The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Prof Abou-Alfa*

Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

Lung Cancer Faculty

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

Christine M Lovly, MD, PhD
Associate Professor of Medicine
Division of Hematology and Oncology
Ingram Associate Professor of Cancer Research
Co-Leader, Translational Research and Interventional Oncology Program
Vanderbilt University Medical Center and
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

RTP
RESEARCH TO PRACTICE

Lung Cancer Agenda

Module 1: Targeted Therapy

Module 2: Immunotherapeutic and Other Novel Strategies

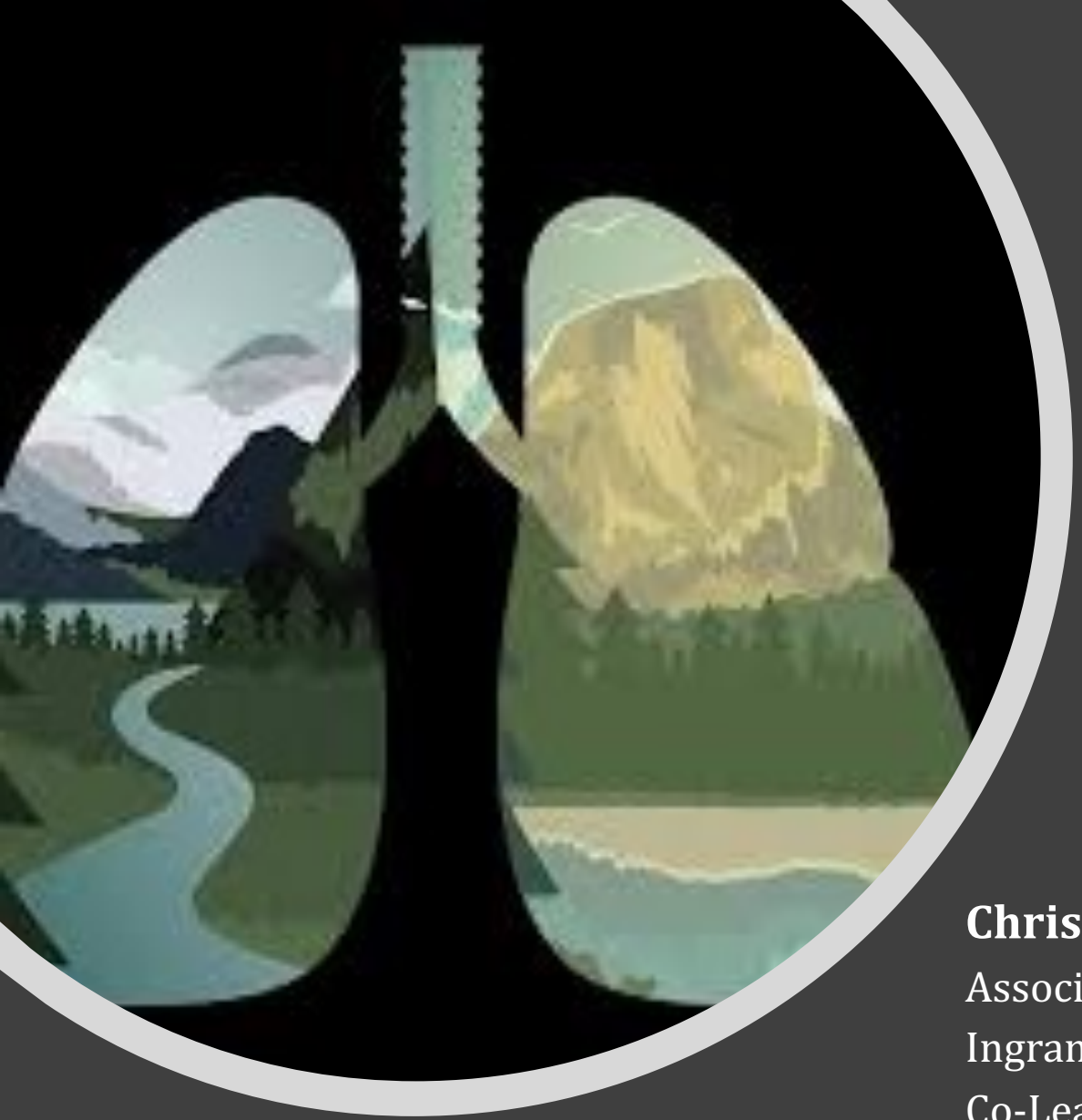
RTP
RESEARCH
TO PRACTICE

Lung Cancer Agenda

Module 1: Targeted Therapy

Module 2: Immunotherapeutic and Other Novel Strategies

RTP
RESEARCH
TO PRACTICE



Updates on management of EGFR-mutant and HER2-mutant lung cancer

Christine M. Lovly, MD, PhD
Associate Professor of Medicine, Division of Hematology and Oncology
Ingram Associate Professor of Cancer Research
Co-Leader, Translational Research and Interventional Oncology Program
Vanderbilt University and Vanderbilt Ingram Cancer Center
Nashville, TN

@Christine_Lovly

OBJECTIVES

- Discuss therapeutic strategies for patients with metastatic **EGFR-mutant lung cancer** that experience disease progression on 1st line osimertinib

- Review options for management of metastatic NSCLC harboring **EGFR exon 20 insertion mutations**

- Outline emerging strategies for management of **HER2-mutant** NSCLC

Distinguishing between *EGFR* mutations in NSCLC

"EGFR mutation positive" is not enough detail

SENSITIZING

Common EGFR Mutations

Exon 19 Deletions (~45%)

Most commonly between AA L747 and E749:
E746_A750del, L747_P753insS, L747_T751del, L747_A750insP, E746-S752insV, etc.

L858R point mutation (exon 21), (~40%)

Approved Therapies:
- **Osimertinib (preferred, 1L)**
- Erlotinib, Gefitinib, Afatinib, Dacomitinib

Atypical EGFR Mutations

L861Q, G719X, S768I, etc

Others (TKI sensitivity varies)

Approved Therapies:
- **Afatinib**
- (Osimertinib may also have some activity)

RESISTANT to standard EGFR TKIs

Exon 20 Insertions (AA 761-775)

A767_V769dup

S768_D770dupSVD

V769_D770insASV

D770_N771ins…

D770_P772dup

N771_H773dup

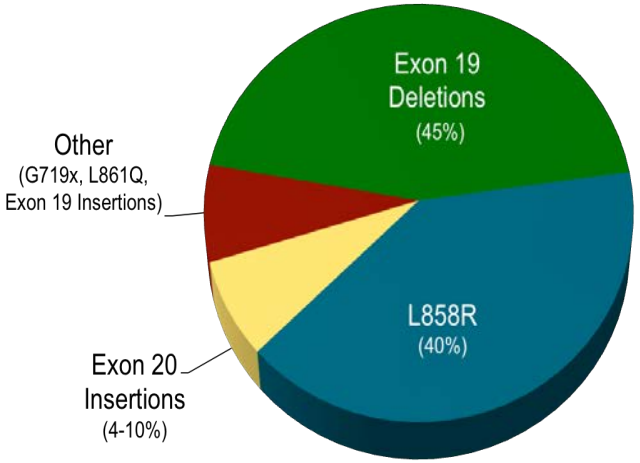
N771_P772ins…

P772_H773dupPH

V774ins

Others…

Approved Therapies:
- **Mobocertinib (2L, post-platinum)**
- **Amivantamab (2L, post-platinum)**



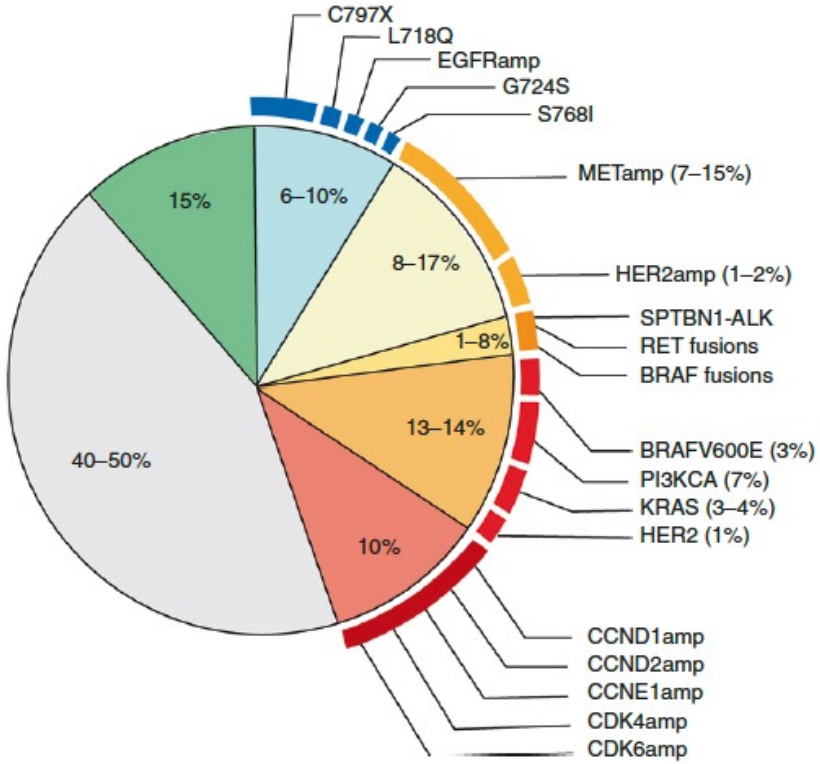
Yasuda H et al. *Lancet Oncol.* 2012;13(1):e23-e31.
Yasuda H et al. *Sci Transl Med.* 2013;5(2216):216ra177.

For EGFR-mutant NSCLC patients, disease progression on osimertinib is now a major challenge

1st line Osimertinib
mPFS 18.9 mos

2nd line therapies after 1st line osimertinib?

Selecting optimal post-Osimertinib therapies requires an understanding of resistance mechanisms and effective strategies to target these mechanisms



- **On-target resistance**
  - *EGFR* C797S, G724S, etc.
  - 5-10%
- **Histologic Transformation**
  - SCLC, squamous, and other histologies
  - Tissue biopsy is critical in the evaluation of osimertinib resistance
  - Up to 15%
- **Bypass pathway activation**
  - most notably *MET* amplification
  - up to 15% pts
- **50-60% of patients don't have a targetable resistance mechanism**

Schoenfeld AJ et al. *Clin Cancer Res.* 2020;26(11):2654-2663.
Leonetti A et al. *Br J Cancer.* 2019;121(9):725-737.

Treatment Options after First-Line Osimertinib

General Principles

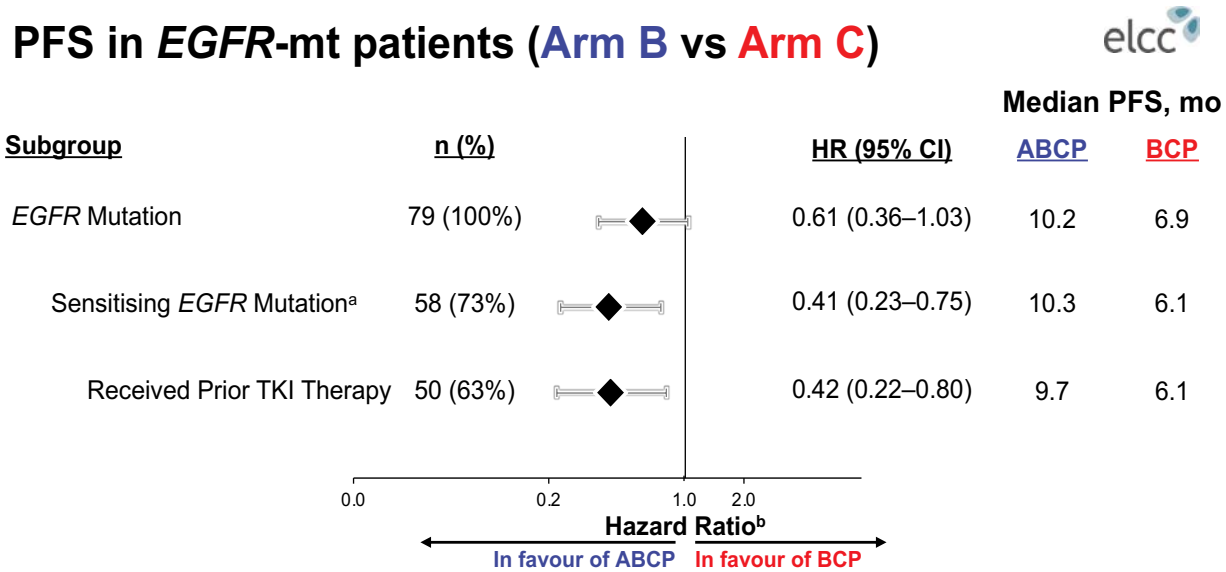
- Platinum-pemetrexed remains the standard of care after 1st line Osimertinib.
- Consider treatment options directed at resistance mechanisms when available
  - Histology-specific chemotherapy
- Enroll patients on clinical trials

To continue Osimertinib or not with chemotherapy?

- Role of continued Osimertinib with carboplatin/pemetrexed is unknown.
  - Carbo/Pem/Osi vs. Carbo/Pem/Placebo being evaluated (COMPEL; NCT04765059)
- Chemo + Osi is generally well tolerated, with more myelosuppression
  - White M, Piotrowska Z, *Clinical Lung Cancer* 2021.
- Consider continuing Osimertinib with carboplatin/pemetrexed for patients with CNS disease which remains controlled on osimertinib.

Role of Immunotherapy After Osimertinib?

- The efficacy of single-agent anti-PD1/PD-L1 inhibitors among EGFR+ NSCLC is low (ORR ~3-12%)[1]
- KEYNOTE-189 *excluded* pts with sensitizing EGFR mutations.
- ImPower150 (Carbo/Pac/Bev/Atezo) is an option. Patients with EGFR-mutant tumors had improvement in PFS/OS with ABCP vs. BCP (small numbers).
- Osi *should not* be given concurrently with IO (↑ pneumonitis risk).



- The addition of atezolizumab to bevacizumab and chemotherapy increased PFS benefit across all *EGFR*-mut patient subgroups, especially those who have received prior TKI

[a] Defined as exon 19 deletions or L858R mutations. [b] Unstratified HR.
Data cutoff 22 Jan 2018.

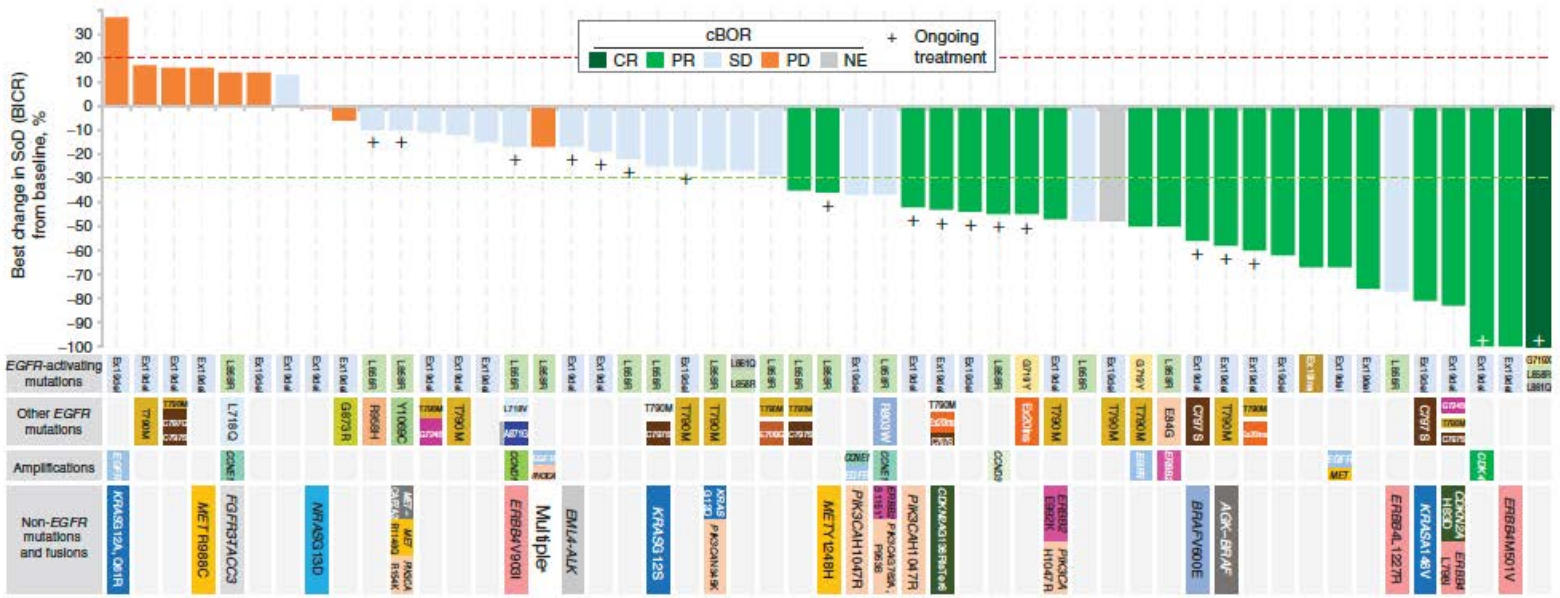
EUROPEAN LUNG CANCER CONFERENCE 2019
Reck et al. IMpower150 in *EGFR*-mt pts

1. Gainor, et all, CCR 2016; 2. Reck, ELCC 2019

Patritumab Deruxtecan
(HER3-DXd; HER3 Antibody-Drug Conjugate)

- HER3 is expressed in most NSCLC tumors.
- Patritumab Deruxtecan (HER3-DXd) is an antibody drug conjugate with a topoisomerase I inhibitor payload.
- HER3 mutation is not a known mechanism of resistance to EGFR TKI in *EGFR*m NSCLC.
- Reference: Janne et al. ASCO 2021

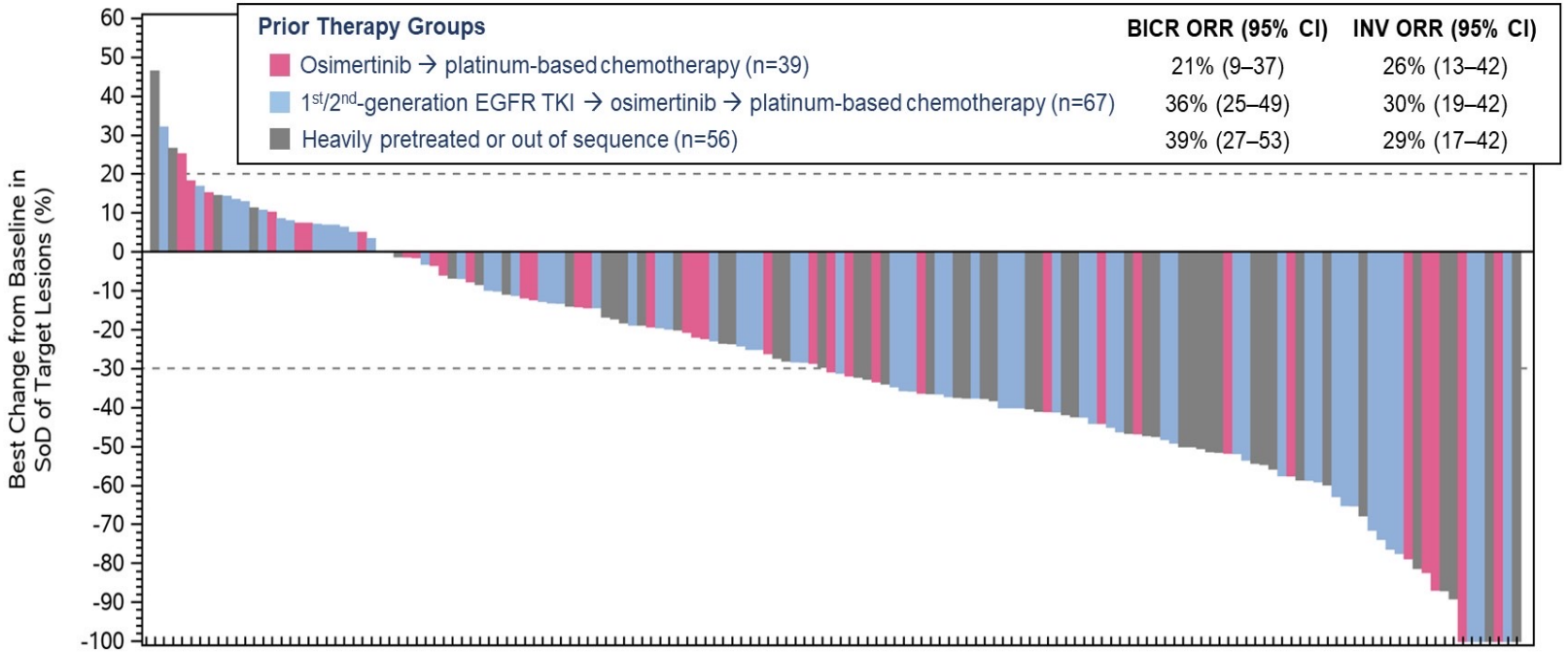
	All (n=57)	Prior PBC + Osi (n=44)
Confirmed ORR (BICR)	39%	39%
mDOR, mo (range)	6.9 (3.1-NE)	7.0 (3.1-NE)
mPFS, mo (range	8.2 (4.4-8.3)	8.2 (4.0-NE)



Responses observed regardless of osimertinib resistance mechanism.

Amivantamab + Lazertinib

Amivantamab (bispecific MET/EGFR antibody) + Lazertinib (3rd gen EGFR TKI)



- 10 efficacy-evaluable patients did not have any evaluable post-baseline target lesion measurements

BICR-assessed Response	n=162
ORR	33% (95% CI, 26–41)
Median DOR	9.6 mo (95% CI, 7.0–NE)
Best response, n (%)	
Complete response	2 (1)
Partial response	52 (32)
Unconfirmed partial response	1 (0.6)
Stable disease	69 (43)
Progressive disease	28 (17)
NE	10 (6)
Clinical benefit rate[a]	57% (95% CI, 49–65)

Investigator-assessed ORR=28% (95% CI, 22–36)
Investigator-assessed median DOR=8.4 mo (95% CI, 5.6–NE)

Median follow-up=10.0 mo (range, 0.3–20.2)
Median progression free survival=5.1 mo (95% CI, 4.2–6.9)
Median overall survival=14.8 mo (95% CI, 12.1–NE)

Amivantamab + Lazertinib – Biomarker Selection?

- ORR 47% (8/17) in patients with identified EGFR/MET mechanism of resistance
- ORR 29% (8/28) in patients without an identified EGFR/MET mechanism of resistance

Shu C, ASCO 2022
Chul B et al. ASCO 2021

Summary: therapeutic strategies after progression on 1st line osimertinib

- The therapeutic approach to patients who progress on osimertinib should be guided by 1) sites of progression (consider local therapy for oligoprogressive disease) and 2) resistance mechanisms, if possible.

- Tissue biopsy should be considered, particularly for patients with baseline EGFR/TP53/Rb1 mutations who are at increased risk of SCLC transformation.

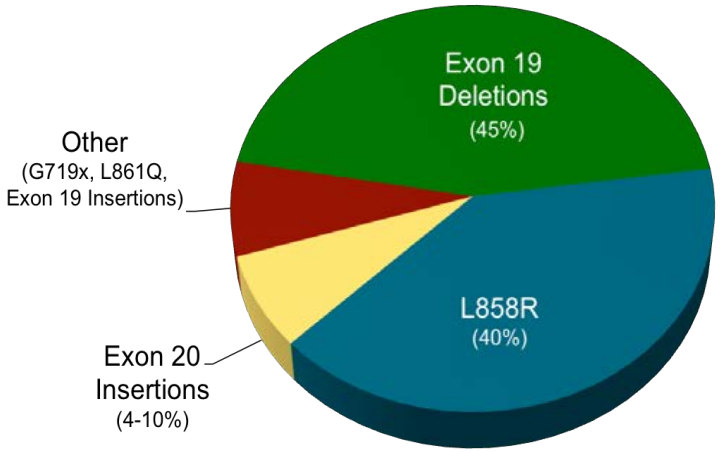
- Outside of clinical trials, I use **platinum doublet chemotherapy +/- osimertinib.**
  - In particular, consider continuing osimertinib with chemotherapy (e.g., carbo/pem/osi) for patients with CNS disease controlled with Osimertinib.

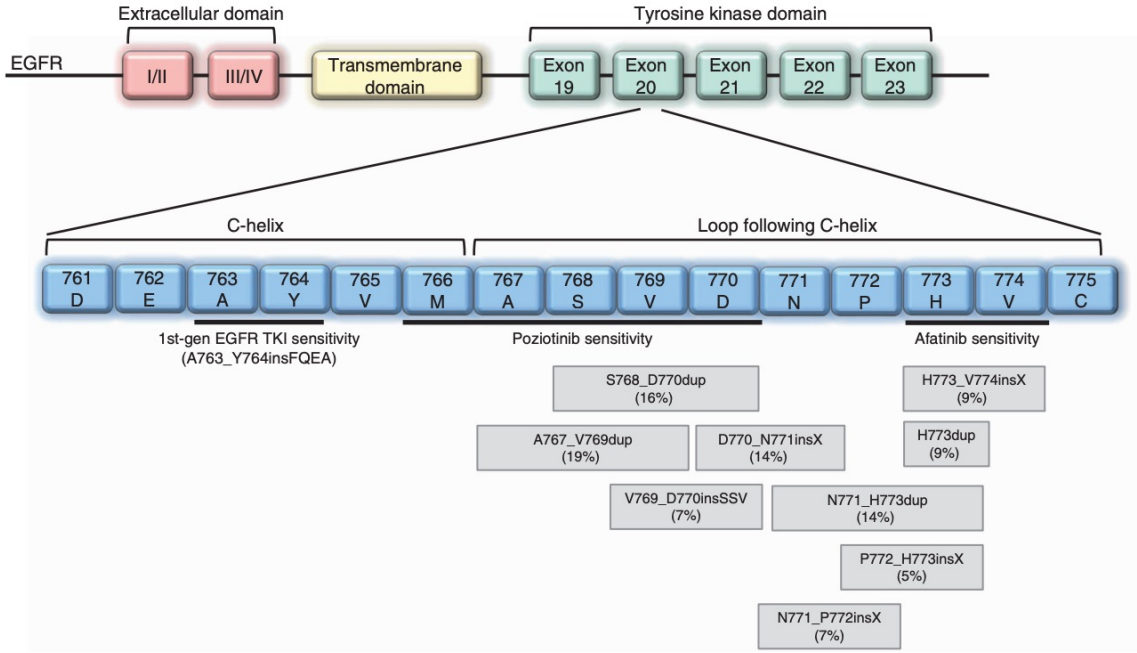
- Numerous agents in development: HER3-DxD, Amivantamab + Lazertinib, "4th generation" EGFR TKIs.

- Also look for "risk adapted" clinical trials based on ctDNA clearance.

EGFR Exon 20 Insertion Mutations

- Like other mutations, can be detected with NGS
- More commonly seen in specific populations
  - Female sex
  - Never smokers
  - Adenocarcinoma histology
- Like EGFR del19/L858R, poor responses to immunotherapy
- Unlike EGFR del19/L858R, poor responses to standard TKIs
- Standard treatment is currently 1st line platinum doublet chemotherapy





Vyse et al. Signal Transduction and Targeted Therapy. 2019
Yasuda, et al. Lancet Oncol, 2011; Yasuda, et al. Science Trans Med, 2014
Heymach J, WCLC 2018, Meador CB, Sequist LV, Piotrowska Z, Cancer Discov 2021.

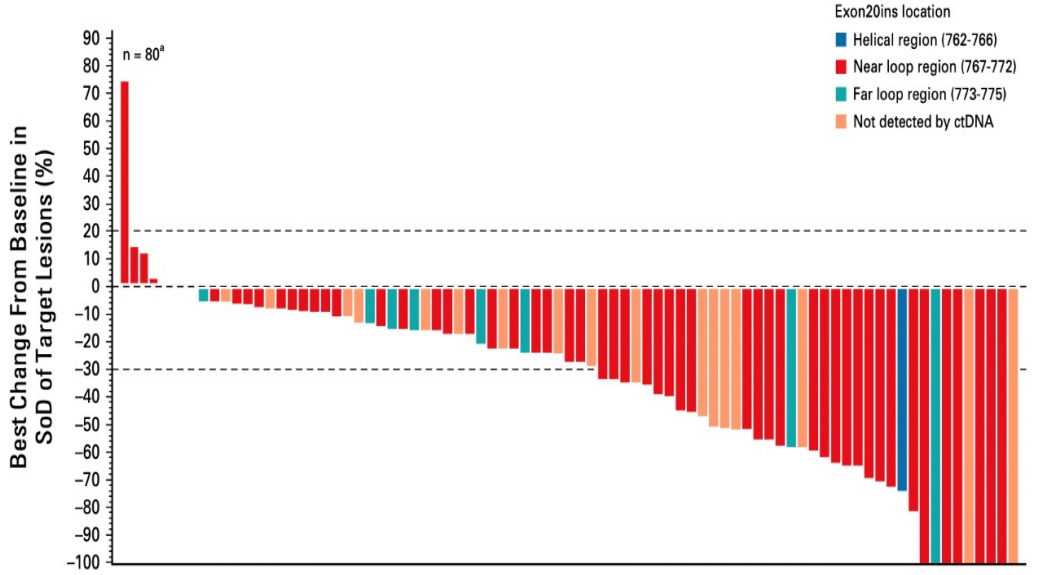
Amivantamab for patients with metastatic lung cancer harboring EGFR exon 20 insertions

Study Population:
- 81 patients
- All with prior platinum-based chemotherapy

Efficacy:
- Confirmed ORR 40%
- mPFS: 8.3 mos; mDOR: 11.1 mos

Toxicity:
- Infusion related reactions (66% Any Grade, 3% Grade > 3) - most commonly on C1D1
- Derm: Rash (86% Any Grade, 4% Grade > 3), Paronychia (45%)
- MET-related: Hypoalbuminemia (27%), Edema (18%)
- Dose Reduction: 13% | Dose discontinuation: 10%

→ **FDA accelerated approval May 21, 2021**



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)

Park K et al. *J Clin Oncol.* 2021;39:3391-3402.
Sabari, WCLC 2020

Mobocertinib for patients with metastatic lung cancer harboring EGFR exon 20 insertions

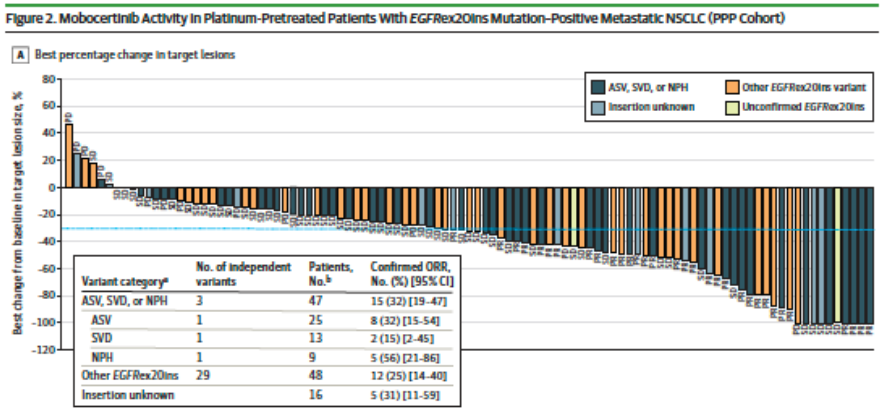
Mobocertinib- Oral, irreversible EGFR TKI (160mg daily)

Study Population:
- 114 patients
- All with prior platinum-based chemotherapy

Efficacy:
- ORR 28% (BIRC)
- mPFS: 7.3 mos; mDOR: 17.5 mos

Toxicity:
- GI: Diarrhea (91% Any Grade, 21% Grade > 3), Decreased Appetite (35%), Nausea (34%)
- Derm: Rash (45% Any Grade, 0% Grade > 3), Paronychia (38%)
- Cardiac: QTc prolongation (11% Any Grade, 3% Grade > 3), one treatment-related death due to cardiac failure
- Dose reduction: 25% | Treatment Discontinuation: 17%

→ **FDA accelerated approval Sept 15, 2021**



	Any Grade	Grade ≥ 3
Diarrhea	**91%**	**21%**
Rash	45%	0%
Paronychia	38%	<1
Anorexia	35%	<1%
Nausea	34%	4%
Dry Skin	31%	0
Vomiting	30%	3%
Cr Increase	25%	2%
Stomatitis	24%	4%

Zhou C et al. *JAMA Oncol.* 2021.

Emerging Drugs for EGFR Exon 20 insertion mutations

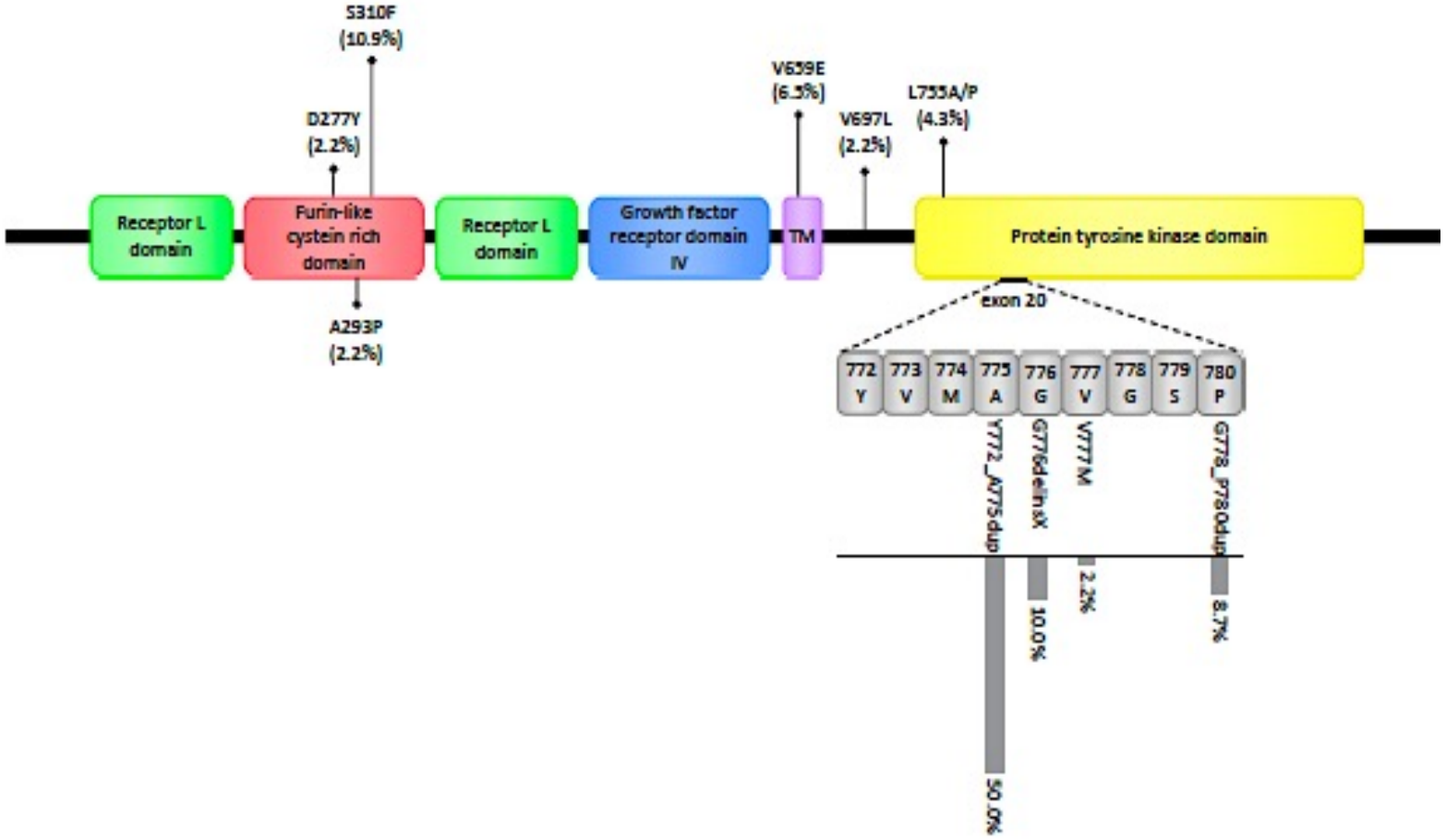
Drug	NCT	Most Recent REF	Notes
Sunvozertinib (DZD9008)	NCT03974022	Janne P, ASCO 2022	Confirmed ORR 37.5 % in overall population presented to date
CLN-081	NCT04036682	Yu HA, ASCO 2022	Confirmed PR 38.4% in overall population presented to date
BDTX-189	NCT04209465	Schram AM, ASCO 2020	*Clinical Development Halted*
BLU-451	NCT05241873	Spira AI, ASCO 2022	CNS Activity Predicted
ORIC-114	NCT05315700	Juntilla MR, AACR 2021	CNS Activity Predicted
HS-10376	NCT05435274		

REF: Clinicaltrials.gov search for “EGFR exon 20” (accessed July 1, 2022) – not an exhaustive list

HER2 mutations in NSCLC

- HER2 mutations occur in 1-3% of NSCLC
  - Exon 20 insertions most common
  - YVMA variant: most common HER2 ex20 insertion variant
  - Point mutations in the tyrosine kinase, transmembrane and extracellular domains also present at lower frequencies.

- HER2 mutations have little to no overlap with gene amplification or protein expression



Jebbink M, et al, Cancer Treatment Rev 2020.
Yu X, et al. Frontiers in Oncol 2022.
Arcila ME, et al. Clin Cancer Re, 2012.
Mazieres J, Annals Oncol, 2016.
Pillai RN, et al. Cancer 2017.

EGFR/HER2 TKIs for HER2-mutant NSCLC

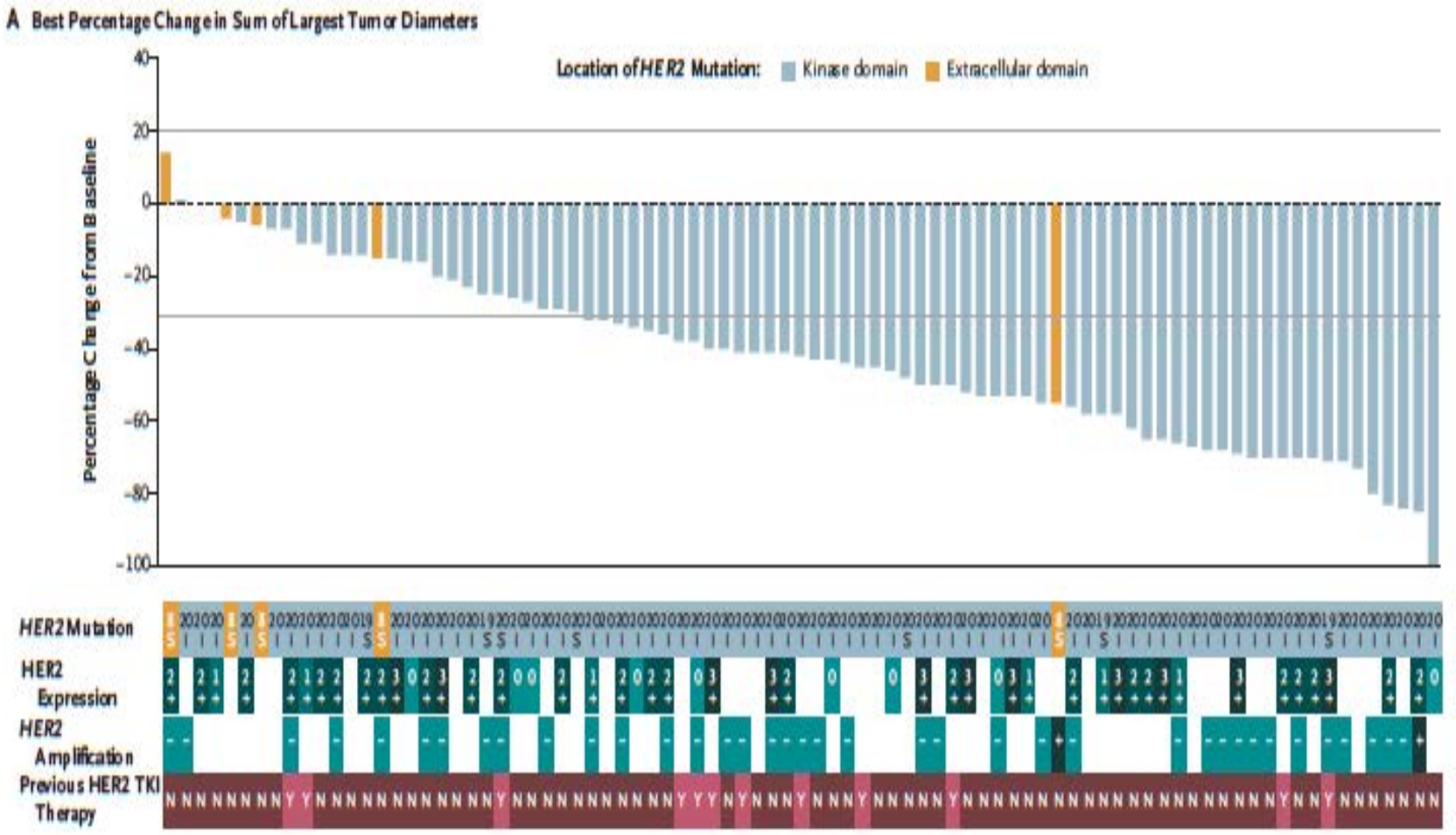
Drug	Target Pop	N	ORR	mPFS	Toxicities
Afatinib[1]	HER2^{mt}	13	8%	16 weeks	Diarrhea, vomiting, rash, paronychia, fatigue, mucositis
Afatinib[2]	HER2^{mt}	27	13%	3 mo	Diarrhea/GI toxicity, skin rash.
Neratinib[3]	HER2^{mt}	26	4%	5.5 mo	Diarrhea (74%), Nausea (43%), Vomiting (41%)
Dacomitinib[4]	HER2^{mt}	26	12%	3 mo	Diarrhea (90%), rash (73%)
Mobocertinib[5]	HER2^{mt}	5	1/5 (20%)		83% Diarrhea, 50% Anorexia
Pyrotinib[6]	HER2^{mt}	60	30%	6.9 mo	92% Diarrhea; 30% Creatinine increase
Poziotinib[7]	HER2^{mt}, Pretreated	90	28%	5.5 mo	49% Gr 3 Rash; 25.6 % Gr 3 Diarrhea
Poziotinib[8]	HER2^{mt}, First-line	48	44%	5.6 mo	49% Gr 3 Rash; 25.6 % Gr 3 Diarrhea

1. Dziadziuszko R, JTO 2019; 2. Lai WCV et al, European Journal of Cancer 2018; 3. Hyman DM, Nature 2018; 4. Kris MG et al. Ann Onc. 2015; 5. Zhou C et al. J Clin Oncol. 2020; 6. Neal JW et al. WCLC 2018. Abstract P1.13-44, 7. Zhou C, JCO 2020, 7. Le X, JCO 2022; 8. Cornelisson R, ESMO 2021

Slide kindly shared by Zofia Piotrowska, MD, MHS

Trastuzumab Deruxtecan (T-DXd) in HER2-mutant NSCLC

DESTINY-Lung01: Single arm, phase 2 study of T-DXd 6.4mg/kg IV q21 days in patients who were "refractory to standard treatment"



	Outcome (95% CI) N=91
ORR	55% (44-65)
mDOR	9.3 mos (5.7-14.7)
mPFS	8.2 mos (6.0-11.9)
mOS	17.8 mos (13.8-22.1)

→ Responses were observed across HER2 mutation sub-types as well as in patients with no detectable HER2 expression or *HER2* gene amplification.

Li BT, NEJM 2022

Trastuzumab Deruxtecan (T-DXd) in HER2-mutant NSCLC

Table 3. Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).

Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
	number of patients (percent)				
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)*	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue†	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia§	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

- **Pneumonitis (ILD)**
  - **Adjudicated drug-related ILD occurred in 24/91 patients (26%)**
  - Grade 1: 3 patients
  - Grade 2: 15 patients
  - Grade 3: 4 patients
  - Grade 5: 2 patients
  - Median duration of onset of ILD – 141 days (range, 14-462)
  - 21 patients required corticosteroids

<u>August 11, 2022: US FDA approved T-DXd (5.4mg/kg) for HER-mutant NSCLC after one prior line of therapy.</u>

- Based on phase DESTINY-Lung02 trial (NCT04644237)
- Interim reports shown at ESMO 2022 meeting, reference: Goto K et. al. Ann Oncol. 2022;33(suppl_7):S808-S869.
- RR similar between 6.4mg and 5.4mg doses, but higher rates of ILD at the 6.4mg dose.

Unanswered Questions for HER2-mutant NSCLC

- What is the optimal first-line therapy for HER2-mutant NSCLC?
  - Should we use chemo alone, or chemo + IO?
  - Is the efficacy of T-DXd sufficient for first-line use?

- How can we minimize (and manage) ADC-related toxicities, particularly ILD with T-DXd?

- Is there a role for HER2—targeting TKIs (poziotinib, pyrotinib), or are their toxicity profiles prohibitive?

- How should currently available therapies be sequenced? Is there a role for combinations?

- Management of CNS Metastases in HER2mutant tumors?

Expanding Precision Medicine in NSCLC

NCCN guidelines for NSCLC, 05/2022

TESTING RESULTS[ll,mm]	
EGFR exon 19 deletion or *L858R* mutation positive	NSCL-20
EGFR S768I, L861Q, and/or *G719X* mutation positive	NSCL-23
EGFR exon 20 insertion mutation positive	NSCL-24
KRAS G12C mutation positive	NSCL-25
ALK rearrangement positive	NSCL-26
ROS1 rearrangement positive	NSCL-29
BRAF V600E mutation positive	NSCL-31
NTRK1/2/3 gene fusion positive	NSCL-32
METex14 skipping mutation positive	NSCL-33
RET rearrangement positive	NSCL-34
ERBB2 (HER2) mutation positive	NSCL-35
PD-L1 ≥50% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 ≥1%–49% and negative for actionable molecular biomarkers above	NSCL-37
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-38

Broad molecular testing of all patients is key for identifying the best treatment strategies for patients with NSCLC.

THANK YOU!
Happy to discuss anytime!

@Christine_Lovly

Christine.lovly@vumc.org

PARIS 2022 ESMO congress

Abstract LBA47

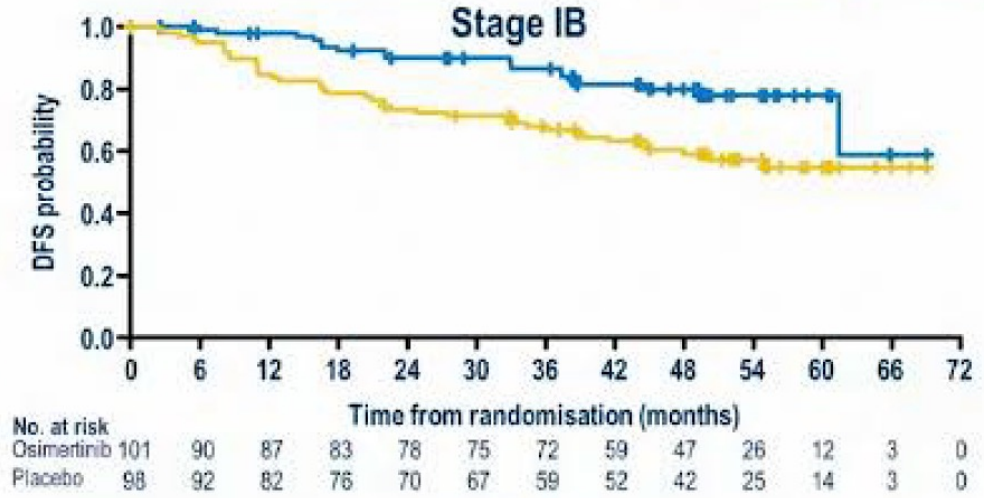
Osimertinib as adjuvant therapy in patients with resected EGFRm stage IB–IIIA NSCLC: updated results from ADAURA

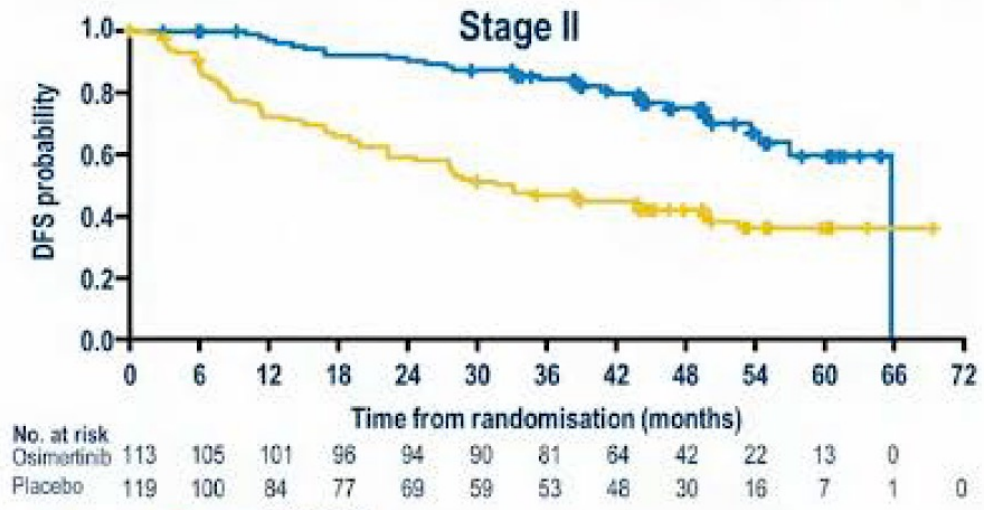
Masahiro Tsuboi[1], Yi-Long Wu[2], Christian Grohe[3], Thomas John[4], Margarita Majem[5], Jie Wang[6], Terufumi Kato[7], Jonathan W. Goldman[8], Sang-We Kim[9], Chong-Jen Yu[10], Huu Vinh Vu[11], Guzel Mukhametshina[12], Charuwan Akewanlop[13], Filippo de Marinis[14], Frances A. Shepherd[15], Damien Urban[16], Marta Stachowiak[17], Ana Bolanos[18], Xiangning Huang[19], Roy S. Herbst[20]

[1]Department of Thoracic Surgery and Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [2]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; [3]Klinik für Pneumologie - Evangelische Lungenklinik Berlin Buch, Berlin, Germany; [4]Department of Medical Oncology, Austin Health, Melbourne, Australia; [5]Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [6]Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [7]Department of Thoracic Oncology, Kanagawa Cancer Center, Asahi Ward, Yokohama, Japan; [8]David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA; [9]Department of Oncology, Asan Medical Center, Seoul, South Korea; [10]Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [11]Department Thoracic Surgery, Choray Hospital, Ho Chi Minh City, Vietnam; [12]Republican Clinical Oncology Center, Kazan, Republic of Tatarstan, Russia; [13]Division of Medical Oncology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand; [14]Thoracic Oncology Division, European Institute of Oncology (IEO), IRCCS, Milan, Italy; [15]Department of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre, Canada; [16]Department of Oncology, Sheba Medical Center, Tel Hashomer, Israel and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [17]Late Oncology Research & Development, AstraZeneca, Warsaw, Poland; [18]Oncology Research & Development, AstraZeneca, Mississauga, Canada; [19]Oncology Biometrics, AstraZeneca, Cambridge, United Kingdom; [20]Medical Oncology, Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA

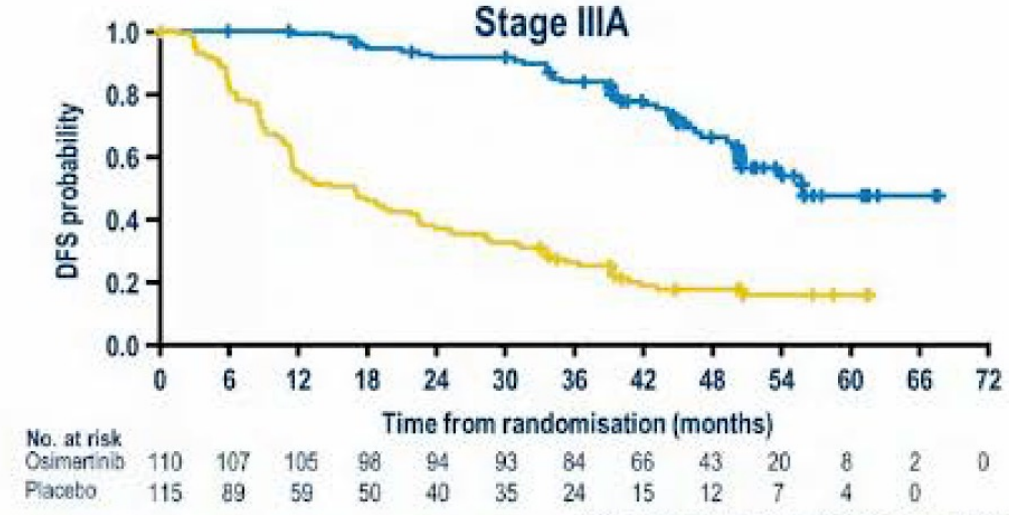
RTP RESEARCH TO PRACTICE

ADAURA Updated Disease-Free Survival (DFS) by Stage (AJCC/UICC 8th Edition*)





	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (69, 87)	75 (65, 83)	66 (55, 75)
– Placebo	60 (49, 69)	43 (34, 52)	16 (10, 24)
Overall HR (95% CI)	0.44 (0.25, 0.76)	0.33 (0.21, 0.50)	0.22 (0.15, 0.31)

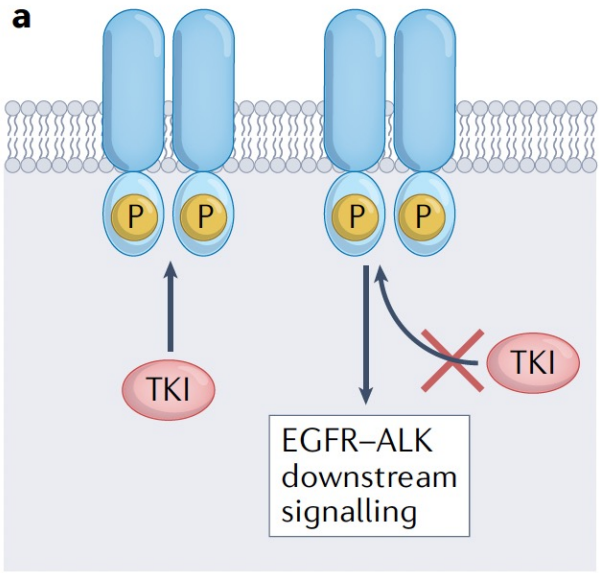
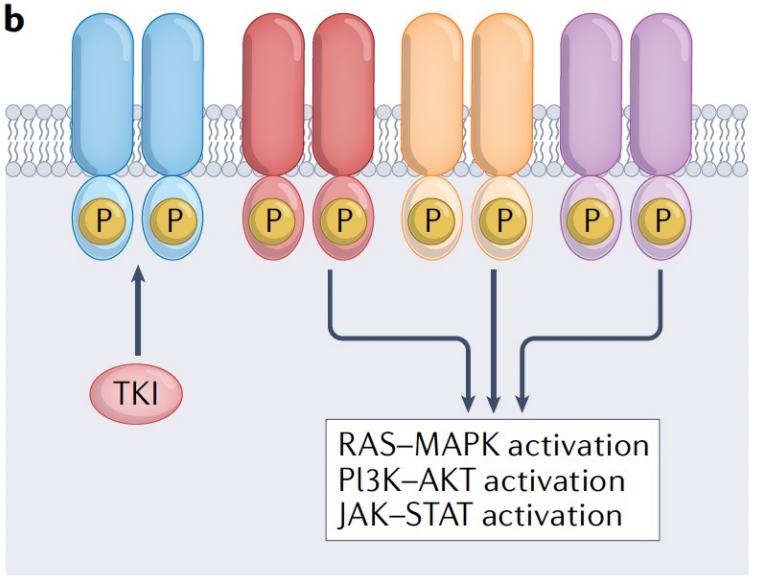
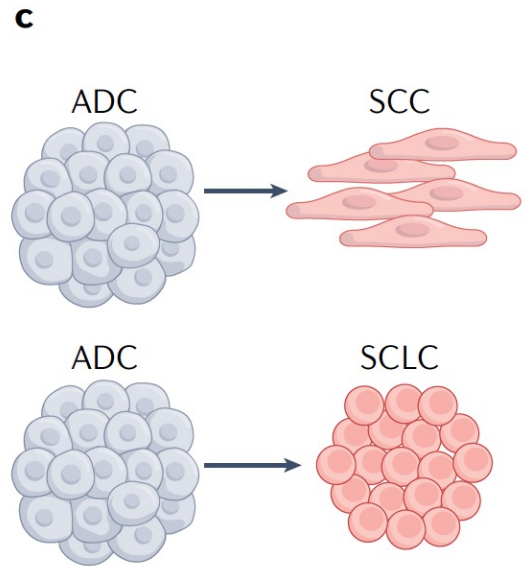


* Staging based on the American Joint Committee on Cancer/Union for International Cancer Control manual, *The Eighth Edition AJCC Cancer Staging Manual.*

Tsuboi M et al. ESMO 2022;Abstract LBA47.

RTP RESEARCH TO PRACTICE

Mechanisms of Acquired Resistance to Osimertinib

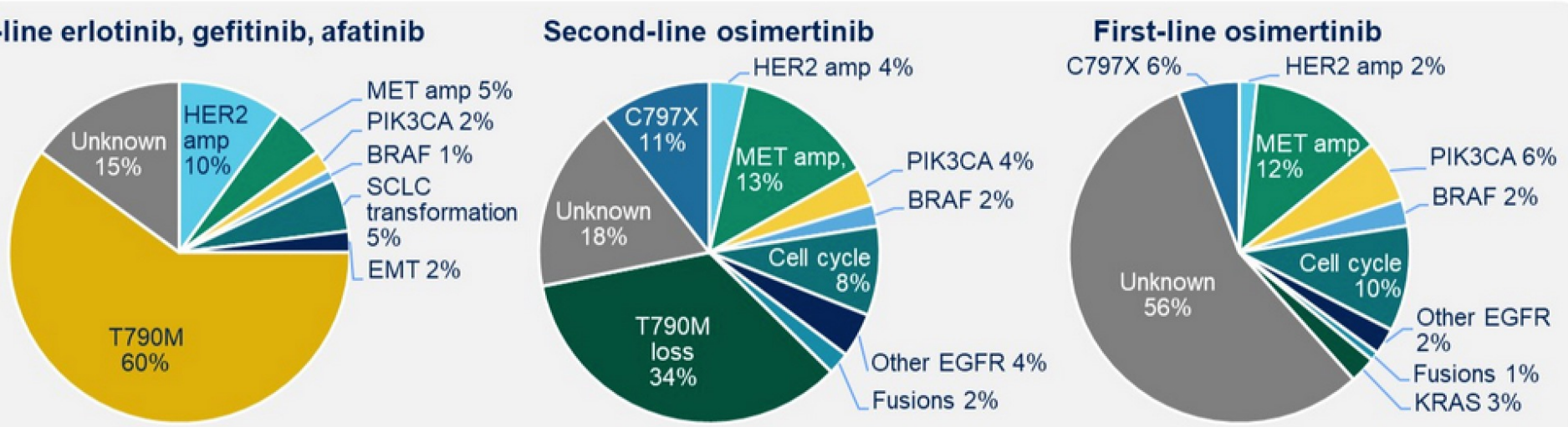
	Alterations that prevent inhibition of the target receptor tyrosine	Activation of bypass and/or downstream signalling pathways	Changes in tumour cell lineage such as transformation
			
Osimertinib resistance	*EGFR* C797X, G796X, L792X, G724S, L718Q	• Amplifications in *MET*, *HER2*, *KRAS*, *NRAS*, *YES1* • Rearrangements in *RET*, *NTRK1*, *ALK*, *BRAF*, *ROS1*, *FGFR3* • Mutations in *BRAF*, *HER2*, *KRAS*, *NRAS*, *PIK3CA* • Others: *AXL* overexpression, IGF1R activation	• Small-cell transformation • Squamous-cell transformation • EMT

Cooper AJ et al. *Nat Rev Clin Oncol* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Broad Range of Resistance Mechanisms in NSCLC with EGFR Mutation After Failure of EGFR Tyrosine Kinase Inhibitor (TKI) Therapy

Wide variety of genomic alterations associated with EGFR TKI resistance[1,2]



1. Engelman JA, et al. *Science*. 2007;316:1039-1043. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15:18-21. 3. Han B, et al. *Onco Targets Ther*. 2018;11:2121-9. 4. Yang CJ, et al. *BMC Pharmacol Toxicol*. 2017;18(1).

Jänne PA et al. ASCO 2021;Abstract 9007.

RESEARCH ARTICLE

Cancer Discov 2022;12(1):74-89.

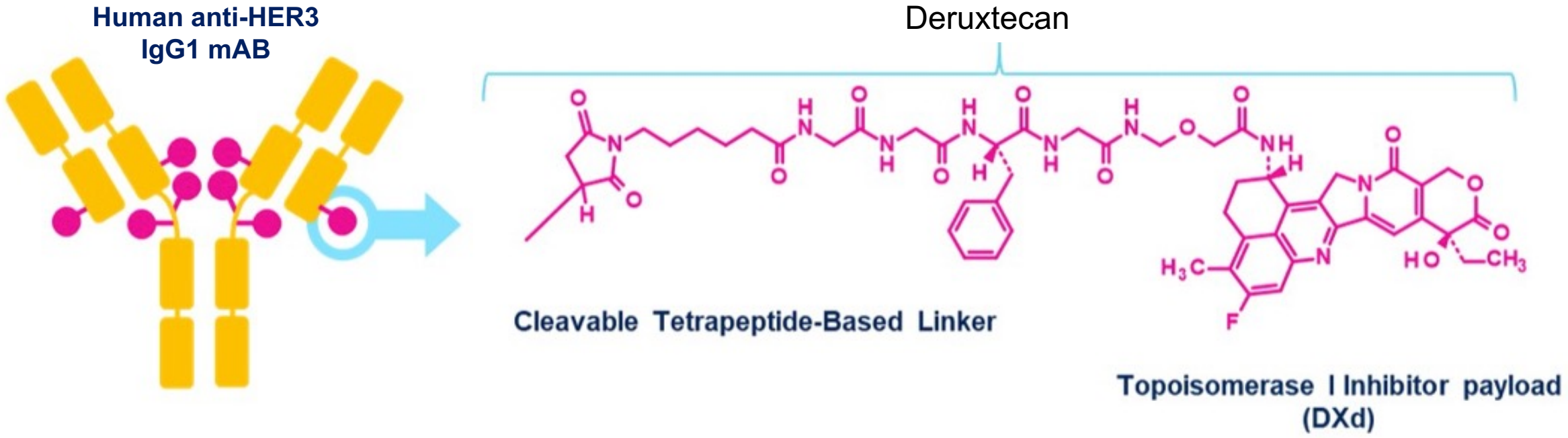
Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer

Pasi A. Jänne[1], Christina Baik[2], Wu-Chou Su[3], Melissa L. Johnson[4], Hidetoshi Hayashi[5], Makoto Nishio[6], Dong-Wan Kim[7], Marianna Koczywas[8], Kathryn A. Gold[9], Conor E. Steuer[10], Haruyasu Murakami[11], James Chih-Hsin Yang[12], Sang-We Kim[13], Michele Vigliotti[14], Rong Shi[14], Zhenhao Qi[14], Yang Qiu[14], Lihui Zhao[14], David Sternberg[14], Channing Yu[14], and Helena A. Yu[15]

Patritumab Deruxtecan (HER3-DXd) Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

HER3-DXd is an antibody-drug conjugate with 3 components

- A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleaver linker



Jänne PA et al. ASCO 2021;Abstract 9007.

RTP RESEARCH TO PRACTICE

Patritumab Deruxtecan: Responses by Blinded Independent Central Review

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

RDE = recommended dose for expansion; PBC = platinum-based chemotherapy; ORR = objective response rate; BOR = best overall response; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated; DCR = disease control rate; TTR = time to response

[a]DCR = rate of confirmed BOR of CR, PR or SD.

Jänne PA et al. *Cancer Discov* 2022;12(1):74-89.

Select Grade ≥3 Treatment-Emergent Adverse Events (TEAEs) with Patritumab Deruxtecan

TEAEs	Pooled RDE 5.6 mg/kg ($n = 57$), n (%)	All patients 3.2/4.8/5.6/6.4 mg/kg ($n = 81$), n (%)
Grade ≥3 TEAEs occurring in ≥5% of patients		
Platelet count decrease/thrombocytopenia	17 (30)	21 (26)
Neutrophil count decrease/neutropenia	11 (19)	12 (15)
Fatigue	8 (14)	8 (10)
Anemia/hemoglobin decrease	5 (9)	6 (7)
Dyspnea	5 (9)	5 (6)
Febrile neutropenia	5 (9)	5 (6)
Adjudicated ILD	5 (9)[e]	5 (6)[e]
Adjudicated treatment-related ILD	4 (7)[f]	4 (5)[f]

RDE = recommended dose for expansion; ILD = interstitial lung disease

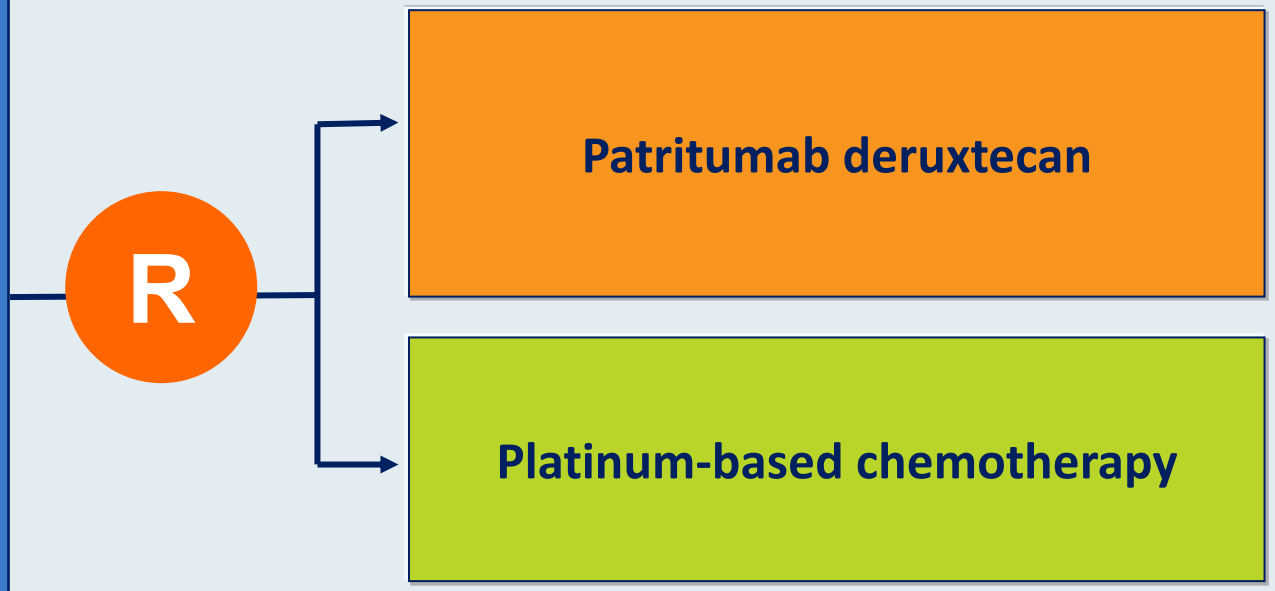
Jänne PA et al. *Cancer Discov* 2022;12(1):74-89.

HERTHENA-Lung02: An Ongoing Phase III Trial of Patritumab Deruxtecan for NSCLC with EGFR Mutation After Failure of an EGFR TKI

Trial identifier: NCT05338970 (Open)
Estimated enrollment: 560

Eligibility

- Locally advanced or metastatic nonsquamous NSCLC with EGFR activating mutation
- 1 or 2 prior lines of an approved EGFR TKI in the metastatic or locally advanced setting, which must include a third-generation EGFR TKI
- Radiographic disease progression while receiving or after receiving a third-generation EGFR TKI



Primary endpoint: Progression-free survival by blinded independent central review

www.clinicaltrials.gov. Accessed June 2022.

2022 ASCO® ANNUAL MEETING

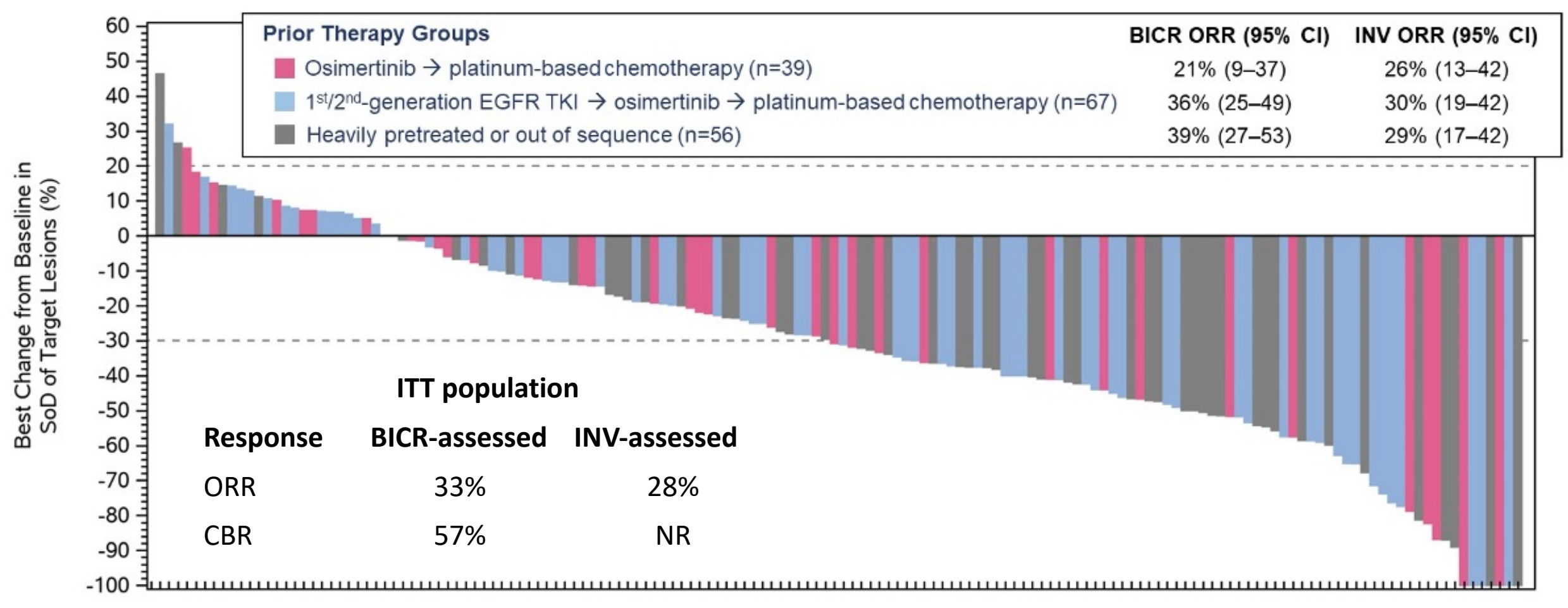
Abstract 9006

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

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

RTP RESEARCH TO PRACTICE

CHRYSALIS-2: Best Antitumor Response and Overall Response Rate (ORR) by Prior Therapy



TKI = tyrosine kinase inhibitor; BICR = blinded independent central review; INV = investigator; ITT = intent-to-treat; CBR = clinical benefit rate

Shu CA et al. ASCO 2022;Abstract 9006.

CHRYSALIS-2: Safety Profile

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

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

Shu CA et al. ASCO 2022;Abstract 9006.

Pivotal Studies of Amivantamab and Mobocertinib for Advanced NSCLC with EGFR Exon 20 Insertion Mutations

	Amivantamab[1]	Mobocertinib[2]
Pivotal study	CHRYSALIS (N = 81)	Study 101 (N = 114)
FDA approval	May 21, 2021	September 15, 2021
ORR	40%	28%
Median duration of response	11.1 months	17.5 months
Common Grade ≥3 adverse events	Rash (4%) Infusion-related reactions (3%) Paronychia (1%)	Diarrhea (21%) Rash (0) Paronychia (<1%)

[1] Park K et al. *J Clin Oncol* 2021;39(30):3391-402. [2] Zhou C et al. *JAMA Oncol* 2021;7(12):e214761.

Key Randomized Trials in Treatment-Naïve Advanced ALK-Rearranged NSCLC

Study	Intervention	Comparator	ORR	CNS ORR
PROFILE 1014	Crizotinib	Platinum/pemetrexed	74% vs 45%	—
PROFILE 1029	Crizotinib	Platinum/pemetrexed	88% vs 46%	—
ASCEND-4	Ceritinib	Platinum/pemetrexed	73% vs 27%	73% vs 27%
ALEX	Alectinib	Crizotinib	83% vs 76%	79% vs 40%
J-ALEX	Alectinib	Crizotinib	92% vs 79%	—
ALESIA	Alectinib	Crizotinib	91% vs 77%	—
ALTA-1L	Brigatinib	Crizotinib	71% vs 60%	78% vs 29%
CROWN	Lorlatinib	Crizotinib	76% vs 58%	82% vs 23%
eXalt3	Ensartinib	Crizotinib	75% vs 67%	64% vs 21%

Tan AC et al. *J Clin Oncol* 2022;40(6):611-25; Soria JC et al. *Lancet* 2017;389(10072):917-29; Peters S et al. *N Engl J Med* 2017;377(9):829-38; Camidge DR et al. *J Thorac Oncol* 2021;16(12):2091-108; Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29; Horn L et al. *JAMA Oncol* 2021;7(11):1617-25; Popat S et al. ESMO 2021;Abstract 1195P.

Common and Unique Adverse Effects of ALK TKIs

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

Crizotinib package insert (PI), rev 1/2021; Ceritinib PI, rev 3/2019; Alectinib PI, rev 1/2021; Brigatinib PI, rev 5/2020; Lorlatinib PI, rev 3/2021; Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-34; Gristina V et al. *Pharmaceuticals* 2020;13(12):474.

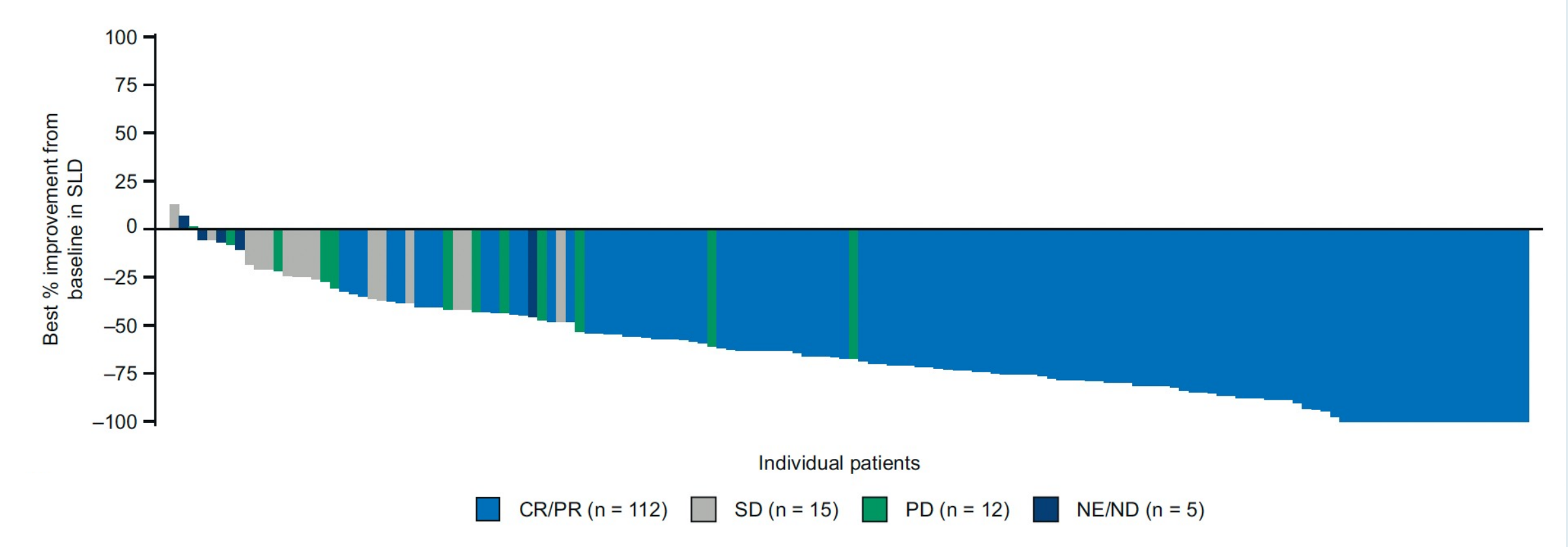
JTO Clin Res Rep 2022;3(6):100332.

ORIGINAL ARTICLE

Long-Term Efficacy and Safety of Entrectinib in *ROS1* Fusion–Positive NSCLC

Alexander Drilon, MD,[a] Chao-Hua Chiu, MD,[b] Yun Fan, MD,[c]
Byoung Chul Cho, MD, PhD,[d] Shun Lu, MD, PhD,[e] Myung-Ju Ahn, MD, PhD,[f]
Matthew G. Krebs, MD, PhD,[g] Stephen V. Liu, MD,[h] Thomas John, MD,[i]
Gregory A. Otterson, MD,[j] Daniel S. W. Tan, MD,[k] Tejas Patil, MD,[l]
Rafal Dziadziuszko, MD, PhD,[m] Erminia Massarelli, MD, PhD,[n] Takashi Seto, MD,[o]
Robert C. Doebele, MD, PhD,[l] Bethany Pitcher, MSc,[p] Nino Kurtsikidze, MD,[q]
Sebastian Heinzmann, PhD,[r] Salvatore Siena, MD[r,s,*]

Best Overall Response with Entrectinib

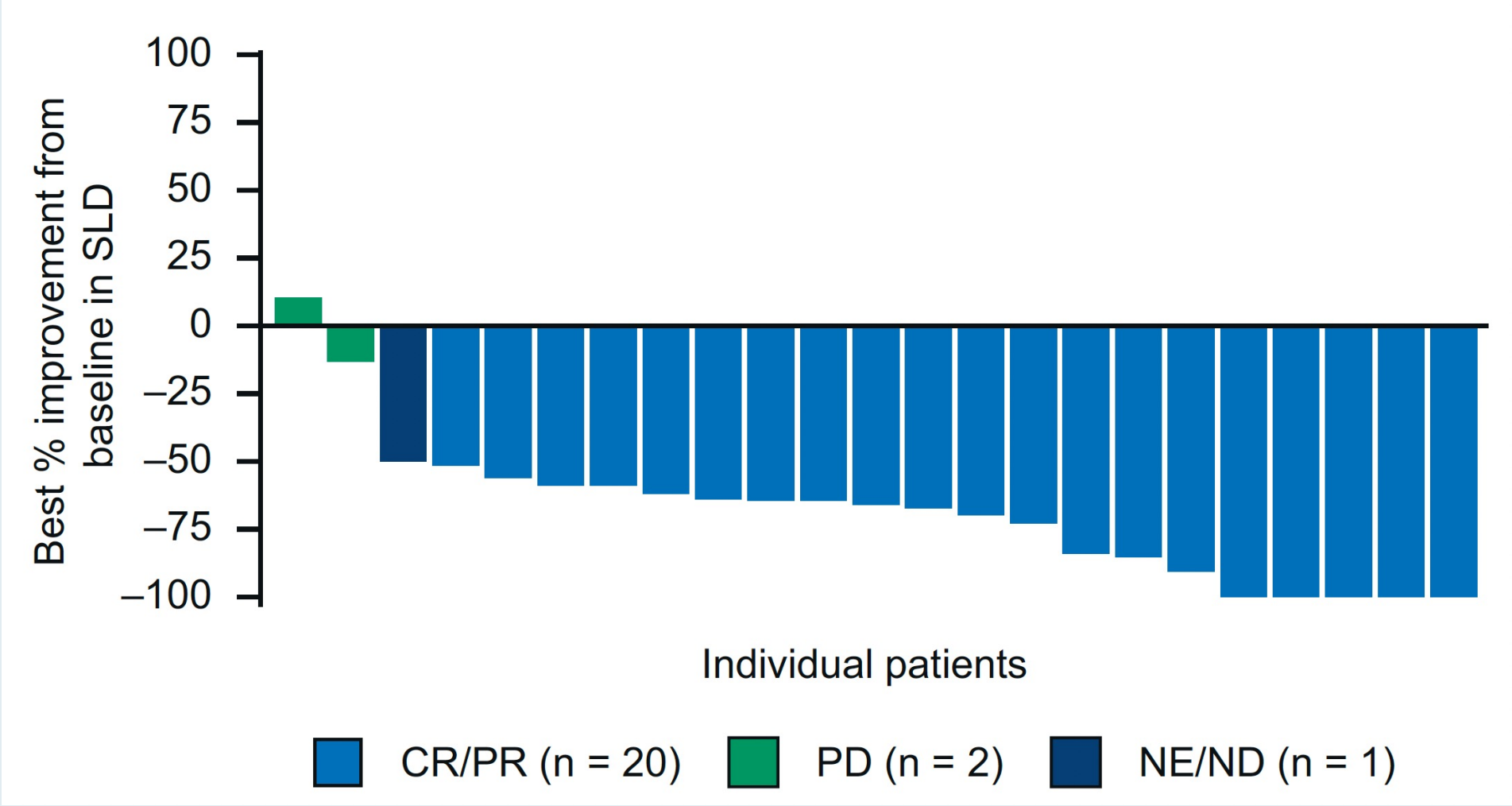


SLD = sum of longest diameters; CR/PR = complete response/partial response; SD = stable disease; PD = progressive disease; NE/ND = not estimable/not determined

Drilon A et al. *JTO Clin Res Rep* 2022;3(6):100332.

RTP RESEARCH TO PRACTICE

Best Intracranial Responses with Entrectinib in Patients with BICR-Assessed Measurable CNS Metastases at Baseline



BICR = blinded independent central review

Drilon A et al. *JTO Clin Res Rep* 2022;3(6):100332.

Key Trials of ROS1 TKIs for TKI-Pretreated NSCLC with ROS1 Fusions

ROS1 TKI	Study	Phase	ORR
Entrectinib (after crizotinib)	Drilon et al	I/II	0/6 (0%)
Ceritinib (after crizotinib)	Lim et al	II	0/2 (0%)
Brigatinib (after crizotinib)	Gettinger et al	I	0/2 (0%)
Lorlatinib	Shaw et al	I/II	After crizotinib: 14/40 (35%) After ≥2 prior TKIs: 0/6 (0%)
Repotrectinib	Drilon et al	I/II	After 1 prior TKI: 7/18 (39%) After ≥2 prior TKIs: 2/7 (29%)
Taletrectinib (after crizotinib)	Fujiwara et al	I	1/3 (33%)

Drilon A et al. *Nat Rev Clin Oncol* 2021;18(1):35-55.

AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

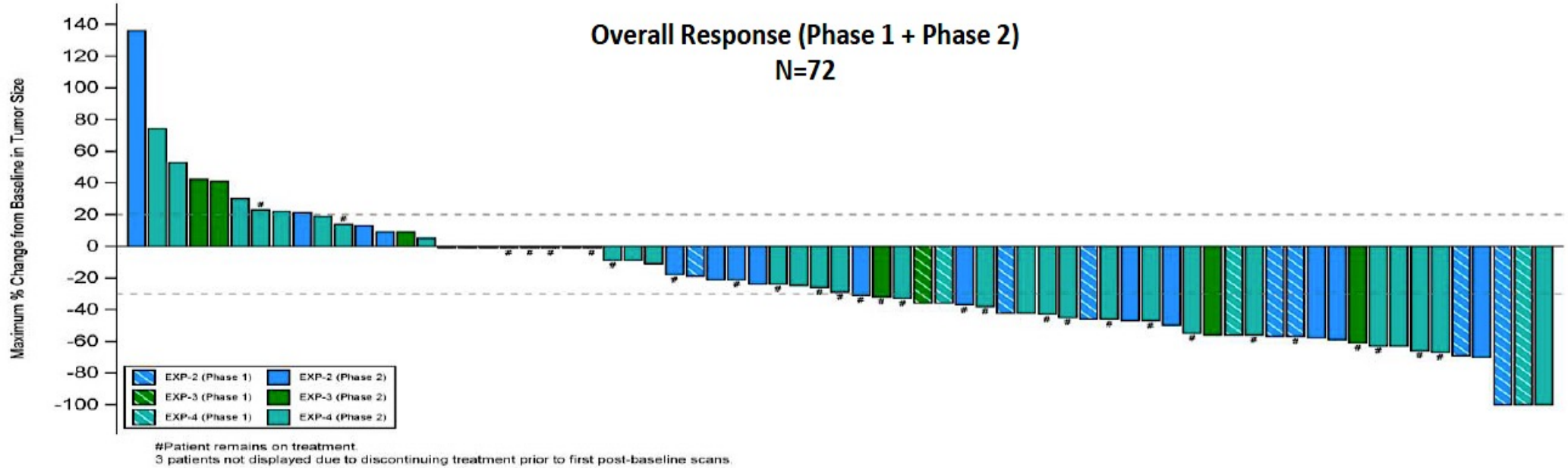
Poster #: P224

Update from the Phase 2 registrational trial of repotrectinib in TKI-pretreated patients with *ROS1+* advanced non-small cell lung cancer and with *NTRK+* advanced solid tumors (TRIDENT-1)

Jessica J. Lin,[1] Byoung Chul Cho,[2] Christoph Springfeld,[3] D. Ross Camidge,[4] Benjamin Solomon,[5] Christina Baik,[6] Vamsidhar Velcheti,[7] Young-Chul Kim,[8] Victor Moreno,[9] Anthonie J. van der Wekken,[10] Enriqueta Felip,[11] Dipesh Uprety,[12] Denise Trone,[13] Shanna Stopatschinskaja,[13] Alexander Drilon[14]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Heidelberg University Hospital, National Center for Tumor Diseases, Department of Medical Oncology, Heidelberg, Germany; [4]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; [5]Peter MacCallum Cancer Center, Melbourne, Australia; [6]University of Washington School of Medicine, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [7]NYU Perlmutter Cancer Center, New York, NY, USA; [8]Chonnam National University Medical School, and CNU Hwasun Hospital, Hwasun-gun, Republic of Korea; [9]Fundación Jiménez Díaz - START Madrid, Madrid, Spain; [10]University of Groningen, University Medical Centre Groningen, Groningen, Netherlands; [11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [12]Karmanos Cancer Institute, Detroit, MI, USA; [13]Turning Point Therapeutics Inc, San Diego, CA, USA; [14]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA.

TRIDENT-1: Preliminary Efficacy in Patients with TKI-Pretreated Advanced NSCLC with ROS1 Fusions



	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

Lin JJ et al. AACR 2021;Abstract P224.

FDA Grants Accelerated Approval to Trastuzumab Deruxtecan for NSCLC with HER2 Mutation

Press Release – August 11, 2022

"On August 11, 2022, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating human epidermal growth factor receptor 2 HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. This is the first drug approved for HER2-mutant NSCLC.

FDA also approved the Life Technologies Corporation's Oncomine™ Dx Target Test (tissue) and the Guardant Health, Inc.'s Guardant360® CDx (plasma) as companion diagnostics for trastuzumab deruxtecan. If no mutation is detected in a plasma specimen, the tumor tissue should be tested."

"The accelerated approval by the FDA was based on the results from the DESTINY-Lung02 Phase II trial. An interim efficacy analysis in a pre-specified patient cohort showed trastuzumab deruxtecan (5.4mg/kg) demonstrated a confirmed ORR of 57.7% (n=52), as assessed by blinded independent central review (BICR), in patients with previously treated unresectable or metastatic non-squamous HER2-mutant NSCLC. Complete responses (CR) were seen in 1.9% of patients and partial responses (PR) in 55.8% of patients with a median DoR of 8.7 months. Results from the DESTINY-Lung02 trial will be presented at an upcoming medical meeting."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-her2-mutant-non-small-cell-lung
https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-approved-in-us-for-her2-mutant-nsclc.html

RTP RESEARCH TO PRACTICE

N Engl J Med 2022;386:241-51.

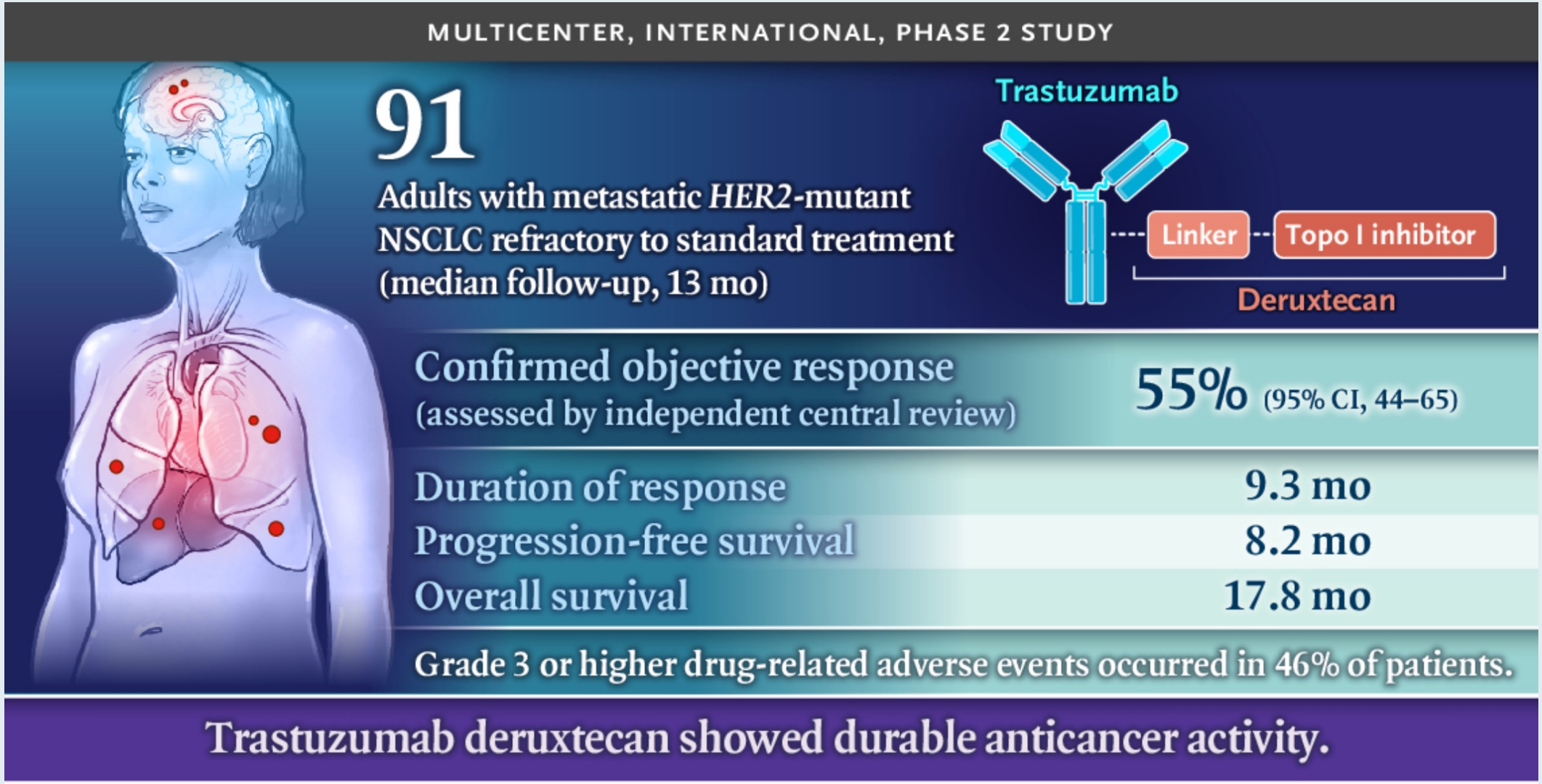
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

Bob T. Li, M.D., Ph.D., M.P.H., Egbert F. Smit, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Hibiki Udagawa, M.D., Julien Mazières, M.D., Misako Nagasaka, M.D., Ph.D., Lyudmila Bazhenova, M.D., Andreas N. Saltos, M.D., Enriqueta Felip, M.D., Ph.D., Jose M. Pacheco, M.D., Maurice Pérol, M.D., Luis Paz-Ares, M.D., Kapil Saxena, M.D., Ryota Shiga, B.Sc., Yingkai Cheng, M.D., Ph.D., Suddhasatta Acharyya, Ph.D., Patrik Vitazka, M.D., Ph.D., Javad Shahidi, M.D., David Planchard, M.D., Ph.D., and Pasi A. Jänne, M.D., Ph.D., for the DESTINY-Lung01 Trial Investigators*

DESTINY-Lung01 Study



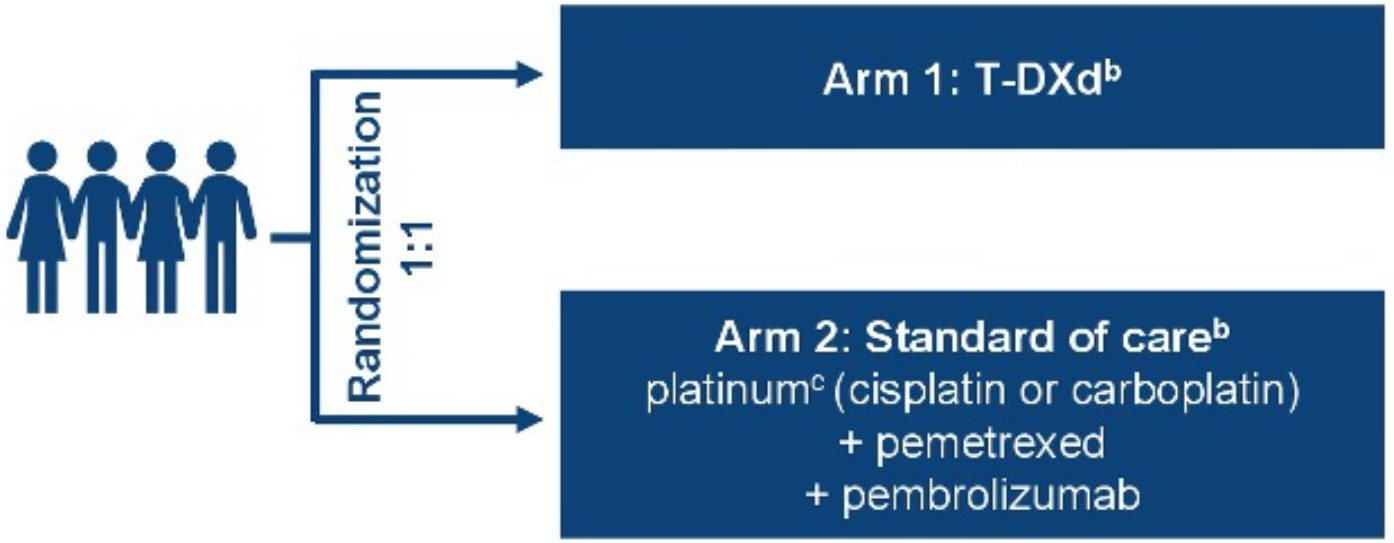
Li BT et al. *N Engl J Med* 2022;386(3):241-51.

RTP RESEARCH TO PRACTICE

DESTINY-Lung04 Phase III Study Design

Patient population (N≈264)

- Unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with *HER2* exon 19 or 20 mutations[a]
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations



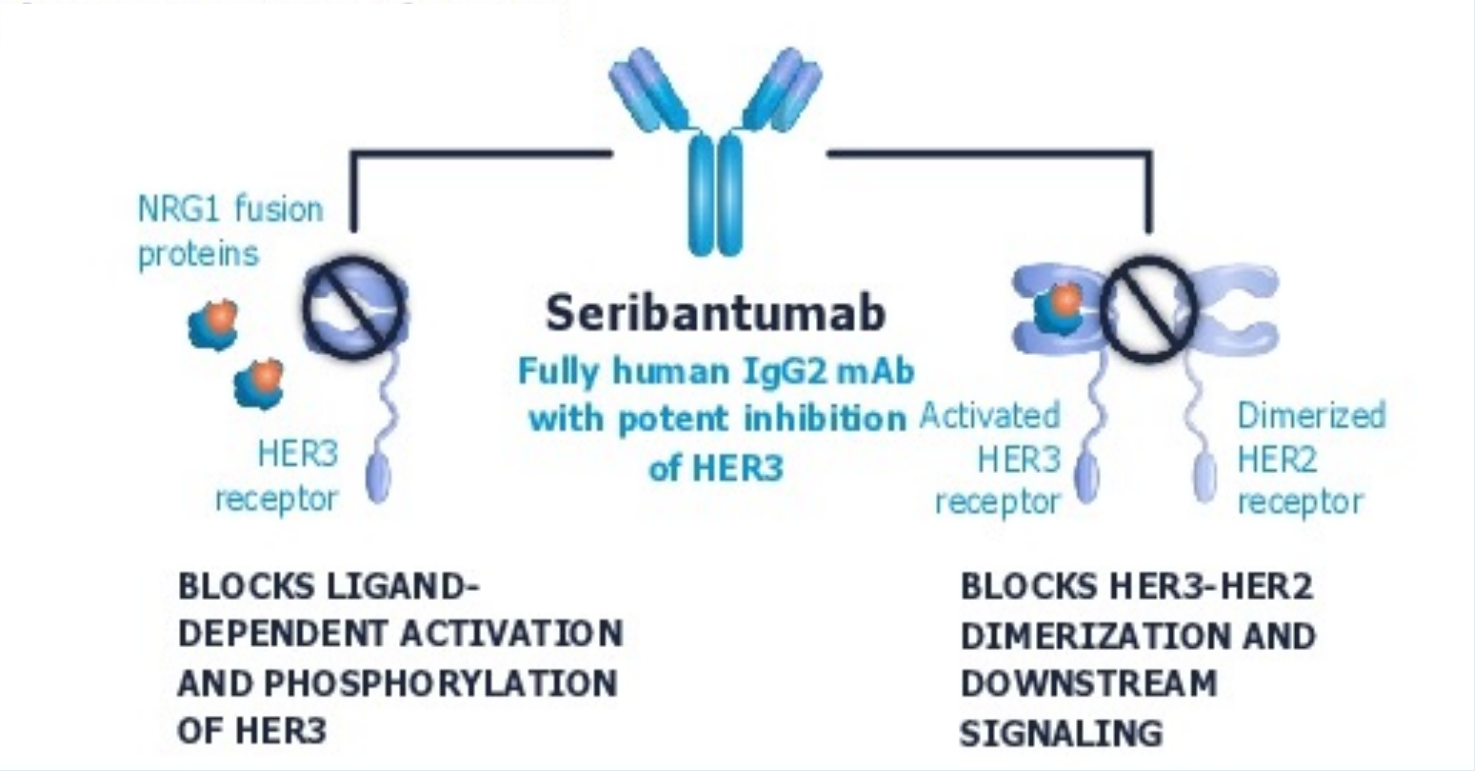
[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

Primary Endpoint: PFS by BICR

Li BT et al. ASCO 2022;Abstract TPS9137.

Neuregulin-1 (NRG1) Gene Fusions and Seribantumab Mechanism of Action

- NRG1 gene fusions are rare oncogenic drivers found in 0.2% of solid tumors including lung, colorectal, breast and ovarian
- NRG1 fusion proteins predominantly retain an active EGF-like domain, which drives tumorigenesis and proliferation through aberrant HER3 activation
- Seribantumab is a fully human monoclonal antibody against HER3



Bendell JC et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS449.

2022 ASCO® ANNUAL MEETING

Abstract 3006

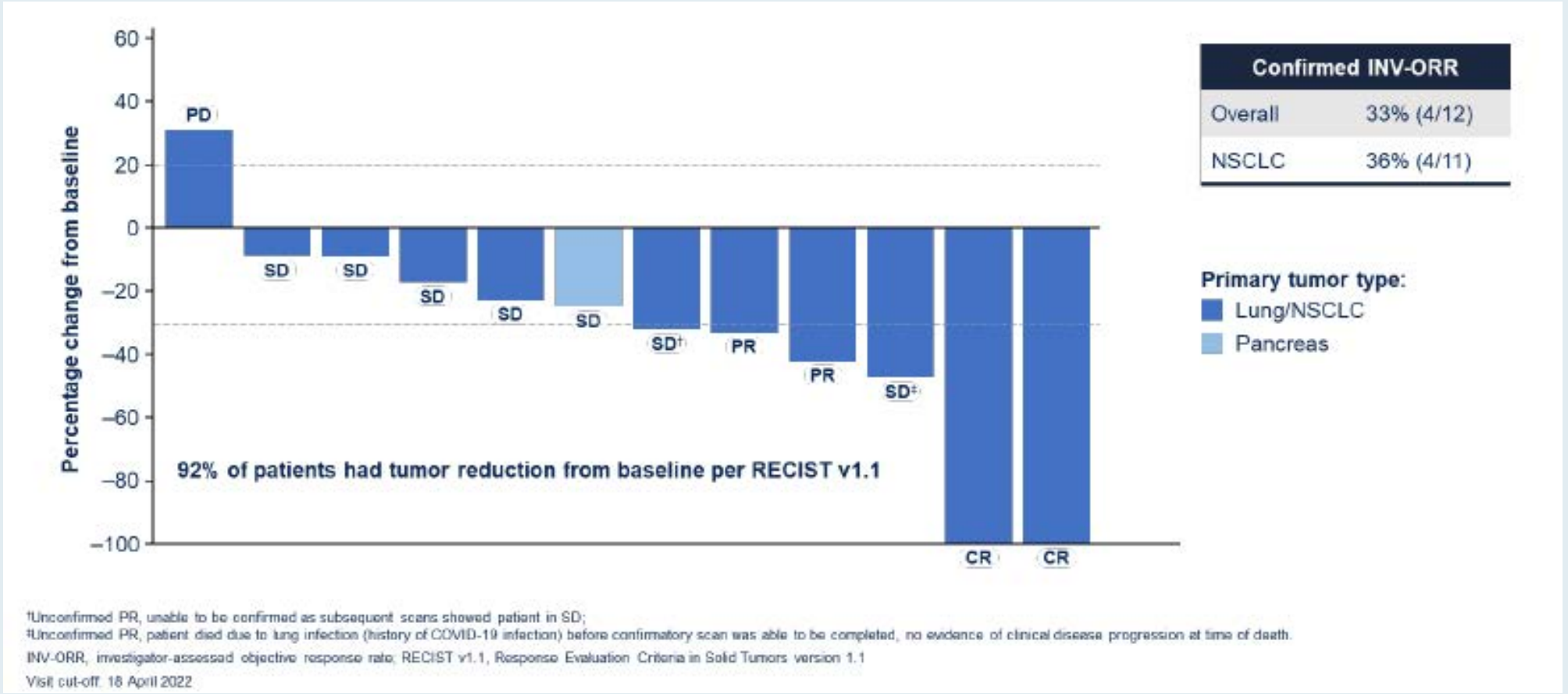
CRESTONE: Initial Efficacy and Safety of Seribantumab in Solid Tumors Harboring NRG1 Fusions

Daniel R. Carrizosa,[1] Mark E. Burkard,[2] Yasir Y. Elamin,[3] Jayesh Desai,[4] Shirish M. Gadgeel,[5] Jessica J. Lin,[6] Saiama N. Waqar,[7] David R. Spigel,[8] Young Kwang Chae,[9] Parneet K. Cheema,[10] Eric B. Haura,[11] Stephen V. Liu,[12] Danny Nguyen,[13] Karen L. Reckamp,[14] Frank Yung-Chin Tsai,[15] Valerie M. Jansen,[16] Alexander Drilon,[17] Sai-Hong Ignatius Ou,[18] D Ross Camidge,[19] Tejas Patil[19]

[1]Levine Cancer Institute/Atrium Health, Charlotte, NC; [2]University of Wisconsin Carbone Cancer Center, Madison, WI; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Peter MacCallum Cancer Centre, Melbourne, Australia; [5]Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI; [6]Massachusetts General Hospital, Boston, MA; [7]Washington University School of Medicine, St. Louis, MO; [8]Sarah Cannon Research Institute, Nashville, TN; [9]Northwestern University, Chicago, IL; [10]William Osler Health System, Calgary, Canada; [11]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [12]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; [13]City of Hope, Huntington Beach and Irvine, CA; [14]Cedars-Sinai Medical Center, Los Angeles, CA; [15]HonorHealth, Scottsdale, AZ; [16]Elevation Oncology, Inc. New York, NY; [17]Memorial Sloan Kettering Cancer Center, New York, NY; [18]Chao Family Comprehensive Cancer Center, University of CA-Irvine, Orange, CA; [19]University of Colorado Cancer Center, Aurora, CO

RTP RESEARCH TO PRACTICE

CRESTONE: Efficacy of Seribantumab for Patients with Advanced Solid Tumors Harboring NRG1 Fusions

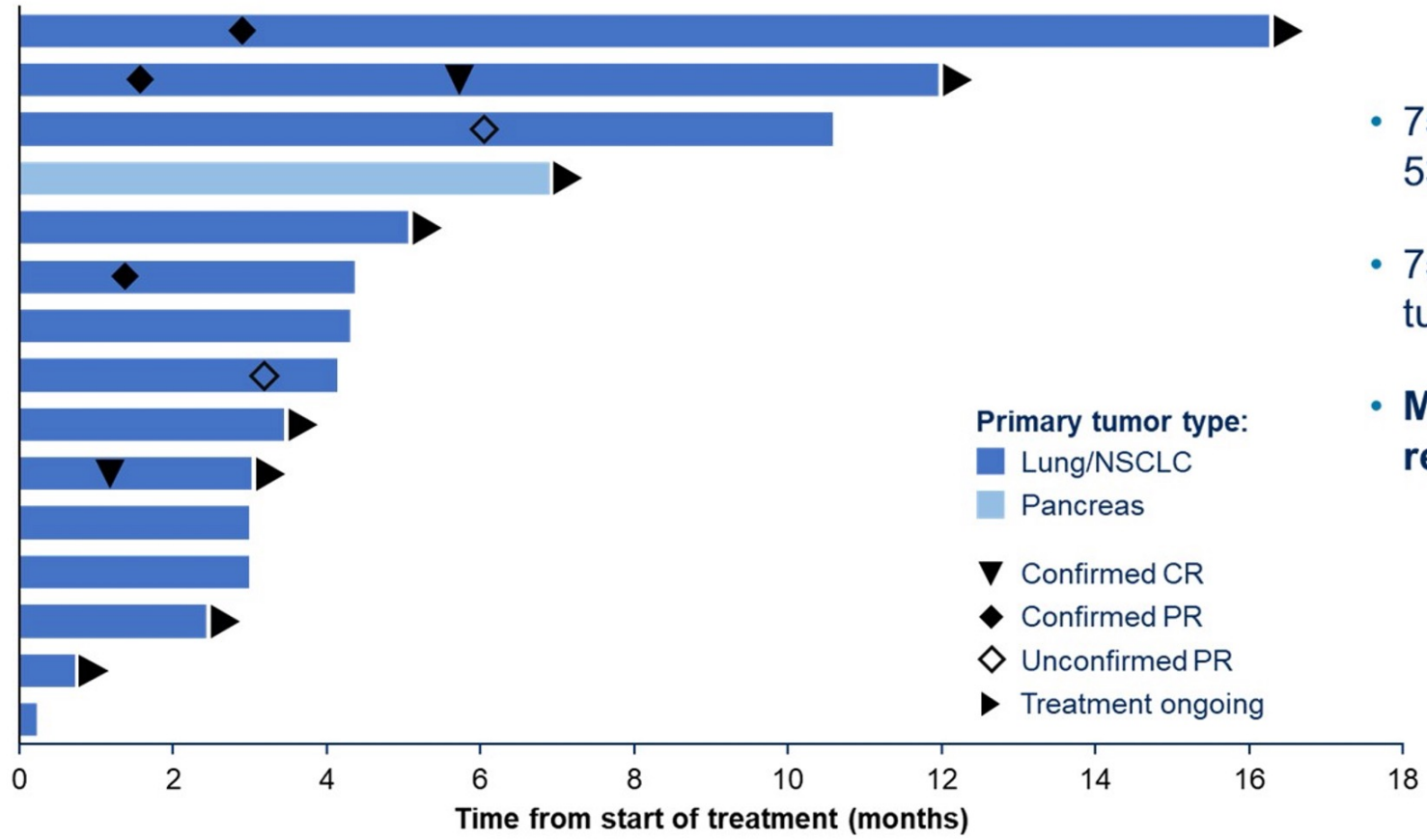


PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response

- Median DoR has not been reached

Carrizosa DR et al. ASCO 2022;Abstract 3006.

CRESTONE: Duration of Seribantumab Therapy for Patients with NRG1 Fusions



- 75% of **responding** patients and 53% of **all** patients remain on treatment
- 75% of **responses** occurred by first tumor assessment (Week 6 ± 2 weeks)
- **Median DOR has not yet been reached** (range: 1.4–11.5 months)

DoR = duration of response; CR = complete response; PR = partial response

Carrizosa DR et al. ASCO 2022;Abstract 3006.

CRESTONE: Select Treatment-Related Adverse Events with Seribantumab in Patients with Advanced Solid Tumors Harboring NRG1 Fusions

Treatment-related adverse event (N = 35)	Any grade	Grade ≥3
Patients with ≥1 AE	30 (86%)	2 (6%)
Diarrhea	14 (40%)	1 (3%)
Fatigue	10 (29%)	0
Rash	9 (26%)	0
Hypokalemia	3 (9%)	0

Carrizosa DR et al. ASCO 2022;Abstract 3006.

Lung Cancer Agenda

Module 1: Targeted Therapy

Module 2: Immunotherapeutic and Other Novel Strategies

RTP
RESEARCH
TO PRACTICE

Systemic Management of Resectable and LA- NSCLC:
2022 Update

Corey J. Langer MD, FACP
Director of Thoracic Oncology
Abramson Cancer Center
Professor of Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA 19104
Corey.langer@uphs.upenn.edu

The unmet need in resectable NSCLC persists

Most patients who receive adjuvant chemotherapy will experience disease recurrence within 5 years

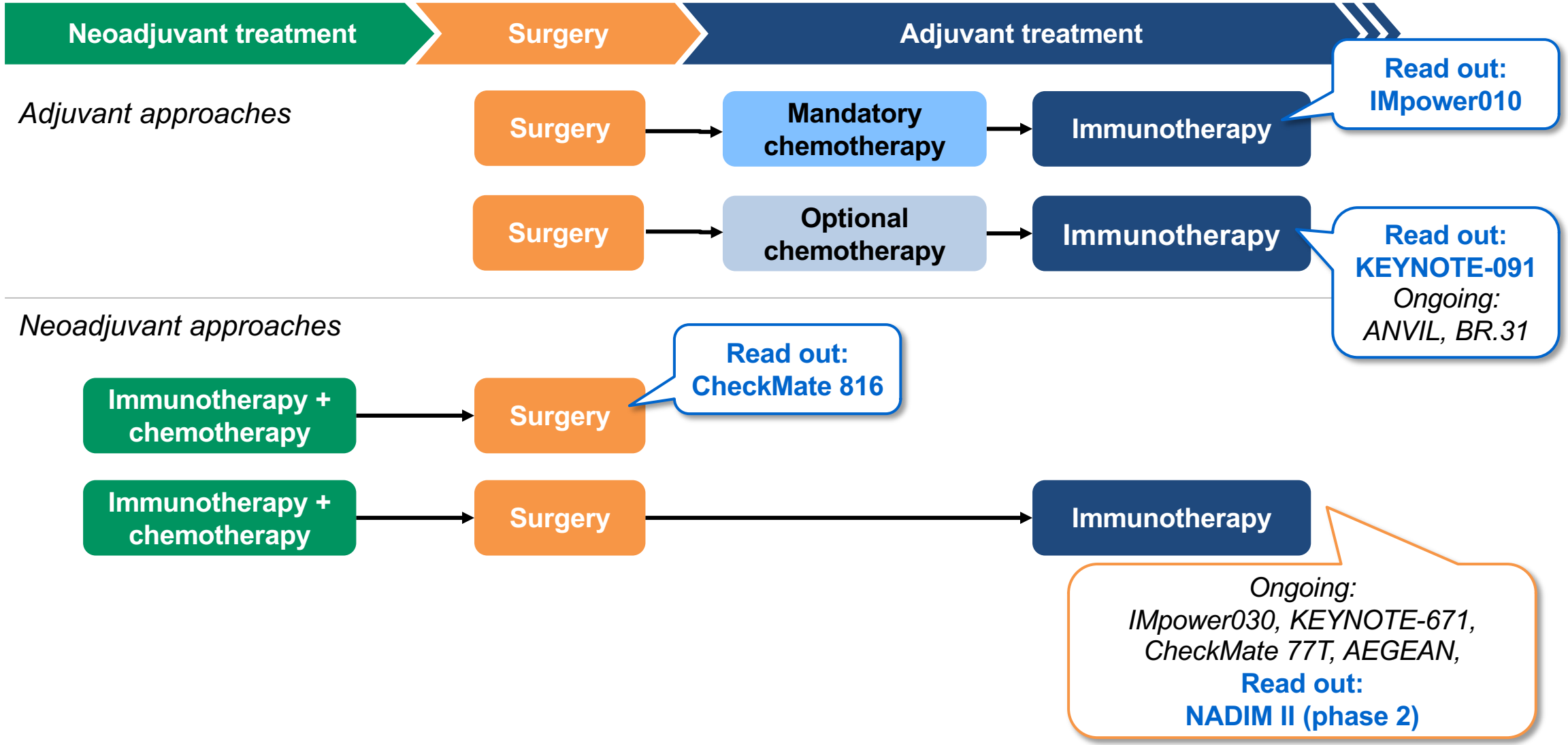
Early stage[1,2]	Regional / locally advanced disease[1,2]	
Stage IB	Stage II	Stage III
		
~45% chance of recurrence or death[a]	~62% chance of recurrence or death[a]	~76% chance of recurrence or death[a]

[a]Median follow-up: 5.2 years, data based on AJCC Staging Manual 6th edition

AJCC, American Joint Committee on Cancer; NSCLC, non-small cell lung cancer

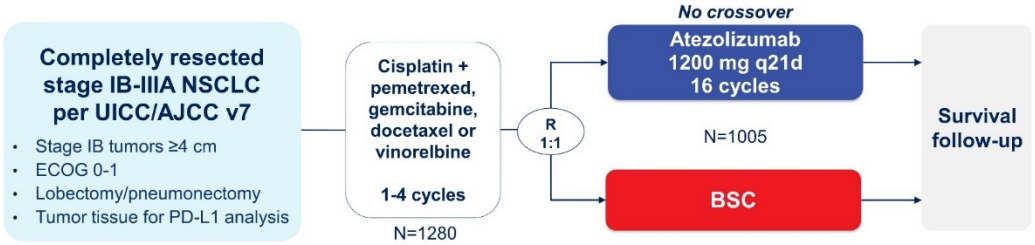
1. Pignon JP, et al. J Clin Oncol 2008;26:3552–59; 2. Edge SB, et al. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010

Phase III studies with immunotherapy in resectable NSCLC are taking different approaches



Adjuvant IO Phase III randomised trials

IMpower010[1]

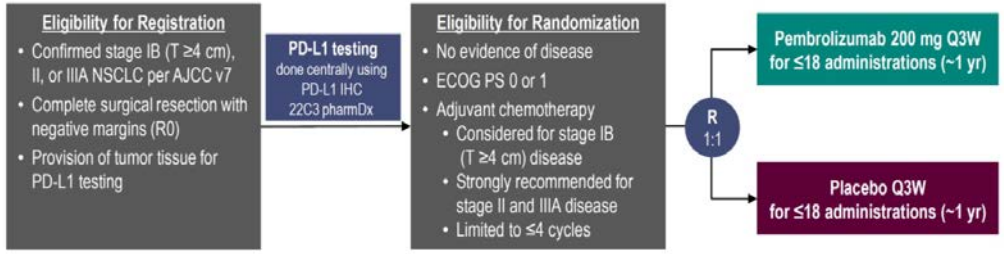


Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

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

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

PEARLS/KEYNOTE 091[2]

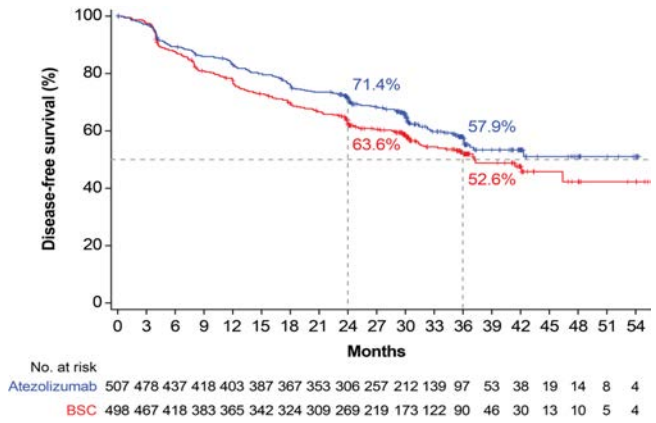


Stratification Factors
- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

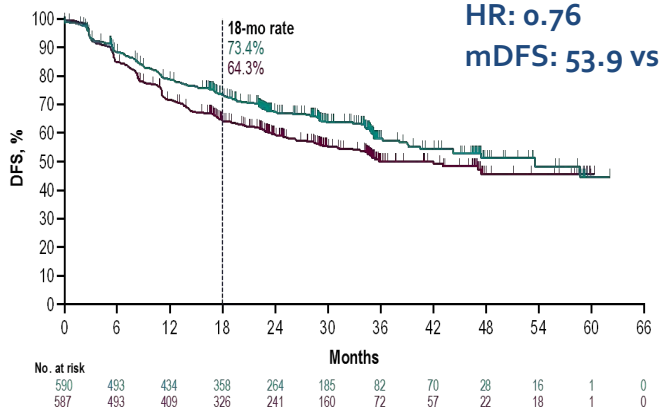
Secondary End Points
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

Stage IB to IIIA



HR: 0.81
mDFS: NE vs 37.2 months

Stage IB to IIIA



HR: 0.76
mDFS: 53.9 vs 42 months

1. Felip E, et al. Lancet 2021;398:1344–57; 2. Paz-Ares L, et al. Presented at ESMO Congress 2022 (Abstract VP3-2022)

Adjuvant IO Phase III randomised trials
DFS and PD-L1 TPS data - consistent data?

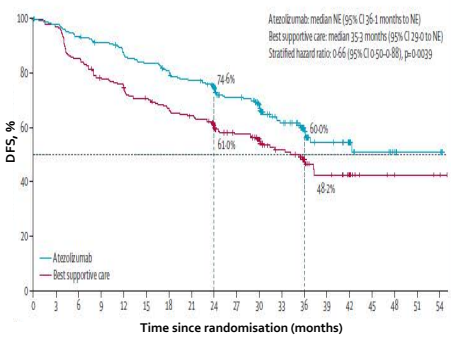
Effect of PD-L1 expression

IMpower010 Stage II/IIIA[1]

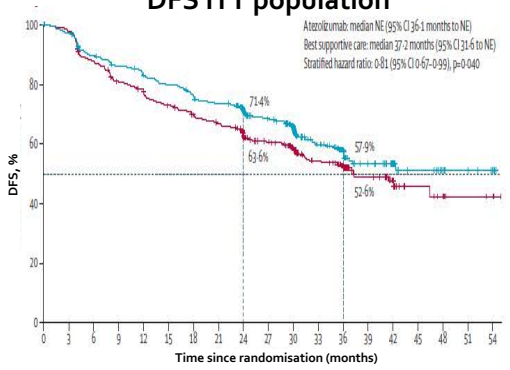
A DFS benefit with atezolizumab vs. BSC was observed in the PD-L1 ≥1% population but not in the ITT population

	HR (95% CI)
PD-L1 TPS ≥1%	0.66 (0.50, 0.88); p=0.0039
ITT population	0.81 (0.67, 0.99); p=0.040

DFS PD-L1 TC ≥1% population



DFS ITT population

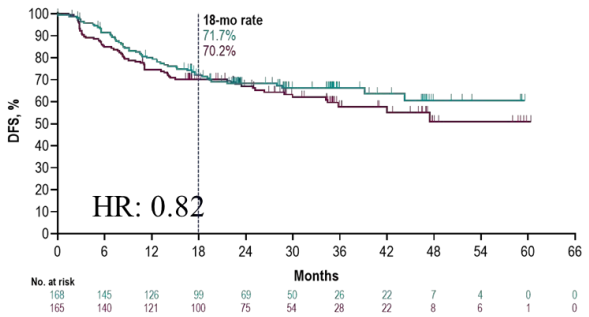


PEARLS/KEYNOTE 091 Stage IB–IIIA[2]

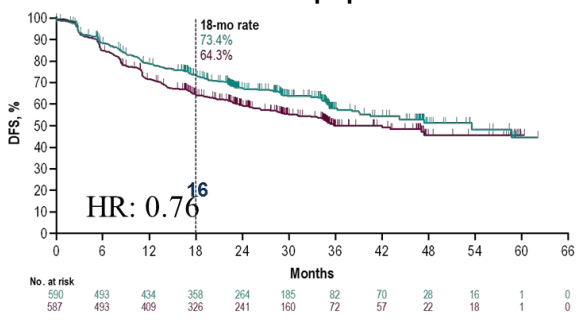
DFS was significantly improved with pembrolizumab in the all-comers population but not in the PD-L1 TPS ≥50% population

	HR (95% CI)
All comers	0.76 (0.63, 0.91); p=0.0014
PD-L1 TPS ≥50%	0.82 (0.57, 1.18); p=0.14

DFS PD-L1 TPS ≥50% population



DFS ITT population



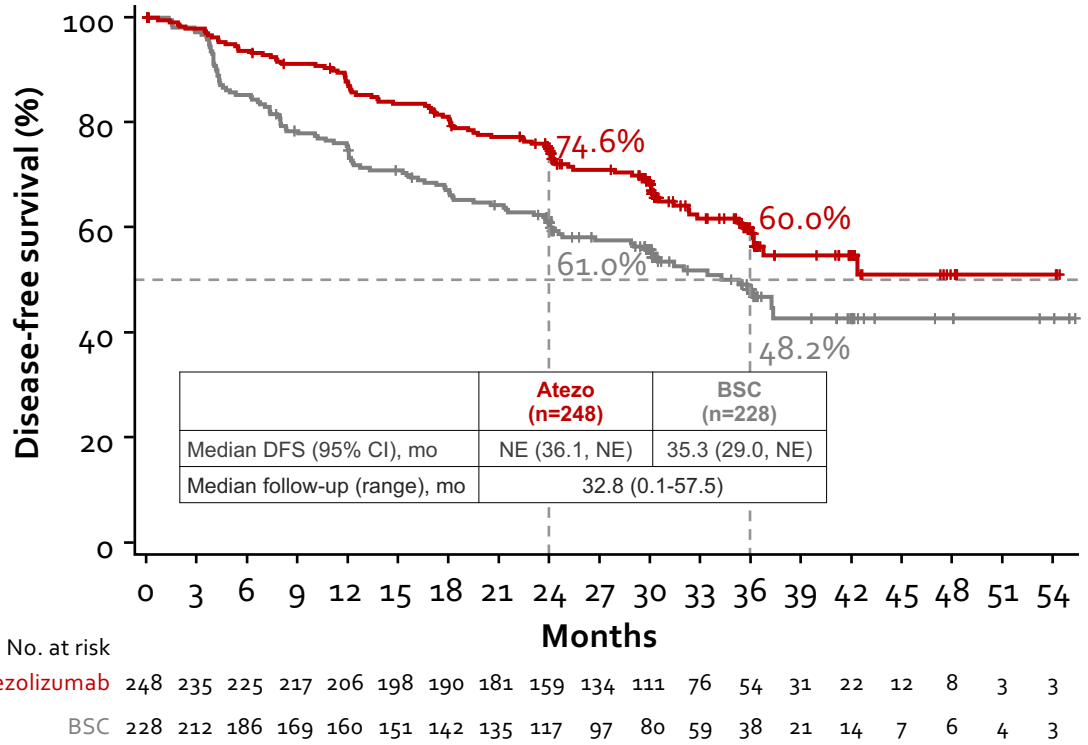
Approvals

PD-L1 ≥1% PD-L1 ≥50%

and other countries

IMpower010: the primary endpoint of improved DFS in patients with PD-L1 TC ≥1%, stage II–IIIA* NSCLC was met

DFS in PD-L1 TC ≥1%, stage II–IIIA, completely resected NSCLC



Primary analysis populations

Population analysed for DFS	n	HR (95% CI)§
PD-L1 TC ≥1%, stage II–IIIA	476	0.66 (0.50, 0.88)
All-randomised, stage II–IIIA	882	0.79 (0.64, 0.96)
ITT (all randomised, stage IB–IIIA)	1005	0.81 (0.67, 0.99)

Endpoint was met at DFS IA

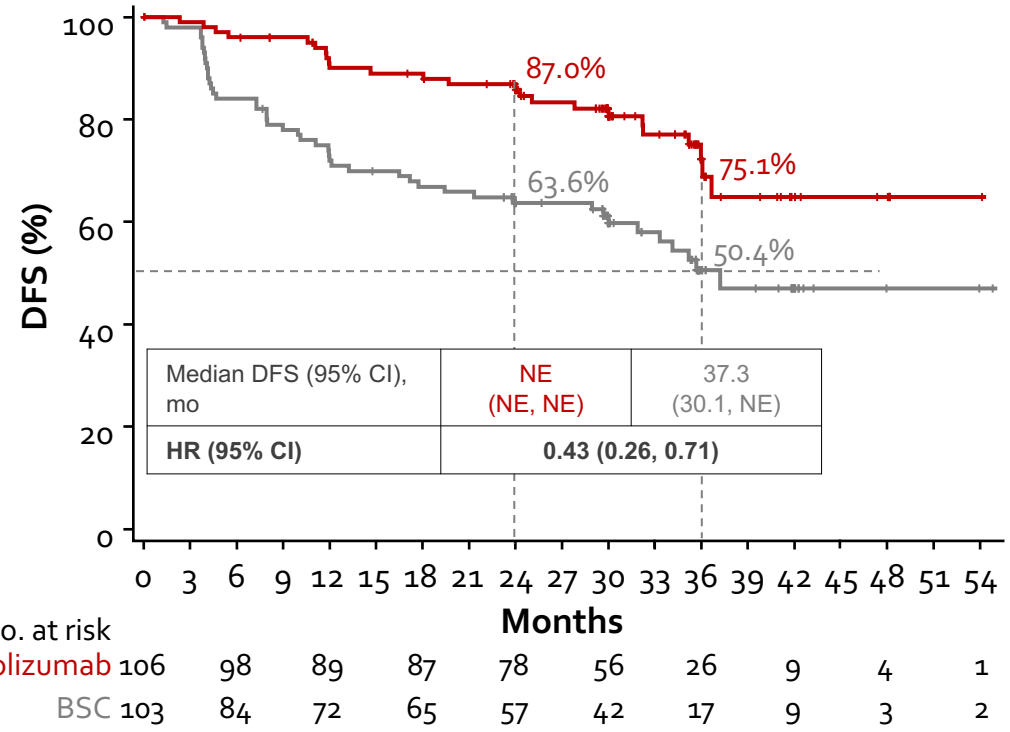
Endpoint was not met at DFS IA, and follow-up is ongoing

***Per TNM 7th edition (select stage II–IIIB per TNM 8th edition)**

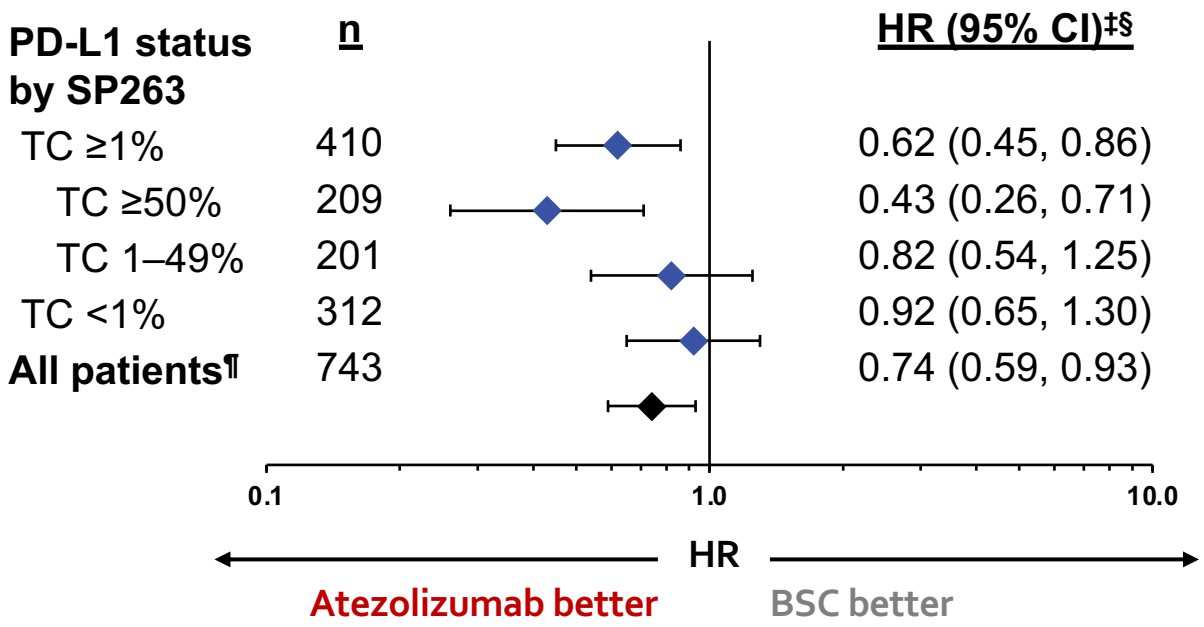
Wakelee, et al. ASCO 2021 (Abs 8500); Felip, et al. Lancet 2021

Greatest magnitude of DFS benefit with adjuvant atezolizumab over BSC was in PD-L1 TC ≥50%, stage II–III NSCLC

DFS in PD-L1 TC ≥50%, stage II–IIIA population (excluding *EGFR*+/*ALK*+ NSCLC)[1]



DFS by PD-L1 status in the all-randomised, stage II–IIIA population (excluding *EGFR*+/*ALK*+ NSCLC)[2]



OS data are not yet mature

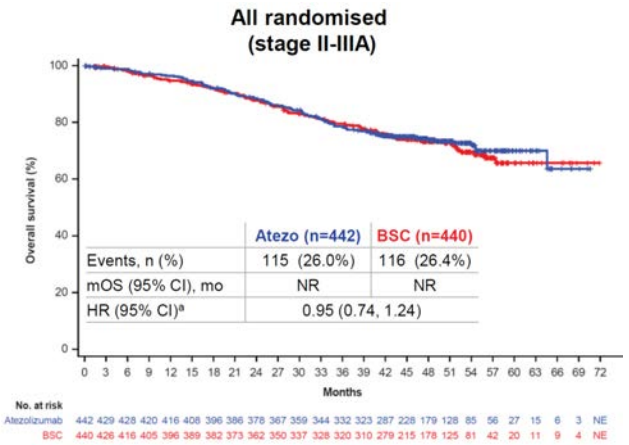
Clinical cut-off: 21 January 2021

*Unstratified HR; ‡Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups; §DFS analyses in the PD-L1 TC <1% and TC 1–49% subgroups were exploratory; ¶23 patients had unknown PD-L1 status as assessed by SP263

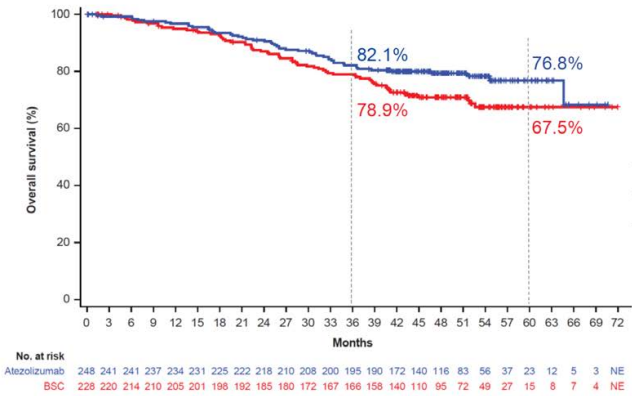
1. Felip, et al. ELCC 2022 (Abs 8oO)
2. Felip, et al. ESMO 2021 (Abs LBA9)

IMpower010: OS trend of atezolizumab in PD-L1 ≥1% Stage II–IIIA (interim OS analysis)

No OS benefit in the all-randomised Stage II–IIIA



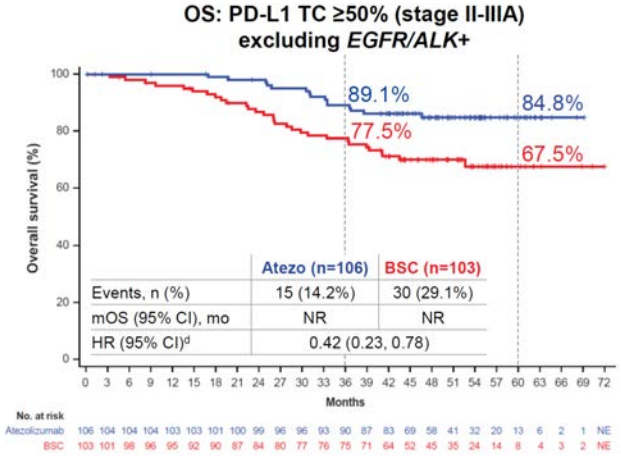
OS interim analysis in PD-L1 TC ≥1% (Stage II–IIIA)



mOS, median overall survival; NR, not reached. [a]By SP263 assay. [b]Stratified.

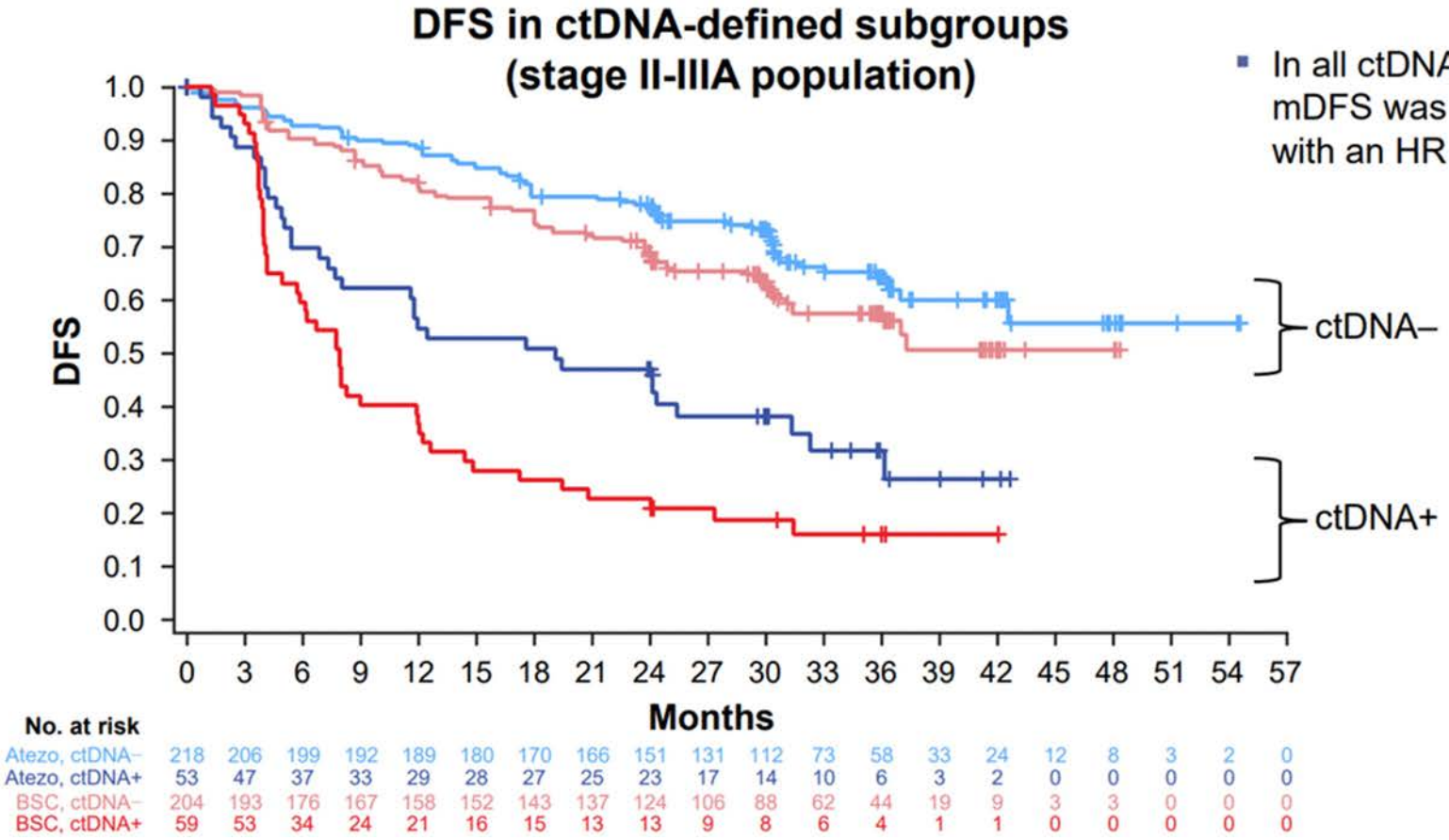
	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[-]	0.71 (0.49, 1.03)	

Clinically meaningful OS trend in PD-L1 ≥50%



Wakelee H, et al. Presented at WCLC 2022 (Abstract PL03.09)

IMpower-010: ctDNA is prognostic but neither predictive nor sufficiently sensitive for de-escalation decisions



- 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)

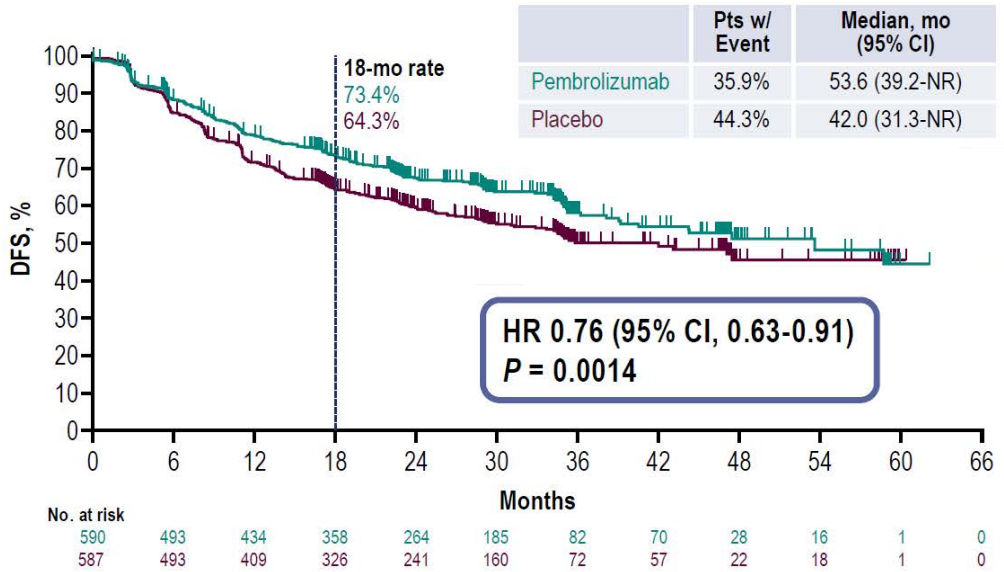
ctDNA−	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

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

Zhang, Cancer Disc 2022

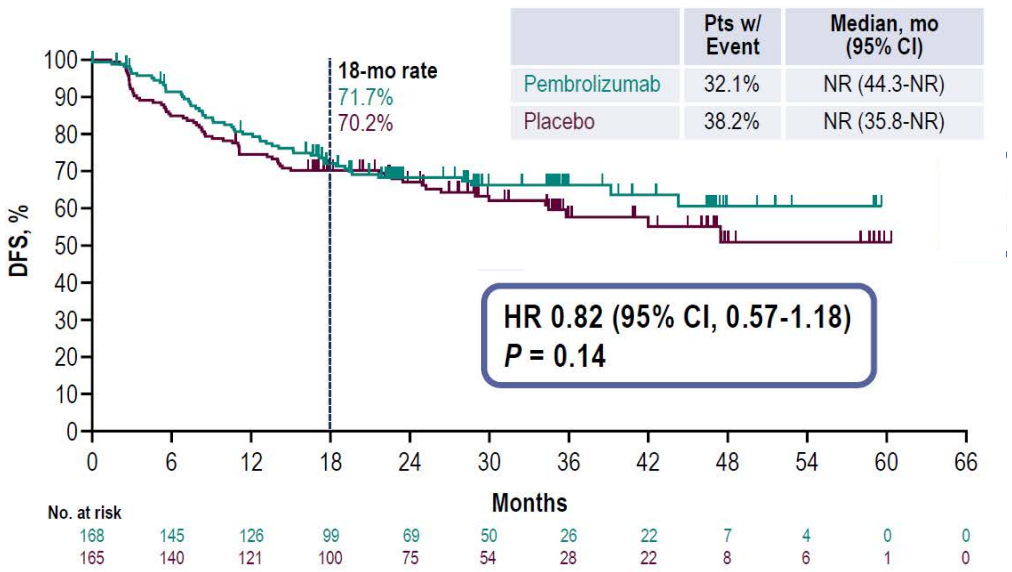
KEYNOTE-091: one dual primary endpoint of a DFS benefit in the overall population was met

DFS in the overall population (PD-L1 unselected, stage IB–III, completely resected NSCLC



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

DFS in PD-L1 TPS ≥50%, stage IB–III, completely resected NSCLC*



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

OS data are not yet mature

Data cut-off: 20 September, 2021; response assessed per RECIST v1.1 by investigator review

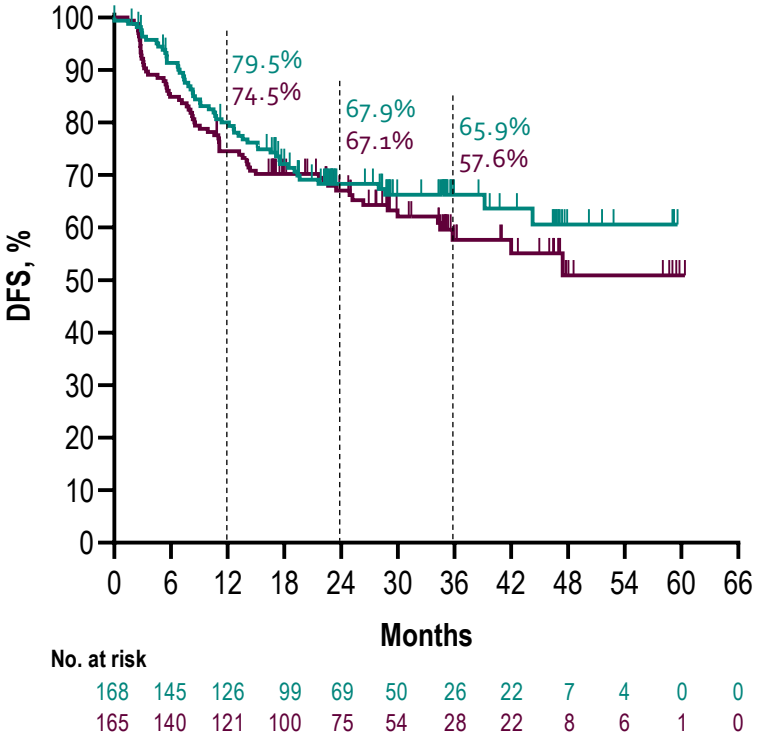
*At the interim analysis, this dual primary endpoint did not meet statistical significance

Paz-Ares, et al. ESMO Plenary 2022 (Abs VP3-2022)

DFS: Pembrolizumab vs Placebo by PD-L1 TPS

TPS ≥50%
HR 0.82 (95% CI, 0.57-1.18)
***P* = 0.14**

Median (95% CI), mo
Pembrolizumab: NR (44.3-NR)
Placebo: NR (35.8-NR)

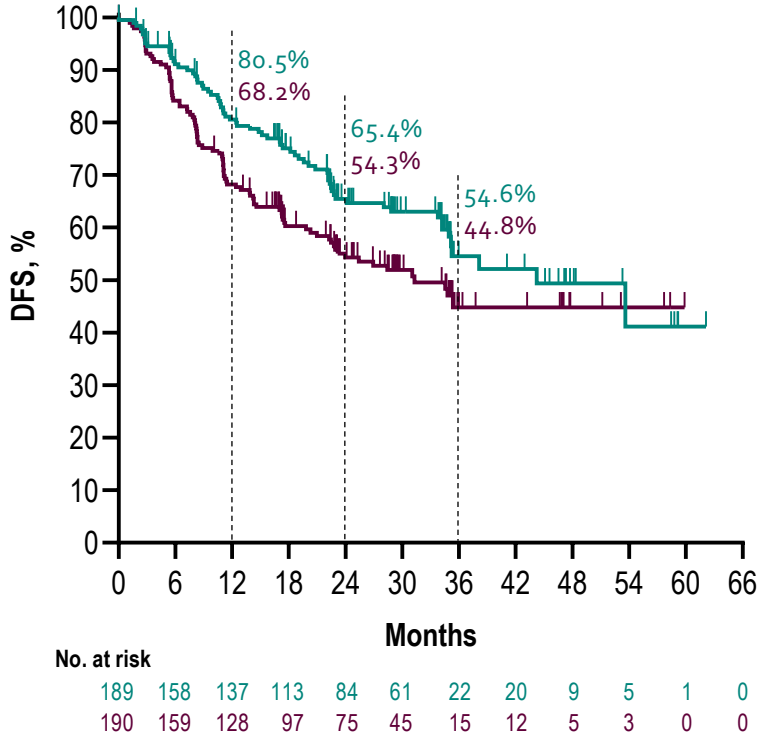


No. at risk

168	145	126	99	69	50	26	22	7	4	0	0
165	140	121	100	75	54	28	22	8	6	1	0

TPS 1-49%
HR 0.67 (95% CI, 0.48-0.92)

Median (95% CI), mo
Pembrolizumab: 44.2 (34.9-NR)
Placebo: 31.3 (22.5-NR)

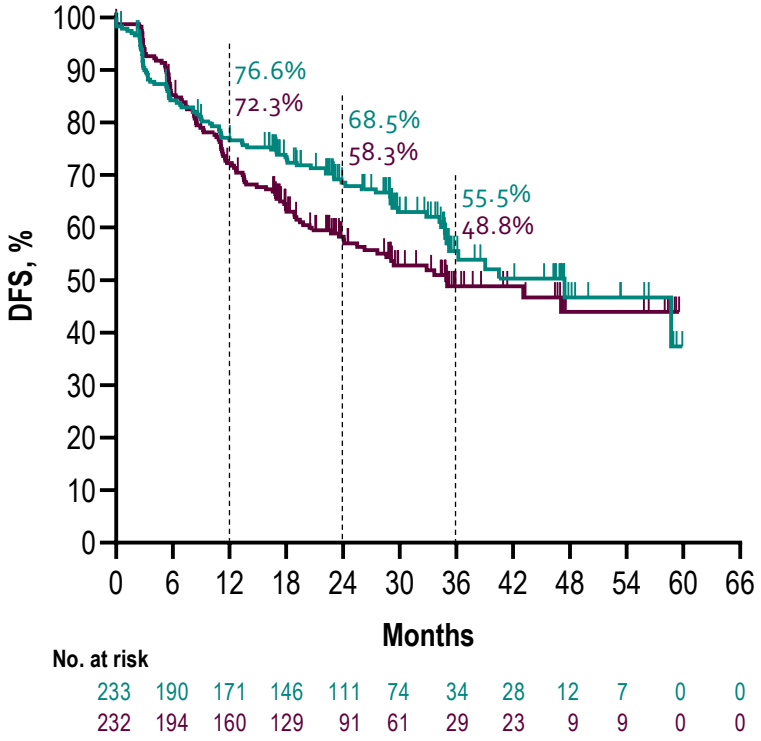


No. at risk

189	158	137	113	84	61	22	20	9	5	1	0
190	159	128	97	75	45	15	12	5	3	0	0

TPS <1%
HR 0.78 (95% CI, 0.58-1.03)

Median (95% CI), mo
Pembrolizumab: 47.4 (35.0-NR)
Placebo: 34.9 (25.5-NR)



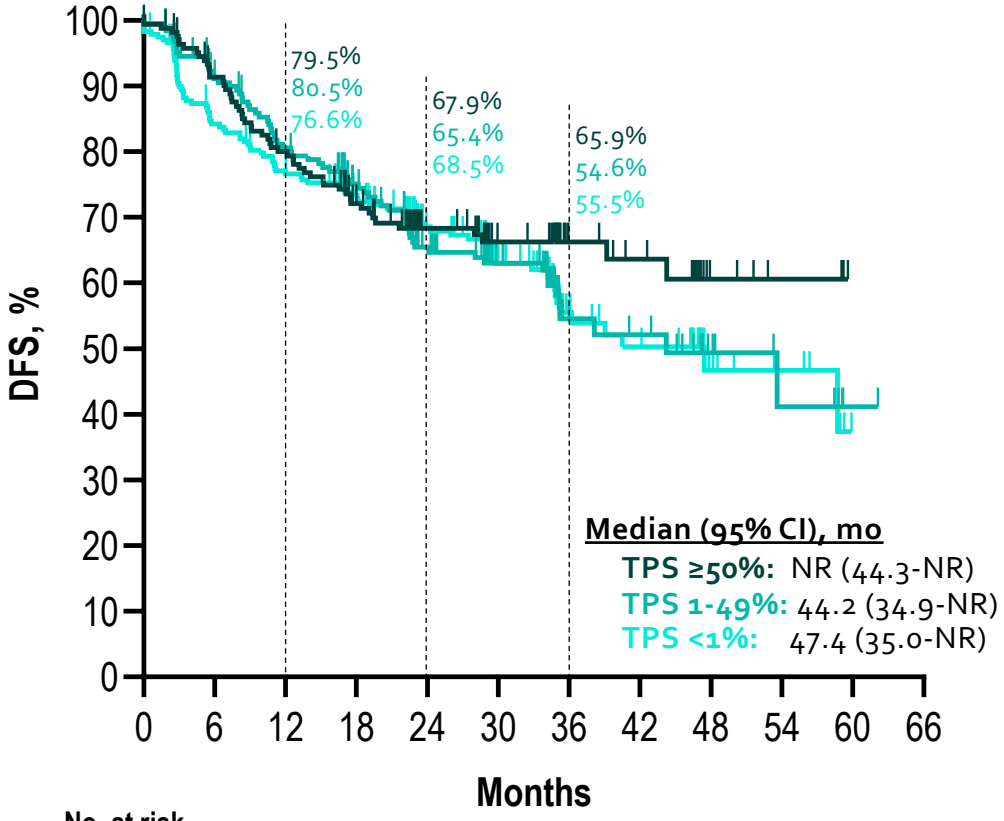
No. at risk

233	190	171	146	111	74	34	28	12	7	0	0
232	194	160	129	91	61	29	23	9	9	0	0

DFS: Overperformance of high PD-L1 in placebo arm

(no imbalance in baseline characteristics or toxicity)

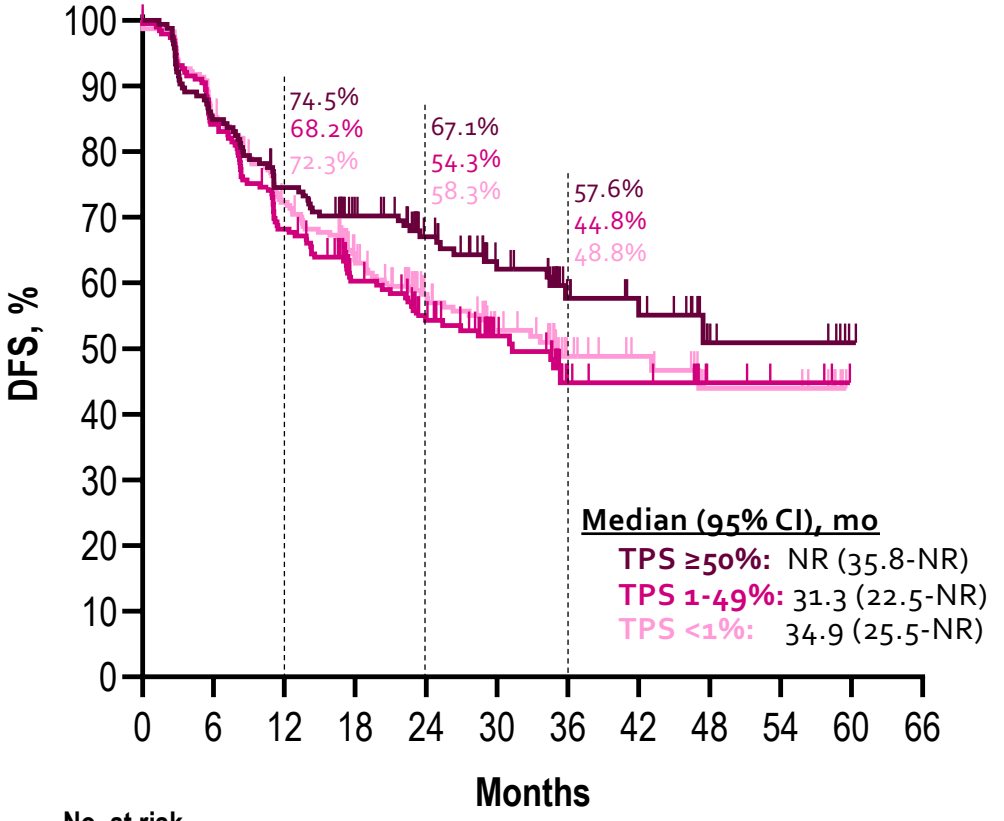
Pembrolizumab



No. at risk

168	145	126	99	69	50	26	22	7	4	0	0
189	158	137	113	84	61	22	20	9	5	1	0
233	190	171	146	111	74	34	28	12	7	0	0

Placebo



No. at risk

165	140	121	100	75	54	28	22	8	6	1	0
190	159	128	97	75	45	15	12	5	3	0	0
232	194	160	129	91	61	29	23	9	9	0	0

Neoadjuvant immunotherapy clinical trials

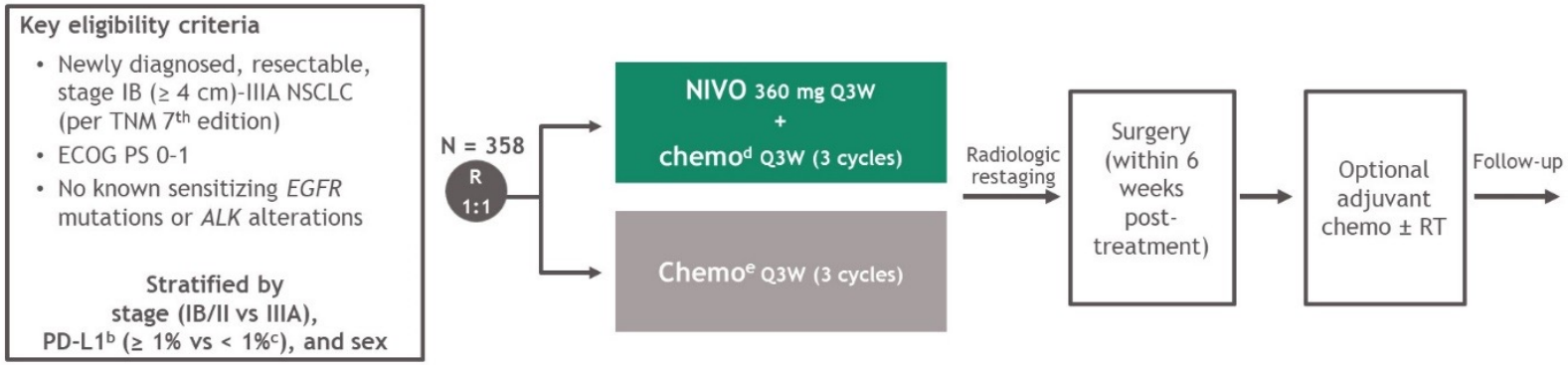
Study	Total n= Squam, %	Stage I/II III	Drug # of preoperative cycles	# taken to surgery (%) #Ro	ORR DCR	pCR	MPR
			PD-L1 monotherapy				
Forde NEJM 2018	21 6 (29%)	66% 33%	Nivo 3 mg/kg x 2	21 (100) 20 Ro	10% 95%	10%	45%
Gao JTO 2021	40 33 (83%)	55% 45%	Sintilimab 200 mg x 2	37 (92.5) 36 Ro	20% 90%	16.2%	40.5%
LCMC3	181 69 (38%)	51% 49%	Atezo 1200 mg x 2	159 (88) 145 Ro	7% 95%	7%	21%
NEOSTAR	23 10 (43%)	78% 22%	Nivo 3 mg/kg x 3	22 (96) 22 Ro	22% 87%	10%	19%
MK3475-223	15 NR	100% 0%	Pembro 200 mg x 1-2	13 (87) NR	13% NR	15%	31% 40% (2 doses)
IFCT-1601 IONESCO	50 21 (42%)	96% 4%	Durva 750 mg x 3	43 (93) 41 Ro	9% 87%	7%	18.6%
PRINCEPS	30 NR	70% 30%	Atezo 1200mg x 1	30 (100) 29 Ro	7% 100%	0%	14%
			Dual checkpoint inhibitors				
Reuss JITC 2020	9 1 (11%)	33% 66%	Nivo 3 mg/kg x 3, Ipi 1 mg/kg x 1	6 (67%) Ro NR	11% 55%	33%	33% (all pCR)
NEOSTAR	21 7 (83%)	81% 19%	Nivo 3 mg/mg x 3, Ipi 1 mg/kg x 1	17 (81) 17 Ro	19% 81%	38%	44%
			IO + chemotherapy				
Shu Lancet Onc 2020	30 12 (40%)	23% 77%	Carbo AUC 5, Nab-pac 100 mg/m^2, Atezo 1200 mg x 4	29 (97%) 26 Ro	63% 93%	33%	57%
NADIM	46 16 (35%)	0% 100%	Carbo AUC 6, Taxol 200 mg/m^2, Nivo 360 mg x 3	41 (89) 41 Ro	76% 100%	63%	83%
SAKK 16/14	68 22 (33%)	0% 100%	Cis 100 mg/m^2, Doce 85 mg/m^2 x 3, Durva 750 mg x 2	55 (82%) 50 Ro	58% 84%	18.2%	60%

CT, chemotherapy; DCR, disease control rate; IO, immuno-oncology; NR, not reached; MPR, major pathological response; ORR, objective response rate; pCR, pathological complete response; PD-L1, programmed cell death-ligand 1

1. Forde PM, et al. N Engl J Med 2018;378:1976–86; 2. Gao S, et al. J Thorac Oncol 2020;15:816–26; 3. Lee J, et al. Presented at WCLC 2020 (Abstract PS01.05);
4. Cascone T, et al. Nat Med 2021;27:505–14; 5. Bar J, et al. Presented at ASCO 2019; 6. Wislez M, et al. Presented at ESMO 2020 (Abstract 1214O);
7. Besse B, et al. Presented at ESMO 2020 (Abstract 1215O); 8. Reuss JE, et al. J Immunother Cancer 2020;8:e001282; 9. Shu CA, et al. Lancet Oncol 2020;21:786–95;
10. Provencio M, et al. Lancet Oncol 2020;21:1413–22; 11. Rothschild SI, et al. J Clin Oncol 2021;39:2872–80

Neoadjuvant nivolumab: CheckMate 816 and NADIM II

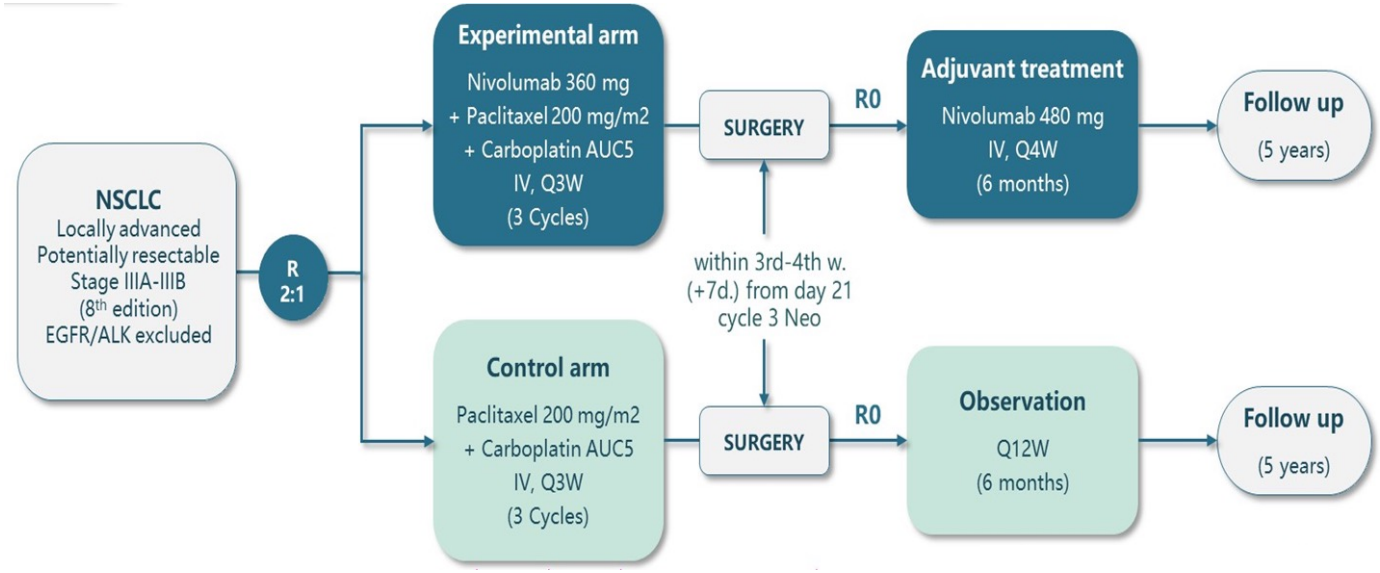
CheckMate 816



Primary endpoints:

- pCR by BICR
- EFS by BICR

NADIM II

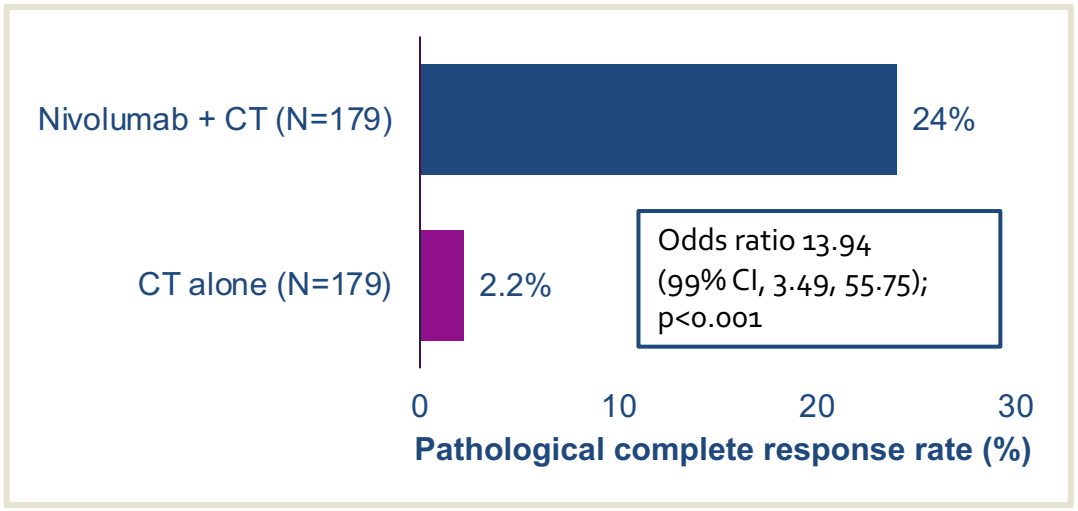


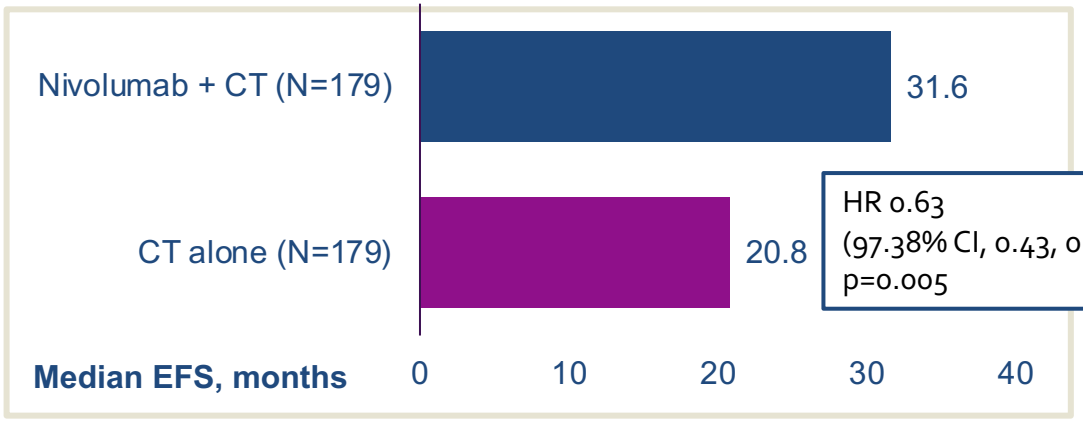
Primary endpoints:

- pCR

Neoadjuvant nivolumab: Odds ratio and EFS

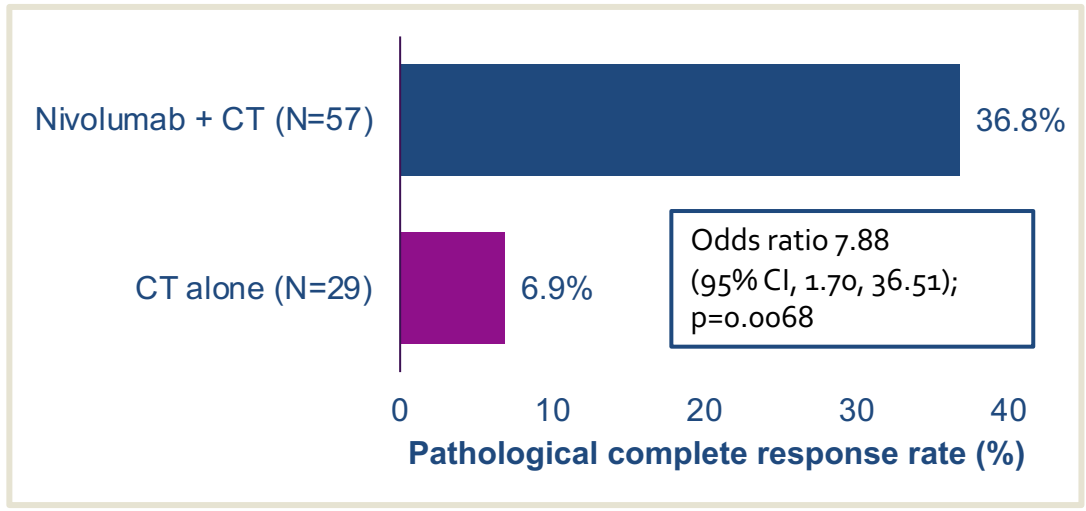
CheckMate 816[1]

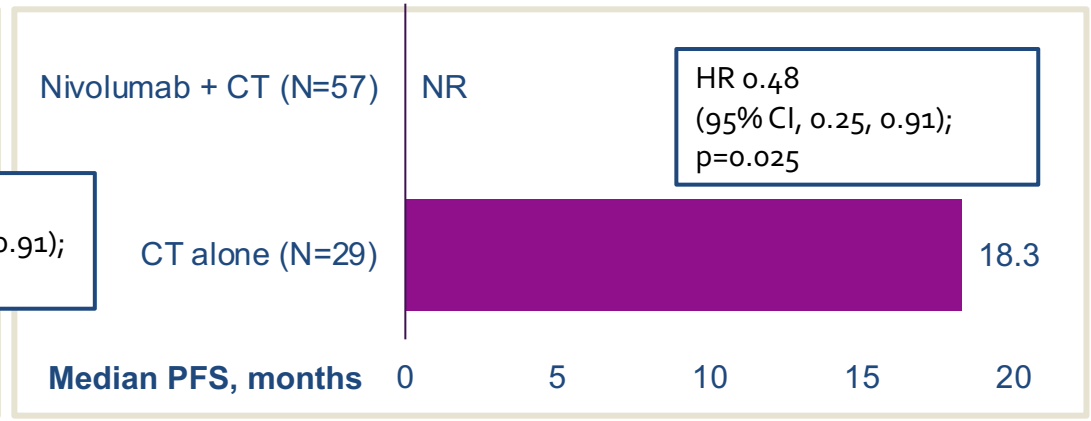




mOS: NR (HR 0.57)

NADIM II[2]



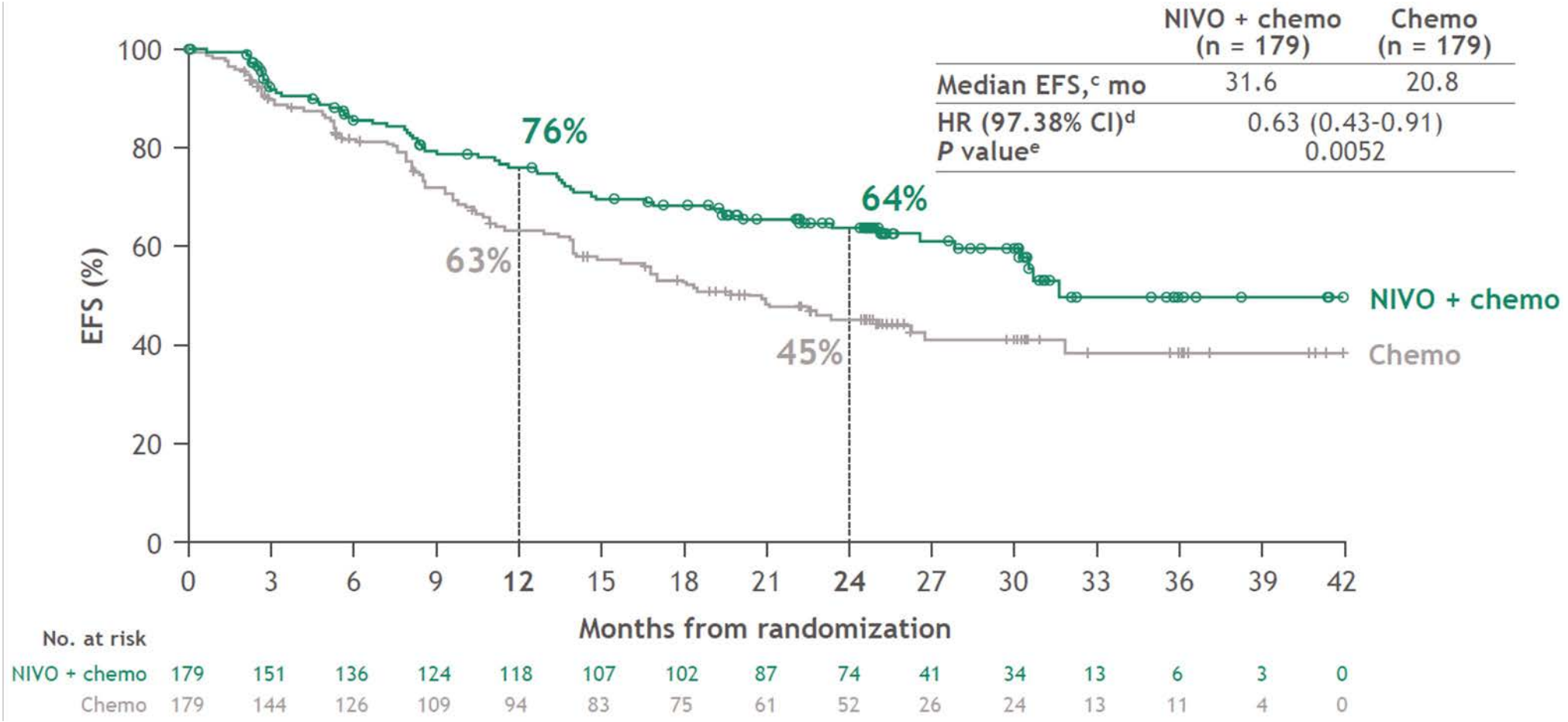


mOS: NR (HR 0.40)

CI, confidence interval; CT, chemotherapy; EFS, event-free survival; HR, hazard ratio; NR, not reached

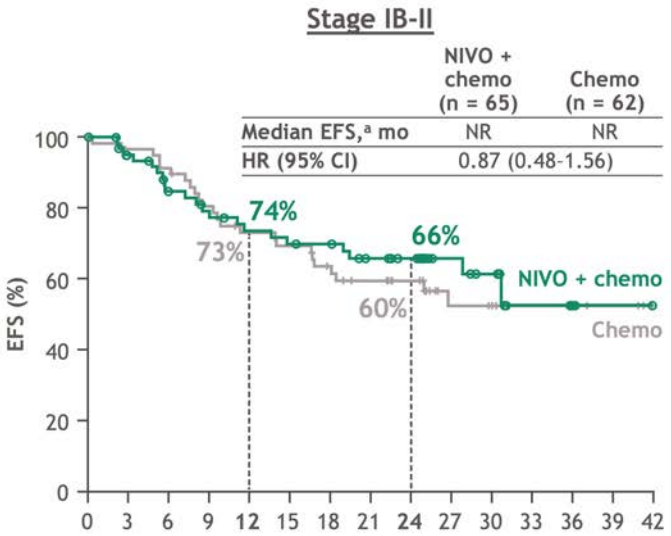
1. Forde PM, et al. N Engl J Med 2018;378:1976–86; 2. Provencio M, et al. Presented at ASCO 2022 (Abstract 8501)

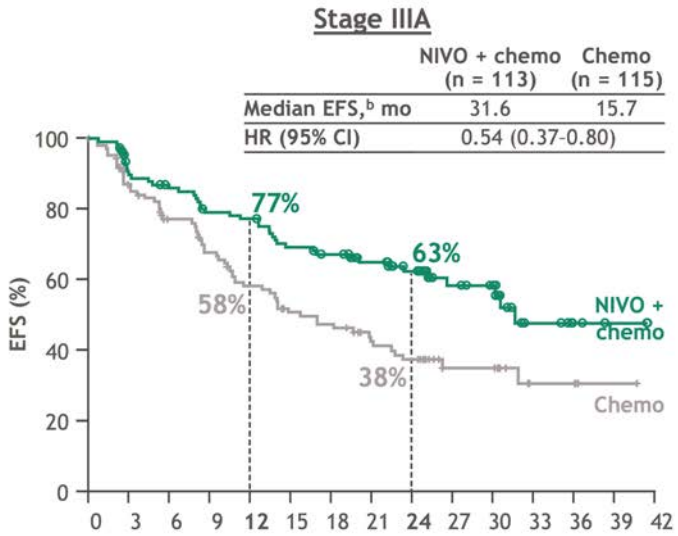
CheckMate 816: neoadjuvant nivolumab + chemotherapy improved EFS compared with chemotherapy alone

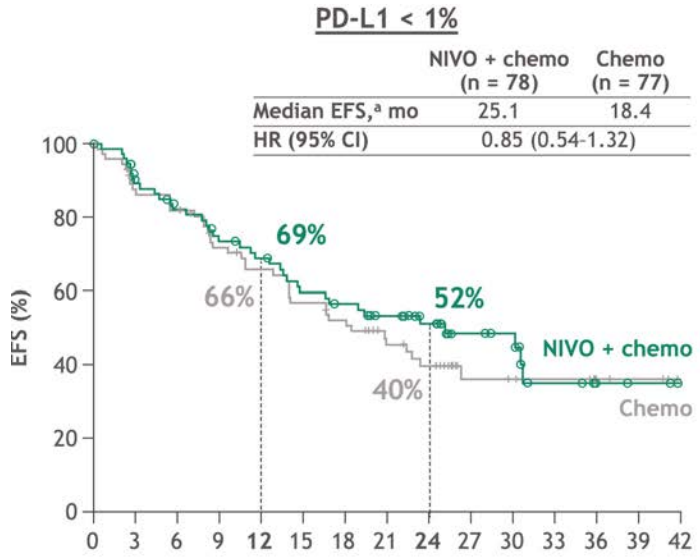


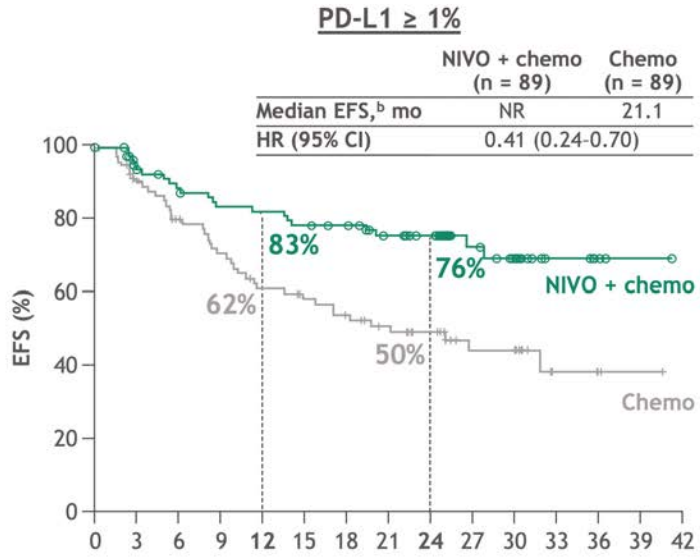
Girard, et al. AACR 2022 (Abs CT012)
Forde, et al. N Engl J Med 2022

CheckMate 816: an EFS by stage and PD-L1

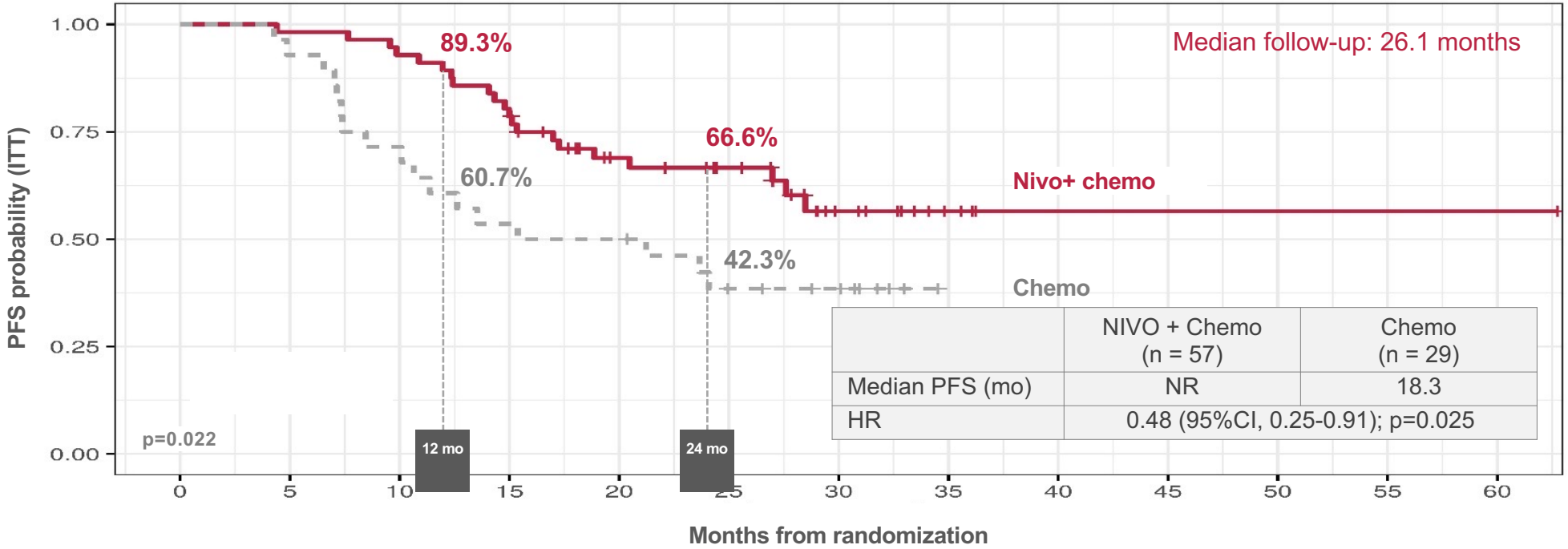








SECONDARY ENDPOINTS – Progression-free survival



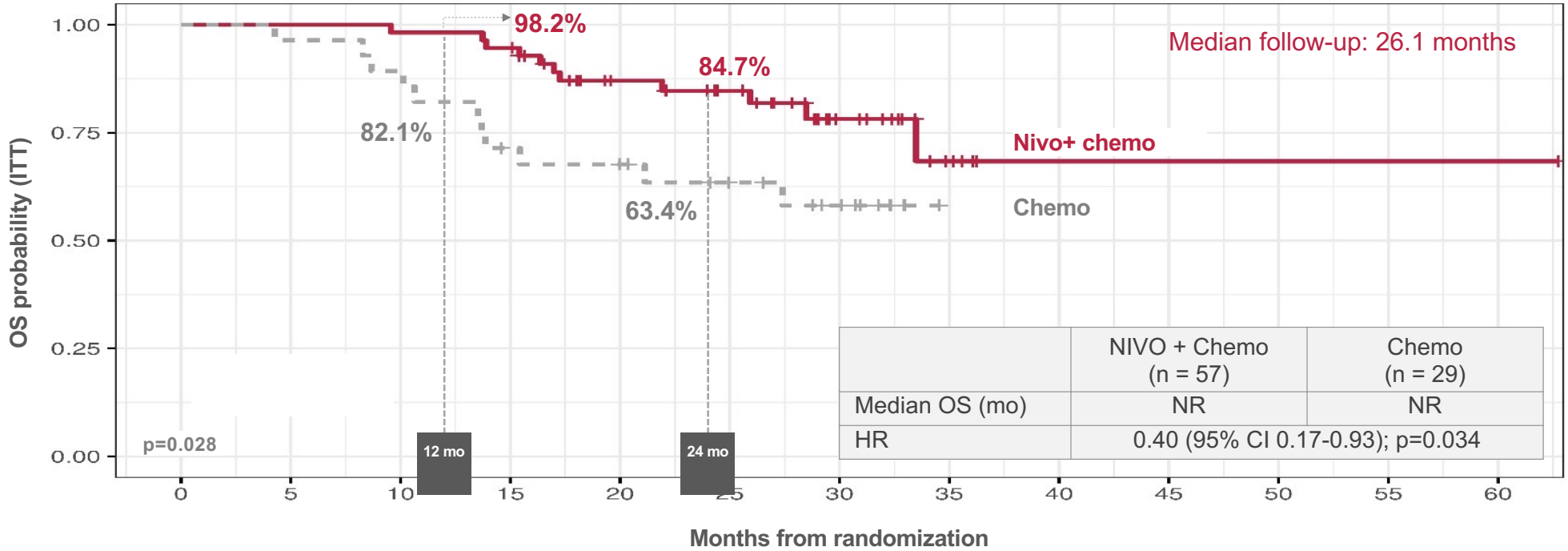
	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median PFS (mo)	NR	18.3
HR	0.48 (95%CI, 0.25-0.91); p=0.025	

Number at risk

Nivo + chemo	56	55	52	44	30	24	11	4	1	1	1	1	1
Chemo	28	26	20	15	14	9	7	0	0	0	0	0	0

Progression-free survival was defined as the time from randomization to any of the following events: progression of disease, recurrence disease, or death due to any cause. Progression/recurrence will have determined by RECIST 1.1

SECONDARY ENDPOINTS – Overall survival



	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median OS (mo)	NR	NR
HR	0.40 (95% CI 0.17-0.93); p=0.034	

Number at risk													
Nivo + chemo	56	56	55	53	37	31	15	5	1	1	1	1	1
Chemo	28	27	25	19	17	13	9	0	0	0	0	0	0

Overall survival was defined as the time from randomization to death. OS was censored on the last date a participant was known to be alive

The risk of toxicity and non-operability

7–18%

AE Grade 3/4: 13–33%

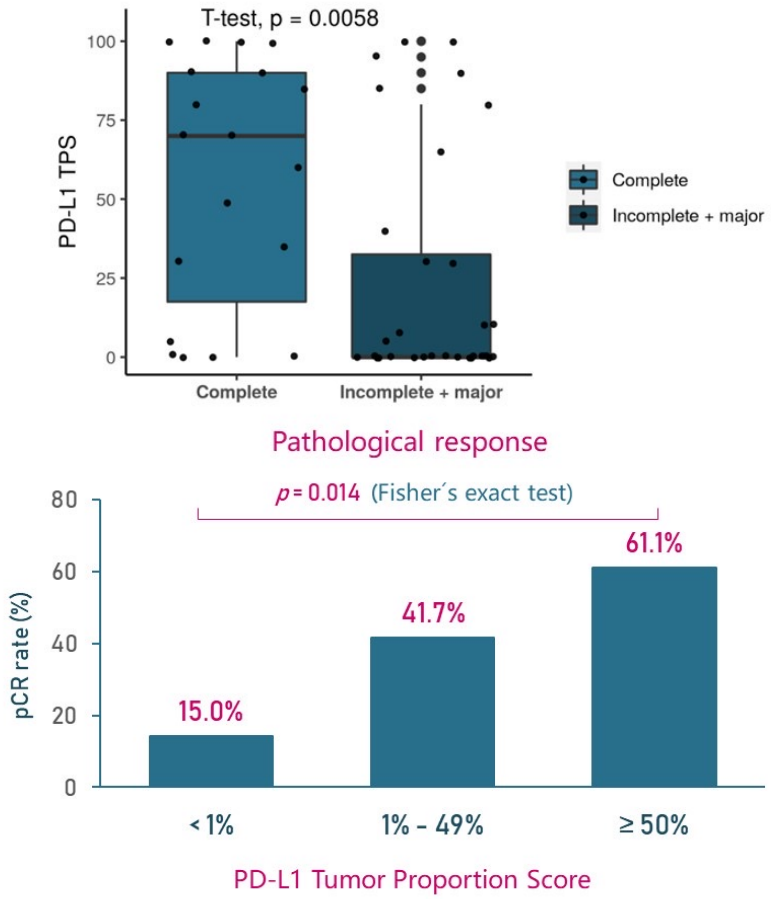
	Rate of unperformed surgery	30 days mortality	Treatment-related AE
NADIM I [1]	11%	Non	G3/4: 13.5% in adjuvant phase
SAKK 16/14 [2]	18%	2% (fatal bronchopulmonary Bleeding)	G3/4: 29% in perioperative phase G3/4: 50% in adjuvant phase
NADIM II [3]	7%	Non	Grade 3/4 AEs: 25%, nivolumab + CT; 10.3%, CT alone (OR: 2.82; 95% CI: 0.74-10.76; Chi-squared *P* = .201)
CheckMate 816 [4]	17%	1.1% (pulmonary embolism, aortic rupture)	Surgery-related G3/4: 11.4% G3/4: 33.5%

AE, adverse event; CI, confidence interval; CT, chemotherapy; G, grade; OR, odds ratio

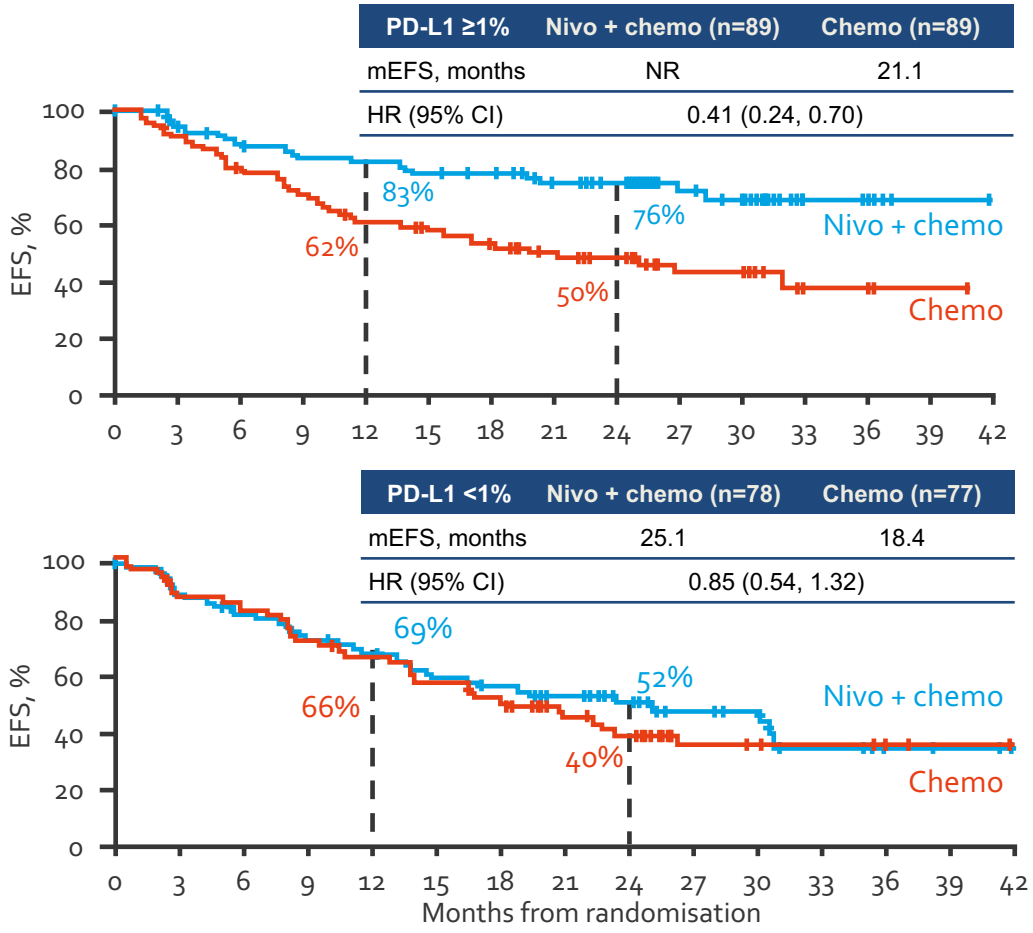
1. Provencio M, et al. Lancet Oncol 2020;21:1413–22; 2. Rothschild SI, et al. J Clin Oncol 2021;39:2872–80; 3. Provencio M, et al. Presented at ASCO 2022 (Abstract 8501); 4. Forde PM, et al. N Engl J Med 2018;378:1976–86

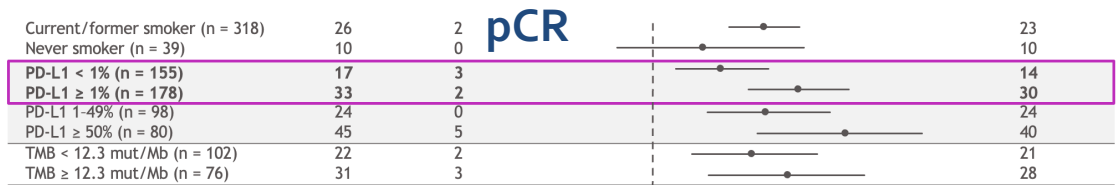
Correlation between tumour response and PD-L1 expression

NADIM II (pCR)[1]



CheckMate 816 (EFS)[2]

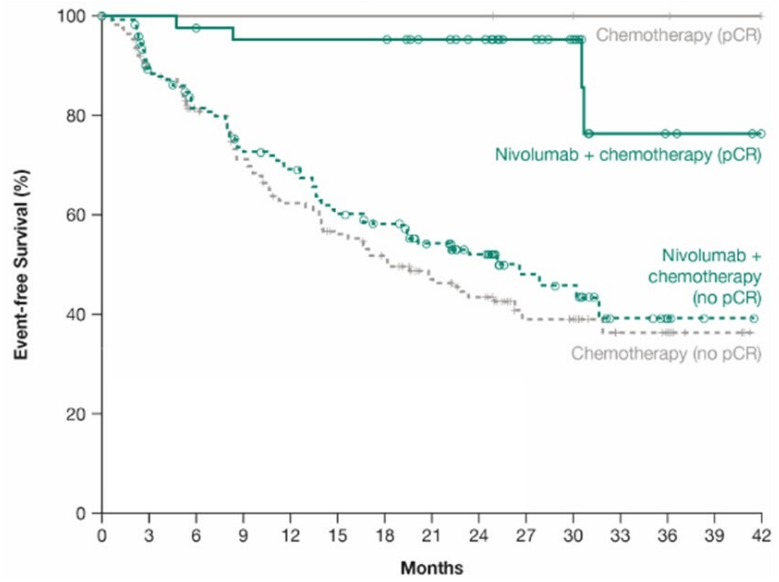




1. Provencio M, et al. Presented at ASCO 2022 (Abstract 8501); 2. Girard N, et al. Presented at AACR 2022 (Abstract CT012)

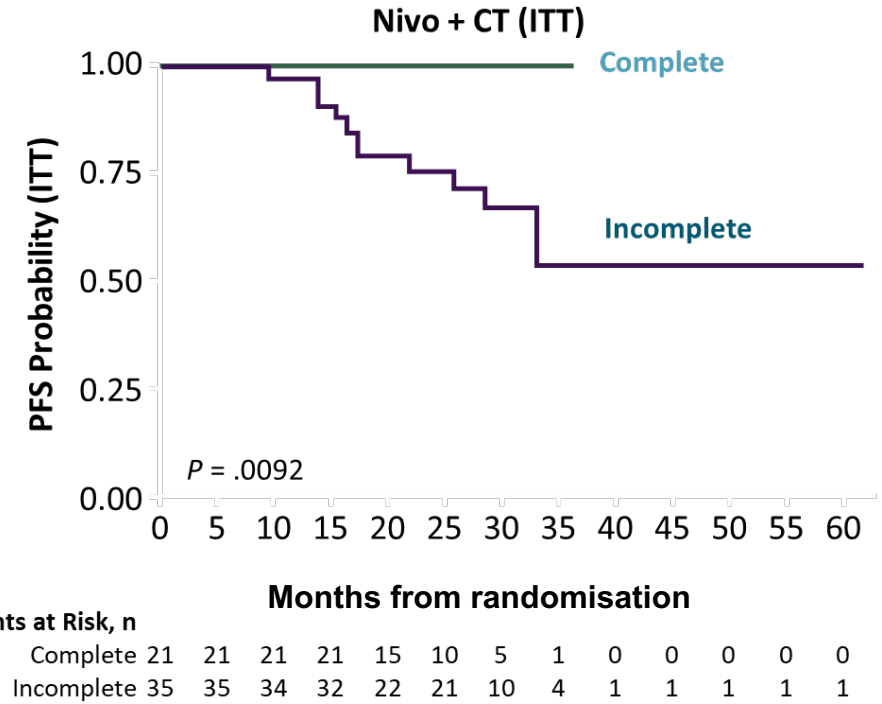
Pathologic response correlates with EFS outcomes

CheckMate 816[1]



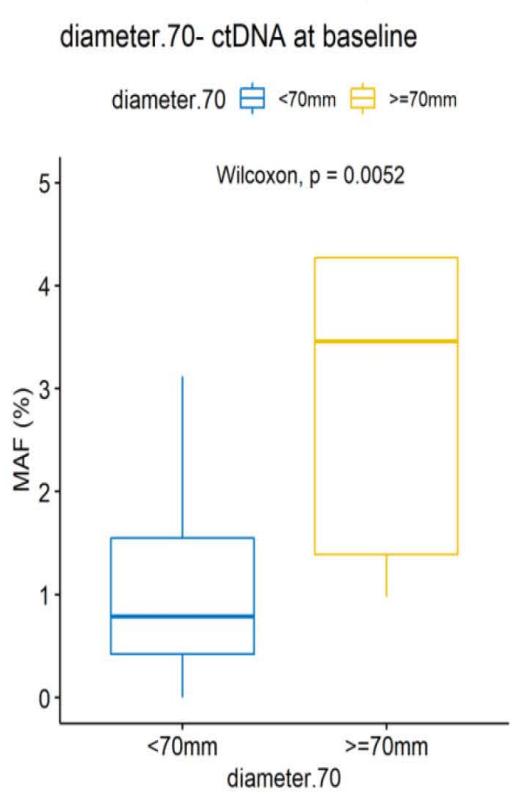
	Nivo + CT		CT	
	pCR	No pCR	pCR	No pCR
mEFS, months	NR	26.6	NR	18.4
HR (95% CI)	0.13 (0.05, 0.37)		Not computed*	

NADIM II[2]

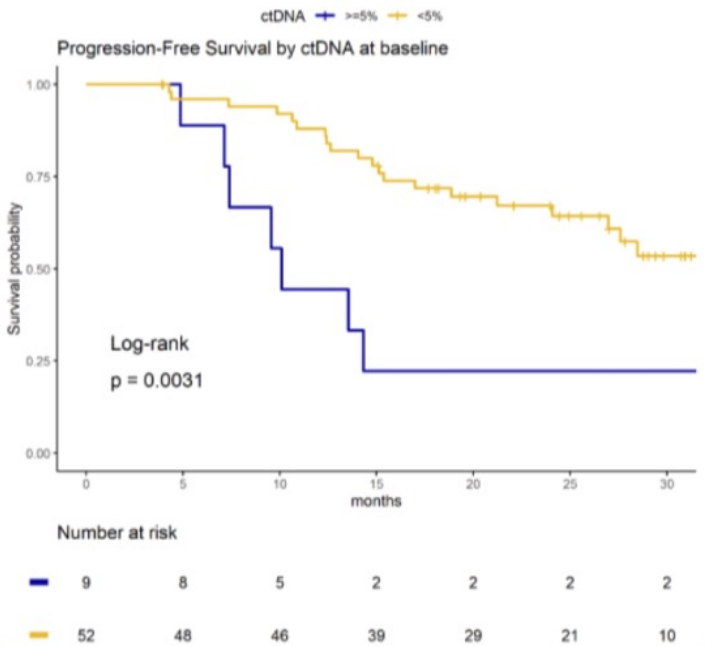


1. Forde PM, et al. N Engl J Med 2022;386:1973–85; 2. Provencio M, et al. Presented at WCLC 2022 (Abstract PL03.12)

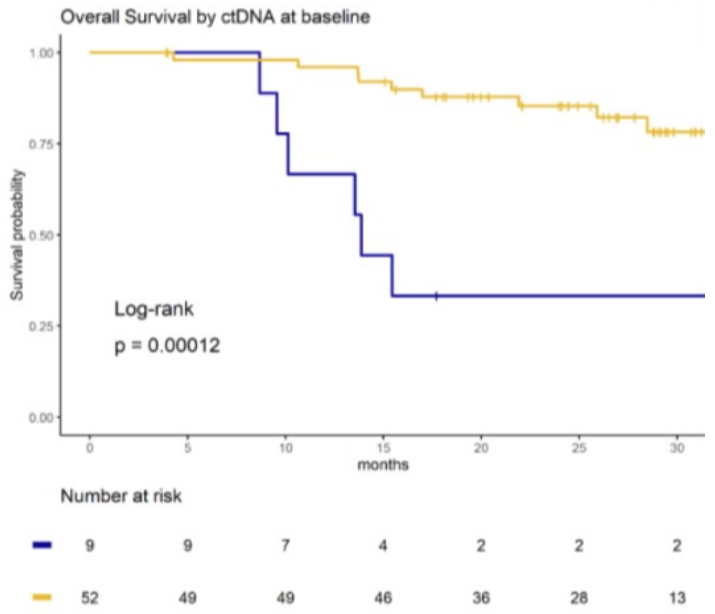
NADIM II: pre-treatment ctDNA levels significantly associated with tumour size and can predict PFS and OS outcomes



PFS by ctDNA at baseline



OS by ctDNA at baseline



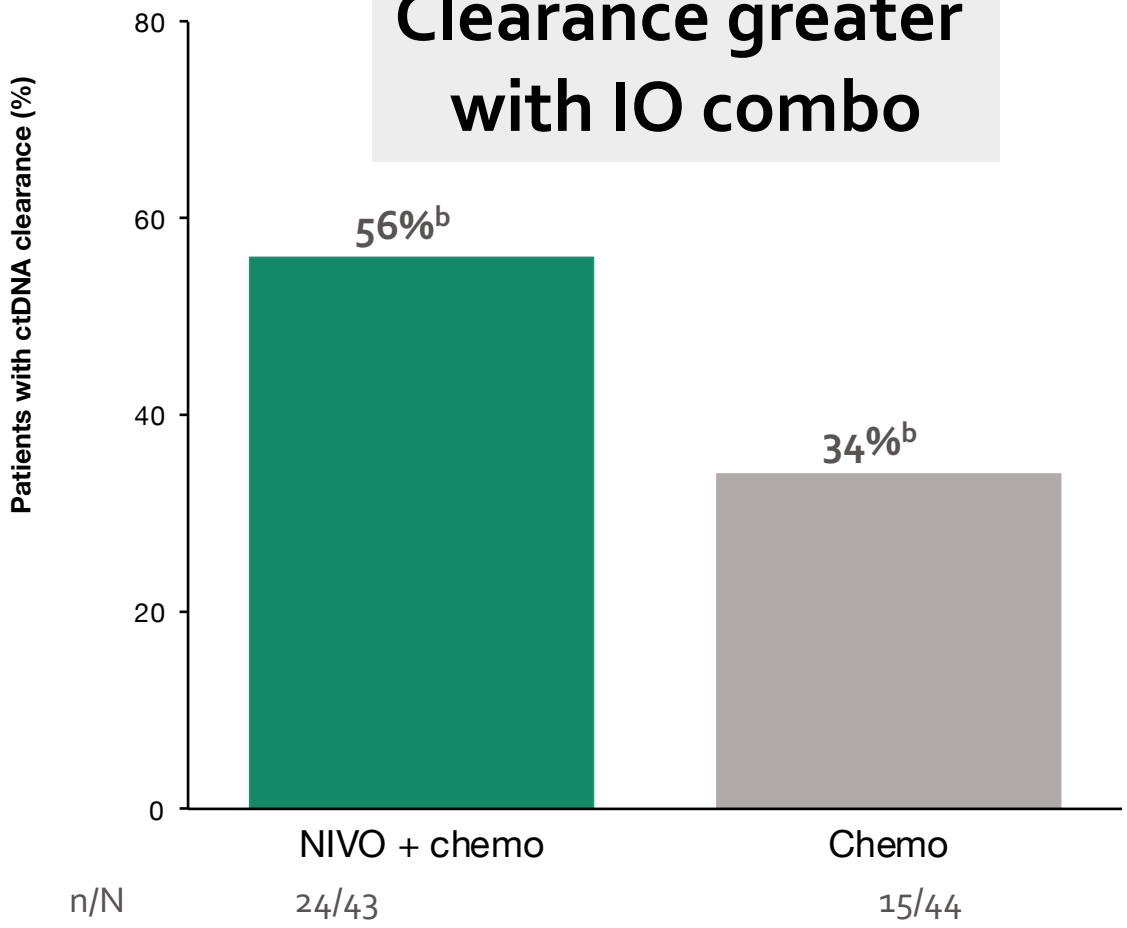
Median follow up time was 26.1 (IQR: 17.6-30.9) months

Romero A, et al. Presented at WCLC 2022 (Abstract MA06.03)

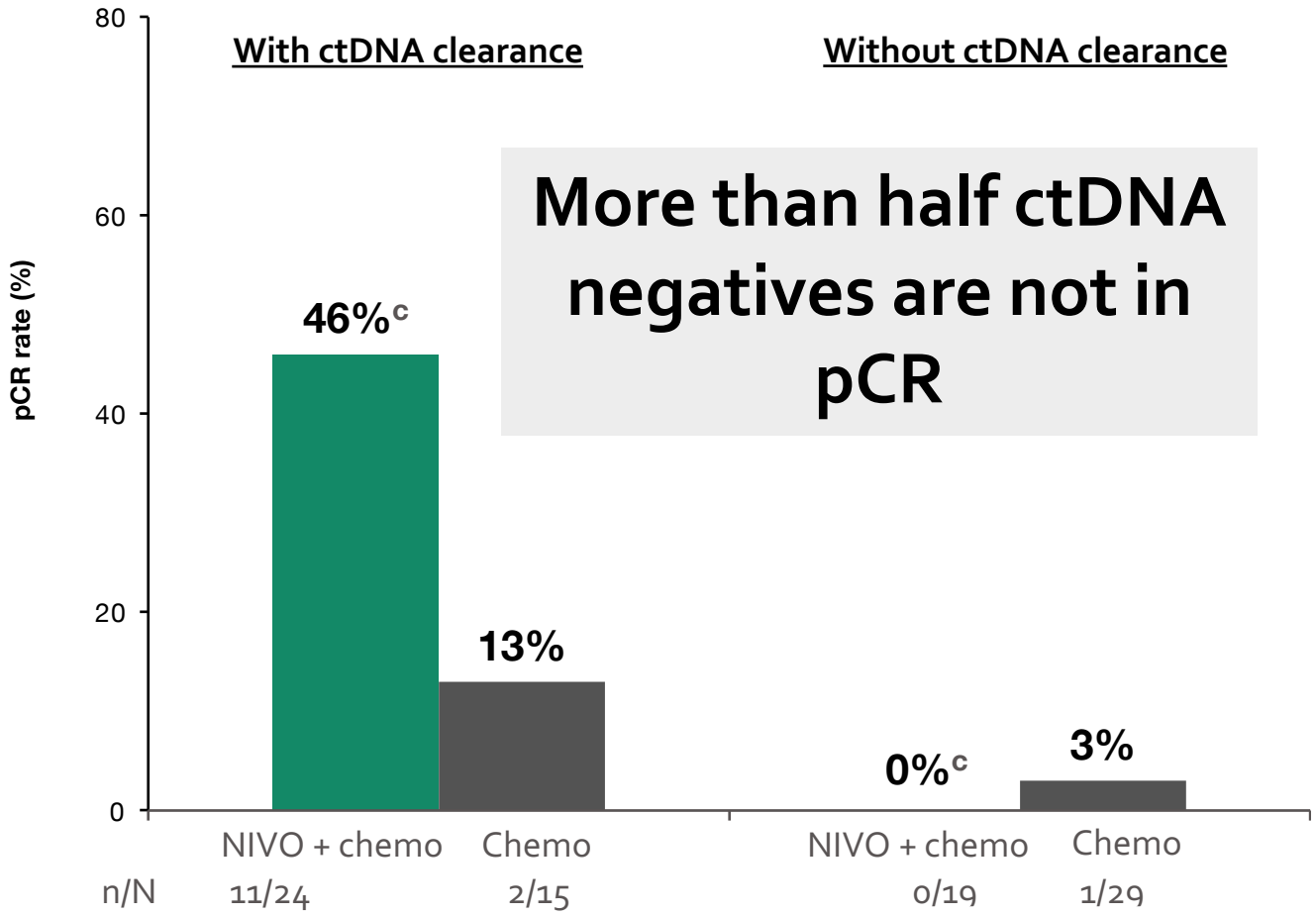
CM816: ctDNA clearance and association with pathological response

ARCHER private test - 1 ctDNA assessment before surgery after neo-adjuvant treatment

Clearance greater with IO combo



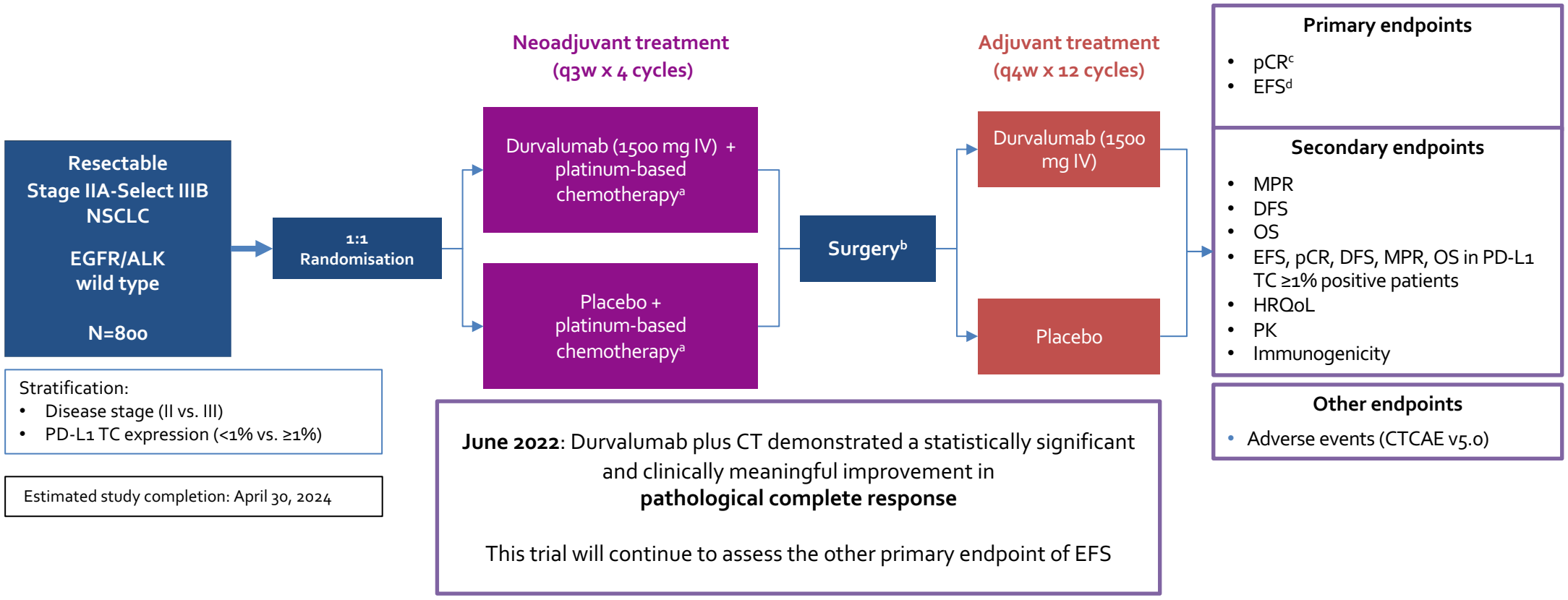
More than half ctDNA negatives are not in pCR



[a]Performed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring); 90 patients were ctDNA evaluable and 87 had detectable ctDNA at C1D1; main reason for sample attrition were lack of tissue for WES and lack of quality control pass for tissue and plasma; [b]ctDNA clearance 95% CI: NIVO + chemo, 40–71; chemo, 20–50; [c]pCR rates 95% CI: NIVO + chemo, 26–67; chemo, 0–18.

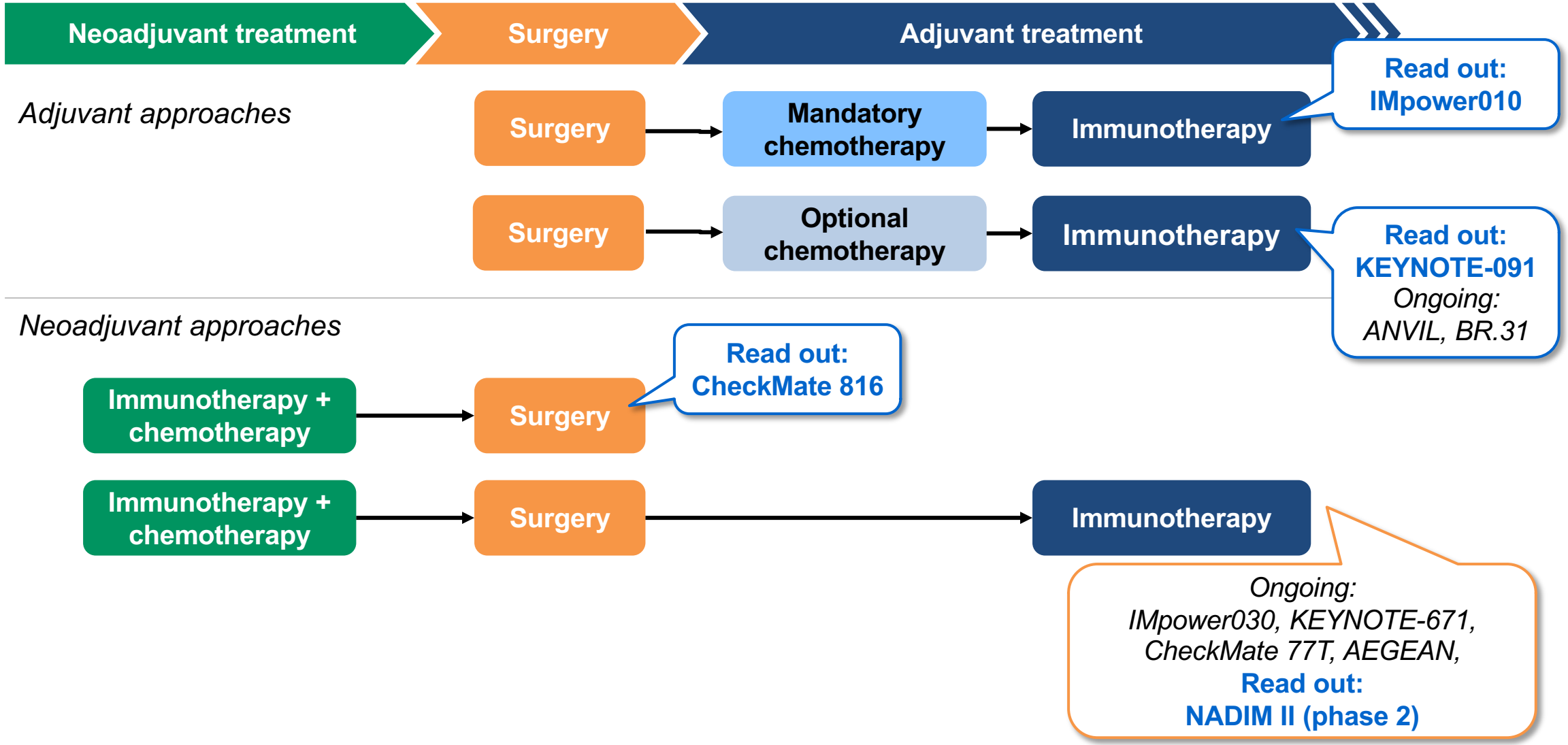
AEGEAN: further positive results with a perioperative regimen

Phase III, placebo-controlled, double-blind, randomised, multicenter study[1,2]



1. Study NCT03800134. ClinicalTrials.gov; 2. Heymach JV, et al. Clin Lung Cancer 2022;23(3):247–51

Several phase III studies with immunotherapy in resectable NSCLC will read soon…



Arguments for Neoadjuvant Immune Checkpoint Inhibition Followed by Surgical Resection

Higher antigen load and release from dying cells in untreated tumors

- ✓ Better priming of immune system

Fit host immune system, intact nodal stations

No significant clonal evolution

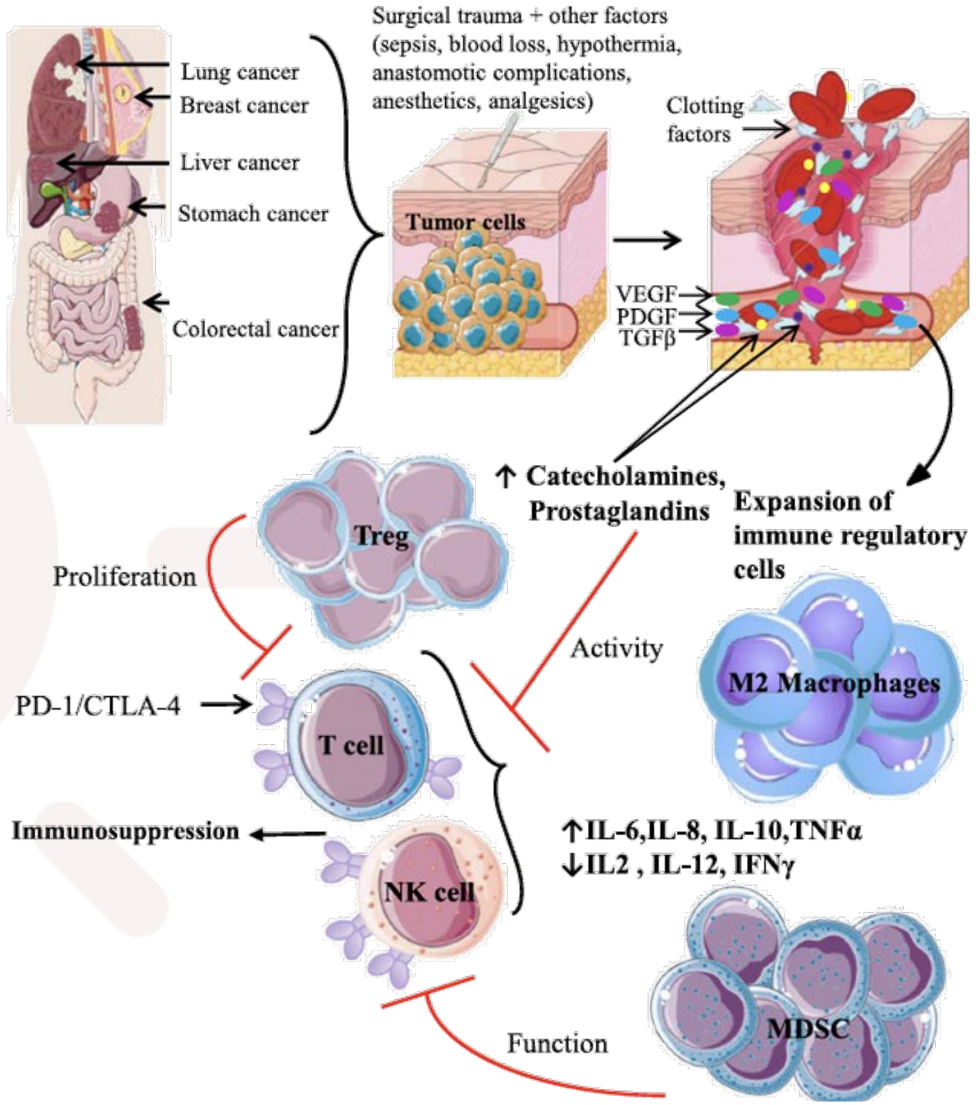
- ✓ Tumor less heterogeneous

Opportunity to accurately study the effects of IO

- ✓ Access to pre and post tissue

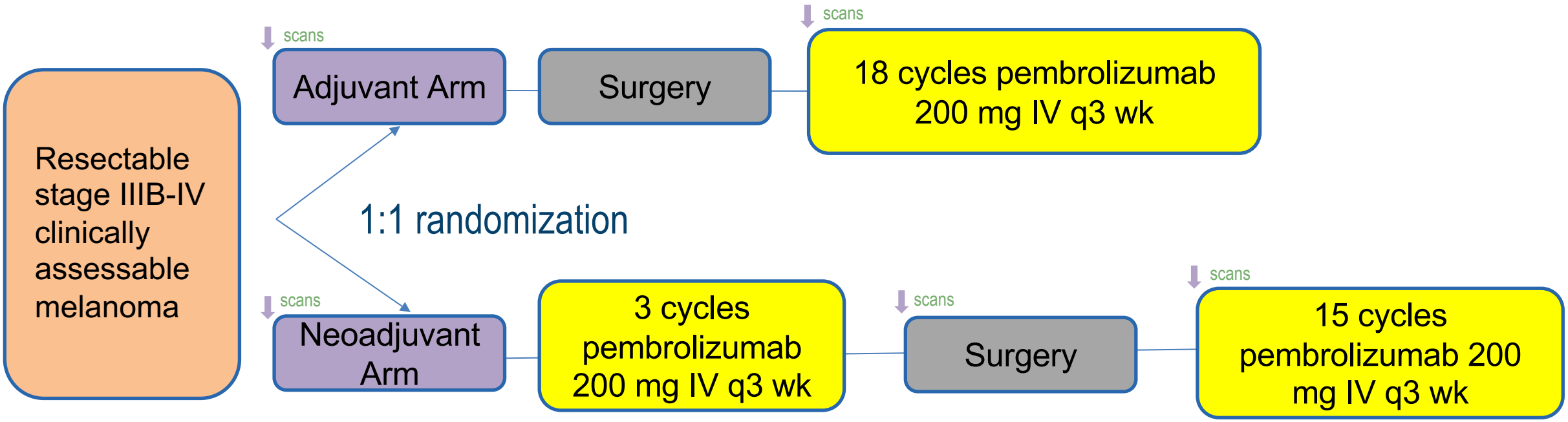
Ability to access efficacy of the therapy

Shorten timeframe to completion of trials (early surrogate for survival?)



S1801 Study Schema

Primary endpoint: Event-free survival

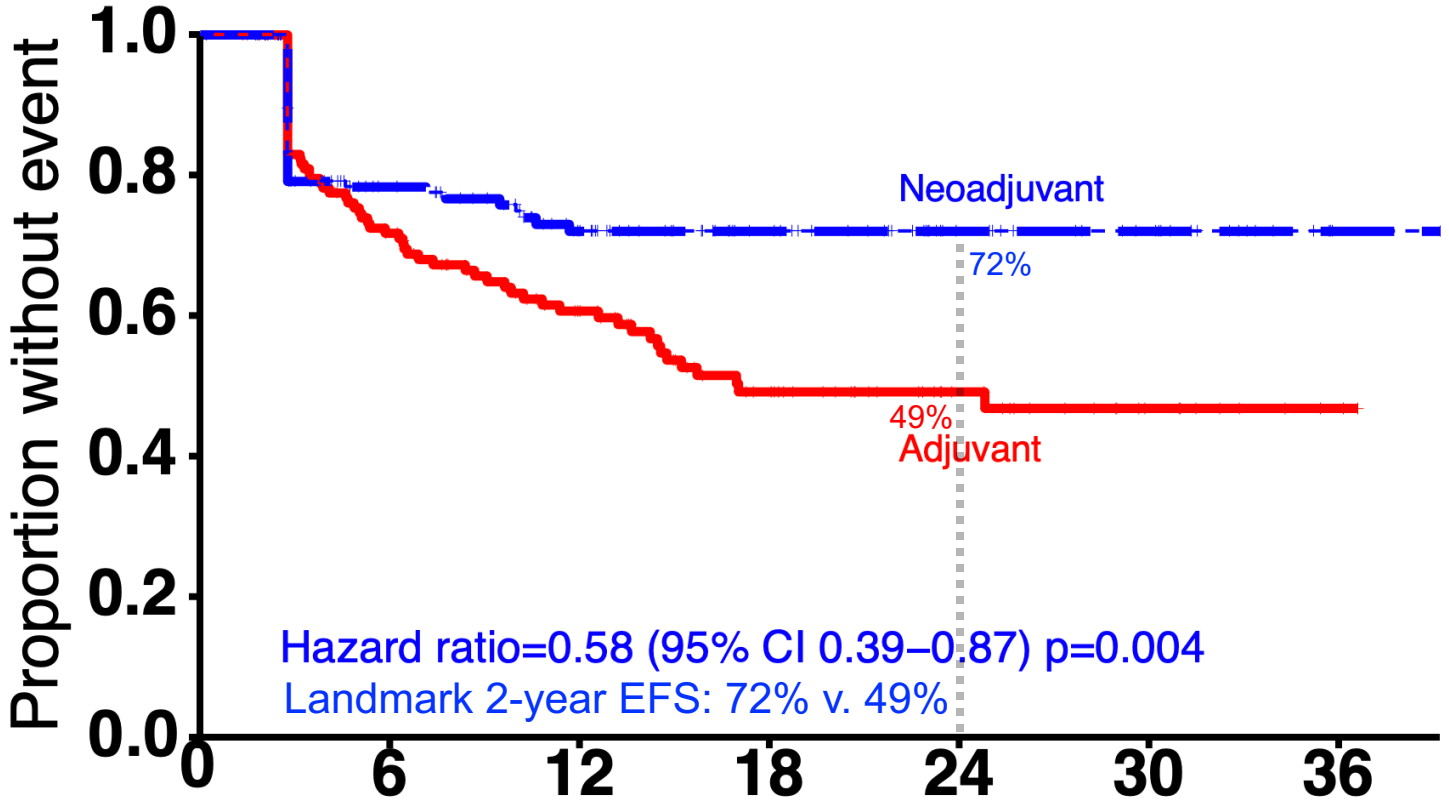


radiographic assessment (scans)

Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded

Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy

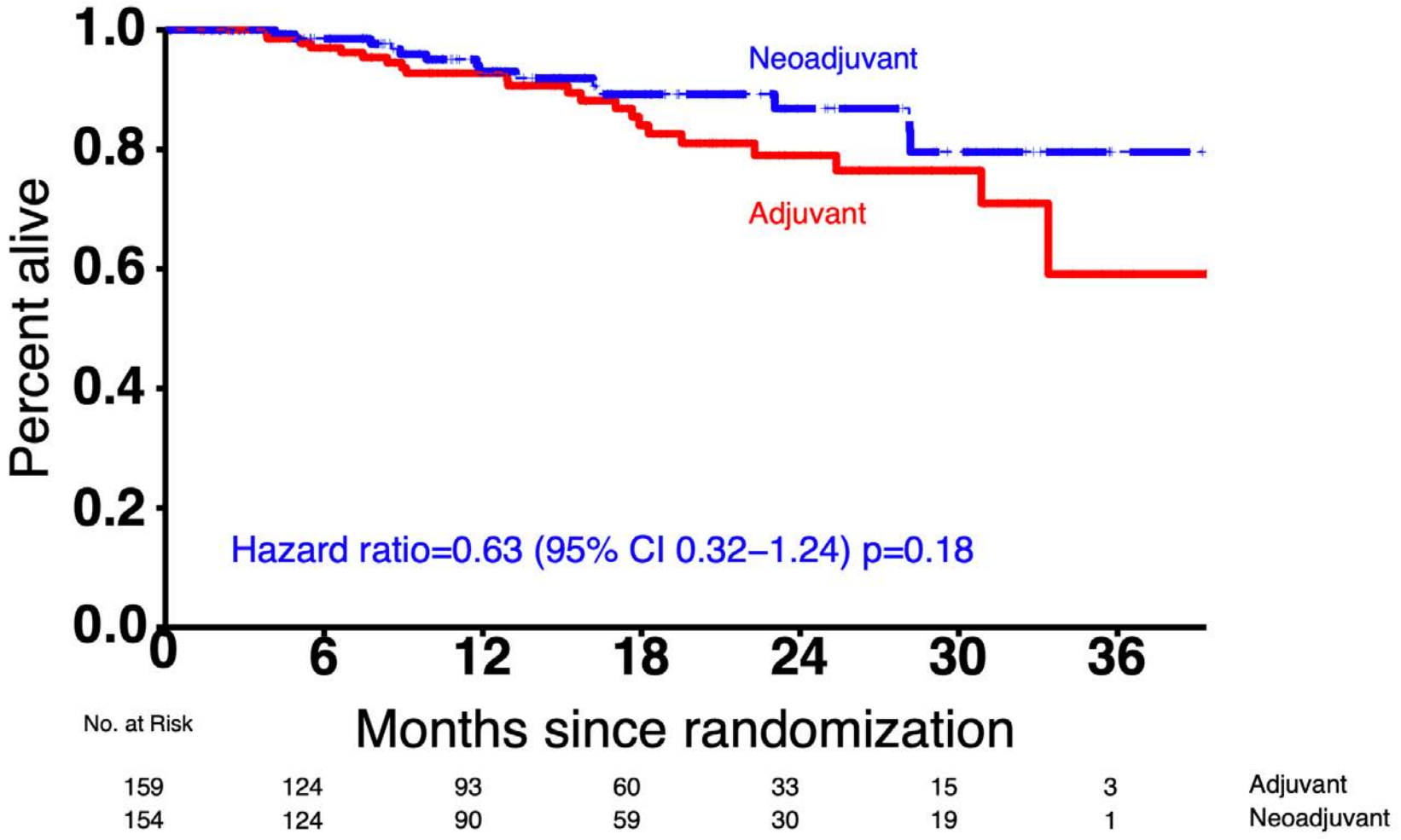
S1801 primary endpoint: Event-free survival



No. at Risk

159	98	67	40	22	10	2	Adjuvant
154	96	69	46	25	17	1	Neoadjuvant

Overall survival



PHASE III ADAURA STUDY DESIGN

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC
- Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Max. interval between surgery and randomisation:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomisation 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II / IIIA patients, designed for superiority under the assumed DFS HR of 0.70
- **Key secondary endpoints:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Pre-specified exploratory endpoints:** Patterns of recurrence, time to CNS disease recurrence or death (CNS DFS)

Masahiro Tsuboi, MD

*At the time of recruitment, staging was determined by the AJCC / UICC 7th edition staging manual. †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment. ¶Stage IB / II / IIIA.

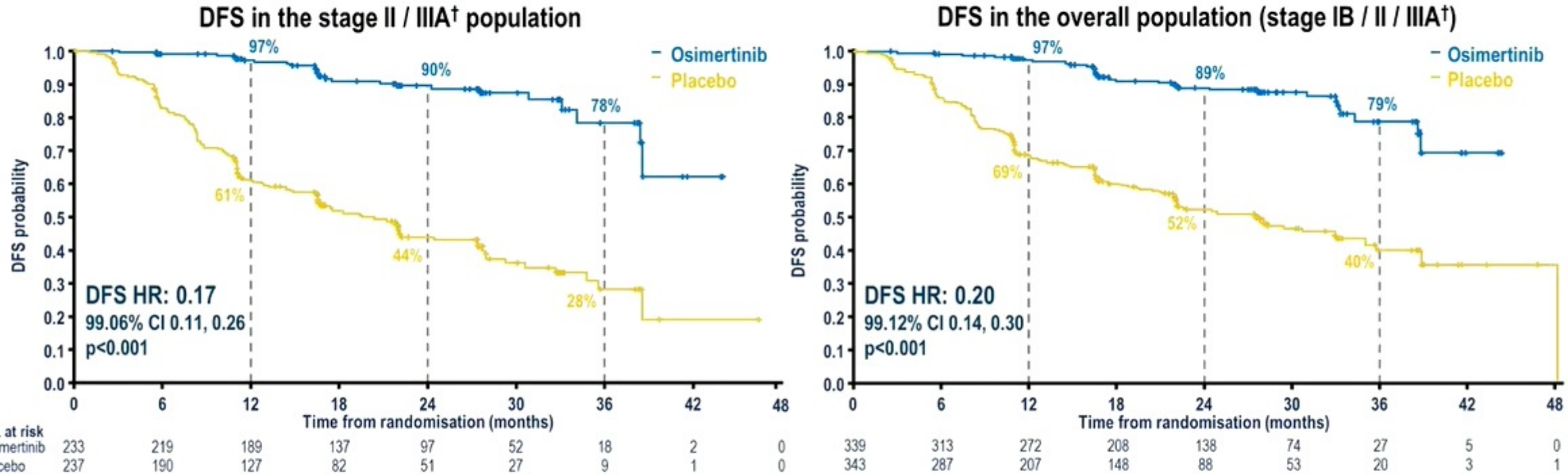
AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CNS, central nervous system; CT, computerized tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; WHO, World Health Organization

Balanced Demographic and Clinical Characteristics at Baseline

Characteristic, %	Osimertinib (n = 339)	Placebo (n = 343)
Female	68	72
Median age, yrs (range)	64 (30-86)	62 (31-82)
Smoker/nonsmoker*	32/68	25/75
Asian/non-Asian	64/36	64/36
WHO PS 0/1	64/36	64/36
AJCC staging at diagnosis (7th edition)		
▪ IB	31	31
▪ II	35	34
▪ IIIA	34	35
Adenocarcinoma/other histology†	95/5	96/4
EGFR ex19del/L858R	55/45	56/44
Prior adjuvant CT	55	56

DFS BENEFIT WITH ADJUVANT OSIMERTINIB: ADAURA PRIMARY ANALYSIS

- The ADAURA primary analysis* showed a highly statistically significant and clinically meaningful improvement in DFS with adjuvant osimertinib vs placebo[1,2]



Here we will present an updated analysis of the final DFS data at the protocol-specified maturity of 50%, a pre-specified exploratory analysis of recurrence patterns and updated safety data, after 2 years of further follow up, in which all patients have had the opportunity to receive the full 3 years of adjuvant treatment

PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

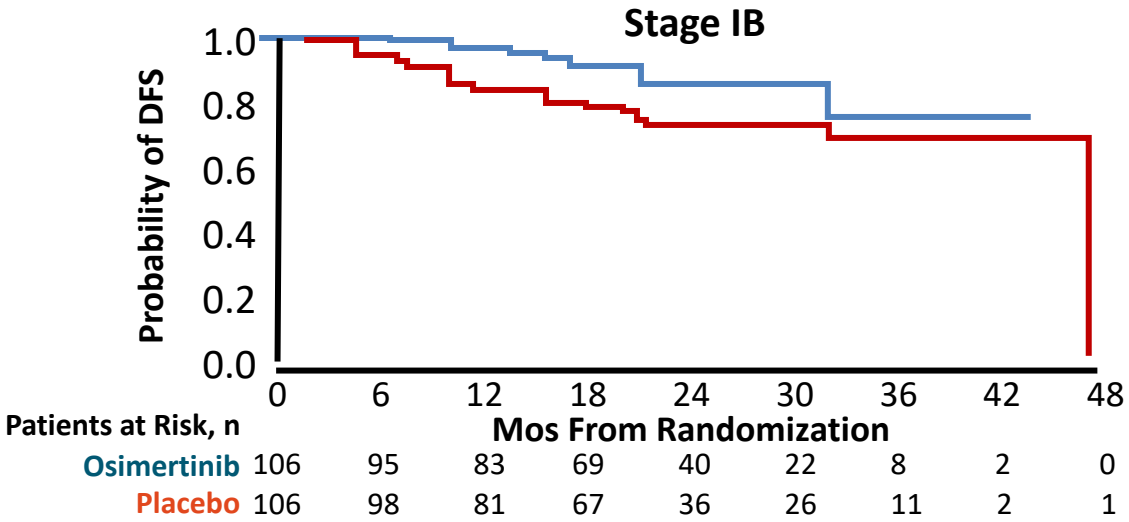
Tick marks indicate censored data. *Reported ~2 years earlier than planned following IDMC recommendation. †AJCC / UICC 7th edition staging.

1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38:18_suppl LBA5.

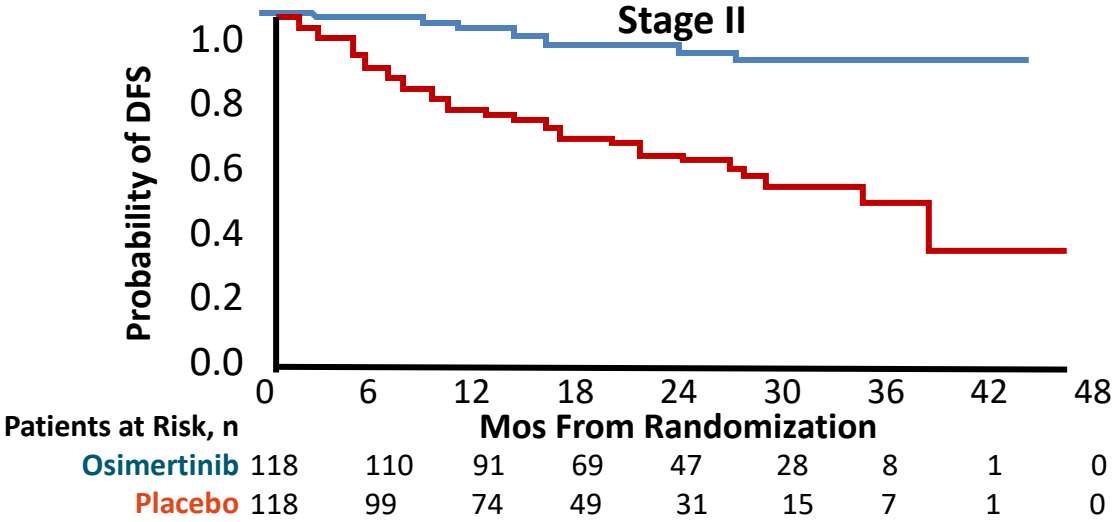
AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IDMC, Independent Data Monitoring Committee

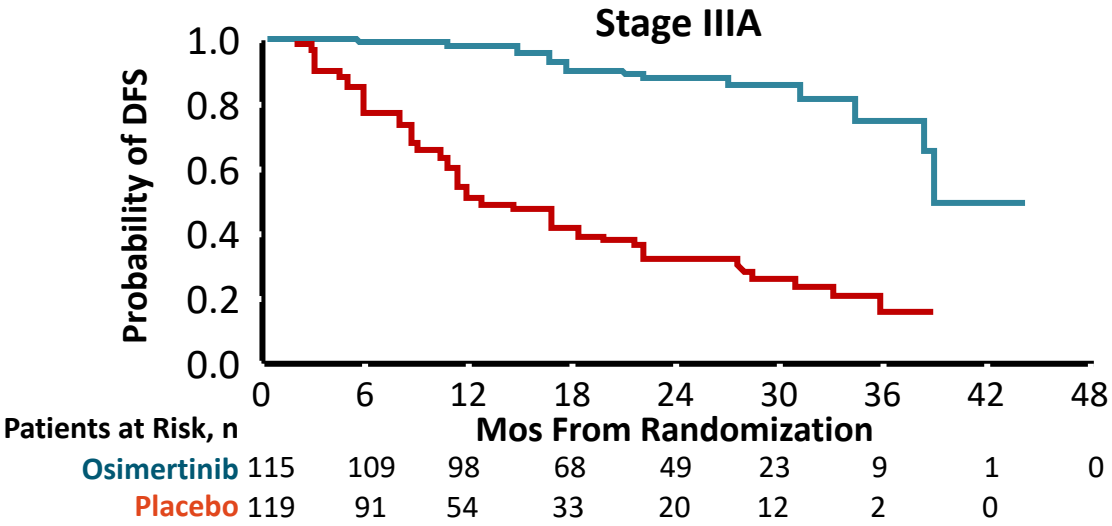
Data cut-off: January 17, 2020.

ADAURA: DFS is superior with Osimertinib across all stages IB-IIIA



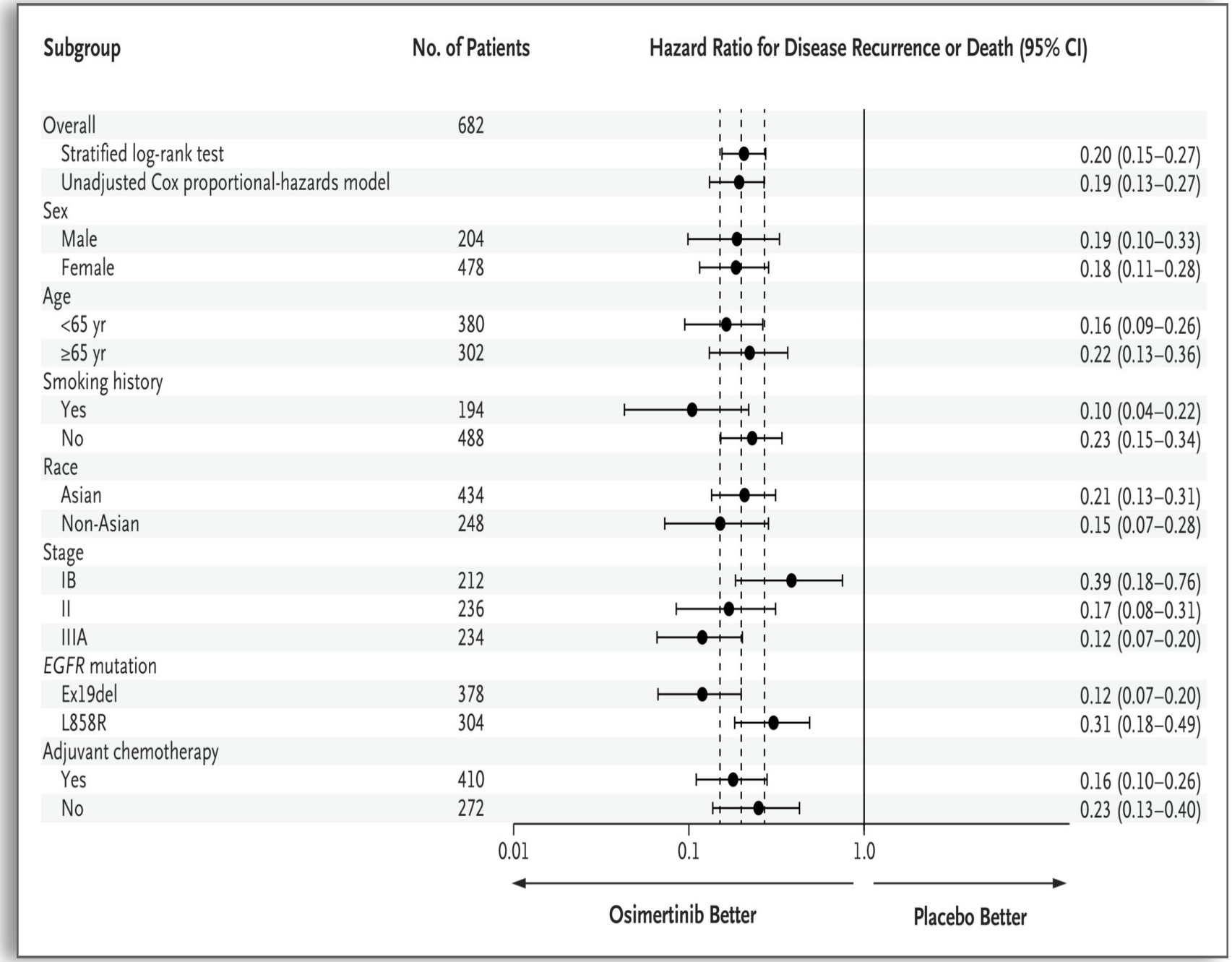
	Stage IB	Stage II	Stage IIIA
2-yr DFS rate, %			
Osimertinib	87	91	88
Placebo	73	56	32
Overall HR (95% CI)	0.39 (0.18-0.76)	0.17 (0.08-0.31)	0.12 (0.07-0.20)





Wu Y-L, et al. N Engl J Med 2020;383:1711-1723

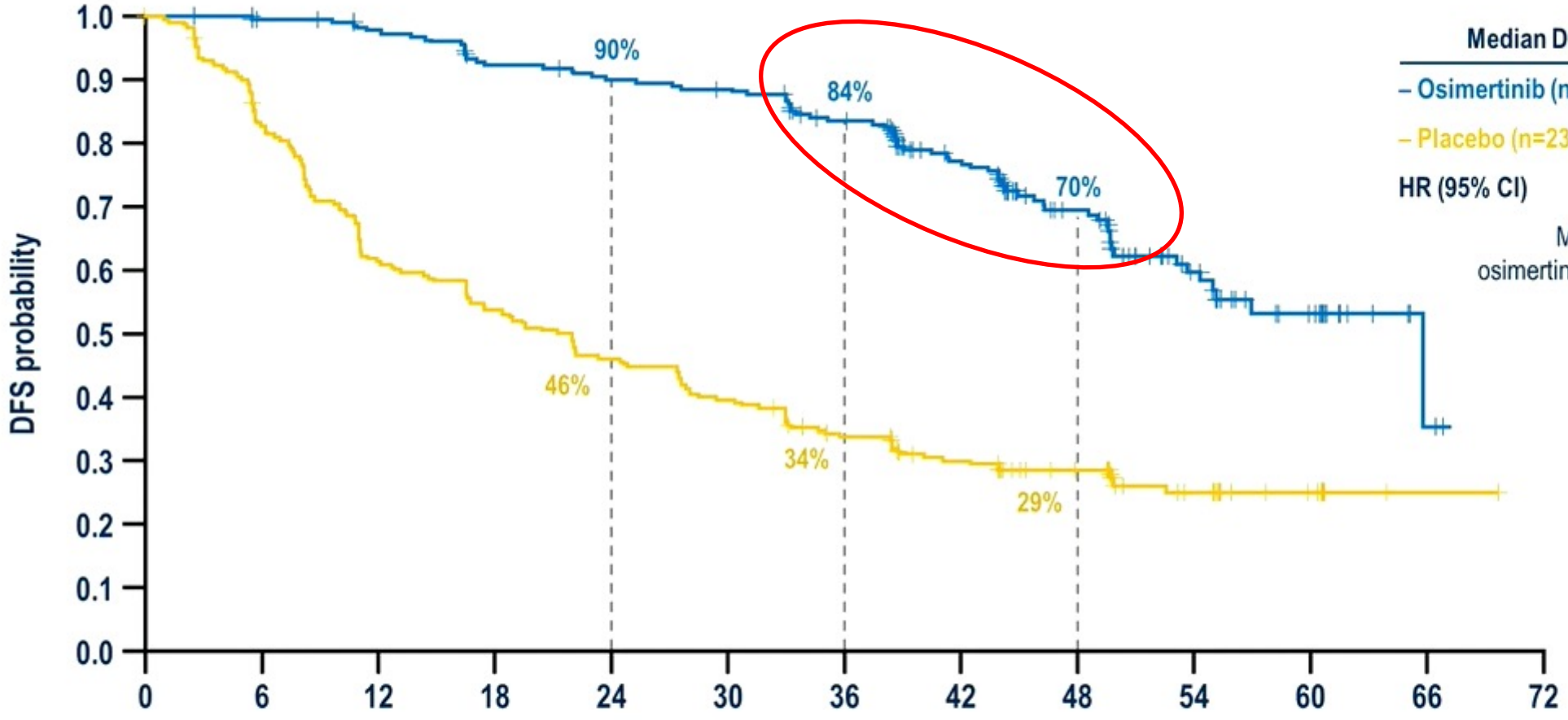
Subgroup Analysis
Disease Recurrence or Death



The benefit favoring osimertinib observed consistently across all predefined subgroups.

Wu Y-L, et al. N Engl J Med 2020;383:1711-1723

PRIMARY ENDPOINT: UPDATED DFS IN STAGE II / IIIA DISEASE



Median DFS, months (95% CI)	
– Osimertinib (n=233)	65.8 (54.4, NC)
– Placebo (n=237)	21.9 (16.6, 27.5)
HR (95% CI)	**0.23 (0.18, 0.30)**

Maturity:* 51%
osimertinib 32%, placebo 70%

No. at risk													
Osimertinib	233	222	216	202	196	192	174	138	90	45	20	2	0
Placebo	237	191	141	124	106	91	74	61	41	23	11	1	0

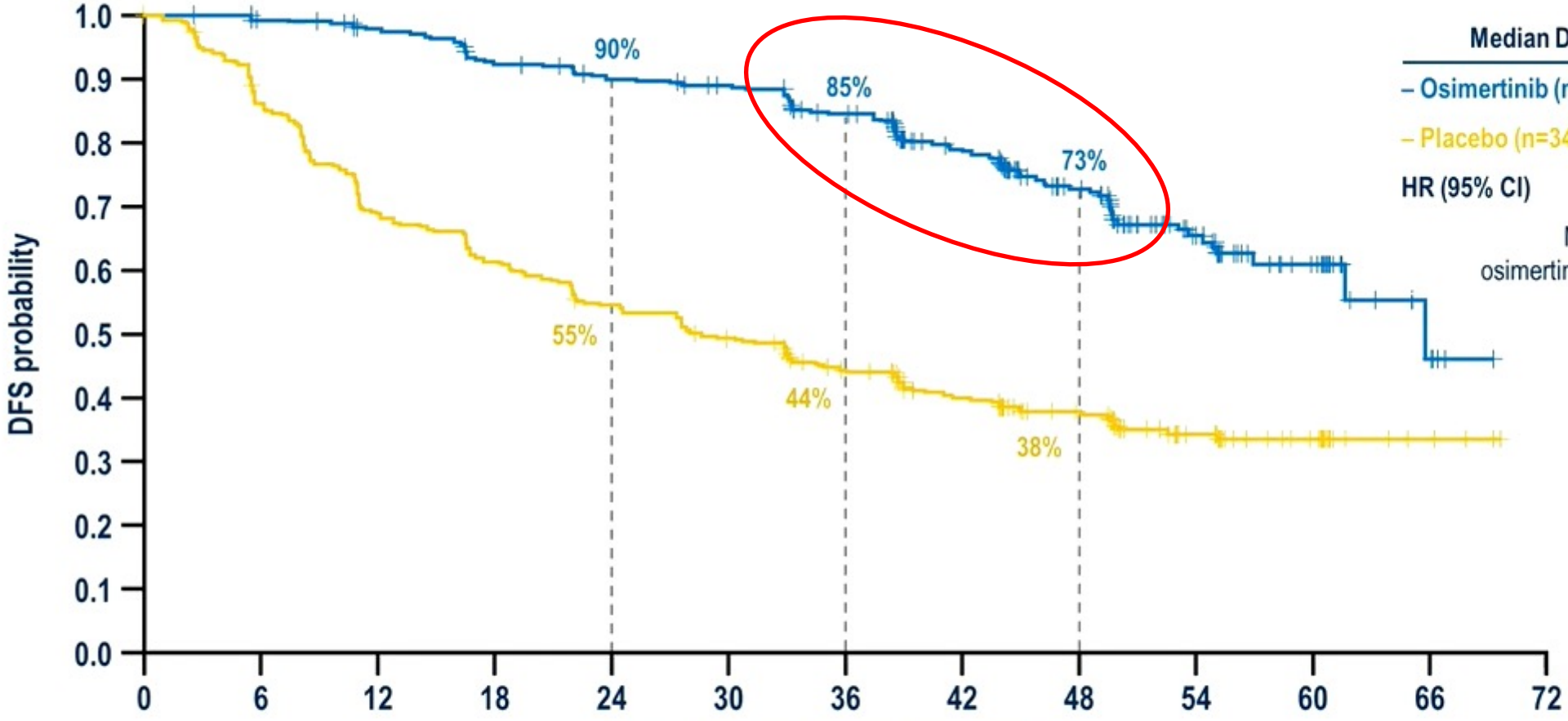
PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

Median follow-up: osimertinib 44.2 months (range 0 to 67), placebo 19.6 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data. *Planned maturity for DFS analysis: 50%.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable
Data cut-off: April 11, 2022.

UPDATED DFS IN THE OVERALL POPULATION (STAGE IB / II / IIIA DISEASE)



Median DFS, months (95% CI)	
– Osimertinib (n=339)	65.8 (61.7, NC)
– Placebo (n=343)	28.1 (22.1, 35.0)
HR (95% CI)	**0.27 (0.21, 0.34)**

Maturity 45%:
osimertinib 28%, placebo 62%

No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

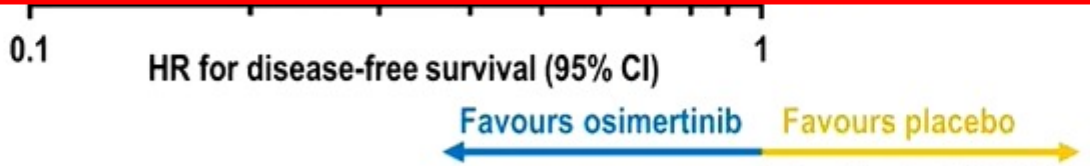
Median follow-up: osimertinib 44.2 months (range 0 to 69), placebo 27.7 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data.

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable
Data cut-off: April 11, 2022.

UPDATED DFS ACROSS SUBGROUPS IN THE OVERALL POPULATION

- A DFS benefit with osimertinib was observed across all predefined subgroups

Subgroup		HR	95% CI
Overall (N=682)	Stratified log-rank	0.27	0.21, 0.34
	Unadjusted Cox PH	0.32	0.25, 0.40
Sex	Male (n=204)	0.31	0.20, 0.48
	Female (n=478)	0.31	0.23, 0.42
Age	<65 yr (n=380)	0.31	0.22, 0.42
	≥65 yr (n=302)	0.33	0.23, 0.48
Smoking history	Yes (n=194)	0.26	0.16, 0.40
	No (n=488)	0.34	0.26, 0.45
Race	Asian (n=434)	0.34	0.25, 0.45
	Non-Asian (n=248)	0.28	0.18, 0.43
Stage*	IB (n=212)	0.41	0.23, 0.69
	II (n=236)	0.34	0.23, 0.52
	IIIA (n=234)	0.20	0.14, 0.29
EGFR mutation	Ex19Del (n=378)	0.24	0.17, 0.33
	L858R (n=304)	0.45	0.31, 0.64
Adjuvant chemotherapy	Yes (n=410)	0.29	0.21, 0.39
	No (n=272)	0.36	0.24, 0.55



Overall population: stage IB / II / IIIA; DFS by investigator assessment. *AJCC / UICC 7th edition.

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; yr, year.
Data cut-off: April 11, 2022.

Table 2. Adverse Events.*

Adverse Event	Osimertinib (N=337)				Placebo (N=343)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
	number of patients (percent)							
Diarrhea	156 (46)	116 (34)	32 (9)	8 (2)	68 (20)	54 (16)	13 (4)	1 (<1)
Paronychia	85 (25)	31 (9)	50 (15)	3 (1)	5 (1)	3 (1)	2 (1)	0
Dry skin	79 (23)	75 (22)	3 (1)	1 (<1)	22 (6)	18 (5)	4 (1)	0
Pruritus	65 (19)	49 (15)	16 (5)	0	30 (9)	28 (8)	2 (1)	0
Cough	62 (18)	43 (13)	19 (6)	0	57 (17)	42 (12)	15 (4)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)	14 (4)	10 (3)	4 (1)	0
Nasopharyngitis	47 (14)	30 (9)	17 (5)	0	35 (10)	25 (7)	10 (3)	0
Upper respiratory tract infection	45 (13)	24 (7)	19 (6)	2 (1)	35 (10)	19 (6)	16 (5)	0
Decreased appetite	44 (13)	29 (9)	13 (4)	2 (1)	13 (4)	9 (3)	4 (1)	0
Mouth ulceration	39 (12)	32 (9)	7 (2)	0	8 (2)	6 (2)	2 (1)	0
Dermatitis acneiform	37 (11)	29 (9)	8 (2)	0	16 (5)	12 (3)	4 (1)	0

* Listed are adverse events that were reported in at least 10% of the patients in either trial group, according to the maximum Common Terminology Criteria for Adverse Events grade and preferred term. The safety analyses included all the patients who received at least one dose of osimertinib or placebo (safety analysis set). None of the adverse events reported in at least 10% of the patients in either trial group were determined to be grade 4 or higher.

Adverse Events

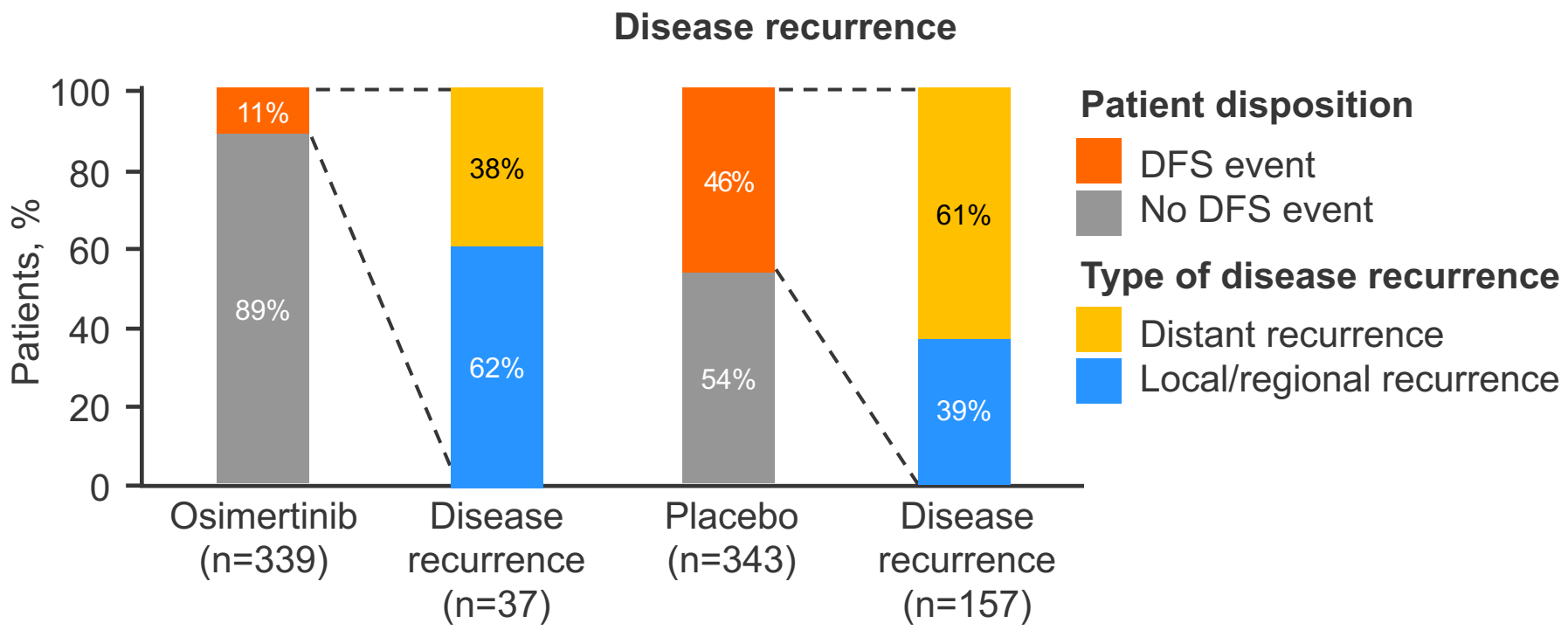
	O	P
Discontinue:	11% vs 3%	
Reduction:	9% vs 1%	
G3+:	20% vs 13%	
G5:	0 vs 1 (PE)	
ILD:	3% vs 0%	
QTc:	7% vs 1%	

Wu Y-L, et al. N Engl J Med 2020;383:1711-1723

WHERE ARE THE RECURRENCES?

ADAURA: Osimertinib associated with reduced distant metastasis upon relapse vs placebo

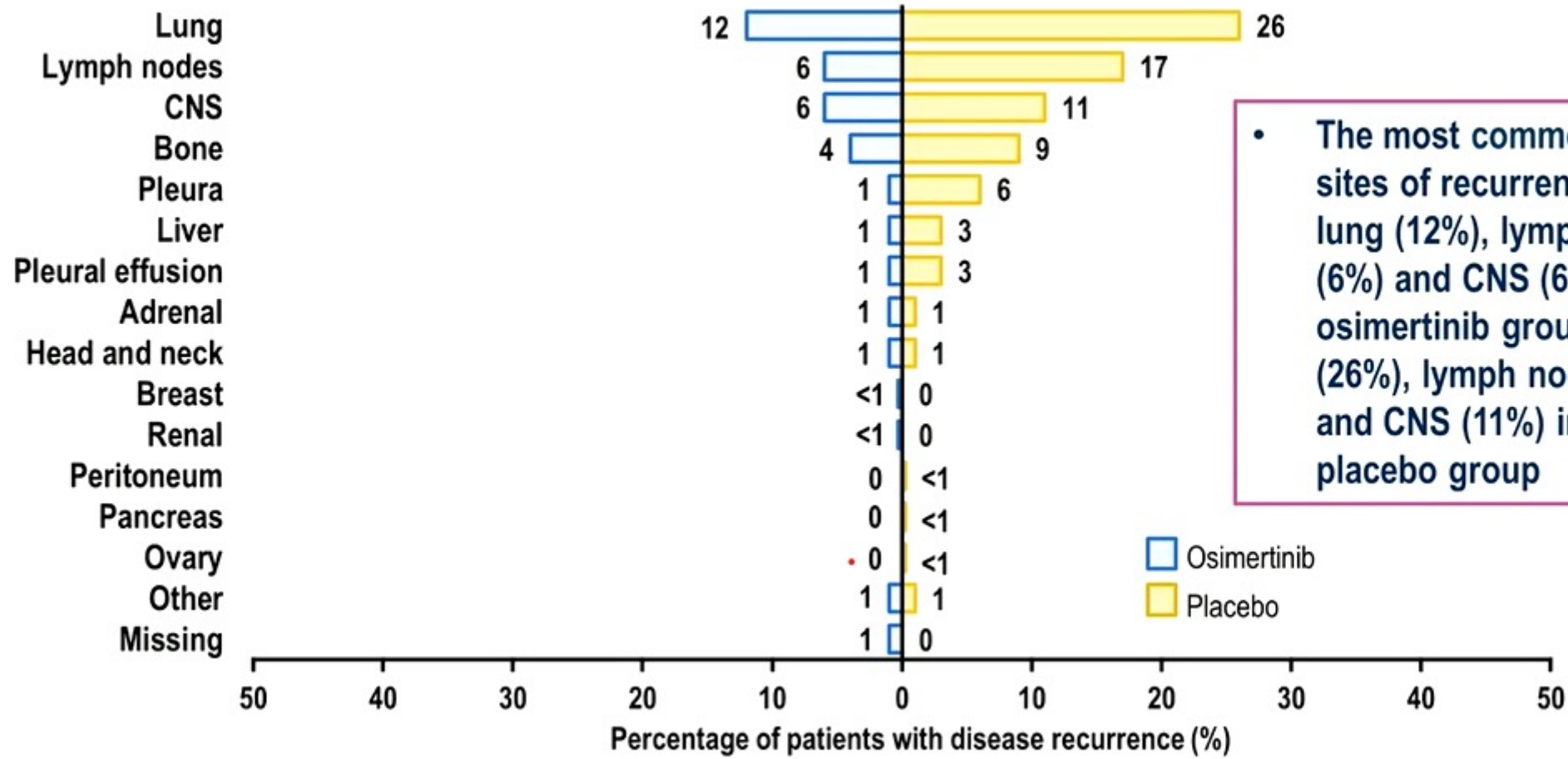
Updated Median DFS (95%CI), months	Osimertinib	Placebo	HR
Stage II/IIIA	NR (38.8, NC)	19.6 (16.6, 24.5)	0.17 (99.06%CI 0.11, 0.26); p<0.0001
Stage IB/II/IIIA	NR (NC, NC)	27.5 (22.0, 35.0)	0.20 (99.21%CI 0.14, 0.30); p<0.0001



Tsuboi M, et al. Ann Oncol 2020;31(suppl):Abstr LBA1

PATTERNS OF DISEASE RECURRENCE (OVERALL POPULATION)

- In the overall population, fewer patients treated with osimertinib had disease recurrence (93/339; 27%) compared with placebo (205/343; 60%)*



- **The most common first sites of recurrence were lung (12%), lymph nodes (6%) and CNS (6%) in the osimertinib group, and lung (26%), lymph nodes (17%) and CNS (11%) in the placebo group**

PARIS 2022 ESMO congress

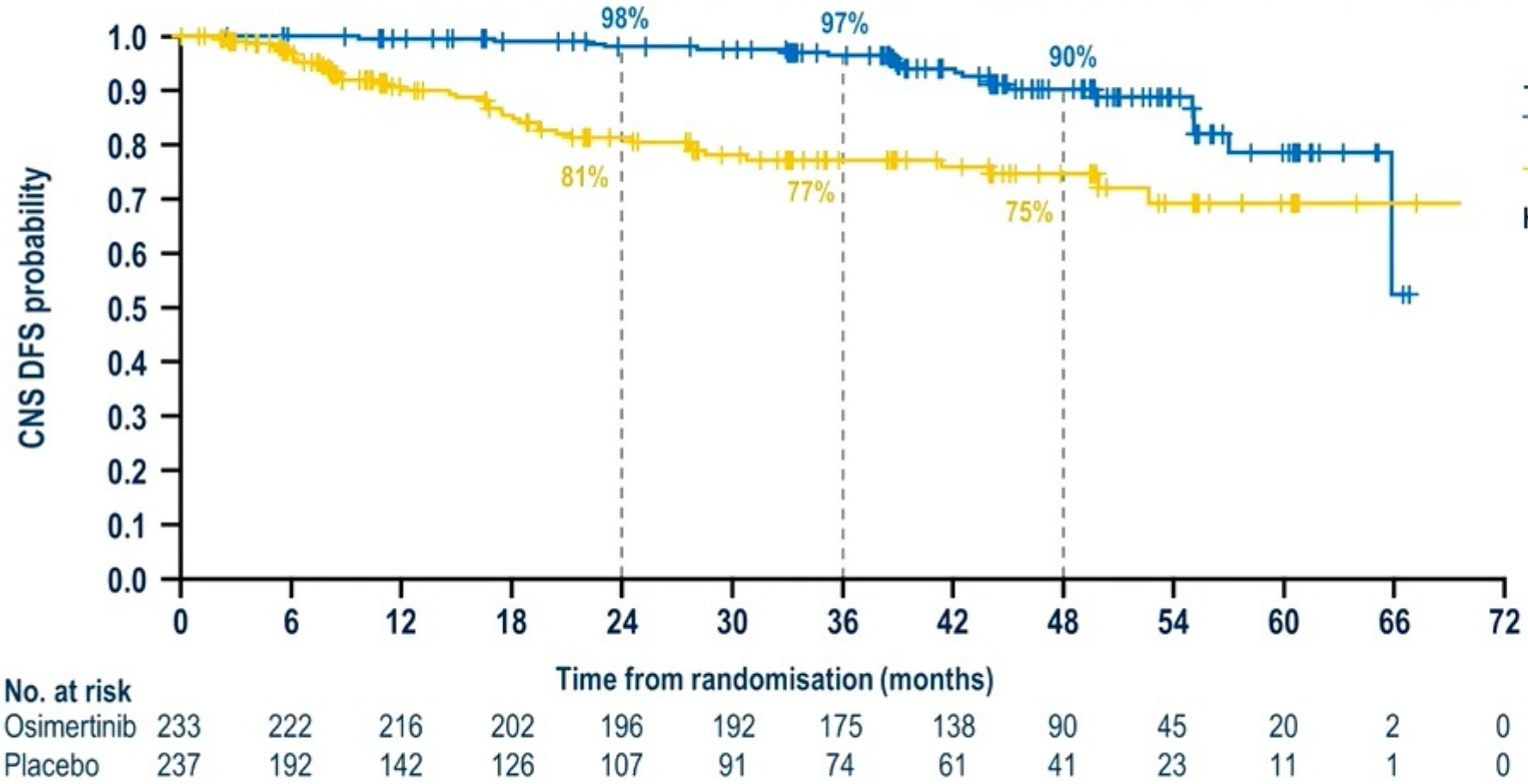
Masahiro Tsuboi, MD

*Distant recurrence only: osimertinib 45/339 (13%), placebo 107/343 (31%); local/regional only: osimertinib 42/339 (12%), placebo 78/343 (23%); local/regional and distant: osimertinib 6/339 (2%), placebo 20/343 (6%).

CNS, central nervous system
Data cut-off: April 11, 2022.

UPDATED CNS DFS IN PATIENTS WITH STAGE II / IIIA DISEASE

- Overall, 63 patients (osimertinib n=22, placebo n=41) had CNS DFS events:*
  - 3 (14%) patients were on treatment at the time of CNS recurrence with osimertinib, versus 29 (71%) with placebo



No. at risk													
Osimertinib	233	222	216	202	196	192	175	138	90	45	20	2	0
Placebo	237	192	142	126	107	91	74	61	41	23	11	1	0

Median CNS DFS, months (95% CI)	
– Osimertinib	NR (65.8, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.24 (0.14, 0.42)**

Maturity 13%:
osimertinib 9%, placebo 17%

PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

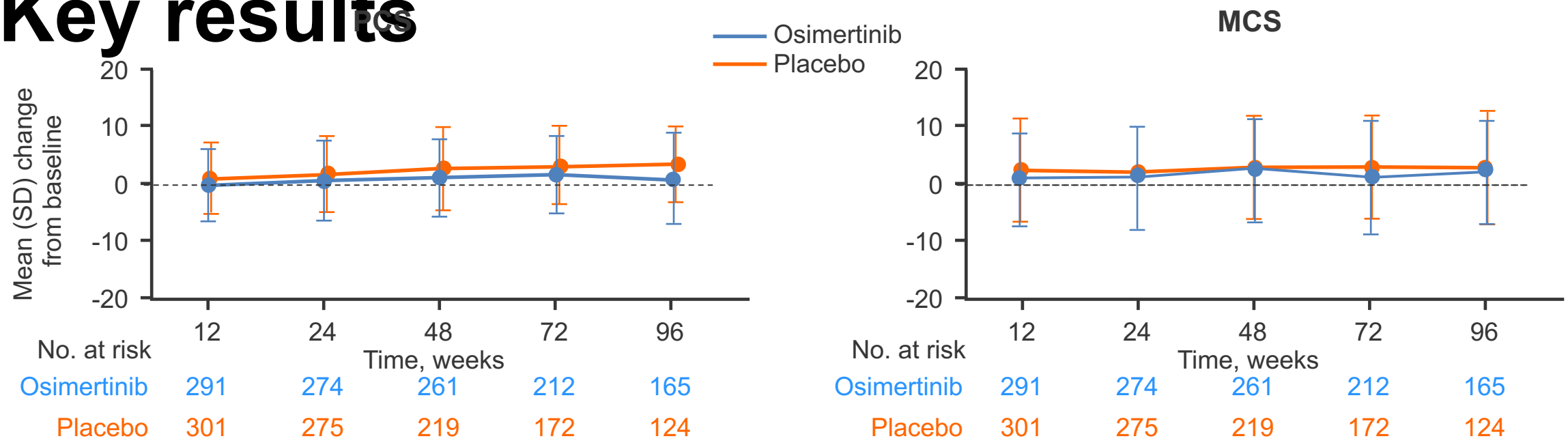
Median follow-up: osimertinib 44.2 months, placebo 20.4 months; DFS by investigator assessment; Tick marks indicate censored data.
*Defined as CNS as the first site of disease recurrence, or death without any disease recurrence.

CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio; NC, not calculable; NR, not reached
Data cut-off: April 11, 2022.

QUALITY OF LIFE?

Patient-Reported Outcomes from ADAURA: Osimertinib as Adjuvant Therapy in Patients with Resected EGFR Mutated (EGFRm) NSCLC

- **Key results**

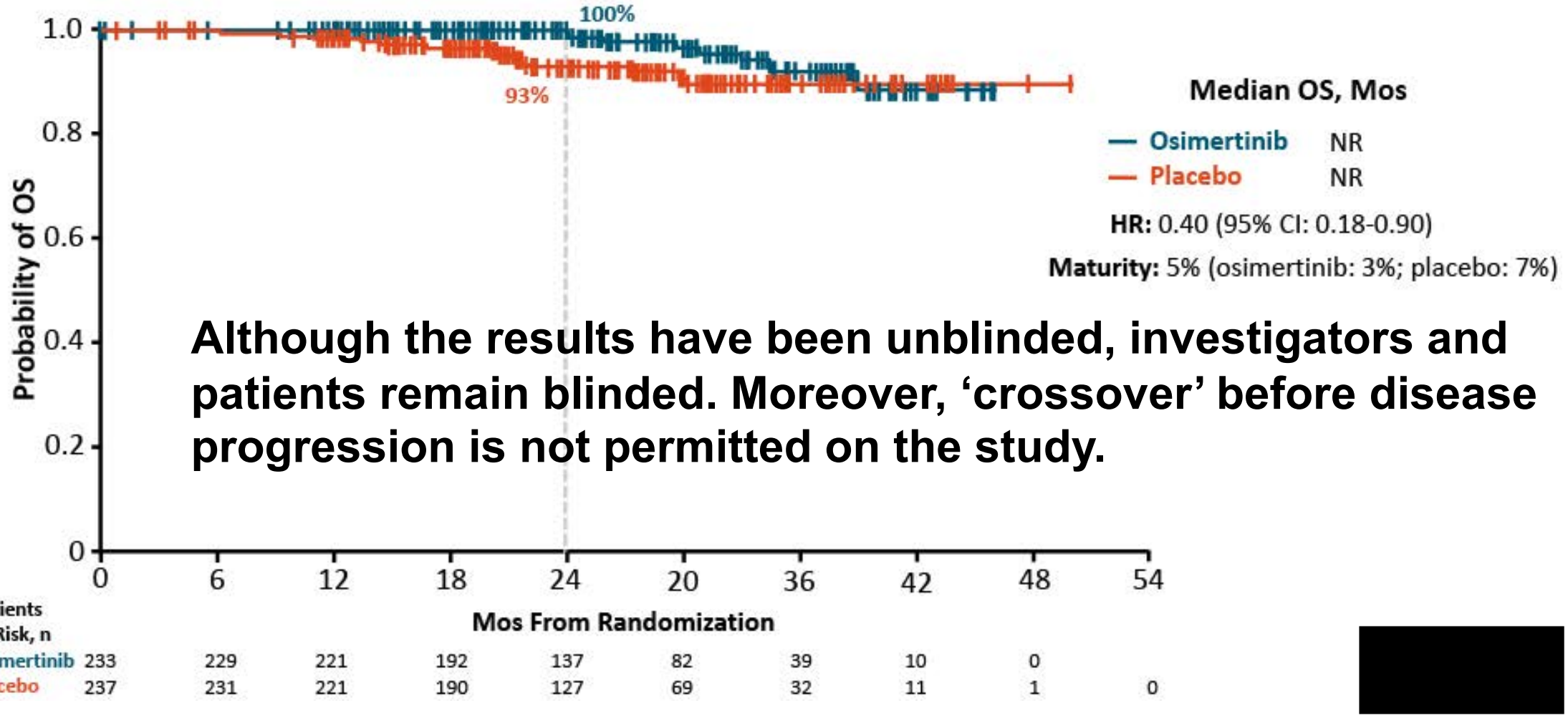


SF-36 component	Mixed model of repeated measures – adjusted mean change from baseline (95%CI)			Definition of clinically meaningful change based on the 3rd edition of the SF-36 scoring manual
	Osimertinib	Placebo	Osimertinib - placebo	
PCS	1.13 (0.54, 1.72)	2.31 (1.70, 2.91)	-1.18 (-2.02, -0.34)	±2
MCS	1.34 (0.60, 2.08)	2.68 (1.92, 3.44)	-1.34 (-2.40, -0.28)	±3

Majem M, et al. J Thorac Oncol 2021;16(suppl):Abstr OA06.03

OVERALL SURVIVAL?

ADAURA: Early OS in stage II-IIIA NSCLC

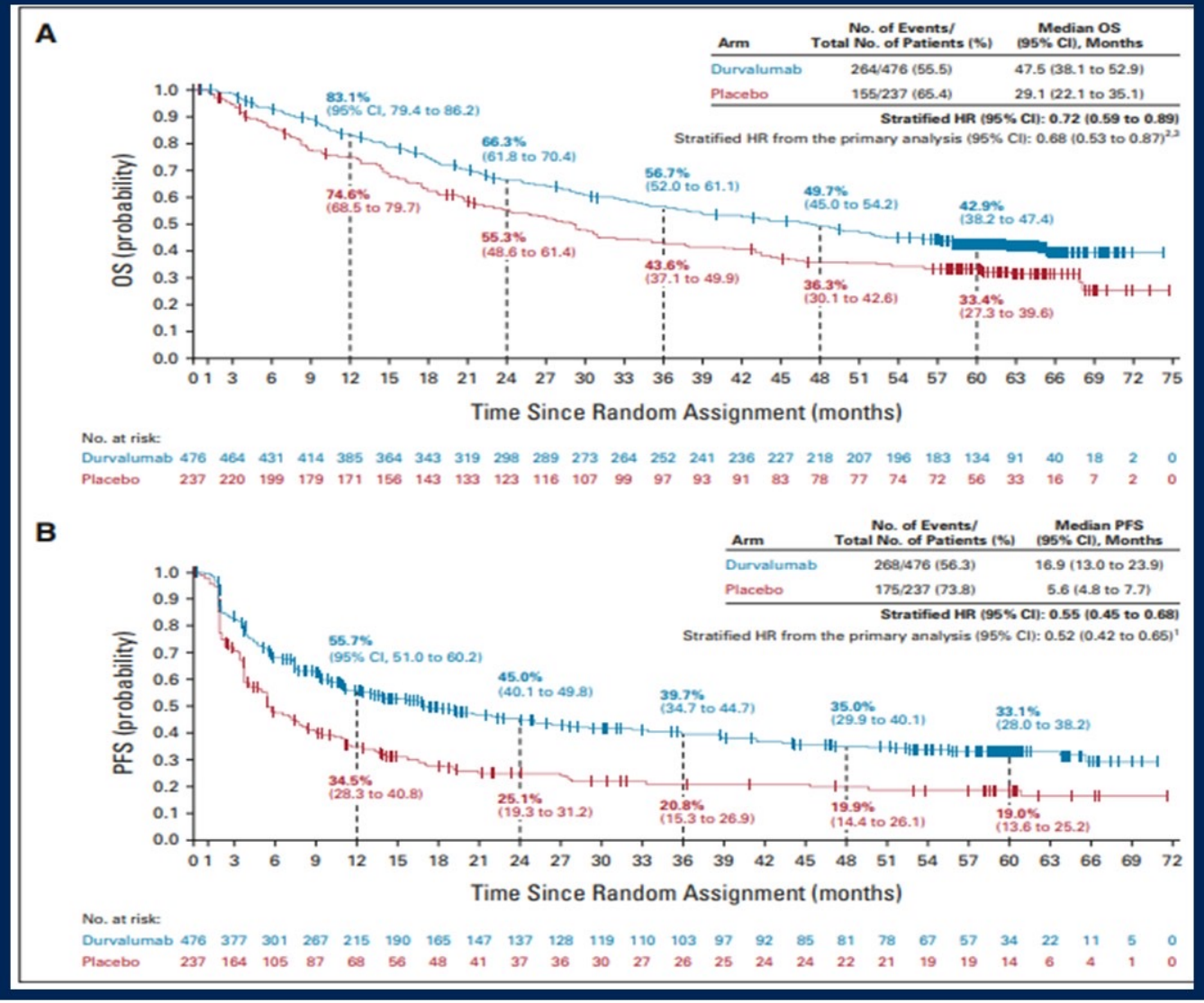


Although the results have been unblinded, investigators and patients remain blinded. Moreover, 'crossover' before disease progression is not permitted on the study.

[redacted]

Wu Y-L, et al. N Engl J Med 2020;383:1711-1723

PACIFIC TRIAL



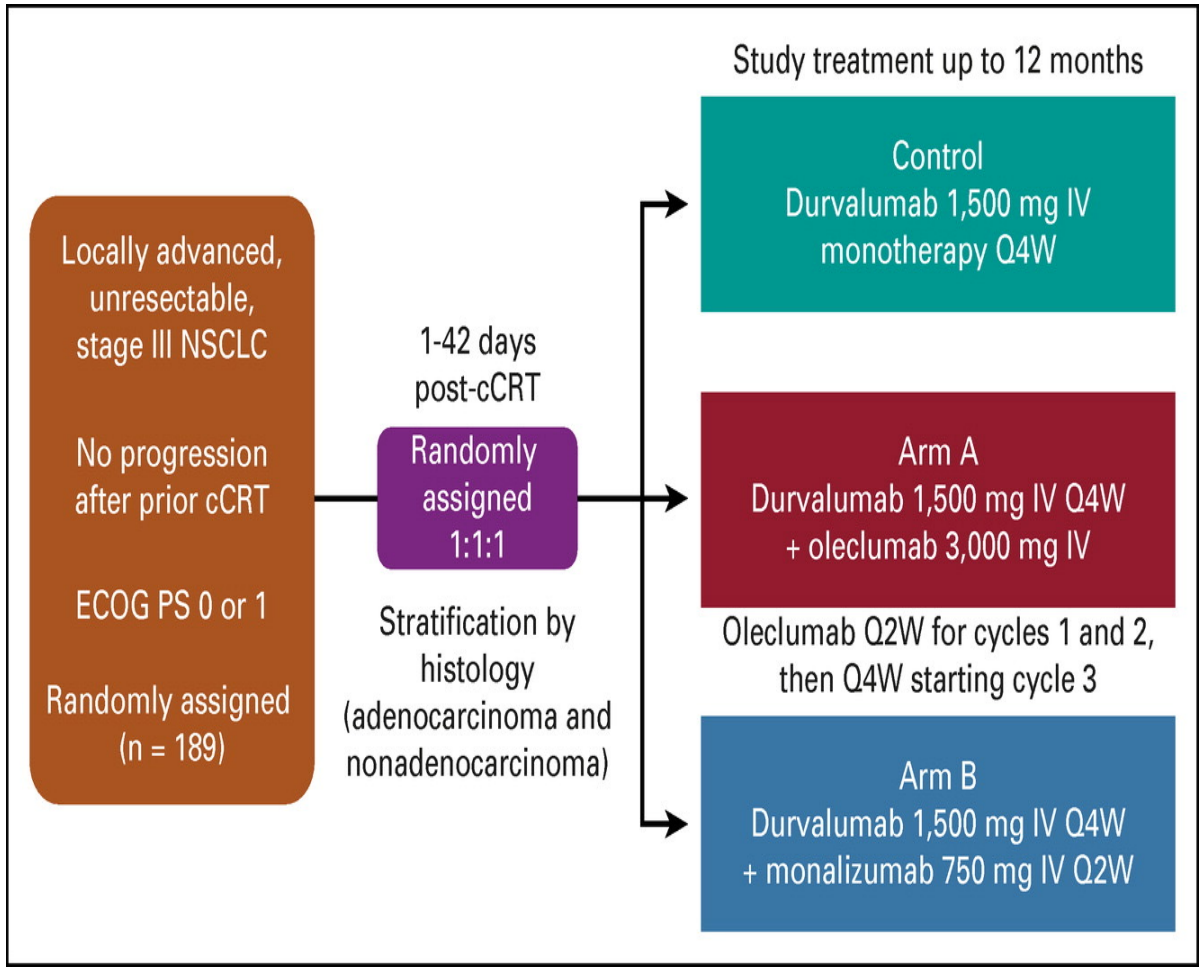
HR = 0.72 OS
Median 47.5 vs 29.1mn

HR = 0.55 PFS
Median 16.9 vs 5.6 mn

Entry Criteria

- No progression during the course of CHEMO/RT
- No unresolved > Grade 2 toxicities
- No Grade ≥ 2 Pneumonitis

COAST - Ph II trial – 1^0 Endpoint - ORR



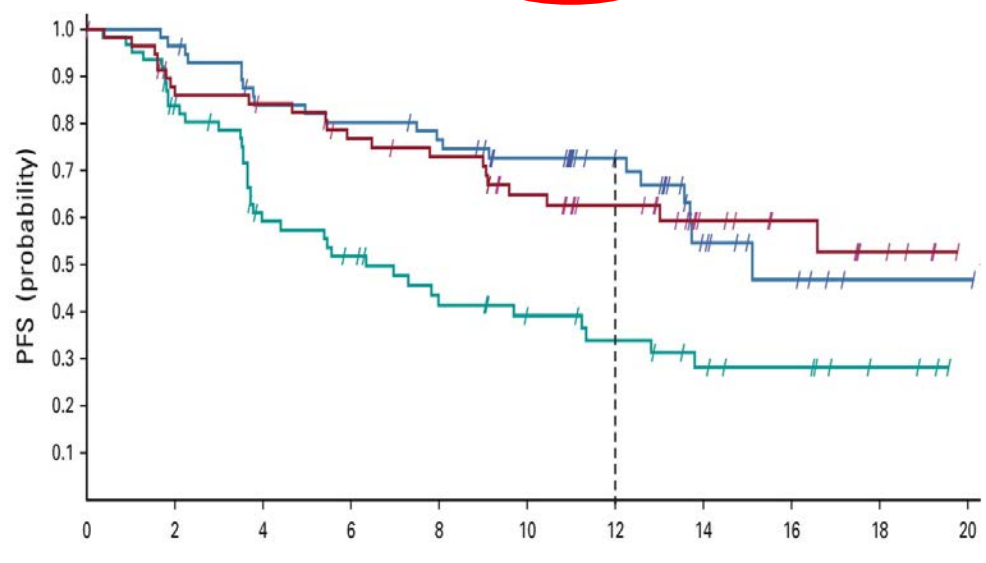
ORR

18%

36%

30%

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

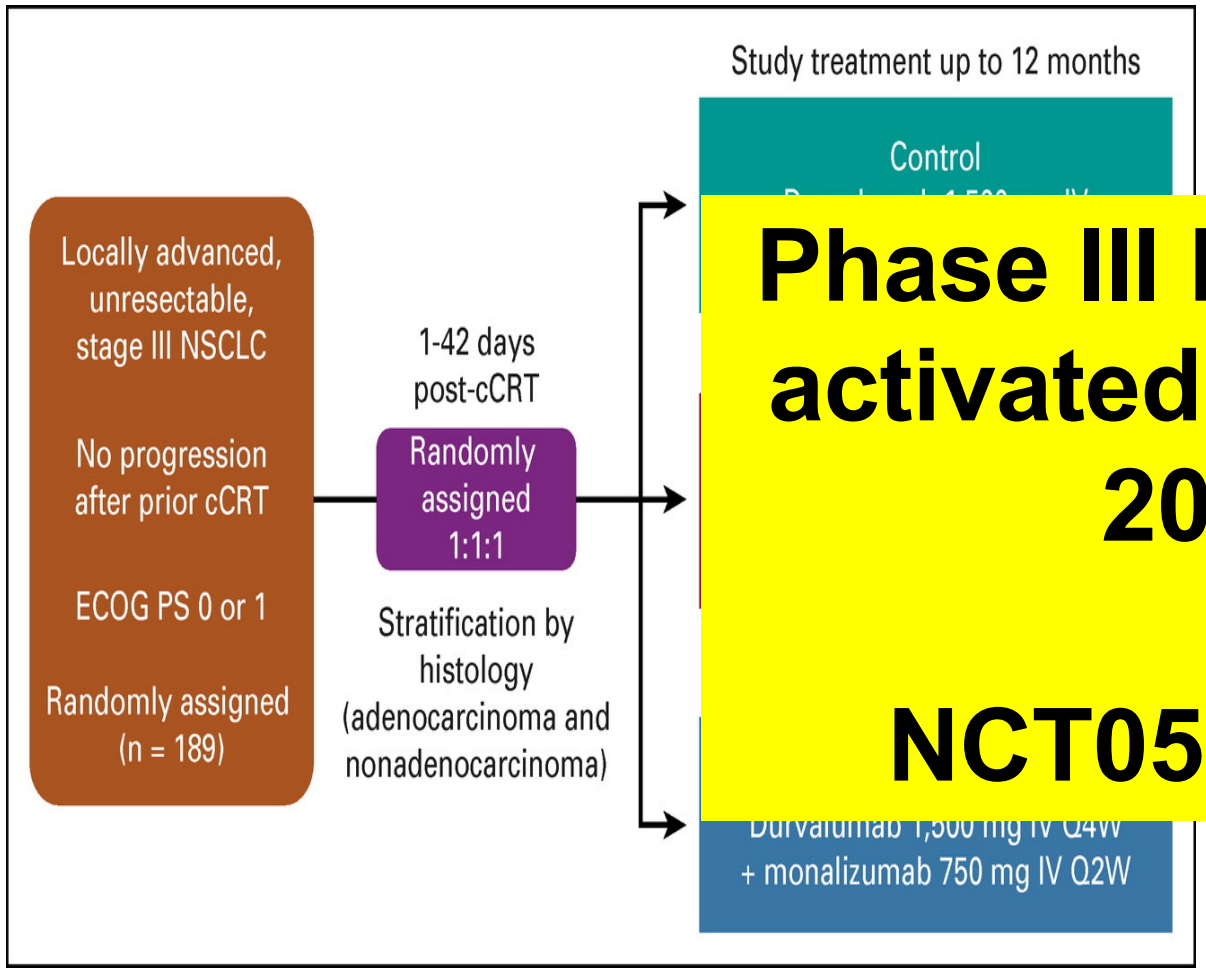


No. at risk:

Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

Oleclumab – inhibits CD73 (adenosine pathway); Monalizumab – blocks NKG2A
Herbst et al. J Clin Oncol 2022

COAST - Ph II trial – 1^0 Endpoint - ORR



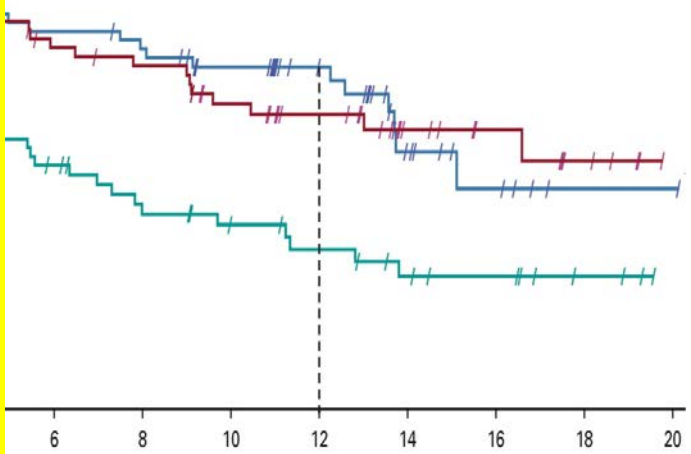
Phase III PACIFIC-9 activated February 2022

NCT05221840

ORR

30%

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

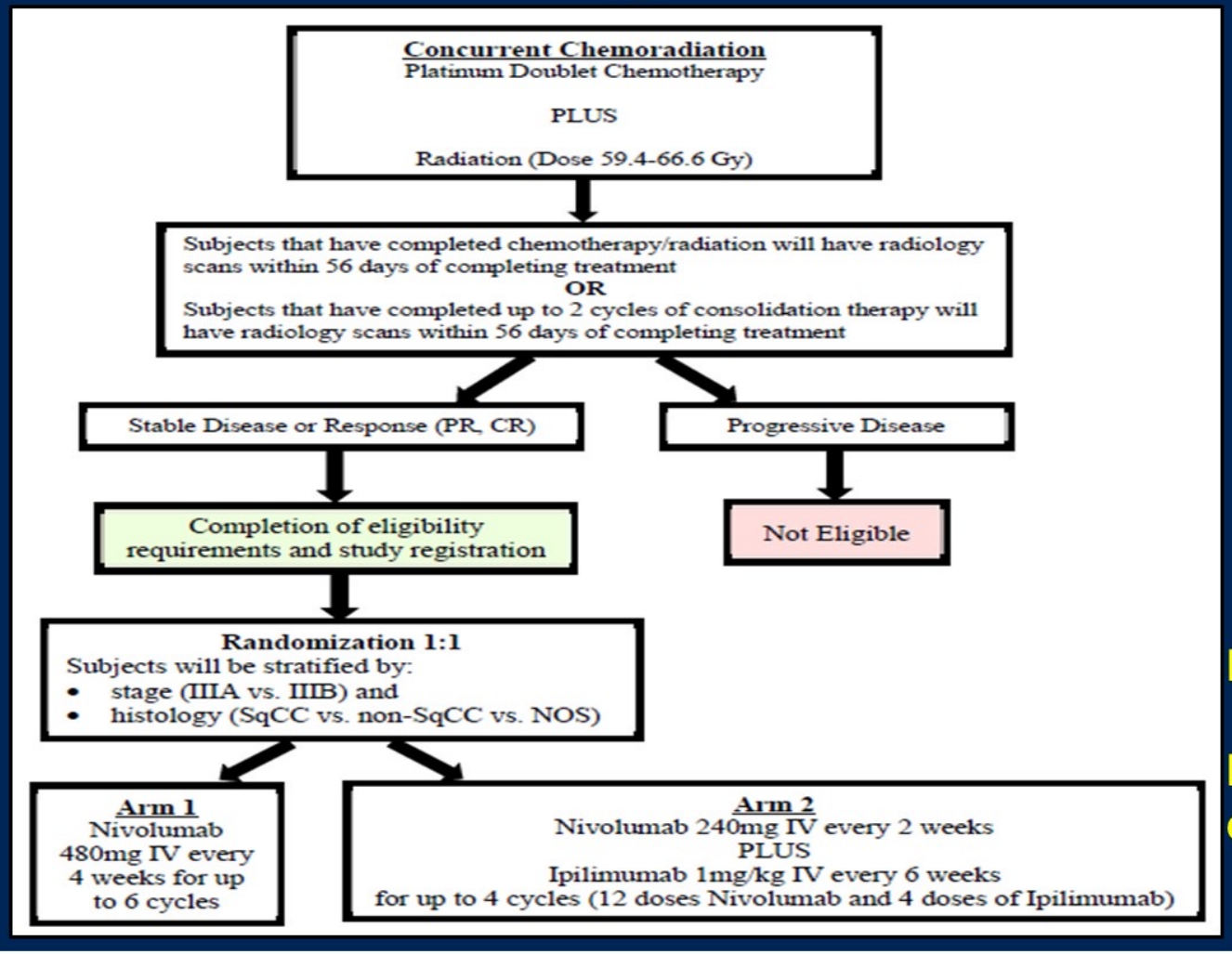


No. at risk:

Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

Oleclumab – inhibits CD73 (adenosine pathway); Monalizumab – blocks NKG2A
Herbst et al. J Clin Oncol 2022

Consolidation Nivolumab Plus Ipilimumab or Nivolumab Alone Following Concurrent Chemoradiation for Patients with Unresectable Stage III Non-Small Cell Lung Cancer. Durm et al



Primary Endpoint-
18- months PFS

1. **Nivo vs historic chemoRT**

2. **Nivo/Ipi vs historic Pacific data**

Big question-

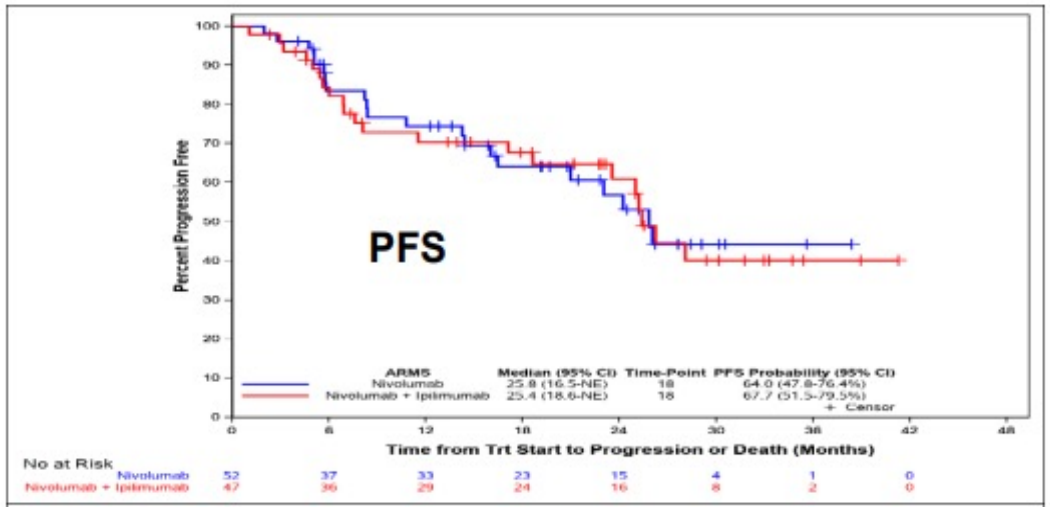
Is 6 months of consolidative immunotherapy enough?

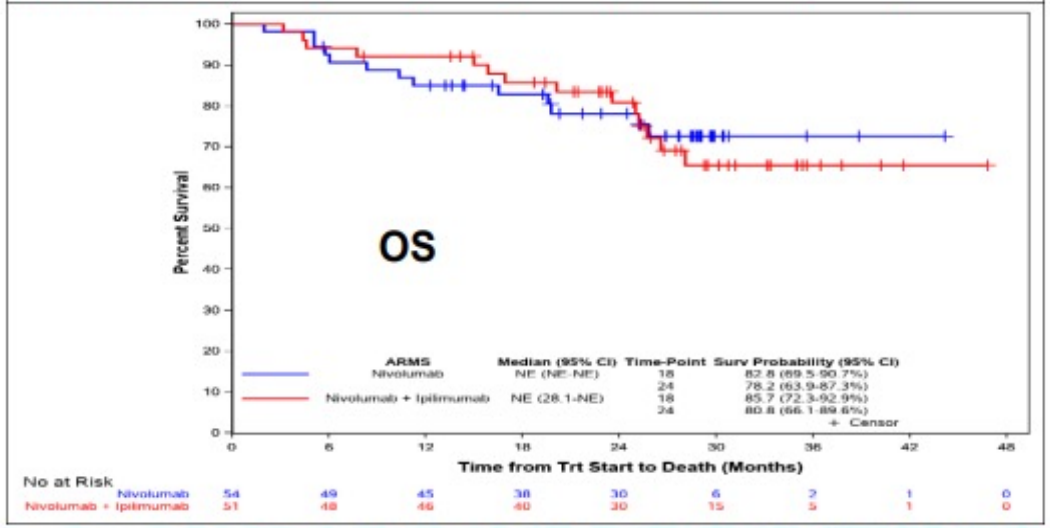
Abstract 8509

IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Results



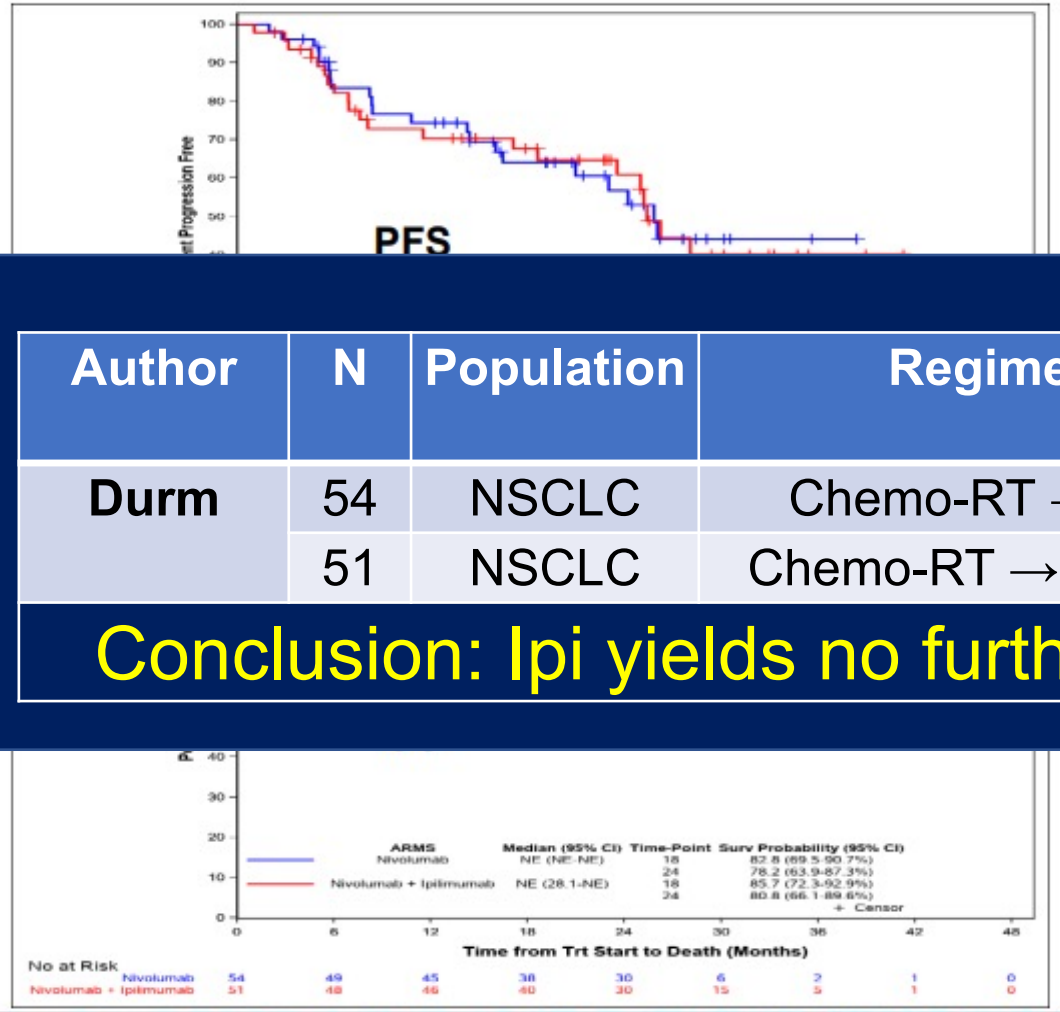


	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	28.5 (2-44.2)	29.4 (3.2-46.8)
Progression Free Survival*		
18- Month (95% CI)	64.0 (53.8-72.6)	67.7 (57.6-75.9)
P-value	<0.1	<0.1
Median, months (95% CI)	25.8 (23.0-NR)	25.4 (25.0-NR)
Overall Survival		
18- Month (95% CI)	82.8 (69.5-90.7)	85.7 (72.3-92.9)
24- Month (95% CI)	78.2 (63.9-87.3)	80.8 (66.1-89.6)
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Results

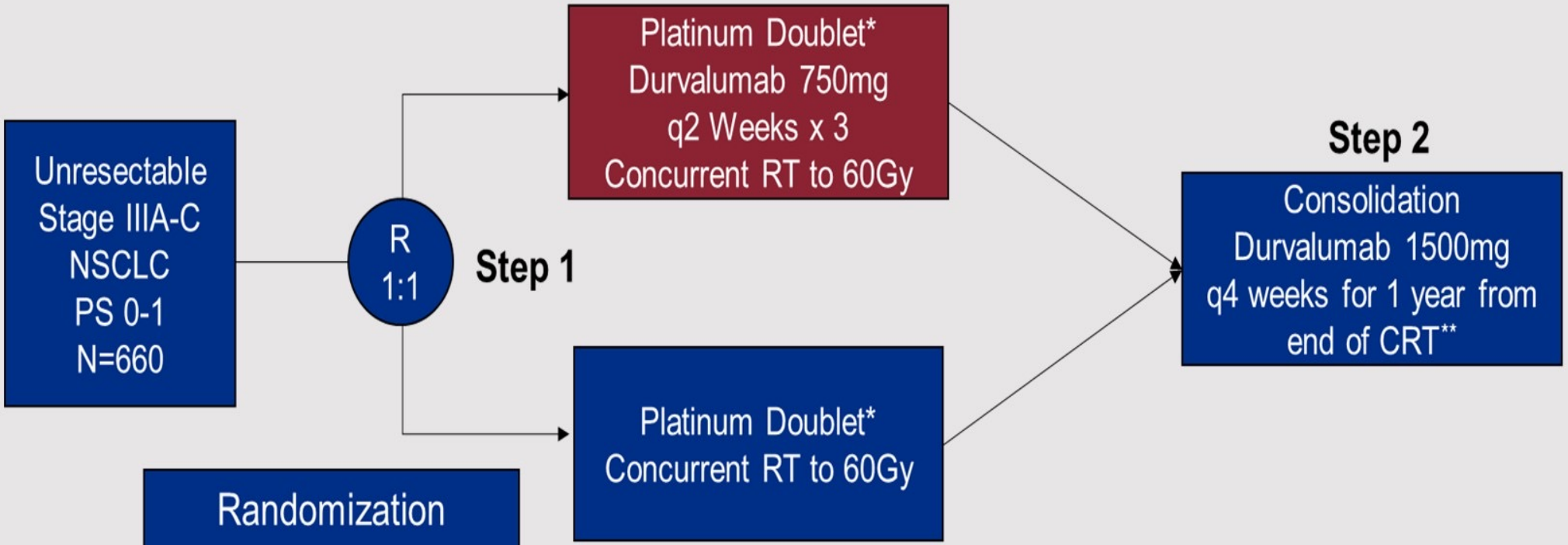


	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	28.5 (2-44.2)	29.4 (3.2-46.8)
Progression Free Survival*		
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

Author	N	Population	Regimen	ORR (%)	PFS, med (mos)	Pneumontis G3+ (%)	trAEs Gr ≥ 3 (%)
Durm	54	NSCLC	Chemo-RT → Nivo	**NR**	**25.8**	**9.3**	**38.5**
	51	NSCLC	Chemo-RT → Nivo/Ipi	**NR**	**25.4**	**15.7**	**52.9**

Conclusion: Ipi yields no further Tx benefit, just heightened toxicity

ECOG-ACRIN EA5181



Randomization

Stratified by:

1) Planned chemotherapy
2) Age
3) Sex
4) Stage (IIIA vs IIIB vs IIIC)

Investigator choice

Cisplatin 50 mg/m2 D1, 8, 29, 36; etoposide 50 mg/m2 D1-5, 29-33
Cisplatin 75 mg/m2 D1, 22; pemetrexed 500 mg/m2 D1, 22 (nonsquamous only)
Carboplatin AUC 2 D1, 8, 15, 22, 29, 36; paclitaxel 45 mg/m2 D1, 8, 15, 22, 29, 36

**Starting within 14 days of CRT unless toxicity has not resolved to ≤ grade 2, but not later than 45 days post-CRT

Conclusions

- After an additional 2 years of follow-up, a significant improvement in DFS for adjuvant Osimertinib in stages IB/II/IIIA EGFR mut (+) NSCLC persisted
- An improvement was seen whether or not patients received adjuvant chemotherapy
- A clinically meaningful improvement in CNS DFS was observed
- Does the benefit of Osimertinib wane after 3 years?????
- Will we observe an OS benefit?

General Conclusions:
Peri-operative Therapy in Early Stage NSCLC

- Adjuvant atezolizumab confers a clear PFS advantage in stage II/IIIA PDL1 (+) NSCLC post resection and adjuvant chemoetherapy
  - PDL1 > 50% realize an OS advantage
  - Adjuvant Pembrolizumab yields similar benefits
- Neoadjuvant Chemo and IO (Nivolumab) has resulted in a pCR, MPR, and EFS advantage vs chemo alone in resectable stage I-IIIA NSCLC. Long term OS data are pending
- Osimertinib as consolidation for 3 yrs post resection of EGFR mt (+) NSCLC +/- advjuvant chemo yields significant PFS benefit compared to placebo with CNS “protection” and preservation of QoL, but benefits may wane once TKI is stopped

Thank You

Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

The NEW ENGLAND JOURNAL of MEDICINE

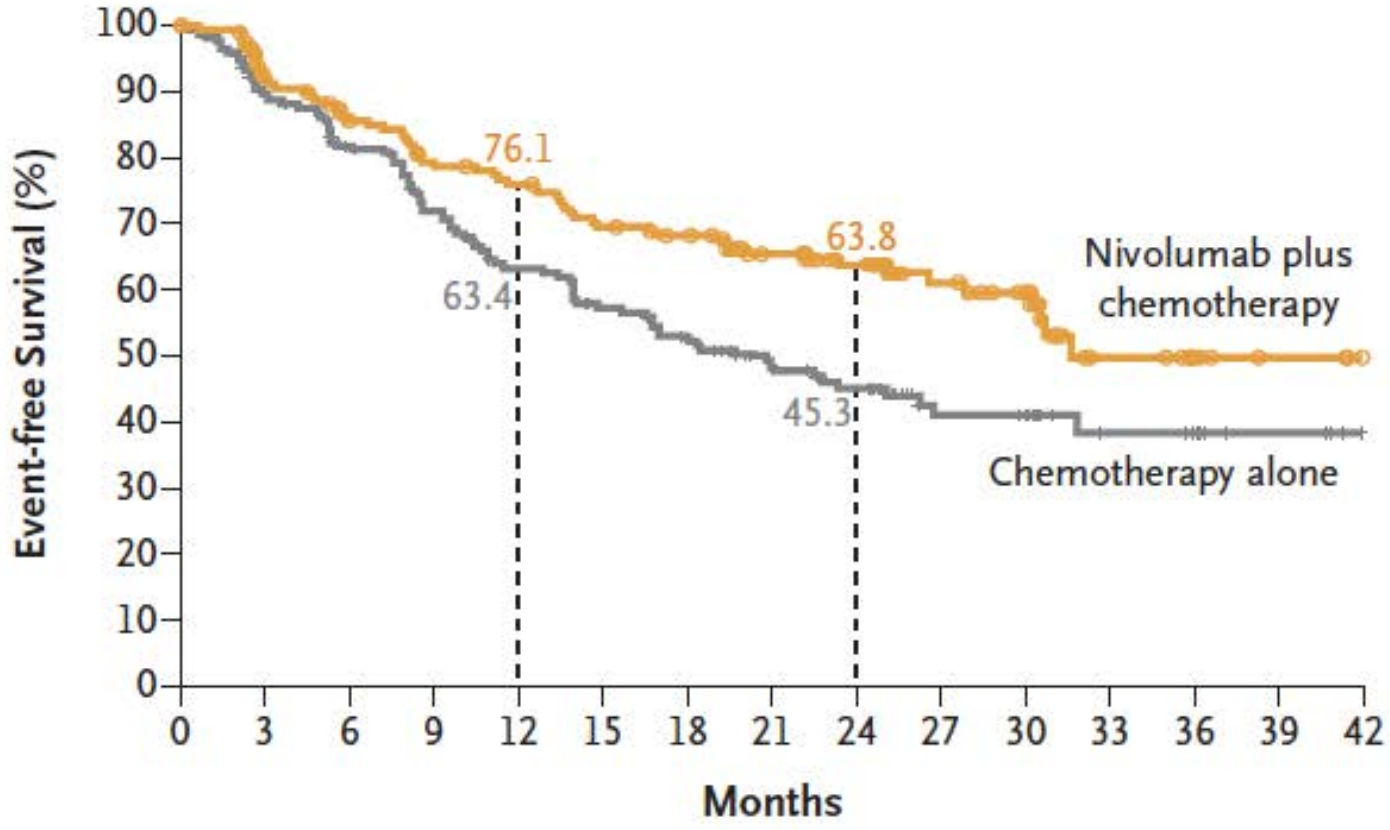
ORIGINAL ARTICLE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

***N Engl J Med* 2022 May 26;386(21):1973-85.**

CheckMate 816 Coprimary Endpoint: Event-Free Survival



	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

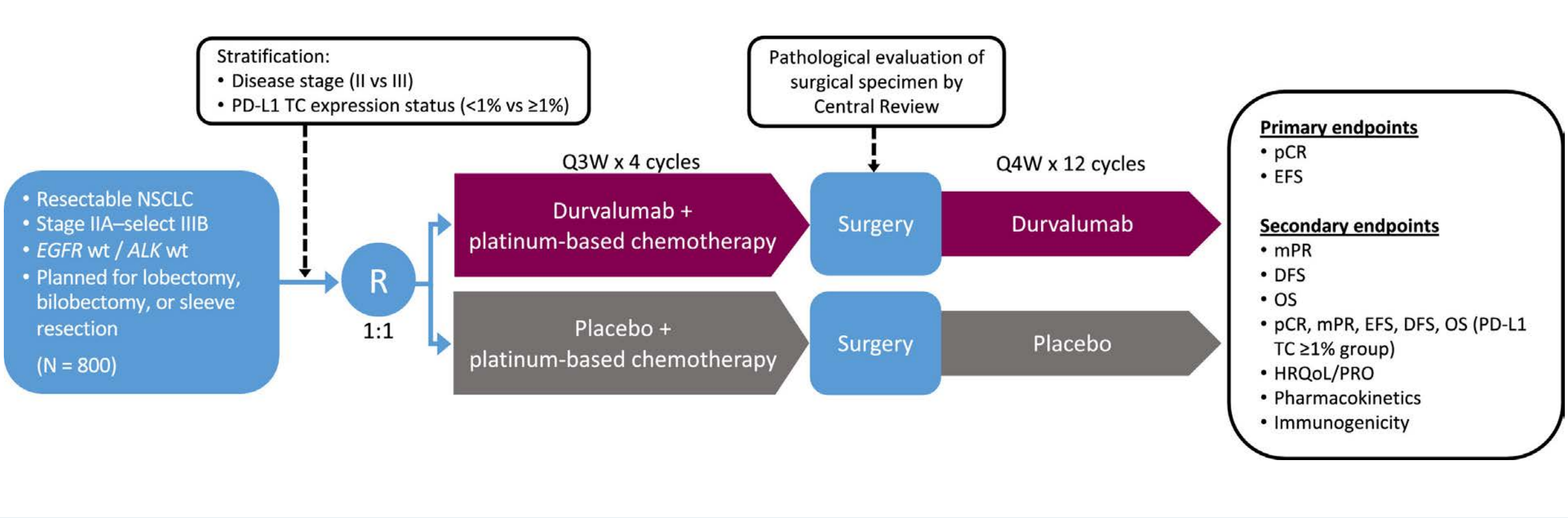
Forde PM et al. *N Engl J Med* 2022 May 26;386(21):1973-85.

Design and Rationale for a Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III non-small-cell Lung Cancer: The AEGEAN Trial

John V. Heymach, MD, PhD,[1] Tetsuya Mitsudomi,[2] David Harpole,[3] Mike Aperghis,[4] Stephanie Jones,[4] Helen Mann,[4] Tamer M. Fouad,[5] Martin Reck[6]

Clin Lung Cancer 2022 May;23(3):e247-51.

AEGEAN: Phase III Trial Design



Wt = wild-type; TC = tumor cells; pCR = pathologic complete response; EFS = event-free survival; mPR = major pathologic response; DFS = disease-free survival; HRQoL = health-related quality of life; PRO = patient-reported outcome

Heymach JV et al. *Clin Lung Cancer* 2022 May;23(3):e247-51.

Positive High-Level Results Announced from the Phase III AEGEAN Trial Evaluating Durvalumab with Chemotherapy for Resectable NSCLC

Press Release – June 30, 2022

"Positive high-level results from a planned interim analysis of the AEGEAN Phase III trial showed treatment with durvalumab in combination with neoadjuvant chemotherapy before surgery demonstrated a statistically significant and meaningful improvement in pathologic complete response (pCR) compared to neoadjuvant chemotherapy alone for patients with resectable non-small cell lung cancer (NSCLC).

A statistically significant improvement in major pathologic response (MPR) was also observed. The trial will continue as planned to assess the additional primary endpoint of event-free survival (EFS) to which the Company, investigators and participants remain blinded.

The safety and tolerability of adding durvalumab to neoadjuvant chemotherapy was consistent with the known profile for this combination and did not decrease the number of patients able to undergo successful surgery versus chemotherapy alone."

https://finance.yahoo.com/news/imfinzi-durvalumab-plus-chemotherapy-significantly-110000161.html

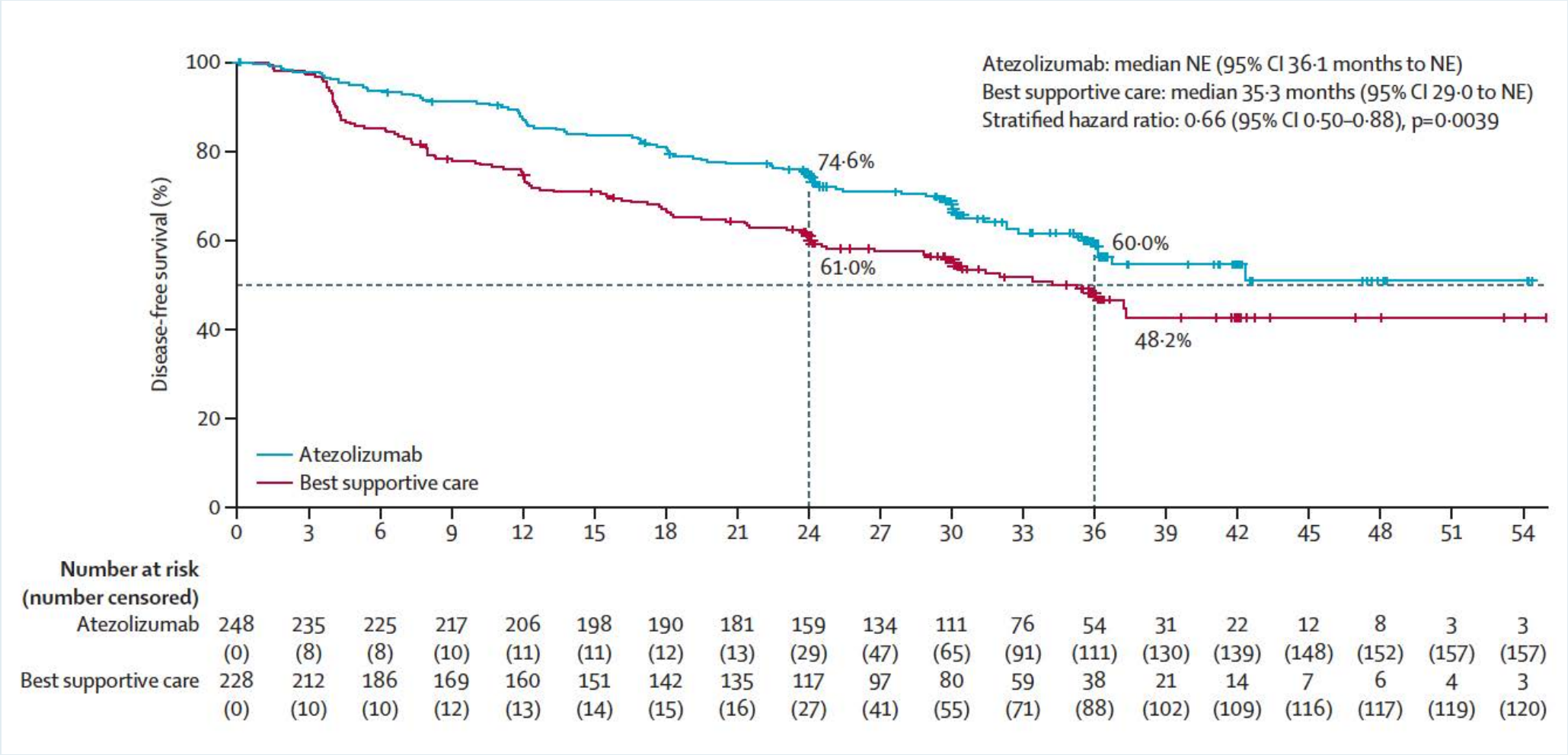
RTP RESEARCH TO PRACTICE

Lancet 2021;398(10308):1344-57.

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators**

IMpower010 Primary Endpoint: Disease-Free Survival in the PD-L1 ≥1% Tumor Cells Stage II-IIIA Population



Felip E et al. *Lancet* 2021;398(10308):1344-57.

IASLC 2022 World Conference on Lung Cancer

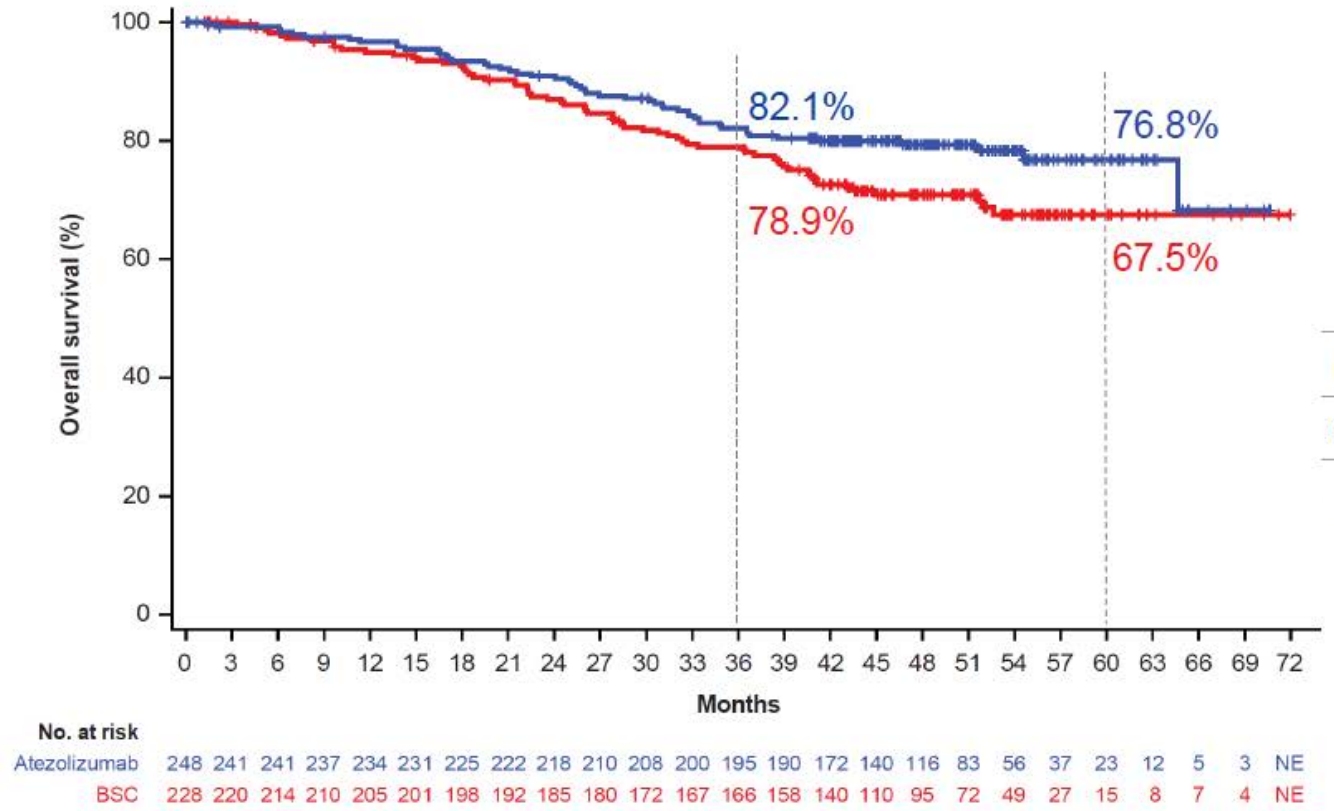
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Abstract PL03.09

IMpower010: Overall survival interim analysis of a phase III study of atezolizumab vs best supportive care in resected NSCLC

Enriqueta Felip,[1] Nasser Altorki,[2] Eric Vallieres,[3] Ihor O. Vynnychenko,[4] Andrey Akopov,[5] Alex Martinez-Marti,[1] Antonio Chella,[6] Igor Bondarenko,[7] Shunichi Sugawara,[8] Yun Fan,[9] Hirotsugu Kenmotsu,[10] Yuh-Min Chen,[11] Yu Deng,[12] Meilin Huang,[12] Virginia McNally,[13] Elizabeth Bennett,[12] Barbara J. Gitlitz,[12] Caicun Zhou,[14] Heather A. Wakelee[15]

IMpower010: Overall Survival Interim Analysis in the PD-L1 ≥1% Tumor Cells, Stage II to IIIA Population



	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)	0.71 (0.49, 1.03)	

Data cutoff: Apr 18, 2022
Median follow-up: 46 months

Atezo = atezolizumab; BSC = best supportive care

Felip E et al. WCLC 2022;Abstract PL03.09.

RTP RESEARCH TO PRACTICE

ESMO VIRTUAL PLENARY

EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

etop
Information | Research

Pembrolizumab Versus Placebo For Early-Stage NSCLC Following Complete Resection and Adjuvant Chemotherapy When Indicated: Randomized, Triple-Blind, Phase 3 EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Study

L. Paz-Ares,[1*] M. O'Brien,[2*] M. Mauer,[3] U. Dafni,[4] K. Oselin,[5] L. Havel,[6] E. Esteban,[7] D. Isla,[8] A. Martinez-Marti,[9] M. Faehling,[10] M. Tsuboi,[11] J.S. Lee,[12] K. Nakagawa,[13] J. Yang,[14] S.M. Keller,[14] N. Jha,[3] S. Marreaud,[3] R. Stahel,[15] S. Peters,[16**] B. Besse[17**] on behalf of the PEARLS/KEYNOTE-091 Investigators

[1]Hospital Universitario 12 de Octubre, CNIO, Ciberonc & Universidad Complutense, Madrid, Spain; [2]Royal Marsden Hospital, London, UK; [3]European Organisation for Research and Treatment of Cancer, Headquarters Brussels, Belgium; [4]National and Kapodistrian University of Athens and Frontier Science Foundation Hellas; [5]North Estonia Medical Centre, Tallinn, Estonia; [6]Charles University and Thomayer Hospital, Prague, Czech Republic; [7]Hospital Universitario Central de Asturias, Oviedo, Spain; [8]University Hospital Lozano Blesa, IIS Aragon, Zaragoza, Spain; [9]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; [10]Klinikum Esslingen, Esslingen, Germany; [11]National Cancer Center Hospital East, Kashiwa, Japan; [12]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; [13]Kindai University Faculty of Medicine, Osaka, Japan; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]European Thoracic Oncology Platform, Bern, Switzerland; [16]Lausanne University Hospital, Lausanne, Switzerland; [17]Institut Gustave Roussy, Villejuif, France
*Drs. Paz-Ares and O'Brien contributed equally to this presentation. **Drs. Peters and Besse contributed equally to this presentation.

ESMO

Abstract VP3-2022

RTP RESEARCH TO PRACTICE

PEARLS/KEYNOTE-091: Author Summary and Conclusions

- Pembrolizumab provided statistically significant, clinically meaningful DFS improvement versus placebo in the overall population
  - Median DFS of 53.6 months with pembrolizumab vs 42.0 months with placebo (HR, 0.76)
  - Generally consistent DFS benefit in participants with PD-L1 TPS <1%, 1-49%, and ≥50%
  - OS data are immature
  - DFS in the PD-L1-defined populations and OS will be tested at future analyses according to the analysis plan
- Pembrolizumab safety profile as expected
- **Data suggest pembrolizumab has the potential to be a new adjuvant treatment option for patients with stage IB (T ≥4 cm) to IIIA NSCLC following complete resection and adjuvant chemotherapy when recommended, regardless of PD-L1 expression**

TPS = tumor proportion score

Paz-Ares L et al. ESMO Virtual Plenary Sessions 2022;Abstract VP3-2022.

original reports

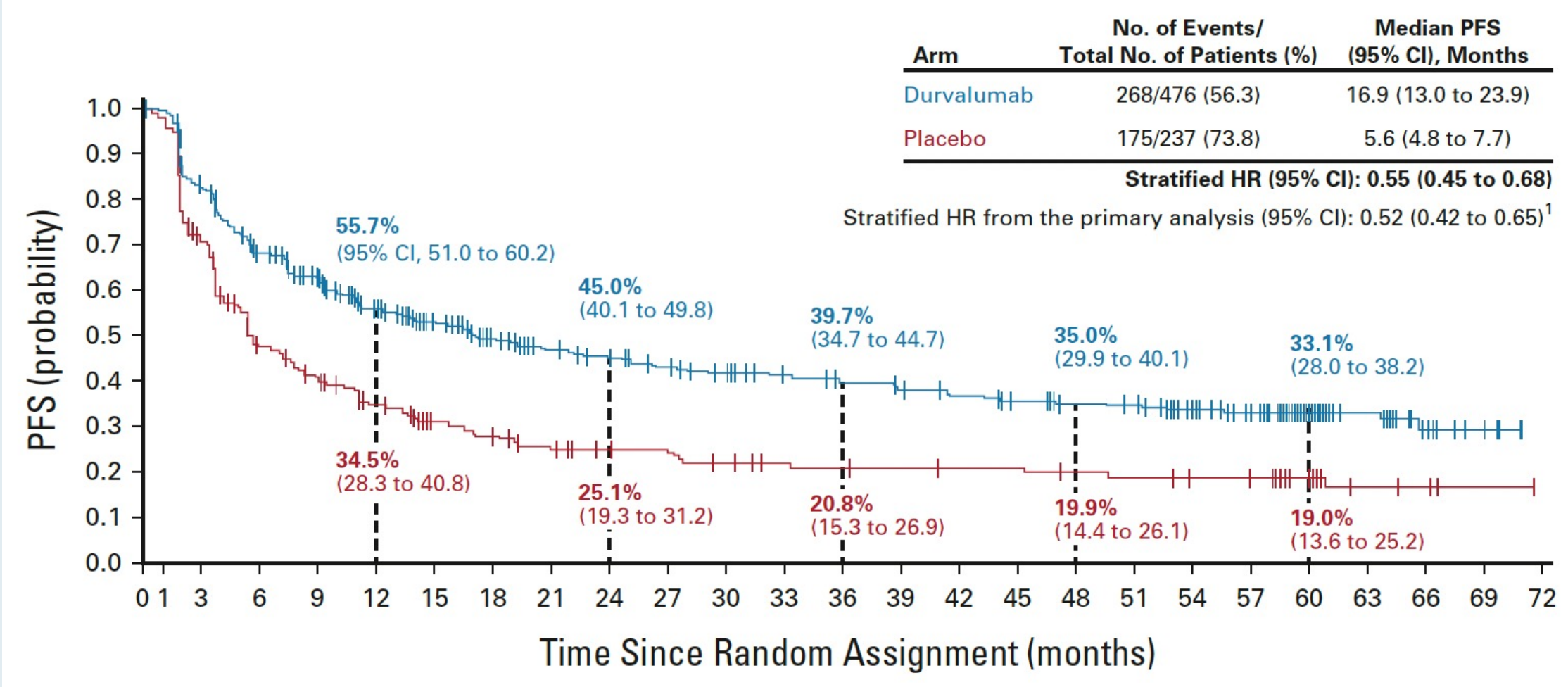
Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

David R. Spigel, MD[1]; Corinne Faivre-Finn, MD, PhD[2]; Jhanelle E. Gray, MD[3]; David Vicente, MD[4]; David Planchard, MD, PhD[5]; Luis Paz-Ares, MD, PhD[6]; Johan F. Vansteenkiste, MD, PhD[7]; Marina C. Garassino, MD[8,9]; Rina Hui, PhD[10]; Xavier Quantin, MD, PhD[11]; Andreas Rimner, MD[12]; Yi-Long Wu, MD[13]; Mustafa Özgüroğlu, MD[14]; Ki H. Lee, MD[15]; Terufumi Kato, MD[16]; Maike de Wit, MD, PhD[17]; Takayasu Kurata, MD[18]; Martin Reck, MD, PhD[19]; Byoung C. Cho, MD, PhD[20]; Suresh Senan, PhD[21]; Jarushka Naidoo, MBBCH, MHS[22]; Helen Mann, MSc[23]; Michael Newton, PharmD[24]; Piruntha Thiyagarajah, MD[23]; and Scott J. Antonia, MD, PhD[3]; on behalf of the PACIFIC Investigators

J Clin Oncol 2022;40(12):1301-11.

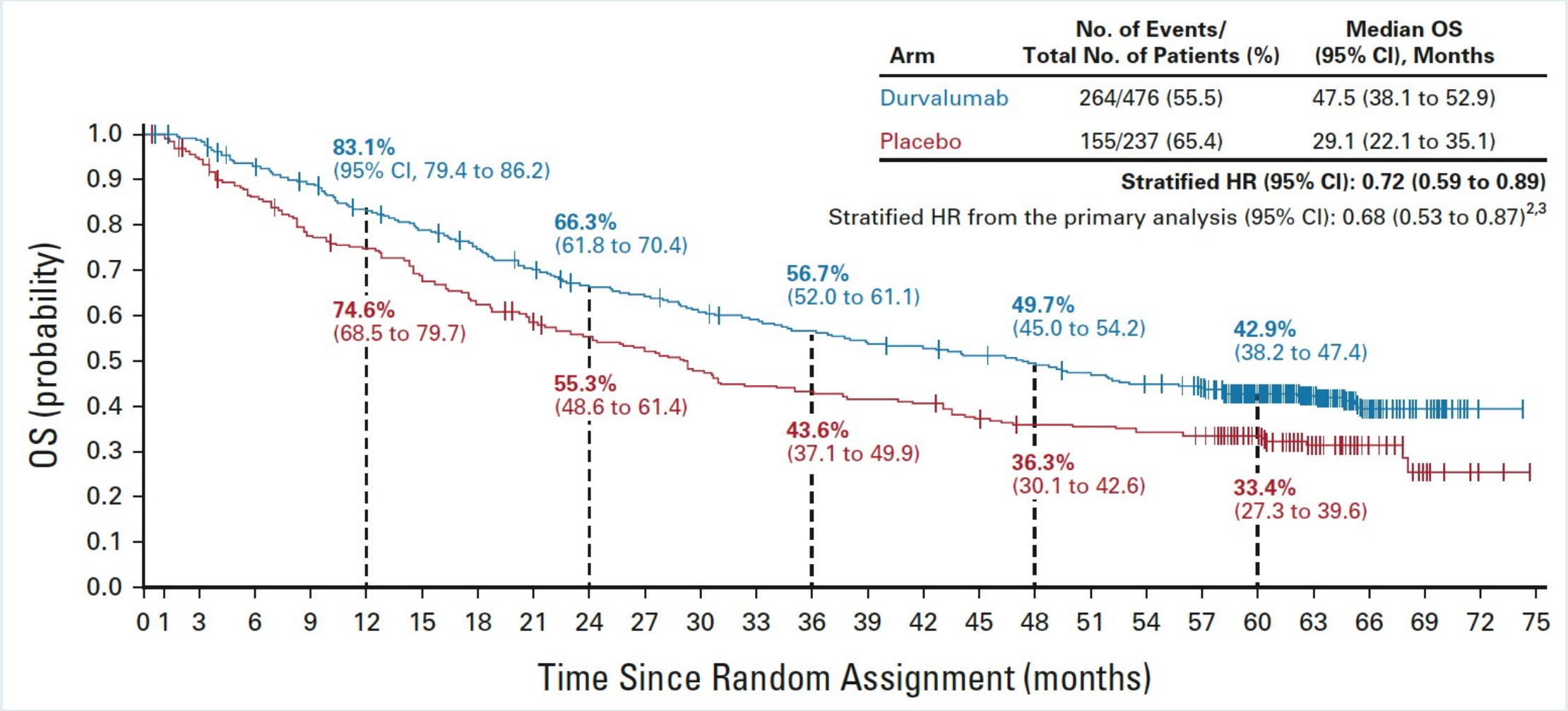
RTP RESEARCH TO PRACTICE

PACIFIC: Five-Year Progression-Free Survival (PFS) with Durvalumab After Chemoradiation Therapy for Stage III NSCLC



Spigel DR et al. *J Clin Oncol* 2022;40(12):1301-11.

PACIFIC: Five-Year Overall Survival (OS) with Durvalumab After Chemoradiation Therapy for Stage III NSCLC



Spigel DR et al. *J Clin Oncol* 2022;40(12):1301-11.

original reports

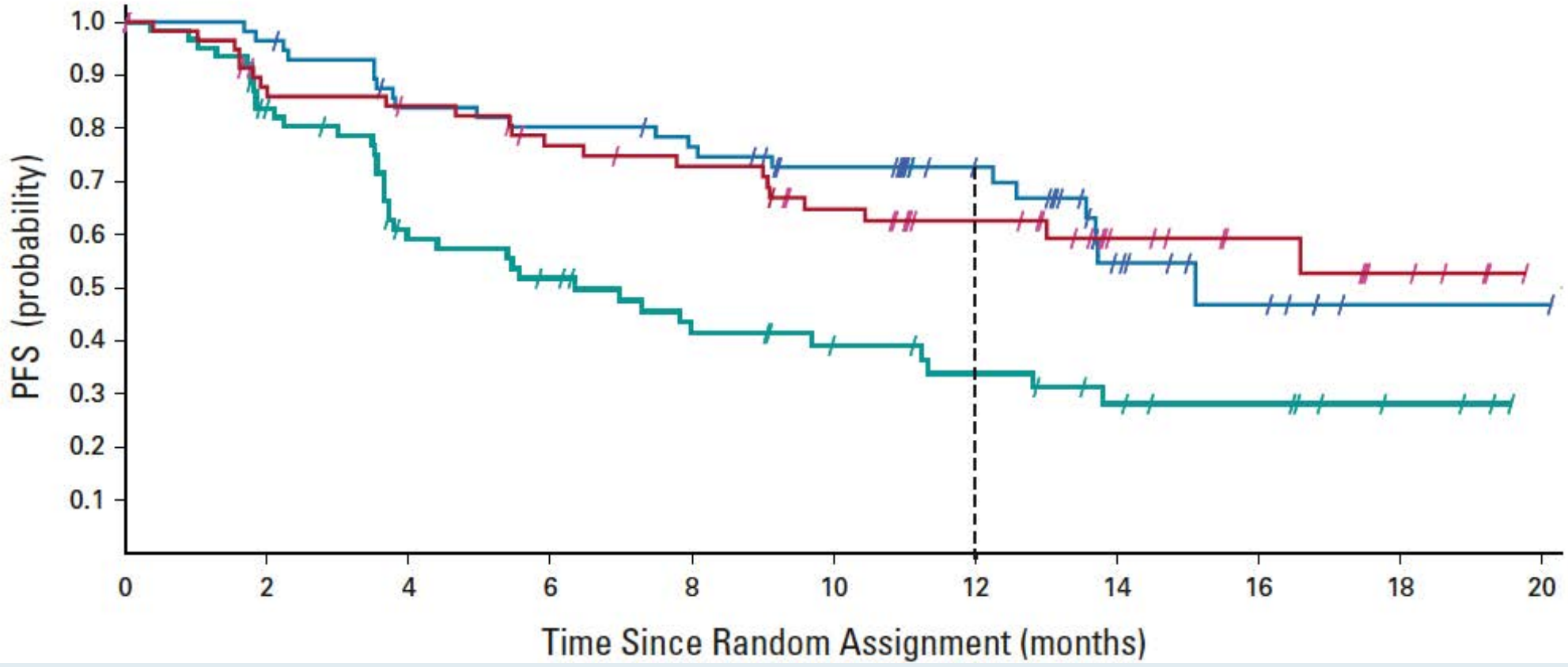
COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non–Small-Cell Lung Cancer

Roy S. Herbst, MD, PhD[1]; Margarita Majem, MD, PhD[2]; Fabrice Barlesi, MD, PhD[3]; Enric Carcereny, MD[4]; Quincy Chu, MD[5]; Isabelle Monnet, MD, PhD[6]; Alfredo Sanchez-Hernandez, MD[7]; Shaker Dakhil, MD[8]; D. Ross Camidge, MD, PhD[9]; Leanne Winzer, MSc[10]; Yee Soo-Hoo, MPH[11]; Zachary A. Cooper, PhD[11]; Rakesh Kumar, MD, PhD[11]; John Bothos, PhD[11]; Charu Aggarwal, MD, MPH[12]; and Alex Martinez-Marti, MD[13]

J Clin Oncol 2022;40(29):3383-93.

COAST: Progression-Free Survival

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–



Herbst RS et al. *J Clin Oncol* 2022;40(29):3383-93.

RTP RESEARCH TO PRACTICE

COAST: Antitumor Activity and Safety Summary

Antitumor Activity	Durvalumab (n = 67)	Durvalumab + Oleclumab (n = 60)	Durvalumab + Monalizumab (n = 62)
Confirmed ORR, % (95% CI)[a] (No.)	17.9 (9.6 to 29.2) (12)	30.0 (18.8 to 43.2) (18)	35.5 (23.7 to 48.7) (22)
Difference in confirmed ORR, % (95% CI)[b]	—	12.1 (–2.7 to 26.9)	16.7 (1.5 to 32.0)
Best overall response by RECIST,[c,d] No. (%)			
CR	2 (3.0)	1 (1.7)	3 (4.8)
PR	10 (14.9)	17 (28.3)	19 (30.6)
SD	37 (55.2)	32 (53.3)	31 (50.0)
PD	11 (16.4)	6 (10.0)	4 (6.5)
NE	7 (10.4)	4 (6.7)	4 (6.5)
DCR at 16 weeks, % (95% CI)[c,e] (No.)	55.2 (42.6 to 67.4) (37)	80.0 (67.7 to 89.2) (48)	77.4 (65.0 to 87.1) (48)
Median DoR, months (95% CI)[c] Range	NR (7.4 to NA) 1.9+ to 17.5+	NR (12.9 to NA) 1.8+ to 16.9+	NR (9.0 to NA) 1.9+ to 18.4+

Incidence	Durvalumab	Durvalumab + Oleclumab	Durvalumab + Monalizumab
Any TEAEs, No. (%)	65 (98.5)	57 (96.6)	61 (100)
Grade ≥ 3 TEAEs, No. (%)	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs, No. (%)	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs, No. (%)	6 (9.1)	7 (11.9)	5 (8.2)
TEAEs leading to treatment discontinuation, No. (%)	11 (16.7)	9 (15.3)	9 (14.8)
Deaths[a,b], No. (%)	7 (10.6)	4 (6.8)	3 (4.9)

NE = not evaluable; NR = not reached; NA = not applicable

Herbst RS et al. *J Clin Oncol* 2022;40(29):3383-93.

RTP RESEARCH TO PRACTICE

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

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

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

FDA-Approved Immunotherapy Combination Options for First-Line Therapy

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

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

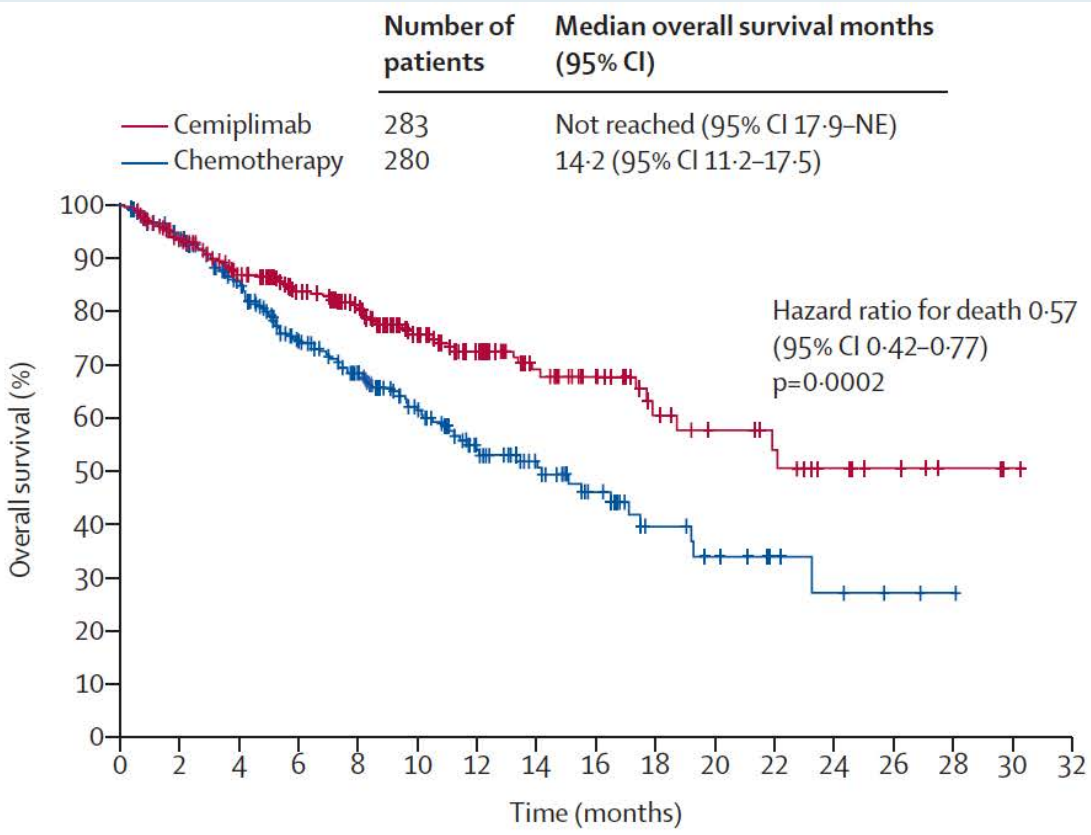
Lancet 2021;397(10274):592-604.

Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial

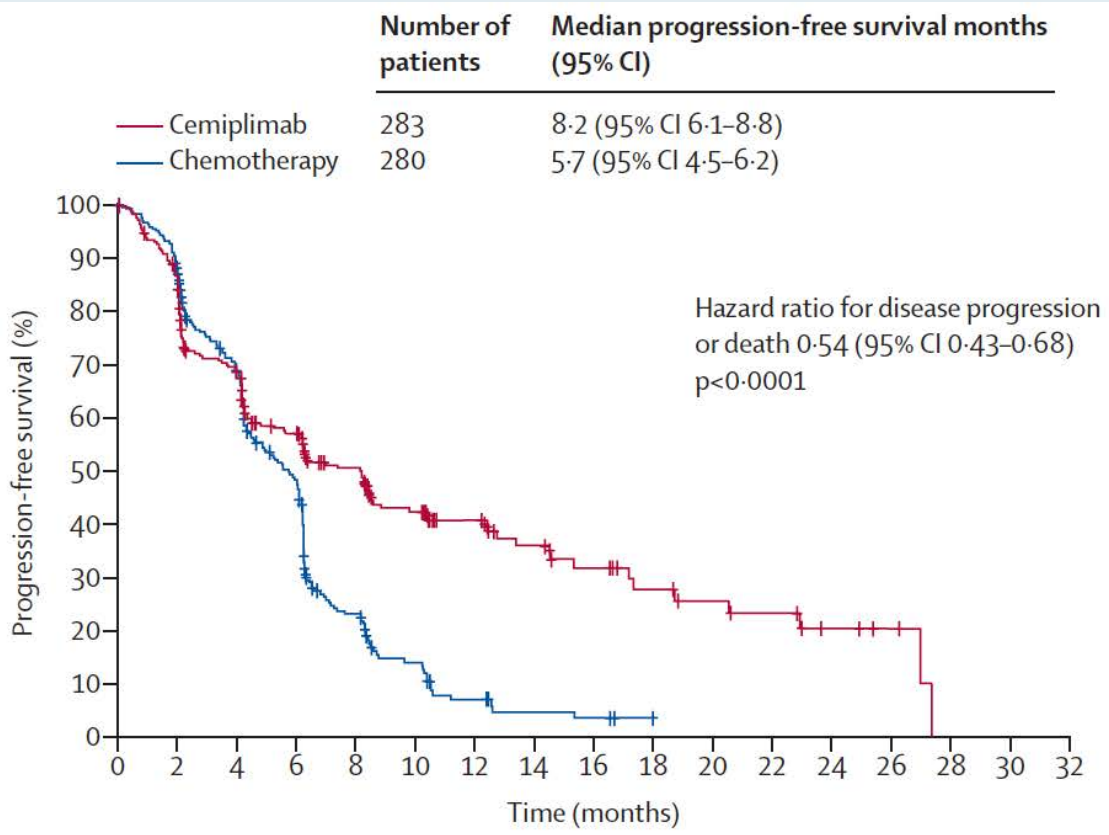
Ahmet Sezer, Saadettin Kilickap, Mahmut Gümüş, Igor Bondarenko, Mustafa Özgüroğlu, Miranda Gogishvili, Haci M Turk, Irfan Cicin, Dmitry Bentsion, Oleg Gladkov, Philip Clingan, Virote Sriuranpong, Naiyer Rizvi, Bo Gao, Siyu Li, Sue Lee, Kristina McGuire, Chieh-I Chen, Tamta Makharadze, Semra Paydas, Marina Nechaeva, Frank Seebach, David M Weinreich, George D Yancopoulos, Giuseppe Gullo, Israel Lowy, Petra Rietschel

EMPOWER-Lung 1: A Phase III Trial of Cemiplimab Monotherapy for First-Line Treatment of NSCLC with PD-L1 ≥50%

Overall Survival



Progression-Free Survival



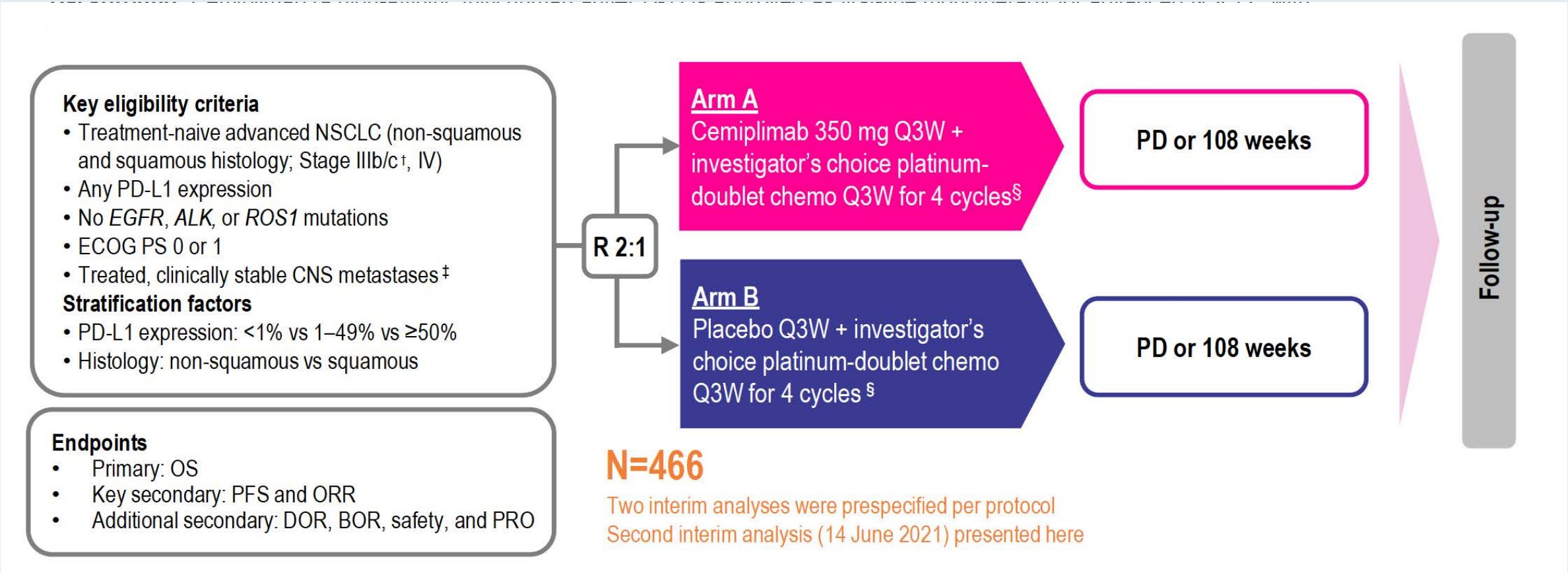
Sezer A et al. *Lancet* 2021;397(10274):592-604.

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

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

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

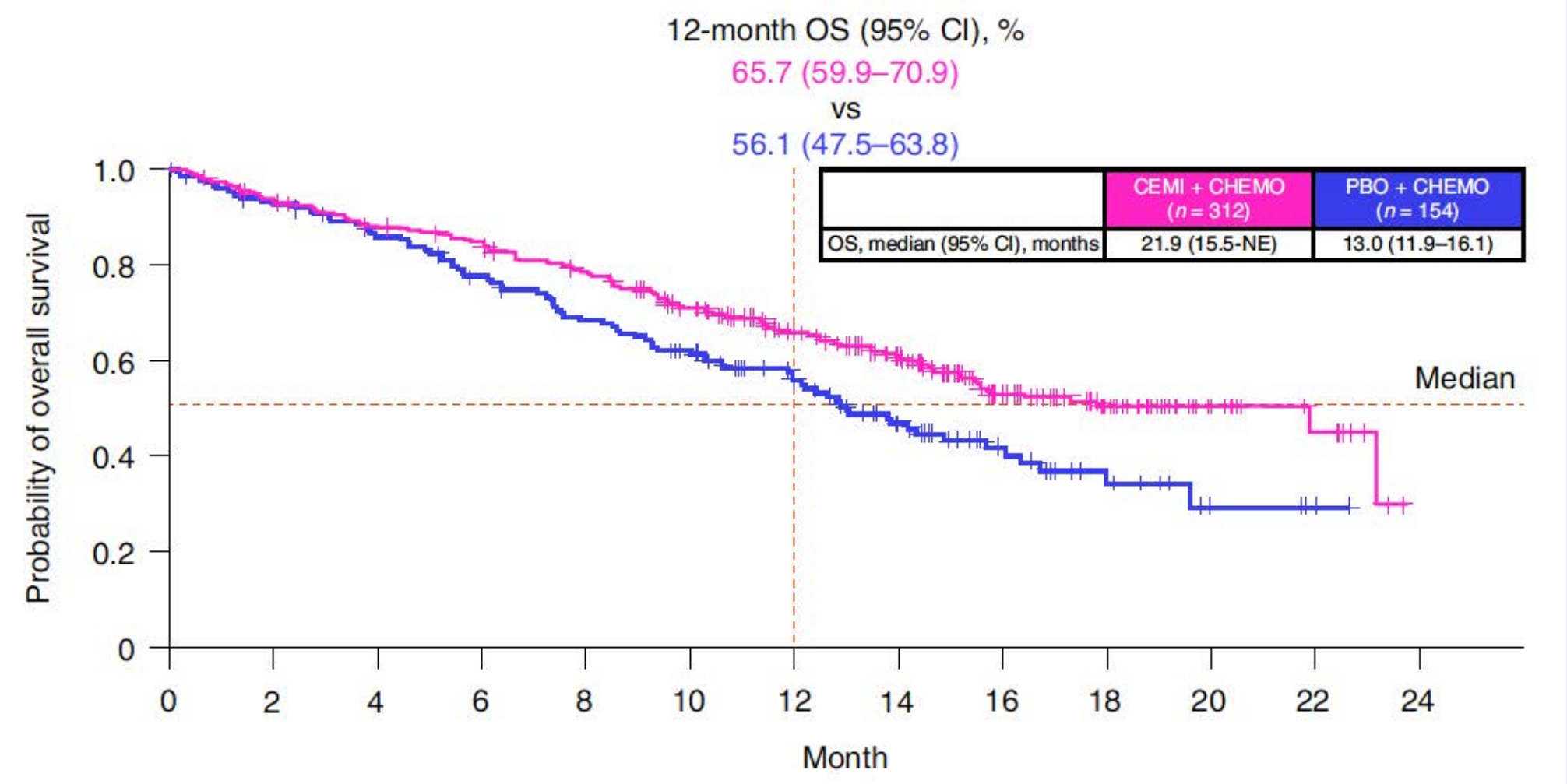
EMPOWER-Lung 3: First-Line Cemiplimab with Platinum-Doublet Chemotherapy for Advanced NSCLC



BOR = best overall response; PRO = patient-reported outcome

Gogishvili M et al. ESMO 2021;Abstract LBA51.

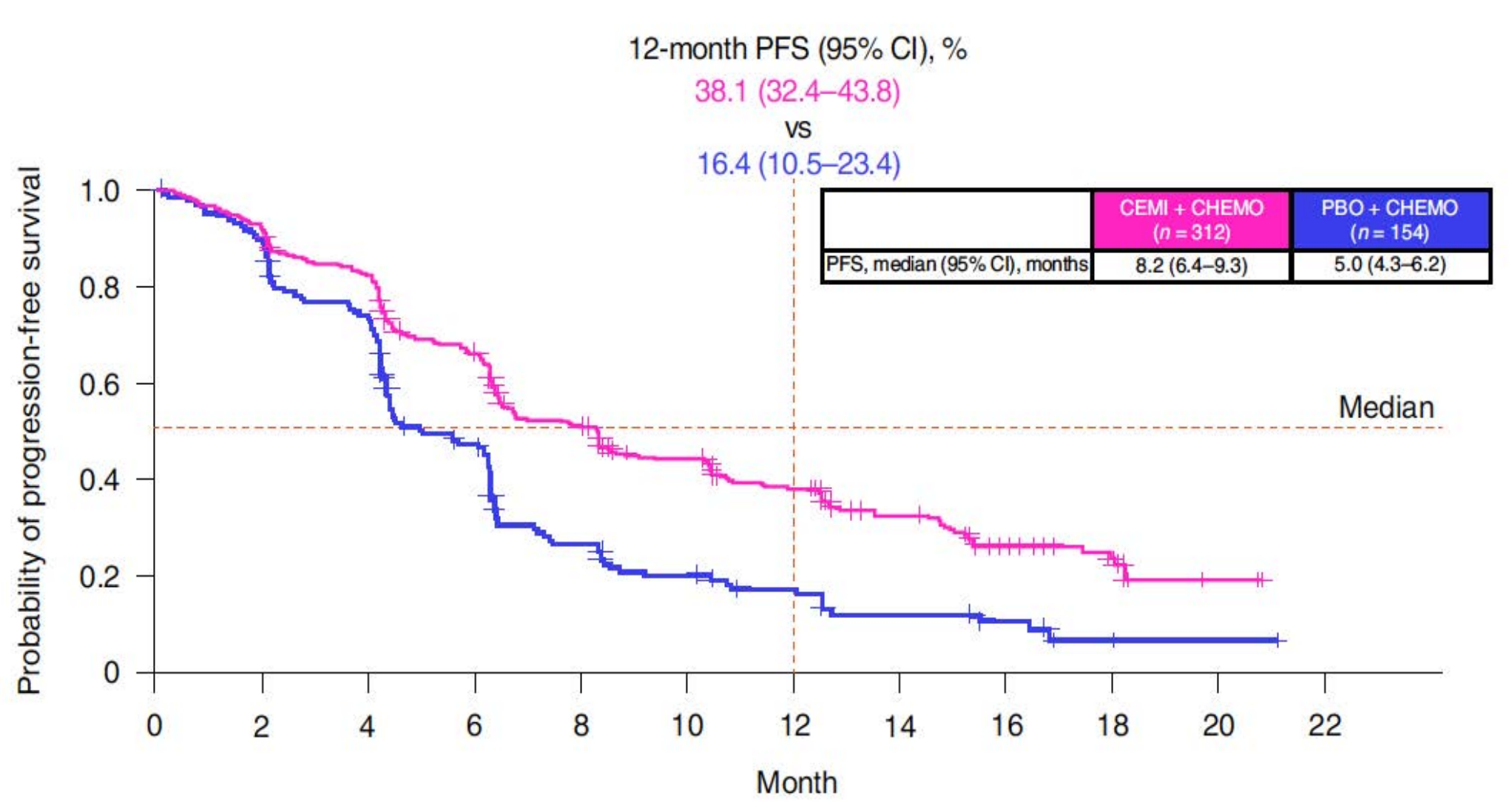
EMPOWER-Lung 3: Overall Survival with First-Line Cemiplimab and Platinum-Doublet Chemotherapy for Advanced NSCLC



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

RTP RESEARCH TO PRACTICE

EMPOWER-Lung 3: Progression-Free Survival with First-Line Cemiplimab and Platinum-Doublet Chemotherapy for Advanced NSCLC



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

RTP RESEARCH TO PRACTICE

EMPOWER-Lung 3: Select Adverse Events

	Cemiplimab + chemotherapy ($n = 312$)		Placebo + chemotherapy ($n = 153$)	
Event, n (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any	299 (95.8)	136 (43.6)	144 (94.1)	48 (31.4)
Led to discontinuation	16 (5.1)	13 (4.2)	4 (2.6)	4 (2.6)
Led to death	19 (6.1)	19 (6.1)	12 (7.8)	12 (7.8)
Events that occurred in ≥10% of patients in either group				
Anemia	136 (43.6)	31 (9.9)	61 (39.9)	10 (6.5)
Alopecia	115 (36.9)	0	66 (43.1)	0
Nausea	78 (25.0)	0	25 (16.3)	0
Hyperglycemia	55 (17.6)	6 (1.9)	18 (11.8)	0
Decreased appetite	53 (17.0)	3 (1.0)	18 (11.8)	0
Alanine aminotransferase increased	51 (16.3)	7 (2.2)	22 (14.4)	3 (2.0)
Arthralgia	48 (15.4)	2 (0.6)	20 (13.1)	0
Neutropenia	48 (15.4)	18 (5.8)	19 (12.4)	9 (5.9)
Aspartate aminotransferase increased	46 (14.7)	1 (0.3)	18 (11.8)	3 (2.0)
Constipation	43 (13.8)	1 (0.3)	17 (11.1)	0
Thrombocytopenia	41 (13.1)	8 (2.6)	19 (12.4)	2 (1.3)
Dyspnea	39 (12.5)	7 (2.2)	10 (6.5)	1 (0.7)
Asthenia	38 (12.2)	6 (1.9)	18 (11.8)	2 (1.3)
Fatigue	38 (12.2)	7 (2.2)	11 (7.2)	1 (0.7)
Vomiting	38 (12.2)	0	15 (9.8)	0

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

Durvalumab ± Tremelimumab + Chemotherapy as First-Line Treatment for mNSCLC: Results from the Phase 3 POSEIDON Study

Melissa L Johnson,[1] Byoung Chul Cho,[2] Alexander Luft,[3] Jorge Alatorre-Alexander,[4] Sarayut Lucien Geater,[5] Konstantin Laktionov,[6] Aleksandr Vasiliev,[7] Dmytro Trukhin,[8] Sang-We Kim,[9] Grygorii Ursol,[10] Maen Hussein,[11] Farah Louise Lim,[12] Cheng-Ta Yang,[13] Luiz Henrique Araujo,[14] Haruhiro Saito,[15] Niels Reinmuth,[16] Xiaojin Shi,[17] Lynne Poole,[18] Solange Peters,[19] Edward B Garon,[20] Tony Mok[21]

[1]Sarah Cannon Research Institute, Tennessee Oncology, PLLCC, Nashville, TN, USA; [2]Yonsei Cancer Center, Seoul, Korea; [3]Leningrad Regional Clinical Hospital, St Petersburg, Russia; [4]Health Pharma Professional Research, Mexico City, Mexico; [5]Prince of Songkla University, Songkhla, Thailand; [6]Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia; [7]"Private Health Institution "Clinical Hospital" RZD-Medicine", St Petersburg, Russia; [8]Odessa Regional Oncological Dispensary, Odessa, Ukraine; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Acinus, Kropyvnytskyi, Ukraine; [11]Florida Cancer Specialists – Sarah Cannon Research Institute, Leesburg, FL, USA; [12]Queen Mary University of London, London, United Kingdom; [13]Chang Gung Memorial Hospital, Taoyuan City, Taiwan; [14]Instituto Nacional de Cancer-INCA, Rio de Janeiro, Brazil; [15]Kanagawa Cancer Center, Yokohama, Japan; [16]Asklepios Lung Clinic, Munich-Gauting, Germany; [17]AstraZeneca, Gaithersburg, MD, USA; [18]AstraZeneca, Cambridge, UK; [19]Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland; [20]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [21]Chinese University of Hong Kong, Hong Kong, China

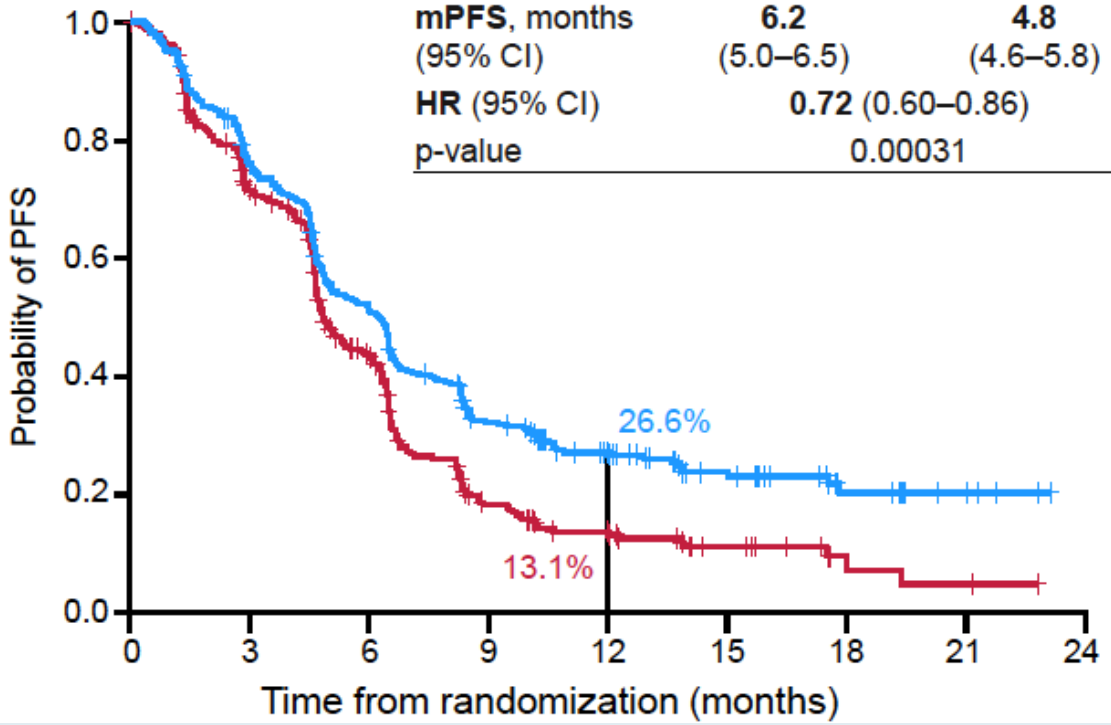
IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

Abstract PL02.01

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

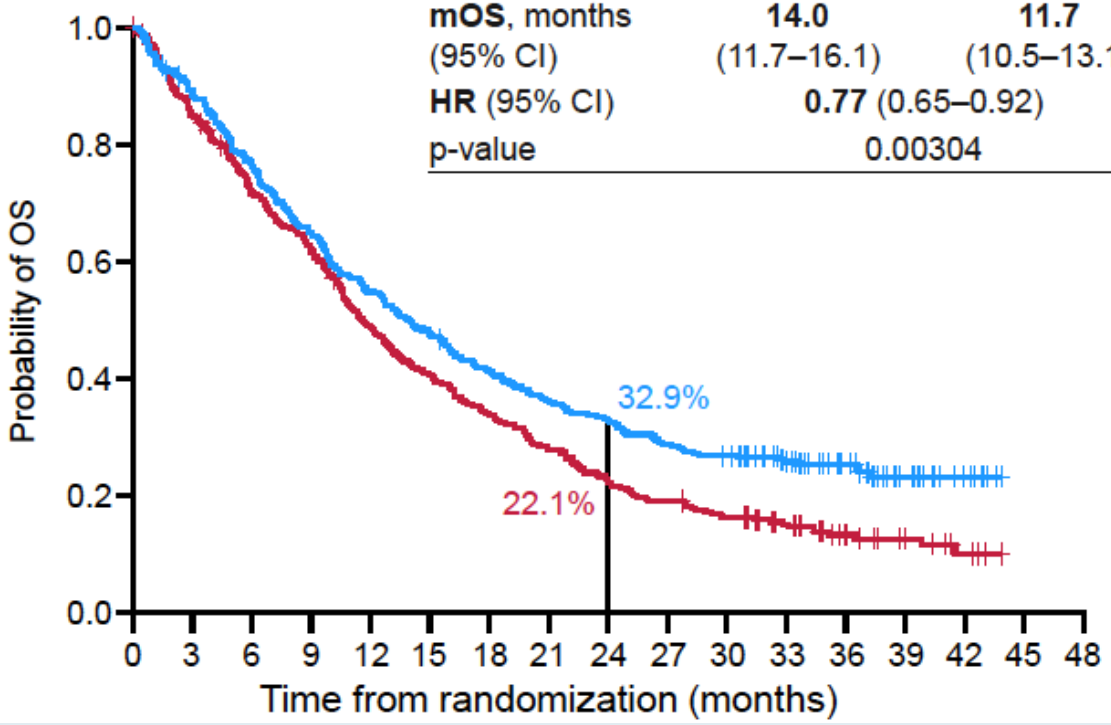
PFS

	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	



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	

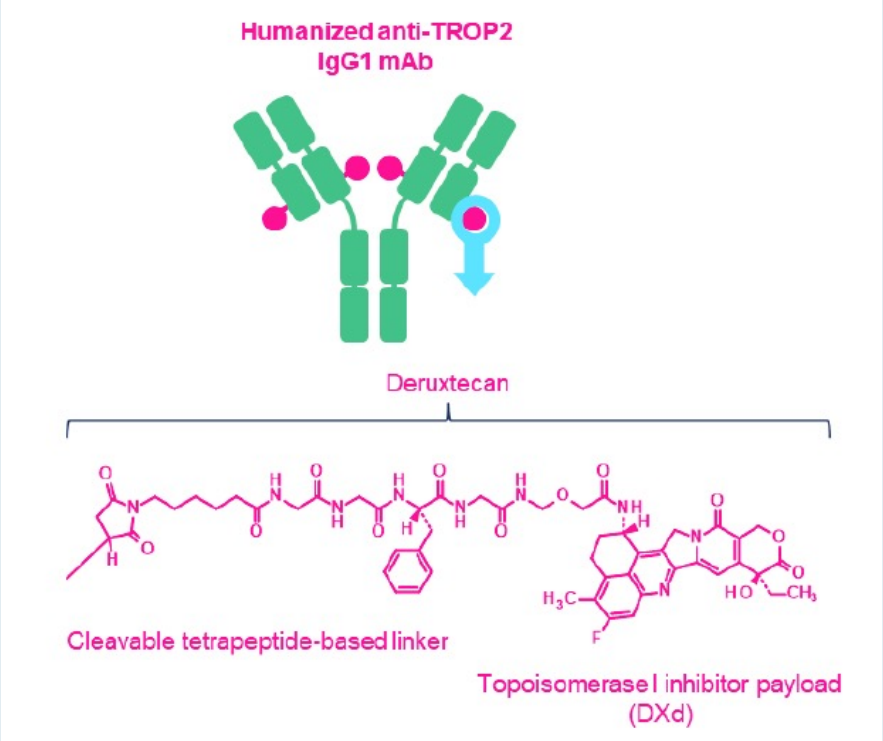


Johnson ML et al. WCLC 2021;Abstract PL02.01.

RTP RESEARCH TO PRACTICE

Targeting TROP2 with Datopotamab Deruxtecan (Dato-DXd)

- TROP2 is highly expressed in NSCLC, regardless of genomic mutation status, and has been associated with poor prognosis
- Dato-DXd is an antibody-drug conjugate composed of a humanized anti-TROP2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor payload via a stable tetrapeptide-based cleaver linker



Garon EB et al. 2021 WCLC;Abstract MA03.02.

2021 ESMO congress

Abstract LBA49

Efficacy of Datopotamab Deruxtecan (Dato-DXd) in Patients With Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC) and Actionable Genomic Alterations (AGAs): Preliminary Results From the Phase 1 TROPION-PanTumor01 Study

Edward B. Garon,[1] Melissa L. Johnson,[2] Aaron E. Lisberg,[1] Alexander Spira,[3] Noboru Yamamoto,[4] Rebecca S. Heist,[5] Jacob M. Sands,[6] Kiyotaka Yoh,[7] Funda Meric-Bernstam,[8] Satoru Kitazono,[9] Jonathan Greenberg,[10] Fumiaki Kobayashi,[11] Yui Kawasaki,[11] Lori Jukofsky,[10] Kota Nakamura,[10] Toshio Shimizu[4]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Sarah Cannon Research Institute, Tennessee Oncology, PLLC/OneOncology, Nashville, TN, USA; [3]Virginia Cancer Specialists, Fairfax, VA, USA; [4]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; [5]Massachusetts General Hospital, Boston, MA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]National Cancer Center Hospital East, Chiba, Japan; [8]The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [9]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [10]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [11]Daiichi Sankyo Co, Ltd, Tokyo, Japan

RTP RESEARCH TO PRACTICE

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

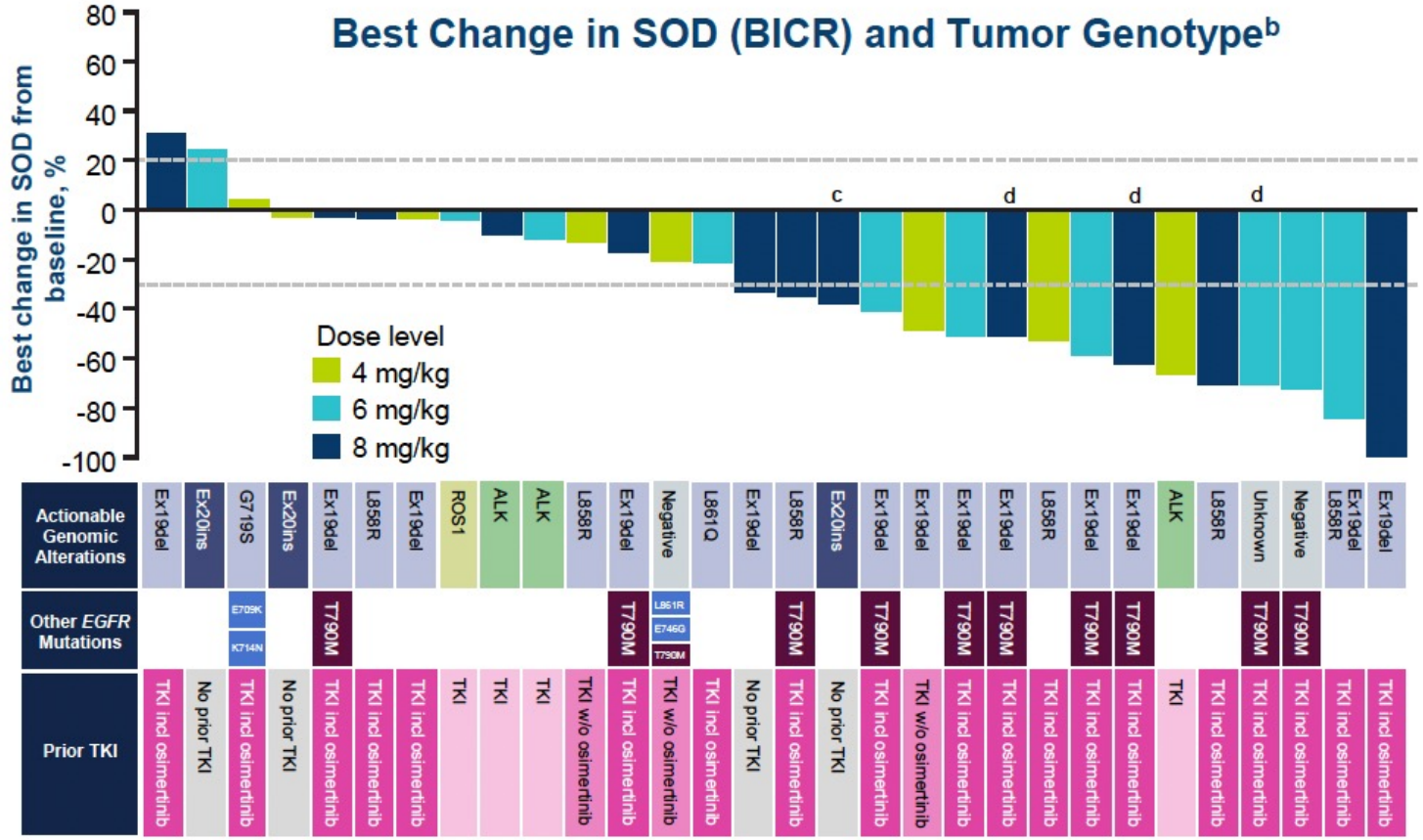
Best Overall Response (BICR)

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]



SOD: sum of diameter

Garon EB et al. ESMO 2021;Abstract LBA49.

Thank you for joining us!

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

RTP
RESEARCH
TO PRACTICE