What General Medical Oncologists Want to Know About Targeted Therapy for Non-Small Cell Lung Cancer

Tuesday, July 27, 2021
5:00 PM – 6:00 PM ET

Faculty

Professor Solange Peters, MD, PhD
Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

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Faculty

Professor Solange Peters, MD, PhD
Head, Medical Oncology
Chair, Thoracic Malignancies
Oncology Department
Lausanne University Hospital
Lausanne, Switzerland

Gregory J Riely, MD, PhD
Associate Attending
Memorial Sloan Kettering Cancer Center
New York, New York

Zofia Piotrowska, MD, MHS
Assistant Professor of Medicine
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc and Turning Point Therapeutics Inc.

Dr Love — Disclosures

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, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, 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, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc and Verastem Inc.

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Dr Piotrowska — Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Blueprint Medicines, C4 Therapeutics, Genentech, a member of the Roche Group, Incyte Corporation, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Medtronic Inc, Takeda Oncology
Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Cullinan Oncology, Daiichi Sankyo Inc, Janssen Biotech Inc, Novartis, Spectrum Pharmaceuticals Inc, Takeda Oncology, Tesaro, A GSK Company

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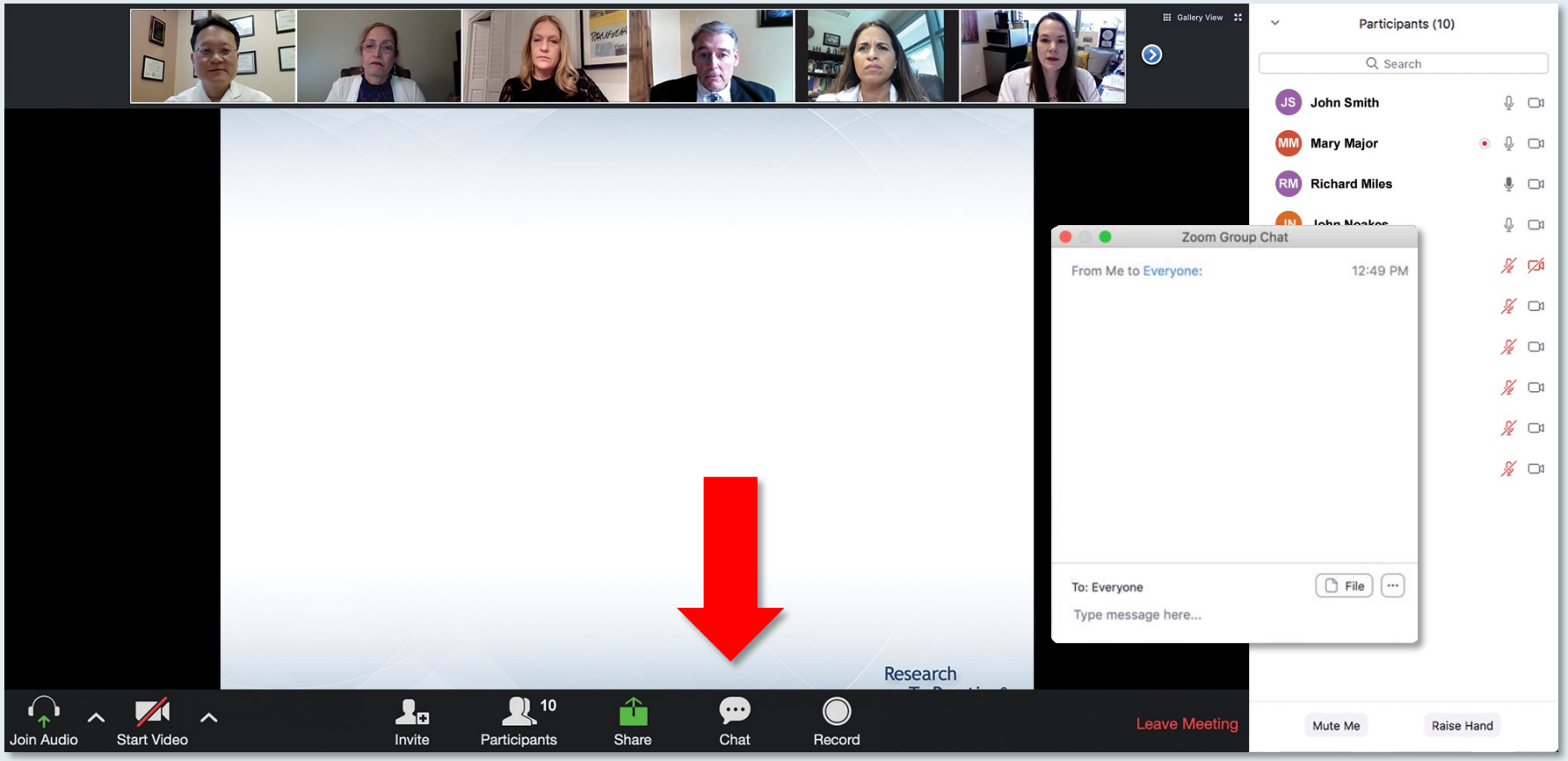
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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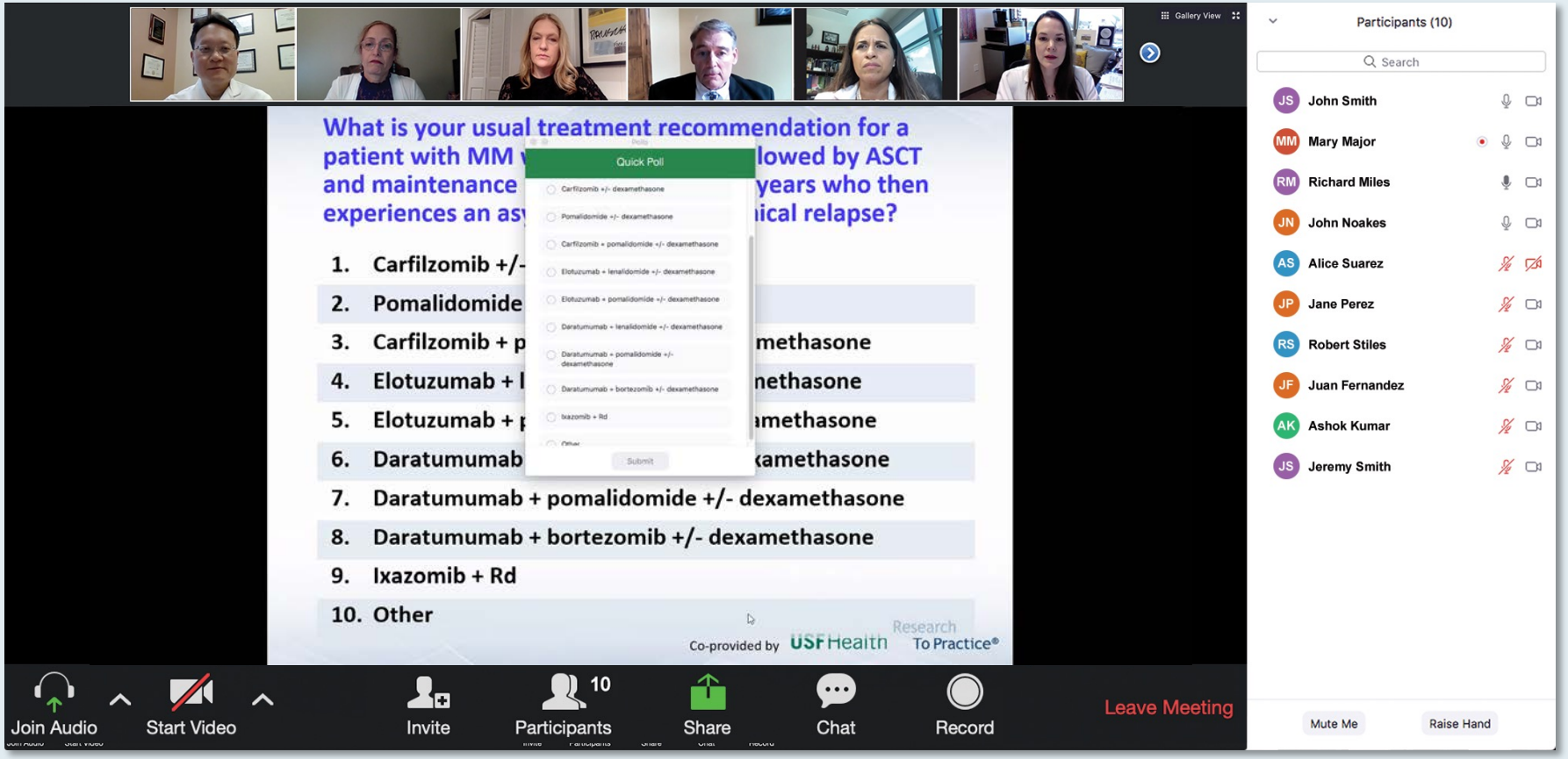
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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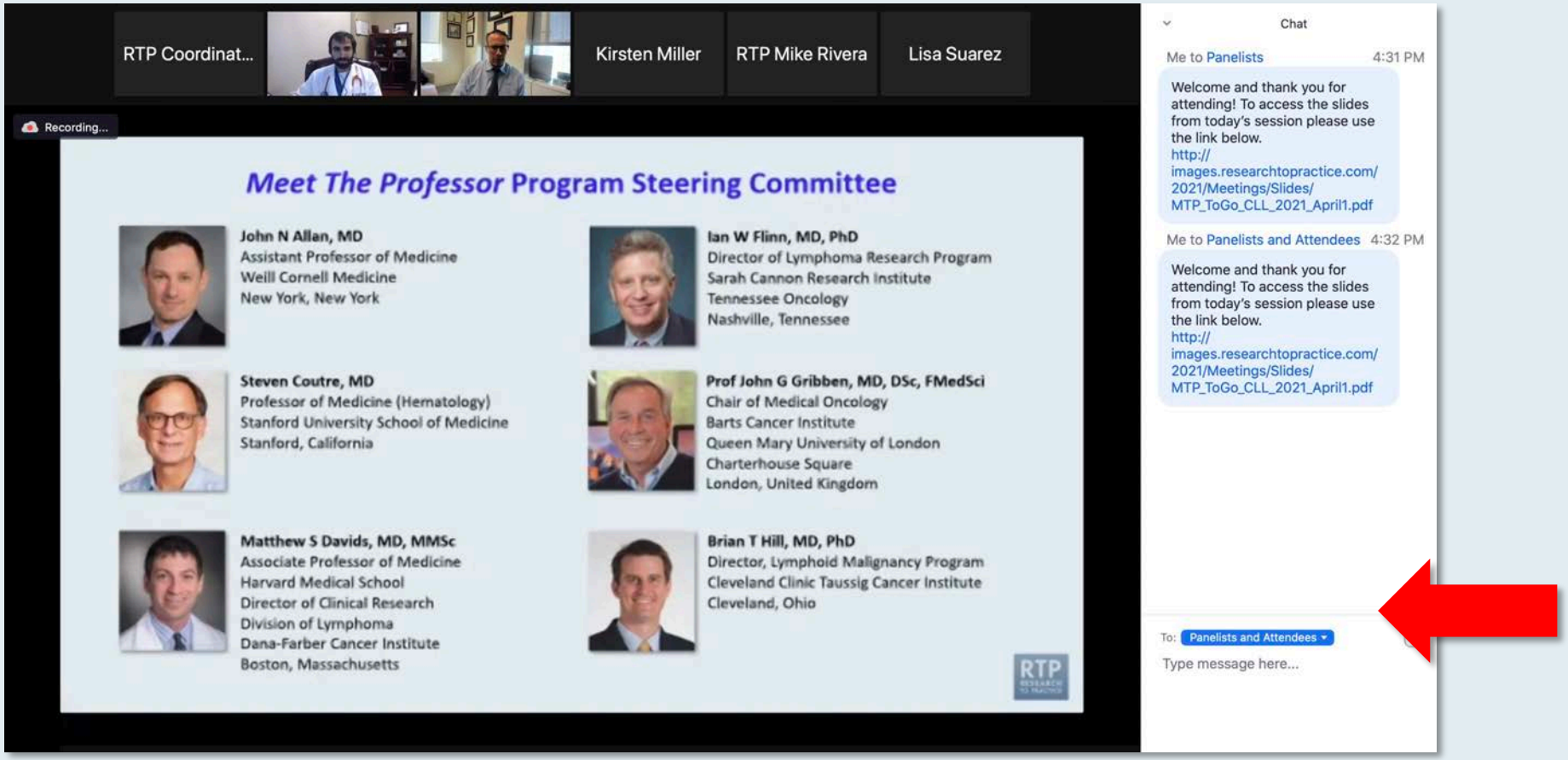
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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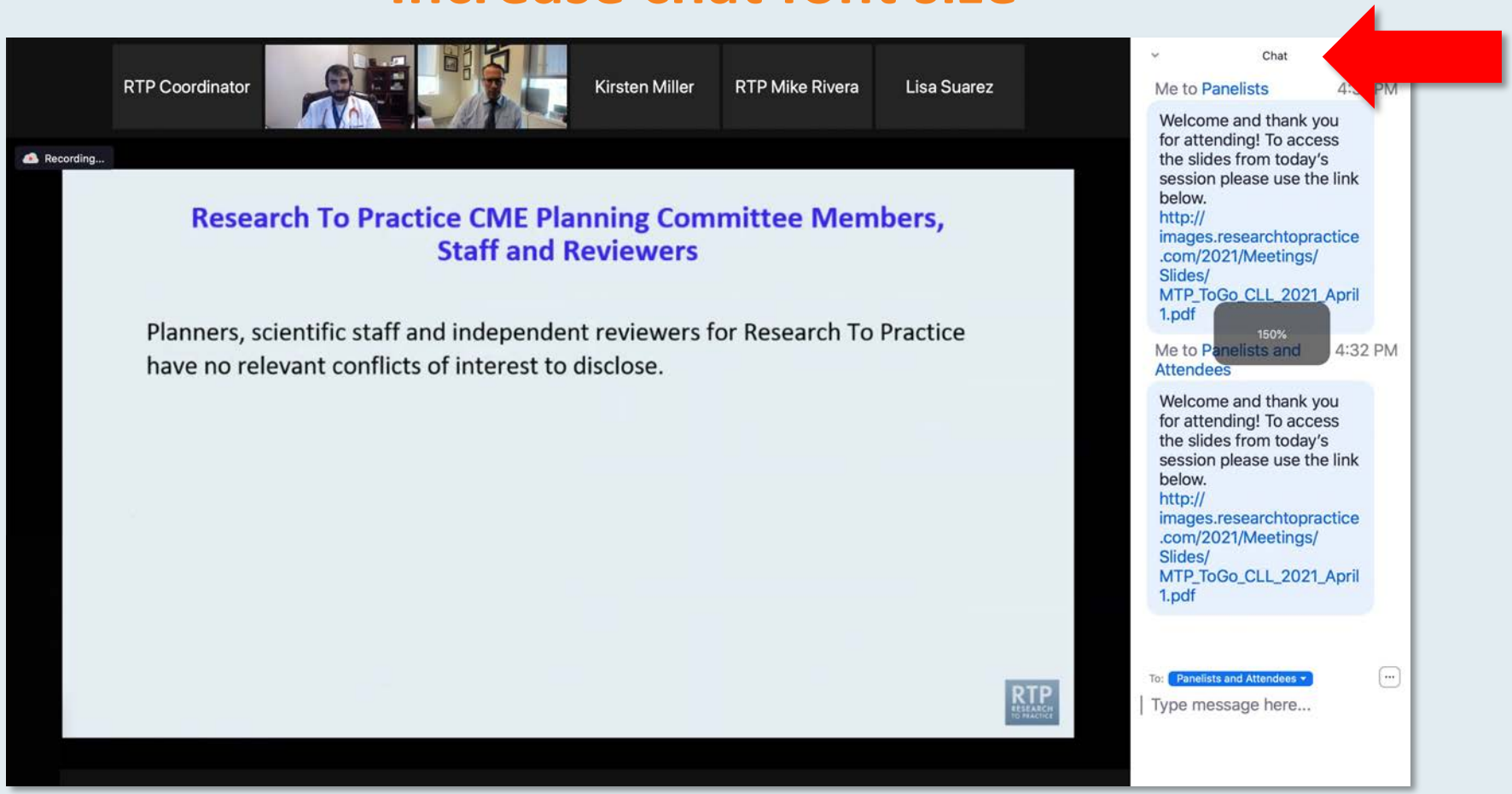
Familiarizing Yourself with the Zoom Interface

Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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WITH DR NEIL LOVE

Management of Localized Non-Small Cell Lung Cancer with EGFR Tumor Mutations

DR ROY HERBST

YALE CANCER CENTER

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Wednesday, August 4
5:00 PM – 6:30 PM ET

Head and Neck Cancer
Wednesday, August 11
5:00 PM – 6:00 PM ET

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Wednesday, July 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Mark Awad, MD, PhD
David R Spigel, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

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Consensus or Controversy? Clinical Investigator Perspectives on the Current and Future Management of Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma

Monday, August 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Stephen M Ansell, MD, PhD
Craig Moskowitz, MD
Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

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Consensus or Controversy? Clinical Investigator Perspectives on the Current and Future Management of Colorectal and Gastroesophageal Cancers

Tuesday, August 3, 2021
5:00 PM – 6:30 PM ET

Faculty

Chloe E Atreya, MD, PhD
Dustin Deming, MD
Eric Van Cutsem, MD, PhD
Zev Wainberg, MD, MSc

Moderator

Neil Love, MD

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Consensus or Controversy? Clinical Investigator Perspectives on the Current and Future Management of Hepatocellular Carcinoma and Pancreatic Cancer

Wednesday, August 4, 2021
5:00 PM – 6:30 PM ET

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Kim A Reiss Binder, MD
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP

Moderator

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Three Exciting Educational Events Held in Conjunction with the 2021 Pan Pacific Lymphoma Conference

In Partnership with the University of Nebraska Medical Center

Expert Second Opinion — Acute Myeloid Leukemia and Myelodysplastic Syndromes

Monday, August 9, 2021
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Eunice S Wang, MD

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Sonali M Smith, MD
Julie M Vose, MD, MBA

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Cases from the Community — Multiple Myeloma

Thursday, August 12, 2021
7:00 PM – 8:30 PM ET

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Joseph Mikhael, MD
Nina Shah, MD

Moderator
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Meet The Professor

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

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.

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Research To Practice
Miami, Florida

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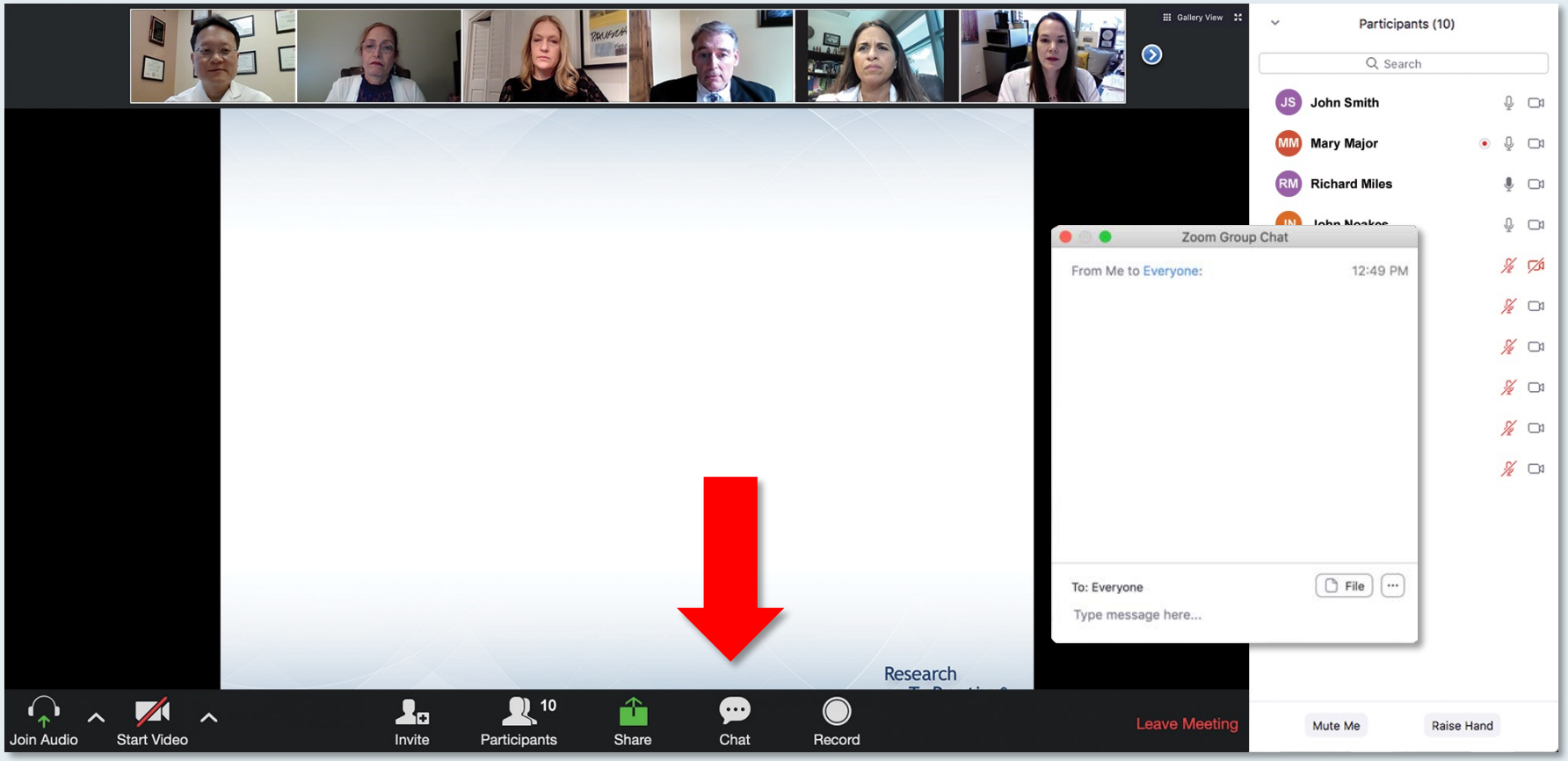

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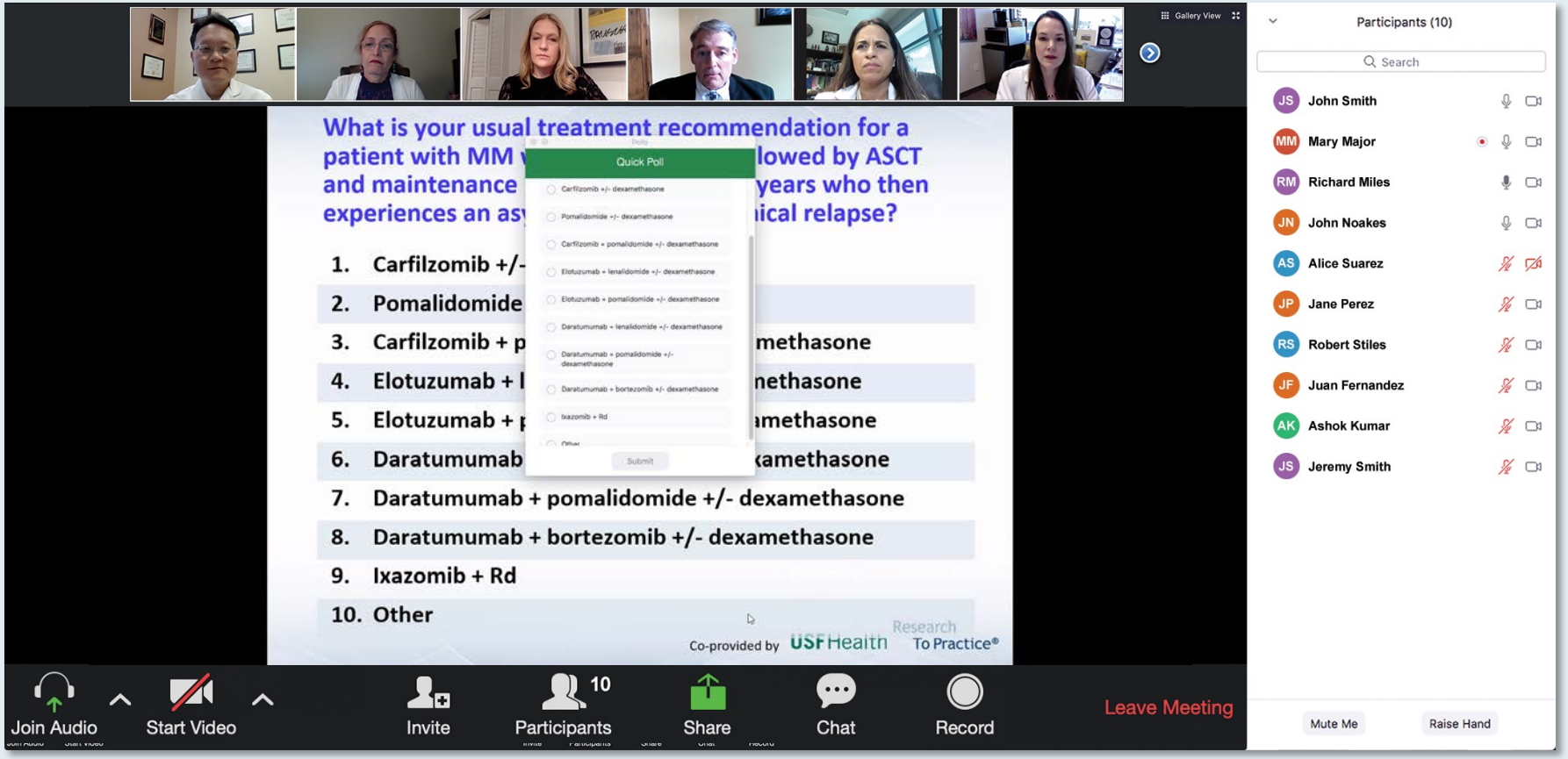

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ASCO 2021 Targeted Therapies for Non-Small Cell Lung Cancer Presentation Library

Key Data Guiding the Management of Localized and Metastatic EGFR Mutation-Positive NSCLC

Zofia Piotrowska, MD, MHS

Download Slides

Research Advances Shaping the Current and Future Treatment of NSCLC with ALK and ROS1 Rearrangements

Professor Solange Peters, MD, PhD

Download Slides

Optimal Therapeutic Approaches for Patients with Genomic Aberrations Beyond EGFR, ALK and ROS1

Gregory J Riely, MD, PhD

Download Slides

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Contributing Oncologists

Gigi Chen, MD
Diablo Valley Oncology and Hematology Medical Group
Pleasant Hill, California

Sulfi Ibrahim, MD
Hematology/Oncology
Reid Health
Richmond, Indiana

Margaret Deutsch, MD
Duke Raleigh Cancer Center Raleigh
Raleigh, North Carolina

Raymond Lobins, DO
Hematology/Oncology
Lake County University Hospitals
Mentor, Ohio

Maria Regina Flores, MD
Advent Health Orlando
Orlando Regional Hospital
HCA Oviedo Medical Center
UCF Lake Nona
Orlando, Florida

Mohamed K Mohamed, MD, PhD
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina

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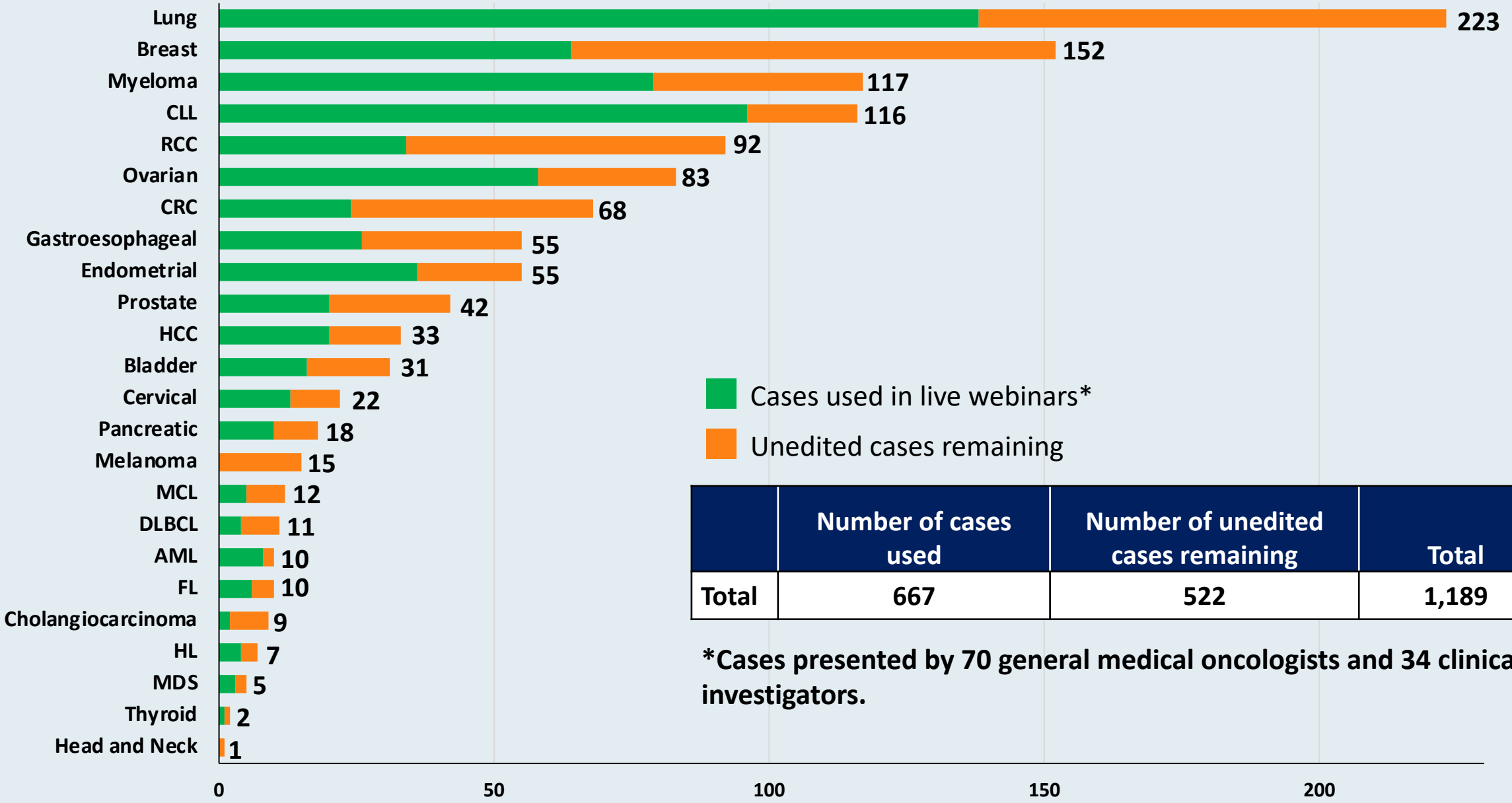

	Number of cases used	Number of unedited cases remaining	Total
Total	667	522	1,189

***Cases presented by 70 general medical oncologists and 34 clinical investigators.**

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Agenda

Introduction: Targeted Treatment in the Adjuvant Setting

Module 1: Current and Future Treatment of NSCLC with ALK and ROS1 Rearrangements

- Dr Deutsch: A 67-year-old man with metastatic adenosquamous carcinoma of the lung – PD-L1 >95%, ROS1 rearrangement
- Dr Lobins: A 74-year-old woman with metastatic adenocarcinoma of the lung and cancer in the right breast – TMB 14 mut/Mb, ALK mutation
- Key relevant data sets

Module 2: Management Strategies for Patients with NSCLC with RET Fusions or MET Alterations

- Dr Mohamed: A 63-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 0%, RET KIF5B fusion
- Key relevant data sets

Module 3: Key Data Guiding the Management of Metastatic NSCLC with EGFR Mutations

- Dr Chen: A 66-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 60%, EGFR exon 19 deletion
- Dr Flores: A 70-year-old man with metastatic NSCLC – EGFR L858R mutation
- Key relevant data sets

Module 4: Therapeutic Approaches for Patients with NSCLC with HER2 or KRAS Mutations

- Dr Lobins: A 62-year-old woman with recurrent metastatic adenocarcinoma of the lung – HER2 mutation
- Dr Ibrahim: A 46-year-old woman with metastatic adenocarcinoma of the lung – KRAS G12C mutation
- Key relevant data sets

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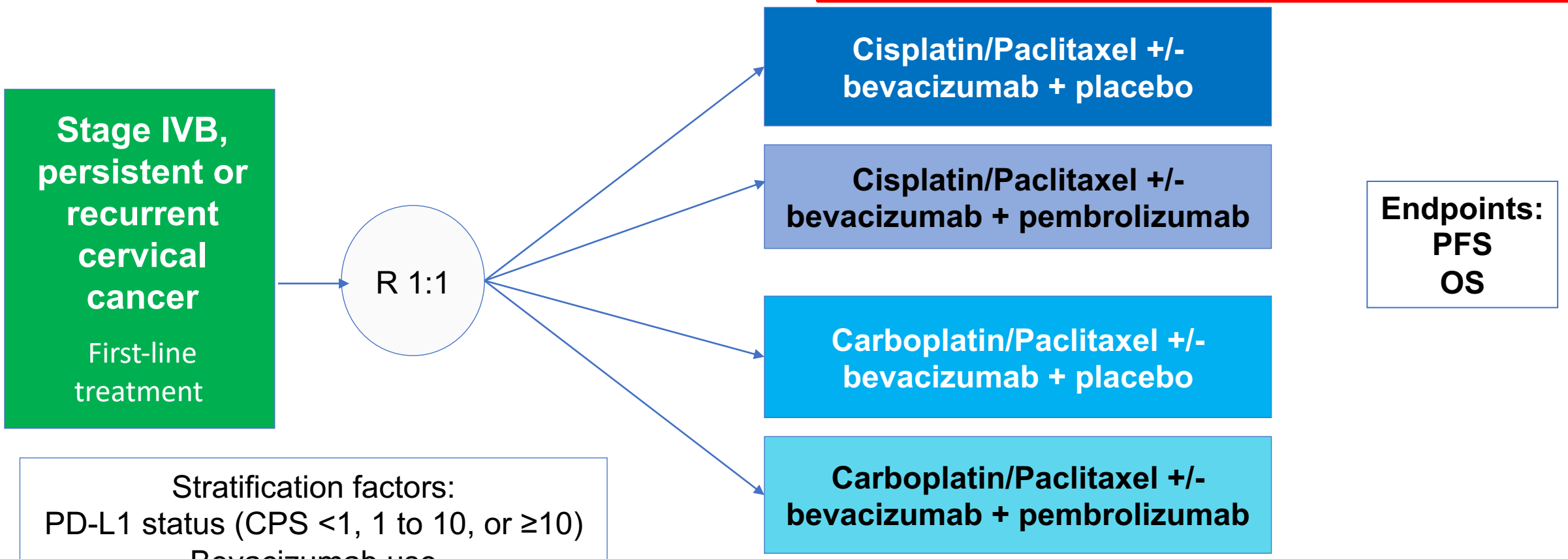
KEYNOTE 826: Schema

Phase 3 KEYNOTE-826

Trial Met Dual Primary Endpoints of Overall Survival (OS) and Progression-Free Survival (PFS) in Patients With Persistent, Recurrent or Metastatic Cervical Cancer June 22, 2021 6:45 am ET



NCT03635567

Shapira-Frommer R. ASCO 2019.

Courtesy of Angeles Alvarez Secord, MD, MHSc

Agenda

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Hi Dr Love,

If time allows, I wanted to see if we can get opinion from the panel about the following case this evening. I just saw her this morning. Sorry for the short notice.

60 yr old Caucasian lady, 40py h/o smoking presented with solitary RLL lung lesion (27x24mm), bx proven adeno, PET neg elsewhere, pt underwent lobectomy and MLND, Path showed T2a (visc pleural inv), N0 margins neg adeno.

Surgeon noticed small pleural nodule during the surgery (separate/not attached to the primary mass), path from that 2mm pleural nodule showed adeno ca, similar histology.

So, by definition Stage IVA NED. EGFR-mutated (exon 21 L858R); PDL1 5-10%; rest of the panel negative. She is now recovering from surgery. NED otherwise.

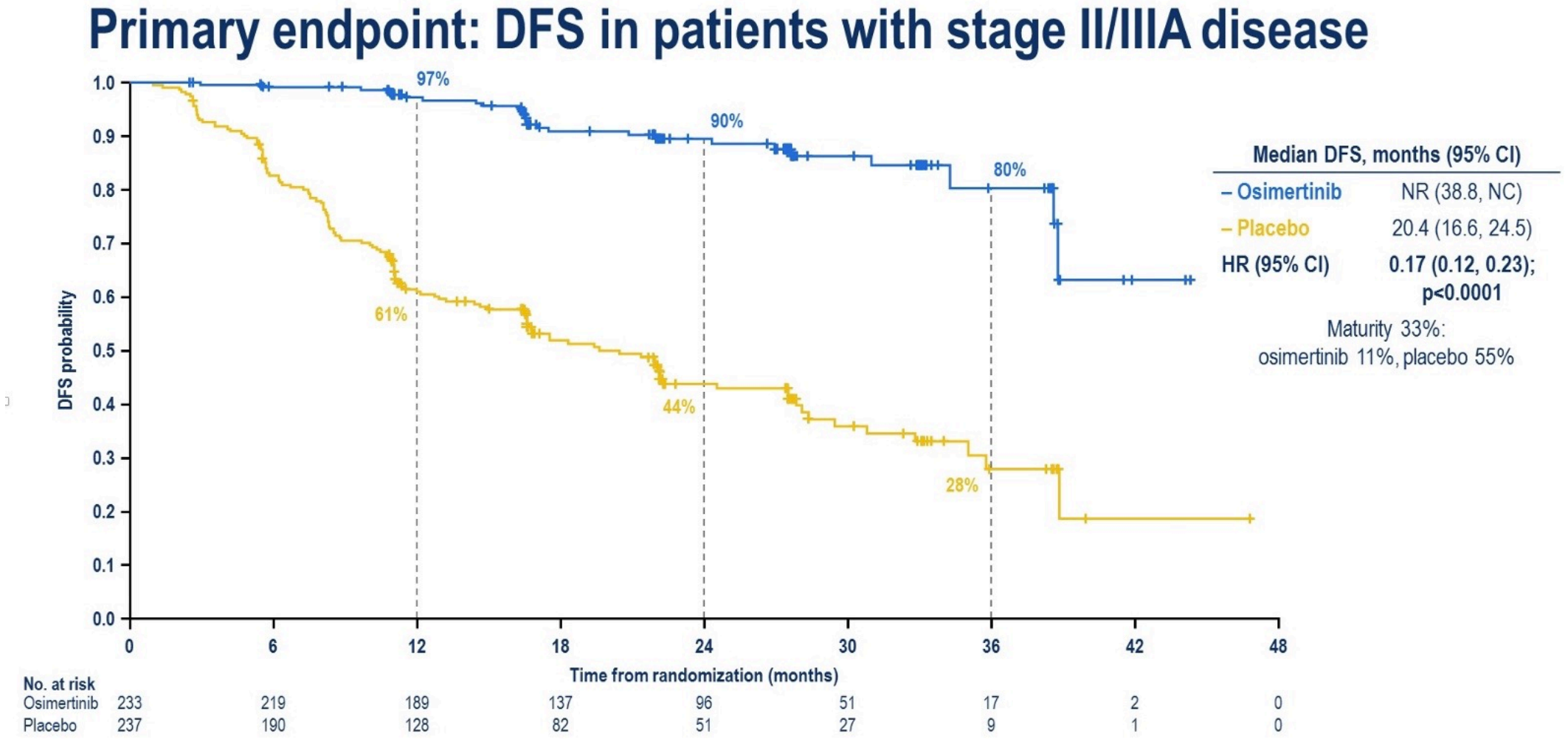
Questions:

- Role of systemic therapy now or later – Osimertinib – if so the duration of osimertinib?
- Long term as long as she tolerates and remain ds free (as it is stage IV) or any specific duration?

Thank you very much!

Padma Mallidi

ADAURA:
Adjuvant Osimertinib in Resected Stage IB-IIIA EGFR+ NSCLC



Courtesy of Zofia Piotrowska, MD, MHS

Herbst R et al. ASCO 2020; Wu TL et al. NEJM 2020

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

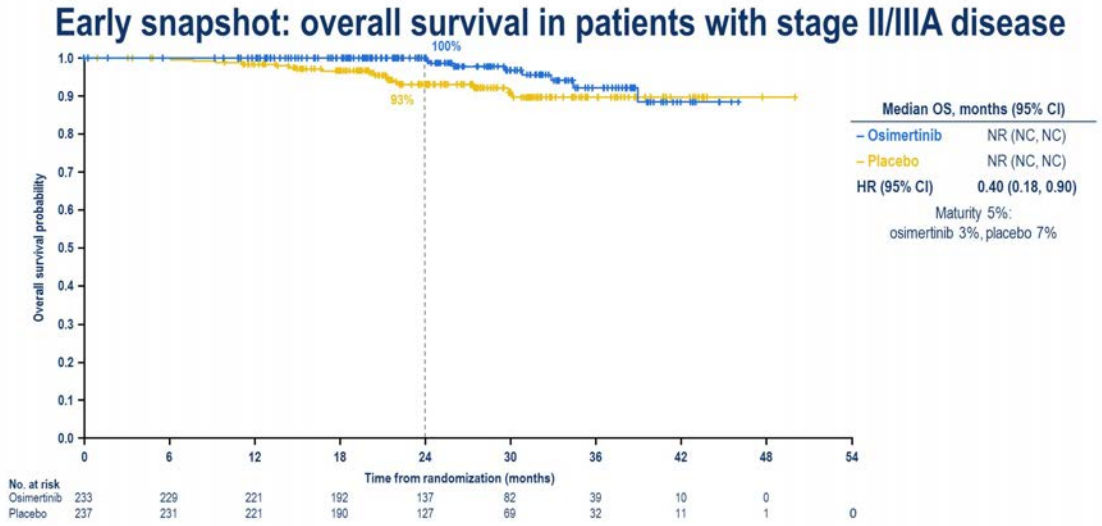
ADAURA:
Adjuvant Osimertinib in Resected Stage IB-IIIA EGFR+ NSCLC

DFS by stage

	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	**0.50 (0.25, 0.96)**	**0.17 (0.08, 0.31)**	**0.12 (0.07, 0.20)**

- In the osimertinib arm, 2 year DFS rates were consistent across stages IB, II, and IIIA disease
- Maturity (overall population: stage IB / II / IIIA) 29%: osimertinib events 12%, placebo events 46%

DFS benefit increases consistently with stage



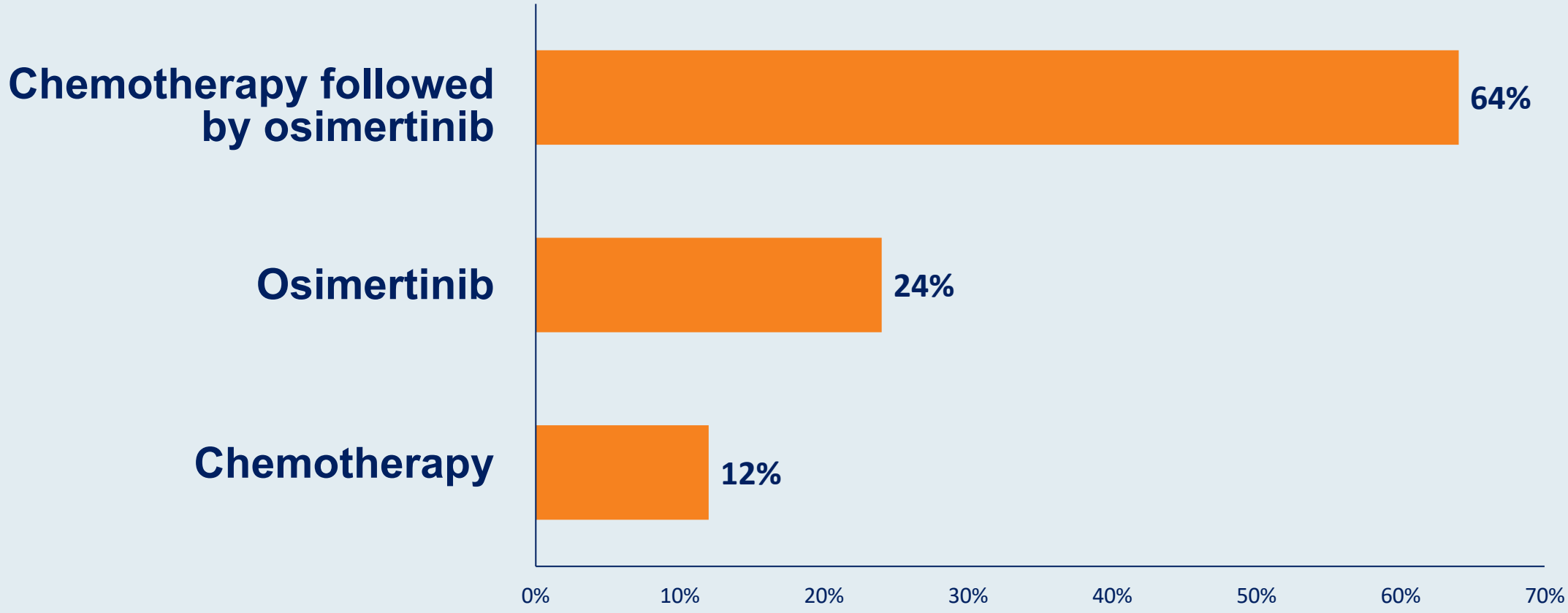
***OS remains very immature (5% maturity)**

Courtesy of Zofia Piotrowska, MD, MHS

Herbst R et al. ASCO 2020; Wu TL et al. NEJM 2020

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Regulatory and reimbursement issues aside, which adjuvant systemic therapy would you generally recommend for a patient with Stage IIB nonsquamous non-small cell lung cancer (NSCLC) and an EGFR exon 19 deletion?



Premeeting survey: July 2021

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 3, 2009 VOL. 361 NO. 10

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

N Engl J Med 2009;361(10):947-57.

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Introduction: Targeted Treatment in the Adjuvant Setting

Module 1: Current and Future Treatment of NSCLC with ALK and ROS1 Rearrangements

- Dr Deutsch: A 67-year-old man with metastatic adenosquamous carcinoma of the lung – PD-L1 >95%, ROS1 rearrangement
- Dr Lobins: A 74-year-old woman with metastatic adenocarcinoma of the lung and cancer in the right breast – TMB 14 mut/Mb, ALK mutation
- Key relevant data sets

Module 2: Management Strategies for Patients with NSCLC with RET Fusions or MET Alterations

- Dr Mohamed: A 63-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 0%, RET KIF5B fusion
- Key relevant data sets

Module 3: Key Data Guiding the Management of Metastatic NSCLC with EGFR Mutations

- Dr Chen: A 66-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 60%, EGFR exon 19 deletion
- Dr Flores: A 70-year-old man with metastatic NSCLC – EGFR L858R mutation
- Key relevant data sets

Module 4: Therapeutic Approaches for Patients with NSCLC with HER2 or KRAS Mutations

- Dr Lobins: A 62-year-old woman with recurrent metastatic adenocarcinoma of the lung – HER2 mutation
- Dr Ibrahim: A 46-year-old woman with metastatic adenocarcinoma of the lung – KRAS G12C mutation
- Key relevant data sets

Case Presentation – Dr Deutsch: A 67-year-old man with metastatic adenosquamous carcinoma of the lung – PD-L1 >95%, ROS1 rearrangement

Dr Margaret Deutsch

- December 2020: Presented with progressive left chest discomfort and shortness of breath
- PMH: Never-smoker, parents were heavy smokers
- PET: Large left upper lobe mass, left pleural effusion, extensive pleural disease, lymphadenopathy
- Biopsy: Adenocarcinoma, PD-L1 >95%
- Patient anxious for immediate treatment

Case Presentation – Dr Deutsch: A 67-year-old man with metastatic adenosquamous carcinoma of the lung – PD-L1 >95%, ROS1 rearrangement (continued)

Dr Margaret Deutsch

- December 2020: Presented with progressive left chest discomfort and shortness of breath
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- Biopsy: Adenocarcinoma, PD-L1 >95%
- Patient anxious for immediate treatment
- ***Carboplatin/pemetrexed/pembrolizumab initiated***
- ***Genetic analysis results: ROS1 rearrangement***
- ***Plan to administer entrectinib for CNS coverage***

Case Presentation – Dr Lobins: A 74-year-old woman with metastatic adenocarcinoma of the lung and cancer in the right breast – TMB 14 mut/Mb, ALK mutation

Dr Raymond Lobins

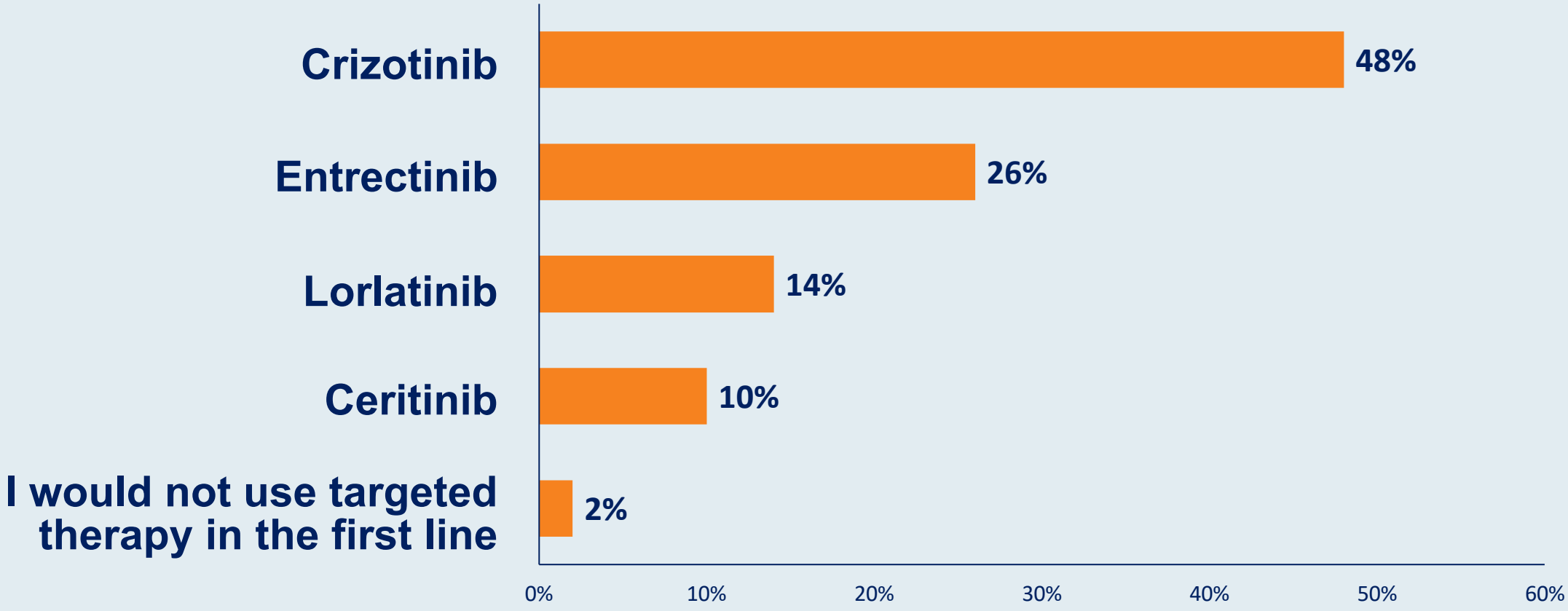
- December 2020: Diagnosed with 3-mm breast cancer in the right breast, lymph node positive
- Workup detects multiple lung nodules that on biopsy are found to be adenocarcinoma (lung primary)
- Molecular studies: ALK mutation, TMB 14 mut/Mb
- AC x 4 → radiation to the breast
- Alectinib also initiated

Questions

- Is there any interaction with alectinib and radiation therapy?
- If she does progress with her breast cancer, is there any data on the use of alectinib for treatment of her lung cancer when I have to use chemotherapy to treat her breast cancer?
- If her lung cancer progresses, which ALK inhibitor would you recommend next?

RTP RESEARCH TO PRACTICE

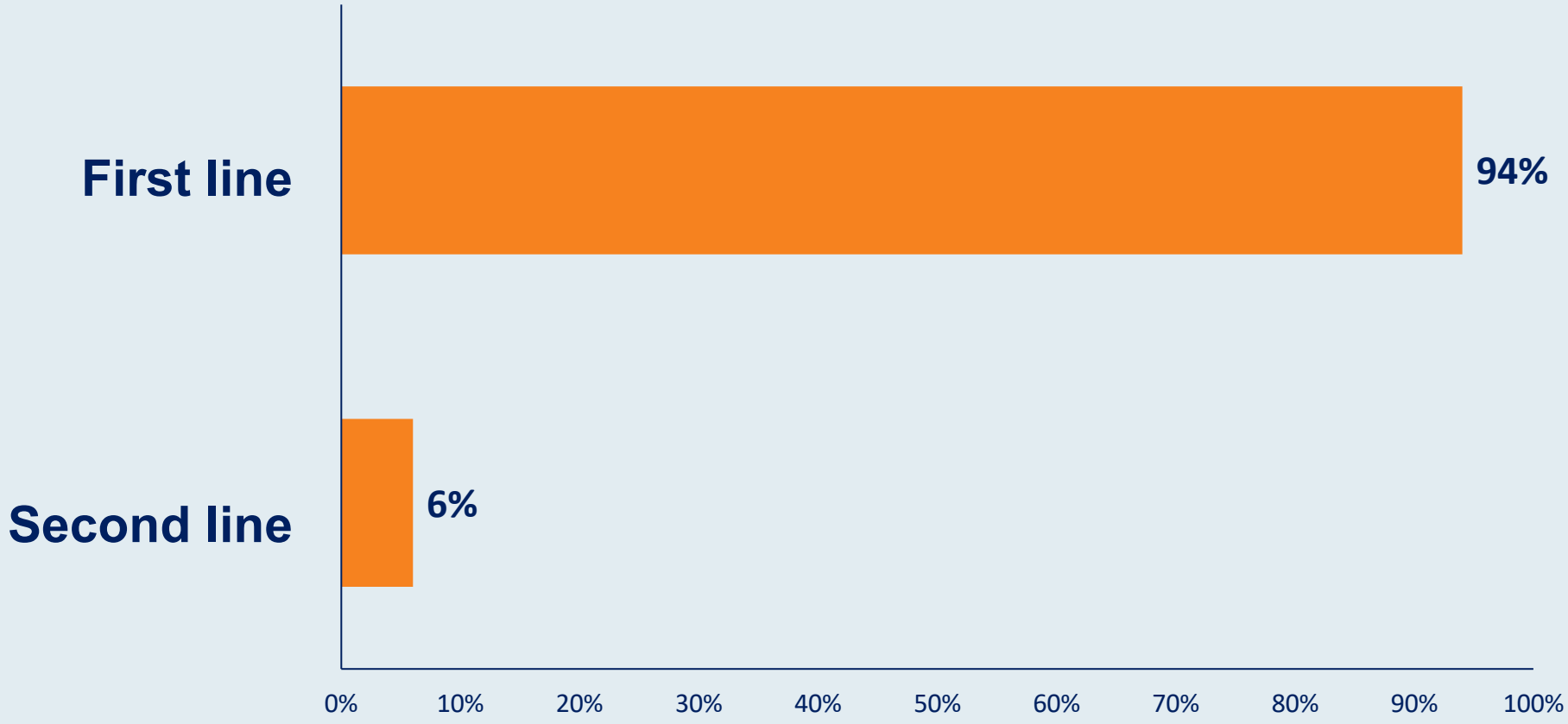
Which of the following targeted treatments are you most likely to use as first-line therapy for metastatic nonsquamous NSCLC with a ROS1 rearrangement?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

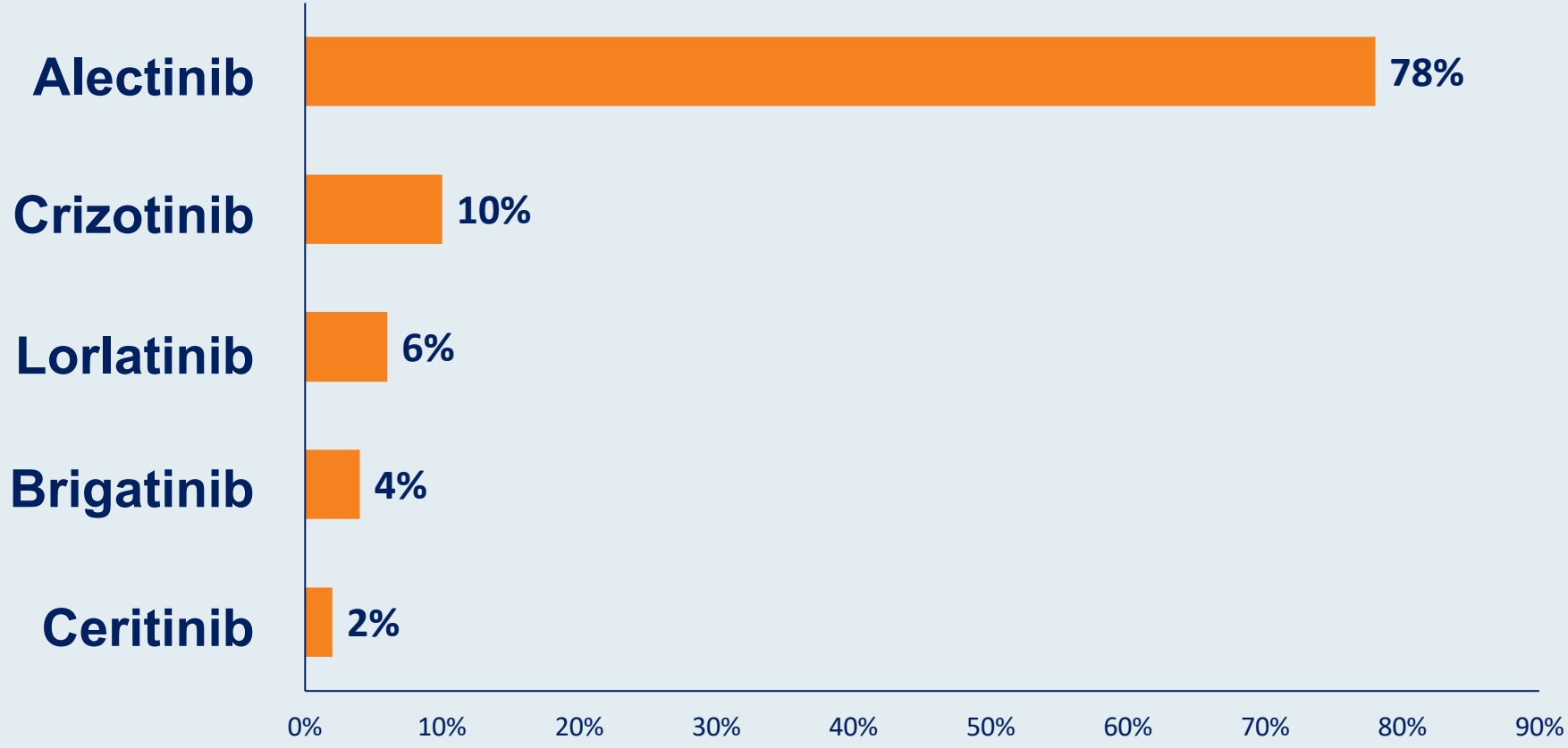
For a patient with newly diagnosed metastatic adenocarcinoma of the lung with a ROS1 rearrangement and a PD-L1 tumor proportion score (TPS) of 10%, in which line of therapy would you most likely administer targeted treatment?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

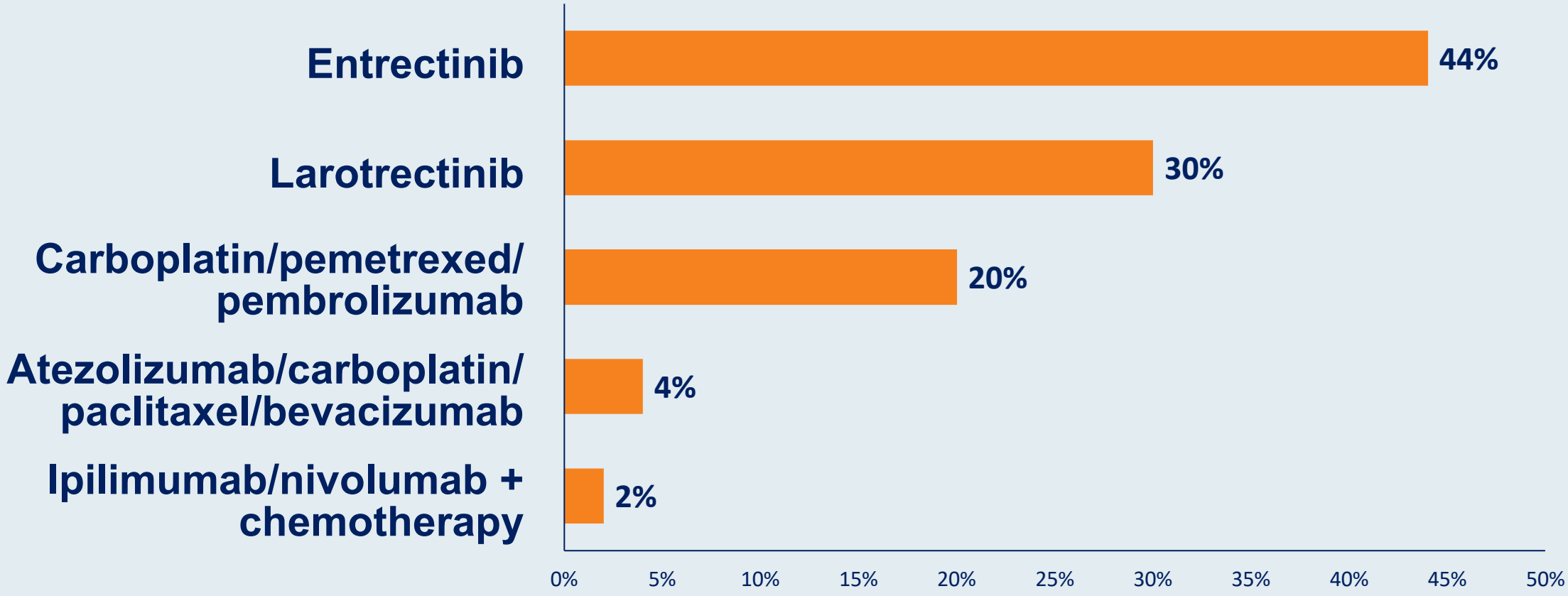
Which of the following ALK inhibitors are you most likely to use as first-line treatment for metastatic nonsquamous NSCLC with an ALK rearrangement?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with metastatic nonsquamous NSCLC with an NTRK gene fusion and a TPS of 10%?



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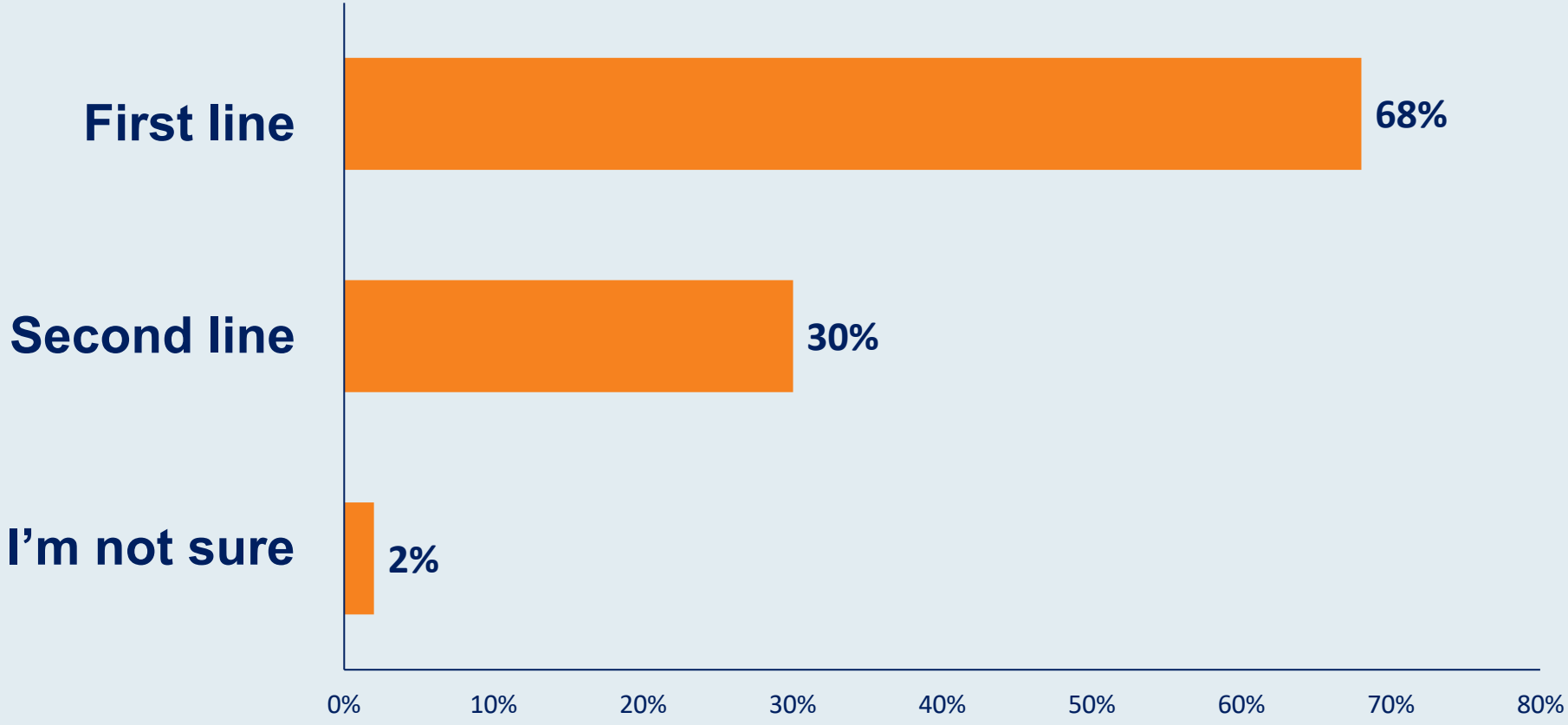
RTP RESEARCH TO PRACTICE

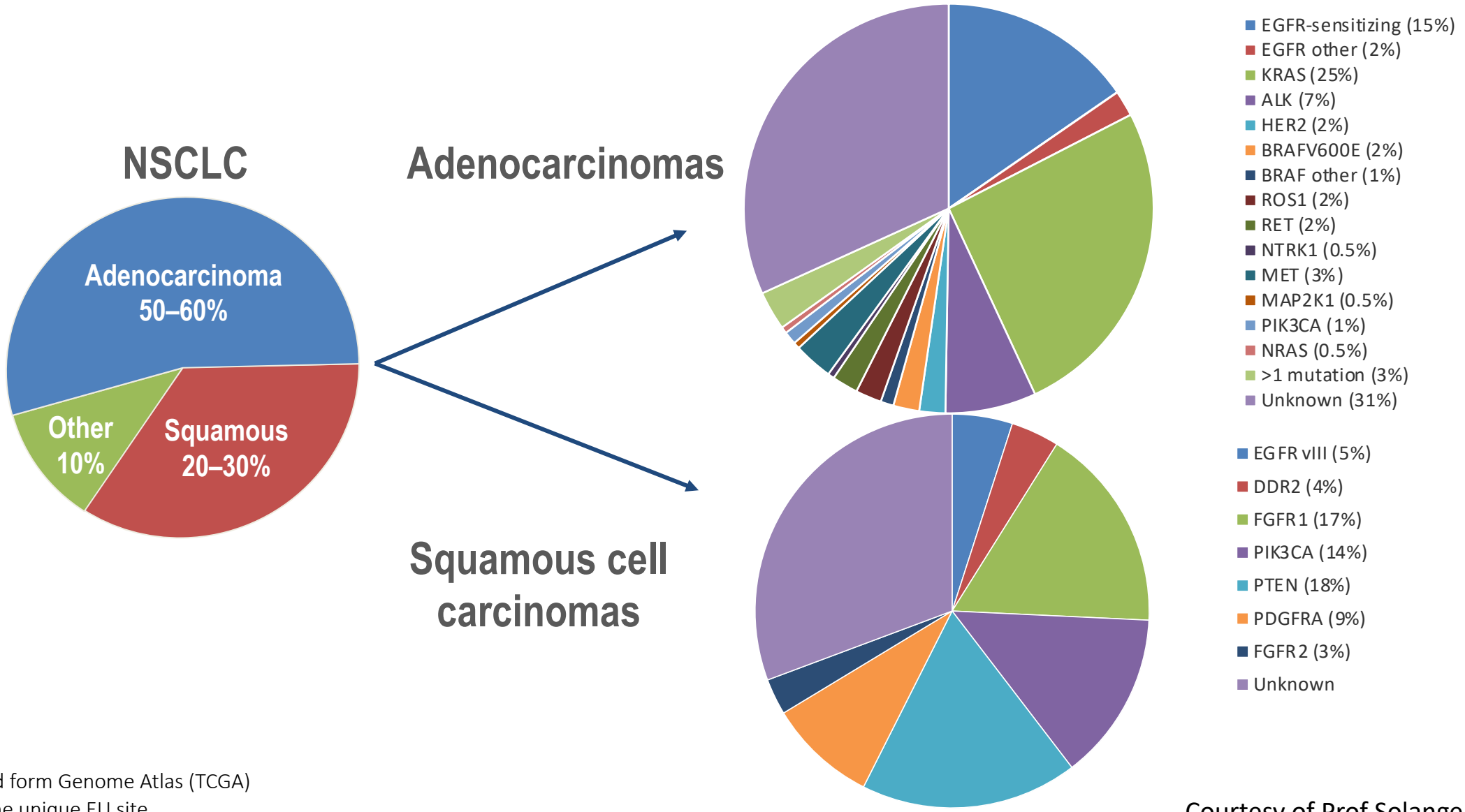
For a patient with metastatic nonsquamous NSCLC with an NTRK gene fusion and a PD-L1 TPS of 10%, in which line of therapy should targeted treatment (eg, larotrectinib, entrectinib) be used?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

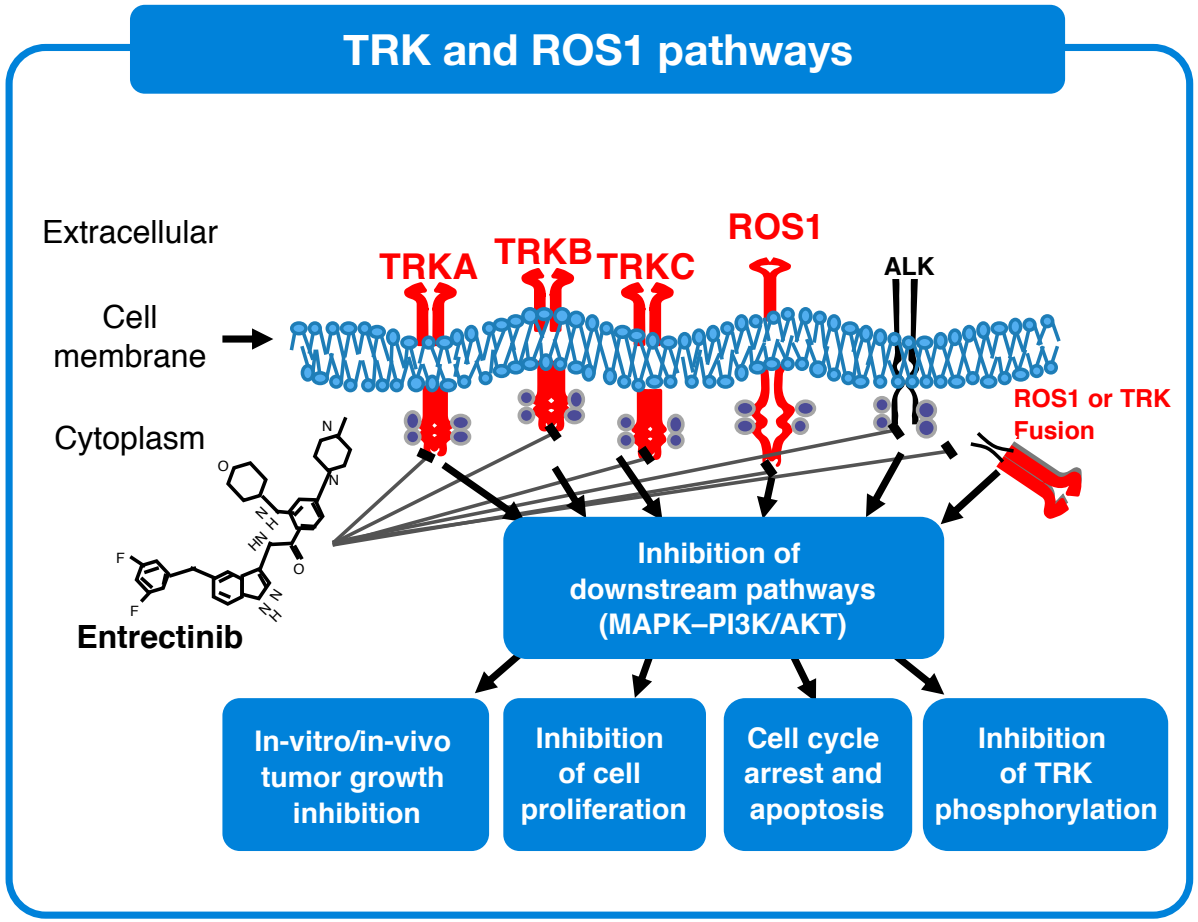
Driver alterations in NSCLC



Adapted form Genome Atlas (TCGA)
Lausanne unique EU site

Courtesy of Prof Solange Peters, MD, PhD

Entrectinib is a potent ROS1 and TRK inhibitor



Target	ROS1	TRKA	TRKB	TRKC
IC_{50} (nM)	0.2	1.7	0.1	0.1

Entrectinib is an oral, potent and selective ROS1/NTRK/ALK tyrosine kinase inhibitor that is CNS active[1,2]

- More potent ROS1 inhibitor than crizotinib in preclinical studies[1]
- Potent pan-TRK inhibitor in clinical development
- Designed to cross the blood–brain barrier and remain within CNS, with demonstrated clinical activity in primary brain tumors and secondary CNS metastases

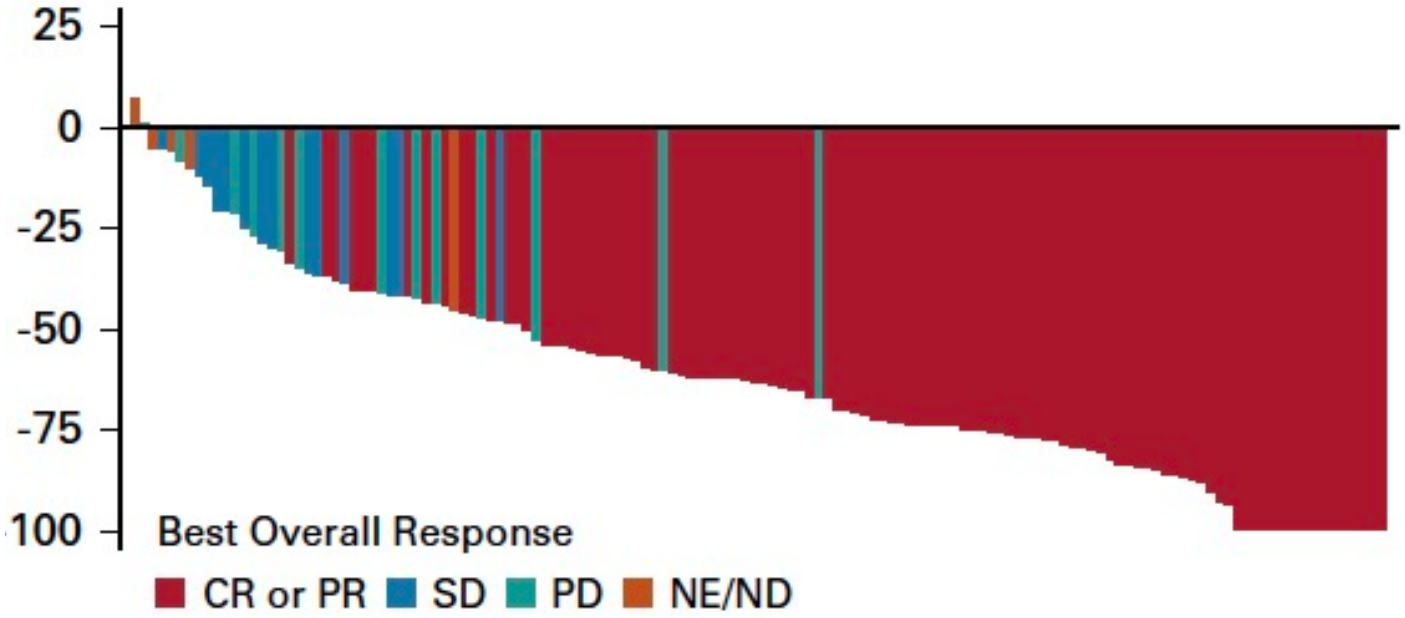
Courtesy of Prof Solange Peters, MD, PhD

Activity of Entrectinib in ROS1 rearranged NSCLC – combined analysis of ALKA-372-001, STARTRK-1, and STARTRK-2 (n=161)

Overall response ITT

ORR = 67.1%

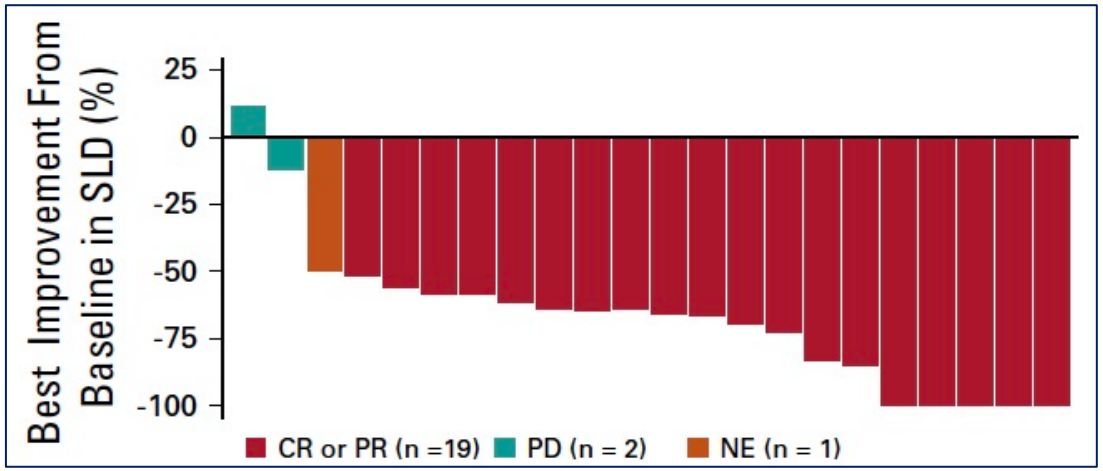
mPFS = 15.7 months



Intracranial Activity

IC ORR: 79.2%

IC PFS: 12 months



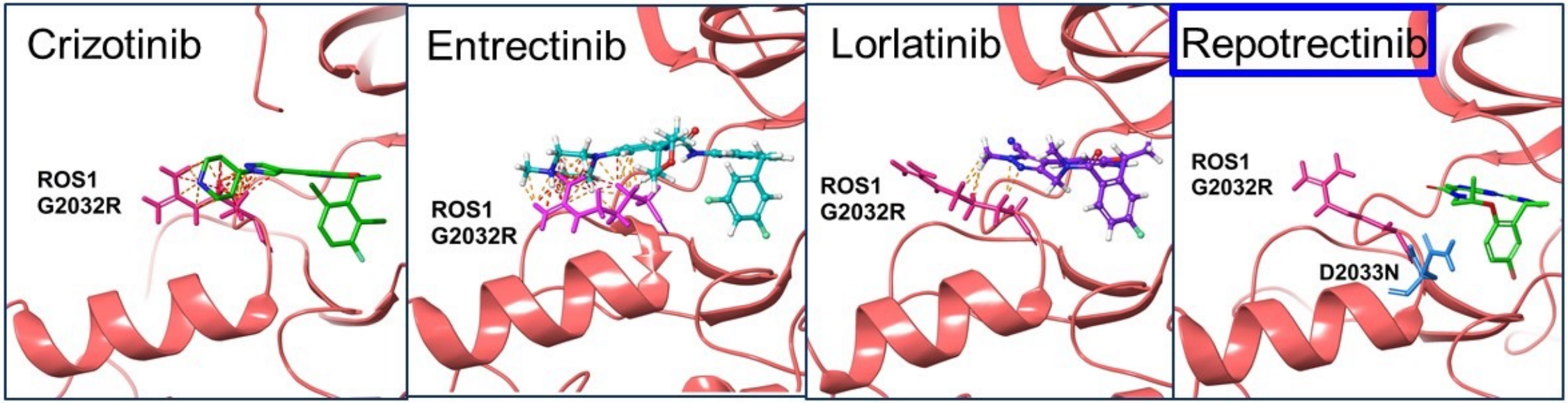
Prior lines of systemic therapy, n (%)[a]	
0	60 (37.3)
1	64 (39.8)
≥ 2	37 (23.0)

No ROS TKI resistance

Courtesy of Prof Solange Peters, MD, PhD

Dzaidziuszko JCO 2021

Repotrectinib is a Small, Rigid Macrocycle Designed to Overcome the *ROS1* G2032R Solvent Front Mutation



CD74-ROS1 Ba/F3 Cell Proliferation IC_{50} (nM)*

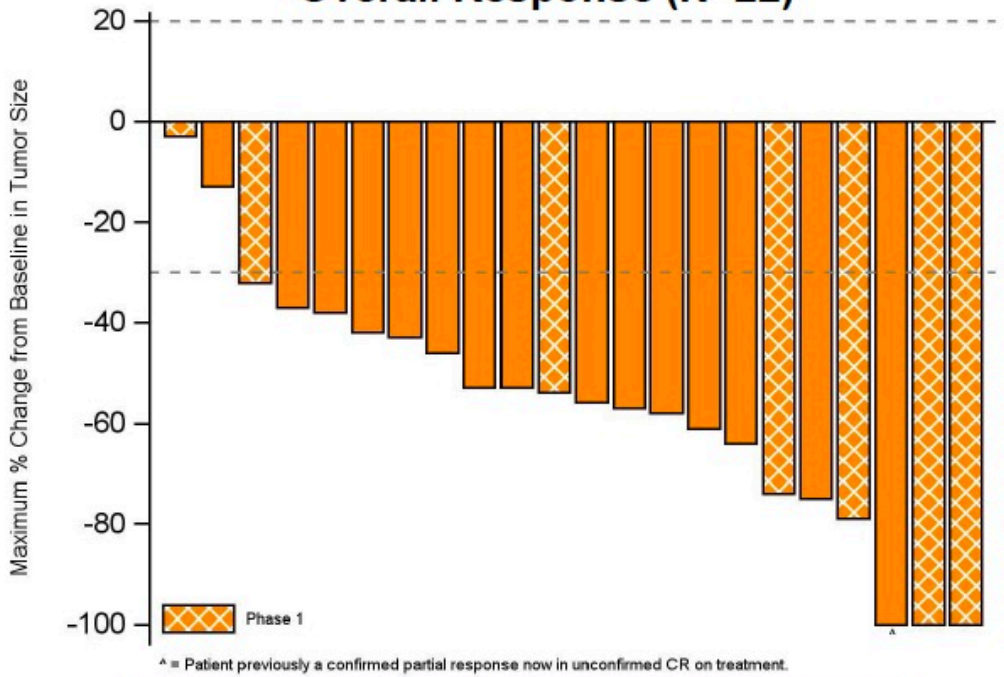
ROS1	Crizotinib	Ceritinib	Cabozantinib	Entrectinib	Lorlatinib	Repotrectinib
WT	14.6	42.8	0.5	10.5	0.2	<0.2
G2032R	266.2	1391	11.3	1813	160.7	3.3

*Data based on evaluation of comparable proxy chemical reagents purchased from commercial sources except repotrectinib

Courtesy of Prof Solange Peters, MD, PhD

Repotrectinib (TPX-0005): Clinical activity in TKI-naïve ROS1+ NSCLC (TRIDENT-1)

Overall Response (N=22)



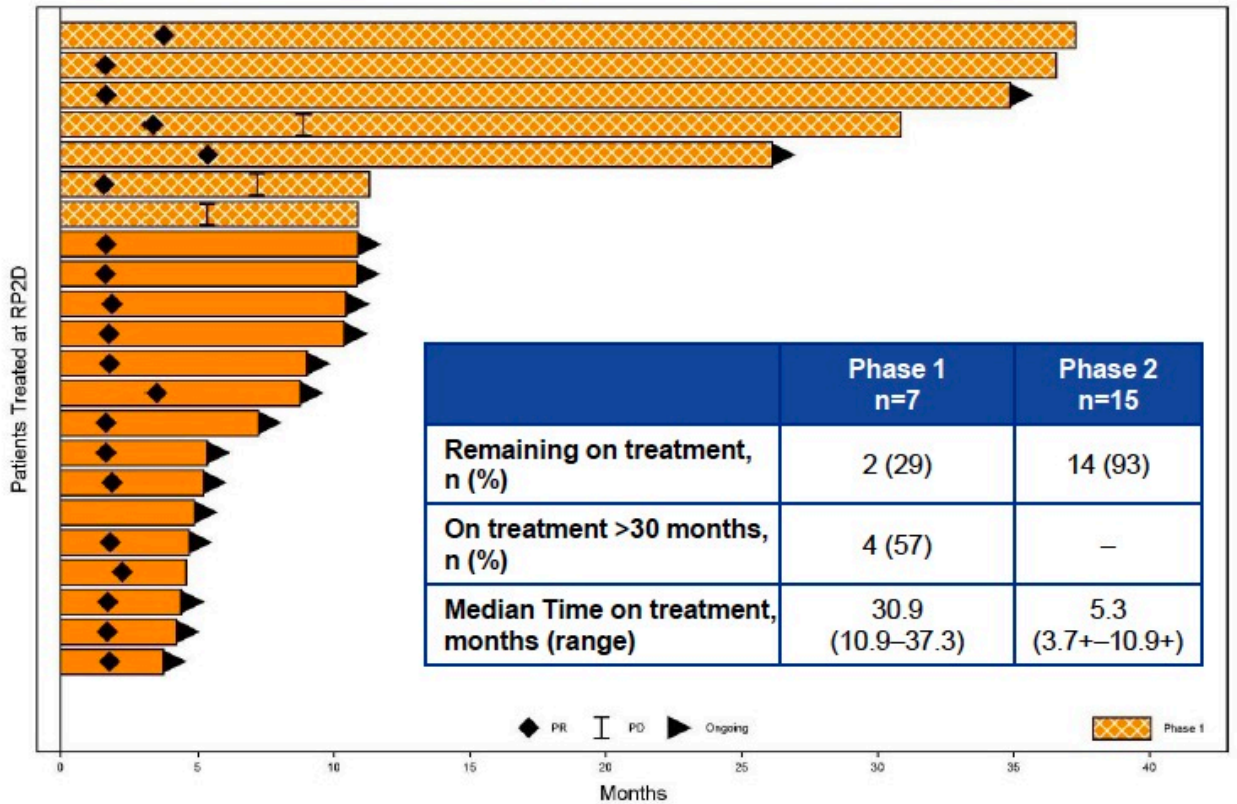
^ = Patient previously a confirmed partial response now in unconfirmed CR on treatment.

	Phase 2 N=15	Phase 1+2 N=22
Confirmed ORR, % (95% CI)	93% (68–100)	91% (71–99)

N=22 patients with baseline and at least two post baseline scans
- *N=15 Phase 2 patients*
- *N=7 Phase 1 patients treated at or above the Phase 2 recommended dose*

As of 31 December 2020, the 16th patient in Phase 2 has an unconfirmed PR and is on treatment awaiting a second post-baseline confirmatory scan.

Duration of Treatment (N=22)



	Phase 1 n=7	Phase 2 n=15
Remaining on treatment, n (%)	2 (29)	14 (93)
On treatment >30 months, n (%)	4 (57)	–
Median Time on treatment, months (range)	30.9 (10.9–37.3)	5.3 (3.7+–10.9+)

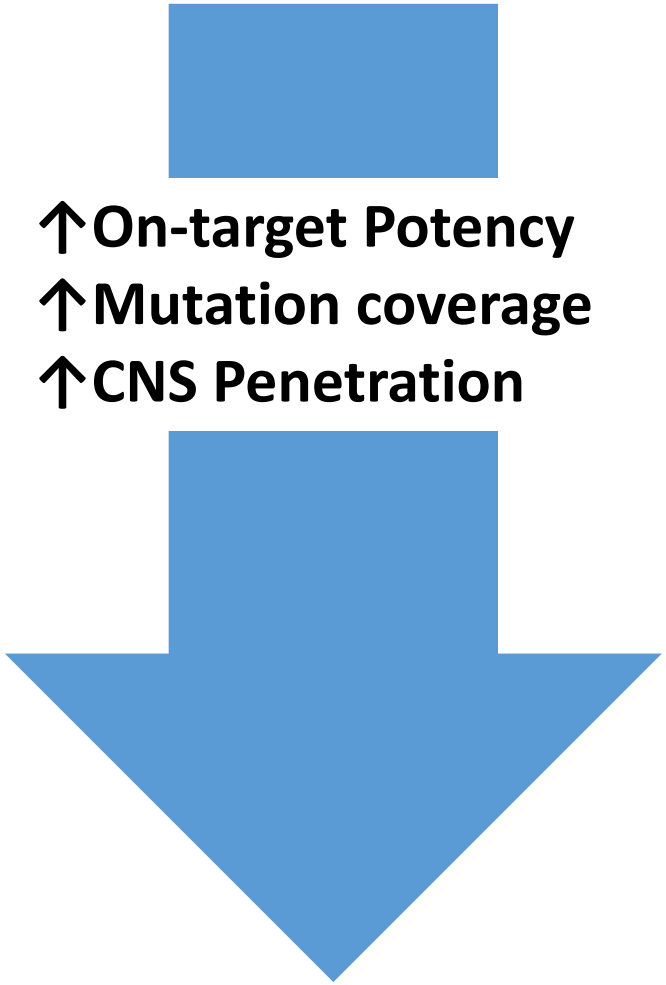
†Includes patients with a baseline and at least two post-baseline scans; Phase 1 data includes only patients treated at or above repotrectinib RP2D.
PD, progressive disease; PR, partial response; RP2D, recommended Phase 2 dose

Equivalent brain activity

Cho BC et al., WCLC 2020

Courtesy of Prof Solange Peters, MD, PhD

Landscape of ALK inhibitors in clinical use



ALK TKI		STATUS
1st generation	Crizotinib	▪ FDA-approved, EMA-approved
2nd generation	Ceritinib	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Alectinb	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Brigatinib	▪ FDA / EMA approved, post crizotinib ▪ FDA / EMA approved, first line
	Ensartinib	▪ *Investigational*
3rd generation	Lorlatinib	▪ FDA / EMA approved, in patients who have received 1 or more ALK inhibitors

Courtesy of Prof Solange Peters, MD, PhD

Currently approved first-line treatments for advanced *ALK*+ NSCLC

Key trial: PROFILE 1014[1]
FDA approval in 1L: Aug 2011
EMA approval in 1L: Nov 2015

mPFS 10.9 months[1†]

Key trial: ASCEND-4[2]
FDA approval in 1L: May 2017
EMA approval in 1L: Jun 2017

mPFS 16.6 months[2‡]

Key trial: ALEX[3–5]
FDA approval in 1L: Nov 2017
EMA approval in 1L: Dec 2017

mPFS 34.8 months[5 §]

Key trial: ALTA-1L[6,7]
FDA approval in 1L: May 2020
EMA approval in 1L: Apr 2020

mPFS 29.4 months[7 § ,¶]

1. Solomon, et al. N Engl J Med 2014
2. Soria, et al. Lancet 2017; 3. Peters, et al. N Engl J Med 2017
4. Camidge, et al. J Thorac Oncol 2019; 5. Mok, et al. Ann Oncol 2020
6. Camidge, et al. N Engl J Med 2018; 7. Camidge, et al. ESMO Asia 2019

†Median PFS by IRC; ‡Median PFS by BIRC; §Median PFS by INV
¶INV-assessed, however the 1° endpoint of ALTA-1L is PFS by BIRC assessment (**24.0 months**)[7]

Courtesy of Prof Solange Peters, MD, PhD

Investigational ALK inhibitors in development and not yet approved for first-line treatment of advanced *ALK*+ NSCLC*

***Lorlatinib received FDA approval as first-line therapy on March 3, 2021**

Lorlatinib

Key trial: CROWN[1]
mPFS not reached

Ensartinib

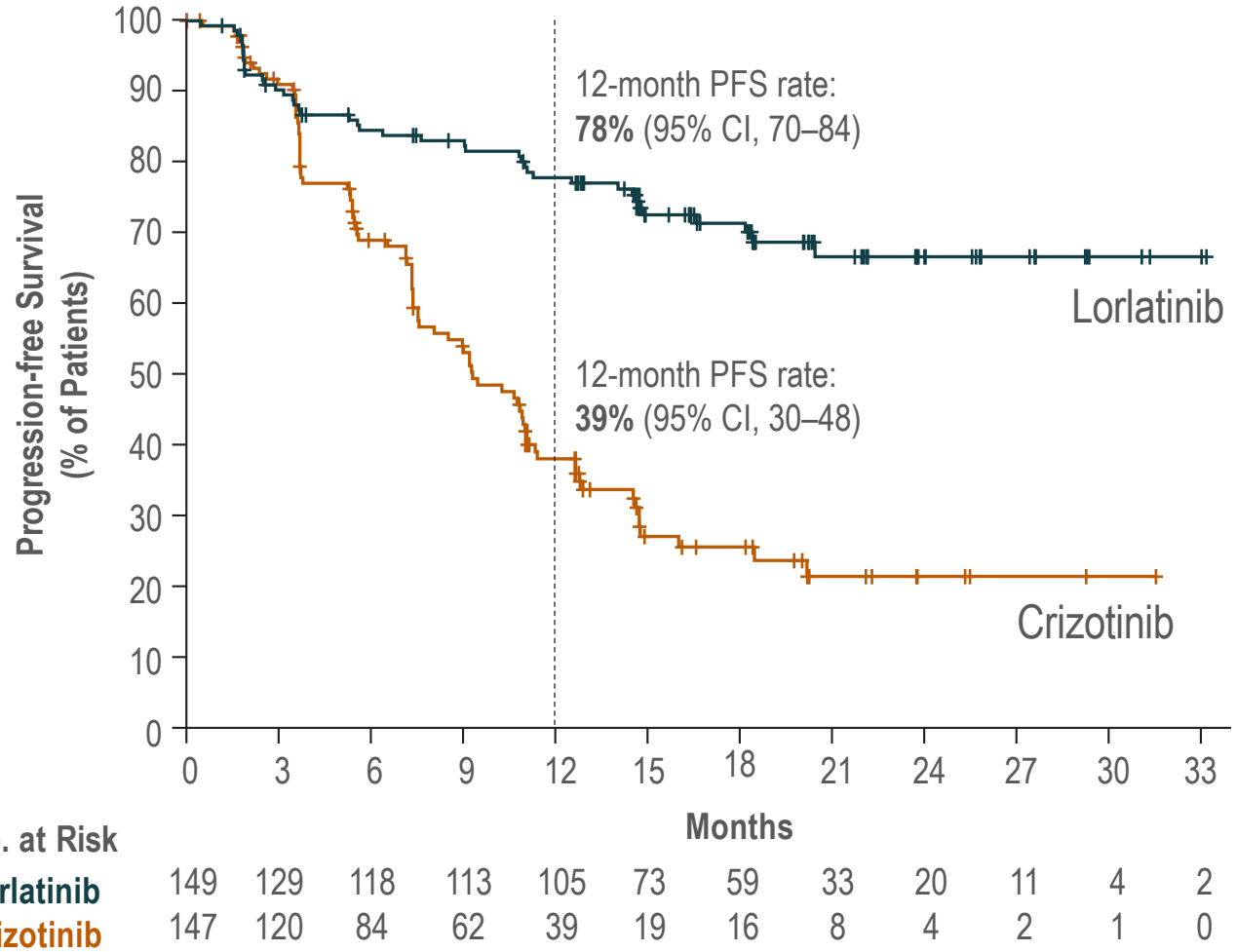
Key trial: eXalt3[2,3]
Investigational
(not yet approved)

ENSARTINIB IS NOT EMA-APPPROVED
LORLATINIB IS NOT EMA-APPPROVED IN FIRST LINE – ONLY IN LATER LINES

1. Shaw, et al. WCLC 2018; 2. Wu, et al. WCLC 2017
3.Horn, et al. WCLC 2020

Courtesy of Prof Solange Peters, MD, PhD

CROWN: Primary Endpoint – PFS by BICR



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	41 (28)	86 (59)
Median PFS, months (95% CI)	NE (NE–NE)	9.3 (7.6-11.1)
HR (95% CI) 1-sided P value*	**0.28** (0.19-0.41) <0.001	

*By stratified log-rank test.

LORLATINIB IS NOT EMA-APPPROVED IN FIRST LINE – ONLY IN LATER LINES

BICR, blinded independent central review; Solomon B, ESMO 2020

Courtesy of Prof Solange Peters, MD, PhD

Agenda

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- Dr Ibrahim: A 46-year-old woman with metastatic adenocarcinoma of the lung – KRAS G12C mutation
- Key relevant data sets

Case Presentation – Dr Mohamed: A 63-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 0%, RET KIF5B fusion

Dr Mohamed Mohamed

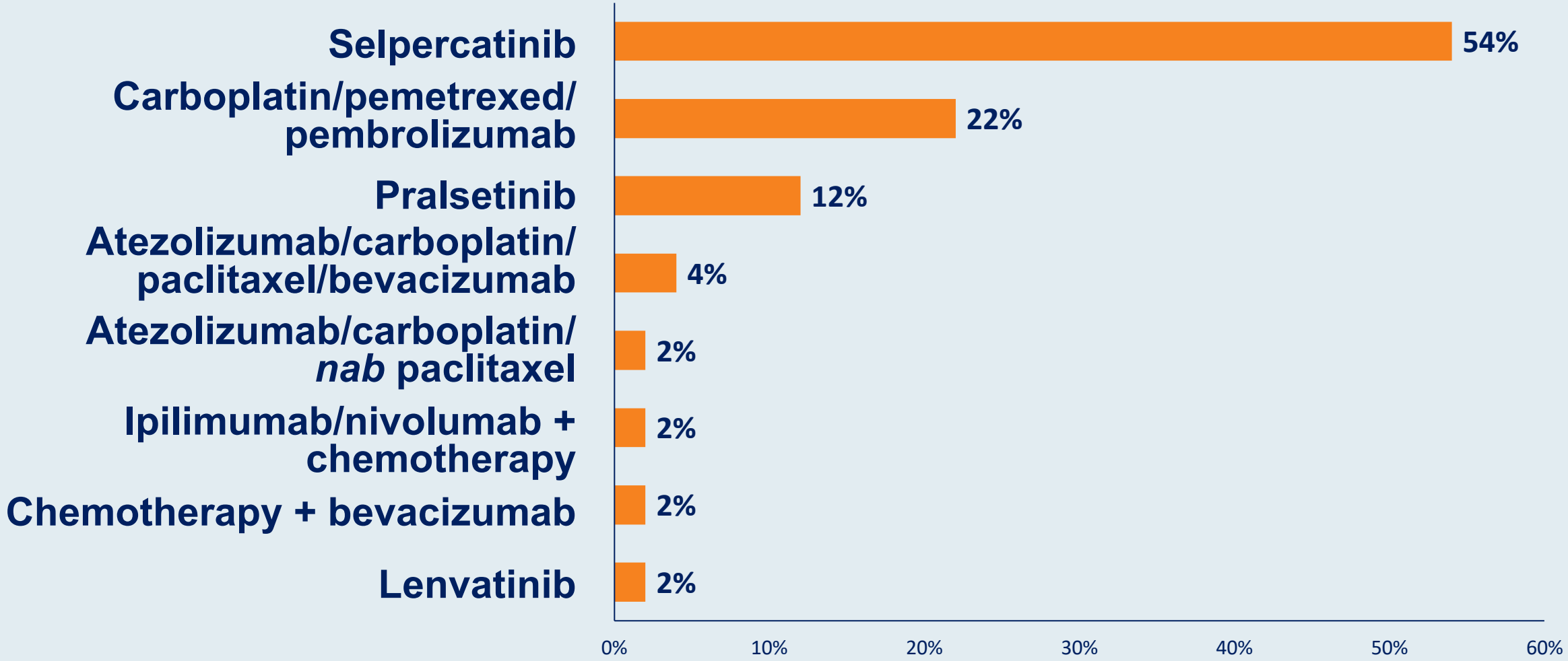
- PMH: Never smoker, rheumatoid arthritis, dyslipidemia
- Presented 3 years ago with chest pressure and tightness in her throat
- Imaging: Left upper lobe lung mass abutting the mediastinum and anterior chest wall, mediastinal lymphadenopathy, bone and solitary brain metastases (0.6 cm)
- Molecular studies: PD-L1 0%, RET KIF5B fusion
- Palliative XRT to the LUL mass and SRS to the solitary brain metastasis
- Carboplatin/pemetrexed/bevacizumab x 4 cycles → SD
- Selpercatinib on clinical trial x 3 years, no evidence of progression

Question

- If she progresses on selpercatinib, would pralsetinib be considered as her next treatment option, or would you administer chemotherapy?

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with metastatic nonsquamous NSCLC with a RET rearrangement and a TPS of 10%?



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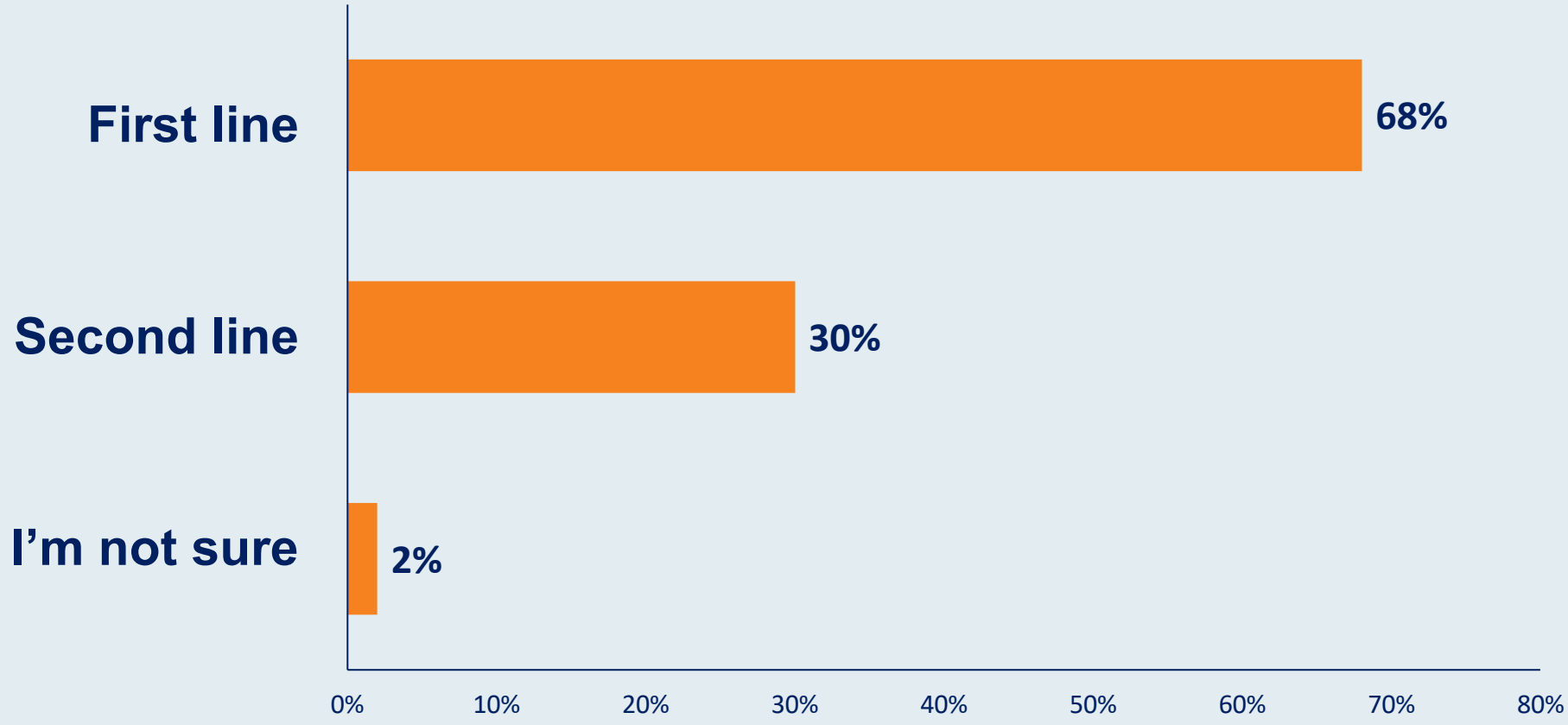
RTP RESEARCH TO PRACTICE

For a patient with metastatic nonsquamous NSCLC with a RET rearrangement and a PD-L1 TPS of 10%, in which line of therapy should targeted treatment (eg, selpercatinib, pralsetinib) be used?



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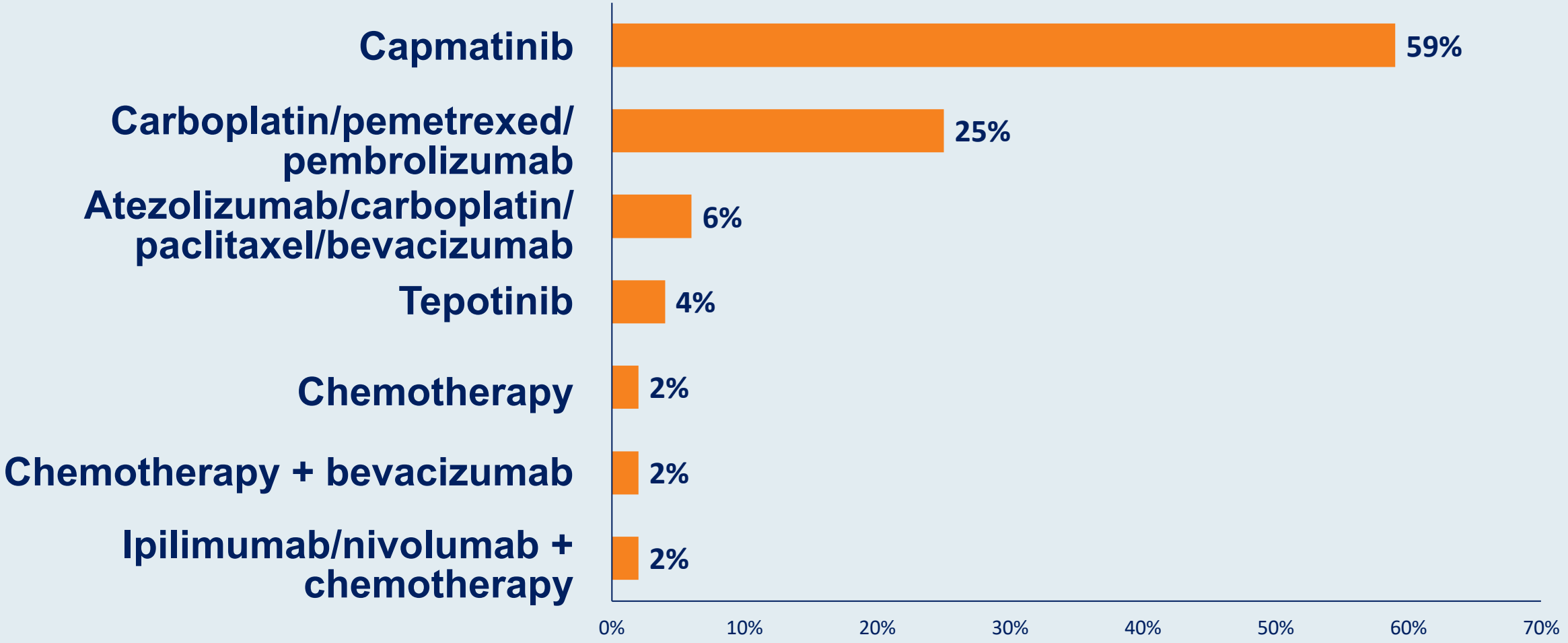
RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with metastatic nonsquamous NSCLC with a MET exon 14 skipping mutation and a TPS of 10%?



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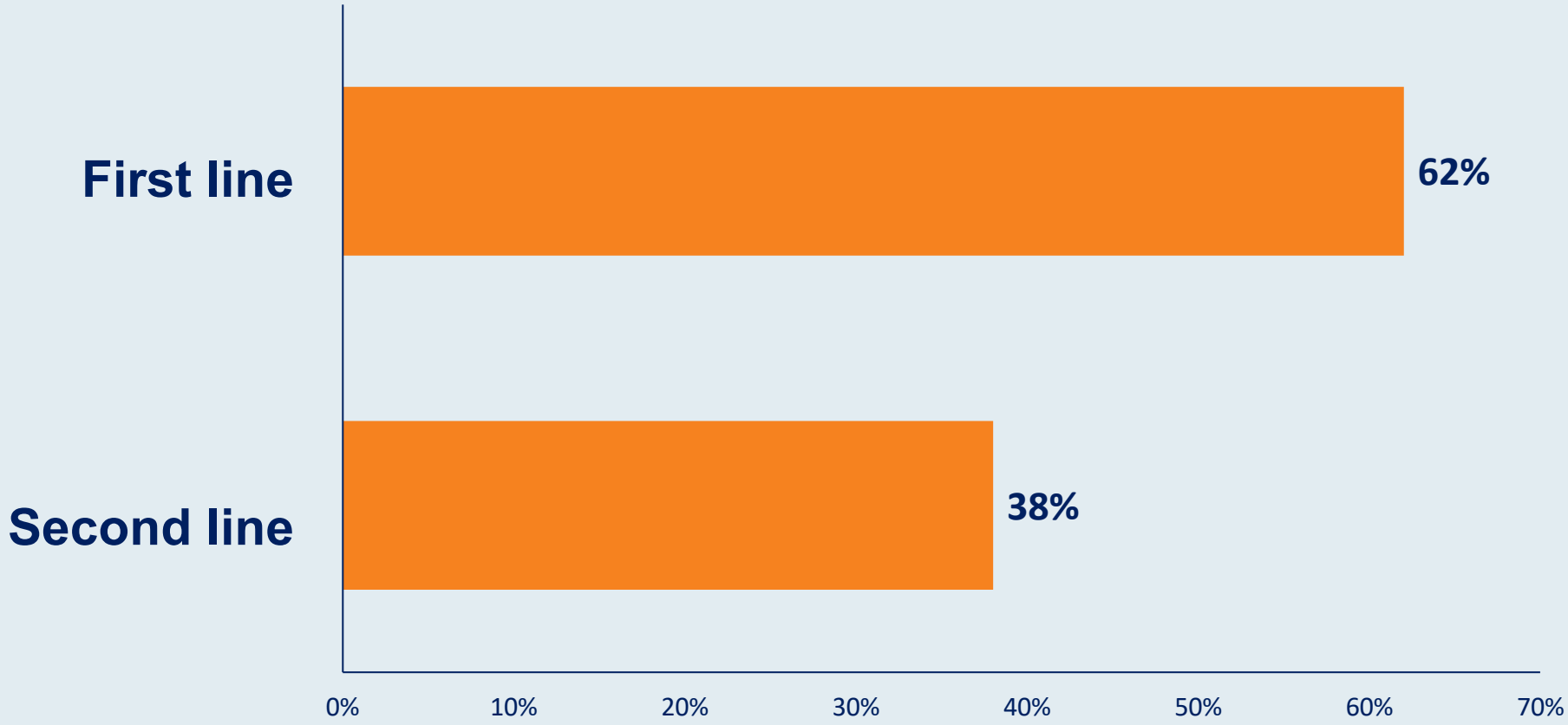
RTP RESEARCH TO PRACTICE

For a patient with metastatic nonsquamous NSCLC with a MET exon 14 skipping mutation and a PD-L1 TPS of 10%, in which line of therapy should targeted treatment (eg, capmatinib, tepotinib) be used?



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RTP RESEARCH TO PRACTICE

RET Fusions

- First identified in patients with thyroid cancer
- Fusions with a variety of partner genes lead to inappropriate expression of RET protein
- Occur in ~2% of patients with NSCLC
- Initial work showed activity of cabozantinib, but recently more specific RET inhibitors, with better CNS penetration

Courtesy of Gregory J Riely, MD, PhD

LIBRETTO-001: Selpercatinib in Patients with RET positive NSCLC

	Previous platinum chemotherapy		Treatment-naive
Response	PAS (N=105)	IAS (N=218)	(N=48)
Overall response rate by IRC – % (95% CI)	64 (54–73)	57 (50–64)	85 (72–94)
Best response – no. (%)			
Complete response	3 (3)	9 (4)	1 (2)
Partial response	64 (61)	115 (53)	40 (83)
Stable disease	30 (29)	81 (37)	4 (8)
Duration of response			
Median duration of response – mo (95% CI)	17.5 (12.1–NE)	17.5 (12.1–NE)	NE (12.0–NE)
Censoring rate, no. (%)	39 (58)	86 (69)	31 (76)
Median follow-up – mo	15.7	12.0	9.8
Progression-free survival			
Median progression-free survival – mo (95% CI)	19.3 (13.9–NE)	19.3 (16.5–NE)	NE (13.8–NE)
1-yr progression-free survival – % (95% CI)	66 (56–74)	70 (62–76)	68 (50–80)
Censoring rate, no. (%)	55 (52)	144 (66)	34 (71)
Median follow-up – mo	16.8	13.6	10.8
Overall survival			
2-yr overall survival – % (95% CI)	68 (55.3–77.8)	67 (55.4–76.7)	88 (68.6–95.8)
Censoring rate, no. (%)	77 (73)	177 (81)	44 (92)
Median follow-up – mo	19.9	14.3	12.6

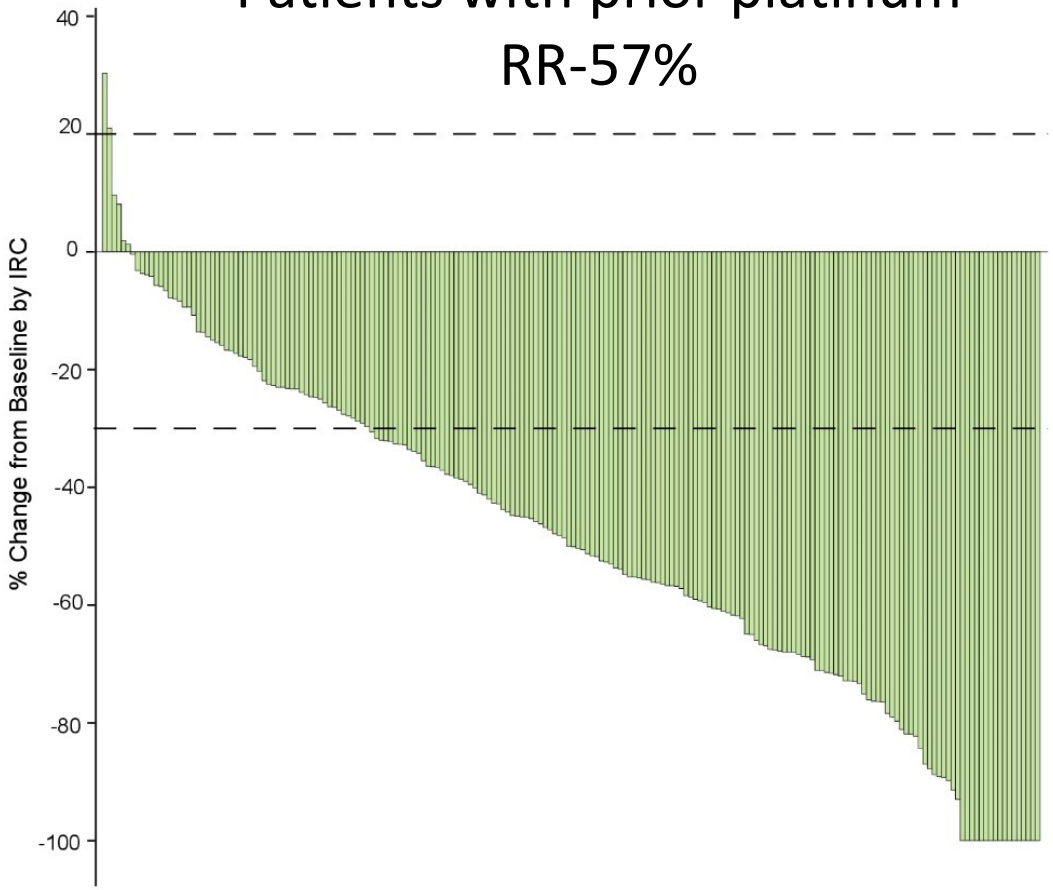
Percentages may not total 100 because of rounding. Abbreviations: NE, could not be evaluated; IRC, independent review committee; IAS, integrated analysis set; no, number; mo, months; CI, confidence interval; PAS, primary analysis set.

Courtesy of Gregory J Riely, MD, PhD

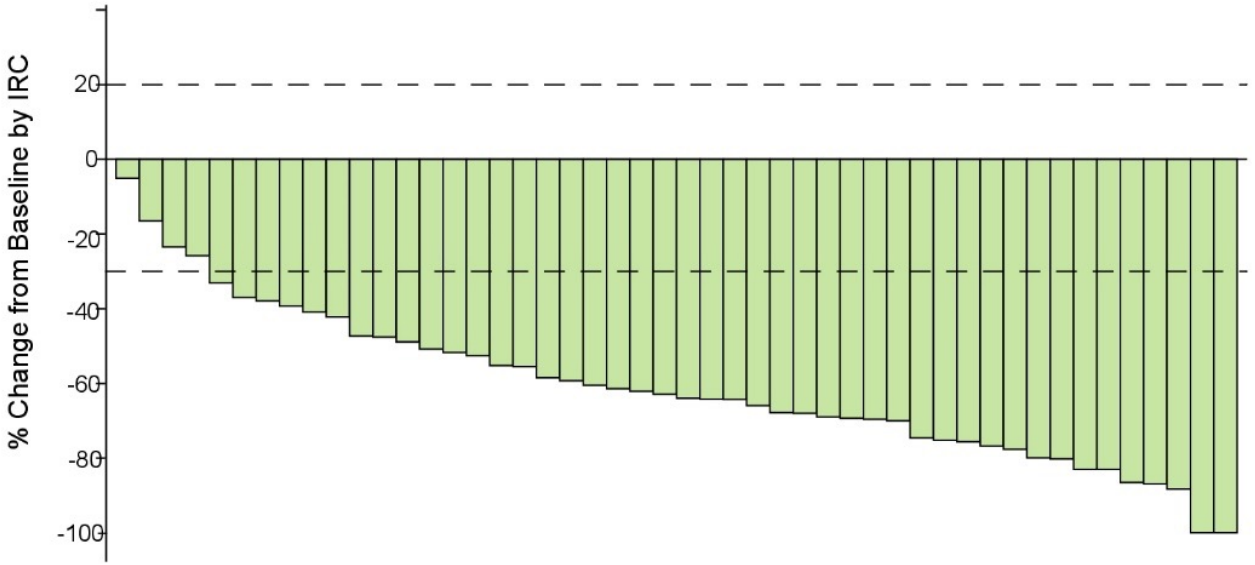
Besse et al, ASCO 2021

LIBRETTO-001: Selpercatinib in Patients with RET positive NSCLC

Patients with prior platinum
RR-57%



Patients with selpercatinib
as initial treatment
RR-85%



Courtesy of Gregory J Riely, MD, PhD

Besse et al, ASCO 2021

ARROW: Pralsetinib in patients with RET positive NSCLC

Efficacy summary (blinded independent central review)

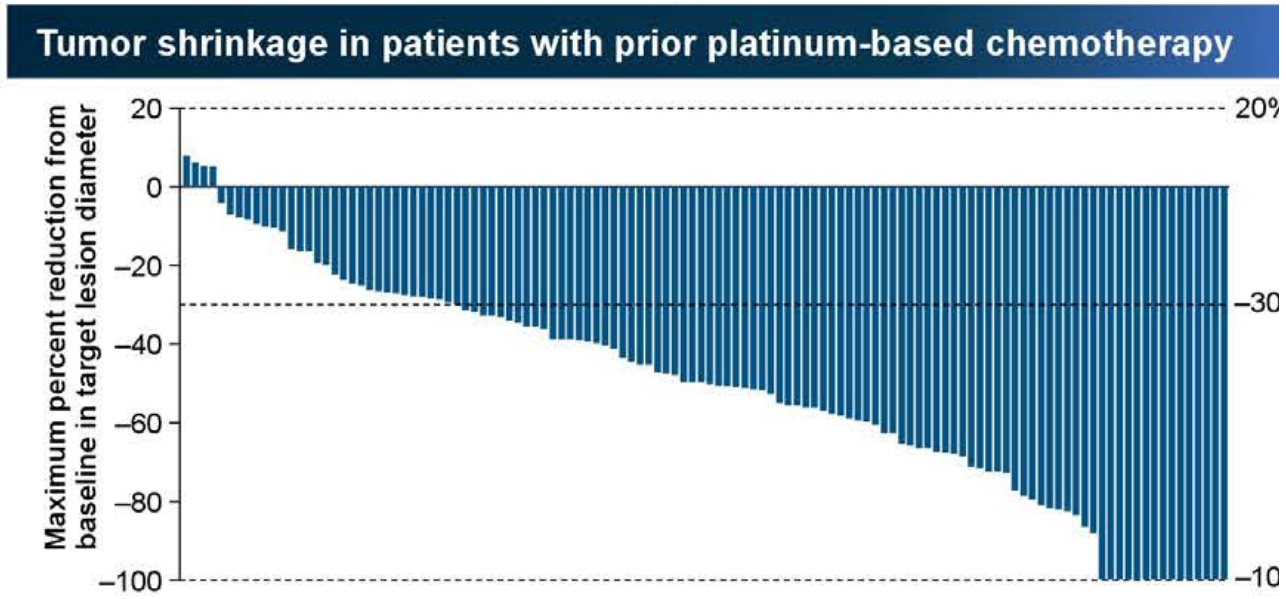
	Measurable disease population					
		Treatment-naïve			Prior treatment	
	RET fusion–positive NSCLC (n=216)	All (n=68)	Pre-eligibility revision (n=43)[a]	Post eligibility revision (n=25)[a]	Prior platinum (n=126)	Prior non-platinum (n=22)
ORR, % (95% CI)	**69** (62–75)	**79** (68–88)	**74** (59–87)	**88** (69–98)	**62** (53–70)	**73** (50–89)
Best overall response, n (%)						
CR	9 (4)	4 (6)	4 (9)	0	5 (4)	0
PR	139 (64)	50 (74)	28 (65)	22 (88)	73 (58)	16 (73)
SD	50 (23)	9 (13)	7 (16)	2 (8)	37 (29)	4 (18)
PD	10 (5)	3 (4)	3 (7)	0	5 (4)	2 (9)
NE	8 (4)	2 (3)	1 (2)	1 (4)	6 (5)	0
DCR, % (95% CI)[b]	92 (87–95)	93 (84–98)	91 (78–97)	96 (80–100)	91 (85–96)	91 (71–99)
CBR, % (95% CI)[c]	77 (71–82)	82 (71–91)	79 (64–90)	88 (69–98)	74 (65–81)	77 (55–92)
mDOR, mo (95% CI)	22.3 (15.1–NR)	NR (9.0–NR)	11.0 (7.4–NR)	NR (NR–NR)	22.3 (15.1–NR)	NR (9.2–NR)
mPFS, mo (95% CI)[d]	16.4 (11.0–24.1) n=233	13.0 (9.1–NR) n=75	10.9 (7.7–NR) n=47	NR (NR–NR) n=28	16.5 (10.5–24.1) n=136	12.8 (9.1–NR) n=22

[a]Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naïve patients eligible for standard platinum-based therapy who had previously not been permitted. [b]Confirmed CR or PR or SD. [c]CR or PR or SD of ≥16 weeks. [d]Evaluated in all patients with *RET* fusion–positive NSCLC who initiated 400 mg QD pralsetinib by May 22, 2020.
CI, confidence interval; mDOR, median duration of response; mo, month; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; PD, progressive disease.

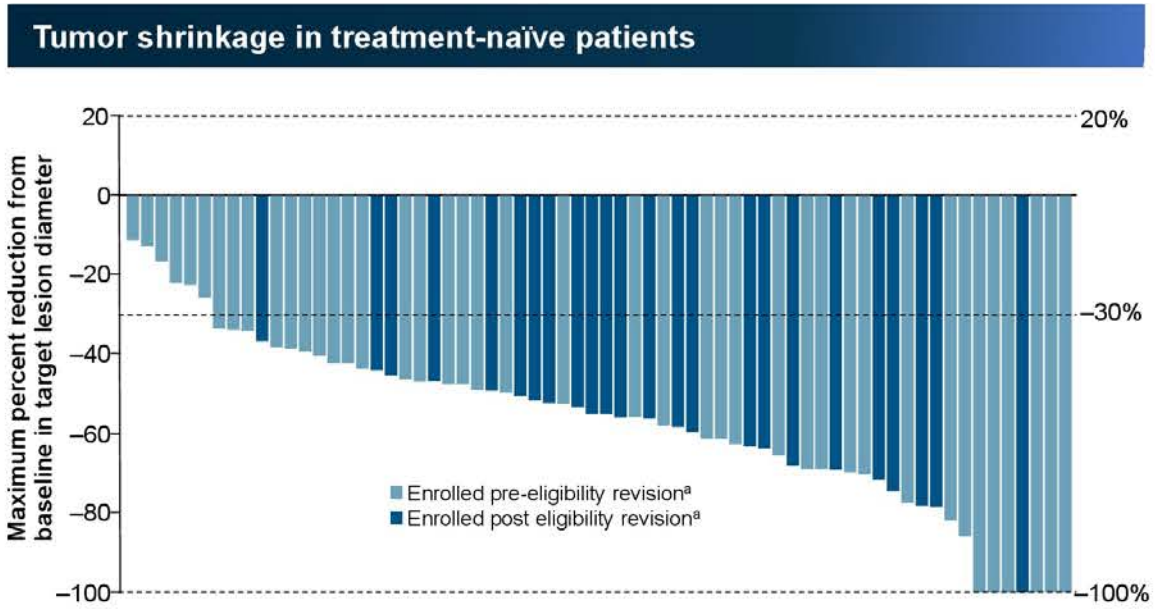
Courtesy of Gregory J Riely, MD, PhD

Curigliano et al, ASCO 2021

ARROW: Pralsetinib in patients with RET positive NSCLC



Response Rate 62%

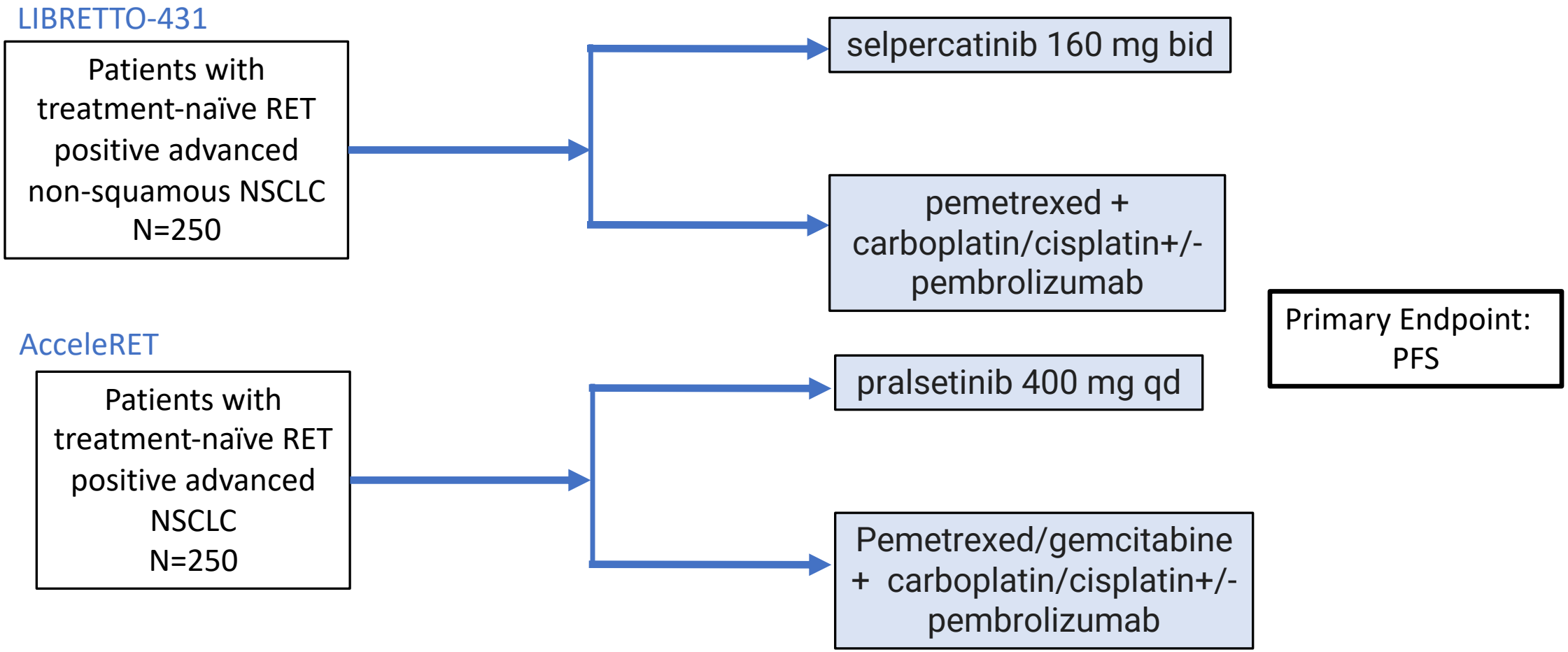


Response Rate 79%

Courtesy of Gregory J Riely, MD, PhD

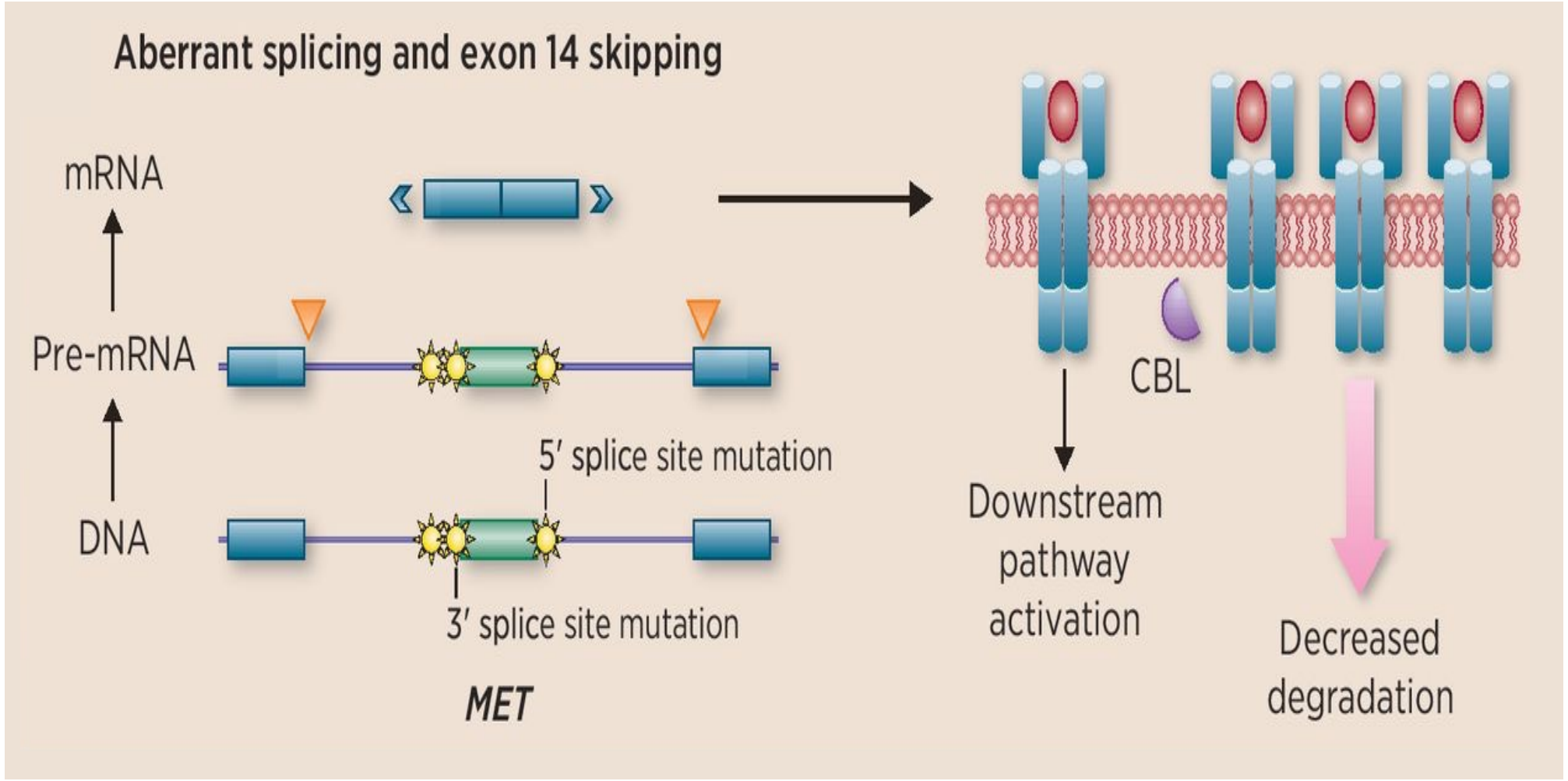
Curigliano et al, ASCO 2021

Ongoing randomized phase III trials to evaluate first line RET inhibitors



Courtesy of Gregory J Riely, MD, PhD

MET Exon 14 Alterations in NSCLC



Drilon A, et al. *Clin Cancer Res*. 2016;22(12):2832-2834.

Courtesy of Gregory J Riely, MD, PhD

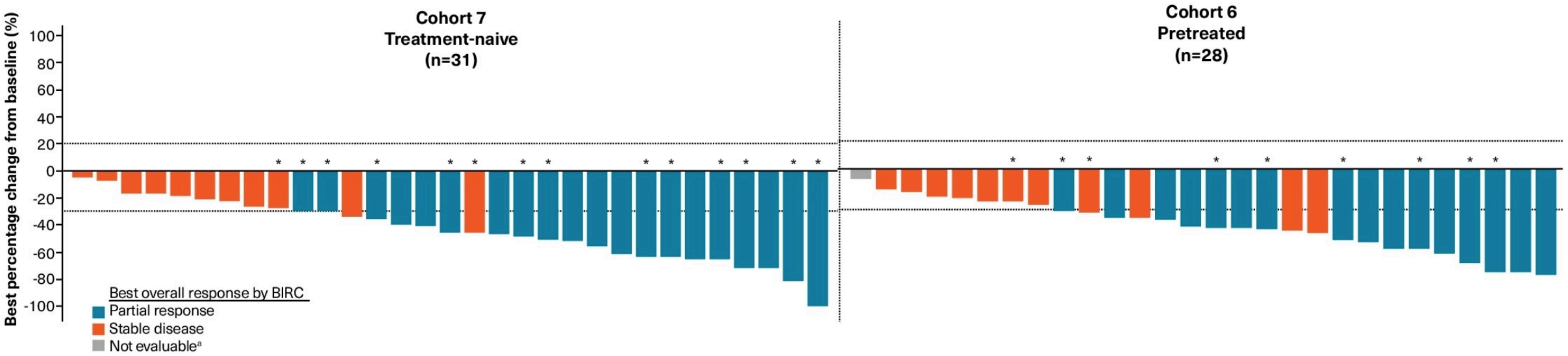
GEOMETRY mono-1: Capmatinib in Patients with MET exon 14 NSCLC

	Treatment-naive			Pretreated		
	Cohort 5b N = 28	Cohort 7 N = 32	Al Patients N = 60	Cohort 4 (2/3L) N = 69	Cohort 6 (2L) N = 31	All Patients N = 100
ORR	67.9%	65.6%	66.7%	40.6%	51.6%	44.0%
DCR	96.4%	100%	98.3%	78.3%	90.3%	82.0%
DOR events	12 (63.2%)	5 (23.8%)	17 (42.6%)	23 (82.1%)	11 (68.8%)	34 (77.3%)
Median DOR	12.6 mo	NE	12.6 mo	9.7 mo	8.4 mo	9.7 mo
PFS events	18 (64.3%)	14 (43.8%)	32 (53.3%)	60 (87.0%)	22 (71.0%)	82 (82.0%)
Median PFS	12.4 mo	10.8 mo	12.3 mo	5.4 mo	6.9 mo	5.5 mo

Courtesy of Gregory J Riely, MD, PhD

Wolf et al ASCO 2021; Abstract 9020.

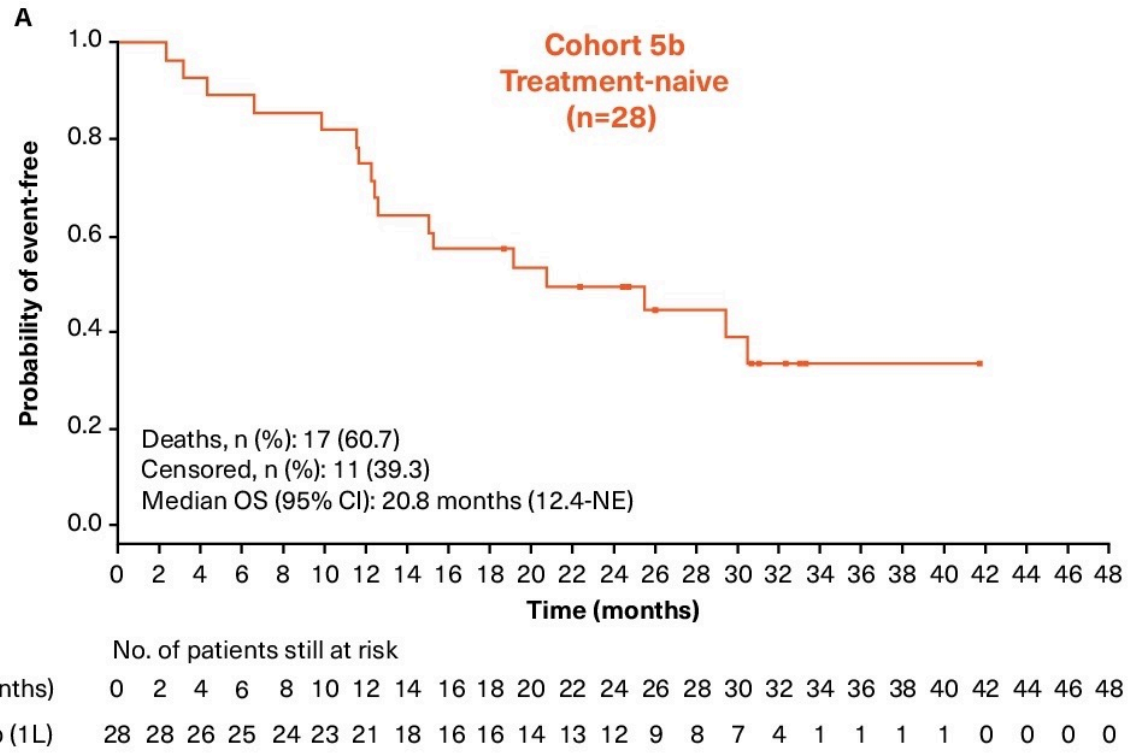
GEOMETRY mono-1: BIRC-Determined Change in Tumor Size from Baseline for Treatment-Naïve (Cohort 7) and Pretreated (Cohort 6) patients with MET Exon 14 NSCLC Receiving Capmatinib

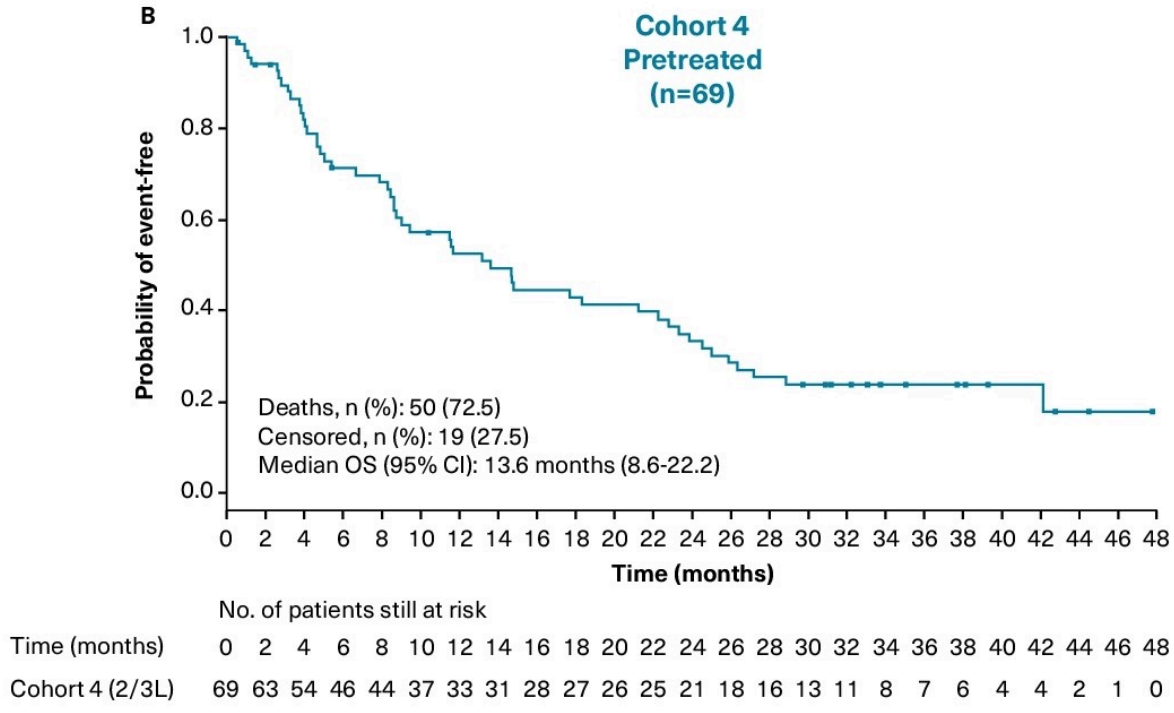


Courtesy of Gregory J Riely, MD, PhD

Wolf et al ASCO 2021; Abstract 9020.

GEOMETRY mono-1: Overall Survival for Treatment-Naïve (Cohort 5b and Pretreated (2/3L) (Cohort 4) Patients with MET Exon 14 NSCLC Receiving Capmatinib

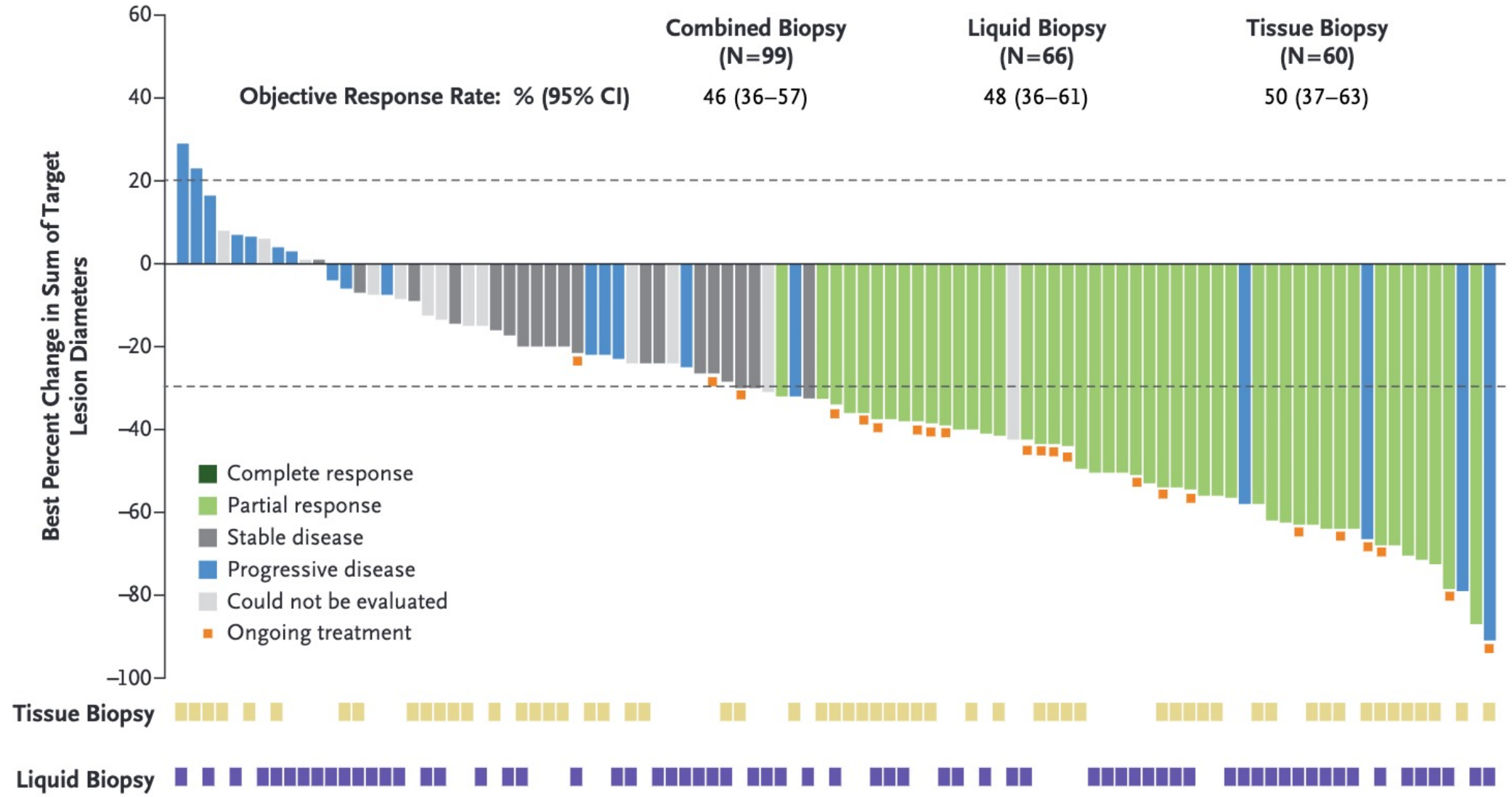




Courtesy of Gregory J Riely, MD, PhD

Wolf et al ASCO 2021; Abstract 9020.

VISION: Tepotinib in Patients with MET exon 14



Courtesy of Gregory J Riely, MD, PhD

Paik et al, NEJM 2020

VISION: Evaluation of Tepotinib in MET exon 14 NSCLC

Efficacy (investigator-assessed)	Overall (n=99)	Treatment-naïve (n=44)	Previously treated (n=55)
ORR, % (95% CI)	52.5 (42.2, 62.7)	59.1 (43.2, 73.7)	47.3 (33.7, 61.2)
Median DOR, months (95% CI)	14.0 (8.3, NE)	10.9 (6.6, NE)	14.0 (8.3, NE)
Median PFS, months (95% CI)	7.4 (5.8, 9.7)	7.4 (5.5, 11.1)	6.9 (4.9, 11.0)

Courtesy of Gregory J Riely, MD, PhD

Paik et al, ASCO 2021

Agenda

Introduction: Targeted Treatment in the Adjuvant Setting

Module 1: Current and Future Treatment of NSCLC with ALK and ROS1 Rearrangements

- Dr Deutsch: A 67-year-old man with metastatic adenosquamous carcinoma of the lung – PD-L1 >95%, ROS1 rearrangement
- Dr Lobins: A 74-year-old woman with metastatic adenocarcinoma of the lung and cancer in the right breast – TMB 14 mut/Mb, ALK mutation
- Key relevant data sets

Module 2: Management Strategies for Patients with NSCLC with RET Fusions or MET Alterations

- Dr Mohamed: A 63-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 0%, RET KIF5B fusion
- Key relevant data sets

Module 3: Key Data Guiding the Management of Metastatic NSCLC with EGFR Mutations

- Dr Chen: A 66-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 60%, EGFR exon 19 deletion
- Dr Flores: A 70-year-old man with metastatic NSCLC – EGFR L858R mutation
- Key relevant data sets

Module 4: Therapeutic Approaches for Patients with NSCLC with HER2 or KRAS Mutations

- Dr Lobins: A 62-year-old woman with recurrent metastatic adenocarcinoma of the lung – HER2 mutation
- Dr Ibrahim: A 46-year-old woman with metastatic adenocarcinoma of the lung – KRAS G12C mutation
- Key relevant data sets

RTP
RESEARCH TO PRACTICE

Case Presentation – Dr Chen: A 66-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 60%, EGFR exon 19 deletion

Dr Gigi Chen

- February 2018: Presented with hemoptysis and diagnosed with Stage IV poorly differentiated adenocarcinoma in right lung and multiple thoracic bone metastases
- May 2018: Switched to osimertinib initiated after initial treatment with erlotinib with zoledronic acid
- December 2019: Progression in RLL mass, other sites of disease stable
- SBRT to right lung mass → CT scan shows increase in 3 lung nodules

Questions

- What would be the best course of treatment at this time – additional SBRT or switch to chemotherapy? What chemotherapy regimen would you offer to her?
- If we change her treatment to chemotherapy, what would be the role of continuing osimertinib?

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Case Presentation – Dr Flores: A 70-year-old man with metastatic NSCLC – EGFR L858R mutation

Dr Regina Flores

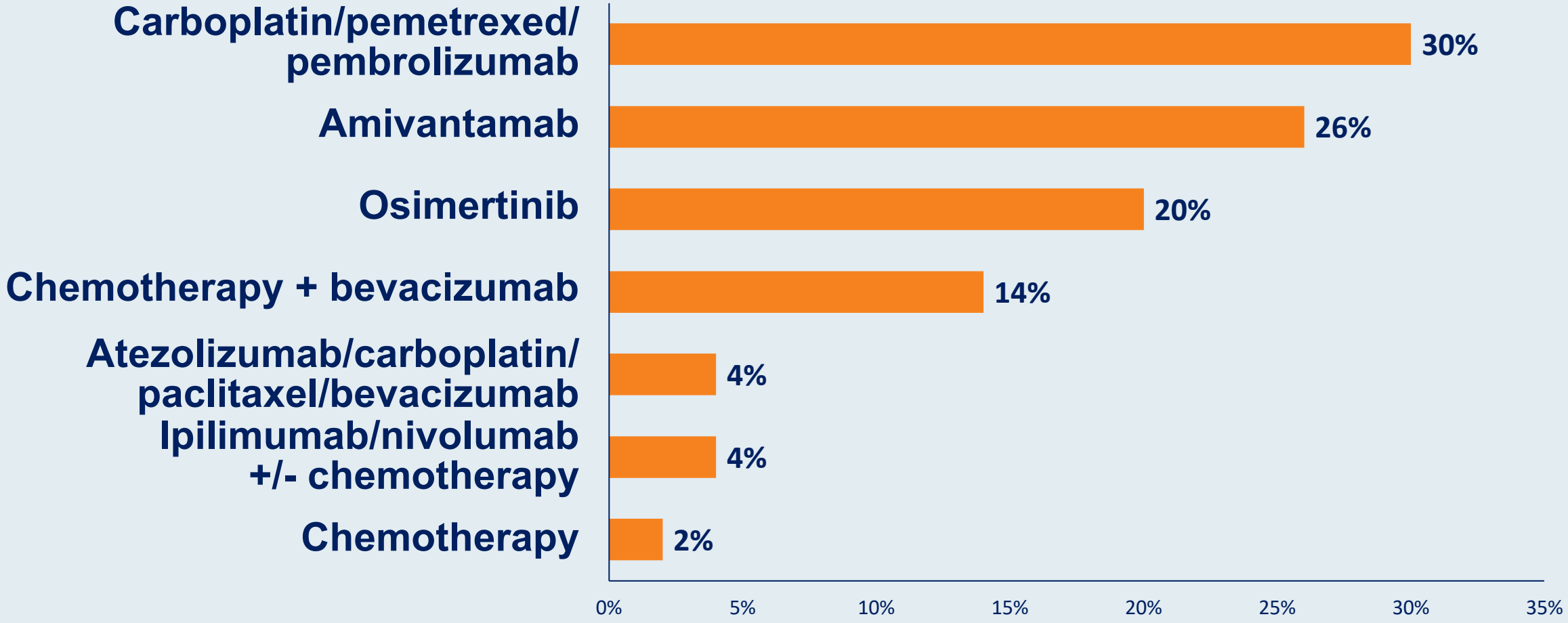
- PMH: Diabetes
- Diagnosed with Stage IV lung cancer with liver, bone and brain metastases
- Molecular studies: EGFR L858R mutation
- Osimertinib initiated

Questions

- What would prompt you to radiate the brain up front instead of waiting to start radiation after osimertinib?
- Does degree of vasogenic edema, size or location of brain metastases or seizure activity influence your decision?

RTP RESEARCH TO PRACTICE

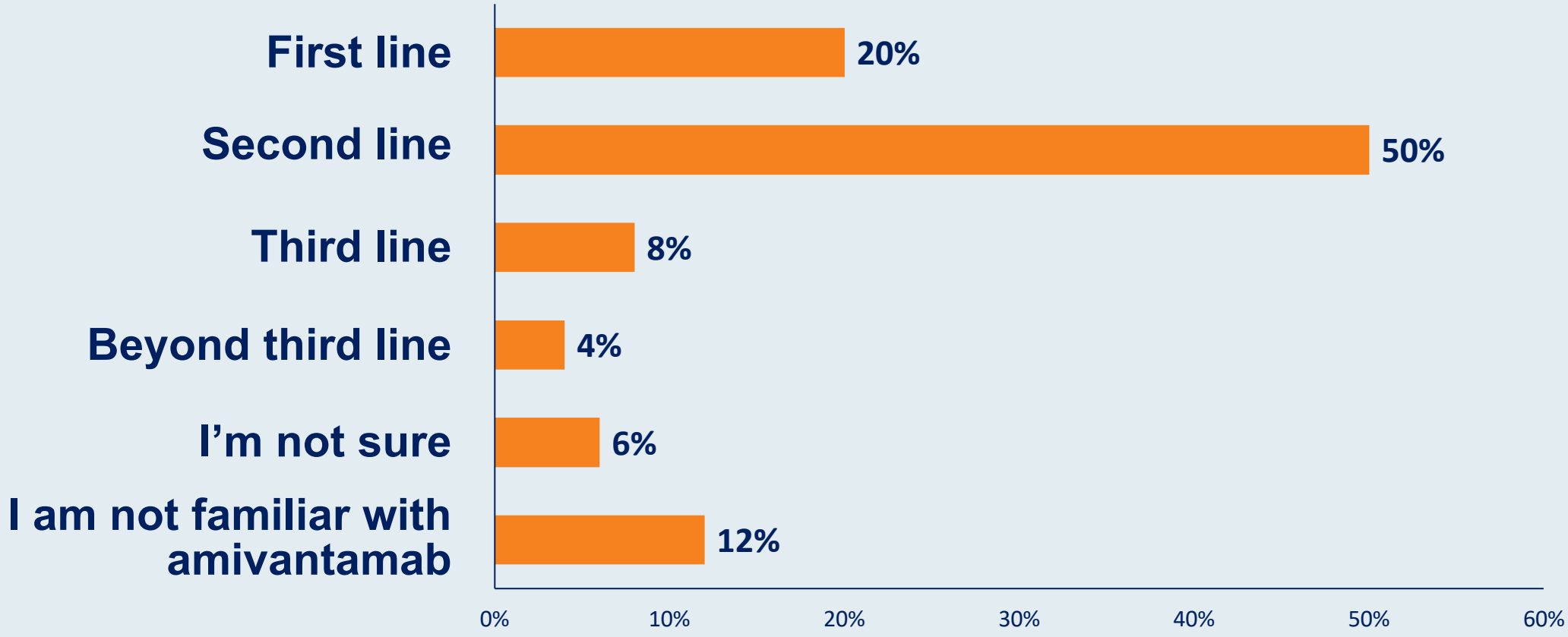
Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with metastatic nonsquamous NSCLC with an EGFR exon 20 insertion mutation and a TPS of 10%?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer amivantamab to a patient with metastatic NSCLC and an EGFR exon 20 insertion mutation?

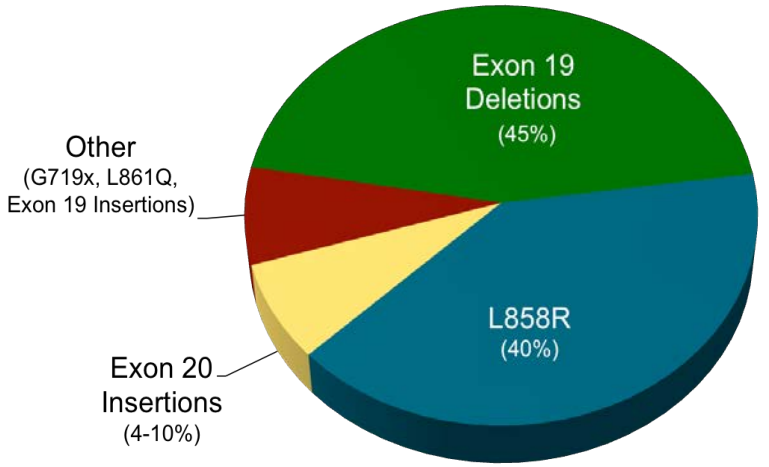


Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

The Diversity of EGFR Mutations in NSCLC

	EGFR Mutation Subtypes	Preferred First-Line Treatment
SENSITIZING	**Exon 19 Deletion (~45%)**	Osimertinib
	L858R (~40%)	
	Rare but sensitizing mutations (~5%):	
	L861Q*	Afatinib (FDA-approved) or Osimertinib
	G719X*	
	S768I*	
	A763_Y764insFQEA	
RESISTANT to 1st/2nd gen TKIs	***Exon 20 Insertions (~5-10%)***	
	A767_V769dup	**Chemotherapy +/- immunotherapy** (Amivantamab now approved for second-line use)
	S768_D770dupSVD	
	V769_D770insASV	
	D770_N771ins…	
	D770_P772dup	
	N771_H773dup	
	N771_P772ins…	
	P772_H773dupPH	
	V774ins	



Courtesy of Zofia Piotrowska, MD, MHS

Yasuda, et al. Lancet Oncol, 2011; Yasuda, et al. Science Trans Med, 2014.

For EGFR+ NSCLC patients, progression on osimertinib is now a major challenge

1st line Osimertinib
mPFS 18.9 mos

2L therapies after 1L osimertinib
???

Selecting Optimal Post-Osimertinib Rx Requires:

1. Molecular testing at progression
2. Understanding resistance mechanisms to first-line osimertinib
3. Effective treatment strategies aimed at these resistance mechanisms

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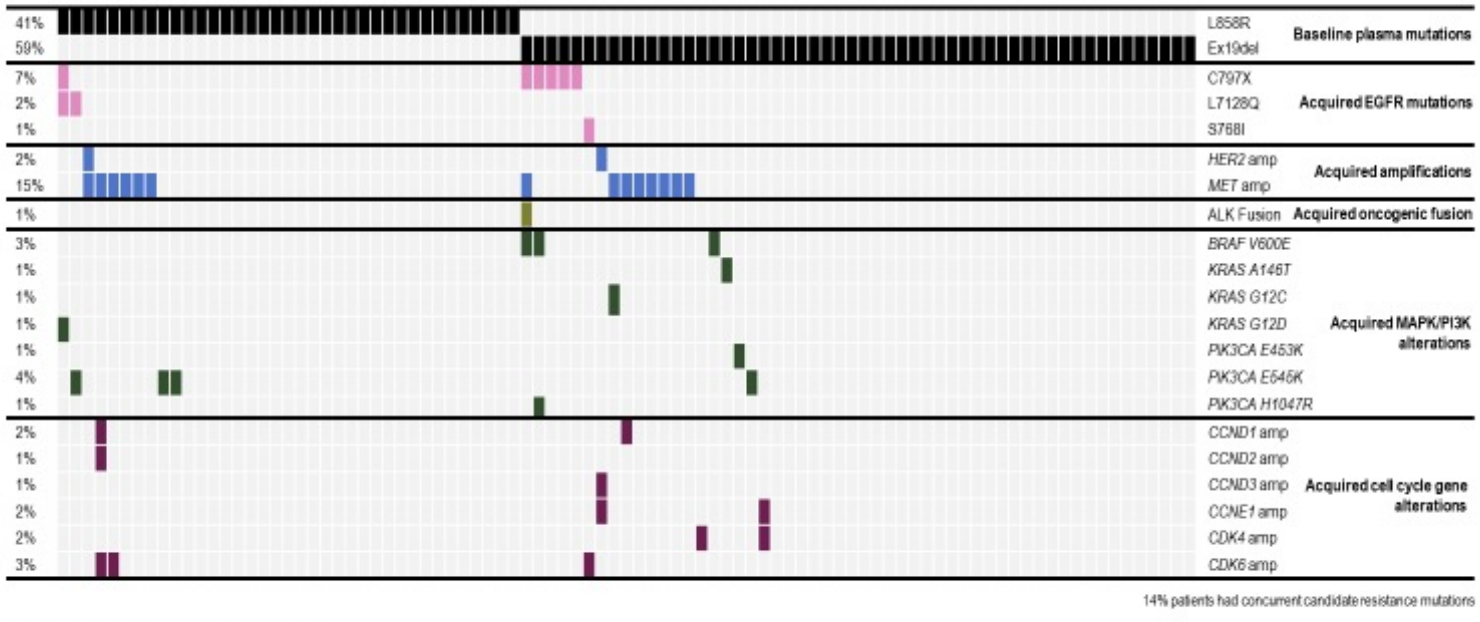
Courtesy of Zofia Piotrowska, MD, MHS

Resistance to First-Line Osimertinib

Osimertinib Resistance in FLAURA
(n=91, ctDNA analysis)

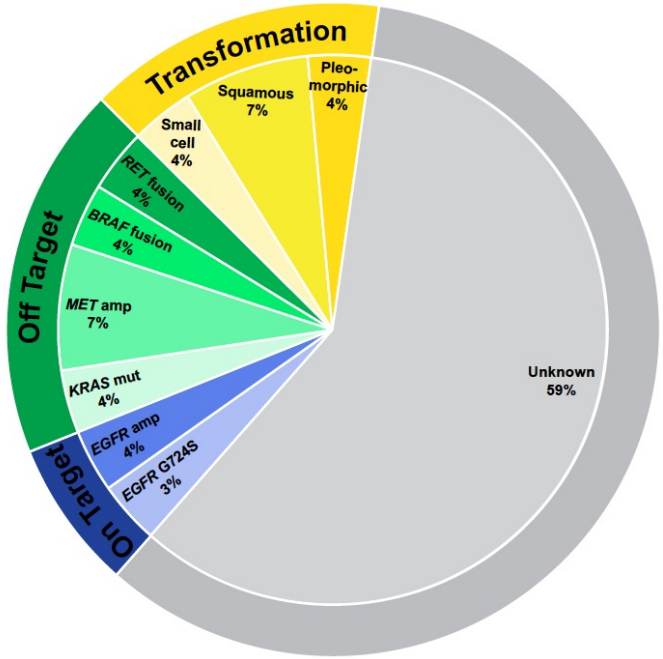


- Lower rate of C797S (7%) than was seen in 2L Osi Resistance
- 15% MET amplification
- ctDNA so no histologic changes detected.
- Acquired alterations in the MAP kinase pathway and cell cycle genes.

Ramalingam S et al. ESMO 2018; Schoenfeld A et al. CCR 2020

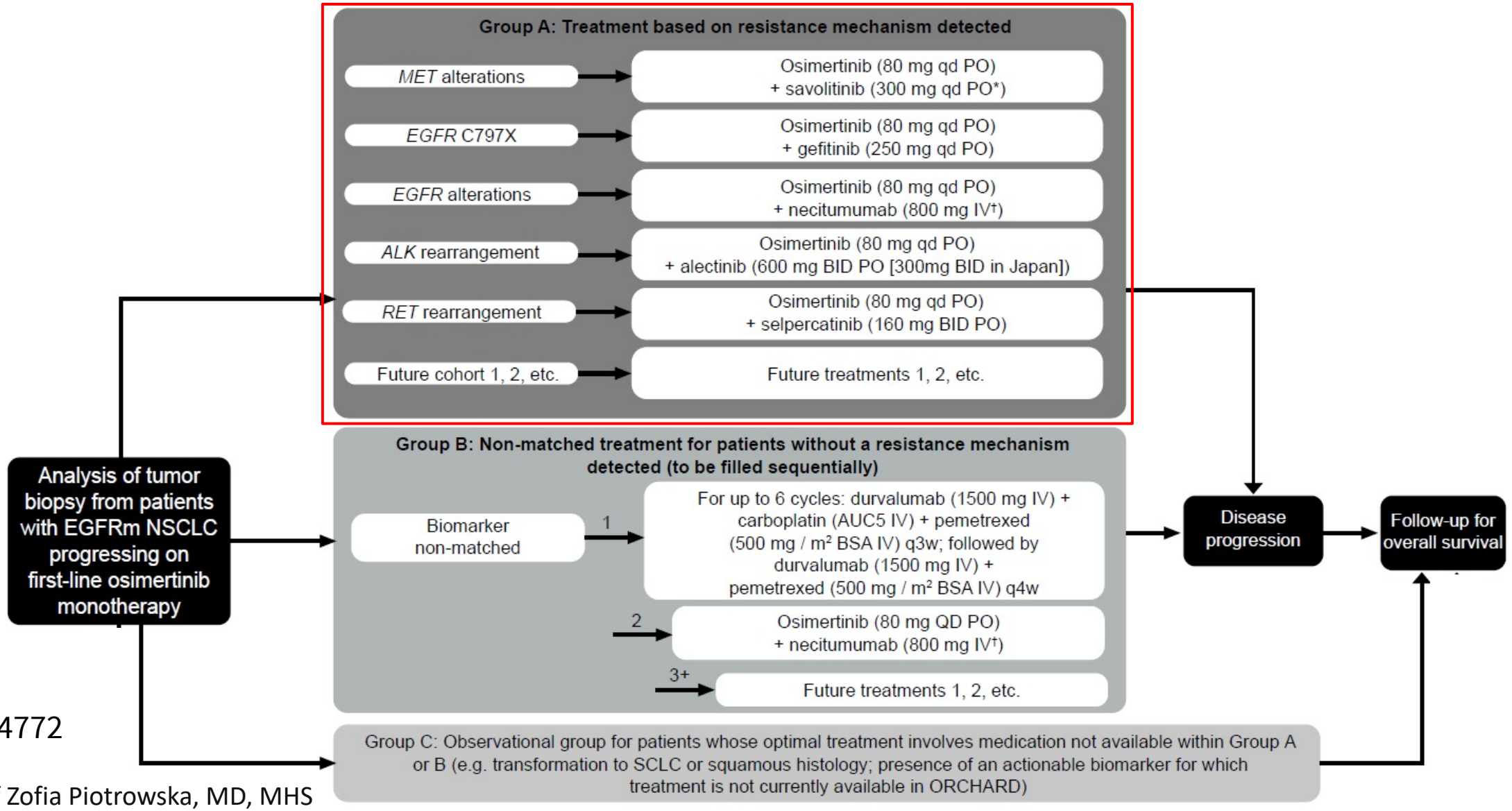
Courtesy of Zofia Piotrowska, MD, MHS

MSKCC 1L Cohort
(n=27, tissue biopsies)



- 15% histologic transformation
  - SCLC, Squamous, Pleomorphic
- 7% MET amplification
- On-target resistance mechanisms were uncommon; no EGFR C797S and one EGFR G724S

Post-Osimertinib Clinical Trials: ORCHARD

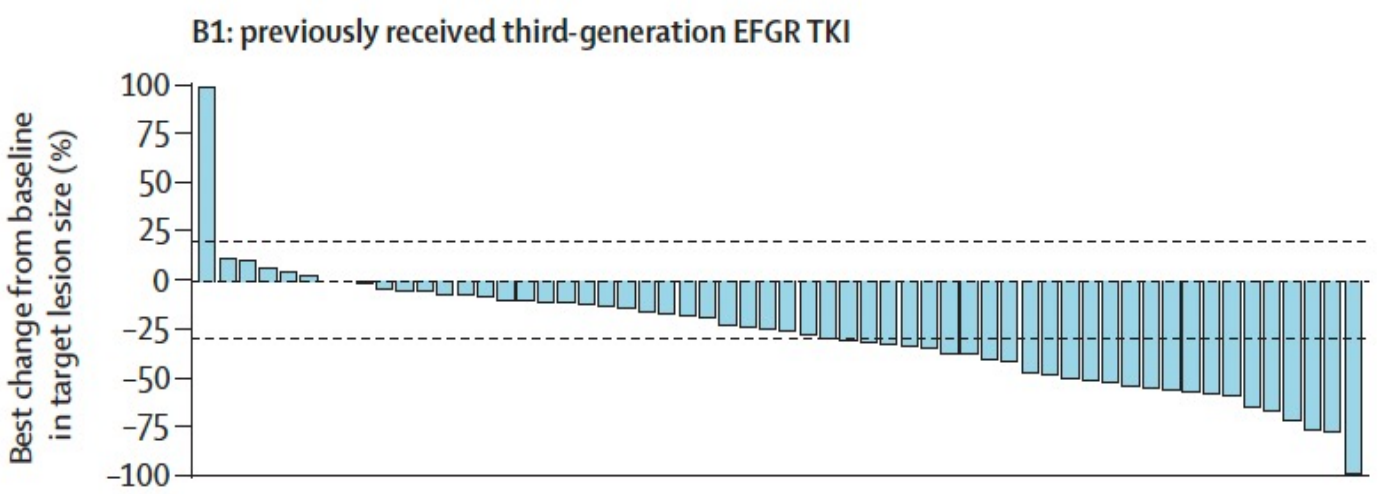


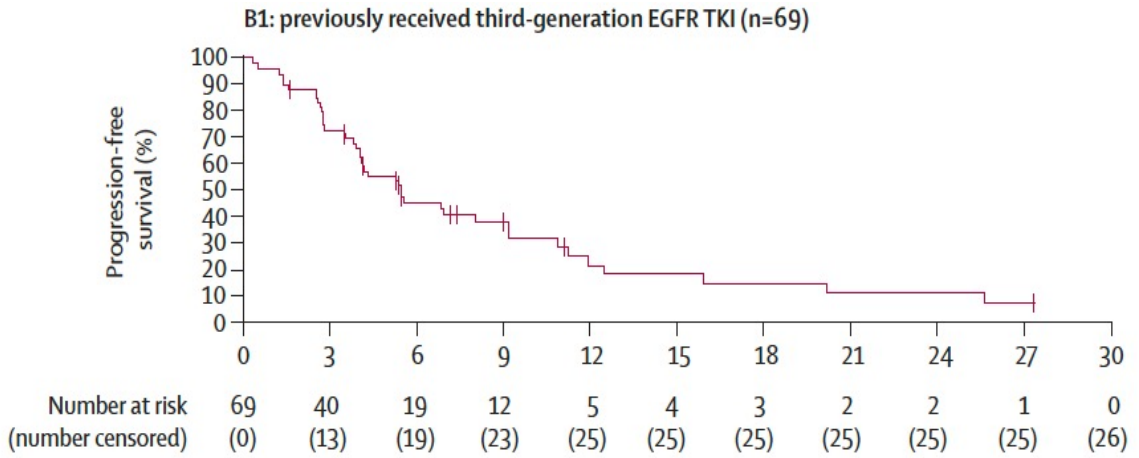
NCT03944772

Courtesy of Zofia Piotrowska, MD, MHS

Targeting MET Amplification after Osimertinib

- The TATTON trial evaluated Osimertinib + Savolitinib (METi) in pts with MET amp after osimertinib[1]
  - ORR 30%, mPFS 5.4 months



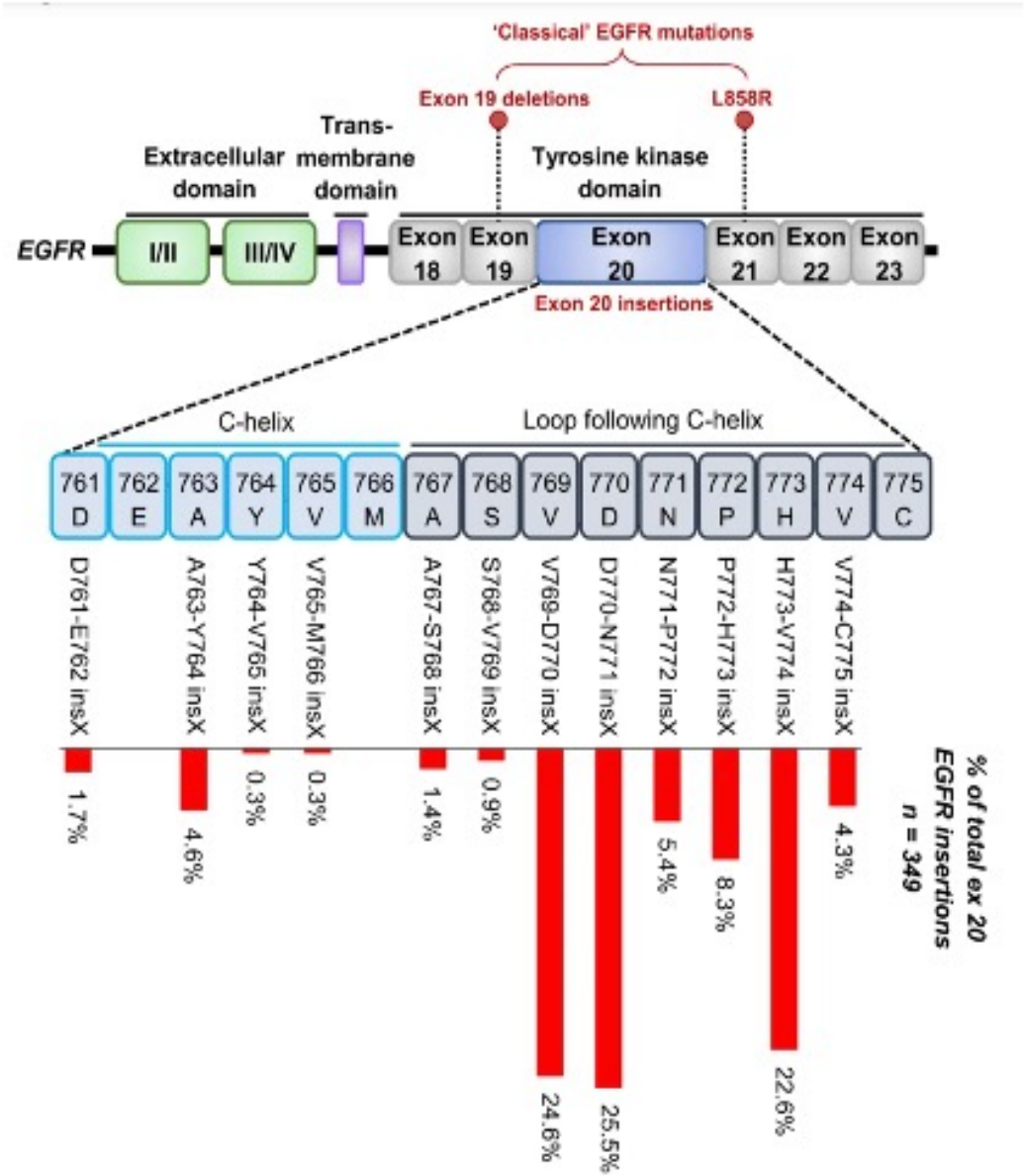


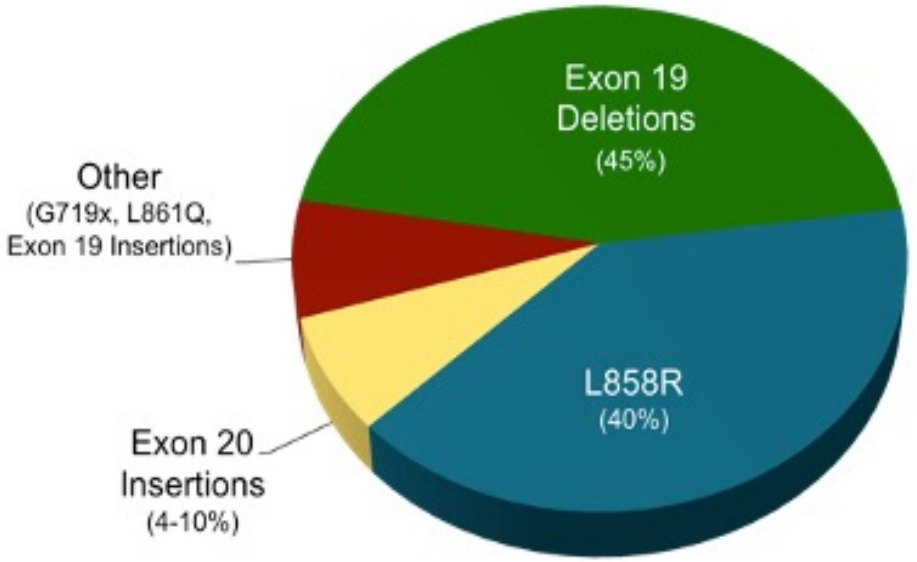
- Case reports of response to osimertinib + crizotinib[2,3] and osimertinib + capmatinib[3] have also been reported.

Courtesy of Zofia Piotrowska, MD, MHS

1. Sequist et al. Lancet Onc 2020; 2. York ER et al. JTO 2017 ; 3. Deng L et al. JTO 2018; 4. Gautschi O et al. JTO 2020

Frequency of EGFR Exon 20 Mutations





Exon 20 NSCLC: US and China				
		Exon 20 Frequency	Total Number of NSCLC Patients/year	
United States	EGFR HER2	2.1% 1.5%	3.6%	7700
China	EGFR HER2	2.4% 3.9%	6.3%	41100

Courtesy of Zofia Piotrowska, MD, MHS

Emerging Targeted Therapies for EGFR Exon 20 Mutations

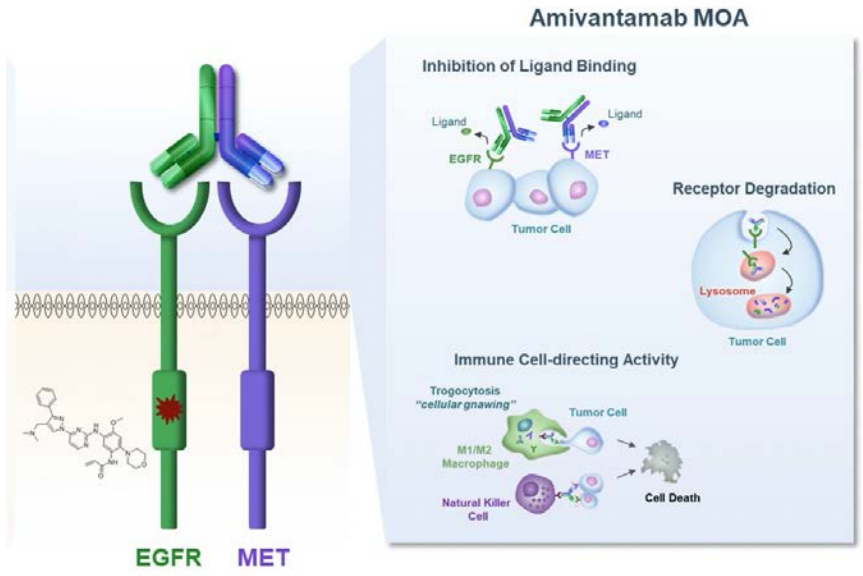
Drug	MOA	N	ORR	mPFS	Major toxicities	Discont due to toxicities	FDA status re exon 20
Poziotinib[1,2]	TKI	115	15%	4.2 mo	Diarrhea Rash	12%	Fast track designation March 2021
Mobocertinib[3,4,5]	TKI	114	35%	7.3 mo	Diarrhea Rash Nausea	14%	Breakthrough therapy designation April 2020
Amivantamab[6]	EGFR/ MET Ab	81	40%	8.3 mo	Rash Infusion reaction Paronychia	4%	FDA accelerated approval May 2021
Osimertinib[7]	TKI	17	24%	9.6 mo	Diarrhea Rash Platelets	6%	No indication in exon 20
CLN-081[8]	TKI	22	35%	NR	Rash Stomatitis	0%	Investigational

1. Le X. AACR 2020, 2. Socinski M. ESMO 2020; 3. Riely G. ESMO 2020; 4. Zhou C. IASLC 2020; 5. Zhou C. IASLC/WCLC 2020. 6. Sabari JK. IASLC WCLC 2020; 7. Piotrowska Z. ASCO 2020; 8. Piotrowska Z. ESMO 2020.

Courtesy of Zofia Piotrowska, MD, MHS

Amivantamab

Amivantamab is a bispecific antibody targeting EGFR + MET

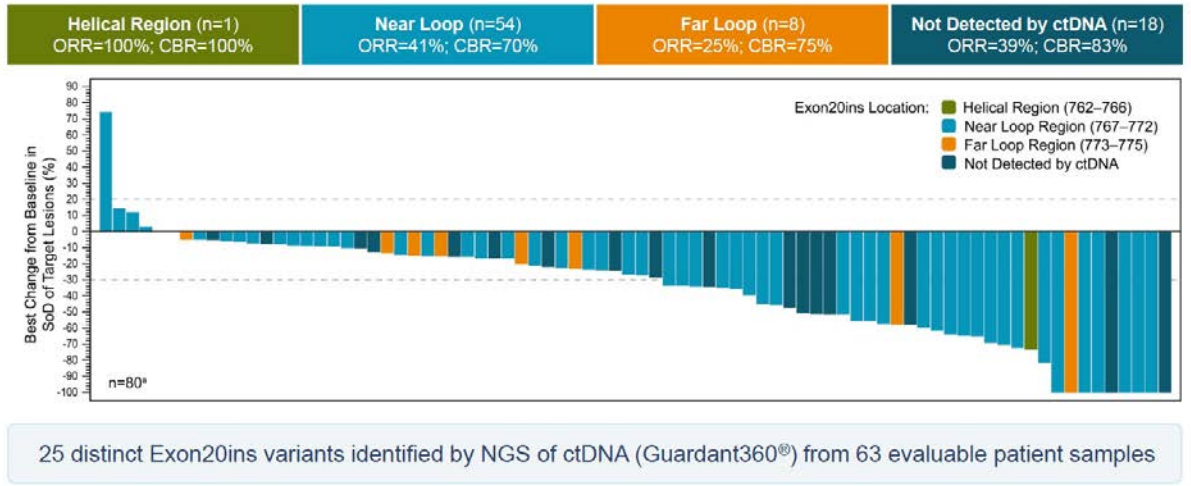


- Amivantamab recently received FDA approval for EGFR exon 20 insertion+ NSCLC

CHRYSALIS Trial

	N=81 (EGFR ins20)
ORR	40%
mDOT	11.1 mo (95% CI, 6.9-NR)
mPFS	8.3 mo (95% CI, 6.5-10.9)

Best ORR by Insertion Region of Exon 20 (detected by ctDNA)



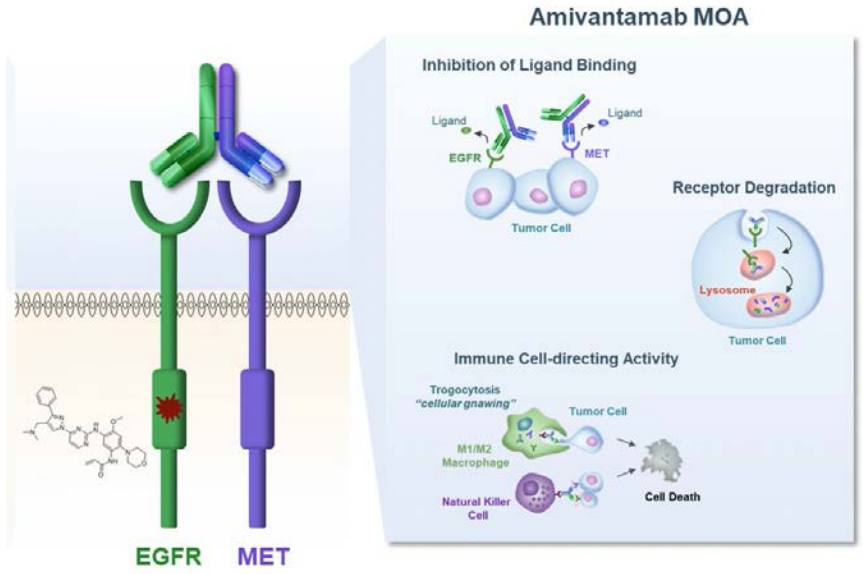
25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

Courtesy of Zofia Piotrowska, MD, MHS

Chul B et al. ASCO 2021; Sabari J et al. WCLC 2021

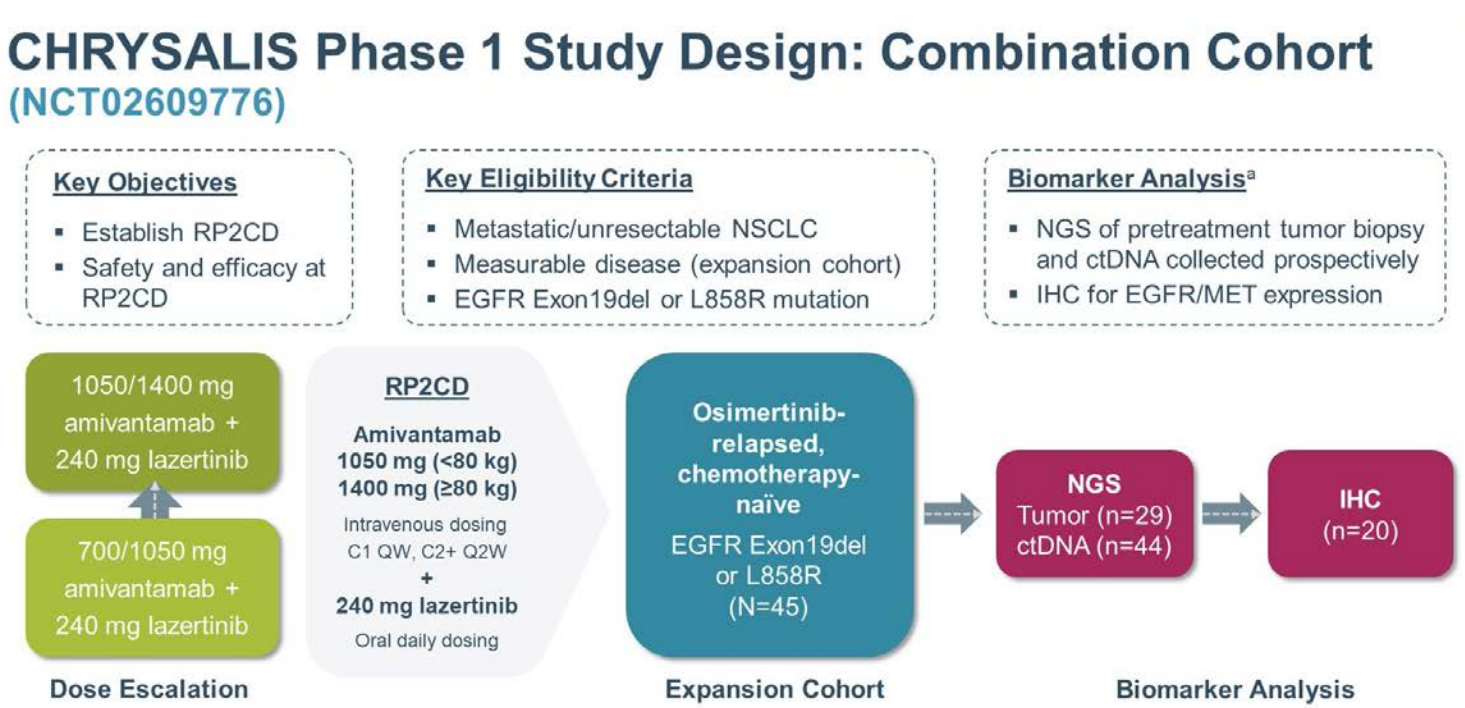
Amivantamab + Lazertinib

Amivantamab is a bispecific antibody targeting EGFR + MET



- Amivantamab recently received FDA approval for EGFR exon 20 insertion+ NSCLC
- Amivantamab + Lazertinib (3rd gen EGFR TKI) is being evaluated in TKI-resistant EGFR+ NSCLC

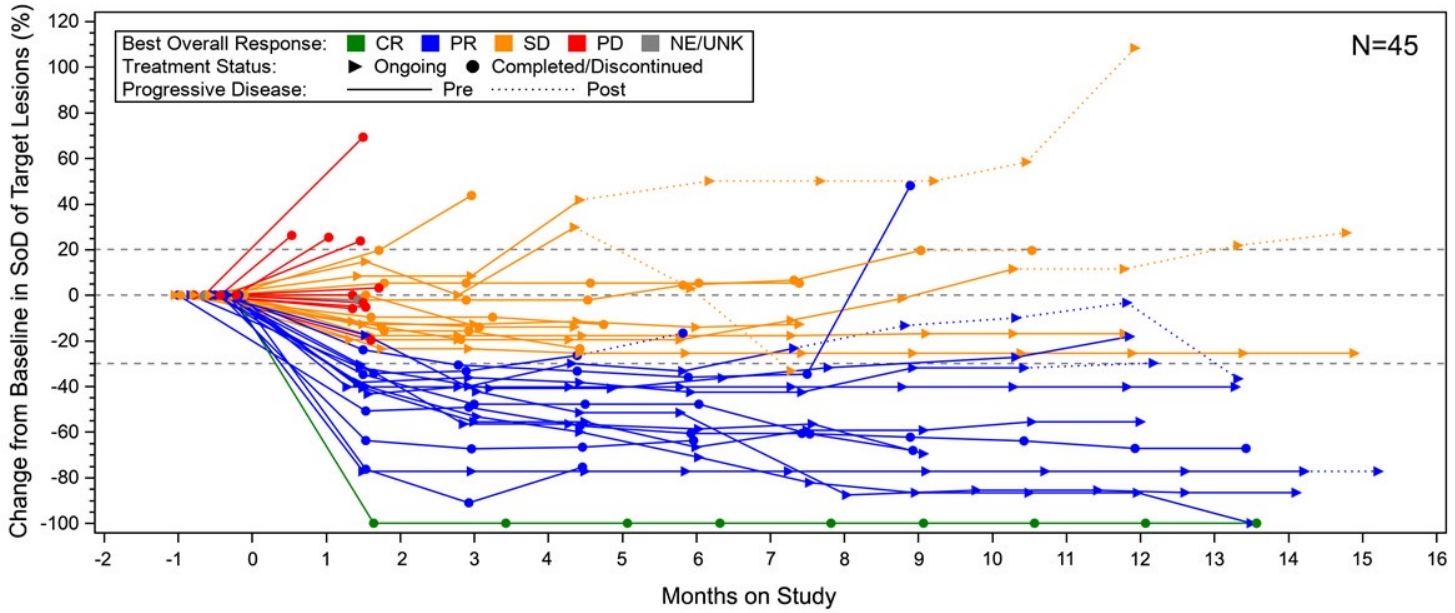
Amivantamab + Lazertinib in TKI-resistant EGFR+ NSCLC



Courtesy of Zofia Piotrowska, MD, MHS

1. Chul B et al. ASCO 2021

Amivantamab + Lazertinib



Investigator-assessed Response (N=45) *mF/U: 11.0 months (range, 1.0–15.0)* *mDOT: 5.6 months (range, 0.5–14.8)*	
ORR	36% (95% CI, 22–51)
mDOR, months	9.6 (95% CI, 5.3–NR)
DOR ≥6 months	69%
CBR	64% (95% CI, 49–78)
mPFS, months	4.9 (95% CI, 3.7–9.5)

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

1. Chul B et al. ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

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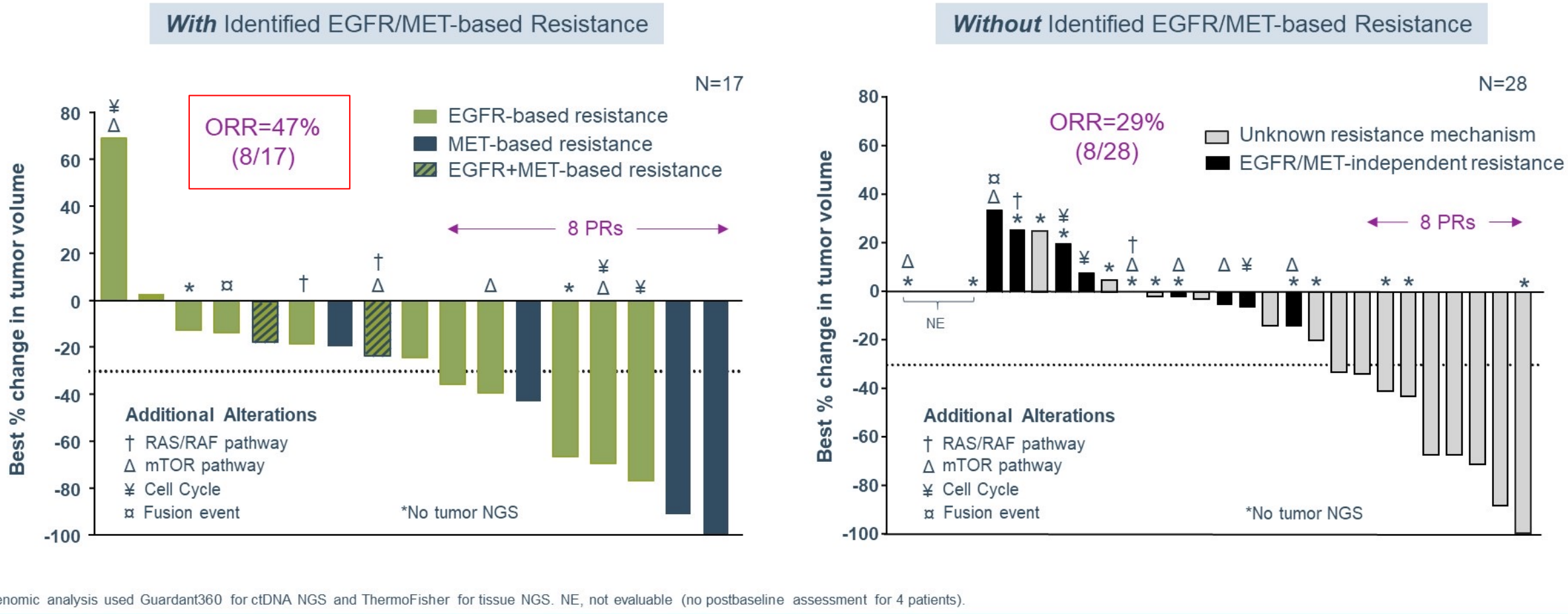
Amivantamab + Lazertinib

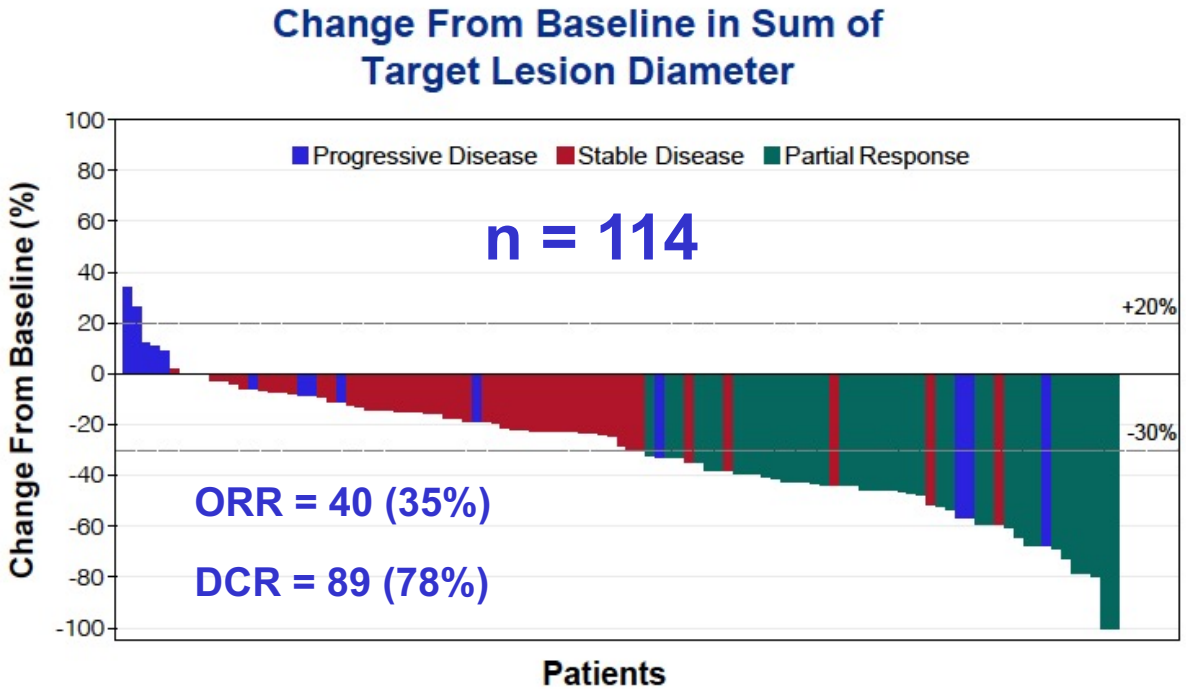


Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS. NE, not evaluable (no postbaseline assessment for 4 patients).

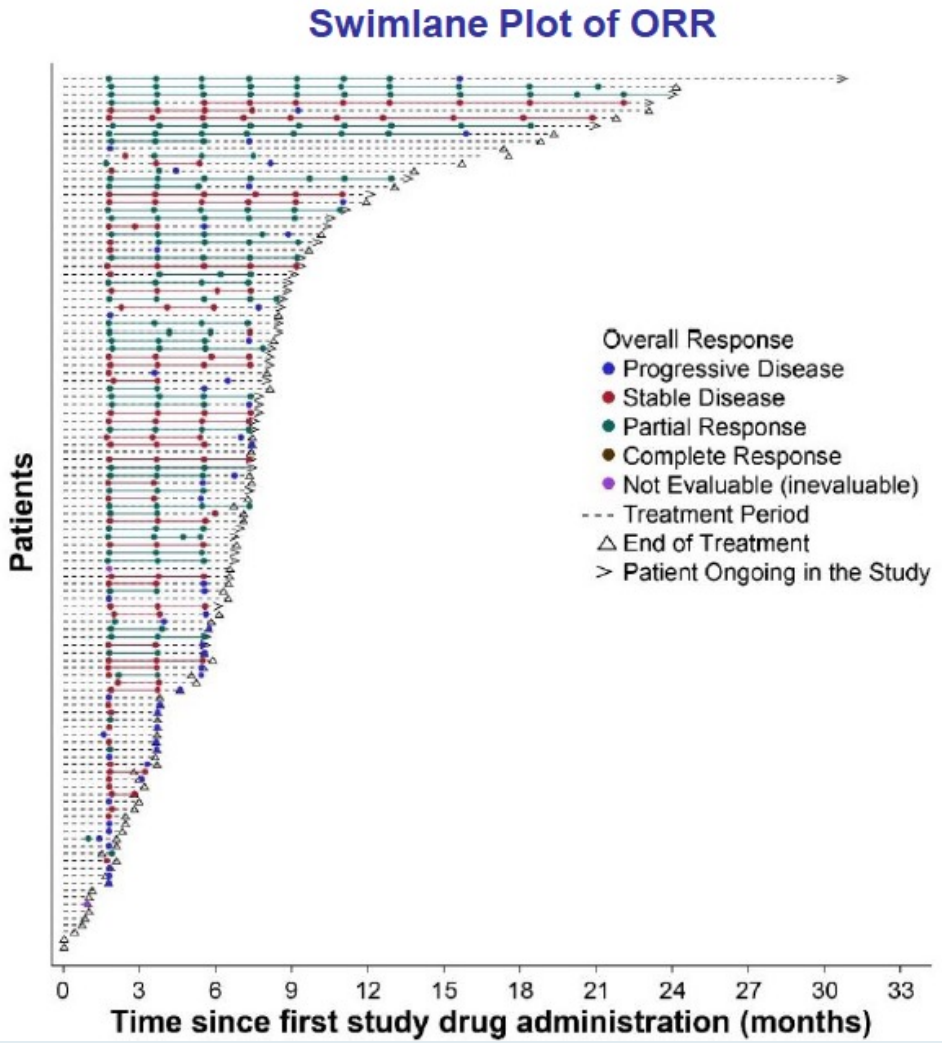
1. Chul B et al. ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

EXCLAIM: Mobocertinib in Platinum-Pretreated NSCLC with EGFR Exon 20 Insertions



- 94 patients (82%) had a reduction from baseline in the sum of target lesion diameter



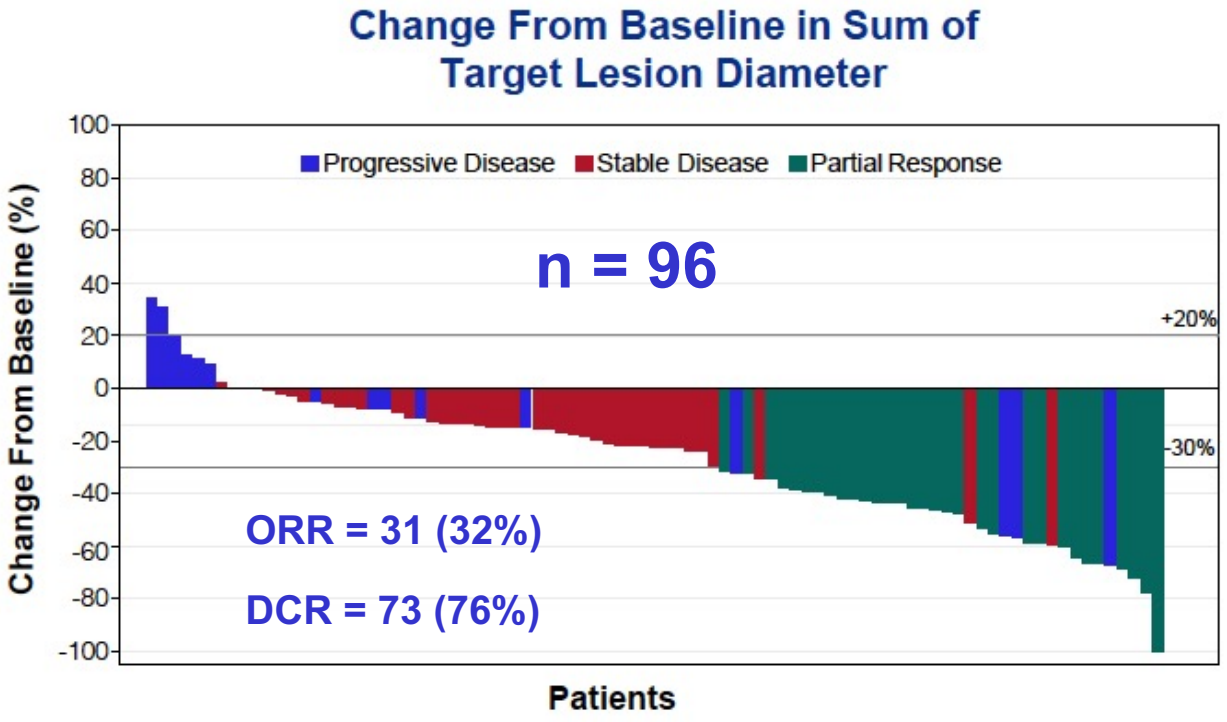
ORR, objective response rate; PPP, platinum-pretreated patients

Zhou C et al. IASLC/WCLC 2020;Abstract OA04.03

Courtesy of Zofia Piotrowska, MD, MHS

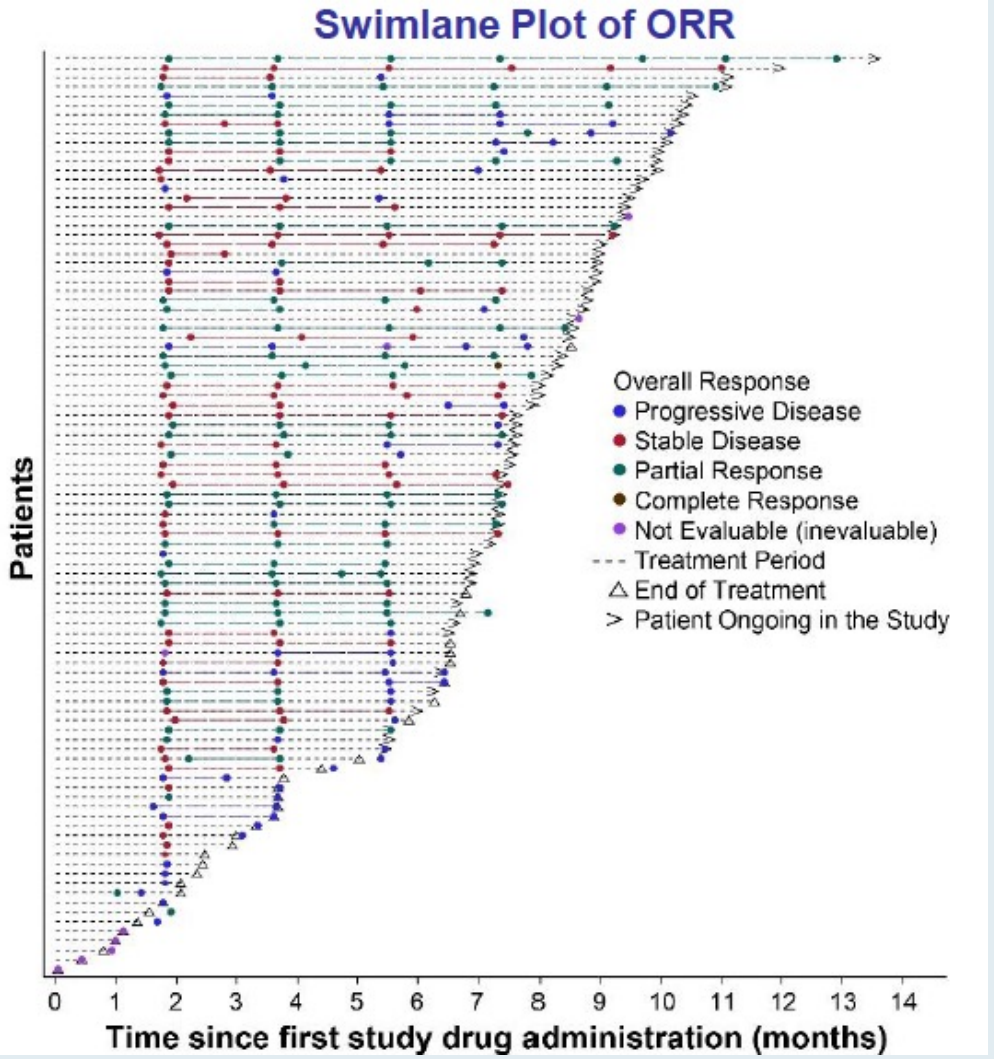
RTP RESEARCH TO PRACTICE

Mobocertinib Resulted in Reductions in Target Lesion Volume in EXCLAIM Cohort



- 77 patients (80%) had a reduction from baseline in the sum of target lesion diameter

ORR, objective response rate

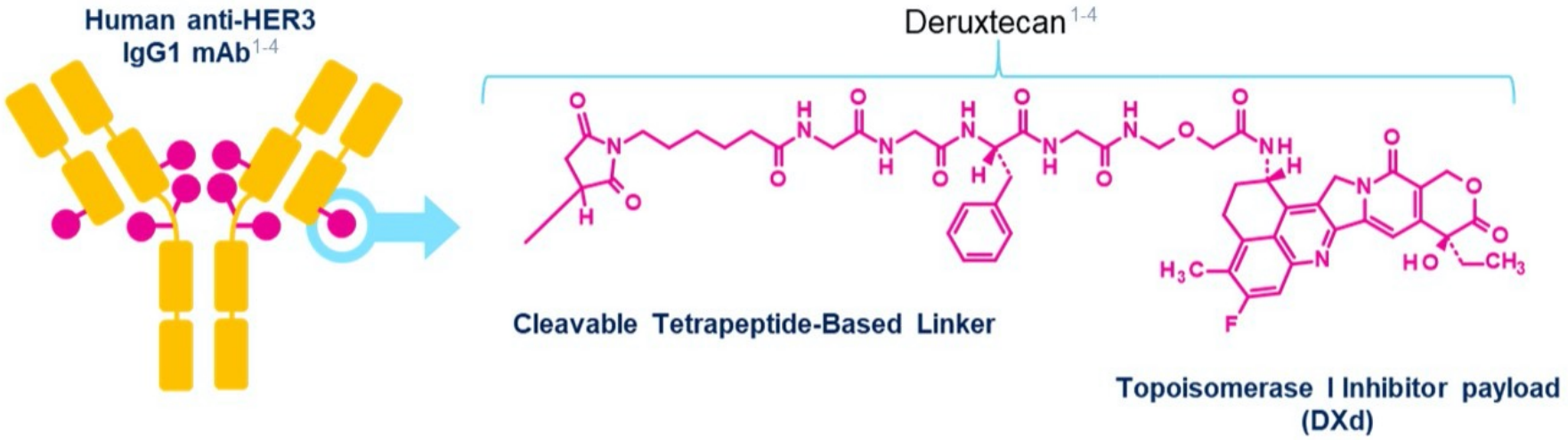


Zhou C et al. IASLC/WCLC 2020;Abstract OA04.03

Courtesy of Zofia Piotrowska, MD, MHS

RTP RESEARCH TO PRACTICE

Patritumab Deruxtecan (U3-1402; HER3-DXd)



- HER3 is expressed in 83% of NSCLC
- Patritumab Deruxtecan RP2D- 5.6mg/kg IV q21d

Janne P, ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

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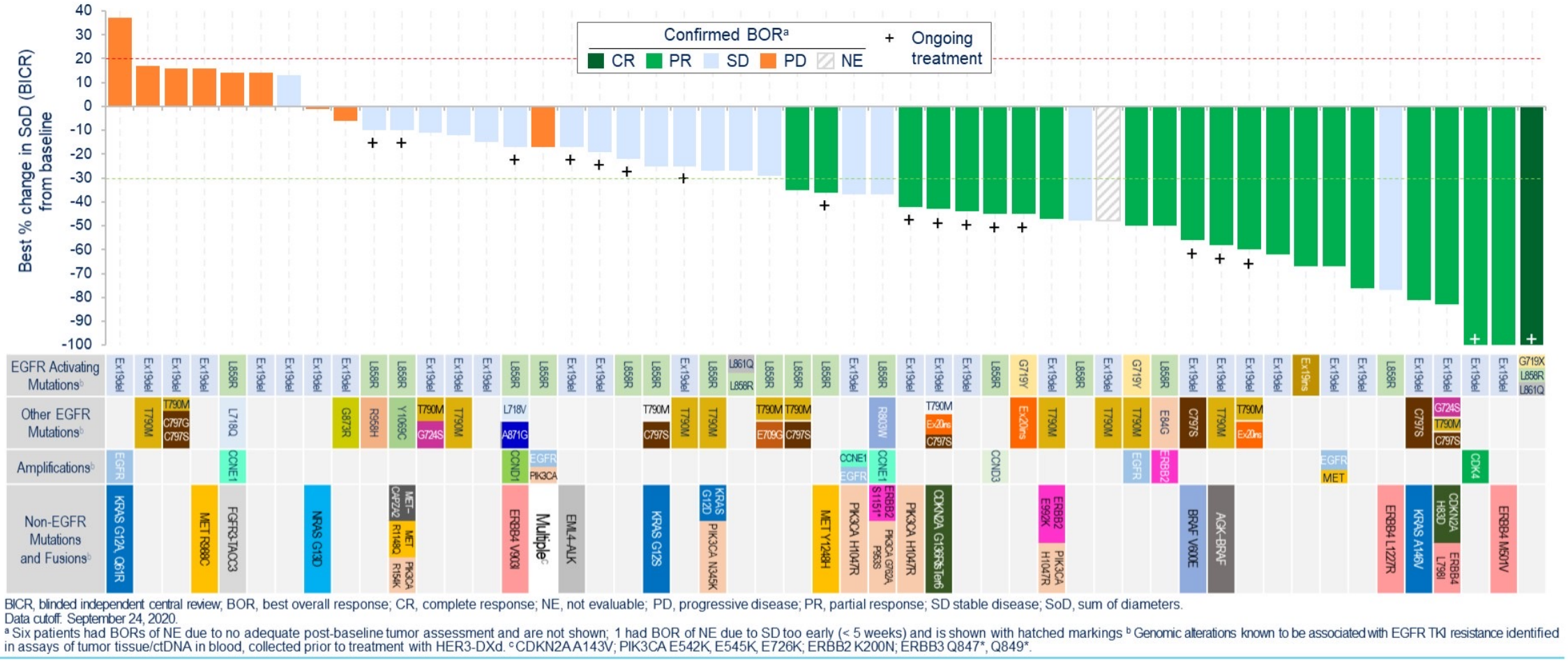
Patritumab Deruxtecan (U3-1402; HER3-DXd) has activity across diverse resistance mechanisms



BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD stable disease; SoD, sum of diameters.
Data cutoff: September 24, 2020.
[a] Six patients had BORs of NE due to no adequate post-baseline tumor assessment and are not shown; 1 had BOR of NE due to SD too early (< 5 weeks) and is shown with hatched markings [b] Genomic alterations known to be associated with EGFR TKI resistance identified in assays of tumor tissue/ctDNA in blood, collected prior to treatment with HER3-DXd. [c] CDKN2A A143V; PIK3CA E542K, E545K, E726K; ERBB2 K200N; ERBB3 Q847*, Q849*.

Janne P, ASCO 2021

Courtesy of Zofia Piotrowska, MD, MHS

Agenda

Introduction: Targeted Treatment in the Adjuvant Setting

Module 1: Current and Future Treatment of NSCLC with ALK and ROS1 Rearrangements

- Dr Deutsch: A 67-year-old man with metastatic adenosquamous carcinoma of the lung – PD-L1 >95%, ROS1 rearrangement
- Dr Lobins: A 74-year-old woman with metastatic adenocarcinoma of the lung and cancer in the right breast – TMB 14 mut/Mb, ALK mutation
- Key relevant data sets

Module 2: Management Strategies for Patients with NSCLC with RET Fusions or MET Alterations

- Dr Mohamed: A 63-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 0%, RET KIF5B fusion
- Key relevant data sets

Module 3: Key Data Guiding the Management of Metastatic NSCLC with EGFR Mutations

- Dr Chen: A 66-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 60%, EGFR exon 19 deletion
- Dr Flores: A 70-year-old man with metastatic NSCLC – EGFR L858R mutation
- Key relevant data sets

Module 4: Therapeutic Approaches for Patients with NSCLC with HER2 or KRAS Mutations

- Dr Lobins: A 62-year-old woman with recurrent metastatic adenocarcinoma of the lung – HER2 mutation
- Dr Ibrahim: A 46-year-old woman with metastatic adenocarcinoma of the lung – KRAS G12C mutation
- Key relevant data sets

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Case Presentation – Dr Lobins: A 62-year-old woman with recurrent metastatic adenocarcinoma of the lung – HER2 mutation

Dr Raymond Lobins

- December 2017: Initial diagnosis of Stage IIa adenocarcinoma of the right lung (2 of 3 hilar nodes positive) and treated with cisplatin/pemetrexed x 4
- July 2019: Local recurrence in mediastinum → chemoRT followed by durvalumab → PD in 3 months
- Molecular studies: HER2 mutation
- Docetaxel/ramucirumab → PD in 3 months
- May 2020: Gemcitabine/trastuzumab with good response but has developed CHF and renal insufficiency
- March 2021: Observation

Questions

- Would you recommend trastuzumab deruxtecan for this patient given her heart failure? Where in the treatment sequence would you introduce this agent?

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Case Presentation – Dr Ibrahim: A 46-year-old woman with metastatic adenocarcinoma of the lung – KRAS G12C mutation

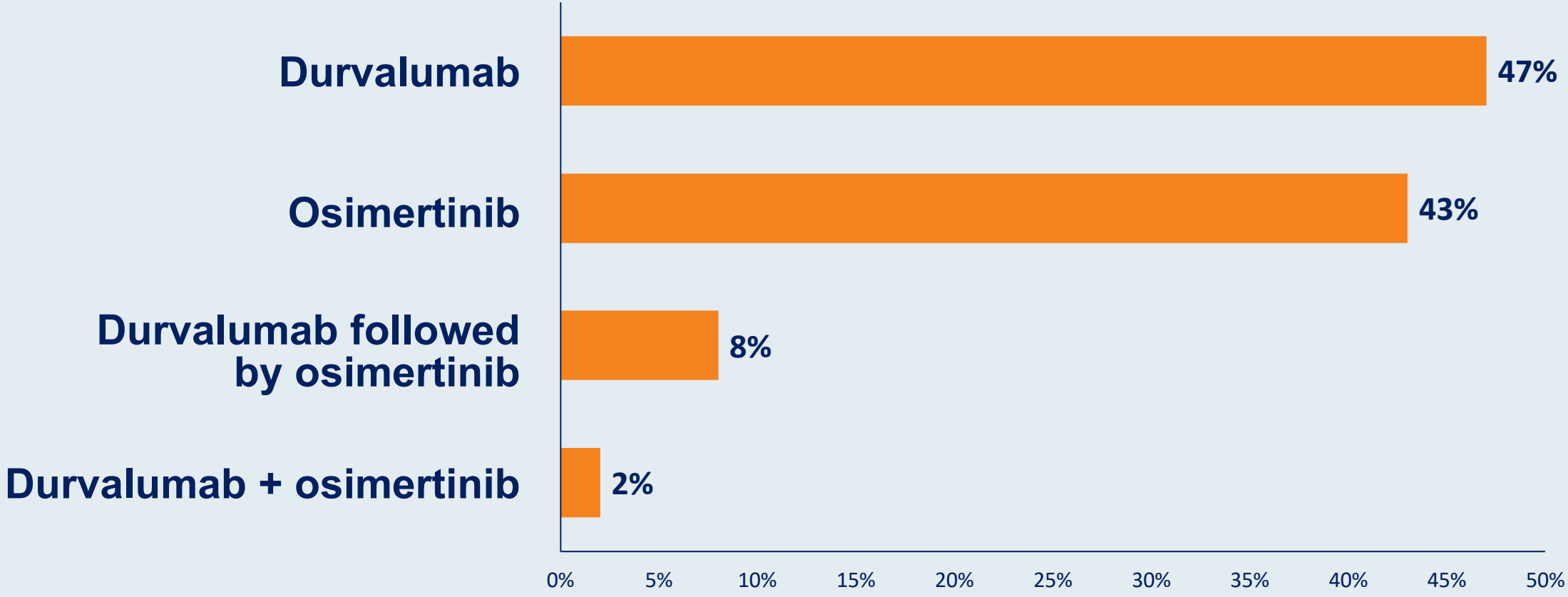
Dr Sulfi Ibrahim

- Initially diagnosed with stage III adenocarcinoma of the left lung
  - Concurrent chemoradiation with CR, followed by consolidation durvalumab x 1 year
- Develops PD about 3 months after completion of durvalumab
- Molecular studies: KRAS G12C mutation
- CodeBreak 100 trial with sotorasib → responded to therapy and has had no toxicity
- Remains on sotorasib 18 months later

Questions

- In the future, do you anticipate sotorasib may be moved up to the front-line setting for patients with KRAS mutations in a similar manner as osimertinib has been for patients with EGFR mutations?
- Is there any concern about a patient who receives sotorasib a few months after the completion of immunotherapy? Is there a risk of increased pneumonitis as there is in patients who receive osimertinib after receiving immunotherapy?
- Is there any data regarding the CNS activity of sotorasib?

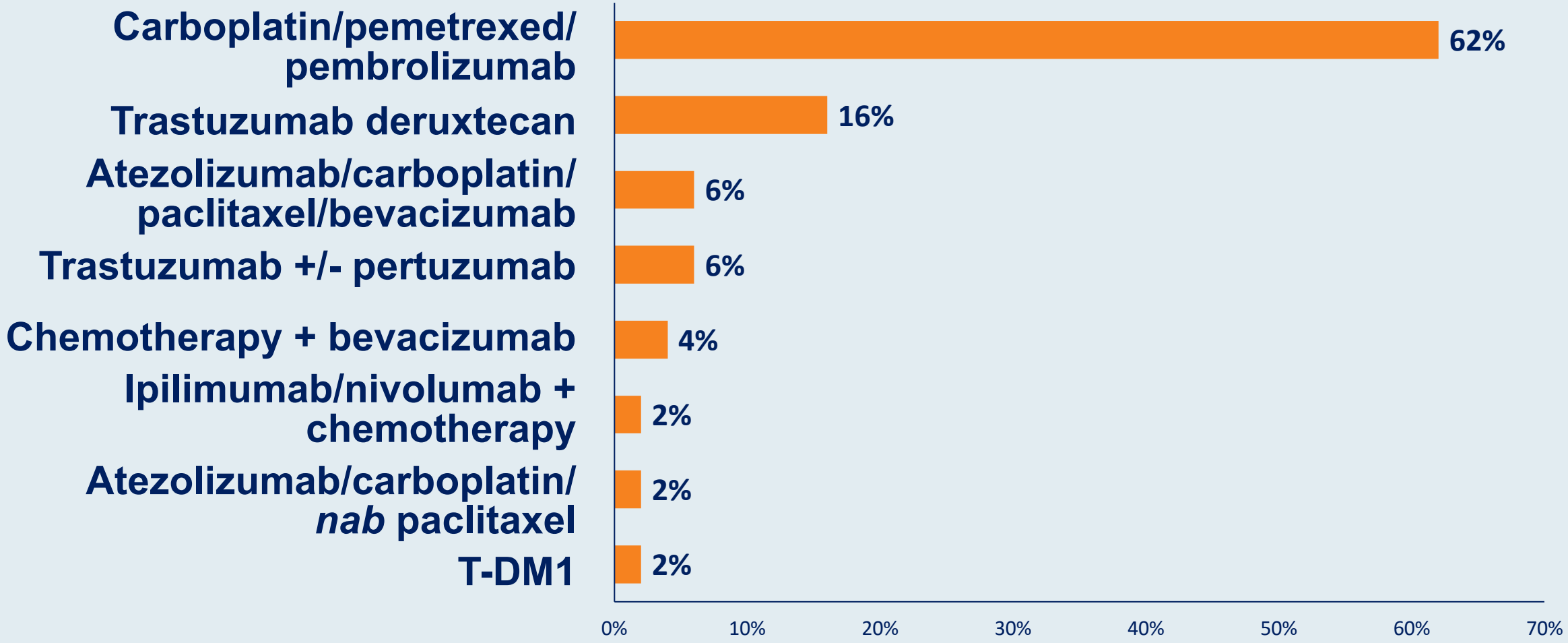
What would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who has completed chemoradiation therapy and is found to have an EGFR activating mutation?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

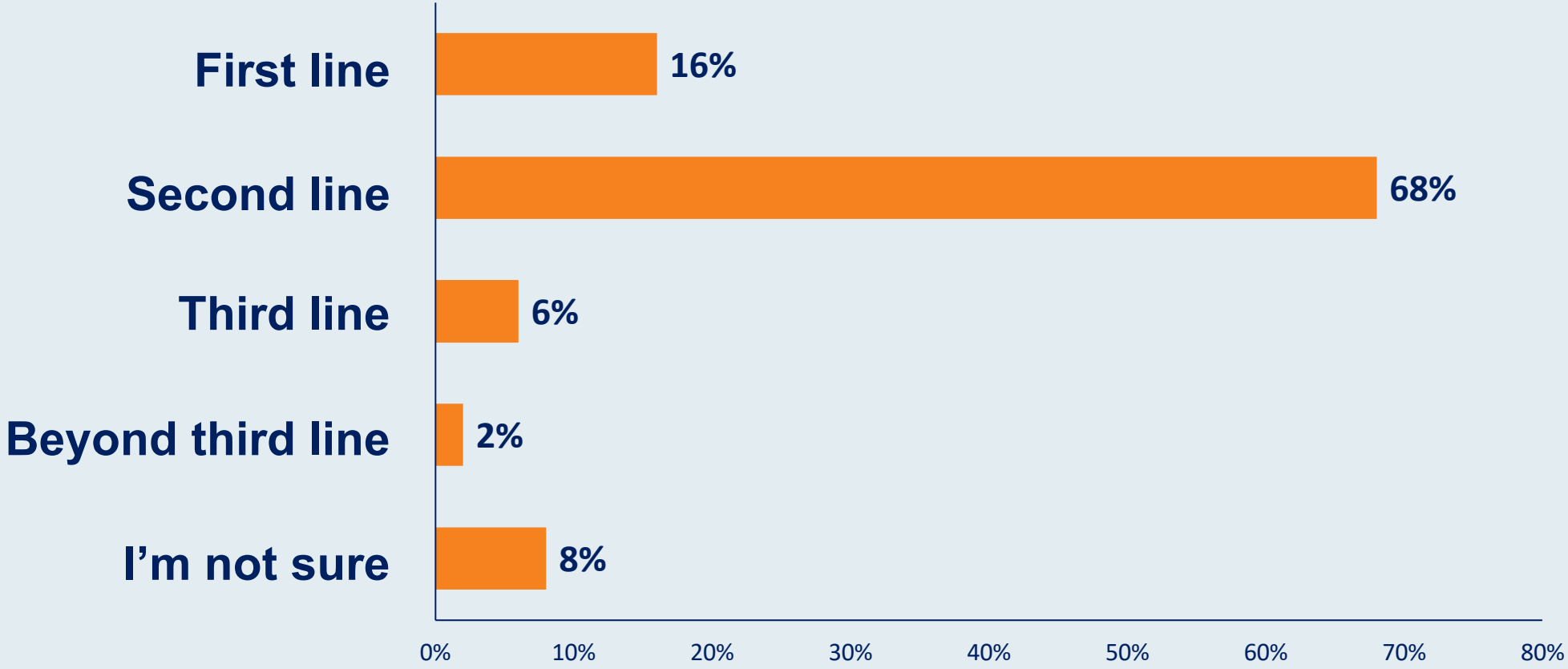
Regulatory and reimbursement issues aside, what would be your preferred first-line treatment for a patient with metastatic nonsquamous NSCLC with a HER2 mutation and a TPS of 10%?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

For a patient with metastatic nonsquamous NSCLC with a HER2 mutation and a PD-L1 TPS of 10%, in which line of therapy should targeted treatment (eg, trastuzumab, trastuzumab deruxtecan) be used?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

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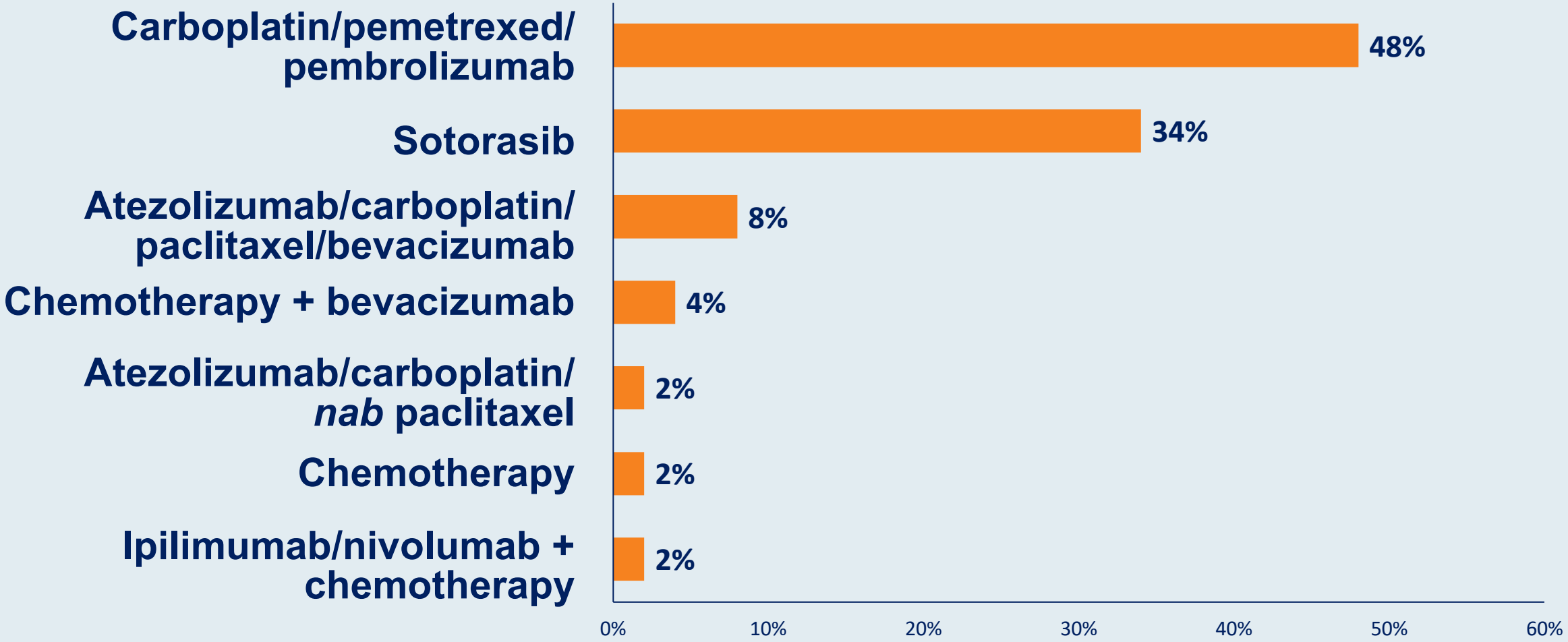

Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

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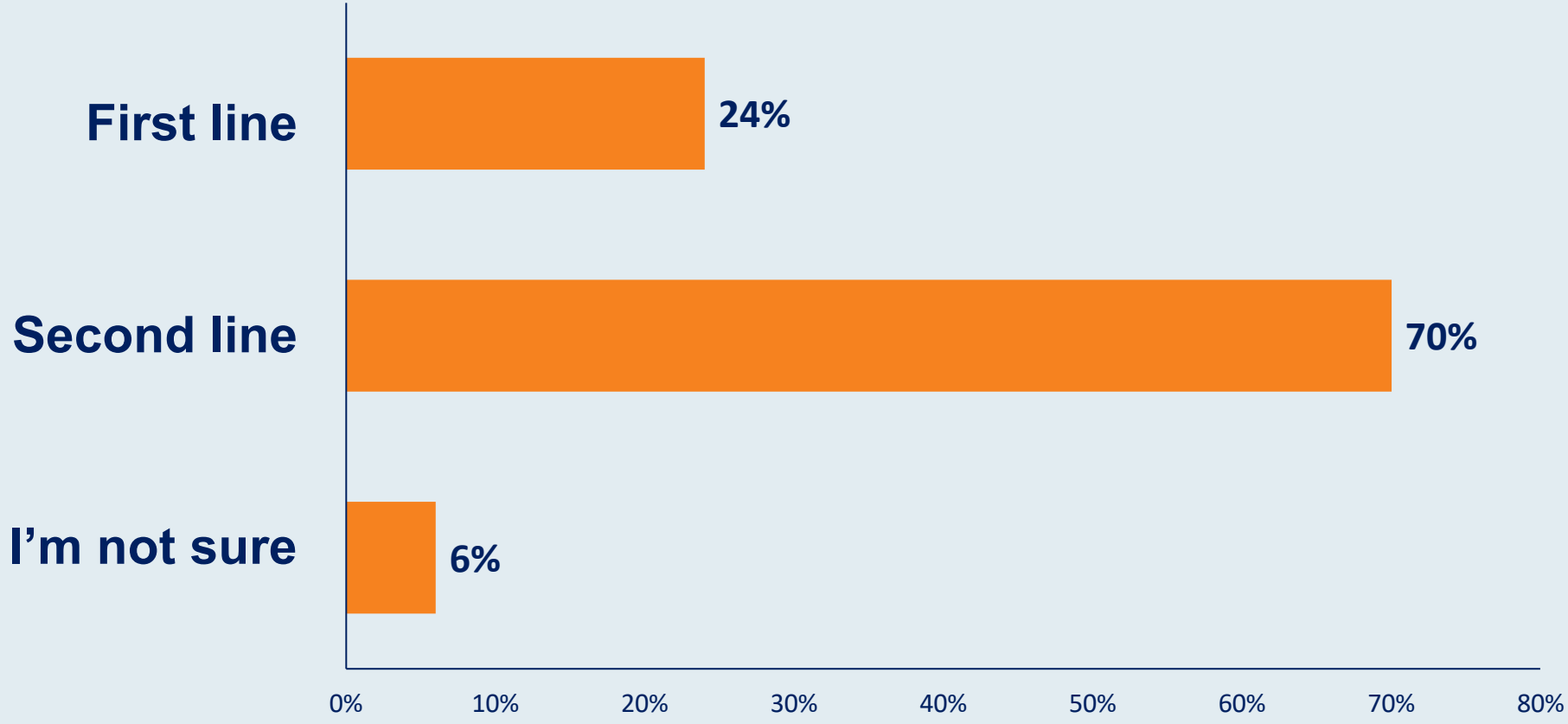

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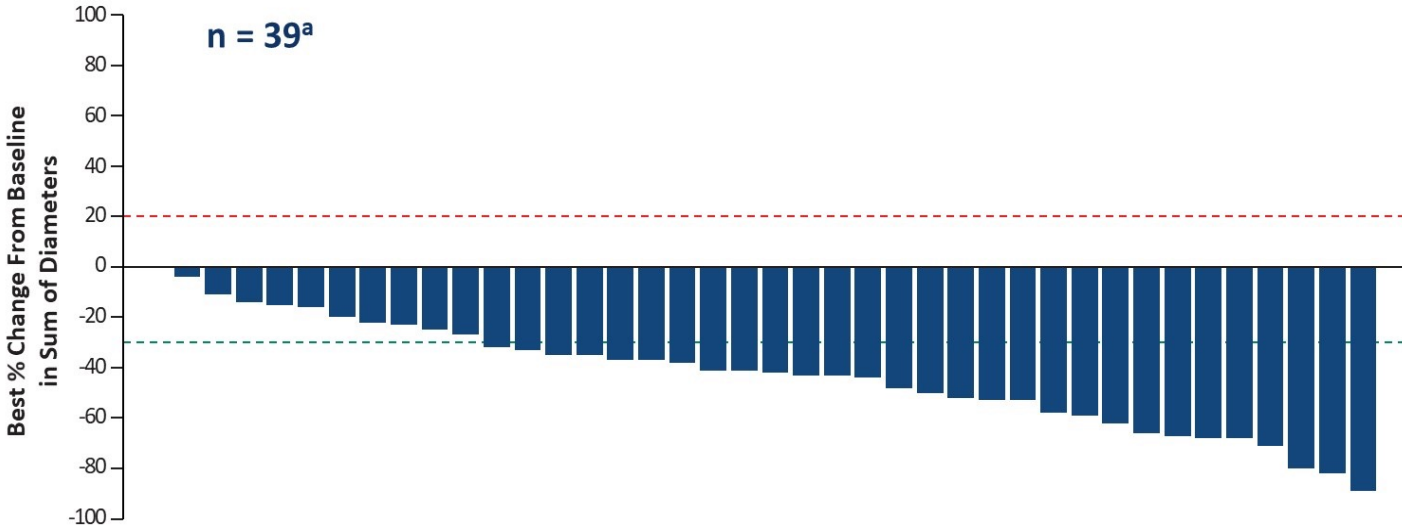
ERBB2 (HER2)-mutant NSCLC

- Occurs in 1-2% of patients with NSCLC
- Distinct from HER2 expression
- Distinct from HER2 amplification

Courtesy of Gregory J Riely, MD, PhD

DESTINY-Lung01: Evaluation of Trastuzumab Deruxtecan in HER2-mutant NSCLC

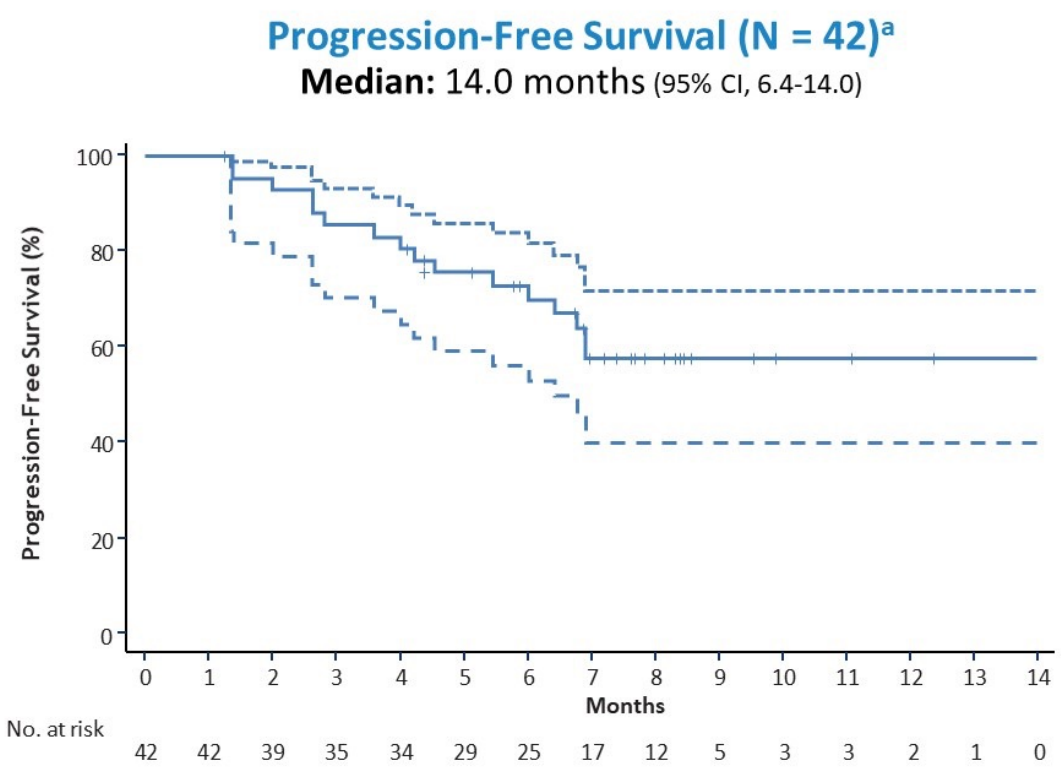
	Patients (N = 42)
Confirmed ORR by ICR	**61.9% (n = 26)** (95% CI, 45.6%-76.4%)
CR	2.4% (n = 1)
PR	59.5% (n = 25)
SD	28.6% (n = 12)
PD	4.8% (n = 2)
Not evaluable	4.8% (n = 2)
Disease control rate	90.5% (95% CI, 77.4%-97.3%)
Duration of response, median	Not reached (95% CI, 5.3 months-NE)
PFS, median	14.0 mo (95% CI, 6.4-14.0 months)

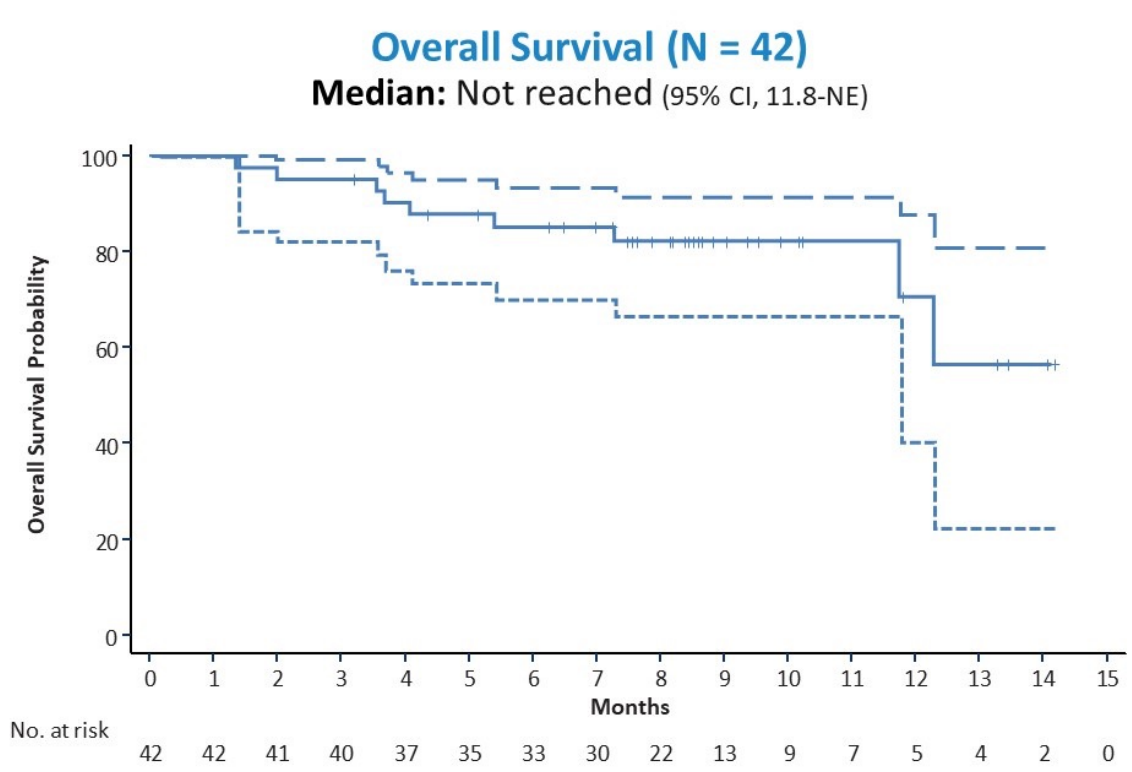


Courtesy of Gregory J Riely, MD, PhD

Smit et al, ASCO 2020

DESTINY-Lung01: Evaluation of Trastuzumab Deruxtecan in HER2 mutant NSCLC





Courtesy of Gregory J Riely, MD, PhD

Smit et al, ASCO 2020

KRAS-mutant NSCLC

- ~25% of Patients with NSCLC have KRAS mutations
- The most common KRAS mutation is G12C

Courtesy of Gregory J Riely, MD, PhD

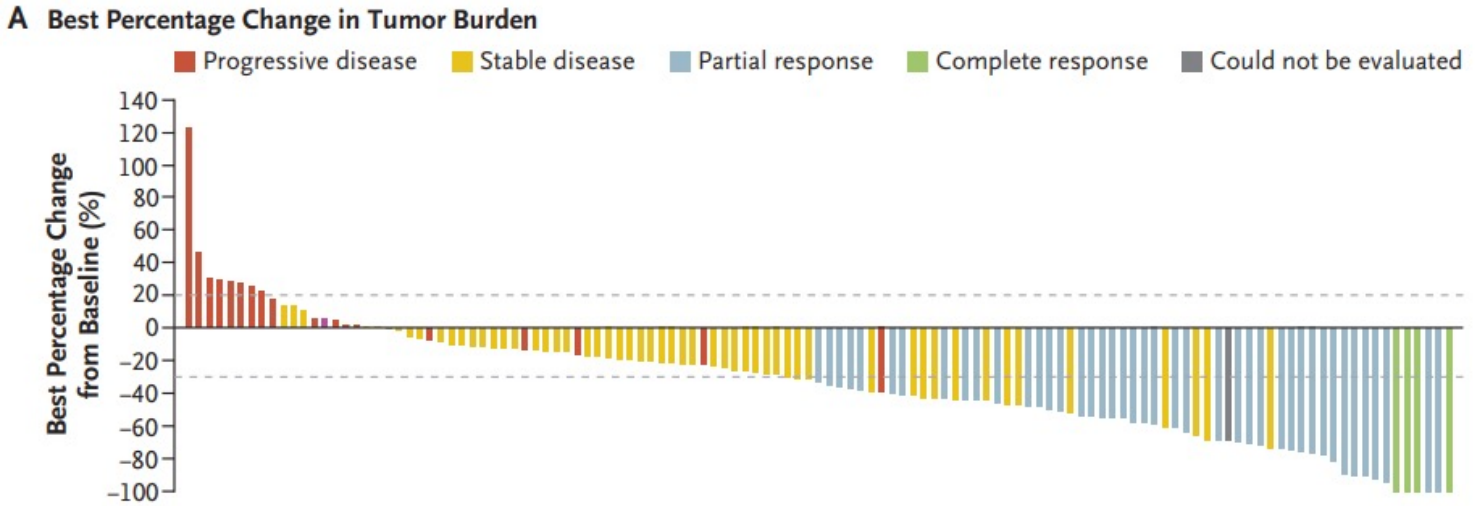
CodeBreak100 Trial

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

Table 2. Tumor Response to Sotorasib Therapy According to Independent Central Review.*

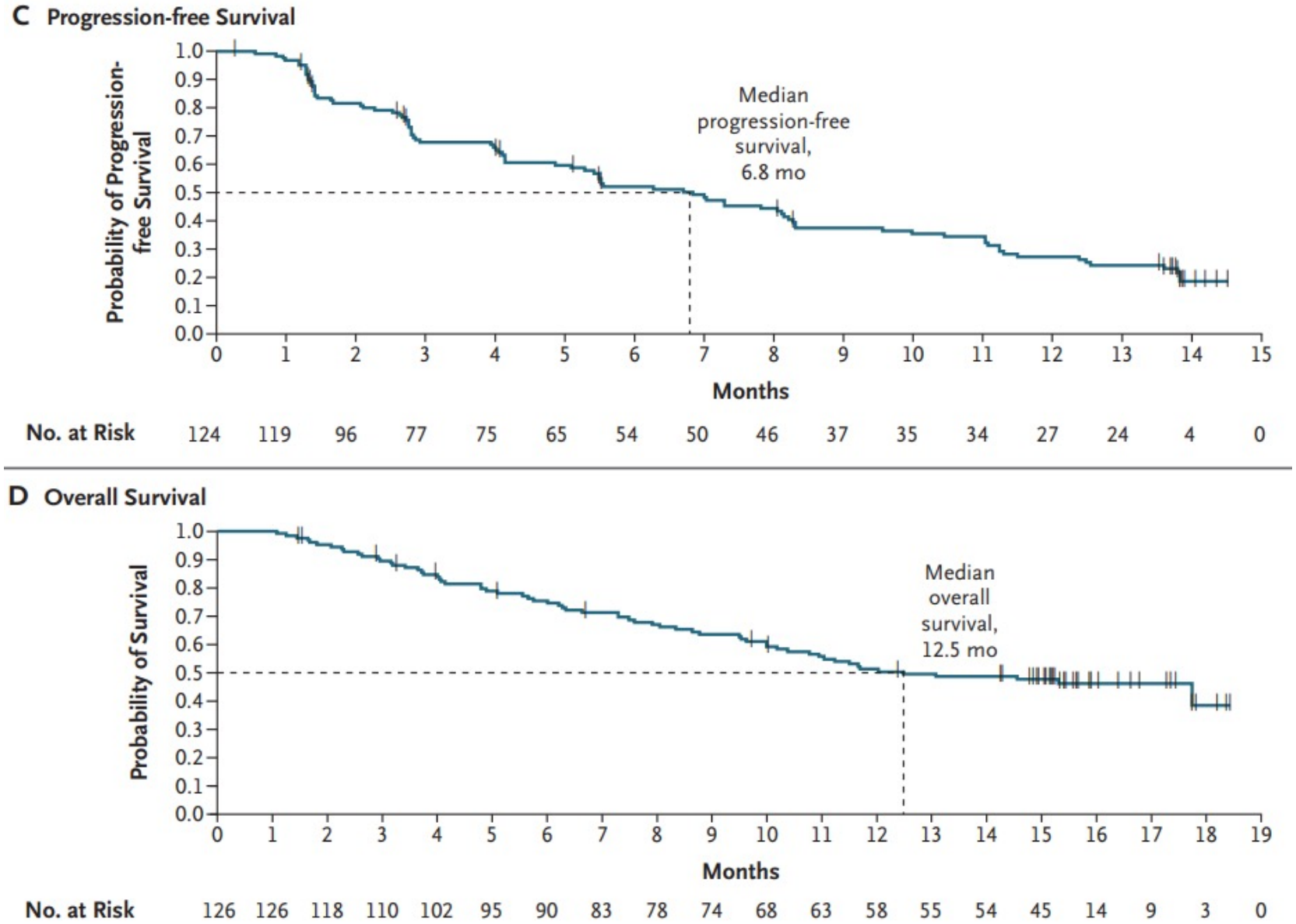
Variable	Patients (N = 124)
Objective response — % (95% CI)†	37.1 (28.6–46.2)
Disease control — % (95% CI)‡	80.6 (72.6–87.2)
Best response — no. (%)	
Complete response	4 (3.2)
Partial response	42 (33.9)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
Could not be evaluated	2 (1.6)
Missing scan	2 (1.6)
Median duration of objective response (95% CI) — mo§	11.1 (6.9–NE)
Kaplan–Meier estimate of objective response (95% CI) — %	
At 3 mo	90.5 (76.7–96.3)
At 6 mo	70.8 (54.3–82.2)
At 9 mo	57.3 (40.4–71.0)



NEJM 2021;384(25):2371-2381.

Courtesy of Gregory J Riely, MD, PhD

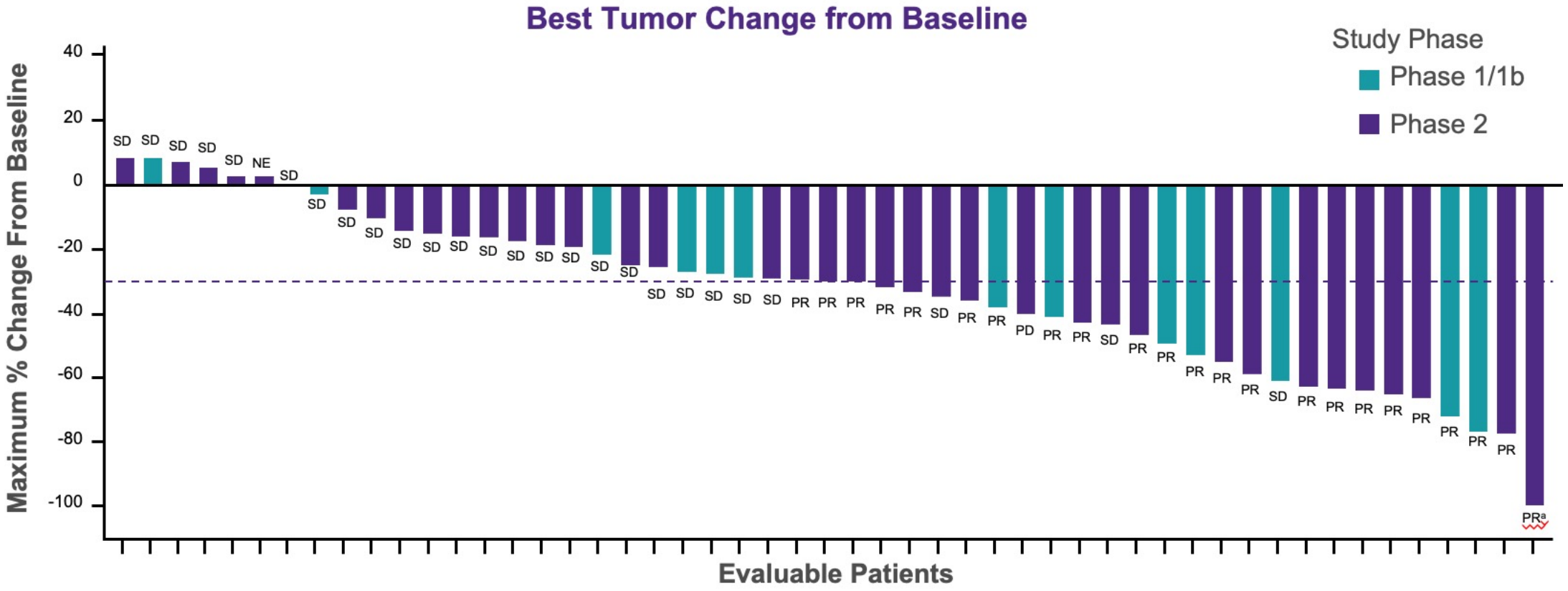
CodeBreak100 Trial: Sotorasib in Patients with KRAS G12C NSCLC



Courtesy of Gregory J Riely, MD, PhD

Skoulidis et al, NEJM 2021

KRYSTAL-1: Adagrasib in Patients with KRAS G12C NSCLC



- Clinical benefit (DCR) observed in 96% (49/51) of patients

Courtesy of Gregory J Riely, MD, PhD

Riely et al, ELCC 2021

KRYSTAL-1: Adagrasib in Patients with KRAS G12C 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%)

Courtesy of Gregory J Riely, MD, PhD

Riely et al, ELCC 2021

What General Medical Oncologists Want to Know About Immunotherapy and Other Nontargeted Approaches for Lung Cancer

Wednesday, July 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Mark Awad, MD, PhD
David R Spigel, MD
Heather Wakelee, 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 2 to 3 business days.

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