NOSCM™
NEW ORLEANS SUMMER CANCER MEETING

June 24-26, 2022
The Roosevelt Hotel
New Orleans, LA

17TH ANNUAL
New Orleans Summer Cancer Meeting

CONFERENCE CHAIRMAN
Edgardo S. Santos Castillero, MD, FACP

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FAU MEDICINE
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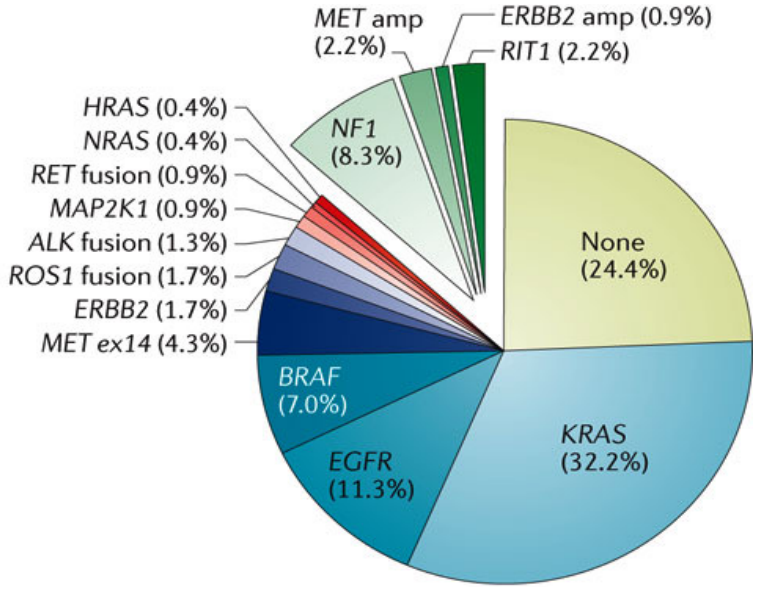
Targeted Therapy in NSCLC: FDA approvals

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*
- [?]*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, 03/16/2022

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EGFR Pathway
Salvage Osimertinib

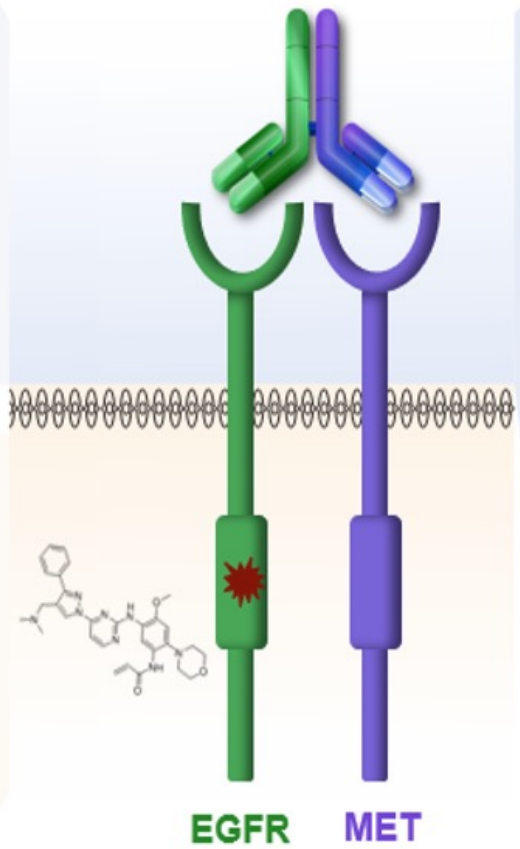
Amivantamab and Lazertinib CHRYSALIS Study

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

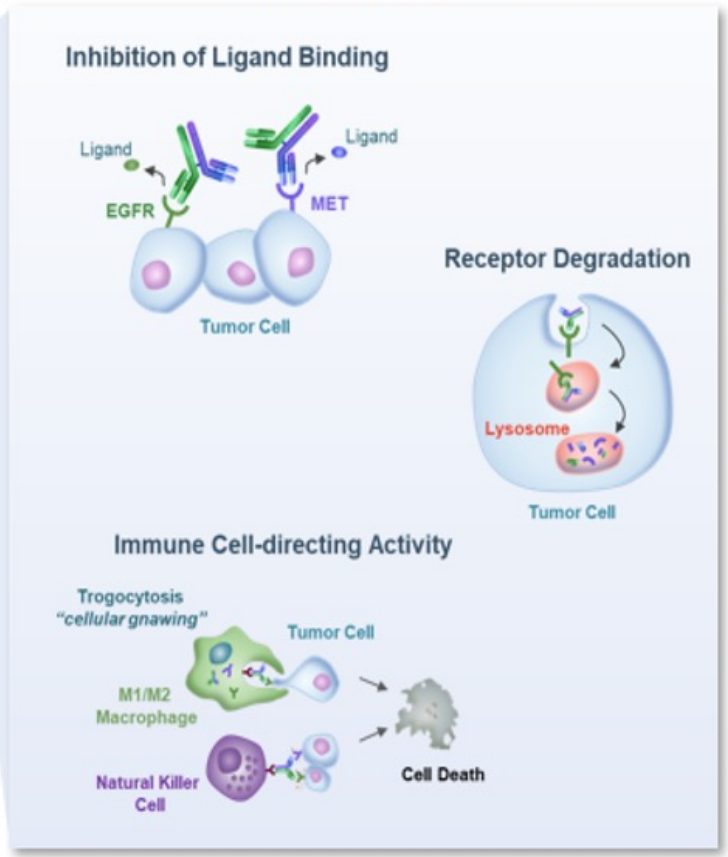
- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

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 et al. 2021 ASCO, abstr 9006.

CHRYSALIS Phase 1 Study Design: Combination Cohort (NCT02609776)

Key Objectives

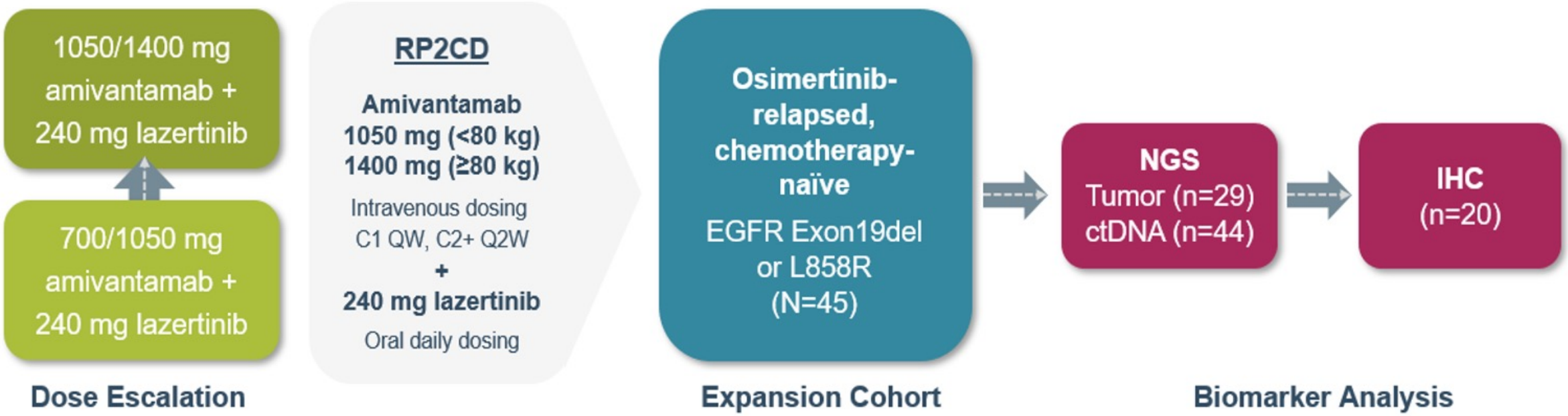
- Establish RP2CD
- Safety and efficacy at RP2CD

Key Eligibility Criteria

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

Biomarker Analysis[a]

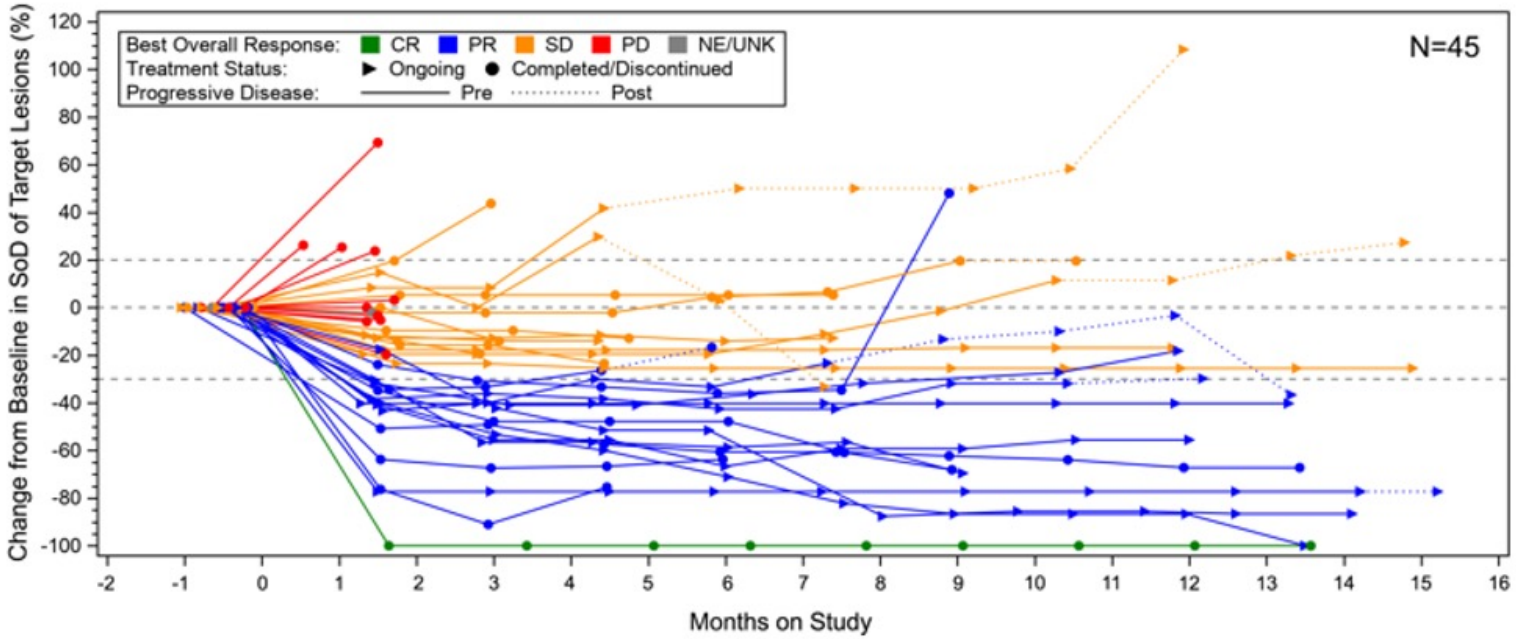
- NGS of pretreatment tumor biopsy and ctDNA collected prospectively
- IHC for EGFR/MET expression



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

Durable Responses Observed with Amivantamab + Lazertinib with Manageable Safety

CHEMO-NAIVE



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)

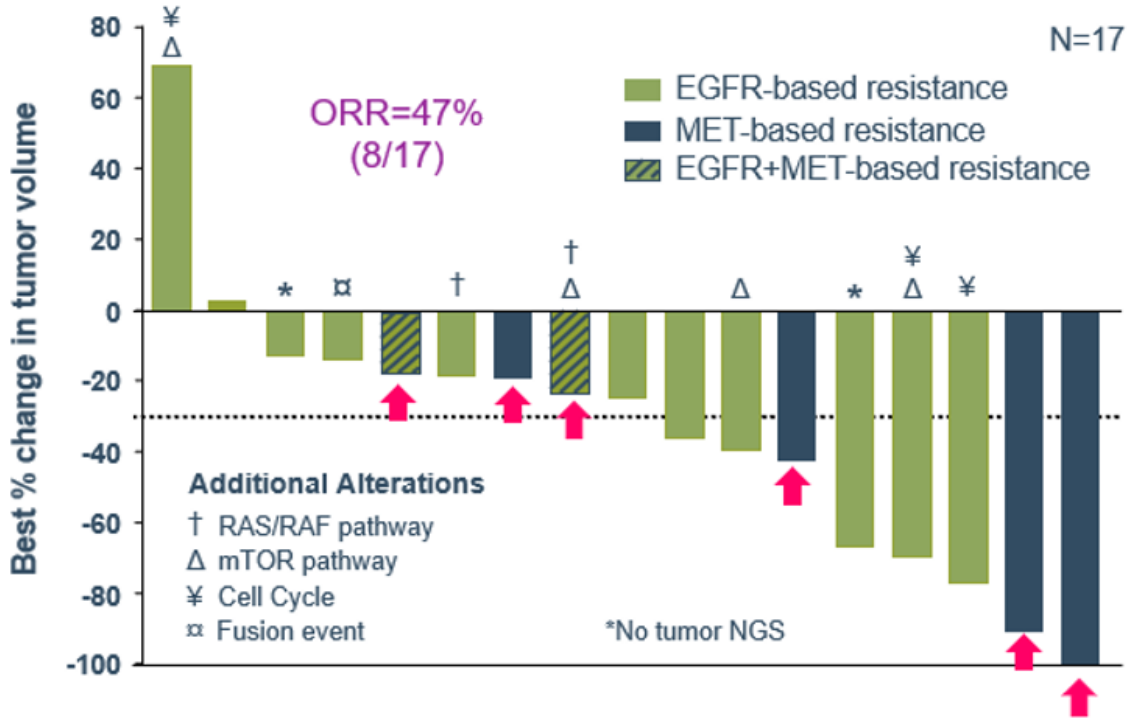
- Safety profile consistent with previous experience with amivantamab + lazertinib[1]
- Most common AEs were IRR (78%), rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%)
  - Majority were grade 1–2
- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

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

BC Cho et al. 2021 ASCO, abstr 9006.

Response Among Patients with Identified EGFR/MET-based Resistance

- **17 of 45** patients were **identified with either EGFR/MET-based resistance** by NGS[a] (ctDNA/tissue)
- **ORR in this subgroup was 47%,** mDOR was 10.4 months, CBR was 82%, and mPFS was 6.7 months

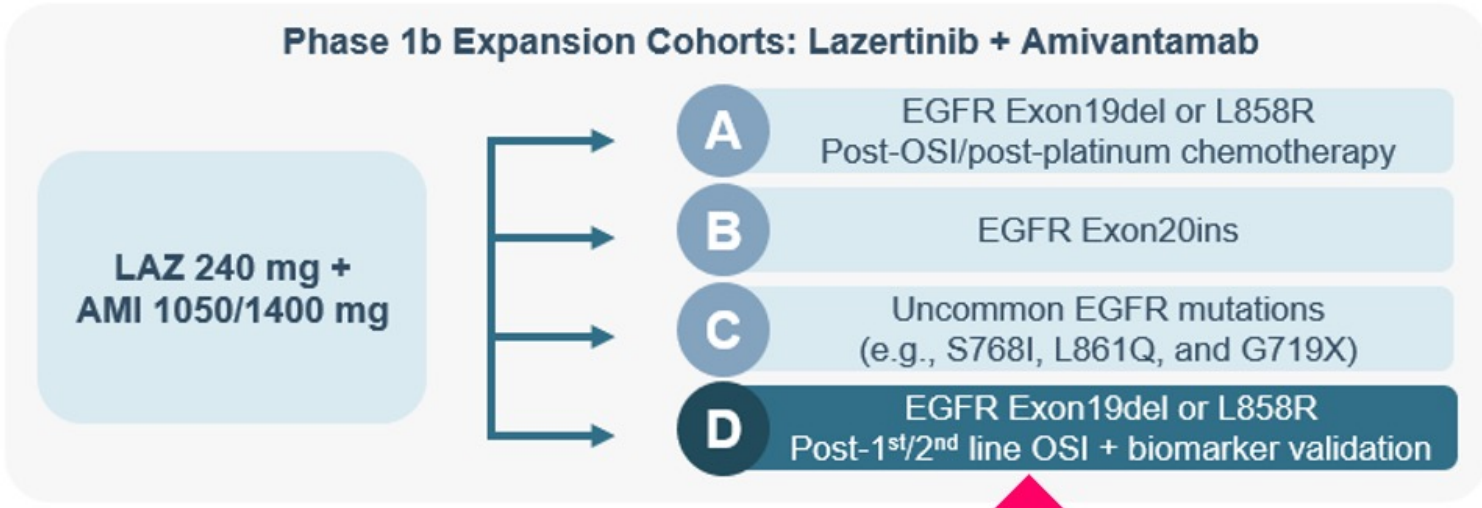


Resistance[b]	Alterations[c]	
EGFR-based	C797S (n=7) Amp (n=3) L718X (n=3) G724S (n=2)	L792H (n=1) G796S (n=1) E709K (n=1)
MET-based	Amp (n=5)	METex14 (n=1)
Additional	PIK3CA E542X (n=2) CCNE1 Amp (n=1) PIK3CA Amp (n=1) CCND1 Amp (n=1) CDK4 (n=1)	KRAS Amp (n=1) FGFR3-TACC3 fusion (n=1) KRAS G12D (n=1) CDKN2A G101W (n=1)

[a]Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS; [b]EGFR amp (CNV ≥7) and MET amp (CNV ≥3) were based on tumor NGS; other amps were based on tumor NGS (CNV ≥7) or ctDNA NGS (CNV ≥3). Single nucleotide variants, insertion/deletions, and insertion call threshold was ≥1% allele frequency with >250 reads. [c]Eight patients had ≥1 alteration. Amp, amplification; CNV, copy number variation

BC Cho et al. 2021 ASCO, abstr 9006.

CHRYSALIS-2 Study Design: Phase 1b Expansion Cohorts
(NCT04077463)



looking to validate biomarkers identified at CHRYSALIS
In a prospective fashion

Key Inclusion Criteria

Phase 1b Expansion Cohorts

A	▪ EGFR Exon19del or L858R ▪ Post-osimertinib (1st/2nd line) *and* ▪ Progression on platinum-based chemotherapy as last line
B	▪ EGFR Exon20ins ▪ Prior SOC platinum-based chemotherapy or alternatively, EGFR TKI[a] or IO ▪ ≤3 prior lines of therapy
C	▪ Uncommon non-Exon20ins mutation[b] ▪ Treatment-naïve or 1 prior 1st/2nd-gen EGFR TKI as last line ▪ ≤2 prior lines of therapy
D	▪ EGFR Exon19del or L858R ▪ Post-osimertinib (1st/2nd line) as last line ▪ Amenable to tumor biopsy[c] for biomarker validation

[a]Includes investigational EGFR-TKI targeting Exon20ins (e.g., mobocertinib and poziotinib). [b]e.g., S768I, L861Q, G719X. [c]After progression on most recent system treatment or from initial biopsy in metastatic setting.
AMI, amivantamab; Exon20ins; exon 20 insertion; IO, immuno-oncology therapy; LAZ, lazertinib; OSI, osimertinib; SOC, standard of care

BC Cho et al. ASCO 2022, abstr 9006

CHRYSALIS-2 (ClinicalTrails.gov Identifier: NCT04077463) Study Design

Dose Expansion Cohorts

RP2CD: Lazertinib 240 mg PO +
Amivantamab 1050 mg (1400 mg for ≥80 kg) IV

Cohort A: EGFR ex19del or L858R
Post-osimertinib and platinum-based chemotherapy (n=162)

Cohort B: EGFR ex20ins
Post-standard of care and platinum-based chemotherapy

Cohort C: Uncommon EGFR mutations
Treatment naïve or post-1st or 2nd generation EGFR TKI

Cohort D: EGFR ex19del or L858R
Post-osimertinib, chemotherapy naïve, biomarker validation

Endpoints

- Overall response rate (primary)
- Duration of response
- Clinical benefit rate[a]
- Progression-free survival
- Overall survival
- Adverse events

Here we present updated **safety** and **efficacy** results
of the **amivantamab and lazertinib combination** from **fully enrolled Cohort A**

[a]Percentage of patients with confirmed response or durable stable disease (duration of ≥11 weeks).

EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; ex20ins, exon 20 insertion; IV, intravenous; PO, per oral; RP2CD, recommended phase 2 combination dose; TKI, tyrosine kinase inhibitor.

CA Shu et al. ASCO 2022

Demographics and Baseline Characteristics

Characteristic, n (%)	n=162
Median age, years (range)	61.5 (31–83)
Male / female	57 (35) / 105 (65)
Race	
White	42 (26)
Asian	99 (61)
Black	1 (0.6)
Not reported	20 (12)
ECOG PS 0 /1	49 (30) / 113 (70)
Brain metastases at baseline[a]	66 (41)
Untreated	30 (19)
Treated	36 (22)

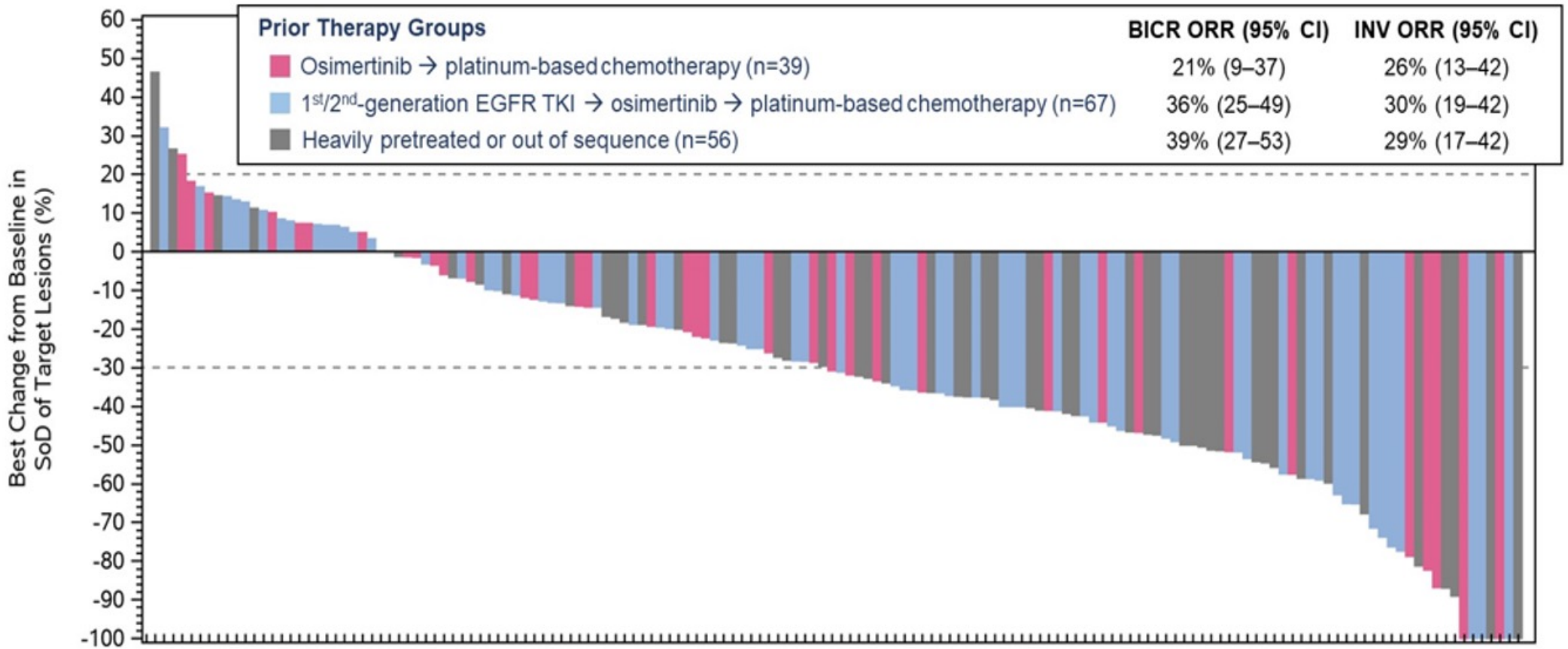
Characteristic, n (%)	n=162
Smoking history	
Non-smoker	111 (69)
Smoker	49 (30)
Unknown	2 (1)
Median number of prior therapy lines (range)	3 (2–14)
2–3	117 (72)
≥4	45 (28)
Prior therapy regimens	
Frontline osimertinib → platinum-based chemo	39 (23)
1st/2nd-gen EGFR TKI → osimertinib → platinum-based chemo	67 (42)
Heavily pretreated or out of sequence	56 (35)

[a]Study initially allowed stable/asymptomatic treated or untreated brain metastases at baseline and was later amended to allow for treated brain metastases only.

Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; gen, generation; TKI, tyrosine kinase inhibitor.

CA Shu et al. ASCO 2022

Best Antitumor Response and ORR by Prior Therapy Group



- 10 efficacy-evaluable patients did not have any evaluable post-baseline target lesion measurements

BICR, blinded independent central review; CI, confidence interval; EGFR, epidermal growth factor receptor; INV, investigator-assessed; ORR, overall response rate; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

CA Shu et al. ASCO 2022

CNS Antitumor Activity of Amivantamab + Lazertinib

Retrospective, Exploratory CNS Analysis

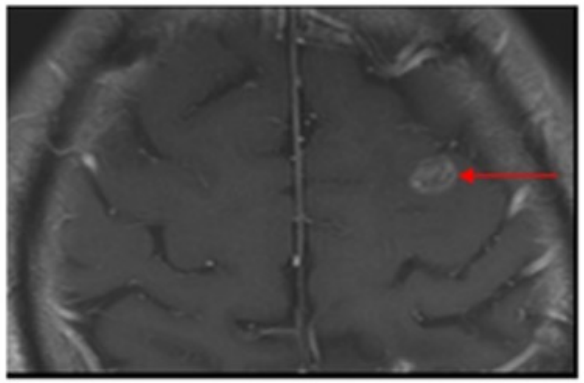
- CHRYSALIS-2 Cohort A allowed stable treated and untreated brain metastases during its conduct; in addition to baseline brain imaging, follow-up imaging was required for those with baseline lesions
- Among the 66 patients with baseline brain lesions,[a] 30 were untreated (no prior brain radiation/surgery), of which 27 completed ≥1 post-baseline brain scan

Best CNS Lesion Assessment/evaluation	Untreated Brain Metastases (n=27)
Complete clearance ("absent")	7 (26%)
Non-CR/non-PR ("present")	20 (74%)
Progressive disease ("unequivocal progression")	0

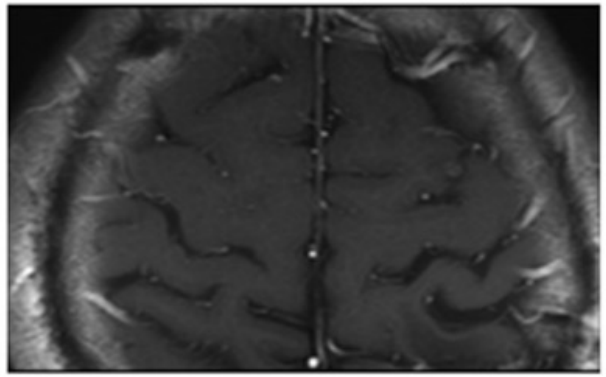
Of the 27 patients, 5 had documented non-target intracranial progression at the time of clinical cutoff[b]

Images courtesy of Prof. Se-Hoon Lee
Samsung Medical Center, Seoul, Republic of Korea

52-yo M, ECOG PS 1, with distant history of brain mets treated with gamma knife surgery, previously treated with afatinib, followed by cisplatin-pemetrexed, followed by osimertinib presents with new CNS lesion and demonstrated intracranial response at Week 6, which was maintained through Week 54



Baseline



Week 54

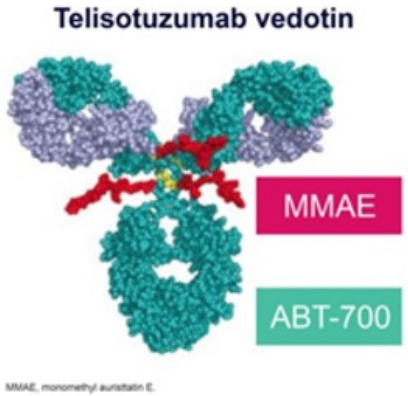
[a]Of these 66 patients, 65 had non-target lesions and 1 patient had a target lesion (see vignette).
[b]Clinical cutoff was March 15, 2022.
CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; M, male; PR, partial response; yo, year old.

CA Shu et al. ASCO 2022

Telisotuzumab vedotin and osimertinib in EGFR+

- Teliso-V is an antibody drug conjugate (ADC) directed against MET.
- As monotherapy in MET intermediate/high expressing NSCLC (EGFRwt) the ORR 36.5%
- Lower activity in **EGFR mutant** NSCLC **ORR 11.6%**

ASCO22 Abstract #9016

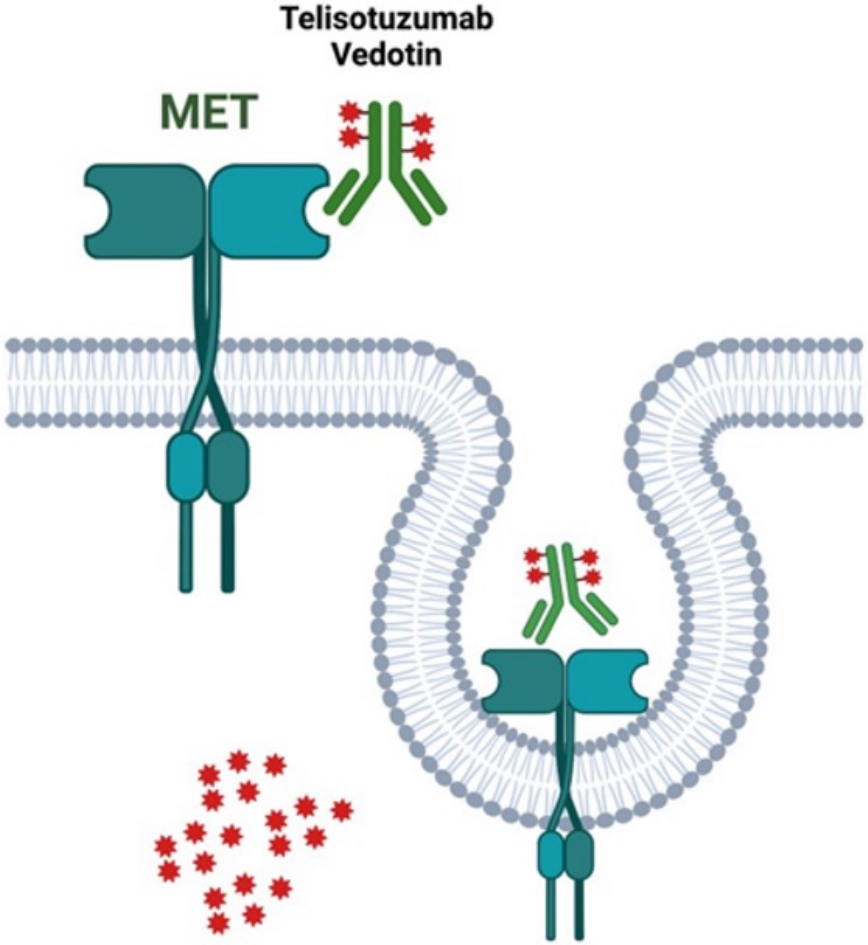


MET IHC+ = 39%

≠

MET amp 2%

MET exon 14 1%



DR Camidge et al. Presented at WCLC 2021
R Guo et al. JTO 2019

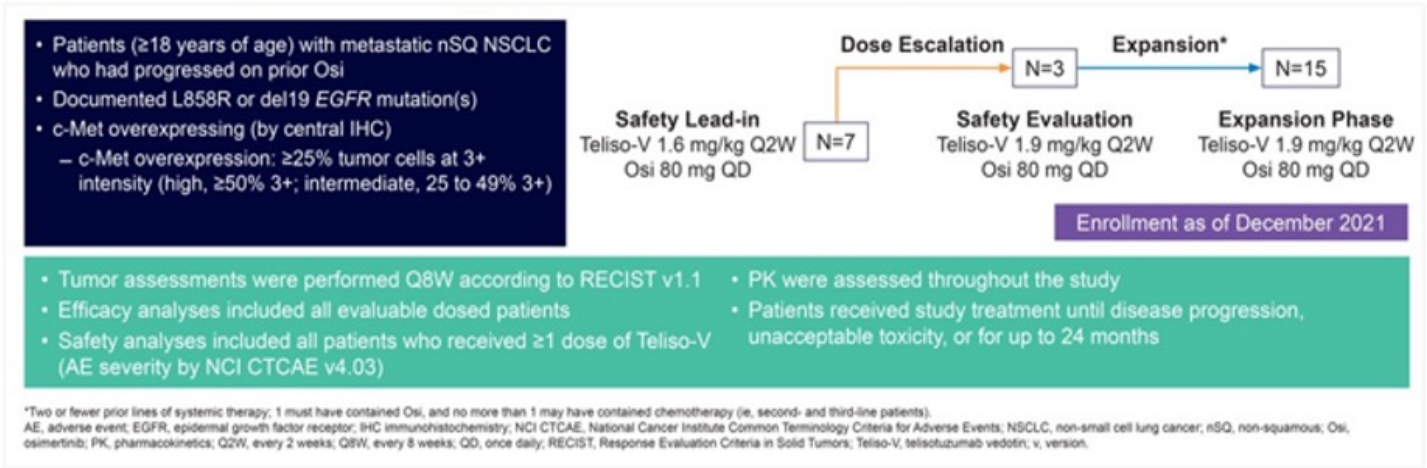
JW Goldman et al. 2022 ASCO, abstr 9013.

Telisotuzumab vedotin and osimertinib in EGFR+

- EGFR L858R, ex 19 deletion
- Prior Osimertinib
- c-MET overexpression:
- Intermediate: MET IHC 3+ in 25%-49% cells
- High: MET IHC 3+ ≥ 50% cells

Objective: safety, PK, and preliminary efficacy

Arm E: Phase 1/1b Multicenter, Open-Label Study Design (NCT02099058)



*Two or fewer prior lines of systemic therapy; 1 must have contained Osi, and no more than 1 may have contained chemotherapy (ie, second- and third-line patients).
AE, adverse event; EGFR, epidermal growth factor receptor; IHC immunohistochemistry; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; nSQ, non-squamous; Osi, osimertinib; PK, pharmacokinetics; Q2W, every 2 weeks; Q8W, every 8 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; Teliso-V, telisotuzumab vedotin; v, version.

MET expression	N = 25
Intermediate (25%-49% cells MET IHC 3+)	11 (44%)
High (≥ 50% cells MET IHC 3+)	13 (52%)
Other	1 (4%)

Prior Therapies	N = 25
Prior Platinum-based chemotherapy	15 (60%)
Duration of prior Osimertinib	
< 6 months	6 (25%)
6-12 months	4 (17%)
>12 months	14 (58%)
Missing	1
Time since end of prior osimertinib to start of therapy	
< 1 month	10 (45%)
1-6 months	7 (32%)
>6 months	5 (23%)
Missing	3

JW Goldman et al. 2022 ASCO, abstr 9013.

Teliso-V and osimertinib: Preliminary Efficacy

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

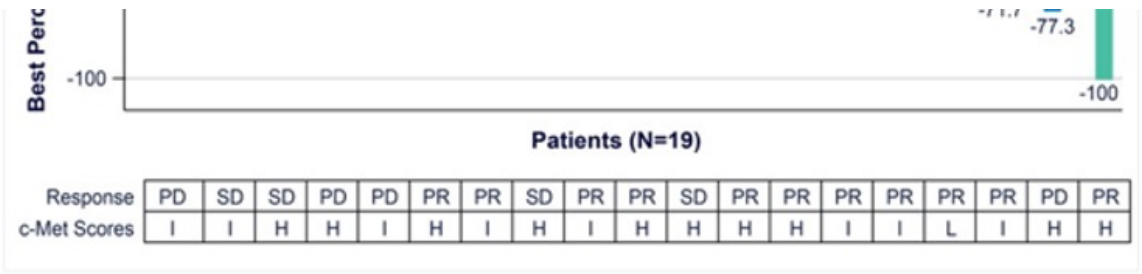
Best Percentage Change From Baseline in Target Lesion

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]

Studies currently enrolling

NCT02099058; phase 1b Teliso-V + Osi combo (2022 ASCO, Goldman et al)
NCT03539536; phase 2 Teliso-V mono (LUMINOSITY; 2022 ASCO, Camidge et al)
NCT04928846; phase 3 Teliso-V mono vs docetaxel (TeliMET NSCLC-01)



Response	PD	SD	SD	PD	PD	PR	PR	SD	PR	PR	SD	PR	PR	PR	PR	PR	PR	PD	PR
c-Met Scores	I	I	H	H	I	H	I	H	I	H	H	H	H	I	I	L	I	H	H

H, c-Met high (≥50%, 3+ staining); I, c-Met intermediate (25–49%, 3+ staining); L, c-Met low (<25, 3+ staining); PD, progressive disease; PR, partial response; Q2W, every 2 weeks; SD, stable disease.

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]

EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; Int, intermediate; ORR, objective response rate; Osi, osimertinib; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; Teliso-V, telisotuzumab vedotin.
*RECIST v1.1; ORR (confirmed responses, all PR); data not mature for duration of response and progression-free survival. †As of December 2021, 25 patients enrolled, 19 with available RECIST assessment. ‡c-Met IHC score <25% 3+, n=1. §*G719S* mutation, n=1.

Jonathan W. Goldman et al. Abstract 9013

JW Goldman et al. 2022 ASCO, abstr 9013.

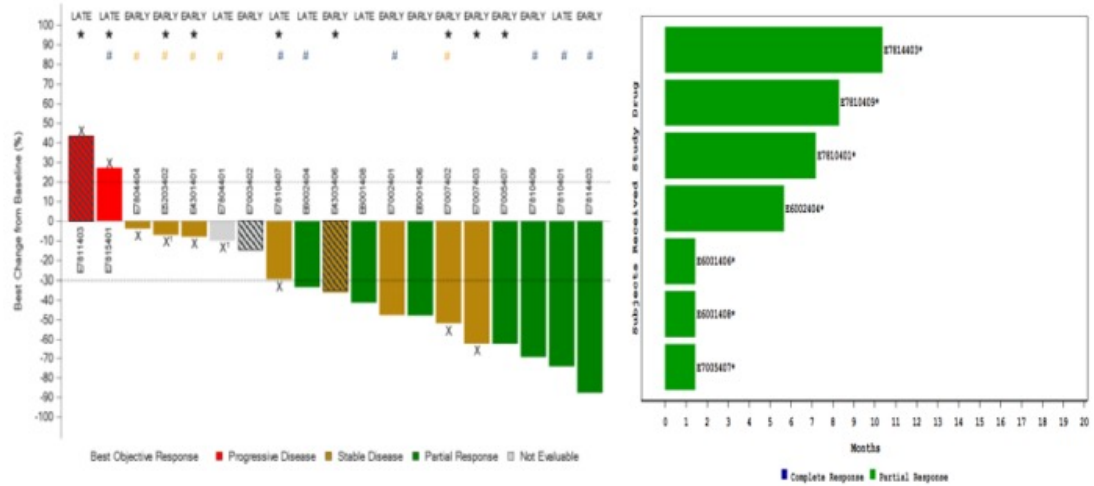
METamp EGFR Mutant NSCLC → Other Efforts (will help define the METamp Landscape)

❖ Clinical preliminary data (in osimertinib frontline era)

- ORCHARD trial (osimertinib+savolitinib arm)

All osimertinib first-line progressors (n=17)
Biopsy at osimertinib progression: acquired EGFR C797S, fusion drivers, small cell transformation excluded
Well-tolerated toxicity profile

- Confirmed ORR (41%) 7/17
- Unconfirmed ORR (59%) 10/17



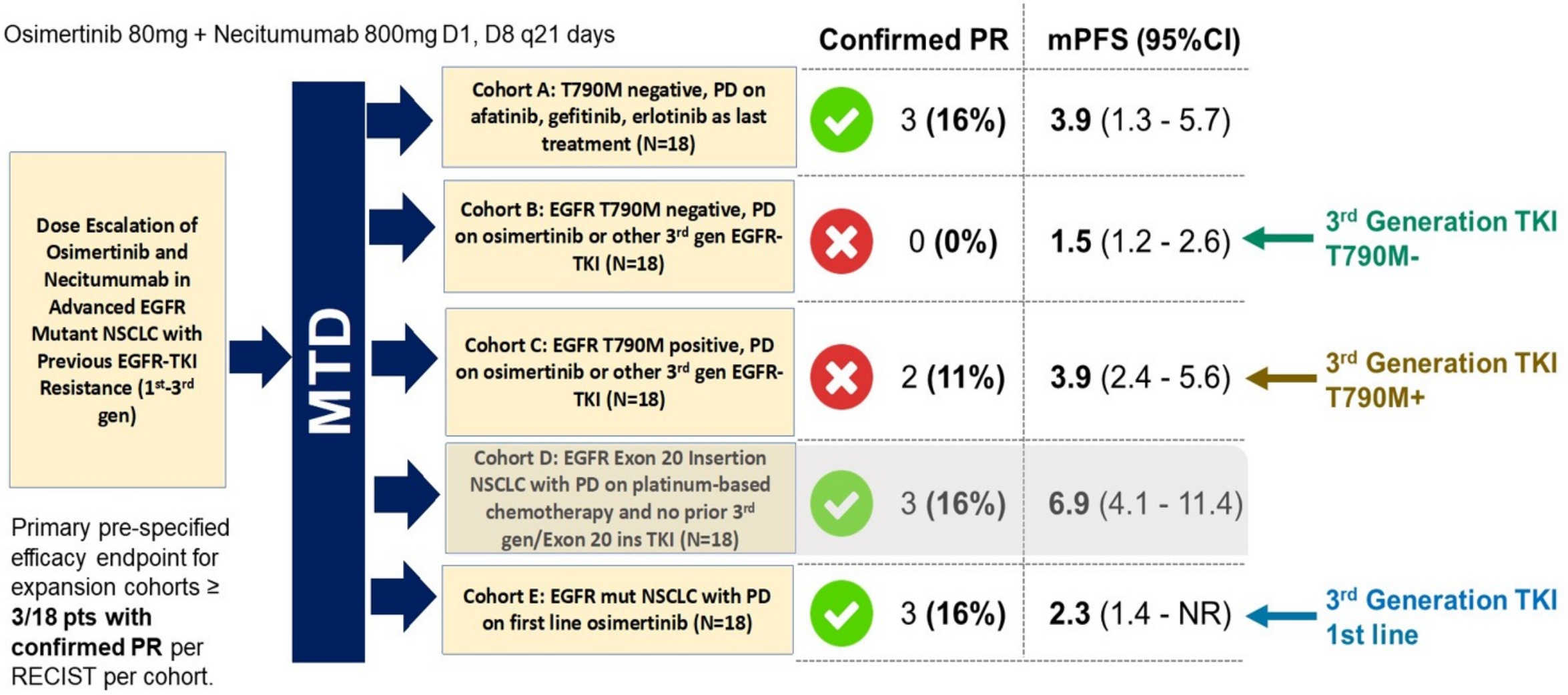
Yu and Le ESMO 2021

SAVANNAH trial (NCT03778229)
activated in early 2019
Savolitinib + osimertinib
MET amp by FISH
Completed trial accrual

INSIGHT2 trial (NCT03944772)
Tepotinib + osimertinib
MET amp by ctDNA or FISH
Completed interim analysis accrual

GEOMETRY-E (NCT04816214)
activated in March 2021
Capmatinib + osimertinib
Compared to platinum-pemetrexed
MET amp (method unclear)

Osimertinib and Necitumumab in EGFR+ NSCLC

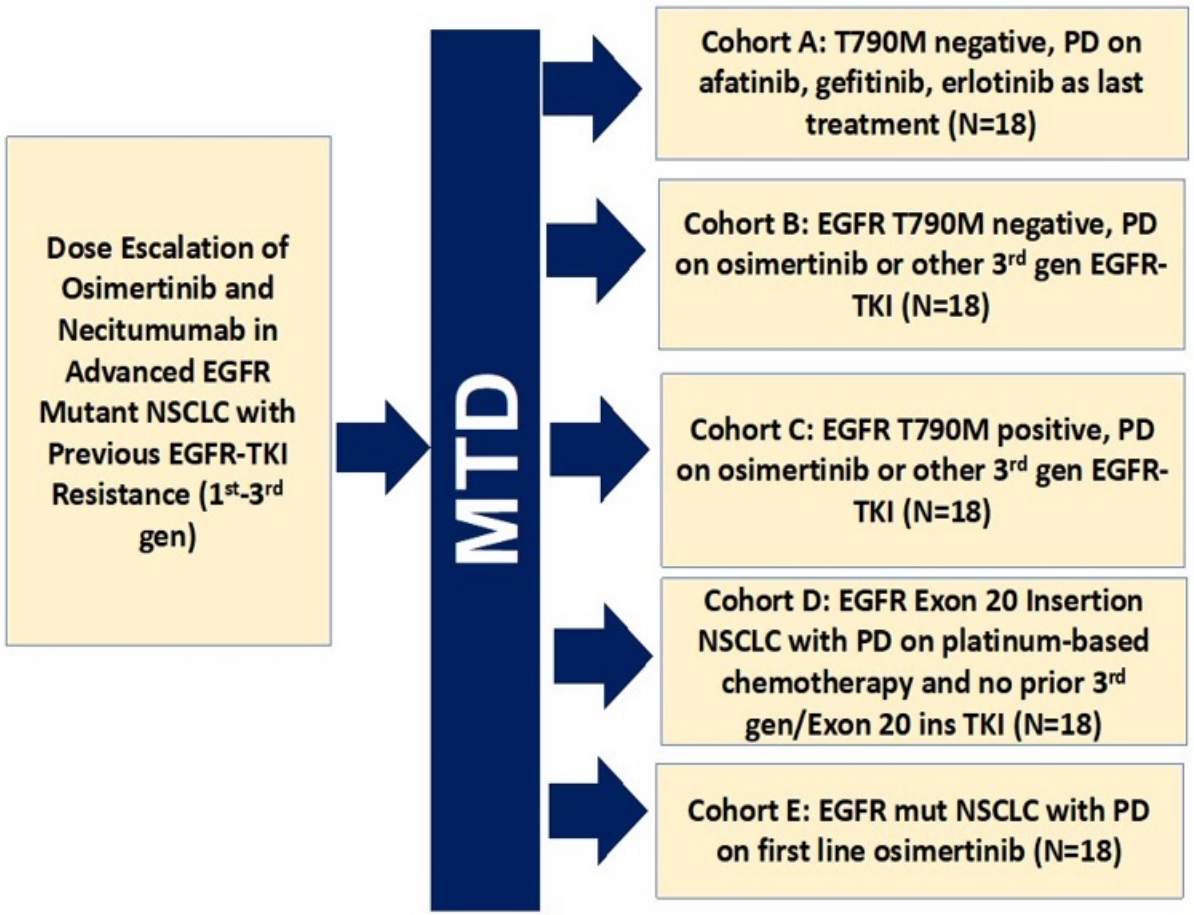


- Primary pre-specified efficacy endpoint for expansion cohorts ≥ **3/18 pts with confirmed PR** per RECIST per cohort.

JW Riess et al. 2022 ASCO, abstr 9014.

Osimertinib and Necitumumab: Safety

Osimertinib 80mg + Necitumumab 800mg D1, D8 q21 days



Drug related ≥Gr 3 AE: 38%

	Number of Patients with this Grade (N=97)	
Toxicity	Grade 1-2	≥Grade 3
Rash maculo-papular/acneiform/pustular	64	20
Diarrhea	32	1
Mucositis oral	23	2
Lymphocyte count decreased	12	4
Dyspnea	1	2
Hypophosphatemia	9	1
Hypokalemia	8	1
Infusion related reaction	7	1
Lipase Increased	0	1
AST/ALT Elevation	11	1
Sinus bradycardia	2	1
Thromboembolic event	3	1
Pneumonitis	1	2
Dehydration	0	1
Bone pain	0	1
Dry skin	50	1
Facial Abrasion	35	1
Fatigue	41	2
Electrocardiogram QT corrected interval prolonged	19	2
White blood cell decreased	13	1
Anemia	14	1
Weight loss	13	1

21%

JW Riess et al. 2022 ASCO, abstr 9014.

Overcoming Osimertinib Resistance

Outcomes	Amivantanab + Lazertinib N= 45			Necitumumab + Osimertinib N = 18	Savolitinib + Osimertinib N = 69	Patritumab Deruxtecan N =44	Datopotomab Deruxtecan* N = 34	Teliso-V + Osimertinib N = 25
Target	EGFR + MET Post Osi			EGFR Post 1st line Osi	EGFR + MET Post 3rd Gen TKI	HER3 Post Osi	TROP2 Post EGFR ,ALK, ROS1	EGFR + MET Post Osi
Biomarker	EGFR/MET resistance	Unknown resistance	Other resistance	No	MET amplification	No	No	MET expression
ORR (%)	47%	29%	0%	16%	30%	39%	35%	58%
mDOR, median (months)	10.4	8.3		Not reported	7.9	7.0	9.5	Not reported
mPFS, median (months)	6.7	4.1		2.3	5.4	8.2	Not reported	Not reported
Grade ≥ 3 TRAE	16%			38%	57%	54%	38%	32%

Cross-trial comparisons have significant limitations. This information is presented to generate discussion, not to make comparisons between study results.

* Includes post Osimertinib, and other targets (ALK,ROS1) and therapies

BC Cho et al. Presnted at ASCO 2021L. Sequist et al. Lancet Oncology 2020
P. Janne et al Presented at ASCO 2021EB Garon et al. Presented at ESMO 2021

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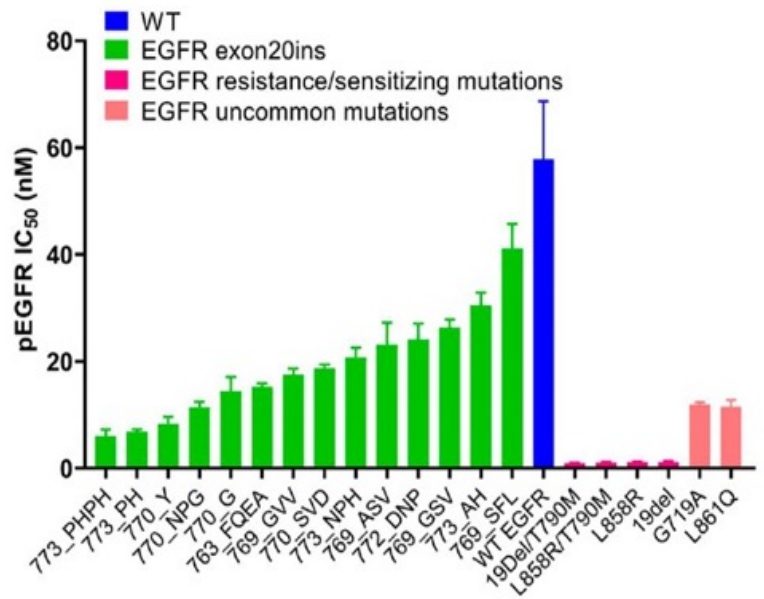
EGFR Pathway

EGFRex20ins

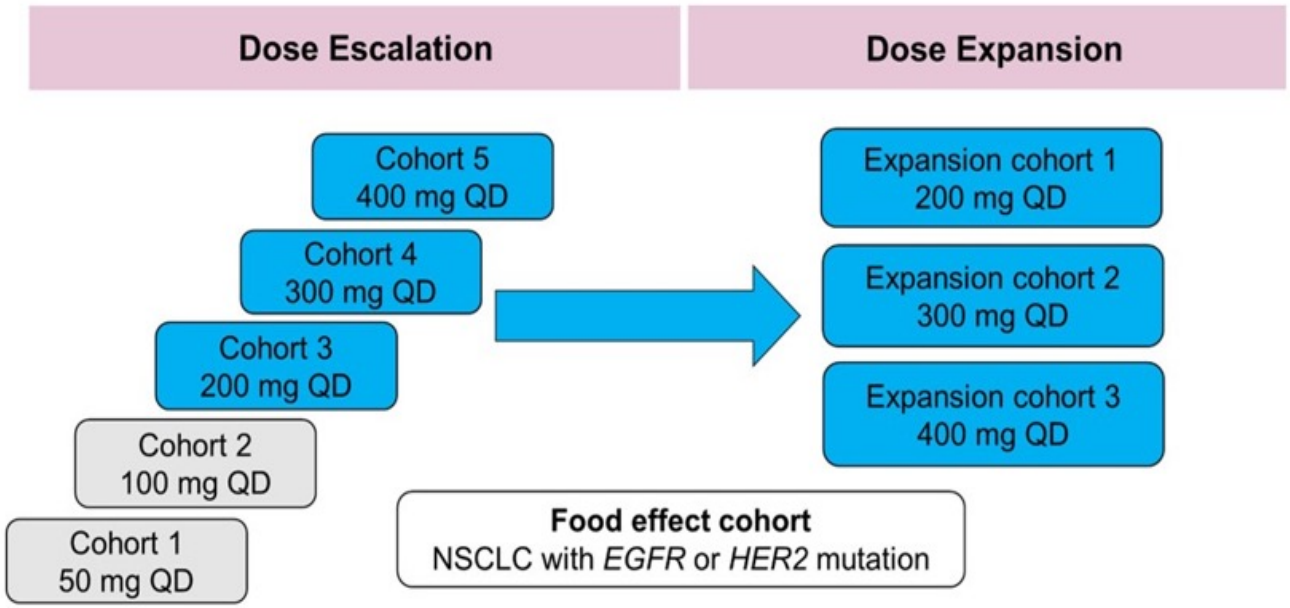
Sunvozertinib in EGFR exon 20 mutant NSCLC

Sunvozertinib is an oral, irreversible, selective EGFR TKI:

- Exon 19 deletions/L858R
- T790M
- EGFR exon 20 insertions



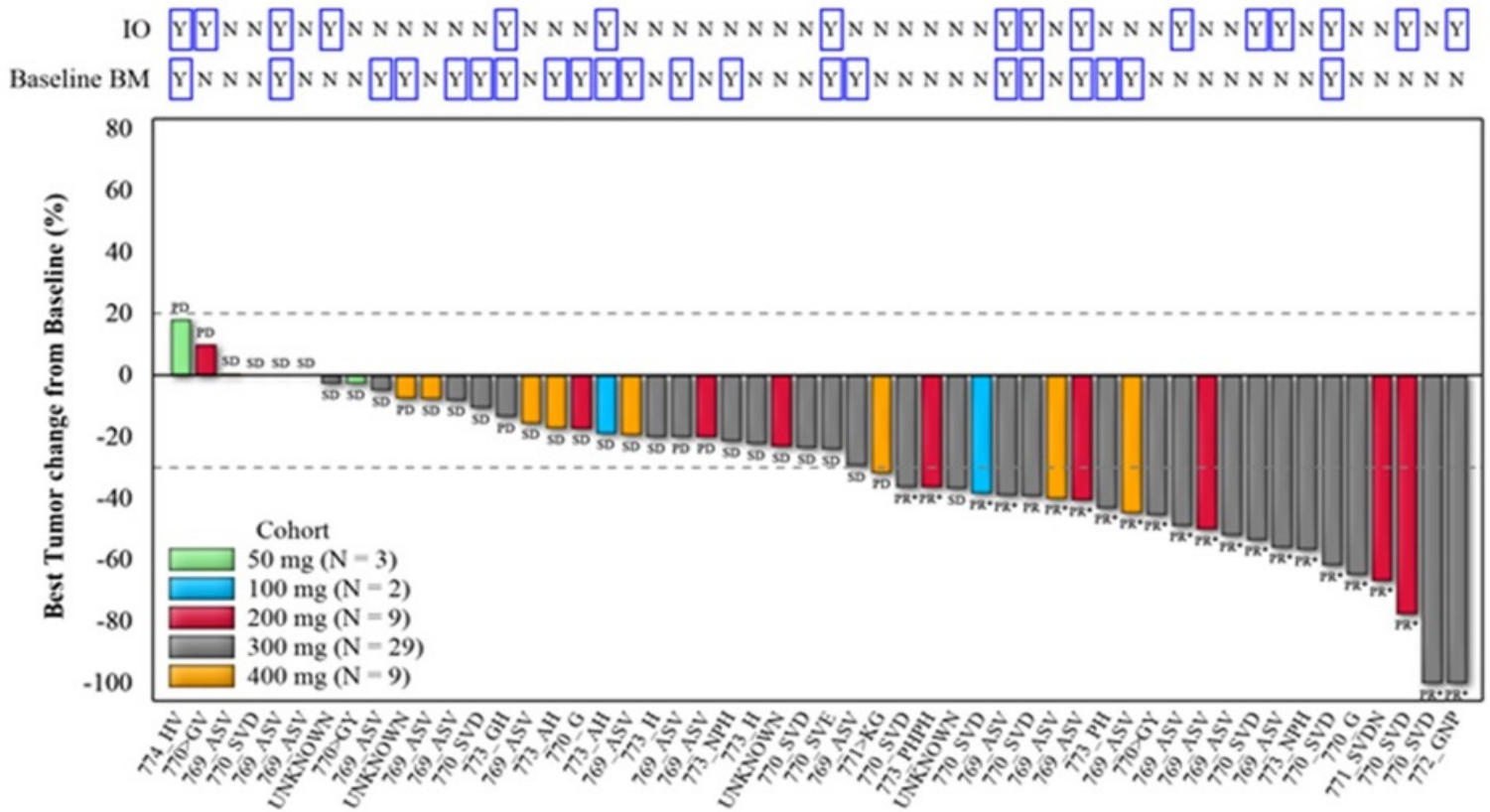
Phase 1 study design (WU-KONG1 and WU-KONG2 trials)



Mengzhao Wang et al Cancer Discov. 2022 Apr 11;candisc.1615.2021
. Pasi A. Janne et al. Abstract 9015: Antitumor activity of sunvozertinib in NSCLC patients with EGFR Exon20 insertion mutations after platinum and anti-PD(L)1 treatment failures

Sunvozertinib in platinum pretreated NSCLC with EGFR Exon20ins

Results	N = 52
Previous therapies median (range)	3 (1-10)
Brain Mets	21 (40%)
Prior Immunotherapy	15 (29%)
ORR (%)	40.4%
DCR. (%)	84.6%
mDOR (months)	5.9



Median follow-up time: 10.5 months

. Pasi A. Janne et al. Abstract 9015: Antitumor activity of sunvozertinib in NSCLC patients with EGFR Exon20 insertion mutations after platinum and anti-PD(L)1 treatment failures

Sunvozertinib and prior immunotherapy

	N	PR	Drug related Grade ≥ 3 AE	Dose Reduction	Dose Interruption	Treatment Discontinuation
PD-(L)1 therapy	15	53.3%	38.9%	25%	41.7%	2.8%
No anti PD-(L)1	34	38.2%	43.8%	6.3%	31.3%	6.3%

Dose ≥ 100mg

K. Park JCO 2021, C. Zhou Jama Onc 2021, PA Janne ASCO 2022,
Piotrowskaet al, ASCO 2021, R Cornelissen WCLC 2020, Z. Wierenga ESMO 2021

Efficacy of EGFR exon 20 targeted therapies

Post platinum-based chemotherapy

	Amivantamab n = 81	Mobocertinib N = 114	Poziotinib N = 115	Osimertinib* N = 25	CLN-081 N = 39	Sunvozertinib# N = 52	Necitumumab Osimertinib N = 18
ORR (%)	**40%**	**28%**	**15%**	**28%**	**41%**	**40.4%**	**16%**
mDOR (months)	11.1	17.5	7.4	4,2	>21	5.9	---
mPFS (months)	8.3	7.3	4.2	6.8	12.0	---	6.9
mOS (months)	22.8	24.0	---	15.2	---	---	---
Grade ≥ 3 AE	35%	47%	---	---	5%	40%	38%^

Cross-trial comparisons have significant limitations. This information is presented to generate discussion, not to make comparisons between study results.

K. Park JCO 2021, C. Zhou Jama Onc 2021, PA Janne ASCO 2022, Piotrowskaet al, ASCO 2021, R Cornelissen WCLC 2020, Z. Wierenga ESMO 2021

*Osimertinib dose 160mg/day # Sunvozertinib all doses
^ in all patients included EGFR sensitizing mutationsand exón 20 insertions

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K-RAS Pathway

2022 ASCO® ANNUAL MEETING

KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients with Advanced/Metastatic Non-Small Cell Lung Cancer Harboring a $KRAS^{G12C}$ Mutation

Alexander I. Spira[1], Gregory J. Riely[2], Shirish M. Gadgeel[3], Rebecca S. Heist[4], Sai-Hong Ignatius Ou[5], Jose M. Pacheco[6], Melissa L. Johnson[7], Joshua K. Sabari[8], Konstantinos Leventakos[9], Edwin Yau[10], Lyudmila Bazhenova[11], Marcelo V. Negrao[12], Nathan A. Pennell[13], Jun Zhang[14], Karen Velastegui[15], James G. Christensen[15], Xiaohong Yan[15], Kenna Anderes[15], Richard C. Chao[15], Pasi A. Jänne[16]

[1]Virginia Cancer Specialists, Fairfax, VA; US Oncology Research, The Woodlands, TX; NEXT Oncology Virginia, Fairfax, VA; [2]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY; [3]Henry Ford Cancer Institute, Detroit, MI; [4]Massachusetts General Hospital, Boston, MA; [5]University of California, Irvine, Chao Family Comprehensive Cancer Center, Orange, CA; [6]University of Colorado Anschutz Medical Campus, Aurora, CO; [7]Sarah Cannon Research Institute Tennessee Oncology, Nashville, TN; [8]Perlmutter Cancer Center, New York University Langone Health, New York, NY; [9]Mayo Clinic, Rochester, MN; [10]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [11]UC San Diego Moores Cancer Center, La Jolla, CA; [12]MD Anderson Cancer Center, Houston, TX; [13]Cleveland Clinic, Cleveland, OH; [14]University of Kansas Medical Center, Kansas City, KS; [15]Mirati Therapeutics, Inc., San Diego, CA; [16]Dana-Farber Cancer Institute, Boston, MA

KRYSTAL-1 (849-001) Phase 2 Cohort A Study Design

Phase 2
NSCLC Monotherapy Treatment

Key Eligibility Criteria

- NSCLC with KRAS^{G12C} mutation[a]
- Unresectable or metastatic disease
- Prior treatment with a PD-1/L1 inhibitor in combination or in sequence with chemotherapy
- Treated, stable CNS metastases were allowed

Adagrasib 600 mg BID (Capsule, Fasted)

Study Objectives

- Primary endpoint: ORR (RECIST 1.1) per BICR
- Secondary endpoints: DOR, PFS, OS, safety

Here we report data from a registrational Phase 2 cohort evaluating adagrasib 600 mg BID in previously treated patients with NSCLC harboring a KRAS^{G12C} mutation (N=116)

Enrollment period, January 2020 to December 2020

[a]KRAS^{G12C} mutation detected in tumor tissue by sponsor-approved local laboratory testing
ClinicalTrials.gov. NCT03785249

Al Spira et al. 2022 ASCO, abstr 9002

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Tumor Response by BICR

Efficacy Outcome	Adagrasib Monotherapy (n=112)[a]
Objective response rate, n (%)	48 (43%)
Best overall response, n (%)	
Complete response	1 (1%)
Partial response	47 (42%)
Stable disease	41 (37%)
Progressive disease	6 (5%)
Not evaluable	17 (15%)
Disease control rate, n (%)	89 (80%)

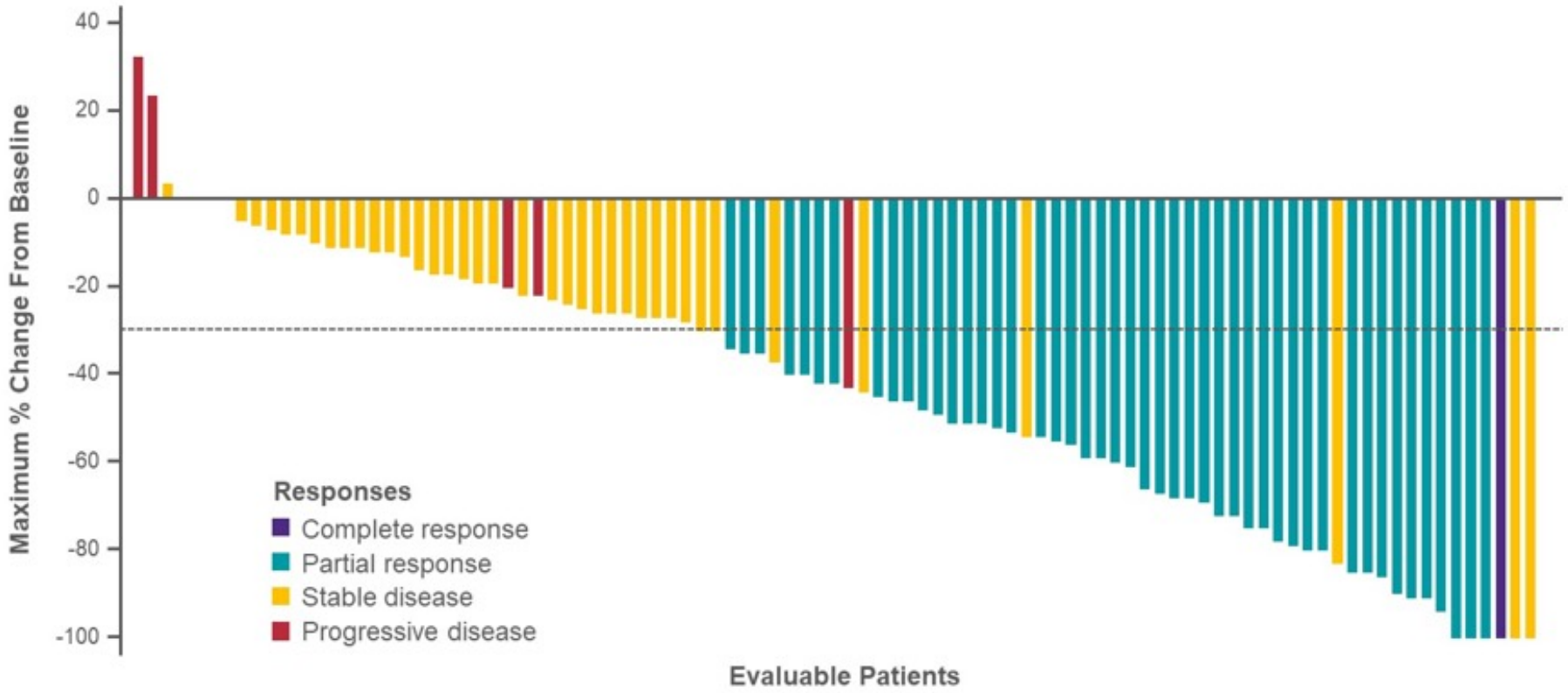
- 17 patients were not evaluable due to having received post-baseline scans too early (n=3) or study withdrawal prior to first scheduled assessment (n=14)[b]
- For evaluable patients (on treatment and who had a scan at ~6 weeks[c]), ORR was 51% (48/95)

[a]Full analysis set as per BICR excludes 4 patients who did not have measurable disease at baseline; [b]Due to reasons of: withdrawal by patient (n=5), AEs (n=3; 2 patients experienced AEs not related to treatment, 1 patient experienced a TRAE), global deterioration of health (n=3), death (n=2), non-compliance (n=1); [c]6 weeks ± 10 days

Data as of October 15, 2021 (median follow-up: 12.9 months)

Al Spira et al. 2022 ASCO, abstr 9002

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

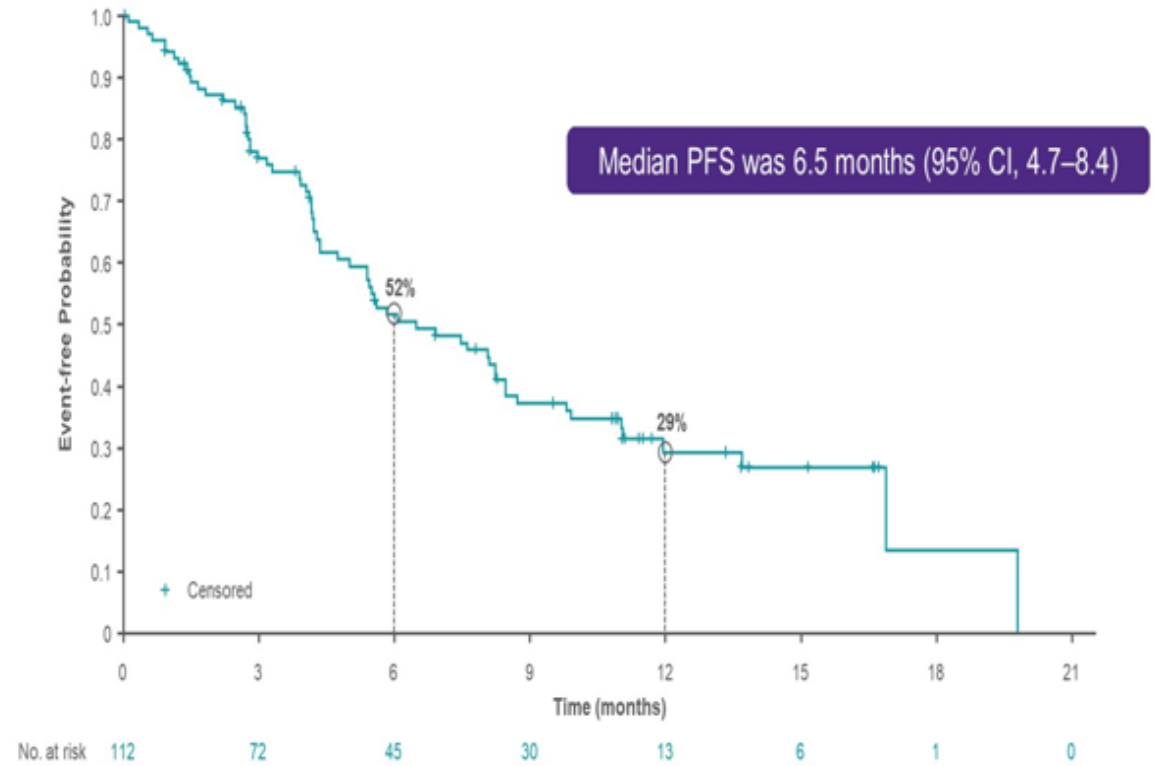


- Objective responses were observed in 43% (95% CI, 33.5–52.6); DCR was 80% (95% CI, 70.8–86.5)
- Responses were deep with 75% of responders achieving >50% tumor reduction

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

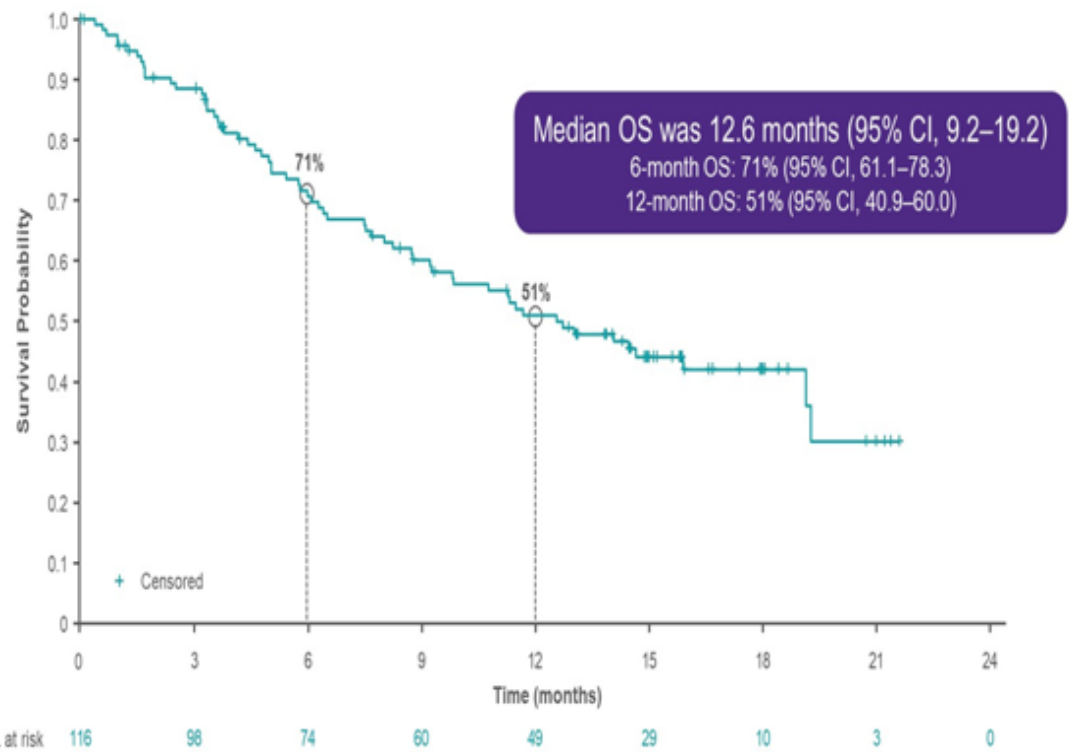
Al Spira et al. 2022 ASCO, abstr 9002

Adagrasib in Previously Treated Patients with K-Ras^{G12C}-mutated NSCLC: Median Progression-free Survival and Median Overall Survival



All results are based on BICR

Data as of October 15, 2021 (median follow-up: 12.9 months)



As of October 15, 2021, median OS was 11.7 months (95% CI, 9.2–NE); median follow-up: 12.9 months

Data as of January 15, 2022 (median follow-up: 15.6 months)

Al Spira et al. 2022 ASCO, abstr 9002

Efficacy KRAS G12C inhibitor: Adagrasib vs. Sotorasib

Parameter	Adagrasib (KRYSTAL-1)	Sotorasib (CodeBreaK100)[1]
N=	116 (112 for efficacy)	126 (124 for efficacy)
Prior Platinum Chemo + IO	**98%**	**81%**
ORR	**43%** (95% CI 33.5-52.6)	**37.1%** (95% CI 28.6-46.2)
DCR	**80%** (95% CI 70.8-86.5)	**80.6%** (95% CI 72.6-87.2)
TTR, median (range)	**1.4 mo** (0.9-7.2)	**1.4 mo** (1.2-10.1)
DOR, median	**8.5 mo** (95% CI 6.2-13.8)	**11.1 mo** (95% CI 6.9-NE)
PFS, median	**6.5 mo** (95% CI 4.7-8.4)	**6.8 mo** (95% CI 5.1-8.2)
OS, median	**12.6 mo** (95% CI 9.2-19.2)	**12.5 mo**[2] (95% CI 10.0-NE)
Follow-up, median	12.9 mo	15.3 mo[2]

1= Skoulidis et al. N Engl J Med. 2021 Jun 24;384(25):2371-2381; 2=Pooled phase 1/2 of 174 pts with median f/u 24.9 mo, median OS 12.5 mo (95% CI 10.0-17.8), 1-year OS 50.8%, 2-year OS 32.5% (Dy G et al. AACR 2022)

Sukhmani K. Padda. 2022 ASCO.

Treatment-Related Adverse Event (TRAE)

ADAGRASIB

	Adagrasib (N=116)[1]	
TRAEs, n (%)	**Any Grade**	**Grades 3–4[2]**
Any TRAEs	113 (97%)	50 (43%)
Most frequent TRAEs, n (%)		
**Diarrhea*	73 (63%)	1 (<1%)
**Nausea*	72 (62%)	5 (4%)
**Vomiting*	55 (47%)	1 (<1%)
**Fatigue*	47 (41%)	5 (4%)
**ALT increase*	32 (28%)	5 (4%)
Blood creatinine increase	30 (26%)	1 (<1%)
**AST increase*	29 (25%)	4 (3%)
Decreased appetite	28 (24%)	4 (3%)
Anemia	21 (18%)	6 (5%)
Amylase increase	20 (17%)	1 (0.9%)
QT prolongation	19 (16%)	5 (4%)

1=Capsule, Fasted
2=3 Grade 4 TRAEs. 2 Grade 5 TRAE (1 Cardiac Failure, 1 Pulmonary Hemorrhage)

SOTORASIB

	Sotorasib (N=126)	
TRAEs, n (%)	**Any Grade**	**Grades 3–4[1]**
Any TRAEs	88 (70%)	26 (21%)
Most frequent TRAEs, n (%)		
Diarrhea	40 (32%)	5 (4%)
Nausea	24 (19%)	0
ALT increase[2]	19 (15%)	8 (6%)
AST increase[2]	19 (15%)	7 (6%)
Fatigue	14 (11%)	0
Vomiting	10 (8%)	0

1= Only 1 patient with Grade 4 TRAE of dyspnea & pneumonitis. No Grade 5 TRAE.
2=TRAE (Any Grade/G3): Blood alk phos increase 9 (7%)/1 (<1%); Drug-induced liver injury 3 (2.4%)/ 2 (1.6%); Gamma-GGT increase 3 (2.4%)/3 (2.4%); Abnl hepatic function 2 (1.6%)/1 (<1%); 1 G3 event each of Hepatotoxic Event, Increase liver function level, Abnormal aminotransferase level

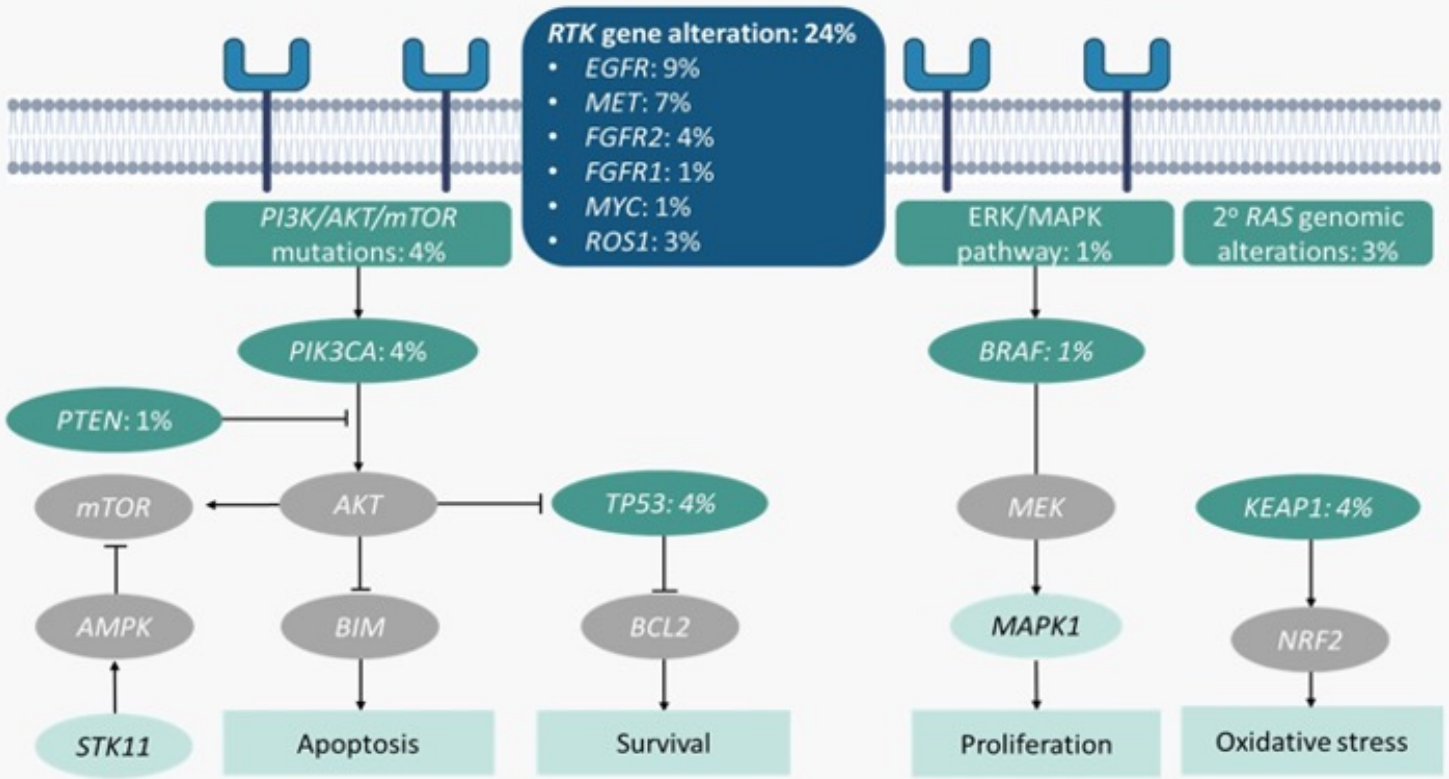
- **Dose Reduction/Interruption**
- Adagrasib: **52%** Dose Reduction, 61% Dose Interruption
  - 33% 400 mg bid, 11% 600 mg qd, 14% (200 mg bid or 400 mg qd)
- Sotorasib (both interruption/reduction): 22.2%
- **TRAEs led to dose discontinuation**: Adagrasib 7%, Sotorasib 7.1%

Skoulidis F et al. N Engl J Med. 2021 Jun 24;384(25):2371-2381.

Sukhmani K. Padda. 2022 ASCO.

NSCLC

Putative Acquired Resistance Mechanisms To Sotorasib*



OncoKB[1]

10/31 alterations were potentially targetable†

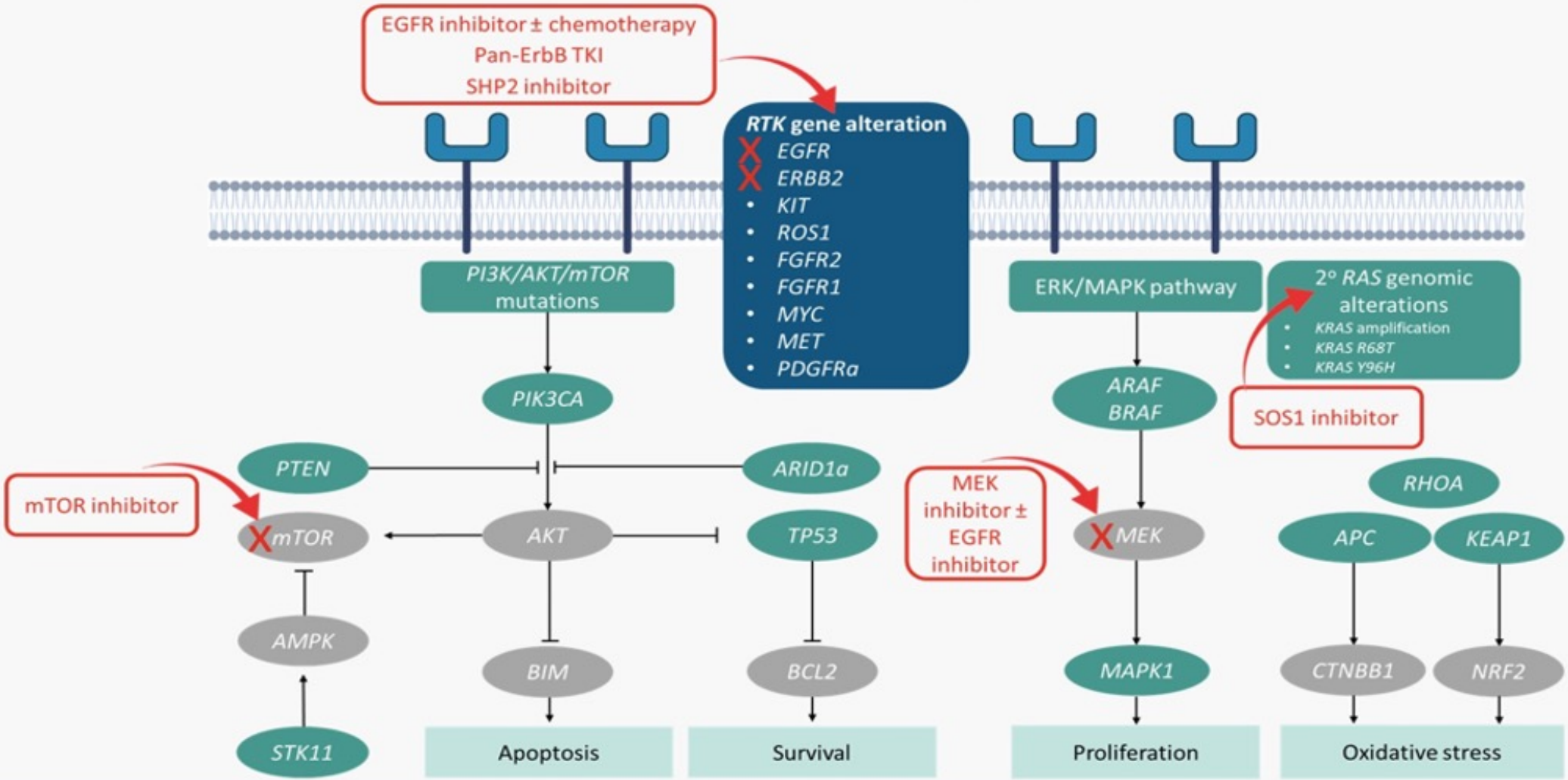
- Level 1: *PIK3CA* E542K (1)
  PIK3CA E545K (1)
- Level 2: *MET* amp. (3)‡
  BRAF K601E (1)‡
- Level 3: *FGFR1* amp. (1)
- Level 4: *EGFR* amp. (2)
  PTEN deletion (1)

RTK gene alterations: the most prevalent acquired genomic alteration in NSCLC patients (16/67 [24%])

1. Chakravarty D, et al. *JCO Precis Oncol*. 2017:doi:10.1200/PO.17.00011.
*Mutation rate presented based on 67 evaluable patients.
†Actionability levels defined in full at https://www.oncokb.org/levels; actionable variants are based on evidence from any cancer indication.
‡Evidence of targetability in NSCLC: *MET* amp., Level 2; *BRAF* K601E, Level 4.
amp., amplification; NSCLC, non-small cell lung cancer.

Bob T. Li. 2022 ASCO.

Acquired Resistance Mechanisms May Inform Potential Sotorasib Combination Therapies (CodeBreaK 101)



Bob T. Li. 2022 ASCO.

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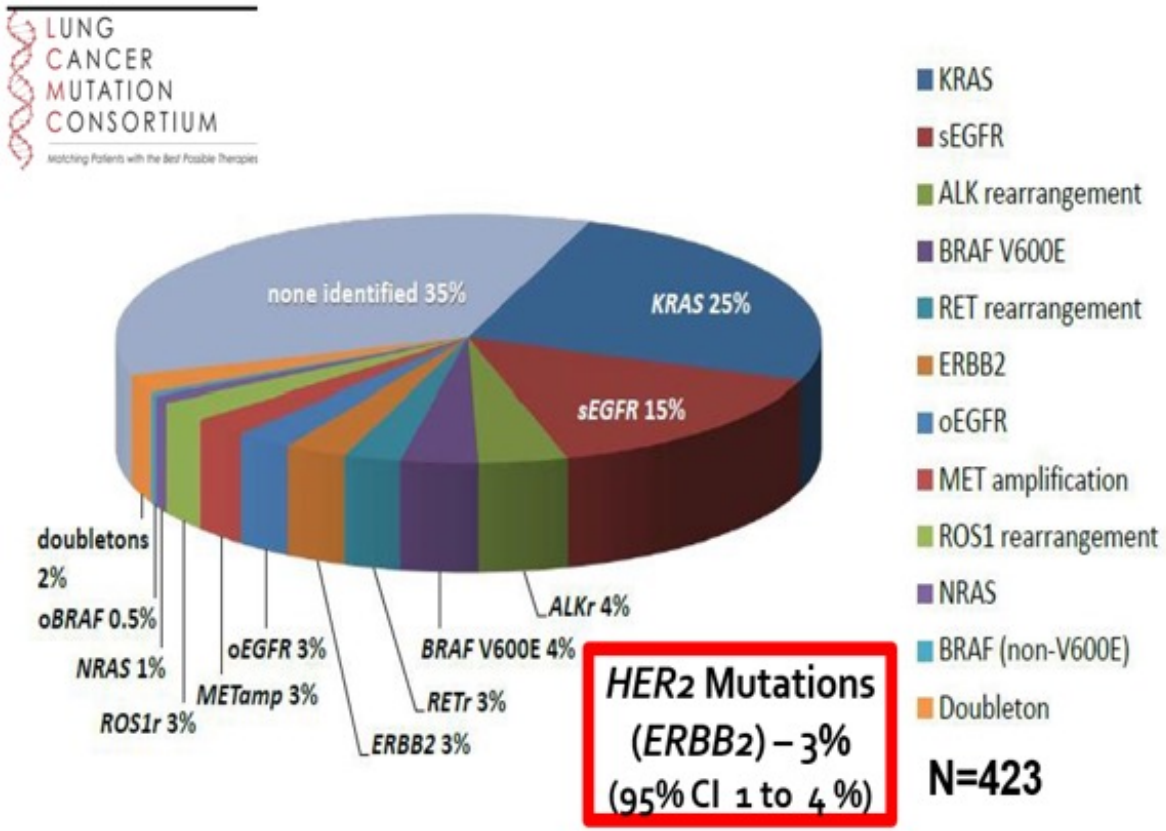
ERBB2 Pathway

HER2 in Lung Cancers

Mechanisms Underlying HER2 Dependency in Lung Cancers

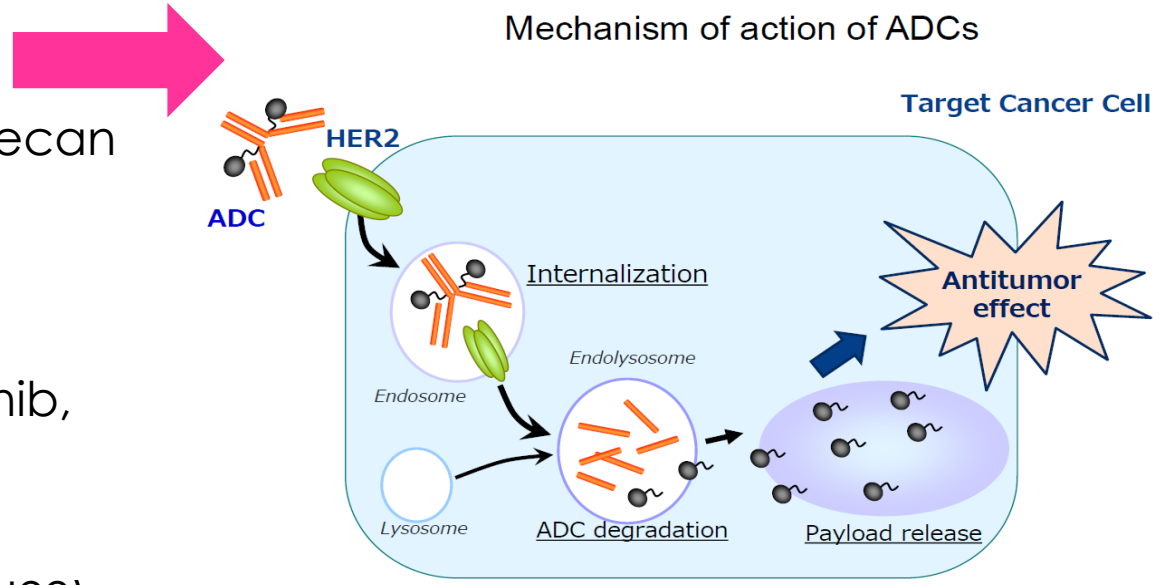
Available tissue and blood NGS panels adequately detect *HER2* mutations and amplification (Ross J Mol Diagn 2017)
No need for additional IHC or FISH testing



DL Aisner et al. Clin Cancer Research 2018

HER2 (ERBB2) in Lung Cancers

- Anti-HER2 Antibody Drug Conjugates (ADCs)
  - Ado trastuzumab emtansine, trastuzumab deruxtecan (DS8201A), trastuzumab duocarmazine, ZW-49, DHES0815A, RC48-ADC, A166
- HER2 Kinase Inhibitors
  - Afatinib, dacomitinib, neratinib, poziotinib, lapatinib, pyrotinib, AP32788
- Anti-HER2 MoAbs
  - Trastuzumab, pertuzumab, margetuximab (MGAH22)
- Anti-HER2 MoAb Bispecific Antibodies
  - GO40311 (HER2-CD3)
- Cytotoxic Chemotherapies
  - Pemetrexed, vinorelbine, paclitaxel
- Immune Checkpoint Blockade



Phase 2 Trials in *HER2*-Mutant Lung Cancers

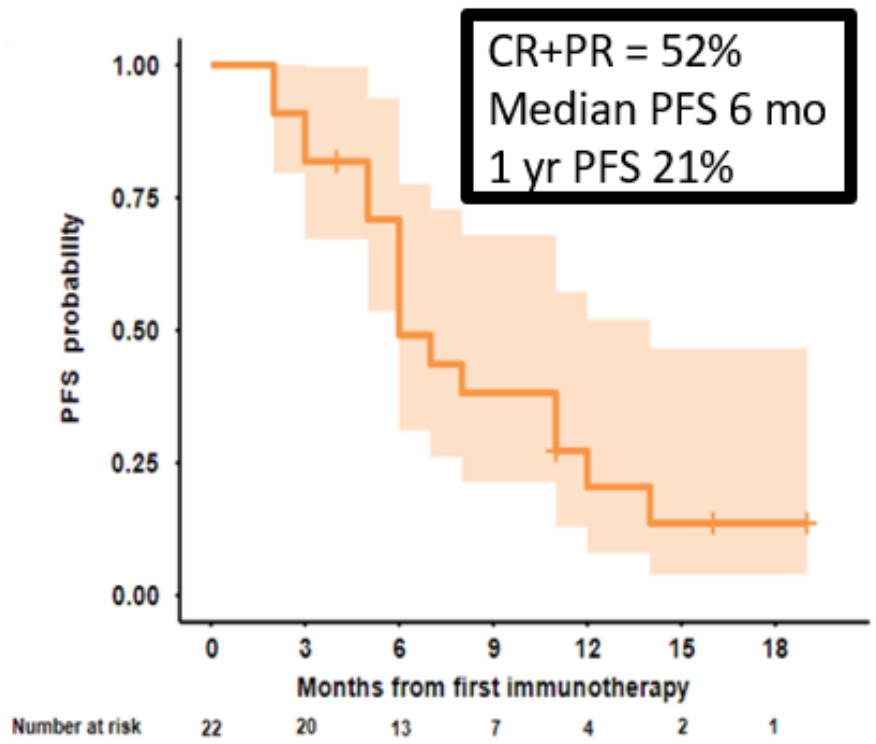
Drug Type and Reference†	No. of Patients	Agent or Agents	Objective Response	Disease Control	Median Progression-free Survival (95% CI)	Median Overall Survival (95% CI)
			no. of patients (%)		*mo*	*mo*
Pan–ErbB family TKIs						
Kris et al. 2015	26	Dacomitinib	3 (12)	—	3 (2–4)	9 (7–21)
Hyman et al. 2018	26	Neratinib	1 (4)	11 (42)	5.5‡	—
Dziadziuszko et al. 2019	13	Afatinib	1 (8)	7 (54)	3.7 (1.4–8.1)§	12.9 (3.7–NR)§
Wang et al. 2019	15	Pyrotinib	8 (53)	11 (73)	6.4 (1.6–11.2)	12.9 (2.1–23.8)
Zhou et al. 2020	60	Pyrotinib	18 (30)¶	51 (85)	6.9 (5.5–8.2)	14.4 (12.3–21.3)
Selective HER2 TKIs						
Liu et al. 2020	9	Tarloxotinib	2 (22)	6 (67)	—	—
Le et al. 2021	74‖	Poziotinib	26 (35)	61 (82)	5.5 (0.6–17.6)	—
Cornelisson et al. 2021	48**	Poziotinib	21 (44)	36 (75)	5.6 (0–20.2)	—
Elamin et al. 2021	30	Poziotinib	8 (27)	22 (73)	5.5 (4.0–7.0)	15 (9.0–NR)
Trastuzumab						
Hainsworth et al. 2018	14	Trastuzumab and pertuzumab	3 (21)	6 (43)	—	—
Mazieres et al. 2021	45	Trastuzumab, pertuzumab, and docetaxel	13 (29)	39 (87)	6.8 (4.0–8.5)	—
Antibody–drug conjugates						
Li et al. 2018[4]	18	Trastuzumab emtansine	8 (44)	15 (83)	5 (3–9)	—
Li et al. 2021[6]	91	Trastuzumab deruxtecan	50 (55)	84 (92)	8.2 (6.0–11.9)	17.8 (13.8–22.1)

Passaro N Engl J Med 2022

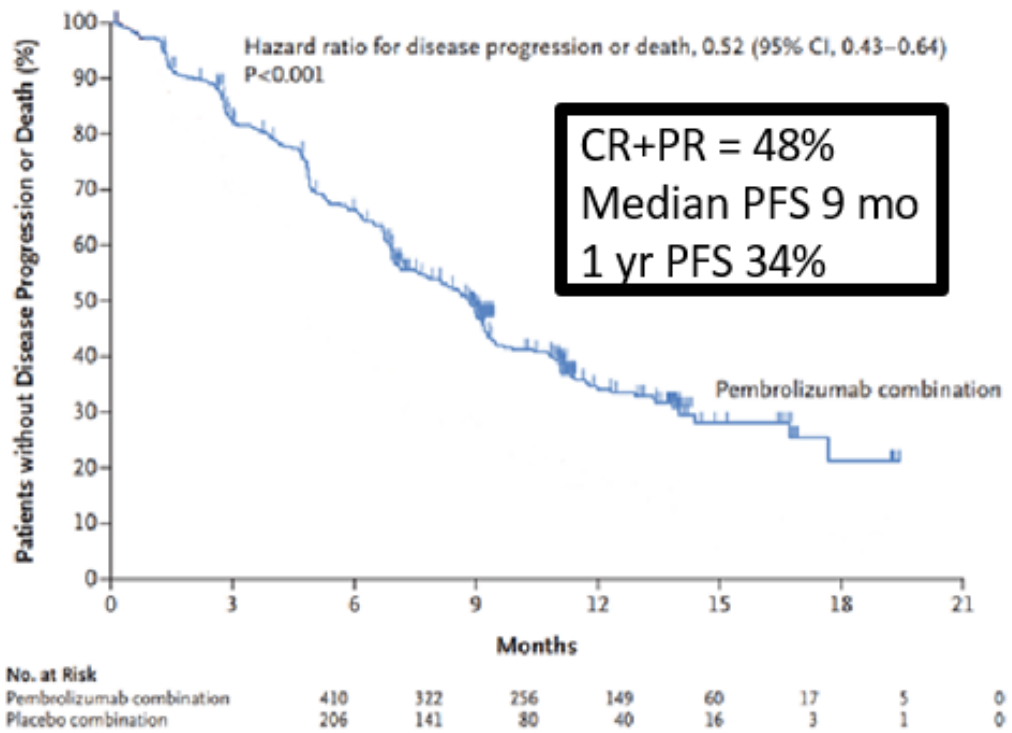
Outcomes with Initial Chemoimmunotherapy

HER2 Mutant vs All NSCLCs

HER2 Mutant



All NSCLCs



Saalfeld. J Thorac Oncol 2021, Gandhi N Engl J Med 2018

Open-Label, Randomized, Multicenter, Phase 3 Study Evaluating Trastuzumab Deruxtecan (T-DXd) as First-Line Treatment in Patients With Unresectable, Locally Advanced, or Metastatic Non-Small Cell Lung Cancer (NSCLC) Harboring *HER2* Exon 19 or 20 Mutations (DESTINY-Lung04)

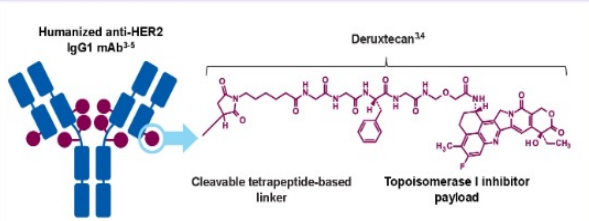
Bob T. Li, MD, PhD, MPH[1]; Myung-Ju Ahn, MD, PhD[2]; Koichi Goto, MD, PhD[3]; Julien Mazieres, MD[4]; Sukhmani K. Padda, MD[5]; William Nassib William Jr, MD[6]; Yi-Long Wu, MD[7]; Simon Dearden, MSc[8]; Alejandra Ragone, MD[9]; Natasha Viglianti, MSc[8]; Amaya Gascó Hernández, MD, PhD[10]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]Hôpital Larrey, Service de Pneumologie, Toulouse, France; [5]Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [6]Hospital BP, a Beneficência Portuguesa de São Paulo, São Paulo, Brazil; [7]Guangdong Provincial People's Hospital, Guangzhou, Guangdong, China; [8]AstraZeneca Pharmaceuticals, Cambridge, UK; [9]AstraZeneca Pharmaceuticals, Mississauga, ON, Canada; [10]AstraZeneca Pharmaceuticals, Gaithersburg, MD, USA

Background

- The standard of care for patients with metastatic NSCLC is guided by specific molecular characterization and includes chemotherapy, immunotherapy, chemoimmunotherapy, and oncogene-directed targeted therapies[1,2]
- Although HER2-targeted therapies have transformed the care of patients with breast and gastric cancers, there is currently no approved HER2-targeted therapy for NSCLC
- T-DXd is an antibody-drug conjugate composed of an anti-HER2 antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload[3,4]

Structure of T-DXd



T-DXd demonstrated durable and robust anticancer activity in pretreated (median, 2 prior lines) patients with unresectable or metastatic *HER2*-mutant NSCLC in the DESTINY-Lung01 trial[5]

- In DESTINY-Lung01, T-DXd demonstrated a confirmed ORR of 55%, median DOR of 9.3 months, median PFS of 8.2 months, and median OS of 17.8 months[6]
- Given the efficacy observed in later-line settings and the unmet need for targeted therapies in patients with *HER2*-mutant NSCLC, evaluating the efficacy of T-DXd vs standard of care in the first-line setting is important to determine the optimal treatment approach

Here we describe DESTINY-Lung04, an open-label, randomized, phase 3 trial evaluating the efficacy and safety of first-line T-DXd in patients with unresectable, locally advanced, or metastatic NSCLC harboring *HER2* mutations

- For more information, please visit ClinicalTrials.gov (NCT05048797)

Study Design and Population

Patient population (N≈264)

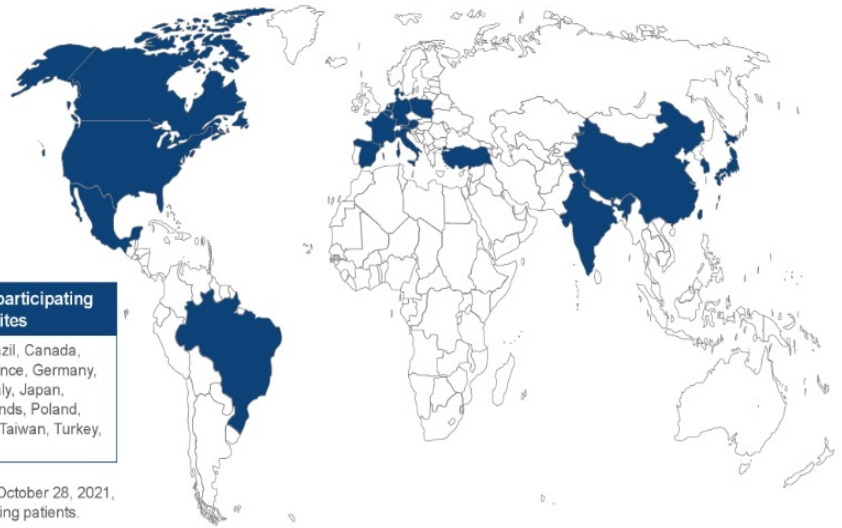
- Unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with *HER2* exon 19 or 20 mutations[a]
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations

Randomization 1:1

- **Arm 1: T-DXd[b]**
- **Arm 2: Standard of care[b]** platinum[c] (cisplatin or carboplatin) + pemetrexed + pembrolizumab

[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

Countries With Enrollment Sites



Countries with participating study sites

Austria, Belgium, Brazil, Canada, China, Denmark, France, Germany, Hong Kong, India, Italy, Japan, Mexico, the Netherlands, Poland, South Korea, Spain, Taiwan, Turkey, United States

This study started on October 28, 2021, and is currently recruiting patients.

Key Inclusion Criteria

- Age ≥18 years
- Locally advanced (not amenable to curative therapy) or metastatic NSCLC
- Histologically documented nonsquamous NSCLC with *HER2* mutation in exon 19 or 20 detected by tissue sequencing or plasma ctDNA (local or central testing)
- Naive to systemic therapy in the locally advanced or metastatic setting
- Left ventricular ejection fraction ≥50%
- Measurable disease based on RECIST v1.1
- Adequate organ function, including cardiac, renal, and hepatic function, as defined in the protocol
- ECOG performance status of 0 or 1
- Tumor tissue available for central testing

Key Exclusion Criteria

- Tumors with other known targetable mutations/alterations[a]
- Clinically active brain metastases (previously treated and asymptomatic brain metastases are allowed)
- Active autoimmune or inflammatory disorders
- Pleural effusion, ascites, or pericardial effusion that requires drainage
- Medical history of myocardial infarction within 6 months prior to randomization
- History of noninfectious ILD/pneumonitis that required steroids or current or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Lung-specific, intercurrent, clinically significant severe illness
- Contraindication to platinum-based doublet chemotherapy or pembrolizumab

[a] If routinely tested for approved available therapy, including, but not limited, to alterations to *EGFR* and *ALK* fusions.

Key Study Endpoints

1° Primary endpoint

- Progression-free survival (PFS) by blinded independent central review (BICR)[a,b]

2° Secondary endpoints

- Overall survival (OS)[b]
- PFS by investigator[a]
- Overall response rate (ORR) by BICR and investigator[a]
- Duration of response (DOR) by BICR and investigator[a]
- Time to second progression[c] or death
- Landmark PFS at 12 months by BICR and investigator[a]
- Landmark OS at 24 months
- CNS-PFS by BICR[a]
- Safety and tolerability[d]
- Pharmacokinetics, including serum concentrations of T-DXd, total anti-HER2 antibody, and DXd
- Immunogenicity assessed by presence of anti-drug antibodies for T-DXd
- Patient-reported pulmonary symptoms[e]
- Patient-reported tolerability[f]

[a] According to RECIST version 1.1.
[b] Endpoint statistically controlled in the multiple testing procedure.
[c] Assessed by the investigator per local standard clinical practice.
[d] Assessed per the occurrence of AEs, SAEs, and changes from baseline in laboratory parameters, vital signs, ECG, and ECHO/MUGA scan results.
[e] Assessed using the NSCLC-SAQ.
[f] Described using symptomatic AEs (assessed via the PRO-CTCAE and items from the EORTC library), overall side-effect bother (assessed via the PGI-TT), and physical function (assessed via the EORTC QLQ-C30).

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Conclusions

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- In my opinion, combination of Ami + Laz should be discussed for approval based on CHRYSALIS and CHRYSALIS-2 (Coh-A) data; this is a critical ***Unmet Need in NSCLC!***
- Sunvozertinib showed comparable efficacy to standard therapies with comparable safety profile to other TKIs; Osi + Neci showed activity but lower than other agents.
- Based on the ORR, DCR and 1-yr OS DOR as well as comparable safety profile of adagrasib reported in the KRYSTAL study, NDA has been accepted and is under accelerated review for its approval.
- Confirmatory phase III trial KRYSTAL-12 is undergoing comparing adagrasib vs docetaxel.
- New RTK alterations have been found as mechanism of resistance to sotorasib in NSCLC and CRC, opening the concept of combining sotorasib with upstream inhibitors of RTK such as EGFR and SHP2.
- ADC looks as the most promising agents against HER2-mutant NSCLC; Trastuzumab deruxtecan is entering into a phase 3 front-line against chemo/io combo.