Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Lung Cancer

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Friday, June 3, 2022
6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)

Faculty

Justin F Gainor, MD
Corey J Langer, MD
Luis Paz-Ares, MD, PhD
Heather Wakelee, MD
Jared Weiss, MD
Helena Yu, MD

Moderator

Neil Love, MD

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Faculty

Justin F Gainor, MD
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
Massachusetts General Hospital
Boston, Massachusetts

Corey J Langer, MD
Director of Thoracic Oncology
Abramson Cancer Center
Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Luis Paz-Ares, MD, PhD
Chair of the Medical Oncology Department at the Hospital Universitario 12 de Octubre
Associate Professor at the Universidad Complutense
Head of the Lung Cancer Unit at the National Oncology Research Center
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Professor of Medicine
Chief, Division of Oncology
Interim Medical Director, Stanford Cancer Center
Deputy Director, Stanford Cancer Institute
President, International Association for the Study of Lung Cancer (IASLC)
Stanford, California

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Professor of Medicine
UNC School of Medicine
Lineberger Comprehensive Cancer Center
Chapel Hill, North Carolina

Helena Yu, MD
Medical Oncologist
Associate Attending
Memorial Sloan Kettering Cancer Center
New York, New York

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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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 premeeting survey before the meeting. Survey results will be presented and 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 CME 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 premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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

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

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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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Friday June 3	**Acute Myeloid Leukemia and Myelodysplastic Syndromes** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 4	**Prostate Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Gastrointestinal Cancers 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Sunday June 5	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 6	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 7	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Lung Cancer

Friday, June 3, 2022
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Luis Paz-Ares, MD, PhD
Heather Wakelee, MD
Jared Weiss, MD
Helena Yu, MD

Gastrointestinal Cancers

Saturday, June 4, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
John Strickler, MD
Eric Van Cutsem, MD, PhD

Prostate Cancer

Saturday, June 4, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Andrew J Armstrong, MD, ScM
Alan H Bryce, MD
Alicia K Morgans, MD, MPH

Ovarian Cancer

Sunday, June 5, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Antonio González-Martín, MD, PhD
Joyce F Liu, MD, MPH
Kathleen N Moore, MD, MS

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

Sunday, June 5, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Ian W Flinn, MD, PhD
Brian T Hill, MD, PhD
John P Leonard, MD
Matthew Lunning, DO
Laurie H Sehn, MD, MPH
Mitchell R Smith, MD, PhD

Breast Cancer

Monday, June 6, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Javier Cortés, MD, PhD
Matthew P Goetz, MD
Erika Hamilton, MD
Ian E Krop, MD, PhD
Hope S Rugo, MD
Sara M Tolaney, MD, MPH

Urothelial Bladder Cancer

Monday, June 6, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Yohann Loriot, MD, PhD
Elizabeth R Plimack, MD, MS
Jonathan E Rosenberg, MD

Multiple Myeloma

Tuesday, June 7, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Ajai Chari, MD
Elizabeth O'Donnell, MD
Robert Z Orlowski, MD, PhD

Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Philip L Brooks, MD
Northern Light Eastern Maine Medical Center and Lafayette Family Cancer Institute
Brewer, Maine

Shams Bufalino, MD
Advocate Aurora Health
Park Ridge, Illinois

Lionel A Kankeu Fonkoua, MD
Mayo Clinic
Rochester, Minnesota

Shaachi Gupta, MD, MPH
Florida Cancer Specialists
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Florida Cancer Specialists
Naples, Florida

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Atlantic Health System
Summit, New Jersey

Vignesh Narayanan, MD
Colorado Permanente Medical Group (CPMG)
Lone Tree, Colorado

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Fort Worth, Texas

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Namrata I Peswani, MD
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Comprehensive Cancer Center
Richardson, Texas

Matthew R Strickland, MD
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Cancer Center
Boston, Massachusetts

Commercial Support

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Research To Practice CME Planning Committee Members, Staff and Reviewers

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

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Dr Gainor — Disclosures

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Contracted Research	Adaptimmune, ALX Oncology, Array BioPharma Inc, a subsidiary of Pfizer Inc, Blueprint Medicines, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Jounce Therapeutics, Merck, Moderna, Novartis, Scholar Rock, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company
Employment (Immediate Family Member)	Ironwood Pharmaceuticals

Dr Langer — Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, GlaxoSmithKline, Guardant Health, Lilly, Merck, Pfizer Inc, Takeda Pharmaceuticals USA Inc
Consulting Agreements	AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Lilly, Merck, Novartis, Novocure Inc, Regeneron Pharmaceuticals Inc
Contracted Research	Advantagene Inc, Amgen Inc, Lilly, Merck, Takeda Pharmaceuticals USA Inc, Trizell
Data and Safety Monitoring Board/Committee	US Department of Veterans Affairs, OncocyteRx

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Dr Paz-Ares — Disclosures

Board	GENOMICA SAU
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Merck Sharp & Dohme Corp, Pfizer Inc
Speakers Bureau	Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, GlaxoSmithKline, Janssen Biotech Inc, Lilly, Merck, Merck Sharp & Dohme Corp, Mirati Therapeutics, Novartis, Pfizer Inc, PharmaMar, Roche Laboratories Inc, Sanofi Genzyme, Servier Pharmaceuticals LLC, Takeda Pharmaceuticals USA Inc

Dr Wakelee — Disclosures

Advisory Board	AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Janssen, Biotech Inc, Merck, Mirati Therapeutics
Research Funding	ACEA Biosciences Inc, Arrys Therapeutics, a wholly owned subsidiary of Kyn Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Clovis Oncology, Genentech, a member of the Roche Group, Helsinn Healthcare SA, Merck, Novartis, Seagen Inc, Xcovery

Dr Weiss — Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Azitra, Boehringer Ingelheim Pharmaceuticals Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Jazz Pharmaceuticals Inc, Lilly, Nanobiotix, Pfizer Inc, Regeneron Pharmaceuticals Inc, Saatchi & Saatchi Wellness, Sumitomo Dainippon Pharma Oncology Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, G1 Therapeutics Inc, Inspirna, Merck
Data and Safety Monitoring Board/Committee	BeiGene Ltd, EMD Serono Inc, Jounce Therapeutics
Ownership Interest	Achilles Therapeutics, Lyell, Nuvalent, Vesselon (warrants)

Dr Yu — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Blueprint Medicines, C4 Therapeutics, Cullinan Oncology, Daiichi Sankyo Inc, Janssen Biotech Inc
Research Funding (to Institution)	AstraZeneca Pharmaceuticals LP, Cullinan Oncology, Daiichi Sankyo Inc, Erasca, Janssen Biotech Inc, Pfizer Inc, Novartis

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Moderator

Neil Love, MD

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Agenda

Module 1 – Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Wakelee

Module 2 – Contemporary Treatment for Localized and Metastatic NSCLC with EGFR Mutations — Dr Yu

Module 3 – Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Gainor

Module 4 – Targeting Alterations in MET, HER2, KRAS and Other Oncogenes in NSCLC — Dr Weiss

Module 5 – Current and Future Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Langer

Module 6 – Current Treatment Paradigm for Small Cell Lung Cancer (SCLC) — Dr Paz-Ares

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Lung Cancer Survey Respondents

Christina Baik, MD, MPH

Julie Brahmer, MD

Paul Bunn Jr, MD

D Ross Camidge, MD, PhD

Justin F Gainor, MD

Edward B Garon, MD, MS

Matthew Gubens, MD, MS

John V Heymach, MD, PhD

Corey J Langer, MD

Stephen V Liu, MD

Joel W Neal, MD, PhD

Luis Paz-Ares, MD, PhD

Nathan A Pennell, MD, PhD

Zofia Piotrowska, MD, MHS

Gregory J Riely, MD, PhD

Charles Rudin, MD, PhD

Tawee Tanvetyanon, MD, MPH

Heather Wakelee, MD

Jared Weiss, MD

Helena Yu, MD

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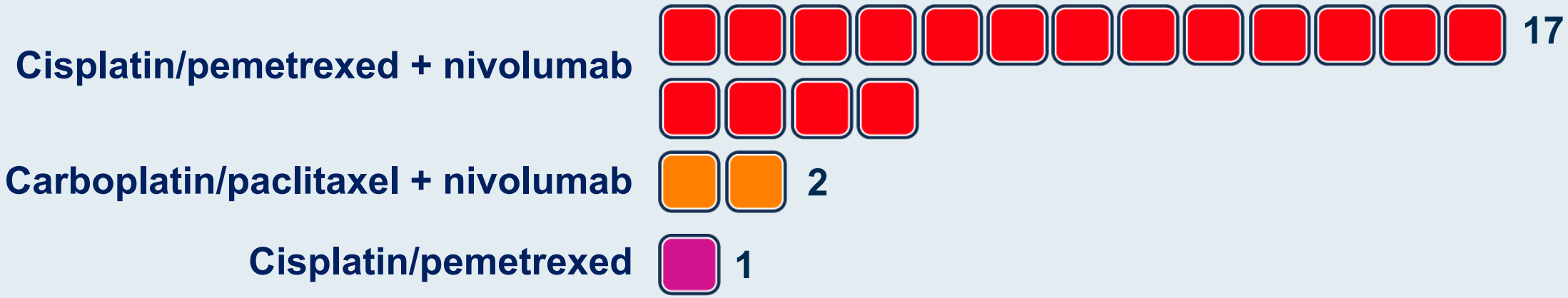
MODULE 1: Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC) — Dr Wakelee

What neoadjuvant systemic therapy would you most likely recommend to a 65-year-old patient with adenocarcinoma of the lung in whom the surgeon would like to see tumor shrinkage before proceeding to surgery (PD-L1 TPS = 40%)?



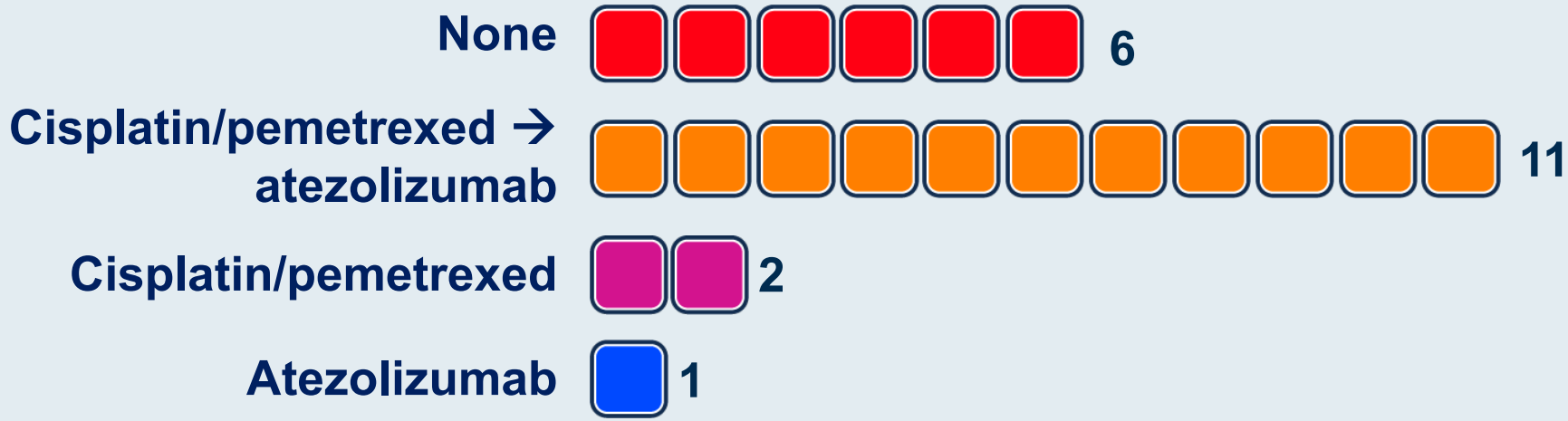
Number of patients with NSCLC who received neoadjuvant chemotherapy alone or combined with an anti-PD-1/PD-L1 antibody in the past year…

Off protocol (Median)
3 patients

On protocol (Median)
2 patients

Survey of lung cancer clinical investigators

In general, what adjuvant treatment, if any, would you recommend for an otherwise healthy 65-year-old patient with Stage IB (4-cm) nonsquamous NSCLC with no identified targetable mutations and a PD-L1 TPS of 50%?



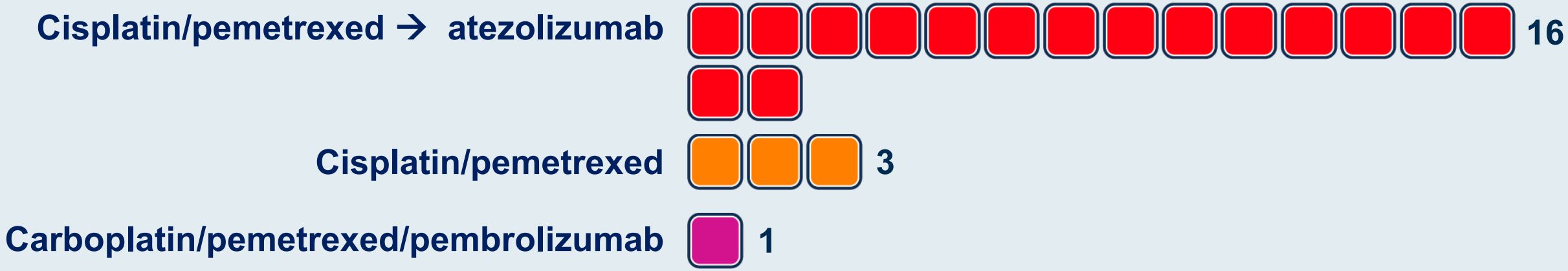
Number of patients with NSCLC who received an adjuvant anti-PD-1/PD-L1 antibody in the past year…

Off protocol (Median)
3 patients

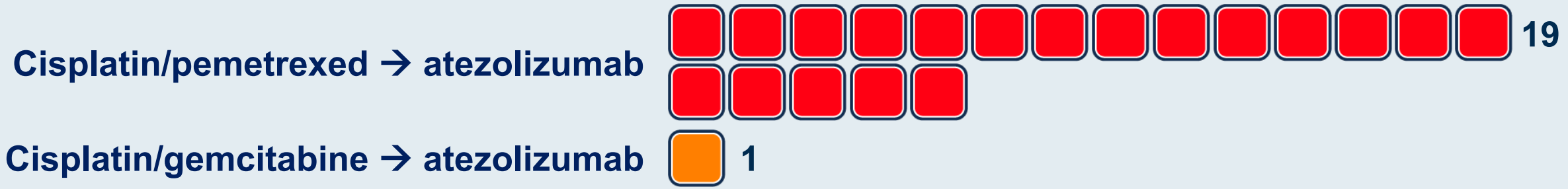
On protocol (Median)
None

Survey of lung cancer clinical investigators

In general, what adjuvant treatment, if any, would you recommend for an otherwise healthy 65-year-old patient with Stage IIB nonsquamous NSCLC with no identified targetable mutations and a PD-L1 TPS of 1%?

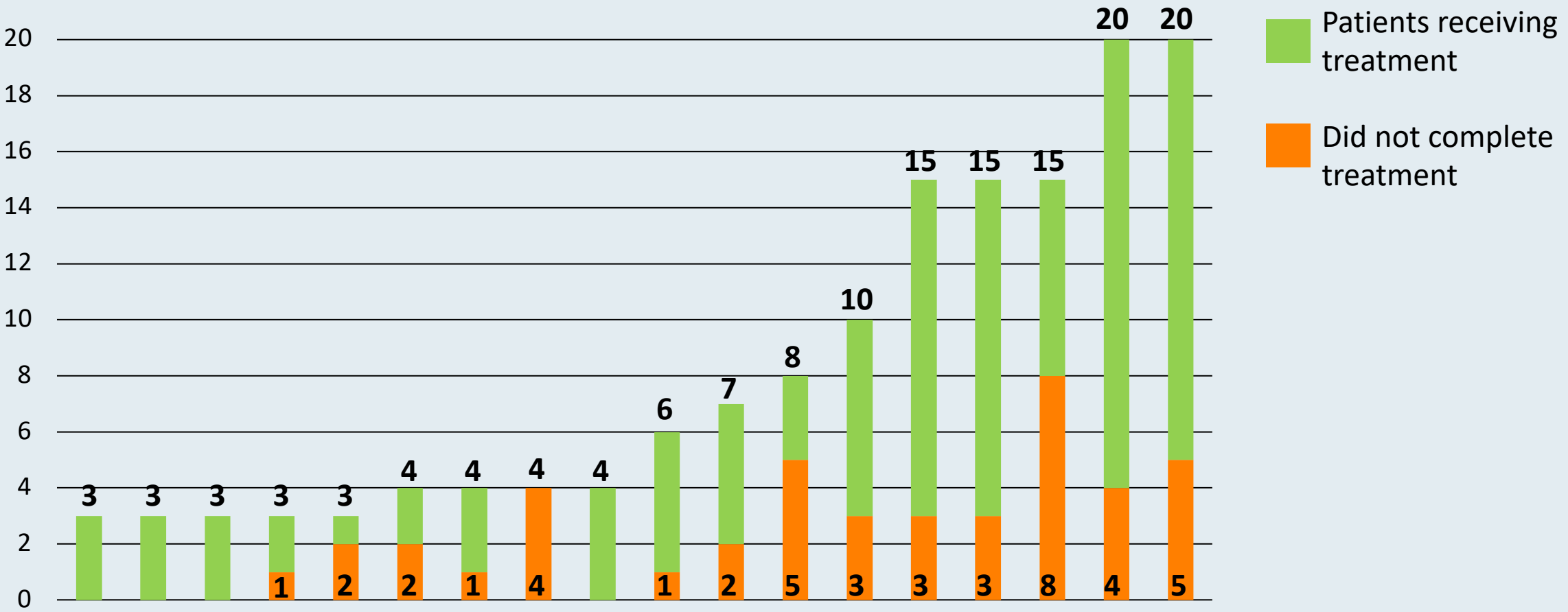


In general, what adjuvant treatment, if any, would you recommend for an otherwise healthy 65-year-old patient with Stage IIB nonsquamous NSCLC with no identified targetable mutations and a PD-L1 TPS of 50%?



Survey of lung cancer clinical investigators

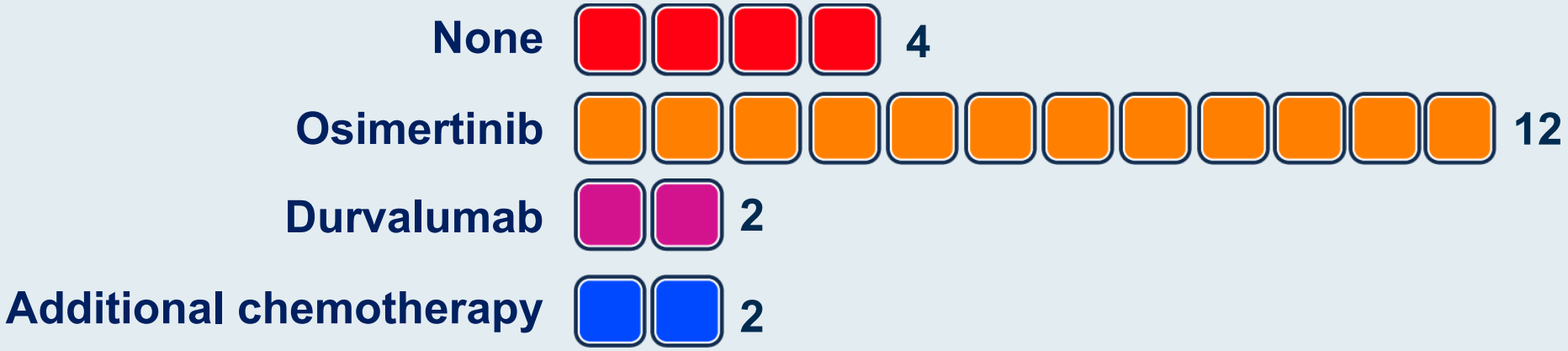
In the past year, to approximately how many patients with unresectable locally advanced NSCLC have you administered durvalumab consolidation after chemoradiation therapy? (Mean)
Approximately how many of these patients were not able to complete the full course of durvalumab consolidation?



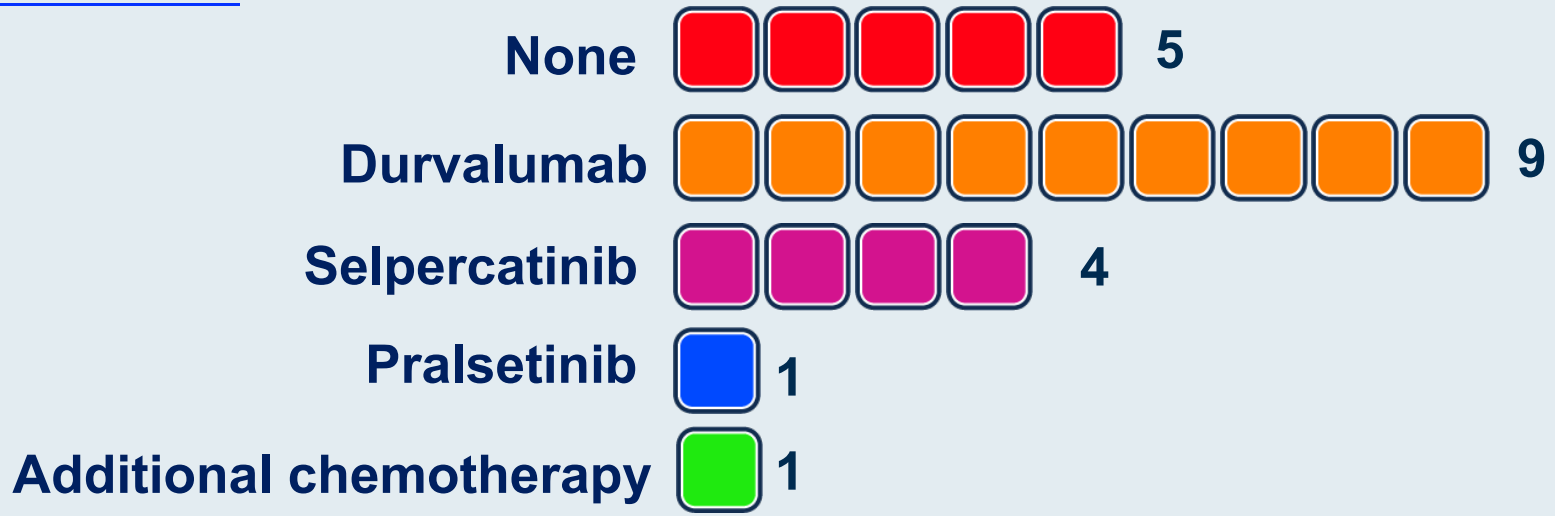
Survey of lung cancer clinical investigators

What would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who had completed chemoradiation therapy and was found to have…

An EGFR mutation?



A RET fusion?



Survey of lung cancer clinical investigators

Incorporation of Immunotherapeutic Strategies into the Management of Nonmetastatic Non-Small Cell Lung Cancer (NSCLC)

Heather Wakelee, MD, FASCO
Professor of Medicine, Oncology
Chief, Division of Medical Oncology
Interim Medical Director, Stanford Cancer Center
Stanford University School of Medicine
Deputy Director, Stanford Cancer Institute
President, International Association for the Study of Lung Cancer (IASLC)

Adjuvant Chemotherapy:
LACE and NSCLC Meta-analysis Collaborative Group

LACE: 5 trials - 4,584 patients
DFS HR 0.84 (95% CI: 0.78, 0.91); p<.001
OS HR 0.89 [0.82-0.96], p= .005
5% OS benefit at 5 yrs
Grade 3/4 toxicity was 66%, 32% Gr4, 0.9% Grade 5 toxicity

Updated individual patient data of adj chemo trials from 1965+
34 trials - 8,447 patients
OS HR 0.86 [0.81-0.92], p= <.0001
4% absolute OS benefit at 5 yrs

NO Selection (despite years of trying)
Became Standard of Care

Pignon JCO 26:3552, 2008; Lancet 375:1267, 2010

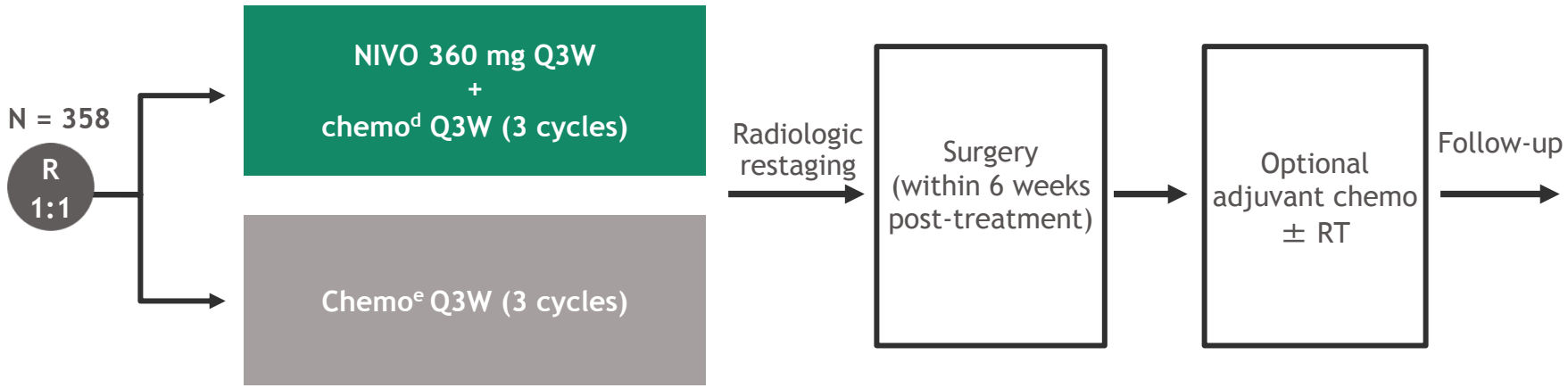
Neo-Adjuvant IO Therapy

Neoadjuvant Nivolumab + Chemotherapy CheckMate 816

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Primary endpoints
- pCR by BIPR
- EFS by BICR

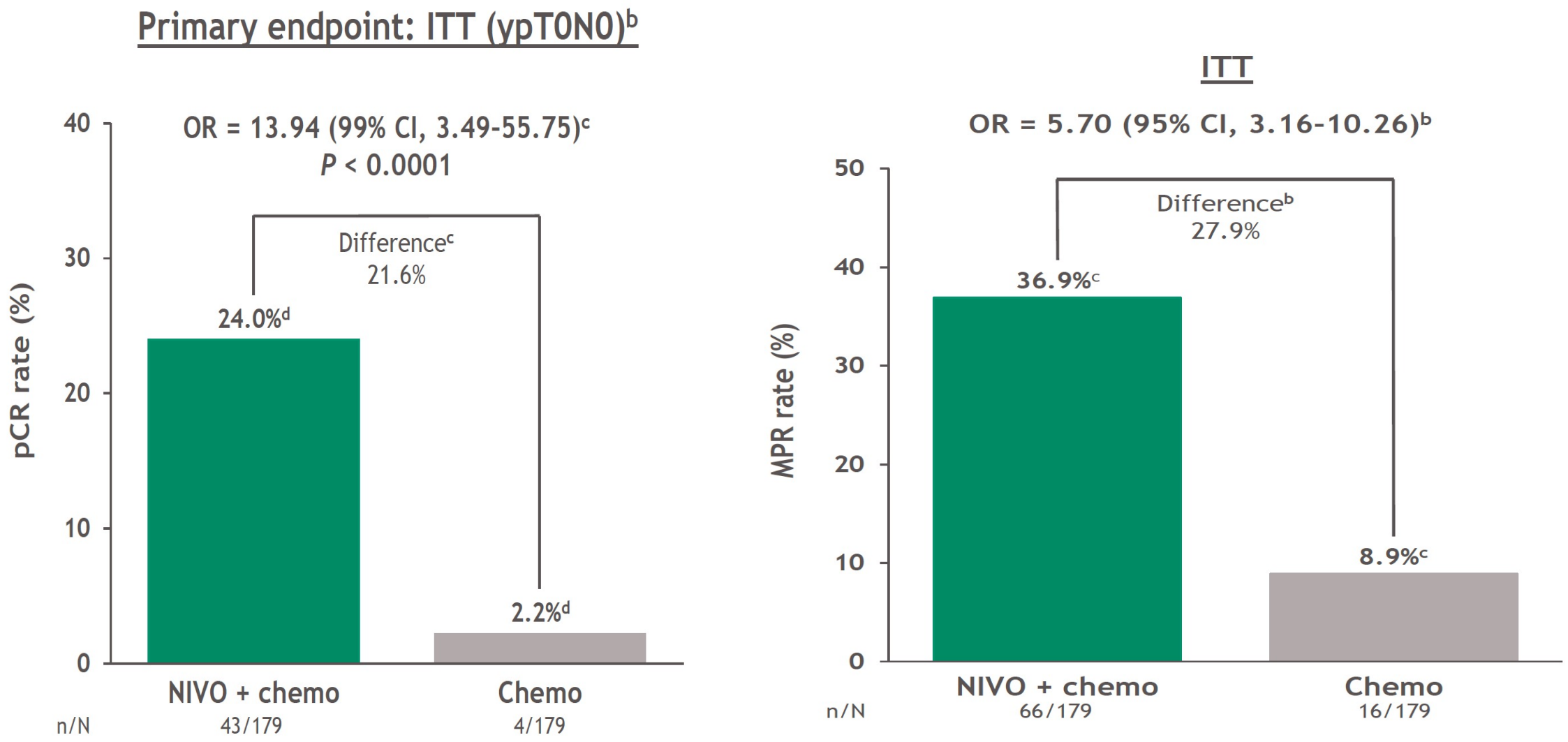
Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

63% Stage IIIA
50% PD-L1 >1%

Spicer ASCO 2021 abstr: 8503

CM816 – pCR and MPR in ITT population



- pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

Forde CM816, AACR2021

CM816: PD-L1 and TMB data

pCR subgroup analysis

	pCR[a] rate, %		Unweighted pCR difference, % (95% CI)	Unweighted pCR difference, %
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	24	2		22
< 65 years (n = 176)	27	0		27
≥ 65 years (n = 182)	21	4		17
Male (n = 255)	23	2		20
Female (n = 103)	28	2		26
North America (n = 91)	22	2		20
Europe (n = 66)	24	0		24
Asia (n = 177)	28	3		25
Stage IB-II (n = 128)	**26**	**5**		**21**
Stage IIIA (n = 228)	**23**	**1**		**22**
Squamous (n = 182)	**25**	**4**		**21**
Non-squamous (n = 176)	**23**	**0**		**23**
Current/former smoker (n = 318)	26	2		23
Never smoker (n = 39)	10	0		10
PD-L1 < 1% (n = 155)	**17**	**3**		**14**
PD-L1 ≥ 1% (n = 178)	**33**	**2**		**30**
PD-L1 1-49% (n = 98)	24	0		24
PD-L1 ≥ 50% (n = 80)	45	5		40
TMB < 12.3 mut/Mb (n = 102)	22	2		21
TMB ≥ 12.3 mut/Mb (n = 76)	31	3		28
Cisplatin (n = 258)	22	2		20
Carboplatin (n = 72)	31	0		31

[a]Per BIPR in ITT.

Forde CM816 AACR

CM816 EFS + US FDA approval

EFS HR 0.63 (97.38% CI: 0.43, 0.91; p=0.0052)

Median EFS:
31.6 mo (95% CI: 30.2, NR) nivo + chemo
20.8 mo (95% CI: 14.0, 26.7) chemo alone

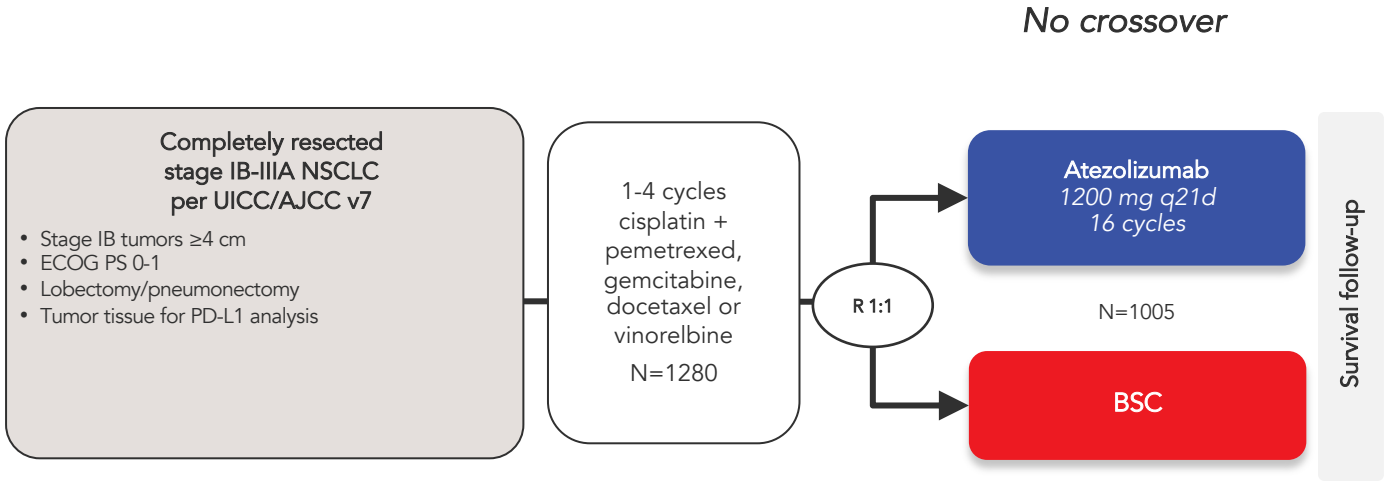
CheckMate 816 trial (NCT02998528)
US FDA Approval March 4, 2022

Phase 3 Neo-Adjuvant PD-(L)1 IO trials

Drug	N	Stages	Description	Primary Endpoint
Nivo + platinum chemo (**ipi/nivo closed**) CM816	350	Stage IB–IIIA, resectable NSCLC	Neo-adjuvant, no adjuvant	MPR / RFS
Atezo + platinum chemo IMpower030	374	Stage II–IIIB (T3N2), resectable NSCLC	Neo-adjuvant chemo-ICI, then adjuvant IO	MPR / RFS
Pembro + platinum chemo KN671	786	Stage IIB–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	RFS / OS
Durva + platinum chemo	300	Stage II–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	MPR

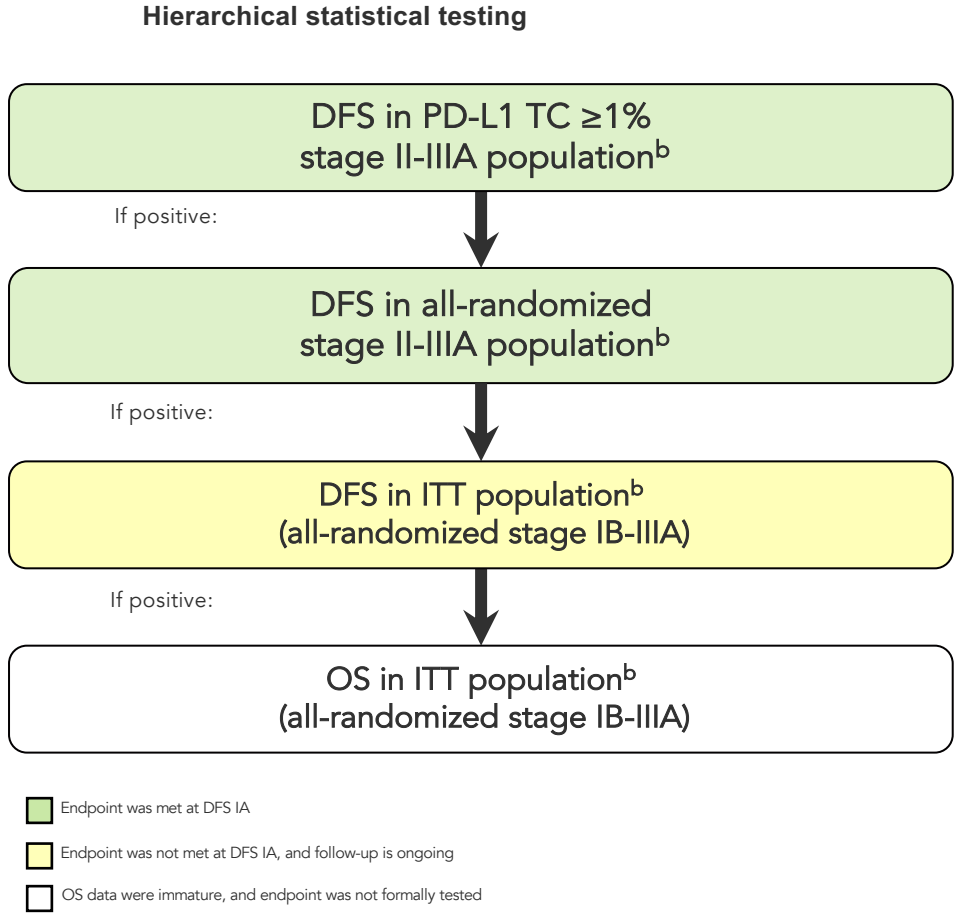
Adjuvant IO Therapy

IMpower010 study design



Stratification factors
- Male vs female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomized stage II-IIIA population
  3. ITT (all-randomized stage IB-IIIA) population



Both arms included observation and regular scans for disease recurrence on the same schedule.
IC, tumor-infiltrating immune cells. [a] Per SP142 assay. [b] Two-sided α=0.05.

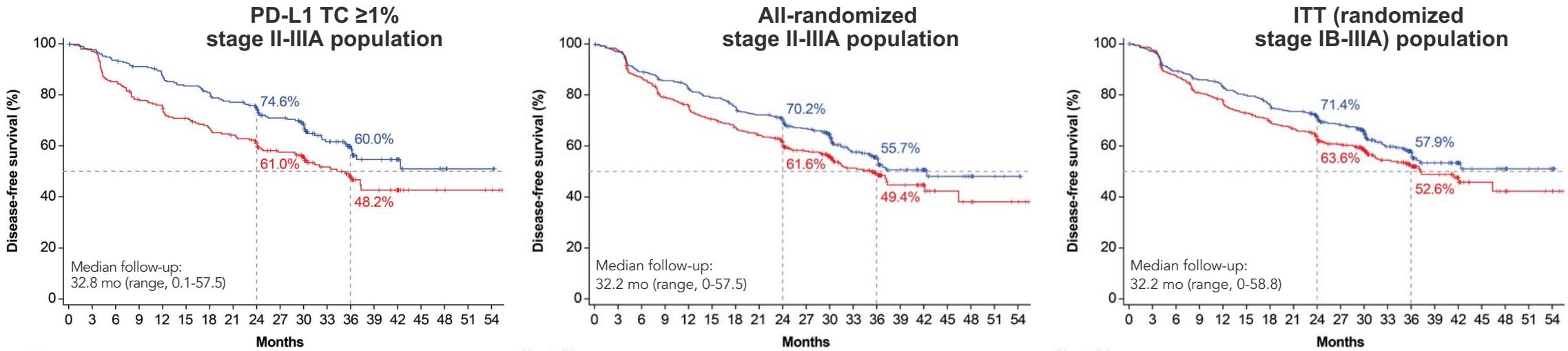
Dr. Heather A. Wakelee ASCO 2021, abstr 8500:IMpower010 Interim Analysis; https://bit.ly/33t6JJ; Felip Lancet 2021

IMpower010: Baseline characteristics

Characteristic	All patients (N=1005)	PD-L1 TC ≥1% (SP263) (stage II-IIIA)		All randomized (stage II-IIIA)		ITT (stage IB-IIIA)	
		Atezo (n=248)	BSC (n=228)	Atezo (n=442)	BSC (n=440)	Atezo (n=507)	BSC (n=498)
Median (range) age,	**62 (26-84)**	61 (34–82)	62 (26–84)	62 (33–82)	62 (26–84)	62 (33–83)	62 (26–84)
Age ≥65 y, n (%)	**382 (38.0)**	92 (37.1)	97 (42.5)	161 (36.4)	177 (40.2)	184 (36.3)	198 (39.8)
Sex, male, n (%)	**672 (66.9)**	171 (69.0)	147 (64.5)	295 (66.7)	294 (66.8)	337 (66.5)	335 (67.3)
Race, n (%)							
White	**738 (73.4)**	162 (65.3)	166 (72.8)	307 (69.5)	324 (73.6)	362 (71.4)	376 (75.5)
Asian	**242 (24.1)**	78 (31.5)	56 (24.6)	121 (27.4)	106 (24.1)	130 (25.6)	112 (22.5)
Other	**25 (2.5)**	8 (3.2)	6 (2.6)	14 (3.2)	10 (2.3)	15 (3.0)	10 (2.0)
Histology, non-SQ	**659 (65.6)**	152 (61.3)	143 (62.7)	292 (66.1)	296 (67.3)	328 (64.7)	331 (66.5)
Stage, n (%)							
IB	**123 (12.2)**	–	–	–	–	65 (12.8)	58 (11.6)
IIA	**295 (29.4)**	85 (34.3)	76 (33.3)	147 (33.3)	148 (33.6)	147 (29.0)	148 (29.7)
IIB	**174 (17.3)**	46 (18.5)	37 (16.2)	90 (20.4)	84 (19.1)	90 (17.8)	84 (16.9)
IIIA	**413 (41.1)**	117 (47.2)	115 (50.4)	205 (46.4)	208 (47.3)	205 (40.4)	208 (41.8)
Tobacco use, n (%)							
Never	**222 (22.1)**	51 (20.6)	41 (18.0)	100 (22.6)	96 (21.8)	114 (22.5)	108 (21.7)
Current/previous	**783 (77.9)**	197 (79.4)	187 (82.0)	342 (77.4)	344 (78.2)	393 (77.5)	390 (78.3)
PD-L1 by SP263, TC≥1%, n (%)[a]	**535 (54.6)**	248 (100)	228 (100)	248 (57.8)	228 (53.0)	283 (57.4)	252 (51.9)

Wakelee ASCO 2021 abstr 8500; Felip Lancet 2021

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA, all-randomized stage II-IIIA and ITT populations (primary endpoint)



	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

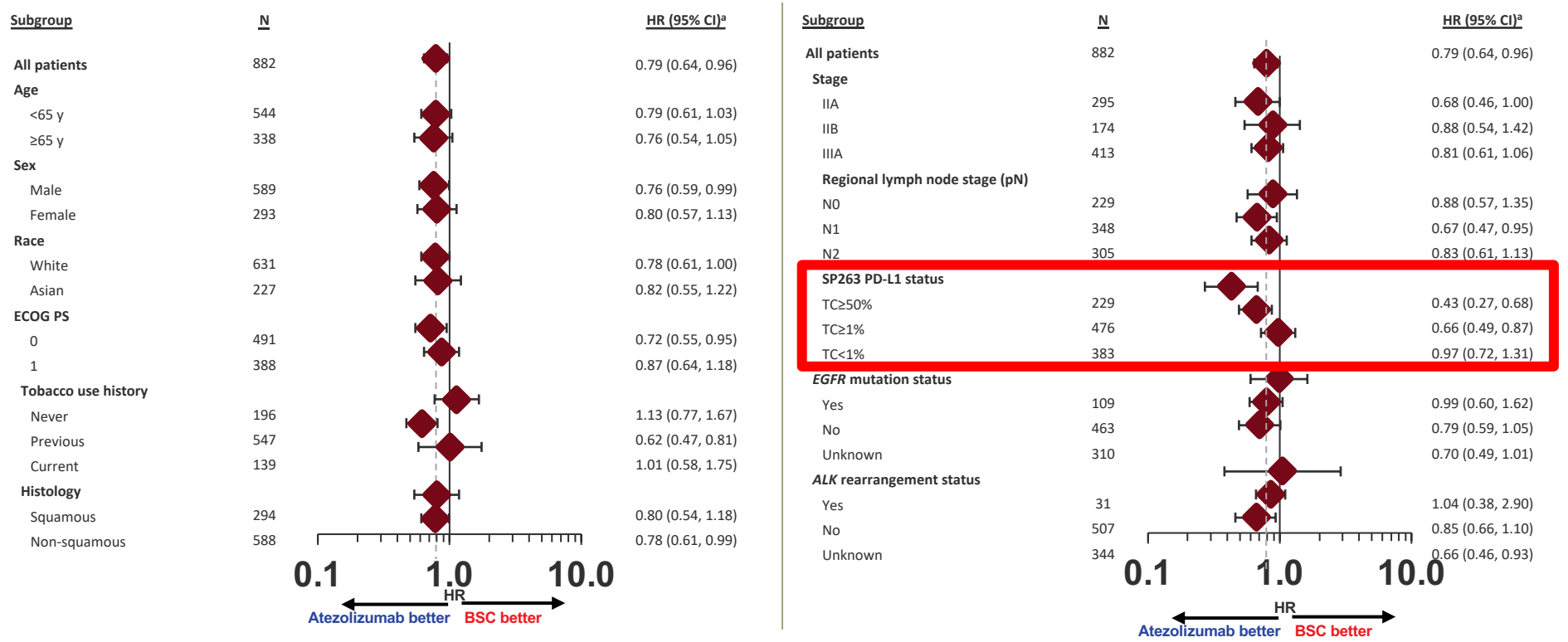
	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS. [d] The statistical significance boundary for DFS was not crossed.

Wakelee ASCO 2021 abstr 8500; Felip Lancet 2021

IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population



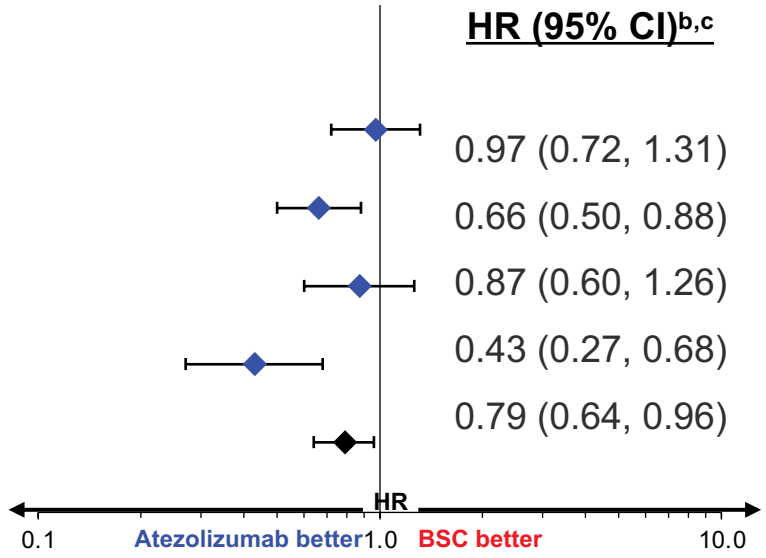
Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

Wakelee ASCO 2021 abstr 8500; Felip Lancet 2021

IMpower010 DFS by PD-L1 status[a]

All-randomized stage II-IIIA population (with and without known EGFR/ALK+ disease)

Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)

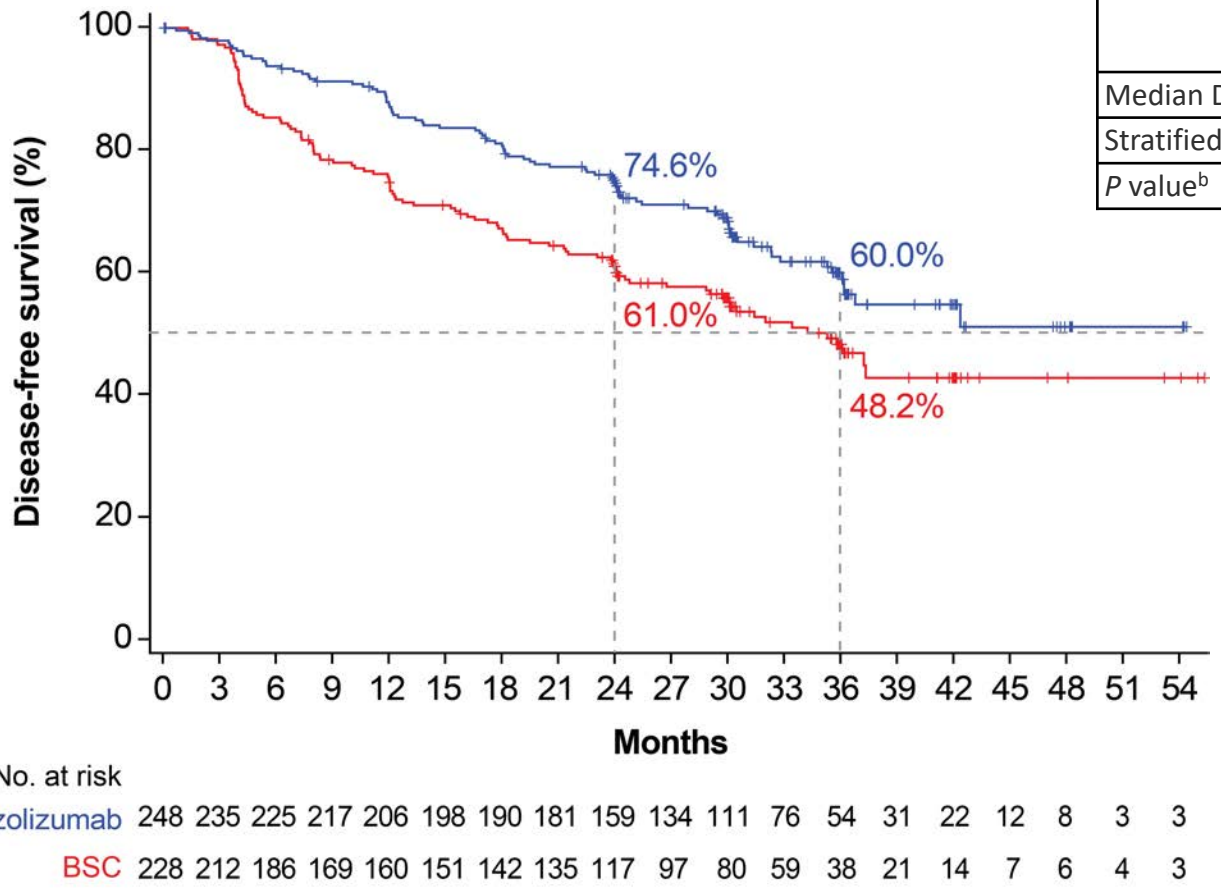


Clinical cutoff: 21 January 2021. [a] Per SP263 assay.
[b] Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups. [c] DFS analyses in the PD-L1 TC <1% and TC 1-49% subgroups were exploratory. [d] 23 patients had unknown PD-L1 status as assessed by SP263. [e] Excluding patients with known *EGFR/ALK*+ NSCLC. [f] Unstratified for all subgroups. [g] EGFR/ALK+ exclusion analyses were post hoc. [h] 21 patients had unknown PD-L1 status as assessed by SP263.

Felip ESMO2021

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint)

US FDA approval Oct 15, 2021



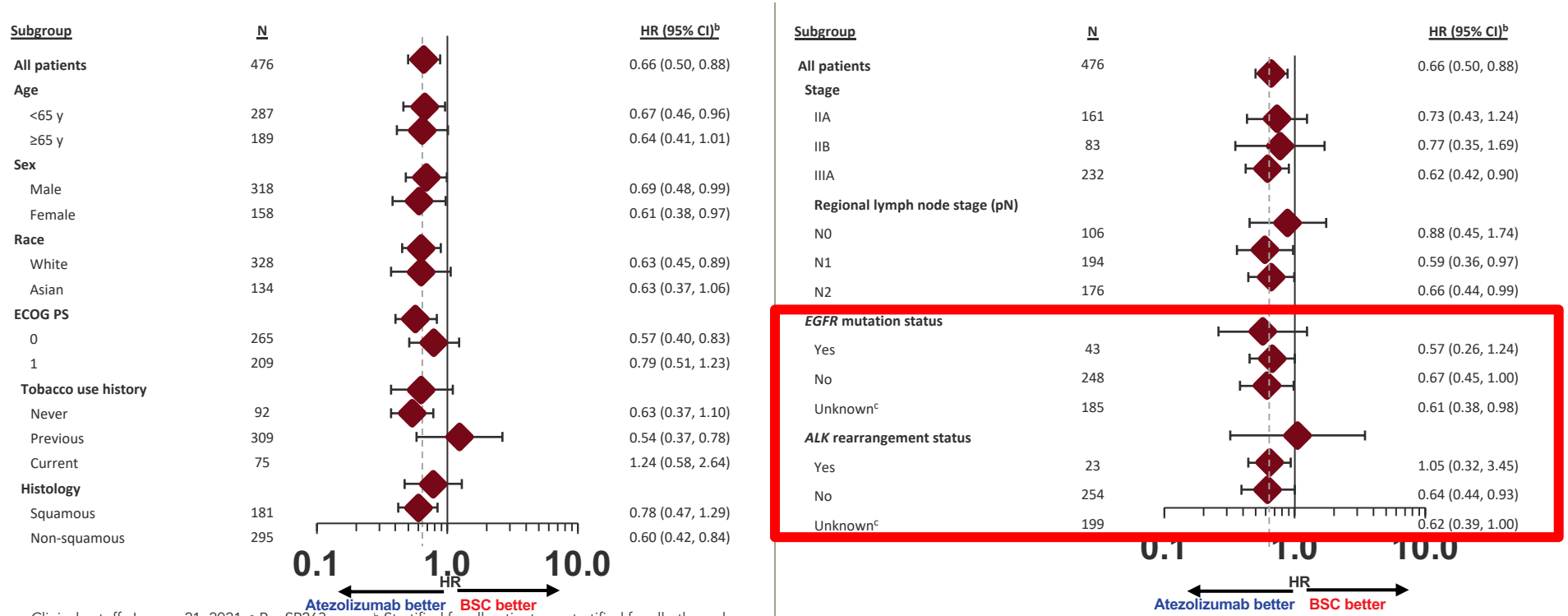
	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

Dr. Heather A. Wakelee ASCO 2021, abstr 8500
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

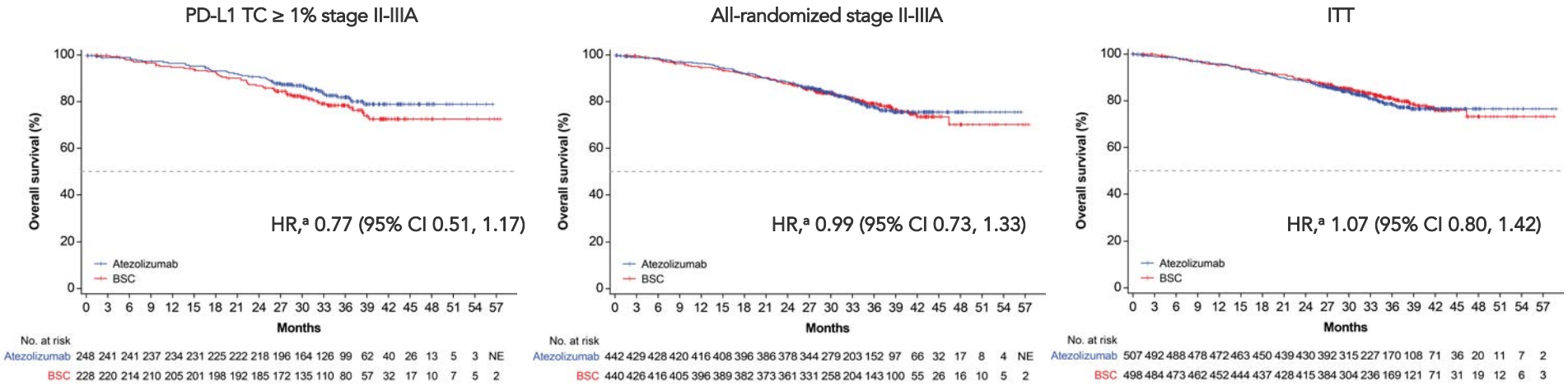
IMpower010: DFS in key subgroups of the PD-L1 TC ≥1%[a] stage II-IIIA population



Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified for all patients; unstratified for all other subgroups.
[c] 89.2% and 80.7% of patients in the ITT population with unknown *EGFR* or *ALK* status, respectively, had squamous NSCLC and were not required to undergo local or central testing.

Dr. Heather A. Wakelee ASCO 2021, abstr 8500
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

IMpower010: Early OS data at interim- Exploratory DFS analysis



OS data were immature at this pre-planned DFS interim analysis

- OS in the ITT population was not formally tested
- A trend toward OS improvement with atezolizumab was seen in the PD-L1 TC ≥1% stage II-IIIA population

Clinical cutoff: January 21, 2021. [a] Stratified.

Wakelee ASCO 2021, abstr 8500; Felip Lancet 2021

IMpower010: Safety summary[a]

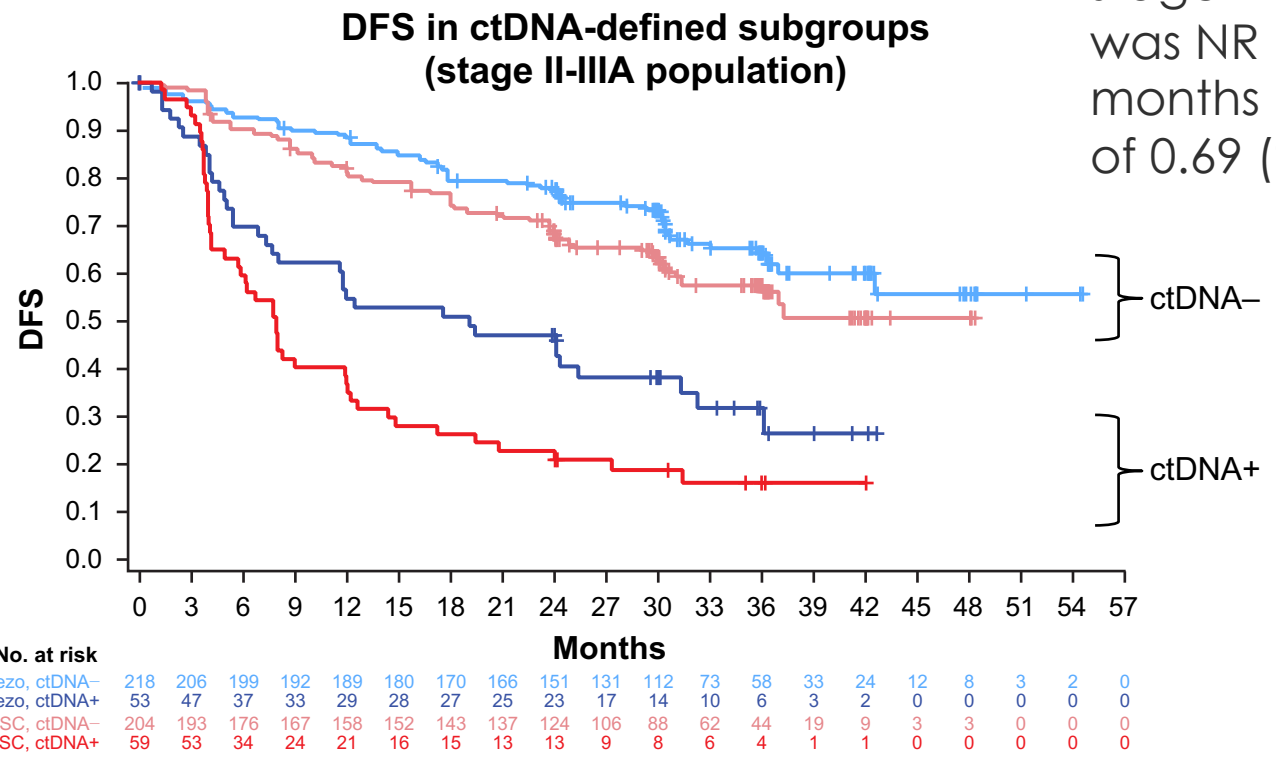
n (%)	Atezolizumab (n=495)	BSC (n=495)
Any-cause AE	459 (92.7)	350 (70.7)
Treatment-related AE	335 (67.7)	–
Grade 3-4 AE	108 (21.8)	57 (11.5)
Treatment-related grade 3-4 AE	53 (10.7)	–
Serious AE	87 (17.6)	42 (8.5)
Treatment-related serious AE	37 (7.5)	–
Grade 5 AE	8 (1.6)[b]	3 (0.6)[c]
Treatment-related grade 5 AE	4 (0.8)	–
AE leading to dose interruption of atezolizumab	142 (28.7)	–
AE leading to atezolizumab discontinuation	90 (18.2)	–
Immune-mediated AEs	256 (51.7)	47 (9.5)
Grade 3-4 immune-mediated AEs	39 (7.9)	3 (0.6)
Immune-mediated AEs requiring the use of systemic corticosteroids	60 (12.1)	4 (0.8)

Clinical cutoff: January 21, 2021. AE, adverse event; [a] Data are from the safety population (all randomized patients who received ≥1 atezolizumab dose or for BSC, had ≥1 post-baseline assessment). [b] Interstitial lung disease*; pneumothorax; multiple organ dysfunction syndrome*; cerebrovascular accident; arrhythmia; myocarditis*; acute myeloid leukemia*; acute cardiac failure. [c] Pneumonia; pulmonary embolism; cardiac tamponade and septic shock in the same patient. *, Treatment related per investigator.

Wakelee ASCO 2021, abstr 8500; Felip Lancet 2021

IMpower010 – Exploratory ctDNA results

- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)



ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

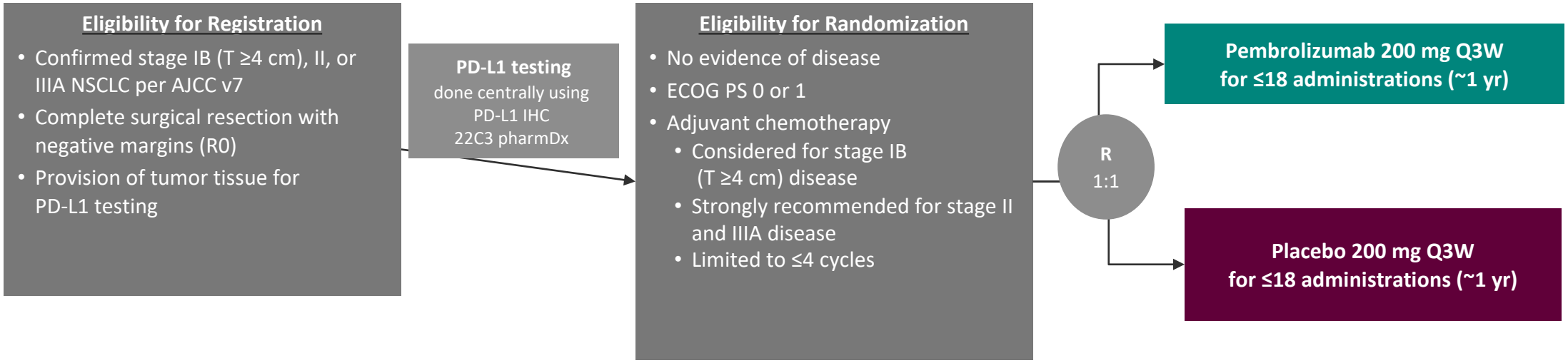
ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Clinical cutoff: 21 January 2021. Unstratified HRs are shown.

Zhou C et al, ESMO IO 2021

PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial



Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

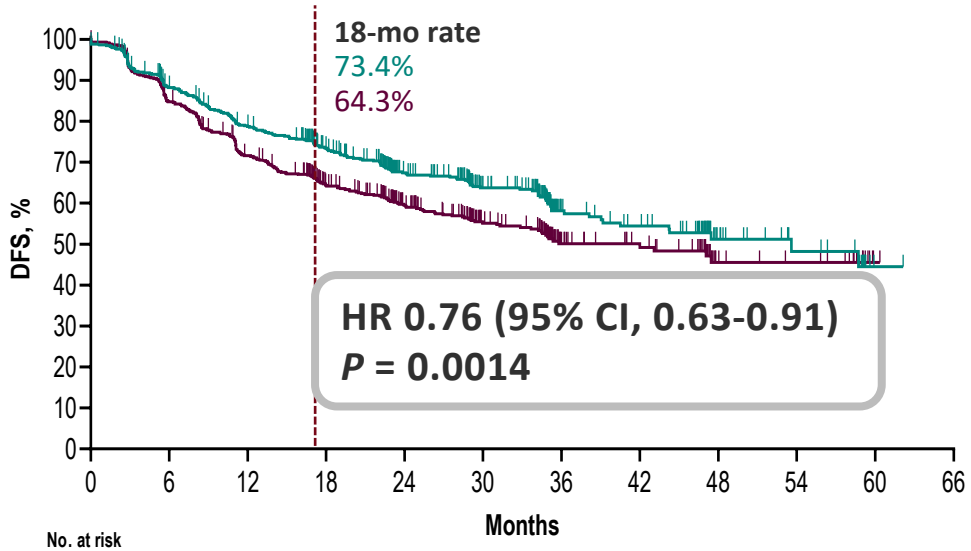
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

ClinicalTrials.gov number, NCT02504372.

Paz Ares – ESMO Virtual Plenary March 2022

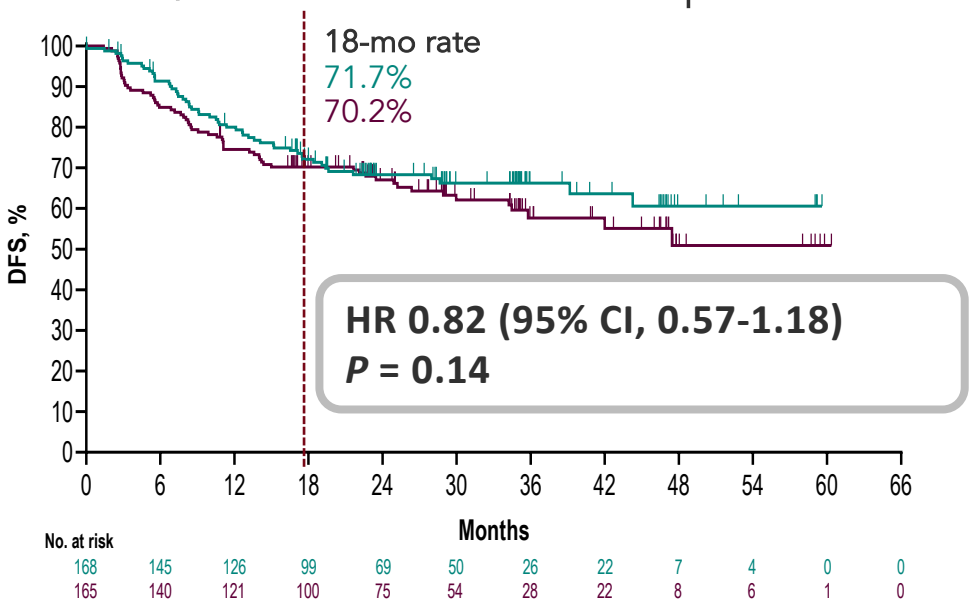
KN-091 DFS curves

DFS, Overall Population



	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)

DFS, PD-L1 TPS ≥50% Population



	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	32.1%	NR (44.3-NR)
Placebo	38.2%	NR (35.8-NR)

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

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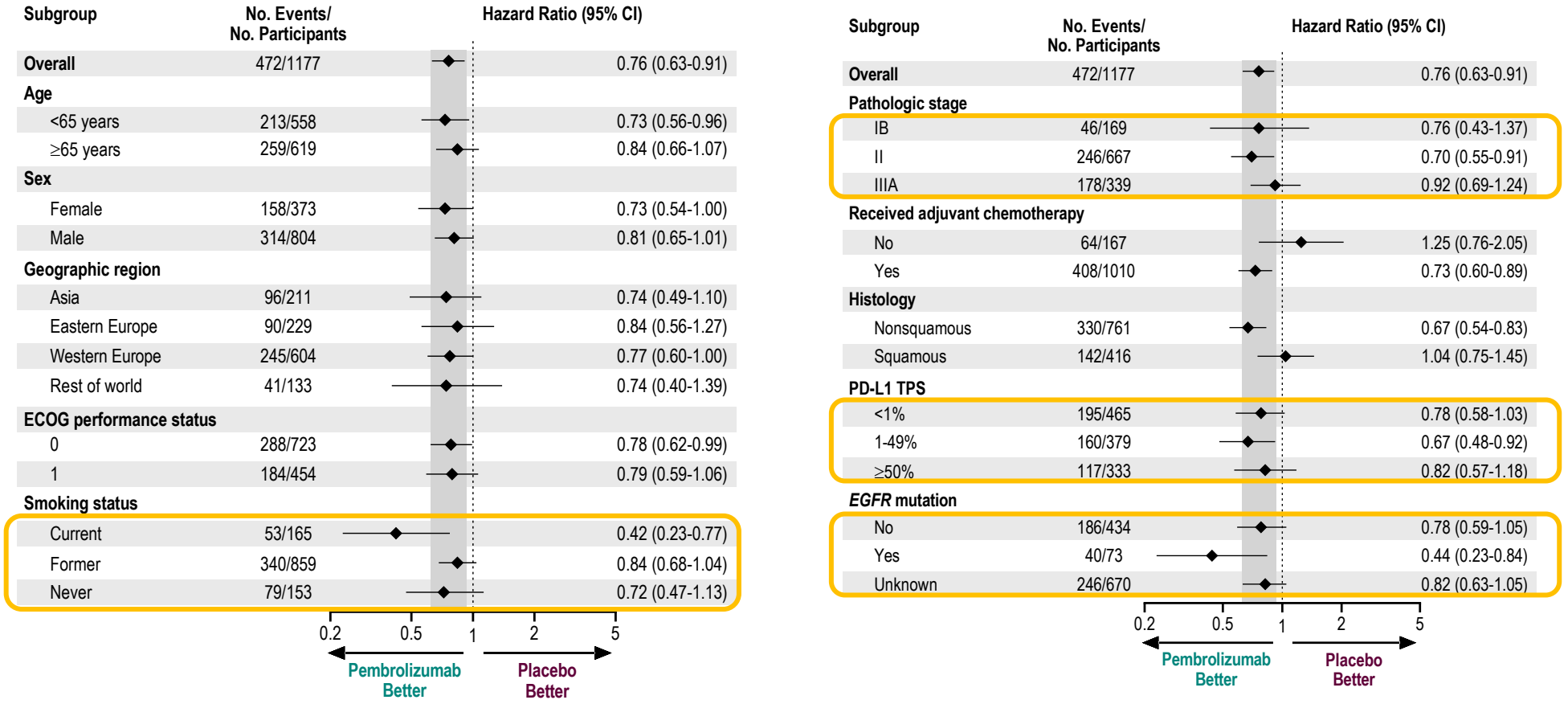
KN-091 DFS in Key Subgroups, Overall Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

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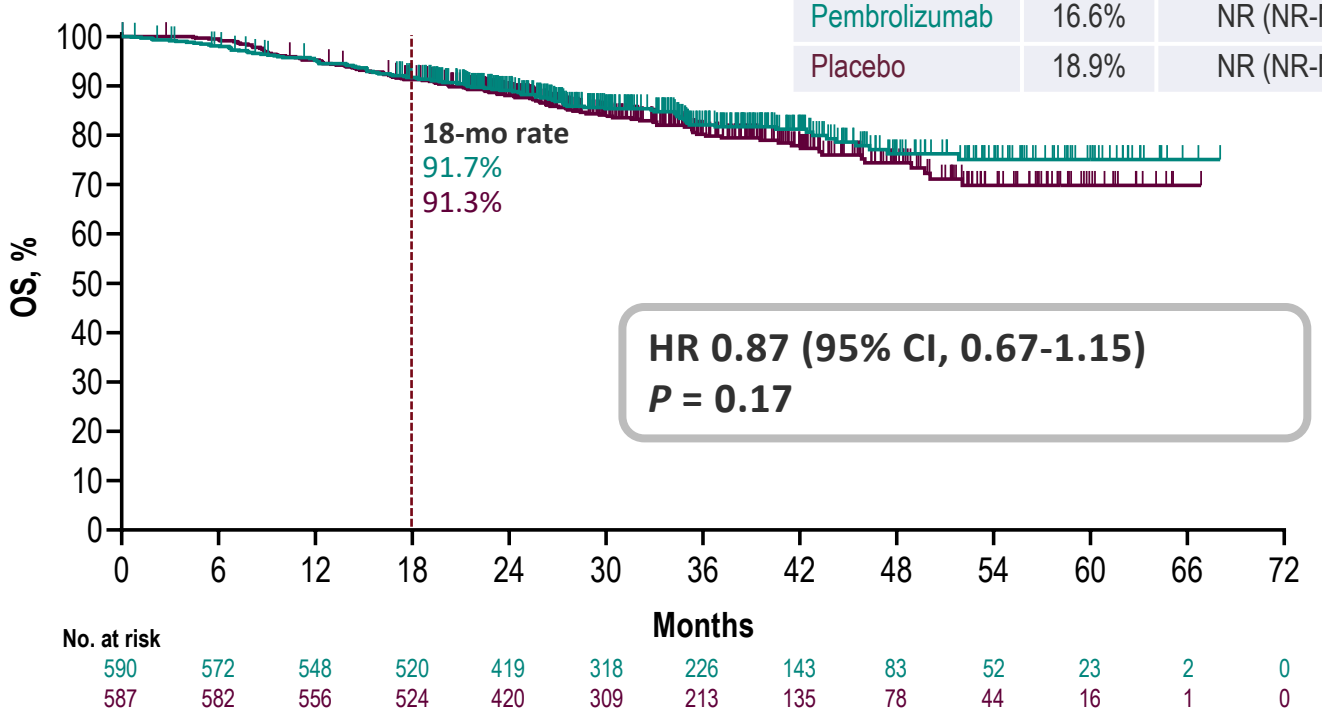
KN-091 OS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	16.6%	NR (NR-NR)
Placebo	18.9%	NR (NR-NR)



Data cutoff date: September 20, 2021

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Adjuvant PD-1/PD-L1 IO trials

Drug/Trial	Description	Stages entered	Description	Primary endpoint
Nivolumab ANVIL arm of ALCHEMIST	US, NCI (ECOG), Observational control	IB (4cm)-IIIA After Adj Chemo +/- radiation	Phase 3 Allows PD-L1 +/-	OS/DFS
Atezolizumab IMpower010	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Durvalumab	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Pembrolizumab PEARLS KN-091	ETOP/EORTC, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS

Locally Advanced IO Therapy

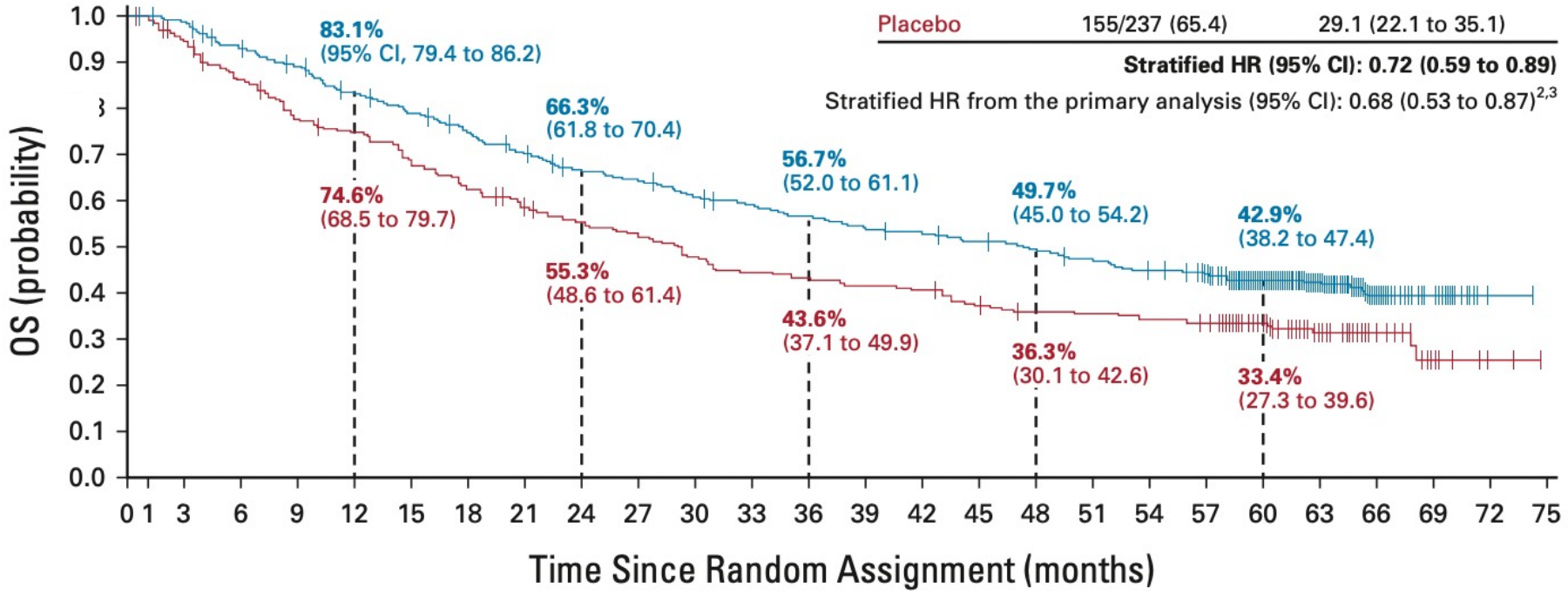
PACIFIC: Updated OVERALL SURVIVAL (ITT)

A

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

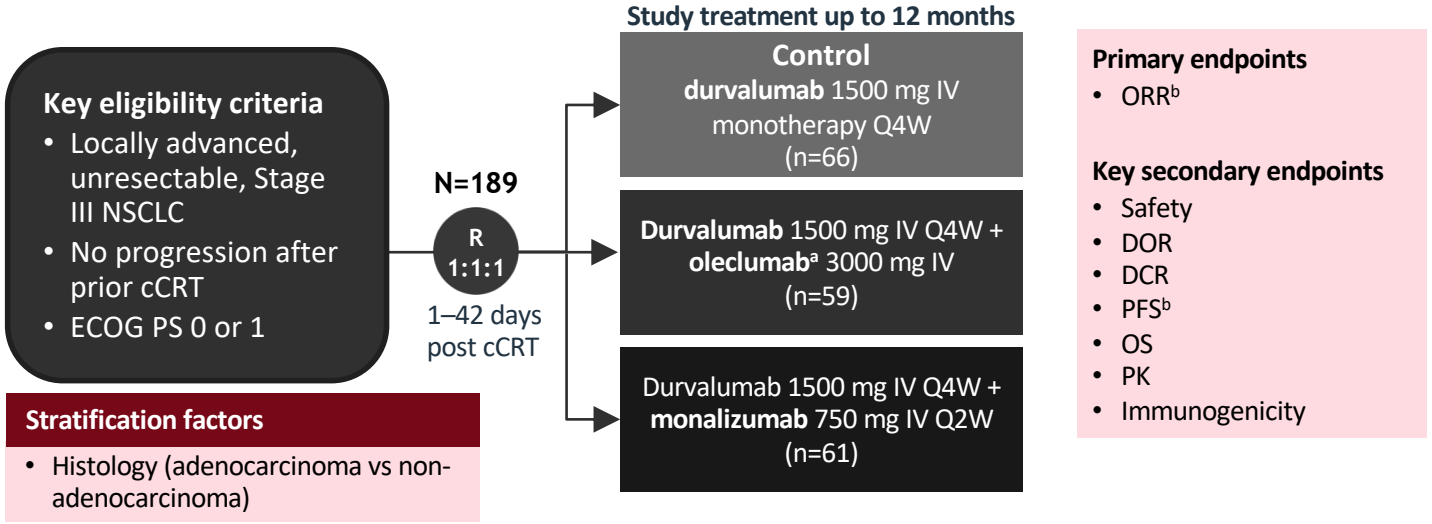
Spigel D, JCO, 2022.

PACIFIC: Prognostic baseline factors for OS (ITT)

Baseline Variable	Comparator Group	Comparator No. of Events/Total No. of Patients (%)	Reference Group	Reference No. of Events/Total No. of Patients (%)	HR (95% CI)
Treatment arm	Durvalumab	264/476 (55.5)	Placebo	155/237 (65.4)	0.71 (0.58 to 0.87)[a]
Age, years	≥ 65	210/322 (65.2)	< 65	209/391 (53.5)	1.30 (1.06 to 1.59)[a]
Disease stage[b]	IIIB	182/319 (57.1)	IIIA	227/377 (60.2)	1.03 (0.84 to 1.26)
Best response to prior treatment[c]	CR/PR	195/365 (53.4)	SD	216/338 (63.9)	0.88 (0.72 to 1.08)
Tumor histologic type	Squamous	205/326 (62.9)	Nonsquamous	214/387 (55.3)	1.28 (1.04 to 1.58)[a]
WHO PS	1[d]	233/365 (63.8)	0	186/348 (53.4)	1.23 (1.01 to 1.50)[a]
Prior platinum CT agent[e]	Cisplatin	215/395 (54.4)	Carboplatin	190/301 (63.1)	0.84 (0.69 to 1.03)
Race	Asian	95/192 (49.5)	White	310/494 (62.8)	0.63 (0.49 to 0.81)[a]
	Black or African American	7/14 (50.0)			0.81 (0.38 to 1.73)
	Other[f]	7/13 (53.8)			0.91 (0.41 to 1.99)
Sex	Male	304/500 (60.8)	Female	115/213 (54.0)	1.27 (1.01 to 1.61)[a]
Smoking status	Smoker	384/649 (59.2)	Nonsmoker	35/64 (54.7)	0.83 (0.56 to 1.22)
Time from CRT to random assignment, days	≥ 14	312/531 (58.8)	< 14	107/182 (58.8)	0.97 (0.77 to 1.22)
EGFR or *ALK* aberration status	Positive[g]	25/43 (58.1)	Negative	275/482 (57.1)	1.06 (0.69 to 1.64)
	Unknown	119/188 (63.3)			0.95 (0.73 to 1.23)
PD-L1 expression level	TC ≥ 25%	78/159 (49.1)	TC < 25%	175/292 (59.9)	0.82 (0.62 to 1.07)
	Unknown	166/262 (63.4)			1.19 (0.92 to 1.54)

Spigel, D JCO, 2022.

COAST (phase 2, open label): Durvalumab ± novel agents in patients with locally advanced, unresectable, Stage III NSCLC



Monalizumab is a humanized IgG4 that inhibits NKG2A, an inhibitory cell surface receptor covalently bound to CD94, and expressed on tumor infiltrating NK cells and CD8 + T cells, which interacts with HLA-E

Oleclumab is a mAb that binds to CD73 and inhibits production of immunosuppressive adenosine

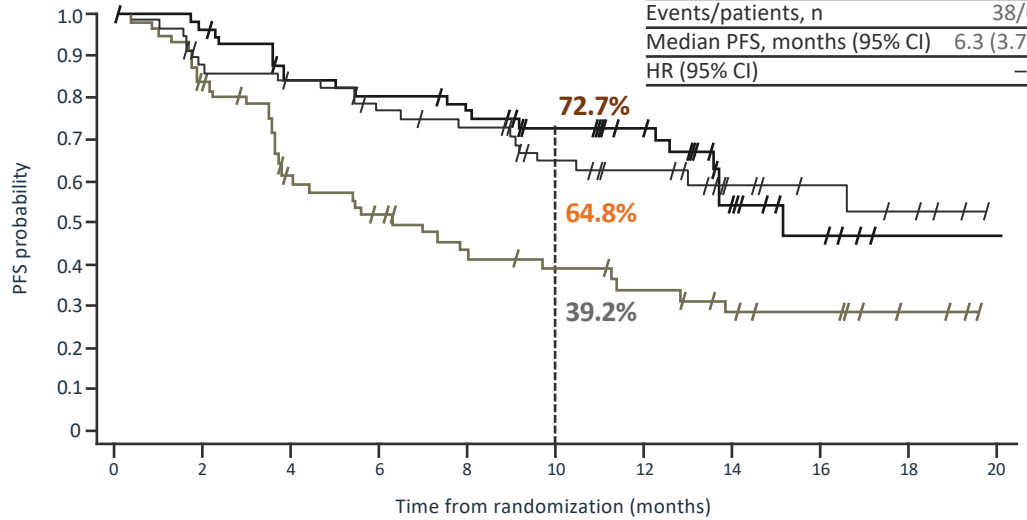
Data cutoff May 17, 2021; all patients had ≥10 months potential follow-up and median follow-up was 11.5 months (range 0.4–23.4; all patients). [a]Oleclumab Q2W for cycles 1 and 2 then Q4W; [b]Investigator assessment by RECIST v1.1. cCRT, concurrent chemoradiotherapy; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NK, natural killer; ORR, objective response rate; PK, pharmacokinetics.

Martinez-Marti A, et al. ESMO 2021. Abstract LBA42. Herbst RA, et al. JCO 2022.

COAST: Investigator assessed PFS

PFS: interim analysis (ITT population)

	Durvalumab	Durvalumab + oleclumab	Durvalumab + monalizumab
Events/patients, n	38/67	22/60	21/62
Median PFS, months (95% CI)	6.3 (3.7, 11.2)	NR (10.4, NE)	15.1 (13.6, NE)
HR (95% CI)	–	0.44 (0.26, 0.75)	0.65 (0.49, 0.85)



No. at risk											
Durvalumab	67	50	32	32	20	16	13	9	7	3	0
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1

ORRs:

- Durvalumab: 18%
- Durvalumab + oleclumab: 30%
- Durvalumab + monalizumab: 36%

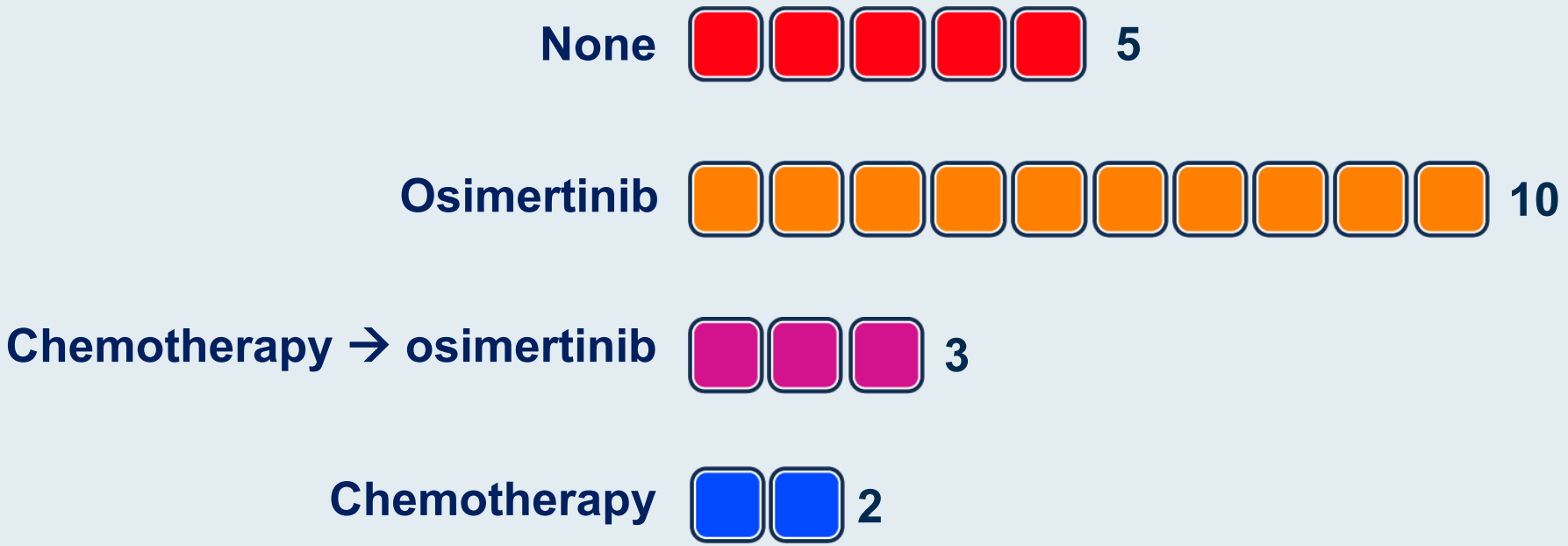
NO SIGNIFICANT INCREASE IN TOXICITY

Data cutoff: May 17, 2021 (median follow-up 11.5 months (range 0.4–23.4)).
ITT, intent-to-treat; NE, not evaluable; NR, not reached; ORR, objective response rate.

Martinez-Marti A, et al. ESMO 2021. Abstract LBA42. Herbst RA, et al. JCO 2022.

MODULE 2: Contemporary Treatment for Localized and Metastatic NSCLC with EGFR Mutations — Dr Yu

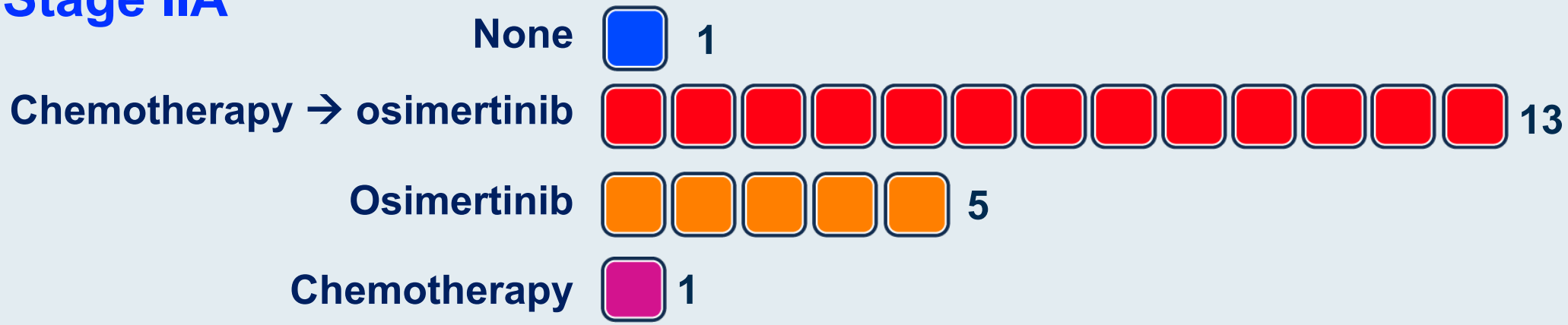
Regulatory and reimbursement issues aside, in general, what adjuvant treatment, if any, would you recommend for an otherwise healthy 65-year-old patient with Stage IB nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 50%?



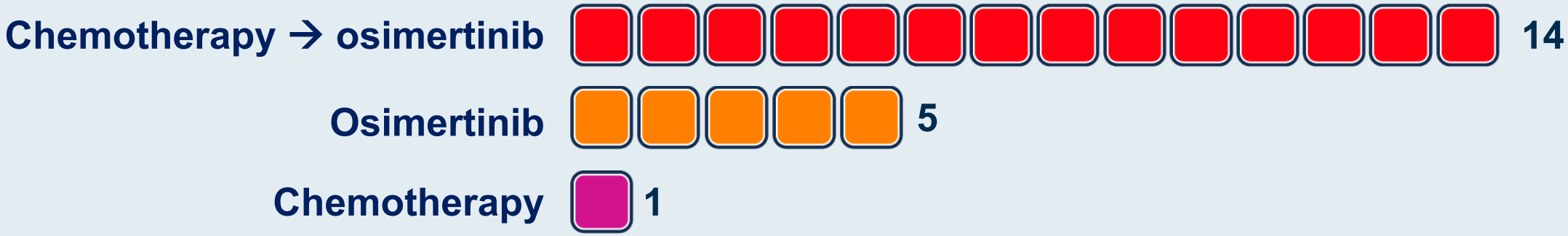
Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, in general, what adjuvant treatment would you recommend for an otherwise healthy 65-year-old patient with nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 50% if...?

Stage IIA

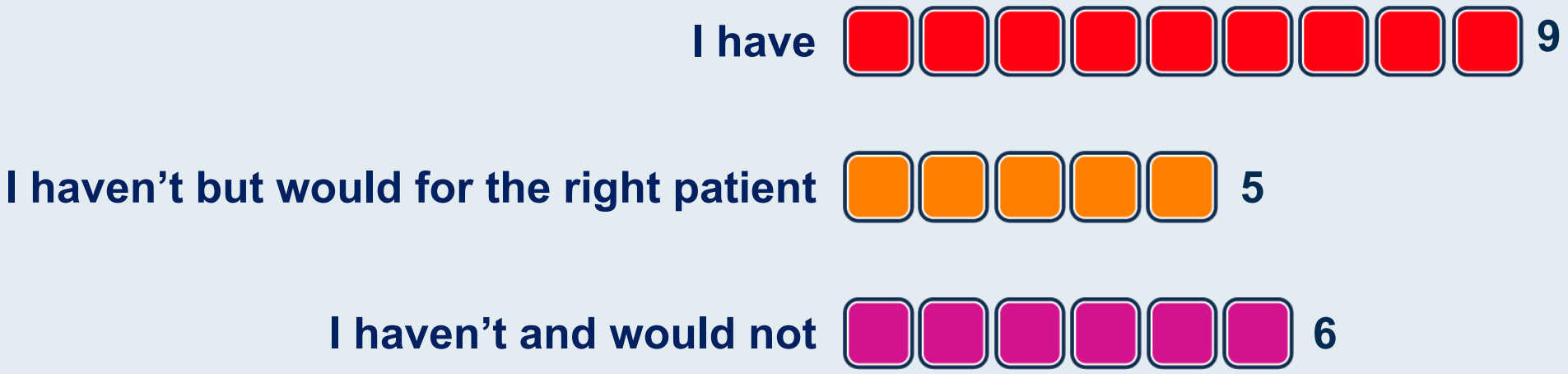


Stage IIIA



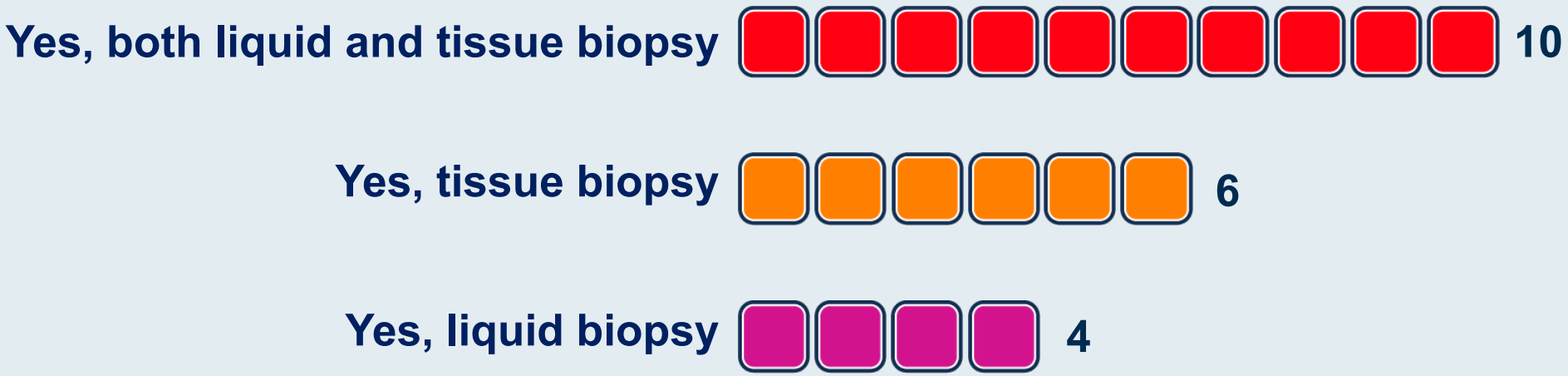
Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, outside of a protocol setting, have you administered or would you administer targeted treatment in the adjuvant setting for a patient with a targetable mutation beyond EGFR?



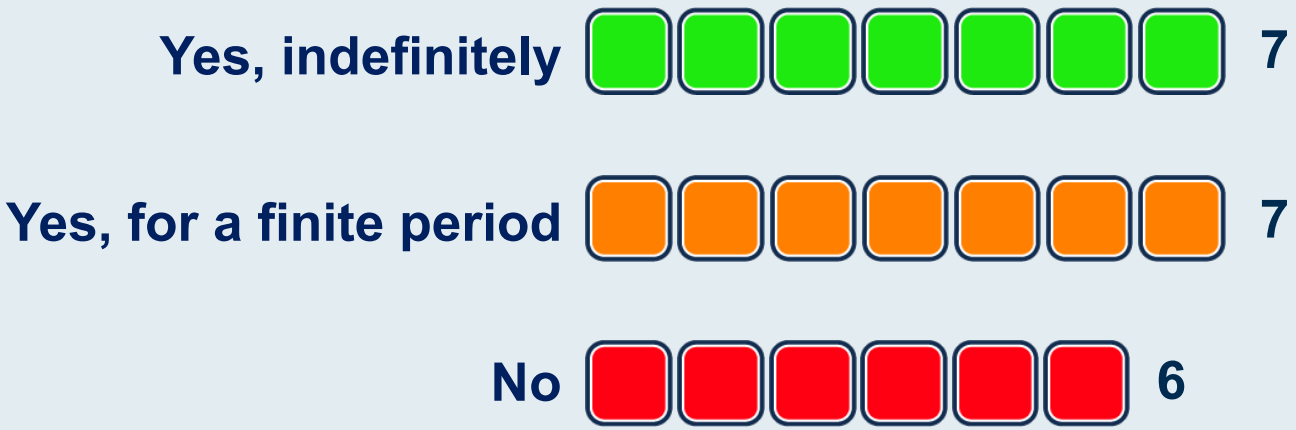
Survey of lung cancer clinical investigators

For a patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 50% who receives first-line osimertinib with response followed by disease progression, would you recommend repeat mutation testing?



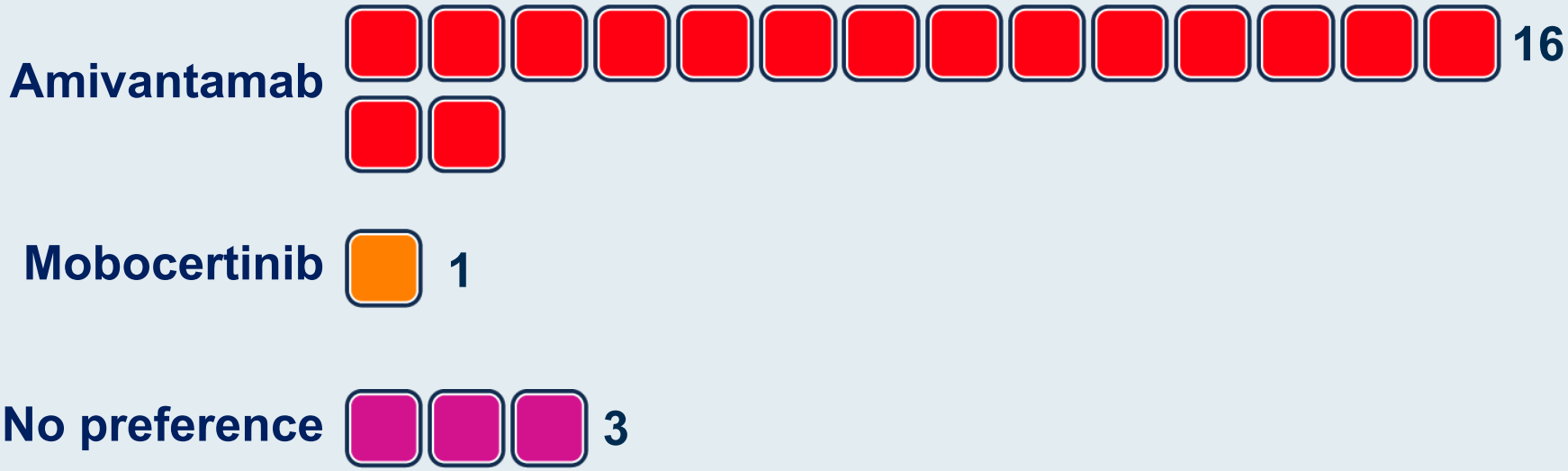
Survey of lung cancer clinical investigators

A patient with nonsquamous NSCLC with an EGFR exon 19 deletion and systemic and brain metastases has a good response to first-line osimertinib but experiences disease progression and is switched to chemotherapy. Would you continue the osimertinib?



Survey of lung cancer clinical investigators

For a patient with metastatic nonsquamous NSCLC with an EGFR exon 20 insertion mutation to whom you've made the determination to administer targeted therapy, which agent do you prefer?



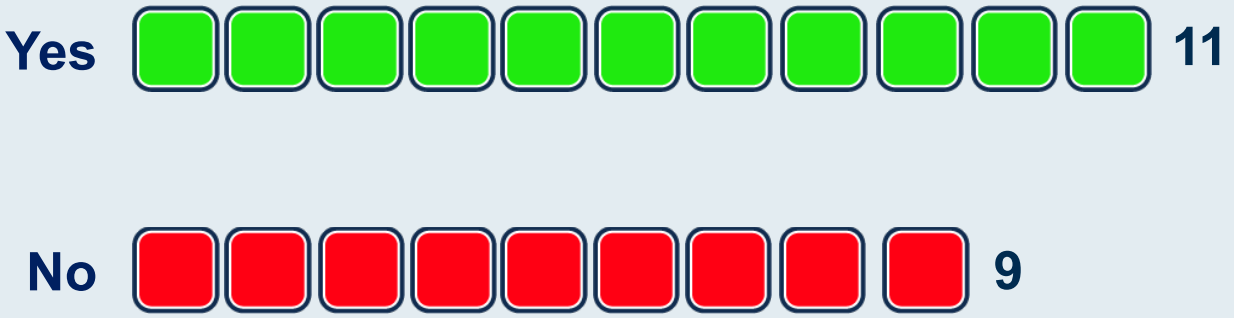
Survey of lung cancer clinical investigators

What are your most important tolerability concerns when a patient is about to begin treatment with…

Amivantamab	**Mobocertinib**
Infusion reaction	Rash
Rash	Diarrhea
Edema	Malaise
Fatigue	Stomatitis
Paronychia	QT prolongation
Mucositis	

Survey of lung cancer clinical investigators

If you could access amivantamab/lazertinib today, would you attempt to administer it prior to chemotherapy in select situations for your patients with metastatic nonsquamous NSCLC with an EGFR mutation experiencing disease progression on osimertinib?



Survey of lung cancer clinical investigators

Memorial Sloan Kettering Cancer Center

Contemporary treatment for EGFR-mutant localized and metastatic NSCLC

Helena Yu, MD
Associate Attending
Research Director, Thoracic Oncology Service
Memorial Sloan Kettering Cancer Center

Outline

- Targeted therapy in early-stage EGFR+ NSCLC
- First-line treatment for metastatic EGFR+ NSCLC
- Mechanisms of resistance to osimertinib
- Targeted therapies after osimertinib
- Treatment of metastatic EGFR exon 20 positive NSCLC

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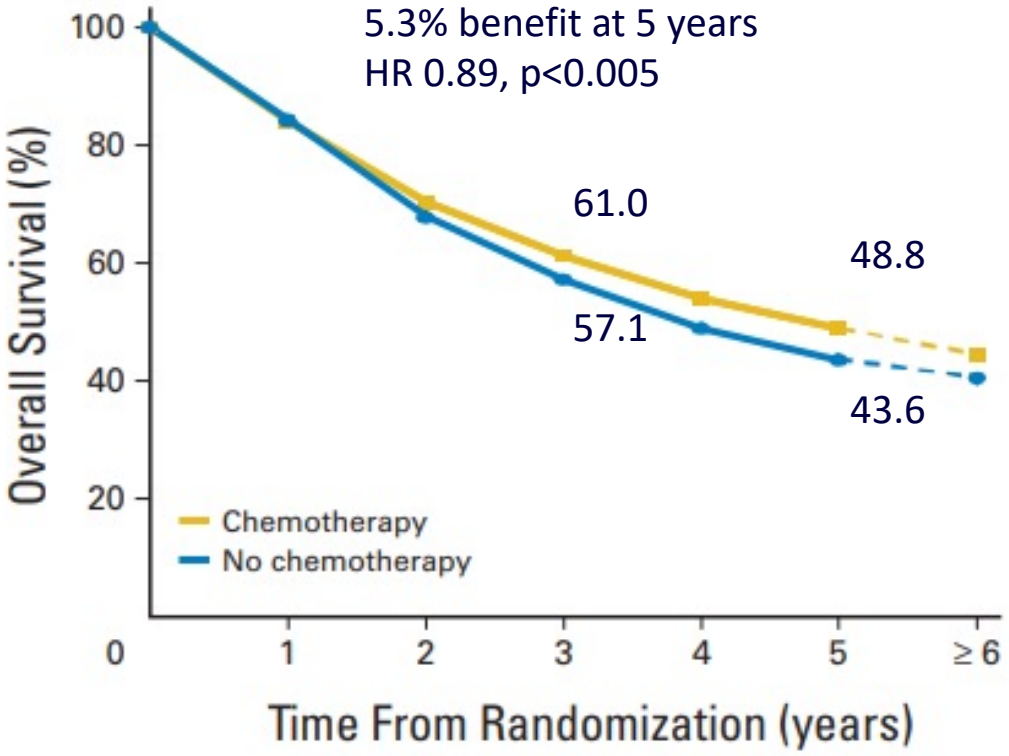
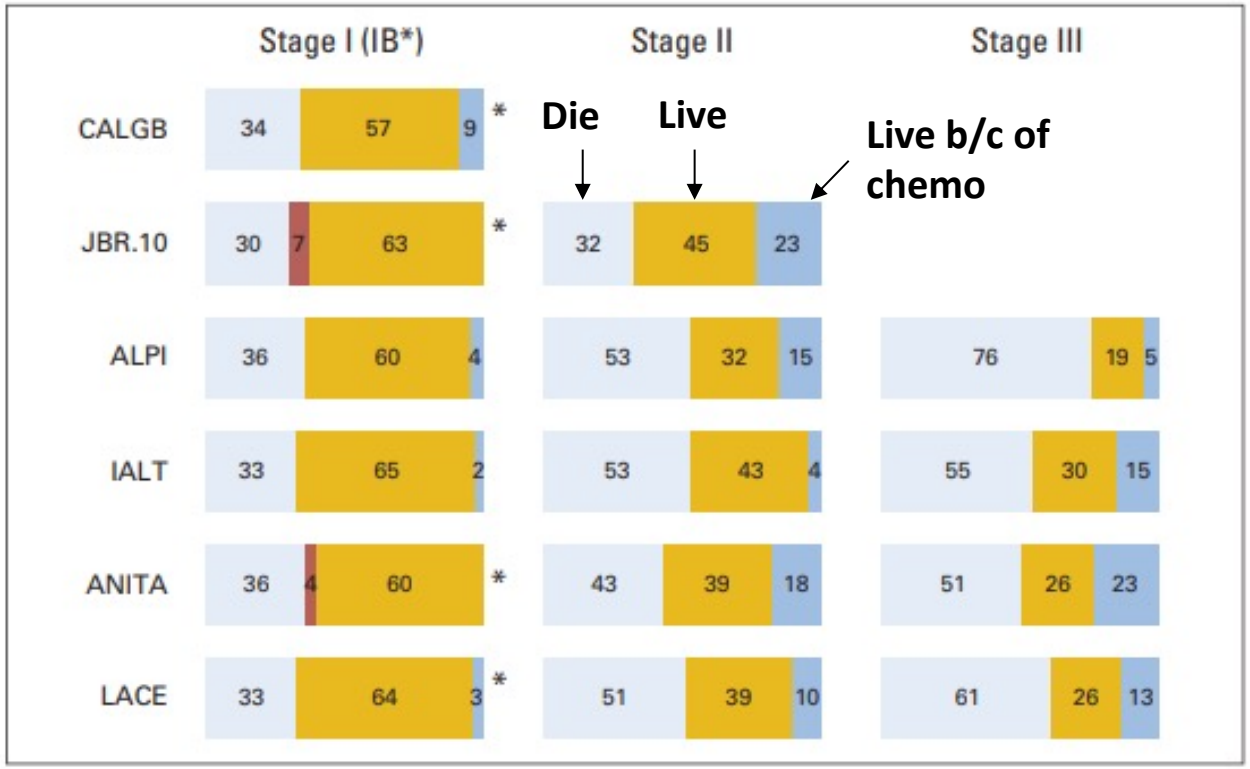
Adjuvant treatment for early-stage disease

Benefit of adjuvant platinum-doublet chemotherapy





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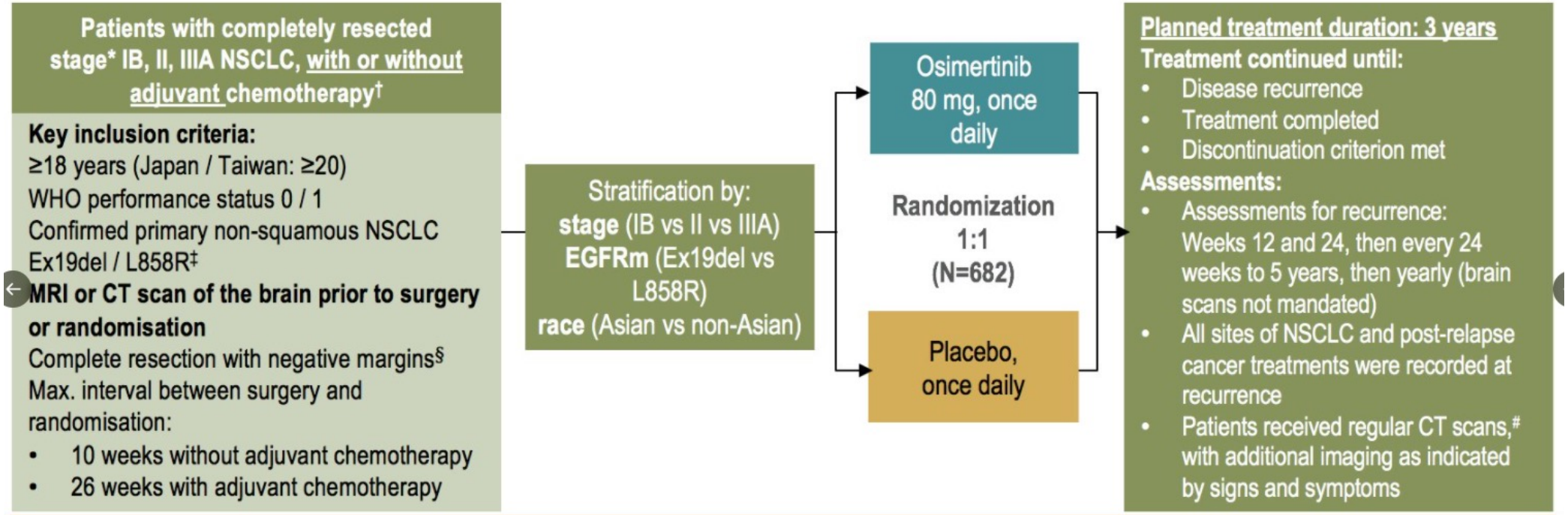
Pignon JCO 2008, Pisters JCO 2008

Osimertinib in early-stage disease

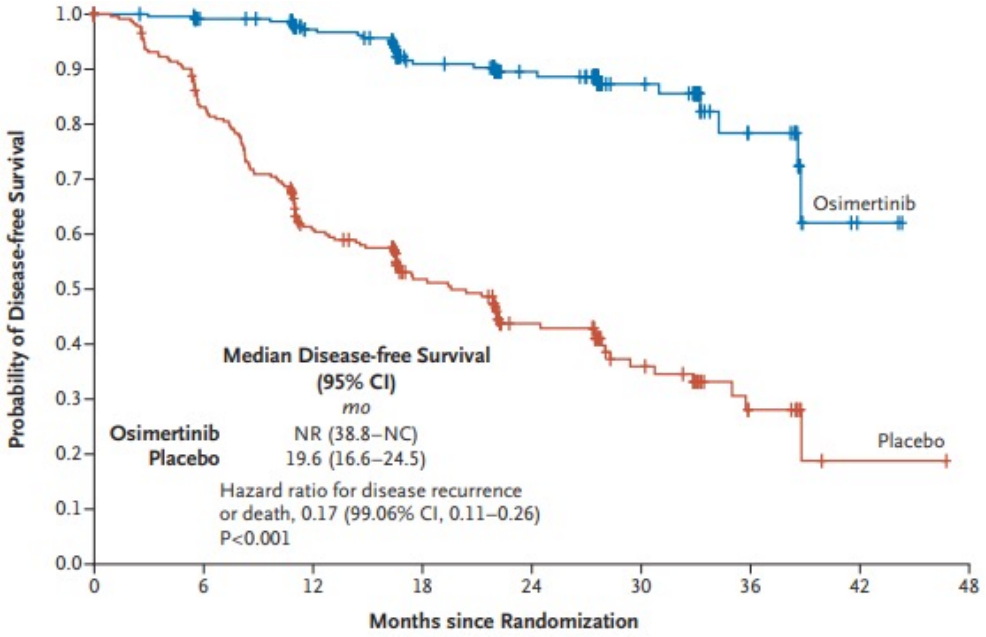
ADAURA: Phase III double-blind study design



- The primary and key secondary endpoints of DFS¶ in stage II/IIIA patients and the overall population, respectively, have been reported previously[1]
- **Here we report results from a pre-specified exploratory analysis of disease recurrence patterns in ADAURA, including CNS**

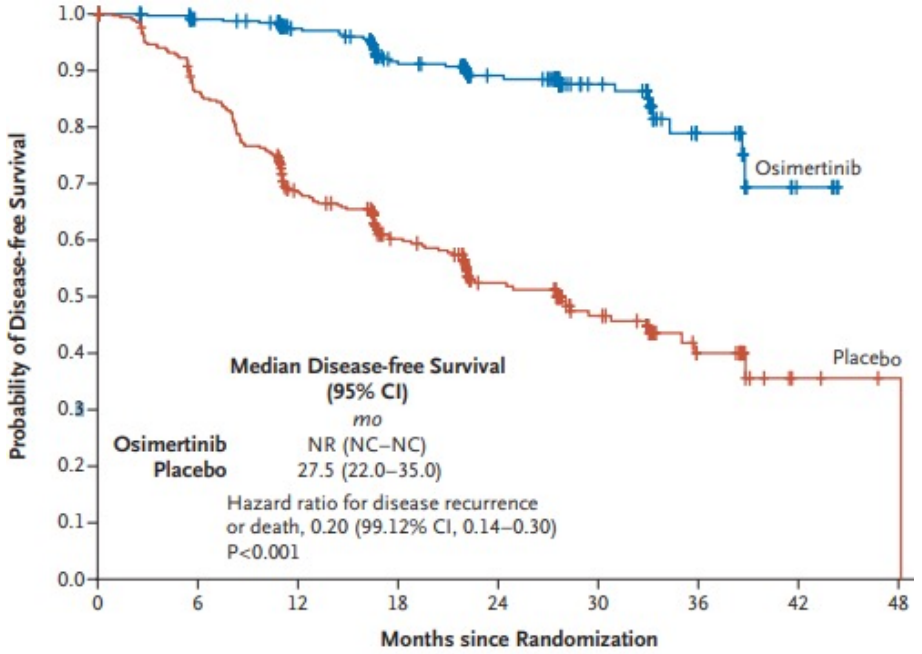
Osimertinib in early-stage disease

Stage 2-3A



	Median DFS, months (95% CI)	HR (99.06% CI)
– Osimertinib	NR (38.8, NC)	0.17 (0.11, 0.26) P<0.0001
– Placebo	19.6 (16.6, 24.5)	

Stage 1B-3A



	Median DFS, months (95% CI)	HR (99.12% CI)
– Osimertinib	NR (NC, NC)	0.20 (0.14, 0.30) P<0.0001
– Placebo	27.5 (22.0, 35.0)	

- Benefit deepened with higher stage but remained across all stages, all subgroups and with/without adjuvant chemotherapy

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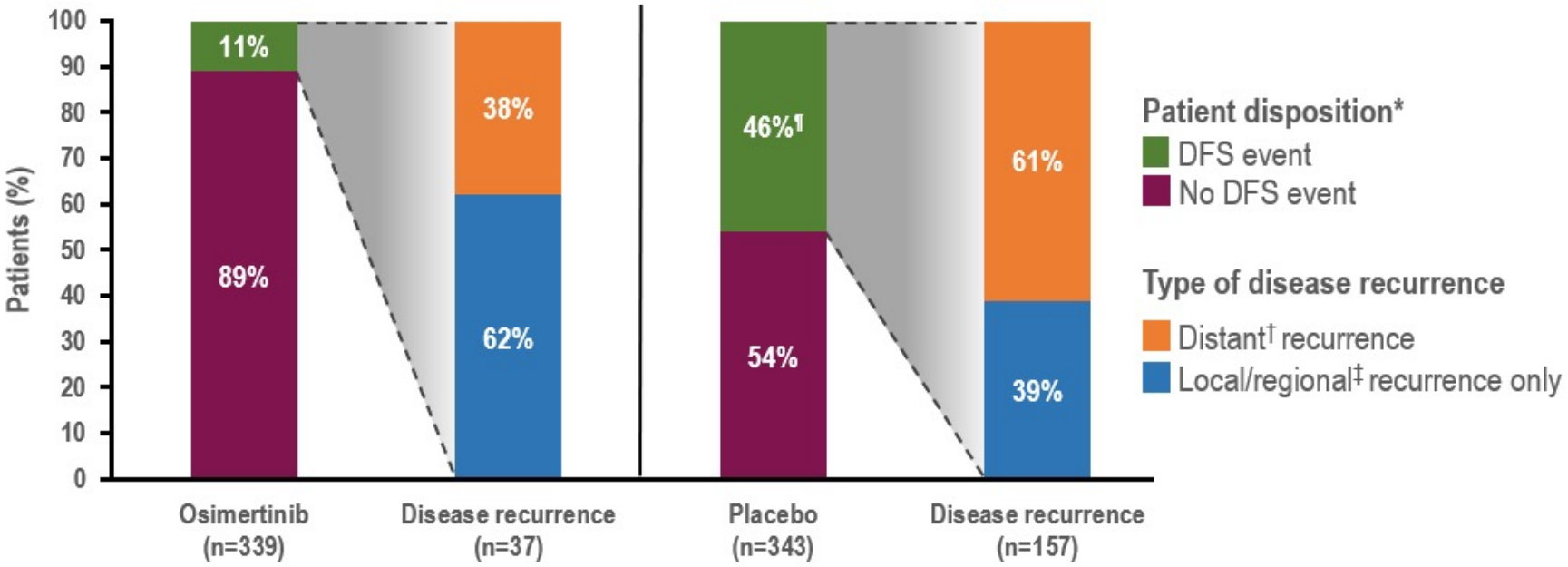
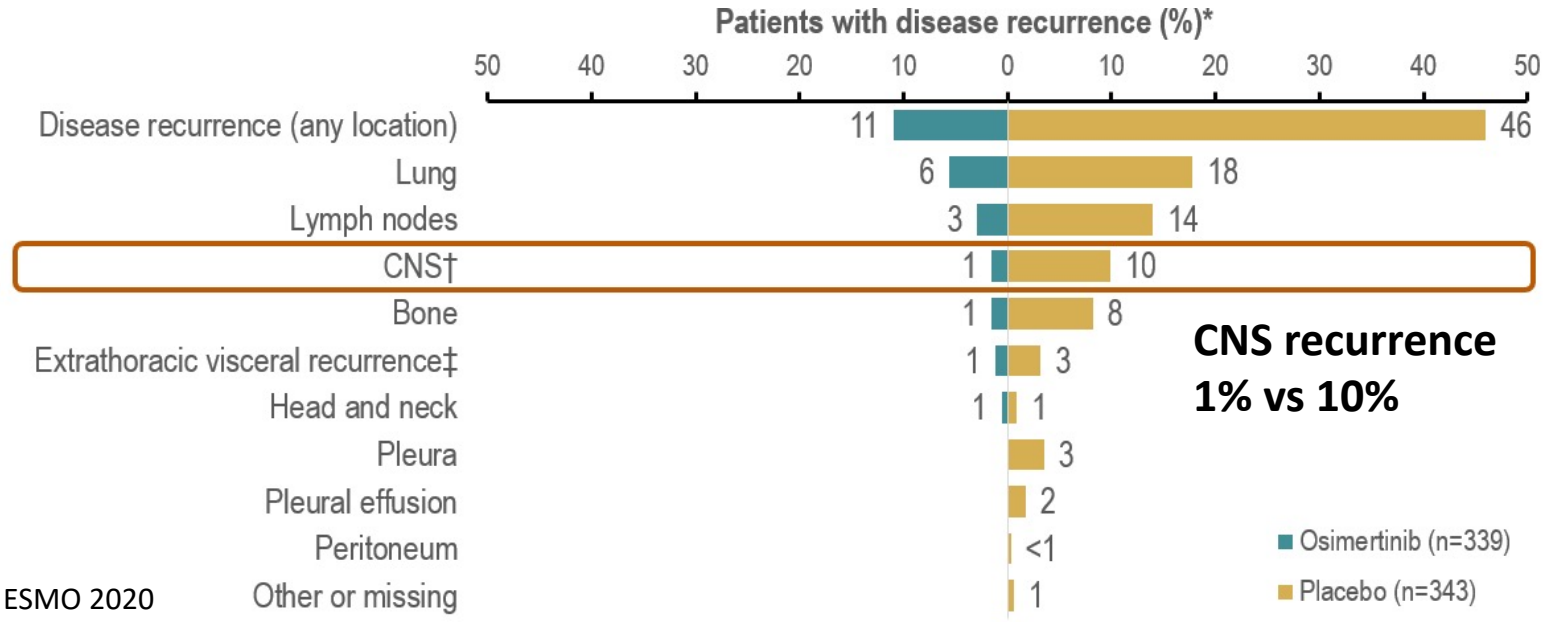
Wu NEJM 2020

Osimertinib in early-stage disease





CNS recurrence
1% vs 10%

Memorial Sloan Kettering Cancer Center

Tsuboi ESMO 2020

Outline

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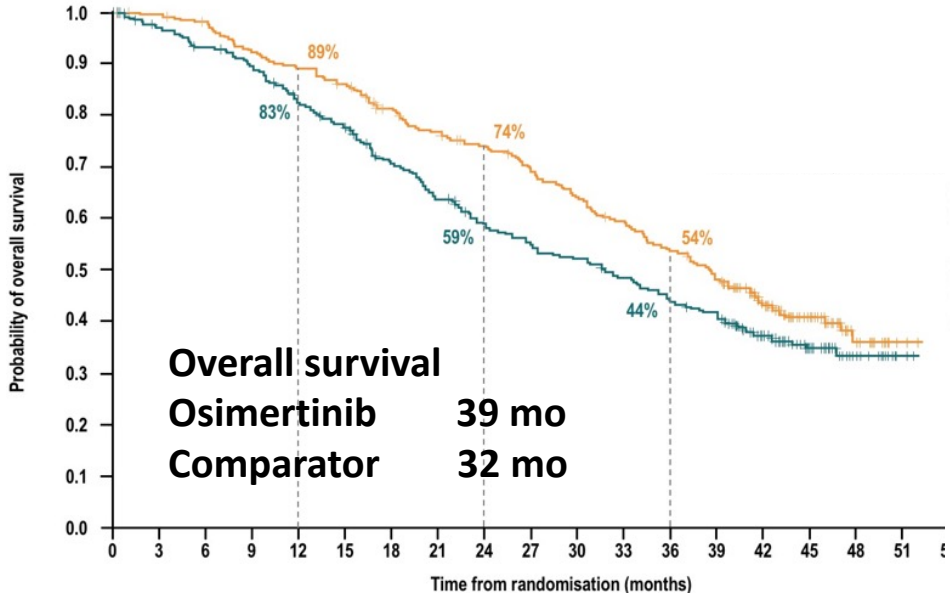
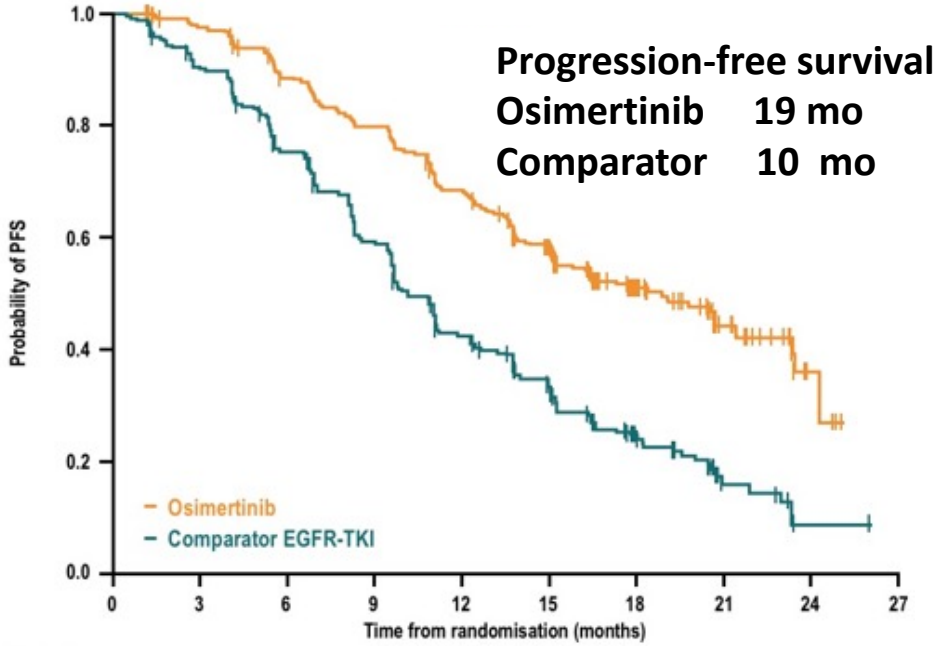
Osimertinib as best in class EGFR TKI





- Osimertinib is a third-generation, irreversible, mutant-specific EGFR TKI
- Osimertinib initially approved for use after earlier generation EGFR TKIs with acquisition of EGFR T790M
- Improved PFS and OS compared to earlier generation EGFR TKIs
- Even so, PFS and OS still relatively short with acquired resistance a certainty

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Soria NEJM 2018, Ramalingam ESMO 2019

Osimertinib better at treating and preventing CNS metastases

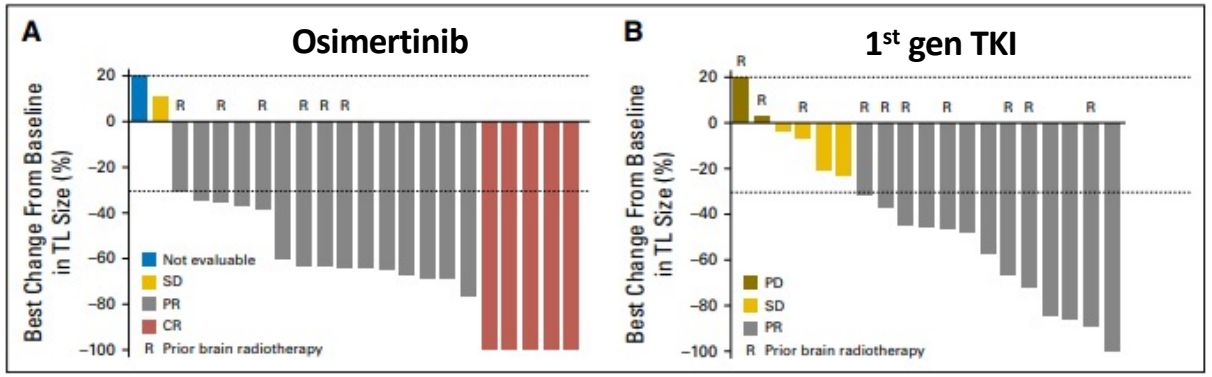
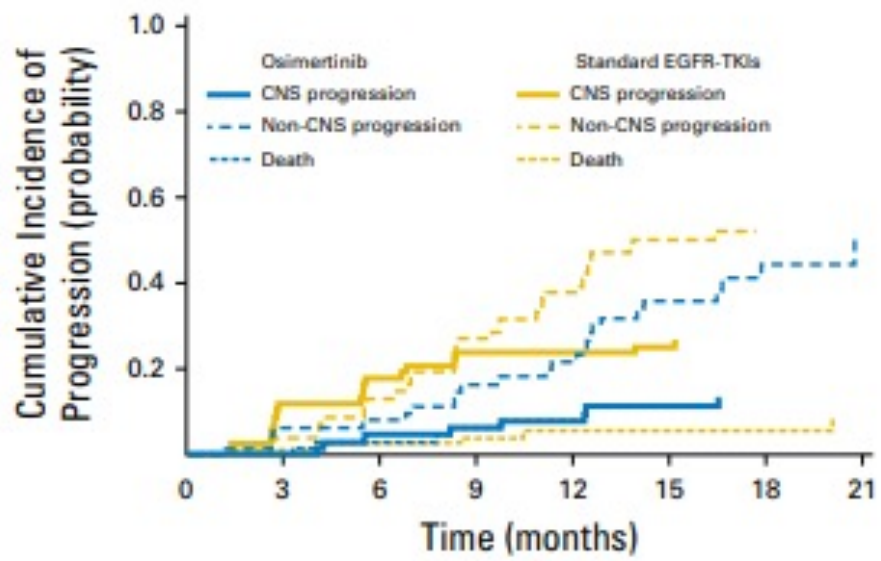


Fig 3. Best percentage change from baseline in CNS target lesion (TL) size (cEFR) with (A) osimertinib and (B) standard epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs).



CNS Progression
Osimertinib: 20%
1st gen TKI: 39%

- FLAURA assessed osimertinib vs SOC TKI as 1st line treatment (mPFS 19 vs 10mo)
- Baseline MRI not mandated, and interval MRIs only in pts with known BM (128 with BM/200 baseline scan/556 total pts)
- Rate of symptomatic CNS PD lower with osimertinib (15 vs 6%)
- CNS progression was mostly in new lesions

Evaluation of new therapies should include routine CNS imaging as CNS efficacy is a key factor in treatment choice. Lack of routine imaging seriously limits interpretation.

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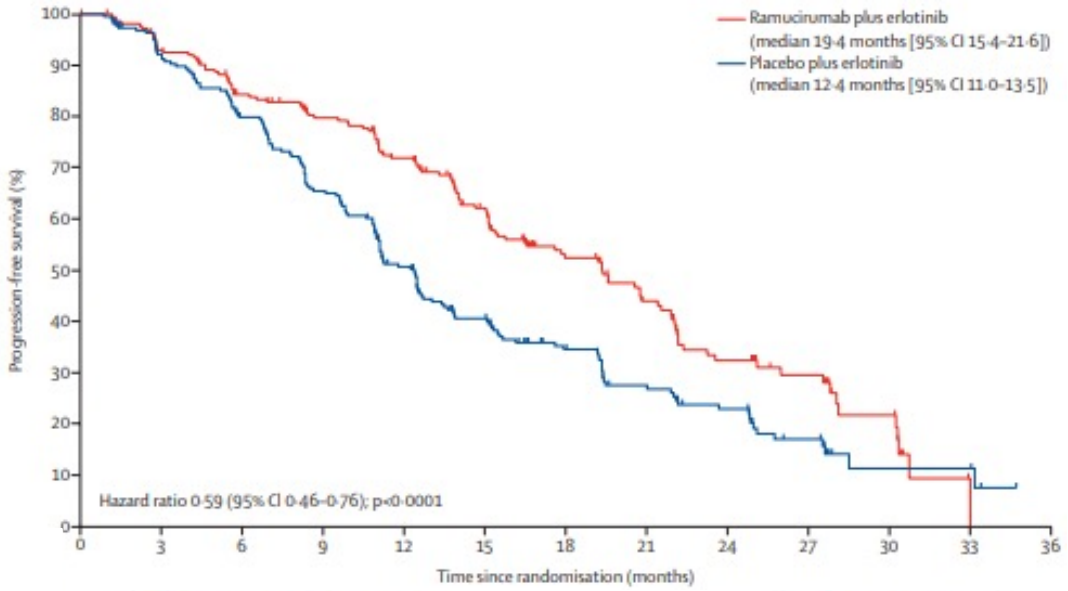
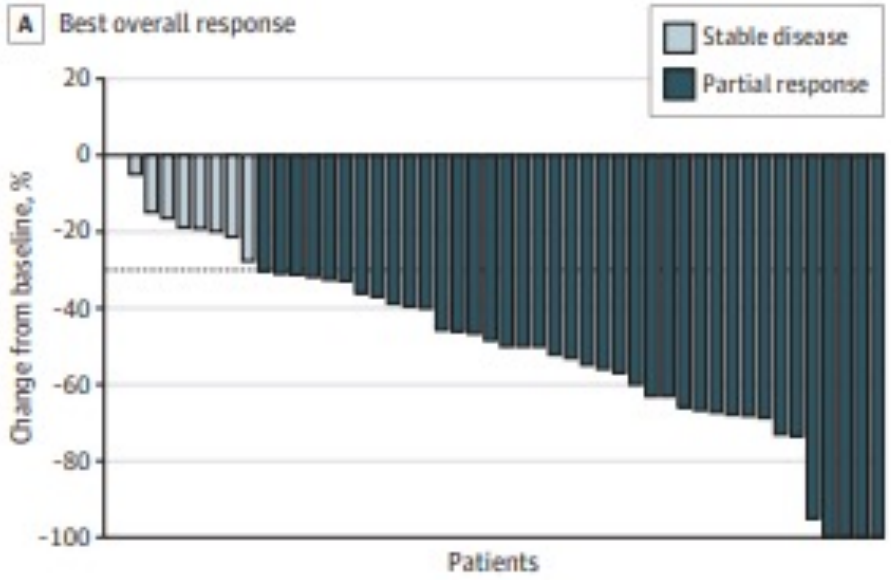
Soria 2018, Reungwetwattana 2018

Osimertinib first-line combinations - VEGF





- Erlotinib and bevacizumab in Phase 2/3 studies have demonstrated clear PFS but no OS benefit
- Erlotinib and bevacizumab has approval in EU, Japan
- Erlotinib and ramucirumab in phase 3 study demonstrated improved PFS compared to erlotinib alone (19.4 vs 12.4mo) leading to US approval
- Osimertinib and bevacizumab single-arm Phase 1 study demonstrated safety and feasibility

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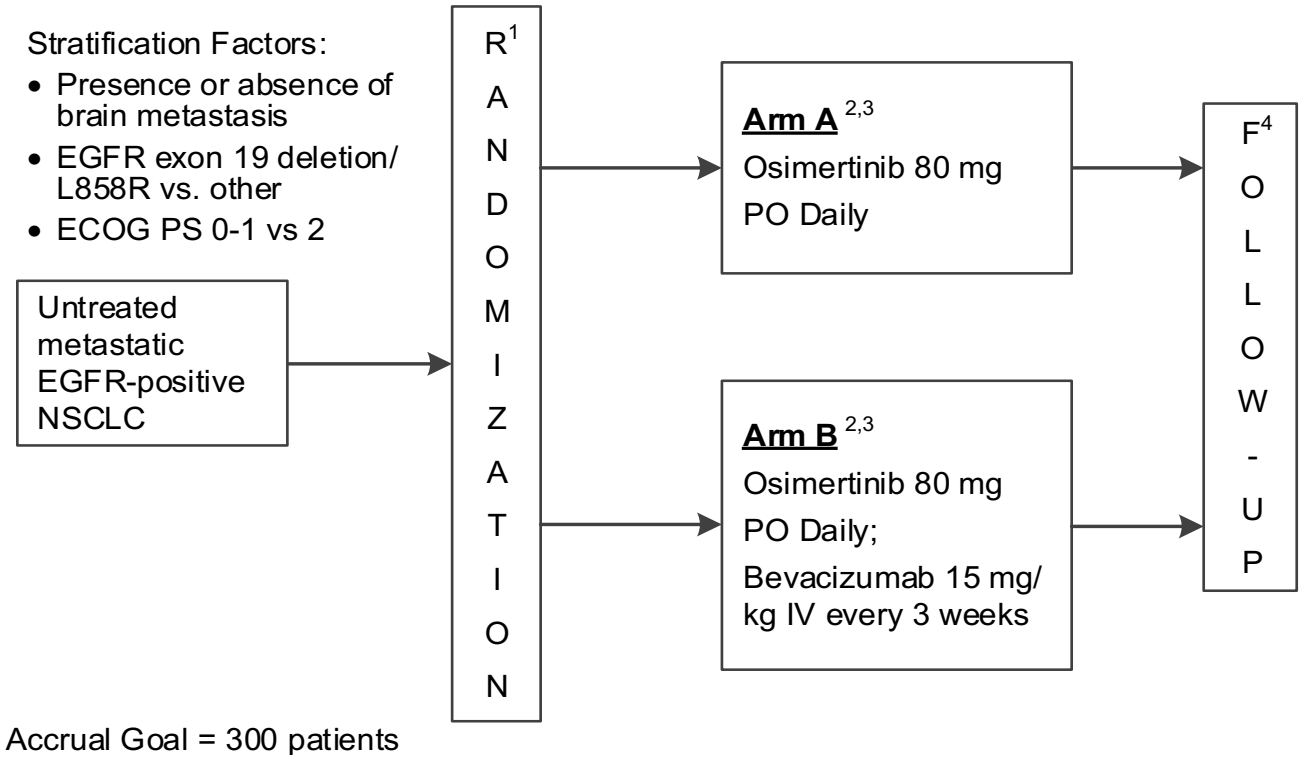
Nakagawa Lancet Onc 2019 Yu JAMA Onc 2020

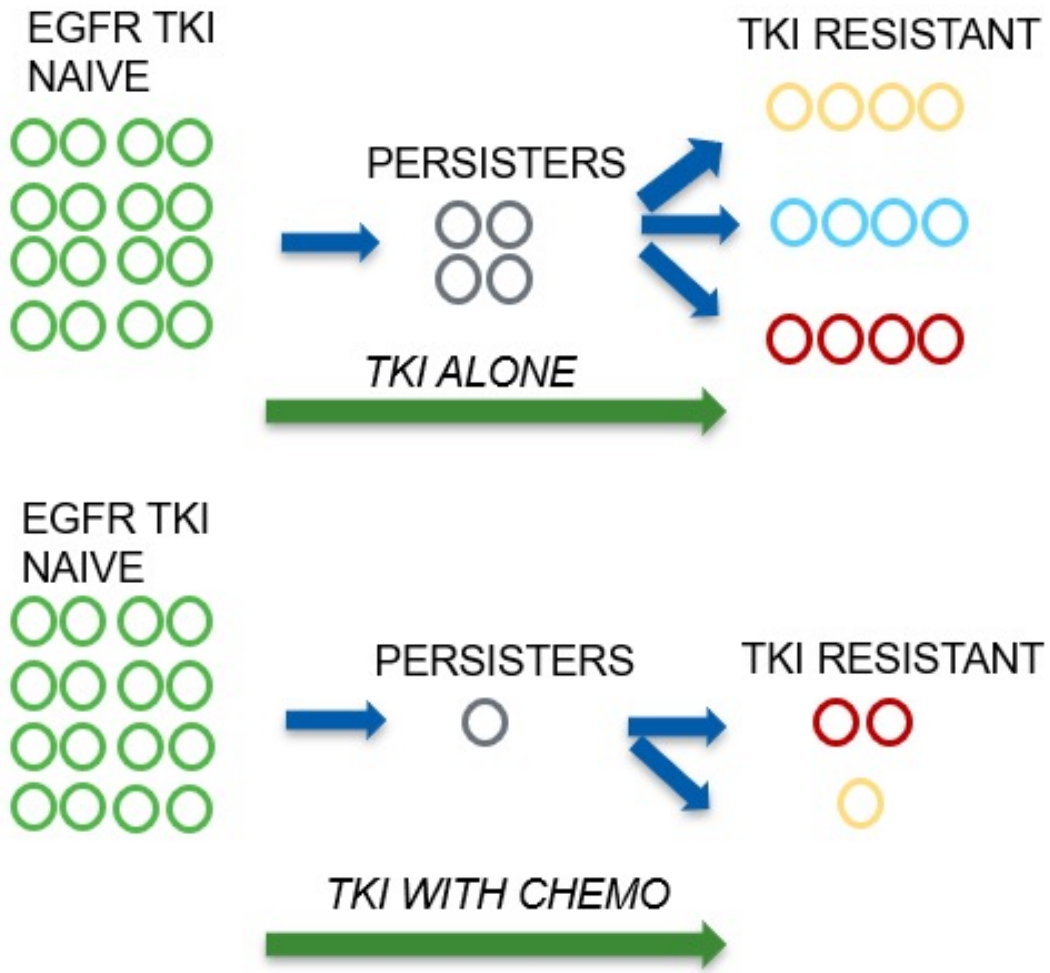
Osimertinib first-line combinations - VEGF

EA5182



- Multiple studies assessing EGFR TKI +/- VEGF inhibitor in the first-line setting
- EA5182 is assessing osimertinib vs osimertinib/bevacizumab. Hoosier Oncology study assessing osimertinib vs osimertinib/ramucirumab
- Study allows for CNS metastases and interval MRI imaging will be obtained
- Ongoing randomized studies will definitively demonstrate whether there is utility in EGFR TKI/VEGF inhibition combination

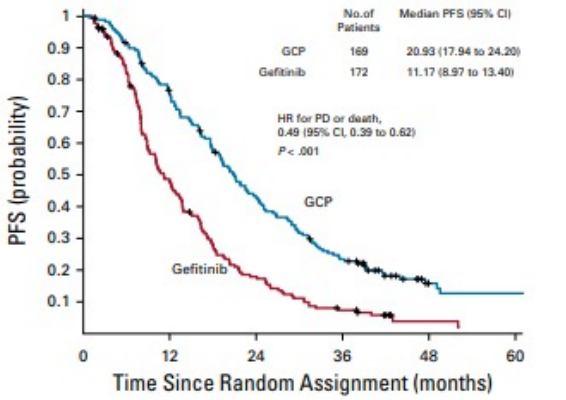
Osimertinib first-line combinations - Chemo



- To combine two active therapies, there needs to be clear improvement in PFS more than the sum of sequencing OR improvement in overall survival
- EGFR TKI and chemotherapy combination therapy may further eradicate subclones that survive EGFR TKI monotherapy (PERSISTERS)
- Studies with earlier gen EGFR TKIs suggest improvement in OS with the combination suggesting that further eradication of persister subclones changes natural history

Osimertinib first-line combinations - Chemo

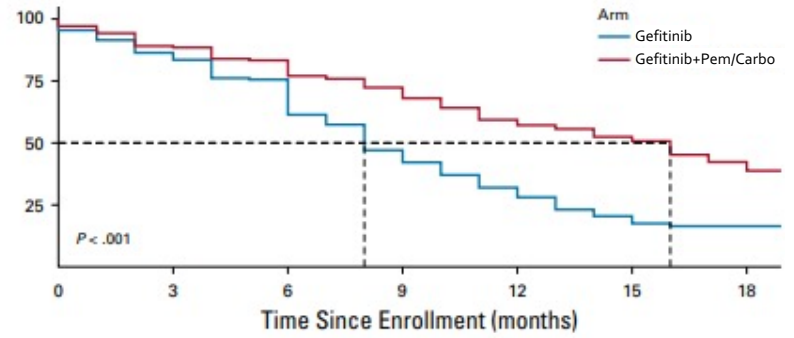
Hosomi JCO 2019, Noronha JCO 2019

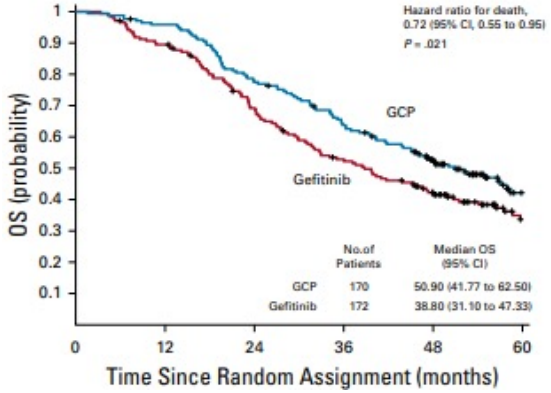


PFS

NEJ009: 11 vs 21 mo (HR 0.49)

Tata: 8 vs 16 mo (HR 0.51)

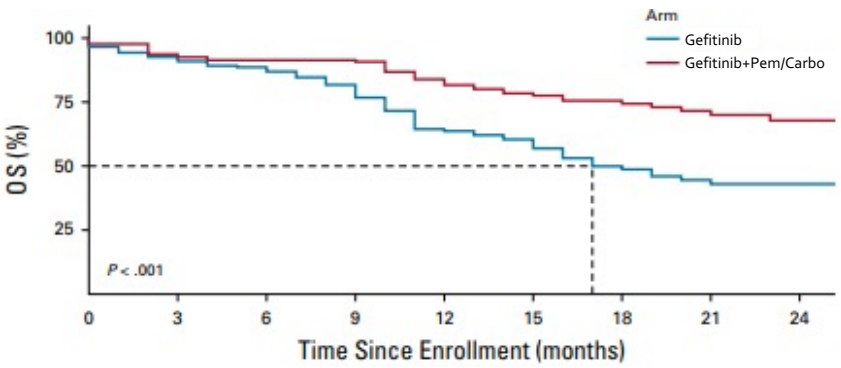




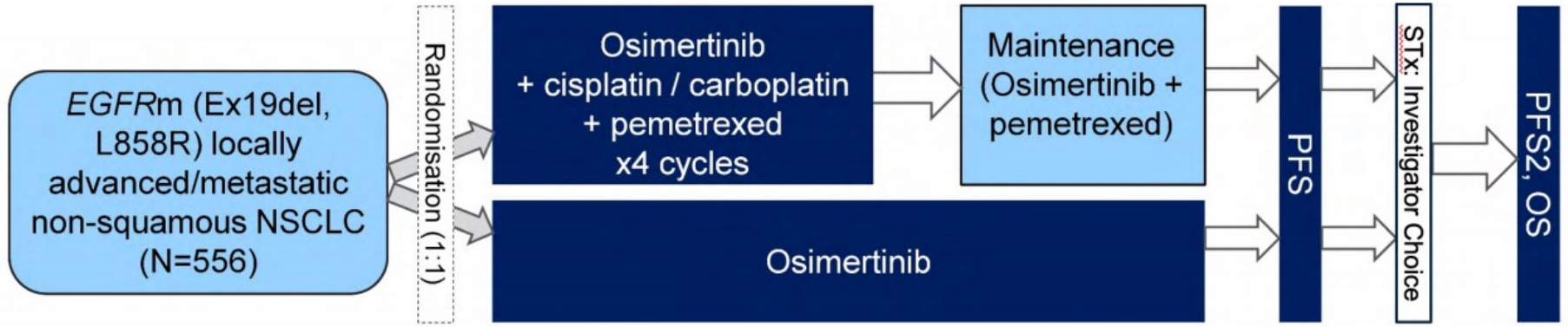
OS

NEJ009: 39 vs 51mo (HR 0.72)

Tata: 17 v NR (HR 0.45)



FLAURA2



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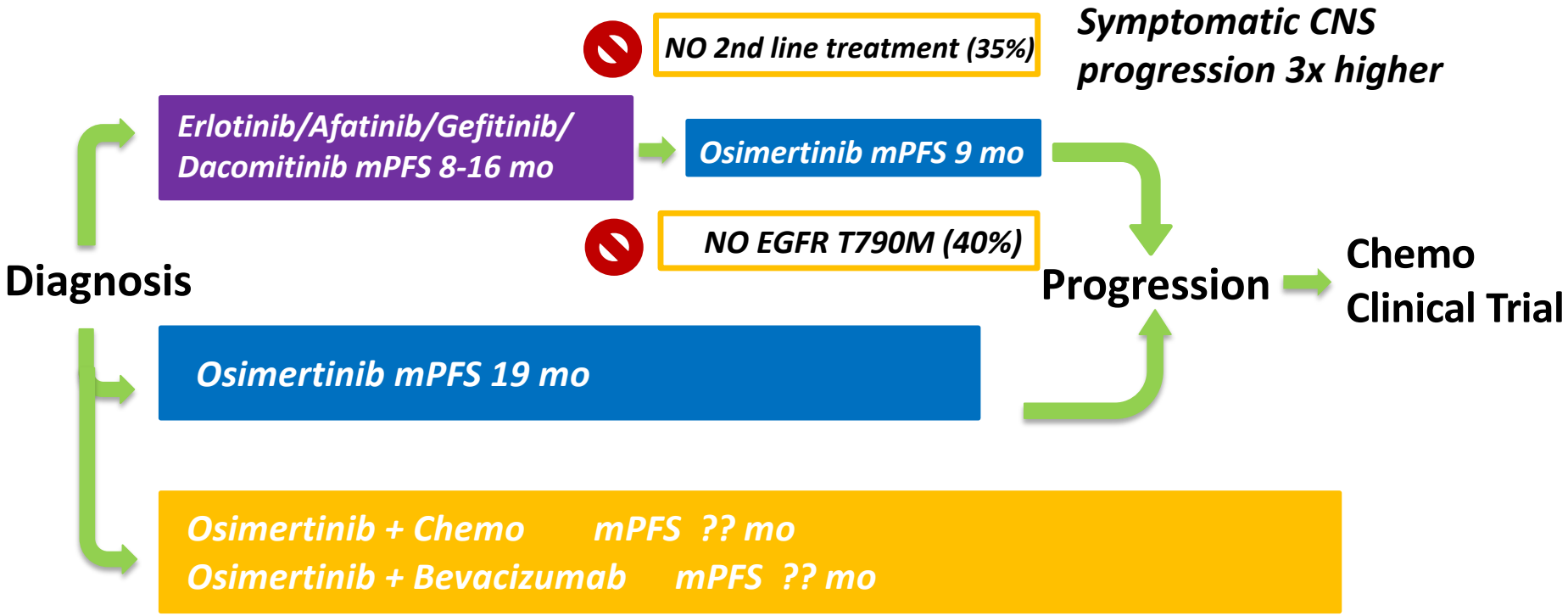
Sequencing therapy



- *Always give your best treatments first. Not everyone gets second line treatment*
- *No approved targeted agents after osimertinib, but that's the case either way*
- *Osimertinib with better CNS efficacy*

Outline

- Targeted therapy in early-stage EGFR+ NSCLC
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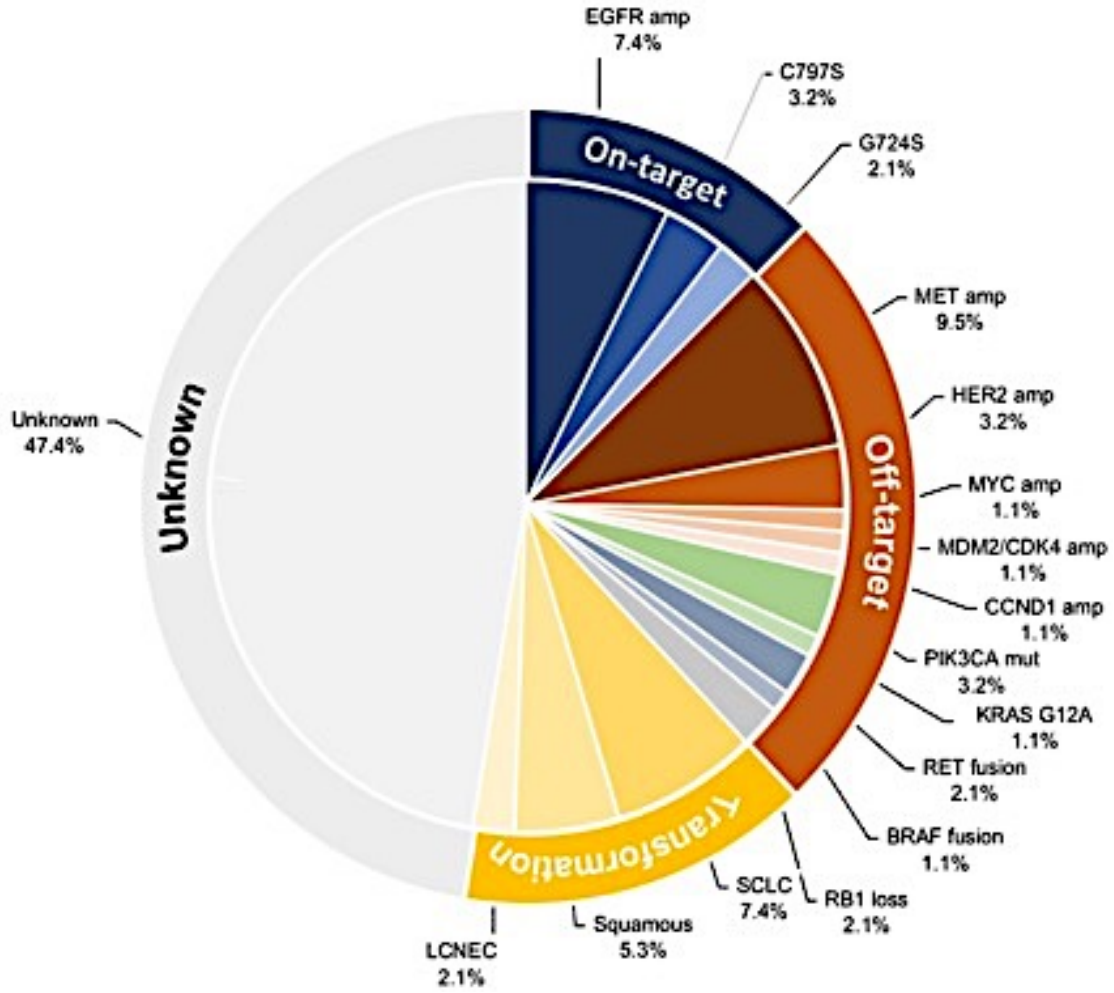
- Targeted therapies after osimertinib
- Treatment of metastatic EGFR exon 20 positive NSCLC

Mechanisms of resistance to first-line osimertinib



- Mechanisms of resistance to first-line osimertinib are diverse, with no dominant mechanism so upfront combinations to prevent resistance not appropriate without a biomarker
- With development of better EGFR inhibitors, there is more off target resistance seen
- High incidence of lineage plasticity including both small cell and squamous transformation
- Frequent acquired gene alterations such as gene fusions which are rare de novo
- There will be a role for non-biomarker selected therapies that focus on enhanced EGFR on-target inhibition or address general tumor biology

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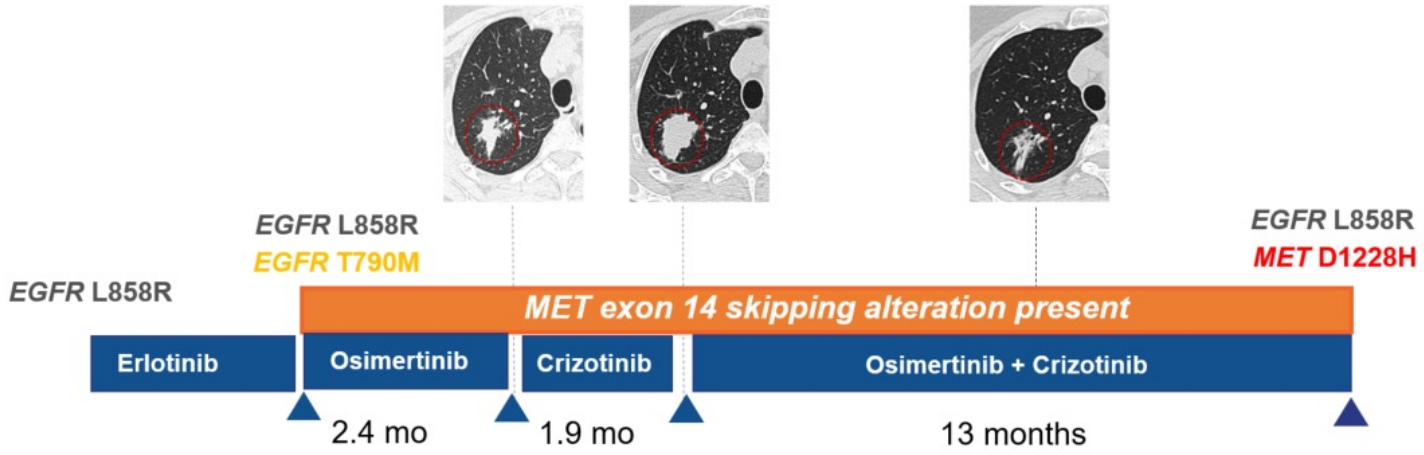
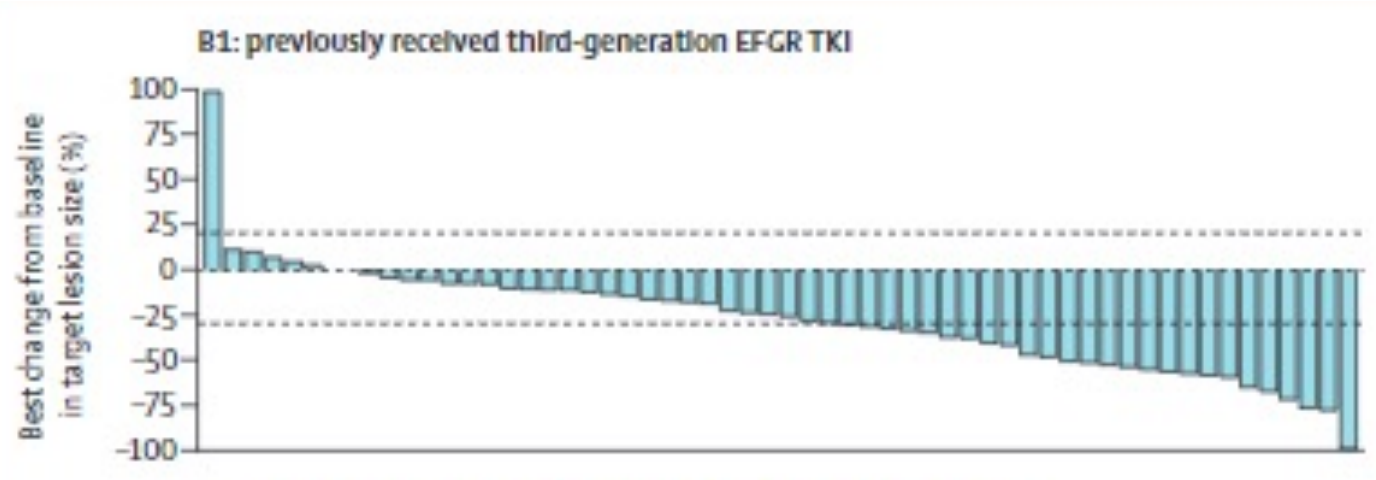
Yu, submitted paper

Mechanisms of resistance to osimertinib

On target	EGFR 2nd mtn: 1st/2nd gen EGFR TKI
Off target	MET amp: crizotinib, capmatinib
	RET fusion: selpercatinib
	ALK fusion: alectinib
	BRAF mtn: trametinib +/- dabrafenib
	HER2 amp/mtn: T-DM1, TDXd
None identified	Chemo or clinical trial
Lineage plasticity	SCLC transform: chemo
	Squamous transform: chemo

Acquired MET amplification/mutation drives resistance to osimertinib





- Approved/available MET inhibitors include crizotinib, tepotinib and capmatinib
- Osimertinib and savolitinib studied in TATTON study with relevant cohort that received prior 3rd gen EGFR TKI (57% had 3 or more prior treatments)
- ORR was 30%, median PFS 5.4 months
- Multiple studies ongoing looking at osimertinib + MET inhibitor combination (tepotinib NCT03940703, savolitinib SAVANNAH NCT03778229, ORCHARD NCT03944772)

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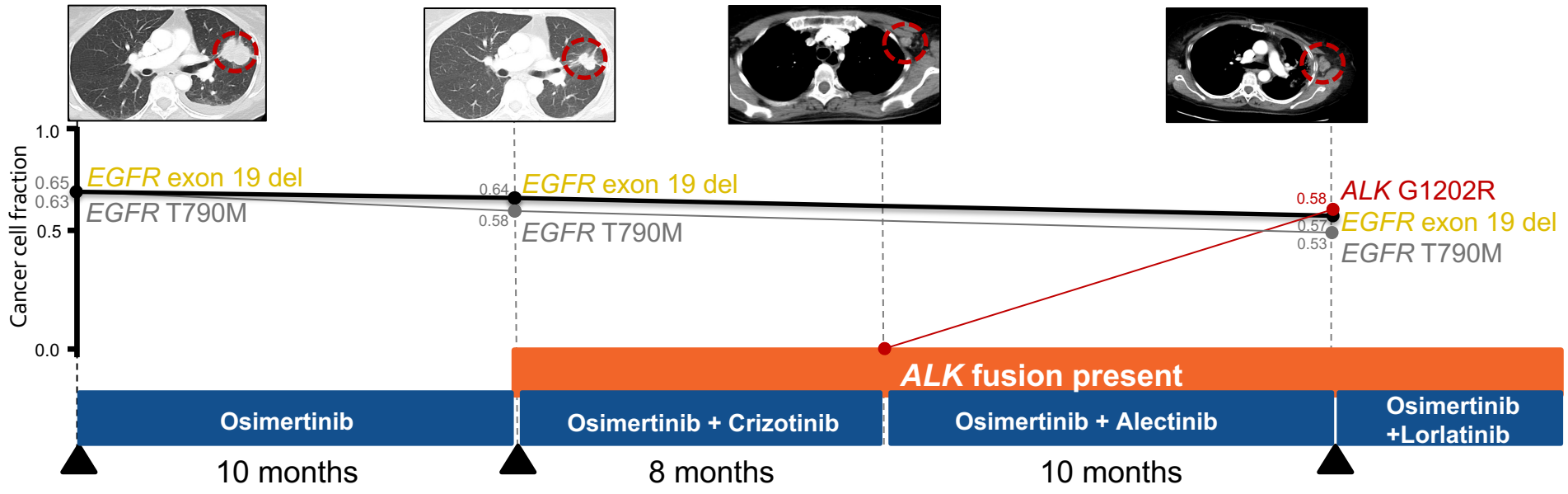
Sequist Lancet Onc 2020, Suzawa JCO PO 2019

Acquired ALK fusion drives resistance to osimertinib

Combined inhibition of *ALK* and *EGFR* overcomes *ALK*-mediated resistance



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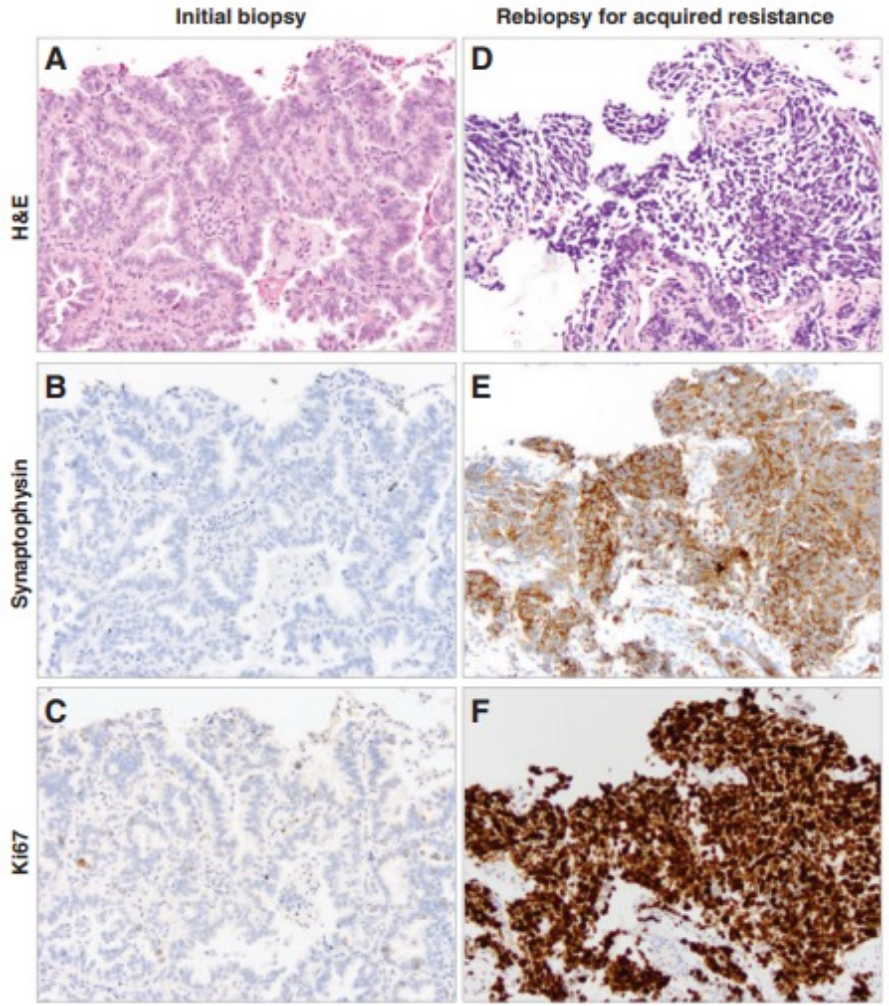
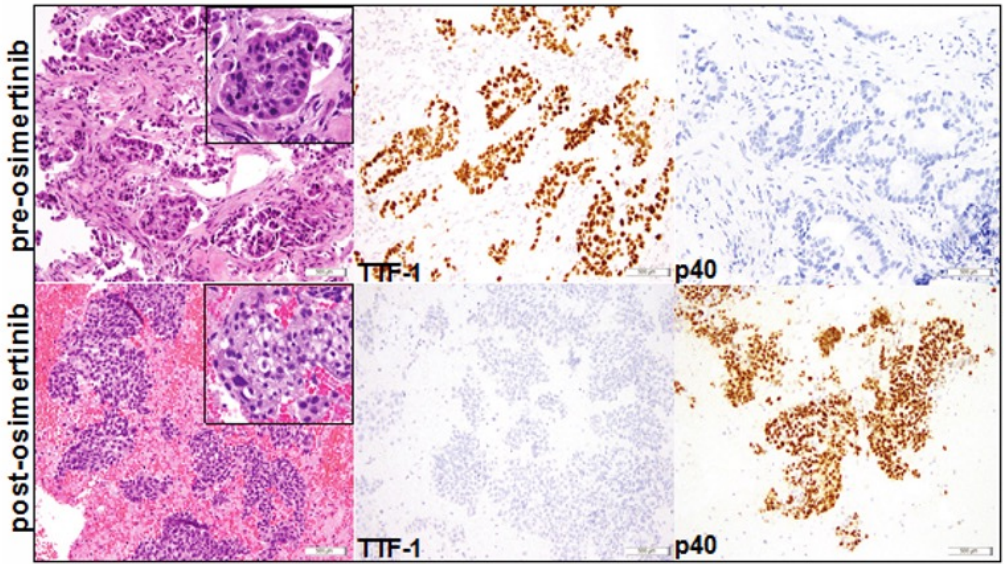
Schoenfeld CCR 2020

Histologic transformation

Small cell transformation



Squamous cell transformation



-With first-line osimertinib, we see more lineage plasticity (~15%). This is a complete histologic transformation that makes the tumor no longer dependent on EGFR signaling.
-Once transformation occurs, outcomes are poor (median OS 10.9mo) and treatment options limited. Work ongoing to try to prevent transformation.
-Presence of EGFR/TP53/RB1 alterations increases risk.

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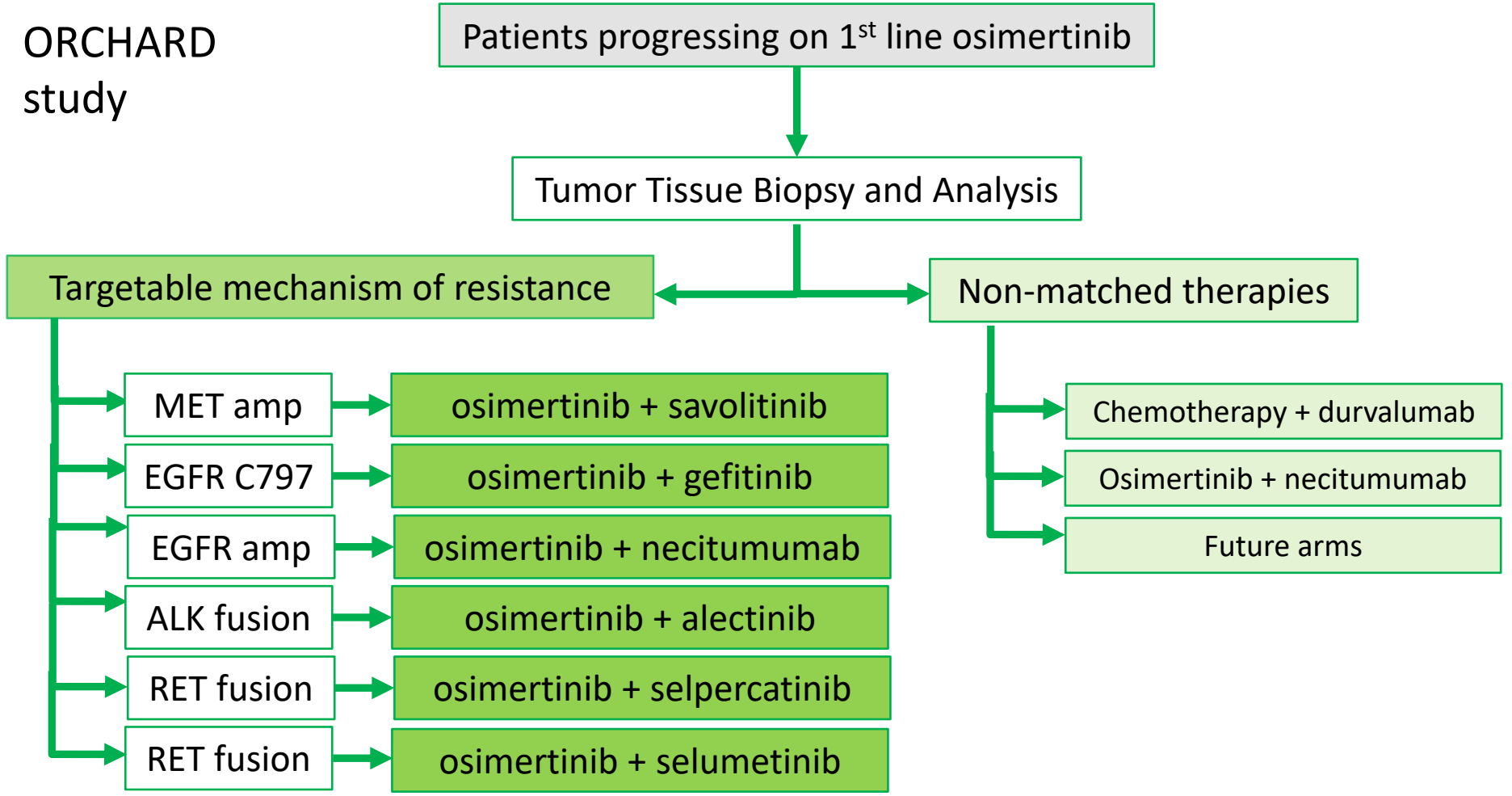
Yu CCR 2013, Schoenfeld CCR 2020

Exploring biomarker-driven treatment of osimertinib resistance

ORCHARD study



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MSK IRB# 19-312, NCT03944772
Global PI: Yu

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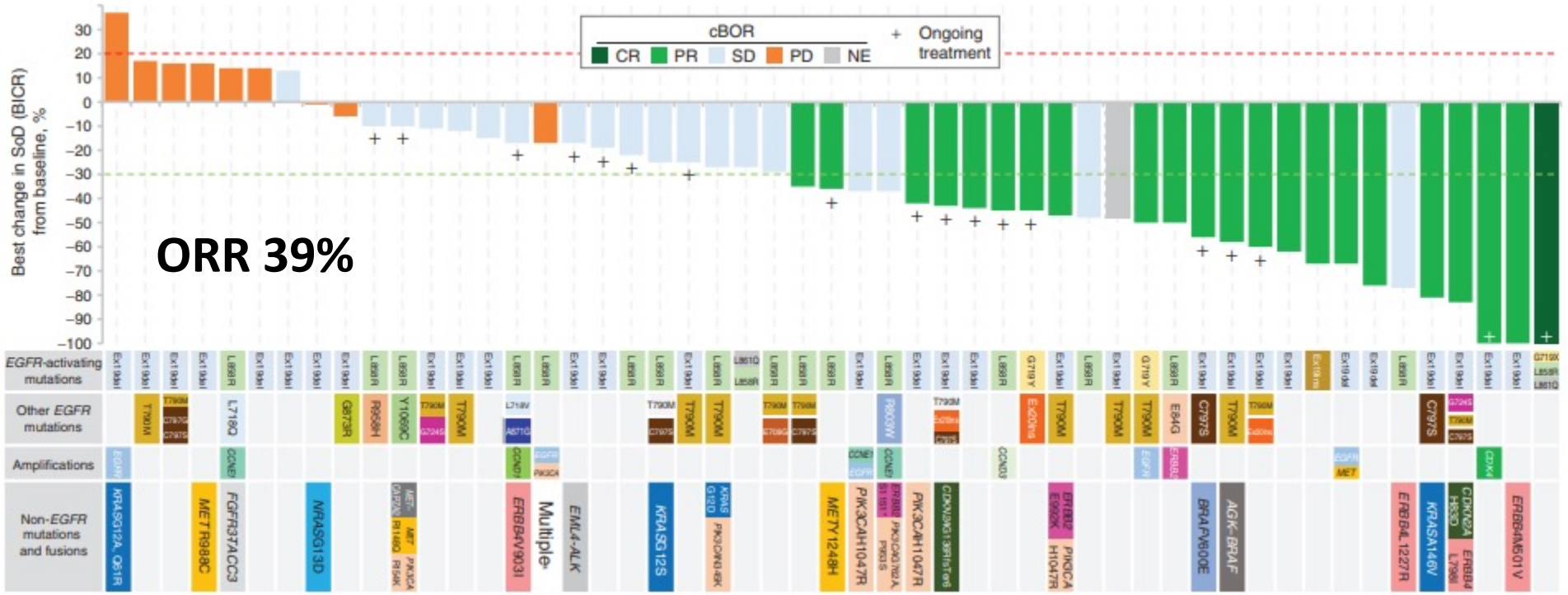
Treatments post osimertinib: Patritumab deruxtecan



- Platinum-based chemotherapy is the standard of care post osimertinib.
- HER3-DxD is a HER3-directed antibody drug conjugate. HER3 is expressed in the majority of EGFR-mutant NSCLCs.
- After osimertinib and after chemotherapy, patritumab deruxtecan was active.
- It is now being assessed in further studies as monotherapy and in combination with osimertinib.

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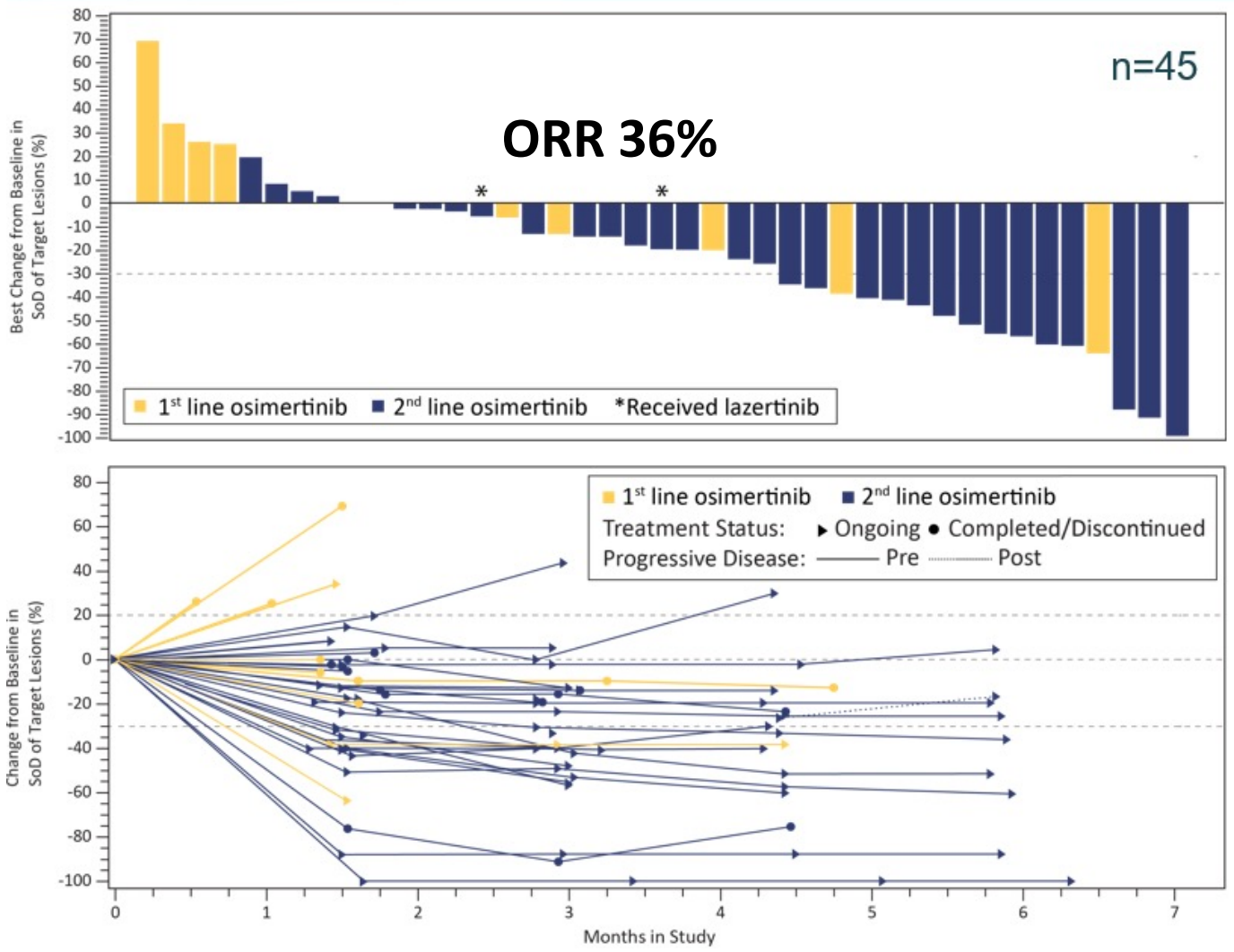
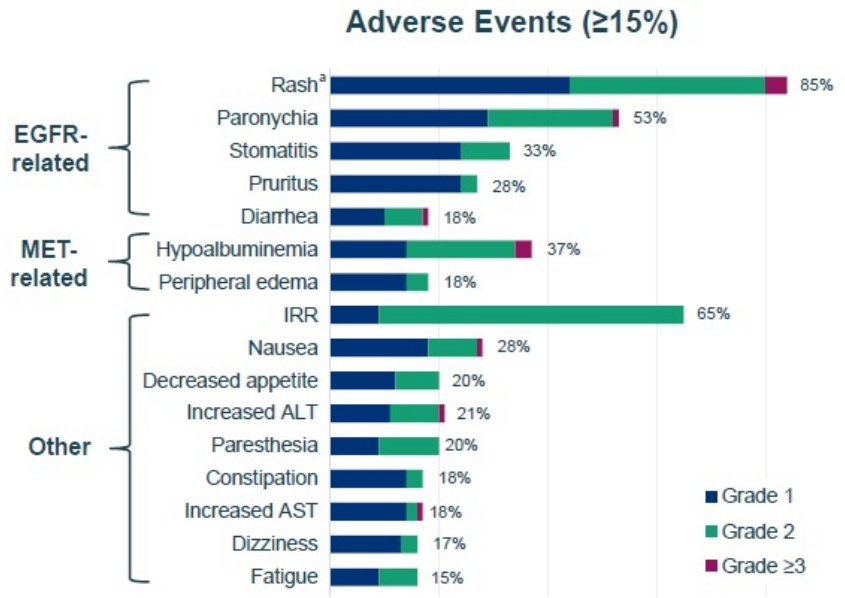
Jänne Canc Disc 2022

Treatments post osimertinib: amivantamab and lazertinib



- Amivantamab is a MET/EGFR antibody and lazertinib is a 3rd gen EGFR TKI
- The combo was assessed after osimertinib before chemo
- Ongoing and future studies are looking at first-line and later-line treatment



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Cho ESMO 2020

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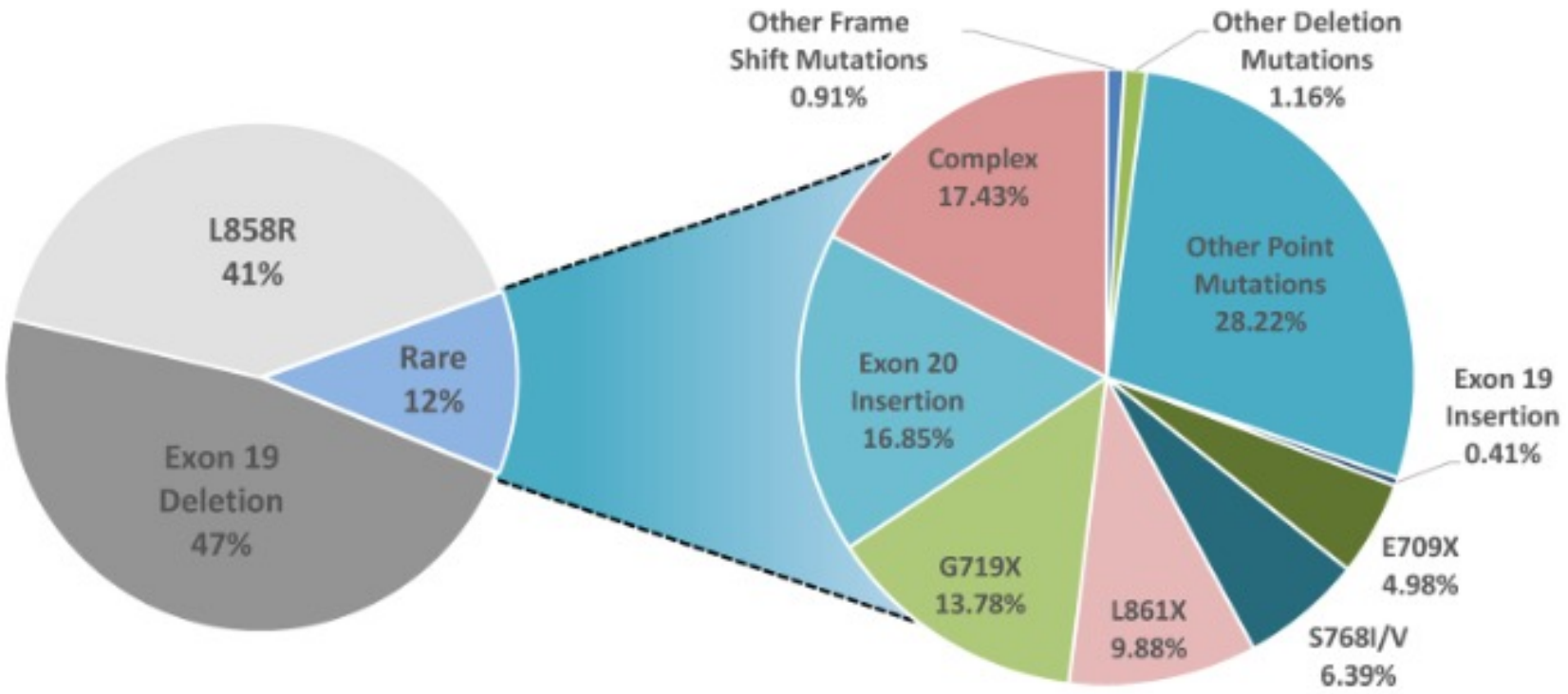
EGFR exon 20 insertions



- Subset of EGFR mutations that are activating but not sensitizing to traditional EGFR TKIs (erlotinib, osimertinib)
- Recent first approvals for targeted therapies for these lung cancers

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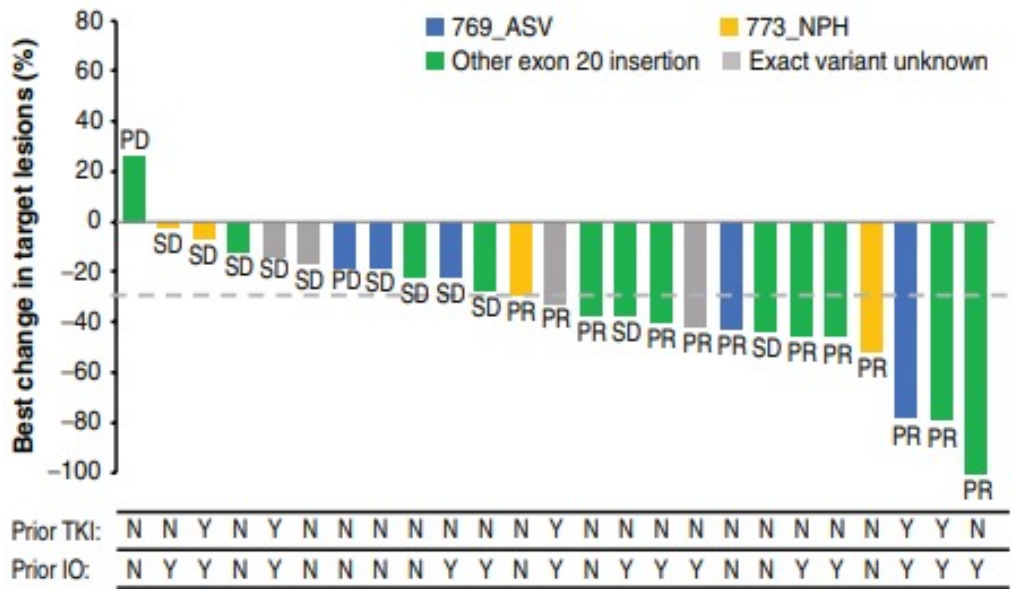
Harrison Sem Canc Bio 2019

Mobocertinib



Efficacy endpoint	5–40 mg/d (*n* = 12)	80 mg total daily dose[a] (*n* = 9)	120 mg/d (*n* = 21)	160 mg/d[b] (*n* = 28)
Best confirmed response, *n* (%)[c]				
Complete response	0	1 (11)	1 (5)	0
Partial response	0	1 (11)	3 (14)	12 (43)
Stable disease[d]	3 (25)	6 (67)	11 (52)	12 (43)
Progressive disease	7 (58)	1 (11)	3 (14)	2 (7)
Not evaluated	2 (17)	0	3 (14)	2 (7)
Confirmed ORR, *n* (%) [95% CI]	0 [0–26]	2 (22) [3–60]	4 (19) [5–42]	12 (43) [24–63]
Confirmed disease control rate, *n* (%) [95% CI]	3 (25) [5–57]	8 (89) [52–100]	15 (71) [48–89]	24 (86) [67–96]

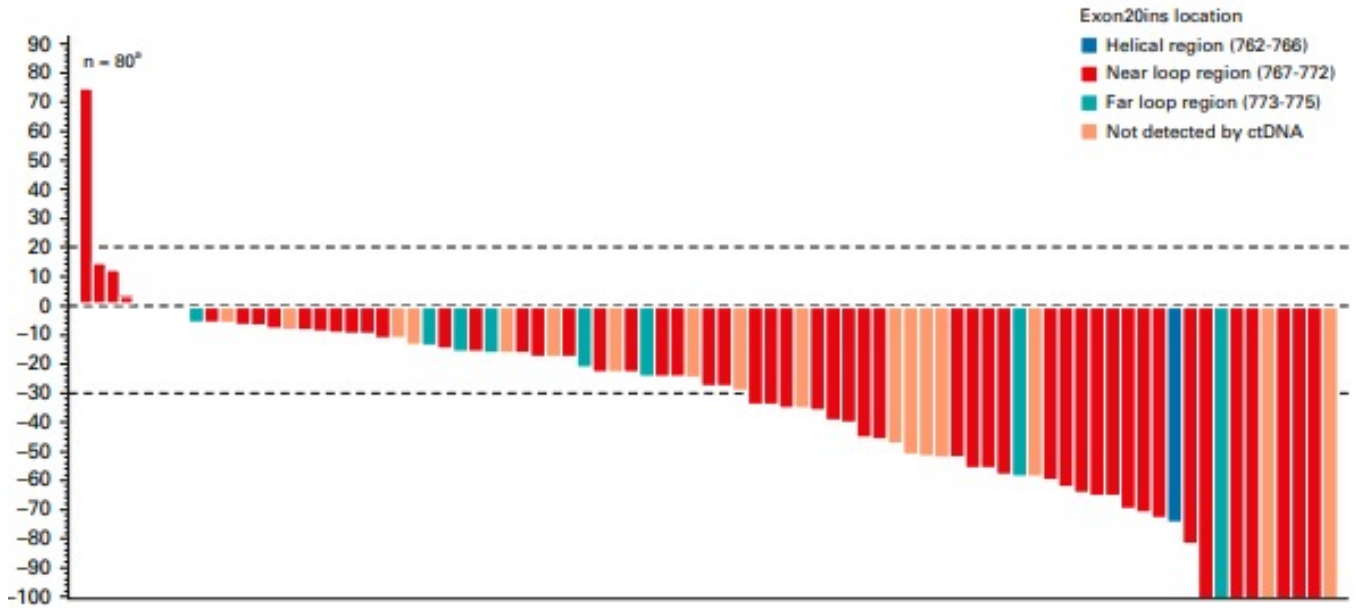
	Patients with *EGFR*ex20ins treated at 160 mg/d[a] (*n* = 28)	
TEAE	Any grade	Grade ≥3
Diarrhea	23 (82)	9 (32)
Nausea	11 (39)	3 (11)
Rash	13 (46)	0
Vomiting	10 (36)	2 (7)
Dry skin	5 (18)	0
Decreased appetite	11 (39)	0
Stomatitis	6 (21)	2 (7)
Fatigue	4 (14)	1 (4)
Rash maculopapular	7 (25)	1 (4)
Paronychia	8 (29)	0
Anemia	5 (18)	0
Dermatitis acneiform	5 (18)	0
GERD	3 (11)	0
Dyspepsia	6 (21)	0
Increased lipase	7 (25)	2 (7)
Pruritus	5 (18)	0

- Oral EGFR exon 20 inhibitor
- ORR at 160mg was 43% (0-19% ORR at lower doses), mPFS 7.3mo
- ORR 56% in pts w/o brain mets, 25% in pts with brain mets

Memorial Sloan Kettering Cancer Center

Riely Canc Disc 2021

Amivantamab

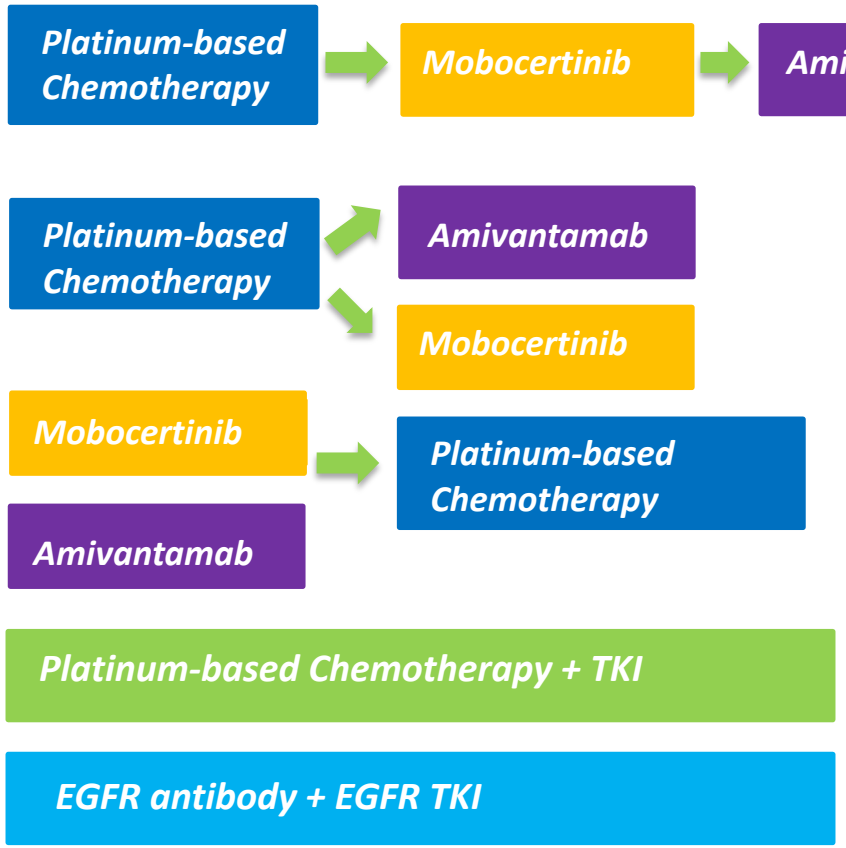


AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[a]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0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

-Bispecific EGFR/MET antibody that is given intravenously
-ORR 40%, DoR 11.1mo, mPFS 8.3mo, mOS 22.8mo
-Also being assessed in sensitizing EGFR mutations

Park JCO 2021

Outstanding questions for EGFR exon 20



-First-line treatment versus second-line treatment

-Sequencing, especially with EGFR TKI and antibody

-CNS penetration and efficacy

-Combination strategies

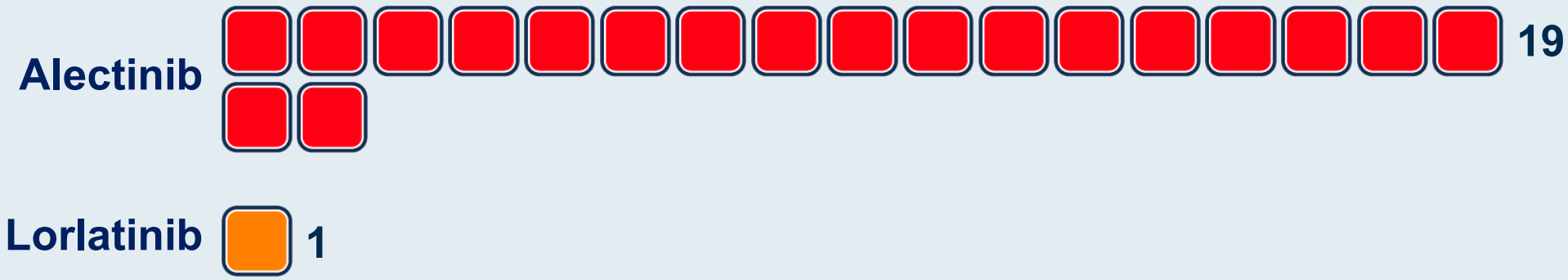
-New exon 20 inhibitors in development and their role

Conclusions

- **Early-stage EGFR+ NSCLC**
  - Make sure to do molecular testing, use osimertinib when appropriate
- **First-line treatment**
  - Osimertinib monotherapy is the standard of care but studies are ongoing looking at osimertinib-based combinations. Risk stratifying will be important when making treatment choices
- **Mechanisms of resistance**
  - No dominant mechanism, off-target and histologic transformation are common
- **Targeted therapies after osimertinib**
  - Focus on targeted therapies that transcend resistance mechanism, interest in patritumab deruxtecan and amivantamab/lazertinib
- **EGFR exon 20**
  - Amivantamab and mobocertinib are both approved but with limitations. New inhibitors also currently in development

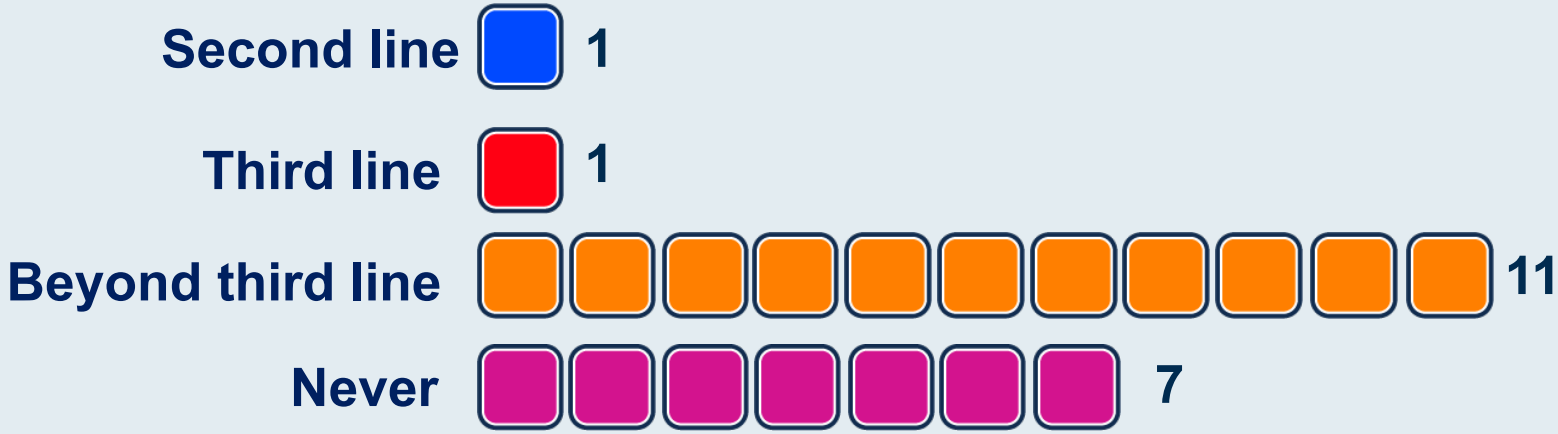
MODULE 3: Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK Rearrangements, ROS1 Rearrangements or RET Fusions — Dr Gainor

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and an ALK rearrangement?



Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer an immune checkpoint inhibitor (alone or in combination with chemotherapy) to a patient with metastatic nonsquamous NSCLC and an ALK rearrangement?



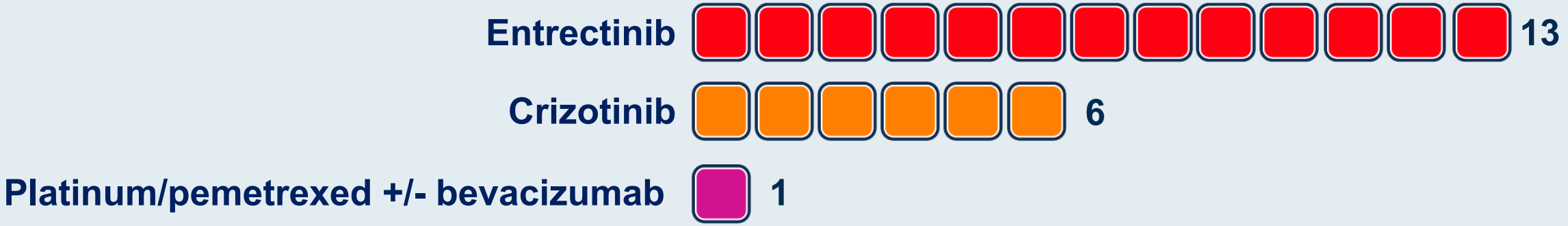
Would level of PD-L1 expression have any bearing on this decision?

Survey of lung cancer clinical investigators

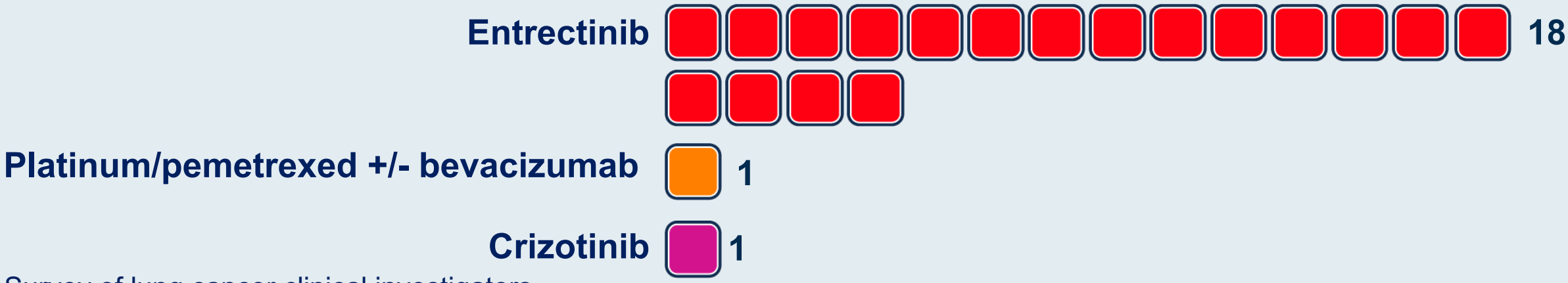
In general, what would be your preferred second-line therapy for a patient with metastatic nonsquamous NSCLC with an ALK rearrangement and a TPS of 50% who experienced disease progression on alectinib?

Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a ROS1 rearrangement?



What would be your preferred treatment if the patient had brain metastases?



Survey of lung cancer clinical investigators

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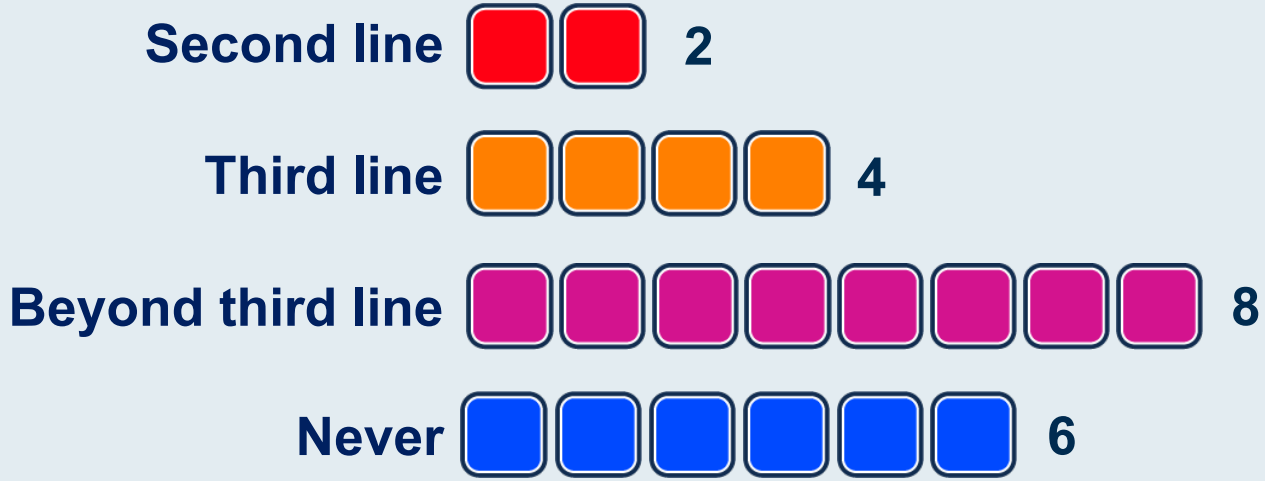
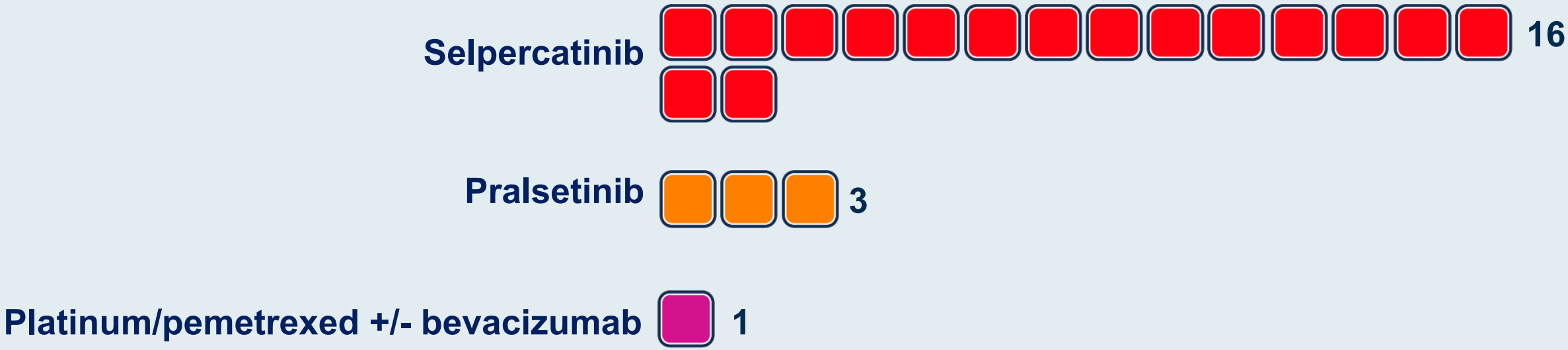


Would level of PD-L1 expression have any bearing on this decision?

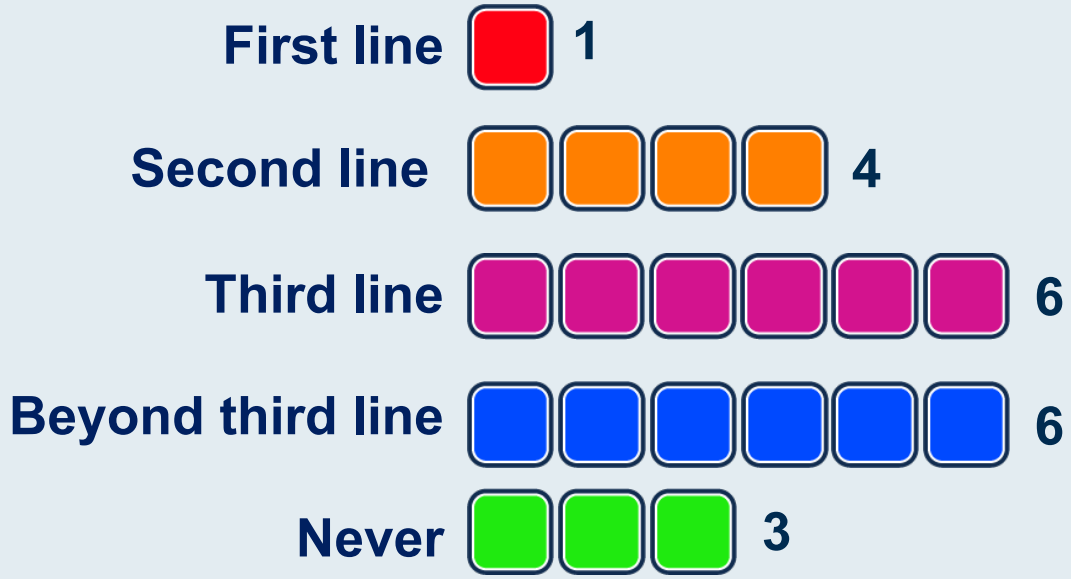
Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a RET fusion?

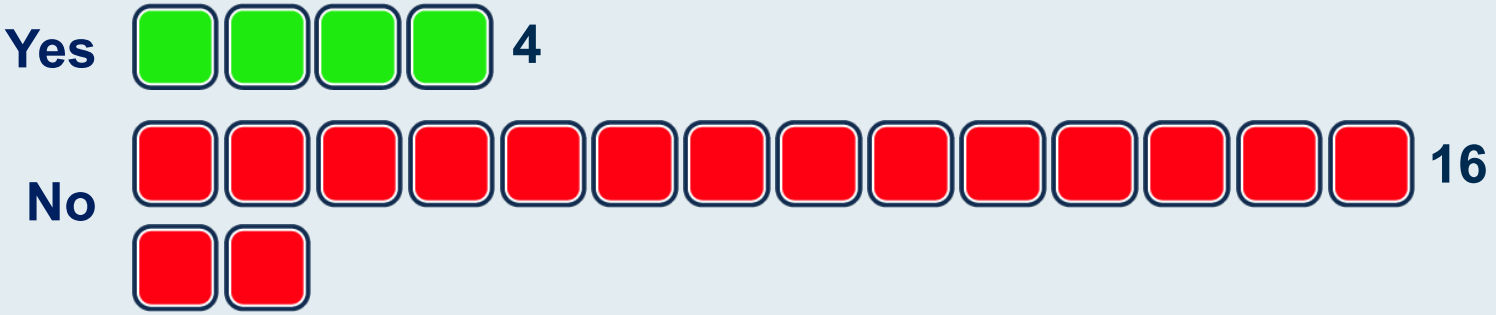


Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer an immune checkpoint inhibitor (alone or in combination with chemotherapy) to a patient with metastatic nonsquamous NSCLC and a RET fusion?



Would level of PD-L1 expression have any bearing on this decision?



Survey of lung cancer clinical investigators

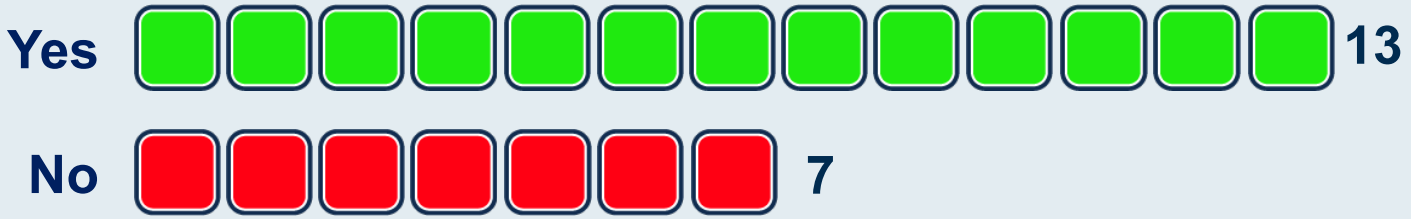
What are your most important tolerability concerns when a patient is about to begin treatment with…

Selpercatinib	**Pralsetinib**
Hepatotoxicity	Myelosuppression
Hypertension	Hepatoxicity
Xerostomia	Dysgeusia
Rash	Hypertension
Diarrhea	Rash
Fatigue	GI toxicity
QT prolongation	Pneumonitis

Survey of lung cancer clinical investigators

A patient who has never smoked presents with highly symptomatic metastatic nonsquamous NSCLC requiring immediate treatment, and chemotherapy is started while awaiting next-generation sequencing. PD-L1 TPS is 90%. Would you recommend adding an anti-PD-1/PD-L1 antibody as well?

A patient with a long smoking history presents with highly symptomatic metastatic nonsquamous NSCLC requiring immediate treatment, and chemotherapy is started while awaiting next-generation sequencing. PD-L1 TPS is 90%. Would you recommend adding an anti-PD-1/PD-L1 antibody as well?



Survey of lung cancer clinical investigators

Research Advances Shaping the Current and Future Treatment of Metastatic NSCLC with ALK, ROS1 and RET Fusions

Justin F. Gainor, M.D.
Director, Center for Thoracic Cancers
Director, Targeted Immunotherapy
Massachusetts General Hospital
Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

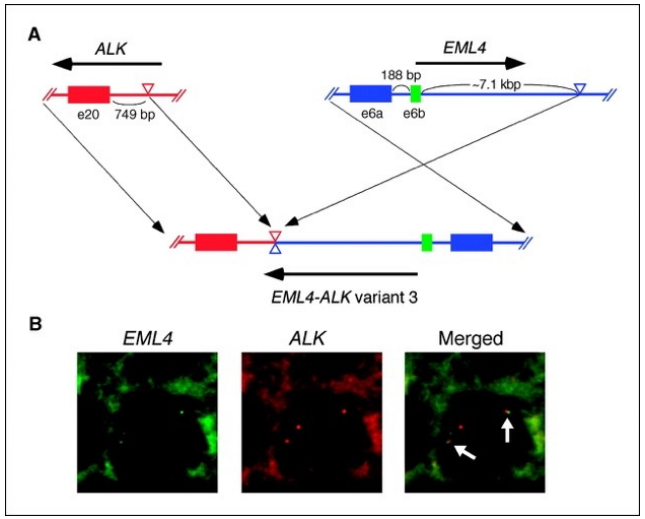
ALK Rearrangements

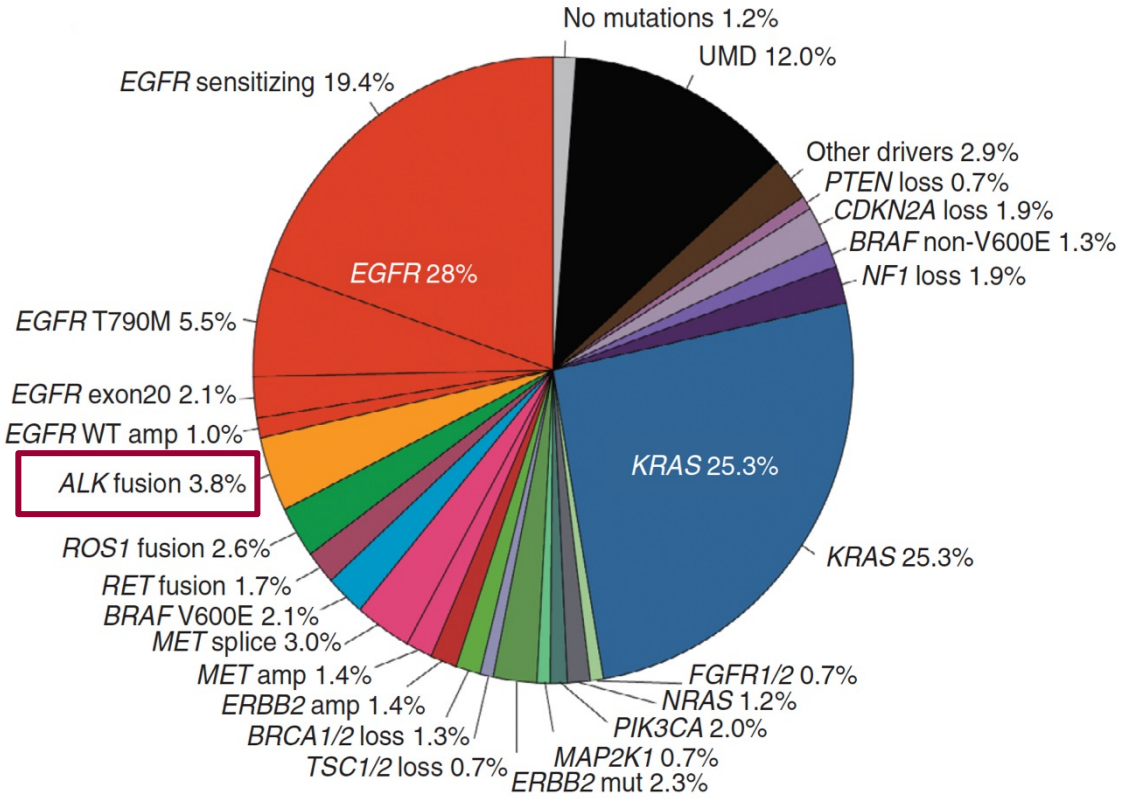
Vol 448|2 August 2007|doi:10.1038/nature05945 nature

ARTICLES

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



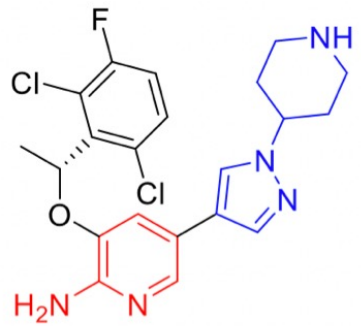


Soda M, et al. Nature 2007; Jordan EM, et al. Cancer Discov 2017

Evolution of ALK Tyrosine Kinase Inhibitors (TKIs)

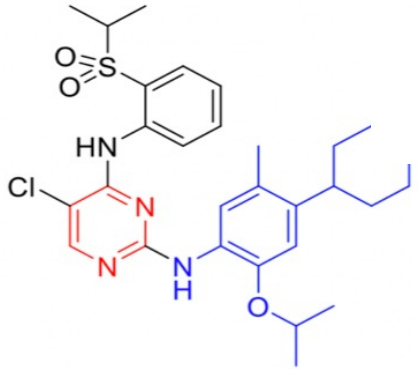
First-Generation

Crizotinib

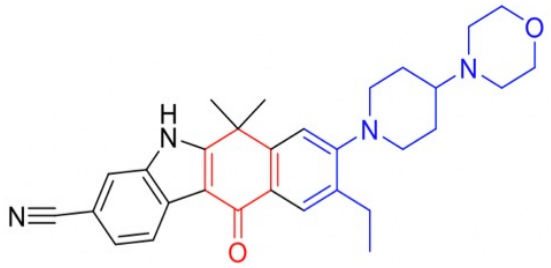


Second-Generation

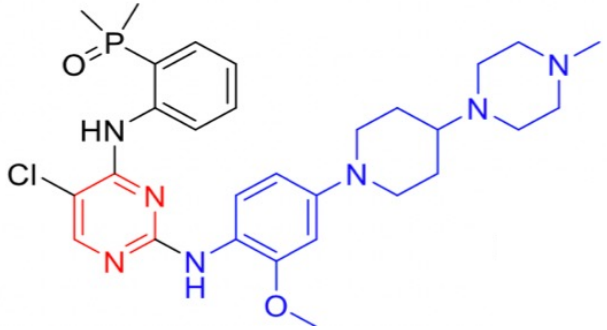
Ceritinib



Alectinib

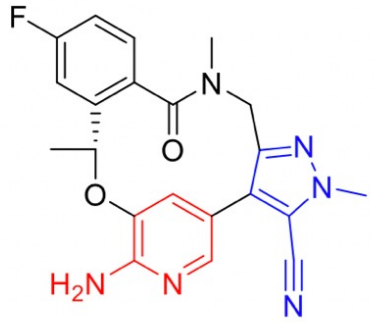


Brigatinib



Third-Generation

Lorlatinib



*Only FDA-approved ALK inhibitors depicted

Second-Generation ALK Inhibitors in the First-Line Setting

	ASCEND-4 (N=376)	J-ALEX (N=207)	ALEX (N=303)	ALESIA (N=187)	ALTA-1L (N=275)
ALK Inhibitor	Ceritinib	Alectinib	Alectinib	Alectinib	Brigatinib
Control Arm	Plat/Pemetrexed	Crizotinib	Crizotinib	Crizotinib	Crizotinib
Median f/u	19.7 months	42.4 months	37.8 months	16.2 months	40.4 months
PFS (median)	16.6 months*	34.1 months*	34.8 months¥	NR¥	24.0 months*
PFS (HR)	0.55	0.37	0.43	0.22	0.48
ORR	72.5%	92%	83%	91%	74%

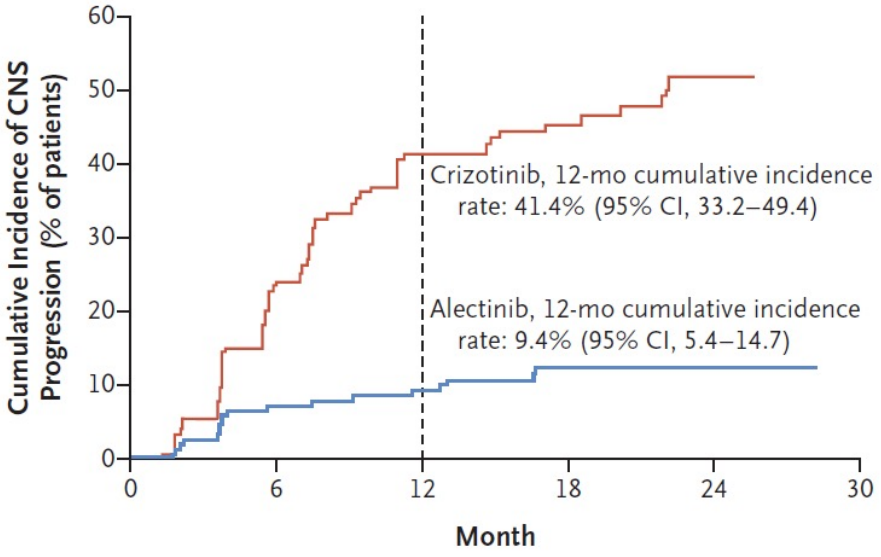
*BIRC assessed
¥Investigator-assessed

References: 1. Soria JC, et al. Lancet 2017; 2. Hida et al. Lancet 2017; 3. Takiguchi et al. ASCO 2017; 4. Peters S, et al. NEJM 2017; 5. Camidge DR, et al. ASCO 2018; 6. Zhou et al. Lancet Resp Med 2019; 7. Camidge DR, et al. NEJM 2018; 8. Nakagawa K, et al. Lung Cancer 2020; 9. Mok T, et al. Ann Oncol 2020; 10. Camidge DR, et al. J Clin Oncol 2020. 11. Camidge DR, et al. JTO 2021.

Second-Generation ALK TKIs Have Improved CNS Activity Compared to Crizotinib

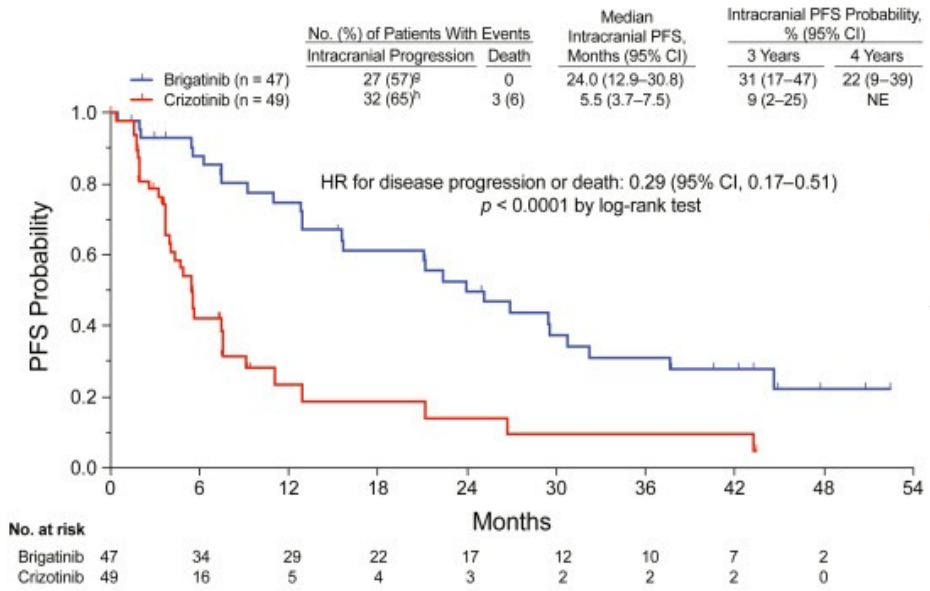
Global ALEX Study

Cumulative Incidence of CNS Progression



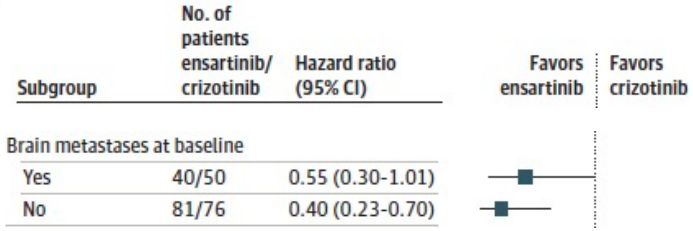
ALTA-1L Study

Survival w/o Intracranial Disease Progression in Patients with Baseline Brain Metastases



eXalt2 Trial

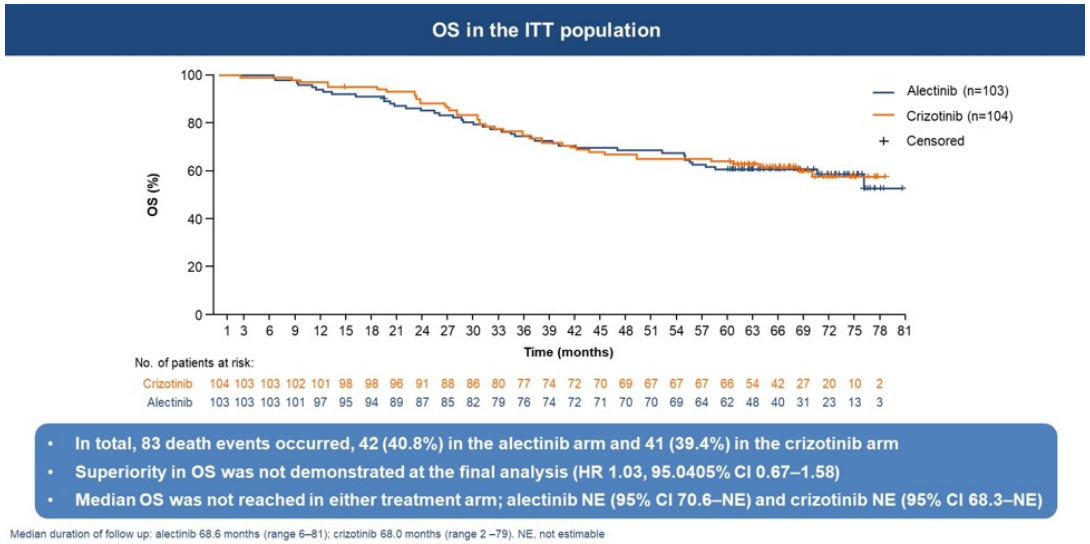
Intracranial ORR 63.6% vs. 21.1%



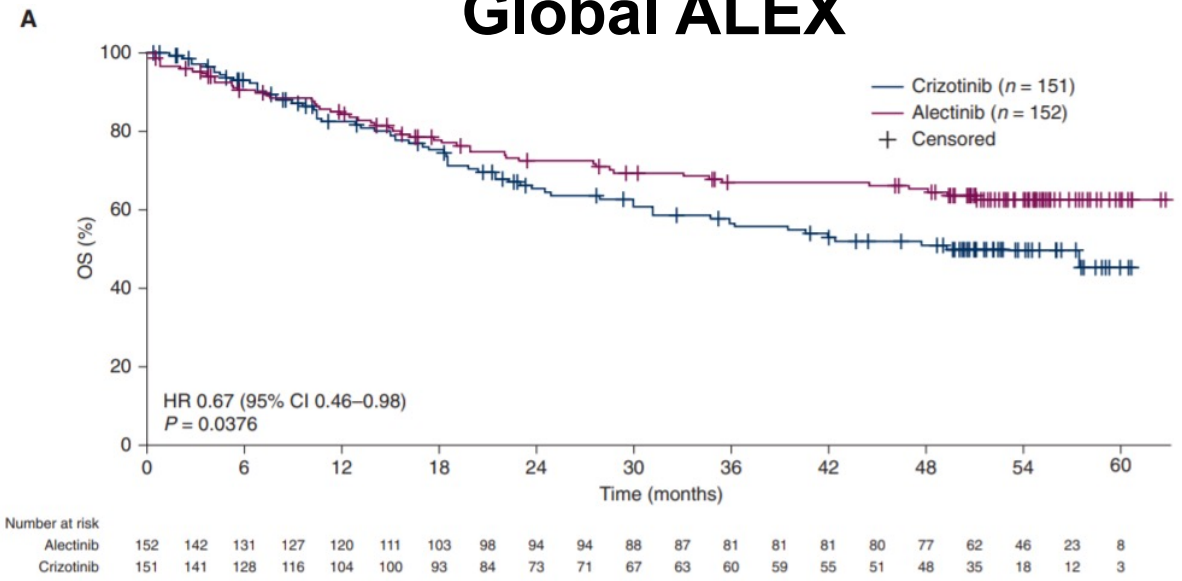
1. Peters S, et al. NEJM 2017; 2. Camidge DR, et al. NEJM 2018; 3. Horn L, et al. JAMA Oncol 2021 4. Camidge DR, et al. JTO 2021.

Second Generation ALK TKI: Overall Survival

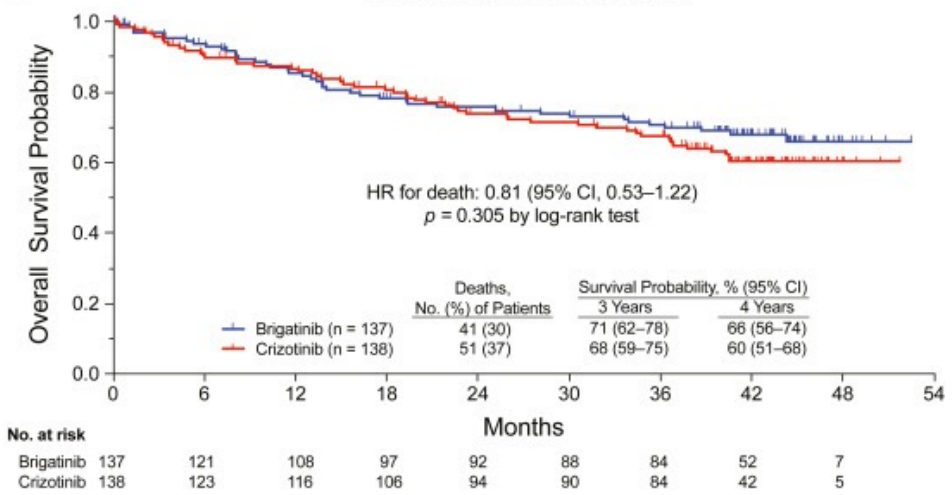
J-ALEX



Global ALEX

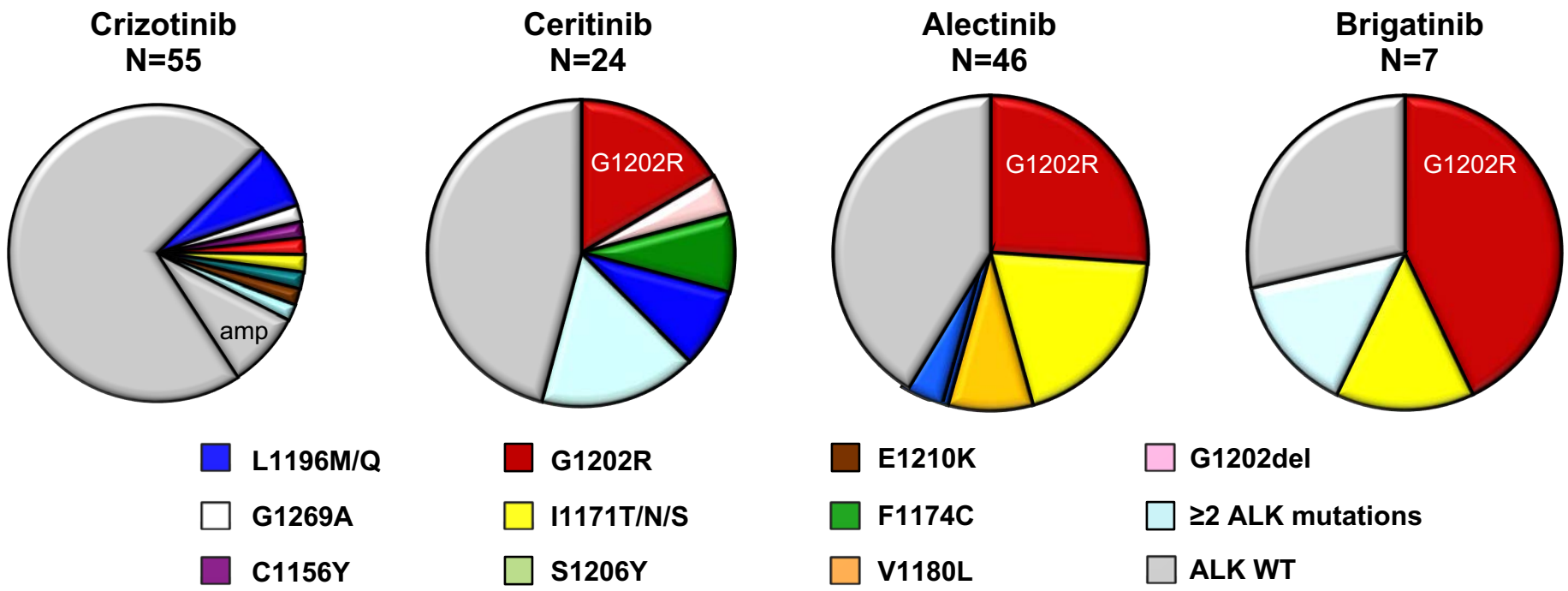


ALTA-1L



Yoshioka et al, ASCO 2021
Mok T et al. Ann Oncol 2020
Camidge DR, et al. JCO 2020
Camidge DR, et al. JTO 2021

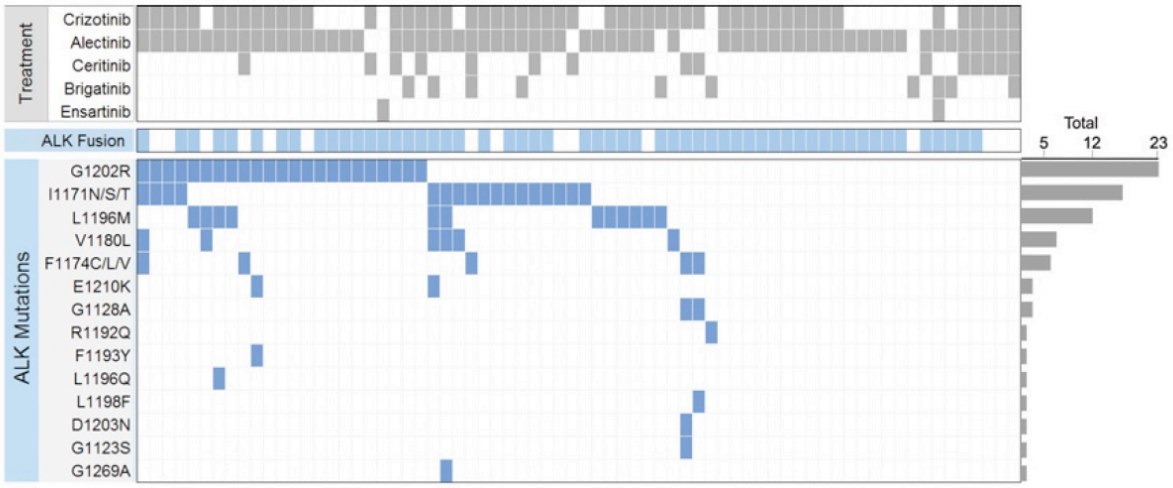
ALK Resistance Mutations are More Common After Progression on Second-Generation ALK inhibitors

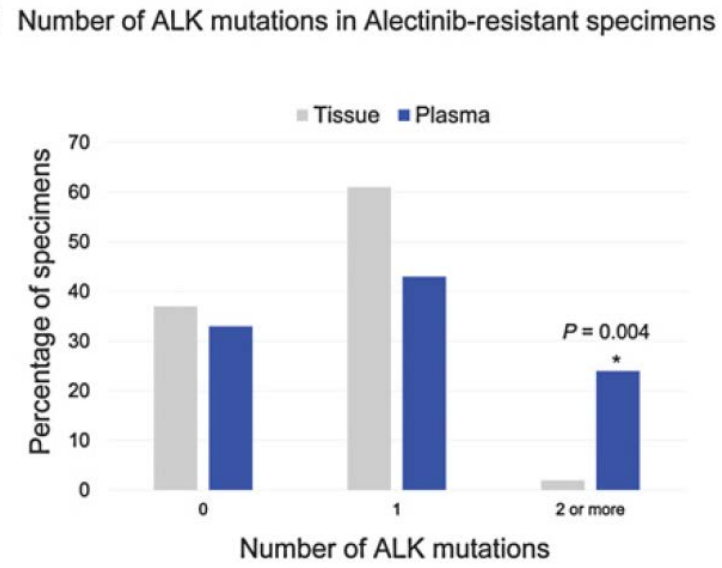


1. Updated from Gainor JF, Dardaei L, et al. Cancer Discovery 2016; 2. Lin JJ, et al. ASCO 2018.

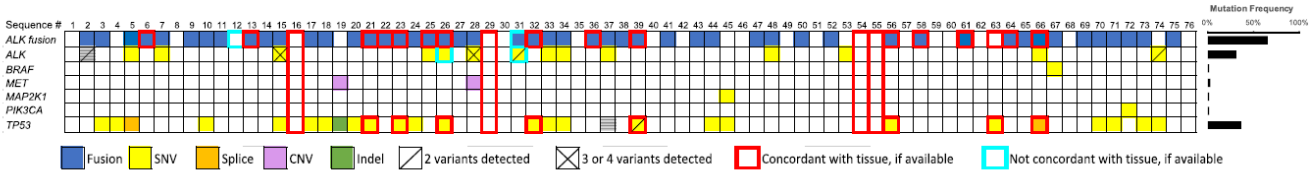
ALK Resistance Mutations in ctDNA

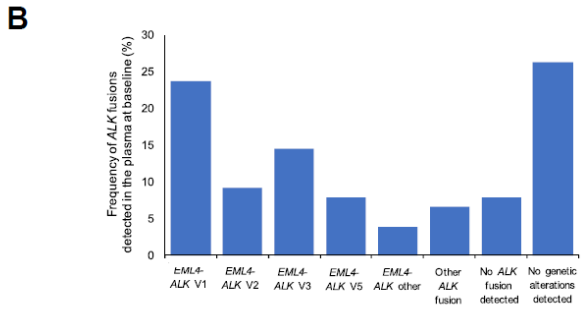
Dagogo-Jack I, et al. Clin Cancer Res 2019

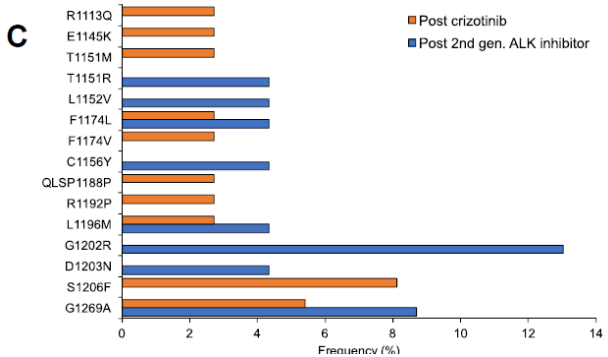




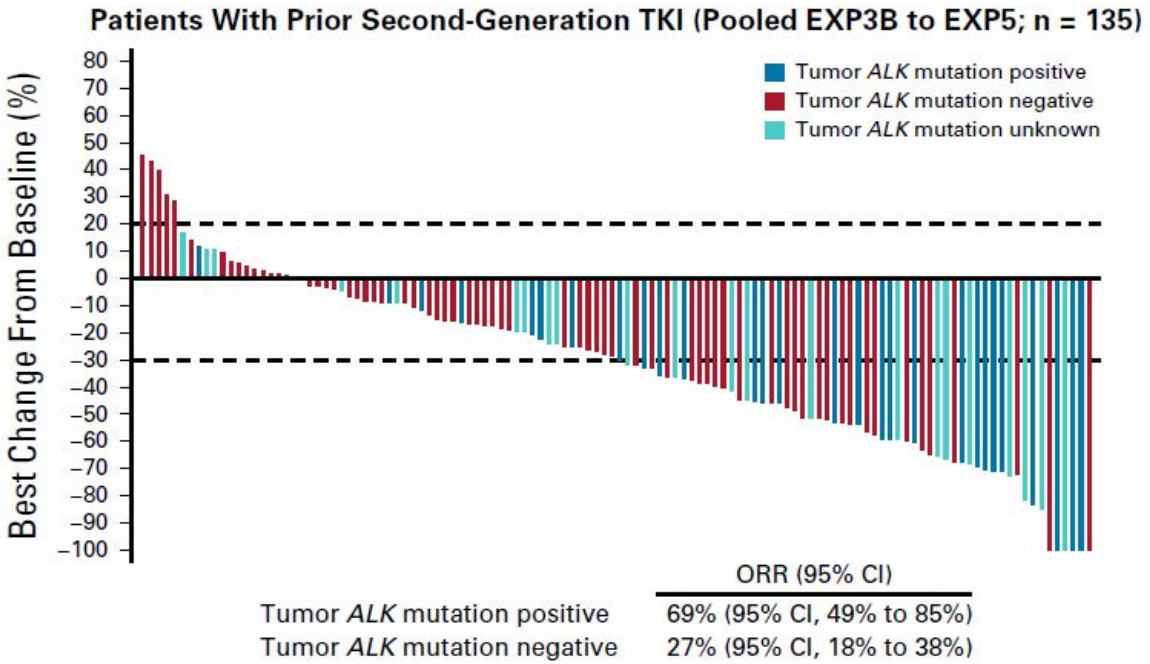
Horn L, et al. J Thorac Oncol 2019

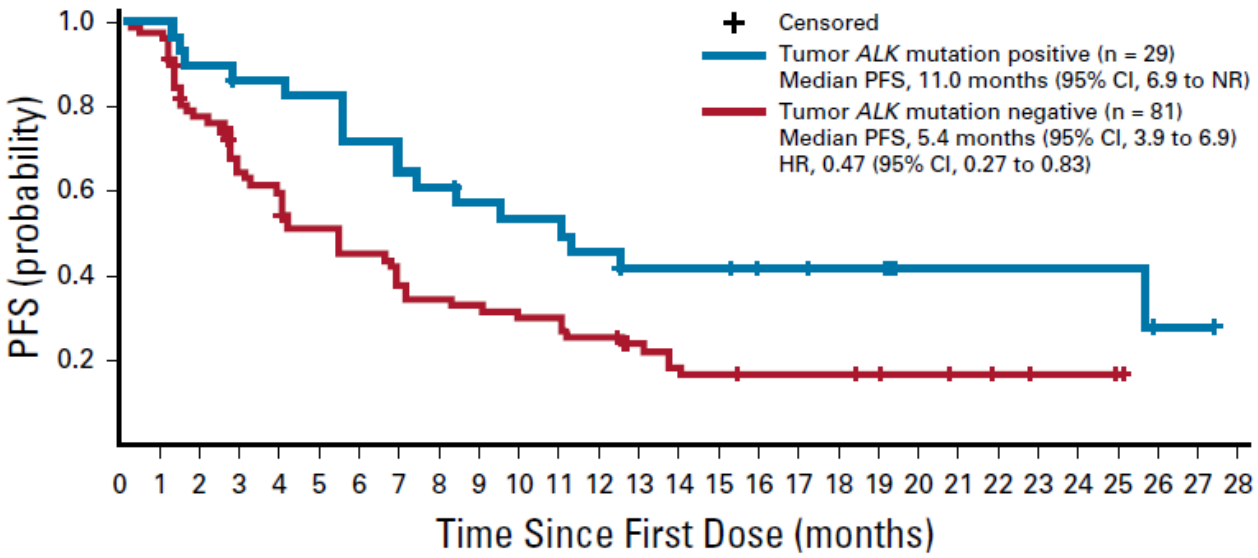






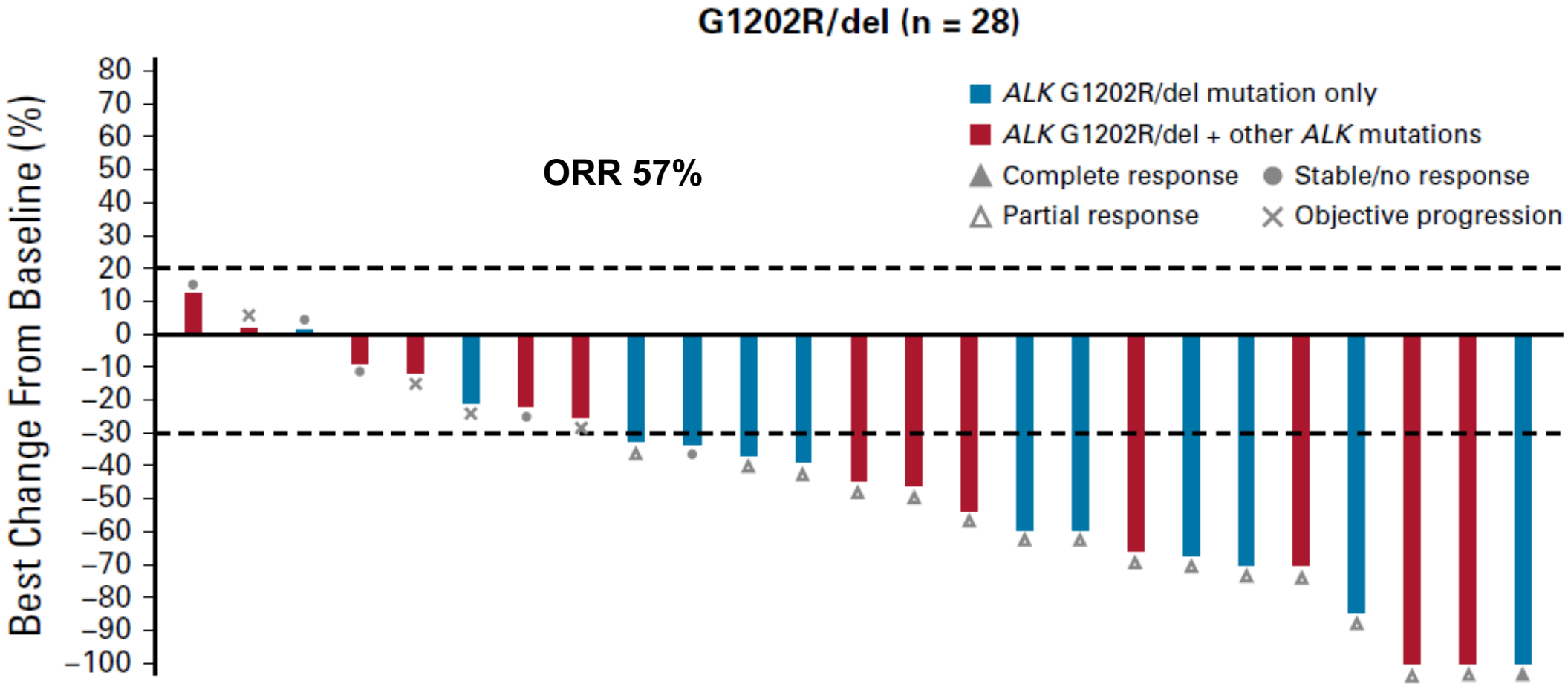
Activity of Lorlatinib by ALK Resistance Mutation Status[1]





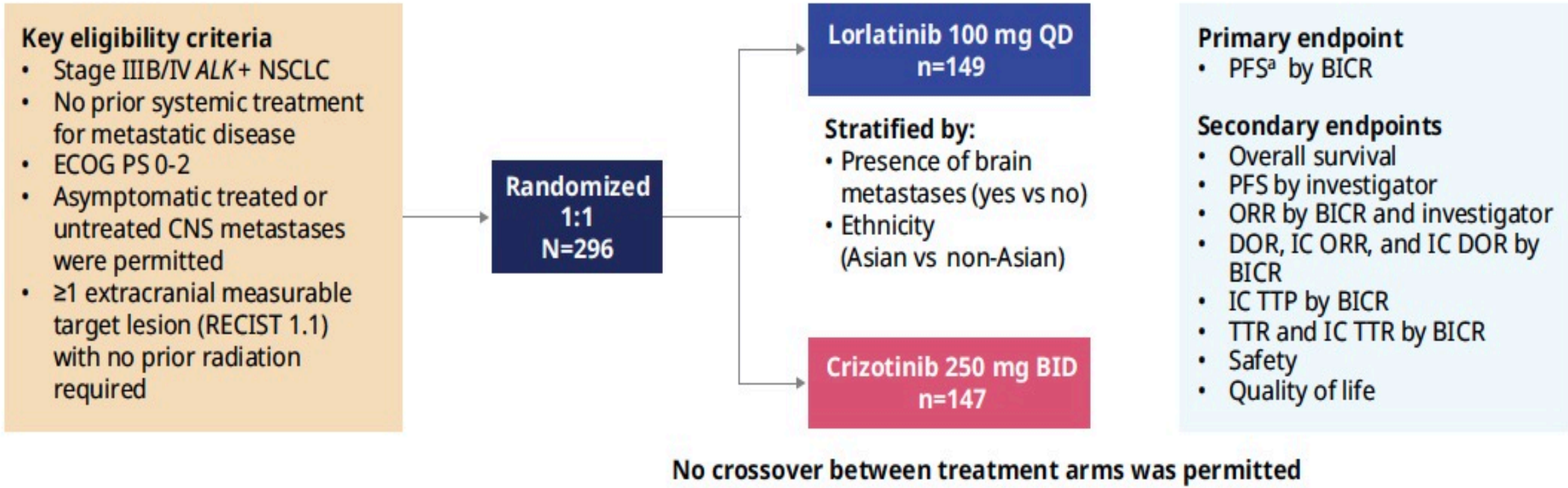
1. Shaw AT, et al. J Clin Oncol 2019

Lorlatinib is Active Against ALK G1202R[1]



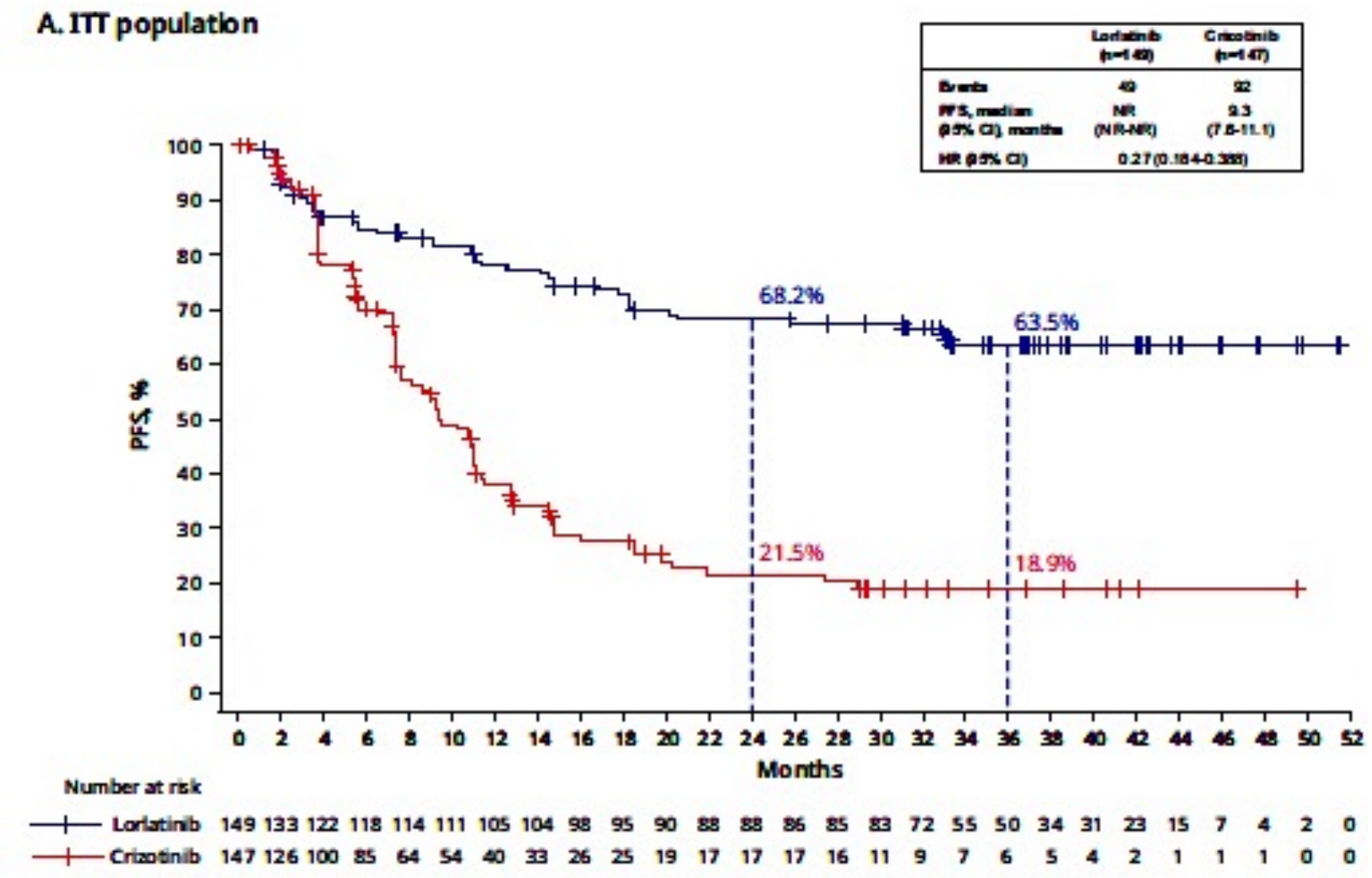
1. Shaw AT, et al. J Clin Oncol 2019

CROWN Study



Solomon B, et al. AACR 2022

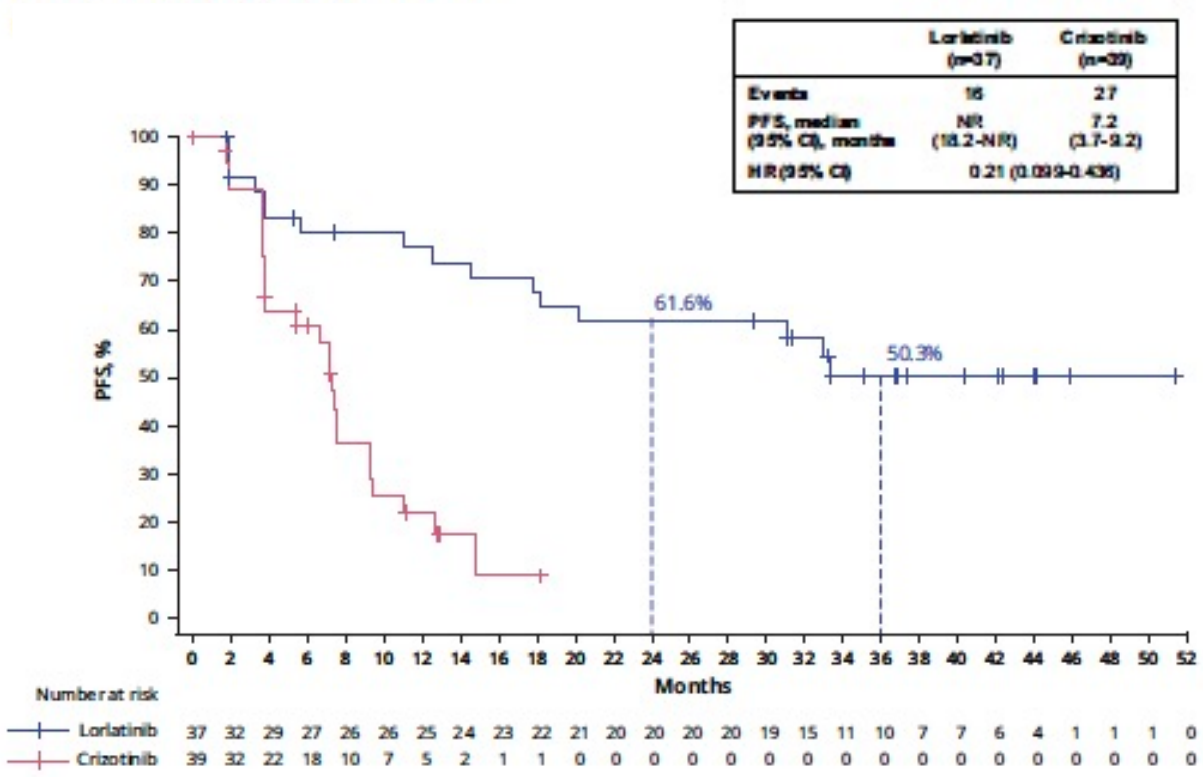
CROWN: AACR Update



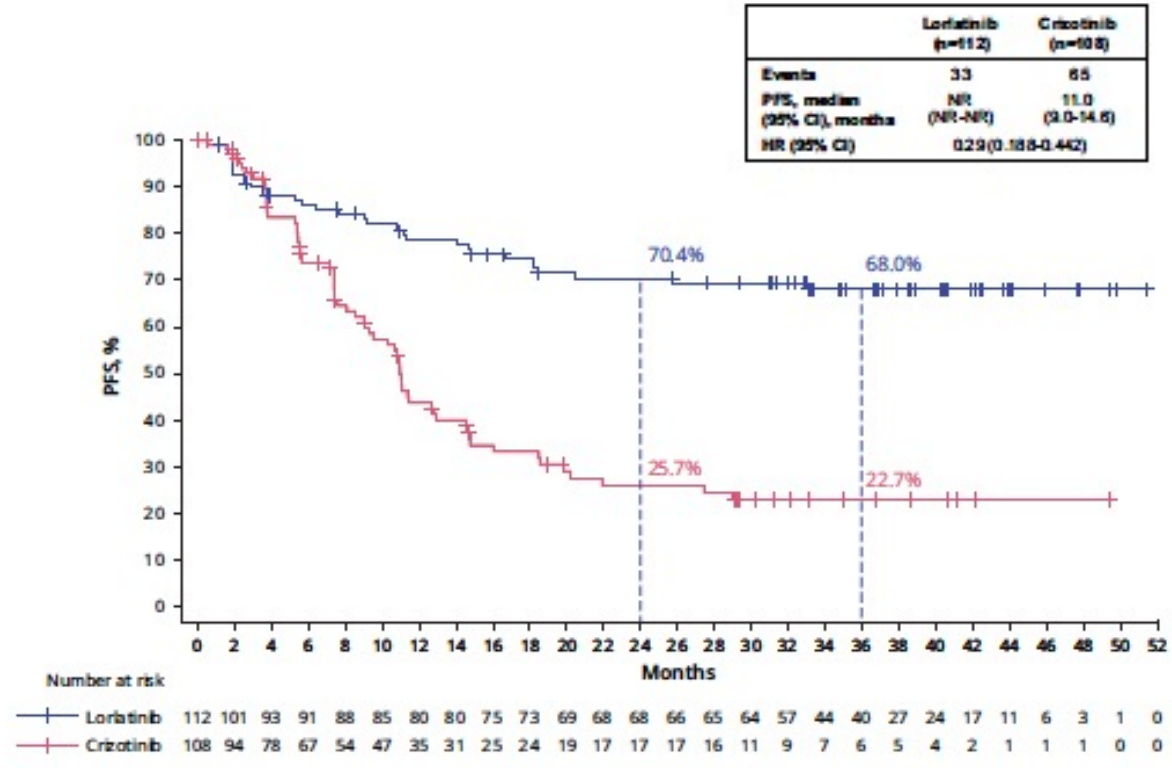
Solomon B, et al. AACR 2022

CROWN: AACR Update

Patients with Brain Metastases

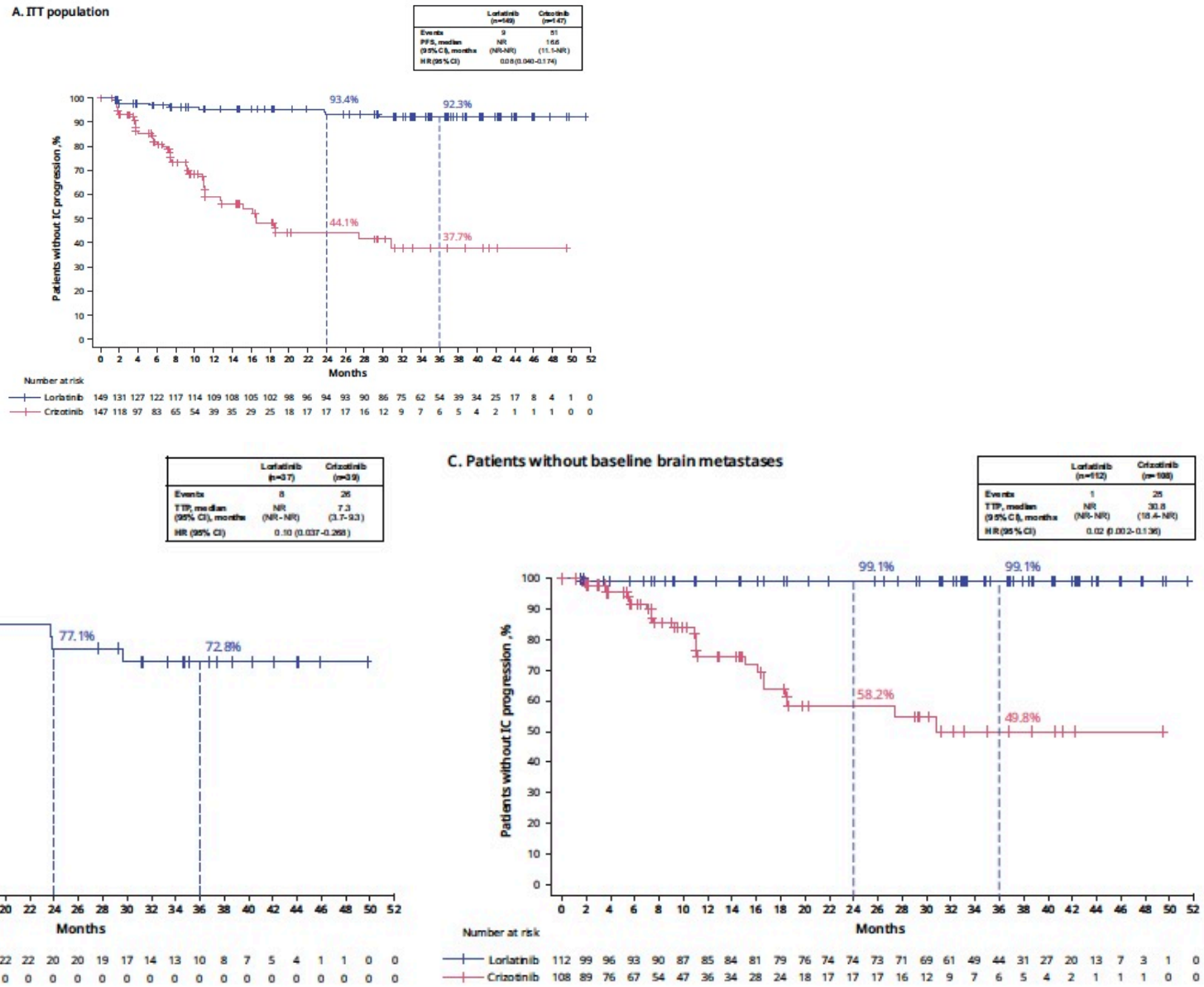


Patients without Brain Metastases



Solomon B, et al. AACR 2022

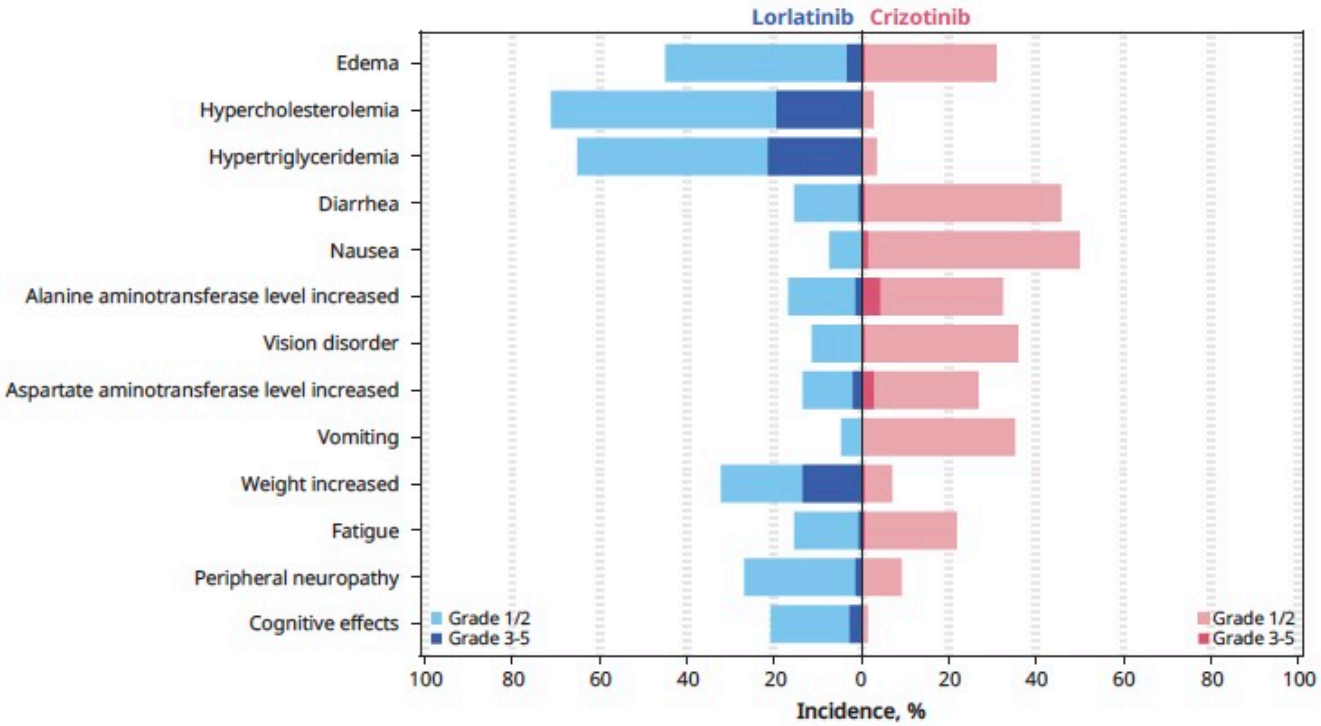
CROWN: AACR Update



Solomon B, et al. AACR 2022

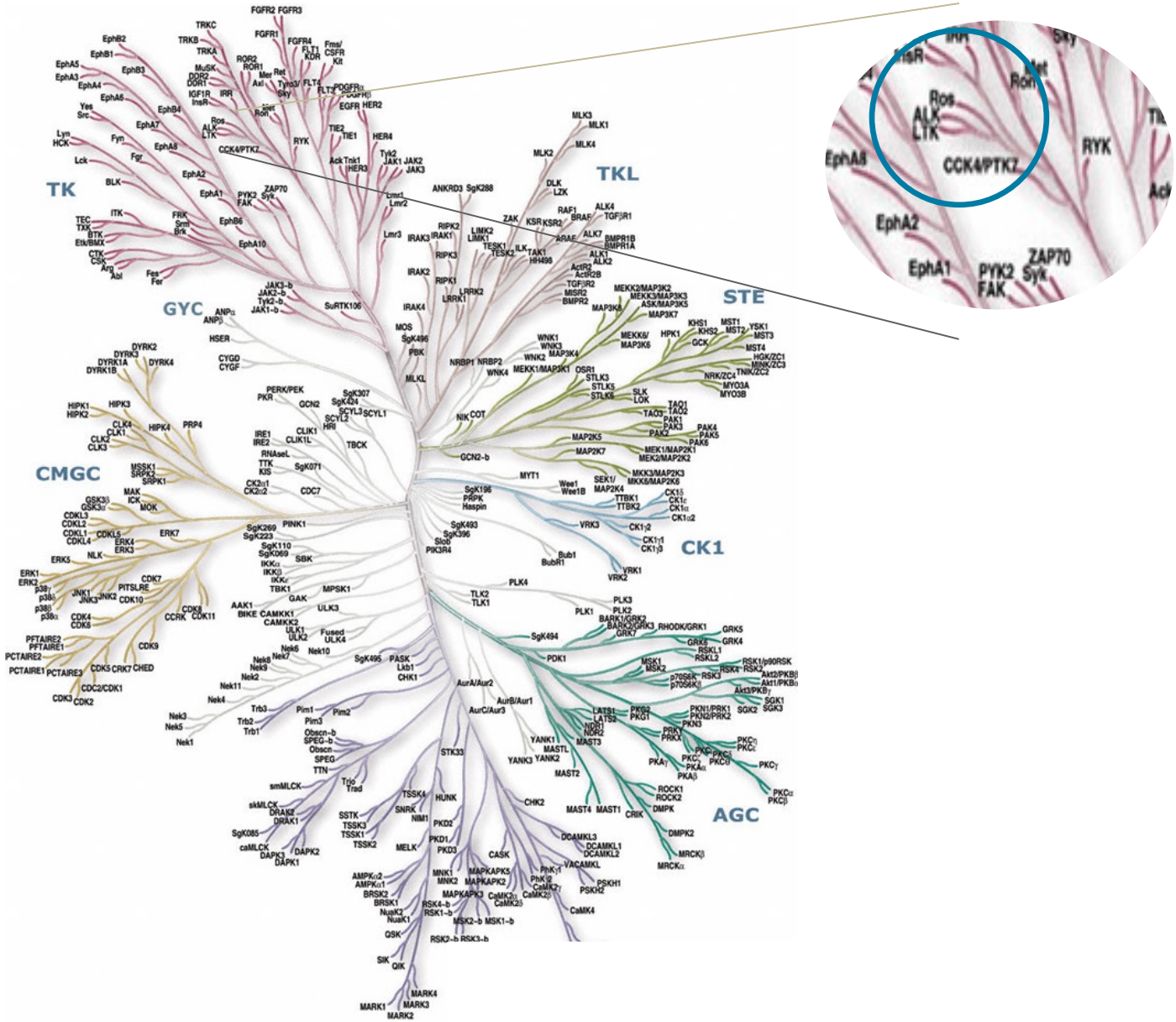
CROWN – AACR Update

Table 2: Summary of AEs	n (%)	
	Lorlatinib (n=149)	Crizotinib (n=142)
Any-grade AE	149 (100.0)	140 (98.6)
Treatment related	145 (97.3)	133 (93.7)
Grade 3/4 AE	113 (75.8)	81 (57.0)
Treatment related	94 (63.1)	54 (38.0)
Death	10 (6.7)	7 (4.9)
Treatment related	2 (1.3)	0
Any serious AE	57 (38.3)	44 (31.0)
Treatment related	13 (8.7)	9 (6.3)
AEs leading to dose reduction	32 (21.5)	21 (14.8)
AEs leading to temporary discontinuations	84 (56.4)	69 (48.6)
AEs leading to permanent treatment discontinuation	11 (7.4)	14 (9.9)



Solomon B, et al. AACR 2022

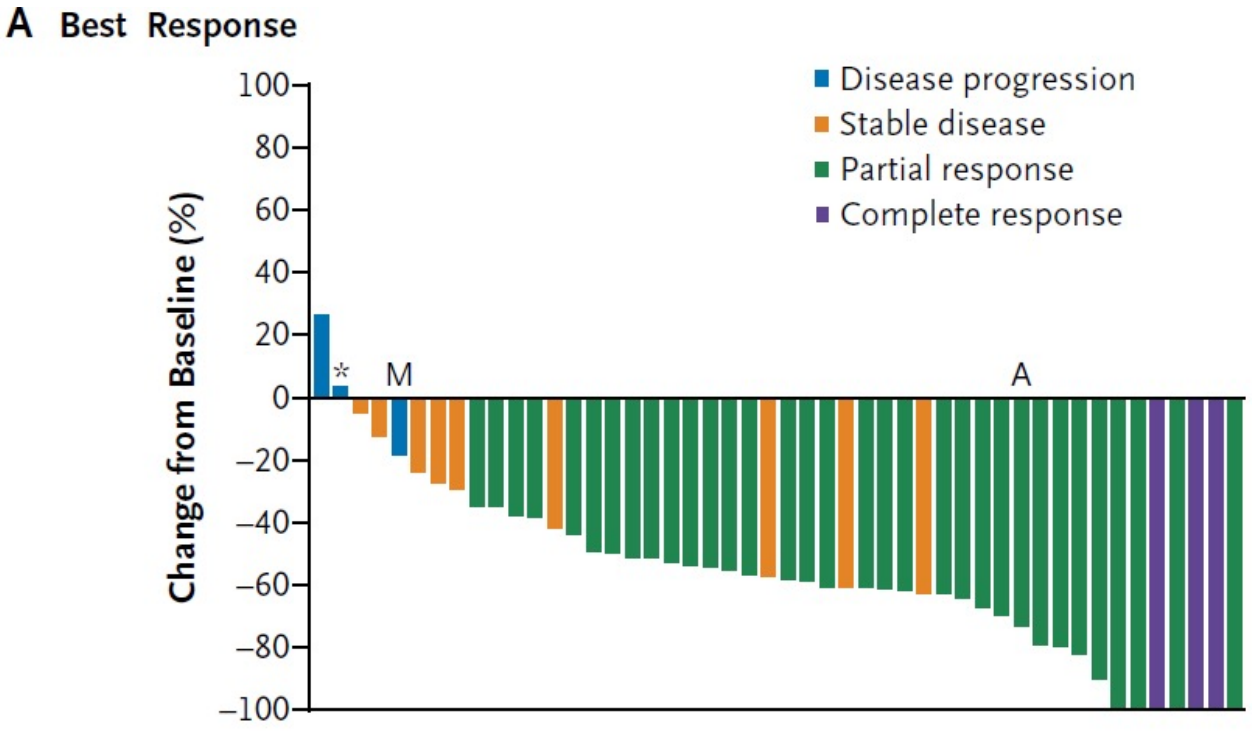
ROS1 and ALK Share Homology

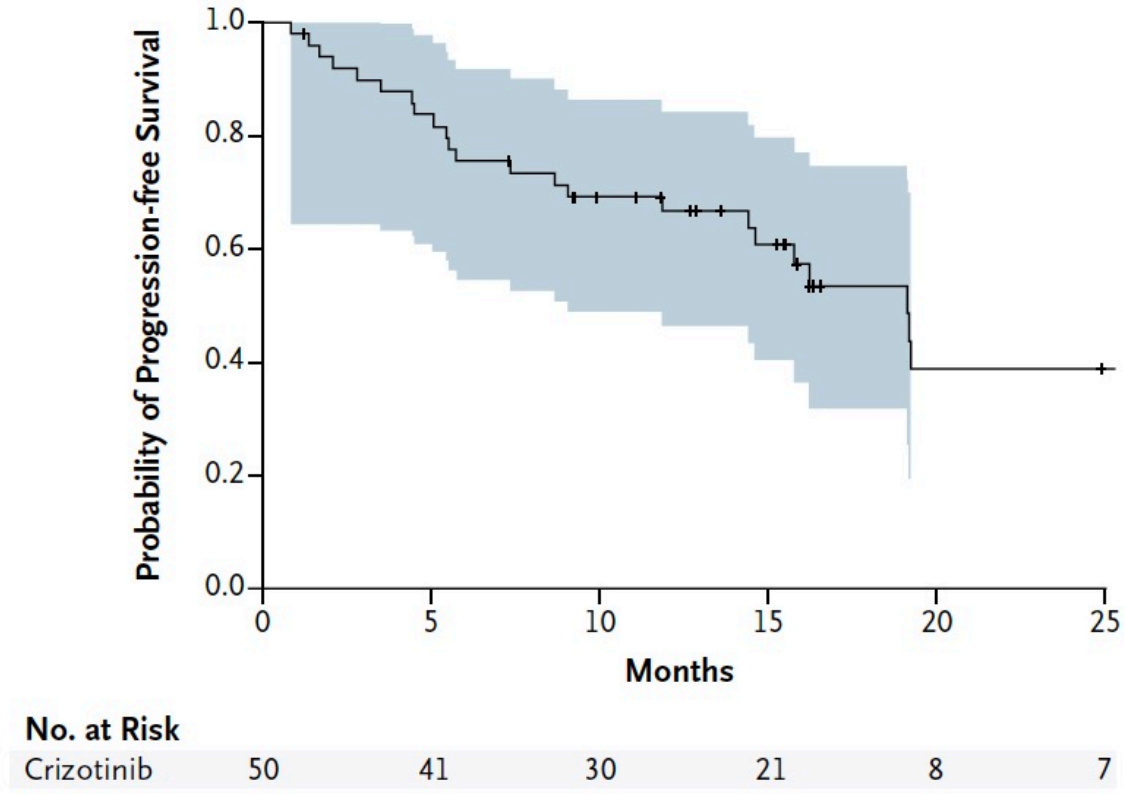


Shaw et al. NEJM 2014

Crizotinib in ROS1-Rearranged NSCLC

ORR 72%
Median PFS 19.2 months

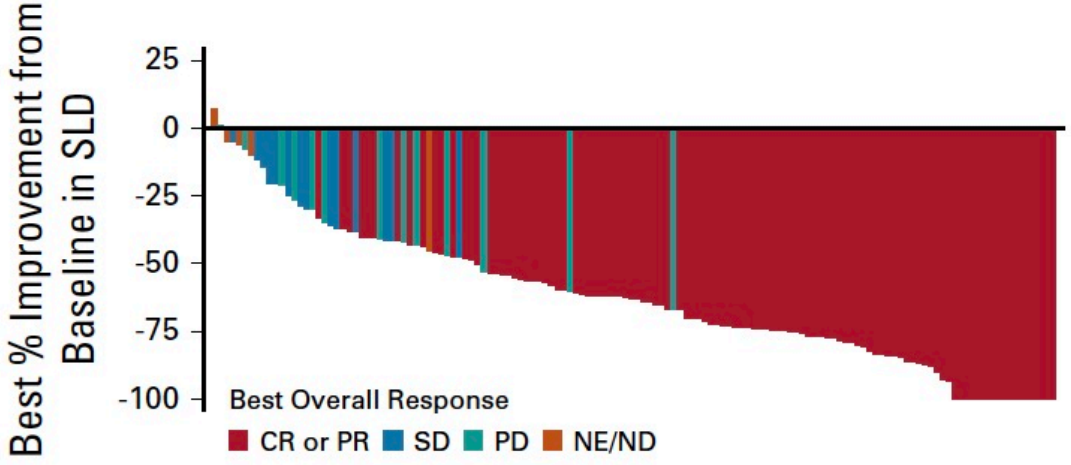




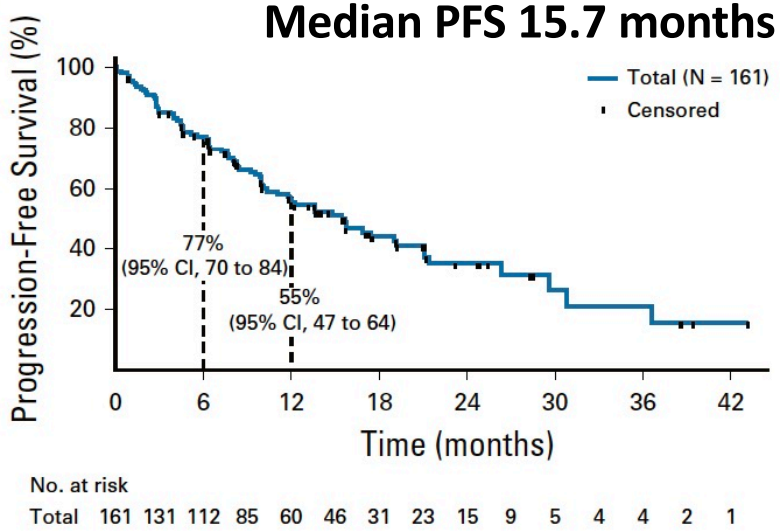
Shaw AT, et al. NEJM 2014

Entrectinib in ROS1+ NSCLC

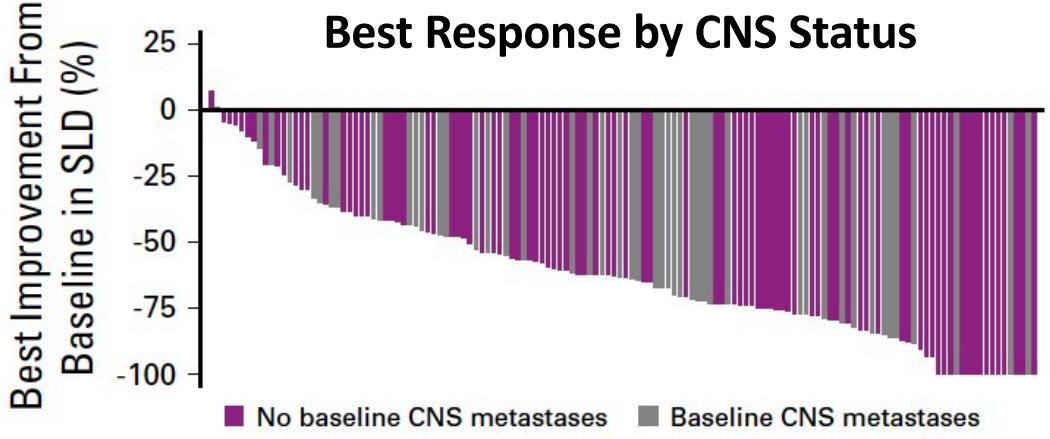
ORR 67.1%



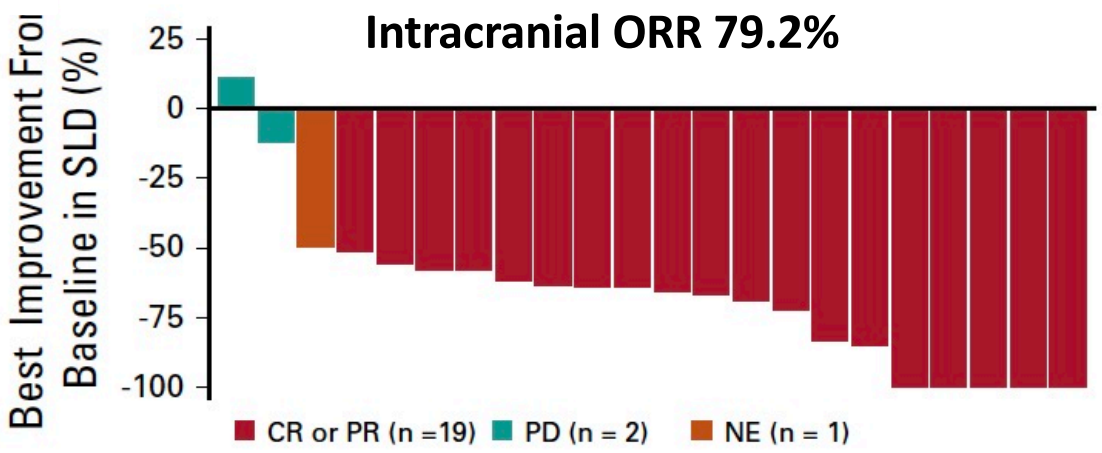
Median PFS 15.7 months



Best Response by CNS Status



Intracranial ORR 79.2%

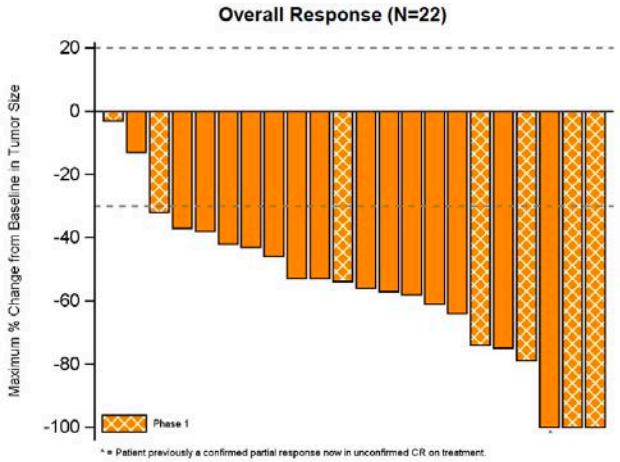


Dziadziuszko R, et al. JCO 2021

Other ROS1 Inhibitors

Repotrectinib

TKI-Naive

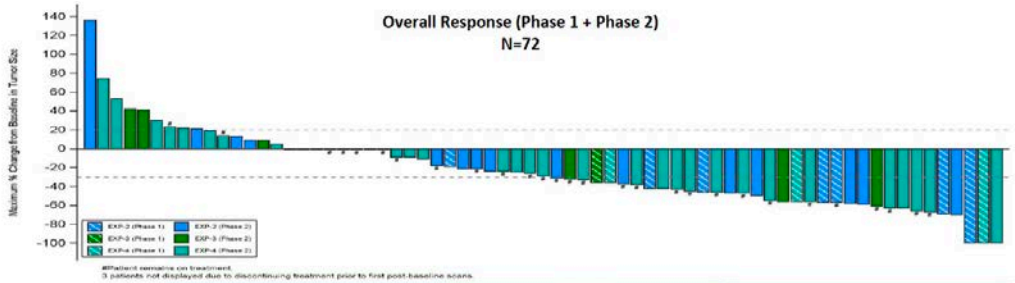


	Phase 2 N=15	Phase 1+2 N=22
Confirmed ORR, % (95% CI)	93% (68–100)	91% (71–99)

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

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

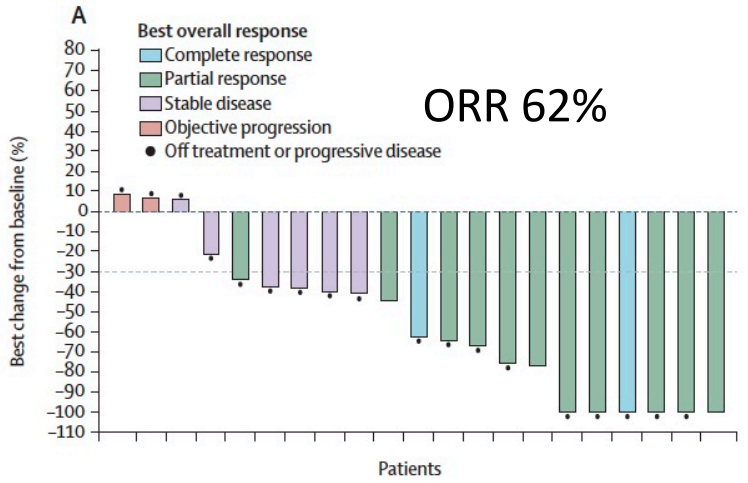
TKI-Treated



	EXP-2		EXP-3		EXP-4	
	Phase 2 (N=16)	Phase 1 + 2 (N=23)	Phase 2 (N=9)	Phase 1 + 2 (N=10)	Phase 2 (N=36)	Phase 1 + 2 (N=39)
Confirmed ORR (cORR) (95% CI)	31% (11 - 59)	39% (20 - 61)	33% (7 - 70)	30% (7 - 65)	31%* (16 - 48)	33%* (19 - 50)
Duration of Response (range in months)	1.8+ - 9.2 n=5	1.8+ - 11.1 n=9	1.9+ - 12.9+ n=3	1.9+ - 12.9+ n=3	1.7+ - 15.0+ n=11	0.8+ - 15.0+ n=13

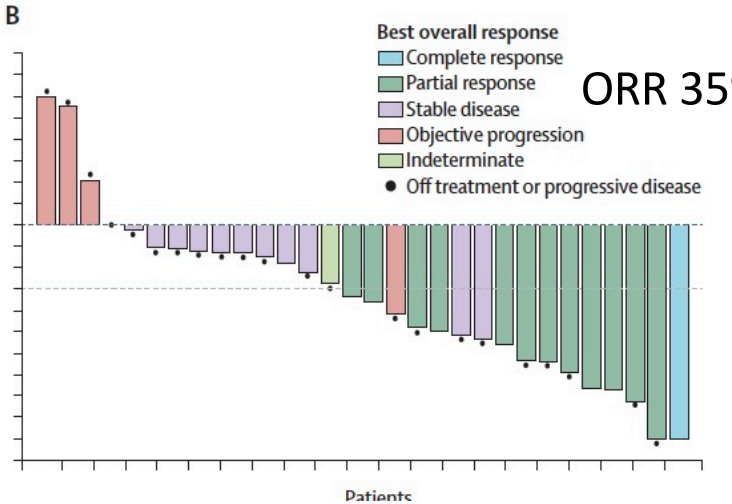
Lorlatinib

TKI-Naive



ORR 62%

Crizotinib-Treated

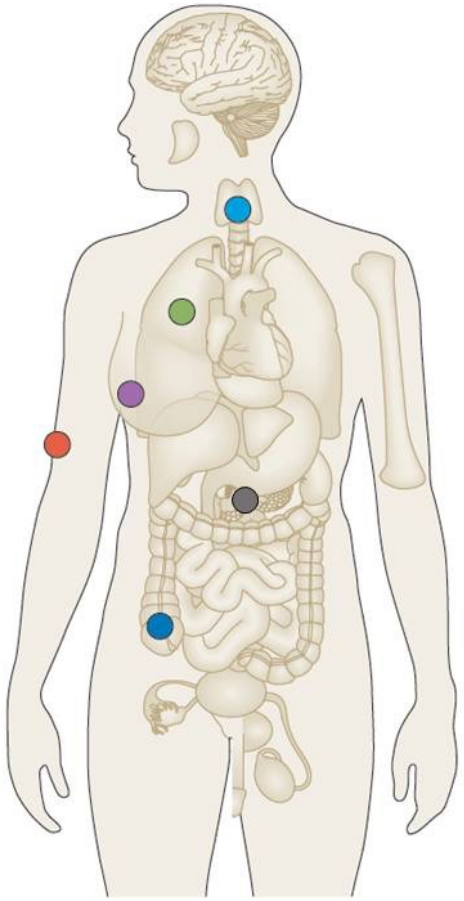


ORR 35%

Cho BC, et al. WCLC 2021; Lin JJ, et al. AACR-NCI-EORTC 2021; Shaw AT, et al. Lancet Oncol 2019

RET Fusions Across Cancers

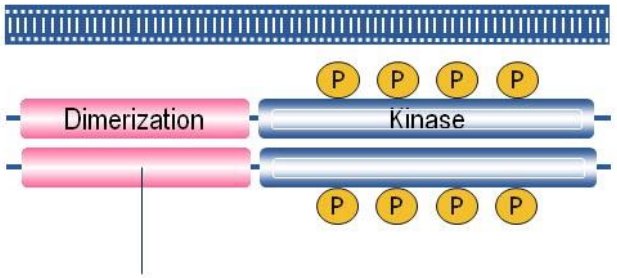
RET fusions



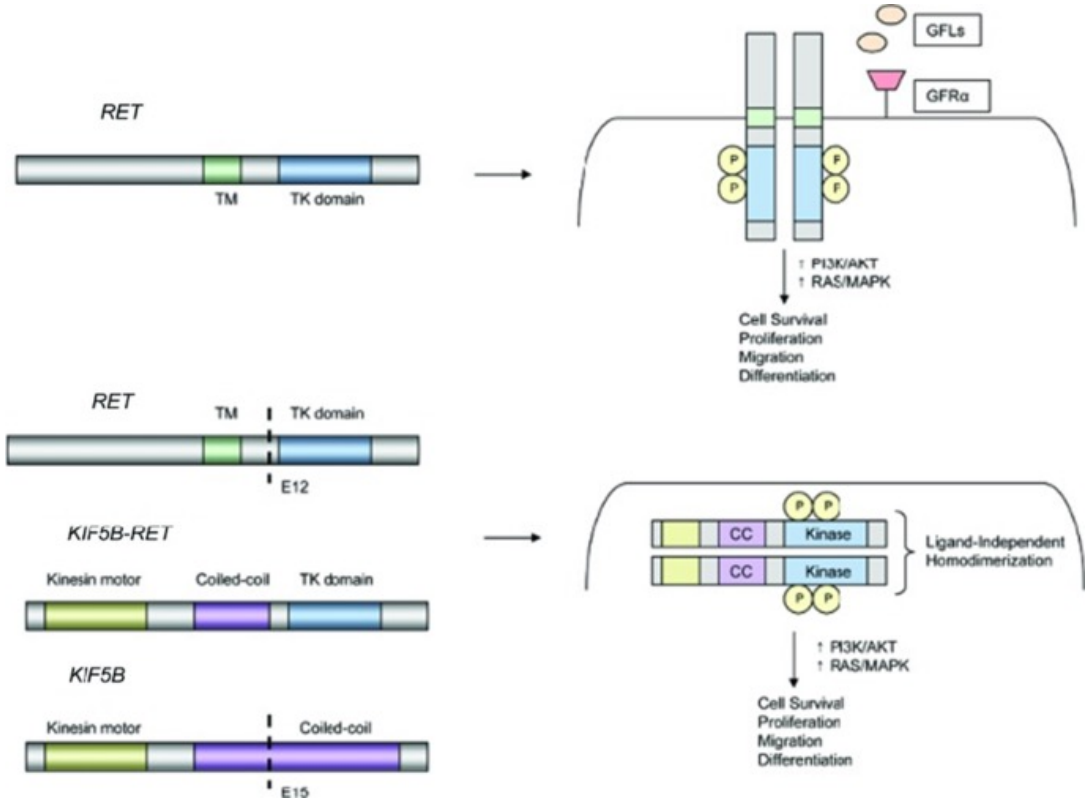
Non-small cell lung cancer (2%)

Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)

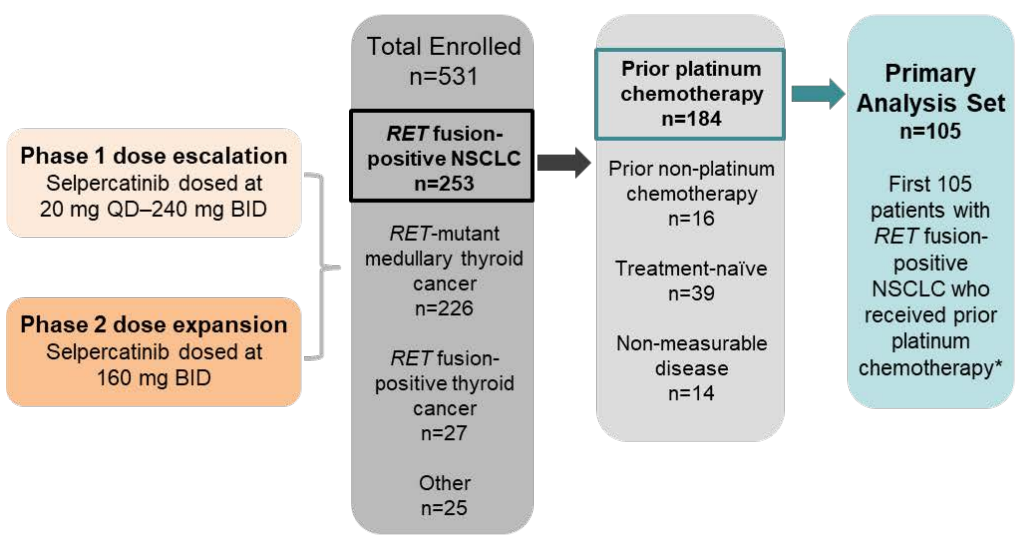


KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

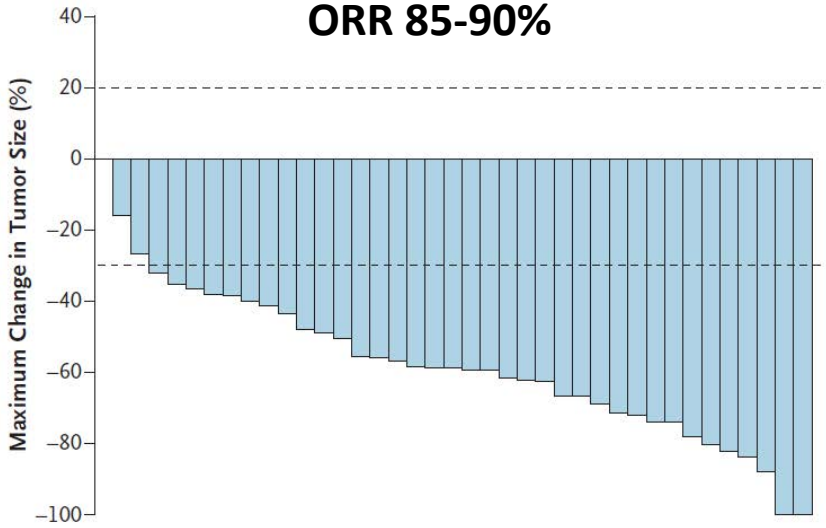


Drilon A et al. ASCO 2018; Gainor JF, et al. Oncologist 2013

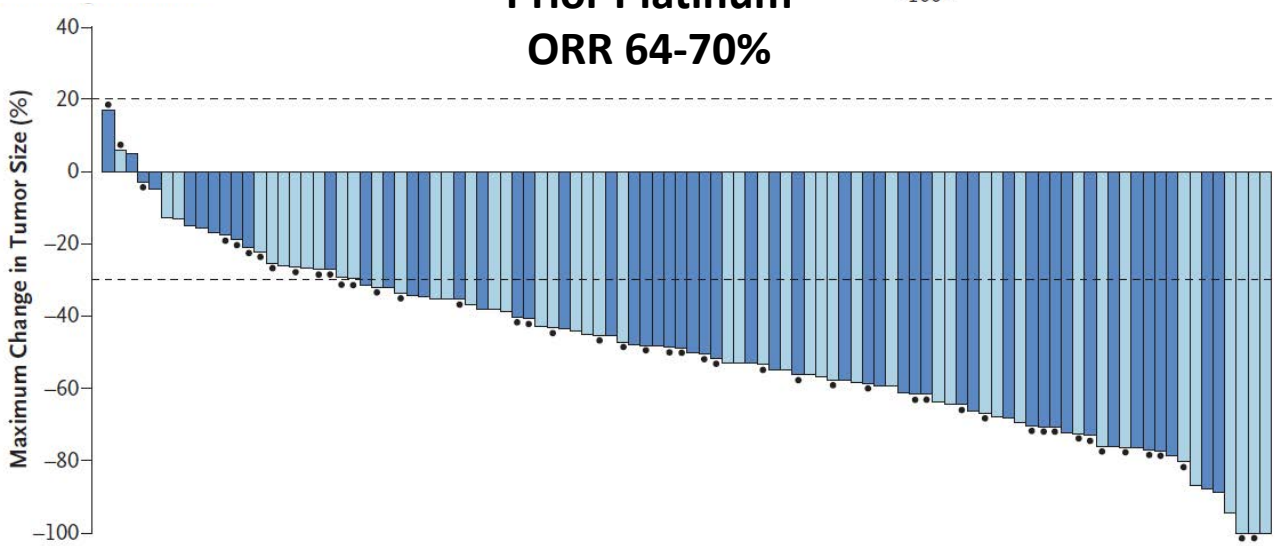
Libretto-001: Selpercatinib



Treatment-naïve
ORR 85-90%



Prior Platinum
ORR 64-70%



Drilon A, et al. NEJM 2020; Drilon A, WCLC 2019

Selective RET TKIs

Agent	Ref	Post-Platinum			Treatment-naïve			Most Common AEs
		N	ORR[#]	Median PFS	N	ORR[#]	Median PFS	Treatment-Related[^]
Selpercatinib	Drilon A, et al. NEJM 2020	105	64%	16.5 mo	39	85%	NR	Dry mouth (36%), Diarrhea (22%), HTN (25%), elevated ALT/AST (20-22%), fatigue (19%)
	Besse B, et al. ASCO 2021 Update	218	57%	19.3 mo	48	85%	NR	
	Drilon A, et al. ELCC 2022 Update	247	61%	24.9 mo	69	84%	22.0 mo	

Based upon blinded independent review; ^ Data from 2021 report

ARROW: Pralsetinib

Phase 2 study design

- Advanced solid tumors
- RET-altered (local testing)
- No other driver mutations
- ECOG PS 0-1

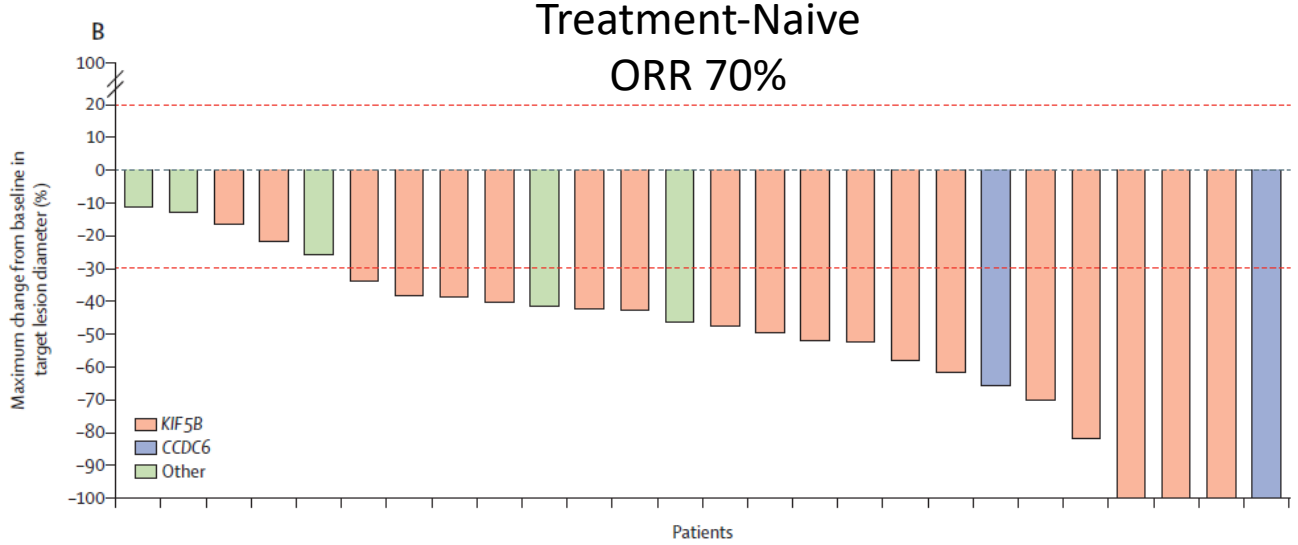
Pralsetinib dosing:
400 mg PO QD

- *RET* fusion-positive NSCLC
- *RET* mutation-positive MTC
- *RET* fusion-positive other tumors

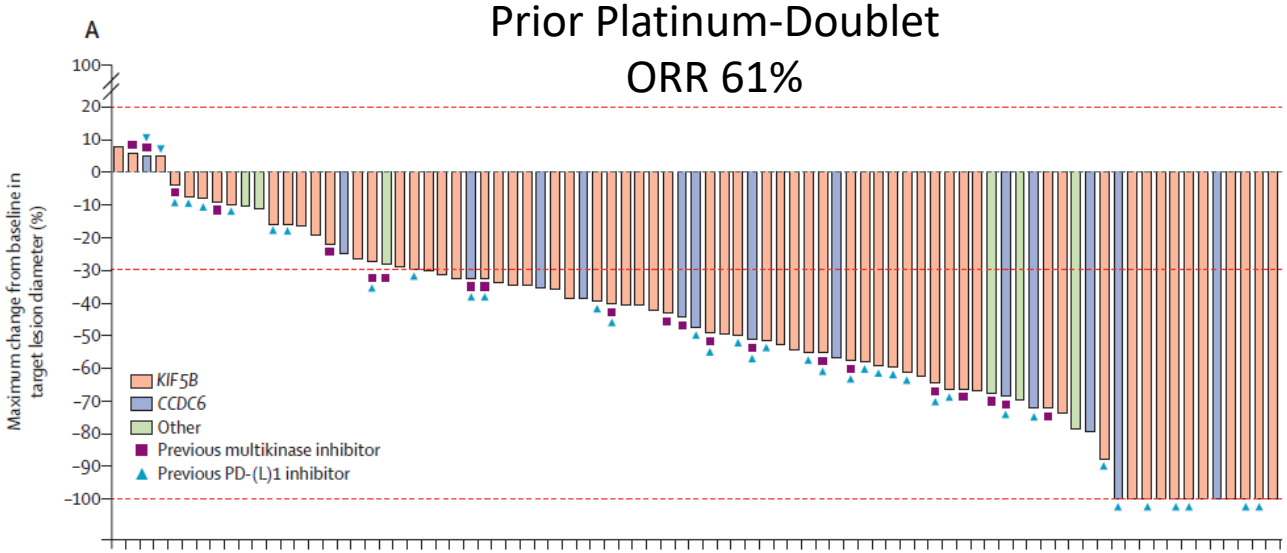
Primary endpoints

- Centrally reviewed ORR per RECIST v1.1
- Safety

Treatment-Naive
ORR 70%



Prior Platinum-Doublet
ORR 61%



Gainor JF, et al. Lancet Oncol 2021

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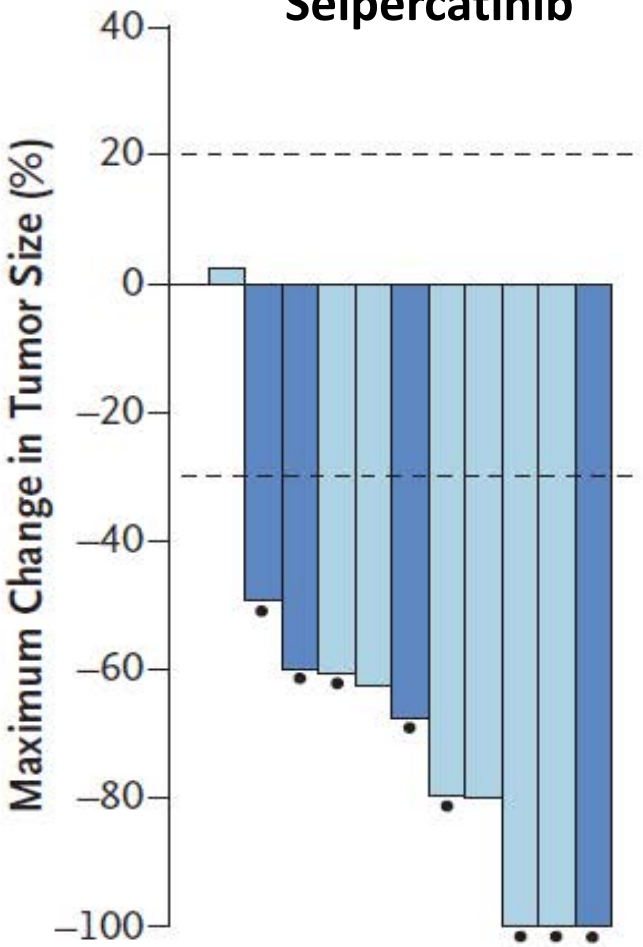
	Drilon A, et al. ELCC 2022 Update	247	61%	24.9 mo	69	84%	22.0 mo	
Pralsetinib	Gainor JF, et al. Lancet Oncol 2021	87	61%	17.1 mo	27	70%	9.1 mo	Neutropenia (42%), AST increase (39%), anemia (38%), WBC decreased (30%), ALT increase (27%) HTN (25%)
	Curigliano G, et al. ASCO 2021 Update	126	62%	16.5 mo	43[*] 25**	74% 88%	10.9 mo NR	

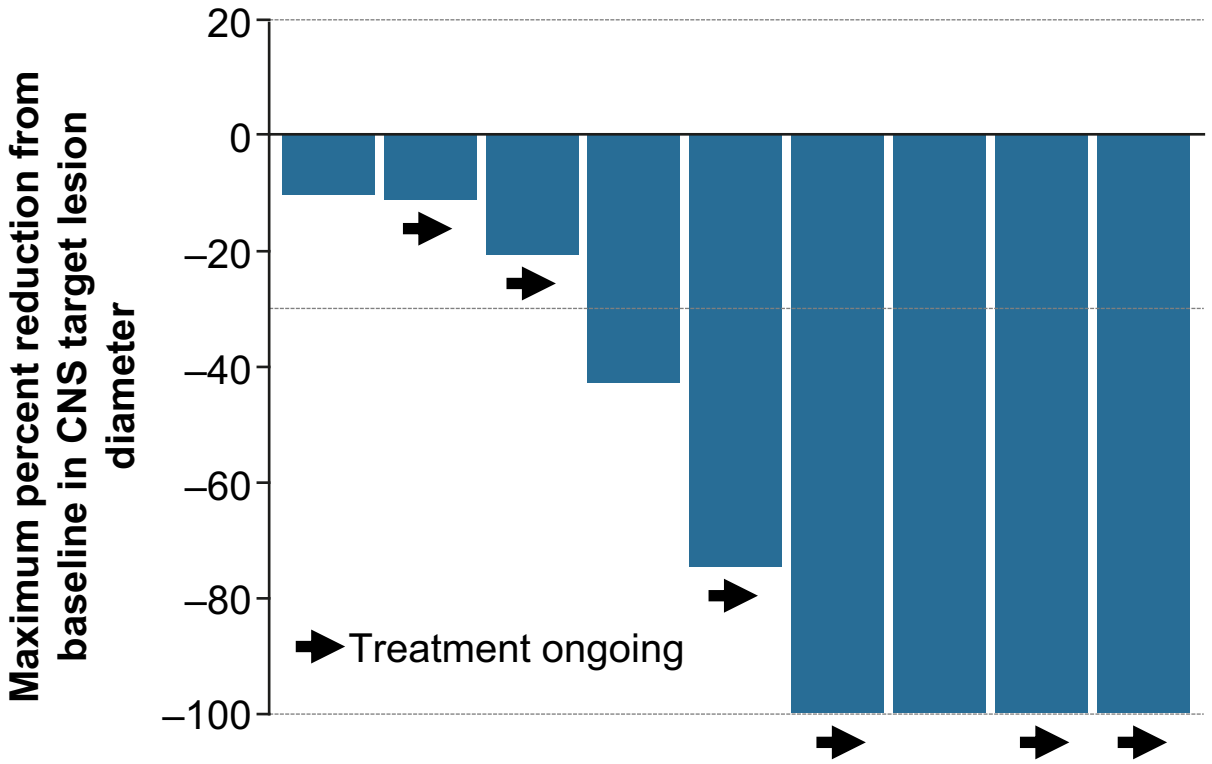
Based upon blinded independent review; ^ Data from 2021 reports; * Pre-eligibility revision; ** Post-eligibility revision

CNS Activity of Selective RET TKIs

Selpercatinib



Pralsetinib



Drilon A, et al. NEJM 2020; Curigliano G, et al. AIMO 2020

Novel RET Inhibitors in Development

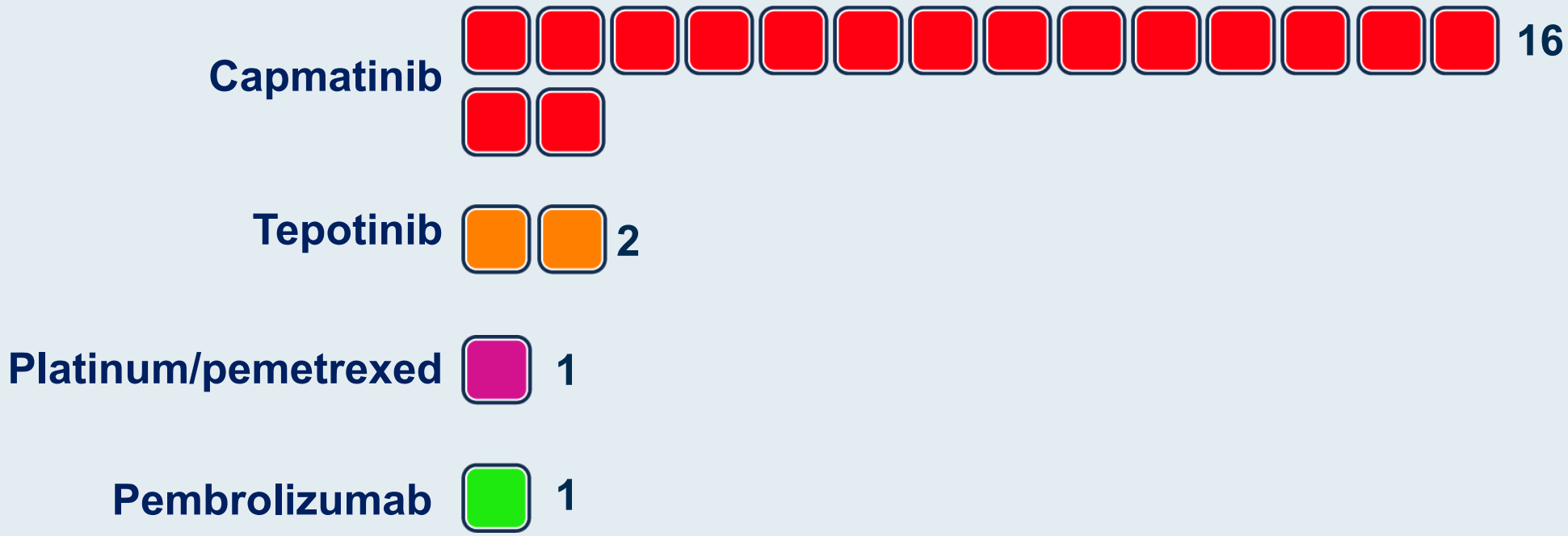
Agent	Target(s)	Resistance Coverage	Clinical Data	NCT
TPX-0046	RET, SRC	RET G810C/S/R	SWORD-1 Phase I/II: 2/5 TKI-naïve pts with PRs, 2/9 RET TKI-pretreated pts with SD[1]	NCT04161391
BOS172738 (DS-5010)	RET	RET V804M	Phase I: 9/30 responses (ORR 30%) in dose escalation (all RET selective TKI-naïve)[2]	NCT03780517
TAS0953/HM06	RET	RET V804M/L & RET G810R/S	Phase I/II ongoing	NCT04683250
LOXO-260	RET, TrkC	RET V804M/L & RET G810S	Phase I ongoing	NCT05241834

1. Turning Point Therapeutics announces initial clinical data from phase 1/2 SWORD-1 study of RET inhibitor TPX-0046. News release. Turning Point Therapeutics, Inc. April 5, 2021. 2. Schoffski P, et al. ASCO 2021. 3. Miyazaki I, et al. Mol Cancer Ther 2021. 4. Kolakowski GR, et al. AACR 2021

MODULE 4: Targeting Alterations in MET, HER2, KRAS and Other Oncogenes in NSCLC — Dr Weiss

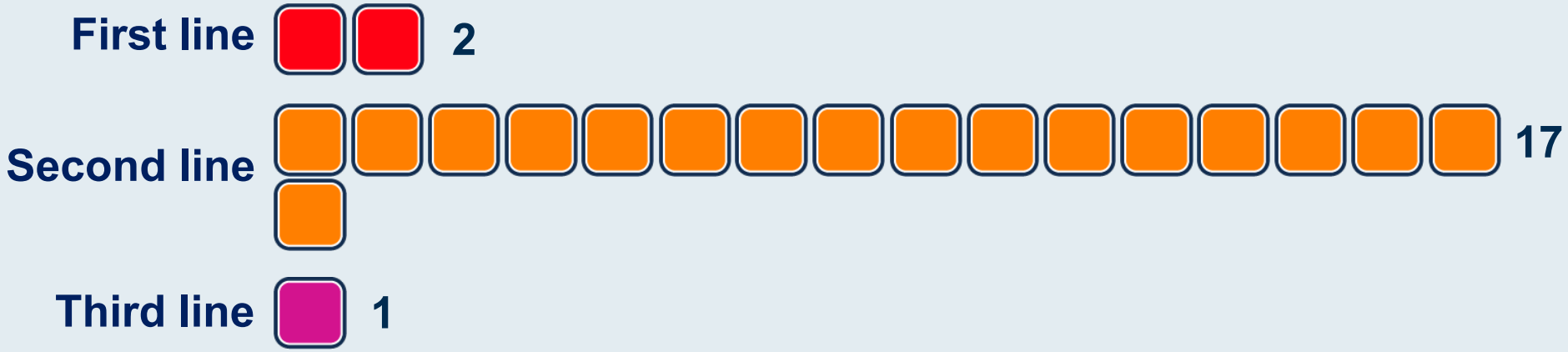
RTP
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a MET exon 14 skipping mutation?

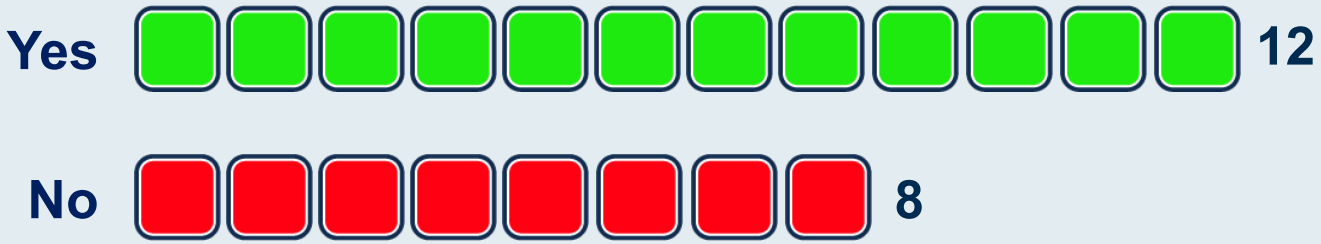


Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer an immune checkpoint inhibitor (alone or in combination with chemotherapy) to a patient with metastatic nonsquamous NSCLC and a MET exon 14 skipping mutation?



Would level of PD-L1 expression have any bearing on this decision?



Survey of lung cancer clinical investigators

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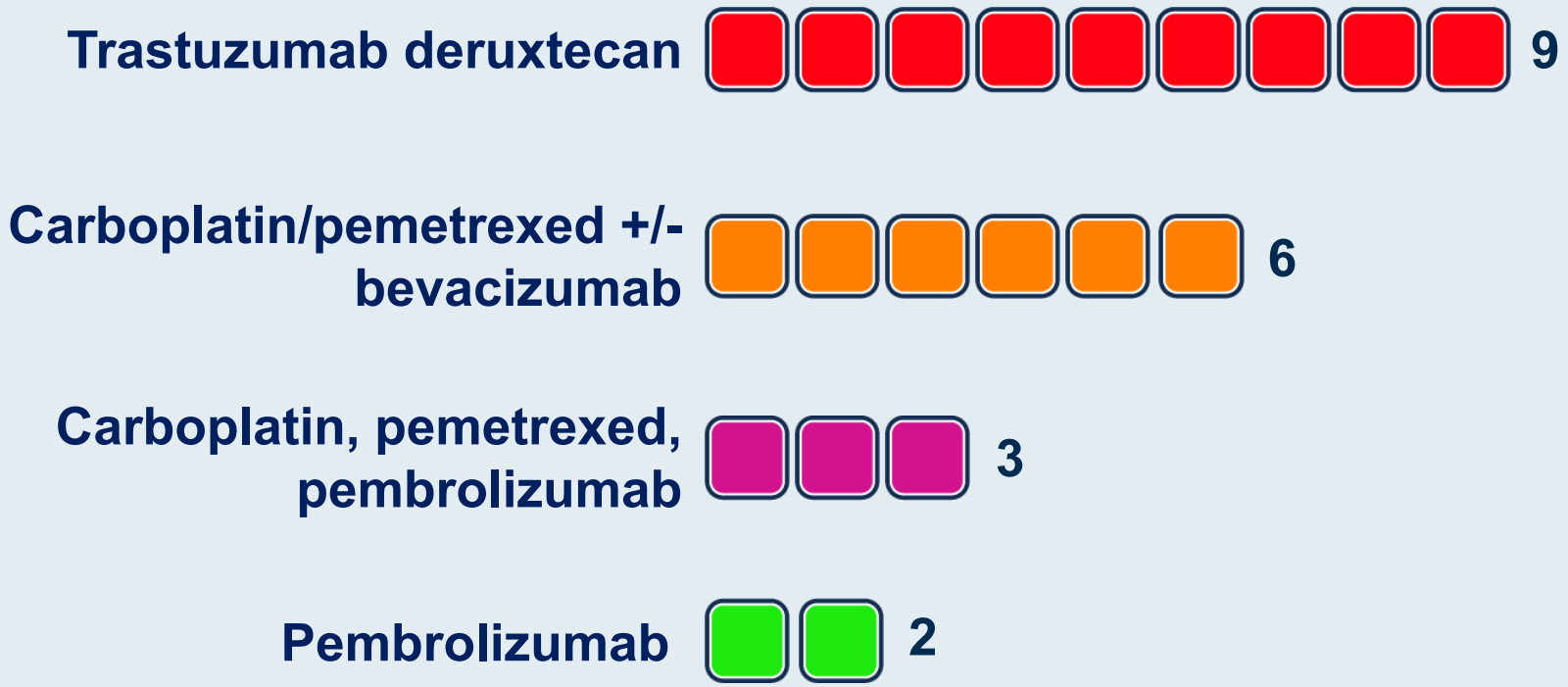
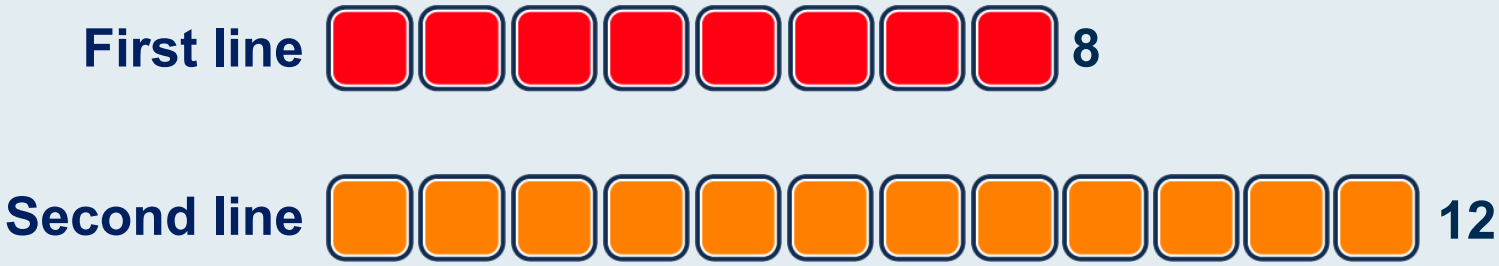


Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, in which line of therapy would you generally offer targeted treatment to a patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a HER2 mutation?



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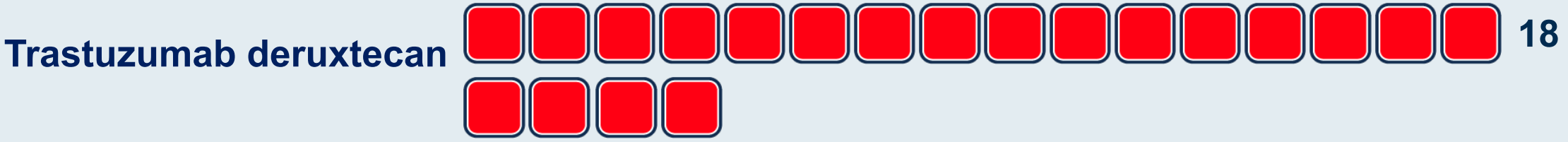

Survey of lung cancer clinical investigators

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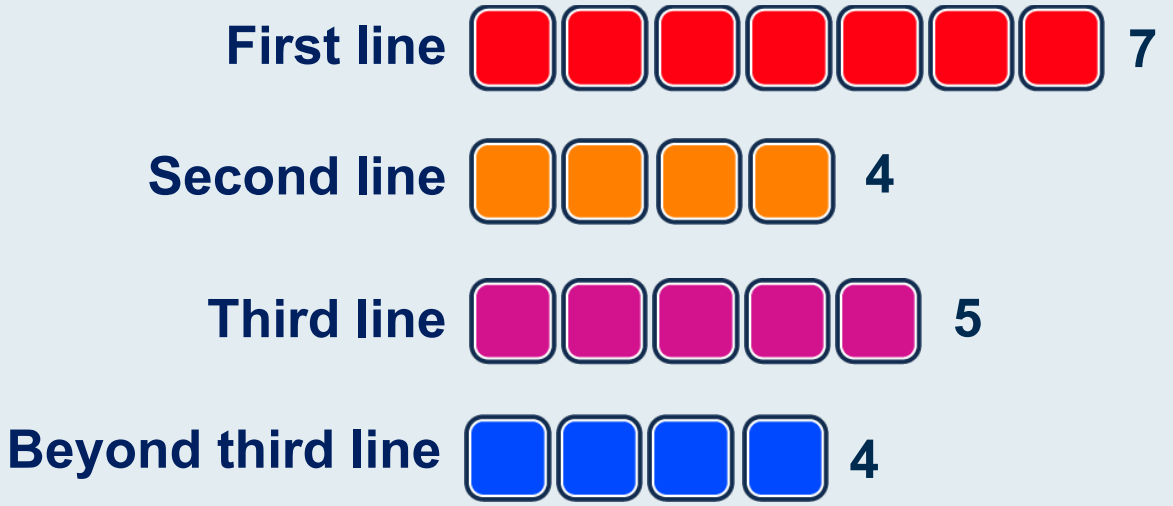

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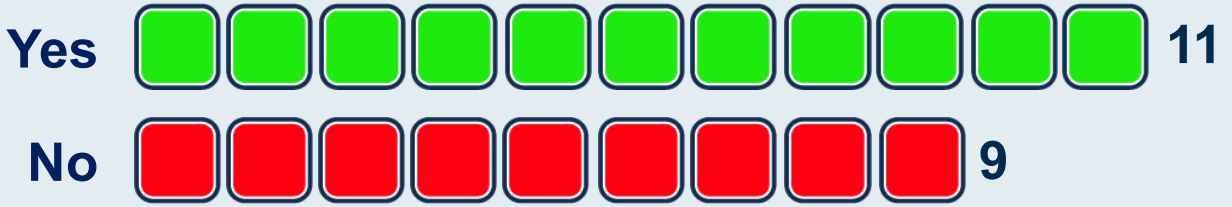


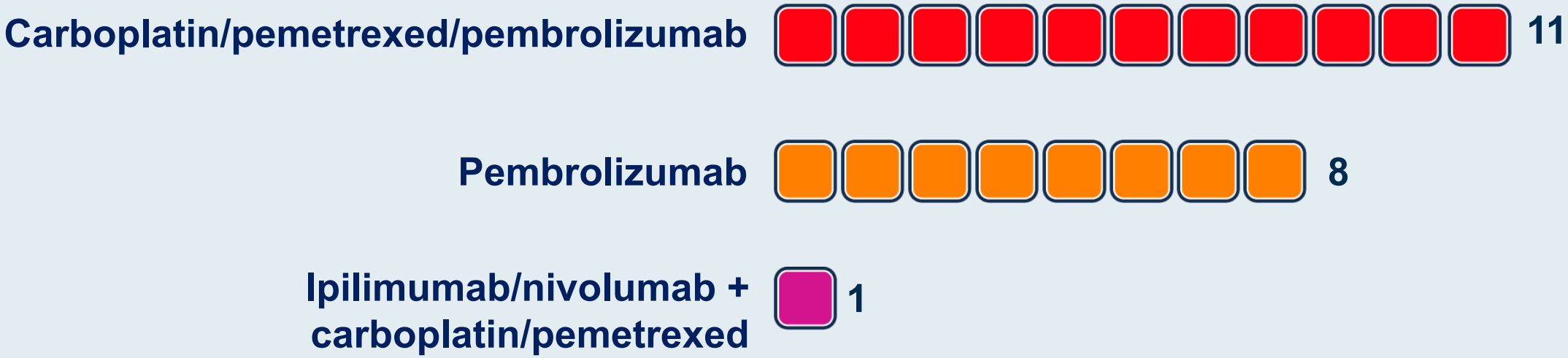
Survey of lung cancer clinical investigators

Do you use adjunctive methods other than imaging and clinical evaluation to detect interstitial lung disease from trastuzumab deruxtecan?

What do you generally advise your patients who are about to begin treatment with trastuzumab deruxtecan regarding the potential for chemotherapy-like side effects?

Survey of lung cancer clinical investigators

Regulatory and reimbursement issues aside, what would be your preferred first-line therapy for a 65-year-old asymptomatic patient with metastatic nonsquamous NSCLC (PD-L1 TPS 50%) and a KRAS G12C mutation?



Survey of lung cancer clinical investigators

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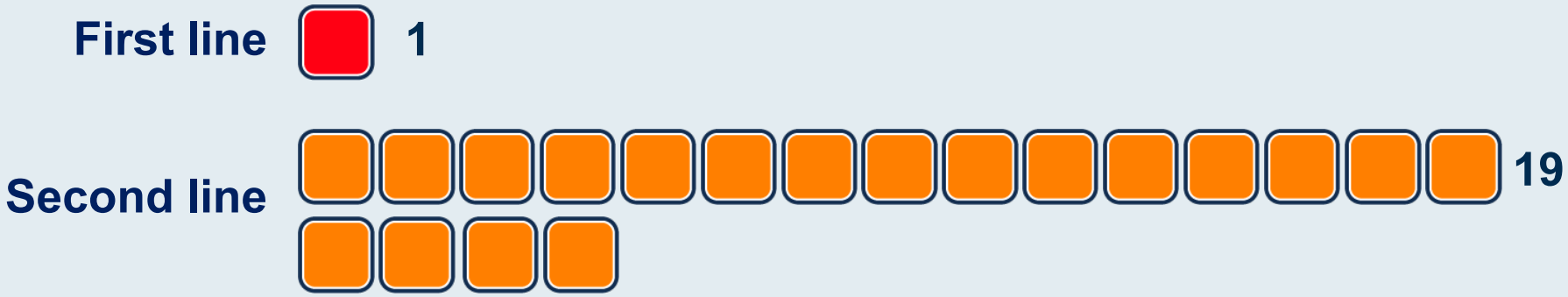
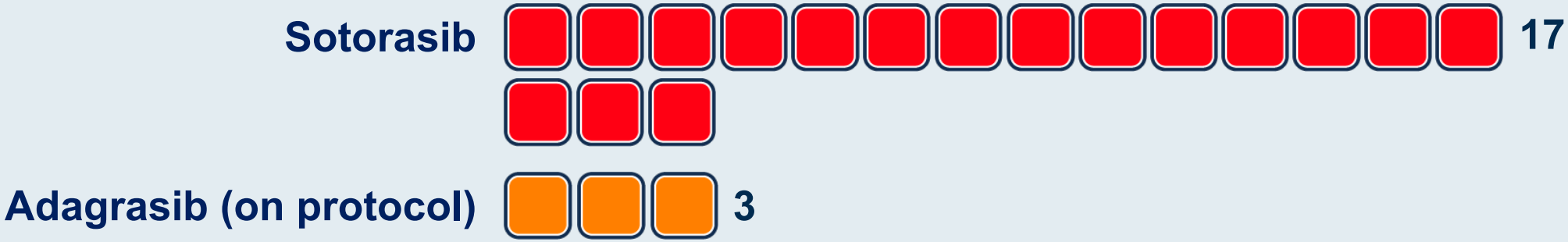


Which targeted treatment would you generally offer?



Survey of lung cancer clinical investigators

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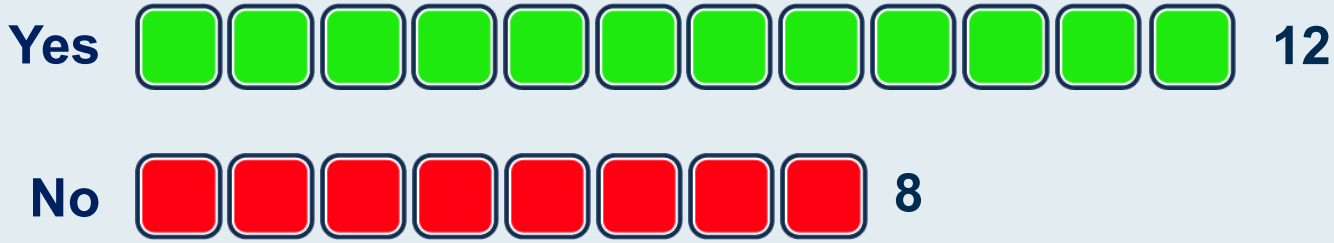


Survey of lung cancer clinical investigators

UNC | LINEBERGER COMPREHENSIVE CANCER CENTER

UNC CANCER CARE

Targeting Alterations in *MET, HER2, KRAS* and Other Oncogenes in NSCLC

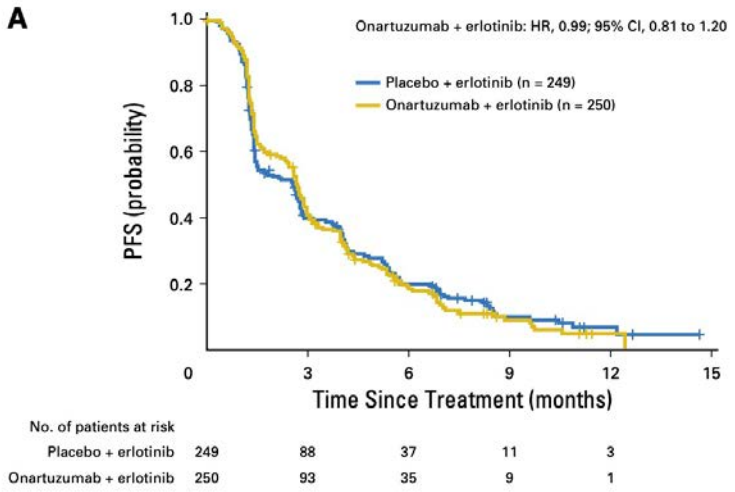
Jared Weiss, MD
Professor of Medicine
Section Chief of Thoracic and Head/Neck Oncology
Fri, June 3, 2022

Topics to be covered

- Key efficacy and safety findings with the use of capmatinib and tepotinib in patients with MET exon 14 mutation-positive NSCLC
- Early data with amivantamab in patients with NSCLC with MET exon 14 skipping mutations
- Principal efficacy and safety findings with sotorasib and adagrasib in pretreated KRAS G12C-mutated NSCLC
- Results from the Phase II DESTINY-Lung01 study evaluating trastuzumab deruxtecan in HER2-mutated NSCLC
- Early data with and ongoing investigations of other novel agents and strategies (eg, telisotuzumab vedotin, datopotamab deruxtecan, seribantumab) in patients with actionable genomic abnormalities

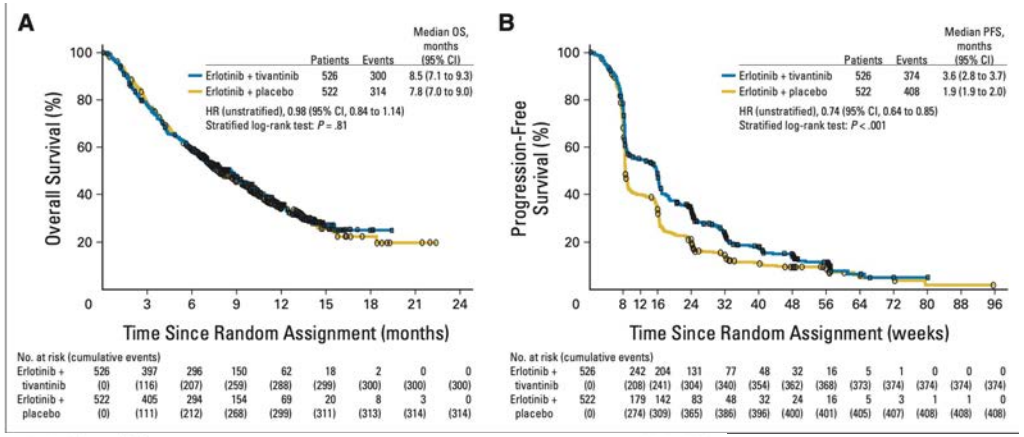
MET—A Critical Lesson That Testing Methods Matter (and re the follies of believing subgroup analysis of phase II studies)

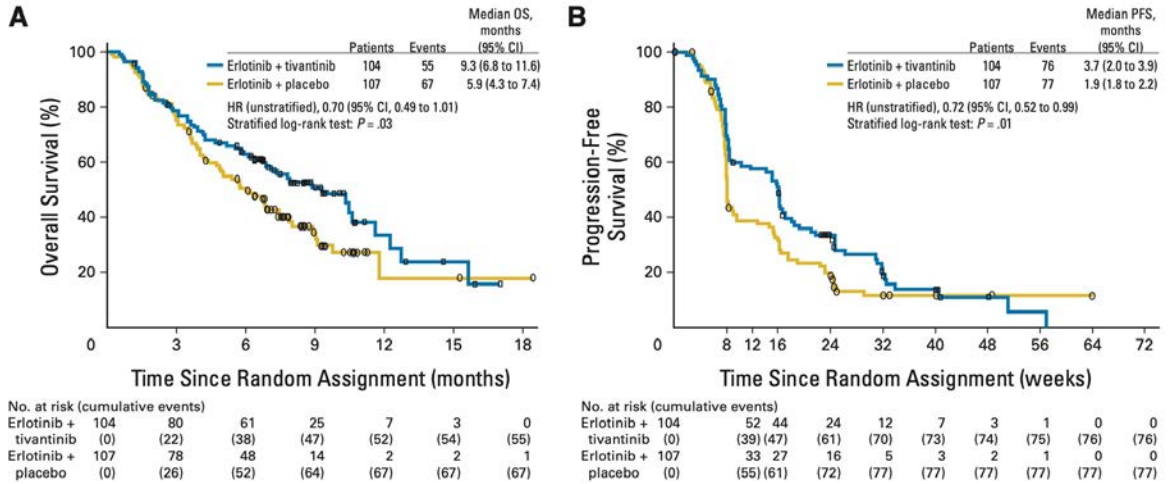
Onartuzumab



Spigel DR, Edelman MJ, O'Byrne K et al. JCO 2017

Tivantinib

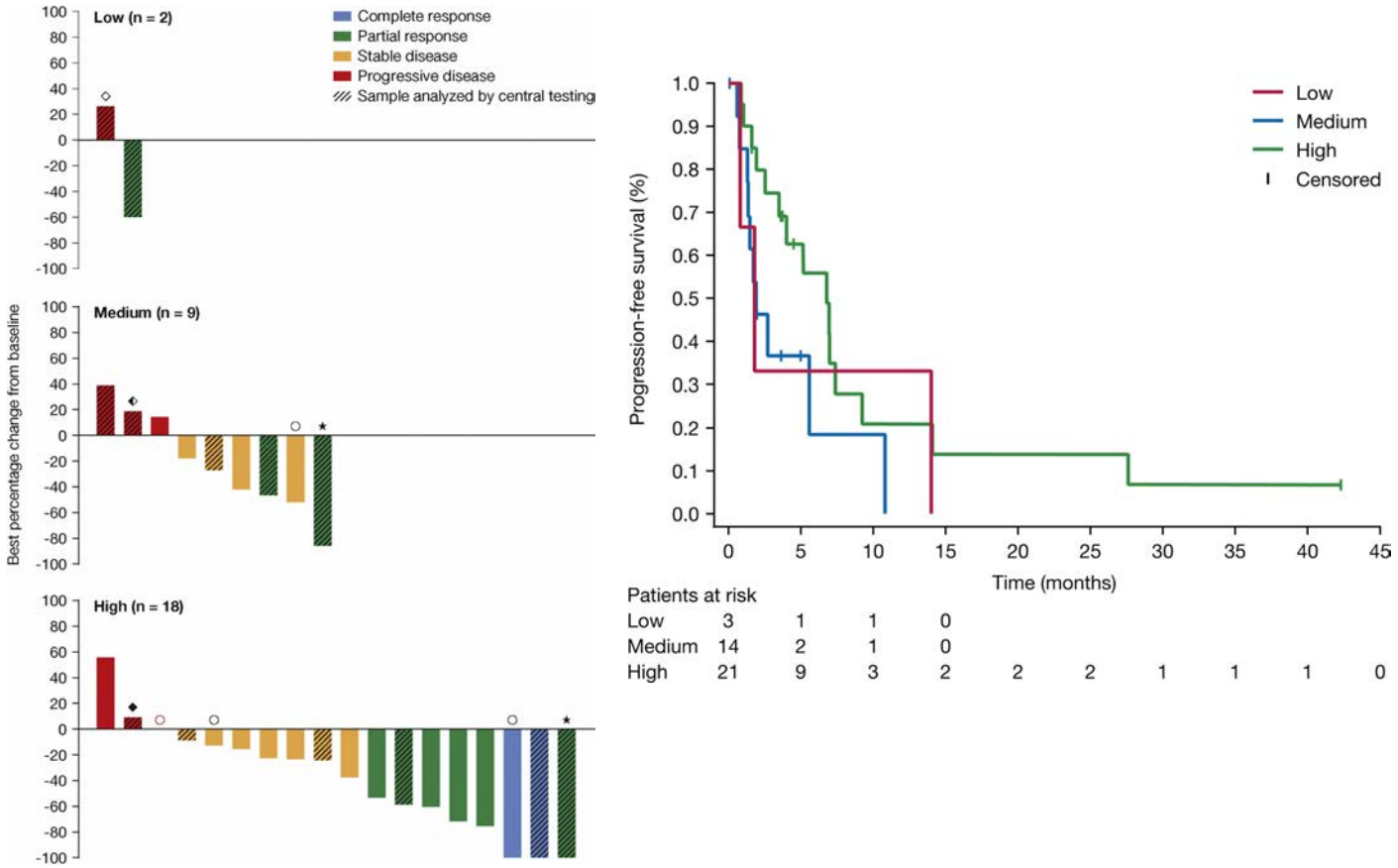




Scagliott G, Pawel J, Novello S et al. JCO 2015

MET and biomarkers, cont.

Crizotinib



Camidge DR, Otterson GA, Clark JW et al. JTO 2021

Capmatinib

IHC	0/1+ (n=3)	2+ (n=14)	3+ (n=37)
RR	0	14	24
PFS			7.3m

MET/CEP7	<2 (n=32)	≥2(n=9)
RR	16	33
PFS		5.6

MET CGN	<4 (n=17)	4-5 (n=15)	≥6 (n=15)
RR	0	17	47
PFS			9.3

Schuler M, Berardi R, Lim W-T, Annals of Oncology 2020

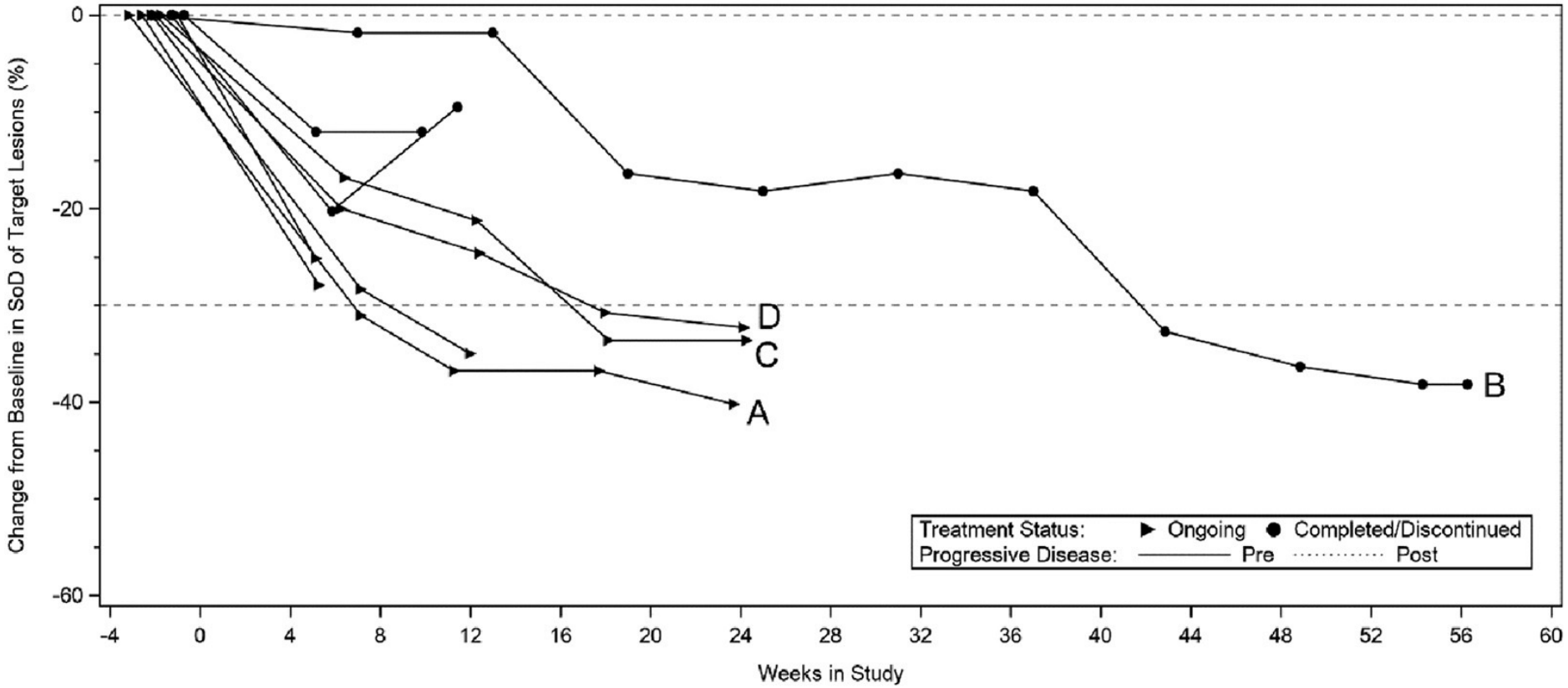
MET del 14 clinical outcomes data with crizotinib, capmatinib and tepotinib

Drug/Context	RR	PFS	OS
Crizotinib, pre-Rx	37%	7.3m	
Crizotinib 1L	25%		
Capmatinib, pre-Rx	41-48%		
Capmatinib, 1L	66-68%	10.8-12.4m	20.8-NE
Tepotinib, pre-Rx	45%		
Tepotinib, 1L	46%		

1. Drilon A, Clark JW, Weiss J, et al: Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. Nat Med 26:47-51, 2020
2. Wolf J, Garon EB, Groen HJM et al. Capmatinib in MET exon 14-mutated, advanced NSCLC: Updated results from the GEOMETRY mono-1 study. ASCO 2021
3. Paik P, Sakai H, Felip E. VISION Cohort A. WCLC 2021.

Amivantamab

Figure. Spider Plot of Response-evaluable Patients (n=9)



Spira A, Krebs M, Cho BC. CHRYSALIS. WCLC 2021;Abstract OA15.03

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

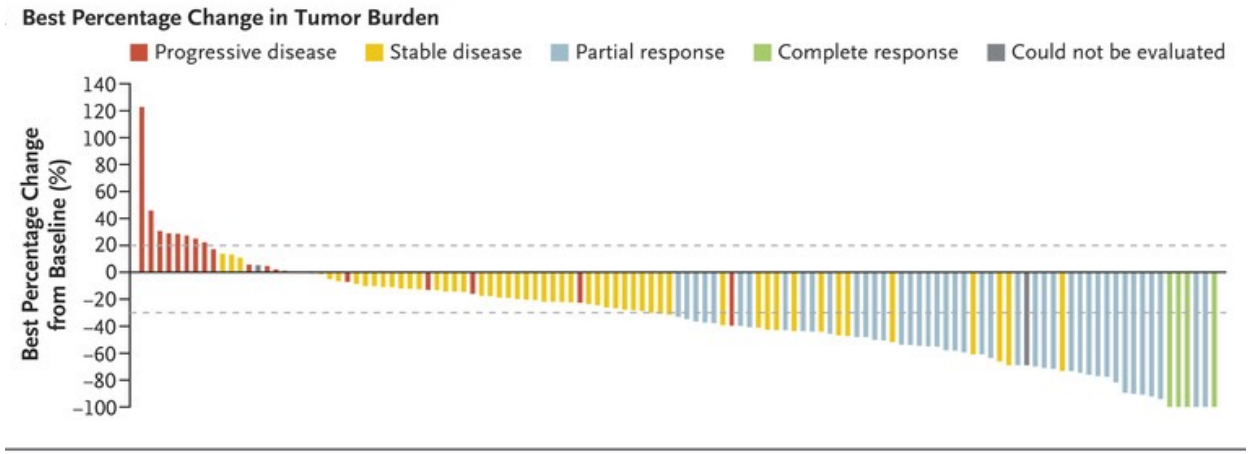
Matthew Krebs et al.
ASCO 2022;Abstract 367168.

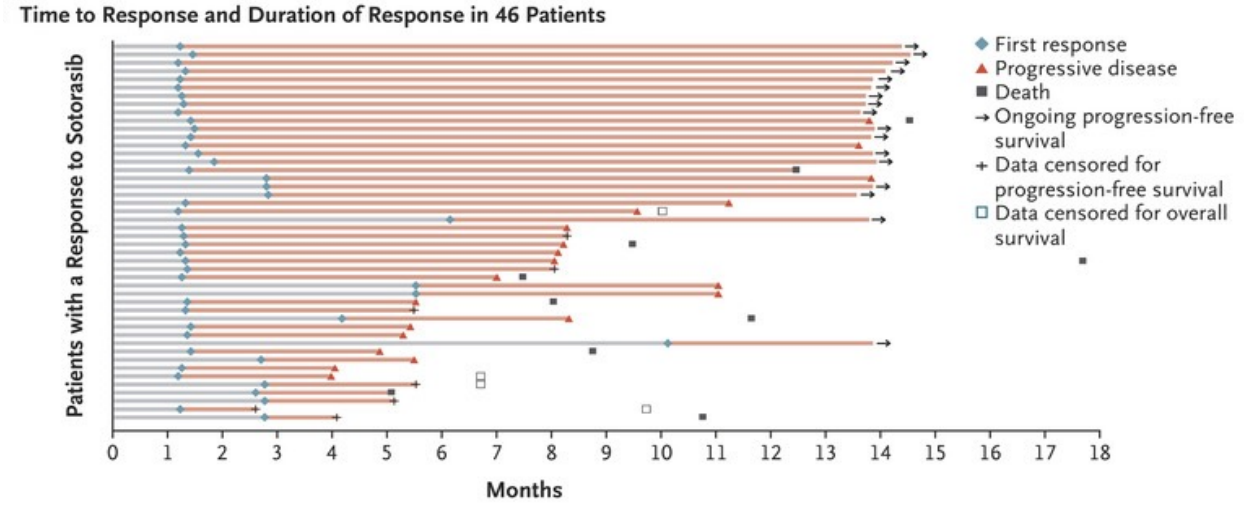
Telisotuzumab vedotin

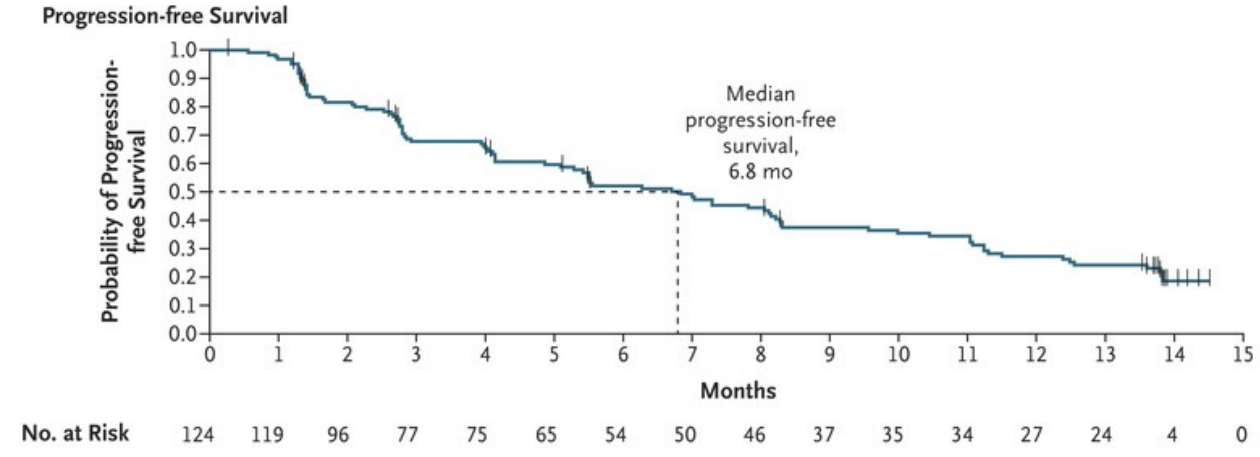
NSCLC Group	N(Total=88)	Confirmed Responses	ORR(95% CI)
NSQ EGFR WT	37	13	35.1% (20,53)
c-Met high (≥ 50% positive, 3+ staining)	13	7	53.8% (25, 81)
c-Met int(25-49%, 3+ staining)	24	6	25.0% (10,47)
NSQ EGFR MU	30	4	13.3% (4,31)
c-Met high (≥ 50%, 3+ staining)	22	4	18.2% (5, 40)
c-Met int (25-49%, 3+ staining)	8	0	0 (-,-)
SQUAMOUS(≥ 75%, 1+ staining)	21	3	14.3% (3, 36)

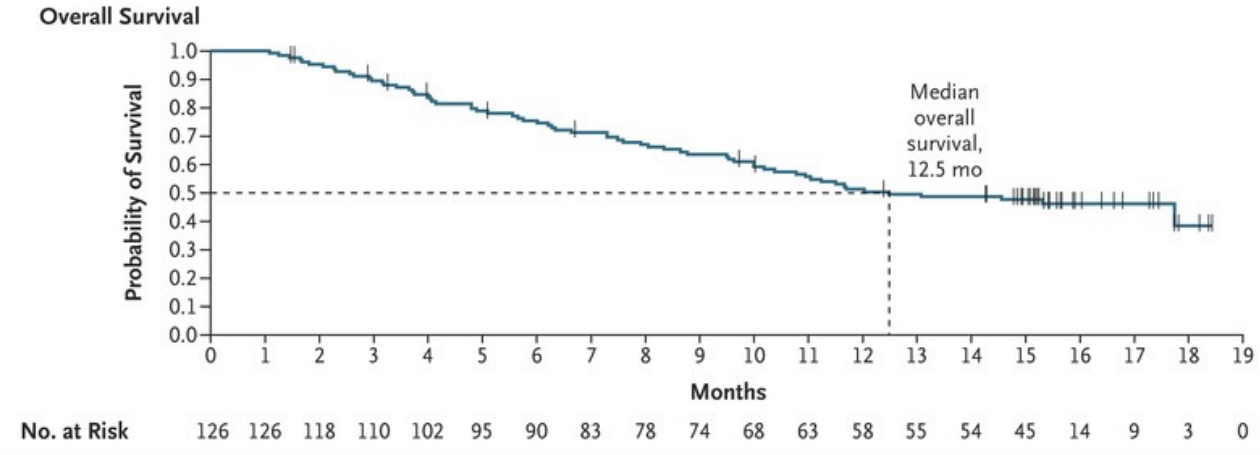
Camidge DR, Moiseenko F, Cicin I et al, AACR 2021

Sotorasib for *kRAS G12C* NSCLC





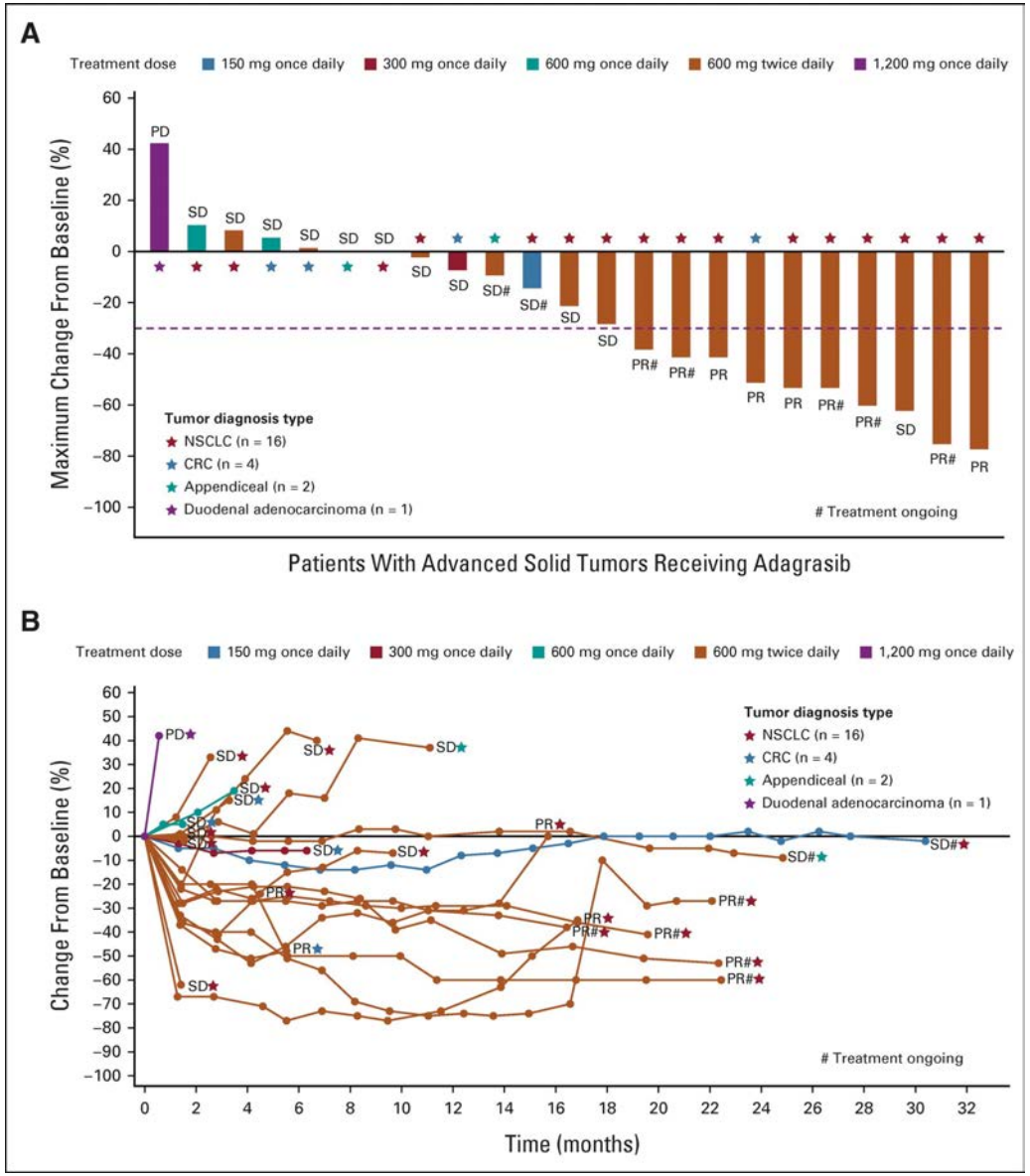




Skoulidis, NEJM 2021

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

Adagrasib for *kRAS G12C*



ASCO 2022

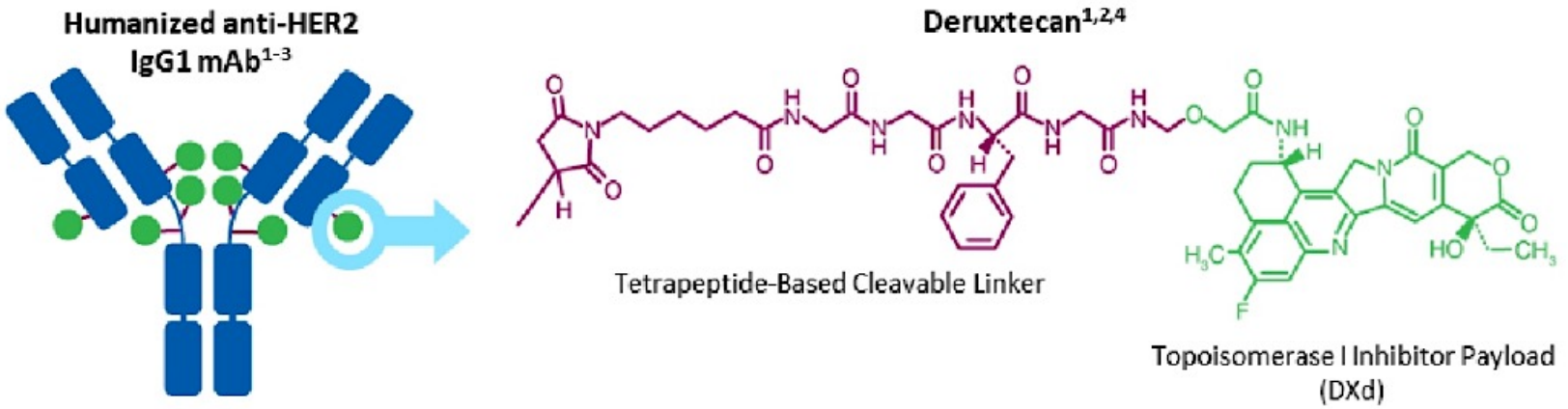
- Full results from the registration-enabling Phase 2 cohort of the KRYSTAL-1 study evaluating *adagrasib* in patients with pre-treated non-small cell lung cancer (NSCLC) harboring a $KRAS^{G12C}$ mutation
- Late-breaking data on *adagrasib* in patients with $KRAS^{G12C}$-mutated NSCLC with active and untreated central nervous system (CNS) metastases

Ou SI, Janne PA, Leal TA et al. KRYSTAL-1, JCO 2022

Antibody-Drug Conjugate Trastuzumab Deruxtecan (T-DXd)

T-DXd is an ADC with 3 components:

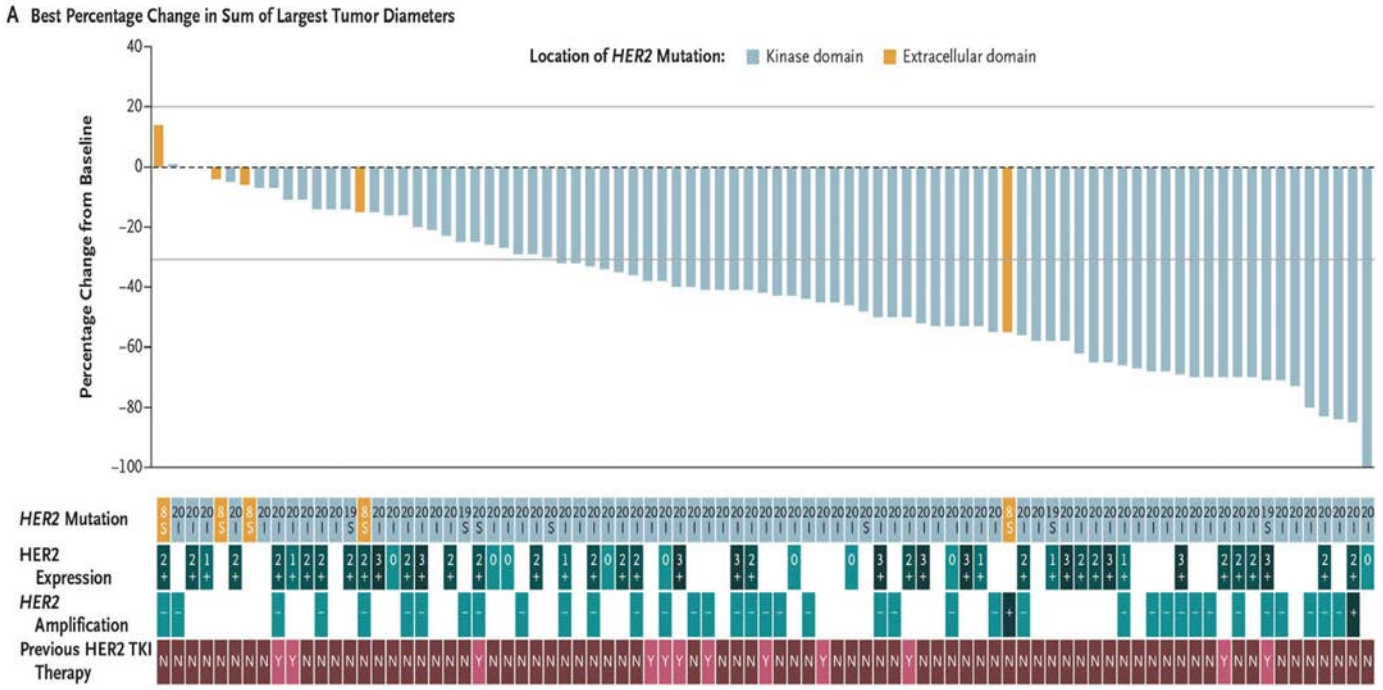
- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

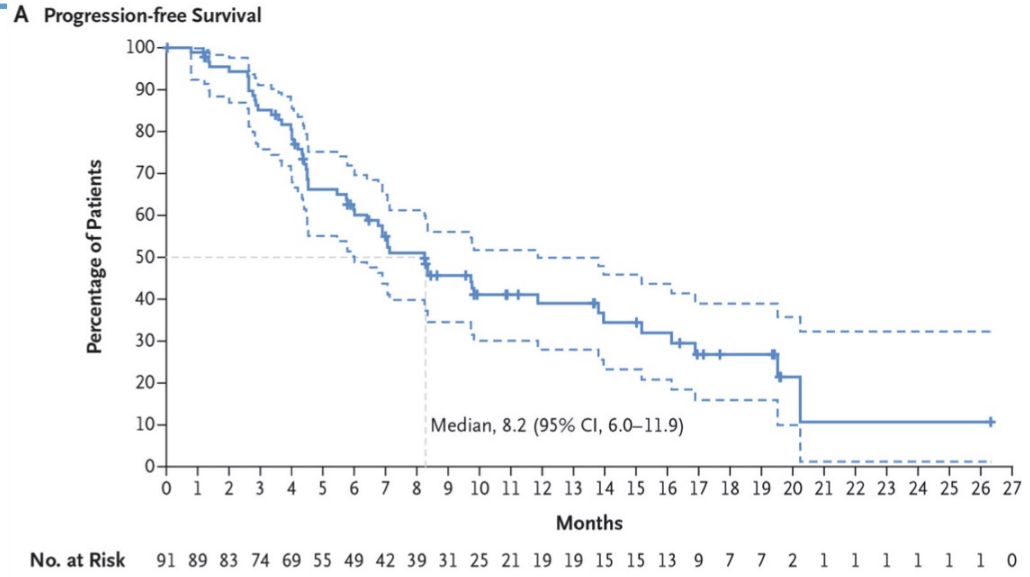


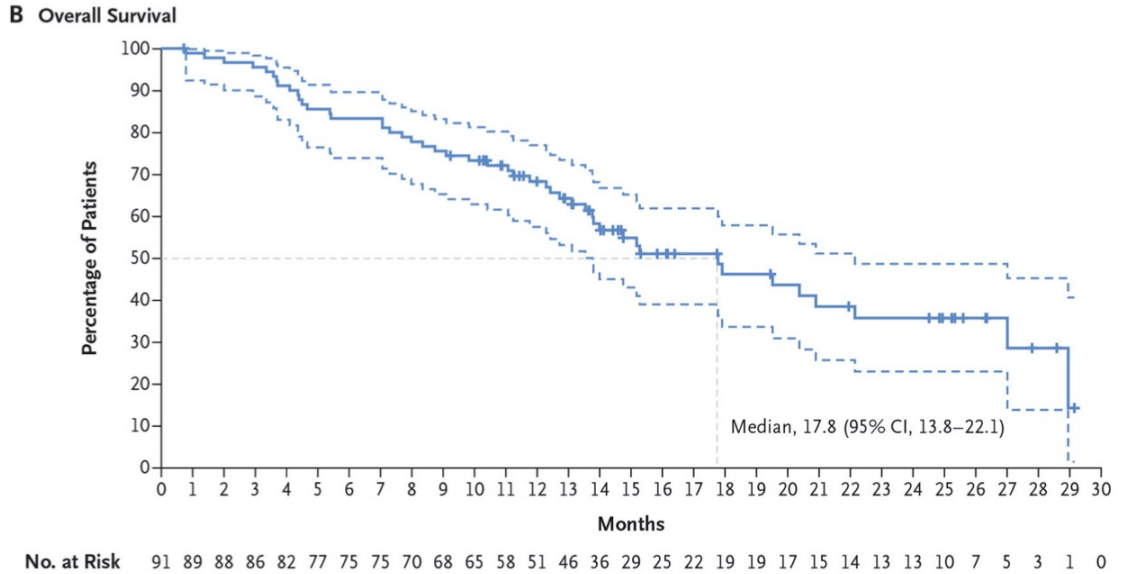
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

Smit EF et al. ASCO 2020;Abstract 9504.

Trastuzumab deruxtecan in HER2-mutated NSCLC







Li BT, Smit EF, Goto Y et al. Destiny-Lung01, NEJM 2022

DESTINY-Lung01: Summary of Adverse Events and AEs of Clinical Interest

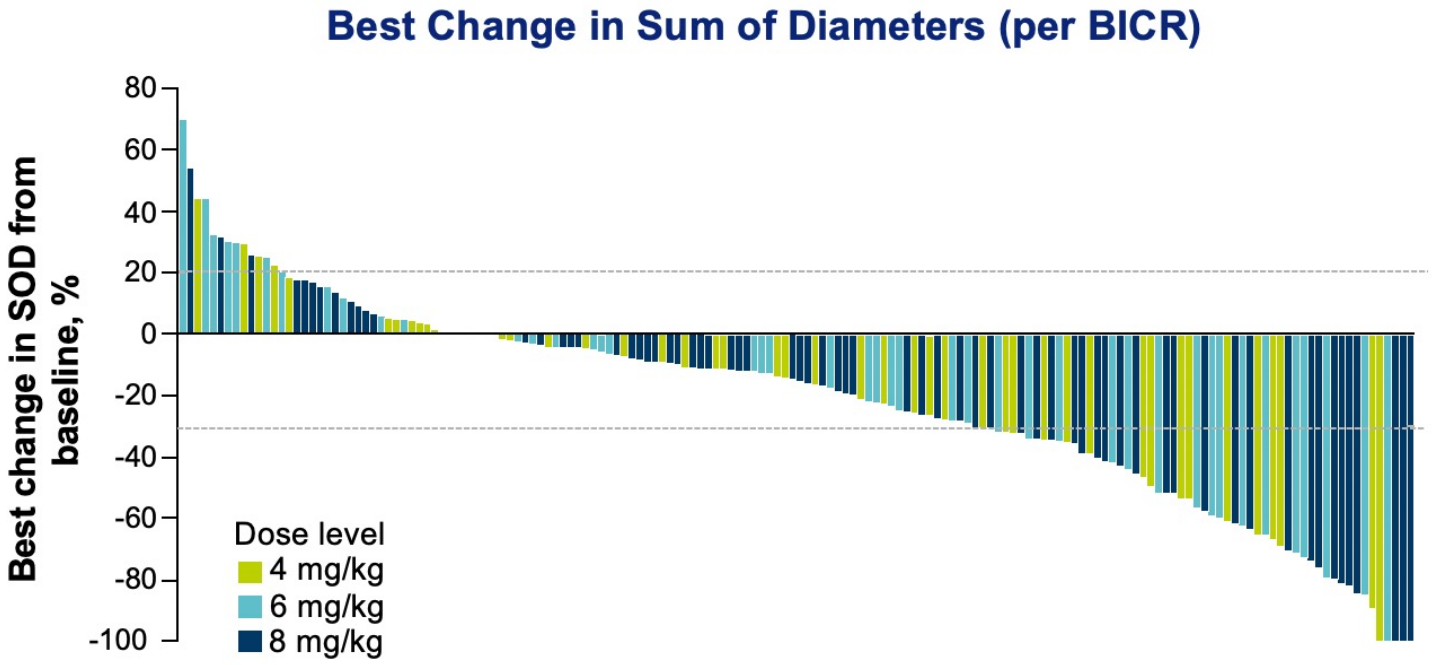
Event	N = 91
Discontinued due to AEs	25%
Dose reduction due to AEs	34%
Dose interruption due to AEs	32%
Drug-related interstitial lung disease (ILD)	26% (N = 24)
Grade 1	3 pts
Grade 2	15 pts
Grade 3	4 pts
Grade 5	2 pts
Median time to onset of ILD	141 days
Median duration of ILD	43 days

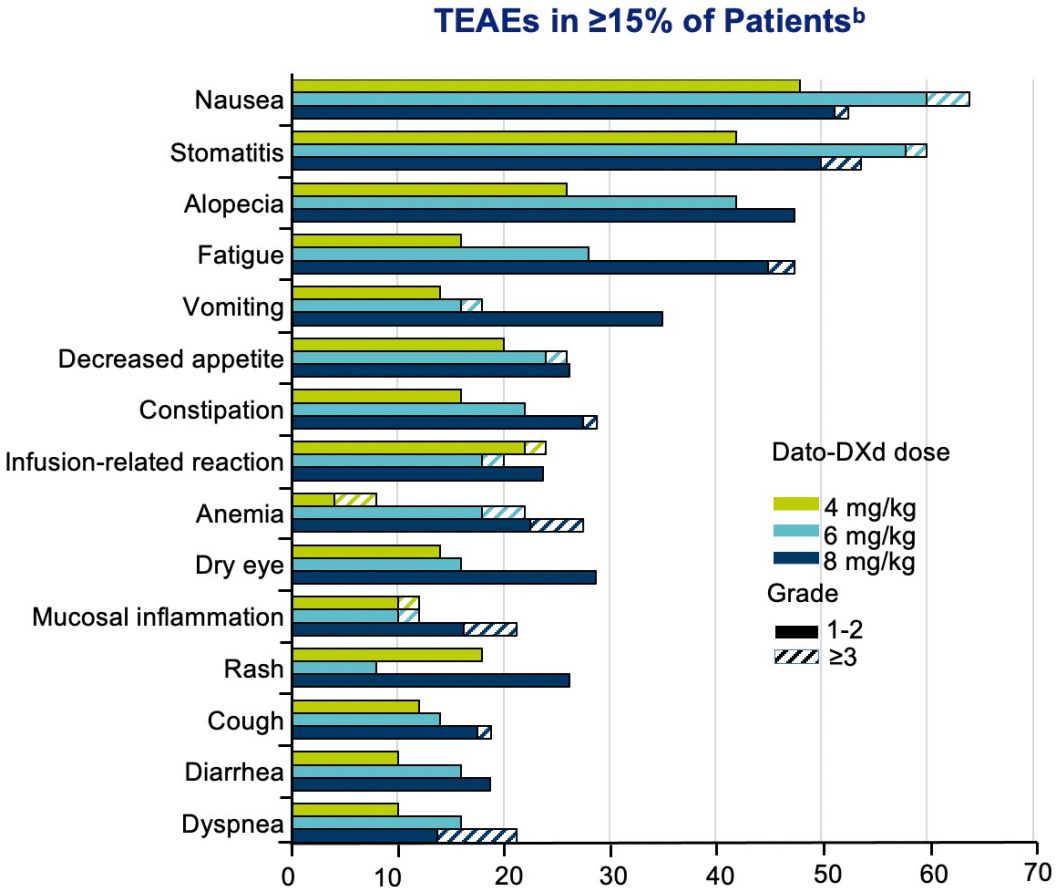
Li BT et al. *N Engl J Med* 2022;386(3):241-51.

Should these new targets be 1L?

- What is the bar?
- How well does IO or chemo/IO work in the population?
- Greater toxicity of TKI post IO?
- Patient preferences

Datopotamab Deruxtecan-- TROPION-PanTumor01





Garon et al. WCLC 2021;Abstract MA03.02

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

Phase I TROPION-PanTumor01 (NSCLC Cohort): Antitumor Activity of Dato-DXd in NSCLC with Actionable Genomic Alterations

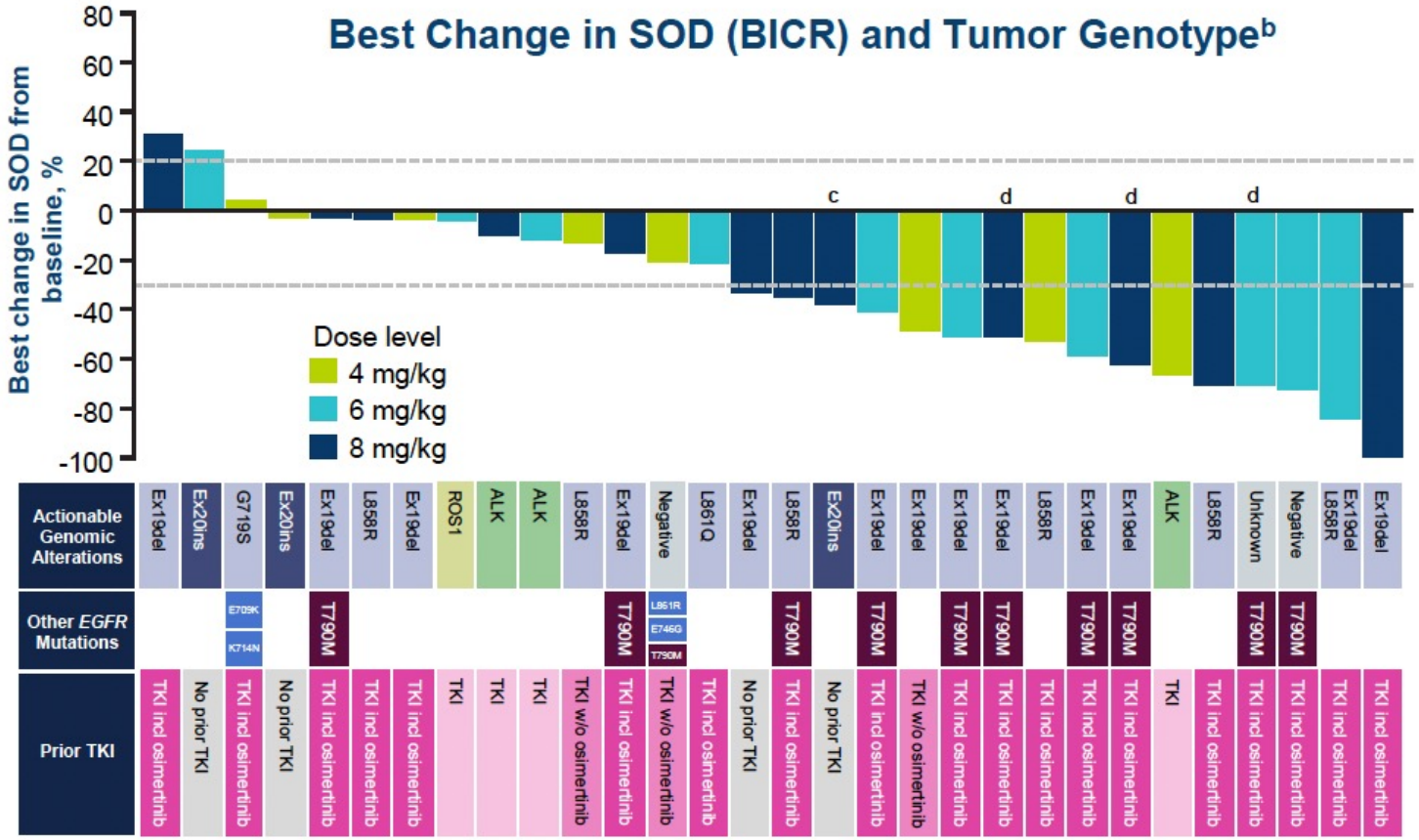
Best Overall Response (BICR)

Patients[a]	Dato-DXd n=34
ORR, n (%)	12 (35)
CR	0
PR	12 (35)
SD, n (%)	14 (41)
Non-CR/PD, n (%)	2 (6)
PD, n (%)	2 (6)
NE, n (%)	4 (12)
DOR, median (95% CI), mo	9.5 (3.3-NE)

- Clinical activity was observed in *EGFR* (Ex19del, L858R) including after osimertinib and across other AGAs

Data cutoff: April 6, 2021.

Best Change in SOD (BICR) and Tumor Genotype[b]



TROPION-PanTumor01: Safety Summary

Overall Safety Summary

Patients, n (%)	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
TEAE	49 (98)	49 (98)	80 (100)
Grade ≥3	15 (30)	27 (54)	46 (58)
Drug-related TEAE	47 (94)	41 (82)	78 (98)
Grade ≥3	7 (14)	13 (26)	28 (35)
Serious TEAE	10 (20)	24 (48)	40 (50)
Grade ≥3	10 (20)	18 (36)	37 (46)
Dose adjustments			
TEAEs associated with discontinuation	8 (16)	7 (14)	19 (24)
TEAEs associated with dose interruption	4 (8)	15 (30)	29 (36)
TEAEs associated with dose reduction	1 (2)	5 (10)	23 (29)
ILD adjudicated as drug related[a]	5 (10)	3 (6)	11 (14)
Grade ≤2	4 (8)	2 (4)	7 (9)
Grades 3-4	1 (2)	1 (2)	1 (1)
Grade 5	0	0	3 (4)

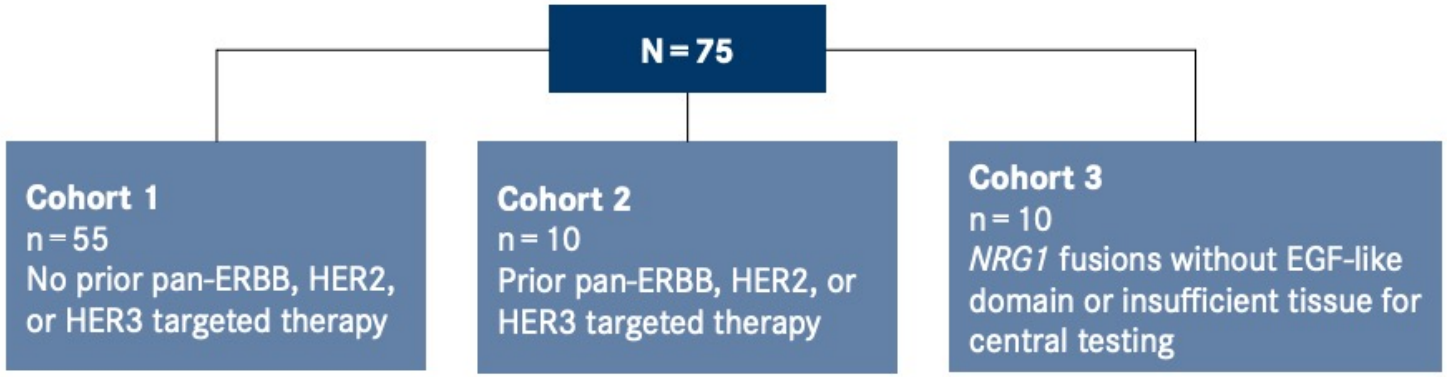
- The safety profile was manageable with mainly mild/moderate toxicity; TEAEs were primarily nonhematologic

Seribantumab

Phase 2 CRESTONE Study

Eligibility criteria

- Locally advanced or metastatic solid tumor with an *NRG1* gene fusion
- Minimum of 1 prior standard therapy
- Progressed on or lack of response to prior therapy
- ECOG performance status of 0 to 2
- At least 1 measurable extracranial lesion defined by RECIST v1.1
- Adequate hepatic function[a] and hematologic status[b]
- Adequate hematologic status



Therapy
Seribantumab 1-hour IV infusion at various doses once weekly, every 2 weeks, and every 3 weeks, during the induction, consolidation, and maintenance dosing phases, respectively.

End points

Primary
- ORR

Secondary
- DOR
- PFS
- CBR
- OS
- safety

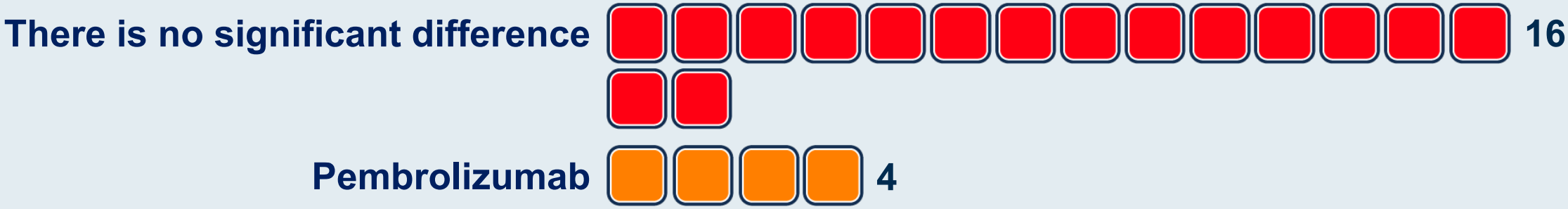
ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; CBR, clinical benefit rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, profession-free survival; ULN, upper limit normal.
[a]Defined as serum AST and ALT < 2.5 x ULN or AST and ALT < 5 x ULN; total bilirubin < 2.0 ULN.
[b]Defined as ANC ≥ 1.5 x 10^9/L and platelet count ≥ 100.0 x 10^9/L with no transfusion support for at least 7 days prior to screening.

NCT04383210

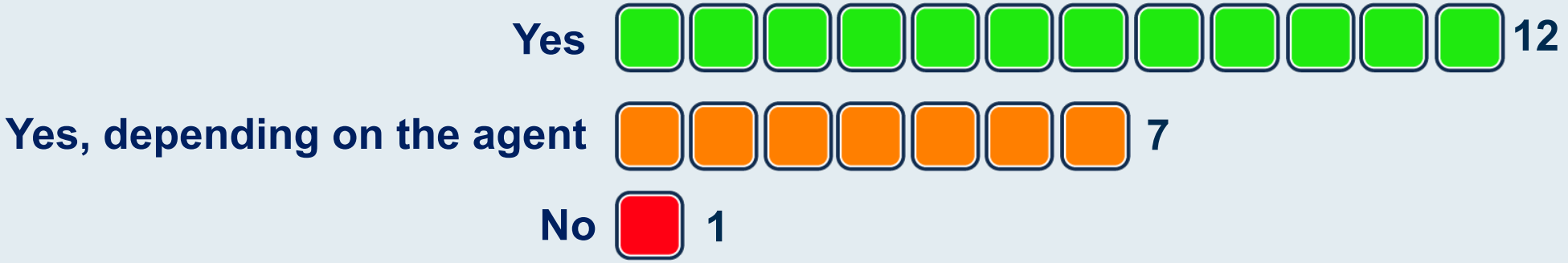
MODULE 5: Current and Future Management of Metastatic NSCLC without a Targetable Tumor Mutation — Dr Langer

RTP
RESEARCH
TO PRACTICE

Of the 3 agents pembrolizumab, atezolizumab and cemiplimab, which has the best risk-benefit profile when administered as monotherapy for a patient with metastatic NSCLC with no targetable mutations and a high PD-L1 TPS (≥50%)?



For a patient with metastatic NSCLC and a high PD-L1 TPS (≥50%) to whom you've decided to administer anti-PD-1/PD-L1 antibody monotherapy, if one of the 3 approved agents were priced 50% below the others, would you preferentially use it?



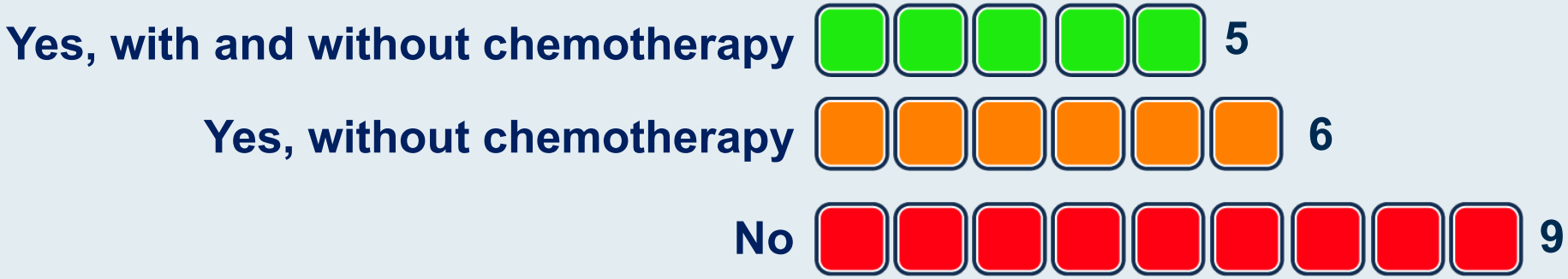
Survey of lung cancer clinical investigators

Which first-line treatment regimen would you recommend for an asymptomatic 65-year-old patient with metastatic nonsquamous lung cancer with modest disease burden, no identified targetable mutations and a PD-L1 TPS of 50%?

Which first-line treatment regimen would you recommend for an asymptomatic 80-year-old patient with metastatic nonsquamous lung cancer with modest disease burden, no identified targetable mutations and a PD-L1 TPS of 50%?

Survey of lung cancer clinical investigators

Outside of a clinical trial, have you administered first-line ipilimumab/nivolumab to a patient with metastatic NSCLC?



Do you believe that a correlation exists between autoimmune toxicity and treatment benefit in patients receiving immune checkpoint inhibitors?

Approximately what proportion of your patients receiving an anti-PD-1/PD-L1 antibody for metastatic NSCLC develop dermatologic toxicity requiring local or systemic therapy? (Median) 20%

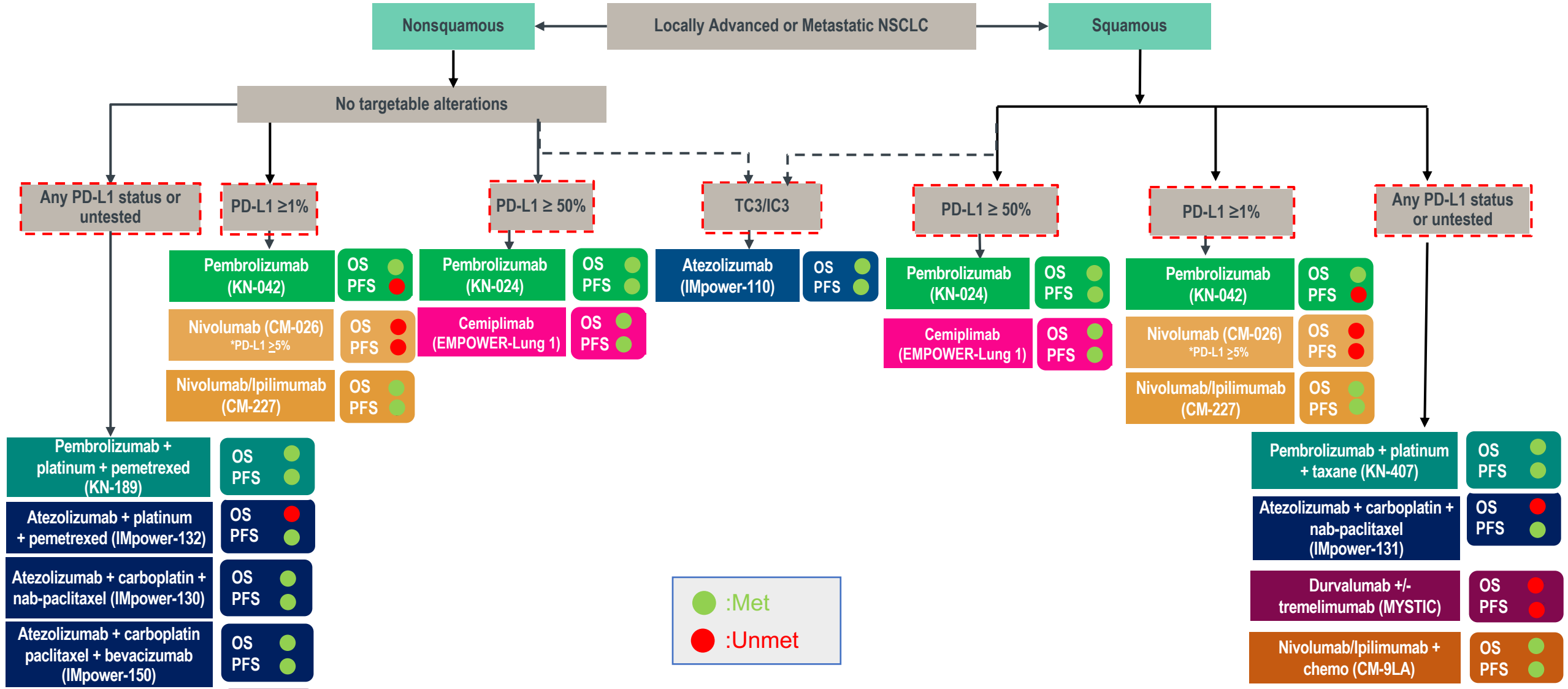
Survey of lung cancer clinical investigators

Current and Future Management of Metastatic NSCLC without a Targetable Tumor Mutation

Corey J. Langer, MD, FACP
Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA 19104

These visuals are not intended to make direct comparisons between trials or to show one's superiority, but to acknowledge the context of data within the landscape of the disease

Front-line Treatment Landscape in Advanced and Metastatic "wt" NSCLC

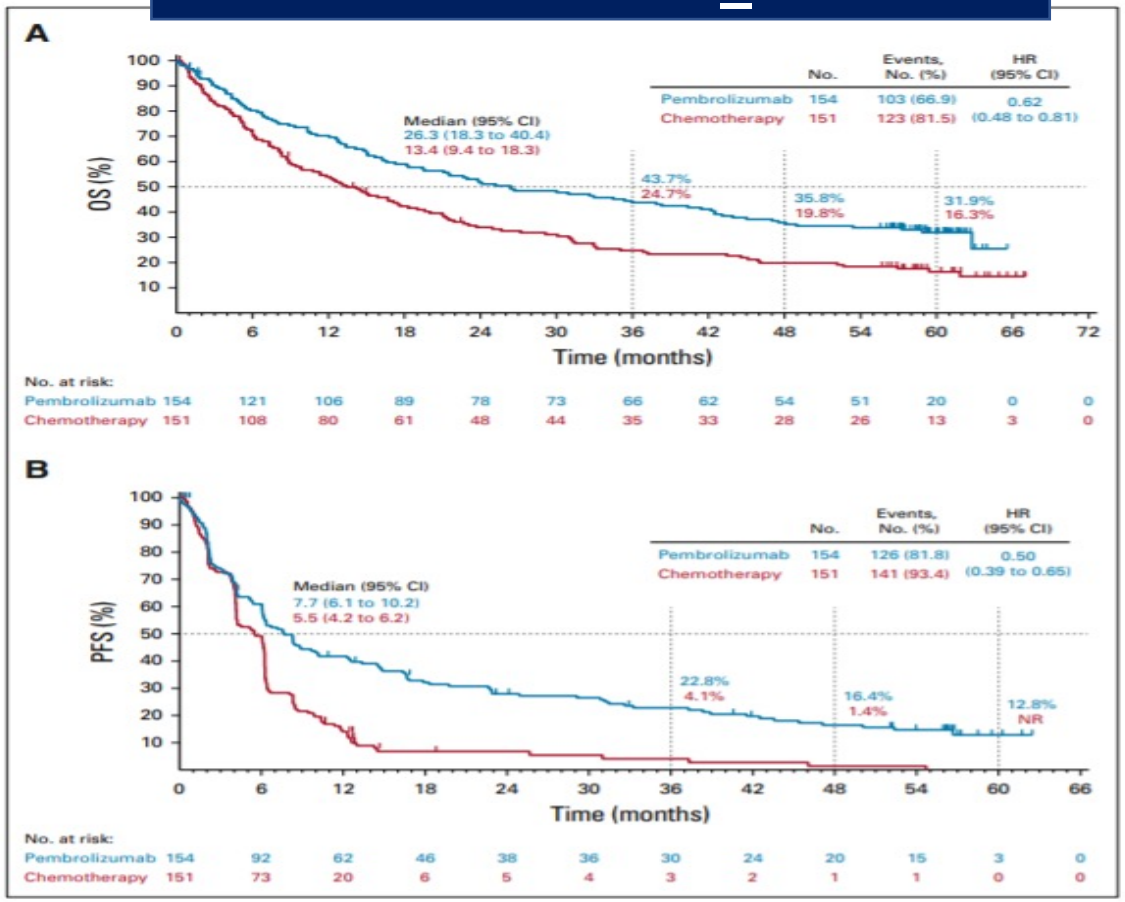


1L = first line; ALK = anaplastic lymphoma kinase; BRAF = serine/threonine-protein kinase B-Raf; ChT = chemotherapy; EGFR = epidermal growth factor receptor; KN = KEYNOTE; Mb = megabase; NSCLC = non–small cell lung cancer;
PD-L1 = programmed death ligand 1; ROS-1 = receptor tyrosine kinase ROS; TMB = tumor mutational burden; VEGFR = vascular endothelial growth factor receptor.

Planchard D et al; ESMO Guidelines Committee. Ann Oncol. 2018;29 (suppl 4): iv192–iv237.
NCCN clinical practice guidelines in oncology https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

"Standard of Care" in North America

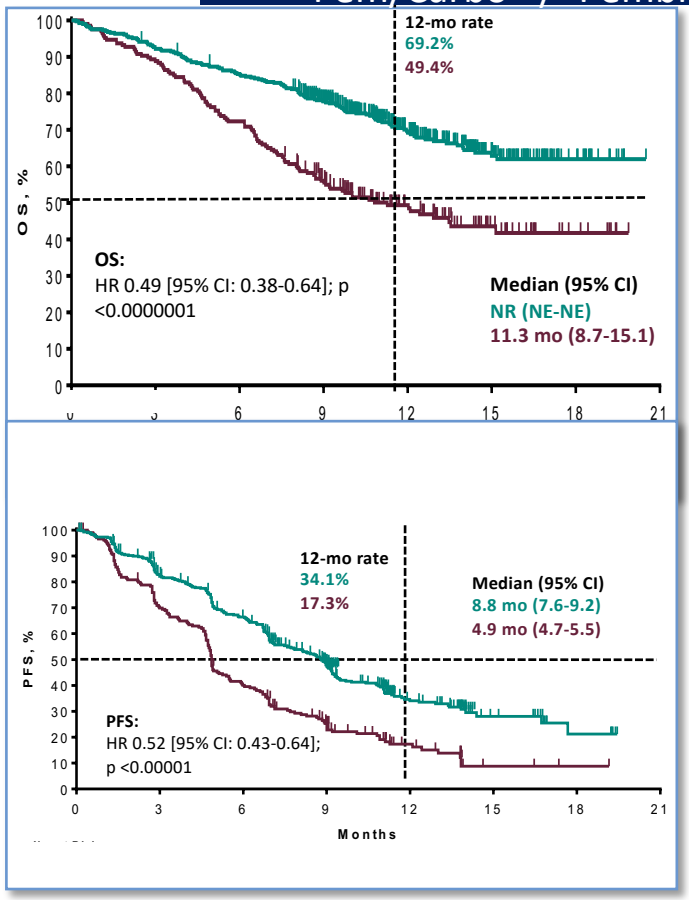
KN 024 – PDL1 ≥ 50%

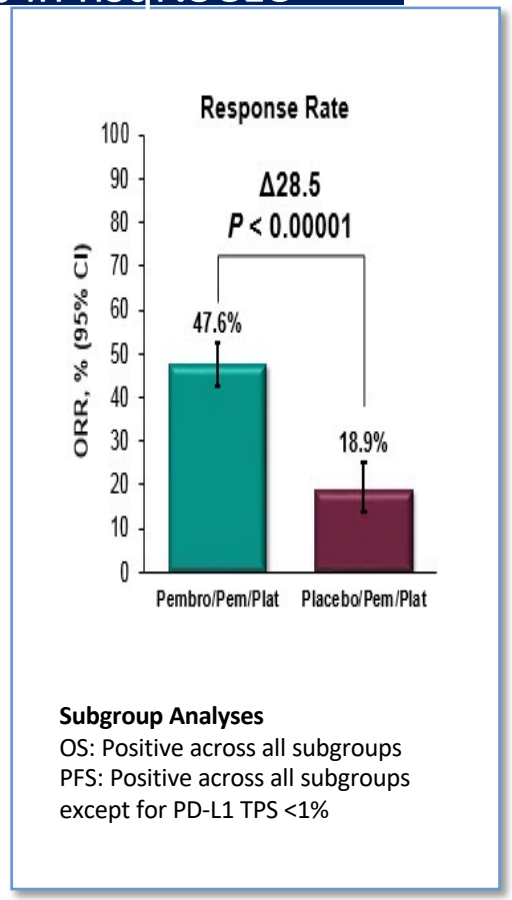


Brahmer ESMO 2020, Reck JCO 2021

KEYNOTE-189: Results

Pem/Carbo +/- Pembro in nsqNSCLC

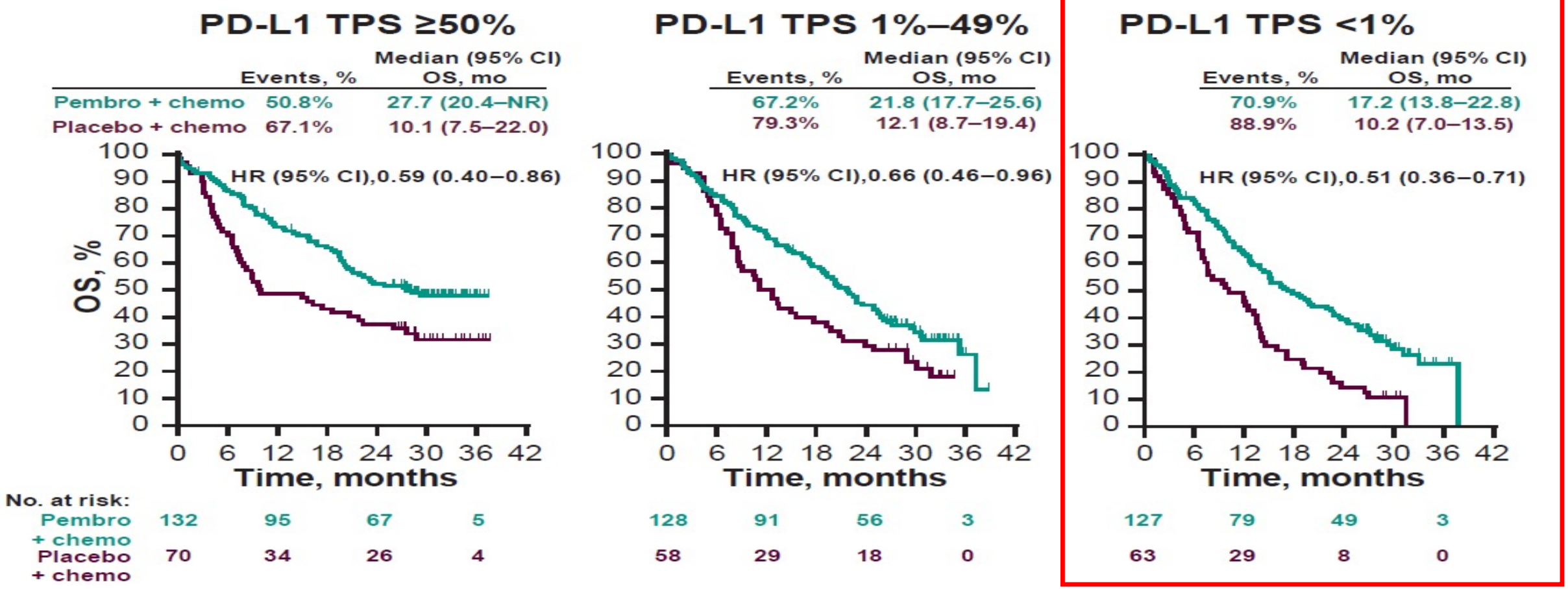




Subgroup Analyses
OS: Positive across all subgroups
PFS: Positive across all subgroups except for PD-L1 TPS <1%

Gandhi et al, AACR 2018, NEJM 2018

Kaplan-Meier Estimates of OS in Subgroups Defined by Baseline PD-L1 TPS



Chemo, chemotherapy with pemetrexed + platinum; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Pembro, pembrolizumab.

Rodríguez-Abreu KN189 ASCO 2020

"Standard of Care" in North America

KEYNOTE-407 in SqNSCLC (NCT02775435)

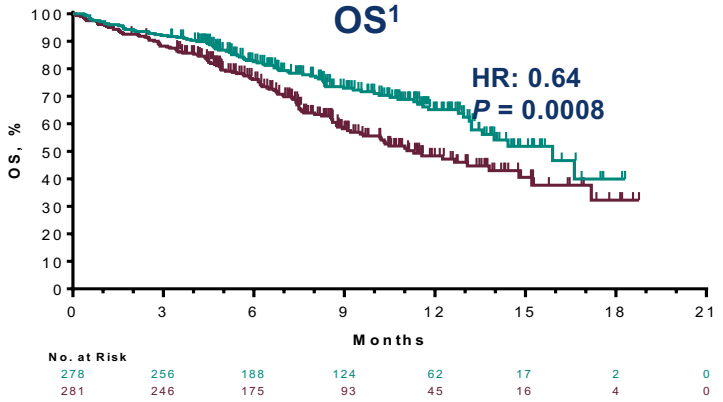
Key Eligibility Criteria

- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

R (1:1)

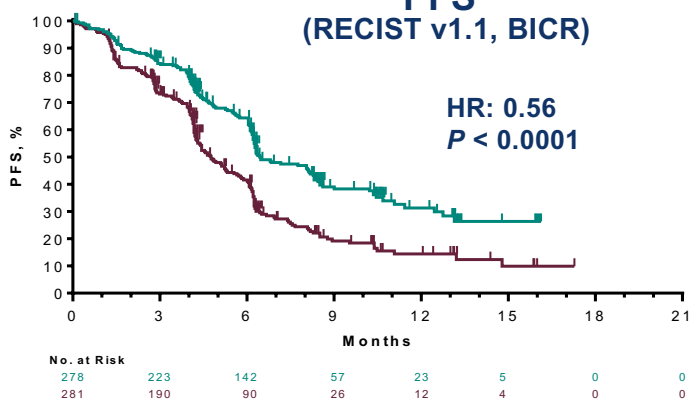
- Pembrolizumab 200 mg Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 31 cycles
- Placebo (normal saline) Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk) → Placebo (normal saline) Q3W for up to 31 cycles → PD → Optional Crossover[b] Pembrolizumab 200 mg Q3W for up to 35 cycles

OS[1]



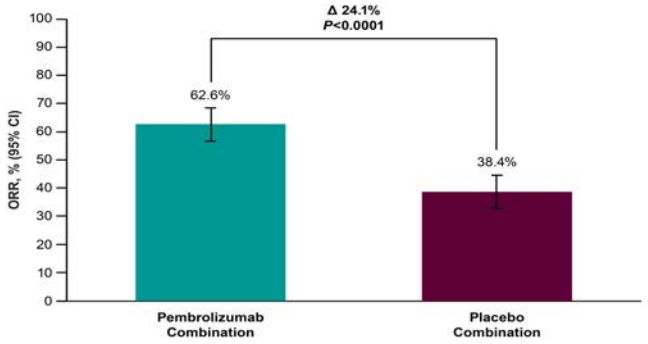
Median (95% CI)
15.9 mo (13.2-NE)
11.3 mo (9.5-14.8)

PFS[1]
(RECIST v1.1, BICR)



Median (95% CI)
6.4 mo (6.2-8.3)
4.8 mo (4.3-5.7)

ORR[1]



Paz-Ares L et al. *J Clin Oncol* 2018;36(15_suppl): abstr 105.

Is there any role for other Checkpoint Inhibitors?

EMPOWER-Lung 3 (Part 2) Study Design (NCT03409614)

Background: Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

Key eligibility criteria
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c†, IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases‡

Stratification factors
- PD-L1 expression: <1% vs 1–49% vs ≥50%
- Histology: non-squamous vs squamous

Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

R 2:1

Arm A
Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles§

Arm B
Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles §

PD or 108 weeks

PD or 108 weeks

Follow-up

N=466

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

†Patient not a candidate for definitive chemoradiation. ‡Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). §For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen. *ALK*, anaplastic lymphoma kinase gene; BOR, best overall response; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomised; *ROS1*, c-ros oncogene 1.

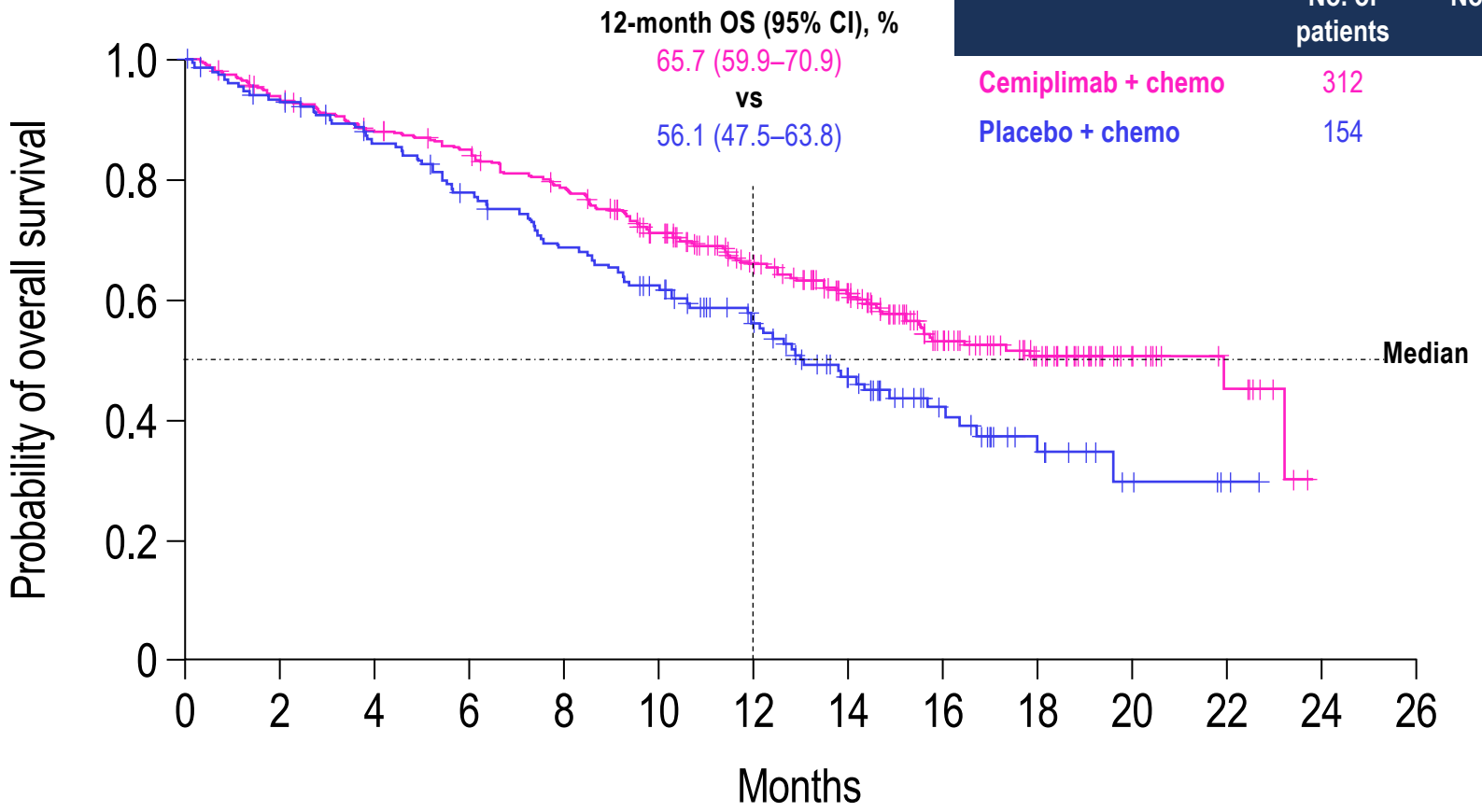
1. Sezer A et al. *Lancet* 2021;397:592–604.

Overall Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014



No. at risk:

Cemiplimab + chemo	312	289	269	256	233	199	162	131	86	52	18	8	0	0
Placebo + chemo	154	141	126	112	98	85	65	46	26	14	5	2	0	0

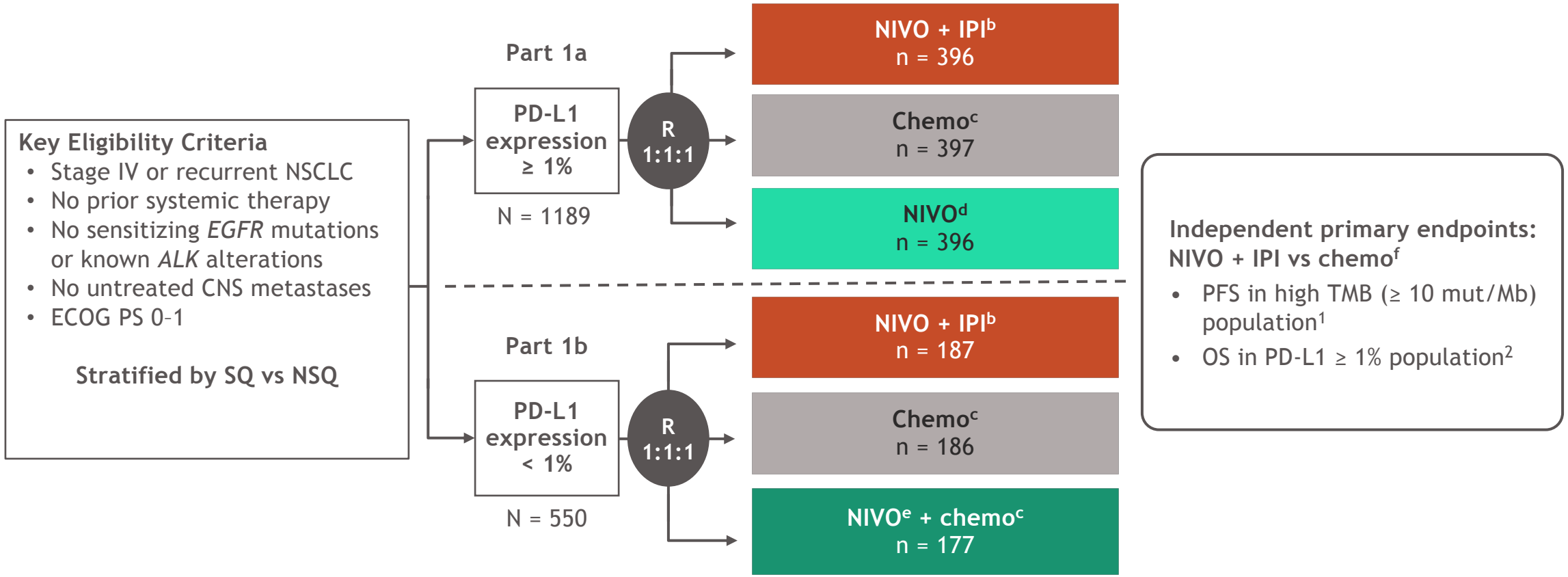
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off date: 14 June 2021

Is there a Niche for Dual CPI with anti CTLA4?

CM227
9LA
POSEIDON

CheckMate 227[a] Part 1 study design



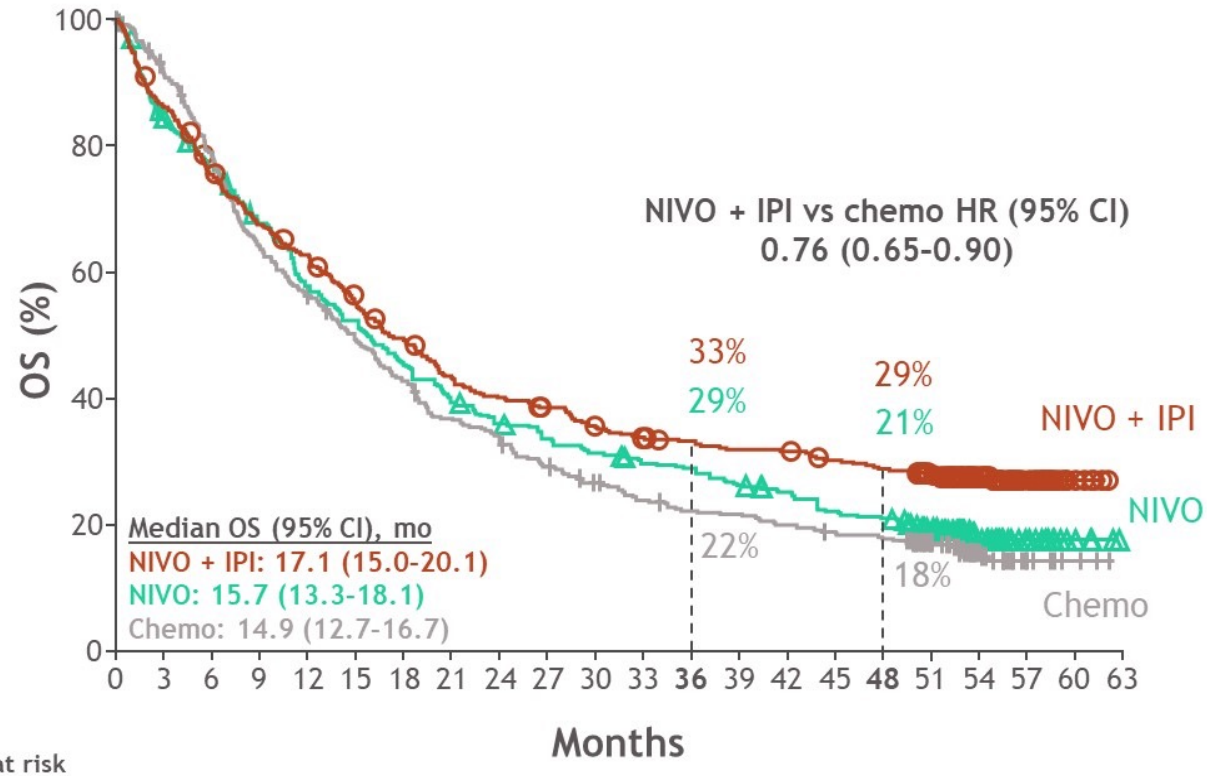
Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.

Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]Both endpoints were met; results were previously reported.

1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093–2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020–2031.

4-year OS in patients with PD-L1 ≥ 1%

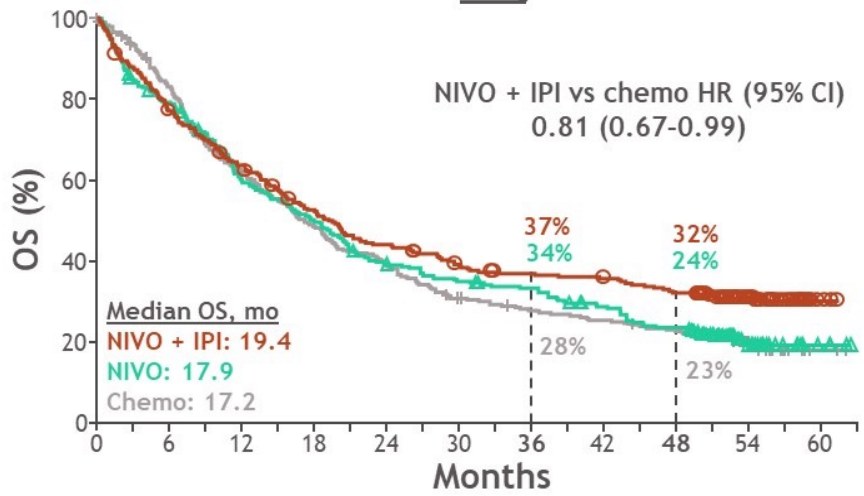
All patients (NSQ + SQ)



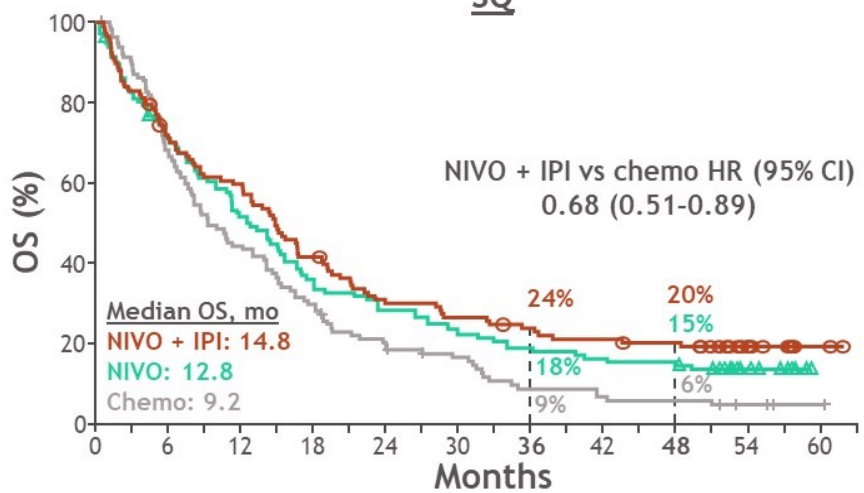
No. at risk

NIVO + IPI	396	341	295	264	244	212	190	165	153	145	132	124	121	116	114	108	103	84	58	23	5	0
NIVO	396	330	299	265	220	201	176	153	139	129	119	112	108	98	91	80	76	61	31	15	4	0
Chemo	397	358	306	250	218	190	166	141	126	112	98	87	80	78	72	66	63	46	24	7	3	0

NSQ



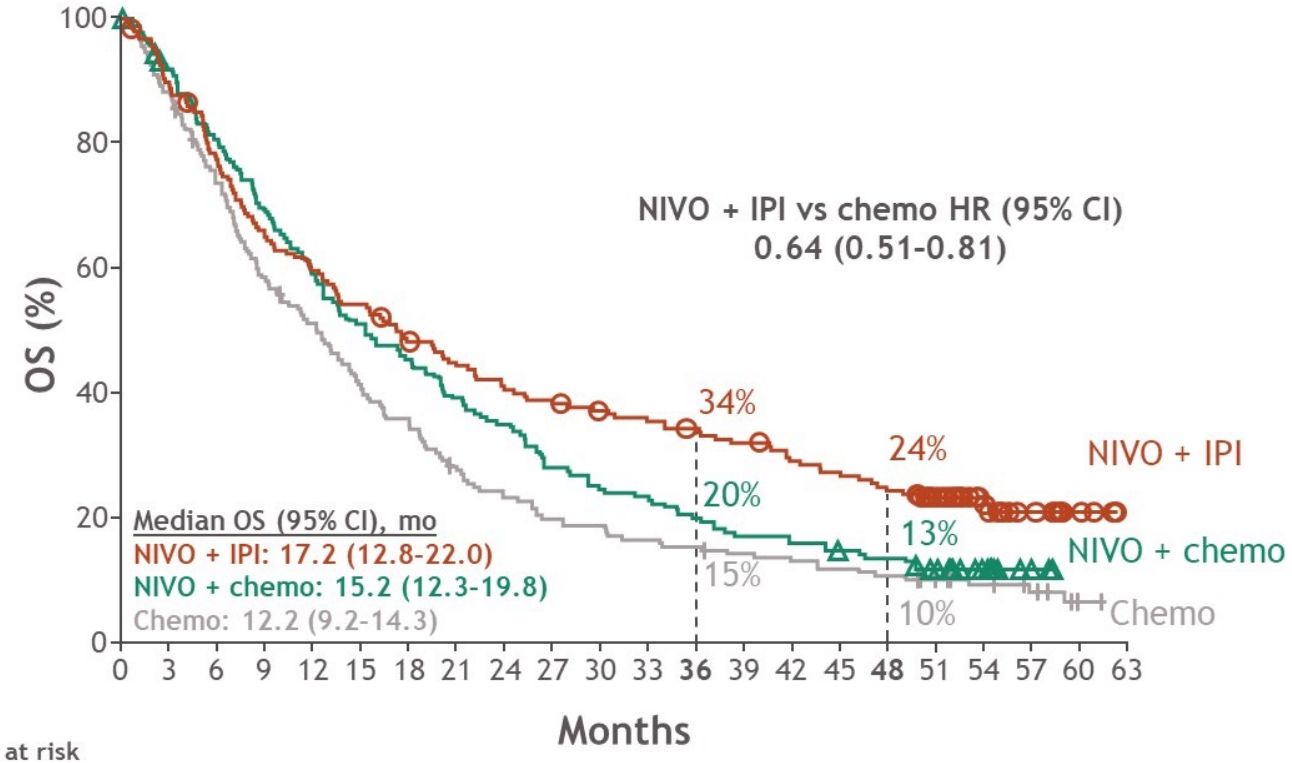
SQ



In all patients with PD-L1 ≥ 1% (NSQ + SQ) with a PFS event (per BICR), subsequent systemic therapy was received by 34% in the NIVO + IPI arm, 46% in the NIVO arm, and 49% in the chemo arm; subsequent immunotherapies by 7%, 9%, and 40%; and subsequent chemo by 32%, 45%, and 25%, respectively.

4-year OS in patients with PD-L1 < 1%

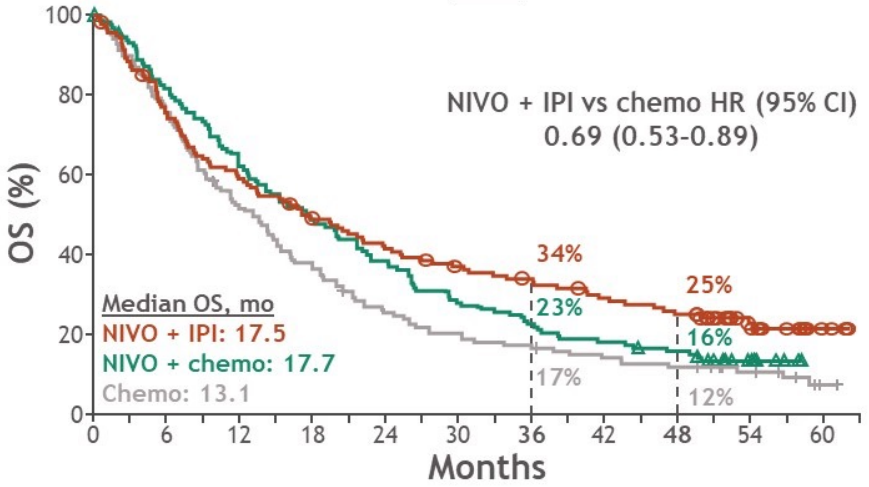
All patients (NSQ + SQ)



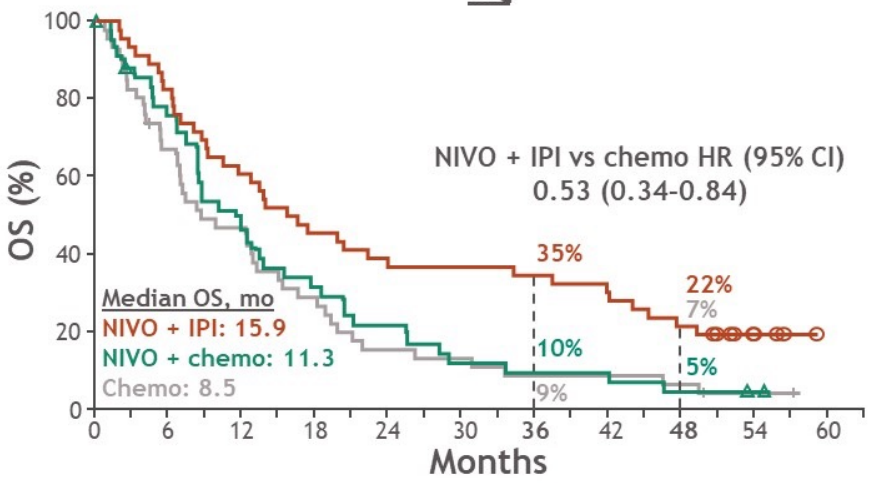
No. at risk

NIVO + IPI	187	165	142	120	110	100	87	80	73	69	65	62	59	55	49	45	41	31	19	12	4	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	42	39	34	29	27	24	22	17	10	2	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	33	29	27	24	22	20	18	13	10	7	1	0

NSQ



SQ



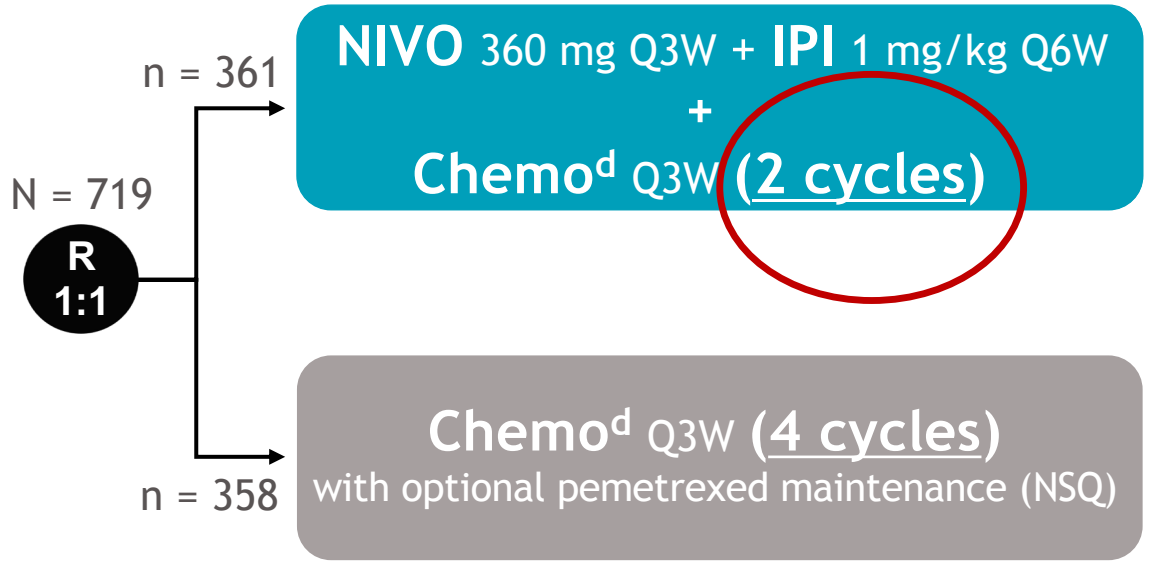
In all patients with PD-L1 < 1% (NSQ + SQ) with a PFS event (per BICR), subsequent systemic therapy was received by 46% in the NIVO + IPI arm, 39% in the NIVO + chemo arm, and 48% in the chemo arm; subsequent immunotherapies by 9%, 5%, and 33%; and subsequent chemo by 44%, 37%, and 33%, respectively.

CheckMate 9LA study design[a]

Key eligibility criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0–1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Exploratory endpoints
- Safety

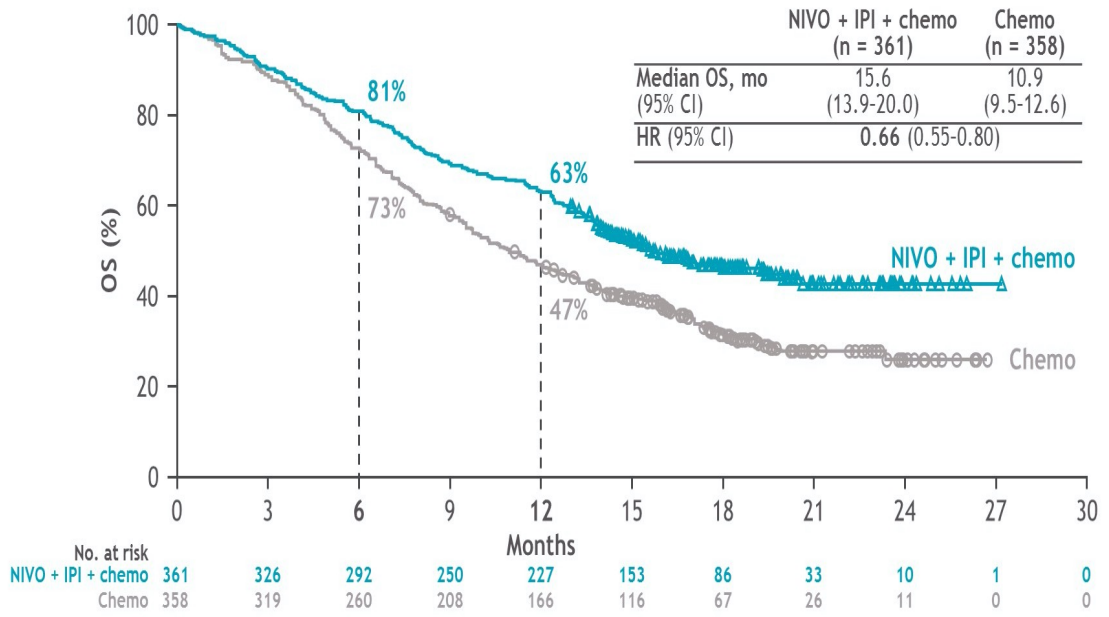
DBL: February 18, 2021; minimum / median follow-up for OS: 24.4 months / 30.7 months.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

9LA with long(er) term follow-up

CheckMate 9LA: NIVO + IPI + 2 cycles of chemo in 1L NSCLC

Primary endpoint (updated): Overall survival[a]



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	0.66 (0.55-0.80)	

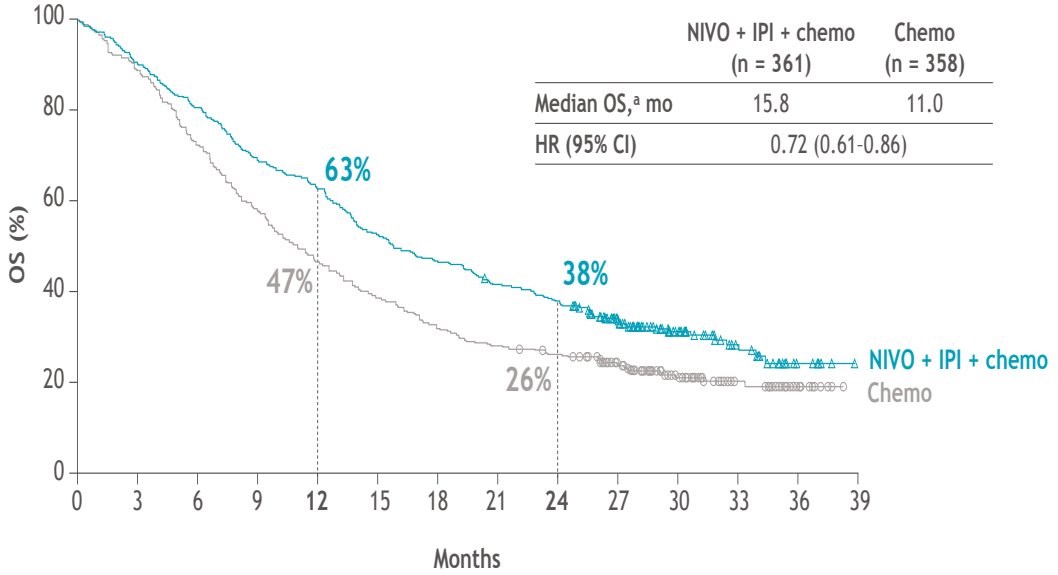
No. at risk											
NIVO + IPI + chemo	361	326	292	250	227	153	86	33	10	1	0
Chemo	358	319	260	208	166	116	67	26	11	0	0

Minimum follow-up 12.7 months

ASCO 2020

CheckMate 9LA (NIVO + IPI + chemo vs chemo in 1L NSCLC): 2-year update

2-Year update: OS in all randomized patients



	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[a] mo	15.8	11.0
HR (95% CI)	0.72 (0.61-0.86)	

No. at risk														
NIVO + IPI + chemo	361	326	292	250	227	191	170	150	137	95	50	23	7	0
Chemo	358	319	260	208	168	139	115	102	93	69	40	18	8	0

Minimum follow-up: 24.4 months.
[a]95% CI = 13.9-19.7 (NIVO + IPI + chemo) and 9.5-12.7 (chemo).

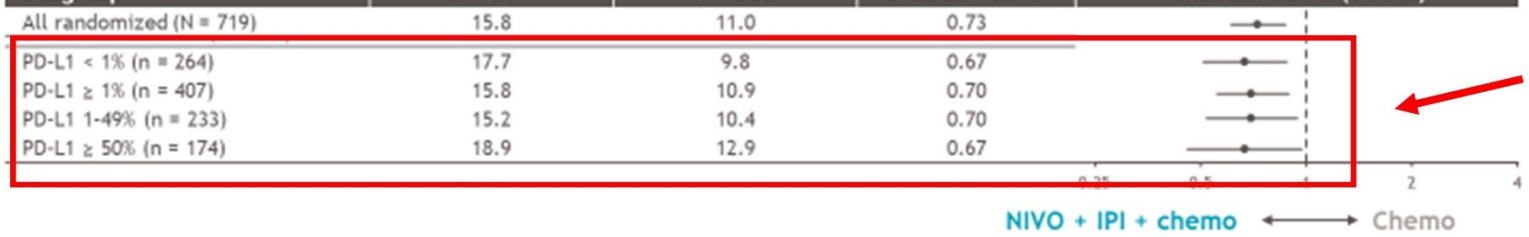
38

ASCO 2021

Reck M et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. ESMO Open 2021; 6(5):100273 [Epub Oct 2021]

Checkmate 9LA Update

Subgroup	Median OS, mo: NIVO + IPI + chemo n = 361	Median OS, mo: Chemo n = 358	Unstratified HR	Unstratified HR (95% CI)
All randomized (N = 719)	15.8	11.0	0.73	
PD-L1 < 1% (n = 264)	17.7	9.8	0.67	
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.70	
PD-L1 1-49% (n = 233)	15.2	10.4	0.70	
PD-L1 ≥ 50% (n = 174)	18.9	12.9	0.67	



No difference in treatment effect by PD-L1 status alone

PD-L1	Non-squamous	Squamous	All
< 1%	0.75 (0.54-1.04)	0.48 (0.28-0.81)	0.67 (0.51-0.88)
≥ 1%	0.71 (0.53-0.95)	0.70 (0.48-1.01)	0.70 (0.56-0.89)
All	0.78	0.63	0.72 (0.61-0.86)

Do patients with PD-L1 negative squamous disease do better?

- Chemo-IO in PD-L1 < 1%:
  - 0.59 for non-squamous (KN 189)
  - 0.61 for squamous (KN 407)
- NIVO/IPI in < 1% (CM 227)
  - 0.67 for non-squamous
  - 0.49 for squamous

L Gandhi et al. N Engl J Med 2018;378:2078-2092., L Paz-Ares et al. N Engl J Med 2018;379:2040-2051., MD Hellmann et al. N Engl J Med 2019;381:2020-2031

POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study

- Stage IV NSCLC
- No *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- Treatment-naïve for metastatic disease

N=1013 (randomized)

R 1:1:1

Stratified by:
- PD-L1 expression (TC ≥50% vs <50%)
- Disease stage (IVA vs IVB)
- Histology

Durvalumab 1500 mg + CT* q3w (4 cycles) → **Durvalumab 1500 mg q4w + pemetrexed† until PD**

Durvalumab 1500 mg + tremelimumab 75 mg + CT* q3w (4 cycles) → **Durvalumab 1500 mg q4w + tremelimumab 75 mg (week 16 only)‡ + pemetrexed† until PD**

Platinum-based CT* q3w (up to 6 cycles) → **Pemetrexed† until PD**

Primary endpoints
- PFS by BICR (D+CT vs CT)
- OS (D+CT vs CT)

Key secondary endpoints
- PFS by BICR (D+T+CT vs CT)
- OS (D+T+CT vs CT)
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)

Additional secondary endpoints
- ORR, DoR, and BOR by BICR
- PFS at 12 months
- HRQoL
- Safety and tolerability

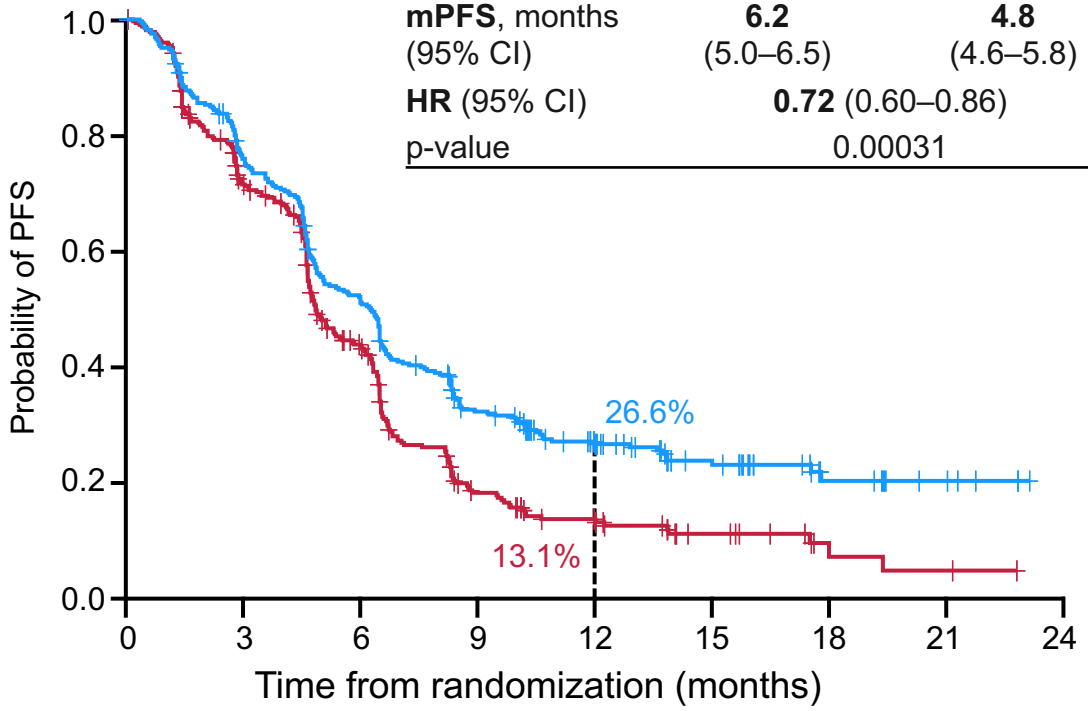
*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology);
†Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

BICR, blinded independent central review; BOR, best objective response; bTMB, blood tumor mutational burden; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumor cell

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	

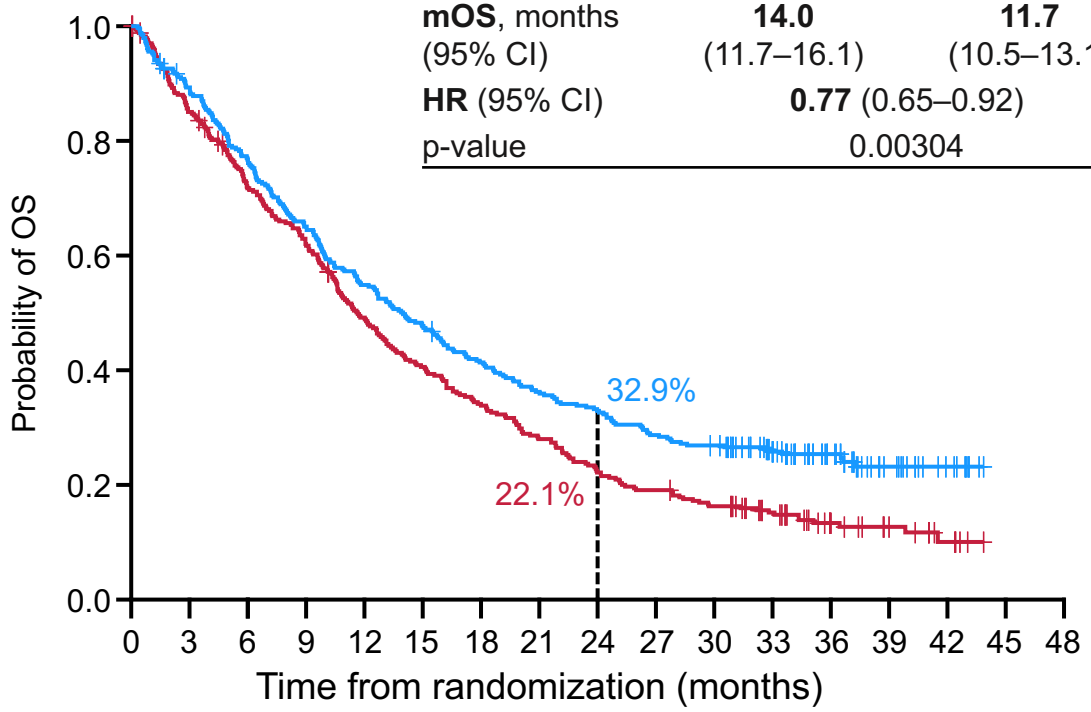


No. at risk									
D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



No. at risk																	
D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

Options in PDL1 > 50%

- CITYSCAPE
- INSIGNA

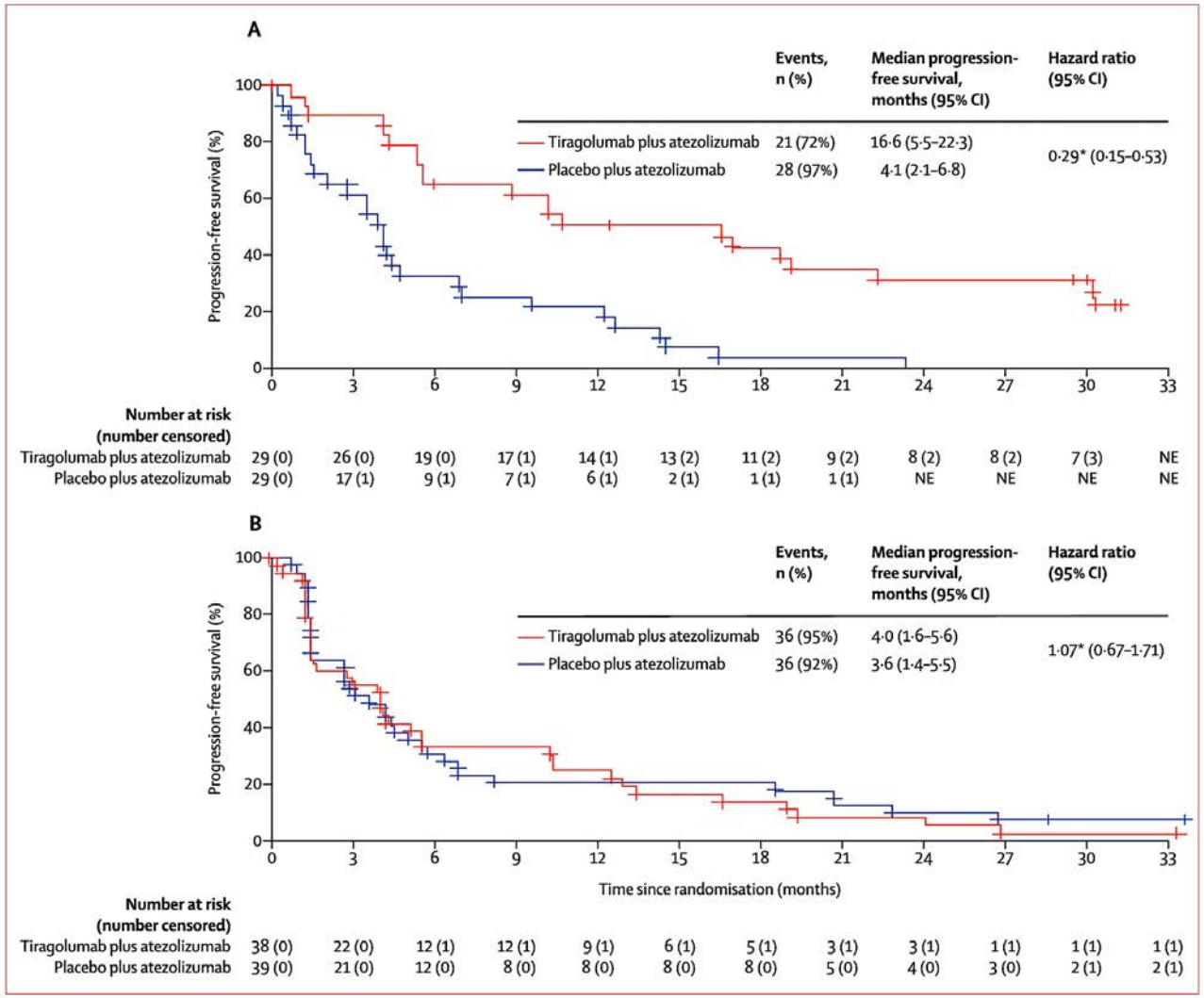


Figure 3: **Investigator-assessed progression-free survival in (A) the PD-L1 TPS ≥50% population and (B) the PD-L1 TPS 1–49% population**
Updated analysis as of data cutoff on Aug 16, 2021 (median follow-up 30·4 months [29·4–33·0]). NE=not evaluable. TPS=tumour proportion score. *Unstratified.

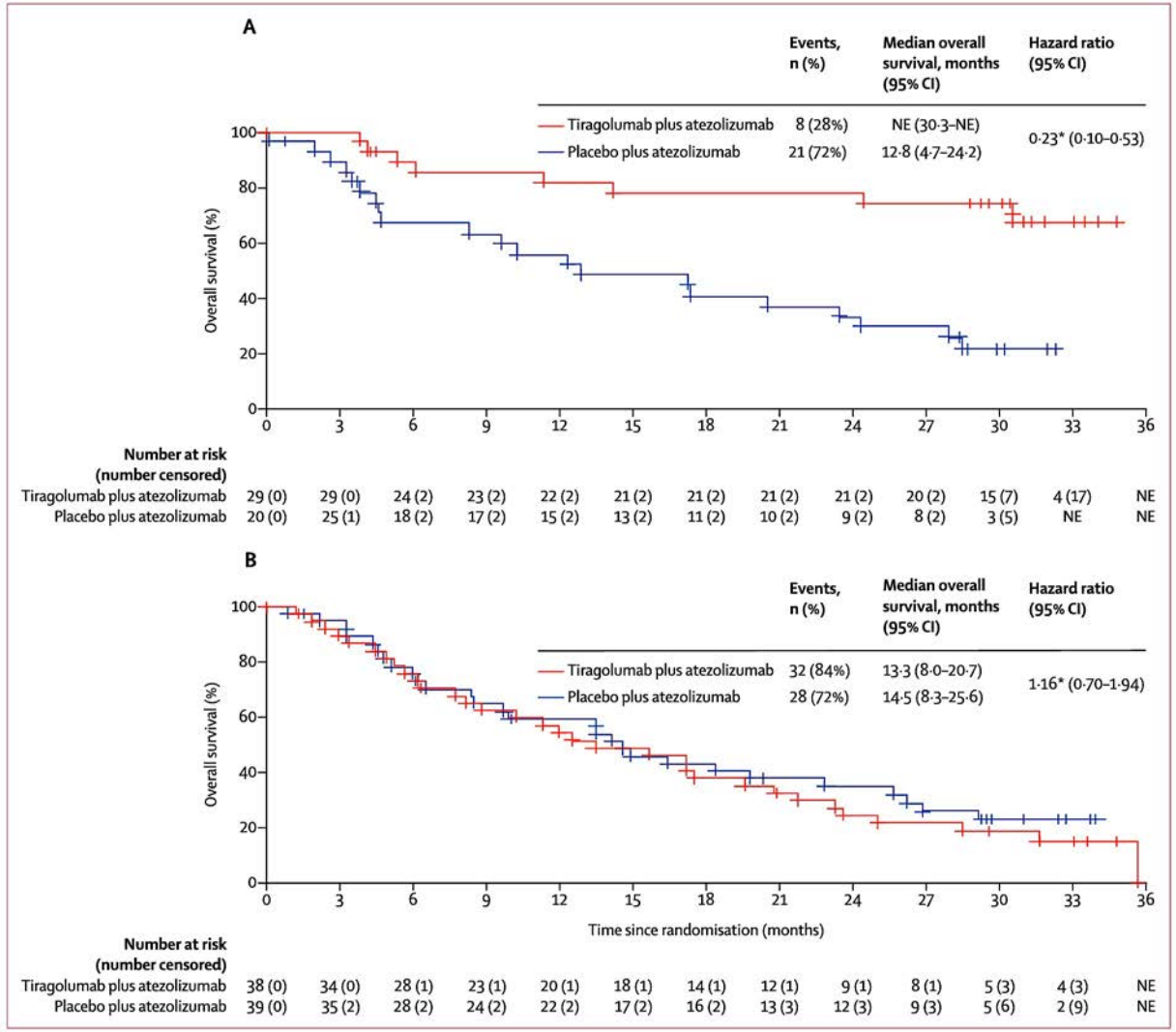
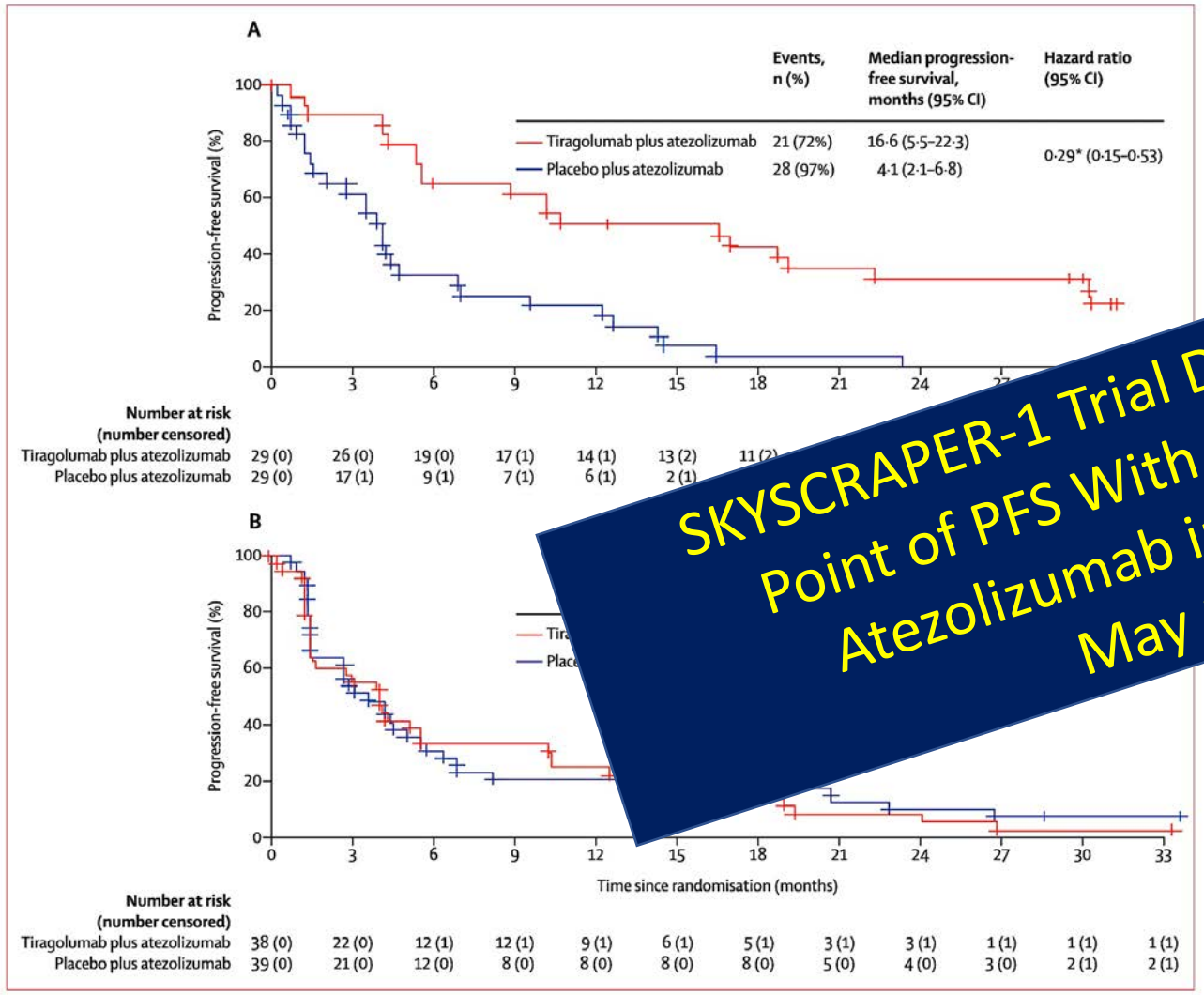


Figure 4: **Kaplan-Meier plots for investigator-assessed overall survival in (A) the PD-L1 TPS ≥50% population and (B) the PD-L1 TPS 1–49% population**
Updated analysis as of data cutoff on Aug 16, 2021 (median follow-up 30·4 months [29·4–33·0]). NE=not evaluable. TPS=tumour proportion score. *Unstratified.

Cho et al, LANCET 05/22



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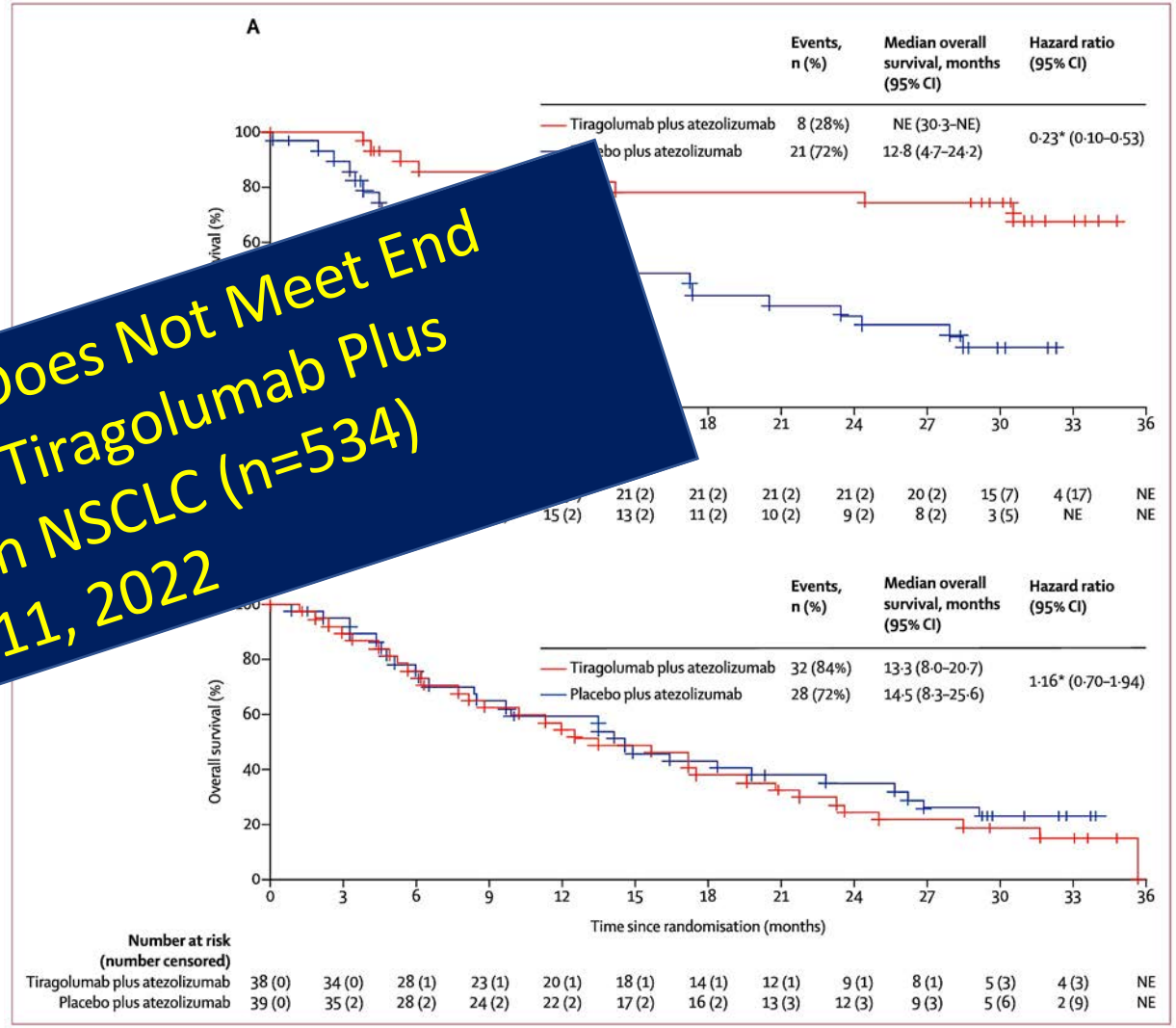


Figure 4: **Kaplan-Meier plots for investigator-assessed overall survival in (A) the PD-L1 TPS ≥50% population and (B) the PD-L1 TPS 1–49% population**
Updated analysis as of data cutoff on Aug 16, 2021 (median follow-up 30·4 months [29·4–33·0]). NE=not evaluable. TPS=tumour proportion score. *Unstratified.

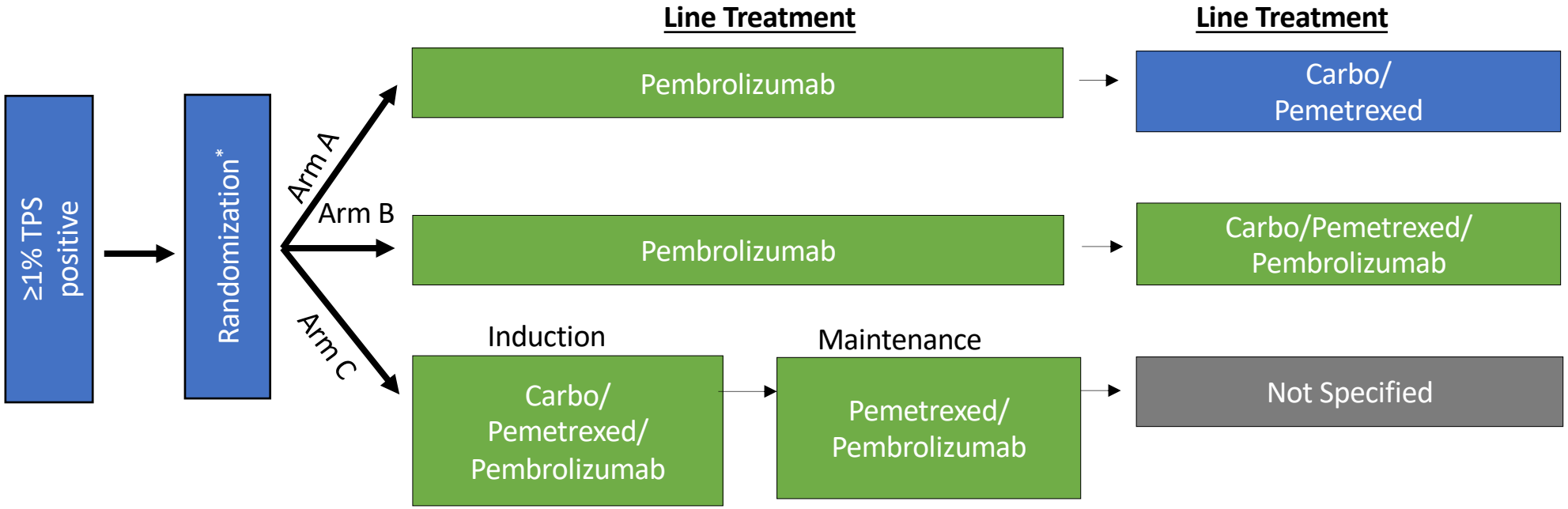
SKYSCRAPER-1 Trial Does Not Meet End Point of PFS With Tiragolumab Plus Atezolizumab in NSCLC (n=534)
May 11, 2022

Cho et al, LANCET 05/22

INSIGNA TRIAL

Sequential vs Combination Therapy: INSIGNA

A Randomized, Phase III Study of Firstline Immunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker SIGNature-driven Analysis



SWOG-ECOG collaboration NCTN NCI network (A. Chiang, H. Borghaei)

Other Promising Strategies

- **ADCs**
  - **TROP2**
  - **HER3**

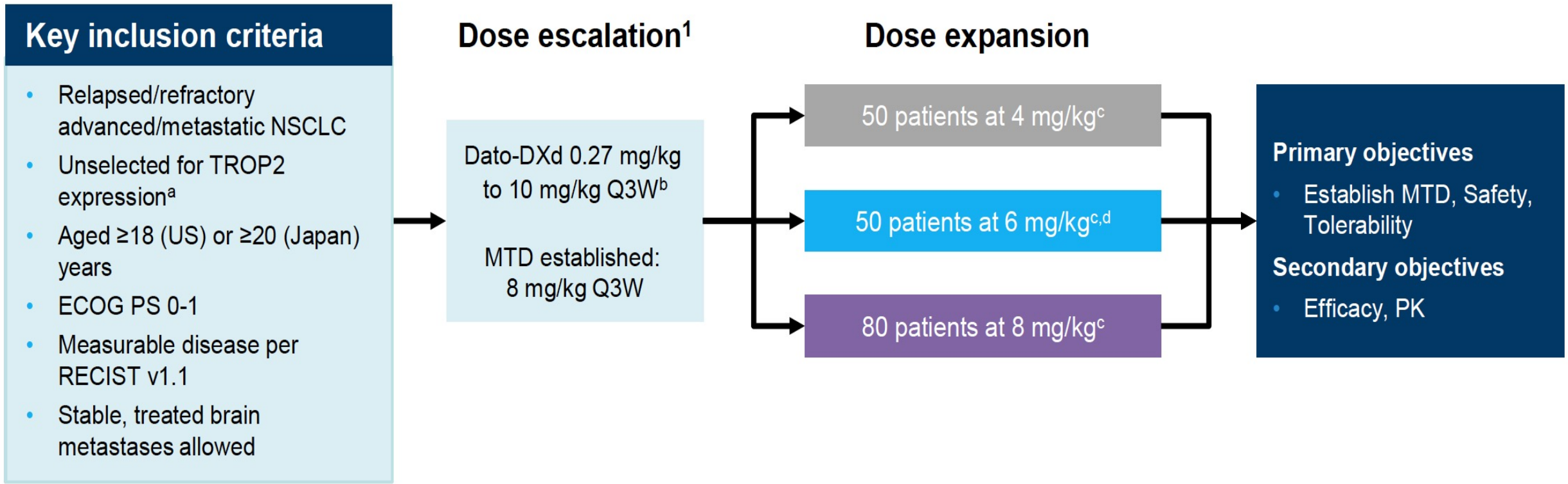
Datopotamab Deruxtecan (Dato-DXd; DS-1062), a TROP2 ADC, in Patients With Advanced NSCLC: Updated Results of TROPION-PanTumor01 Phase 1 Study

Alexander Spira, MD
Virginia Cancer Specialists, US Oncology Research,
Clinical Assistant Professor, Johns Hopkins Medicine, USA

Alexander Spira,[1] Aaron E. Lisberg,[2] Jacob M. Sands,[3] Jonathan Greenberg,[4] Penny Phillips,[4]
Ferdinand Guevara,[4] Naoyuki Tajima,[5] Yui Kawasaki,[5] Jessie Gu,[4] Fumiaki Kobayashi,[5] Noboru Yamamoto,[6]
Melissa Johnson,[7] Funda Meric-Bernstam,[8] Kiyotaka Yoh,[9] Edward B. Garon,[2]
Rebecca S. Heist,[10] Toshio Shimizu[11]

TROPION-PanTumor01 (NCT03401385) Study Design

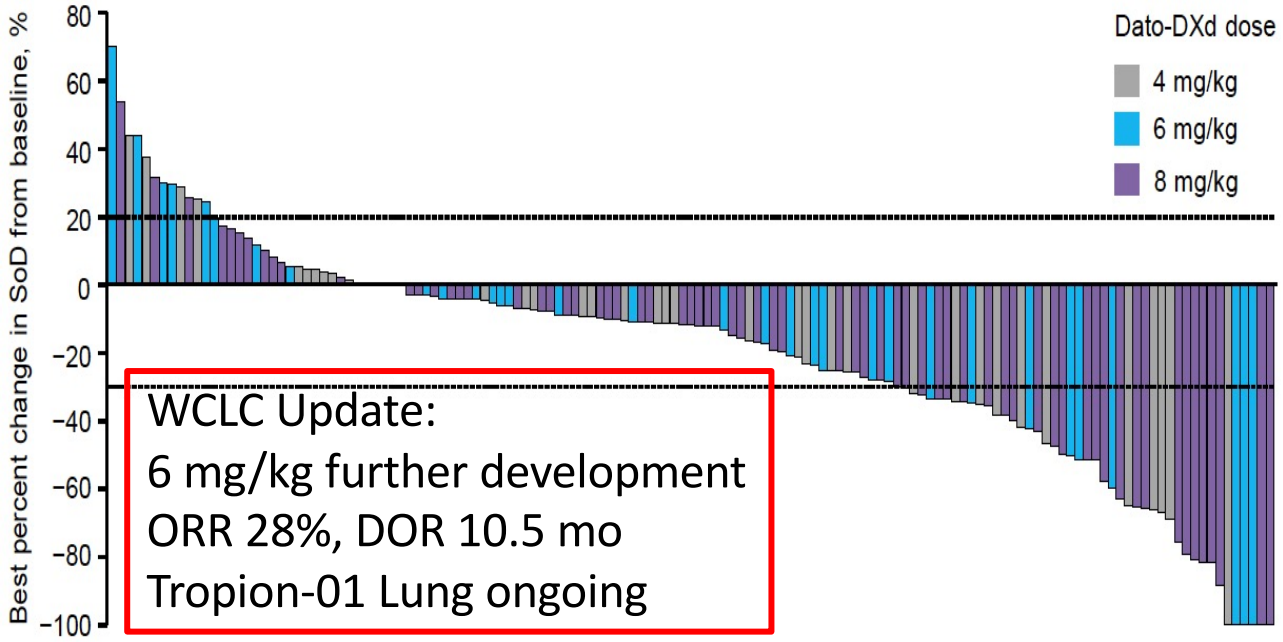
Phase 1 FIH Dose Escalation and Expansion Study



Spira A et al ASCO 2021

Datopotamab deruxtecan (Dato-DXd)

Best Change in Sum of Diameters and Overall Response (BICR)

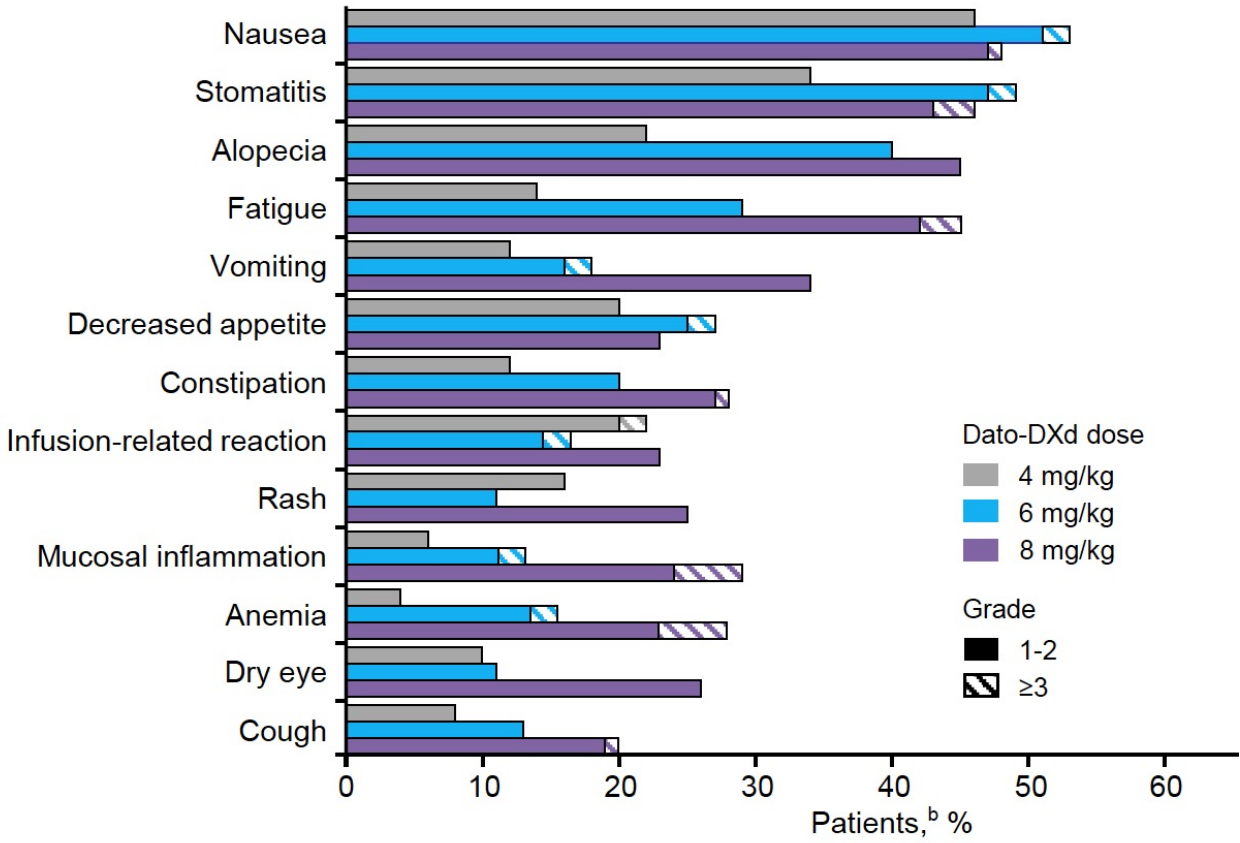


WCLC Update:
6 mg/kg further development
ORR 28%, DOR 10.5 mo
Tropion-01 Lung ongoing

Dato-DXd dose	Response-evaluable patients,[a] n	Confirmed CR/PR,[b] n	CR/PR (too early to be confirmed),[b] n	ORR,[b] % (n)	DCR, % (n)	PD, % (n)
4 mg/kg	40	7	2	23 (9)	73 (29)	15 (6)
6 mg/kg	39	6	2	21 (8)	67 (26)	21 (8)
8 mg/kg	80	19	1	25 (20)	80 (64)	9 (7)

8% ILD mostly in the 8 mg/kg cohort

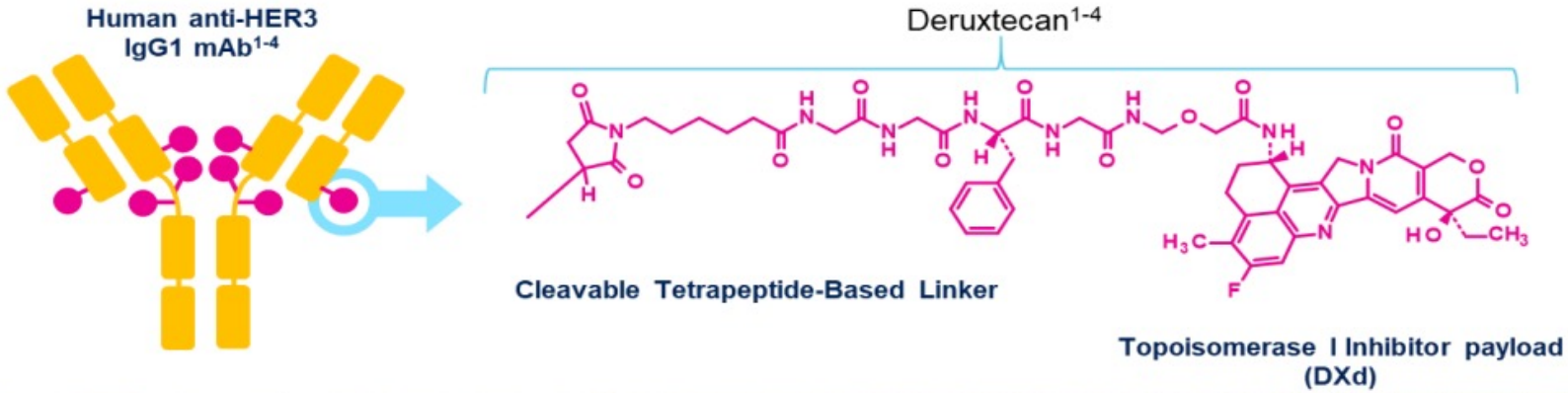
TEAEs in ≥15% of Patients[a]



Spira A et al ASCO 2021; Garon E et al WCLC 2021

Patritumab Deruxtecan (HER3-DXd)

- HER3-DXd is an ADC with 3 components:[1-6]
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to:
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker
- HER3-DXd is in clinical evaluation for NSCLC,[1-4] metastatic breast cancer, and colorectal cancer



Jänne et al. Cancer Discovery 2022

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

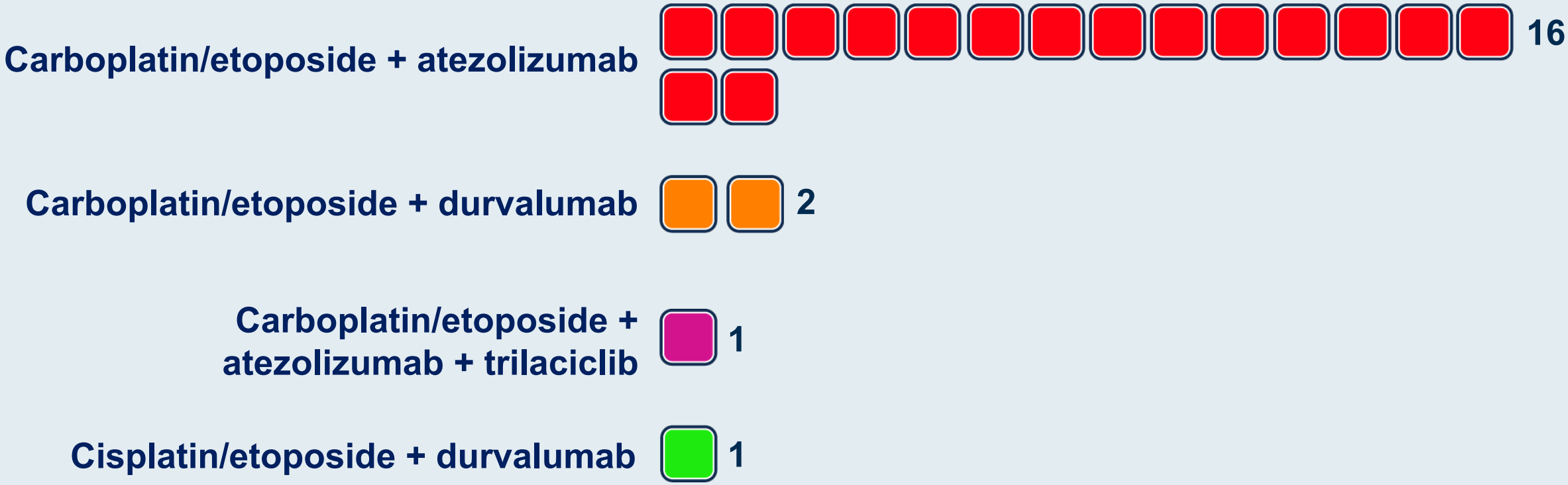
Immunotherapy in mNSCLC: Unanswered Questions

- Are there biomarkers beyond PDL1 to aid patient selection?
- How to choose monotherapy vs combination?
- Role of CPI combinations vs Pembro/Chemo?
  - Need a trial comparing 9LA to Pembro + Histology-specific Chemo
- What is the role of ADCs?
- **Other unanswered questions:**
  - Optimal number of chemo cycles
  - Maintenance pemetrexed in those with high PDL1 expression
  - Mechanisms of resistance
  - Additional compounds – immunotherapy or TKIs

MODULE 6: Current Treatment Paradigm for Small Cell Lung Cancer (SCLC) — Dr Paz-Ares

RTP
RESEARCH
TO PRACTICE

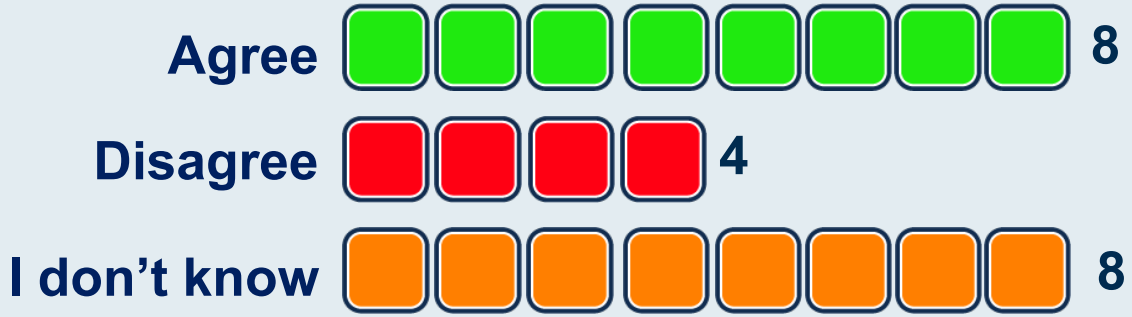
In general, what would be your preferred first-line treatment regimen for a 65-year-old patient with extensive-stage small cell lung cancer (SCLC)?



Survey of lung cancer clinical investigators

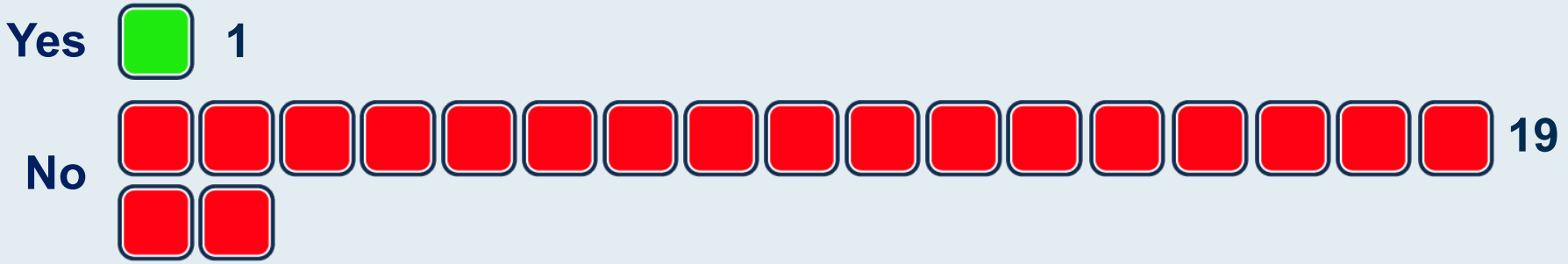
The benefits and risks of adding durvalumab to platinum/etoposide and of adding atezolizumab to carboplatin/etoposide are very similar, and from a clinical point of view selecting between the 2 regimens as first-line treatment for a patient with extensive-stage SCLC can be considered a "coin flip."

Patients who are receiving antibiotics may derive less benefit from anti-PD-1/PD-L1 antibodies than those who are not.

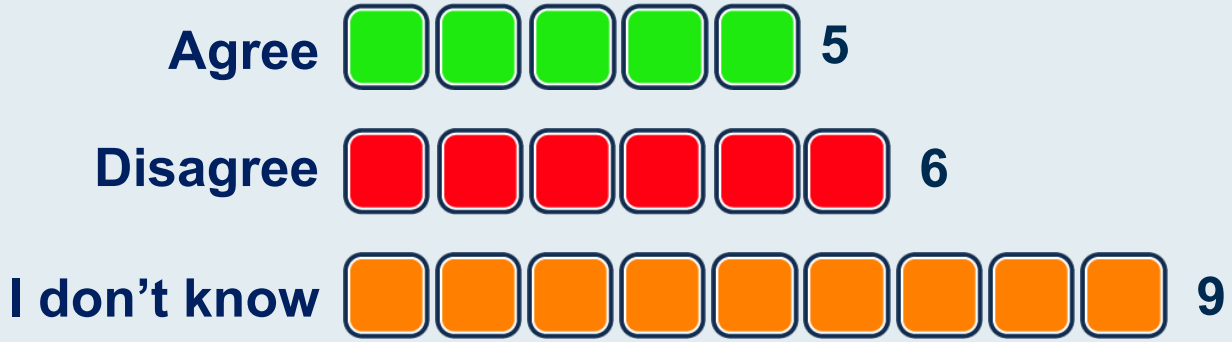


Survey of lung cancer clinical investigators

Have you administered trilaciclib to patients with extensive-stage SCLC?

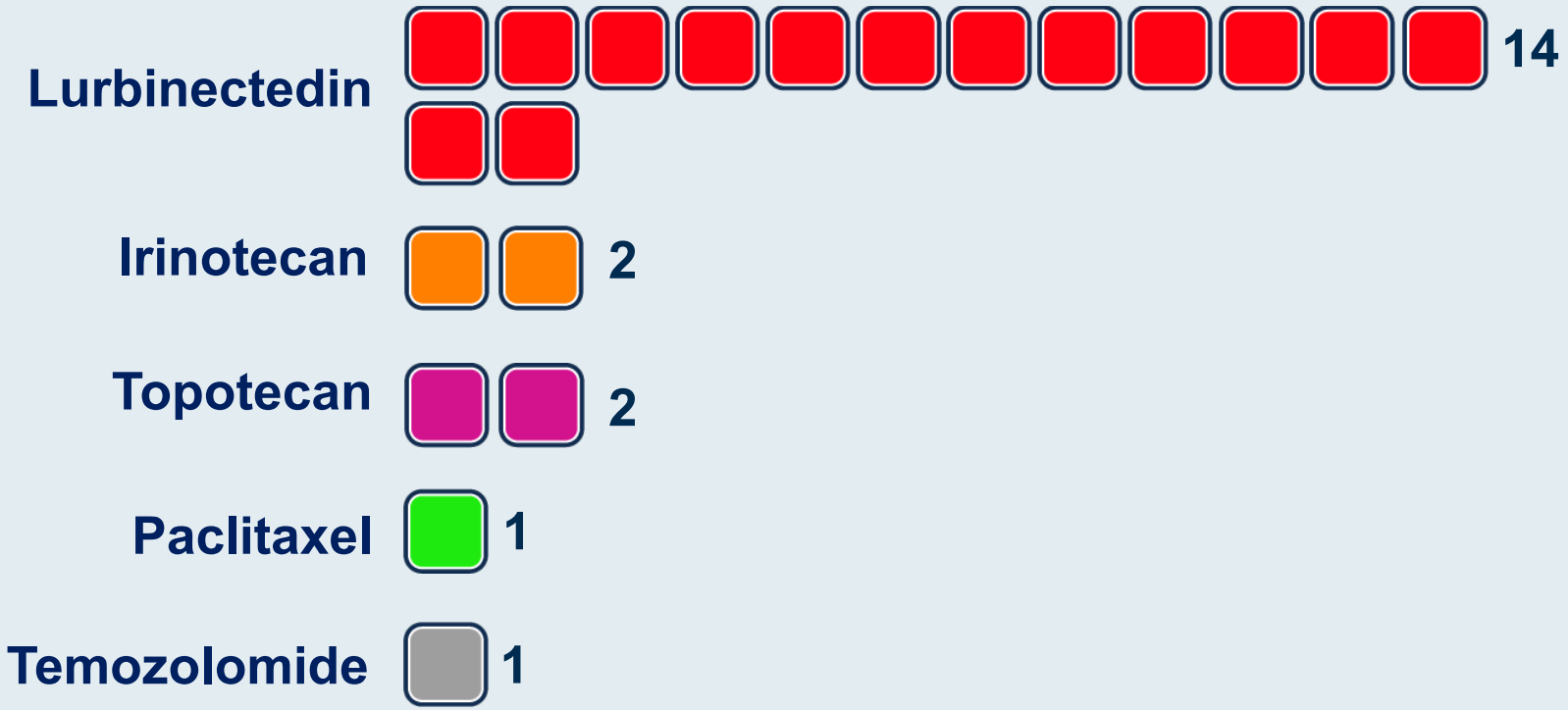


Based on current clinical trial data and your personal experience: The addition of trilaciclib to a platinum/etoposide- or topotecan-containing regimen improves the quality of life for patients with extensive-stage SCLC.



Survey of lung cancer clinical investigators

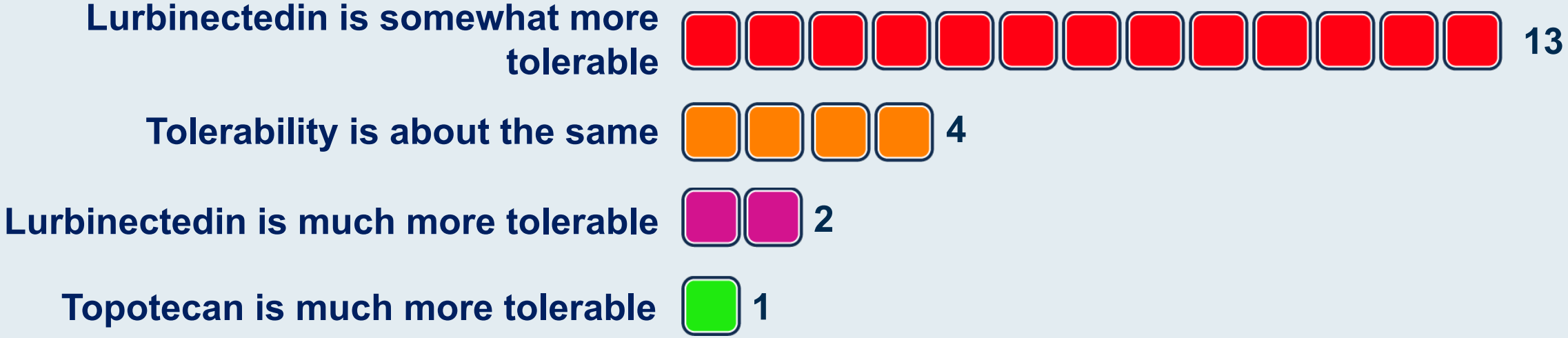
In general, what is your preferred second-line treatment for a patient with extensive-stage SCLC after disease progression on first-line chemotherapy/atezolizumab?



To approximately how many patients with SCLC have you administered lurbinectedin? (Median) **4 patients**

Survey of lung cancer clinical investigators

Based on current clinical trial data and your personal experience, how would you compare the global tolerability of lurbinectedin to that of topotecan?



Have you observed any significant responses in your patients with SCLC receiving lurbinectedin?

Survey of lung cancer clinical investigators

i+12
Instituto de Investigación
Hospital 12 de Octubre

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

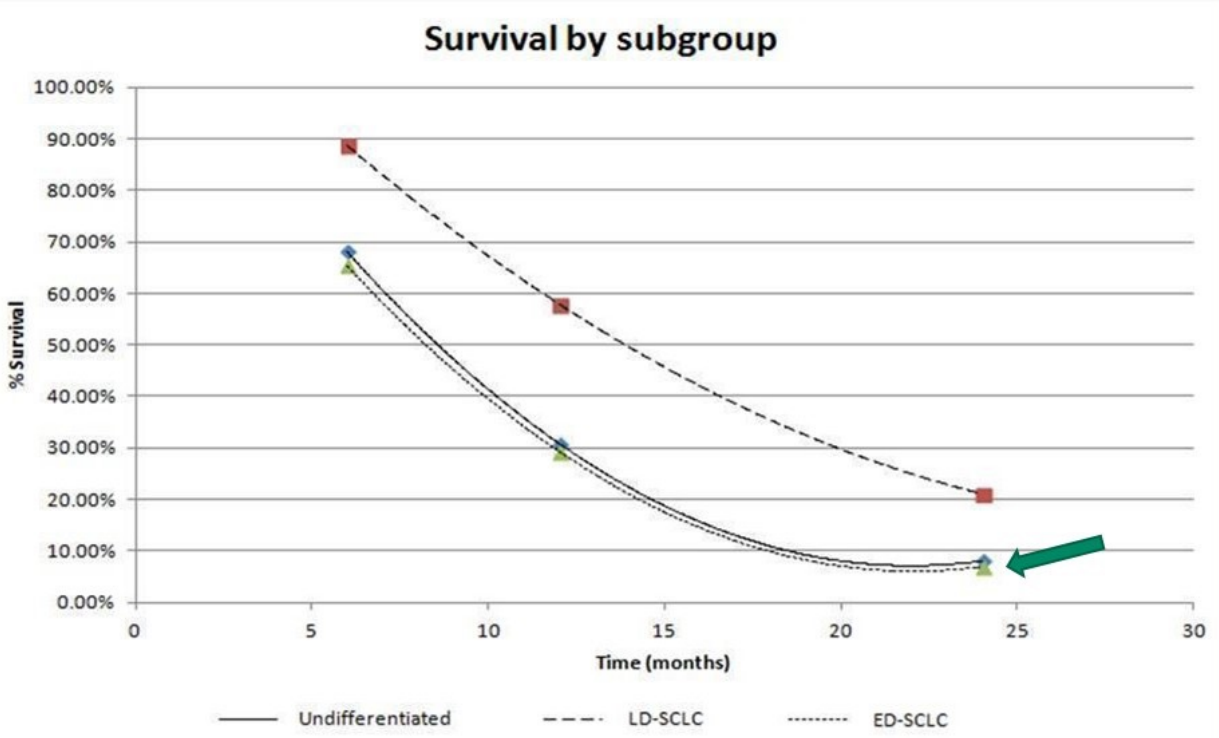
UNIVERSIDAD COMPLUTENSE MADRID

Current Treatment Paradigms for Small Cell Lung Cancer (SCLC)

Luis Paz-Ares

Hospital Universitario 12 de Octubre

Cochrane analysis - outcome prior to ICB

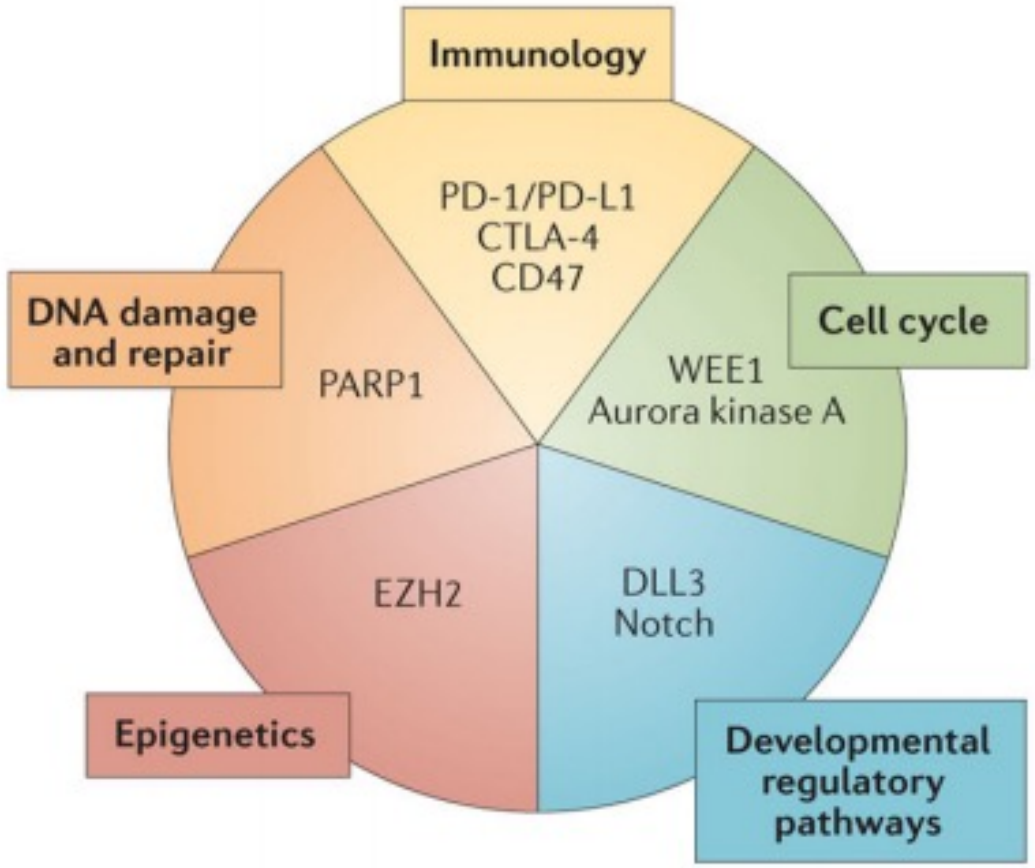


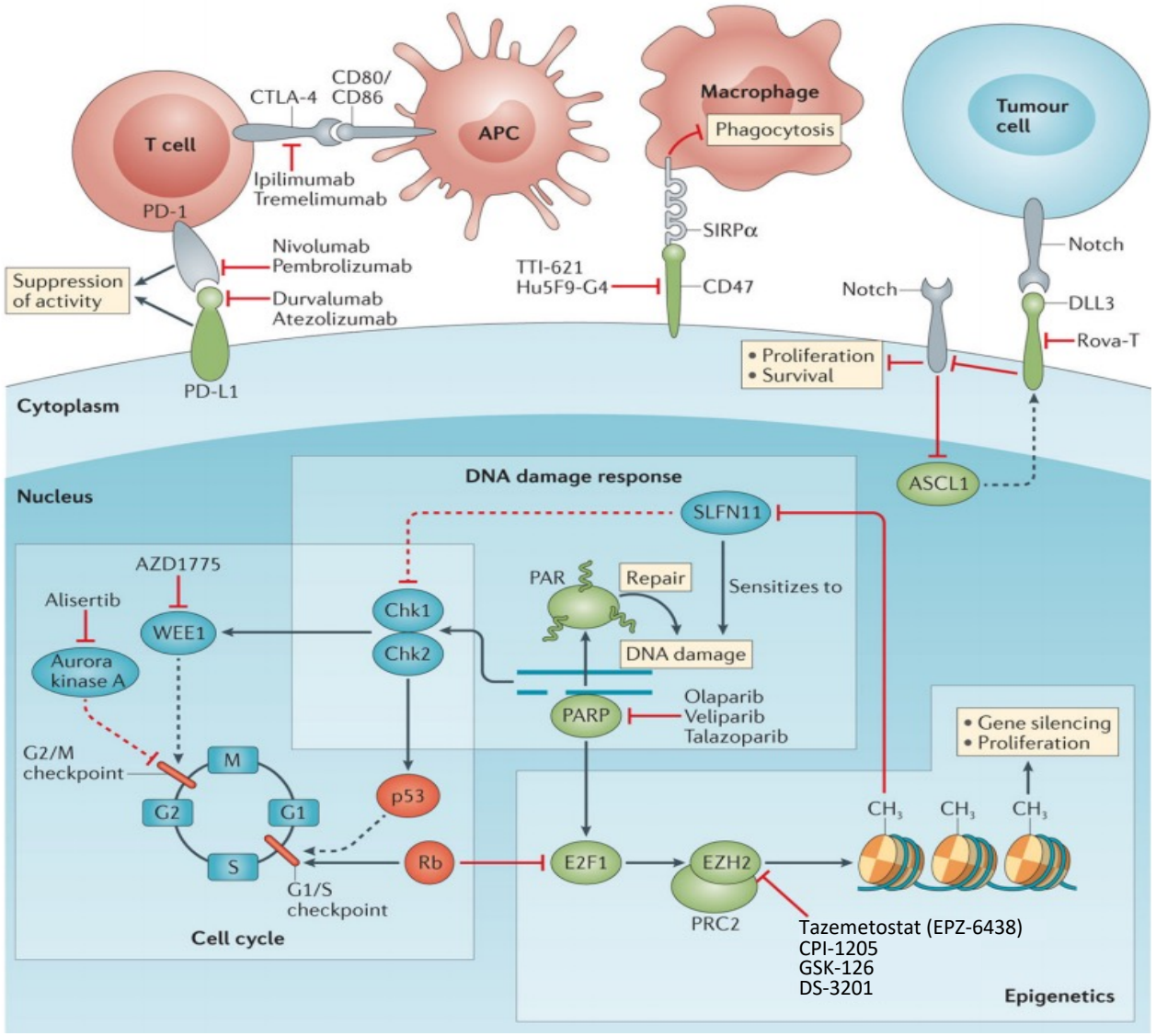
% Survival	Subgroups		
	LD and ED SCLC	LD-SCLC	ED-SCLC
6 months	68.09%	88.70%	**65.36%**
12 months	30.92%	57.98%	**29.37%**
24 months	8.08%	21.09%	**6.93%**

Survival data from 32 randomized studies analyzed 6075 SCLC patients; 3036 treated with platinum-based chemotherapy and 3039 with non-platinum-based chemotherapy.

- ED, extensive disease; ICB, Immune checkpoint blockade; LD, limited disease.
- Amarasena IU, et al. Cochrane Database of Syst Rev. 2015; 8: CD006849.
- Owonikoko TK presentation at ASCO 2020.

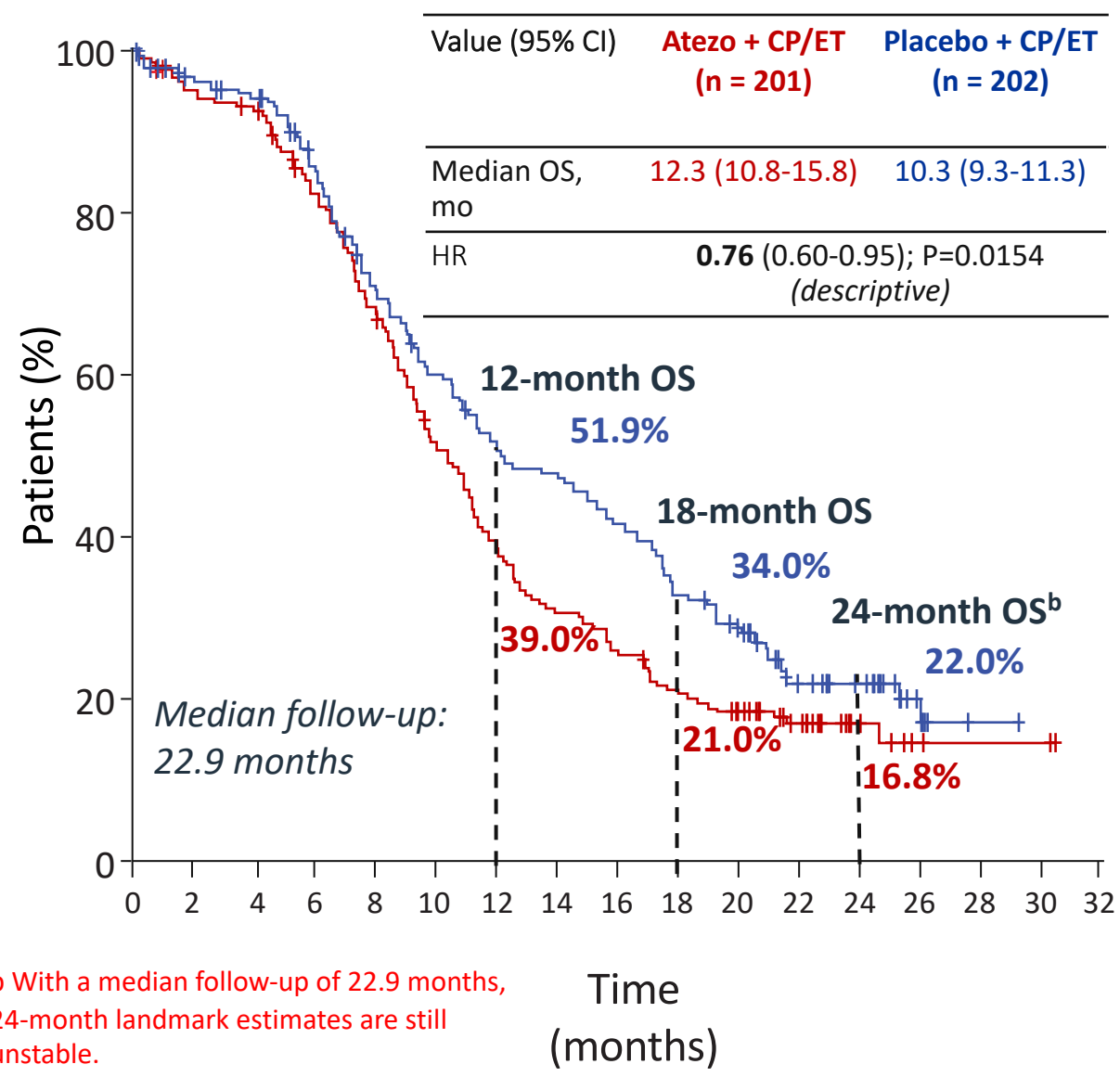
SCLC: main therapeutic areas of interest



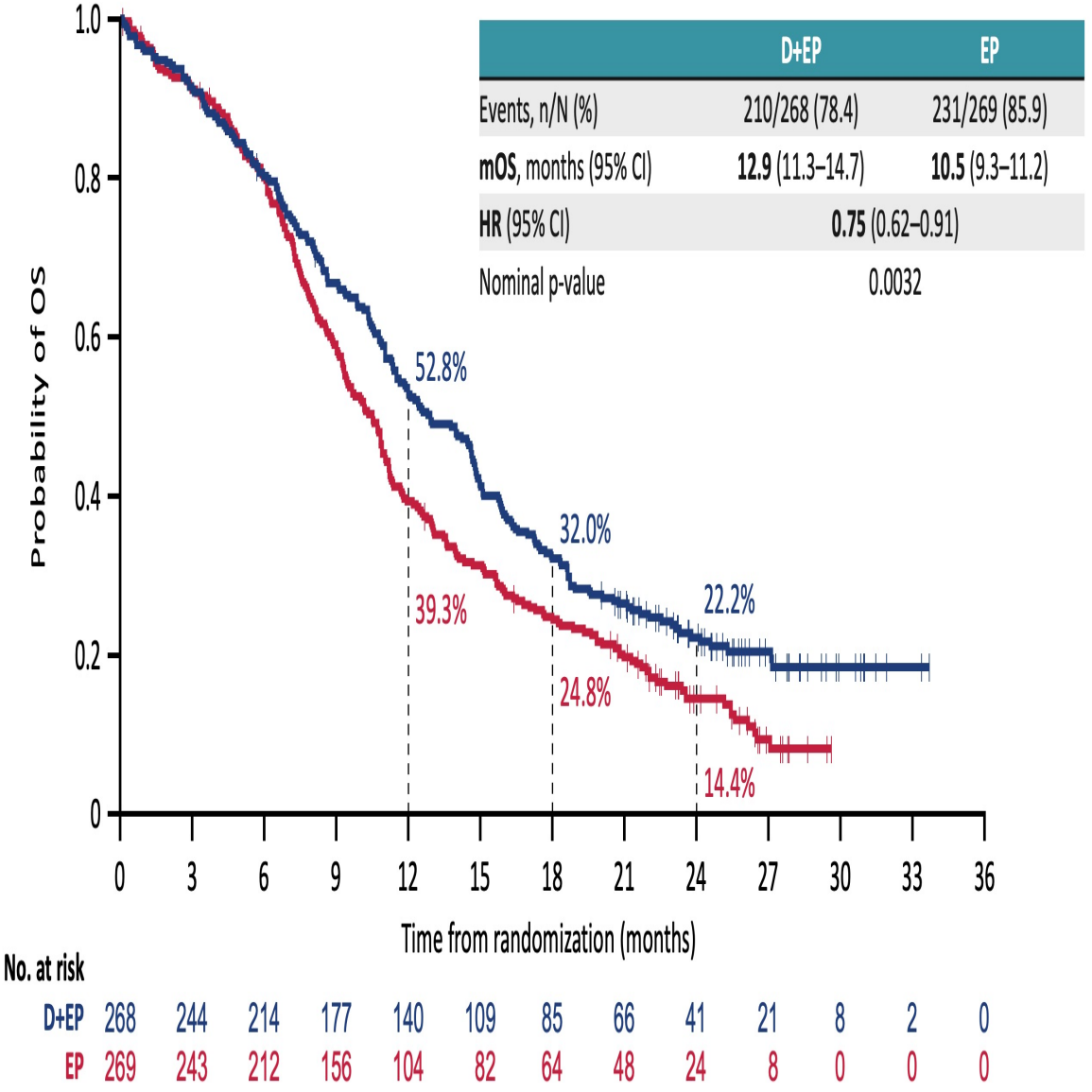


Sabari JK, et al. Nat Rev Clin Oncol 2017;14:549-61.

ES-SCLC – Chemo plus PD-L1 blockade

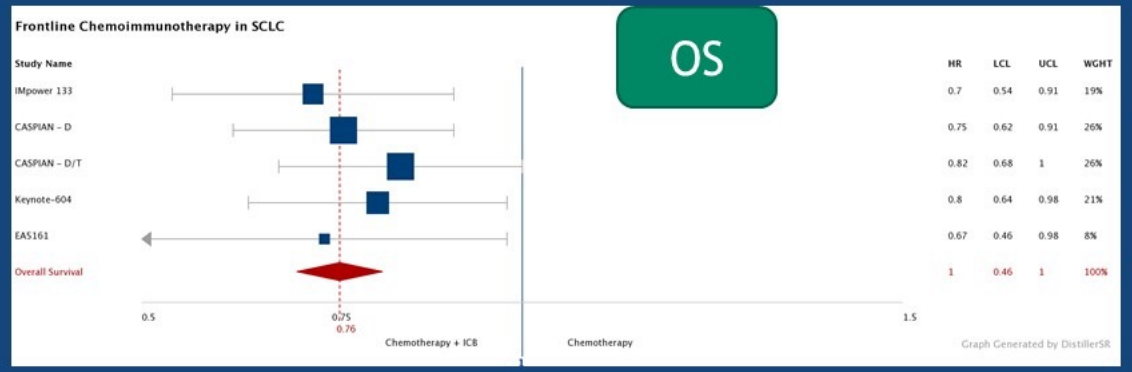


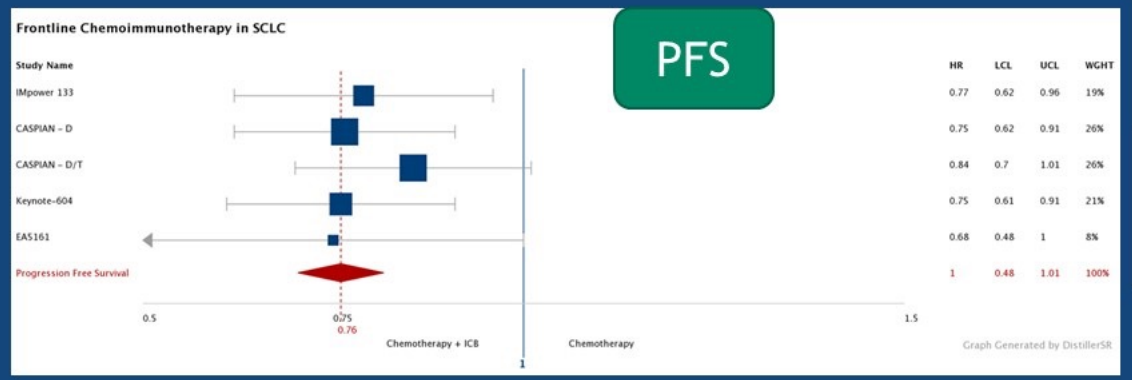
b With a median follow-up of 22.9 months, 24-month landmark estimates are still unstable.



Horn, NEJM 2018; Liu, ESMO 2020; Paz-Ares et al Lancet 2019 & Lancet Oncol 2021

Summary: Chemo-Immunotherapy in SCLC



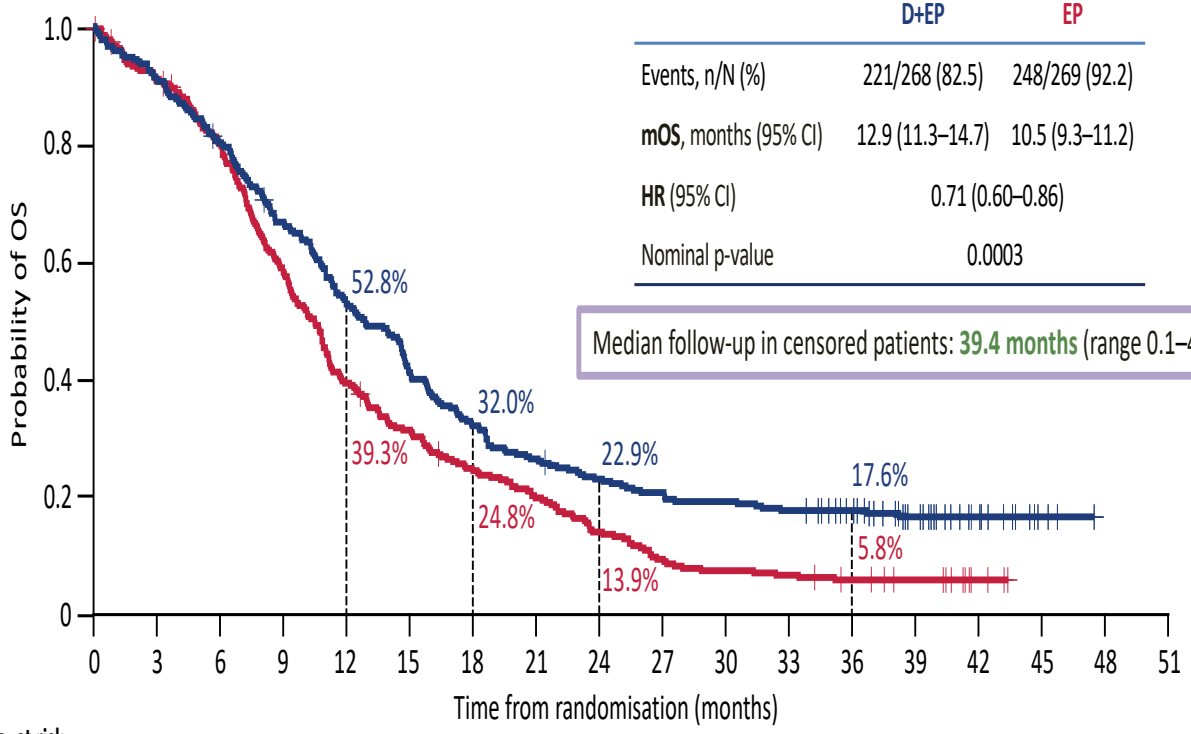


	IMpower133	Caspian D	Caspian D/T	KN-604	EA5161
Median PFS	5.2	5.1	4.9	4.5	5.5
Median OS	12.3	13	10.4	10.8	11.3
12-month OS	**51.7**	**52.8**	**43.8**	**45.1**	**≈48**
24-month OS	**≈22**	**22.2**	**23.4**	**22.5**	**NR**
HR PFS 95% CI	0.77 0.62-0.96	0.78 0.65-0.94	0.84 0.70-1.01	0.75 0.61-0.91	0.68 0.48-1.0
HR OS 95% CI	0.70 0.54-0.91	0.73 0.59-0.91	0.82 0.68-1.00	0.80 0.64-0.98	0.67 0.46-0.98

Owonikoko TK presentation at ASCO 2020.

CASPIAN Trial – OS after 3 years

3-year Overall Survival Update: D+EP vs EP



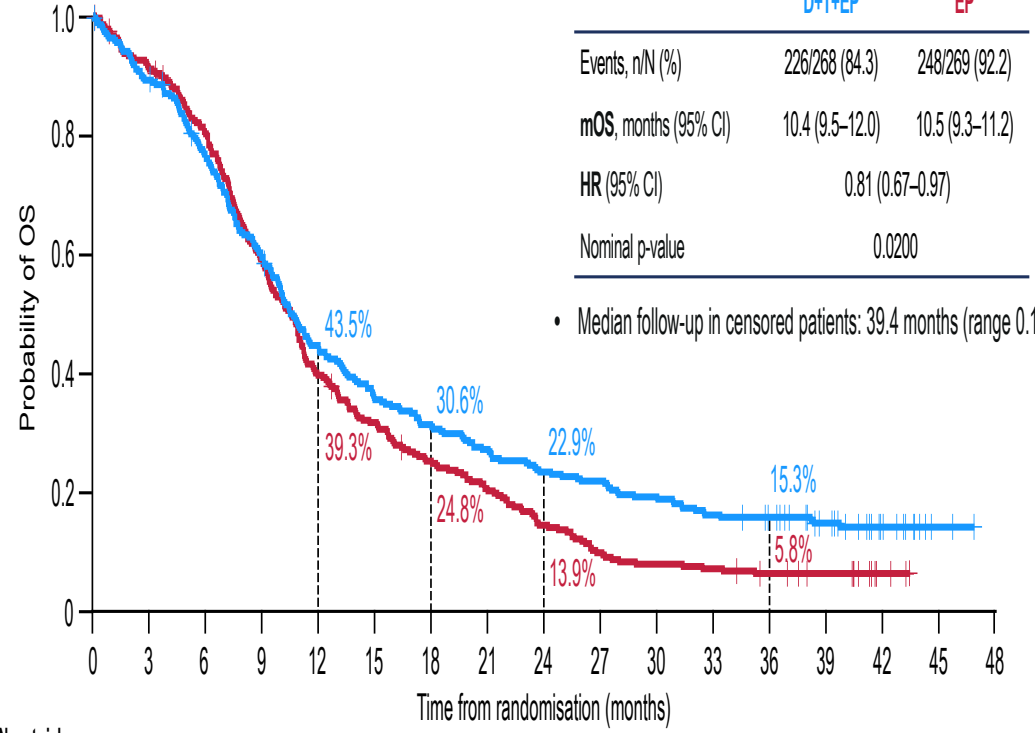
	D+EP	EP
Events, n/N (%)	221/268 (82.5)	248/269 (92.2)
mOS, months (95% CI)	12.9 (11.3–14.7)	10.5 (9.3–11.2)
HR (95% CI)	0.71 (0.60–0.86)	
Nominal p-value	0.0003	

Median follow-up in censored patients: **39.4 months** (range 0.1–47.5)

No. at risk

D+EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

3-year Overall Survival Update: D+T+EP vs EP



	D+T+EP	EP
Events, n/N (%)	226/268 (84.3)	248/269 (92.2)
mOS, months (95% CI)	10.4 (9.5–12.0)	10.5 (9.3–11.2)
HR (95% CI)	0.81 (0.67–0.97)	
Nominal p-value	0.0200	

- Median follow-up in censored patients: 39.4 months (range 0.1–47.5)

No. at risk

D+T+EP	268	238	200	156	114	92	80	70	60	56	48	41	37	26	11	2	0	
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	

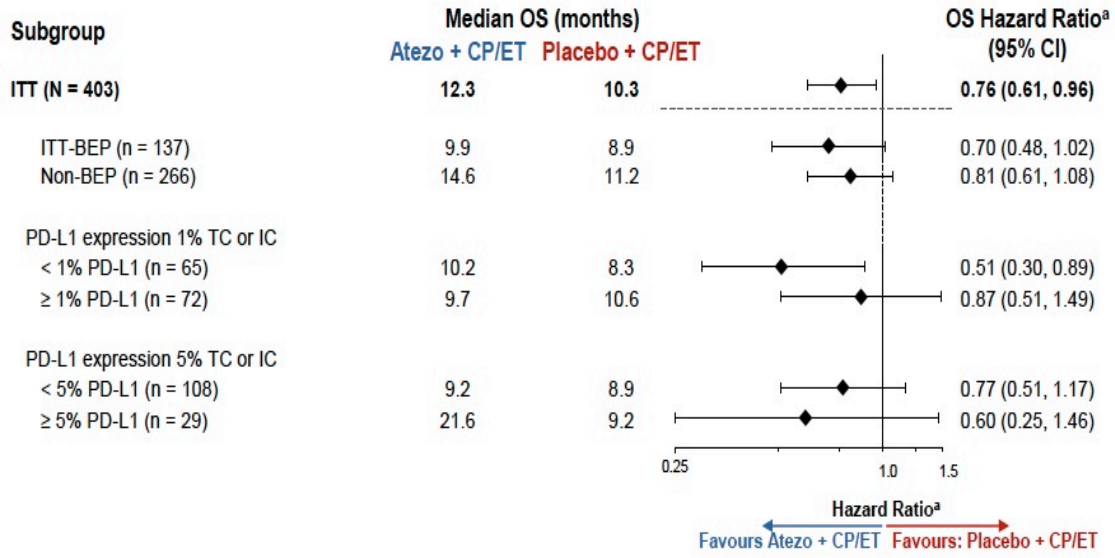
L Paz-Ares et al., ESMO 2021

Data cutoff: 22 March 2021

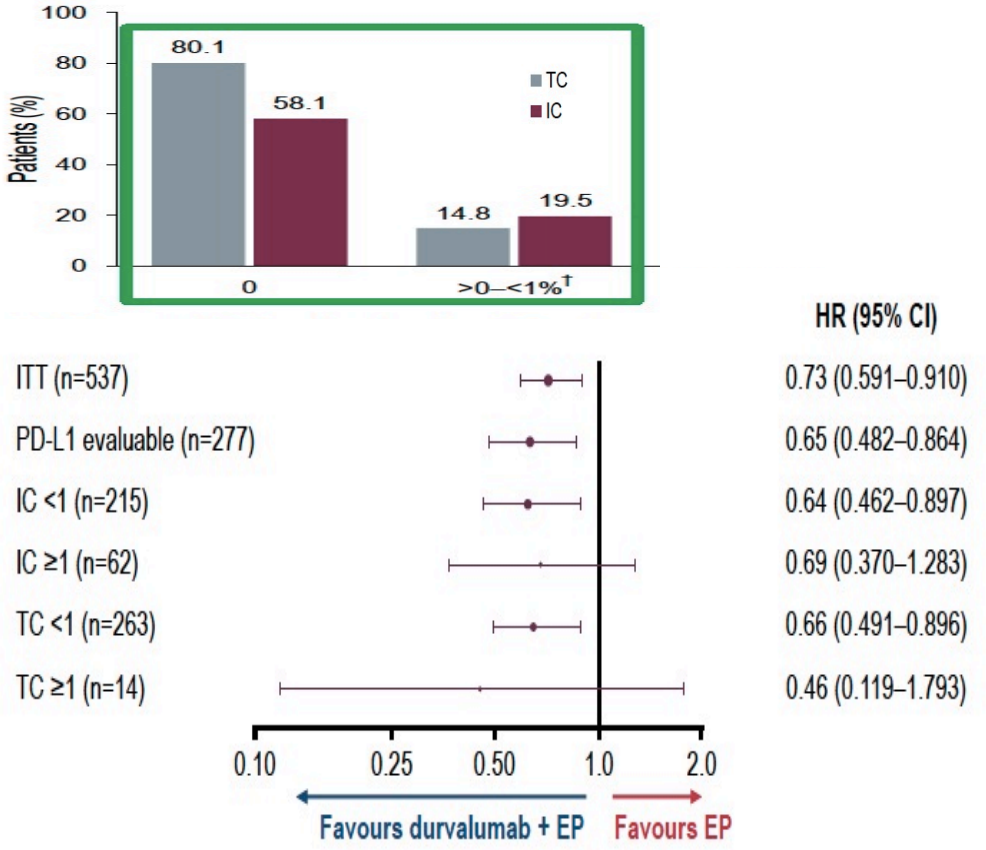
PD-L1 expression and outcome

IMpower133 PD-L1 (SP263) evaluable in 34% of ITT

PD-L1 IHC expression in ES-SCLC (n = 137)			
IC	% BEP (n)	TC	% BEP (n)
< 1%	49.6% (68)	< 1%	94.2% (129)
≥ 1%	50.4% (69)	≥ 1%	5.8% (8)



CASPIAN PD-L1 (SP263) evaluable in 59% of pts. in 3 arms

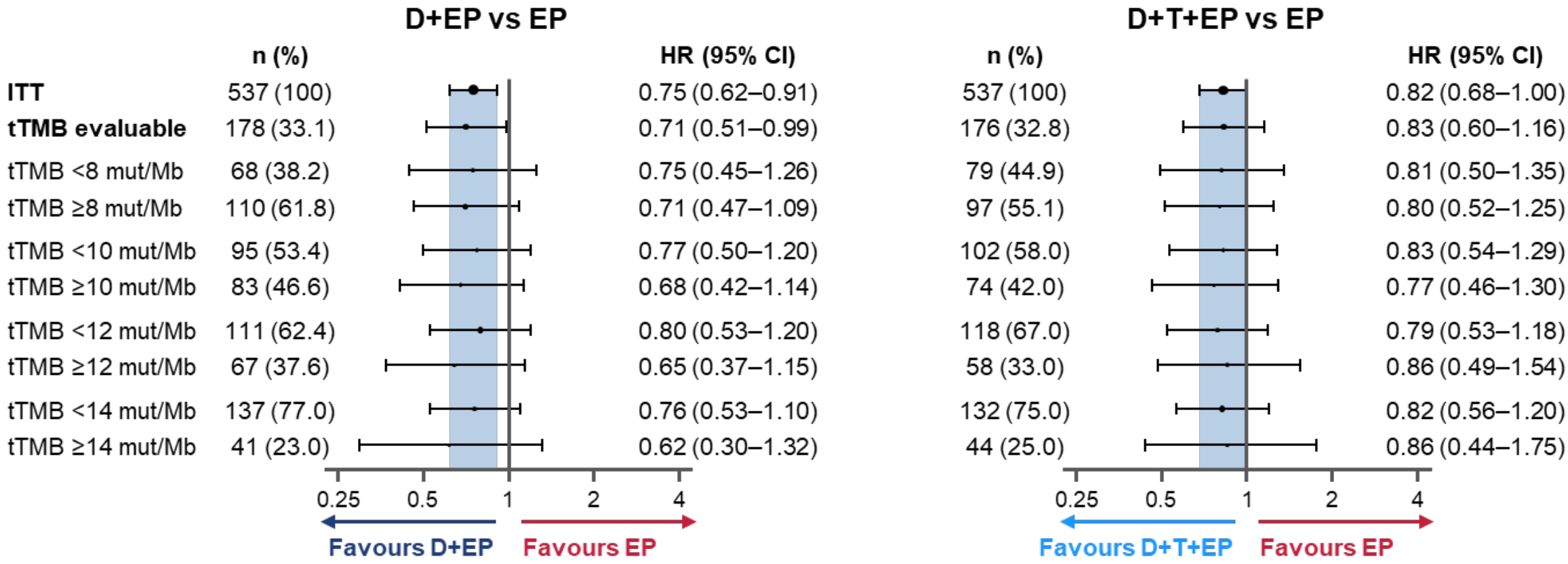


PD-L1 expression in TC is low and no significant interaction PD-L1 and outcome

- BEP, biomarker evaluable population; IC, immune cells; TC, tumor cells.
- Reck M, et al. Presented at: ESMO 2019; Abstract 2374. Paz-Ares, et al. Presented at: ESMO 2019; Abstract 3837.

CASPIAN: Overall survival based on tTMB

tTMB was not predictive of an improvement in OS for durvalumab ± tremelimumab + EP vs EP

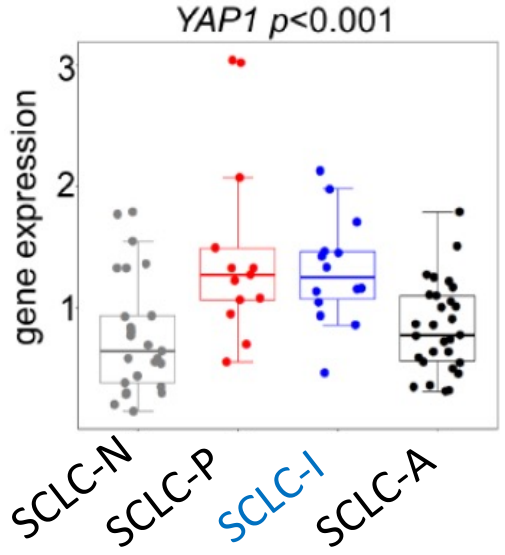


CI, confidence interval; D, durvalumab; EP, platinum-etoposide; HR, hazard ratio; ITT, intent-to-treat; T, tremelimumab; tTMB, tissue tumour mutational burden.

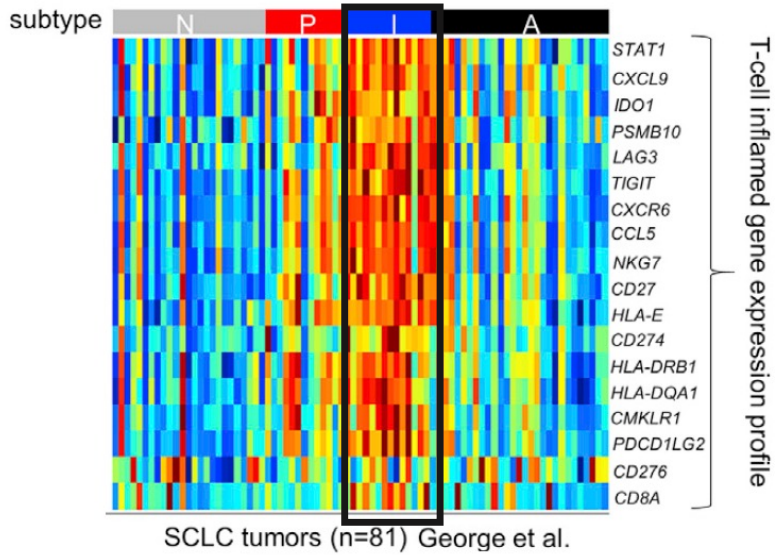
Ji JH et al. ESMO Asia 2020;Abstract 379MO.

SCLC-I: a new subtype with therapeutical implications?

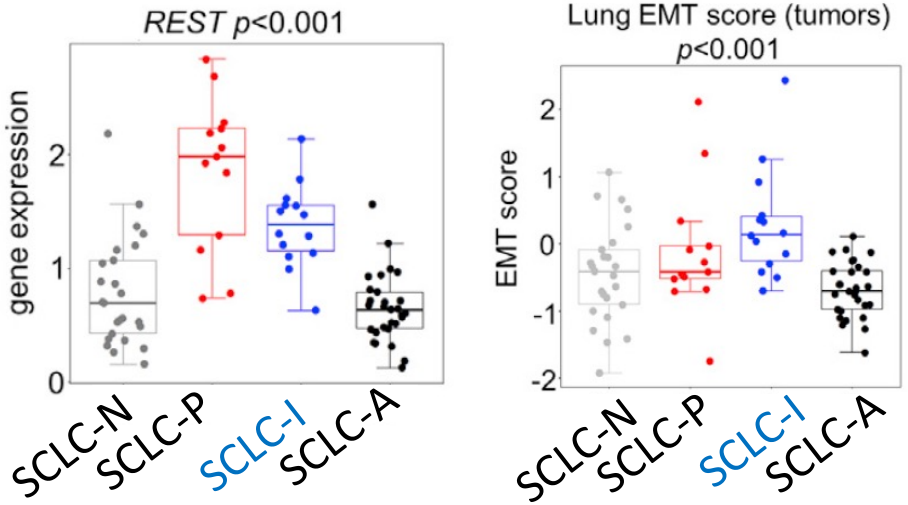
YAP1 expression does not define a particular subtype



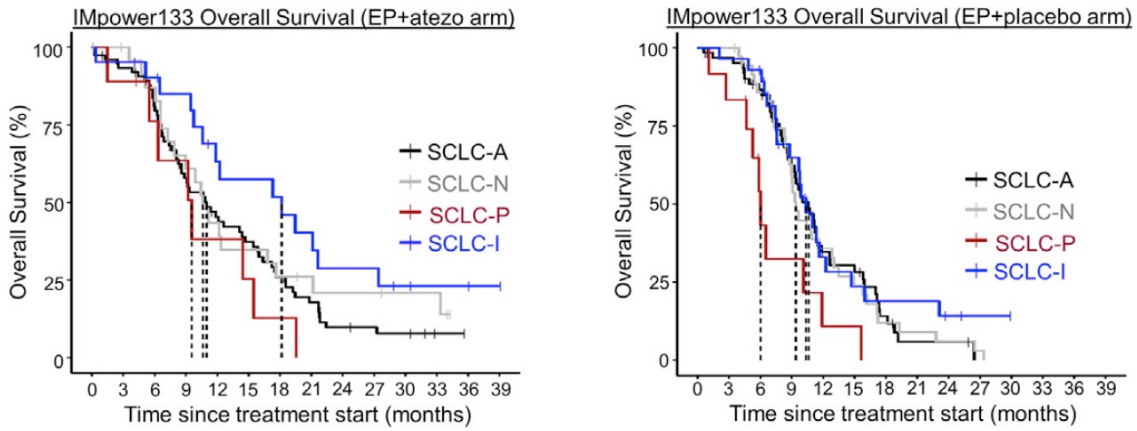
SCLC-I shows an "*immune hot*" phenotype…



SCLC-I subtype shows Notch activation and EMT phenotype



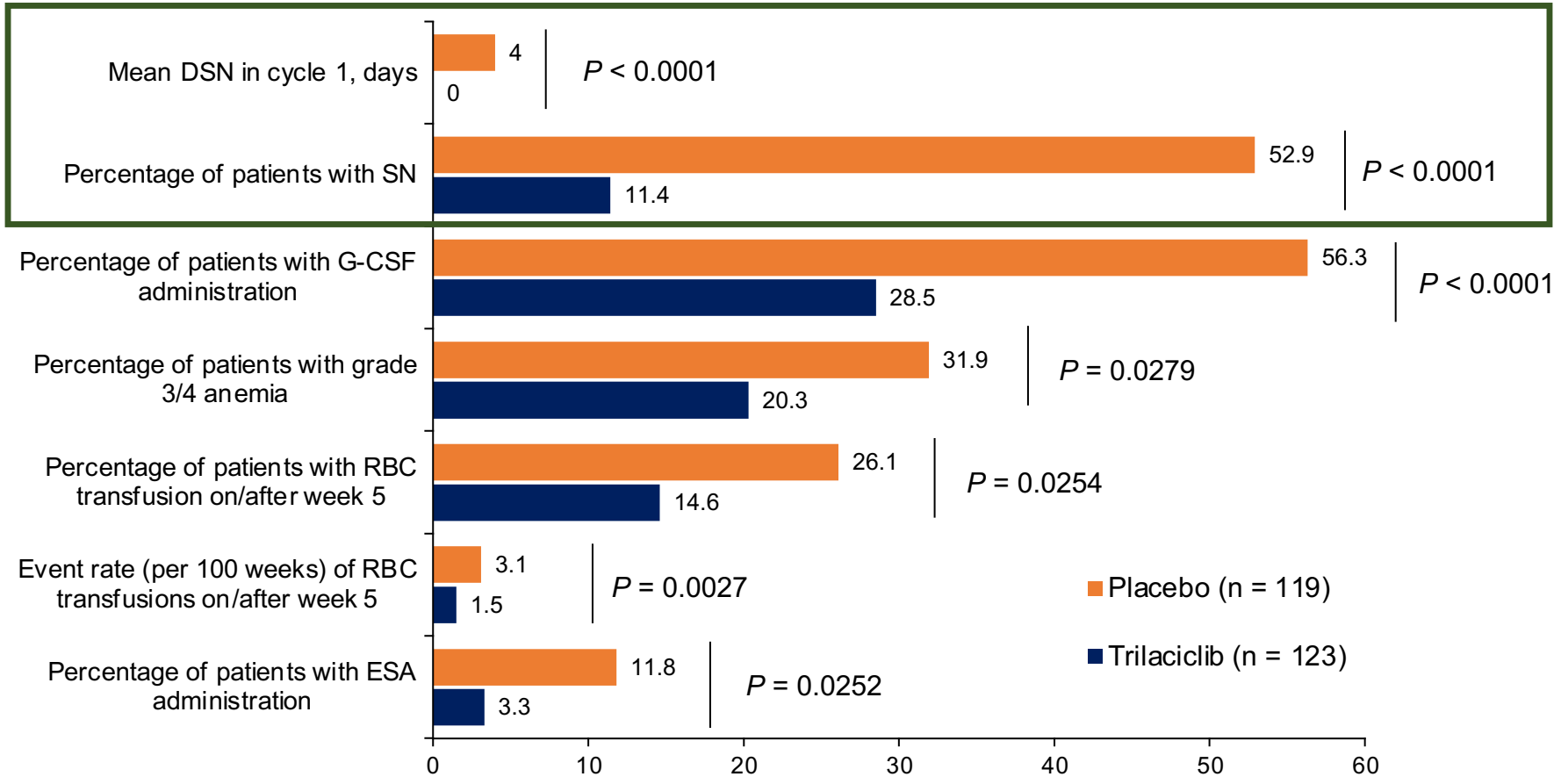
…correlating with better response to immunotherapy



Gay et al., *Cancer Cell* 2021

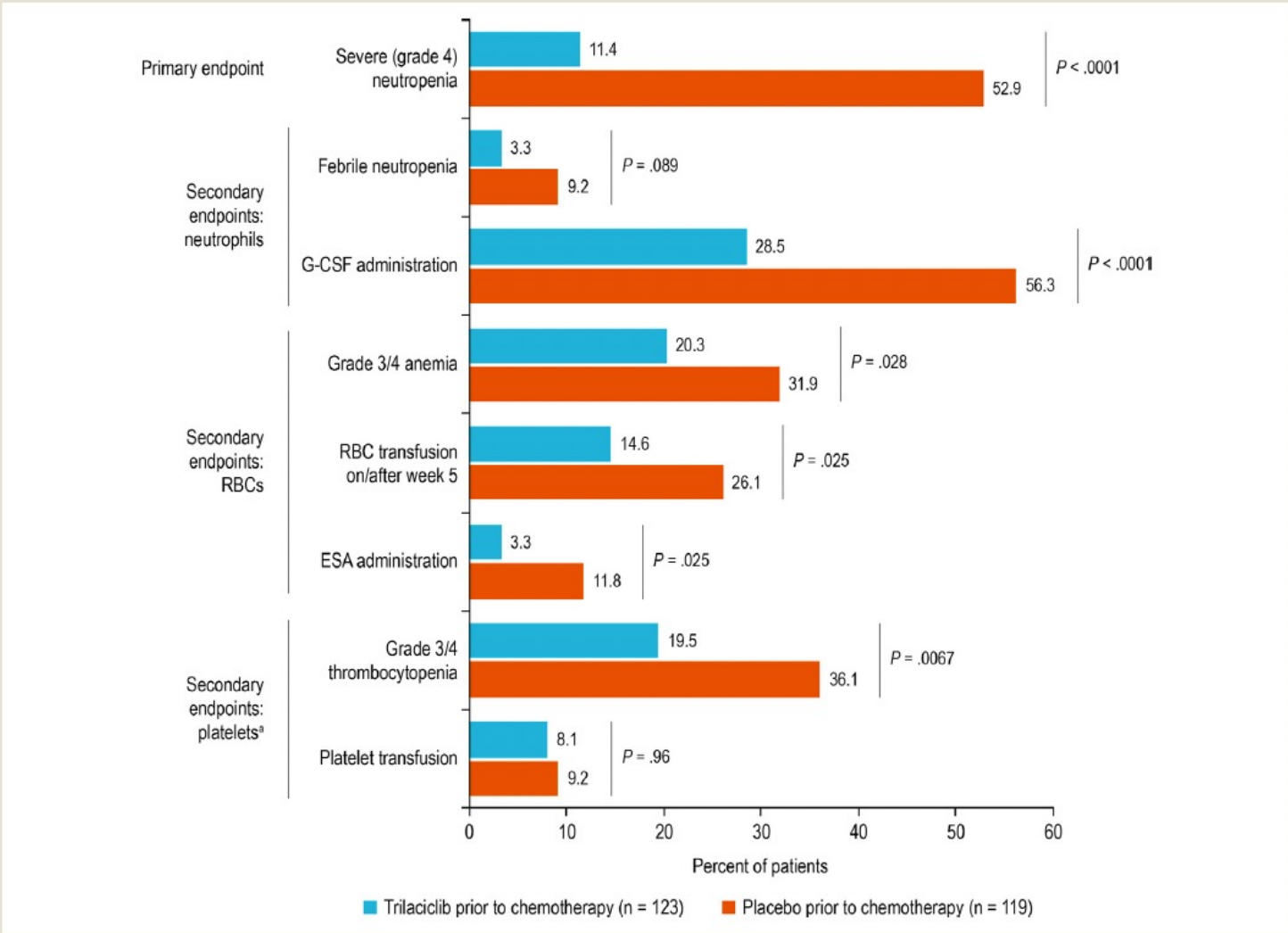
Trilaciclib: Randomized, double-blind, placebo-controlled studies in ES-SCLC

- Overall, 123 patients received trilaciclib prior to chemotherapy and 119 patients received placebo
- Fewer patients receiving trilaciclib had SN or grade 3/4 anemia, and the use of supportive care interventions was reduced



Ferraroto et al. NACLC 2020

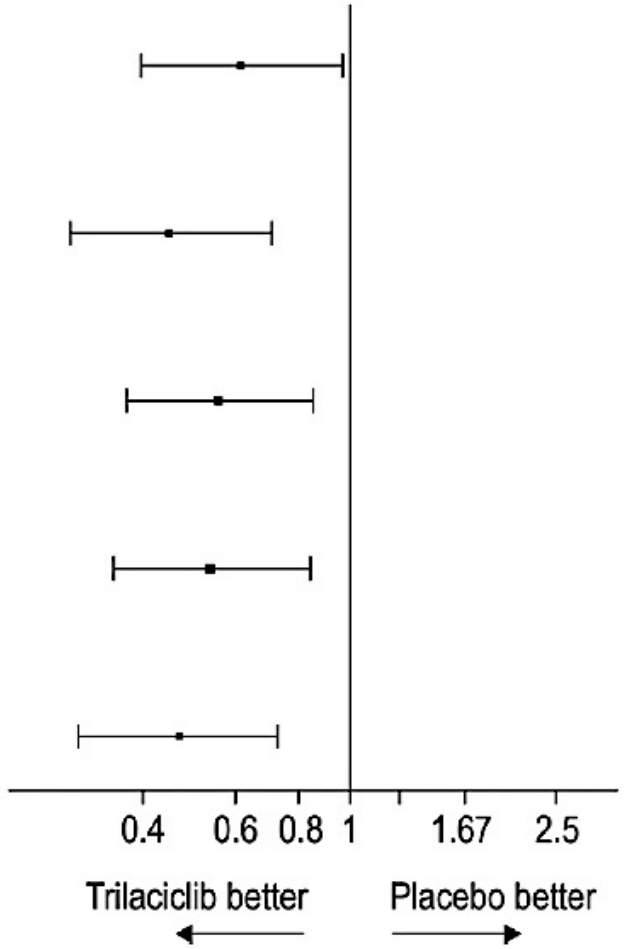
Myelopreservation Benefits with Trilaciclib Administered Prior to Chemotherapy



Weiss J et al. *Clin Lung Cancer* 2021;22(5):449-60.

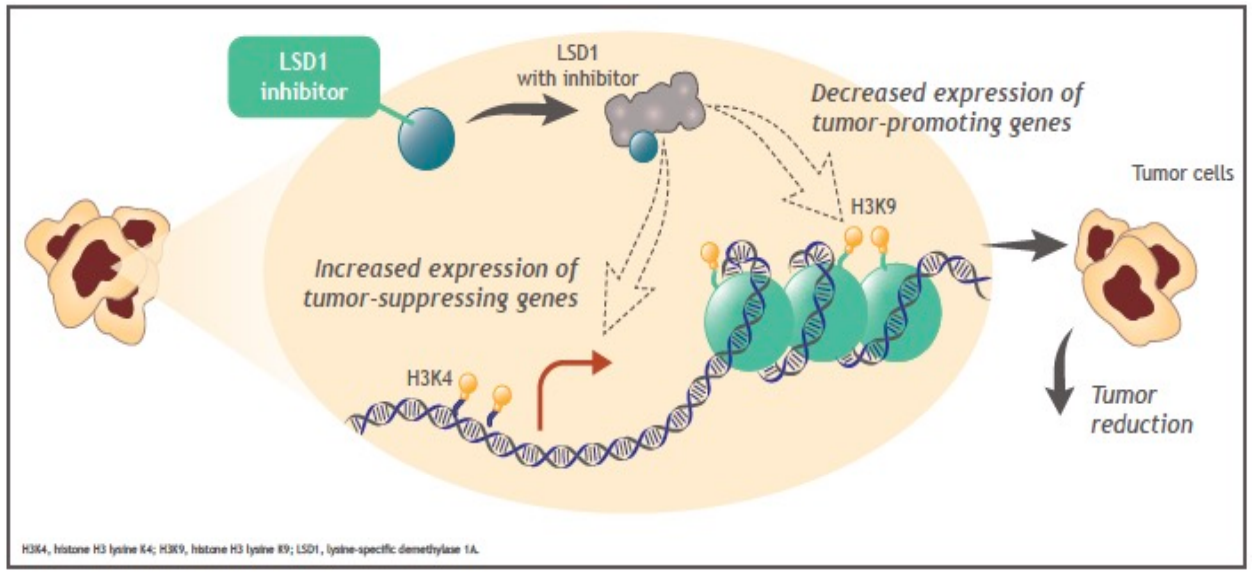
Time to Confirmed Deterioration (TTCD) in Selected Patient-Reported Outcome Measures with Trilaciclib

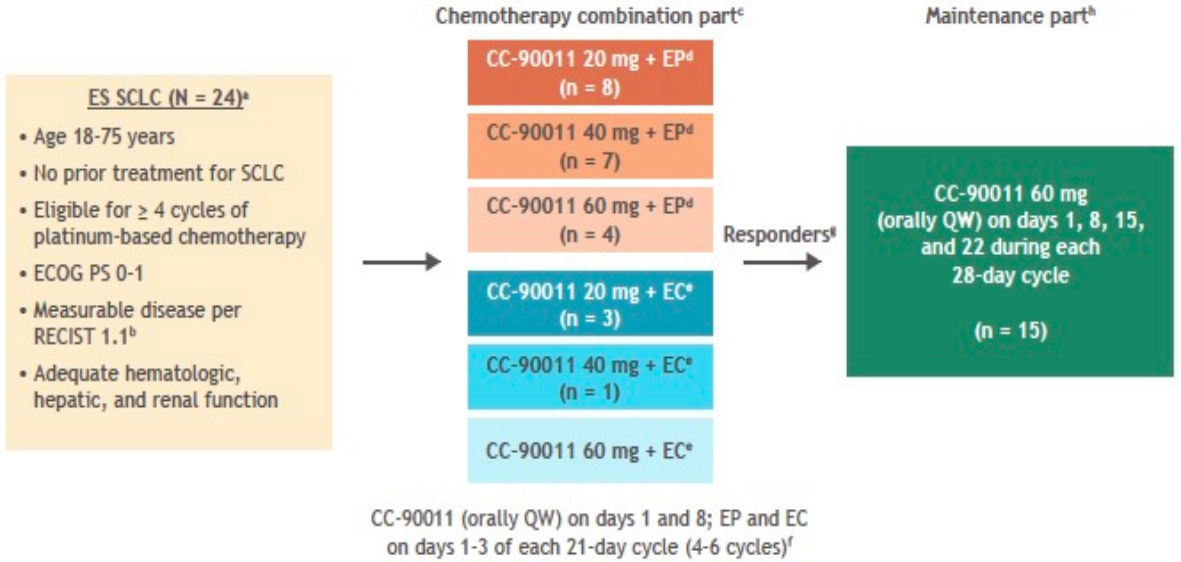
Domain	Events, n Trilaciclib/placebo	TTCD, months Trilaciclib/placebo	Hazard ratio (95% CI)
Physical wellbeing	32/51	NYR/5.16	0.62 (0.40–0.97)
Functional wellbeing	31/55	7.62/3.78	0.45 (0.29–0.71)
Fatigue	39/61	7.03/2.33	0.56 (0.37–0.85)
Anemia trial outcome index	33/55	7.20/3.78	0.54 (0.35–0.84)
FACT-An total	31/58	NYR/3.48	0.47 (0.30–0.73)

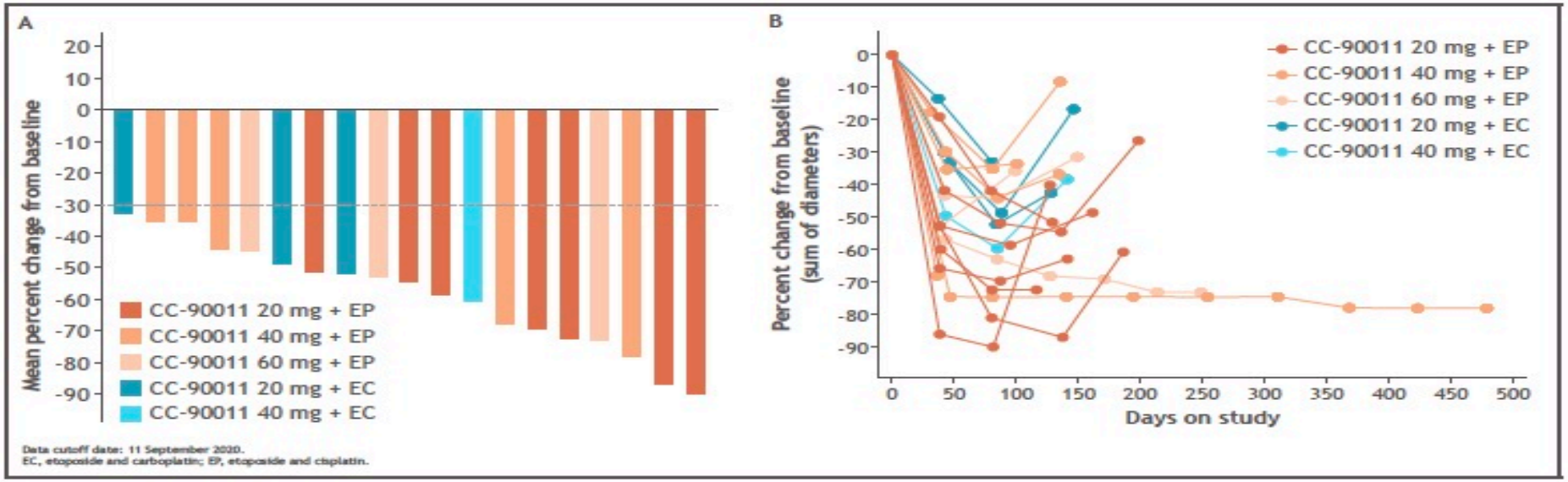


Weiss J et al. *Clin Lung Cancer* 2021;22(5):449-60.

LSD1 Inhibition





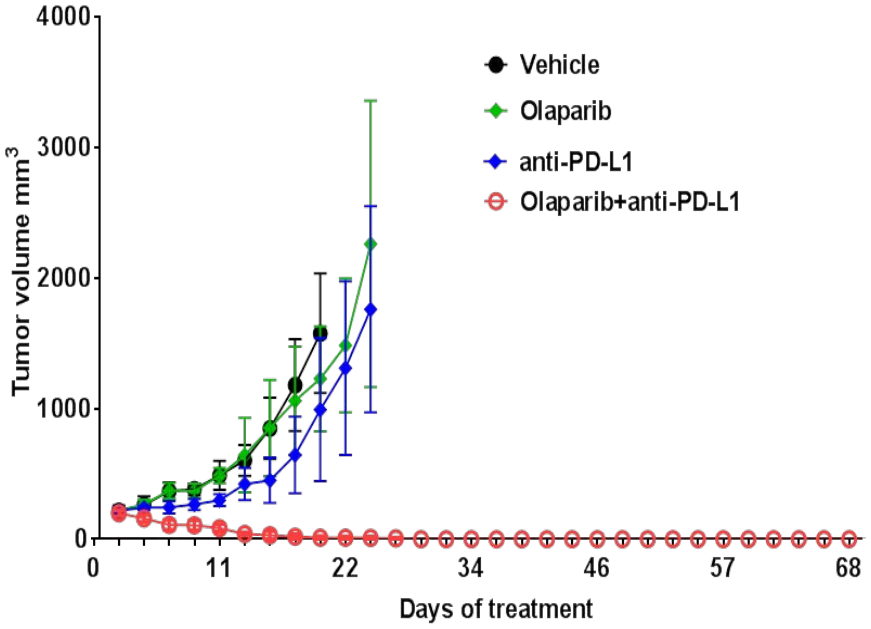


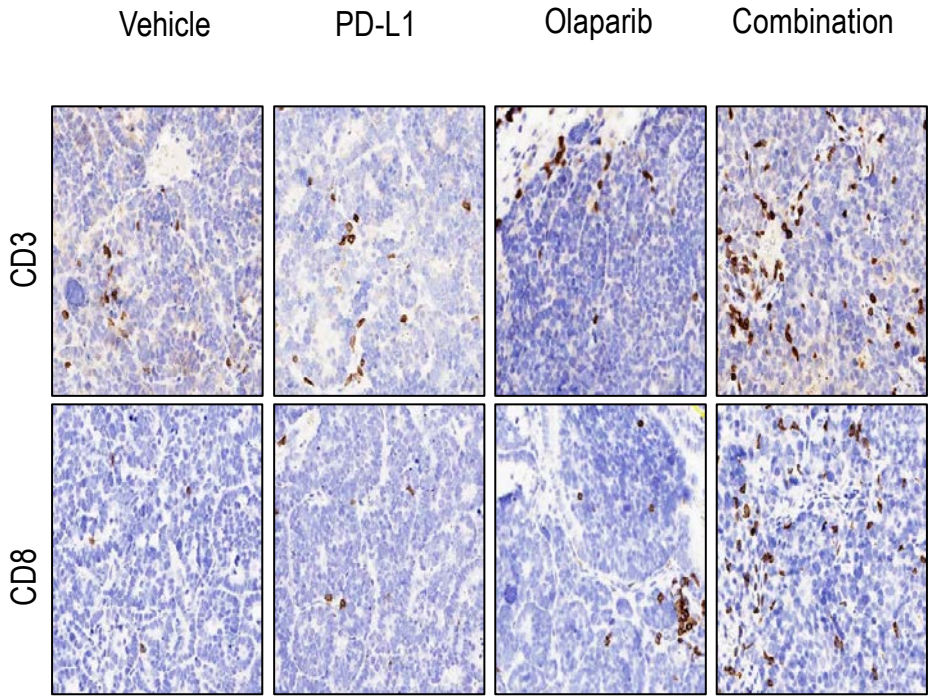
Ponce et al. ELCC 2021

Targeting DNA damage response promotes anti-tumor immunity through STING-mediated T-cell activation

- Despite typically having high TMB, SCLC paradoxically shows lower expression of PDL1 and relatively immunosuppressed TME with limited infiltrating T-cells

- Targeting PARP/CHK1 promotes the expression of PD-L1





Cytotoxic T-cell infiltrates increased in SCLC tumors treated with PARPi plus PDL1i

Sen et al. Cancer Discov 2019

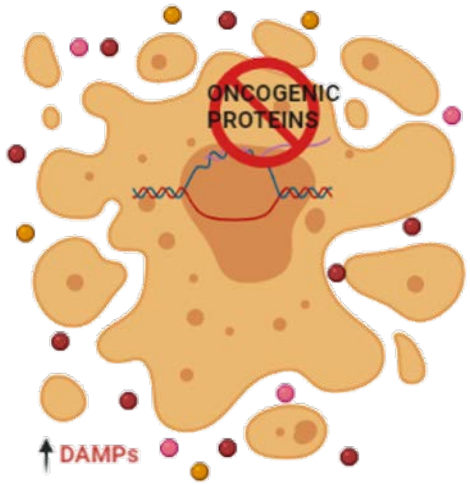
PARP Inhibitor studies in SCLC

Study Population	Drug(s)	Response Rate	PFS (Months)	OS (Months)	Unique Trial Data
Patients with ≤1 prior treatment regimen[30]	Talazoparib	9%	11.1 weeks		
First-line ES-SCLC[32]	CE + veliparib vs. CE + placebo	71.9% vs. 65.6%	6.1 vs. 5.5	10.3 vs. 8.9	Elevated LDH and male gender correlated with benefit
First-line ES-SCLC[45]	(A) CE+ veliparib -> veliparib (B) CE + veliparib -> placebo (C) CE + placebo -> placebo	77% 59.3% 63.9%	5.8 5.7 5.6	10.1 10.0 12.4	
Relapsed ES-SCLC[36]	TMZ + veliparib vs. TMZ + placebo	39% vs. 14%	3.8 vs. 2.0	8.2 vs. 7.0	SLFN11 positive tumors prolonged PFS and OS
Relapsed ES-SCLC[39]	TMZ + olaparib	41.7%	4.2	8.5	Co-clinical PDX trial
Relapsed ES-SCLC[65]	Durvalumab + olaparib	10.5%	1.8	4.1	Inflamed phenotype→ response
Relapsed ES-SCLC[66]	Durvalumab + olaparib	5.3%			Olaparib run in

PFS = progression-free survival, OS = overall survival, ES-SCLC = extensive-stage small-cell lung cancer, CE = cisplatin/etoposide, LDH = lactate dehydrogenase, TMZ = temozolomide, SLFN11 = schlafen family member 11, and PDX = patient-derived xenograft.

Knelson et al. Cancers 2021

Lurbinectidin regulates SCLC transcription and reshapes the TME



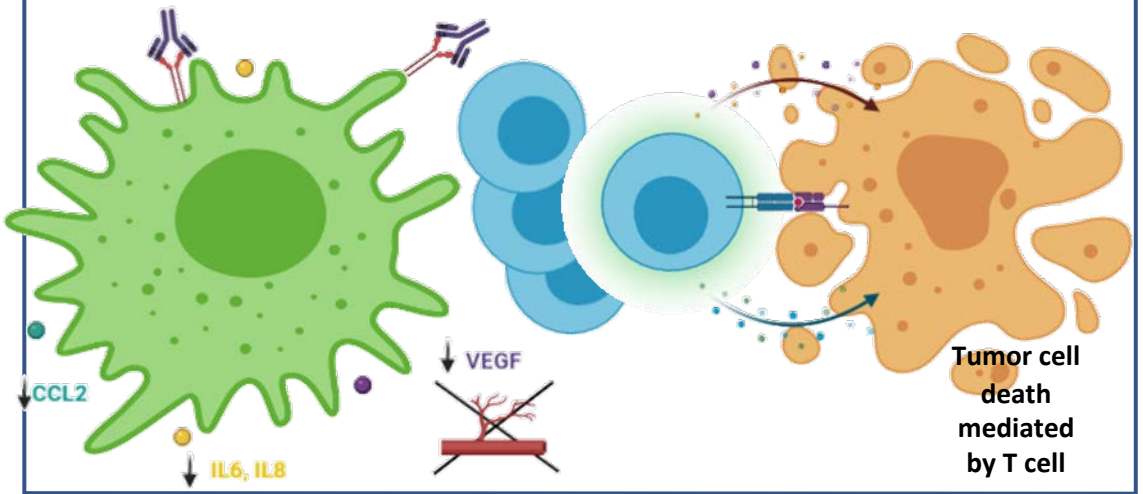
Tumor cell death mediated by LUR

Tumor cells ⬇ **Tumor cells**

- **Lurbinectedin inhibits production of oncogenic proteins and kills the tumor cell**

Tumor cells ⬇ **Immune cells**

- **Lurbinectedin produces immunogenic tumor cell death and decreases the number of TAMs within the tumor**



Immune cells ⬇ **Tumor cells**

- **Lurbinectedin inhibits the production of tumorigenic and immuno-suppressive chemokines by TAMs**

Immune cells ⬇ **Immune cells**

- **αPD-1/PD-L1 block causes the T-cells to remain active and kill the tumor cells**

Tumor Cell Death and Immune Response

Santamaría *et al*., Mol Cancer Ther. 2016
Belgiovine *et al*., Br J Can 2017
Xie W *et al*., Oncoimmunology. 2019

Germano *et al*., Cancer Res 2010
Germano *et al*., Cancer Cell 2013
Povo-Retana *et al*., Cancers. 2020

BASKET Trial | Lurbinectedin monotherapy
Efficacy in Patients With SCLC

	All patients (n=105)	Chemotherapy-free interval <90 days (n=45)	Chemotherapy-free interval ≥90 days (n=60)
RECIST responses, %			
CR / PR / SD,* %	0 / 35 / 33	0 / 22 / 29	0 / 45 / 37
PD, %	27	40	17
Not evaluable,‡ %	5	9	2
Overall response, %	35.2	22.2	45.0
Disease control, %†	68.6	51.1	81.7
Duration of response			
Median DoR, months (95% CI)	5.3 (4.1–6.4)	4.7 (2.6–5.6)	6.2 (3.5–7.3)
Progression-free survival			
Median PFS, months (95% CI)	3.5 (2.6–4.3)	2.6 (1.3–3.9)	4.6 (2.8–6.5)
4-month PFS rate, %	46.6	29.1	59.9
6-month PFS rate, %	32.9	18.8	43.5
Overall survival			
Median OS, months (95% CI)	9.3 (6.3–11.8)	5.0 (4.1–6.3)	11.9 (9.7–16.2)
6-month OS rate, %	67.1	45.8	83.6
12-month OS rate, %	34.2	15.9	48.3

**Includes five patients with partial response not confirmed; ‡ five patients were not evaluable because they had no radiological assessment during treatment due to early death from malignant disease (n=2), symptomatic deterioration because of disease progression (n=2), and patient refusal (n=1); † partial response or stable disease*

Median follow-up of 17.1 months (as of data cut-off January 15, 2019)

Trigo et al. Lancet Oncol 2020

BASKET Trial | Lurbinectedin monotherapy
Safety and tolerability

n=105	n (%)
AEs	89 (84.8)
- Gr ≥3	36 (34.3)
SAEs	11 (10.5)
AEs leading to death	0 (0.0)
AEs leading to treatment discontinuation	2 (1.9)
Dose delays treatment related	21 (22.1*)
Dose reductions #	25 (26.3*)
G-CSF	23 (21.9)
Transfusions (red blood cells and/or platelets)	10 (9.5)

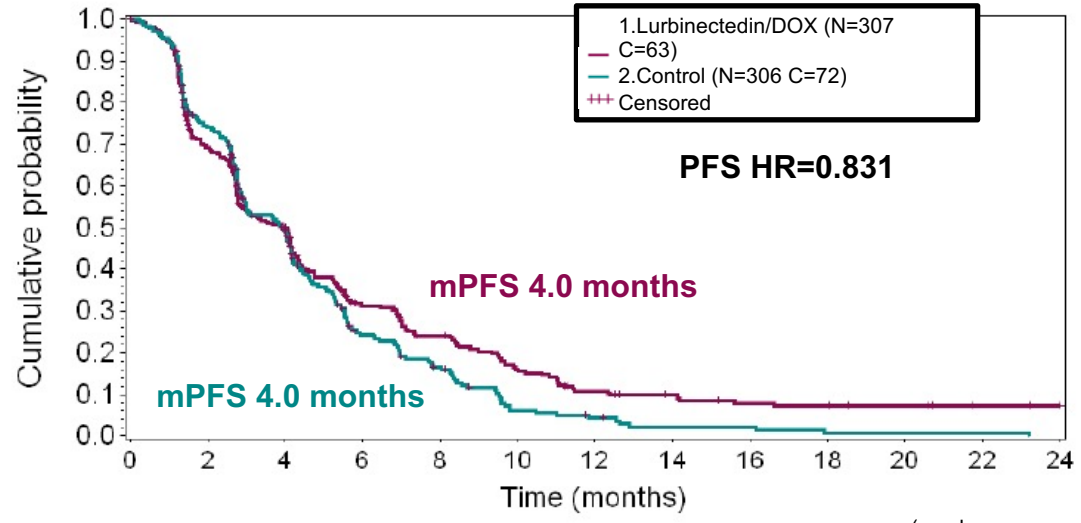
	n=105	Gr 1-2 n (%)	Gr 3-4 n (%)	Gr 1-4 n (%)
Hematological AEs *	Neutropenia	6 (5.7)	24 (22.9)	30 (28.6)
	Anemia	2 (1.9)	7 (6.7)	9 (8.7)
	Thrombocytopenia	2 (1.9)	5 (4.8)	7 (6.7)
Non-Hematological AEs	Febrile neutropenia	.	5 (4.8)	5 (4.8)
	Fatigue	54 (51.4)	7 (6.7)	61 (58.1)
	Nausea	34 (32.4)	.	34 (32.4)
	Decreased appetite	22 (21.0)	.	22 (21.0)
	Vomiting	19 (18.1)	.	19 (18.1)
	Diarrhea	13 (12.4)	1 (1.0)	14 (13.4)
	Constipation	10 (9.5)	.	10 (9.5)
	Pneumonia	.	2 (1.9)	2 (1.9)
	Alanine aminotransferase increased *	.	2 (1.9)	2 (1.9)
	Skin ulcer	.	1 (1.0)	1 (1.0)

Paz-Ares LG et al. ASCO 2019;Abstract 8506.

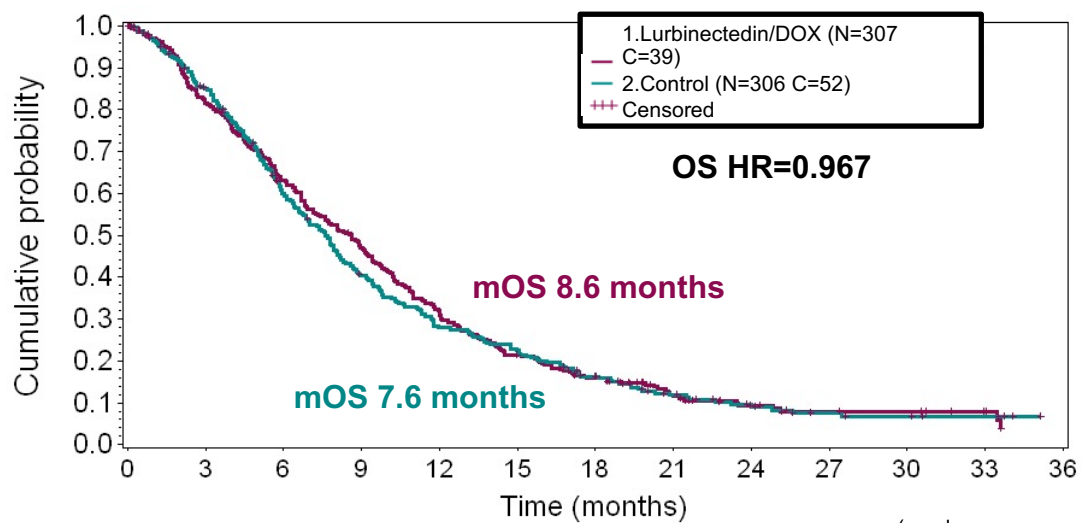
ATLANTIS Trial | Lurbinectedin + Doxorubicin
Overall Survival and Progression-free Survival

IMforte GO43104

Progression-free Survival



Overall Survival



Paz-Ares et al. WCLC 2021 (PL02.03)

ATLANTIS Trial | Lurbinectedin + Doxorubicin
Safety

Hematological	Lurbinectedin+DOX (n=303)	Control (n=289)	
	Grade ≥3	Grade ≥3	p-value
Anaemia	44 (14.5)	90 (31.1)	<0.0001
Neutropenia	112 (37.0)	200 (69.2)	<0.0001
Febrile neutropenia	12 (4.0)	24 (8.3)	0.0377
Thrombocytopenia	42 (13.9)	90 (31.1)	<0.0001

Non hematological	Lurbinectedin+DOX (n=303)	Control (n=289)	
	Grade ≥3	Grade ≥3	p-value
ALT increased	6 (2.0)	3 (1.0)	0.5057
AP increased	2 (0.7)	3 (1.0)	0.6783
AST increased	7 (2.3)	4 (1.4)	0.5463
Fatigue	26 (8.6)	31 (10.7)	0.4051
Nausea	6 (2.0)	4 (1.4)	0.7525
Vomiting	4 (1.3)	0	0.1242

	Lurbinectedin+DOX (n=303) n (%)	Control (n=289) n (%)
Any AE treatment-related	268 (88.4)	266 (92.0)
Any grade ≥3 AE	**143 (47.2)**	**218 (75.4)**
Any grade 4 AE	**49 (16.2)**	**158 (54.7)**
Any grade ≥3 SAE	38 (12.5)	83 (28.7)
Death associated with AEs	**1 (0.3)**	**10 (3.5)**
Treatment discontinuations associated with AEs	23 (7.6)	45 (15.6)
Delays associated with AEs	79 (26.1)	99 (34.3)
Reductions associated with AEs	66 (21.8)	138 (47.8)

Paz-Ares et al. WCLC 2021 (PL02.03)

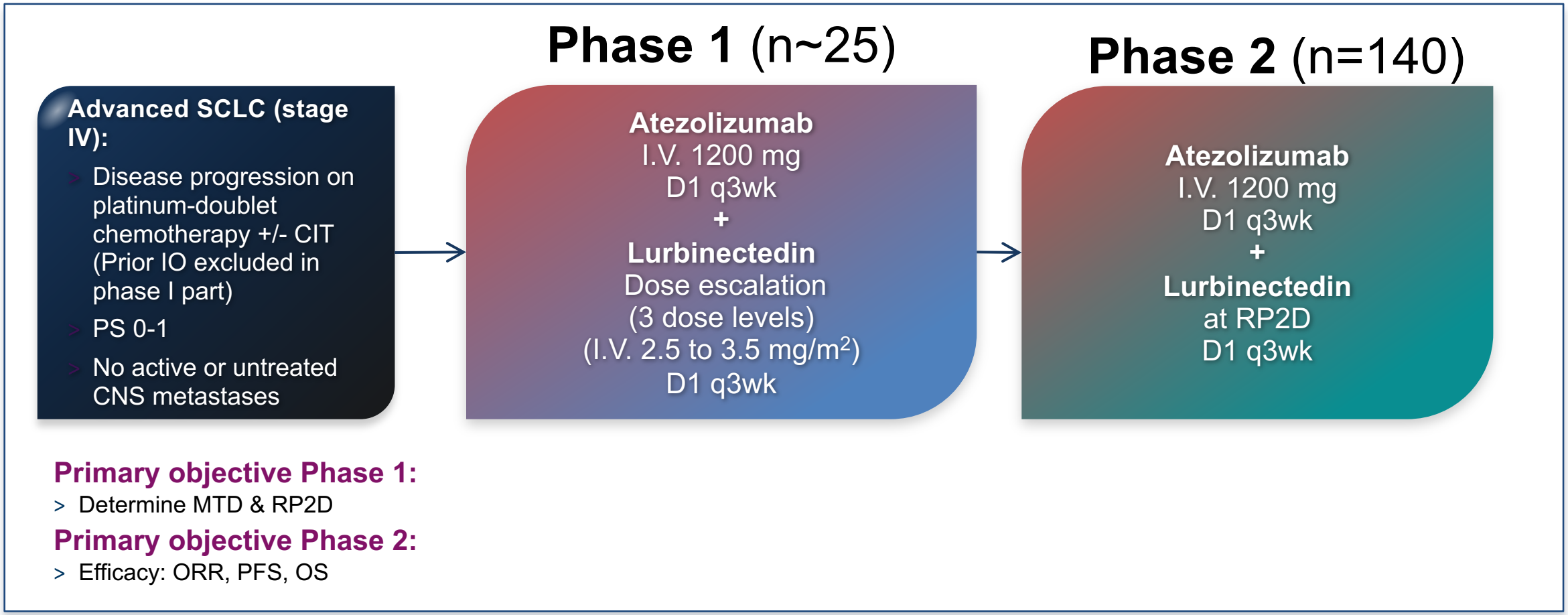
Phase 1b/2 Trial | Lurbinectedin + Irinotecan
Efficacy in the SCLC Cohort

	All patients (n = 21)	CTFI		Setting		CNS	
		≥90 days (n = 13)	<90 days (n = 8)	2nd line (n = 13)	3rd line (n = 8)	YES (n = 5)	NO (n = 16)
Median number of cycles (range)	8+ (1-20)	10+ (6-20)	5.5+ (1-8)	8+ (3-20)	7.5+ (1-17)	7+ (2-10)	8+ (1-20)
Overall response rate (PR)	**62%**	**69%**	**50%**	**77%**	**37%**	**20%**	**75%**
Clinical benefit rate (PR + SD >4m)	81%	92.3%	62.5%	92.3%	62.5%	60%	87.5%
Disease control rate (PR + SD)	90%	100%	75%	100%	75%	80%	93.8%
Median DOR (m) (95% CI)	6.7+ (3.0, nr)	7.5+ (3.0, nr)	3.7+ (2.8, 3.7)	6.7+ (3.0, nr)	3.0+ (2.8, nr)	–	6.7+ (3.0, nr)
Median PFS (m) (95% CI)	**6.2+ (4.3, 8.5)**	**8.1+ (4.3, nr)**	**4.8+ (0.7, 5.0)**	**8.3+ (4.8, nr)**	**4.2+ (0.7, 7.2)**	**7.2+ (1.1, 7.2)**	**6.2+ (4.3, 9.7)**

Ponce-Aix S. Presented at WCLC 2020. Oral OA11.04.

SCLC, small-cell lung cancer; CTFI, chemotherapy-free interval; CNS, central nervous system; PR, partial response; SD, stable disease; DOR, duration of response; CI, confidence interval; PFS, progression-free survival.

2SMALL: Phase I/II trial



Primary objective Phase 1:

> Determine MTD & RP2D

Primary objective Phase 2:

> Efficacy: ORR, PFS, OS

MTD: maximum tolerated dose; RP2D: recommended PhII dose

Ponce et al. SITC 2021

2SMALL: Phase I/II trial – Early Results

Objective responses (ORR) were observed in 15 pts (57.7%), including complete responses (CR) in 2 pts (7.7%), partial response (PR) in 13 pts (50%). Stable disease (SD) was observed in 7 pts (26.9%) and 3 pts (11.54%) were in progressive disease (PD). Disease control rate (DC) was 84.61%.

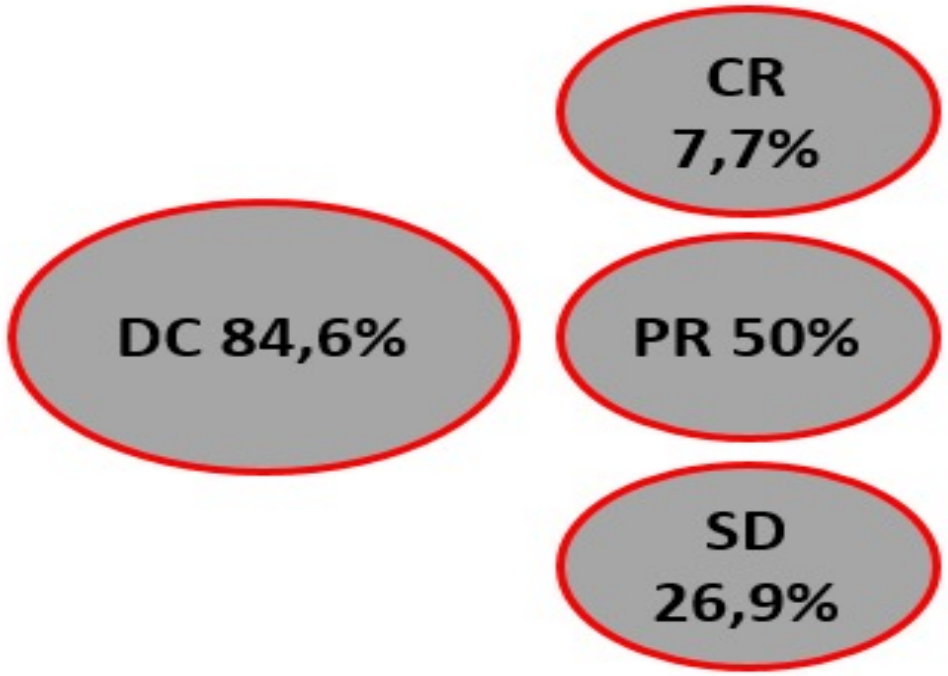


FIGURE 1 Disease Control Rate and ORR

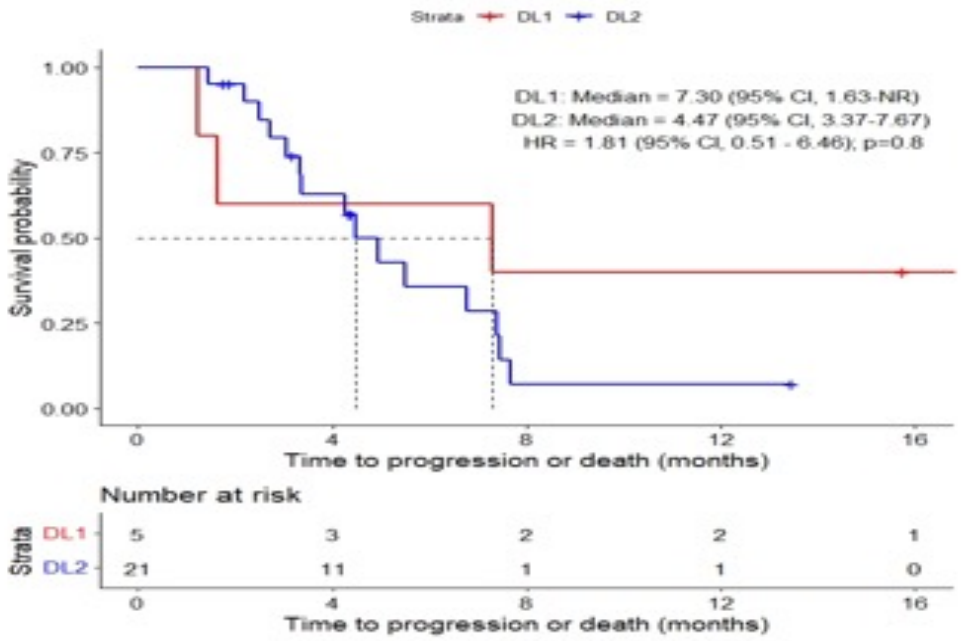


FIGURE 2 **Progression-free Survival** curve for DL1 and DL2 dosing limiting toxicity patients.

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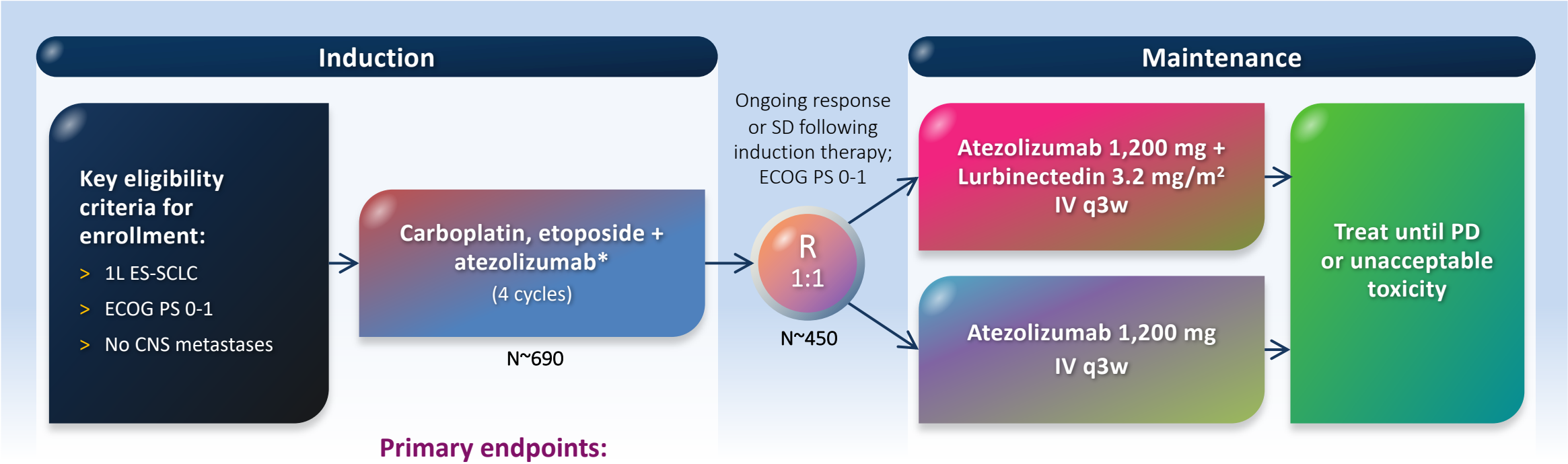
IMforte trial design



Primary endpoints:

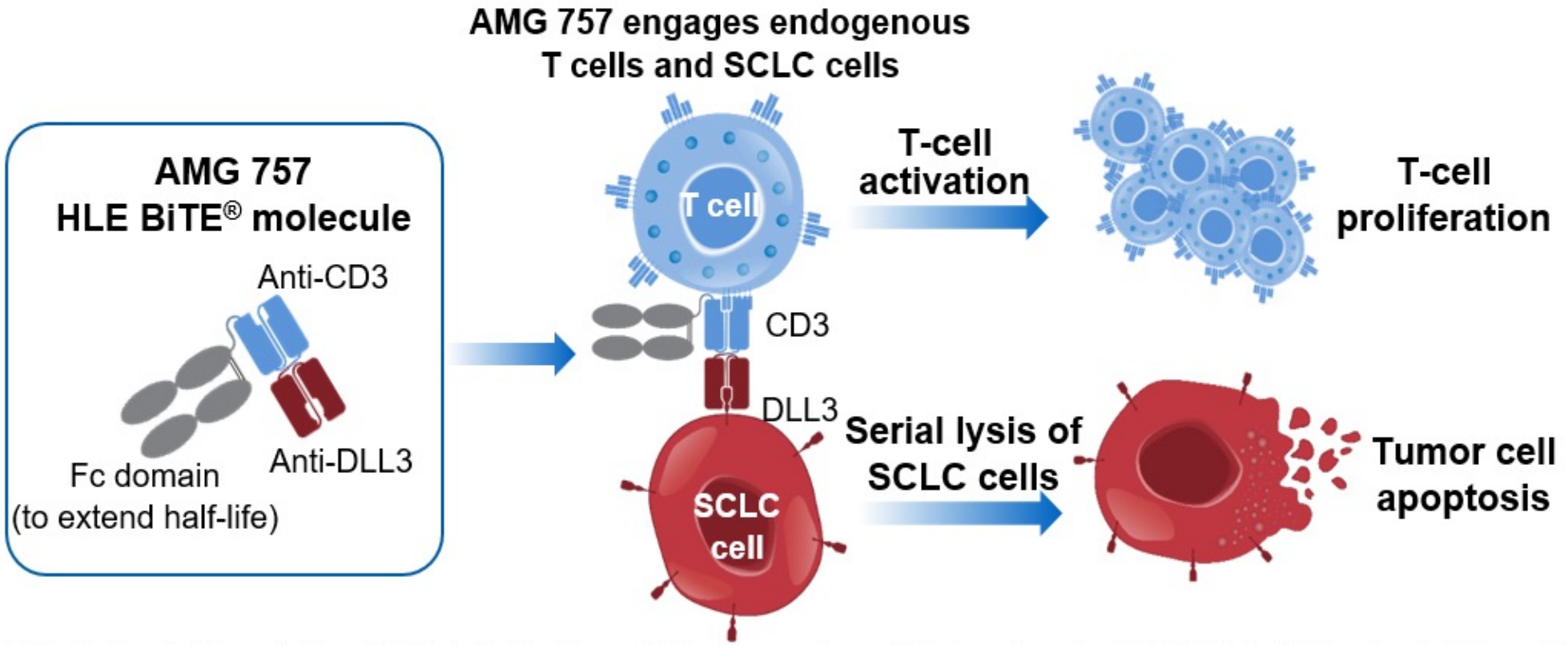
> IRF-assessed PFS and OS

Secondary endpoints:

> Inv-assessed PFS, ORR, DOR, landmark PFS & OS, safety

- *PCI allowed following induction treatment*
- ***DOR**, duration of response; **Inv**, investigator; **IRF**, independent review facility; **ORR**, objective response rate; **OS**, overall survival; **PCI**, prophylactic cranial irradiation; **PD**, disease progression; **PFS**, progression-free survival; **SD**, stable disease*

AMG 757: A Half-life Extended BiTE® (bispecific T-cell engager) Immuno-oncology Therapy Targeting DLL3 for SCLC



CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

- BiTE molecules engage a patient's own T cells to attack and eradicate cancer cells[1-3]

1.Stieglmaier J, et al. *Expert Opin Biol Ther.* 2015;15:1093-1099. 2. Einsele H, et al. *Cancer.* 2020;126:3192-3201. 3. Bargou R, et al. *Science.* 2008;321:974-977.

Safety profile

Treatment-related AEs	Patients (N = 66)	
	All Grades, n (%)	Grade ≥ 3, n (%)*
Any treatment-related AE	56 (85)	18 (27)
Treatment-related AEs in ≥ 10% of patients		
CRS	29† (44)	1 (2)
Pyrexia	17 (26)	2 (3)
Fatigue	11 (17)	0 (0)
Asthenia	7 (11)	1 (2)
Dysgeusia	7 (11)	0 (0)
Nausea	7 (11)	0 (0)

- Treatment-related AEs resulted in discontinuation in 3 (5%) patients
  - DLT: grade 5 pneumonitis (1 [2%] patient; 0.3 mg); grade 3 encephalopathy (1 [2%] patient; 100 mg)
- CRS was typically reversible, manageable, and associated with fever, tachycardia, nausea, fatigue, and hypotension‡
  - One CRS event led to treatment discontinuation
  - CRS typically occurred in cycle 1 and did not recur in subsequent cycles
  - CRS management could include supportive care, corticosteroids, and/or anti-IL-6R

*Includes one patient with grade 5 pneumonitis. †Of the 29 patients, 21 had grade 1, 7 had grade 2, and 1 had grade 3 CRS. ‡Lee 2014 grading. AE, adverse event; CRS, cytokine release syndrome; DLT, dose limiting toxicity.

Tarlatamab monotherapy demonstrated a favorable safety profile

Owonikoko et al, ASCO 2021

“Take home”

- Chemotherapy-plus PD-L1 inhibitors (atezolizumab, durvalumab) combinations represent the standard of care in first line EE-SCLC
- Further biomarker evaluation is warranted
- Ongoing exploration of novel IO strategies in SCLC include
  - Maintenance combos (lurbenectidin, Parp or ATR inh) with PD-L1 inhibitors in EE-SCLC
  - Concurrent/sequential IO with CT/RT in LS-SCLC
  - Novel CPI (Tigit inh, CD47 inh,…)
  - T cell engagers (AMG 757)

Breakfast with the Investigators: Prostate Cancer

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Saturday, June 4, 2022

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Andrew J Armstrong, MD, ScM

Alan H Bryce, MD

Alicia K Morgans, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME links will be posted in the chat (Zoom participants only) and emailed to all participants within 24 hours of the program.