Implications of Recent Data Sets for the Current and Future Management of Lung Cancer

Part 3 of a 3-Part Post-ESMO Congress 2023 CME/MOC-Accredited Live Webinar Series

Tuesday, November 14, 2023
5:00 PM – 6:30 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Zofia Piotrowska, MD, MHS
David R Spigel, MD

Moderator

Neil Love, MD

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Faculty

Luis Paz-Ares, MD, PhD
Chair of the Medical Oncology Department at the Hospital Universitario 12 de Octubre
Associate Professor at the Universidad Complutense
Head of the Lung Cancer Unit at the National Oncology Research Center
Madrid, Spain

David R Spigel, MD
Chief Scientific Officer
Sarah Cannon Research Institute
Nashville, Tennessee

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

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

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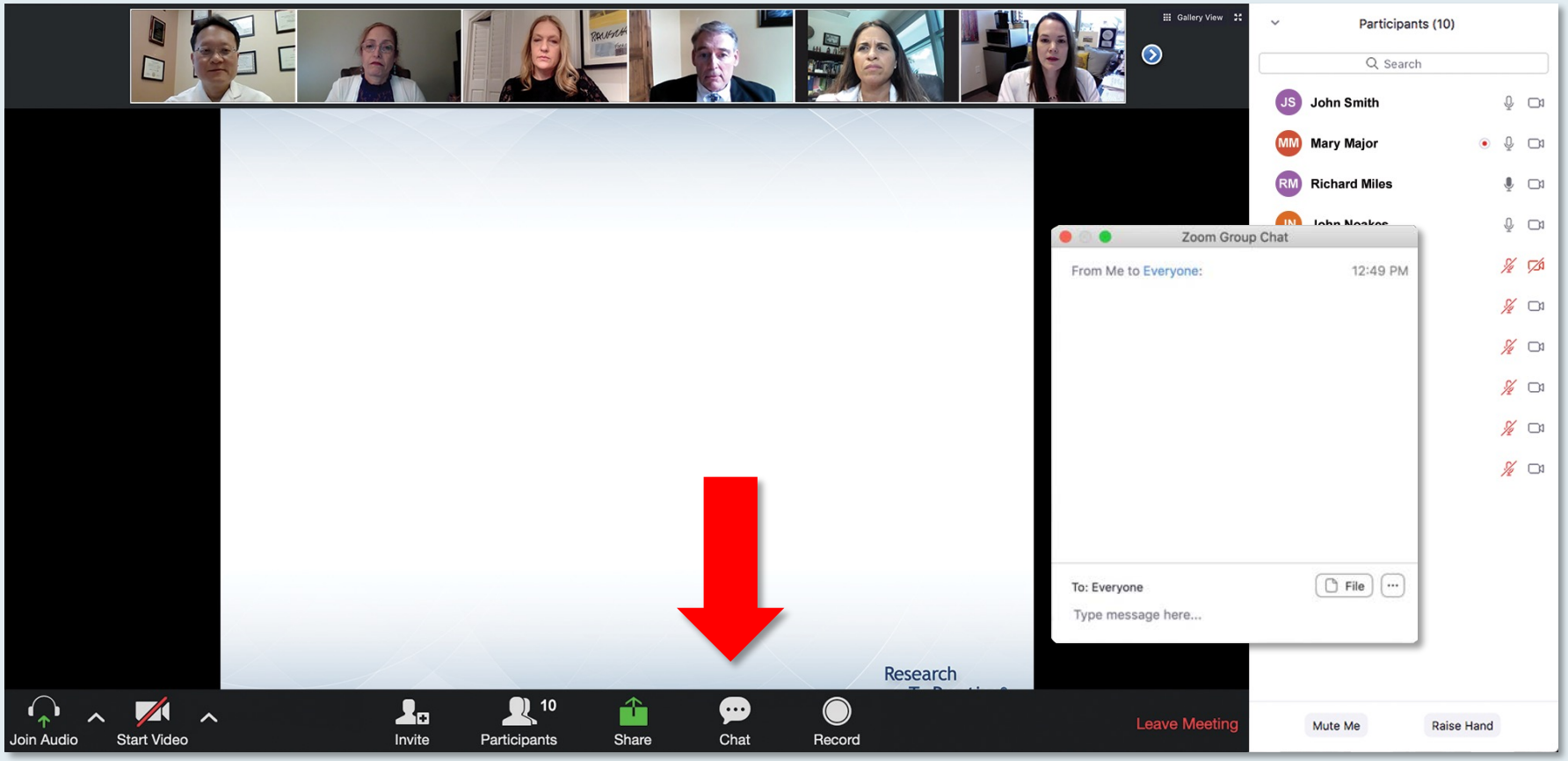

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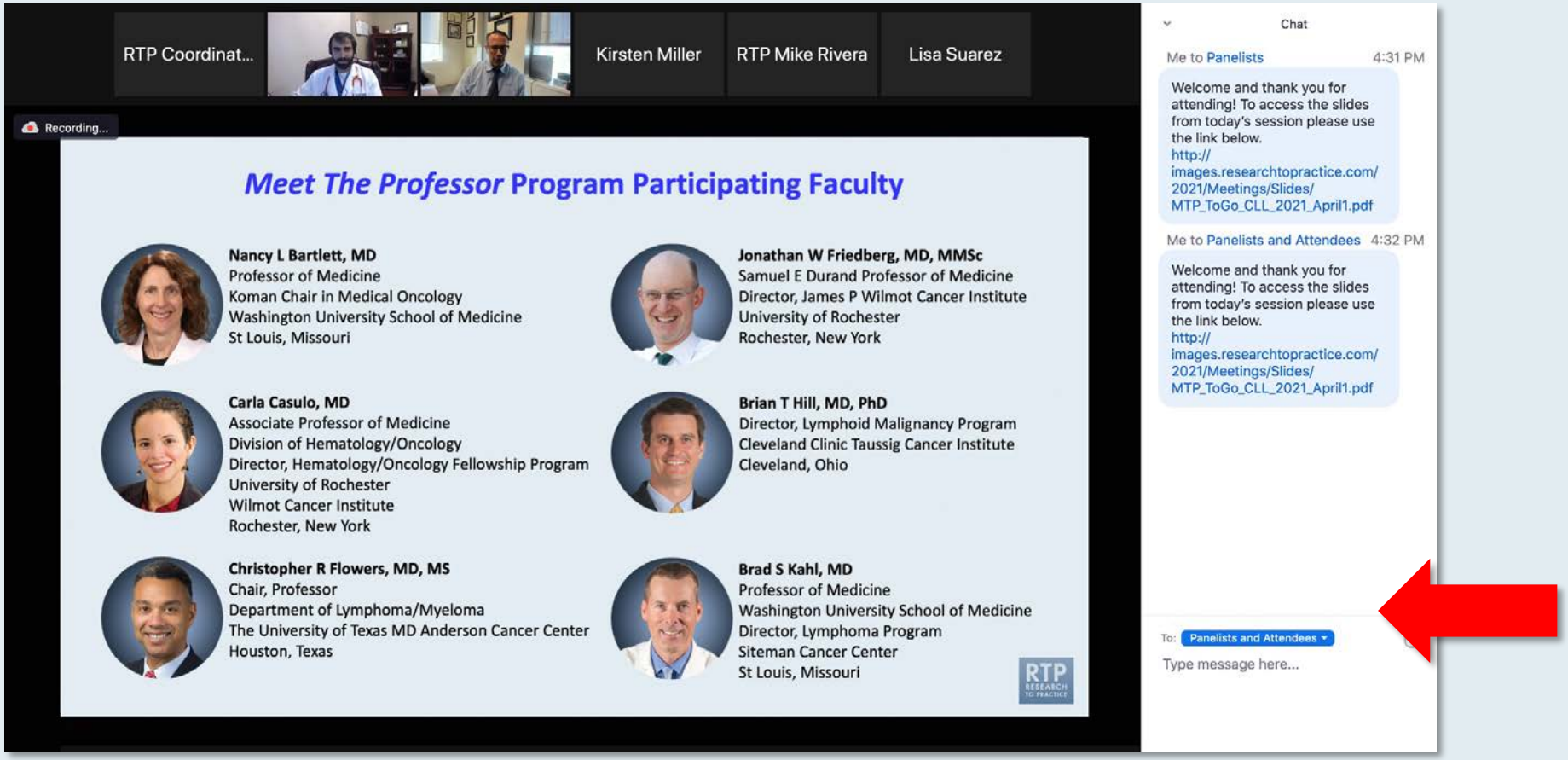

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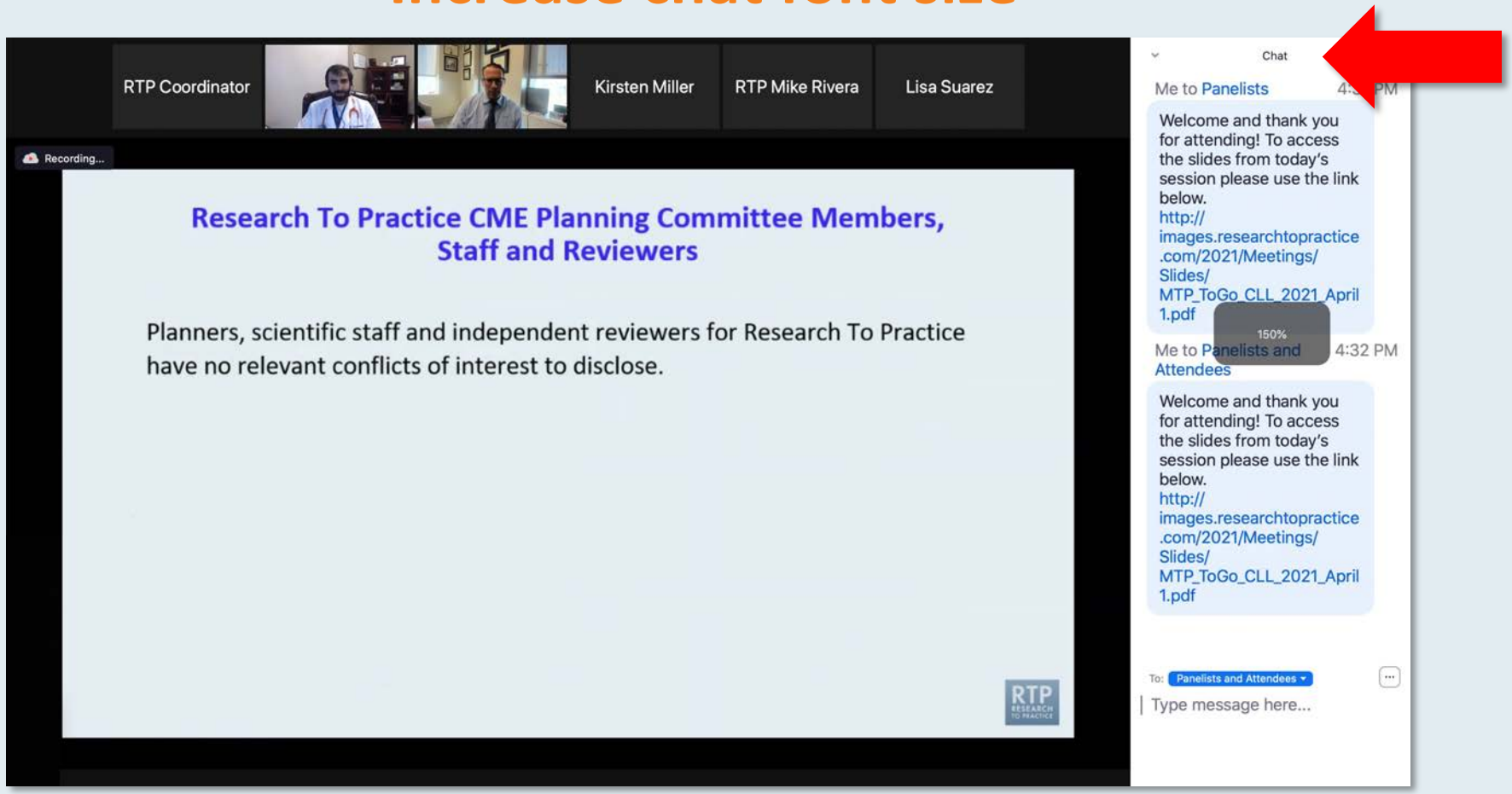

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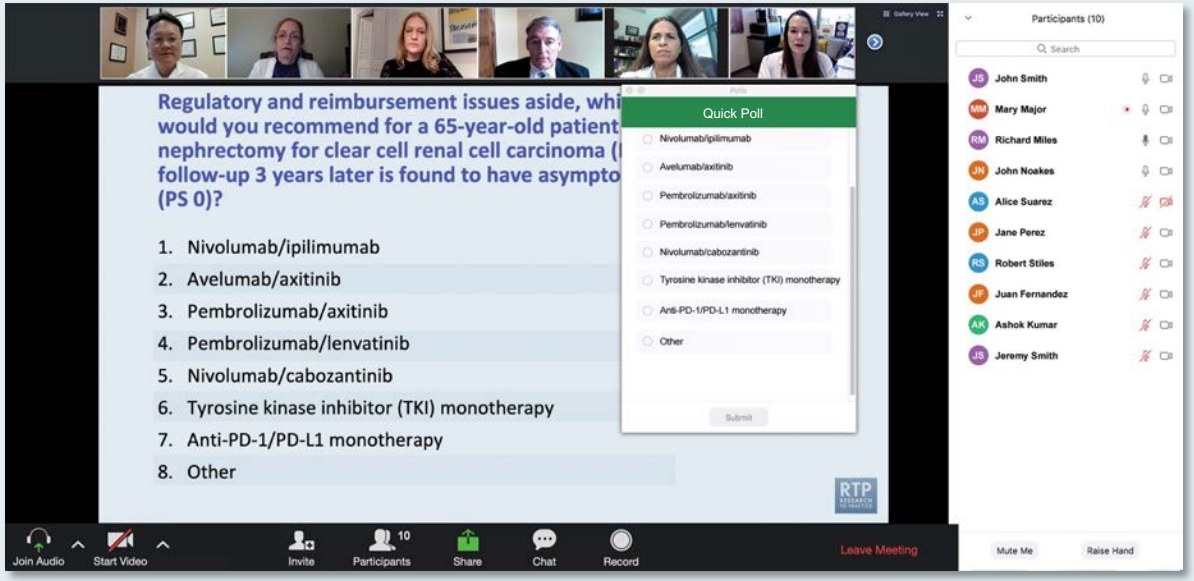

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DR MATTHEW GUBENS

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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Optimizing the Management of Gastroesophageal Cancers

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5:00 PM – 6:00 PM ET

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Moderator

Neil Love, MD

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Inside the Issue: Targeted and Immunotherapeutic Approaches for Biliary Tract Cancers

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Wednesday, November 29, 2023
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Lipika Goyal, MD, MPhil
Milind Javle, MD

Moderator

Neil Love, MD

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

A 3-Part CME Satellite Symposium Series Held in Partnership with the 2023 San Antonio Breast Cancer Symposium®

ER-Positive Metastatic Breast Cancer

Tuesday, December 5, 2023

7:15 PM – 9:15 PM CT

Localized HER2-Negative Breast Cancer

Wednesday, December 6, 2023

7:15 PM – 9:15 PM CT

HER2-Low Breast Cancer

Thursday, December 7, 2023

7:15 PM – 8:45 PM CT

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of ER-Positive Metastatic Breast Cancer

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Erika Hamilton, MD
Komal Jhaveri, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Localized HER2-Negative Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Wednesday, December 6, 2023

7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)

Faculty

Harold J Burstein, MD, PhD
Matthew P Goetz, MD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Lajos Pusztai, MD, DPhil, FASCO

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of HER2-Low Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series in Partnership with the 2023 San Antonio Breast Cancer Symposium®

Thursday, December 7, 2023

7:15 PM – 8:45 PM CT (8:15 PM – 9:45 PM ET)

Faculty

Aditya Bardia, MD, MPH

Lisa A Carey, MD, ScM, FASCO

Shanu Modi, MD

Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hematologic Cancers

A 4-Part CME Friday Satellite Symposium Series Preceding the 65th ASH Annual Meeting and Exposition

Friday, December 8, 2023

Follicular, Mantle Cell and Hodgkin Lymphoma
7:30 AM – 10:00 AM PT

Diffuse Large B-Cell Lymphoma
11:30 AM – 1:30 PM PT

Chronic Lymphocytic Leukemia
3:15 PM – 5:15 PM PT

Multiple Myeloma
7:00 PM – 9:00 PM PT

Moderator
Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Follicular, Mantle Cell and Hodgkin Lymphoma (Part 1 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

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Jeremy S Abramson, MD, MMSc
Stephen M Ansell, MD, PhD
Nancy L Bartlett, MD
Jonathon B Cohen, MD
Jonathan W Friedberg, MD, MMSc
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Friday, December 8, 2023

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Michael Dickinson, MD
Grzegorz S Nowakowski, MD
Gilles Salles, MD, PhD
Laurie H Sehn, MD, MPH
Jason Westin, MD, MS

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

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Friday, December 8, 2023

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

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Noopur Raje, MD
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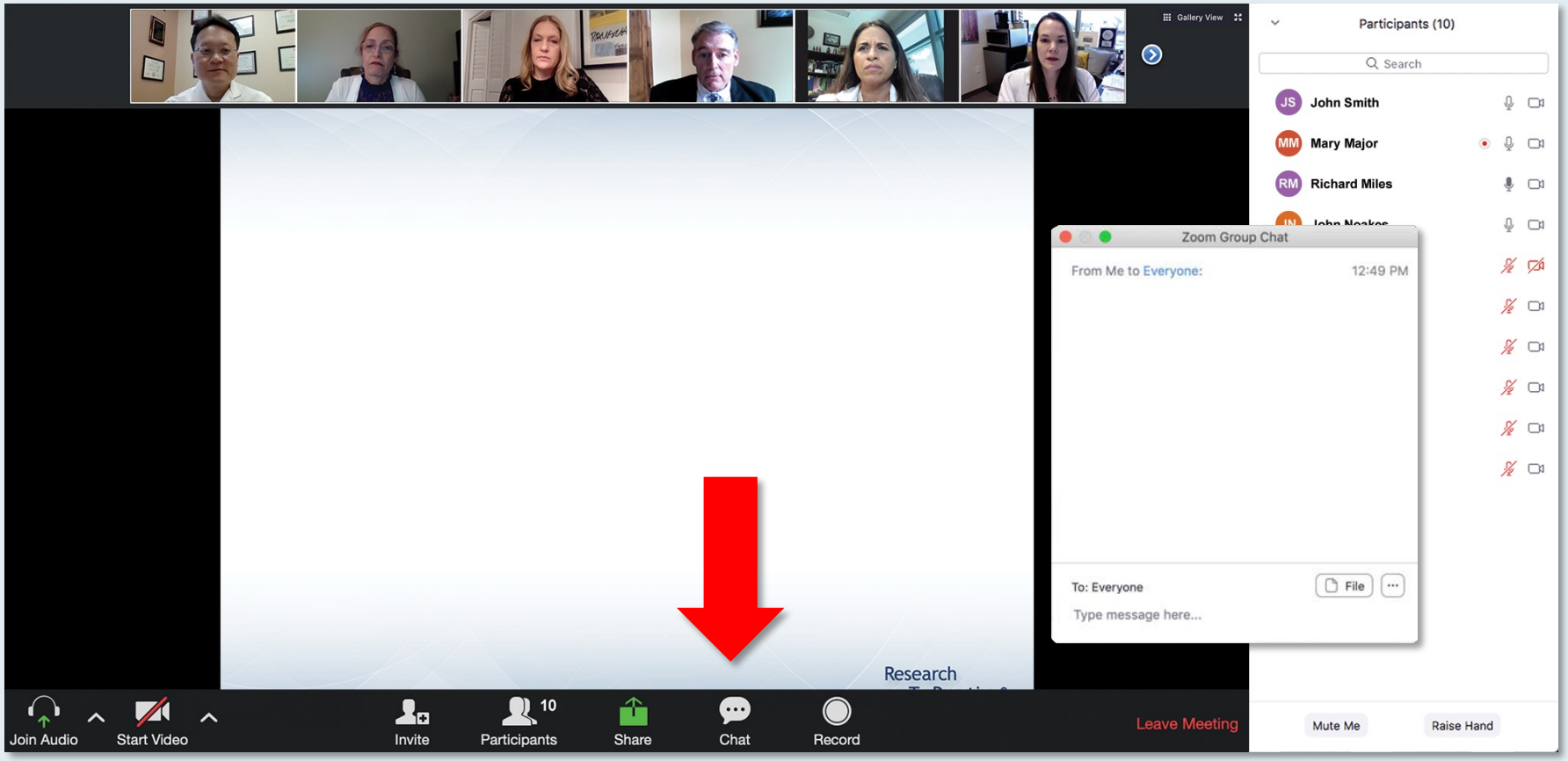

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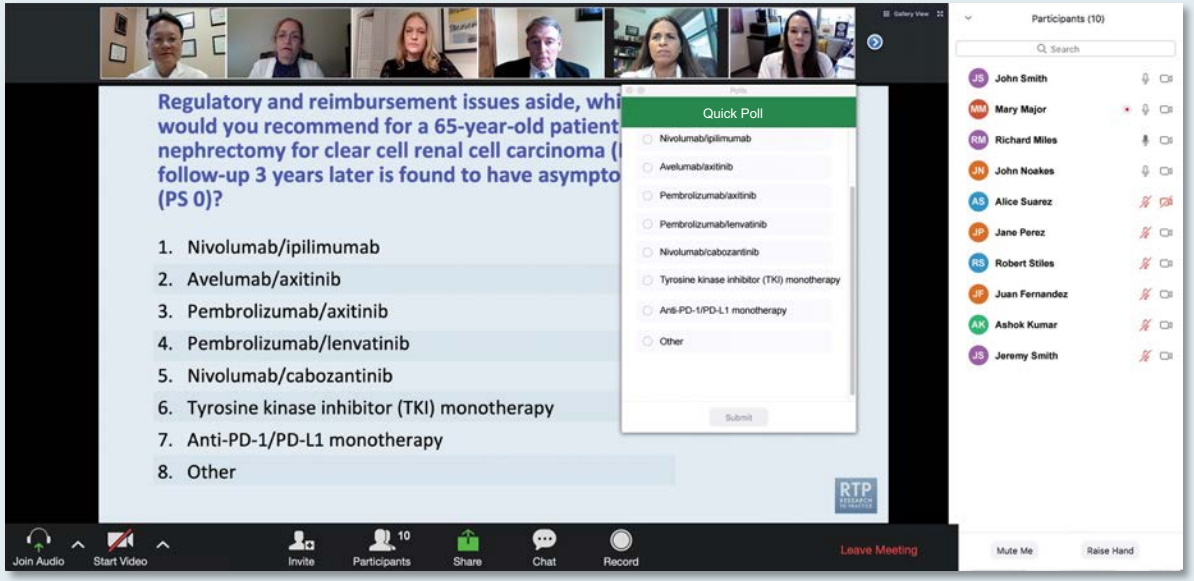

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Implications of Recent Data Sets for the Current and Future Management of Lung Cancer

ESMO 2023

Luis Paz-Ares
Hospital Universitario 12 de Octubre

Targeted Therapies for Metastatic NSCLC

Updates from WCLC and ESMO 2023

Zosia Piotrowska, MD, MHS
Massachusetts General Hospital

Key Data Sets from the 2023 World Conference on Lung Cancer and ESMO Meetings

Immunotherapeutic and Other Novel Strategies for Metastatic Non-Small Cell and Small Cell Lung Cancer

Aaron Lisberg, MD
University of California, Los Angeles
Santa Monica, California

November 14, 2023

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Key Data Sets

Luis Paz-Ares, MD, PhD

- Herbst RS et al. Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC). ASCO 2023;Abstract LBA3.
- Nassar AH et al. Consolidation EGFR-tyrosine kinase inhibitor (TKI) vs durvalumab vs observation in unresectable EGFR-mutant Stage III NSCLC. WCLC 2023;Abstract MA16.11.
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- Pulla MP et al. Neoadjuvant nivolumab (N) + chemotherapy (C) in the phase 3 CheckMate 816 study: 3-y results by tumor PD-L1 expression. ESMO 2023;Abstract LBA57.
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Key Data Sets

Luis Paz-Ares, MD, PhD (continued)

- Mitsudomi T et al. Surgical outcomes with neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in resectable NSCLC (AEGEAN). WCLC 2023;Abstract OA12.05.
- Reck M et al. Associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase 3 AEGEAN trial. ESMO 2023;Abstract LBA59.
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Key Data Sets

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- Garassino MC et al. Durvalumab (durva) after sequential chemoradiotherapy (CRT) in patients (pts) with unresectable Stage III NSCLC: Final analysis from PACIFIC-6. ESMO 2023;Abstract LBA61.
- Filippi ARR et al. Durvalumab after radiotherapy (RT) in patients with unresectable Stage III NSCLC ineligible for chemotherapy (CT): Primary results from the DUART study. ESMO 2023;Abstract LBA62.

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Zofia Piotrowska, MD, MHS

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- Planchard D et al. FLAURA2: Safety and CNS outcomes of first-line (1L) osimertinib (osi) ± chemotherapy (CTx) in EGFRm advanced NSCLC. ESMO 2023;Abstract LBA68.
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- Cho BC et al. Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results from MARIPOSA, a phase 3, global, randomized, controlled trial. ESMO 2023;Abstract LBA14.

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Key Data Sets

Zofia Piotrowska, MD, MHS (continued)

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Key Data Sets

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Key Data Sets

Zofia Piotrowska, MD, MHS (continued)

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- Planchard D et al. Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2 (ERBB2)-mutant (HER2m) metastatic non-small cell lung cancer (NSCLC) with and without brain metastases (BMs): Pooled analyses from DESTINY-Lung01 and DESTINY-Lung02. ESMO 2023;Abstract 1321MO.

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- Gandara DR et al. Predictive utility of patient-reported outcomes for survival in 1st-line treated patients with aNSCLC in EMPOWER-Lung 1 and 3. WCLC 2023;Abstract MA05.11.
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Key Data Sets

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Aaron Lisberg, MD (continued)

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Key Data Sets

Aaron Lisberg, MD (continued)

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A 74-year-old Taiwanese non-smoking woman presented to a nearby hospital with shortness of breath and was found to have a large burden of metastatic disease on scans (I can include pictures). She had bulky masses in her lungs bilaterally.

Due to the large burden of pulmonary disease, was hypoxic and she required 6 L of oxygen in order to saturate around 90%. She had lost 30 pounds and had a severe cough. At this outside hospital, she was put on hospice without any tissue diagnosis. After a few months she had a family friend suggest she reach out and was seen at my office while still on hospice.

Obviously, my concern at this time was for a possible sensitizing mutation lung cancer.
She underwent tissue biopsy as well as liquid biopsy that showed a lung adenocarcinoma and she was positive for EGFR exon 19 deletion mutation.

She revoked her hospice and I immediately started her on osimertinib.

4 weeks later, she was completely off of oxygen and clinically doing great. She had the standard incredible response to osimertinib. However, about 4 weeks later, she started requiring oxygen again and became short of breath and had a cough. She ended up in the emergency room with hypoxia, cough, and new atrial fibrillation. Her imaging showed the previous sites of cancer had improved drastically, however she developed a new pneumonitis bilaterally. She required IV antibiotics and intravenous steroids and slowly improved.

My question:
Osimertinib induced pneumonitis or interstitial lung disease is relatively uncommon but a serious complication. We are used to dealing with this with immunotherapy.

In this case, for a patient that is frail, and her cancer is having a remarkable response to her EGFR targeted therapy, once the patient has improved, would experts rechallenge her? Would they use osimertinib again at a reduced dose? Would they leave on a small steroid dose in the beginning? Would they reach for another EGFR TKI?

Unfortunately she is not a great candidate for systemic chemotherapy and my understanding is these patients do not do as well on immunotherapy.

Happy to provide more details or info at request!

Thank you

Eric Fox, MD

Philadelphia, Pennsylvania

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ADAURA trial: Overall Survival

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§
Maximum interval between surgery and randomization:
- 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)

Randomization 1:1 (N=682)

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

Planned treatment duration: 3 years

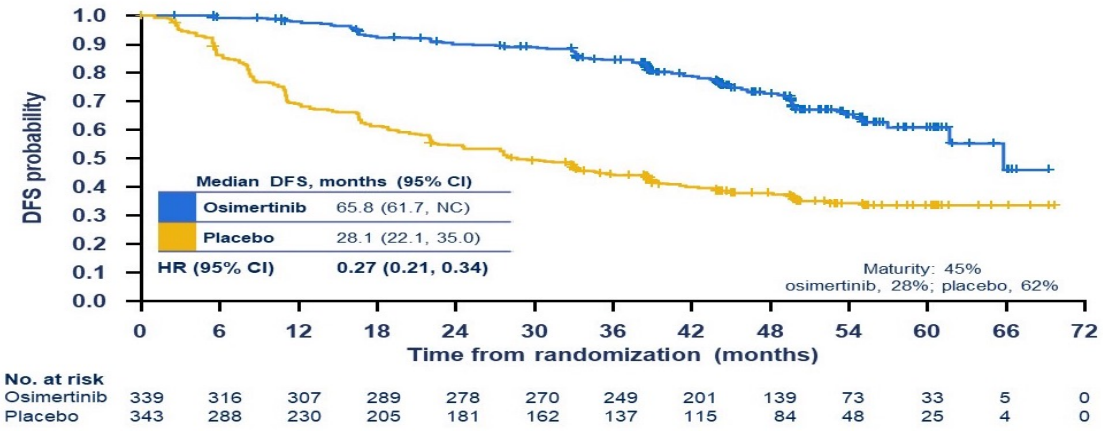
Treatment continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

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

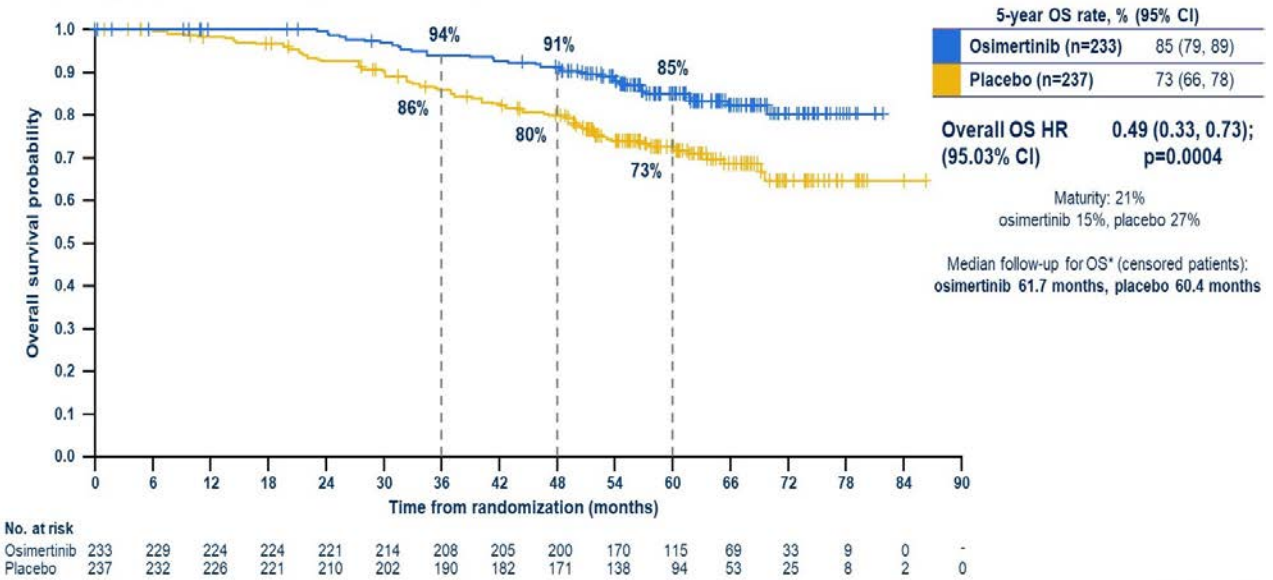
Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

ADAURA updated DFS analysis[3,4] (stage IB—IIIA)†

JCO January 2023



Subsequent treatments, n (%)	Osimertinib (n=339)	Placebo (n=343)
Patients who received subsequent anti-cancer treatment*	76 (22)	184 (54)
EGFR-TKIs	58 (76)	162 (88)
Osimertinib	31 (41)	79 (43)
Other EGFR-TKIs	28 (37)	114 (62)
Chemotherapy	20 (26)	46 (25)
Radiotherapy	30 (39)	53 (29)
Other anti-cancer treatments	12 (16)	29 (16)

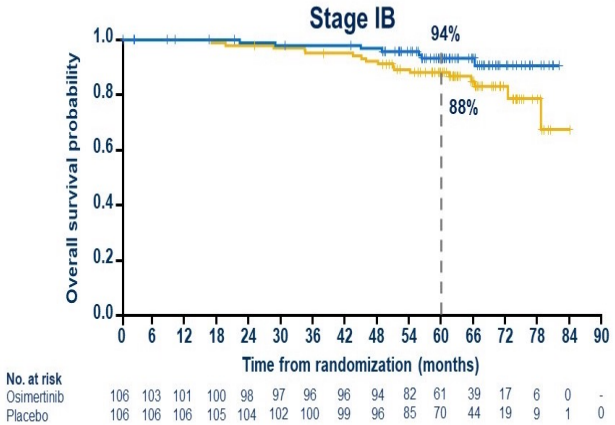


Courtesy of Luis Paz-Ares, MD, PhD

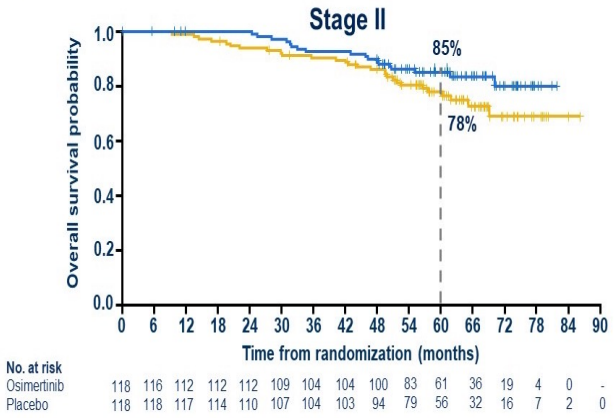
Herbst et al. ESMO 2023

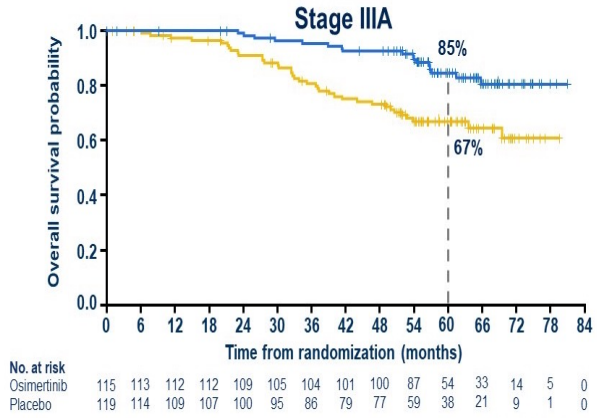
ADAURA trial: Overall Survival

Overall survival by disease stage

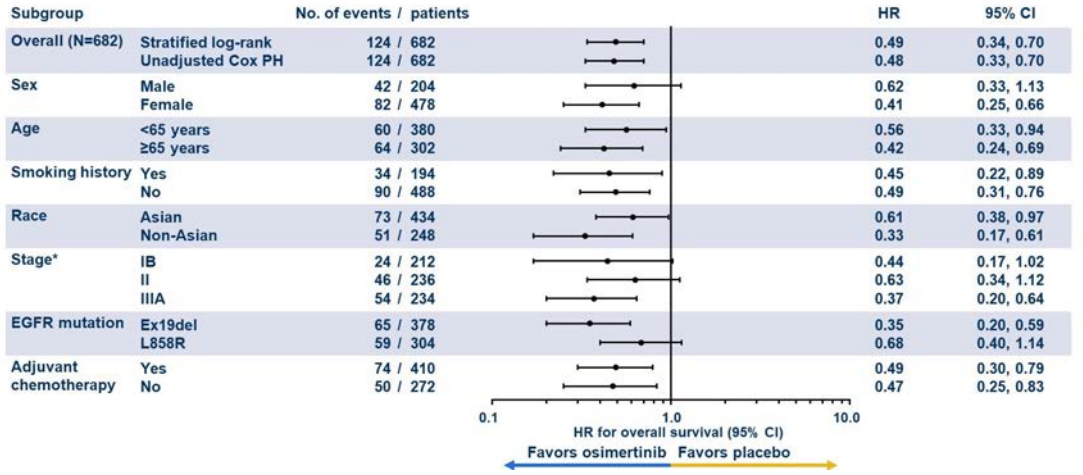


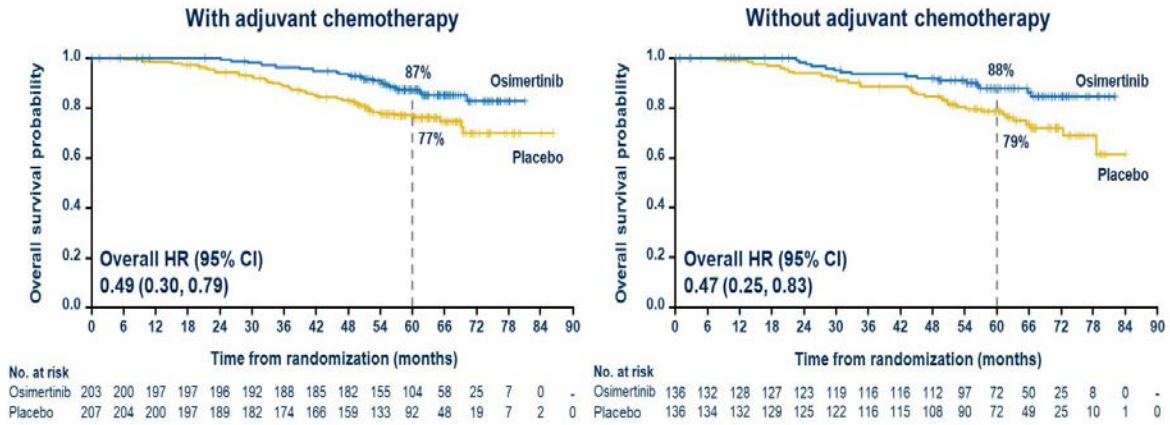
	Stage IB	Stage II	Stage IIIA
5 year OS rate, % (95% CI)			
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	0.44 (0.17, 1.02)	0.63 (0.34, 1.12)	0.37 (0.20, 0.64)





OS across subgroups: patients with stage IB / II / IIIA disease





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Herbst et al. ESMO 2023

ALINA trial: Adjuvant Alectinib

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

N=257

Alectinib 600 mg BID 2 years → Recurrence

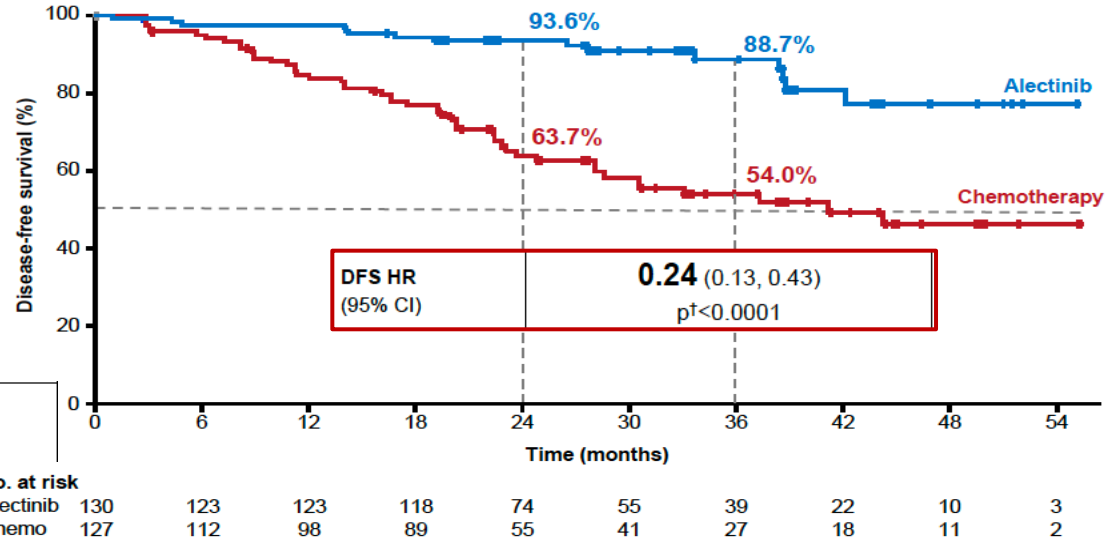
Platinum-based chemotherapy† Q3W; 4 cycles → Recurrence

Further treatments at investigator's choice and survival follow-up

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease-free survival: stage II–IIIA*

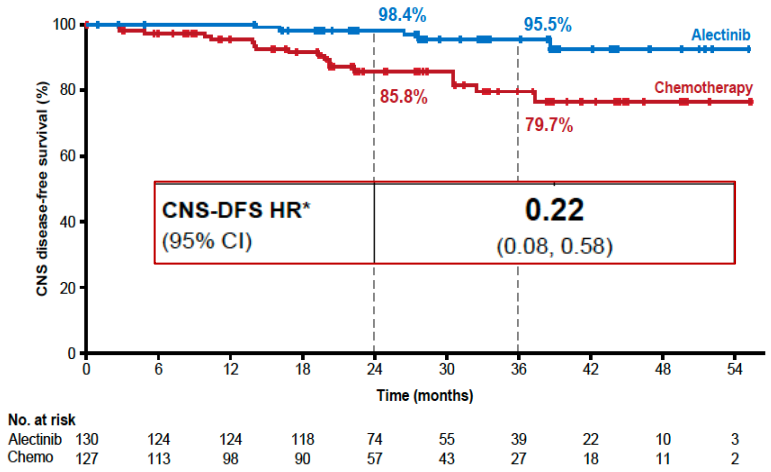


No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

CNS-DFS HR* (95% CI) 0.22 (0.08, 0.58)

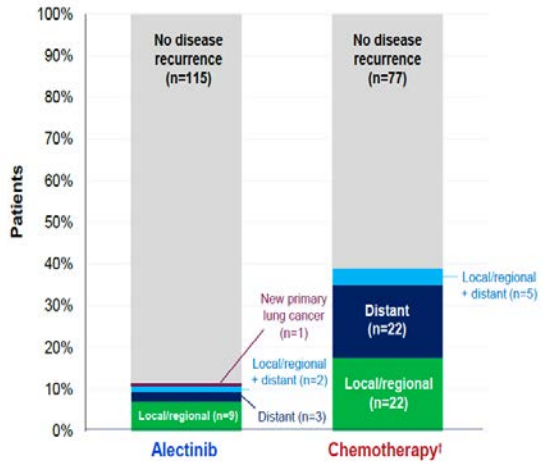
Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

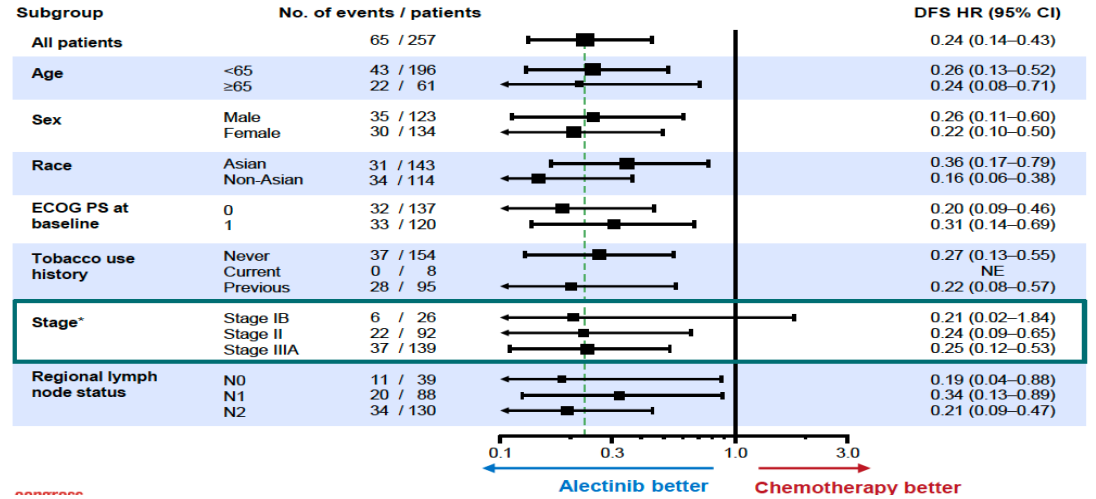


No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

Sites of disease recurrence (ITT)





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Solomon et al. ESMO 2023

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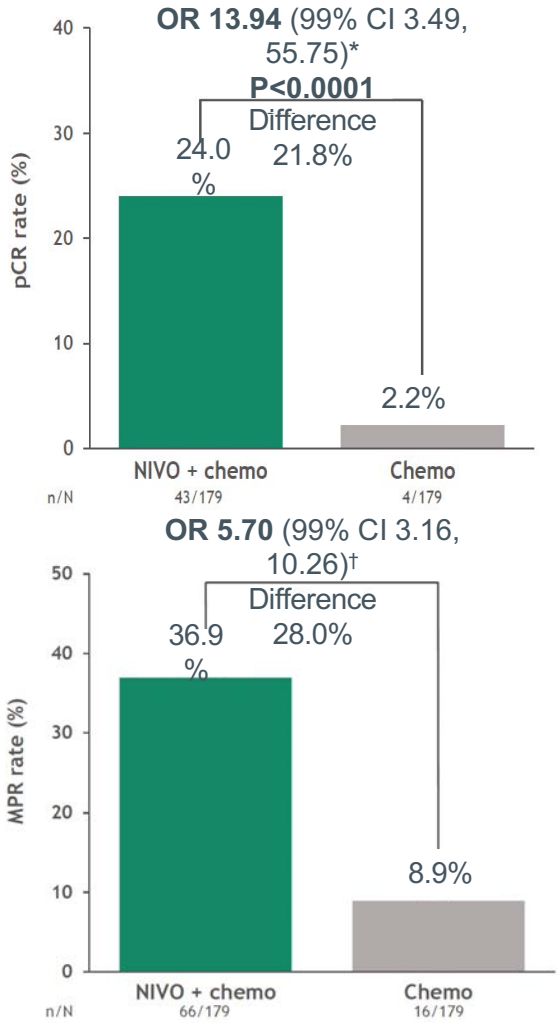
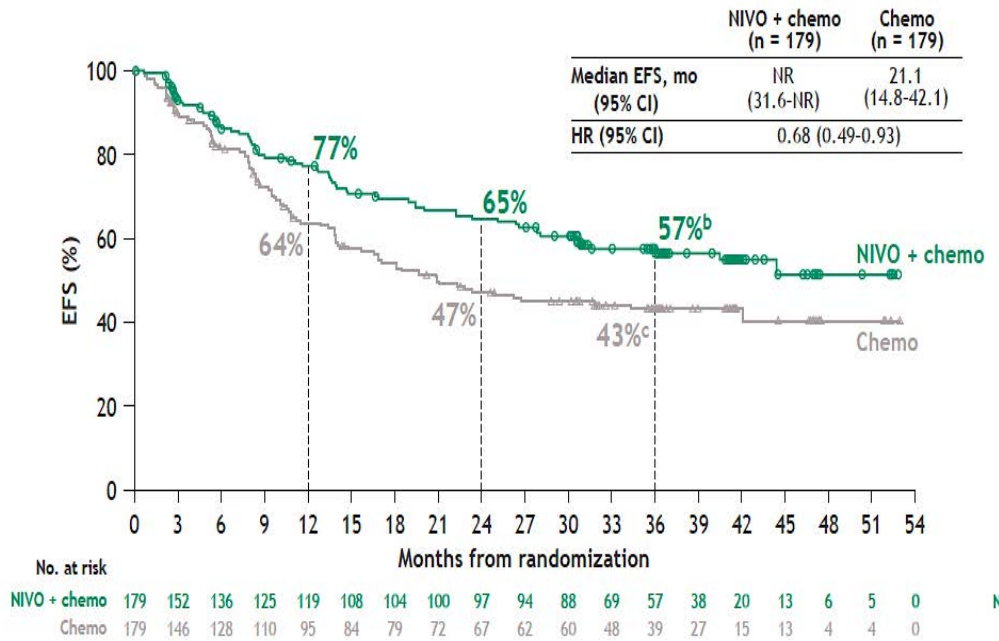
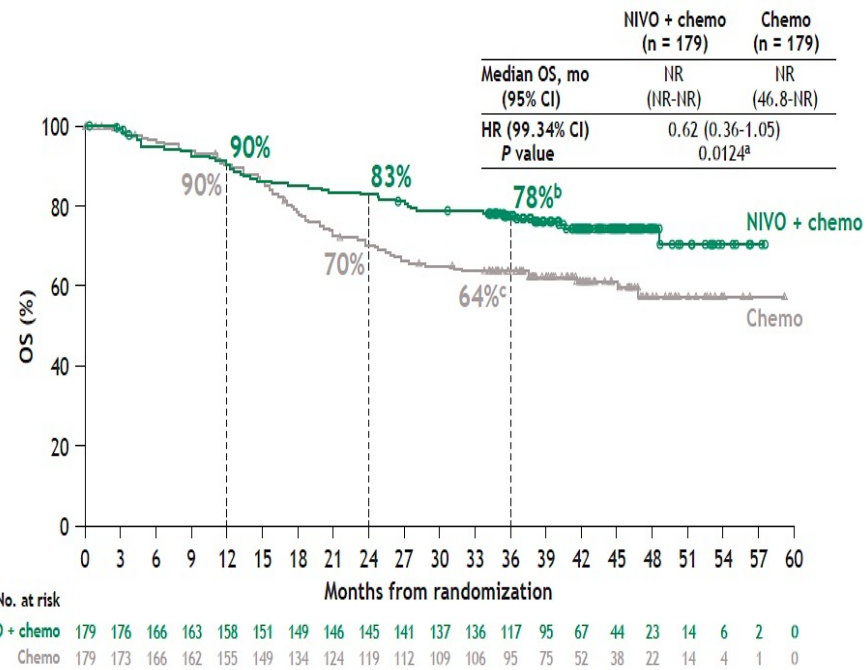
CheckMate 816: efficacy results with 3 years follow-up

Pathological outcomes



EFS and OS outcomes‡§





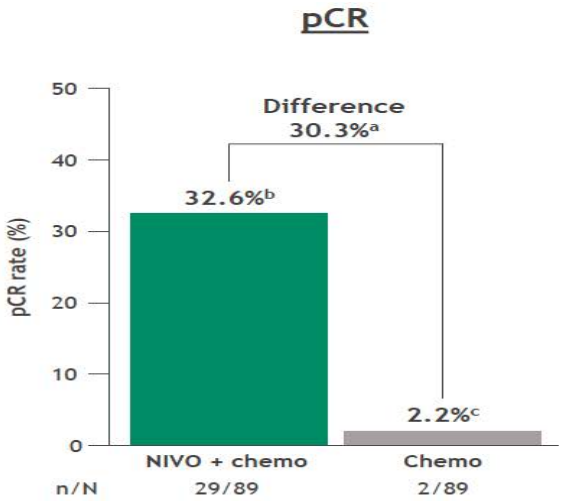
Courtesy of Luis Paz-Ares, MD, PhD

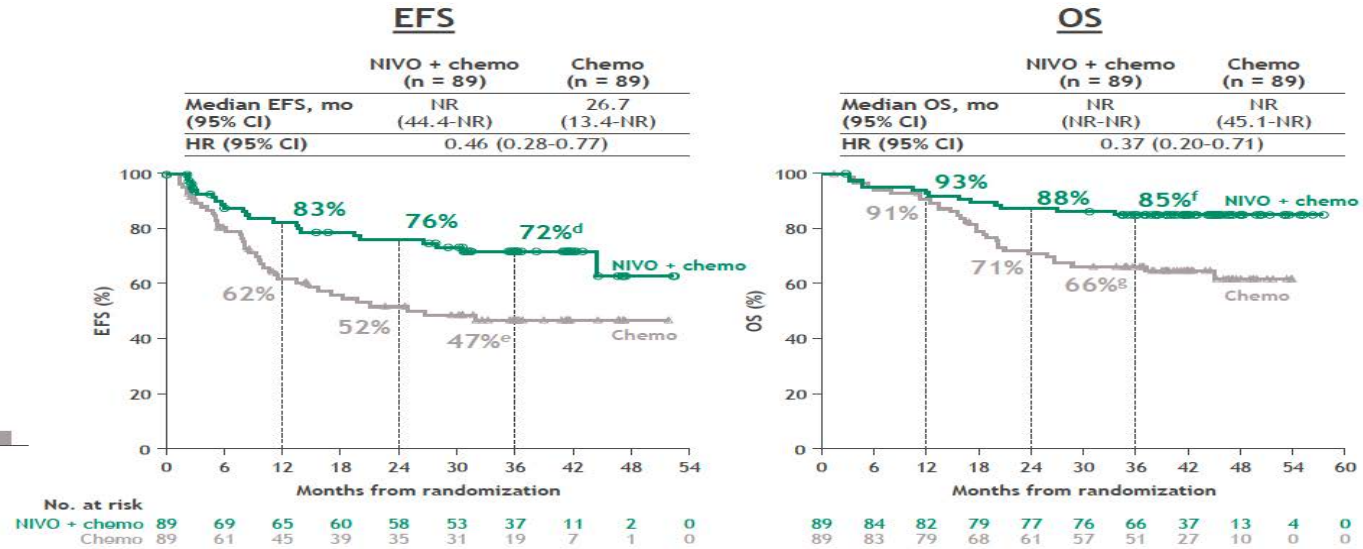
Hospital Universitario 12 de Octubre

Spicer J, et al. Oral presentation at ASCO 2021 (Abstract 8503); Girard N, et al. Oral presentation at AACR 2022 (Abstract CT012); Forde PM, et al. N Engl J Med 2022;386:1973–1985; Forde ELCC 2023

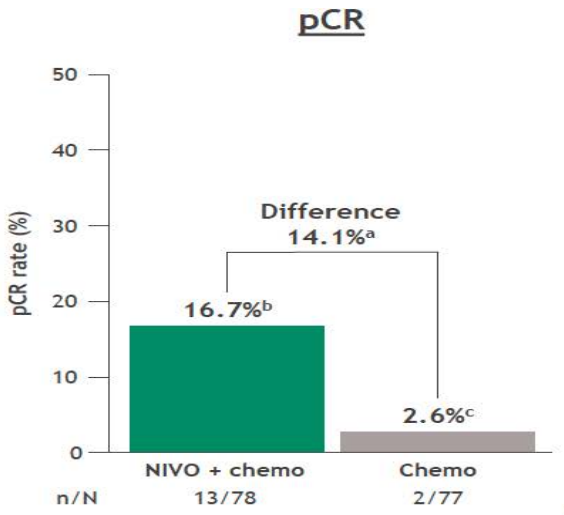
CheckMate 816 trial: Neoadjuvant CT+Nivo by PD-L1 status

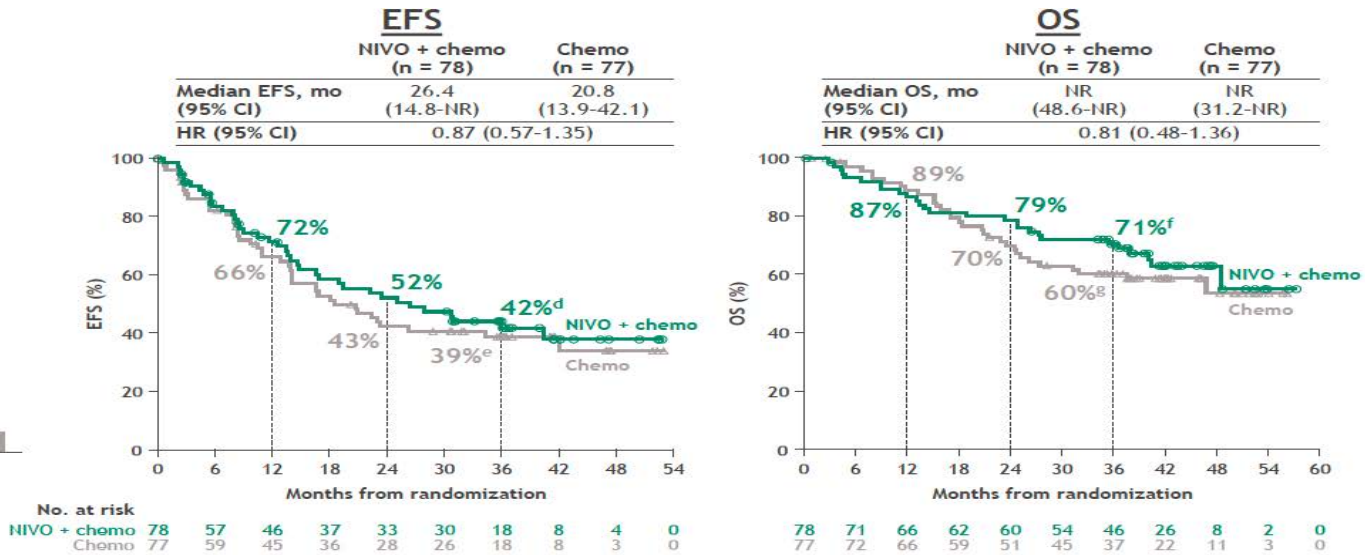
PD-L1 +





PD-L1 -





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Pulla MP et al. ESMO 2023

CheckMate 816 trial: Neoadjuvant CT+Nivo by PD-L1 status

	Tumor PD-L1 ≥ 1%		Tumor PD-L1 < 1%	
	NIVO + chemo (n = 89)	Chemo (n = 89)	NIVO + chemo (n = 78)	Chemo (n = 77)
Disease stage prior to definitive surgery,[a] %				
IIA	14	14	15	10
IIB	7	6	12	9
IIIA	48	48	45	46
Underwent definitive surgery,[b] %	84	74	81	77
Cancelled definitive surgery, %	16	24	17	20
Disease progression	6	9	6	12
AE	1	1	1	0
Other[c]	9	14	9	8
Surgical approach,[d] %				
Minimally invasive	39	21	19	19
Thoracotomy	57	65	64	63
Minimally invasive to thoracotomy	4	14	18	19
Extent of resection,[d,e] %				
Lobectomy	79	59	81	64
Pneumonectomy	17	24	11	22
Completeness of resection,[d,f] %				
R0	91	82	79	76

Courtesy of Luis Paz-Ares, MD, PhD

Pulla MP et al. ESMO 2023

Agenda

INTRODUCTION

MODULE 1: Localized NSCLC

- Adjuvant Targeted Therapy
- Perioperative Immunotherapy
- Locally Advanced Unresectable NSCLC

MODULE 2: EGFR-Mutated Metastatic NSCLC

MODULE 3: Other Targeted Treatment for Metastatic NSCLC

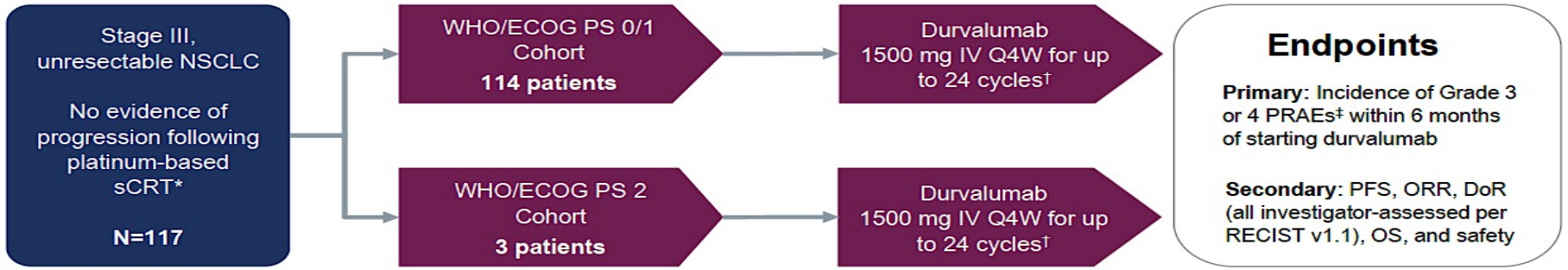
MODULE 4: Updates on Immunotherapy in Metastatic NSCLC

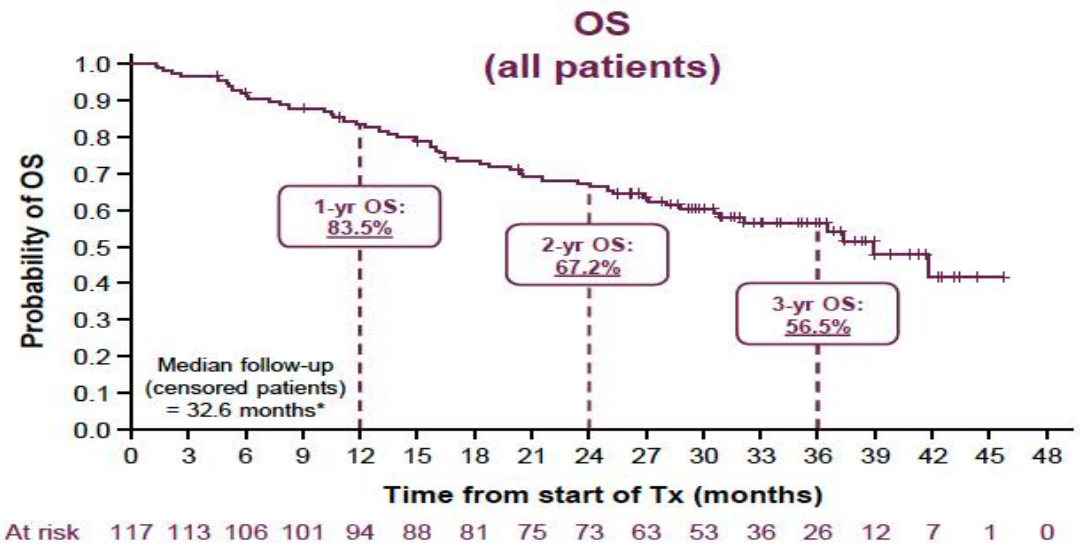
MODULE 5: Emerging Antibody-Drug Conjugates for Metastatic NSCLC

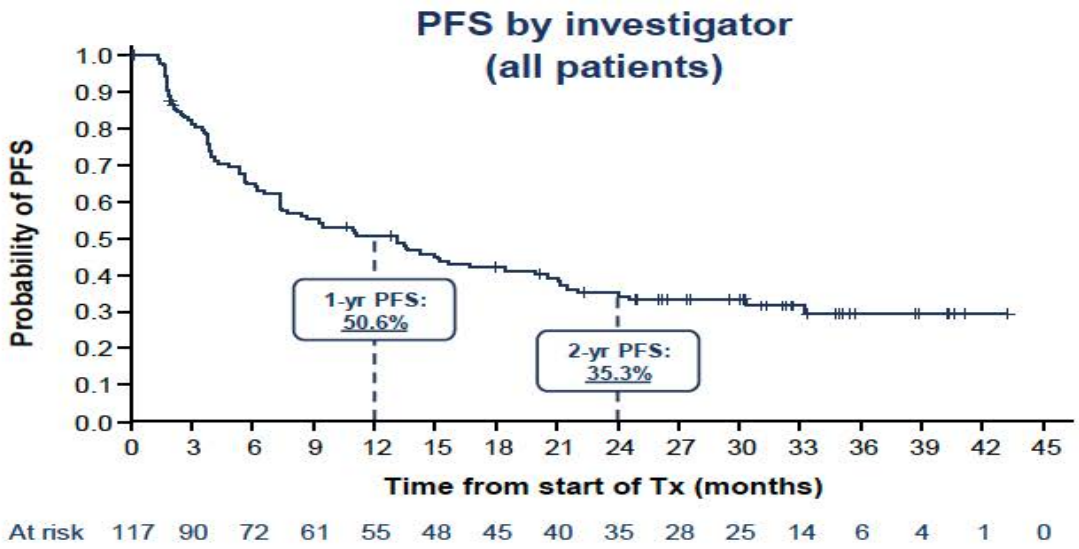
MODULE 6: Small Cell Lung Cancer

RTP
RESEARCH
TO PRACTICE

PACIFIC-6 trial – Durvalumab following sequential CT/RT





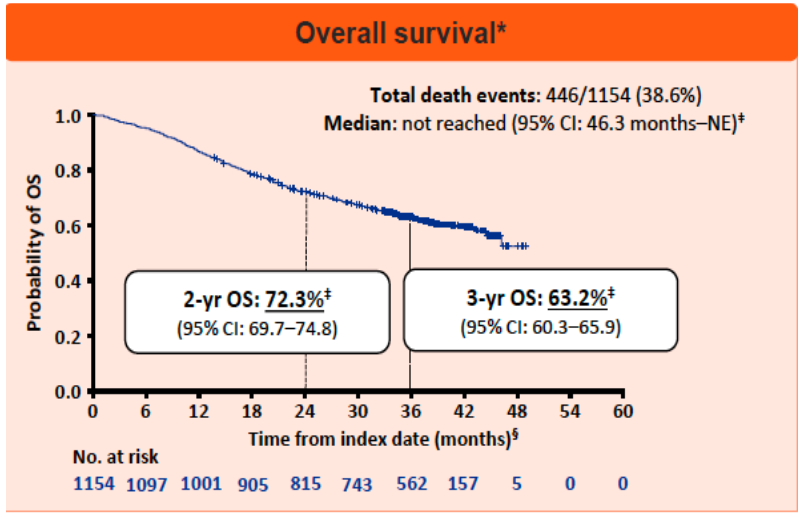


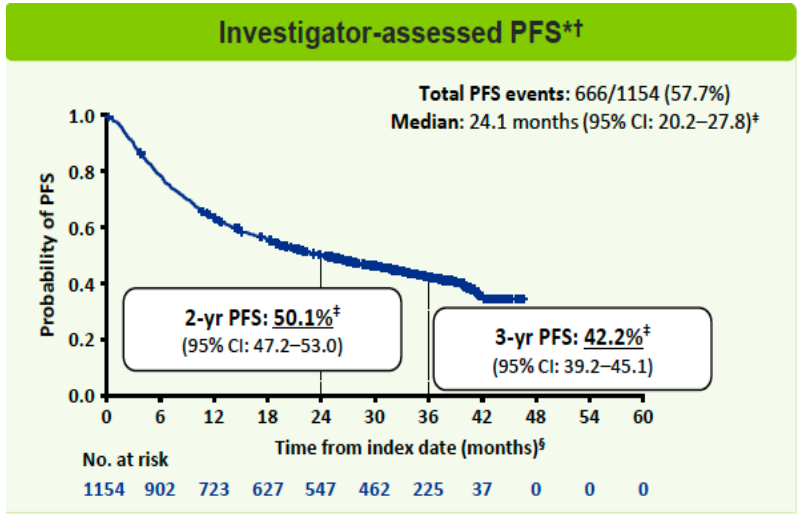
Endpoint		All patients (N=117)	PS 0/1 cohort (n=114)†
OS	Median, months (95% CI)	39.0 (30.6–NC)	39.0 (30.6–NC)
	3-yr rate, % (95% CI)	56.5 (46.4–65.5)	57.2 (46.9–66.2)
PFS by investigator	Median, months (95% CI)	13.1 (7.4–19.9)	13.1 (7.4–19.9)
	2-yr rate, % (95% CI)	35.3 (26.5–44.3)	35.4 (26.4–44.5)
Confirmed ORR by investigator	n (%)	24 (20.5)‡	24 (21.1)‡
	[95% CI]§	[13.6–29.0]	[14.0–29.7]

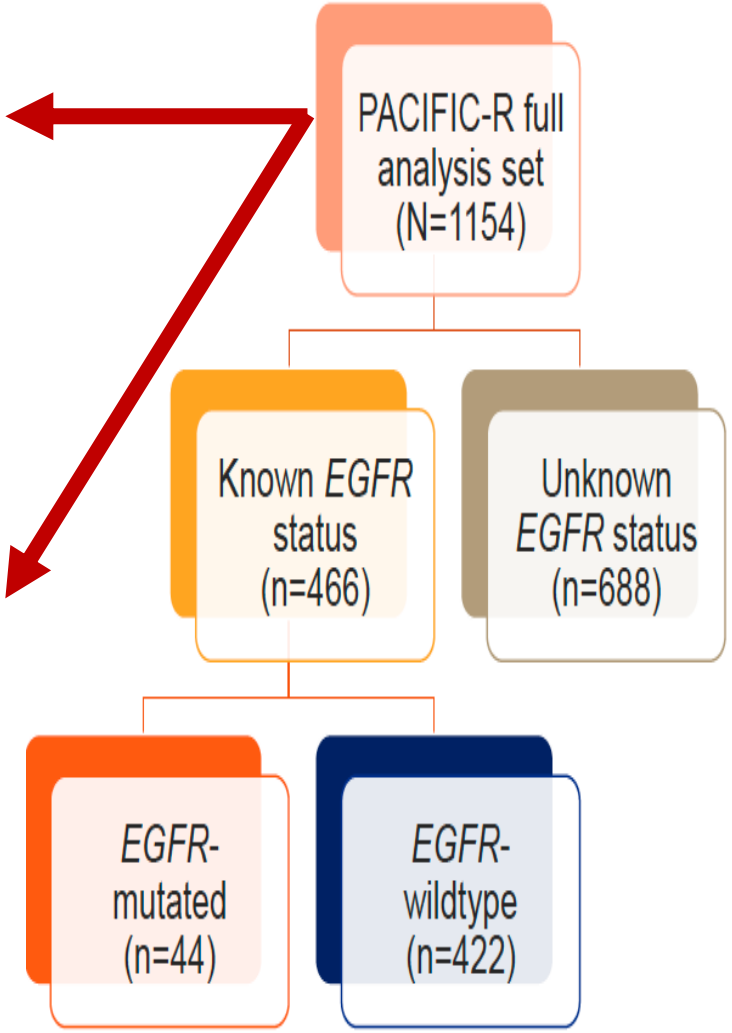
Courtesy of Luis Paz-Ares, MD, PhD

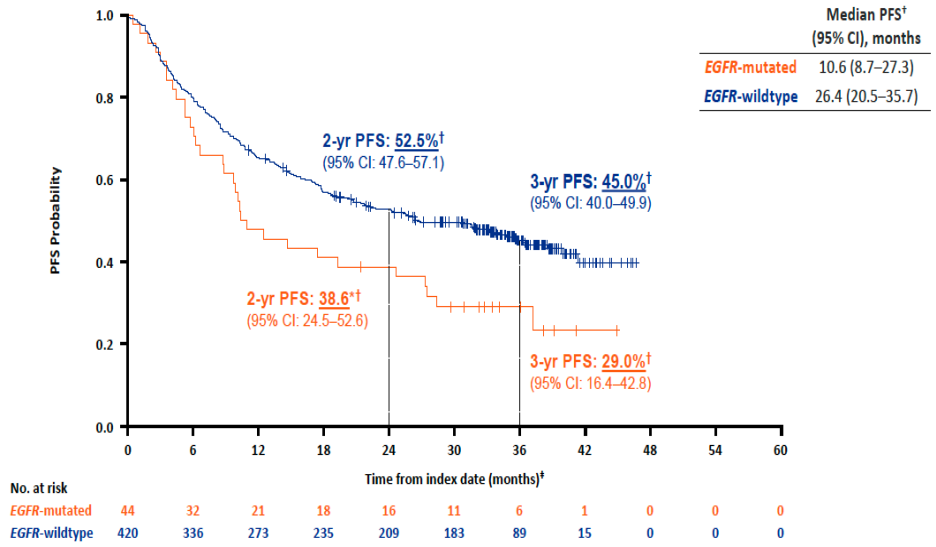
Garassino et al. ESMO 2023

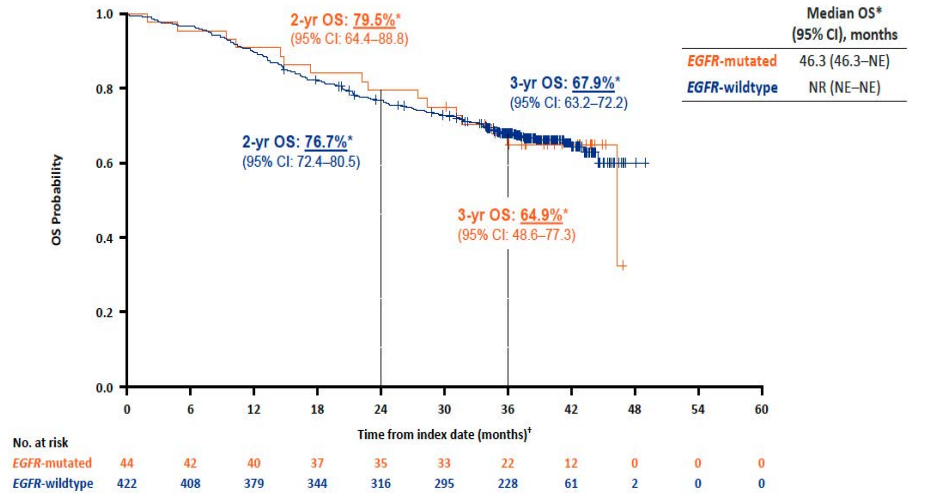
PACIFIC-R – Durvalumab following sequential CT/RT in EGFR mutant stage III NSCLC











Courtesy of Luis Paz-Ares, MD, PhD

Peters et al. ESMO 2023

Earlier Use of Durvalumab with Chemoradiotherapy Fails in Lung Cancer Study

Press Release – November 14, 2023

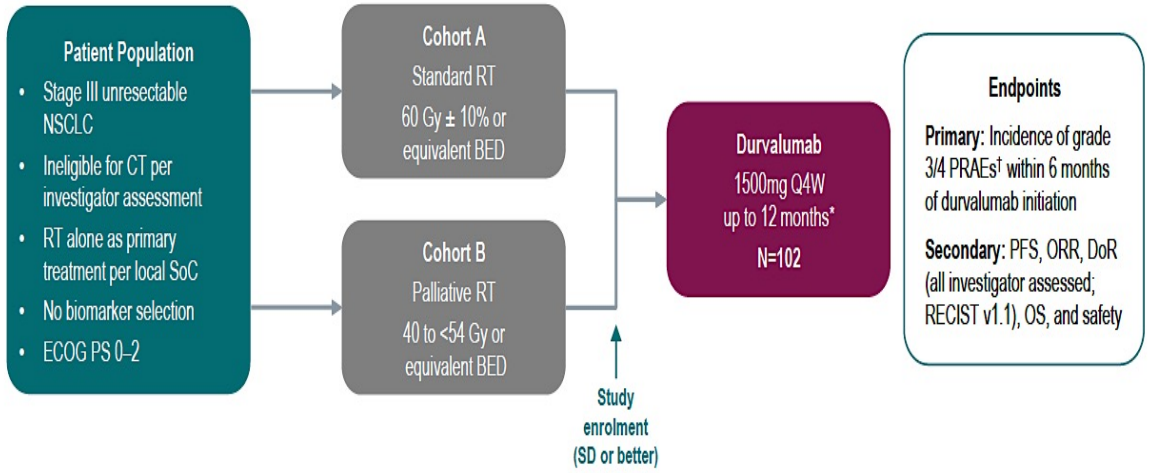
"[The manufacturer] announced Tuesday that the Phase III PACIFIC-2 study of durvalumab in patients with unresectable, Stage III non-small-cell lung cancer (NSCLC) failed to meet its primary endpoint of progression-free survival (PFS). The trial investigated concurrent durvalumab administration with chemoradiotherapy (CRT), with the aim of addressing patients who progress or discontinue treatment during CRT.

Durvalumab sequentially administered after platinum-based CRT is the established, global standard of care for the treatment of unresectable, Stage III NSCLC based on results from the Phase III PACIFIC study. 'Our goal with the PACIFIC-2 trial was to address a remaining unmet need for patients in this setting by introducing immunotherapy even earlier and concurrently administering durvalumab with chemoradiotherapy,' remarked Susan Galbraith, executive vice president of oncology R&D."

https://firstwordpharma.com/story/5800631?aid=5800631

RTP RESEARCH TO PRACTICE

DUART Trial
Durva following RT in stage III NSCLC ineligible to CT



- All patients had past/present medical conditions, mostly vascular (76.5%), metabolic (53.9%), respiratory (53.9%), or cardiac (52.0%) disorders

Characteristic		Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)
Age	Median (range), years	78.0 (43–87)	80.0 (56–87)	79.0 (43–87)
	≥75 years, %	59.3	72.1	64.7
Sex, %	Male	69.5	74.4	71.6
	Female	30.5	25.6	28.4
Race, %*	White	94.5	95.0	94.7
	Other	1.8	0	1.1
	Unknown	3.6	5.0	4.2
ECOG PS, %*	0	27.6	7.0	18.8
	1	70.7	76.7	73.3
	2	1.7	16.3	7.9
Disease stage, %†	IIIA	61.0	60.5	60.8
	IIIB	33.9	30.2	32.4
	IIIC	5.1	7.0	5.9
PD-L1 expression, %*	TC <1%	44.2	45.2	44.6
	TC ≥1%	53.5	48.4	51.4
Smoking status, %	Current	23.7	16.3	20.6
	Former	64.4	72.1	67.6
	Never	11.9	11.6	11.8

Courtesy of Luis Paz-Ares, MD, PhD

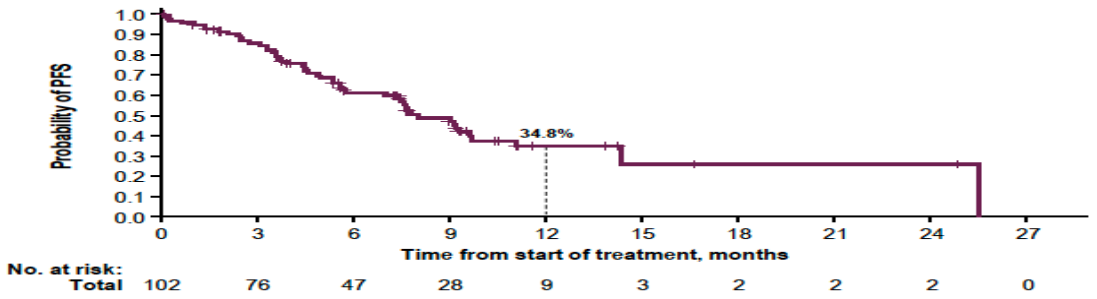
Filippi et al. WLCC 2023

DUART Trial
Durva following RT in stage III NSCLC ineligible to CT

Endpoint	Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)
Confirmed ORR*, % (95% CI)†	28.8 (17.8–42.1)	23.3 (11.8–38.6)	26.5 (18.2–36.1)

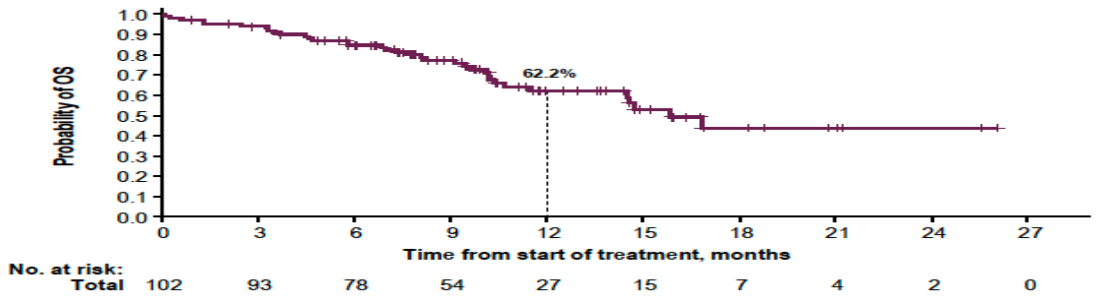
PFS

	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	26/59 (44.1)	25/43 (58.1)	51/102 (50.0)
Median PFS (95% CI)*, months	9.0 (5.6–NC)	7.6 (5.3–11.0)	8.0 (7.0–9.7)
12-month PFS rate (95% CI)†, %	40.2 (23.6–56.3)	29.3 (13.8–46.7)	34.8 (23.0–46.9)



OS

	Cohort A (standard RT)	Cohort B (palliative RT)	Total
No. events / no. patients (%)	16/59 (27.1)	19/43 (44.2)	35/102 (34.3)
Median OS (95% CI)*, months	NC (14.5–NC)	14.8 (10.1–NC)	15.9 (11.5–NC)
12-month OS rate (95% CI)†, %	67.0 (50.1–79.2)	56.3 (37.3–71.6)	62.2 (49.8–72.4)



	All-cause AEs			PRAEs*		
	Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)	Cohort A (standard RT; n=59)	Cohort B (palliative RT; n=43)	Total (N=102)
Any AE, n (%)	56 (94.9)	43 (100)	99 (97.1)	40 (67.8)	21 (48.8)	61 (59.8)
Grade 3/4	25 (42.4)	15 (34.9)	40 (39.2)	9 (15.3)	3 (7.0)	12 (11.8)
Within 6 months	—	—	—	7 (11.9)	3 (7.0)	10 (9.8)
SAE	25 (42.4)	13 (30.2)	38 (37.3)	7 (11.9)	2 (4.7)	9 (8.8)
Outcome of death‡	5 (8.5)	2 (4.7)	7 (6.9)	1 (1.7)	0	1 (1.0)
Leading to Tx discontinuation	11 (18.6)	7 (16.3)	18 (17.6)	7 (11.9)	3 (7.0)	10 (9.8)
Leading to Tx interruption	31 (52.5)	17 (39.5)	48 (47.1)	8 (13.6)	5 (11.6)	13 (12.7)

Courtesy of Luis Paz-Ares, MD, PhD

Filippi et al. WLCC 2023

Osimertinib *v* Durvalumab v Observation following CT/RT in EGFR mutant stage III NSCLC

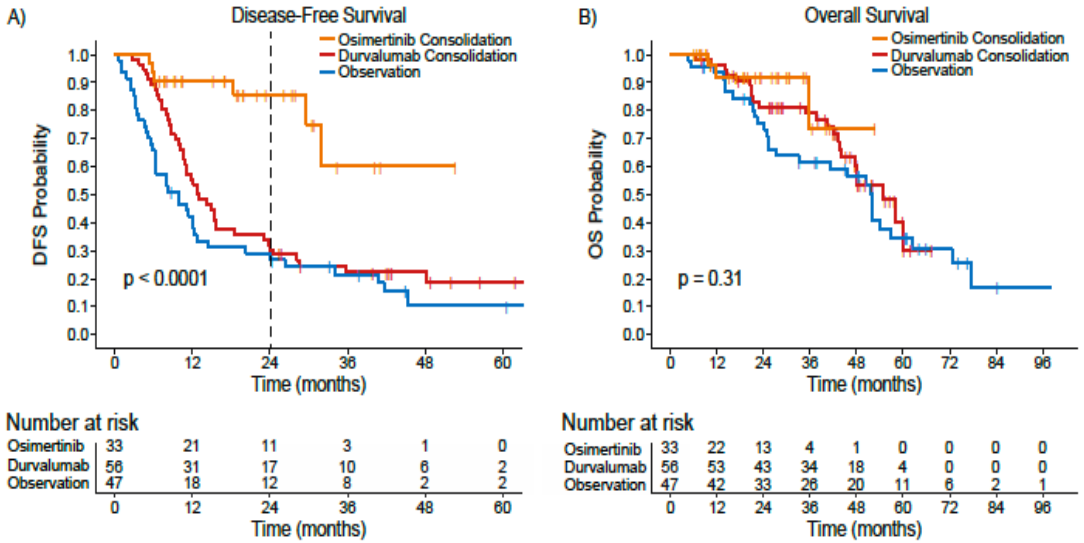
Multi-institutional retrospective analysis including 24 institutions

Inclusion Criteria:
(1) ≥ age 18 treated years 2015 or later
(2) Stage III, locally advanced, unresectable NSCLC with *EGFR*-sensitizing mutation
(3) Received ≥2 cycles of platinum-based concurrent chemoradiation
(4) No disease progression at time of initiation of consolidation treatments

→ Consolidation Osimertinib
→ Consolidation Durvalumab
→ Observation

Co-primary endpoints: Disease-free survival (DFS) and overall survival (OS)#
Secondary endpoints: Consolidation treatment-related adverse events (trAE), central nervous system disease-free survival (CNS DFS)

#multivariable including nodal status (N stage), stage III A/B/C AJCC 8th, and age



Baseline characteristics

	Total (N=136)	Osimertinib (N=33)	Durvalumab (N=56)	Observation (N=47)	P-value
Age – Median (IQR)	66 [57, 72]	65 [60, 72]	67 [56, 71]	64 [57, 72]	0.8
Sex – Female	88 (64.7%)	22 (66.7%)	34 (60.7%)	32 (68.1%)	0.7
Race					0.2
White	88 (64.7%)	22 (66.7%)	33 (58.9%)	33 (70.2%)	
Asian	36 (26.5%)	9 (27.3%)	20 (35.7%)	7 (14.9%)	
Black	6 (4.4%)	1 (3.0%)	2 (3.6%)	3 (6.4%)	
Smoking					0.06
Former/Current	55 (40.4%)	10 (30%)	32 (1.8%)	27 (57.4%)	
Never	81 (59.6%)	23 (69.7%)	38 (67.9%)	20 (42.6%)	
PD-L1 TPS*					0.4
<1%	35 (37.2%)	10 (40%)	15 (31.3%)	10 (47.6%)	
≥1%	59 (62.8%)	15 (60%)	33 (68.8%)	11 (52.4%)	
Stage					0.31
IIIA	52 (38.2%)	11 (33.3%)	20 (35.7%)	21 (44.7%)	
IIIB	68 (50.0%)	15 (45.5%)	30 (53.6%)	23 (48.9%)	
IIIC	16 (11.8%)	7 (21.2%)	6 (10.7%)	3 (6.4%)	

	Osimertinib (N=33)		Durvalumab (N=56)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any trAE#	16 (48%)	2 (6.1%)	27 (48%)	10 (18%)
Rash	1 (3.0%)	0 (0%)	1 (1.8%)	0 (0%)
Pneumonitis^	5 (15%)	1 (3.0%)	14 (25%)	7 (13%)
Diarrhea	1 (3.0%)	0 (0%)	2 (3.6%)	1 (1.8%)
Endocrine	0 (0%)	0 (0%)	5 (8.9%)	0 (0%)
AST/ALT elevation	1 (3.0%)	0 (0%)	2 (3.6%)	1 (1.8%)
Other	11 (33%)	1 (3.0%)	3 (5.4%)	1 (1.8%)*
trAE leading to discontinuation	4 (12%)		15 (27%)	
Steroid use	7 (21%)		20 (36%)	

*grade 3 myocarditis
^ Does not include radiation pneumonitis
#Consolidation treatment-related adverse events

Subsequent systemic therapy after consolidation treatment or observation

Subsequent systemic therapy

Arm	EGFR TKI	IO	Other	Total
Osimertinib	1 (3%)	1 (3%)	1 (3%)	3 (3.7%)
Durvalumab	37 (66%)	1 (1.8%)	3 (5.4%)	41 (51%)
Observation	35 (74%)	1 (2.2%)	1 (2.2%)	37 (46%)
Total	73 (90%)	3 (3.7%)	5 (6.2%)	81

Courtesy of Luis Paz-Ares, MD, PhD

Nassar et al. WLCC 2023

Dr Paz-Ares: Clinical Case – Non-SCC NSCLC T1N3

- 42 yo male
- Heavy smoker – 63 py
- PMH
  - Pneumothorax: right lung (1993 - drainage), bilateral (2013 – resection)
  - Migraine

- Current Problem
  - March 2015: Right supraclavicular lymph node
  - Diagnosed of RUL **Squamous Cell Carcinoma T1N3M0**

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Dr Paz-Ares: Clinical Case – Non-SCC NSCLC T1N3

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  - March 2015: Right supraclavicular lymph node
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  - **PD-L1 ??**

Courtesy of Luis Paz-Ares, MD, PhD

Dr Paz-Ares: Clinical Case – Non-SCC NSCLC T1N3

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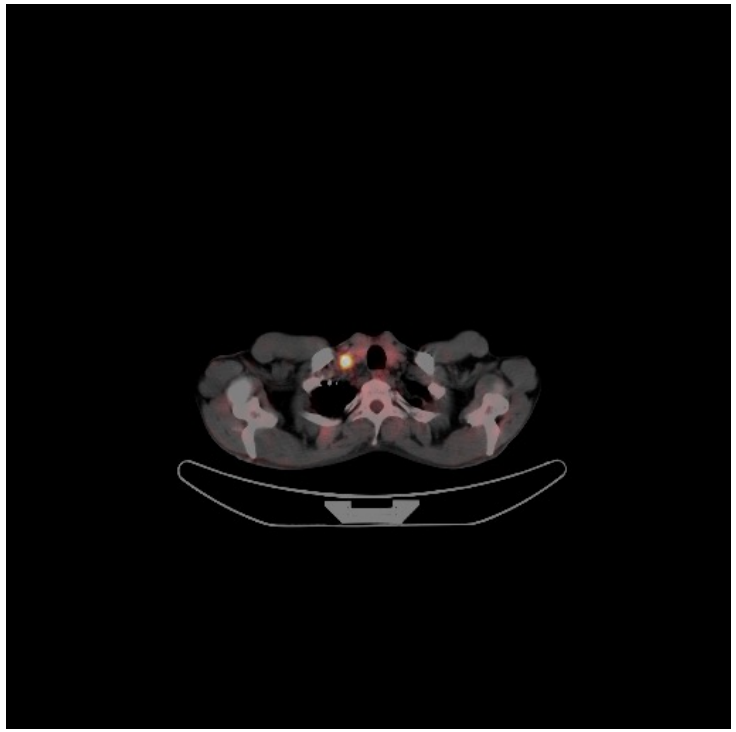
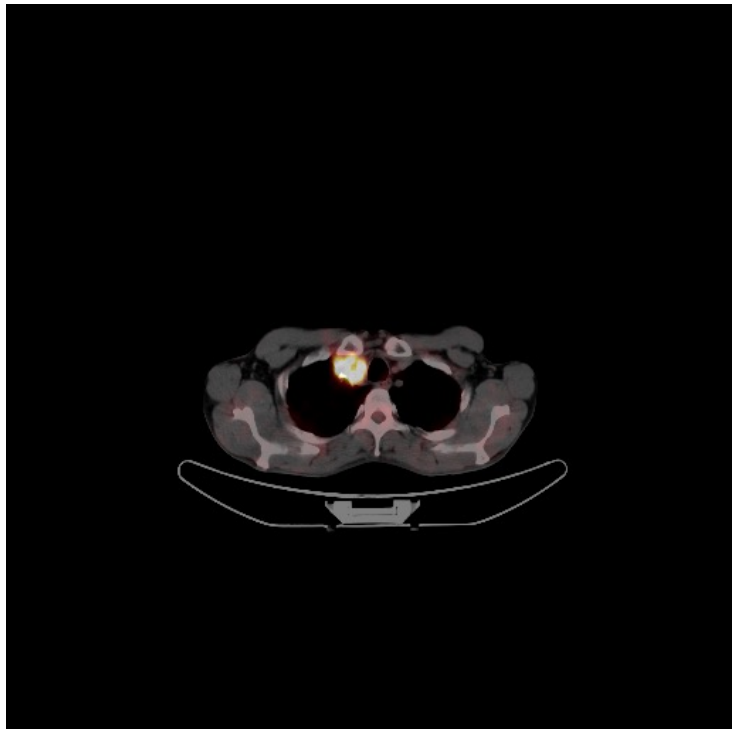
- PMH
  - Pneumothorax: right lung (1993 - drainage), bilateral (2013 – resection)
  - Migraine

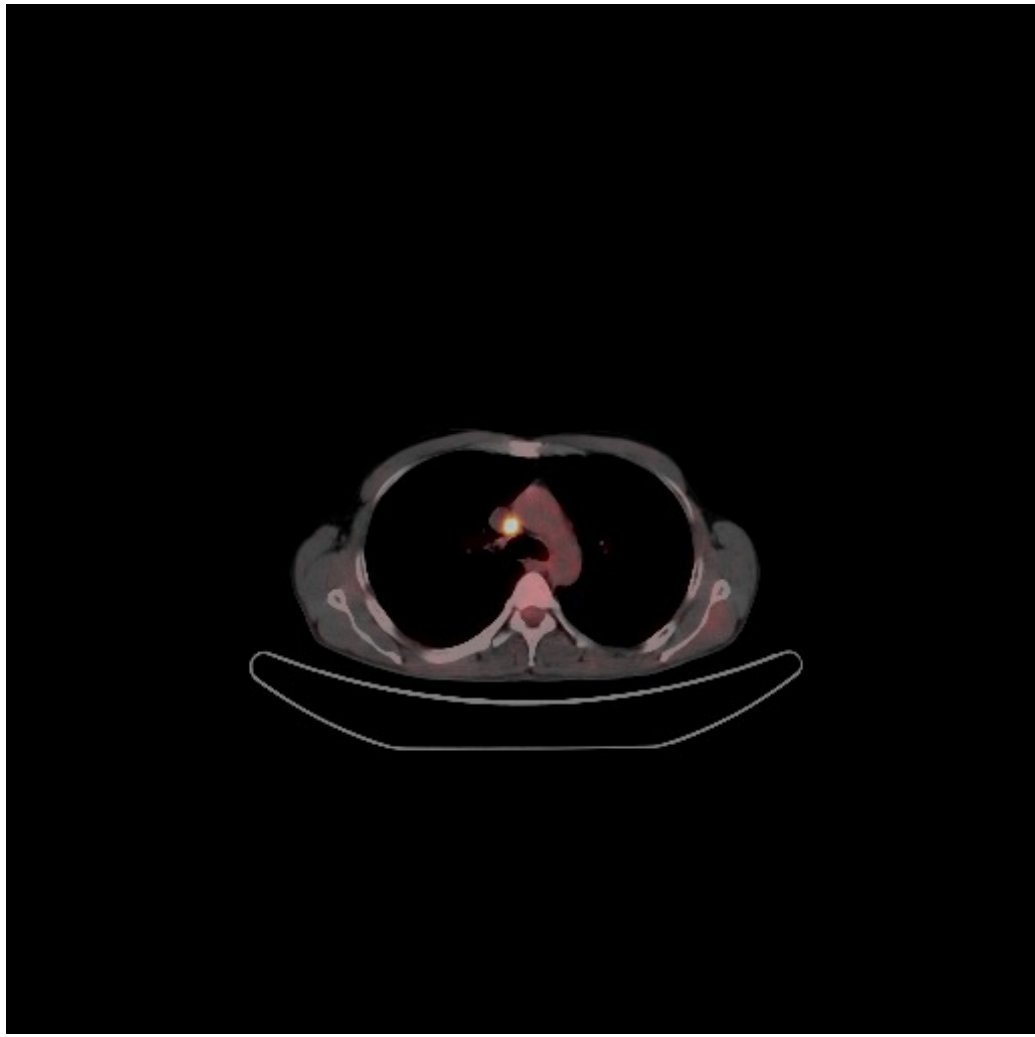
- Current Problem
  - March 2015: Right supraclavicular lymph node
  - Diagnosed of RUL **Squamous Cell Carcinoma T1N3M0**
  - **PD-L1 + (5% of cells)**

Courtesy of Luis Paz-Ares, MD, PhD

Baseline PET/TC
March 2015





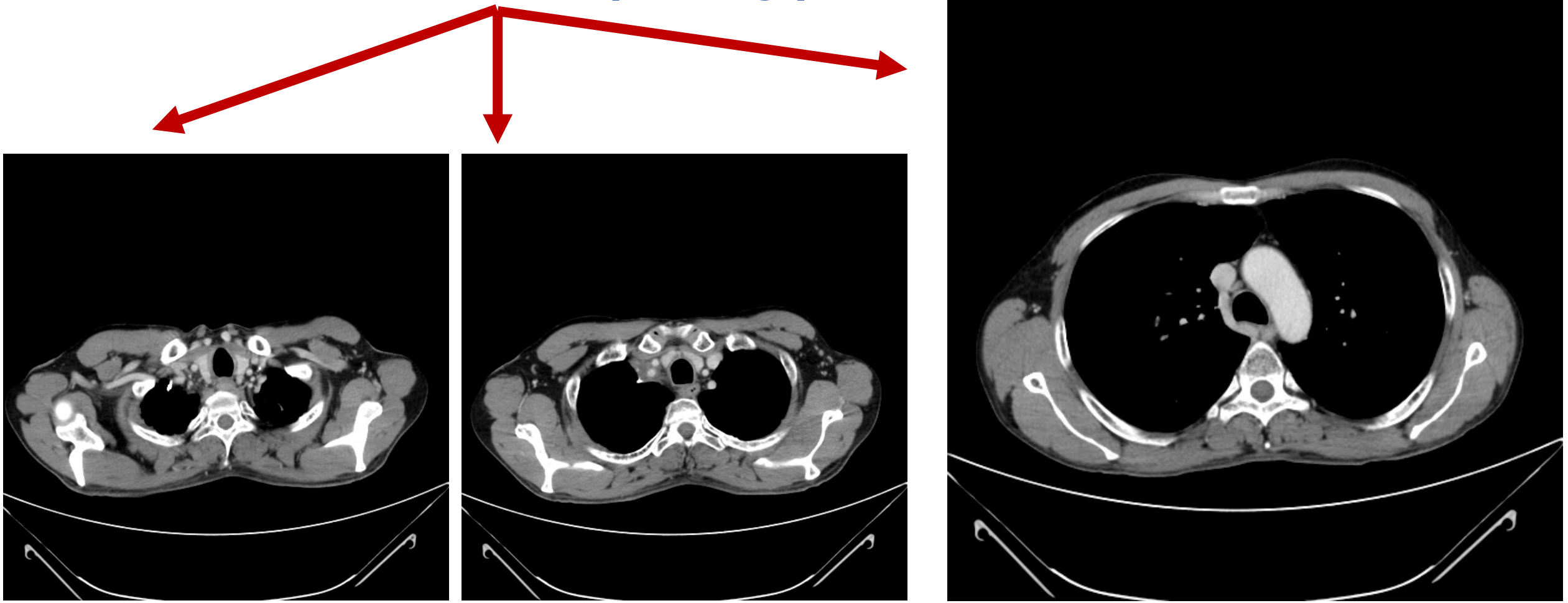


Courtesy of Luis Paz-Ares, MD, PhD

Chemo/xRT Treatment
Cb-Pem x3/xRT (60Gy)

Courtesy of Luis Paz-Ares, MD, PhD

Chemo/xRT Treatment
Cb-Pem x3/xRT (60Gy)



Courtesy of Luis Paz-Ares, MD, PhD

EC PACIFIC

C1 Durvalumab 30/06/15

C5 Durvalumab 24/08/15

26/8/15 Admission due to GI bleeding

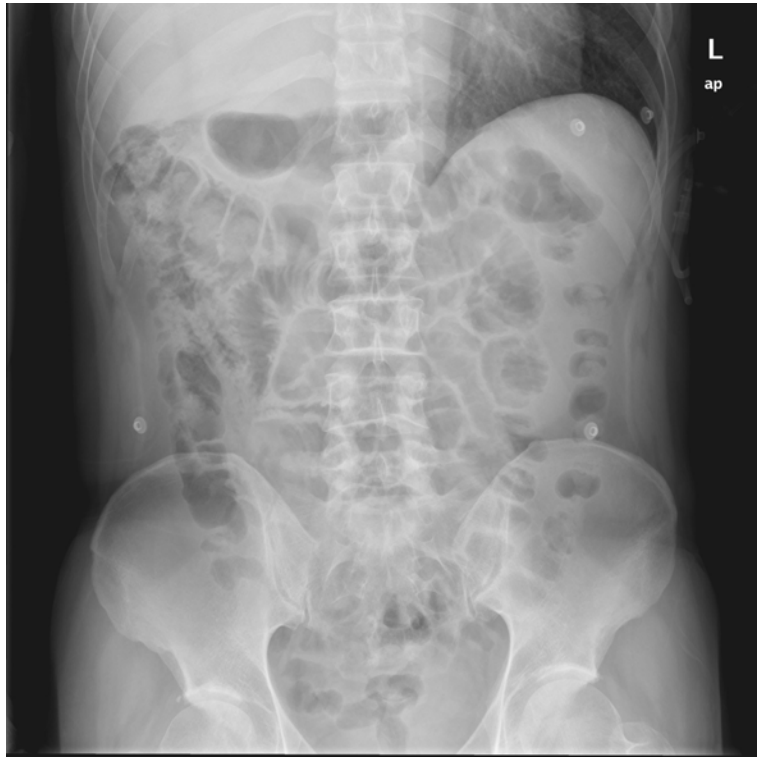
Courtesy of Luis Paz-Ares, MD, PhD

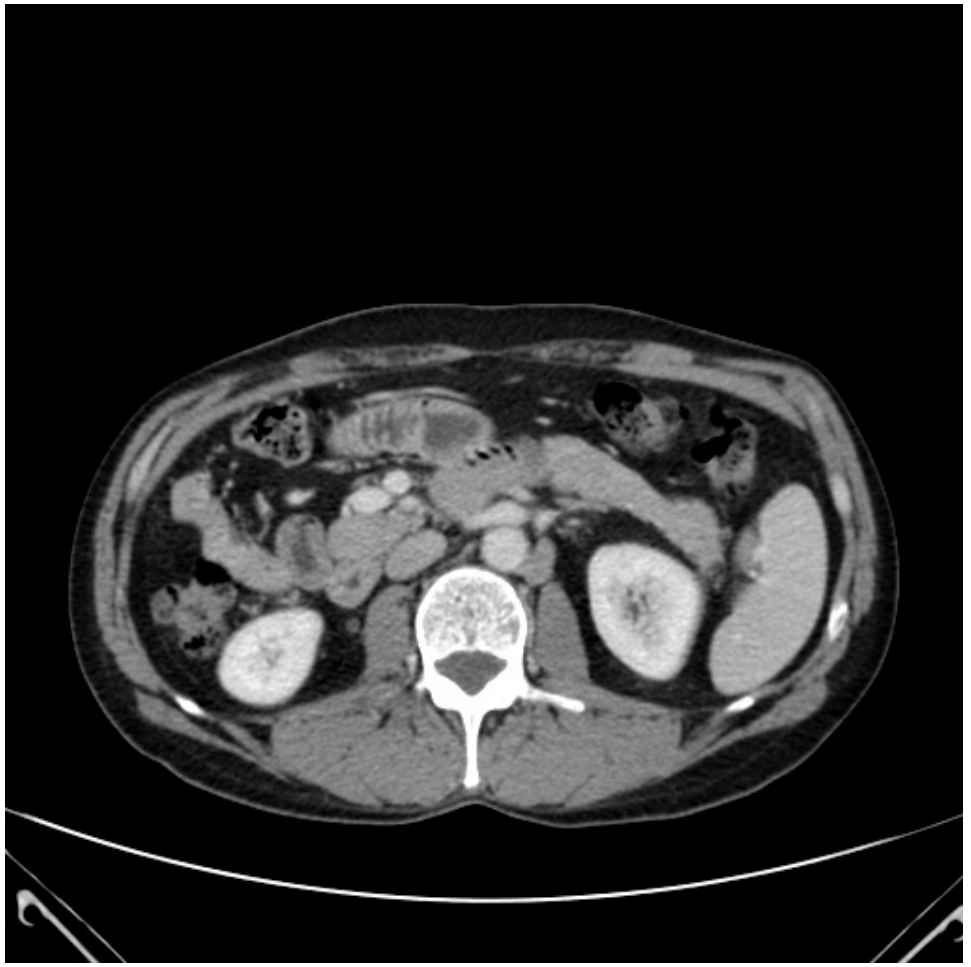
EC PACIFIC

C1 Durvalumab 30/06/15

C5 Durvalumab 24/08/15

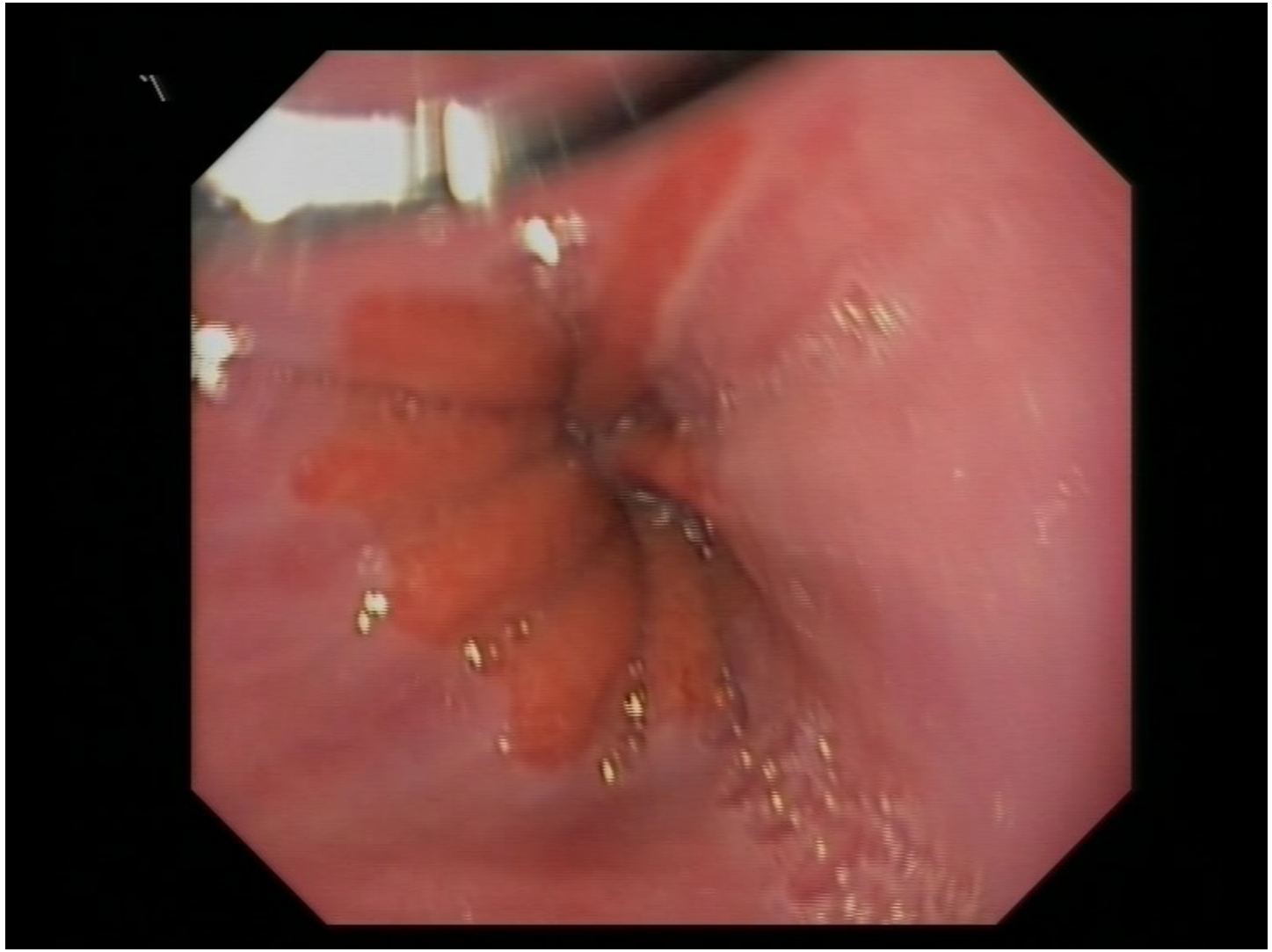
26/8/15 Admission due to GI bleeding





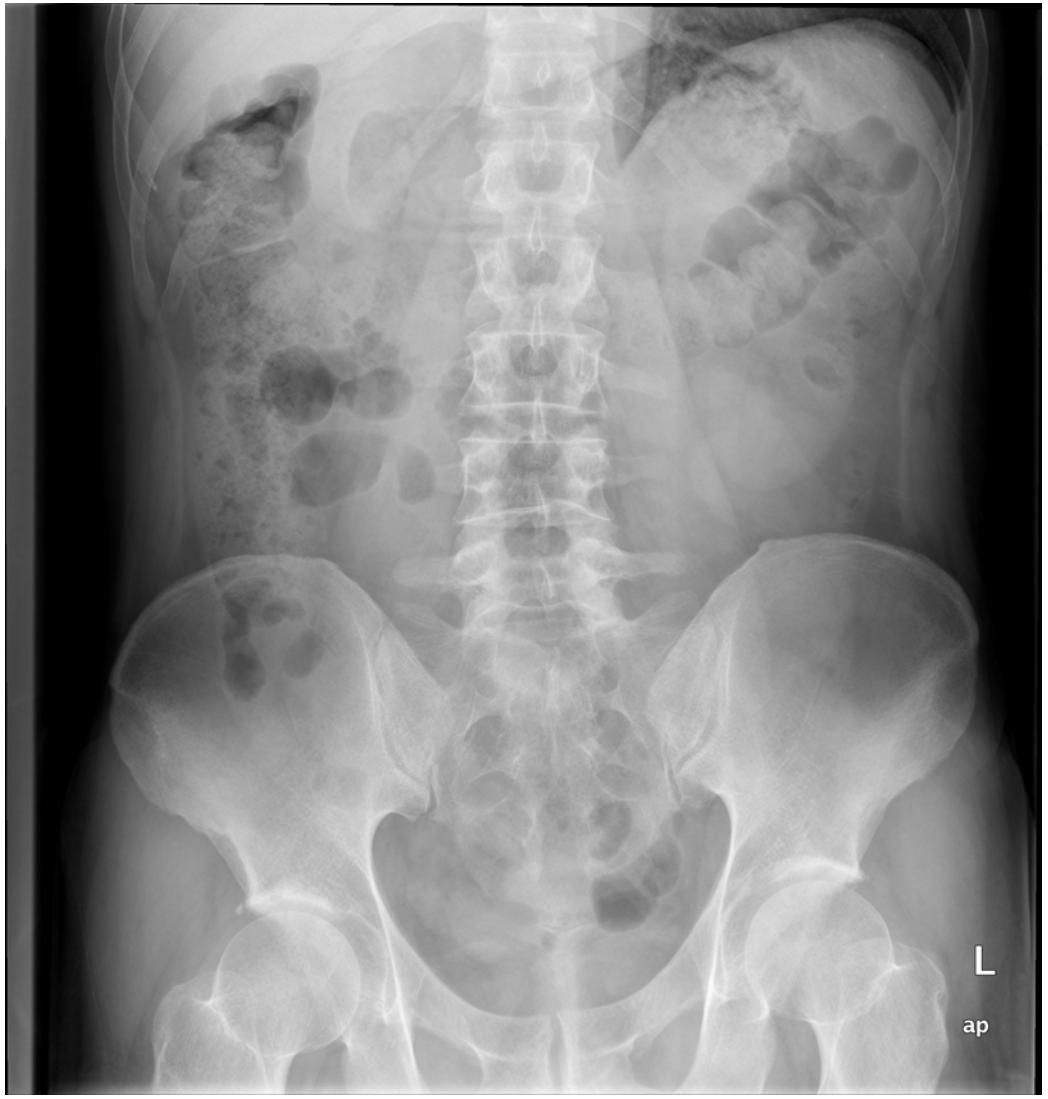
Courtesy of Luis Paz-Ares, MD, PhD

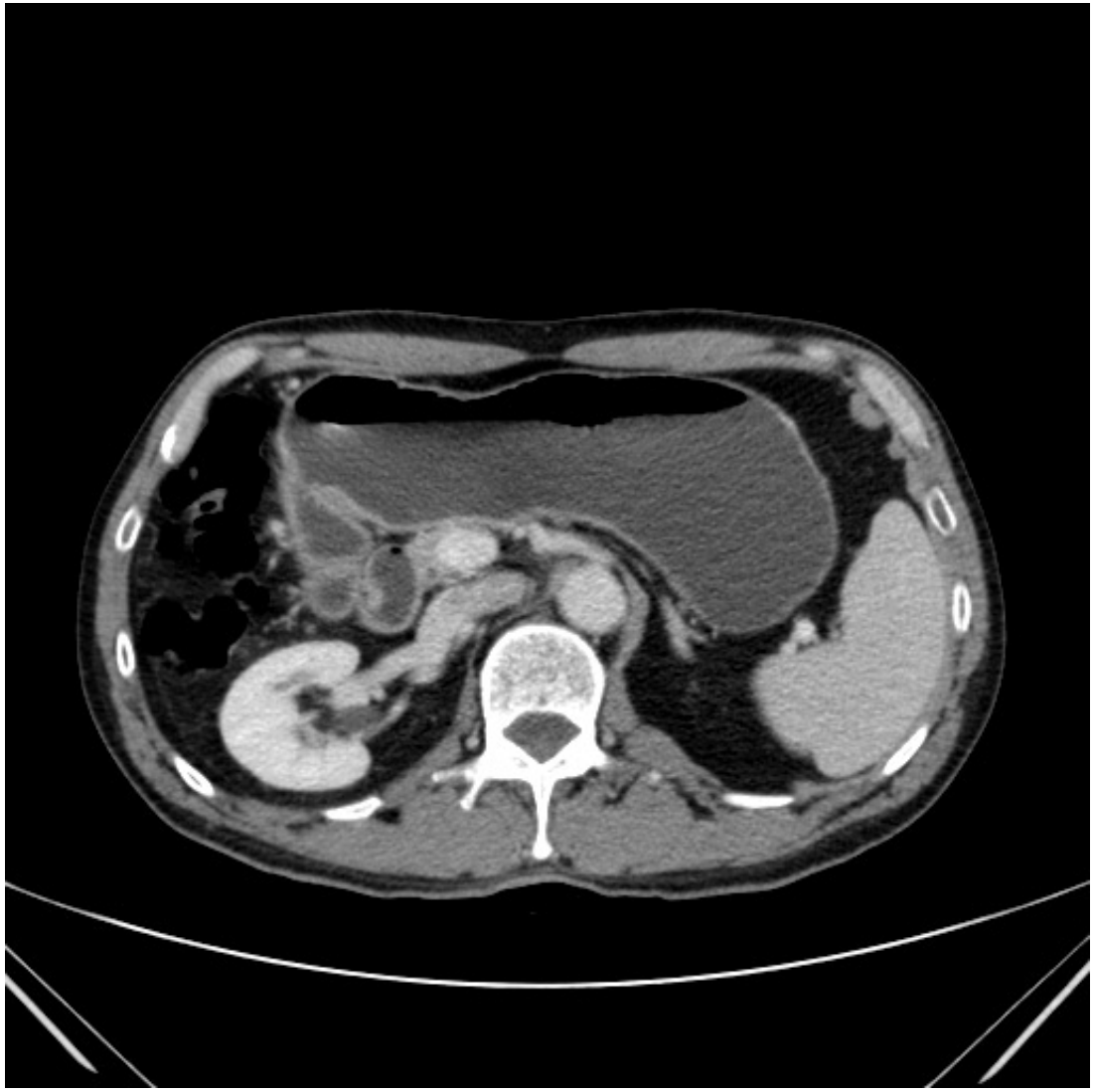
Grade III Jejunitis



Courtesy of Luis Paz-Ares, MD, PhD

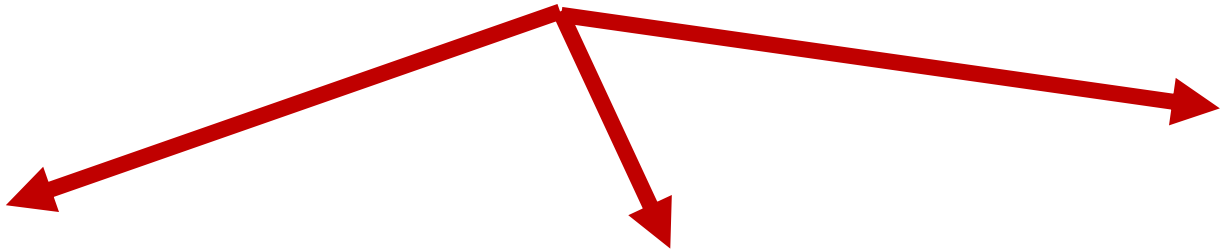
After Prednisolone 1mg/kg
At discharge on 10/9/19

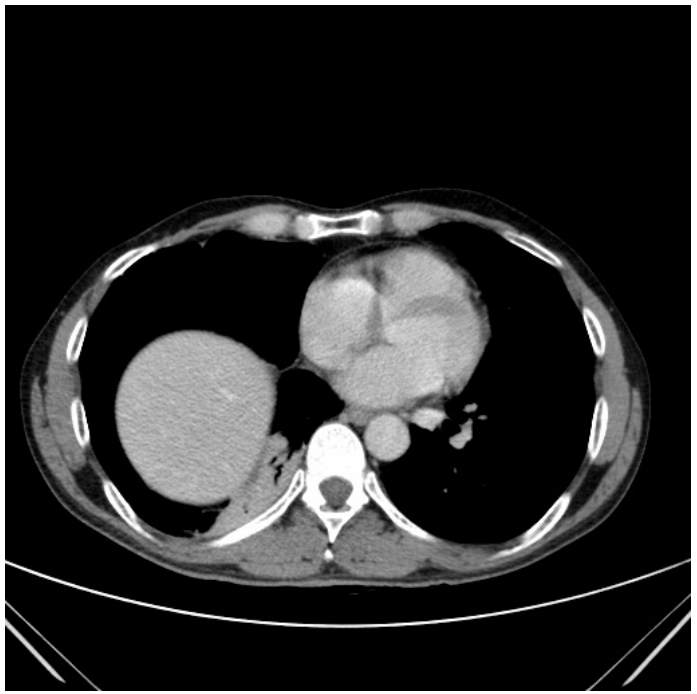


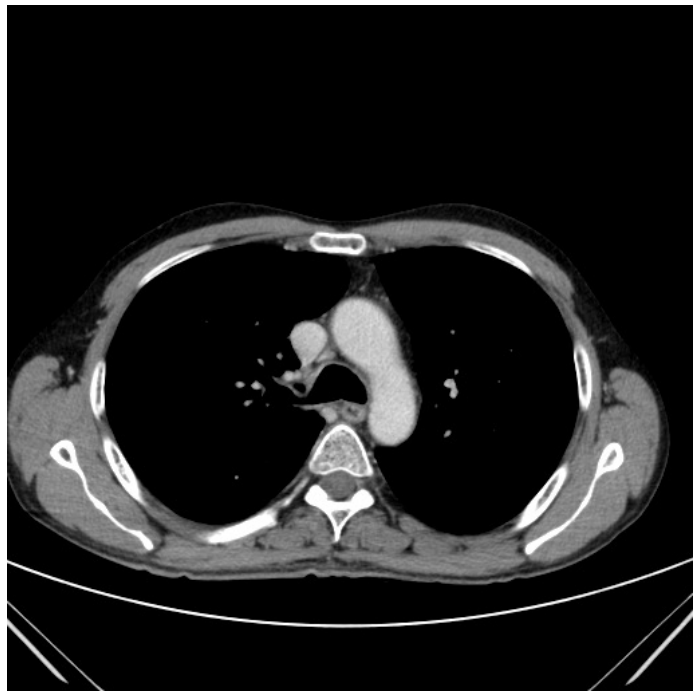


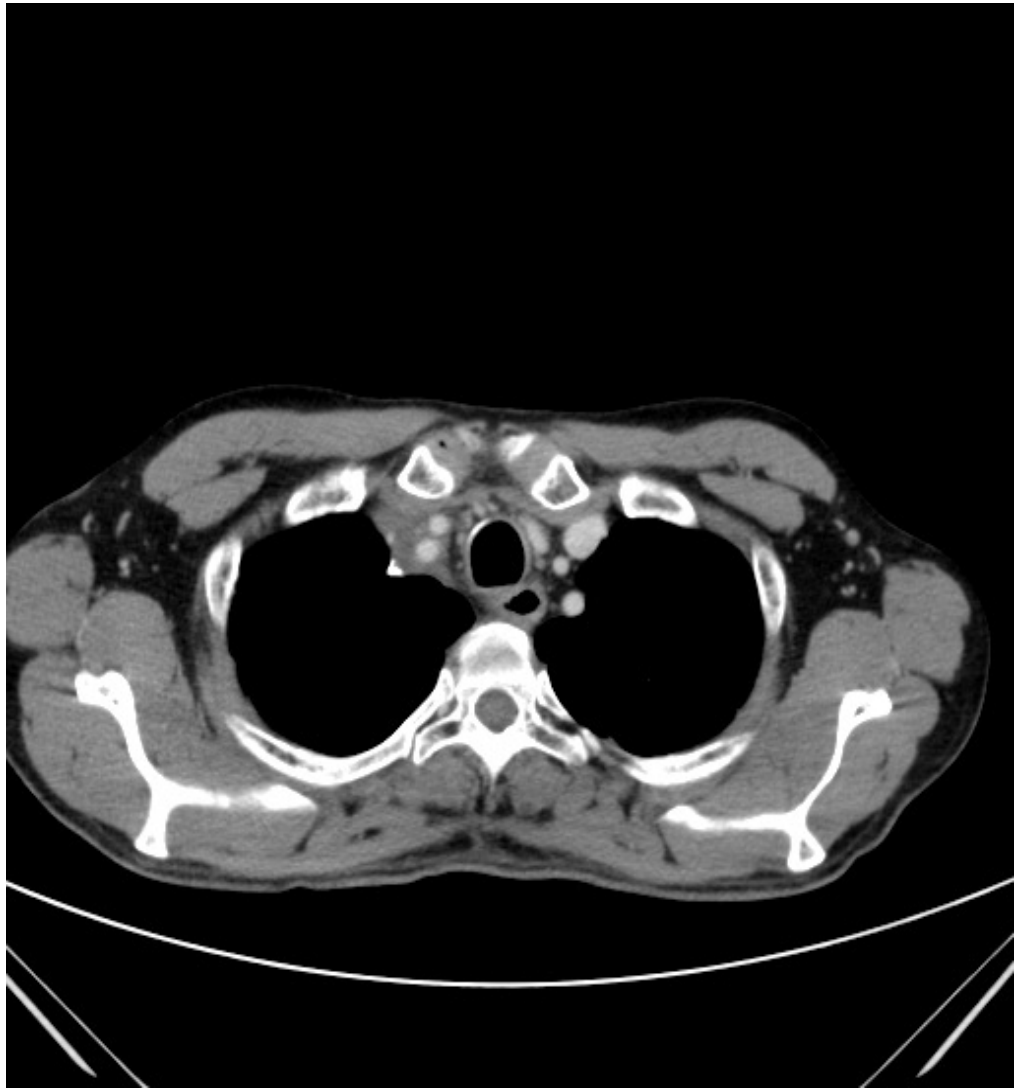
Courtesy of Luis Paz-Ares, MD, PhD

CT Scan in Sept 2015







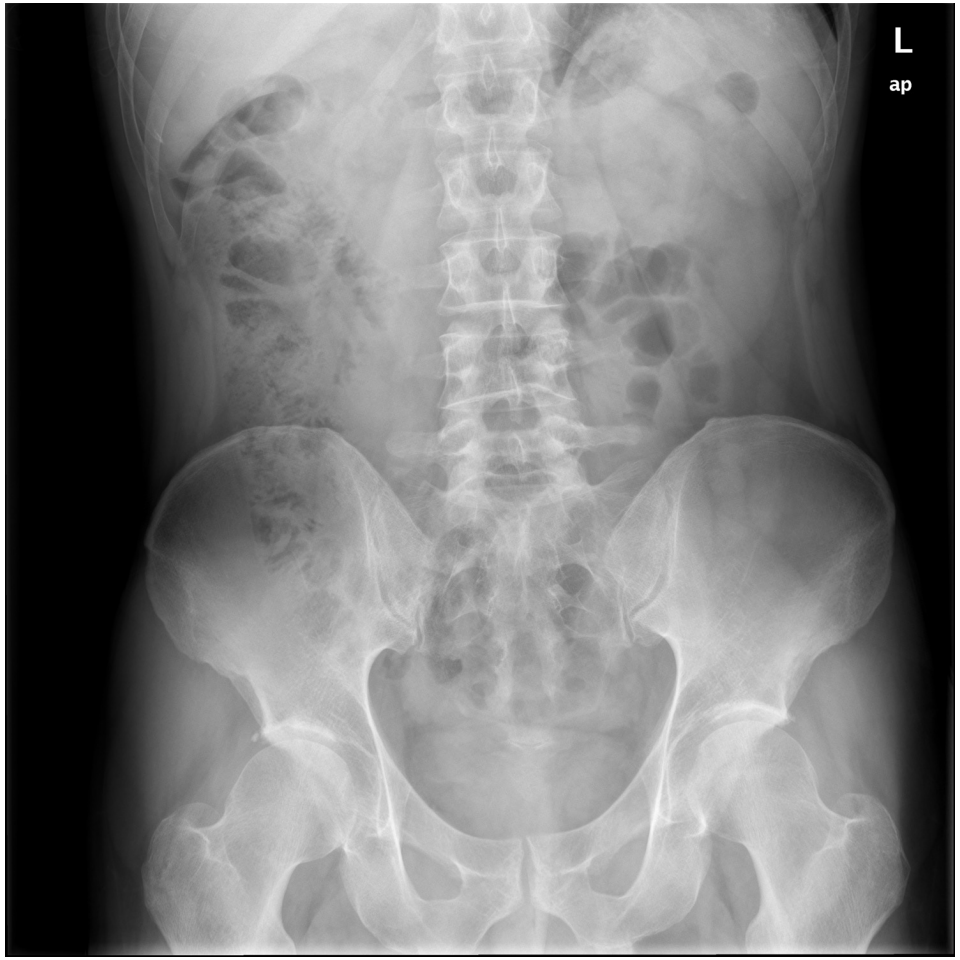


Courtesy of Luis Paz-Ares, MD, PhD

No rechallenge to Durvalumab

After tapering steroids:

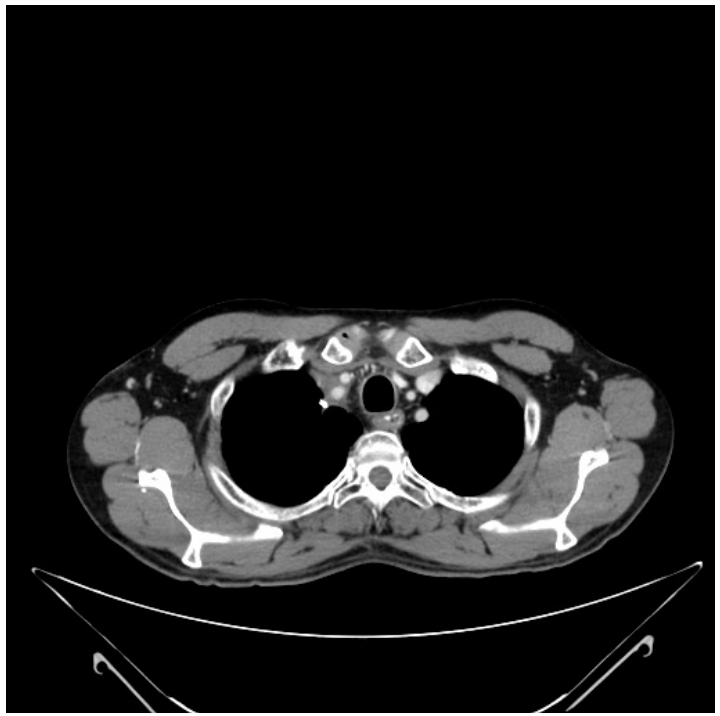
New episode of GI inflammation in Oct 2015

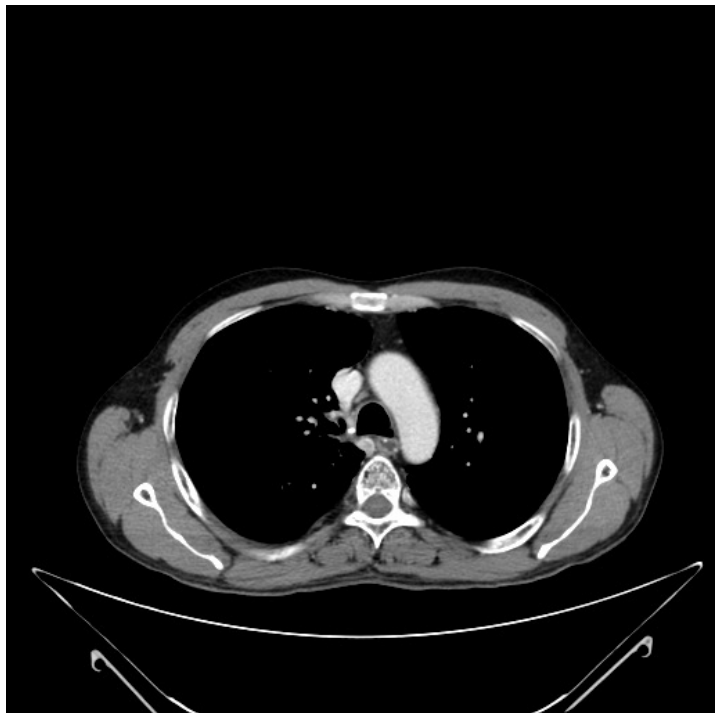


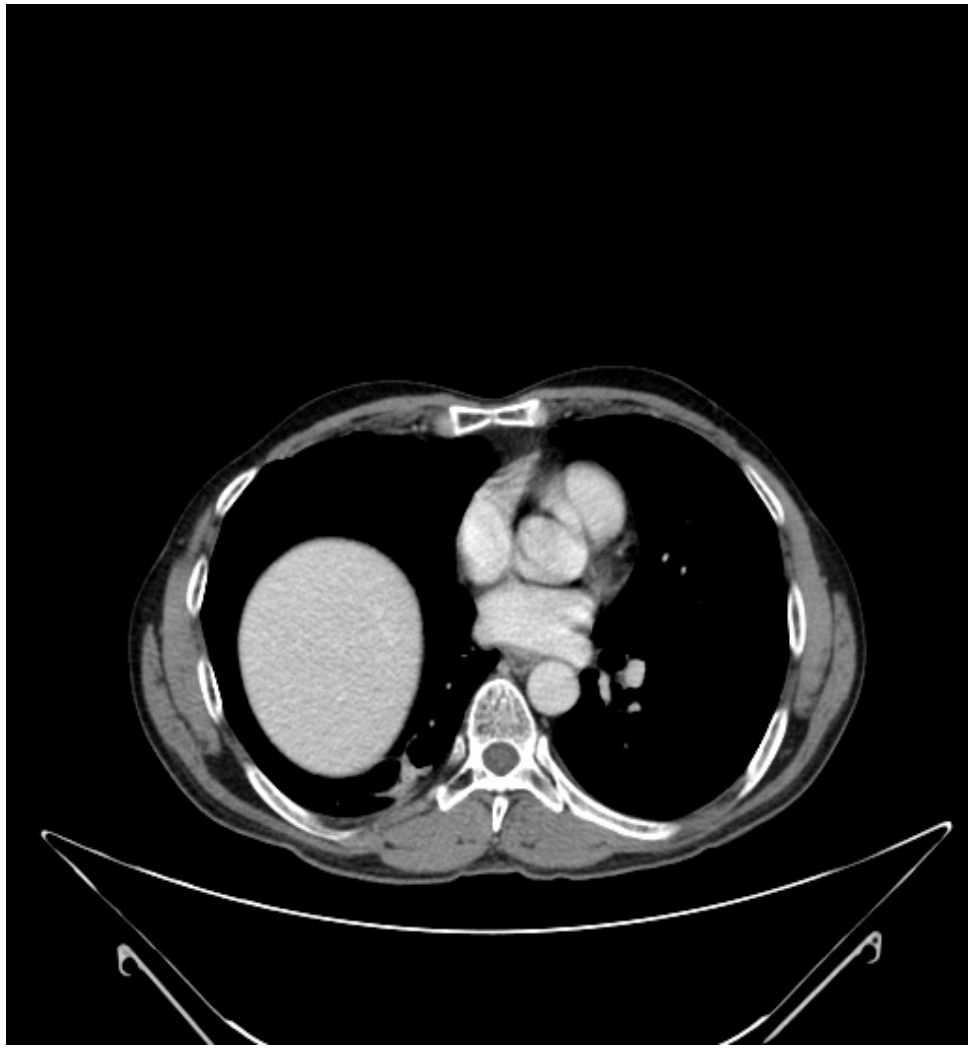
Courtesy of Luis Paz-Ares, MD, PhD

More than 8 years later…

CT Scan in June 3, 2023







Courtesy of Luis Paz-Ares, MD, PhD

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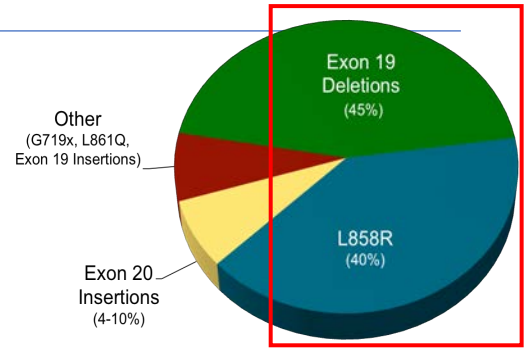
RTP RESEARCH TO PRACTICE

Management of NSCLC with classical EGFR mutations



1st Line

Current SOC

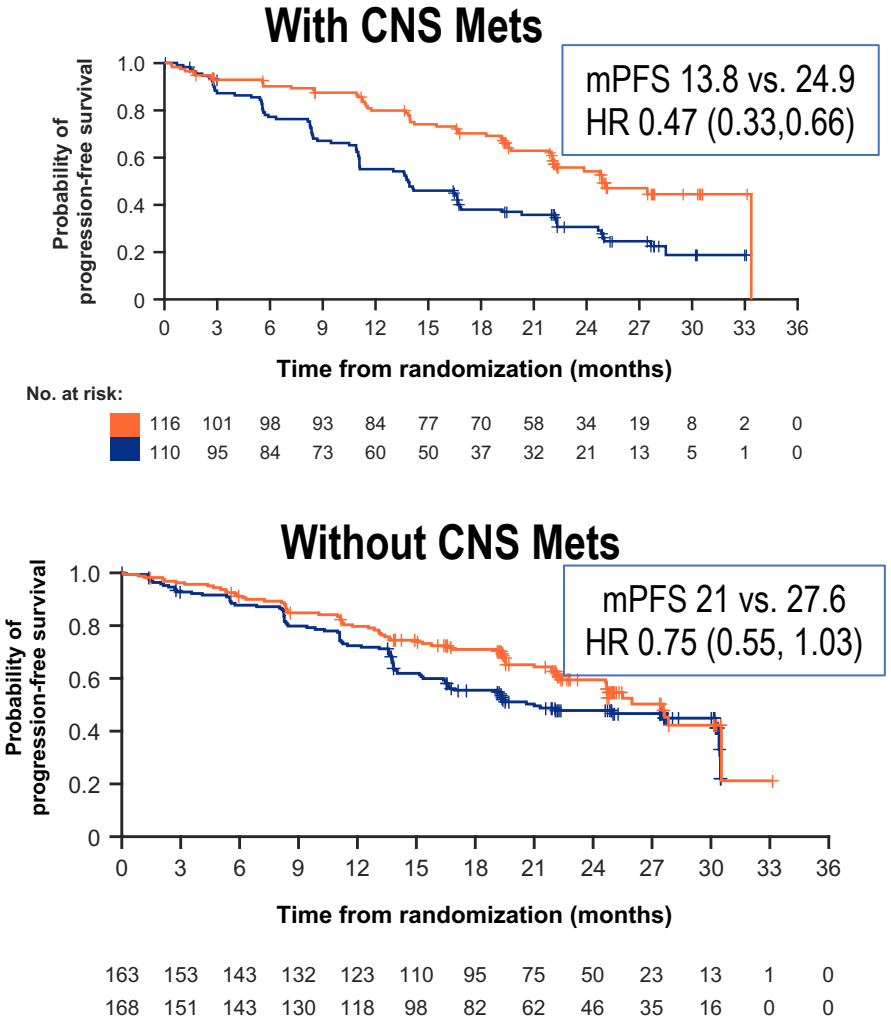
OSIMERTINIB[1]
(mPFS 18.9 mo, oral therapy, well-tolerated)

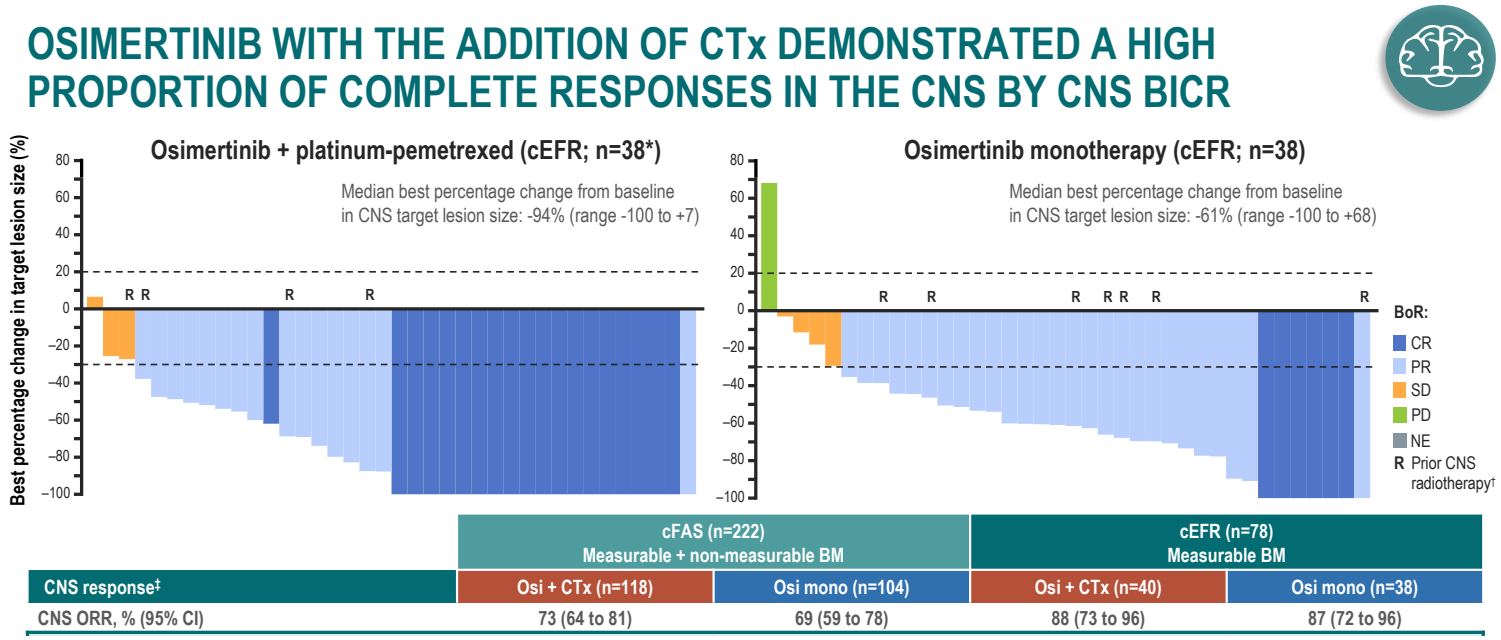
TKI + Chemotherapy	Osimertinib + Carboplatin/Pemetrexed FLAURA2
TKI + Bispecific Antibody	Lazertinib + Amivantamab MARIPOSA
TKI + anti-VEGF therapy	Osimertinib + Ramucirumab OSIRAM, RAMOSE

1. FLAURA Soria NEJM 2018

Courtesy of Zofia Piotrowska, MD, MHS

FLAURA2 – Outcomes in pts with baseline CNS mets





These exploratory analyses suggest that patients with baseline CNS metastases may have particular benefit from addition of chemotherapy to osimertinib.

Janne P, WCLC 2023 and Planchard D, ESMO 2023.

Courtesy of Zofia Piotrowska, MD, MHS

MARIPOSA

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

Stratification Factors

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

2:2:1 Randomization (N=1074)

Serial brain MRIs were required for all patients[a]

- **Amivantamab + Lazertinib** (n=429; open-label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, t
Lazertinib: 240 mg daily
Osimertinib: 80 mg daily

Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:

- **Amivantamab + lazertinib** vs **osimertinib**

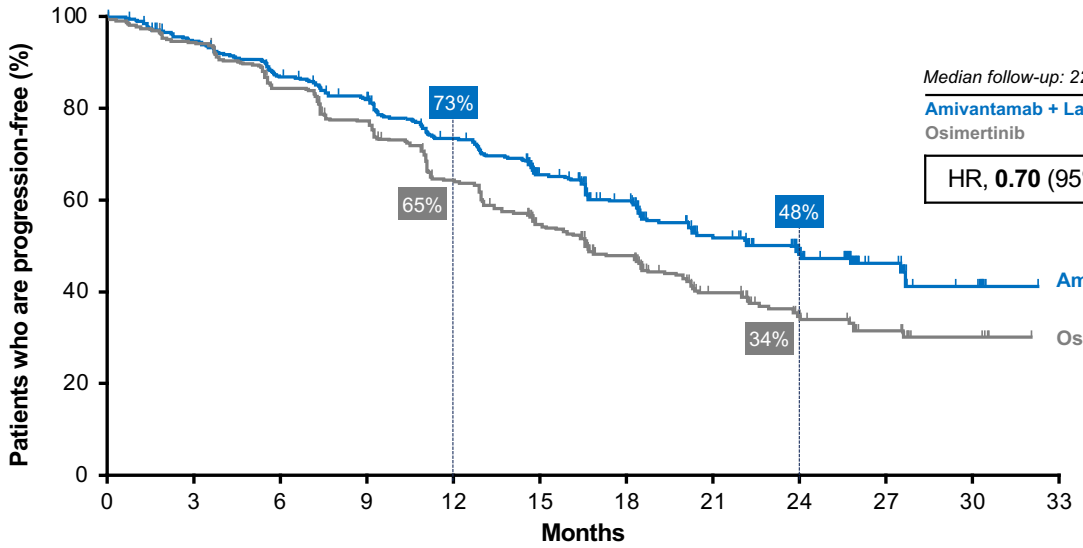
Secondary endpoints of amivantamab + lazertinib vs osimertinib:

- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)

MARIPOSA

Primary Endpoint: Progression-free Survival by BICR[a]

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 months	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

No. at risk												
Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

Overall Survival (Interim Analysis:)
HR 0.80 (95% CI, 0.61-1.05), p=0.11

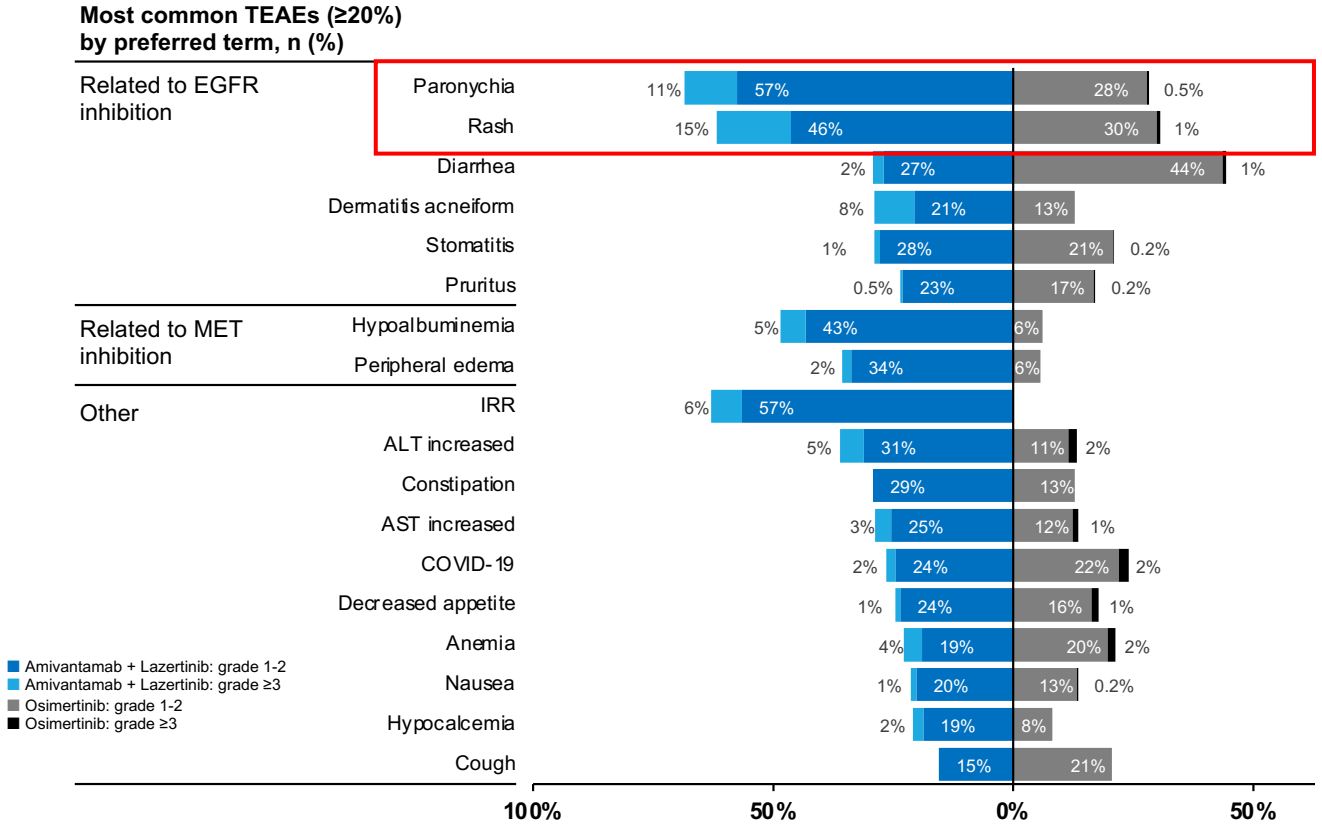
Landmark 2-year survival: 74% vs 69%

Cho BC, ESMO 2023, Abstract LBA14.

Courtesy of Zofia Piotrowska, MD, MHS

MARIPOSA

Safety Profile



Amivantamab/Lazertinib:

- 83% Interruption
- 59% Dose reduction (any agent)
- 35% Discontinuation (any agent)

Osimertinib:

- 39% Interruption
- 5% Dose reduction (any agent)
- 14% Discontinuation (any agent)

- **37% patients had VTE on Ami/Lazertinib** (median onset 84 days)
- **Prophylactic anticoagulation** is now recommended for the first 4 months of treatment with amivantamab + lazertinib

Cho BC, ESMO 2023, Abstract LBA14.

Courtesy of Zofia Piotrowska, MD, MHS

MARIPOSA

Clinical Implications:

- Amivantamab + Lazertinib extends PFS (7.1 month PFS gain, HR 0.70) compared to osimertinib, but requires IV q2 week infusions and increases toxicities (dermatologic, IRRs, VTE).
- If approved, Ami/Lazer will represent another first-line treatment option to be discussed with patients, but given toxicity concerns and lack of OS benefit with either MARIPOSA or FLAURA2 thus far, osimertinib monotherapy remains a reasonable first-line option.

Future Directions:

- OS data are needed
- Better biomarkers and risk stratification strategies are needed.

Courtesy of Zofia Piotrowska, MD, MHS

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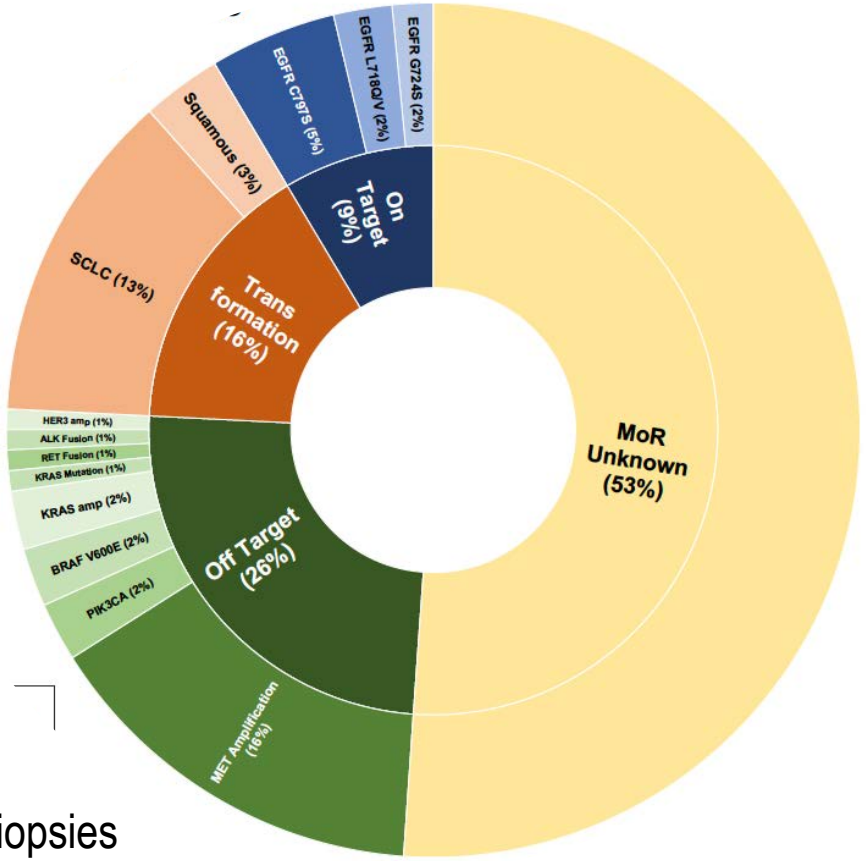
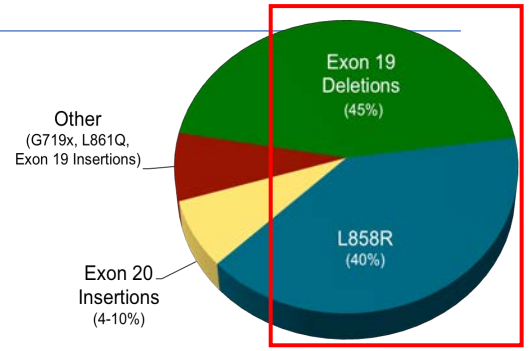
RTP RESEARCH TO PRACTICE

Managing Progression on EGFR TKIs

Resistance Mechanisms to First-Line Osimertinib



N=129
Tissue Biopsies



Treatment Options for Patients with no Targetable Resistance Mechanisms:

- **MARIPOSA-2** (Chemo + Amivantamab +/- Lazertinib)
- **HERTHENA-Lung 01** - Patritumab Deruxtecan (HER23 ADC)

Treatment Options for Patients with MET Amp after Osimertinib

- Tepotinib + Osimertinib (Final Analysis of **INSIGHT-2**)

Piotrowska Z, ASCO 2023 Abstract 9108

Courtesy of Zofia Piotrowska, MD, MHS

MARIPOSA-2 - Summary

Clinical Implications:

- Adding Amivantamab or Ami/Lazertinib to Carbo/Pem post-TKIs improves ORR, mPFS and intracranial PFS, but also increases toxicities.
- If approved, Amivantamab/Chemotherapy will be a post-TKI option, and will be particularly appealing for high risk patients (e.g., CNS mets, high disease burden)

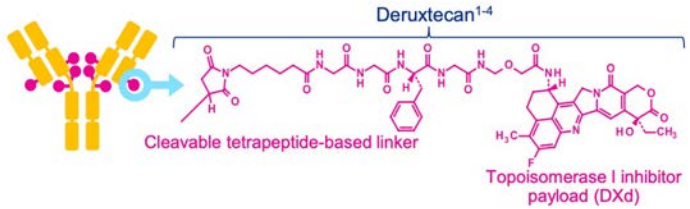
Future Directions:

- A delayed regimen with Lazertinib added after carboplatin is complete is being evaluated.
- Biomarker analyses will be important for patient selection.

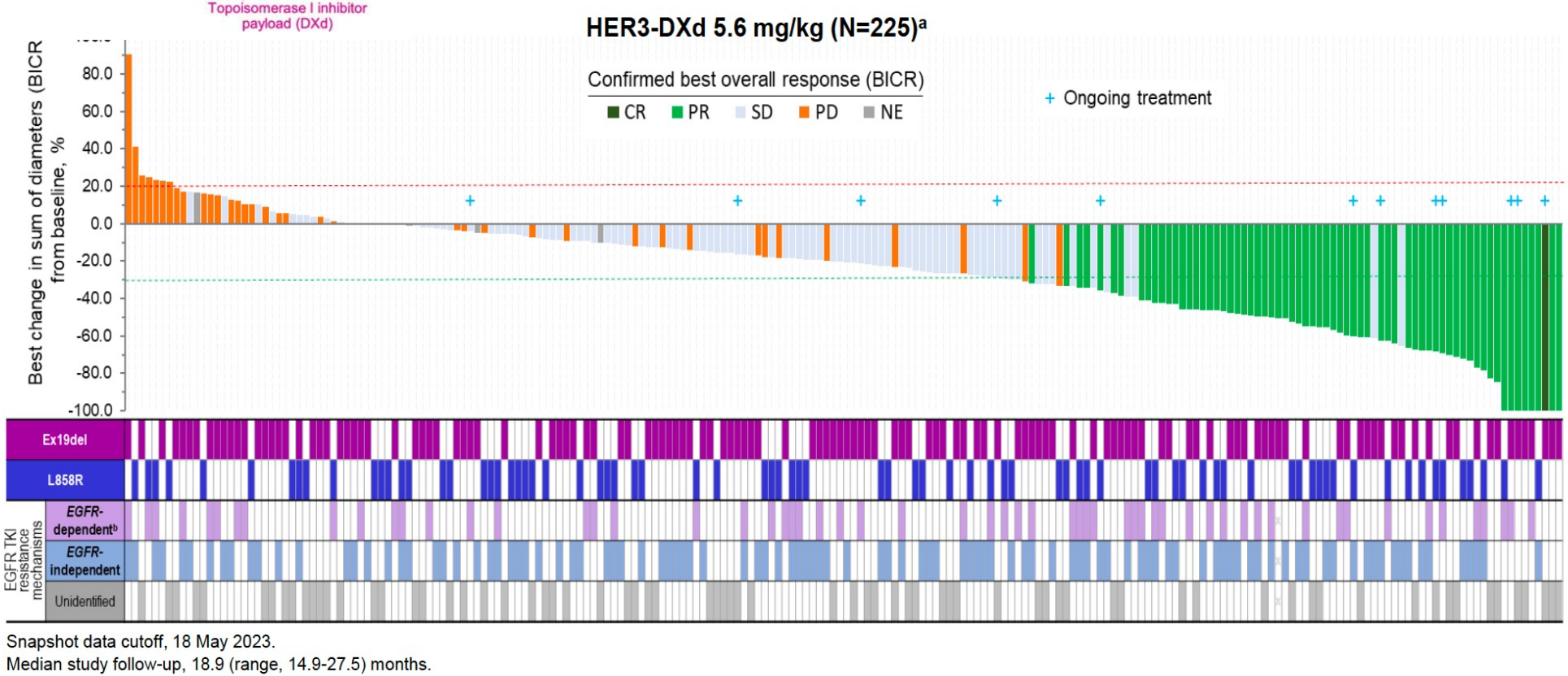
Courtesy of Zofia Piotrowska, MD, MHS

HERTHENA-Lung01: Patritumab Deruxtecan

Patritumab Deruxtecan: HER3-directed ADC with Topoisomerase I Inh payload



Prior EGFR TKI and PBC (n=225):
Confirmed ORR: 29.8% (23.9-36.2)
mPFS: 5.5 months (5.1-5.9)



Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

Courtesy of Zofia Piotrowska, MD, MHS

Yu HA, WCLC 2023

HERTHENA-Lung01: CNS Outcomes

Patritumab Deruxtecan appears to have intracranial activity, with a CNS ORR 33%, and may delay intracranial progression.

Responses by CNS BICR	All patients with baseline BM by CNS BICR (n=95)	No Radiotherapy to the Brain (n=30)[a]
CNS cORR, n (%) [95% CI]	19 (20.0) [12.5, 29.5]	10 (33.3) [17.3-52.8]
CR, n (%)	15 (15.8)	9 (30.0)[b]
PR, n (%)	4 (4.2)	1 (3.3)
SD/non-CR/non-PD, n (%)	57 (60.0)	13 (43.3)
PD, n (%)	13 (13.7)	4 (13.3)
NE, n (%)	6 (6.3)	3 (10.0)
CNS DCR (95% CI), %	80.0 (70.5, 87.5)	76.7 (57.7-90.1)
CNS DOR, median (95% CI), mo	9.2 (8.1-11.1)	8.4 (5.8-9.2)

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

	History of brain metastasis		
Site of first PD (by BICR)	Yes (n=115)	No (n=110)	All patients (N=225)
All sites, n (%)	75 (65)	67 (61)	142 (63)
Non-CNS, n (%)	63 (55)	65 (59)	128 (57)
CNS, n (%)	23 (20)	3 (3)	26 (12)
CNS and non-CNS, n (%)	11 (10)	1 (1)	12 (5)

80% of patients with a history of brain metastasis did not have progression in the brain

97% of patients without a history of brain metastasis did not have progression in the brain

Among 8 pts with CR, 8 had non-target lesions.

Courtesy of Zofia Piotrowska, MD, MHS

Johnson M, ESMO 2023

HERTHENA-Lung 01 - Summary

Clinical Implications:

- Patritumab deruxtecan has broad activity in EGFRm NSCLC post-TKI and post-chemotherapy, including patients with various resistance mechanisms.
- Intracranial responses have been observed, which will be important as post-osimertinib options with CNS activity are very limited.
- If approved, this drug will represent a new post-TKI treatment option for EGFRm lung cancer.

Future Directions:

- Combination studies of Patritumab +/- Osimertinib are ongoing in the first and second line.

Courtesy of Zofia Piotrowska, MD, MHS

INSIGHT 2

Key inclusion criteria

- Locally advanced/metastatic *EGFR*m NSCLC
- Acquired resistance to 1L osimertinib
- ***MET*amp** by:
  - **TBx FISH** (GCN ≥5 and/or *MET*:*CEP7* ≥2) and/or **LBx NGS** (≥2.3 Archer®)
- ECOG PS of 0 or 1

Tepotinib 500 mg QD + **Osimertinib** 80 mg QD

Tepotinib monotherapy 500 mg QD*

Endpoints

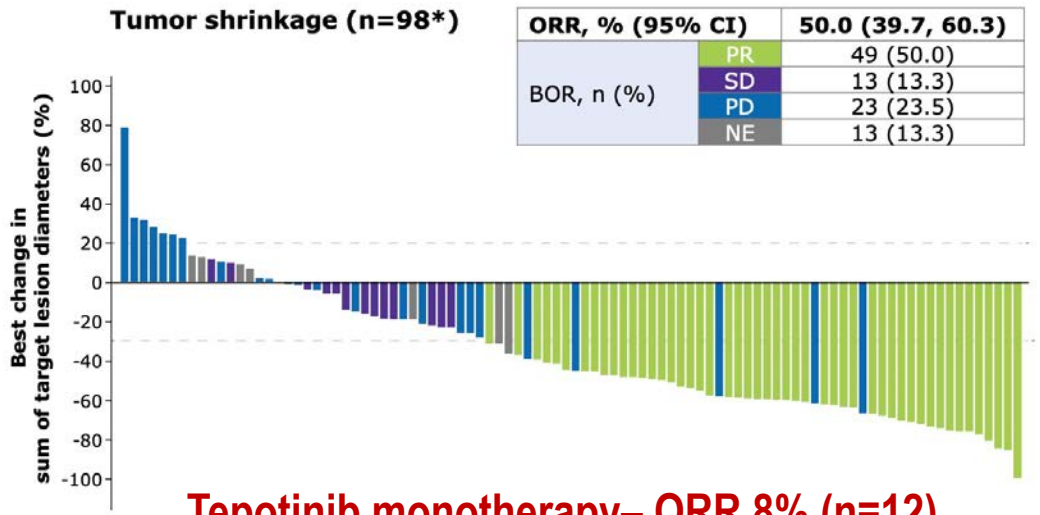
Primary endpoint
- **Objective response by IRC** in patients with **TBx FISH** *MET*amp

Selected secondary endpoints
- Objective response in patients with LBx NGS *MET*amp
- DOR
- PFS
- OS
- HRQoL
- Safety
- Biomarkers

Selected tertiary endpoints
- RANO-BM

Outcomes were similar whether MET amp was detected by tissue testing (FISH) or ctDNA (NGS), with highest response rates observed in patients with high-level MET amp.

Osimertinib + Tepotinib – ORR 50%, mPFS 5.6 mos



ORR, % (95% CI)		50.0 (39.7, 60.3)
BOR, n (%)	PR	49 (50.0)
	SD	13 (13.3)
	PD	23 (23.5)
	NE	13 (13.3)

Tepotinib monotherapy– ORR 8% (n=12)

Osimertinib + Tepotinib had intracranial activity

RANO-BM (IRC)		TBx FISH (N=24)
Intracranial ORR	% (95% CI)	29.2 (12.6, 51.1)
Intracranial BOR, n (%)	CR	6 (25.0)
	PR	1 (4.2)
	SD	12 (50.0)
	PD	2 (8.3)
	NE	3 (12.5)
Intracranial DCR	% (95% CI)	79.2 (57.8, 92.9)
Intracranial mDOR	Months (95% CI)	ne (3.6, ne)
Intracranial mPFS	Months (95% CI)	7.8 (3.9, ne)

Courtesy of Zofia Piotrowska, MD, MHS

Kim TM, WCLC 2023, Abstract OA21.05

INSIGHT 2: Summary

Clinical Implications:

- MET amplification is among the most commonly observed resistance mechanisms to first-line osimertinib (~15-20% patients) and can be detected by tissue and ctDNA (though ctDNA sensitivity is limited.)
- The primary results of INSIGHT 2 are consistent with other studies (TATTON, SAVANNAH), demonstrating the efficacy of combined EGFR + MET inhibition for patients with acquired MET amp after osimertinib.
- If approved, combined MET + EGFR will likely become the preferred treatment for patients with MET amp (off-label use can be considered in select patients.)

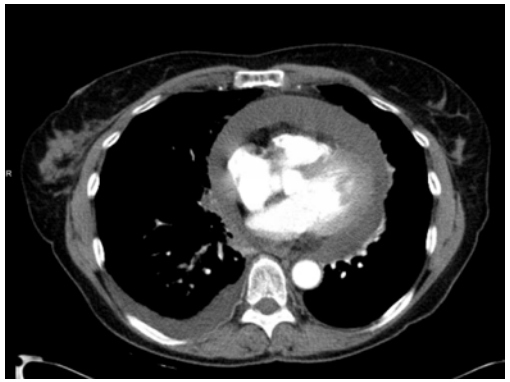
Future Directions:

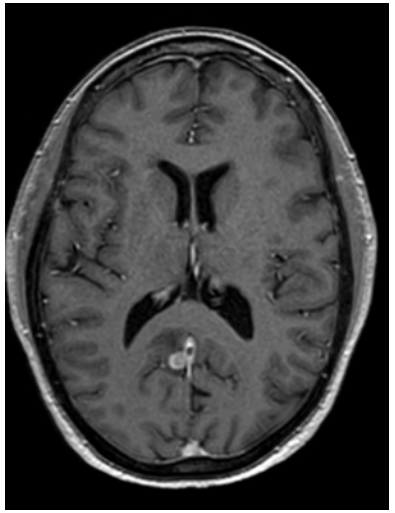
- Randomized studies of EGFR/MET inhibitors vs. Carboplatin/Pemetrexed are ongoing.

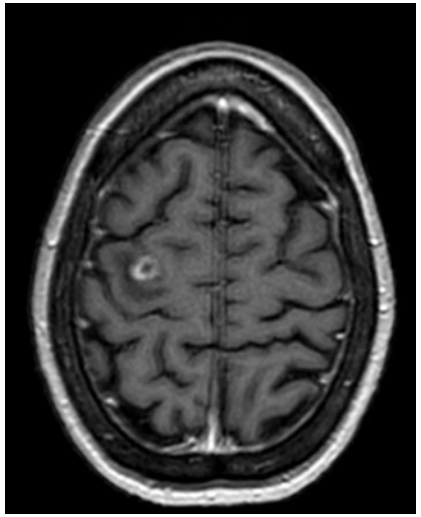
Courtesy of Zofia Piotrowska, MD, MHS

Dr Piotrowska: EGFR-mutated metastatic NSCLC

- 68yo F with no history of tobacco use, h/o mild anxiety, presented to a local ED with several weeks of progressive dyspnea on exertion. She was found to have a large pericardial effusion with tamponade physiology.
- Underwent emergent pericardiocentesis.
  - Pleural fluid cytology + for **adenocarcinoma**.
- Full staging scans:
  - PET/CT: FDG-avid, 3cm RUL mass, R hilar and mediastinal LAD, adrenal nodule.
  - Brain MRI: 7mm occipital lesion, 9 mm R frontal lobe lesion.
- ctDNA NGS: **EGFR L858R**, TP53 mutation.
- She initiated first-line osimertinib with good systemic and CNS response.
- After 14 months, she was noted to have progressive systemic disease with increased pericardial nodules. Brain MRI remained stable.





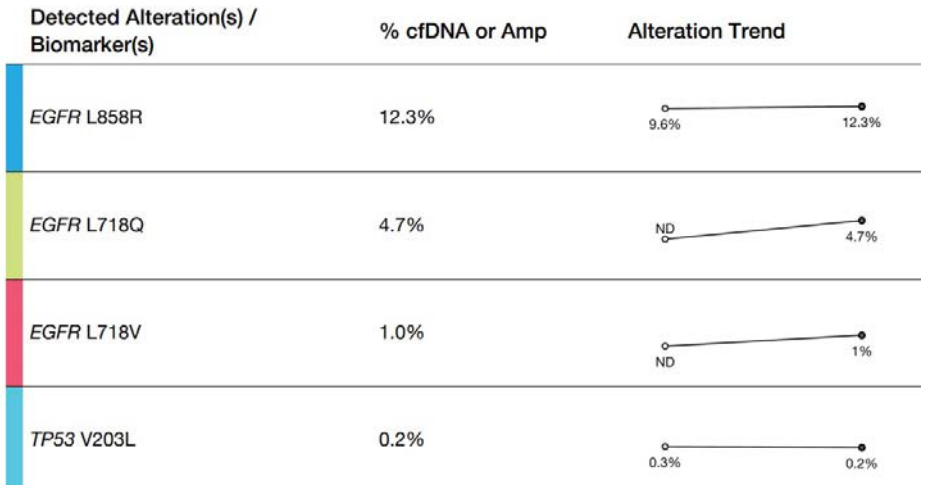


Dr Piotrowska: EGFR-mutated metastatic NSCLC, continued

- Post-osimertinib ctDNA NGS: EGFR L858R, TP53 mutation and **acquired EGFR L718Q, L718V mutations**.
- She initiated **second-line carboplatin/pemetrexed**, followed by pemetrexed maintenance (10 total cycles) with further disease progression in the thorax.

- **What treatment options should be considered now?**
  - Patritumab deruxtecan (if available)
  - Amivantamab/Lazertinib (if available)
  - Docetaxel
  - Afatinib

ctDNA testing after first-line osimertinib



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- **EGFR Exon 20 Insertions**
- **HER2 Mutations**
- **RET Fusions**

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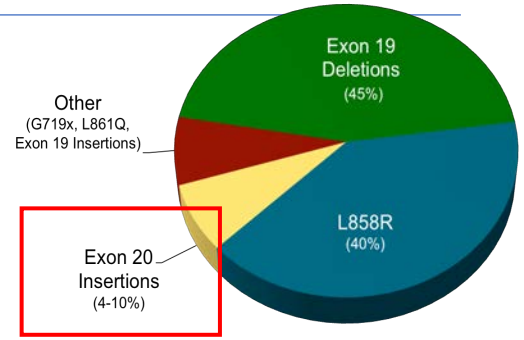
Management of EGFR Exon 20 Insertions

Management of EGFR exon 20 insertions pre-ESMO:

- The current first-line standard of care for EGFR exon 20 insertions is platinum-pemetrexed chemo (+/- immunotherapy).
- Amivantamab (bispecific EGFR/MET ab) has accelerated approval in the post-chemotherapy setting (ORR 40%, mPFS 8.3 mo[1])
- Mobocertinib (oral EGFR inhibitor) is being voluntarily withdrawn from the US market after randomized first-line trial was stopped for futility[2].
- Other new EGFR exon 20-directed TKIs are in clinical trials.



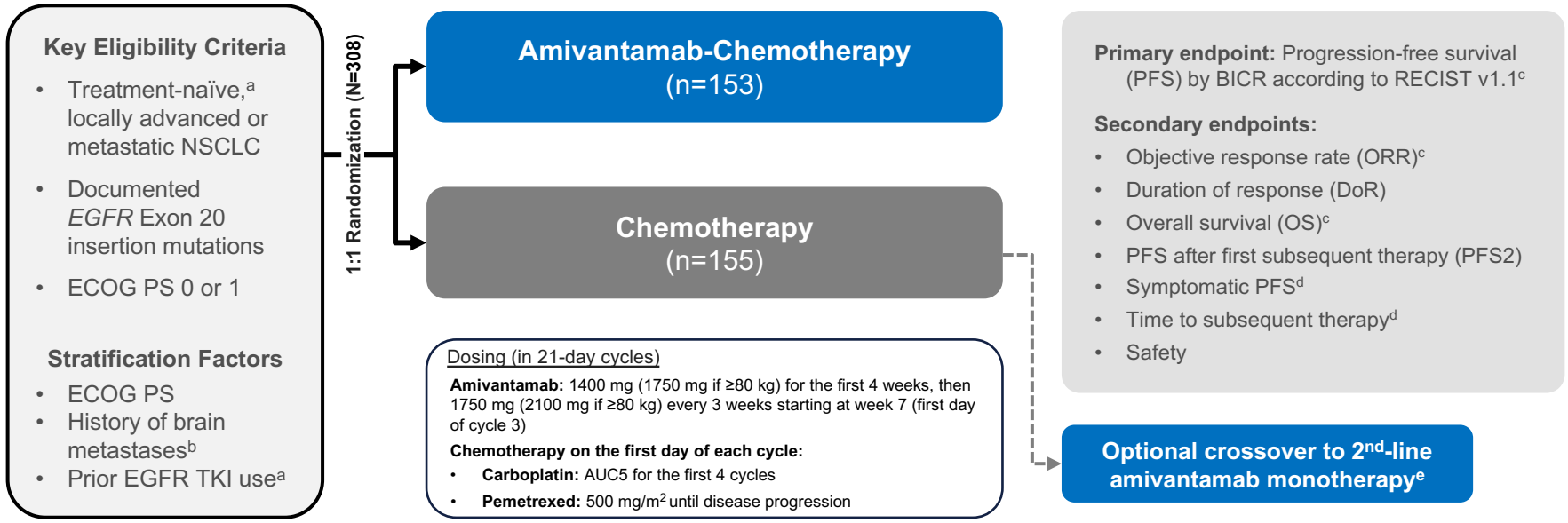
1. Park K, et al, JCO 2021; 2. https://www.takeda.com/newsroom/newsreleases/2023/Takeda-Provides-Update-on-EXKIVITY-mobocertinib/

Courtesy of Zofia Piotrowska, MD, MHS

PAPILLON: Amivantamab + Chemo for EGFR ex20ins

PAPILLON

PAPILLON: Phase 3 Study Design



PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

[a]Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
[b]Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
[c]Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
[d]These secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
[e]Crossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

AUC, area under the curve; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

MADRID 2023 ESMO congress

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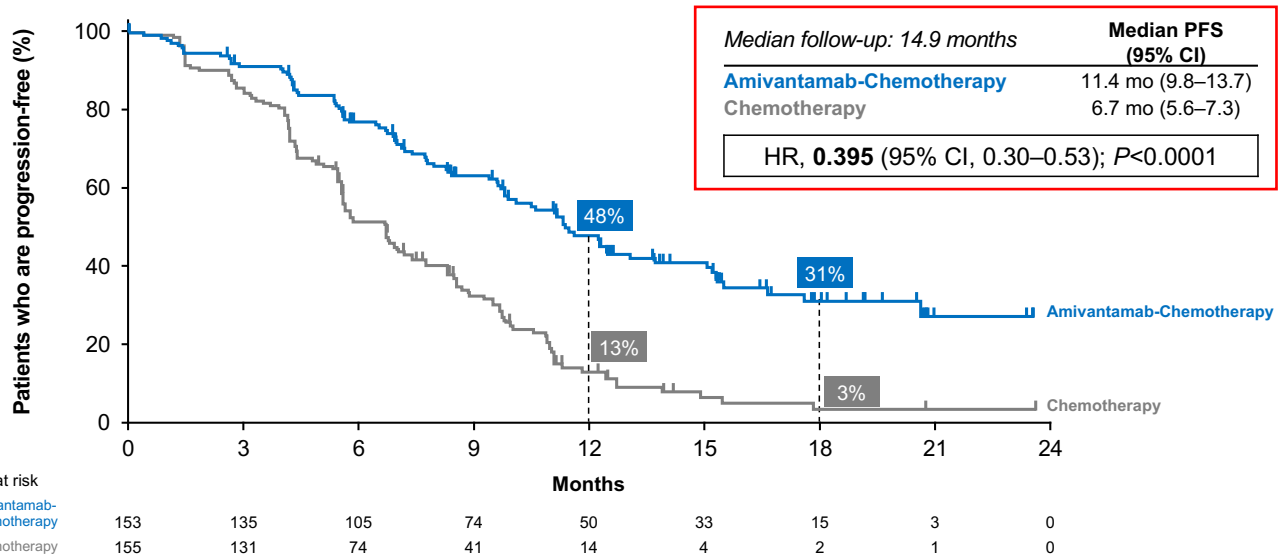
Girard N, ESMO 2023.

Courtesy of Zofia Piotrowska, MD, MHS

PAPILLON: Amivantamab + Chemo for EGFR ex20ins

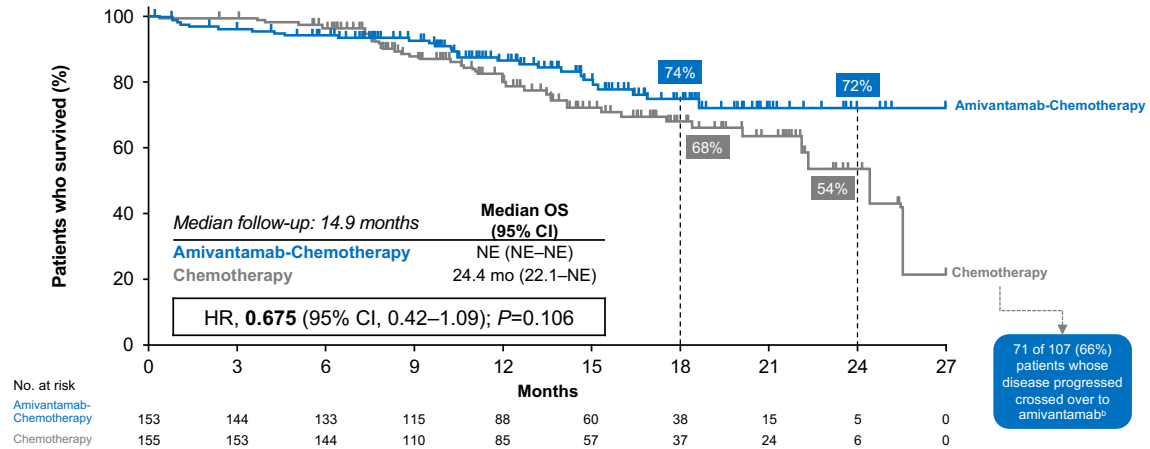
Primary Endpoint: Progression-free Survival by BICR

Amivantamab-chemotherapy reduced risk of progression or death by 60%

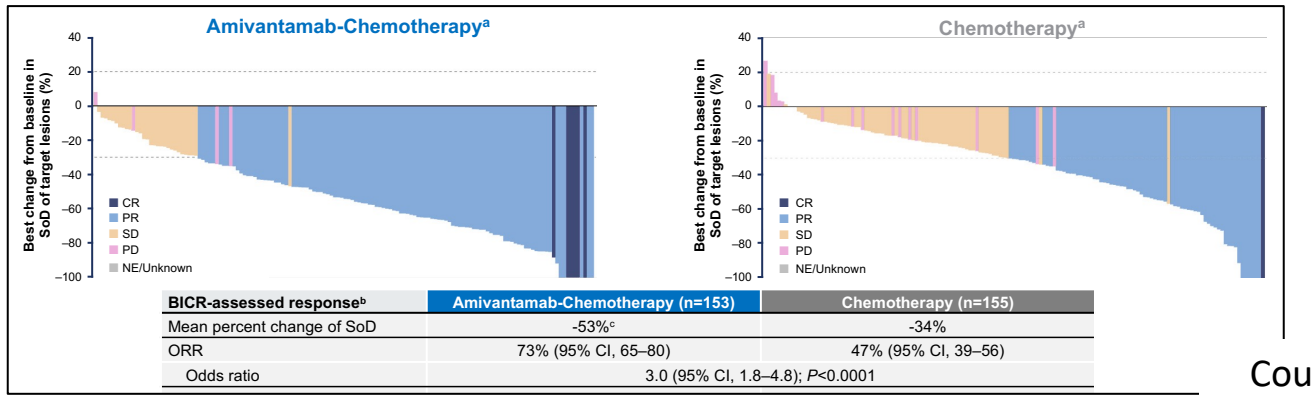


Interim Overall Survival[a]

Amivantamab-chemotherapy shows trend in reducing risk of death by over 30%



ORR 73 vs 47%



Girard N, ESMO 2023.

Courtesy of Zofia Piotrowska, MD, MHS

PAPILLON Safety

Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Other				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increased	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

- Lazertinib adds dermatologic toxicities, edema, and increases risk of neutropenia vs. chemotherapy.
- Dose reductions were required in 48% Ami/Chemo vs. 23% of Chemo pts.
- 24% pts on Ami/Chemo discontinued an agent, vs. 10% on chemo.

Girard N, ESMO 2023.

Courtesy of Zofia Piotrowska, MD, MHS

PAPILLON - Summary

Clinical Implications:

- Adding Amivantamab to Chemotherapy significantly improved ORR and PFS for patients with EGFR exon 20 insertion+ NSCLC.
- Testing for EGFR exon 20 is critical for selection of optimal therapy.
- If approved, Chemo + Ami will likely become the preferred first-line treatment for patients (acknowledging increased toxicities)

Future Directions:

- Multiple studies of novel, selective exon 20-specific TKIs are ongoing and may change our first-line standard of care in the future.

Courtesy of Zofia Piotrowska, MD, MHS

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- HER2 Mutations
- RET Fusions

MODULE 4: Updates on Immunotherapy in Metastatic NSCLC

MODULE 5: Emerging Antibody-Drug Conjugates for Metastatic NSCLC

MODULE 6: Small Cell Lung Cancer

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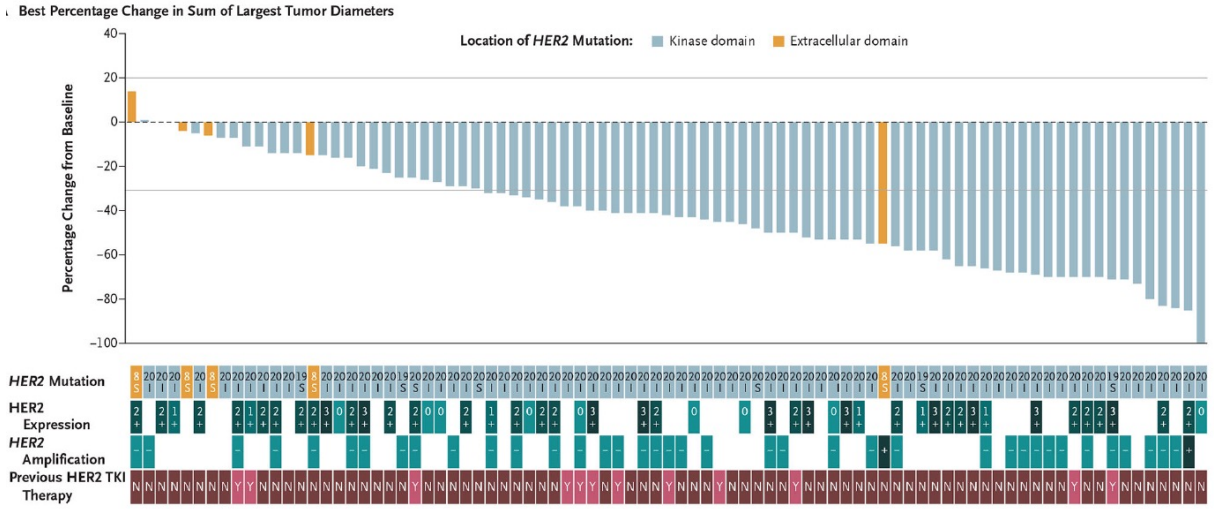
HER2-mutant NSCLC

DESTINY-Lung 01

- HER2-mutated cohort (N=91):
  - ORR 55% (95% CI, 44–65%)
  - mPFS 8.2 mo (95% CI, 6.0–11.9 mo)
  - mOS 17.8 mo (95% CI, 13.8–22.1 mo)
- Adjudicated drug-related ILD occurred in 26% pts, with 2/91 deaths.

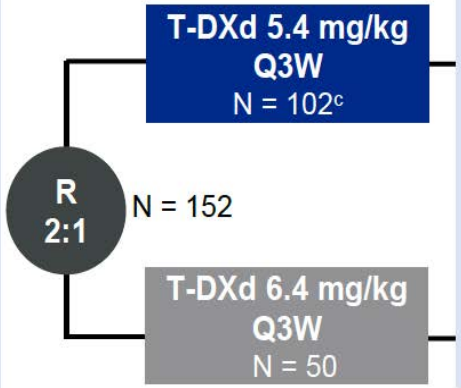


Li B, et al, NEJM 2022

DESTINY-Lung02: Study Design

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment



Primary Endpoint
- Confirmed ORR by BICR

Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

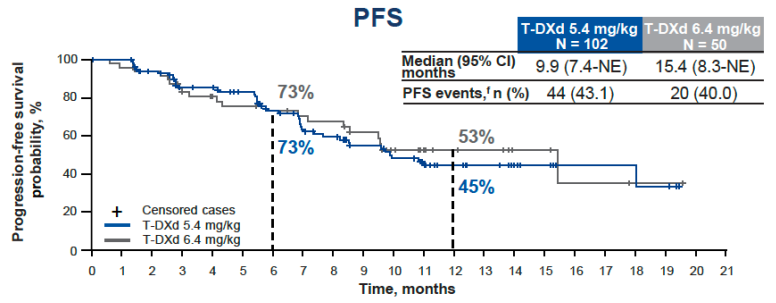
Courtesy of Zofia Piotrowska, MD, MHS

Janne P, WCLC 2023, Abstract MA13.20

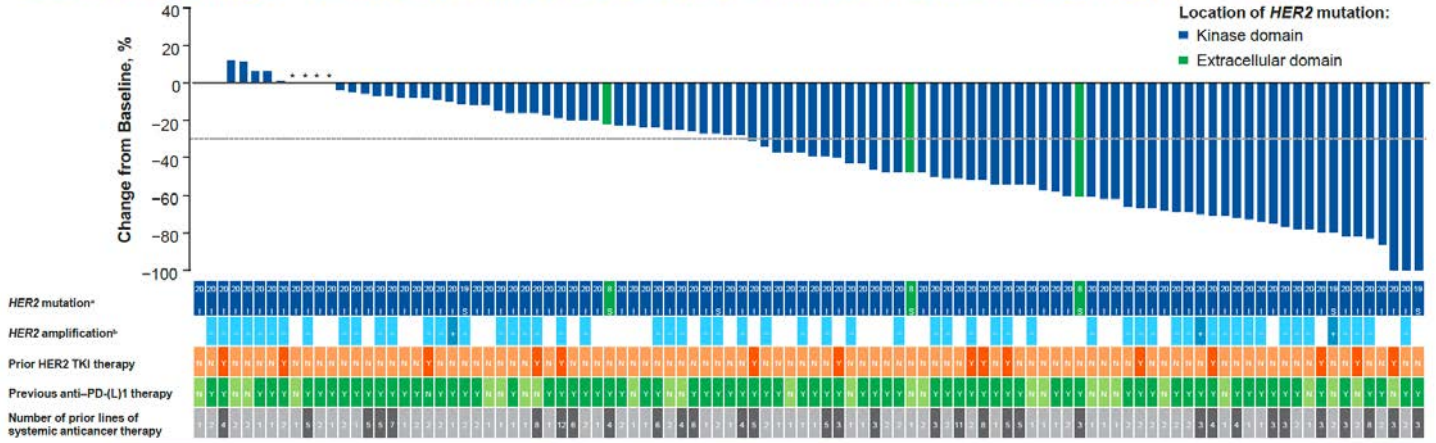
DESTINY-Lung02

Janne P, WCLC 2023, Abstract MA13.20

	5.4mg/kg N=102	6.4mg/kg N=50
Conf ORR	49% (39-59.1)	56% (41.3-70)
mDOR	16.8 mo (6.4-NE)	NE (8.3-NE)
Median PFS	9.9 mo (7.4-NE)	15.4 mo (8.3-NE)
Median F/U	11.5 mo	11.8mo

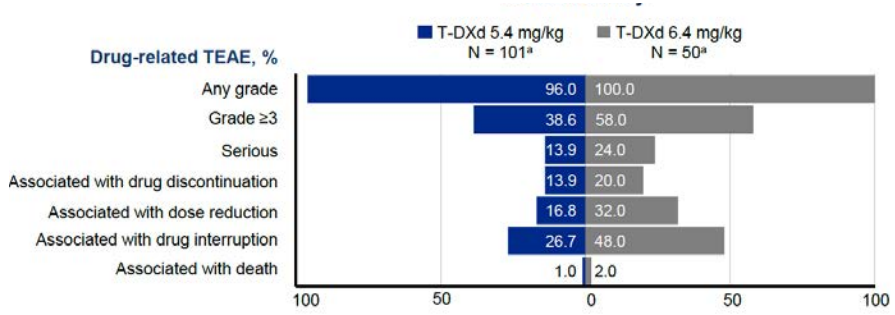


Best Percentage Change in Tumor Size by BICR With T-DXd 5.4 mg/kg (N = 102)



Responses were observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

Safety in DL-02



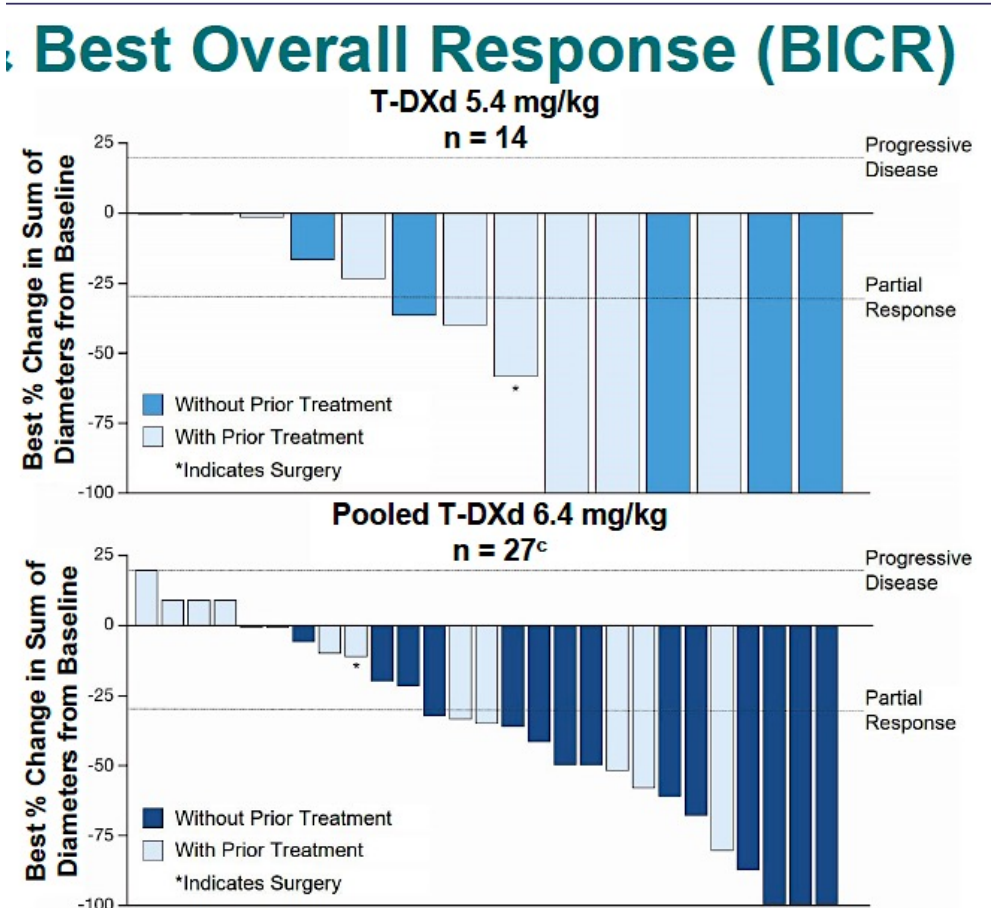
Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

8/11/22: US FDA granted accelerated approval to T-DXd for NSCLC with activating HER2 mutations, who have received a prior systemic therapy. The recommended dose is 5.4mg/kg IV q3 weeks.

Courtesy of Zofia Piotrowska, MD, MHS

CNS Outcomes with Trastuzumab Deruxtecan



Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM n = 14	Pooled T-DXd 6.4 mg/kg DL-01 *HER2m*/DL-02 BM n = 30
IC-cORR, n (%)[a]	**7 (50.0)**	**9 (30.0)**
95% CI[b]	23.0-77.0	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30.0)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE[c]	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%)[a]	**13 (92.9)**	**22 (73.3)**
95% CI[b]	66.1-99.8	54.1-87.7
IC-DoR, months[d]		
Median, (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

	5.4mg/kg (DL02) No prior Rx N=6	Pooled 6.4mg/kg (DL-01/DL-02) No prior Rx N=16
IC –cORR	3/6 (50%)	6/16 (37.5%)
IC- DoR, median	9.5 mo	5.6 mo

Planchard D, ESMO 2023

Courtesy of Zofia Piotrowska, MD, MHS

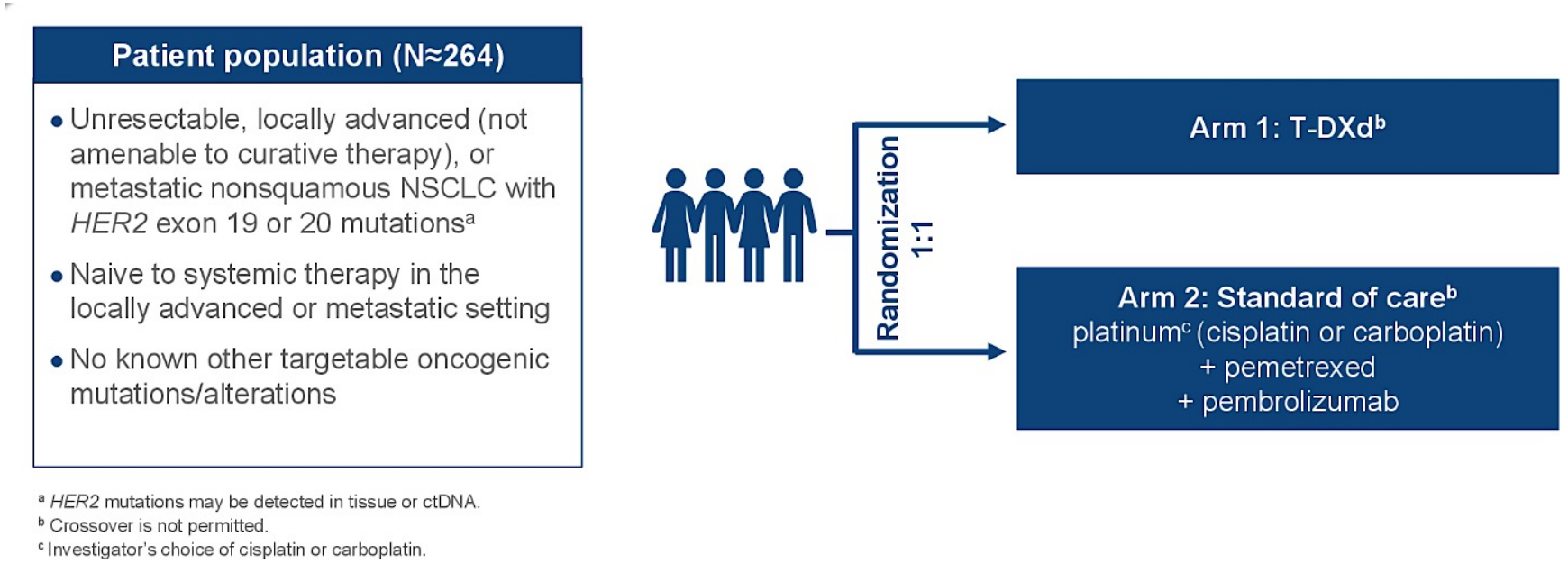
Trastuzumab Deruxtecan in HER2-mutant NSCLC

Clinical Implications:

- DESTINY-Lung02 confirms efficacy of T-DXd in HER2m NSCLC at the approved dose of 5.4mg/kg IV q3 weeks, with lower rates of toxicities, especially ILD (12%).
- T-DXd has CNS activity with an intracranial ORR of 50% (7/14 pts) including 3 CRs at 5.4mg/m2.

Future Directions:

- **DESTINY-Lung04**
- HER2-selective, EGFR-sparing TKIs are also now in clinical trials



Courtesy of Zofia Piotrowska, MD, MHS

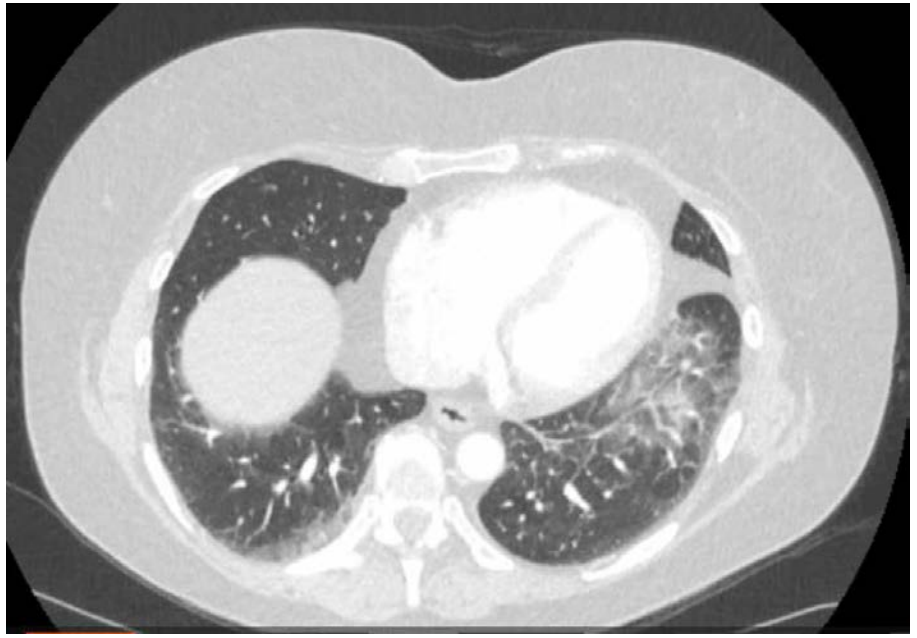
Li B, J Clin Oncol 40, 2022 (suppl 16; abstr TPS9137)

Dr Piotrowska: HER2-mutated metastatic NSCLC

- 65 yo F with no history of tobacco use, history of hypothyroidism who presented with subacute cough and shortness of breath.
- Scans showed a 4cm LUL lung mass with mediastinal adenopathy and a lytic lesion of T10. Brain MRI at diagnosis showed 3 subcentimeter metastases.
- Bronchoscopy/EBUS and biopsy of level 4L LN: **lung adenocarcinoma**, PDL1 negative.
- NGS– **HER2 exon 20 insertion, A775_G776insYVMA**, TP53 mutation
- She received first-line **Carboplatin/Pemetrexed/Pembroli**zumab x 4 cycles, followed by 6 cycles of Pemetrexed/Pembrolizumab maintenance.
- She developed progressive bone metastases, new CNS metastasis.

Dr Piotrowska: HER2-mutated metastatic NSCLC, continued

- She received SRS to the new CNS metastasis.
- She started second-line **Trastuzumab Deruxtecan, 5.4mg/kg IV q3 weeks**.
- Restaging scans showed decrease in LUL mass, stable osseous and CNS metastases.
- After 6 months on Trastuzumab Deruxtecan, she was noted to have new groundglass opacities in the RLL. She had no associated shortness of breath, cough or respiratory symptoms.
- What is the most appropriate course of action at this point?



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LIBRETTO-431

Key Eligibility Criteria

- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

Stratification factors:

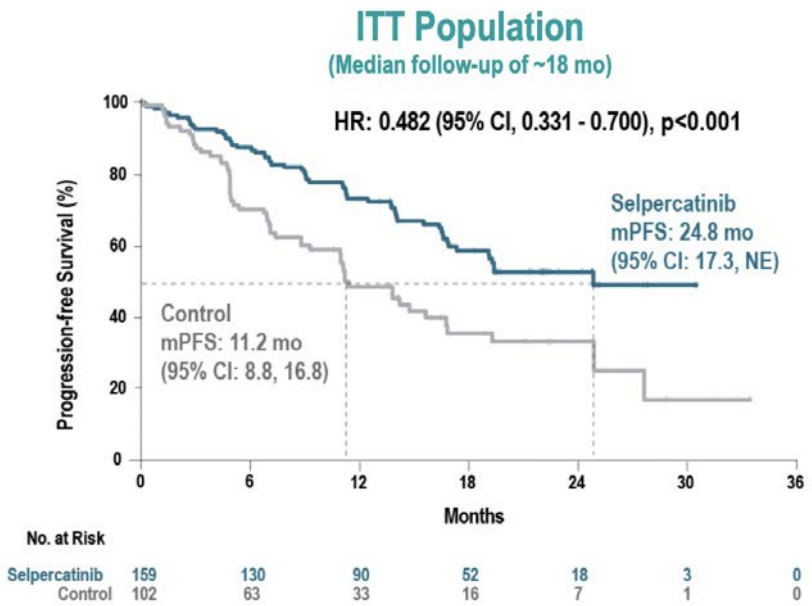
- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

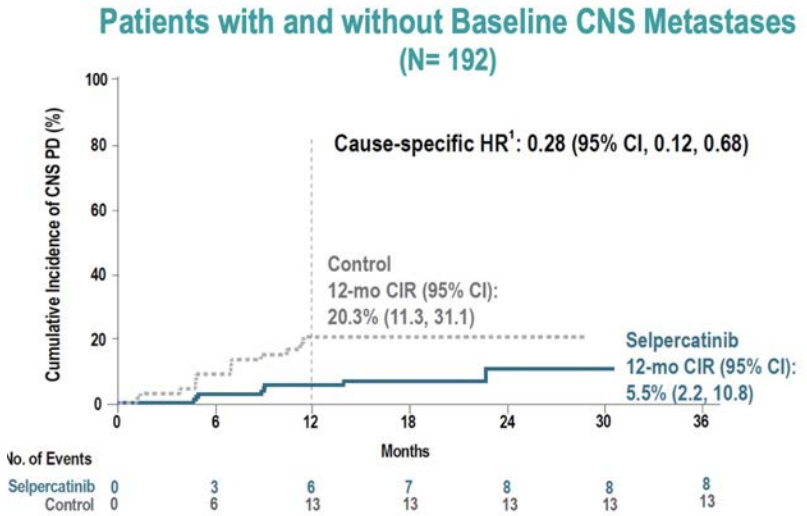
R 2:1[3]

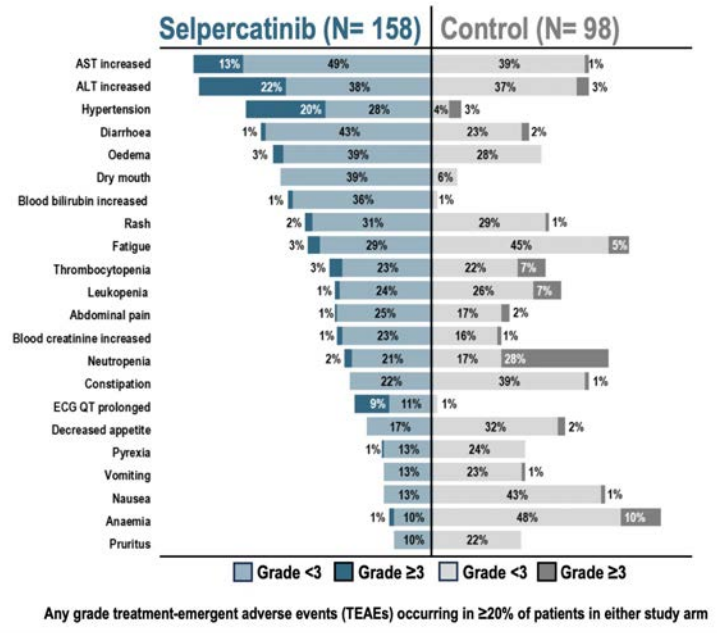
Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Optional Crossover → **Selpercatinib** (Upon BICR confirmed PD)







Courtesy of Zofia Piotrowska, MD, MHS

Loong H, ESMO 2023

LIBRETTO-431 Summary

Clinical Implications:

- LIBRETTO-431 confirms our practice of using selective RET inhibitors as first-line therapy for patients with RET+ NSCLC.
- Similar outcomes were observed in the control arm, regardless of whether pembro was given, highlighting the limited role of immunotherapy in RET+ patients.

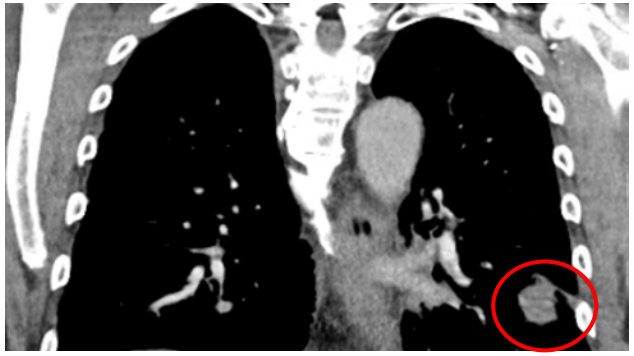
Future Directions:

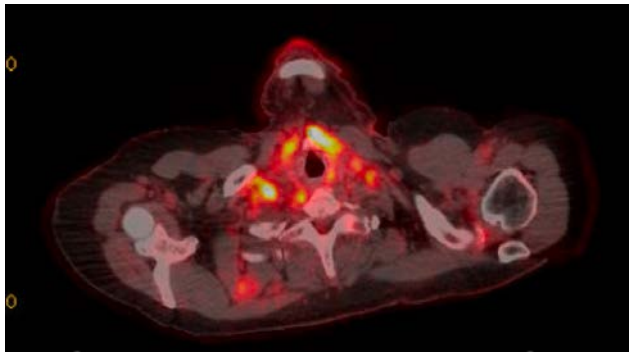
- Unclear if confirmatory, randomized studies are needed for rare patient subgroups with highly-active TKIs.

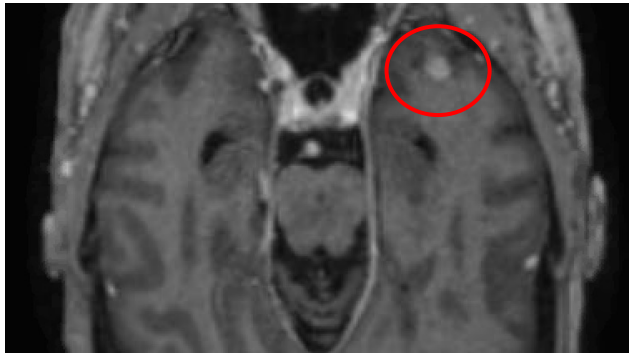
Courtesy of Zofia Piotrowska, MD, MHS

Dr Piotrowska: Metastatic NSCLC with a RET Fusion

- 58yo M with 10 py history of tobacco use, HTN, s/p gastric bypass presented with neck discomfort.
- CT neck/chest/abd/pelvis showed a 2.4cm LLL lung mass, extensive L hilar, mediastinal, supraclavicular, cervical lymphadenopathy and multiple hepatic metastases.
- Brain MRI showed a 1cm temporal lobe metastasis.
- Liver biopsy demonstrated adenocarcinoma.
- DNA NGS was negative; RNA NGS showed a **KIF5B-RET fusion.**
- He was started on first-line selpercatinib 160mg BID.

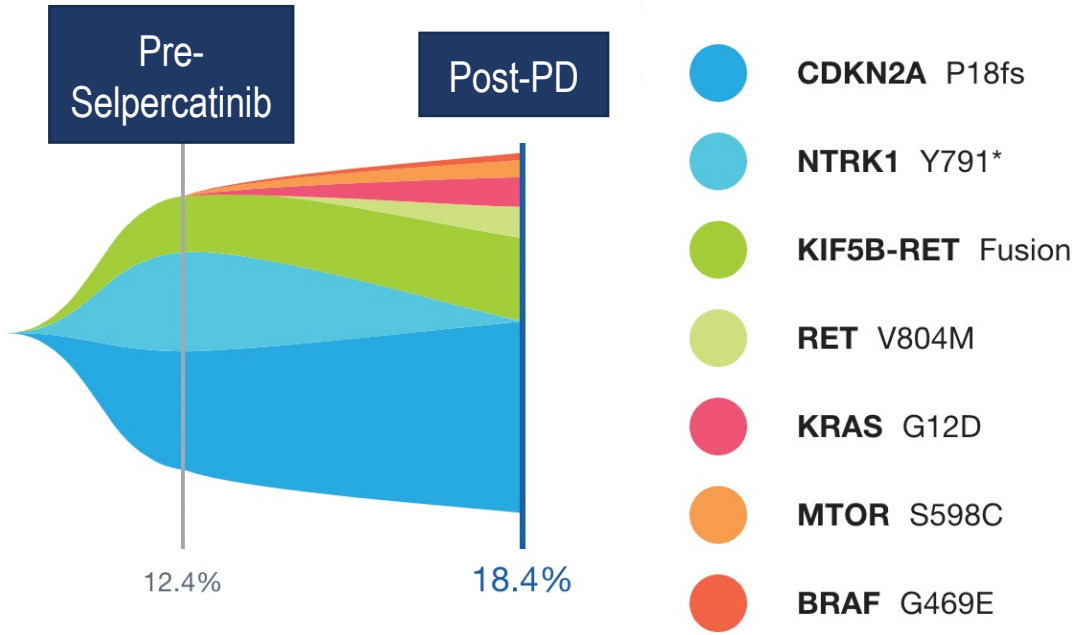






Dr Piotrowska: Metastatic NSCLC with a RET Fusion, continued

- Best response to selpercatinib was stable disease, lasting 9 months.
- He received SRS to the L temporal lesion.
- After about 9 months on selpercatinib, he developed progressive low back pain.
- Restaging CT scans showed progressive hepatic and LN metastases, new L5 metastasis. Brain MRI remained stable.
- What treatment options should be considered now?



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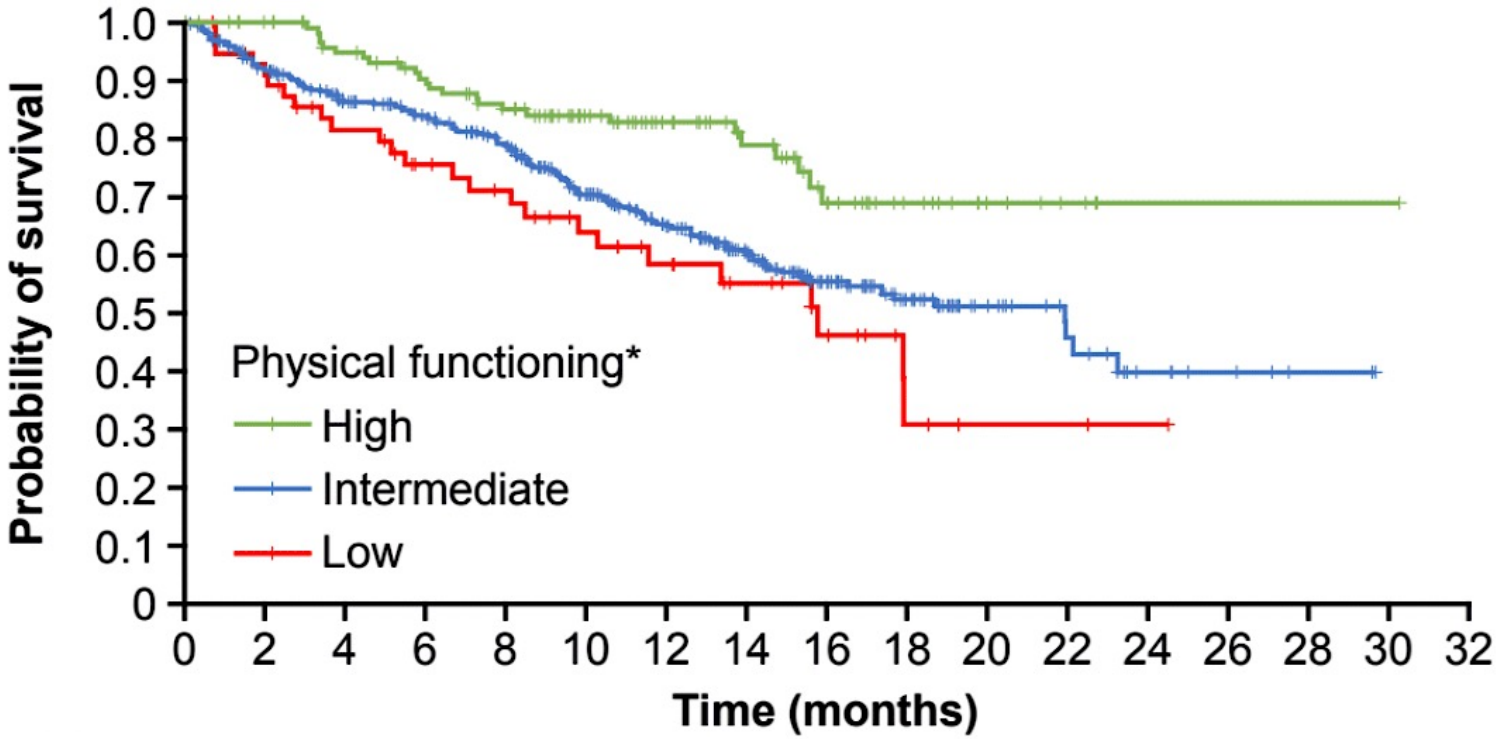
IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Predictive Utility of Patient-Reported Outcomes for Survival in 1st-Line Treated Patients with aNSCLC in EMPOWER-Lung 1 and 3

David Gandara,[1] Miranda Gogishvili,[2] Ahmet Sezer,[3] Tamta Makharadze,[4] Mahmut Gumus,[5] Debra AG McIntyre,[6] Xuanyao He,[6] Eric Yan,[6,7] Giuseppe Gullo,[6] Petra Rietschel,[6] Ruben GW Quek[6]

[1]Division of Hematology/Oncology, Department of Medicine, UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [2]High Technology Medical Centre, University Clinic Ltd, Tbilisi, Georgia; [3]Department of Medical Oncology, Başkent University, Adana, Turkey; [4]LTD High Technology Hospital Med Center, Batumi, Georgia; [5]Department of Medical Oncology, School of Medicine, Istanbul Medeniyet University, Istanbul, Turkey; [6]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [7]Cyan Global Inc., San Diego, CA, USA

Predictive Utility of PROs for Survival in the EMPOWER-Lung 1 and 3 Trials: Overall Survival (OS) by Physical Function at Baseline



Patients with higher baseline physical functioning* had more favorable OS (high vs low, HR [95% CI]: 0.41 [0.24–0.72]; *P*=0.002). This represents a predicted 59% reduction in the risk of death

PROs = patient-reported outcomes

Gandara D et al. WCLC 2023;Abstract MA05.11.

Cemiplimab for Advanced Non-Small Cell Lung Cancer: Squamous Subgroup Analysis for EMPOWER-Lung 1 and 3

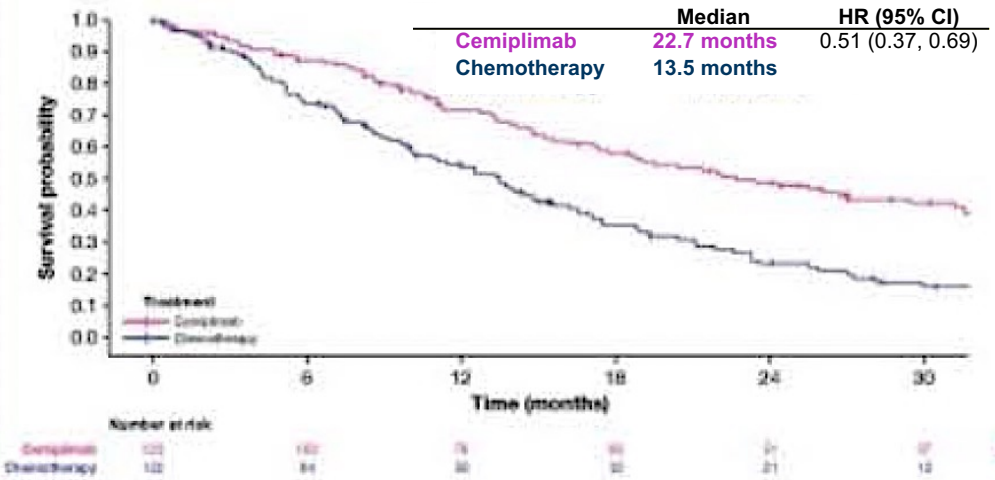
Makharadze T et al.

ESMO 2023;Abstract 1438P.

Subgroup Analysis for EMPOWER-Lung 1 and 3

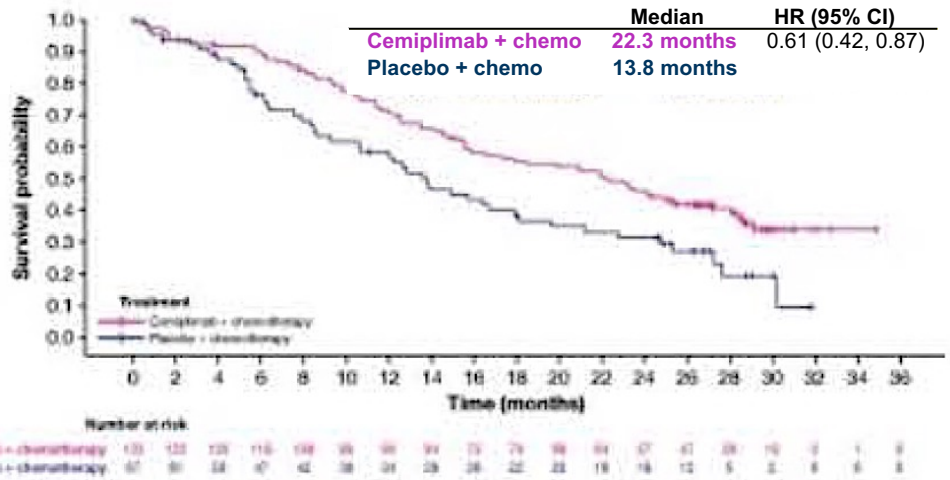
EMPOWER-Lung1: OS

	Median	HR (95% CI)
Cemiplimab	22.7 months	0.51 (0.37, 0.69)
Chemotherapy	13.5 months	



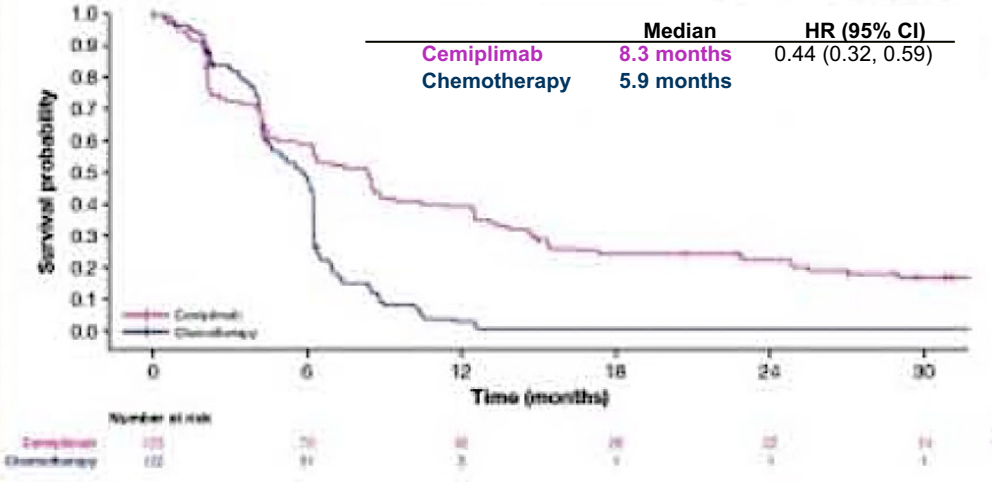
EMPOWER-Lung3 Part 2: OS

	Median	HR (95% CI)
Cemiplimab + chemo	22.3 months	0.61 (0.42, 0.87)
Placebo + chemo	13.8 months	



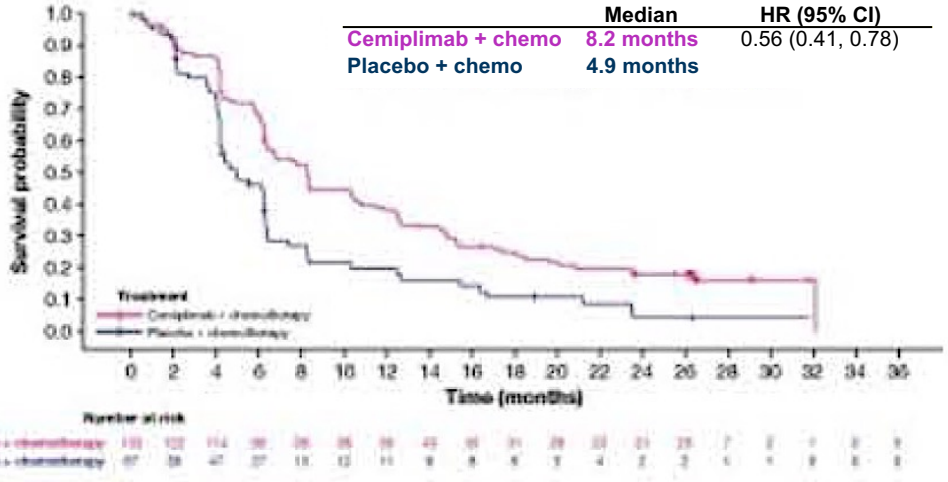
EMPOWER-Lung1: PFS

	Median	HR (95% CI)
Cemiplimab	8.3 months	0.44 (0.32, 0.59)
Chemotherapy	5.9 months	



EMPOWER-Lung3 Part 2: PFS

	Median	HR (95% CI)
Cemiplimab + chemo	8.2 months	0.56 (0.41, 0.78)
Placebo + chemo	4.9 months	



Makharadze T et al. ESMO 2023;Abstract 1438P.

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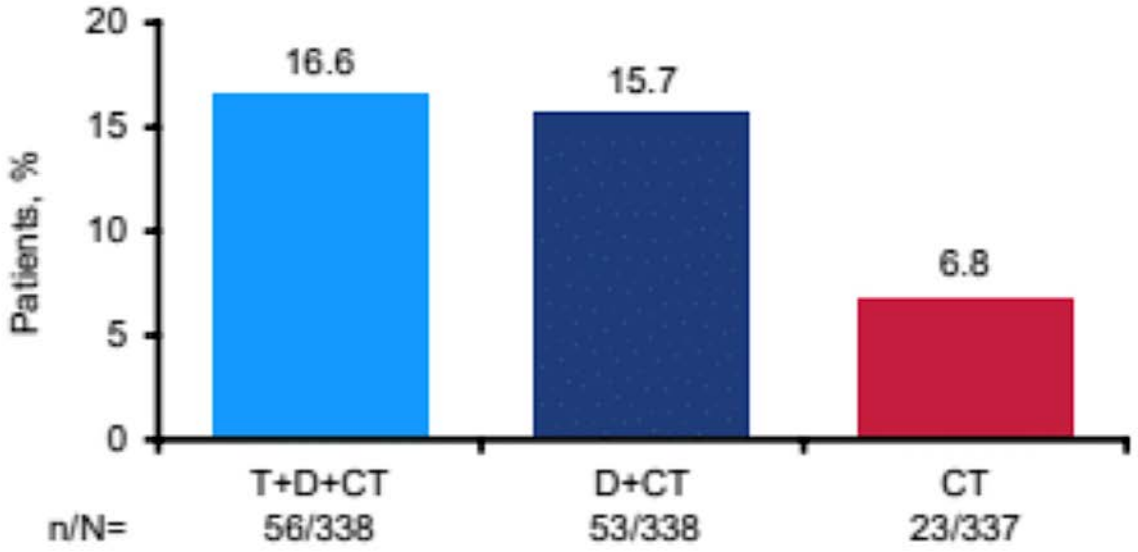
Durvalumab ± Tremelimumab + Chemotherapy in 1L Metastatic NSCLC: Characterization of Patients with PFS ≥12 Months in POSEIDON

Cho BC et al.

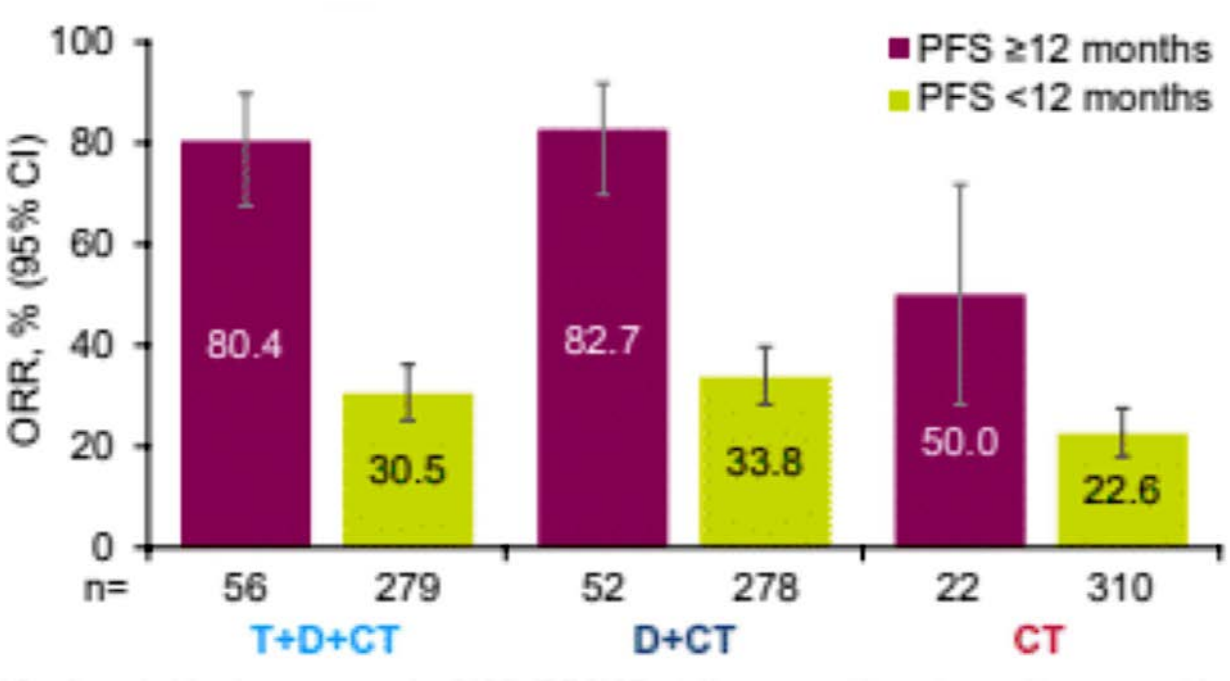
WCLC 2023;Abstract P2.06-05.

Patients with PFS ≥12 Months in the POSEIDON Trial

Patients with PFS ≥12 months



ORR in the PFS ≥12 and <12 months subgroups



T = tremelimumab; D = durvalumab; CT = chemotherapy; ORR = objective response rate

Cho BC et al. WCLC 2023;Abstract P2.06-05.

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MODULE 5: Emerging Antibody-Drug Conjugates for Metastatic NSCLC

- Datopotamab Deruxtecan
- Sacituzumab Govitecan

MODULE 6: Small Cell Lung Cancer

RTP RESEARCH TO PRACTICE

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RTP RESEARCH TO PRACTICE

MADRID 2023 ESMO congress

Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase 3 study TROPION-Lung01

Myung-Ju Ahn,[1,a] Aaron Lisberg,[2,a,b] Luis Paz-Ares,[3] Robin Cornelissen,[4] Nicolas Girard,[5] Elvire Pons-Tostivint,[6] David Vicente Baz,[7] Shunichi Sugawara,[8] Manuel Angel Cobo Dols,[9] Maurice Pérol,[10] Céline Mascaux,[11] Elena Poddubskaya,[12] Satoru Kitazono,[13] Hidetoshi Hayashi,[14] Jacob Sands,[15] Richard Hall,[16] Yong Zhang,[17] Hong Zebger-Gong,[18] Deise Uema,[17] Isamu Okamoto[19]

[a]Equal contribution as first author. [b]Indicates presenting author.

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TROPION-Lung01 Study Design

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations[a]

- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd
6 mg/kg Q3W
(N=299)

Docetaxel
75 mg/m² Q3W
(N=305)

Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

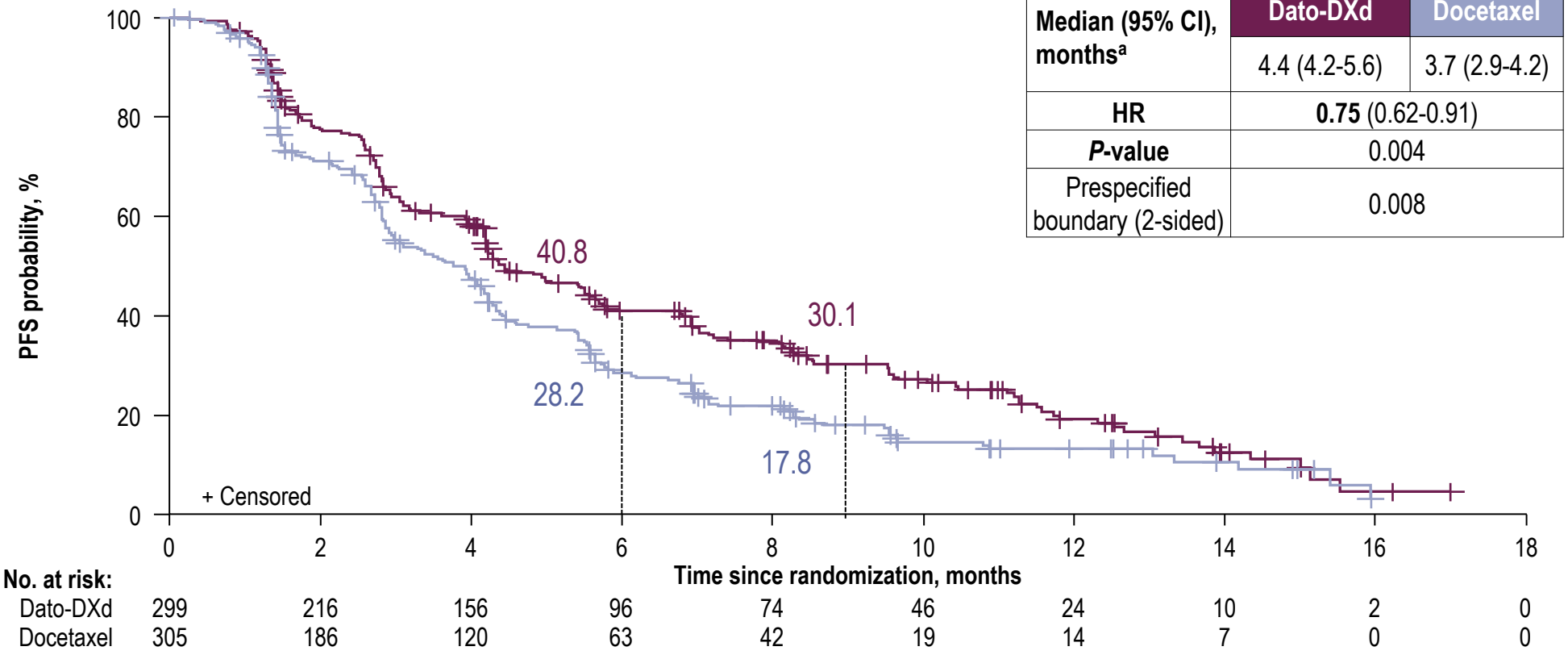
Enrollment period: 19 February 2021 to 7 November 2022.

BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.

[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs non-squamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.

Progression-Free Survival: ITT

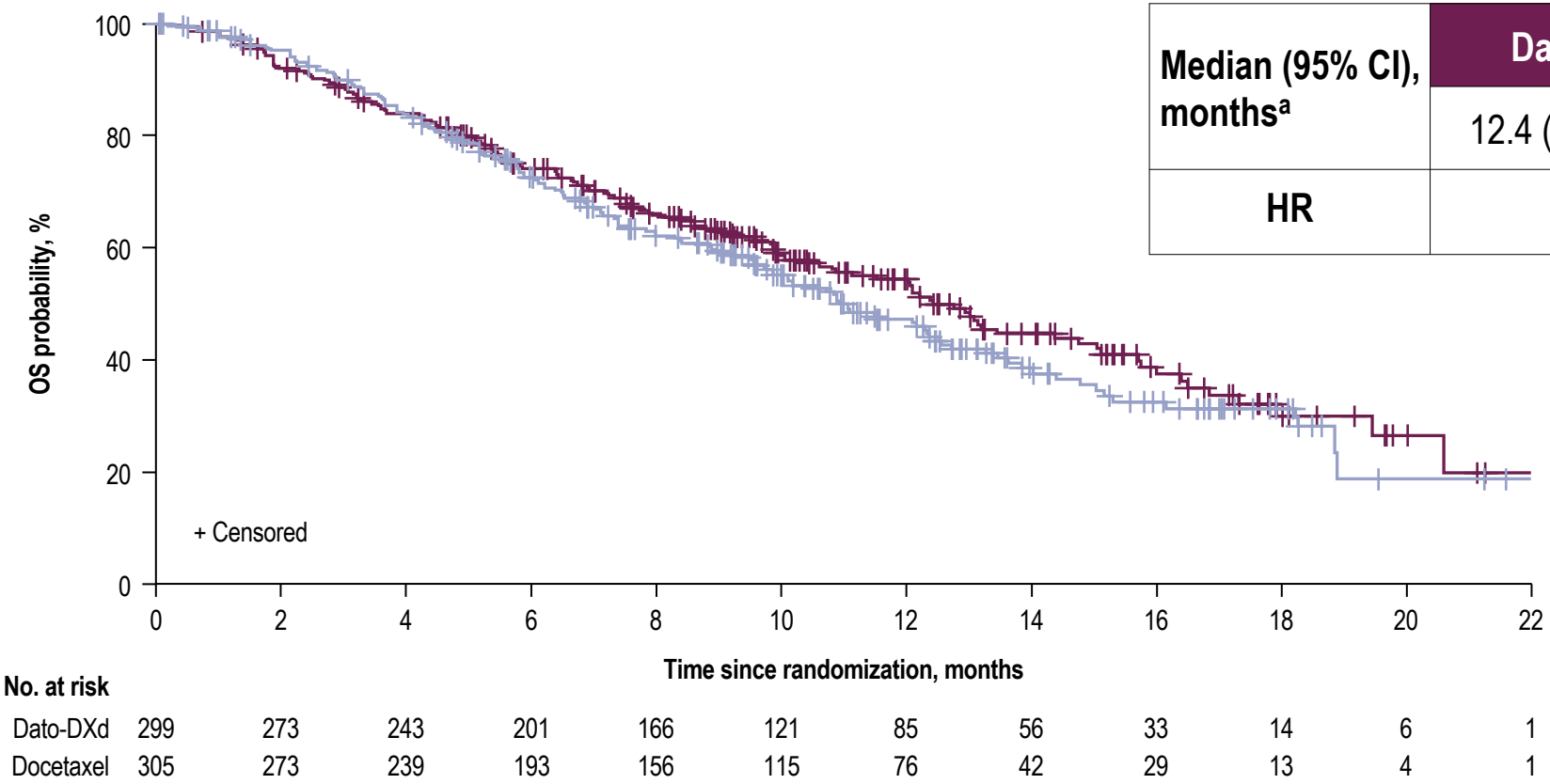
Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
***P*-value**	0.004	
Prespecified boundary (2-sided)	0.008	



	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Median PFS follow-up was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and docetaxel, respectively. [b]Included 4 CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

Interim Overall Survival: ITT



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	**0.90** (0.72-1.13)	

Information fraction at interim analysis (events/total events required): **74%.**

Non-squamous HR (95% CI): **0.77** (0.59-1.01); **Squamous HR** (95% CI): **1.32** (0.87-2.00)

Trial is continuing to final OS analysis

HR, hazard ratio; ITT, intention to treat; OS, overall survival.

[a]Median OS follow-up was 11.8 (95% CI, 11.3-12.7) and 11.7 (95% CI, 10.9-12.9) months for Dato-DXd and docetaxel, respectively.

MADRID 2023 ESMO congress

Aaron Lisberg

Abstract LBA12.

Adverse Events of Special Interest

AESI, n (%)	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis[a]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events[b]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[c]	0
Adjudicated drug-related ILD[d]		
All grades	25 (8)	12 (4)
Grade ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

- Stomatitis/oral mucositis associated with Dato-DXd resulted in a low rate of discontinuation (0.7%)
- Dry eye was the most common ocular event seen with Dato-DXd (6.1%; primarily grade ≤2), followed by increased lacrimation (5.4%)
- Seven adjudicated drug-related grade 5 ILD events
  - Primary cause of death in 4 out of 7 was attributed to disease progression by investigator
  - Non-squamous: 4 of 232 patients (1.7%); Squamous: 3 of 65 patients (4.6%)[e]
- IRRs were observed in 8% of patients in each arm, all were grade ≤2 with the exception of 1 grade 3 event with Dato-DXd

AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, standardized MedDRA query; SOC, system organ class. AESIs listed in this slide are treatment emergent and include all PTs that define the medical concept.

[a]Events included the selected PTs oral mucositis/stomatitis, oropharyngeal pain, mouth ulceration, odynophagia, dysphagia, oral pain, glossitis, pharyngeal inflammation, aphthous ulcer, and oral mucosa erosion. [b]Ocular events included selected PTs from the corneal disorder SMQ and selected relevant PTs from the eye disorder SOC. [c]Included 4 cases of keratitis and 1 case of ulcerative keratitis. [d]ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or docetaxel (includes cases of potential ILD/pneumonitis based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). [e]Among treated patients, histology information per the case report form.

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Datopotamab Deruxtecan (Dato-DXd) + Durvalumab ± Carboplatin in Advanced/Metastatic NSCLC: Initial Results from the Phase 1b TROPION-Lung04 Study

Kyriakos P. Papadopoulos,[1] Debora S. Bruno,[2] Satoru Kitazono,[3] Shuji Murakami,[4] Martin Gutierrez,[5] Kazushige Wakuda,[6] Alexander Spira,[7] Kristof Cuppens,[8,9] Susan Lovick,[10] Adriana Hepner,[11] Gabriel Mak,[11] Saiama N. Waqar[12]

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TROPION-Lung04 Design: A Phase Ib, Multicenter, Open-Label, Dose Escalation/Confirmation and Expansion Study

TROPION-Lung04 is investigating Dato-DXd in combination with different immunotherapy agents ± carboplatin across 11 cohorts. This interim analysis reports the first data from Cohorts 2 and 4

Key eligibility

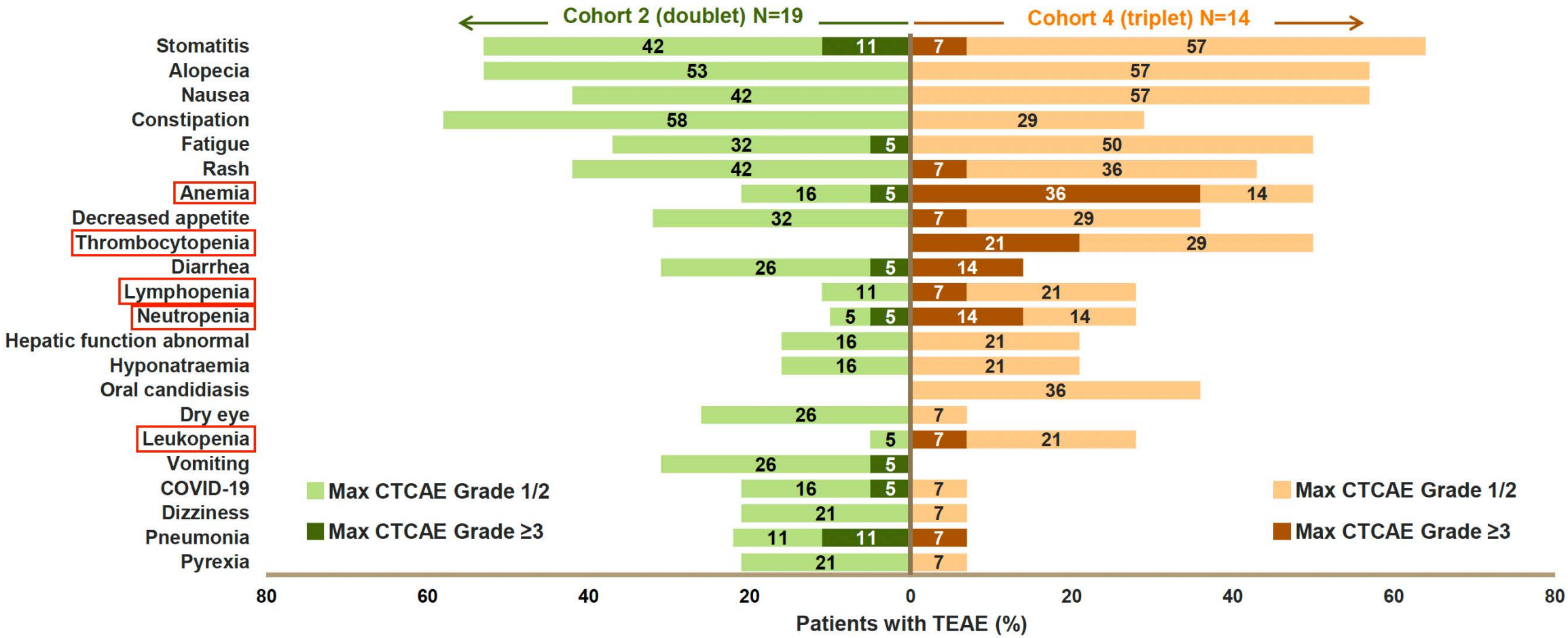
- Adults (≥18 years) with previously treated or treatment-naïve advanced or metastatic NSCLC[a]
- No actionable genomic alterations
- ECOG PS 0–1

	1 Part 1: Sequential dose escalation[b]	2 Part 2: Dose expansion
Cohort 1 (Doublet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg, Q3W (n=5)	
Cohort 2 (Doublet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=3)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=16)
Cohort 3[c] (Triplet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W	
Cohort 4 (Triplet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=6)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=8)

- **Primary endpoint:** Safety and tolerability
- **Key secondary endpoints:** ORR and disease control rate by investigator assessment per RECIST v1.1

Papadopoulos KP et al. WCLC 2023;Abstract OA05.06.

TROPION-Lung04: TEAEs in ≥15% of Patients



Data cut-off: March 6 2023.
TEAEs by preferred term/grouped preferred term. TEAEs in ≥15% of patients is based on the total number of safety subjects in Cohort 2 and Cohort 4. Red boxes indicate hematological events.
CTCAE, Common Terminology Criteria for Adverse Events.

Papadopoulos KP et al. WCLC 2023;Abstract OA05.06.

TROPION-Lung04: Antitumor Activity

Response in patients in the 1L setting,[a] n (%)		Cohort 2 (doublet) N=14	Cohort 4 (triplet) N=13
Objective response rate (confirmed)		**7 (50.0)**	**10 (76.9)[b]**
[95% CI]		[23.0, 77.0]	[46.2, 95.0]
Best objective response	Complete response	0	0
	Partial response	7 (50.0)	10 (76.9)[b]
	Stable disease	6 (42.9)	2 (15.4)
	Progressive disease	1 (7.1)	1 (7.7)
Disease control rate		**13 (92.9)**	**12 (92.3)**
[95% CI]		[66.1, 99.8]	[64.0, 99.8]

- In the 1L setting, ORRs were **50.0%** for Cohort 2 and **76.9%[b]** for Cohort 4
- In the overall population (1L/2L+), ORRs were **47.4%** for Cohort 2 (N=19) and **71.4%[b]** for Cohort 4 (N=14)
- Responses were numerically higher with the triplet versus doublet combination and were observed across all PD-L1 expression levels

Data cut-off: March 6 2023.
All subjects must have had at least one scan (6 weeks of follow-up) to be included in the ORR interim analysis set. The 2-sided 95% CIs are exact Clopper-Pearson intervals. [a] As assessed by investigator per RECIST v1.1. [b] One of the 10 partial responses in Cohort 4 was confirmed after data cut-off.

Papadopoulos KP et al. WCLC 2023;Abstract OA05.06.

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Sacituzumab Govitecan + Pembrolizumab in 1L Metastatic Non-Small Cell Lung Cancer: Preliminary Results of the EVOKE-02 Study

Byoung Chul Cho,[1] Manuel Cobo Dols,[2] Roxana Reyes Cabanillas,[3] David Vicente,[4] Jose Fuentes Pradera,[5] Salvatore Grisanti,[6] Afshin Eli Gabayan,[7] Ki Hyeong Lee,[8] Eun Kyung Cho,[9] Sabeen Mekan,[10] Farnoush Safavi,[10] Nelumka Fernando,[10] Michael J. Chisamore,[11] Martin Reck[12]

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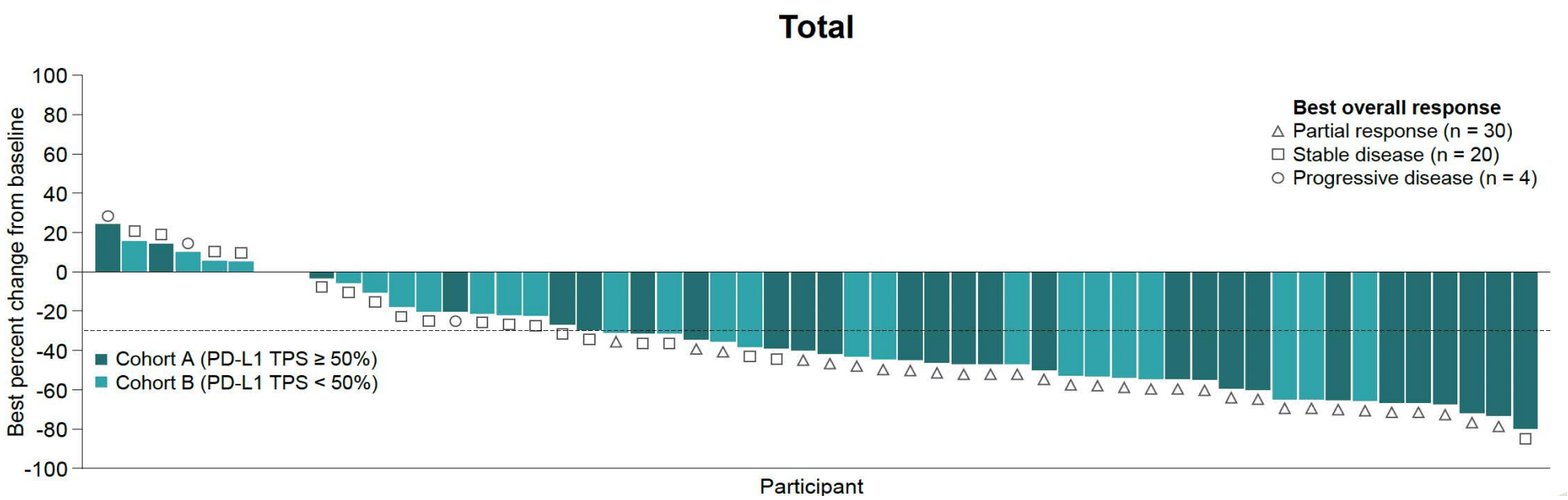
EVOKE-02: Efficacy by Investigator Assessment

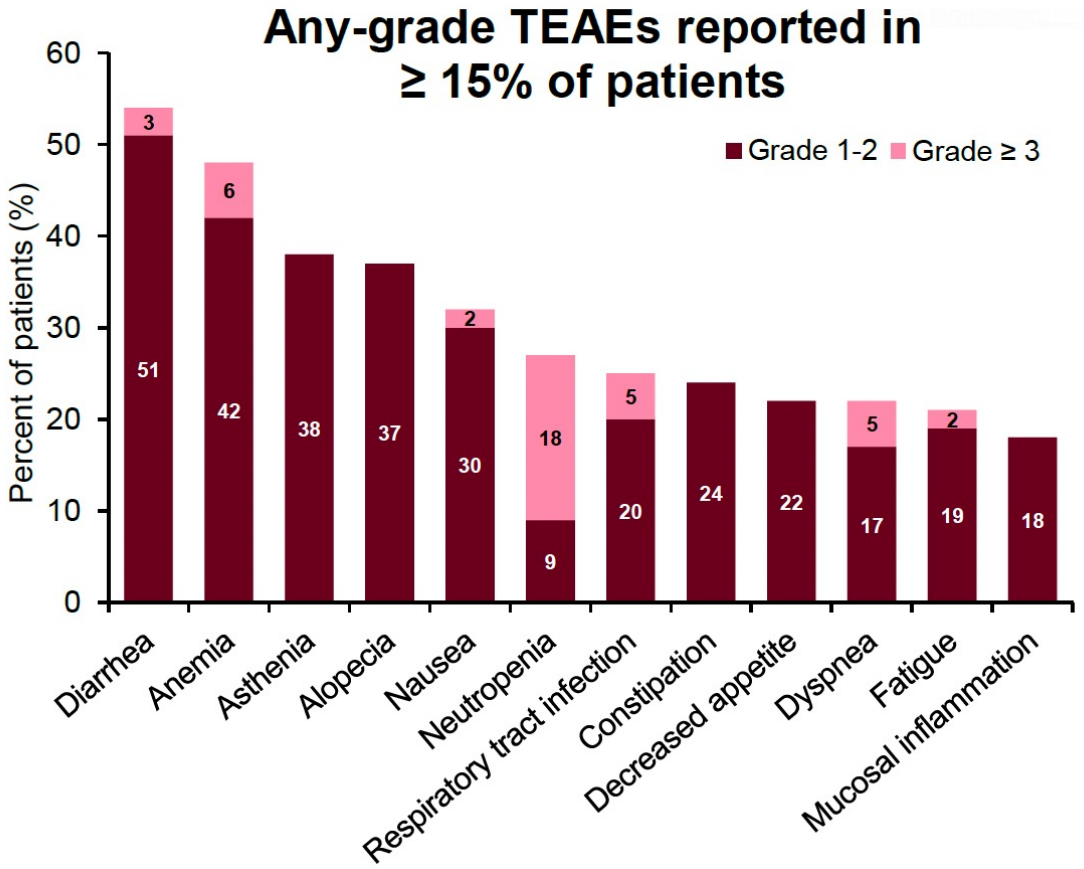


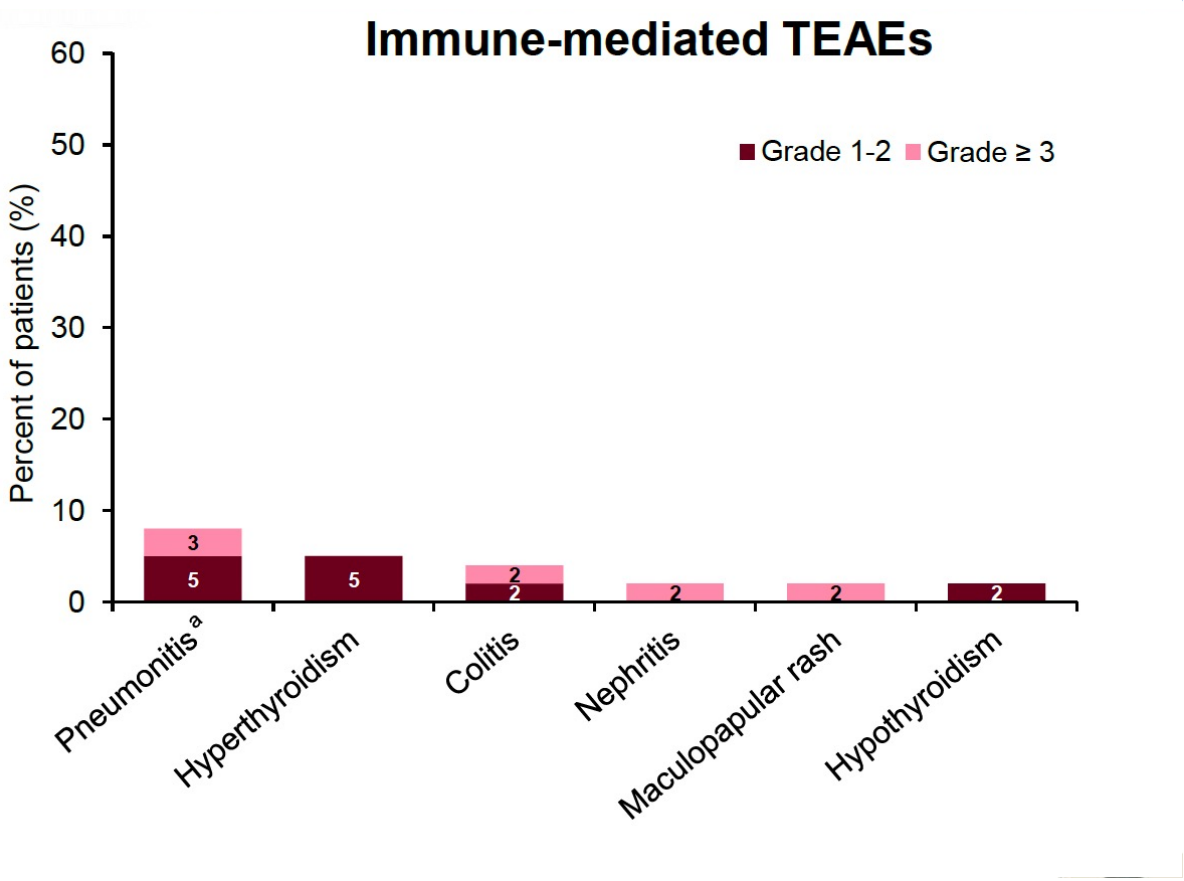
Efficacy by INV[a]	Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 29	Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 32	Total SG + Pembro n = 61
ORR[b] (95% CI), %	**69 (49-85)**	**44 (26-62)**	**56 (42-69)**
PR, n (%) – confirmed and unconfirmed	20 (69)	14 (44)	34 (56)
Confirmed PR, n (%)	18 (62)	12 (38)	30 (49)
SD, n (%)	5 (17)	11 (34)	16 (26)
PD, n (%)	3 (10)	2 (6)	5 (8)
DCR[c] (95% CI), %	86 (68-96)	78 (60-91)	82 (70-91)
Median DOR[d,e] (95% CI), months	NR (5.6-NR)	NR (3.5-NR)	NR (7.9-NR)
DOR rate at 6 months[d,e] (95% CI), %	88 (39-98)	88 (39-98)	87 (58-97)

SG = sacituzumab govitecan; Pembro = pembrolizumab; ORR = objective response rate; DCR = disease control rate

Cho BC et al. WCLC 2023;Abstract OA05.04.

EVOKE-02: Safety Profile of Sacituzumab Govitecan/Pembrolizumab





TEAEs = treatment-emergent adverse events

Cho BC et al. WCLC 2023;Abstract OA05.04.

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- Immunotherapy
- Novel Agents

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- **Immunotherapy**
- **Novel Agents**

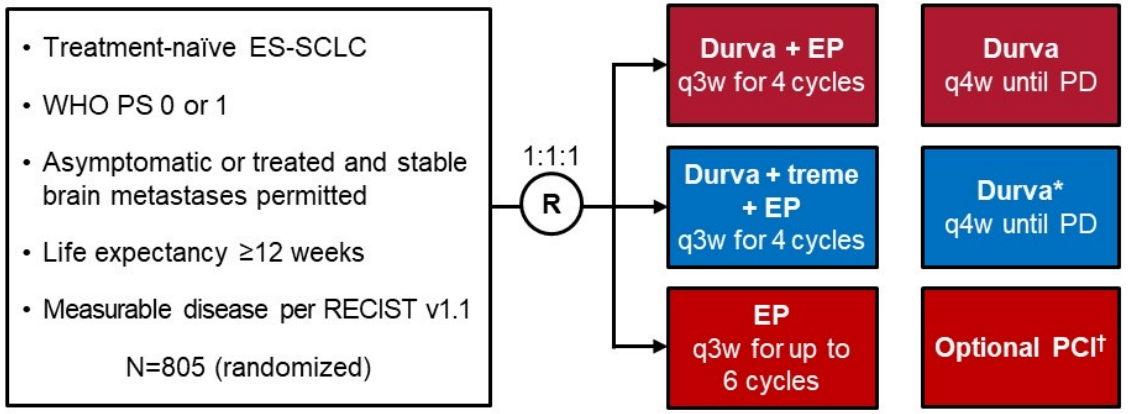
RTP RESEARCH TO PRACTICE

The Prognostic Value of Patient Reported Outcomes (PROs) and Clinical/Demographic Variables in the CASPIAN Study

Ganti AK et al.

ASCO 2023;Abstract 8516.

CASPIAN: Prognostic Value of PROs and Clinical/Demographic Variables



	Median OS	3 year survival
Durva + EP	12.9 mo	17.6%
EP	10.4 mo	5.8%

EORTC QLQ-C30

1 Global heath status/QoL scale	5 Functioning scales	3 Symptom scales	6 Single items
• Overall health • Overall QoL	• Physical • Role • Emotional • Cognitive • Social	• Fatigue • Nausea and vomiting • Pain	• Dyspnea • Insomnia • Appetite loss • Constipation • Diarrhea • Financial difficulties
7-point Likert scales	4-point Likert scales	4-point Likert scales	
Rescaled to 0–10 (minimally important change) Higher scores are better		Rescaled to 0–10 (minimally important change) Higher scores are worse	

ES-SCLC = extensive-stage small cell lung cancer; Durva = durvalumab; EP = platinum-etoposide; QoL = quality of life

Ganti AK et al. ASCO 2023;Abstract 8516.

CASPIAN: Prognostic Value of PROs and Clinical/Demographic Variables

	PFS			OS		
	A: Baseline only	B: Baseline & treatment	C: Baseline, treatment, other covariates	A: Baseline only	B: Baseline & treatment	C: Baseline, treatment, other covariates
Global health status/QoL	0.942	0.943	0.943	0.926	0.927	0.929
Functional scales						
Physical functioning	0.962	0.963	0.953	0.922	0.925	0.920
Role functioning	0.953	0.953	0.940	0.938	0.939	0.929
Emotional functioning	0.973	0.975	0.959	0.965	0.968	0.955
Cognitive functioning	0.987	0.988	0.987	0.964	0.968	0.965
Social functioning	0.960	0.960	0.956	0.956	0.957	0.958
Symptom scales/items						
Fatigue	1.033	1.033	1.040	1.061	1.060	1.066
Nausea and vomiting	1.027	1.025	1.036	1.040	1.040	1.056
Pain	1.041	1.040	1.054	1.059	1.059	1.069
Dyspnea	1.000	0.999	1.008	1.024	1.023	1.030
Insomnia	1.004	1.002	1.010	1.021	1.018	1.024
Appetite loss	1.043	1.040	1.052	1.058	1.057	1.066
Constipation	1.018	1.014	1.020	1.021	1.020	1.028
Diarrhea	0.971	0.973	0.975	0.933	0.933	0.934
Financial difficulties	1.035	1.032	1.032	1.029	1.028	1.030

Other co-variates in Cox Proportional Hazard Model

Durvalumab + EP Durvalumab + tremelimumab + EP EP
Cisplatin Carboplatin
Male vs female
≥65 years vs <65 years
1 vs 0
Yes vs no
Yes vs no
Asian vs non-Asian
III vs IV
Asia Europe North America/South America

Ganti AK et al. ASCO 2023;Abstract 8516.

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- **– Immunotherapy**
- **– Novel Agents**

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3258

Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with refractory SCLC: a subgroup analysis of a phase 1/2 study

Melissa Johnson,[1] Mark Awad,[2] Takafumi Koyama,[3] Martin Gutierrez,[4] Gerald S Falchook,[5] Sarina A Piha-Paul,[6] Toshihiko Doi,[7] Taroh Satoh,[8] Naoko Okamoto,[9] Jasmeet Singh,[9] Naoto Yoshizuka,[9] Meng Qian,[9] Xiaozhong Qian,[9] Brittany P Tran,[9] Ololade Dosunmu,[1] Rakesh Mucha,[1] Hillarie Windish,[1] Manish R Patel[1,10]

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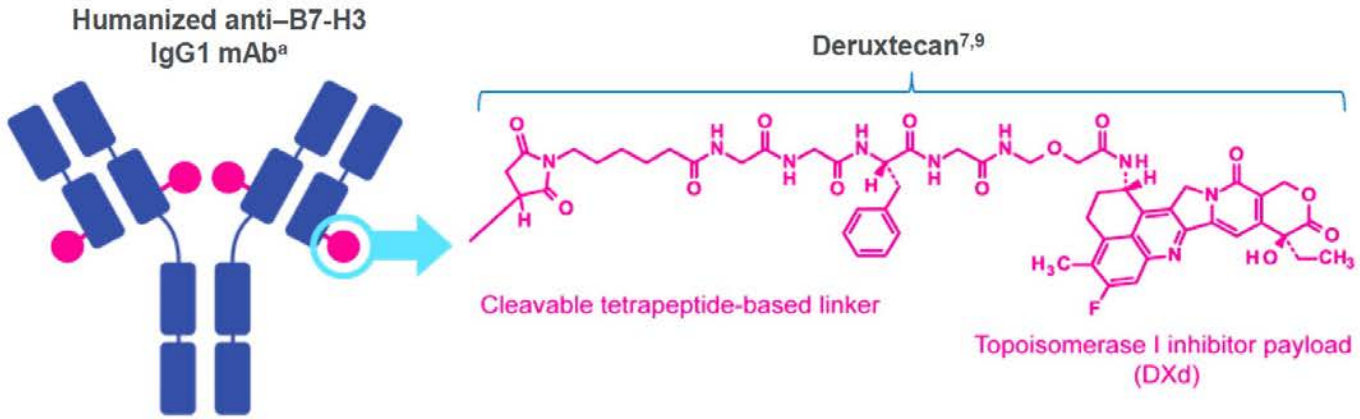
Ifinatamab Deruxtecan

Ifinatamab Deruxtecan (I-DXd; DS-7300) Was Designed With 7 Key Attributes

- B7-H3 is overexpressed in a wide range of cancer types and is associated with disease progression and lower survival[1–5]
- I-DXd is a B7-H3 (CD276)-directed ADC composed of 3 parts:[6–9,11]
  - A humanized anti–B7-H3 IgG1 monoclonal antibody[9,11]
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



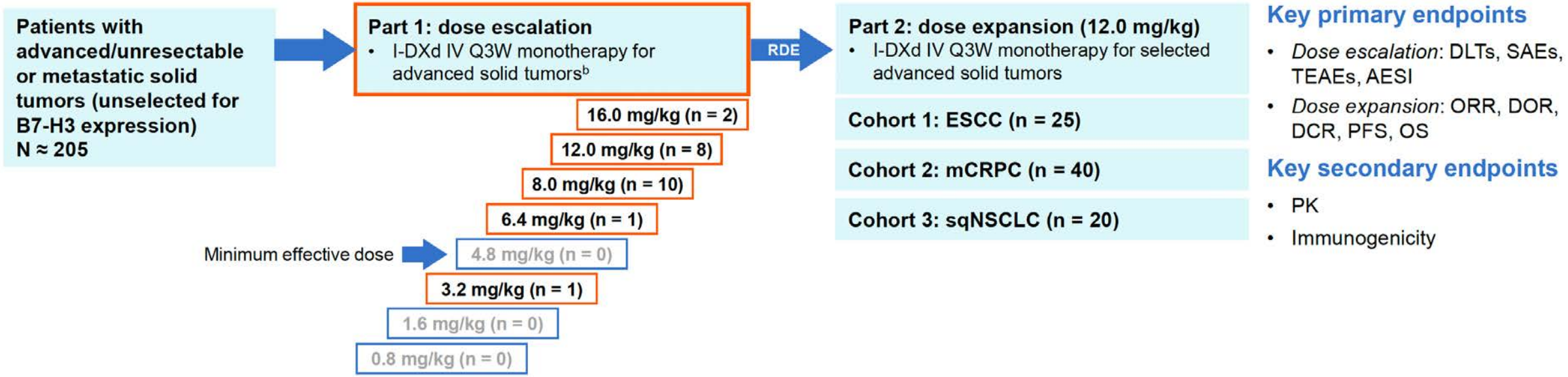
Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]

ADC = antibody-drug conjugate

Johnson M et al. WCLC 2023;Abstract OA05.05.

DS7300-A-J101 (NCT04145622) Study Design

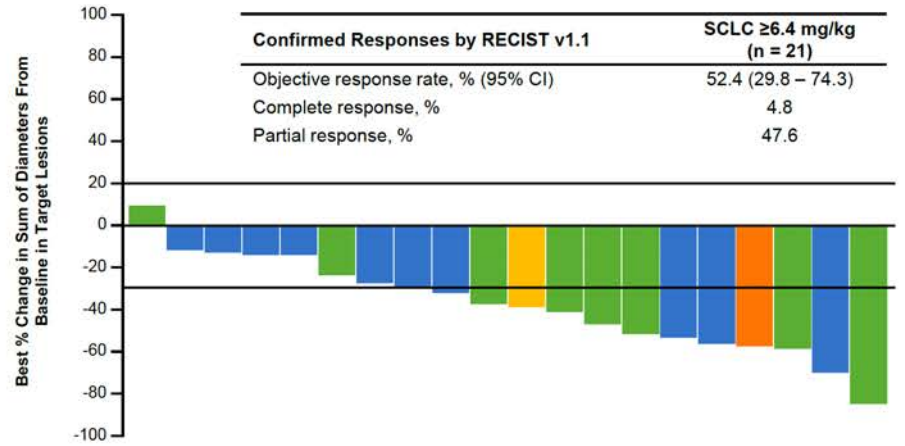
- I-DXd is generally well tolerated with early signs of antitumor activity[1,2]
- **We present a subgroup analysis of patients with SCLC (N = 22[a]) from part 1 treated with I-DXd at all doses studied**
  - Patients dosed at ≥6.4 mg/kg (n = 21) were evaluable for efficacy
  - Baseline tumor biopsies were retrospectively examined for B7-H3 protein level by IHC and used for correlative analysis in biomarker-evaluable patients dosed at ≥6.4 mg/kg (n = 17)

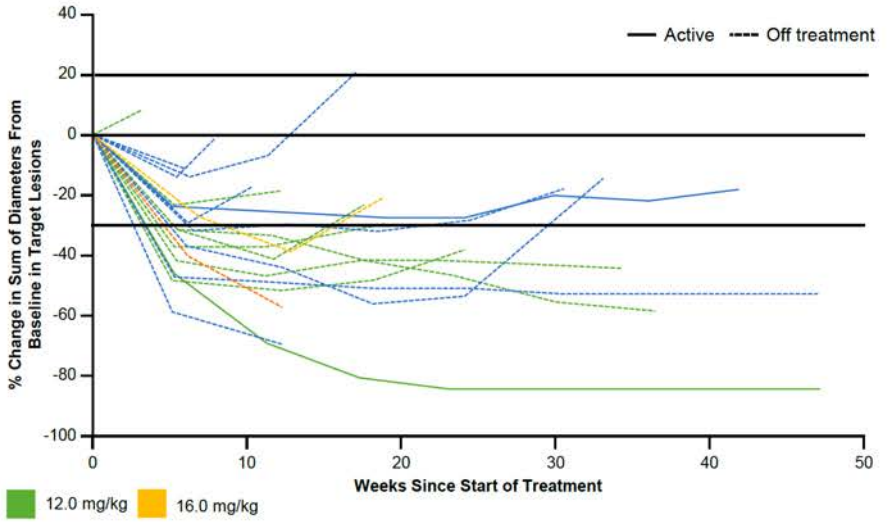


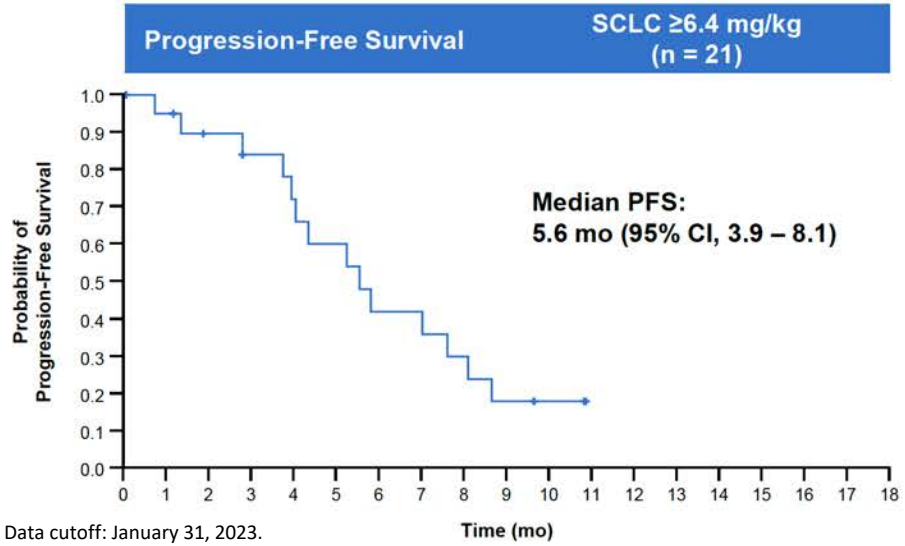
Johnson M et al. WCLC 2023;Abstract OA05.05.

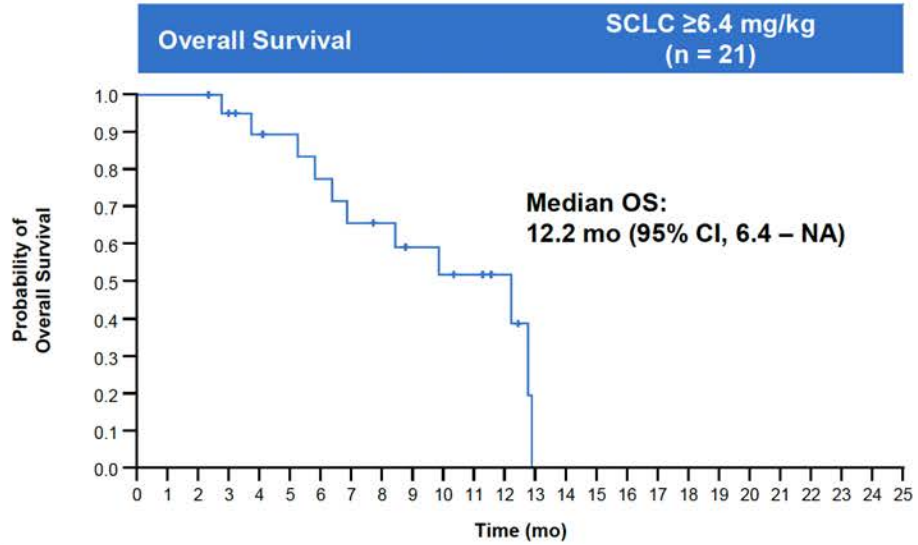
DS7300-A-J101: Ifinatamab Deruxtecan Antitumor Activity

- Nearly all patients with post-baseline scans had a reduction in target lesions
- Median time to response was 1.2 months (95% CI, 1.2-1.4)
- Median duration of response was 5.9 months (95% CI, 2.8-7.5); two patients remain on treatment
- Median follow-up was 11.7 months (95% CI, 4.63-12.88)









Data cutoff: January 31, 2023.

Johnson M et al. WCLC 2023;Abstract OA05.05.

DS7300-A-J101: Ifinatamab Deruxtecan – Most Common (≥10%) All-Grade TEAEs Regardless of Causality

System Organ Class Preferred Term, n (%)	SCLC (N = 22)	
	Any Grade	Grade ≥3
Nausea	13 (59.1)	1 (4.5)
Fatigue	11 (50.0)	0 (0.0)
Anemia	6 (27.3)	1 (4.5)
Vomiting	6 (27.3)	0 (0.0)
Decreased appetite	5 (22.7)	1 (4.5)
Pyrexia	4 (18.2)	0 (0.0)
Constipation	4 (18.2)	1 (4.5)
IRR	3 (13.6)	0 (0.0)
Diarrhea	3 (13.6)	0 (0.0)
Dehydration	3 (13.6)	0 (0.0)
Dyspnea	3 (13.6)	0 (0.0)
Platelet count decreased	3 (13.6)	0 (0.0)
Arthralgia	3 (13.6)	0 (0.0)
Hyponatremia	3 (13.6)	0 (0.0)

- A total of 3 patients (13.6%) experienced an interstitial lung disease (ILD) or pneumonitis event (two Grade 1, one Grade 2).
  - All events were adjudicated by the ILD adjudication committee, of which one was adjudicated as drug-related ILD (Grade 2, 8.0 mg/kg), and treatment was discontinued per protocol.[a]
- Prophylactic premedication for nausea, vomiting and IRR (infusion-related reaction) were not permitted for primary prophylaxis during cycle 1 of dose escalation.

Johnson M et al. WCLC 2023;Abstract OA05.05.

Data cutoff: January 31, 2023. [a] Outcome was reported as "not recovered" for 2 events (Gr 1, Gr2) and "recovered" for 1 event (Gr 1).

Tarlatamab for Patients (pts) with Previously Treated Small Cell Lung Cancer (SCLC): Primary Analysis of the Phase 2 DeLLphi-301 Study

Paz-Ares L et al.

ESMO 2023;Abstract LBA92.

DeLLphi-301: Efficacy Analysis Set per ITT Analysis

	10 mg (n = 100)*	100 mg (n = 88)*
ORR, % (97.5% CI)	40.0 (29.1—51.7)	31.8 (21.1—44.1)
Complete response, n (%)	1 (1.0)	7 (8.0)
Partial response, n (%)	39 (39.0)	21 (23.9)
Stable disease, n (%)	30 (30.0)	27 (30.7)
Progressive disease, n (%)	20 (20.0)	13 (14.8)
Not evaluable, n (%)	2 (2.0)	4 (4.5)
Death before post-baseline scan, n (%)	6 (6.0)	13 (14.8)
No post-baseline scan, n (%)	2 (2.0)	3 (3.4)
mDoR, mo (95% CI)	NE (5.9—NE)	NE (6.6—NE)
Disease control rate % (95% CI)	70.0 (60.0, 78.8)	62.5 (51.5, 72.6)
mOS, mo (95% CI)	14.3 (10.8—NE)	NE (12.4—NE)
mPFS, mo (95% CI)	4.9 (2.9—6.7)	3.9 (2.6—4.4)

ITT = intent to treat; ORR = objective response rate

Paz-Ares L et al. ESMO 2023;Abstract LBA92.

Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Thursday, November 16, 2023
5:00 PM – 6:00 PM ET

Faculty

Samuel J Klempner, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

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

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

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