Expert Second Opinion: Investigators Discuss Available Clinical Research in the Care of Patients with Non-Small Cell Lung Cancer and Validated Targets Beyond EGFR

A Live Webinar Held as a Satellite CME/MOC Symposium During the IASLC 2021 World Conference on Lung Cancer Worldwide Virtual Event

Friday, September 10, 2021
5:45 AM – 6:45 AM MDT / 7:45 AM – 8:45 AM ET

Faculty

D Ross Camidge, MD, PhD
Alexander E Drilon, MD
Justin F Gainor, MD

Moderator

Neil Love, MD

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Faculty

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Denver, Colorado

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Director, Center for Thoracic Cancers at Massachusetts General Hospital
Director of Targeted Immunotherapy in the Henri and Belinda Termeer Center for Targeted Therapies
Associate Professor of Medicine
Harvard Medical School
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Associate Attending Physician
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Moderator

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Miami, Florida

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Commercial Support

This activity is supported by educational grants from Genentech, a member of the Roche Group, and Lilly.

This program was approved by the IASLC 2021 World Conference on Lung Cancer Program Committee as an independent activity held in conjunction with the IASLC 2021 World Conference on Lung Cancer. This program is not sponsored or endorsed by IASLC and is not part of the official IASLC accredited program.

Dr Love — Disclosures

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Dr Drilon — Disclosures

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Employment (Immediate Family Member)	Ironwood Pharmaceuticals

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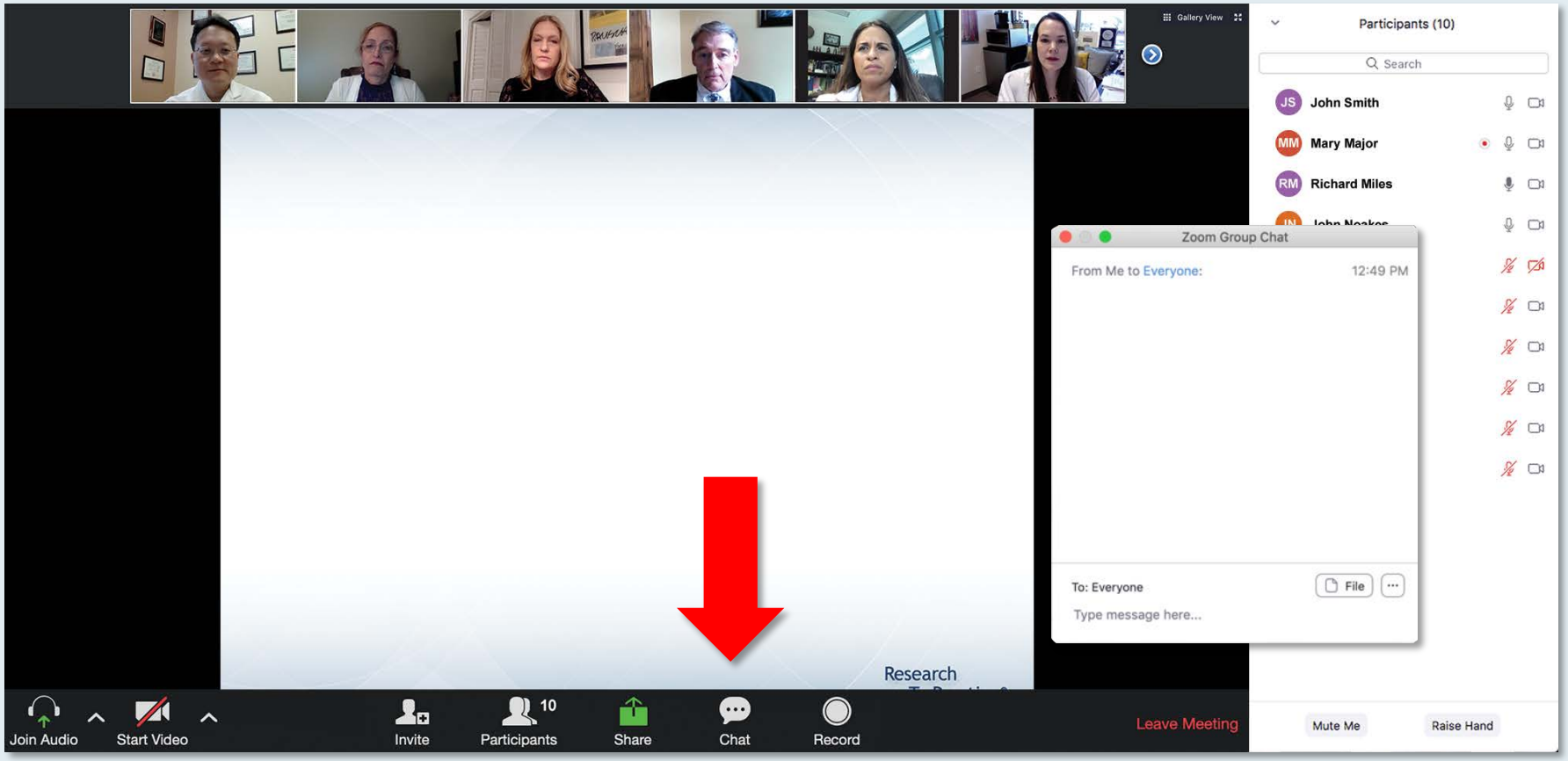

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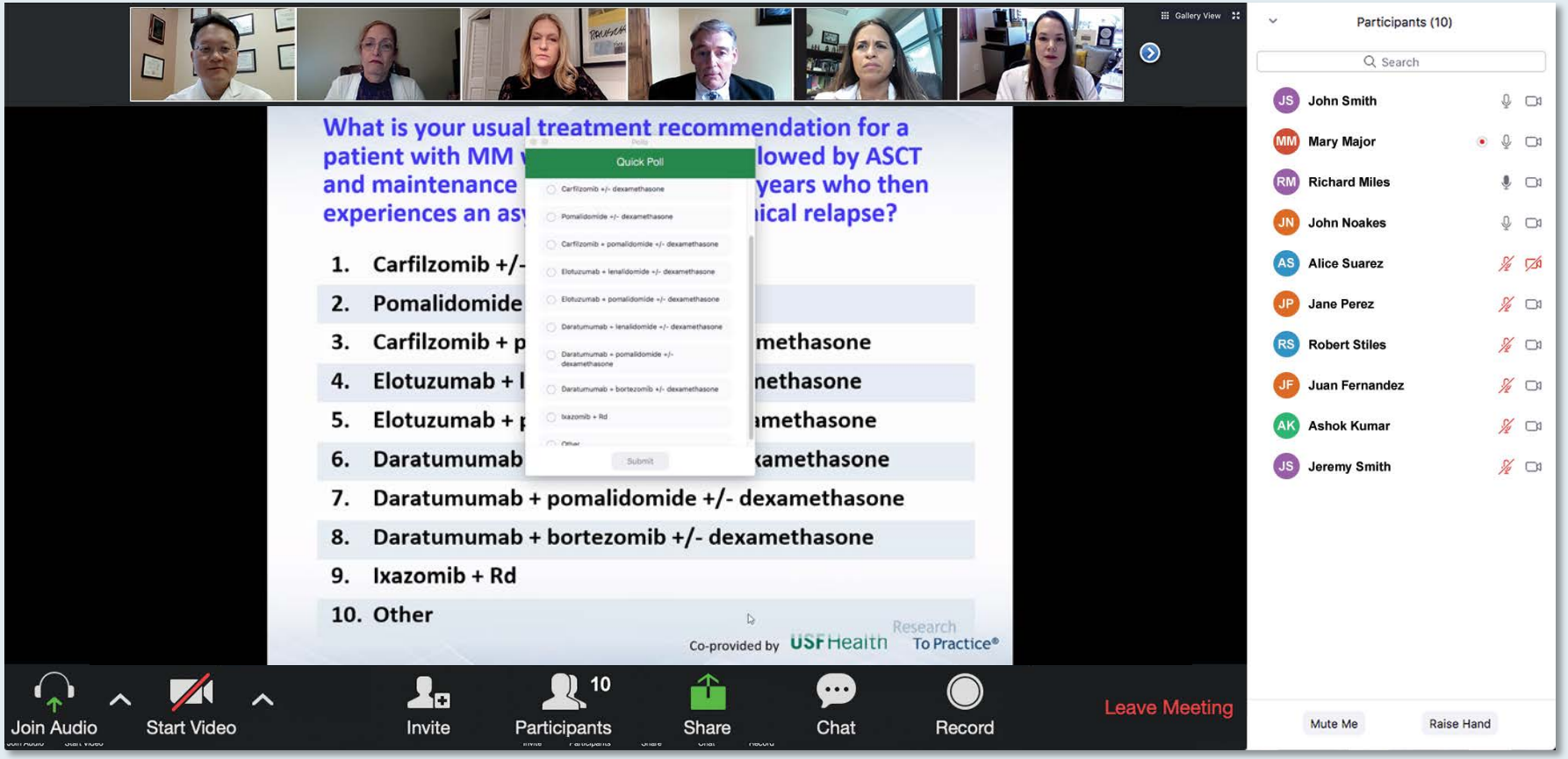

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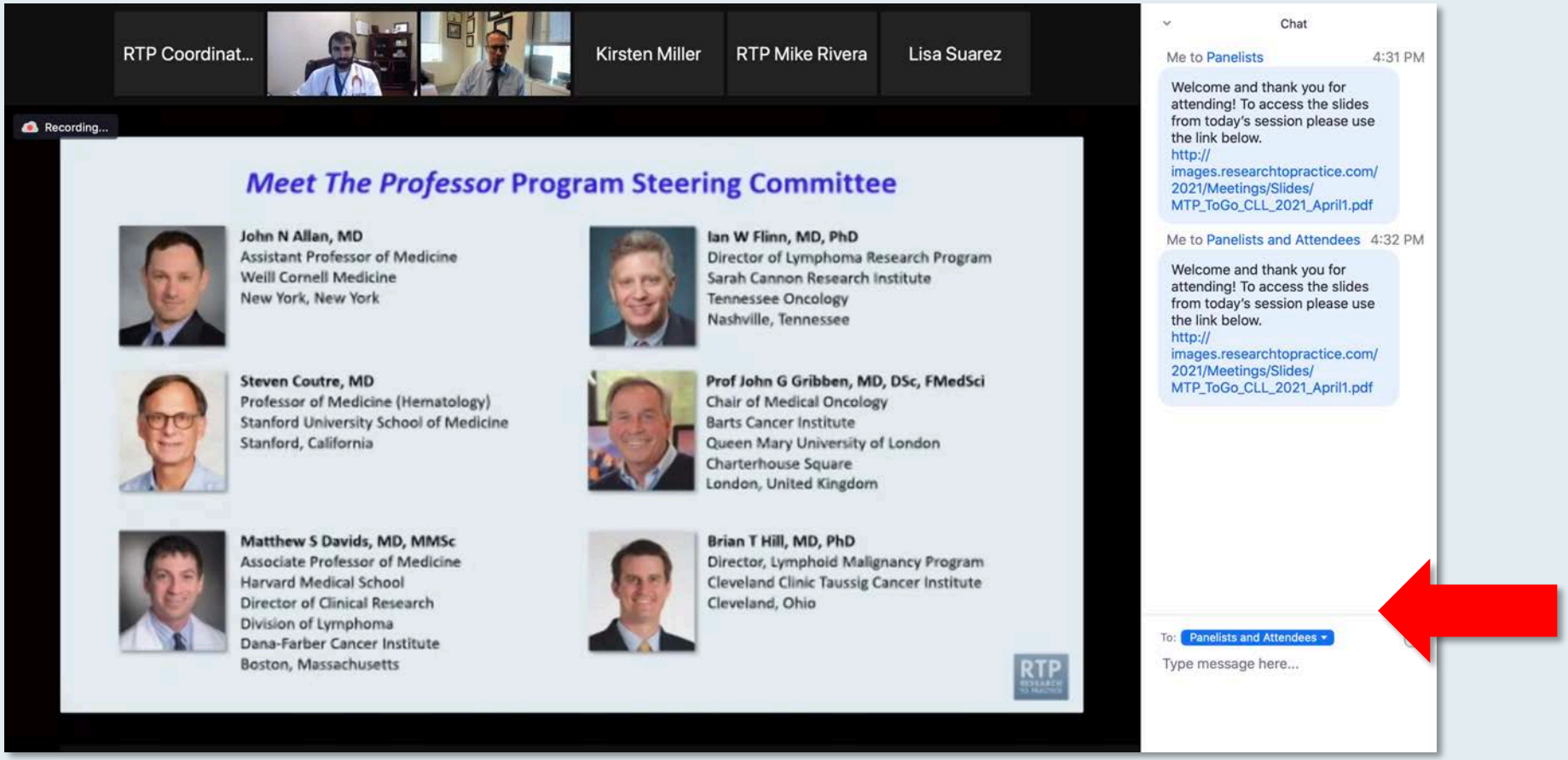

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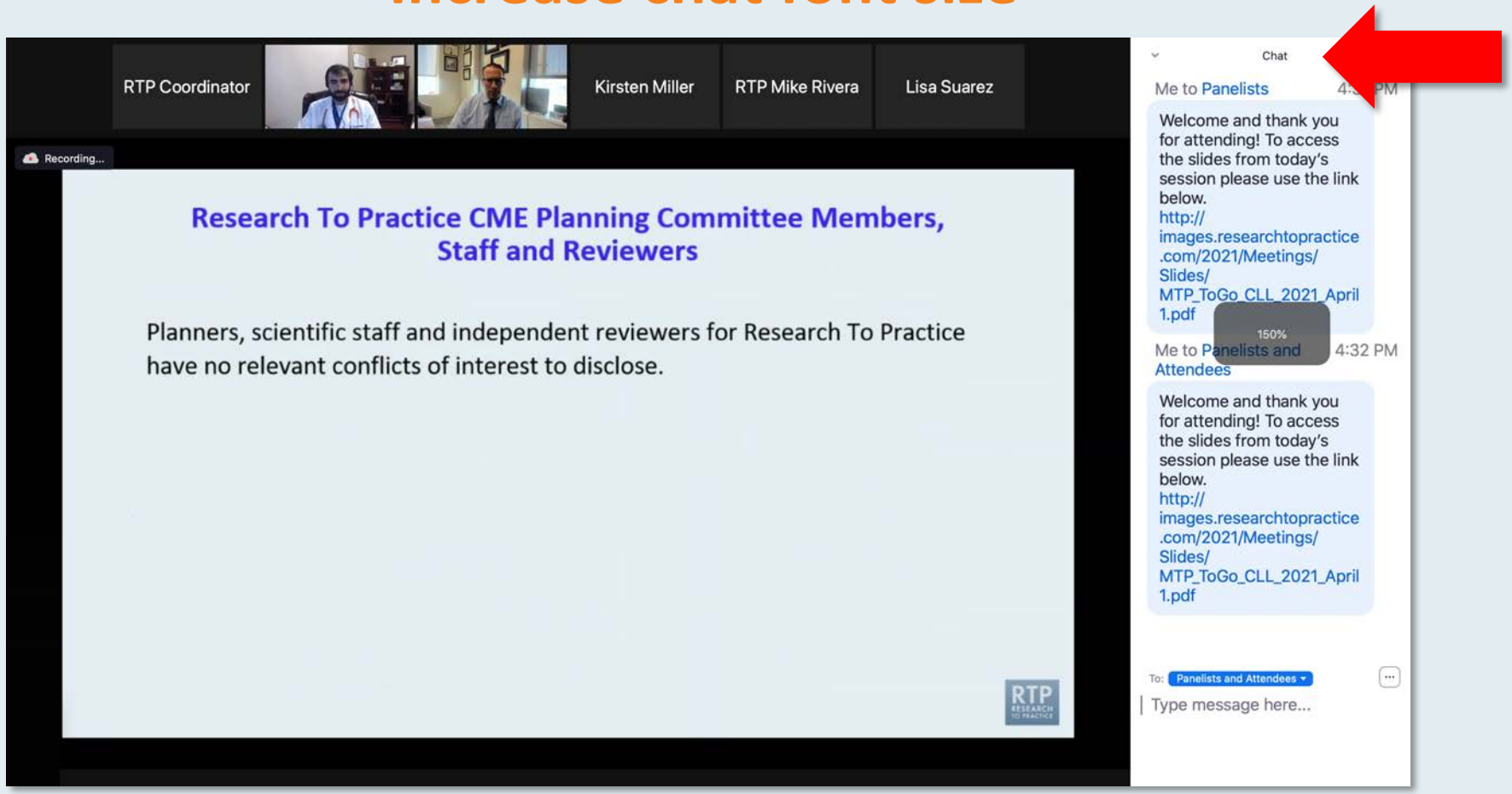

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Management of Localized Non-Small Cell Lung Cancer with EGFR Tumor Mutations

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9:15 PM – 10:15 PM MDT / 11:15 PM – 12:15 AM ET

Faculty

Edward B Garon, MD, MS
Harvey I Pass, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

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What Urologists Want To Know: Addressing Current Questions and Controversies in the Management of Bladder Cancer

A Virtual CME Satellite Symposium During the American Urological Association (AUA) 2021 Annual Meeting

Monday, September 13, 2021
11:00 AM – 12:30 PM ET / 8:00 AM – 9:30 AM PT

Faculty

Arjun Balar, MD
Ashish M Kamat, MD, MBBS
Guru Sonpavde, MD
Robert Svatek, MD

Moderator

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Faculty

Leonard G Gomella, MD
Maha Hussain, MD, FACP, FASCO
A Oliver Sartor, MD
Neal D Shore, MD

Moderator

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RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Tuesday, September 14, 2021
5:00 PM – 6:00 PM ET

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Neeraj Agarwal, MD

Moderator

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Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Thursday, September 16, 2021
5:00 PM – 6:00 PM ET

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Loretta J Nastoupil, MD

Moderator

Neil Love, MD

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Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Friday, September 17, 2021
12:00 PM – 1:00 PM ET

Faculty

Philip A Philip, MD, PhD, FRCP

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

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

Wednesday, September 22, 2021
5:00 PM – 6:00 PM ET

Faculty

Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Thank you for joining us!

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

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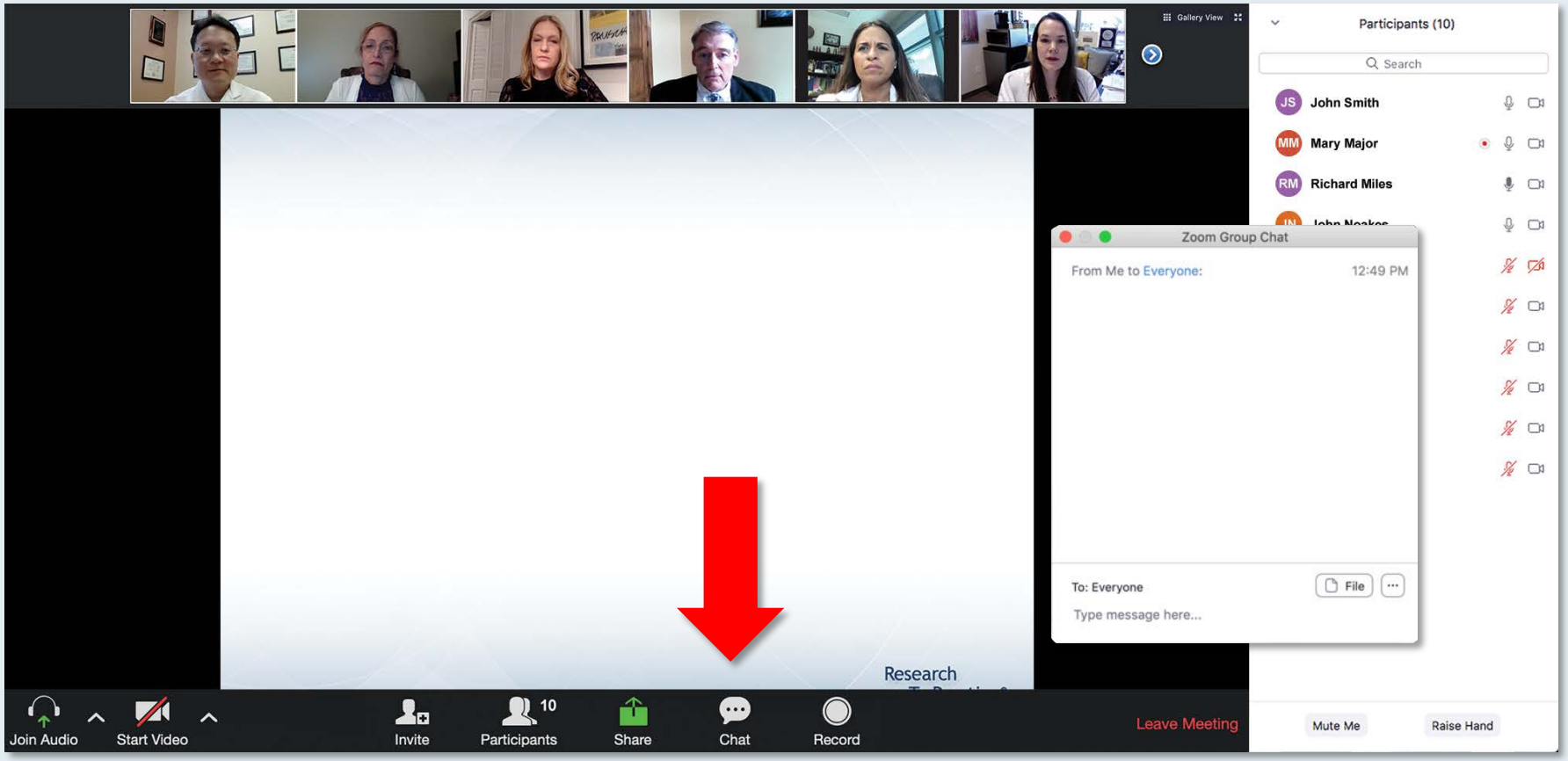

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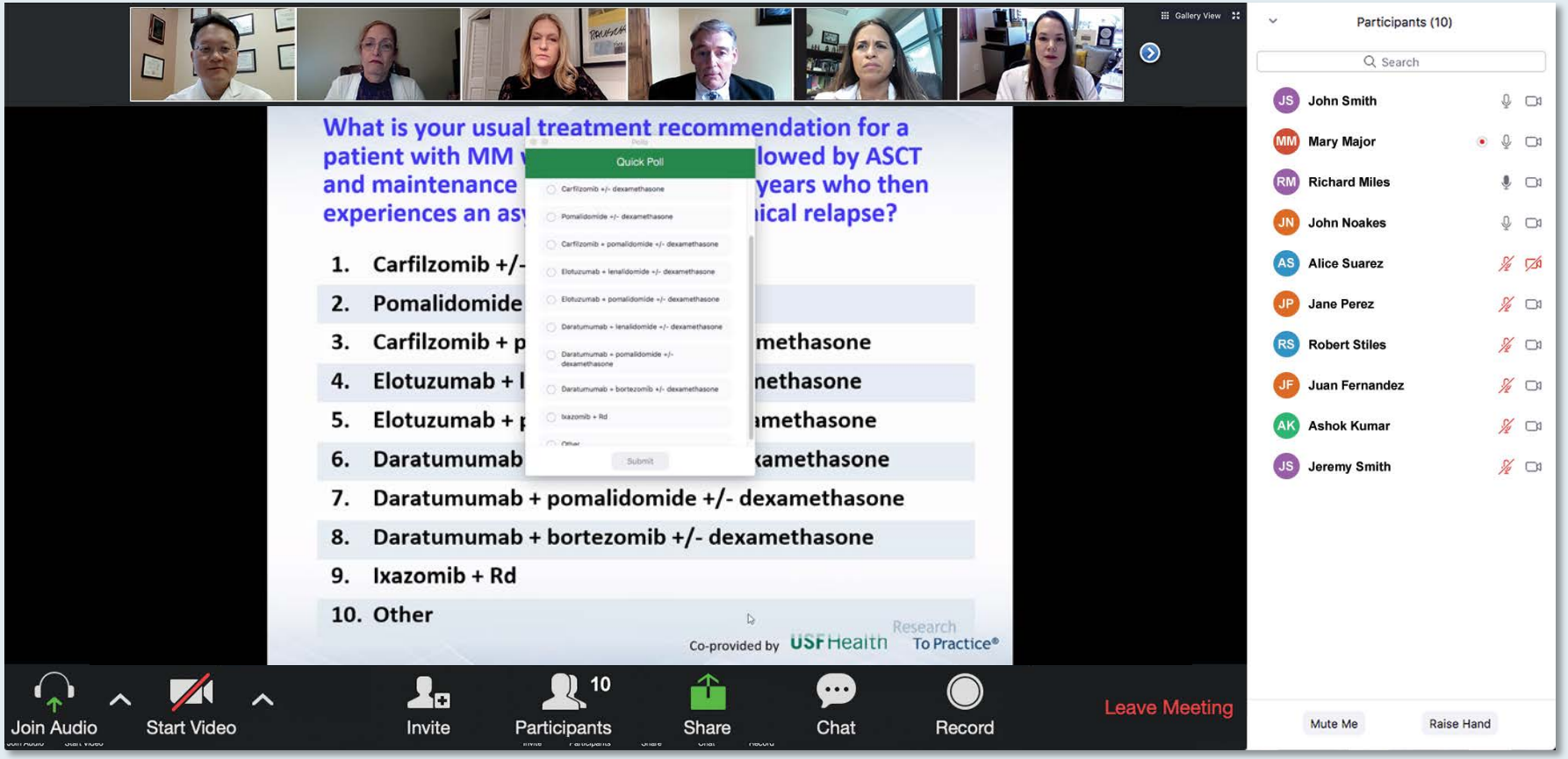

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KS Kumar, MD
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Florida Cancer Specialists and
Research Institute
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Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey

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Agenda

Module 1: Selection and Sequencing of Therapy for Patients with Non-Small Cell Lung Cancer (NSCLC) and an ALK Rearrangement

Module 2: Optimal Use of Recently Approved RET Inhibitors in the Care of Patients with NSCLC with RET Alterations

Module 3: Current and Future Directions in the Management of NSCLC with ROS1 Rearrangement

Module 4: Rational Approaches to Targeting BRAF in Patients with NSCLC

Module 5: Other Validated Targets Beyond EGFR (eg, MET, KRAS G12C)

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Case Presentation – Dr Jasani: A 35-year-old woman with newly diagnosed metastatic NSCLC – ALK mutation

Dr Nikesh Jasani

- Presented with cough, chest pain, and fatigue
- Diagnosed with stage IV NSCLC adenocarcinoma with right hilar mass, with metastases to multiple mediastinal nodes, bone and a solitary brain mass
- Molecular studies: ALK FISH+
- Stereotactic RT to brain lesion
- 1/2021: Alectinib → excellent response with resolution of all symptoms

Questions

- What is the optimal first-line therapy for NSCLC that is ALK mutation-positive?
- If her disease progresses, what would be the best next steps — repeat biopsy and assessment of resistance mutations to determine ideal treatment?
- How do you manage CNS disease in patients with NSCLC that is ALK mutation-positive?
- What are the side effects of note with the newer ALK inhibitors such as lorlatinib and brigatinib?

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Case Presentation – Dr Hart: A 53-year-old woman with metastatic adenocarcinoma of the lung and an ALK rearrangement

Dr Lowell Hart

- Presents with back and chest pain → CT: LUL mass, bilateral nodules, numerous osseous lesions
  - Bronchoscopic biopsy: Adenocarcinoma
  - ALK rearrangement
- 12/2015: Crizotinib
  - Bilateral lower extremity edema

Question

- In a situation like this, where the patient is stable on first-line therapy — but we know that in general the next-generation drugs are better — is it worthwhile switching somebody or should we save it in reserve?

Activity of ALK TKIs in the First-Line Setting for Advanced NSCLC with ALK Rearrangement

ALK TKI	Median PFS	ORR	Intracranial response
Crizotinib	10.9 mo	74%	NA
Ceritinib	16.6 mo	72.5%	72.7%
Alectinib	34.8 mo	82.9%	82.9%
Brigatinib	29.4 mo	71%	78%
Lorlatinib	Not reached	90%	66.7%
Ensartinib	26.2 mo	80%	64.3%

Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-253.

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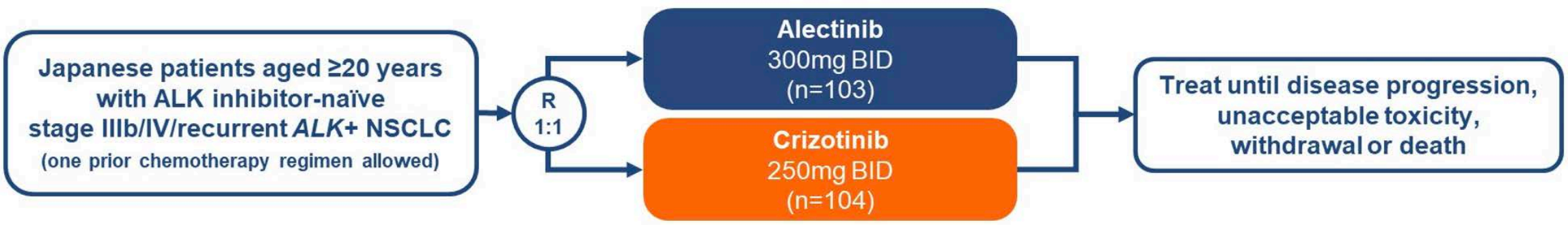
Common and Unique Adverse Effects of ALK TKIs

ALK TKI	Most common adverse effects
Crizotinib	Vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy
Ceritinib	Diarrhea, nausea, vomiting, fatigue, abdominal pain, decreased appetite, and weight loss
Alectinib	Constipation, fatigue, edema, myalgia and anemia
Brigatinib	Diarrhea, fatigue, nausea, rash , cough, myalgia, headache, hypertension, vomiting, and dyspnea
Lorlatinib	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, weight gain, cognitive effects, fatigue, dyspnea, arthralgia, diarrhea
Ensartinib	Rash, nausea, pruritis, and vomiting

Crizotinib PI, rev 1/2021; Ceritinib PI, rev 3/2019; Alectinib PI, rev 1/2021; Brigatinib PI, rev 5/2020; Lorlatinib PI, rev 3/2021
Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-253; Gristina V et al. *Pharmaceuticals* 2020;13:474.

Final Overall Survival Analysis from the Phase III J-ALEX Study of Alectinib versus Crizotinib



Primary endpoint: IRF-assessed PFS

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

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

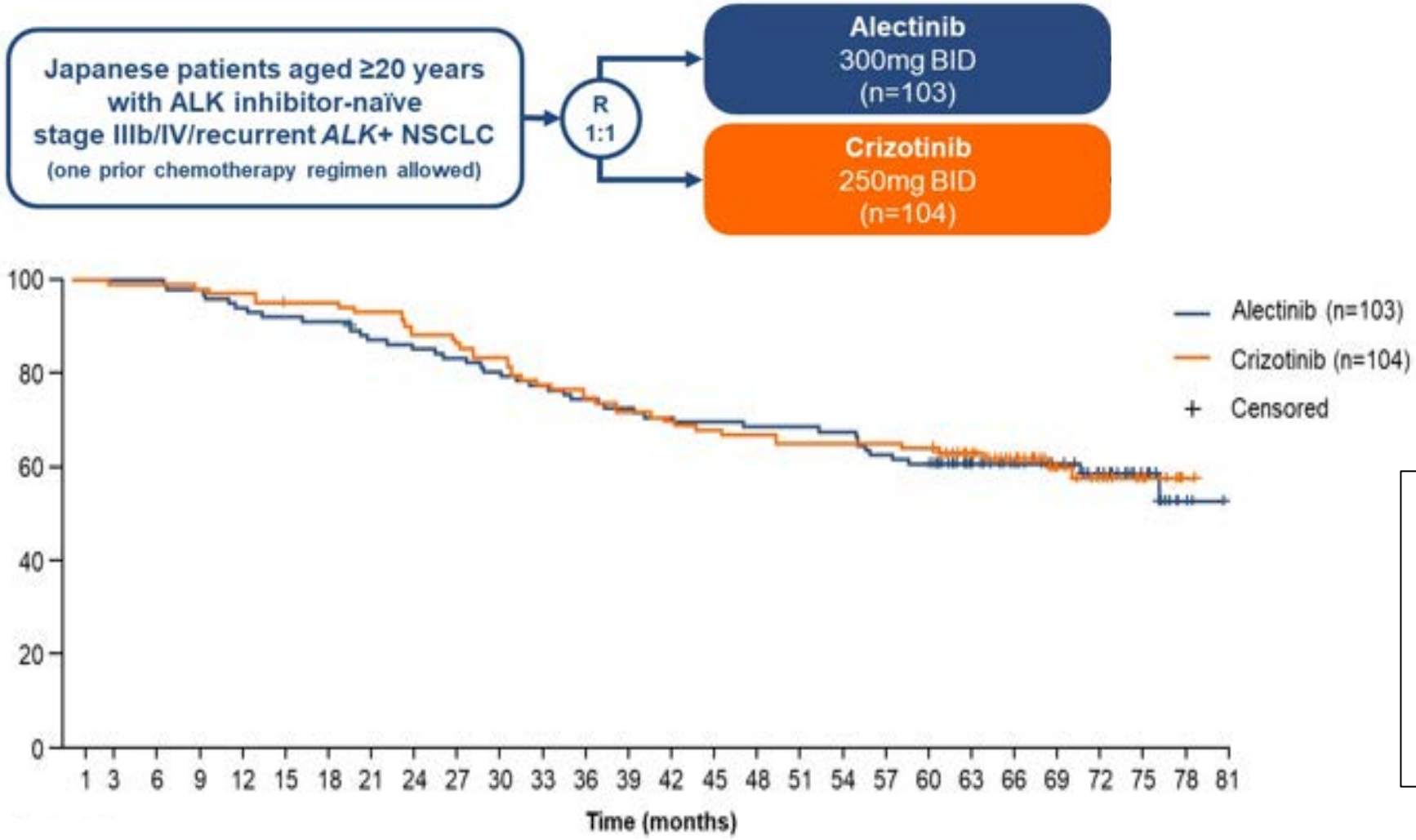
Median duration of OS follow-up:
68.6 months alectinib vs 68.0 months crizotinib

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

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

Yoshioka et al. ASCO 2021;Abstract 9022

J-ALEX: Final OS Analysis of Alectinib versus Crizotinib



Post crizotinib therapy:

79% alectinib

3% lorlatinib

1% brigatinib

Yoshioka et al. ASCO 2021;Abstract 9022

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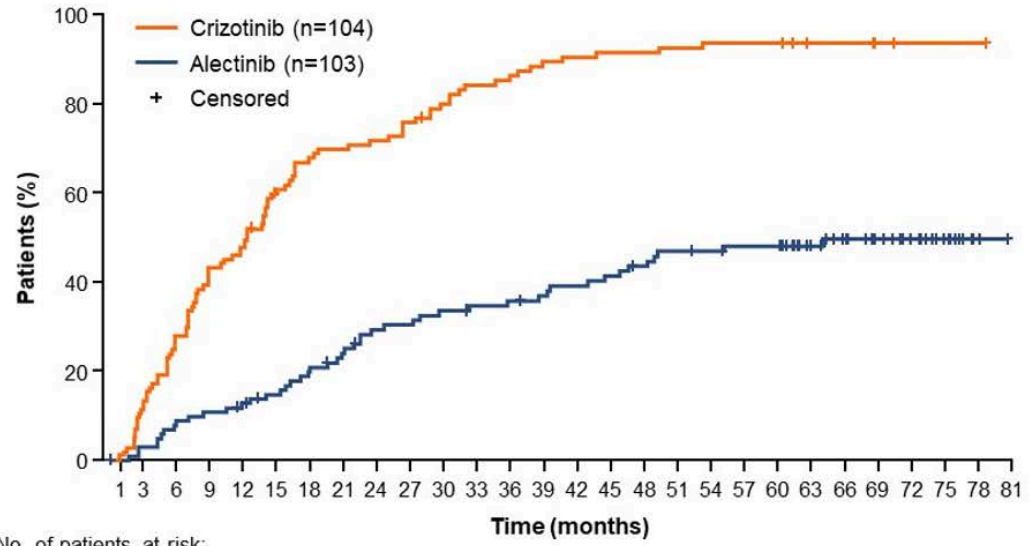
J-ALEX: Time from Randomization of First Change of Treatment and OS After Change of Treatment

Time from randomization to first change of treatment

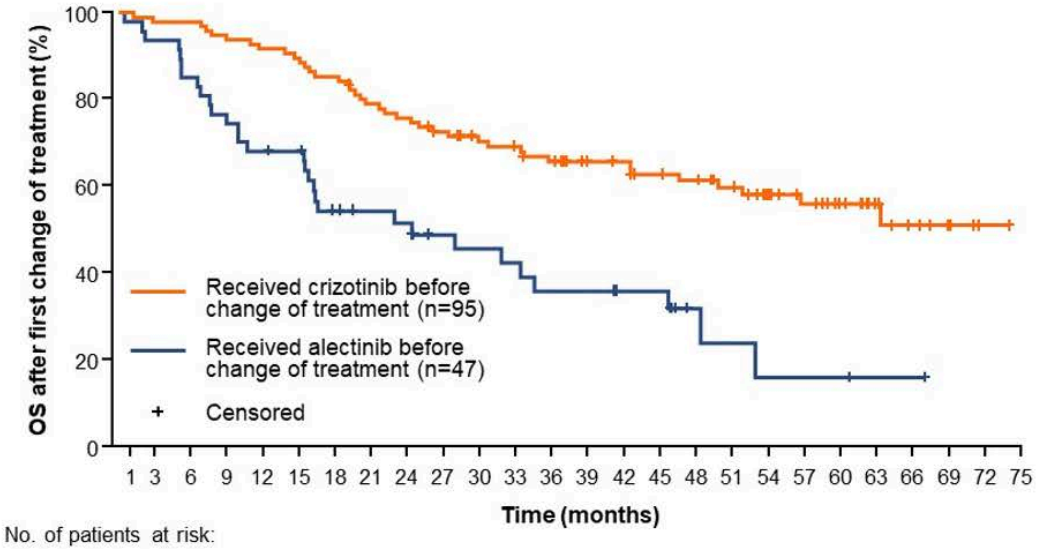


No. of patients at risk:

Crizotinib	103	90	75	59	54	40	32	30	28	24	19	15	13	10	9	8	8	7	6	6	6	3	3	2	1	1	1
Alectinib	102	99	93	91	88	84	78	71	66	65	62	60	59	57	55	53	50	47	46	44	44	34	28	22	16	9	2

Patients in the crizotinib arm tended to change their treatment earlier than patients in the alectinib arm (median time from randomization to first change of treatment: 12.3 months for the crizotinib arm [95% CI 8.7–14.6] and NE for the alectinib arm [95% CI 42.8–NE])

OS after first change of treatment in patients who received a subsequent anticancer therapy[a]



No. of patients at risk:

Crizotinib	95	93	93	90	87	85	81	74	71	66	61	59	55	48	47	43	41	37	31	26	19	12	7	4	1	
Alectinib	46	44	40	35	32	31	22	20	19	15	14	13	11	11	9	9	4	3	2	2	2	1	1			

In a non-randomized subset of patients who received a subsequent anticancer therapy, median OS from first change of treatment was 24.3 months for the alectinib arm (95% CI 15.4–45.6) and NE for the crizotinib arm (95% CI 49.8–NE)

- **This suggests that alectinib as a subsequent therapy may have substantially impacted OS in the crizotinib arm**

[a]Patient characteristics at treatment change may vary from baseline.

Yoshioka et al. ASCO 2021;Abstract 9022

FDA Expands Lorlatinib Approval to Front-Line Treatment of Metastatic NSCLC with ALK Fusion

Press Release – March 3, 2021

"The Food and Drug Administration granted regular approval to lorlatinib for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive, detected by an FDA-approved test. The FDA also approved the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc) as a companion diagnostic for lorlatinib.

Lorlatinib received accelerated approval in November 2018 for the second- or third-line treatment of ALK-positive metastatic NSCLC.

This current approval is based on data from Study B7461006 (NCT03052608), a randomized, multicenter, open-label, active-controlled trial conducted in 296 patients with ALK-positive metastatic NSCLC who had not received prior systemic therapy for metastatic disease. Patients were required to have ALK-positive tumors detected by the VENTANA ALK (D5F3) CDx assay. Patients were randomized 1:1 to receive lorlatinib 100 mg orally once daily (n=149) or crizotinib 250 mg orally twice daily (n=147). Study B7461006 demonstrated an improvement in progression-free survival (PFS) as assessed by blinded independent central review (BICR), with a hazard ratio of 0.28 (95% CI: 0.19, 0.41; p<0.0001)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-lorlatinib-metastatic-alk-positive-nsclc?utm_medium=email&utm_source=govdelivery

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

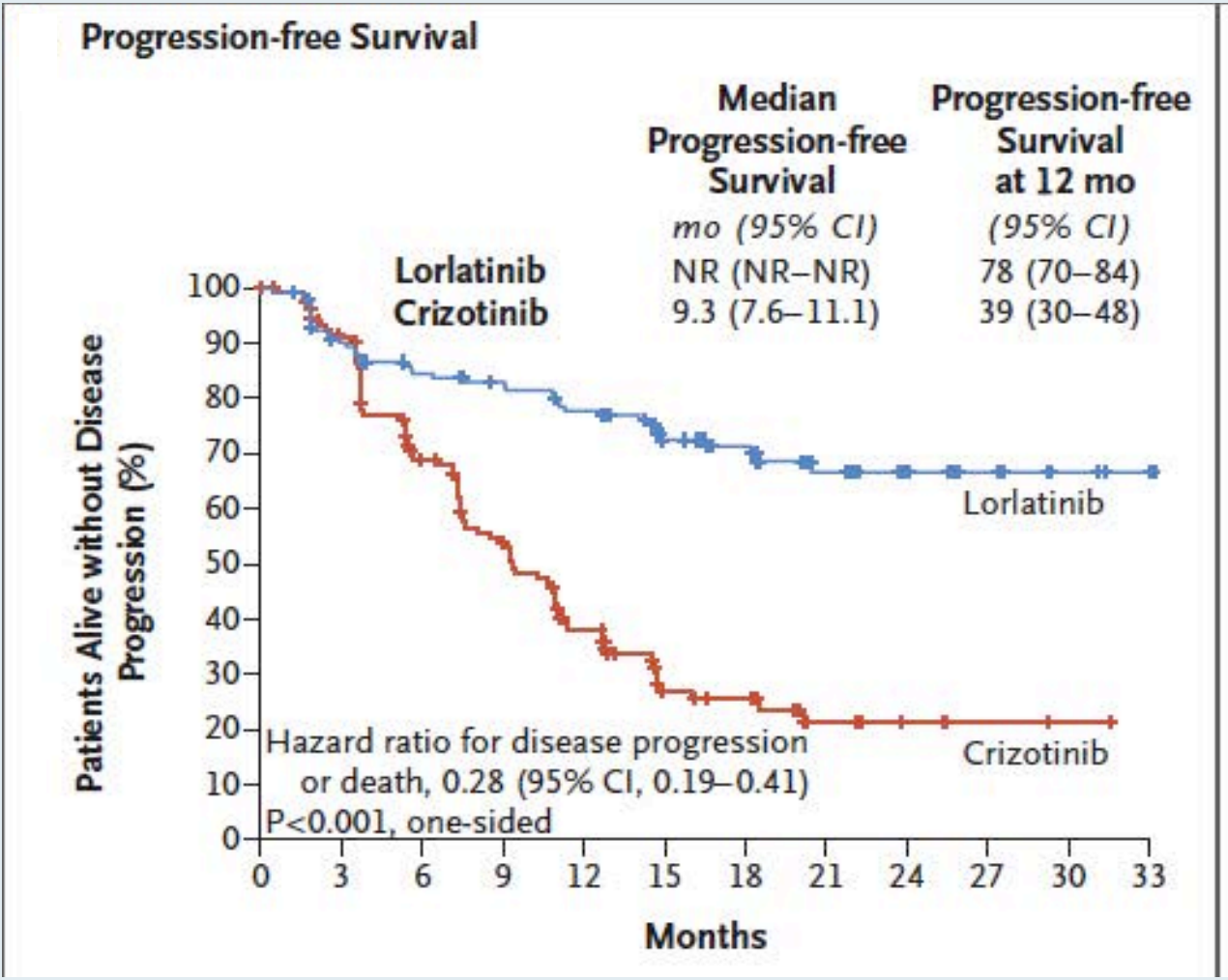
ORIGINAL ARTICLE

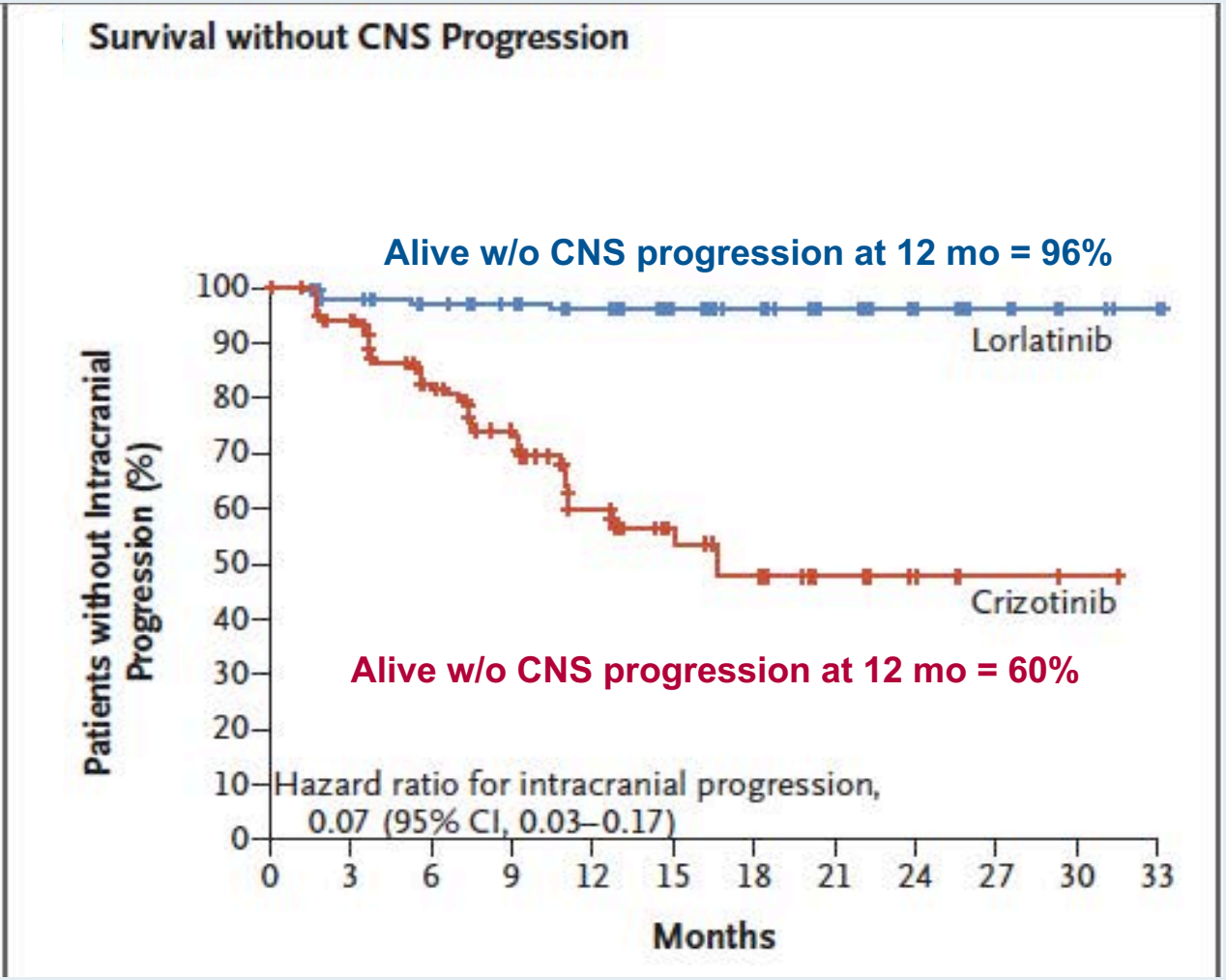
First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D., Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D., Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D., Gerson Peltz, M.D., M.P.H., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the CROWN Trial Investigators*

N Engl J Med 2020;383(21):2018-29.

CROWN: PFS and Survival without Intracranial Progression



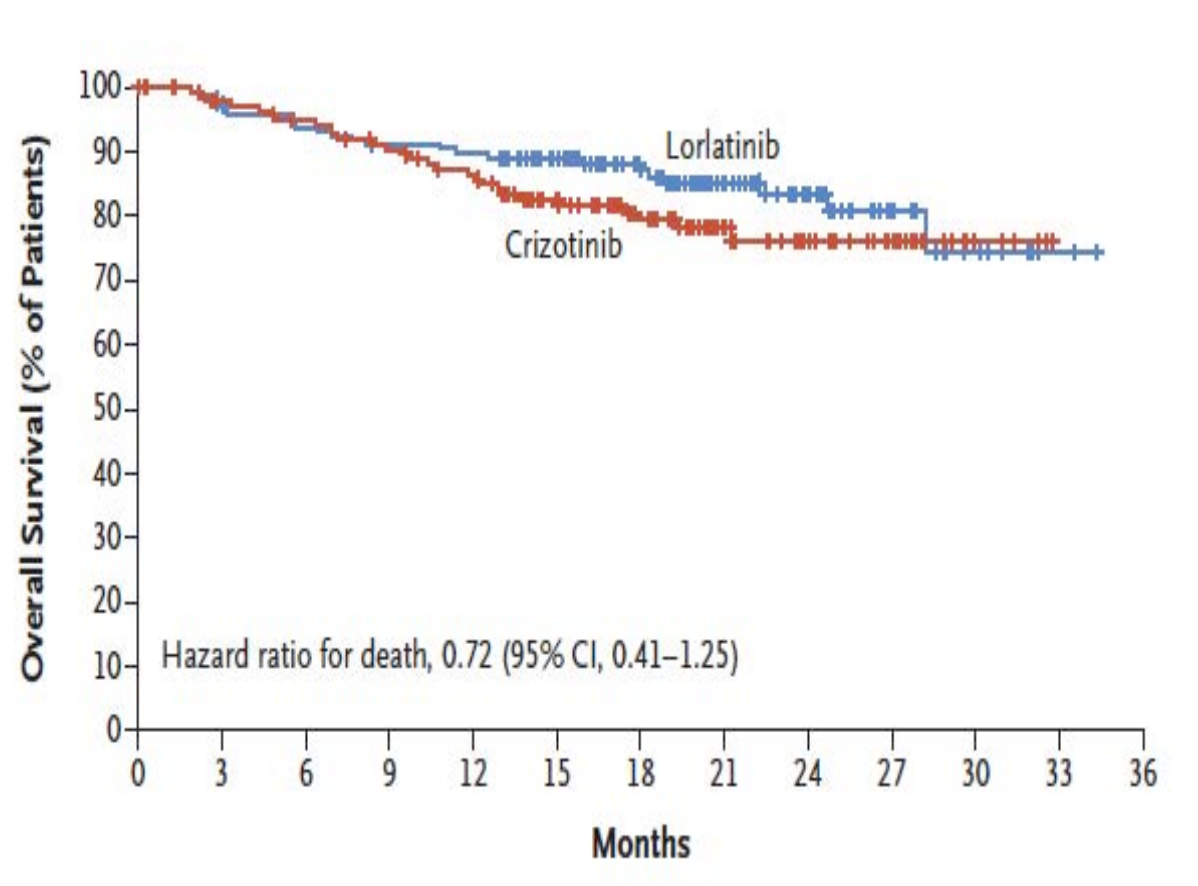


Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29.

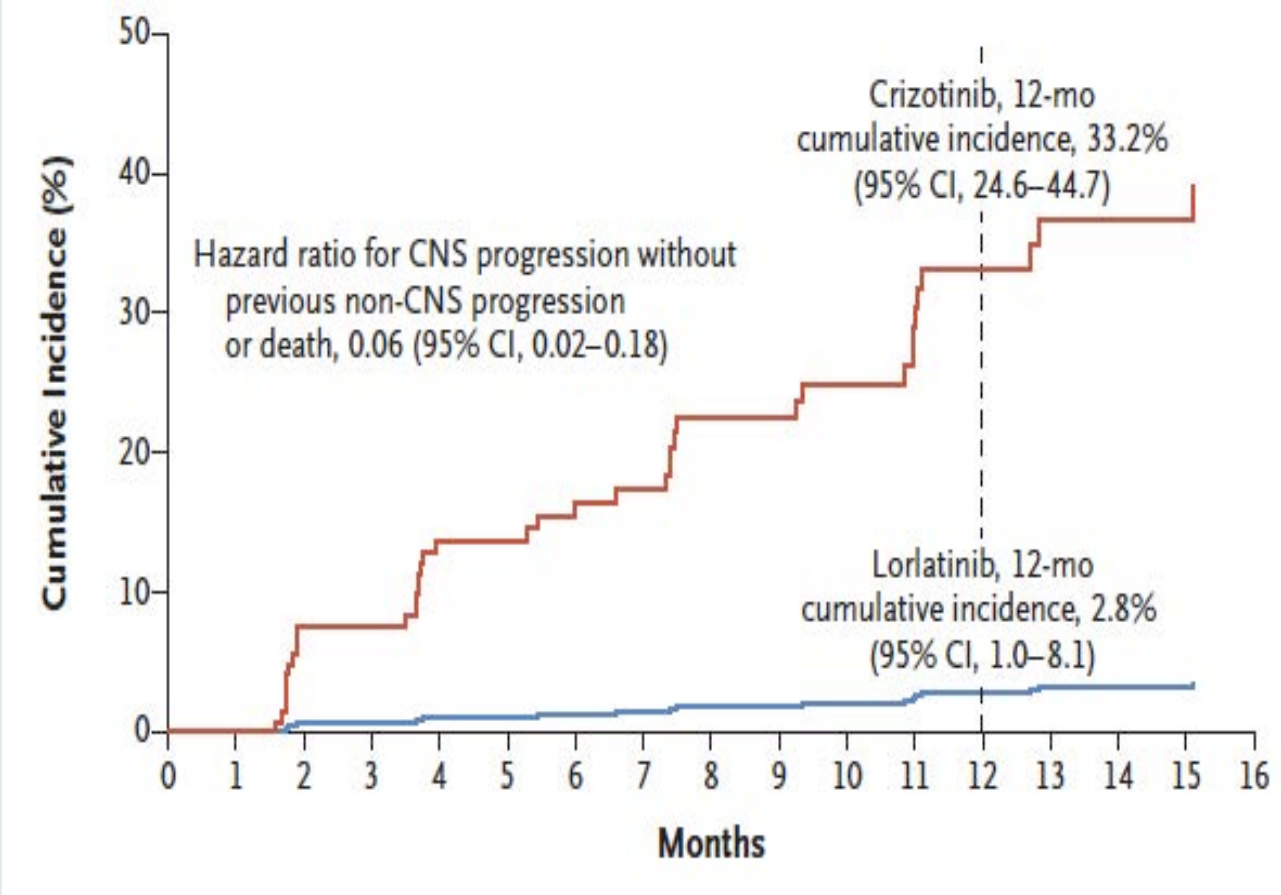
RTP RESEARCH TO PRACTICE

CROWN: OS and Cumulative Incidence of CNS Progression

Overall Survival



Cumulative Incidence of CNS Progression as First Event



Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29.

RTP RESEARCH TO PRACTICE

2020 Presidential Symposium

AUGUST 8, 2020 | WORLDWIDE

IASLC/WCLC 2020;Abstract 2

Phase 3 Randomized Study of Ensartinib vs Crizotinib in Anaplastic Lymphoma Kinase (ALK)–Positive NSCLC Patients: eXalt3

Horn L,[1] Wang Z,[2] Wu G,[3] Poddubskaya E,[4] Mok T,[5] Reck M,[6] Wakelee H,[7] Chiappori A,[8] Lee DH,[9] Breder V,[10] Orlov S,[11] Cicin I,[12] Cheng Y,[13] Liu Y,[14] Fan Y,[15] Zhou J,[16] Oertel V,[16] Mao L,[16] Selvaggi G,[16] and **Wu Y**[17]

[1]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [2]Beijing Cancer Hospital, Beijing China; [3]Cancer Center of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [4]Sechenov University, Moscow, Russia and VitaMed LLC, Carson City, NV, USA; [5]The Chinese University of Hong Kong, Hong Kong, China; [6]LungClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [7]Stanford Cancer Institute, Stanford University, Stanford, CA, USA; [8]Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [9]Asan Medical Center, Seoul, South Korea; [10]Russian Cancer Research Center n.a. N.Blokhin, Moscow, Russia; [11]Pavlov First Saint Petersburg State Medical University, St Petersburg, Russia; [12]Trakya University, Edirne, Turkey; [13]Jilin Cancer Hospital, Changchun, China; [14]The First Hospital of China Medical University, Shenyang, China; [15]Zhejiang Cancer Hospital, Hangzhou, China; [16]Xcovery Holdings, Inc., Palm Beach Gardens, FL, USA; [17]Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

Agenda

Module 1: Selection and Sequencing of Therapy for Patients with Non-Small Cell Lung Cancer (NSCLC) and an ALK Rearrangement

Module 2: Optimal Use of Recently Approved RET Inhibitors in the Care of Patients with NSCLC with RET Alterations

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Module 4: Rational Approaches to Targeting BRAF in Patients with NSCLC

Module 5: Other Validated Targets Beyond EGFR (eg, MET, KRAS G12C)

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

Case Presentation – Dr Bauml: A 70-year-old man with metastatic adenocarcinoma of the lung – PD-L1 65%, KIF5B-RET mutation

Dr Joshua Bauml

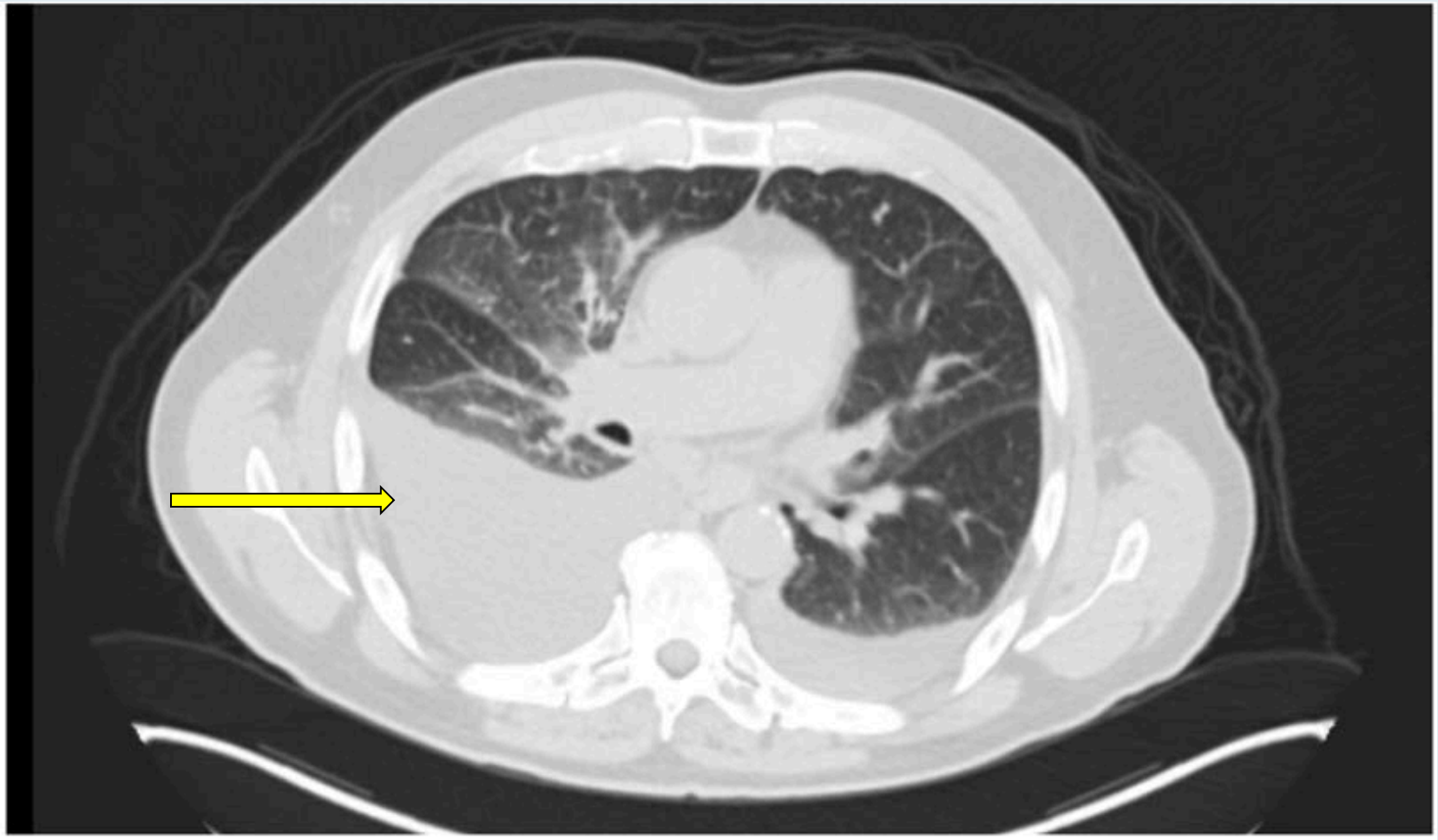
- Presents with cough and worsening SOB
- Chest x-ray: Pleural effusion (cytology negative)
- Effusion re-accumulated: Adenocarcinoma, PD-L1 65%, NGS: KIF5B-RET mutation
- Original oncologist recommends immunotherapy
- Selpercatinib, with symptom improvement and no side effects
  - Continues on treatment one year later

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Bauml: A 70-year-old man with metastatic adenocarcinoma of the lung – PD-L1 65%, KIF5B-RET mutation

Dr Joshua Bauml

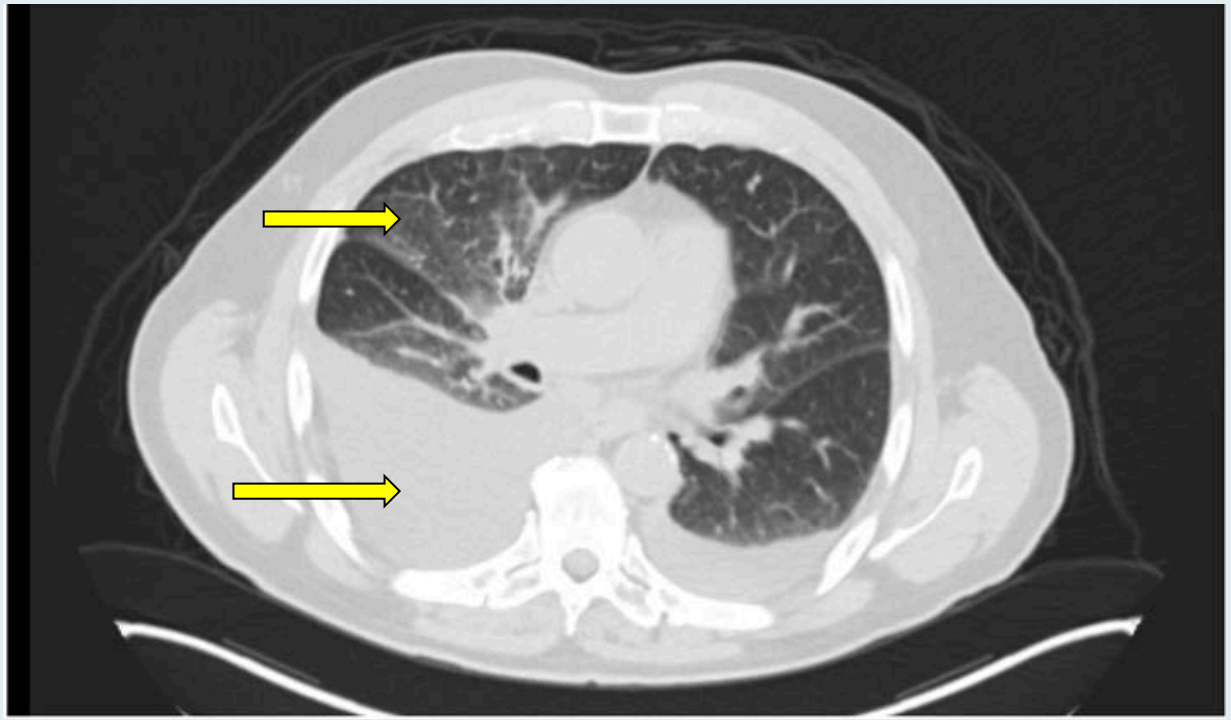
Pleural effusion at diagnosis

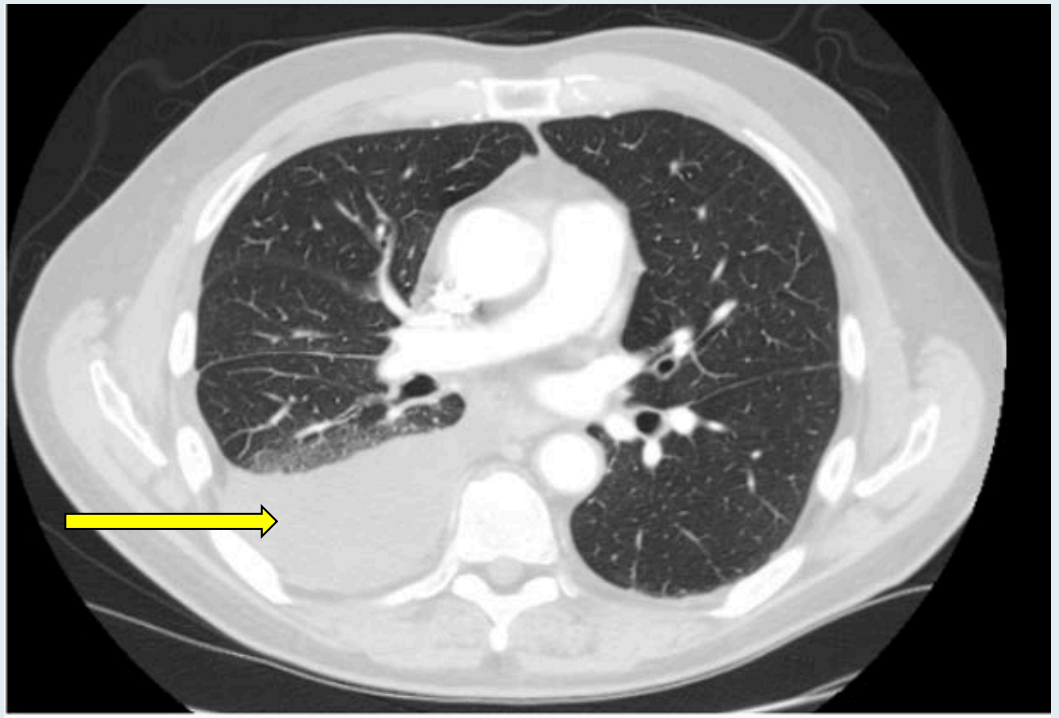


Case Presentation – Dr Bauml: A 70-year-old man with metastatic adenocarcinoma of the lung – PD-L1 65%, KIF5B-RET mutation

Dr Joshua Bauml

Pleural effusion remains after selpercatinib
Ground glass opacities in the anterior aspect of his right lung





FDA Approves Selpercatinib for Lung and Thyroid Cancer with RET Gene Mutations or Fusions

Press Release — May 8, 2020

"On May 8, 2020, the Food and Drug Administration granted accelerated approval to selpercatinib for the following indications:

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC);
- Adult and pediatric patients ≥12 years of age with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy;
- Adult and pediatric patients ≥12 years of age with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Efficacy was investigated in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001) in patients whose tumors had RET alterations."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions

The NEW ENGLAND JOURNAL of MEDICINE

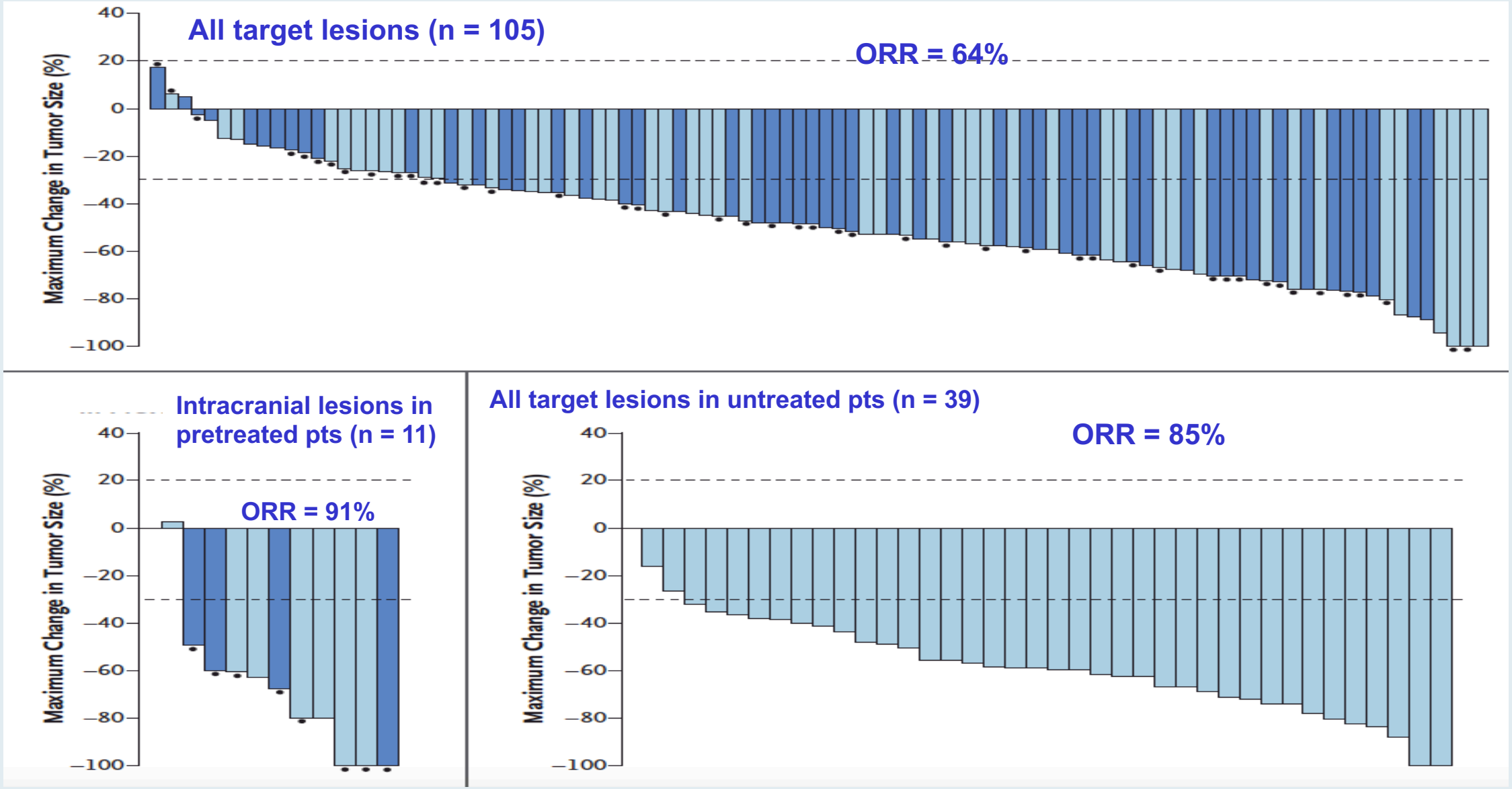
ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C.E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.-J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P.A. Cassier, L. Bazhenova, F. De Braud, E. Garralda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.M. Rothenberg, K. Goto, and V. Subbiah

N Engl J Med 2020;383(9):813-24.

LIBRETTO-001: Response by Independent Review



Drilon A et al. *N Engl J Med* 2020;383(9):813-24.

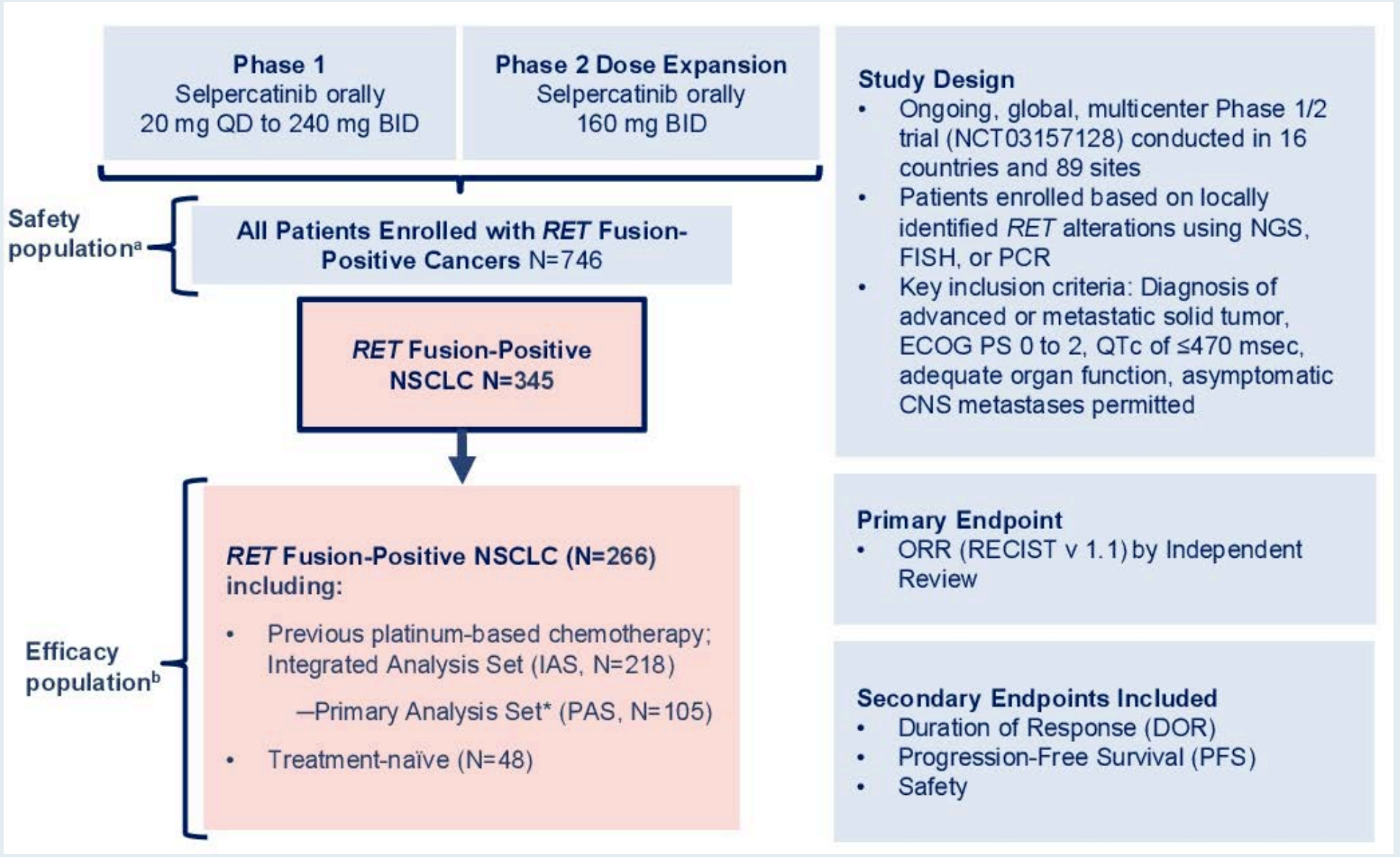
RTP RESEARCH TO PRACTICE

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.

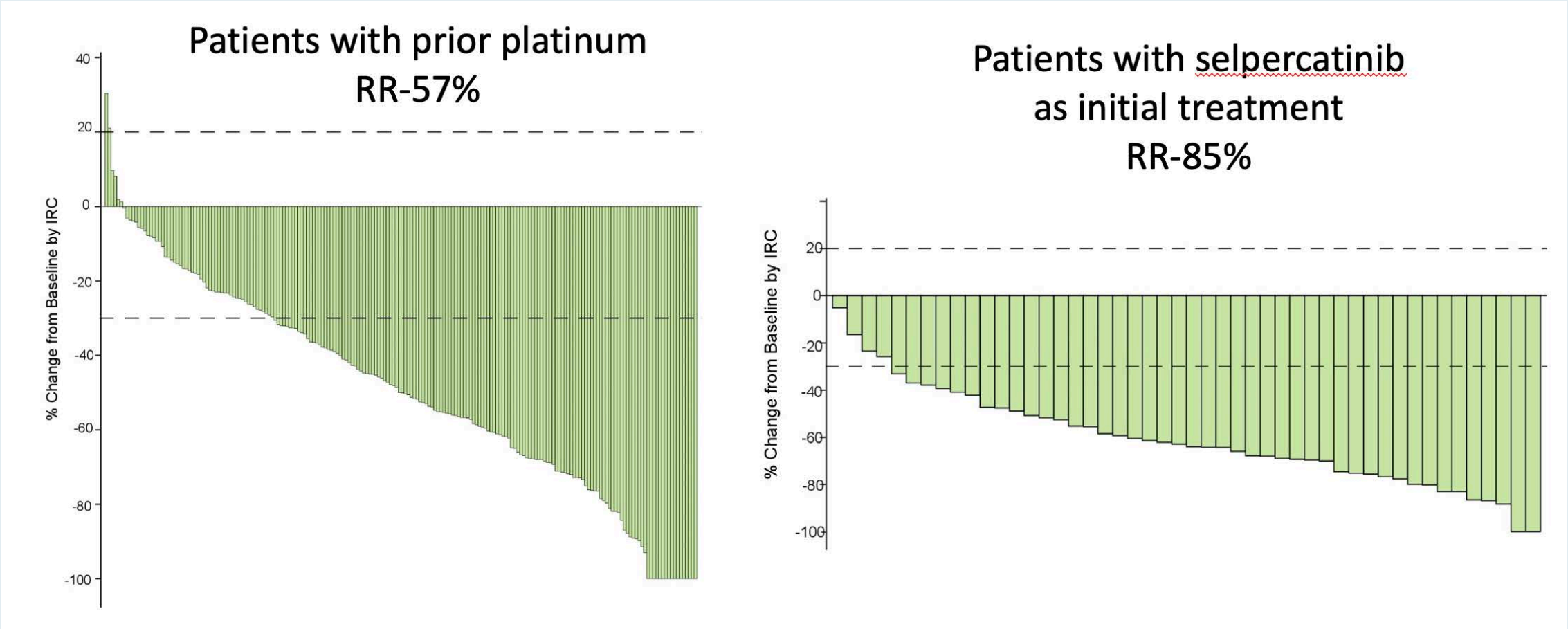
ASCO 2021;Abstract 9065.

LIBRETTO-001 Study Design



Besse B et al. ASCO 2021;Abstract 9065.

LIBRETTO-001: Response to Selpercatinib



Besse B et al. ASCO 2021;Abstract 9065.

RTP RESEARCH TO PRACTICE

FDA Grants Approval of Pralsetinib for the Treatment of Metastatic NSCLC with RET Fusion

Press Release – September 4, 2020

"On September 4, 2020, the Food and Drug Administration granted accelerated approval to pralsetinib for adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

Today, FDA also approved the Oncomine Dx Target (ODxT) Test as a companion diagnostic for pralsetinib.

Efficacy was investigated in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385) in patients whose tumors had RET alterations. Identification of RET gene alterations was prospectively determined in local laboratories using either next generation sequencing, fluorescence in situ hybridization, or other tests. The main efficacy outcome measures were overall response rate (ORR) and response duration determined by a blinded independent review committee using RECIST 1.1."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-lung-cancer-ret-gene-fusions

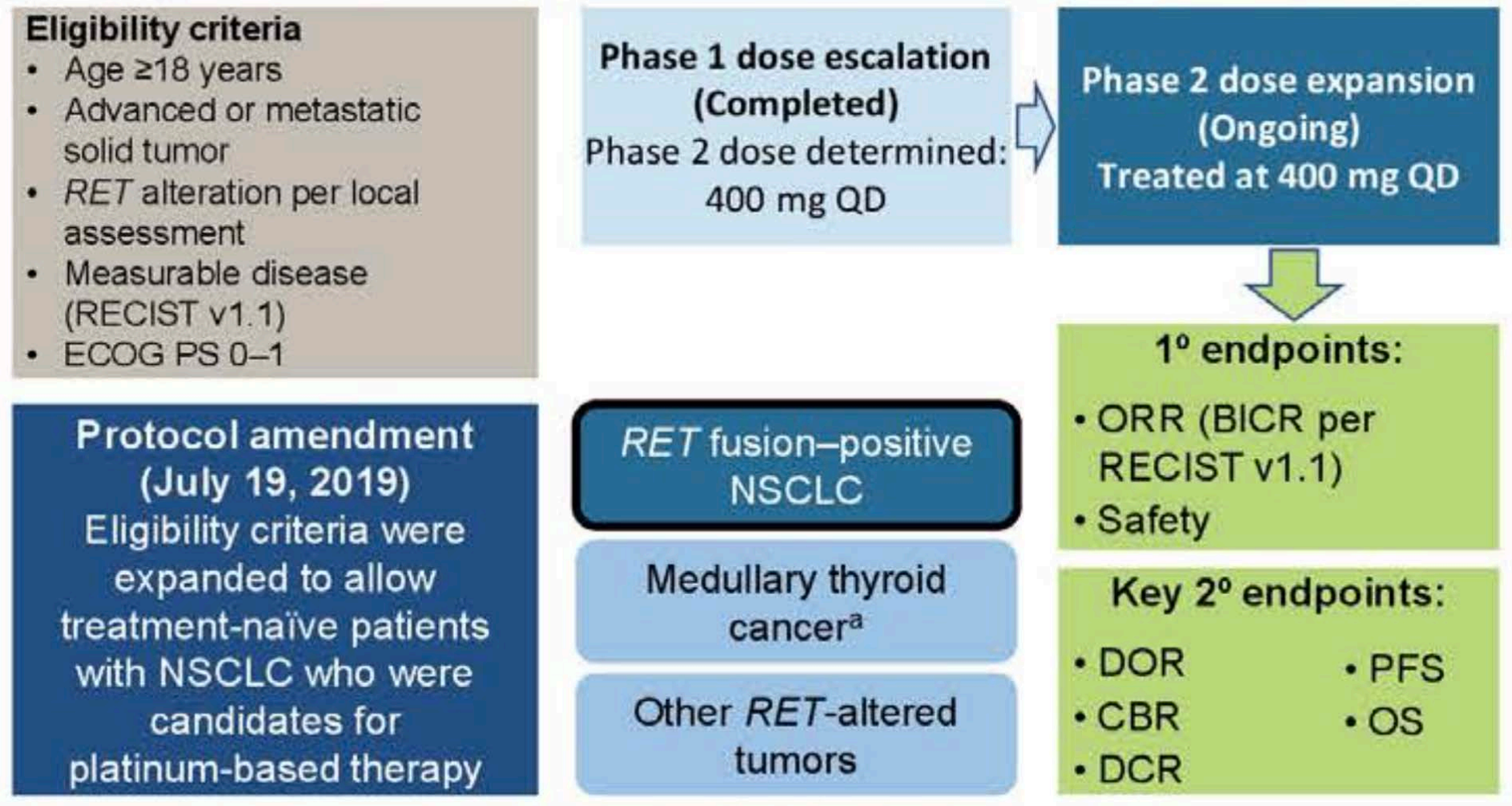
RTP RESEARCH TO PRACTICE

Safety and Efficacy of Pralsetinib in Patients with Advanced *RET* Fusion-Positive Non-Small Cell Lung Cancer: Update from the ARROW Trial

Curigliano G et al.

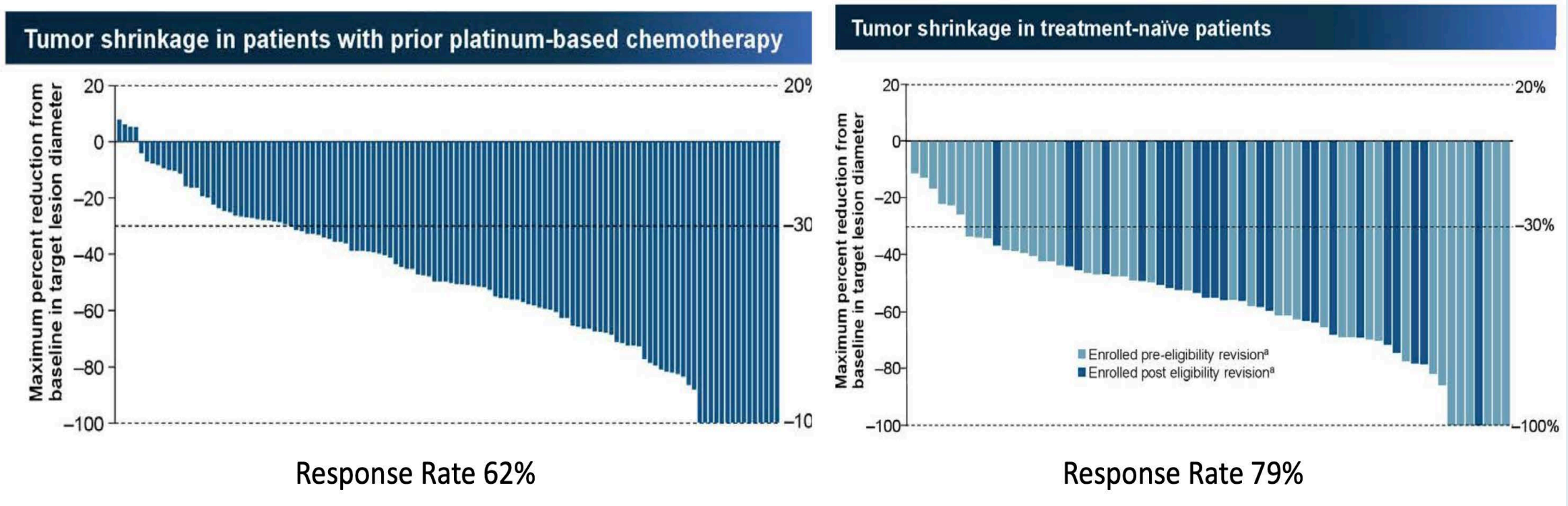
ASCO 2021;Abstract 9089.

ARROW Study Design



Curigliano J et al. ASCO 2021;Abstract 9089.

ARROW Primary Endpoint: Response to Pralsetinib



ORR (response-evaluable): All – 69%, Prior platinum – 62%, Treatment-naïve – 79%

Curigliano J et al. ASCO 2021;Abstract 9089.

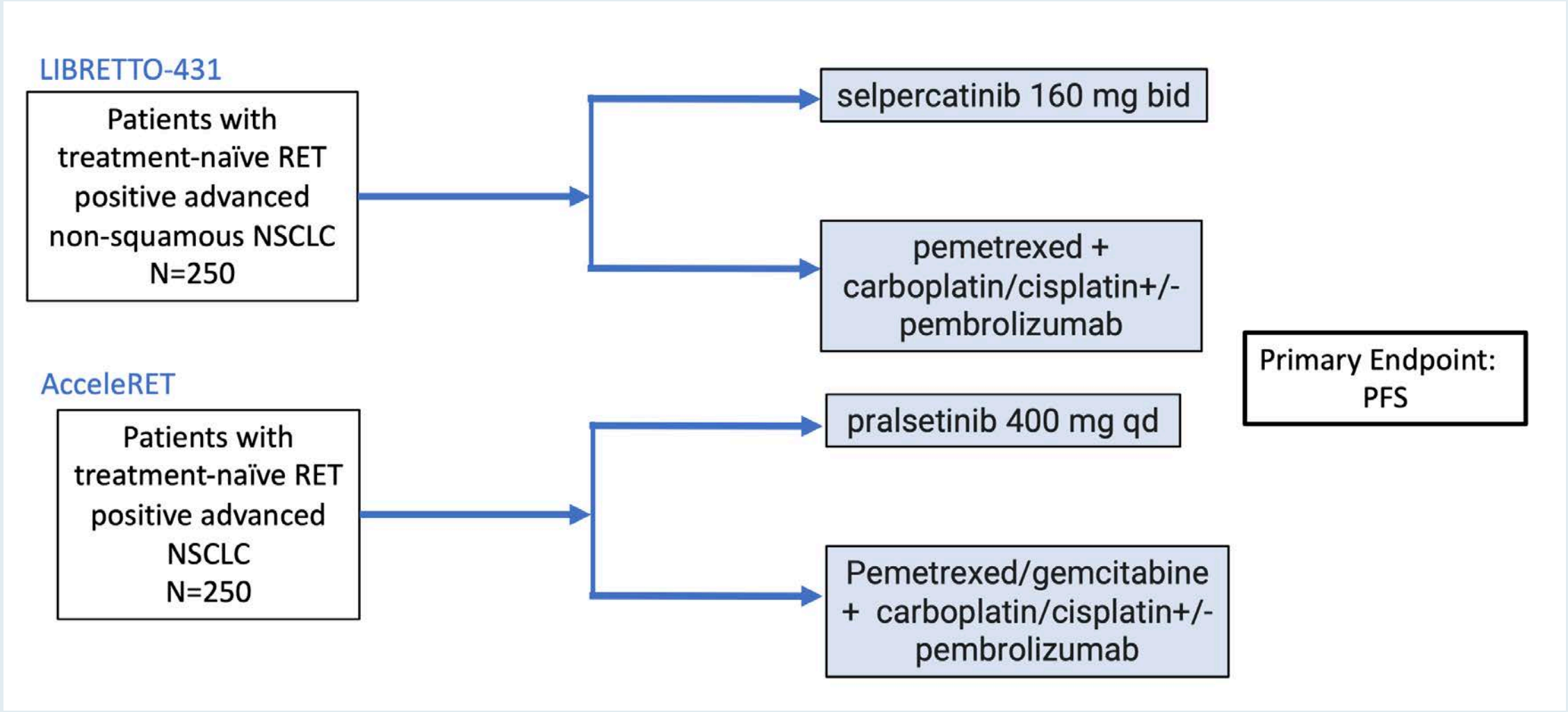
RTP RESEARCH TO PRACTICE

ARROW: Efficacy Summary

	Measurable disease population					
	RET fusion–positive NSCLC (n=216)	Treatment-naïve			Prior treatment	
		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

Curigliano J et al. ASCO 2021;Abstract 9089.

Ongoing Randomized Phase III Trials to Evaluate First-Line RET Inhibitors



Courtesy of Gregory J Riely, MD, PhD

Agenda

Module 1: Selection and Sequencing of Therapy for Patients with Non-Small Cell Lung Cancer (NSCLC) and an ALK Rearrangement

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Module 4: Rational Approaches to Targeting BRAF in Patients with NSCLC

Module 5: Other Validated Targets Beyond EGFR (eg, MET, KRAS G12C)

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
- Carboplatin/pemetrexed/pembrolizumab initiated
- Genetic analysis results: ROS1 rearrangement
- Plan to administer entrectinib for CNS coverage

Case Presentation – Dr Chen: A 59-year-old woman with metastatic adenocarcinoma of the lung with a ROS1 fusion and severe rheumatoid arthritis

Dr Gigi Chen

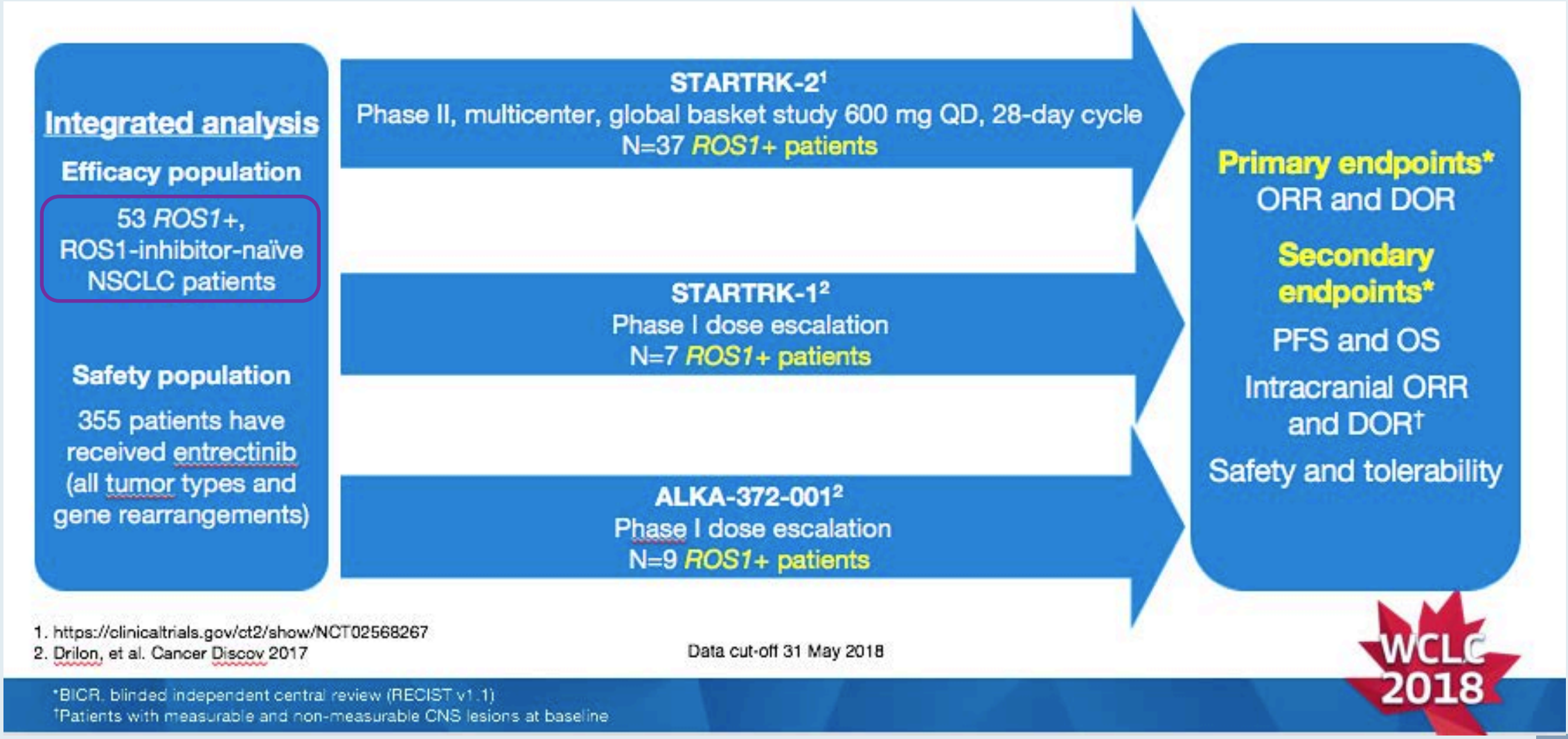
- Never smoker presents with persistent cough
- RLL lung mass, mediastinal adenopathy and multiple bone lesions; MRI brain: Negative
- CT-guided biopsy: Adenocarcinoma, CD 74 ROS1 fusion
- Crizotinib and denosumab x 9 months → Headache → MRI brain: 3-mm parietal lobe and 2-mm frontal lobe lesions
- Systemic disease is well controlled

Questions

- What is the next step in her treatment?
- Would it be best to change to a different TKI versus chemotherapy in this patient who has had brain progression only? What would be the best choices in terms of the TKIs?

RTP RESEARCH TO PRACTICE

Integrated Analysis of 3 Studies: Entrectinib for NSCLC with ROS1 Rearrangement



Doebele et al. Lancet Oncology, 2019

Courtesy of D Ross Camidge, MD, PhD

RTP RESEARCH TO PRACTICE

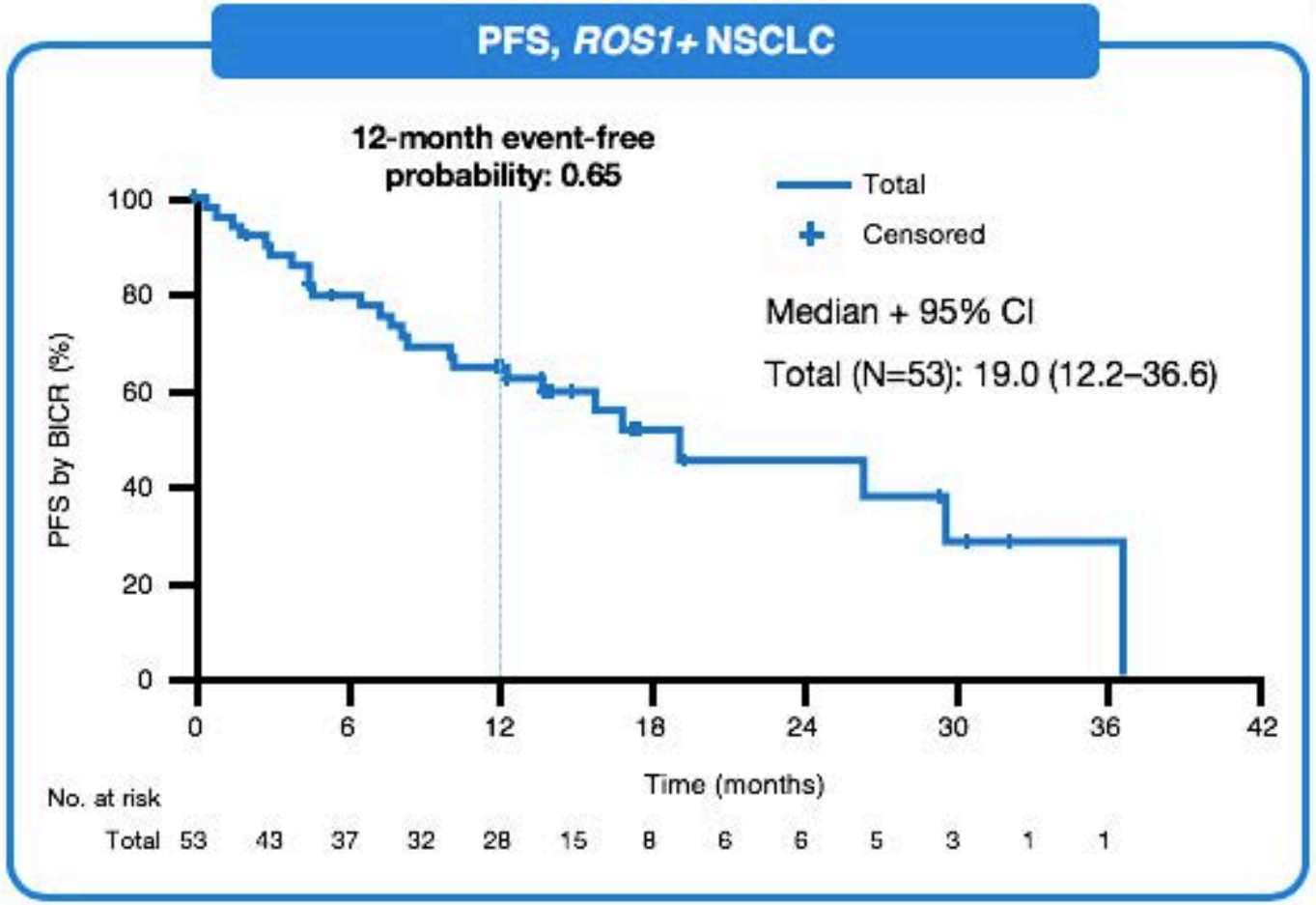
Integrated Analysis of Entrectinib: Intracranial ORR and DOR (BICR assessment)

Intracranial response – CNS metastases at baseline by BICR (n=20*)	
Intracranial ORR, n (%) (95% CI)	**11 (55)** (31.53, 76.94)
CR PR SD PD Non CR/PD-Non evaluable	**4 (20.0)** 7 (35.0) 0 3 (15.0) 6 (30.0)
Intracranial median DOR, months (95% CI)	**12.9** (5.6, NE)
Patients with event, n (%) Disease progression, n Death, n	5 (45.5) 3 2
6 months Patients remaining at risk Event-free probability	 7 0.71

Doebele et al. Lancet Oncology, 2019

Courtesy of D Ross Camidge, MD, PhD

Integrated Analysis of Entrectinib: Progression-free survival (BICR assessment)



	Total N=53	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
Pts with event, n (%)	25 (47.2)	11 (47.8)	14 (46.7)
PD, n	20	8	12
Death, n	5	3	2
Time to event (months)			
Median (95% CI)	**19.0** (12.2, 36.6)	**13.6** (4.5, NE)	**26.3** (15.7, 36.6)

Median PFS 19.0 months (95% CI 12.2, 36.6)

Median follow up: 15.5 months

Doebele et al. Lancet Oncology, 2019

Courtesy of D Ross Camidge, MD, PhD

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Case Presentation – Dr Morganstein: A 62-year-old man with metastatic adenocarcinoma of the lung with a BRAF V600E mutation – PD-L1 TPS 80%

Dr Neil Morganstein

- Heavy smoker presents with shortness of breath
- Workup reveals lung adenocarcinoma with metastases to the liver and bone
- PD-L1 TPS: 80%
- Carboplatin/paclitaxel/pembrolizumab initiated (pembrolizumab not given due to renal insufficiency)
- Molecular analysis results returned after treatment initiated → BRAF V600E mutation

Questions

- In patients with BRAF V600E mutations, is BRAF-targeted therapy recommended in the first line?
- How imperative is it to have molecular study results before initiating therapy?
- Is BRAF considered a classic driver mutation? Should I be concerned about the efficacy of immunotherapies in patients whose tumors harbor BRAF mutations?
- How would you characterize the type of clinical response that I may expect from BRAF-targeted therapies? What is the standard-of-care for BRAF-directed therapy – dabrafenib/trametinib?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Kumar: A 70-year-old man with metastatic NSCLC – BRAF V600E mutation

Dr KS Kumar

- 6/2020: Presented to primary care physician with abdominal pain and shortness of breath
- Workup confirms pulmonary carcinoma with post-obstructive pneumonitis and a large pleural effusion
  - Extensive peritoneal mass effects and extensive studding of the mid and lower mesentery was noted
- NGS: BRAF V600E mutation
- Smoking history: Previously smoked 2-3 ppd for 10 years, currently only smokes an occasional cigar
- Dabrafenib plus trametinib → patient faring well for the past 7 months

Question

- What would be your approach on progression in addition to repeating NGS? An IO doublet regimen or chemotherapy with an IO?

Agenda

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Module 5: Other Validated Targets Beyond EGFR (eg, MET, KRAS G12C)

Case Presentation – Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%

Dr Mohamed Mohamed

- Never smoker presents with bilateral flank pain and 5-month history of weight loss and fatigue
- Workup reveals Stage IV poorly differentiated adenocarcinoma of the lung; lung obstructions and 2 small, subcentimeter lesions in brain detected
- Molecular analyses: MET exon 14 skipping mutation, MET amplification
- PD-L1: 95%
- Palliative RT to the lung; SRS to the brain
- Capmatinib initiated

Questions

- If she didn't need to receive RT due to the lung obstructions, should I have initiated treatment with targeted therapy alone? Does capmatinib work on brain lesions by itself?
- With a PD-L1 of 95%, should she have been considered for immunotherapy, or should targeted therapy precede that as first-line therapy?
- Are mutations in MET regarded in the same way as mutations in EGFR and ALK in terms of immune therapy? Or are they regarded like BRAF mutations in that you could use immune therapy?

RTP RESEARCH TO PRACTICE

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?
- Are there any data regarding the CNS activity of sotorasib?

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Capmatinib for Metastatic NSCLC

Press Release — May 6, 2020

"On May 6, 2020, the Food and Drug Administration granted accelerated approval to capmatinib for adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved teste C.

The FDA also approved the FoundationOnDx assay as a companion diagnostic for capmatinib.

Efficacy was demonstrated in the GEOMETRY mono-1 trial (NCT02414139), a multicenter, non-randomized, open-label, multicohort study enrolling 97 patients with metastatic NSCLC with confirmed MET exon 14 skipping.

The recommended capmatinib dose is 400 mg orally twice daily with or without food."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-capmatinib-metastatic-non-small-cell-lung-cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

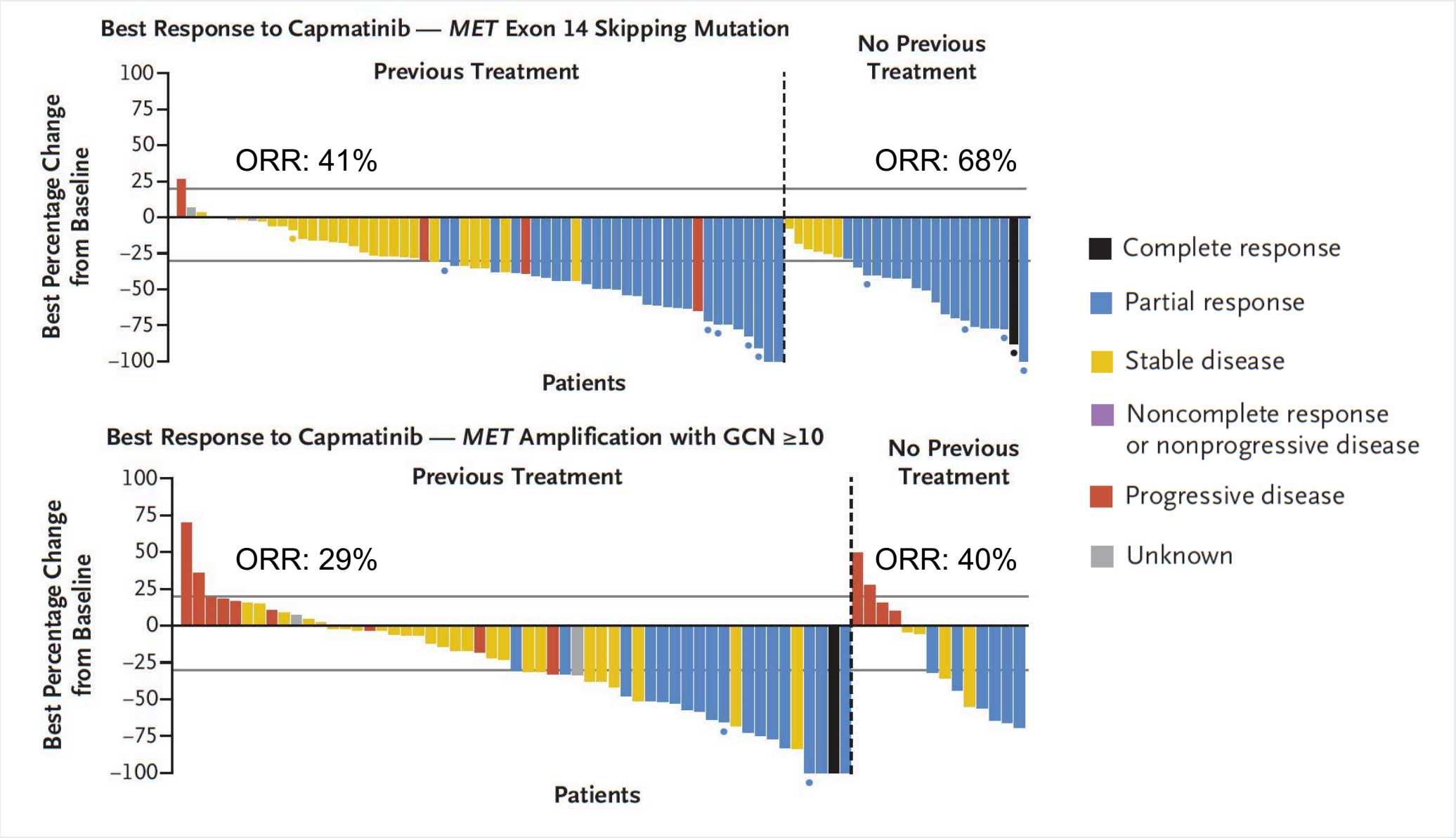
Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

J. Wolf, T. Seto, J.-Y. Han, N. Reguart, E.B. Garon, H.J.M. Groen, D.S.W. Tan, T. Hida, M. de Jonge, S.V. Orlov, E.F. Smit, P.-J. Souquet, J. Vansteenkiste, M. Hochmair, E. Felip, M. Nishio, M. Thomas, K. Ohashi, R. Toyozawa, T.R. Overbeck, F. de Marinis, T.-M. Kim, E. Laack, A. Robeva, S. Le Mouhaer, M. Waldron-Lynch, B. Sankaran, O.A. Balbin, X. Cui, M. Giovannini, M. Akimov, and R.S. Heist, for the GEOMETRY mono-1 Investigators*

ABSTRACT

N Engl J Med 2020;383(10):944-57.

Capmatinib: Response Rate and Change from Baseline in Tumor Burden



Wolf J et al. *N Engl J Med* 2020;383(10):944-57.

FDA Grants Accelerated Approval to Tepotinib for Metastatic NSCLC

Press Release — February 3, 2021

"On February 3, 2021, the Food and Drug Administration granted accelerated approval to tepotinib for adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

Efficacy was demonstrated in the VISION trial (NCT02864992), a multicenter, non-randomized, open-label, multicohort study enrolling 152 patients with advanced or metastatic NSCLC with MET exon 14 skipping alterations. Patients received tepotinib 450 mg orally once daily until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-tepotinib-metastatic-non-small-cell-lung-cancer

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

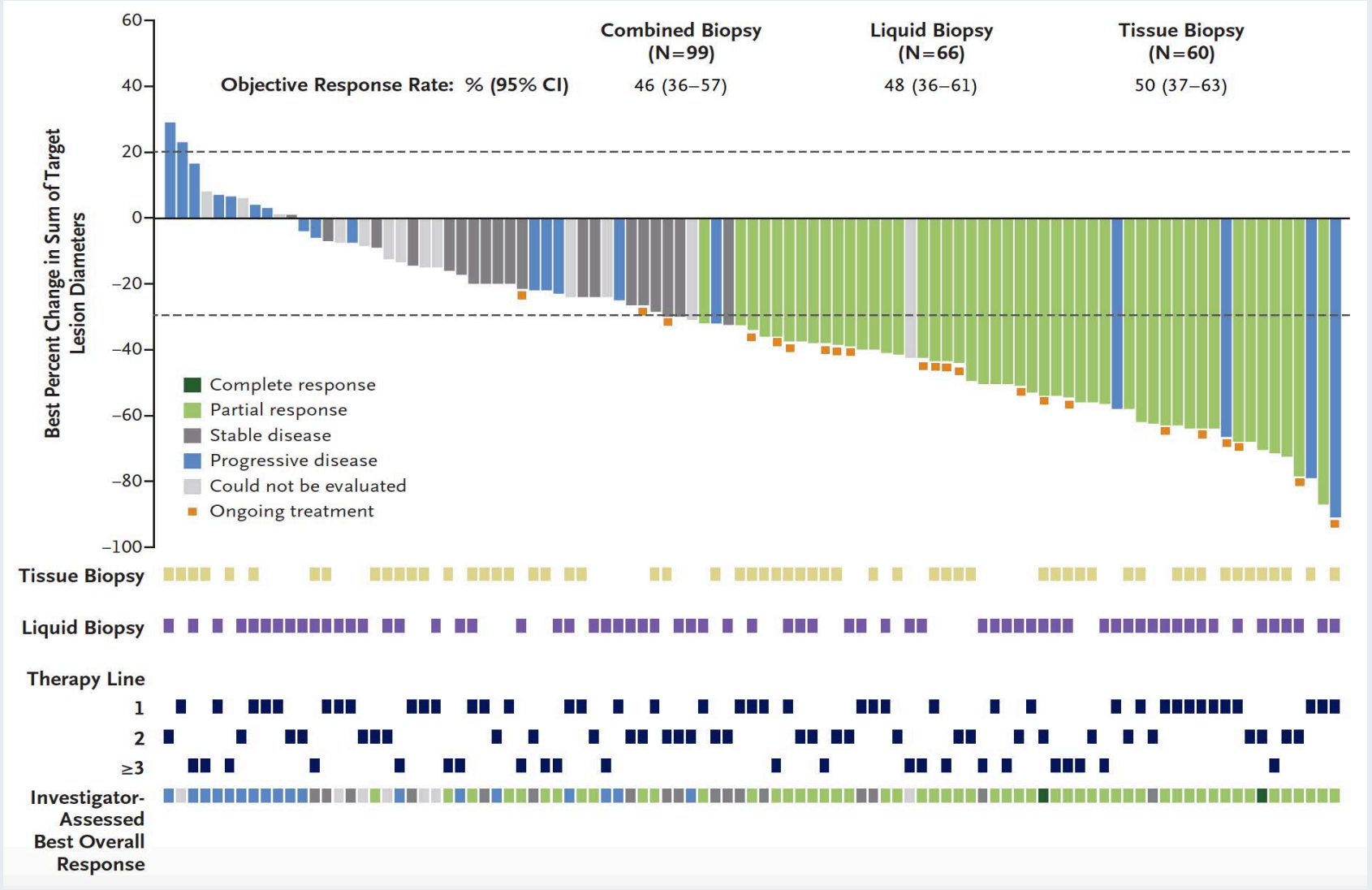
ORIGINAL ARTICLE

Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations

P.K. Paik, E. Felip, R. Veillon, H. Sakai, A.B. Cortot, M.C. Garassino, J. Mazieres, S. Viteri, H. Senellart, J. Van Meerbeeck, J. Raskin, N. Reinmuth, P. Conte, D. Kowalski, B.C. Cho, J.D. Patel, L. Horn, F. Griesinger, J.-Y. Han, Y.-C. Kim, G.-C. Chang, C.-L. Tsai, J.C.-H. Yang, Y.-M. Chen, E.F. Smit, A.J. van der Wekken, T. Kato, D. Juraeva, C. Stroh, R. Bruns, J. Straub, A. Johne, J. Scheele, J.V. Heymach, and X. Le

N Engl J Med 2020;383(10):931-43.

VISION Trial of Tepotinib: Response Rate and Change from Baseline in Tumor Burden



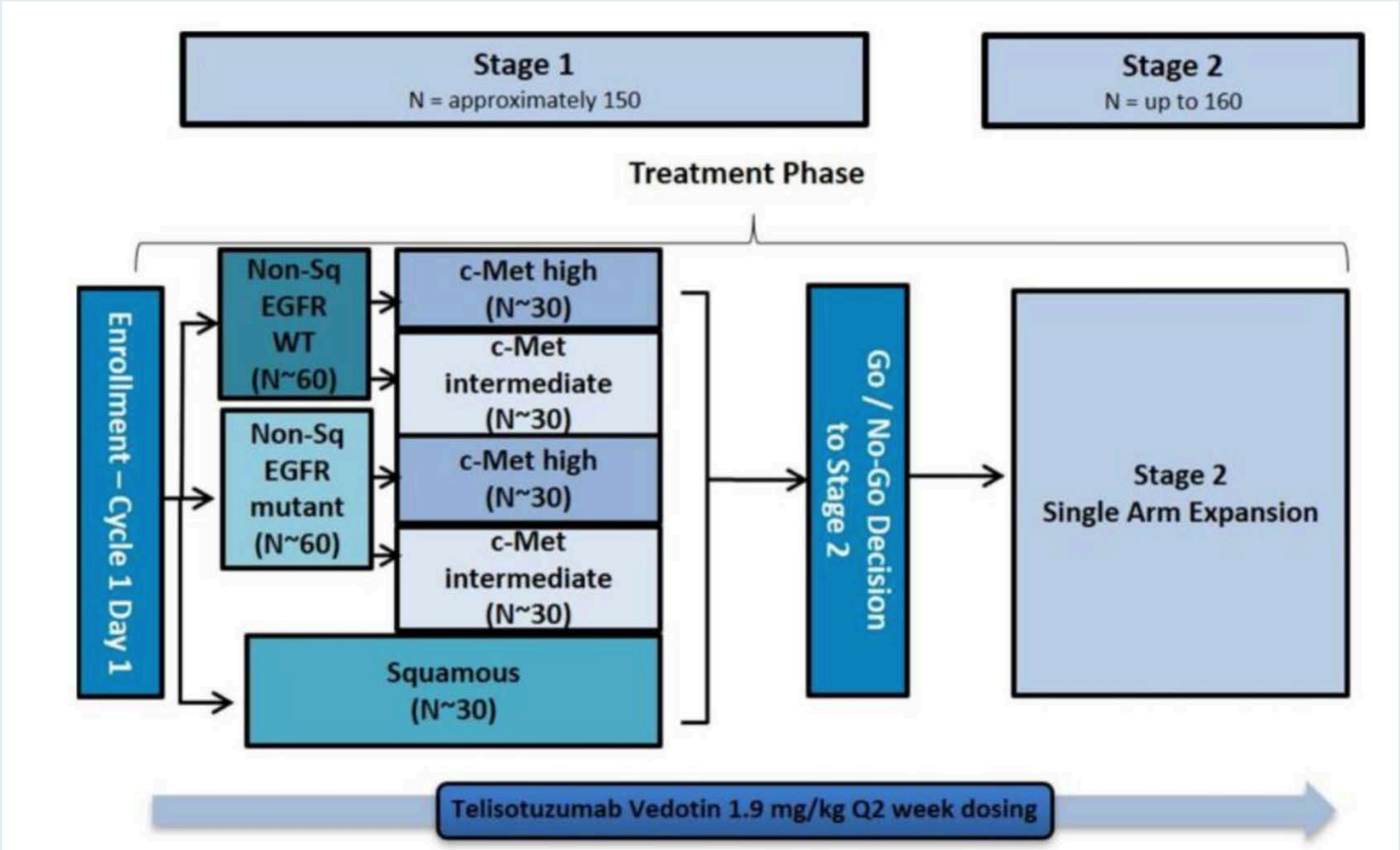
Paik PK et al. *N Engl J Med* 2020;383(10):931-43.

Telisotuzumab Vedotin (Teliso-v) Monotherapy in Patients with Previously Treated c-Met+ Advanced Non-Small Cell Lung Cancer

Camidge DR et al.

IASLC 2021;Abstract OA15.04.

Teliso-v Monotherapy Trial Enrollment



Camidge DR et al. IASLC 2021;Abstract OA15.04.

Teliso-v Monotherapy Trial Efficacy Endpoints by NSCLC Group

NSCLC Group	ORR (CR+PR)[a] by ICR, n/N (%) [95% CI]	ORR (CR+PR) by INV, n/N (%) [95% CI]	mDoR by ICR[b], months [95% CI]	mDoR by INV[c], months [95% CI]
NSQ EGFR WT	13/37 (35.1) [20.2, 52.5]	13/36 (36.1) [20.8, 53.8]	6.9 [3.8, -]	5.5 [4.2, 9.6]
c-Met high	7/13 (53.8) [25.1, 80.8]	6/12 (50.0) [21.1, 78.9]	---	---
c-Met int	6/24 (25.0) [9.8, 46.7]	7/24 (29.2) [12.6, 51.1]	---	---
NSQ EGFR MU	4/30 (13.3) [3.8, 30.7]	8/31 (25.8) [11.9, 44.6]	NA	5.9 [2.6, -]
c-Met high	4/22 (18.2) [5.2, 40.3]	8/22 (36.4) [17.2, 59.3]	---	---
c-Met int	0/8 (0) [-, -]	0/9 (0) [-, -]	---	---
SQ	3/21 (14.3) [3.0, 36.3]	1/22 (4.5) [0.1, 22.8]	4.4 [3.0, -]	4.4 [-, -]

- *ORR was 13/37 (35.1%) in the non-squamous EGFR wild type cohort, 7/13 (53.8%) in c-Met high group and 6/24 (25.0%) in c-Met intermediate group, but was modest in the non-squamous EGFR mutant and squamous cohorts*
- *At the time of this interim analysis, no patients had achieved a complete response, 26/88 (30%) had achieved a partial response, and 9/88 (10%) experienced disease progression*

Camidge DR et al. IASLC 2021;Abstract OA15.04.

FDA Grants accelerated approval to Sotorasib for KRAS G12C-Mutated NSCLC

Press Release – May 28, 2022

- "The FDA has granted accelerated approval to sotorasib, a RAS GTPase family inhibitor, for adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

- Approval was based on CodeBreaK 100, a multicenter, single-arm, open label clinical trial (NCT03600883) which included patients with locally advanced or metastatic NSCLC with KRAS G12C mutations. Efficacy was evaluated in 124 patients whose disease had progressed on or after at least one prior systemic therapy. Patients received sotorasib 960 mg orally daily until disease progression or unacceptable toxicity.

- The main efficacy outcome measures were objective response rate (ORR) according to RECIST 1.1, as evaluated by blinded independent central review and response duration. The ORR was 36% (95% CI: 28%, 45%) with a median response duration of 10 months (range 1.3+, 11.1)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sotorasib-kras-g12c-mutated-nsclc

RTP RESEARCH TO PRACTICE

IASLC/WCLC 2020;Abstract PS01.07

CodeBreaK 100: Registrational Phase 2 Trial of Sotorasib in *KRAS* p.G12C Mutated Non-small Cell Lung Cancer

Bob T. Li,[1] Ferdinandos Skoulidis,[2] Gerald Falchook,[3] Adrian Sacher,[4] Vamsidhar Velcheti,[5] Grace K. Dy,[6] Timothy J. Price,[7] Hossein Borghaei,[8] Martin Schuler,[9] Terufumi Kato,[10] Toshiaki Takahashi,[11] Alexander Spira,[12] Suresh Ramalingam,[13] Benjamin Besse,[14] Fabrice Barlesi,[15] Qui Tran,[16] Agnes Ang,[16] Abraham Anderson,[16] Haby Henary,[16] Gataree Ngarmchamnanrith,[16] Ramaswamy Govindan,[17] Jürgen Wolf[18]

[1]Memorial Sloan Kettering Cancer Center, New York, New York, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [3]Sarah Cannon Research Institute at HealthONE, Denver, Colorado, USA; [4]Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada; [5]Thoracic Medical Oncology, Perlmutter Cancer Center, New York University, New York, New York, USA; [6]Roswell Park Cancer Institute, Buffalo, New York, USA; [7]The Queen Elizabeth Hospital and University of Adelaide, Woodville South, Australia; [8]Fox Chase Cancer Center, Philadelphia, PA, USA; [9]Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, German Cancer Consortium (DKTK), Germany; [10]Kanagawa Cancer Center, Yokohama, Japan; [11]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan; [12]Virginia Cancer Specialists Research Institute, Fairfax, VA, The US Oncology Network, TX; Johns Hopkins Medicine, Baltimore, MD, USA [13]Division of Medical Oncology, Emory University School of Medicine, Winship Cancer Institute, Atlanta, GA, USA; [14]Department of Cancer Medicine, Gustave Roussy, Villejuif, France; [15]Gustave Roussy, Villejuif, France; [16]Amgen Inc. Thousand Oaks, California, USA; [17]Alvin J Siteman Cancer Center at Washington University School of Medicine, St Louis, Missouri, USA. [18]Department of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany

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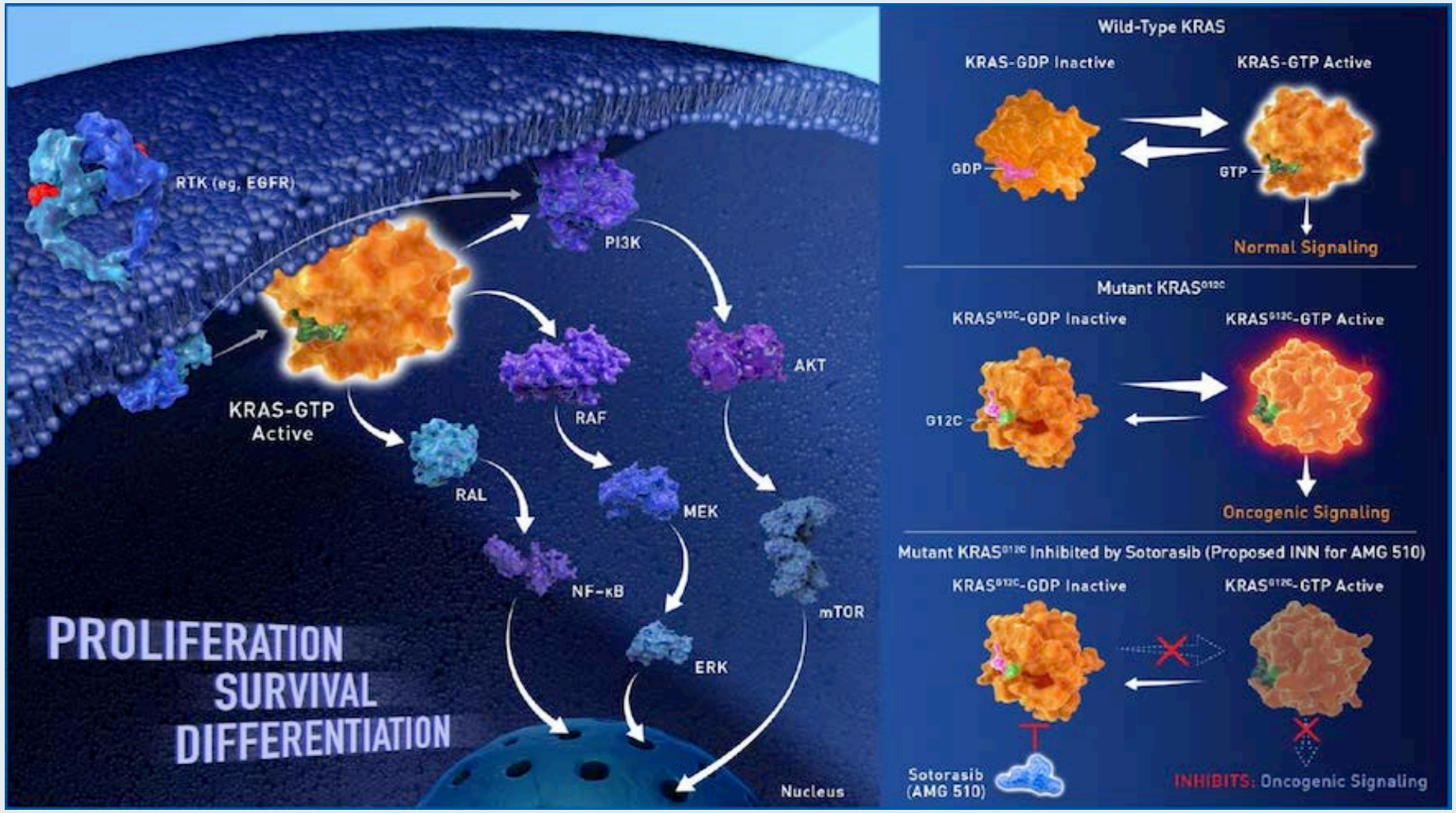
Mechanism of Action of Sotorasib (AMG 510) – A KRAS G12C Inhibitor



Fakih M et al. ASCO 2020;Abstract 4018.

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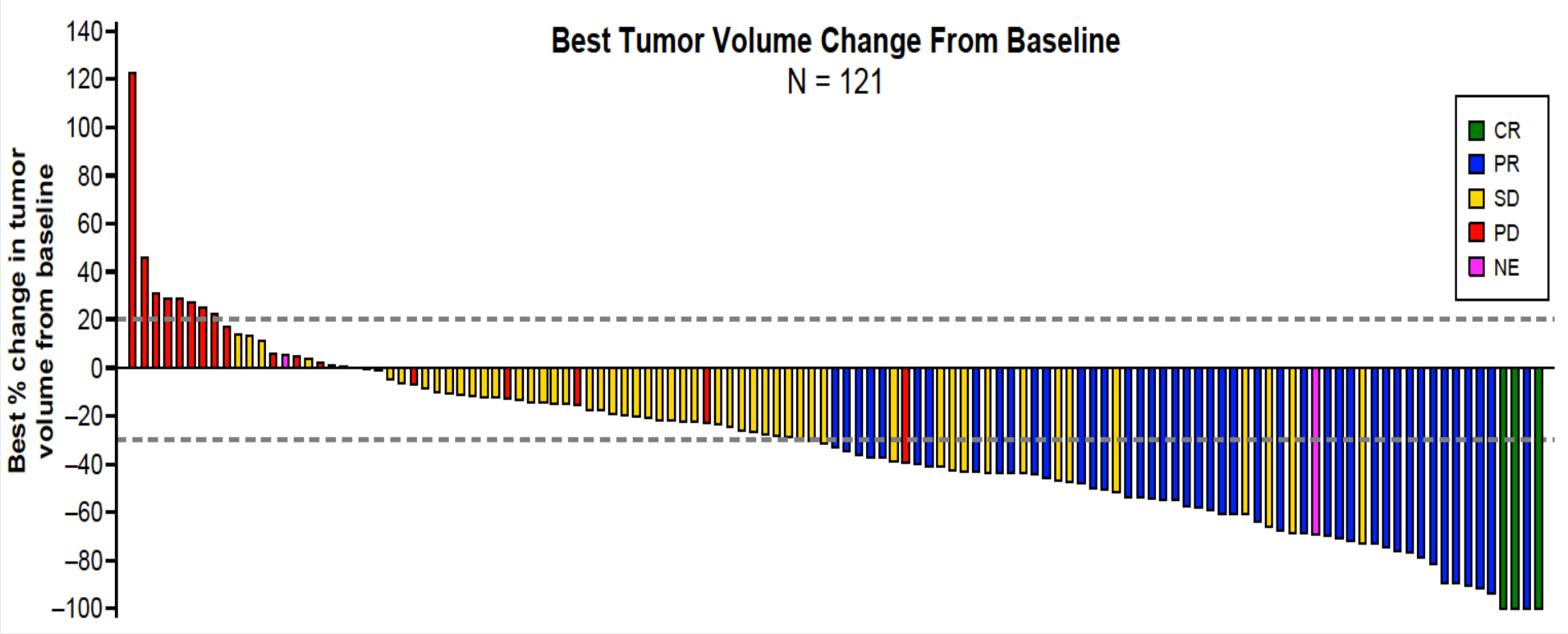
CodeBreak 100: Response and Survival Outcomes



Outcome	960 mg (n = 124)
ORR	37.1%
DCR	80.6%
PR	43.0%
mPFS	6.8 mo
mOS	Not evaluable

Data cutoff: December 1, 2020; median follow-up time: 12.2 months

Li BT et al. IASLC/WCLC 2021;Abstract PS01.07.

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Expert Second Opinion: Investigators Discuss Available Clinical Research in the Care of Patients with Localized Non-Small Cell Lung Cancer

A Live Webinar Held as a Satellite CME/MOC Symposium During the IASLC 2021 World Conference on Lung Cancer Worldwide Virtual Event

Sunday, September 12, 2021
9:15 PM – 10:15 PM MDT / 11:15 PM – 12:15 AM ET

Faculty

Edward B Garon, MD, MS
Harvey I Pass, MD
Heather Wakelee, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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