What I Tell My Patients:
Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Fifteenth Annual RTP Symposium Series Held During the Annual ONS Congress

Lung Cancer

Friday, April 28, 2023
6:00 PM – 8:00 PM

Faculty

Stephen V Liu, MD
Tara Plues, APRN, MSN
Jillian Thompson, MSN, ANP-BC, AOCNP
Anne S Tsao, MD, MBA

Moderator

Neil Love, MD

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Faculty

Stephen V Liu, MD
Associate Professor of Medicine
MedStar Georgetown University Hospital
Washington, DC

Tara Plues, APRN, MSN
Hematology and Medical Oncology
Cleveland Clinic
Cleveland, Ohio

Jillian Thompson, MSN, ANP-BC, AOCNP
Nurse Practitioner
MedStar Georgetown University Hospital
Lombardi Comprehensive Cancer Center
Washington, DC

Anne S Tsao, MD, MBA
Vice President, Academic Affairs
Chief Academic Office
Professor, Thoracic/Head and Neck Medical Oncology
Director, Mesothelioma Program
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Dr Liu — Disclosures

Advisory Committee	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Regeneron Pharmaceuticals Inc, Sanofi, Takeda Pharmaceuticals USA Inc
Consulting Agreements	AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Catalyst Pharmaceuticals, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology, Genentech, a member of the Roche Group, Gilead Sciences Inc, Guardant Health, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Merck, Merus BV, Mirati Therapeutics Inc, Novartis, Regeneron Pharmaceuticals Inc, Sanofi, Takeda Pharmaceuticals USA Inc, Turning Point Therapeutics Inc
Contracted Research	Alkermes, Elevation Oncology, Genentech, a member of the Roche Group, Gilead Sciences Inc, Merck, Merus BV, Nuvalent, RAPT Therapeutics, Turning Point Therapeutics Inc
Data and Safety Monitoring Board/Committee	Candel Therapeutics

Ms Plues — Disclosures

No relevant conflicts of interest to disclose

Ms Thompson — Disclosures

Advisory Committee	Janssen Biotech Inc
Nonrelevant Financial Relationship	Targeted Oncology (virtual tumor board)

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Dr Tsao — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, EMD Serono Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Lilly, Merck, Novartis, Pfizer Inc, Roche Laboratories Inc, Seagen Inc, Summit Therapeutics, Takeda Pharmaceuticals USA Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Epizyme Inc, Genentech, a member of the Roche Group, Lilly, Merck, Novartis, Polaris Pharmaceuticals, Seagen Inc, Takeda Pharmaceuticals USA Inc

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Commercial Support

This activity is supported by educational grants from Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Lilly, Mirati Therapeutics Inc, and Novocure Inc.

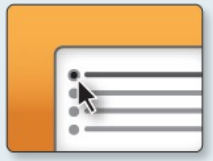
Research To Practice NCPD Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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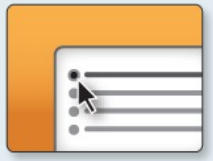
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get NCPD Credit: An NCPD credit link will be provided in the chat room at the conclusion of the program.

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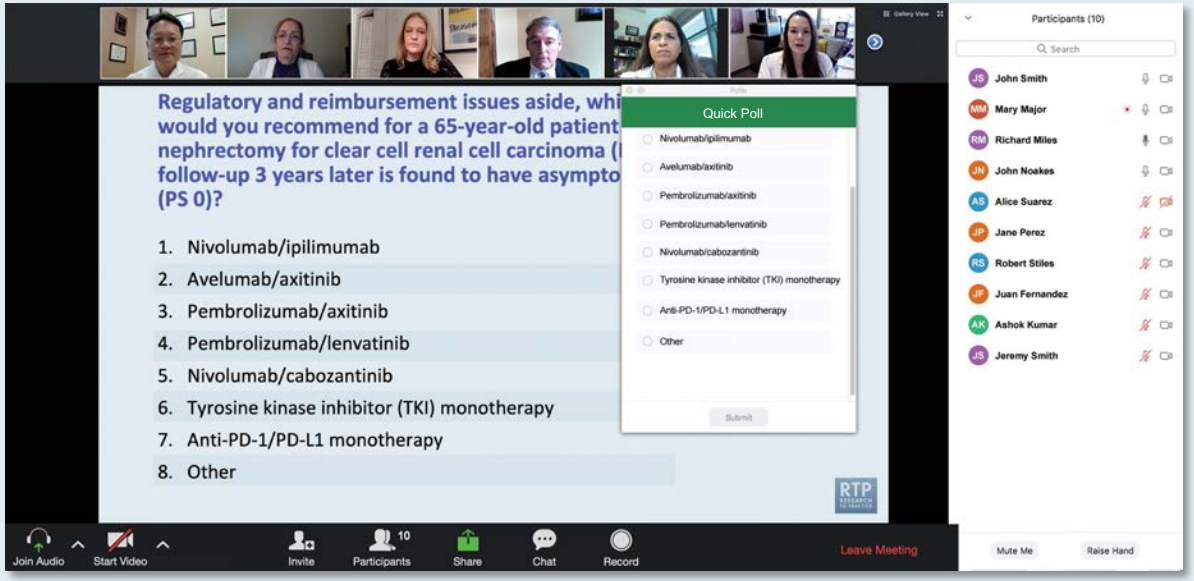
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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“What I Tell My Patients”
Fifteenth Annual RTP-ONS NCPD Symposium Series
ONS Congress, San Antonio, Texas — April 26 to 29, 2023

Wednesday April 26	**Cervical and Endometrial Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Breast Cancer 6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)
Thursday April 27	**Diffuse Large B-Cell Lymphoma** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Chronic Lymphocytic Leukemia 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)
	HER2-Targeted Antibody-Drug Conjugates 6:00 PM – 7:30 PM CT (7:00 PM – 8:30 PM ET)
Friday April 28	**Hepatobiliary Cancers** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Ovarian Cancer 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)
	Lung Cancer 6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)
Saturday April 29	**Acute Myeloid Leukemia, Myelodysplastic Syndromes and Myelofibrosis** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Prostate Cancer 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)

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What I Tell My Patients

2023 ONS Congress

San Antonio, Texas

Symposia Themes

- New agents and therapies; ongoing trials related to specific clinical scenarios
- Patient education: Preparing to receive new therapies
- The bond that heals
- THANKS! (Great job)

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How was it different to take care of this patient versus another patient in the same oncologic setting?

What unique biopsychosocial factors (eg, attitude, comorbidities, social support) were considered in the overall management of this case?

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The University of Texas
MD Anderson Cancer Center
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Neil Love, MD
Research To Practice
Miami, Florida

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Agenda

Module 1: Immunotherapy for Nonmetastatic and Metastatic NSCLC

Module 2: Future Directions — Tumor Treating Fields

Module 3: Overview of Targeted Treatment for NSCLC

Module 4: Targeted Treatment for NSCLC with an EGFR Mutation

Module 5: EGFR Exon 20 Insertion Mutations

Module 6: Targeted Treatment for NSCLC with a RET Fusion

Module 7: Targeted Treatment for NSCLC with a KRAS G12C Mutation

Agenda

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Jillian Thompson, MSN, ANP-BC, AOCNP

79-year-old woman with metastatic NSCLC who received carboplatin/pemetrexed/atezolizumab followed by atezolizumab maintenance and experienced an extended response

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Dr Liu
Washington, DC

Clinical Research Background

Dr Tsao
Houston, Texas

- **Role of immunotherapy in non-small cell lung cancer (NSCLC)**
  - **Neoadjuvant and adjuvant treatment**
  - **Consolidation treatment for unresectable locally advanced disease**
  - **First-line therapy for metastatic disease**
  - **Toxicity in patients with lung cancer**

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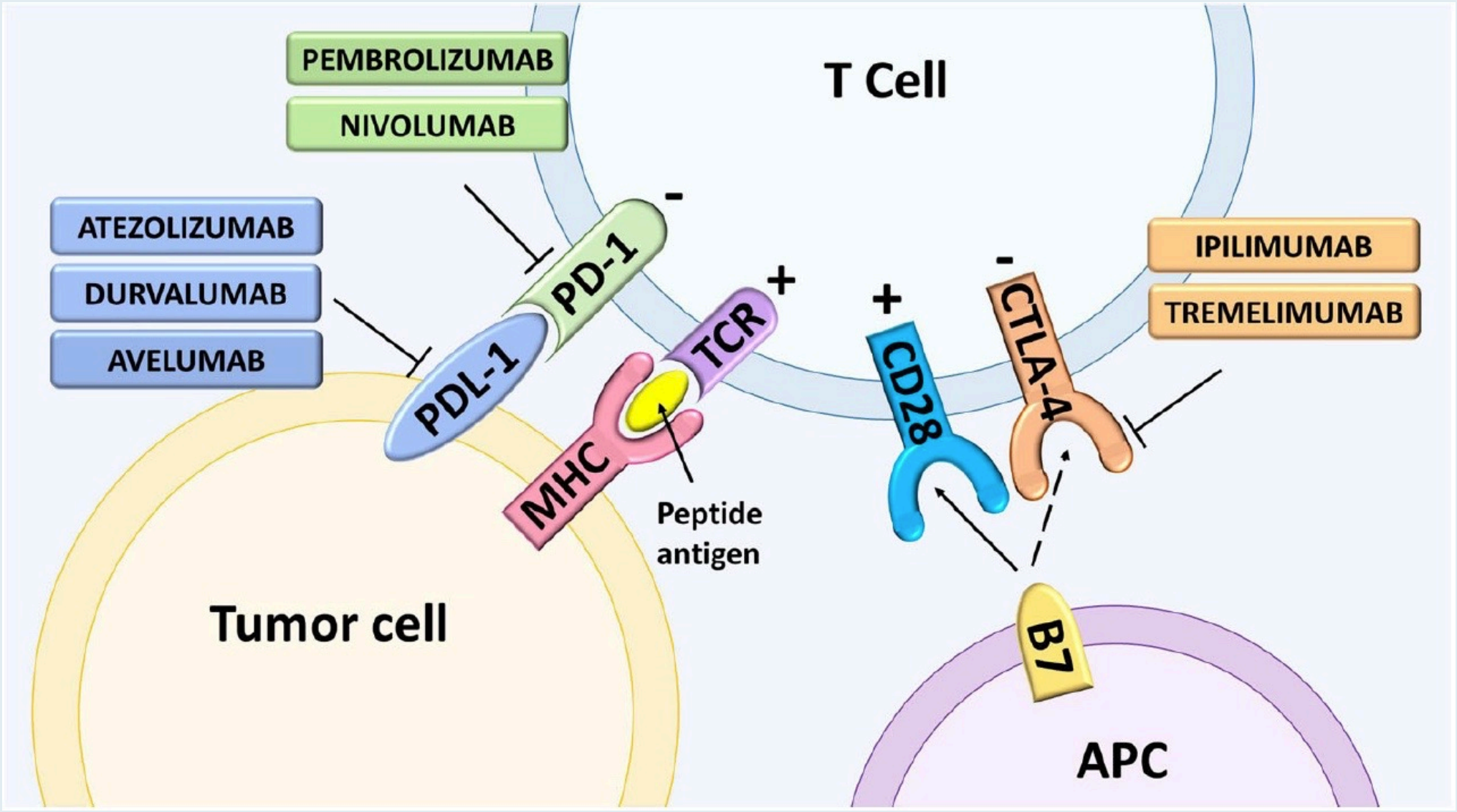
Mechanism of Action of Immune Checkpoint Inhibitors



Seebacher NA et al. *Clin Cancer Res* 2019;38(1):156.

FDA-Approved Immunotherapy for Nonmetastatic NSCLC

Regimen	FDA approval	Pivotal study	Setting	Primary Endpoint(s)
Nivolumab + platinum-doublet chemotherapy[1]	3/4/22	CheckMate-816	Neoadjuvant Resectable, Stage IB , II, or IIIA	Median EFS: 31.6 mo pCR: 24.0%
Atezolizumab[2]	10/15/21	IMpower010	Adjuvant Stage II-IIIA PD-L1 ≥1%	Median DFS: NR
Pembrolizumab[3]	1/26/23	PEARLS/KEYNOTE-091	Adjuvant Stage IB, II, or IIIA	Median DFS (overall): 53.6 mo Median DFS (PD-L1 TPS ≥50%): NR
Durvalumab[4]	2/6/18	PACIFIC	Consolidation Unresectable, Stage III	Median PFS: 16.9 mo Median OS: 47.5 mo

NR, not reached

[1] Forde PM et al. *N Engl J Med* 2022;386(21):1973-85. [2]Felip E et al. *Lancet* 2021;398(10308):1344-57. [3]O'Brien M et al. Lancet Oncol 2022; 23(10):1274-86. [4]Spigel DR et al. *J Clin Oncol* 2022;40(12):1301-11.

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FDA-Approved Single-Agent Immunotherapy Options for First-Line Therapy

Monotherapy	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab[1,2] (q3wk or q6wk)	4/11/19 10/24/16	KEYNOTE-042 KEYNOTE-024	PD-L1 TPS ≥1%	0.63
Atezolizumab[3] (q2wk, q3wk or q4wk)	5/18/20	IMpower110	PD-L1 TPS ≥50, EGFR and/or ALK wt	0.59
Cemiplimab[4] (q3wk)	2/22/21	EMPOWER-Lung 1 (Study 1624)	PD-L1 TPS ≥50, EGFR and/or ALK and/or ROS1 wt	0.57

wt = wild type

[1] Mok. *Lancet* 2019. [2] Reck. *J Clin Oncol* 2019. [3] Herbst. *N Engl J Med* 2020. [4] Sezer. *Lancet* 2021.

FDA-Approved Immunotherapy Combination Options for First-Line Therapy

Combination regimen	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab (q3wk or q6wk) + platinum and pemetrexed[1]	8/20/18	KEYNOTE-189	Nonsquamous	0.56
Pembrolizumab (q3wk or q6wk) + carboplatin, paclitaxel or *nab* paclitaxel[2]	10/30/18	KEYNOTE-407	Squamous	0.71
Atezolizumab (q3wk) + carboplatin and paclitaxel and bevacizumab[3]	12/6/18	IMpower150	Nonsquamous	0.80
Atezolizumab (q3wk) + carboplatin and *nab* paclitaxel[4]	12/3/19	IMpower130	Nonsquamous	0.79
Nivolumab (q2wk) + ipilimumab[5]	5/15/20	CheckMate 227	PD-L1 TPS ≥1, EGFR and/or ALK wt	0.76
Nivolumab (q3wk) + ipilimumab and chemotherapy[6]	5/26/20	CheckMate 9LA	EGFR and/or ALK wt	0.72
Durvalumab (q4wk) + tremelimumab and chemotherapy[7]	11/10/20	POSEIDON	EGFR and/or ALK wt	0.77

[1] Rodriguez-Abreu. *Ann Oncol* 2021. [2] Paz-Ares. *J Thorac Oncol* 2020. [3] Socinski *J Thorac Oncol* 2021. [4] West. *Lancet Oncol* 2019.
[5] Paz-Ares. ASCO 2021;Abstract 9016. [6] Reck. ASCO 2021;Abstract 9000. [7] Johnson. *J Clin Oncol* 2023.

Tara Plues, APRN, MSN

59-year-old man with metastatic NSCLC who received ipilimumab/nivolumab and rejected a transplanted kidney

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Dr Liu
Washington, DC

Clinical Research Background

Dr Tsao
Houston, Texas

- **Role of immunotherapy in NSCLC**
  - **Neoadjuvant and adjuvant treatment**
  - **Consolidation treatment for unresectable locally advanced disease**
  - **First-line therapy for metastatic disease**
  - **Toxicity in patients with lung cancer**

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Symptoms of Immunotherapy Toxicity

Hypophysitis
(fatigue)

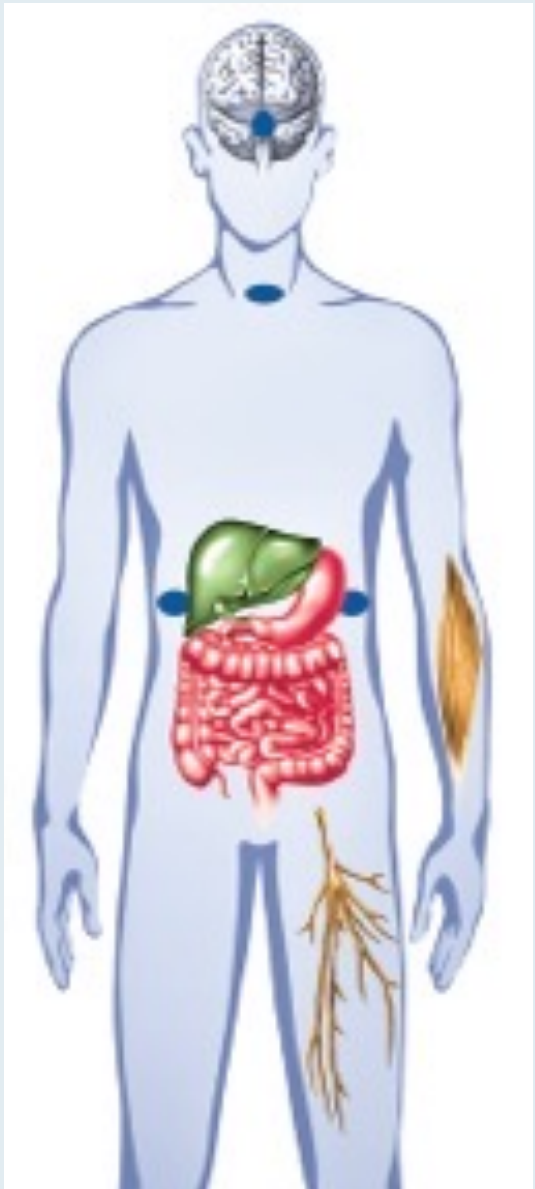
Thyroiditis
(over/underactive thyroid)

Adrenal Insufficiency
(fatigue)

Diabetes Mellitus
(Type I, II, fatigue, DKA)

Colitis
(diarrhea, abdominal pain)

Dermatitis
(rash, itch, blistering)



Pneumonitis
(dyspnea, cough)

Myocarditis
(chest pain, dyspnea)

Hepatitis
(abnornal LFTs, jaundice)

Pancreatitis
(abdominal pain)

Neurotoxicities
(MG, encephalitis)

Arthritis
(joint pain)

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Jillian Thompson, MSN, ANP-BC, AOCNP

75-year-old woman who received neoadjuvant chemotherapy and adjuvant pembrolizumab, developed recurrent disease with a MET exon 14 mutation and was started on capmatinib

Dr Liu
Washington, DC

Clinical Research Background

Dr Tsao
Houston, Texas

- **Tumor treating fields**
  - **Mechanism of action**
  - **Emerging Phase III LUNAR study results**
  - **Tolerability**

Tumor Treating Fields (TTFields)

Mechanism of action

- **Alternating electric fields which interfere with dividing cells by disrupting mitosis**

Indication

- **Investigational**

Pivotal clinical data

- **Press release (January 5, 2023): Primary OS endpoint met in pivotal Phase III LUNAR study of TTFields with immune checkpoint inhibitors or docetaxel (experimental arm) versus immune checkpoint inhibitors or docetaxel alone (control arm) for patients with Stage IV NSCLC whose disease progressed during or after platinum-based therapy**
- **KEYNOTE-B36: A pilot study of first-line TTFields (150 kHz) with pembrolizumab for advanced or metastatic NSCLC**

https://www.novocure.com/novocure-announces-pivotal-lunar-study-in-non-small-cell-lung-cancer-met-primary-overall-survival-endpoint/; Kotecha R et al. WCLC 2022;Abstract EP08.01-076; www.clinicaltrials.gov. NCT04892472. Accessed April 2023.

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Tara Plues, APRN, MSN

24-year-old man with metastatic NSCLC with an ALK rearrangement who received crizotinib

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Dr Liu
Washington, DC

Clinical Research Background

Dr Tsao
Houston, Texas

- **Overview of targeted treatment for NSCLC**
  - **Frequency of targetable tumor mutations**
  - **Approaches to genetic testing**

Targetable Oncogenic Drivers

EGFR sensitizing
- Gefitinib[4]
- Erlotinib[4]
- Afatinib[4]
- Osimertinib[4]
- Necitumumab[4]
- Rociletinib[3]

ALK
- Crizotinib[4]
- Alectinib[4]
- Ceritinib[4]
- Lorlatinib[2]
- Brigatinib[2]

MET
- Crizotinib[2]
- Cabozantinib[2]

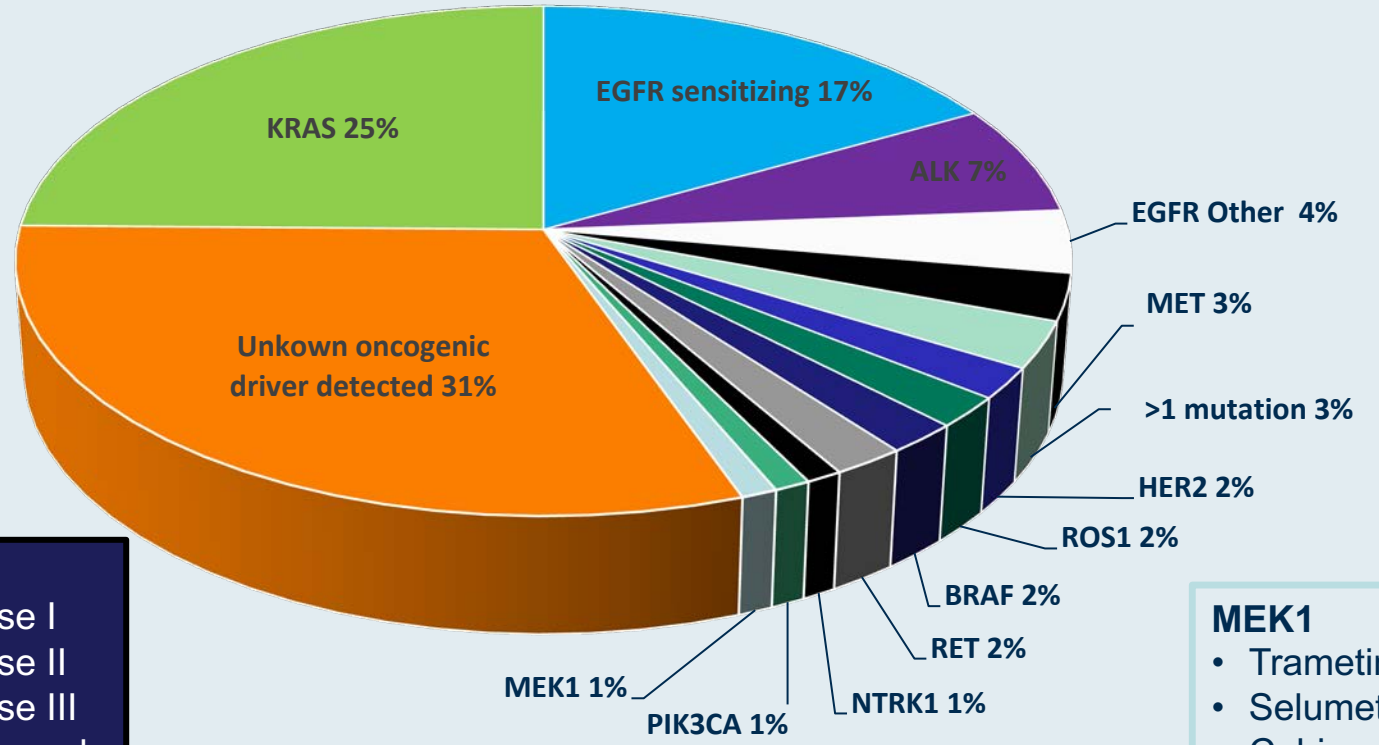
HER2
- Trastuzumab emtansine[2]
- Afatinib[2]
- Dacomitinib[2]

ROS1
- Crizotinib[4]
- Cabozantinib[2]
- Ceritinib[2]
- Lorlatinib[2]
- DS-6051b[1]

BRAF
- Vemurafenib[2]
- Dabrafenib[2]

RET
- Cabozantinib[2]
- Alectinib[2]
- Apatinib[2]
- Vandetanib[2]
- Ponatinib[2]
- Lenvatinib[2]

NTRK1
- Entrectinib[2]
- LOXO-101[2]
- Cabozantinib[2]
- DS-6051b[1]



KEY
1 - Phase I
2 - Phase II
3 - Phase III
4 - Approved

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

PIK3CA
- LY3023414[2]
- PQR 309[1]

Presented By Frances Shepherd at 2019 ASCO Annual Meeting.

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Jillian Thompson, MSN, ANP-BC, AOCNP

74-year-old man with resected Stage IIA NSCLC with an EGFR L858R mutation who received adjuvant osimertinib

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Dr Liu
Washington, DC

Clinical Research Background

Dr Tsao
Houston, Texas

- **Targeted treatment for NSCLC with an EGFR mutation**
  - **Selection of patients for adjuvant osimertinib**
  - **First-line therapy for metastatic disease**
  - **Therapeutic considerations for patients with metastatic NSCLC after disease progression on first-line osimertinib**

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Jillian Thompson, MSN, ANP-BC, AOCNP

73-year-old man with metastatic NSCLC with an EGFR exon 20 mutation who received amivantamab

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Dr Liu
Washington, DC

Clinical Research Background

Dr Tsao
Houston, Texas

- **NSCLC with EGFR exon 20 insertion mutations**
  - **Selection and sequencing of amivantamab and mobocertinib**
  - **Tolerability of targeted agents**

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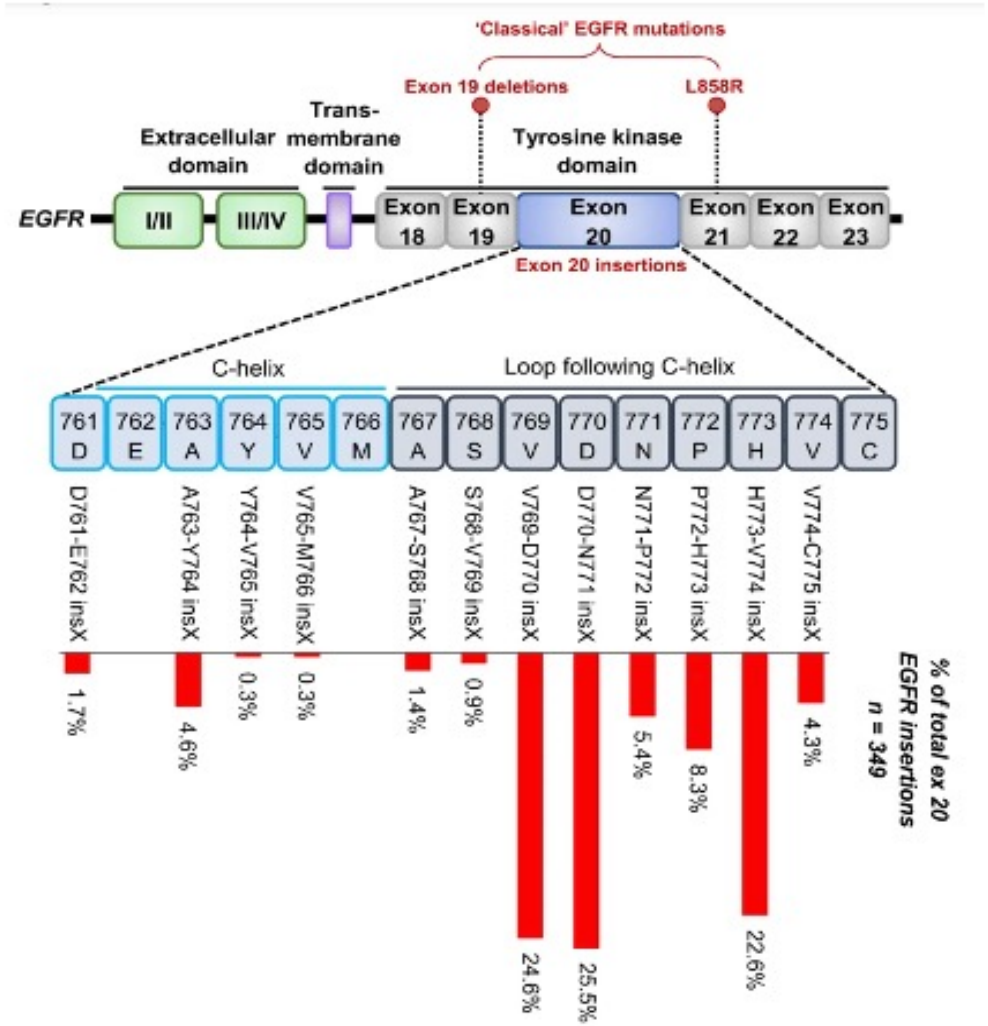
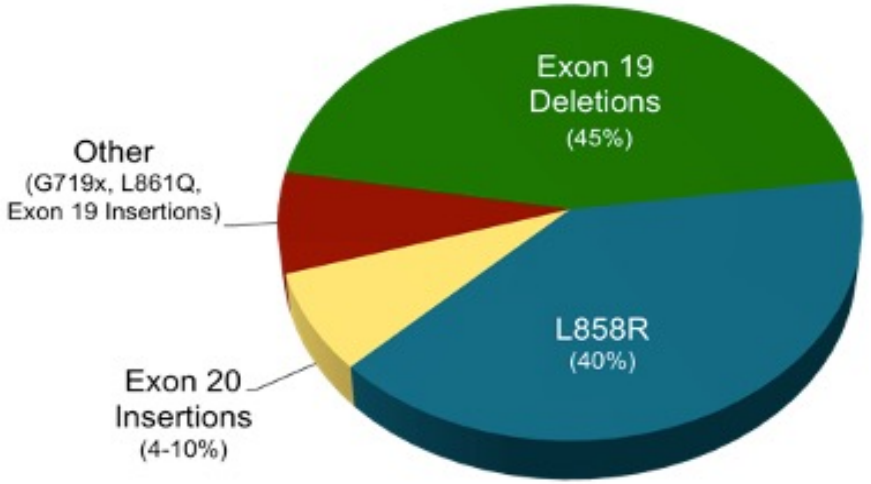
Frequency of EGFR Exon 20 Mutations





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

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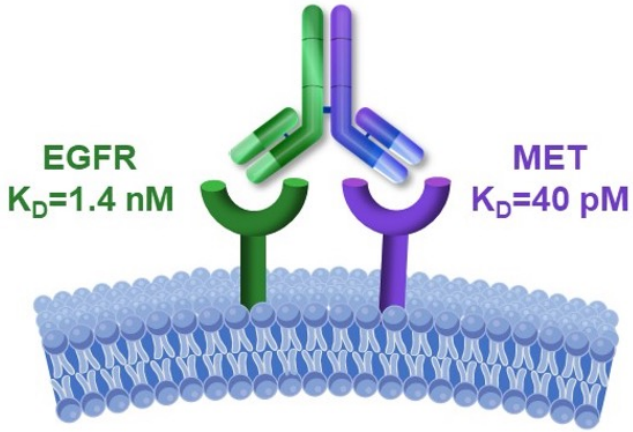
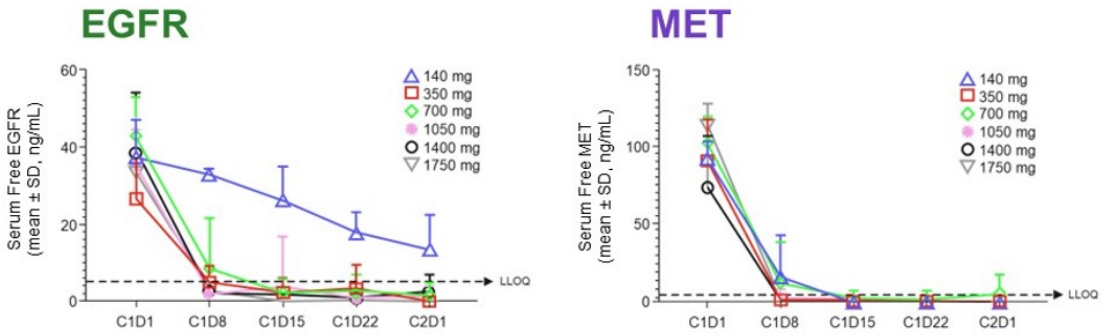
Amivantamab: EGFR-MET Bispecific Antibody

- Demonstrated monotherapy activity in EGFR ex20ins NSCLC following progression on platinum-based chemotherapy (ORR, 40%; DOR, 11.1 months)[1]
- Demonstrated activity in TKI-resistant EGFRm NSCLC with MET amplification[2,3]
- Has higher affinity for MET (40 pM) than EGFR (1.4 nM)
- Depletion of free soluble target proteins, suggesting total body target engagement, occurs at ≥140 mg for sMET and ≥350 mg for sEGFR
- Evaluation in primary MET-driven tumors is ongoing





C, cycle; D, day; DOR, duration of response; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; ex20ins, exon 20 insertion mutations; K_D, dissociation constant; LLOQ, lower limit of quantification; NSCLC, non-small cell lung cancer; ORR, overall response rate; SD, standard deviation; sEGFR, soluble EGFR; sMET, soluble MET; TKI, tyrosine kinase inhibitor.

1. Park K, et al. *J Clin Oncol*. 2021;39(30):3391-3402. 2. Haura EB, et al. Presented at: ASCO; May 31-June 4, 2019. 9009 (oral). 3. Bauml J, et al. Presented at: ASCO; June 4-8, 2021. 9006 (oral).

Krebs MG et al. ASCO 2022;Abstract 9008.

Amivantamab

Mechanism of action

- **Bispecific EGFR-directed and MET receptor-directed antibody**

Indication

- **For adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy**

Recommended dose

- **Administered weekly for 4 weeks, with the initial dose as a split infusion in week 1 on day 1 and day 2, then administer every 2 weeks thereafter, starting at week 5, until disease progression or unacceptable toxicity**
- **Body weight less than 80 kg = 1,050 mg; greater than or equal to 80 kg = 1,400 mg**

Amivantamab package insert, 11/2022.

Mobocertinib

Mechanism of action

- **Bispecific EGFR-directed and MET receptor-directed antibody**

Indication

- **For the treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in patients whose disease has progressed on or after platinum-based chemotherapy**

Recommended dose

- **160 mg orally once daily, with or without food**

Mobocertinib package insert, 3/2023.

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Tara Plues, APRN, MSN

60-year-old woman with metastatic NSCLC with a RET fusion who received selpercatinib and experienced an extended response

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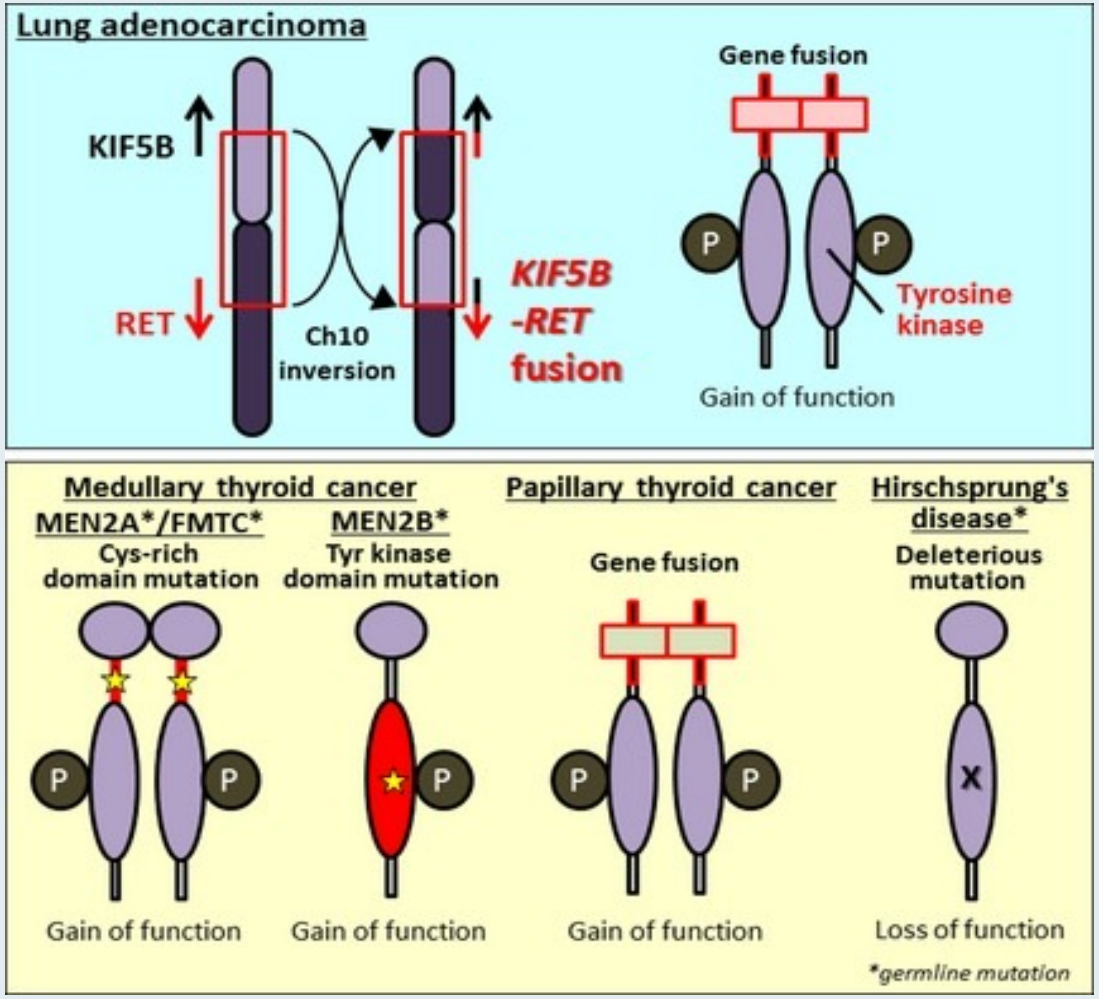
Dr Liu
Washington, DC

Clinical Research Background

Dr Tsao
Houston, Texas

- **Targeted treatment for NSCLC with a RET fusion**
  - **Selection and sequencing of selpercatinib and pralsetinib**
  - **Tolerability of targeted agents**

RET Fusions in NSCLC



- **Intact tyrosine kinase domain fused to an upstream gene partner**
  - **Most common: KIF5B**
  - **Others: CCDC6, NCOA4, TRIM33, KIAA1468**
- **Ligand-independent dimerization and downstream growth pathway activation**
- **Oncogenic in vitro and in vivo**
- **1%-2% NSCLC; younger; never/light smokers; adenocarcinoma/poorly differentiated**

Drilon AD, *Cancer Discov* 2013;3:630-5, Kohno T, *Nat Med* 2012;18:375-7, Saito M, *Carcinogenesis* 2014;35:2452-6; Suehara Y, *Nat Med* 2012;18;6599-608, Lipson D, *Nat Med* 2012;18:382-40, Takeuchi K, *Nat Med* 2012;18:378-81

RTP RESEARCH TO PRACTICE

Selpercatinib

Mechanism of action

- RET Inhibitor

Indication

- For adult patients with locally advanced or metastatic NSCLC with a rearranged during transfection (RET) gene fusion as detected by an FDA-approved test

Recommended dose

- 50 kg or greater: 160 mg orally twice daily
- Less than 50 kg: 120 mg orally twice daily

Selpercatinib package insert, 9/2022.

Pralsetinib

Mechanism of action

- **Oral, next-generation, small-molecule selective RET inhibitor**

Indication

- **For adult patients with metastatic NSCLC with RET fusion as detected by an FDA-approved test**

Recommended dose

- **400 mg orally once daily on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after)**

Pralsetinib package insert, 9/2022.

Agenda

Module 1: Immunotherapy for Nonmetastatic and Metastatic NSCLC

Module 2: Future Directions — Tumor Treating Fields

Module 3: Overview of Targeted Treatment for NSCLC

Module 4: Targeted Treatment for NSCLC with an EGFR Mutation

Module 5: EGFR Exon 20 Insertion Mutations

Module 6: Targeted Treatment for NSCLC with a RET Fusion

Module 7: Targeted Treatment for NSCLC with a KRAS G12C Mutation

Tara Plues, APRN, MSN

58-year-old woman with metastatic NSCLC with a KRAS G12C mutation who received first-line carboplatin/pemetrexed/ pembrolizumab → second-line adagrasib

RTP
RESEARCH
TO PRACTICE

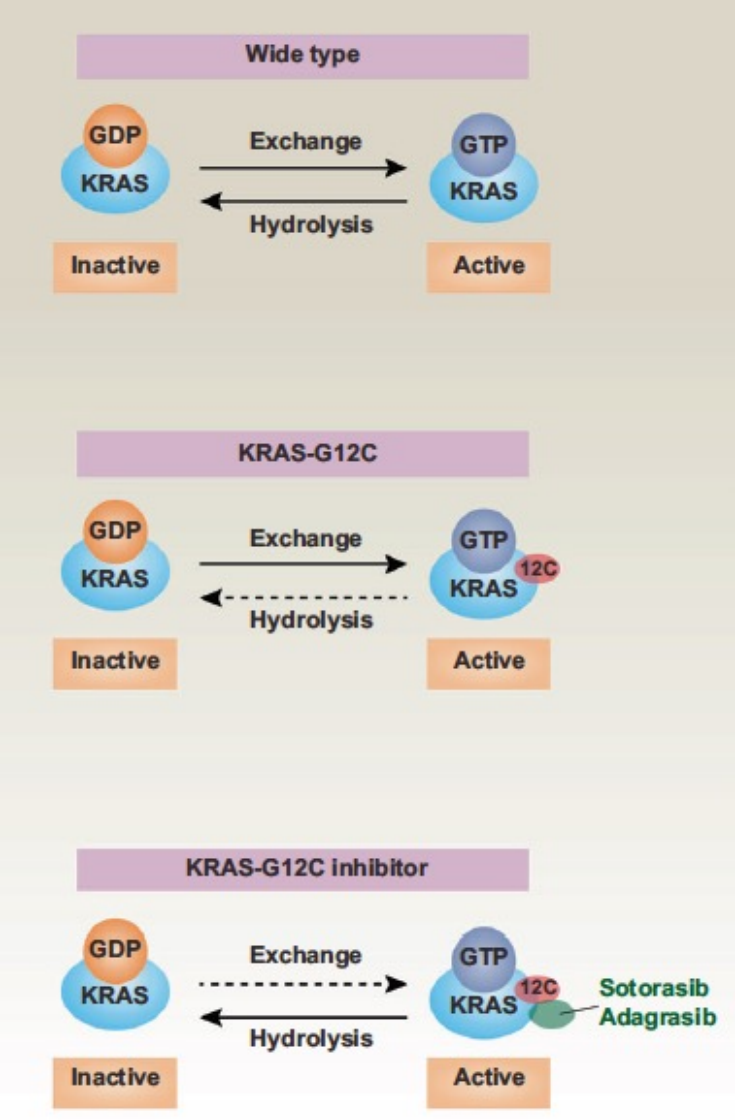
Dr Liu
Washington, DC

Clinical Research Background

Dr Tsao
Houston, Texas

- **Targeted treatment for NSCLC with a KRAS G12C mutation**
  - **Selection and sequencing of adagrasib and sotorasib**
  - **Tolerability of targeted agents**

Mechanism of Action of KRAS G12C Inhibitors



Compared with wild-type KRAS, which maintains a balance between inactive and activated states, cysteine 12 (C12) mutations destroys GTPase activity of KRAS and locks in the GTP-bound active state.

In contrast, the small molecule drug sotorasib or adagrasib can form a covalent bond with C12 in the KRAS G12C protein, causing KRAS to be in an inactive state.

Liu J et al. *Cancer Gene Ther* 2022;29:875-78.

RTP RESEARCH TO PRACTICE

Sotorasib

Mechanism of action

- **Direct inhibitor of the enzyme KRAS with the G12C mutation**

Indication

- **For the treatment of locally advanced or metastatic NSCLC with a KRAS G12C mutation in patients who have received at least 1 prior systemic therapy**

Recommended dose

- **960 mg orally once daily**

Sotorasib package insert, 1/2023.

Adagrasib

Mechanism of action

- **Orally bioavailable, highly selective, small-molecule, irreversible covalent inhibitor of KRAS G12C**

Indication

- **For the treatment of locally advanced or metastatic NSCLC with a KRAS G12C mutation in patients who have received at least 1 prior systemic therapy**

Recommended dose

- **600 mg orally twice daily**

Adagrasib package insert, 12/2022.

APPENDIX

Immunotherapy as Up-Front Treatment for NSCLC

2022 ASCO® ANNUAL MEETING

FDA

Abstract 9000

Outcomes of anti-PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score ≥50%: FDA Pooled Analysis

Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Oncology Center of Excellence, U.S. Food and Drug Administration

RTP RESEARCH TO PRACTICE

FDA-Approved Regimens for Advanced NSCLC Not Harboring Tumor Genomic Alterations

PD-L1 level	Regimen	Histology	Approval endpoint
≥ 50%	**Pembrolizumab**	NSCLC	**OS** & PFS
	Atezolizumab [a]	NSCLC	**OS**
	Cemiplimab	NSCLC	**OS** & PFS
≥ 1%	**Pembrolizumab**	NSCLC	**OS**
	Nivolumab + Ipilimumab	NSCLC	**OS**
None	**Pembrolizumab** + Platinum + Pemetrexed [b]	NSq-NSCLC	**OS** & PFS
	Pembrolizumab + Carboplatin + Paclitaxel	Sq-NSCLC	**OS** & PFS
	Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel	NSq-NSCLC	**OS** & PFS
	Atezolizumab + Carboplatin + Nab-paclitaxel	NSq-NSCLC	**OS** & PFS
	Nivolumab + Ipilimumab + Platinum doublet	NSCLC	**OS**

Akinboro O et al. ASCO 2022;Abstract 9000.

Clinical Trials of First-Line Chemotherapy/Immuno-Oncology (IO) and IO Regimens Included in FDA Pooled Analysis

Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

Akinboro O et al. ASCO 2022;Abstract 9000.

FDA Pooled Analysis: Author Conclusions and Summary

- Our pooled analysis does not suggest a difference in OS for Chemo-IO vs IO-alone though there appears to be a slight numerical advantage favoring Chemo-IO
- Observed differences in PFS and ORR between Chemo-IO and IO-alone to be interpreted in the context of the OS findings and the exploratory nature of this analysis
- Older adults aged ≥75 years may have better OS and PFS outcomes with IO-only regimens
- These support shared decision-making in selecting a therapeutic approach

Akinboro O et al. ASCO 2022;Abstract 9000.

FDA Pooled Analysis: Limitations

- Retrospective exploratory pooled analyses
  - Results only hypothesis-generating
- Analyses do not explain the lack of concordance between OS and PFS/ORR results
  - Subsequent therapies in the IO-only arm
  - Deaths and treatment-discontinuation due to toxicity
- Potential heterogeneity across trials
  - Differences in PD-L1 assays
- Notable differences between clinical trial populations and real-world patients

Akinboro O et al. ASCO 2022;Abstract 9000.

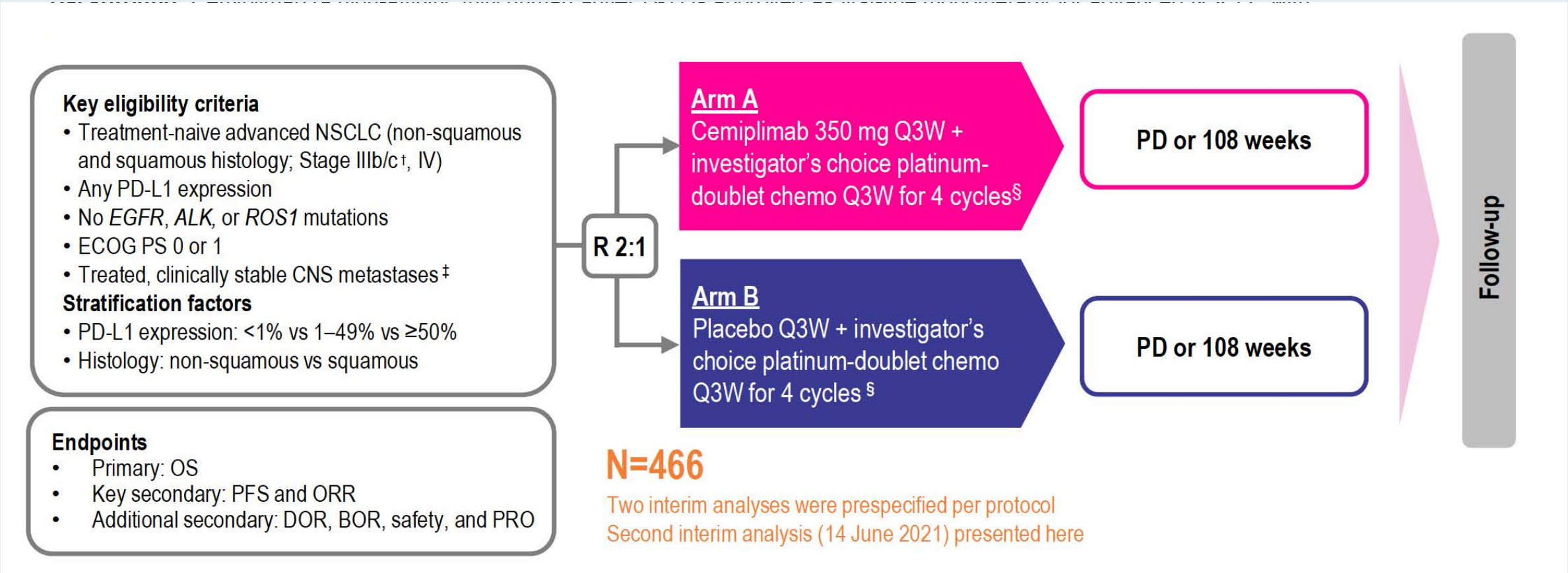
Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial

Miranda Gogishvili[1], Tamar Melkadze[2], Tamta Makharadze[3], Davit Giorgadze[4], Mikhail Dvorkin[5], Konstantin Penkov[6], Konstantin Laktionov[7], Gia Nemsadze[8], Marina Nechaeva[9], Irina Rozhkova[10], Ewa Kalinka[11], Christian Gessner[12,13], Brizio Moreno-Jaime[14], Rodolfo Passalacqua[15], Siyu Li[16], Kristina McGuire[16], Manika Kaul[16], Anne Paccaly[16], Ruben G. W. Quek[16], Bo Gao[16], Frank Seebach[16], David M. Weinreich[16], George D. Yancopoulos[16], Israel Lowy[16], Giuseppe Gullo[16] and Petra Rietschel[16]

Nat Med 2022 August 25;[Online ahead of print].

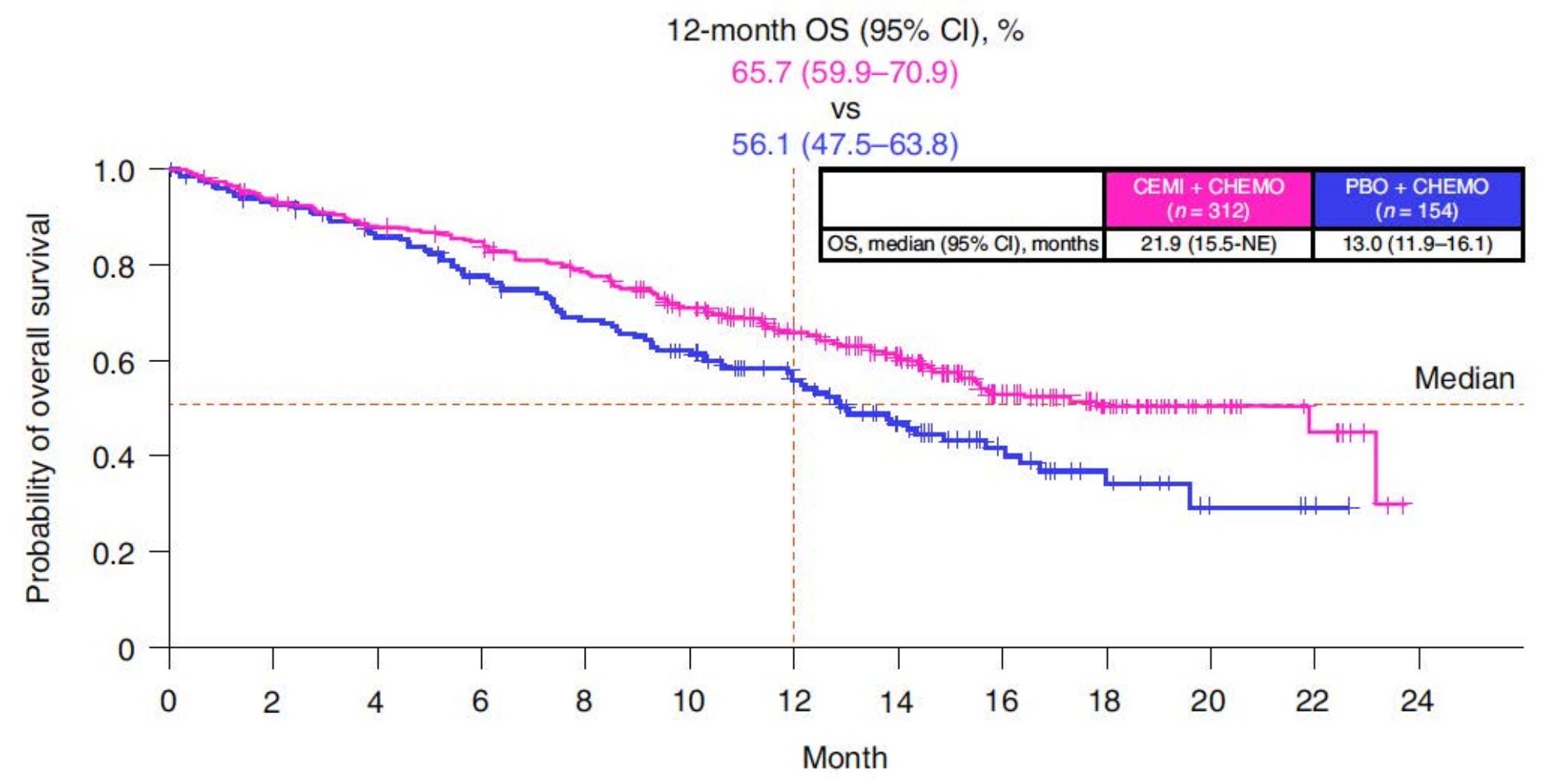
RTP RESEARCH TO PRACTICE

EMPOWER-Lung 3: First-Line Cemiplimab with Platinum-Doublet Chemotherapy for Advanced NSCLC



Gogishvili M et al. ESMO 2021;Abstract LBA51.

EMPOWER-Lung 3: First-Line Cemiplimab with Platinum-Doublet Chemotherapy for Advanced NSCLC



Gogishvili M et al. *Nat Med* 2022 August 25;[Online ahead of print].

RTP RESEARCH TO PRACTICE

original reports

Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study

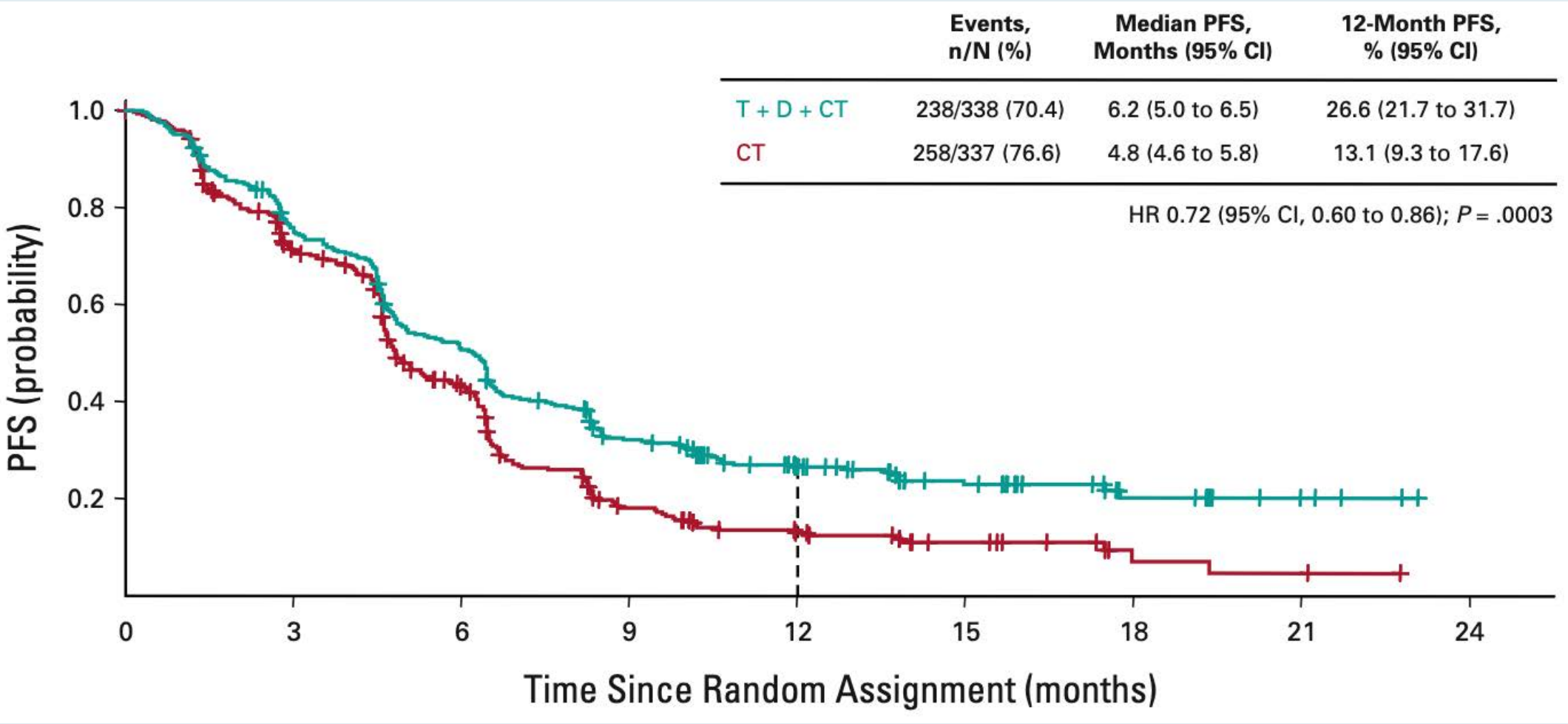
Melissa L. Johnson, MD[1]; Byoung Chul Cho, MD, PhD[2]; Alexander Luft, MD[3]; Jorge Alatorre-Alexander, MD[4]; Sarayut Lucien Geater, MD[5]; Konstantin Laktionov, MD[6]; Sang-We Kim, MD, PhD[7]; Grygorii Ursol, MD[8]; Maen Hussein, MD[9]; Farah Louise Lim, MBBS, MRCP[10]; Cheng-Ta Yang, MD[11]; Luiz Henrique Araujo, MD, PhD[12]; Haruhiro Saito, MD, PhD[13]; Niels Reinmuth, MD, PhD[14]; Xiaojin Shi, MD[15]; Lynne Poole, MSc[16]; Solange Peters, MD, PhD[17]; Edward B. Garon, MD[18]; and Tony Mok, MD[19] for the POSEIDON investigators

J Clin Oncol 2023;41:1213-27.

POSEIDON: PFS with First-Line Durvalumab with Tremelimumab and Chemotherapy for Advanced NSCLC

	Events, n/N (%)	Median PFS, Months (95% CI)	12-Month PFS, % (95% CI)
T + D + CT	238/338 (70.4)	6.2 (5.0 to 6.5)	26.6 (21.7 to 31.7)
CT	258/337 (76.6)	4.8 (4.6 to 5.8)	13.1 (9.3 to 17.6)

HR 0.72 (95% CI, 0.60 to 0.86); $P = .0003$



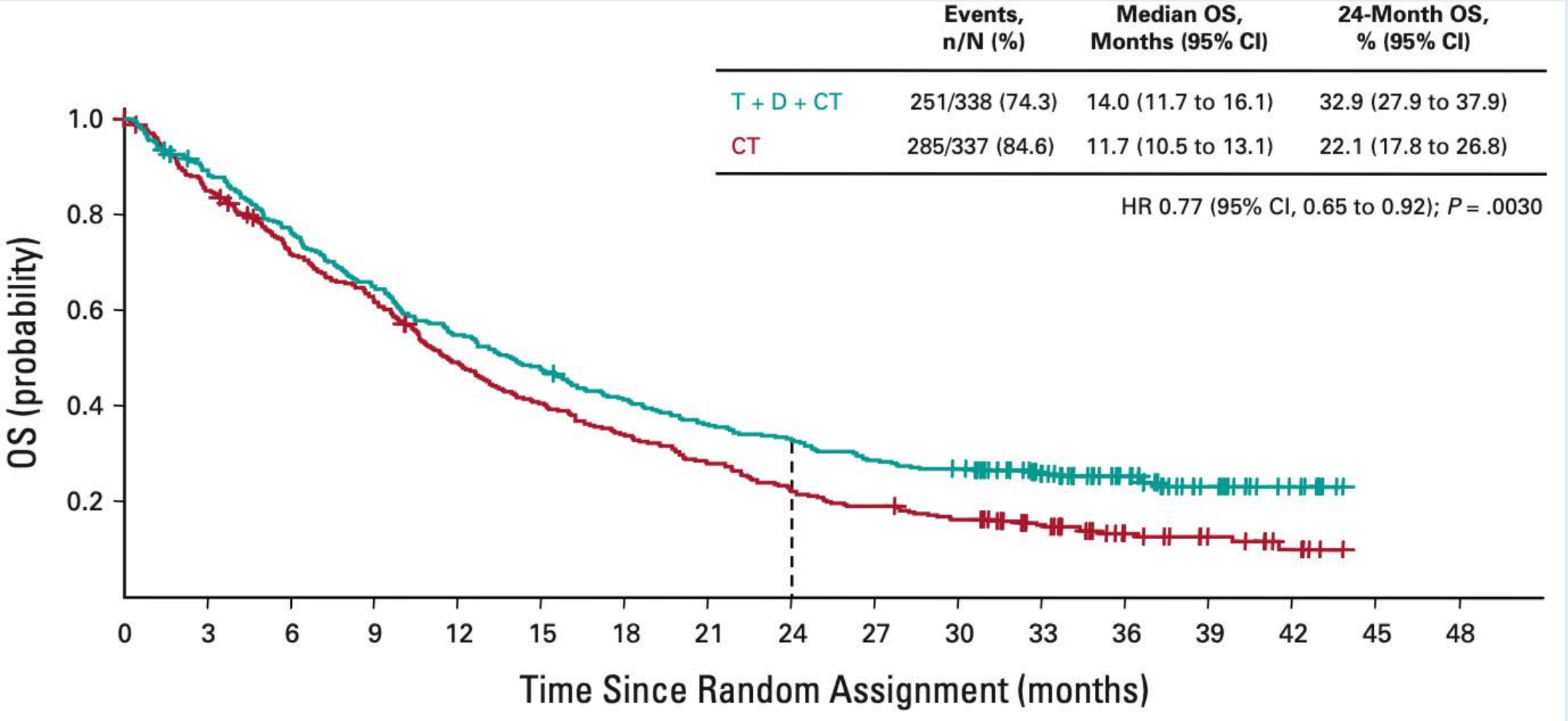
Johnson ML et al. *J Clin Oncol* 2023;41:1213-27.

RTP RESEARCH TO PRACTICE

POSEIDON: OS with First-Line Durvalumab with Tremelimumab and Chemotherapy for Advanced NSCLC

	Events, n/N (%)	Median OS, Months (95% CI)	24-Month OS, % (95% CI)
T + D + CT	251/338 (74.3)	14.0 (11.7 to 16.1)	32.9 (27.9 to 37.9)
CT	285/337 (84.6)	11.7 (10.5 to 13.1)	22.1 (17.8 to 26.8)

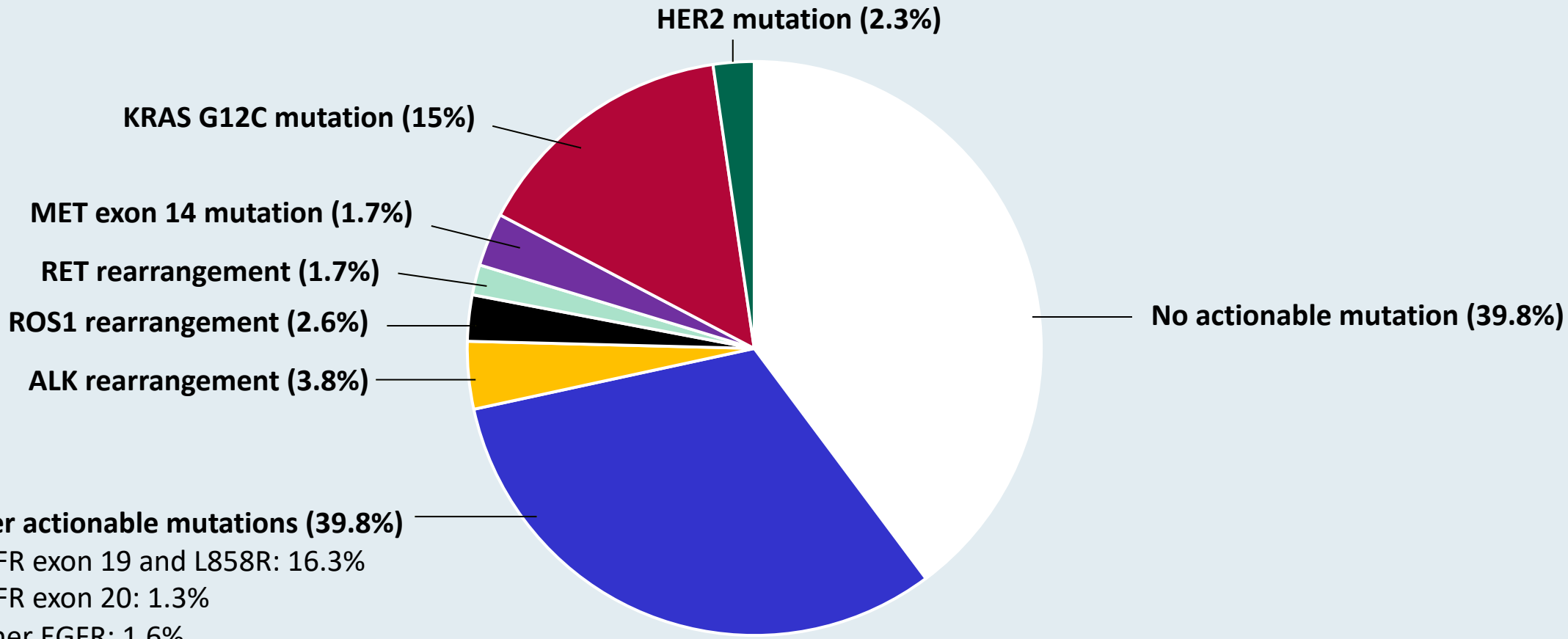
HR 0.77 (95% CI, 0.65 to 0.92); $P = .0030$



Johnson ML et al. *J Clin Oncol* 2023;41:1213-27.

NSCLC with EGFR Mutation

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



Other actionable mutations (39.8%)
--EGFR exon 19 and L858R: 16.3%
--EGFR exon 20: 1.3%
--Other EGFR: 1.6%
--Other KRAS: 10.3%
--BRAF V600E: 2.1%
--NTRK rearrangement: 0.23%

Derived from: Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

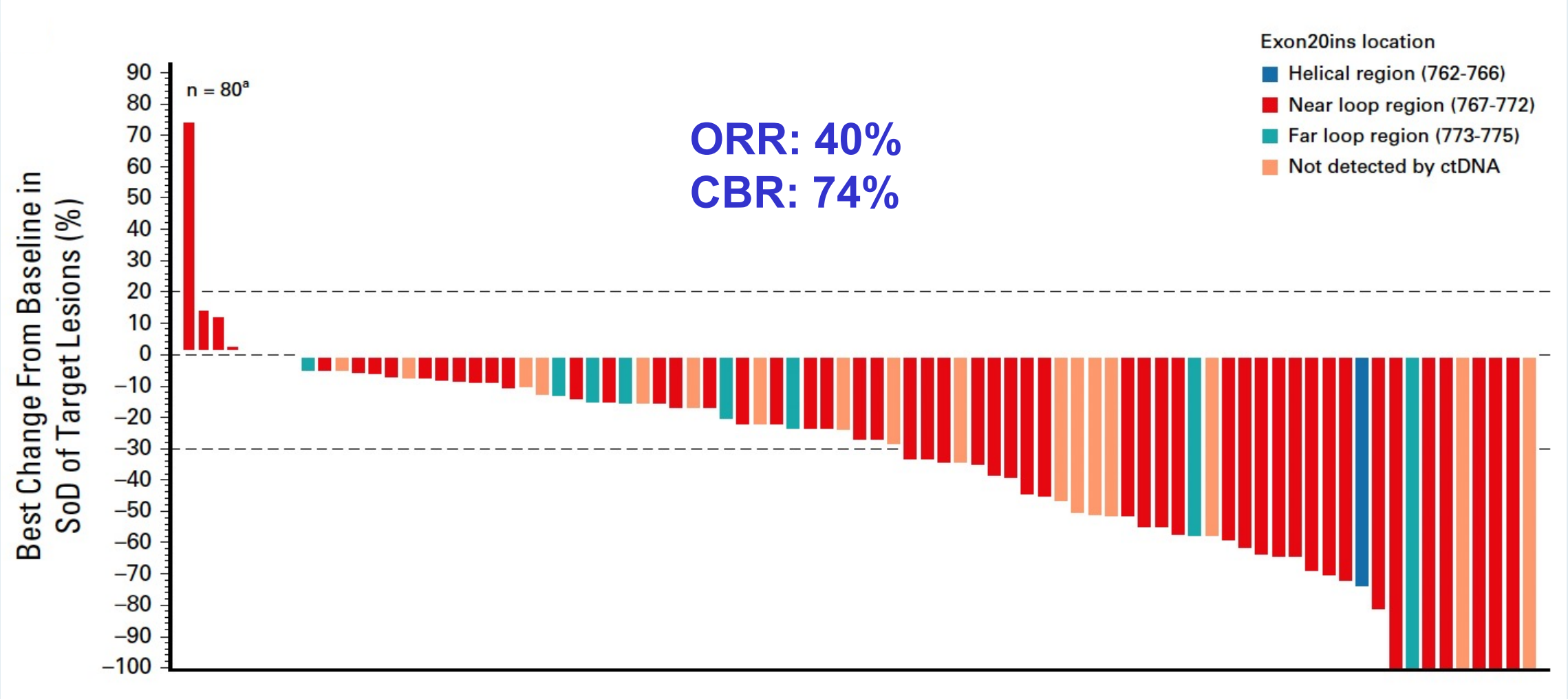
original reports

Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study

Keunchil Park, MD, PhD[1]; Eric B. Haura, MD[2]; Natasha B. Leighl, MD[3]; Paul Mitchell, MD[4]; Catherine A. Shu, MD[5]; Nicolas Girard, MD, PhD[6]; Santiago Viteri, MD[7]; Ji-Youn Han, MD, PhD[8]; Sang-We Kim, MD, PhD[9]; Chee Khoon Lee, MD[10]; Joshua K. Sabari, MD[11]; Alexander I. Spira, MD, PhD[12]; Tsung-Ying Yang, MD, PhD[13]; Dong-Wan Kim, MD, PhD[14]; Ki Hyeong Lee, MD, PhD[15]; Rachel E. Sanborn, MD[16]; José Trigo, MD[17]; Koichi Goto, MD, PhD[18]; Jong-Seok Lee, MD, PhD[19]; James Chih-Hsin Yang, MD, PhD[20]; Ramaswamy Govindan, MD[21]; Joshua M. Bauml, MD[22]; Pilar Garrido, MD, PhD[23]; Matthew G. Krebs, MD, PhD[24]; Karen L. Reckamp, MD[25]; John Xie, PhD[26]; Joshua C. Curtin, PhD[26]; Nahor Haddish-Berhane, PhD[26]; Amy Roshak, BS[26]; Dawn Millington, MS[26]; Patricia Lorenzini, MS[26]; Meena Thayu, MD[26]; Roland E. Knoblauch, MD, PhD[26]; and Byoung Chul Cho, MD, PhD[27]

J Clin Oncol 2021;39:3391-402.

CHRYSALIS: Tumor Reduction and Response



ORR = overall response rate; CBR = clinical benefit rate

Park K et al. *J Clin Oncol* 2021;39:3391-402.

RTP RESEARCH TO PRACTICE

CHRYSALIS: Summary of Adverse Events (AEs) and Most Common AEs

Event	Safety Population (n = 114), No. (%)	Patients Treated at the RP2D (n = 258), No. (%)
Any AE	113 (99)	257 (100)
Grade ≥ 3 AE	40 (35)	101 (39)
Serious AE	34 (30)	79 (31)
AE leading to death	8 (7)	13 (5)
AE leading to discontinuation	11 (10)	17 (7)
AE leading to dose reduction	15 (13)	26 (10)
AE leading to dose interruption[a]	40 (35)	88 (34)

Most Common AEs in the Safety Population

Adverse Events	Any Grade	Grade ≥3
Rash	86%	4%
Infusion-related reactions	66%	3%
Paronychia	45%	1%

Park K et al. *J Clin Oncol* 2021;39:3391-402.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

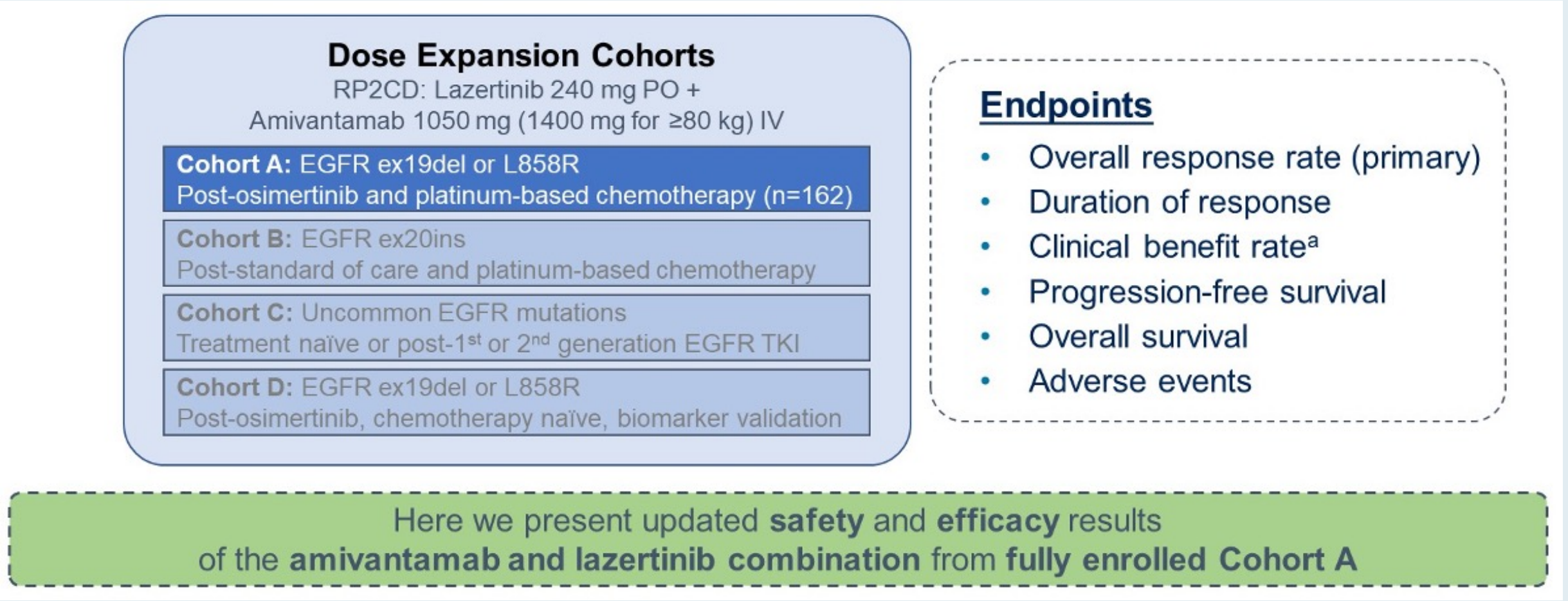
Abstract 9006

Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung cancer (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2

Catherine A. Shu,[1] Koichi Goto,[2] Yuichiro Ohe,[3] Benjamin Besse,[4] Se-Hoon Lee,[5] Yongsheng Wang,[6] Frank Griesinger,[7] James Chih-Hsin Yang,[8] Enriqueta Felip,[9] Rachel E. Sanborn,[10] Reyes Bernabe Caro,[11] Joshua C. Curtin,[12] Jun Chen,[12] Janine Mahoney,[12] Leonardo Trani,[12] Joshua M. Bauml,[12] Meena Thayu,[12] Roland E. Knoblauch,[12] Byoung Chul Cho[13]

RTP RESEARCH TO PRACTICE

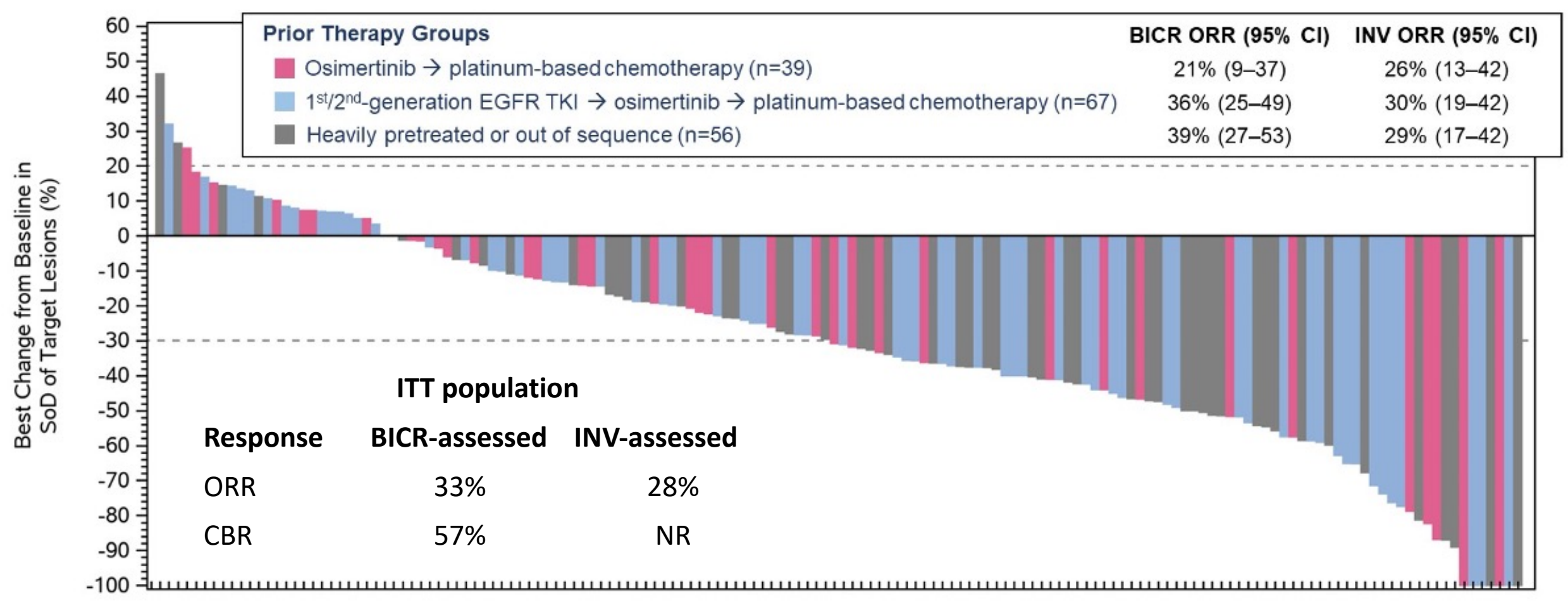
CHRYSALIS-2: Study Design



Shu CA et al. ASCO 2022;Abstract 9006.

RTP RESEARCH TO PRACTICE

CHRYSALIS-2: Best Antitumor Response and ORR by Prior Therapy



ORR = overall response rate; BICR = blinded independent central review; INV = investigator; CBR = clinical benefit rate

Shu CA et al. ASCO 2022;Abstract 9006.

RTP RESEARCH TO PRACTICE

CHRYSALIS-2: Safety Profile

TEAEs (≥15%) by Preferred Term, n (%)	n=162	
	All grade	Grade ≥3
EGFR-related		
Rash	71 (44)	4 (2)
Dermatitis acneiform	55 (34)	8 (5)
Paronychia	84 (52)	6 (4)
Stomatitis	63 (39)	2 (1)
Diarrhea	36 (22)	1 (1)
Pruritus	30 (19)	1 (1)
MET-related		
Hypoalbuminemia	70 (43)	11 (7)
Peripheral edema	43 (27)	2 (1)
Other		
Infusion related reaction	108 (67)	13 (8)
Increased ALT	46 (28)	5 (3)
Nausea	40 (25)	3 (2)
Decreased appetite	39 (24)	1 (1)
Constipation	38 (23)	0
Asthenia	37 (23)	7 (4)
Dry skin	37 (23)	0
Vomiting	36 (22)	1 (1)
Increased AST	35 (22)	3 (2)
Dyspnea	33 (20)	13 (8)
Thrombocytopenia	33 (20)	2 (1)
Fatigue	32 (20)	4 (2)
Headache	29 (18)	2 (1)
Anemia	27 (17)	4 (2)
Hypocalcemia	26 (16)	1 (1)

- Individual AEs were mostly grade 1-2
- Dose interruptions, reductions, and discontinuations of both amivantamab and lazertinib due to toxicity were seen in 57 (35%), 15 (9%), and 12 (7%) patients, respectively
- Pneumonitis/ILD was seen in 11 (7%) patients, of which 6 (4%) were grade ≥3 (no grade 5)
- Cumulative grouped rash-related AEs[a] occurred in 129 (80%) patients, with 17 grade ≥3 (10%)
- Safety profile consistent with what was previously reported; no new safety signals identified

Shu CA et al. ASCO 2022;Abstract 9006.

Select Ongoing Phase III Studies of First-Line Therapy for Patients with Metastatic NSCLC and Activating EGFR Mutations

Study	No. of patients	Randomization	Est primary completion
FLAURA2	587	• Osimertinib • Osimertinib + platinum-based chemo	April 2023
MARIPOSA	1,000	• Amivantamab + lazertinib • Osimertinib + placebo • Lazertinib + placebo	April 2024
ECOG-ACRIN EA5182	300	• Osimertinib • Osimertinib + bevacizumab	September 2025
SANOVO*	320	• Osimertinib + savolitinib • Osimertinib + placebo	November 2024
FLETEO	680	• Osimertinib • TY-9591	May 2025

* Sensitizing EGFR mutation and c-MET overexpression

www.clinicaltrials.gov. Accessed June 2022.

RTP RESEARCH TO PRACTICE

Lazertinib

Mechanism of action

- **Oral third-generation, irreversible EGFR TKI**

Indication

- **Investigational**

Pivotal clinical data

- **Phase III MARIPOSA study evaluating lazertinib and amivantamab combination therapy versus osimertinib versus lazertinib as first-line therapy for patients with EGFR-mutated locally advanced or metastatic NSCLC**

www.clinicaltrials.gov. Accessed April 2023.

Select Ongoing Studies to Overcome Mechanisms of Resistance to EGFR TKIs for Advanced NSCLC

Study/phase	No. of patients	Eligibility	Treatment
SAVANNAH Phase II	294	• Locally advanced/metastatic • EGFR mutation • MET amplified/overexpressed • PD on osimertinib	• Osimertinib + savolitinib
SAFFRON Phase III	324	• Locally advanced/metastatic • EGFR mutation • MET amplified/overexpressed • PD on osimertinib	• Osimertinib + savolitinib • Platinum-based doublet
COMPEL Phase III	204	• Locally advanced/metastatic • EGFR mutation • Extracranial PD on first-line osimertinib	• Platinum/pemetrexed + osimertinib • Platinum/pemetrexed + placebo
MARIPOSA-2 Phase III	500	• Locally advanced/metastatic • EGFR mutation • PD on osimertinib	• Platinum-based chemotherapy + amivantamab + lazertinib • Platinum-based chemotherapy

PD = disease progression

www.clinicaltrials.gov. Accessed June 2022.

Research

JAMA Oncol 2021;7(12):e214761.

JAMA Oncology | Original Investigation

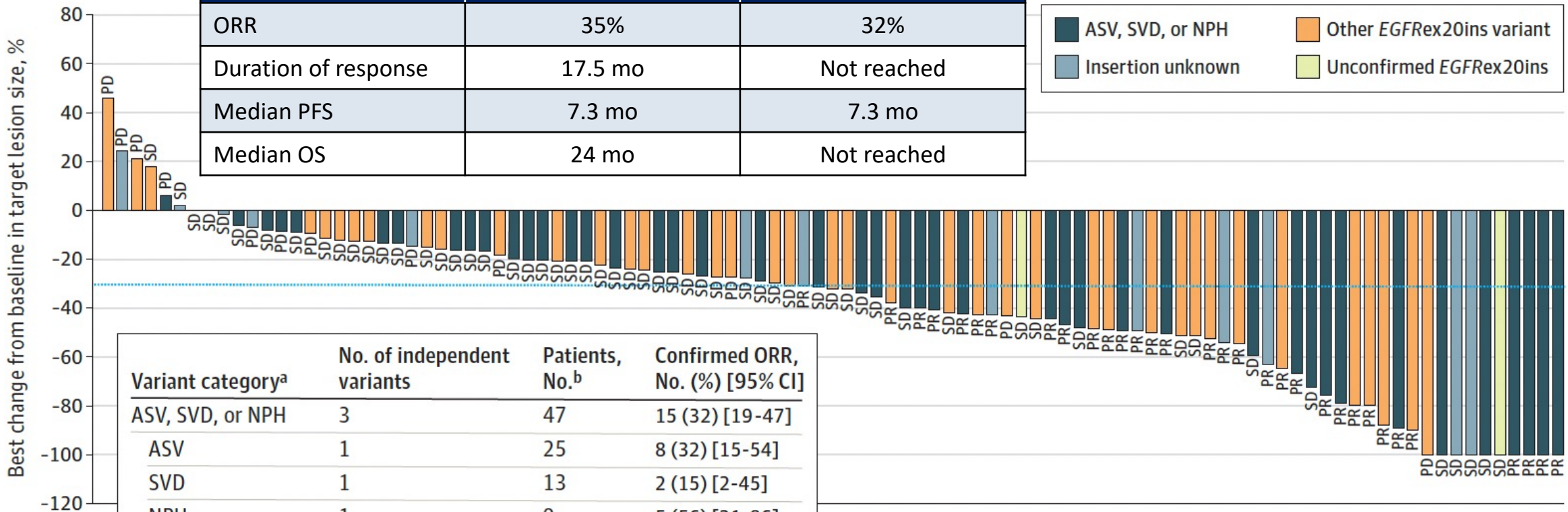
Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With *EGFR* Exon 20 Insertion–Positive Metastatic Non–Small Cell Lung Cancer

A Phase 1/2 Open-label Nonrandomized Clinical Trial

Caicun Zhou, PhD, MD; Suresh S. Ramalingam, MD; Tae Min Kim, MD, PhD; Sang-We Kim, MD; James Chih-Hsin Yang, MD; Gregory J. Riely, MD; Tarek Mekhail, MD; Danny Nguyen, MD; Maria R. Garcia Campelo, MD; Enriqueta Felip, MD; Sylvie Vincent, PhD; Shu Jin, MS; Celina Griffin, PharmD; Veronica Bunn, PhD; Jianchang Lin, PhD; Huamao M. Lin, PhD; Minal Mehta, MBBS; Pasi A. Jänne, MD, PhD

Mobocertinib Activity in Patients with Platinum-Pretreated Metastatic NSCLC with EGFR Exon 20 Insertion Mutation (PPP Cohort)

	PPP cohort (n = 114)	EXCLAIM cohort (n = 96)
ORR	35%	32%
Duration of response	17.5 mo	Not reached
Median PFS	7.3 mo	7.3 mo
Median OS	24 mo	Not reached



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

Zhou C et al. *JAMA Oncol* 2021;7(12):e214761.

RTP RESEARCH TO PRACTICE

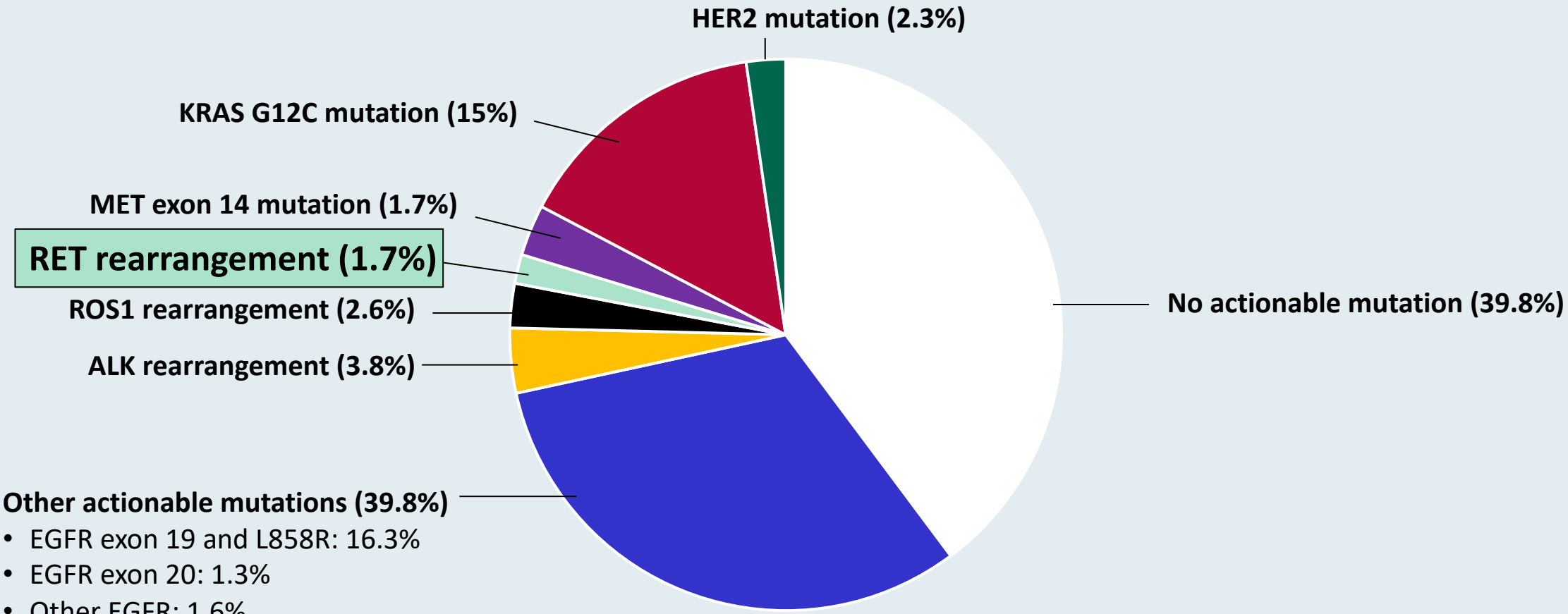
Mobocertinib: Summary of Adverse Events (AEs) and Most Common AEs

Adverse event	Patients, No. (%)			
	PPP cohort (n = 114)		EXCLAIM cohort (n = 96)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Overview of AEs				
Any	114 (100)	79 (69)	96 (100)	63 (66)
Any treatment-related	113 (99)	54 (47)	95 (99)	40 (42)
Serious	56 (49)	52 (46)	45 (47)	42 (44)
Leading to dose reduction	29 (25)	NA[a]	21 (22)	NA[a]
Leading to treatment discontinuation	19 (17)	NA[a]	10 (10)	NA[a]
Treatment-related AEs of any grade reported in ≥10% or of grade ≥3 reported in ≥3% of patients				
Diarrhea	104 (91)	24 (21)	89 (93)	15 (16)
Rash	51 (45)	0	43 (45)	0
Paronychia	43 (38)	1 (<1)	37 (39)	1 (1)

Zhou C et al. *JAMA Oncol* 2021;7(12):e214761.

RET-Rearranged NSCLC

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



Other actionable mutations (39.8%)

- EGFR exon 19 and L858R: 16.3%
- EGFR exon 20: 1.3%
- Other EGFR: 1.6%
- Other KRAS: 10.3%
- BRAF V600E: 2.1%
- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40:611-25.

RTP RESEARCH TO PRACTICE

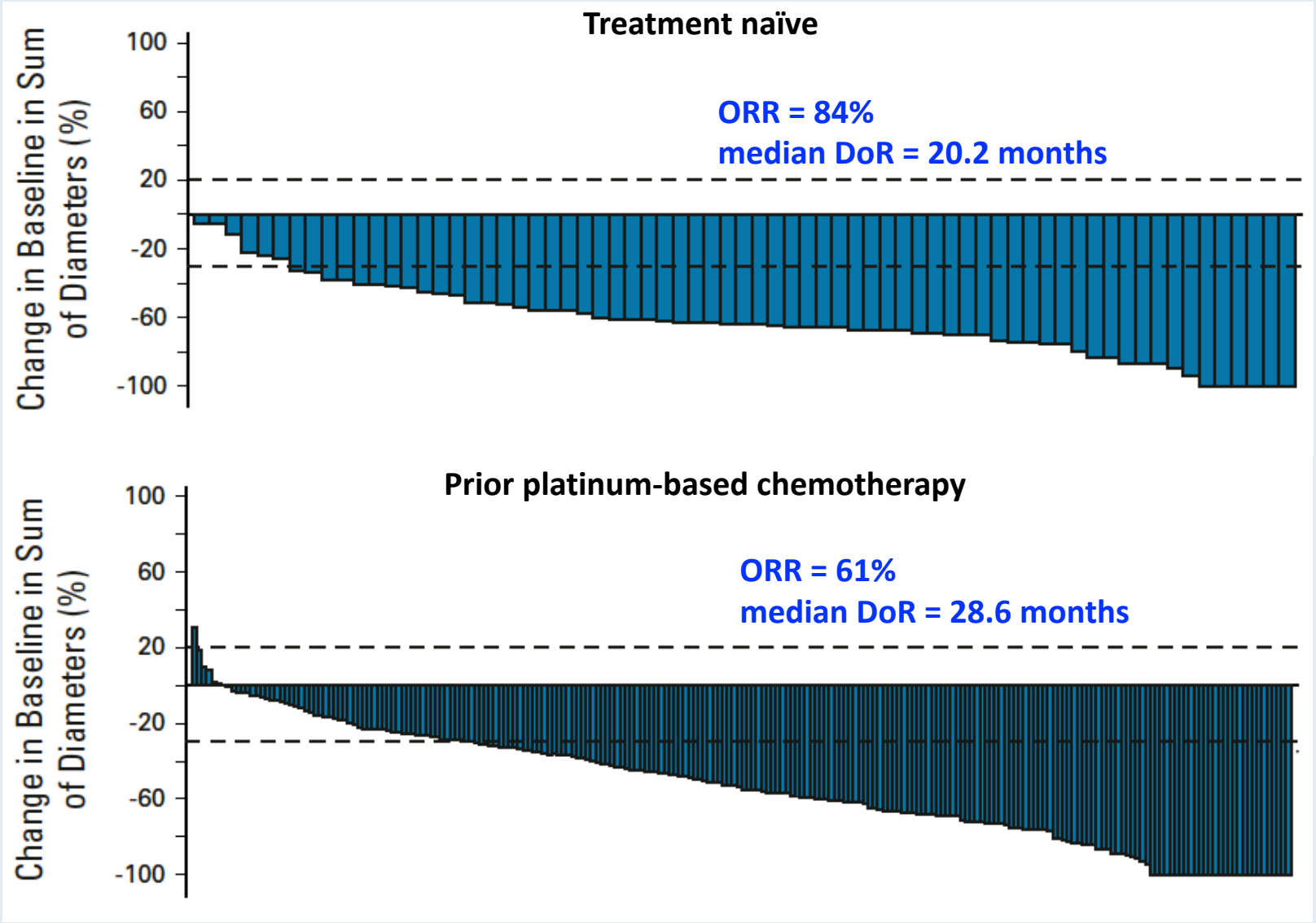
original reports

Selpercatinib in Patients With *RET* Fusion–Positive Non–Small-Cell Lung Cancer: Updated Safety and Efficacy From the Registrational LIBRETTO-001 Phase I/II Trial

Alexander Drilon, MD[1]; Vivek Subbiah, MD[2]; Oliver Gautschi, MD[3]; Pascale Tomasini, MD, MSc[4]; Filippo de Braud, MD[5]; Benjamin J. Solomon, MBBS, PhD[6]; Daniel Shao-Weng Tan, MBBS, PhD[7]; Guzmán Alonso, MD[8]; Jürgen Wolf, MD[9]; Keunchil Park, MD, PhD[10]; Koichi Goto, MD[11]; Victoria Soldatenkova, MSc[12]; Sylwia Szymczak, PhD[13]; Scott S. Barker, PhD[12]; Tarun Puri, MD[12]; Aimee Bence Lin, PhD[12]; Herbert Loong, MBBS[14]; and Benjamin Besse, MD, PhD[15]

J Clin Oncol 2023;41(2):385-94.

LIBRETTO-001: Updated Responses with Selpercatinib for Advanced NSCLC with RET Fusion



Drilon A et al. *J Clin Oncol* 2023;41(2):385-94.

RTP RESEARCH TO PRACTICE

Management of Localized NSCLC with an EGFR Mutation

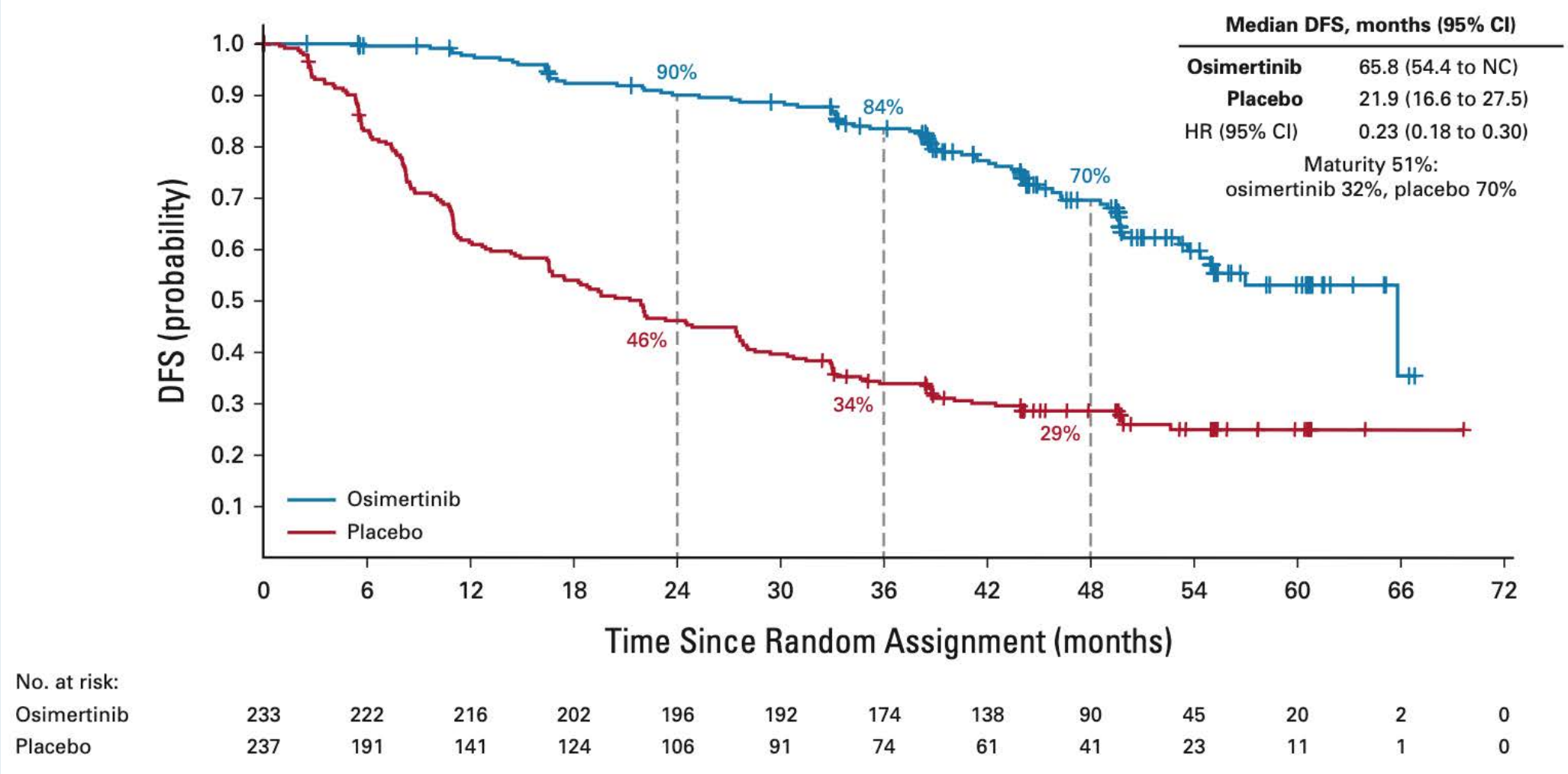
clinical trial updates

Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non–Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial

Roy S. Herbst, MD, PhD[1]; Yi-Long Wu, MD[2]; Thomas John, PhD[3]; Christian Grohe, MD[4]; Margarita Majem, MD, PhD[5]; Jie Wang, MD, PhD[6]; Terufumi Kato, MD[7]; Jonathan W. Goldman, MD[8]; Konstantin Laktionov, PhD[9]; Sang-We Kim, MD, PhD[10]; Chong-Jen Yu, MD, PhD[11,12]; Huu Vinh Vu, MD, PhD[13]; Shun Lu, MD[14]; Kye Young Lee, MD, PhD[15]; Guzel Mukhametshina, MD[16]; Charuwan Akewanlop, MD[17]; Filippo de Marinis, MD[18]; Laura Bonanno, MD[19]; Manuel Domine, MD, PhD[20]; Frances A. Shepherd, MD[21]; Damien Urban, MBBS[22,23]; Xiangning Huang, PhD[24]; Ana Bolanos, MD[25]; Marta Stachowiak, MPharm[26]; and Masahiro Tsuboi, MD, PhD[27]

J Clin Oncol 2023;41:1830-40.

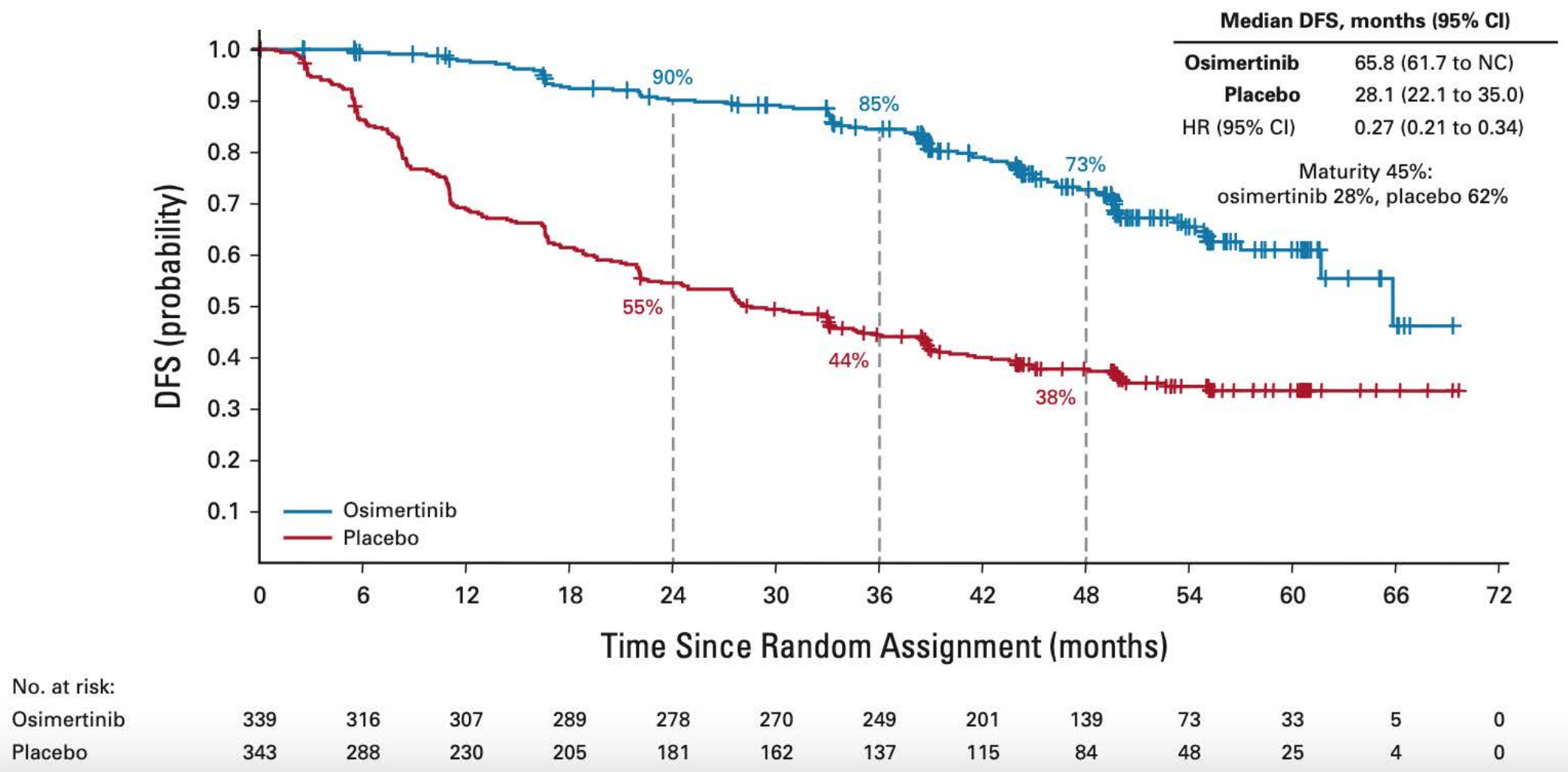
ADAURA Updated Results: DFS in Stage II/IIIA Disease



Herbst RS et al. *J Clin Oncol* 2023;41:1830-40.

RTP RESEARCH TO PRACTICE

ADAURA Updated DFS Results in the Overall Population (Stage IB/II/IIIA Disease)



Herbst RS et al. *J Clin Oncol* 2023;41:1830-40.

RTP RESEARCH TO PRACTICE

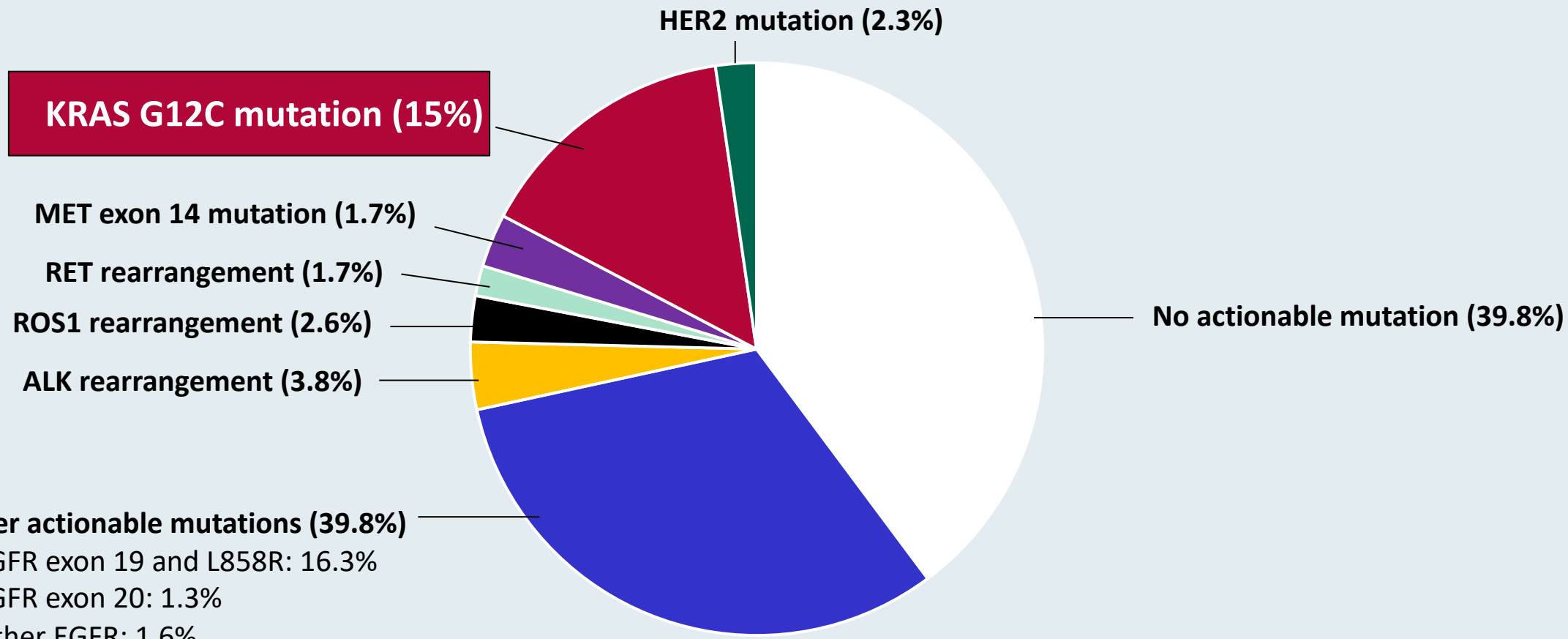
ADAURA Updated Results: Most Common All Causality Adverse Events

Most Common All-Causality AE[d]	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
Diarrhea	159 (47)	114 (34)	36 (11)	9 (3)	70 (20)	55 (16)	14 (4)	1 (< 1)
Paronychia	92 (27)	33 (10)	56 (17)	3 (1)	5 (1)	2 (1)	3 (1)	0
Dry skin	84 (25)	79 (23)	4 (1)	1 (< 1)	23 (7)	19 (6)	4 (1)	0
Pruritus	70 (21)	52 (15)	18 (5)	0	30 (9)	28 (8)	2 (1)	0
Cough	66 (20)	45 (13)	21 (6)	0	61 (18)	44 (13)	17 (5)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)	15 (4)	11 (3)	4 (1)	0
Upper respiratory tract infection	53 (16)	29 (9)	22 (7)	2 (1)	37 (11)	19 (6)	18 (5)	0
Nasopharyngitis	50 (15)	31 (9)	19 (6)	0	36 (10)	25 (7)	11 (3)	0
Decreased appetite	48 (14)	33 (10)	13 (4)	2 (1)	13 (4)	9 (3)	4 (1)	0
Dermatitis acneiform	41 (12)	31 (9)	10 (3)	0	16 (5)	12 (3)	4 (1)	0
Mouth ulceration	39 (12)	32 (9)	7 (2)	0	10 (3)	7 (2)	3 (1)	0
Weight decreased	35 (10)	19 (6)	14 (4)	2 (1)	9 (3)	7 (2)	2 (1)	0
Nausea	34 (10)	28 (8)	5 (1)	1 (< 1)	20 (6)	15 (4)	5 (1)	0
Rash	33 (10)	24 (7)	9 (3)	0	12 (3)	10 (3)	2 (1)	0
Arthralgia	23 (7)	18 (5)	5 (1)	0	37 (11)	32 (9)	5 (1)	0
Headache	26 (8)	24 (7)	2 (1)	0	34 (10)	27 (8)	7 (2)	0

Herbst RS et al. *J Clin Oncol* 2023;41:1830-40.

NSCLC with KRAS G12C Mutations

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



Other actionable mutations (39.8%)

- EGFR exon 19 and L858R: 16.3%
- EGFR exon 20: 1.3%
- Other EGFR: 1.6%
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- BRAF V600E: 2.1%
- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

2022 ASCO ANNUAL MEETING

Abstract 9002

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

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

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2022 July 14;387(2):120-31.

ORIGINAL ARTICLE

Adagrasib in Non–Small-Cell Lung Cancer Harboring a *KRAS*^{G12C} Mutation

Pasi A. Jänne, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Shirish M. Gadgeel, M.D., Rebecca S. Heist, M.D., M.P.H., Sai-Hong I. Ou, M.D., Ph.D., Jose M. Pacheco, M.D., Melissa L. Johnson, M.D., Joshua K. Sabari, M.D., Konstantinos Leventakos, M.D., Ph.D., Edwin Yau, M.D., Ph.D., Lyudmila Bazhenova, M.D., Marcelo V. Negrao, M.D., Nathan A. Pennell, M.D., Ph.D., Jun Zhang, M.D., Ph.D., Kenna Anderes, Ph.D., Hirak Der-Torossian, M.D., Thian Kheoh, Ph.D., Karen Velastegui, B.Sc., Xiaohong Yan, Ph.D., James G. Christensen, Ph.D., Richard C. Chao, M.D., and Alexander I. Spira, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

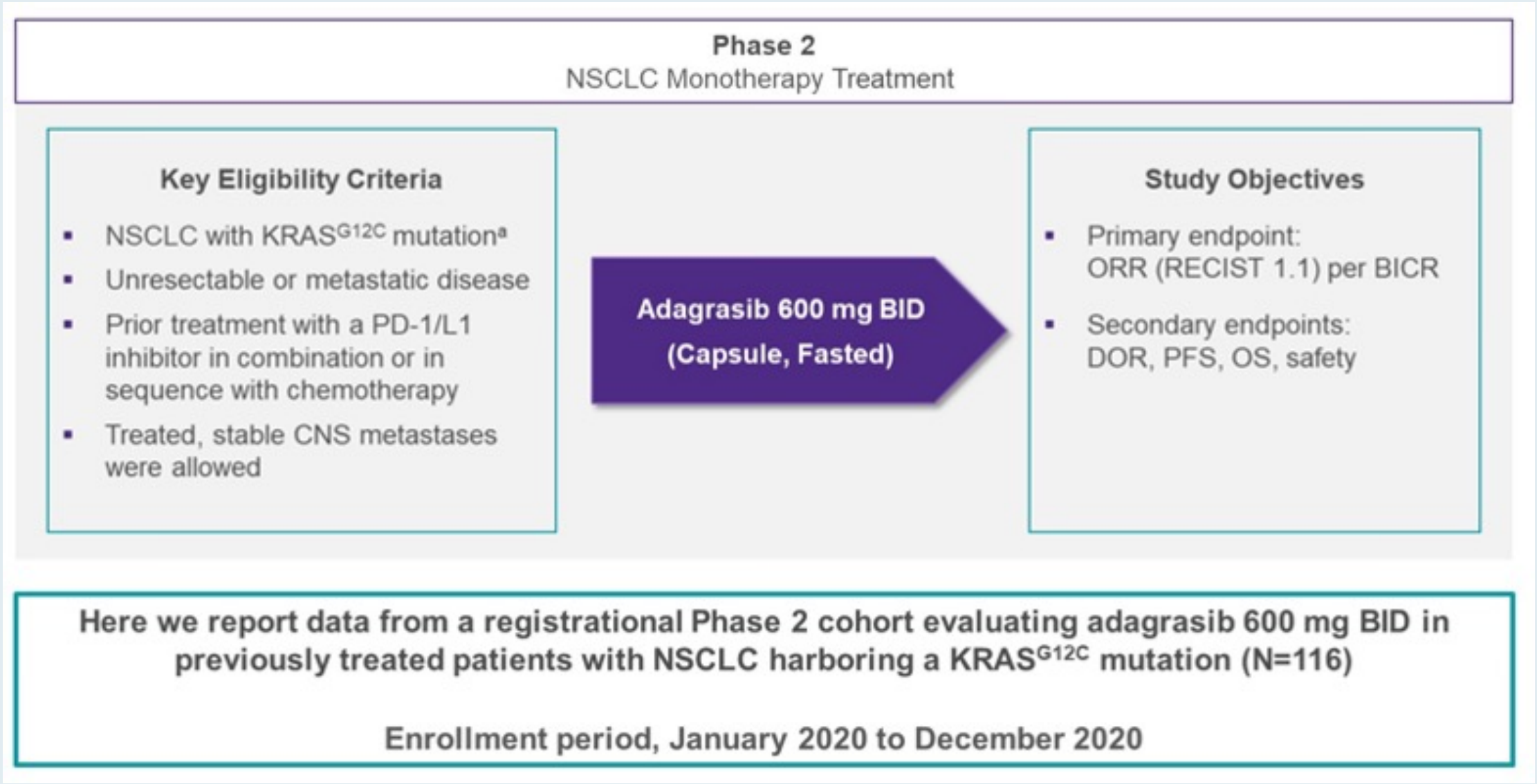
Setting the Benchmark for *KRAS*^{G12C}-Mutated NSCLC

Antonio Passaro, M.D., Ph.D., and Solange Peters, M.D., Ph.D.

N Engl J Med 2022 July 14;387(2):180-3.

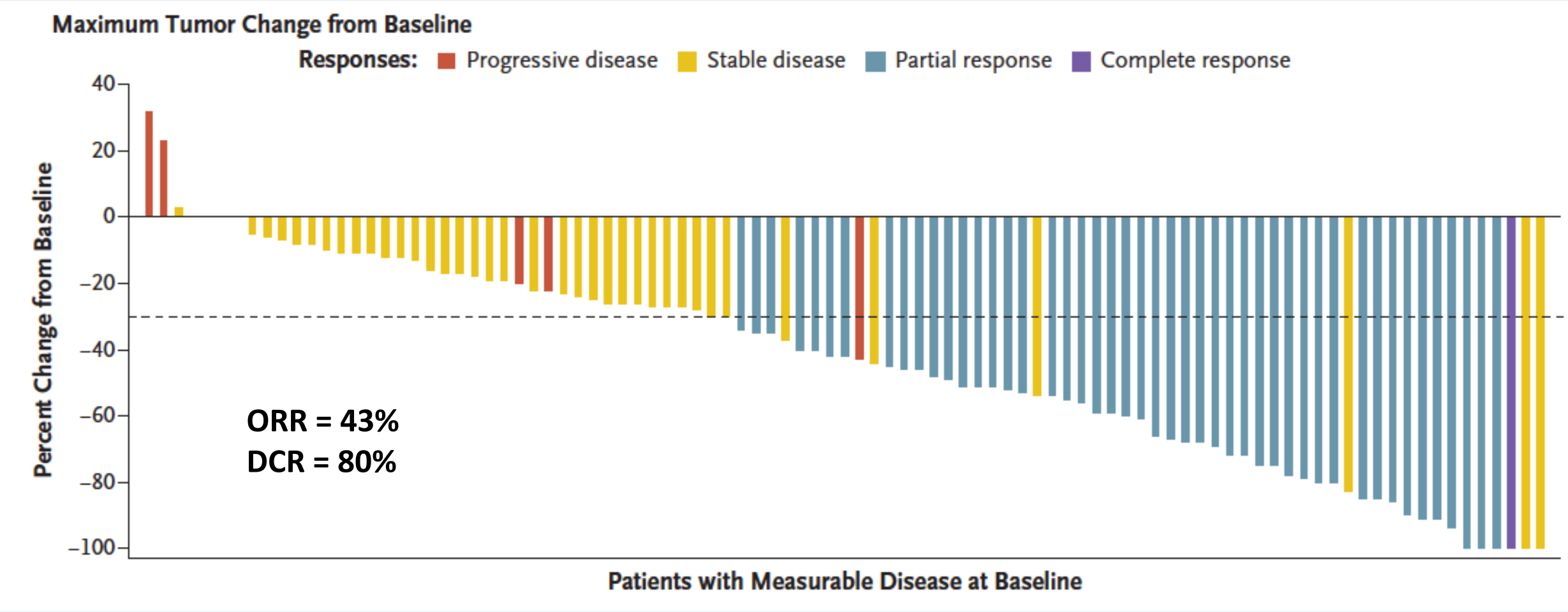
RTP RESEARCH TO PRACTICE

KRYSTAL-1: Phase II Cohort A Study Design



Spira AI et al. ASCO 2022;Abstract 9002.

KRYSTAL-1: Tumor Response with Adagrasib in Advanced NSCLC Harboring a KRAS G12C Mutation



Jänne PS et al. *N Engl J Med* 2022 July 14;387(2):120-31; Spira AI et al. ASCO 2022;Abstract 9002.

KRYSTAL-1: Treatment-Related Adverse Events with Adagrasib in Patients with Advanced NSCLC Harboring a KRAS G12C Mutation

	Adagrasib Monotherapy (N=116) Capsule, Fasted	
TRAEs, n (%)	**Any Grade**	**Grades 3–4**
Any TRAEs	113 (97%)	50 (43%)
Most frequent TRAEs[a], n (%)		
Diarrhea	73 (63%)	1 (<1%)
Nausea	72 (62%)	5 (4%)
Vomiting	55 (47%)	1 (<1%)
Fatigue	47 (41%)	5 (4%)
ALT increase	32 (28%)	5 (4%)
Blood creatinine increase	30 (26%)	1 (<1%)
AST increase	29 (25%)	4 (3%)
Decreased appetite	28 (24%)	4 (3%)

- Grade 1–2 TRAEs occurred in 53% of patients
- There were 2 grade 5 TRAEs (cardiac failure [n=1] and pulmonary hemorrhage [n=1])
- TRAEs led to dose reduction in 60/116 (52%) patients[b] and to dose interruption in 71/116 (61%) patients
- TRAEs led to discontinuation of study drug in 8/116 (7%) patients

Spira AI et al. ASCO 2022;Abstract 9002.

Abstract CT008

AACR American Association for Cancer Research ANNUAL MEETING 2022 New Orleans

Long-term Outcomes With Sotorasib in Pre-treated *KRAS* p.G12C Mutated NSCLC: 2-year Analysis of CodeBreaK 100

Presenter: Grace K. Dy[1], MD

[1]Roswell Park Comprehensive Cancer Center

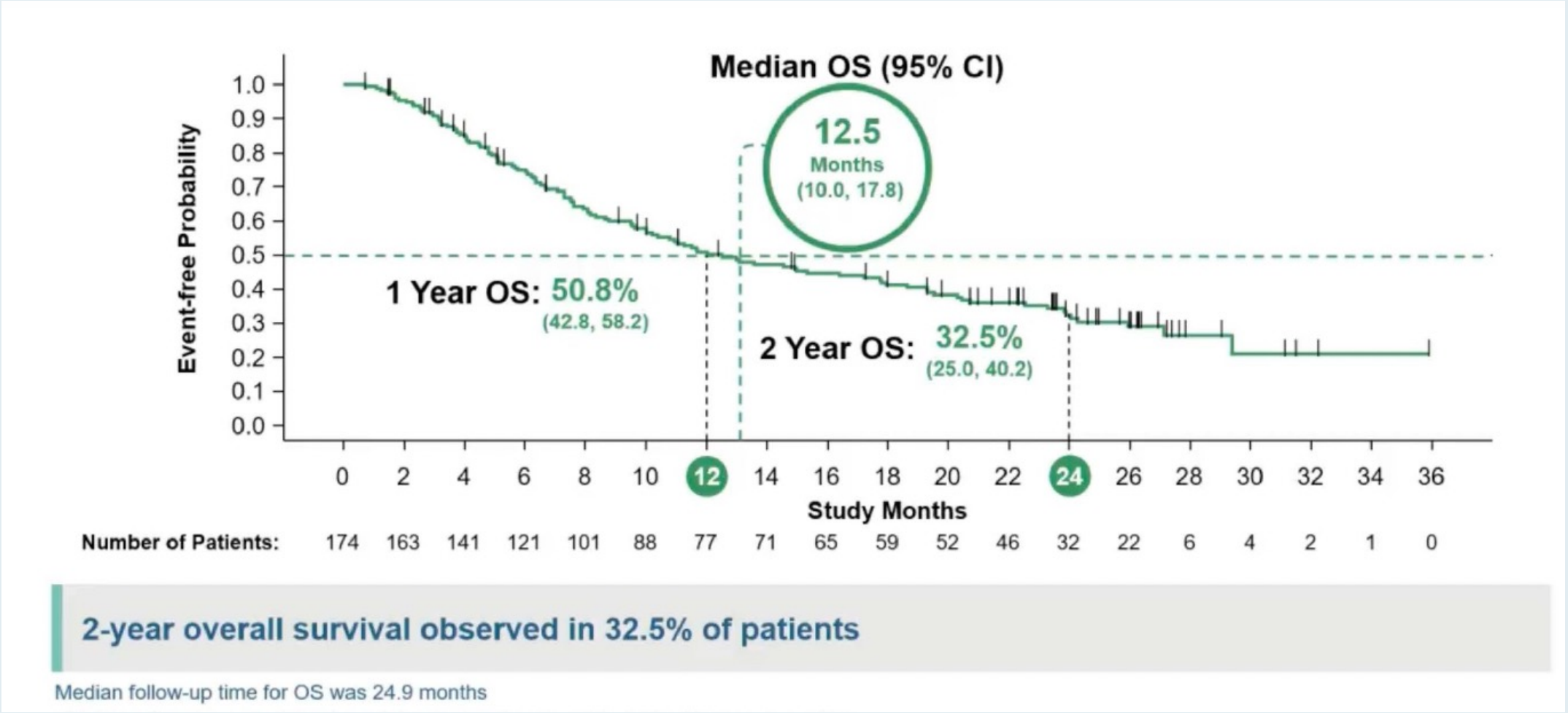
On behalf of: Ramaswamy Govindan[2], Vamsidhar Velcheti[3], Gerald S. Falchook[4], Antoine Italiano[5], Juergen Wolf[6], Adrian G. Sacher[7], Toshiaki Takahashi[8], Suresh S. Ramalingam[9], Christophe Dooms[10], Dong-Wan Kim[11], Alfredo Addeo[12], Jayesh Desai[13], Martin Schuler[14], Pascale Tomasini[15], Qui Tran[16], Simon Jones[16], Agnes Ang[16], Abraham Anderson[16], Antreas Hindoyan[16], David S. Hong[17], Bob T. Li[18]

[2]Washington University in St Louis, [3]New York University Langone, [4]Sarah Cannon Research Institute, [5]Institut Bergonie, [6]Universitatsklinikum Koln, [7]Princess Margaret Cancer Centre, [8]Shizuoka Cancer Center [9]Winship Cancer Institute, [10]Universitair Ziekenhuis Leuven [11]Seoul National University Hospital, [12]Hopitaux Universitaires de Geneve, [13]Peter MacCallum Cancer Centre, [14]Universitatsklinikum Essen, [15]Hopital de la Timone, [16]Amgen Inc., [17]MD Anderson Cancer Center, [18]Memorial Sloan Kettering Cancer Center

RTP RESEARCH TO PRACTICE

CodeBreaK 100: Long-Term Outcomes with Sotorasib for Pretreated Metastatic NSCLC with KRAS G12C Mutation

— *Overall Survival*

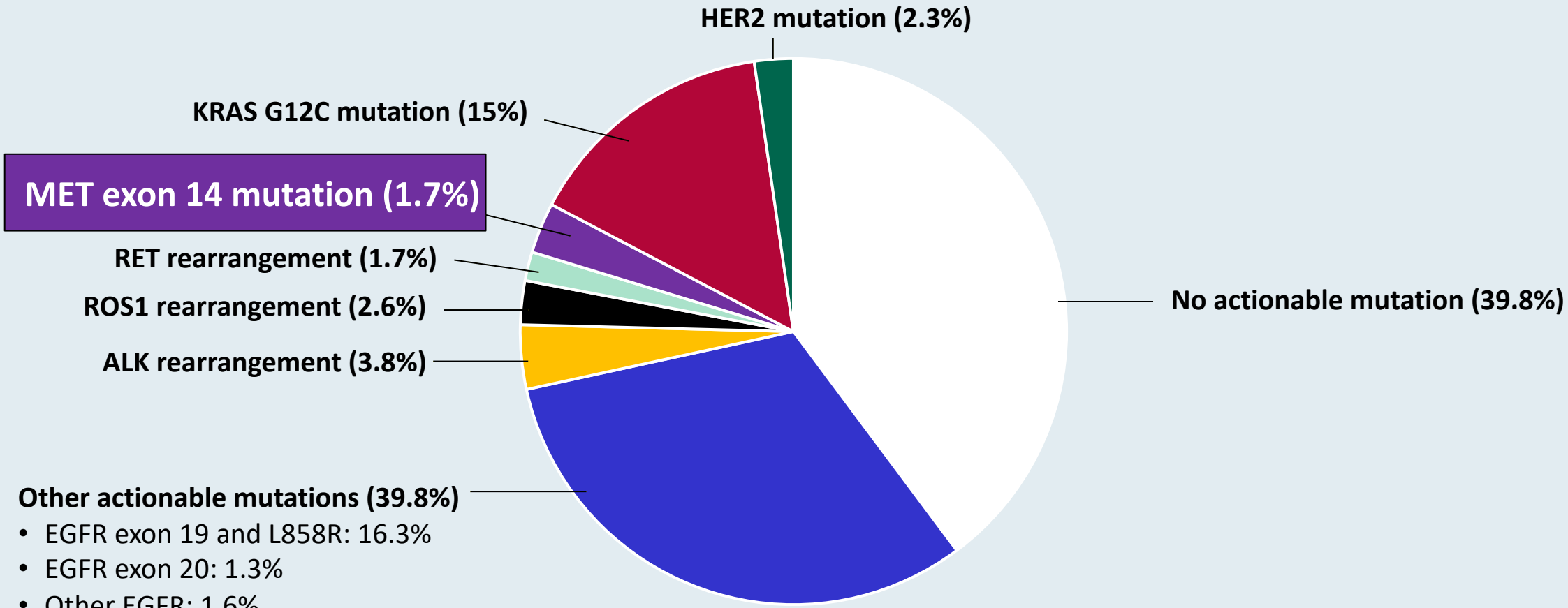


Dy GK et al. AACR 2022;Abstract CT008.

RTP RESEARCH TO PRACTICE

MET Exon 14 Mutations

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



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- NTRK rearrangement: 0.23%

Derived from Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

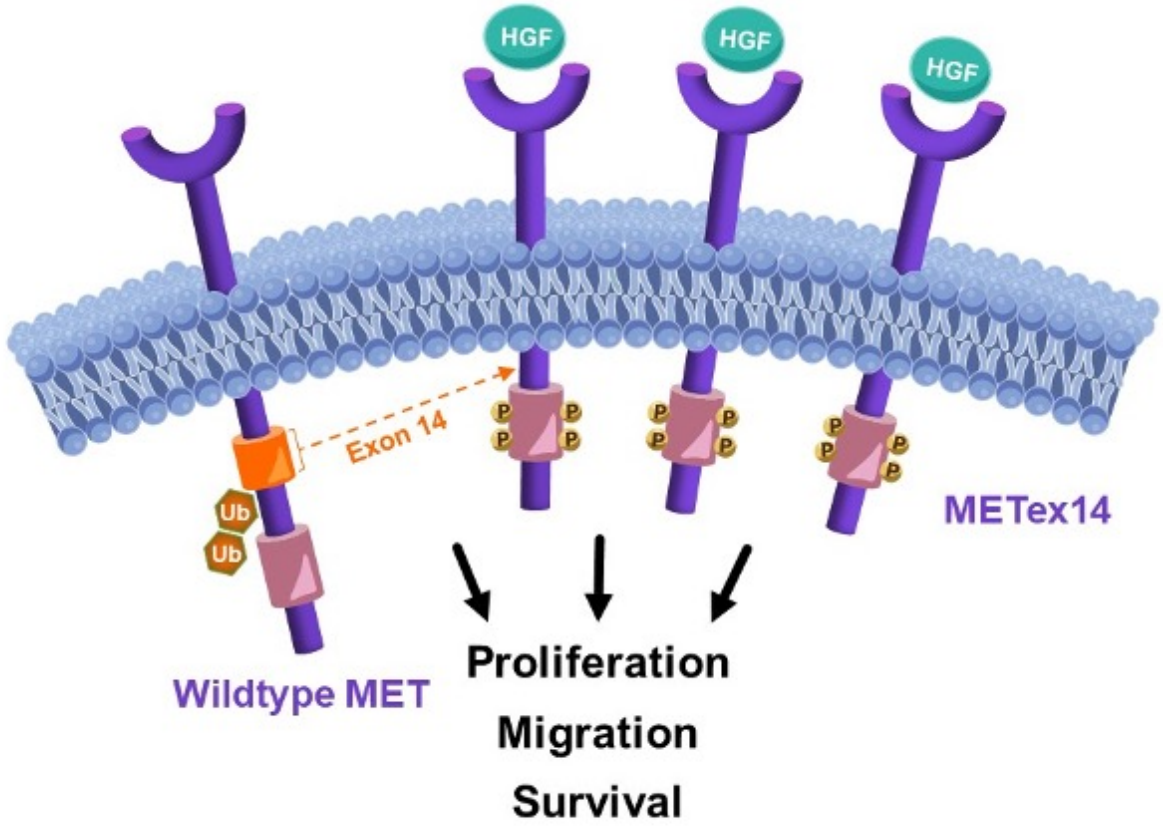
MET Exon 14 Skipping Mutations in NSCLC

MET Exon 14 Skipping Mutations (METex14)

- Found in ~3% of NSCLCs[1]
- Are generally more common in older patients (≥70 years), women, and non-smokers[2]
- Aberrant splicing of exon 14 disrupts degradation of MET receptors, resulting in constitutive activation of the MET pathway[3]

MET TKIs (Capmatinib and Tepotinib)

- Have accelerated approval
- ORR 41% to 43% in previously treated, MET TKI-naïve populations[4,5]
- Most patients develop acquired resistance[6]
  - Mechanisms may include secondary MET mutations or activation of bypass signalling



Krebs MG et al. ASCO 2022;Abstract 9008.

Review Article

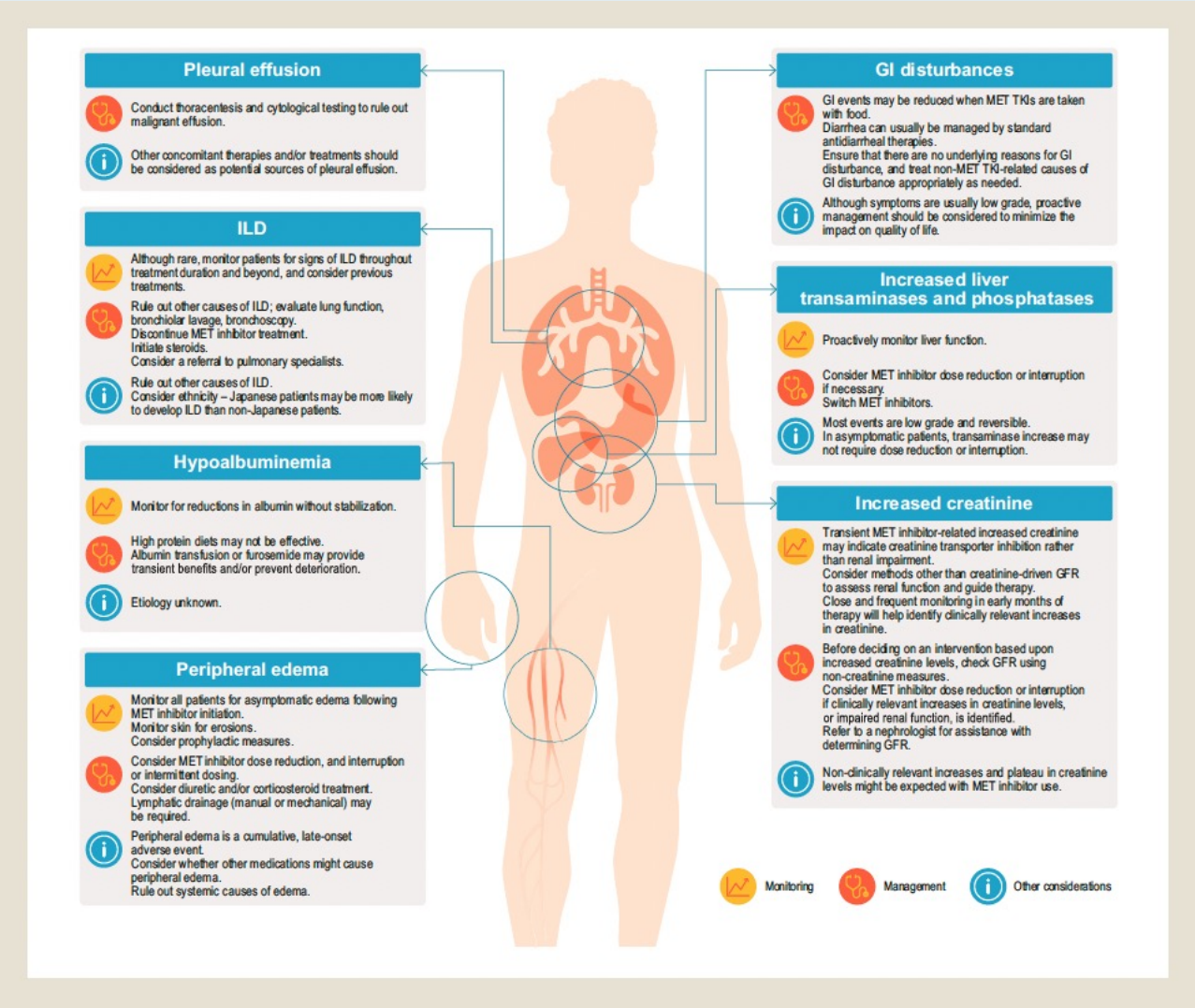
Safety of MET Tyrosine Kinase Inhibitors in Patients With *MET* Exon 14 Skipping Non-small Cell Lung Cancer: A Clinical Review

Alexis Cortot, MD, PhD,[1] Xiuning Le,[2] Egbert Smit,[3] Santiago Viteri,[4] Terufumi Kato,[5] Hiroshi Sakai,[6] Keunchil Park,[7] D. Ross Camidge,[8] Karin Berghoff,[9] Soetkin Vlassak,[9] Paul K. Paik[10,11]

Clin Lung Cancer 2022 May;23(3):195-207.

RTP RESEARCH TO PRACTICE

Monitoring and Management Consideration for Key MET Exon 14 Inhibitor Related Adverse Events



Cortot A et al. *Clin Lung Cancer* 2022 May;23(3):195-207.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 9008

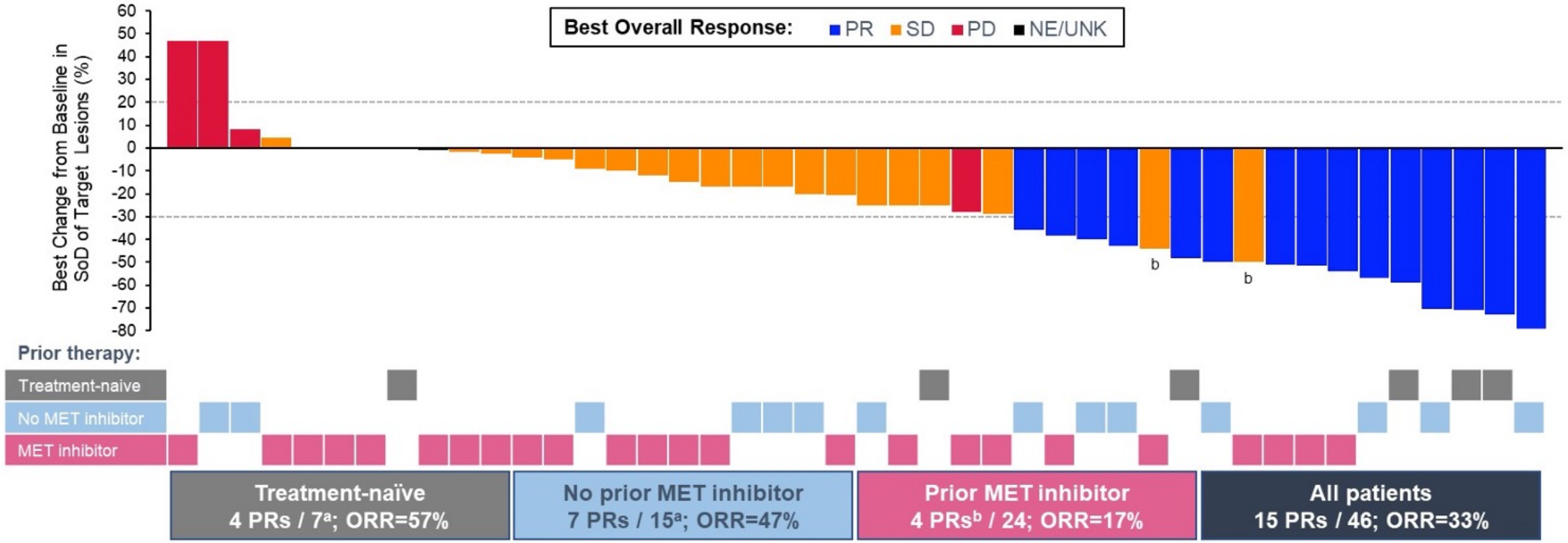
Amivantamab in NSCLC patients with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study

Matthew G. Krebs,[1] Alexander I. Spira,[2] Byoung Chul Cho,[3] Benjamin Besse,[4] Jonathan W. Goldman,[5] Pasi A. Jänne,[6] Zhiyong Ma,[7] Aaron S. Mansfield,[8] Anna Minchom,[9] Sai-Hong Ignatius Ou,[10] Ravi Salgia,[11] Zhijie Wang,[12] Casilda Llacer Perez,[13] Grace Gao,[14] Joshua C. Curtin,[14] Amy Roshak,[14] Robert W. Schnepp,[14] Meena Thayu,[14] Roland E. Knoblauch,[14] Chee Khoon Lee[15]

RTP RESEARCH TO PRACTICE

CHRYSALIS: Antitumor Activity of Amivantamab Monotherapy in Advanced NSCLC with MET Exon 14 Skipping Mutations

- A total of 46 patients were efficacy evaluable



Krebs MG et al. ASCO 2022;Abstract 9008.

RTP RESEARCH TO PRACTICE

CHRYSALIS: Safety Profile of Amivantamab Monotherapy in Advanced NSCLC with MET Exon 14 Skipping Mutations

TEAE (≥15%) by Preferred Term, n (%)	RP2D (n=425) Median follow-up 11.8 months		METex14 Subset (n=55) Median follow up 5.1 months	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion related reaction	283 (67)	11 (3)	38 (69)	3 (5)
Rash	155 (36)	8 (2)	17 (31)	1 (2)
Dermatitis acneiform	155 (36)	4 (1)	22 (40)	0
Paronychia	193 (45)	7 (2)	21 (38)	0
Fatigue	93 (22)	8 (2)	17 (31)	2 (4)
Hypoalbuminemia	135 (32)	10 (2)	15 (27)	1 (2)
Stomatitis	91 (21)	2 (0.5)	15 (27)	0
Decreased appetite	76 (18)	2 (0.5)	12 (22)	0
Dyspnea	96 (23)	21 (5)	12 (22)	4 (7)
Peripheral edema	104 (24)	4 (1)	11 (20)	0
Pruritus	79 (19)	0	12 (22)	0
Nausea	104 (24)	2 (0.5)	11 (20)	0
Constipation	105 (25)	0	10 (18)	0
Hypomagnesemia	41 (10)	0	9 (16)	0
Aspartate aminotransferase increased	64 (15)	5 (1)	9 (16)	1 (2)
Alanine aminotransferase increased	72 (17)	10 (2)	8 (15)	1 (2)
Cough	78 (18)	0	3 (5)	0

- Treatment modifications due to toxicity (n=425): interruptions in 21%, reductions in 12%, and discontinuations in 5% of patients
  - Rates of pneumonitis/ILD was 4%
  - Cumulative grouped rash-related AEs[a] occurred in 322 (76%) patients, with 16 grade ≥3 (4%)
- Safety profile for METex14 subset is consistent with the larger CHRYSALIS safety population, with majority of events grade 1-2
- No new safety signals found

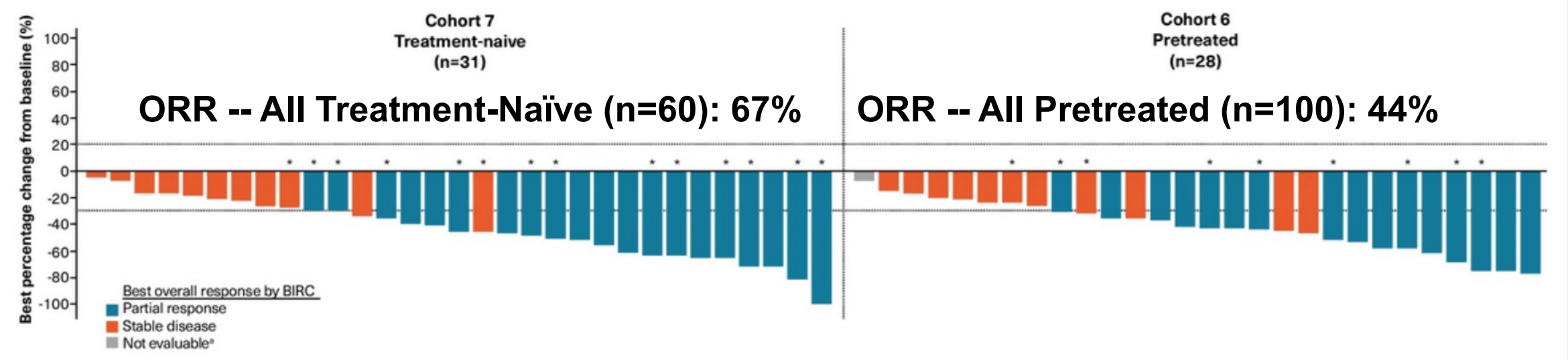
Krebs MG et al. ASCO 2022;Abstract 9008.

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

Wolf J et al.

ASCO 2021;Abstract 9020.

GEOMETRY mono-1



Wolf J et al. ASCO 2021;Abstract 9020.

RTP RESEARCH TO PRACTICE

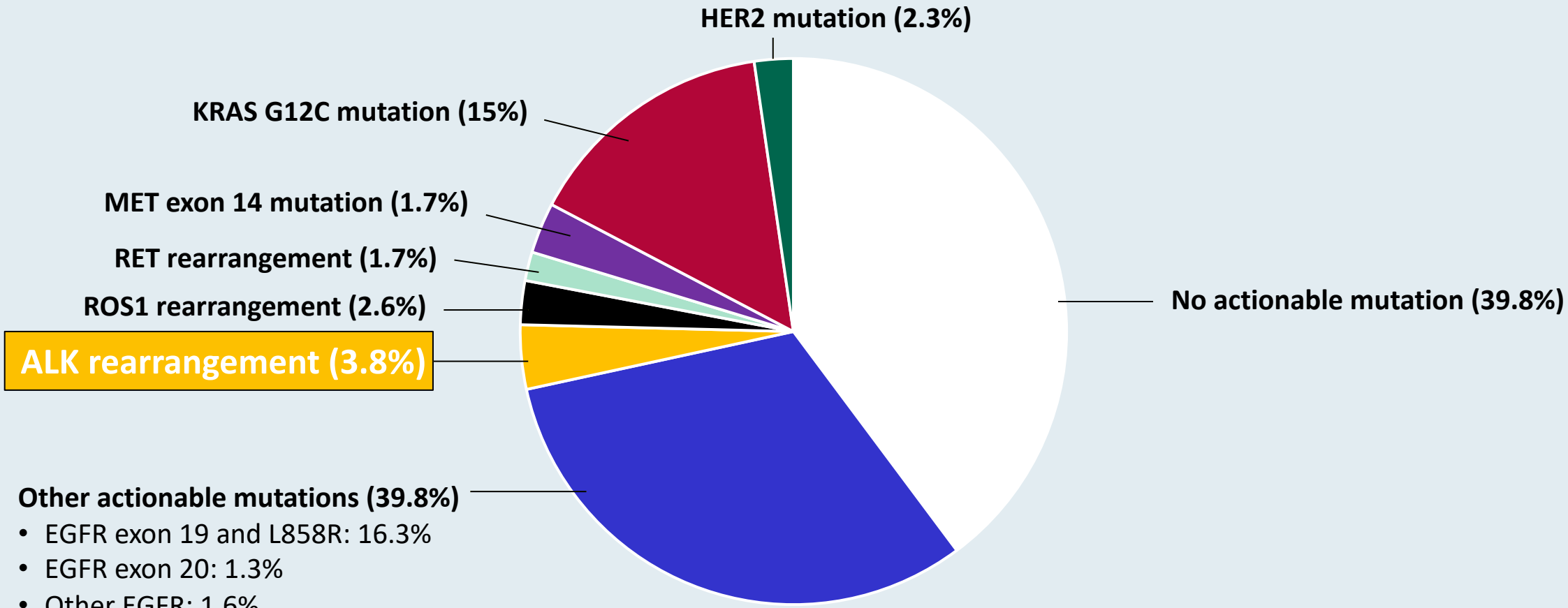
GEOMETRY mono-1: Most Common Adverse Events (Cohorts 7 and 6)

Adverse event	Cohort 7 — treatment naïve N = 32		Cohort 6 — second line N = 31	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Peripheral edema	72%	13%	71%	13%
Nausea	44%	0	32%	3%
Vomiting	15%	3%	26%	0
Increase blood creatinine	31%	0	29%	0
Dyspnea	6%	3%	10%	0
Fatigue	19%	0	29%	0
Decreased appetite	16%	3%	16%	0

Wolf J et al. ASCO 2021;Abstract 9020.

ALK-Rearranged NSCLC

Frequency of Targetable Oncogenic Driver Molecular Alterations in Adenocarcinoma of the Lung



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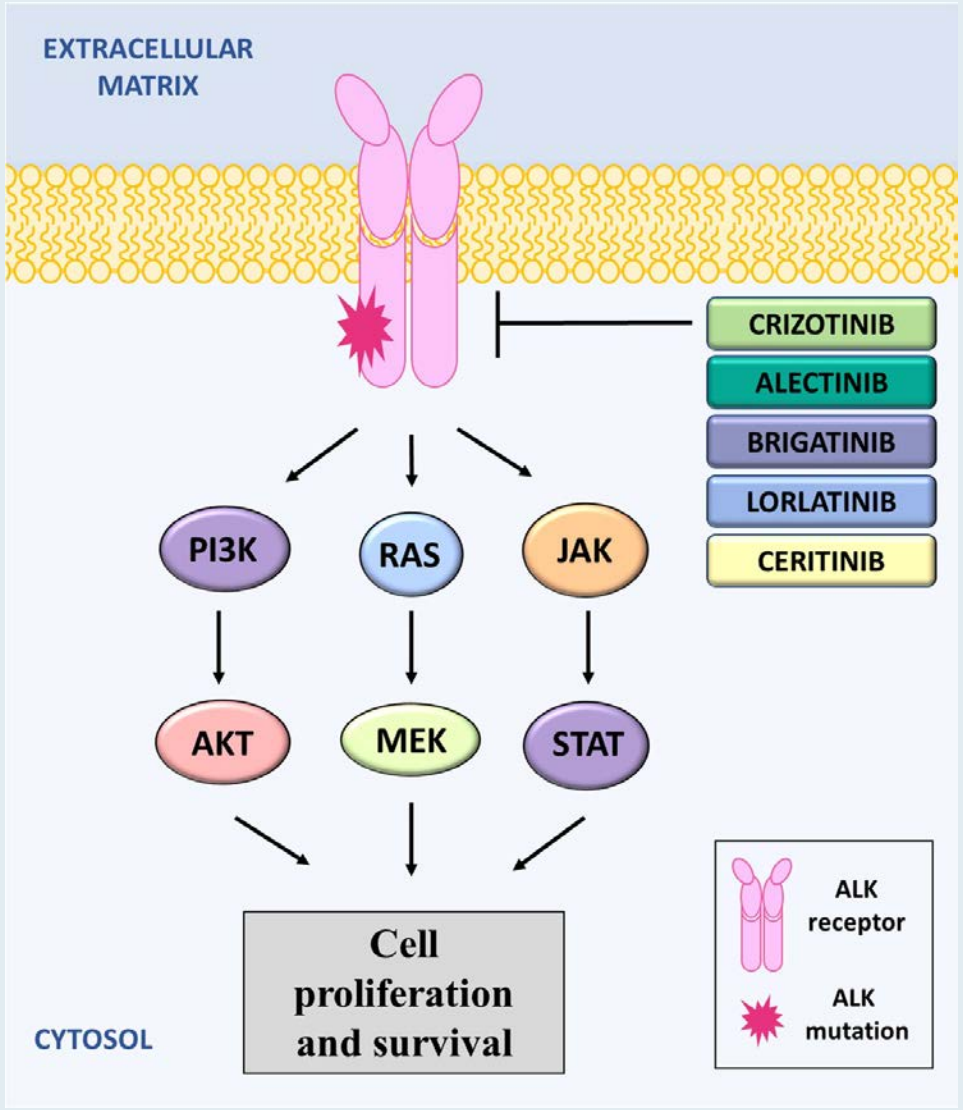
Derived from Tan AC et al. *J Clin Oncol* 2022;40(6):611-25.

RTP RESEARCH TO PRACTICE

Mechanism of Action of ALK Inhibitors



3%-13% of NSCLCs

Seebacher NA et al. *Clin Cancer Res* 2019;38(1):156.

Timeline of FDA Approvals for ALK Tyrosine Kinase Inhibitors (TKIs)

Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-34.

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 and diarrhea
Ensartinib	Rash, nausea, pruritus 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):2521-34; Gristina V et al. *Pharmaceuticals* 2020;13:474.

Brigatinib

Mechanism of action

- Tyrosine kinase inhibitor against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R) and FLT3 as well as EGFR deletion and point mutations

Indication

- For adult patients with ALK-positive metastatic NSCLC

Recommended dose

- 90 mg orally once daily for the first 7 days, then increase the dose to 180 mg orally once daily

Brigatinib package insert, 2/2022.

Lorlatinib

Mechanism of action

- **Reversible potent third-generation tyrosine kinase inhibitor targeting ALK and ROS1**

Indication

- **For the treatment of metastatic NSCLC in adult patients whose tumors are ALK-positive**

Recommended dose

- **100 mg once daily**

Lorlatinib package insert, 5/2022.

Activity of ALK Tyrosine Kinase Inhibitors (TKIs) in the First-Line Setting for Advanced NSCLC with ALK Rearrangement

ALK TKI	Median PFS	Overall response rate	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):2521-34.

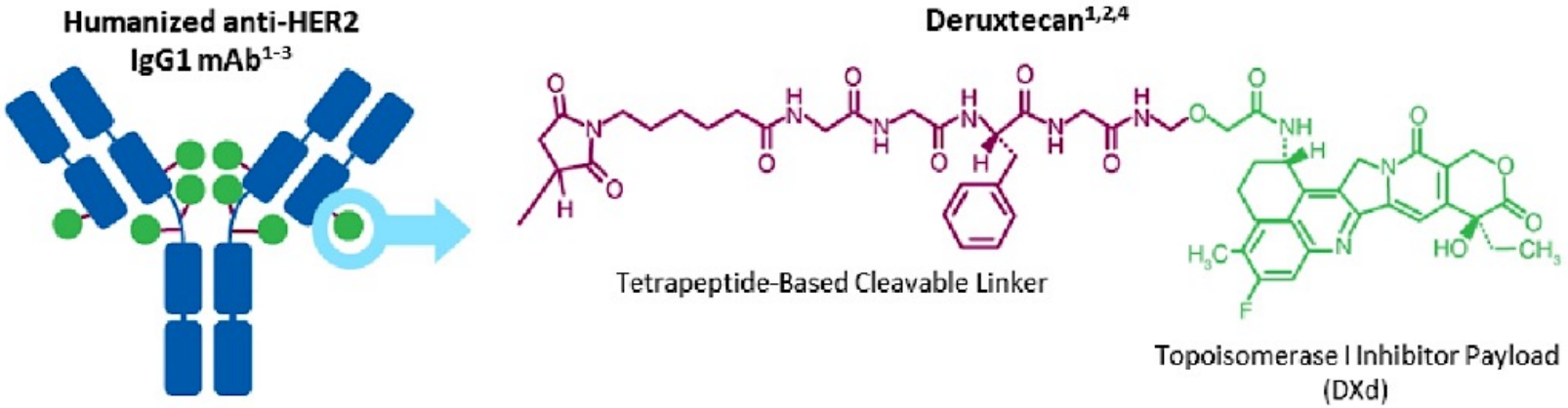
RTP RESEARCH TO PRACTICE

HER2-Mutant NSCLC

Antibody-Drug Conjugate
Trastuzumab Deruxtecan (T-DXd)

T-DXd is an ADC with 3 components:

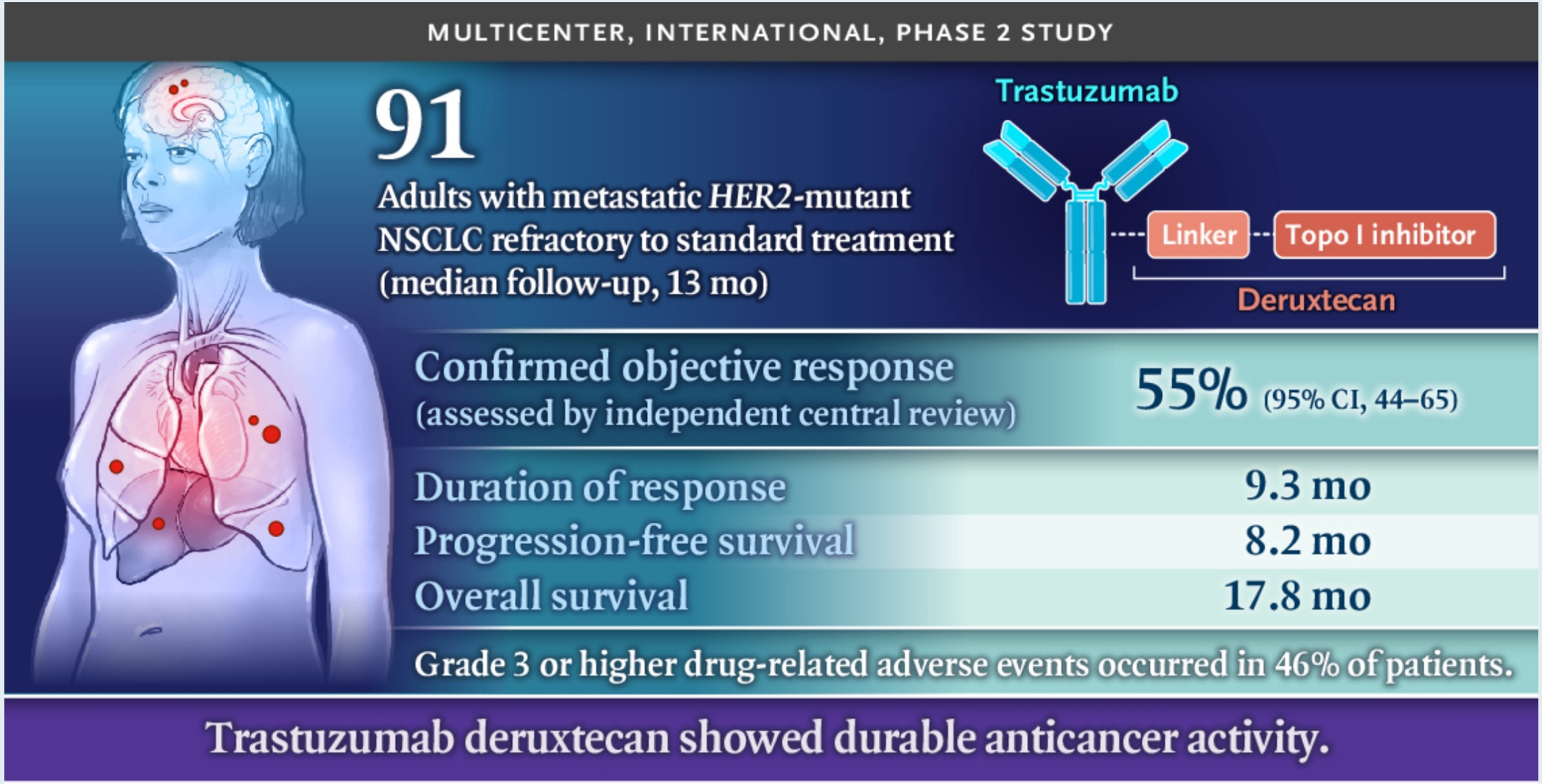
- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

Smit EF et al. ASCO 2020;Abstract 9504.

DESTINY-Lung01: Activity of Trastuzumab Deruxtecan in Patients with Advanced NSCLC with HER2 Mutations



Li BT et al. *N Engl J Med* 2022;386(3):241-51.

Trastuzumab Deruxtecan

Mechanism of action

- **Antibody-drug conjugate directed against HER2**

Indication

- **For patients with unresectable or metastatic NSCLC whose tumors have activating HER2 mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy**

Recommended dose

- **5.4 mg/kg IV infusion q3wk until disease progression or unacceptable toxicity**

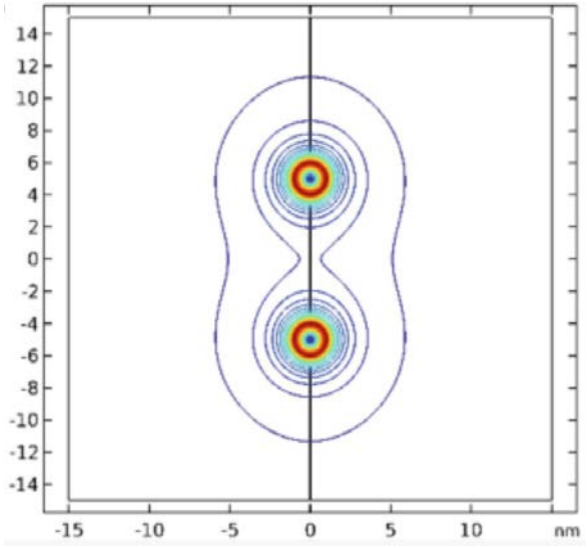
Trastuzumab deruxtecan package insert, 11/2022.

Tumor Treating Fields

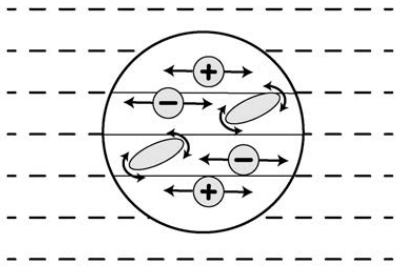
RTP
RESEARCH
TO PRACTICE

Tumor Treatment Fields

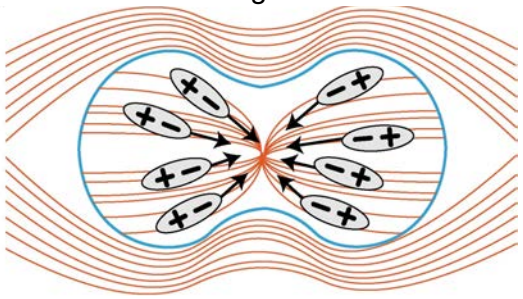
Dividing Cell under TTF
Selective Electric Field Sensitivity

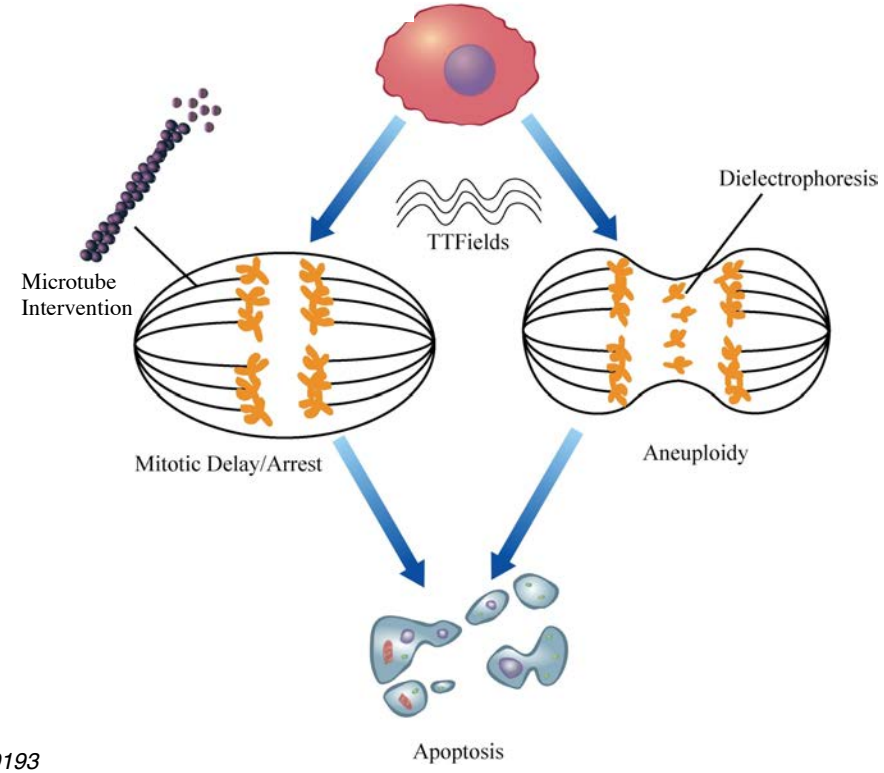


Non-dividing Cells



Dividing Cells

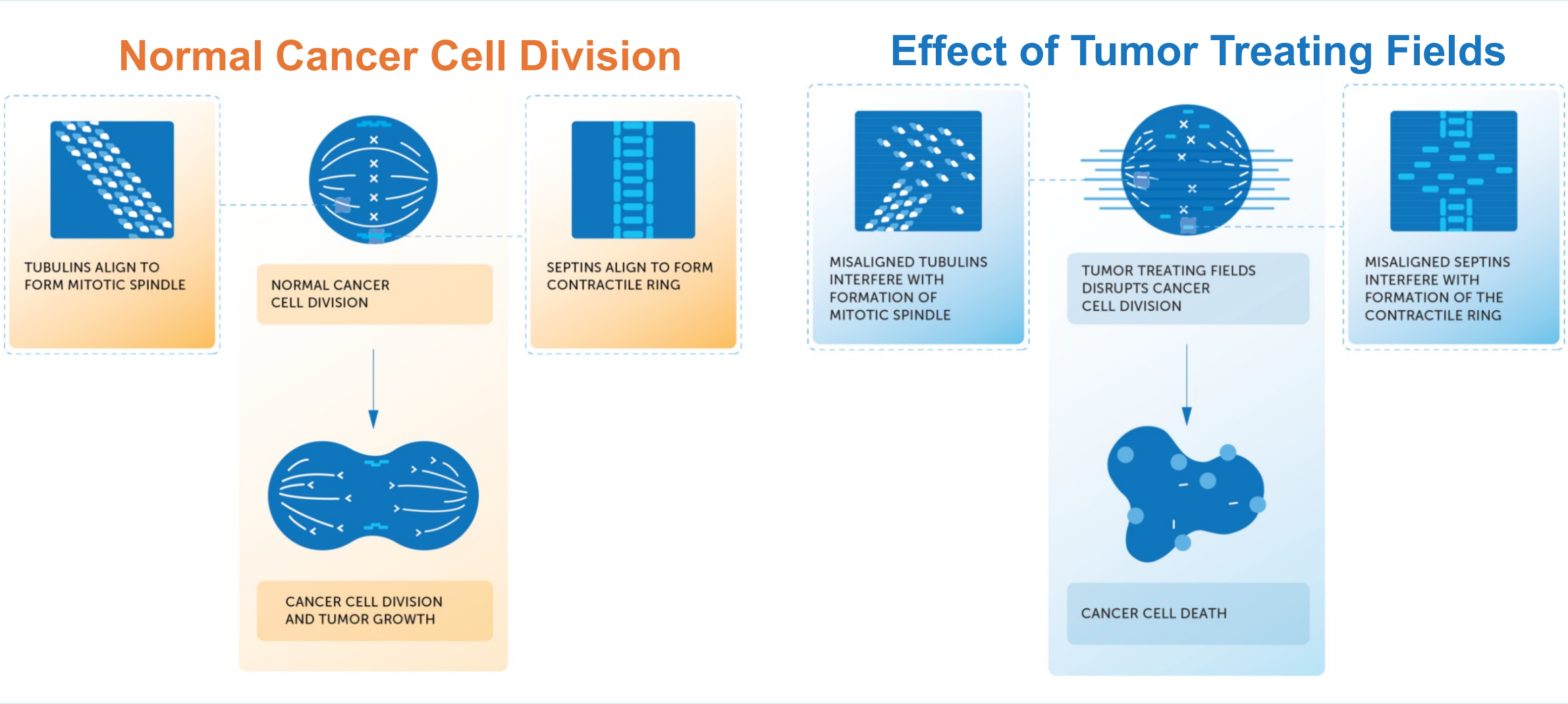




Luo et al. *Biomedicine and Pharmocotherapy 2020; 127:110193*

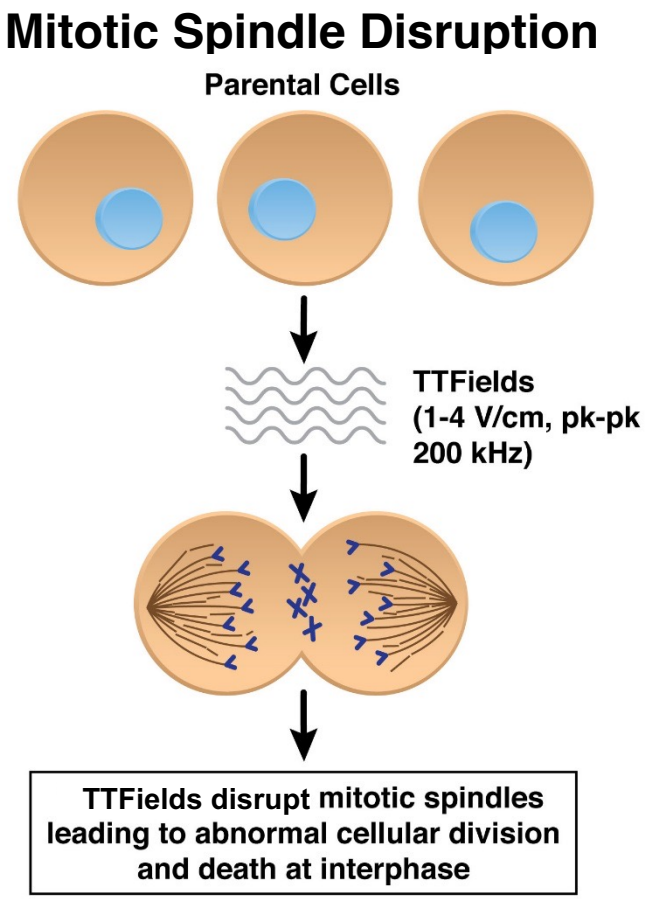
Luo et al. *Biomedicine and Pharmacotherapy* 2020;127:11013.

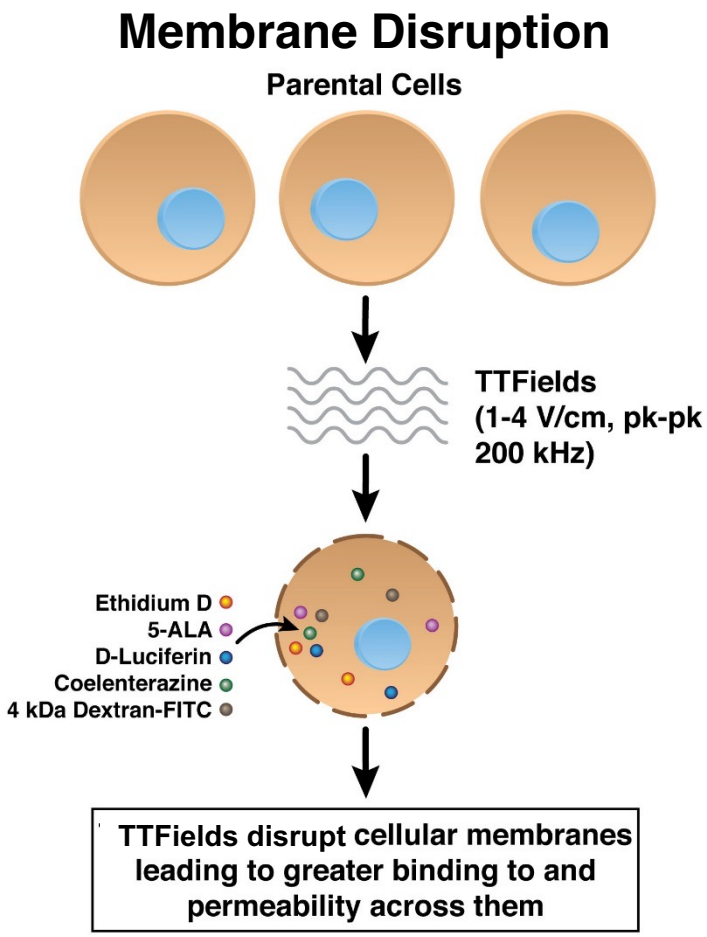
Effect of Tumor Treating Fields on Dividing Cancer Cells



www.novocure.com/our-therapy/

Tumor Treating Fields (TTFields): Alternative Mechanism of Action





Chang*, Patel*, et al., 2018, *CDD*

Pivotal LUNAR Study of Tumor Treating Fields Combined with Standard Therapies in NSCLC Meets its Primary Overall Survival Endpoint

Press Release – January 5, 2023

It was announced that the LUNAR study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in overall survival over standard therapies alone. The LUNAR study is a pivotal, open-label, randomized study evaluating the safety and efficacy of tumor treating fields (TTFields) together with standard therapies for Stage IV non-small cell lung cancer (NSCLC) following progression while on or after treatment with platinum-based therapy.

The LUNAR study also showed a statistically significant and clinically meaningful improvement in overall survival when patients were treated with TTFields and immune checkpoint inhibitors (ICI), as compared to those treated with immune checkpoint inhibitors alone, and a positive trend in overall survival when patients were treated with TTFields and docetaxel versus docetaxel alone. Patient enrollment was well balanced between the ICI and docetaxel cohorts of the experimental and control arms, and control arms performed in line with prior studies. TTFields therapy was well tolerated by patients enrolled in the experimental arm of the study.

https://www.novocure.com/novocure-announces-pivotal-lunar-study-in-non-small-cell-lung-cancer-met-primary-overall-survival-endpoint/

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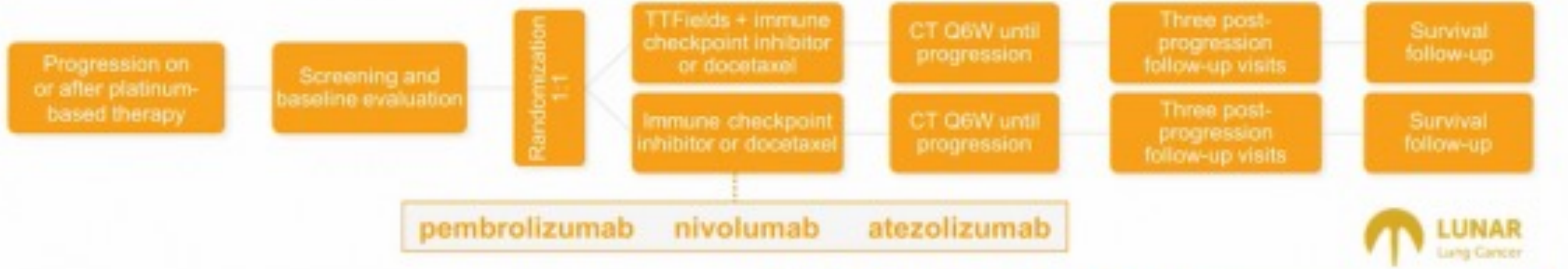
LUNAR Phase III Trial Schema



ORIGINAL STUDY DESIGN

- 534 patients with 18 months of follow-up
- Anticipated final data in 2023
- Primary endpoint: OS
- Designed to detect hazard ratio of 0.75 (+4 months in OS)

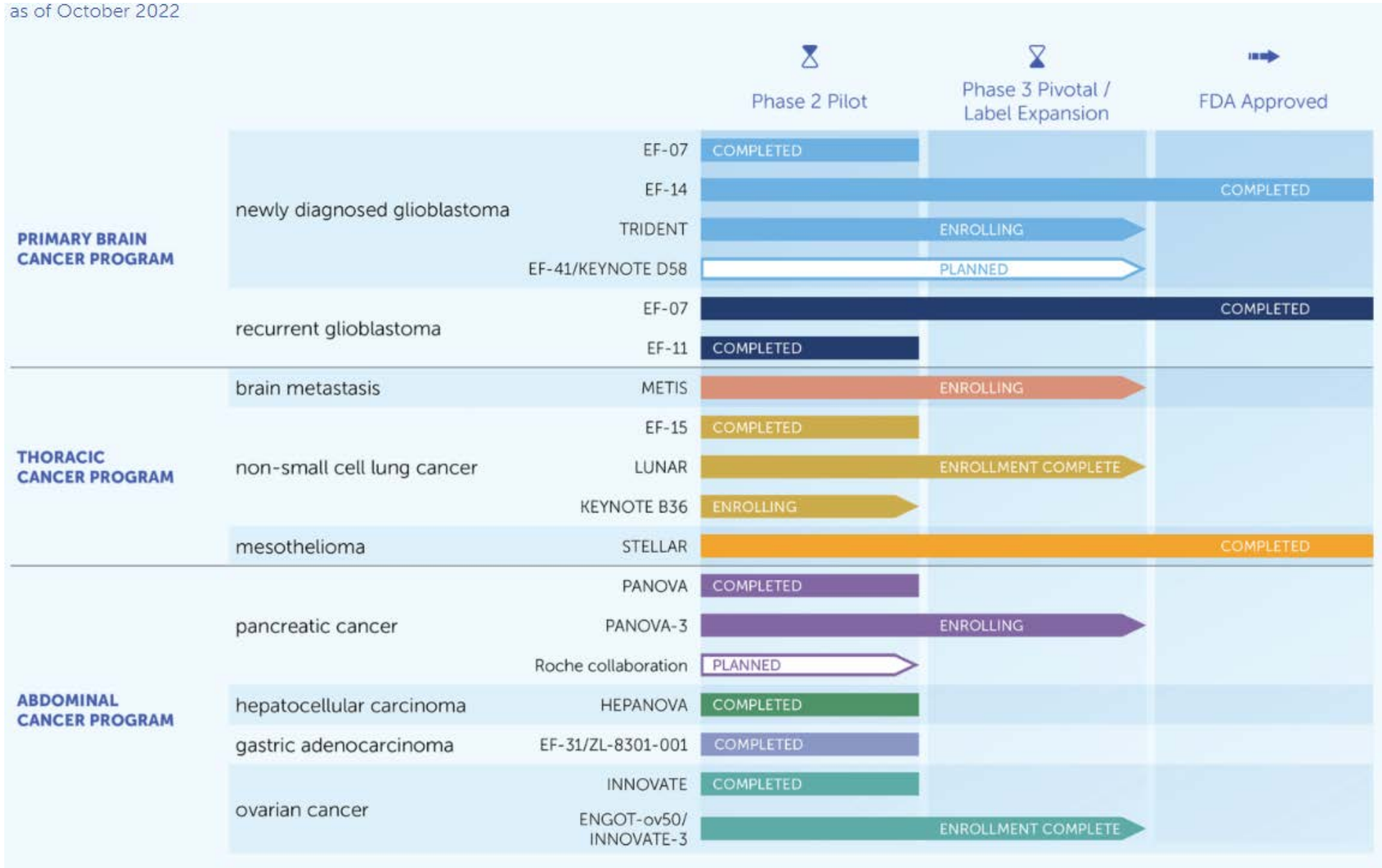
ADJUSTED PROTOCOL[2]

- 276 patients with 12 months of follow-up
- FDA approved recommended changes in May 2021
- Final data anticipated in 2022
- Statistical considerations remain unchanged

M Cobo Dols. ELCC 2022 Industry Satellite Symposium.

RTP RESEARCH TO PRACTICE

TTFields Pipeline



Novocure, Ltd.

What I Tell My Patients:
Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Fifteenth Annual RTP Symposium Series Held During the Annual ONS Congress

Lung Cancer

Friday, April 28, 2023
6:00 PM – 8:00 PM

Faculty

Stephen V Liu, MD
Tara Plues, APRN, MSN
Jillian Thompson, MSN, ANP-BC, AOCNP
Anne S Tsao, MD, MBA

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

What I Tell My Patients:
Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Fifteenth Annual RTP Symposium Series Held During the Annual ONS Congress

Acute Myeloid Leukemia, Myelodysplastic Syndromes and Myelofibrosis

Saturday, April 29, 2023
6:00 AM – 7:30 AM

Faculty

Ilene Galinsky, NP
Ruben A Mesa, MD (Virtual)
Daniel A Pollyea, MD, MS
Richard M Stone, MD
Sara Tinsley-Vance, PhD, APRN, AOCN

Moderator

Neil Love, MD

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Thank you for joining us! Please take a moment to complete the survey currently up on Zoom. Your feedback is very important to us. The survey will remain open up to 5 minutes after the meeting ends.

In-person attendees can use the networked iPads® to claim NCPD credit or use the QR code as instructed in the program syllabus.

Virtual attendees: The NCPD credit link is posted in the chat room.

NCPD/ONCC credit information will be emailed to each participant within 1 to 2 business days.

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