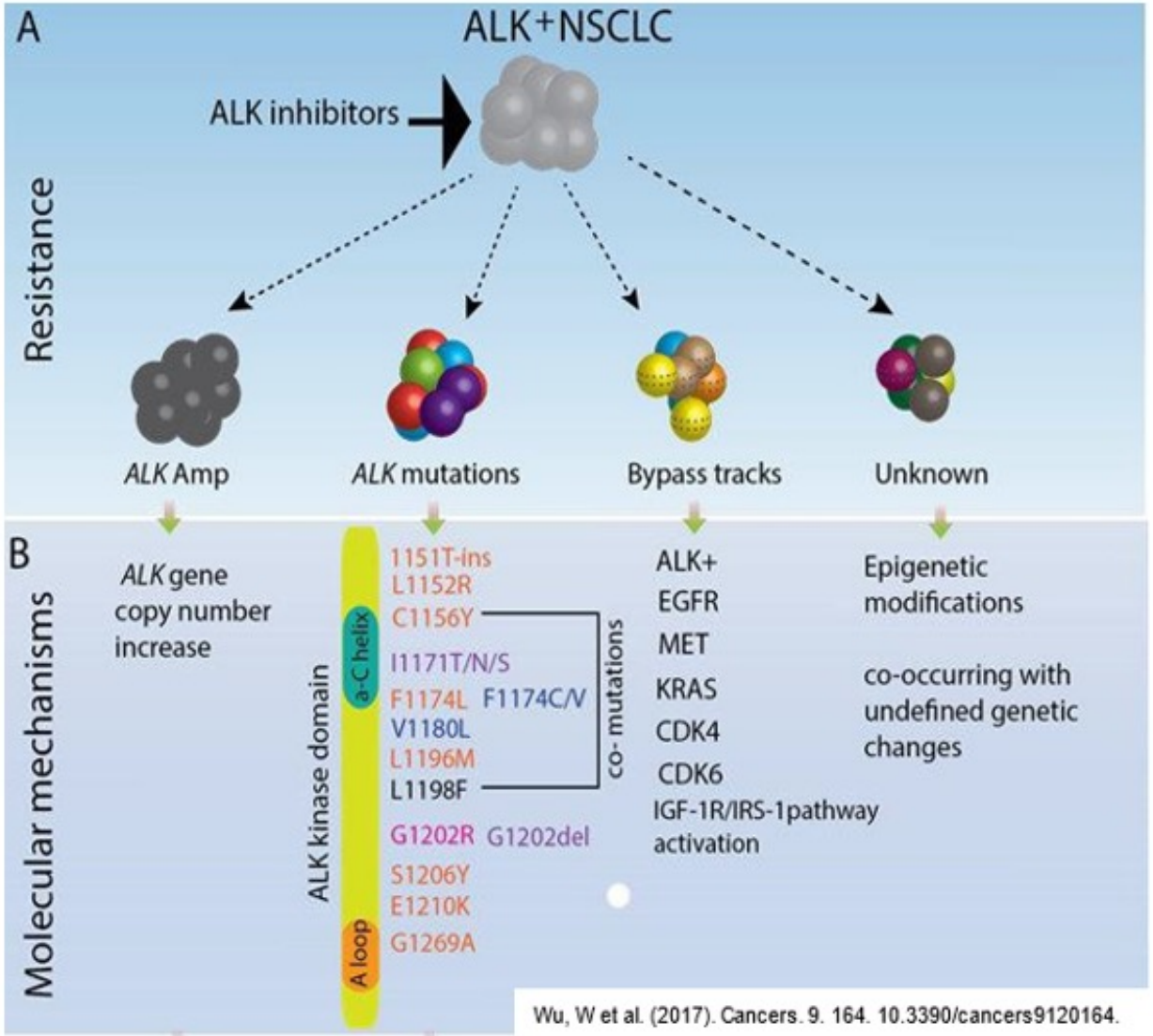
Different Clinical Scenarios for Treatment of ALK+ NSCLC Patients



*Note: There are scenarios where brigatinib should have activity after alectinib (ALK V1180L, ALK 1171N/S/T)

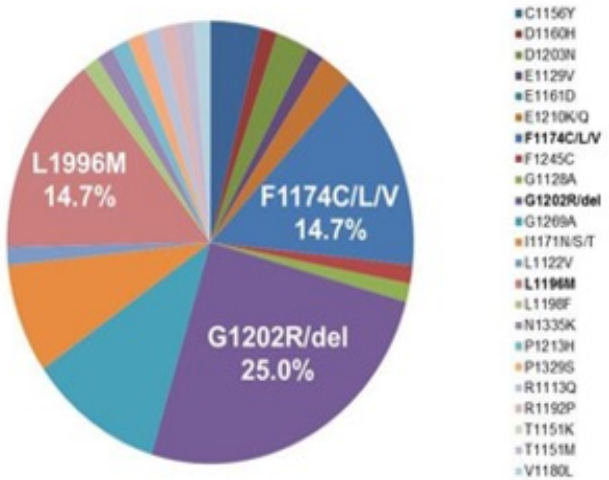
Slide adapted from Ignatius Ou, MD PhD

Resistance to ALK TKI Therapy



Wu, W et al. (2017). Cancers. 9. 164. 10.3390/cancers9120164.

ALK Kinase Domain mutations –
Data from the Lorlatinib phase 1/2 trial

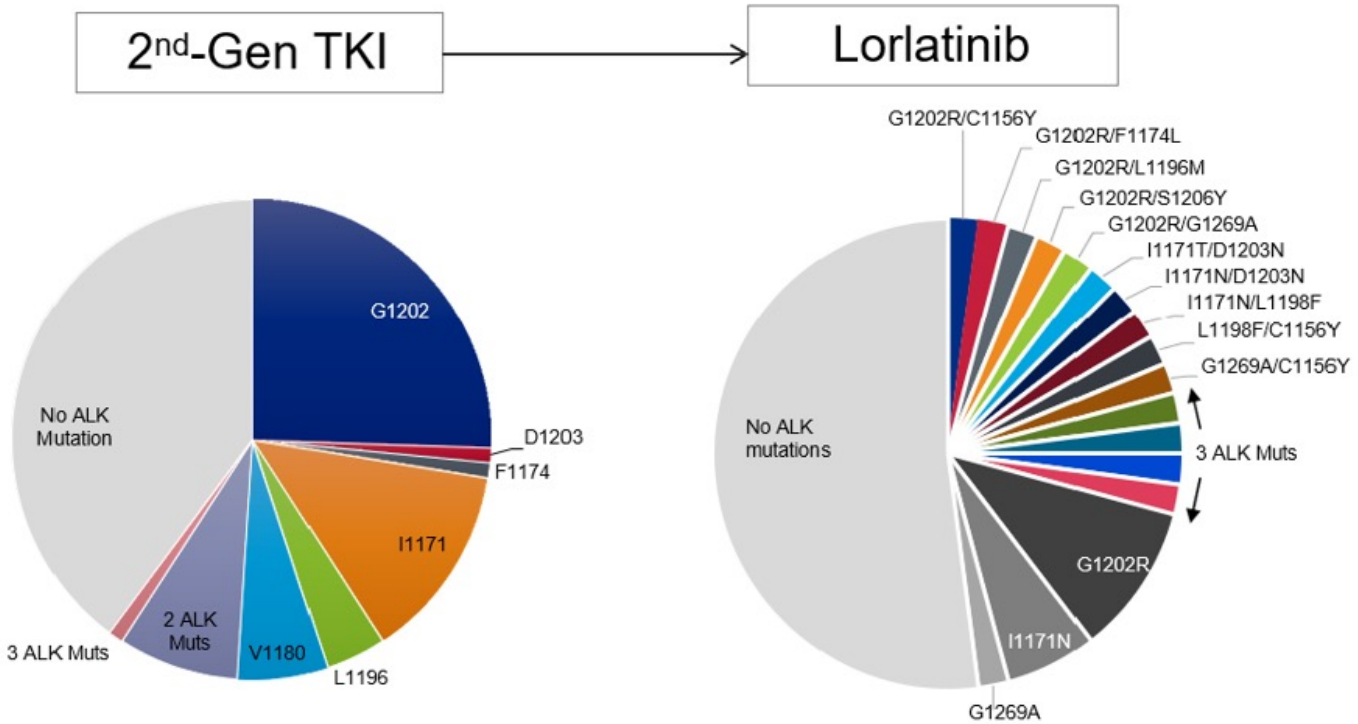


cfDNA analysis (EXP 2-5 from the Lorlatinib phase 1/2 trial):
- 45/190 patients (24%) with 1 or more ALK kinase domain mutations
- 75 mutations detected (used for the frequency denominator)

Shaw AT AACR 2018
Lovly C AACR 2018

Dr. Christine Lovly. 2020 Presidential Symposium, WCLC; August 8, 2020.

Overcoming ALK-Independent ("Off-Target") Resistance



- Off-target mechanisms of resistance occur in a **significant proportion** of cases following 2G/3G ALK TKIs (up to 75% following lorlatinib used later-line)
- Certain off-target resistance mechanisms are known and may be clinically **actionable**

Shiba-Ishii A et al., biorxiv 2021. doi: https://doi.org/10.1101/2021.07.16.452681

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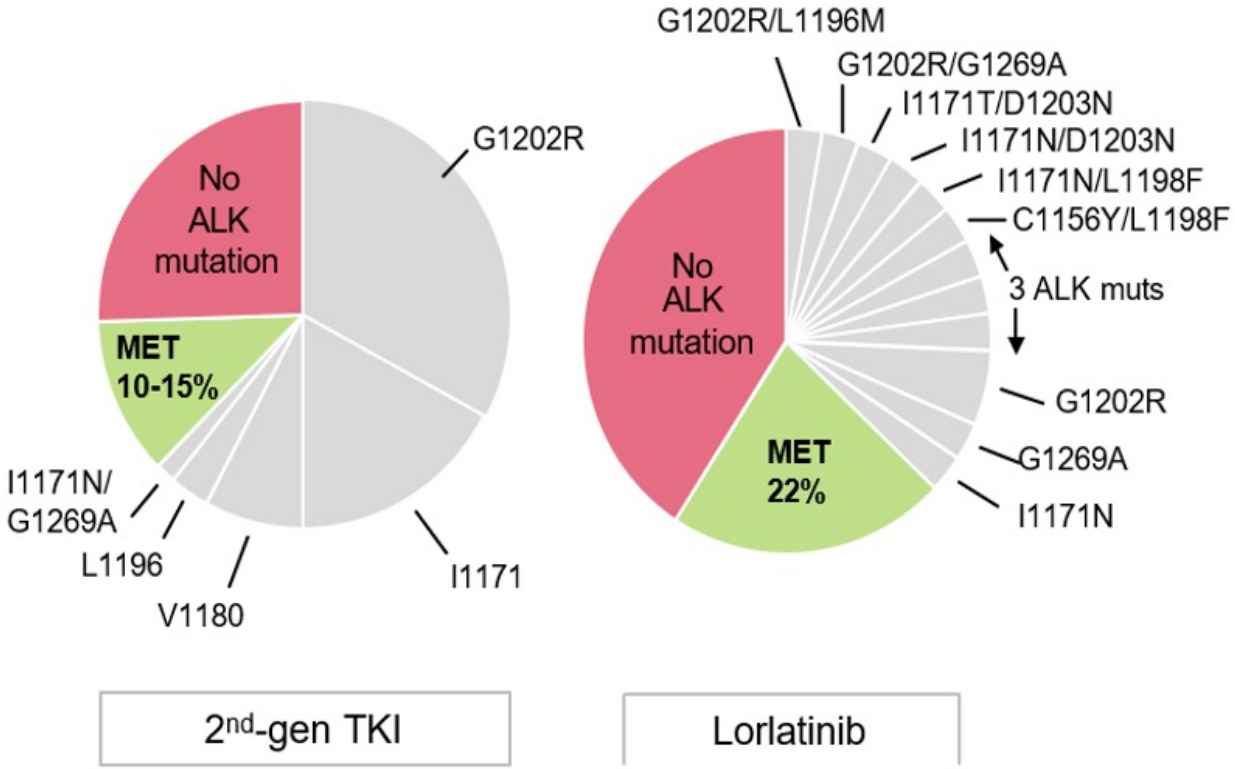
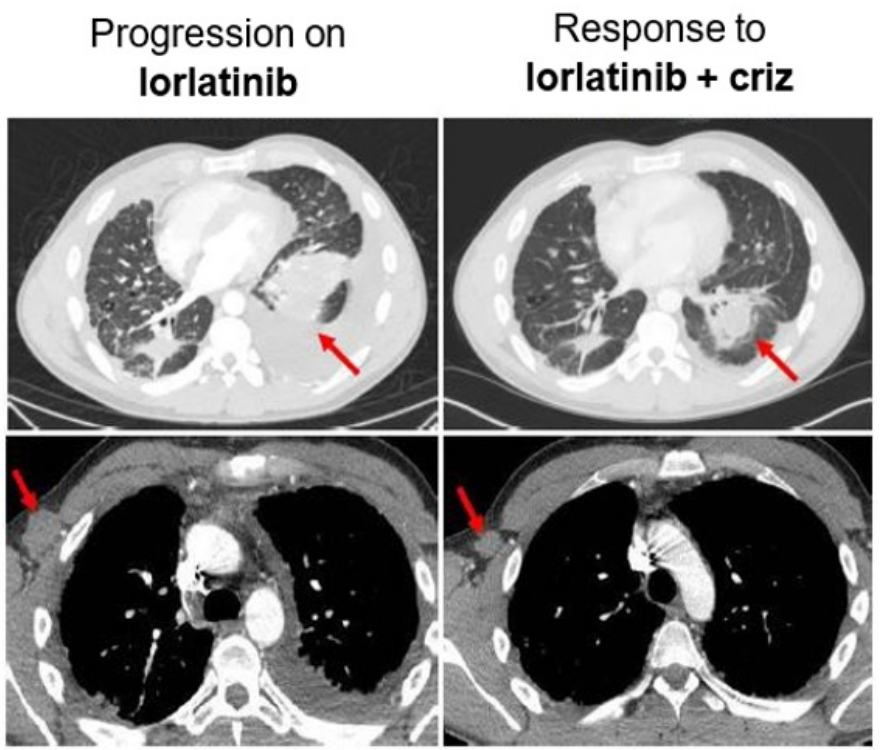
MET Amplification Post-2G/3G ALK TKIs





Dagogo-Jack I et al. Clin Cancer Res 2020;26:2535-45

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Overcoming ALK-Independent Resistance: Combinatorial Strategies

Combination	ALKi Anchor	Partner	Sponsor	ClinicalTrials.gov
ALKi+METi	Lorlatinib	Crizotinib	MGH	NCT04292119
ALKi+MEKi	Alectinib	Cobimetinib	MGH	NCT03202940
	Brigatinib	Binimetinib	UCSF	NCT04005144
	Ceritinib	Trametinib	UCSF	NCT03087448
	Lorlatinib	Binimetinib	MGH	NCT04292119
ALKi+SHP2i	Lorlatinib	PF-07284892	Pfizer	NCT04800822
	Lorlatinib	TNO155	MGH	NCT04292119
ALKi+mTORi	Ceritinib	Everolimus	MD Anderson	NCT02321501
ALKi+VEGFi	Brigatinib	Bevacizumab	City of Hope	NCT04227028

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Emerging ALK Inhibitors and Combinations

- On-target resistance to 3G ALK TKI lorlatinib is mediated by compound *ALK* kinase domain mutations; novel 4G ALK TKIs with potency against double/triple ALK mutants are therefore being developed.

- **TPX-0131** is a 4G compact, macrocyclic ALK inhibitor with preclinical potency against *ALK* wild-type, G1202R, L1198F, and a broad range of *ALK* compound mutations, currently phase 1 testing (FORGE-1).

- **NVL-655** is a 4G highly selective and CNS-penetrant ALK inhibitor with preclinical potency against *ALK* wild- type, G1202R, and G1202R-based compound mutations, anticipated to enter phase 1 testing in 2022.

- Off-target resistance to next-generation ALK TKIs is common.

- Clinical trials of **combination regimens** to overcome some of the known off-target mechanisms of resistance to ALK TKIs (e.g., ALKi+METi, ALKi+MEKi, ALKi+SHP2i) are enrolling patients with goals to assess safety and preliminary efficacy.

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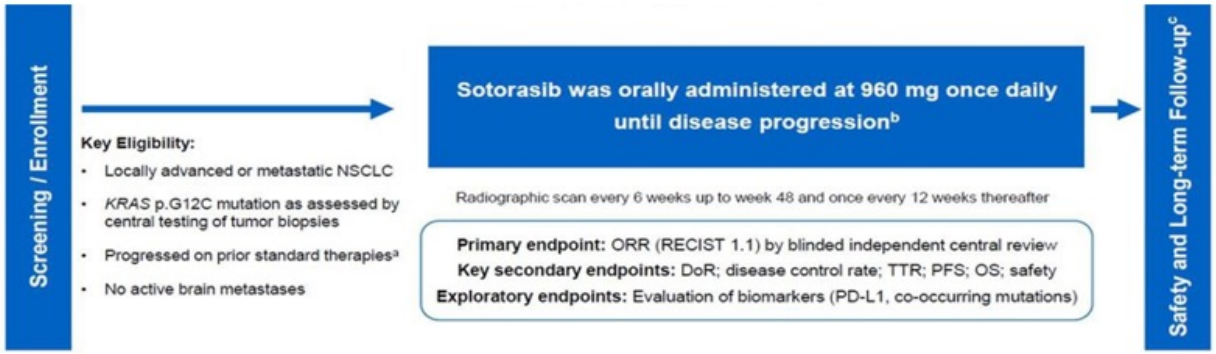
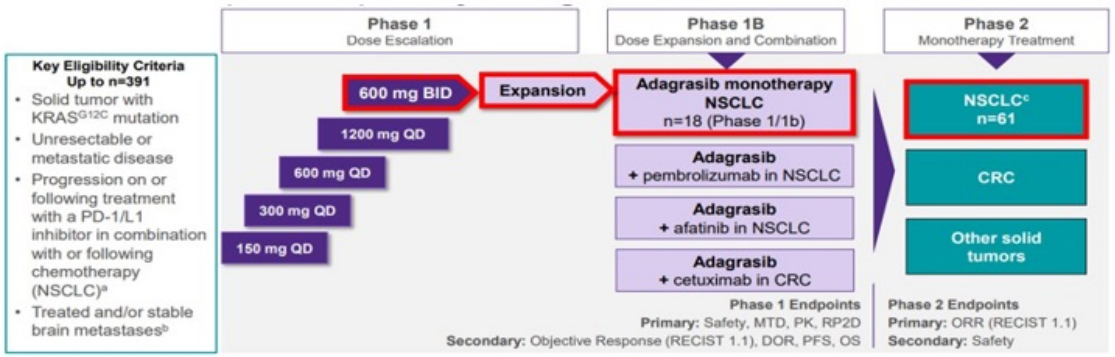
K-Ras^{G12C} **Pathway**

AMG510 Sotorasib



MRTX849 Adagrasib



Li et al, WCLC 2020; Riely et al, ELCC 2021

Rebecca S. Heist, MD. IASLC 2022 Targeted Therapies in Lung Cancer Meeting, Feb 22-26, 2022.

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Toxicity Profile→ Sotorasib and Adagrasib

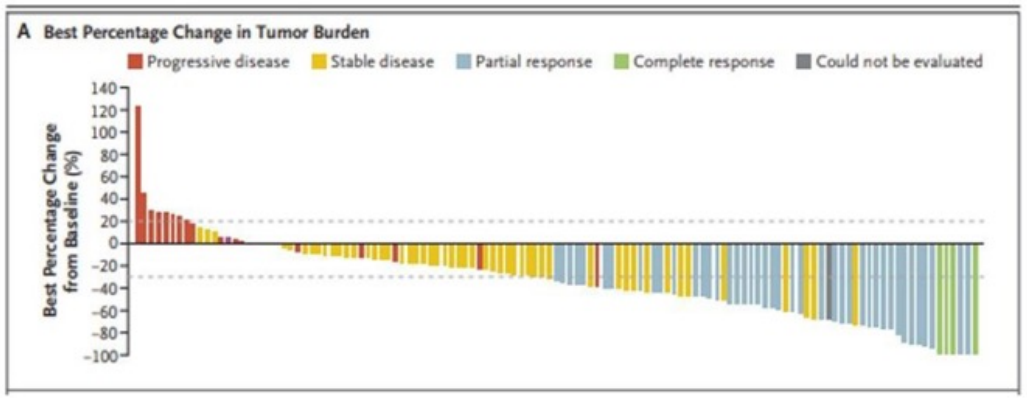
Treatment Related AEs	Sotorasib Phase II (n= 126)		Adagrasib Phase I/II (all cohorts pooled, n = 110)	
Treatment Related AEs Any Grade ≥ Grade 3 Leading to treatment D/C	69.8% 20.6% 7.1%		85% 32% 4.5%	
Most Common TRAEs				
	Any Grade	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Nausea	19%	0	54%	2%
Diarrhea	31.7%	4%	51%	0
Vomiting	7.9%	0	35%	2%
Fatigue	11.1%	0	32%	6%
ALT increase	15.1%	6.3%	20%	5%
AST increase	15.1%	5.6%	17%	5%

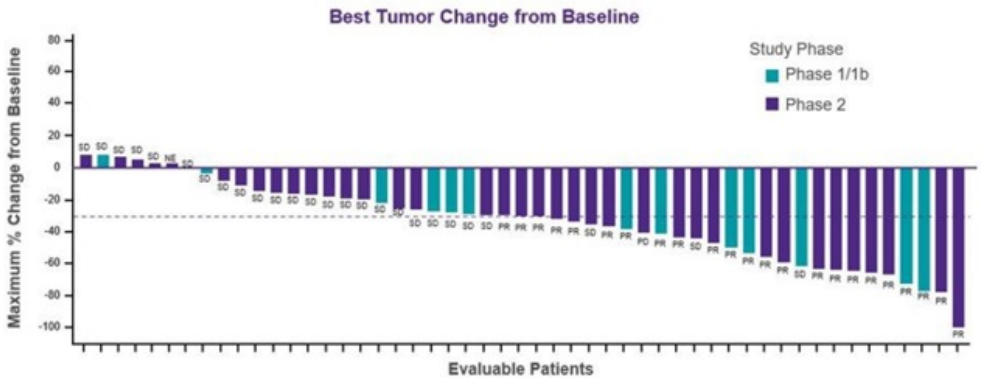
Skoulidis et al, NEJM 2021; Riely et al, ELCC 2021

Rebecca S. Heist, MD. IASLC 2022 Targeted Therapies in Lung Cancer Meeting, Feb 22-26, 2022.

Efficacy of KRasG12C Inhibitors:

Drug	Phase	n	RR	DCR	PFS	OS
Sotorasib	II	126	37.1%	80.6%	6.8 mo	12.5 mo
Adagrasib	I/II	51	45%	96%	Pending data	





Skoulidis et al, NEJM 2021; Riely et al, ELCC 2021

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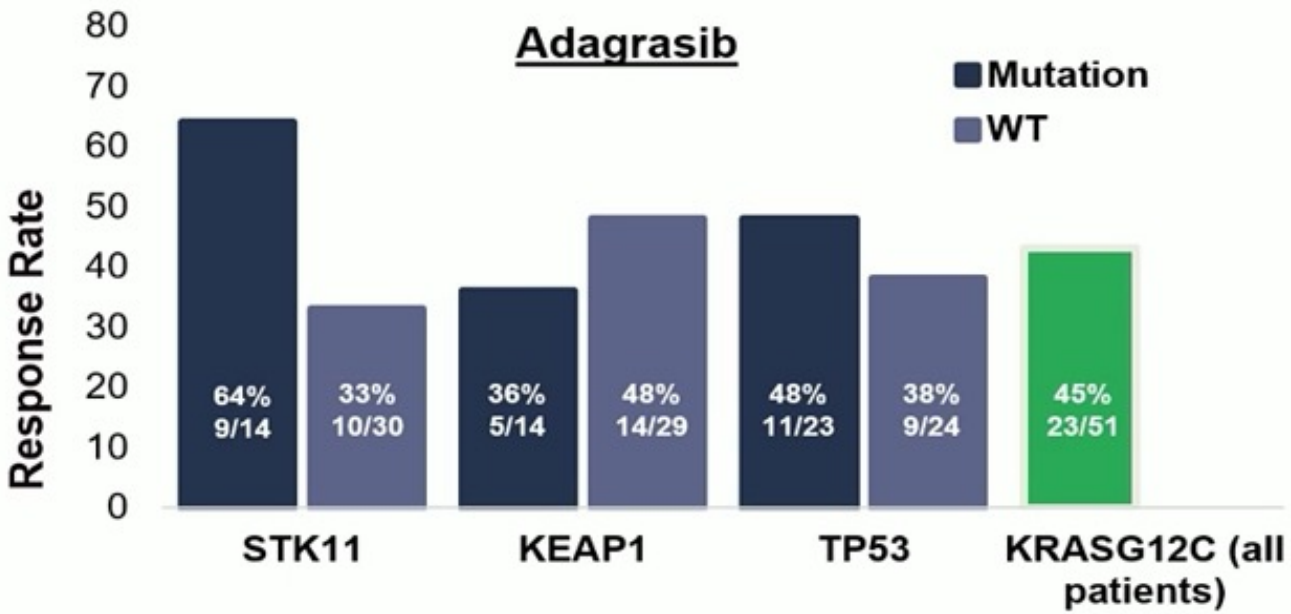
K-RAS G12C Inhibitors: Difficult-to-Treat Subsets

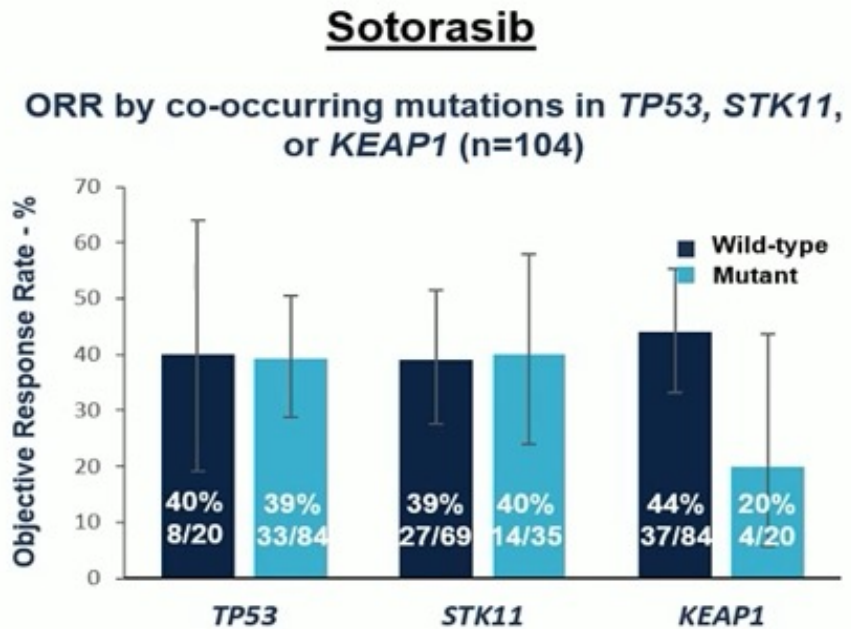
STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in *KRAS*-Mutant Lung Adenocarcinoma

Skoulidis et al, Ca Discovery 2018

KEAP1/NFE2L2 Mutations Predict Lung Cancer Radiation Resistance That Can Be Targeted by Glutaminase Inhibition

Binkley et al, Ca Discovery 2020





➡ G12C inhibitors appear to work in subsets where other treatment modalities struggle

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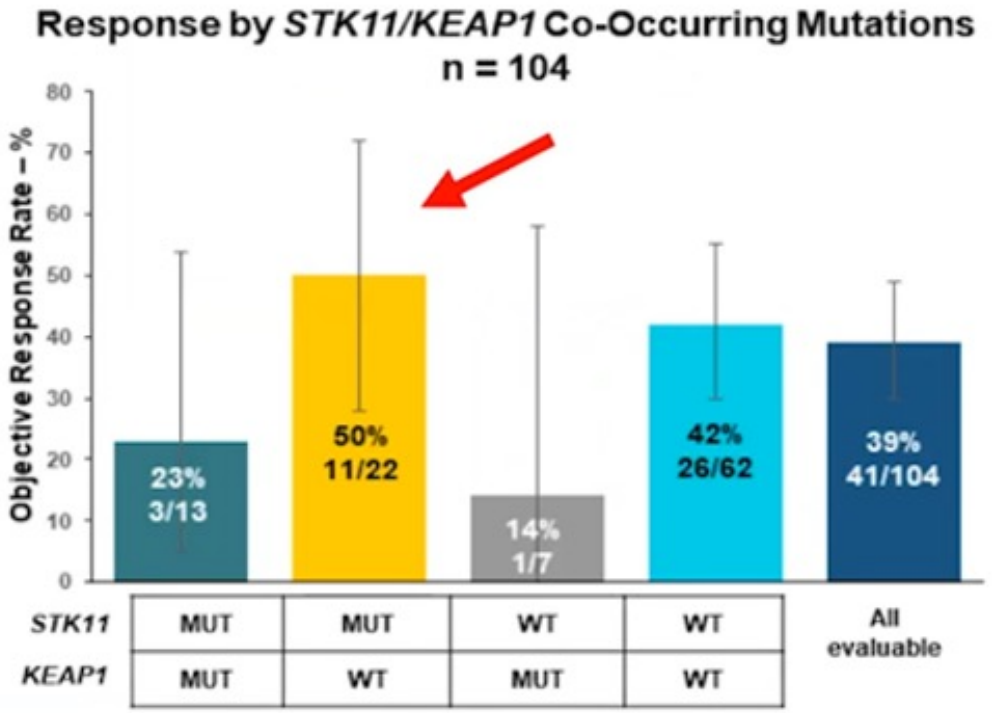
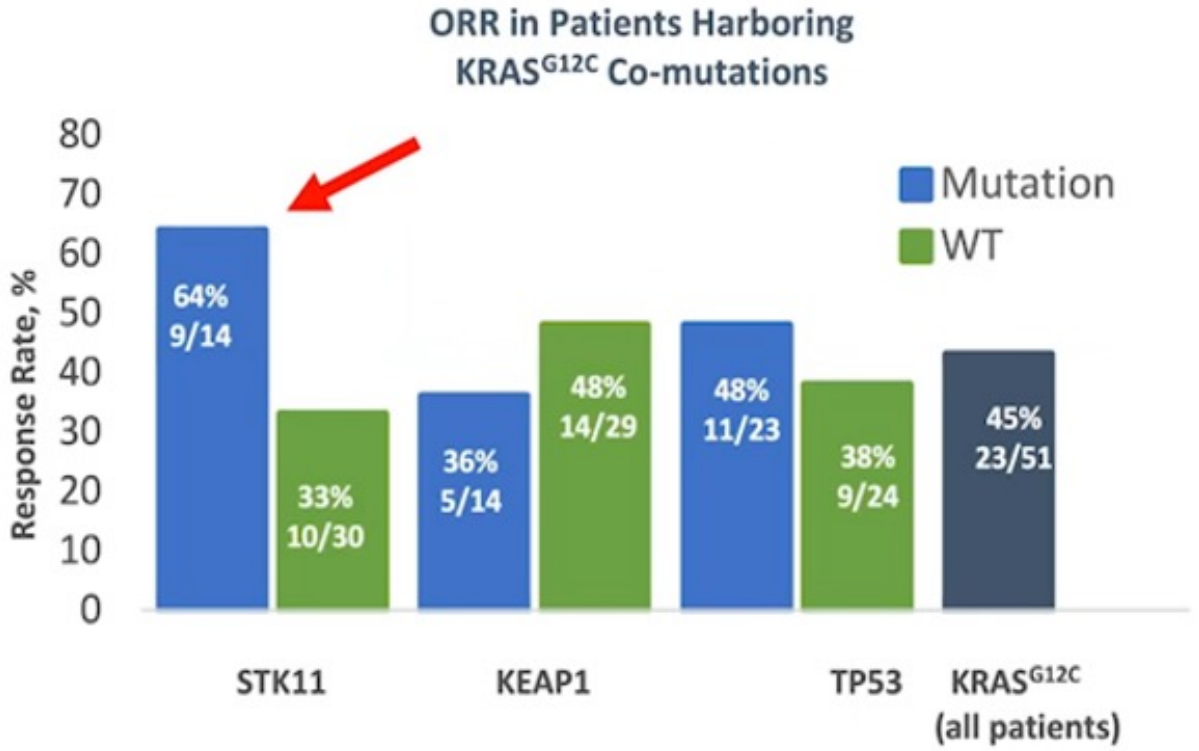
KRAS G12C inhibitors active in patients with STK11mt/KRASmt tumours

18th Annual
MIAMI CANCER MEETING
Breakthrough to Excellence in Cancer Care: Digging More Into Personalized Medicine
JW MARRIOTT MIAMI | MIAMI, FLORIDA
APRIL 1-3, 2022





Li et al PS01.07 WCLC 2020; Janne et al 32nd ENA Symposium 2020

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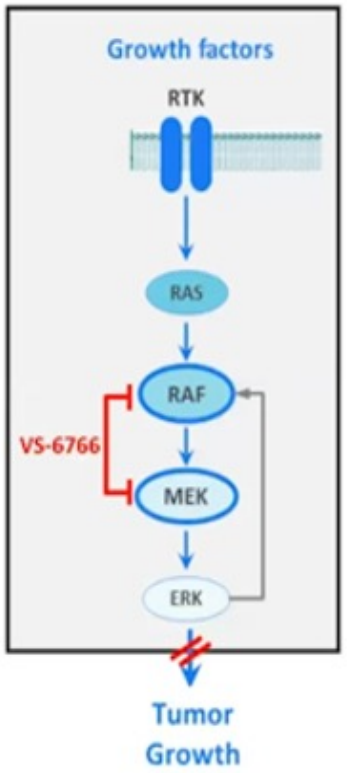
Ongoing KRAS G12C inhibitor combinations

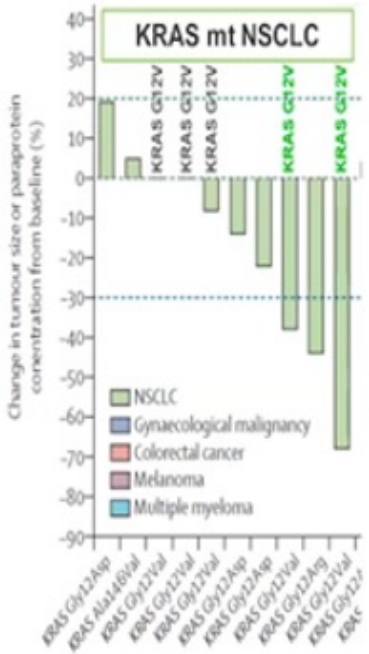
	Sotorasib	Adagrasib	GDC-6036	JDQ-443	D-1553	mRNA-5671/V941
Anti-PD-1/L-1	✓	✓	✓	✓	✓	✓
Shp2 inhibitor	✓	✓	✓	✓		
EGFR inhibitor	✓	✓	✓			
SOS-1 inhibitor		✓				
MEK inhibitor	✓					
VEGF inhibitor	✓		✓			
Chemotherapy	✓				✓	
mTOR inhibitor	✓					
CDK inhibitor	✓	✓				

Updated from Dr. Greg Riely, IASLC TTLC2021; clinicaltrials.gov

VS-6766 (RAF/MEK inhibitor) + Defactinib (FAK inhibitor) – activity in *KRAS* G12V mutant cancers



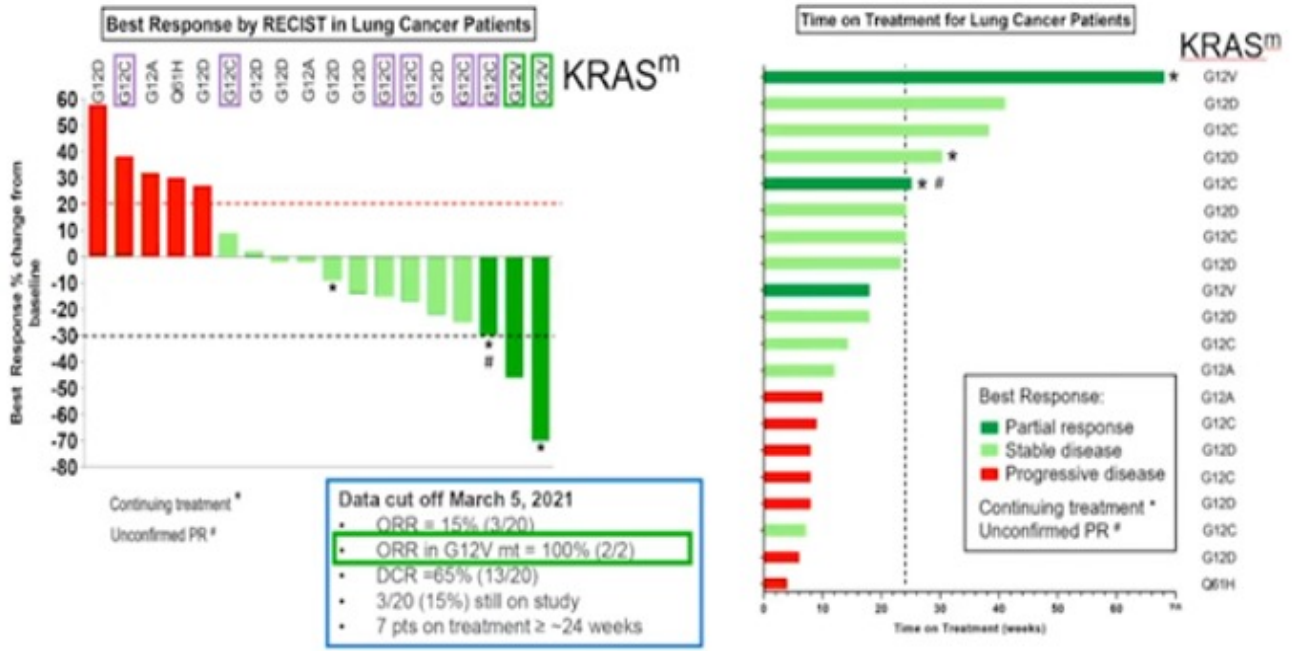
Decreases ERK signaling



Single agent activity VS-6766

Confirmed responses in 2/2 patients with KRAS-G12V NSCLC

Tumor reduction in 4/6 patients with KRAS-G12C NSCLC



VS-6766 + Defactinib

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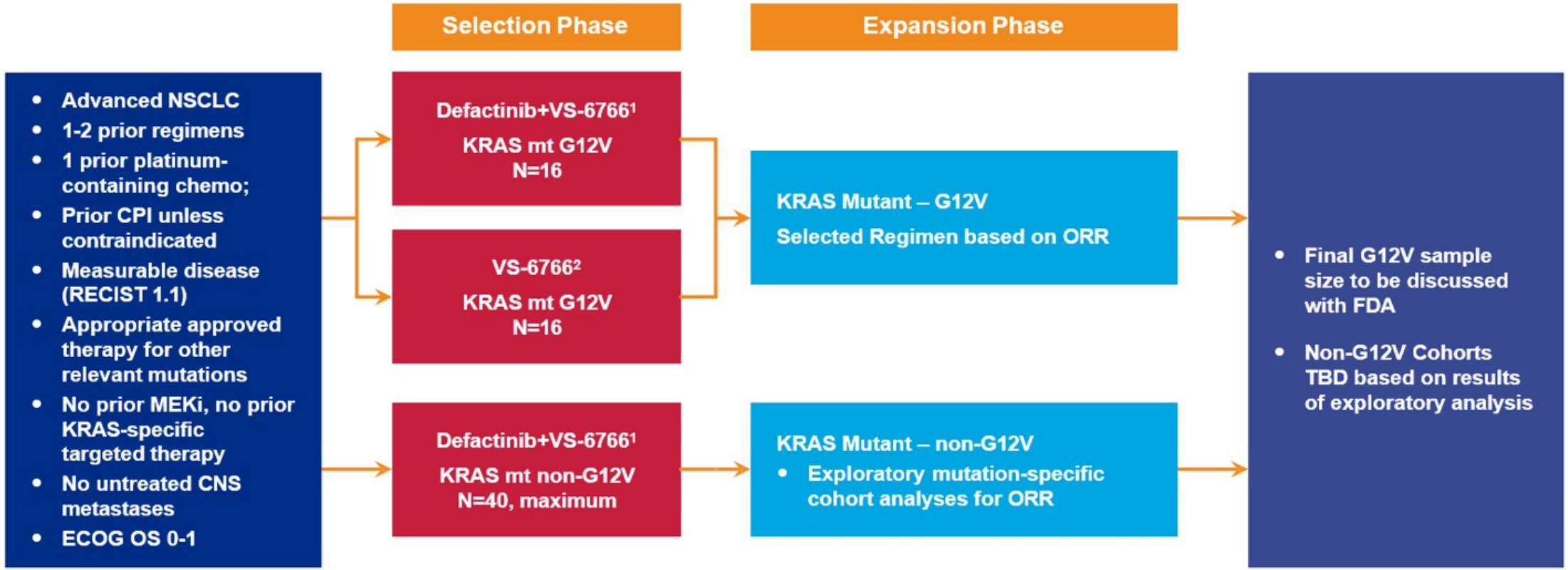
Guo et al Lancet Oncol 2020; Krebs et al AACR 2021; Pachter et al WCLC2021 P52.05

Phase 2 Trial of VS-6766+/- Defactinib in KRAS mutant NSCLC



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Thank You !

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Conclusions

- Single agent Osi is standard of care as 1st line treatment for EGFR+ lung cancers.
- Addition of VEGF inhibition to Osi of unclear benefit with randomized studies ongoing.
- Addition of chemo to OSI being assessed in FLAURA2 to see if PFS/OS benefit redemonstrated with Osi.
- Start with a 2nd/3rd generation ALK TKI-choose based on safety, tolerability, efficacy, cost, convenience.
- At extra-CNS progression, consider re-biopsy and re-analysis ALK mutation status. If no actionable change→ pemetrexed-based chemo (add in vs swap out) +/- local ablative therapy.
- KRAS is druggable; studies also start to understand co-mutations effects on KRAS G12C mutant tumors (KEAP1, STK11).

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