Lung Cancer UPDATES
ASCO HIGHLIGTHS
04-08 JUNIO 2021

Iniciativa científica de:
GECP
lung cancer research

CPNCP metastásico. Terapias dirigidas EGRF/ALK

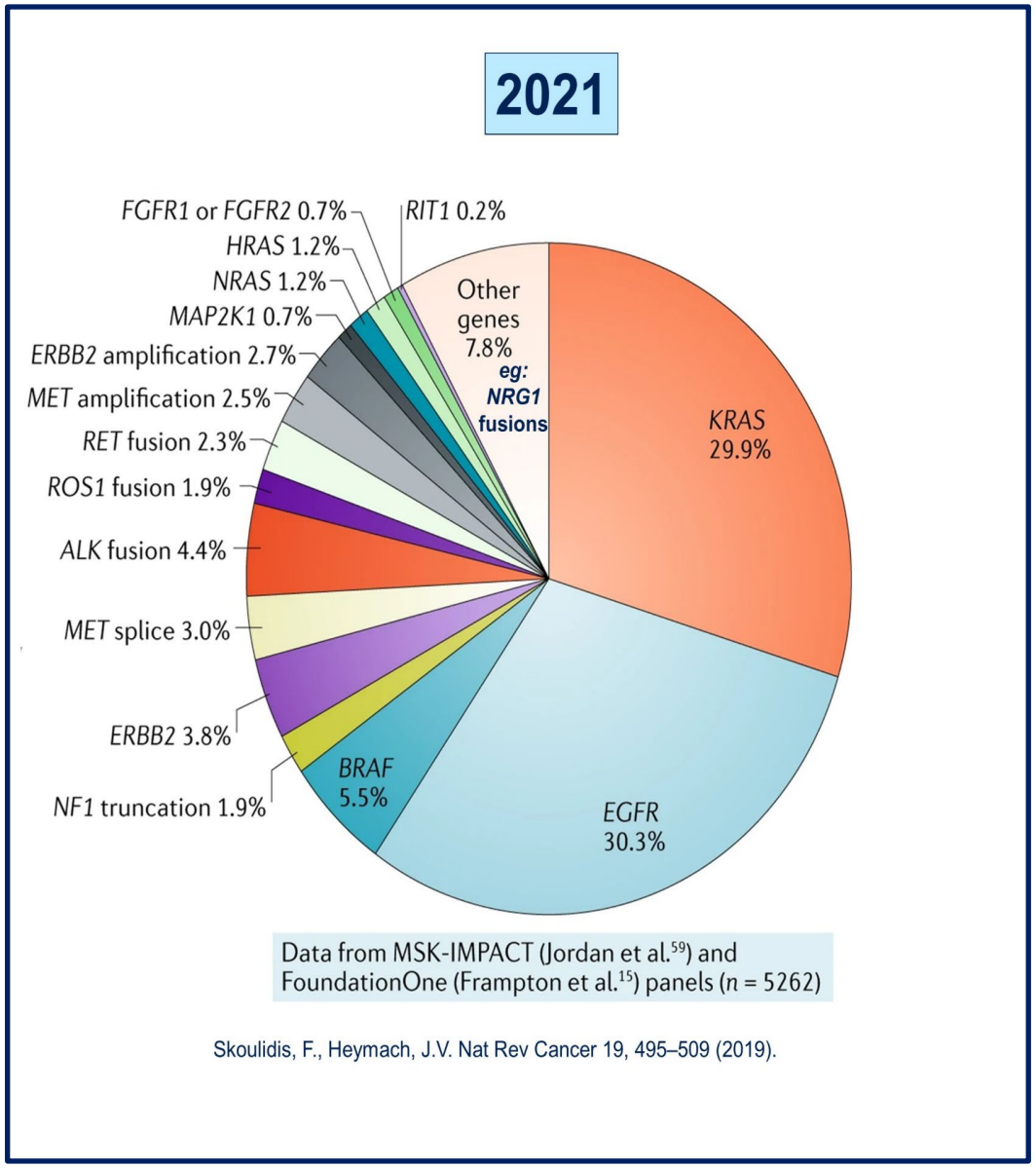
Delvys Rodríguez Abreu, MD, PhD
Hospital Universitario Insular de Gran Canaria.

Disclosure Information

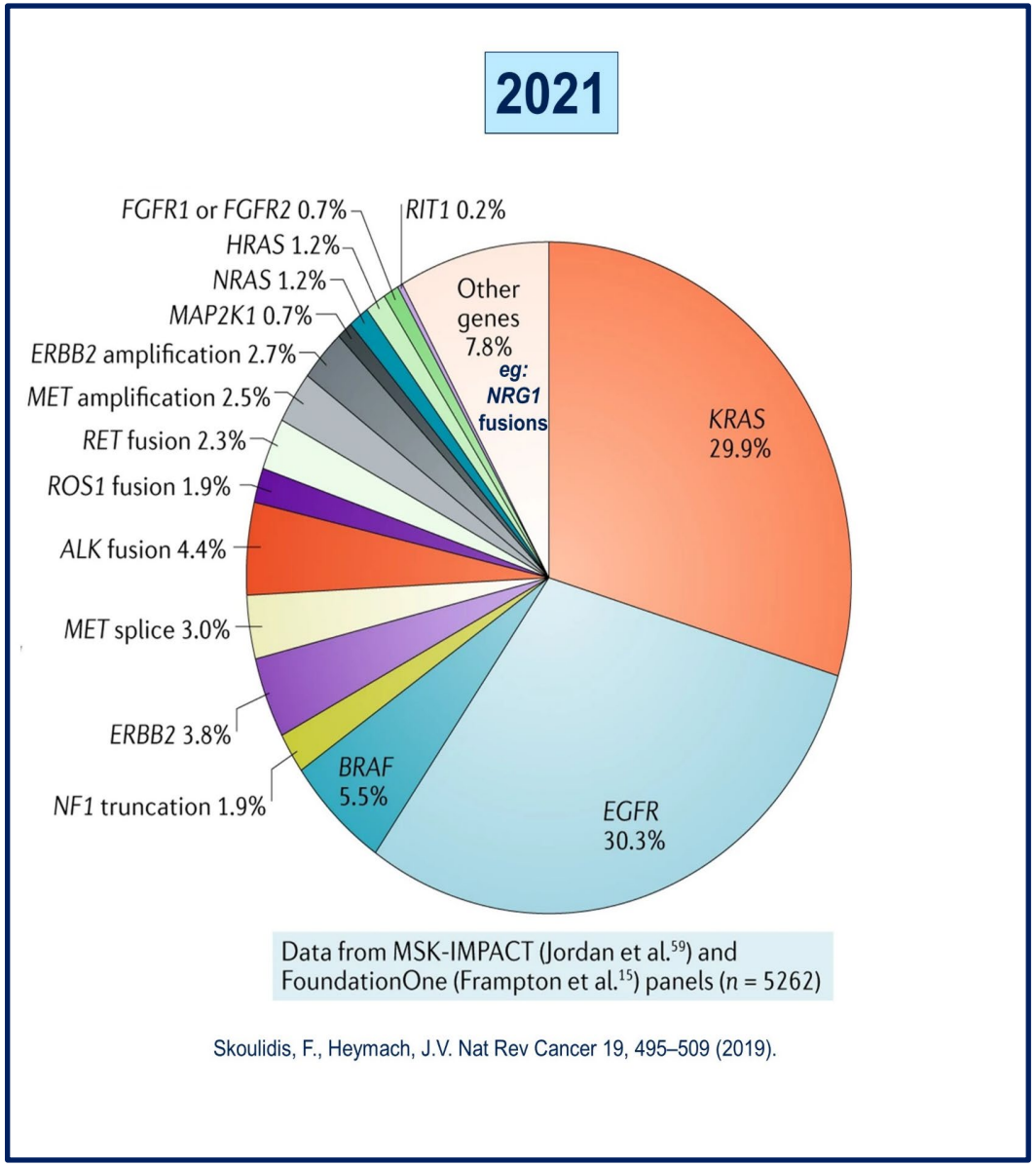
Consultant or Advisory Role: BMS, MSD, ROCHE, ASTRA ZENECA, BOEHRINGER INGELHEIM, NOVARTIS, Lilly.

Lectures: BMS, MSD, ROCHE, ASTRA ZENECA, BOEHRINGER INGELHEIM, Lilly.

Lung cancer never again ONE disease



Lung cancer never again ONE disease



15% EGFR Sensitizing
- Gefitinib[4]
- Erlotinib[4]
- Afatinib[4]
- Dacomitinib
- Osimertinib[4]
- Nazartinib
- Avimantanab

4-5% ALK
- Crizotinib[4]
- Alectinib[4]
- Ceritinib[4]
- Lorlatinib[2]
- Brigatinib[2]
- Ensartinib

<1% MEK1
- Trametinib[2]
- Selumetinib[3]
- Cobimetinib[1]

1-3% MET
- Crizotinib
- Cabozantinib
- **Capmatinib**
- **Savolitinib**
- **Tepotinib**
- Merestinib
- Glesatinib

2% RET
- Cabozantinib
- Vandetanib
- Sunitinib
- Lenvetanib
- Alectinib
- Ponatinib
- RXDX-105
- Selpercatinib
- Pralsetinib

1% NTRK1
- **Entrectinib**
- **Larotrectinib**
- Loxo-195
- Cabozantinib
- DS-6051b
- Repotrectinib

1% PIK3CA
- LY3023414[4]
- PQR 309[4]

12% KRAS (G12C)
- AMG510
- MRTX849

2% ROS1
- Crizotinib
- Ceritinib
- Lorlatinib
- Cabozantinib
- Entrectinib
- Ropotrectinib
- DS-6051b

2% BRAF
- Vemurafenib[2]
- Dabrafenib[2]
- Encorafenib

1% HER2
- Neratinib+/-Temsirolimus
- Afatinib
- Dacomatinib
- **Poziotinib**
- **Pyrotinib**
- **TAK-788**
- Trastuzumab
- **TDM-1**
- **DS-8201a**

- Biomarker tissue journey among patients (pts) with untreated metastatic non-small cell lung cancer (mNSCLC) in the U.S. Oncology Network community practices. **Nicholas J. Robert, et al. on behalf of MYLUNG Consortium Collaborators**

- Racial disparities in biomarker testing and clinical trial enrollment in non-small cell lung cancer (NSCLC). **Debora S. Bruno et al.**

The MYLUNG Consortium™

- The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) Consortium™ study assessed **real-world biomarker testing patterns**.

- Data from practices within the US Oncology Network.
  - 46.4% of the overall cohort from the South-eastern USA
  - 3,474 patients
  - 65.3% White, 8.3% Black / AA, 5.8% 'other', 20.7% not documented
  - 74.4% adenocarcinoma

- Patients with metastatic NSCLC initiating first line systemic therapy between April 1, 2018 and March 31, 2020.

- Objectives:
  - Testing rates for ALK, BRAF, EGFR, ROS1, PDL1.
  - Timing of biomarker test results relative to initiation of 1L systemic therapy
  - Turnaround times for biomarker testing results and initiation of 1L therapy

Test types	Overall N=3474	Nonsquamous N=2820
EGFR	70%	76%
ALK	70%	76%
ROS1	68%	73%
BRAF	55%	59%
PD-L1	83%	83%
Any biomarker	90%	91%
All 5 biomarker tests	46%	49%
NGS	37%	39%

The MYLUNG Consortium™

- The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) Consortium™ study assessed **real-world biomarker testing patterns**.

- Data from practices within the US Oncology Network.
  - 46.4% of the overall cohort from the South-eastern USA
  - 3,474 patients
  - 65.3% White, 8.3% Black / AA, 5.8% 'other', 20.7% not documented
  - 74.4% adenocarcinoma

- Patients with metastatic NSCLC initiating first line systemic therapy between April 1, 2018 and March 31, 2020.

- Objectives:
  - Testing rates for ALK, BRAF, EGFR, ROS1, PDL1.
  - Timing of biomarker test results relative to initiation of 1L systemic therapy
  - Turnaround times for biomarker testing results and initiation of 1L therapy

Test types	Overall N=3474	Nonsquamous N=2820
EGFR	70%	76%
ALK	70%	76%
ROS1	68%	73%
BRAF	55%	59%
PD-L1	83%	83%
Any biomarker	90%	91%
All 5 biomarker tests	46%	49%
NGS	37%	39%

50%

The MYLUNG Consortium™

- The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) Consortium™ study assessed **real-world biomarker testing patterns**.

- Data from practices within the US Oncology Network.
  - 46.4% of the overall cohort from the South-eastern USA
  - 3,474 patients
  - 65.3% White, 8.3% Black / AA, 5.8% 'other', 20.7% not documented
  - 74.4% adenocarcinoma

- Patients with metastatic NSCLC initiating first line systemic therapy between April 1, 2018 and March 31, 2020.

- Objectives:
  - Testing rates for ALK, BRAF, EGFR, ROS1, PDL1.
  - Timing of biomarker test results relative to initiation of 1L systemic therapy
  - Turnaround times for biomarker testing results and initiation of 1L therapy

20% started treatment without biomarker

Test types	Overall N=3474	Nonsquamous N=2820
EGFR	70%	76%
ALK	70%	76%
ROS1	68%	73%
BRAF	55%	59%
PD-L1	83%	83%
Any biomarker	90%	91%
All 5 biomarker tests	46%	49%
NGS	37%	39%

50%

Presented By: Christine Lovly, MD, PhD
@Christine_Lovly

The MYLUNG Consortium™

- The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) Consortium™ study assessed **real-world biomarker testing patterns**.

- Data from practices within the US Oncology Network.
  - 46.4% of the overall cohort from the South-eastern USA
  - 3,474 patients
  - 65.3% White, 8.3% Black / AA, 5.8% 'other', 20.7% not documented
  - 74.4% adenocarcinoma

- Patients with metastatic NSCLC initiating first line systemic therapy between April 1, 2018 and March 31, 2020.

- Objectives:
  - Testing rates for ALK, BRAF, EGFR, ROS1, PDL1.
  - Timing of biomarker test results relative to initiation of 1L systemic therapy
  - Turnaround times for biomarker testing results and initiation of 1L therapy

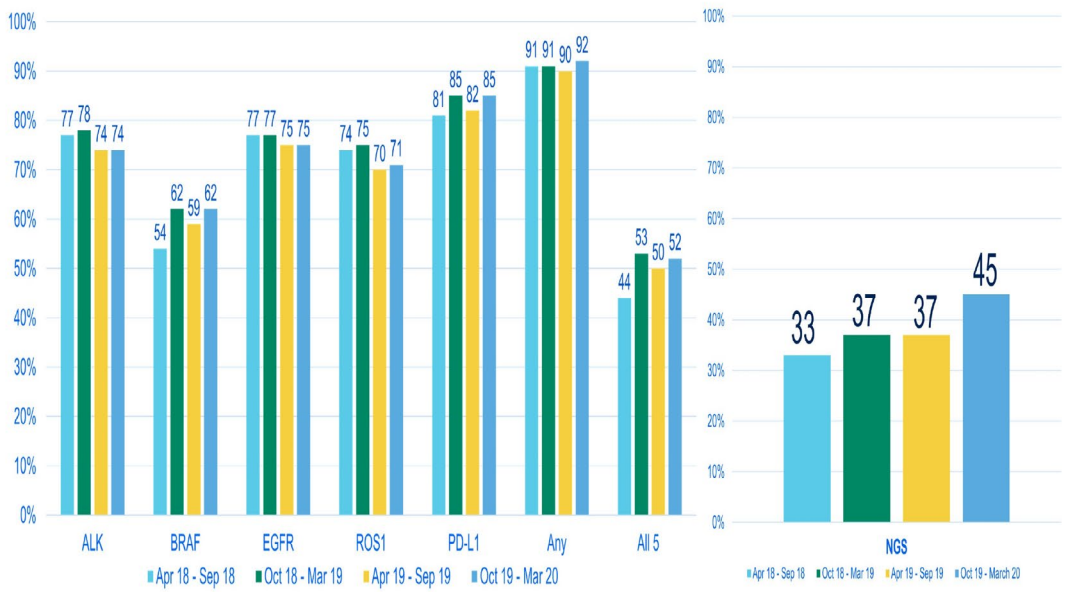
20% started treatment without biomarker

Test types	Overall N=3474	Nonsquamous N=2820
EGFR	70%	76%
ALK	70%	76%
ROS1	68%	73%
BRAF	55%	59%
PD-L1	83%	83%
Any biomarker	90%	91%
All 5 biomarker tests	46%	49%
NGS	37%	39%

50%

Modest improvements in testing for all 5 biomarkers (ALK, BRAF, EGFR, ROS1, PDL1) and use of NGS during the study period

Study Period: April 2018 to March 2020



The MYLUNG Consortium™

- The MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) Consortium™ study assessed **real-world biomarker testing patterns**.

- Data from practices within the US Oncology Network.
  - 46.4% of the overall cohort from the South-eastern USA
  - 3,474 patients
  - 65.3% White, 8.3% Black / AA, 5.8% 'other', 20.7% not documented
  - 74.4% adenocarcinoma

- Patients with metastatic NSCLC initiating first line systemic therapy between April 1, 2018 and March 31, 2020.

- Objectives:
  - Testing rates for ALK, BRAF, EGFR, ROS1, PDL1.
  - Timing of biomarker test results relative to initiation of 1L systemic therapy
  - Turnaround times for biomarker testing results and initiation of 1L therapy

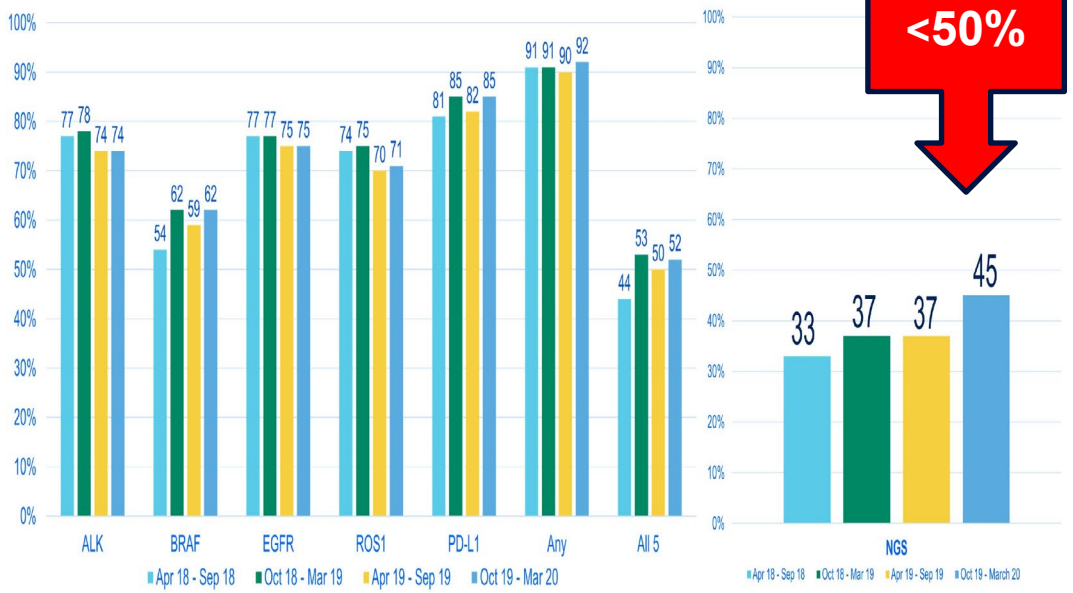
20% started treatment without biomarker

Test types	Overall N=3474	Nonsquamous N=2820
EGFR	70%	76%
ALK	70%	76%
ROS1	68%	73%
BRAF	55%	59%
PD-L1	83%	83%
Any biomarker	90%	91%
All 5 biomarker tests	46%	49%
NGS	37%	39%

50%

Modest improvements in testing for all 5 biomarkers (ALK, BRAF, EGFR, ROS1, PDL1) and use of NGS during the study period

Study Period: April 2018 to March 2020



Flatiron Health de-identified database

Presented by Debora Bruno ASCO. 2021

- 800 sites
- Retrospective cohort study of patients with advanced/metastatic NSCLC: Jan 2017 – October 2020
- Goal: Investigate racial differences in biomarker testing, use of targeted therapies, and clinical trial enrollment among patients in the USA diagnosed with advanced /metastatic NSCLC

Variable	White N = 9,793	Black/AA N = 1,288	p-value
All NSCLC			
Age, mean (SD) years	68.9 (9.7)	66.5 (9.7)	<0.0001
Sex, n (%)*			
Female	4727 (48.3)	633 (49.1)	0.56
Male	5065 (51.7)	655 (50.9)	
Smoking, n (%)	8666 (88.5)	1122 (87.1)	0.16
US geographic region, n(%)			
Midwest	1655 (16.9)	129 (10.0)	<0.0001
Northeast	1939 (19.8)	134 (10.4)	
South	4113 (42.0)	849 (65.9)	
West	1042 (10.6)	52 (4.0)	
Unknown	1044 (10.7)	124 (9.6)	
Payer, n(%)			0.01
Private	3851 (39.3)	495 (38.4)	
Public	1957 (20.0)	307 (23.8)	
Unknown	3985 (40.7)	486 (37.7)	
Practice type, n (%)			
Academic	994 (10.2)	118 (9.2)	0.27
Community	8799 (89.8)	1170 (90.8)	

In this dataset, there were:

- More lung cancer patients overall in the South.
- The South had the highest percentage of Black/AA patients.

Disparities in Biomarker Testing with NGS

Patients with non-squamous NSCLC				
	Non-squamous N=10,333	White N=6,705	Black/AA N=922	P-value, White vs Black/AA
Ever tested	8,786 (85.0%)	5,699 (85.0%)	764 (82.9%)	0.09
Tested prior to first line therapy		4,881 (72.8%)	662 (71.8%)	0.52
Ever NGS tested	5,494 (53.2%)	**3,668 (54.7%)**	**404 (43.8%)**	**<0.0001**
NGS tested prior to first line therapy		**2,452 (36.6%)**	**274 (29.7%)**	**<0.0001**

Race unknown >11%

Social status ???

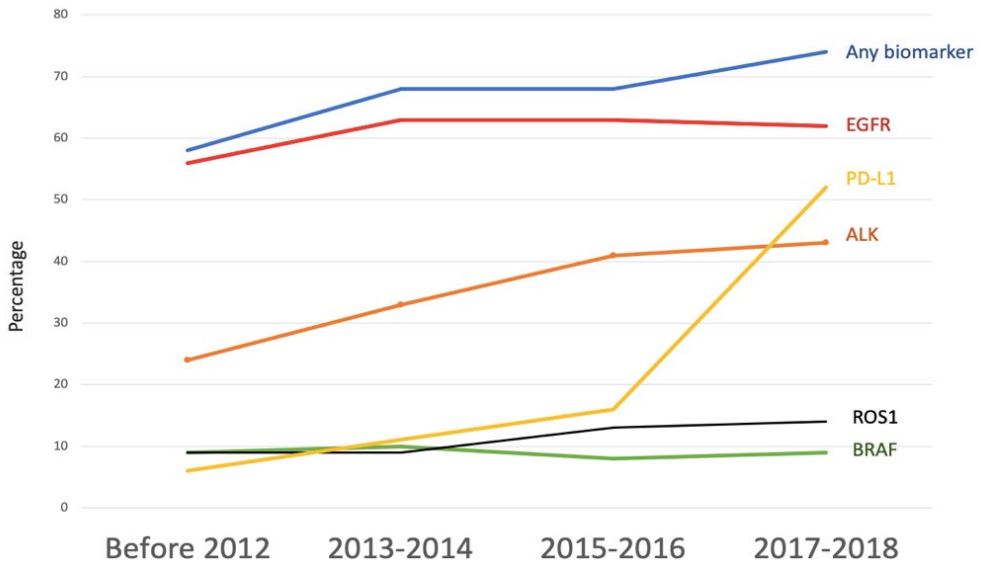
Insurance status?

- *If the prevalence of mutations are analogous, why these differences?*
- *The data also reveal that patients whose tumors were NGS tested were ~2x as likely to be involved in a clinical trial.*
- *Less black/AA patients get NGS = another barrier to achieving equality and equity in clinical trial participation.*

REGISTRO DE TUMORES TORÁCICOS GECP: BIOMARCADORES

EVOLUCIÓN DE % PACIENTES TESTADOS

58% → 74%

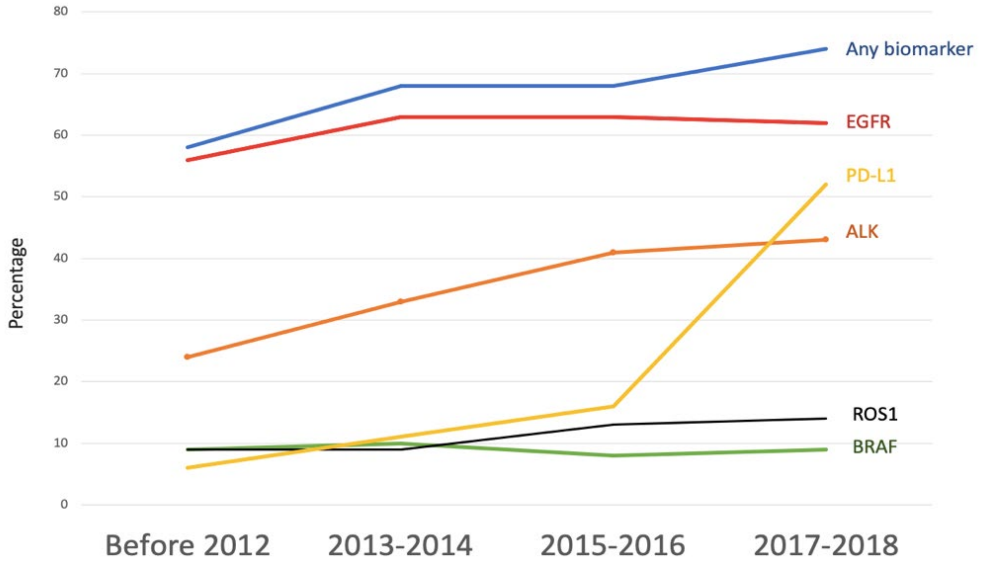


Rodriguez-Abreu D, et al. Presented at World Conference on Lung Cancer, JTO 2019

REGISTRO DE TUMORES TORÁCICOS GECP: BIOMARCADORES

EVOLUCIÓN DE % PACIENTES TESTADOS

58% → 74%



PACIENTES TESTADOS POR COMUNIDADES (%)

Rodriguez-Abreu D, et al. Presented at World Conference on Lung Cancer, JTO 2019

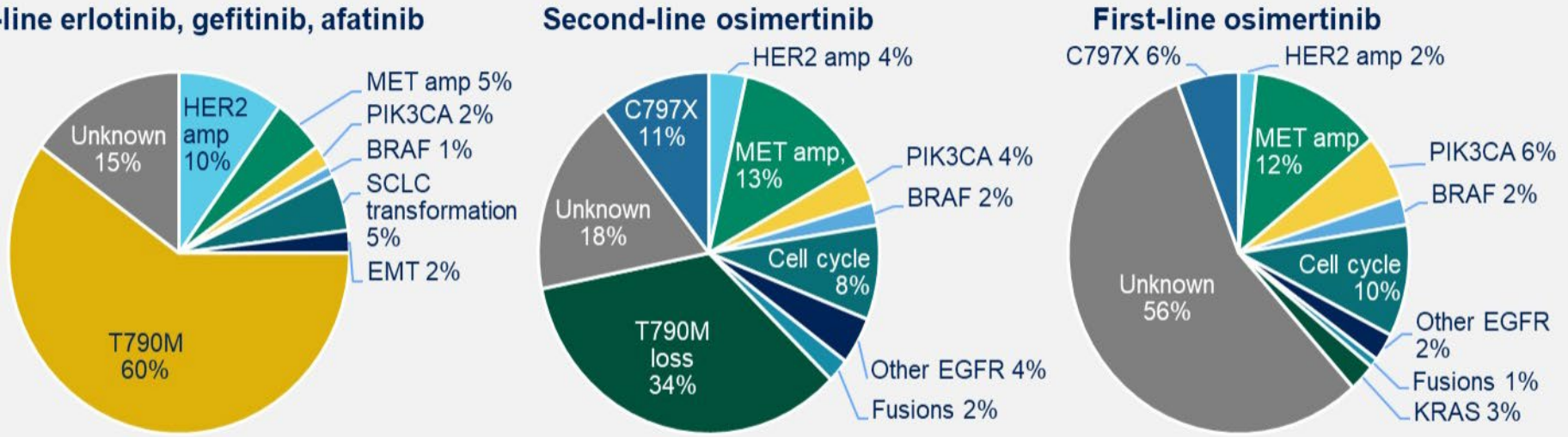
- Amivantamab in combination with lazertinib for the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC) and potential biomarkers for response. **Joshua Bauml, Byoung Chul Cho, et al.**

- Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC). **Pasi A. Janne, et al.**

EGFR TKI Resistance an Unmet need in EGFR mutant NSCLC

- Efficacy of EGFR TKI in *EGFR*m NSCLC has been established; however, the development of various resistance mechanisms commonly leads to disease progression[1-2]
- Platinum-based chemotherapy following EGFR TKI failure has limited efficacy (ORR, 25%–44%; PFS, 2.7–6.4 months)[3]
- Salvage therapies after EGFR TKI and platinum-based chemotherapy have not been effective (PFS, 2.8–3.2 months)[4]

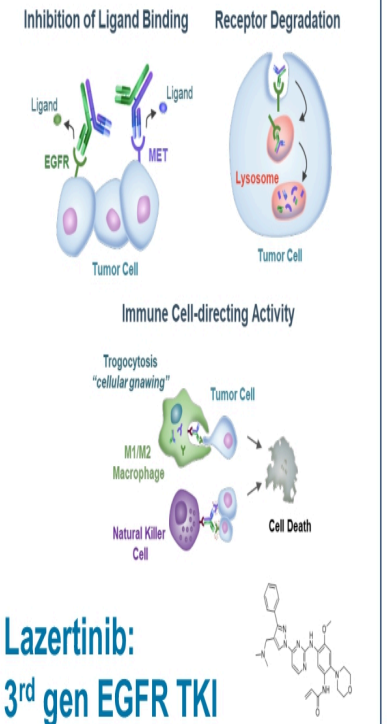
Wide variety of genomic alterations associated with EGFR TKI resistance[1,2]



1. Engelman JA, et al. *Science*. 2007;316:1039-1043. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15:18-21. 3. Han B, et al. *Onco Targets Ther*. 2018;11:2121-9. 4. Yang CJ, et al. *BMC Pharmacol Toxicol* 2017;18(1).

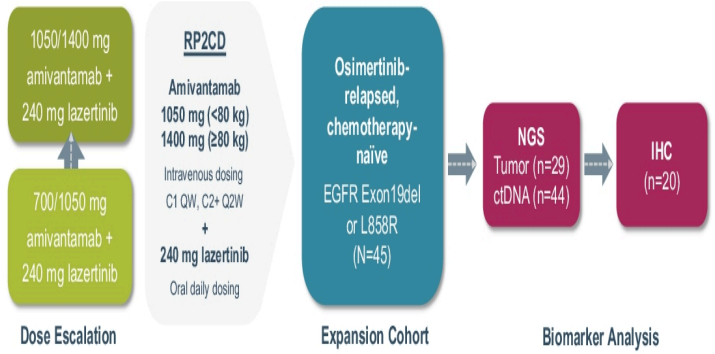
EGFR TKI RESISTANCE: LAZERTINIB PLUS AMIVANTAMAB
ASCO 2021: CHRYSALIS phase I trial

Amivantamab: Fully human bispecific antibody that targets EGFR and MET



Lazertinib: 3rd gen EGFR TKI

- Standard design for dose expansion cohort



- Efficacy dataset (investigator assessed): n=45

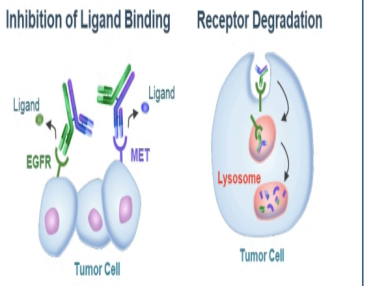
- Brain metastases: 29%
- Prior 1st or 2nd-gen TKI before osimertinib:73%

- Safety as previously reported:

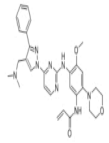
- Majority of grade 1-2, only 16% grade≥3
- IRR (78%), acneiform dermatitis (51%), paronychia (49%)
- Discontinuation rate: 4%

EGFR TKI RESISTANCE: LAZERTINIB PLUS AMIVANTAMAB
ASCO 2021: CHRYSALIS phase I trial

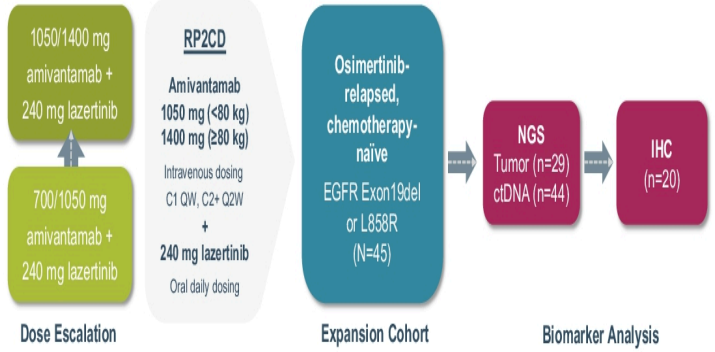
Amivantamab: Fully human bispecific antibody that targets EGFR and MET



Lazertinib: 3rd gen EGFR TKI



- Standard design for dose expansion cohort



- Efficacy dataset (investigator assessed): n=45

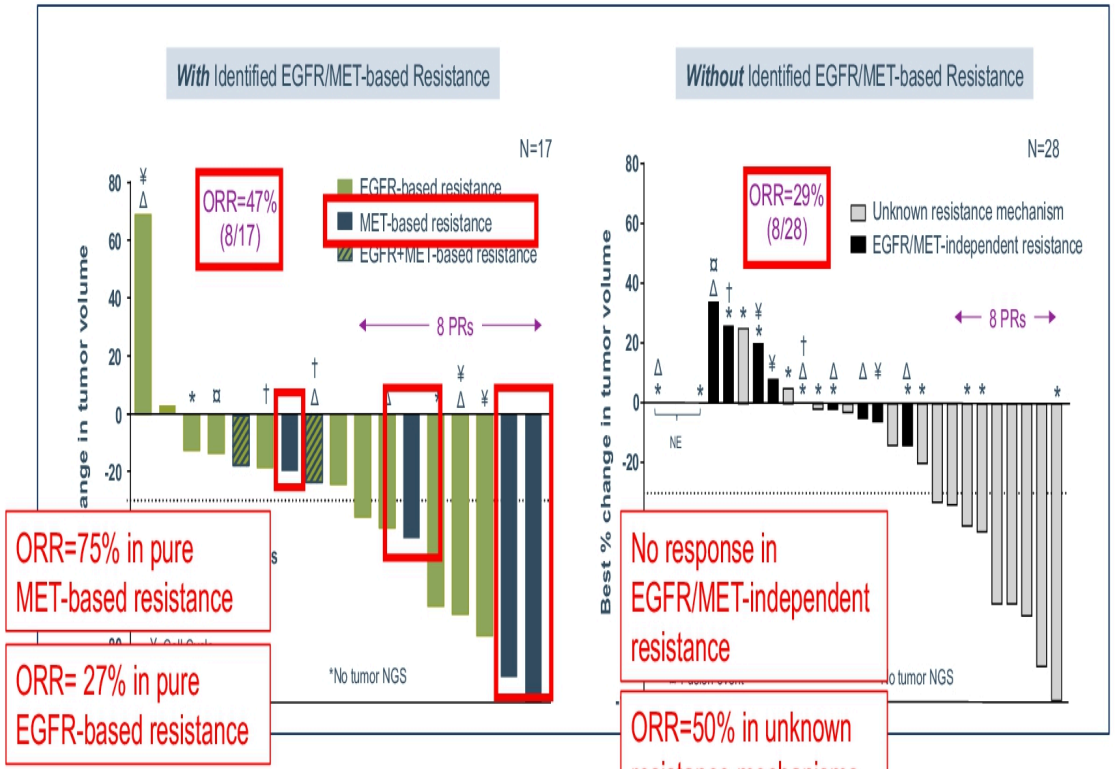
- Brain metastases: 29%
- Prior 1st or 2nd-gen TKI before osimertinib:73%

- Safety as previously reported:

- Majority of grade 1-2, only 16% grade≥3
- IRR (78%), acneiform dermatitis (51%), paronychia (49%)
- Discontinuation rate: 4%

EGFR TKI RESISTANCE: LAZERTINIB PLUS AMIVANTAMAB
ASCO 2021: CHRYSALIS phase I trial

#1: While ORR in the whole cohort is 36%, efficacy is driven by resistance mechanisms

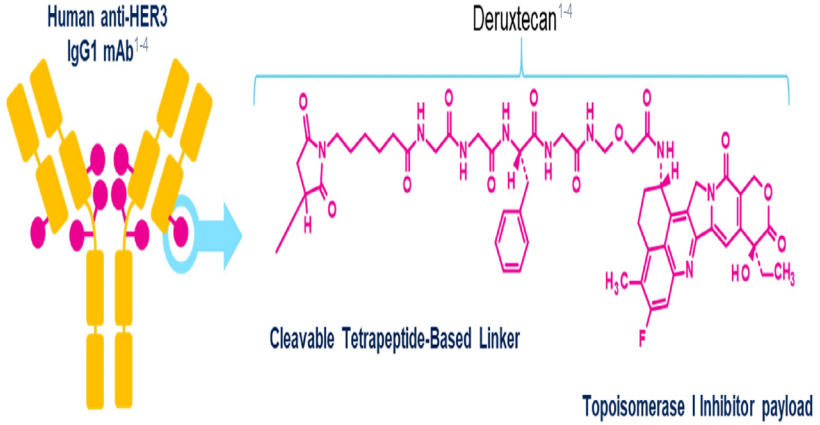


Patritumab Deruxtecan (HER3-DXd)—Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

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

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

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



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

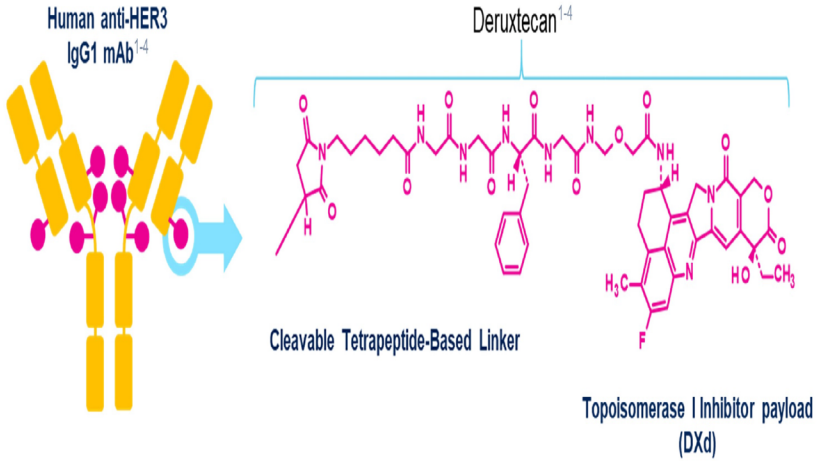
1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388.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

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

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

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

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

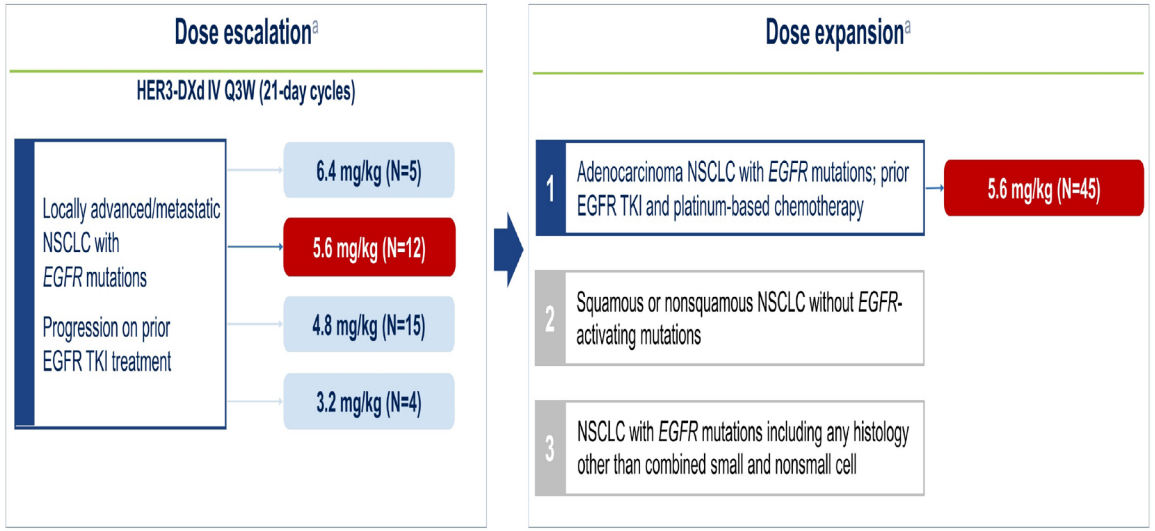


[a]HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC.

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

Patritumab Deruxtecan
U31402-A-U102

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



Recommended dose for expansion: HER3-DXd 5.6 mg/kg IV Q3W

Data cutoff: September 24, 2020

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

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

Clinicaltrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868.

[a]Patients with stable brain metastases were permitted to enroll; A tumor biopsy was required prior to study entry but patients were not selected for inclusion based on measurement of HER3.

Presented By: Marina Chiara GARASSINO

#ASCO21 | Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

2021 ASCO ANNUAL MEETING

Patritumab Deruxtecan
U31402-A-U102

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

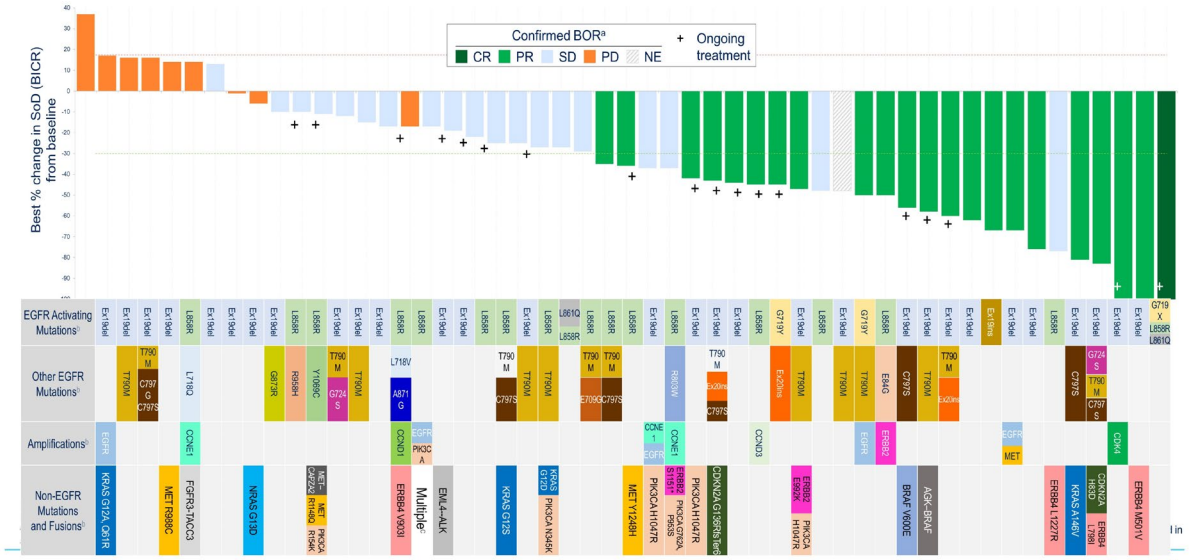
Outcomes (BICR per RECIST 1.1) Median Follow Up: 10.2 (range, 5.2-19.9) mo[a]	HER3-DXd 5.6 mg/kg Prior TKI, ± PBC (N=57)	 Prior OSI, PBC (N=44)
Confirmed ORR, % (95% CI)	39 (26-52)	39 (24-55)
Best overall response, n (%)		
CR	1 (2)	1 (2)
PR	**21 (37)**	**16 (36)**
SD, Non-CR/Non-PD	19 (33)	13 (30)
PD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

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

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

Patritumab Deruxtecan
U31402-A-U102

HER3-DXd Demonstrated Activity in Patients With Diverse Mechanisms of EGFR TKI Resistance



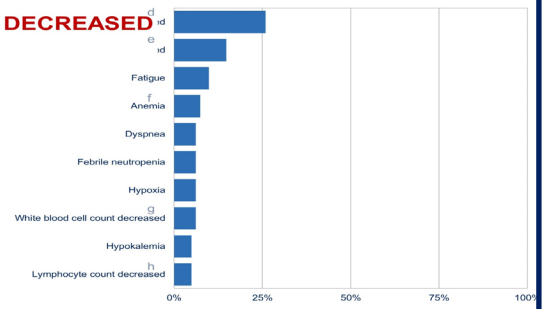
Patritumab Deruxtecan
U31402-A-U102

HER3-DXd Was Associated With a Manageable Safety Profile and a Low Rate of Discontinuations Due to Adverse Events

TEAEs, n (%) Median treatment duration: 5.7 (range, 0.7-28.3) mo	5.6 mg/kg (N=57)	All Doses (N=81)
Any TEAE	57(100)	81 (100)
Associated with treatment discontinuation[a]	6 (11)	7 (9)
Associated with treatment dose reduction	12 (21)	18 (22)
Associated with treatment dose interruption	21 (37)	30 (37)
Associated with death[b]	4 (7)	5 (6)
Grade ≥3 TEAE	42 (74)	52 (64)
Treatment-related TEAE:	55 (96)	78 (96)
Associated with death	0	0
Grade ≥3	31 (54)	38 (47)
Serious TEAE	12 (21)	15 (19)
Interstitial lung disease[c]	**4 (7)**	**4 (5)**
Grade 1	2 (4)	2 (2)
Grade 2	1 (2)	1 (1)
Grade 3	1 (2)	1 (1)
Grade 4/5	0	0

- The rate of adjudicated treatment-related interstitial lung disease was 5%; none were grade 4/5
- Median time to adjudicated onset of treatment-related interstitial lung disease was 53 (range, 13-130) days

TEAEs grade ≥3 in ≥5% of patients (N=81)

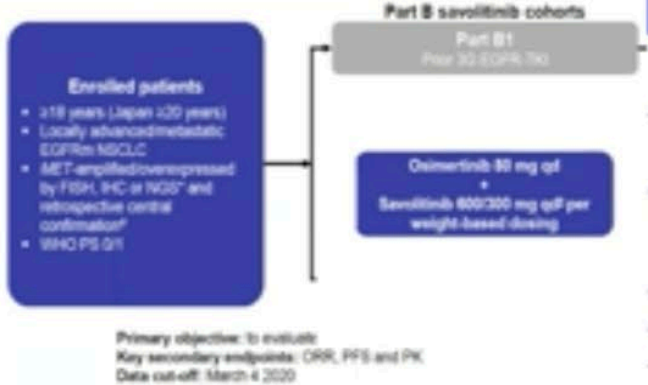


Data cutoff: September 24, 2020.
[a] TEAEs associated with treatment discontinuation were fatigue (2); nausea, decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection; none were for thrombocytopenia (1 each). [b] TEAEs associated with death were: disease progression (2), respiratory failure (2), and shock (1). [c] One additional occurrence of Grade 5 ILD was determined by adjudication to be unrelated to study treatment. [d] Includes thrombocytopenia. [e] Includes neutropenia. [f] Includes hemoglobin decreased. [g] Includes leukopenia. [h] Includes lymphopenia.

EGFR TKI RESISTANCE: TARGETING MET

SAVOLITINIB

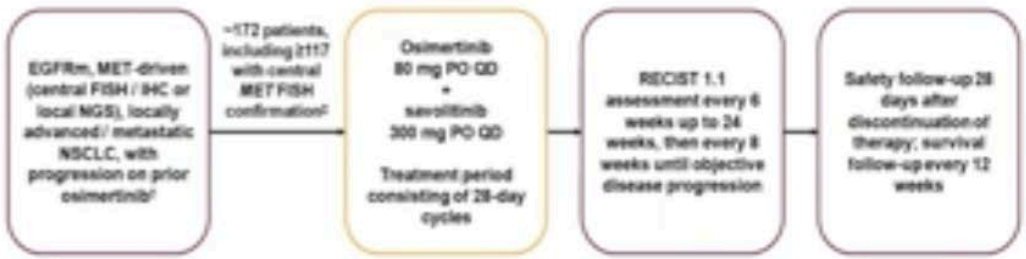
TATTON, part B1



Primary objective: to evaluate
Key secondary endpoints: ORR, PFS and PK
Data cut-off: March 4 2020

Endpoint	Part B1 (n=69) Prior 3G EGFR-TKI
Median treatment duration, months	
Savolitinib	4.6
Osimertinib	4.6
ORR,* n (%) [95% CI]	23 (33) [22, 46]
Complete response	0
Partial response	23 (33)
Non-response, n (%)	
Stable disease (≥ 6 weeks)	29 (42)
Progressive disease	8 (12)
Not evaluable	9 (13)
Disease control rate,* n (%) [95% CI]	52 (75) [64, 85]
Median DoR, months [95% CI]	9.5 [4.2, 14.7]
Median PFS, months [95% CI]	5.5 [4.1, 7.7]

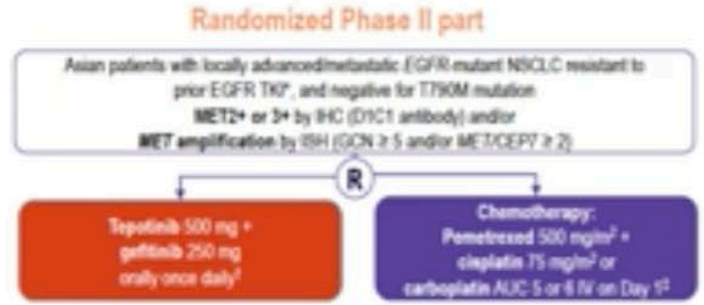
SAVANNAH (ongoing)

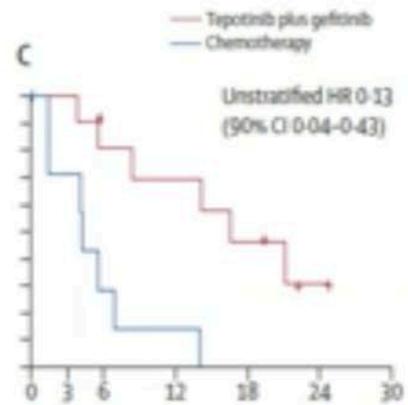


Sequist, et al. Lancet Oncol 2020; 21:373
Oxnard, et al. TPS9119. ASCO 2019

TEPOTINIB

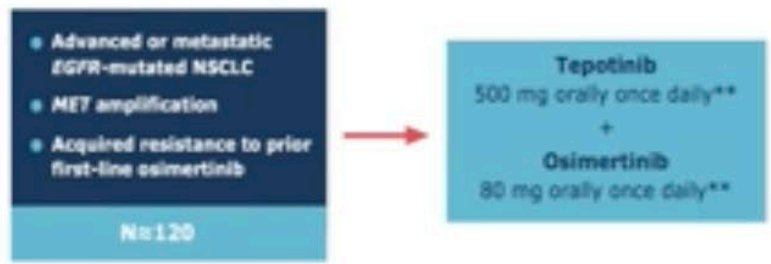
INSIGHT-1





Wu, et al. Lancet Respir Med 2020;8:1132

INSIGHT-2 (ASCO 2021 poster session)



Endpoints

Key Endpoints include:
ORR (by independent and investigator review), **DLTs** (safety run-in only), **safety, PFS, DOR, DC, OS, HRQoL, PK**

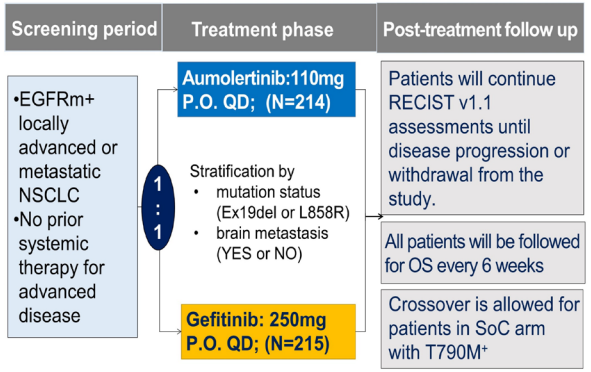
EGFR First Line

Randomized phase III trial of aumolertinib (HS-10296, Au) versus gefitinib (G) as first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and EGFR exon 19 del or L858R mutations (EGFRm). **Shun Lu, et al**. *J Clin Oncol 39, 2021 (suppl 15; abstr 9013)*

Update analysis of NEJ009: Gefitinib alone (G) versus gefitinib plus chemotherapy (GCP) for non-small cell lung cancer with mutated EGFR. **Eisaku Miyauchi, et al.** *J Clin Oncol 39, 2021 (suppl 15; abstr 9081)*

Abstract 9013: AENEAS: Randomized Phase III Trial of Aumolertinib (Almonertinib; Au) versus gefitinib (G) as first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and EGFR exon 19 del or L858R mutations (EGFRm)

S. Lu[1*], X. Dong[2], H. Jian[1], J. Chen[3], G. Chen[4], Y. Sun[5], Y. Ji[6], Z. Wang[7], J. Shi[8], J. Lu[9], S. Chen[10], G. Zhang[11], D. Lv[12], C. Liu[13], J. Li[14], X. Yu[15], Z. Lin[16], Z. Yu[17], Z. Wang[18], J. Cui[19], Hansoh Pharma Clinical Development Group



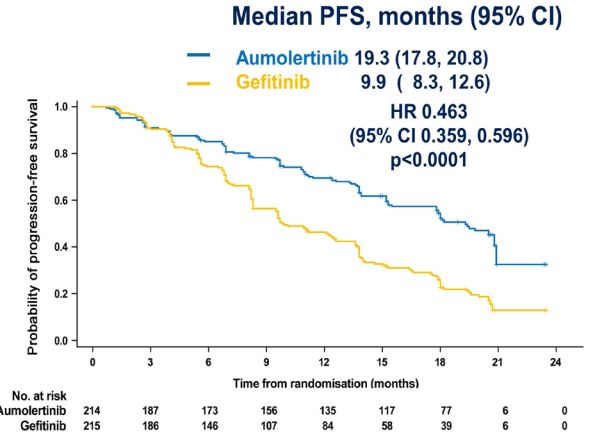
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DoR, DCR, DepOR, AE.

Characteristic %	Aumolertinib (N=214)	Gefitinib (N=215)
Age, median(range),years	59 (32-78)	62(25-81)
Gender: male/female	37.4/62.6	37.2/62.8
Smoking status-ever/never	27.1/72.9	33.0/67.0
Adenocarcinoma	98.1	98.1
Cancer staging IIIB/IV	5.6/94.4	7.9/92.1
ECOG score 0/1	23.8/74.8	25.1/74.0
Brain metastasis	26.2	27.4
EGFR mutation Ex19del/L858R	65.4/34.6	65.6/34.4

Between Nov 30, 2018 and Sept 6, 2019, 429 patients across 53 sites in China were enrolled and randomized, with patient characteristics being well-balanced.

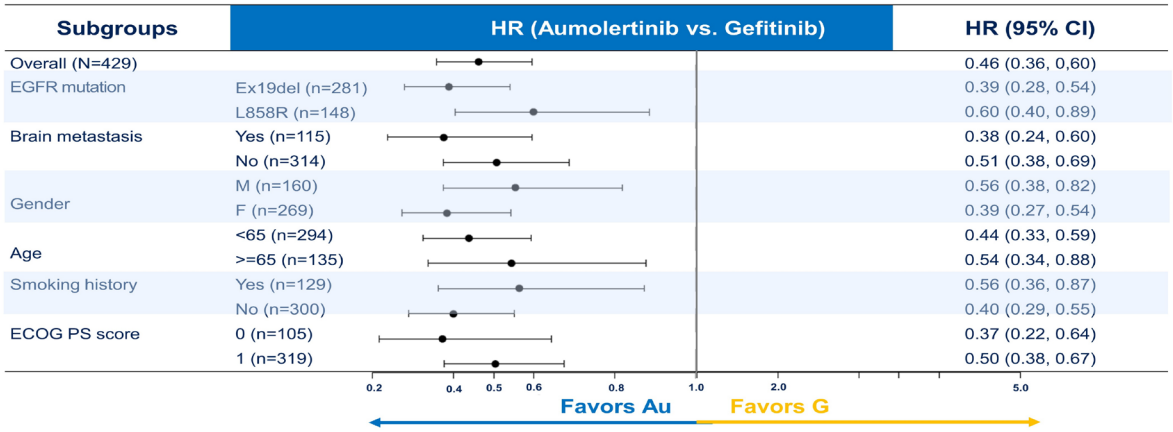
EFFICACY: PFS, OS, DoR, AND ORR IN ITT

Endpoint	Aumolertinib (N=214)	Gefitinib (N=215)	Hazard ratio (HR)/ Odds ratio (OR)
PFS (primary endpoint)	19.3 months (median)	9.9 months (median)	HR 0.463 (95%CI, 0.359-0.596) p<0.0001
OS at 29% maturity	N/A	N/A	HR 0.82 (95%CI, 0.57-1.17) p=0.28
DoR	18.1 months (median)	8.3 months (median)	HR 0.38 (95%CI, 0.28-0.51) p<0.0001
ORR	74%	72%	OR 1.09 (0.70-1.69), p=0.69



- The data cut off is January 15, 2021 with 302 patients now off study treatment: Au-121(56.5%), G-181(84.2%).
- Events number 263 occurred (262 planned), including 258 instances of disease progression and 5 deaths, Au-105 Events(49.1%), G-158 Events (73.5%)

EFFICACY: PFS ACROSS SUBGROUPS



SAFETY SUMMAY

Median exposure: 458 days on Au compared to 254 days on G

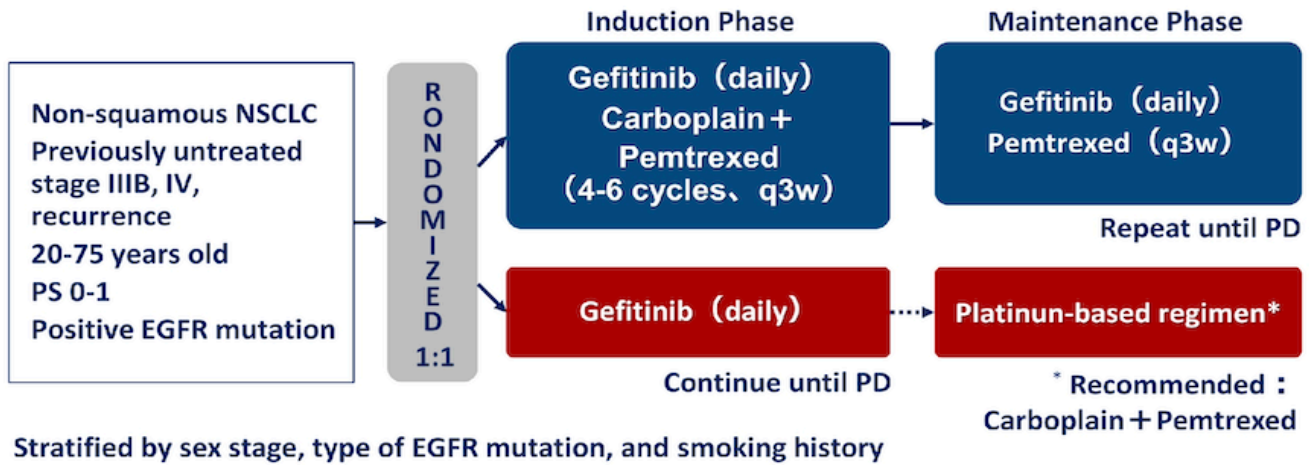
AE n (%)	Aumolertinib (N=214)	Gefitinib (N=215)
At least one AE	211 (98.6)	213 (99.1)
At least one Grade≥3 AE	78 (36.4)	77 (35.8)
At least one SAE	47 (22.0)	46 (21.4)
AE leading to treatment discontinuation	8 (3.7)	11 (5.1)
AE leading to death	5 (2.3)	3 (1.4)

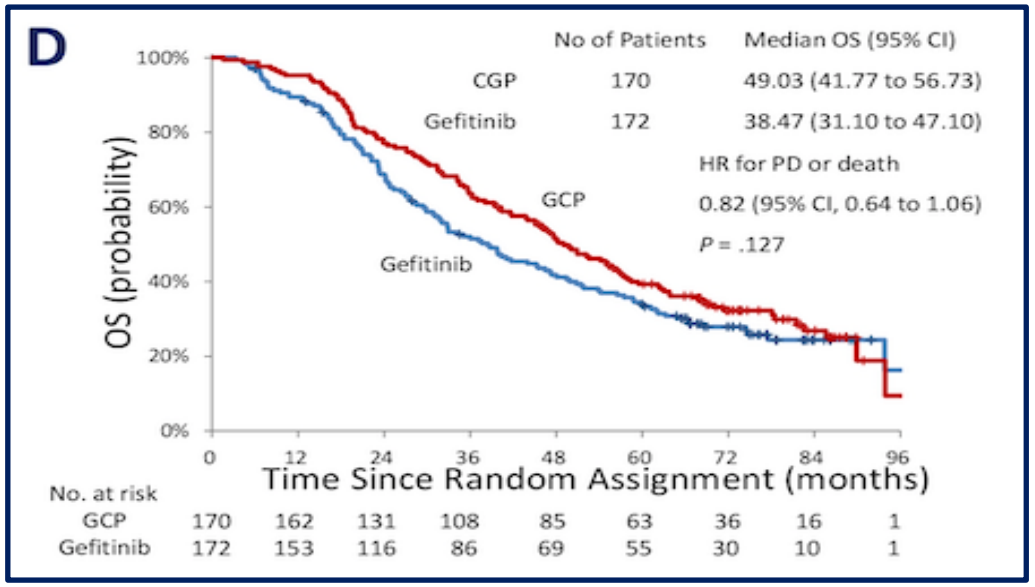
Commonly reported AEs (≥20%, all causality), n (%)	Aumolertinib (N=214)		Gefitinib (N=215)	
	Any Gr	CTCAE≥Gr 3	Any Gr	CTCAE≥Gr 3
Any AEs	211(98.6)	78(36.4)	213(99.1)	77(35.8)
Alanine aminotransferase increased	63(29.4)	6(2.8)	120(55.8)	26(12.1)
Aspartate aminotransferase increased	64(29.9)	3(1.4)	116(54.0)	20(9.3)
Blood white cell count decreased	51(23.8)	5(2.3)	30(14.0)	0
Creatine phosphokinase increased	76(35.5)	15(7.0)	20(9.3)	1(0.5)
Platelet count decreased	47(22.0)	3(1.4)	17(7.9)	2(0.9)
Rash	50(23.4)	0	89(41.4)	0
Diarrhea	35(16.4)	3(1.4)	77(35.8)	2(0.9)
Urinary tract infection	46(21.5)	1(0.5)	37(17.2)	2(0.9)
Anemia	43(20.1)	2(0.9)	21(9.8)	0

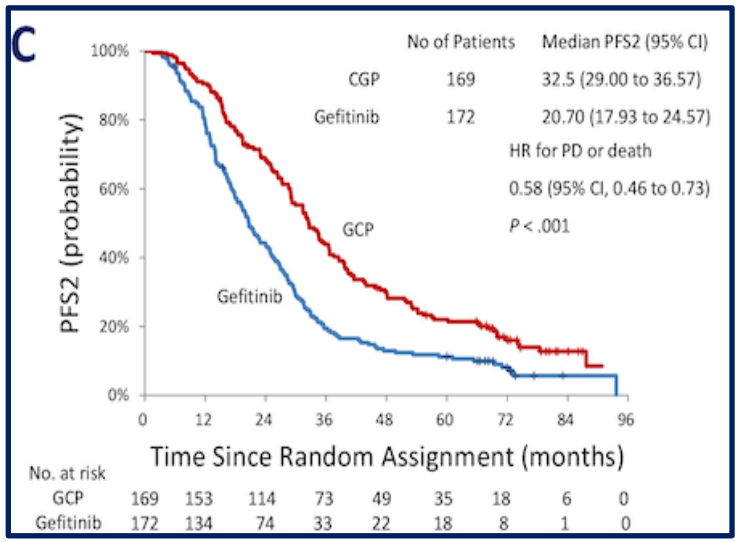
#9081: Update Analysis of NEJ009: Gefitinib Alone (G) versus Gefitinib plus Chemotherapy (GCP) for Non-Small-Cell Lung Cancer with Mutated EGFR

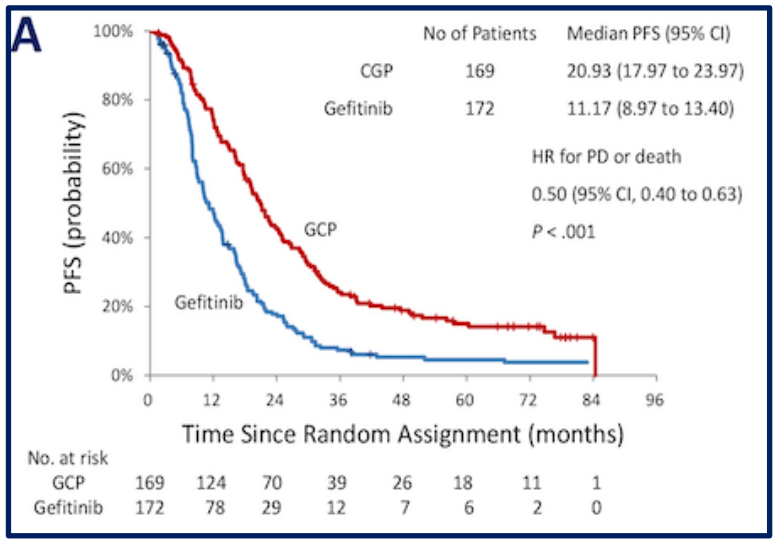
Eisaku Miyauchi[1], Satoshi Morita[2], Atsushi Nakamura[3], Yukio Hosomi[4], Kana Watanabe[5], Satoshi Ikeda[6], Masahiro Seike[7], Yuka Fujita[8], Koichi Minato[9], Ryo Ko[10], Toshiyuki Harada[11], Koichi Hagiwara[12], Kunihiko Kobayashi[13], Toshihiro Nukiwa[14], Akira Inoue[15], North East Japan Study Group (NEJSG)

Figure 1. Study Design









Conclusion

- This updated analysis confirmed that the GCP regimen achieved significantly better PFS and PFS2 with an acceptable safety profile compared with gefitinib alone.
- GCP was tolerated, with no cumulative toxicities and no new- or late-onset safety signals.
- The efficacy outcome of GCP is more favorable than gefitinib monotherapy as first-line treatment of NSCLC with EGFR mutation.

Exon 20 insertions therapy

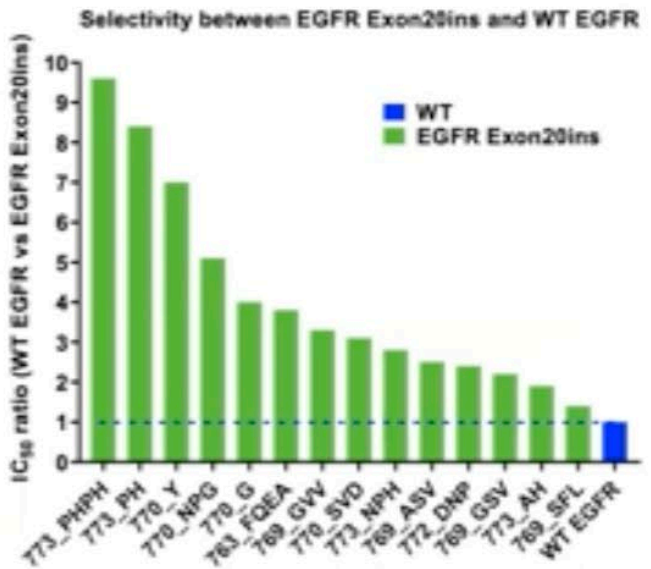
Preliminary safety and efficacy results from phase 1 studies of DZD9008 in NSCLC patients with EGFR Exon20 insertion mutations. **James Chih-Hsin Yang et al.** J Clin Oncol 39, 2021 (suppl 15; abstr 9008)

Mobocertinib (TAK-788) in EGFR exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): Additional results from platinum-pretreated patients (pts) and EXCLAIM cohort of phase 1/2 study.

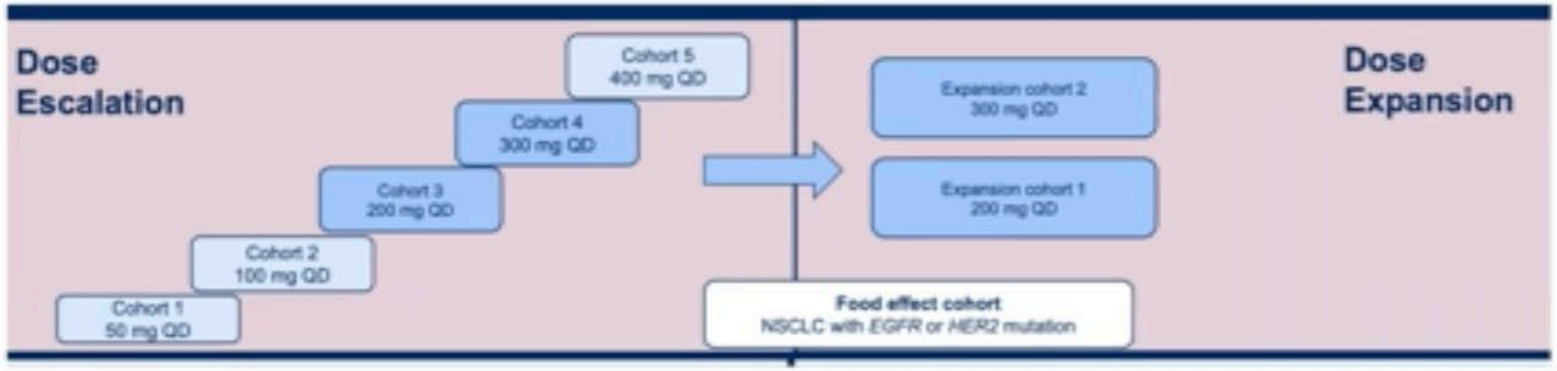
Suresh S. Ramalingam et al. J Clin Oncol 39, 2021 (suppl 15; abstr 9014)

Phase 1 studies of DZD9008 in NSCLC patients with EGFR Exon20 insertion mutations

DZD9008: selective, irreversible EGFR inhibitor targeting EGFR or HER2 mutations



- Standard design for dose escalation/expansion phase 1 trials



- Efficacy dataset on EGFR exon 20 insertion patients: n=56

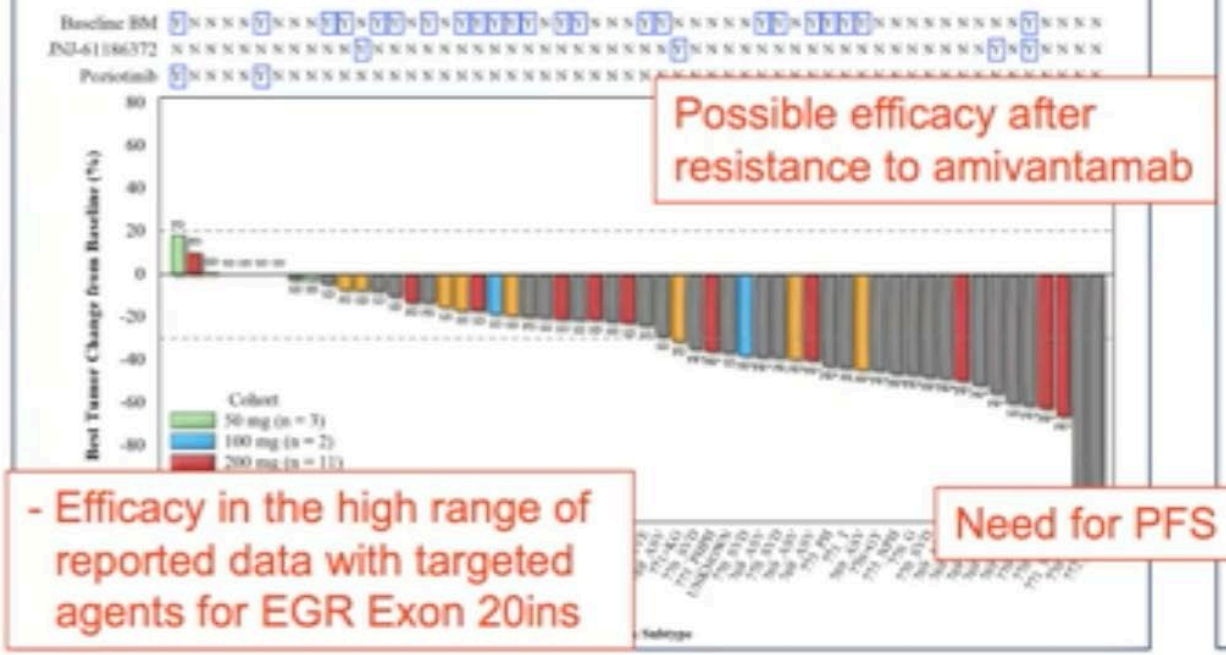
- PS1+: 38%, brain mets: 41%
- median number of previous line: 2
- only 6 patients with previous EGFR exon 20ins treatment

- Safety dataset on all enrolled patients: n=102

Phase 1 studies of DZD9008 in NSCLC patients with EGFR Exon20 insertion mutations

RESPONSE

- Response rate per investigator: 39.6%
- Disease control rate: 85.7%



Possible efficacy after resistance to amivantamab

- Efficacy in the high range of reported data with targeted agents for EGR Exon 20ins

Need for PFS

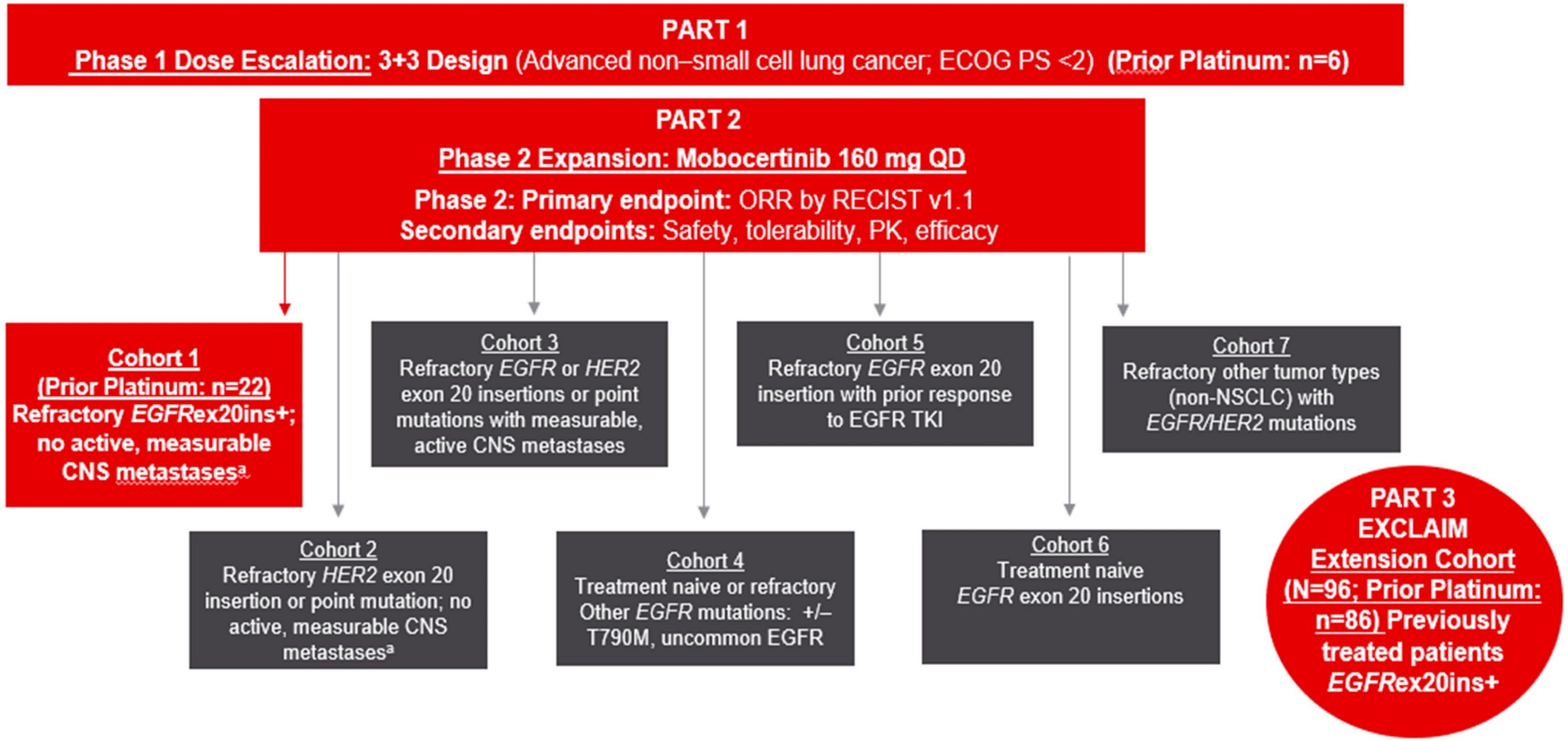
SAFETY

Expected profile of AEs

AE summary n (%)	All (N = 102)
Treatment emergent AE	
Any grade	102 (100.00)
≥ Grade 3	40 (39.2)
Drug-related AE	
Any grade	99 (97.1)
≥ Grade 3	34 (33.3)
Dose reduction due to drug-related AE	16 (15.7)
Dose interruption due to drug-related AE	24 (23.5)
Discontinuation due to drug-related AE	6 (5.9)

Suresh S. Ramalingam,[1] Caicun Zhou,[2] Tae Min Kim,[3] Sang-We Kim,[4] James Chih-Hsin Yang,[5] Gregory J. Riely,[6] Tarek Mekhail,[7] Danny Nguyen,[8] Maria R. Garcia Campelo,[9] Enriqueta Felip,[10] Sylvie Vincent,[11] Shu Jin,[11] Veronica Bunn,[11] Jianchang Lin,[11] Huamao M. Lin,[11] Minal Mehta,[11] Pasi A. Jänne[12]

Mobocertinib in EGFR Exon 20 insertions



Abstract 9014

Mobocertinib (TAK-788) in *EGFR* exon 20 insertion+ metastatic NSCLC: Additional results from platinum-pretreated patients and EXCLAIM cohort of phase 1/2 study

Suresh S. Ramalingam,[1] Caicun Zhou,[2] Tae Min Kim,[3] Sang-We Kim,[4] James Chih-Hsin Yang,[5] Gregory J. Riely,[6] Tarek Mekhail,[7] Danny Nguyen,[8] Maria R. Garcia Campelo,[9] Enriqueta Felip,[10] Sylvie Vincent,[11] Shu Jin,[11] Veronica Bunn,[11] Jianchang Lin,[11] Huamao M. Lin,[11] Minal Mehta,[11] Pasi A. Jänne[12]

Mobocertinib in EGFR Exon 20 insertions

Characteristic	PPP Cohort (n=114)	EXCLAIM Cohort (n=96)
Median age, years (range)	60 (27–84)	59 (27–80)
Female, %	66	65
Race: Asian/White/Black/Other, %	60/37/3/1	69/29/2/0
Histology: Adenocarcinoma/Squamous/Large cell, %	98/1/1	99/1/0
ECOG PS: 0/1, %	25/75	29/71
History of smoking: Never/Current/Former, %	71/2/27	73/2/25
Prior systemic anticancer regimens, 1/2/≥3, %	41/32/27	51/31/18
Median number of prior regimens	2	1
Prior platinum-based chemotherapy, %	100	90
Prior immunotherapy, %	43	34
Prior EGFR TKI, %	25	31
Baseline brain metastases, %	35	34

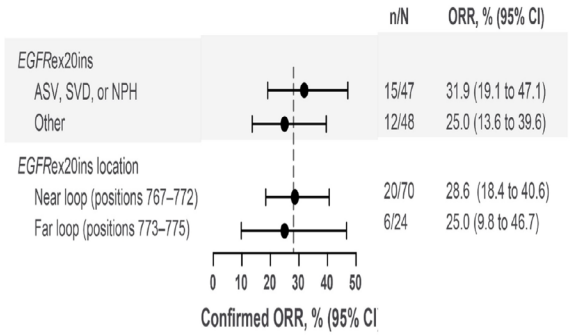
	PPP Cohort n=114	EXCLAIM Cohort n=96
IRC assessments		
Confirmed ORR (95% CI)	28% (20%–37%)	25% (17%–35%)
CR, %	0%	0%
PR, %	28%	25%
Median DoR (95% CI)[a]	17.5 months (7.4–20.3)	NE (5.6–NE)
Confirmed DCR (95% CI)[b]	78% (69%–85%)	76% (66%–84%)
Investigator assessments		
Confirmed ORR, % (95% CI)	35% (26%–45%)	32% (23%–43%)
CR, %	<1%	1%
PR, %	34%	31%
Median DoR, months (95% CI)[a]	11.2 months (5.6–NE)	11.2 months (7.0–NE)
Confirmed DCR (95% CI)[b]	78% (69%–85%)	75% (65%–83%)

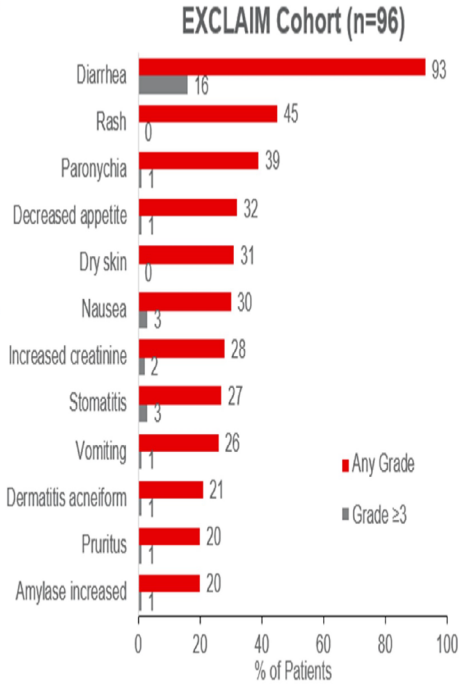
Median ORR 25-28%
Median PFS 7.3 months
Median DoR 17.5 months
Median OS 24 months

Abstract 9014

Mobocertinib in EGFR Exon 20 insertions

	All Patients (n=96)	Patients With Brain Metastases at Baseline (n=33)
PD by investigator, n/N (%)	58/96 (60%)	25/33 (76%)
First site of PD in brain	22/58 (38%)	17/33 (68%)
Continued mobocertinib ≥3 mo after initial PD, n (%)[a]	5/22 (23%)	NA
Median time on treatment beyond initial PD (95% CI)	1.6 months (~0.2–6.7)	NA
First site of PD not in brain	36/58 (62%)	NA
Continued mobocertinib ≥3 mo after initial PD, n (%)[a]	2/36 (6%)	NA
Time on treatment beyond initial PD, median (95% CI)	0.1 months (~1.0–10.0)	NA





-CNS was common site of PD on study
-Mobocertinib effective against all types of EGFR ex20ins
-Dose reduction in 22-25% due to AE
-Study drug discontinuation in 10-17% due to AE

Abstract 9014

Landscape of Targeting EGFR Exon 20 Insertion

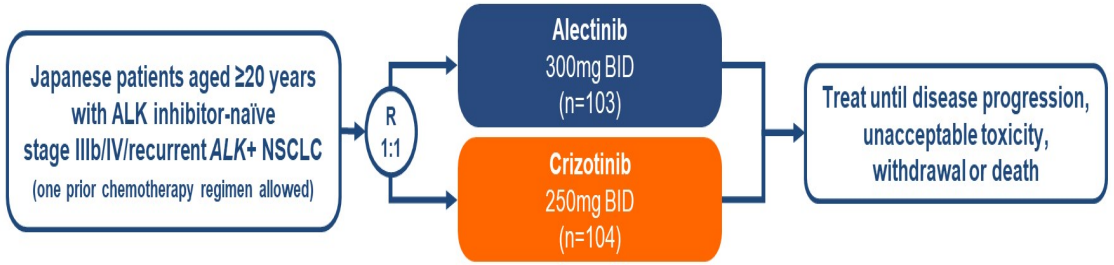
	Mobocertinib	Amivantamab	Osimertinib	CLN-081	Poziotinib
Type of drug	EGFR TKI	EGFR/MET antibody	EGFR TKI	EGFR TKI	EGFR TKI
Clinical trial setting	After platinum chemo Active brain mets OK (35%)	After platinum chemo Brain mets (22%)	1 prior line of treatment Stable brain mets OK	After platinum chemo Stable brain mets OK	After chemo Stable brain mets OK (10%)
Number of pts	PPP N=114 EXCLAIM N=96	N=81	N=21	N=43	N=87
Prior TKI	25% (PPP) 31% (EXCLAIM)	25%	Prior TKI unknown Median prior therapy = 2	Prior 1st/2nd gen=18% Prior osi=20% Prior pozi/mobo=9%	Prior EGFR TKI=25%
Prior IO	43% (PPP) 34% (EXCLAIM)	46%	Unknown	56%	Unknown
Toxicity (Treatment-related) >30%	91-93% Diarrhea 45% Rash 39% Paronychia 32-35% Anorexia 30-34% Nausea 31% Dry skin	66% infusion reaction 86% rash 42% paronychia	76% Diarrhea 67% Fatigue 67% thrombocytopenia 43% anemia 43% leukopenia 43% anorexia 38% mucositis 38% rash	73% Rash	79% Diarrhea 60% Rash 52% Stomatitis 45% Paronychia 38% Nausea 31% Anorexia
Dose Modifications	Dose reduction 25% PPP 22% EXCLAIM Drug discontinue 17% PPP 10% EXCLAIM	Dose reduction 13% Drug discontinue 4%	Dose reduction Unknown Drug discontinue 5%	Dose reduction 11% Drug discontinue 9%	Dose reduction 68% Drug discontinue 10%
ORR	28% (PPP) 25% (EXCLAIM)	40%	24%	31% at all levels 46% at 100 BID	15%
PFS/DOR	DOR 17.5 mo (PPP) mPFS 7.3mo (PPP) OS 24 mo (PPP)	DOR 11.1 mPFS 8.3mo OS 22.8 mo	mPFS 9.6mo	Unknown	PFS 4.2mo DOR 7.4mo
CNS as Site of PD	All: CNS 38%, Not CNS (62%) Baseline brain mets: CND 68%	Not reported	Not reported	Not reported	Not reported
EGFR ex20ins Position	Efficacy across all EGFRex20ins subtypes	Efficacy across all EGFRex20ins subtypes	Not reported	Efficacy across all EGFRex20ins subtypes	Efficacy across all EGFRex20ins subtypes

ALK disease

Yoshioka H, et al.

Abstract number #9022

Final OS analysis from the phase III J-ALEX study of alectinib (ALC) vs. crizotinib (CRZ) in Japanese ALK-inhibitor naïve *ALK*-positive non-small cell lung cancer (*ALK*+ NSCLC)



Primary endpoint: IRF-assessed PFS

Secondary endpoints: OS, ORR, DoR, time to response, CNS PFS, HRQoL, safety and PK

Objective of this analysis: To report the final OS analysis from J-ALEX after a minimum of 5 years of follow up

Median duration of OS follow-up:
68.6 months alectinib vs 68.0 months crizotinib

	ITT population (N=207)[1]	
Baseline demographics	**Alectinib (n=103)**	**Crizotinib (n=104)**
Median age, years (range)	61.0 (27–85)	59.5 (25–84)
Female / Male, %	60.2 / 39.8	60.6 / 39.4
ECOG PS 0 / 1 / 2, %	52.4 / 45.6 / 1.9	46.2 / 51.9 / 1.9
First / second treatment line, %	64.1 / 35.9	64.4 / 35.6
Stage IIIB / Stage IV / recurrent, %	2.9 / 73.8 / 23.3	2.9 / 72.1 / 25.0
Brain metastases by IRF, %	13.6	27.9

Mature PFS data from J-ALEX was previously reported; alectinib demonstrated superiority in IRF-assessed PFS vs crizotinib (HR 0.37, 95% CI 0.26–0.52; median PFS 34.1 vs 10.2 months)[2]

BID, twice daily; CI, confidence interval; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status
HRQoL, health-related quality of life; HR, hazard ratio; IRF, independent review facility; ITT, intent to treat; NSCLC, non-small cell lung cancer
ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; OS, overall survival

1. Hida T, et al. Lancet 2017
2. Nakagawa K, et al. Lung Cancer 2020

ALK disease

Yoshioka H, et al.

Abstract number #9022

Final OS analysis from the phase III J-ALEX study of alectinib (ALC) vs. crizotinib (CRZ) in Japanese ALK-inhibitor naïve *ALK*-positive non-small cell lung cancer (*ALK*+ NSCLC)

Japanese patients aged ≥20 years with ALK inhibitor-naïve stage IIIb/IV/recurrent *ALK*+ NSCLC (one prior chemotherapy regimen allowed)

R 1:1

- Alectinib 300mg BID (n=103)
- Crizotinib 250mg BID (n=104)

Treat until disease progression, unacceptable toxicity, withdrawal or death

Primary endpoint: IRF-assessed PFS

Secondary endpoints: OS, ORR, DoR, time to response, CNS PFS, HRQoL, safety and PK

Objective of this analysis: To report the final OS analysis from J-ALEX after a minimum of 5 years of follow up

Median duration of OS follow-up:
68.6 months alectinib vs 68.0 months crizotinib

	ITT population (N=207)[1]	
Baseline demographics	**Alectinib (n=103)**	**Crizotinib (n=104)**
Median age, years (range)	61.0 (27–85)	59.5 (25–84)
Female / Male, %	60.2 / 39.8	60.6 / 39.4
ECOG PS 0 / 1 / 2, %	52.4 / 45.6 / 1.9	46.2 / 51.9 / 1.9
First / second treatment line, %	64.1 / 35.9	64.4 / 35.6
Stage IIIB / Stage IV / recurrent, %	2.9 / 73.8 / 23.3	2.9 / 72.1 / 25.0
Brain metastases by IRF, %	13.6	27.9

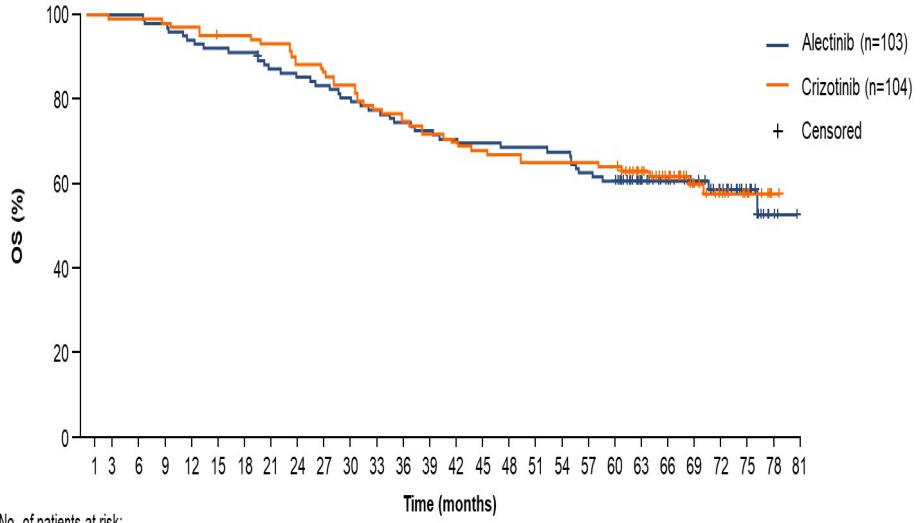
Mature PFS data from J-ALEX was previously reported; alectinib demonstrated superiority in IRF-assessed PFS vs crizotinib (HR 0.37, 95% CI 0.26–0.52; median PFS 34.1 vs 10.2 months)[2]

BID, twice daily; CI, confidence interval; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status HRQoL, health-related quality of life; HR, hazard ratio; IRF, independent review facility; ITT, intent to treat; NSCLC, non-small cell lung cancer ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; OS, overall survival

1. Hida T, et al. Lancet 2017
2. Nakagawa K, et al. Lung Cancer 2020

Final OS

OS in the ITT population



No. of patients at risk:

Crizotinib	104	103	103	102	101	98	98	96	91	88	86	80	77	74	72	70	69	67	67	67	66	54	42	27	20	10	2
Alectinib	103	103	103	101	97	95	94	89	87	85	82	79	76	74	72	71	70	70	69	64	62	48	40	31	23	13	3

- In total, 83 death events occurred, 42 (40.8%) in the alectinib arm and 41 (39.4%) in the crizotinib arm
- Superiority in OS was not demonstrated at the final analysis (HR 1.03, 95.0405% CI 0.67–1.58)
- Median OS was not reached in either treatment arm; alectinib NE (95% CI 70.6–NE) and crizotinib NE (95% CI 68.3–NE)

Median duration of follow up: alectinib 68.6 months (range 6–81); crizotinib 68.0 months (range 2 –79). NE, not estimable

ALK disease

Yoshioka H, et al.

Abstract number #9022

Final OS analysis from the phase III J-ALEX study of alectinib (ALC) vs. crizotinib (CRZ) in Japanese ALK-inhibitor naïve *ALK*-positive non-small cell lung cancer (*ALK*+ NSCLC)

Japanese patients aged ≥20 years with ALK inhibitor-naïve stage IIIb/IV/recurrent *ALK*+ NSCLC (one prior chemotherapy regimen allowed)

R 1:1

- Alectinib 300mg BID (n=103)
- Crizotinib 250mg BID (n=104)

Treat until disease progression, unacceptable toxicity, withdrawal or death

Primary endpoint: IRF-assessed PFS

Secondary endpoints: OS, ORR, DoR, time to response, CNS PFS, HRQoL, safety and PK

Objective of this analysis: To report the final OS analysis from J-ALEX after a minimum of 5 years of follow up

Median duration of OS follow-up:
68.6 months alectinib vs 68.0 months crizotinib

	ITT population (N=207)[1]	
Baseline demographics	**Alectinib (n=103)**	**Crizotinib (n=104)**
Median age, years (range)	61.0 (27–85)	59.5 (25–84)
Female / Male, %	60.2 / 39.8	60.6 / 39.4
ECOG PS 0 / 1 / 2, %	52.4 / 45.6 / 1.9	46.2 / 51.9 / 1.9
First / second treatment line, %	64.1 / 35.9	64.4 / 35.6
Stage IIIB / Stage IV / recurrent, %	2.9 / 73.8 / 23.3	2.9 / 72.1 / 25.0
Brain metastases by IRF, %	13.6	27.9

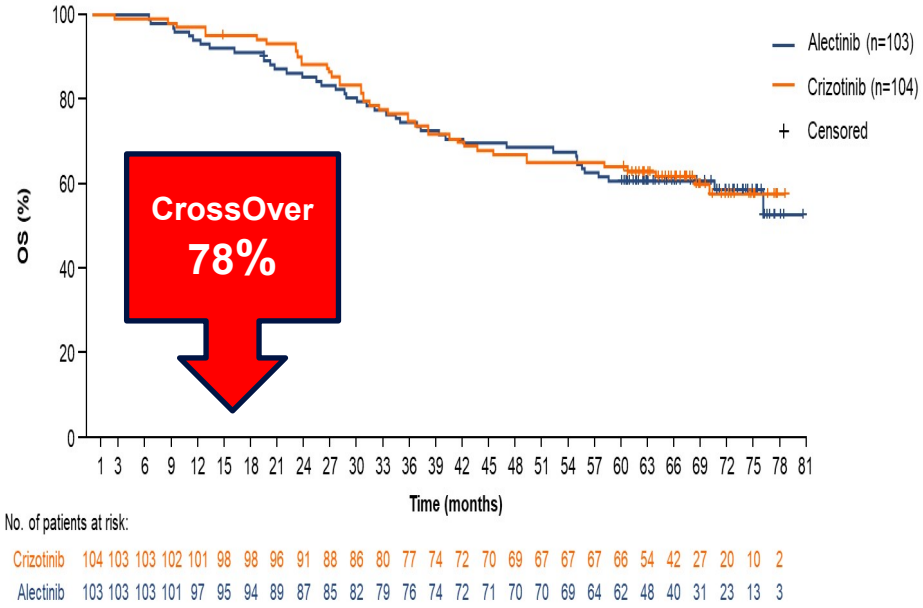
Mature PFS data from J-ALEX was previously reported; alectinib demonstrated superiority in IRF-assessed PFS vs crizotinib (HR 0.37, 95% CI 0.26–0.52; median PFS 34.1 vs 10.2 months)[2]

BID, twice daily; CI, confidence interval; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status HRQoL, health-related quality of life; HR, hazard ratio; IRF, independent review facility; ITT, intent to treat; NSCLC, non-small cell lung cancer ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; OS, overall survival

1. Hida T, et al. Lancet 2017
2. Nakagawa K, et al. Lung Cancer 2020

Final OS

OS in the ITT population



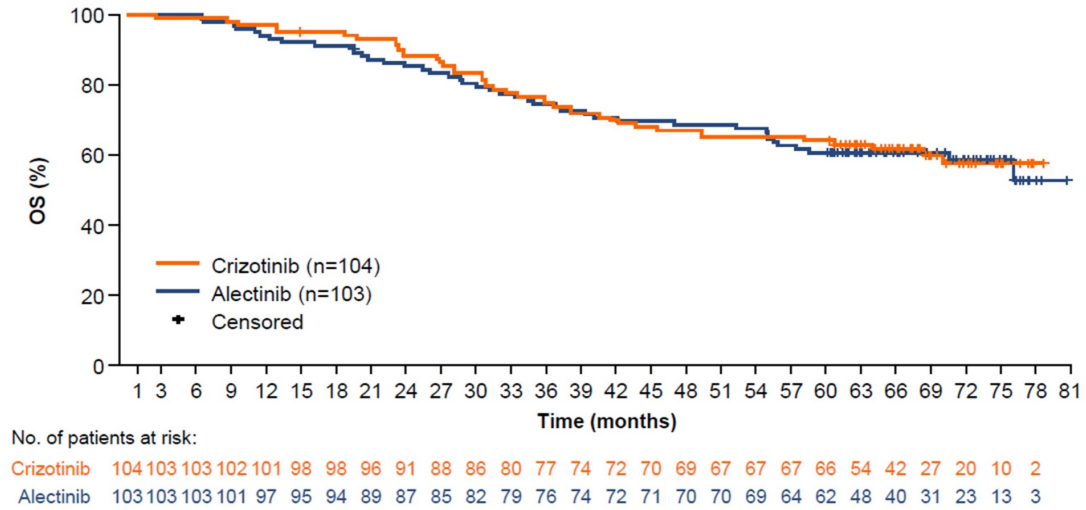
- In total, 83 death events occurred, 42 (40.8%) in the alectinib arm and 41 (39.4%) in the crizotinib arm
- Superiority in OS was not demonstrated at the final analysis (HR 1.03, 95.0405% CI 0.67–1.58)
- Median OS was not reached in either treatment arm; alectinib NE (95% CI 70.6–NE) and crizotinib NE (95% CI 68.3–NE)

Median duration of follow up: alectinib 68.6 months (range 6–81); crizotinib 68.0 months (range 2 –79). NE, not estimable

Final OS Analysis from J-ALEX

J-ALEX

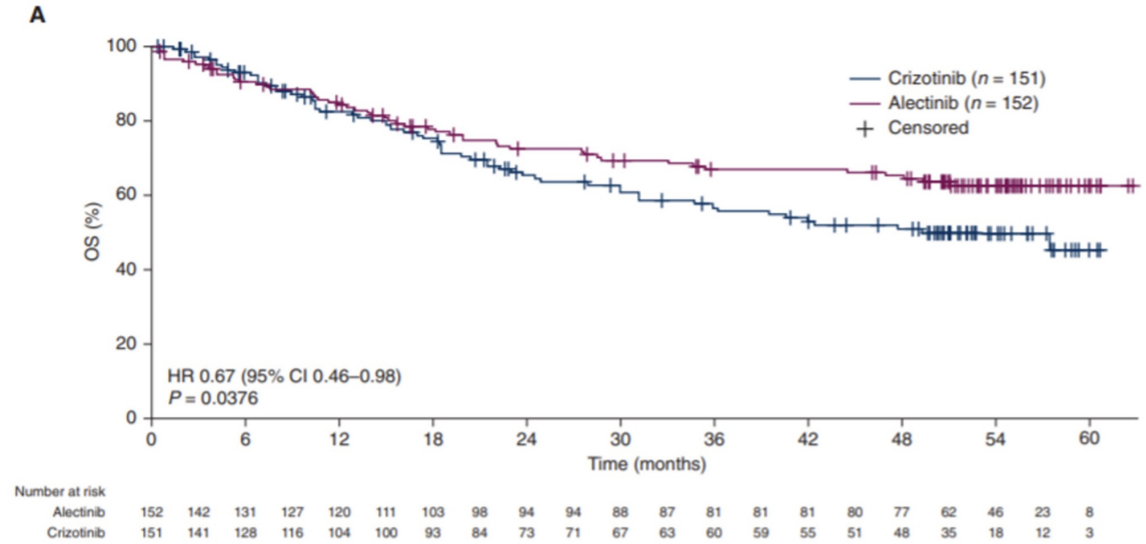
Figure 2. OS in the ITT population



No. of patients at risk:

Crizotinib	104	103	103	102	101	98	98	96	91	88	86	80	77	74	72	70	69	67	67	67	66	54	42	27	20	10	2
Alectinib	103	103	103	101	97	95	94	89	87	85	82	79	76	74	72	71	70	70	69	64	62	48	40	31	23	13	3

ALEX



Number at risk

Alectinib	152	142	131	127	120	111	103	98	94	94	88	87	81	81	81	80	77	62	46	23	8
Crizotinib	151	141	128	116	104	100	93	84	73	71	67	63	60	59	55	51	48	35	18	12	3

5-year OS rate

Alectinib: 60.85% (95% CI 51.38–70.32)
Crizotinib: 64.11% (95% CI 54.85–73.37)

Median follow-up ~68 months for each arm
Median OS not reached in either treatment arm

5-year OS rate

Alectinib: 62.5% (95% CI 54.3–70.8)
Crizotinib: 45.5% (95% CI 33.6–57.4)

Yoshioka H, et al, ASCO 2021 Annual Meeting. Mok T, et al, *Ann Oncol* 2020 Aug;31(8):1056-1064.