Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Targeted Therapy for Non-Small Cell Lung Cancer

Tuesday, January 11, 2022
5:00 PM – 6:00 PM ET

Faculty

John V Heymach, MD, PhD
Zofia Piotrowska, MD, MHS

Moderator

Neil Love, MD

RTP Year in Review 2022

YiR Targeted Therapy for Non-Small Cell Lung Cancer Faculty

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, EMD Serono Inc, Genentech, a member of the Roche Group and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC.

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Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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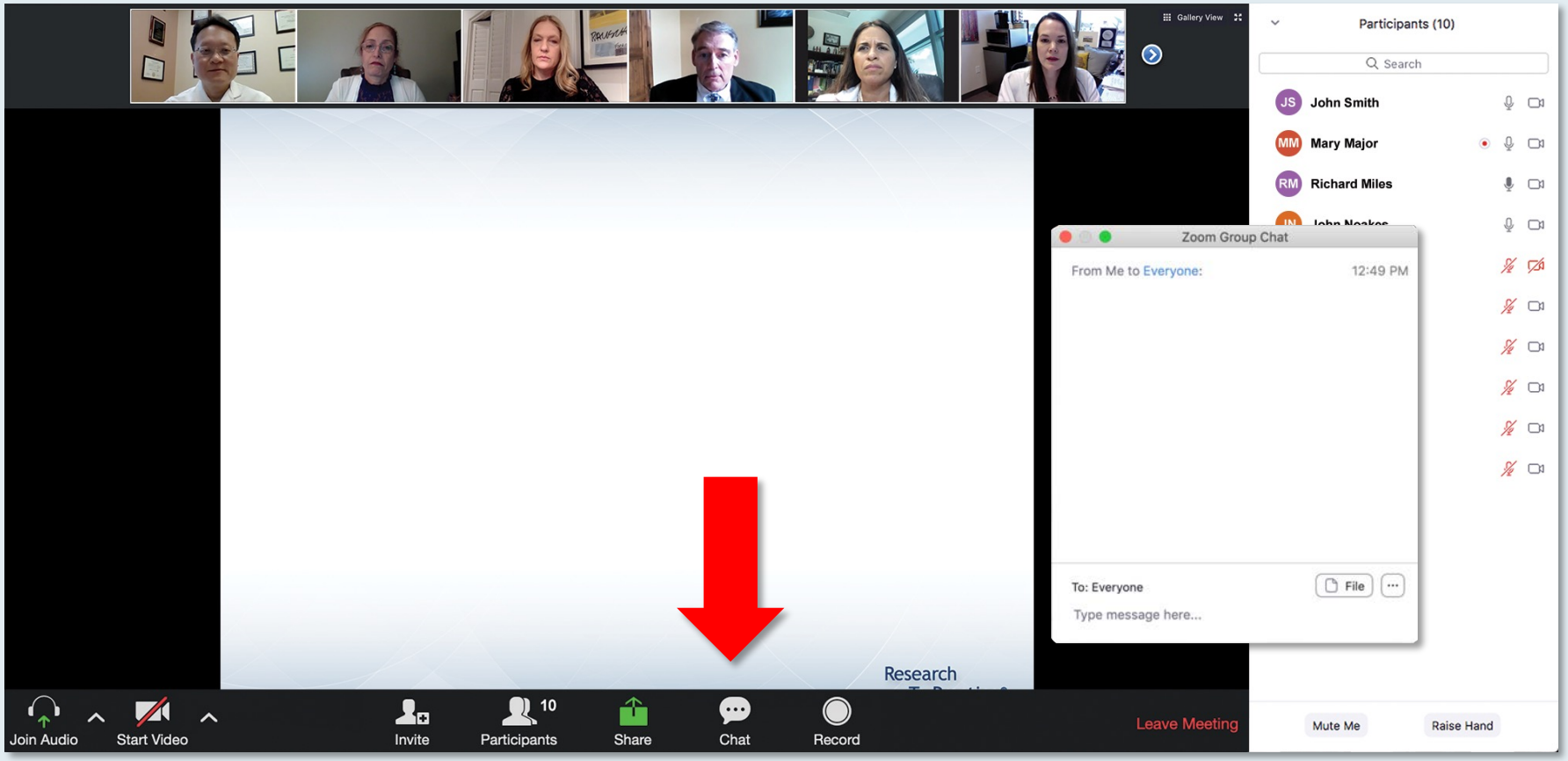
We Encourage Clinicians in Practice to Submit Questions



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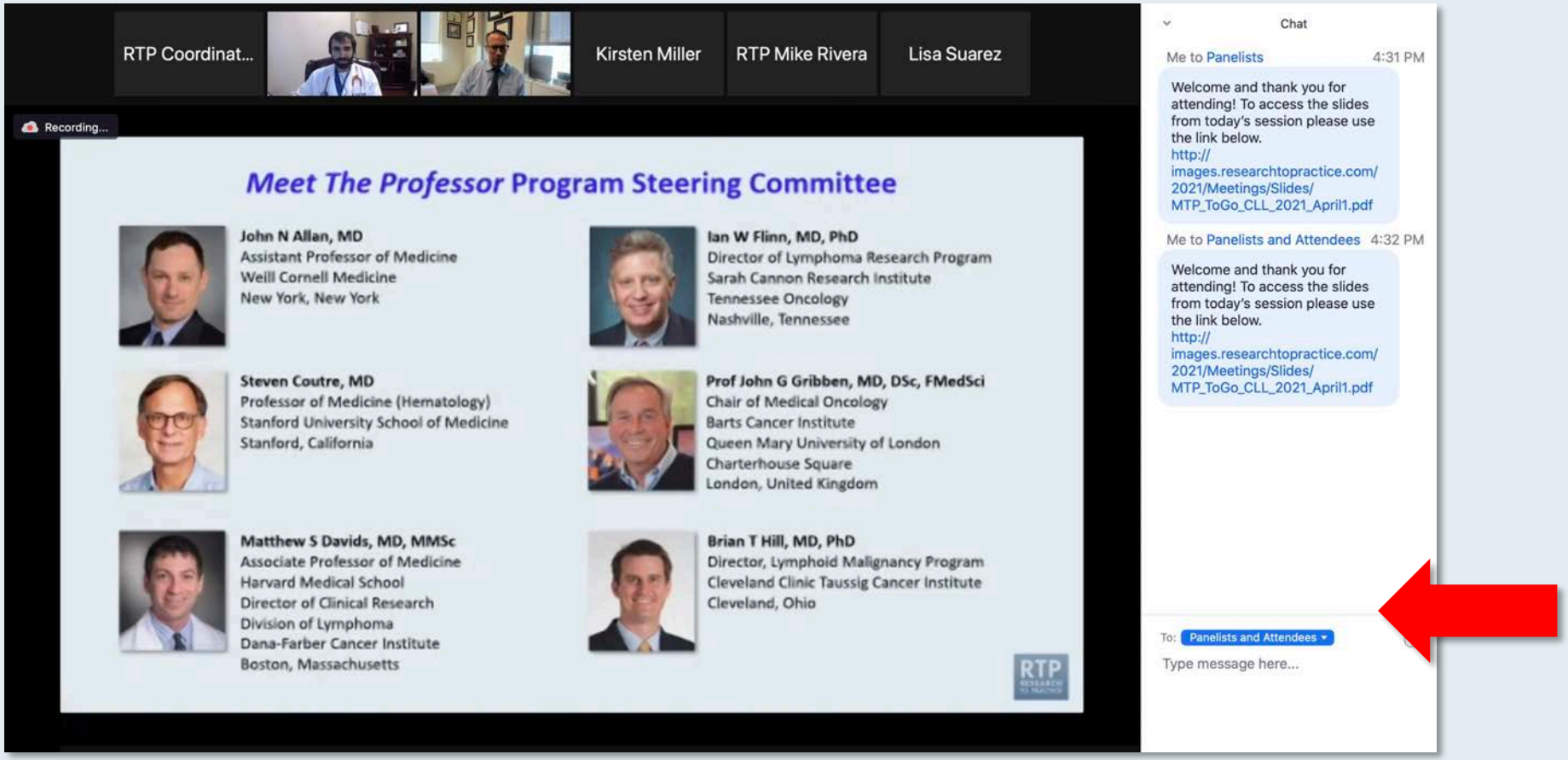

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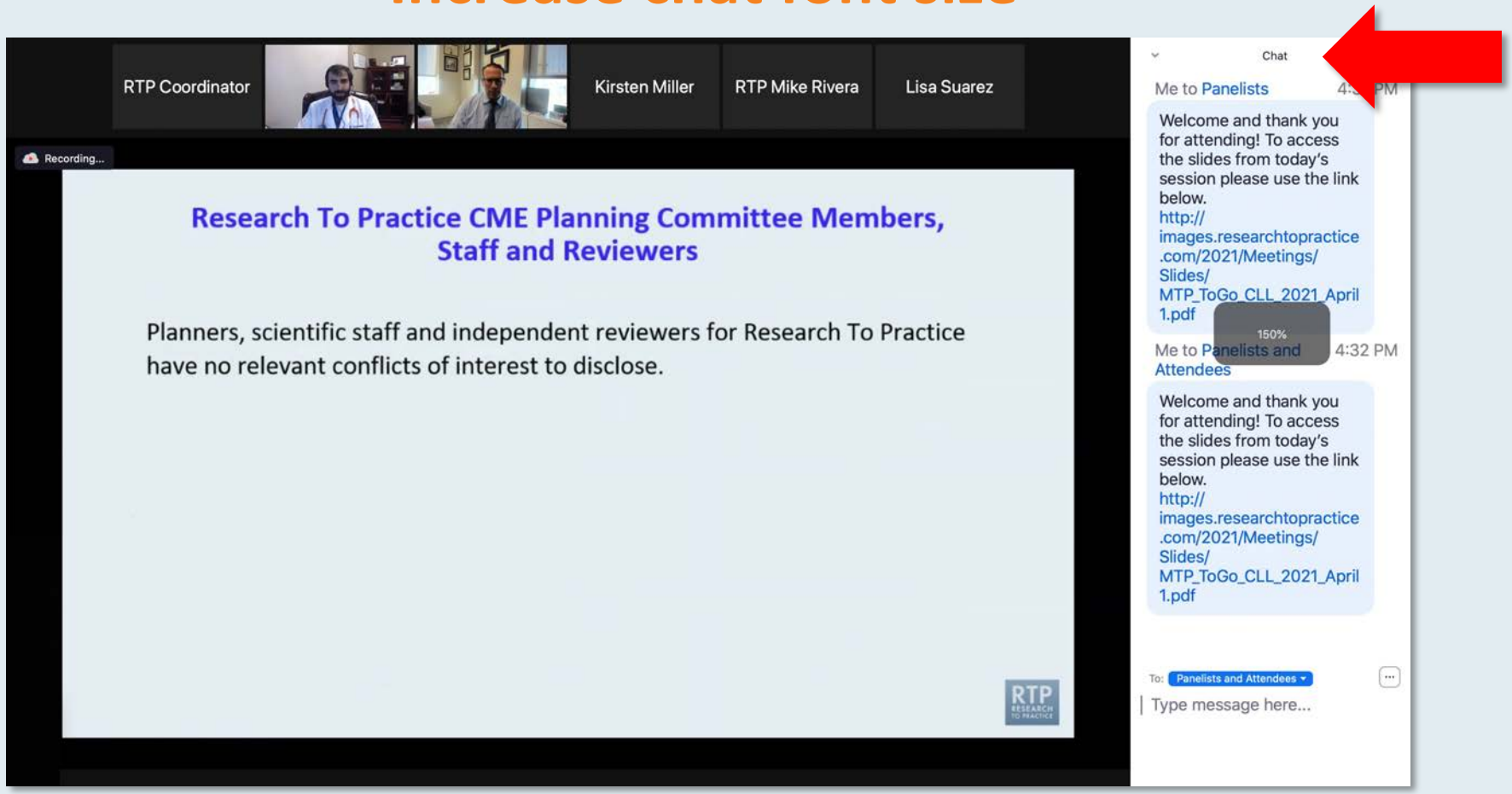

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WITH DR NEIL LOVE

NSCLC with EGFR Exon 20 Insertion Mutations

DR GREGORY RIELY
MEMORIAL SLOAN KETTERING CANCER CENTER

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Wednesday, January 12, 2022
5:30 PM – 6:30 PM ET

Faculty

Tiffany A Traina, MD

Moderator

Neil Love, MD

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Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Immunotherapy and Other Nontargeted Approaches for Lung Cancer

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Corey J Langer, MD

Anne S Tsao, MD, MBA

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Colorectal Cancer (Part 1 of a 3-Part Series)

Wednesday, January 19, 2022
10:15 PM – 11:45 PM ET

Faculty

Cathy Eng, MD
Christopher Lieu, MD
Alan P Venook, MD

Moderator

Kristen K Ciombor, MD, MSCI

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Gastroesophageal Cancers (Part 2 of a 3-Part Series)

Thursday, January 20, 2022
9:15 PM – 10:45 PM ET

Faculty

Yelena Y Janjigian, MD
Eric Van Cutsem, MD, PhD
Harry H Yoon, MD

Moderator

Samuel J Klempner, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hepatobiliary Cancers (Part 3 of a 3-Part Series)

Friday, January 21, 2022
9:15 PM – 10:45 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD
Robin K Kelley, MD

Moderator

Tanios Bekaii-Saab, MD

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Lindsey Roeker, MD

Jeff Sharman, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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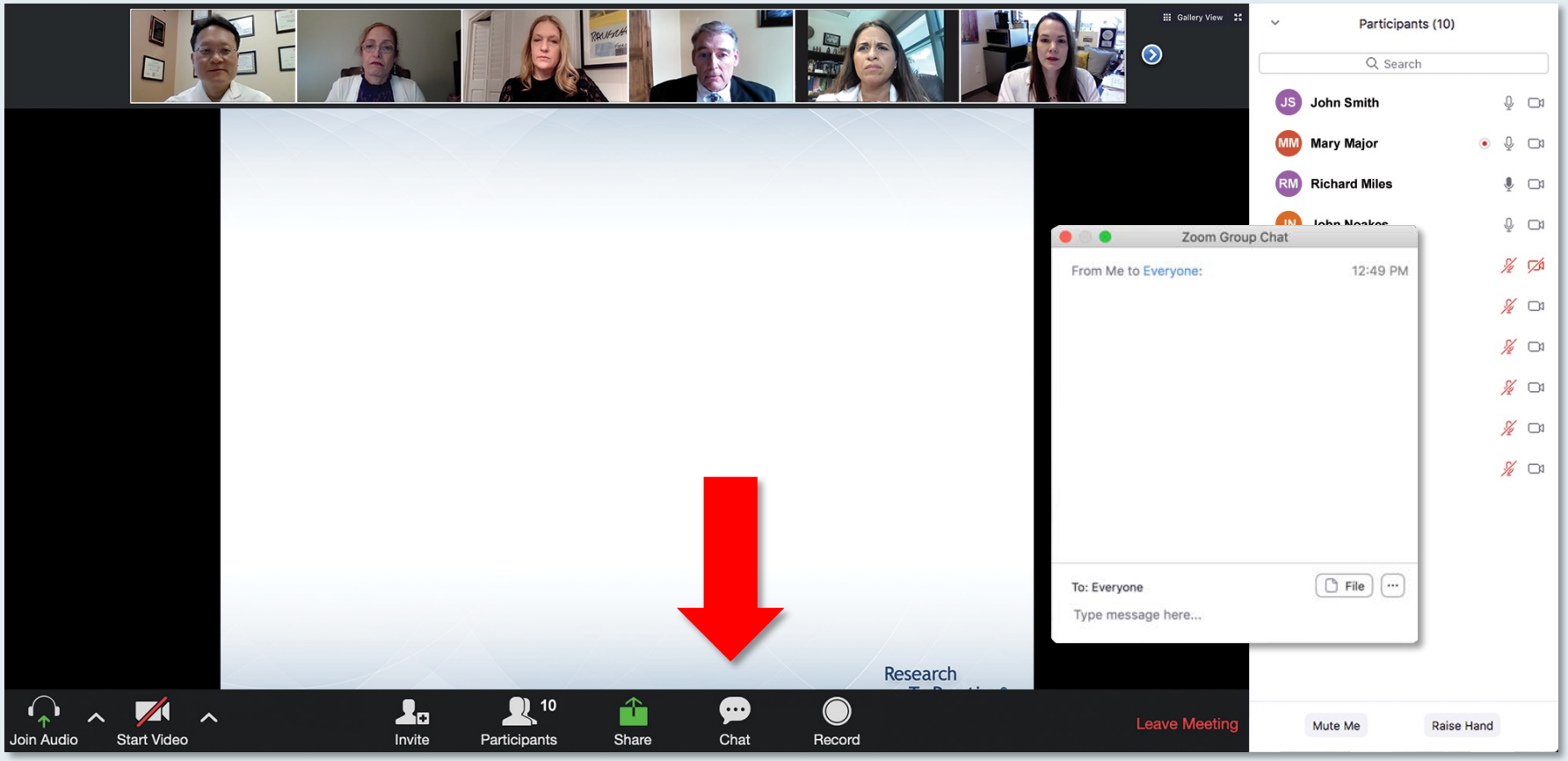

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RTP Year in Review 2022

Targeted Treatment for NSCLC

What did we learn this year?

EGFR (common)
EGFR exon 20
ALK
ROS1
HER2
TROP2
MET exon 14
RET
KRAS
NTRK

- Testing
- Agents
- Sequencing
- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
- New directions

RTP Year in Review 2022

Targeted Treatment for NSCLC

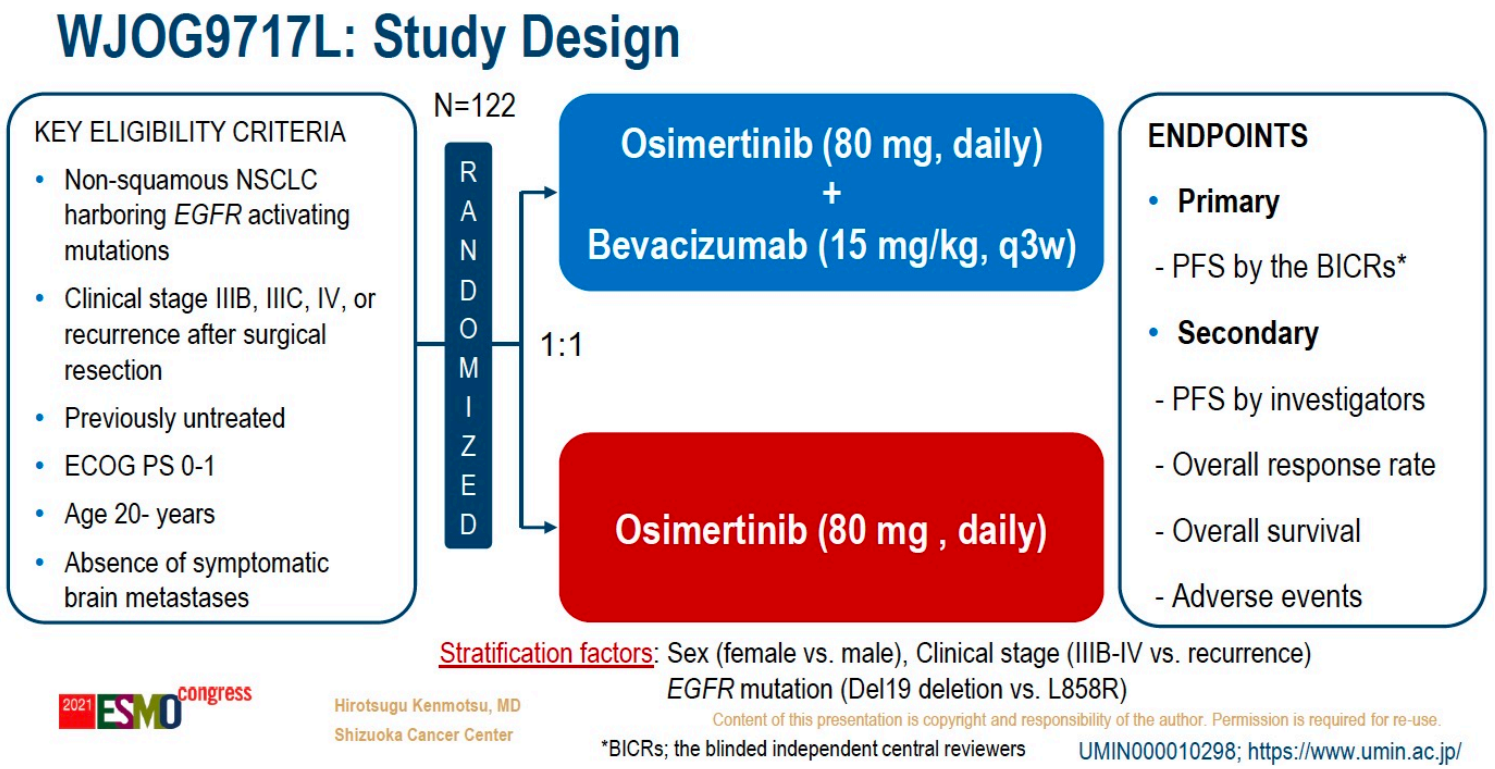
What did we learn this year?

- **EGFR (common)**
- **EGFR exon 20**
- **ALK**
- **ROS1**
- **HER2**
- **TROP2**
- **MET exon 14**
- **RET**
- **KRAS**
- **NTRK**

- **Testing**
- **Agents:** ***Erlotinib, gefitinib, afatinib, osimertinib, patritumab deruxtecan, amivantamab, lazertinib***
- **Sequencing**
- **Tolerability**
- **Resistance**
- **Immunotherapy**
- **Brain metastases**
- **New directions**

EGFR TKI + anti-VEGF Abs

Trial	Ph	n	EGFR TKI	Country	Anti-VEGF	PFS	OS
JO25567[1,2]	Ph 2	154	Erlotinib	Japan	Bevacizumab	16.0 vs 9.7 (HR 0.54)	47.4 vs 47 (HR 0.81)
NEJ026[3]	Ph 3	228	Erlotinib	Japan	Bevacizumab	16.9 vs. 13.3 (HR 0.605)	50.7 vs. 46.2 (HR 1.007)
RELAY[4]	Ph 3	449	Erlotinib	US/Europe/Asia	Ramucirumab	19.4 vs 12.4 (HR 0.591)	Immature



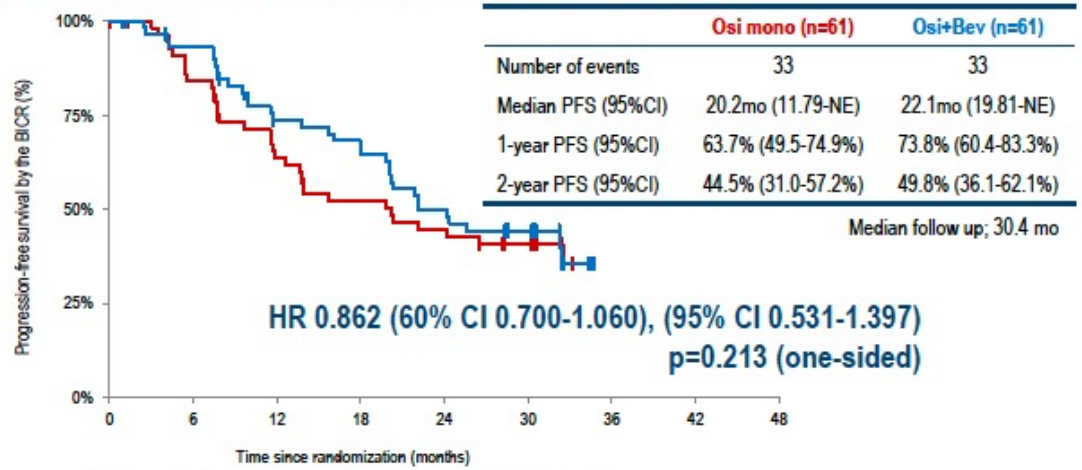
Courtesy of Zofia Piotrowska, MD, MHS

Kenmotsu H et al, ESMO 2021

1. Seto T, Lancet Oncol 2014; ; 2. Yamamoto N, ASCO 2019 Abstract 9007; 3. Saito H et al, Lancet Onc 2019; 4. Nakagawa, Lancet Onc 2019.

WJOG9717L: Osimertinib +/- bevacizumab for untreated EGFR-mutant NSCLC

Primary Endpoint: PFS (ITT), assessed by BICRs



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

2021 ESMO congress

Hirotsugu Kenmotsu, MD
Shizuoka Cancer Center

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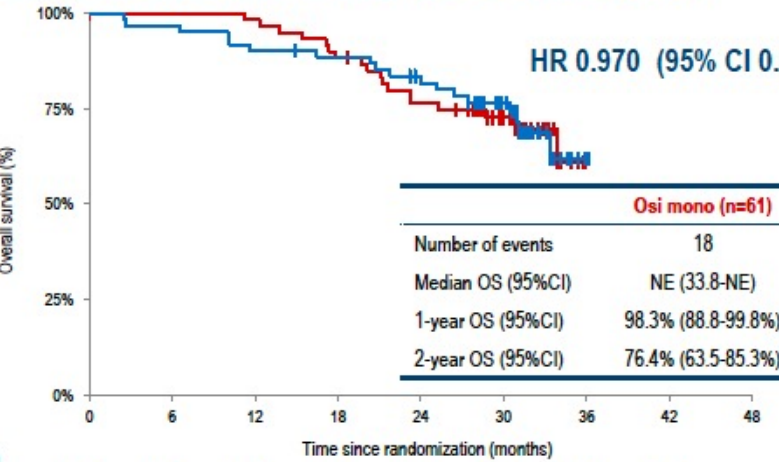
Secondary Endpoint: Overall survival (ITT)



	Osi mono (n=61)	Osi+Bev (n=61)
Number of events	18	18
Median OS (95%CI)	NE (33.8-NE)	NE (33.3-NE)
1-year OS (95%CI)	98.3% (88.8-99.8%)	90.2% (79.4-99.5%)
2-year OS (95%CI)	76.4% (63.5-85.3%)	81.7% (69.5-89.5%)

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Hirotsugu Kenmotsu, MD
Shizuoka Cancer Center

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Kenmotsu H et al, ESMO 2021

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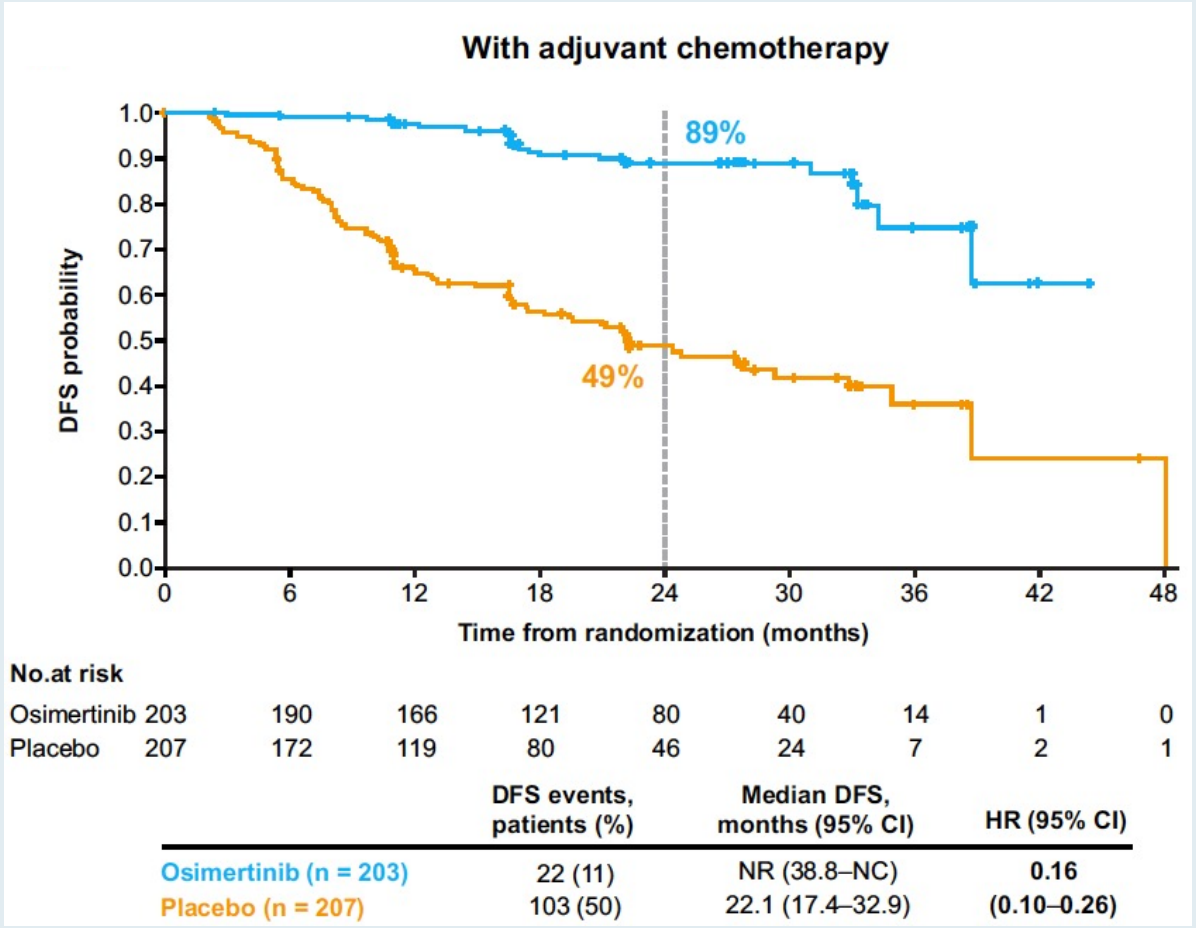
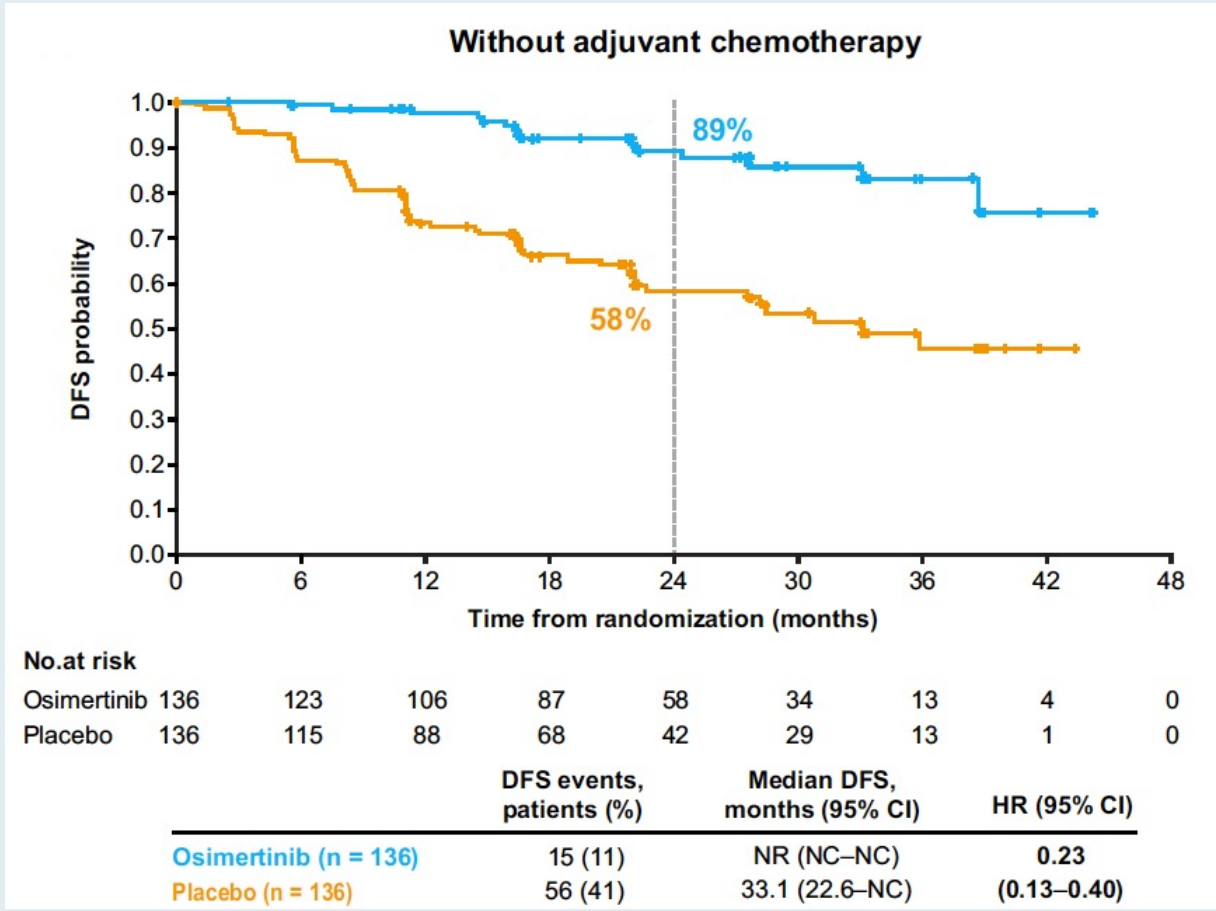
ADAURA: DFS for Patients with and without Adjuvant Chemotherapy



	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n = 203)	22 (11)	NR (38.8–NC)	0.16
Placebo (n = 207)	103 (50)	22.1 (17.4–32.9)	(0.10–0.26)



	DFS events, patients (%)	Median DFS, months (95% CI)	HR (95% CI)
Osimertinib (n = 136)	15 (11)	NR (NC–NC)	0.23
Placebo (n = 136)	56 (41)	33.1 (22.6–NC)	(0.13–0.40)

Wu JT et al. *J Thorac Oncol* 2021;[Online ahead of print].

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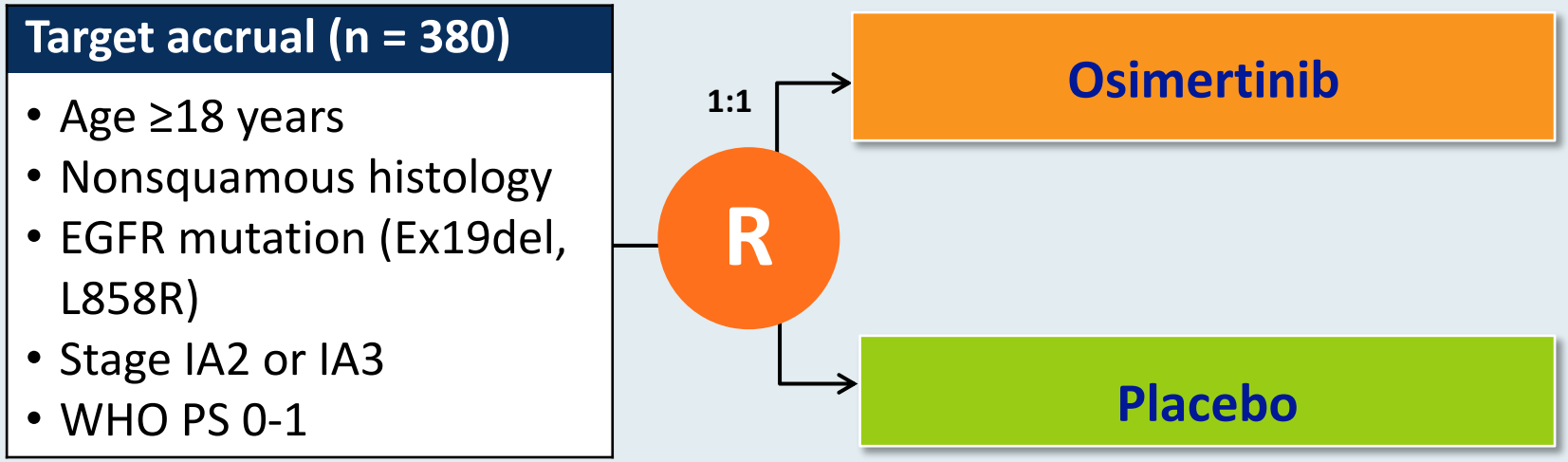
ADAURA-2: Phase III Trial Schema



www.clinicaltrials.gov. Accessed January 2022.

IASLC | 2020 World Conference on Lung Cancer Singapore
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CONQUERING THORACIC CANCERS WORLDWIDE

P03.02

Neoadjuvant osimertinib with/without chemotherapy vs chemotherapy for EGFR mutated resectable NSCLC: NeoADAURA

Masahiro Tsuboi[1], Walter Weder[2], Carles Escriu[3], Collin Blakely[4], Jianxing He[5], Sanja Dacic[6], Yasushi Yatabe[7], Lingmin Zeng[8], Andrew Walding[9], Jamie Chaft[10]

[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Klinik Bethanien, Zürich, Switzerland; [3]The Clatterbridge Cancer Centre, Liverpool, UK; [4]University of California, San Francisco, CA, USA; [5]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [6]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [7]National Cancer Center, Tokyo, Japan; [8]AstraZeneca, Gaithersburg, MD, USA; [9]AstraZeneca, Alderley Park, UK; [10]Memorial Sloan Kettering Cancer Center, New York, USA

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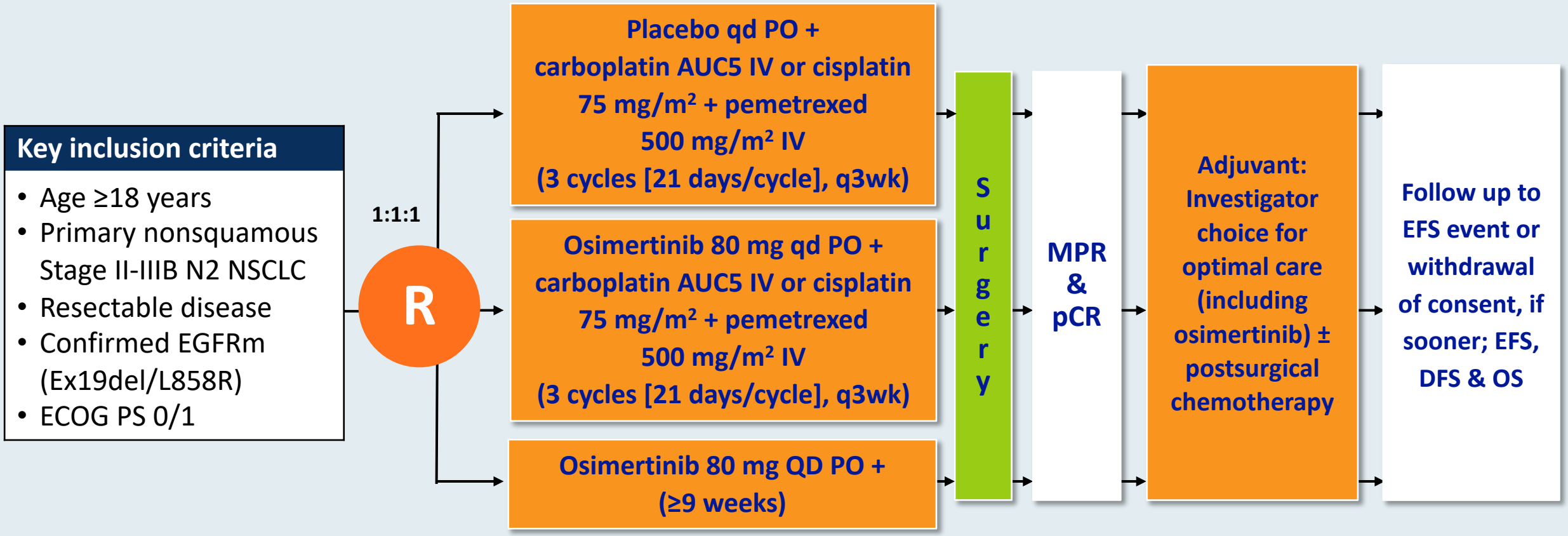
NeoADAURA: Phase III Trial Schema



Tsuboi M et al. IASLC 2020;Abstract P03.02; *Future Oncol* 2021;17(31):4045-55.

NeoADAURA: Key Inclusion and Exclusion Criteria

Key inclusion criteria

- Age ≥18 years*
- Primary non-squamous stage II—IIIB N2 NSCLC†
- Confirmed EGFRm (Ex19del/L858R) via baseline tumor biopsy sample
- Primary NSCLC deemed completely resectable by MDT evaluation including a thoracic surgeon
- ECOG PS 0/1
- Adequate organ and bone marrow function
- Life expectancy of >6 months before randomization

Key exclusion criteria

- Prior treatment with systemic anti-cancer therapy for NSCLC
- Mixed small cell and NSCLC histology
- Pre-operative radiotherapy
- Candidates for segmentectomies or wedge resections only
- T4 tumors infiltrating the aorta, esophagus and/or heart
- Bulky N2 disease
- History of, or current, ILD, drug-induced ILD or radiation pneumonitis
- Severe or uncontrolled systemic diseases / active infections, history of allogeneic organ transplantation, history of primary immunodeficiency, history of another primary malignancy
- Refractory nausea/vomiting, chronic GI disease, significant bowel resection that may prevent absorption of osimertinib
- QTc >470 msec, clinically important abnormalities in resting ECG, factors increasing risk of QT prolongation or arrhythmias

*Written informed consent of patients and their legally acceptable representative required in Japan for patients <20 years old
†By IASLC Cancer Staging Manual v8

Tsuboi M et al. IASLC 2020;Abstract P03.02.

Efficacy and safety of patritumab deruxtecan (HER3-DXd) in TKI-resistant, EGFRm NSCLC

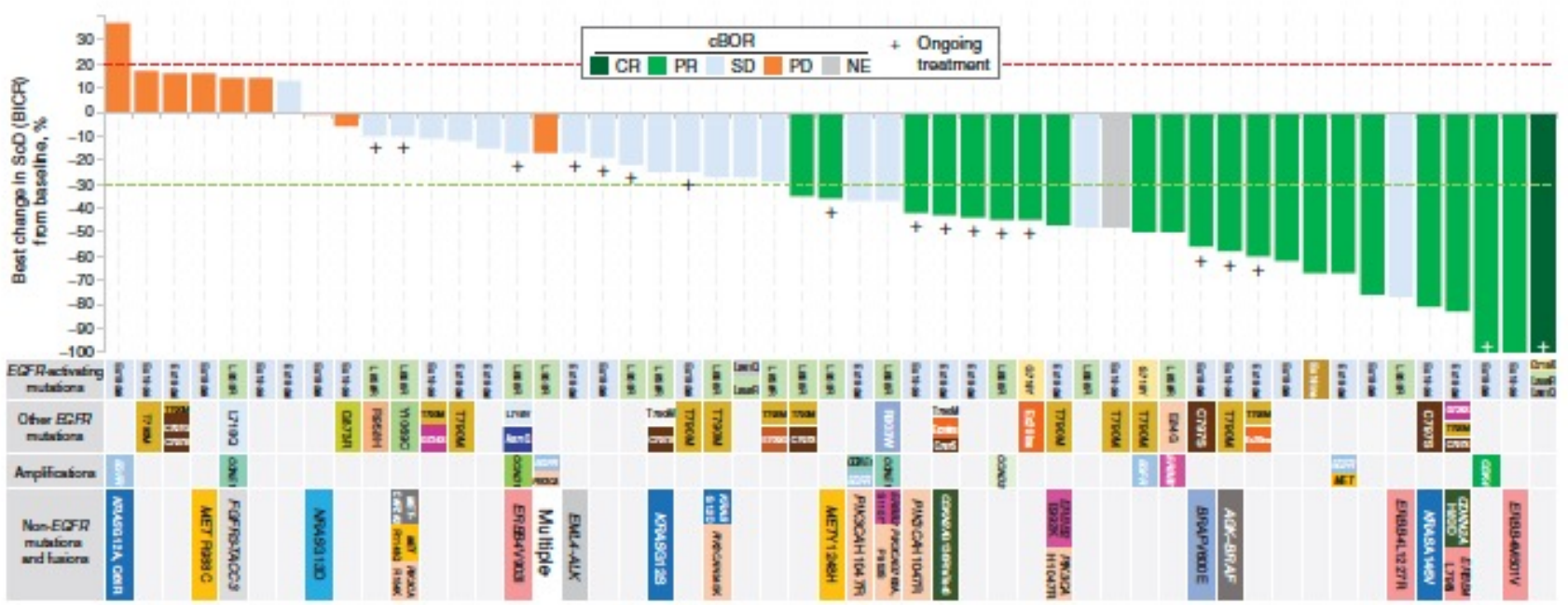


Table 3. Responses by BICR per RECIST 1.1

Characteristics	Pooled RDE (5.6 mg/kg) All pooled (*n* = 57)	Pooled RDE (5.6 mg/kg) Prior PBC and osimertinib (*n* = 44)
Confirmed ORR, % (*n*) [95% CI]	39 (22) [26.0–52.4]	39 (17) [24.4–54.5]
BOR, *n* (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD	19 (33)	13 (30)
PD	9 (16)	8 (18)
NE	7 (12)	6 (14)
DCR,[a] % (*n*) [95% CI]	72 (41) [58.5–83.0]	68 (30) [52.4–81.4]
TTR, median (range), months	2.6 (1.2–5.4)	2.7 (1.2–5.4)
Duration of response, median (95% CI), months	6.9 (3.1–NE)	7.0 (3.1–NE)
Progression-free survival, median (95% CI), months	8.2 (4.4–8.3)	8.2 (4.0–NE)
Overall survival, median (95% CI), months	NE (9.4–NE)	NE (8.2–NE)

Abbreviation: PBC, platinum-based chemotherapy.
[a]DCR = rate of confirmed BOR of CR, PR, or SD.

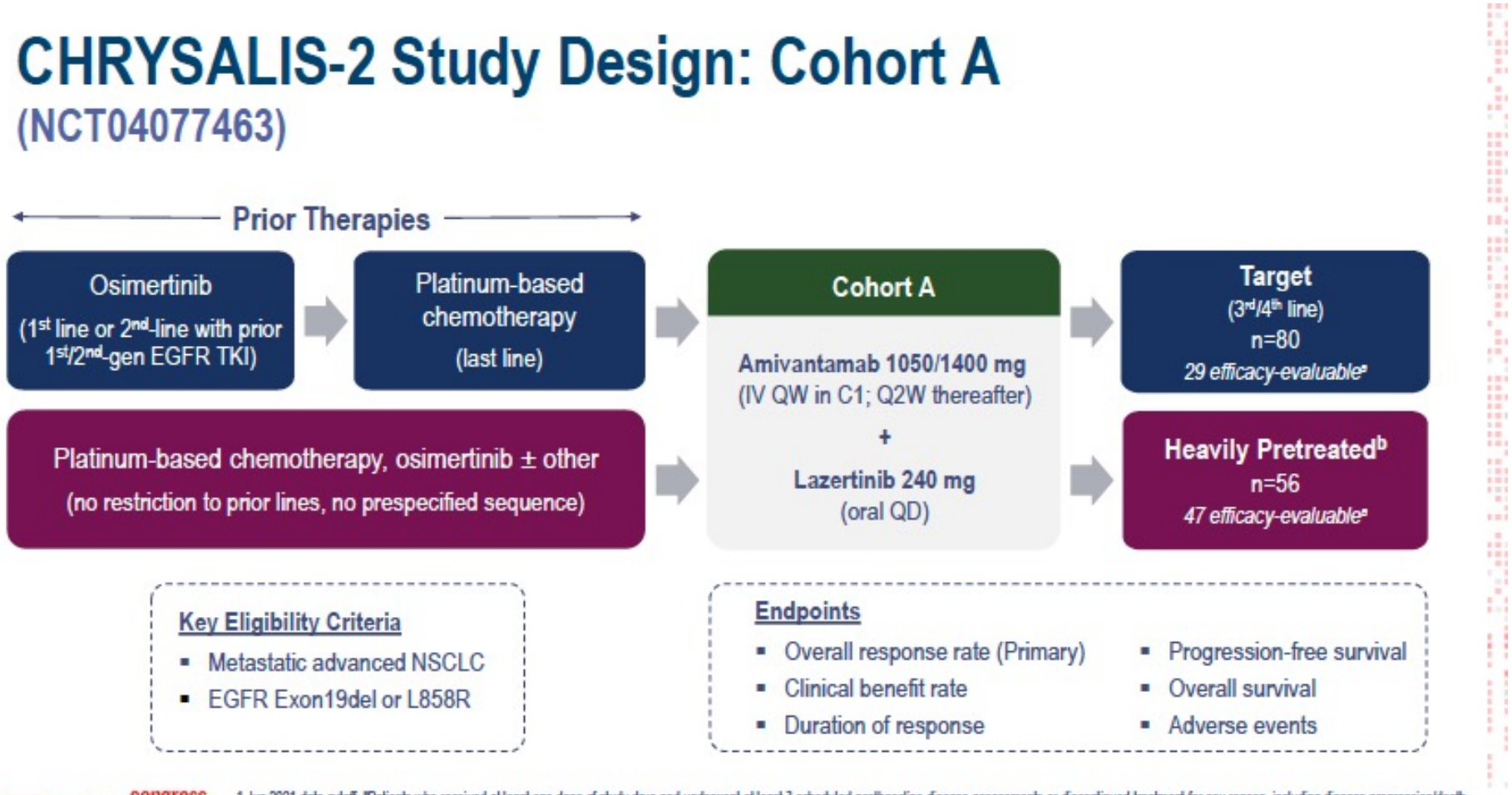
Toxicities:

- Most common grade ≥ 3 toxicities were primarily hematologic (thrombocytopenia, neutropenia, anemia, febrile neutropenia), fatigue, dyspnea.
- ILD in 5% (none grade 4/5.)
- Treatment discontinuation 9%; dose reduction 22%.

Janne P, Cancer Discovery 2021
Janne P, ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

CHRYSALIS 2: Amivantamab + Lazertinib in post-osimertinib, post-platinum EGFRm NSCLC



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1 Jun 2021 data cutoff. [a]Patients who received at least one dose of study drug and underwent at least 3 scheduled postbaseline disease assessments or discontinued treatment for any reason, including disease progression/death, prior to the clinical cutoff. [b]Early eligibility allowed for heavily-pretreated patients who were enrolled prior to protocol amendment, which specified the target population.
C, cycle; EGFR, epidermal growth factor receptor; gen, generation; Exon19del, exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; QD, daily; QW, weekly; Q2W, every 2 weeks

Shu et al. #1193MO

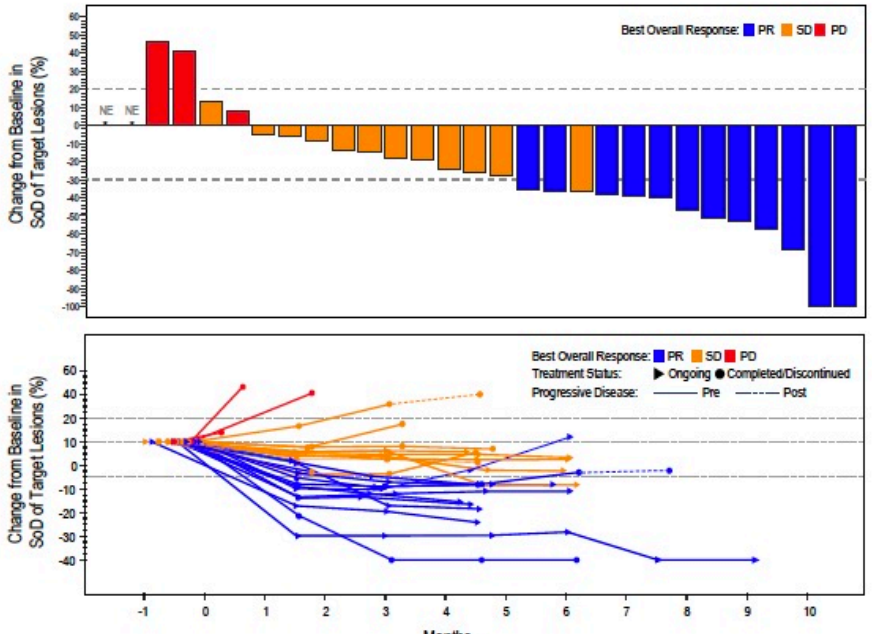
Shu C et al, ESMO 2021

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Courtesy of Zofia Piotrowska, MD, MHS

CHRYSALIS 2: Amivantamab + Lazertinib in post-osimertinib, post-platinum EGFRm NSCLC

Target Population: Antitumor Activity of Amivantamab + Lazertinib



Among 29 efficacy-evaluable[a] patients at a median follow-up of 4.6 mo (range, 0.4–9.6):

- ORR = 41% (95% CI, 24–61)
- CBR = 69% (95% CI, 49–85)
- Median time on treatment = 4.2 mo (range, 0.03–8.4)
- Responses observed early
  - mTTR = 1.4 mo (range, 1.4–4.4)
- 8/12 patients who responded are progression-free and remain on treatment
- 5/12 patients with stable disease remain on treatment (longest at 6.9+ mo)

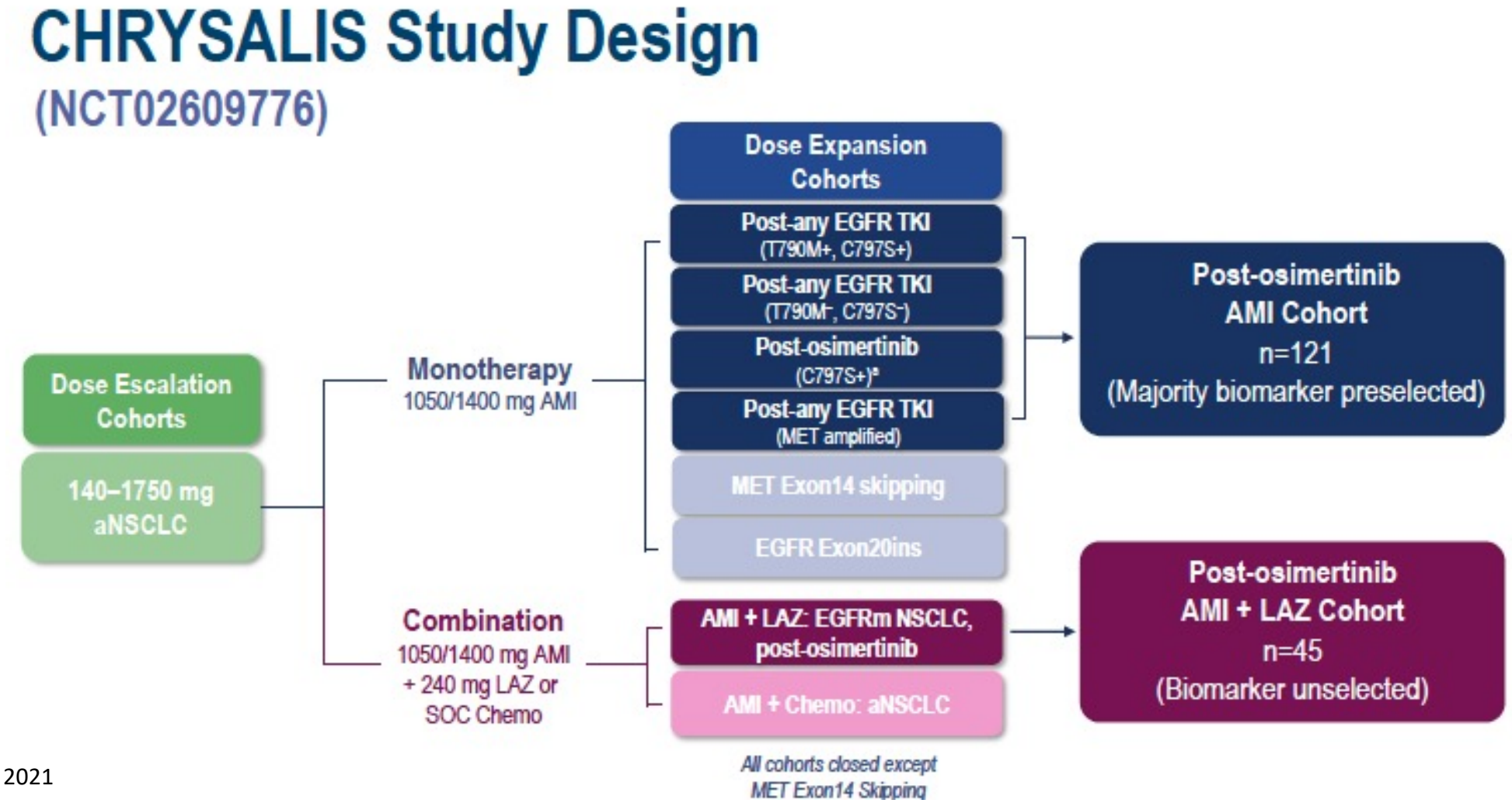
(Target Population: 3rd/4th line only)

- Among 47 "heavily pre-treated" pts (70% ≥ 4 prior lines of rx), activity was more modest with ORR 21%
- Safety:
  - Most common AEs (any grade) include IRR (67%), stomatitis (37%), acneiform dermatitis (35%), paronychia (35%), rash (34%), hypoalbuminemia (29%).
  - Pneumonitis/ILD in 3%

Shu C et al, ESMO 2021

Courtesy of Zofia Piotrowska, MD, MHS

CHRYSALIS: Amivantamab and Amivantamab + Lazertinib in Post-Osimertinib EGFRm NSCLC



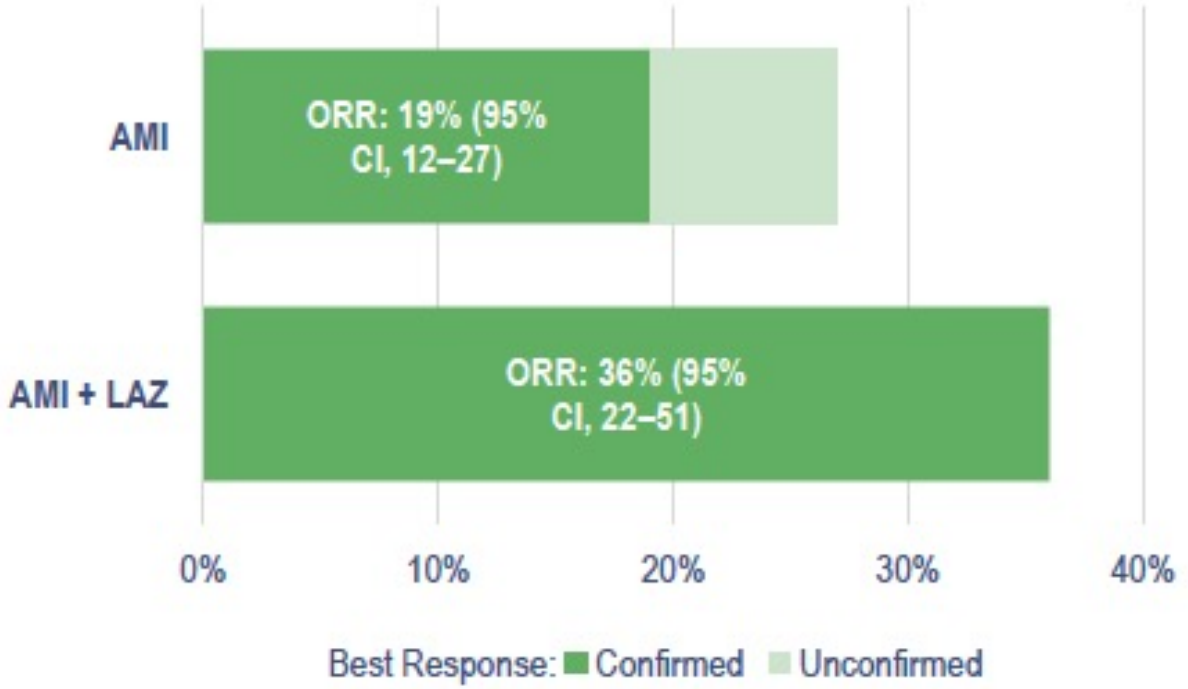
Leighl N et al, ESMO 2021

Courtesy of Zofia Piotrowska, MD, MHS

CHRYSALIS: Amivantamab and Amivantamab + Lazertinib in Post-Osimertinib EGFRm NSCLC

Efficacy: AMI Monotherapy and AMI + LAZ

(descriptive cross-cohort analysis)



	AMI (n=121)	AMI + LAZ (n=45)
Best response[a]	27%	36%
Confirmed ORR* (95% CI)	19% (12–27)	36% (22–51)
CR	0	1 (2%)
PR	23 (19%)	15 (33%)
SD	53 (44%)	14 (31%)
PD	39 (32%)	11 (24%)
NE	6 (5%)	4 (9%)
mDOR (95% CI)	5.9 mo (4.2–12.6)	9.6 mo (5.3–NR)
CBR (95% CI)	48% (39–57)	64% (49–78)
mPFS (95% CI)	4.2 mo (3.2–5.3)	4.9 mo (3.7–9.5)
mF/U (range)	6.9 mo (0.7–38.6)	11.1 mo (1.0–15.0)

*ORR among patients with identified EGFR/MET-based osimertinib resistance was 18% for AMI and 47% for AMI + LAZ[1]

CNS progression was observed among 17% of AMI pts (13% new CNS lesions), and 7% of AMI + LAZ pts (3% new CNS lesions.)

Courtesy of Zofia Piotrowska, MD, MHS

Leighl N et al, ESMO 2021

Targeted Treatment for NSCLC

What did we learn this year?

- EGFR (common)
- **EGFR exon 20**
- ALK
- ROS1
- HER2
- TROP2
- MET exon 14
- RET
- KRAS
- NTRK

- Testing
- Agents:
  Amivantamab,
  mobocertinib
- Sequencing
- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
- New directions

RTP Year in Review 2022

Article

Structure-based classification predicts drug response in *EGFR*-mutant NSCLC

https://doi.org/10.1038/s41586-021-03898-1

Received: 13 April 2021

Accepted: 11 August 2021

Published online: 15 September 2021

Open access

Check for updates

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MD Anderson Cancer Center
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Robichaux et al, Nature 2021

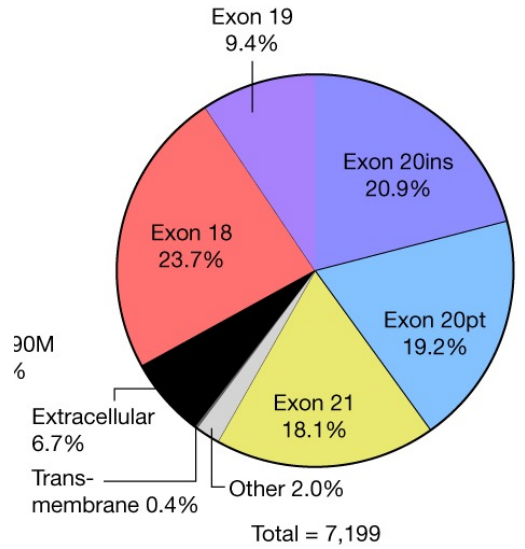
Courtesy of John V Heymach, MD, PhD

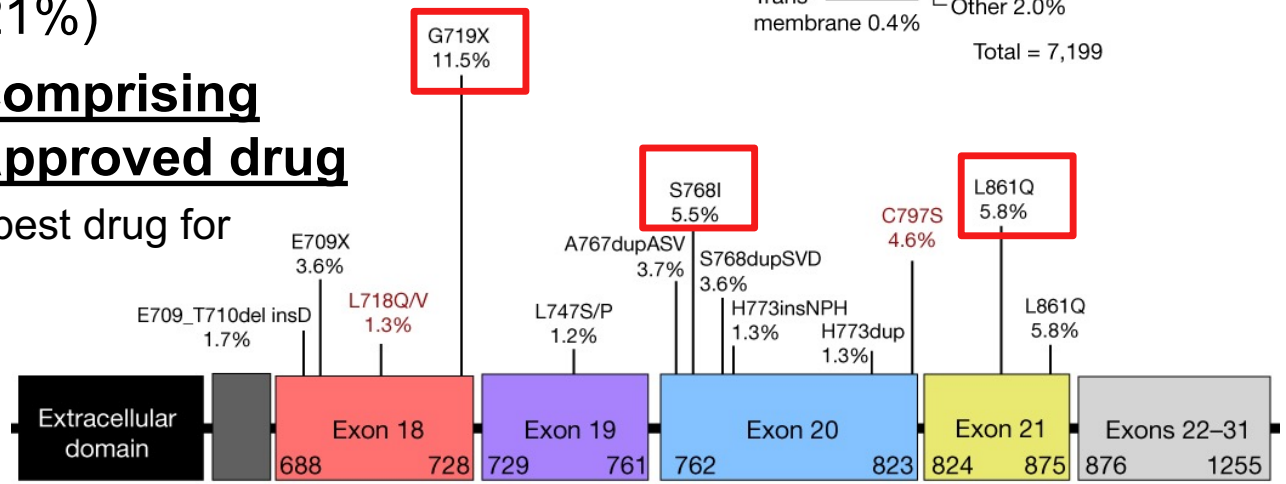
Landscape of atypical EGFR mutant NSCLC

- >70 different recurrent mutations in exons 18-21
- ~40 % exon 20, half of which are insertions
- ~24% are exon 18

- Drugs approved for atypicals:
  - Afatinib: G719X, S768I, L861Q (23%)
  - Amivantamab, mobocertinib: ex20 ins (21%)
  - **<u>>50 commonly recurrent mutations, comprising more than half of atypicals, have no approved drug</u>**
    - In absence of data, clinicians will typically try best drug for classical mutations: 3rd gen osimertinib

Atypical EGFR mutant NSCLC





Courtesy of John V Heymach, MD, PhD

Robichaux et al 2021 Nature

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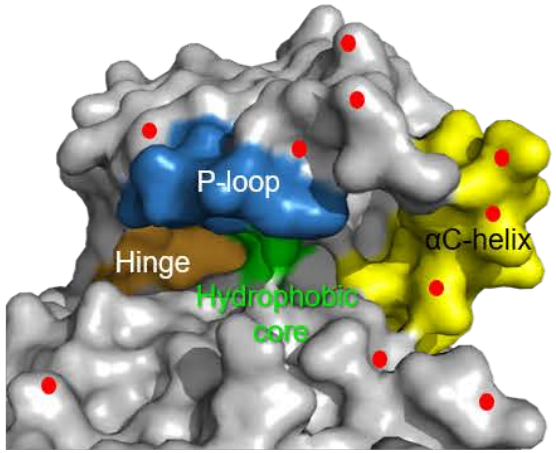
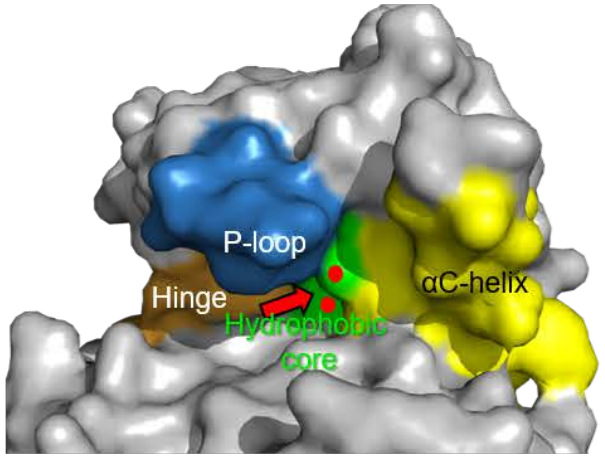
Classical-like



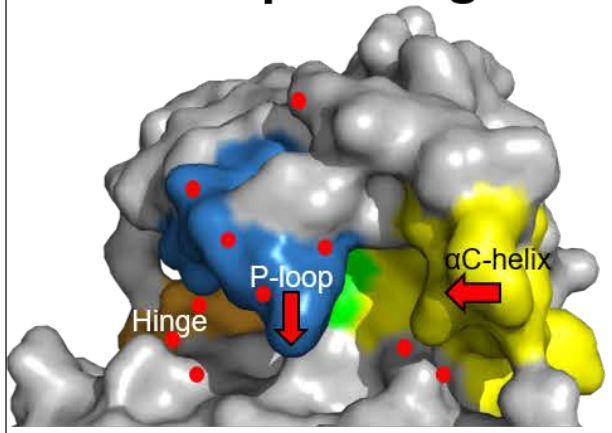
- Distal to drug binding pocket
- Modest to no impact on drug binding

T790M-like



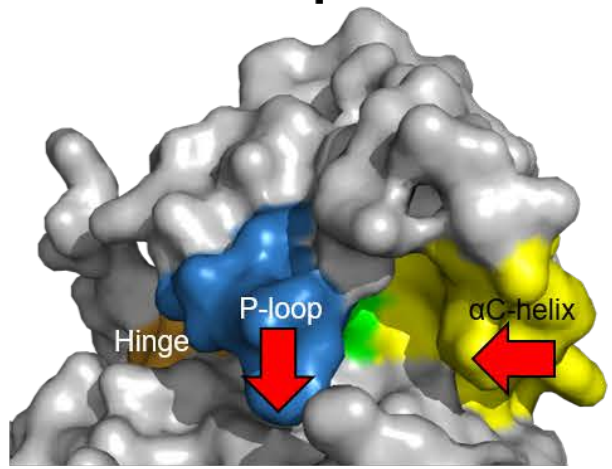
- At least one mutation in hydrophobic core
- Increased affinity for ATP compared to classical-like mutations
- Two subgroups:
  - T790M-like-3S
  - T790M-like-3R

P-loop αC-helix compressing



- Proximal to drug binding pocket
- Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix

Exon 20 loop insertions



- C-terminal loop of αC-helix
- Indirect and substantial impact on drug binding (both P-loop and αC-helix)
- Two subgroups:
  - Ex20ins-near loop (light red)
  - Ex20ins- far loop (dark red)

Representative Mutations

L858R	K754E
Exon 19 deletions	T725M
S720P	L833F/V
L861Q/R	A763insFQEA
S811F	A763insLQEA

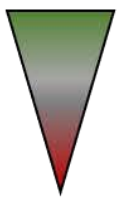
T790M-3S	T790M-3R
Classical/T790M	Ex19del/T790M/L792H
G719X/T790M	L858R/T790M/L718X
L747_K745delinsATSPE	Classical/T790M/C797S
S768I/T790M	

Primary	Acquired
G719X	C797S
S768I	L792H
L747P/S	G724S
E709_T710del insD	L718X
V769L	T854I

Ex20ins-NL	Ex20ins-FL
S768dupSVD	H773insNPH
A767dupASV	H773dupH
D770insNPG	V774insAV
D770del insGY	V774insPR

Drug Sensitivity/Selectivity

Sensitive & Selective



Resistant

Third-generation
Second-generation
First-generation
Exon20ins-specific

T790M-3S	T790M-3R
Third-generation	PKCi
PKCi	ALKi
ALKi	Third-generation
Second-generation	Second-generation
First-generation	First-generation

Second-generation
First-generation
Ex20ins-specific
Third-generation

Ex20ins-NL	Ex20ins-FL
Ex20ins-specific	
Second-generation	Ex20ins-specific
	Second-generation
Third-generation	Third-generation
First-generation	First-generation

Courtesy of John V Heymach, MD, PhD

Structure-based classification of EGFR mutations in NSCLC

Clinical Implications:

- Largest catalogue of common and uncommon EGFR mutations to date, with structure-based classification of these mutations and their specific therapeutic vulnerabilities.
- While clinical data for many of the rare mutations are lacking, this paper is a useful resource when rare EGFR mutations are identified on NGS testing.

Future Directions:

- Further clinical data will be needed to determine optimal treatment strategies for rare EGFR mutations.

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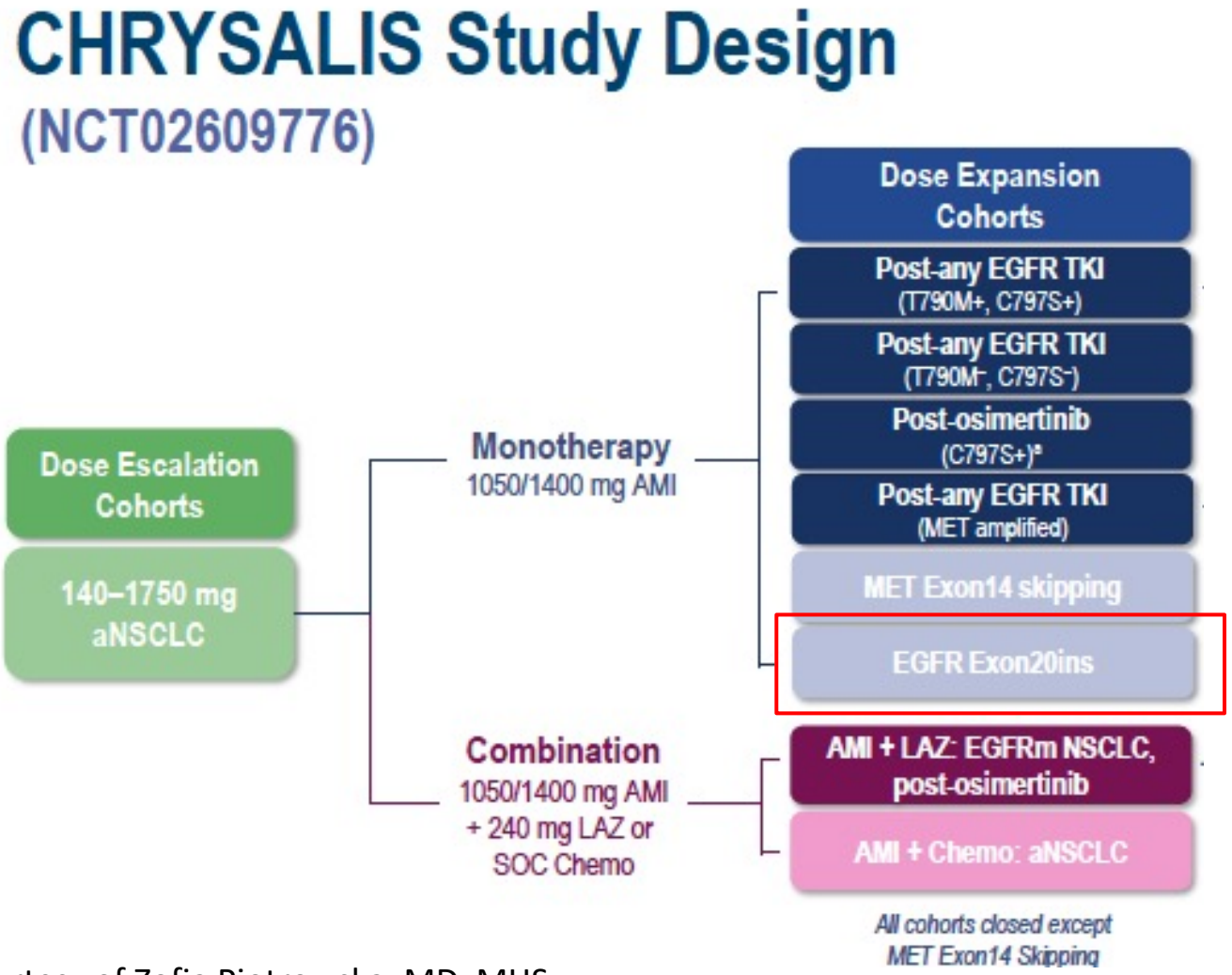
Courtesy of Zofia Piotrowska, MD, MHS

CHRYSALIS: Amivantamab for EGFR Exon 20 Insertions

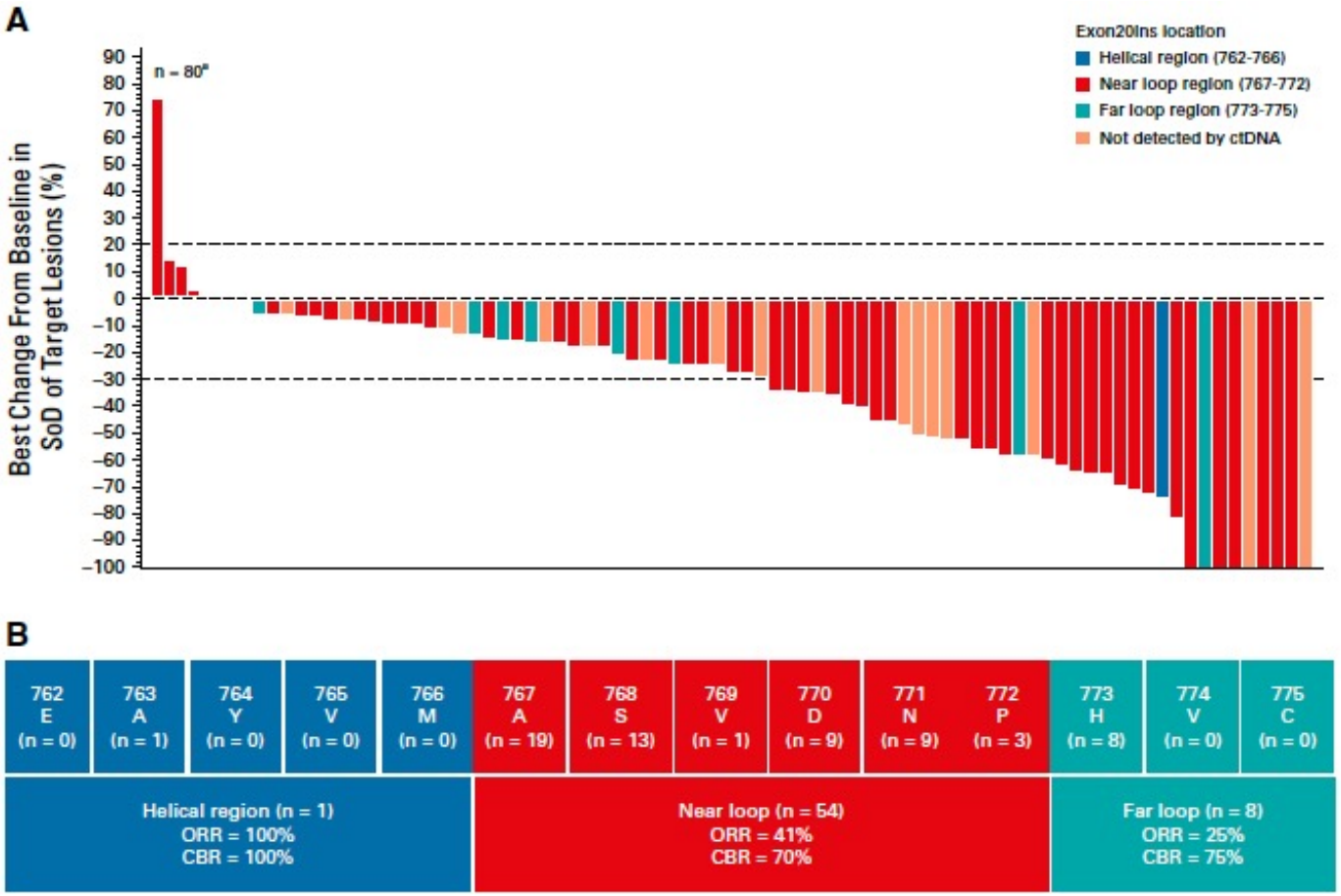


Characteristic	Efficacy Population n=81
Median age, years (range)	62 (42–84)
History of brain metastases	18 (22)
Median number of prior lines (range)	2 (1–7)
Prior systemic therapy	81 (100)
Platinum-based doublet chemotherapy	81 (100)
Immuno-oncology therapy	37 (46)
EGFR TKI	20 (25)
1st-genTKI	7 (9)
2nd-gen TKI	6 (7)
3rd-genTKI	6 (7)
Poziotinib	1 (1)

Courtesy of Zofia Piotrowska, MD, MHS

Adapted from Park K, JCO 2021

CHRYSALIS: Amivantamab for EGFR Exon 20 Insertions



	Post-Platinum EGFR Ins20 N=81
ORR (IRC)	40% (95% CI, 29-51)
mDOR (IRC)	11.1 mos (95% CI, 6.9-NR)
mPFS (IRC)	8.3 mos (95% CI, 5.5-10.6)

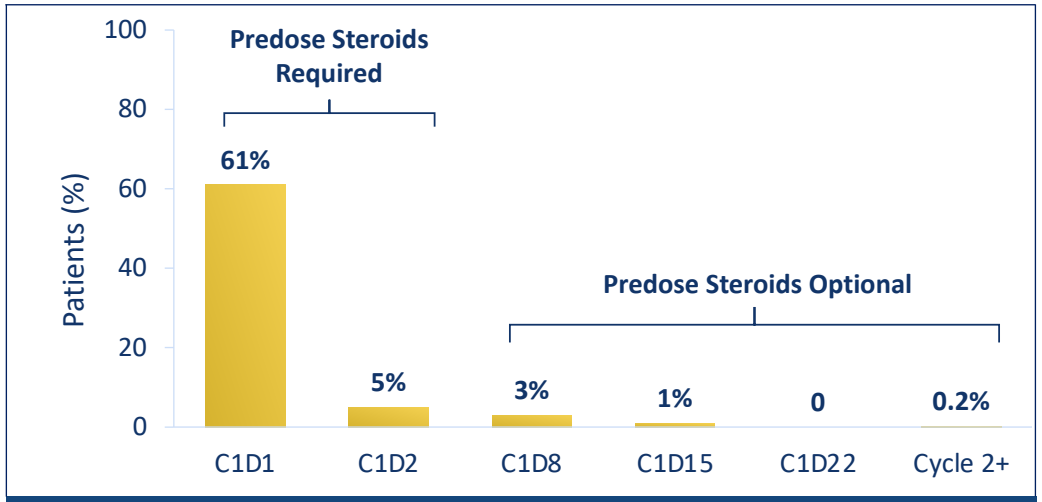
Park K et al. *J Clin Oncol.* 2021.

Courtesy of Zofia Piotrowska, MD, MHS

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

CHRYSALIS: Amivantamab for EGFR Exon 20 Insertions

AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[a]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
MET-related				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral edema	21 (18)	0	11 (10)	0
Other				
Infusion related reaction	75 (66)	3 (3)	75 (66)	3 (3)
Constipation	27 (24)	0	7 (6)	0
Nausea	22 (19)	0	13 (11)	0
Dyspnea	22 (19)	2 (2)	6 (5)	0
Fatigue	21 (18)	2 (2)	14 (12)	1 (1)
Increased ALT	17 (15)	1 (1)	14 (12)	1 (1)



	C1D1	C1D2	C1D8	C1D15	C1D22	Cycle 2+
# Infusions	142	117	133	122	115	1024
# Pts with IRR	87[a]	6	4	1	0	2

- IRR Severity: 98% Gr 1-2; 2% Gr 3
- Chills, SOB, nausea, flushing
- Primarily limited to first infusion
- Improves with split dosing (C1D1, C1D2)

Park K et al. *J Clin Oncol.* 2021;39:3391-3402.
Sabari J et al. WCLC 2020. Abstract OA04.04
Haura EB et al. ASCO 2019. Abstract 9009.

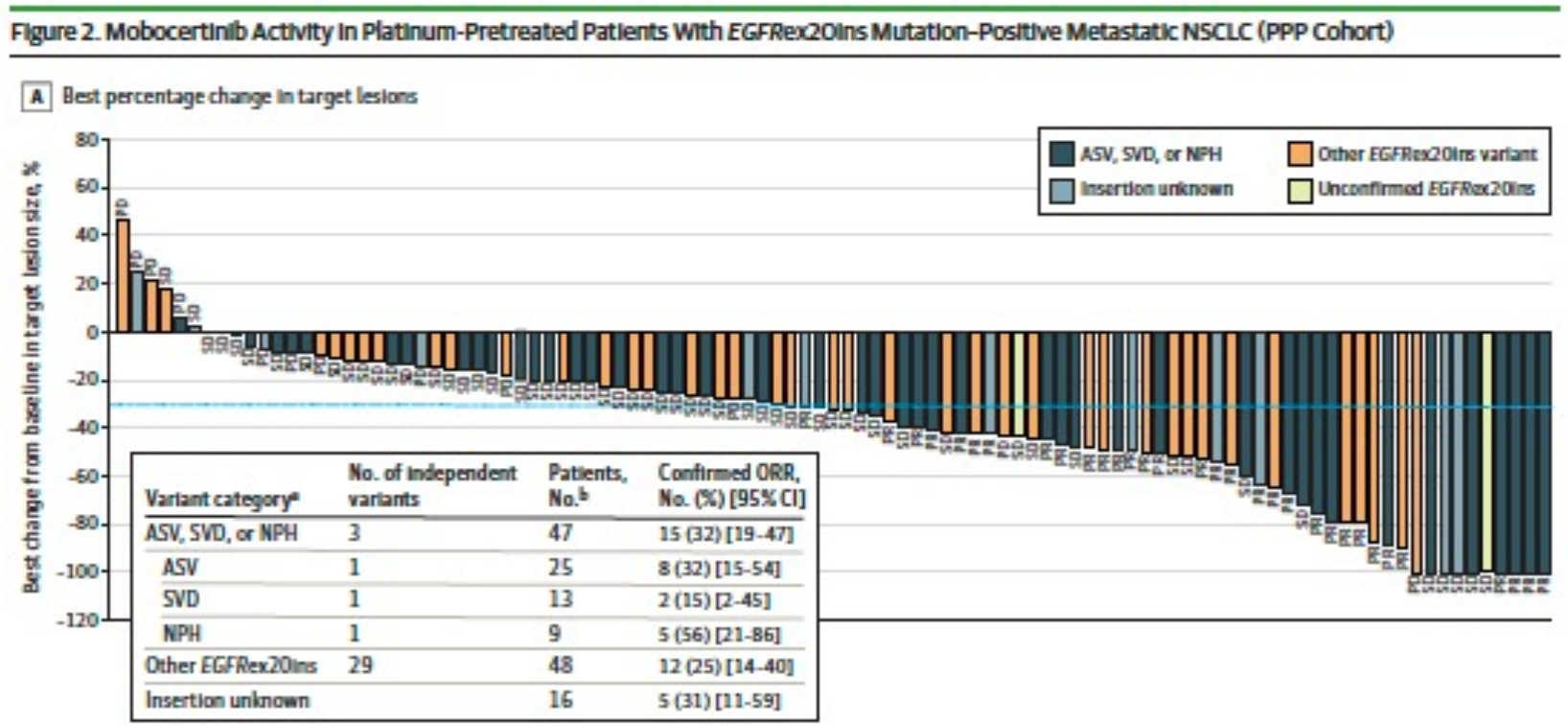
Courtesy of Zofia Piotrowska, MD, MHS

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Mobocertinib in Platinum-Pretreated EGFR Exon 20 Insertion-Positive NSCLC

Mobocertinib- Oral *EGFR* TKI (160mg daily)

	EGFR exon 20 Ph 1/2 Prior Platinum* N=114
Confirmed ORR (IRC)	32 (28%)
Confirmed ORR (Investigator)	40 (35%)
mDOR (IRC)	17.5 mo (8.3-NE)
mPFS (IRC)	7.3 mos (5.5-10.2)



- > 50% responses ongoing at time of data cutoff.
- Responses were more common among pts without baseline brain mets (23/74, 31%), than those with baseline BMs (7/40, 18%)

Zhou C et al. *JAMA Oncol.* 2021;[Epub]:E1-E10.

Courtesy of Zofia Piotrowska, MD, MHS

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Mobocertinib in Platinum-Pretreated EGFR Exon 20 Insertion-Positive NSCLC

	Any Grade n=114	Grade ≥ 3
Diarrhea	**104 (91%)**	**24 (21%)**
Rash	51 (45%)	0
Paronychia	43 (38%)	1 (<1%)
Anorexia	40 (35%)	1 (<1%)
Nausea	39 (34%)	5 (4%)
Dry Skin	35 (31%)	0
Vomiting	34 (30%)	3 (3%)
Creatinine Increase	29 (25%)	2 (2%)
Stomatitis	27 (24%)	5 (4%)

Dose reduction: 29 (25%); Discontinuation: 19 (17%)

Special Considerations:

- QTc prolongation (11% any grade, 3% Gr 3+)
- Cardiomyopathy (2.7%)
- Pneumonitis (4.3%)

Zhou C et al. *JAMA Oncol.* 2021;[Epub]:E1-E10
Mobocertinib package insert.

Courtesy of Zofia Piotrowska, MD, MHS

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Targeted Treatment for NSCLC

What did we learn this year?

- EGFR (common)
- EGFR exon 20
- **ALK**
- ROS1
- HER2
- TROP2
- MET exon 14
- RET
- KRAS
- NTRK

- Testing
- Agents: Alectinib, brigatinib, lorlatinib
- Sequencing
- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
- New directions

Background: ALK + ROS1 alterations in NSCLC

- ALK-positive NSCLC:
  - In the US, crizotinib, ceritinib, alectinib, brigatinib and lorlatinib are all approved for front-line use in ALK-positive NSCLC.
  - Randomized, phase 3 trials of second-generation (alectinib, brigatinib) and recently, third-generation (lorlatinib) ALK inhibitors have all shown superiority to crizotinib in the front-line setting.

- ROS1-positive NSCLC:
  - Crizotinib received FDA approval for ROS1+ NSCLC based on ORR 72% and mPFS 19.2 months in the single arm PROFILE 1001 trial.
  - Recently, entrectinib also received FDA approval based on pooled results of the phase I/II ALKA, STARTRK-1, and STARTRK-2 trials (updated this year)

Shaw. NEJM. 2014;371:1963. Shaw. Ann Oncol. 2019;30:1121.

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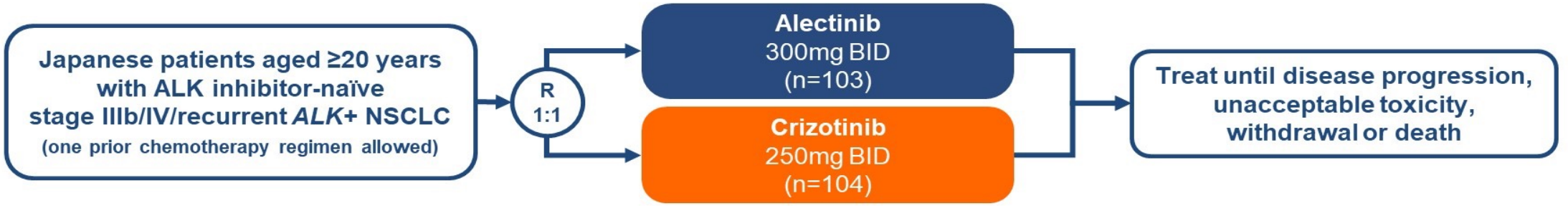
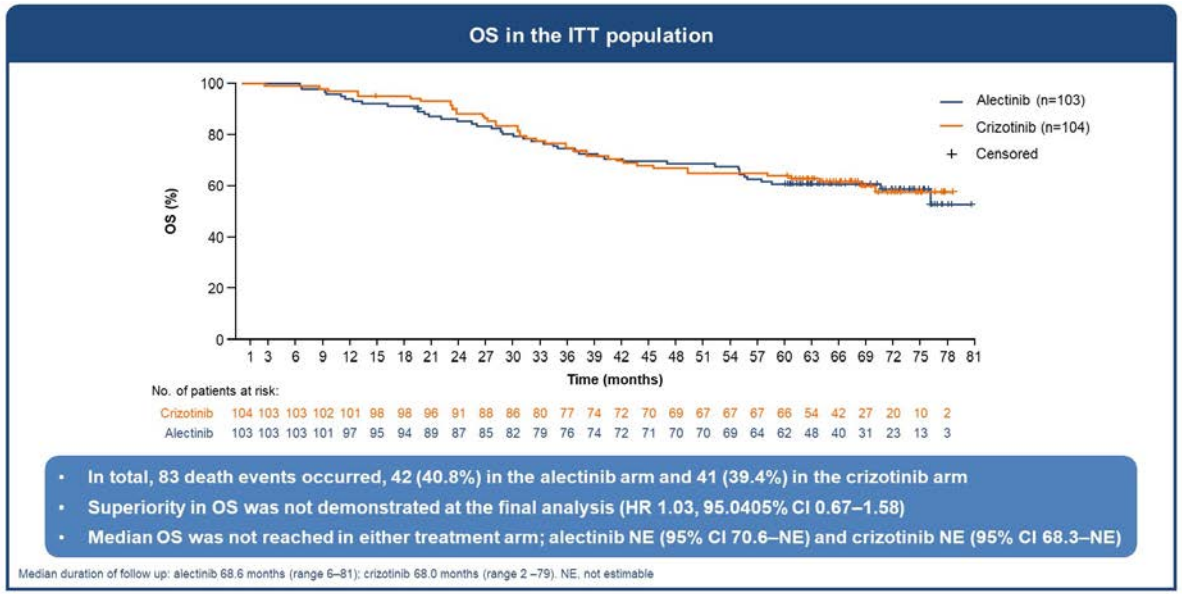
Courtesy of Zofia Piotrowska, MD, MHS

Final OS analysis from the Phase III J-ALEX study of alectinib versus crizotinib





First subsequent anticancer therapies after alectinib or crizotinib

n (%)	Alectinib (n=103)	Crizotinib (n=104)
Patients with at least one treatment	48 (46.6)	95 (91.3)
ALK inhibitors	26 (25.2)	86 (82.7)
Alectinib	0	82 (78.8)
Crizotinib	11 (10.7)	0
Brigatinib	6 (5.8)	1 (1.0)
Lorlatinib	4 (3.9)	3 (2.9)
Ceritinib	5 (4.9)	0
Chemotherapy	18 (17.5)	7 (6.7)
Pemetrexed	13 (12.6)	5 (4.8)
VEGF inhibitor	4 (3.9)	1 (1.0)
Cancer immunotherapy	2 (1.9)	0
RANKL inhibitor[a]	2 (1.9)	2 (1.9)

Yoshioka H, ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

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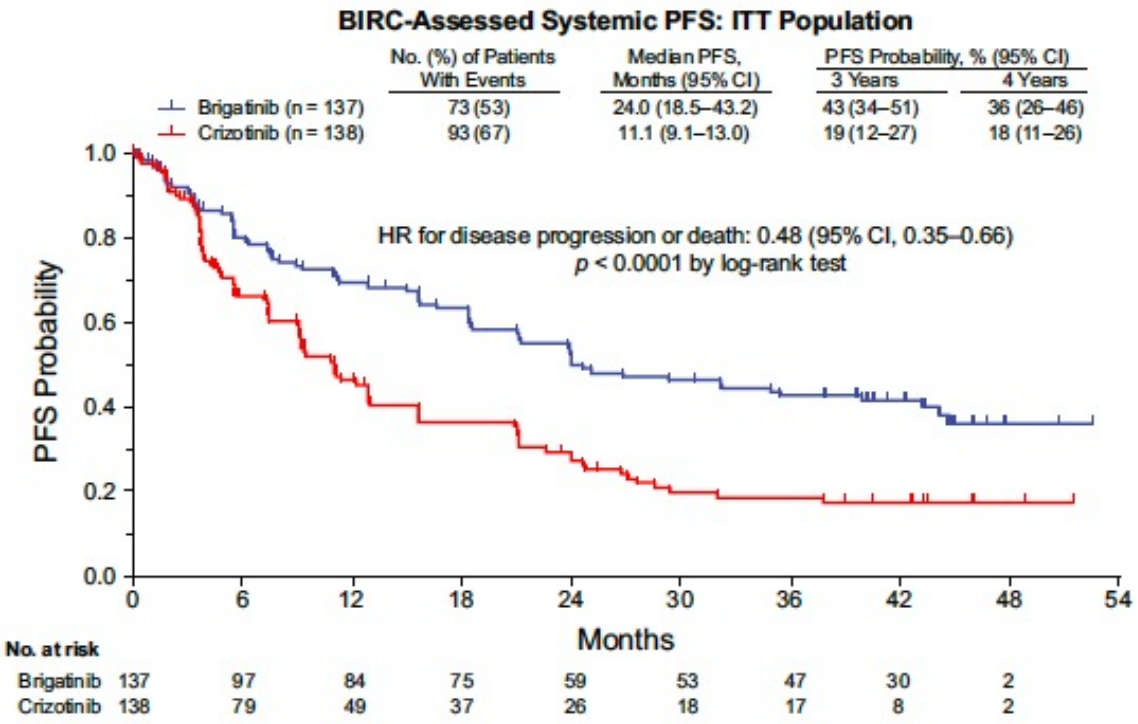
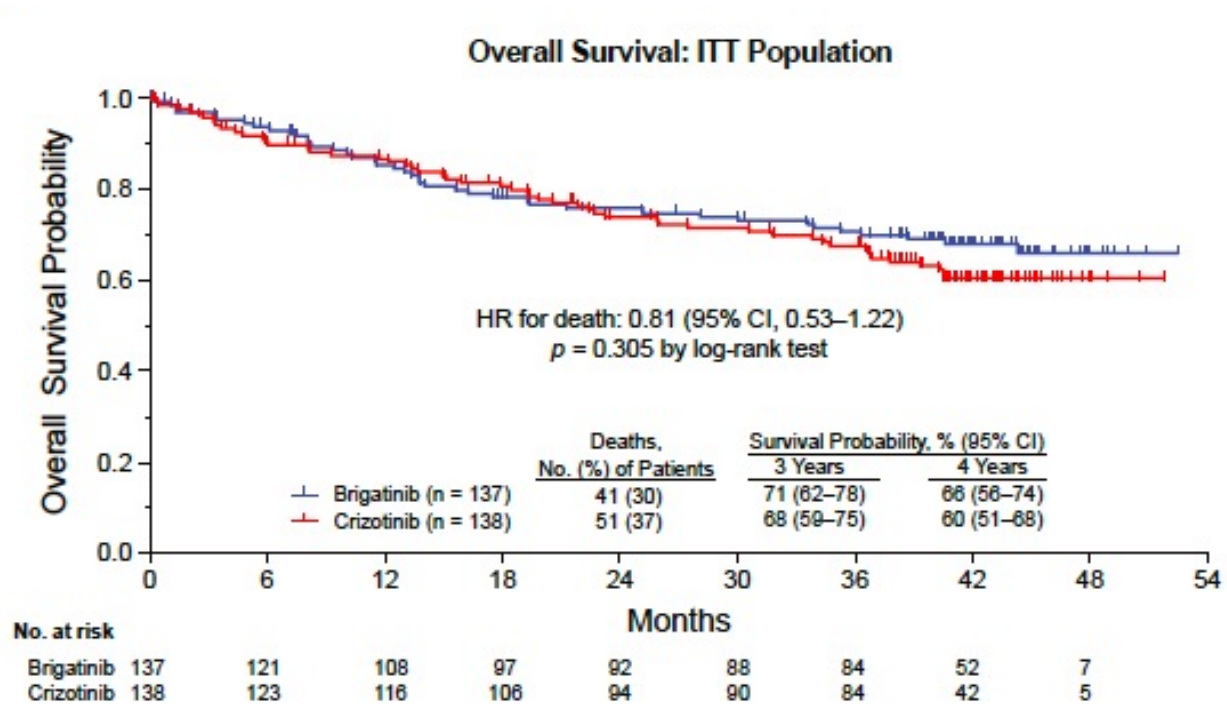
Final Results of Phase 3 ALTA-1L Trial (Brigatinib vs Crizotinib)





Courtesy of Zofia Piotrowska, MD, MHS

Camidge DR, JTO 2021.

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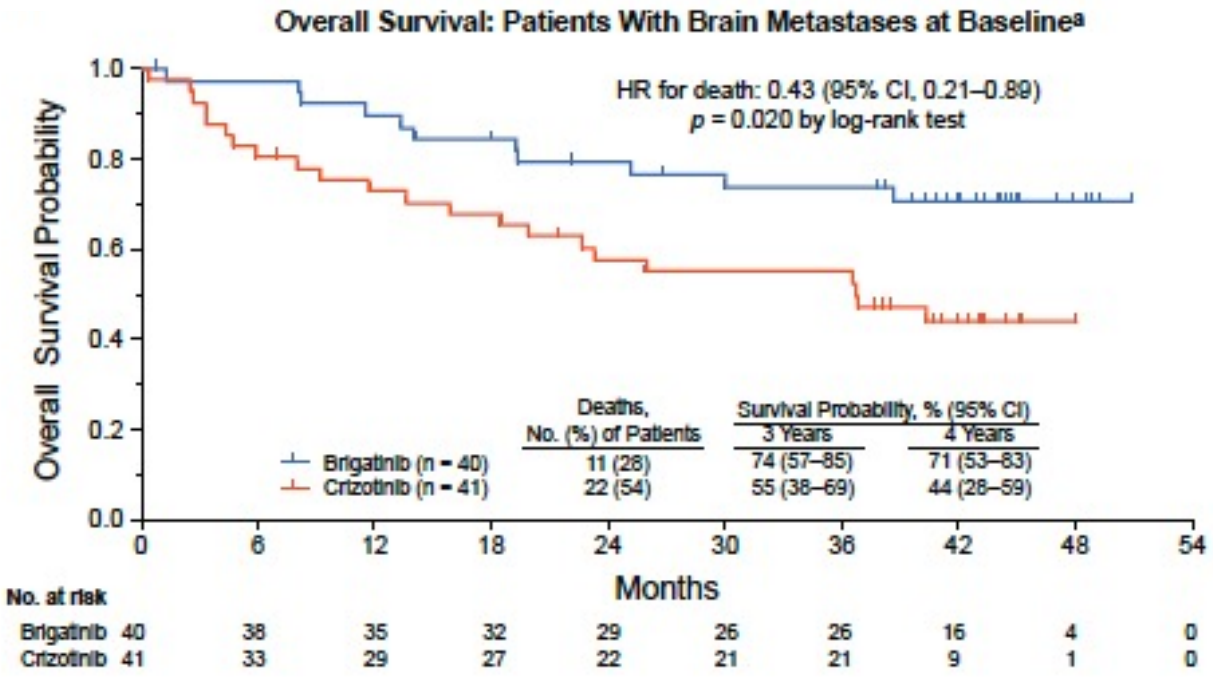

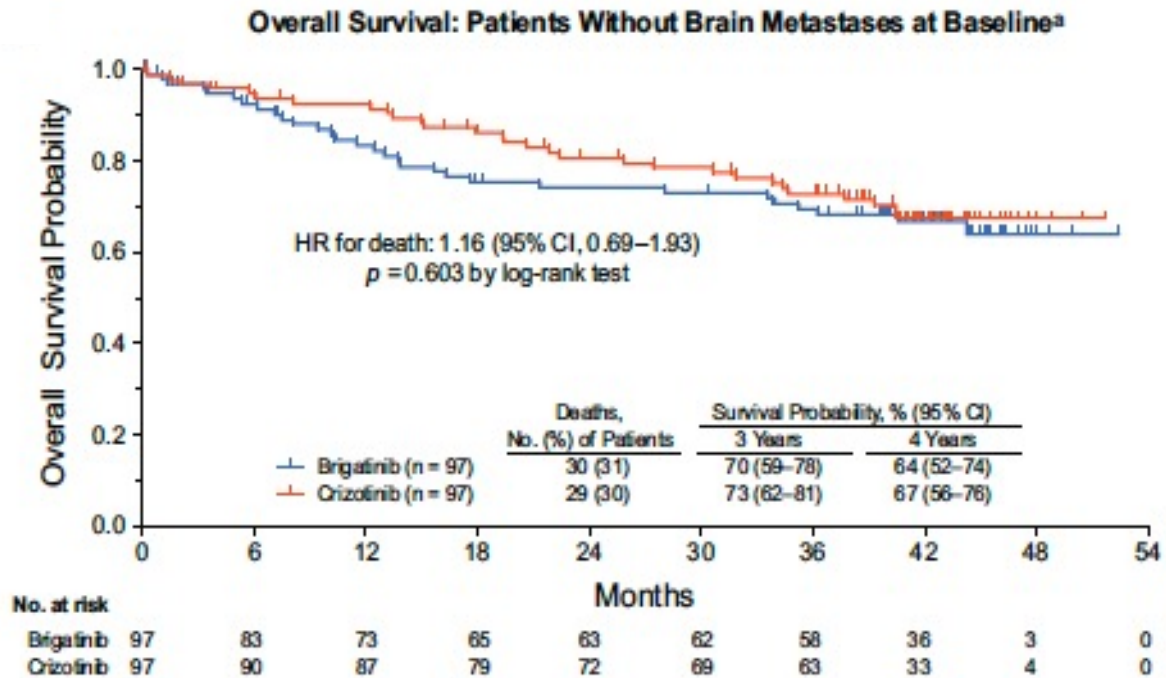

Courtesy of Zofia Piotrowska, MD, MHS

Camidge DR, JTO 2021.

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What did we learn this year?

- EGFR (common)
- EGFR exon 20
- ALK
- **ROS1**
- HER2
- TROP2
- MET exon 14
- RET
- KRAS
- NTRK

- Testing
- Agents: *Entrectinib*
- Sequencing
- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
- New directions

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Shaw. NEJM. 2014;371:1963. Shaw. Ann Oncol. 2019;30:1121.

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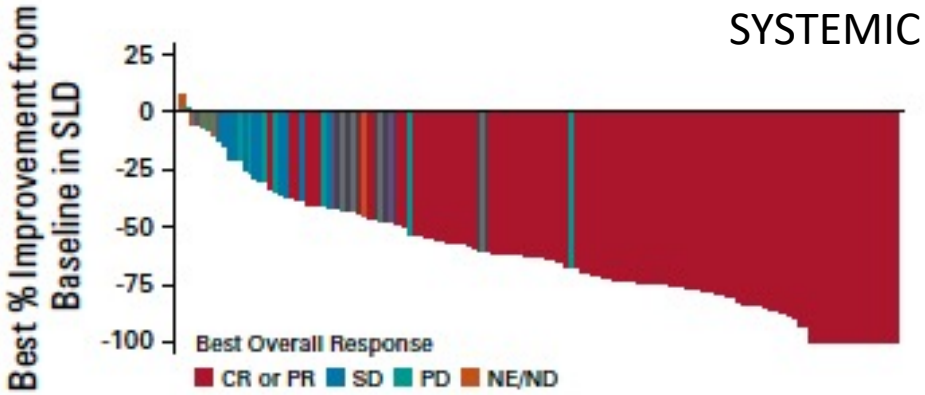
Courtesy of Zofia Piotrowska, MD, MHS

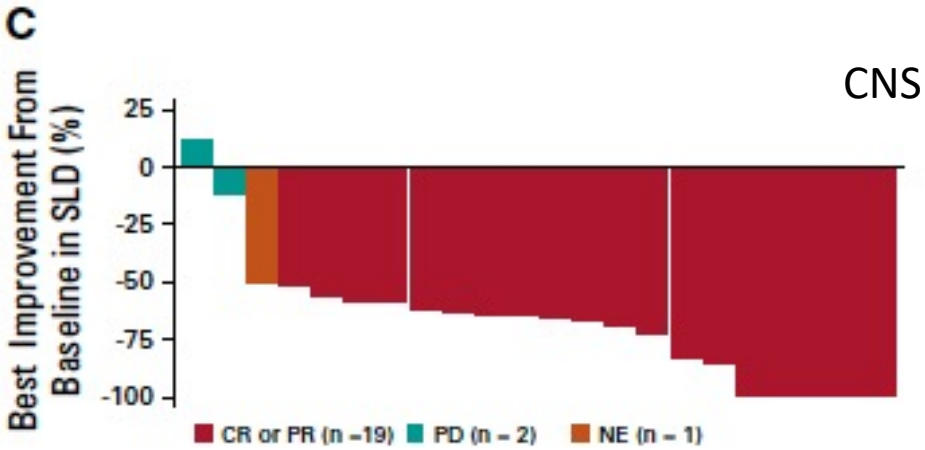
Updated integrated analysis of entrectinib in locally advanced or metastatic ROS1 fusion-positive NSCLC.

- Pooled analysis of 3 phase I/II trials of entrectinib among 161 evaluable patients ROS1+ NSCLC.
- 37% pts first-line; 23% ≥ 2 prior lines of therapy.
- 34.8% pts with baseline brain mets (7.5% measurable)
- Systemic ORR 67.1%, mPFS 15.7 mos
- Among 24 pts with measurable CNS mets, intracranial ORR 79.2% and median intracranial DoR 12.9 mo
- Common toxicities include dysgeusia, dizziness, constipation, fatigue, diarrhea, weight gain.

SYSTEMIC



CNS



Dziadziuszko R, JCO 2021.

Courtesy of Zofia Piotrowska, MD, MHS

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- EGFR (common)
- EGFR exon 20
- ALK
- ROS1
- **HER2**
- TROP2
- MET exon 14
- RET
- KRAS
- NTRK

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- Agents: *Trastuzumab deruxtecan, poziotinib*
- Sequencing
- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
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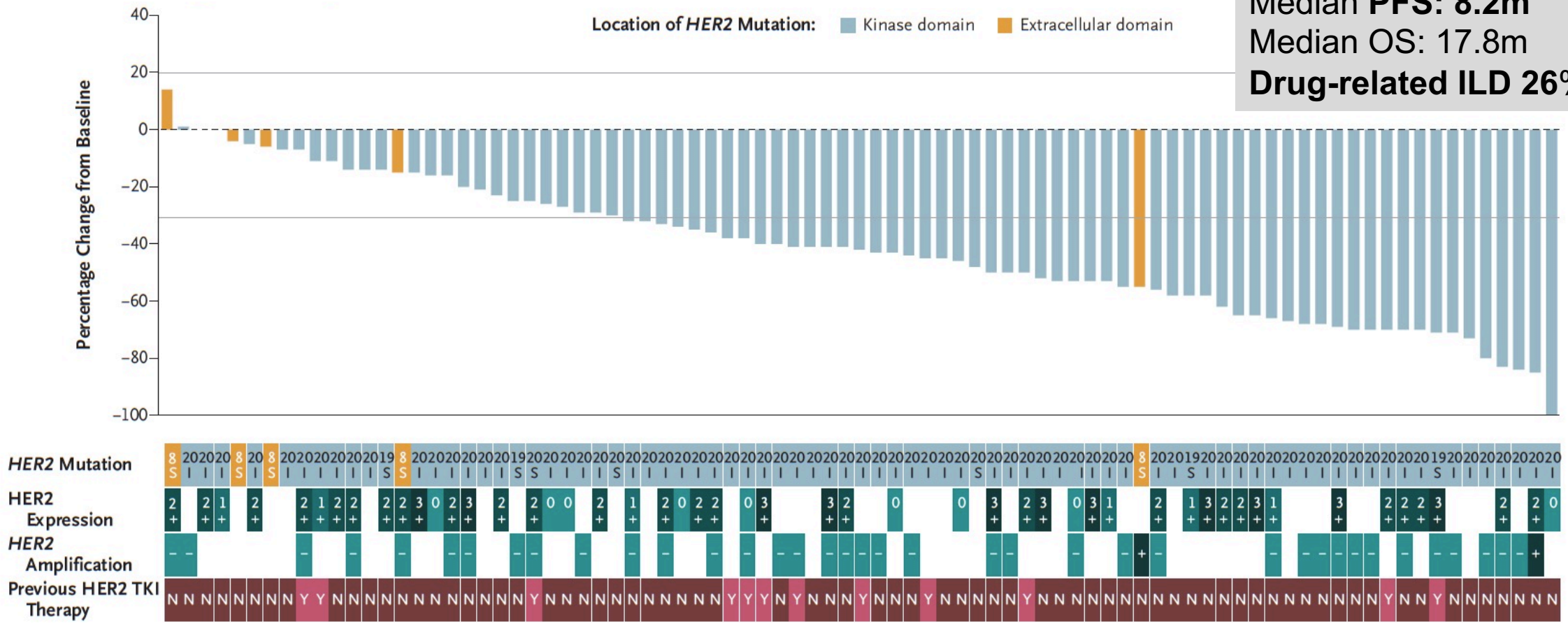
RTP Year in Review 2022

Trastuzumab-deruxtecan for HER2-mutant NSCLC

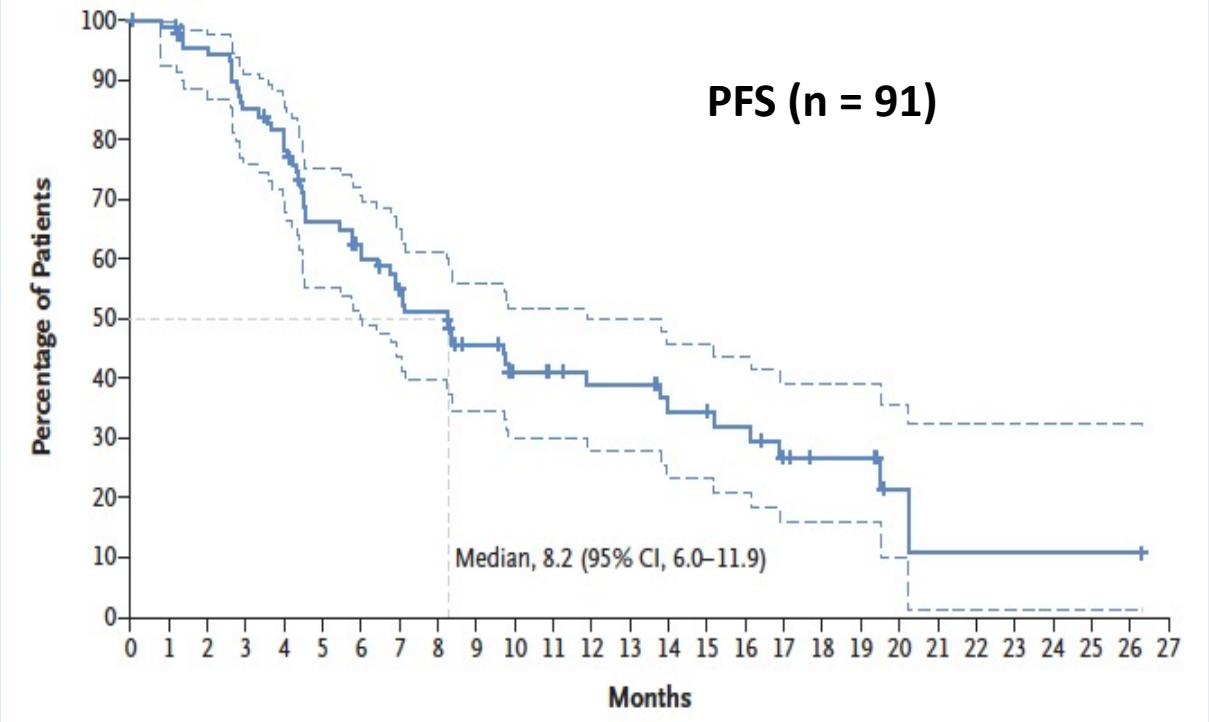
N=91
Confirmed **ORR**: **55%**
Median **PFS: 8.2m**
Median OS: 17.8m
Drug-related ILD 26% (Gr5 in 2)

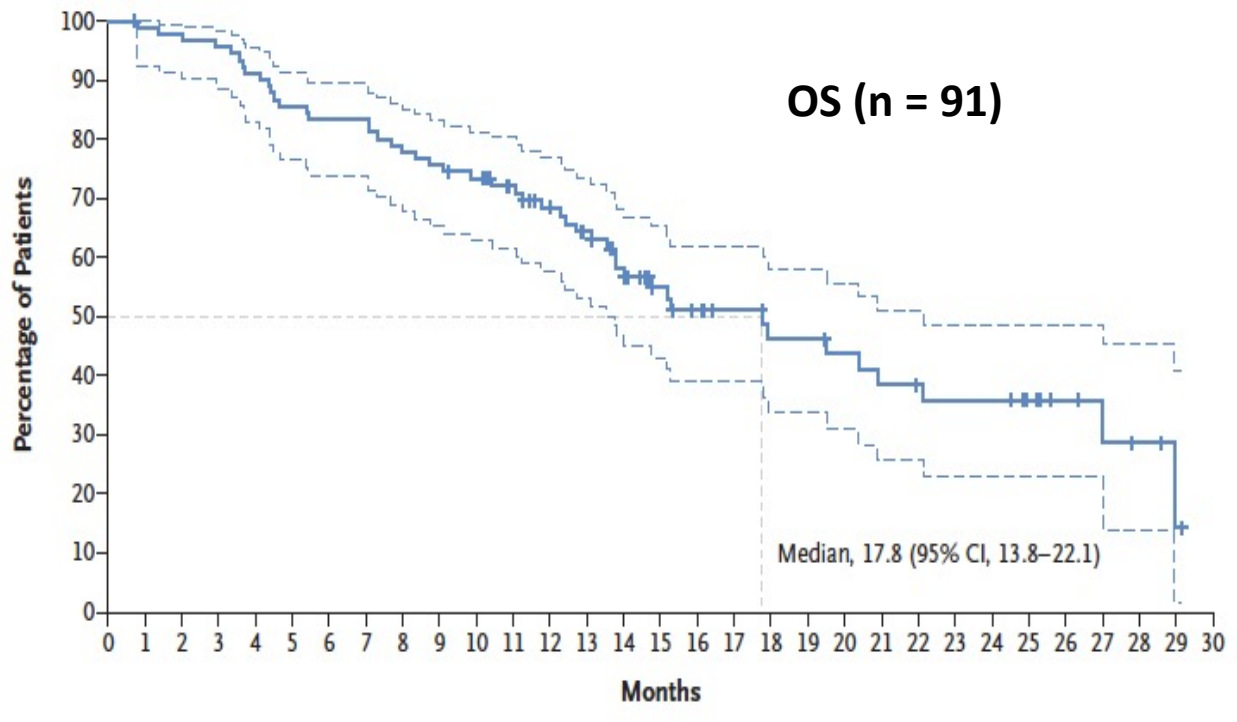


Courtesy of John V Heymach, MD, PhD

Li et al, NEJM 2021

DESTINY-Lung01: Survival in the Overall Population



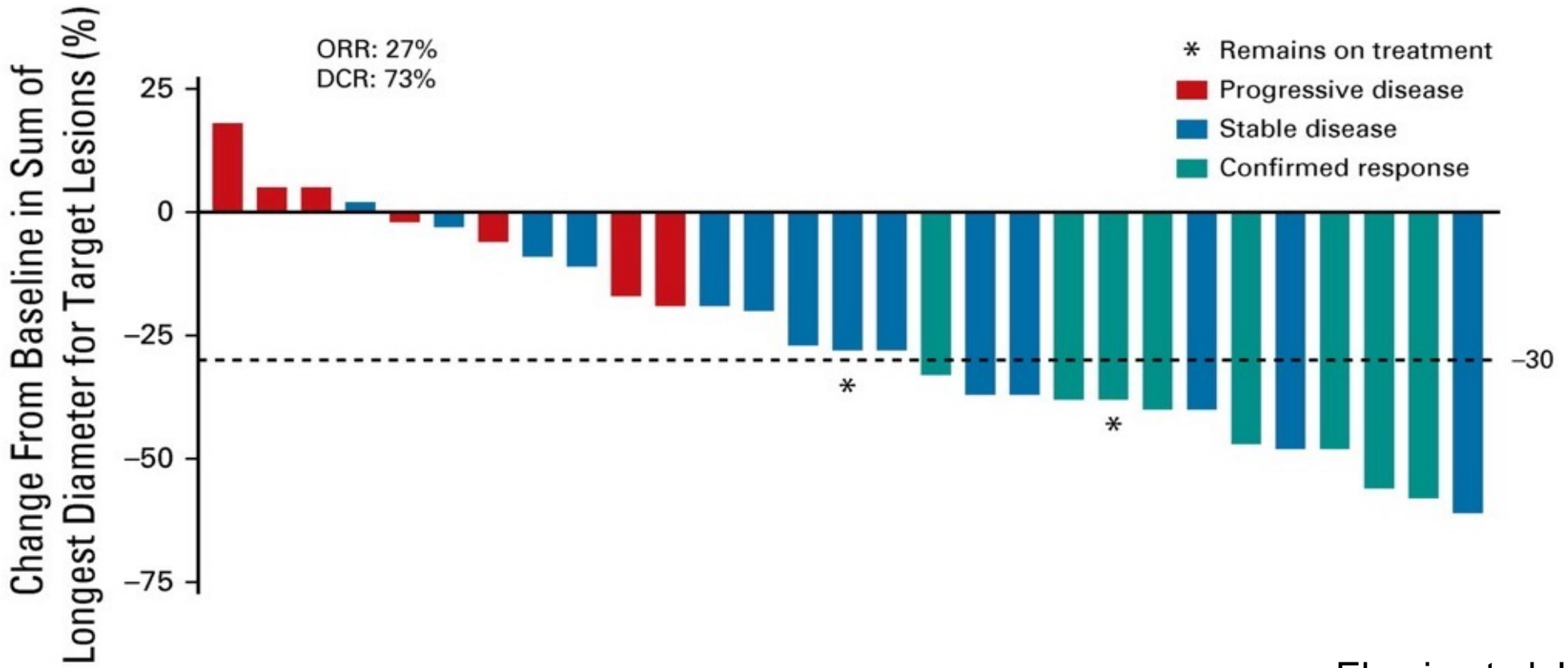


Li BT et al. *N Engl J Med* 2021;[Online ahead of print].

RTP Year in Review 2022

Poziotinib for Patients with HER2 Exon 20 mutant Non-Small Cell Lung Cancer: Results from MDA Phase II Trial

MDA study: Confirmed ORR 27%, mPFS 5.5m, DCR 73%



Elamin et al JCO 2021

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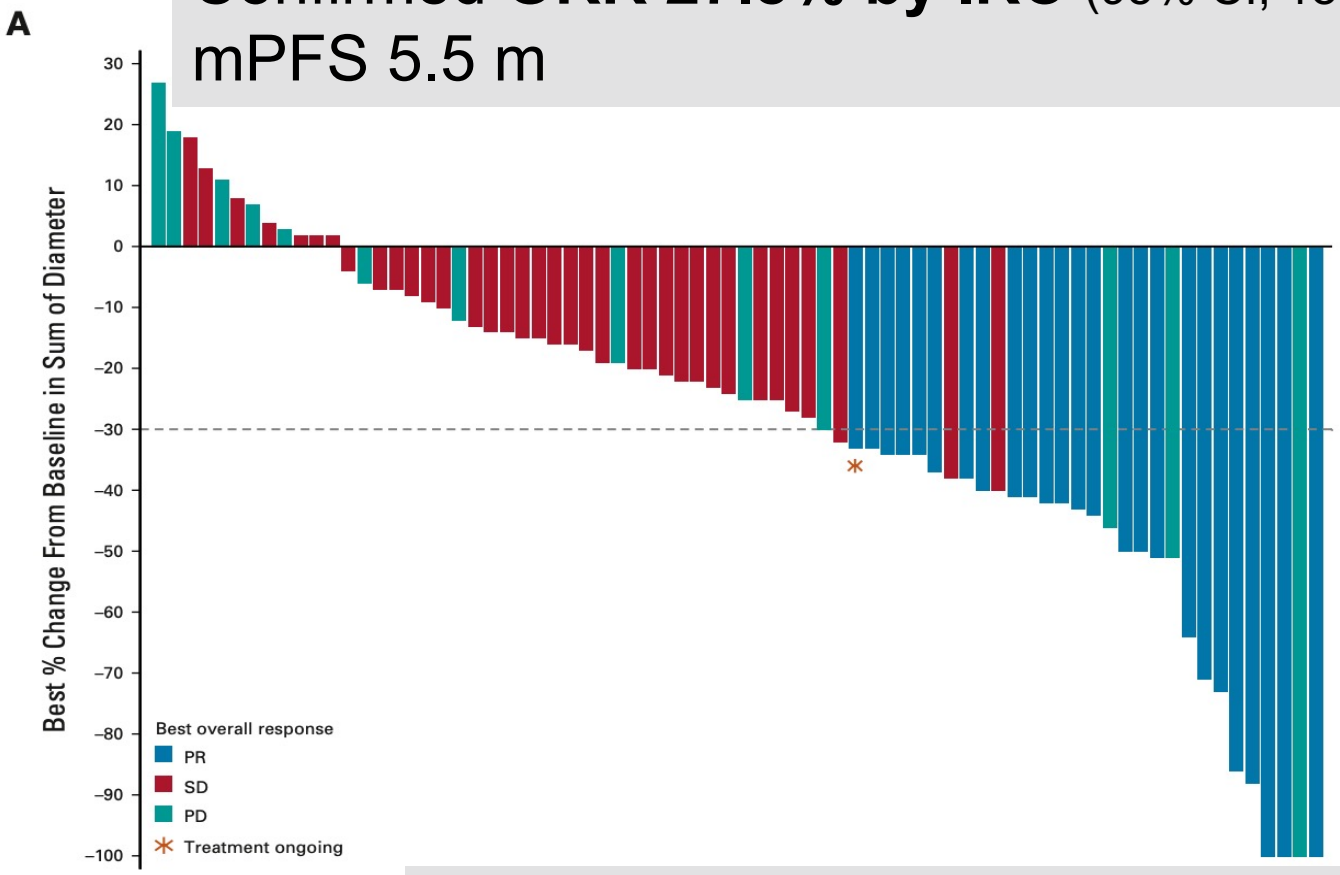
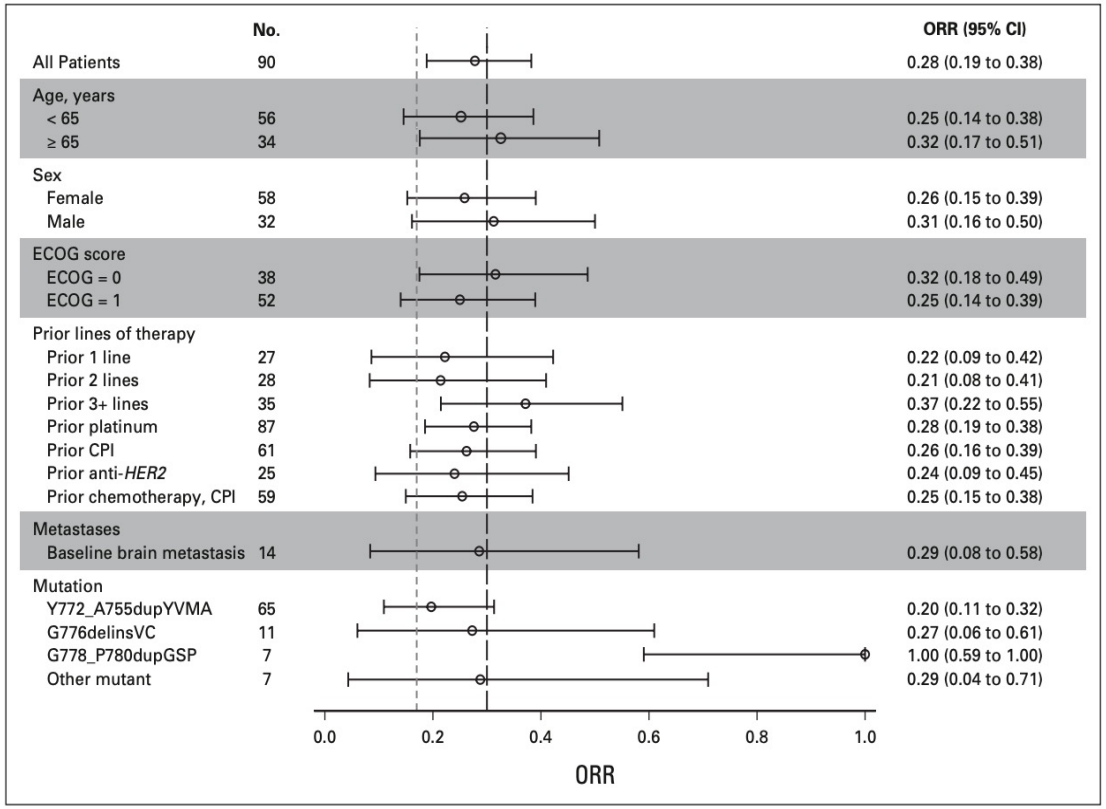
Courtesy of John V Heymach, MD, PhD

Poziotinib in HER2 Exon 20 insertion mutant NSCLC after prior therapies: ZENITH20-2

Confirmed **ORR 27.8% by IRC** (95% CI, 18.9 to 38.2)
mPFS 5.5 m





Dose reductions in 76.7%,
Dose intensity 71%

Le et al., JCO 2021

Courtesy of John V Heymach, MD, PhD

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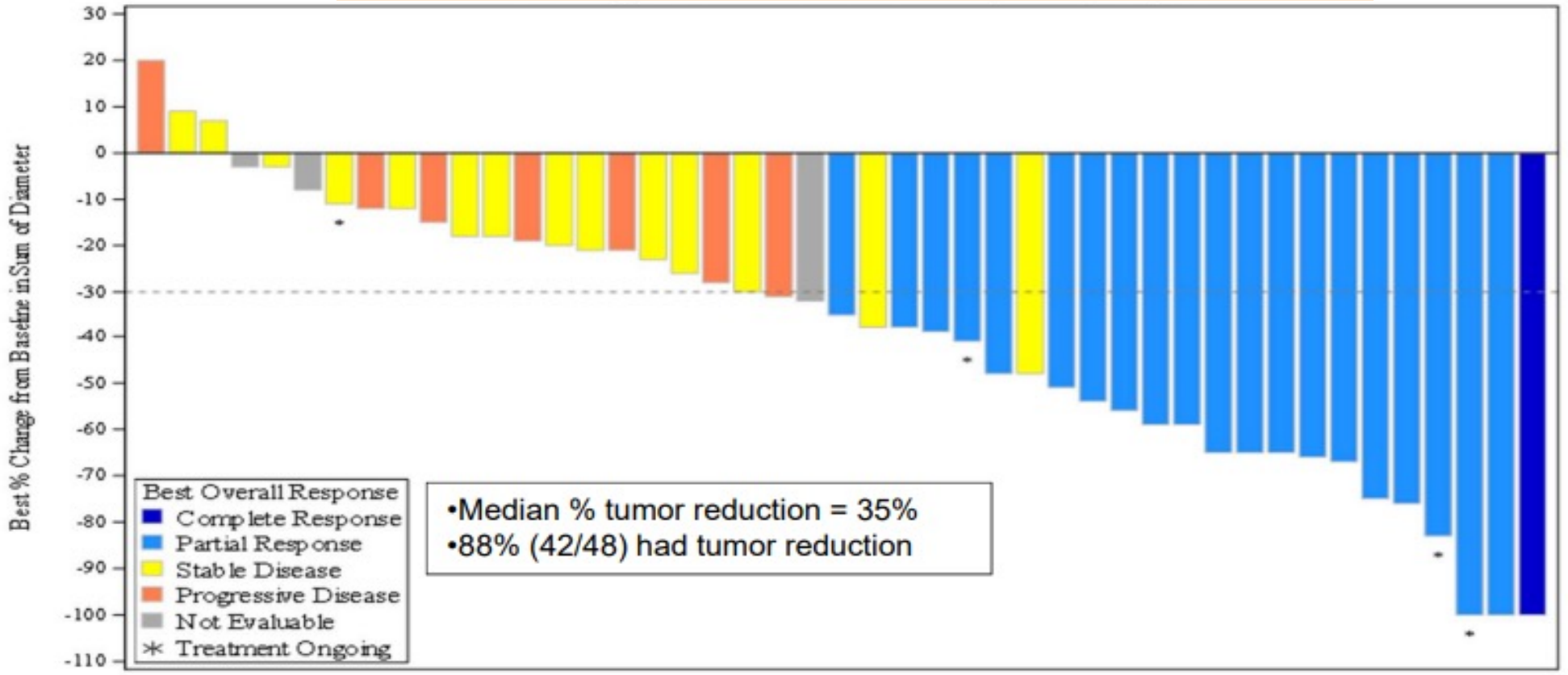
Poziotinib in Treatment-naïve HER2 exon 20 mutant NSCLC: A Multinational Phase 2 Study (ZENITH20-4)

Confirmed ORR 43.8% by BICR



Cornelissen ESMO 2021

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Courtesy of John V Heymach, MD, PhD

Targeted Treatment for NSCLC

What did we learn this year?

- EGFR (common)
- EGFR exon 20
- ALK
- ROS1
- HER2
- **TROP2**
- MET exon 14
- RET
- KRAS
- NTRK

- **Testing**
- **Agents:**
  Datopotamab deruxtecan
- **Sequencing**
- **Tolerability**
- **Resistance**
- **Immunotherapy**
- **Brain metastases**
- **New directions**

RTP Year in Review 2022

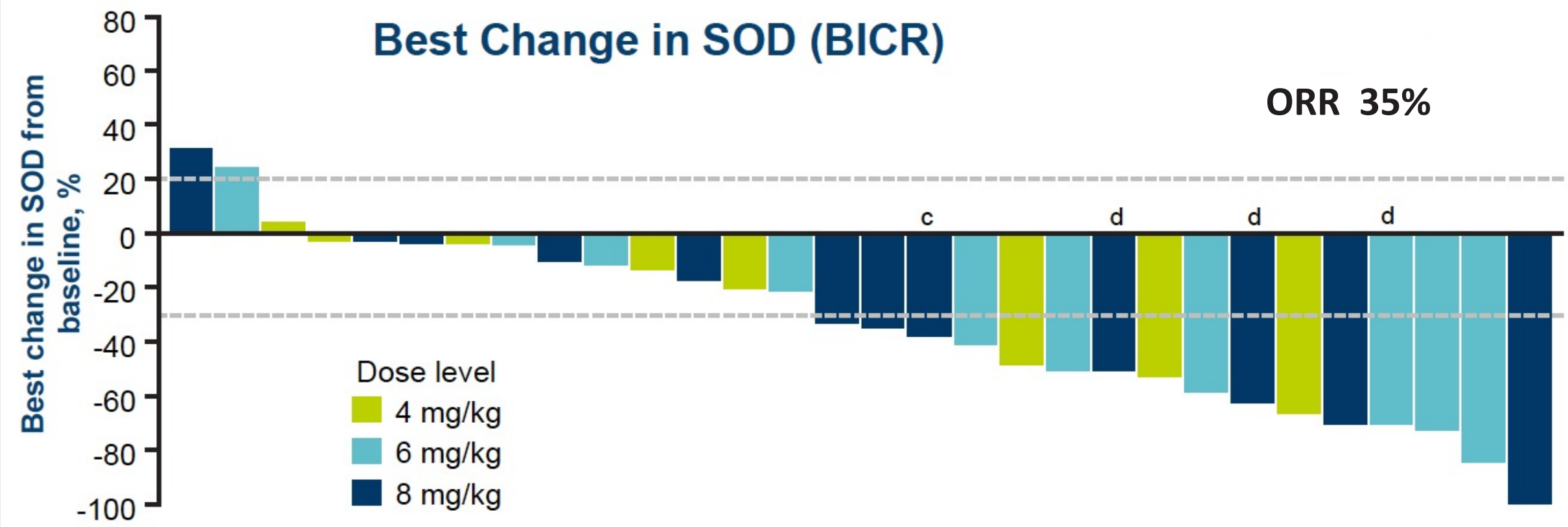
Efficacy of Datopotamab Deruxtecan (Dato-DXd) in Patients with Advanced/Metastatic NSCLC and Actionable Genomic Alterations (AGAs): Preliminary Results from the Phase I TROPION-PanTumor01 Study

Garon EB et al.

ESMO 2021;Abstract LBA49.

RTP Year in Review 2022

TROPION-PanTumor01: Response to Dato-DXd in Tumors with Actionable Genomic Alterations



Actionable genomic alterations: EGFR mutation, 85% (of which 10% were exon 20 insertions); ALK fusion, 9%; ROS1 fusion, 3%; RET fusion, 3%

Garon EB et al. ESMO 2021;Abstract LBA49.

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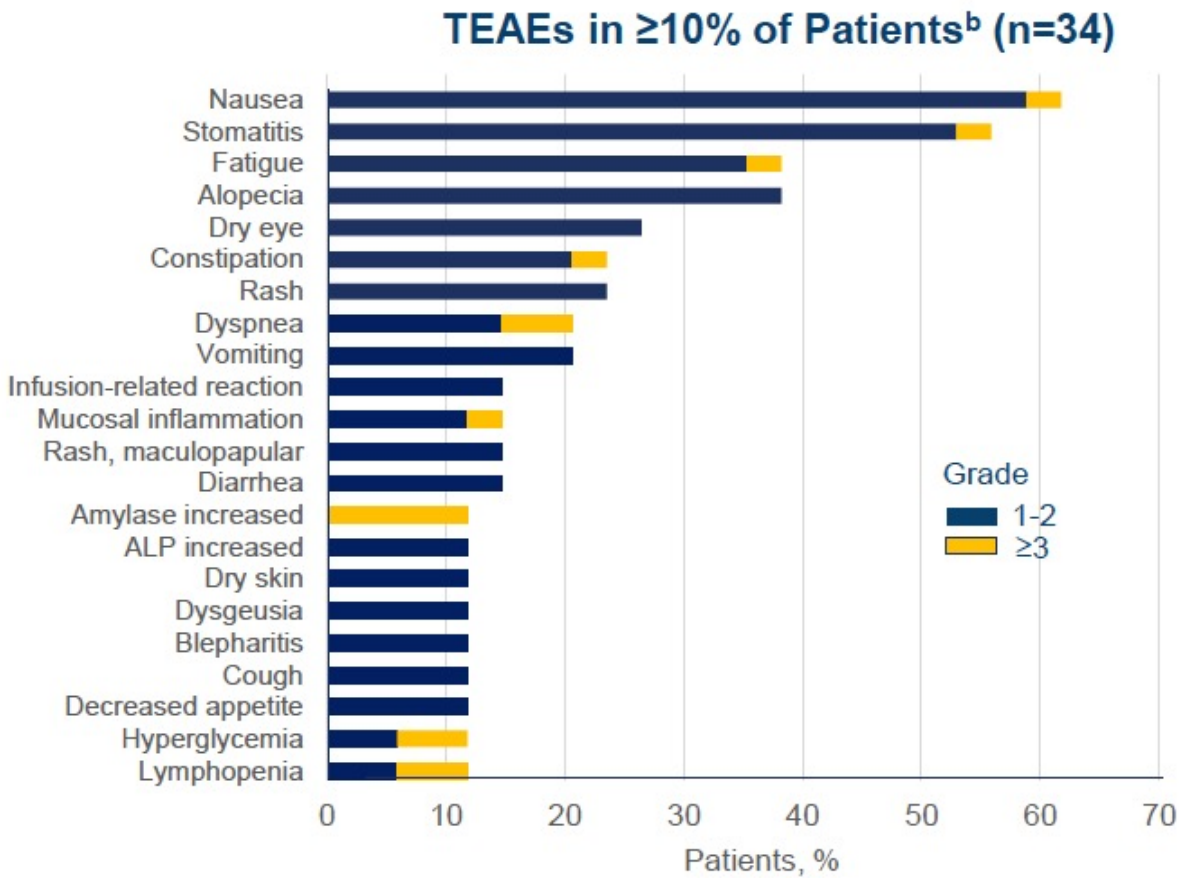
TROPION-PanTumor01: Adverse Events and Safety

Adverse events, n (%)	Dato-DXd n=34
TEAE, %	100
Grade ≥3	53
Drug-related TEAE, %	88
Grade ≥3	38
Serious TEAE, %	35
Grade ≥3	29
Dose adjustments, %	
TEAEs associated with discontinuation	15
TEAEs associated with dose interruption	27
TEAEs associated with dose reduction	15
ILD adjudicated as drug related, n[a]	1
Grade ≤2	0
Grade 3/4	0
Grade 5	1



The safety profile of Dato-DXd was manageable and consistent with that observed in the overall NSCLC population in TROPION-PanTumor01; treatment-emergent adverse events (TEAEs) were primarily nonhematologic

Garon EB et al. ESMO 2021;Abstract LBA49.

RTP Year in Review 2022

Targeted Treatment for NSCLC

What did we learn this year?

- EGFR (common)
- EGFR exon 20
- ALK
- ROS1
- HER2
- TROP2
- **MET exon 14**
- RET
- KRAS
- NTRK

- Testing
- Agents: *Tepotinib, capmatinib*
- Sequencing
- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
- New directions

RTP Year in Review 2022

Tepotinib Efficacy and Safety in Patients with *MET* Exon 14 Skipping NSCLC: Outcomes in Patient Subgroups from the VISION Study with Relevance for Clinical Practice

Xiuning Le[1], Hiroshi Sakai[2], Enriqueta Felip[3], Remi Veillon[4], Marina Chiara Garassino[5,6], Jo Raskin[7], Alexis B. Cortot[8], Santiago Viteri[9], Julien Mazieres[10], Egbert F. Smit[11], Michael Thomas[12], Wade T. Iams[13], Byoung Chul Cho[14], Hye Ryun Kim[14], James Chih-Hsin Yang[15], Yuh-Min Chen[16], Jyoti D. Patel[17], Christine M. Bestvina[18], Keunchil Park[19], Frank Griesinger[20], Melissa Johnson[21], Maya Gottfried[22], Christian Britschgi[23], John Heymach[1], Elif Sikoglu[24], Karin Berghoff[25], Karl-Maria Schumacher[26], Rolf Bruns[27], Gordon Otto[26], and Paul K. Paik[28,29]

***Clin Cancer Res* 2021;[Online ahead of print]**

RTP Year in Review 2022

METex14 ctDNA Dynamics and Resistance Mechanisms Detected in Liquid Biopsy from Patients with METex14 Skipping NSCLC Treated with Tepotinib

Paik PK et al.

ASCO 2021;Abstract 9012.

RTP Year in Review 2022

VISION: Association Between Molecular and Clinical Response

79 patients had ≥1 on-treatment profile available;
65 had two consecutive on-treatment profiles (30 1L, 35 ≥2L)

	Confirmed **molecular response*** (n=46; 71%) *>75% depletion in MET exon 14 VAF ctDNA from baseline*			Confirmed **molecular progression*** (n=5; 8%) *VAF increase >0 from baseline*			No change in VAF or lacked confirmation (n=14; 22%)†
Clinical response (investigator-assessed)	Overall (n=46)	1L (n=20)	≥2L (n=26)	Overall (n=5)	1L (n=4)	≥2L (n=1)	
ORR, n (%)	35 (76)	18 (90)	15 (58)	0	0	0	
DCR, n (%)	42 (91)	18 (90)	24 (92)	3 (60)	2 (50)	1	
mDOR, months (95% CI)	**14** (9.8, NE)	**18** (7.2, NE)	**14** (9.7, NE)	n/a	n/a	n/a	
mPFS, months (95% CI)	**11.0** (8.6, 17.7)	**19.7** (9.7, NE)	**9.9** (6.9, 13.8)	5.5 (2.8, NE)	4.8 (2.8, NE)	5.8	

- Molecular responses were associated with clinical response
- Molecular progression was associated with no response/short PFS

Paik PK et al. ASCO 2021;Abstract 9012.

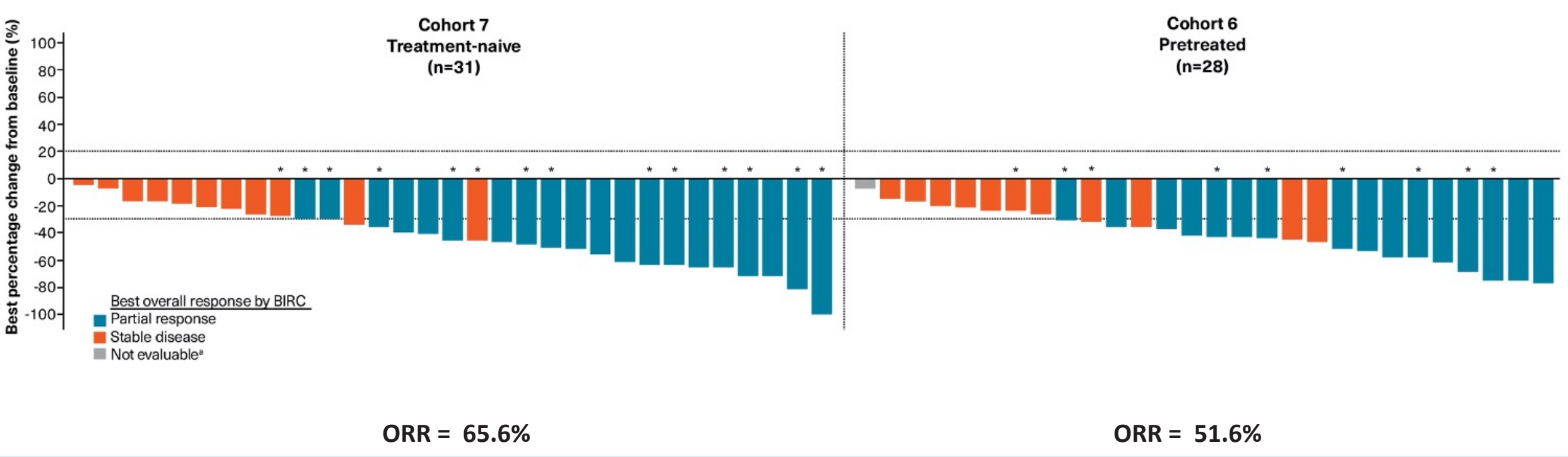
Capmatinib in MET Exon 14-Mutated, Advanced NSCLC: Updated Results from the GEOMETRY mono-1 Study

Wolf J et al.

ASCO 2021;Abstract 9020.

RTP Year in Review 2022

GEOMETRY mono-1: Response to Capmatinib



ORR = 65.6%

ORR = 51.6%

Wolf J et al. ASCO 2021;Abstract 9020.

Targeted Treatment for NSCLC

What did we learn this year?

- EGFR (common)
- EGFR exon 20
- ALK
- ROS1
- HER2
- TROP2
- MET exon 14
- **RET**
- KRAS
- NTRK

- Testing
- Agents: *Pralsetinib, selpercatinib*
- Sequencing
- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
- New directions

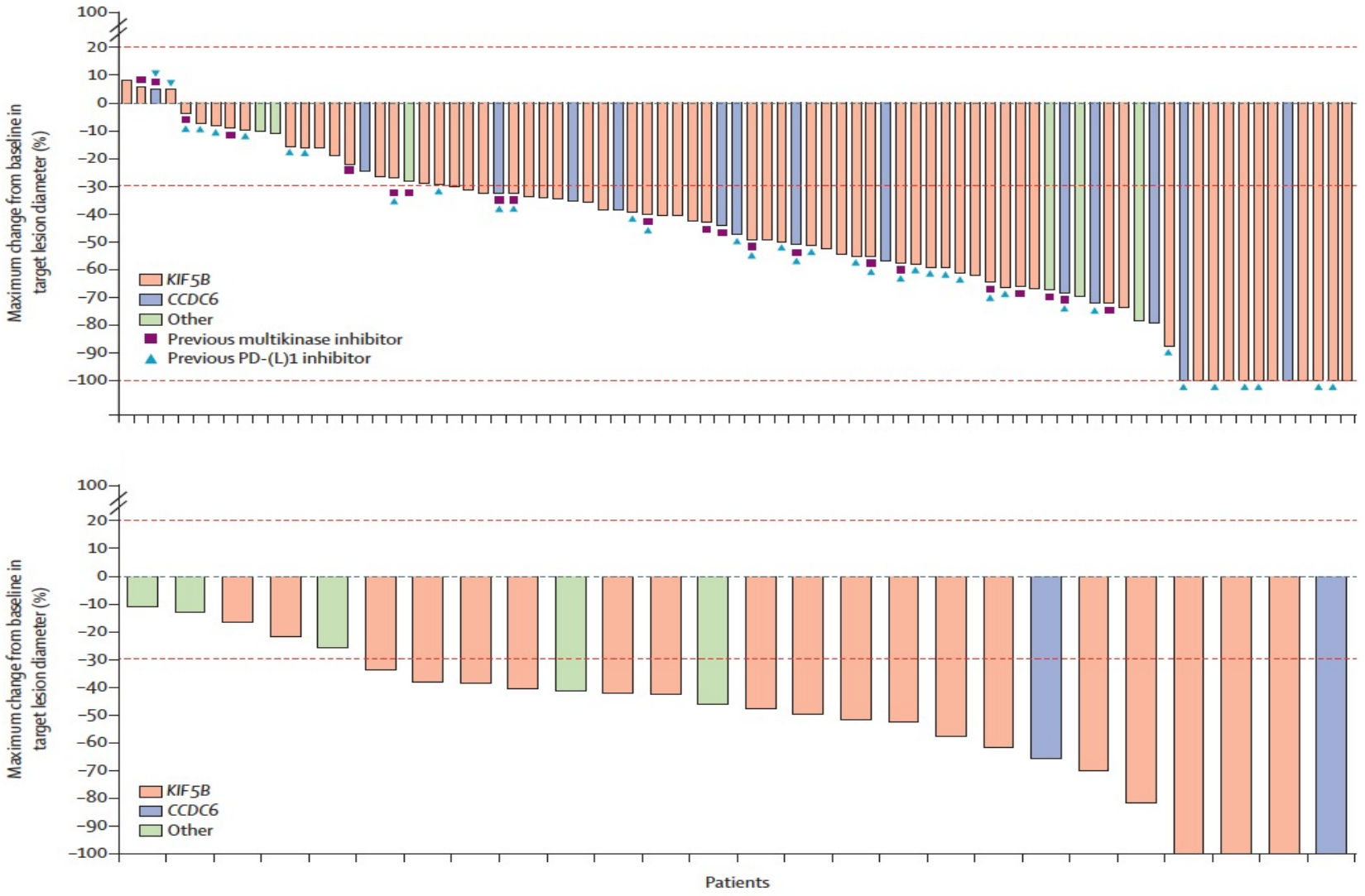
RTP Year in Review 2022

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

Justin F Gainor, Giuseppe Curigliano, Dong-Wan Kim, Dae Ho Lee, Benjamin Besse, Christina S Baik, Robert C Doebele, Philippe A Cassier, Gilberto Lopes, Daniel S W Tan, Elena Garralda, Luis G Paz-Ares, Byoung Chul Cho, Shirish M Gadgeel, Michael Thomas, Stephen V Liu, Matthew H Taylor, Aaron S Mansfield, Viola W Zhu, Corinne Clifford, Hui Zhang, Michael Palmer, Jennifer Green, Christopher D Turner, Vivek Subbiah

Lancet Oncol **2021; 22: 959–69**

ARROW: Response to Pralsetinib



Previous platinum-based therapy

ORR = 61%

No prior therapy

ORR = 70%

Gainor JF et al. *Lancet Oncol* 2021;22(7):959-69.

RTP Year in Review 2022

ARROW: Response Summary

	Previous platinum group (n=87)	No previous systemic treatment group (n=27)†
Overall response rate	53 (61%; 50–71)‡	19 (70%; 50–86)
Disease control rate	79 (91%; 83–96)	23 (85%; 66–96)
Best overall response		
Complete response	5 (6%)	3 (11%)
Partial response	48 (55%)‡	16 (59%)
Stable disease	26 (30%)	4 (15%)
Progressive disease	4 (5%)	3 (11%)
Not evaluable	4 (5%)	1 (4%)
Median duration of response, months	NR (15·2–NE)	9·0 (6·3–NE)
Rate at 6 months	83%; 73–94	74%; 52–96
Rate at 12 months	74%; 61–87	26%; 0–52
Clinical benefit rate§	69% (58–79)	70% (50–86)

Gainor JF et al. *Lancet Oncol* 2021;22(7):959-69.

RTP Year in Review 2022

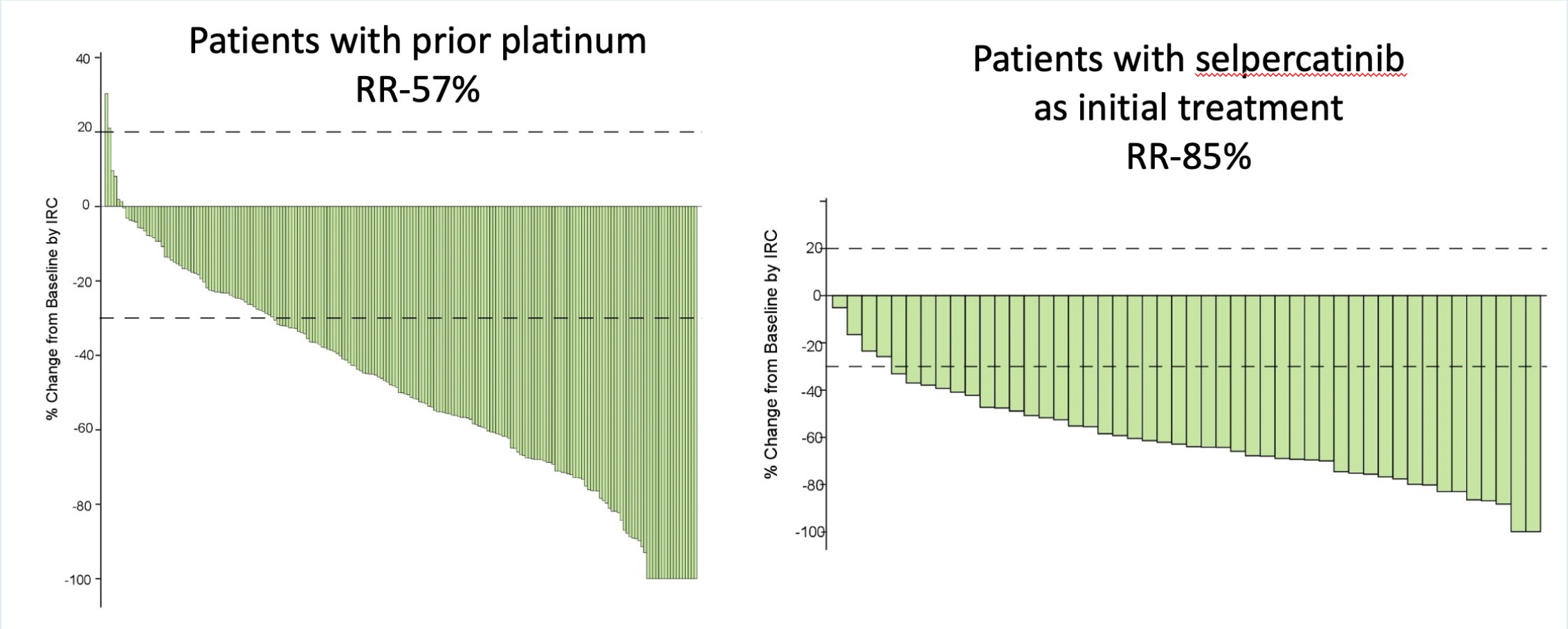
Updated Overall Efficacy and Safety of Selpercatinib in Patients with RET Fusion-Positive Non-Small-Cell Lung Cancer (NSCLC): LIBRETTO-001 Study

Besse B et al.

ASCO 2021;Abstract 9065.

RTP Year in Review 2022

LIBRETTO-001: Response to Selpercatinib



Besse B et al. ASCO 2021;Abstract 9065.

RTP Year in Review 2022

Targeted Treatment for NSCLC

What did we learn this year?

- EGFR (common)
- EGFR exon 20
- ALK
- ROS1
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- **KRAS**
- NTRK

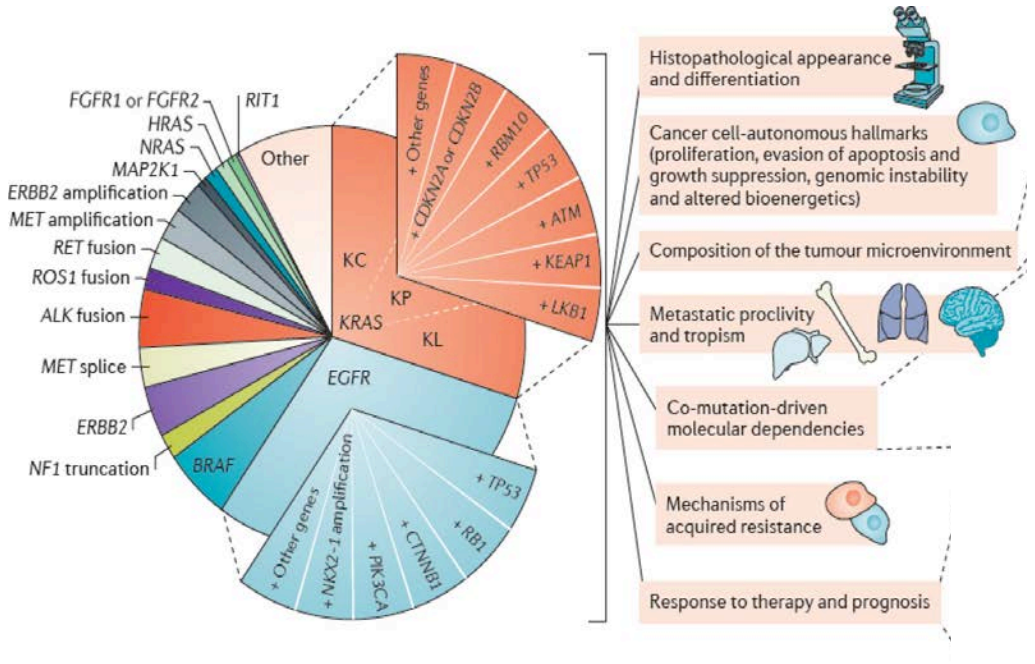
- Testing
- Agents: *Sotorasib, adagrasib*
- Sequencing
- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
- New directions

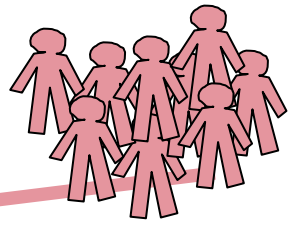
RTP Year in Review 2022

KRAS mutant NSCLC subgroups based on alleles (e.g. G12C) and co-mutations

NSCLC

KRAS co-mutations





KRAS mutant ~25%

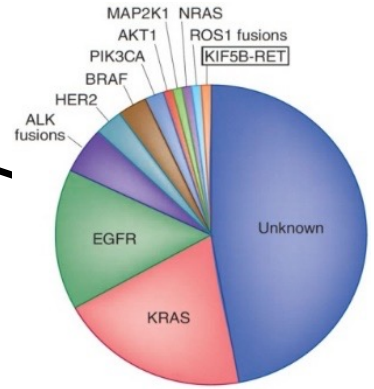
G12C ~13%

G12V ~6%

G12D ~3%

Other

Driver positive: the genomic pie (40-50%)



KRAS Alleles in NSCLC

Skoulidis and Heymach, Nat Rev Cancer 2019

Courtesy of John V Heymach, MD, PhD

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Making Cancer History®

Phase 2 CodeBreaK 100 trial evaluating sotorasib in pretreated KRAS p.G12C mutated

The NEW ENGLAND JOURNAL of MEDICINE

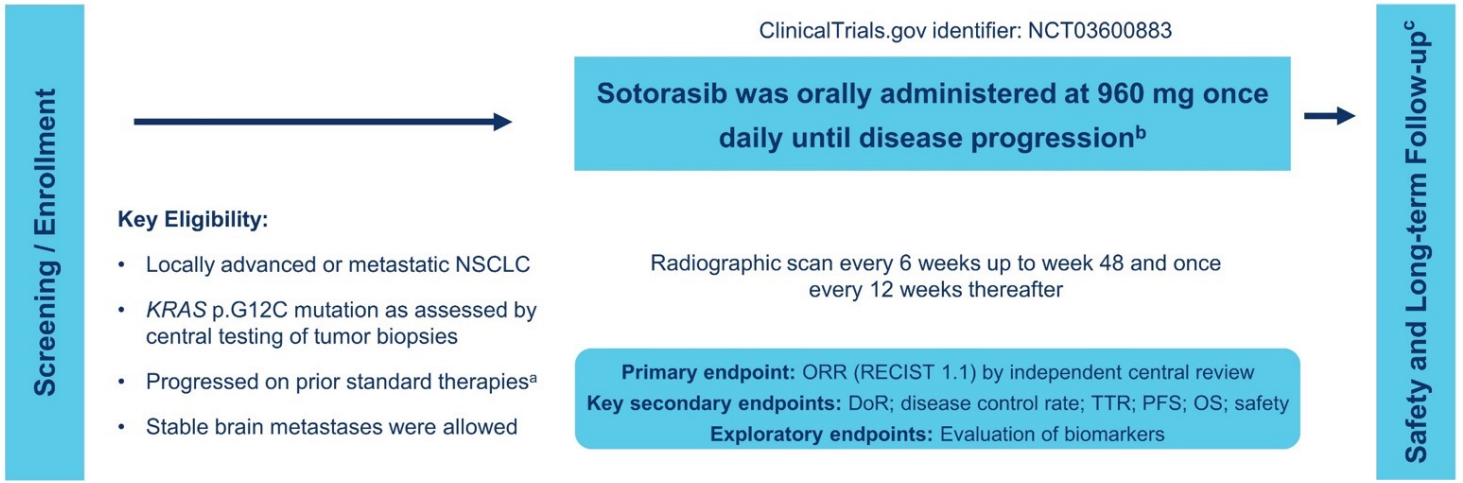
ESTABLISHED IN 1812 JUNE 24, 2021 VOL. 384 NO. 25

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

Skoulidis NEJM 2021

Phase 2 CodeBreaK100 Trial Design



Skoulidis ASCO 2021

Courtesy of John V Heymach, MD, PhD

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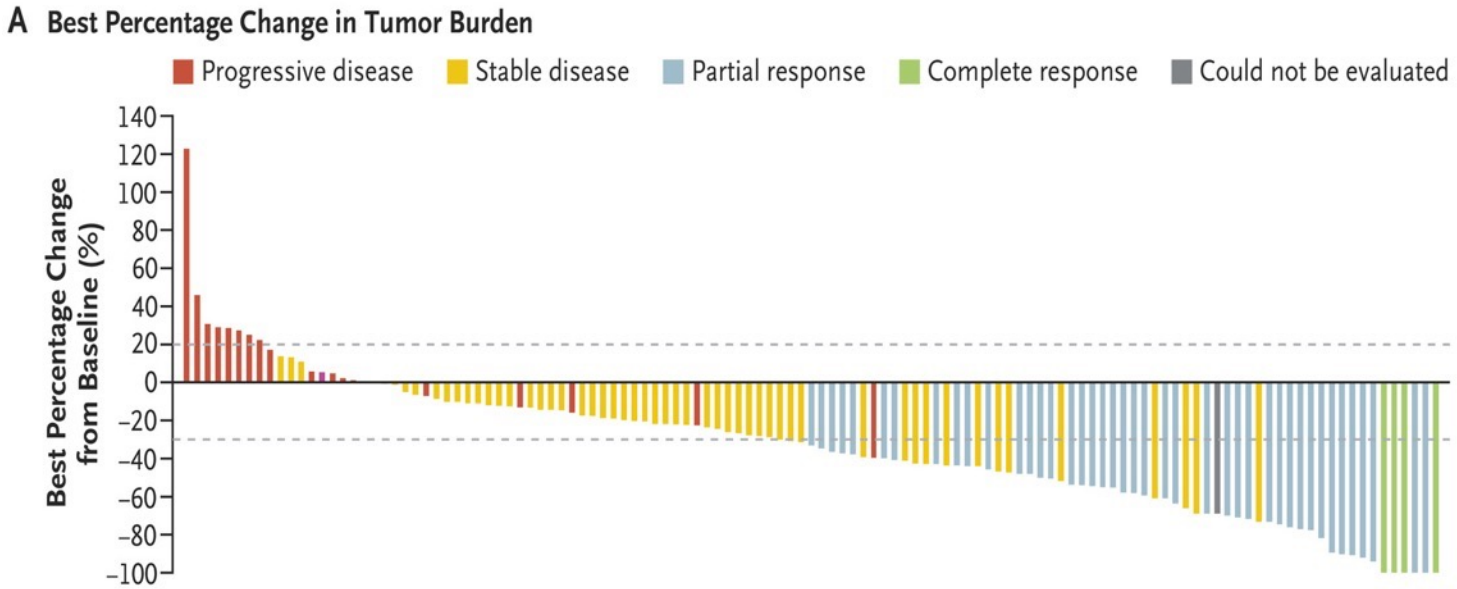
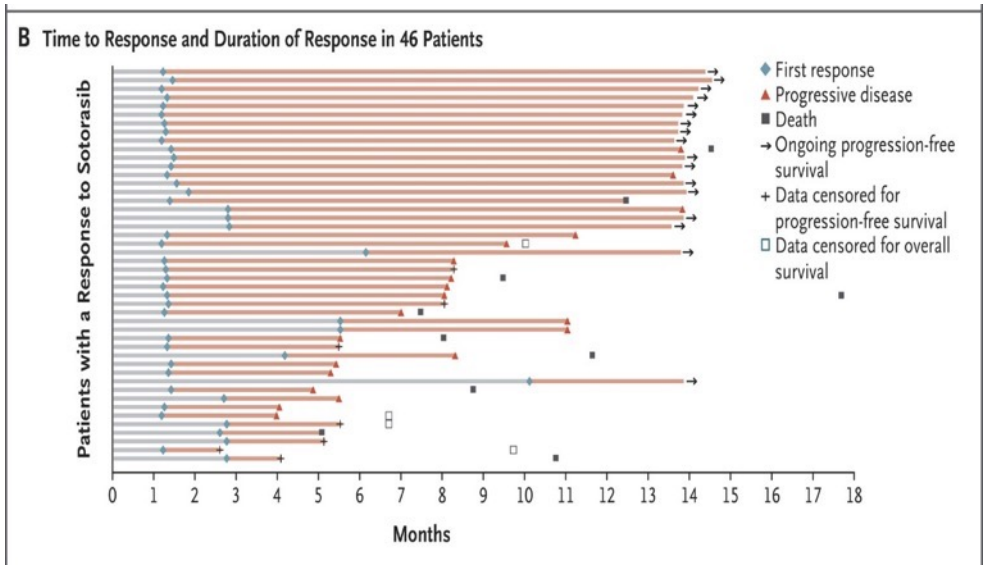
Sotorasib therapy led to a durable clinical benefit

objective response 37.1% median PFS 6.8m



median duration of response 11.1 months



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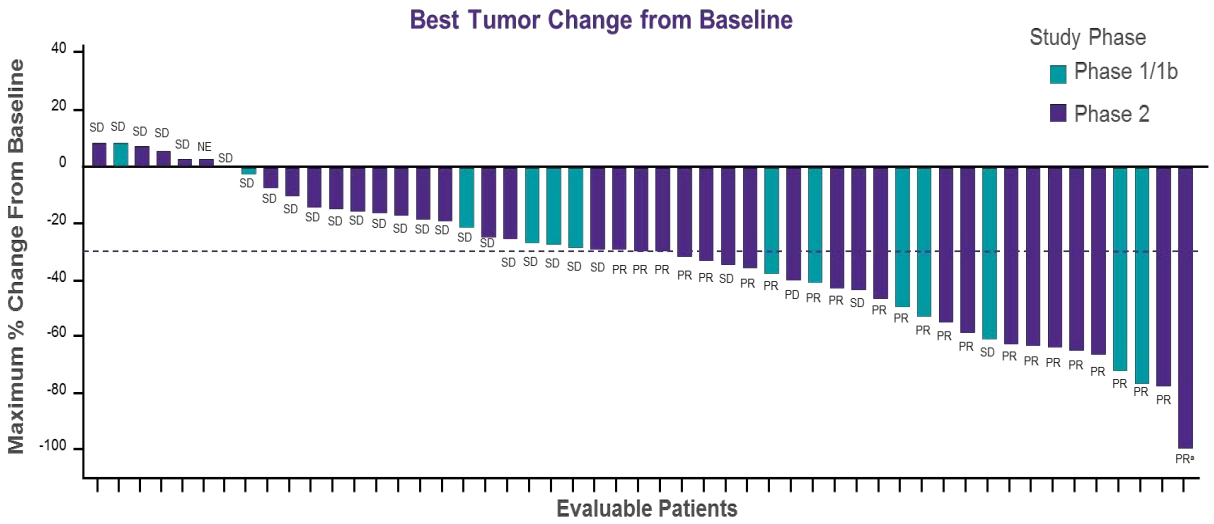
Skoulidis NEJM 2021

Courtesy of John V Heymach, MD, PhD

KRYSTAL-1: a phase 1/2 Study of MRTX849 (adagrasib) in KRAS G12C mutant NSCLC



Efficacy Outcome[a], n (%)	Phase 1/1b, NSCLC 600 mg BID (n=14)	Phase 1/1b and 2, NSCLC 600 mg BID (n=51)
Objective Response Rate	6 (43%)	23 (45%)[b]
Best Overall Response		
Complete Response (CR)	0 (0%)	0 (0%)
Partial Response (PR)	6 (43%)	23 (45%)
Stable Disease (SD)	8 (57%)	26 (51%)
Progressive Disease (PD)	0 (0%)	1 (2%)
Not Evaluable (NE)	0 (0%)	1 (2%)[c]
Disease Control	14 (100%)	49 (96%)

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NCT03785249

Riely et al., ESMO 2021

Courtesy of John V Heymach, MD, PhD

Targeted Treatment for NSCLC

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- EGFR (common)
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- Testing
- Agents: *Entrectinib, larotrectinib*
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- Tolerability
- Resistance
- Immunotherapy
- Brain metastases
- New directions

RTP Year in Review 2022

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Wednesday, January 12, 2022
5:30 PM – 6:30 PM ET

Faculty

Tiffany A Traina, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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