Data + Perspectives: Clinical Investigators Discuss the Current and Future Role of Immunotherapy and Antibody-Drug Conjugates in Lung Cancer

Friday, May 30, 2025
11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)

Faculty

Marina Chiara Garassino, MBBS
John V Heymach, MD, PhD
Professor Solange Peters, MD, PhD

Moderator

Jacob Sands, MD

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Prof Garassino — Disclosures
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Dr Sands — Disclosures
Moderator

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Dr Love — Disclosures

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Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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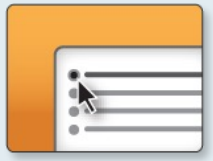
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys.

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

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

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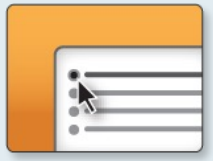

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Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

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

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
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Agenda

Module 1: Role of Immune Checkpoint Inhibitors in Metastatic Non-Small Cell Lung Cancer (NSCLC) without a Targetable Tumor Mutation — Prof Peters

Module 2: Targeted and Other Novel Therapeutic Strategies for Relapsed Metastatic NSCLC — Prof Garassino

Module 3: Potential Role of TROP2-Targeted Antibody-Drug Conjugates in Advanced NSCLC — Dr Sands

Module 4: Evolving Role of Immune Checkpoint Inhibitors in the Care of Patients with Nonmetastatic NSCLC — Dr Heymach

Agenda

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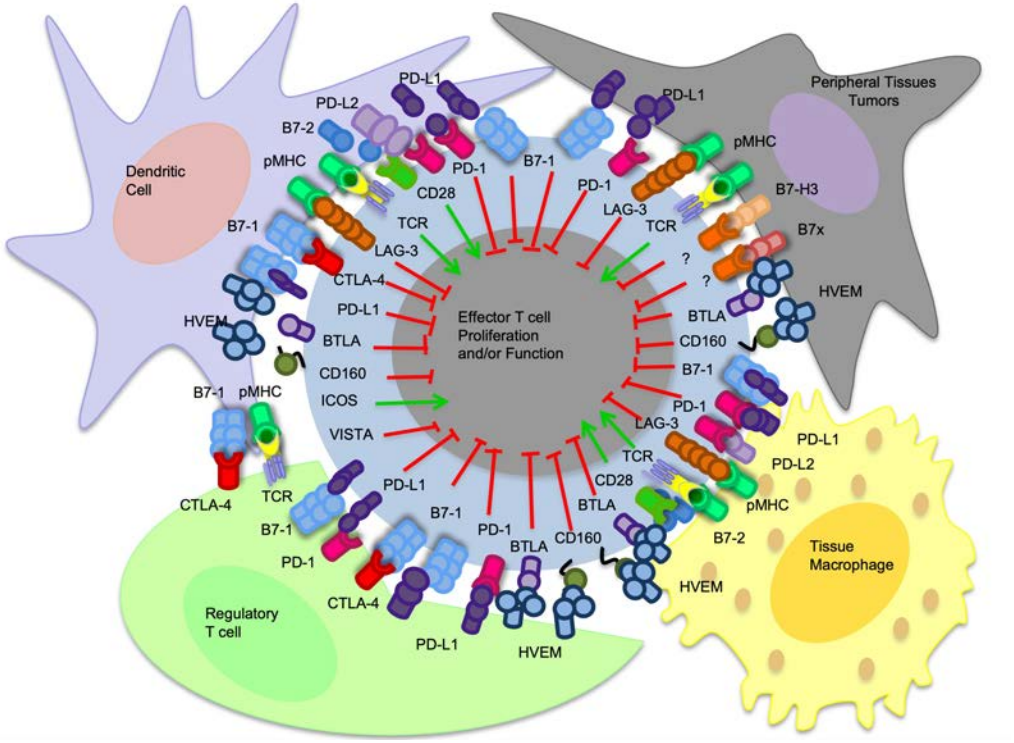
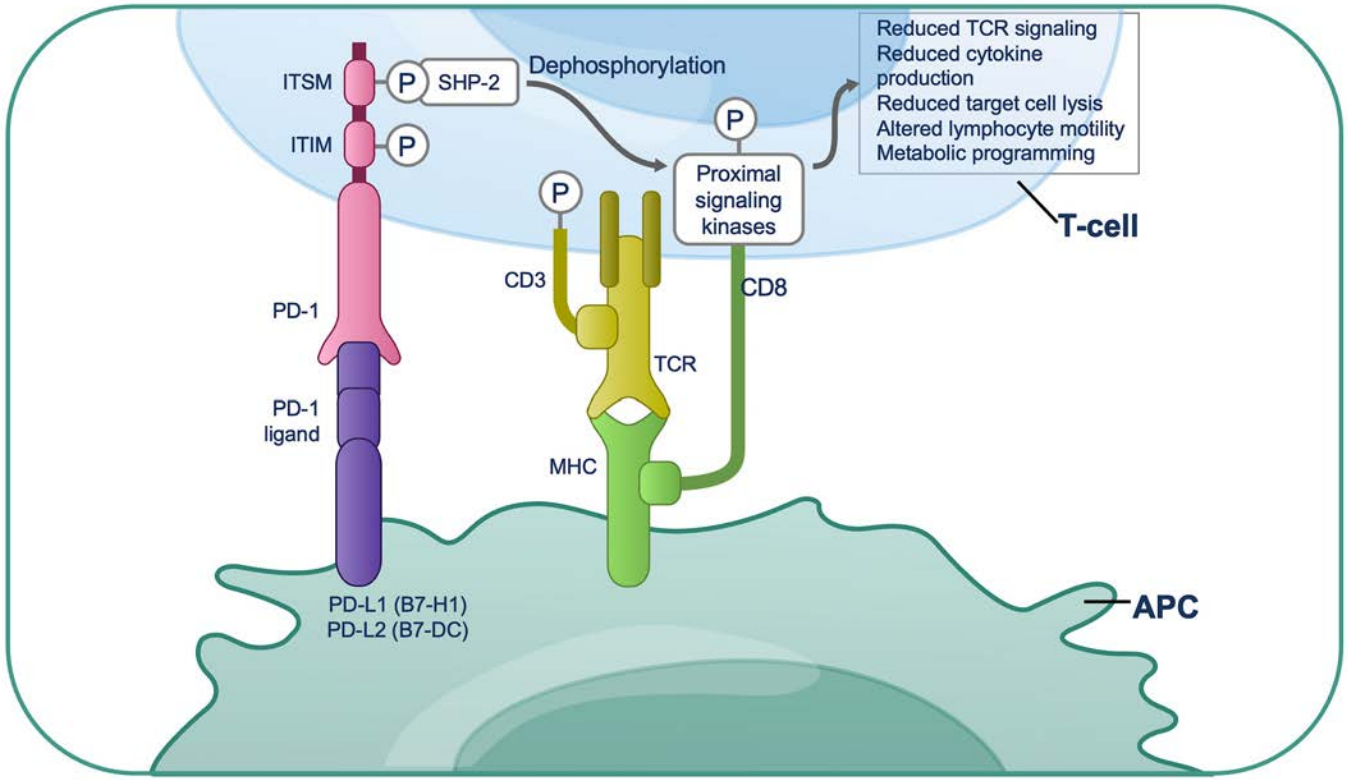


A Role of Immune Checkpoint Inhibitors for Metastatic NSCLC without a Targetable Tumor Mutation

Pr Solange Peters, MD-PhD
Lausanne University Hospital & Ludwig Institute
Switzerland

ICI-based 1L strategies in mNSCLC



Anti-PD1/PD-L1

Monotherapy

With chemotherapy

With anti-CTLA-4

With anti-CTLA-4 and chemotherapy

New combinations

Anti-PD(L)-1 **monotherapy** in 1L mNSCLC (PD-L1 ≥50%)

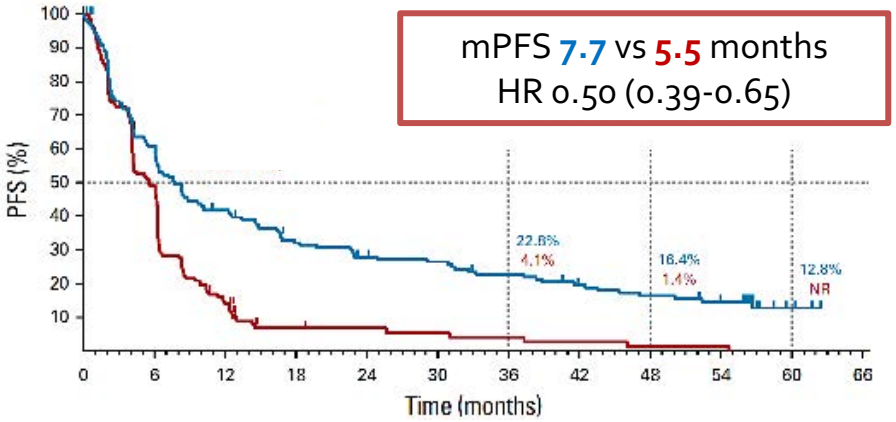
	Patients	PFS (months)	OS (months)	ESMO MCBS score[8]
KEYNOTE-024[1,2] (pembrolizumab vs chemo)	305	7.7 vs 5.5, HR 0.50	5 year OS 31.9%	**A/5**
IMpower110[3,4] (atezolizumab vs chemo)	205	8.2 vs 5.0, HR 0.59	20.2 vs 14.7, HR 0.76	5
EMPOWER-Lung 1[5,6,7] (cemiplimab vs chemo)	712	8.1 vs 5.3, HR 0.50	5 years OS 29%	4

1) Reck, et al. JCO. 8 Jan 2019.; 2) Brahmer J, et al. Presented at ESMO 2020. Abstract LBA51; 3) Spigel D, et al. Presented at ESMO 2019. Abstract LBA78. 4) Herbst R, et al. Presented at WCLC 2020. Abstract FP13.03. 5) Sezer A, et al. Presented at ESMO 2020. Abstract LBA52. 6) Özgüroğlu M, et al. Presented at ESMO 2022. Abstract LBA54. 7) Baramidze A, et al. Presented at WCLC 2024. Abstract OA11.06.; 8) https://www.esmo.org/living-guidelines/esmo-non-oncogene-addicted-metastatic-non-small-cell-lung-cancer-living-guideline, Jan, 2025

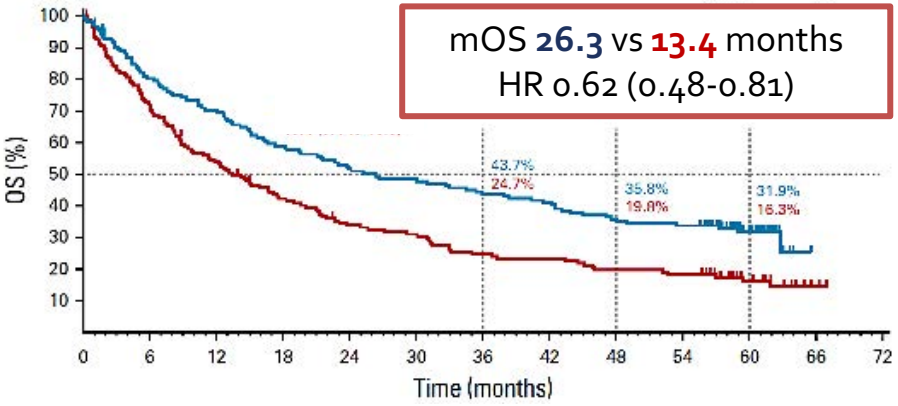
The 50% TC cut-off is validated first line in NSCLC

KEYNOTE-024

mPFS **7.7** vs **5.5** months
HR 0.50 (0.39-0.65)

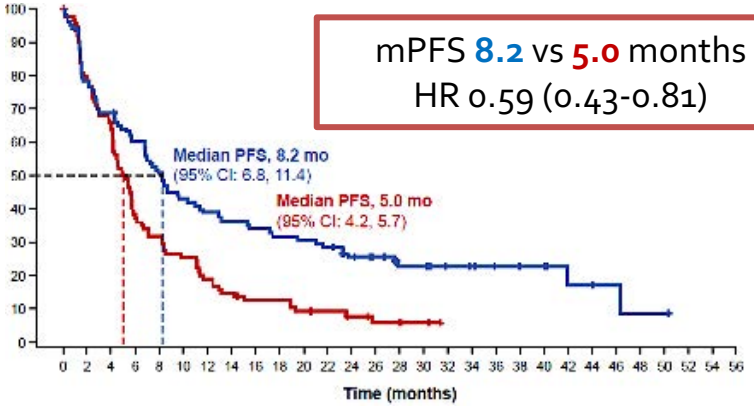


mOS **26.3** vs **13.4** months
HR 0.62 (0.48-0.81)

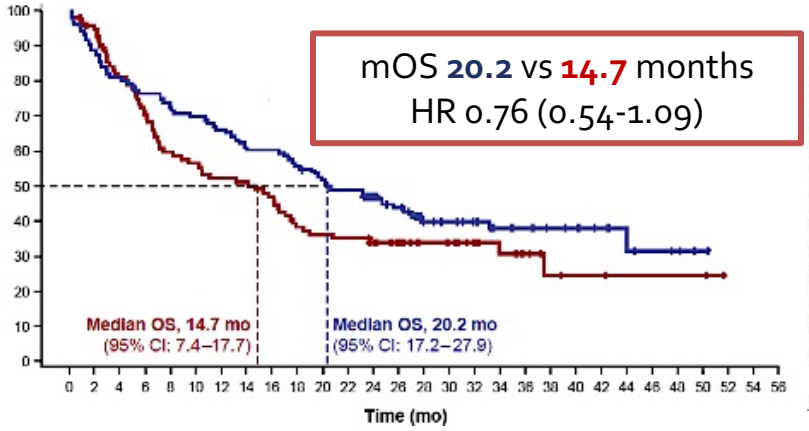


IMpower110 WT

mPFS **8.2** vs **5.0** months
HR 0.59 (0.43-0.81)

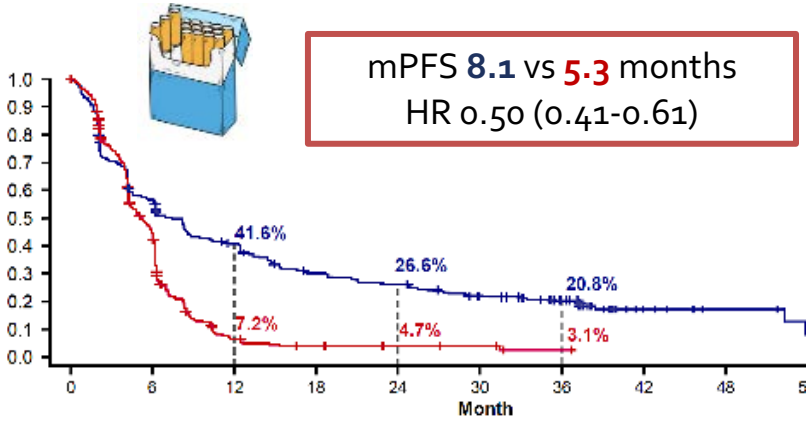


mOS **20.2** vs **14.7** months
HR 0.76 (0.54-1.09)

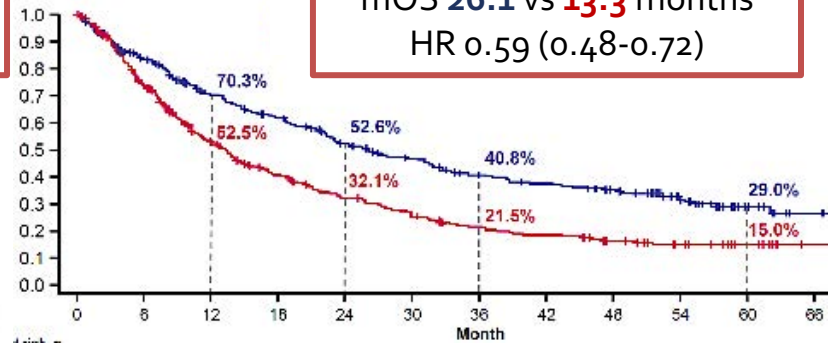


EMPOWER-Lung 1

mPFS **8.1** vs **5.3** months
HR 0.50 (0.41-0.61)

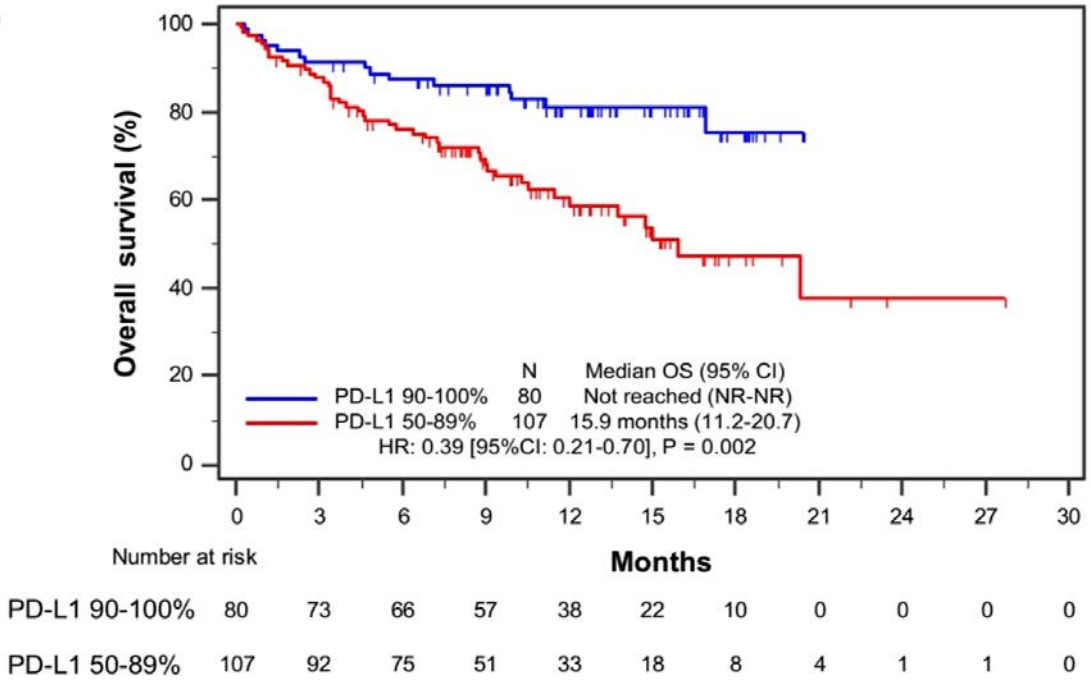


mOS **26.1** vs **13.3** months
HR 0.59 (0.48-0.72)

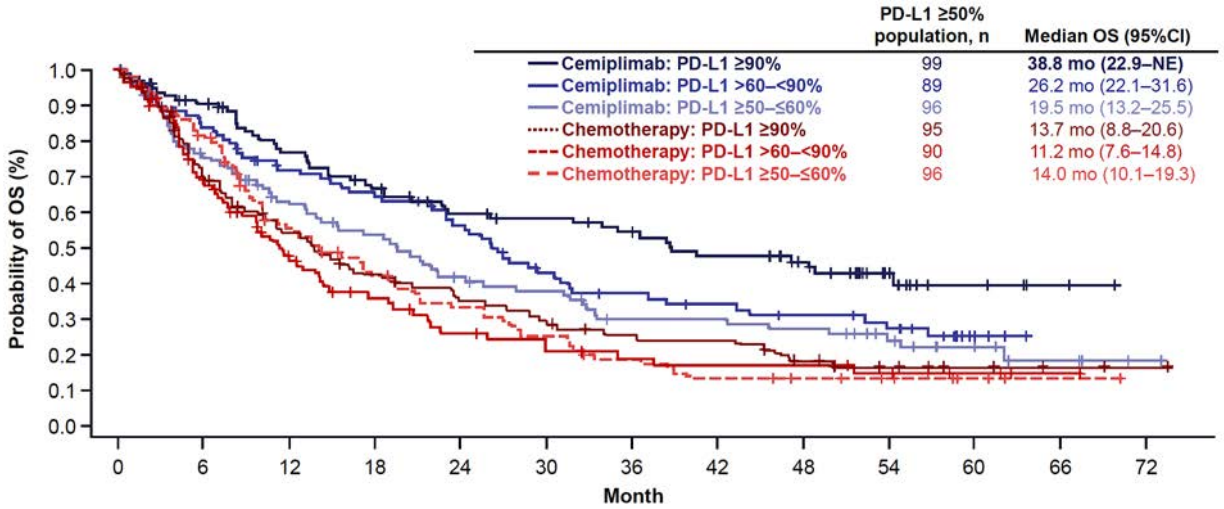


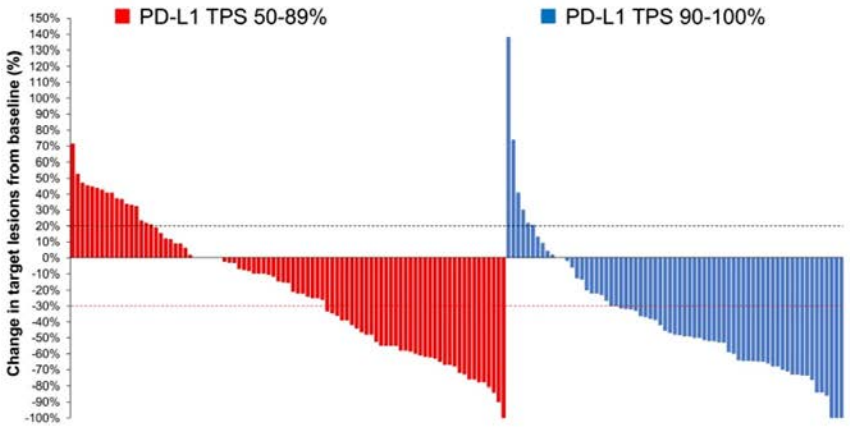
Reck, et al. JCO. 8 Jan 2019.; Brahmer J, et al. Presented at ESMO 2020. Abstract LBA51; Spigel D, et al. Presented at ESMO 2019. Abstract LBA78.; Herbst R, et al. Presented at WCLC 2020. Abstract FP13.03; Sezer A, et al. Presented at ESMO 2020. Abstract LBA52.; Özgüroğlu M, et al. Presented at ESMO 2022. Abstract LBA54.; Baramidze A, et al. Presented at WCLC 2024. Abstract OA11.06.

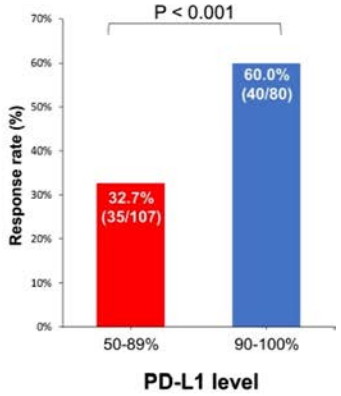
Clinical continuum: anti PD(L)-1 in very high PD-L1



EMPOWER-Lung 1

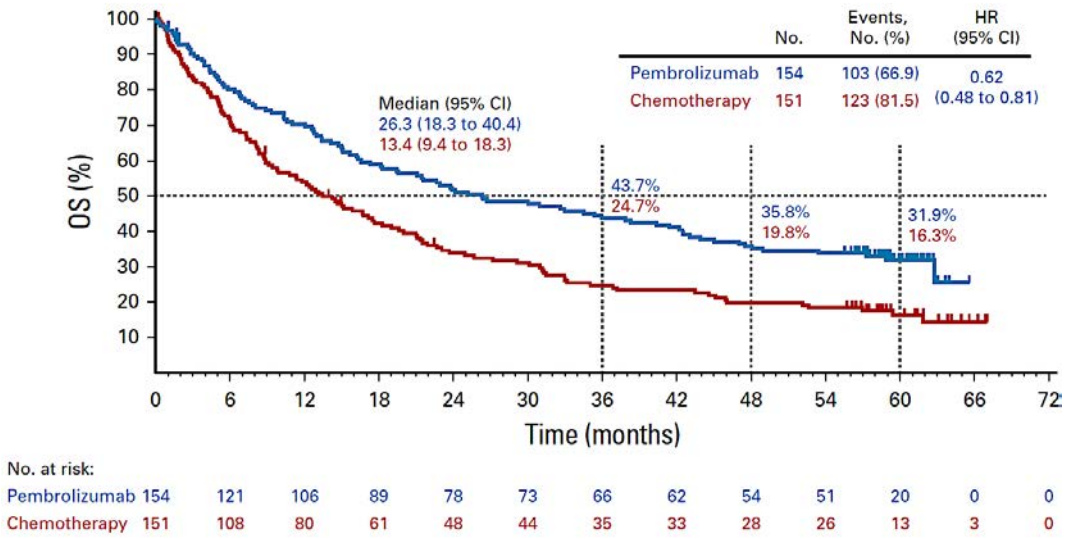


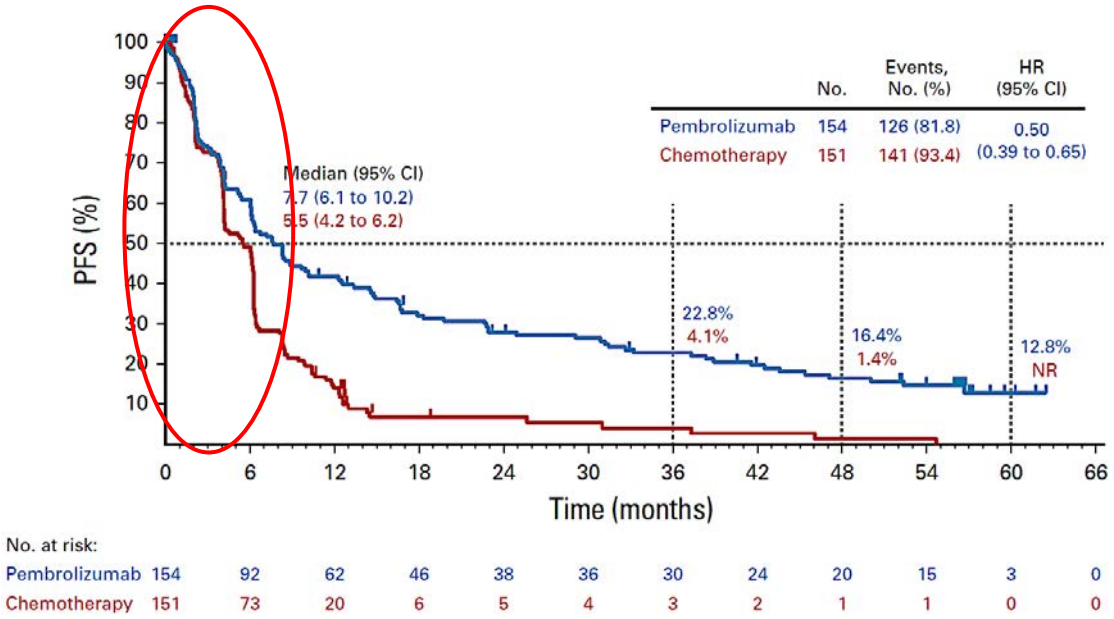




Aguilar, Ann Oncol 2019; Kilickap, WCLC 2024

KEYNOTE-024: A word of caution?

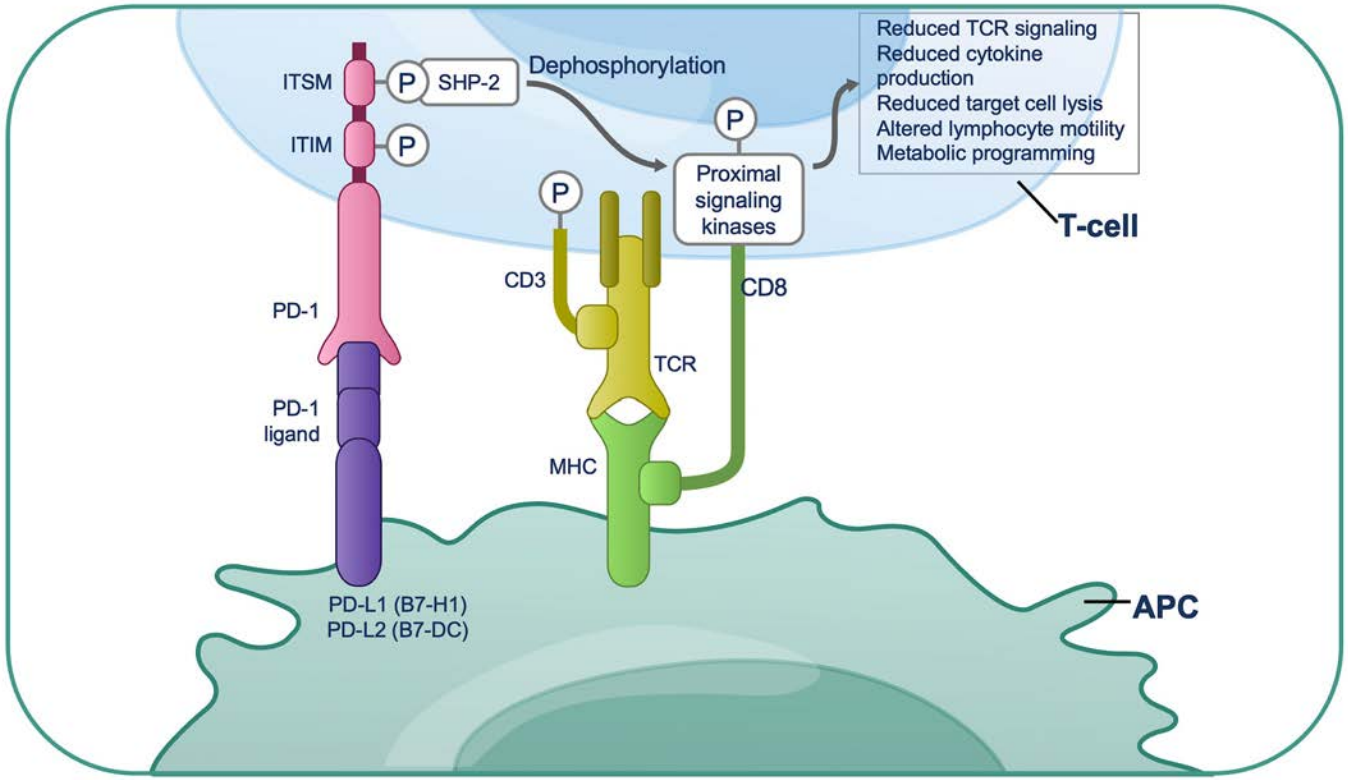




- 1/3 of patients experience **progressive disease at first assessment**
- A surprisingly **small proportion of patients receive second-line therapy**
  - RWD **25%**
  - KEYNOTE-024: **53%**
  - KEYNOTE-042: **46%**
  - EMPOWER-Lung 1: **32%**

Reck M, et al. J Clin Oncol 2021;39:2339-49

IO-based 1L strategies in mNSCLC



Anti-PD1/PD-L1

Monotherapy

With chemotherapy

With anti-CTLA-4

With anti-CTLA-4 and chemotherapy

New combinations

ChT ± (dual) anti-PD(L)-1 in 1L Non-Sq mNSCLC

ICI	± ChT	Patients	PFS (months)	OS (months)	ESMO MCBS score[12]
KEYNOTE-189[1,2,3,4] (pembrolizumab)	CisP/CbP + pemetrexed	616	9.0 vs 4.9, HR 0.50	5 years OS 19.4%	**A/4**
IMpower150[5,6] (atezolizumab)	CbP-paclitaxel ± bevacizumab	697	8.3 vs 6.8, HR 0.59	19.5 vs 14.7, HR 0.80	4
IMpower130[7,8] (atezolizumab)	CbP + nab-paclitaxel	723	7.0 vs 5.5, HR 0.64	18.6 vs 13.9, HR 0.79	4
EMPOWER-Lung 3[9] (cemiplimab)	Platinum doublet	266*	7.9 vs 5.7, HR 0.53*	19.4 vs 12.4, HR 0.64*	4
GEMSTONE-302[10] (sugemalimab)	CbP + pemetrexed	191*	9,6 vs 5,9, HR 0,57*	26.0 vs 19.8, HR 0,72*	4
RATIONALE-304[11] (tislelizumab)	CisP/CbP + pemetrexed	334	9.8 vs 7.6, HR 0.47	21.6 vs 20.1, HR 0.85	4 (for PD-L1 ≥50%)

* Non Sq subgroup analysis

1) Gadgeel S, et al. Presented at ASCO 2019. Abstract 9013. 2) Rodriguez-Abreu D. Presented at ASCO 2020. Abstract 9582. 3) Gray JE, et al. Presented at WCLC 2020. Abstract FP13.02. 4) Garassino M, et al. Presented at ESMO 2022. Abstract 973MO. 5) Socinski M, et al. *N Engl J Med*.4 Jun 2018. 6) Socinski M, et al. Presented at AACR 2020. Abstract CT126. 7) Cappuzzo, et al. Presented at ESMO 2018. Abstract LBA53. 8) West HJ, et al. *Lancet*. 20 May 2019. 9) Makharadze T, et al. Presented at ELCC 2023. Abstract 5O. 10) Zhou C, et al. Presented at ESMO 2024. Abstract 1318P. 11) Lu S, et al. Presented at ESMO IO 2022. Abstract 138P. 12) https://www.esmo.org/living-guidelines/esmo-non-oncogene-addicted-metastatic-non-small-cell-lung-cancer-living-guideline, Jan, 2025

ChT ± (dual) anti-PD(L)-1 in 1L Sq. mNSCLC

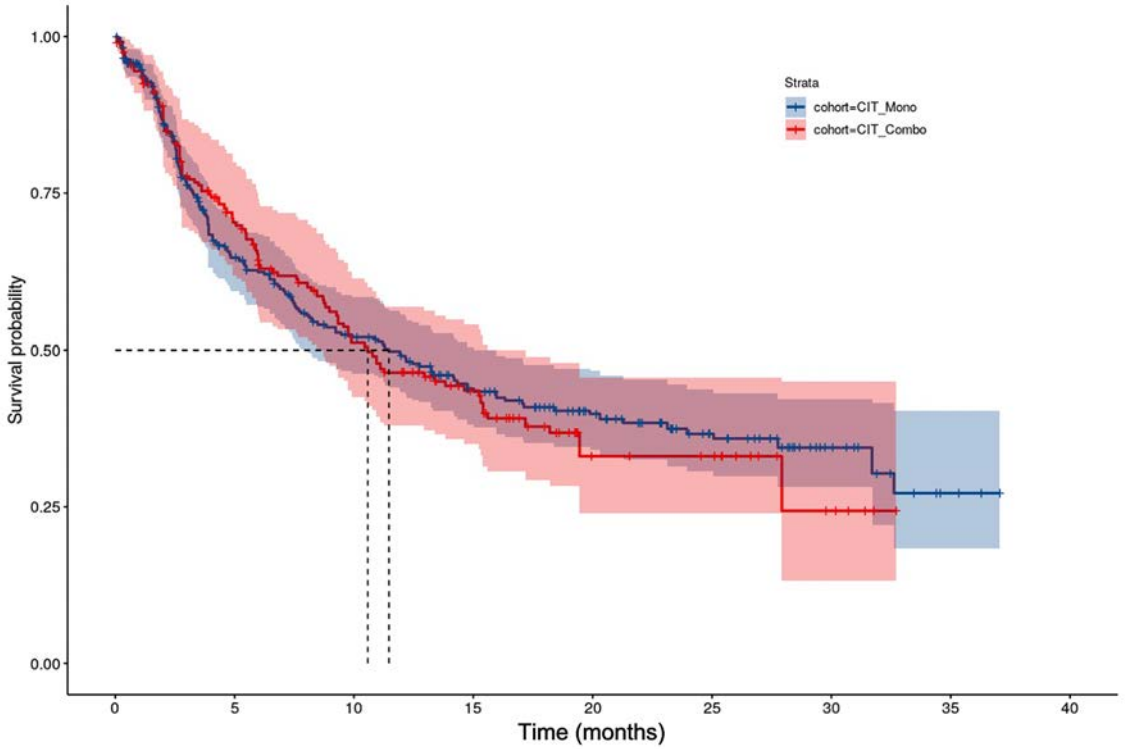
(Dual) Anti-PD-L1	± ChT	Patients	PFS (months)	OS (months)	ESMO MCBS score[10]
KEYNOTE-407[1,2,3] (pembrolizumab)	CisP/CbP + paclitaxel or nab-paclitaxel	559	8.0 vs 5.1, HR 0.62	5 years OS 18.4%	**4/A**
EMPOWER-Lung 3[4]	Platinum based ChT	200*	8.2 vs 4.9, HR 0.56*	22.3 vs 13.8, HR 0.61*	4
RATIONALE-307[5,6,7,8] (tislelizumab)	CbP-(nab)paclitaxel	360	7.7 vs 9.5 vs 5.5 HR 0.45 and 0.45	26.1 vs 23.3 vs 19.4 HR 0.67 and 0.82	4 (pacli), 3 (nab-pacli)
GEMSTONE-302[9] (sugemalimab)	CbP + paclitaxel	192*	8.3 vs 4.8, HR 0.37*	23.6 vs 12.2, HR 0.61*	4

* Sq subgroup analysis

1) Paz-Ares L, et al. Presented at ESMO 2019. Abstract LBA82. 2) Robinson A, et al. Presented at ELCC 2021. Abstract 97O. 3) Novello S, et al. Presented at ESMO 2022. Abstract 974MO. 4) Makharadze T, et al. Presented at ELCC 2023. Abstract 5O. 5) Wang J, et al. Presented at Chinese Society of Clinical Oncology Congress 2020. 6) Wang J, et al. JAMA Oncol. 2021;7:709. 7) Wang J, et al. Presented at ESMO IO 2022. Abstract 132P. 8) Wang Z, et al. Presented at ESMO 2024. Abstract 1323P. 9) Zhou C, et al. Presented at ESMO 2024. Abstract 1318P. 10) https://www.esmo.org/living-guidelines/esmo-non-oncogene-addicted-metastatic-non-small-cell-lung-cancer-living-guideline, Jan, 2025

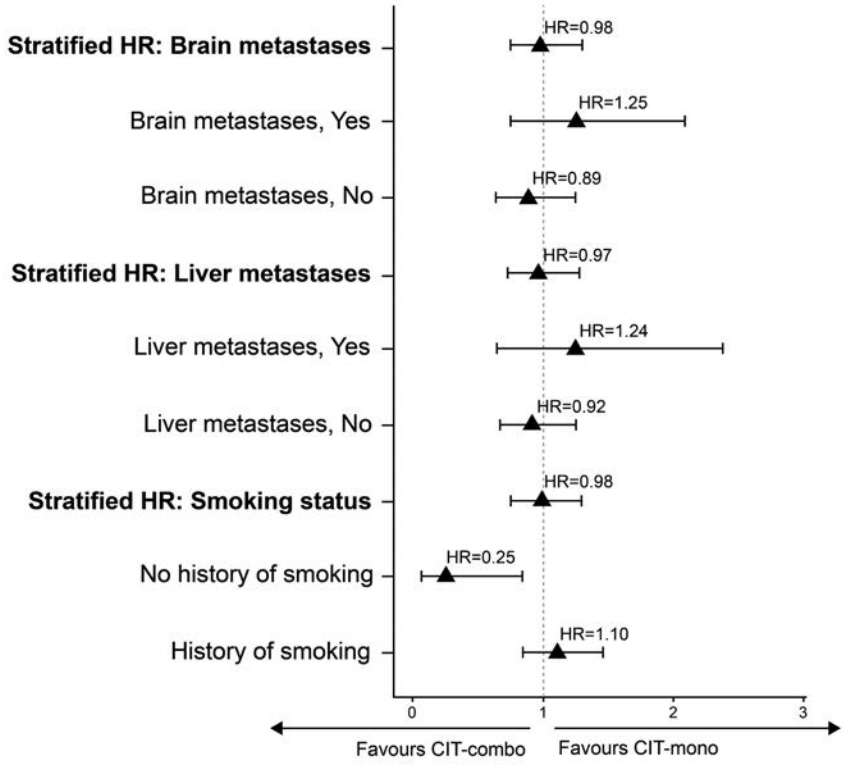
Chemotherapy might not be needed in PD-L1 ≥50%

Adjusted analysis (rwPFS)



Overall survival

Unadjusted anlaysis



CIT-combo vs CIT-mono (reference)	Hazard ratio (95% CI)	*P* value
Unadjusted analysis	1.01 (0.78, 1.05)	0.957
Adjusted analysis	1.04 (0.78, 1.37)	0.811

Group	Patients	Events, n (%)	Median rwPFS (95% CI), mo
CIT-mono	351	170 (48)	11.5 (8.12, 15.01)
CIT-combo	169	87 (52)	10.8 (8.97, 15.31)

[a] Proportional hazards assumption is violated in the unadjusted model (Schoenfeld residual test).

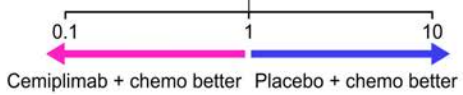
The propensity score model included metastatic type, age, race, ECOG performance status score, brain metastases, smoking status, sex, liver metastases, time to 1L treatment start.

Pérol M et al. Ann Oncol. 2022 May;33(5):511-521.

EMPOWER-Lung 3: outcomes across PD-L1 subgroups

OS

	Cemiplimab + chemo (OS events/patients)	Placebo + chemo (OS events/patients)	Hazard ratio (95% CI)
All patients	180/312	111/154	0.65 (0.51–0.82)
Age group			
<65 years	100/184	70/94	0.53 (0.39–0.72)
≥65 years	80/128	41/60	0.81 (0.55–1.18)
Sex			
Male	155/268	92/123	0.55 (0.42–0.71)
Female	25/44	19/31	0.98 (0.54–1.78)
Race			
White	155/267	102/138	0.61 (0.47–0.78)
Non-White	25/45	9/16	0.81 (0.38–1.74)
Histology			
Squamous	79/133	47/67	0.61 (0.42–0.87)
Nonsquamous	101/179	64/87	0.64 (0.47–0.88)
PD-L1 level			
<1%	66/95	34/44	0.94 (0.62–1.42)
1–49%	62/114	43/61	0.50 (0.34–0.74)
≥50%	52/103	34/49	0.56 (0.36–0.86)
ECOG performance status			
0	15/51	14/18	0.24 (0.12–0.51)
1	163/259	96/134	0.70 (0.54–0.90)
Geographic region			
Europe	157/270	102/138	0.61 (0.48–0.79)
Asia	23/42	9/16	0.78 (0.36–1.69)
Brain metastasis at baseline			
Yes	12/24	7/7	0.29 (0.11–0.75)
No	168/288	104/147	0.65 (0.51–0.83)
Cancer stage at screening			
Locally advanced	21/45	18/24	0.50 (0.27–0.95)
Metastatic	159/267	93/130	0.64 (0.49–0.83)
Smoking history			
Smokers	155/269	96/130	0.58 (0.45–0.75)
Non-smokers	25/43	15/24	0.85 (0.45–1.62)



PFS

	Cemiplimab + chemo (PFS events/patients)	Placebo + chemo (PFS events/patients)	Hazard ratio (95% CI)
All patients	234/312	133/154	0.55 (0.44–0.68)
Age group			
<65 years	134/184	84/94	0.50 (0.38–0.66)
≥65 years	100/128	49/60	0.60 (0.42–0.85)
Sex			
Male	203/268	107/123	0.48 (0.38–0.62)
Female	31/44	26/31	0.71 (0.42–1.20)
Race			
White	208/267	119/138	0.55 (0.44–0.69)
Non-White	26/45	14/16	0.53 (0.28–1.02)

Feb 24, 2023
Kristi Rosa

The European Medicines Agency's Committee for Medicinal Products for Human Use has recommended the approval of cemiplimab-rwlc in combination with platinum-based chemotherapy as frontline treatment for adult patients with advanced non–small cell lung cancer with PD-L1 expression of 1% or higher.

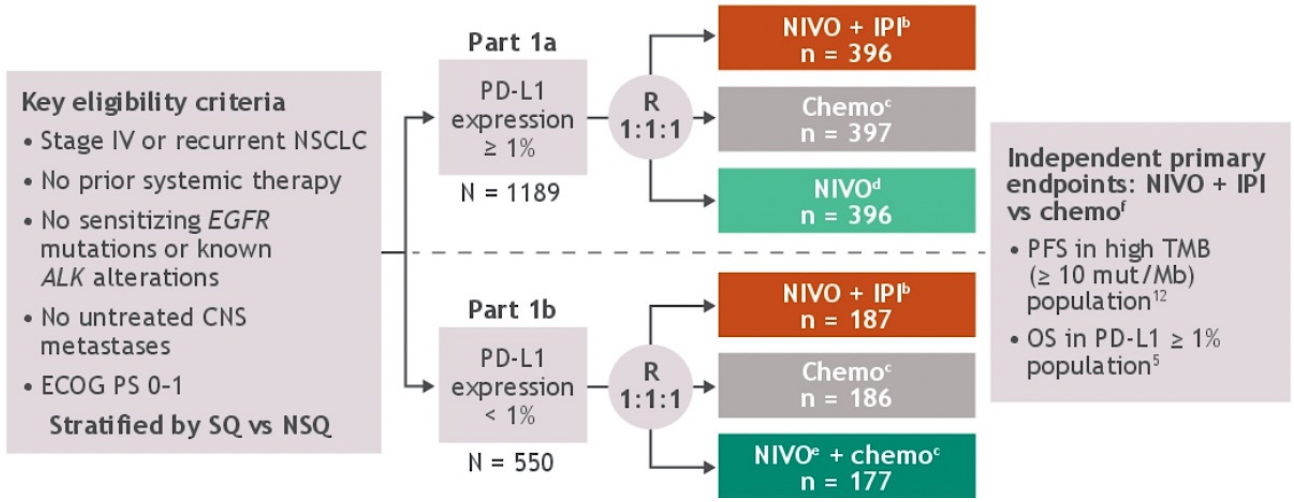
The European Medicines Agency's Committee for Medicinal Products for Human Use has recommended the approval of cemiplimab-rwlc in combination with platinum-based chemotherapy as frontline treatment for adult patients with advanced non–small cell lung cancer (NSCLC) with PD-L1 expression of 1% or higher in the European Union.[1]

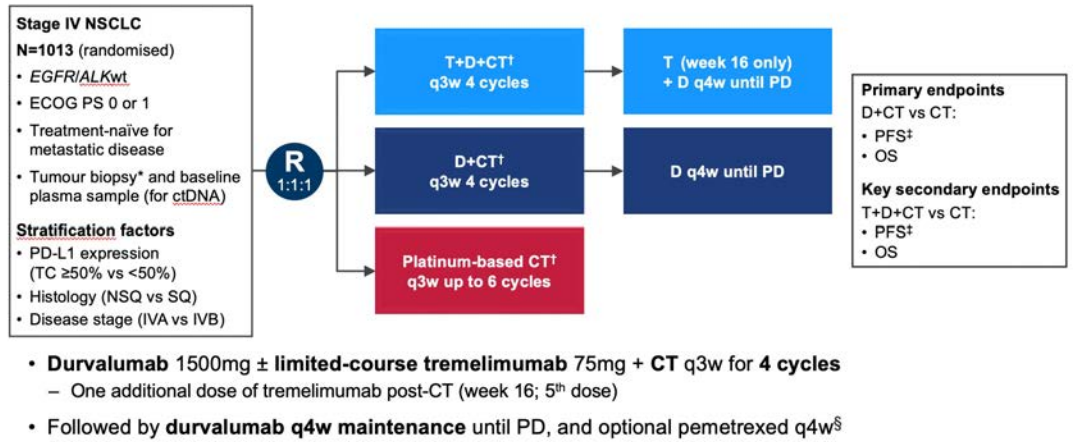
The approval would include patients who are not candidates to receive definitive chemoradiation, whose tumors are metastatic or locally advanced, and who do not harbor *EGFR*, *ALK*, or *ROS1* aberrations.

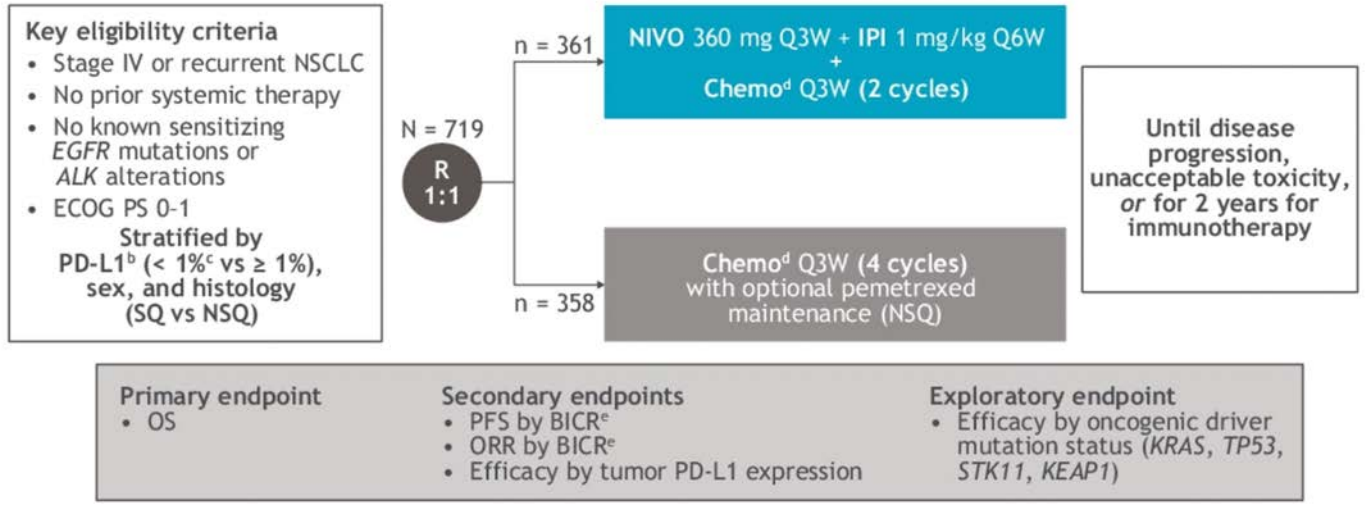
The positive opinion is based on data from the phase 3 Study 16113/EMPOWER-Lung 3 trial (NCT03409614). Of the 466 patients enrolled to the trial, 327 had tumors with a PD-L1 expression of at least 1%. In this subgroup, cemiplimab plus chemotherapy (n = 217) resulted in a median overall survival (OS) of 22 months vs 13 months with chemotherapy alone (n = 110) at a median follow-up of 16 months; this translated to a 45% relative reduction in the risk of death (HR, 0.55; 95% CI, 0.39-0.78). With a longer median follow-up of 28 months, cemiplimab/chemotherapy continued to showcase a meaningful survival benefit in this group (HR, 0.51; 95% CI, 0.38-0.69).

Makharadze T et al. J Thorac Oncol. 2023 Jun;18(6):755-768.

ChT + anti-PD(L)-1: Why adding an anti-CTLA-4?







ChT, chemotherapy; PD-L1, programmed death-ligand 1.
[1]Peters S. Presented at IASLC 2023 WCLC; [2]Johnson ML, et al. Presented at ESMO Congress 2022; [3]Paz-Ares LG, et al. Presented at ASCO 2022.

Cancer Therapy: Clinical

Clinical Cancer Research

CTLA4 Blockade Broadens the Peripheral T-Cell Receptor Repertoire

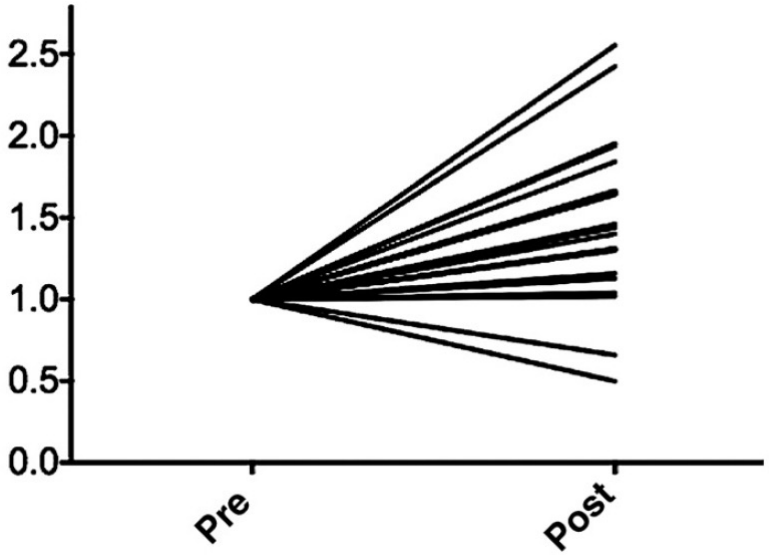
Lidia Robert[1], Jennifer Tsoi[2], Xiaoyan Wang[1,3], Ryan Emerson[7,8], Blanca Homet[1,9], Thinle Chodon[1], Stephen Mok[1,2], Rong Rong Huang[4], Alistair J. Cochran[4], Begoña Comin-Anduix[5,6], Richard C. Koya[5,6], Thomas G. Graeber[2,6], Harlan Robins[7,8], and Antoni Ribas[1,2,5,6]

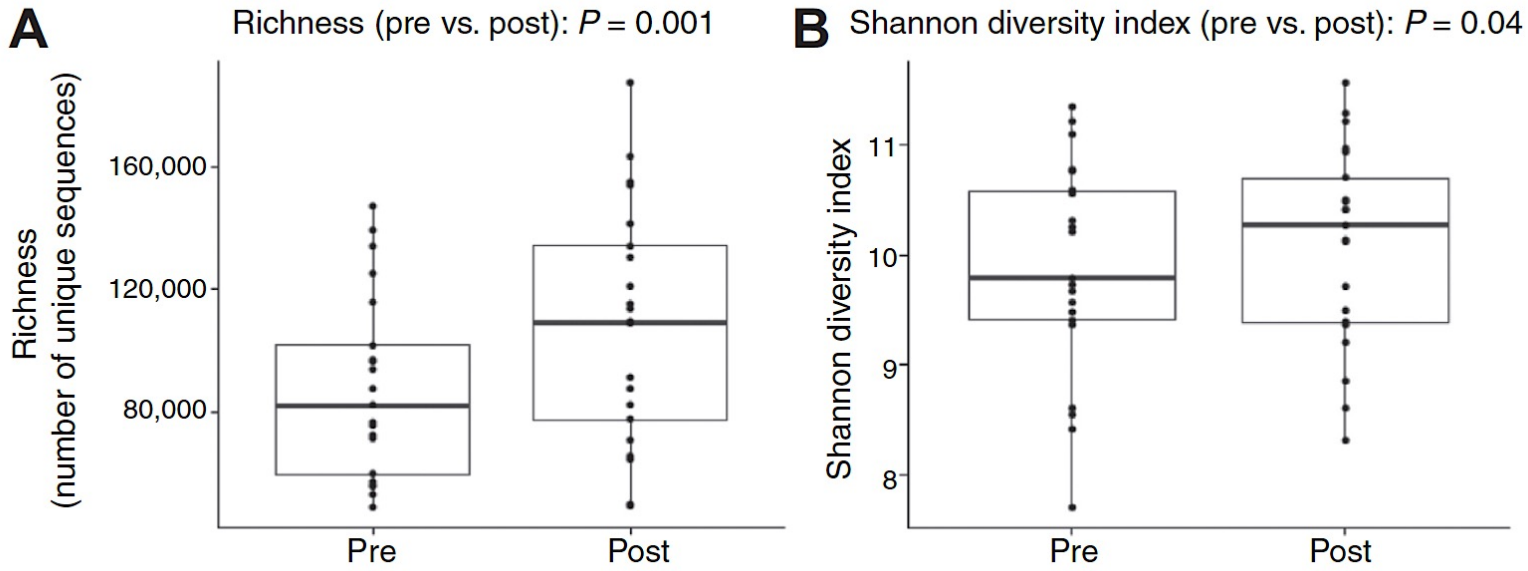
Science Translational Medicine AAAS

Anti–CTLA-4 therapy broadens the melanoma-reactive CD8+ T cell response

Pia Kvistborg *et al.*

Sci Transl Med **6**, 254ra128 (2014);
DOI: 10.1126/scitranslmed.3008918





Normalized TCR V-beta CDR3 repertoire diversity.
Analysis comparing baseline and post-tremelimumab PBMC samples, Richness and Shannon index for diversity. Differences in richness for total number of unique productive sequences (P . 0.001;A) and Shannon index for diversity of the repertoire (P . 0.04; B).

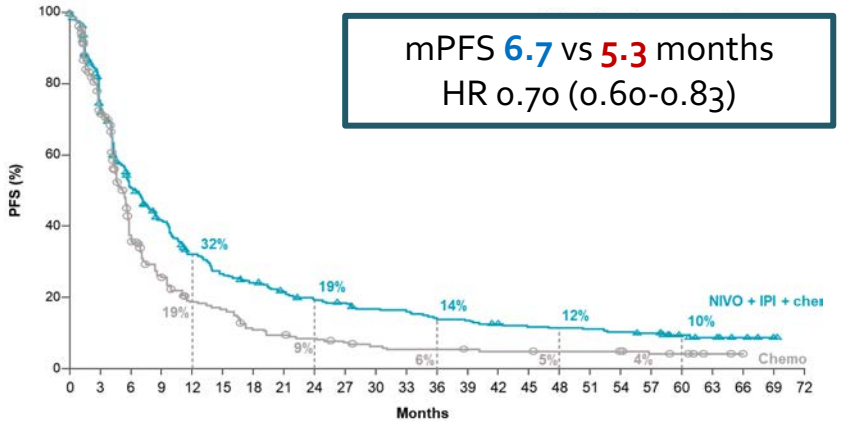
Kvistborg P, et al. Sci Transl Med. 2014 Sep 17;6(254):254ra128.

Robert L, et al. Clin Cancer Res. 2014 May 1;20(9):2424-32.

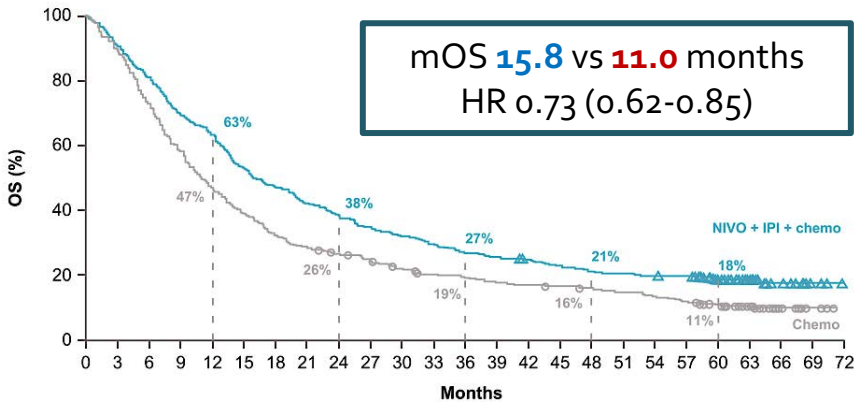
DUAL ICB +/- chemo phIII trial data

CheckMate 9LA

mPFS **6.7** vs **5.3** months
HR 0.70 (0.60-0.83)

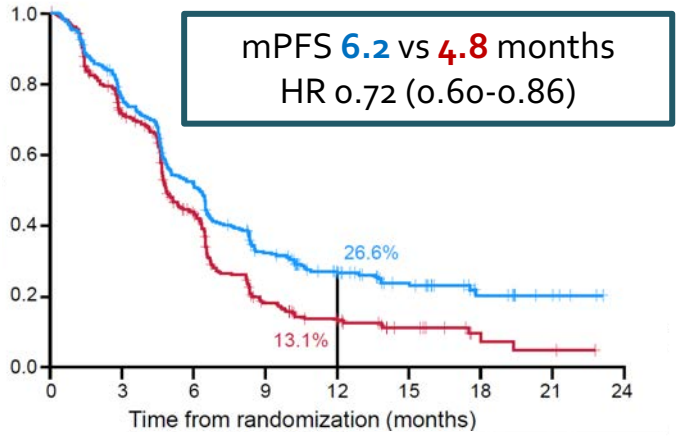


mOS **15.8** vs **11.0** months
HR 0.73 (0.62-0.85)

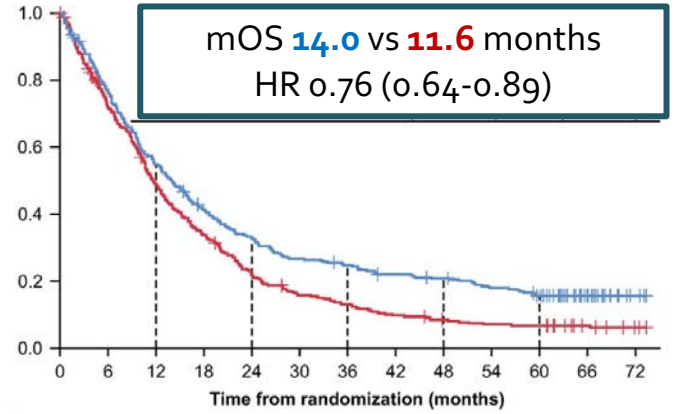


POSEIDON

mPFS **6.2** vs **4.8** months
HR 0.72 (0.60-0.86)

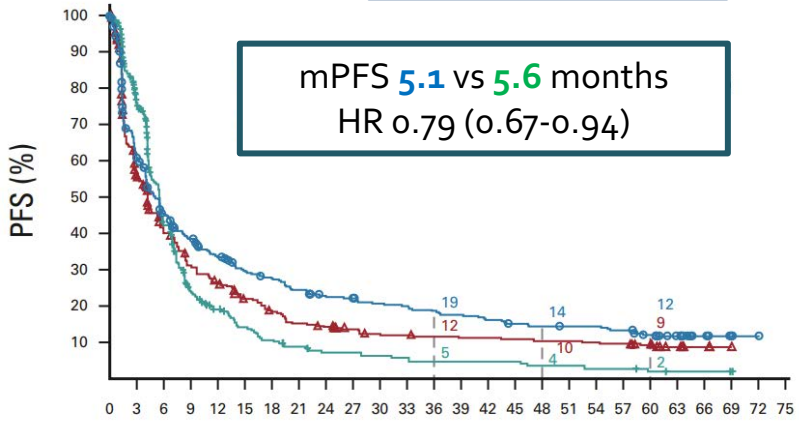


mOS **14.0** vs **11.6** months
HR 0.76 (0.64-0.89)

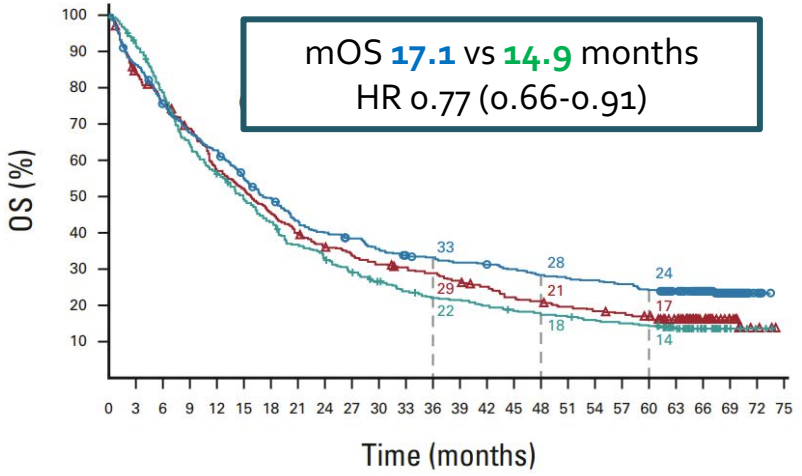


CheckMate 227 PD-L1+

mPFS **5.1** vs **5.6** months
HR 0.79 (0.67-0.94)

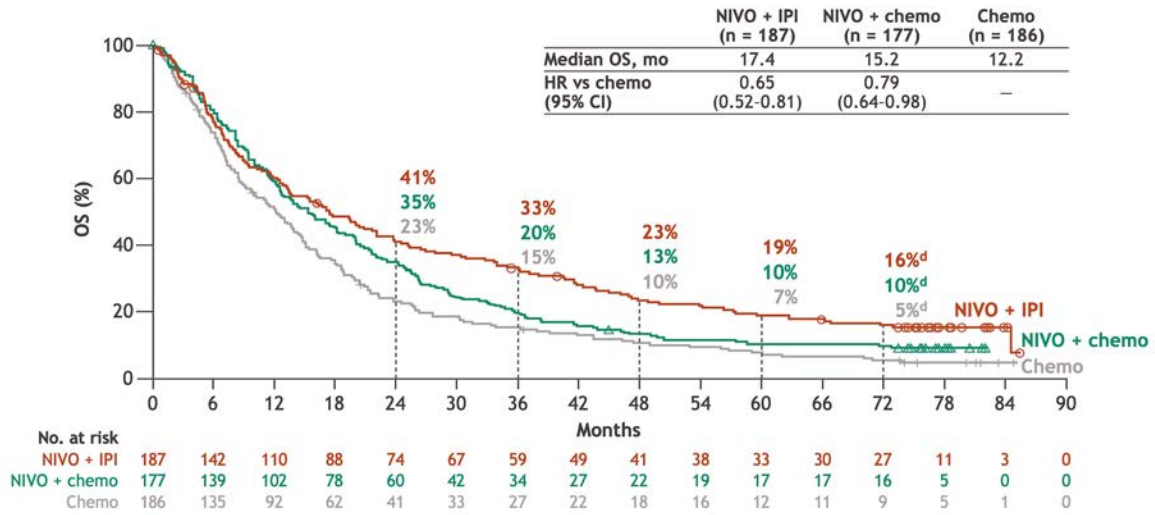


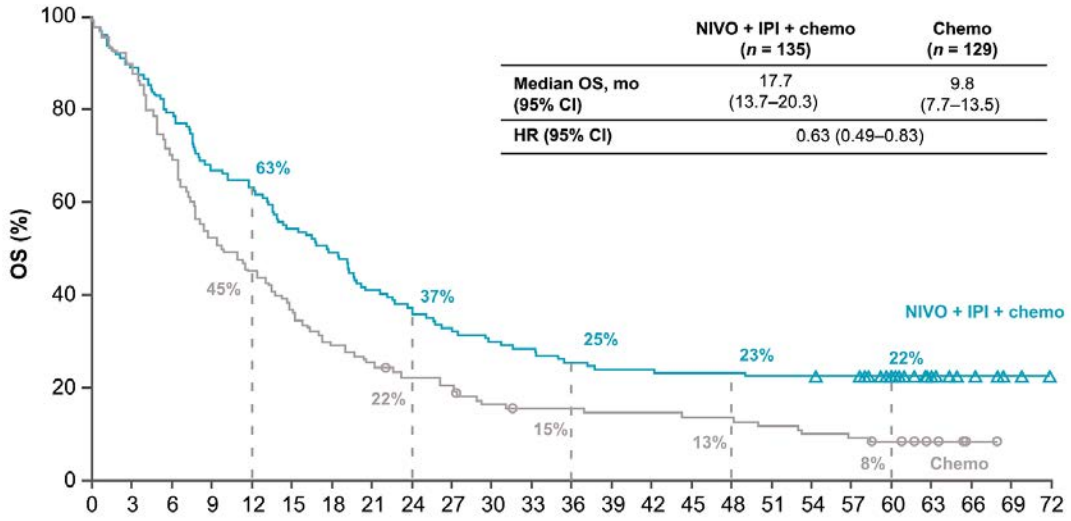
mOS **17.1** vs **14.9** months
HR 0.77 (0.66-0.91)



Reck EJC 2024; Brahmer JCO 2022; Peters JTO 2025; Johnson JCO 2021

CheckMate 227: adding a CTLA-4 is active in negative PD-L1



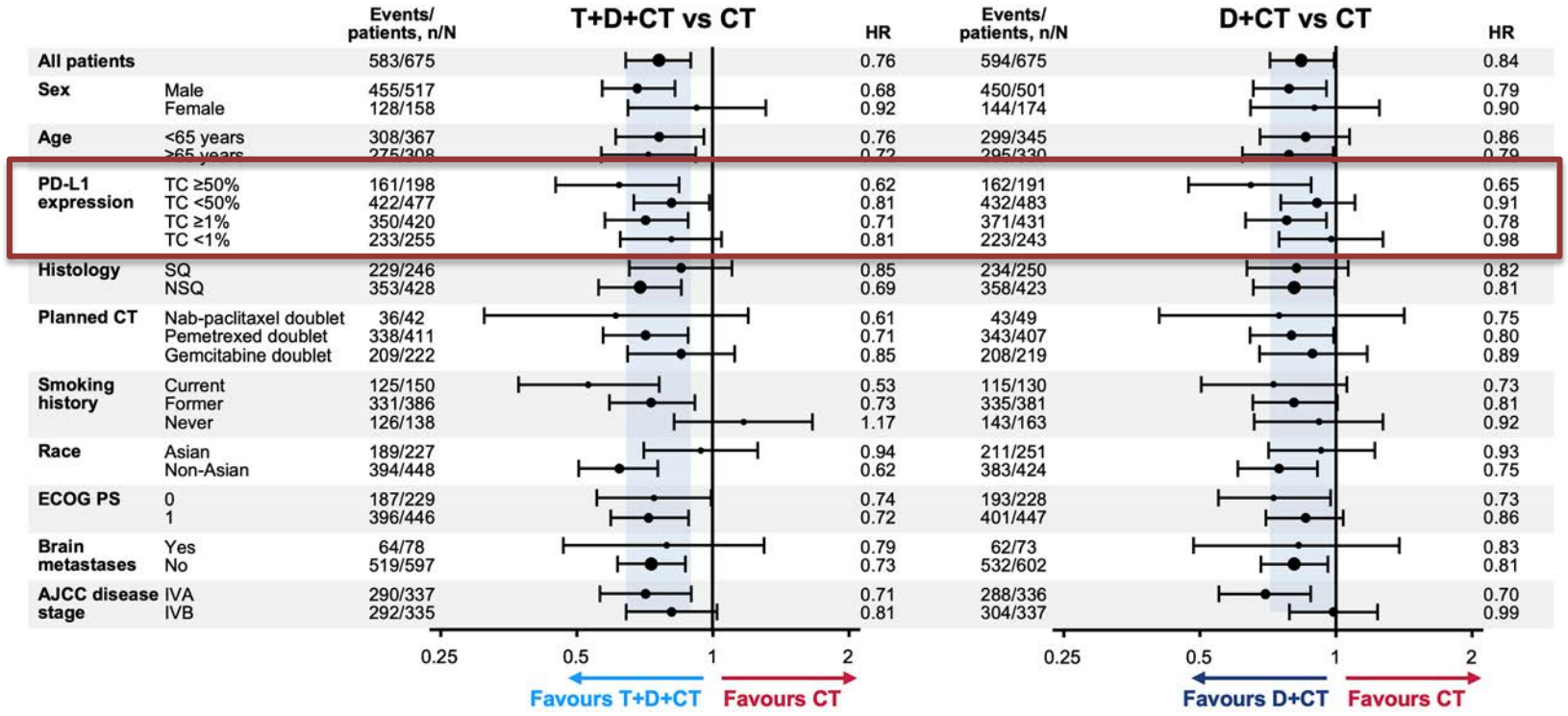


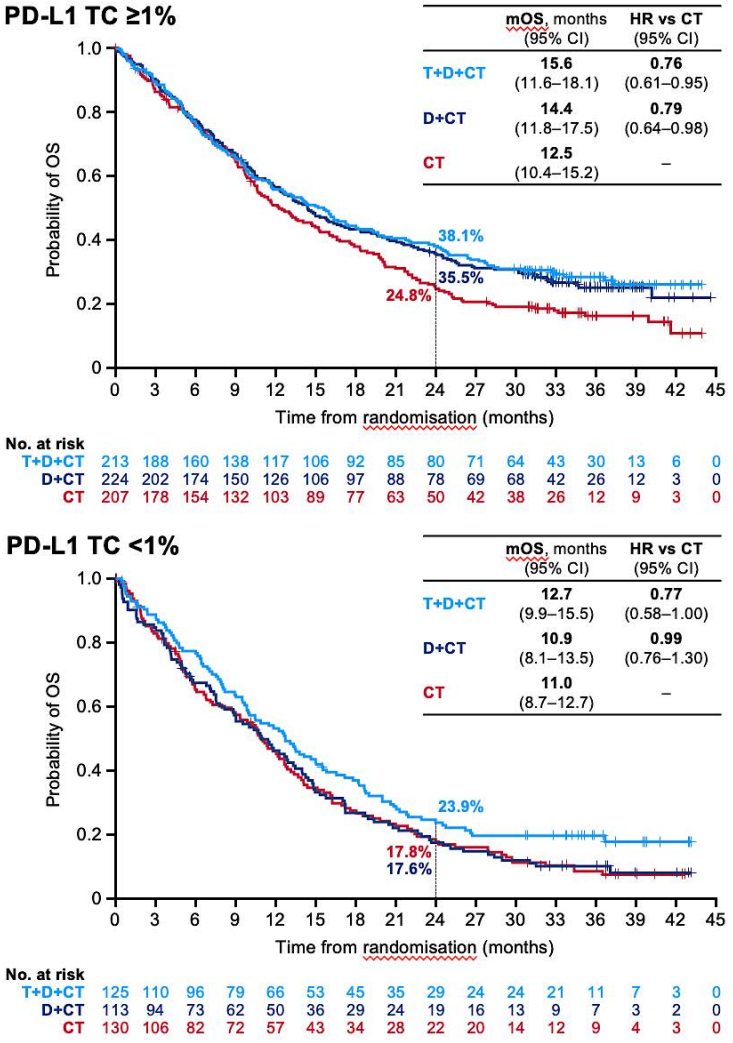
Subgroup analysis of OS	Events / patients, n/N (%) T+D+CT	CT	HR	(95% CI)
All patients, ITT analysis	279/338 (82.5)	304/337 (90.2)	0.76	(0.64–0.89)
Sex				
Male	223/269 (82.9)	232/248 (93.5)	0.68	(0.57–0.82)
Female	56/69 (81.2)	72/89 (80.9)	0.92	(0.65–1.31)
Age at randomization, years				
<65	152/191 (79.6)	156/176 (88.6)	0.76	(0.61–0.96)
≥65	127/147 (86.4)	148/161 (91.9)	0.72	(0.57–0.92)
Tumor PD-L1 expression				
TC ≥50%	75/101 (74.3)	86/97 (88.7)	0.62	(0.45–0.84)
TC <50%	204/237 (86.1)	218/240 (90.8)	0.81	(0.67–0.98)
TC 1–49%	91/112 (81.3)	98/110 (89.1)	0.81	(0.61–1.08)
TC ≥1%	166/213 (77.9)	184/207 (88.9)	0.71	(0.58–0.88)
TC <1%	113/125 (90.4)	120/130 (92.3)	0.81	(0.62–1.05)
Tumor histologic type				
Squamous	112/124 (90.3)	117/122 (95.9)	0.85	(0.65–1.10)
Nonsquamous	167/214 (78.0)	186/214 (86.9)	0.69	(0.56–0.85)
Planned chemotherapy				
Nab-paclitaxel doublet	19/23 (82.6)	17/19 (89.5)	0.61	(0.31–1.20)
Pemetrexed doublet	159/204 (77.9)	179/207 (86.5)	0.71	(0.57–0.88)
Gemcitabine doublet	101/111 (91.0)	108/111 (97.3)	0.85	(0.65–1.12)
Smoking history				
Current	65/84 (77.4)	60/66 (90.9)	0.53	(0.37–0.76)
Former	158/195 (81.0)	173/191 (90.6)	0.73	(0.59–0.91)
Never	56/59 (94.9)	70/79 (88.6)	1.17	(0.82–1.66)
Race				
Asian	80/99 (80.8)	109/128 (85.2)	0.94	(0.70–1.26)
Non-Asian	199/239 (83.3)	195/209 (93.3)	0.62	(0.51–0.76)
ECOG performance status				
0	83/110 (75.5)	104/119 (87.4)	0.74	(0.55–0.99)
1	196/228 (86.0)	200/218 (91.7)	0.72	(0.59–0.88)
Brain metastasis				
Yes	24/33 (72.7)	40/45 (88.9)	0.79	(0.47–1.30)
No	255/305 (83.6)	264/292 (90.4)	0.73	(0.61–0.87)
AJCC disease stage				
IVA	141/171 (82.5)	149/166 (89.8)	0.71	(0.56–0.89)
IVB	138/165 (83.6)	154/170 (90.6)	0.81	(0.64–1.02)

5 years POSEIDON

Peters, WCLC 2023 & JTO 2025

Adding a CTLA-4 improves OS in negative PD-L1 in POSEIDON



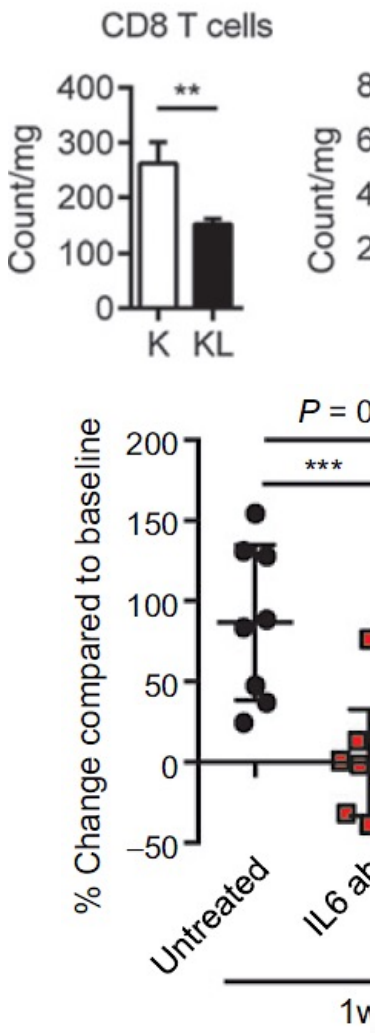


HRs calculated using an unstratified Cox proportional hazards model; DCO 12 Mar 2021.

Johnson, WCLC 2021; Garon Clin Lung Cancer 2024; Peters ESMO IO 2023

Possible mechanisms of *STK11* loss-mediated immune escape

Recruitment of



Repression of

Article

CTLA4 blockade abrogates *KEAP1/STK11*-related resistance to PD-(L)1 inhibitors

https://doi.org/10.1038/s41586-024-07943-7

Received: 27 October 2023

Accepted: 13 August 2024

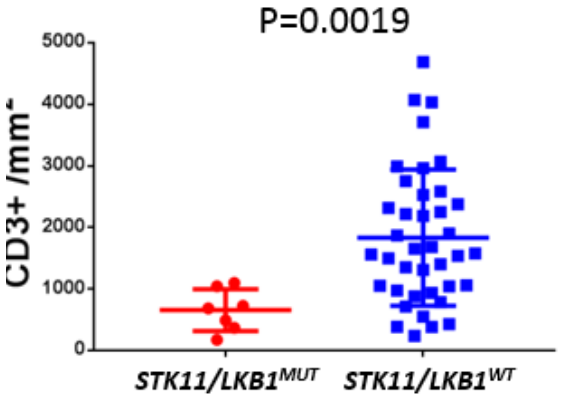
Published online: 09 October 2024

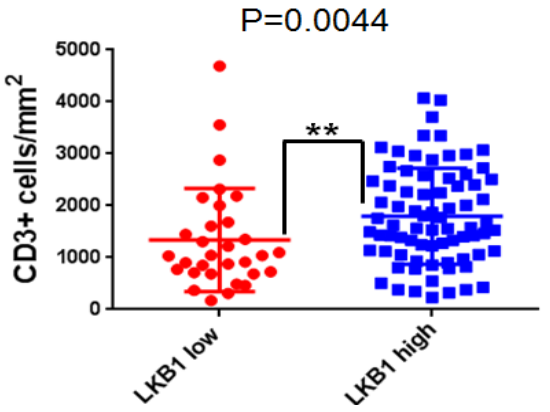
Open access

Check for updates

For patients with advanced non-small-cell lung cancer (NSCLC), dual immune checkpoint blockade (ICB) with CTLA4 inhibitors and PD-1 or PD-L1 inhibitors (hereafter, PD-(L)1 inhibitors) is associated with higher rates of anti-tumour activity and immune-related toxicities, when compared with treatment with PD-(L)1 inhibitors alone. However, there are currently no validated biomarkers to identify which patients will benefit from dual ICB[1,2]. Here we show that patients with NSCLC who have mutations in the *STK11* and/or *KEAP1* tumour suppressor genes derived clinical benefit from dual ICB with the PD-L1 inhibitor durvalumab and the CTLA4 inhibitor tremelimumab, but not from durvalumab alone, when added to chemotherapy in the randomized phase III POSEIDON trial[3]. Unbiased genetic screens identified loss of both of these tumour suppressor genes as independent drivers of resistance to PD-(L)1 inhibition, and showed that loss of *Keap1* was the strongest genomic predictor of dual ICB efficacy—a finding that was confirmed in several mouse models of *Kras*-driven NSCLC. In both mouse models and patients, *KEAP1* and *STK11* alterations were associated with an adverse tumour microenvironment, which was characterized by a preponderance of suppressive myeloid cells and the depletion of $CD8^+$ cytotoxic T cells, but relative sparing of $CD4^+$ effector subsets. Dual ICB potently engaged $CD4^+$ effector cells and reprogrammed the tumour myeloid cell compartment towards inducible nitric oxide synthase (iNOS)-expressing tumoricidal phenotypes that—together with $CD4^+$ and $CD8^+$ T cells—contributed to anti-tumour efficacy. These data support the use of chemo-immunotherapy with dual ICB to mitigate resistance to PD-(L)1 inhibition in patients with NSCLC who have *STK11* and/or *KEAP1* alterations.

Low CD3





Koyama S et al., *Cancer Research*, 2016

Kitajima S et al., *Cancer Discovery*, 2018

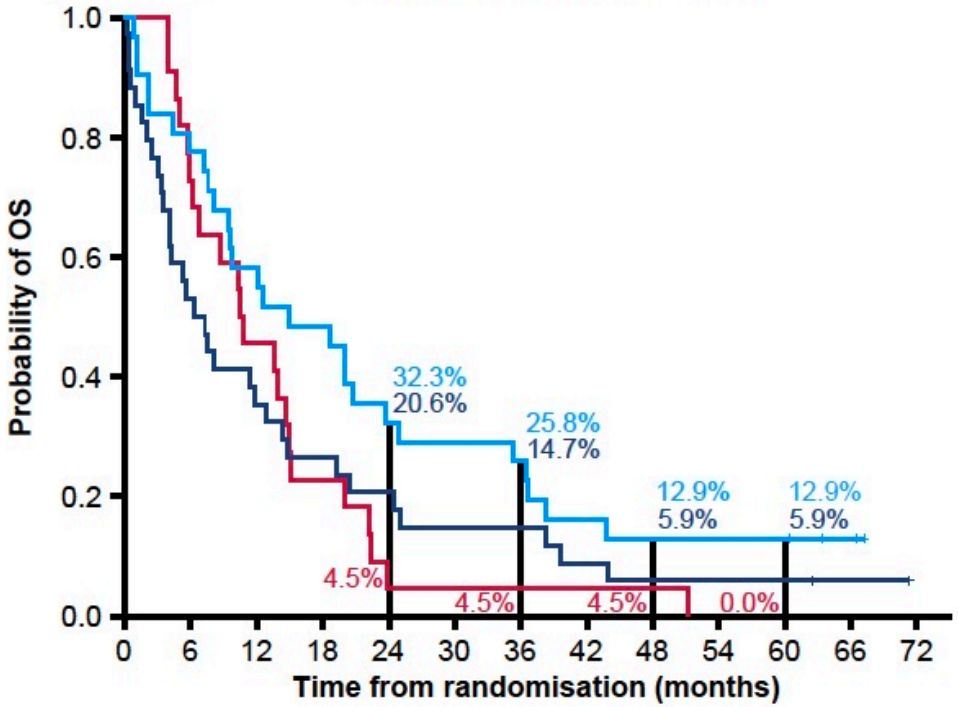
Skoulidis F et al, *Cancer Discovery*, 2018

Exploratory analyses suggest addition of a CTLA-4 might improve outcomes in biomarker-defined subgroups

POSEIDON: *STK11*m and *KRAS*m sub-analyses

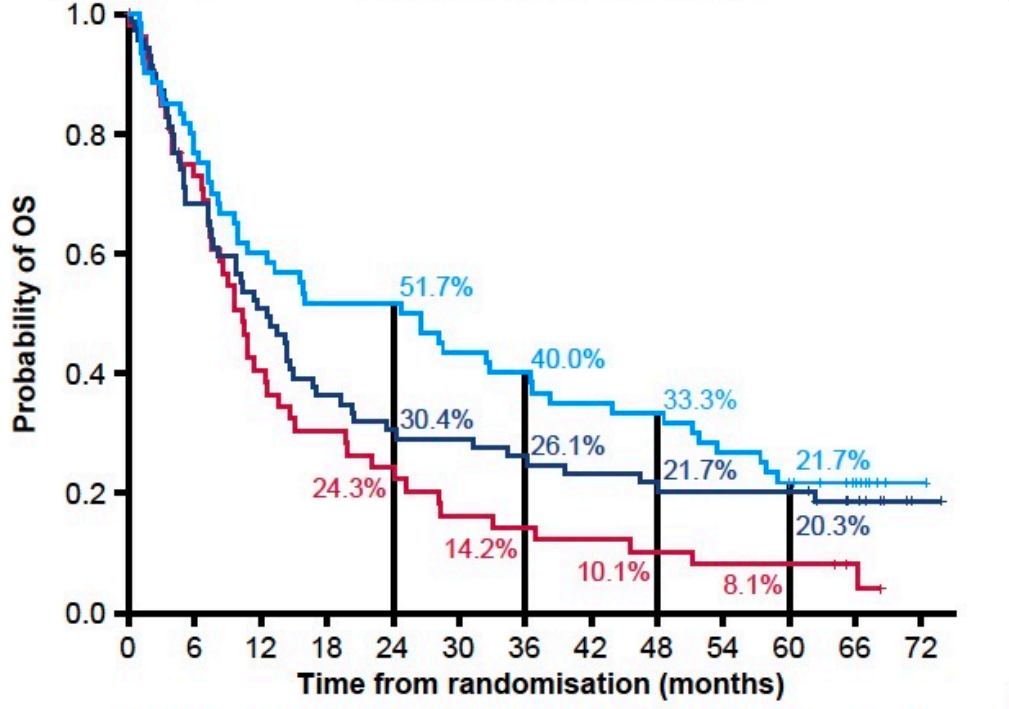
***STK11*m**

	T+D+CT	D+CT	CT
Events/patients, n/N	27/31	32/34	22/22
mOS, months (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.57** (0.32–1.04)	**1.02** (0.59–1.80)	–



***KRAS*m**

	T+D+CT	D+CT	CT
Events/patients, n/N	47/60	56/69	47/53
mOS, months (95% CI)	**25.7** (9.9–36.7)	**12.6** (7.5–16.9)	**10.4** (7.3–12.6)
HR* (95% CI)	**0.55** (0.36–0.83)	**0.74** (0.50–1.09)	–



The same is seen:

- For KEAP-1 alterations
- In CheckMate 9LA and 227

Peters S et al. ESMO IO 2023;Abstract LBA3.

TRITON: An ongoing phase III trial

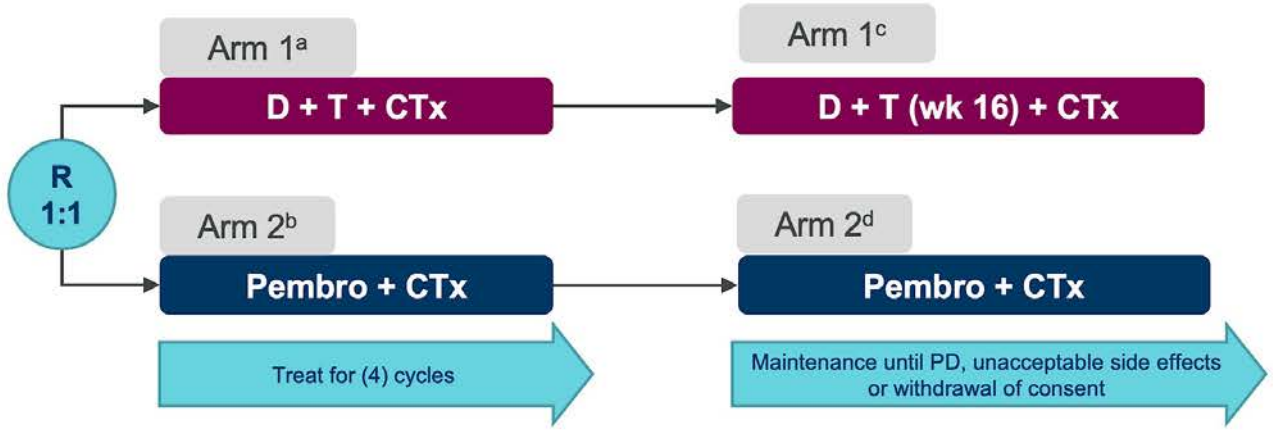
TRITON

Phase IIIb randomized, open-label, multicenter study

Study Population

STK11 +/- KEAP1 +/- KRASm

- **N = 280**
- Metastatic non-squamous NSCLC
- No prior systemic treatment for metastatic disease
- No EGFR or ALK alterations
- **Local testing**
- ECOG PS 0 or 1
- Tissue Sample requirement (TBC)



Primary endpoints
- OS in ITT
- OS in STK11/KEAP1

Key secondary endpoints
- PFS
- ORR, DoR
- Safety/Tolerability
- PRO/QoL

Exploratory Analysis
- Outcomes by PD-L1 expression
- Outcomes by different commutations

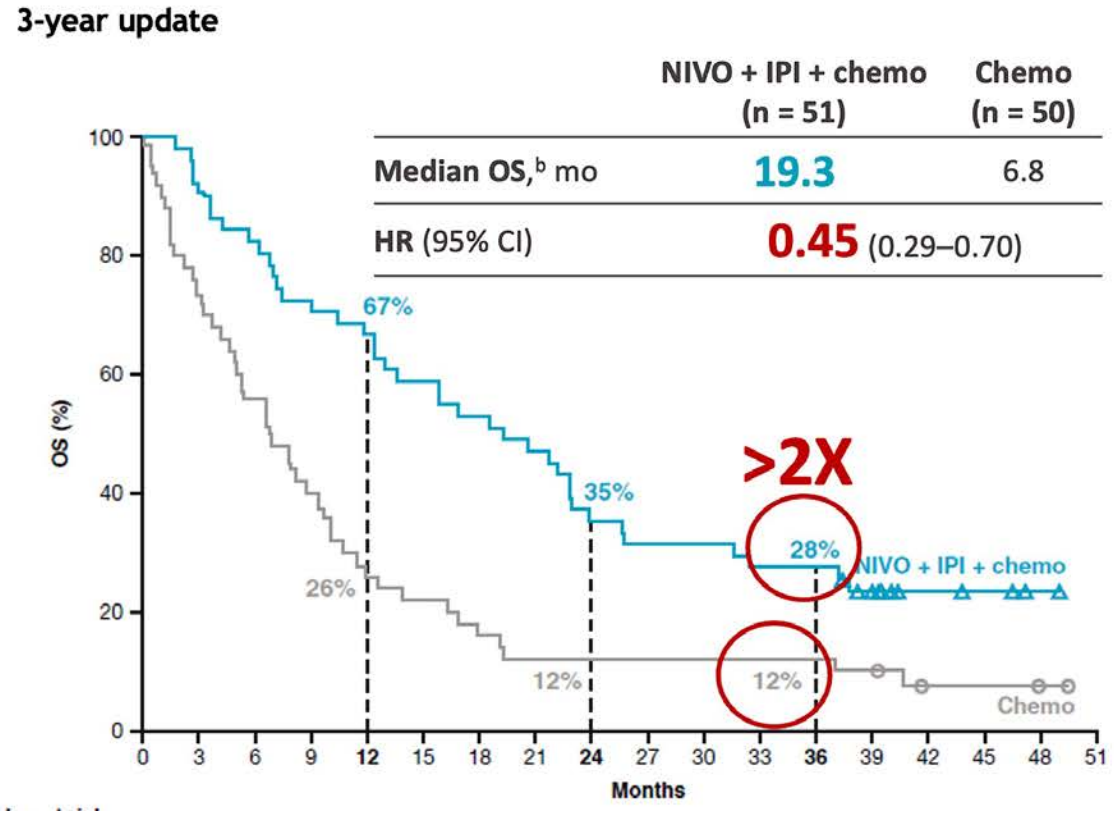
[a]Durvalumab 1500 mg Q3W + tremelimumab 75 mg Q3W + (platinum + pemetrexed 500 mg/m^2 Q3W); tremelimumab (permitted up to 5 cycles). [b]Pembrolizumab 200 mg Q3W + (platinum + pemetrexed 500 mg/m^2 Q3W).
[c]Durvalumab 1500 mg Q4W + tremelimumab 75 mg (one dose at week 16 only) + pemetrexed 500 mg/m^2 Q3W. [d]Pembrolizumab 200 mg Q3W + pemetrexed 500 mg/m^2 Q3W.

Participants must have tumors with STK11 or KEAP1 or KRAS mutations. Co-mutations are also allowed

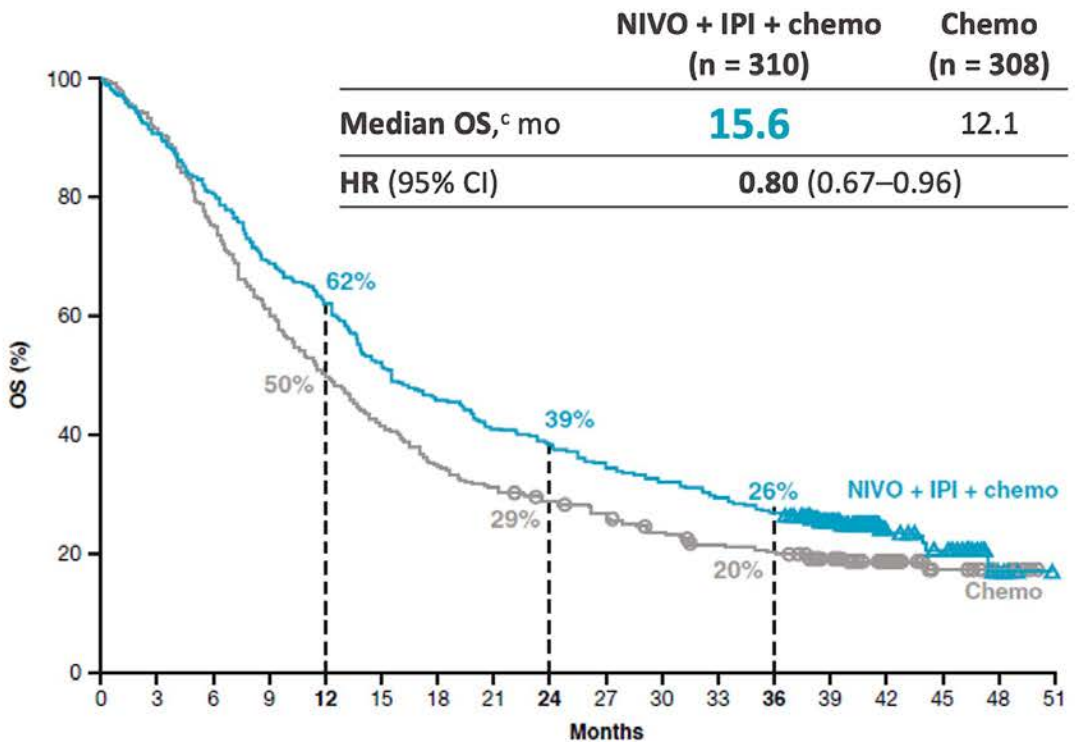
ClinicalTrials.gov. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT06008093 (Accessed: 15 February 2024).

CheckMate 9LA: a higher magnitude of benefit if brain mets

Postohoc analysis of patients treated in CheckMate 9LA, 3 years update



With baseline treated brain mets



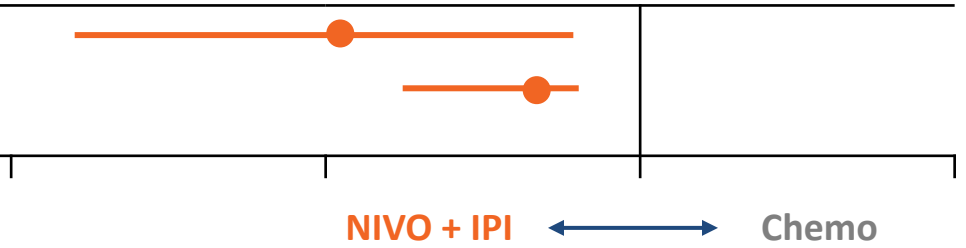
Without brain mets

Paz-Ares LG, et al. J Thorac Oncol. 2023 Feb; 18(2): 204-222

Ipi/nivo + 2 cycles of chemo demonstrated efficacy in patients with advanced NSCLC and CNS metastases[1,2]

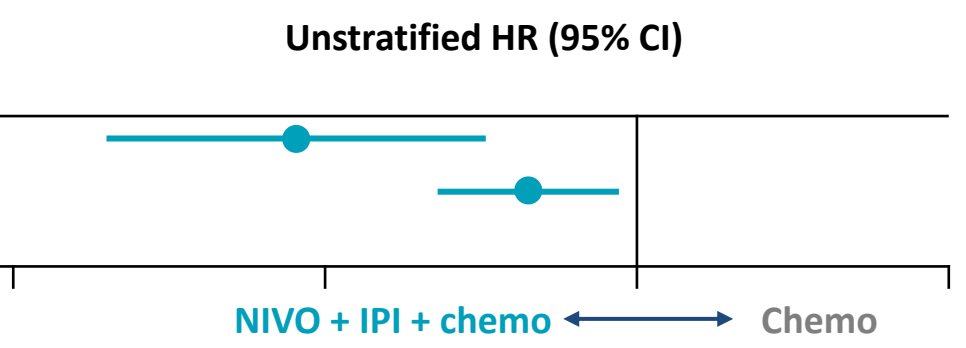
Checkmate 227

Subgroup	Median OS, mo NIVO + IPI (n = 583)	Chemo (n = 583)	Unstratified HR
CNS metastases (n = 135)	17.4	13.7	0.60
No CNS metastases (n = 1031)	17.1	13.9	0.77



Checkmate 9LA

Subgroup	Median OS, mo NIVO + IPI + chemo (n = 361)	Chemo (n = 358)	Unstratified HR
CNS metastases (n = 123)	19.9	7.9	0.49
No CNS metastases (n = 596)	15.6	11.8	0.81



chemo=chemotherapy; CI=confidence interval; CNS=central nervous system; HR=hazard ratio; IPI=ipilimumab; mets=metastases; mo=month; NIVO=nivolumab; NSCLC=non-small cell lung cancer; OS=overall survival.

1. Borghaei H, et al. AACR Annual Meeting 2020. Abstract CT221 (CheckMate 227). 2. Reck M, et al. 2021 ASCO. Abstract 9000 (CheckMate 9LA).

ChT ± (dual) anti-PD(L)-1 in 1L Non-Sq mNSCLC

ICI	± ChT	Patients	PFS (months)	OS (months)	ESMO MCBS score[21]
Keynote 189[1,2,3,4] (pembrolizumab)	CisP/CbP + pemetrexed	616	9.0 vs 4.9, HR 0.50	5 years OS 19.4%	**A/4**
IMPower 150[5,6] (atezolizumab)	CbP-paclitaxel ± bevacizumab	697	8.3 vs 6.8, HR 0.59	19.5 vs 14.7, HR 0.80	4
IMPower 130[7,8] (atezolizumab)	CbP + nab-paclitaxel	723	7.0 vs 5.5, HR 0.64	18.6 vs 13.9, HR 0.79	4
EMPower-Lung-3[9] (cemiplimab)	Platinum doublet	266*	7.9 vs 5.7, HR 0.53*	19.4 vs 12.4, HR 0.64*	4
Gemstone-302[10] (sugemalimab)	CbP + pemetrexed	191*	9,6 vs 5,9, HR 0,57*	26.0 vs 19.8, HR 0,72*	4
Rationale-304[11] (tislelizumab)	CisP/CbP + pemetrexed	334	9.8 vs 7.6, HR 0.47	21.6 vs 20.1, HR 0.85	4 (for PD-L1 ≥50%)
CM-9LA[12,13,14] (nivolumab + ipilimumab)	2 cycles platinum + pemetrexed	492*	6.9 vs 5.6, HR 0.75*	5 year OS 19%*	4
POSEIDON[15,16,17] (durvalumab + tremelimumab)	4 cycles platinum doublet ChT	428*	6.8 vs 5.5, HR 0.66*	5 year OS 20.5%*	4
Check-Mate 227[18,19,20] (nivo+ipi vs chemo) TPS ≥ 1%	-	557*	5.5 vs 5.9, HR 0.83*	6 year OS 25%*	4

* Non Sq subgroup analysis

1) Gadgeel S, et al. Presented at ASCO 2019. Abstract 9013. 2) Rodriguez-Abreu D. Presented at ASCO 2020. Abstract 9582. 3) Gray JE, et al. Presented at WCLC 2020. Abstract FP13.02. 4) Garassino M, et al. Presented at ESMO 2022. Abstract 973MO. 5) Socinski M, et al. *N Engl J Med*.4 Jun 2018. 6) Socinski M, et al. Presented at AACR 2020. Abstract CT126. 7) Cappuzzo, et al. Presented at ESMO 2018. Abstract LBA53. 8) West HJ, et al. *Lancet*. 20 May 2019. 9) Makharadze T, et al. Presented at ELCC 2023. Abstract 5O. 10) Zhou C, et al. Presented at ESMO 2024. Abstract 1318P. 11) Lu S, et al. Presented at ESMO IO 2022. Abstract 138P. 12) Paz-Ares L, et al. Presented at ASCO 2022. Abstract LBA9026. 13) Carbone D, et al. Presented at ASCO 2023. Abstract LBA9023. 14) Reck M, et al. Presented at ASCO 2024. Abstract 8560. 15) Johnson M, et al. Presented at ESMO 2022. Abstract LBA59. 16) Johnson M, et al. *JTO 2023.* 3 Nov 2022. 17) Peters S, et al. Presented at ESMO IO 2023. Abstract LBA3. 18) Paz-Ares, et al. *JTO*. 20 Sept 2021. 19) Brahmer J, et al. Presented at ASCO 2022. Abstract LBA9025. 20) Peters S, et al. Presented at WCLC 2023. Abstract OA14.03; 21) https://www.esmo.org/living-guidelines/esmo-non-oncogene-addicted-metastatic-non-small-cell-lung-cancer-living-guideline, Jan, 2025

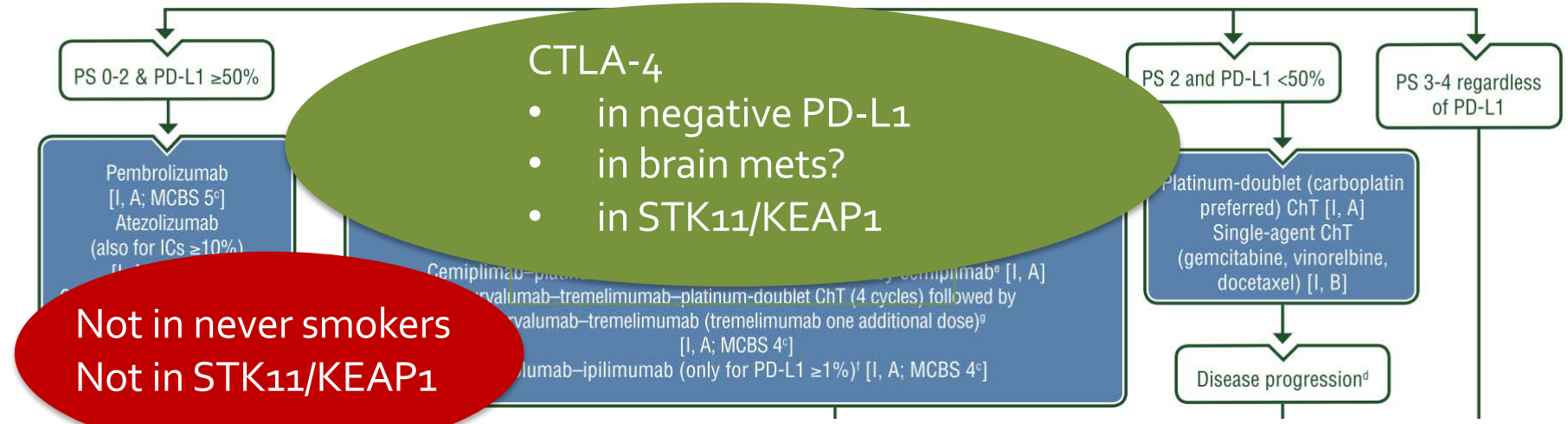
ChT ± (dual) anti-PD(L)-1 in 1L Sq. mNSCLC

(Dual) Anti-PD-L1	± ChT	Patients	PFS (months)	OS (months)	ESMO MCBS score[19]
Keynote 407[1,2,3] (pembrolizumab)	CisP/CbP + paclitaxel or nab-paclitaxel	559	8.0 vs 5.1, HR 0.62	5 years OS 18.4%	**4/A**
Empower-Lung 3[4]	Platinum based ChT	200*	8.2 vs 4.9, HR 0.56*	22.3 vs 13.8, HR 0.61*	4
Rationale-307[5,6,7,8] (tislelizumab)	CbP-(nab)paclitaxel	360	7.7 vs 9.5 vs 5.5 HR 0.45 and 0.45	26.1 vs 23.3 vs 19.4 HR 0.67 and 0.82	4 (pacli), 3 (nab-pacli)
Gemstone-302[9] (sugemalimab)	CbP + paclitaxel	192*	8.3 vs 4.8, HR 0.37*	23.6 vs 12.2, HR 0.61*	4
CM-9LA[10,11,12] (nivolumab + ipilimumab)	2 cycles platinum + paclitaxel or pemetrexed	227*	5.6 vs 4.3 HR 0.65*	5 years OS 18%*	4
POSEIDON[13,14,15] (durvalumab + tremelimumab)	4 cycles platinum doublet ChT	246*	4.6 vs 4.6, HR 0.68*	5 years OS 7.3%*	4
Check-Mate 227[16,17,18] (nivo+ipi vs chemo) TPS ≥ 1%	-	236*	4.1 vs 4.3, HR 0.77*	6 year OS 14%*	4

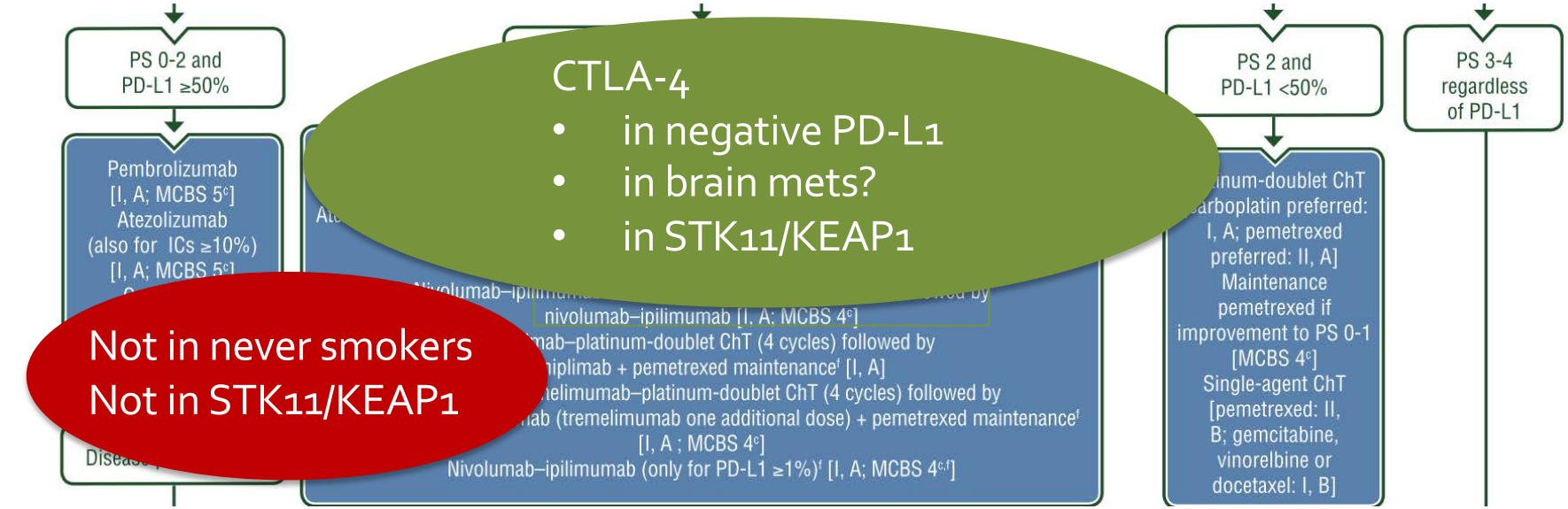
* Sq subgroup analysis

1) Paz-Ares L, et al. Presented at ESMO 2019. Abstract LBA82. 2) Robinson A, et al. Presented at ELCC 2021. Abstract 97O. 3) Novello S, et al. Presented at ESMO 2022. Abstract 974MO. 4) Makharadze T, et al. Presented at ELCC 2023. Abstract 5O. 5) Wang J, et al. Presented at Chinese Society of Clinical Oncology Congress 2020. 6) Wang J, et al. JAMA Oncol. 2021;7:709. 7) Wang J, et al. Presented at ESMO IO 2022. Abstract 132P. 8) Wang Z, et al. Presented at ESMO 2024. Abstract 1323P. 9) Zhou C, et al. Presented at ESMO 2024. Abstract 1318P. 10) Paz-Ares L, et al. Presented at ASCO 2022. Abstract LBA9026. 11) Carbone D, et al. Presented at ASCO 2023. Abstract LBA9023. 12) Reck M, et al. Presented at ASCO 2024. Abstract 8560. 13) Johnson M, et al. Presented at ESMO 2022. Abstract LBA59. 14) Johnson M, et al. JTO 2023. 3 Nov 2022. 15) Peters S, et al. Presented at ESMO IO 2023. Abstract LBA3. 16) Paz-Ares, et al. JTO. 20 Sept 2021. 17) Brahmer J, et al. Presented at ASCO 2022. Abstract LBA9025. 18) Peters S, et al. Presented at WCLC 2023. Abstract OA14.03; 19) https://www.esmo.org/living-guidelines/esmo-non-oncogene-addicted-metastatic-non-small-cell-lung-cancer-living-guideline, Jan, 2025

ESMO CPG: some nuances



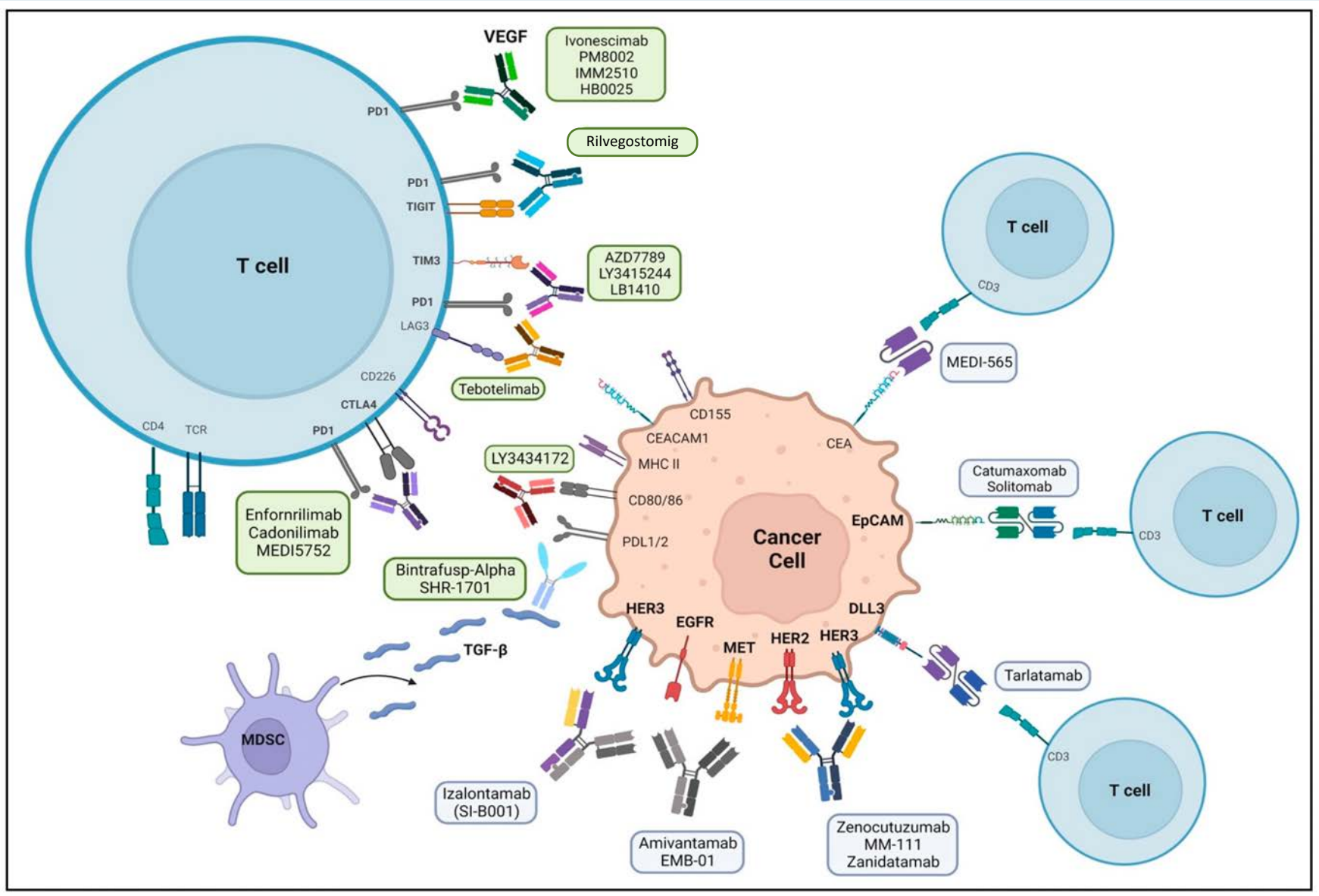
squamous



Non-squamous

Hendriks Ann Oncol 2023

Bispecific Antibodies under Investigation in Lung



Khosla AA et al. Pharmaceuticals (Basel). 2023 Oct 14;16(10):1461.

RTP RESEARCH TO PRACTICE

Ongoing Phase III Trials Investigating Immune Checkpoint Bispecific Antibodies

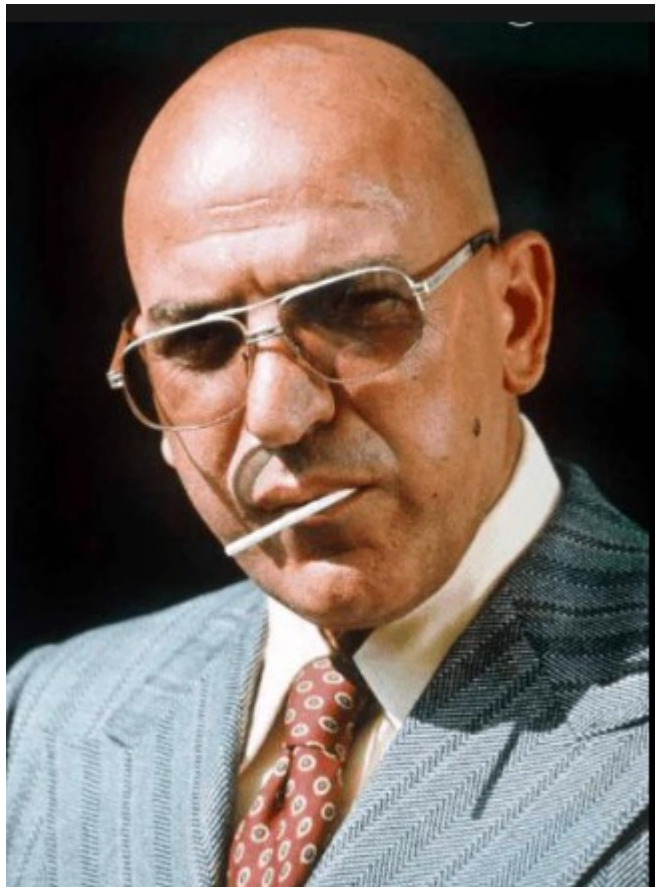
Trial	Phase	Bispecific Antibody (targets)	Eligibility	Intervention	Primary Endpoint	Interim Results
HARMONi-7 (NCT06767514)	III	Ivonescimab (PD-1 and VEGF)	First-line metastatic NSCLC with PD-L1 expression (TPS ≥50%)	Ivonescimab *v* pembrolizumab	PFS, OS	
HARMONi (NCT06396065)	III	Ivonescimab (PD-1 and VEGF)	*EGFR*-mutant locally advanced or metastatic NSCLC that has progressed on EGFR inhibitor	Ivonescimab (SMT112/AK112) + pemetrexed + carboplatin *v* placebo + pemetrexed + carboplatin	PFS, OS	
HARMONi-3 (NCT05899608)	III	Ivonescimab (PD-1 and VEGF)	First-line metastatic NSCLC	Ivonescimab + chemotherapy *v* pembrolizumab + chemotherapy	PFS, OS	
NCT06020352	II/III	KN046 (PD-1 and CTLA-4)	Neoadjuvant therapy for resectable stage IB to IIIB NSCLC	KN046 + axitinib followed by surgery	MPR and surgical resection rate	
NCT05756972	II/III	PM8002 (PD-1 and VEGF-A)	*EGFR*-mutant locally advanced or metastatic nonsquamous NSCLC who have failed EGFR-TKI treatment	PM8002 + chemotherapy *v* chemotherapy alone	ORR, PFS	ORR was 54.7% (35/64, 95% CI, 41.8 to 67.2) and DCR was 95.3% (61/64, 95% CI, 86.9 to 99.0)[62]
ABBIL1TY NSCLC-06 (NCT06635824)	III	Acasunlimab (PD-1 and 4-1BB)	PD-L1–positive metastatic NSCLC who have been treated with PD-1/PD-L1 inhibitor and platinum-containing chemotherapy, administered either in combination or sequentially in the metastatic setting	Acasunlimab + pembrolizumab *v* docetaxel	OS	
NCT06617416	III	Cadonilimab (PD-1 and CTLA-4)	Unresectable locally advanced NSCLC	Cadonilimab *v* sugemalimab	PFS	
ARTEMIDE-Lung02 (NCT06692738)	III	Rilvegostomig (PD-1 and TIGIT)	First-line treatment of squamous metastatic NSCLC with PD-L1 ≥1%	Rilvegostomig *v* pembrolizumab, both in combination with platinum-based doublet chemotherapy	PFS, OS	
ARTEMIDE-Lung04 (NCT06868277)	III	Rilvegostomig (PD-1 and TIGIT)	First-line treatment of PD-L1–high metastatic NSCLC	Rilvegostomig *v* pembrolizumab	PFS, OS	

Carlisle JW et al. Am Soc Clin Oncol Educ Book. 2025 Jun;45(3):e472792.

Faculty Case Presentations

Case Presentation – Dr Sands: Metastatic lung adenocarcinoma

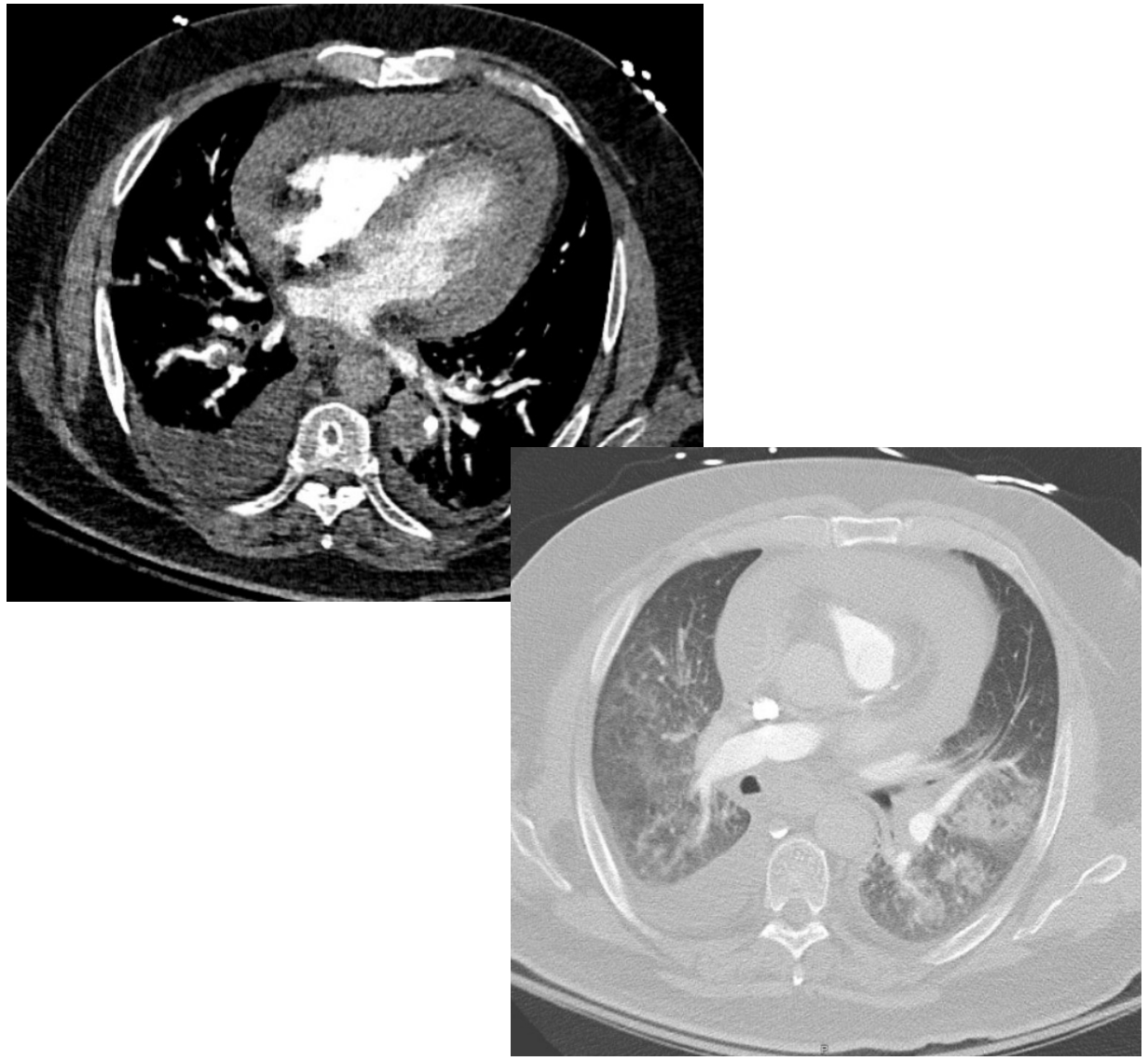
- 69 yr old man experienced worsening shortness of breath over 3 months leading to presentation to PCP. Diagnosed with pneumonia and treated without improvement.
- Referred to cardiology and pulmonology. Diagnosed with restrictive/obstructive disease and prescribed steroids and albuterol inhaler with some relief.
- About 1 month later, presented to PCP with worsening symptoms. CT scan showed bilateral pulmonary emboli, extensive infiltrates, “mass-like features”, and adenopathy. Wife drove him to BWH for worsening symptoms where he was admitted.
- Lung adenocarcinoma diagnosed from EBUS nodes and pericardial fluid. No actionable alterations. PD-L1 = 20%



Not the actual patient

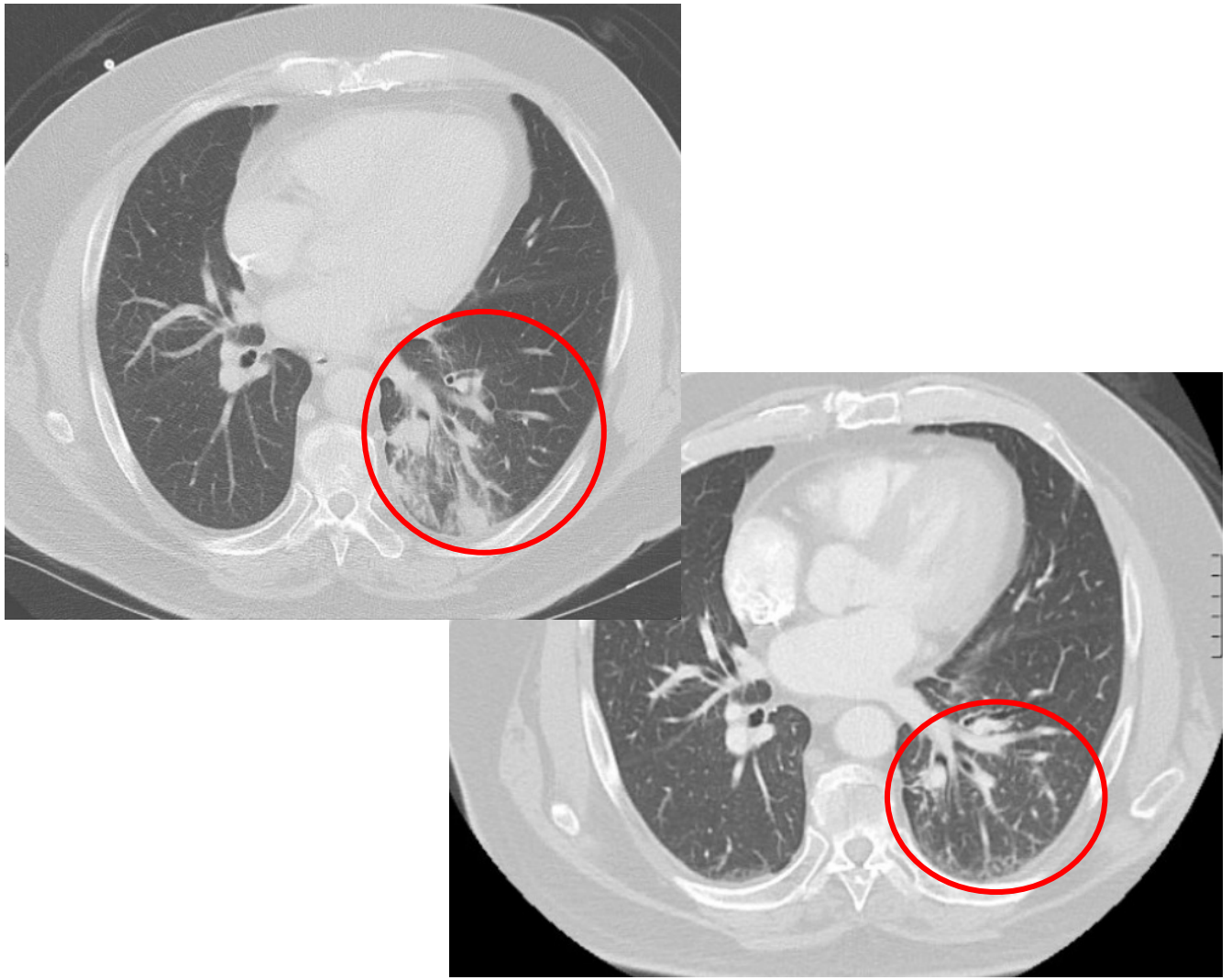
Case Presentation – Dr Sands: Metastatic lung adenocarcinoma (cont'd)

- 1L treatment: carboplatin, pemetrexed, and pembrolizumab and had partial response with total ~10 months disease control
- 2L treatment: Initiated DS-1062 (Dato-DXd) on clinical trial
- Tolerated treatment well with only significant toxicity being ocular. He did not like using eye drops and did not consistently start using until being told that if symptoms worsened, he might have to stop the treatment.



Case Presentation – Dr Sands: Metastatic lung adenocarcinoma (cont'd)

- These scans show baseline to 9 months into treatment with a 72% reduction in measurable tumor volume.
- Had partial response with disease control for ~21 months
- At progression, he was treated on docetaxel as next line therapy with early progression and then with gemcitabine with brief disease control.



Questions for the Faculty

Do you view pembrolizumab, atezolizumab and cemiplimab monotherapy as equivalent options for patients with a PD-L1 TPS ≥50%? Do you have a preference for a particular agent for patients with nonsquamous or squamous disease?

In which situations, if any, are you currently recommending anti-PD-1/PD-L1 monotherapy for patients with a PD-L1 TPS <50%?

Questions for the Faculty

In which situations are you currently recommending an anti-PD-1/ PD-L1 antibody in combination with chemotherapy for patients with a PD-L1 TPS ≥50%?

How do you think through therapeutic selection after disease progression on first-line chemoimmunotherapy? Would you ever rechallenge with an alternative immune checkpoint inhibitor-containing regimen?

Questions for the Faculty

Do you believe immune checkpoint bispecific antibodies will replace anti-PD-1/PD-L1 antibodies as first-line treatment?

Which particular immune checkpoint bispecific antibodies (PD-1 x VEGF, PD-1 x CTLA-4, PD-1 x TIGIT), if any, are you particularly enthusiastic about?

Which ongoing trials evaluating novel immune checkpoint bispecific antibodies are you recommending for your patients?

Questions for the Faculty

In which situations are you currently recommending an anti-PD-1/PD-L1 antibody in combination with an anti-CTLA-4 antibody as first-line treatment for metastatic NSCLC? What about an anti-PD-1/PD-L1 antibody in combination with an anti-CTLA-4 antibody and chemotherapy?

Do you believe these regimens might be preferential in patients with PD-L1-negative disease? What about in those with symptomatic, high tumor-volume disease? What about in patients with CNS involvement?

Questions for the Faculty

Beyond negative PD-L1, are there any biomarkers (eg, STK11/KEAP1 mutations, KRAS mutations) that would make you more inclined to favor an anti-PD-1/PD-L1 antibody in combination with an anti-CTLA-4 antibody with or without chemotherapy as first-line therapy?

Should community-based oncologists be testing for STK11/KEAP1 mutations in their patients with metastatic NSCLC and considering them when making decisions regarding first-line therapy?

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1: Role of Immune Checkpoint Inhibitors in Metastatic Non-Small Cell Lung Cancer (NSCLC) without a Targetable Tumor Mutation — Prof Peters

Module 2: Targeted and Other Novel Therapeutic Strategies for Relapsed Metastatic NSCLC — Prof Garassino

Module 3: Potential Role of TROP2-Targeted Antibody-Drug Conjugates in Advanced NSCLC — Dr Sands

Module 4: Evolving Role of Immune Checkpoint Inhibitors in the Care of Patients with Nonmetastatic NSCLC — Dr Heymach

Targeted and Other Novel Therapeutic Strategies for Relapsed Metastatic NSCLC

Marina Chiara GARASSINO
Professor of Medicine
Director, Thoracic Oncology Program
University of Chicago

Two new targets

- HER2
- c-Met

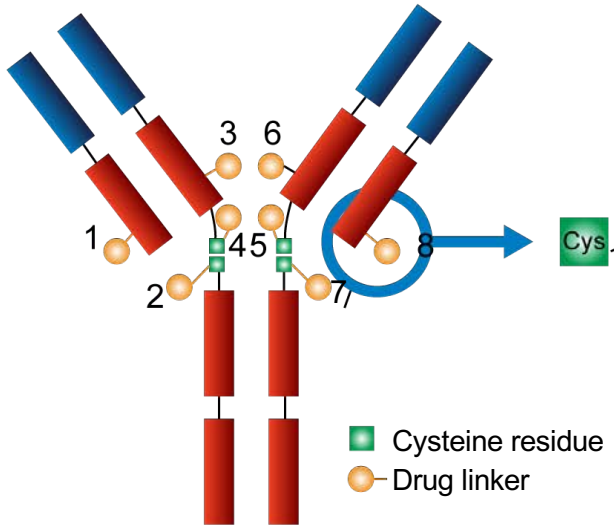
HER2

Select Phase 2 Trials in *HER2*-Altered NSCLC

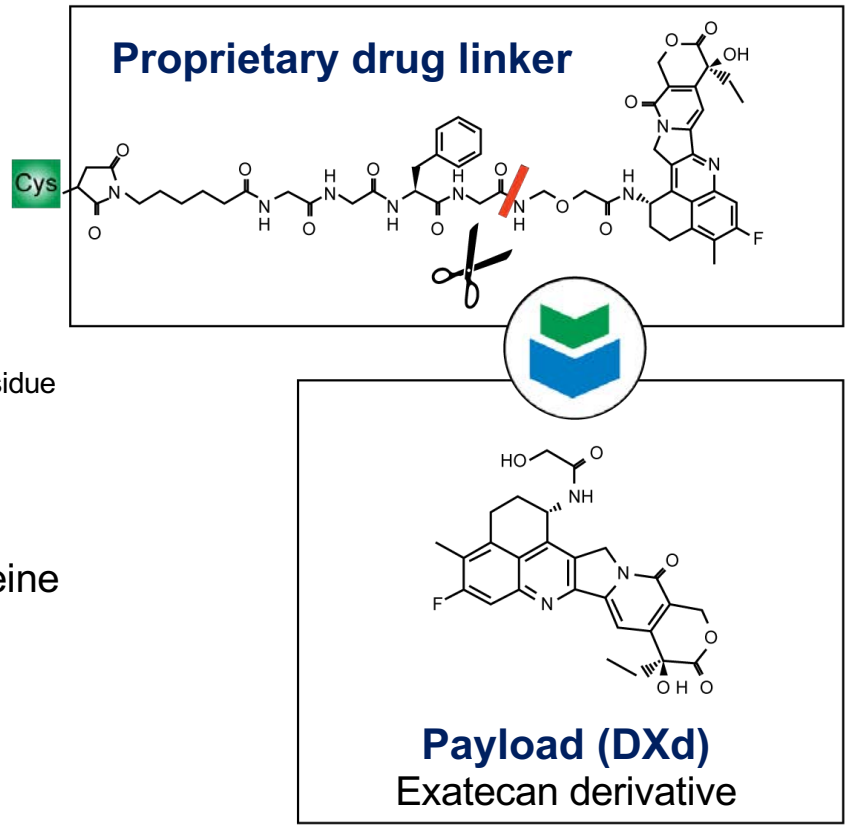
Drug	Phase	N	RR, %	PFS, mo
TKIs				
Afatinib	2	13	7.7	4
Dacomitinib	2	30	11.5	3
Poziotinib	2	12	50	5.6
Pyrotinib	2	15	53.3	6.4
Monoclonal antibodies/ADCs				
Ado-trastuzumab emtansine	2	18	44	5.0
Trastuzumab deruxtecan	2	42	61	14

Peters S et al. *Clin Cancer Res* 2019;25(1):64-72. Smit E et al. *J Thorac Oncol* 2021.

Trastuzumab Deruxtecan (T-DXd)



Conjugation Chemistry
The linker is connected to cysteine residue of the antibody



- ADC composed of three components
  - Humanized HER2-targeted mAb
  - Topoisomerase I inhibitor "payload"
  - Tetrapeptide-based cleavable linker

- High drug-to-antibody ratio (~8:1)
- High potency payload that is membrane permeable → nearby cells in tumor targeted regardless of HER2 expression ("bystander antitumor effect")

Li B et al. ESMO 2022;Abstract 976P.

DESTINY-Lung01: Study Design

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS 0 or 1
- Locally reported *HER2* mutation (cohort 2)[b]

→ **Cohort 1**[c] (n = 49)
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg Q3W

→ **Cohort 1a**[c] (n = 41)
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg Q3W

→ **Cohort 2** (n = 42)
***HER2* mutated**
T-DXd 6.4 mg/kg Q3W

Cohort 2 (n = 49)
***HER2* mutated**
T-DXd 6.4 mg/kg Q3W

- **Primary endpoint:** confirmed ORR by ICR[d]
- **Secondary endpoints:** DOR, PFS, OS, DCR, and safety
- **Exploratory endpoint:** biomarkers of response

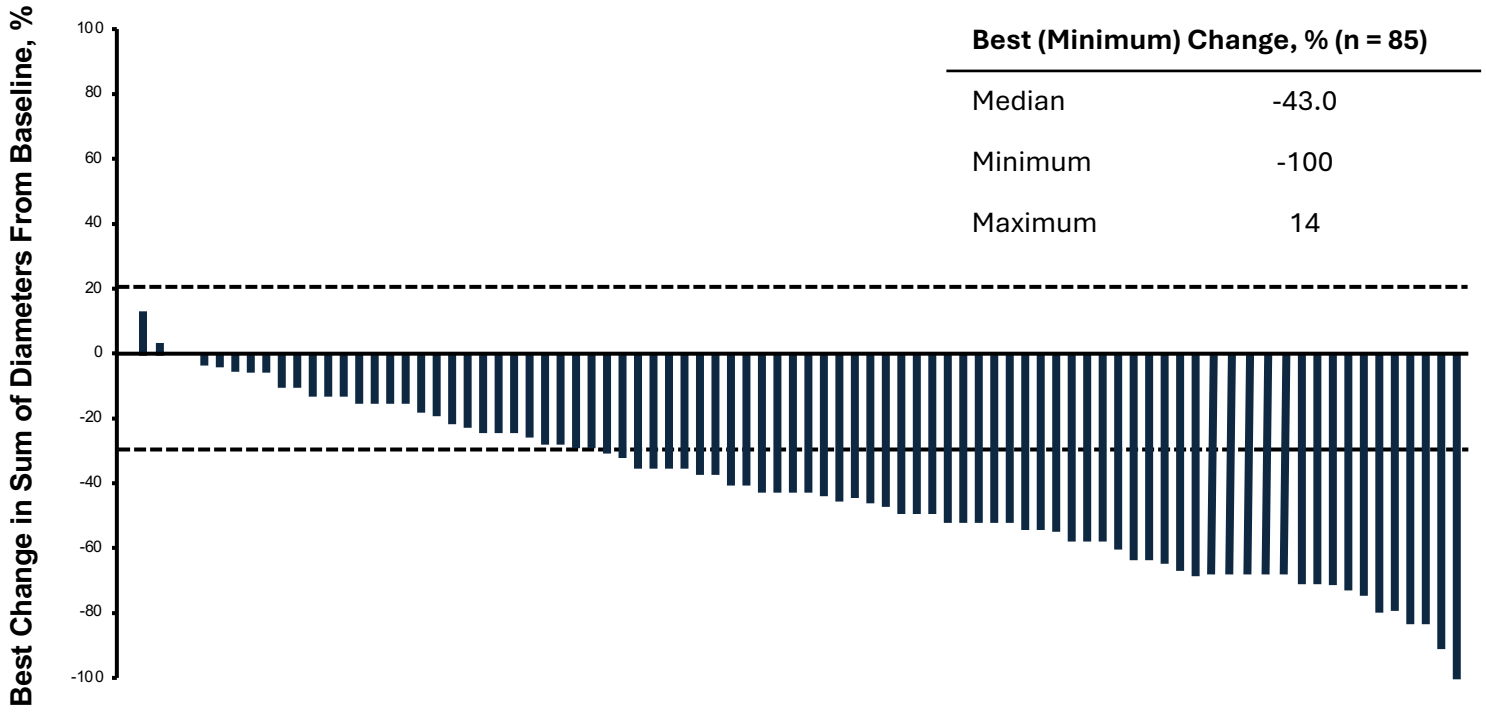
Li B et al. ESMO 2022;Abstract 976P.

DESTINY-Lung01 Cohort 2 (*HER2*-Mutated NSCLC): Updated Efficacy Results

1. Confirmed ORR by ICR in overall population: **54.9%** (95% CI, 44.2%-65.4%)
2. Confirmed ORR by ICR similar across subgroups (54.5% [95% CI, 36.4%-71.9%] and 55.2% [95% CI, 41.5%-68.3%] in pts with/without CNS metastases; 55.7% [95% CI, 42.5%-68.5%] in pts with ≤2 prior lines of therapy and 53.3% [95% CI, 34.3%-71.1%] in pts with >2 prior lines)
3. **Median DOR in overall population: 10.6 mo**
4. Median DOR in pts with/without CNS metastases at baseline: 7.2 mo (95% CI, 5.3-11.1 mo)/14.7 mo (95% CI, 5.7 mo-NE)
5. Median DOR 14.1 mo (95% CI, 5.9-NE mo) with ≤2 prior lines of therapy vs 5.8 mo (95% CI, 4.2-12.0 mo) with >2 prior lines

Updated data: 7 mo additional follow-up

Best Percentage Change From Baseline in Target Lesions by ICR for the Overall NSCLC *HER2*m Population (DCO December 3, 2021)



Li B et al. ESMO 2022;Abstract 976P.

DESTINY-Lung01 Cohort 2 (*HER2*-Mutated NSCLC): Updated Safety Results

Safety Summary of T-DXd in the Overall *HER2*mut NSCLC Population (DCO December 3, 2021)

n, %	Overall Population (N = 91)
Any-grade TEAEs	91 (100)
Drug-related TEAEs	88 (96.7)
Drug-related grade ≥3 TEAEs	42 (46.2)
Serious drug-related TEAEs	18 (19.8)
Drug-related TEAEs associated with	
Drug discontinuation	24 (26.4)
Dose reduction	33 (36.3)
Drug interruption	31 (34.1)
Drug-related TEAEs associated with an outcome of death	2 (2.2)

Adjudicated Drug-Related ILD in the Overall *HER2*mut NSCLC Population (DCO December 3, 2021)

	Overall Population (N = 91)
Any grade, n (%)	25 (27.5)
Grade 1	3 (3.3)
Grade 2	16 (17.6)
Grade 3	4 (4.4)
Grade 4	0
Grade 5	2 (2.2)
Median time to first onset, days (range)	125 (14-461)
Median duration, days (95% CI)	43 (29-94)
Outcome of event as reported by investigator, n (%)	
Fatal	1 (4)
Not recovered/not resolved	8 (32)
Recovering/resolved	1 (4)
Recovered/resolved with sequelae	2 (8)
Recovered/resolved	13 (52)

Li B et al. ESMO 2022;Abstract 976P.

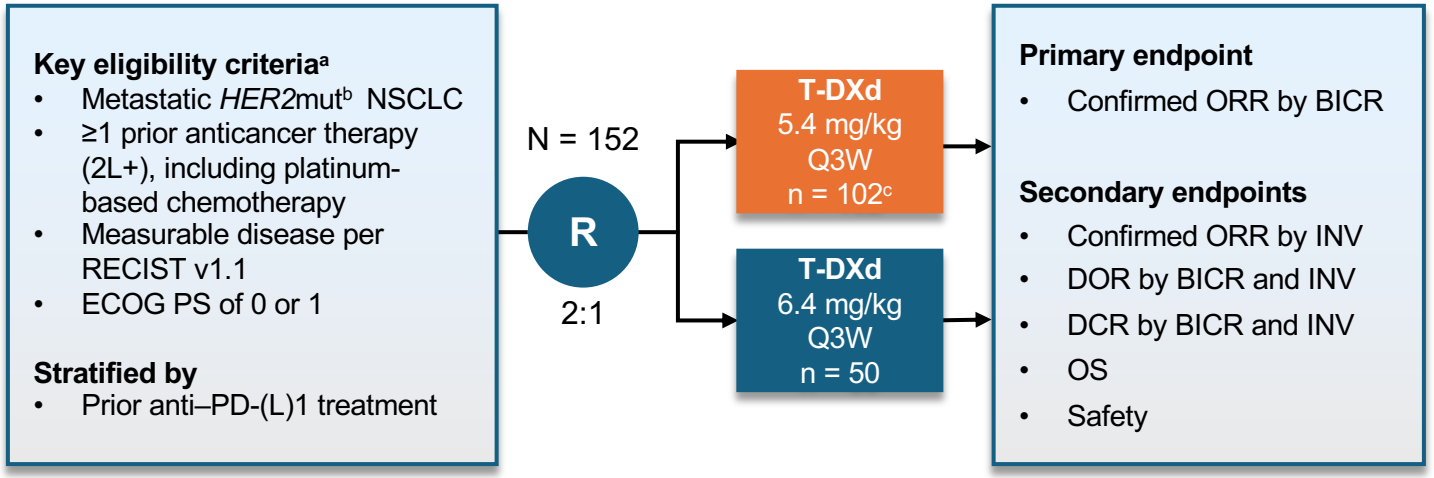
DESTINY-Lung02: Study Design

A Blinded, Randomized, Multicenter, International, Noncomparative, Phase 2 Trial (NCT04644237)

Background

- T-DXd 5.4 mg/kg and 6.4 mg/kg showed robust antitumor activity in multiple cancer types; however, T-DXd 5.4 mg/kg has not been evaluated in patients with previously treated *HER2*mut mNSCLC
- DESTINY-Lung02 assessed the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with *HER2*mut mNSCLC
  - In the interim analysis, T-DXd showed deep and durable responses and an acceptable and generally manageable safety profile[3]
- Following are the **primary analysis results** of DESTINY-Lung02

Study Design



Statistical considerations

- Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper–Pearson CI of confirmed ORR of a T-DXd dose with a benchmark ORR of 26.4% (upper limit of the ORR 95% CI in the ramucirumab plus docetaxel arm of the REVEL trial)[4]
- The study was not powered to statistically compare between arms

Janne P et al. ASCO 2024;Abstract 8543.

DESTINY-Lung02: Baseline Characteristics and Efficacy Summary

Baseline characteristics

In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively

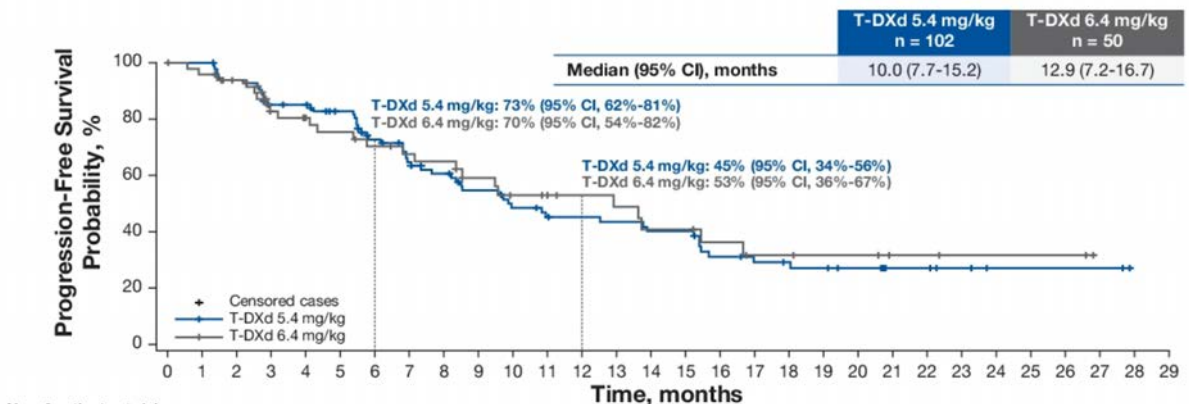
- Median age was 59.4 y (range, 31-84) and 61.3 y (range 28-86)
- Most patients were female (63.7% and 68.0%), from Asia (61.8% and 60.0%), had never smoked (53.9% and 58.0%), and received prior anti–PD-(L)1 therapy (73.5% and 78.0%)
- *HER2* mutations were primarily in the kinase domain (97.1% and 100%)
- Baseline CNS metastasis was present in 34.3% and 44.0% of patients
- Median prior lines of treatment was 2 (range, 1-12) and 2 (range, 1-7)

Table 2. Summary of Efficacy Results of T-DXd

	T-DXd 5.4 mg/kg n = 102	T-DXd 6.4 mg/kg n = 50
cORR,[a,b] n (% [95% CI])	51 (50.0 [39.9-60.1])	28 (56.0 [41.3-70.0])
CR	3 (2.9)	4 (8.0)
PR	48 (47.1)	24 (48.0)
SD	44 (43.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Non-evaluable	3 (2.9)	2 (4.0)
DCR,[c] n (% [95% CI])	95 (93.1 [86.4-97.2])	46 (92.0 [80.8-97.8])
DoR,[b] median (95% CI), months	12.6 (6.4 to NE)	12.2 (7.0 to NE)

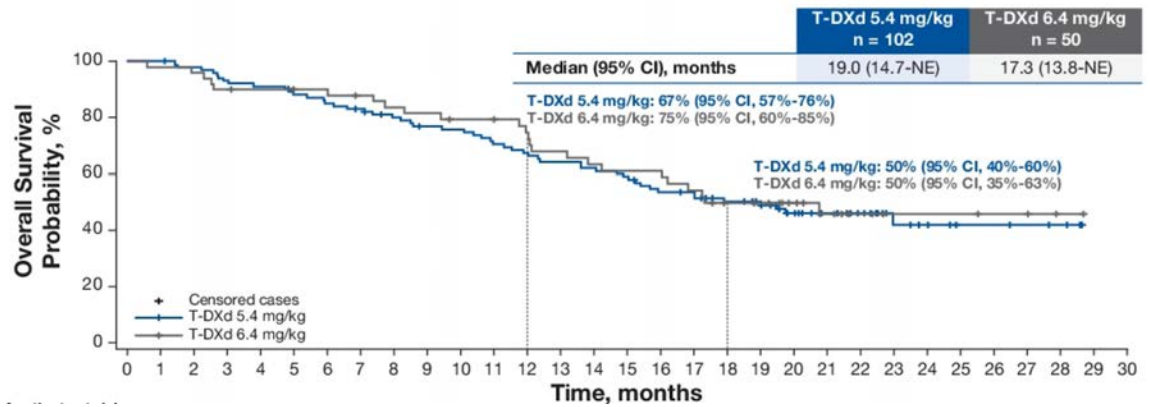
PFS

Figure 3. Kaplan-Meier Plot of PFS by BICR in the T-DXd 5.4 mg/kg and 6.4 mg/kg Arms



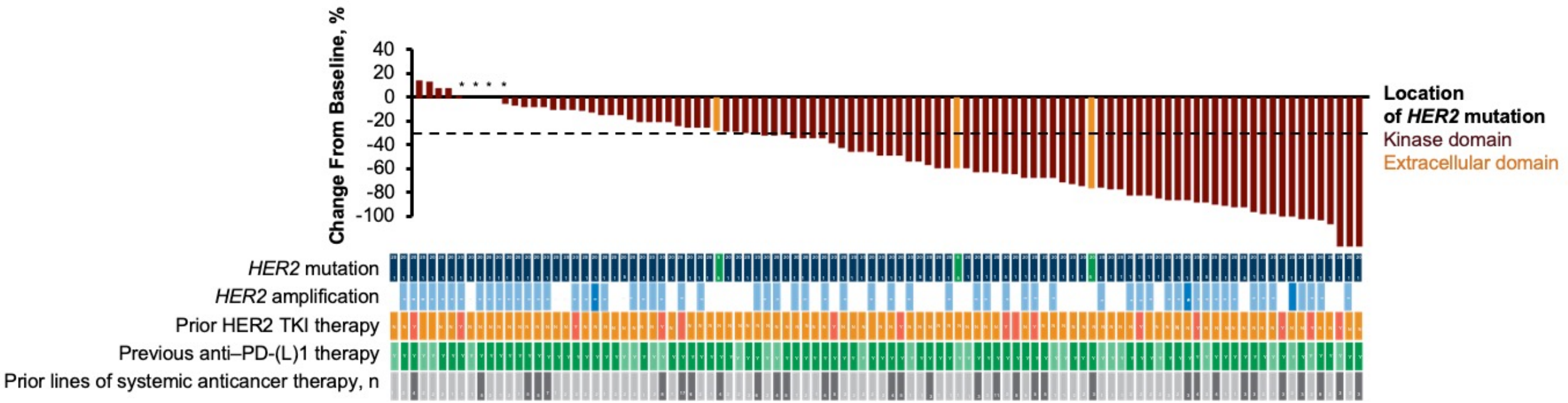
OS

Figure 4. Kaplan-Meier Plot of OS in the T-DXd 5.4 mg/kg and 6.4 mg/kg Arms



Janne P et al. ASCO 2024;Abstract 8543.

DESTINY-Lung02: Best Percentage Change in Tumor Size by BICR With T-DXd 5.4 mg/kg (N = 102)

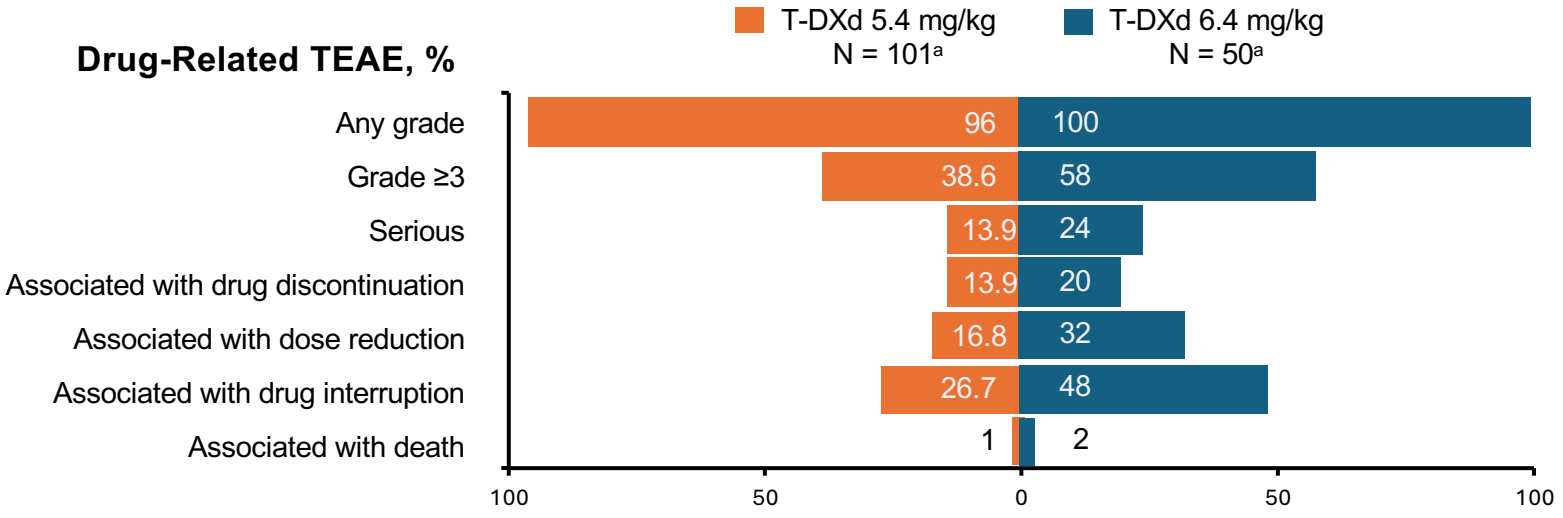


Responses were observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

Janne P et al. ASCO 2024;Abstract 8543.

DESTINY-Lung02: Overall Safety Summary

Overall Safety



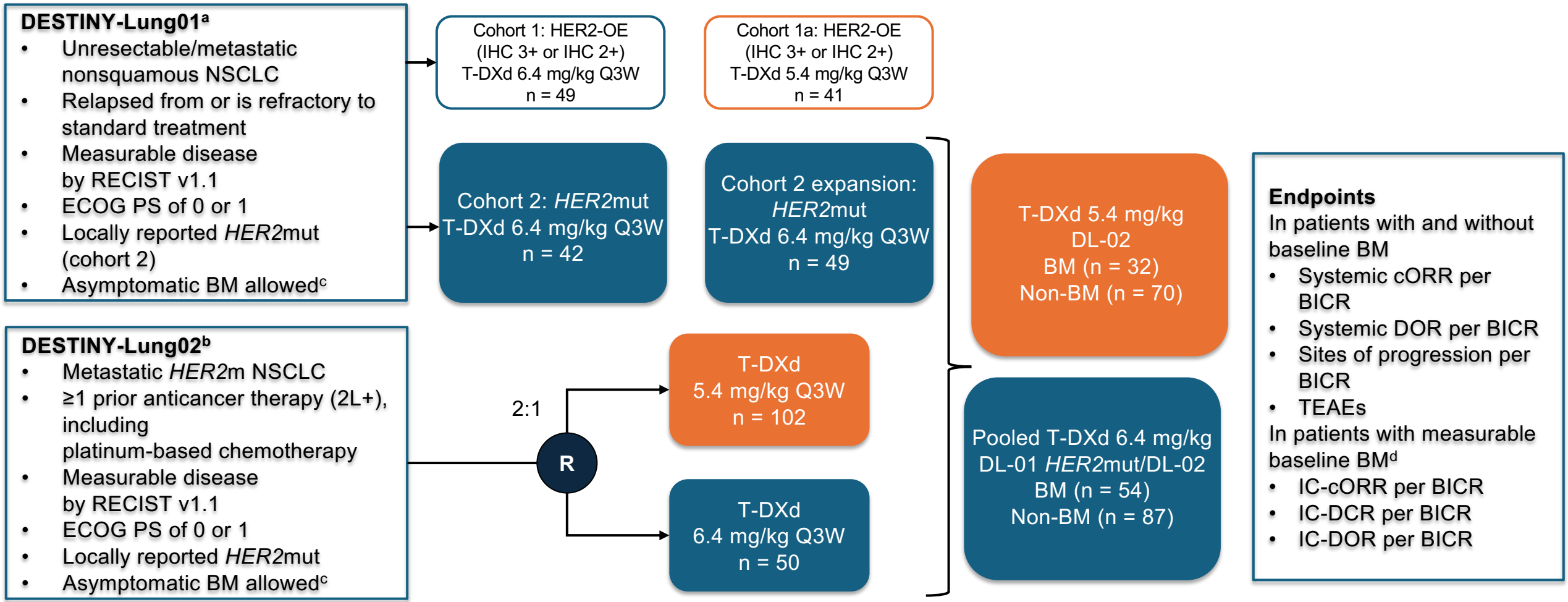
Adjudicated Drug-Related ILD

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)**
Grade 1	4 (4)	4 (8)
Grade 2	7 (6.9)	9 (18)
Grade 3	1 (1)	0
Grade 4	0	0
Grade 5	1 (1)	1 (2)

- **Median treatment duration** was 7.7 mo (range, 0.7-20.8) with T-DXd 5.4 mg/kg and 8.3 mo (range, 0.7-20.3) with T-DXd 6.4 mg/kg
- The **most common any-grade TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **nausea** (67.3% and 82.0%), **neutropenia** (42.6% and 56.0%), and **fatigue** (44.6% and 50.0%)
- The **most common grade ≥3 TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **neutropenia** (18.8% and 36.0%) and **anemia** (10.9% and 16.0%)

Janne P et al. ASCO 2024;Abstract 8543.

Exploratory Pooled Brain Metastases Analyses of DESTINY-Lung01 and DESTINY-Lung02



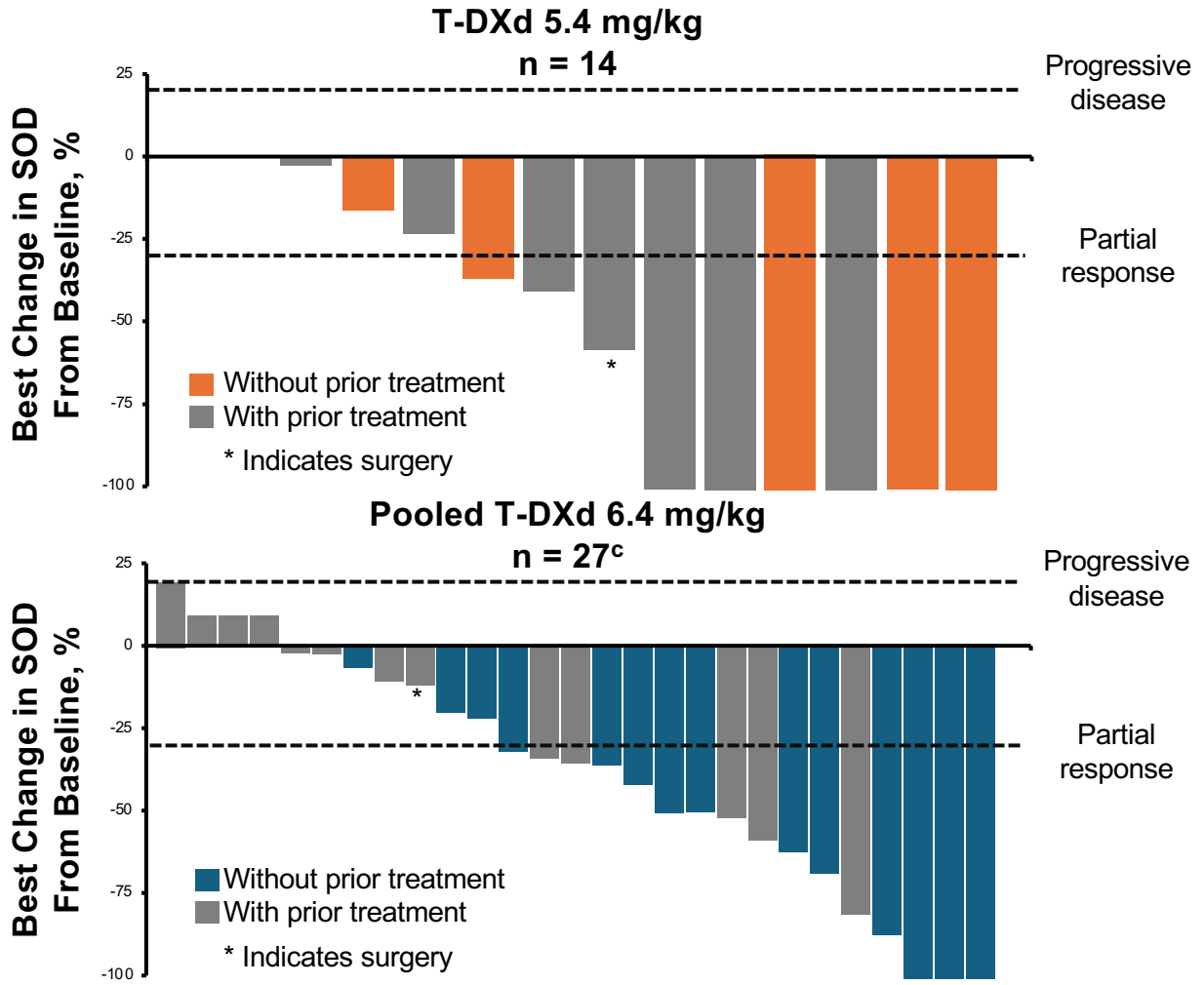
Planchard D et al. ESMO 2023;Abstract 1321MO.

DESTINY-Lung01 and DESTINY-Lung02: IC Objective Response Rates and Best Overall Response (BICR)

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)**	**9 (30)**
95% CI[b]	23-77	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30)
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, mo[d]		
Median (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response



[a] Denominator for percentage is the number of patients in the full analysis set who have at least 1 target lesion at baseline per BICR. [b] Based on the Clopper–Pearson method for single proportion. [c] For 1 patient deemed NE in the 6.4 mg/kg group, it was not possible to derive objective response due to missing data of 1 target lesion; the patient's best overall response however was calculated from available target lesion assessments and included in the waterfall plot. [d] Calculated as time from first response in brain until progression in brain. [e] Based on Kaplan–Meier analysis and computed with the Brookmeyer–Crowley method.

1. Li BT et al. ESMO 2023. Abstract 1321MO.

Planchard D et al. ESMO 2023;Abstract 1321MO.

DESTINY-Lung03: T-DXd Monotherapy in Pretreated HER2-overexpressing NSCLC

Patient population

- Aged ≥18 years
- Centrally assessed HER2-OE (IHC 3+/2+)* unresectable, locally advanced or metastatic nonsquamous NSCLC
- Measurable disease per RECIST v1.1
- WHO/ECOG performance status 0–1
- Patients in Part 1 had one or two prior lines of therapy; those with therapy-targetable alterations must have had prior appropriate targeted therapy

Part 1: dose escalation† (enrollment complete)

Arm 1A: T-DXd + durvalumab + cisplatin
Arm 1B: T-DXd + durvalumab + carboplatin

Part 1: T-DXd monotherapy (enrollment complete)

Arm 1D: T-DXd 5.4 mg/kg IV Q3W (N=36)

Part 3: dose confirmation and expansion (currently recruiting)

T-DXd + volrustomig ± carboplatin

Part 4: safety run-in and expansion (currently recruiting)

T-DXd + rilvegostomig ± carboplatin

Key endpoints: T-DXd monotherapy (arm 1D)

Secondary:

- ORR
- DOR
- DCR
- PFS

(Investigator assessed)

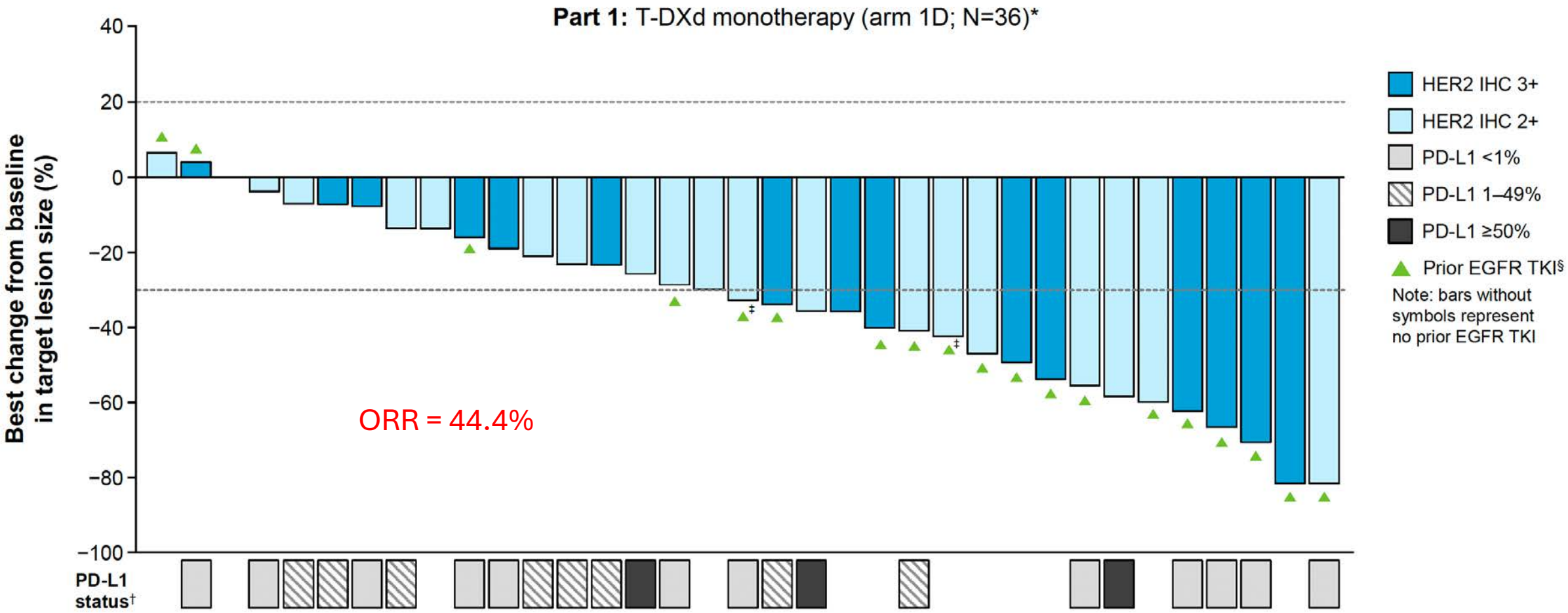
- OS
- Safety and tolerability

Exploratory:

- Efficacy outcomes by:
  - HER2 IHC status
  - Prior EGFR TKI exposure‡

Planchard D et al. WCLC 2024;Abstract OA16.05.

DESTINY-Lung03: T-DXd Monotherapy in Pretreated HER2-overexpressing NSCLC

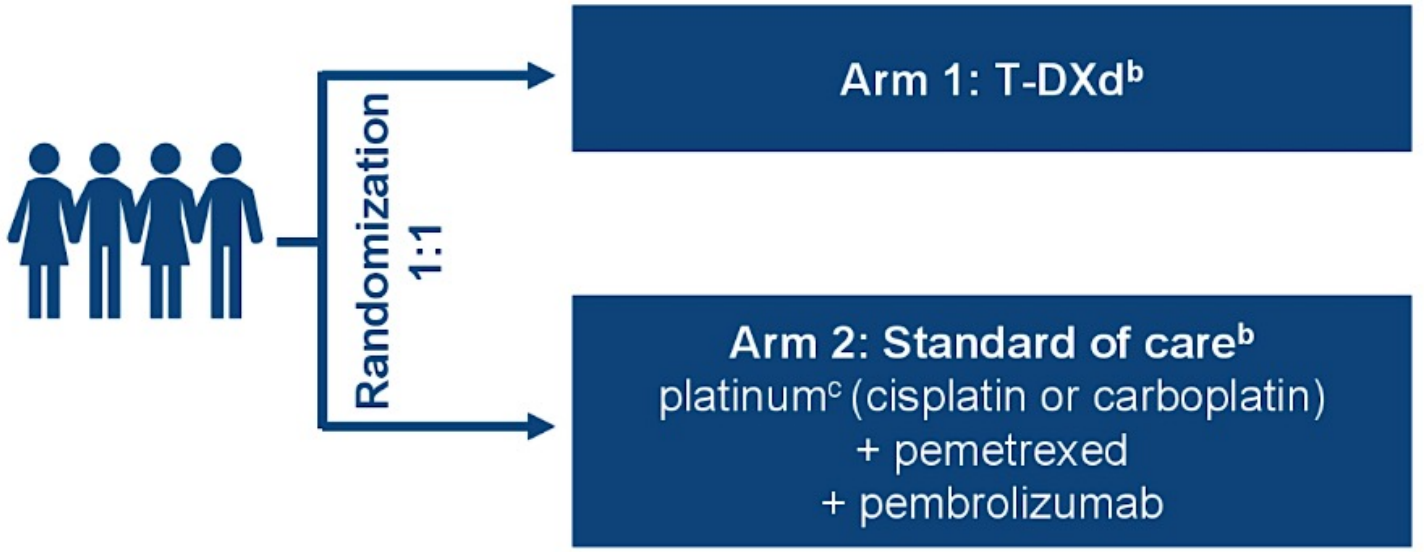


Planchard D et al. WCLC 2024;Abstract OA16.05.

DESTINY-Lung04: Study Design

Patient population (N≈264)

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

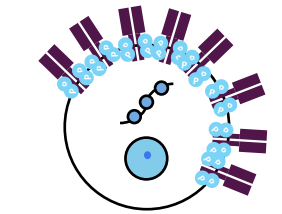


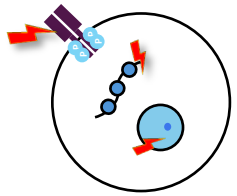
[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

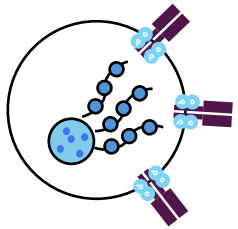
Li B et al. ASCO 2022;Abstract TPS9137.

c-Met

c-Met overexpression, MET ex 14 mutations and MET amplification







Alteration	*NSCLC Prevalence*	*Biological Effects*	*Test*	
c-Met Overexpression[1-3]	~25% *(NSQ EGFRwt)*	✓ Increased c-Met expression ✓ May result from other *MET* alterations (e.g., *MET*ex14 or *MET* amplification) X Not <u>always</u> an indicator of *MET* oncogenic dependency	IHC	***Teliso-V** (in development)[5]*
***MET* Mutations[1,4]** (e.g., *MET*ex14)	2-4%	✓ Reduced c-Met degradation, which may lead to c-Met expression ✓ Oncogenic signaling ✓ *MET* dependency	NGS PCR	***Approved MET TKI** (e.g., capmatinib, tepotinib)[6]*
***MET* Amplification[1,4]**	2-5%	✓ Increased c-Met expression ✓ Extended signaling ✓ *MET* dependency	NGS PCR FISH	***MET TKI** per NCCN Guidelines[6]*

<u>Target Domain</u>: Extracellular[4]

<u>MOA</u>: Toxin introduction to c-Met-expressing cells; Downregulation of signaling pathway also occurs, but cell death is not dependent on signal addiction[4]

<u>Target Domain</u>: Intracellular[4]

<u>MOA</u>: Anti-tumor activity in tumors dependent on or addicted to c-Met signaling[4]

FISH, fluorescence in situ hybridization; NGS, next generation sequencing; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.

1. Van Der Steen N, et al. *Cancers.* 2015;7, 556-573. 2. Lee et al. *Expert Opin Ther Targets.*2021;25(4):249-268. 3. Ansell PJ, et al. CRUK Lung Cancer Conference. Nov 15-17, 2022. Manchester. 4. Liang H, Wang M. *Onco Targets Ther* 2020; 13:2491–2510; 5. Wang J, et al. *BMC Cancer.*2016; 16:105. 6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V5.2023.

MET as a negative prognostic factor

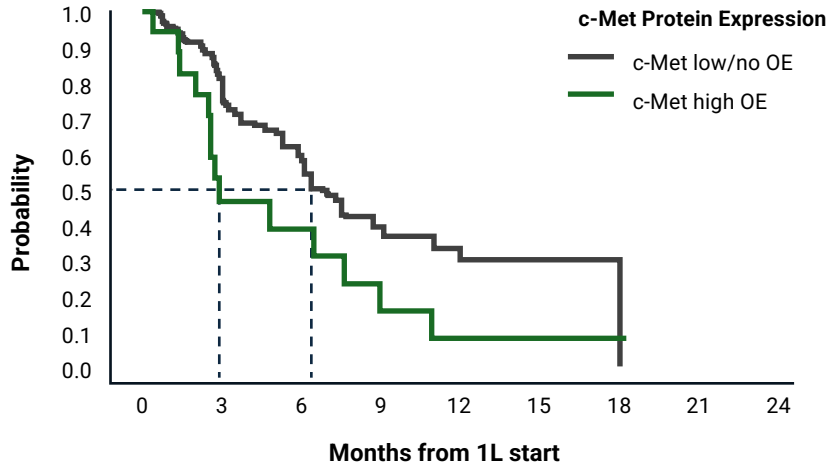
Archived tissue samples from patients with NSQ NSCLC at Caris Life Sciences™ and linked patient data from ConcertAI Real World Data 360® database were used to determine clinical outcomes among patients with 1L therapy and c-Met OE.

1L TTNT-D: Unadjusted and Adjusted KM Analysis by c-Met OE Status

	n	Events	Median	95% LCL	95% UCL
Unadjusted					
c-Met high OE	23	17	2.9	2.6	9.0
c-Met OE	27	19	3.0	2.6	9.0
c-Met low/no OE	124	71	4.2	3.3	6.1
Adjusted*					
c-Met high OE	17	14	2.9	2.6	10.9
c-Met OE	21	16	4.8	2.6	9.3
c-Met low/no OE	17	9	6.4	5.9	12.0

*Doubly robust multivariable Cox proportional hazard models considering propensity score weighting and adjustment of potential confounders were used to determine the association between c-Met IHC results and TTNT-D. The multivariate regression was adjusted for the following covariates: 1L regimen, PD-L1 status, ECOG at 1L initiation, age at 1L initiation, race, biological sex, smoking status, and presence of brain metastasis at 1L initiation.

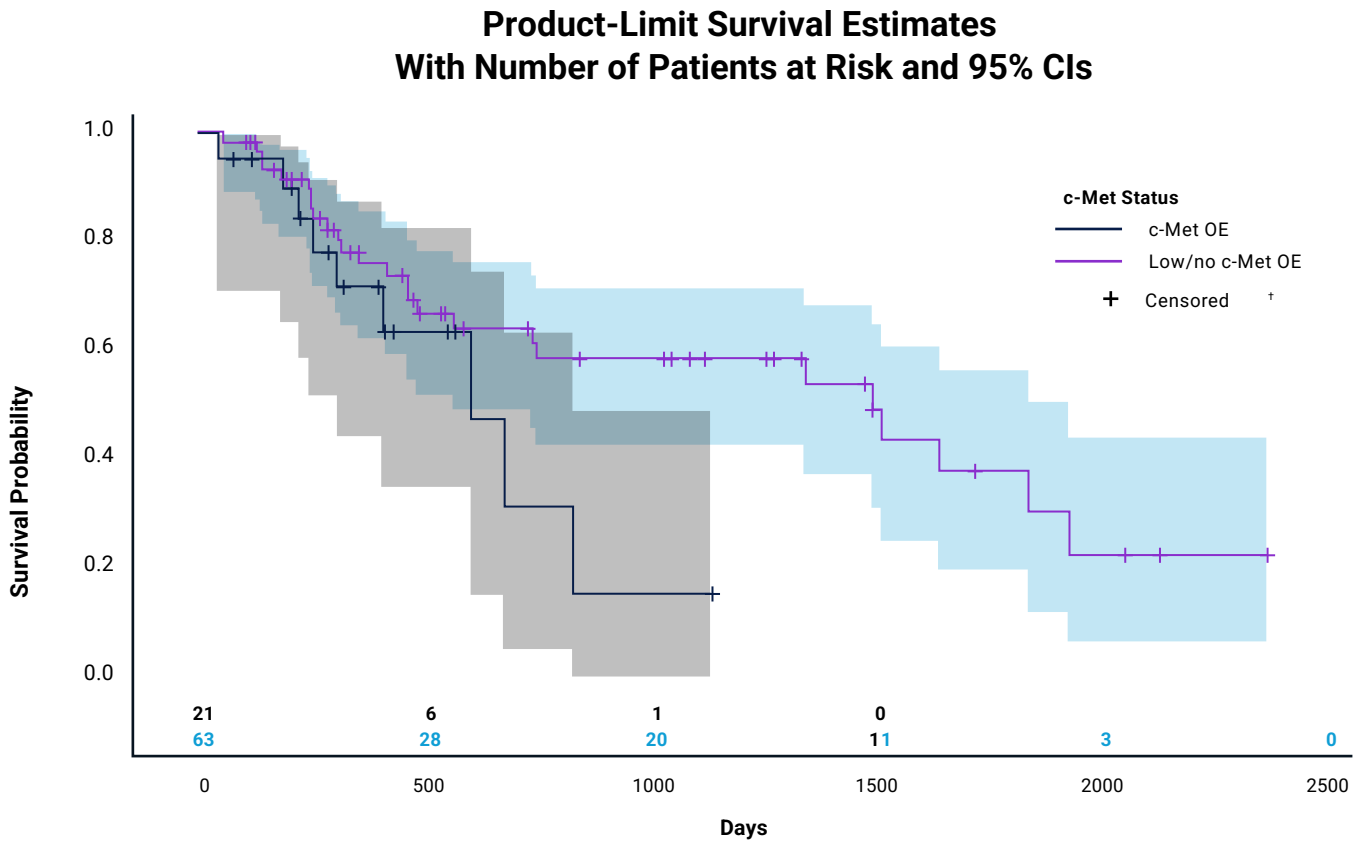
1L TTNT-D: Adjusted KM Analysis by c-Met OE Status*



Patients at Risk:									
c-Met low/no OE	17	11	7	4	2	0	0	0	0
c-Met high OE	17	7	5	2	1	1	1	0	0

1L=first line; ECOG=Eastern Cooperative Oncology Group; IHC=immunohistochemistry; KM=Kaplan-Meier; LCL=lower confidence limit; NSCLC=non-small cell lung cancer; NSQ=non-squamous; OE=overexpression; PD-L1=programmed death-ligand 1; PFS=progression-free survival; TTNT-D=time to next treatment or death; UCL=upper confidence limit. **1.** Le X, et al. METPRO: Evaluating prognostic value of c-Met protein overexpression and concurrent biomarker presence. Poster presented at: 2024 European Society for Medical Oncology (ESMO), 13–17 September, 2024; Barcelona, Spain [Ref DV-012467].

Poor Patient Prognosis by c-Met Overexpression



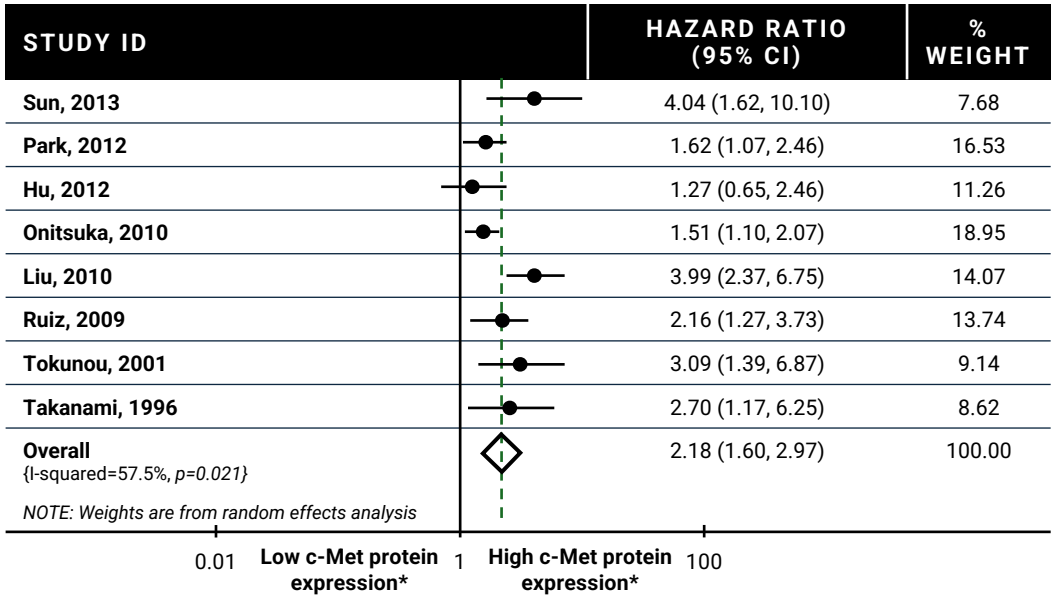
The unadjusted hazard ratio for death in patients with NSCLC and c-Met OE vs low/no c-Met OE was 2.04 (95% CI: 1.02, 4.10)

- Samples collected in 2016 or later. Patients receiving targeted therapy as first-line treatment were excluded. †Patients censored at clinical trial enrollment, last follow-up or development of a new primary lung cancer, whichever occurred first. CI=confidence interval; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; NSQ=non-squamous; OE=overexpression; SOC=standard of care; WT=wildtype. **1.** Bar J, et al. Prevalence, molecular characterization, and prognosis of MET-overexpressing non-small cell lung cancer (NSCLC) in a real-world patient cohort. Poster presented at: European Society for Medical Oncology (ESMO) 2023 Annual Congress, 20–24 October 2023, Madrid, Spain, and Online.

Negative Prognostic Impact of Elevated c-Met Protein Expression in NSCLC

- A study of 5516 patients with surgically resected NSCLC found that increased c-Met protein expression was significantly associated with poor OS[2]*
- Other meta-analyses have supported these findings and observed that increased c-Met expression was a prognostic indicator of shorter OS in patients with surgically resected stage IV NSCLC[3,4]*

Overall Survival in Patients with High vs Low c-Met Expression[2]*



- *Expression cutoffs varied across studies. CI=confidence interval; NSCLC=non-small cell lung cancer; OS=overall survival. **1.** Strickler JH, et al. *J Clin Oncol*. 2018;36(33):3298-3306. **2.** Guo B, et al. *PLoS One*. 2014;9(6):e99399. **3.** Ma G, et al. *Front Oncol*. 2019;9:1441. **4.** Pyo JS, et al. *Pathol Res Pract*. 2016;212(8):710-716.

Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Overexpressing Advanced Non-Small Cell Lung Cancer

D. Ross Camidge[1], Jair Bar[2], Hidehito Horinouchi[3], Jonathan Goldman[4], Fedor Moiseenko[5], Elena Filippova[6], Irfan Cicin[7], Penelope Bradbury[8], Nathalie Daaboul[9], Pascale Tomasini[10], Tudor Ciuleanu[11], David Planchard[12], Mor Moskovitz-Mutsafy[13], Nicolas Girard[14], Janet Jin[15], Martin Dunbar[15], Ellen Bolotin[15], Jim Looman[15], Christine Ratajczak[15], Shun Lu[16]

[1]University of Colorado Cancer Center, Aurora, CO, USA; [2]Sheba Medical Center, Ramat Gan, Israel; [3]National Cancer Center Hospital, Tokyo, Japan; [4]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [5]St. Petersburg City Cancer Center, St. Petersburg, Russia; [6]Center of Palliative Medicine De Vita, St. Petersburg, Russia; [7]Trakya University Medical Center, Edirne, Turkey; [8]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [9]CICM, Charles-LeMoyne Hospital, University of Sherbrooke, Quebec, QC, Canada; [10]Aix Marseille University, APHM, INSERM, CNRS, CRCM, Hôpital Nord, Multidisciplinary Oncology and Therapeutic Innovations Department, Marseille, France; [11]Institutul Oncologic, Cluj-Napoca, Romania; [12]Medical Oncology Department, Thoracic Group, Gustave Roussy, Villejuif, France; [13]Rambam Health Care Campus, Haifa, Israel; [14]Département d'Oncologie Médicale, Institut Curie, Paris, France; [15]AbbVie Inc, North Chicago, IL, USA; [16]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai, China.

American Society of Clinical Oncology (ASCO) Annual Meeting, June 3–7, 2022, Chicago, IL, USA, and Online

Telisotuzumab Vedotin (ABBV-399)

Structure:

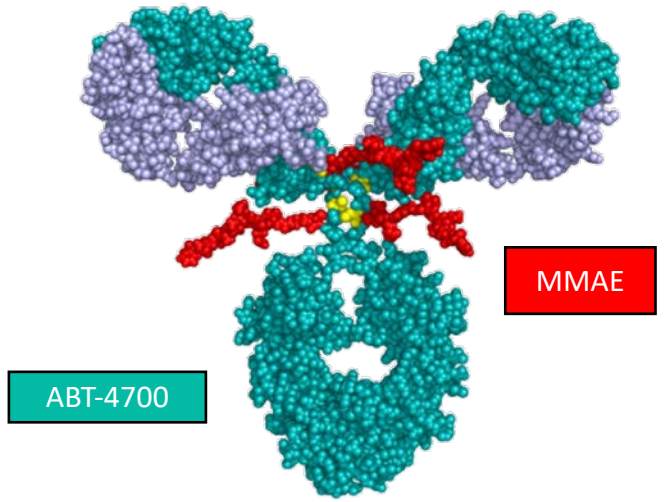
- ✓ Antagonist **anti–c-Met antibody** (ABT-700) **linked to cytotoxin** monomethyl auristatin E (MMAE) through a cleavable linker (VC), with an average drug:antibody ratio of approximately 3.1

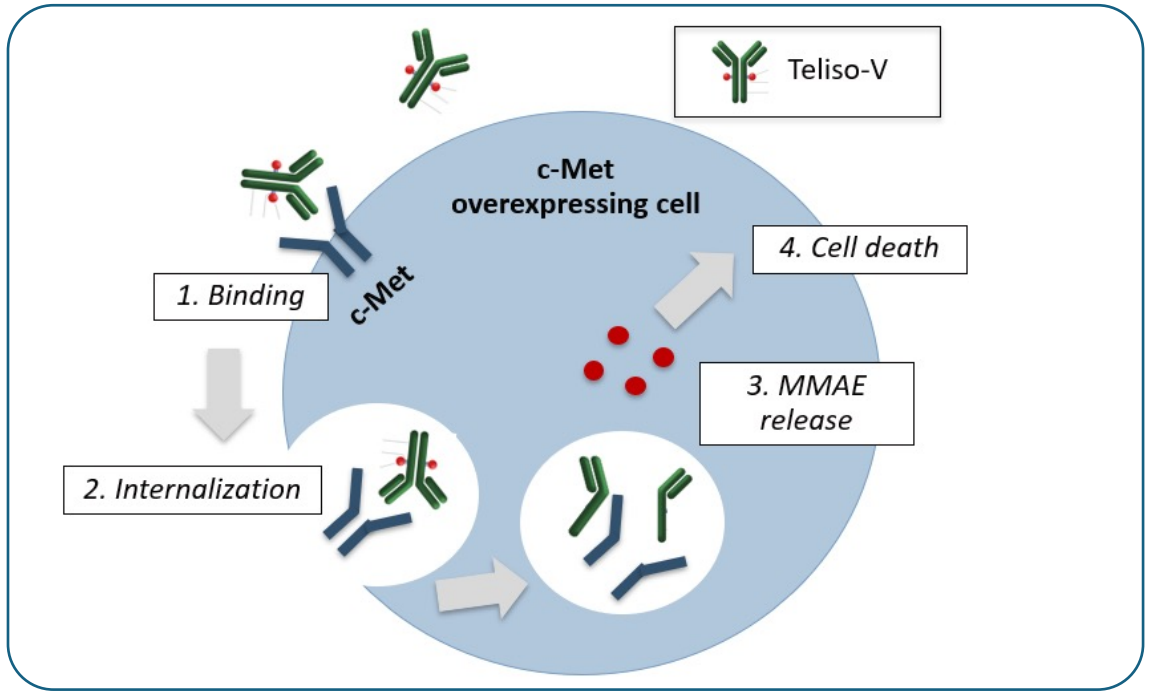
Target: c-Met

- ✓ Cell surface tyrosine kinase receptor that provides pro-survival and proliferation signaling
- ✓ Overexpressed in high proportion of select tumor types (NSCLC, H&N, gastric, esophageal)

Mechanism of Action:

- ✓ Targeted delivery of cytotoxin MMAE to cells via c-Met binding





ADC, antibody drug conjugate; c-Met, mesenchymal epithelial transition; H&N, head and neck.

Wang J, et al. *Clin Cancer Res*. 2017:15;23(4):992-1000.

c-Met

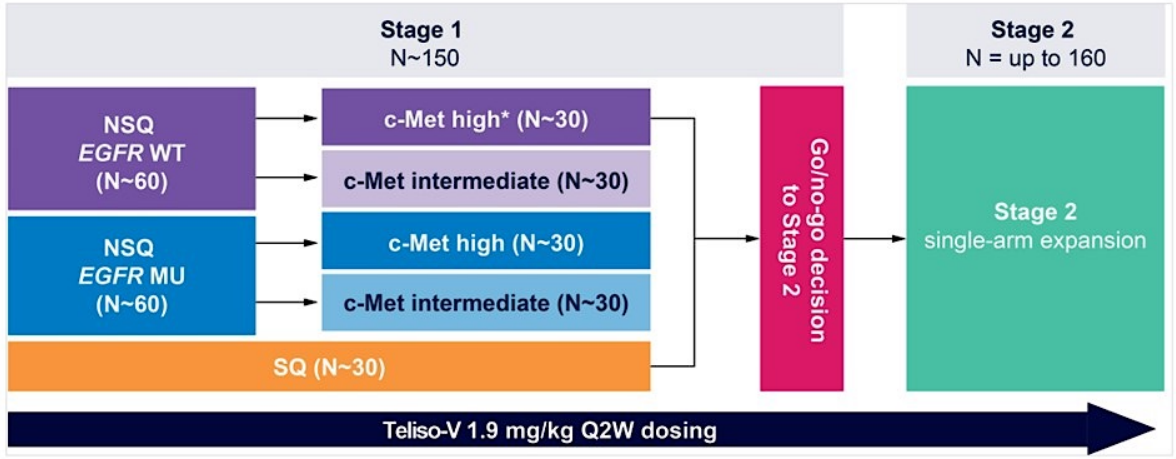
- c-Met protein overexpression (clinical trial assay for MET [SP44]) was defined as ≥25% tumor cells with 3+ staining intensity
  - c-Met high: ≥50%, 3+
  - c-Met intermediate: ≥25% to <50%, 3+

Study Design and Patient Characteristics

Objective: To identify the target c-Met OE NSCLC population(s) best suited for Teliso-V monotherapy in the 2L/3L setting, and then to expand the selected population(s) to further evaluate efficacy

Patient population: Patients with previously treated c-Met OE advanced/metastatic NSCLC

LUMINOSITY (Study M14-239) Design



*c-Met overexpression was defined for the NSQ cohort as ≥25% tumor cells at 3+ intensity (high, ≥50% 3+; intermediate, 25 to <50% 3+), and for the SQ cohort as ≥75% of tumor cells at 1+ intensity. *EGFR*, epidermal growth factor receptor; MU, mutant; NSQ, non-squamous; Q2W, every 2 weeks; Teliso-V, telisotuzumab vedotin; WT, wild-type.

- As of May 27, 2021, 136 patients with c-Met OE NSCLC were treated with Teliso-V; 130 were efficacy evaluable, of whom 122 patients had ≥12 weeks of follow-up (or had progressed or died before the first post-baseline assessment) and were evaluable for ORR

Patient Demographics and Clinical Characteristics

Characteristic	NSQ *EGFR* WT N=58	NSQ *EGFR* MU N=44	SQ N=28
Age, median [range]	64 [33, 81]	61.5 [36, 81]	66 [45, 76]
Sex			
Male, n (%)	41 (71)	19 (43)	17 (61)
ECOG performance status, n (%)			
0	11 (19)	15 (34)	4 (14)
1	46 (79)	29 (66)	24 (86)
2	1 (2)	0	0
Stage IV at study entry, n (%)	55 (95)	42 (95)	19 (68)
Number of prior systemic cancer therapies, median [range]	1 [1, 3]	2 [1, 4]	1.5 [1, 4]
Prior systemic cancer therapies, n (%)			
Microtubule inhibitor	19 (33)	4 (9)	22 (79)
EGFR TKI	0	43 (98)	1 (4)
Platinum based	56 (97)	38 (86)	28 (100)
Immune checkpoint inhibitor based	43 (74)	8 (18)	26 (93)
Platinum and immune checkpoint inhibitor based	42 (72)	8 (18)	26 (93)
c-Met inhibitor	4 (7)	0	0

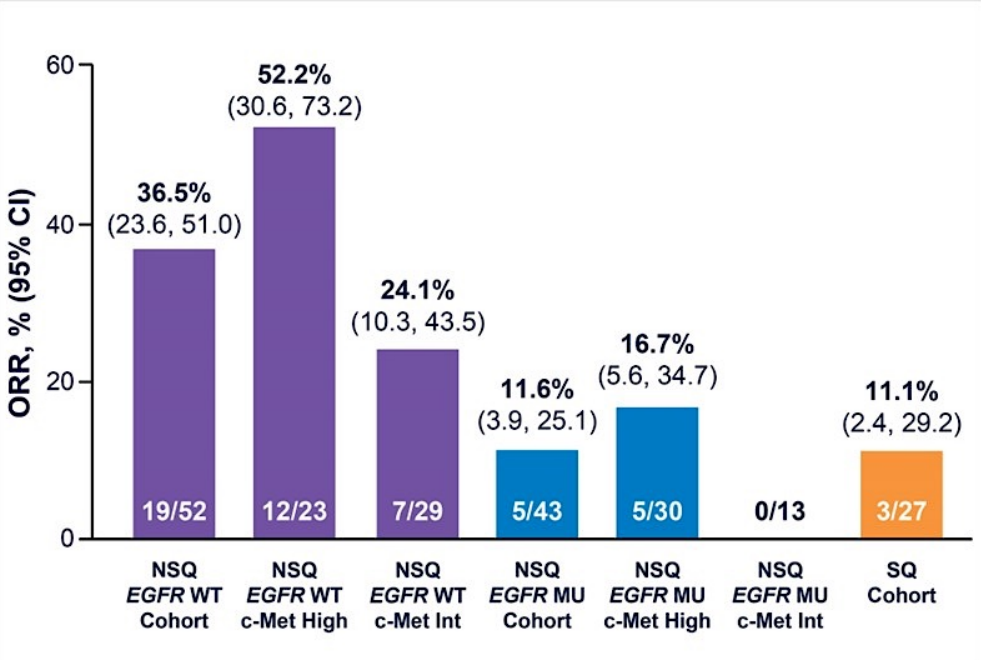
ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; MU, mutant; NSCLC, non-small cell lung cancer; NSQ, non-squamous; SQ, squamous; TKI, tyrosine kinase inhibitor; WT, wild-type.

2L, second-line; 3L, third-line; EGFR, epidermal growth factor receptor; MU, mutant; NSCLC, non-small cell lung caner; NSQ, non-squamous; OE, overexpressing; SQ, squamous; Teliso-V, telisotuzumab vedotin; WT, wild-type.

Camidge D et al. ASCO 2022;Abstract 9016.

Interim Efficacy

ORR per Central Review by Cohort/Group



CI, confidence interval; *EGFR*, epidermal growth factor receptor; Int, intermediate; MU, mutant; NSQ, non-squamous; ORR, overall response rate; SQ, squamous; WT, wild-type.

- The NSQ *EGFR* WT NSCLC cohort met protocol-specified criteria for expansion in Stage 2 at interim analysis 3. Updated data at the time of interim analysis 4 are shown
- The NSQ *EGFR* MU NSCLC cohort met protocol-specified criteria for futility at interim analysis 4. The SQ cohort met criteria for futility at the previous interim analysis; final data shown

DOR per Central Review by Cohort/Group

Cohort/Group	mDOR by ICR, No. of Events/No. of Responders, Months [95% CI]
NSQ *EGFR* WT	8/19, 6.9 [4.1, NR]
c-Met high	5/12, 6.9 [2.4, NR]
c-Met int	3/7, NR [4.1, NR]
NSQ *EGFR* MU	2/5, NR [3.0, NR]
c-Met high	2/5, NR [3.0, NR]
c-Met int	NA
SQ	2/3, 4.4 [3.0, NR]

CI, confidence interval; DOR, duration of response; *EGFR*, epidermal growth factor receptor; ICR, independent central review; int, intermediate; mDOR, median duration of response; MU, mutant; NA, not available; NR, not reached; NSQ, non-squamous; SQ, squamous; WT, wild-type.

Objective Response Rate per Central Review for Subgroups Defined by Prior Therapies: NSQ *EGFR* WT Cohort

Cohort/Group	Prior Platinum, n/N (%)	Prior Platinum and Immune Checkpoint Inhibitor, n/N (%)
NSQ *EGFR* WT	18/50 (36.0)	15/37 (40.5)
c-Met high	11/21 (52.4)	9/16 (56.3)
c-Met int	7/29 (24.1)	6/21 (28.6)

EGFR, epidermal growth factor receptor; int, intermediate; NSQ, non-squamous; WT, wild-type.

Molecular oncogene analyses in tumors of patients with available tissue are underway.

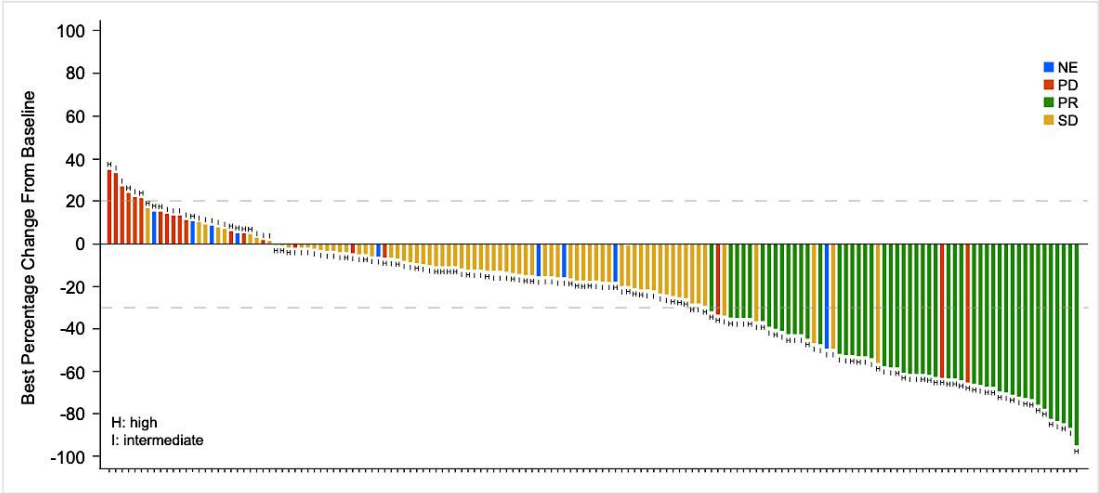
DOR, duration of response; EGFR, epidermal growth factor receptor; MU, mutant; NSCLC, non-small cell lung caner; NSQ, non-squamous; OE, overexpressing; ORR, overall response rate; SQ, squamous; Teliso-V, telisotuzumab vedotin; WT, wild-type.

Camidge D et al. ASCO 2022;Abstract 9016.

Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein–Overexpressing Non-Squamous *EGFR* Wildtype Advanced NSCLC: Updated Analysis of the LUMINOSITY Trial

Nicolas Girard[1], D. Ross Camidge[2], Jair Bar[3], Hidehito Horinouchi[4], Jonathan Goldman[5], Nathalie Daaboul[6], Chunling Liu[7], Irfan Çiçin[8], Nuran Katgi[9], Alona Zer[10], Tudor Ciuleanu[11], Niels Reinmuth[12], David Planchard[13], Aaron Mansfield[14], Shobhit Baijal[15], Nancy Zhang[16], Shilpen Patel[16], Summer Xia[16], Christine Ratajczak[16], Shun Lu[17]

Best Reductions in Target Lesions[a] per ICR (n=152)



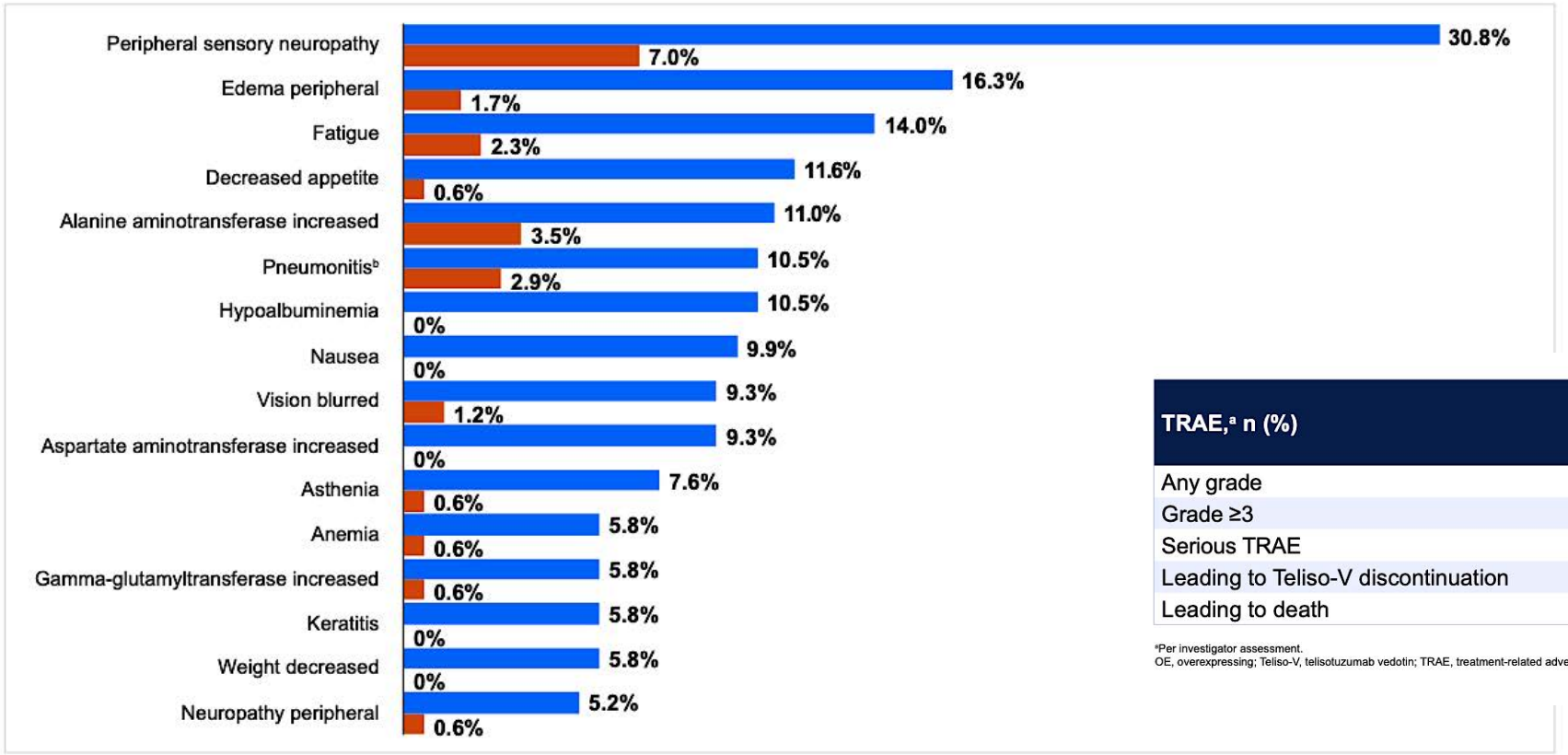
[a]Only patients who had measurable disease at baseline and who had at least 1 measurable post-baseline assessment were included in this analysis.
ICR, independent central review; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

- DCR was 59.5% for c-Met high, 58.3% for c-Met intermediate, and 58.9% for c-Met OE total

Girard et al. ELCC 2025.

Toxicity

TRAEs[a] Occurring in >5% of Patients



TRAE,[a] n (%)	c-Met OE Total (N=172)
Any grade	140 (81.4)
Grade ≥3	49 (28.5)
Serious TRAE	21 (12.2)
Leading to Teliso-V discontinuation	39 (22.7)
Leading to death	2 (1.2)

[a]Per investigator assessment.
OE, overexpressing; Teliso-V, telisotuzumab vedotin; TRAE, treatment-related adverse event.

[a]Per investigator assessment. [b]Pneumonitis events shown are those with a MedDRA preferred term of "pneumonitis" according to the investigative site reporting. TRAEs with a preferred term of "ILD" according to investigative site reporting were noted in 4 (2.3%) patients.
ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; TRAEs, treatment-related adverse events.

Girard et al. ELCC 2025.

Interim Safety and Efficacy

Summary of Treatment-Emergent Adverse Events

TEAEs, n (%)	Total N=136	
	Any Grade	Grade ≥3
Any TEAE	131 (96)	65 (48)
Most common any-grade TEAEs (≥10%)		
Peripheral sensory neuropathy	34 (25)	6 (4)
Nausea	30 (22)	1 (1)
Hypoalbuminemia	28 (21)	1 (1)
Peripheral edema	25 (18)	0
Blurred vision	25 (18)	1 (1)
Decreased appetite	24 (18)	0
Fatigue	22 (16)	5 (4)
Anemia	19 (14)	3 (2)
Dyspnea	19 (14)	4 (3)
Asthenia	18 (13)	3 (2)
Increased gamma-glutamyl transferase	18 (13)	3 (2)
Keratitis	18 (13)	0
Constipation	16 (12)	1 (1)
Cough	14 (10)	0
Diarrhea	14 (10)	0
Dizziness	14 (10)	0
Malignant neoplasm progression	14 (10)	11 (8)
Vomiting	14 (10)	1 (1)

*Per investigator assessment. TEAEs, treatment-emergent adverse events; Teliso-V, telisotuzumab vedotin.

Any TEAE related to Teliso-V*	104 (76)
Any serious TEAE	41 (30)
Any TEAE leading to Teliso-V discontinuation	45 (33)
Any TEAE leading to Teliso-V discontinuation possibly related to Teliso-V*	18 (13)
Any TEAE leading to death possibly related to Teliso-V*	2 (1)

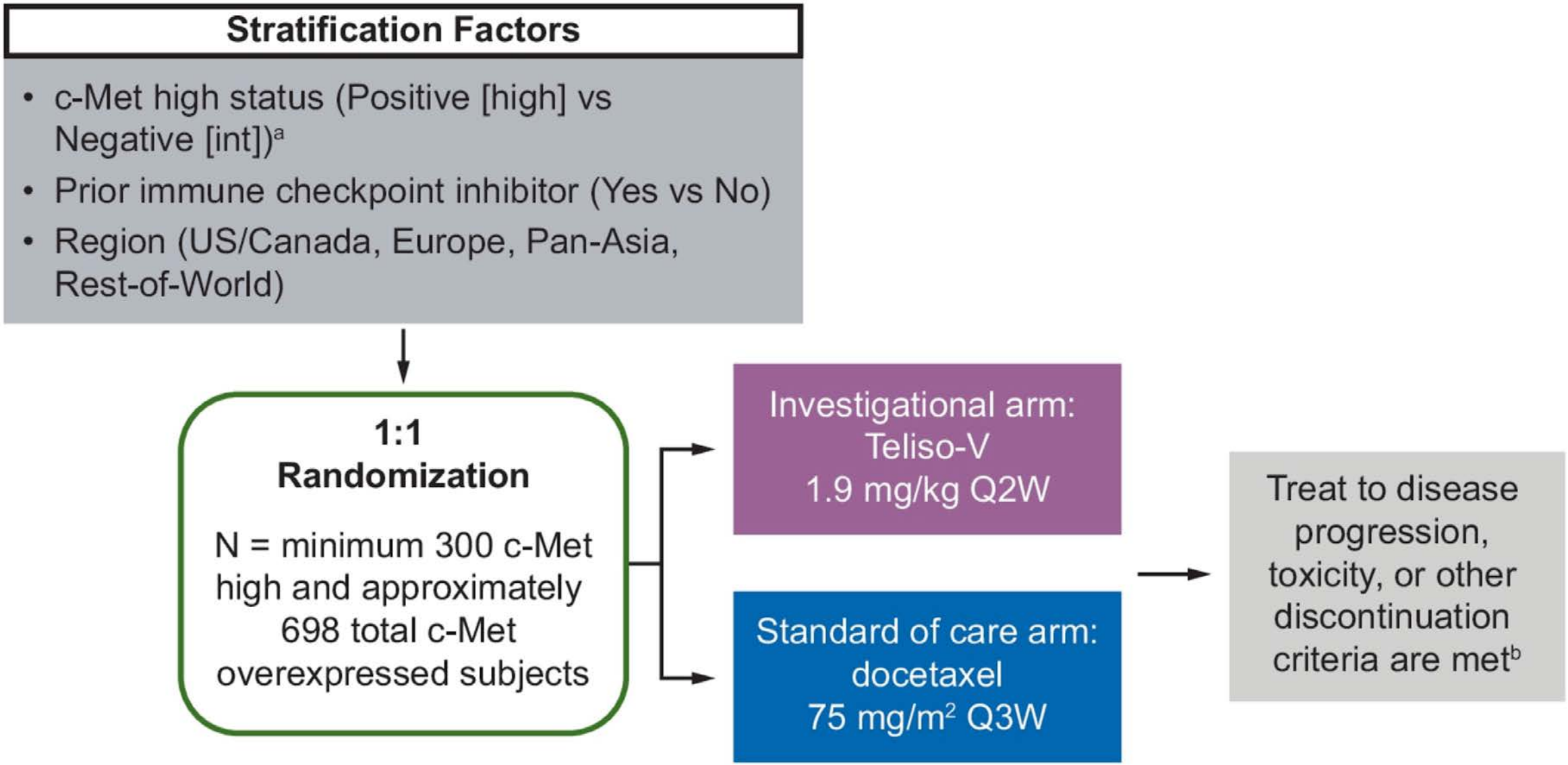
*Per investigator assessment.
TEAEs, treatment-emergent adverse events; Teliso-V, telisotuzumab vedotin.

- Treatment-emergent adverse events leading to death assessed by investigator as possibly related to Teliso-V were sudden death and pneumonitis, in 1 patient each. Both were in the squamous cohort
- Any-grade pneumonitis was reported in 9 patients (6.6%) and grade ≥3 pneumonitis was reported in 3 patients (2.2%)

*Per investigator assessment. TEAEs, treatment-emergent adverse events; Teliso-V, telisotuzumab vedotin.

Camidge D et al. ASCO 2022;Abstract 9016.

TeliMET NSCLC-01 Study Design



Lu S et al. ASCO 2024;Abstract TPS8656.

Faculty Case Presentations

Case Presentation – Dr Sands: 52-year-old woman

- 52 yr old woman presented to PCP with dry cough that had persisted for 1 year.
- CXR showed right lower lobe mass
- CT chest: 5.3 x 4.4 cm right lower lobe mass with right hilar adenopathy.
- PET showed RLL mass, hilar, mediastinal, and supraclavicular adenopathy as well as T10 vertebral body lesion.
- MRI brain showed 2 brain mets, which were treated with SRS prior to starting systemic therapy
- Started treatment on Carboplatin, pemetrexed, and pembrolizumab

Pathology:
metastatic adenocarcinoma
TTF-1 +, p40 rare +
negative for GATA-3, ER, PR, HER2).
ALK and ROS1 IHC negative
PD-L1 20%
EGFR exon 19 del/L858R negative from cfDNA.

Case Presentation – Dr Sands: 52-year-old woman (cont'd)

- About 8 months into systemic therapy, progression was noted in previously radiated brain mets. Treated with SRS again.
- About 9 months after starting systemic therapy, progression was noted in multiple sites throughout brain.
- Genomic testing showed RET fusion. Patient started LOXO-292 (selpercatinib).
- After >2 years on treatment, progression noted in multiple brain mets, underwent whole brain radiation.
- 6 months later, palliative radiation to C6 – T2.
- After >3 years LOXO-292, progression noted.

Case Presentation – Dr Sands: 52-year-old woman (cont'd)

- Genomics testing on sample from liver biopsy showed HER2 amplification, leading to IHC that was HER2 3+
- Started Trastuzumab deruxtecan with concurrent selpercatinib
- About 18 months of disease control was noted before progression seen on CT scans and evidence of leptomeningeal disease seen on MRI.

Genomics:

- Two copy deletion CDKN2A/B MTAP
- RET gain (supports presence of RET fusion with breakpoint in intron 11)
- ERBB2 amp (36 copies)

- HER2 IHC performed, 3+

Questions for the Faculty

In what line of therapy are you typically offering T-DXd for HER2-mutant NSCLC? What about HER2-overexpressing (IHC 3+) disease?

How often do you encounter patients like this one with HER2 mutations or HER2 overexpression and another actionable genomic alteration? How do you sequence T-DXd relative to other targeted therapies in those cases? How, if at all, does that vary based on the other biomarker that is present?

In your experience, how effective is T-DXd for patients with CNS metastases?

Questions for the Faculty

Are there scenarios in which you would recommend T-DXd in the first-line setting?

Are there scenarios in which you would recommend T-DXd for patients with HER2-amplified but not HER2-overexpressing NSCLC? What about HER2 IHC 1+ or 2+ disease?

Where do you see HER2-targeted tyrosine kinase inhibitors such as zongertinib fitting into the management of HER2-mutant NSCLC?

Case presentation – Prof Garassino

A 64-year-old man, with a 40-pack-year smoking history, who quit five years ago, presents with chest pain and dyspnea.

Computed tomography (CT) and positron emission tomography (PET) scans reveal a right lower lobe mass, mediastinal and hilar adenopathy, and hepatic lesions concerning for metastases.

CT guided biopsy of one of the hepatic lesions reveals non-small-cell lung cancer (NSCLC), adenocarcinoma histology.

Magnetic resonance imaging (MRI) of the brain is negative for metastases.

The PD-L1 tumor proportion score (TPS) is 50%.

This patient’s tumor is negative for EGFR mutations, ALK, ROS-1 or RET rearrangements, MET exon 14 skipping mutation, BRAF V600E mutation, or NTRK1/2/3 gene fusion. HER2 positive (IHC).

Patient started pembrolizumab single agent.

Case presentation – Prof Garassino (cont'd)

The patient progressed after 12 months on pembrolizumab with an initial response.

Started Trastuzumab deruxtecan 5.4 mg/Kg.

After a month, the patient developed ILD and was treated with steroids with some benefit.

Unfortunately, the patient had a deterioration of his general condition and died.

Questions for the Faculty

How do you prevent and manage gastrointestinal toxicities with T-DXd?

How do you screen for interstitial lung disease (ILD) in patients receiving T-DXd? How do you manage Grade 1 ILD? What about Grade 2 ILD? Will you rechallenge with T-DXd after ILD symptoms have resolved in either case?

How do you factor in the presence of coexisting cardiopulmonary morbidities (COPD, CAD) when making decisions about T-DXd, and how problematic are nonspecific pulmonary densities on imaging?

Questions for the Faculty

When and how do you test for c-Met overexpression in patients with NSCLC? How is "high c-Met overexpression" defined for the purposes of using telisotuzumab vedotin (teliso-V)?

In what line of therapy are you typically offering teliso-V for high c-Met-overexpressing NSCLC?

Would you offer teliso-V to a patient with lower c-Met expression under any circumstances?

What are the most common adverse events associated with teliso-V, and how do you monitor for and manage them?

Agenda

Module 1: Role of Immune Checkpoint Inhibitors in Metastatic Non-Small Cell Lung Cancer (NSCLC) without a Targetable Tumor Mutation — Prof Peters

Module 2: Targeted and Other Novel Therapeutic Strategies for Relapsed Metastatic NSCLC — Prof Garassino

Module 3: Potential Role of TROP2-Targeted Antibody-Drug Conjugates in Advanced NSCLC — Dr Sands

Module 4: Evolving Role of Immune Checkpoint Inhibitors in the Care of Patients with Nonmetastatic NSCLC — Dr Heymach

RTP RESEARCH TO PRACTICE

Potential Role for TROP2-Targeting ADCs In Advanced NSCLC

Jacob Sands, MD

May 2025

Trophoblast-Cell Surface Antigen 2 (TROP2)

- Initially discovered in human trophoblast and choriocarcinoma cells
- An intracellular calcium signal transducer overexpressed in various epithelial cancers
- Associated with poor prognosis in some data sets
- Not expressed in normal tissue
- Encoded by TACSTD2
- Role is not fully understood but thought to have a role in growth and proliferation of carcinoma cells
- Thought to be an oncogene with a role in initiating signaling mechanisms that can increase tumorigenicity, aggressiveness, and metastasis

Basu A, et al. Int J Cancer. 1995
Lipinski M, et al. Proc Natl Acad Sci U S A. 1981
Shvartsur A, et al. Genes Cancer. 2015
Wang J, et al. Mol Cancer Ther. 2008
Ohmachi, et al. *Clin Cancer Res*. 2006;12:3057

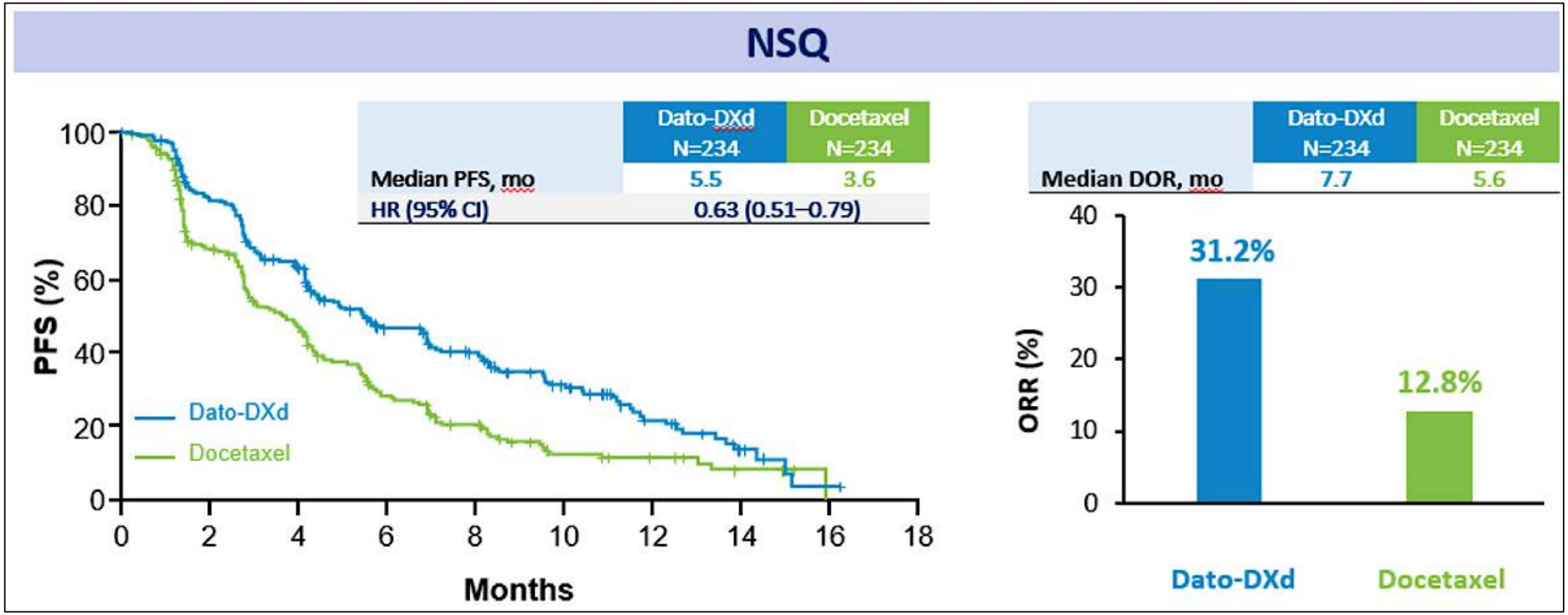
Trop2 Antibody-Drug Conjugates

	Datopotamab Deruxtecan	Sacituzumab Govitecan	Sacituzumab Tirumotecan
Antibody	Trop2	*Trop2	*Trop2
Linker	Hydrolyzable	Hydrolyzable	Hydrolyzable
Payload	+Exetecan derivative	+SN-38	+Belotecan derivative
DAR	4:1	7.6:1	7.4:1

* Same antibody
+ All are topoisomerase I inhibitor payloads

Datopotamab deruxtecan (Dato-DXd)

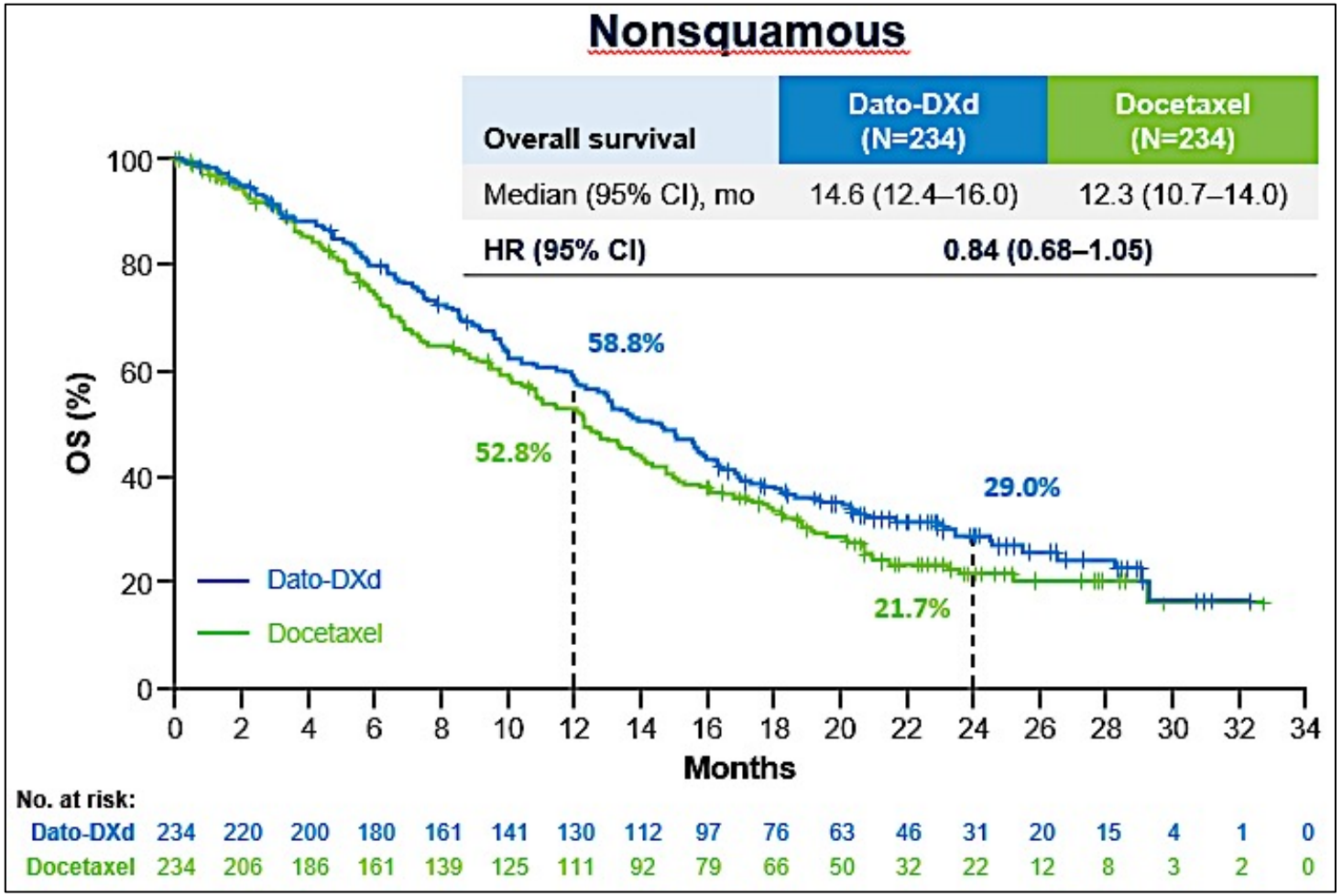
- TROPION Lung-01



Sands et al. WCLC 2024

Datopotamab deruxtecan (Dato-DXd)

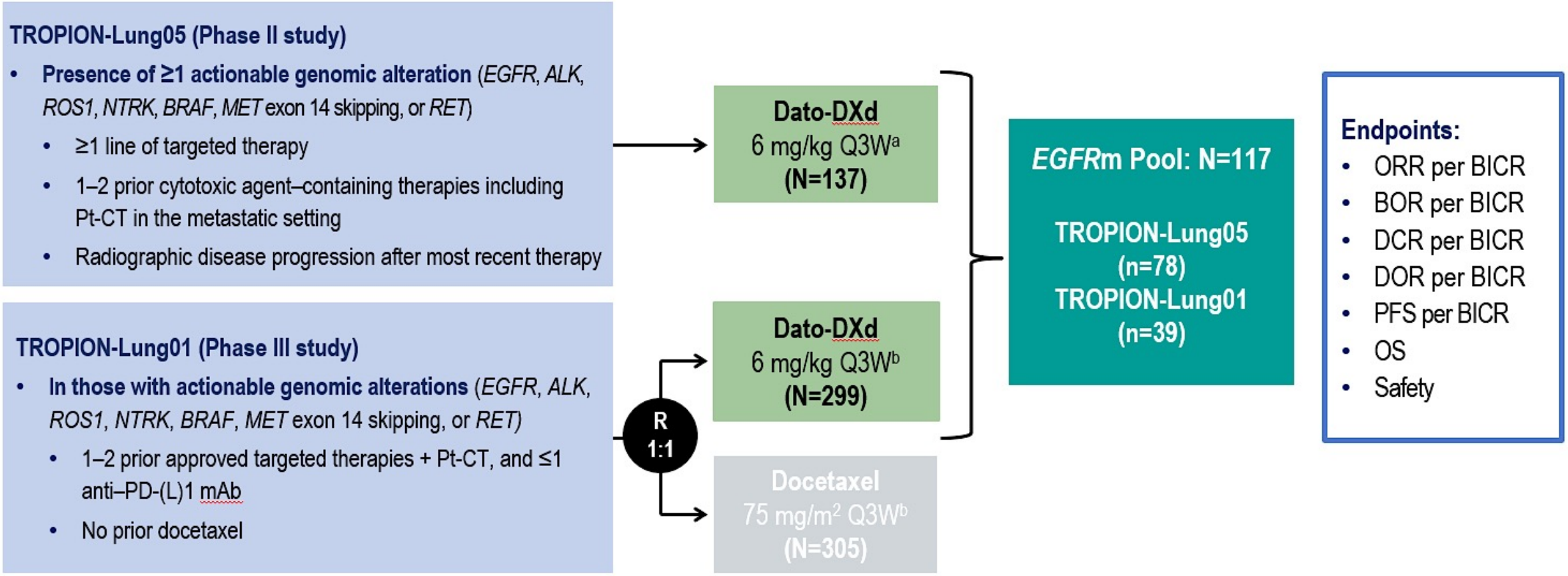
- In the setting of Actionable Genomic Alteration:
  - 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]);



Sands et al. WCLC 2024

Datopotamab deruxtecan (Dato-DXd)

- TROPION Lung-01 and TROPION Lung-05 Combined Cohort

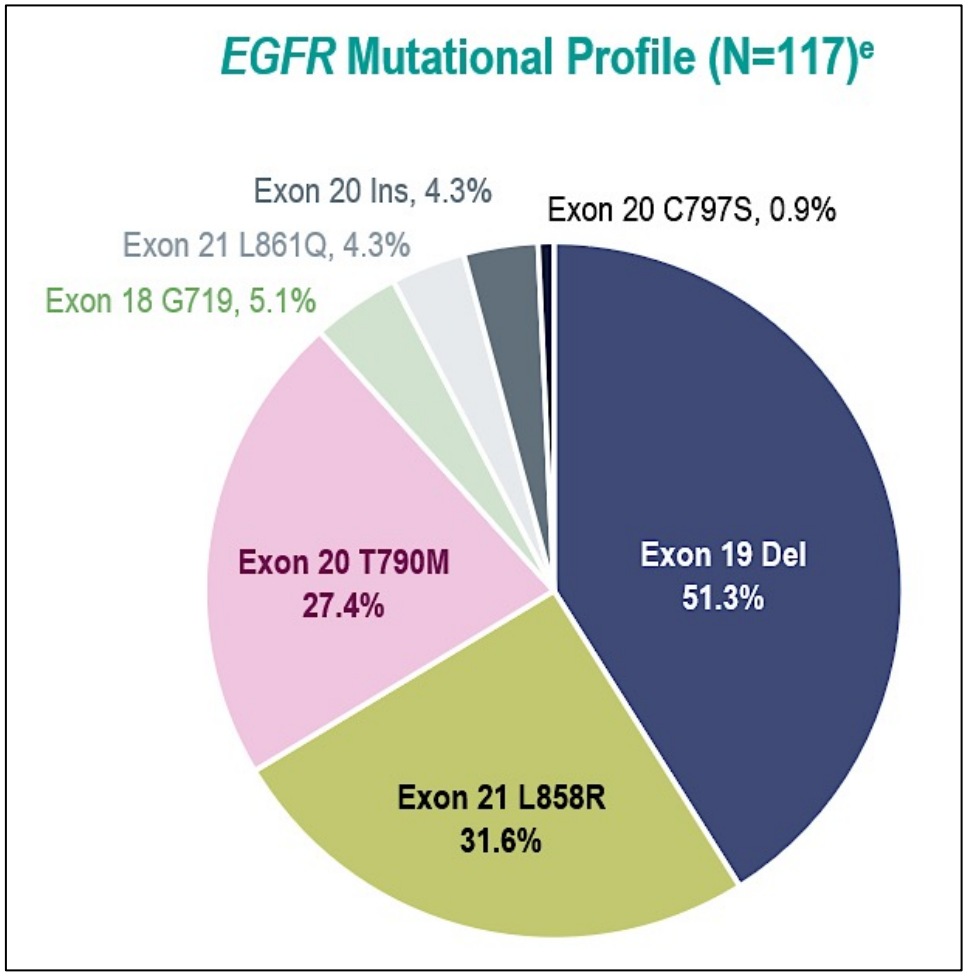


Ahn et al. ESMO Asia 2024

Datopotamab deruxtecan (Dato-DXd)

- TROPION Lung-01 and TROPION Lung-05 Combined Cohort

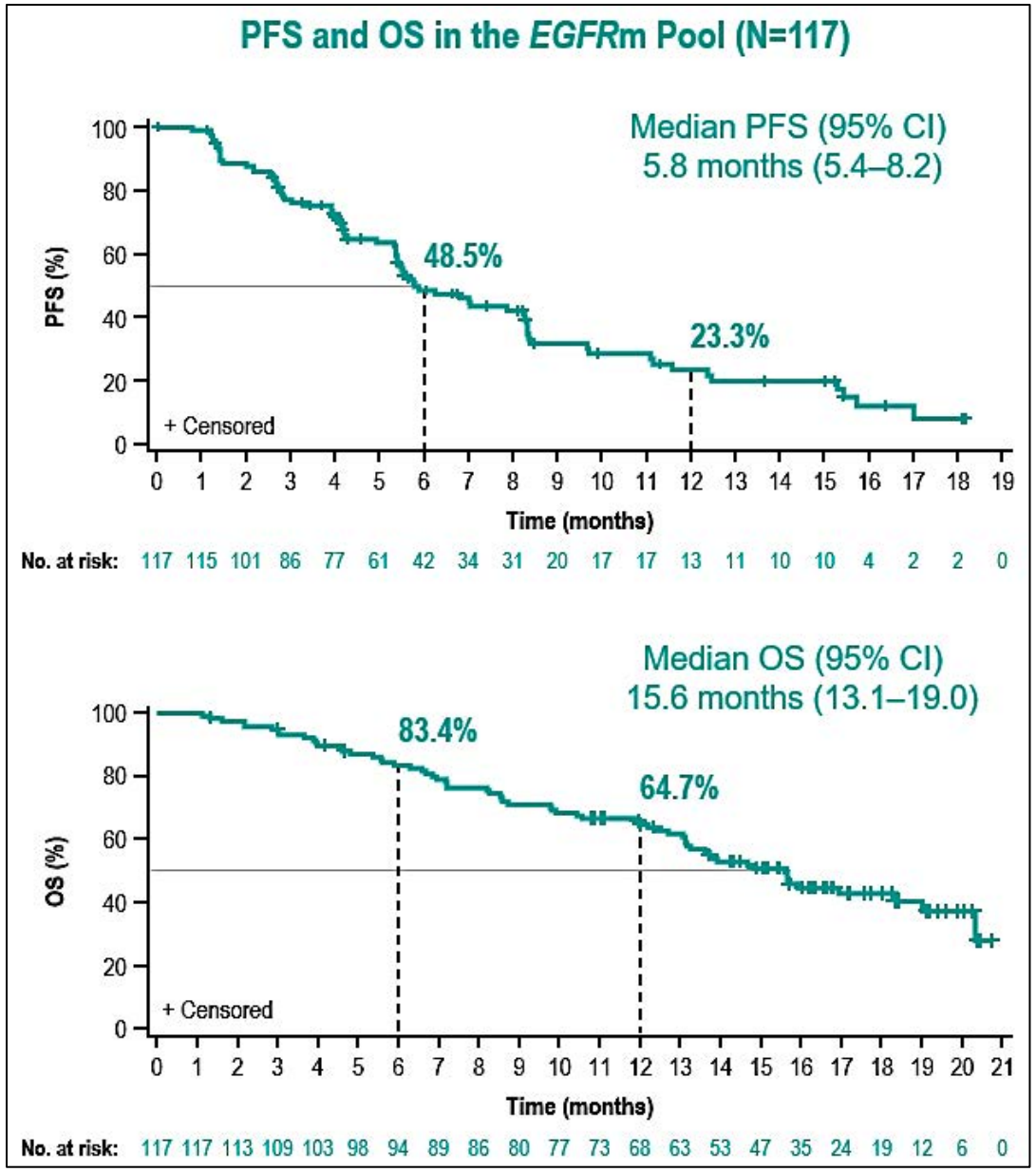
Characteristic, n (%)	*EGFR*m Pool (N=117)	TROPION-Lung05 (N=78)	TROPION-Lung01 (N=39)
Median age (range), years	63 (36–81)	63 (36–77)	62 (39–81)
Sex, female	73 (62.4)	52 (66.7)	21 (53.8)
Race			
Asian	81 (69.2)	55 (70.5)	26 (66.7)
White	27 (23.1)	20 (25.6)	7 (17.9)
Black or African American	1 (0.9)	0	1 (2.6)
Other/missing	8 (6.8)	3 (3.8)	5 (12.8)
ECOG PS			
0	39 (33.3)	24 (30.8)	15 (38.5)
1	78 (66.7)	54 (69.2)	24 (61.5)
Smoker[a]	55 (47.0)	34 (43.6)	21 (53.8)
Nonsquamous histology[b]	115 (98.3)	77 (98.7)	38 (97.4)
Brain metastasis at study entry	36 (30.8)	21 (26.9)	15 (38.5)
Median lines systemic therapy (range)[c]	3 (1–5)	3 (1–5)	2 (1–5)
Prior osimertinib[d]	96 (82.1)	61 (78.2)	35 (89.7)
First line	47 (40.2)	27 (34.6)	20 (51.3)
Second line	34 (29.1)	20 (25.6)	14 (35.9)



Ahn et al. ESMO Asia 2024

Datopotamab deruxtecan (Dato-DXd)

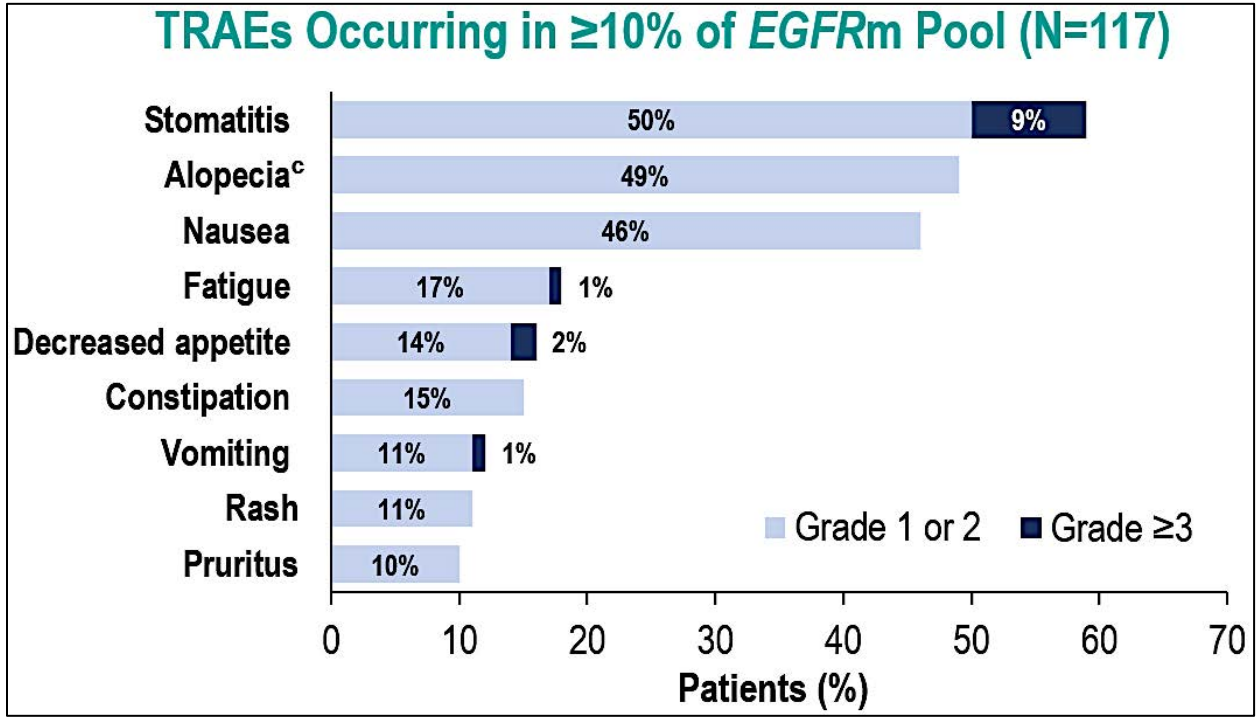
Response	*EGFR*m Pool (N=117)	Prior Osimertinib (N=96)
Confirmed ORR,[a] n (%) [95% CI]	50 (**42.7**) [33.6–52.2]	43 (**44.8**) [34.6–55.3]
BOR, n (%)		
CR	5 (**4.3**)	4 (**4.2**)
PR	45 (**38.5**)	39 (**40.6**)
SD	48 (41.0)	37 (38.5)
Non-CR/Non-PD	3 (2.6)	2 (2.1)
PD	12 (10.3)	10 (10.4)
NE	4 (3.4)	4 (4.2)
Median DOR, months (95% CI)	**7.0** (4.2–9.8)	**6.9** (4.2–9.8)
DCR,[b] n (%) [95% CI]	101 (**86.3**) [78.7–92.0]	82 (**85.4**) [76.7–91.8]
Median PFS, months (95% CI)	**5.8** (5.4–8.2)	**5.7** (5.4–7.9)
Median OS, months (95% CI)	**15.6** (13.1–19.0)	**14.7** (13.0–18.3)



Ahn et al. ESMO Asia 2024

Datopotamab deruxtecan (Dato-DXd)

	*EGFR*m Pool (N=117)
TRAEs, n (%)	111 (95)
Grade ≥3	27 (23)
Associated with dose reduction	26 (22)
Associated with dose delay	27 (23)
Associated with treatment discontinuation	6 (5)
Associated with death	0 (0)
Serious TRAEs	9 (8)
AESIs, n (%)	
Stomatitis/oral mucositis[a]	81 (69)
Grade 3[b]	11 (9)
Ocular surface events[a]	38 (32)
Grade 3[b]	3 (3)
Adjudicated drug-related ILD	5 (4)
Grade 3[b]	1 (1)



[b]No grade 4 or 5 events occurred

Ahn et al. ESMO Asia 2024

Datopotamab deruxtecan granted Priority Review in the US for patients with previously treated advanced EGFR-mutated NSCLC

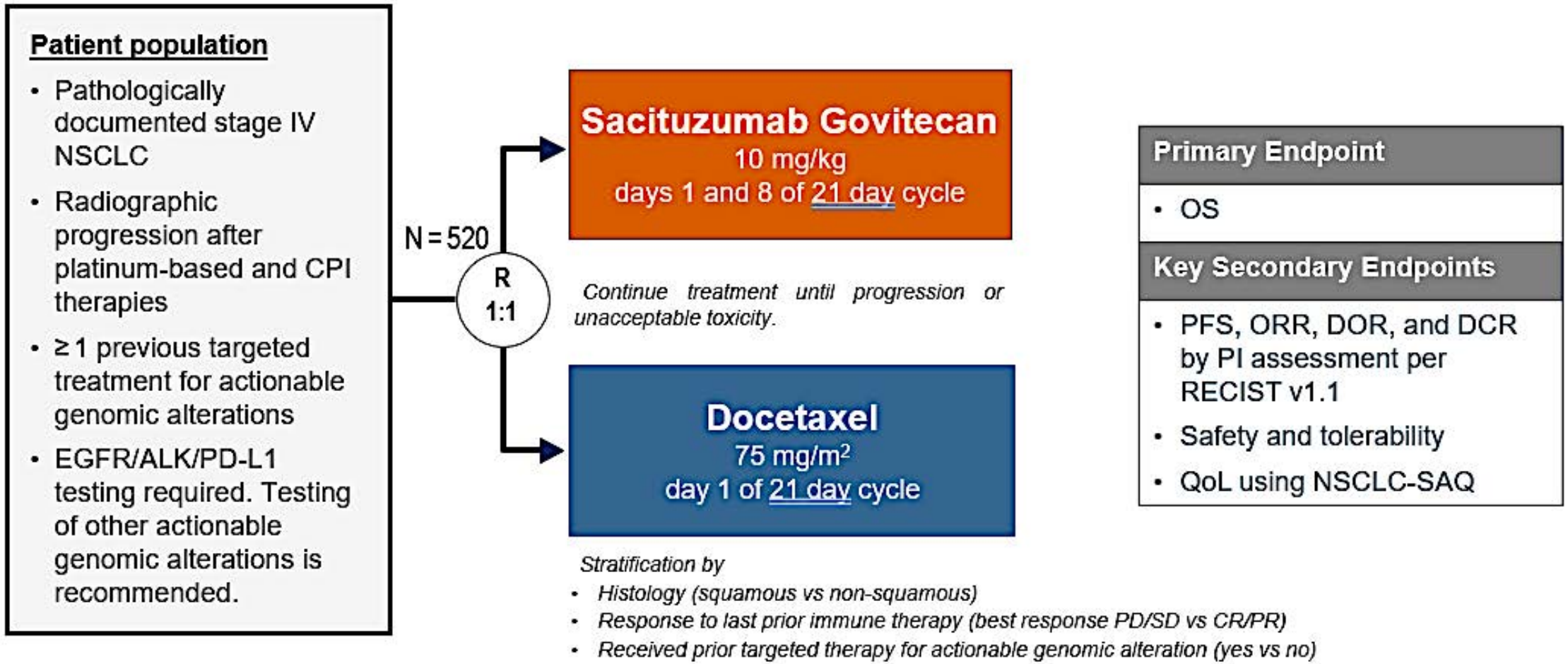
Press Release: January 13, 2025

The Biologics License Application (BLA) for datopotamab deruxtecan (Dato-DXd) has been accepted and granted Priority Review in the US for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) who have received prior systemic therapies, including an EGFR-directed therapy.

In a pooled analysis of patients with previously treated advanced or metastatic EGFRm NSCLC in the TROPION-Lung05 and TROPION-Lung01 trials presented at the European Society for Medical Oncology (ESMO) Asia 2024 Congress, datopotamab deruxtecan demonstrated a confirmed objective response rate (ORR) of 42.7% (95% confidence interval [CI] 33.6-52.2) as assessed by blinded independent central review (BICR) and a median duration of response (DoR) of 7.0 months (95% CI 4.2-9.8). The safety profile of datopotamab deruxtecan was consistent with previous reports from the TROPION-Lung05 and TROPION-Lung01 trials, with no new safety concerns identified.

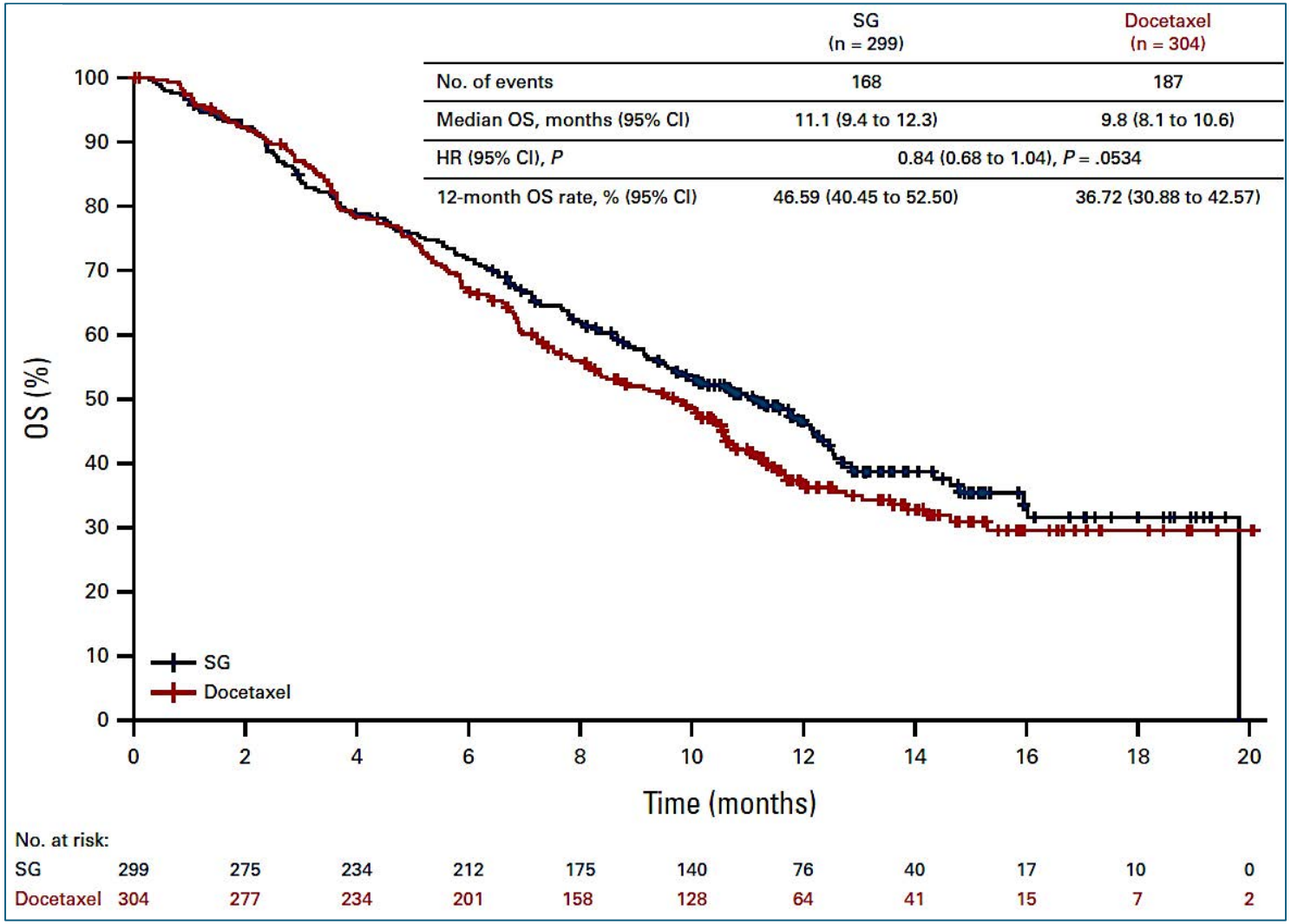
https://www.astrazeneca.com/media-centre/press-releases/2025/datopotamab-deruxtecan-granted-priority-review-in-the-us-for-patients-with-previously-treated-advanced-egfr-mutated-non-small-cell-lung-cancer.html#:~:text=AstraZeneca%20and%20Daiichi%20Sankyo's%20Biologics,small%20cell%20lung%20cancer%20(NSCLC)

Sacituzumab govitecan



Paz Ares et al. JCO 2024

Sacituzumab govitecan

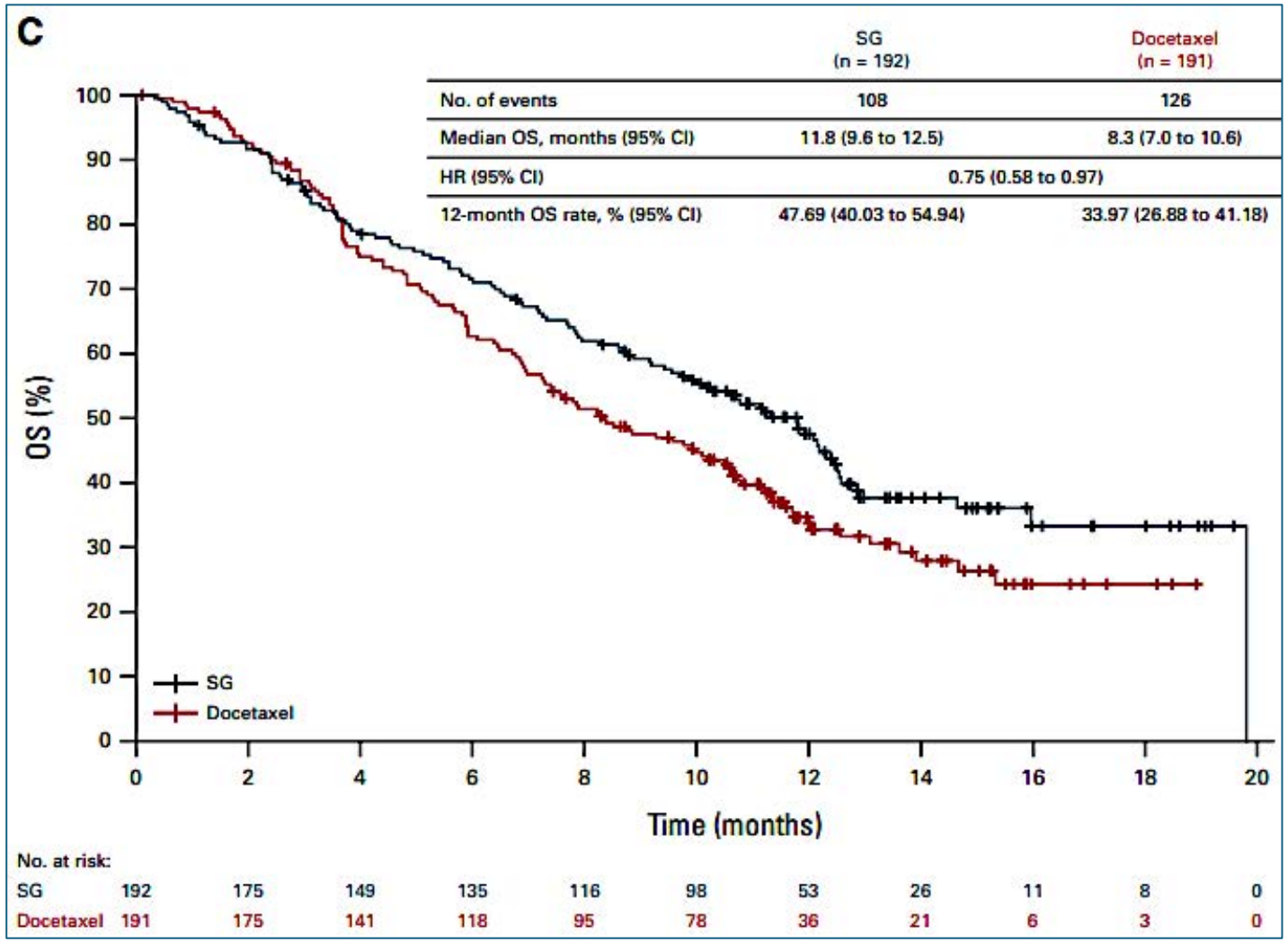


	Sacituzumab govitecan	Docetaxel
ORR	13.7%	18.1%
mDOR	6.7 mos	5.8 mos
mPFS	4.1 mos	3.9 mos
mOS	11.1 mos	9.8 mos

Paz Ares et al. JCO 2024

Sacituzumab govitecan

- Sub-group of those without response to prior line of immunotherapy (may also include chemo).



Paz Ares et al. JCO 2024

Event	SG (n = 296), No. (%)		Docetaxel (n = 288), No. (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAEs[a,b]	295 (99.7)	197 (66.6)	282 (97.9)	218 (75.7)
TEAEs reported in ≥10% in either group[c]				
Fatigue	168 (56.8)	37 (12.5)	161 (55.9)	28 (9.7)
Diarrhea	156 (52.7)	31 (10.5)	97 (33.7)	11 (3.8)
Alopecia	128 (43.2)	2 (0.7)	86 (29.9)	2 (0.7)
Nausea	123 (41.6)	5 (1.7)	75 (26.0)	3 (1.0)
Anemia	119 (40.2)	19 (6.4)	89 (30.9)	17 (5.9)
Neutropenia	111 (37.5)	73 (24.7)	123 (42.7)	106 (36.8)
Constipation	86 (29.1)	0	49 (17.0)	1 (0.3)
Decreased appetite	78 (26.4)	7 (2.4)	69 (24.0)	6 (2.1)
Vomiting	62 (20.9)	7 (2.4)	43 (14.9)	6 (2.1)
Cough	46 (15.5)	0	45 (15.6)	1 (0.3)
Dyspnea	42 (14.2)	4 (1.4)	51 (17.7)	13 (4.5)
Stomatitis	39 (13.2)	3 (1.0)	58 (20.1)	7 (2.4)
Leukopenia	38 (12.8)	15 (5.1)	63 (21.9)	50 (17.4)
Pruritus	37 (12.5)	1 (0.3)	11 (3.8)	0
Pyrexia	37 (12.5)	2 (0.7)	34 (11.8)	2 (0.7)
Back pain	33 (11.1)	2 (0.7)	19 (6.6)	2 (0.7)
Abdominal pain	31 (10.5)	3 (1.0)	14 (4.9)	0
Arthralgia	30 (10.1)	2 (0.7)	29 (10.1)	1 (0.3)
Rash	30 (10.1)	0	19 (6.6)	0
Febrile neutropenia	23 (7.8)	23 (7.8)	29 (10.1)	27 (9.4)
Lymphopenia	23 (7.8)	9 (3.0)	31 (10.8)	12 (4.2)
Peripheral edema	16 (5.4)	0	35 (12.2)	4 (1.4)
Dysgeusia	14 (4.7)	0	30 (10.4)	0
Peripheral neuropathy	11 (3.7)	0	38 (13.2)	2 (0.7)
Treatment-related[c]	279 (94.3)	156 (52.7)	262 (91.0)	173 (60.1)

Paz Ares et al. JCO 2024

Event	SG (n = 296), No. (%)		Docetaxel (n = 288), No. (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAEs[a,b]	295 (99.7)	197 (66.6)	282 (97.9)	218 (75.7)
TEAEs reported in ≥10% in either group[c]				
Fatigue	168 (56.8)	37 (12.5)	161 (55.9)	28 (9.7)
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Cough	46 (15.5)	0	45 (15.6)	1 (0.3)
Dyspnea	42 (14.2)	4 (1.4)	51 (17.7)	13 (4.5)
Stomatitis	39 (13.2)	3 (1.0)	58 (20.1)	7 (2.4)
Leukopenia	38 (12.8)	15 (5.1)	63 (21.9)	50 (17.4)
Pruritus	37 (12.5)	1 (0.3)	11 (3.8)	0
TEAEs leading to discontinuation	29 (9.8)		48 (16.7)	
Treatment-related[c]	20 (6.8)		41 (14.2)	
TEAEs leading to death	10 (3.4)		13 (4.5)	
Treatment-related[d]	4 (1.4)		3 (1.0)	
TEAEs leading to dose reduction	87 (29.4)		112 (38.9)	
TEAEs leading to treatment interruption	171 (57.8)		81 (28.1)	
Peripheral neuropathy	11 (3.7)	0	38 (13.2)	2 (0.7)
Treatment-related[c]	279 (94.3)	156 (52.7)	262 (91.0)	173 (60.1)

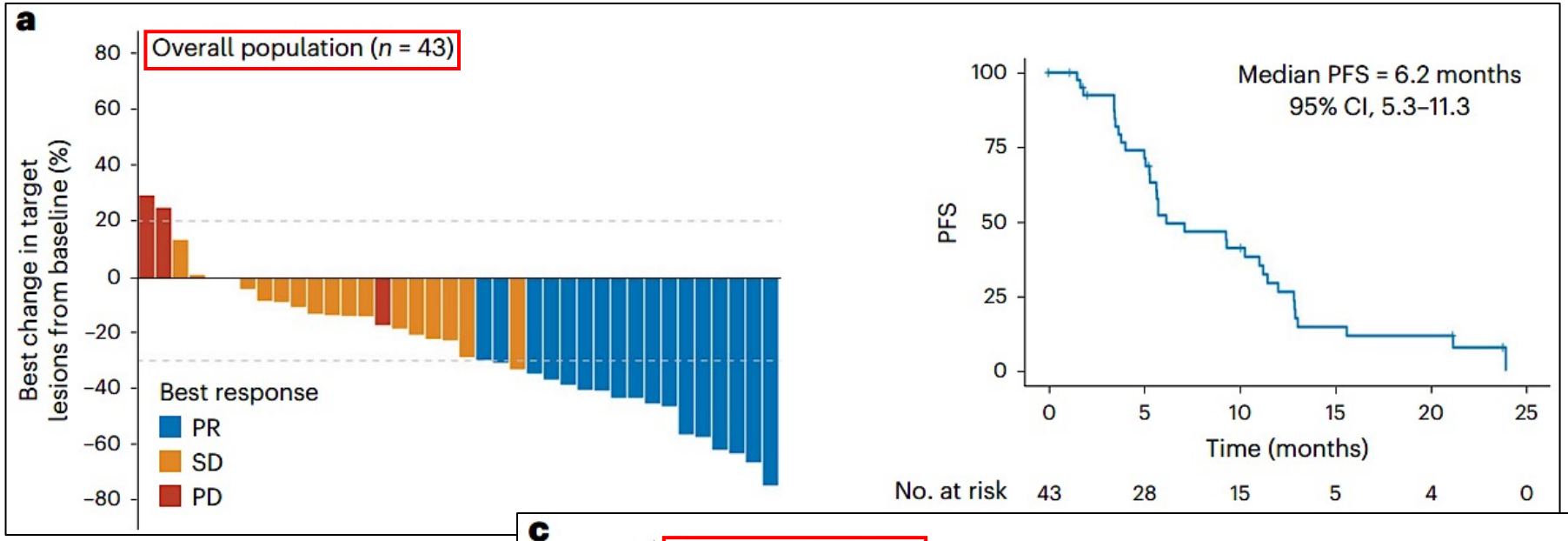
Paz Ares et al. JCO 2024

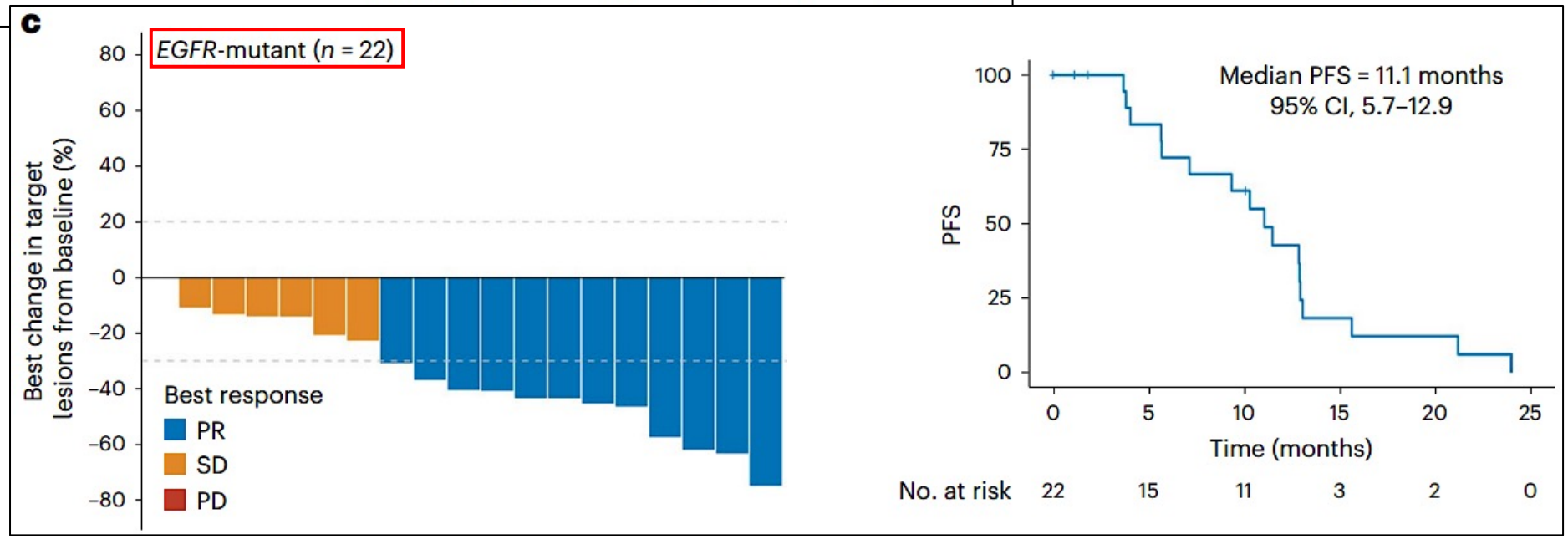
Sacituzumab tirumotecan (Sac-TMT)

	KL264-01 cohort 3A			SKB264-II-08 cohort 1	SKB264-II-08 cohort 2
	Overall (*n*=43)	*EGFR*-WT (*n*=21)	*EGFR*-mutant (*n*=22)	Overall (*n*=32)	Overall (*n*=32)
EGFR primary mutation, *n* (%)[a]					
Exon 19 deletion	–	–	10 (45)	20 (63)	17 (53)
Exon 21 L858R	–	–	8 (36)	10 (31)	15 (47)
Others[b]	–	–	2 (9)	2 (6)	0
Unknown	–	–	2 (9)	0	0
Previous lines of therapy, *n* (%)					
Median (range)	2 (1–10)	2 (1–10)	2 (1–7)	3 (1–5)	1 (1–2)
1	13 (30)	7 (33)	6 (27)	3 (9)	23 (72)
2	14 (33)	7 (33)	7 (32)	11 (34)	9 (28)
≥3	16 (37)	7 (33)	9 (41)	18 (56)	0
Previous systemic therapy, *n* (%)					
Platinum-based chemotherapy	33 (77)	21 (100)	12 (55)	32 (100)	0
Immunotherapy	23 (53)	21 (100)	2 (9)	0	0
3rd generation EGFR TKI	14 (33)	0	14 (64)	28 (88)	28 (88)

Zhao et al. Nature Medicine 2025

Sacituzumab tirumotecan (Sac-TMT)





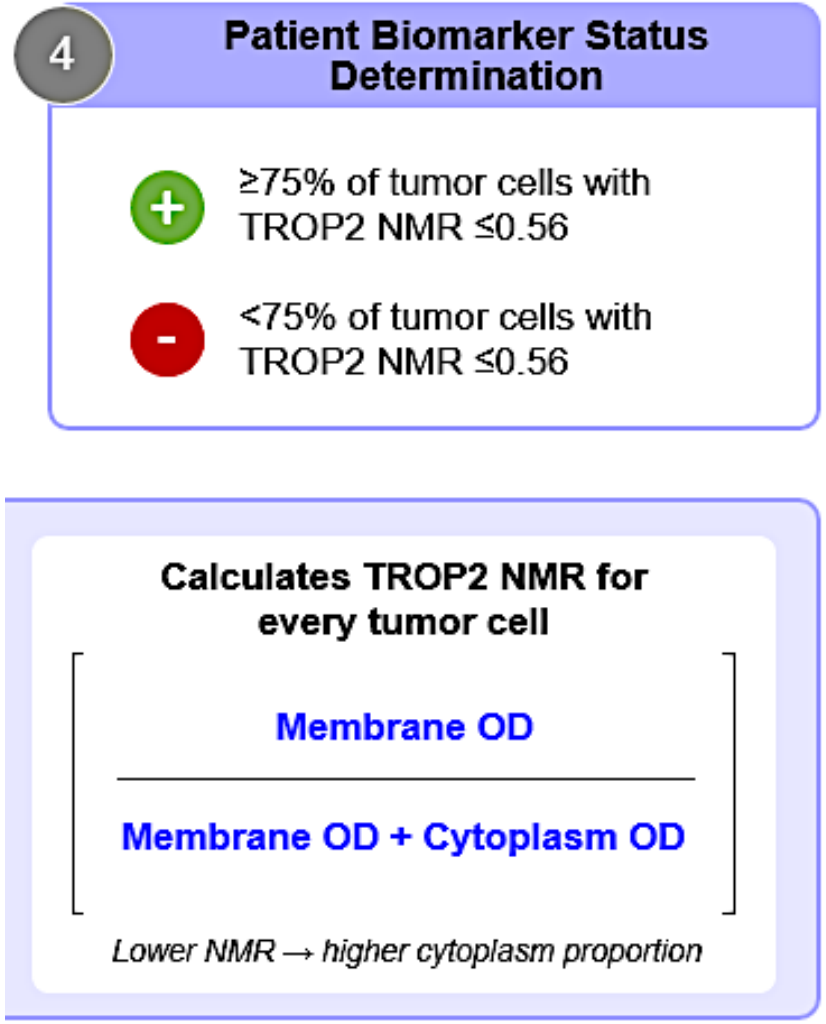
Zhao et al. Nature Medicine 2025

n (%)	KL264-01 cohort 3A (*n*=43)		SKB264-II-08 cohort 1 (*n*=32)		SKB264-II-08 cohort 2 (*n*=32)		Combined (*n*=107)	
	Any-grade	Grade ≥3	Any-grade	Grade ≥3	Any-grade	Grade ≥3	Any-grade	Grade ≥3
Anemia	31 (72)	13 (30)	29 (91)	8 (25)	30 (94)	4 (13)	90 (84)	25 (23)
White blood cell count decreased	24 (56)	11 (26)	23 (72)	5 (16)	29 (91)	7 (22)	76 (71)	23 (21)
Neutrophil count decreased	23 (53)	15 (35)	22 (69)	12 (38)	26 (81)	15 (47)	71 (66)	42 (39)
Stomatitis	22 (51)	4 (9)	23 (72)	8 (25)	20 (63)	3 (9)	65 (61)	15 (14)
Alopecia	23 (53)	0	10 (31)	0	18 (56)	0	51 (48)	0
Nausea	16 (37)	0	12 (38)	0	12 (38)	0	40 (37)	0
Decreased appetite	16 (37)	0	10 (31)	0	10 (31)	0	36 (34)	0
Platelet count decreased	10 (23)	1 (2)	15 (47)	3 (9)	10 (31)	2 (6)	35 (33)	6 (6)
Rash	17 (40)	2 (5)	3 (9)	0	12 (38)	0	32 (30)	2 (2)
Vomiting	15 (35)	2 (5)	9 (28)	1 (3)	7 (22)	0	31 (29)	3 (3)
Weight decreased	6 (14)	1 (2)	15 (47)	0	10 (31)	0	31 (29)	1 (1)
Weakness	3 (7)	1 (2)	11 (34)	1 (3)	11 (34)	1 (3)	25 (23)	3 (3)
Hypoalbuminemia	10 (23)	0	4 (13)	0	4 (13)	0	18 (17)	0
ALT increased	8 (19)	0	4 (13)	0	5 (16)	0	17 (16)	0
AST increased	6 (14)	0	4 (13)	0	6 (19)	0	16 (15)	0
Pruritus	9 (21)	0	2 (6)	0	2 (6)	0	13 (12)	0
Lymphocyte count decreased	8 (19)	2 (5)	2 (6)	0	2 (6)	1 (3)	12 (11)	3 (3)
Hyperglycemia	4 (9)	0	4 (13)	0	3 (9)	0	11 (10)	0
Skin hyperpigmentation	8 (19)	0	0	0	0	0	8 (7)	0
Dizziness	3 (7)	0	4 (13)	0	1 (3)	0	8 (7)	0
Mouth ulceration	5 (12)	0	1 (3)	0	0	0	6 (6)	0
Proteinuria	2 (5)	0	4 (13)	0	1 (3)	0	7 (7)	0
Fatigue	5 (12)	0	0	0	0	0	5 (5)	0

Zhao et al. Nature Medicine 2025

Will a biomarker open treatment population?

- Biomarker developed from Tropion-Lung 01 study (Datopotamab deruxtecan)



Prevalence

Histology subgroup	Prevalence of TROP2 QCS-NMR+, % (n)
BEP, n=352	
NSQ	66% (179/272)
NSQ/non-AGA	63% (140/221)
NSQ/AGA	76% (39/51)
SQ	44% (35/80)

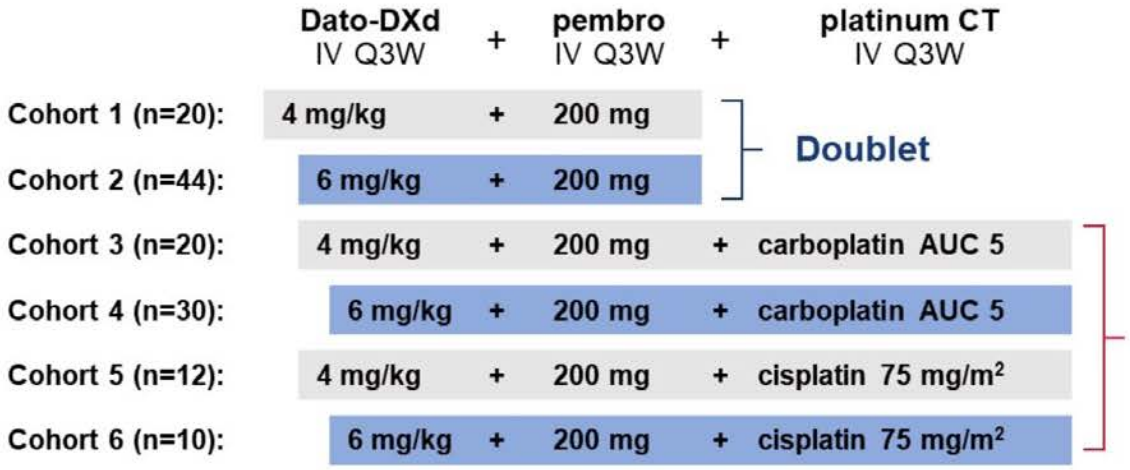
Garassino et al. WCLC 2024

TROPION-Lung02: Dato-DXd + Pembrolizumab ± Chemo

- TROPION-Lung02 is the first study evaluating Dato-DXd + pembrolizumab ± platinum CT[a] in advanced NSCLC without actionable genomic alterations[b] (NCT04526691)
  - The safety of the Dato-DXd + pembrolizumab doublet was established prior to evaluation of the platinum-containing triplet
  - The safety of Dato-DXd 4-mg/kg combinations was established prior to evaluation of 6-mg/kg combinations

Key eligibility criteria

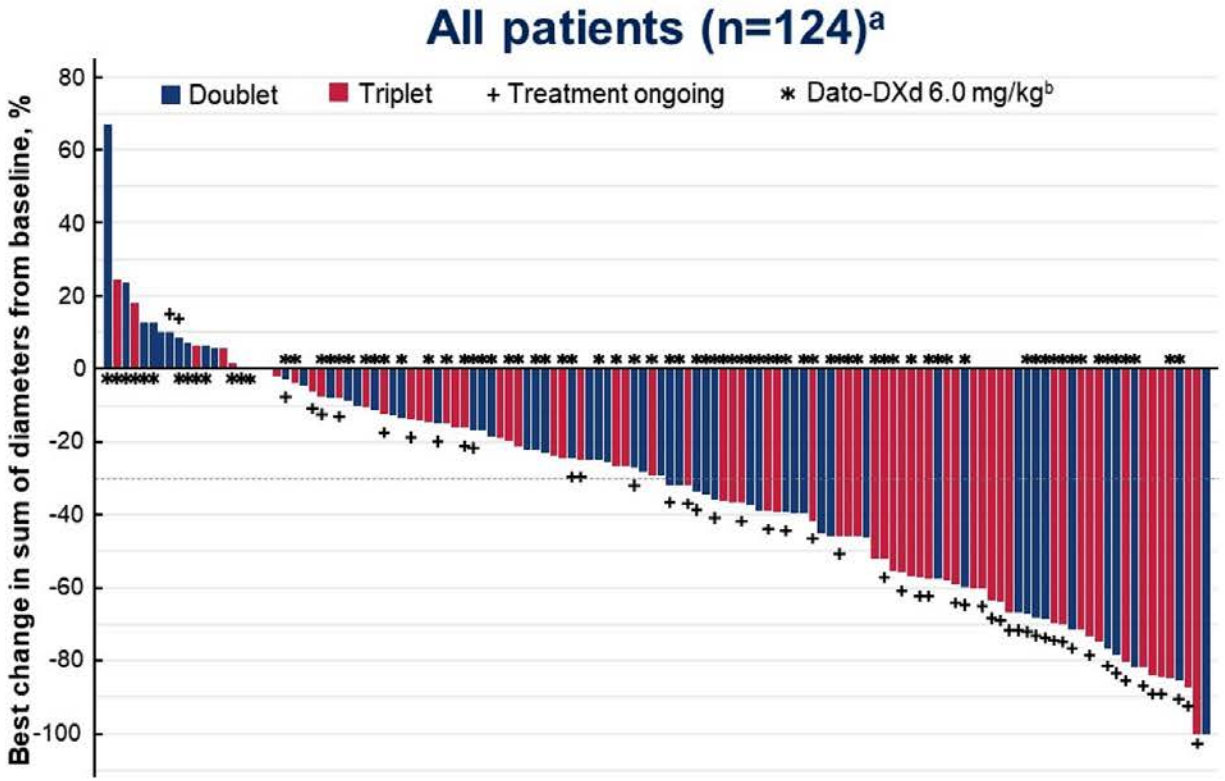
- **Advanced/metastatic NSCLC**
- **Dose escalation**[c]: ≤2 lines of prior therapy[d]
- **Dose expansion**
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[d]
  - Treatment naive (cohort 2; enrollment after Jun 30, 2022)[d]
  - Treatment naive (cohorts 3-6)[d]

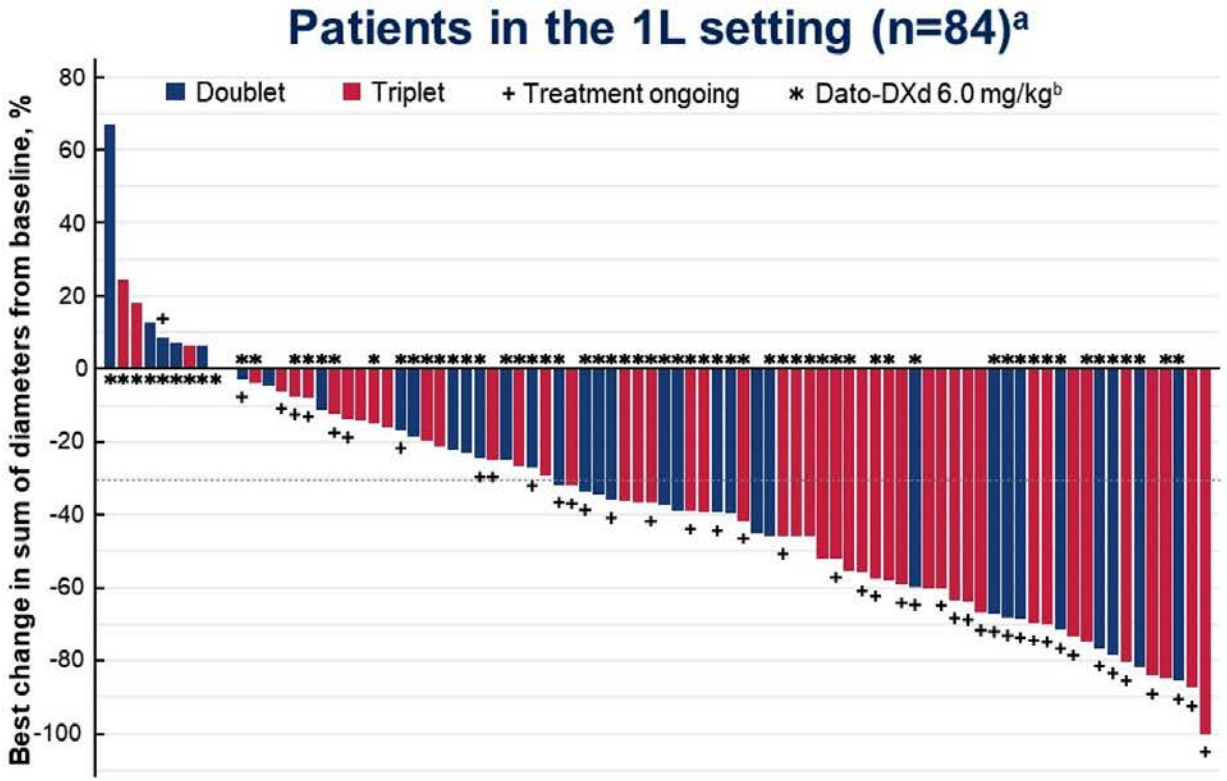


- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and antidrug antibodies

Goto Y et al. ASCO 2023;Abstract 9004.

TROPION-Lung02: Dato-DXd + Pembrolizumab ± Chemo





Goto Y et al. ASCO 2023;Abstract 9004.

TROPION-Lung02: Dato-DXd + Pembrolizumab ± Chemo

	All patients		Patients in 1L	
Response[a]	**Doublet (n=61)[b]**	**Triplet (n=71)[b]**	**Doublet (n=34)[b]**	**Triplet (n=53)[b]**
Confirmed + pending ORR, n (%)[c,d] [95% CI]	23 (38) [26-51]	35 (49) [37-61]	17 (50) [32-68]	30 (57) [42-70]
Confirmed + pending BOR, n (%)[d,e]				
Confirmed CR	0	1 (1)	0	1 (2)
Pending CR[d]	0	0	0	0
Confirmed PR	21 (34)	34 (48)	15 (44)	29 (55)
Pending PR[d]	2 (3)	0	2 (6)	0
SD, n (%)[f]	30 (49)	27 (38)	16 (47)	18 (34)
DCR, n (%)[g]	51 (84)	62 (87)	31 (91)	48 (91)
Median DOR, months [95% CI]	NE [8.8-NE]	NE [5.8-NE]	NE [5.5-NE]	NE [5.7-NE]

Preliminary PFS in all patients, median (95% CI), months: doublet, 8.3 (6.8-11.8); triplet 7.8 (5.6-11.1)[h]

- In the 1L setting, the ORR (confirmed and pending)[d] was 50% in patients receiving doublet therapy and 57% in those receiving triplet therapy
- Among all patients, the DCR was 84% (doublet) and 87% (triplet); in the 1L setting, the DCR was 91% in both therapy subgroups

Goto Y et al. ASCO 2023;Abstract 9004.

TROPION-Lung02: Datopotamab Deruxtecan (Dato-DXd) plus Pembrolizumab (Pembro) with or without Platinum Chemotherapy (Pt-CT) as First-Line (1L) Therapy for Advanced Non-Small Cell Lung Cancer (aNSCLC)

Levy B et al.
ASCO 2025;Abstract 8501.

June 1, 2025
Arie Crown Theater | 8:12 AM CT

Ongoing Trials

- AVANZAR: 1L Non-sq NSCLC: Durva, Dato-DXd, Carbo
- TROPION Lung-07: 1L Non-sq PD-L1 <50%: Dato-DXd+pembro+/-chemo
- TROPION Lung-08: 1L Non-sq PD-L1 ≥50%: Pembro +/- Dato-DXd
- TROPION Lung-15: 2L EGFR: Dato-DXd +/- osi vs chemo
- EVOKE-03: 1L NSCLC, PD-L1 ≥50%: Pembro +/- Sacituzumab govitecan
- 1L Squam NSCLC: Carbo paclitaxel pembro → pembro +/- SacTMT
- 2L EGFR: SacTMT vs chemo (post osi progression)
- Trofuse-007: 1L NSCLC, PD-L1 ≥50%: Pembro +/- SacTMT

Faculty Case Presentations

Case Presentation – Prof Peters: 50-year-old male, never smoker

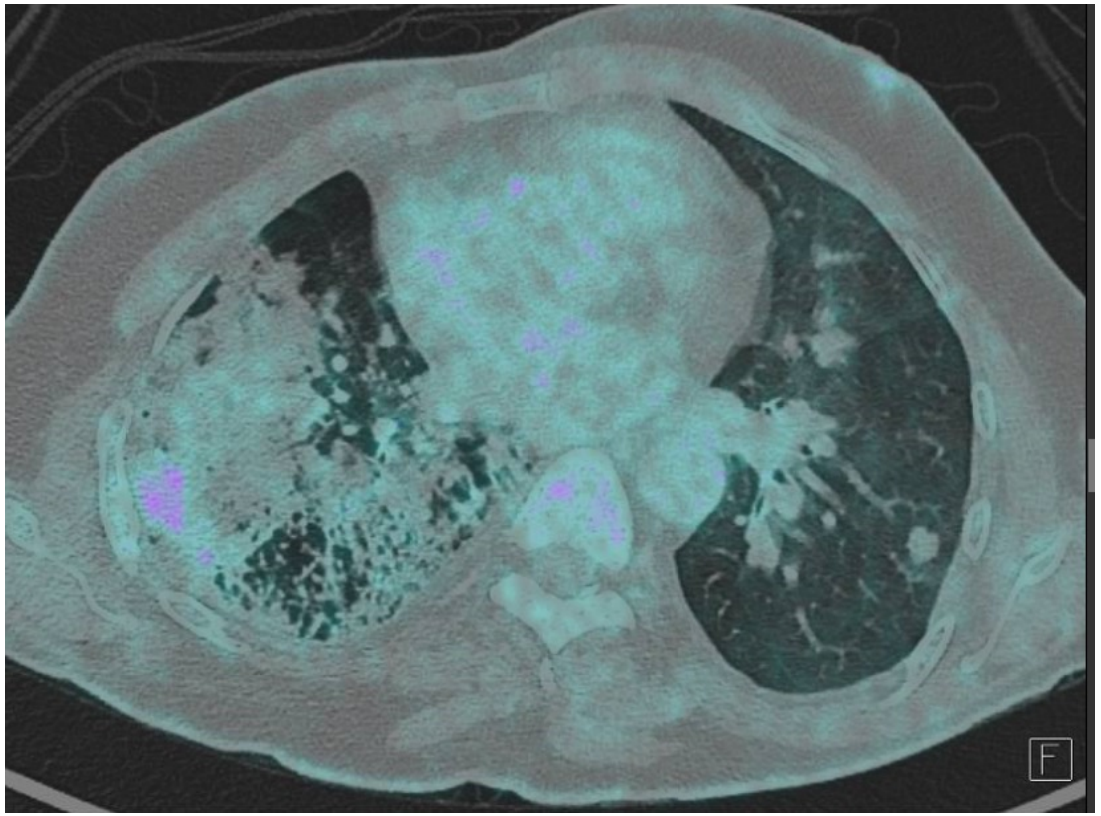
50 years old, never smoker

Mucinous adenocarcinoma of the right lower lobe, cT4 (>7 cm, ipsilateral lung lesions), cN2 (station 7), cM1a (contralateral lung lesions), stage IVA (8th TNM)

IHC: ALK or ROS1 negative, PD-L1 <1%

NGS-52 panel: no EGFR, BRAF or HER2 mutation

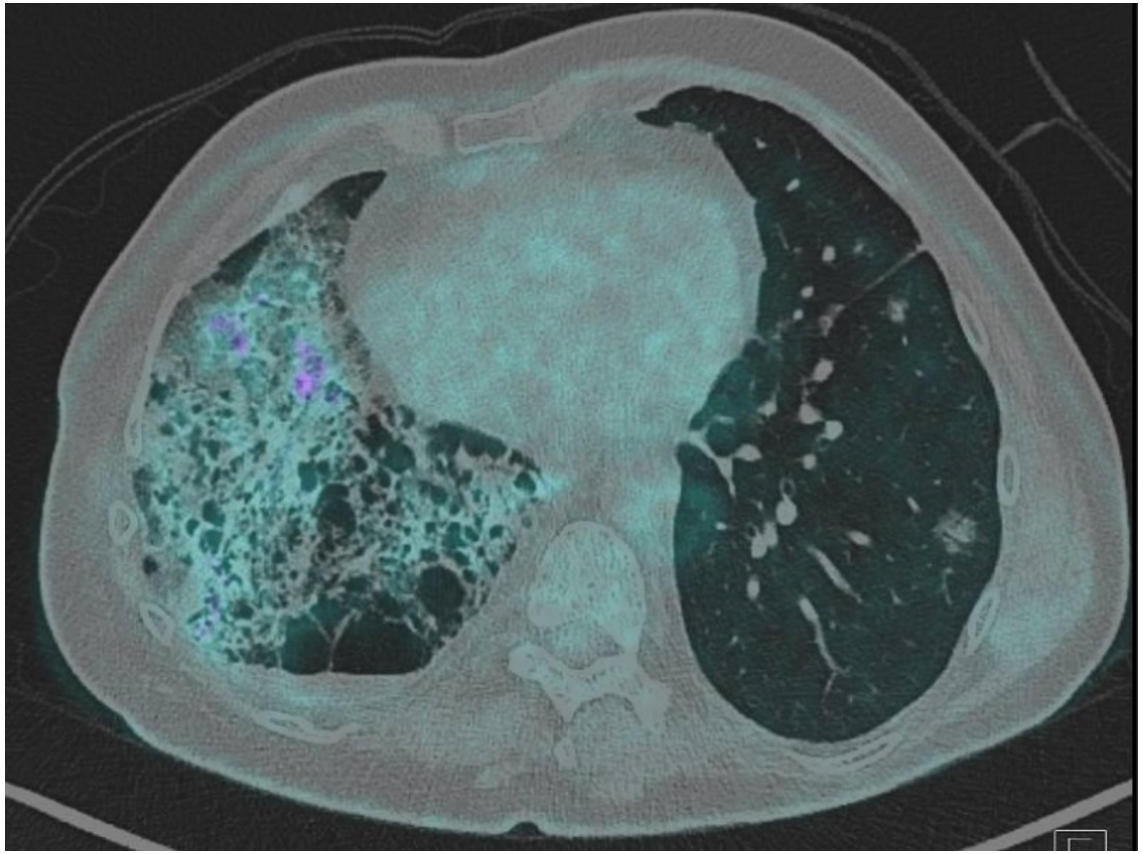
Detected mutations: KRAS (G12D, exon 2), GNAS (R201S, exon 8), RET (V648I, exon 11), FLT3 (S446L, exon 11)



Case Presentation – Prof Peters: 50-year-old male, never smoker (cont'd)

May 2021

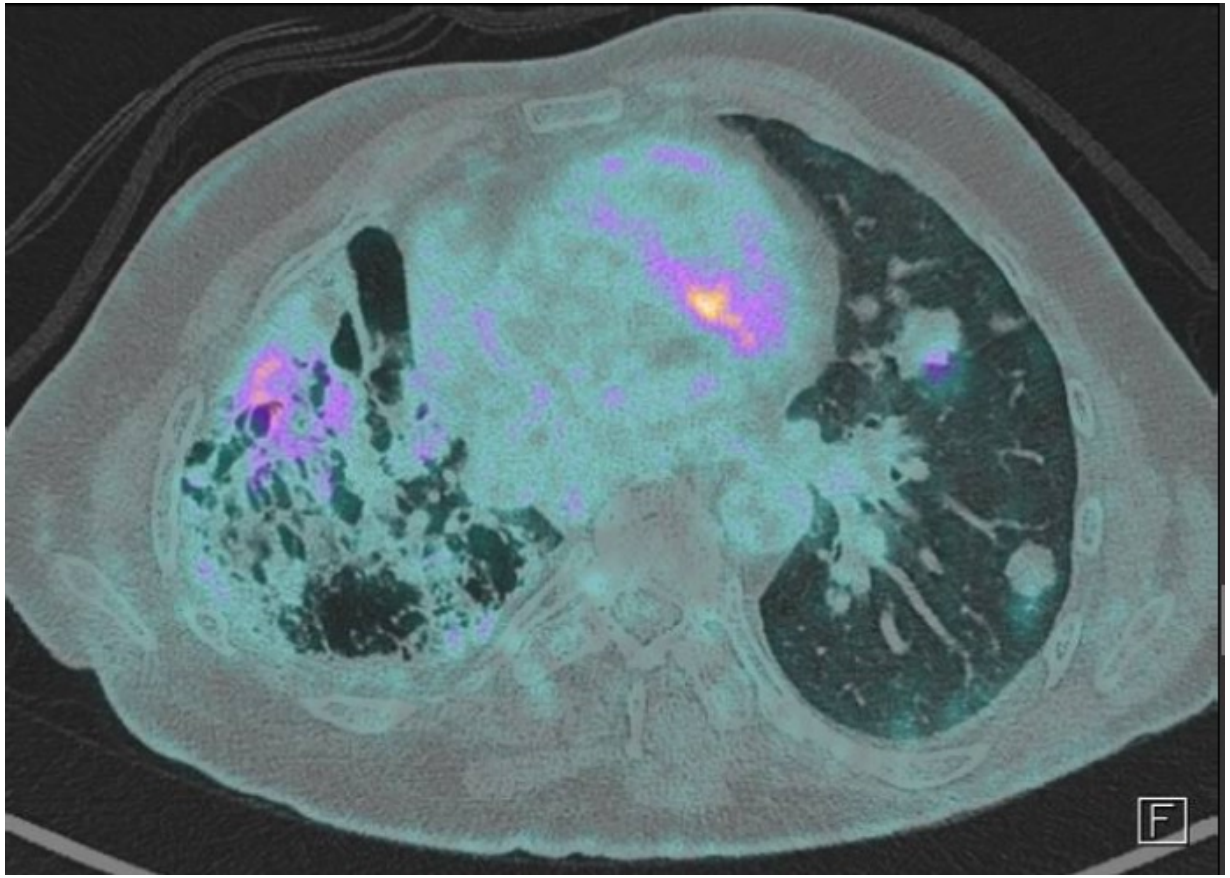
First line - carboplatin-pemetrexed-pembrolizumab according to KEYNOTE-189
Treatment stopped in May 2023



Case Presentation – Prof Peters: 50-year-old male, never smoker (cont'd)

July 2023

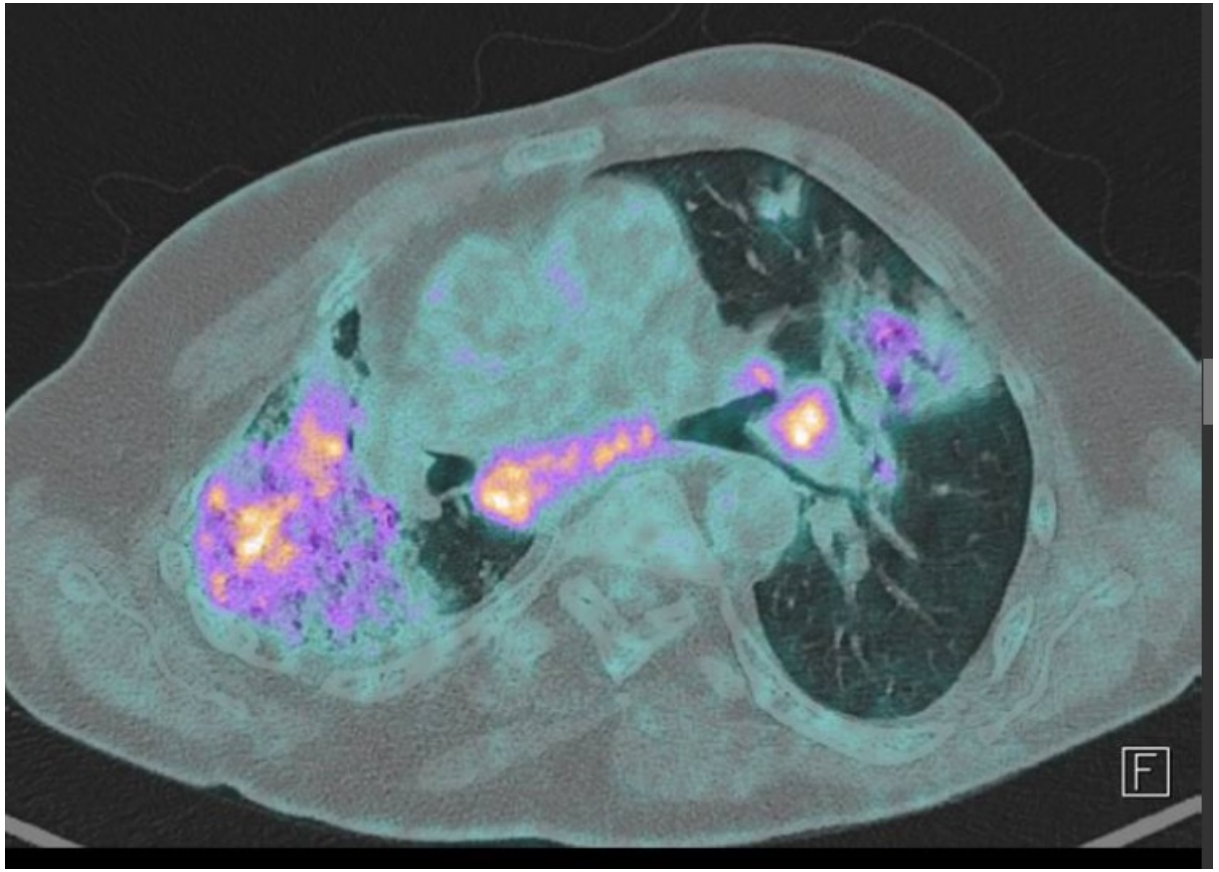
Lung progression



Case Presentation – Prof Peters: 50-year-old male, never smoker (cont'd)

Second line - ipilimumab, nivolumab, carboplatin, and paclitaxel according to CheckMate 9LA

Best response: PD on November 2023

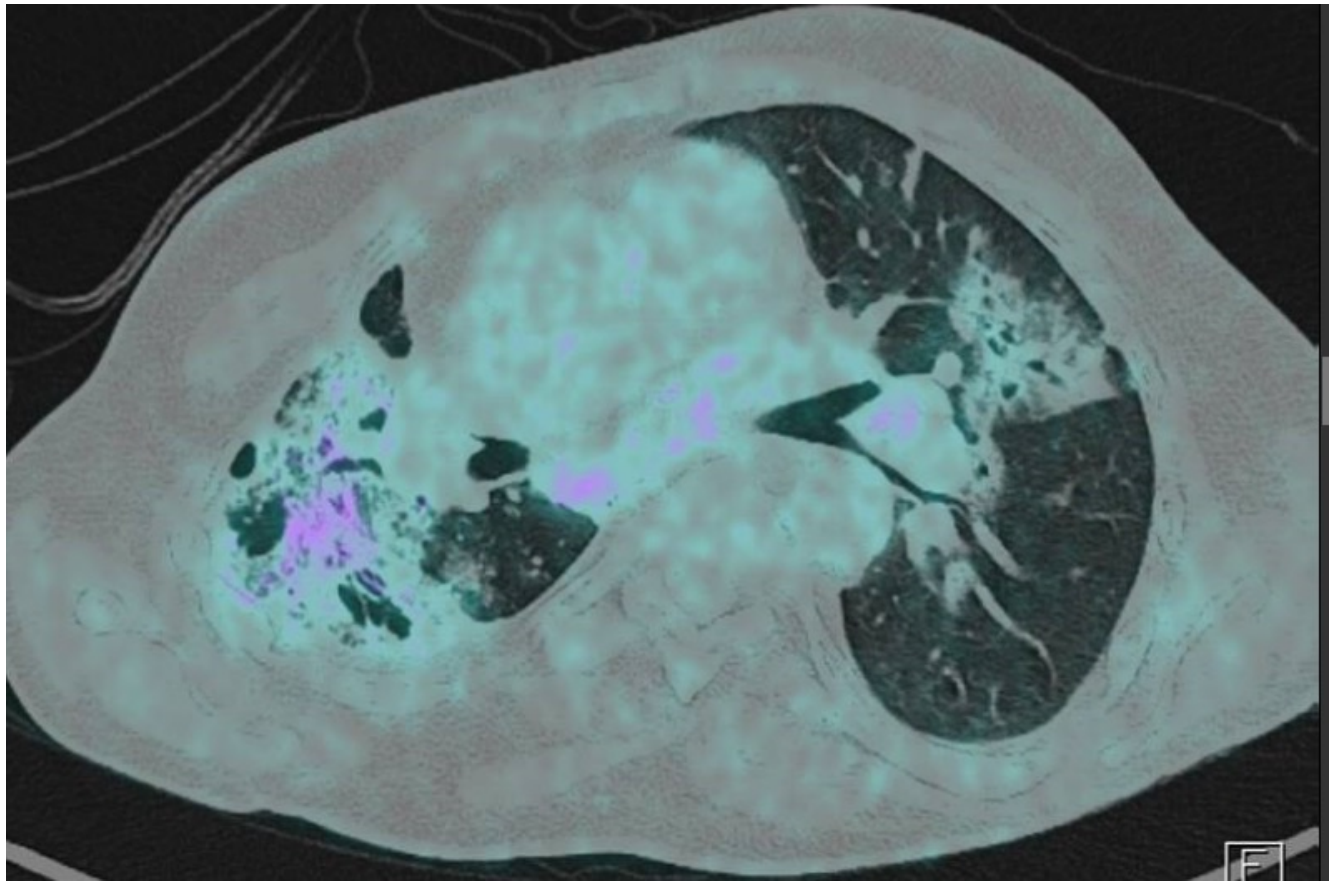


Case Presentation – Prof Peters: 50-year-old male, never smoker (cont'd)

November 2023

Third line: gemcitabine, vinorelbine, ipilimumab and nivolumab

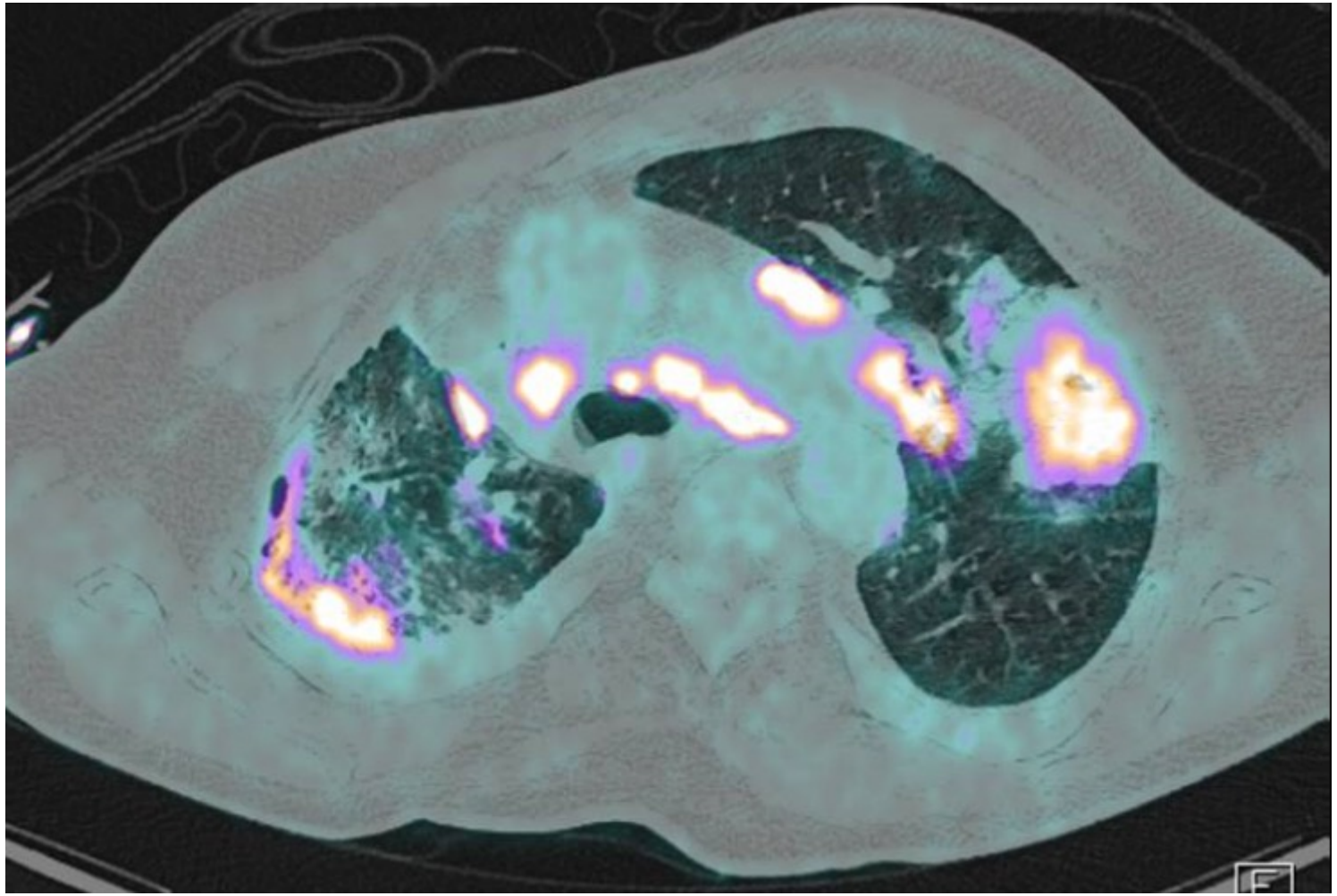
Best response: PR



Case Presentation – Prof Peters: 50-year-old male, never smoker (cont'd)

July 2024

Pulmonary and LN progression

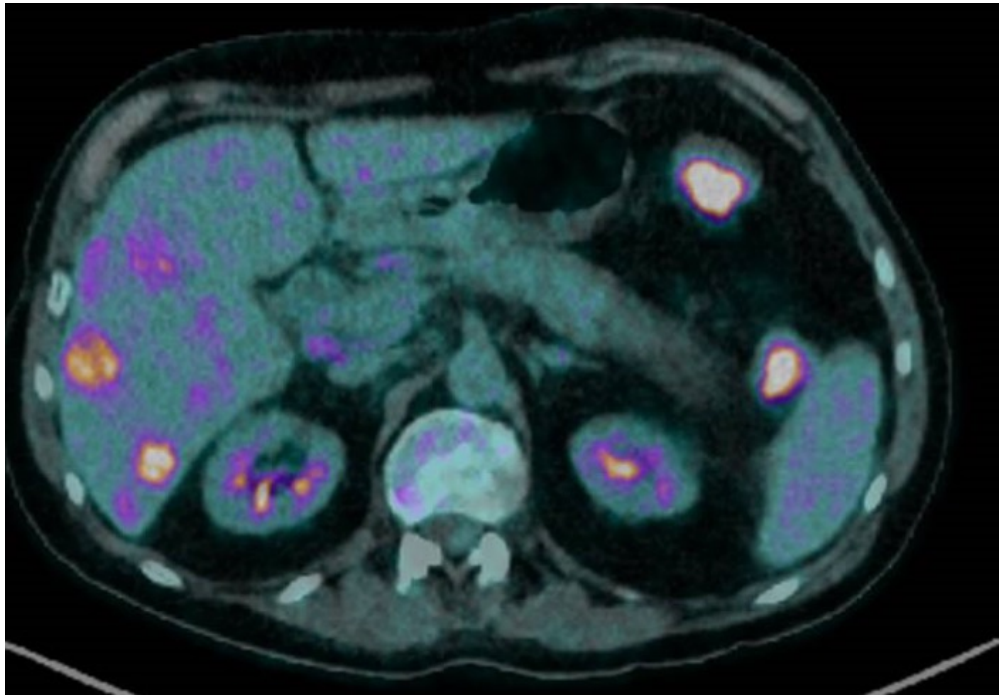


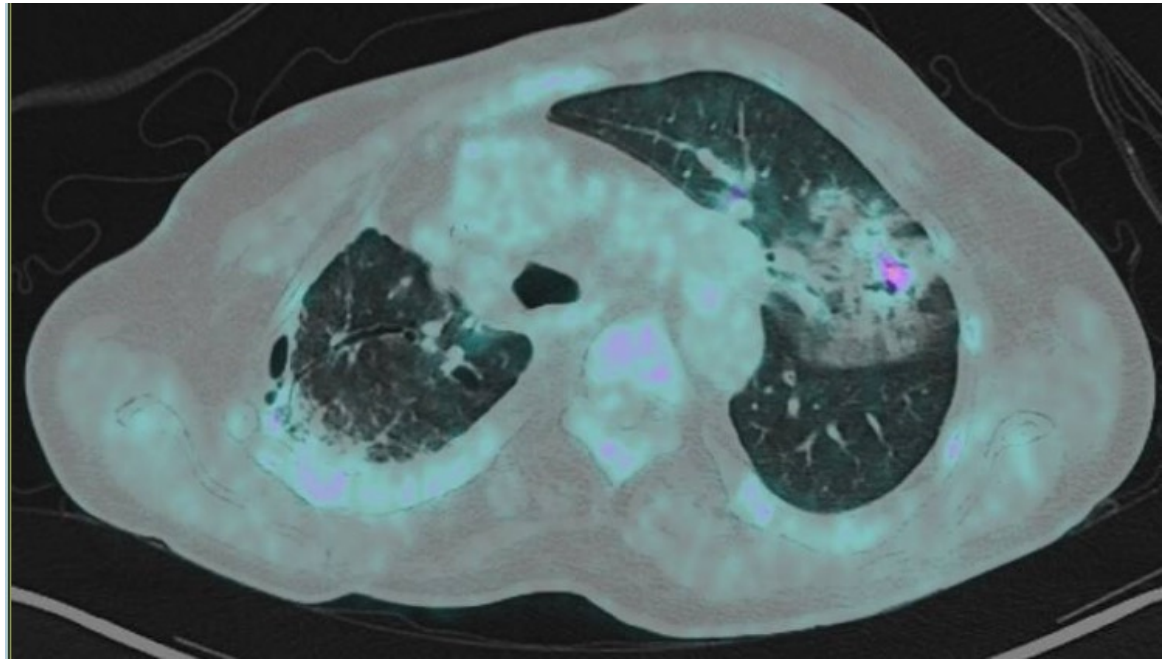
Case Presentation – Prof Peters: 50-year-old male, never smoker (cont'd)

August 2024

Fourth-line - gemcitabine and weekly docetaxel

Best response: hepatic PD, persistent thoracic partial response

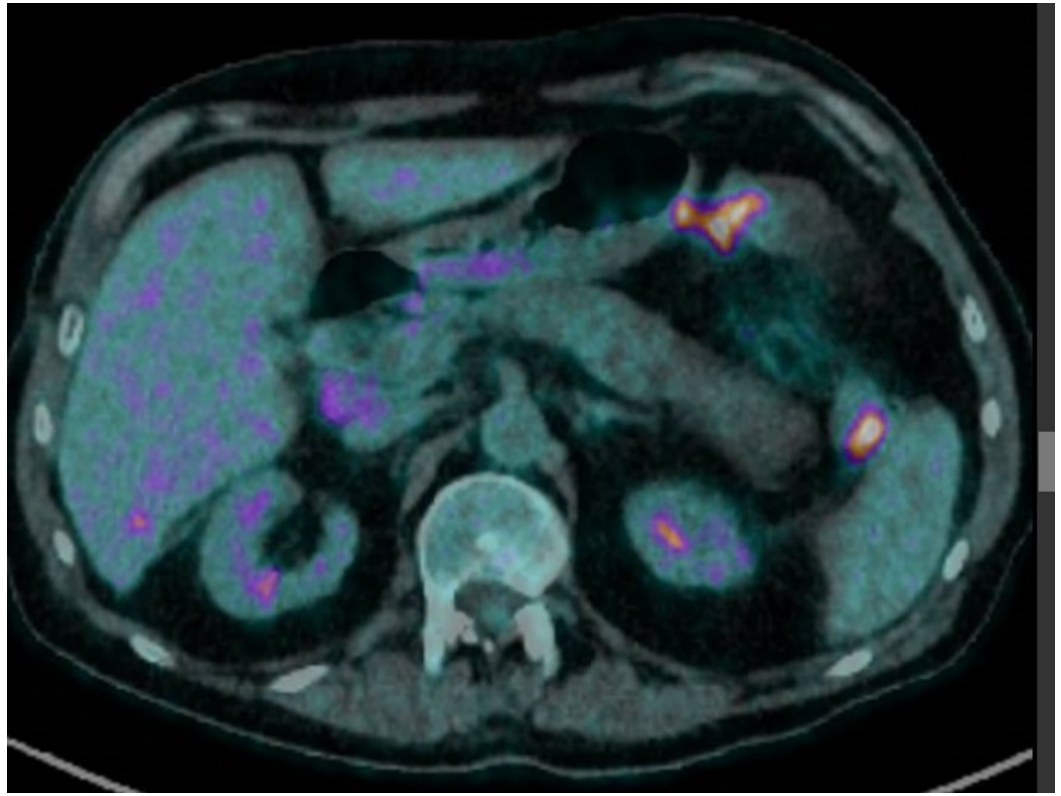


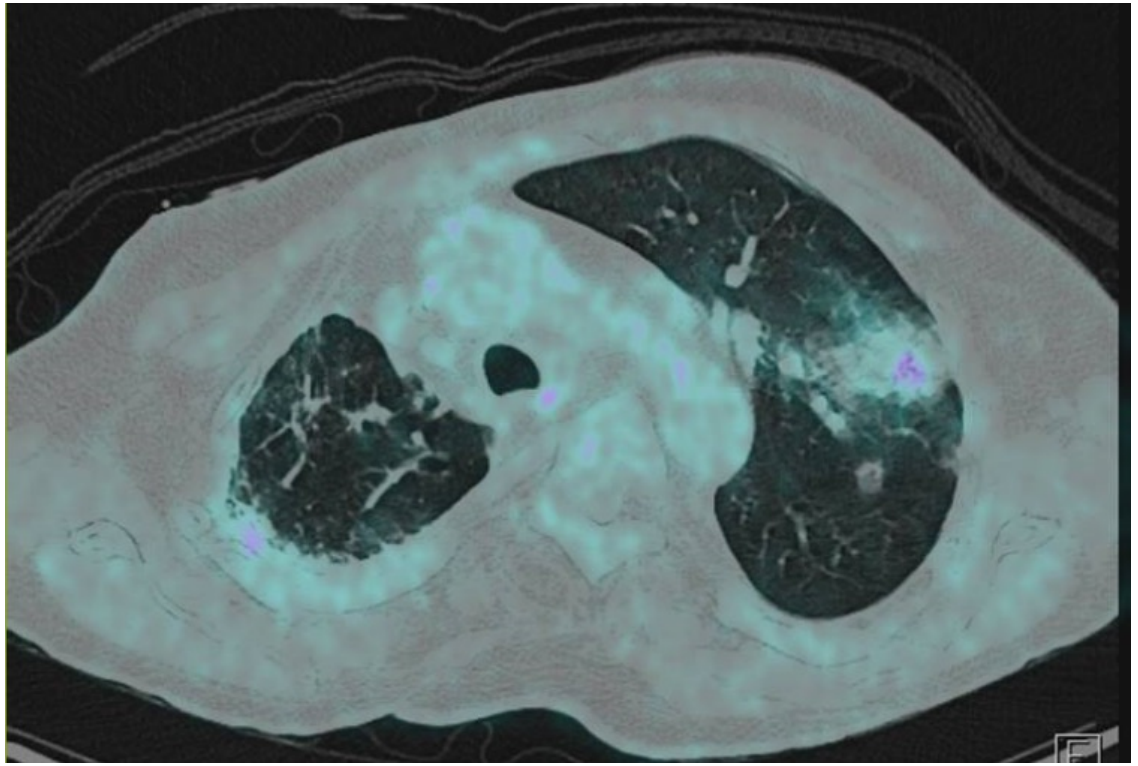


Case Presentation – Prof Peters: 50-year-old male, never smoker (cont'd)

October 2024
Fifth-line with **datopotamab deruxtecan**

Hepatic complete response and persistent thoracic partial response
Toxicity: oral mucositis Grade 1-2



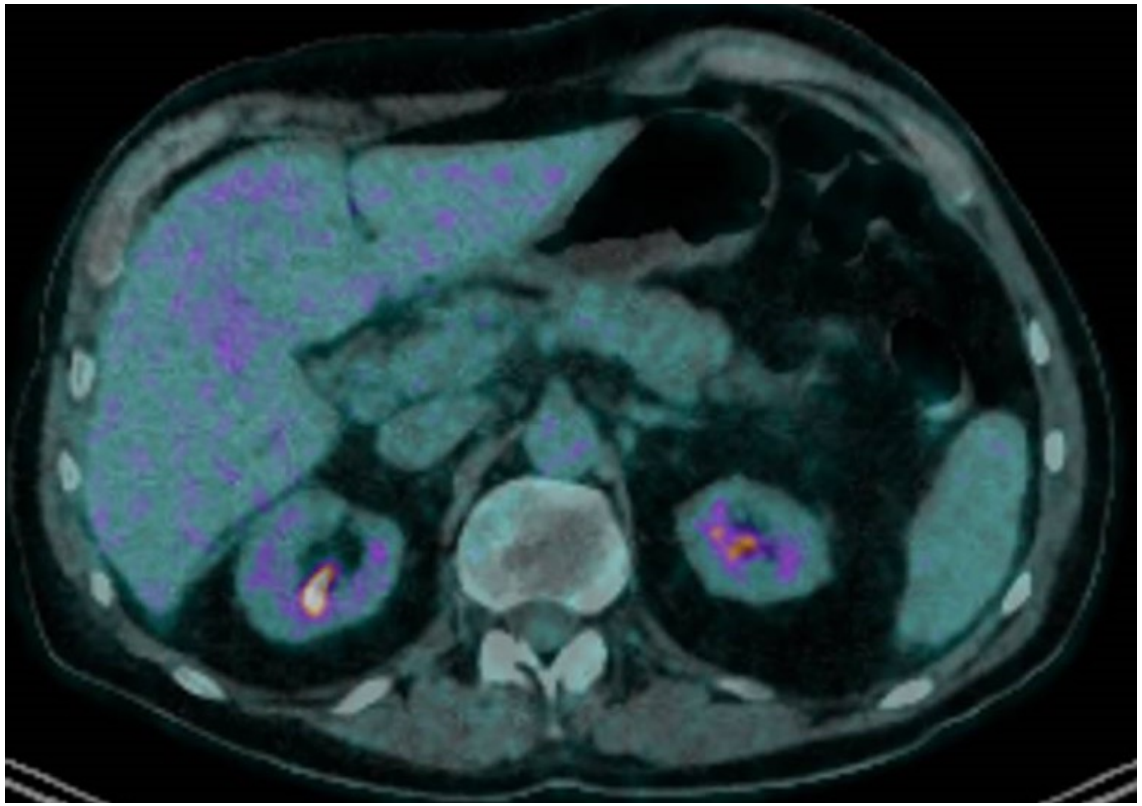


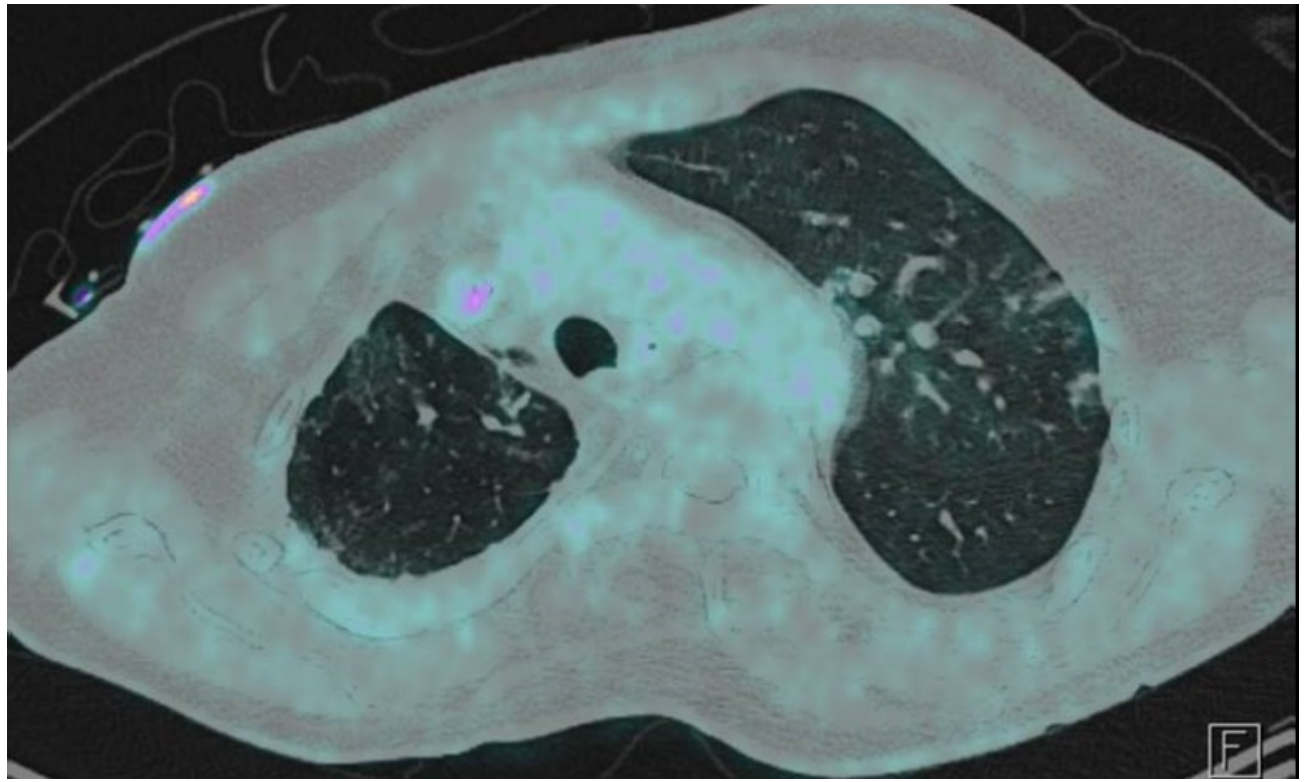
Case Presentation – Prof Peters: 50-year-old male, never smoker (cont'd)

Seven months after initiation of datopotamab deruxtecan

Hepatic & LN complete response and persistent pulmonary partial response

Toxicity: oral mucositis grade 1





Questions for the Faculty

If Dato-DXd were to become available for progressive EGFR-mutant NSCLC, in which line of treatment would you most likely use it, and how would this vary depending on the first-line therapy the patient had received (osimertinib monotherapy versus osimertinib/chemotherapy versus amivantamab/lazertinib)?

Questions for the Faculty

If Dato-DXd were to become available for NSCLC, would you consider it for a patient without a targetable tumor mutation who had exhausted other options? What about for a patient with a genomic alteration beyond EGFR?

How enthusiastic are you about the ongoing studies evaluating Dato-DXd in combination with immune checkpoint inhibition as initial therapy for metastatic NSCLC? Do you think these strategies will eventually reach the clinic?

Do you think we'll eventually be using the TROP2 QCS-NMR to select patients with NSCLC to receive Dato-DXd?

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

What preemptive strategies, if any, do you employ to prevent the development of oral mucositis/stomatitis associated with Dato-DXd? How do you manage oral mucositis/stomatitis when it occurs?

What is your approach to screening for ILD in patients with NSCLC receiving Dato-DXd? Does your approach to monitoring for and managing ILD associated with Dato-DXd differ in any way from ILD associated with T-DXd? If so, how?

What specific ocular adverse events have you encountered with Dato-DXd? How do you monitor for, mitigate and manage them?

Agenda

Module 1: Role of Immune Checkpoint Inhibitors in Metastatic Non-Small Cell Lung Cancer (NSCLC) without a Targetable Tumor Mutation — Prof Peters

Module 2: Targeted and Other Novel Therapeutic Strategies for Relapsed Metastatic NSCLC — Prof Garassino

Module 3: Potential Role of TROP2-Targeted Antibody-Drug Conjugates in Advanced NSCLC — Dr Sands

Module 4: Evolving Role of Immune Checkpoint Inhibitors in the Care of Patients with Nonmetastatic NSCLC — Dr Heymach

The Evolving Role of Immune Checkpoint Inhibitors in the Care of Patients with Non-Metastatic NSCLC

John Heymach, M.D., Ph.D.

Chair, Dept. of Thoracic/Head and Neck
Medical Oncology
Ruth Legett Jones Distinguished Chair

Research To Practice
May 30, 2025

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Multiple Large Randomized Trials Support Substantial Clinical Benefit of Immune Checkpoint Inhibitors in Resectable NSCLC

	Adjuvant[a] (N=2182)				Perioperative (N=1998)				Neoadjuvant (N=358)	
Study	**KEYNOTE-091[1] N=1177**		**IMpower010[2] N=1005**		**KEYNOTE-671[3] N=797**		**AEGEAN N=740**		**CheckMate 77T[4] N=461**		**CheckMate 816[5] N=358**	
Regimen	**Pembro**	**Placebo**	**Atezo**	**BSC**	**Pembro + Chemo →Pembro**	**Placebo + Chemo →Placebo**	**Durva + Chemo →Durva**	**Placebo + Chemo →Placebo**	**Nivo + Chemo →Nivo**	**Placebo + Chemo →Placebo**	**Nivo + Chemo**	**Chemo**
Median EFS/DFS (95% CI), mo	53.9 (46.2-67.0)	43.0 (35.0-51.6)	65.6 (NA, NA)	47.8 (NA, NA)	47.2 (32.9, NR)	18.3 (14.8, 22.1)	NR (42.3, NR)	30.0 (20.6, NR)	NR (28.9, NR)	18.4 (13.6, 28.1)	43.8 (30.6, NR)	18.4 (14.0, 26.7)
EFS/DFS HR (95% CI)	**0.81 (0.68, 0.96)**		**0.85 (0.71, 1.01)**		**0.59 (0.48, 0.72)**		**0.69 (0.55, 0.88)**		**0.58 (0.42, 0.81)**		**0.66 (0.49, 0.90)**	
Maturity	**48%**		**50%**		**53%**		**39%**		**40%**		**52% (planned)[6]**	
Median follow-up	51.7 months		65.0 months		36.6 months		25.9 months		25.4 months		57.6 months	

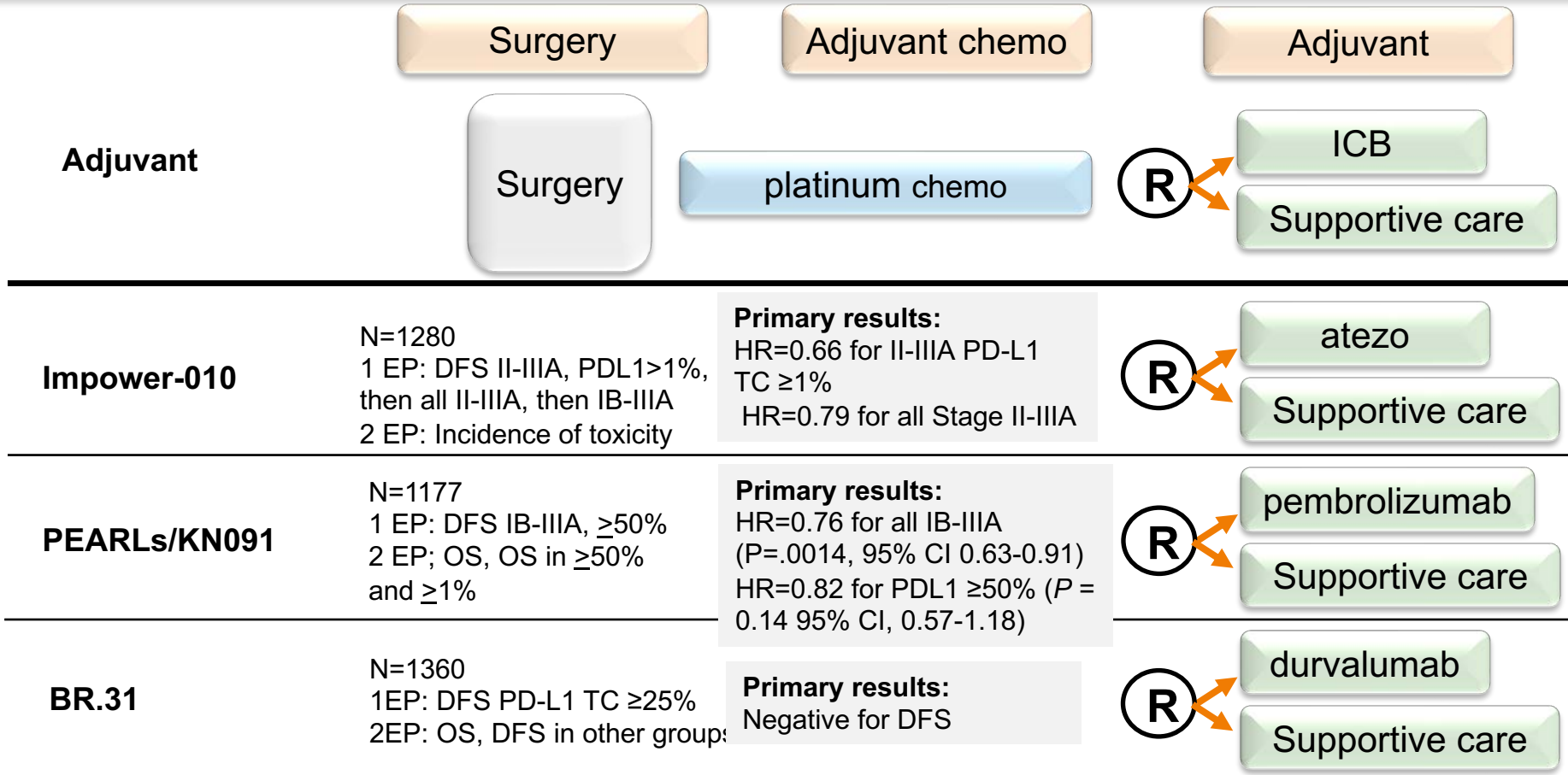
Note: Most recent data from all studies (regardless of PD-L1).

[a] For Adjuvant studies, randomization is after surgery and +/- adjuvant chemotherapy.

Atezo=atezolizumab; BSC=best supportive care; DFS=disease-free survival; Durva=durvalumab; EFS=event free survival; Nivo=nivolumab; NR=not reached/not estimable; NA=not available; Pembro=pembrolizumab.

1. Besse B, et al. ESMO-IO 2023. Abstract 120MO; 2. Wakelee HA, et al. ASCO 2024. Poster 297; 3. Spicer JD, et al. ESMO 2023. Abstract LBA56; 4. Cascone T, et al. ESMO 2023. Abstract LBA1; 5. Spicer JD, et al. ASCO 2024 [oral]. Abstract LBA8010; 6. Forde PM, et al. *N Engl J Med*. 2022;386(21):1973-1985.

Randomized studies of adjuvant ICB for resectable NSCLC



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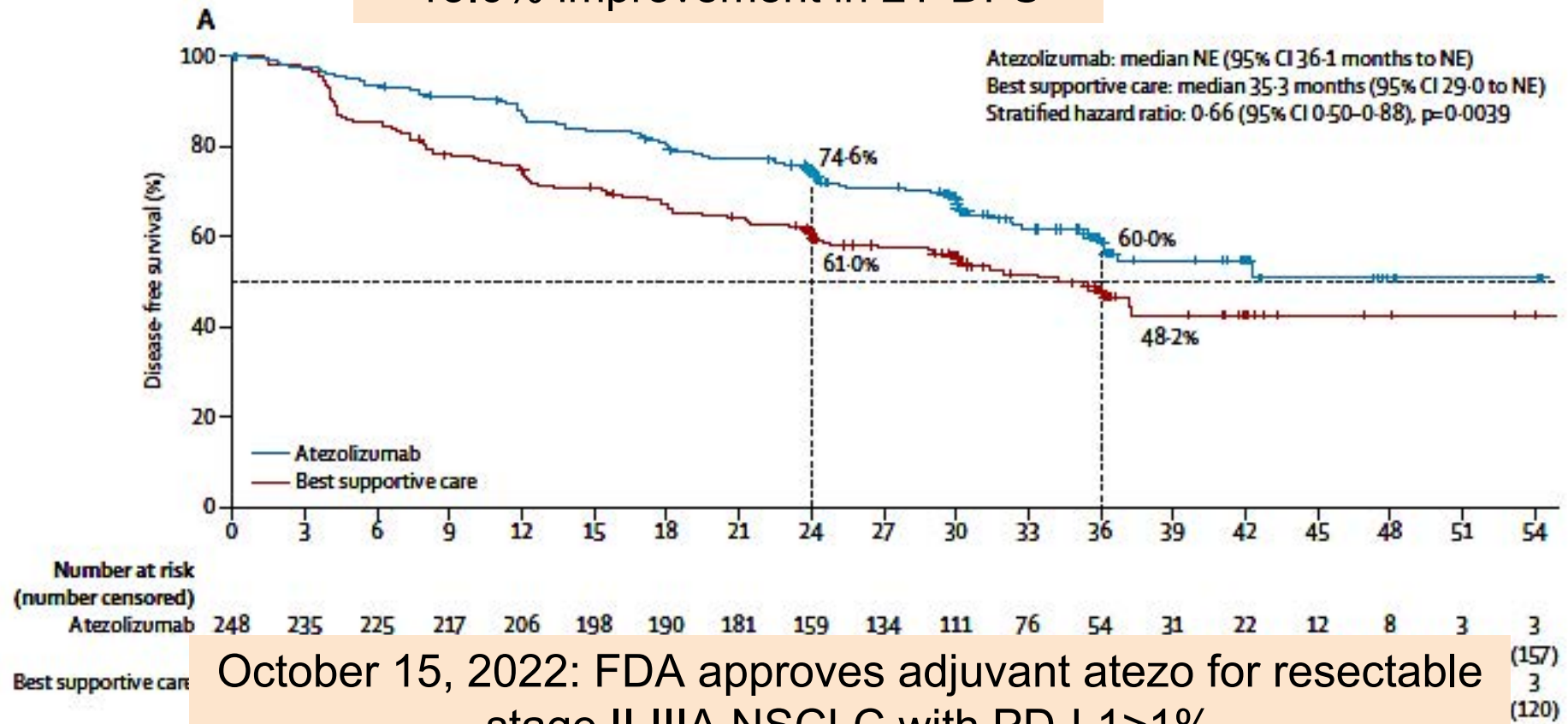
Felip, Lancet 2021; Paz-Ares, et al. *Annals Oncology*. 2022;33(4):451

Impower-010 randomized study of adjuvant atezolizumab vs BSC: Primary endpoint of DFS (PDL1>1%, stage II-IIIA)

HR 0.66 (p=.0039) in PDL1> 1%
13.6% improvement in 2Y DFS



October 15, 2022: FDA approves adjuvant atezo for resectable stage II-IIIA NSCLC with PD-L1≥1%

Felip et al, Lancet 2021

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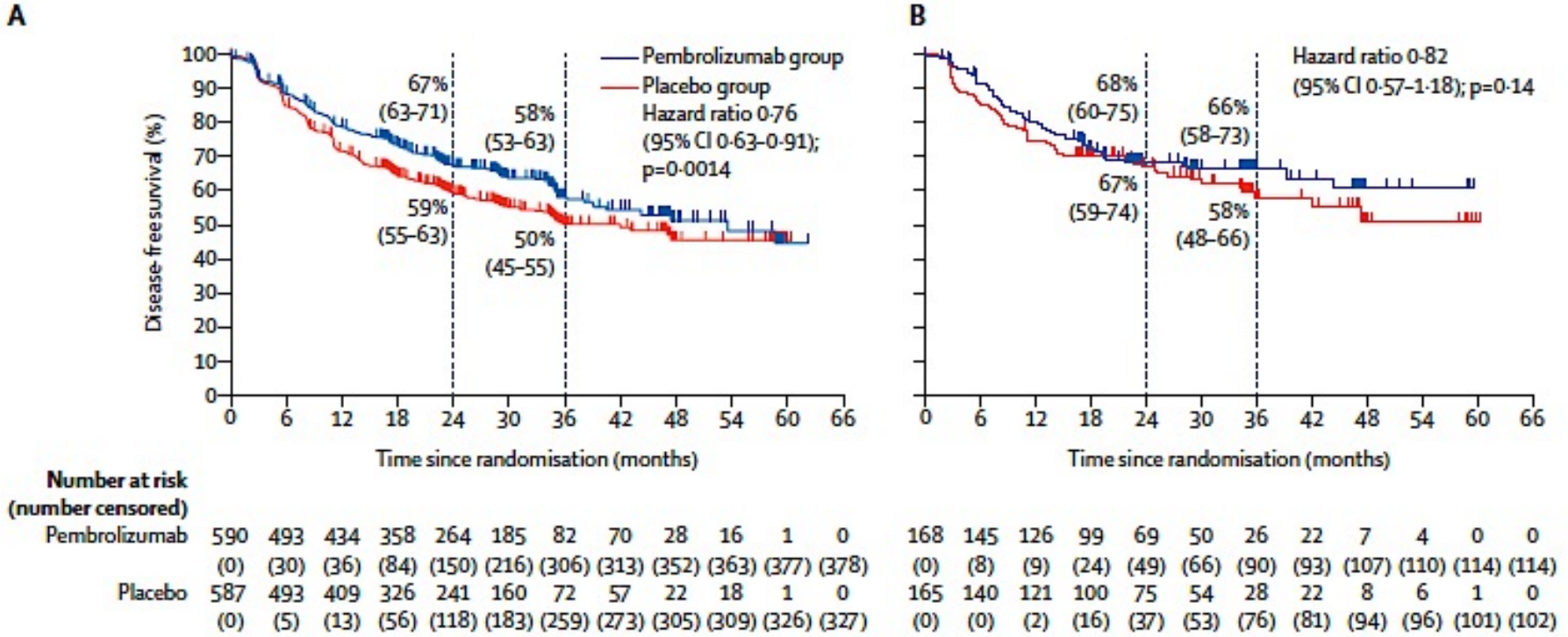
Keynote-91/PEARLs RP3 study of adjuvant pembrolizumab vs BSC for resectable NSCLC

Stage IB-IIIA
HR=0.76 (P=.0014,
95% CI 0.63-0.91)

PD-L1>50%
HR=0.82 (P=.14,
95% CI , 0.57-1.18)



O'Brien et al, Lancet Oncology 2022

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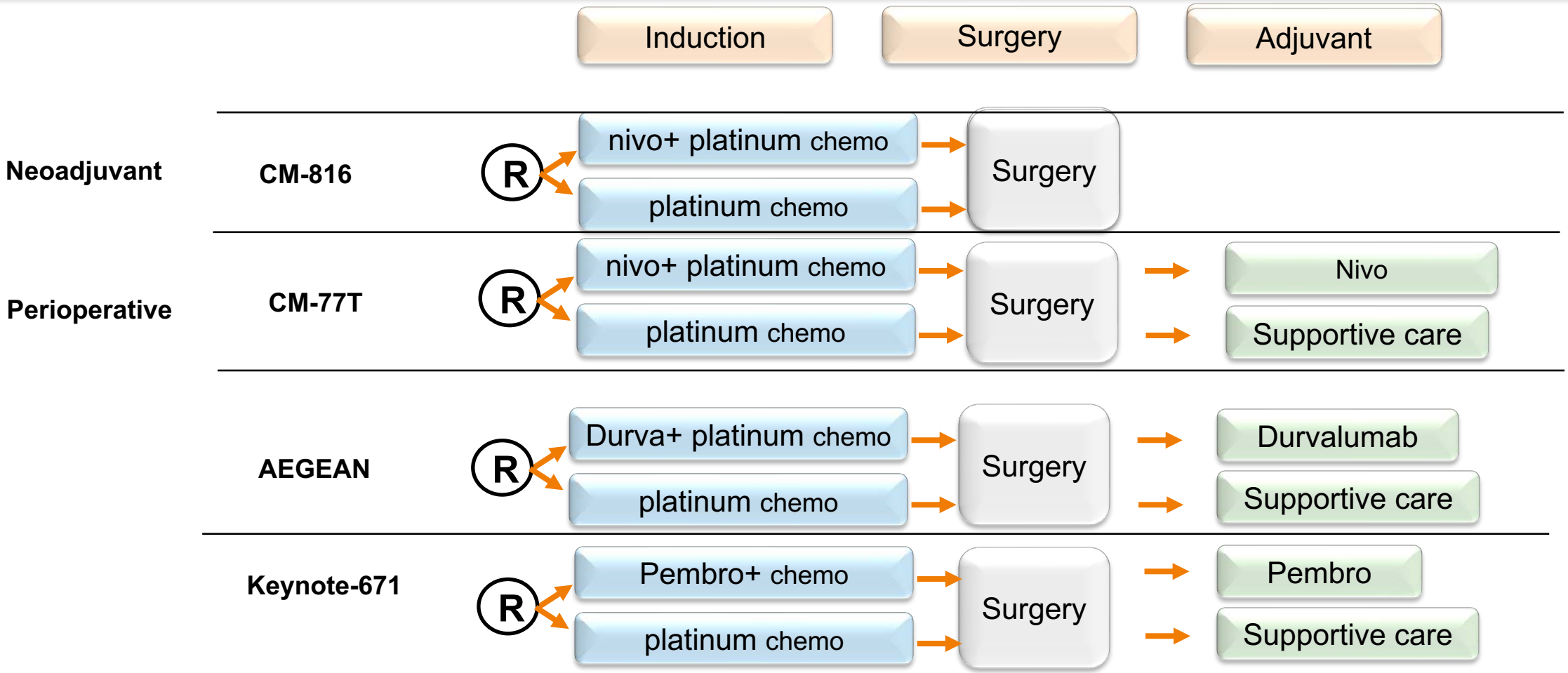
Randomized studies of neoadjuvant or perioperative (neoadjuvant+adjuvant) ICB for resectable NSCLC



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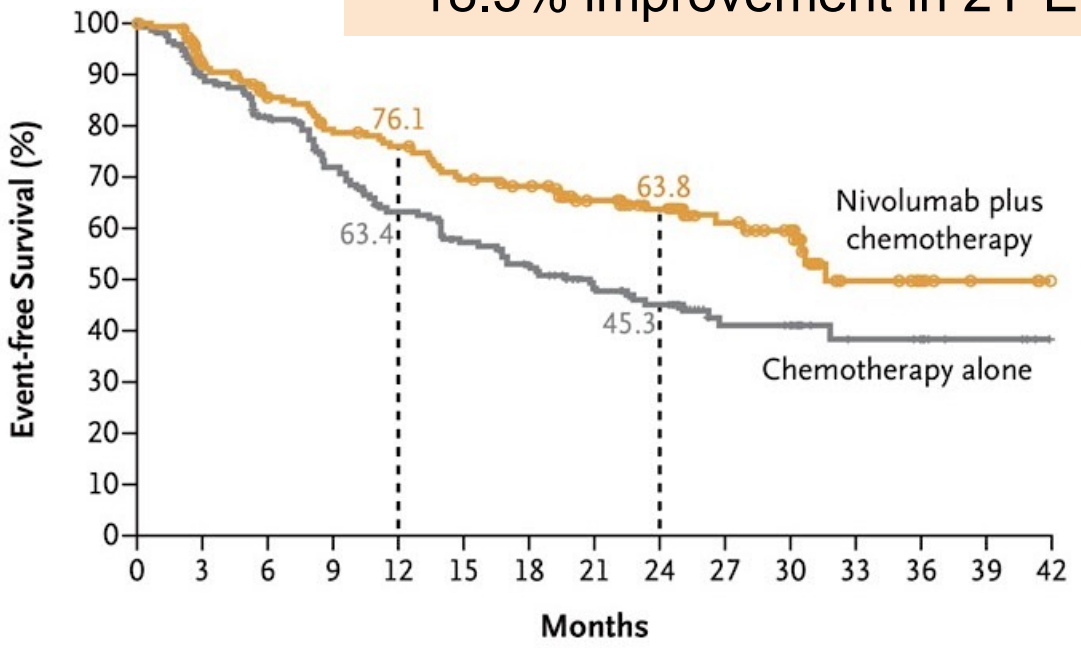
AEGEAN (CT.gov: NCT03800134; WCLC19 abstract P1.18-02), KN671 (CT.gov: NCT03425643, ESMO20 1235 TPS), IMpower030 (CT.gov: NCT03456063, WCLC18 P2.17-27 TPS), CM77T (CT.gov: NCT04025879).

Checkmate 816 study: addition of neoadjuvant nivolumab to CT improves EFS in resectable stage IB-IIIA NSCLC

EFS HR: 0.63 (P=.005)
18.5% improvement in 2Y EFS



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

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

No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

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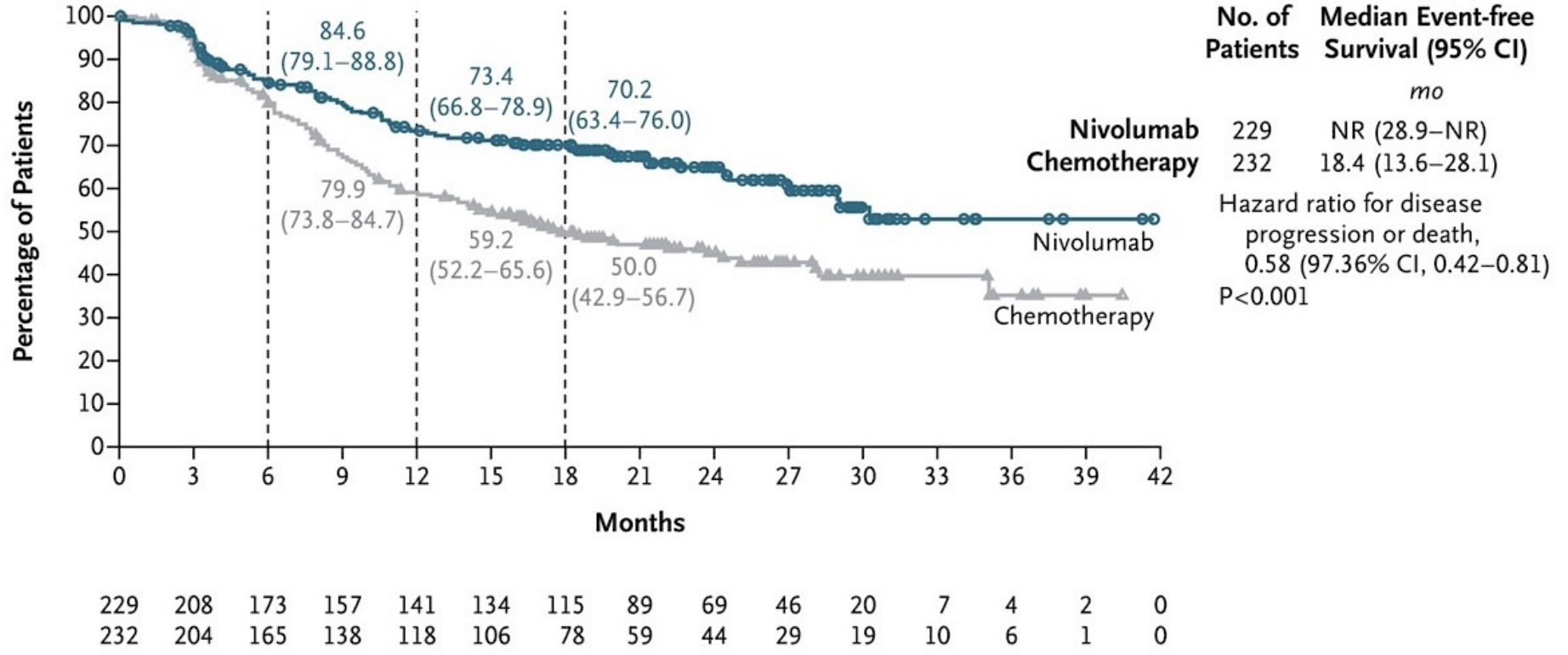
Forde et al. N Engl J Med 2022;386:1973-1985

77T study of perioperative nivolumab in resectable NSCLC

77T achieved primary endpoint of EFS (HR 0.58) with 20% improvement in 18m EFS



Cascone et al, NEJM 2024

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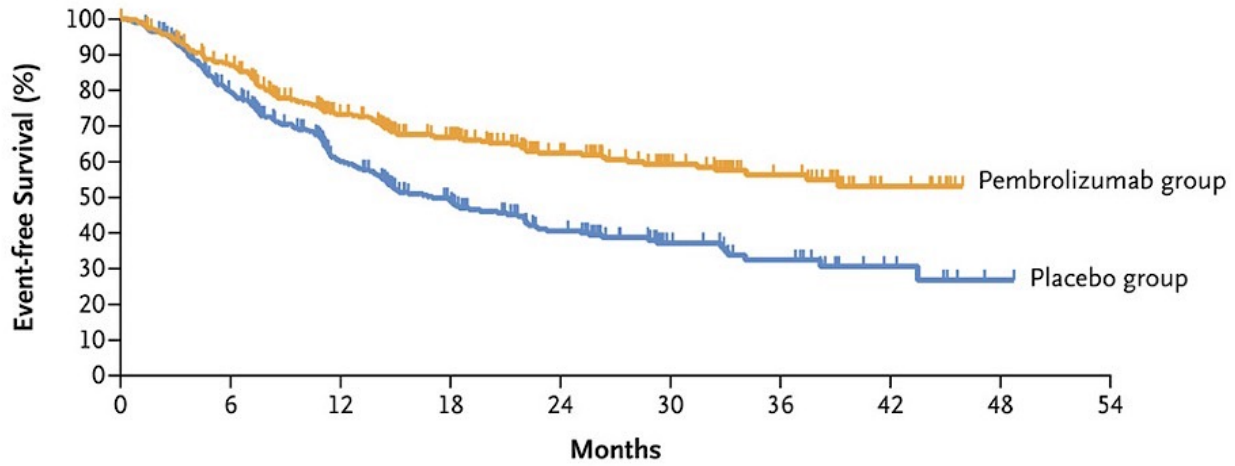
KN 671 of perioperative pembrolizumab: primary endpoint of EFS

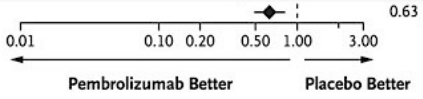


No. at Risk

Pembrolizumab group	397	330	236	172	117	72	42	11	0	0
Placebo group	400	294	183	124	74	38	24	9	1	0

B Subgroup Analysis of Event-free Survival

Subgroup	Pembrolizumab Group	Placebo Group	Hazard Ratio for Event or Death (95% CI)
	no. of events/no. of participants		
All patients	139/397	205/400	0.58 (0.46–0.72)
Age			
<65 yr	74/221	113/214	0.53 (0.39–0.71)
≥65 yr	65/176	92/186	0.64 (0.46–0.88)
Sex			
Female	31/118	55/116	0.44 (0.28–0.68)
Male	108/279	150/284	0.63 (0.49–0.80)
Race			
White	85/250	123/239	0.54 (0.41–0.72)
Other	46/134	70/145	0.62 (0.42–0.89)
Geographic region			
East Asia	43/123	57/121	0.66 (0.45–0.99)
Other	96/274	148/279	0.54 (0.41–0.69)
Smoking status			
Current smoker	37/96	57/103	0.52 (0.34–0.78)
Former smoker	84/247	128/250	0.57 (0.43–0.75)
Never smoked	18/54	20/47	0.68 (0.36–1.30)
Pathological stage			
II	34/118	48/121	0.65 (0.42–1.01)
III	105/279	157/279	0.54 (0.42–0.70)
Histologic features			
Nonsquamous	73/226	107/227	0.58 (0.43–0.78)
Squamous	66/171	98/173	0.57 (0.41–0.77)
PD-L1 TPS (50% cutoff)			
<50%	107/265	142/266	0.64 (0.49–0.82)
≥50%	32/132	63/134	0.42 (0.28–0.65)
PD-L1 TPS (1% cutoff)			
<1%	63/138	80/151	0.77 (0.55–1.07)
≥1%	76/259	125/249	0.47 (0.36–0.63)
PD-L1 TPS			
<1%	63/138	80/151	0.77 (0.55–1.07)
1–49%	44/127	62/115	0.51 (0.34–0.75)
≥50%	32/132	63/134	0.42 (0.28–0.65)
EGFR mutation			
No	31/111	64/127	0.48 (0.31–0.74)
Yes	1/14	10/19	0.09 (0.01–0.74)
Unknown	107/272	131/254	0.64 (0.49–0.83)
ALK translocation			
No	29/104	76/133	0.41 (0.26–0.62)
Unknown	106/281	128/258	0.63 (0.49–0.82)



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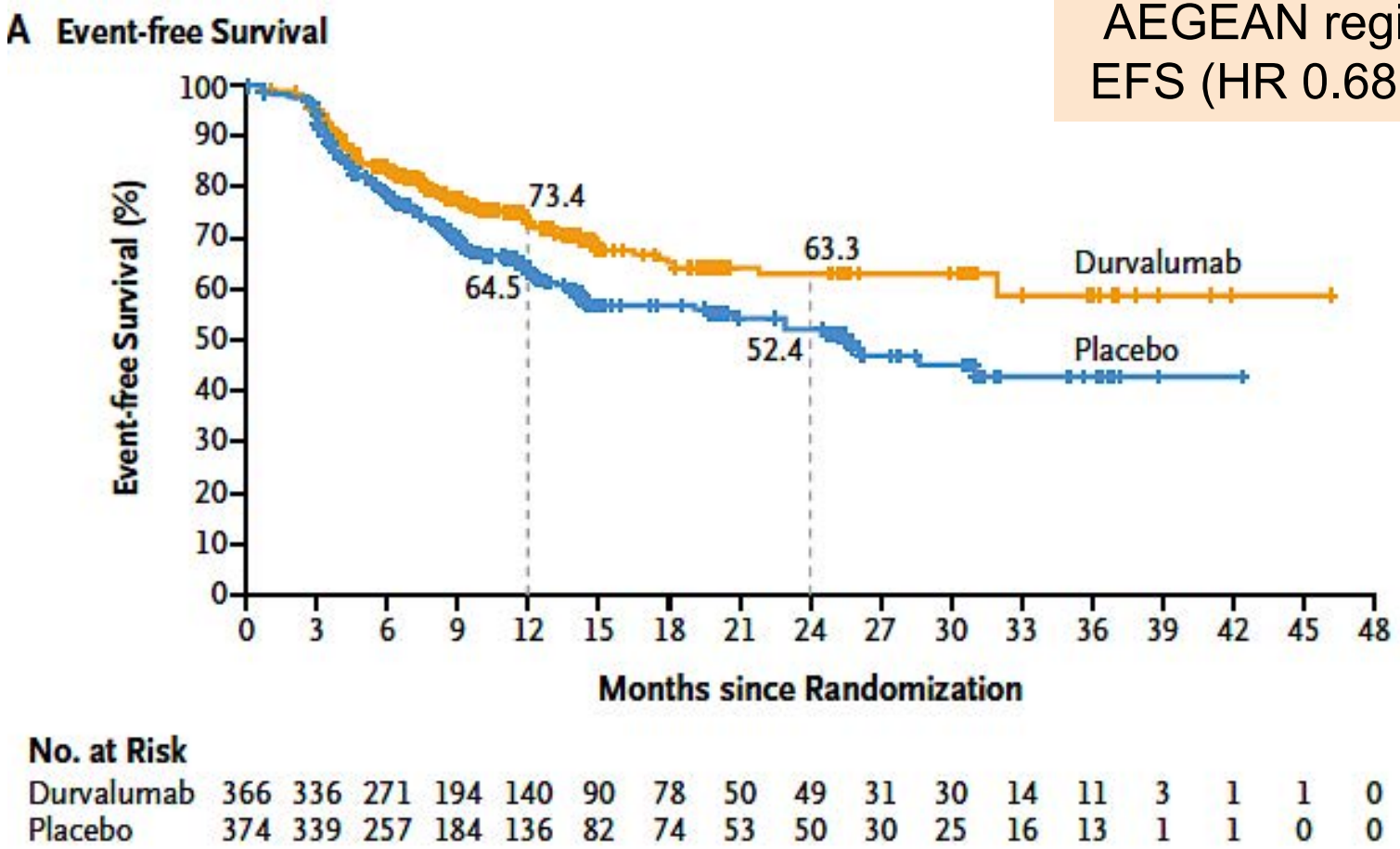
Wakelee et al, NEJM 2023

AEGEAN EFS primary endpoint (BICR in mITT)

First planned interim analysis of EFS

AEGEAN regimen achieved primary endpoint of EFS (HR 0.68) with 11% improvement in 2Y EFS



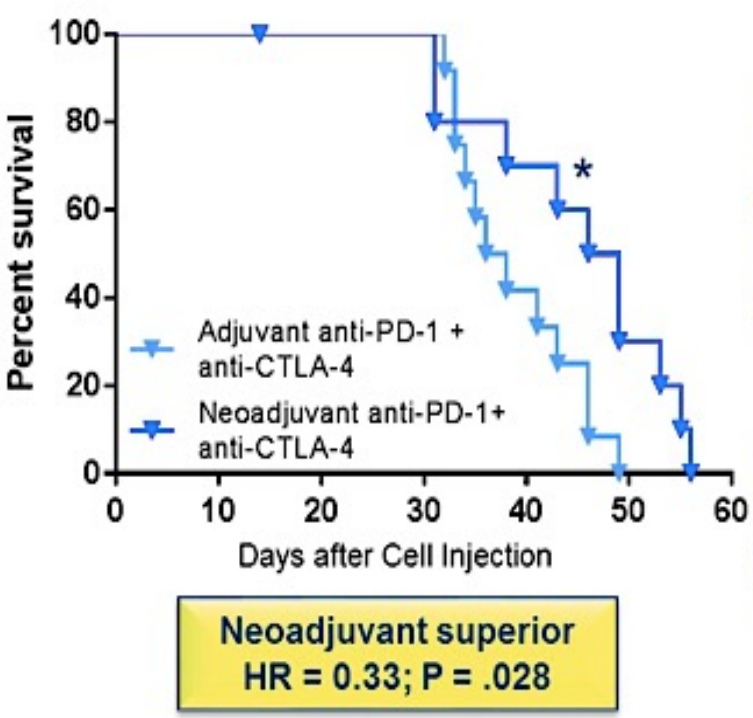
	No. of Events/ No. of Patients	Median Event-free Survival (95%CI)
		mo
Durvalumab	98/366 (26.8)	NR (31.9–NR)
Placebo	138/374 (36.9)	25.9 (18.9–NR)

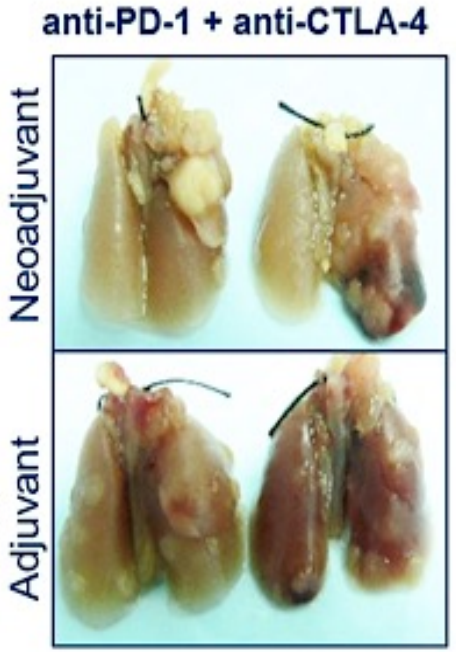
Stratified hazard ratio for disease progression, recurrence, or death, 0.68 (95% CI, 0.53–0.88)
P=0.004 by stratified log-rank test

Heymach et al, NEJM 2023

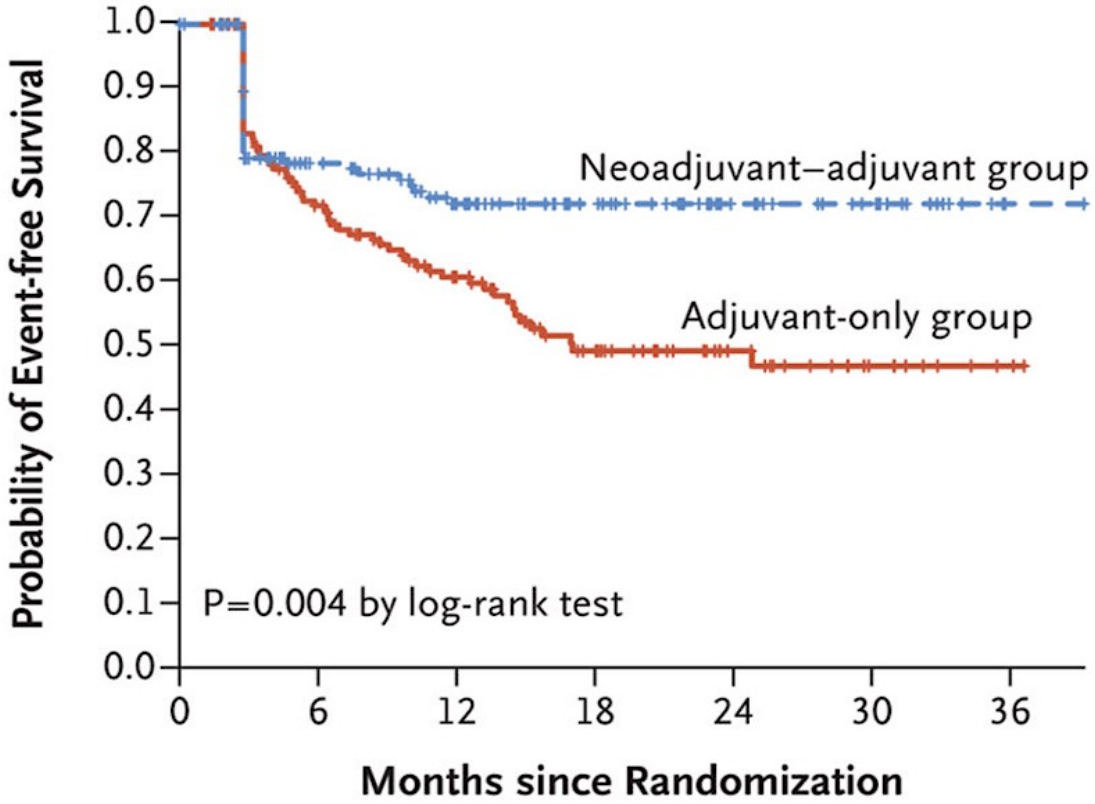
Neoadjuvant, adjuvant, or both? Preclinical and Clinical Studies Support the Superiority of Neoadjuvant or Perioperative ICI vs Adjuvant ICI

NSCLC Model





SWOG S1801 (Melanoma)



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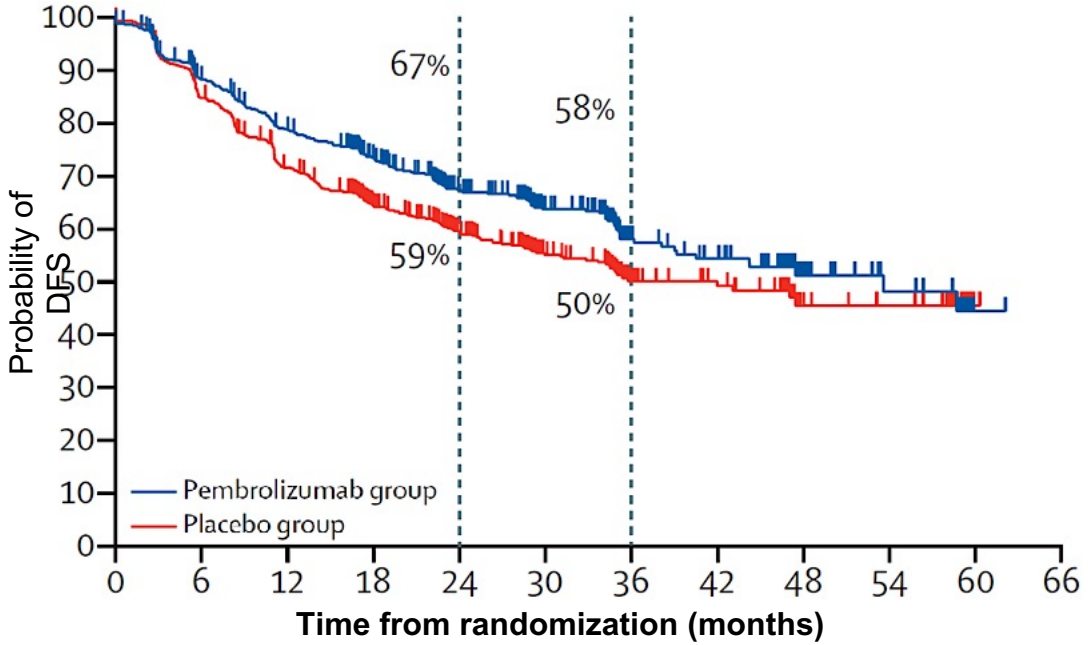
Liu J, et al. *Cancer Discov*. 2016;6(12):1382-1399; Cascone et al, unpublished; Patel SP, et al. *N Engl J Med*. 2023;388(9):813-823

Perioperative pembro appears more effective than adjuvant pembro

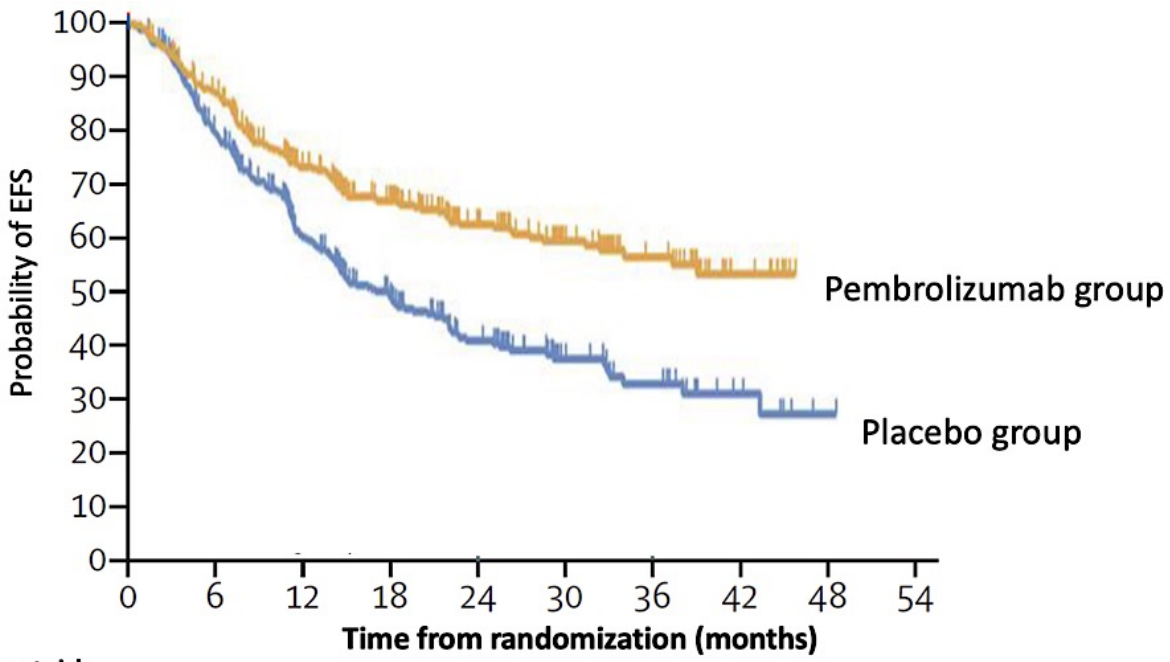
KEYNOTE-091 (Adjuvant Treatment)

HR: 0.76 (95% CI: 0.63, 0.91)



KEYNOTE-671 (Perioperative Treatment)

HR: 0.58 (95% CI: 0.46, 0.72)



No. at risk										
Pembrolizumab group	397	330	236	172	117	72	42	11	0	0
Placebo group	400	294	183	124	74	38	24	9	1	0

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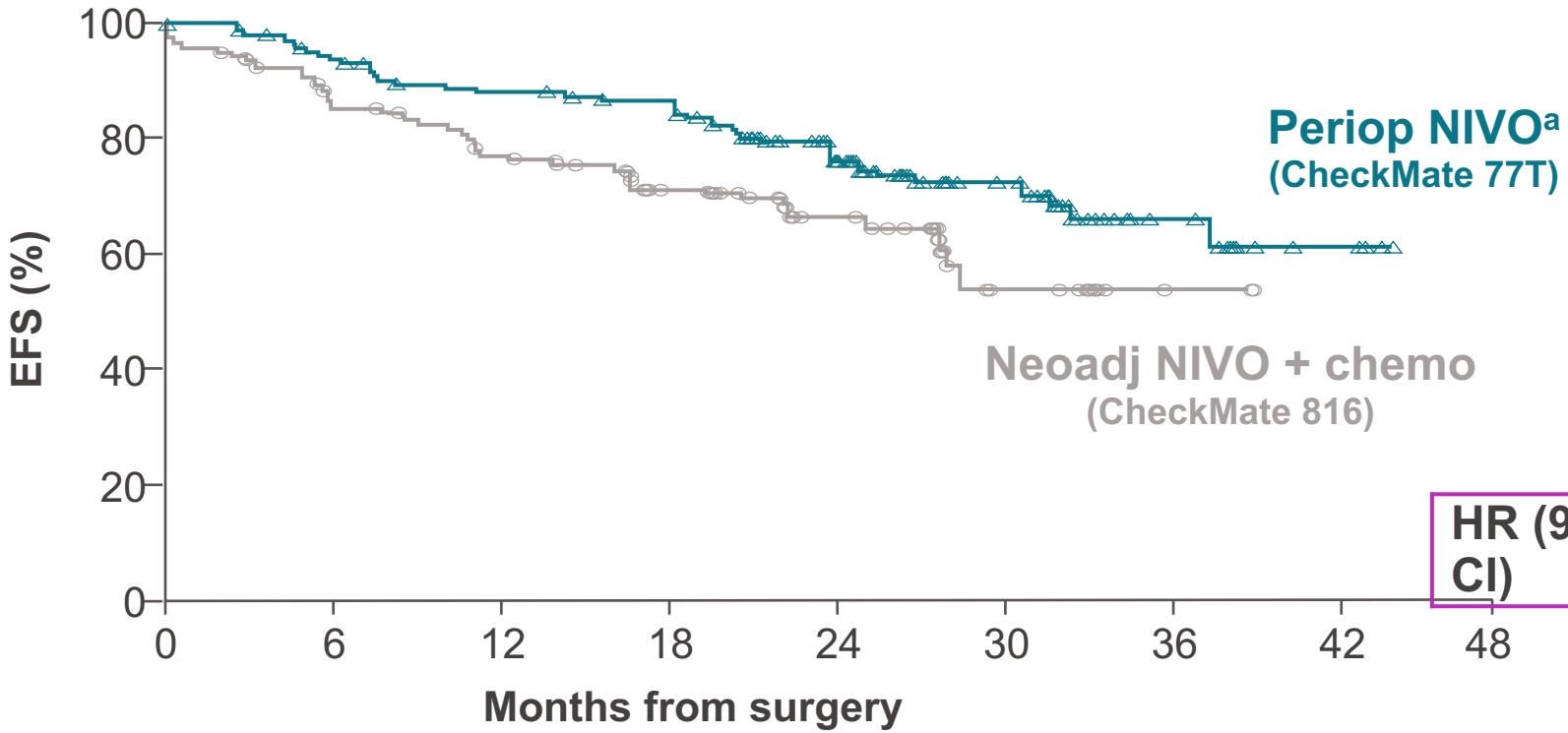
O'Brien M, et al. *The Lancet Oncology*, 23(10), 1274-1286,

Wakelee H, et al. *N Engl J Med*, , Perioperative pembrolizumab for early-stage non-small-cell lung cancer, 389(6), 491-503.

Comparison of neoadjuvant CM816 vs perioperative CM-77T: landmark EFS from definitive surgery



No. at risk

Periop NIVO	139.4	128.0	118.1	112.9	79.7	42.5	13.0	3.1	0
Neoadj N+C	147.5	121.0	106.2	84.2	39.1	12.1	2.2	0	0

	Weighted (ATE)[b]	
	Periop NIVO[a] (n = 139.4[c])	Neoadj NIVO + chemo (n = 147.5[c])
HR (95% CI)	0.61 (0.39–0.97)	

- HR (95% CI): ATT[d] weighted analysis, 0.56 (0.35–0.90); unweighted analysis, 0.59 (0.38–0.92)

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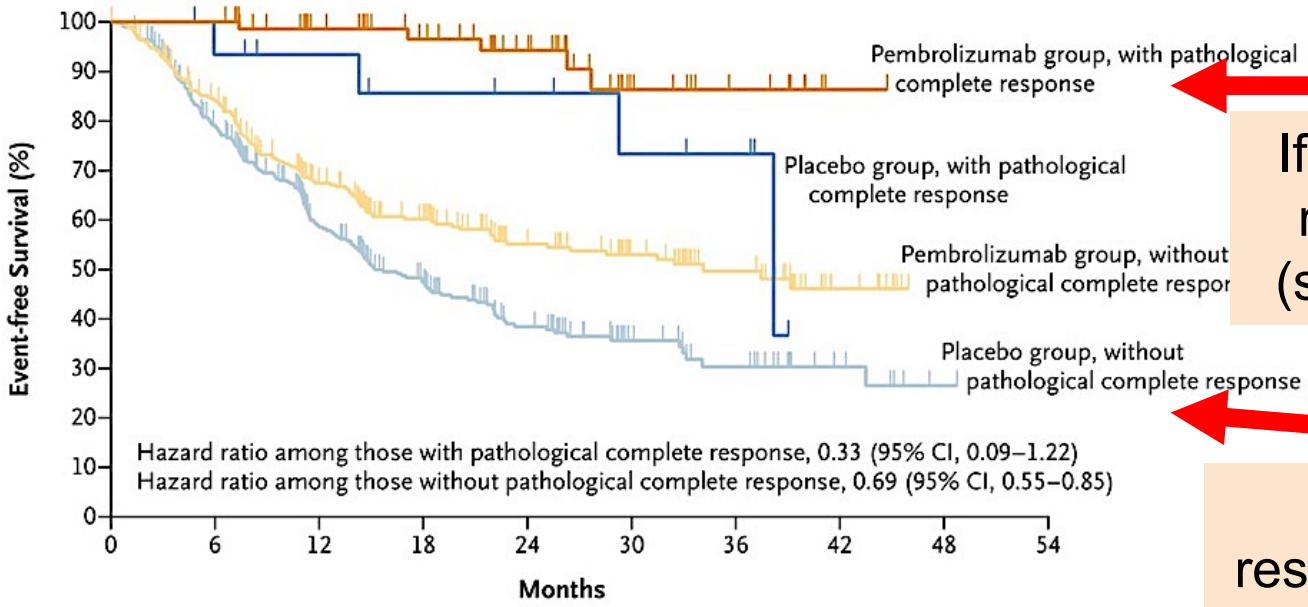
Forde et al, WCLC presentation 2024

Can we select adjuvant therapy based on path CR status? KN 671 suggests benefit for adjuvant in both path CR and non-path CR groups

B Event-free Survival According to Pathological Complete Response



No. at Risk										
With pathological complete response										
Pembrolizumab group	72	72	59	46	33	15	8	1	0	0
Placebo group	16	14	12	10	9	5	4	0	0	0
Without pathological complete response										
Pembrolizumab group	325	258	177	126	84	57	34	10	0	0
Placebo group	384	280	171	114	65	33	20	9	1	0

pCR group: HR 0.33

If the pCR group is benefitting so much, shouldn't they continue? (still >20% chance of recurrence)

Non-pCR group: HR 0.69

If the no pCR group hasn't responded as well, should they get a different type of, or intensified, therapy?

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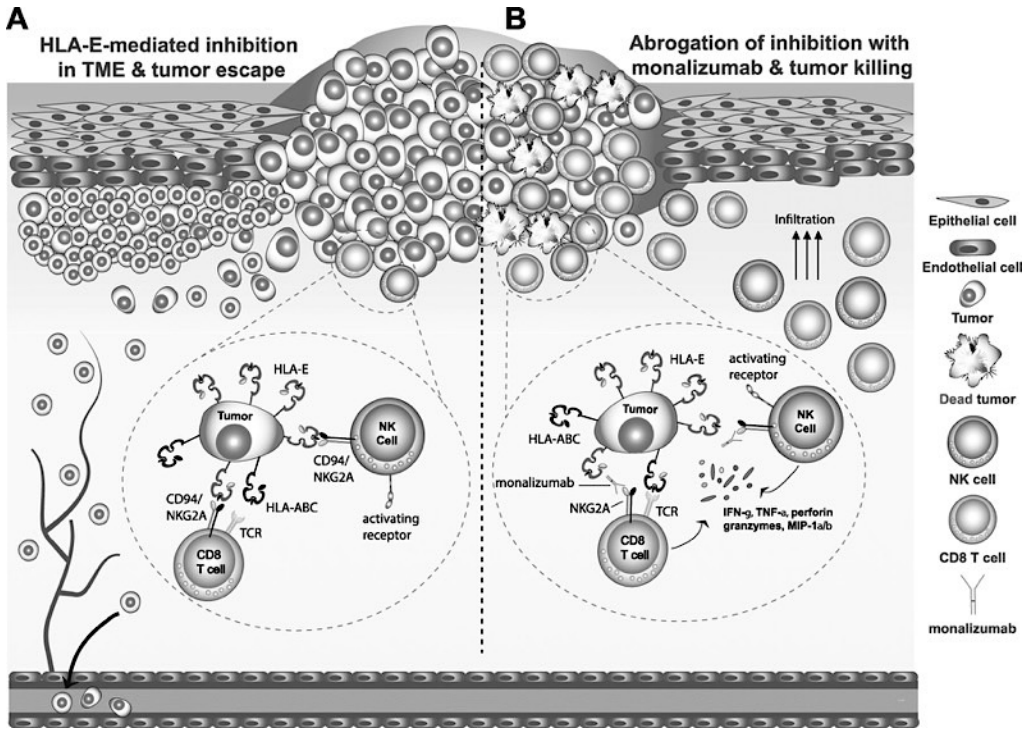
Wakelee et al, NEJM 2023

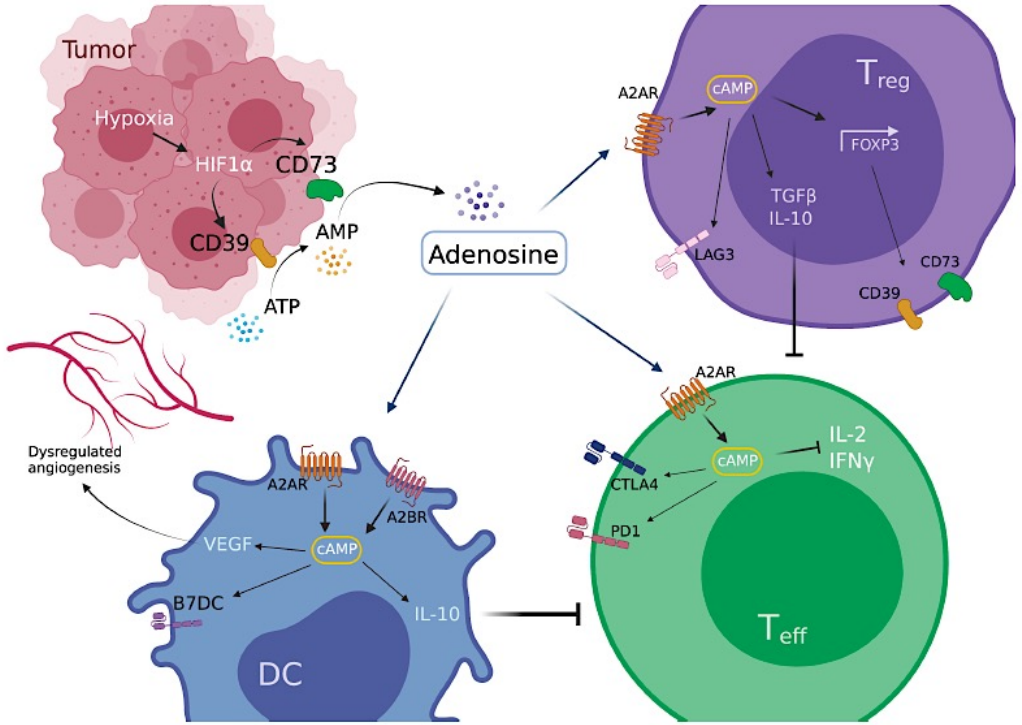
Mechanism of action of monalizumab and oleclumab

Monalizumab blocks the inhibitory interaction between NKG2A and HLA-E, activating NK cells and CD8+ T cells



Thorbald van Hall et al. J Immunother Cancer 2019;7:263

Oleclumab blocks CD73, an enzyme involved in the generation of immunosuppressive adenosine



Augustin et al, JITC 2022; 10:e004089

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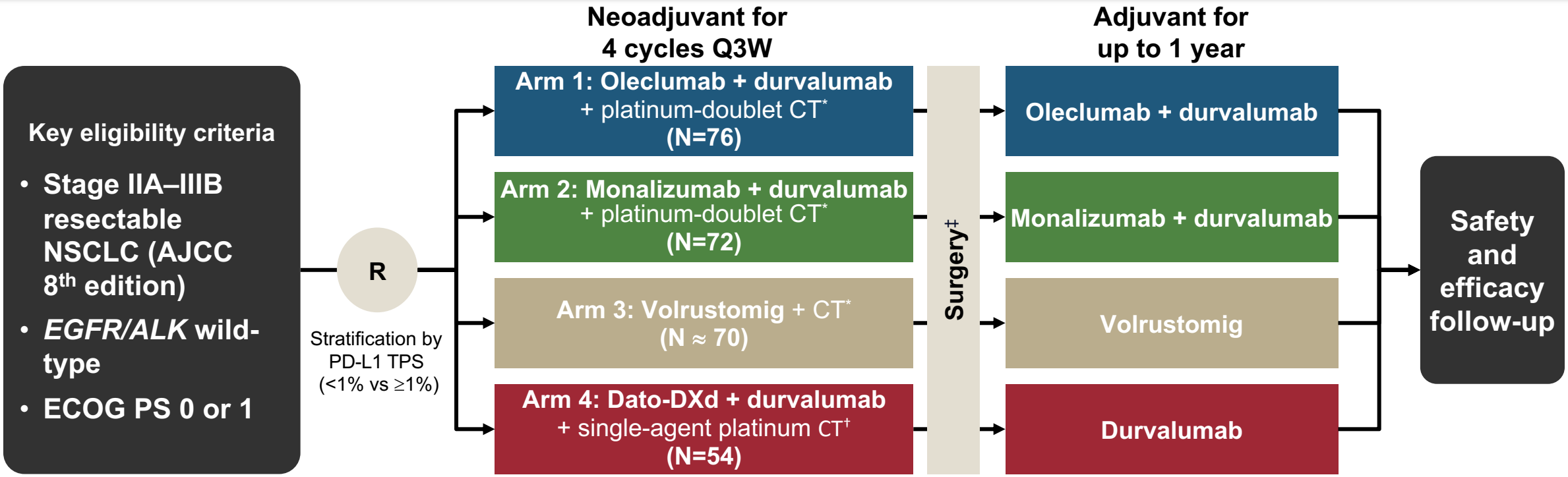
NeoCOAST-2: Open-label, multi-arm platform study in perioperative NSCLC



Primary endpoints
- pCR rate §
- Safety and tolerability

Key secondary endpoints
- mPR rate § and EFS
- Feasibility of surgery

Statistical considerations
- This study was not powered to make direct statistical comparisons between arms.
- Descriptive statistics are summarised and presented.
- The primary intent was to look for preliminary efficacy signals by calculating pCR rates.

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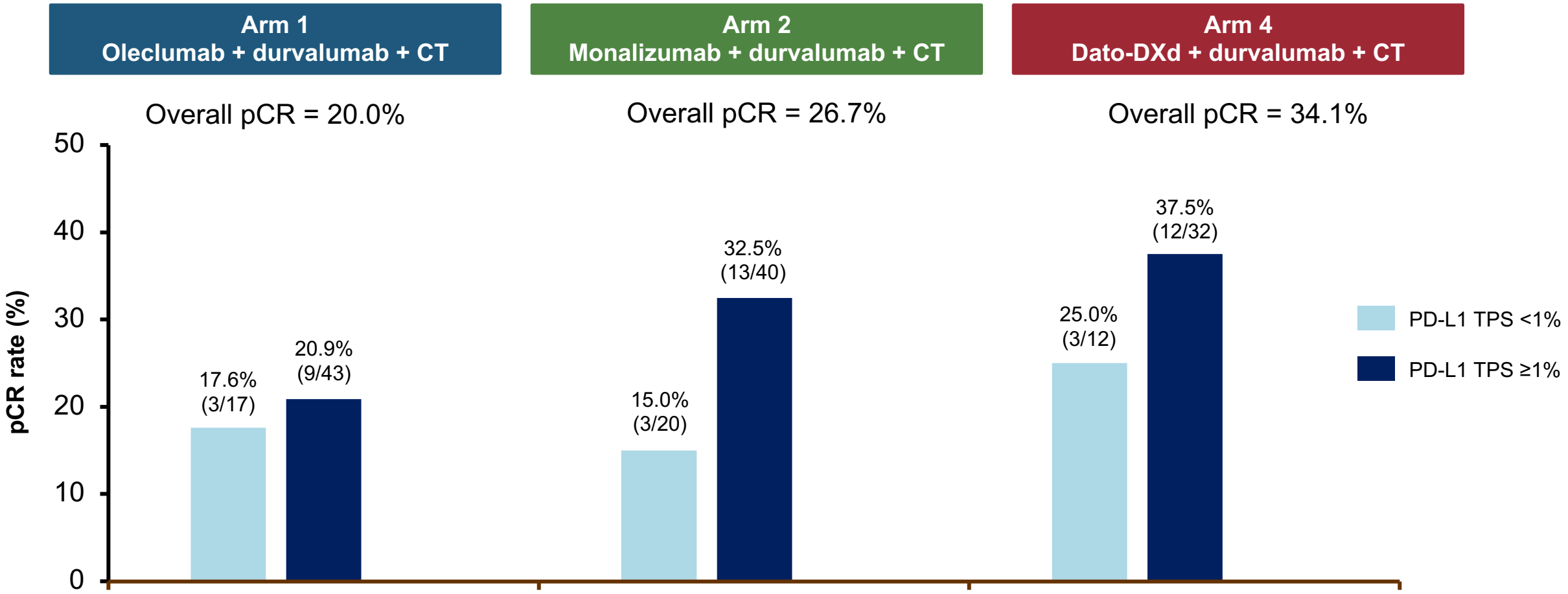
Cascone et al, IASLC 2024 (see updated ASCO 2025 data tomorrow May 31st)

Path CR rates in different durva+chemo combination arms (note: durva+chemo had path CR 17% in Aegean)



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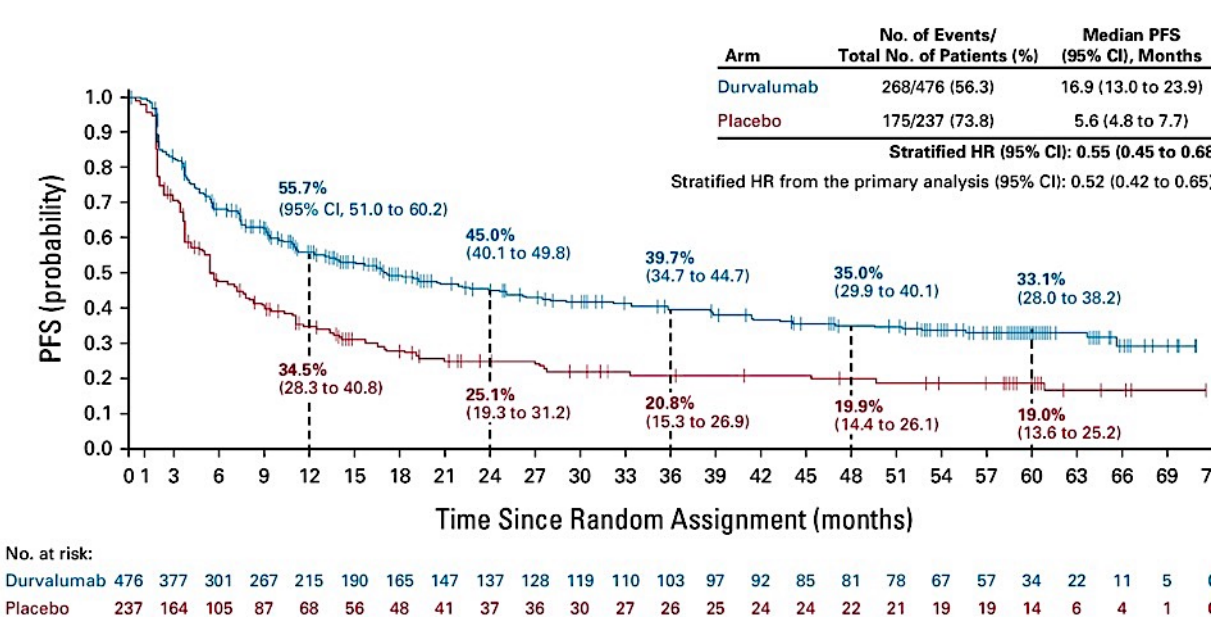
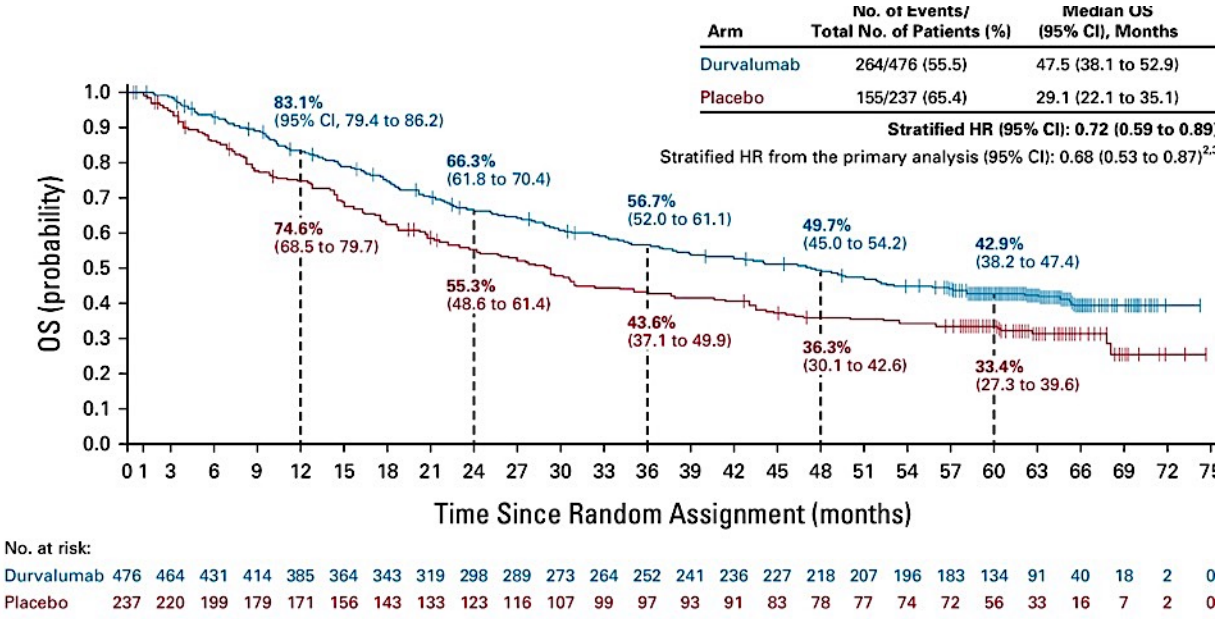
Cascone et al, IASLC 2024 (see updated ASCO 2025 data tomorrow May 31st)

Five year outcomes from PACIFIC: durvalumab after chemoRT for unresectable stage III NSCLC

PFS HR 0.55, 14% improvement in 5Y PFS



OS HR 0.72, 10% improvement in 5Y OS



Spigel et al, JCO 40:12, 2022

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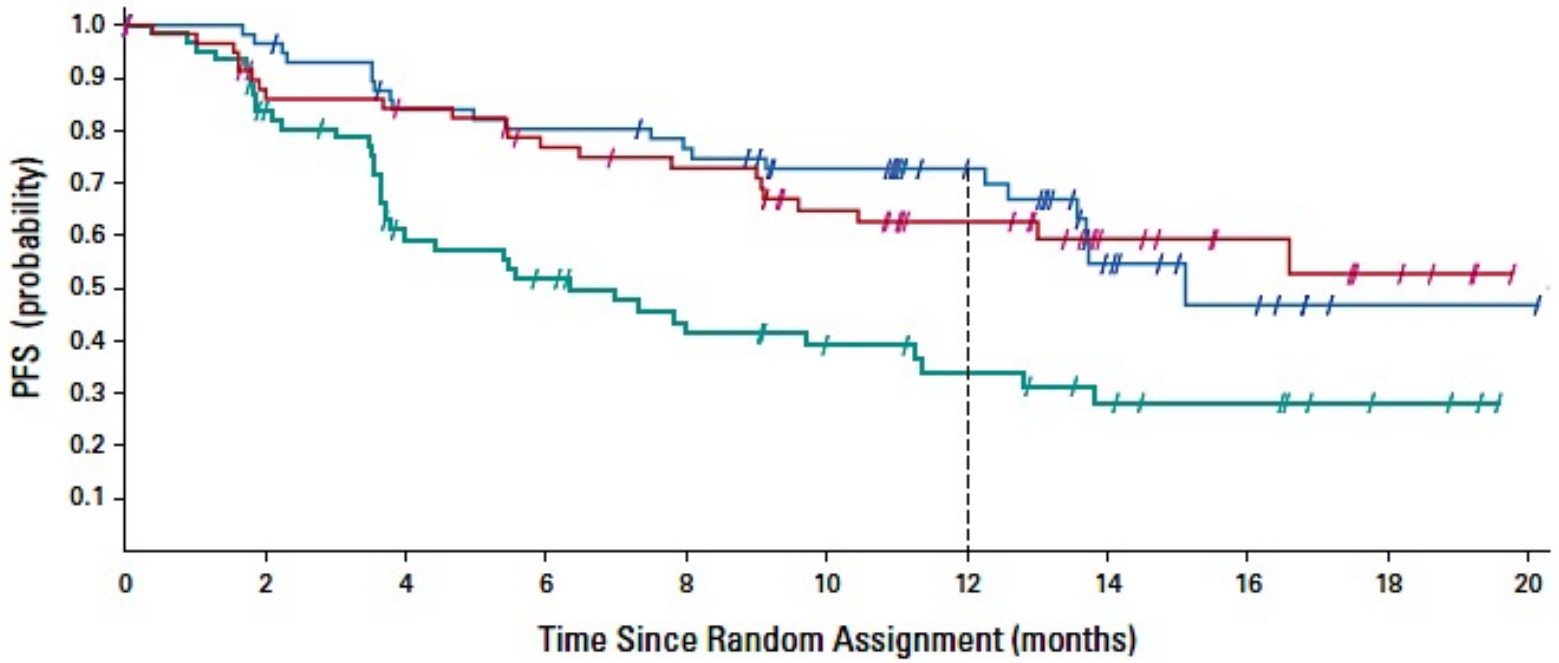
Coast: a randomized phase II study of consolidation durvalumab combinations in unresectable stage III NSCLC

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



No. at risk:											
Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

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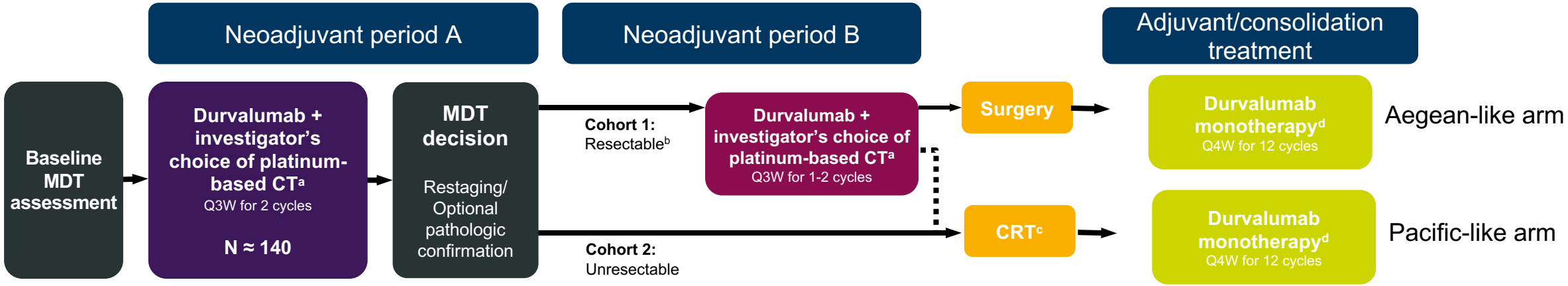
Herbst et al, J Clin Oncol 2022; 40:3383-3393

Given the efficacy of perioperative regimens for N2 disease, can induction chemo-IO be used for borderline resectable cases? The MDT-BRIDGE study

Phase 2 for stage IIB to IIIB, N2+ NSCLC testing induction chemo+ durvalumab, followed by restaging, then assessment of operability with options of surgery→adjuvant durva (Aegean) or chemoRT then durvalumab (Pacific)



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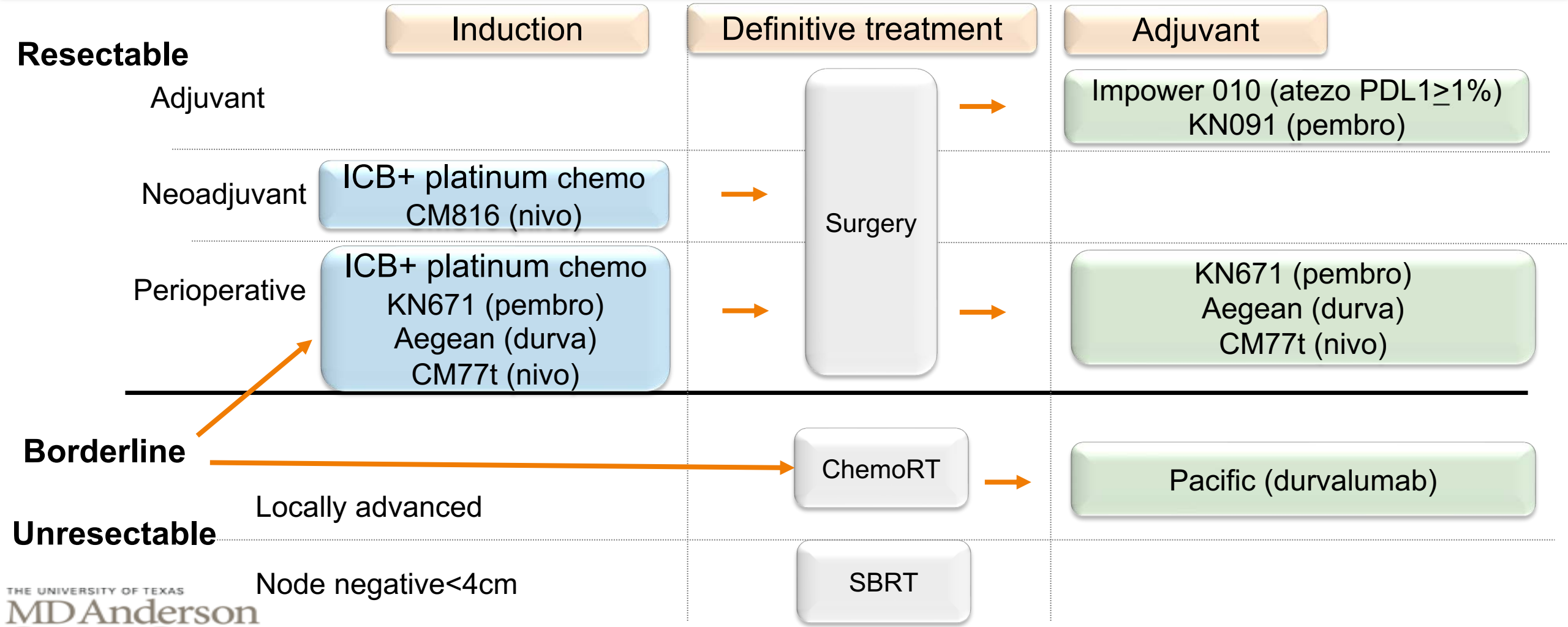
NCT04765709

Evolving paradigm for non-metastatic, non-driver NSCLC



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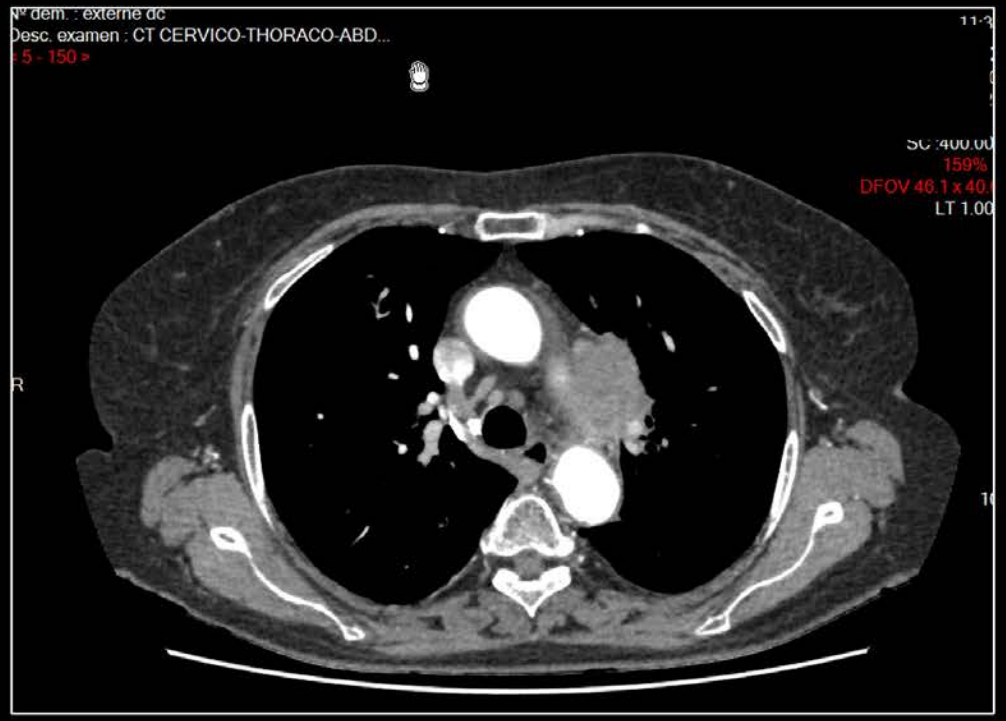
The evolving paradigm for non-metastatic NSCLC: where are we in 2025?

- Neoadjuvant, adjuvant, and perioperative IO regimens are all approved for resectable NSCLC
- We have 3 positive RCT of perioperative IO with similar designs that have generally yielded similar, clinically meaningful benefits
  - AEGEAN (durva), KN671 (pembro), and CM-77T (nivo)
- Multiple lines of evidence suggest that:
  - Neoadjuvant>adjuvant, neoadjuvant+adjuvant > neoadjuvant or adjuvant.
  - There is likely benefit to adjuvant IO after neoadjuvant IO, whether or not patients have had a path CR.
- Key questions for the field include how to intensify non-path CR groups, and how to treat borderline resectable disease

Faculty Case Presentations

Case Presentation – Prof Peters: 77-year-old female, former smoker

- 77-year-old female
- Former smoker (50py)
- September 2019: dysphonia
- H&N exam: left vocal cord paralysis, weight loss 10%
- PS 1
- CT scan and PET-CT (Sept 2019)


N° dem. : externe dc
Desc. examen : CT CERVICO-THORACO-ABD...
159%
LT 1.00
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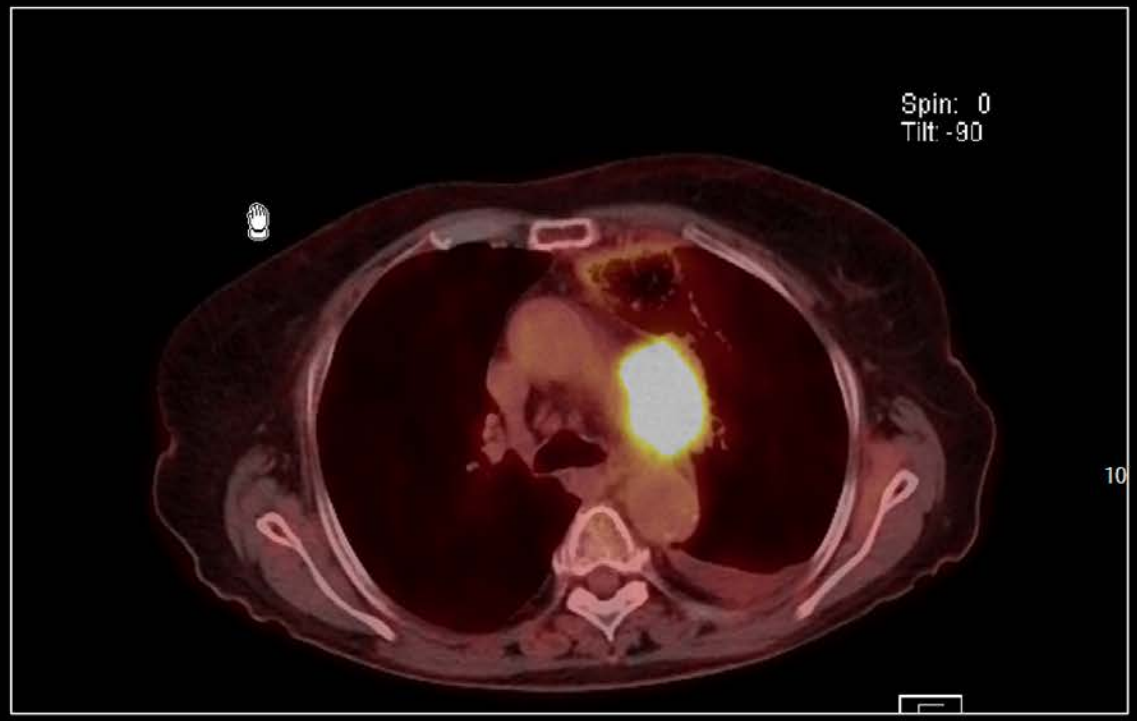
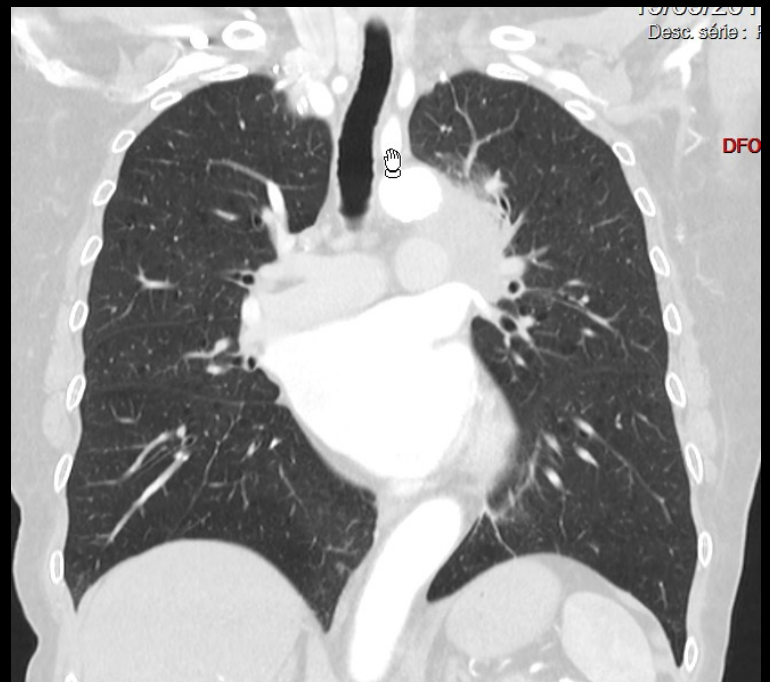

Spin: 0
Tilt: -90


Desc. série :

Case Presentation – Prof Peters: 77-year-old female, former smoker (cont'd)

- 10.2019: Bronchoscopy + EBUS (positive in 4L, 10L)
- Brain MRI (11.2019): No CNS metastases
- Staging: Upper left lung squamous cell carcinoma: cT4 (recurrent) cN2 (4L) cM0: stage IIIB (7^{th} and 8^{th} edition)
- PDL1 1%

Case Presentation – Prof Peters: 77-year-old female, former smoker (cont'd)

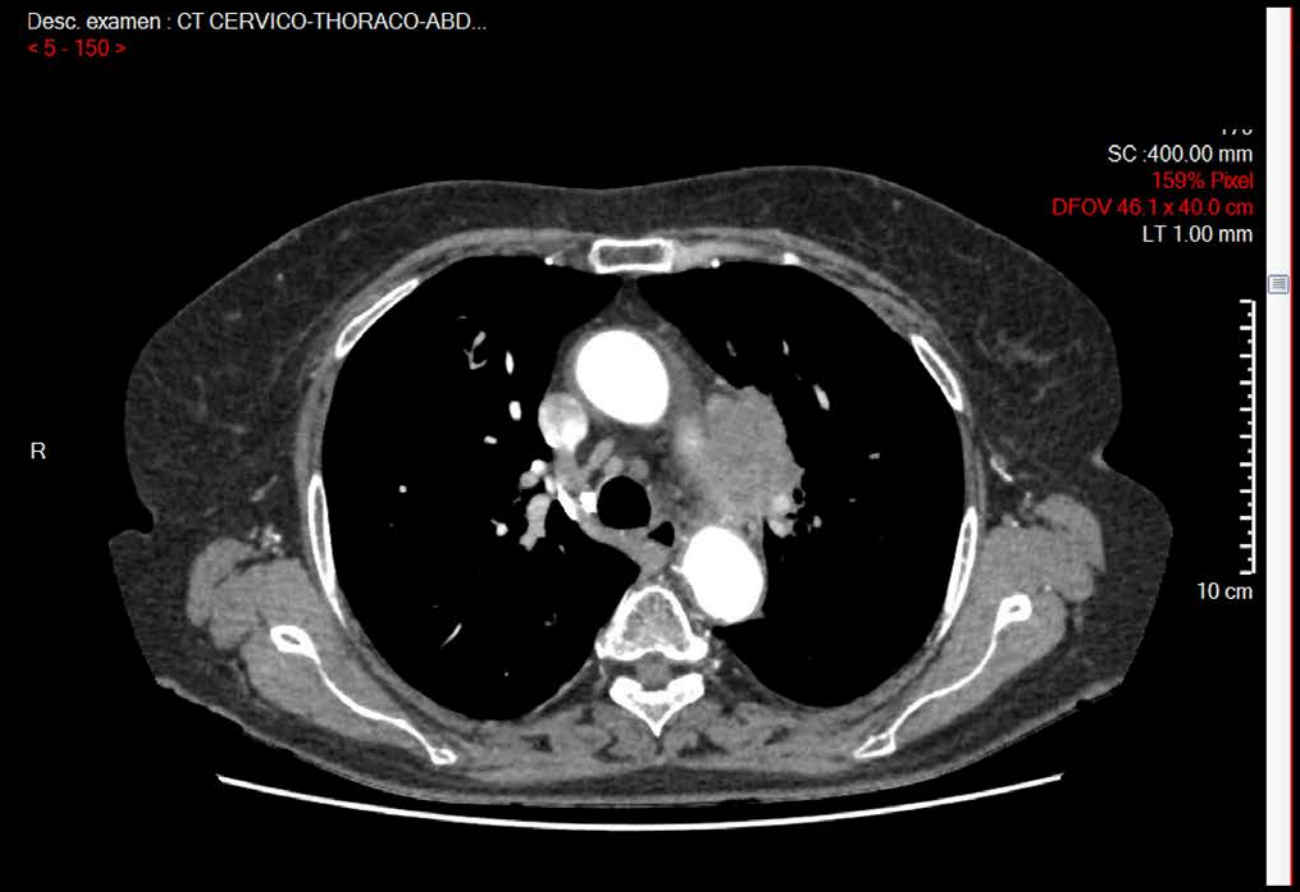
- Multidisciplinary Tumorboard:

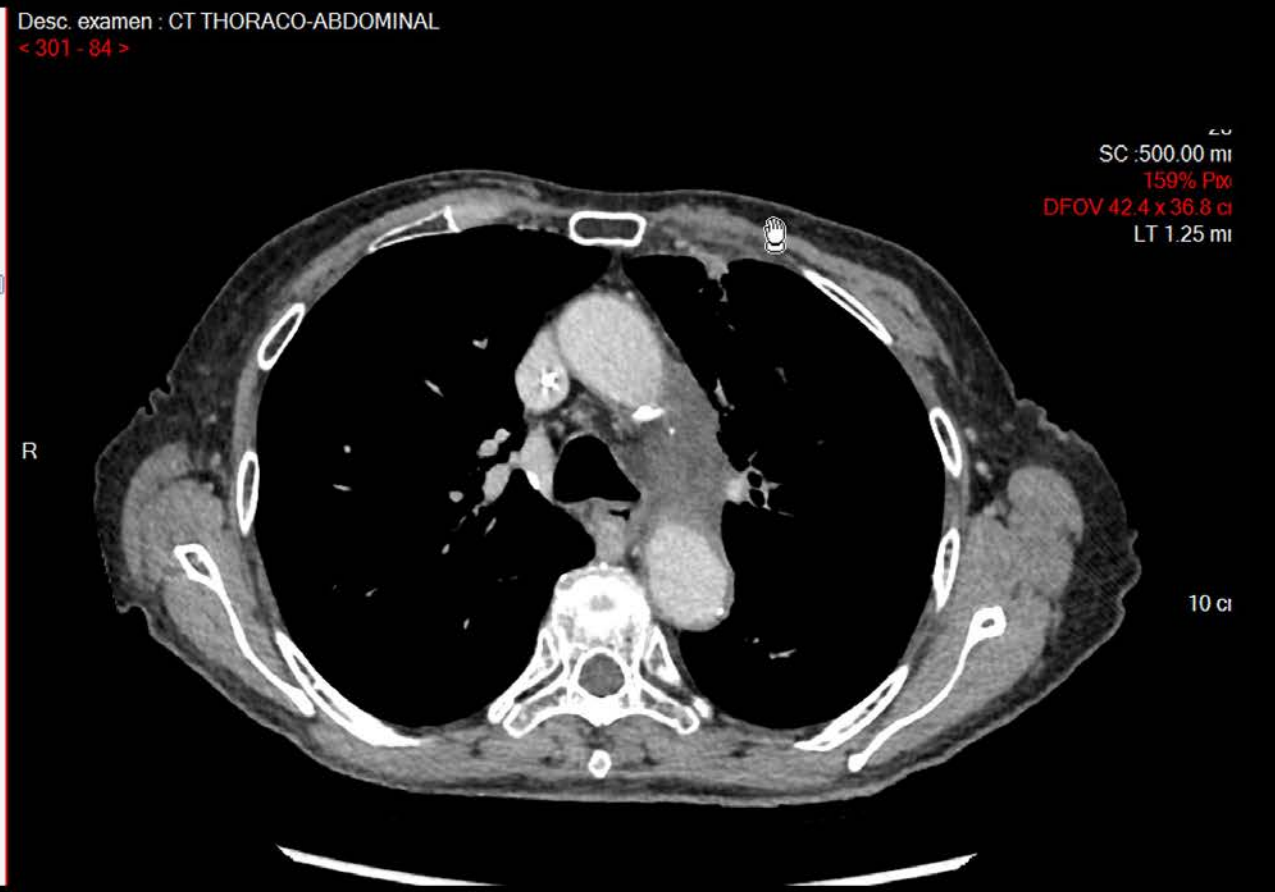
Chemoradiation and consolidation immunotherapy (durvalumab)

- 27.11.2019 au 10.02.2020:

Chemoradiotherapy (60Gy+ carboplatin/vinorelbine: 3 cycles)

1st tumour assessment: CT scan (March 2020)

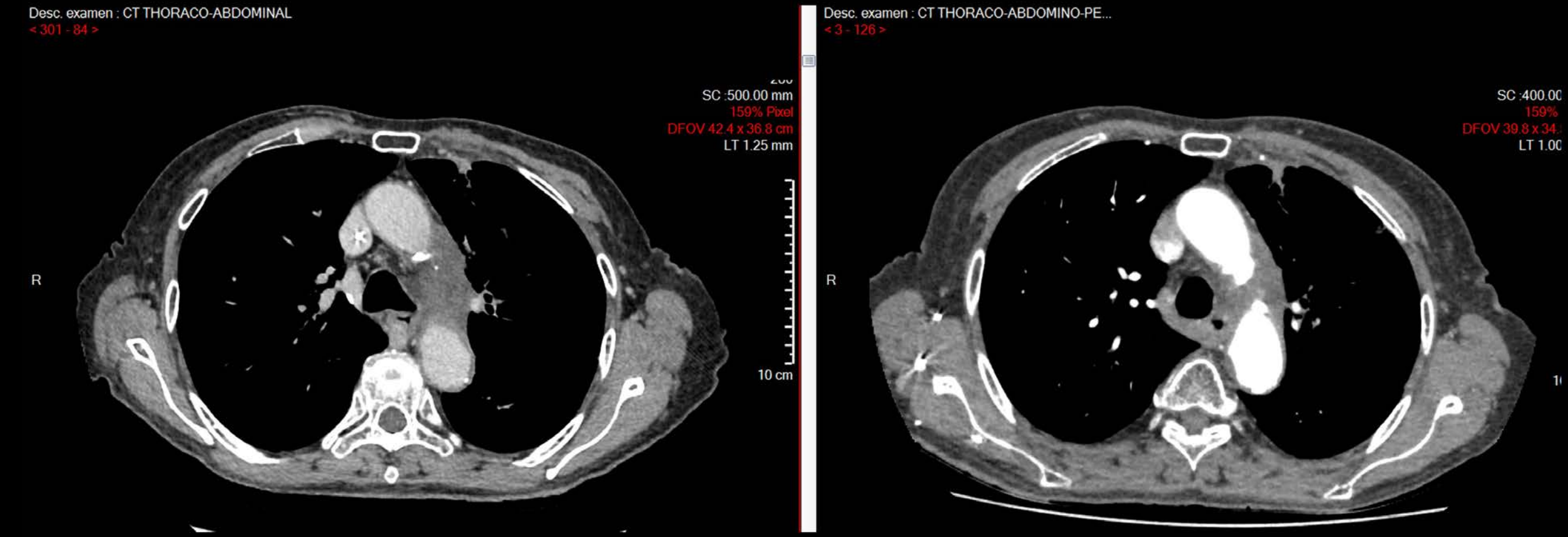




Case Presentation – Prof Peters: 77-year-old female, former smoker (cont'd)

- 06.04.2020: durvalumab 10mg/kg q2w
- 6 infusions with fatigue grade 1, rash grade 1, cough grade 1, dyspnea grade 2

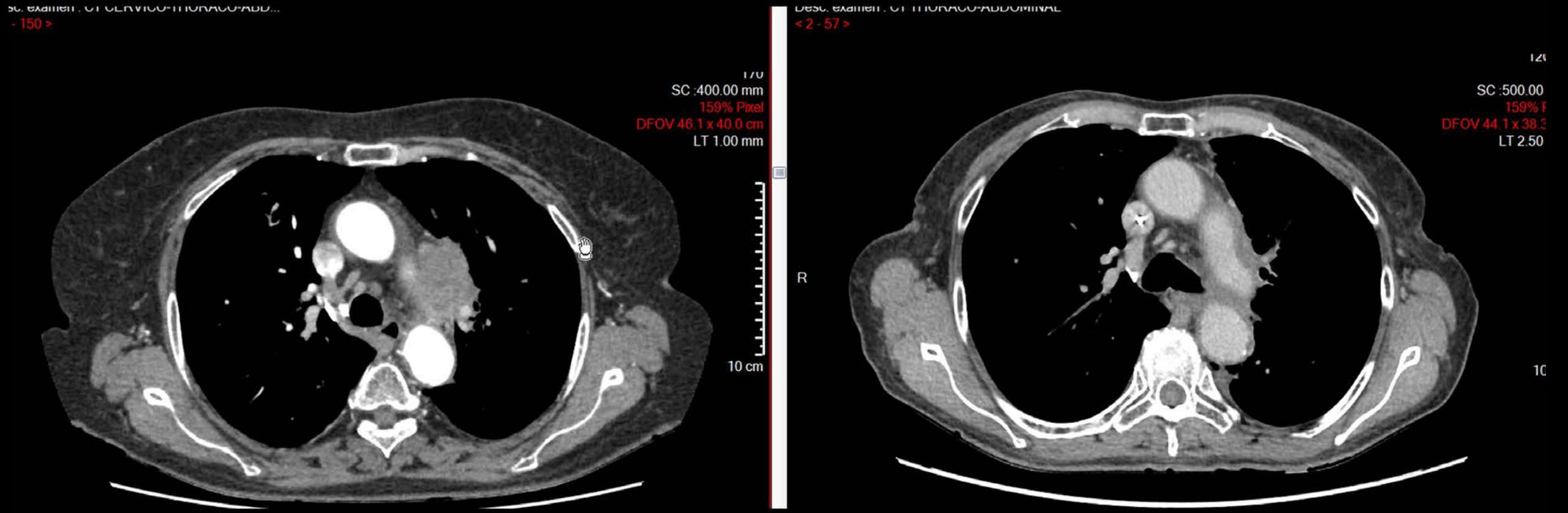
CT scan: June 2020



Case Presentation – Prof Peters: 77-year-old female, former smoker (cont'd)

- Early July 2020: colitis grade 4, proven by colonoscopy/biopsies
- Prednisone iv 3mg/kg and 2 doses of infliximab iv with slow resolution of diarrhoea and pain
- Durvalumab permanently discontinued
- Symptoms lasting 3 months

CT scan: October 2020



Case Presentation – Prof Peters: 77-year-old female, former smoker (cont'd)

- Bran MRI in December 2023: normal
- CT scan in December 2024: CR

Questions for the Faculty

For patients with resectable localized NSCLC, which strategy do you believe generally offers the best risk-benefit ratio — neoadjuvant, perioperative or adjuvant anti-PD-1/PD-L1 antibody therapy?

How do you currently select among the available neoadjuvant, perioperative and adjuvant immunotherapeutic strategies for individual patients with localized NSCLC in your own practice?

How do you think through the use of neoadjuvant/adjuvant anti-PD-1/PD-L1 antibodies for patients with autoimmune disease or a history of transplant?

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

How often do you encounter patients with Stage III NSCLC that is unresectable at initial presentation but might be operable with tumor shrinkage? How do you decide whether to proceed with definitive chemoradiation therapy followed by consolidation durvalumab in these cases versus attempting to downstage the tumor with neoadjuvant immune checkpoint inhibition?

In the absence of an EGFR mutation, are there any situations in which you would NOT employ consolidation durvalumab for a patient with unresectable Stage III NSCLC responding to chemoradiation therapy?

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

How would you think through toxicity management in this patient's case? What would you recommend for a patient with low-grade cough and/or dyspnea while receiving consolidation durvalumab?

In patients receiving consolidation durvalumab, how do you differentiate drug-related pneumonitis from other potential causes of symptoms (nonspecific radiation effects on imaging, symptoms from their disease, infection, etc)?

What grade of various immune-related adverse events will prompt you to discontinue therapy with consolidation durvalumab?

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Colorectal Cancer

A CME Symposium Held in Conjunction with the 2025 ASCO® Annual Meeting

Friday, May 30, 2025
6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Andrea Cercek, MD
Arvind Dasari, MD, MS
Pashtoon Kasi, MD, MS
Eric Van Cutsem, MD, PhD

Moderator

J Randolph Hecht, MD

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Clinical Care of Patients with EGFR Mutation-Positive Non-Small Cell Lung Cancer

A CME Symposium Held in Conjunction with the 2025 ASCO® Annual Meeting

Friday, May 30, 2025

6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Nicolas Girard, MD, PhD

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