EGFR and ALK Resistance

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Objectives

I. Mechanisms of EGFR Resistant NSCLC:

A. Possible Actionable Genomic Alteration

B. Histologic Transformation

II. Management of EGFR Resistant NSCLC

III. Mechanisms of ALK Resistant NSCLC

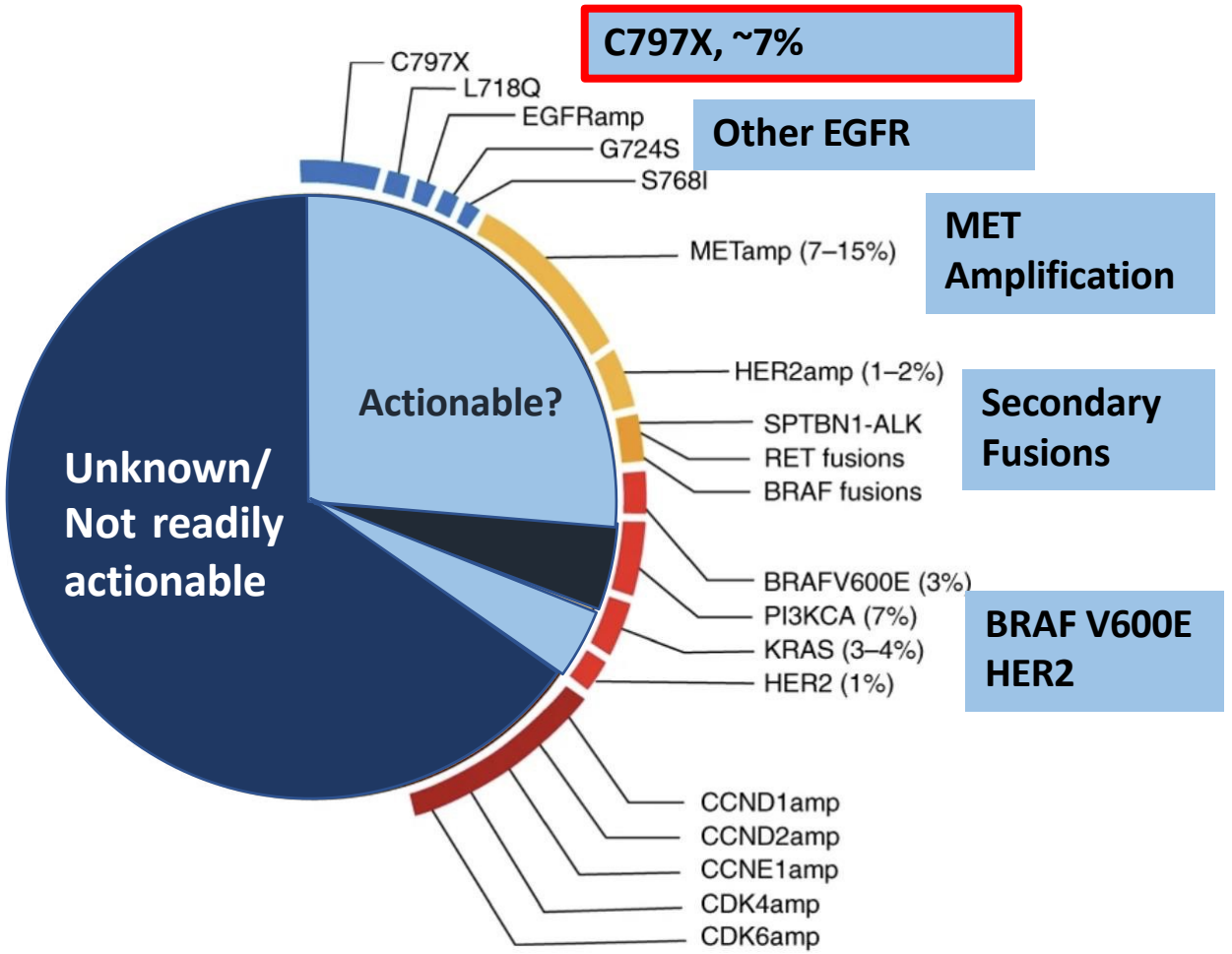
IV. Management of ALK Resistant NSCLC

EGFR Resistant NSCLC

I. Mechanism of EGFR Resistant NSCLC:

- Acquired resistance to 3rd generation EGFR TKIs is **heterogenous**
- Dominant mechanisms include **EGFR C797X mutations** and **MET amplification**
- Fourth generation EGFR TKIs are in development with predicted activity against C797X
- EGFR + MET-targeted therapies are active for high-level acquired MET amplification
- While less common, TKI combinations offer promise for acquired secondary oncogenic driver mutations

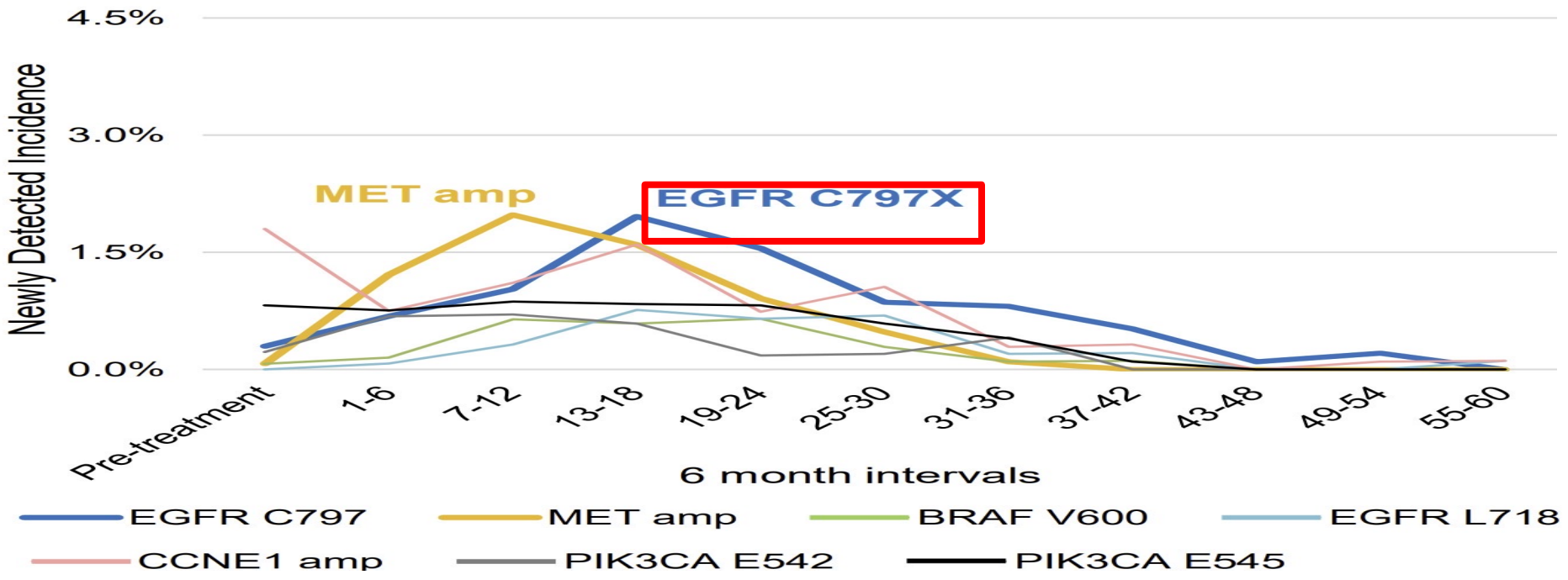
Possible Actionable Genomic Alteration



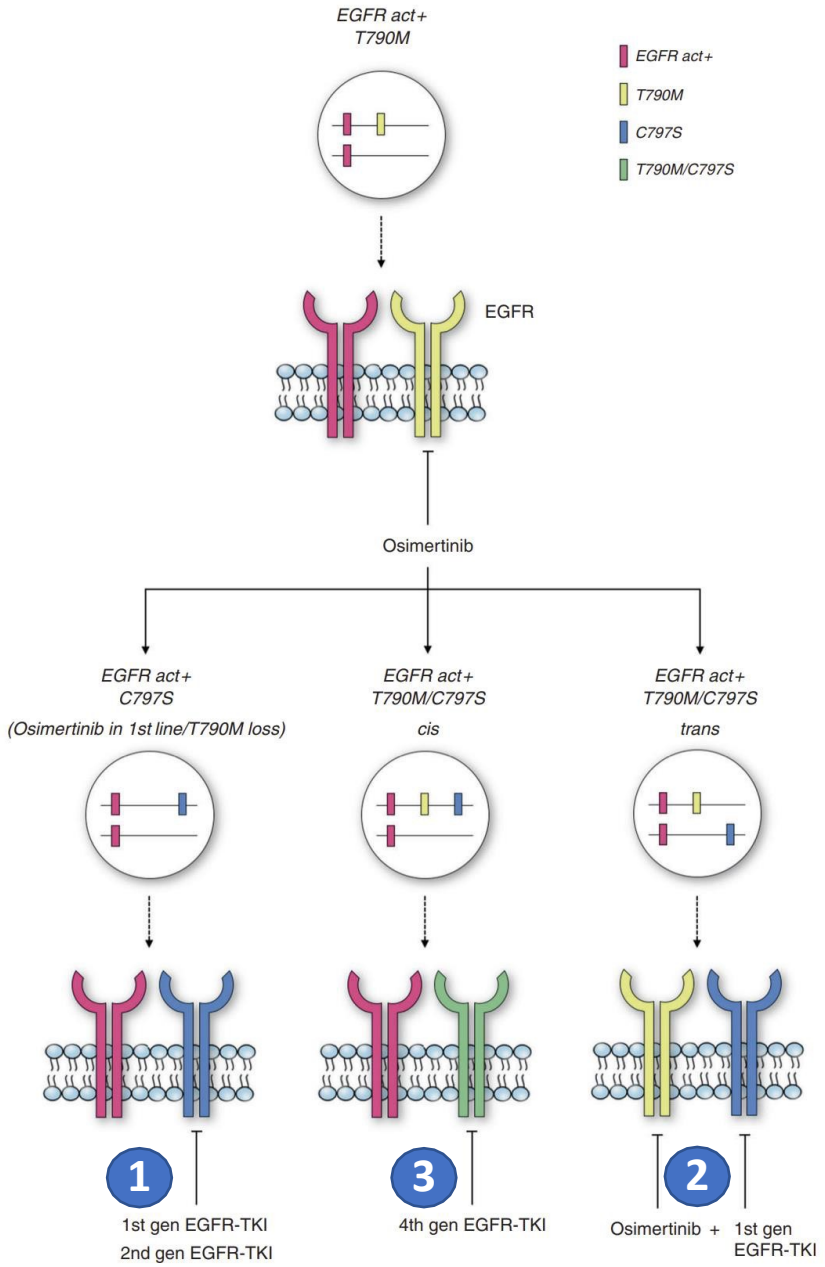
Leonetti et al. BJC. 2019.

What fraction of acquired resistance is associated with an actionable genomic alteration?

cfDNA, 1L Osimertinib



Ramalingam et al, JTO, 2022, MA07.03



EGFR C797X Mutations

1. **<u>EGFRm + EGFR C797X</u> "Double Mutant"**
   e.g. Acquired Resistance to 1L Osimertinib

   Reported Sensitivity to 1st Gen EGFR TKIs (geftinib, erlotinib)

2. **<u>EGFRm + EGFR T790M + EGFR C797X</u> "Triple Mutant" *<u>in trans</u>***
   e.g. Acquired Resistance to sequential 1st and 3rd generation EGFR TKIs.

   Reported sensitivity to combination osimertinib + gefitinib

3. **EGFRm + EGFR T790M + EGFR C797X "Triple Mutant" *<u>in cis</u>***
   Resistant to all approved EGFR TKIs
   Requires a 4th generation EGFR TKI

Leonetti et al. BJC. 2019

C797S-Active Compounds in Development: Preclinical Data

Compound	Del19	L858R	Del19/ T790M	L858R/ T790M	Del19/ C797S	L858R/ C797S	Triple Mutant	Other	CNS?	Status
BLU-945	-	X	X	X	-	X	X		X	Phase 1/2 (NCT04862780)
BLU-701	X	X	-	-	X	X	X		X	Discontinued
BLU-525	X	X	-	-	X	X	X		X	Preclinical
BDTX-1535	X	X	-	-	X	X	X	Uncommon	X	Phase 1 (NCT05256290)
THE-349	X	X	X	X	X	X	X		X	Preclinical
H002	X	X	X	X	X	X	X		X	Phase 1/2 (NCT05552781)
BAY 2927088	X	X			X	X		Ex20ins		Phase 1 (NCT05099172)
JIN-A02	X	X	X	X	X		X		X	Phase 1/2 (NCT05394831)
BBT-176	X	X	X		X	X	X		X	Phase 1/2 (NCT04820023)

Predicted Not Active Predicted Active No available data

Shum et al, AACR 2022; Tavera-Mendoza et al ENA 2022 #177; Lucas et al. ENA 2022. Abstract #64; Zhang et eal. ENA 2022 #236; Siegel et al. ENA 2022 #17; Lim et al ESMO 2021; Yun et al ESMO 2022 #999P

BLU-945 SYMPHONY Phase I/II Study

	1G	3G	Next generation		Potential combinations	
EGFR mutational coverage[a]	Gefitinib	Osimertinib	BLU-701	BLU-945	BLU-945 + osimertinib	BLU-701 + BLU-945
L858R (LR)						
ex19del						
EGFRm / T790M						
LR / C797S						
ex19del / C797S						
EGFRm / T790M / C797S						

IC_{50} ≤10 nM IC_{50}>50 nM

Key eligibility
- Age > 18 years
- Metastatic *EGFRm* NSCLC
- Prior treatment with > 1 TKI
- No known additional tumor drivers
- ECOG PS 0–1

Monotherapy Escalation[a,b]
- 25–400 mg (n=33)
- 600 mg dosing ongoing
- MTD not reached

Combination Escalation[c]
BLU-945 + Osimertinib
Planned starting dose
- 80 mg Osi + 200 mg BLU-945

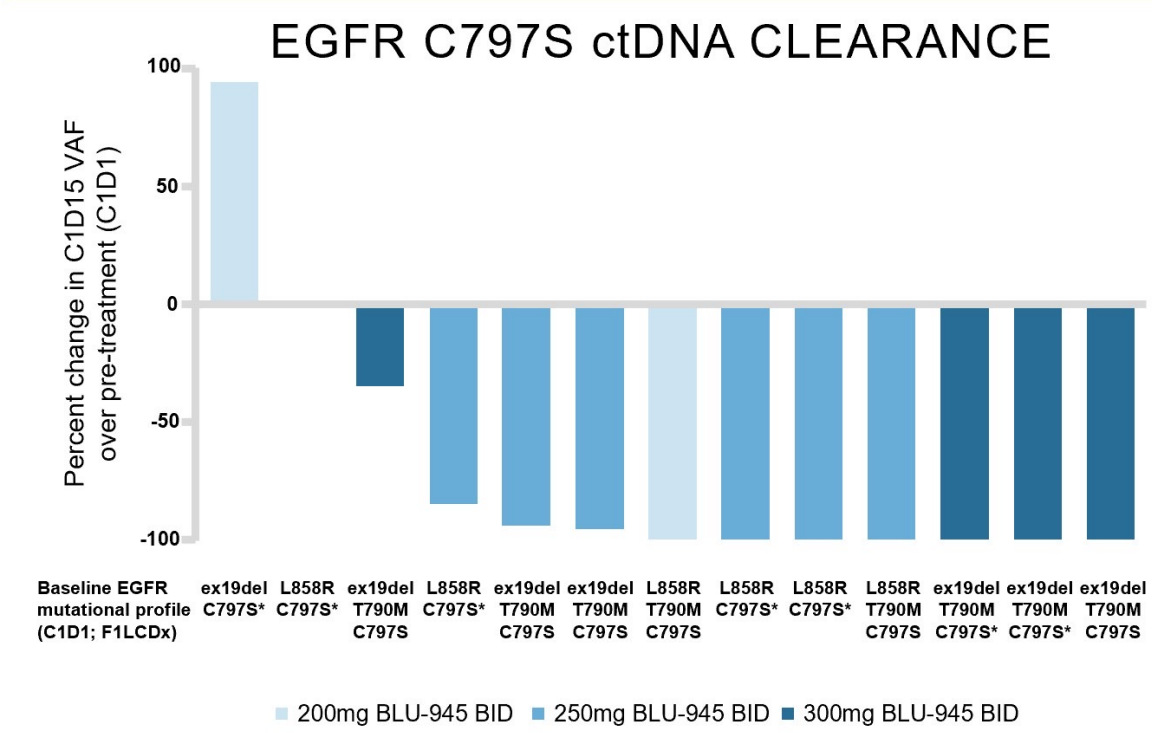
Primary endpoints
MTD, RP2D, Safety

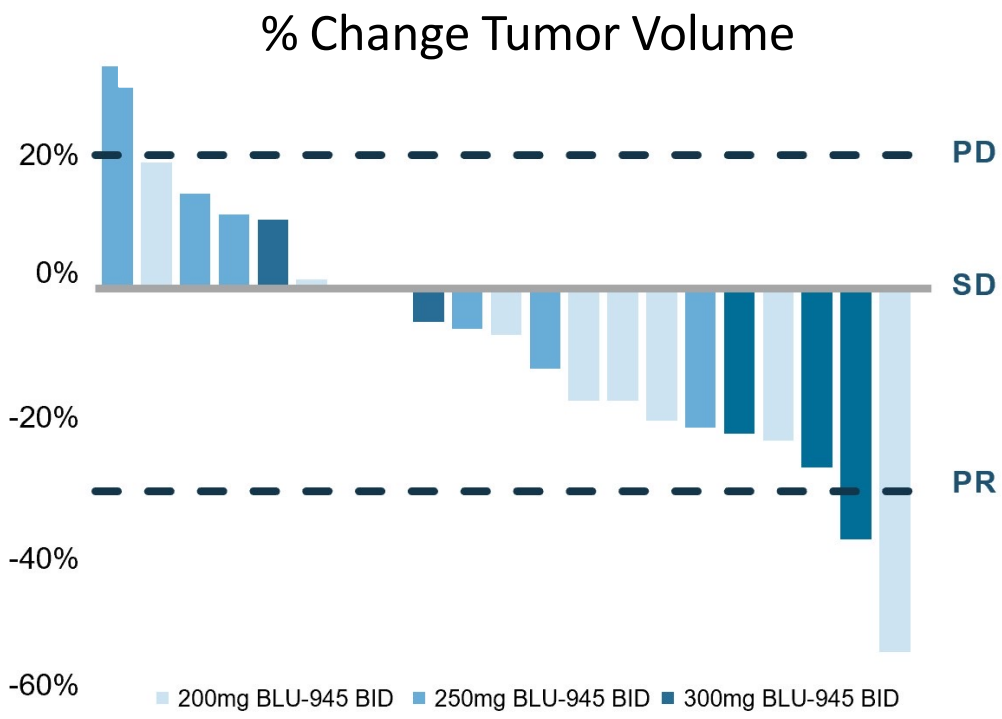
Key secondary endpoints
ctDNA kinetics, PK, ORR
DUSP6 and SPRY4 modulation

→ BLU-945 MONOTHERAPY EXPANSION COHORTS

→ BLU-945 + OSIMERTINIB EXPANSION COHORTS

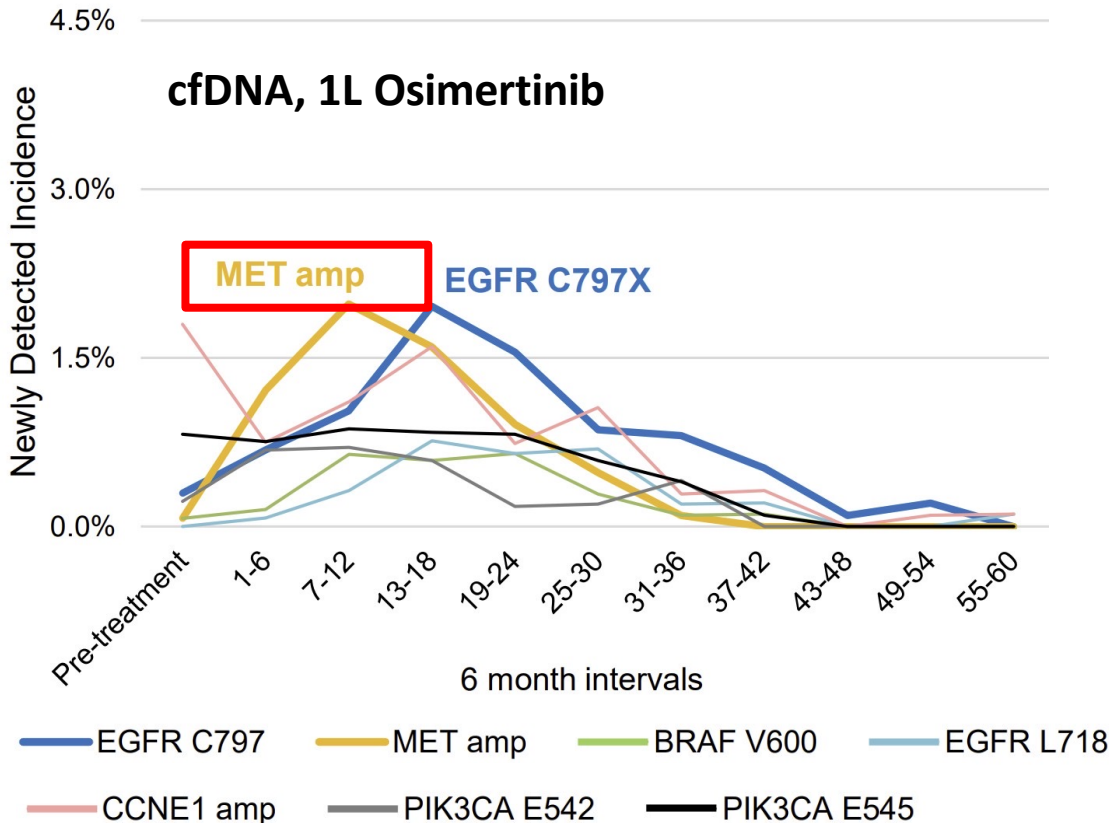
BLU-945: Preliminary Efficacy Data Monotherapy Cohorts, Top Dose Levels

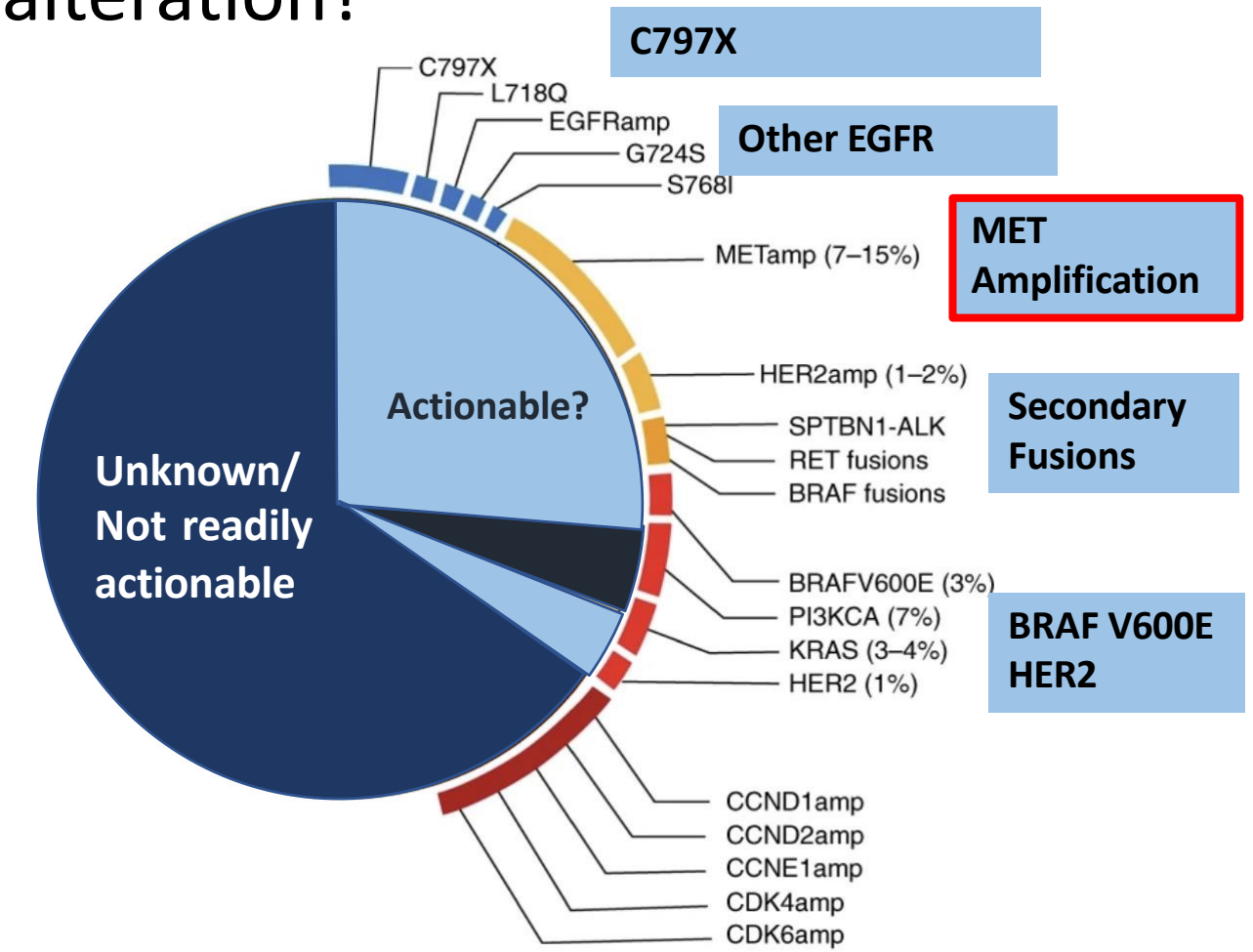




Adapted from: Mar, B. Presented to EGFR Exon 20 Research Consortium

What fraction of acquired resistance is associated with an actionable genomic alteration?





INSIGHT 2: Osimertinib + Tepotinib

EGFRm NSCLC, Acquired Resistance to 1L Osimertinib with a MET amplification (n = 120)

***MET*amp definitions**

TBx FISH: *MET* GCN ≥5 and/or *MET*/*CEP7* ≥2

and/or

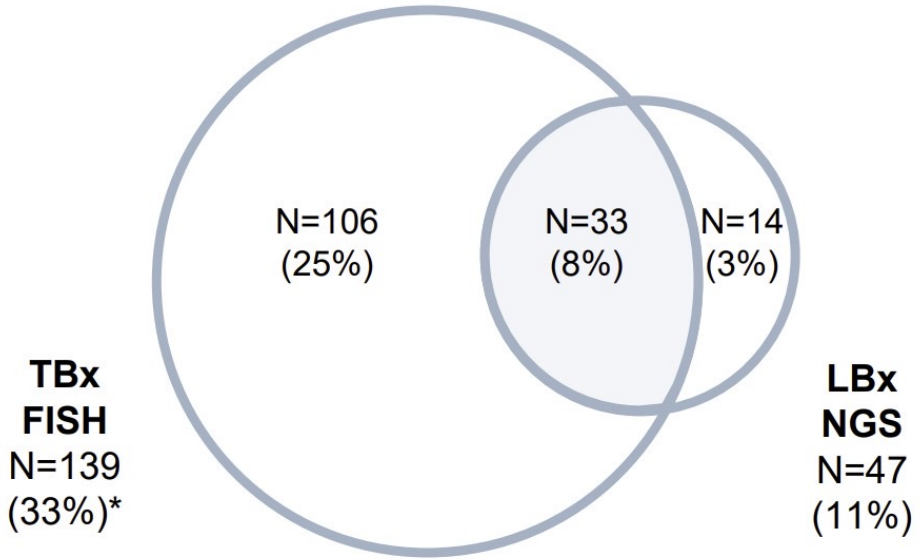
LBx NGS: *MET* GCN ≥2.3; Archer®

Central testing was mandatory for both

Treatment with **osimertinib + tepotinib** or **tepotinib** alone

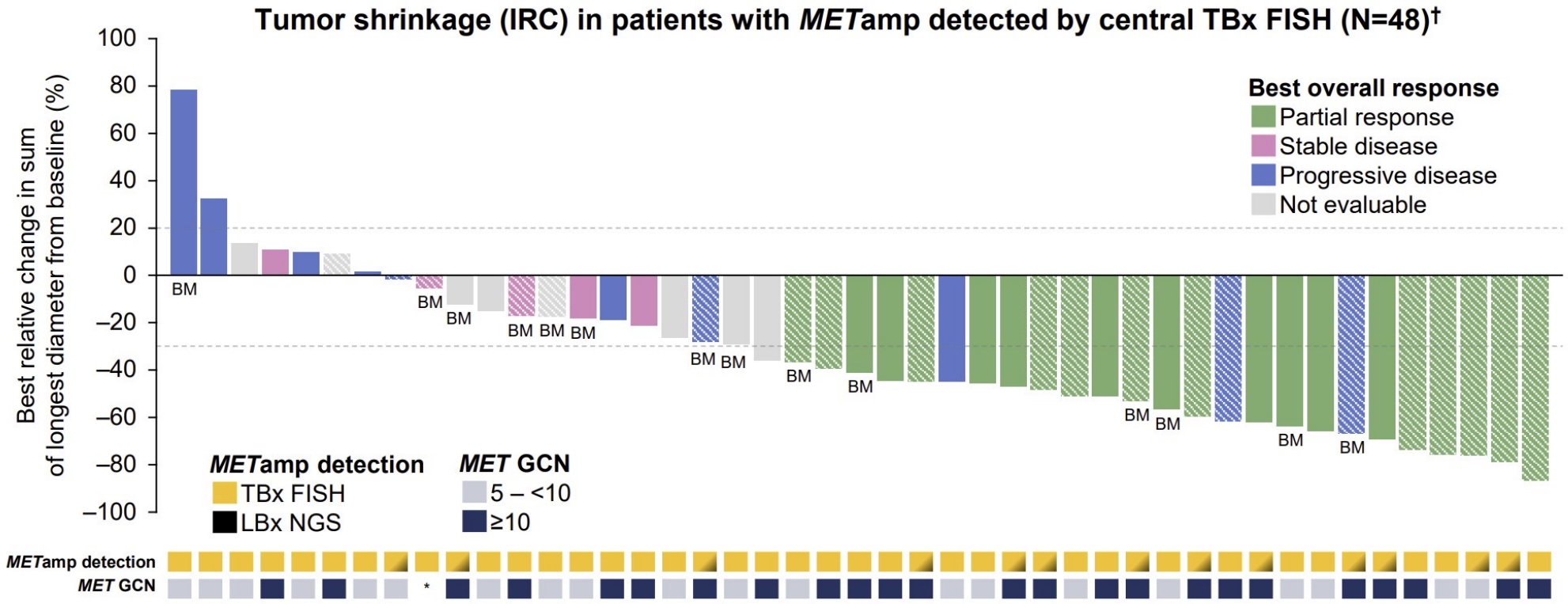
Primary Endpoint: ORR to combination in centrally confirmed MET FISH+ patients

Pre-screened Patients (n = 425)
36% MET-amplified



Mazieres et al. ESMO 2022. LBA

INSIGHT 2: Osimertinib + Tepotinib for MET-amplified EGFRm NSCLC



ORR 45.8%-56.5% osimertinib + tepotinib
ORR 8.3% tepotinib monotherapy

EGFR + MET TKI Combinations

Osimertinib + Savolitinib for MET+ s/p Osimertinib

TATTON Phase Ib
FISH MET/CEP7 2+ or MET 5x+; IHC 3+ in 50%+; NGS 5X CNG)

ORR 30% post 3rd gen EGFRTKI

SAVANNAH Phase II
Definition MET+: IHC 50+ or FISH 5+ (62% screened)
Definition MET-high: IHC 90+/FISH 10+ (34% screened)

ORR 49%, PFS 7.1 mo MET-high
ORR 9% if not MET-high

SAFFRON Phase III
NCT NCT05261399

Osimertinib + Capmatinib for MET+ s/p Osimertinib

Case Reports of Activity

ORR 50% for erlotinib + capmatinib
(MET FISH > ULN, or MET IHC 2+/3+)

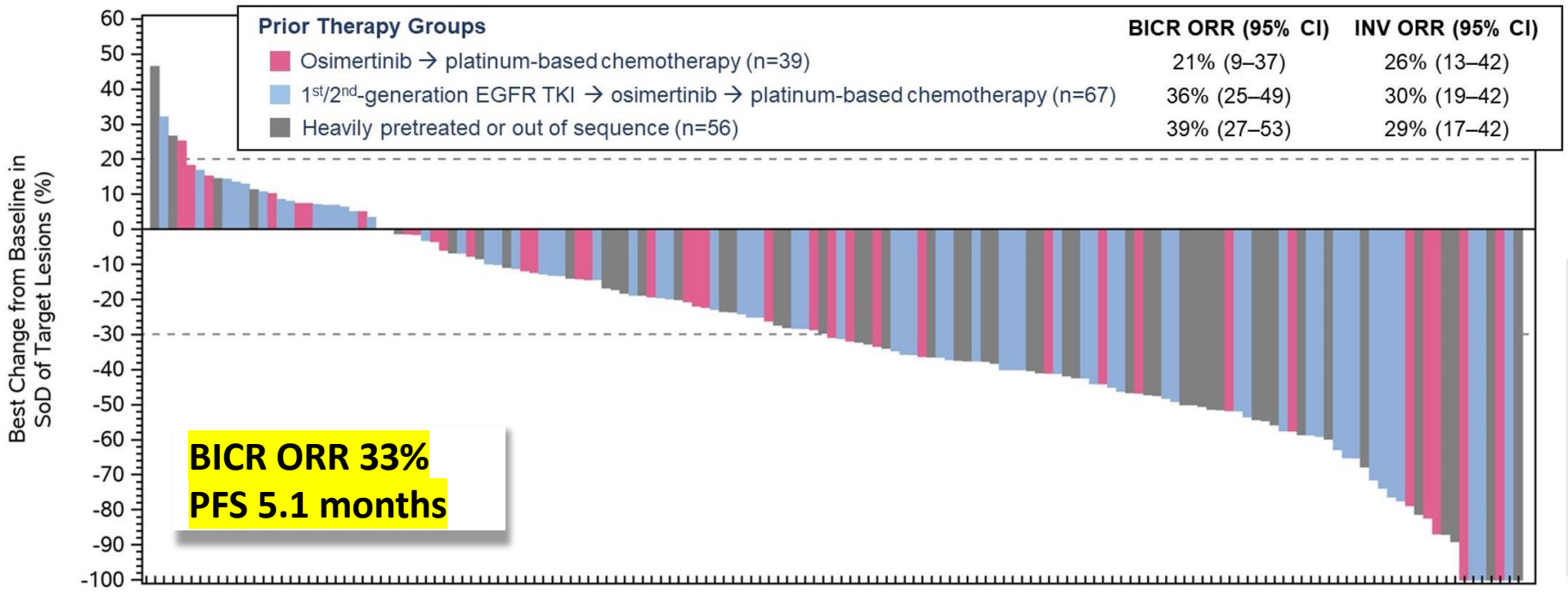
GEOMETRY-E Phase III
Randomized osimertinib + capmatinib vs platinum doublet
NCT 04816214 → study enrollment terminated

Sequist et al, Lancet Oncology, 2020; Ahn et al, IASLC 2022 EP08.01-140; McCoach et al J Precision Oncol. 2021.

Rotow, TTLC 2023

Amivantamab + Lazertinib

EGFR/MET Bispecific +3rd Gen EGFR TKI CHRYSALIS-2



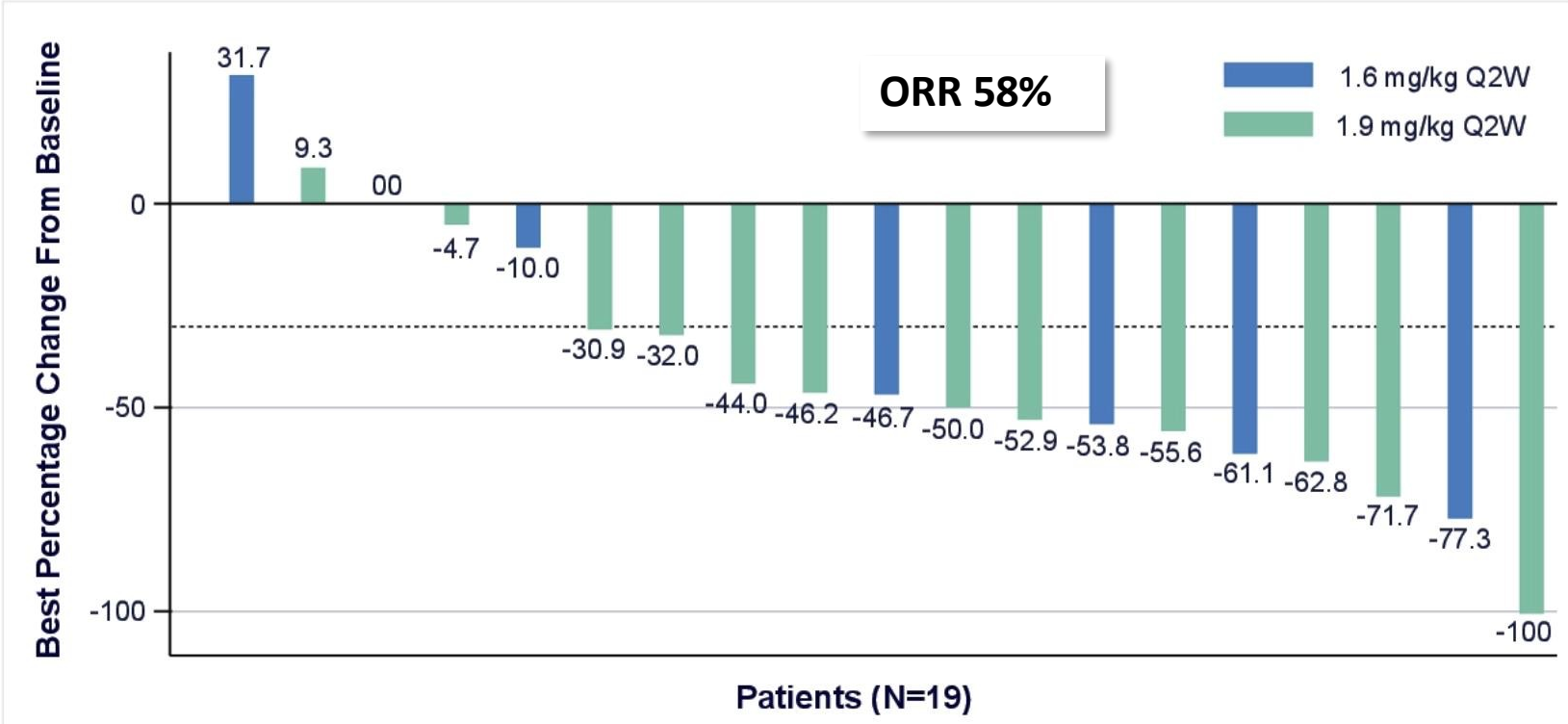
In CHRYSALIS-1, MET/EGFR IHC score correlated with response (n=20)

ORR 90% if IHC+
ORR 10% if IHC-

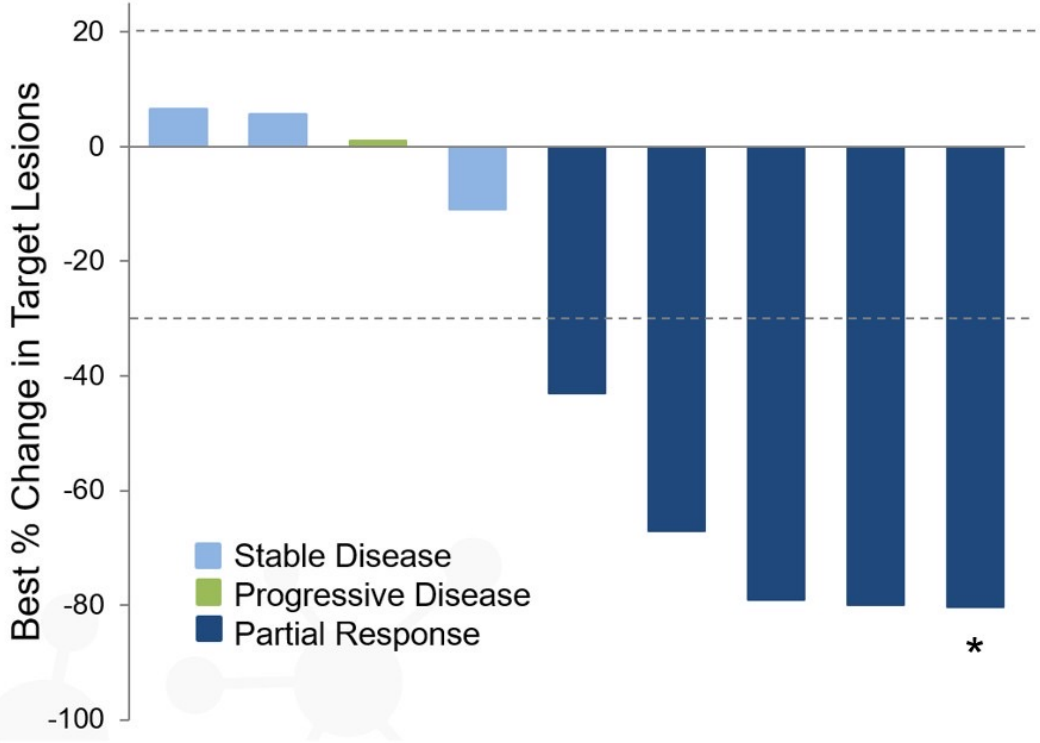
Shu et al. ASCO 2022. #9006.; Bauml et al ASCO 2021 #9006

Telisotuzumab vedotin + Osimertinib MET-ADC + EGFR TKI

MET-overexpression: IHC 3+ in at 25% of tumor cells



Osimertinib + Selpercatinib For Acquired RET Fusions
Patient series from the selpercatinib extended access program



One patient with clinical progression without radiographic evaluation not shown

Best Response (n=10)	
Objective Response n (%)	**5 (50%)**
Partial Response*	5 (50%)
Stable Disease	3 (30%)
Progressive Disease	2 (20%)
Disease Control Rate n (%)	**8 (80%)**
Median Depth of Response (%)	**-43%**

*One partial response unconfirmed

- **Median Treatment Duration:** 7.4 months
- **Median Treatment Duration Responders:** 11 months

Targeting Other Acquired Oncogenic Drivers

ALK Fusions	**Osimertinib + Alectinib** 6 months DoR — Case Reports
HER2 Amplification	**T-DM1 + Osimertinib** HER 2+/3+ IHC or Amp (NGS) ORR 0%, DCR 63% — TRAEMOS Ph II
BRAF Fusions	**Osimertinib + Trametinib** Response, D/c at 5 mo (Tox) — Case Report
BRAF V600E	**Osimertinib + Dabrafenib/Trametinib** 7-8 months DoR **Osimertinib+Vemurafenib** 7+ months DoR — Case Reports

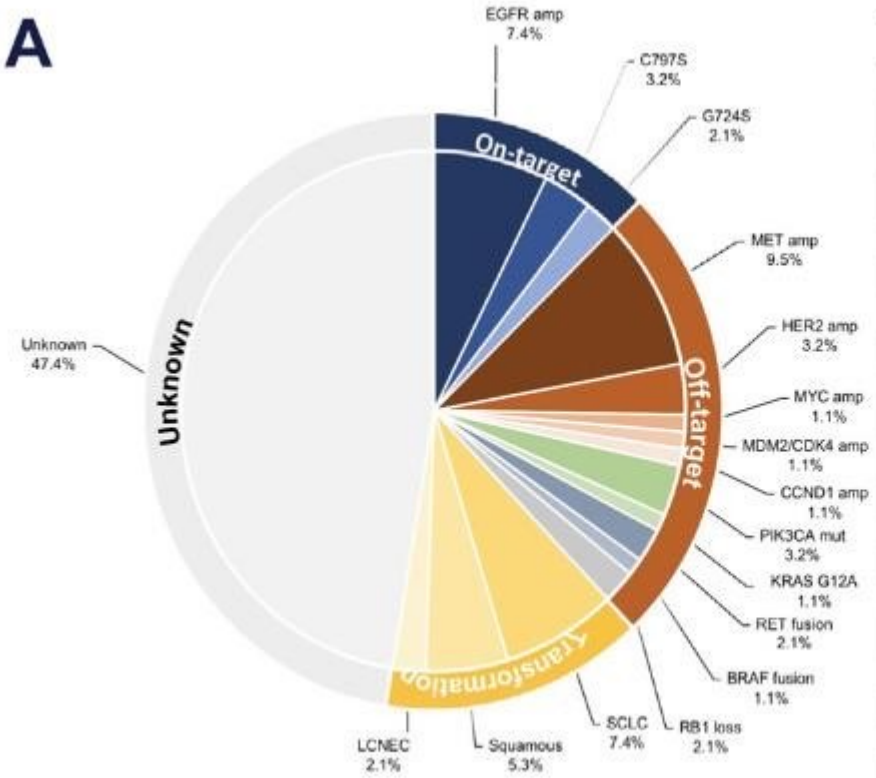
ORCHARD (NCT03944772)

Biomarker-Guided Platform Study for Osimertinib Resistance

- MET ➔ Savolitinib
- C797X ➔ Gefitinib
- ALK ➔ Alectinib
- RET ➔ Selpercatinib
- EGFR Amp ➔ Necitumumab
- BRAF ➔ Selumetinib
- SCLC ➔ Platinum/etoposide/durvalumab
- Unmatched ➔ Datopotamab deruxtecan

Jebbink et al. MA02.07. WCLC 2021; Schrock JTO 2018; Offin et al JCP Precis Oncol. 2018; Ribero et al, npj precision oncology 2021; Huang et al JTO 2019; Sun et al Thorac Cancer 2022; Dagogo-Jack et al. JTO. 2019

Mechanisms of resistance to 1L osimertinib



	Paired	Post-progression	Total (%)
On Target			
EGFR amplification	3	4	7 (7.4)
C797S	1	2	3 (3.2)
G724S	2	0	2 (2.1)
Off Target			
MET amp	7	2	9 (9.5)
HER2 amp	2	1	3 (3.2)
MYC amp	0	1	1 (1.1)
MDM2/CDK4 amp	0	1	1 (1.1)
CCND1 amp	0	1	1 (1.1)
PIK3CA mut	2	1	3 (3.2)
KRAS G12A	1	0	1 (1.1)
RET fusion	1	1	2 (2.1)
BRAF fusion	1	0	1 (1.1)
RB1 loss	1	1	2 (2.1)
Transformation			
SCLC	4	3	7 (7.4)
Squamous	5	0	5 (5.3)
LCNEC	2	0	2 (2.1)
Unknown	35	10	45 (47.4)
Sum	67	28	95

- **Acquired alterations**

- **Histologic Transformation** (15%)

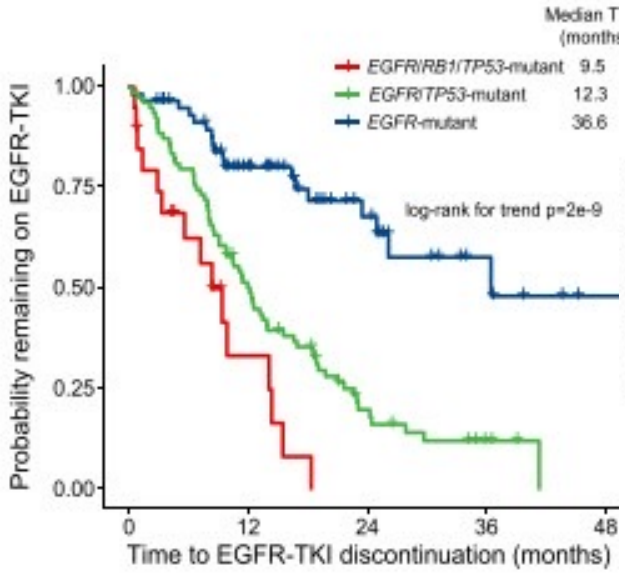
  - ***Neuroendocrine (small cell, large cell)***
  - ***Squamous cell***

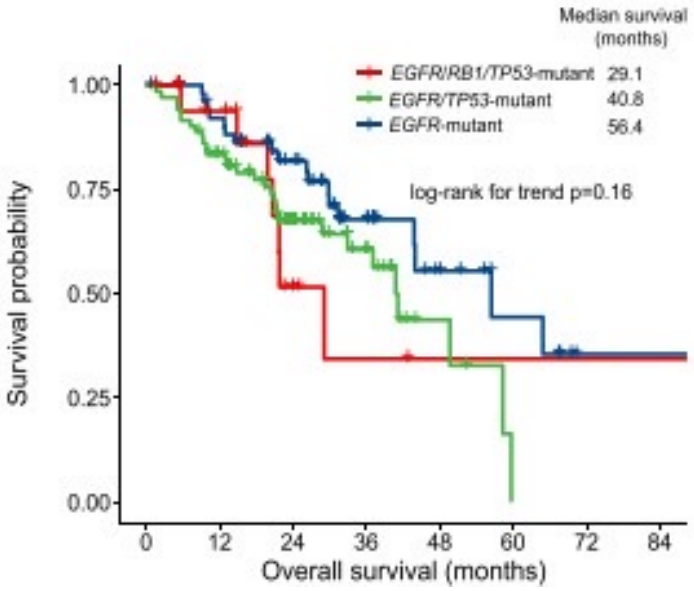
- Only diagnosed by a **tumor tissue biopsy**, and can be seen in the setting of more indolent resistance

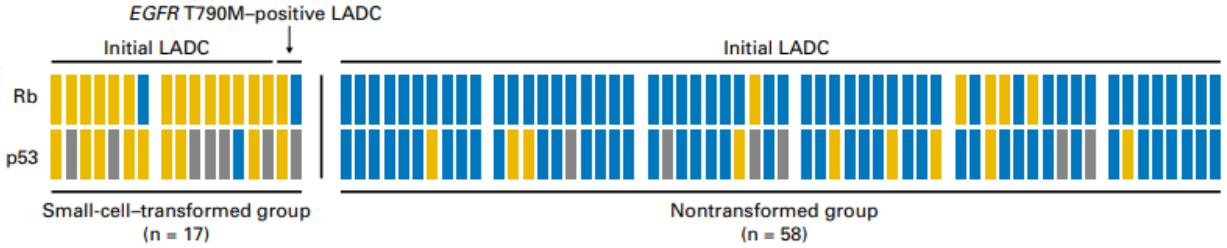
Choudhury JTO 2022

Helena Yu TTLC 2023

Molecular predictors of SCLC transformation





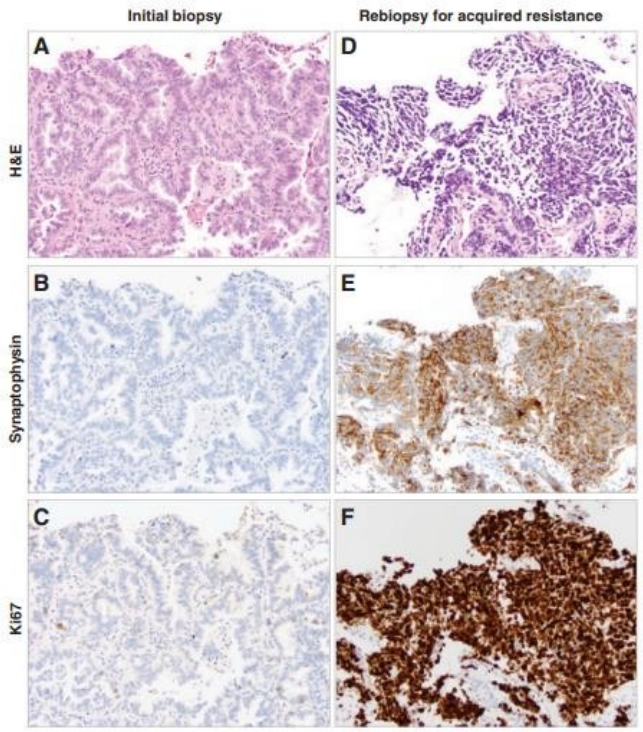


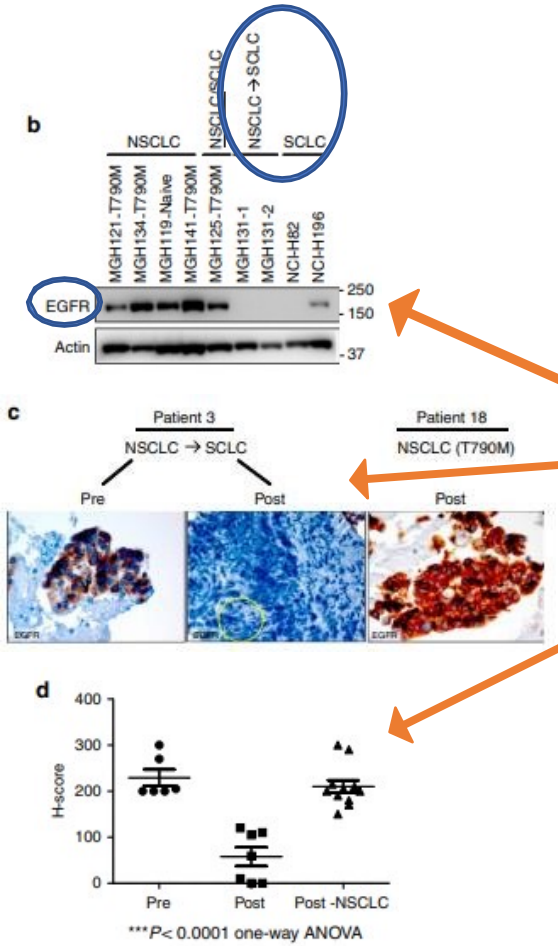
5-10% of EGFR-mutant lung cancers have concurrent RB1 and TP53 loss RB1 and TP53 loss may be detectable by IHC only (intact on NGS, IHC demonstrates protein loss).

RB1 and TP53 loss are necessary but NOT sufficient- 25% likelihood of transformation over disease course with EGFR/TP53/RB1 genotype.

- Concurrent TP53/RB1 alterations also associated with shorter time on EGFR TKI and shorter OS

Histologic Transformation



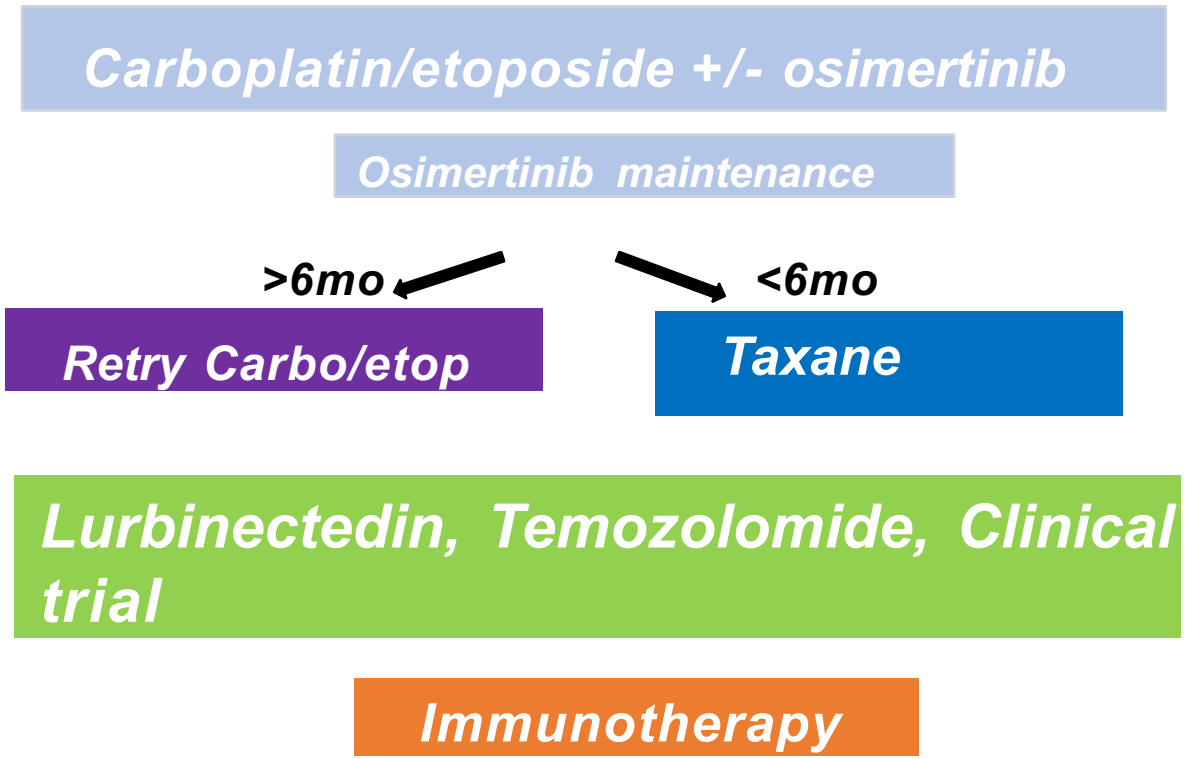


Pre-treatment EGFR+ LC almost always adeno (rare small cell, squamous cell, adenosq seen)

- Transformation is a mechanism of resistance to EGFR TKI because it results in loss of dependence on EGFR signaling.
- **Transformed SCLC does not express EGFR**.
- IHC staining for total EGFR largely lost with **SCLC transformation.**
- H-score of EGFR staining from paired samples pre- treatment with EGFR TKI and post-treatment after SCLC transformation.
- Once transformation occurs, **only targeting EGFR is not effective.** Small cell-directed treatments are required to manage transformed SCLC

Yu CCR 2013, Niederst Nat Comm 2015

Clinical outcomes with SCLC transformation



Multi-center retrospective review

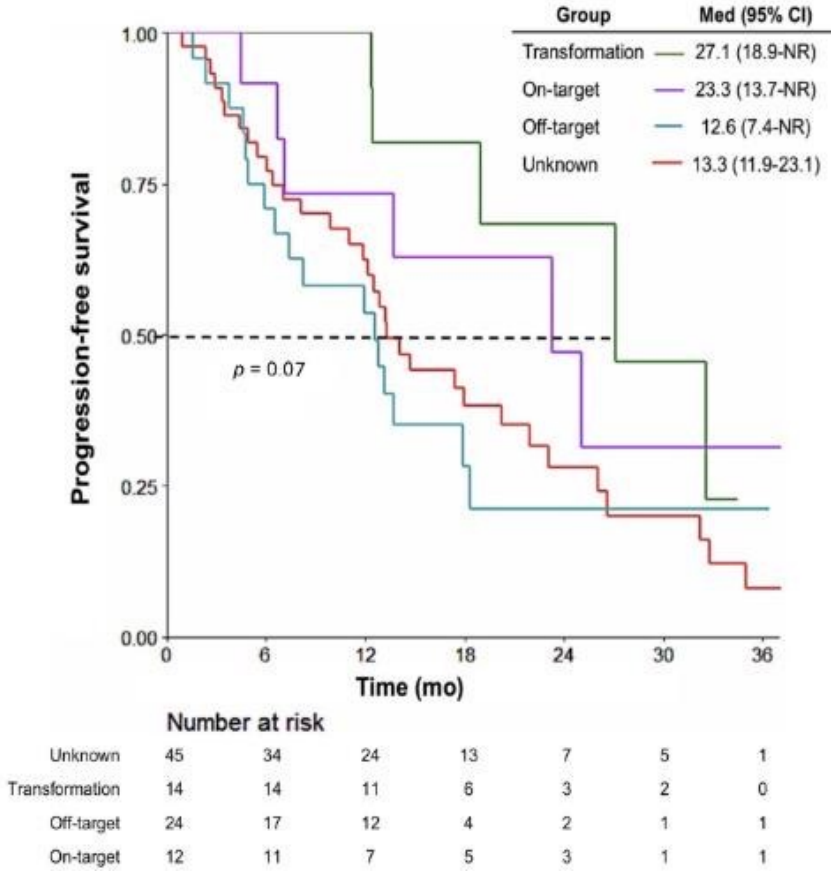
- **67 pts** with EGFR+ SCLC from 8 institutions
- 87% were adeno at dx, 13% small cell/mixed at dx
- All patients retained their EGFR mutation in the transformed SCLC tumor.
- Median time from diagnosis to transformation was 17.8 months (95% CI 14.3-26.2).

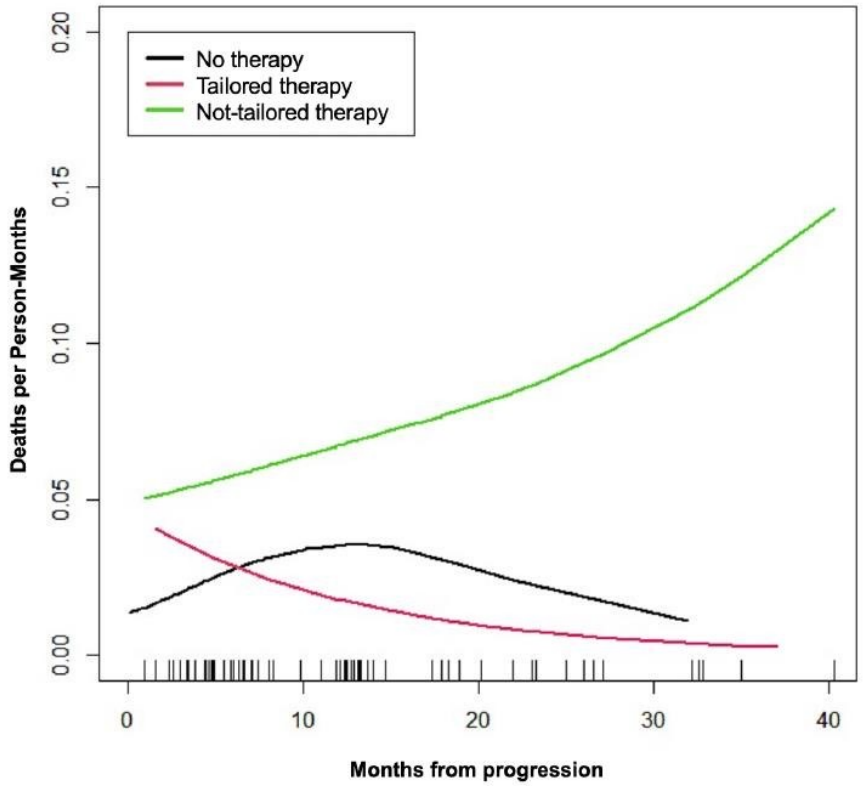
Median OS from time of SCLC transformation was **10.9 months**

- Platinum/etoposide= most common treatment **RR=54% & mPFS = 3.4 months**
- No responses to immunotherapy, with the longest time to progression on IO being 9 weeks
- Taxanes were often used with a clinical response rate of 50% and a median PFS of 2.7 months

Marcoux JCO 2018

Clinical outcomes with SCLC transformation





24 mo HR 0.09 (tailored therapy vs. not tailored therapy)
24 mo HR 0.31 (tailored therapy vs. no therapy)
p<0.001

-If second-line therapy was tailored to mechanism of resistance (including histology directed chemo), risk of death was decreased compared to if 2L therapy was not tailored

Choudhury JTO 2022

Clinical outcomes with SCLC transformation

Continuation of Osimertinib with Chemo after PD

Pros

- CNS activity and protection
- Continued control of sensitive clones

Cons

- Toxicity
- Inconvenience
- No randomized data
- No NCCN endorsement
- Financial Burden

Continuation of Osimertinib with Chemo after PD

Pros

- CNS activity and protection
- Continued control of sensitive clones

Cons

- Toxicity
- Inconvenience
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Benefit of continued TKI in oligoprogressive disease

J Thorac Oncol. Author manuscript; available in PMC 2013 Dec 1.
Published in final edited form as:
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doi: 10.1097/JTO.0b013e3182745948

PMCID: PMC3506112
NIHMSID: NIHMS415046
PMID: 23154552

Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene addicted non-small cell lung cancer

Andrew J. Weickhardt, MBBS DMedSc,[1,*] Benjamin Scheier, MD,[1] Joseph Malachy Burke, MD,[1] Gregory Gan, MD,[2] Xian Lu, MSc,[3] Paul A. Bunn, Jr., MD,[1] Dara L. Aisner, MD PhD,[4] Laurie E. Gaspar, MD MBA,[2] Brian D. Kavanagh, MD MPH,[2] Robert C. Doebele, MD PhD,[1] and D. Ross Camidge, MD PhD[1]

Based on the practices within this study, suggested criteria for considering local ablative therapy of oligoprogressive disease and treatment with a TKI beyond progression include:
1. *ALK* positive or *EGFR* mutant metastatic NSCLC
2. Relevant TKI (e.g. crizotinib or erlotinib) is well tolerated
3. Oligoprogressive disease on TKI therapy, defined as: **a.** CNS progression without leptomeningeal disease amenable to WBRT, SRS or surgical resection **b.** Progression in ≤ 4 extra-CNS sites amenable to SBRT, XRT or surgical resection

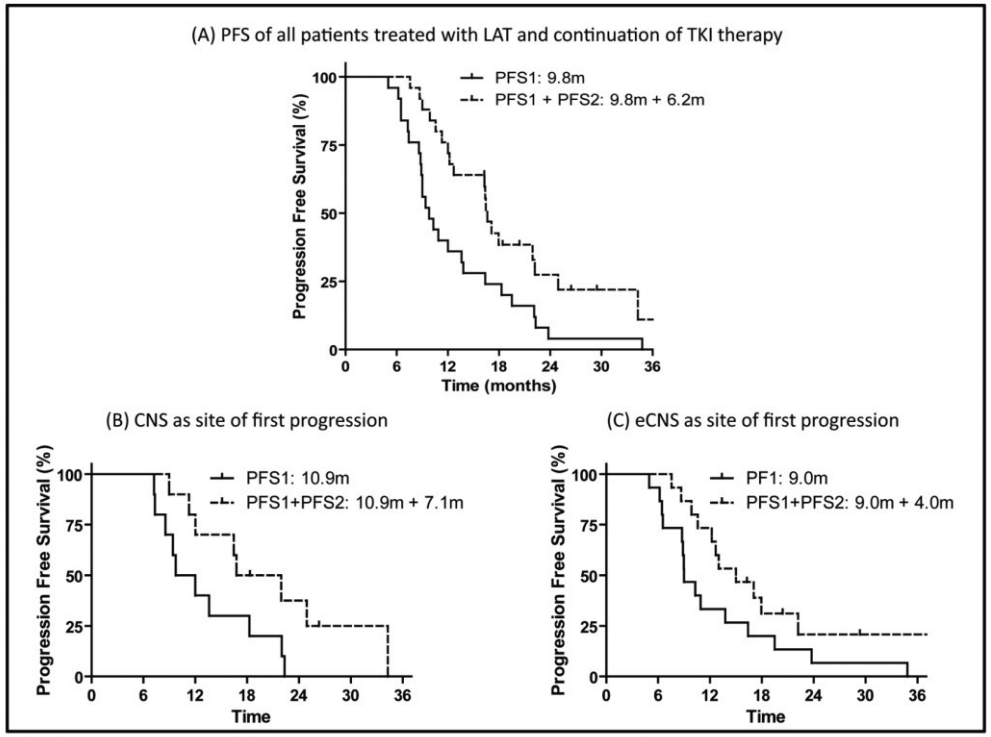


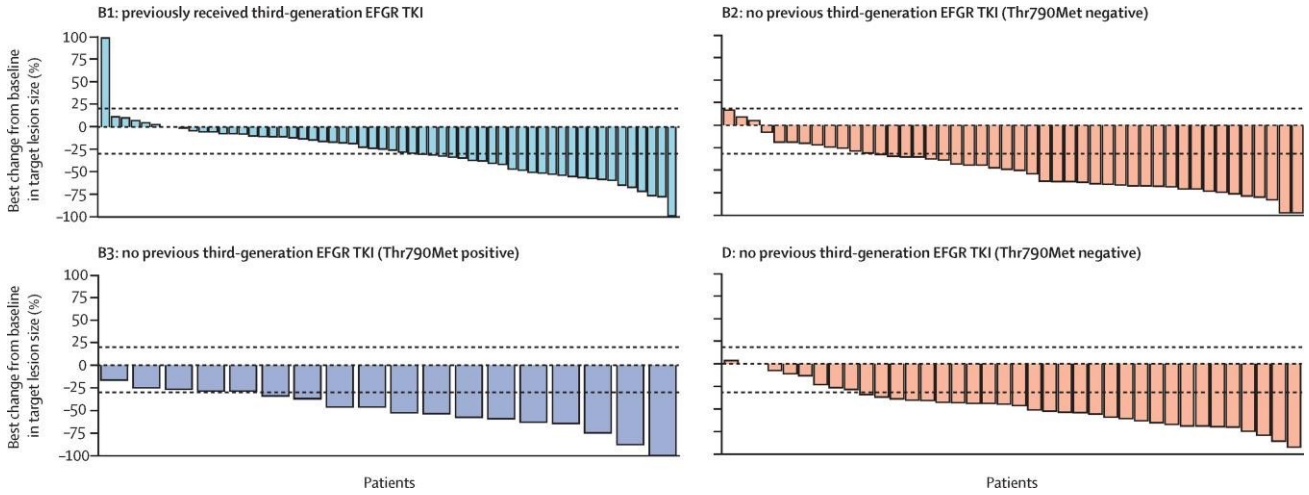
Figure 1.
PFS1 and PFS1+PFS2 survival curves of (A) All 25 patients treated with LAT; (B) 10 patients treated with LAT who first progressed only in the CNS; (C) 15 patients treated with LAT who first progressed in extra-CNS (eCNS) locations, including 3 patients with simultaneous CNS and eCNS progression.

II. Management of EGFR Resistant NSCLC

Continue Osimertinib with MET TKI/ADC

Osimertinib plus savolitinib in patients with *EGFR* mutation-positive, *MET*-amplified, non-small-cell lung cancer after progression on EGFR tyrosine kinase inhibitors: interim results from a multicentre, open-label, phase 1b study

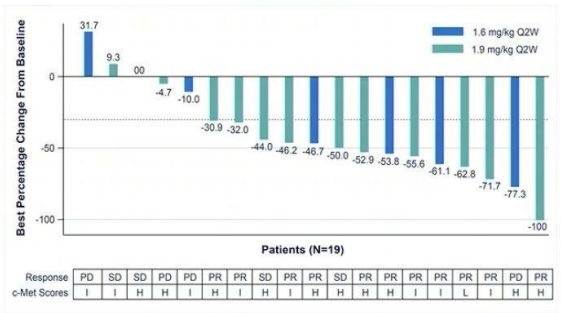
Lecia V Sequist, MD † • Prof Ji-Youn Han, MD † • Prof Myung-Ju Ahn, MD • Byoung Chul Cho, MD • Helena Yu, MD • Prof Sang-We Kim, MD • Prof James Chih-Hsin Yang, MD • Jong Seok Lee, MD • Wu-Chou Su, MD • Dariusz Kowalski, MD • Sergey Orlov, PhD • Mireille Cantarini, MD • Remy B Verheijen, PhD • Anders Mellemgaard, MD • Lone Ottesen, MD • Paul Frewer, MSc • Xiaoling Ou, PhD • Geoffrey Oxnard, MD • Show less • Show footnotes



Teliso-V and osimertinib: Preliminary Efficacy

ORR: 58% (95%CI: 34-80)

Best Percentage Change From Baseline in Target Lesion



Interim Objective Response Rate

Category	N	ORR,* n (%) [95% CI]
Teliso-V dose		
1.6 mg/kg	7	3 (43) [10, 82]
1.9 mg/kg	12	8 (67) [35, 90]
Total	19†	11 (58) [34, 80]
c-Met level		
High (≥50%, 3+ staining)	10	5 (50) [19, 81]
Int (25–49%, 3+ staining)	8	5 (63) [25, 92]
Total	18‡	10 (56) [31, 79]
EGFR mutation		
L858R	9	5 (56) [21, 86]
Del19	9	6 (67) [30, 93]
Total	19¶	11 (58) [34, 80]
Last prior regimen		
Contained Osi	8	4 (50) [16, 84]
Did not contain Osi	11	7 (64) [31, 89]
Total	19	11 (58) [34, 80]

Jonathan W. Goldman et al. Abstract 9013

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY: Gonzalo Recondo MD PhD
Center for Medical Education and Clinical Research (CEMIC)

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Management of EGFR Resistant NSCLC

THE LANCET
Oncology

ARTICLES | VOLUME 16, ISSUE 8, P990-998, AUGUST 2015

Gefitinib plus chemotherapy versus placebo plus chemotherapy in *EGFR*-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial

Prof Jean-Charles Soria, MD • Prof Yi-Long Wu, MD • Prof Kazuhiko Nakagawa, MD • Prof Sang-We Kim, MD • Jin-Ji Yang, MD • Prof Myung-Ju Ahn, MD • et al. Show all authors

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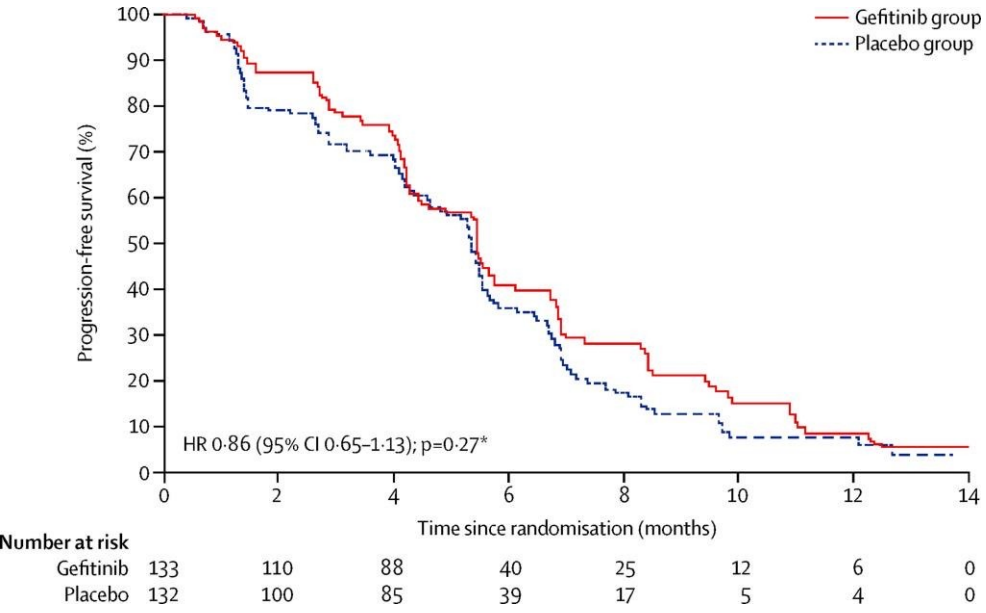

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Randomized Phase II Trial of Erlotinib Beyond Progression in Advanced Erlotinib-Responsive Non-Small Cell Lung Cancer

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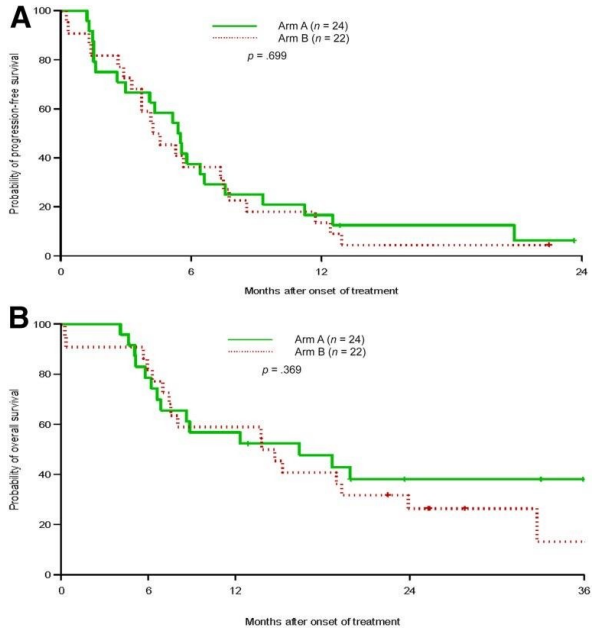
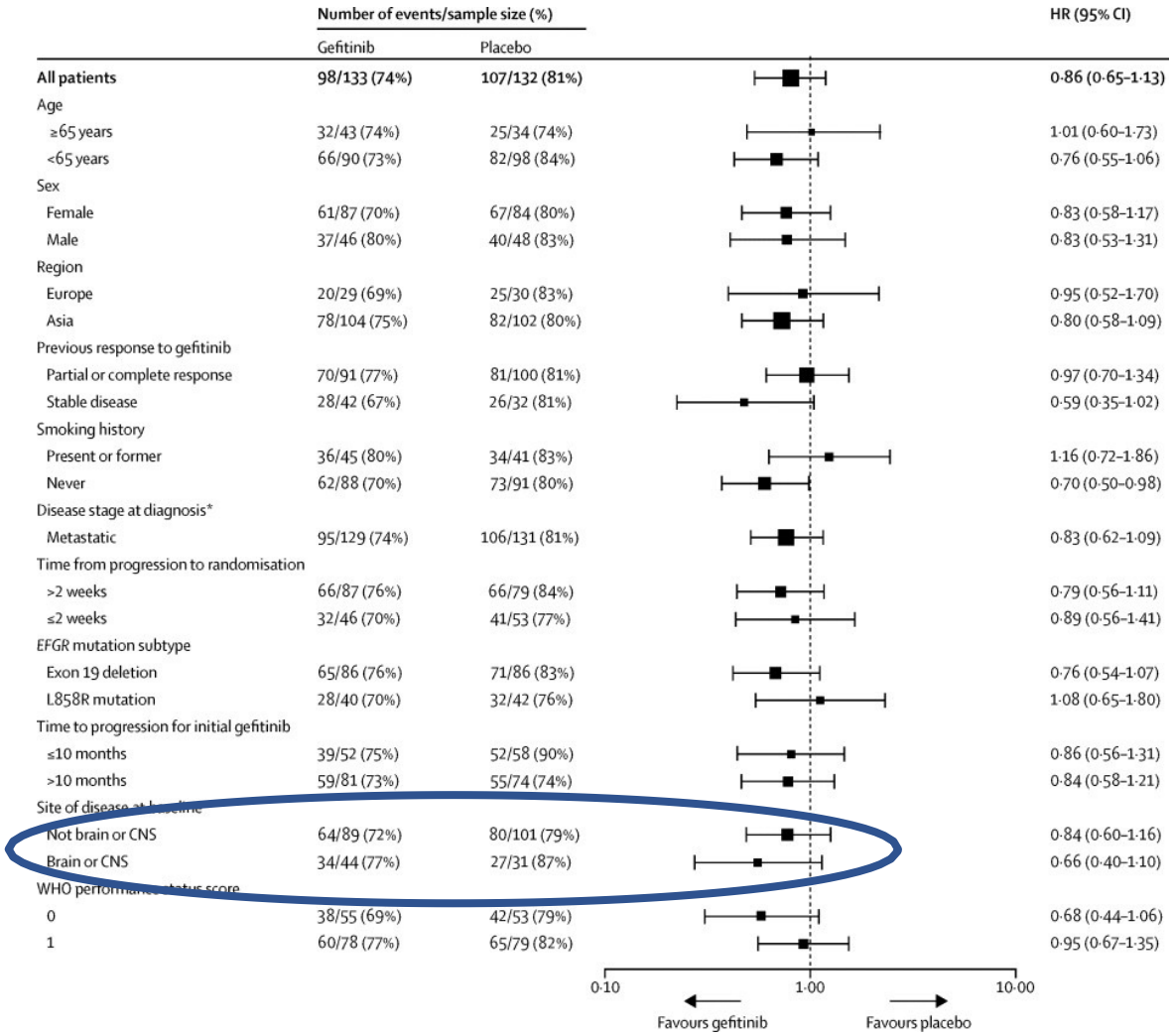


Arm A: median OS, 16.4 months (95% CI: 6.6, 39)
Arm B: median OS, 14.2 months (95% CI: 7, 23.9)



	Number of events/sample size (%)		HR (95% CI)
	Gefitinib	Placebo	
All patients	**98/133 (74%)**	**107/132 (81%)**	**0·86 (0·65–1·13)**
Age			
≥65 years	32/43 (74%)	25/34 (74%)	1·01 (0·60–1·73)
<65 years	66/90 (73%)	82/98 (84%)	0·76 (0·55–1·06)
Sex			
Female	61/87 (70%)	67/84 (80%)	0·83 (0·58–1·17)
Male	37/46 (80%)	40/48 (83%)	0·83 (0·53–1·31)
Region			
Europe	20/29 (69%)	25/30 (83%)	0·95 (0·52–1·70)
Asia	78/104 (75%)	82/102 (80%)	0·80 (0·58–1·09)
Previous response to gefitinib			
Partial or complete response	70/91 (77%)	81/100 (81%)	0·97 (0·70–1·34)
Stable disease	28/42 (67%)	26/32 (81%)	0·59 (0·35–1·02)
Smoking history			
Present or former	36/45 (80%)	34/41 (83%)	1·16 (0·72–1·86)
Never	62/88 (70%)	73/91 (80%)	0·70 (0·50–0·98)
Disease stage at diagnosis*			
Metastatic	95/129 (74%)	106/131 (81%)	0·83 (0·62–1·09)
Time from progression to randomisation			
>2 weeks	66/87 (76%)	66/79 (84%)	0·79 (0·56–1·11)
≤2 weeks	32/46 (70%)	41/53 (77%)	0·89 (0·56–1·41)
EFGR mutation subtype			
Exon 19 deletion	65/86 (76%)	71/86 (83%)	0·76 (0·54–1·07)
L858R mutation	28/40 (70%)	32/42 (76%)	1·08 (0·65–1·80)
Time to progression for initial gefitinib			
≤10 months	39/52 (75%)	52/58 (90%)	0·86 (0·56–1·31)
>10 months	59/81 (73%)	55/74 (74%)	0·84 (0·58–1·21)
Site of disease at baseline			
Not brain or CNS	64/89 (72%)	80/101 (79%)	0·84 (0·60–1·16)
Brain or CNS	34/44 (77%)	27/31 (87%)	0·66 (0·40–1·10)
WHO performance status score			
0	38/55 (69%)	42/53 (79%)	0·68 (0·44–1·06)
1	60/78 (77%)	65/79 (82%)	0·95 (0·67–1·35)

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Combining Osimertinib With Chemotherapy in EGFR-Mutant NSCLC at Progression

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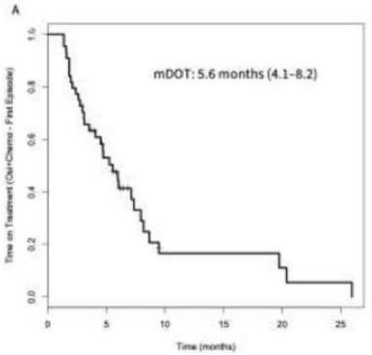
Baseline Characteristics

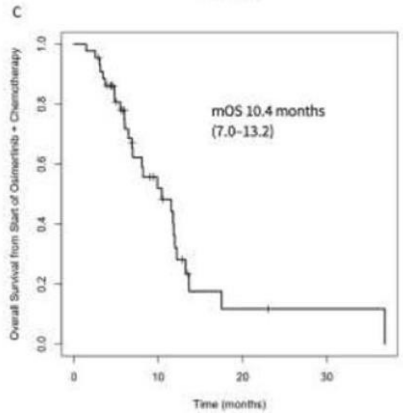
Characteristic	All patients (n=44)
Median age at diagnosis, years (range)	58 (34–82)
Sex – n (%)	
Female	30 (68)
Male	14 (32)
Race – n (%)	
Asian	20 (45)
White	17 (39)
Black	3 (7)
Other	4 (9)
Histologic type – n (%)	
Adenocarcinoma	44 (100)
Stage at initial diagnosis – n (%)	
Stage I-III	3 (7)
Stage IV	41 (93)
EGFR mutation – n (%)	
Exon 19 deletion	28 (64)
L858R	15 (34)
G719A	1 (2)
T790M (ever detected with above) – n (%)	30 (68)
CNS metastases present – n (%)	
At diagnosis of metastatic disease	23 (52)
Prior to start of first osimertinib	35 (80)
Prior to start of osimertinib + chemotherapy	37 (84)
Number of prior lines of therapy (before osimertinib + chemotherapy) – n (%)	
2	22 (50)
3	10 (23)
4	9 (20)
≥5	3 (7)
Prior treatment (before osimertinib + chemotherapy) – n (%)	
Prior EGFR TKI	44 (100)
Prior 3rd generation EGFR TKI	43 (98)
Prior 1st or 2nd generation EGFR TKI	42 (95)
Prior chemotherapy alone	15 (34)
Prior immunotherapy	3 (7)
Immediate prior treatment (directly preceding osimertinib + chemotherapy) – n (%)	
Osimertinib monotherapy	38 (86)
Osimertinib + EGFR mAb	2 (5)
Investigational 3rd generation EGFR TKI	2 (5)
Chemotherapy alone	2 (5)

Continuing Osimertinib with chemotherapy Safe and might have particular benefit for pts with CNSdisease

Adverse Events	Any Grade	Grade 3	Grade 4
AST/ALT elevation	15 (34%)	1 (2%)	0
Anemia	33 (75%)	4 (9%)	0
Neutropenia	14 (32%)	5 (11%)	2 (5%)
Thrombocytopenia	26 (59%)	1 (2%)	1 (2%)
Ejection fraction decreased	1 (2%)	1 (2%)	0
Pneumonitis	0	0	0

Among the 37 patients with CNS metastases present at the time of initiation of concurrent chemotherapy and osimertinib, 9 (24%) had CNS disease progression while on osimertinib plus chemotherapy. Among the 7 patients who did not have CNS metastases at the initiation of concurrent chemotherapy and osimertinib, 2 (29%) developed new CNS metastases while on chemotherapy plus osimertinib – one was 2.6 months and one was 5.3 months after starting combination therapy.





Post-Osimertinib Failure – Current SOC

- Treatment based on acquired resistance
- Chemotherapy – carboplatin + pemetrexed ± bevacizumab
- IMpower150 – Cb/paclitaxel/bevacizumab/atezolizumab
- Clinical trial

- Chemo + IO NOT a standard option
  - Excluded from KN-189
  - CM722 – negative trial (underpowered and minority got osi)
  - KN-789 – pending

II. Management of EGFR Resistant NSCLC
What's Next?

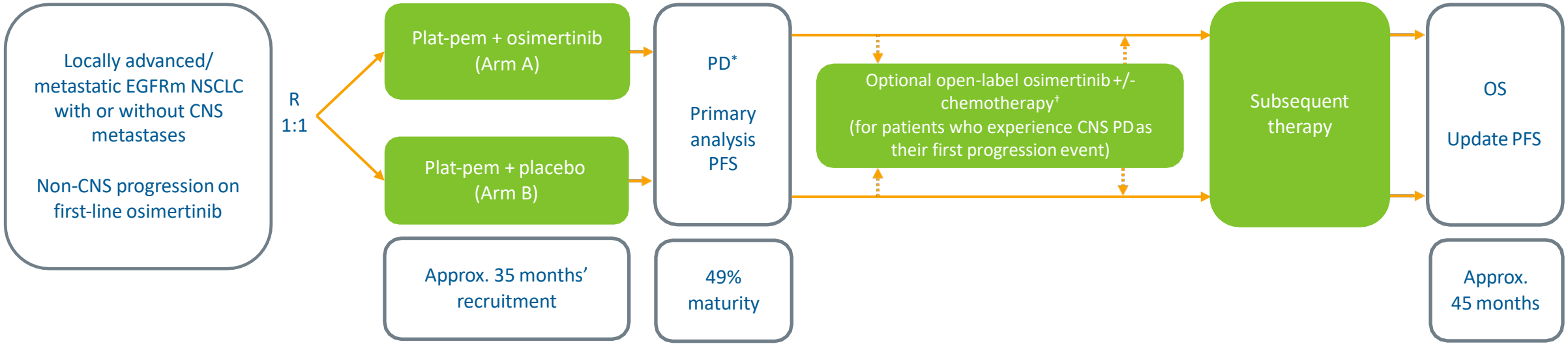
- Pembrolizumab[1-4] and other ICIs, as monotherapy and in combination with chemotherapy changed the treatment paradigm for previously untreated metastatic NSCLC without *EGFR*/*ALK* alterations[5,6]
- EGFR TKIs are standard therapy for previously untreated metastatic NSCLC with sensitizing *EGFR* mutations; however, most patients develop resistance and experience disease progression[5–8]
  - Treatment options following disease progression have limited benefit[9–12]
- Subgroup analysis of 86 patients with TKI-resistant *EGFR*-mutant metastatic NSCLC with PD-L1 TPS ≥1% in the phase 2/3 KEYNOTE-010 study of pembrolizumab monotherapy vs docetaxel: HR for OS, 0.88 (95% CI, 0.45–1.70)[13]
- Subgroup analysis of TKI-resistant, *EGFR*-mutant nonsquamous metastatic NSCLC in phase 3 IMpower150 study indicated a trend in improvement in PFS with atezolizumab and bevacizumab plus chemotherapy[12]
- Studies evaluating the combination of ICIs plus TKIs for previously untreated advanced NSCLC with sensitizing *EGFR* mutations were associated with toxicity concerns[14,15]
- Since pembrolizumab[13] and other ICIs[12,16] demonstrated activity in TKI-resistant, *EGFR*-mutant NSCLC, and to extend the benefit of ICIs in this population, the combination of pembrolizumab plus chemotherapy warranted further exploration in TKI-resistant, *EGFR*-mutant metastatic NSCLC

ICI, immune checkpoint inhibitor.

1. Mok TSK, et al. *Lancet*. 2019;393(10183):1819-1830. 2. Reck M, et al. *N Engl J Med*. 2016;375(19):1823-1833. 3. Gandhi L, et al. *N Engl J Med*. 2018;378(22):2078-2092. 4. Paz-Ares L, et al. *N Engl J Med*. 2018;379(21):2040-2051. 5. Hendriks LE, et al. *Ann Oncol*. 2023;34:339–357. 6. NCCN. *NCCN Guidelines*. Version 2.2023. 7. Qian X, et al. *Front Pharmacol*. 2022;13:926890. 8. Wu L, et al. *Front Oncol*. 2020;10:602762. 9. To KKW, et al. *Front Oncol*. 2021;11:635007. 10. Lee CK, et al. *JAMA Oncol*. 2018;4(2):210–216.11. Gainor JF, et al. *Clin Cancer Res*. 2016;22(18)4585-4593. 12. Reck M, et al. *Lancet Respir Med*. 2019;7:387–401. 13. Herbst RS, et al. *Lancet*. 2016;387:1540–1550 14. Yang J C-H, et al. *J Thorac Oncol*. 2019;14(3):553-559. 15. Creelan BC, et al. *Br J Cancer*. 2021;124(2):383-390. 16. Gettinger S, et al. *J Thorac Oncol*. 2018;13(9):1363-1372.

COMPEL study design (NCT04765059)

Phase III, randomised, double-blind, placebo-controlled study



Randomisation of 204 patients Stratification criteria: Presence of stable CNS metastases per CNS RECIST 1.1 assessments versus no CNS metastases

Endpoints

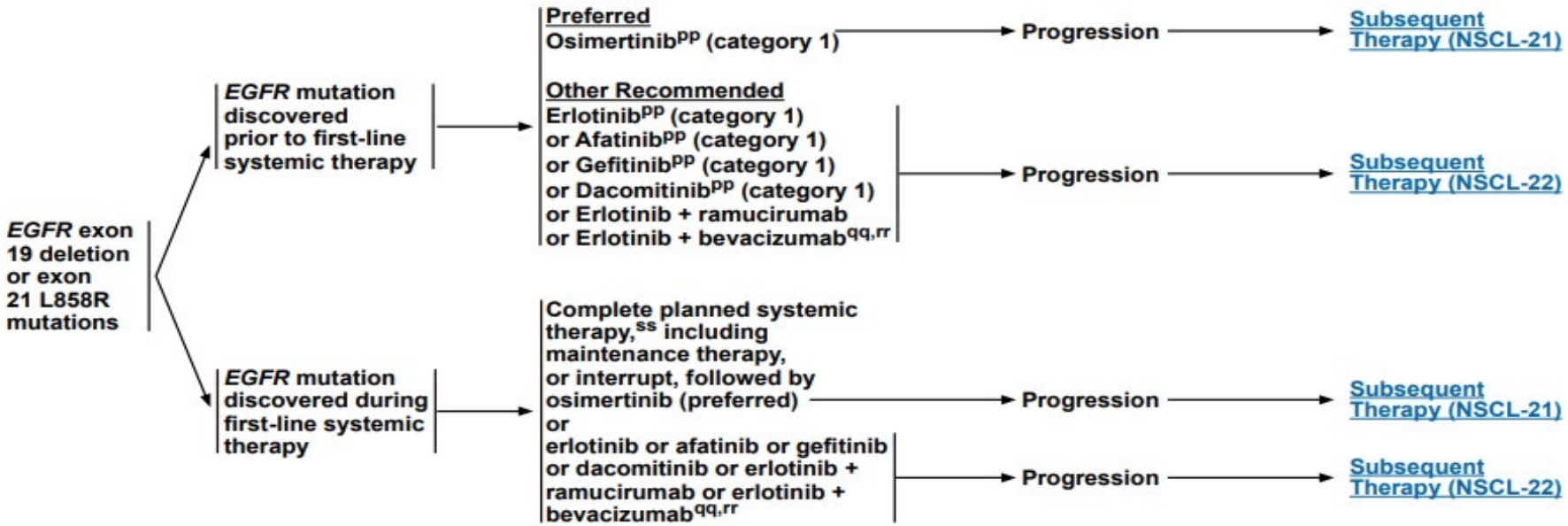
- **Primary:** PFS from randomisation to progression (CNS or non-CNS, whichever occurs first) per RECIST 1.1 and CNS RECIST 1.1
- **Secondary:** CNS PFS per CNS RECIST 1.1, non-CNS PFS per RECIST 1.1, and OS
- **Safety:** AEs, vital signs, clinical laboratory assessments, ECGs, LVEF, and WHO performance status
- **Exploratory:** Key genetic, gene expression and proteomic markers, and efficacy post-re-challenge (third-line osimertinib) in patients with CNS PD as their first progression event

*Patients will receive randomised study treatment until RECIST 1.1- or CNS RECIST 1.1-defined progression, based on Investigator assessment, or until another discontinuation criterion is met. At the Investigator's discretion, study treatment may continue for as long as a patient continues to derive clinical benefit through RECIST 1.1 or CNS-RECIST 1.1 progression in the absence of any discontinuation criteria. Chest and abdominal imaging will continue until RECIST 1.1-defined non-CNS progression; CNS imaging will continue until CNS RECIST 1.1-defined CNS progression (and until second CNS RECIST 1.1-defined CNS progression for patients who receive open-label osimertinib)

†Patients who receive open-label osimertinib may also receive platinum chemotherapy and/or pemetrexed at the Investigator's discretion

EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[ll]

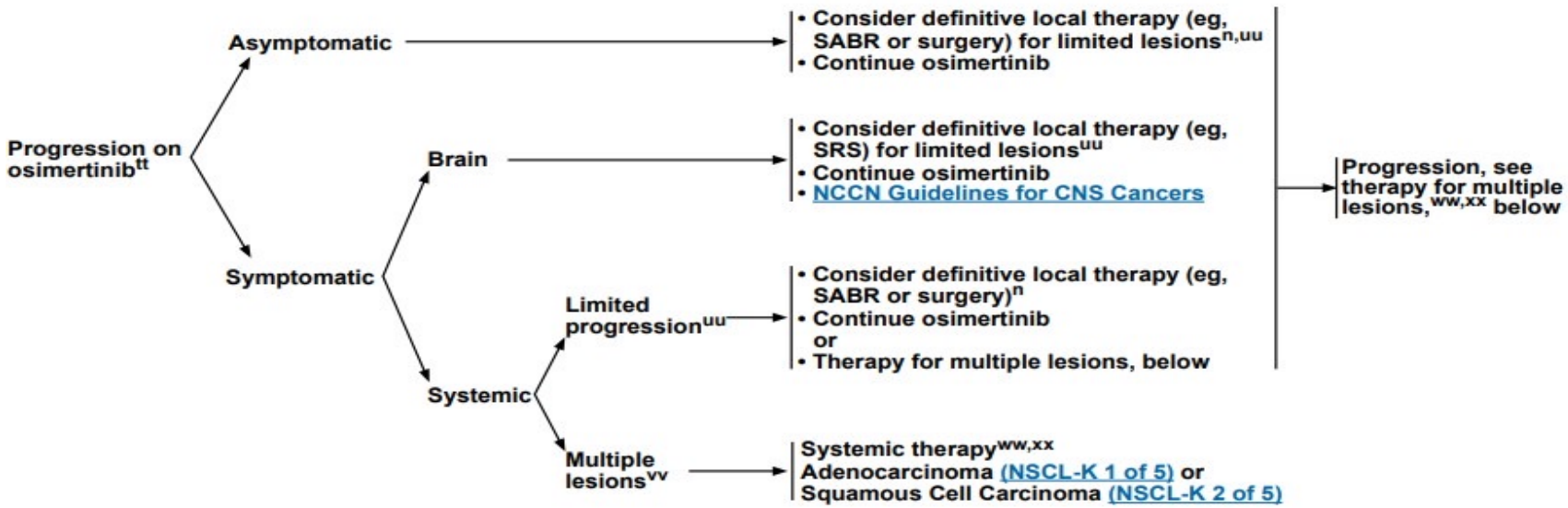
FIRST-LINE THERAPY[oo]



[ll] Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] Moleculer or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[pp] For performance status 0–4.
[qq] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis.
[rr] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[ss] If systemic therapy regimen contains an immune checkpoint inhibitor, physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[ll] **SUBSEQUENT THERAPY[oo]**



[n] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[ll] Principles of Molecular and Biomarker Analysis (NSCL-H).
[oo] Moleculer or Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J).
[tt] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[uu] Clinical trials have included up to 3 to 5 progressing sites.
[vv] Consider a biopsy at time of progression to rule out SCLC transformation (approximately 6%) and evaluate mechanisms of resistance. Principles of Molecular and Biomarker Analysis (NSCL-H) NCCN Guidelines for Small Cell Lung Cancer.
[ww] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
[xx] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR* exon 19 deletion or exon 21 L858R, *ALK*+ NSCLC.

Note: All recommendations are category 2A unless otherwise indicated.
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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred
- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]

Other Recommended
- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1)[6,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]
- Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin) (category 1)[7,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e]
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[8,e]

Contraindications to PD-1 or PD-L1 inhibitors[d]

Useful in Certain Circumstances
- Bevacizumab[f]/carboplatin/paclitaxel (category 1)[9,g,h,i]
- Bevacizumab[f]/carboplatin/pemetrexed[9,10,g,h,i]
- Bevacizumab[f]/cisplatin/pemetrexed[11,g,h,i]
- Carboplatin/albumin-bound paclitaxel (category 1)[12]
- Carboplatin/docetaxel (category 1)[13]
- Carboplatin/etoposide (category 1)[14,15]
- Carboplatin/gemcitabine (category 1)[16]
- Carboplatin/paclitaxel (category 1)[17]
- Carboplatin/pemetrexed (category 1)[18]
- Cisplatin/docetaxel (category 1)[13]
- Cisplatin/etoposide (category 1)[19]
- Cisplatin/gemcitabine (category 1)[17,20]
- Cisplatin/paclitaxel (category 1)[21]
- Cisplatin/pemetrexed (category 1)[20]
- Gemcitabine/docetaxel (category 1)[22]
- Gemcitabine/vinorelbine (category 1)[23]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 2)

Preferred
- Carboplatin/pemetrexed[18]

Other Recommended
- Carboplatin/albumin-bound paclitaxel[25,26]
- Carboplatin/docetaxel[13]
- Carboplatin/etoposide[14,15]
- Carboplatin/gemcitabine[16]
- Carboplatin/paclitaxel[17]

Useful in Certain Circumstances
- Albumin-bound paclitaxel[24]
- Docetaxel[27,28]
- Gemcitabine[29-31]
- Gemcitabine/docetaxel[22]
- Gemcitabine/vinorelbine[23]
- Paclitaxel[32-34]
- Pemetrexed[35]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 3–4)

Best supportive care See NCCN Guidelines for Palliative Care

Maintenance Therapy NSCL-K 3 of 5
Subsequent Therapy NSCL-K 4 of 5
References

[a] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
[b] Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
[c] If first-line systemic therapy completed before treatment for an actionable mutation, and disease has progressed, see Subsequent Therapy NSCL-K 4 of 5.
[d] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR exon 19* deletion *or L858R*, *ALK* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.
[e] If progression on PD-1/PD-L1 inhibitor, using a PD-1/PD-L1 inhibitor is not recommended.
[f] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[g] Bevacizumab should be given until progression.
[h] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[i] Criteria for treatment with bevacizumab: nonsquamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

Continued

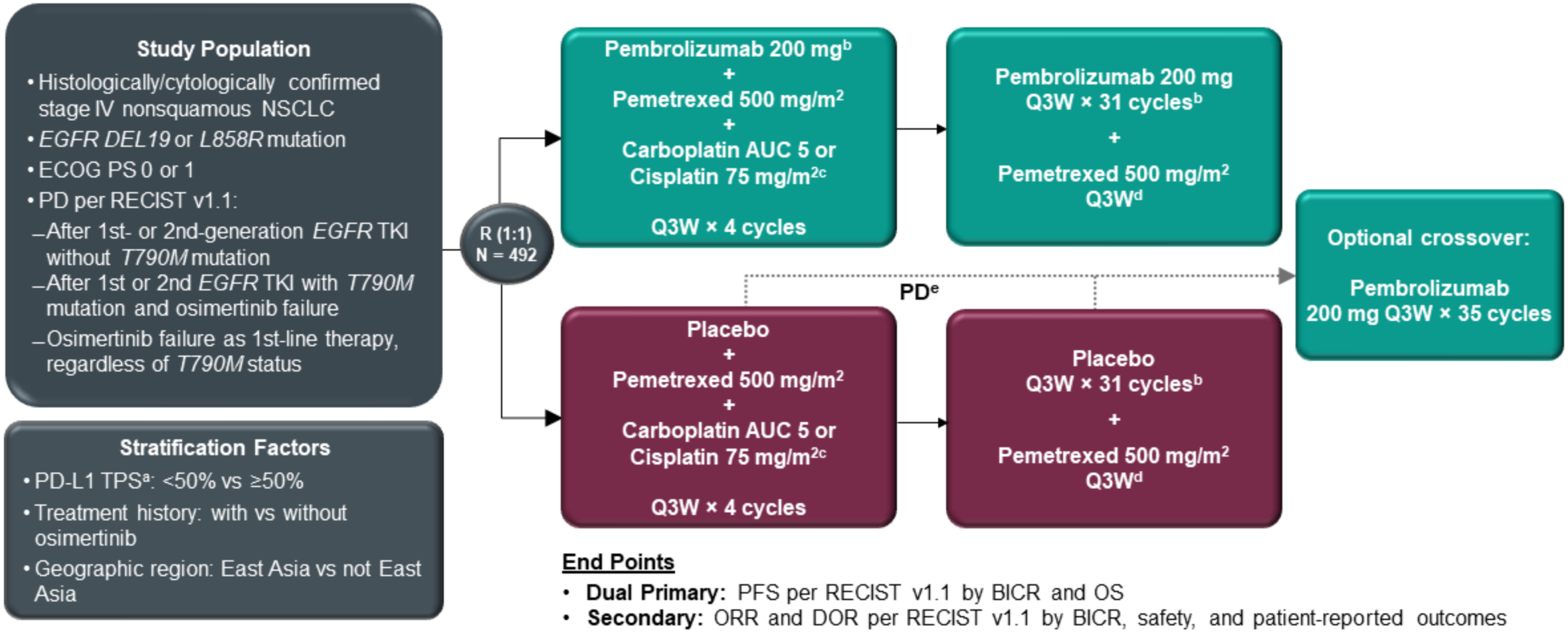
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Pemetrexed and Platinum With or Without Pembrolizumab for Tyrosine Kinase Inhibitor (TKI)-Resistant, *EGFR*-Mutant, Metastatic Nonsquamous NSCLC: Phase 3 KEYNOTE-789 Study

James Chih-Hsin Yang,[1] Dae Ho Lee,[2] Jong-Seok Lee,[3] Yun Fan,[4] Filippo de Marinis,[5] Isamu Okamoto,[6] Takako Inoue,[7] Jerónimo Rodríguez-Cid,[8] Li Zhang,[9] Cheng-Ta Yang,[10] Emmanuel de la Mora Jimenez,[11] Jianying Zhou,[12] Maurice Pérol,[13] Ki Hyeong Lee,[14] David Vicente,[15] Eiki Ichihara,[16] Gregory J. Riely,[17] Yiwen Luo,[18] M. Catherine Pietanza,[18] Niyati Bhagwati,[18] Shun Lu[19]

[1]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan; [2]Asan Medical Center, Seoul, South Korea; [3]Seoul National University Bundang Hospital, Seoul, South Korea; [4]Zhejiang Cancer Hospital, Hangzhou, China; [5]Istituto Europeo di Oncologia, Milan, Italy; [6]Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [7]Osaka International Cancer Institute, Osaka, Japan; [8]Oncology Center, Medica Sur Hospital, Mexico City, Mexico; [9]Peking Union Medical College Hospital, Beijing, China; [10]Chang Gung Memorial Hospital, Taoyuan, Taiwan; [11]Instituto Jalisciense de Cancerología, Guadalajara, Mexico; [12]The First Affiliated Hospital, Zhejiang University, Zhejiang, China; [13]Centre Leon Berard, Lyon, France; [14]Chungbuk National University Hospital, Cheongju-si, South Korea; [15]Hospital Universitario Virgen Macarena, Sevilla, Spain; [16]Okayama University Hospital, Okayama, Japan; [17]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [18]Merck & Co., Inc., Rahway, NJ, USA; [19]Shanghai Chest Hospital, Shanghai, China

KEYNOTE-789: Phase 3 Randomized Study (NCT03515837)



End Points

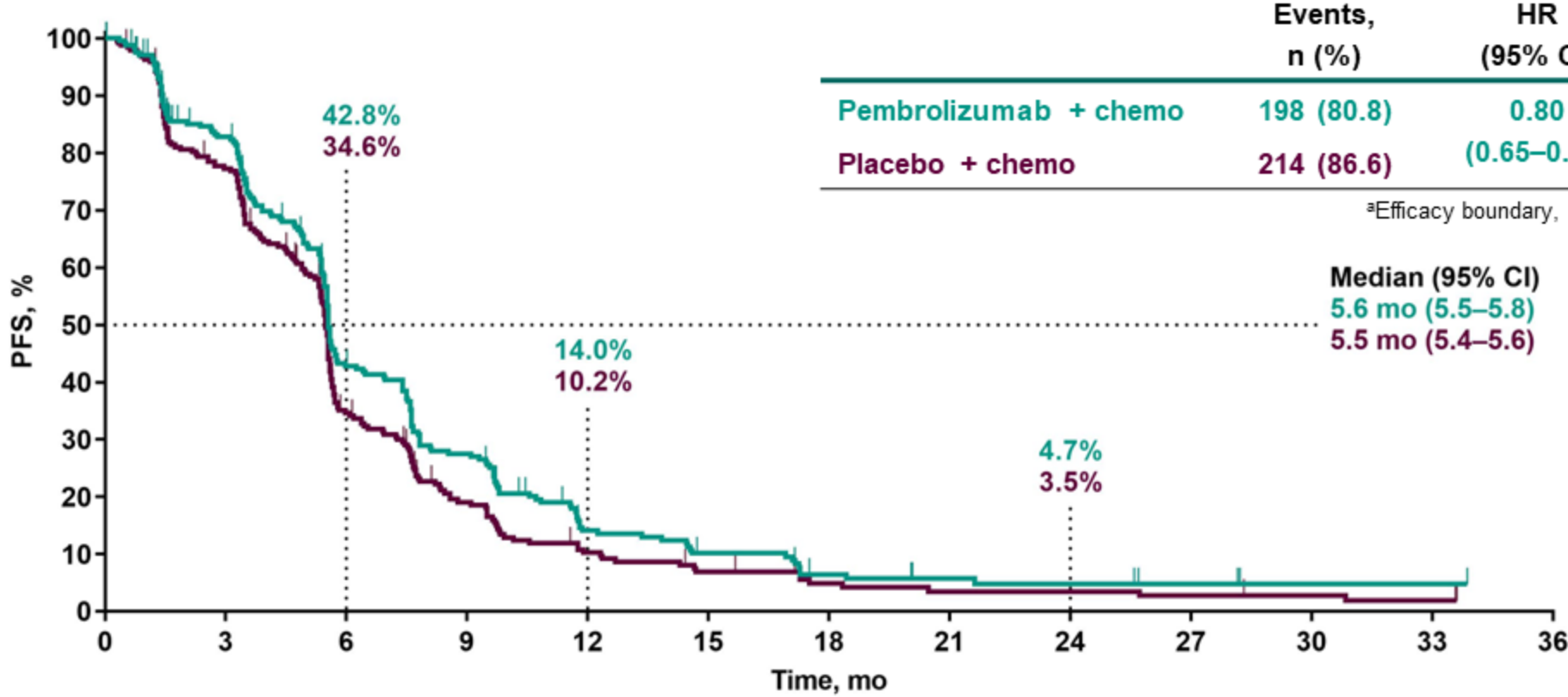
- **Dual Primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR and DOR per RECIST v1.1 by BICR, safety, and patient-reported outcomes

[a]PD-L1 expression was centrally assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). [b]If a patient has documented PD but is benefiting clinically, they may receive pembrolizumab monotherapy to complete a total of 35 pembrolizumab administrations. [c]Carboplatin or cisplatin therapy is at the investigator's choice. [d]Maintenance pemetrexed may continue past 35 cycles until reaching a discontinuation criterion if the patient is receiving benefit; however, pembrolizumab or saline placebo are limited to 35 cycles. [e]Patients could crossover at any time during the treatment. To be eligible for crossover, PD must have been verified by BICR.

Progression-Free Survival at IA2
(RECIST v1.1, BICR)

	Events, n (%)	HR (95% CI)	*P* value[a]
Pembrolizumab + chemo	198 (80.8)	0.80 (0.65–0.97)	0.0122
Placebo + chemo	214 (86.6)		

[a]Efficacy boundary, $P = 0.0117$ for PFS (IA2).



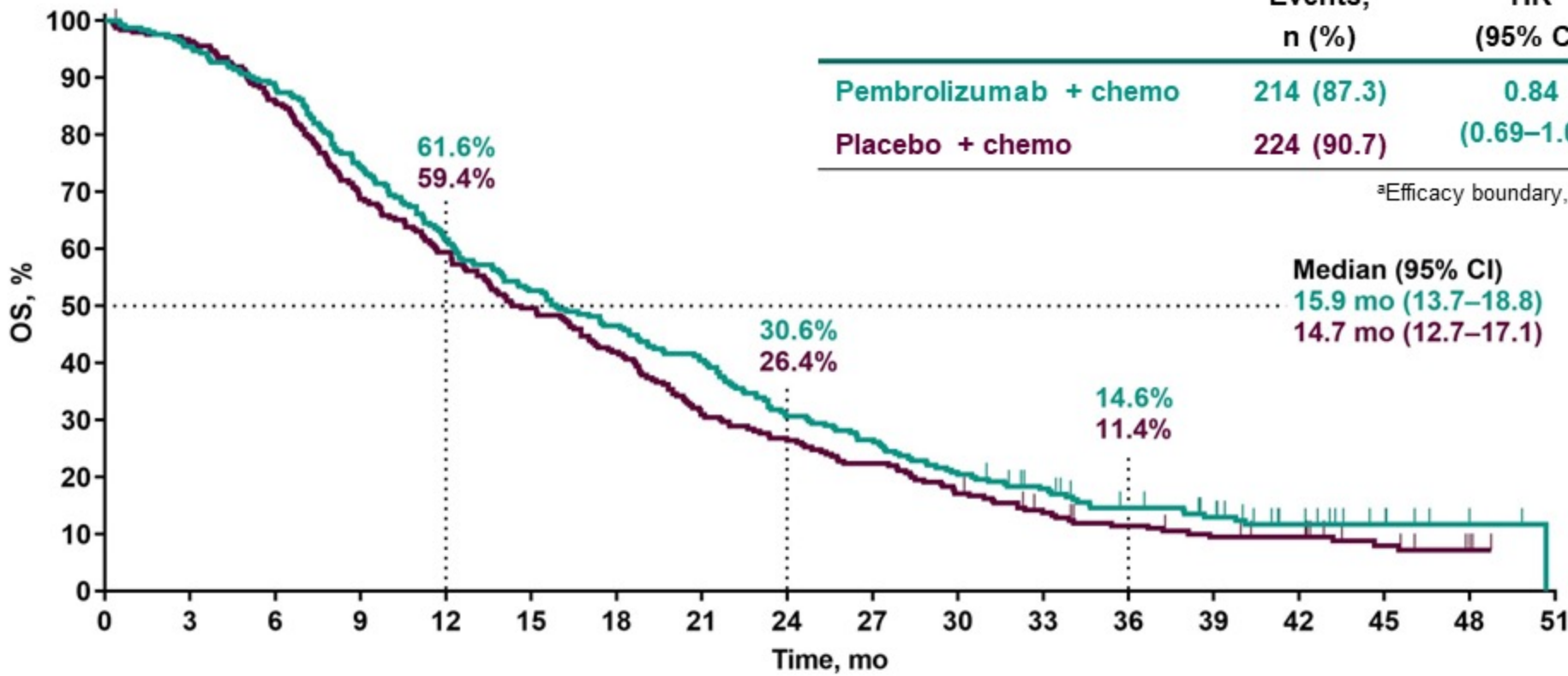
No. at risk													
Pembrolizumab + chemo	245	181	90	57	25	17	9	6	5	3	1	1	0
Placebo + chemo	247	184	75	37	19	12	7	5	5	4	3	2	0

Median time from randomization to data cutoff: 28.6 (16.0–40.4) mo.
Data cutoff date: December 3, 2021.

Overall Survival at FA

	Events, n (%)	HR (95% CI)	*P* value[a]
Pembrolizumab + chemo	214 (87.3)	0.84 (0.69–1.02)	0.0362
Placebo + chemo	224 (90.7)		

[a]Efficacy boundary, $P = 0.0117$ for OS (FA).



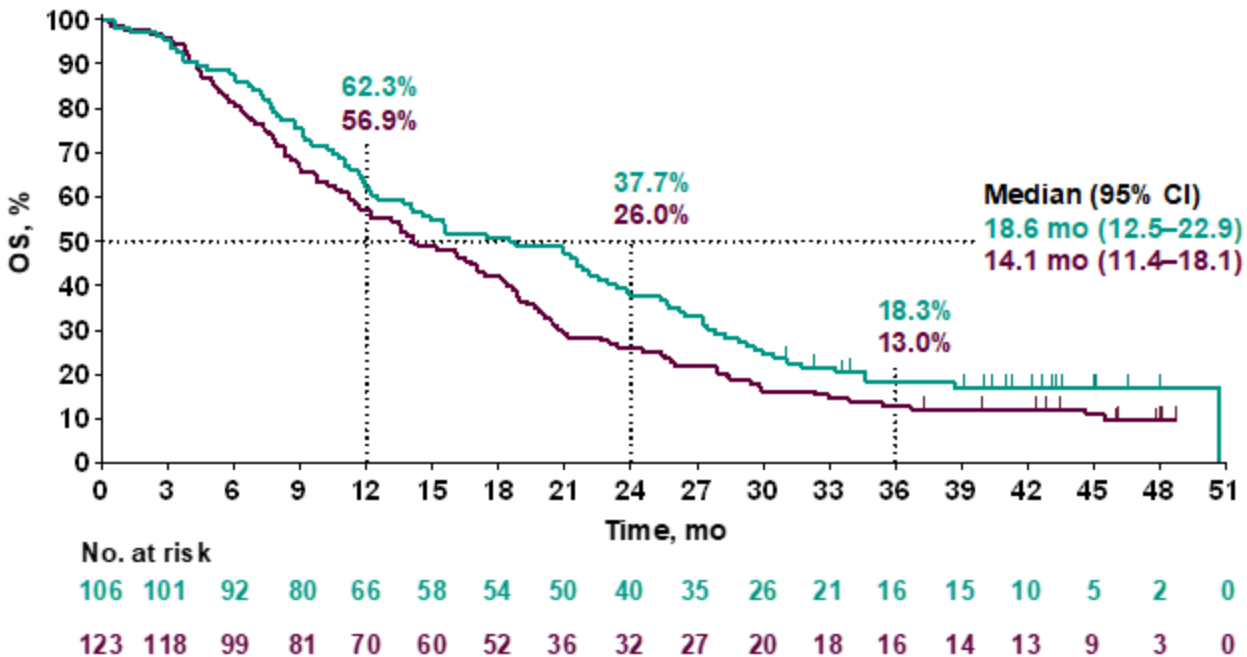
No. at risk																		
Pembrolizumab + chemo	245	234	217	182	151	129	114	99	75	65	50	40	29	23	13	7	3	0
Placebo + chemo	247	237	211	169	146	122	103	76	65	55	42	31	24	19	17	10	3	0

Median (range) time from randomization to data cutoff: 42.0 (29.5–53.9) months.
Data cutoff date: January 17, 2023.

Overall Survival in PD-L1 TPS ≥1% and <1% at FA

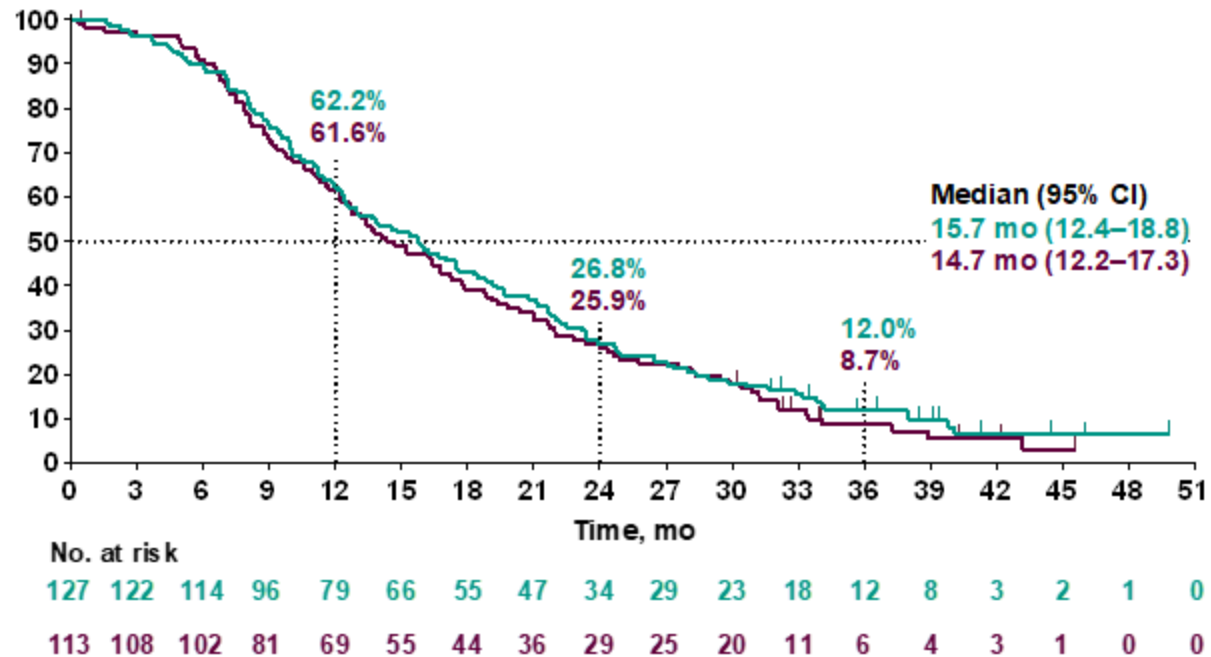
PD-L1 TPS ≥1%

	Events, n (%)	HR (95% CI)
Pembrolizumab + chemo	88 (83.0)	0.77 (0.58–1.02)
Placebo + chemo	110 (89.4)	



PD-L1 TPS <1%

	Events, n (%)	HR (95% CI)
Pembrolizumab + chemo	115 (90.6)	0.91 (0.70–1.19)
Placebo + chemo	104 (92.0)	



Data cutoff date: January 17, 2023.

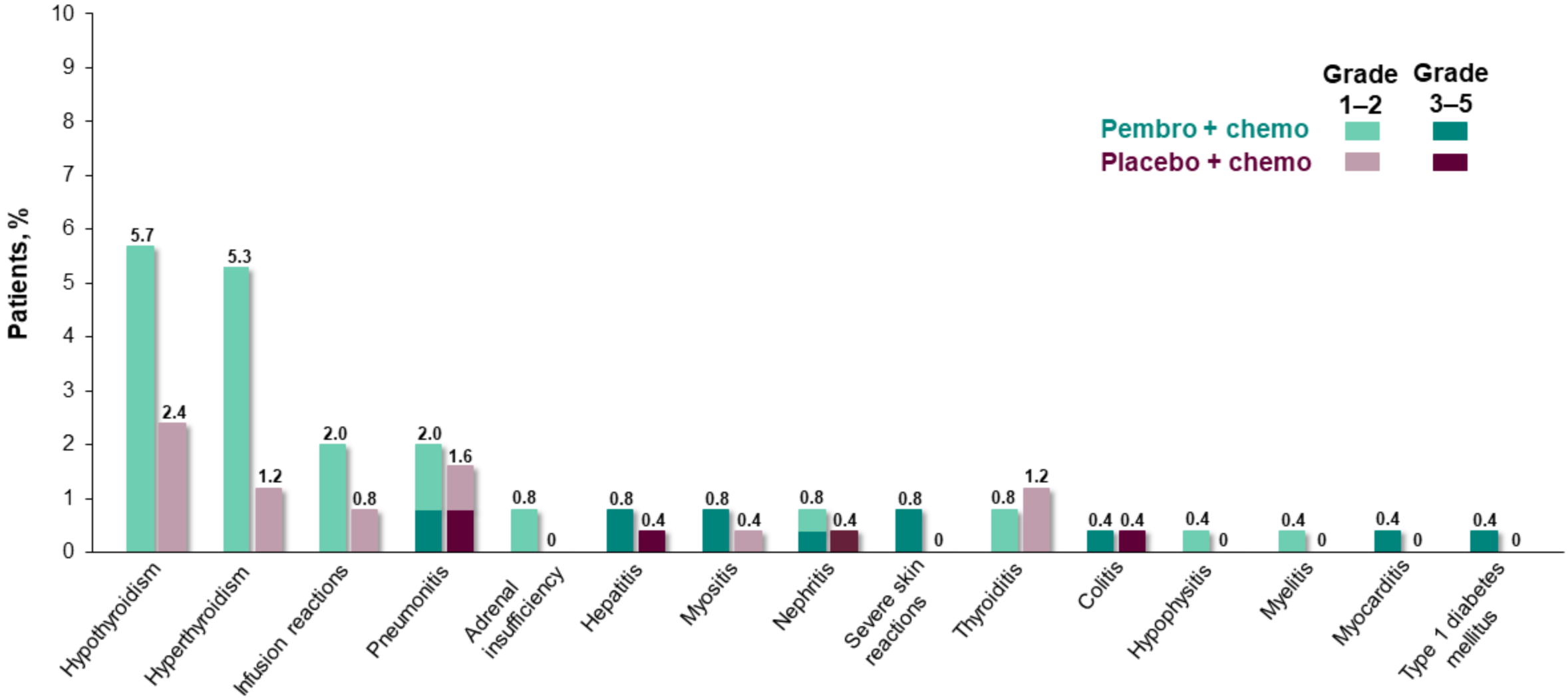
Summary of AEs

- Median (range) number of treatment cycles: 8 (1–62) in pembrolizumab plus chemotherapy; 8 (1–63) in placebo plus chemotherapy group

Patients With AE, n (%)	Pembrolizumab Plus Chemotherapy n = 245	Placebo Plus Chemotherapy n = 246
Any AE (all-cause)	239 (97.6)	241 (98.0)
Grade 3–5	137 (55.9)	143 (58.1)
Led to death	5 (2.0)	12 (4.9)
Treatment related	220 (89.8)	212 (86.2)
Grade 3–5[a]	107 (43.7)	95 (38.6)
Led to discontinuation of any treatment component	40 (16.3)	29 (11.8)
Led to discontinuation of pembrolizumab or placebo	24 (9.8)	11 (4.5)
Led to discontinuation of any chemotherapy	31 (12.7)	29 (11.8)
Led to discontinuation of all treatment components	7 (2.9)	5 (2.0)
Immune-mediated AEs and infusion reactions	49 (20.0)	20 (8.1)
Grade 3–5	11 (4.5)	5 (2.0)

[a]1 patient in the pembrolizumab plus pemetrexed-platinum group died due to a treatment-related AE of myocarditis; 2 patients in the placebo plus pemetrexed-platinum group died due to treatment-related AEs of bone marrow failure (n = 1) and general physical health deterioration (n = 1).
Data cutoff: January 17, 2023.

Immune-Mediated AEs and Infusion Reactions[a]



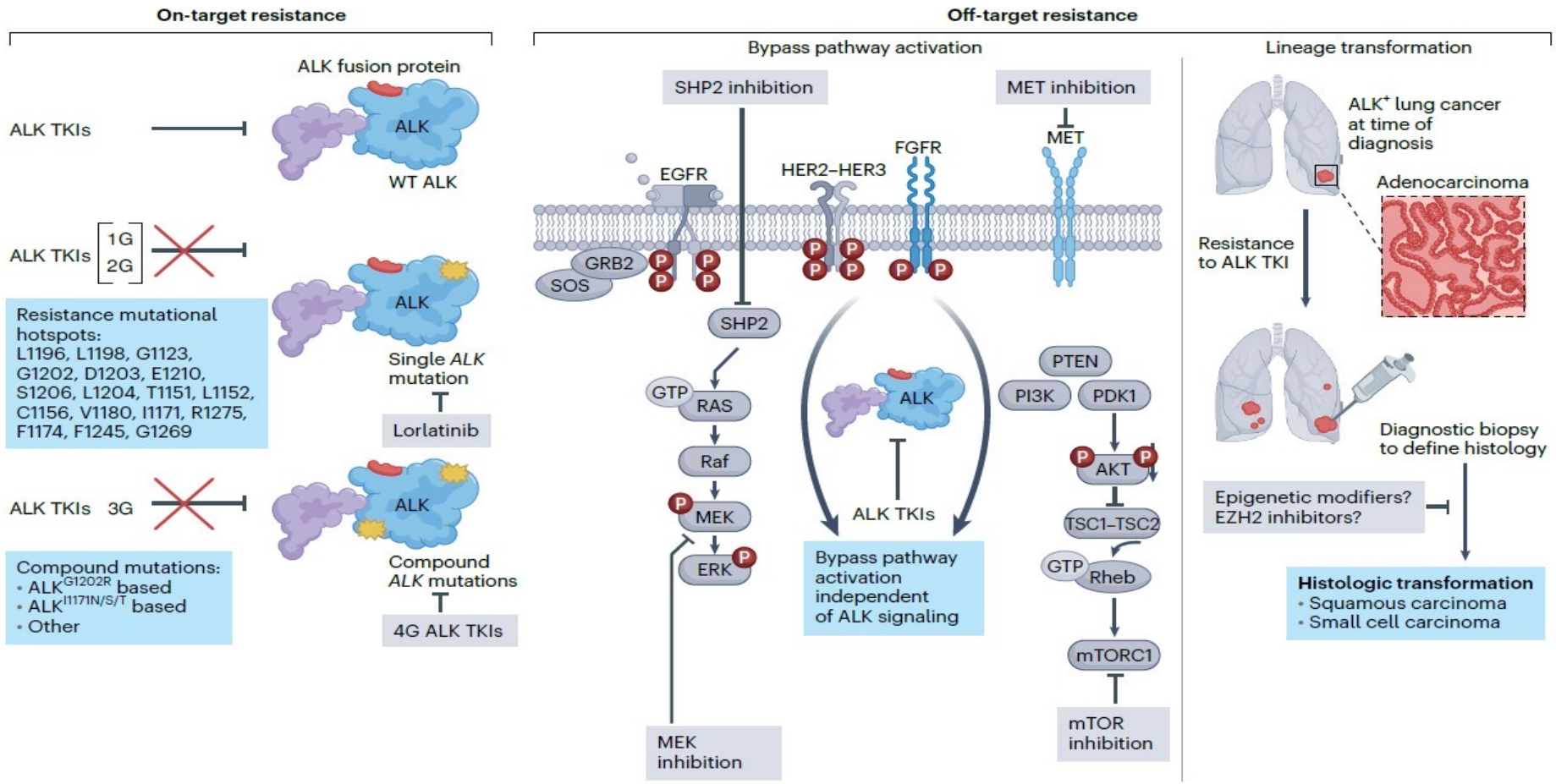
[a]Events were based on a list of terms specified at the time of analysis and were included regardless of attribution to study treatment or immune relatedness by the investigator. Related terms were included.
Data cutoff date: January 17, 2023.

Conclusions

- Addition of pembrolizumab to chemotherapy prolonged PFS and OS vs placebo plus chemotherapy in TKI-resistant, *EGFR*-mutant, metastatic nonsquamous NSCLC, but the results did not reach statistical significance per the prespecified statistical analysis plan
  - PFS (at IA2): median 5.6 mo vs 5.5 mo (HR 0.80; $P = 0.0122$)
  - OS (at FA): median 15.9 mo vs 14.7 mo (HR 0.84; $P = 0.0362$)
- AEs were manageable, with no new safety signals identified
- Results are consistent with prior findings that TKI-resistant, *EGFR*-mutant metastatic NSCLC derives less benefit from anti–PD-(L)1-based treatment than *EGFR* wild-type metastatic NSCLC[1]
  - Additional biomarker research is needed to determine which patients will benefit from ICI therapy in TKI-resistant, *EGFR*-mutant metastatic NSCLC, as there remains a great unmet need for this patient population

1. To KKW, et al. *Front Oncol.* 2021;11:635007.

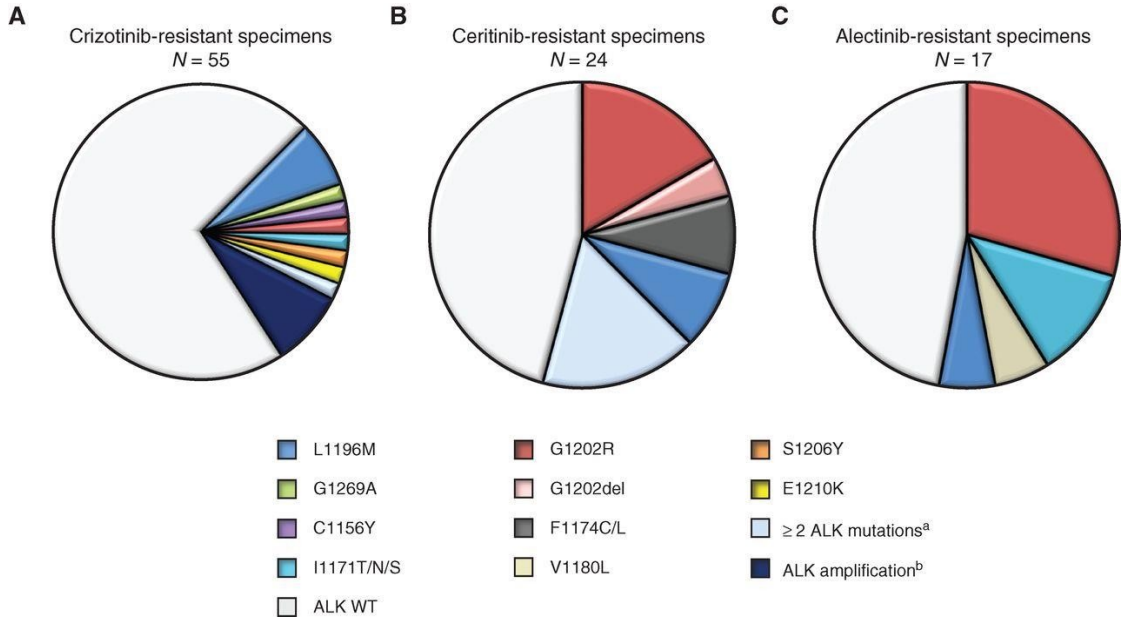
III. Mechanisms of ALK Resistant NSCLC

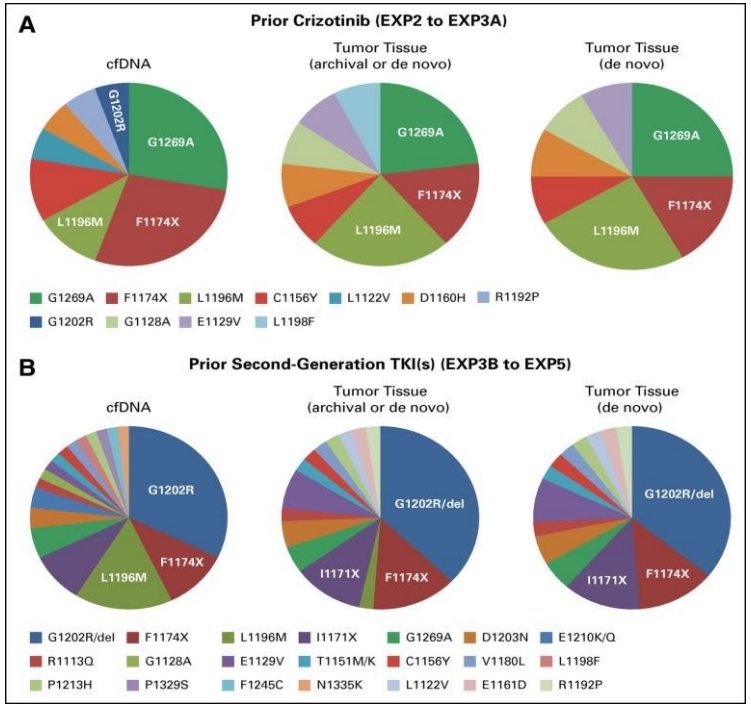


Schneider JL, et al. Nat Cancer 2023.

ALK-mediated resistance

- Dependent on prior ALK TKI exposure
- Resistance on first and second generation ALK TKI → single ALK mutation





Gainor JF et al. Cancer Discov 2016; Shaw AT et al. J Clin Oncol 2019.

- IV. Management of ALK Resistant NSCLC; an area of unmet need

  - Chemotherapy is still the backbone of NSCLC and in ALK-positive patients progressing after ALK TKIs without actionable resistance mutations. Platinum-based chemotherapy is still a valid option.

  - The role of single-agent immune checkpoint inhibitors (ICIs) is still a matter of debate. The combination of an ALK inhibitor and an ICI were studied and resulted in a negative outcome.

  - Phase I/II study combination nivolumab with crizotinib as a first-line treatment (CheckMate 370), the enrollment was discontinued due to significant hepatotoxicity.

  - Similar results were observed in the combination of ceritinib and nivolumab presented ASCO 2017.

  - In contrast, a manageable toxicity profile has been reported with the combinations avelumab with lorlatinib in the phase 1b/2 JAVELIN Lung 101 trial33 and atezolizumab with alectinib34. with no new or unexpected side effects.

  - Encouraging data are emerging with the chemoimmunotherapy combinations in a small subset analysis of the IMpower 150 trial.

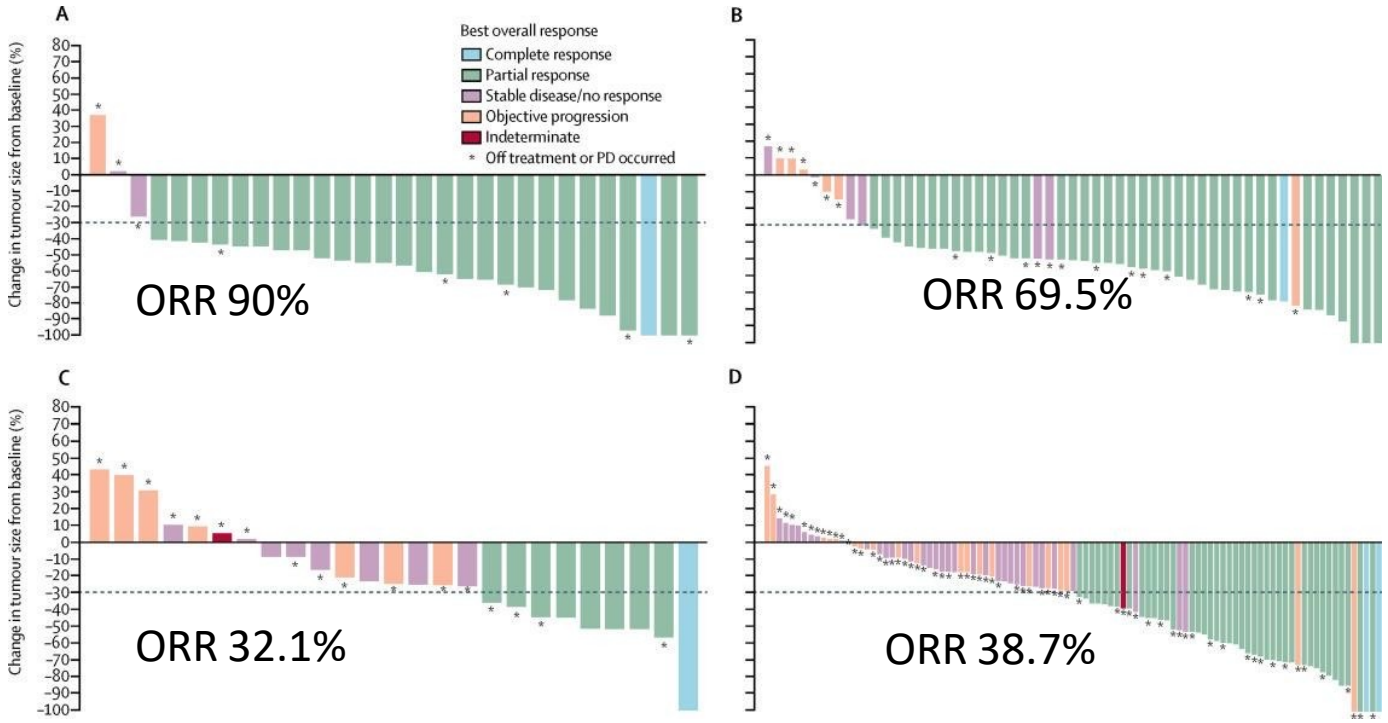
ALK Resistant NSCLC

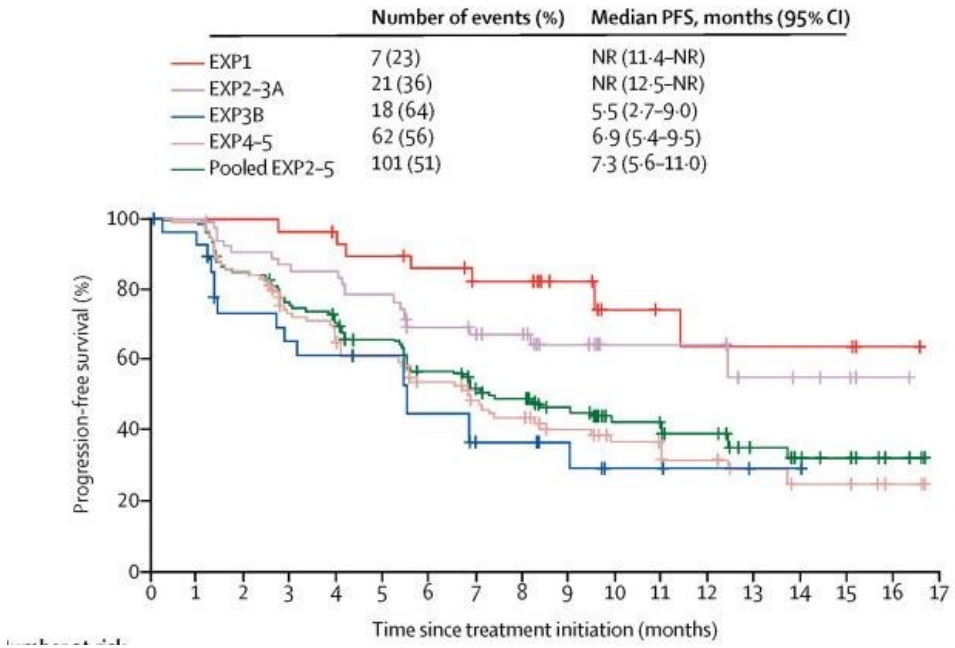
INOVA

- As ctDNA and tissue NGS techniques continue to advance, we expect a better understanding of the optimal treatment sequencing to emerge.

- The role of immunotherapy in combination with chemotherapy should be addressed in prospective clinical trials in order to produce more robust efficacy data in this small subgroup of NSCLC patients and to define their exact place in the therapeutic armamentarium of ALK-rearranged NSCLCs.

The efficacy of lorlatinib after prior ALK TKI

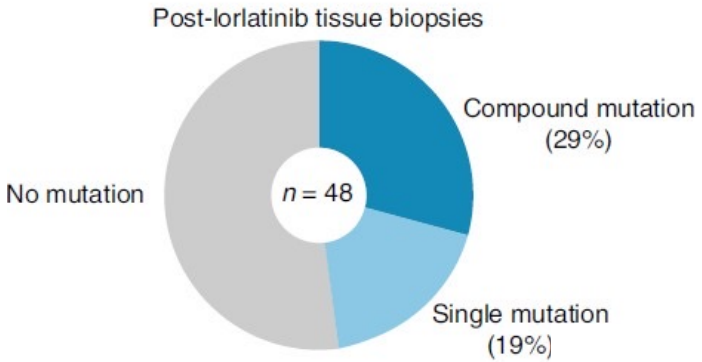


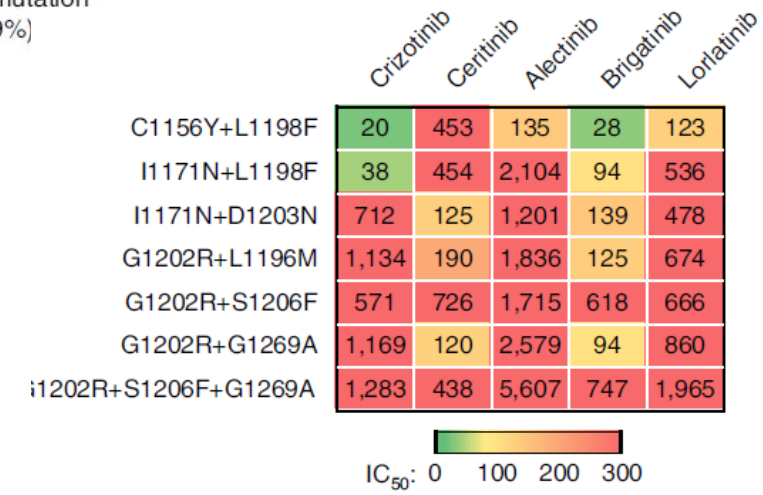


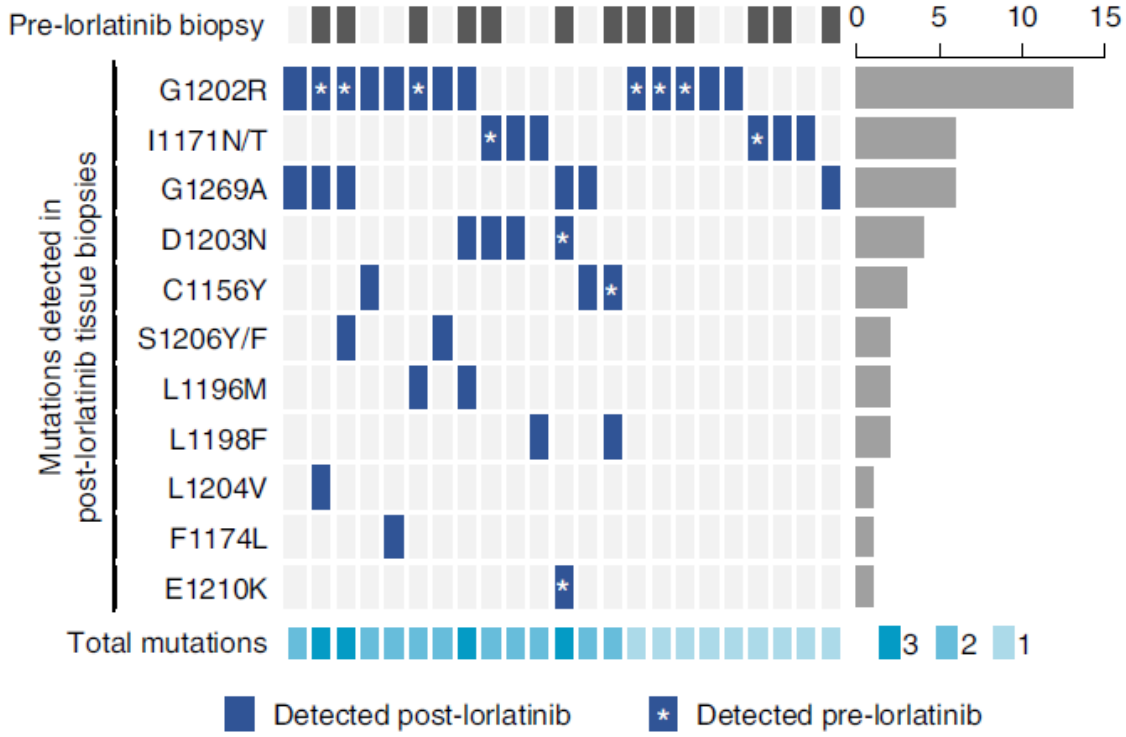
(A) EXP1: treatment-naive patients. (B) EXP2–3A: previous crizotinib with or without 1–2 chemotherapy regimens. (C) EXP3B: previous non-crizotinib ALK TKI with or without chemotherapy. (D) EXP4–5: two or more previous ALK TKIs with or without chemotherapy.

Solomon BJ, et al. Lancet Oncol 2018.

Resistance to lorlatinib is more challenging







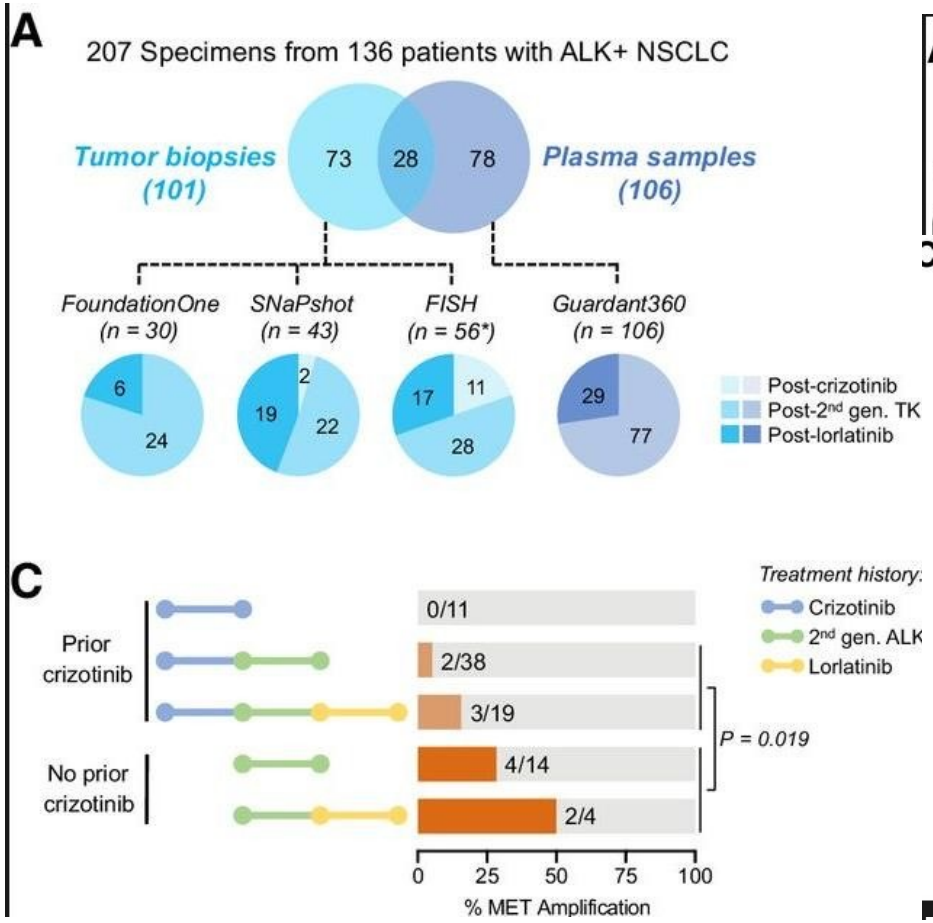
Shiba-Ishii A et al. Nat Cancer 2022.

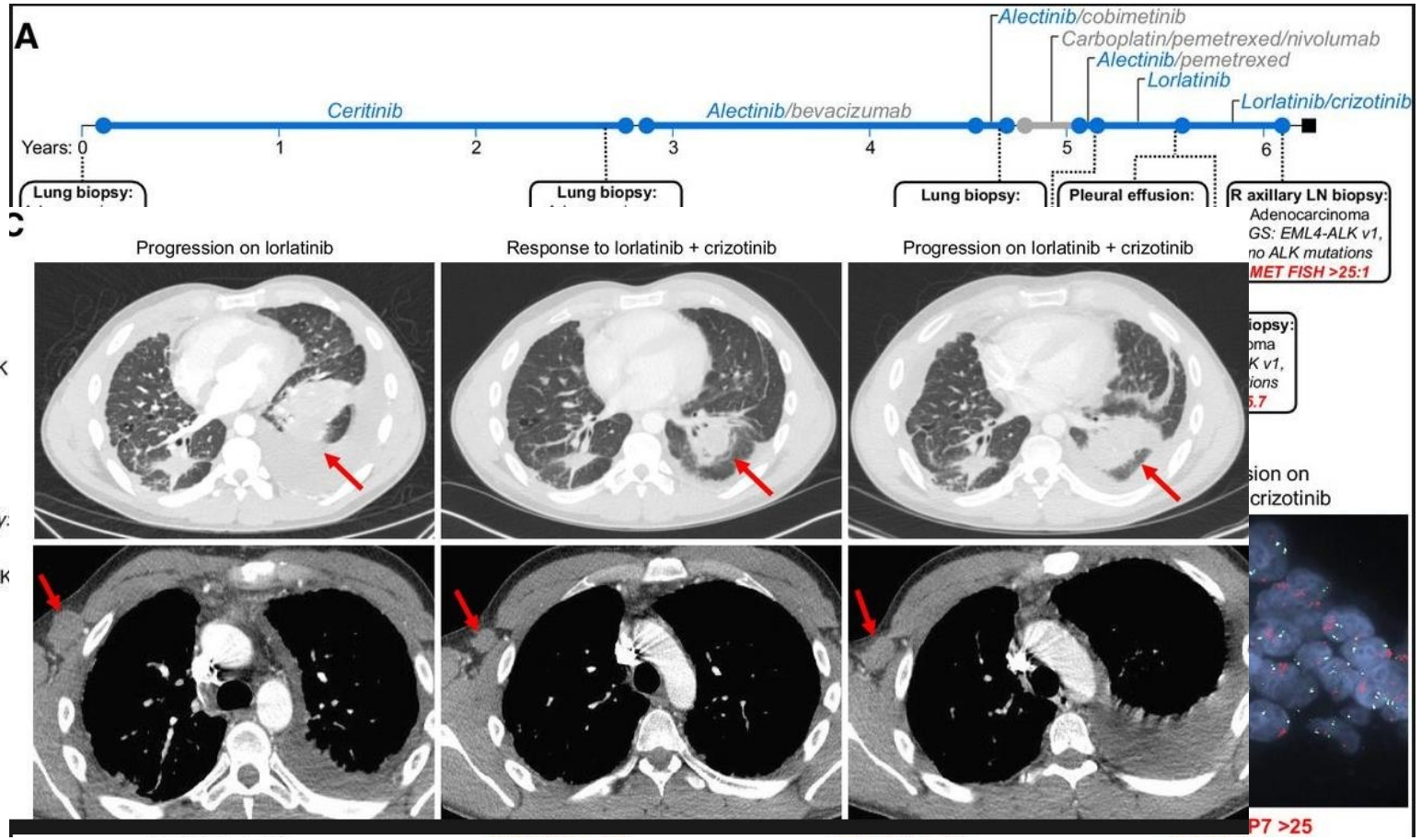
ALK-independent resistance

Bypass mechanism	Prior ALK TKI[a]	Prevalence
MET amplifications	Second-generation TKIs	12% in first or later lines
	Lorlatinib	22% in later lines
MET rearrangements	Alectinib or lorlatinib	3% in later lines
MET exon 14 mutations	Alectinib	Unknown, data limited to case reports
RET rearrangements	Brigatinib	Unknown, data limited to case reports
EGFR activation	Crizotinib	44% in first line
EGFR mutations	Crizotinib	9–14% in first line
HER2 amplifications	Crizotinib, alectinib	Unknown, data limited to case reports
KIT amplifications/activation	Crizotinib	15% in first line
IGF1R activation	Crizotinib	80% in first line
SHP2 signalling	Ceritinib	Preclinical data only
NF2 mutations	Lorlatinib	20% in later lines
YES1 amplifications	Crizotinib, ceritinib	11.8% in later lines
KRAS mutations	Crizotinib	18% in first line
$BRAF^{V600E}$ mutations	Alectinib	Unknown, data limited to case reports
MAP2K1 mutations	Ceritinib	Unknown, data limited to case reports
DUSP6 loss	Crizotinib	83%
PIK3CA mutations	Lorlatinib or ceritinib	Unknown, data limited to case reports
AXL overexpression	Earlier-generation TKIs	Preclinical data only

Cooper AJ, Sequist LV, Lin JJ. Nat Rev Clin Oncol 2022

Treating ALK resistance



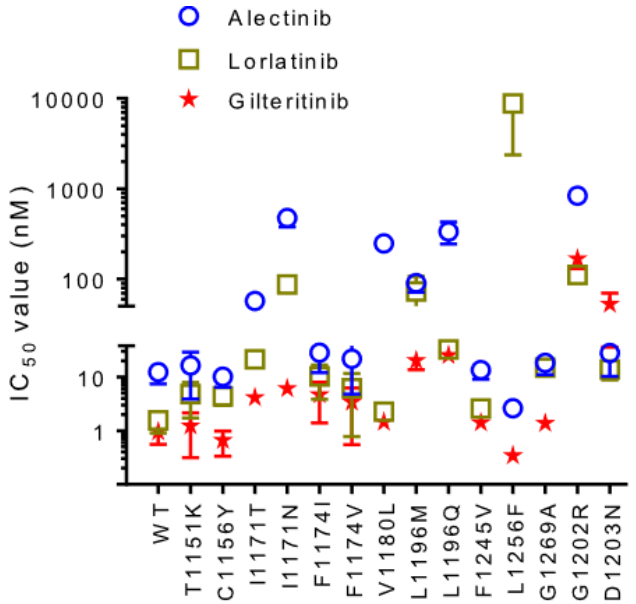


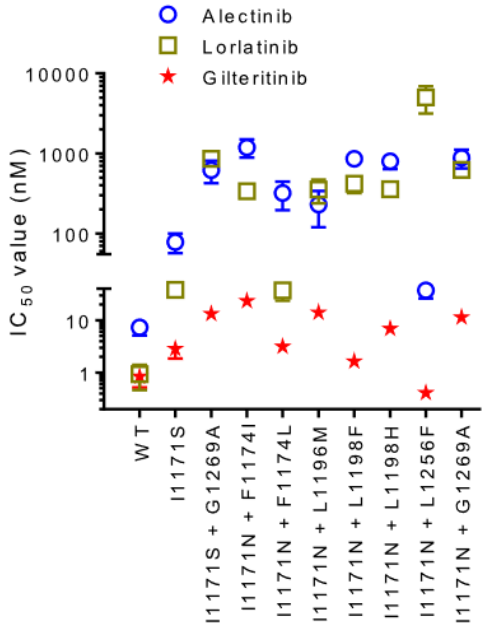
Angel Qin TTLC 2023

Dagogo-Jack I et al. Clin Cancer Res 2020

A Phase I Study of Gilteritinib for ALK Positive NSCLC

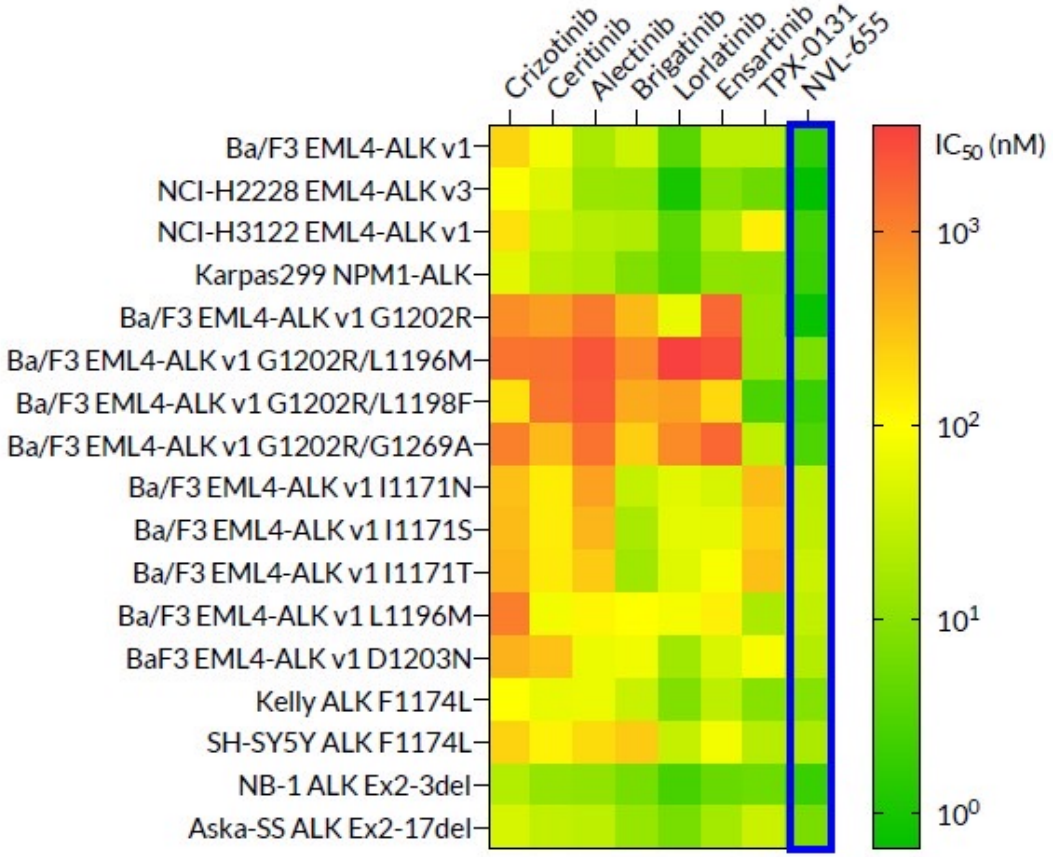
- Gilteritinib is a TKI approved by the FDA for the treatment of relapsed/refractory FLT3 mutated AML
- Activity against FLT3, LRTK, ALK, AXL, tropomyosin receptor kinase A, ROS, RET and MER kinases





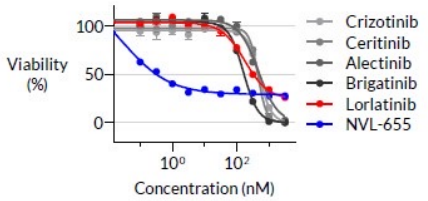
Mizuta H et al. Nat Comm 2021

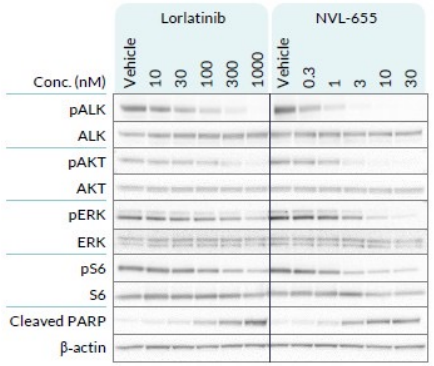
Next generation ALK inhibitor



IN VITRO ACTIVITY

NVL-655 potently suppressed viability (IC_{50} < 1 nM) and ALK pathway signaling (IC_{50} < 3 nM) in MR448re cells. By contrast, lorlatinib had poor activity against MR448re in both assays (IC_{50} > 300 nM).

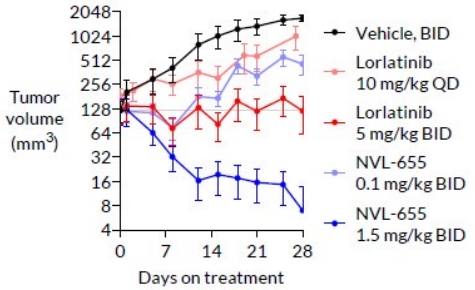


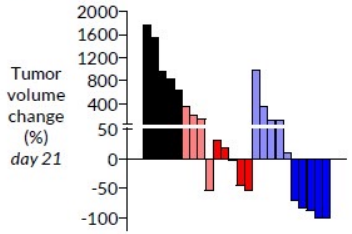


▲ Figure 7 Activity of ALK TKIs in MR448re cells. (Left) Dose-response curves from 3-day viability assays. Mean ± SEM plotted. Data from n ≥ 2 repeat testing. (Right) Western blot showing ALK pathway activity. Cells were treated for 6 hours. Figure adapted from Reference 13.

IN VIVO ACTIVITY

NVL-655 induced regression in the MR448re patient cell line-derived xenograft without causing significant body weight changes (data not shown). MR448re showed reduced sensitivity to lorlatinib, consistent with treatment history.



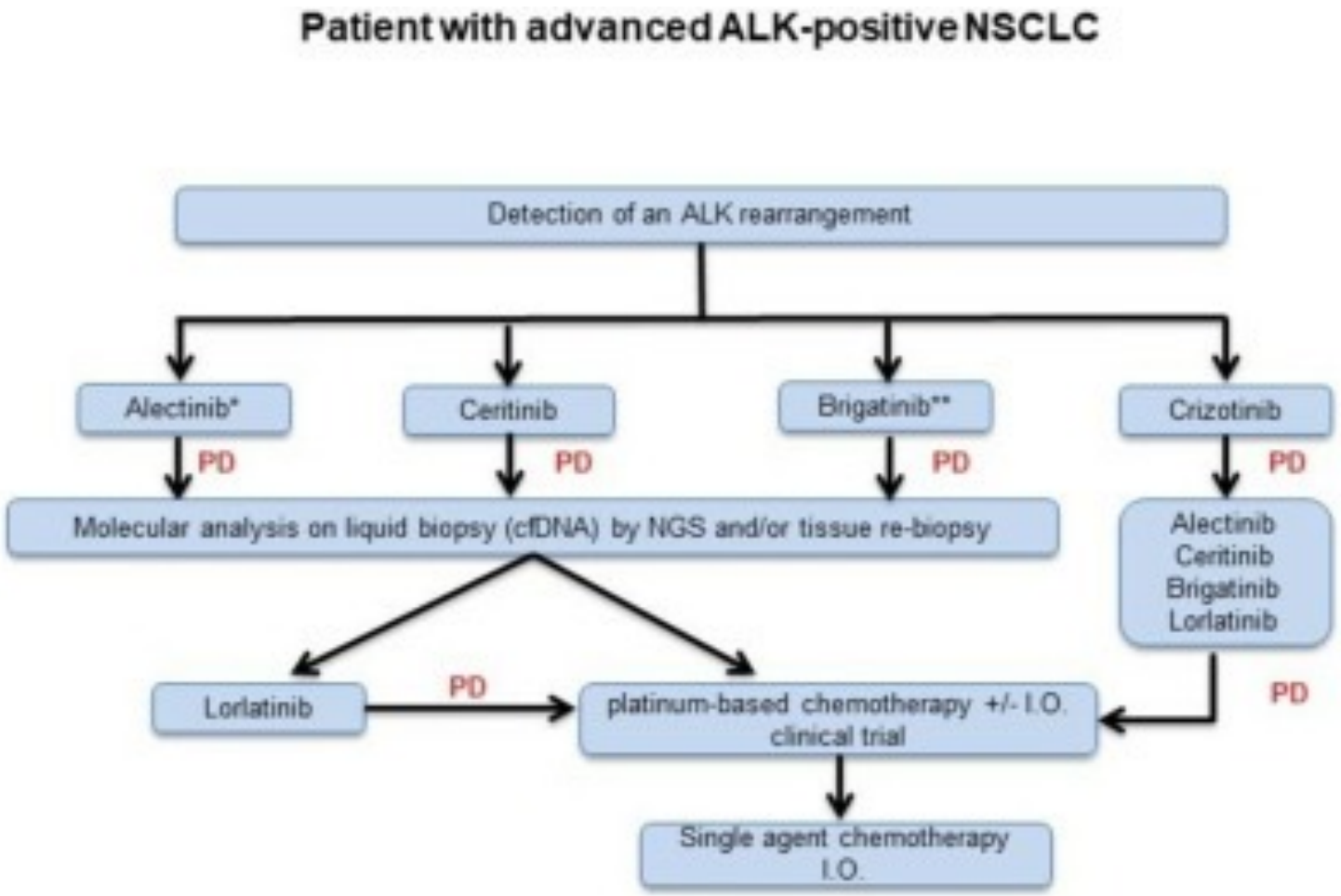


Fujino T et al. EORTC-NCI-AACR 2022

Ongoing clinical trials

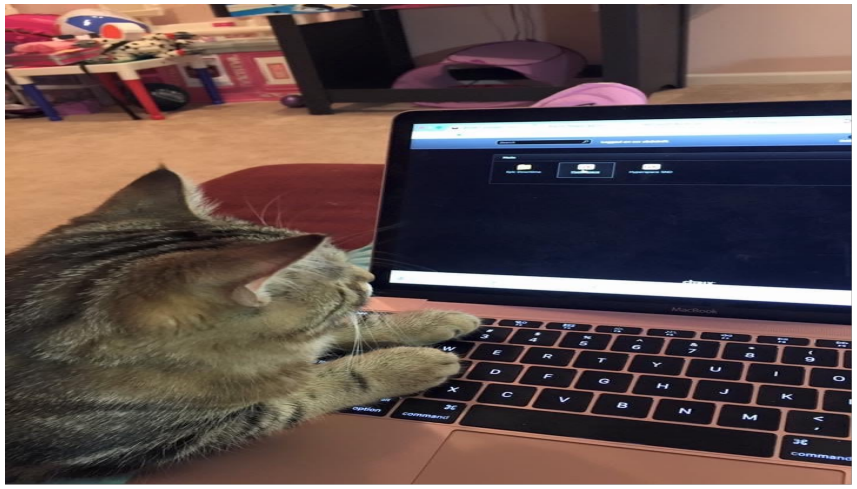
- A Phase IB/II Study of Alectinib Combined With Cobimetinib in Advanced ALK-Rearranged (ALK+) NSCLC. NCT 03202940
- A Study Evaluating Platinum-Pemetrexed-Atezolizumab (+/- Bevacizumab) for Patients With Stage IIIB/IV Non-squamous NSCLC With EGFR Mutations, ALK Rearrangement or ROS1 Fusion Progressing After Targeted Therapies. NCT 04042558
- Clinical Trial of CD40L-Augmented TIL for Patients With EGFR, ALK, ROS1 or HER2-Driven NSCLC. NCT05681780.
- Lorlatinib Combinations in Lung Cancer. NCT04292119.

ALK Resistant NSCLC



*preferred option
**not yet FDA/EMA approved for this indication

I treat ALK-positive non-small cell lung cancer Michael G. McCusker, Alessandro Russo, Katherine A. Scilla, Ranee Mehra, Christian Rolfo ESMO Open 2019



Unleashing Innovations

“Addressing the unmet Needs of EGFR and ALK Resistant NSCLC Patients”