Global Lung Cancer Academy

Global Lung Cancer Academy

Sharing Best Practices to Optimize Patient Care

21 October 2022

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Sponsor: Sanofi Oncology & Regeneron

Global Lung Cancer Academy

Welcome and Meeting Overview

Corey Langer, MD

Meet the faculty

CO-CHAIRS

Corey J. Langer, MD, FACP
University of Pennsylvania, PA, USA

Carlos H. Barrios, MD
Center at Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

FACULTY

Narjust Florez (Duma), MD
Dana-Farber Cancer Institute/ Harvard Cancer Center, MA, USA

Barbara Melosky, MD, FRCP
University of British Columbia, Vancouver, Canada

Edgardo S. Santos, MD
Charles E. Schmidt College of Medicine, Florida Atlantic University, FL, USA

Anne S. Tsao, MD
MD Anderson Cancer Center, Houston, TX, USA

William N. William, MD
Beneficência Portuguesa de São Paulo, Brazil

Ignacio I. Wistuba, MD
MD Anderson Cancer Center, Houston, TX, USA

Global Lung Cancer Academy

Objectives of the program

- Discuss current evidence-based practices in the diagnosis and treatment of lung cancer
- Learn about current genomic testing practices and how these results inform treatment decisions
- Understand advances made in immunotherapy for lung cancer and how these agents are being used in clinical practice
- Gain insights into the latest developments in targeted therapies used for lung cancer
- Promote best practice cancer care via the review of clinical patient cases
- Recognize the major clinical trials underway to further develop treatment in lung cancer
- Learn about the regional challenges and differences in lung cancer treatment patterns in Latin America and Canada

Day 1: Plenary Sessions

Friday, 21 October 2022 from 4.00 PM – 8.00 PM EDT

Time (EDT)	Title	Speaker
4.00 PM – 4.10 PM (10 min)	**Welcome and Meeting Overview** • Introduction to audience response system (ARS)	Corey Langer
4.10 PM – 4.40 PM (30 min)	**Recent Developments in NSCLC – What Is New in Research and Management?** • Overview of recently presented data in NSCLC	Corey Langer
4.40 PM – 5.00 PM (20 min)	**Biomarker and Mutational Testing for NSCLC – What, Where, and When?** • NSCLC heterogeneity, overview of current and emerging biomarkers and co-mutations, and best practices and guidelines for testing at diagnosis and during treatment of NSCLC	Ignacio Wistuba
5.00 PM – 5.20 PM (20 min)	**Neoadjuvant Therapy for NSCLC – Is It Ready for Prime Time?** • Current state of neoadjuvant therapy in resectable NSCLC	Anne Tsao
5.20 PM – 5.50 PM (30 min)	**Debate: Adjuvant or Neoadjuvant Therapy for NSCLC?** • Neoadjuvant therapy (10 min) • Adjuvant therapy (10 min) • Discussion and voting (10 min)	Moderator: Corey Langer Anne Tsao Narjust Florez All faculty
5.50 PM – 6.00 PM (10 min)	***Break***	
6.00 PM – 6.20 PM (20 min)	**Locally Advanced Unresectable NSCLC – What Are the Options?** • Current standard practices and ongoing studies	Edgardo S. Santos
6.20 PM – 6.40 PM (20 min)	**Targeted Therapies for Advanced NSCLC** • Summary of targeted therapies for different NSCLC genotypes	Barbara Melosky
6.40 PM – 7.00 PM (20 min)	**Immunotherapy Approaches for Advanced NSCLC** • Predictive biomarkers, monotherapy vs combination strategies, mechanisms of resistance, and rechallenge	Edgardo S. Santos
7.00 PM – 7.20 PM (20 min)	**De Novo—or at Relapse—Oligometastatic NSCLC: Management of Local and Systemic Disease** • Work-up of first recurrence vs de novo oligometastatic NSCLC, including sites of involvement (isolated vs systemic recurrence)	Narjust Florez
7.20 PM – 7.50 PM (30 min)	**Tumor Board Discussion** • Patient case 1 (10 min) • Patient case 2 (10 min) • Discussion and Q&A (10 min)	Moderator: Corey Langer Vinícius Lorandi Barbara Melosky All faculty
7.50 PM – 8.00 PM (10 min)	**Session Close** • ARS questions	Corey Langer

Day 2: Plenary Sessions

Monday, 24 October 2022 from 4.00 PM – 7.00 PM EDT

Time (EDT)	Title	Speaker
4.00 PM – 4.10 PM (10 min)	**Session Open** • ARS questions	Corey Langer and Carlos Barrios
4.10 PM – 4.40 PM (30 min)	**Interactive Discussion: Regional Challenges in NSCLC Management** • Interactive discussion and Q&A (15 min)	Moderator: Carlos Barrios All faculty
4.40 PM – 5.00 PM (20 min)	**Current Diagnostic Options and Initial Management of Early-Stage NSCLC in Latin America** • Overview of currently available diagnostic methods and treatment options for early-stage NSCLC (resectable vs unresectable)	William William
5.00 PM – 5.20 PM (20 min)	**Current Treatment Options for Metastatic NSCLC in Latin America** • Overview of currently available treatment options for metastatic NSCLC	Carlos Barrios
5.20 PM – 5.50 PM (30 min)	**Tumor Board Discussion** • Patient case 1 (10 min) • Patient case 2 (10 min) • Discussion and Q&A (10 min)	Moderator: Carlos Barrios Caio Abner Leite Alvaro Guimaraes Paula All faculty
5.50 PM – 6.00 PM (10 min)	***Break***	
6.00 PM – 6.20 PM (20 min)	**Monitoring and Managing Immunotherapy-Related AEs** • Optimal monitoring and managing of the most common AEs associated with immunotherapy	Edgardo S. Santos
6.20 PM – 6.50 PM (30 min)	**Tumor Board Discussion** • Patient case (10 min) • Discussion and Q&A (20 min)	Moderator: Corey Langer Barbara Melosky All faculty
6.50 PM – 7.00 PM (10 min)	**Session Close** • ARS questions	Carlos Barrios

Introduction to Voting

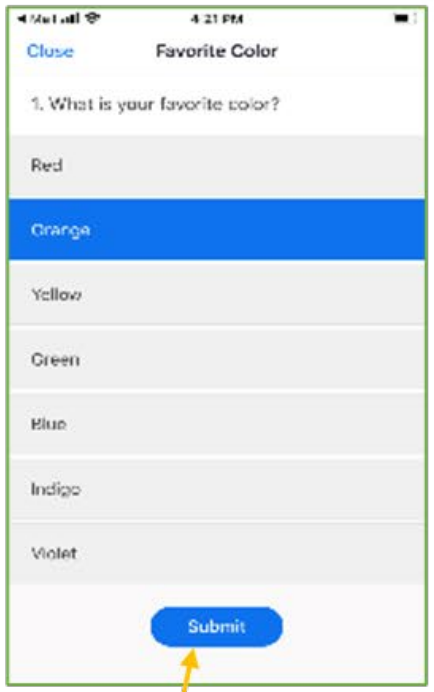
Desktop View

Choose Your Answer
Click on the answer (or answers if multiple choice)

Select Submit
After choosing your answer, select "Submit" to finalize

Mobile View

Choose Your Answer
Click on the answer (or answers if multiple choice)



Select Submit
After choosing your answer, select "Submit" to finalize

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Question 1

In which country do you currently practice?

1. Argentina
2. Brazil
3. Canada
4. Colombia
5. Chile
6. Mexico
7. Peru
8. Other country in LATAM
9. Other country outside LATAM

Question 2

How would you describe your specialty?

1. General oncologist
2. Lung oncologist
3. General internal medicine
4. Fellow
5. Other

Question 3

In what percentage of your patients with lung cancer have you used neoadjuvant therapy?

1. None
2. ≤25%
3. 26%–50%
4. 51%–75%
5. ≥76%

Question 4

In the EMPOWER-Lung 1 trial, cemiplimab showed improvement over chemotherapy in:

1. PFS only
2. OS only
3. PFS and OS
4. Neither

Question 5

In what percentage of your patients with lung cancer do you perform liquid biopsy?

1. None
2. ≤20%
3. 21%–50%
4. 51%–75%
5. ≥76%

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Recent Developments in NSCLC – What Is New in Research and Management?

Corey Langer, MD

Penn Medicine
Abramson Cancer Center

Division of Hematology and Oncology

Recent Advances in Management of Lung Cancer

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October 2022

Disclosures: Past 10 Years

- **Institutional Grant/Research Support**
  - Pfizer, Lilly, Advantagene, Inovio, Celgene, Vertex, Ariad (Takeda), Merck, Stemcentrx, Genentech/Roche, AstraZeneca, Trizell, GSK, Guardant, Fujifilm
- **Scientific Advisor**
  - Bristol Myers Squibb, Lilly, Pfizer, Synta, Boehringer-Ingelheim, AstraZeneca, Novartis, Abbott, Genentech/Roche, Bayer/Onyx, Celgene, Clarient, Clovis, Guardant, Merck, Gilead
- **Data Safety Monitoring Committees**
  - Lilly, Amgen, Peregrine, Incyte, SWOG, Oncocyte, VALOR

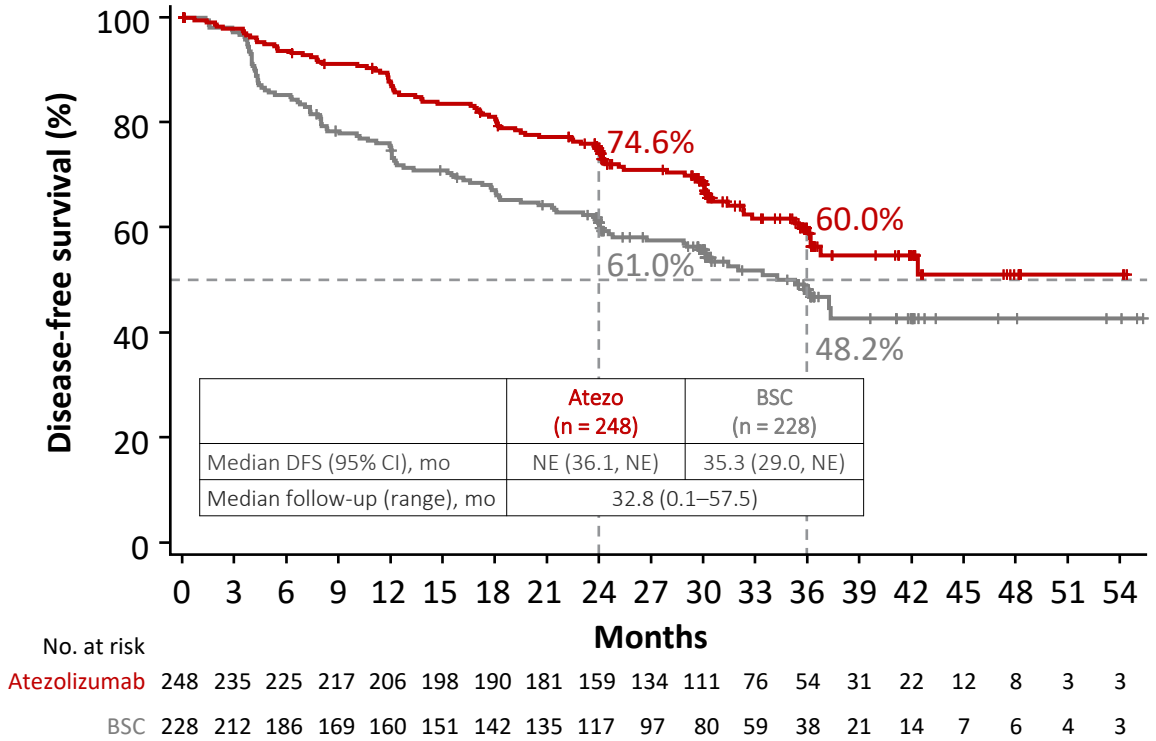
Curable NSCLC: Can We Isolate the Role of Immunotherapy in the Neoadjuvant and Combined Modality Arena?

Exporting CPIs to the Curative Setting

- IMpower010
- CheckMate 816
- NADIM
- PACIFIC

IMpower010: The Primary Endpoint of Improved DFS in Patients With PD-L1 TC ≥1%, Stage II–IIIA* NSCLC Was Met

DFS in PD-L1 TC ≥1%, Stage II–IIIA, Completely resected NSCLC



Primary Analysis Populations

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

Endpoint was met at DFS IA

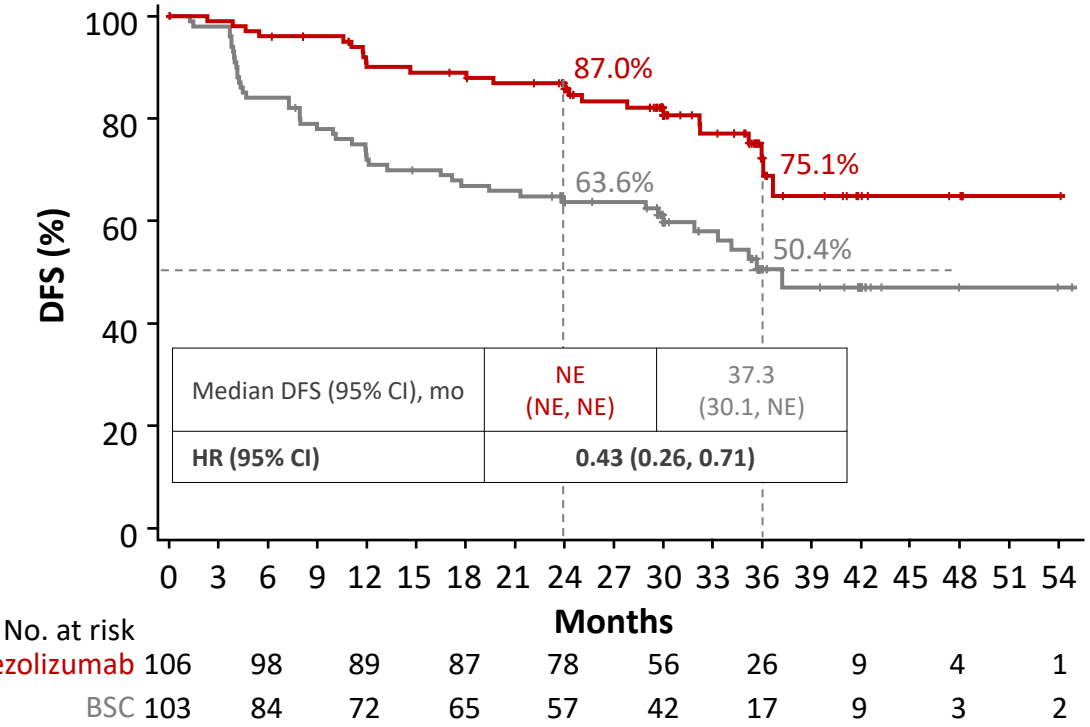
Endpoint was not met at DFS IA, and follow-up is ongoing

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

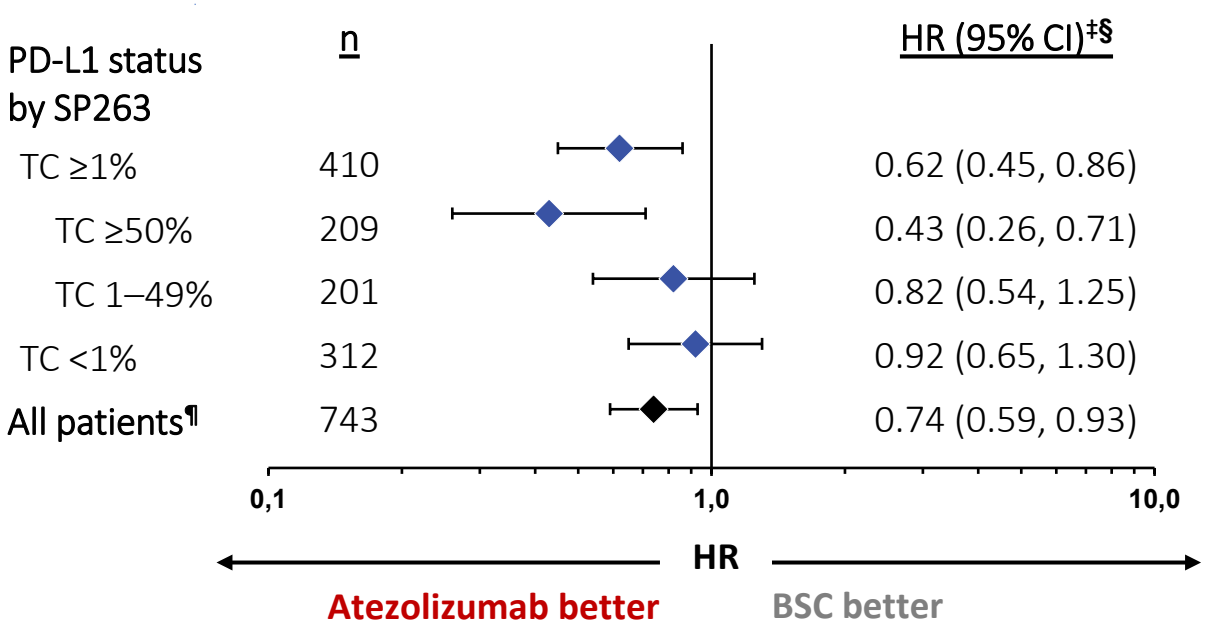
Wakelee H, et al. ASCO 2021. Abstract 8500; Felip E, et al. *Lancet.* 2021;398:1344-1357.

Greatest Magnitude of DFS Benefit With Adjuvant Atezolizumab Over BSC Was in PD-L1 TC ≥50%, Stage II–III NSCLC

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



DFS by PD-L1 Status in the All-Randomized, Stage II–IIIA Population (excluding *EGFR*+/*ALK*+ NSCLC)[2]



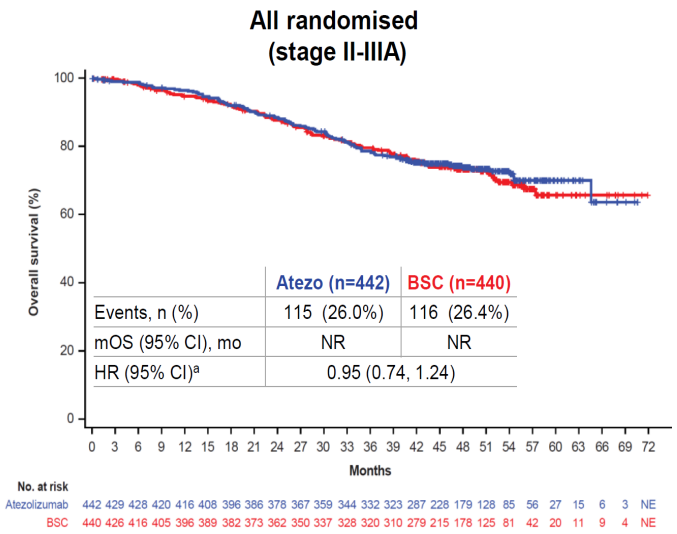
Clinical cut-off: 21 January 2021.

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

1. Felip E, et al. ELCC 2022. Abstract 800; 2. Felip E, et al. ESMO 2021. Abstract LBA9.

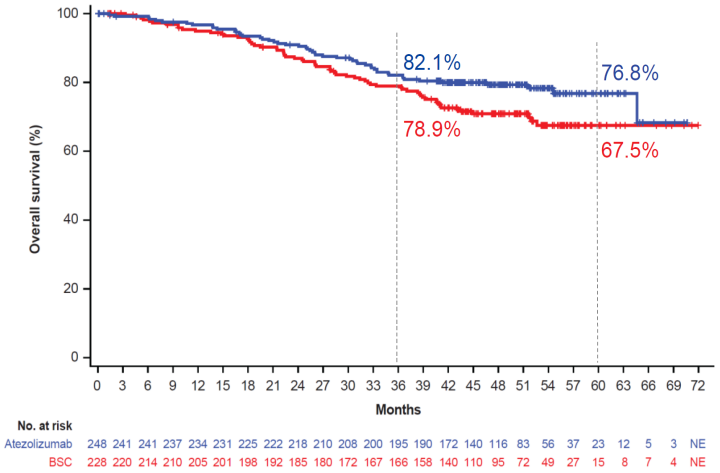
IMpower010: OS Trend of Atezolizumab in PD-L1 ≥1% Stage II–IIIA (interim OS analysis)

No OS Benefit in the All-Randomized Stage II–IIIA



	Atezo (n=442)	BSC (n=440)
Events, n (%)	115 (26.0%)	116 (26.4%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.95 (0.74, 1.24)	

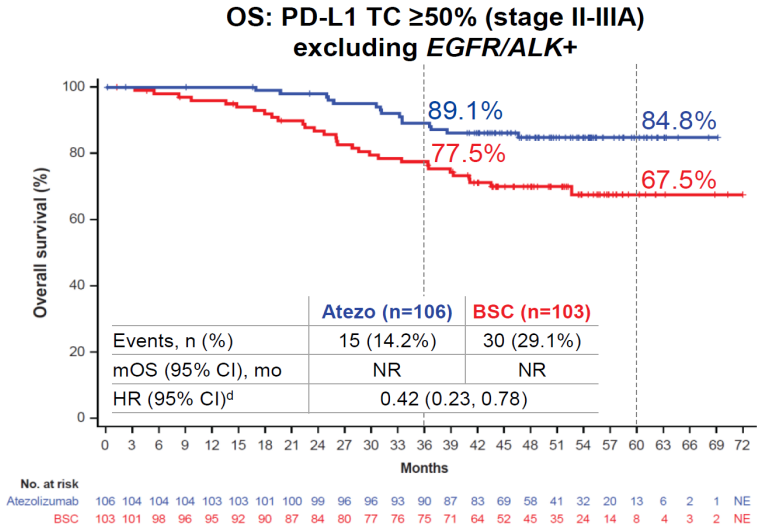
OS Interim Analysis in PD-L1 TC ≥1% (stage II–IIIA)



n

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

Clinically Meaningful OS Trend in PD-L1 ≥50%

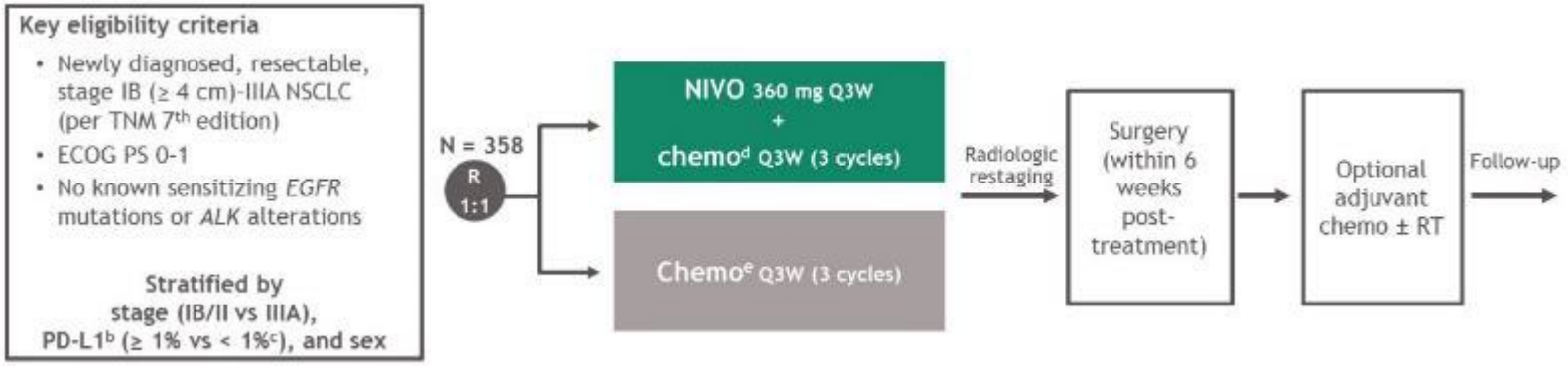


	Atezo (n=106)	BSC (n=103)
Events, n (%)	15 (14.2%)	30 (29.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[d]	0.42 (0.23, 0.78)	

Wakelee H, et al. WCLC 2022. Abstract PL03.09.

Neoadjuvant Nivolumab: CheckMate 816 and NADIM II

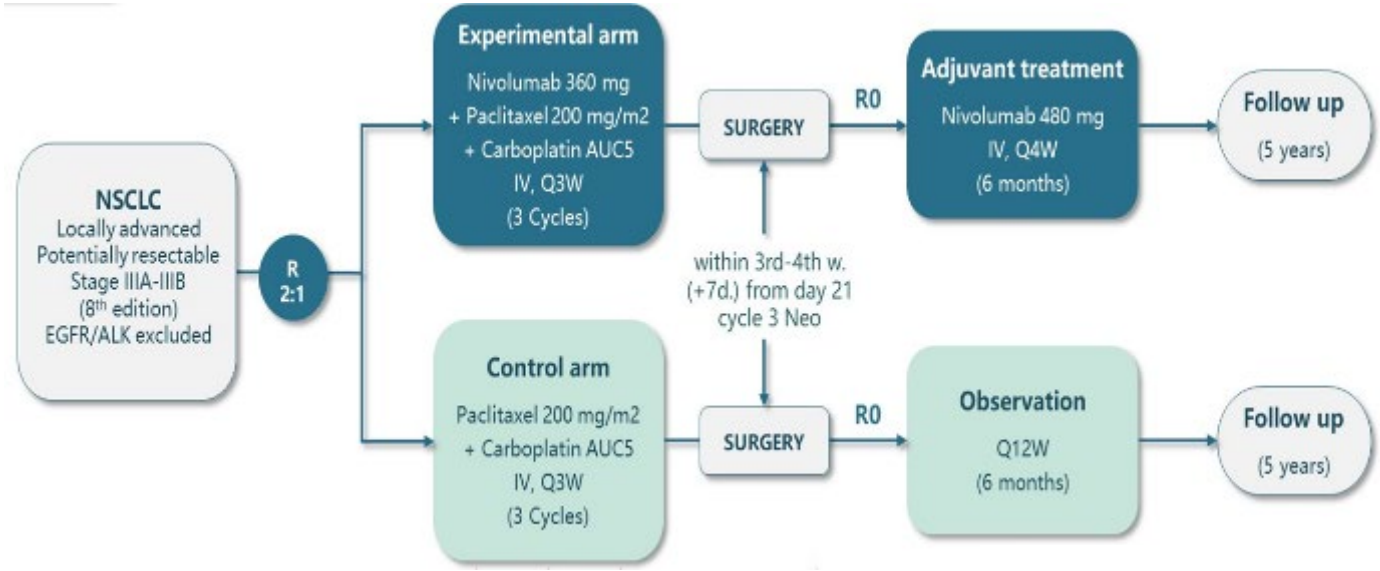
CheckMate 816



Primary Endpoints

- pCR by BICR
- EFS by BICR

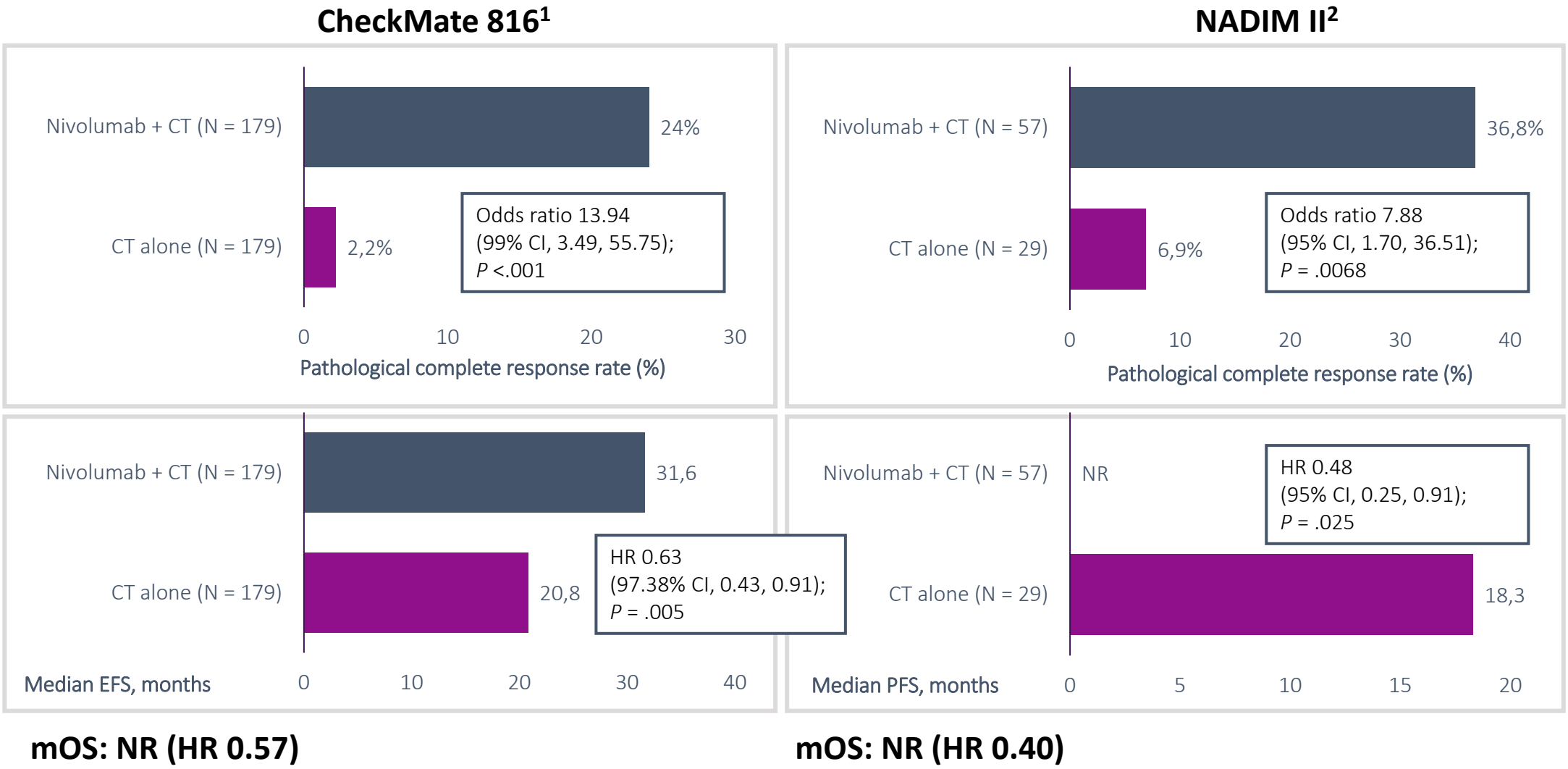
NADIM II



Primary Endpoint

- pCR

Neoadjuvant Nivolumab: Odds Ratio and EFS



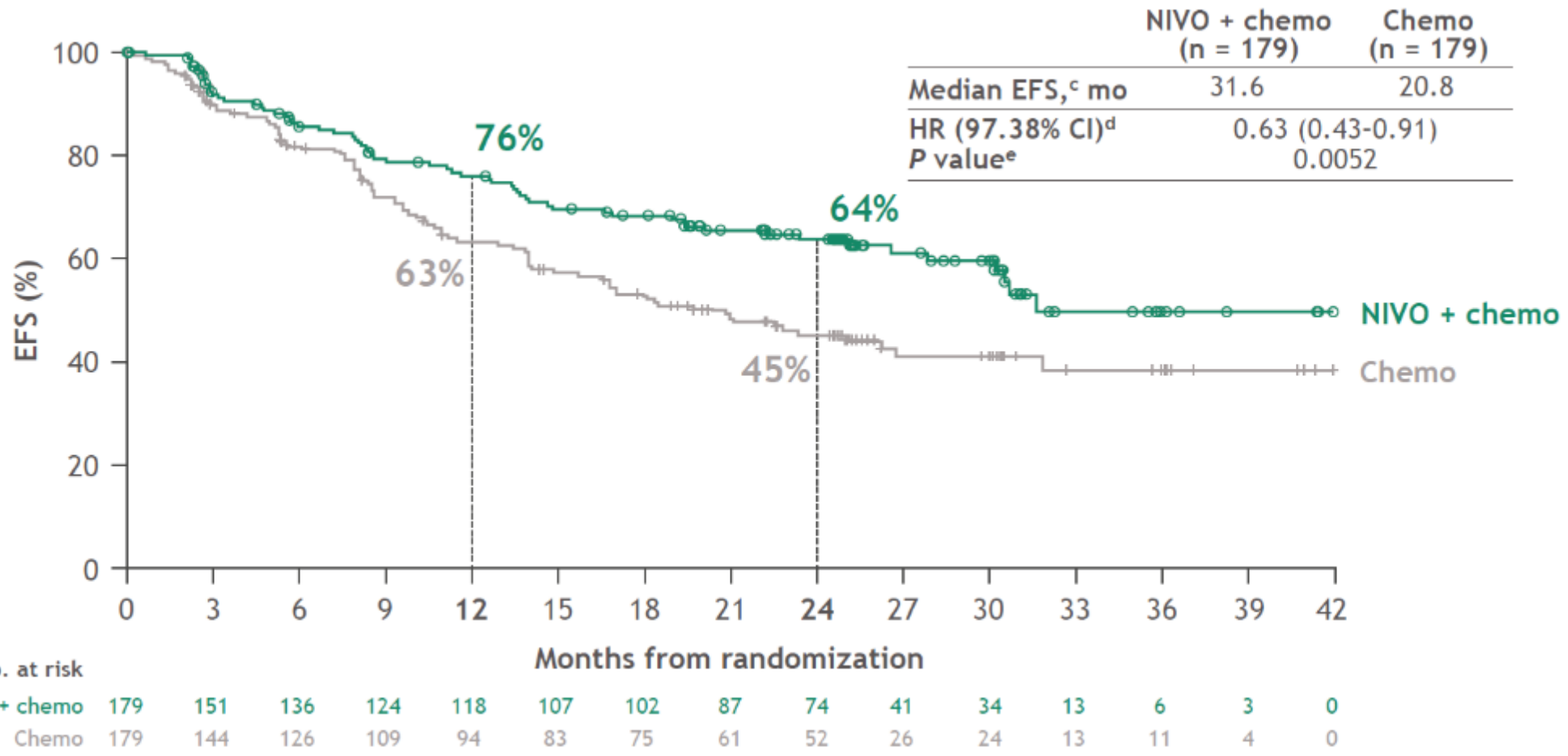
mOS: NR (HR 0.57)

mOS: NR (HR 0.40)

CT, chemotherapy; EFS, event-free survival; HR, hazard ratio; NR, not reached.

1. Forde PM, et al. *N Engl J Med.* 2018;378:1976-86; 2. Provencio M, et al. ASCO 2022. Abstract 8501.

CheckMate 816: Neoadjuvant Nivolumab + Chemotherapy Improved EFS Compared With Chemotherapy Alone

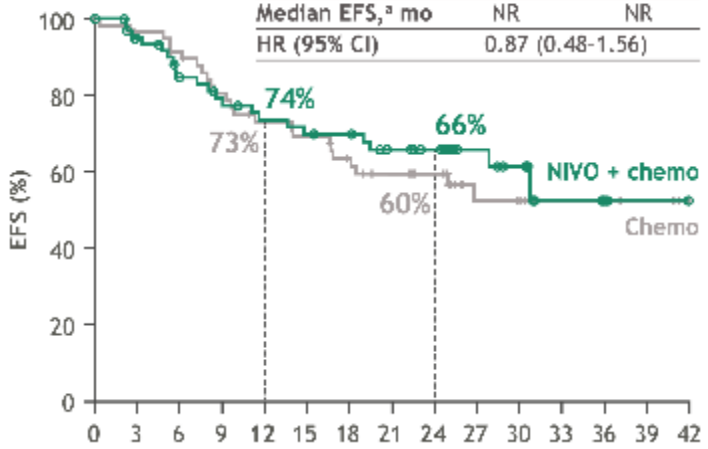


Girard, et al. AACR 2022. Abstract CT012; Forde PM, et al. *N Engl J Med.* 2022;386:1973-1985.

CheckMate 816: An EFS by Stage and PD-L1

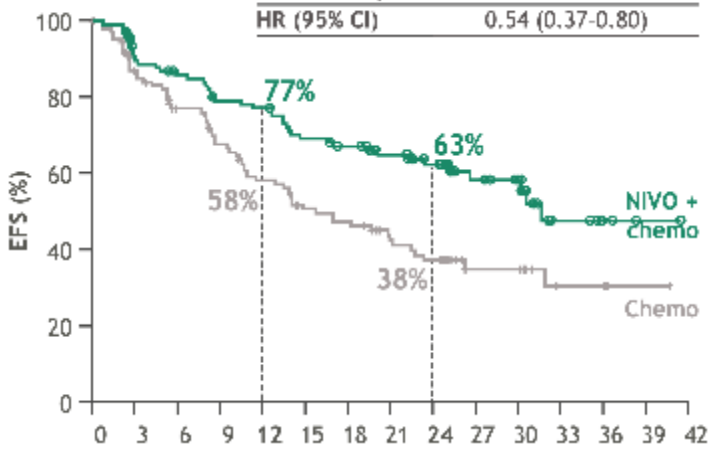
Stage IB-II

	NIVO + chemo (n = 65)	Chemo (n = 62)
Median EFS,[a] mo	NR	NR
HR (95% CI)	0.87 (0.48-1.56)	



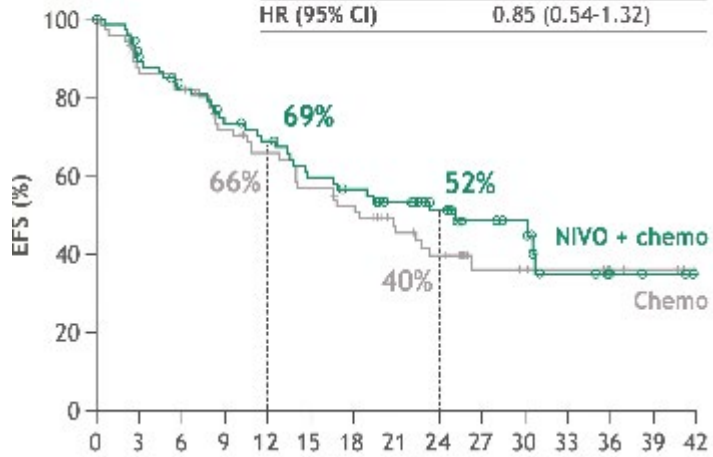
Stage IIIA

	NIVO + chemo (n = 113)	Chemo (n = 115)
Median EFS,[b] mo	31.6	15.7
HR (95% CI)	0.54 (0.37-0.80)	



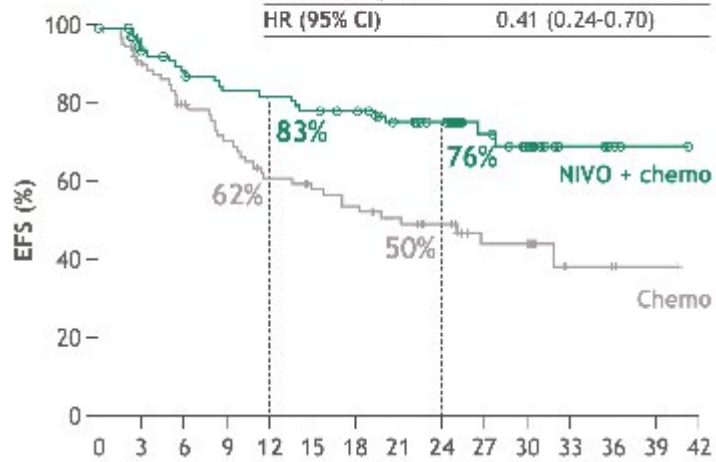
PD-L1 < 1%

	NIVO + chemo (n = 78)	Chemo (n = 77)
Median EFS,[a] mo	25.1	18.4
HR (95% CI)	0.85 (0.54-1.32)	

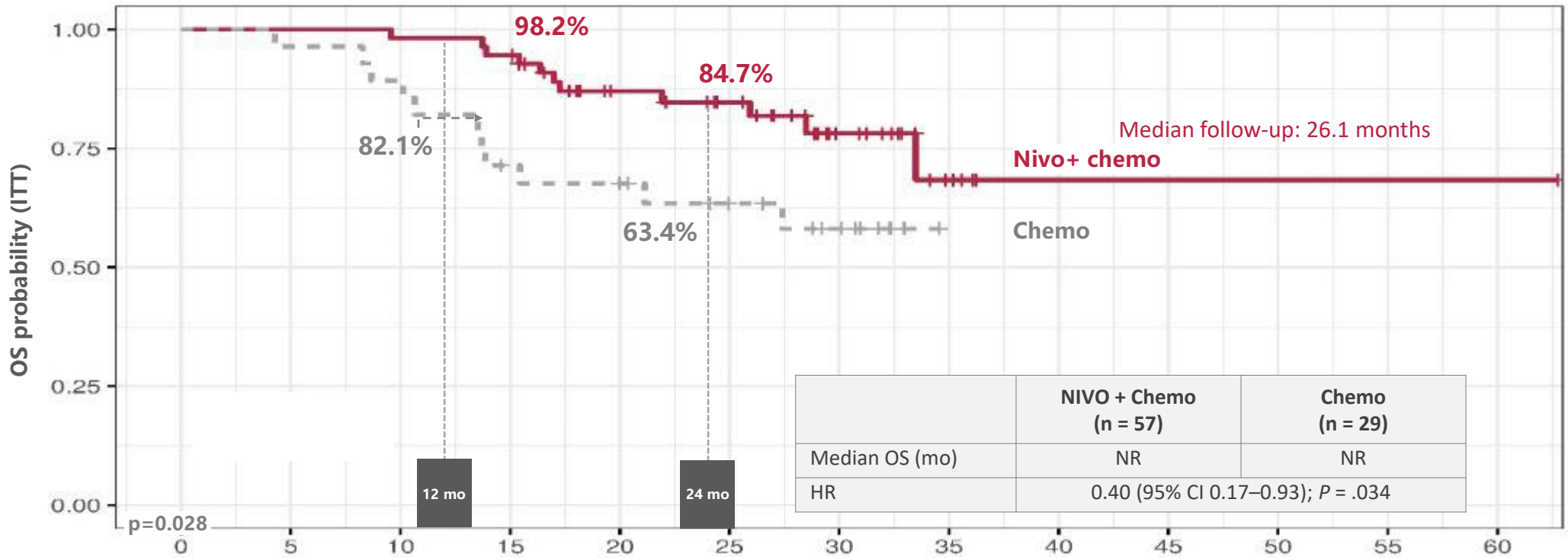


PD-L1 ≥ 1%

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median EFS,[b] mo	NR	21.1
HR (95% CI)	0.41 (0.24-0.70)	



NADIM: Secondary Endpoints – Overall Survival



	NIVO + Chemo (n = 57)	Chemo (n = 29)
Median OS (mo)	NR	NR
HR	0.40 (95% CI 0.17–0.93); *P* = .034	

Number at risk

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

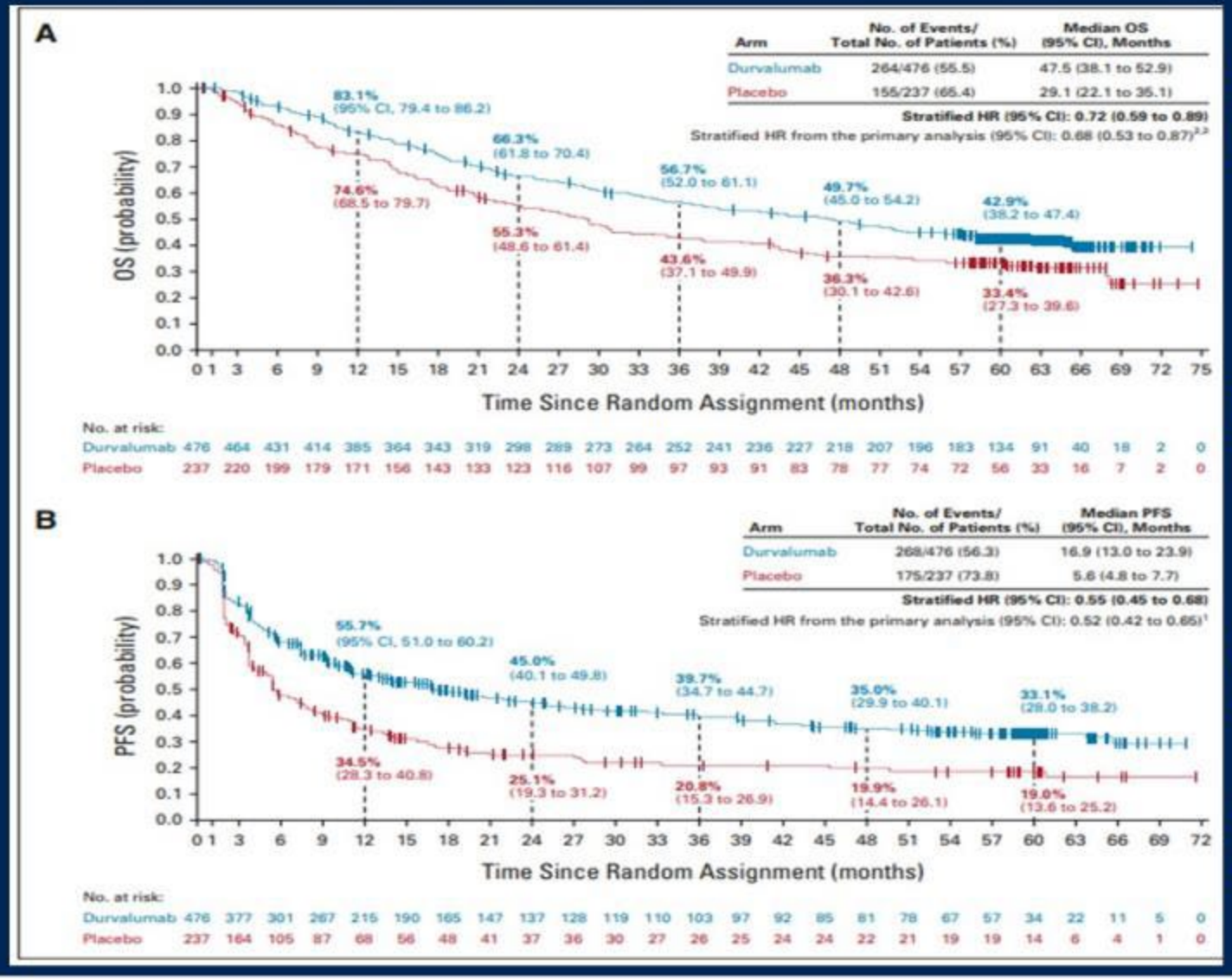
Overall survival was defined as the time from randomization to death. OS was censored on the last date a participant was known to be alive.

Dr Mariano Provencio, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain.

Emerging Paradigms in Care: LA-NSCLC (ASCO)

- PACIFIC
- Abstract 8541 – COAST
- Big Ten Lung Trial
- EA5181

PACIFIC TRIAL



HR = 0.72 OS
Median 47.5 vs 29.1mn

HR = 0.55 PFS
Median 16.9 vs 5.6 mn

Entry Criteria

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

Abstract 8541: Durvalumab (durva) After Chemoradiotherapy (CRT) in Unresectable, Stage III, *EGFR* Mutation-Positive (*EGFR*m) NSCLC: A Post Hoc Subgroup Analysis From PACIFIC

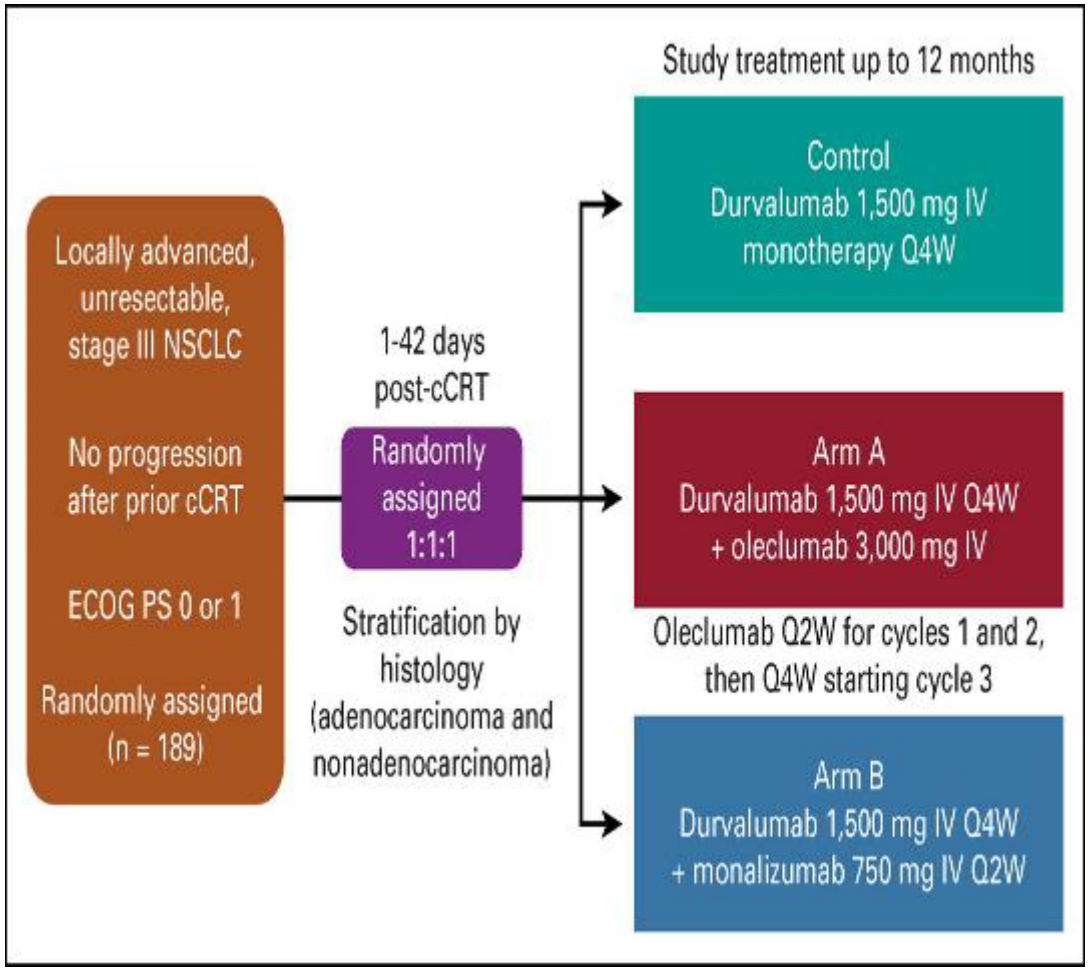
PACIFIC

- 713 pts enrolled, 35 had *EGFR* mutations (2/3 exon 19/21, 1/3 "other")
- For all pts: OS HR 0.68, PFS HR 0.52
- Of 35 EGFR mutation+ pts, 24 received durva, 11 pbo

	Placebo	Durvalumab
Male, %	73	54
IIIA, %	64	46
PS 0, %	64	54
Ind Rx, %	36	8
Asian, %	55	63
PD-L1 <25%	36	67
Med PFS, mo	10.9	11.2*
Med OS, mo	43.0	46.8**
ORR, %	18.2	26.1

*HR 0.91 (0.39, 2.13)
**HR 1.02 (0.39, 2.63)

COAST Phase II Trial: 1^0 Endpoint – ORR

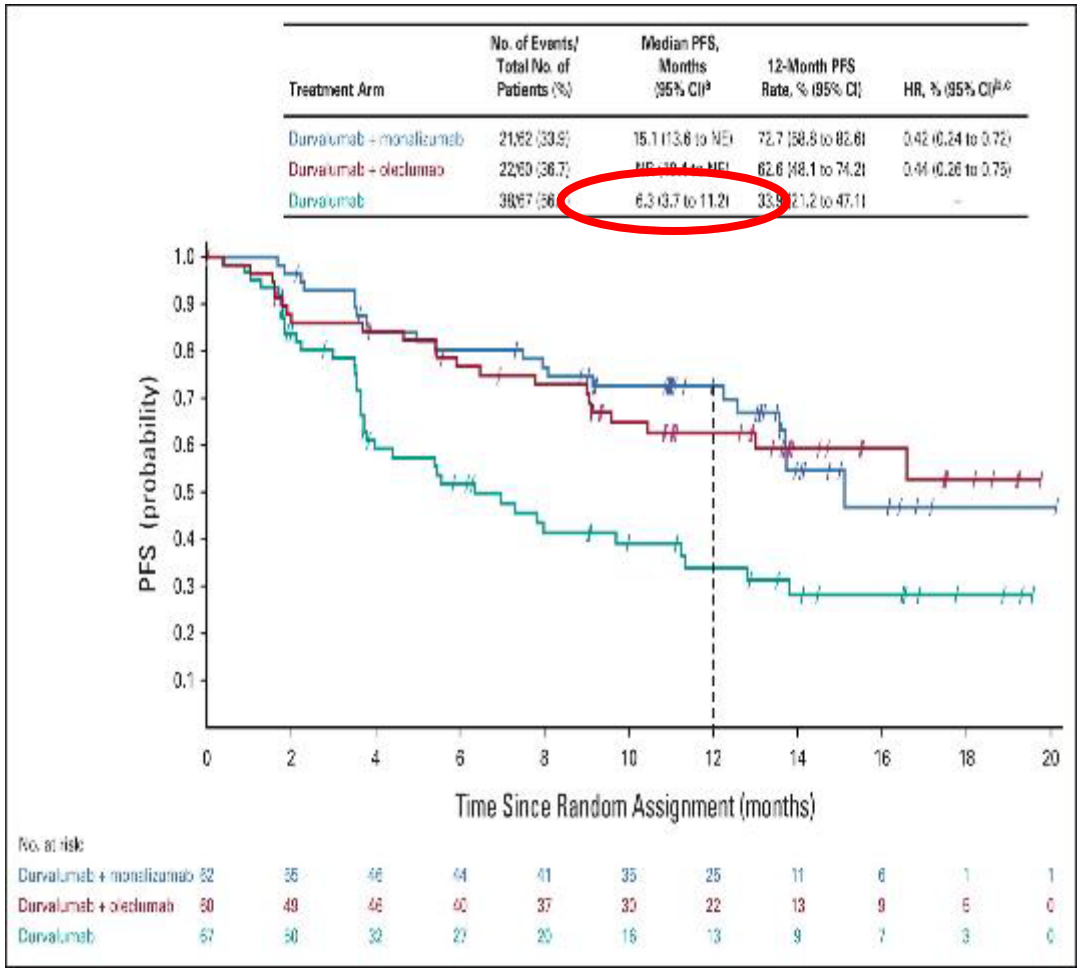


ORR

18%

36%

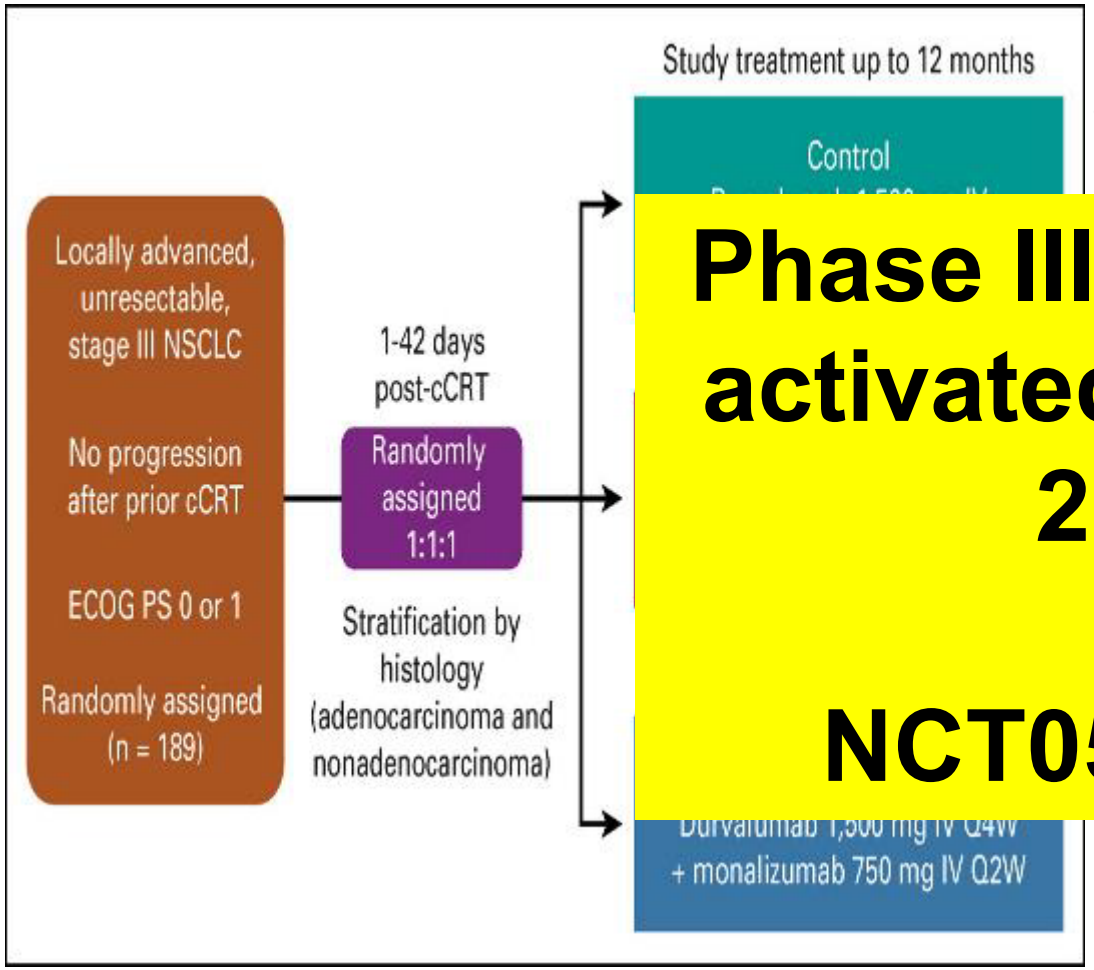
30%



Oleclumab, inhibits CD73 (adenosine pathway); Monalizumab, blocks NKG2A.

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

COAST Phase II Trial: 1^0 Endpoint – ORR

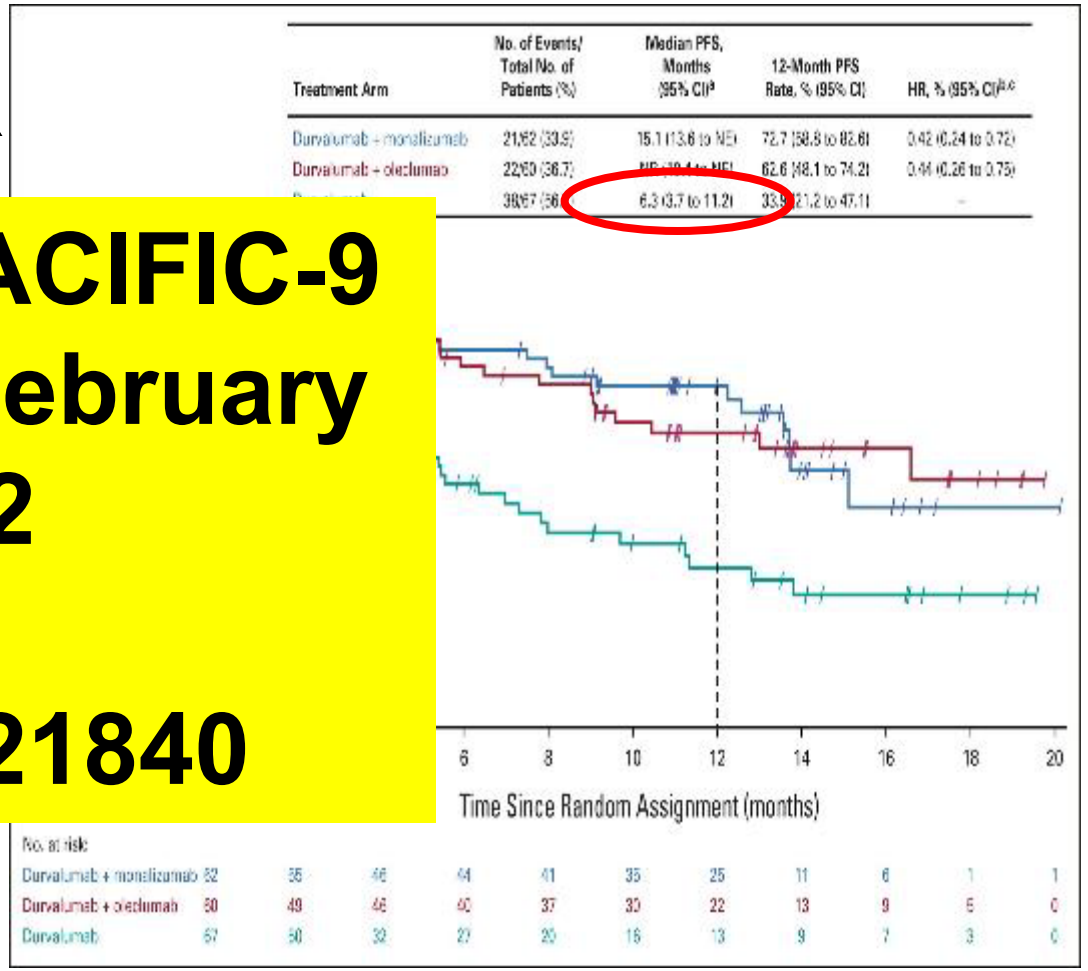


ORR

30%

Phase III PACIFIC-9 activated February 2022

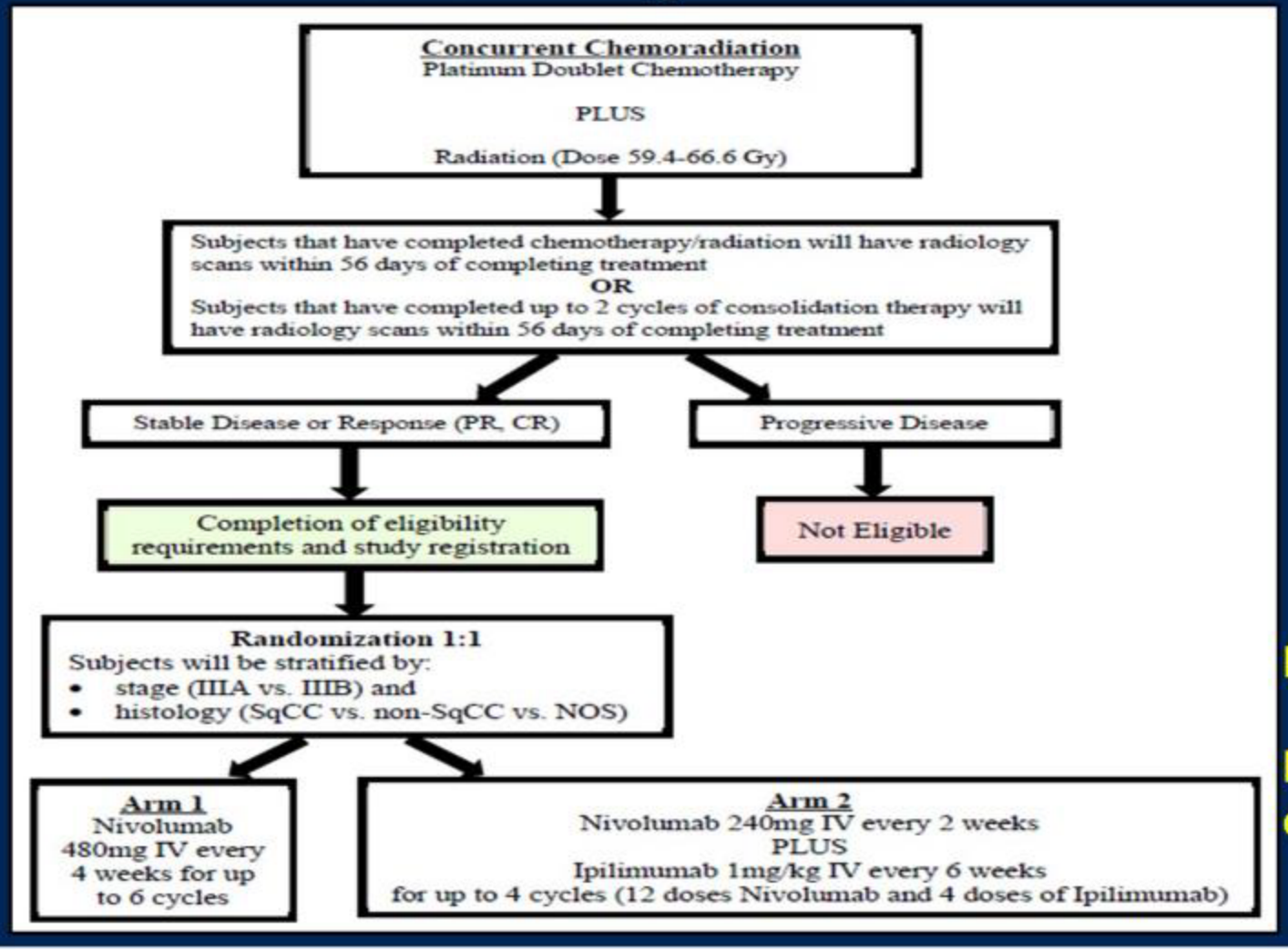
NCT05221840



Oleclumab, inhibits CD73 (adenosine pathway); Monalizumab, blocks NKG2A.

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

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



Primary Endpoint-
18- months PFS

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

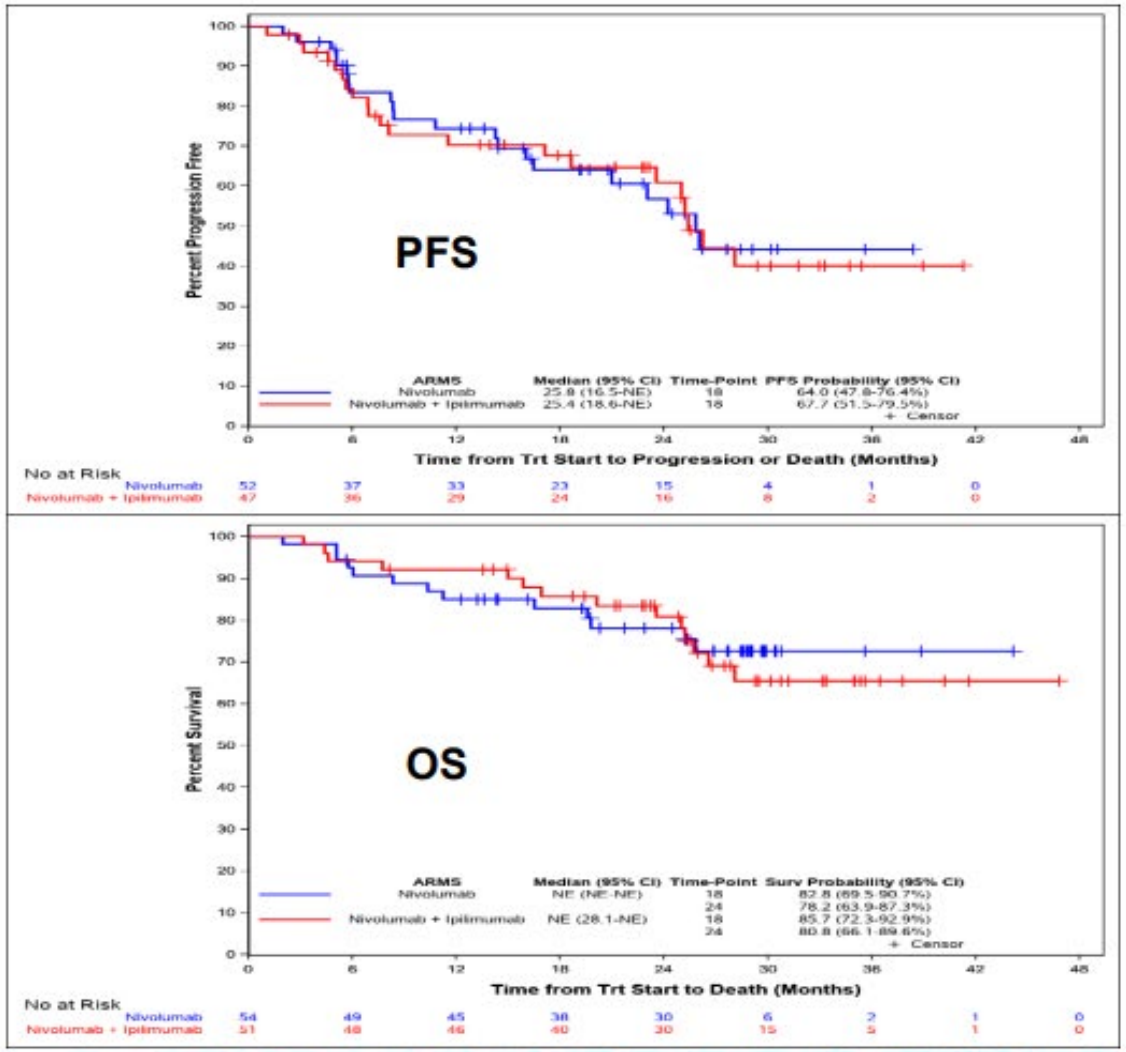
Big question-

Is 6 months of consolidative immunotherapy enough?

Abstract 8509

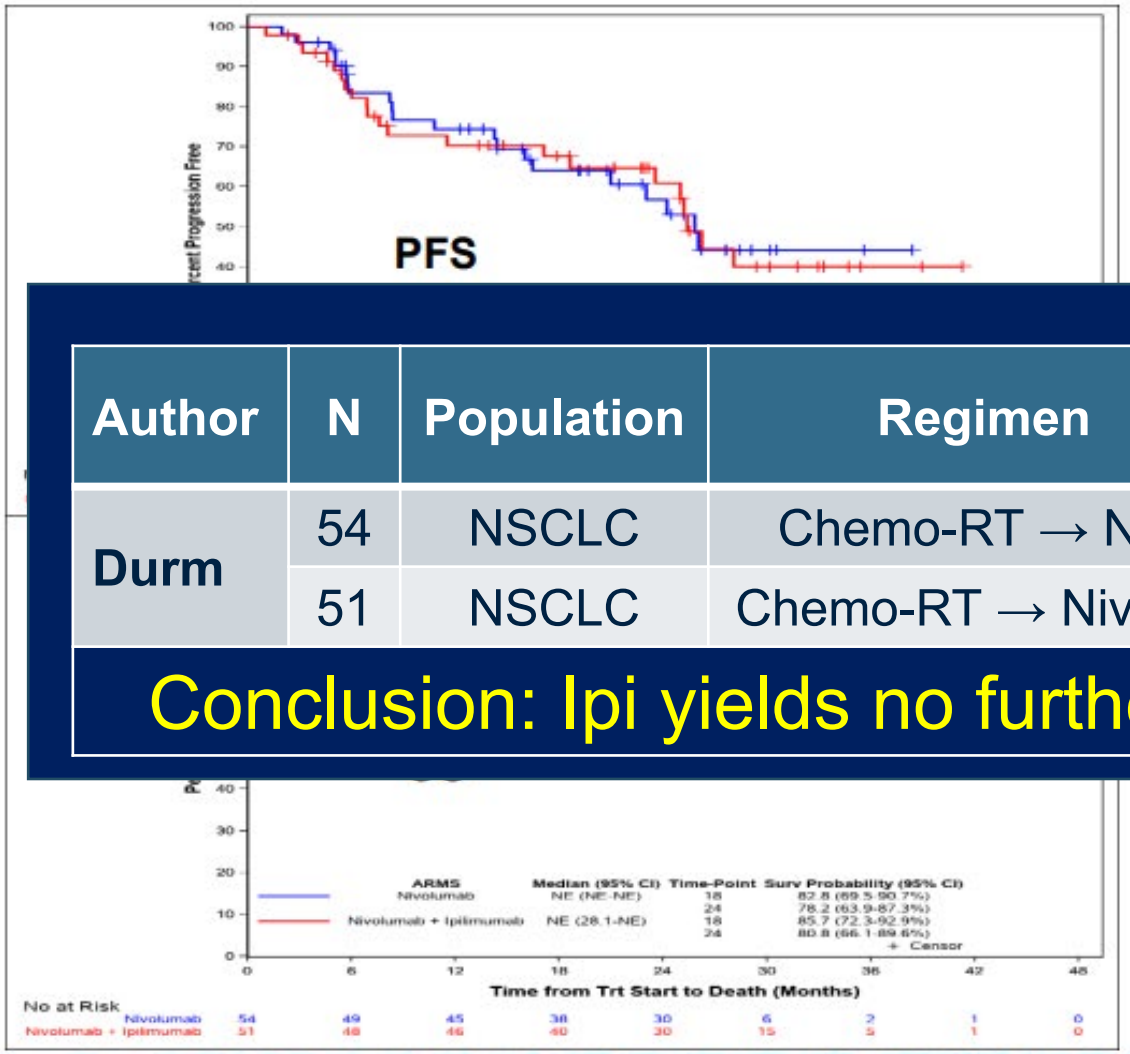
PRESENTED BY:
John Michael Varlotto – Chief Radiation Oncology, Marshall University

Results



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

Results

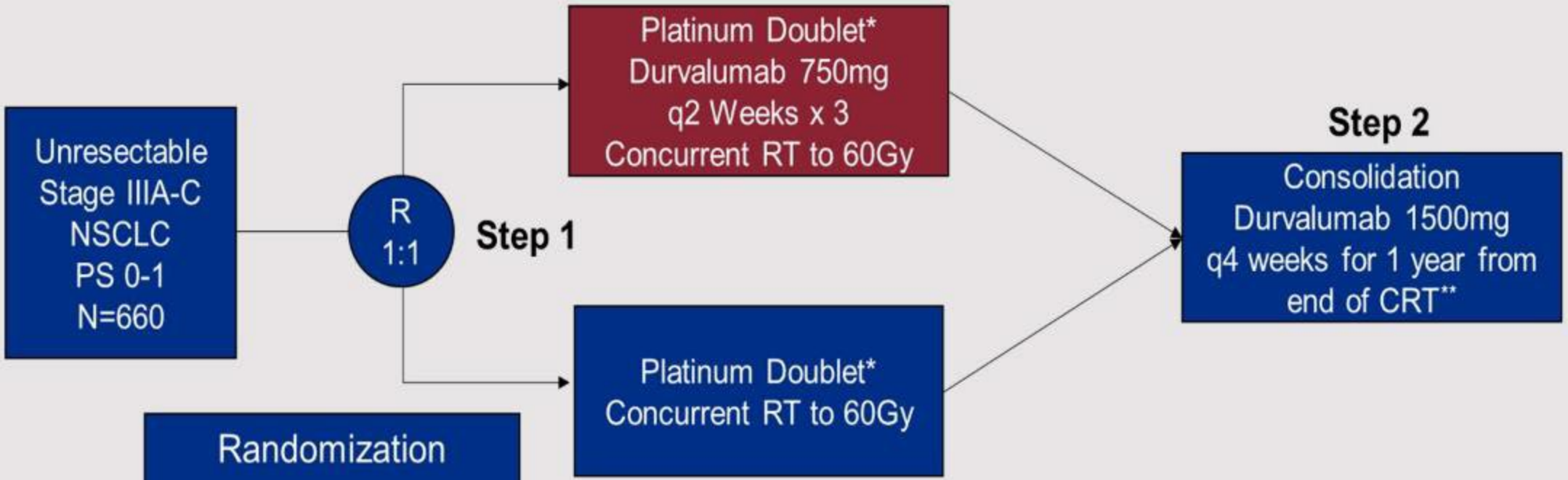


	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	28.5 (2-44.2)	29.4 (3.2-46.8)
Progression Free Survival*		
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

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

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

ECOG-ACRIN EA5181



Randomization

Stratified by:

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

***Investigator choice**

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

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

PRESENTED BY:
John Michael Varlotto – Chief Radiation Oncology, Marshall University

Metastatic NSCLC: Can We Further Personalize First-Line Treatment?

2022 ASCO® ANNUAL MEETING

FDA

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

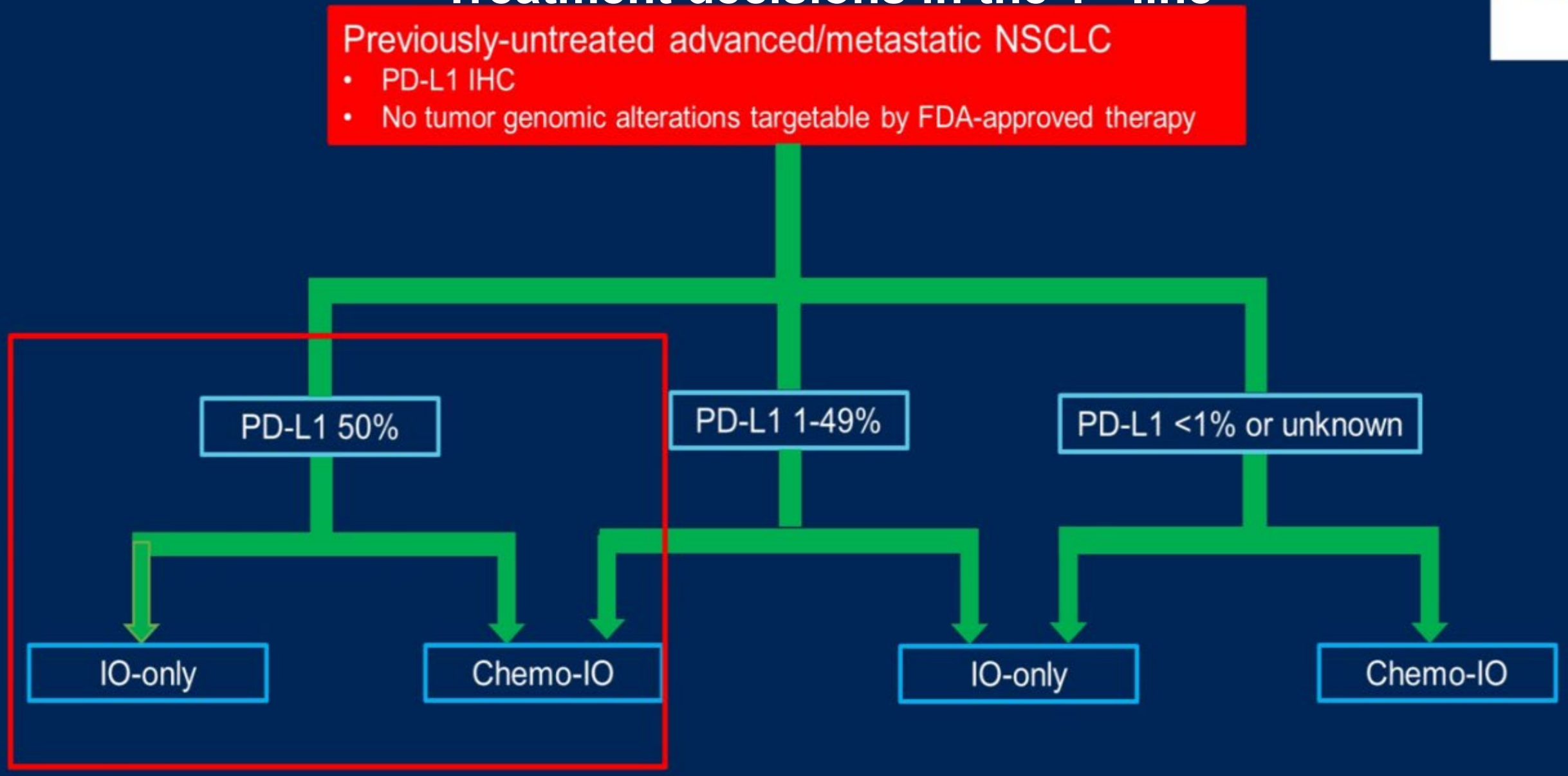
Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

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

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

Oladimeji Akinboro, MD, MPH

Treatment decisions in the 1st line

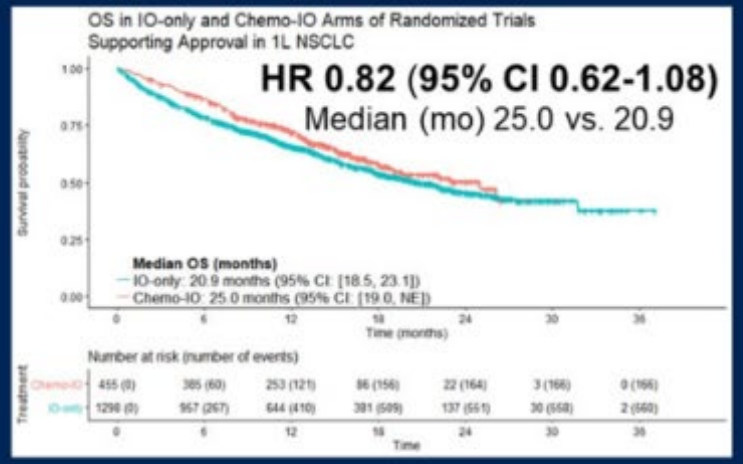


Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; IO=immunotherapy; NSCLC=non-small-cell lung cancer; PD-L1=programmed death ligand-1.

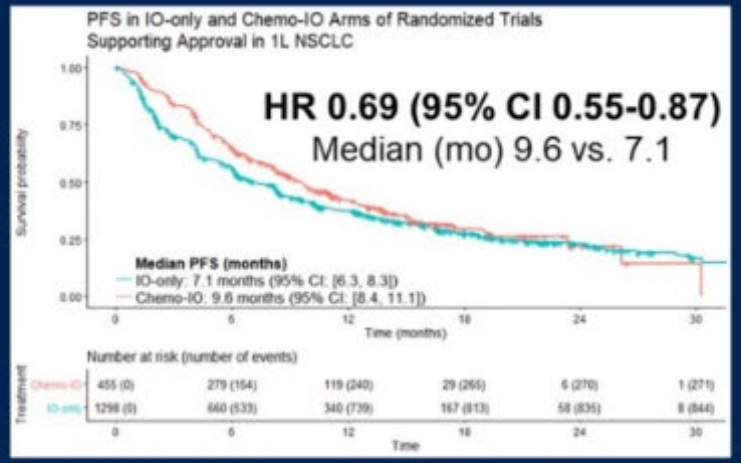
IO vs Chemo-IO in PD-L1 ≥50%

- **Randomized Clinical Trials supporting FDA approved IO-based regimens**
  - **Chemo-IO (6 trials, n=455):** Platinum-Chemo + Pembrolizumab, Atezolizumab (+/- bevacizumab), or Nivolumab/Ipilimumab
  - **IO (6 trials, n=1298):** Nivolumab, Pembrolizumab, Atezolizumab, Cemiplimab, Nivolumab/Ipilimumab
- **Biomarkers[1]: PD-L1 ≥ 50% TPS and *EGFR/ALK* WT**

OS – no difference



PFS – favor chemo-IO



ORR – favor chemo-IO

	Chemo-IO	IO
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio (95% CI)	**1.2** (1.1, 1.3)	

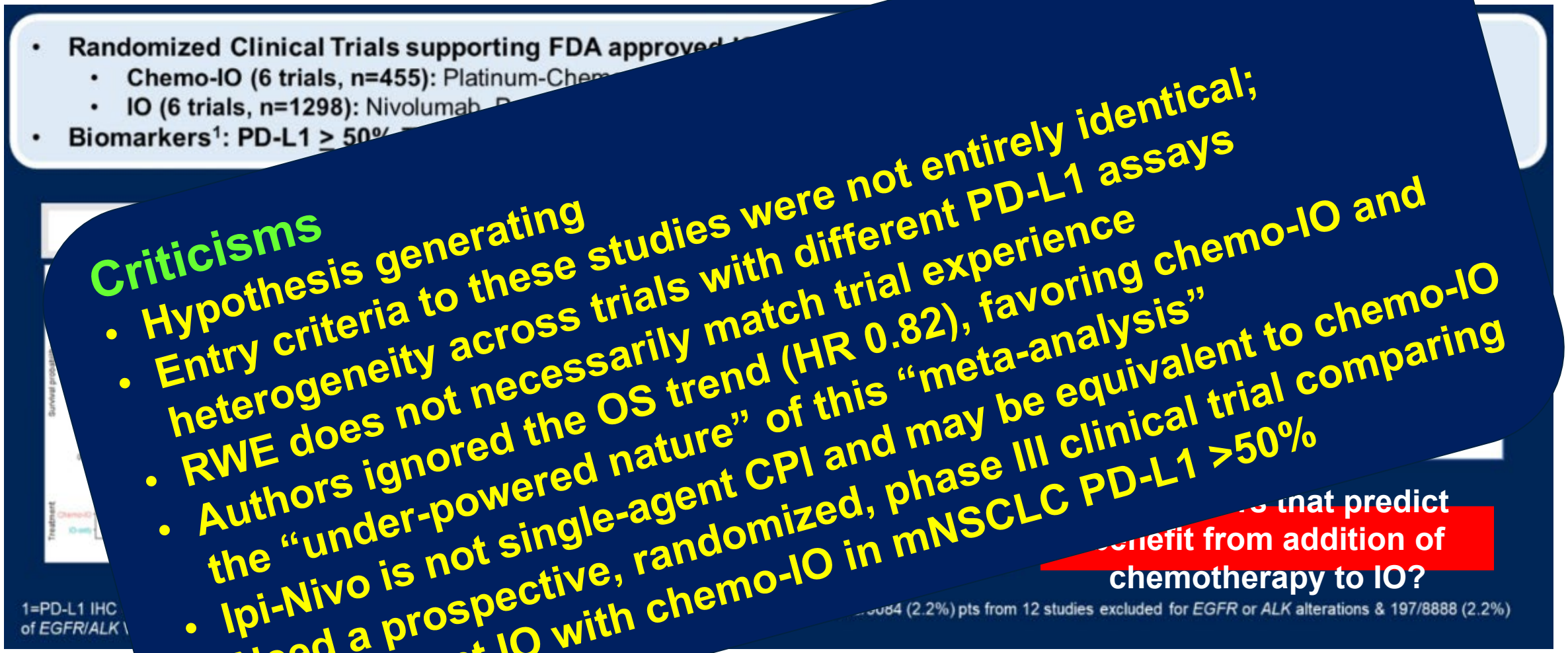
Risk factors that predict benefit from addition of chemotherapy to IO?

1=PD-L1 IHC defined by tumor proportion score (TPS) and excluded staining by tumor infiltrating lymphocytes; 2=196/9084 (2.2%) pts from 12 studies excluded for *EGFR* or *ALK* alterations & 197/8888 (2.2%) of *EGFR/ALK* WT pts excluded as no baseline PD-L1 IHC results.

Adapted from ASCO 2022 presentations by Sukhmani Padda, O. Akinboro.

Penn Medicine Abramson Cancer Center

IO vs Chemo-IO in PD-L1 ≥50%



Criticisms

- Hypothesis generating
- Entry criteria to these studies were not entirely identical; heterogeneity across trials with different PD-L1 assays
- RWE does not necessarily match trial experience
- Authors ignored the OS trend (HR 0.82), favoring chemo-IO and the "under-powered nature" of this "meta-analysis"
- Ipi-Nivo is not single-agent CPI and may be equivalent to chemo-IO
- Need a prospective, randomized, phase III clinical trial comparing single agent IO with chemo-IO in mNSCLC PD-L1 >50%

Adapted from ASCO 2022 presentations by Sukhmani Padda, O. Akinboro.

Penn Medicine Abramson Cancer Center

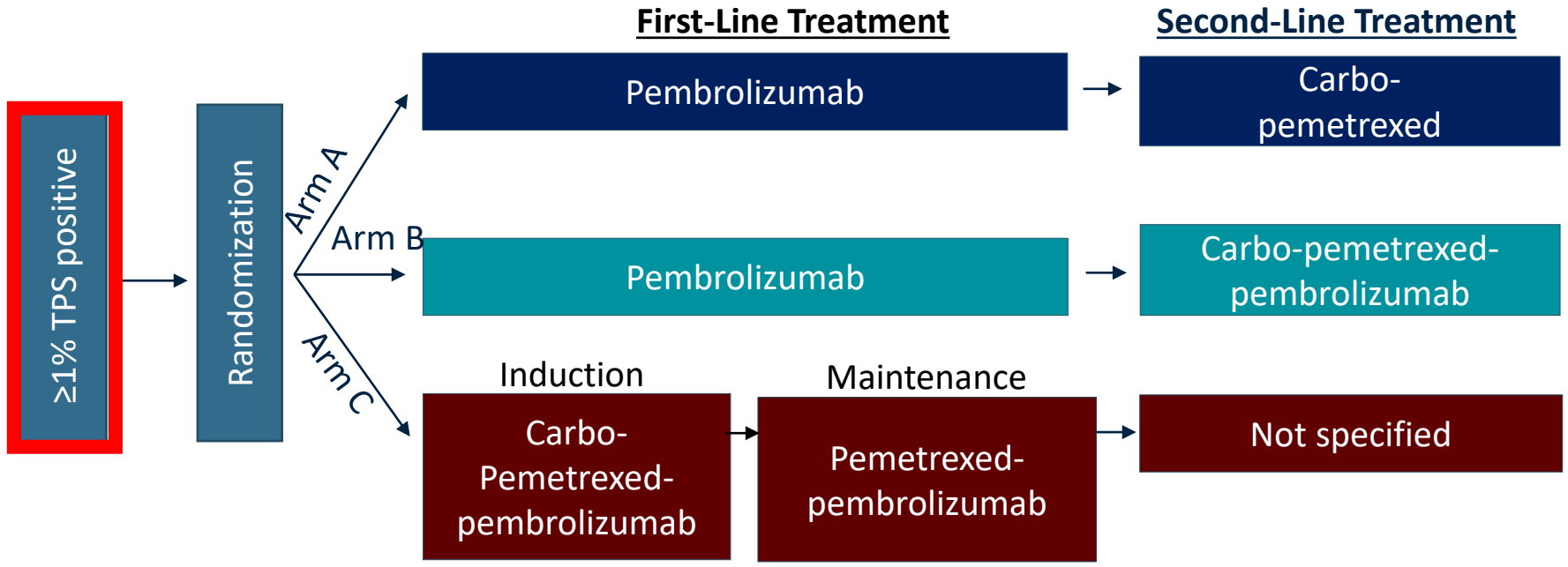
Sequential vs Combination Therapy: INSIGNA

VIEW ALL PRESS RELEASES

And the Landscape Is Changing

KEYTRUDA® (pembrolizumab) Monotherapy Met Primary Endpoint in Phase 3 KEYNOTE-042 Study, Significantly Improving OS as First-Line Therapy in Locally Advanced or Metastatic NSCLC Patients Expressing PD-L1 in at Least 1 Percent of Tumor Cells

APRIL 09, 2018



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

2022 ASCO® ANNUAL MEETING

Randomized phase III study of nivolumab and ipilimumab versus carboplatin-based doublet in first-line treatment of PS 2 or elderly (≥ 70 years) patients with advanced non–small cell lung cancer (Energy-GFPC 06-2015 study).

Hervé Léna[1], Isabelle Monnet [2], Olivier Bylicki[3], Clarisse Audigier-Valette[4], Lionel Falchero[5], Alain Vergnenegre[6], Pierre Demontrond[7], Laurent Greillier[8], Margaux Geier[9], Florian Guisier[10], Stéphane Hominal[11], Chrystele Locher[12], Romain Corre[13], Claire Cropet[14], Christos Chouaid[15], Charles Ricordel[1], Groupe Français de Pneumo Cancérologie;

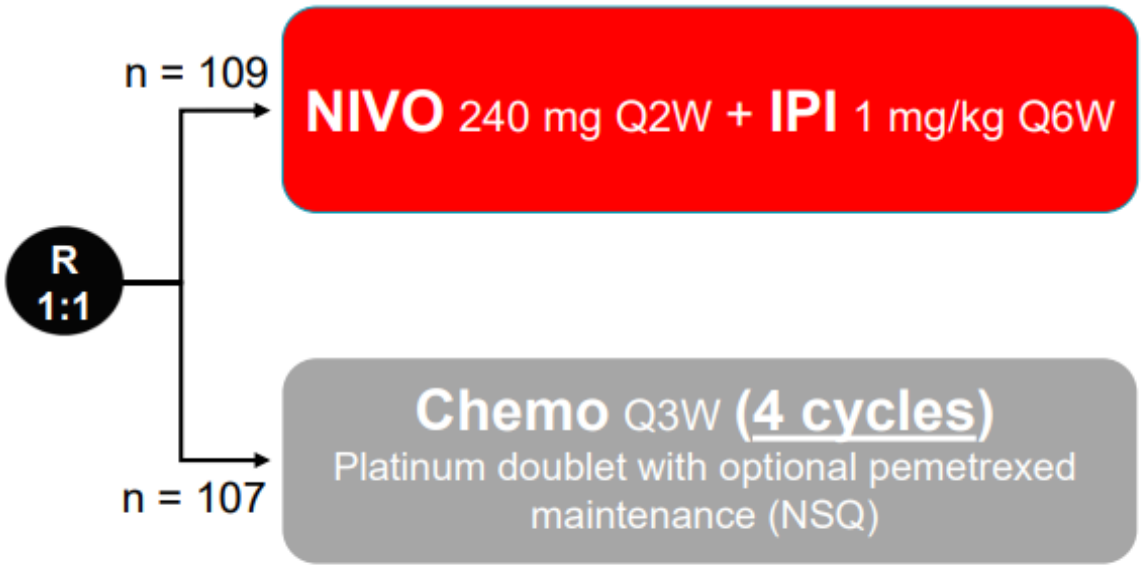
1 CHU, Rennes, France; 2 Pneumologie, CHI Creteil, Creteil, France; 3 HIA Desgenettes, Ampuis, France; 4 Orientation Oncologique, Hôpital Sainte-Musse, Toulon, France; 5 Pneumologie, Hopital Nord Ouest Villefranche Sur Saone, Villefranche Sur Saone, France; 6 Unite d'Oncologie Thoracique, Limoges, France; 7 CLCC Baclesse, Caen, France; 8 Multidisciplinary Oncology and Therapeutic Innovations, Hôpital Nord, Marseille, France; 9 CHU Morvan, Brest, France; 10 CHU Rouen, Rouen, France; 11 CH Annecy Genevois, Epagny Metz-Tessy, France; 12 GHEF site de Meaux, Meaux, France; 13 CHIC, Service de Pneumologie, Quimper, France; 14 Unite de Biostatistique et d'Evaluation des Therapeutiques-Direction de la Recherche et d l'Innovation, Centre Leon Berard, Lyon, France; 15 Centre Hospitalier Intercommunal de Créteil, Créteil, France; Pneumologie

eNerGy : a study dedicated to elderly and PS2 patients

Key Eligibility Criteria

- Stage IV or recurrent
- Squamous or Non-Squamous
- No prior systemic therapy for advanced disease
- No known EGFR mutations or ALK or ROS1 alteration
- Age ≥ 70 ECOG PS 0-1 or PS 2

Stratified by :
· Age ≥ versus < 70 years
· PS 0/1 versus 2
· Histology : squamous/non-squamous



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

Primary endpoint
- OS

Secondary endpoints
- PFS
- ORR
- Efficacy by tumor PD-L1 expression
- QOL, geriatric mini dataset

Statistical Plan

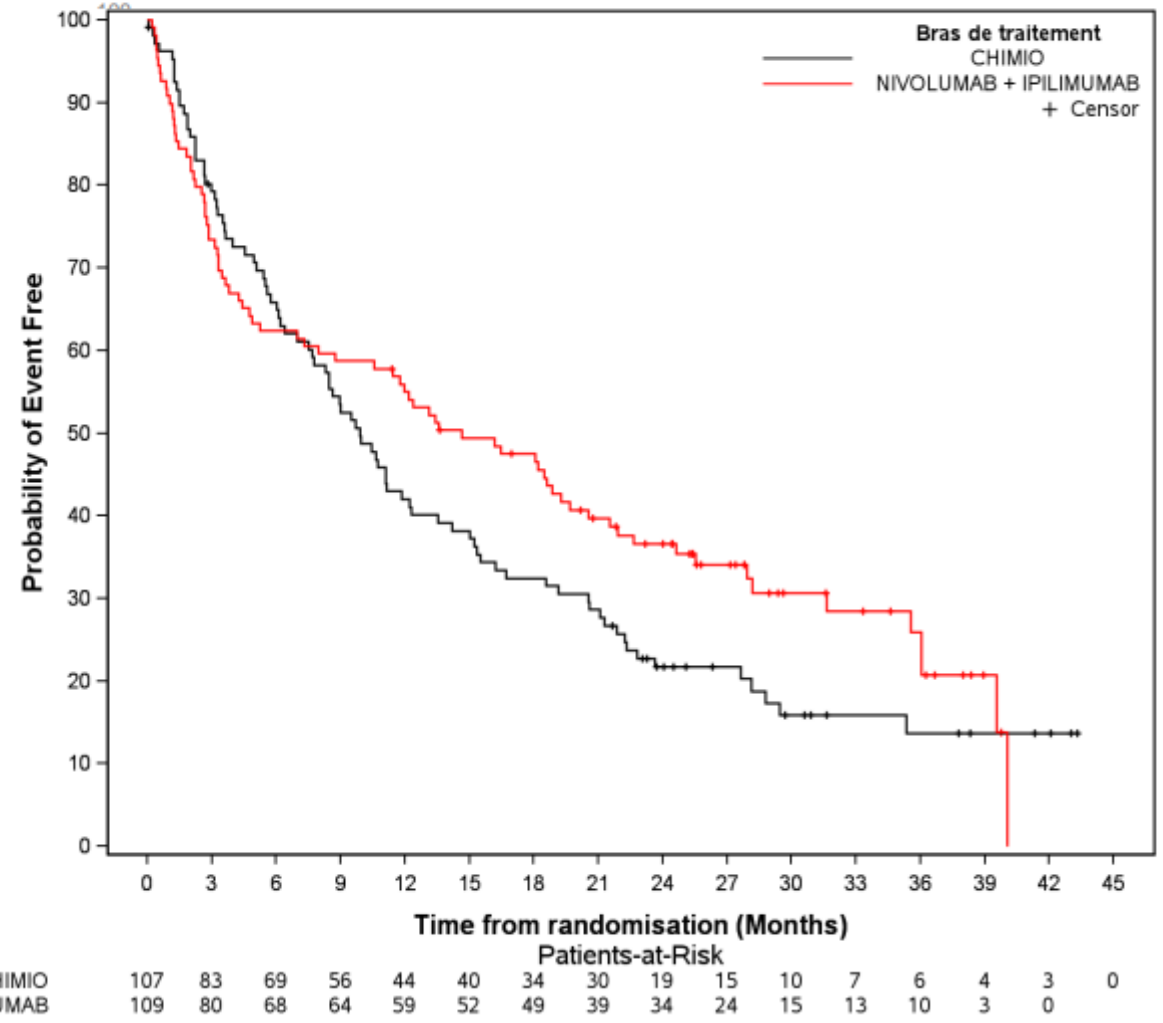
- 242 patients had to be randomized with 199 events to detect a treatment effect hazard ratio (HR) of 0.65 with 85% power, translating in an improvement of 1-year OS rate from 40% (control arm) to 55% (NIVO-IPI), and using a log-rank test at a 2-sided alpha level of 5%.
- One preplanned interim analysis for futility occurred in December 2019, after that 33% of the expected events have occurred.
- Regarding low effect on PS 2 patients, the DMC recommended to stop inclusion, 217 patients had been randomized at that time.
- Final analysis is performed on the ITT population

Baseline characteristics

	NIVO + IPI (n = 109)	Chemo (n = 107)
Age, median (range), years	74 (52-89)	74 (51-88)
≥ 70	78%	79.4%
Female, %	32.1	25.2
ECOG PS, %		
0	26.6	25.2
1	37.6	37.4
2	35.8	37.4
Smoking status, %		
Never smoker	11.9	8.4
Current / former smoker	88.1	91.6
Histology, %		
Squamous	32.1	30.8
Non-squamous	67.9	69.2
Metastases, %		
Bone	37.6	43.9
Liver	14.7	16.8
CNS	8.3	7.5
Tumor PD-L1 expression,%		
<1%	58.7	54.1
1–49%	38.5	37.8
≥ 50%	2.9	8.2
ND	4.5	8.4

Primary endpoint : Overall survival in ITT population

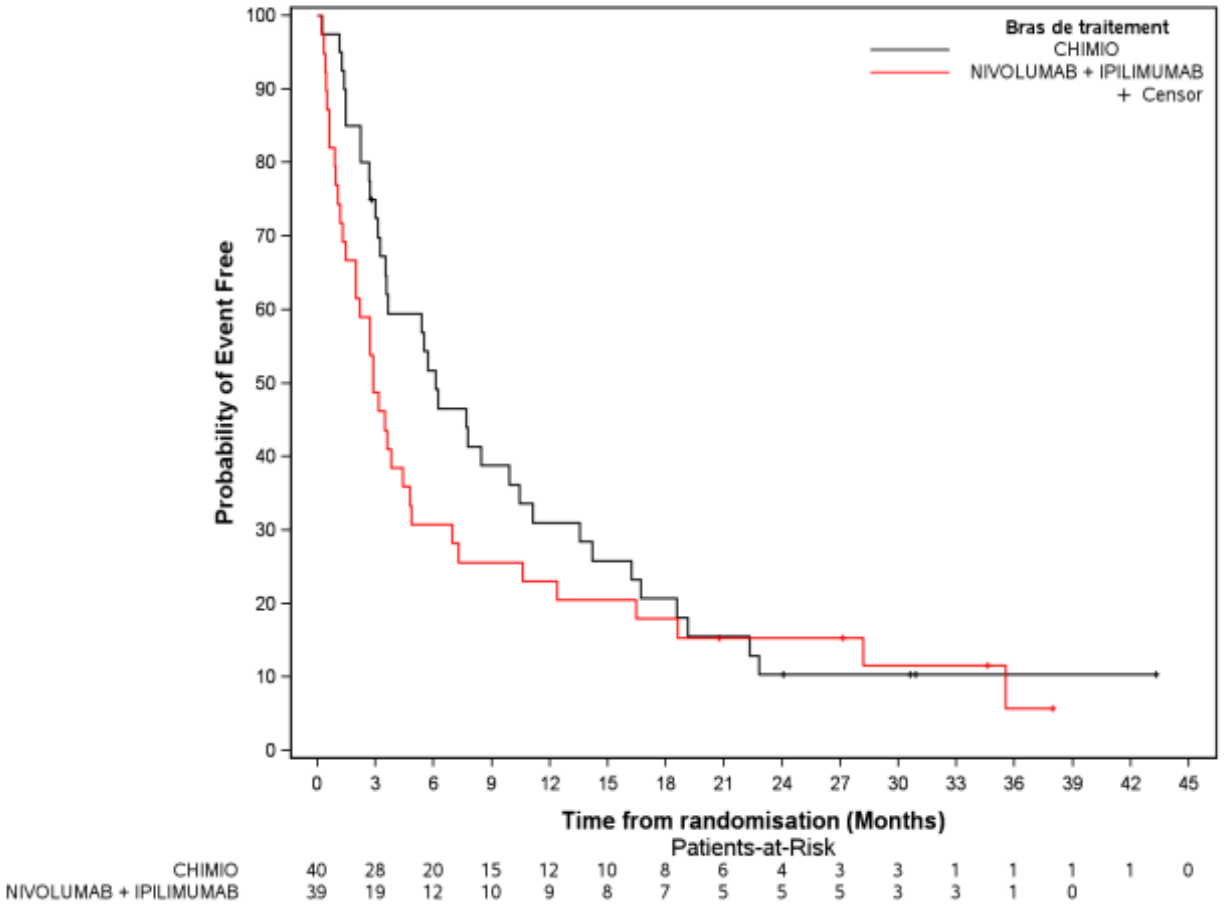
Overall survival whole population



	NIVO IPI n = 109	Chemo n =107
Median OS, mo (95% CI)	14.7 (8-19.7)	9.9 (7.7-12.3)
HR (95% CI)	0.85 (0.62–1.16) *P* = 0.2978	
Survival 1 year	55% 45.2%-63.8%	42% 32.5%-51.2%
Survival 2 years	36.6% 27.5%-45.7%	21% 14.3%-30.0%

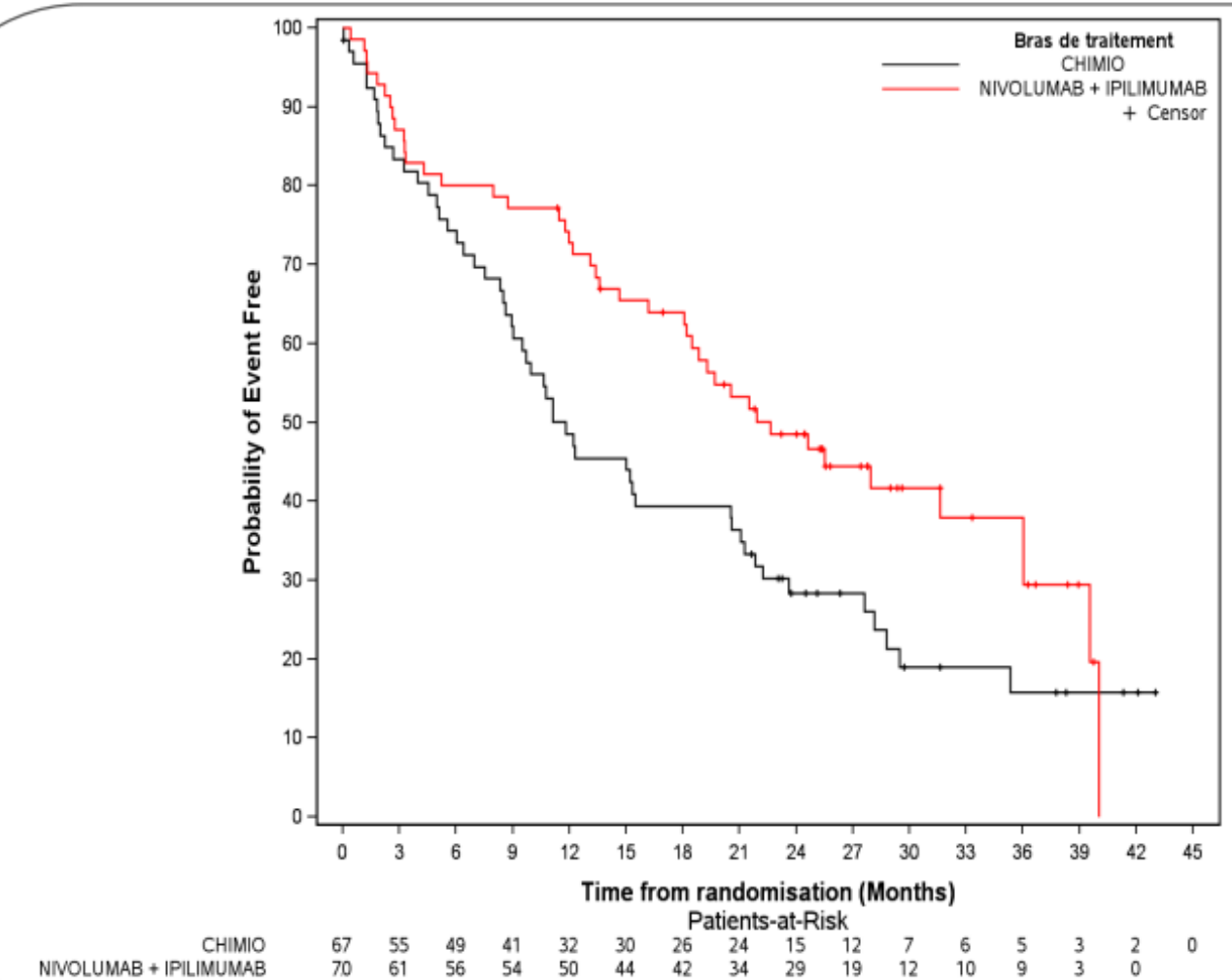
Overall survival PS 2 patients

Overall survival (ITT population) – PS 2



	NIVO IPI n = 40	Chemo n = 39
Median OS (95% CI)	2.9 (1.4-4.8)	6.1 (3.5-10.4)

Overall Survival elderly patients PS 0-1



	NIVO IPI n = 70	Chemo n = 67
Median OS, mo (95% CI)	22.6 (18.1-36)	11.8 (8.9-20.5)
HR (95% CI)	**0.63** (0.42–0.95)	

Safety

	NIVO IPI %	Chemo %
TRAEs all grades	74.3	89.3
TRAEs grade ≥3	31.4	49.5
TRAEs leading to discontinuation of any component of the regimen	54.3	34.0
TRSAEs	39.0	25.2
Treatment-related deaths	3.8*	1.9**

*Hyperprogression 1 (PS 2, 76 yo), Pneumonitis 1 (PS 0 76 yo), Encephalitis 1 (PS 1 74 yo), sudden death 1 (PS 2 63 yo)

**Septic schock 2 (PS 0 79 yo, PS 1 71 yo)

Conclusion

- In this elderly and/or PS2 advanced NSCLC, we observed a non significant advantage of NIVO IPI compared to platinum doublet chemo for OS, PFS 1 year.
- Nivo-Ipi appeared deleterious for PS2 patients compared to chemo.
- In subgroup analysis of elderly PS 0/1 patients, OS was significantly increased with NIVO IPI over chemo :
  - 22.6 (18.1-36) versus 11.8 (8.9-20.5) months.
- No new signal of toxicity of NIVO IPI in elderly and/or PS2 population was observed
- Pending QOL, geriatric parameters analysis and 2nd line therapies will be presented later.

- **Dedicated trials for elderly population, PS 2 are feasible and remain essential**

Langer's Current Paradigm: 2022 (could change at any moment)

Tx Cohort	Non-squamous	Squamous
PD-L1 ≥50%	Pembro > Pem-Carbo-Pembro	Pembro > Taxane-Carbo-Pembro
PD-L1 1%–50%	Pem-Carbo-Pembro > Pembro	Taxane-Carbo-Pembro > Pembro
PD-L1 <1%	Pem-Carbo-Pembro	Taxane-Carbo-Pembro
PD-L1 <1%, TMB >10	Pem-Carbo-Pembro vs Ipi-Nivo*	Taxane-Carbo-Pembro vs Ipi-Nivo*
TKI refractory	Pem-Carbo ± Bev or Pac-Carbo-Bev-Atezo (IMP150)	
Tissue QNS	Pem-Carbo-Pembro	Taxane-Carbo-Pembro

*Ipilimumab-nivolumab ± 2 cycles of histology-appropriate chemotherapy (9LA).

CPIs: Unanswered Questions for First Line

- Are there biomarkers to aid patient selection beyond PD-L1?
- How to choose monotherapy vs combination?
- Role of CPI combinations vs Pembro-chemo?
  - Need a trial comparing 9LA with Pembro + histology-specific chemo
- **Other unanswered questions**
  - Optimal number of chemo cycles?
  - Can we extend Tx intervals?
  - Maintenance pemetrexed in those with high PD-L1 expression?
  - Mechanisms of resistance?
  - Additional compounds?

Metastatic wtNSCLC: Role of Second-Line Immunotherapy

2022 ASCO® ANNUAL MEETING

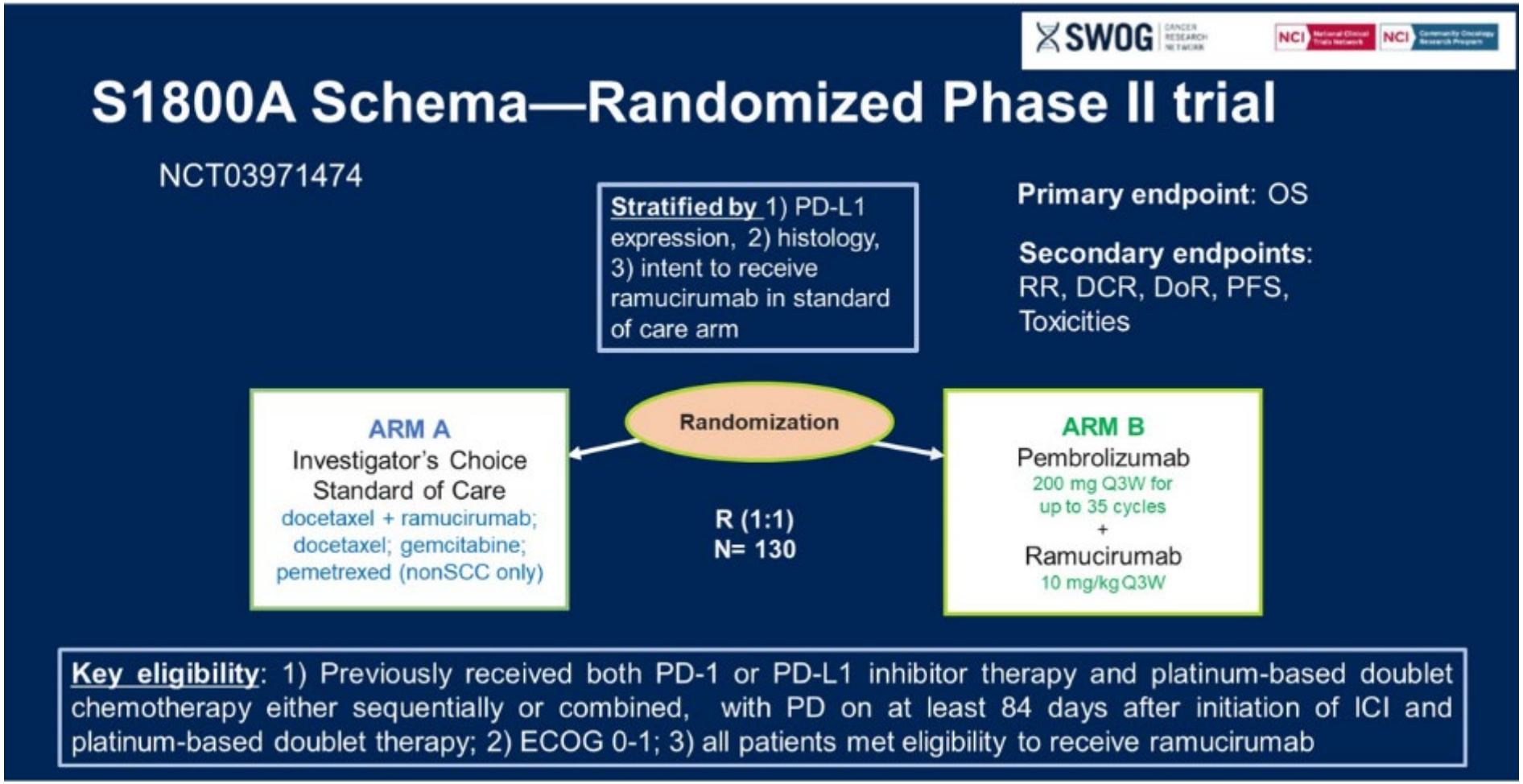
SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network | NCI Community Oncology Research Program

Overall survival from a phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with immunotherapy—Lung-MAP non-matched sub-study S1800A

Karen L. Reckamp, M.D.[1], Mary W. Redman, PhD[2], Konstantin H. Dragnev, M.D.[3], Liza Villaruz, M.D.[4], Bryan Faller, MD[5]; Tareq Al Baghdadi, MD[6], Susan Hines, MD[7], Lu Qian, M.S.[2], Katherine Minichiello, M.S.[2], David R. Gandara, M.D.[8], Karen Kelly, MD[8], Roy S. Herbst, M.D., Ph.D.[9]

[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]SWOG Statistics and Data Management Center & Fred Hutchinson Cancer Research Center, Seattle, WA; [3]Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH/Alliance for Clinical Trials in Cancer; [4]University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center; [5]Missouri Baptist Medical Center, St. Louis, MO/Heartland NCORP; [6]IHA Hematology Oncology Consultants-Ann Arbor/Michigan CRC NCORP; [7]Novant Health Cancer Institute - Mount Airy/Southeast Clinical Oncology Research Consortium NCORP); [8]UC Davis Comprehensive Cancer Center, Sacramento, CA; [9]Yale University, New Haven, CT

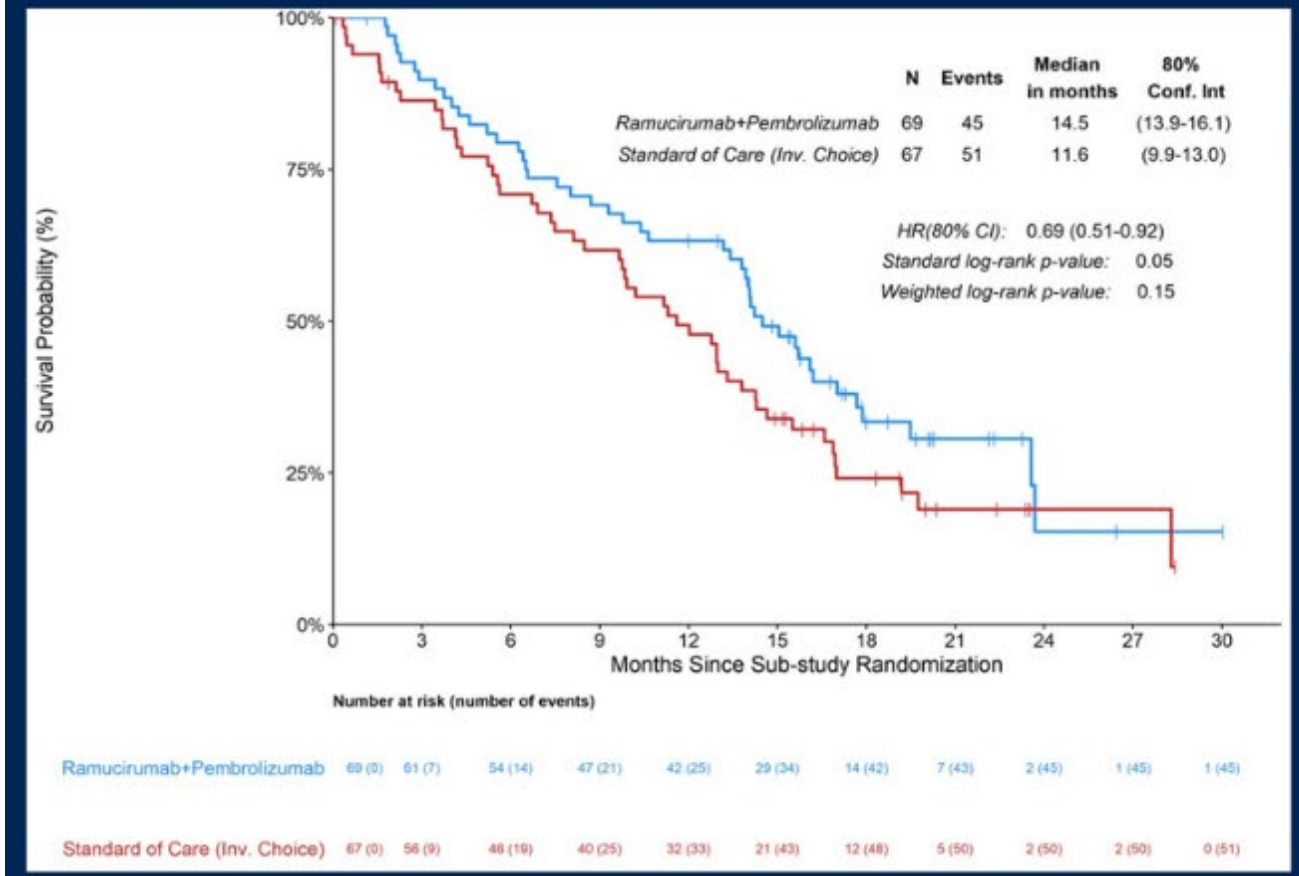
What Is the Best Second-Line Treatment After Chemotherapy and Immunotherapy?

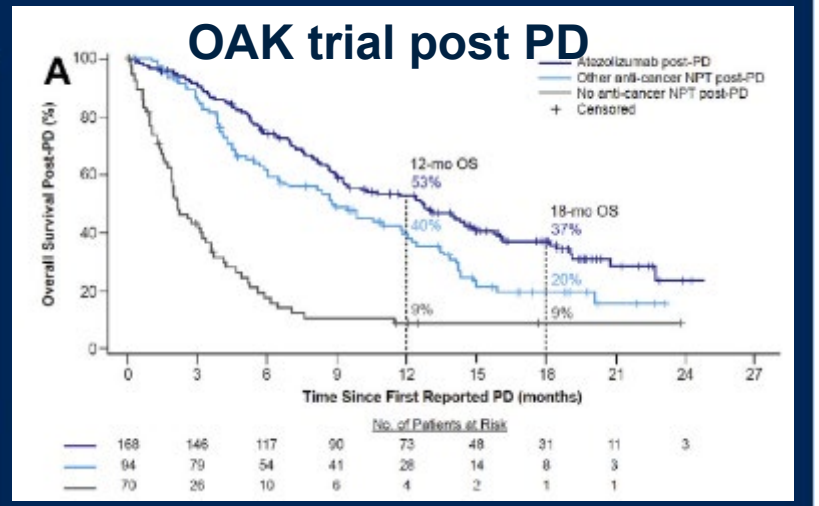


Adapted from ASCO 2022 presentation by Karen Reckamp.

Improved OS for Ramucirumab-Pembrolizumab

Overall survival



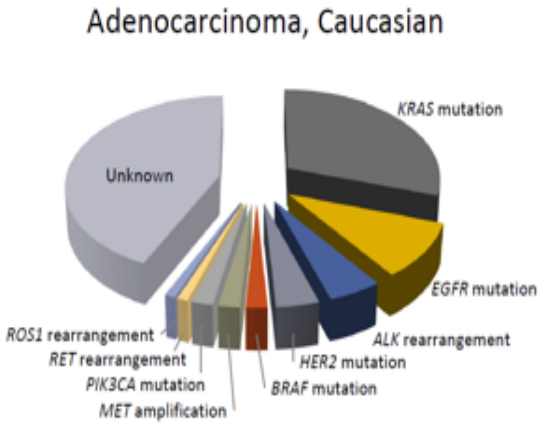


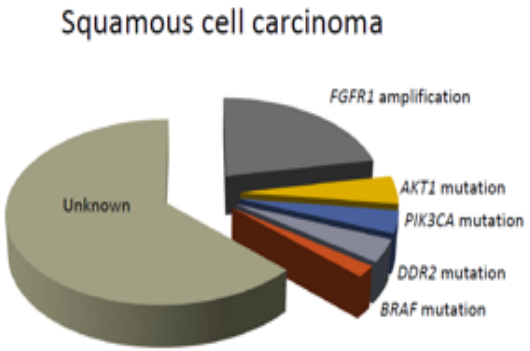
Standard of care therapy received:

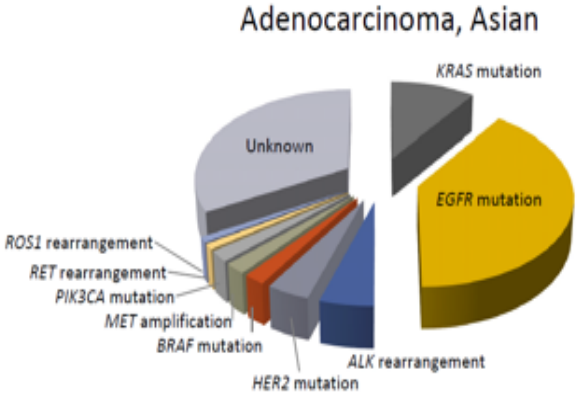
- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

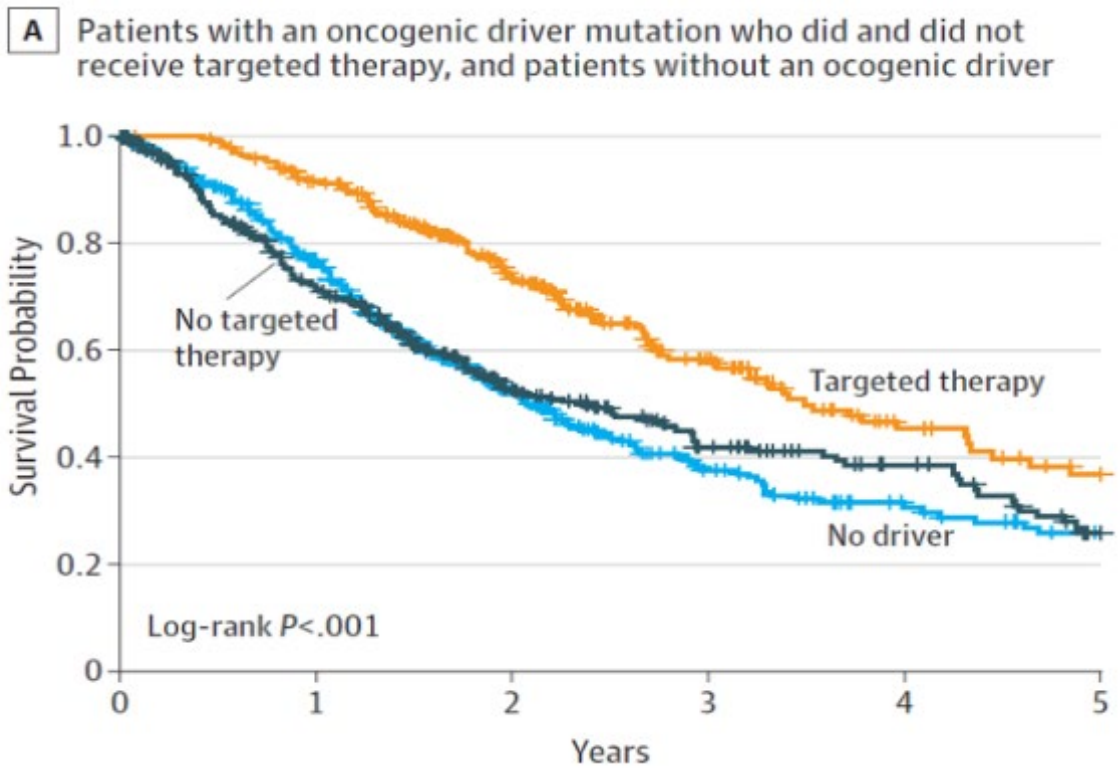
Adapted from ASCO 2022 presentation by Karen Reckamp; Gandara DR, et al. *J Thorac Oncol.* 2018;13:1906-1918.

Target Directed Therapy Improves OS







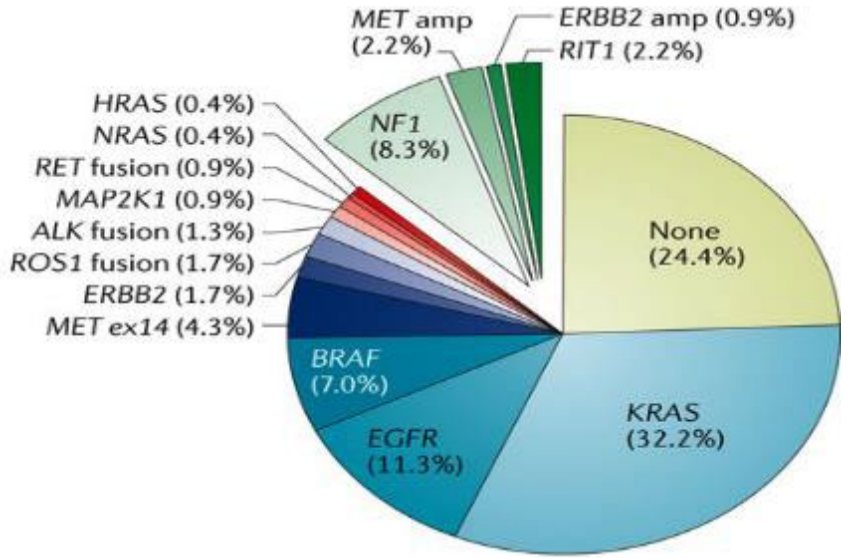


Kris MG, et al. *JAMA.* 2014;21;311:1998-2006.

Targeted Therapy in NSCLC: FDA Approvals

Lung cancer is COMPLEX

Tremendous progress has been made in personalized therapy



EGFR	ALK	ROS1	BRAF	MET	RET	TRK	KRAS G12C	HER-2
Erlotinib	Crizotinib	Crizotinib	Dabrafenib	Crizotinib	Vandetanib	**Larotrectinib**	**Sotorasib**	**TDM-1**
Gefitinib	Ceritinib	**Entrectinib**	Vemurafenib	**Tepotinib**	Cabozantinib	**Entrectinib**		
Afatinib	Brigatinib		Trametinib	**Capmatinib**	**Selpercatinib**			
Osimertinib	Alectinib				**Pralsetinib**			
Dacomitinib	**Lorlatinib**							
Ramu + Erl								
Amivantamab								
Mobocertinib								

2022 ASCO® ANNUAL MEETING

Association of comprehensive molecular genotyping and overall survival in patients with advanced non-squamous non-small cell lung cancer

Charu Aggarwal, Melina E. Marmarelis, Wei-Ting Hwang, Dylan G. Scholes, Tara L. McWilliams, Aditi P. Singh, Lova Sun, John Kosteva, Michael R. Costello, Roger B. Cohen, Corey J. Langer, Peter E. Gabriel, Lawrence N. Shulman, Jeffrey C. Thompson, Erica L. Carpenter

Abramson Cancer Center,
University of Pennsylvania
Philadelphia, PA, United States

Background/Methods:

- We analyzed the impact of concurrent tissue (T) and plasma (P) based next generation sequencing (NGS) upon comprehensiveness of molecular genotyping and overall survival (OS).

Methods:

- Retrospective cohort study of patients with newly diagnosed Stage IV non-squamous NSCLC treated at our institution between 1/2019 -12/2020
- Categories of NCCN guideline concordant testing were defined as follows:
  i. Comprehensive: *EGFR, ALK, BRAF, ROS1, MET, RET, NTRK* testing
  ii. Incomplete: 2-6 genes tested
  iii. No molecular testing

Statistics:

- Proportion of patients with comprehensive molecular testing performed, prior to first line and by modality (T NGS vs. T+P NGS), were compared using Fisher's exact test.
- Median OS was estimated using Kaplan-Meier methodology from diagnosis to death or censored at most recent follow-up.

Figure 1. Consort Diagram

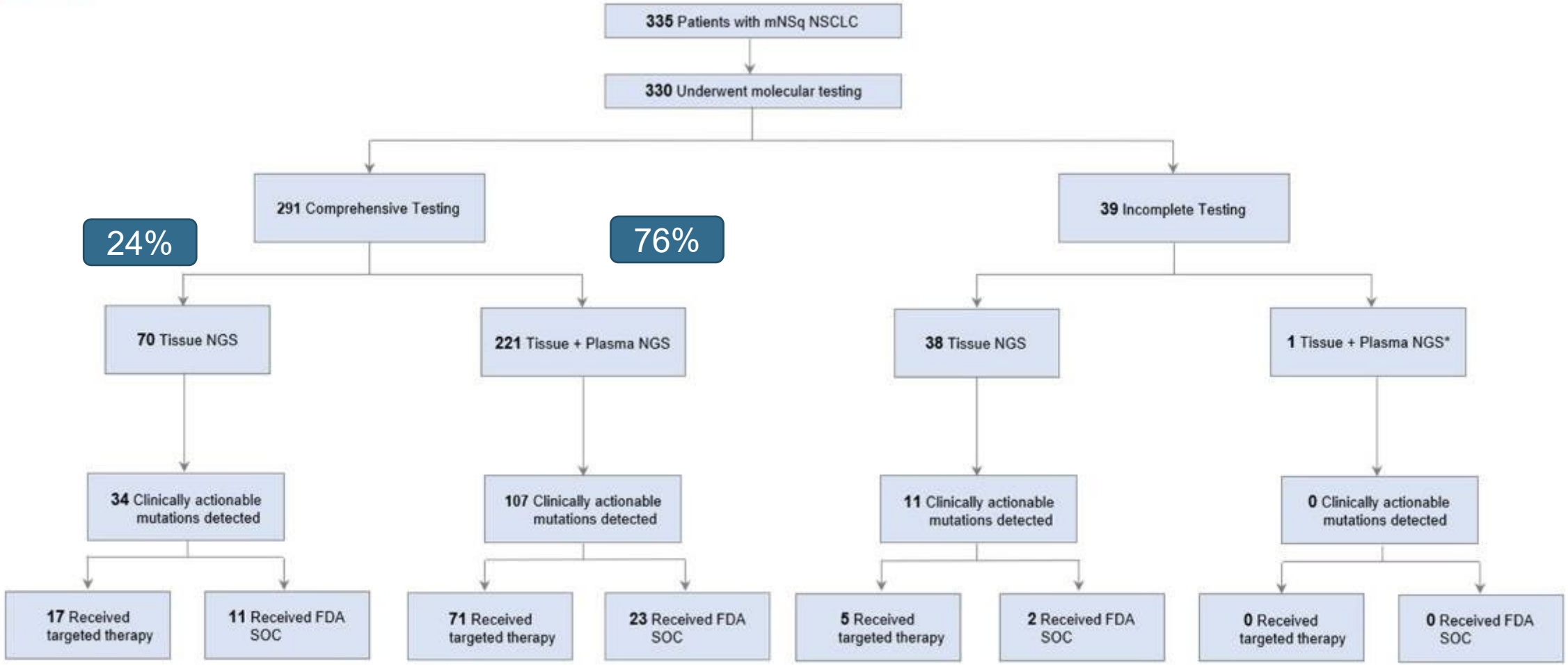


Fig 1.
Flowchart summarizes the overall patient enrollment and the number of clinically actionable mutations detected (*EGFR, ALK, BRAF, ROS1, MET, RET, NTRK1,2* and *3*, *KRAS* G12C, and *ErbB2)* on Tissue vs. Tissue + Plasma NGS for patients with comprehensive testing as well as for those with incomplete/no testing. NGS, next-generation sequencing; FDA, Food and Drug Administration; SOC, standard of care.

Comprehensive molecular genotyping and overall survival

Patients with comprehensive molecular genotyping had superior OS (22.1 months, 95% CI 14.62 – NA), compared to those with incomplete or no testing (11.6 months, 95% CI 3.61 – NA), p=0.02, likely mediated by delivery of targeted therapy

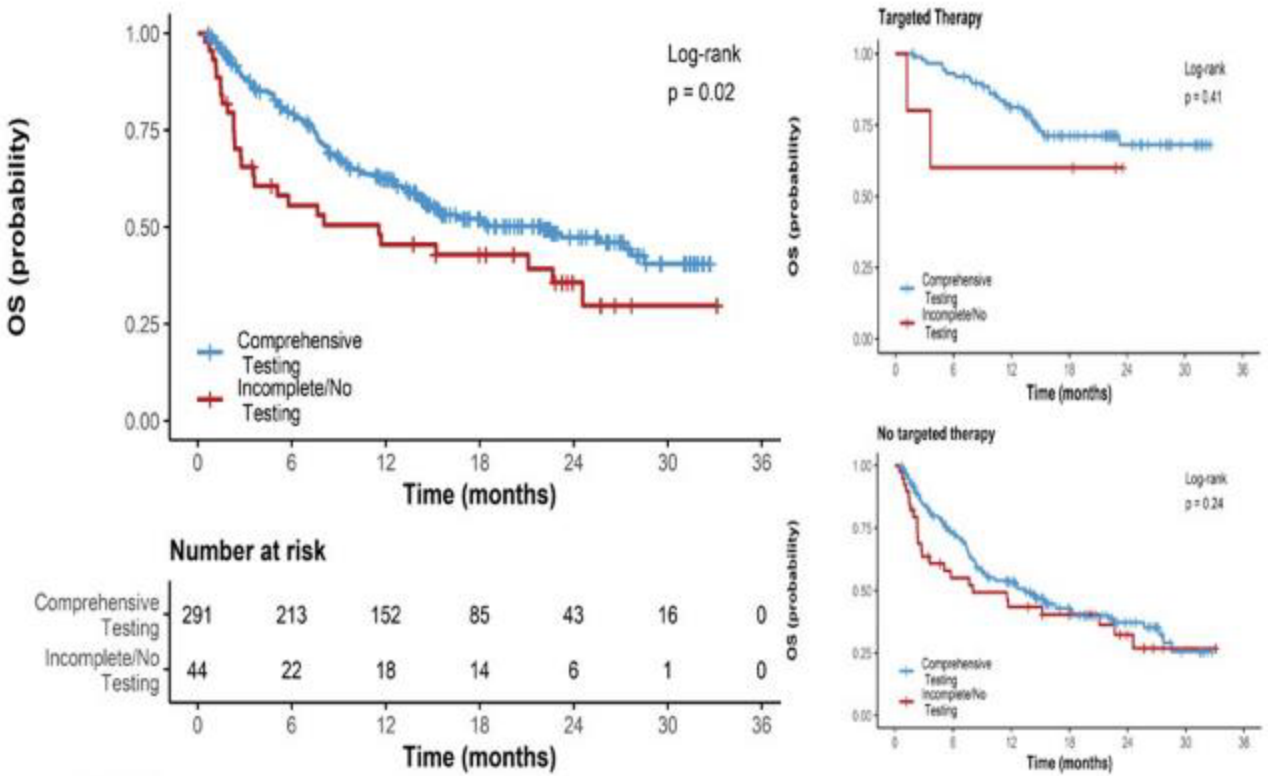


Fig 1.
Kaplan-Meier curve for OS of patients with comprehensive testing compared to patients with incomplete/no testing.

Availability of molecular genotyping results prior to first line therapy was associated with an improvement in OS (24.57 months, 95% CI, 18.56– NR), compared to patients without results available prior to first line therapy (6.18 months, 95% CI, 2.83 – 10.3), p<0.0001

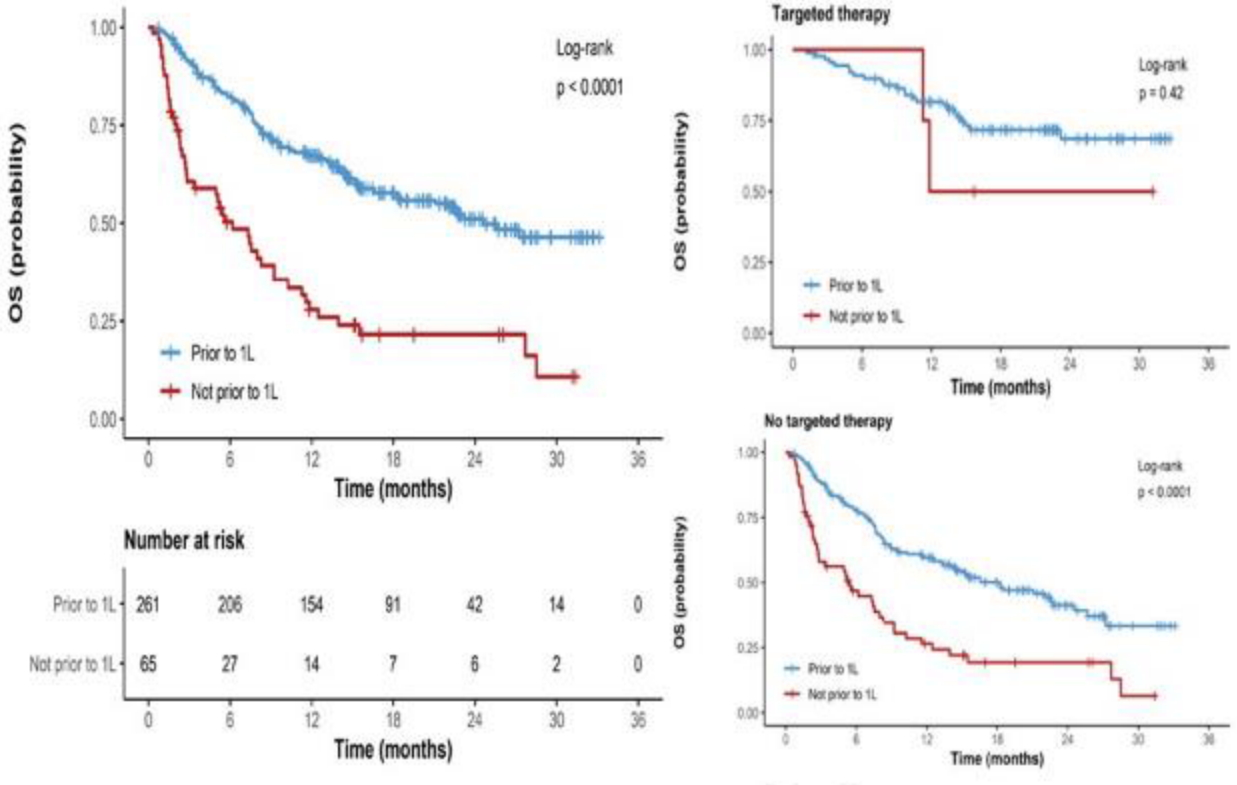


Fig 2.
Kaplan-Meier curve for OS of patients with comprehensive testing back prior to first line treatment compared to patients with results not back prior to first line treatment.

NGS: Implications for Clinical Practice

Tissue for NGS testing

- Should be obtained, if safe and feasible, both at diagnosis as well as at progression after primary targeted therapy
- At a minimum, test all adenocarcinomas regardless of smoking history, all never smokers or remote, former smokers regardless of histology

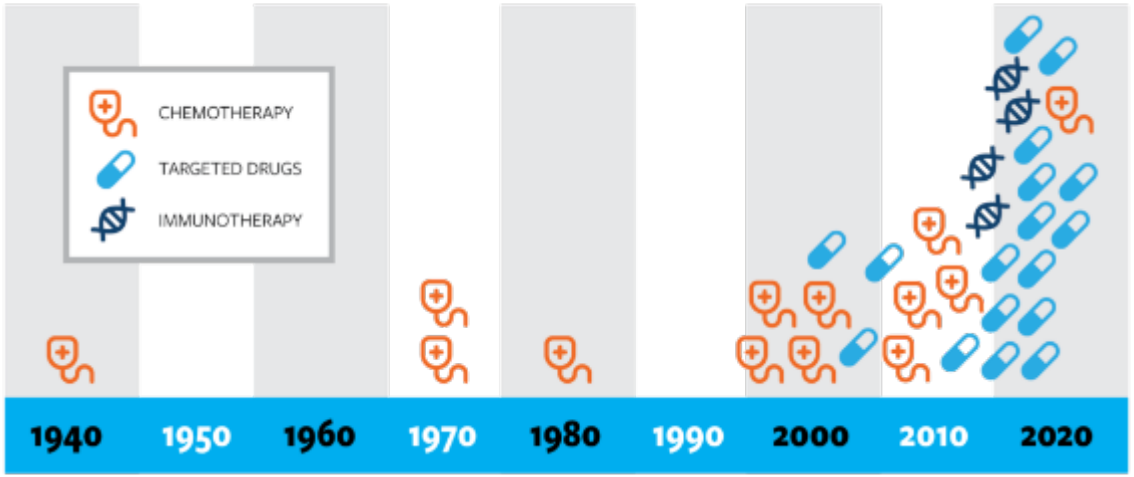
Liquid biopsy for NGS testing

- Obtainable at diagnosis, often concurrently with tissue testing; quick TAT
- Especially useful if burden of disease is on the higher side
- May be negative, especially if disease burden is low or confined to the thorax
- Early institution, in conjunction with standard tissue testing, can lead to improved outcome
- Often useful in detecting mechanisms of resistance after primary TKI therapy
- Evolving role in monitoring efficacy of therapy, both in the neoadjuvant setting and in advanced NSCLC

KRAS-Targeted Therapy: Beyond Sotorasib

KRAS G12C

- *KRAS* mutations are prevalent in NSCLC
- *KRAS* G12C present in 13% of lung adenocarcinoma
- Previously undruggable due to protein shape
- **NOW** with an FDA-approved targeted therapy and others in development



2021
Mobocertinib – *EGFR* exon20
Sotorasib – *KRAS* G12C
Amivantamab – *EGFR* exon 20
Tepotinib – *MET* exon 14 skipping

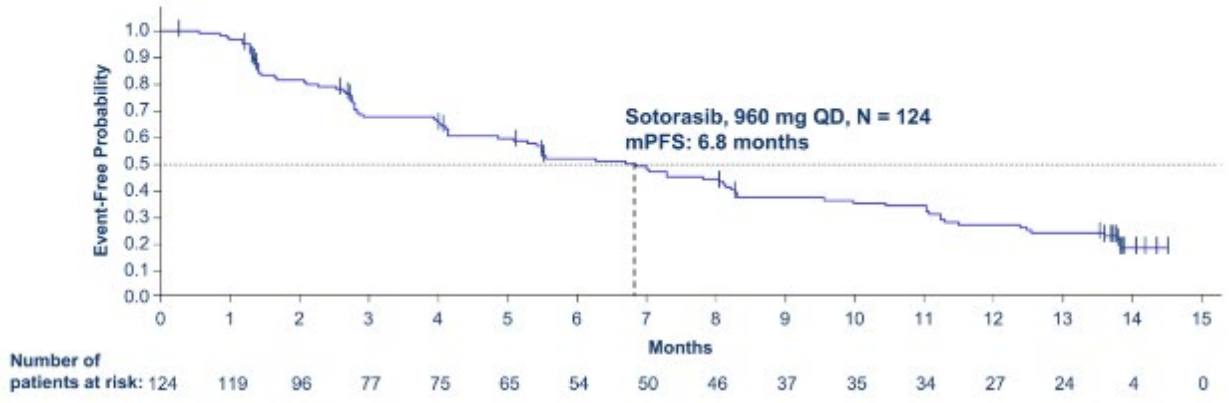
2020
Pralsetinib – *RET*
Brigatinib – *ALK* 1L
Capmatinib – *MET* exon 14 skipping
Selpercatinib – *RET*

2019
Entrectinib – *NTRK*, *ROS1* fusions

2018
Lorlatinib – *ALK*
Larotrectinib – *NTRK* fusion
Dacomitinib – *EGFR*

Progression-Free Survival

Sotorasib
ORR 37.1%



https://www.lungcancerresearchfoundation.org/research/why-research/treatment-advances/;
Nassar AH, et al. *N Engl J Med.* 2021;384:185-187; The Lancet Oncology. *Lancet Oncol.* 2021;22:289. Skoulidis F, et al. *N Engl J Med*. 2021;384:2371-2381.

Adagrasib and Sotorasib Have Similar Efficacy

Parameter	Adagrasib (KRYSTAL-1)	Sotorasib (CodeBreaK100)[1]
N=	116 (112 for efficacy)	126 (124 for efficacy)
Prior Platinum Chemo + IO	**98%**	**81%**
ORR	**43%** (95% CI 33.5-52.6)	**37.1%** (95% CI 28.6-46.2)
DCR	**80%** (95% CI 70.8-86.5)	**80.6%** (95% CI 72.6-87.2)
TTR, median (range)	**1.4 mo** (0.9-7.2)	**1.4 mo** (1.2-10.1)
DOR, median	**8.5 mo** (95% CI 6.2-13.8)	**11.1 mo** (95% CI 6.9-NE)
PFS, median	**6.5 mo** (95% CI 4.7-8.4)	**6.8 mo** (95% CI 5.1-8.2)
OS, median	**12.6 mo** (95% CI 9.2-19.2)	**12.5 mo**[2] (95% CI 10.0-NE)
Follow-up, median	12.9 mo	15.3 mo[2]

1= Skoulidis et al. N Engl J Med. 2021 Jun 24;384(25):2371-2381; 2=Pooled phase 1/2 of 174 pts with median f/u 24.9 mo, median OS 12.5 mo (95% CI 10.0-17.8), 1-year OS 50.8%, 2-year OS 32.5% (Dy G et al. AACR 2022)

Adapted from ASCO 2022 presentations by Sukhmani Padda, Alex Spira.

Adverse Events (AEs)

Treatment-related AEs	Sotorasib phase II (n = 126)	Adagrasib phase II (n = 116)
Treatment-related AEs		
Any grade	69.8%	97.4%
≥Grade 3	20.6%	43.1%
Leading to dose reduction	22.2%	51.7%
Leading to treatment D/C	7.1%	6.9%

Most Common TRAEs

	Any grade	≥Grade 3	Any grade	≥Grade 3
Nausea	19%	0	62.1%	4.3%
Diarrhea	31.7%	4%	62.9%	0.9%
Vomiting	7.9%	0	47.4%	0.9%
Fatigue	11.1%	0	40.5%	4.3%
ALT increase	15.1%	6.3%	27.6%	4.3%
AST increase	15.1%	5.6%	25%	3.4%

ALT, alanine transaminase; AST, aspartate transaminase.

Skoulidis F, et al. *N Engl J Med*. 2021;384:2371-2381; Janne PA, et al. *N Engl J Med*. 2022;387:120-131.

CodeBreaK 200 Phase 3 Study Design

Key eligibility criteria

- Locally advanced/unresectable or metastatic *KRAS* G12C-mutated NSCLC
- **≥ 1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor***
- **No active brain metastases**
- ECOG performance status ≤ 1

Stratification factors

- Prior lines of therapy (1 vs 2 vs > 2)
- Race (Asian vs non-Asian)
- History of CNS involvement (yes vs no)

Randomisation 1:1 (N = 345)

- **Sotorasib 960 mg oral daily N = 171**
- **Docetaxel 75 mg/m² IV Q3W N = 174**

Primary Endpoint: PFS by BICR

Secondary Endpoints: Efficacy (OS†, ORR, DOR, TTR, DCR)**, safety/tolerability, PRO**

ITT population analysis included all randomised patients

Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.

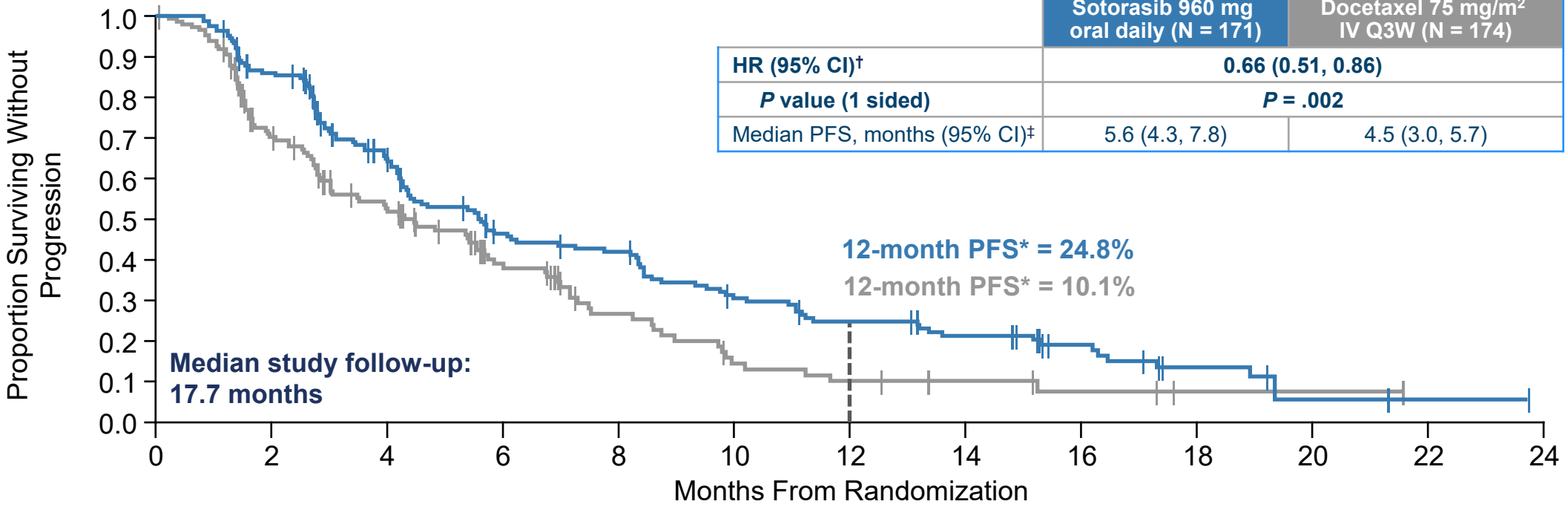
NCT04303780; EudraCT: 2019-003582-18.

*Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval.

†Analysis of OS planned if PFS was found to be statistically significant and when at least 198 OS events have been reached.

Melissa L. Johnson, MD
Twitter: @MLJohnsonMD2

Primary Endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P value (1 sided)	*P* = .002	
Median PFS, months (95% CI)‡	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = .002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model; *P* value calculated using a stratified log-rank test.
‡Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

Key Takeaways From 2021–2022 in Lung Cancer

- **Neoadjuvant:** chemo-Nivo superior pCR, MPR, and EFS vs chemo alone in resectable IB–IIIA NSCLC
- **Adjuvant:** post-resection and adjuvant chemo, atezolizumab yields superior DFS in stage II/IIIA, PD-L1–positive NSCLC and potential OS advantage in pts with ≥50% expression. Pembro yields similar PFS benefit in phase III trial
- **LA-NSCLC:** durvalumab post chemo-XRT remains SOC in absence of PD or untoward toxicity
- **PD-L1 ≥50%:** still on the hunt for high-risk features that predict benefit of adding chemo to IO
  - Ongoing research will prospectively define role of chemo-IO vs IO alone
- **Combination CPIs:** hazardous in PS 2, but fit elderly appear to benefit (vs chemo alone)
  - Trials intermixing these populations will lead to “murky” outcomes
- **Second-line treatment:** post–chemo-IO space poses tremendous, unmet need
  - IO + VEGF may be a viable, less-toxic strategy compared with other options in this space (eg, docetaxel ± Ramu)
- ***KRAS* G12C**: adagrasib will likely be the next addition in the therapeutic portfolio
  - Similar to sotorasib in efficacy but has higher grade 3–4 TRAEs that may require dose reduction
  - However, documented CNS penetrance

https://stock.adobe.com/search?k=key+takeaway

Thank you for your attention

Perelman Center for Advanced Medicine

University of Pennsylvania, Philadelphia, PA

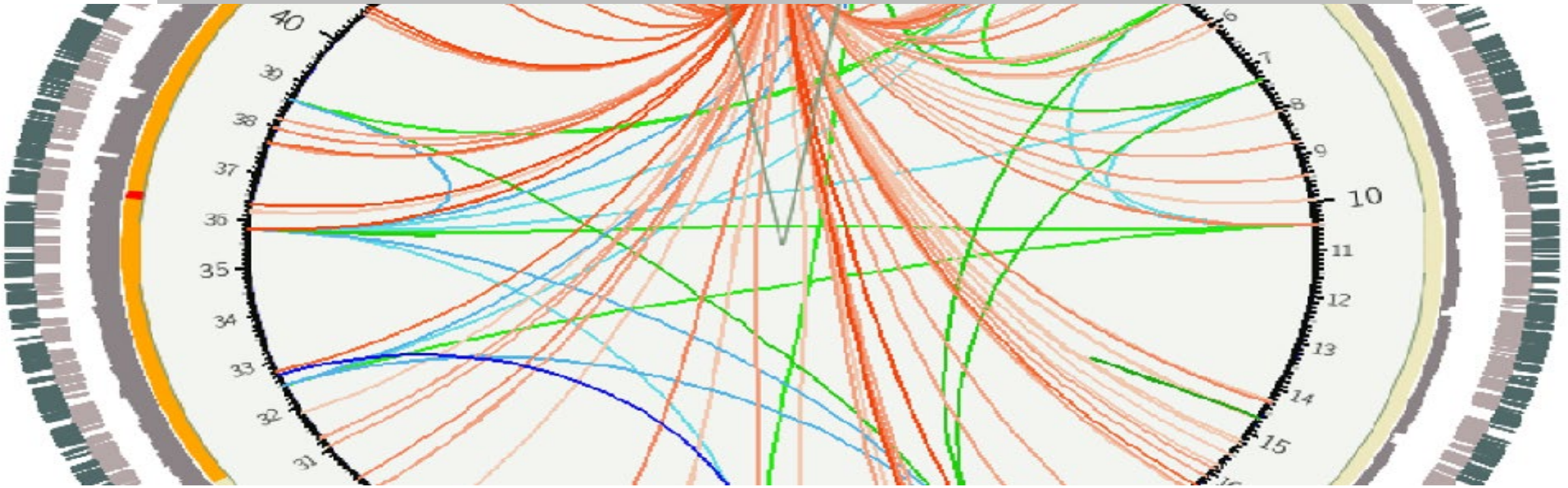
Thank you!

Penn Medicine
Abramson Cancer Center

Global Lung Cancer Academy

Biomarker and Mutational Testing for NSCLC – What, Where, and When?

Ignacio Wistuba, MD



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Biomarker and Mutational Testing for NSCLC: What, Where, and When?

Global Lung Cancer Academy, Virtual Meeting, October 21, 2022

Ignacio I. Wistuba, MD
Professor and Chair, Department of Translational Molecular Pathology
Co-Director, Khalifa Institute for Personalized Cancer Therapy (IPCT)
The University of Texas MD Anderson Cancer Center, Houston, TX

Disclosures

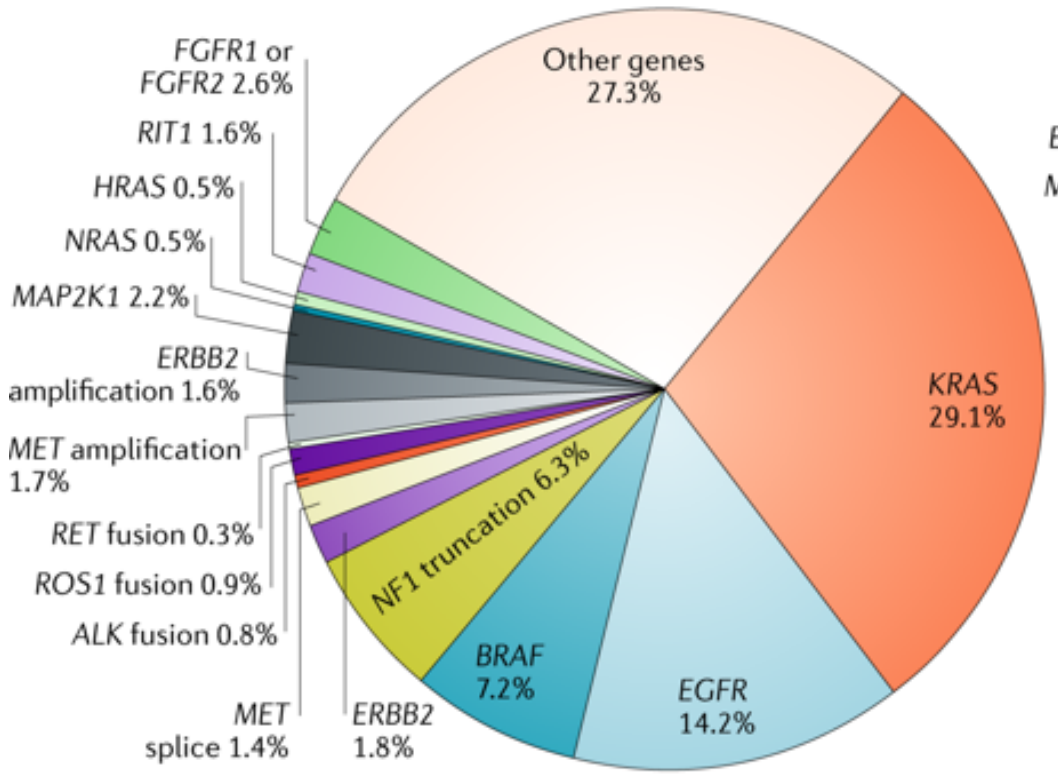
- **Advisory Board:** Genentech/Roche, Bayer, Bristol-Myers Squibb, Astra Zeneca, Pfizer, HTG Molecular, Asuragen, Merck, GlaxoSmithKline, Guardant Health, Flame, Novartis, Sanofi, Daiichi Sankyo, Jansen, Regeneron, Amgen, Oncocyte, and MSD
- **Speaker**: Medscape, MSD, Genentech/Roche, Platform Health, Pfizer, AstraZeneca, Merck
- **Research support**: Genentech, HTG Molecular, DepArray, Merck, Bristol-Myers Squibb, Medimmune, Adaptive, Adaptimmune, EMD Serono, Pfizer, Takeda, Amgen, Karus, Johnson & Johnson, Bayer, Iovance, 4D, Novartis, and Akoya

Paradigms in Cancer Molecular Pathology: 2022

- Histology subtyping of lung cancer is clinically important
- Multiple clinically relevant molecular abnormalities ("driver alterations") have been detected and can be used to direct targeted therapy and improve patients' outcomes
- Liquid biopsy represents an alternative option for molecular testing and potentially early diagnosis
- Immunotherapy-related biomarkers are part of diagnosis (*PD-L1 IHC, microsatellite instability (MSI), and Tumor Mutational Burden (TMB)*. However, additional biomarkers are needed
- As neoadjuvant approaches using immunotherapy and targeted therapy are being adopted, surrogate markers to decide on adjuvant therapy and recurrence such as minimal residual disease are needed
  - Major Pathological Response (MPR)
  - Liquid Biopsy (cfDNA) to assess Minimal Residual Disease (MRD)

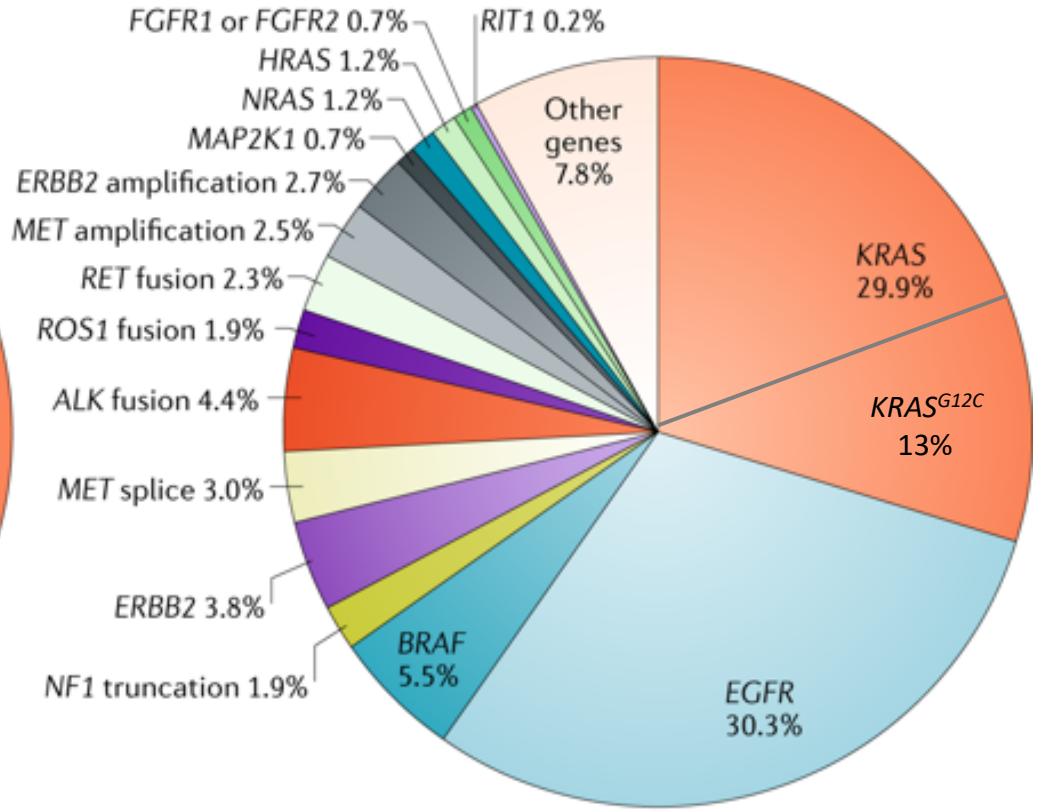
Genomic Abnormalities in Lung Adenocarcinoma

Early Stage



Data from TCGA (Sanchez-Vega et al.[178], Ellrott et al.[179] and Hoadley et al.[180]), Imielinski et al.[62] and Kadara et al.[133] (n = 741)

Metastatic Stage



Data from MSK-IMPACT (Jordan et al.[59]) and FoundationOne (Frampton et al.[15]) panels (n = 5262)

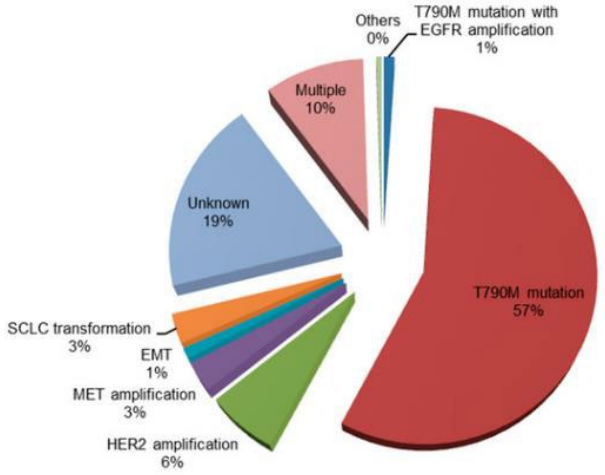
Cancer

Skoulidis F, et al. *Cancer Discov*. 2018;8:822-835.

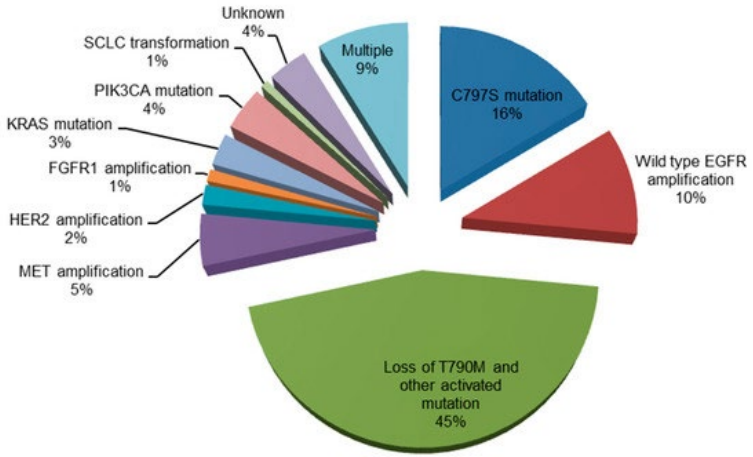
Mechanisms of Resistance to EGFR and ALK TKIs in Lung Adenocarcinoma

EGFR

First Generation TKIs

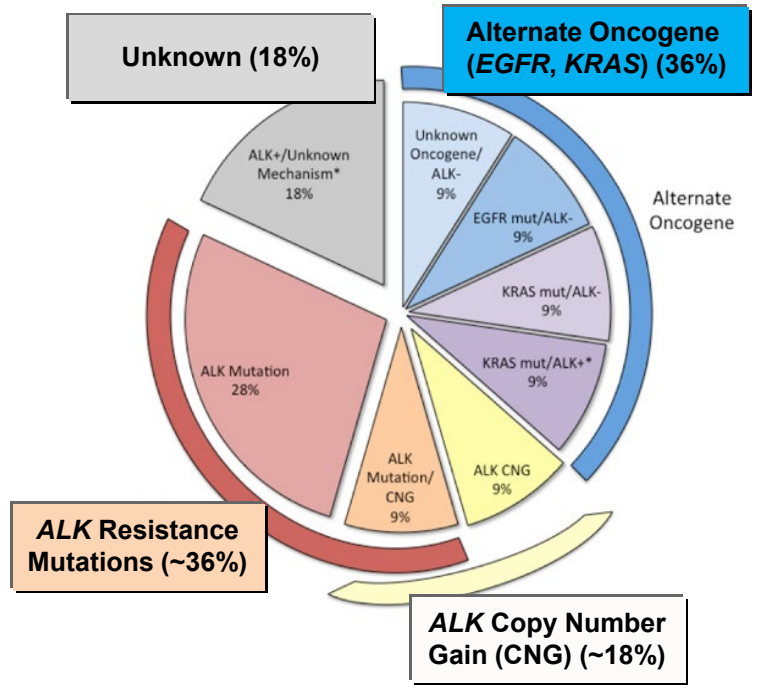


Second Generation TKIs



Nagano T, et al. *Cells.* 2018;7:212.

ALK



Doebele RC, et al. *Clin Cancer Res*. 2012;18:1472-1482.

Biomarker Testing in NSCLC

- Which type of specimens are suitable for comprehensive biomarker testing in NSCLC?

  a) Tissue biopsy

  b) Cytology, only smears

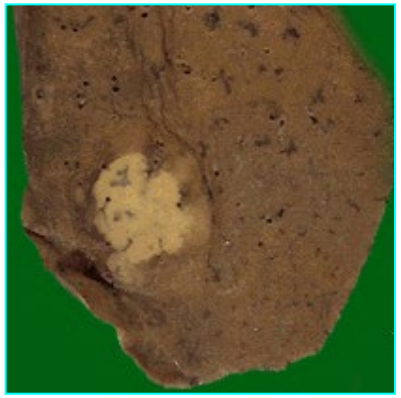
  c) Cytology, smear and cell block

  d) Liquid biopsy (cfDNA)

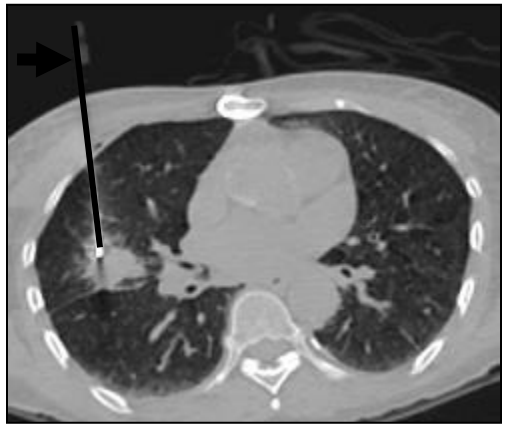
  e) “a” and “c”

Types of Tumor Specimens in Lung Cancer

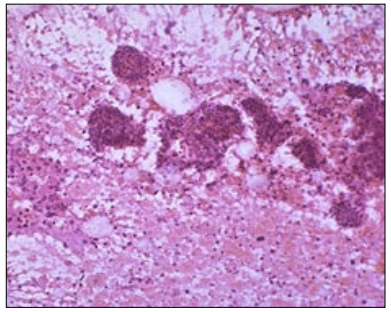
Surgical Resection



Advanced Tumor



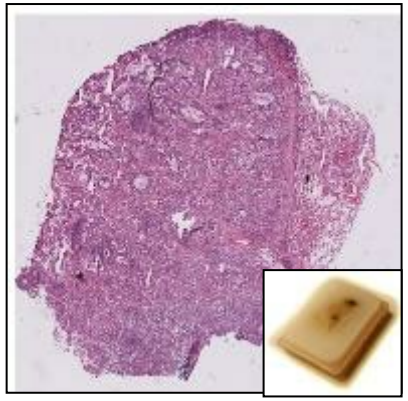
Endobronchial Ultrasound (EBUS) or Pleural Fluid



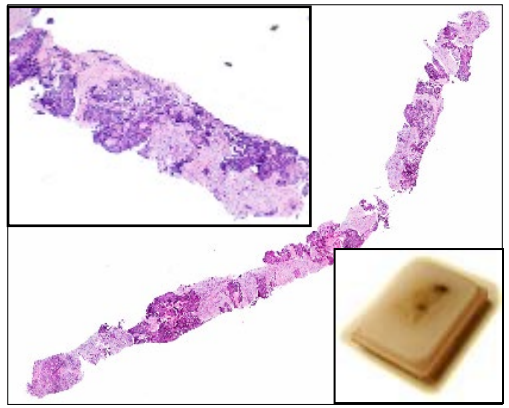
Alcohol-fixed

Alcohol-fixed – Cell Block

Histology

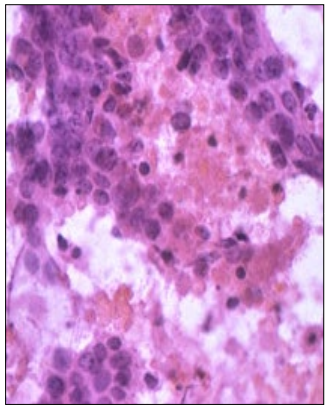


Core Needle Biopsy (CNB)



Formalin-fixed and Paraffin-embedded (FFPE)

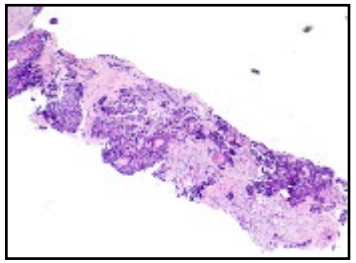
Fine Needle Aspiration (FNA)



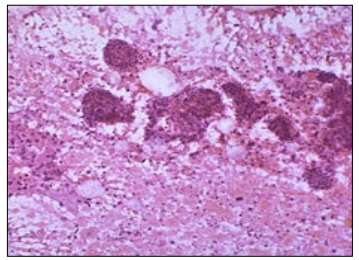
Alcohol-fixed

Diagnostic Algorithm for Lung Cancer Diagnosis 2022

Comprehensive Biomarker Testing



Biopsy

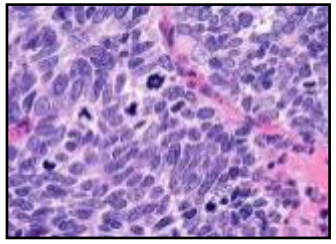


Cytology

Blood

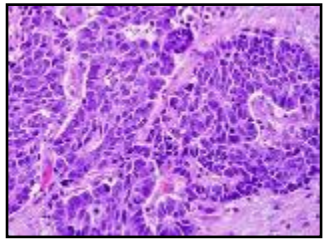
cfDNA Testing
(Liquid Biopsy)

SCLC



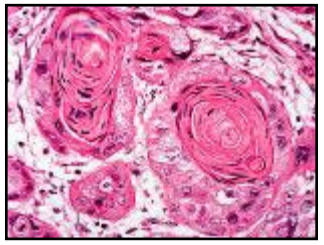
Morphology

LCNEC



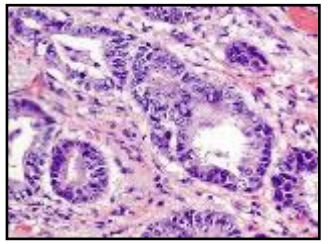
Morphology
IHC NE (+)

Squamous



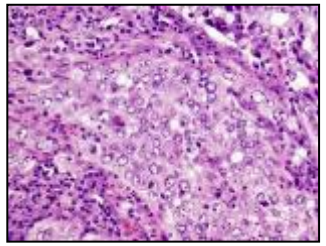
Morphology
IHC p63/p40 (+)

Adenoca



Morphology
IHC TTF1 (+)

NSCLC-NOS



Morphology
IHC (-)

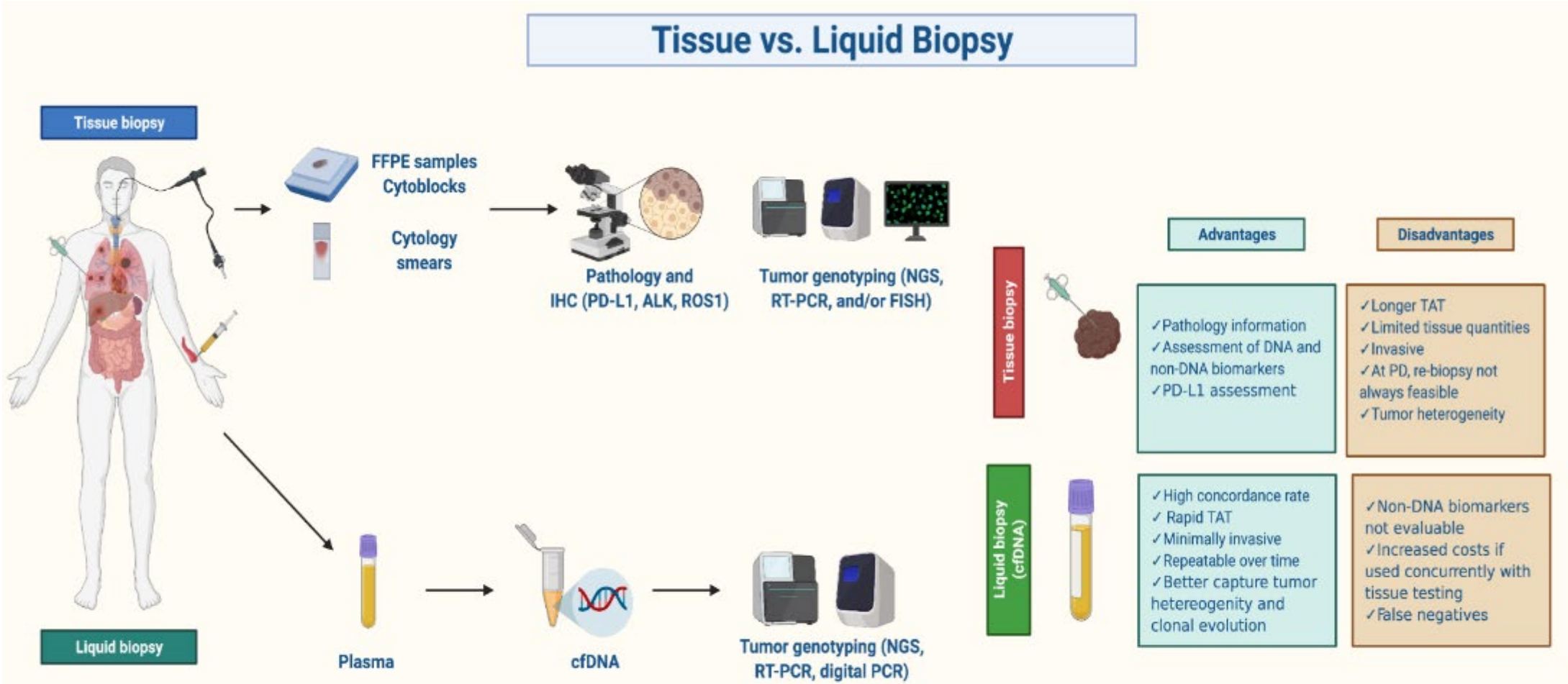
EGFR and *BRAF* mutation, *ALK*, *ROS1* and *NTRK* fusions, *MET ex14* splicing

PD-L1 IHC

Practical Points for Lung Cancer Molecular Biomarker Testing

- **Type of sample**: tissue, cytology (FNA), blood
- **Choice of platform**: single gene vs multiplex small panel vs multiplex expanded panel
  - Low cost and faster TAT single gene testing such as *ALK* IHC, or *ALK/ROS1* FISH, or real-time PCR for *EGFR*, *BRAF* vs NGS
  - There is a need for more than 1 algorithm for testing depending on practice setting and availability of testing platforms
- **Issues specific to type of practice**
  - Large academic centers vs community-based practice
  - In-house testing vs send out reference lab testing
  - Proposed algorithm that can be adopted in various practice settings
  - Availability of reflex testing
- **Stage of the disease in NSCLC**

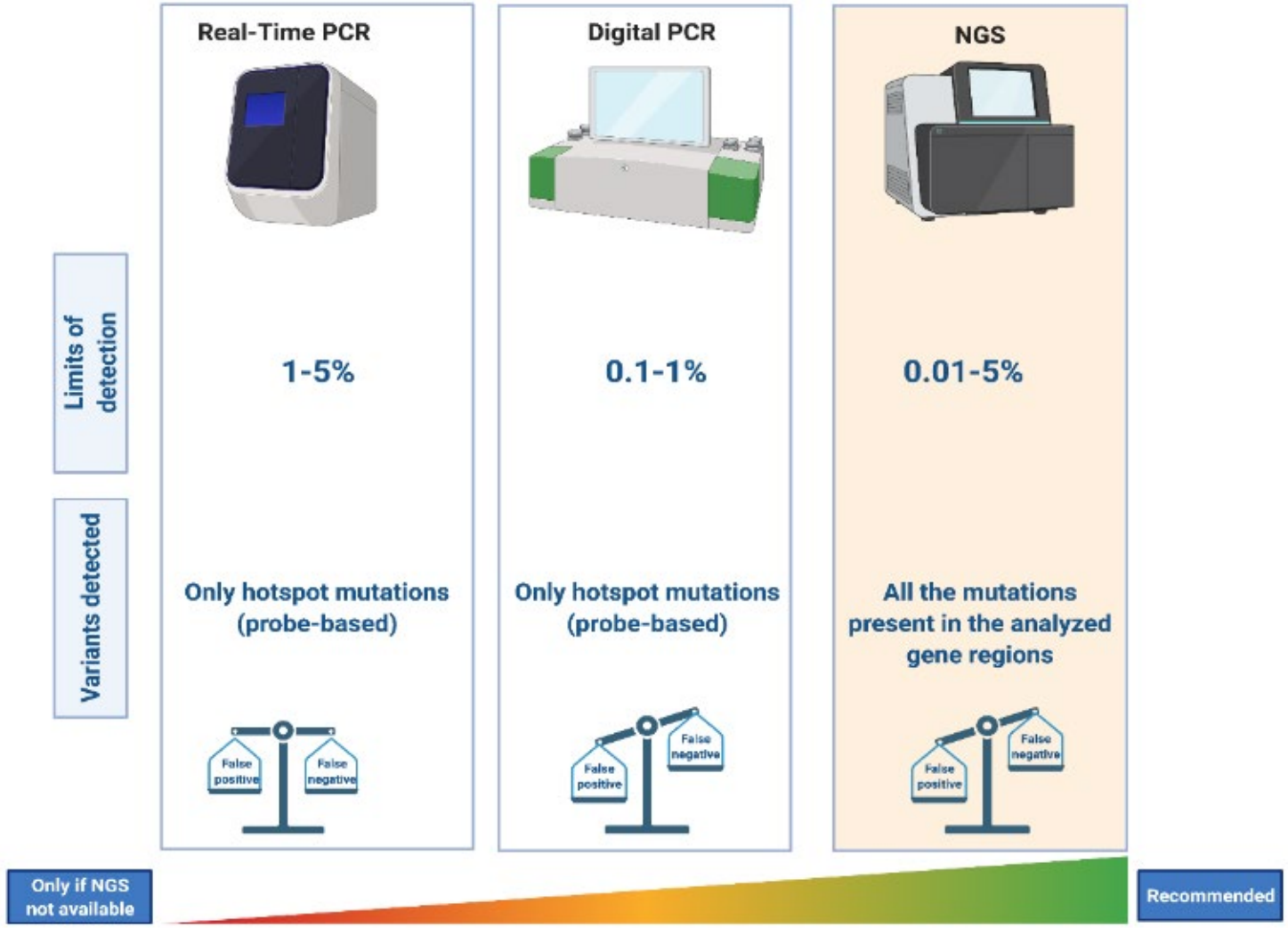
Tissue vs Liquid Biopsy for Molecular Profiling



Cancer

Rolfo C, et al. *J Thorac Oncol*. 2021;16:1647-1662.

Next-Generation Sequencing Panels Major Benefits



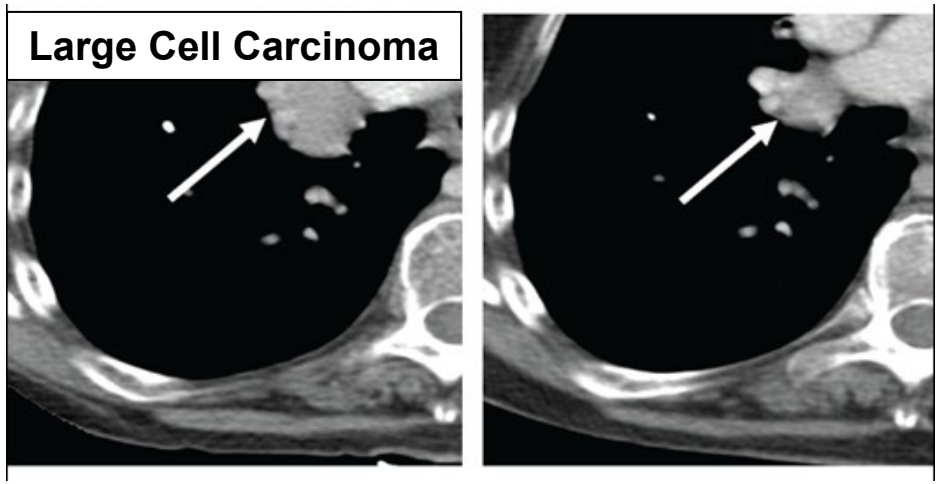
Rolfo C, et al. Unpublished. 2021.

Next-Generation Sequencing Panels Major Benefits

- Provide information in multiple targetable gene abnormalities
- Provide data on mutation, copy number variations, indels, and translocations
- Can be performed in routine, small FFPE tissue samples and liquid biopsy (cfDNA, CTCs, exosome DNA)
- Turnaround time acceptable for clinical management and costs being significantly reduced
- Clinically, they offers to patients more options to get off-label treatment and enter in genomic-based clinical trials
- May provide information on tumor mutational burden (TMB) and immune-suppressive genotypes (eg, *LKB1* mutations)

Benefits of NGS Panels in Lung Cancer

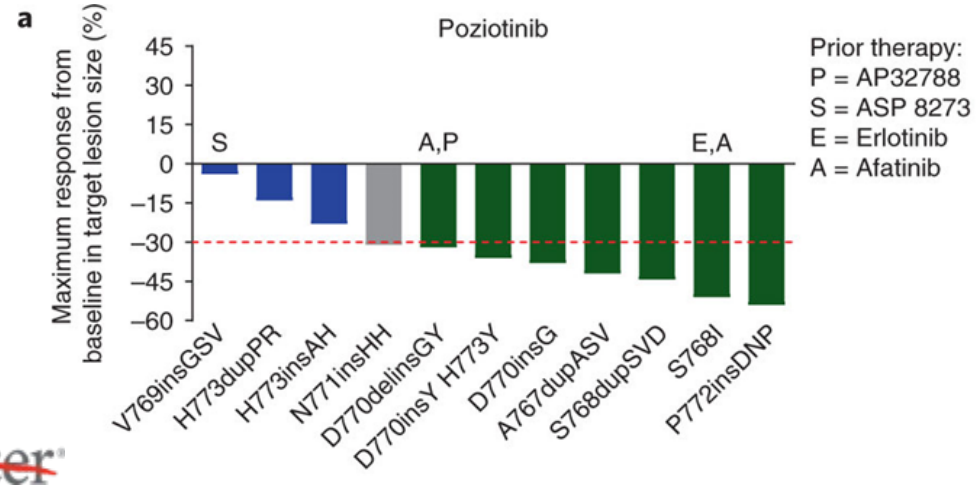
Standard of Care: Treatment with MET inhibitor



- MET exon 14 (*METex14*) is a recurrent somatic splice site
- 0.6% of 38,028 tumors sequenced by FM (3% lung adenocarcinomas)
- Patients' tumor sensitive to MET inhibitor, Capmatinib

Frampton GM, et al. *Cancer Discov.* 2015;5:850-859.

Clinical Research: Treatment with Poziotinib

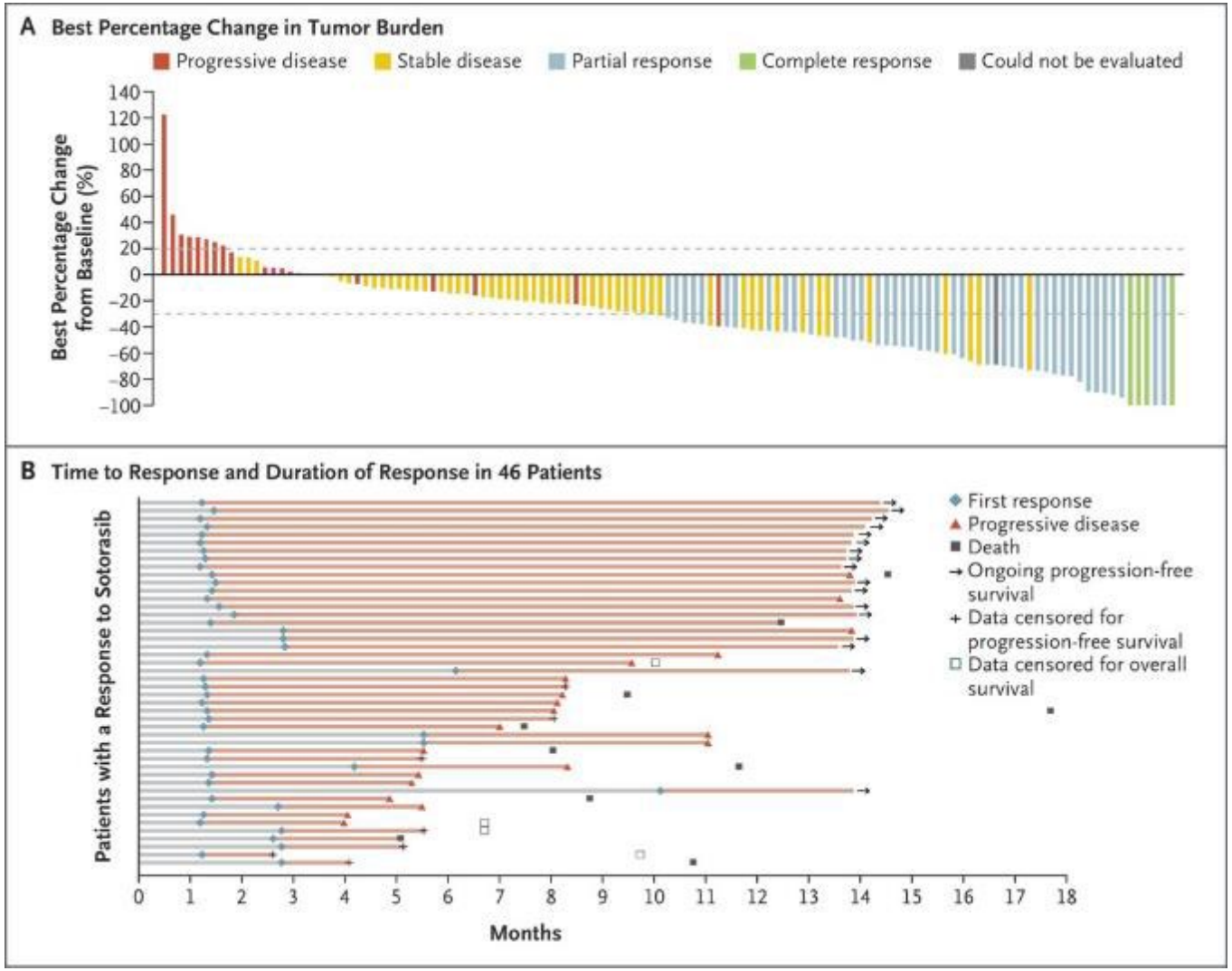


- *EGFR* exon 20 mutations, resistance to TKIs
- Poziotinib, potential active drug against *EGFR* and *HER2* exon 20 mutations
- Study on 11 patients showed objective partial responses in 7 and stable disease in 3

Robichaux JP, et al. *Nat Med.* 2018;24:638-646.

KRAS^{G12C} Inhibition in Advanced NSCLC

- Phase II trial using a KRAS^{G12C} inhibitor (Sotorasib) in 126 patients, *G12C*-mutated advanced NSCLC previously treated with standard therapies
- Objective response was 37.1, including in 4 (3.2%) who had a complete response and in 42 (33.9%) who had a partial response
- Disease control occurred in 100 patients (80.6%)
- Responses were observed in subgroups defined according to PD-L1 expression, tumor mutational burden, and co-occurring mutations in *STK11*, *KEAP1*, or *TP53*

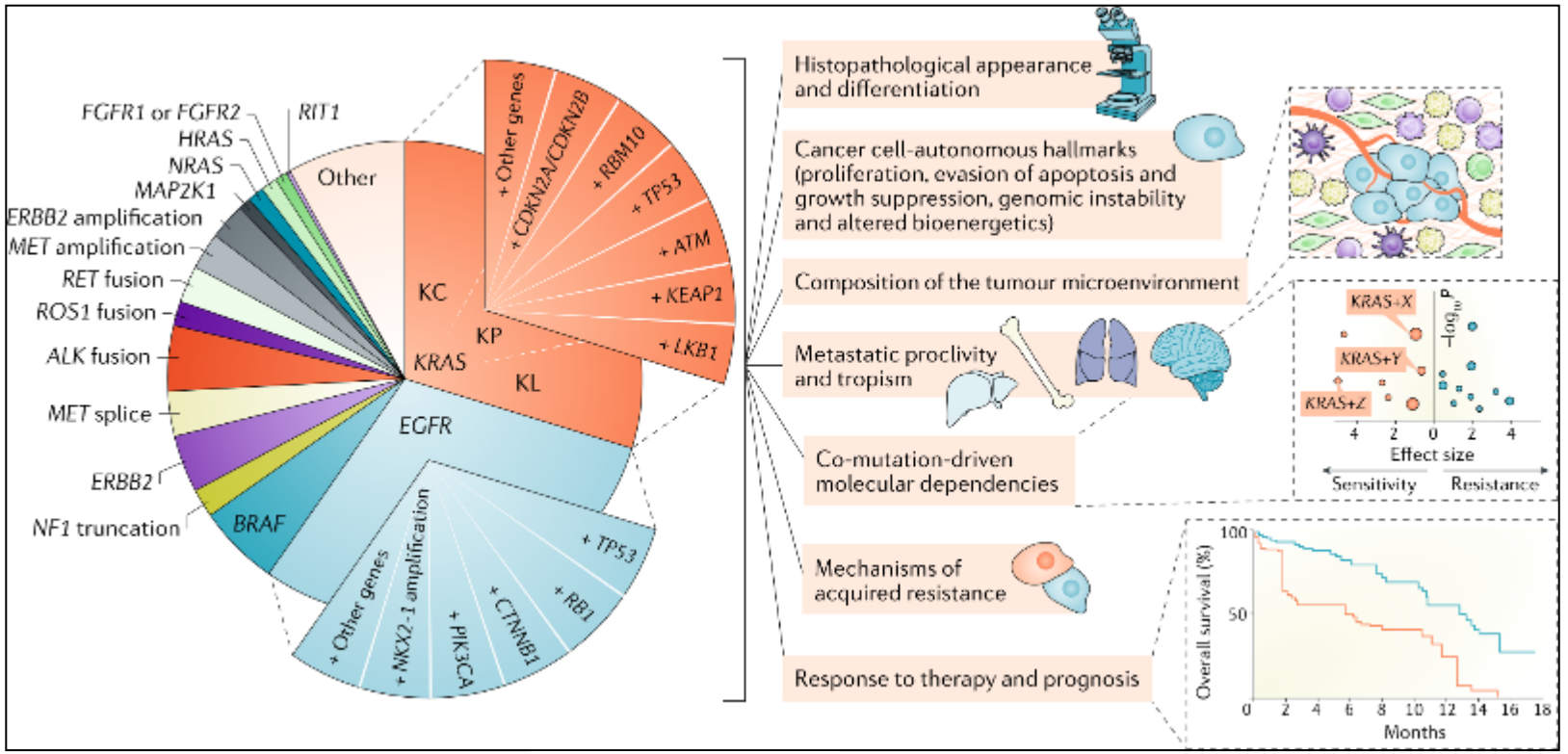


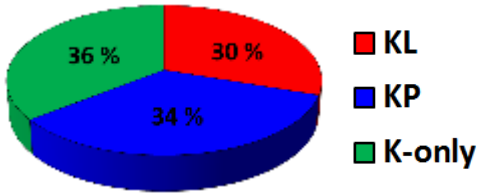
Cancer

Skoulidis F, et al. *N Engl J Med.* 2021;384:2371-2381.

KRAS Co-Mutations in Lung Cancer
TP53, *STK11/LKB1*, *KEAP1*, Other Genes

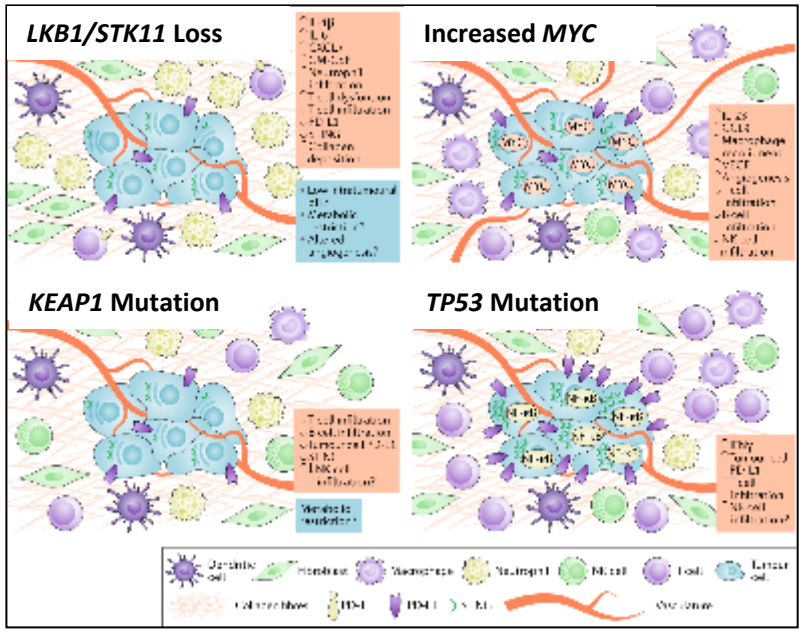
KRAS Co-Mutations





Immune Response

Cold **Hot**

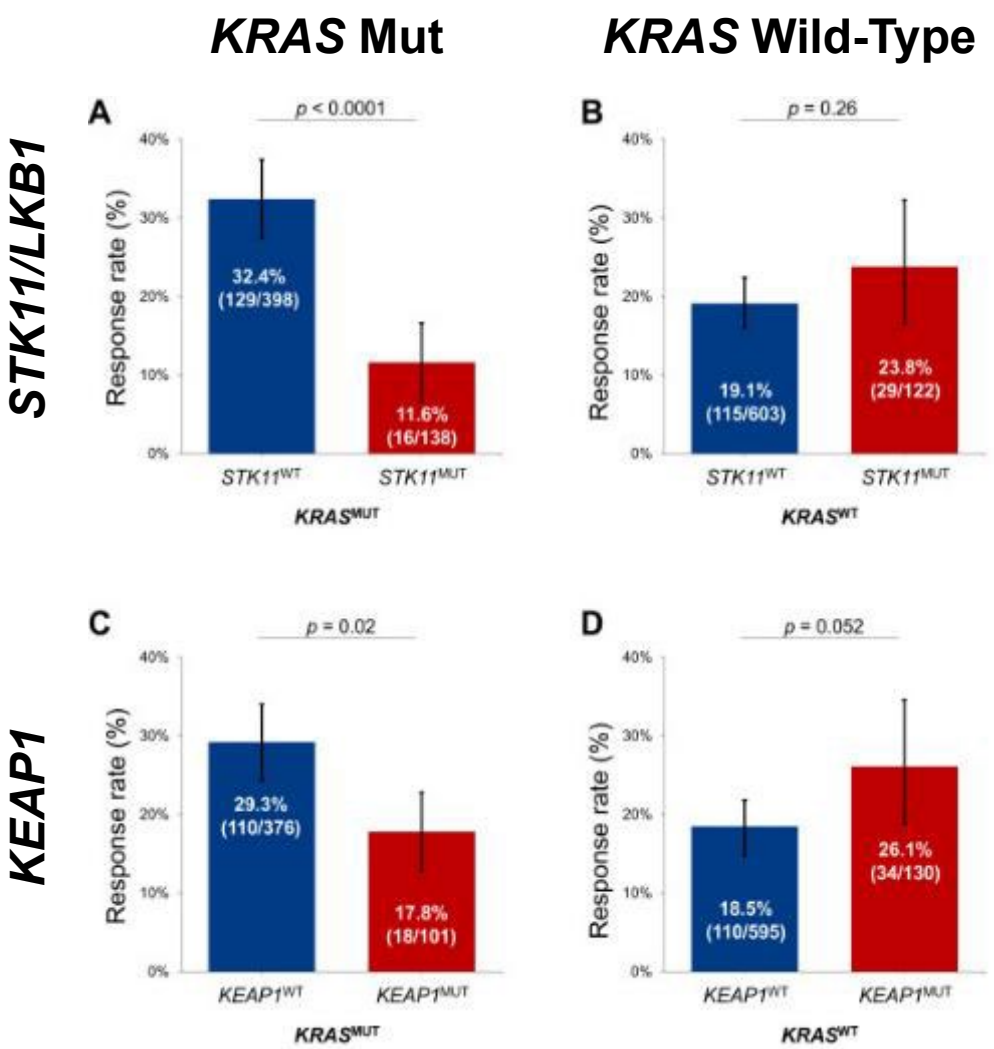


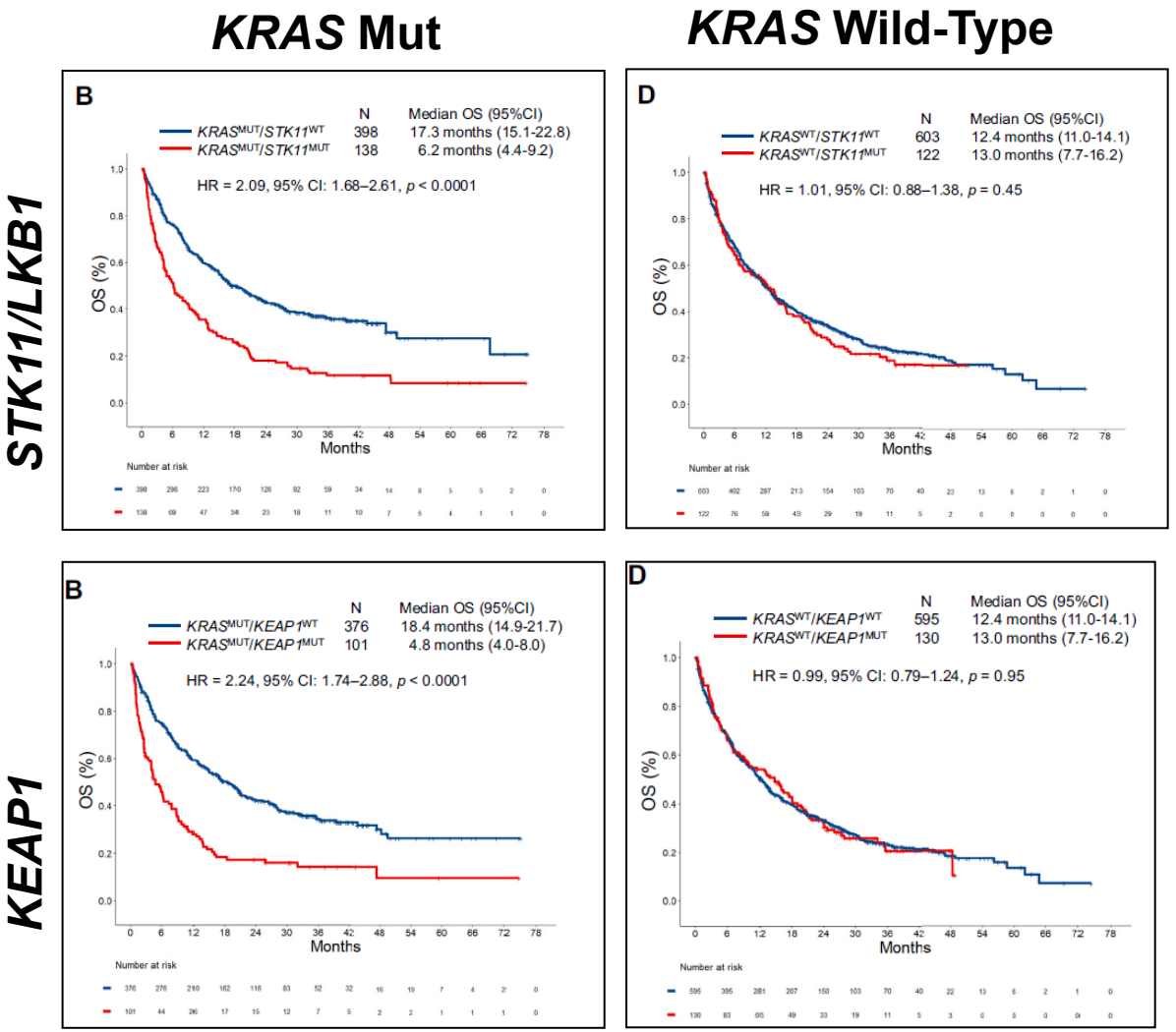
Cancer

Skoulidis F, et al. *Cancer Discov*. 2018;8:822-835.

KRAS Co-Mutations in Lung Cancer

STK11/LKB1 and *KEAP1* – Response to PD-1/PD-L1 Inhibition





Cancer

Ricciuti B, et al. *J Thorac Oncol*. 2022;17:399-410.

Approved PD-L1 IHC Assays

Diagnostic Antibodies

Assay	Anti-PD-1 or anti-PD-L1 antibody	Interpretive scoring	Instrument and detection systems required
28-8 (Dako)	Nivolumab	Tumour cell membrane	EnVision Flex-Autostainer Link 48
22C3 (Dako)	Pembrolizumab	Tumour cell membrane	EnVision Flex-Autostainer Link 48
SP142 (Ventana)	Atezolizumab	Tumour cell membrane and infiltrating immune cells	OptiView Detection and Amplification-Benchmark ULTRA
SP263 (Ventana)	Durvalumab	Tumour cell membrane	OptiView Detection and Benchmark ULTRA

Companion Diagnostic

Table 1 | **FDA-approved PD-L1 companion diagnostic assays**[13]

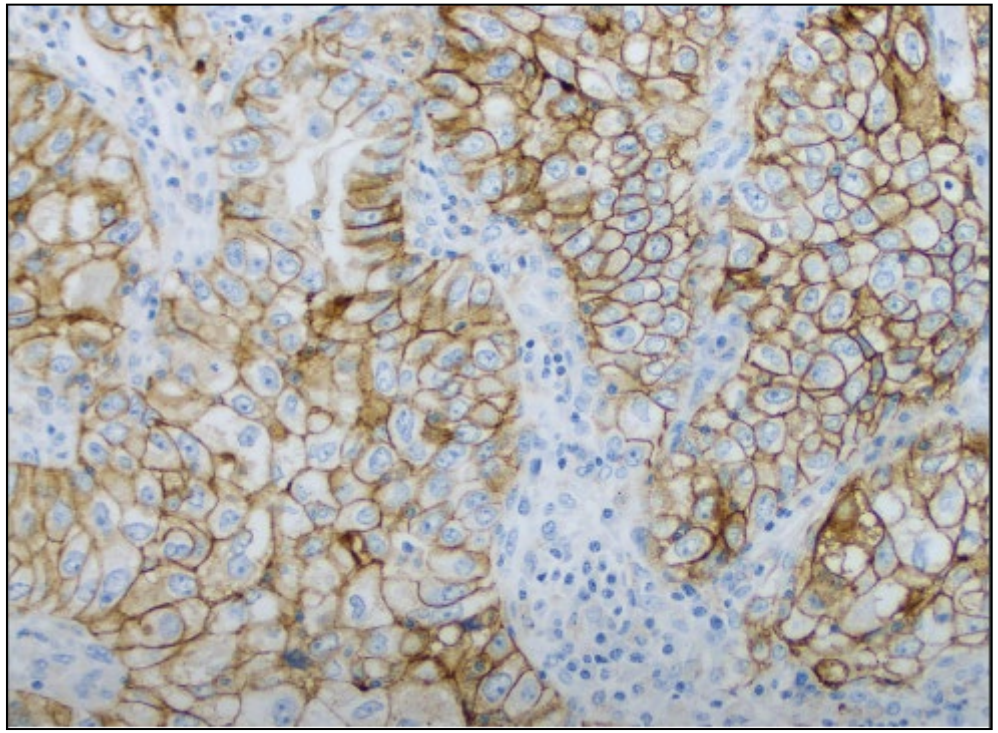
Indication	Treatment setting	PD-L1 positivity threshold	Outcomes in selected population	Refs
22C3 pharmDx (pembrolizumab)				
Stage III and IV NSCLC without *EGFR* mutations or *ALK* fusions	First line	TPS ≥1%	mOS 16.7 months vs 12.1 months in patients receiving chemotherapy, HR 0.81, 95% CI 0.71–0.93, *P* = 0.0036	46
Metastatic or unresectable, recurrent HSNCC	First line	CPS ≥1	mOS 12.3 months vs 10.3 months in patients receiving cetuximab plus chemotherapy, HR 0.78, 95% CI 0.64–0.96, *P* = 0.0086	130
Cisplatin-ineligible locally advanced or metastatic urothelial carcinoma	First line	CPS ≥10	mOS 18.5 months vs 9.7 months in patients with CPS <10 receiving pembrolizumab	159,160
Recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma	Second line	CPS ≥1	mOS 9.3 months vs 6.7 months, HR 0.69, 95% CI 0.52–0.93, *P* = 0.0074	153
Metastatic NSCLC after progression on chemotherapy	Second line	TPS ≥1%	mOS 14.9 months vs 8.2 months, HR 0.54, 95% CI 0.38–0.77, *P* = 0.0002[a]	33
Recurrent or metastatic cervical cancer after progression on chemotherapy	Second line	CPS ≥1	ORR 14.6%	199
Ventana SP142 (atezolizumab)				
Metastatic NSCLC without *EGFR* mutations or *ALK* fusions	First line	TC ≥50% and/or IC ≥10%	mOS 20.2 months vs 13.1 months in patients receiving chemotherapy, HR 0.59, 95% CI 0.40–0.89, *P* = 0.01	87
Cisplatin-ineligible, locally advanced or metastatic urothelial carcinoma	First line	IC ≥5%	ORR 26%	158
28-8 pharmDx (nivolumab)				
Metastatic NSCLC without *EGFR* mutations or *ALK* fusions, in combination with ipilimumab	First line	TC ≥1%	mOS 17.1 months vs 14.9 months in patients receiving chemotherapy, *P* = 0.007	91,92

CPS, combined positive score; GEJ, gastroesophageal junction; HNSCC, head and neck squamous cell carcinoma; IC, tumour-infiltrating immune cells; mOS, median overall survival; NSCLC, non-small-cell lung cancer; ORR, objective response rate; TC, tumour cells; TPS, tumour proportional score. [a]Data reported are for the FDA-approved dose of 2 mg/kg.

Cancer

Doroshow DB, et al. *Nat Rev Clin Oncol*. 2021;18:345-362.

PD-L1 IHC Interpretation in Lung Cancer



www.agilent.com
22C3 PharmDx interpretation manual

- Scoring of percentage of tumor cells with membranous labeling, complete or partial ("TPS/tumor proportion score")
- Cut points
  - **≥50%** → pembrolizumab in **first line**
  - **≥1%** → pembrolizumab in **second line** (after chemo)
  - 0 → no Pembro
- A minimum of **100 viable tumor cells** must be present for the specimen to be considered adequate for PD-L1 evaluation

Cancer

Slide Courtesy of Natasha Rekhtman, Memorial Sloan Kettering, NYC.

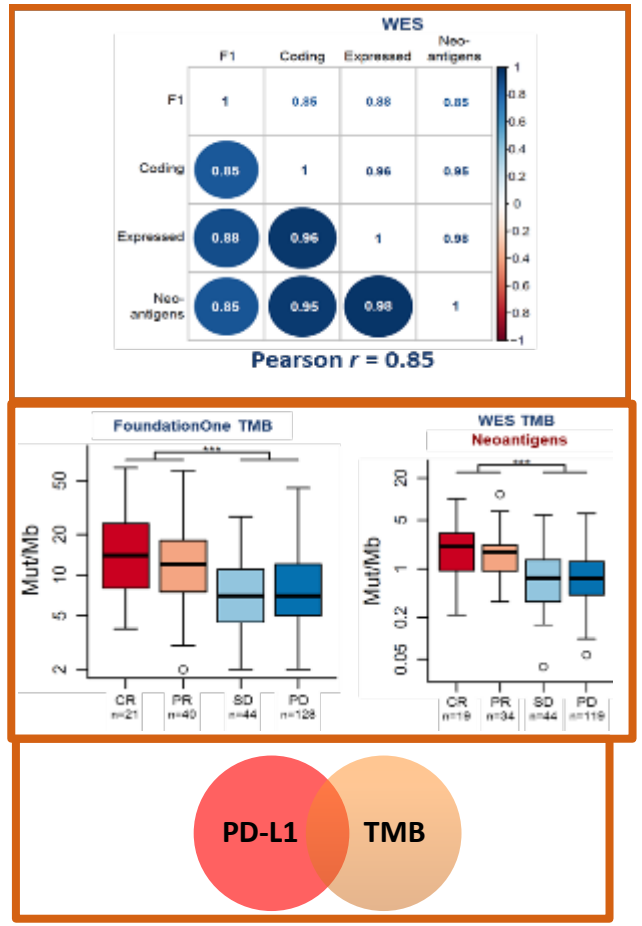
Moving Beyond PD-L1 as a Biomarker for Guiding Immunotherapy

- **Immune Response**
  - Expression of new immune checkpoint targets (IHC and multiplex approaches)
  - Immune cell infiltrates (IHC and multiplex approaches)
  - Gene expression signatures (mRNA assays)

- **Genomic**
  - Microsatellite instability (MSI) High
  - Tumor Mutational Burden (TMB) for combination immune oncology therapies
  - Genomic predictors of response to therapy
    - *STK1/LKB1* loss
    - Genes involved in inactivation of INF-γ pathway (mechanisms of resistance, *JAK* gene)

Tumor Mutational Burden as a Candidate Predictive Biomarker for Cancer Immunotherapy

- **Somatic mutations in cancers** produce **neoantigens** that induce antitumor immune responses
- **TMB is an emerging predictive biomarker** for cancer checkpoint immunotherapy (CIT)
- TMB can be estimated using whole-exome sequencing (WES) or comprehensive genomic profiling by NGS **(eg, FoundationOne and FACT in blood[bTMB], MSK-IMPACT, Guardant OMNI** in blood)[1-8]
  - Studies show that TMB either by WES or CGP correlate with each other & with efficacy of CPI therapy in multiple cancer types[1-3]
- **Predicted neoantigen load (NAL),** a component of TMB most closely linked to immune response, correlates with F1 TMB & OMNI[4,5,7,8]
- **TMB identifies a distinct patient population** not currently captured by PD-L1 IHC or other immune biomarkers[5,6]



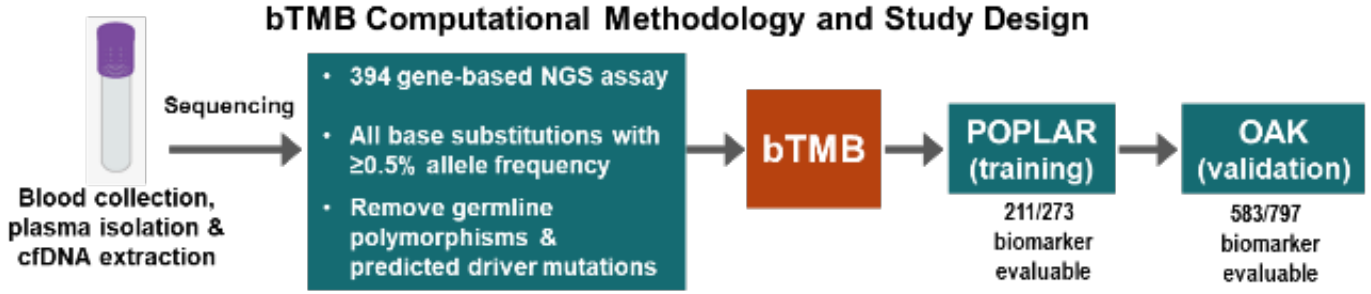
From Gandara D, et al. ASCO 2018.

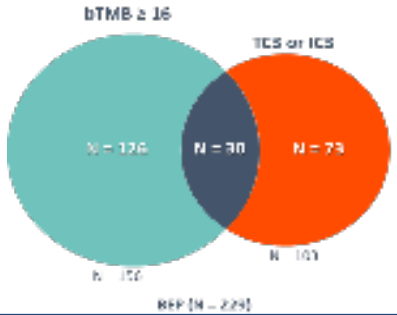
IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.

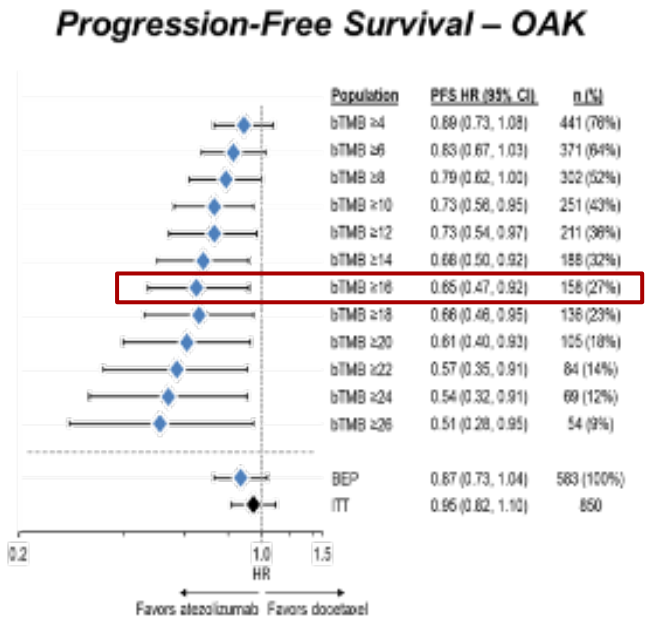
1. Yarchoan M, et al. *N Engl J Med.* 2017;377:2500-2501; 2. Chalmers ZR, et al. *Genome Med.* 2017;9:34; 3. Goodman AM, et al. *Mol Cancer Ther.* 2017;16:2598-2608; 4. Efremova M, et al. *Front Immunol.* 2017;8:1679; 5. Topalian SL, et al. *Nat Rev Cancer.* 2016;16:275-287; 6. Kowanetz M, et al. WCLC 2017. Abstract 0A20.01; 7. Mariathansan S, et al. *Nature.* 2018;554:544-548; 8. Rizvi et al: ESMO IO 2018.

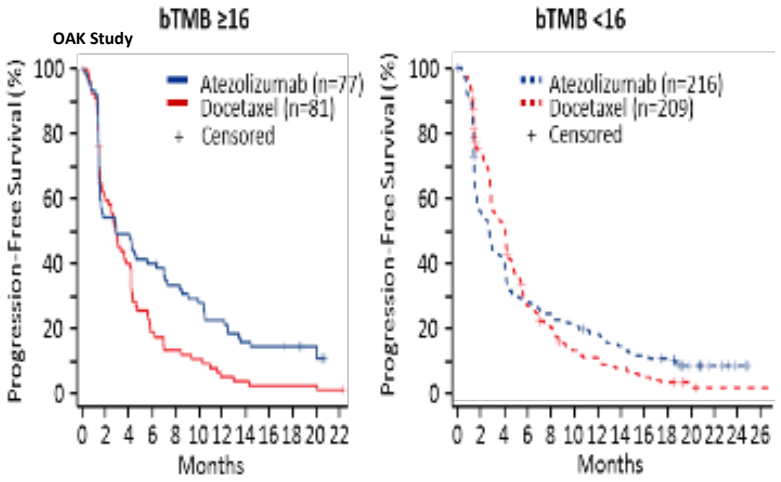
Courtesy of Dr David Gandara, University of California Davis, Comprehensive Cancer Center, Sacramento CA. USA.

Analytical and Clinical Validation of Tumor Mutational Burden in Blood (bTMB) in association with Atezolizumab efficacy in advanced NSCLC (POPLAR and OAK Trials)









Gandara DR, et al. *Nat Med.* 2018.

	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

Courtesy of Dr David Gandara (Master Lecture Series, 2020; University of California Davis, Comprehensive Cancer Center, Sacramento CA. USA)

Biomarker Testing in NSCLC

- Regarding liquid biopsy (cfDNA) molecular testing, please select the incorrect option

  a) Detects mutation, deletions, insertions and translocations

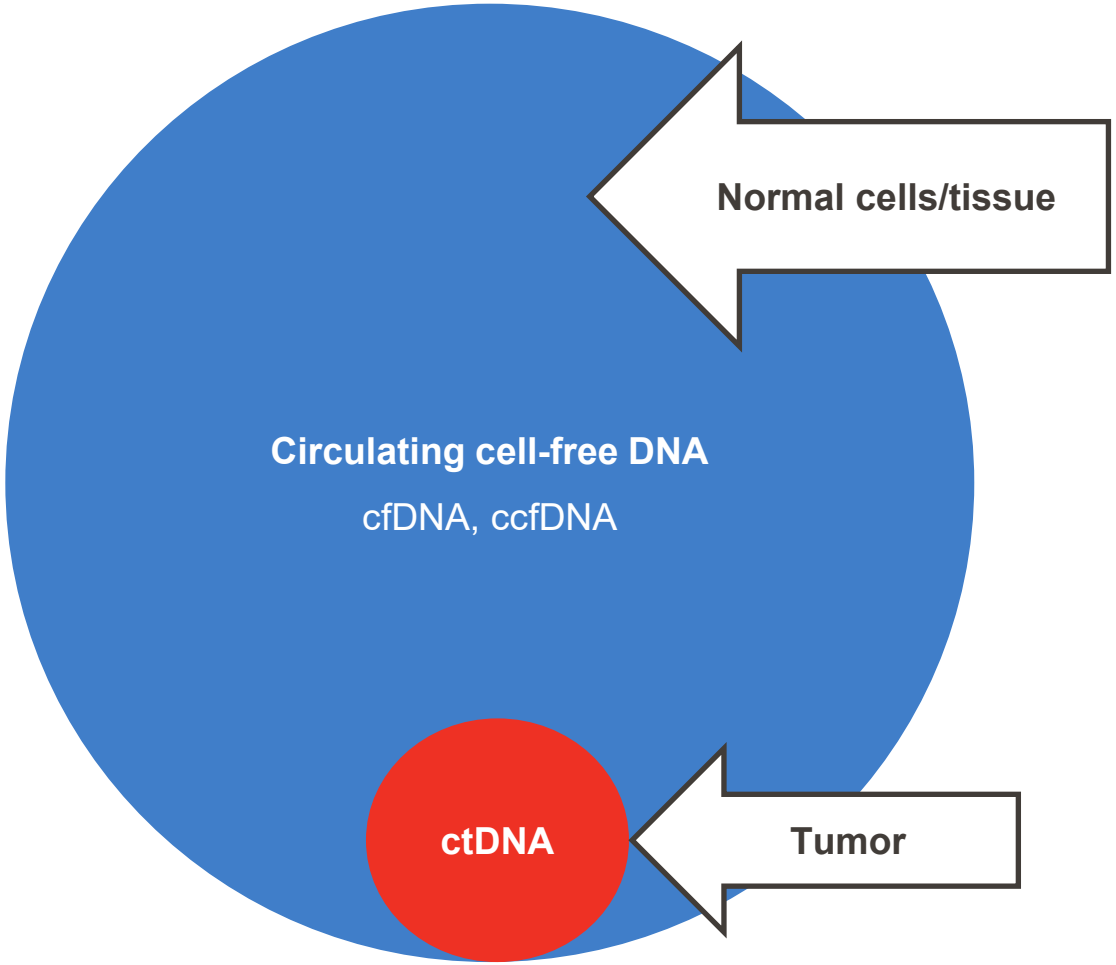
  b) Suitable for NGS panels

  c) Suitable for digital droplet PCR panels

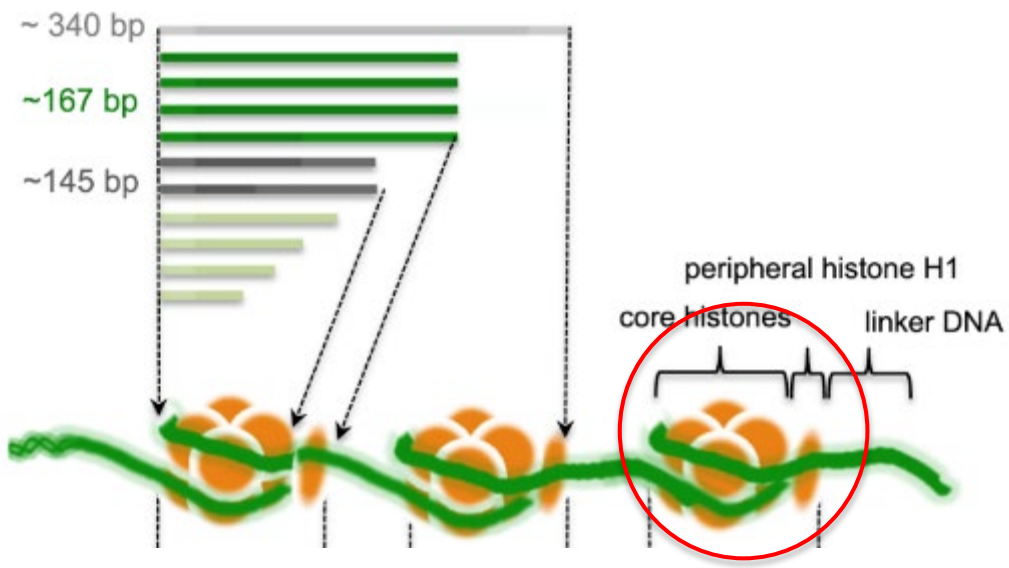
  d) Allows assessment of PD-L1 expression

  e) All above options

Characteristics and Terminology for Circulating Tumor DNA (ctDNA)



167 bp fragments of DNA, a nucleosome



The linker DNA between nucleosomes is cleaved leaving 167 bp cell-free DNA fragments (145 bp plus a ~20 bp segment wrapping histone H1). Originally described by Wyllie in 1980.

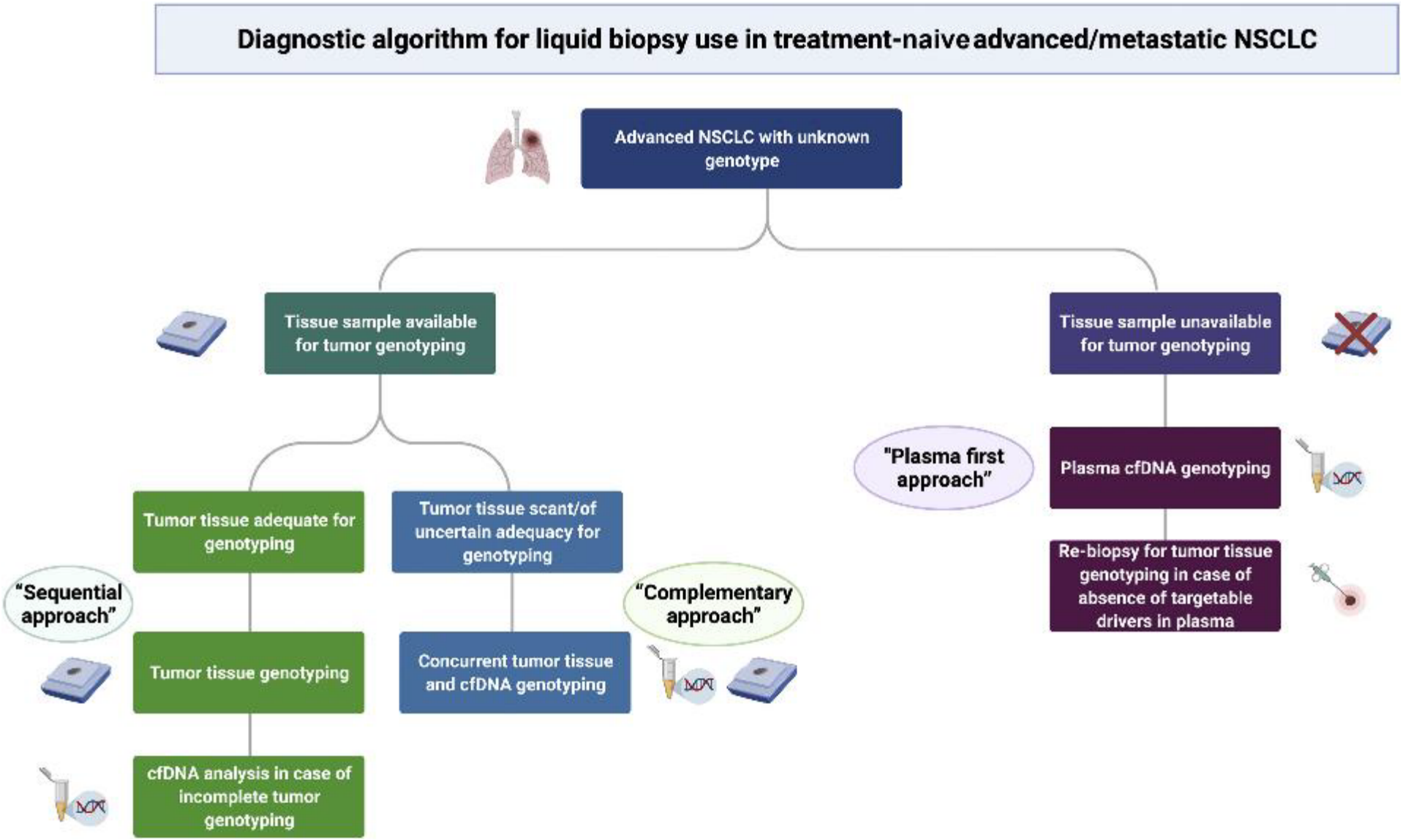
Cancer

Chandrananda D, et al. *BMC Med Genomics.* 2015;8:29;
Wyllie AH. *Nature. 9*80;284:555-556*;* Slide from Rick Lanman.

Liquid Biopsy in Lung Cancer

- **Currently, it is used in metastatic disease to deliver targeted therapy**
  - Can be easily repeated to control treatment efficiency and/or the detection of genomic changes resulting from resistance to therapy (eg, *EGFR T790M*)
  - It is an alternative to patients with solid tumors when biopsies are inaccessible or after more than one attempt the yield was unsatisfactory
- **Other applications**
  - Tumor mutational burden
  - Monitoring response to immunotherapies
  - Minimal residual disease
  - Early detection

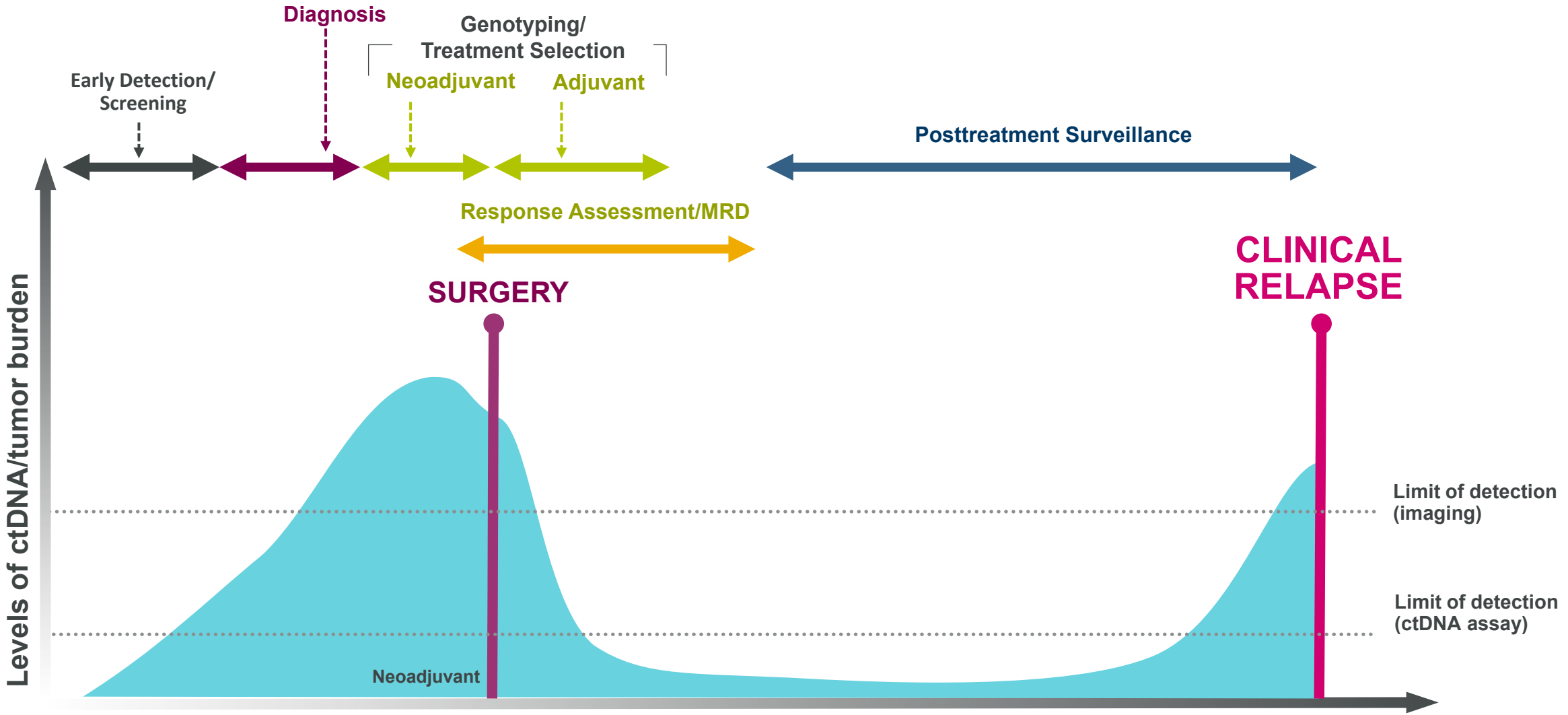
Liquid Biopsy and Diagnostic Algorithm in NSCLC



Cancer

Rolfo C, et al. *J Thorac Oncol*. 2021;16:1647-1662.

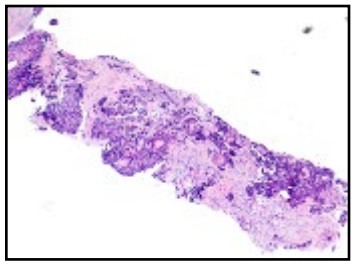
Where Could ctDNA Testing in the Early-Stage Lung Cancer Journey Be Approached?



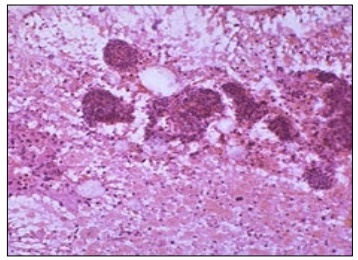
ctDNA = circulating tumor DNA; MRD = minimal residual disease.

Rolfo C, et al. *J Thorac Oncol*. 2021;16:1647-1662.

Diagnostic Algorithm for Lung Cancer Diagnosis 2022



Biopsy

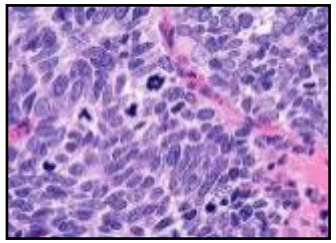


Cytology

Blood

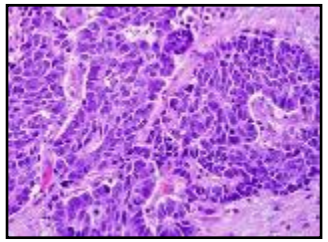
cfDNA Testing
(Liquid Biopsy)

SCLC



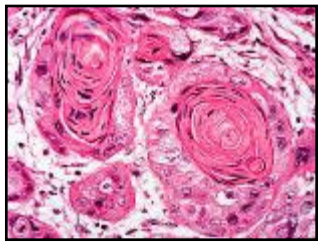
Morphology

LCNEC



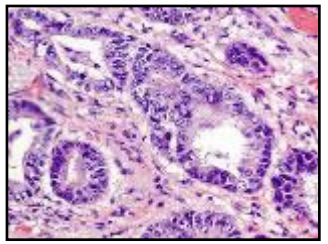
Morphology
IHC NE (+)

Squamous



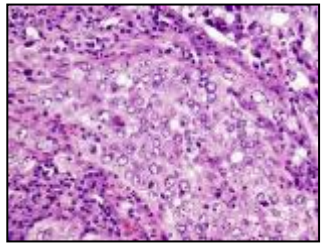
Morphology
IHC p63/p40 (+)

Adenoca



Morphology
IHC TTF1 (+)

NSCLC-NOS



Morphology
IHC (-)

EGFR and *BRAF* mutation, *ALK*,
ROS1 and *NTRK* fusions, *MET ex14*
splicing

PD-L1 IHC


Thank You

Global Lung Cancer Academy

Neoadjuvant Therapy for NSCLC – Is It Ready for Prime Time?

Anne Tsao, MD

Anne Tsao, MD, MBA

Neoadjuvant Therapy in Resectable Disease

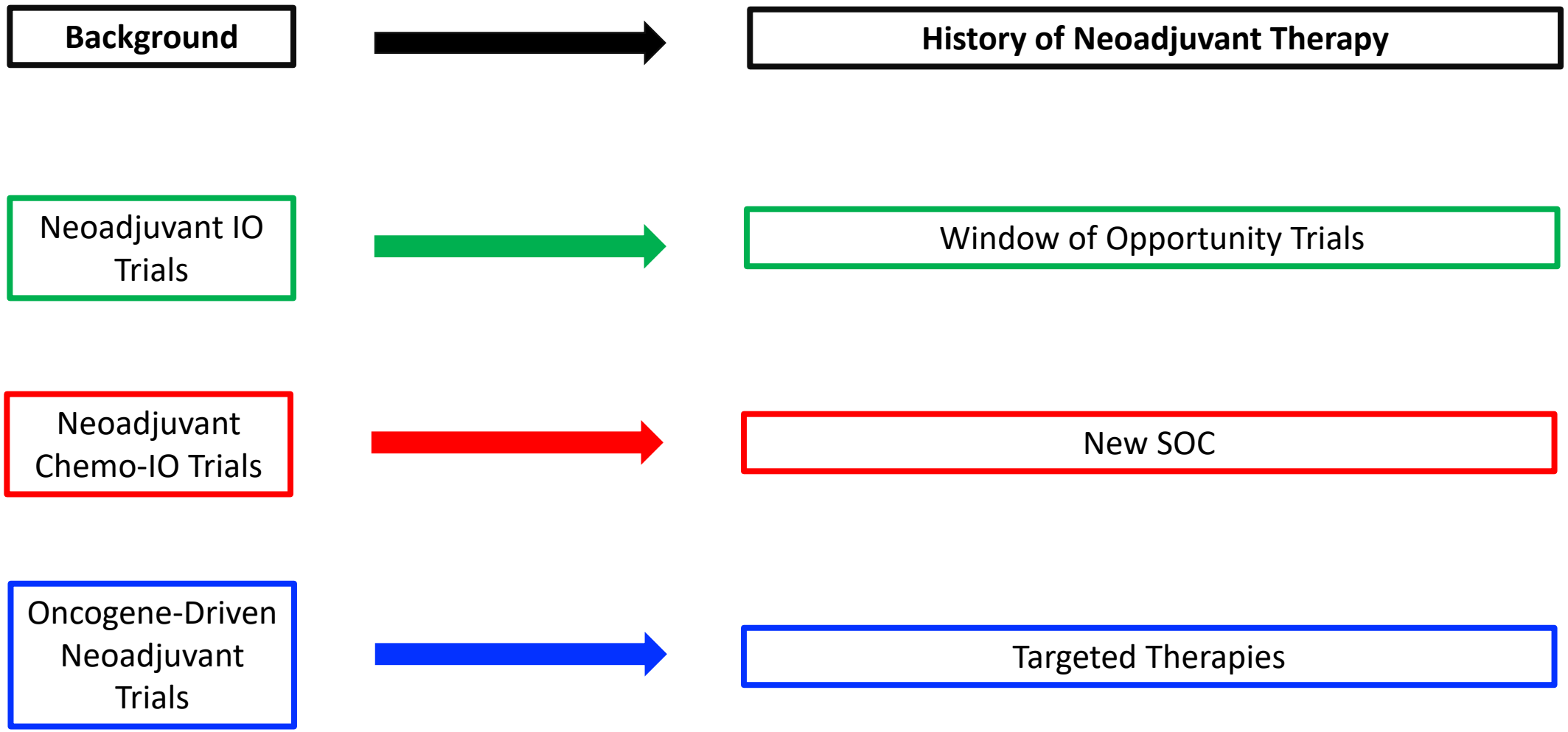
MD Anderson Cancer Center

October 2022

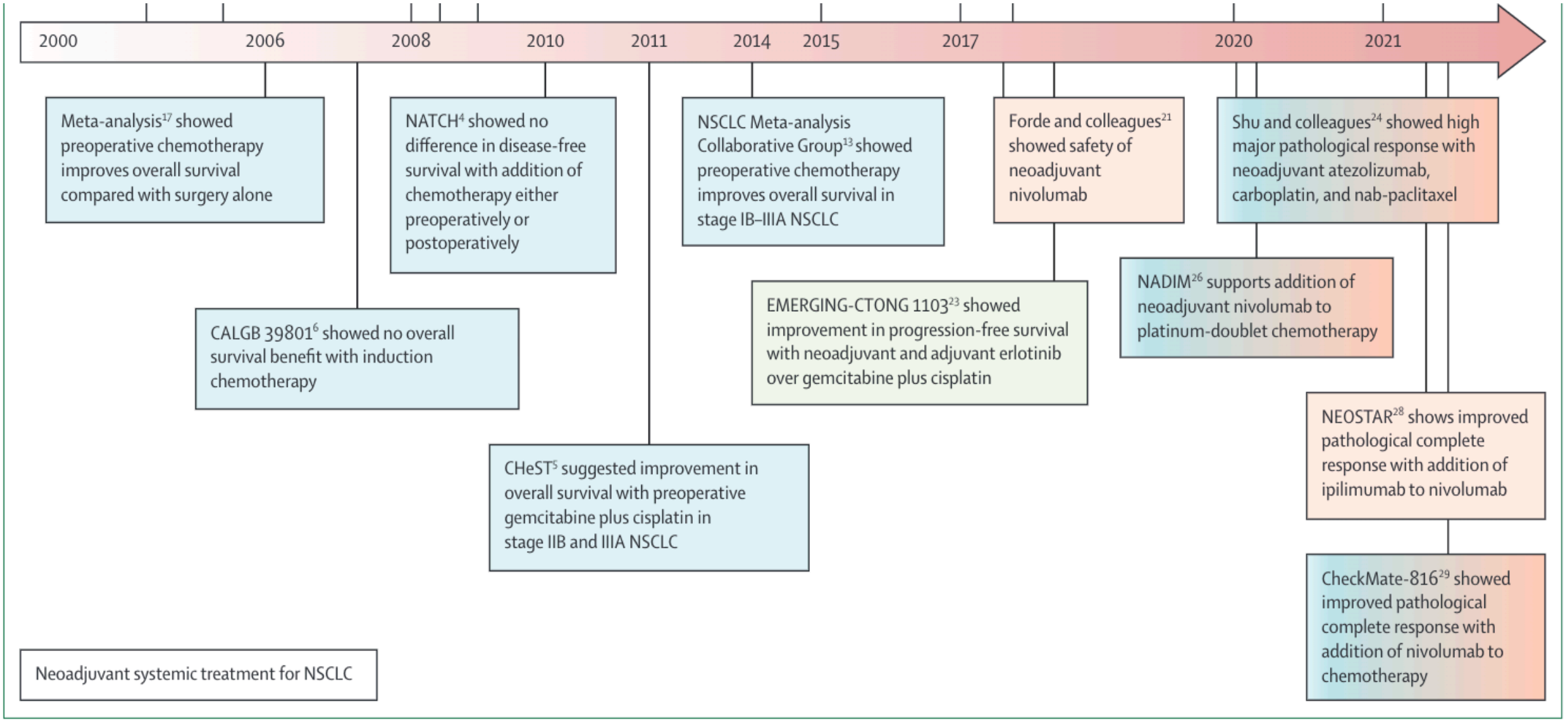
Which of the following is a standard neoadjuvant therapy regimen?

1. Cisplatin-docetaxel
2. Carboplatin-paclitaxel-nivolumab
3. Cisplatin-gemcitabine-nivolumab
4. Cisplatin-pemetrexed-nivolumab
5. All of the above

Outline

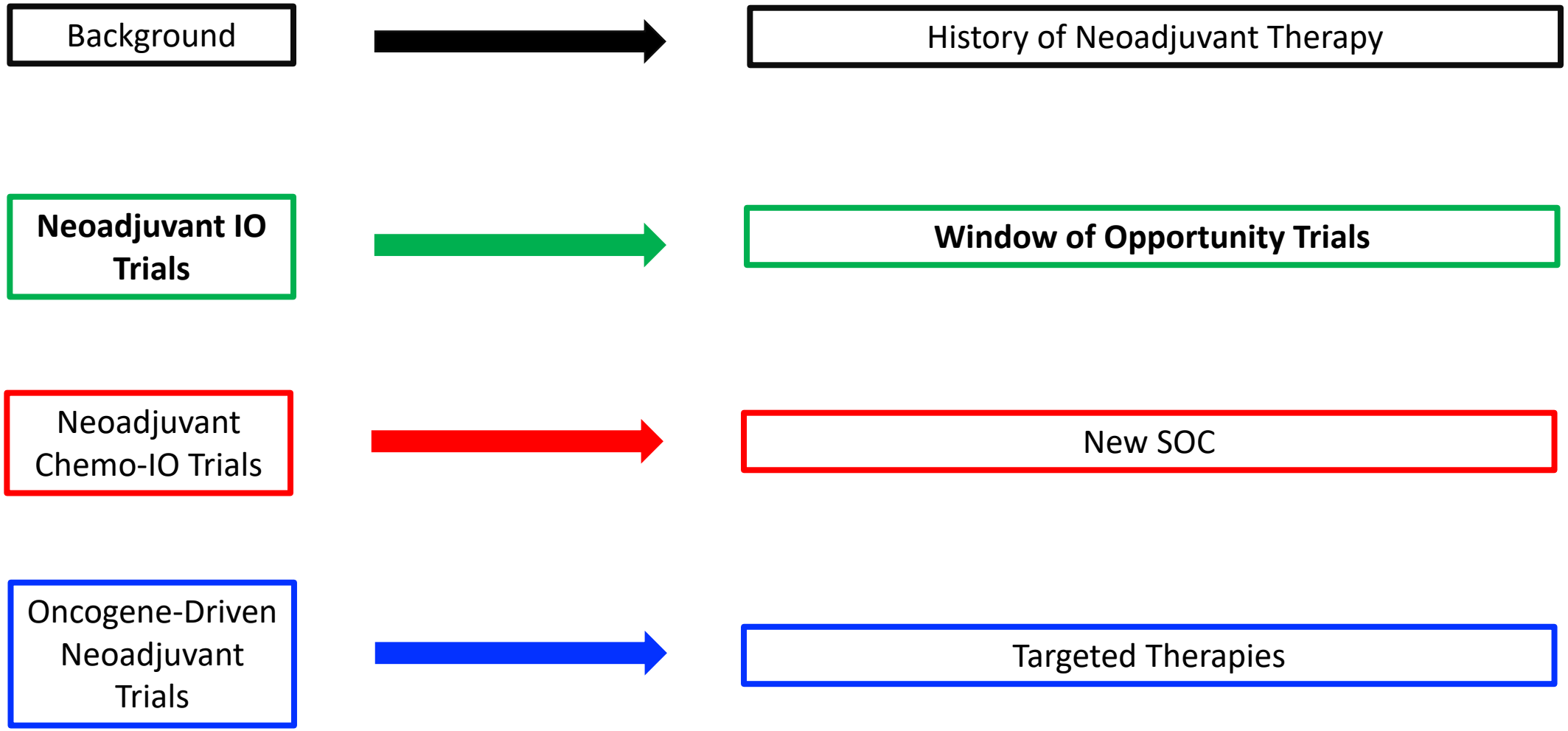

Background
History of Neoadjuvant Therapy
Neoadjuvant IO Trials
Window of Opportunity Trials
Neoadjuvant Chemo-IO Trials
New SOC
Oncogene-Driven Neoadjuvant Trials
Targeted Therapies

Neoadjuvant Therapy Timeline



Saw SPL, et al. *Lancet Oncol*. 2021;22:e501-e516.

Outline


Background
History of Neoadjuvant Therapy
Neoadjuvant IO Trials
Window of Opportunity Trials
Neoadjuvant Chemo-IO Trials
New SOC
Oncogene-Driven Neoadjuvant Trials
Targeted Therapies

Neoadjuvant Immunotherapy Trials

	Population	Study design	Major pathological response	Pathological complete response	Objective response rate	Progression-free survival, event-free survival, or disease-free survival	Median overall survival	Grade 3 or above treatment-related adverse events	R0 surgery	Adjuvant treatment
Immunotherapy trials										
Forde et al (2018)[21]	Resectable stage I–IIIA (n=21)	2 cycles of nivolumab preoperatively	45·0% (9 of 20)	10·0% (2 of 20)	9·5% (2 of 21)	18-months progression-free survival 73·0%	Not reached	4·5% pneumonia*	95·2% (20 of 21)	NR
LCMC3 (2021)[50]†	Resectable stage IB–IIIB (n=181)	2 cycles of atezolizumab preoperatively	20·4%* (30 of 147)	6·8% (10 of 147)	6·9% (11 of 159)	NR	NR	16·6%	82·3% (149 of 181)	NR
Gao et al (2020)[51]	Resectable stage IA–IIIB (n=40)	2 cycles of sintilimab preoperatively	40·5% (15 of 37)	8·1% (3 of 37)	20·0% (8 of 40)	Not reached	Not reached	10·0% (5·0% pneumonitis, 2·5% raised GGT, 2·5% raised creatine kinase, 2·5% pneumonia, and 2·5% hyponatraemia)*	90·0% (36 of 40)	72·5% (29 of 40)
IONESCO (2020)[52]†	Resectable stage IB–IIIA (n=46)	3 cycles of durvalumab preoperatively	NR	NR	8·7% (4 of 46)	18-month disease-free survival 69·7%	Not reached	0·0%	89·1%* (41 of 46)	NR
PRINCEPS (2020)[53]†	Resectable stage IA–IIIA (n=30)	1 cycle of atezolizumab preoperatively	0·0% (0 of 30)	0·0% (0 of 30)	0·0% (0 of 30)	NR	NR	0·0%*	96·7% (29 of 30)	NR
NEOSTAR (2021)[28]	Resectable stage I–IIIA (n=44)	3 cycles of nivolumab preoperatively (n=23) *vs* 1 cycle of nivolumab plus ipilimumab preoperatively (n=21)	21·7%* (5 of 23) with nivolumab *vs* 38·1%* (8 of 21) with nivolumab plus ipilimumab	8·7% (2 of 23) with nivolumab *vs* 28·6% (6 of 21) with nivolumab plus ipilimumab	21·7% (5 of 23) with nivolumab *vs* 19·0% (4 of 21) with nivolumab plus ipilimumab	Not reached with nivolumab *vs* not reached with nivolumab plus ipilimumab	Not reached with nivolumab *vs* not reached with nivolumab plus ipilimumab	4·3% pneumonitis, pneumonia, hypoxia, and hypermagnesaemia with nivolumab *vs* 4·8% diarrhoea, hyponatraemia with nivolumab plus ipilimumab	95·7% (22 of 23) with nivolumab *vs* 81·0% (17 of 21) with nivolumab plus ipilimumab	47·8% (11 of 23) with nivolumab *vs* 28·6% (6 of 21) with nivolumab plus ipilimumab

(Table 3 continues on next page)

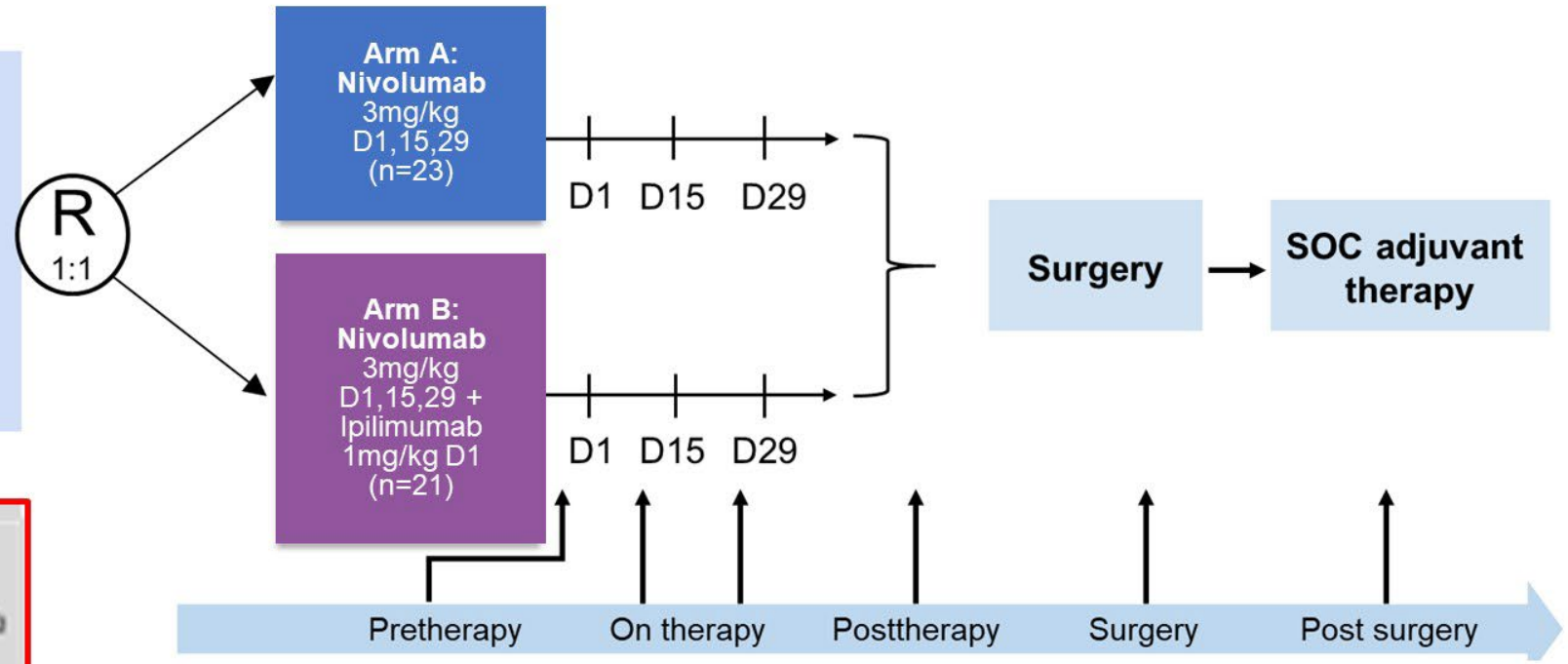
Saw SPL, et al. *Lancet Oncol*. 2021;22:e501-e516.

NEOSTAR: randomized phase II study of induction checkpoint blockade for untreated and resectable stage I-IIIA NSCLC

Key Eligibility Criteria
NSCLC Stage I-IIIA N2 single station (AJCC 7th)
No prior systemic therapy
Surgical resectability
ECOG PS 0-1

Stratification
Stage

Primary endpoint
MPR rate in patients treated with Nivolumab and Nivolumab + Ipilimumab (MPR: ≤10% viable tumor)



PI: Tina Cascone
Co-PI: Boris Sepesi

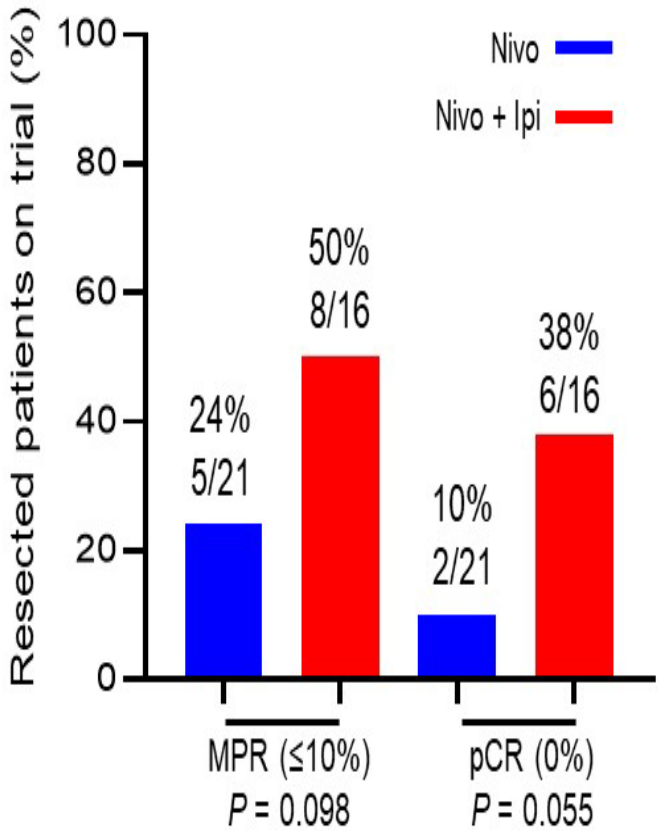
Cascone, T et al. *Nat Med.* 2021

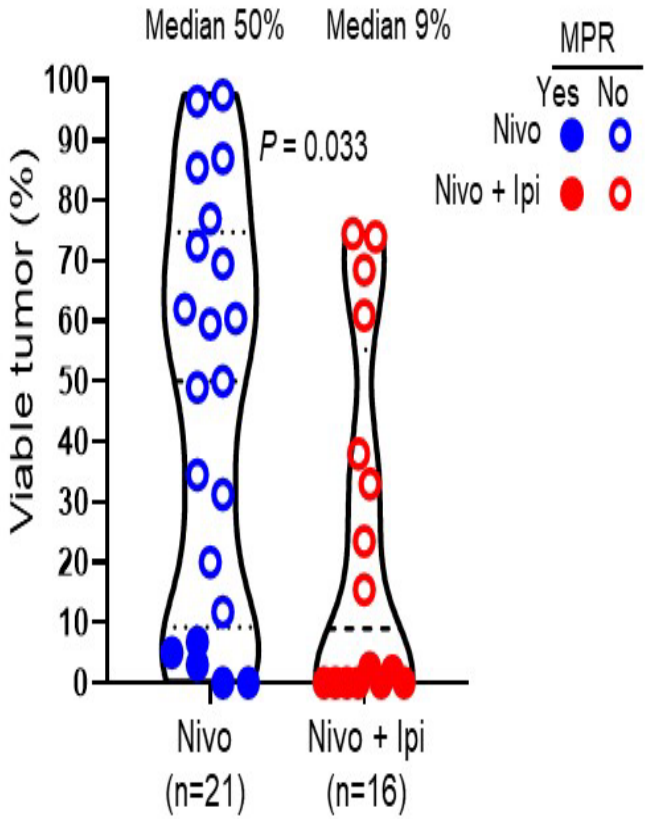
Cascone T, et al. *Nat Med.* 2021;27:504-514.

Combined Blockade Showed Higher MPR and pCR Rates With Less Viable Tumor

MPR RATE (%)		
Percentage viable tumor	**Nivo n=23**	**Nivo + Ipi n=21**
0-10 (MPR)	22 (5/23)	38 (8/21)
0 (pCR)	9 (2/23)	29 (6/21)

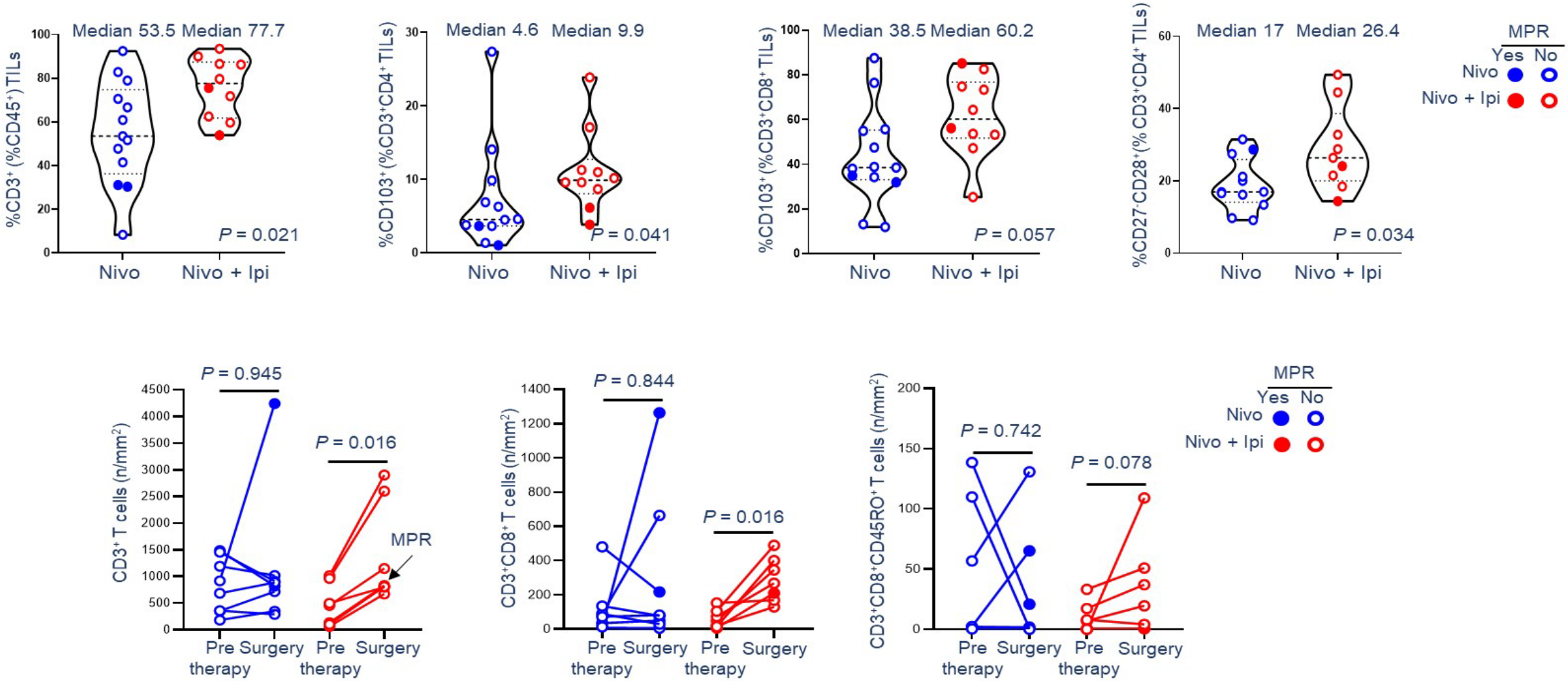
Prespecified trial efficacy boundary: ≥ 6 MPR





Cascone T, et al. *Nat Med.* 2021;27:504-514.

Combined Blockade Increases Tumor Immune Infiltration and Immunological Memory



Cascone T, et al. *Nat Med.* 2021;27:504-514.

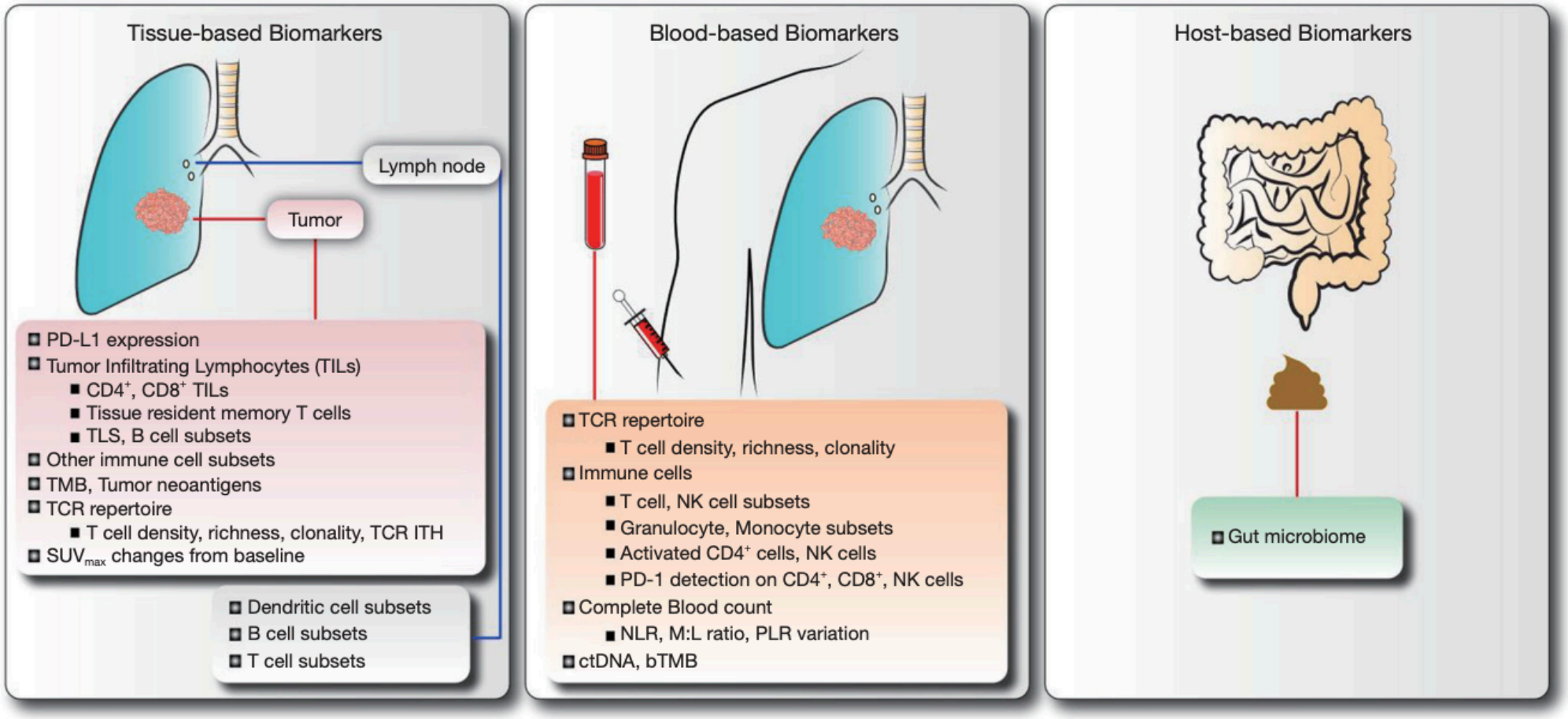
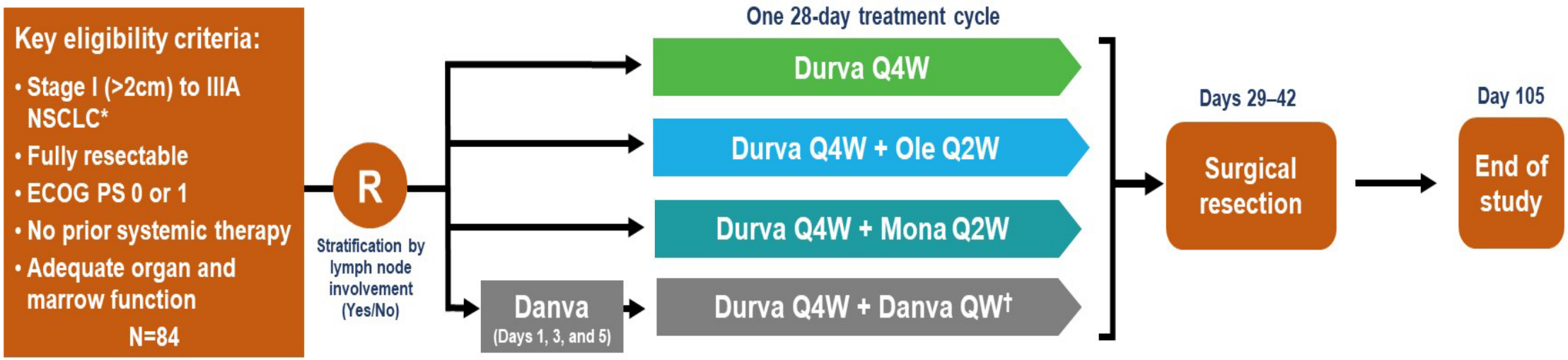


Figure 1 Biomarkers under investigation for neoadjuvant immune checkpoint inhibitors in operable NSCLC. PD-L1, programmed cell death-ligand 1; TILs, tumor infiltrating lymphocytes; TLS, tertiary lymphoid structures; TMB, tumor mutation burden; TCR, T cell receptor; ITH, intratumoral heterogeneity; SUV_{max}, maximum standardized uptake values; NK, natural killer cells; PD-1, programmed cell death-1; NLR, neutrophil to lymphocyte ratio; M,L, myeloid to lymphoid ratio; PLR, platelet to lymphocyte ratio; ctDNA, circulating tumor DNA; bTMB, blood-based tumor mutation burden.

Pradhan M, et al. *Transl Lung Cancer Res*. 2021;10(1):590-606.

NeoCOAST: Study design and objectives



Endpoints:

- **Primary**: MPR rate (proportion of patients with ≤10% residual viable tumor cells in resected tumor specimen and sampled nodes at surgery) per investigator assessment.
- **Secondary**: pCR rate (no viable tumor cells in resected tumor specimen or sampled nodes at surgery), safety and tolerability, feasibility of planned surgery, pharmacokinetics, and immunogenicity.
- **Exploratory**: Tumor, blood, and stool microbiome biomarkers; investigator-assessed best overall response and ORR (per RECIST v1.1).

Cascone T, et al. AACR 2022. Abstract CT011.

NeoCOAST: Efficacy outcomes in the ITT population

	Durva (n=27)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)
Pathologic responses				
MPR, n (%)	**3 (11.1)**	**4 (19.0)**	**6 (30.0)**	**5 (31.3)**
pCR, n (%)	1 (3.7)	2 (9.5)	2 (10.0)	2 (12.5)
Responses by RECIST v1.1				
ORR, n (%)	2 (7.4)	1 (4.8)	3 (15.0)	1 (6.3)
Objective responses, n (%)				
PR	2 (7.4)	1 (4.8)	3 (15.0)	1 (6.3)
SD	22 (81.5)	17 (81.0)	15 (75.0)	14 (87.5)
PD	1 (3.7)	3 (14.3)	1 (5.0)	1 (6.3)
NE	1 (3.7)	0	1 (5.0)	0

MPR and pCR rates in the durva arm were similar to published data for anti-PD-1/PD-L1 antibodies (MPR, 6.7–45%; pCR, 0–16.2%).[1–8]

Numerically higher MPR rates were observed across all combination arms, compared with a single dose of durva monotherapy.

No differences in pCR rates were observed between treatment arms.

No significant differences in ORR rates were observed between treatment arms.

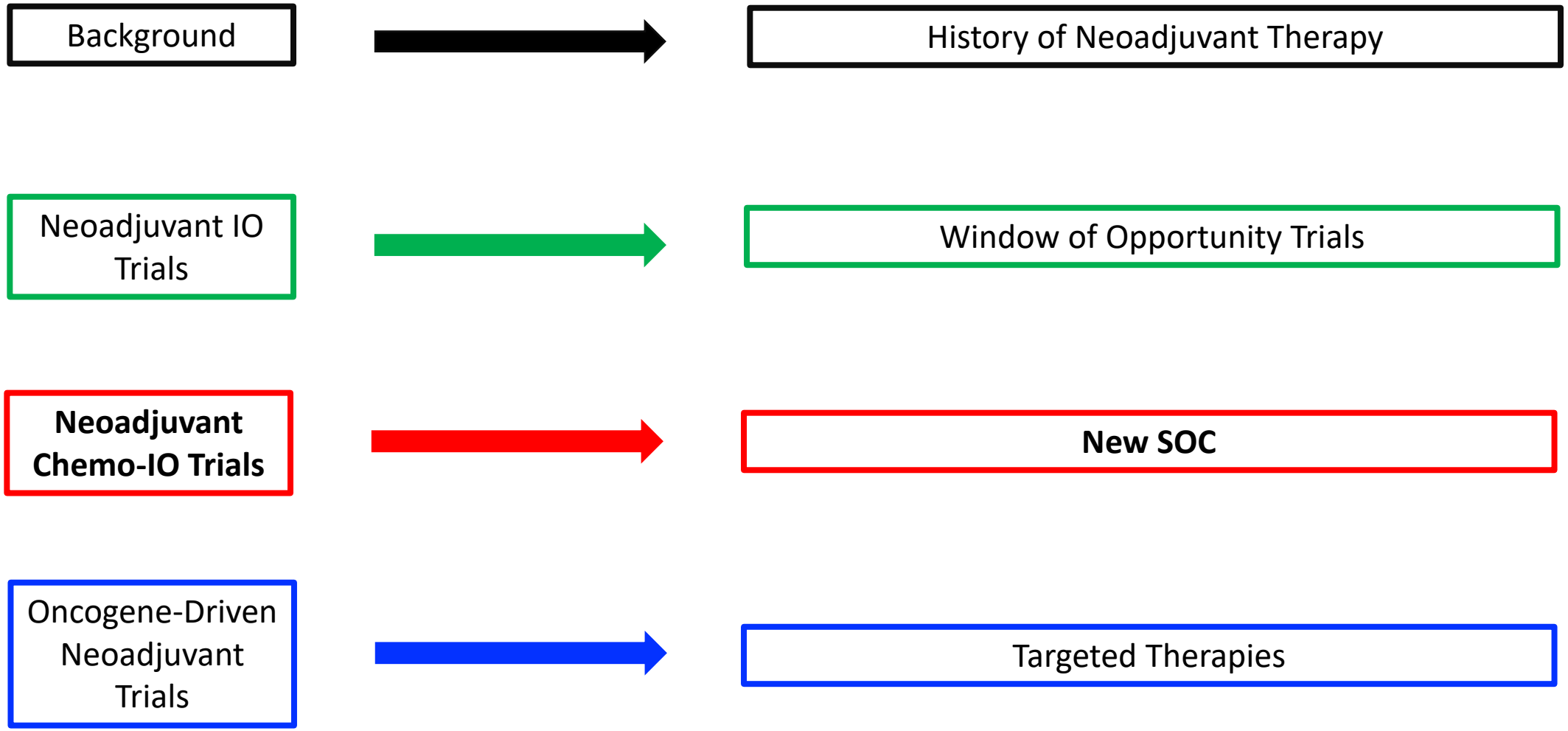
1. Forde PM, et al. N Engl J Med 2018;378:1976–86; 2. Gao S, et al. J Thorac Oncol 2020;15:816–26; 3. Lee JM, et al. WCLC 2020 (presentation PS01.05); 4. Altorki NK, et al. Lancet Oncol 2021;22:824–35; 5. Wislez M, et al. ESMO 2020 (presentation 1214O); 6. Tong BC, et al. J Thorac Cardiovasc Surg 2022;163:427–36; 7. Cascone T, et al. Nat Med 2021;27:504–14; 8. Besse B, et al. ESMO 2020 (presentation 1215O).

Cascone T, et al. AACR 2022. Abstract CT011.

Summary Neoadjuvant IO and IO Combinations

- Not a current standard of care therapeutic strategy
- Trials are critical to identifying patients who may benefit from a chemo-free regimen
  - Stage
  - Biomarker status
  - PS
  - Histology
- Remains investigational strategy for now

Outline


Background
History of Neoadjuvant Therapy
Neoadjuvant IO Trials
Window of Opportunity Trials
Neoadjuvant Chemo-IO Trials
New SOC
Oncogene-Driven Neoadjuvant Trials
Targeted Therapies

Neoadjuvant Chemoimmunotherapy Trials

	Population	Study design	Major pathological response	Pathological complete response	Objective response rate	Progression-free survival, event-free survival, or disease-free survival	Median overall survival	Grade 3 or above treatment-related adverse events	R0 surgery	Adjuvant treatment
(Continued from previous page)										
Immunochemotherapy trials										
Provencio et al (2020)[26]	Resectable stage IIIA (n=46)	3 cycles of nivolumab plus paclitaxel plus carboplatin preoperatively followed by nivolumab 12 months postoperatively	82·9% (34 of 41)	63·4% (26 of 41)	76·1% (35 of 46)	24-month progression-free survival 77·1%*	Not reached	30·4% (6·5% increased lipase, 6·5% febrile neutropenia)	89·1% (41 of 46)	80·4% (37 of 46)
Shu et al (2020)[24]	Resectable stage IB–IIIA (n=30)	4 cycles of atezolizumab plus carboplatin plus nab-paclitaxel preoperatively	56·7%* (17 of 30)	33·3% (10 of 30)	63·3% (19 of 30)	Median progression-free survival 17·9 months	Not reached	50·0% neutropenia, 6·7% increased aspartate amino-transferase and thrombocytopenia, and 3·3% febrile neutropenia, hyperglycaemia, haemorrhage, anaemia, diarrhoea, fatigue, hypo-natraemia, and weight loss	86·7% (26 of 30)	NA
Zinner et al (2020)[54]†	Resectable stage IB–IIIA (n=13)	3 cycles of nivolumab plus cisplatin plus pemetrexed or gemcitabine preoperatively	84·6%* (11 of 13)	38·5% (5 of 13)	46·2% (6 of 13)	NR	NR	15·4% (15·4% neutropenia, 7·7% anaemia, and 7·7% nephro-toxicity)	NR	NR
Rothschild et al (2020)[55]†	Resectable stage IIIA–N2 (n=68)	3 cycles of cisplatin plus docetaxel followed by 2 cycles of durvalumab preoperatively followed by durvalumab 12 months postoperatively	61·8% (34 of 55)	18·2% (10 of 55)	58·2% (39 of 67)	12-month event-free survival 73·3%*	Not reached	NR	NR	NR
CheckMate-816 (2021)[29]†	Resectable stage IB–IIIA (n=358)	3 cycles of platinum doublet chemo-therapy preoperatively (n=179) *vs* 3 cycles nivolumab plus platinum-doublet chemotherapy preoperatively (n=179)	8·9% (16 of 179) with platinum doublet chemo-therapy *vs* 36·9% (66 of 179) with nivolumab plus platinum-doublet chemotherapy	2·2%* (4 of 179) with platinum doublet chemotherapy *vs* 24·0%* (43 of 179) with nivolumab plus platinum-doublet chemotherapy	37·4% (67 of 179) with platinum doublet chemotherapy *vs* 53·6% (96 of 179) with nivolumab plus platinum-doublet chemotherapy	NR with platinum doublet chemotherapy *vs* NR with nivolumab plus platinum-doublet chemotherapy	NR with platinum doublet chemotherapy *vs* NR with nivolumab plus platinum-doublet chemotherapy	NR with platinum doublet chemotherapy *vs* NR with nivolumab plus platinum-doublet chemotherapy	58·7% (105 of 179) with platinum doublet chemotherapy *vs* 69·3% (124 of 179) with nivolumab plus platinum-doublet chemotherapy	NR with platinum doublet chemo-therapy *vs* NR with nivolumab plus platinum-doublet chemo-therapy

R0=resection with negative margins. NR=not reported. GGT=gamma-glutamyltransferase. NA=not applicable. *Primary endpoint. †Represent studies available only in abstract form.

Table 3: **Summary of prospective neoadjuvant immunotherapy and immunochemotherapy trials**

Saw SPL, et al. *Lancet Oncol*. 2021;22:e501-e516.

NADIM Trial

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García-Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem, Delvys Rodríguez-Abreu, Alex Martínez-Martí, Javier De Castro Carpeño, Manuel Cobo, Guillermo López Vivanco, Edel Del Barco, Reyes Bernabé Caro, Nuria Viñolas, Isidoro Barneto Aranda, Santiago Viteri, Eva Pereira, Ana Royuela, Marta Casarrubios, Clara Salas Antón, Edwin R Parra, Ignacio Wistuba, Virginia Calvo, Raquel Laza-Briviesca, Atocha Romero, Bartomeu Massuti, Alberto Cruz-Bermúdez

Summary

Background Non-small-cell lung cancer (NSCLC) is terminal in most patients with locally advanced stage disease. We aimed to assess the antitumour activity and safety of neoadjuvant chemoimmunotherapy for resectable stage IIIA NSCLC.

Methods This was an open-label, multicentre, single-arm phase 2 trial done at 18 hospitals in Spain. Eligible patients were aged 18 years or older with histologically or cytologically documented treatment-naive American Joint Committee on Cancer-defined stage IIIA NSCLC that was deemed locally to be surgically resectable by a multidisciplinary clinical team, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients received neoadjuvant treatment with intravenous paclitaxel (200 mg/m²) and carboplatin (area under curve 6; 6 mg/mL per min) plus nivolumab (360 mg) on day 1 of each 21-day cycle, for three cycles before surgical resection, followed by adjuvant intravenous nivolumab monotherapy for 1 year (240 mg every 2 weeks for 4 months, followed by 480 mg every 4 weeks for 8 months). The primary endpoint was progression-free survival at 24 months, assessed in the modified intention-to-treat population, which included all patients who received neoadjuvant treatment, and in the per-protocol population, which included all patients who had tumour resection and received at least one cycle of adjuvant treatment. Safety was assessed in the modified intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT03081689, and is ongoing but no longer recruiting patients.

Findings Between April 26, 2017, and Aug 25, 2018, we screened 51 patients for eligibility, of whom 46 patients were enrolled and received neoadjuvant treatment. At the time of data cutoff (Jan 31, 2020), the median duration of follow-up was 24·0 months (IQR 21·4–28·1) and 35 of 41 patients who had tumour resection were progression free. At 24 months, progression-free survival was 77·1% (95% CI 59·9–87·7). 43 (93%) of 46 patients had treatment-related adverse events during neoadjuvant treatment, and 14 (30%) had treatment-related adverse events of grade 3 or worse; however, none of the adverse events were associated with surgery delays or deaths. The most common grade 3 or worse treatment-related adverse events were increased lipase (three [7%]) and febrile neutropenia (three [7%]).

Interpretation Our results support the addition of neoadjuvant nivolumab to platinum-based chemotherapy in patients with resectable stage IIIA NSCLC. Neoadjuvant chemoimmunotherapy could change the perception of locally advanced lung cancer as a potentially lethal disease to one that is curable.

original reports abstract

Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non–Small-Cell Lung Cancer (NADIM phase II trial)

Mariano Provencio, MD, PhD[1]; Roberto Serna-Blasco, MSc[1]; Ernest Nadal, MD[2]; Amelia Insa, MD[3]; M. Rosario García-Campelo, MD[4]; Joaquín Casal Rubio, MD[5]; Manuel Dómine, MD[6]; Margarita Majem, MD[7]; Delvys Rodríguez-Abreu, MD[8]; Alex Martínez-Martí, MD[9]; Javier De Castro Carpeño, MD[10]; Manuel Cobo, MD[11]; Guillermo López Vivanco, MD[12]; Edel Del Barco, MD[13]; Reyes Bernabé Caro, MD[14]; Nuria Viñolas, MD[15]; Isidoro Barneto Aranda, MD[16]; Santiago Viteri, MD[17]; Eva Pereira, MSc[18]; Ana Royuela, PhD[1]; Virginia Calvo, MD[1]; Javier Martín-López, MD[1]; Francisco García-García, PhD[19]; Marta Casarrubios, MSc[1]; Fernando Franco, MD[1]; Estela Sánchez-Herrero, MSc[1,20]; Bartomeu Massuti, MD[21]; Alberto Cruz-Bermúdez, PhD[1]; and Atocha Romero, PhD[1]

PURPOSE Neoadjuvant chemotherapy plus nivolumab has been shown to be effective in resectable non–small-cell lung cancer (NSCLC) in the NADIM trial (ClinicalTrials.gov identifier: NCT03081689). The 3-year overall survival (OS) and circulating tumor DNA (ctDNA) analysis have not been reported.

METHODS This was an open-label, multicenter, single-arm, phase II trial in which patients with stage IIIA NSCLC, who were deemed to be surgically resectable, were treated with neoadjuvant paclitaxel (200 mg/m² once a day) and carboplatin (area under curve 6) plus nivolumab (360 mg) once on day 1 of each 21-day cycle, for three cycles, followed by adjuvant nivolumab monotherapy for 1 year (240 mg once every 2 weeks for 4 months, followed by 480 mg once every 4 weeks for 8 months). The 3-year OS and ctDNA analysis were secondary objectives of the trial.

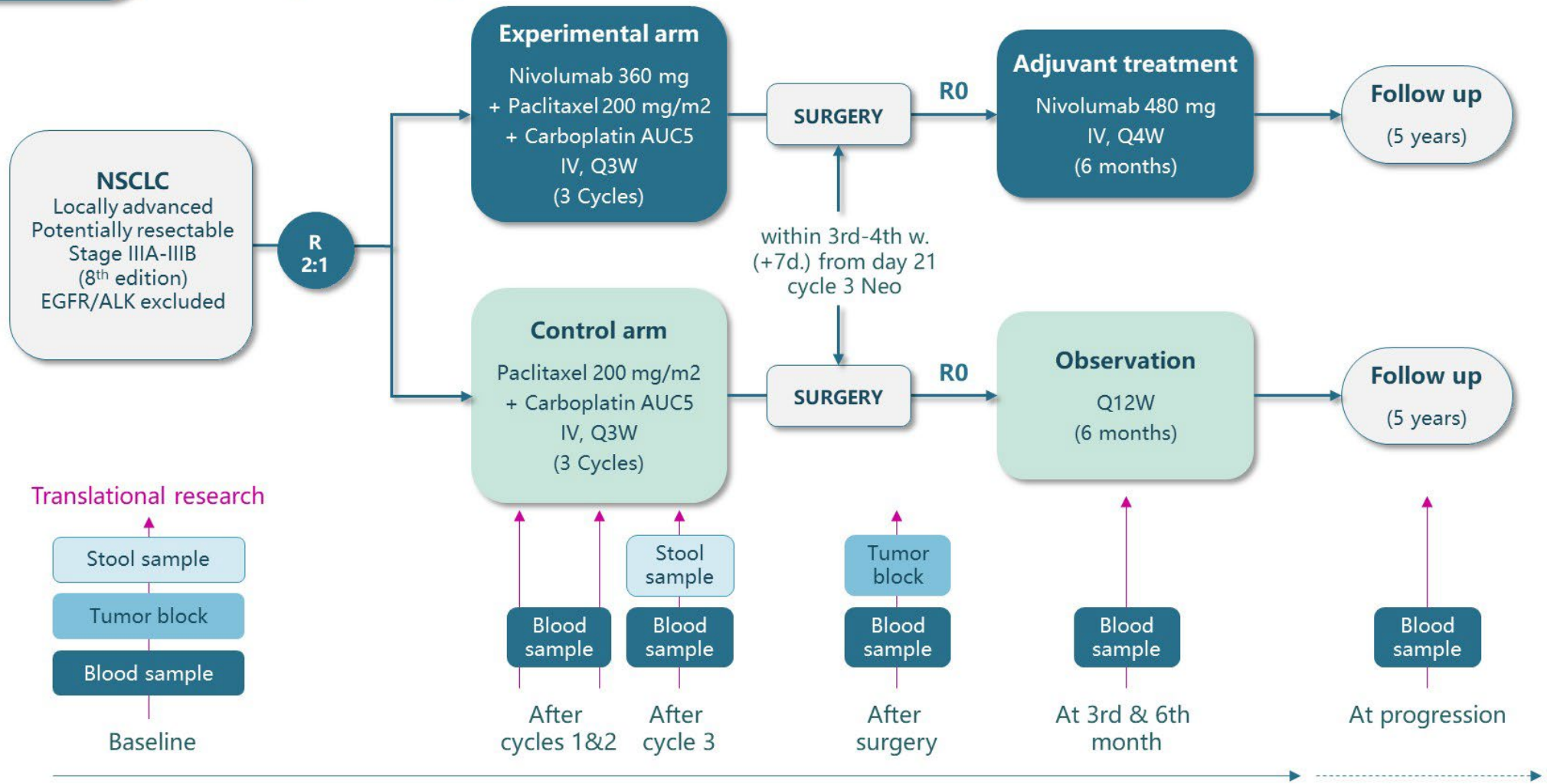
RESULTS OS at 36 months was 81.9% (95% CI, 66.8 to 90.6) in the intention-to-treat population, rising to 91.0% (95% CI, 74.2 to 97.0) in the per-protocol population. Neither tumor mutation burden nor programmed cell death ligand-1 staining was predictive of survival. Conversely, low pretreatment levels of ctDNA were significantly associated with improved progression-free survival and OS (hazard ratio [HR], 0.20; 95% CI, 0.06 to 0.63, and HR, 0.07; 95% CI, 0.01 to 0.39, respectively). Clinical responses according to RECIST v1.1 criteria did not predict survival outcomes. However, undetectable ctDNA levels after neoadjuvant treatment were significantly associated with progression-free survival and OS (HR, 0.26; 95% CI, 0.07 to 0.93, and HR, 0.04; 95% CI, 0.00 to 0.55, respectively). The C-index to predict OS for ctDNA levels after neoadjuvant treatment (0.82) was superior to that of RECIST criteria (0.72).

CONCLUSION The efficacy of neoadjuvant chemotherapy plus nivolumab in resectable NSCLC is supported by 3-year OS. ctDNA levels were significantly associated with OS and outperformed radiologic assessments in the prediction of survival.

- Spain, 18 hospitals (n = 46)
- Single-arm phase II of neoadjuvant Nivo + Carbo-Paclitaxel × 3 and 1-year adjuvant Nivo in IIIA NSCLC resectable patients
- Demonstrated safety and feasibility of chemo-IO strategy in neoadjuvant space
- 36-month OS 81.9%
- Low pretreatment ctDNA and undetectable ctDNA after neoadjuvant treatment predicted for PFS and OS

Provencio M, et al. *Lancet Oncol.* 2020;21:1413-1422; Provencio M, et al. *J Clin Oncol.* 2022; 40:2924-2933.

NADIM II Study design



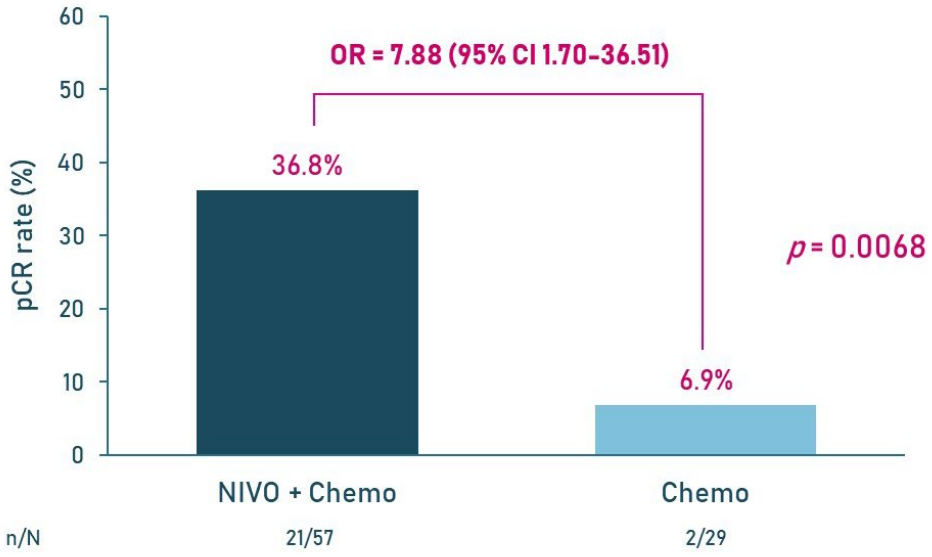
NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

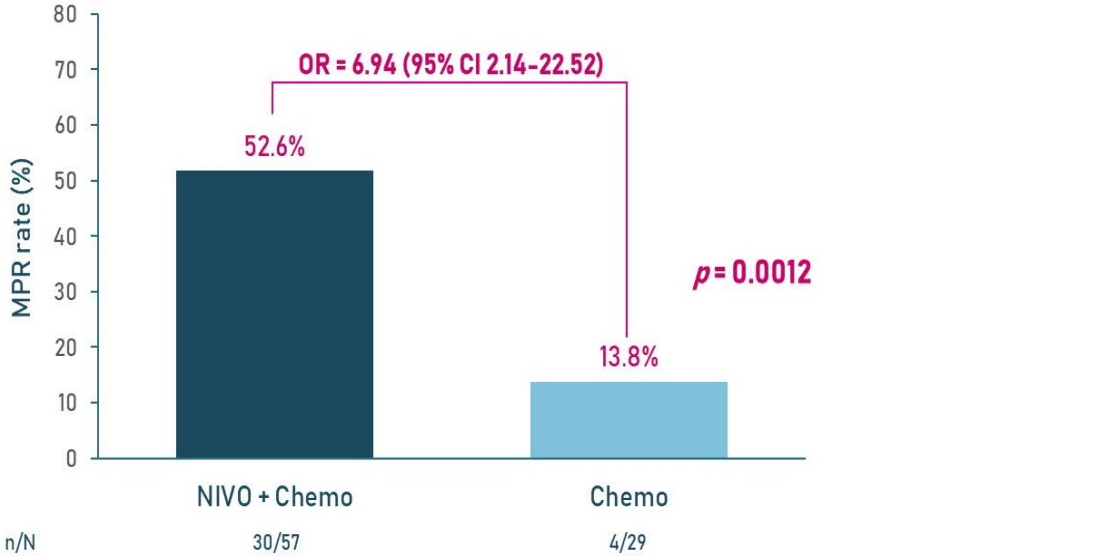
Provencio M, et al. ASCO 2022. Abstract PL03.12.

NADIM II: Pathologic Outcomes

pCR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population[b]



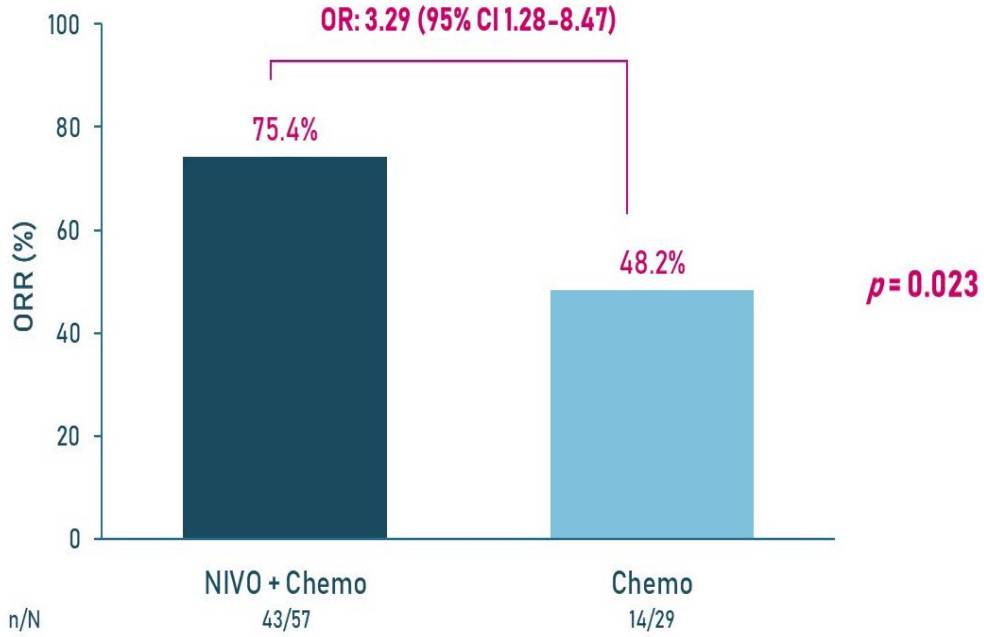
MPR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population[b]



Provencio M, et al. ASCO 2022. Abstract PL03.12.

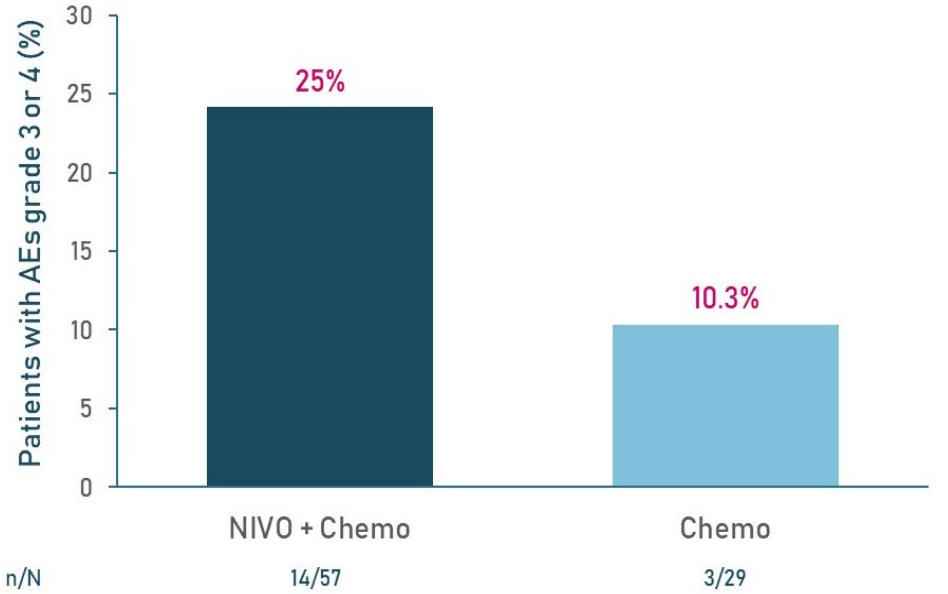
NADIM II: Clinical Outcomes

ORR[a] with neoadjuvant NIVO + Chemo vs Chemo in the ITT population [b]



Percentage of patients with a complete response or a partial response

Adverse events G 3-4 summary (ITT population)

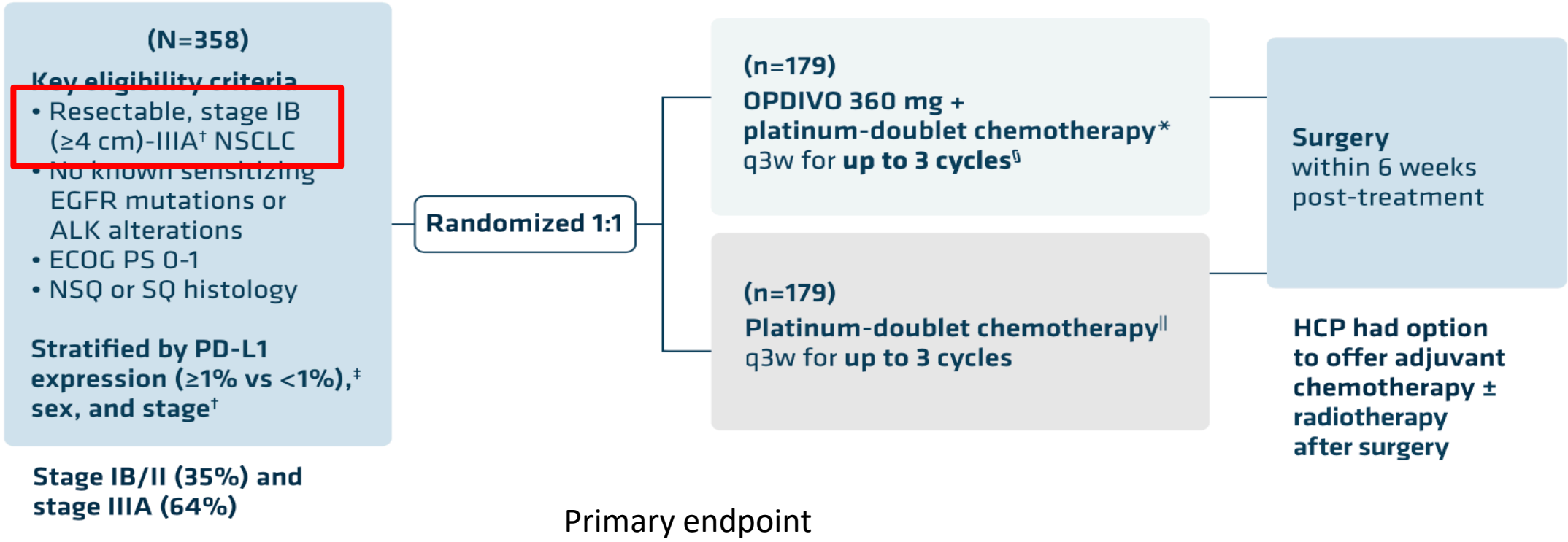


No grade 5 treatment-related adverse events were observed

- Neoadjuvant Nivo + chemo did not impede feasibility of surgery
- PD-L1 TPS positivity predicted for pCR (AUC 0.728 [95% CI 0.59–0.87], *P* = .002)

Provencio M, et al. ASCO 2022. Abstract PL03.12.

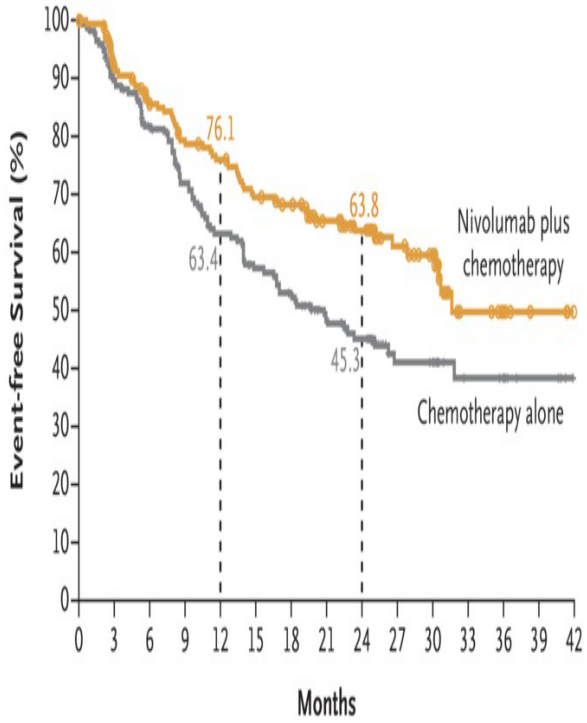
CheckMate 816 International Phase III



Primary endpoint

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

Event-Free Survival Favors Nivolumab + Chemo



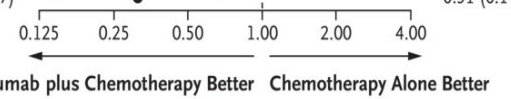
	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

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

No. at Risk

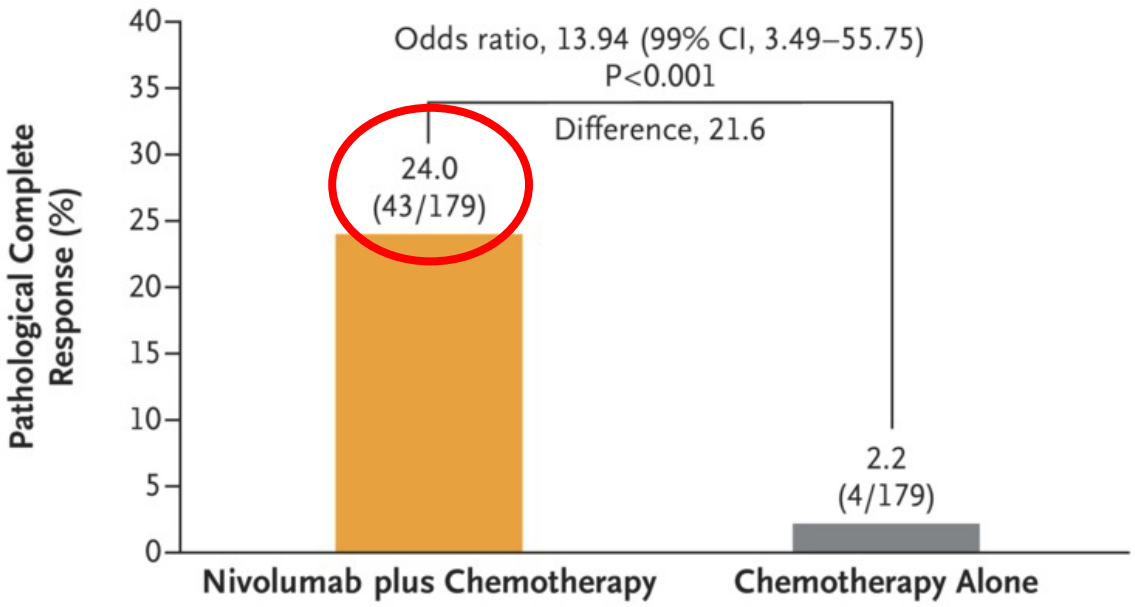
Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

Subgroup	No. of Patients	Median Event-free Survival (95% CI) *mo*		Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
		Nivolumab plus chemotherapy (N=179)	Chemotherapy alone (N=179)	
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)



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

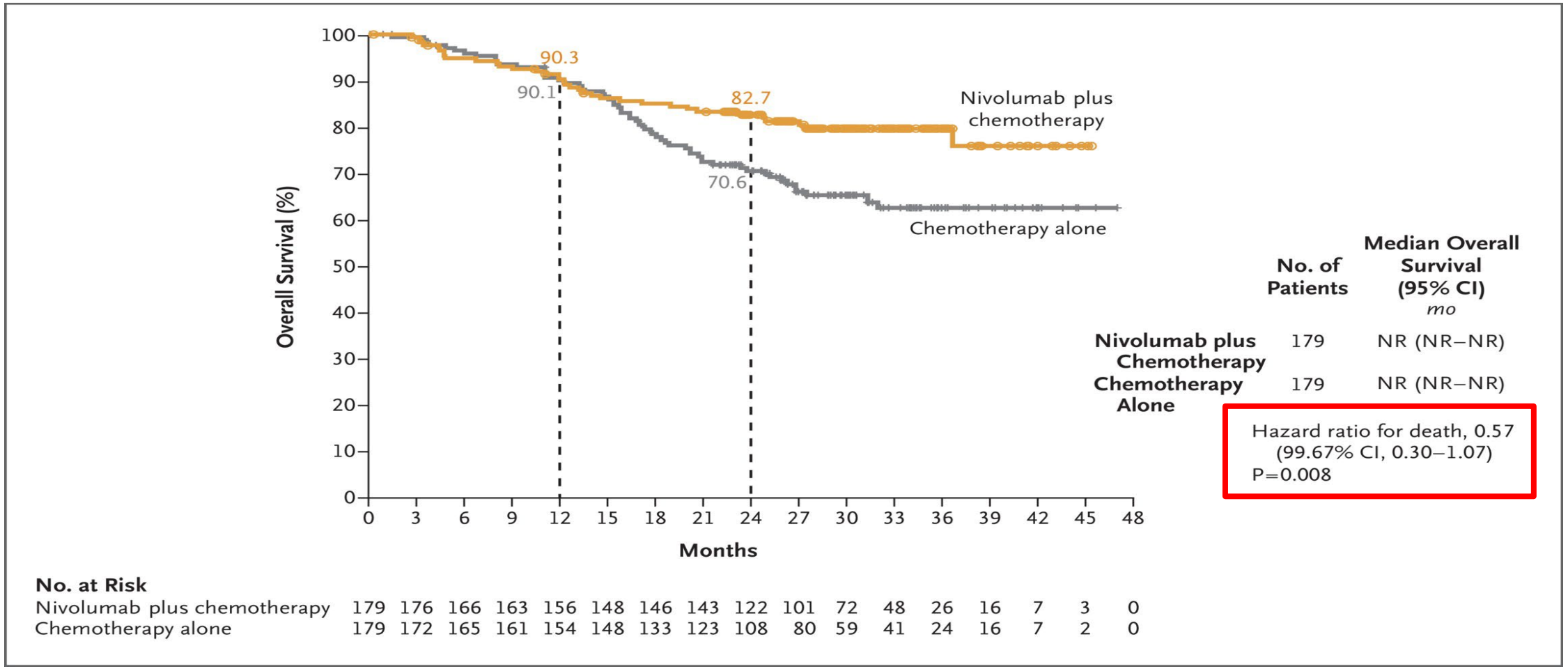
pCR Response Favors Nivolumab + Chemo



Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Unweighted Difference, Nivolumab plus Chemotherapy minus Chemotherapy Alone (95% CI)
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)	
		%		percentage points
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)	21.8 (15.2 to 28.7)
Age				
<65 yr	176	0 (0–4.3)	26.9 (18.2–37.1)	26.9 (17.8 to 36.7)
≥65 yr	182	4.2 (1.1–10.3)	20.9 (12.9–31.0)	17.8 (7.3 to 26.8)
Sex				
Male	255	2.4 (0.5–6.7)	22.7 (15.7–30.9)	20.3 (12.6 to 28.4)
Female	103	1.9 (<0.1–10.3)	27.5 (15.9–41.7)	25.5 (12.3 to 39.1)
Geographic region				
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)	20.0 (6.9 to 34.8)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)	24.4 (7.4 to 39.3)
Asia	177	3.3 (0.7–9.2)	28.2 (19.0–39.0)	25.0 (14.7 to 35.5)
ECOG performance-status score				
0	241	1.7 (0.2–6.0)	26.9 (19.1–35.3)	24.9 (16.7 to 33.4)
1	117	3.2 (0.4–11.2)	18.2 (9.1–30.9)	15.0 (3.8 to 27.3)
Disease stage at baseline				
IB or II	128	4.8 (1.0–13.3)	26.2 (16.0–38.5)	21.4 (9.0 to 33.6)
IIIA	228	0.9 (<0.1–4.7)	23.0 (15.6–31.9)	22.1 (14.3 to 30.7)
Histologic type of tumor				
Squamous	182	4.2 (1.2–10.4)	25.3 (16.6–35.7)	21.1 (11.0 to 31.4)
Nonsquamous	176	0 (0–4.3)	22.8 (14.7–32.8)	22.8 (14.2 to 32.4)
Smoking status				
Current or former smoker	318	2.5 (0.7–6.4)	25.6 (19.1–33.1)	23.1 (15.9 to 30.5)
Never smoked	39	0 (0–16.8)	10.5 (1.3–33.1)	10.5 (−7.3 to 31.4)
PD-L1 expression level				
<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)	14.1 (4.8 to 24.0)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)
TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)
Type of platinum therapy				
Cisplatin	258	2.2 (0.5–6.4)	21.8 (14.9–30.1)	19.5 (12.0 to 27.7)
Carboplatin	72	0 (0–10.6)	30.8 (17.0–47.6)	30.8 (14.7 to 46.4)

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

Preliminary Prespecified Interim Analysis: Overall Survival Favors Nivolumab + Chemo



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

Summary Neoadjuvant Chemo + IO

- Consistent data that neoadjuvant chemo + IO improves pCR and response rates
- No new safety signals
- No major impediment to resection
- CheckMate 816 demonstrates EFS benefit
- Neoadjuvant chemo + nivolumab is now a new standard of care

SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[1]

Preferred (squamous)
- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[2]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[3]

Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[4]
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5,6]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[5]

Useful in Certain Circumstances
- Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[7]
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[8]
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[9] (non-squamous histology)

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

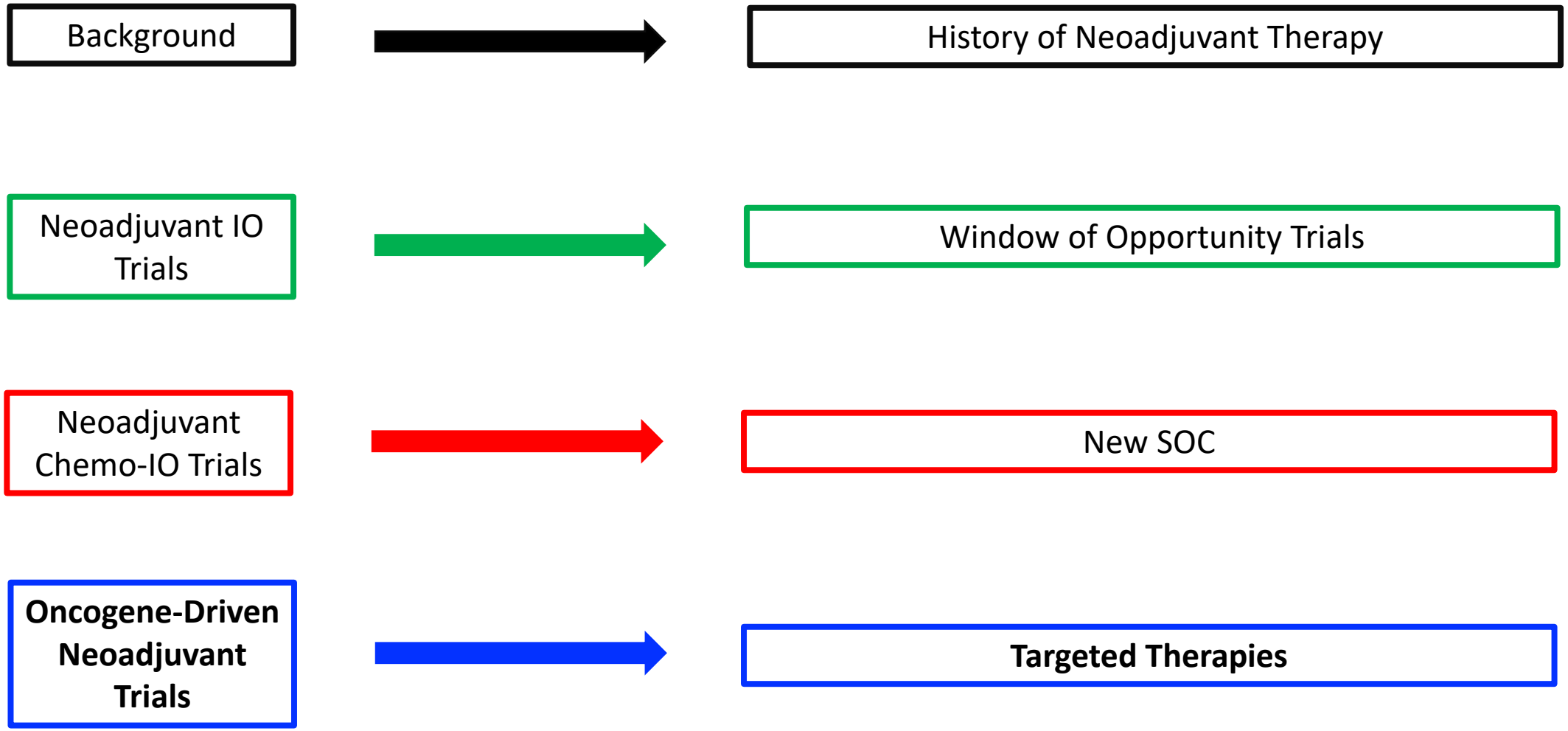
Neoadjuvant Systemic Therapy
- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[10,*]
  - Platinum-doublet chemotherapy options include:
    - ◊ Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
    - ◊ Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (non-squamous histology)
    - ◊ Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)
    - ◊ Cisplatin 75 mg/m² day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
  - Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
    - ◊ Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m² day 1 (non-squamous histology)
    - ◊ Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)

Future Trials to Read Out

Trial	NCT	Phase	N	Eligibility	Agents	Primary Endpoint
AEGEAN	03800134	III	800	IIA–IIIB (N2)	Chemo ± durvalumab (neoadj + adj)	pCR, EFS
BGB-A317-315	04379635	III	450	II–IIIA	Neoadj chemo ± tislelizumab (neoadj + adj)	mPR, EFS
CheckMate77T	04025879	III	452	IIA–IIIB (N2)	Neoadj chemo ± nivolumab (neoadj + adj)	EFS
CIBI308G301	05116462	III	800	IIB (>4 cm), IIIA/B	Neoadj chemo ± sintilimab (neoadj + adj)	EFS, pCR
IMpower 030	03456063	III	453	II, IIIA or IIIB (N2)	Neoadj chemo ± atezolizumab (neoadj + adj)	EFS
KEYNOTE-671	03425643	III	786	II, IIIA or IIIB (N2)	Neoadj chemo ± pembrolizumab (neoadj + adj)	EFS, OS
SHR-1316-III-303	04316364	Ib/III	537	II, IIIA/B	Neoadj chemo ± adebrelimab (neoadj + adj)	mPR, EFS

ClinicalTrials.gov.

Outline


Background
History of Neoadjuvant Therapy
Neoadjuvant IO Trials
Window of Opportunity Trials
Neoadjuvant Chemo-IO Trials
New SOC
Oncogene-Driven Neoadjuvant Trials
Targeted Therapies

Neoadjuvant Targeted Therapy Trials

	Population	Study drugs	Treatment duration	Objective response rate	Major pathological response	Pathological complete response	Median disease-free survival (months)	Median overall survival (months)	Grade 3 or above treatment-related adverse events	R0 surgery	Adjuvant treatment
Zhong et al (2019)[23]	Resectable stage IIIA–N2; Ex19del or L858R (n=72)	Erlotinib *vs* gemcitabine plus cisplatin	Erlotinib: 42 days preoperatively followed by 12 months postoperatively; gemcitabine plus cisplatin: 2 cycles preoperatively and 2 cycles postoperatively	54·1%* (20 of 37) with erlotinib *vs* 34·3%* (12 of 35) with gemcitabine plus cisplatin	9·7% (3 of 31) with erlotinib *vs* 0·0% (0 of 23) with gemcitabine plus cisplatin	0·0% with erlotinib *vs* 0·0% with gemcitabine plus cisplatin	21·5 with erlotinib *vs* 11·4 with gemcitabine plus cisplatin	45·8 with erlotinib *vs* 39·2 with gemcitabine plus cisplatin	None with erlotinib; 29·4% (17·6% neutropenia, 2.9% vomiting, 2.9% elevated blood glucose, and 2.9% bone marrow cell reduction) with gemcitabine plus cisplatin	73·0% (27 of 37) with erlotinib; 62·9% (22 of 35) with gemcitabine plus cisplatin	75·7% (28 of 37) with erlotinib; 62·9% (22 of 35) with gemcitabine plus cisplatin
Xiong et al (2019)[43]	Stage IIIA–N2; Ex19del or L858R (n=19)	Erlotinib	56 days	42·1% (8 of 19)	NR	NR	11·2	51·6	15·8% (5·3% abnormal liver function, 5·3% leukopenia, and 5·3% cerebral infarction)	68·4%* (13 of 19)	Most (exact figure NR)
Zhang et al (2021)[44]	Operable stage II–IIIA Ex19del or L858R (n=33)	Gefitinib	42 days	54·5%* (18 of 33)	24·2% (8 of 33)	NR	33·5	Not reached	None	87·9% (29 of 33)	100·0% (29 of 29; platinum doublet chemo-therapy or radiotherapy)
Tan et al (2019)[45]†	Stage IA–IIIA; Ex19del or L858R (n=13)	Gefitinib	Minimum 4 weeks (median 1·4 months)	61·5% (8 of 13)	7·7% (1 of 13)	NR	20·2	NR	8·0% (abnormal liver function test)	100·0% (13 of 13)	NR

R0=resection with negative margins. NR=not reported. *Primary endpoint. †Study available only in abstract form.

- Mostly *EGFR* focused
- EMERGING-CTONG1103
  - PFS benefit
- ALINA (*ALK* rearranged) ongoing
  - NCT03456076
- Currently no standard recommendation for neoadjuvant targeted therapy

Saw SPL, et al. *Lancet Oncol*. 2021;22:e501-e516.

Window of Opportunity Trials With Targeted Therapies

Advantages

- Smaller trial size can be completed with faster outcomes
- Optimal evaluation of a novel targeted agent – opportunity for "pure" results
  - Clean biomarker analysis pre- and post-neoadjuvant targeted agent
  - Ability for clean assessment of peripheral surrogate biomarkers
- Response to the targeted agent can be directly correlated to radiographic and pathologic results
- Can evaluate tumor heterogeneity response to the targeted agent

Disadvantages

- Experienced centers with multidisciplinary and translational programs
- Small sample size needs a greater effect to be significant
- Target of the novel agent should be known
- Must have a reasonable safety profile and tolerability
- Short window of neoadjuvant treatment may require adjuvant maintenance therapy to really see any survival impact
  - Unknown what the optimal duration of adjuvant maintenance
  - Also, unlikely to see significant response rates unless similar in magnitude of effect of *EGFR* mutations to EGFR TKI
  - May requires alternative endpoints

Clinical Conclusions

- Neoadjuvant therapy is an accepted standard practice
- Choice of when to utilize it should be personalized to each individual patient

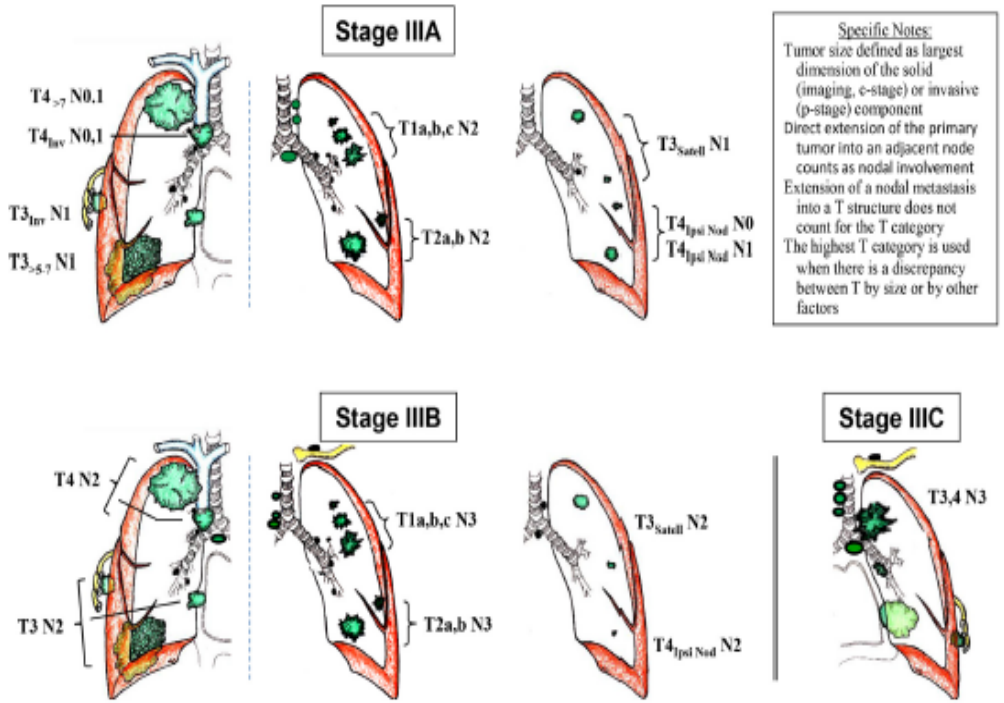


Figure 3 – *Graphic illustration of stage III.*

Hypothetical Future Strategies

Unresectable large T or N3 or bulky or multi-station N2 LN	Neoadjuvant chemoimmunotherapy, concurrent immunoradiation, then 1 year immunotherapy
Small T, **PD-L1 IHC-high,** small multi-station N2 LN	Concurrent immunoradiation, then 1 year immunotherapy
Small T, PD-L1 IHC low, small multi-station N2 LN	Concurrent chemoradiation, then 1 year immunotherapy
Large T single-station N2 LN	Neoadjuvant chemoimmunotherapy, surgery ± XRT, then 1 year immunotherapy
Small T single-station N2 LN	Neoadjuvant immunotherapy, surgery ± XRT, then 1 year immunotherapy

Detterbeck FC, et al. *Chest*. 2017;151:193-203.

Academic Summary

- Window of opportunity neoadjuvant trials are essential to understanding and developing predictive biomarkers
- Trials determining optimal sequence of treatments are needed
  - Which patients only need neoadjuvant? Adjuvant? Or both?
  - What stages should be considered for neoadjuvant? Stage III vs II vs IB
  - What pathologic endpoints can be used as predictive for additional therapy?
  - Who can avoid chemo?
  - Can patients who previously responded to neoadjuvant receive similar regimens when they develop disease recurrence?

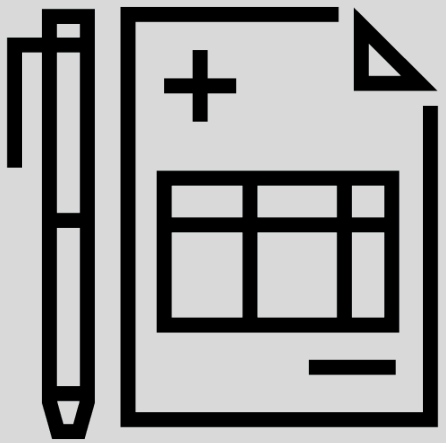
Global Lung Cancer Academy

Debate: Adjuvant vs Neoadjuvant Therapy for NSCLC?

Moderator: Corey Langer, MD

Presenters: Anne Tsao, MD, and Narjust Florez, MD

Patient case



Patient and disease characteristics

- 70-year-old woman
- Former smoker who quit 20 years ago

Diagnosis

- Stage II NSCLC, lymph node positive
- Biopsy shows *P53* mutation positive but no other mutations
- PD-L1 = 15%

What would be your treatment approach for this patient?

- Neoadjuvant therapy
- Adjuvant therapy

Global Lung Cancer Academy

Neoadjuvant Therapy

Anne Tsao, MD

Patient Case Debate

Case for Neoadjuvant Therapy

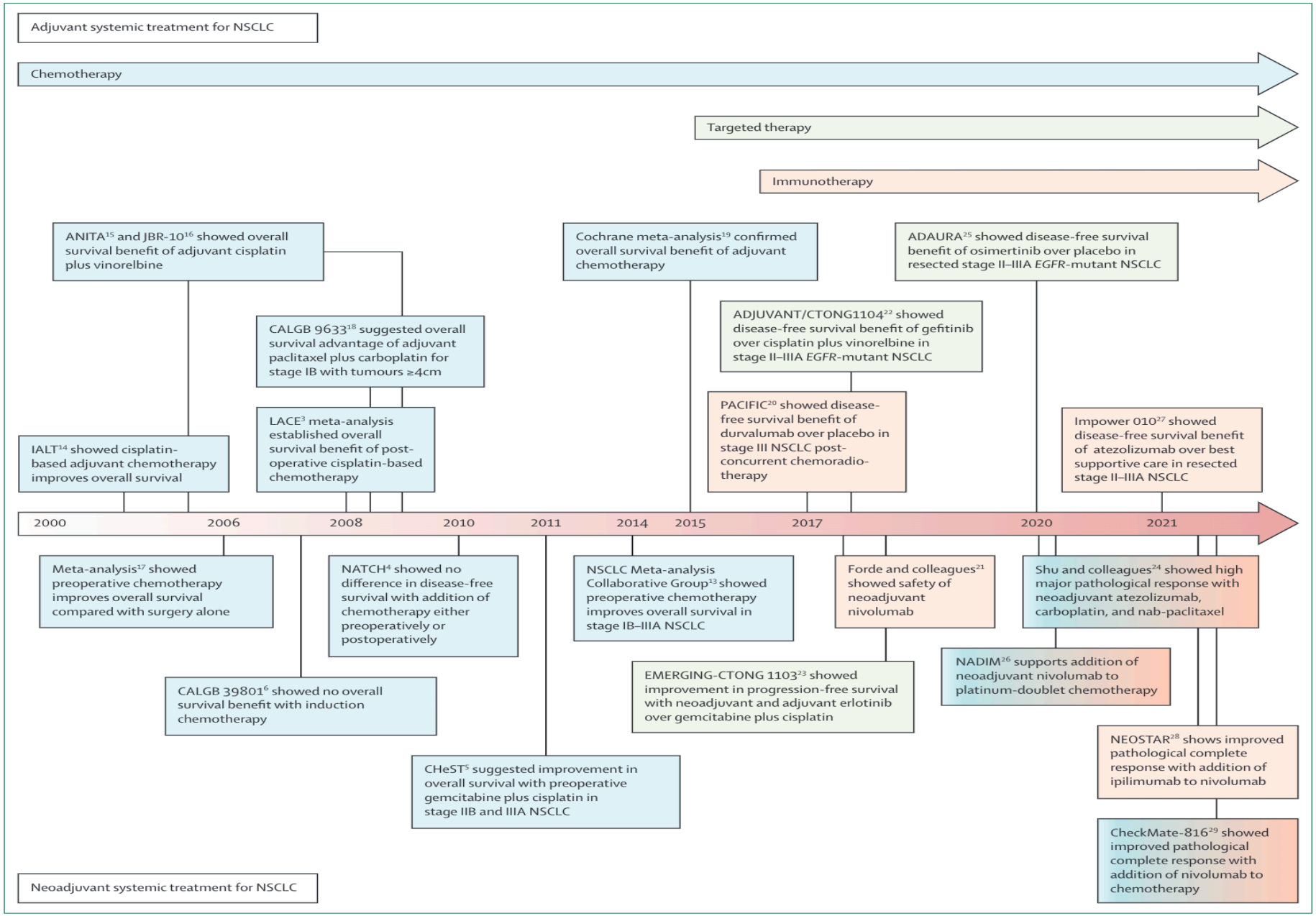


Figure 1: **Timeline of main milestones in adjuvant and neoadjuvant systemic treatment of NSCLC**
NSCLC=non-small-cell lung cancer.

Saw SPL, et al. *Lancet Oncol*. 2021;22:e501-e516.

Neoadjuvant Therapy

ADVANTAGES

- Time to encourage preoperative tobacco abstinence
- Earlier elimination of micrometastatic disease
- Chemotherapy ± IO better tolerated before major surgery than after – higher dose intensity
- Possible downstaging
- Prognostic value – assessment of chemo or chemo-IO sensitivity
- Opportunity for biomarker discovery pretreatment and posttreatment

DISADVANTAGES

- Delay to definitive procedure
- Toxicity of chemotherapy interferes with surgery
- Potential staging ambiguity
- Increased risk of postoperative complications

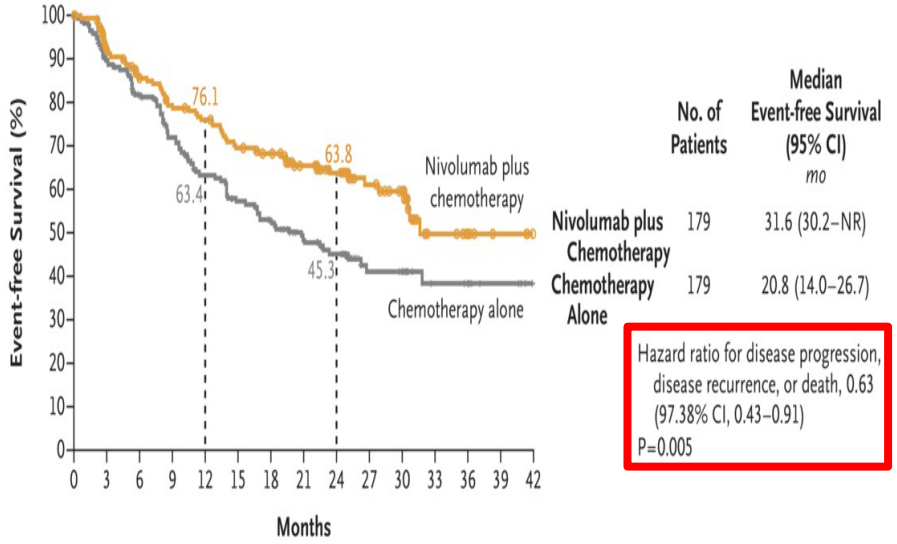
Prognostic Factors for Improved Survival After Neoadjuvant Therapy

- Response to chemotherapy
- Downstage N2 disease
- Single-station N2 is better than multi-station N2 disease
- R0 resection
- Pathologic CR
- Better systemic therapies may lead to improved downstaging and clinical outcomes
- Personalized therapy with targeted agents and molecular profiling
- Window of opportunity trials

CM816 Event-Free Survival Favors Nivo + Chemo

For all patients HR 0.63, *P* = .005

For PD-L1 ≥1% patients HR 0.41



	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

Subgroup	No. of Patients	Median Event-free Survival (95% CI) *mo*		Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
		Nivolumab plus chemotherapy (N=179)	Chemotherapy alone (N=179)	
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
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TMB				
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Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
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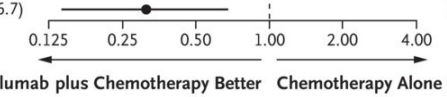


<u>IMpower010 (adjuvant atezolizumab)</u>

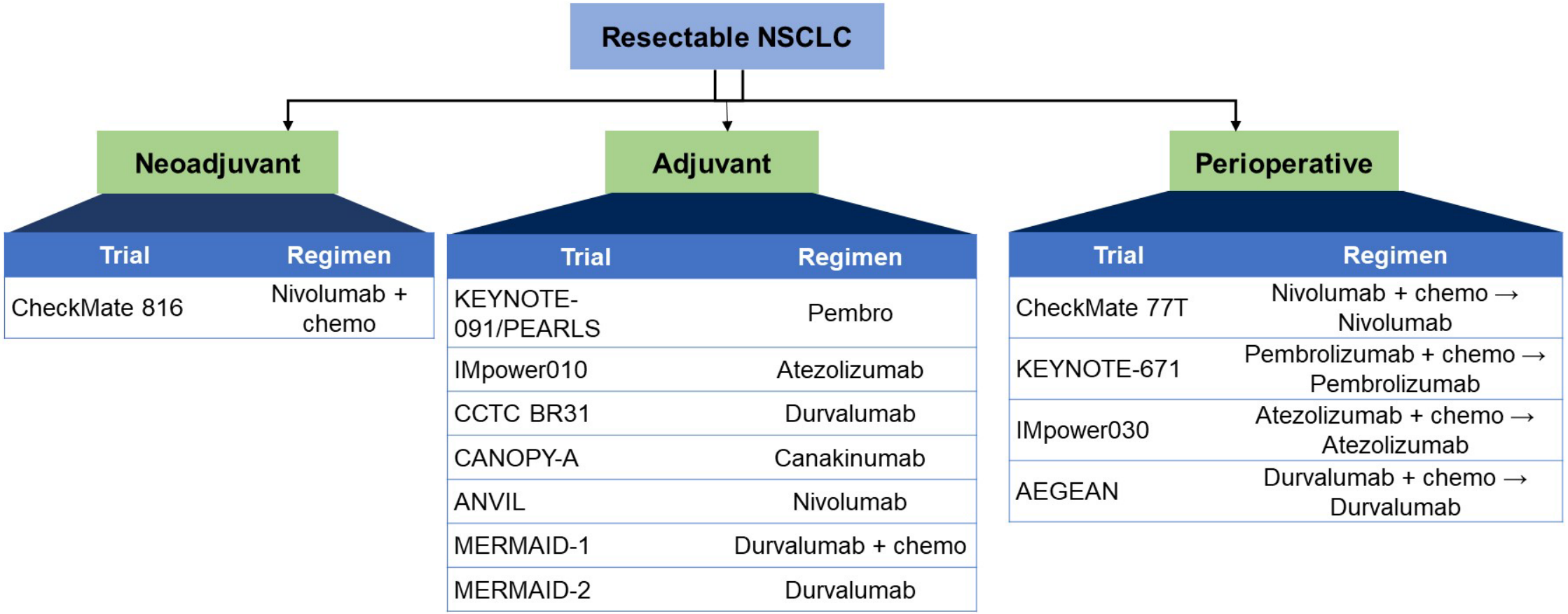
All patients (II–IIIA) adjuvant atezolizumab DFS HR 0.79

II–IIIA PDL1 ≥1% DFS HR 0.66

Forde PM, et al. *N Engl J Med.* 2022;386:1973-1985; Felip E, et al. *Lancet.* 2021;398:1344-1357.

The neo-adjuvant treatment landscape will expand as IO–based therapies are further explored in resectable NSCLC

Completed and Ongoing Select Phase 3 trials



Trial	Regimen
CheckMate 816	Nivolumab + chemo

Trial	Regimen
KEYNOTE-091/PEARLS	Pembro
IMpower010	Atezolizumab
CCTC BR31	Durvalumab
CANOPY-A	Canakinumab
ANVIL	Nivolumab
MERMAID-1	Durvalumab + chemo
MERMAID-2	Durvalumab

Trial	Regimen
CheckMate 77T	Nivolumab + chemo → Nivolumab
KEYNOTE-671	Pembrolizumab + chemo → Pembrolizumab
IMpower030	Atezolizumab + chemo → Atezolizumab
AEGEAN	Durvalumab + chemo → Durvalumab

Cascone T, et al. ASCO 2022. Education Session.

Global Lung Cancer Academy

Adjuvant Therapy

Narjust Florez, MD

Adjuvant Therapy in Lung Cancer

Narjust Florez (Duma), MD
Associate Director, Cancer Care Equity Program
Thoracic Oncologist, Lowe Center for Thoracic Oncology
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Dana-Farber Cancer Institute
Harvard Medical School
October 2022

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Disclosures

Advisory/Consulting: NeoGenomics, Pfizer, Janssen, BMS, Merck, DSI, and AstraZeneca

Speakers Engagement: Clinical Care Options (CCO), OncLive, and Physician Education Resource (PER)

Phase III Adjuvant Immunotherapy Trials

IMpower010[1,2]

Stratified by PD-L1 expression, sex, stage (IB vs II vs IIIA, and histology

Adults with stage IB (T ≥4 cm)/II/IIIA NSCLC per *AJCC* 7th ed. after complete surgical resection (N = 1280)

→ **Cisplatin + pemetrexed, gemcitabine, docetaxel, or vinorelbine** 1–4 cycles

- → **Atezolizumab** 1200 mg IV Q3W × 16
- → **BSC** × 1 yr

Chemotherapy mandatory

- **Primary endpoint:** DFS by investigator (hierarchical design) in PD-L1+ stage II–IIIA > all stage II–IIIA > ITT (stage IB–IIIA)

PEARLS/KEYNOTE-091[3]

Stratified by disease stage (IB vs II vs IIA), PD-L1 TPS (<1% vs 1%–49% vs ≥50%, and geographic region

Adults with stage IB (T ≥4 cm)/II/IIIA NSCLC per *AJCC* 7th ed. after complete surgical resection with provision of tumor tissue for PD-L1 testing (N = 1177)

- → **Pembrolizumab** 200 mg IV Q3W × 1 yr
- → **Placebo** IV Q3W × 1 yr

Chemotherapy not mandatory

- **Primary endpoint:** DFS

Cross-trial comparisons have significant limitations. The information in this section is presented in order to generate discussion, not to make direct comparisons between study results.

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1. Wakelee H, et al. ASCO 2021. Abstract 8500; 2. Felip E, et al. *Lancet.* 2021;398:1344; 3. Paz-Ares L, et al. ESMO 2022. Abstract VP3-2022.

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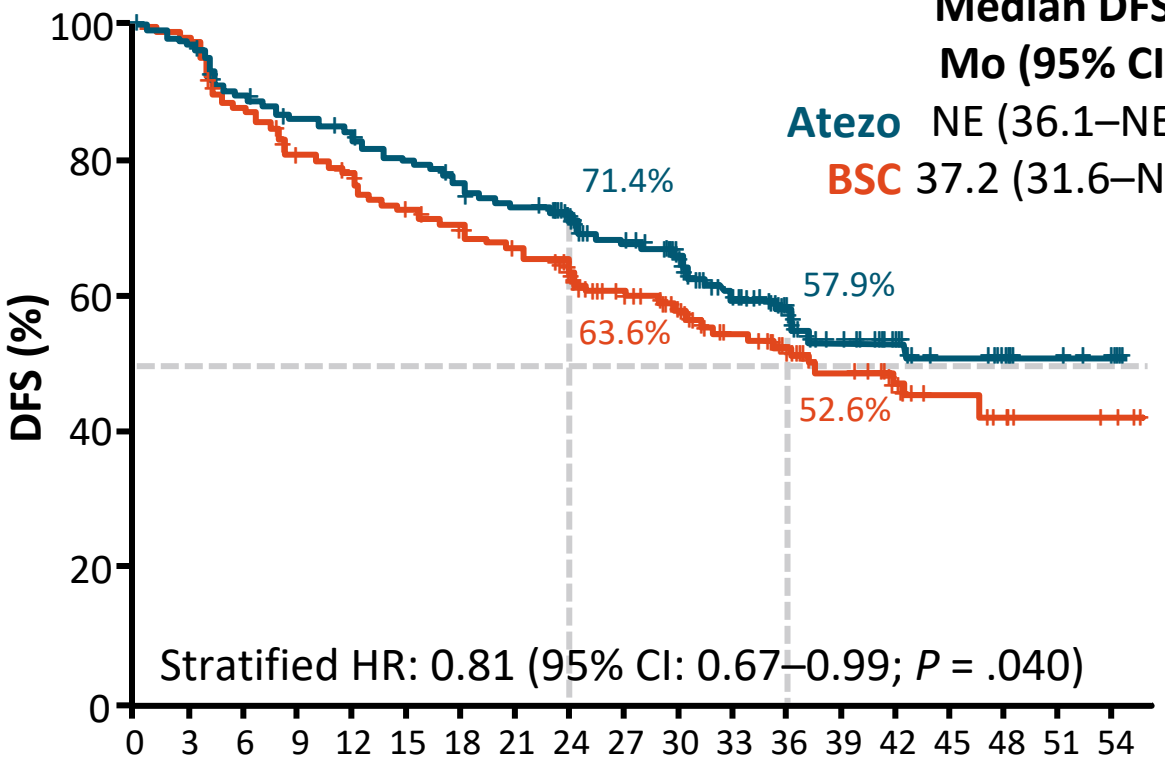
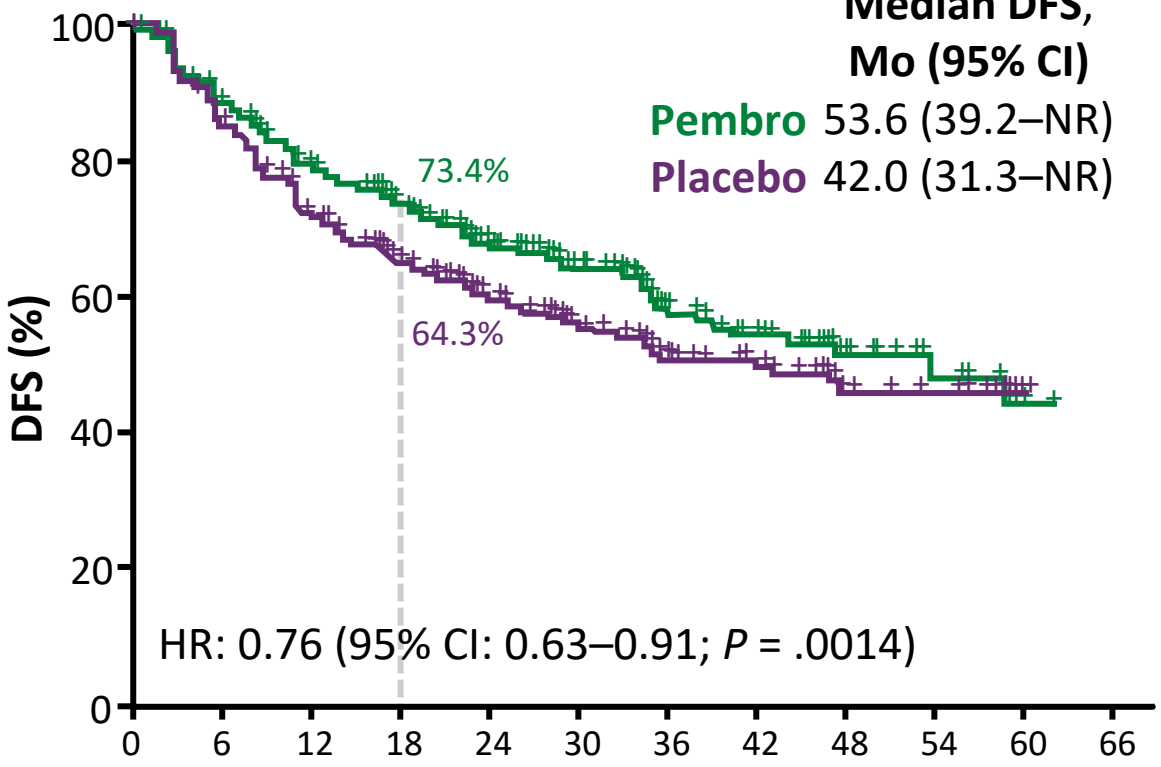
Adjuvant IO Trials: DFS in Overall Population (ITT)

IMpower010[1,2]



Patients at Risk, n																			
Atezo	507	478	437	418	403	387	367	353	306	257	212	139	97	53	38	19	14	8	4
BSC	498	467	418	383	365	342	324	309	269	219	173	122	90	46	30	13	10	5	4

PEARLS/KEYNOTE-091[3]



Patients at Risk, n												
Pembro	590	493	434	358	264	185	82	70	28	16	1	0
Placebo	587	493	409	326	241	160	72	57	22	18	1	0

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1. Wakelee H, et al. ASCO 2021. Abstract 8500; 2. Felip E, et al. *Lancet.* 2021;398:1344; 3. Paz-Ares L, et al. ESMO 2022. Abstract VP3-2022.

IMpower010: OS in Patients With Stage II–IIIA NSCLC and PD-L1 TC ≥1%

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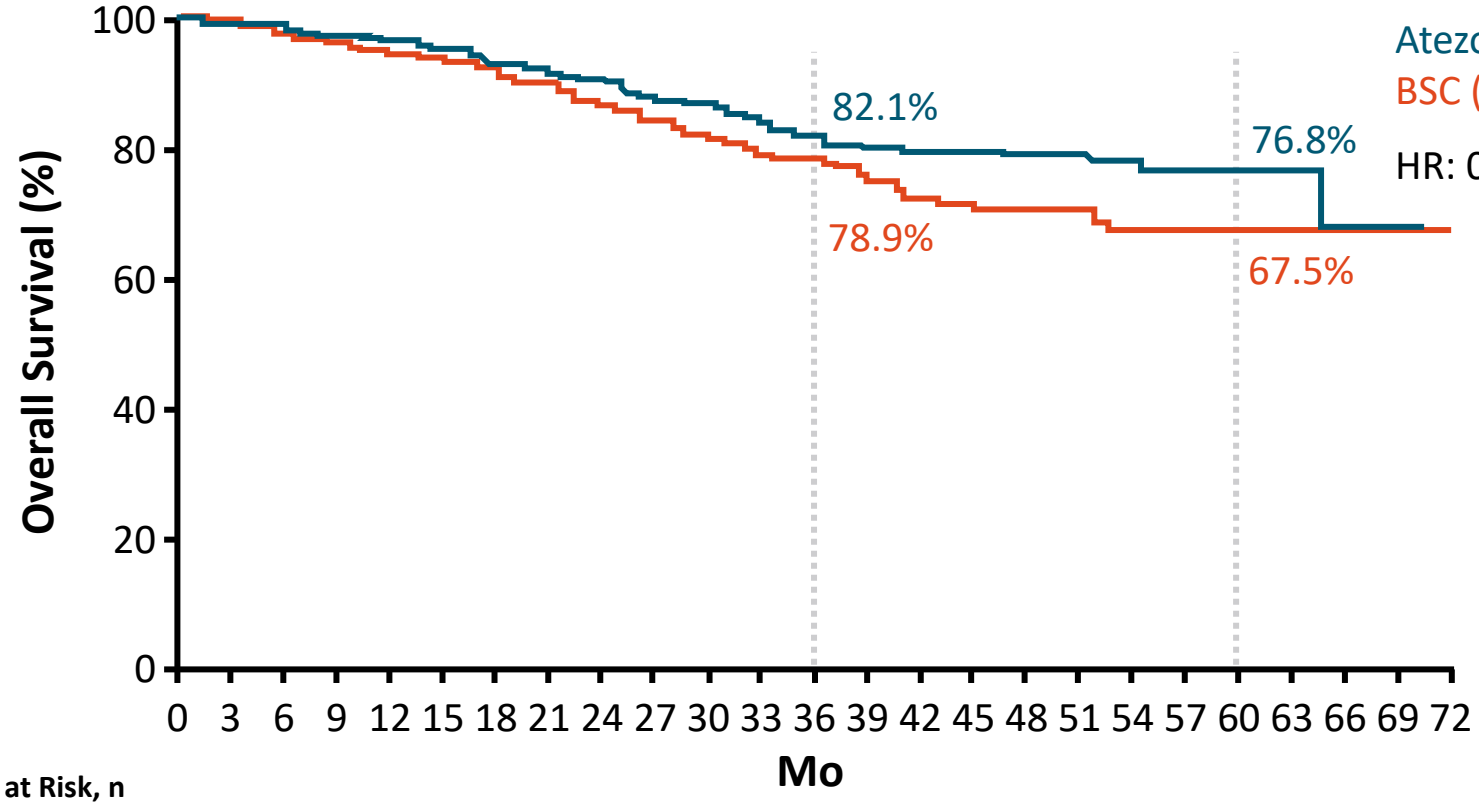
Median follow-up: 46 mo



	Events, n (%)	Median OS, Mo (95% CI)
Atezo (n = 248)	52 (21.0)	NR
BSC (n = 228)	64 (28.1)	NR

HR: 0.71 (95% CI: 0.49–1.03)

Patients at Risk, n

Atezo	248	241	241	237	234	231	225	222	218	210	208	200	195	190	172	140	116	83	56	37	23	12	5	3	NE
BSC	228	220	214	210	205	201	198	192	185	180	172	167	166	158	140	110	95	72	49	27	15	8	7	4	NE

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

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IMpower010: OS By Biomarker Status (Stage II–IIIA)

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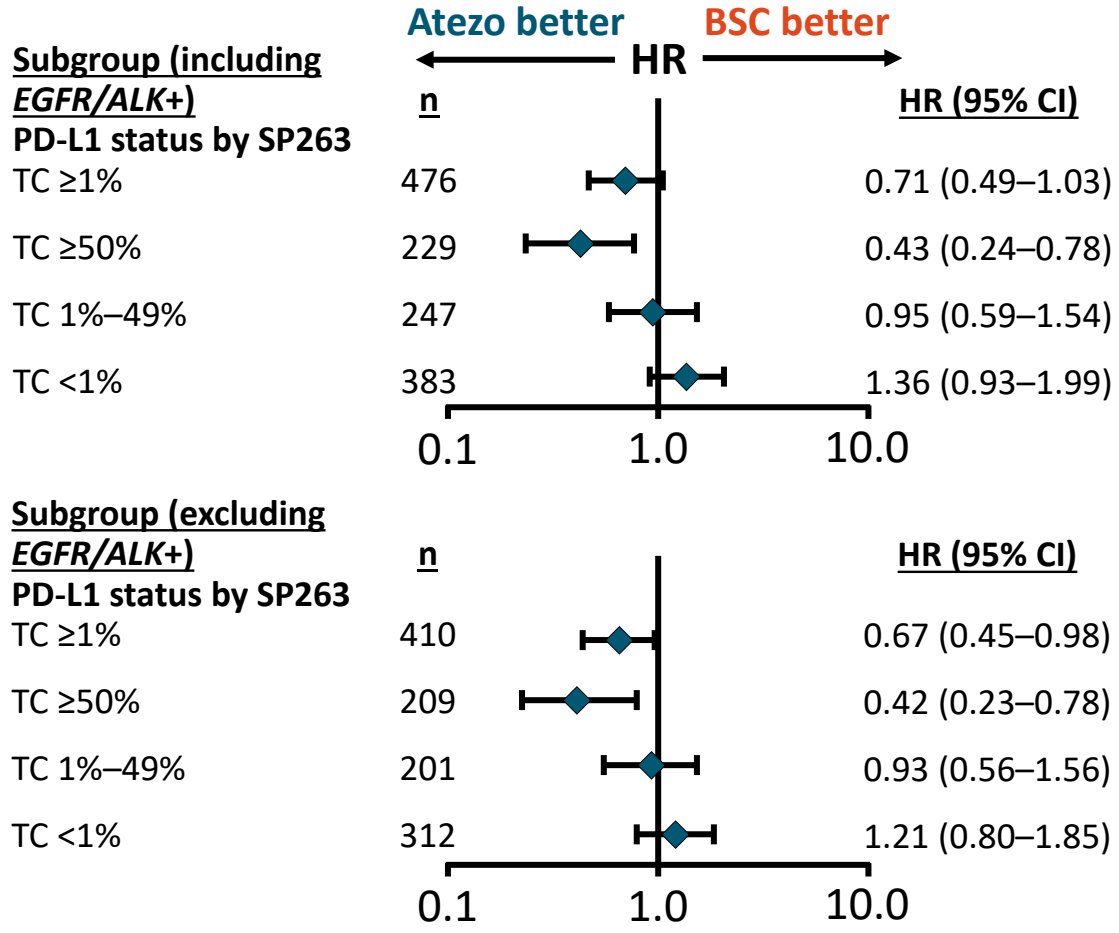
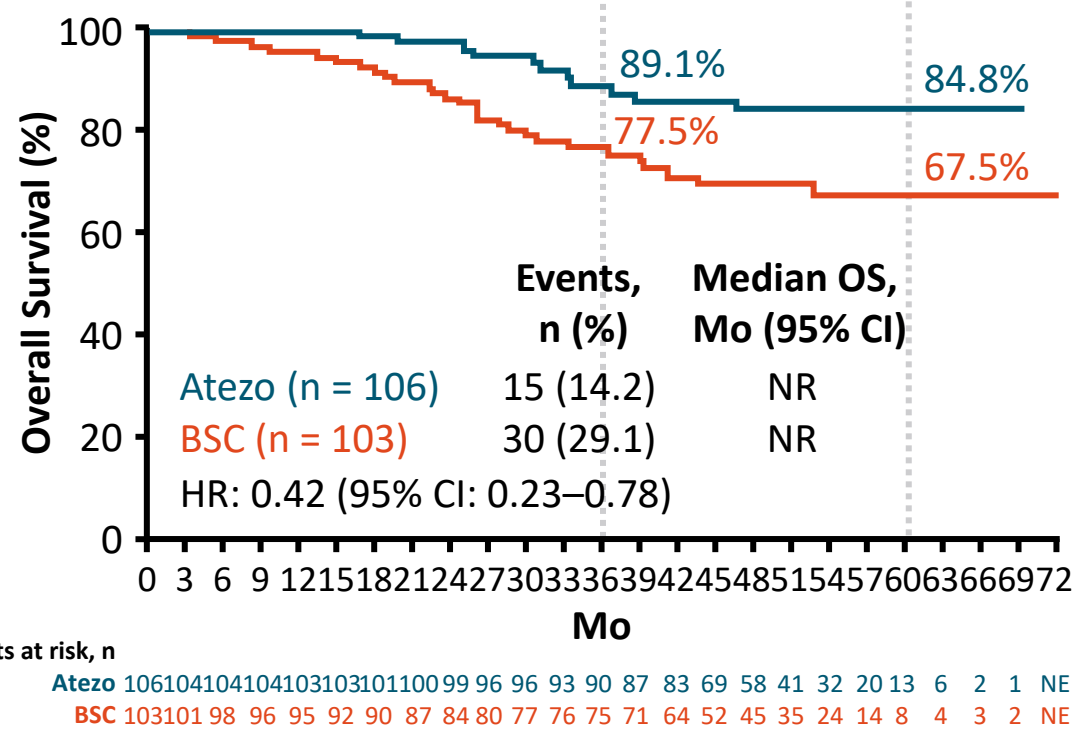


OS in Patients With Stage II-IIIA NSCLC and PD-L1 TC ≥50%, Excluding *EGFR/ALK*+



Patients at risk, n

Atezo	106	104	104	104	103	103	101	100	99	96	96	93	90	87	83	69	58	41	32	20	13	6	2	1	NE
BSC	103	101	98	96	95	92	90	87	84	80	77	76	75	71	64	52	45	35	24	14	8	4	3	2	NE

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

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IMpower010: Safety

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	Median Follow-up: 32 Mo	Median Follow-up: 46 Mo	
Safety Event, %	**Atezolizumab (n = 495)**	**Atezolizumab (n = 495)**	**BSC (n = 495)**
Any-grade AE	92.7	92.5	70.9
▪ Treatment related	67.7	67.9	0
Grade 3/4 AEs	21.8	22.0	11.5
▪ Treatment related	10.7	10.7	0
Serious AEs	17.6	17.8	8.5
▪ Treatment related	7.5	7.5	0
Grade 5 AEs	1.6	1.8*	0.6
▪ Treatment related	0.8	0.8	0
AE leading to atezolizumab dose interruption	28.7	28.7	0
AE leading to any treatment discontinuation	18.2	18.2	0
Atezolizumab-related AEs of interest	51.7	52.1	9.5
▪ Grade 3/4	7.9	7.9	0.6
▪ Requiring use of systemic corticosteroids	12.1	12.3	0.8

*No new deaths occurred between median follow-up of 32 mo and 46 mo, but 1 “other” death was updated to grade 5 AE.

IMpower010: Conclusions

- Trend toward OS benefit in patients with stage II–IIIA NSCLC with PD-L1 TC ≥1% vs BSC
  - OS HR: 0.71 (95% CI: 0.49–1.03) in this patient population
  - Trend toward OS benefit also seen in patients with stage II–IIIA NSCLC with PD-L1 TC ≥50%; OS HR: 0.43 (95% CI: 0.24–0.78)
- Safety profile of adjuvant atezolizumab at median follow-up of 46 mo similar to earlier data
- Investigators concluded that these data continue to support previous findings and currently approved use of atezolizumab as adjuvant treatment for patients with stage II–IIIA NSCLC who are PD-L1 positive after complete resection and adjuvant chemotherapy
  - Additional follow-up required for final DFS analysis and subsequent hierarchical OS analysis

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

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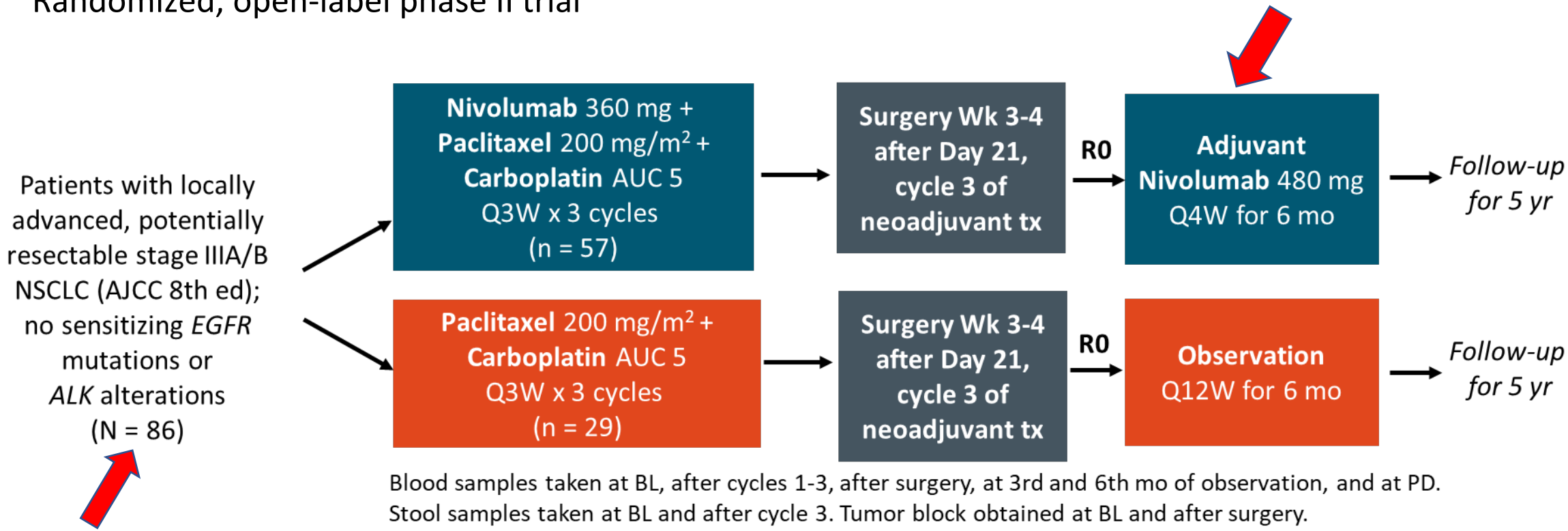
PRO Adjuvant Immunotherapy in Lung Cancer

- Provides the opportunity to treat patients after they already had surgery
- Potential lower percentage of delays to surgery (curative treatment)
- Patients may feel more comfortable receiving therapy after surgery (as well as surgeons)
- Available OS for patients with PD-L1 >50%
- The story for other patients is still developing for IMpower010

What About NADIM II?

- Randomized, open-label phase II trial



Blood samples taken at BL, after cycles 1-3, after surgery, at 3rd and 6th mo of observation, and at PD. Stool samples taken at BL and after cycle 3. Tumor block obtained at BL and after surgery.

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NADIM II: OS (Secondary Endpoint)

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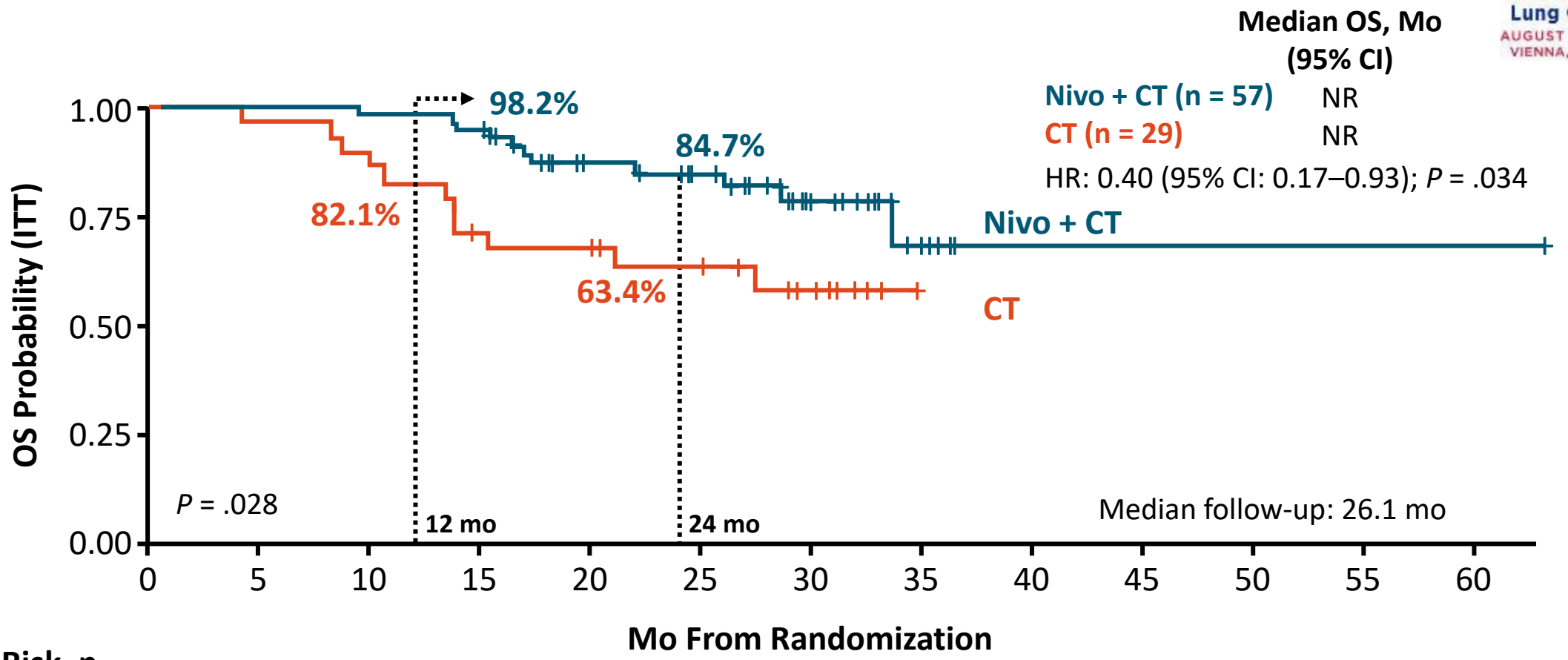

Patients at Risk, n

Nivo + CT	56	56	55	53	37	31	15	5	1	1	1	1	1
CT	28	27	25	19	17	13	9	0	0	0	0	0	0

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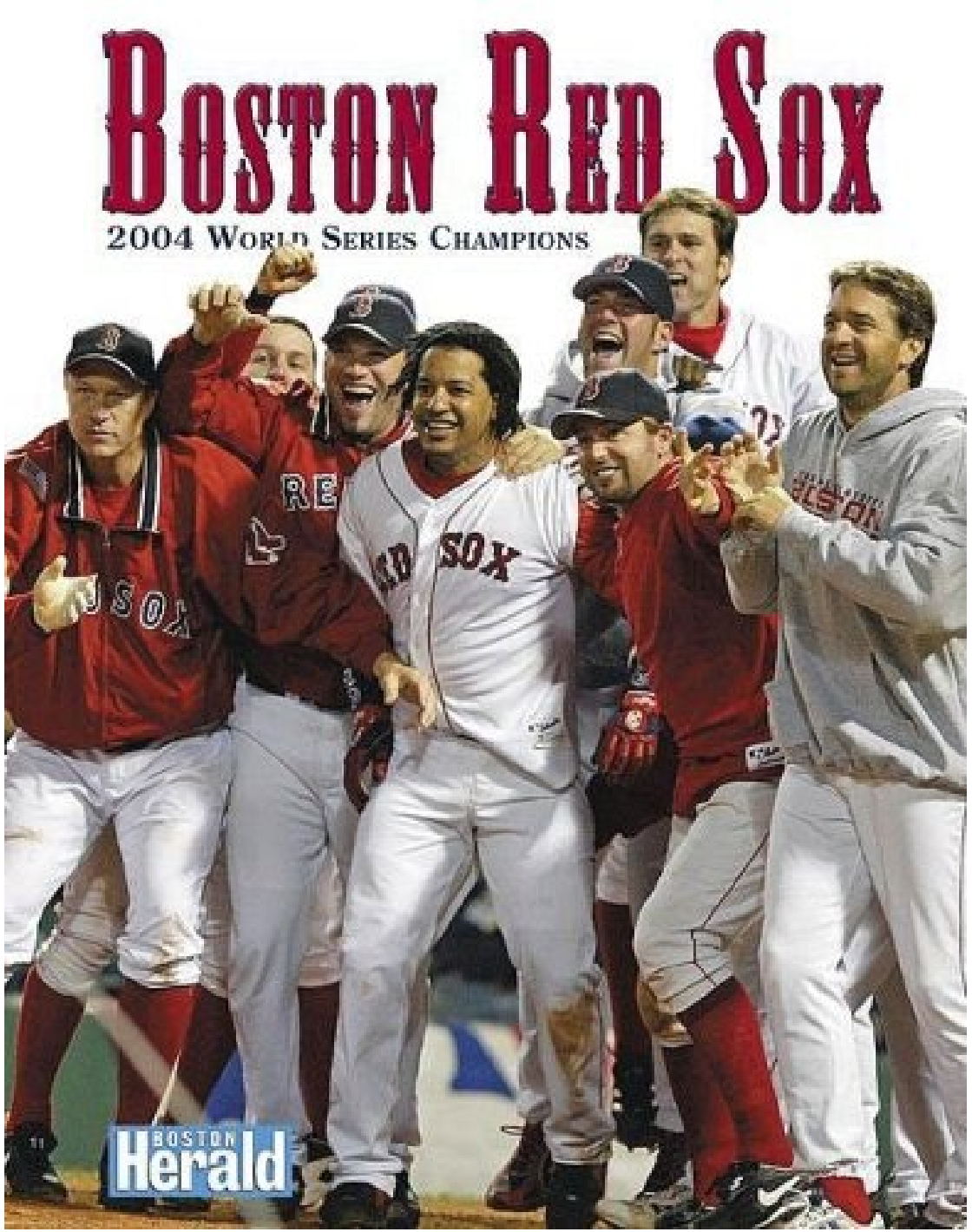
Will you compete knowing that your chances are low?

YES!



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Global Lung Cancer Academy

Debate: Adjuvant vs Neoadjuvant Therapy for NSCLC?

Moderator: Corey Langer, MD

Presenters: Anne Tsao, MD, and Narjust Florez, MD

What would be your treatment approach for this patient?

- Neoadjuvant therapy
- Adjuvant therapy

Global Lung Cancer Academy

BREAK

Coming up

– GLCA Europe (7 and 14 November 2022)

Global Lung Cancer Academy

Locally Advanced Unresectable NSCLC – What Are the Options?

Edgardo S. Santos, MD

Locally Advanced Unresectable NSCLC – What Are the Options?

Edgardo S. Santos, M.D., FACP
Genesis Care US
Medical Director of Research Services/GC Hematology-Oncology
Thoracic Oncology
Clinical Associate Professor
Charles E. Schmidt School of Medicine/Florida Atlantic University
Treasurer, FLASCO & President, FLASCO Foundation

October 21, 2022

GenesisCare

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

Clinical case.

67-year-old female presented with SOB and cough to ER. CXR revealed an opacification in the right mediastinum. CT chest w contrast revealed a RUL lesion 2.5 cm and bulky lymphadenopathy (4 cm) in the R mediastinum and 2.1cm LN in the subcarinal. Patient underwent bronchoscopy and tissue confirm the presence of adenocarcinoma at subcarinal level; PET CT scan revealed no metastatic disease (cT1cN2M0, stage IIIA). ECOG PS 0. Co-morbid conditions: HTN and hyperlipidemia. TMP revealed EGFR(-), ALK (-), and PD-L1 80%.

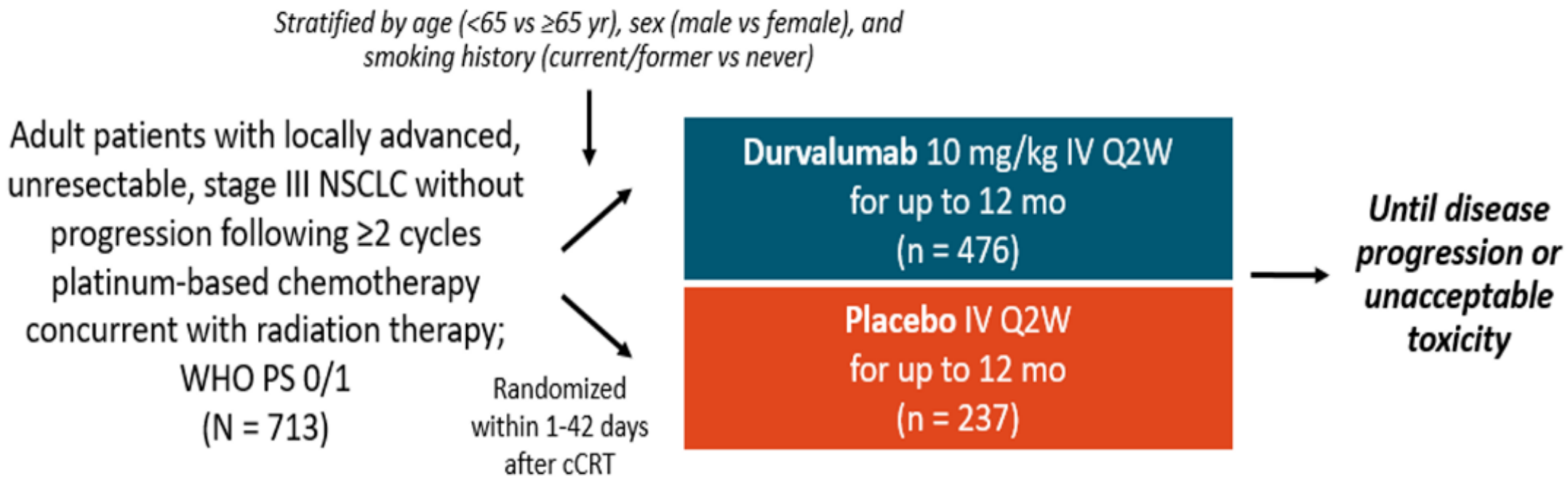
All the following therapeutic approaches may be acceptable except:

1. Neoadjuvant nivolumab plus chemotherapy followed by surgery.
2. cCRT followed by Durvalumab
3. Single agent immunotherapy
4. Sequential chemotherapy followed by cCRT followed by durvalumab.

Background.....

PACIFIC Trial

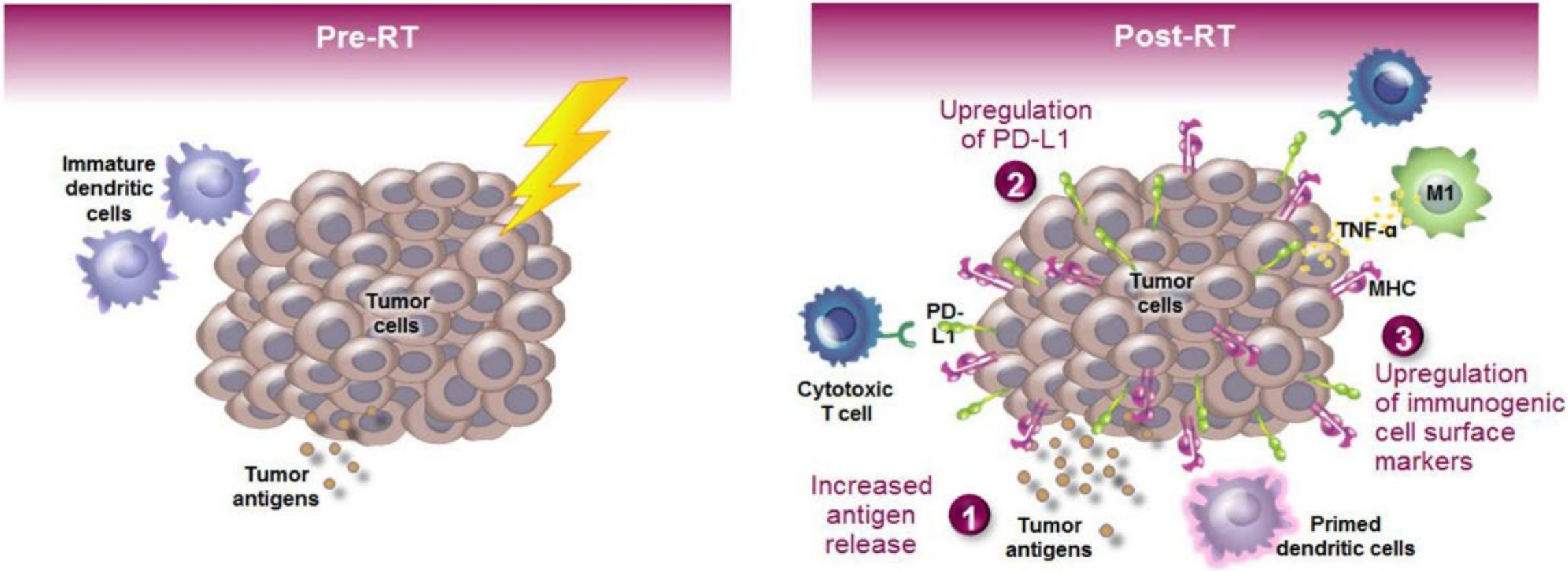
- Randomized, double-blind, placebo-controlled phase III trial



Patients enrolled regardless of PD-L1 status. If available, pre-cCRT tumor tissue archived for PD-L1 testing.

Spigel DR et al. ASCO 2021; abstr 8511

RT Induces Multiple Immunomodulatory Changes That May Influence the Effectiveness of Immunotherapy[1-3]



M1, tumor-associated macrophage; MHC I, major histocompatibility complex I; PD-L1, programmed cell death-ligand 1; TNF-α, tumor necrosis factor alpha.

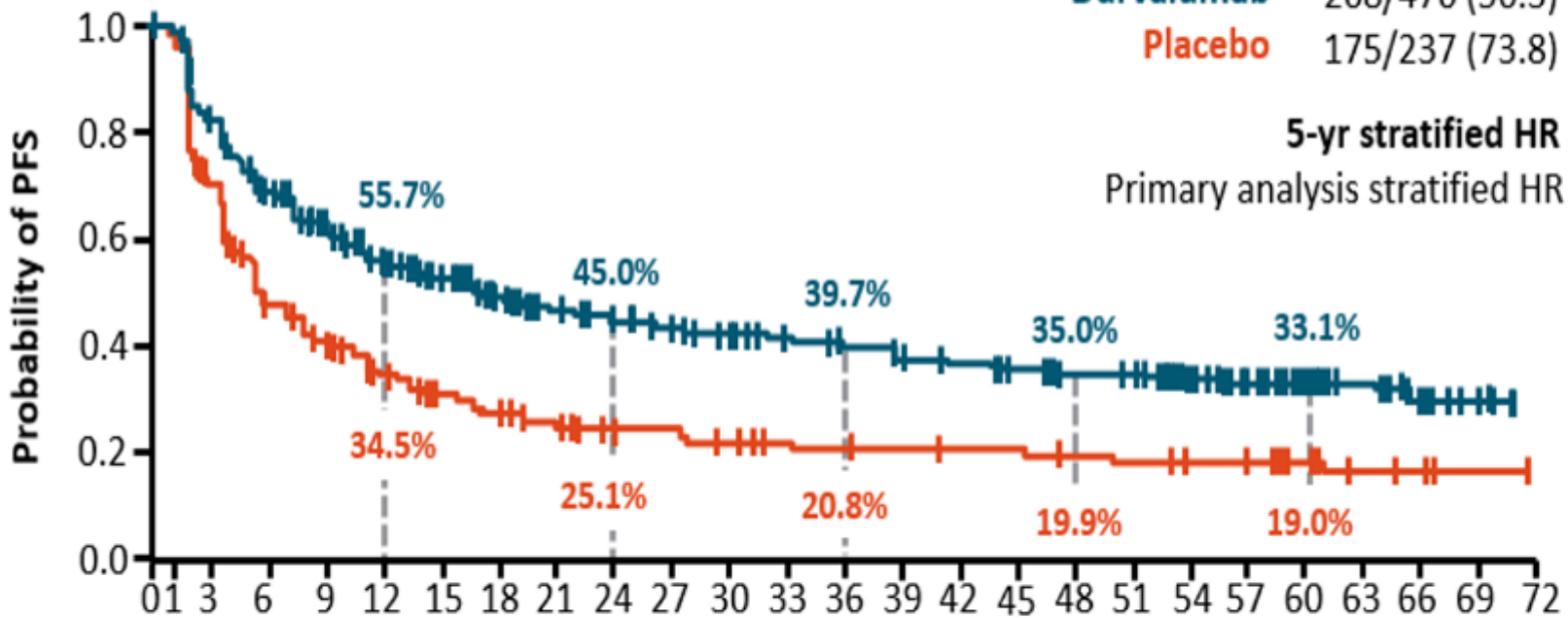
1. Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-1693. 2. Kaur P, Asea A. *Frontiers Oncol*. 2012;2:191. 3. Deng L, et al. *J Clin Invest*. 2014;124(2):687-695.

5-year update: PFS

	Events/Patients, n/N (%)	Median PFS, Mo (95% CI)
Durvalumab	268/476 (56.3)	16.9 (13.0-23.9)
Placebo	175/237 (73.8)	5.6 (4.8-7.7)

5-yr stratified HR (95% CI): 0.55 (0.45-0.68)

Primary analysis stratified HR (95% CI): 0.52 (0.42-0.65)



Patients at Risk, n																									
Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

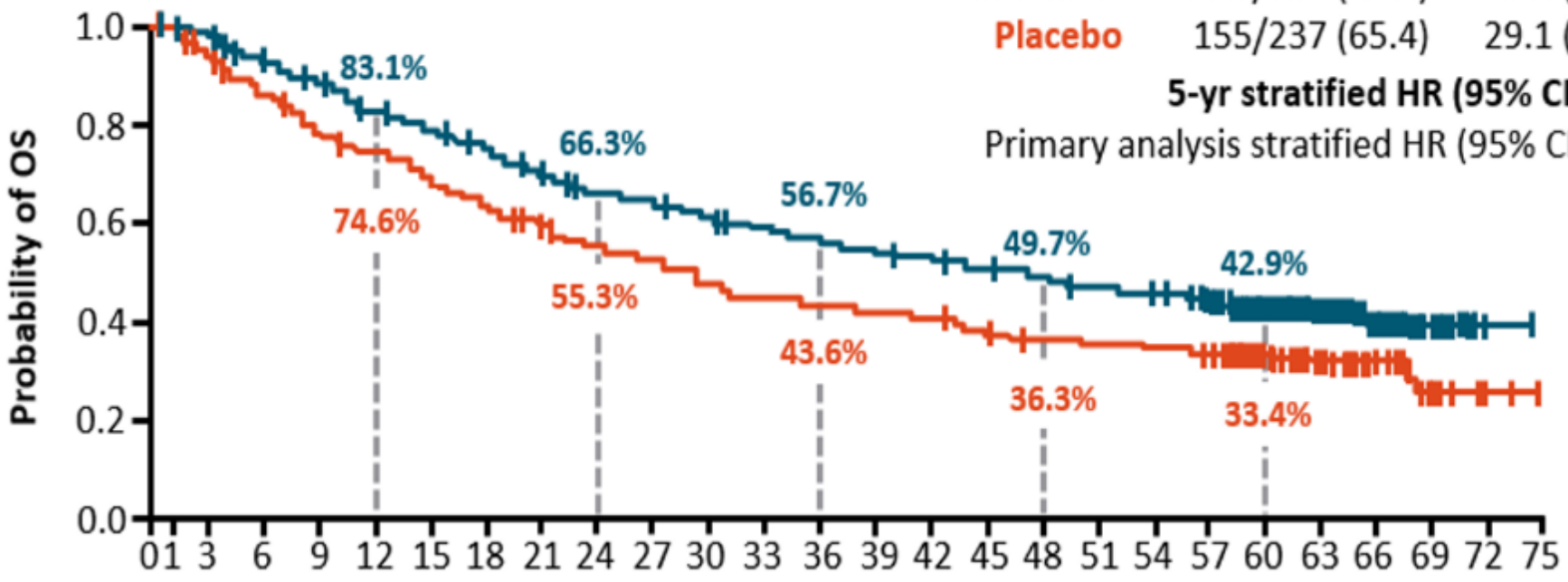
Spigel DR et al. ASCO 2021; abstr 8511

5-year update: Overall Survival

	Events/Patients, n/N (%)	Median OS, Mo (95% CI)
Durvalumab	264/476 (55.5)	47.5 (38.1-52.9)
Placebo	155/237 (65.4)	29.1 (22.1-35.1)

5-yr stratified HR (95% CI): 0.72 (0.59-0.89)

Primary analysis stratified HR (95% CI): 0.68 (0.53-0.87)



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

Spigel DR et al. ASCO 2021; abstr 8511

PACIFIC into Perspective….

	Albain	RTOG 0617	PACIFIC	PACIFIC
Arm	CCRT→Resection	CCRT (60 Gy)	CCRT	CCRT→durva
Median follow up	1.88 yrs	5.1 yrs	5.0 yrs	5.0 yrs
OS (median)	23.6 mos	28.7 mos	29.1 mos	47.5 mos
5-year OS	NR	32.1%	33.4%	42.9%
5-year PFS	22%	23%	19%	33.1%

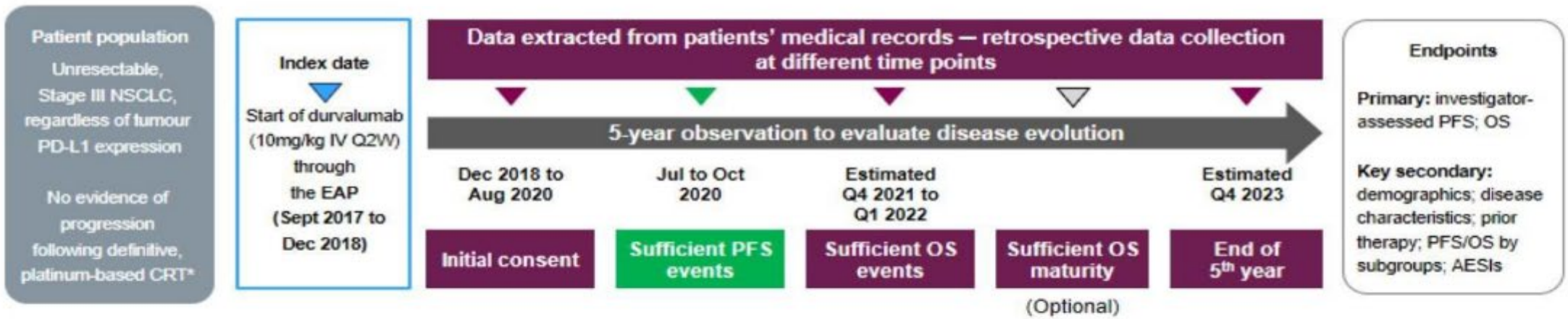
PACIFIC: Summary

- Durvalumab demonstrated improvements in PFS and OS versus placebo.
- Patients who received durvalumab had a lower incidence of new lesions including brain metastases compared with placebo.
- No new safety signals were identified.
- For patients with unresectable Stage III NSCLC who have not progressed post 2 cycles of definitive chemoradiation, durvalumab is FDA approved and category 1 on NCCN.

PACIFIC Real-World Study: ESMO 2021

Study Design & Status (NCT03798535)

PACIFIC-R: An International, Observational Study



- **1,399 patients** included in the **full analysis set (FAS)** from **290 active sites** in **11 participating countries**
  - France (n=342), Spain (244)†, Australia (165), Netherlands (155), Belgium (118), Italy (116), Israel (92), Germany (62), UK (54), Norway (36), and Switzerland (15)

*Patients had completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of disease progression; †Spanish data are from an externally sponsored study integrated in April 2021
AESI, adverse event of special interest; CRT, chemoradiotherapy; EAP, expanded access programme; IV, intravenously; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q2W, every 2 weeks

Girard N, et al ESMO congress 2021. 1171 MO.

PACIFIC-R DATA

Patient Characteristics & Durvalumab Treatment

Characteristics		FAS (N=1,399)
Age at EAP inclusion (years)	Median (range)	66.0 (26–88)
Age categories, %	≤75 years / >75 years	89.6 / 10.4
Sex, %	Male / Female	67.5 / 32.5
Smoking status at EAP inclusion, %	Never / Current / Former	7.9 / 32.6 / 59.5
Stage at diagnosis, %*[A]	Stage IIIA	43.2
	Stage IIIB/C	51.0
Histological subtype, %*[B]	Squamous	35.5
	Non-squamous	63.1
	Unknown	1.4
ECOG/WHO PS at EAP inclusion, %	0 / 1 / 2 / 3	51.4 / 46.6 / 1.9 / 0.1
CRT type, %*[C]	Concurrent	76.6
	Sequential	14.3
	Other	9.1
PD-L1 expression, %*[D] (Based on n=967 tested patients)	≥1%	72.5
	<1%	17.9
	Inconsistent[†]	9.6

- **Median time to durvalumab initiation** from the end of RT = **56 days**
- Overall **median durvalumab treatment duration = 335 days (~11 months)**
  - >12 months' treatment: 20.1%
  - >14 months' treatment: 4.4%
- Patients received a **median of 22 durvalumab infusions**
  - 7.1% received >26 infusions

Cut-off date for data extraction: 8 April 2021
*Percentages based on patients for whom the data were available; †PD-L1 expression tested but not clearly reported.
[A]Disease stage was missing for n=7 and n=74 had were diagnosed at a stage <III; [B]Histology was missing for n=2; [C]CRT type was missing for n=2; [D]PD-L1 was not tested for n=432
CRT, chemoradiotherapy; EAP, expanded access programme; ECOG/WHO PS, Eastern Cooperative Oncology Group/World Health Organization performance status; FAS, full analysis set; PD-L1, programmed cell death-ligand 1; RT, radiotherapy

	PACIFIC-R FAS	PACIFIC trial (durva. arm)[1]
PFS	N=1,399	N=476
Total events, N (%)	737 (52.7)	268 (56.3)[†]
Progression per RECIST	456 (32.6)	
Progression per physician assessment	170 (12.2)	
Progression, assessment unknown	30 (2.1)	
Deaths in absence of progression	81 (5.8)	
Median PFS, months	**21.7**	**16.9**
95% CI	19.2–24.5	13.0–23.9
PFS rate, %		
12 months	62.4	55.7
24 months	48.2	45.0

Girard N, et al ESMO congress 2021. 1171 MO.

PACIFIC-R Toxicity Data

Durvalumab Treatment Discontinuation

FAS (N=1,399)	Discontinuation reason, n (%)*	Median time from durva. start to discontinuation
Patient decision	20 (1.4)	6.1 months
AE	233 (16.7)	2.8 months
Completed treatment†	659 (47.1)	12.0 months
Disease progression	377 (26.9)	5.1 months
Death	21 (1.5)	1.9 months

- **Pneumonitis/interstitial lung disease (ILD)** was the most common AE leading to (% of FAS):
  - **Permanent** discontinuation: 133 (**9.5%**)‡
  - **Temporary** interruption: 73 (**5.2%**)‡

Pneumonitis/ILD

	FAS (N=1,399)
Patients with any pneumonitis/ILD, n (%)§	250 (17.9)
Mild event¶	56 (4.0)
Moderate event¶	118 (8.4)
Severe event¶	41 (2.9)
Life-threatening or fatal event¶	5 (0.4)

- Median **time to onset** of pneumonitis/ILD from durvalumab initiation: **2.5 months**
- **Corticosteroid** administration was required in **71.3%** of events#

*Other discontinuation reason: missing (n=2), 'other' reasons (n=66), lost to follow-up (n=3), and ongoing durvalumab at time of data extraction (n=16); †Investigator's decision per country protocol and, where applicable, was after >12 months' treatment; ‡Categories are not mutually exclusive (i.e. a single patient could both interrupt and permanently discontinue durvalumab due to pneumonitis/ILD); §37/1,399 patients (2.6%) had pneumonitis/ILD events of unknown severity; ¶Categories are not mutually exclusive – patients experiencing ≥2 events of different severity can be counted under both categories. #A total of 279 pneumonitis/ILD events were reported among the 250 patients who experienced pneumonitis/ILD
AE, adverse event; FAS, full analysis set; ILD, interstitial lung disease

Girard N, et al ESMO congress 2021. 1171 MO.

GenesisCare OLA FLASCO FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

Gaps after PACIFIC and How to Improve

- Patients with limited KPS
- Concurrent immunotherapy with chemoRT
- Neoadjuvant chemoimmunotherapy prior to chemoRT
- Novel adjuvant therapies

Patients with limited Karnofsky's PS

Standard of Care: ~~CCRT~~→durvalumab

Sequential therapy: chemo→ RT→durvalumab[1]

RT alone: RT→durvalumab[2]

Study	Type	Cohort 1	Cohort 2	Study Size	Start	Estimated completion
[1]PACIFIC-6	Phase II	chemo→RT→ Durva (PS 0-1)	chemo→RT→ Durva (PS 2)	117	April 2019	April 2023
[2]DUART	Phase II	RT (60 Gy^) →Durva	RT (40-54 Gy^) →Durva	150	Jan 2020	Nov 2022

^hypofractionation allowed

Concurrent immunotherapy with chemoRT

PACIFIC → Standard of Care: CCRT→ Durvalumab

[1,2]Durvalumab + CCRT → Durvalumab ← (PACIFIC 2)

[3]Nivo +CCRT → Nivo ← (NICOLAS)

[4]Nivo/Ipi +CCRT → Nivo ← (Checkmate 73L)

Study	Type	Arm 1	Arm 2	Study Size	Start	Est. completion
[1]PACIFIC-2	Randomized	Durva+CCRT →Durva	Placebo+CCRT →Placebo	328	March 2018	June 2022
[2]NCT04092283	Randomized	Durva+CCRT →Durva	Placebo+CCRT →Durva	660	April 2020	October 2028
[3]NICOLAS	Phase II, Safety/Efficacy	n = 79	mF-U: 21.0 mos	mPFS: 12.7 mos	mOS: 38.8 mos	2-yr OS: 63.7%
CheckMate 73L	Randomized	Nivo + CCRT+ Ipi (Arm A)	Nivo+CCRT (Arm B) Durva + CCRT (Arm C)	888	July 2019	June 2025

Neoadjuvant chemoimmunotherapy prior to chemoRT:

PACIFIC → Standard of Care: CCRT→durvalumab

Chemo[1]Nivo→ CCRT[2] → Nivolumab / Observation

Study	Type	Arm A	Arm B	Study Size	Start	Est. completion
NCT04085250	Phase II, Randomized	ChemoNivo→ CRT→Nivo	ChemoNivo→ CRT→Observe	264	Nov 2019	Nov 2023

[1]chemo: docetaxel+cisplatin

[2]RT: Hypofractionated

Neoadjuvant chemoimmunotherapy prior to chemoRT:

PACIFIC → Standard of Care: CCRT→durvalumab

Pembro/Chemo[1]→ CCRT + Pembro →Pembro

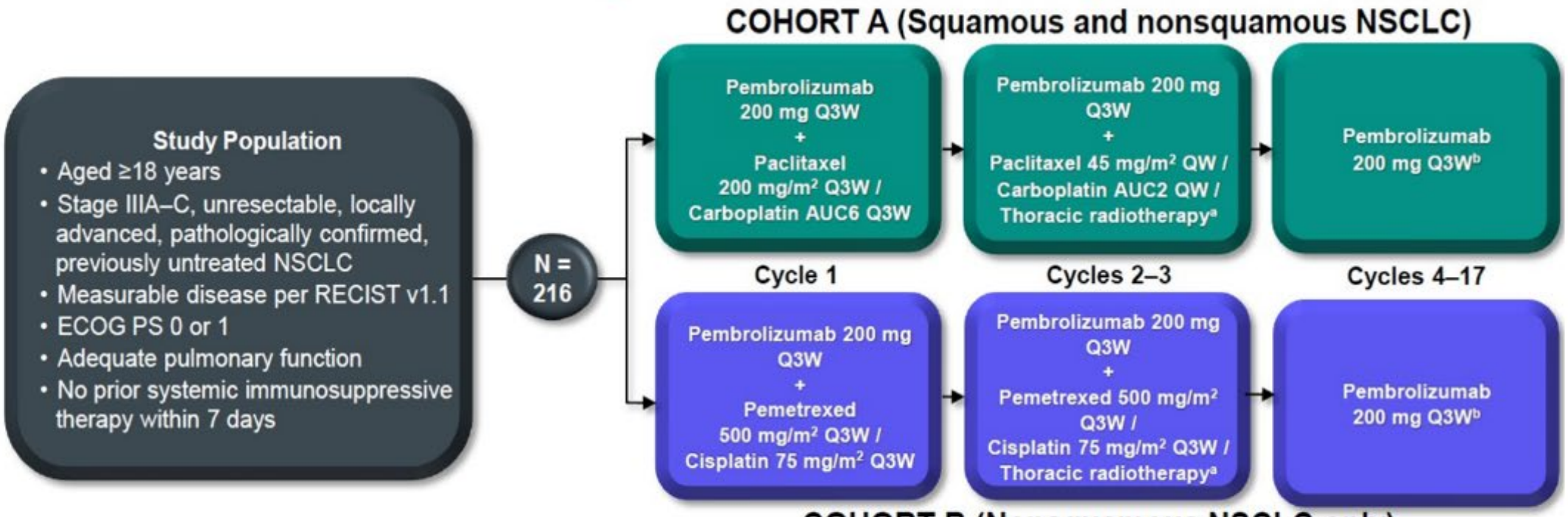
Study	Type	Cohort A	Cohort B	Study Size	Start	Est. completion
[1]Keynote-799	Phase II, nonrandomized	Pembro/Chemo[A] →PembroCRT→ Pembro	Pembro/chemo[B] →PembroCRT→ Pembro	217	Oct 2018	May 2023

[A]chemo: carboplatin+paclitaxel

[B]chemo: cisplatin+pemetrexed

Jabbour SK et al. JAMA Oncol. 2021; 7(9):1-9.

KEYNOTE-799 (NCT03631784)



Primary Objectives

- ORR per RECIST version 1.1 by BICR
- Percentage of patients who develop grade ≥3 pneumonitis

Secondary Objectives

- PFS, OS, safety

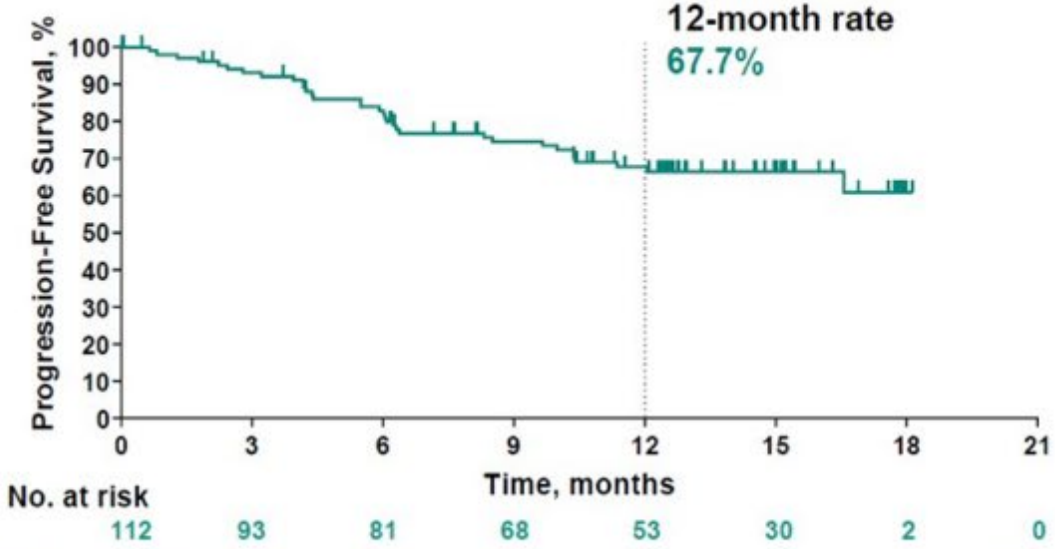
Statistical Analysis Details

- Efficacy assessed in all patients with first study dose before or on October 31, 2019 (PE population)
- Safety assessed in all patients in the as-treated population

Progression-Free Survival
By BICR per RECIST v1.1 (Primary Efficacy Population)

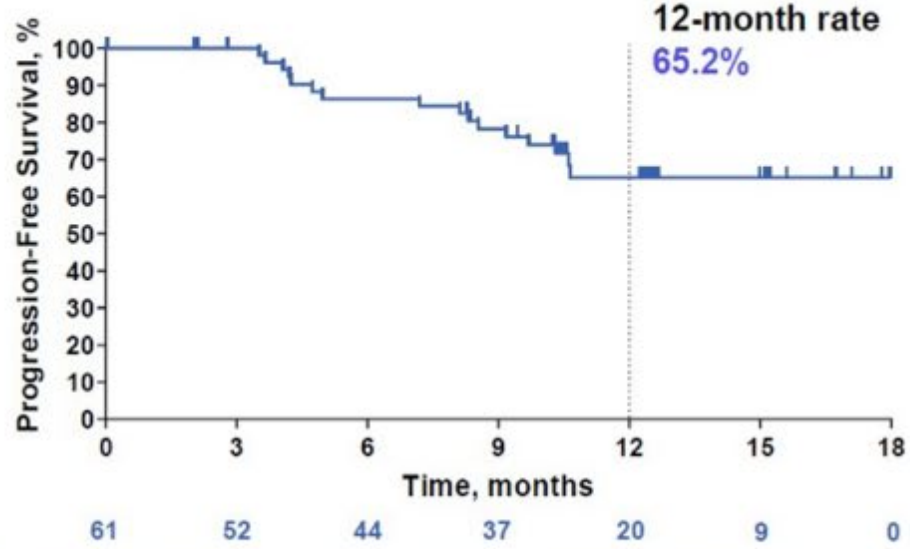
Cohort A[a]

n	Median (95% CI)
112	NR (16.6–NR)



Cohort B[b]

n	Median (95% CI)
61	NR (10.6–NR)

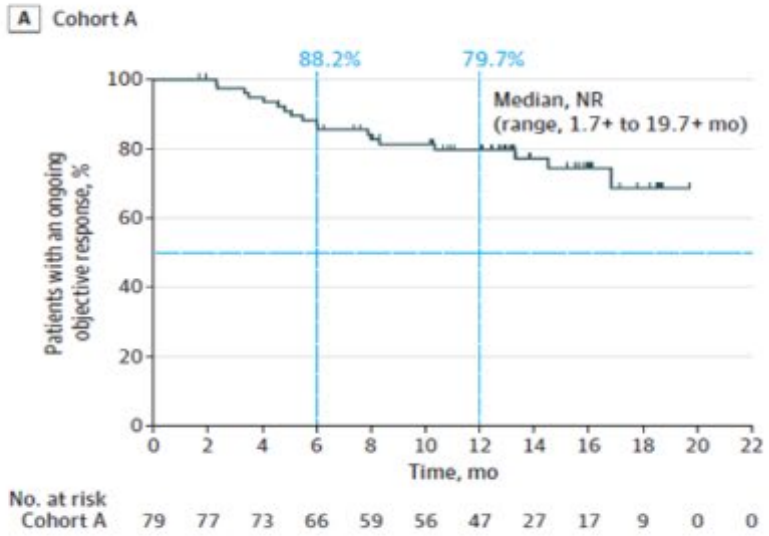


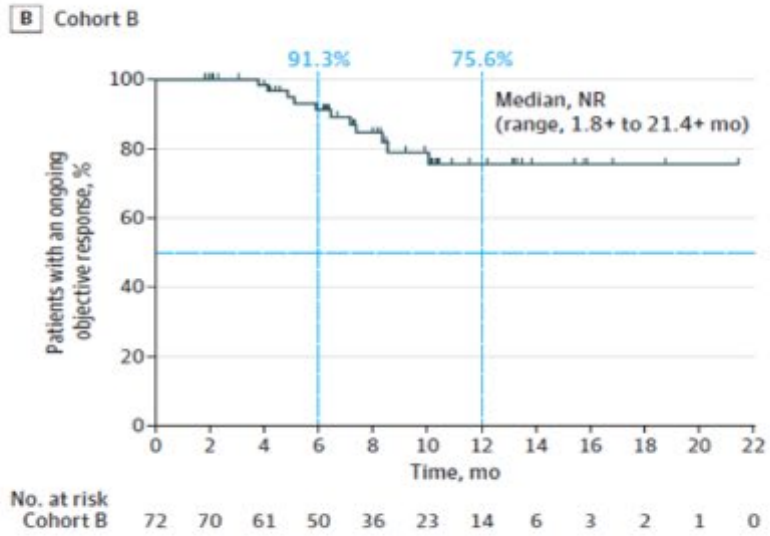
Adverse event	Cohort A (n = 112)		Cohort B (n = 102)	
Occurring in ≥15% of patients in either cohort	Any grade	Grade 3-5	Any grade	Grade 3-5
Radiation pneumonitis	20 (17.9)	2 (1.8)	8 (7.8)	1 (1.0)

KEYNOTE-799

– Primary endpoint:

- Objective response rate
- Grade 3-5 pneumonitis incidence





Jabbour SK et al. JAMA Oncol. 2021; 7(9):1-9.

KEYNOTE-799

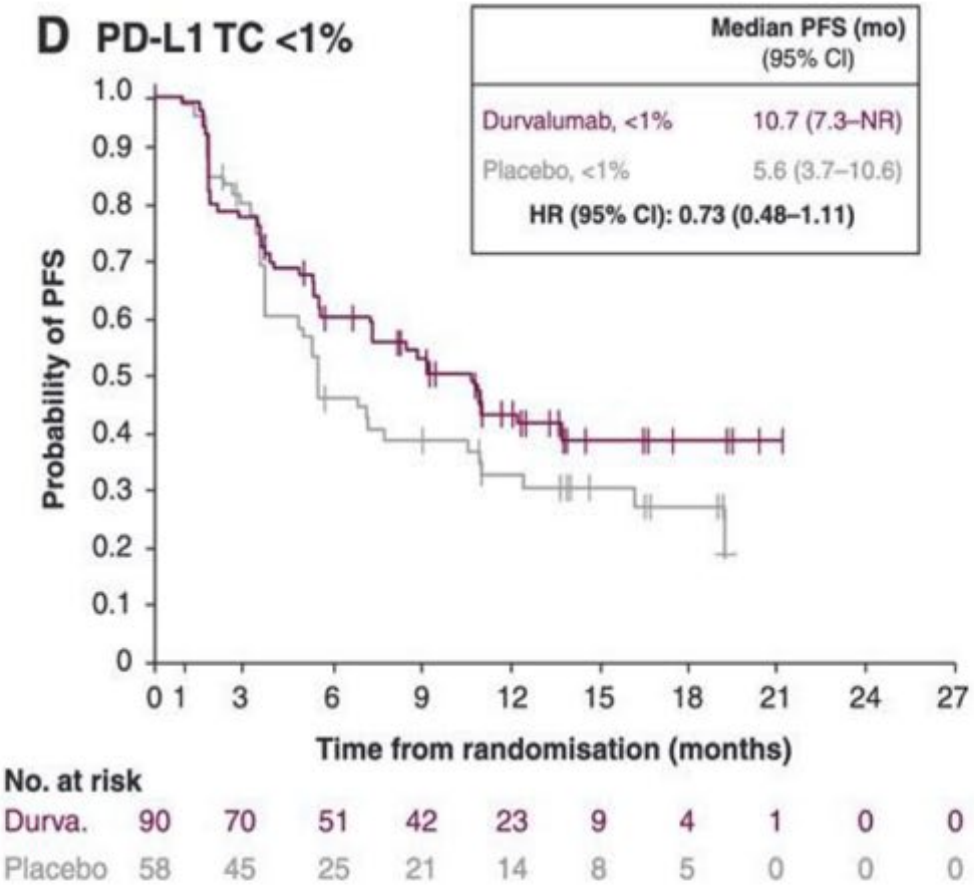
– Primary endpoint:

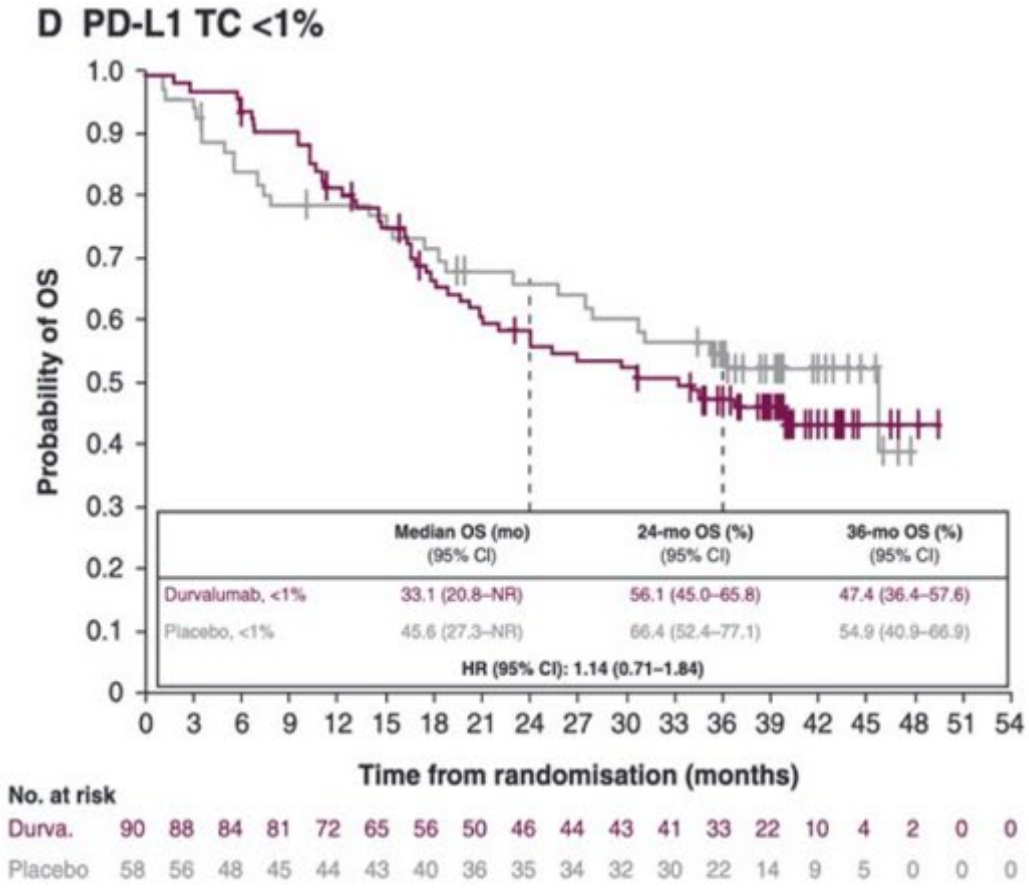
- Objective response rate
- Grade 3-5 pneumonitis incidence

	No. (%)			
Adverse event	Cohort A (n = 112)		Cohort B (n = 102)	
Treatment-related adverse event[a]	105 (93.8)		99 (97.1)	
Grade 3-5	72 (64.3)		51 (50.0)	
Led to discontinuation of any treatment	38 (33.9)		19 (18.6)	
Led to death	4 (3.6)[b]		1 (1.0)[c]	
	Any grade	Grade 3-5	Any grade	Grade 3-5
Pneumonitis	22 (19.6)	7 (6.3)	19 (18.6)	5 (4.9)
Radiation pneumonitis	20 (17.9)	2 (1.8)	8 (7.8)	1 (1.0)

Jabbour SK et al. JAMA Oncol. 2021; 7(9):1-9.

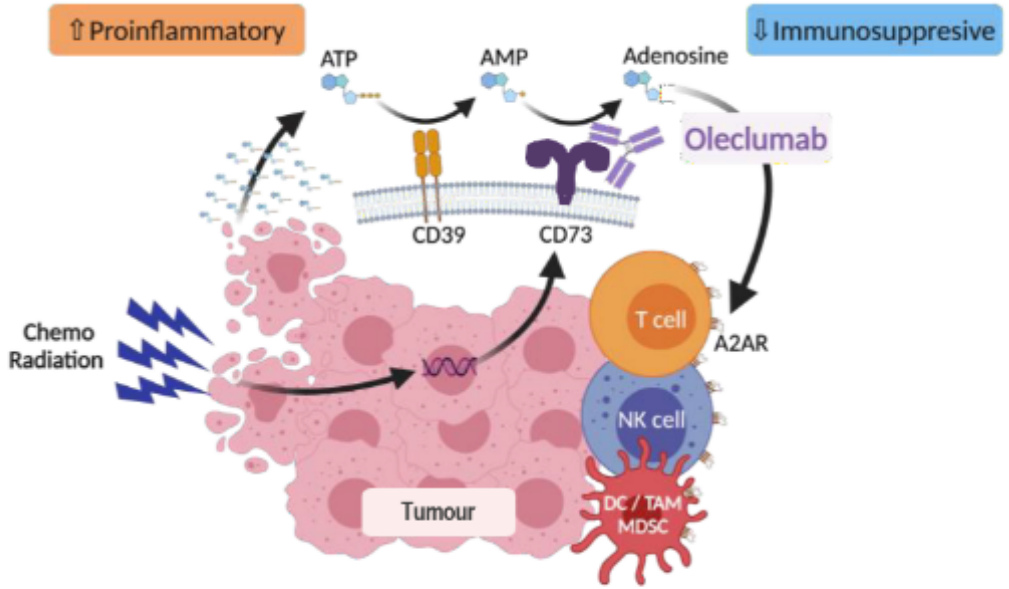
Background from PACIFIC

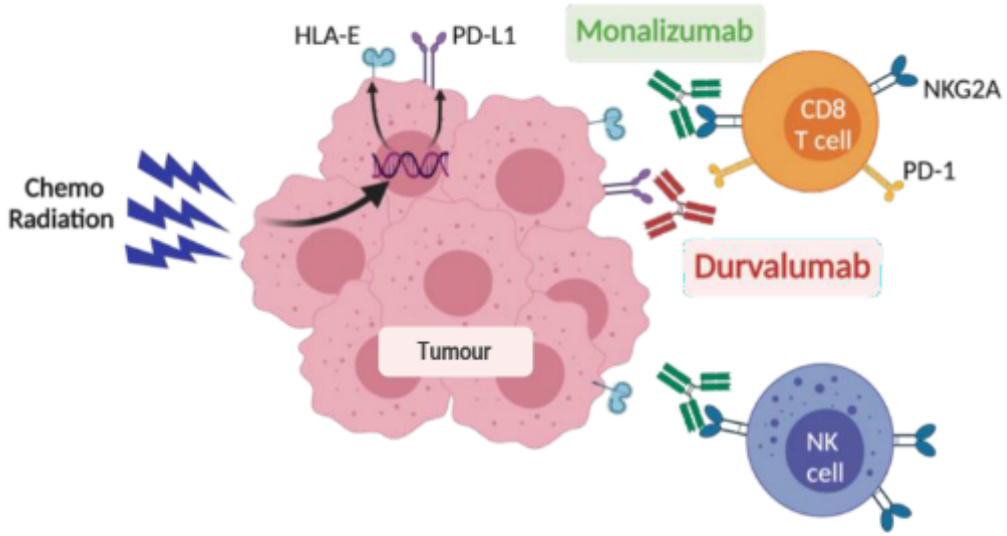




L Paz-Ares, Annals of Oncology, 2020

Rationale for combining durvalumab with oleclumab (anti-CD73) or monalizumab (anti-NKG2A)



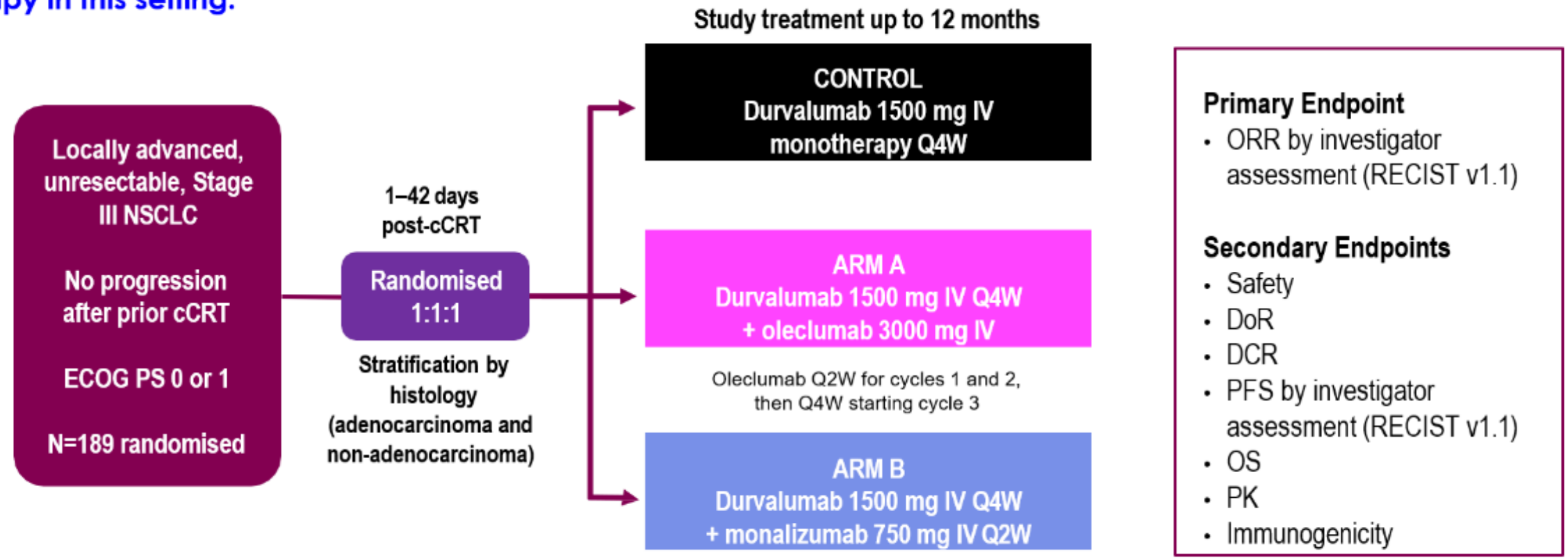


- RT induces expression of CD73 and HLA-E (NKG2A ligand), which inhibit antitumour immune response[1-4]
- Oleclumab inhibits CD73 to reduce extracellular adenosine production, thereby promoting antitumour immunity.[5] Oleclumab combined with durvalumab produced durable responses with manageable safety in a Ph I study of advanced *EGFR*m NSCLC[6]
- Monalizumab blocks NKG2A to reduce inhibition of NK and CD8+ T cells.[7] Monalizumab combined with cetuximab had promising activity with manageable safety in a Ph I/II trial of patients with R/M HNSCC[8]
- Combinations of RT and anti-CD73/NKG2A ± anti-PD-(X) show increased antitumour activity in preclinical models[1,2,4]

ATP, adenosine triphosphate; AMP, adenosine monophosphate; DC, dendritic cell; *EGFR*m, epidermal growth factor receptor mutant; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-(L)1, programmed cell death (ligand) 1; R/M HNSCC, recurrent/metastatic head and neck squamous cell carcinoma; RT, radiotherapy; TAM, tumour-associated macrophages

1. Wennerberg E, et al. Cancer Immunology Res 2020;8:465-478; 2. Tsukui H, et al. BMC Cancer 2020;20:411; 3. Nguyen AM, et al. Mol Cell Proteomics, 2020;19:375-389; 4. Battaglia NG, et al. J Immunol 2020;204:241.24; 5. Geoghegan JC, et al. MAbs 2016;8:454-467; 6. Bendell J, et al. J Clin Oncol 2021;39.no. 15_suppl:9047; 7. André P, et al. Cell 2018;175:1731–1743.e13; 8. Cohen RB et al. J Clin Oncol 38: 2020 (suppl; abstr 6516). Figures created with BioRender.com.

COAST: Combination Platform Study in Unresectable Stage III NSCLC. Phase 2, global, randomized open- label study of durvalumab alone or combined with the anti-CD73 mAb oleclumab or anti-NKG2A mAb monalizumab as consolidation therapy in this setting:



- A planned sample size of 60 patients per arm was designed to provide acceptable precision in estimating antitumour activities in an early phase setting
- Between Jan 2019 and Jul 2020, 189 patients were randomised of whom 186 received D (n=66), D+O (n=59) or D+M (n=61)
- As of 17 May 2021, all patients had a minimum of 10 months potential follow-up and the median actual follow-up was 11.5 months (range, 0.4–23.4; all patients)

D, durvalumab; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; M, monalizumab; O, oleclumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours

Baseline characteristics and prior CRT

Characteristic[a]	D (N=67)	D+O (N=60)	D+M (N=62)
Median age (range), years	66.0 (46–81)	65.0 (37–83)	65.0 (44–87)
Male, %	67.2	70.0	67.7
Race, %			
Asian / White / Other	7.7 / 87.7 / 4.5	6.8 / 79.7 / 13.3	8.1 / 88.7 / 3.2
ECOG PS, %			
0 / 1	45.5 / 54.5	55.9 / 44.1	44.3 / 55.7
Ever smoked, %	94.0	90.0	95.2
Histology, %			
Squamous / Non-squamous	44.8 / 55.2	40.0 / 60.0	43.5 / 56.5
Disease stage at study entry, %			
IIIA / IIIB / IIIC	40.3 / 50.7 / 9.0	45.0 / 48.3 / 6.7	51.6 / 43.5 / 4.8
PD-L1 status, %[b]			
TC ≥1% / TC <1% / Unknown	37.3 / 20.9 / 41.8	38.3 / 11.7 / 50.0	29.0 / 19.4 / 51.6
Prior RT dose, %			
54–66 Gy / >66 Gy	92.5 / 7.5	90.0 / 10.0	91.9 / 8.1
Time from last RT to randomisation, %			
<14 days / 14–28 days / 29–42 days	13.4 / 40.3 / 46.3	6.7 / 45.0 / 48.3	9.7 / 48.4 / 41.9
Prior platinum-based CT, %			
Cisplatin / Carboplatin	34.3 / 64.2	46.7 / 46.7	24.2 / 71.0

Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

[a]One randomised patient in each arm did not receive treatment; [b]28, 30, and 32 patients in the D, D+O, and D+M arms, respectively, were not evaluable for PD-L1 TC expression

CT, chemotherapy; TC, tumour cell

Antitumour activity by investigator assessment (interim analysis; ITT population)

Antitumour activity	D (N=67)	D+O (N=60)	D+M (N=62)
Confirmed ORR (95% CI),[b] %	**17.9 (9.6, 29.2)**	**30.0 (18.8, 43.2)**	**35.5 (23.7, 48.7)**
[n]	[12]	[18]	[22]
Confirmed + unconfirmed ORR (95% CI),[b] %	**25.4 (15.5, 37.5)**	**38.3 (26.1, 51.8)**	**37.1 (25.2, 50.3)**
[n]	[17]	[23]	[23]
ORR odds ratio (95% CI)[a,b]	–	**1.83 (0.80, 4.20)**	**1.77 (0.77, 4.11)**
Objective responses by RECIST,[a] n (%)			
CR	2 (3.0)	1 (1.7)	3 (4.8)
PR	15 (22.4)	22 (36.7)	20 (32.3)
SD	27 (40.3)	25 (41.7)	27 (43.5)
PD	15 (22.4)	7 (11.7)	7 (11.3)
NE	8 (11.9)	5 (8.3)	4 (6.5)
DCR at 16 weeks (95% CI),[a,c] %	**58.2 (45.5, 70.2)**	**81.7 (69.6, 90.5)**	**77.4 (65.0, 87.1)**
[n]	[39]	[49]	[48]
Median DoR (95% CI),[a] months	**NR (2.3, NA)**	**12.9 (6.7, NA)**	**NR (9.0, NA)**
Range	0.0+, 17.5+	0.0+, 16.9+	1.9+, 18.4+

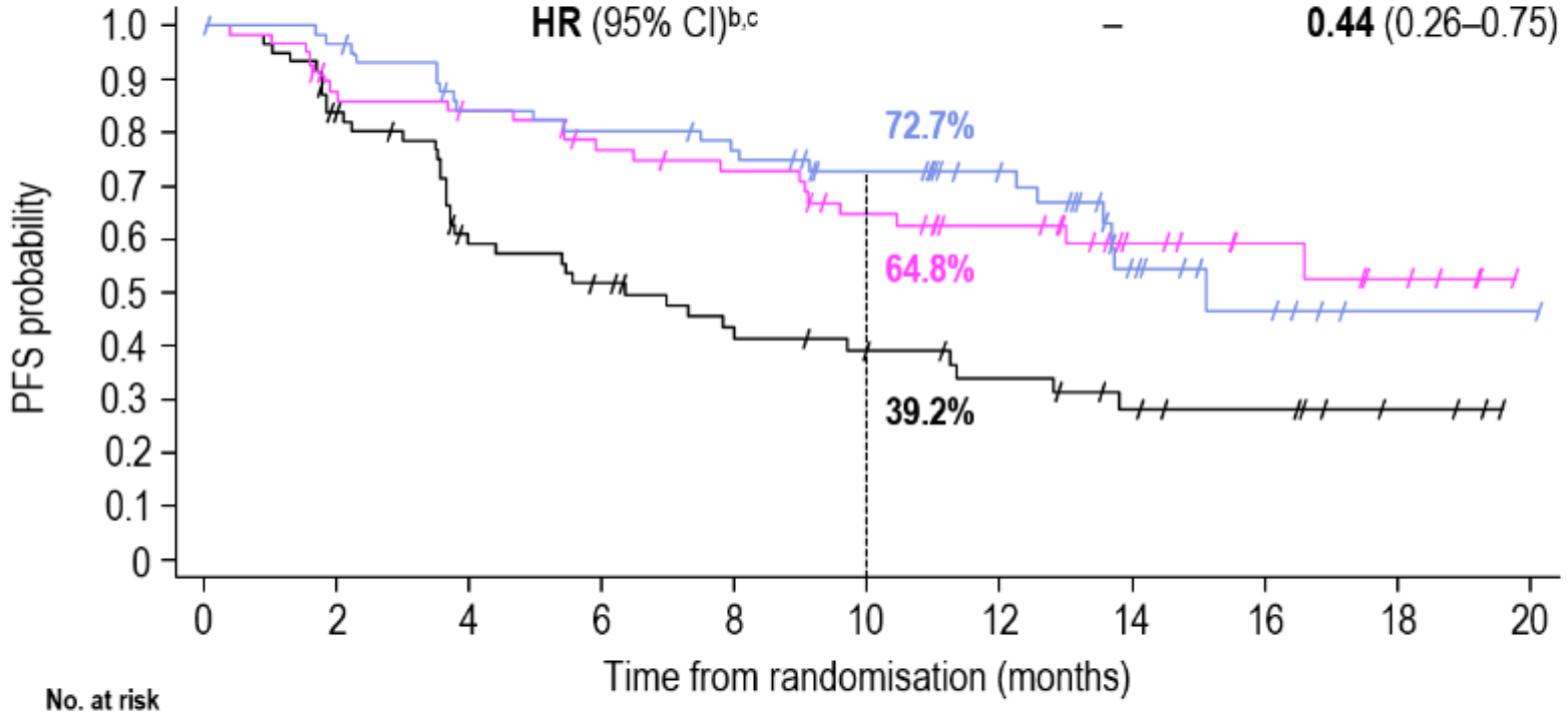
Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

[a]Confirmed and unconfirmed responses; [b]95% CI by Clopper-Pearson exact method; [c]DCR at 16 weeks = CR + PR + SD for ≥16 weeks

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NA, not applicable; NE, not evaluable; NR, not reached; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease

PFS by investigator assessment (interim analysis; ITT population)

	D	D+O	D+M
Events/patients, n	38/67	22/60	21/62
mPFS, months (95% CI)[a]	**6.3** (3.7–11.2)	**NR** (10.4–NE)	**15.1** (13.6–NE)
HR (95% CI)[b,c]	–	**0.44** (0.26–0.75)	**0.65** (0.49–0.85)



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

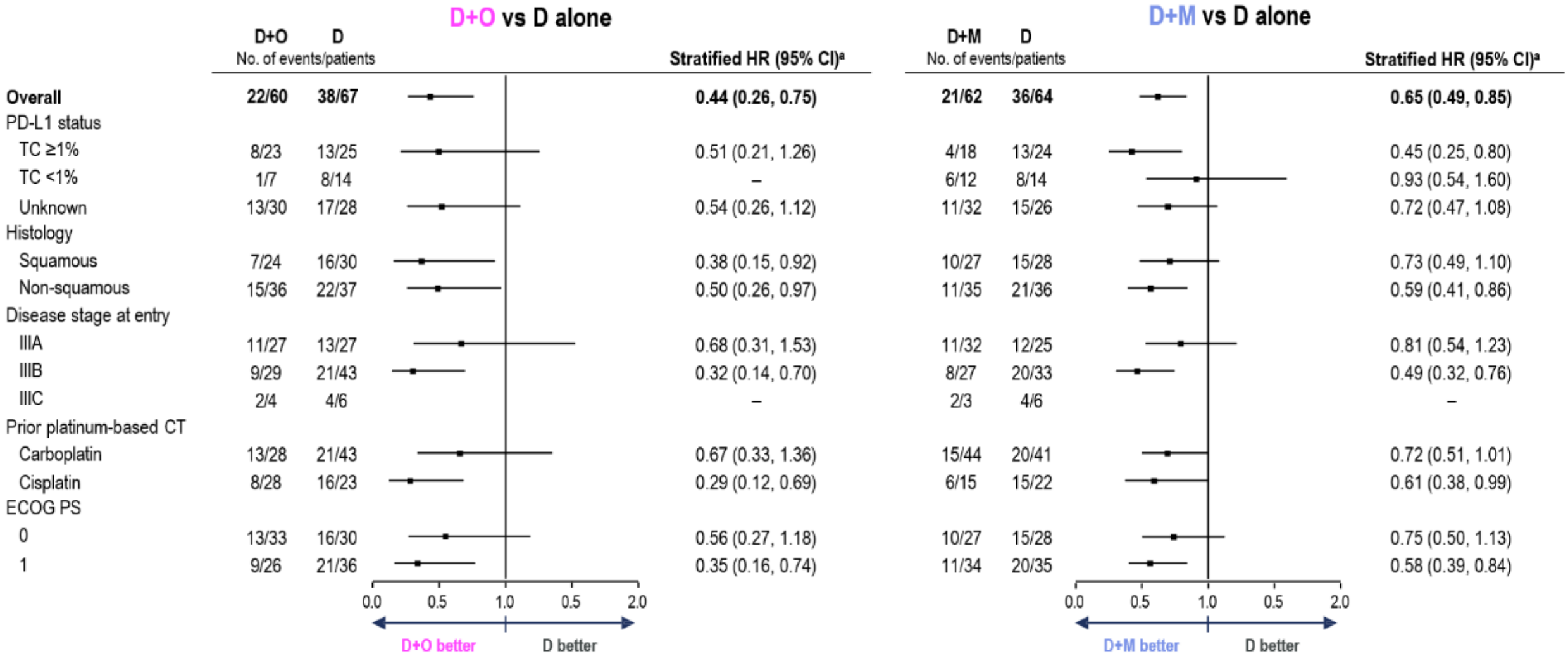
Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

[a]Interim analysis was performed when all patients had a 10-month minimum potential follow-up; Kaplan-Meier estimates for PFS, PFS rate and 95% CIs [b]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and non-adenocarcinoma)

[c]Compared with the 67 and 64 patients in the D arm enrolled concurrently with patients in the D+O and D+M arms, respectively

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; mPFS, median PFS; NE, not estimable; NR, not reached

PFS subgroup analysis by investigator assessment
(interim analysis; ITT population)



Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

[a]PFS HR and 95% CI estimated by Cox regression model, stratified by histology (adenocarcinoma and non-adenocarcinoma)

Safety summary
(as-treated population)

Incidence, n (%)	D (N=66)	D+O (N=59)	D+M (N=61)
Any TEAEs	65 (98.5)	57 (96.6)	61 (100)
Grade ≥3 TEAEs	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs	6 (9.1)	7 (11.9)	5 (8.2)
AEs leading to discontinuation	11 (16.7)	9 (15.3)	9 (14.8)
Deaths[a,b]	7 (10.6)	4 (6.8)	3 (4.9)

[a]All reported deaths within 90 days post-last dose, regardless of relationship to study drug
[b]In total, 4 deaths were related to study drug, 2 (pneumonitis and radiation pneumonitis) in the D arm, 1 (pneumonitis) in the D+O arm, and 1 (myocardial infarction) in the D+M arm

Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

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TEAEs occurring in >15% of patients in any arm (all causality; as-treated population)

Preferred term, n (%)	D (N=66)		D+O (N=59)		D+M (N=61)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Patients with ≥1 TEAE	65 (98.5)	23 (34.8)	57 (96.6)	21 (35.6)	61 (100)	16 (26.2)
Cough	12 (18.2)	0	18 (30.5)	1 (1.7)	27 (44.3)	0
Dyspnoea	17 (25.8)	2 (3.0)	15 (25.4)	1 (1.7)	14 (23.0)	1 (1.6)
Pruritus	7 (10.6)	0	10 (16.9)	0	15 (24.6)	0
Asthenia	10 (15.2)	0	10 (16.9)	0	14 (23.0)	0
Hypothyroidism	10 (15.2)	0	9 (15.3)	0	12 (19.7)	0
Diarrhoea	7 (10.6)	1 (1.5)	7 (11.9)	0	12 (19.7)	0
Pneumonitis[a]	11 (16.7)	0	11 (18.6)	0	10 (16.4)	1 (1.6)
Arthralgia	11 (16.7)	0	9 (15.3)	0	10 (16.4)	0
Pyrexia	6 (9.1)	0	8 (13.6)	0	10 (16.4)	0
Rash	6 (9.1)	0	9 (15.3)	0	8 (13.1)	0
Constipation	10 (15.2)	0	4 (6.8)	0	2 (3.3)	0

[a]In addition, radiation pneumonitis of any grade (grade 3/4) occurred in 3 (1), 7 (0), and 3 (0) patients in the D, D+O, and D+M arms, respectively

Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

AESIs for durvalumab (as-treated population)

Grouped term, n (%)	D (N=66)	D+O (N=59)	D+M (N=61)
	All Grades	All Grades	All Grades
Any AESI	37 (56.1)	36 (61.0)	41 (67.2)
Pneumonitis	12 (18.2)	12 (20.3)	11 (18.0)
Rash	6 (9.1)	12 (20.3)	14 (23.0)
Hypothyroid events	10 (15.2)	9 (15.3)	12 (19.7)
Diarrhoea	7 (10.6)	7 (11.9)	12 (19.7)
Hyperthyroid events	8 (12.1)	6 (10.2)	6 (9.8)
Dermatitis	4 (6.1)	4 (6.8)	2 (3.3)
Hepatic events	3 (4.5)	1 (1.7)	0
Other rare/miscellaneous[a]	0	0	2 (3.3)
Renal events	0	1 (1.7)	0
Infusion related reaction	0	1 (1.7)	0
Type 1 diabetes mellitus	0	0	1 (1.6)
Colitis	1 (1.5)	0	0
Hypersensitivity/anaphylactic reactions	1 (1.5)	0	0
Myositis	1 (1.5)	0	0

[a]Includes iridocyclitis and pericarditis

Data cutoff: 17 May 2021 (median follow-up of 11.5 months; range, 0.4–23.4)

AESI, adverse event of special interest

Global Lung Cancer Academy

SAVE THE DATE

Sharing Best Practices to Optimize Patient Care in Lung Cancer

PACIFIC-9:

A Global Study to Assess the Effects of Durvalumab With Oleclumab or Durvalumab With Monalizumab Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer.

GenesisCare

OLA Oncology Latin American Association

FLASCO

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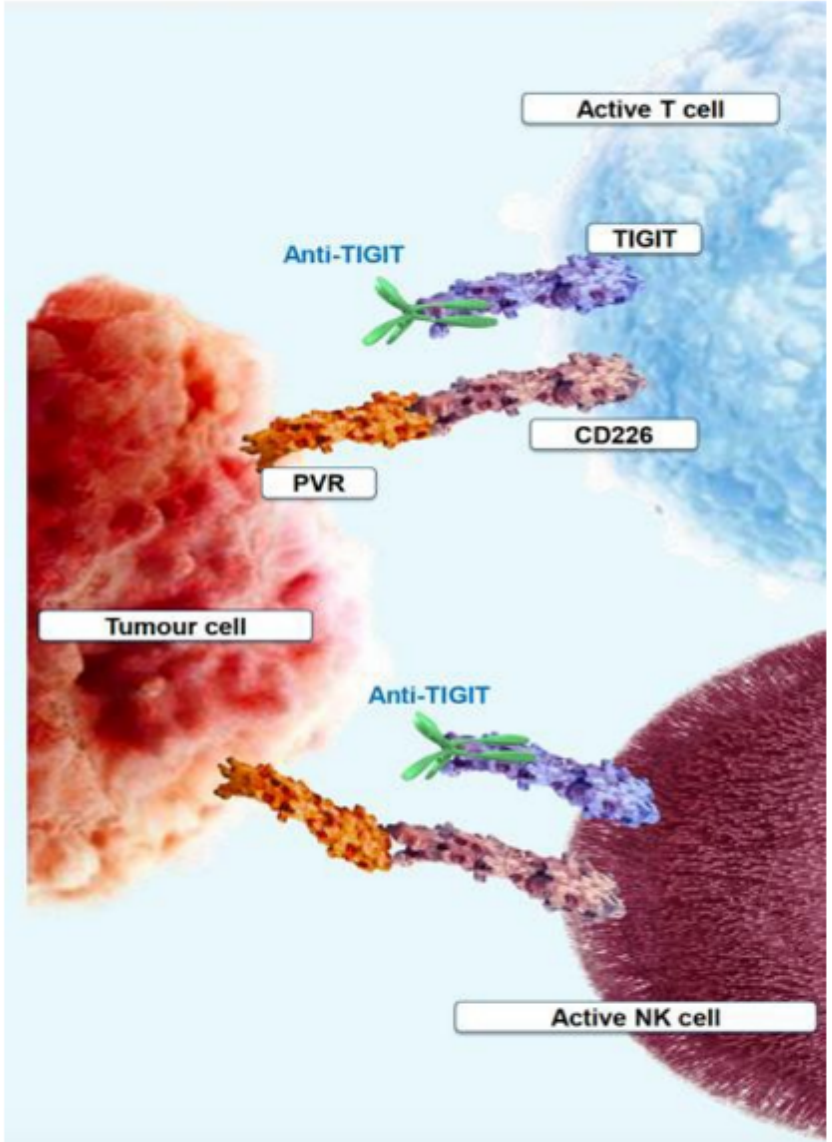
Anti-TIGIT Antibodies:

- TIGIT is a novel inhibitory checkpoint on activated T cells and NK cells.
- Tiragolumab is a fully human IgG1/kappa anti-TIGIT monoclonal antibody; blocks binding to its receptor PVR.
- Inhibition of TIGIT/PVR may amplify the durability / duration of anti-tumor response of anti-PD-L1/PD-1 antibodies



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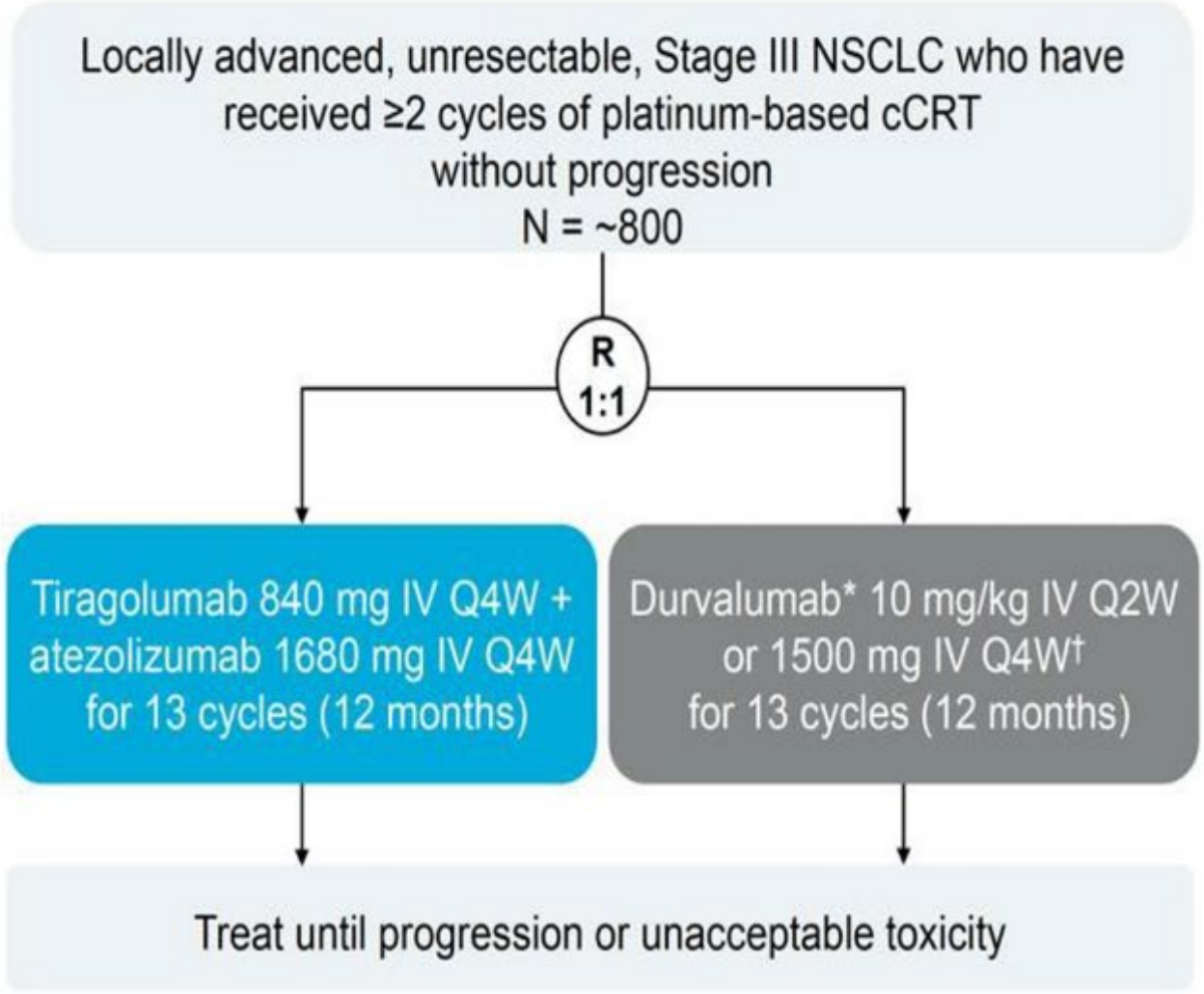

*Durvalumab at Q2W or Q4W based on the investigator in consultation with the patient and/or local standard of care;
†For patients who weigh ≥30 kg; Q2W, once every 2 weeks; Q4W, once every 4 weeks; IV, intravenous

Primary endpoint: PFS by independent review facility assessment per RECIST v1.1

Key secondary endpoints: OS, investigator-assessed PFS, ORR, DOR, PFS and OS rates at 12, 18 and 24 months

Safety, pharmacokinetics, immunogenicity and biomarkers will also be evaluated

Global Lung Cancer Academy

SAVE THE DATE

Sharing Best Practices to Optimize Patient Care in Lung Cancer

PACIFIC-8:

A Global Study to Assess the Effects of Durvalumab + Domvanalimab Following Concurrent Chemoradiation in Participants With Stage III Unresectable NSCLC.

GenesisCare

OLA Oncology Latin American Association

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Global Lung Cancer Academy

Global Lung Cancer Academy

Sharing Best Practices to Optimize Patient Care

21 & 24 October – LATAM and Canada

APTITUDE HEALTH

Role of Targeted Therapies Following Chemo-RT

GenesisCare

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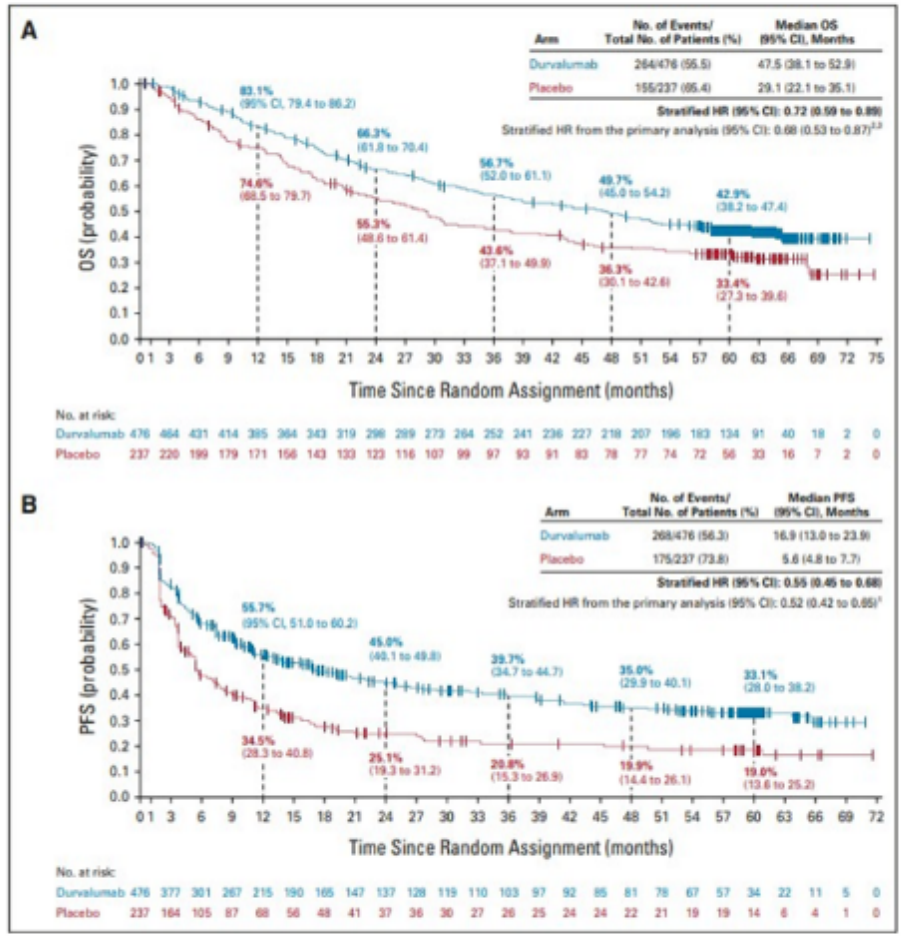
Outcomes in Unresectable Stage III NSCLC

- Despite improvements in chemoRT over the last 2 decades, outcomes for unresectable stage III NSCLC have been poor

- Recently updated outcomes for PACIFIC
  - 5-yr OS- 42.9% vs. 33.4%
  - 5-yr PFS- 33.1% vs. 19%

- Though Durvalumab significantly improves OS and PFS, most patients are still not cured and less than 1/3 are alive without progression at 5 years



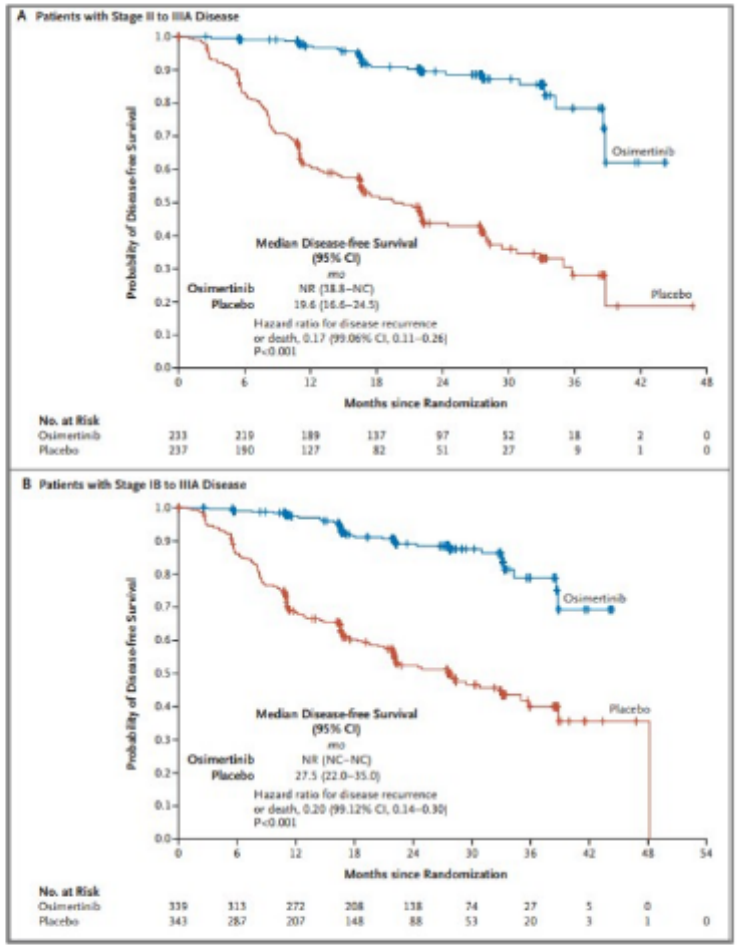
Previous Targeted Therapy Trials

- Unfortunately, prior targeted therapy trials in stage III NSCLC have been unsuccessful in changing the standard of care

- Most have utilized early generation EGFR inhibitors or PARP inhibition
  - EGFR/ALK
    - CALGB 30106
    - SWOG S0023
    - Rigas et al
    - RTOG 1306 (induction TKI)
  - PARP
    - SWOG 1206
    - M14-360

Rationale for Consolidation Targeted Therapy

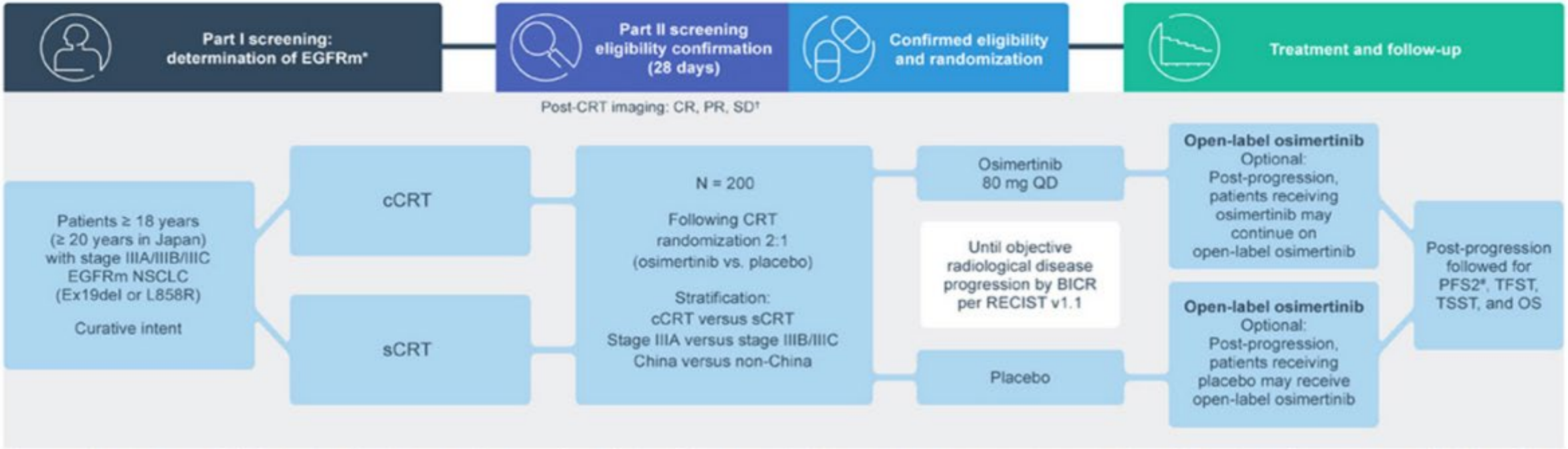
- Some patients are not candidates for consolidation immune therapy (e.g. transplant, autoimmune disease) or are at high risk for AEs.
- EGFR-m patients may have worse outcomes after chemoradiation compared to EGFR-wt.
- Significantly improved DFS in the adjuvant setting (ADAURA) and high rates of activity and improved clinical outcomes in stage IV.



Qin et al. Expert Rev Anticancer Ther 2019;19(6):533-539.
Wu et al. N Eng J Med 2020;383:1711-23.

Ongoing Trials

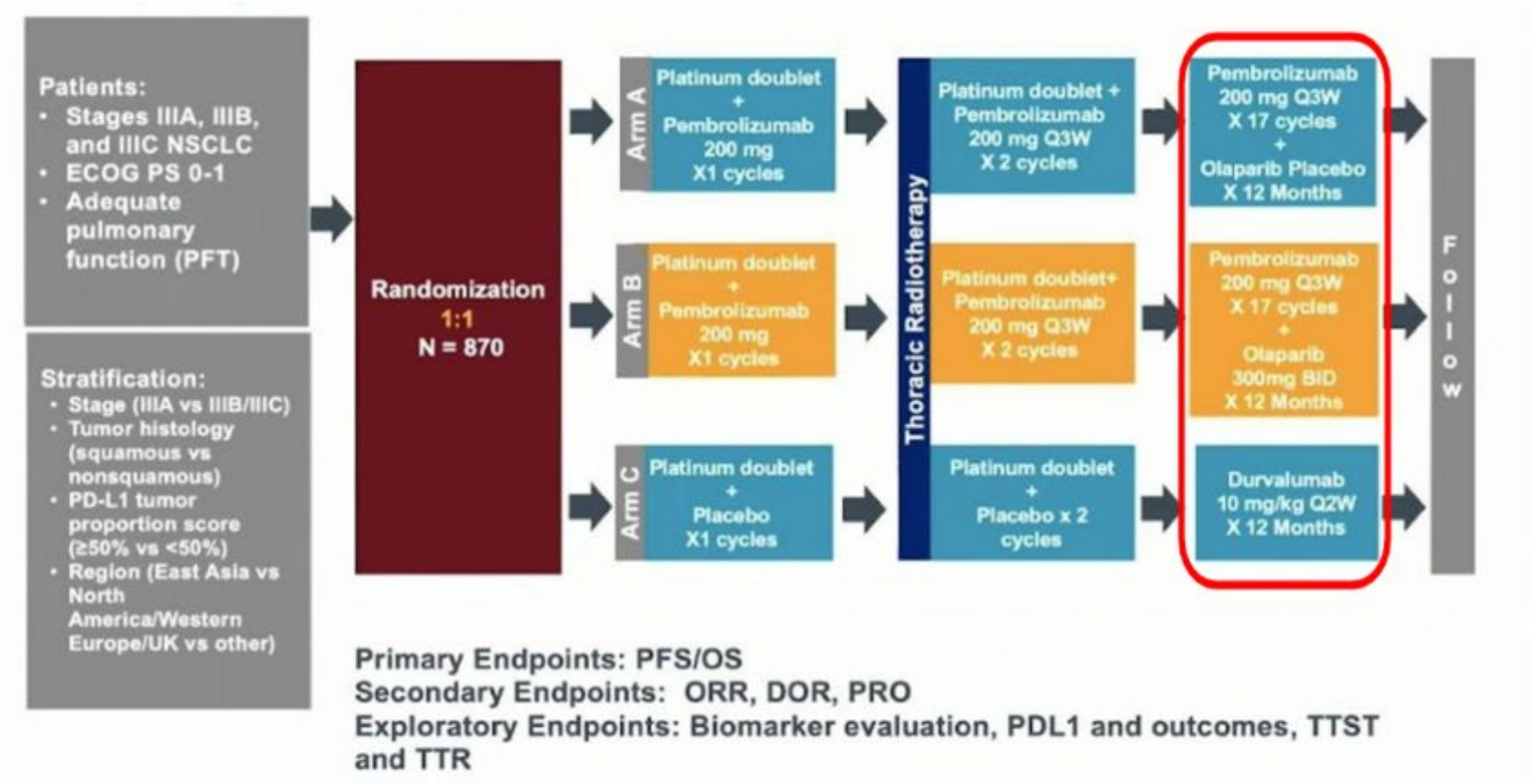
- **LAURA Trial (NCT03521154)**
  - Osimertinib Maintenance After Definitive Chemoradiation in Unresectable EGFR Mutation+ Stage III NSCLC
  - Primary Endpoint- BICR- confirmed PFS
  - Secondary Endpoints- CNS PFS, OS, PFS by mutation status, safety
  - 1st pt- July 2018
  - Expected results- late 2022



*Patients with a local cobas® EGFR Mutation Test v2 tissue positive result from a CLIA-certified or accredited laboratory do not require part I screening. †Post-CRT imaging performed to assess CR, PR and SD up to 28 days before randomization. ‡Assessment of PFS2 will not be collected after the primary PFS analysis.

Ongoing Trials

- KEYLYNK-012 (NCT04380636)
  - ChemoRT +/- Pembro → Pembro +/- Olaparib vs. Durvalumab

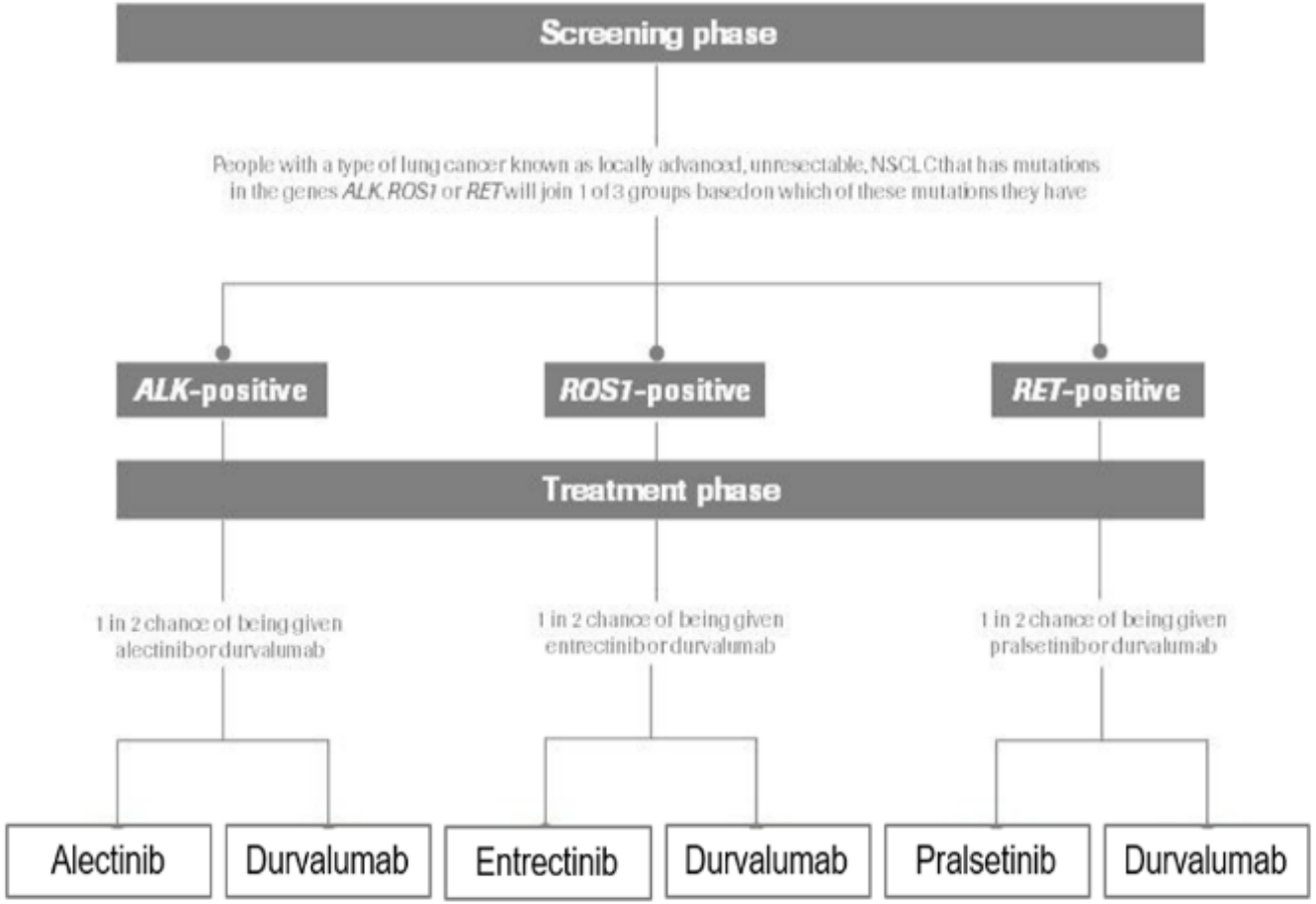


Start date- July 2020

Estimated End- July 2026

Ongoing Trials

- Roche Study
  - Consolidation targeted agent vs. SOC immunotherapy
  - 3 cohorts (ALK, ROS1, and RET positive)
  - All cohorts randomized against Durvalumab
  - Targeted tx duration- 3 years
  - Planned enrollment- 320 pts
  - Not yet open



Conclusion

- The placebo-controlled, Phase 3 PACIFIC study established consolidation durvalumab as SOC for patients with unresectable Stage III NSCLC who have not progressed after cCRT.
  - Five-year data from PACIFIC demonstrated robust and sustained OS plus durable PFS benefit with durvalumab in this patient population
    - **42.9% remain alive** and **33.1% remain alive and progression-free** at 5 years

- COAST is the **first randomised Phase 2 study** to show evidence of improved outcomes with novel IO combinations in the PACIFIC setting ("additional immunomodulation").

- Both combinations (D+O and D+M) numerically increased ORR and significantly improved PFS versus durvalumab alone:
  - PFS benefit with both combinations was observed across various subgroups, including those based on histology, ECOG PS, prior platinum-based CT, and PD-L1 status.

- Addition of an anti-TIGIT antibody to immunotherapy following concurrent chemoradiation is under investigation.

- Consolidation with targeted therapies following chemoradiation for stage III NSCLC is a promising strategy; a number of trials are underway in EGFR, ALK, ROS1, RET, and PARP to evaluate this approach.

- Biomarkers are needed to identify those who may benefit most from escalation of therapy.

GenesisCare OLA FLASCO FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

Global Lung Cancer Academy

Targeted Therapies for Advanced NSCLC

Barbara Melosky, MD, FRCP

Targeted Therapies for NSCLC

Dr Barb Melosky

BC Cancer Vancouver Canada

Conflict of Interest

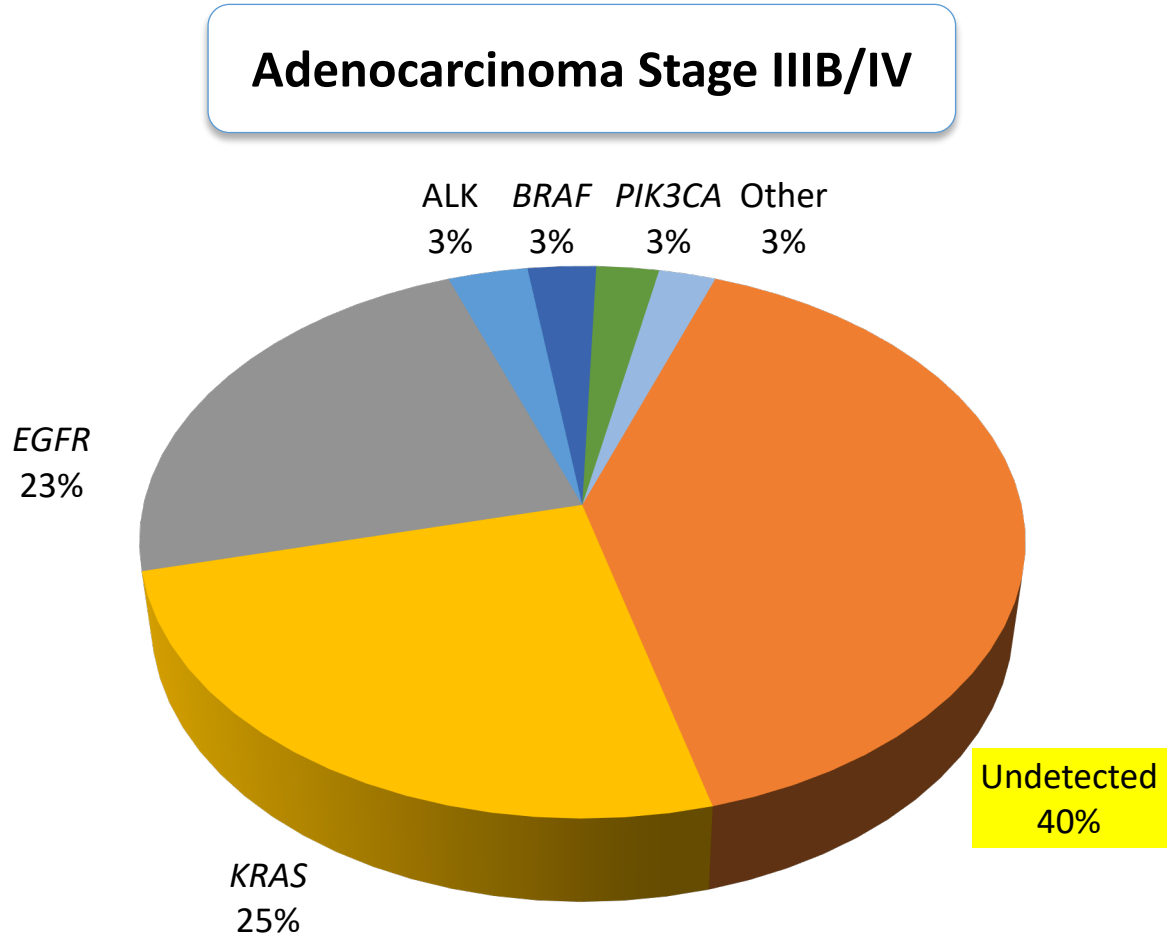
- Advisory Board/Honorarium
  - AstraZeneca, Pfizer, Roche, Janssen, BMS, Merck, Boehringer Ingelheim, Jazz, Novartis, Eisai, Takeda, Merck, Serono

Objectives

- Review the main driver mutations in non-squamous NSCLC
- Discuss targeted therapy that is approved/exists for those driver mutations
- Highlight the “other” driver mutations/targeted therapies that have exploded onto the scene

2011

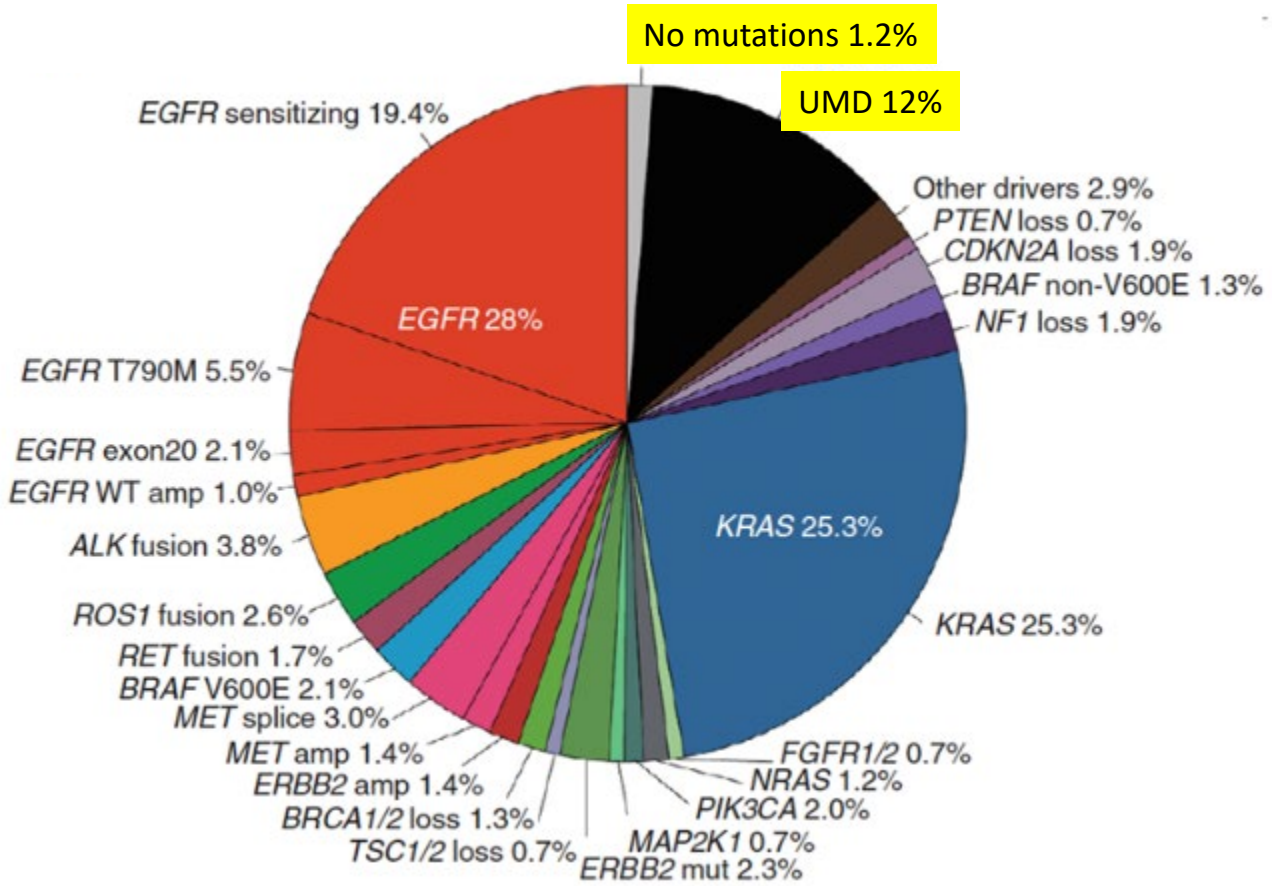
Prevalence of Mutations: Lung Cancer Mutation Consortium (LCMC)



Kris MG, et al. *J Clin Oncol.* 2011;29:CRA7506.

2018

Adenocarcinoma Stage IIIB/IV

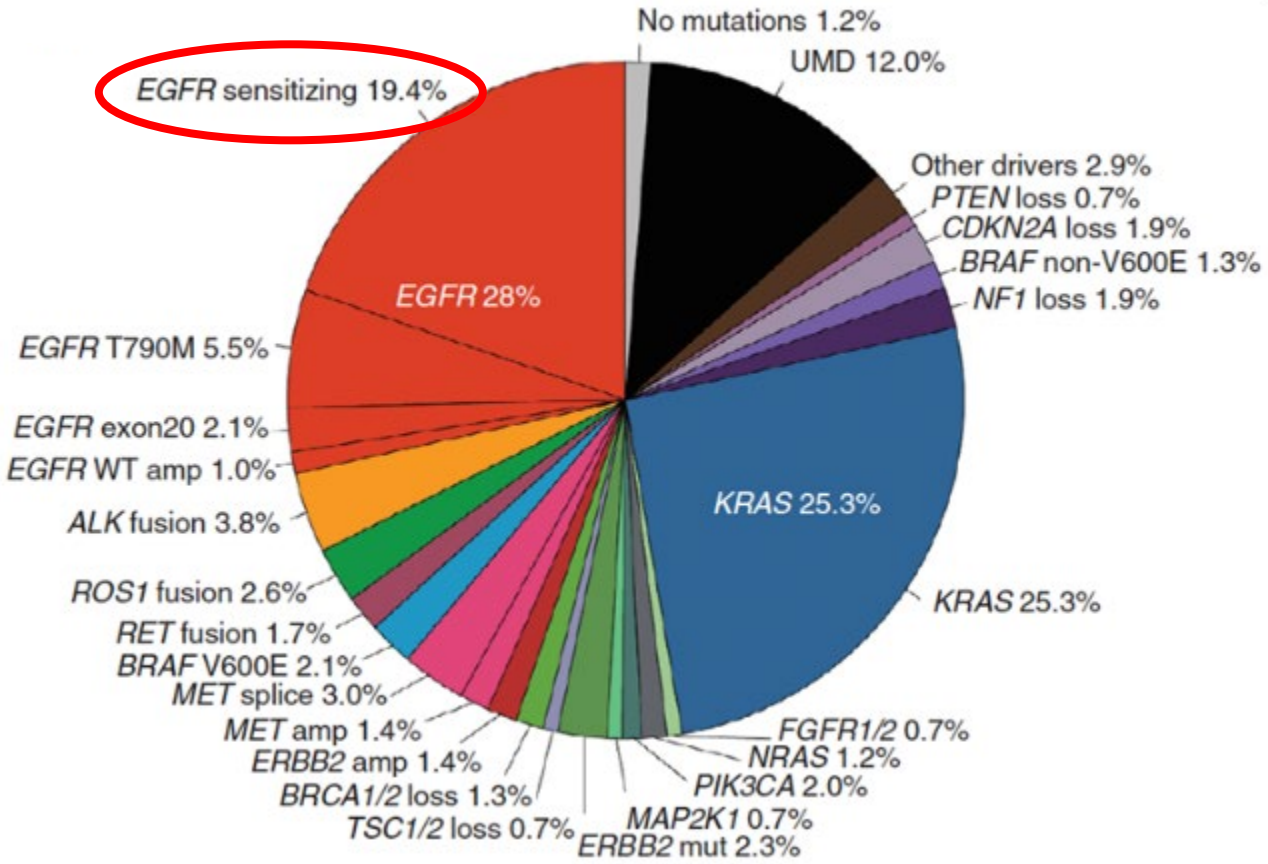


Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

Outline

- The Big 4 that should be standard of care for testing
  - *EGFR, ALK, ROS, BRAF*
- Other
  - *MET, HER2, RET, NTRK,* and *KRAS*

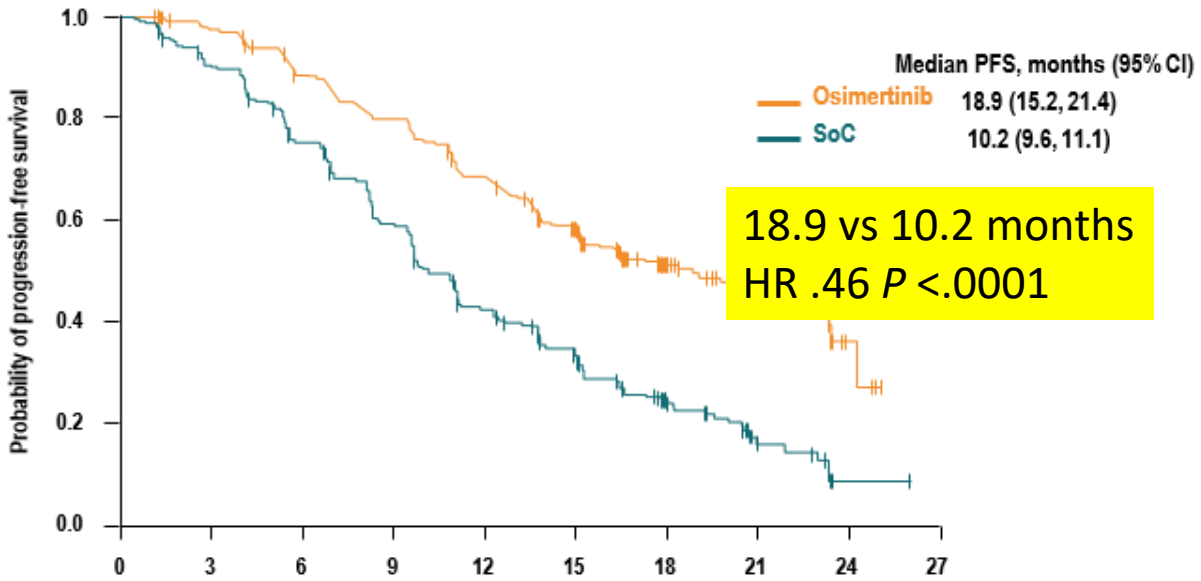
EGFR



Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

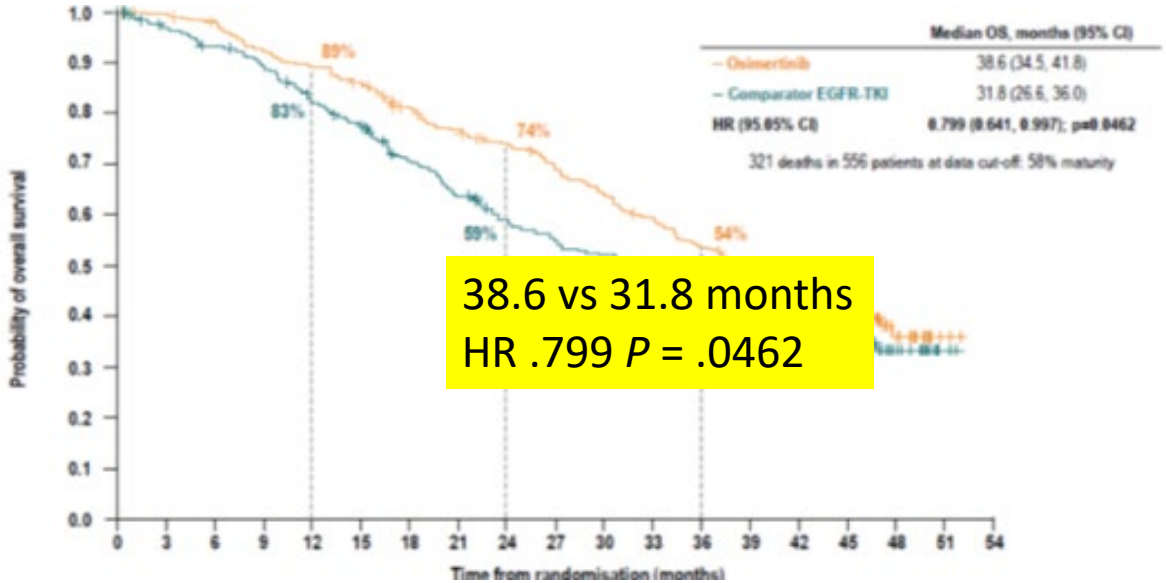
FLAURA

PFS



18.9 vs 10.2 months
HR .46 *P* <.0001

OS

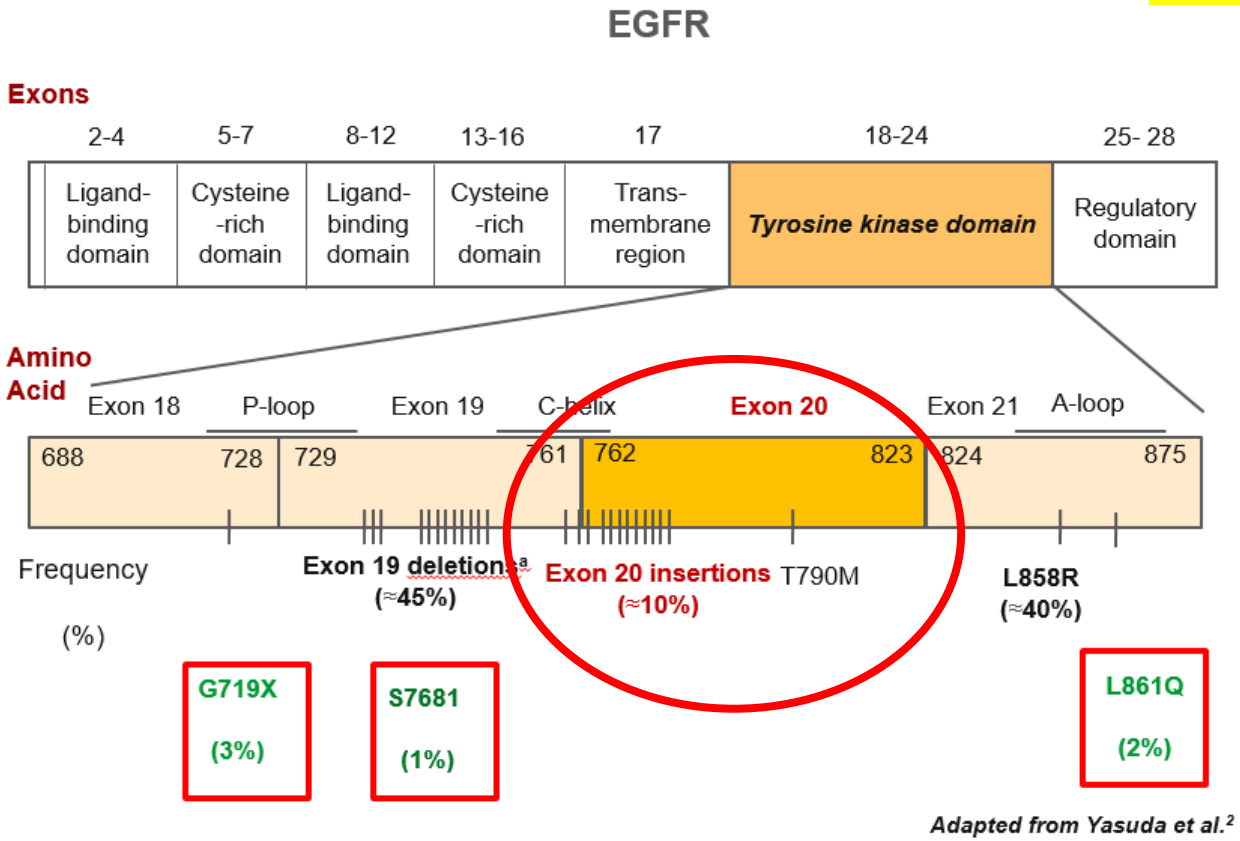


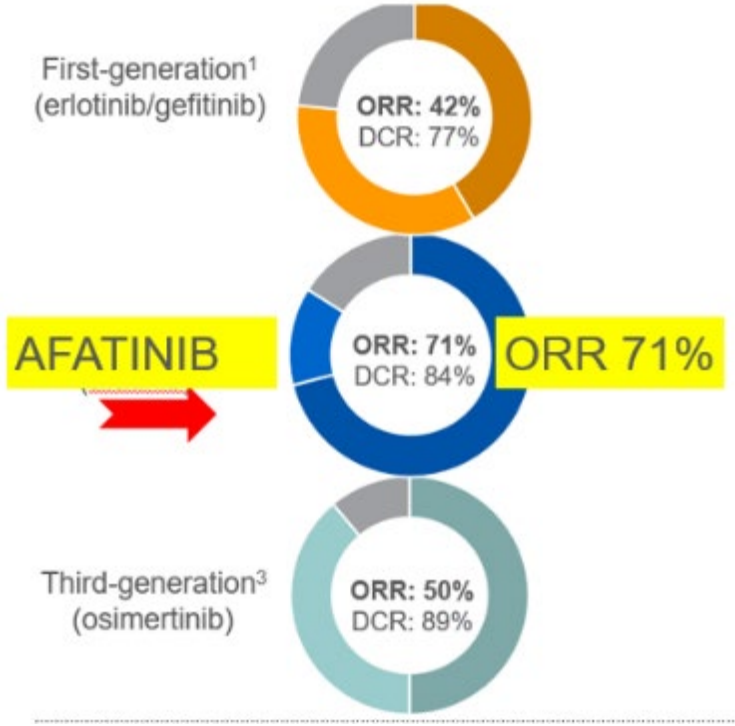
38.6 vs 31.8 months
HR .799 *P* = .0462

Soria JC, et al. *N Engl J Med*. 2018;378:113-125.

Uncommon *EGFR* Mutations

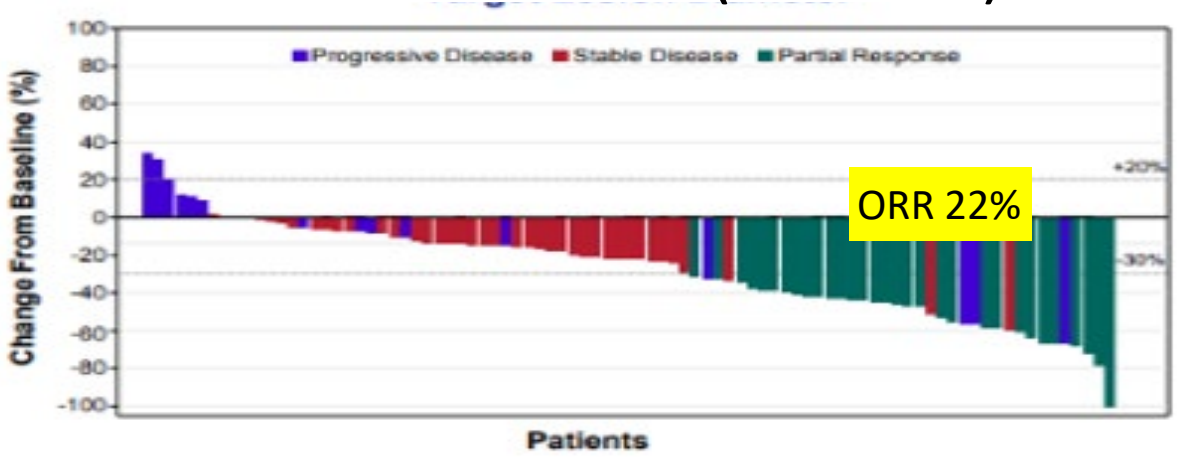
Afatinib is FDA approved for G719X, S768I, and L861Q





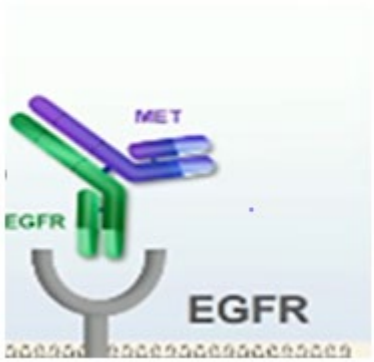
EXON 20 Insertion

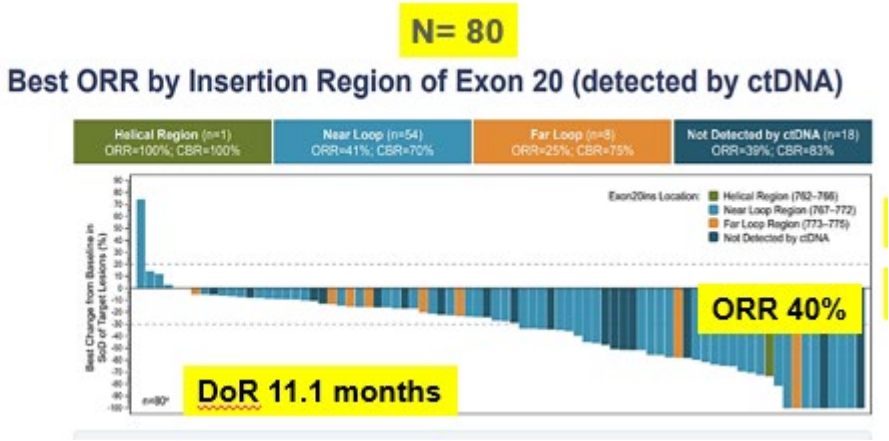
Mobocertinib (TAK-788)



Zhou C, et al. WCLC 2020. OA04.03 (Oral).

Amivantamab





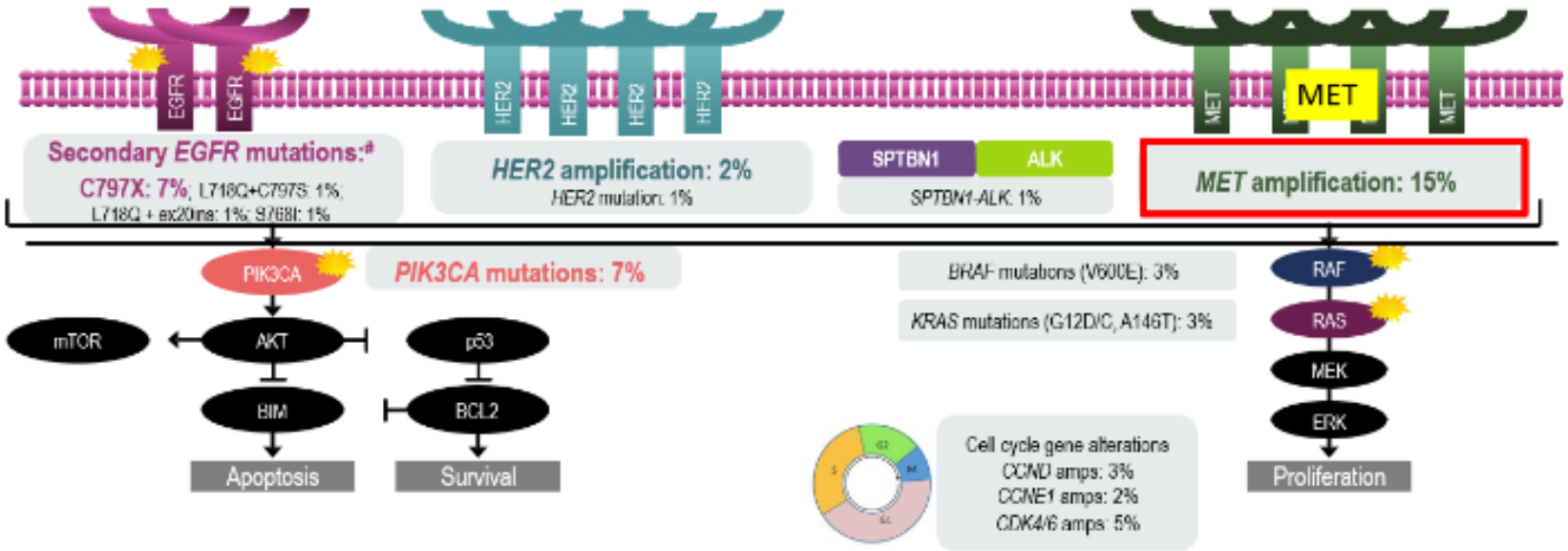
PFS 8.3 months

OS 22.8 months

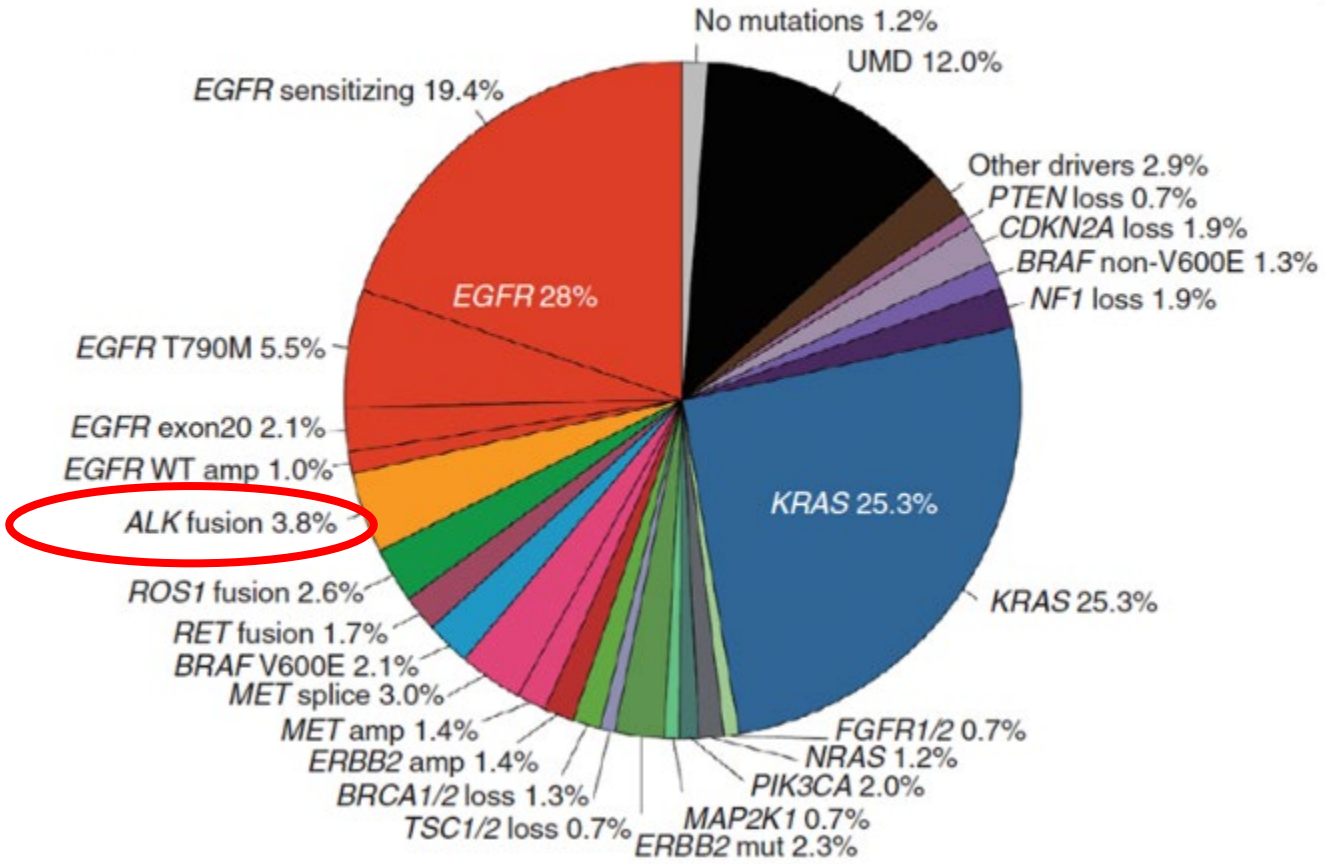
Sabari JK, et al. WCLC 2020. OA04.04 (Oral).

Big Question in *EGFR* Lung

- What do you do when osimertinib stops working?



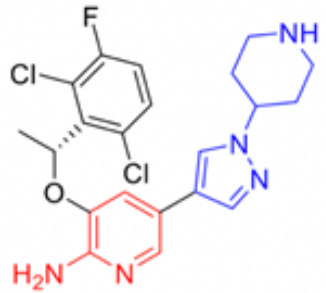
ALK



Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

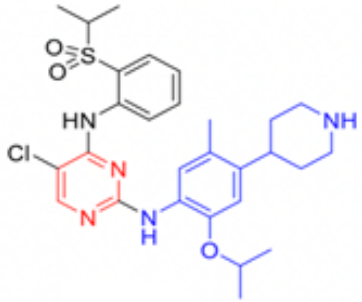
First-Generation

Crizotinib

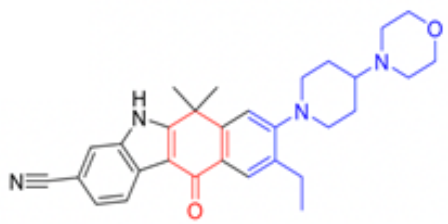


Second-Generation

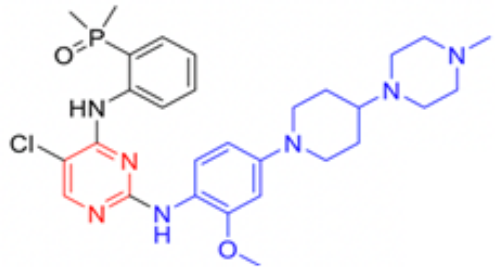
Ceritinib



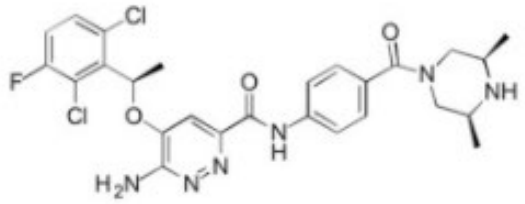
Alectinib



Brigatinib

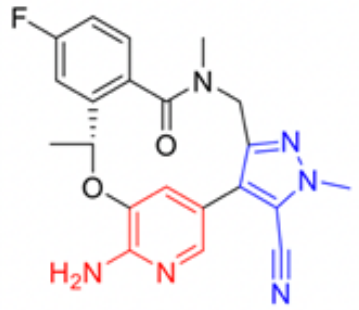


Ensartinib



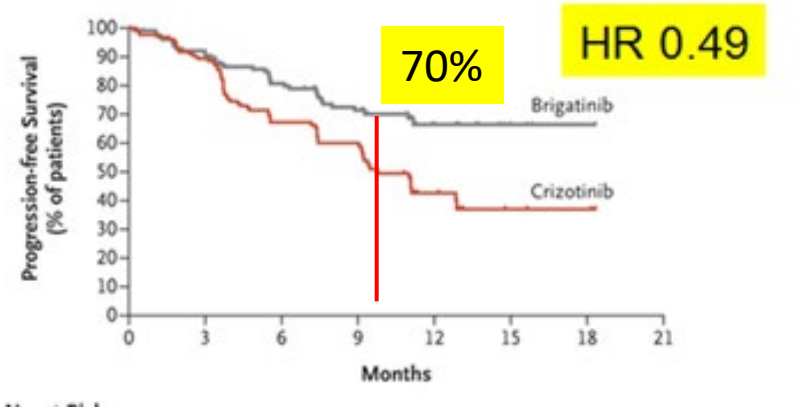
Third-Generation

Lorlatinib

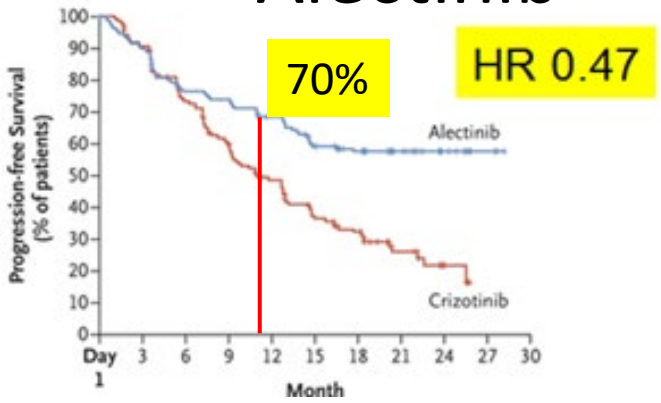


PFS

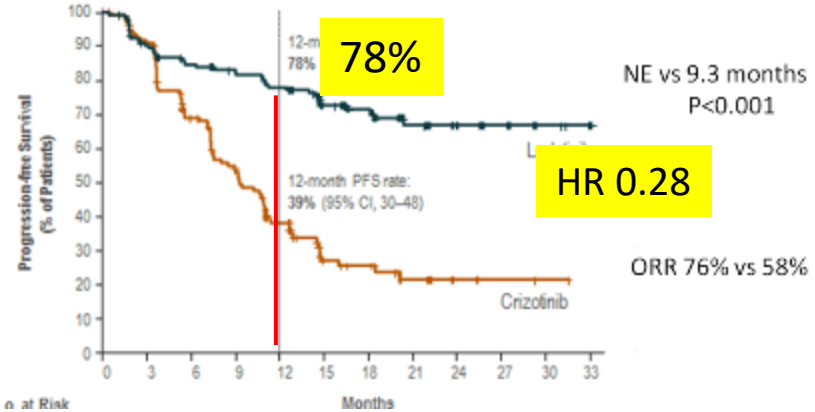
Brigatinib



Alectinib



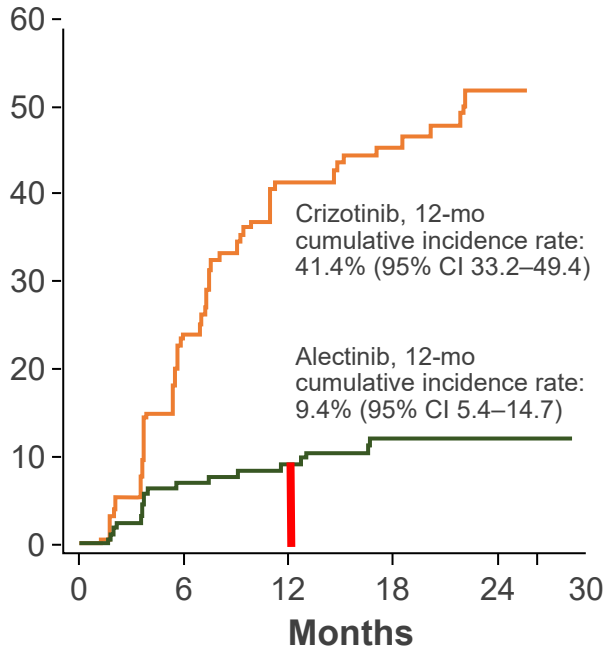
Lorlatinib



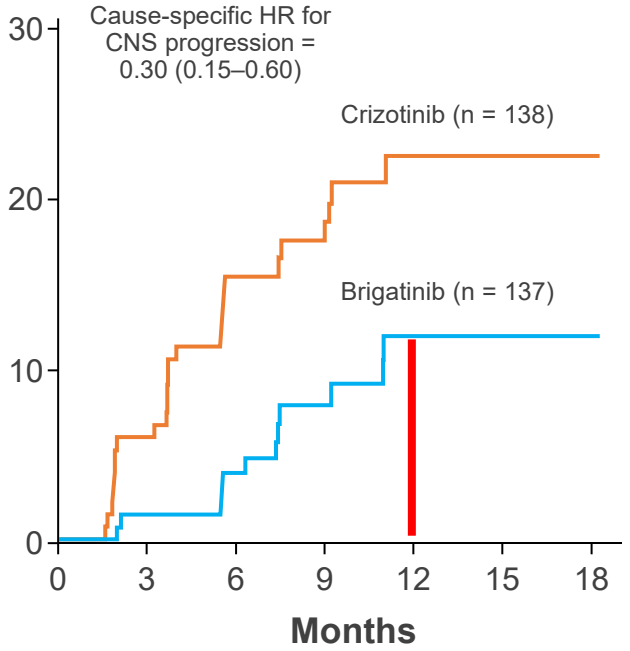
Mok T, et al. *Ann Oncol*. 2020;31:1056-1064; Camidge DR, et al. *J Clin Oncol.* 2020;38:3592-3603; Shaw AT, et al. *N Engl J Med*. 2020;383:2018-2029.

CNS Progression

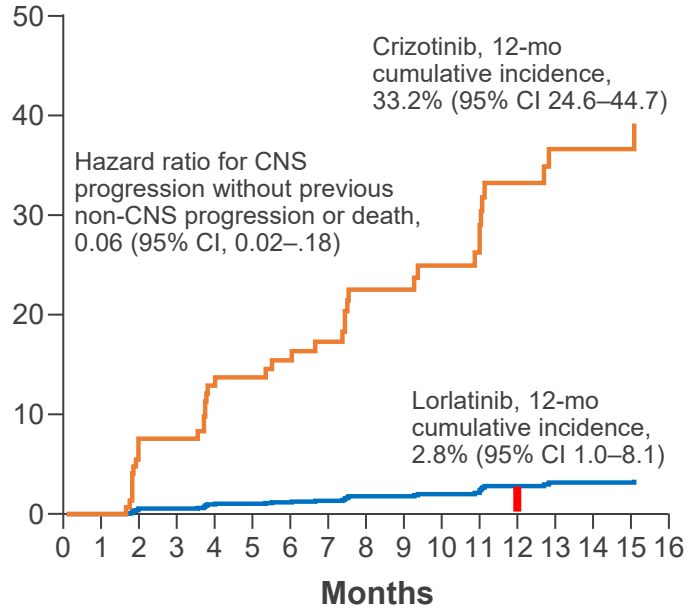
Alectinib (ALEX)[1]



Brigatinib (ALTA-1L)

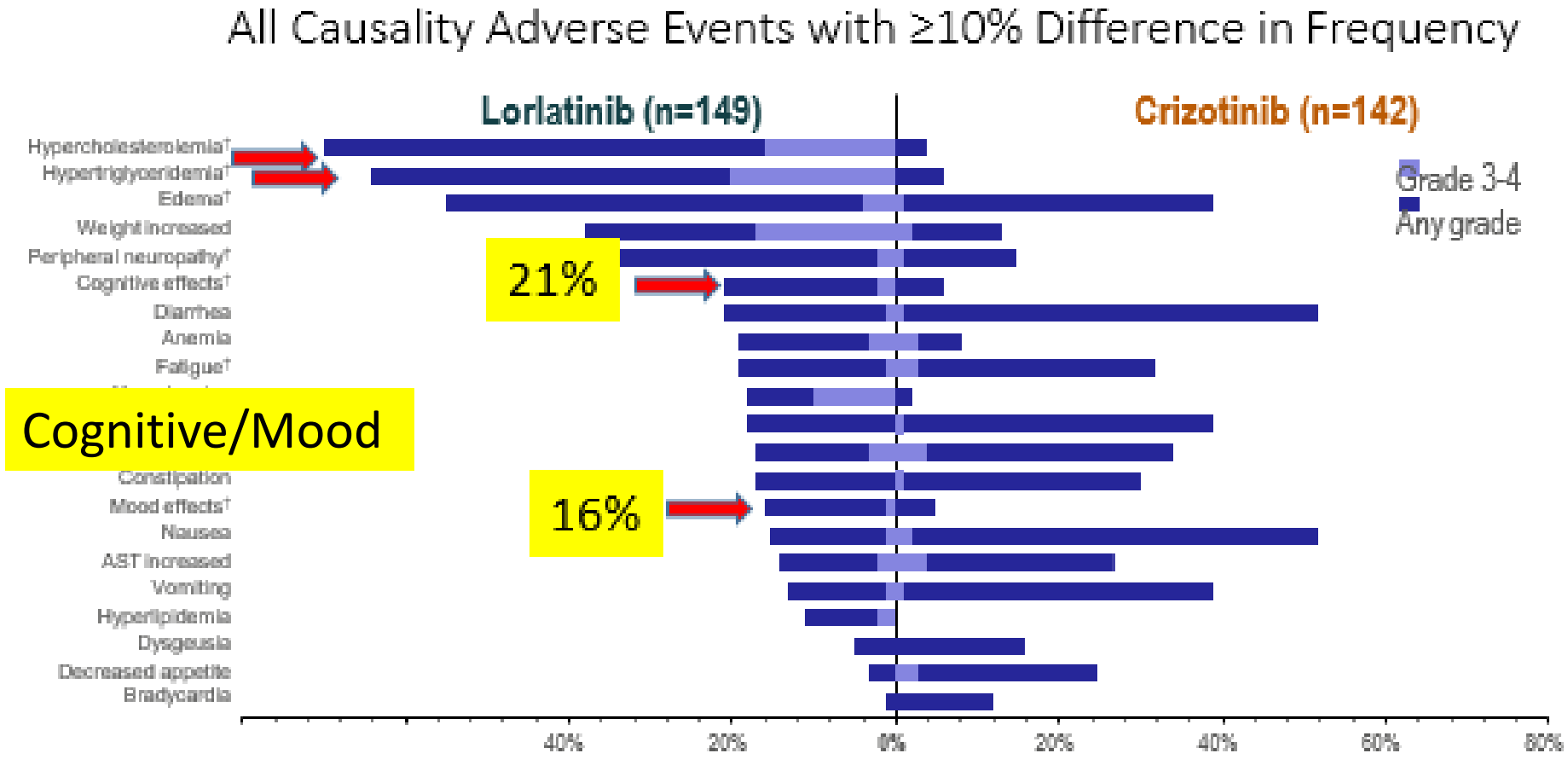


Lorlatinib (CROWN)[3]



Peters S, et al. *N Engl J Med.* 2017;377:829-838; Popat S, et al. *Ann Oncol.* 2018;29(suppl_8):vii76 and presentation at ESMO 2018; Shaw AT, et al. *N Engl J Med.* 2020;383:2018-2029.

Lorlatinib Adverse Events

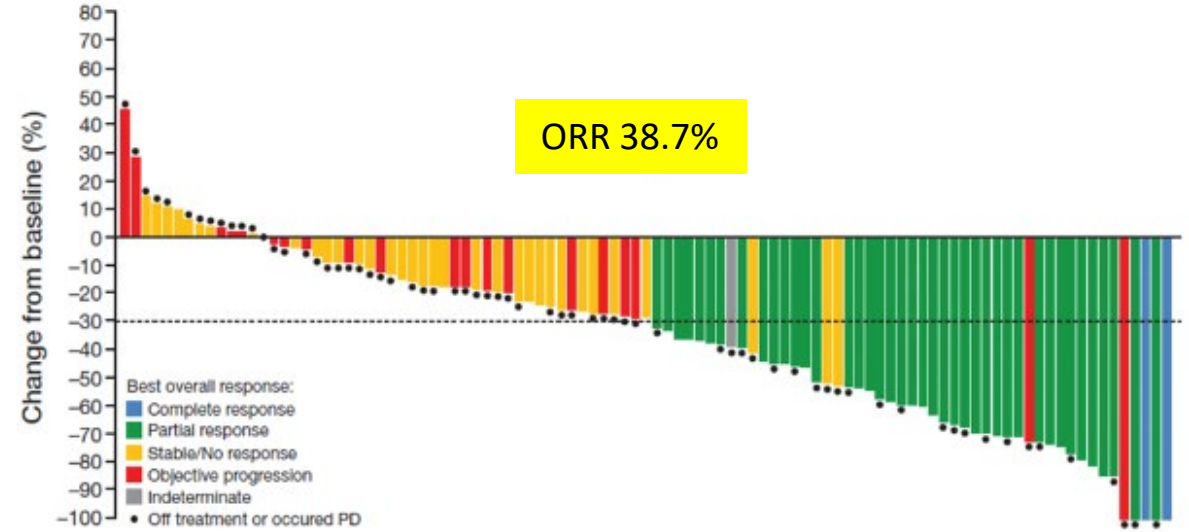


<u>Weight gain</u> reported in <u>38%</u> and associated with increased appetite. (17% grade 3: 20% increase)

Both weight gain and cognitive and mood changes due to off-target inhibition of <u>tropomyosin receptor kinase B in the CNS</u>

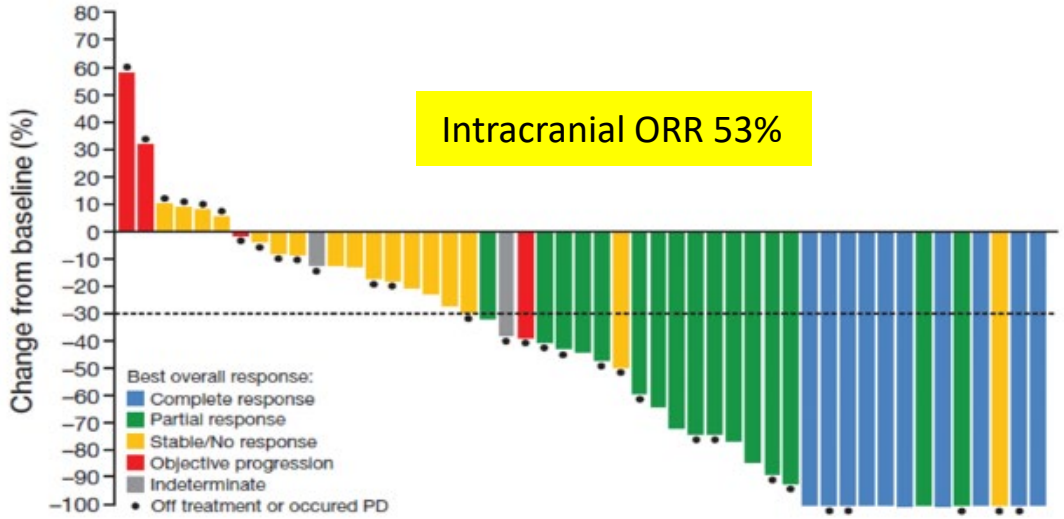
Lorlatinib in *ALK*+ Patients Treated With ≥2 Prior ALK Inhibitors (2–3 ALK TKI ± chemo)

N = 111



ORR 38.7%

PFS 6.9 months



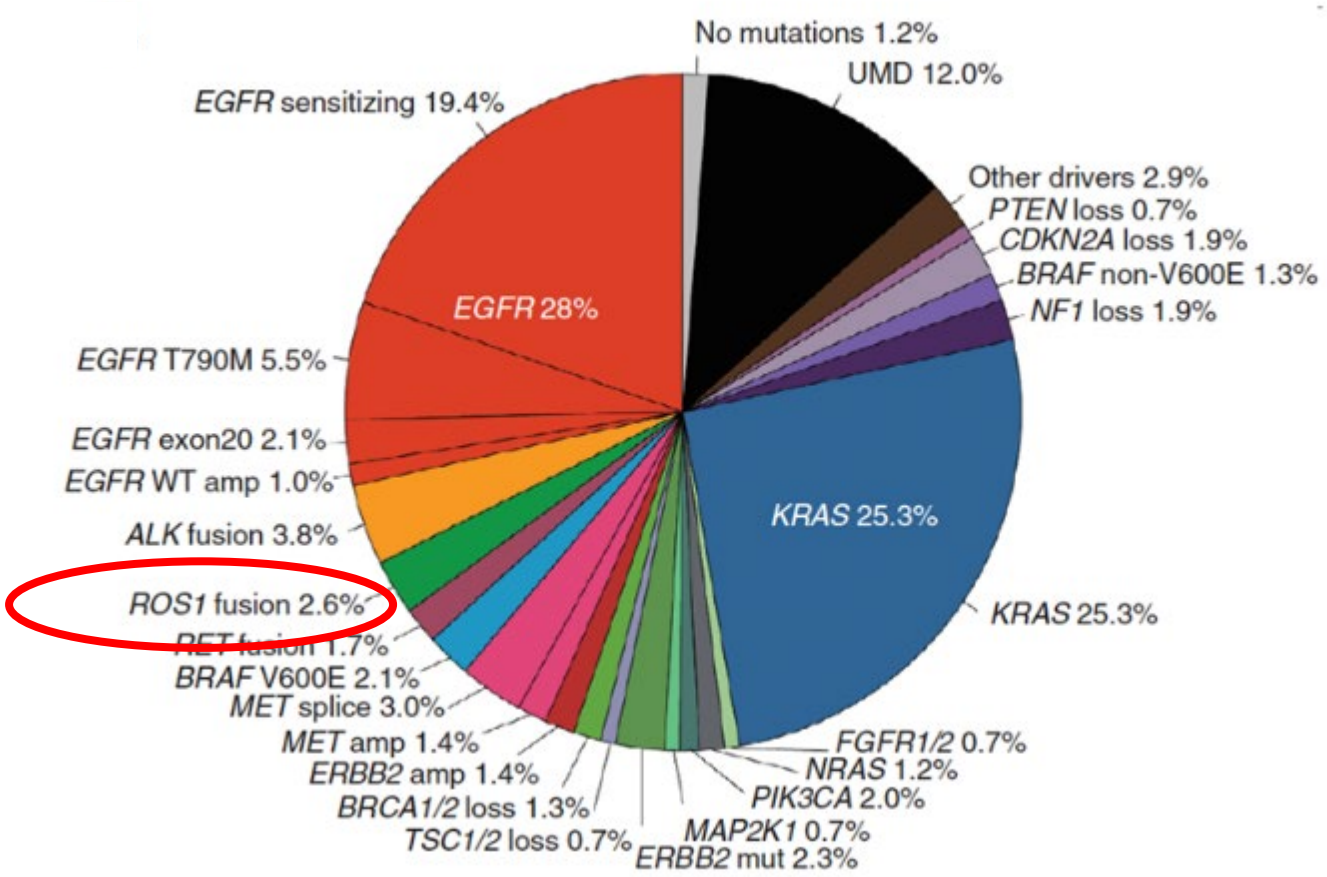
Intracranial ORR 53%

Solomon BJ, et al. *Lancet Oncol*. 2018;19:1654-1667.

Big Question in ALK

- What TKI do we use in the first line?
- In Canada, we have 3 first-line choices
  - Alectinib, brigatinib, lorlatinib
- No drugs approved for second or third line

ROS

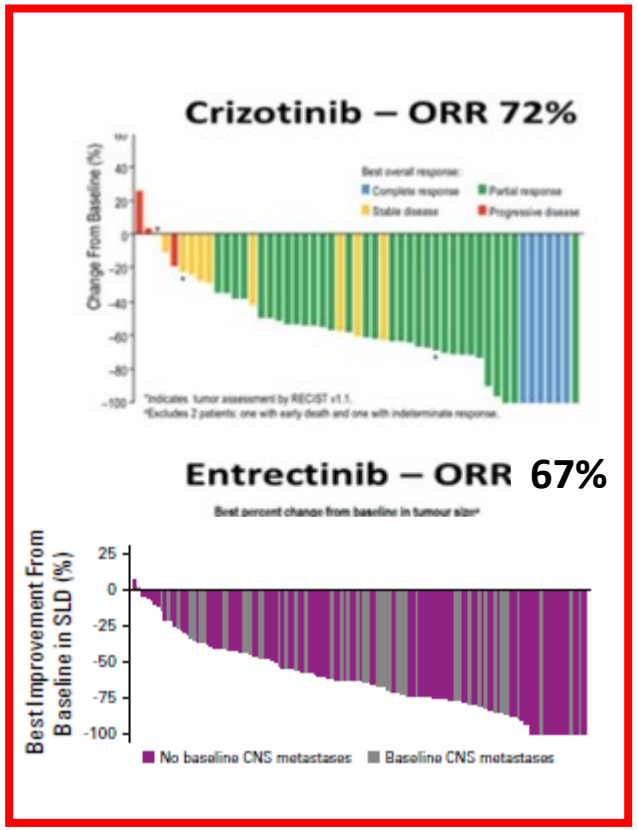


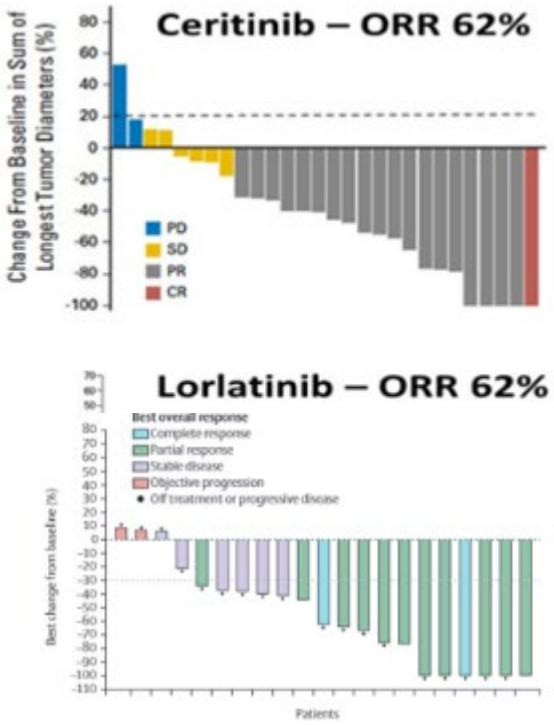
Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

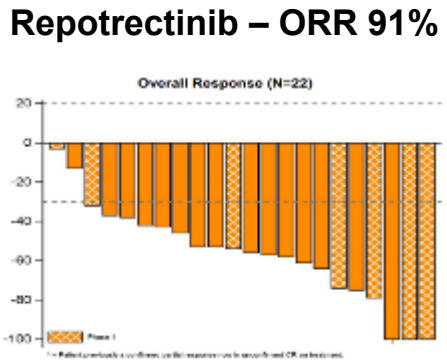
ROS1 Inhibitors

	N	RR (%)	PFS (mo.)	OS (mo.) 1-y OS (%)	Ic-RR (%)
Crizotinib	53	72	19.3	51.4 / 79	50 (ALK)
Ceritinib	32	62	19.3	24 / 56	25[a]
Entrectinib	53	77	19.0 (26.3 w/o BM)	NR / 85	55*
Lorlatinib	13	62	21.0	NR	67@
Repotrectinib	33	82	NR	NR	100#

ROS1 Inhibitors in TKI-Naive Patients







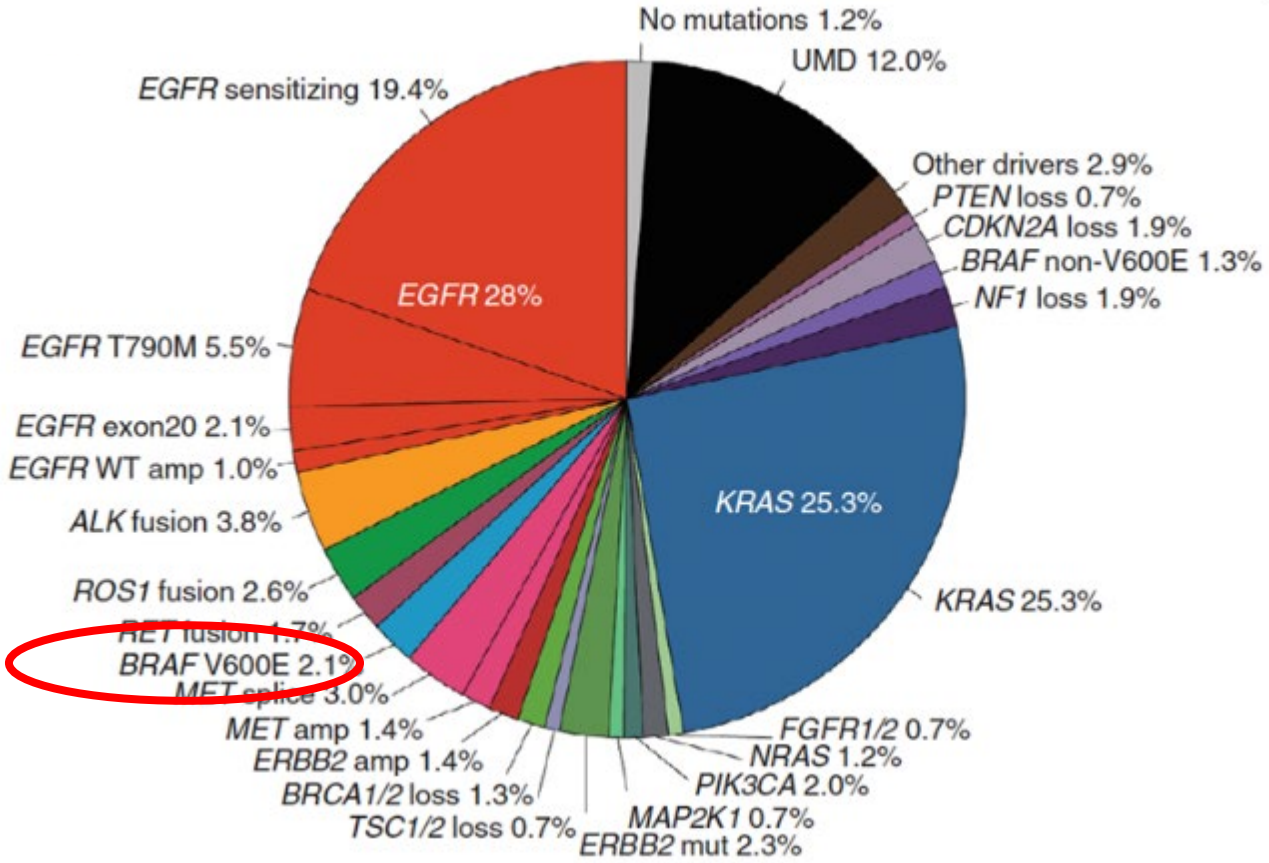
Crizotinib approved by pCODR May 2019

Entrectinib approved by pCODR Jan 2021

Big Question in *ROS*

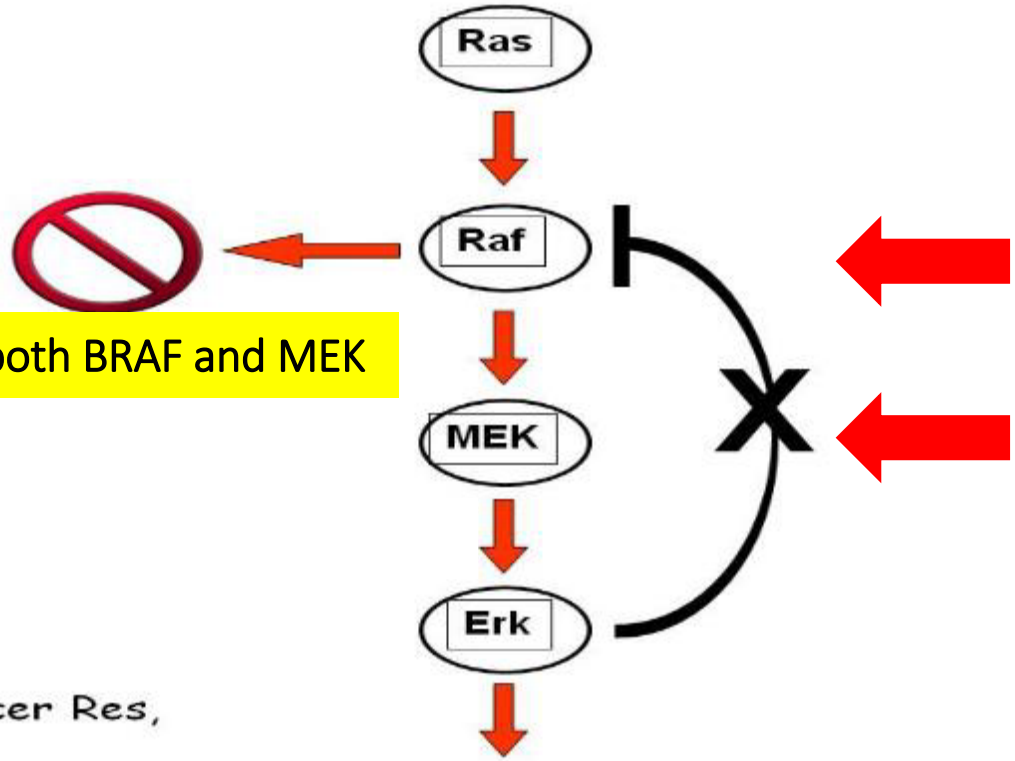
- What do you use in the first line?
- What is the proper sequence?

BRAF



Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

Abrogation of feedback loop of Raf by Erk



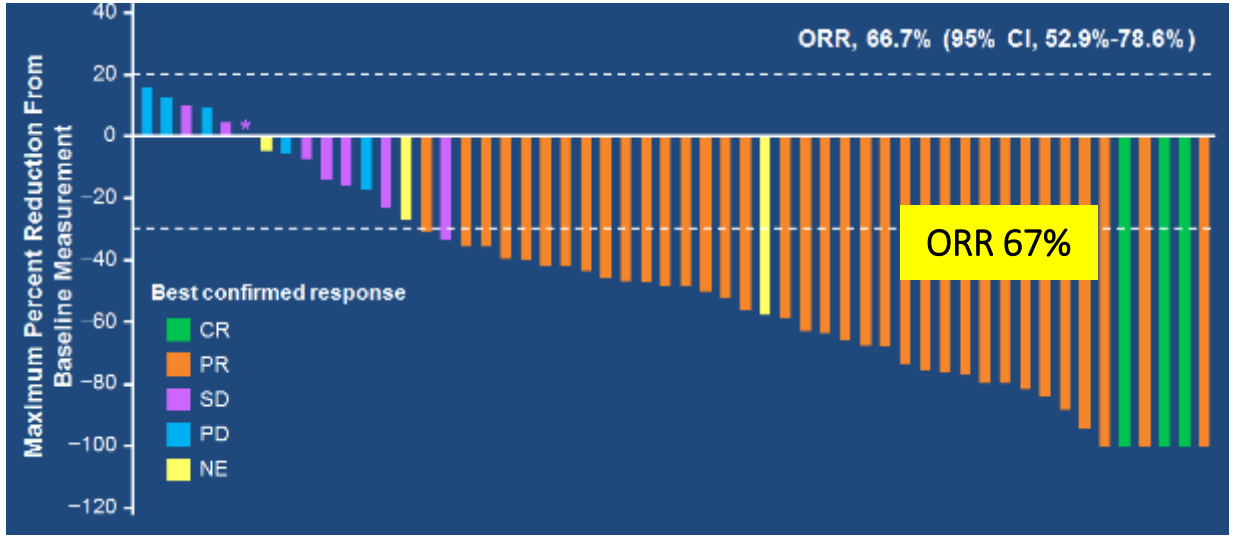
Synergism to block both BRAF and MEK

Friday et al, Cancer Res, 2008
Zhao Y & Adjei AA, Nature

Second Line

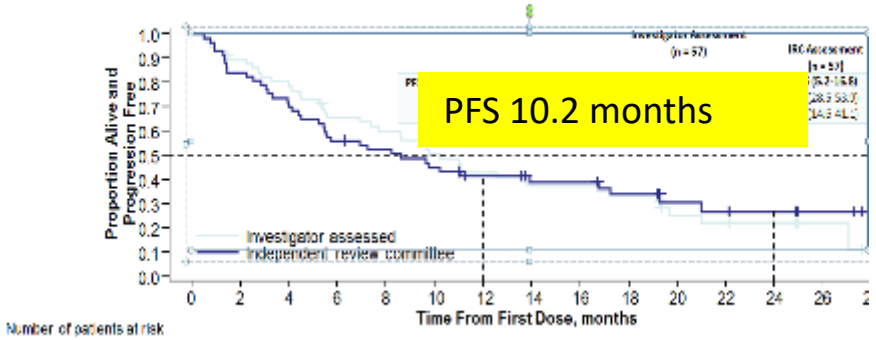
ASCO 2017

Dabrafenib and Trametinib: *BRAF* V600E

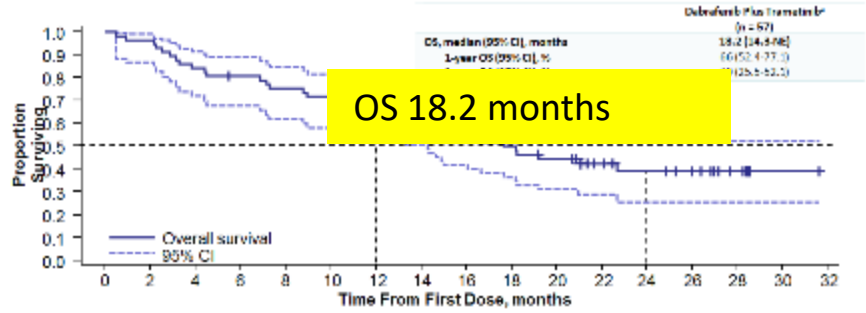


N = 57

Dabrafenib Plus Trametinib Cohort: PFS



Dabrafenib Plus Trametinib :Overall Survival



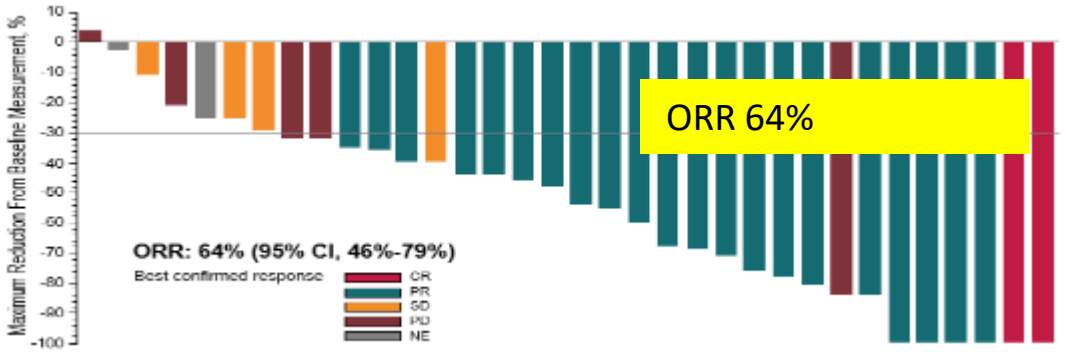
Planchard D, et al. *Lancet Oncol.* 2016;17:984-993.

First Line

ESMO 2017

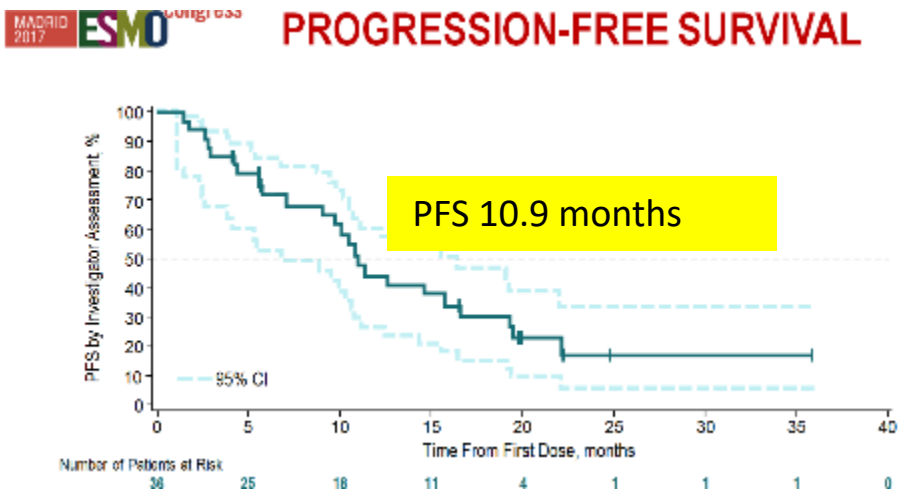
Approved in Canada April 1, 2021

Dabrafenib and Trametinib: *BRAF* V600E

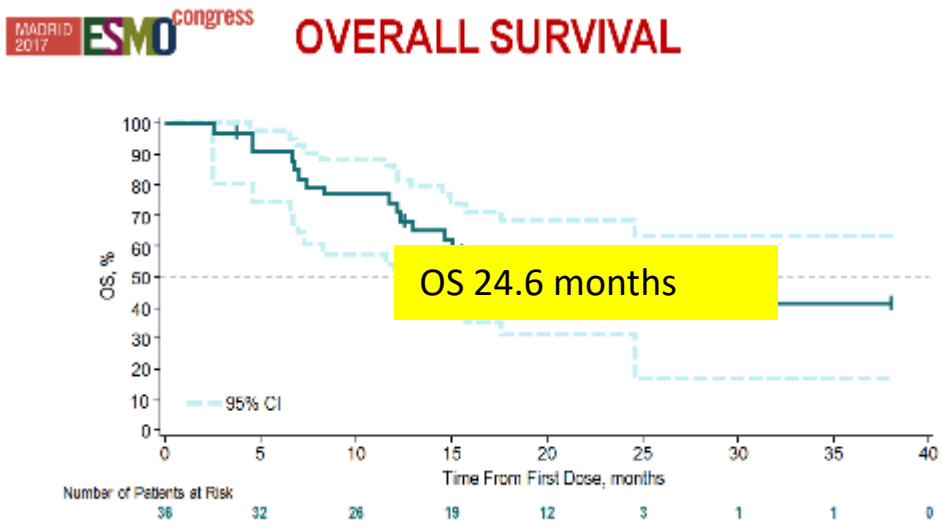


ORR 64%

N = 36



PFS 10.9 months



OS 24.6 months

Planchard D, et al. *Lancet Oncol*. 2017;18:1307-1316.

Big Question in *BRAF*

- What about *BRAF* nonV600E?
- What is the role of immunotherapy?

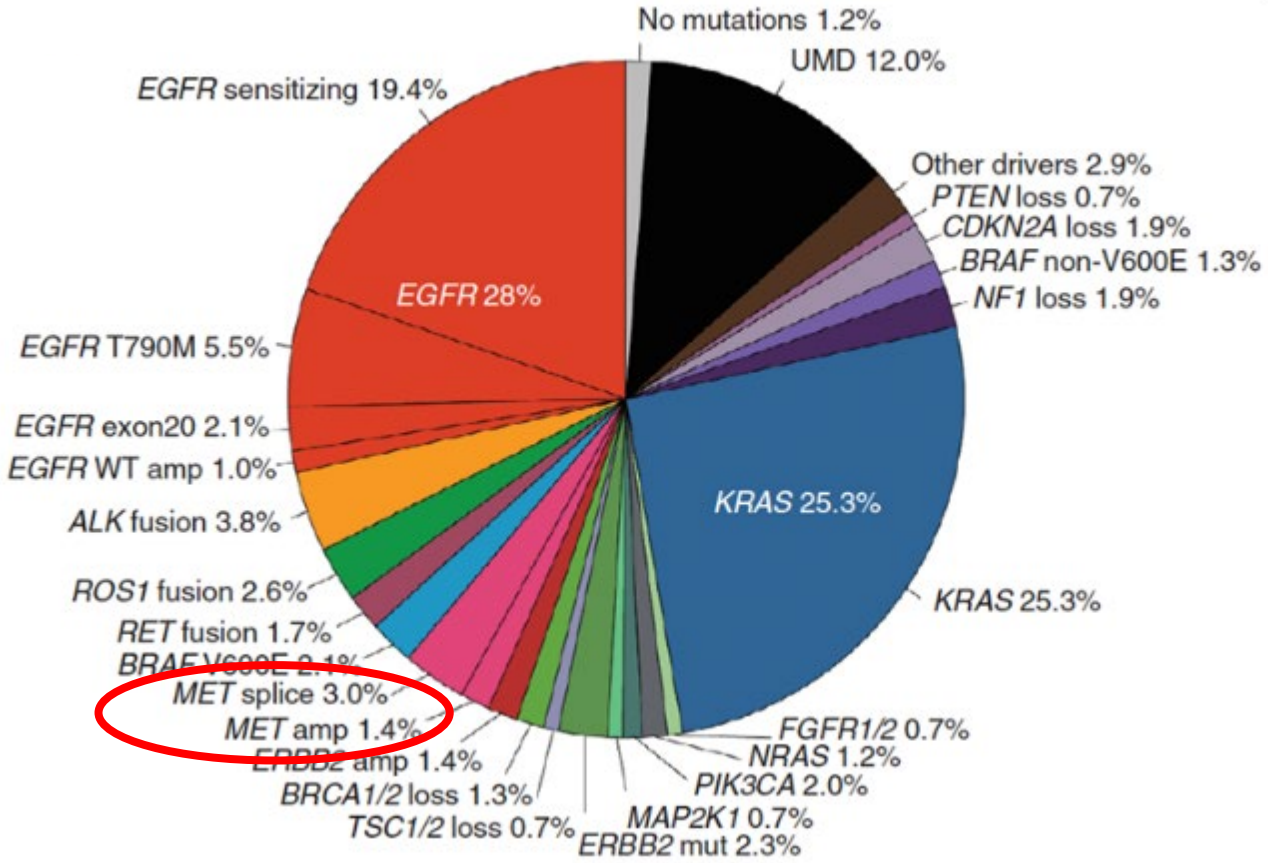
The Big 4

EGFR, ALK, ROS, BRAF

Other

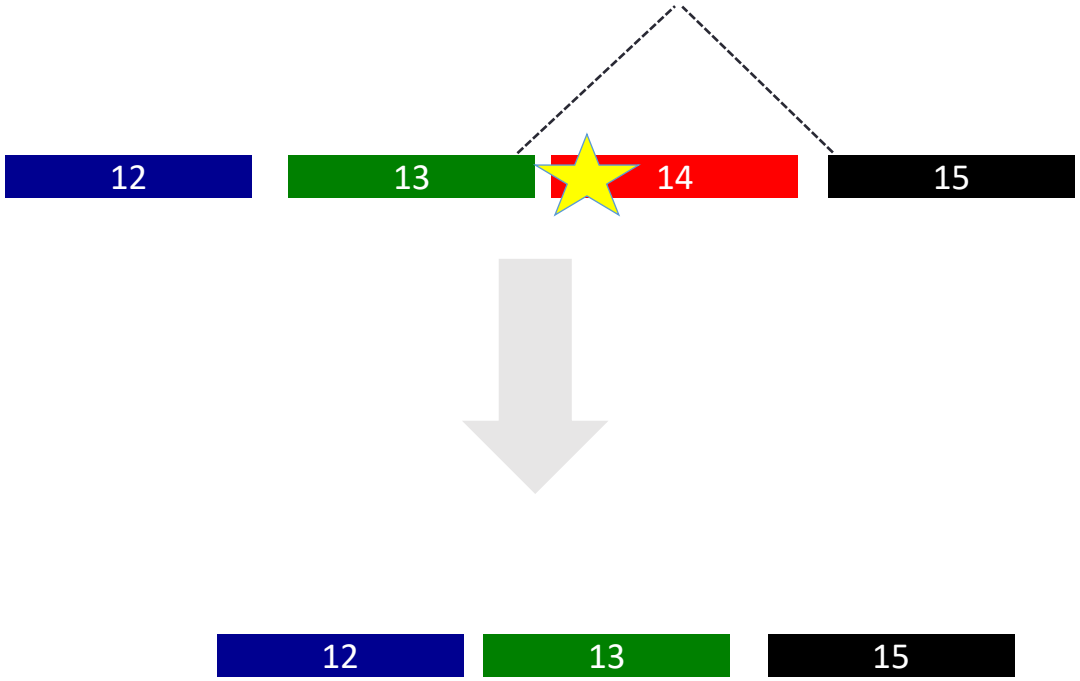
MET, HER2, RET, NTRK, and *KRAS*

MET

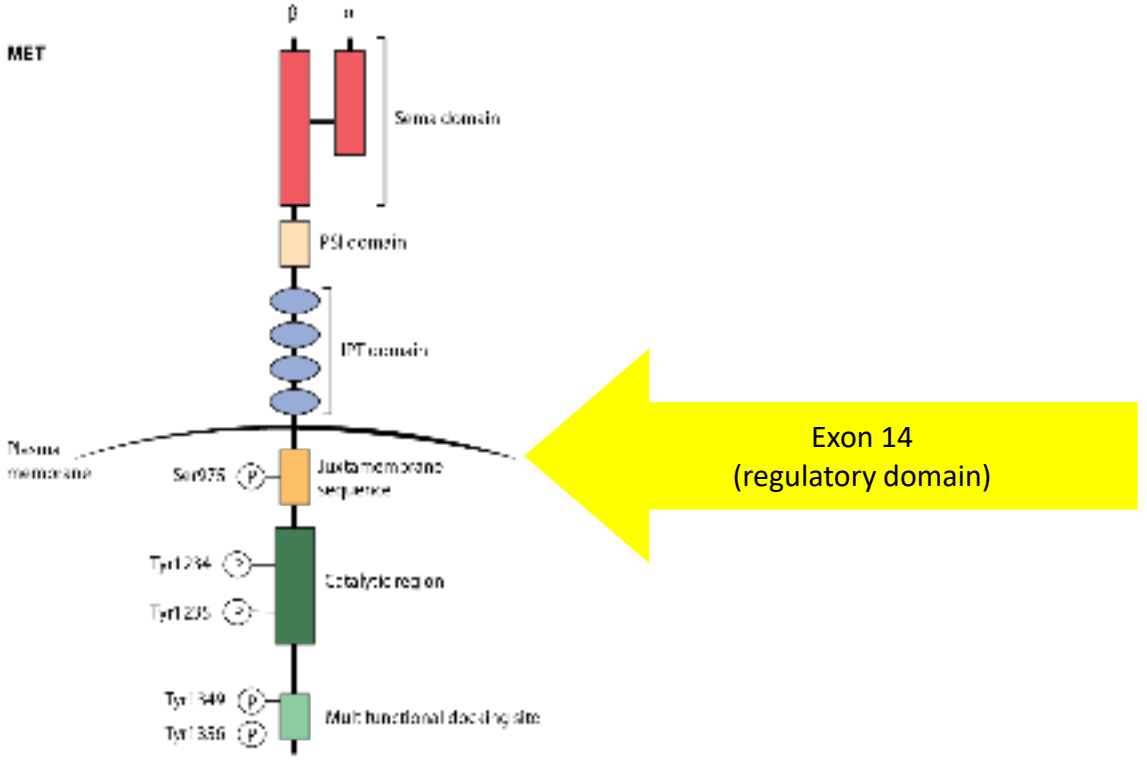


Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

Mechanism of *MET* Exon 14 Skipping



METex14 skipped



MET Inhibitors

Drug	Phase	Clinicaltrials.gov
Crizotinib	Ib	NCT00585195
Mersetinib	I	NCT02920996
Savolitinib	I	NCT02897479
Cabozantinib	II	NCT01639508
Capmantinib	II	NCT02750215
Tepotinib	II	NCT02864992

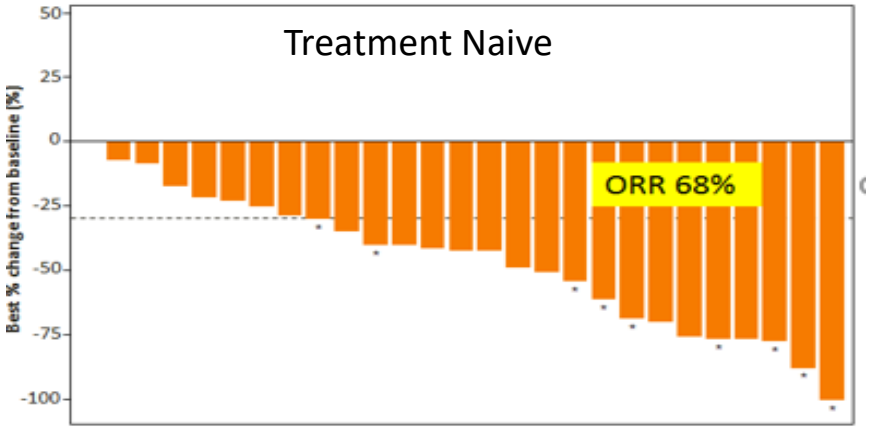
	Capmatinib	Tepotinib	Savolitinib	Cabozantinib	Crizotinib
IC_{50} (nM)	0.6	3.0	2.1	7.8	22.5

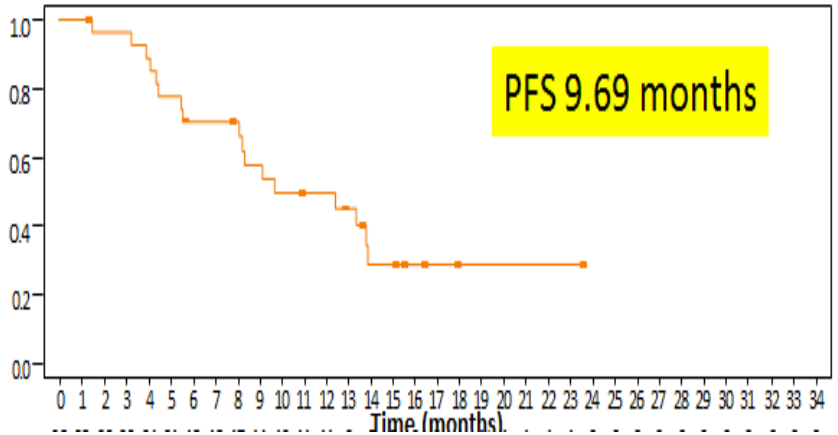
GEOMETRY Phase II – Capmatinib in Exon 14 Skip

ASCO 2019

Cohort 5b (1L)
N=28

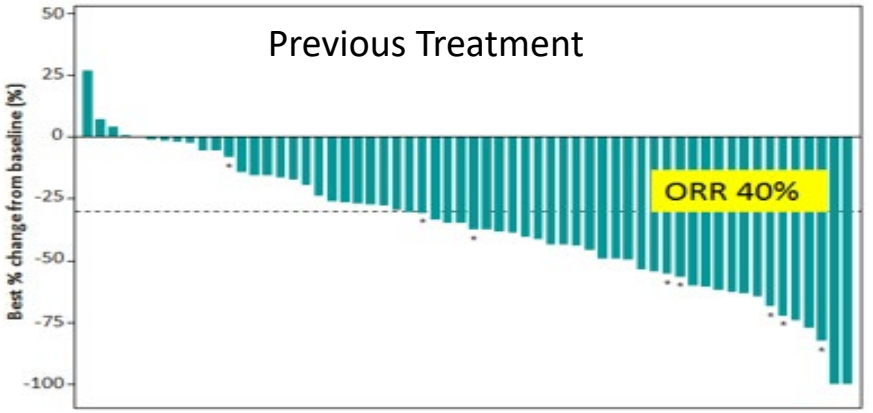
Treatment Naive

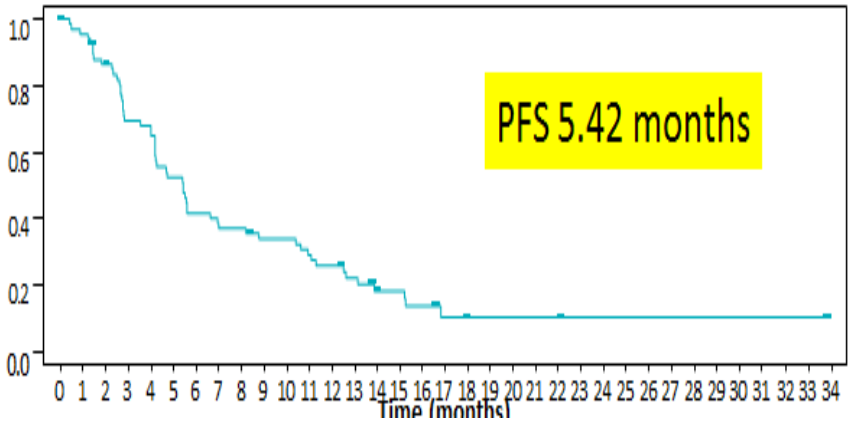




Cohort 4 (2/3L)
N=69

Previous Treatment





VISION Phase II – Tepotinib in Exon 14 Skip

ASCO 2019

Tepotinib 500 mg QD	Tissue biopsy (T+)	
	IRC (n=51)	Investigator (n=51)
ORR,* n (%) [95% CI]		28 (54.9) [40.3, 68.9]
mDOR, months [95% CI]		14.3 [7, ne]

ORR 45 %

DOR 15.7 months

First line

Evidence of tumor shrinkage in 92% of patients by both IRC and Investigator read

Second line

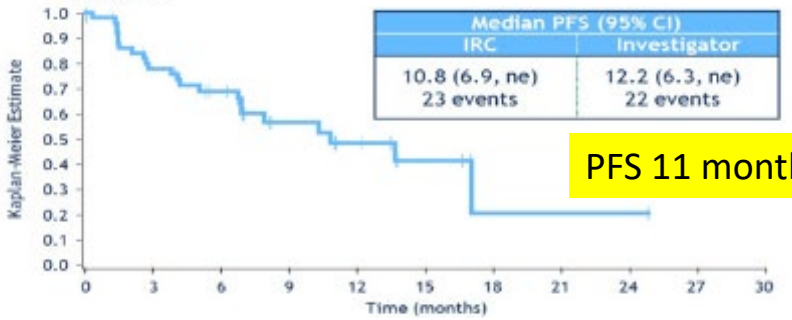
≥Third line

Evidence of tumor shrinkage in ≥75% of patients

Tissue biopsy (T+) (n=58)

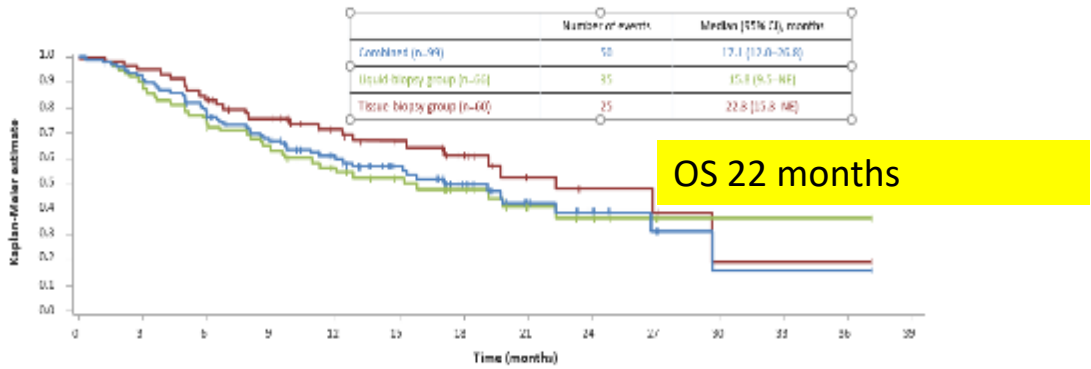
PFS by IRC

Median PFS (95% CI)	
IRC	Investigator
10.8 (6.9, ne) 23 events	12.2 (6.3, ne) 22 events



PFS 11 months

Median OS

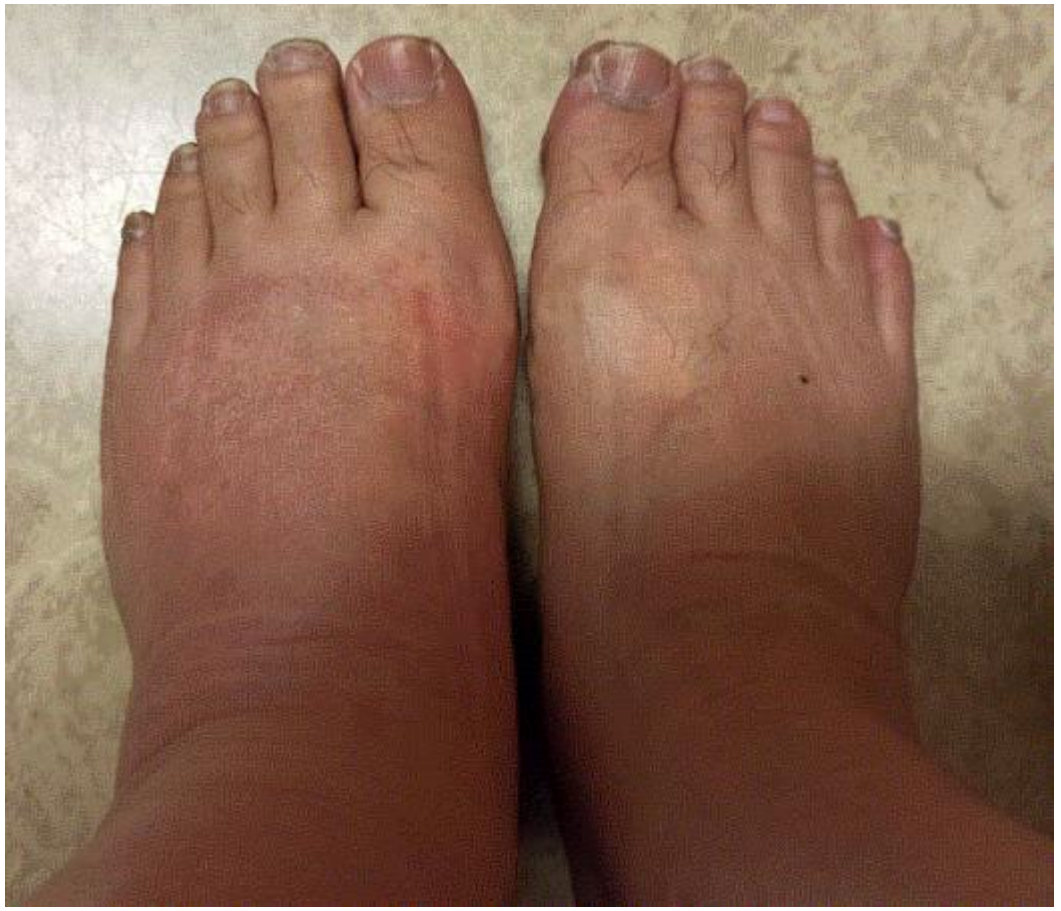


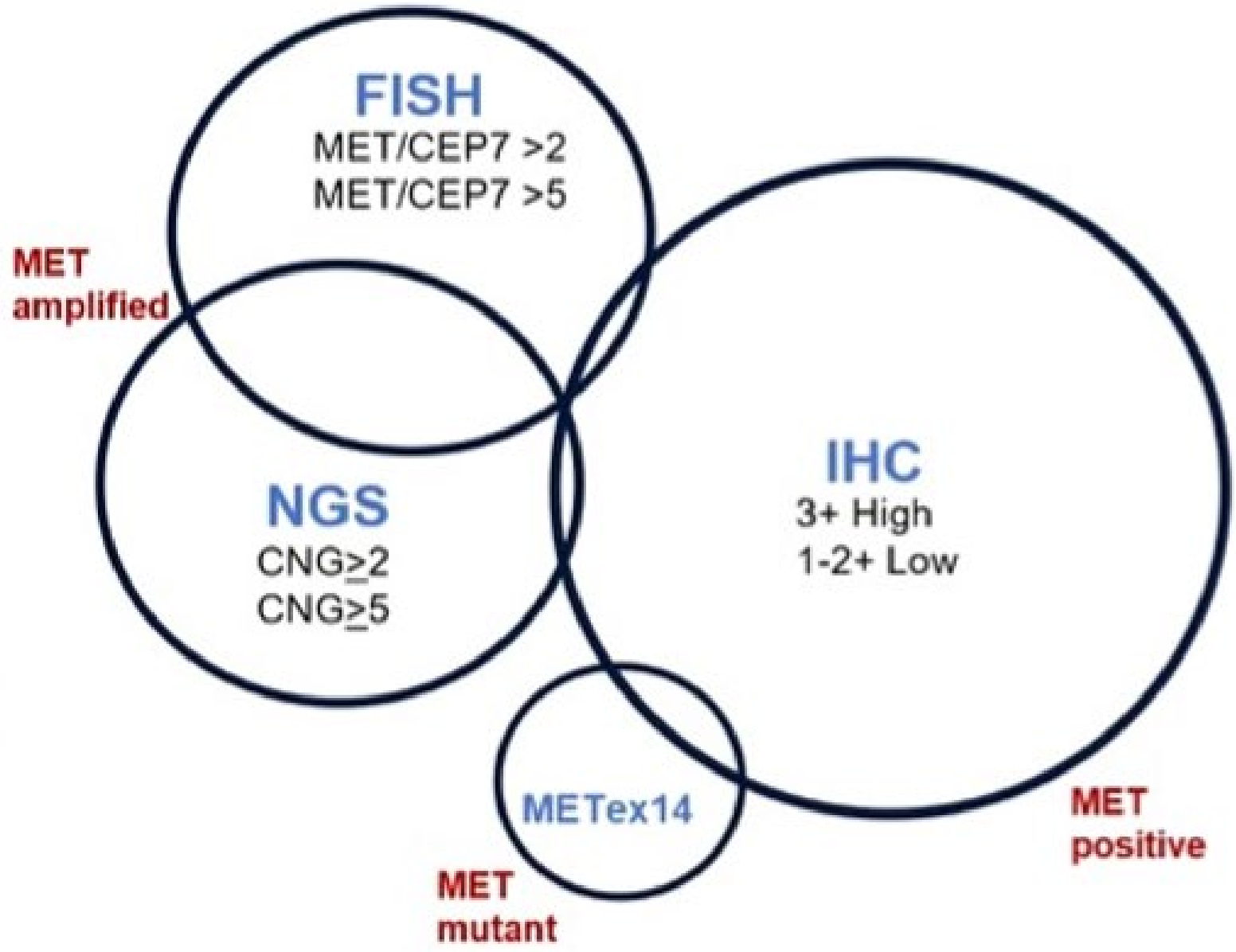
OS 22 months

Paik P, et al. ASCO 2019. Abstract 9005.

Safety: Treatment-Related Adverse Events

	Tepotinib 500 mg QD (N = 87)	
	Any Grade	Grade 3
Any treatment-related AE, n (%)	71 (81.6)	17 (19.5)
Treatment-related AEs reported in ≥5% patients, n (%)		
Peripheral edema	42 (48.3)	7 (8.0)
Nausea	20 (23.0)	0
Diarrhea	18 (20.7)	1 (1.1)
Blood creatinine increased	11 (12.6)	0
Asthenia	8 (9.2)	1 (1.1)
Amylase increase	7 (8.0)	2 (2.3)
ALT increased	6 (6.9)	2 (2.3)
AST increased	5 (5.7)	1 (1.1)
Hypoalbuminemia	5 (5.7)	0



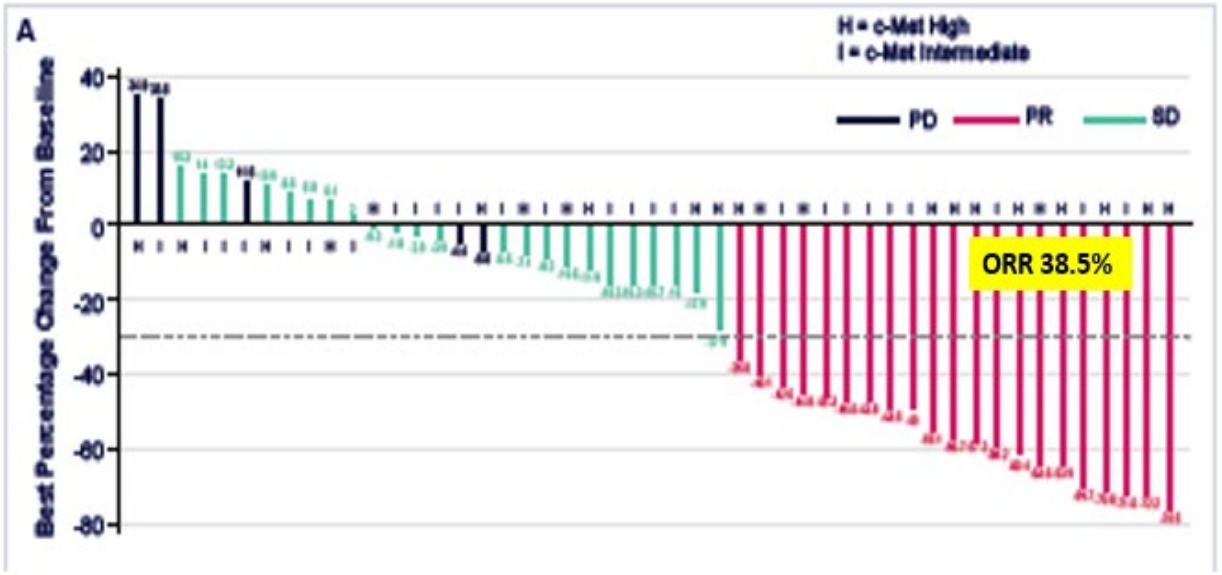

FISH
MET/CEP7 >2
MET/CEP7 >5
MET
amplified
NGS
CNG≥2
CNG≥5
IHC
3+ High
1-2+ Low
METex14
MET
mutant
MET
positive

MET IHC High Expression

ASCO 2022

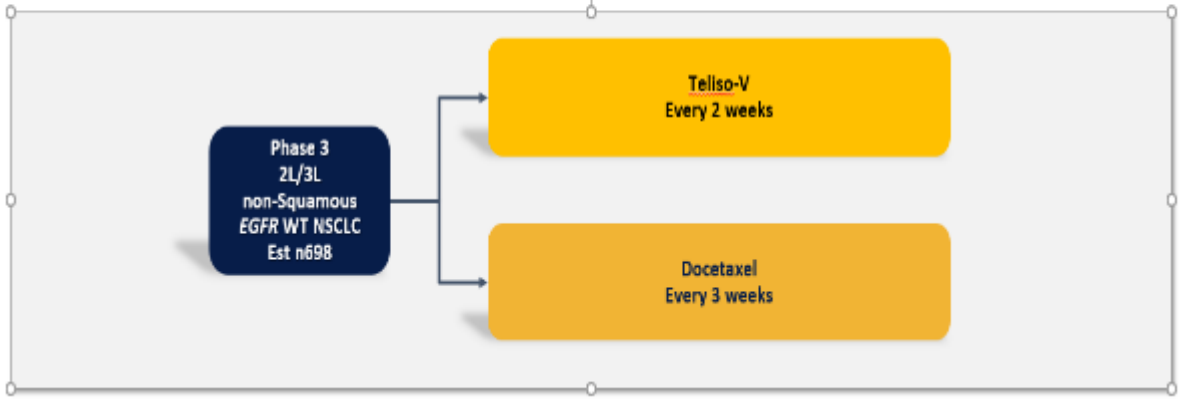
Antibody Drug Conjugate

Telisotuzumab Vedotin (Teliso-V) Monotherapy in Patients (Pts) With Previously Treated c-Met Overexpressing (OE) Advanced Non-Small Cell Lung Cancer (NSCLC)



TeliMET

A Phase 3 Global Study of Telisotuzumab Vedotin Versus Docetaxel EGFR WT High or Int CMET expression



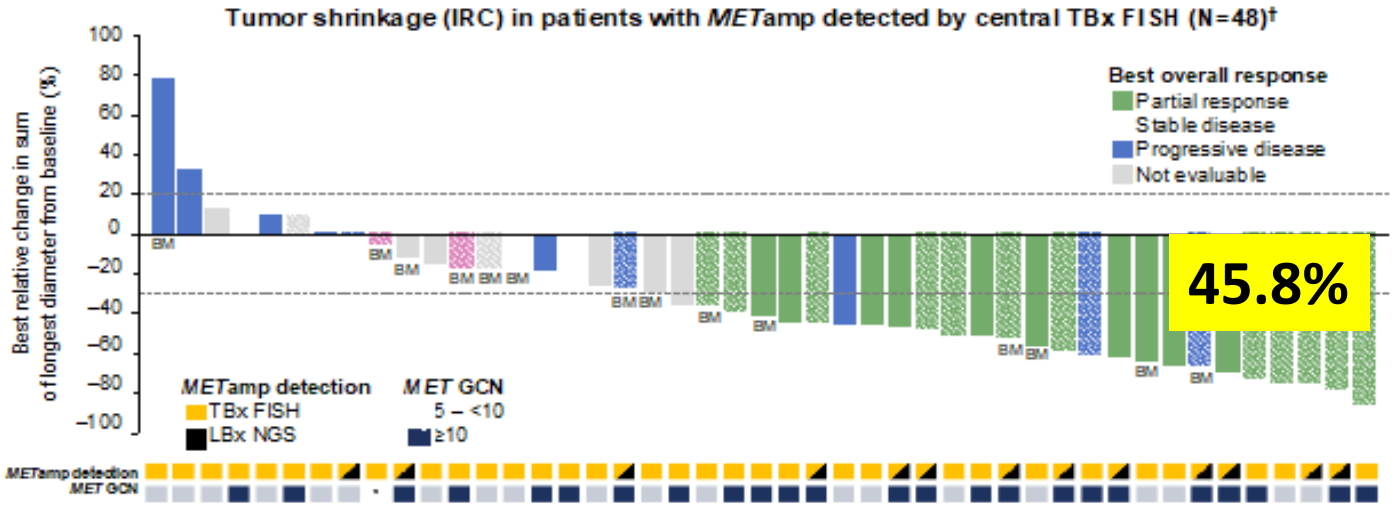
Camidge R, et al. ASCO 2022.

MET Amplification

INSIGHT 2 Study

Tepotinib + osimertinib for *EGFR*m NSCLC with *MET* amplification (*MET*amp) after progression on first-line (1L) osimertinib:

Antitumor Activity of Tepotinib plus Osimertinib



Mazieres J, et al. ESMO 2022. Abstract LBA52.

Big Question in *MET*

- Capmatinib vs tepotinib

NEJM Sept 2020

Capmatinib in MET Exon 14–Mutated or MET-Amplified Non–Small-Cell Lung Cancer

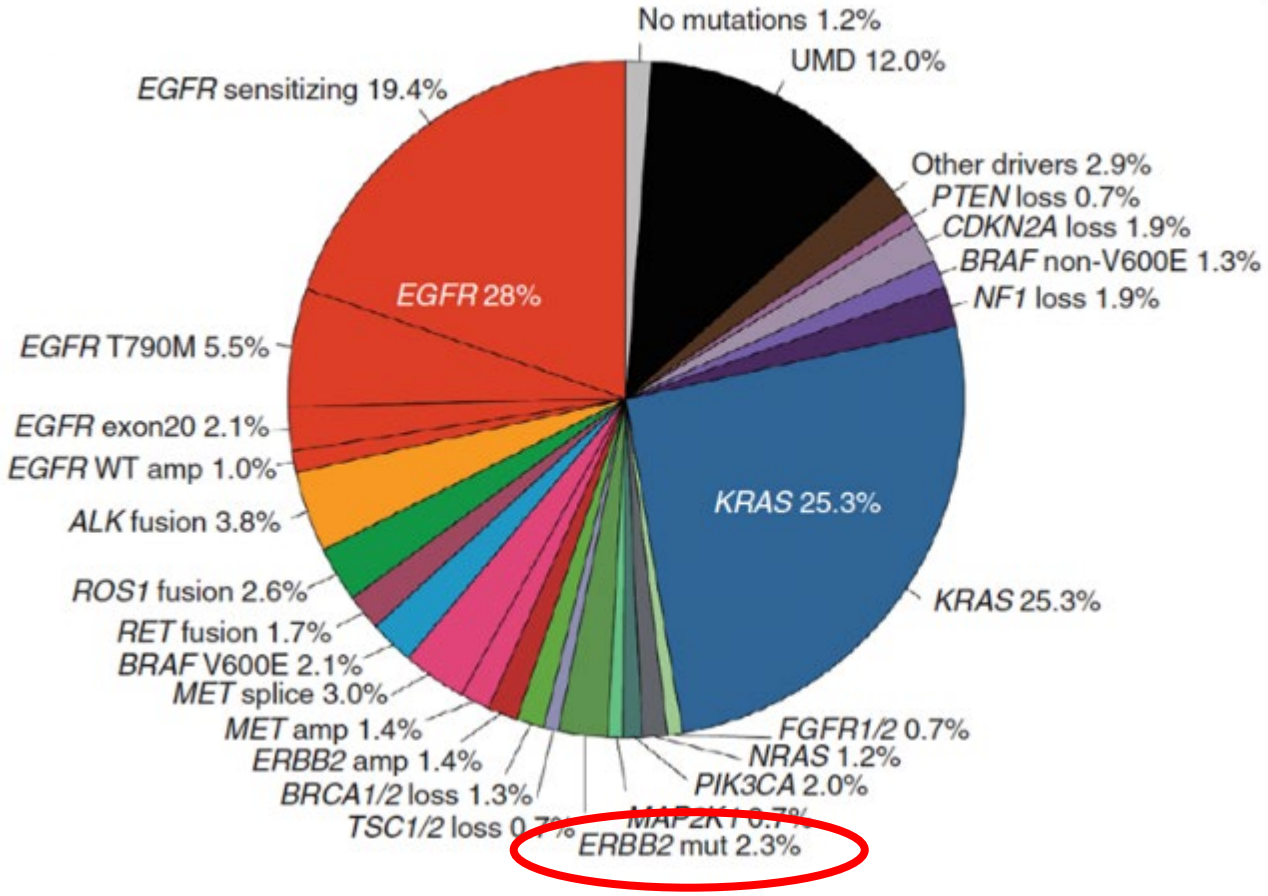
Jürgen Wolf, M.D., Takashi Seto, M.D., Ji-Youn Han, M.D., Ph.D., Noemi Reguart, M.D., Ph.D., Edward B. Garon, M.D., Harry J.M. Groen, M.D., Ph.D., Daniel S.W. Tan, M.D., Ph.D., Toyoaki Hida, M.D., Ph.D., Maja de Jonge, M.D., Ph.D., Sergey V. Orlov, M.D., Egbert F. Smit, M.D., Ph.D., Pierre-Jean Souquet, M.D., et al., for the GEOMETRY mono-1 Investigators*

Tepotinib in Non–Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations

Paul K. Paik, M.D., Enriqueta Felip, M.D., Ph.D., Remi Veillon, M.D., Hiroshi Sakai, M.D., Alexis B. Cortot, M.D., Ph.D., Marina C. Garassino, M.D., Julien Mazieres, M.D., Ph.D., Santiago Viteri, M.D., Helene Senellart, M.D., Jan Van Meerbeeck, M.D., Ph.D., Jo Raskin, M.D., Niels Reinmuth, M.D., Ph.D., et al.

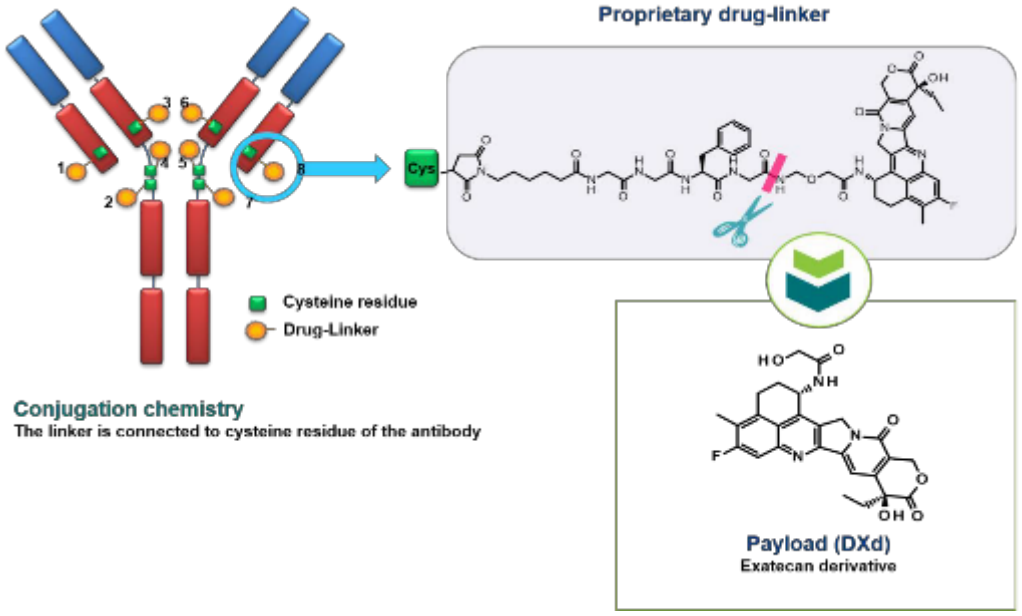
Wolf J, et al. *N Engl J Med*. 2020;383:944-957; Paik PK, et al. *N Engl J Med.* 2020;383:931-943.

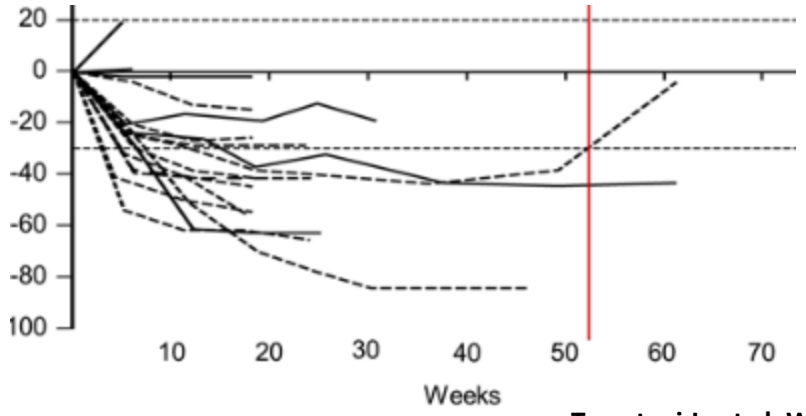
HER2



Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

Trastuzumab Deruxtecan TDX-d Antibody-Drug Conjugate in *HER2*-Mutant NSCLC





Tsurutani J, et al. WCLC 2018. Abstract OA02.07

Cohort 2: *HER2*-mutated

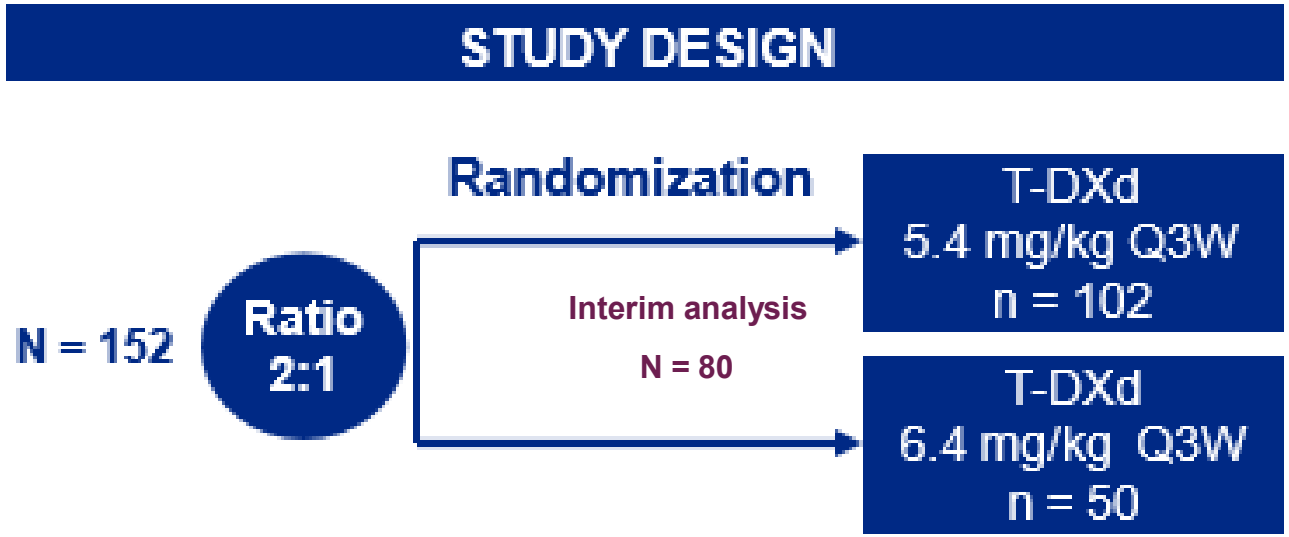
DESTINY-Lung01

Smit E et al, ASCO 2020

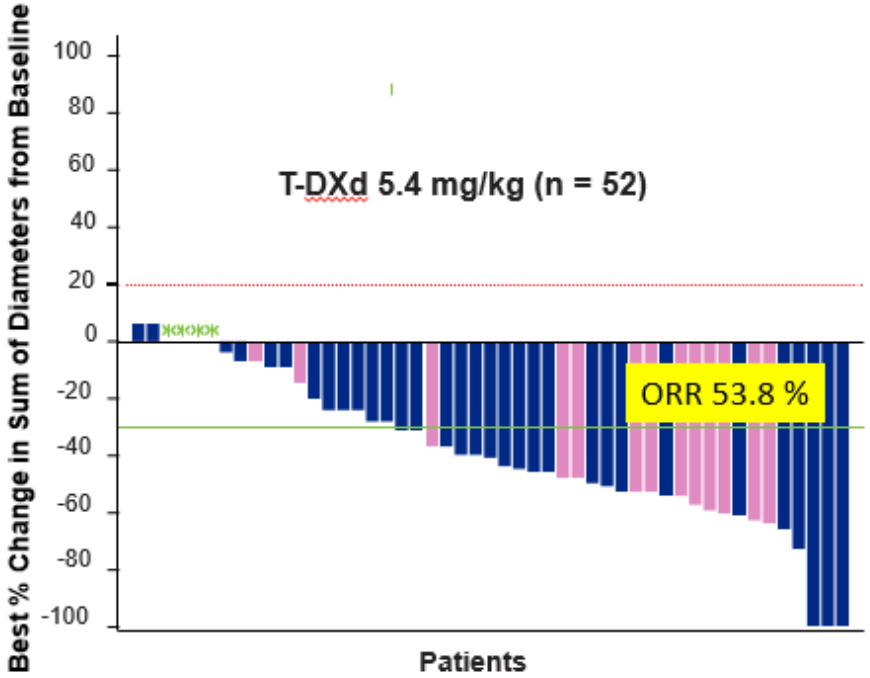
DESTINY-Lung02

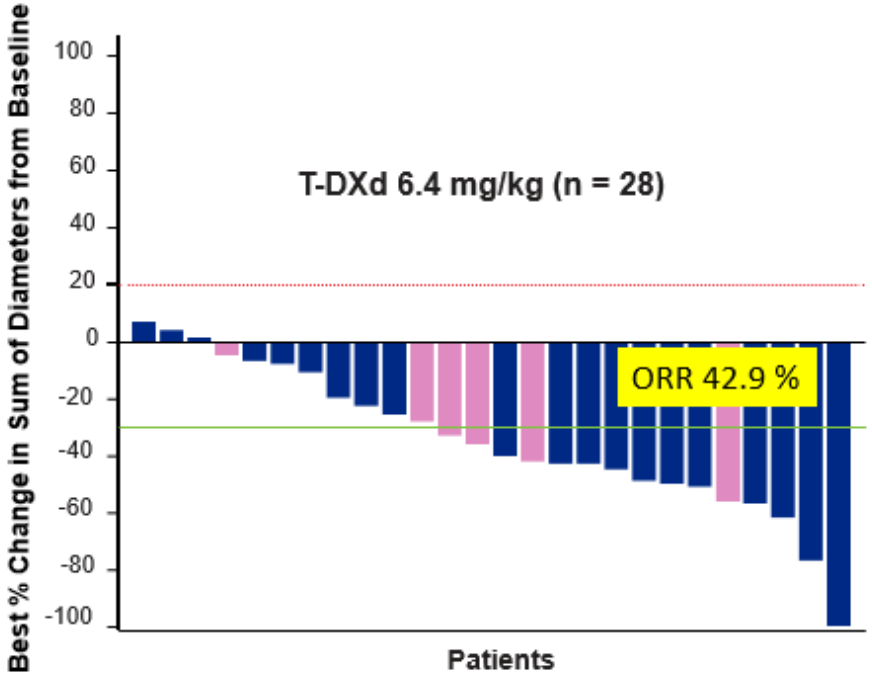
PARIS 2022 ESMO congress

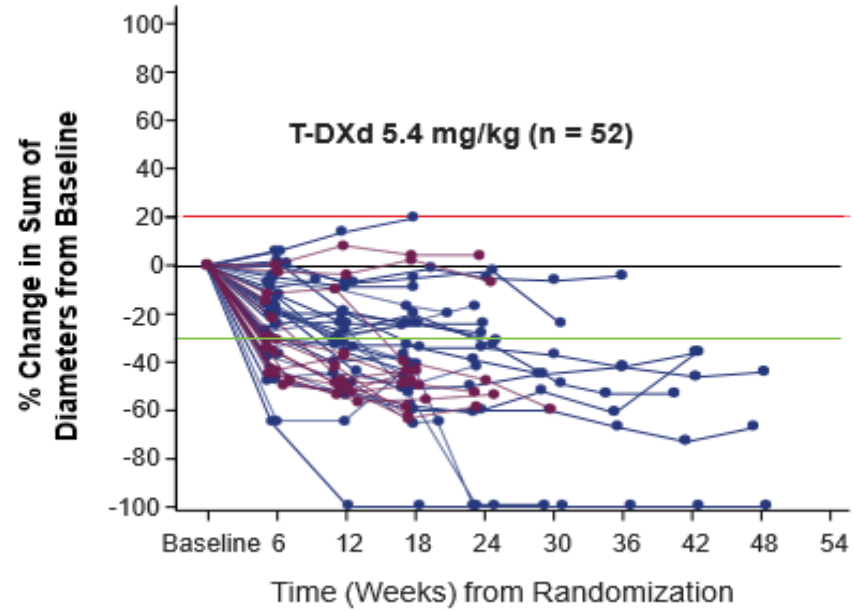
Trastuzumab Deruxtecan in Patients With *HER2* Mutant Metastatic Non-small Cell Lung Cancer: Interim Results From the **Phase II DESTINY-Lung02 Trial**

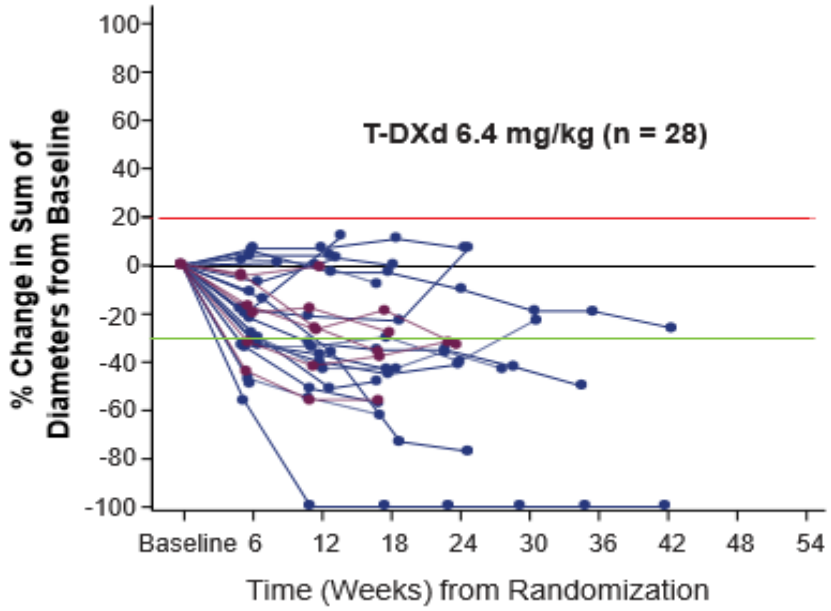


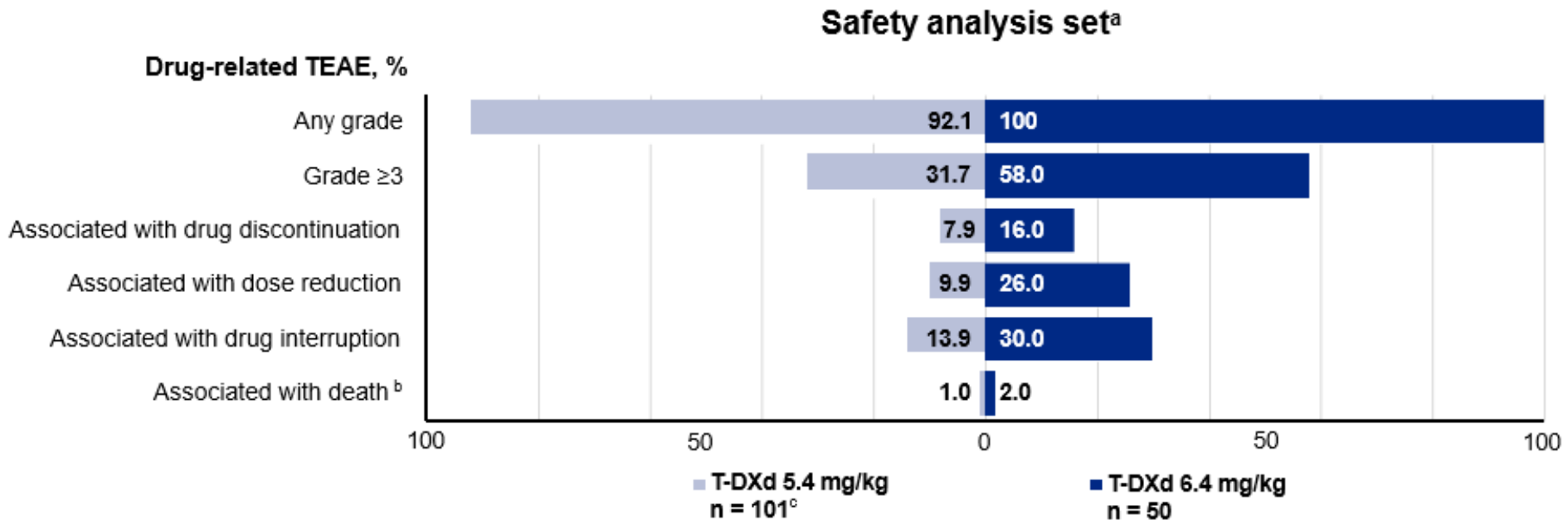
Goto K, et al. ESMO 2022. Abstract LBA55.


T-DXd 5.4 mg/kg (n = 52)
ORR 53.8 %
Best % Change in Sum of Diameters from Baseline
Patients


T-DXd 6.4 mg/kg (n = 28)
ORR 42.9 %
Best % Change in Sum of Diameters from Baseline
Patients


T-DXd 5.4 mg/kg (n = 52)
% Change in Sum of Diameters from Baseline
Time (Weeks) from Randomization


T-DXd 6.4 mg/kg (n = 28)
% Change in Sum of Diameters from Baseline
Time (Weeks) from Randomization



Adjudicated as drug-related ILD[a]	Safety analysis set[b]	
	T-DXd 5.4 mg/kg n = 101	T-DXd 6.4 mg/kg n = 50
Any grade, n (%)	**6 (5.9)**	**7 (14.0)**
Grade 1		
Grade 2		
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)
Median time to onset of first adjudicated ILD, days (range)	67.5 (40–207)	41.0 (36–208)

5.9%

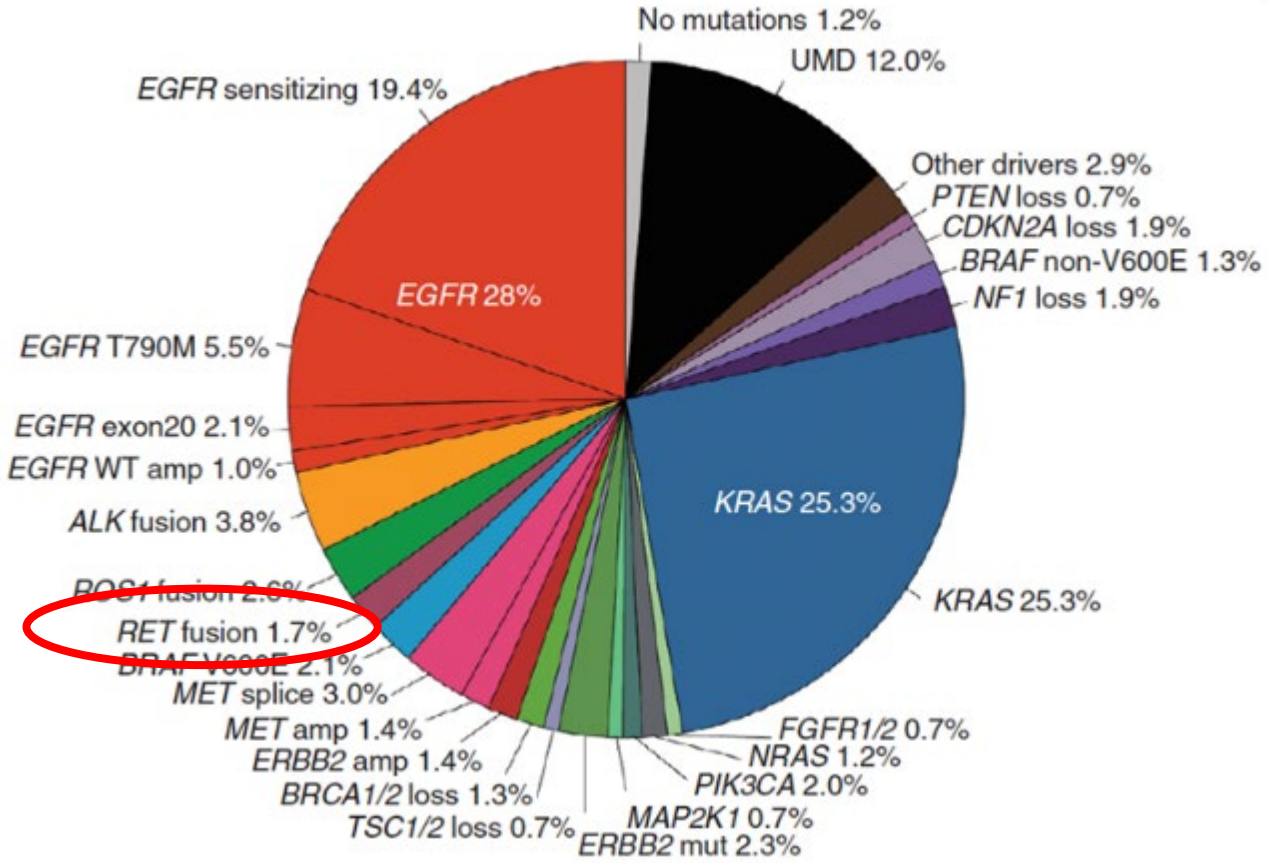
14.0%

Big Question in *HER2*

- How do I get TDX-d for my patients?

2021

RET



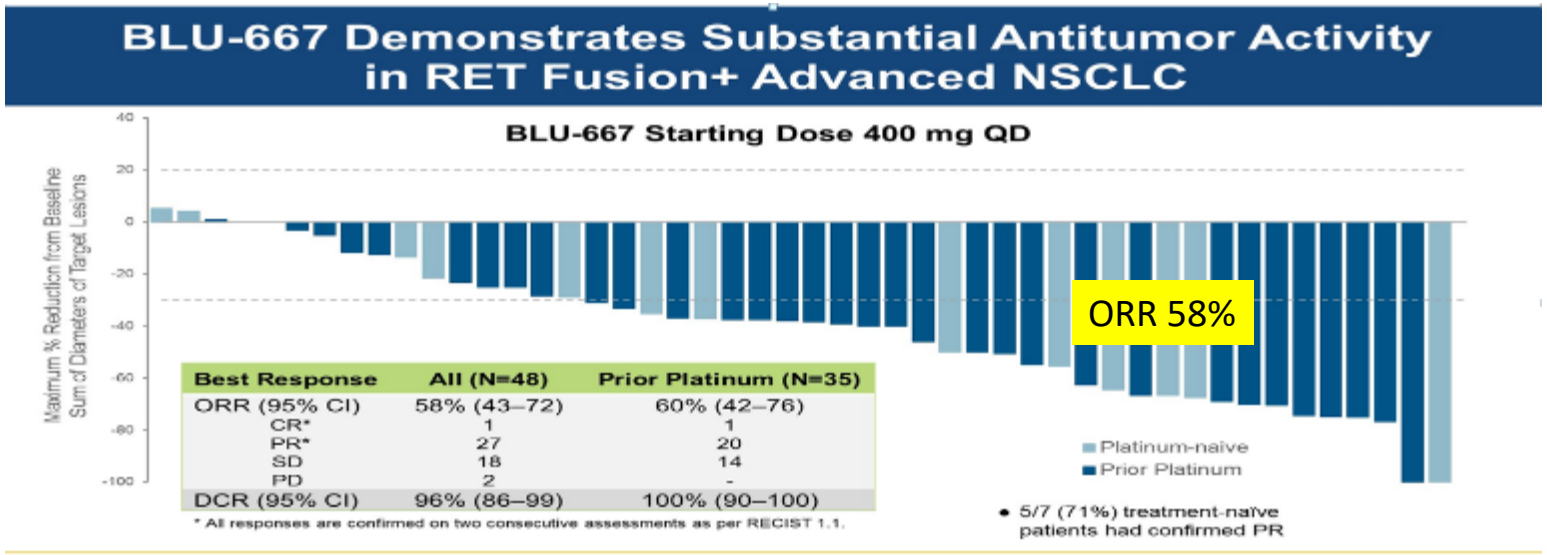
Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

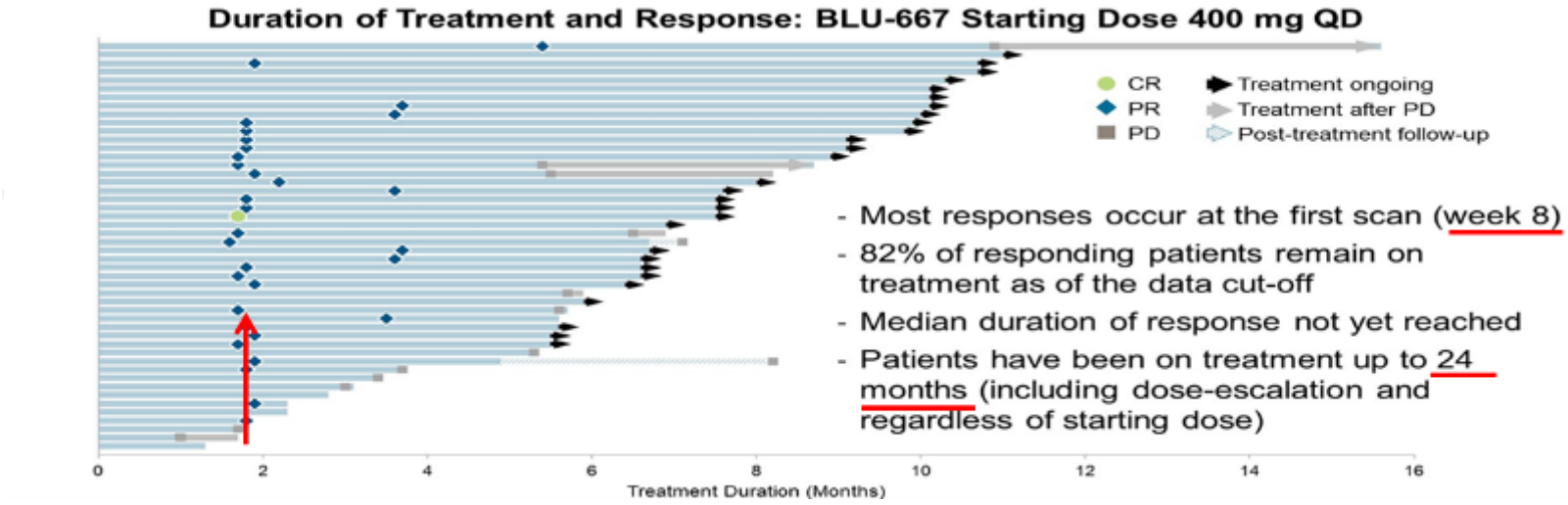
Selective Tyrosine Kinase Inhibitors

RET

	Drug names
First-generation	alectinib, cabozantinib, lenvatinib, vandetanib
Next-generation	BLU-667 Pralsetinib LOXO-292 Selpercatinib

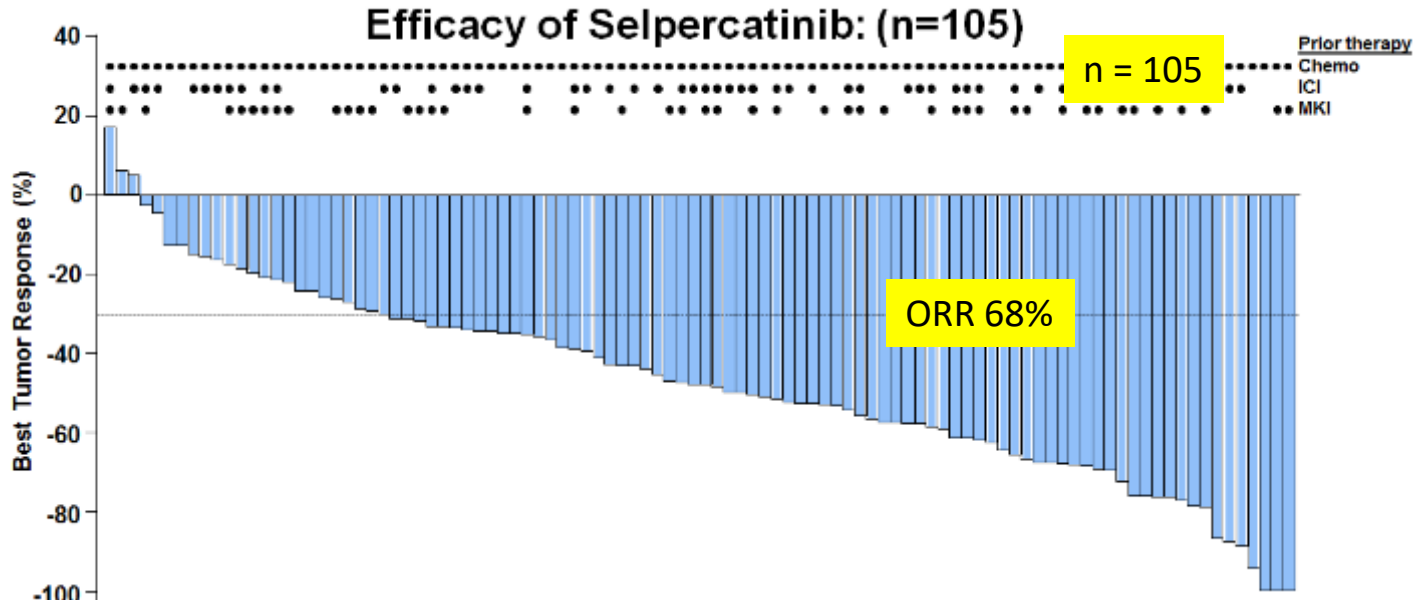
Pralsetinib

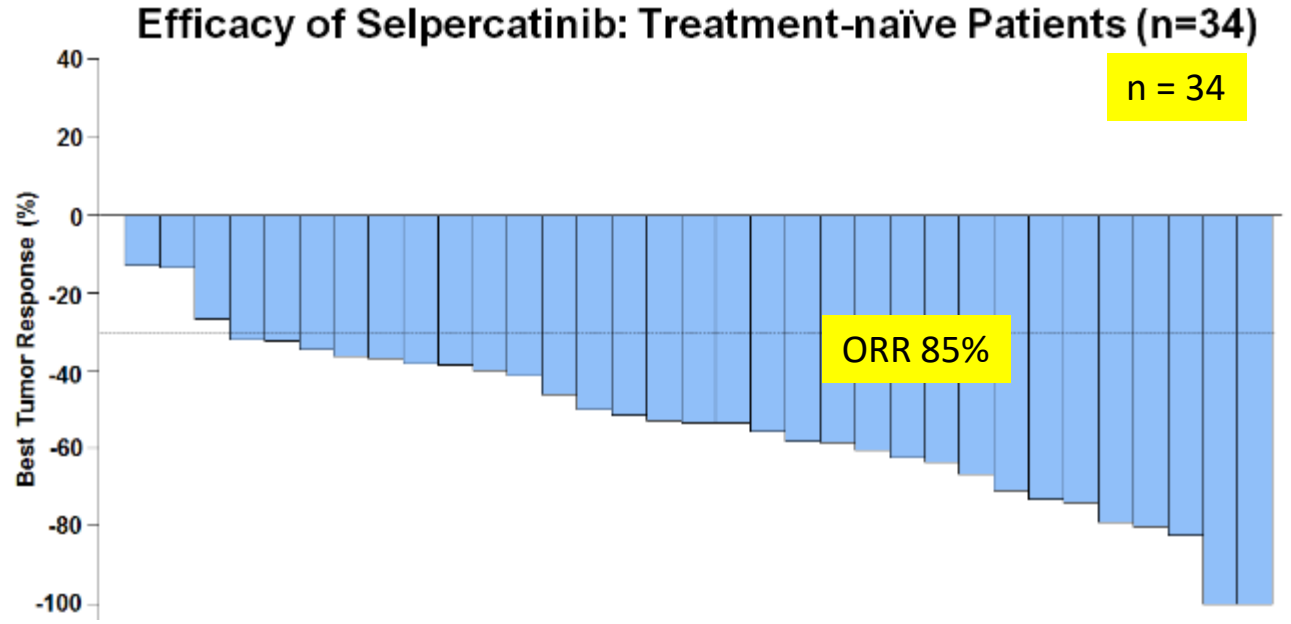




LIBRETTO-001: Selpercatinib in *RET*-Altered Cancers

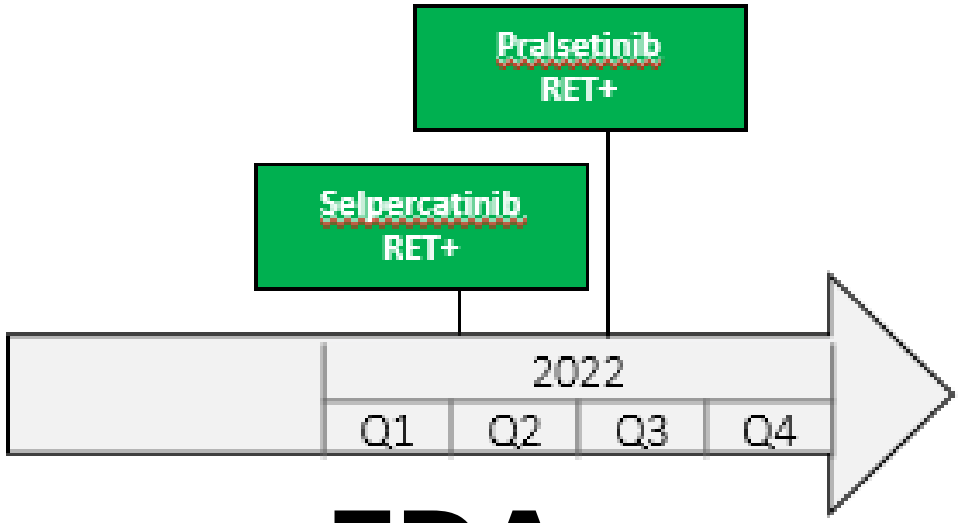
WCLC 2019





Drillon A, et al. WCLC 2019. Abstract PL02.08.

CANADA



FDA

Selpercatinib-pralsetinib

- **Accelerated approval first-line lung and thyroid with *RET* fusion, May/September 2020**

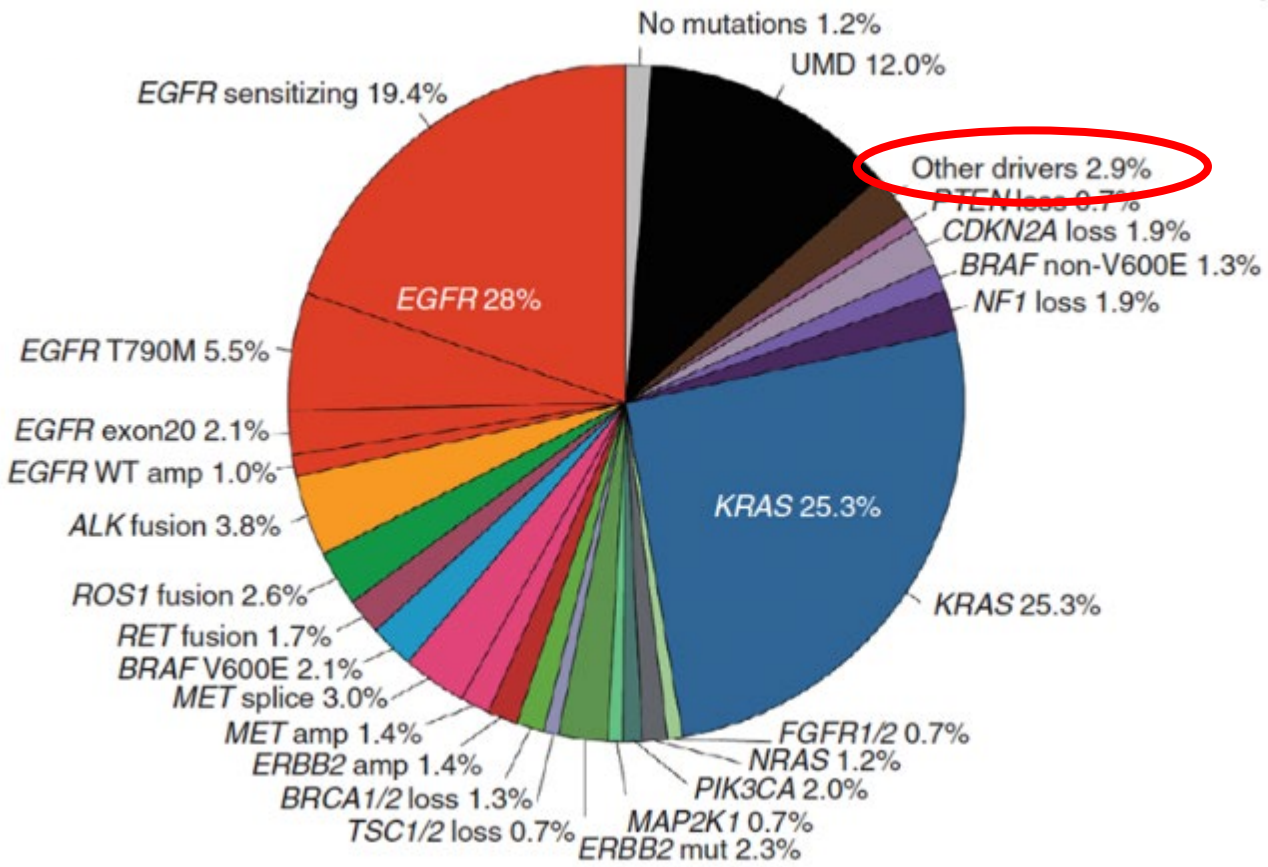
Selpercatinib

- **Accelerated approval <u>agnostic</u> *RET* fusion, September 2022**

Big Question in *RET*

- Selpercatinib or pralsetinib or both?

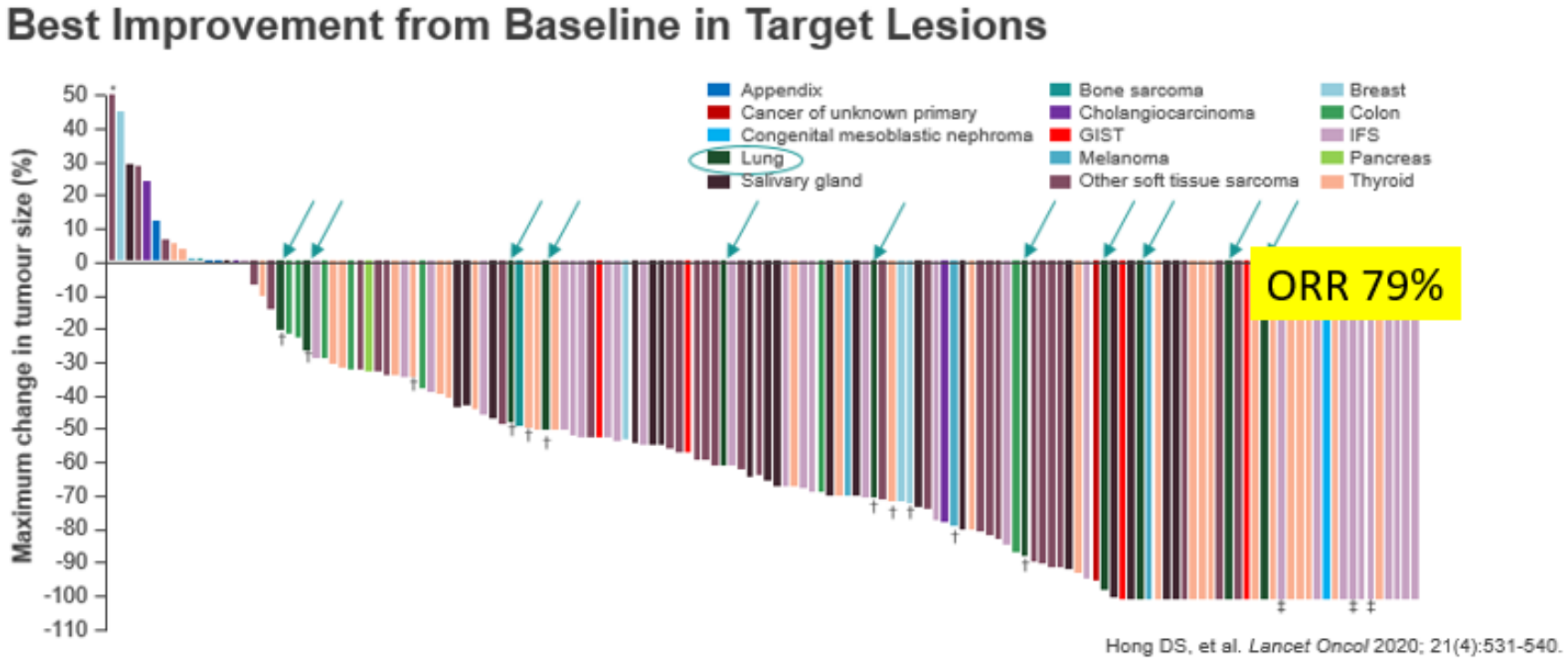
NTRK



Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

Larotrectinib

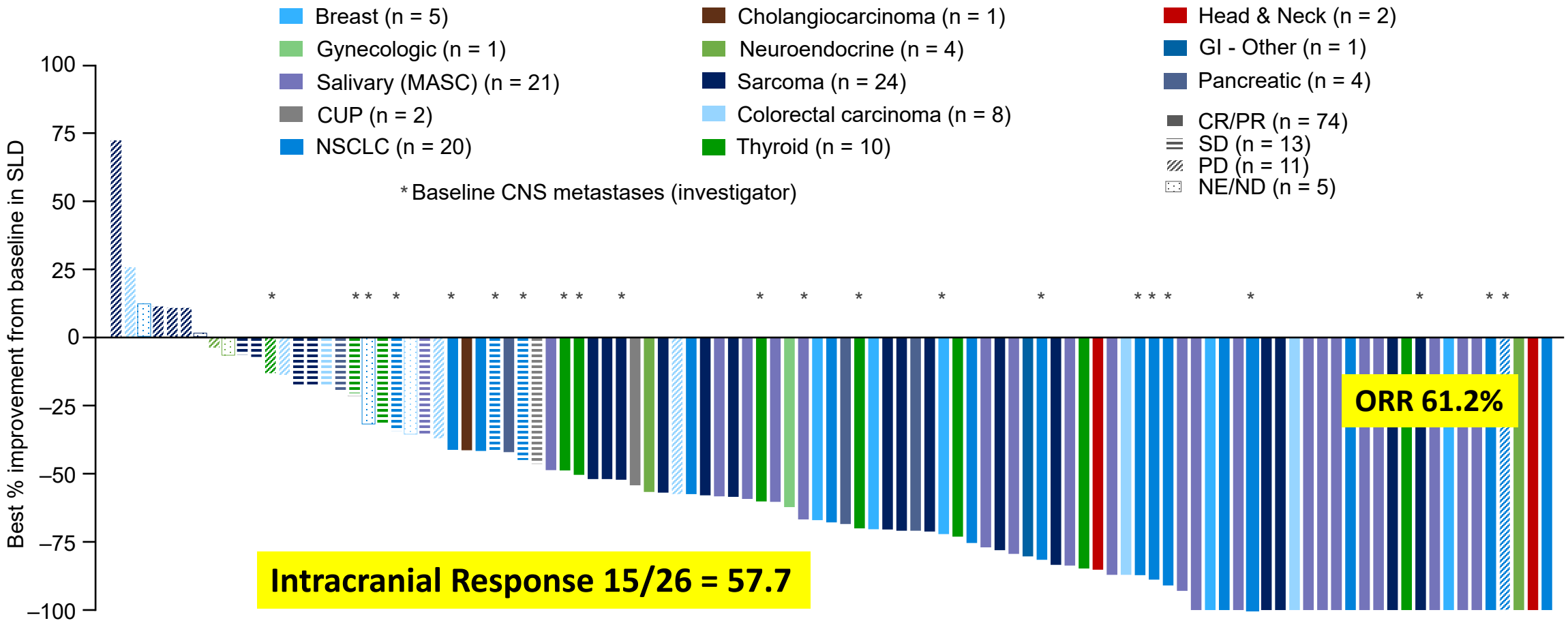
N = 159



Hong DS, et al. *Lancet Oncol*. 2020;21:531-540.

Entrectinib

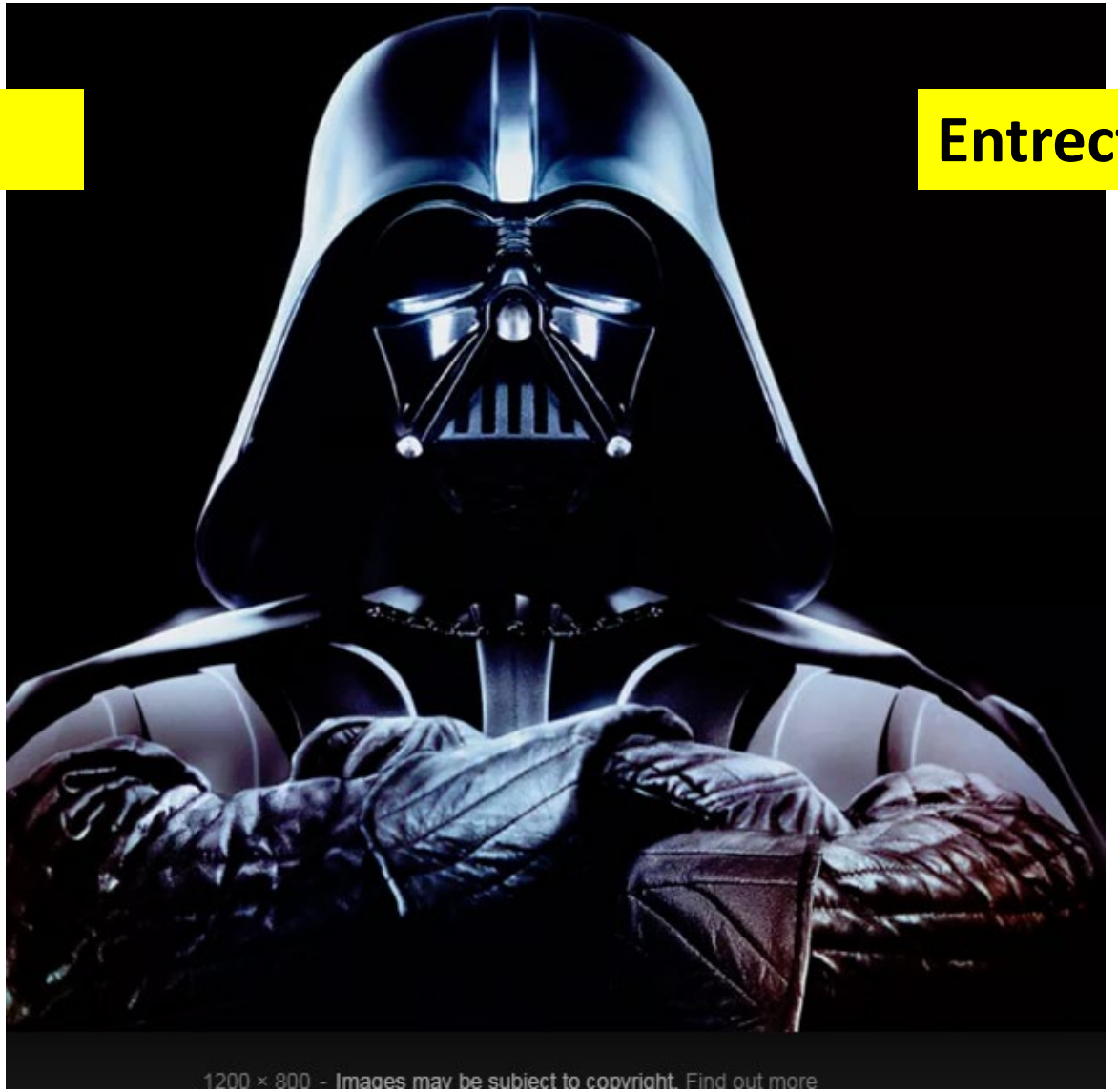
ASCO 2022



Bazhenova, et al. ESMO 2021. Poster 533P.

*NTRK*WARS

Larotrectinib

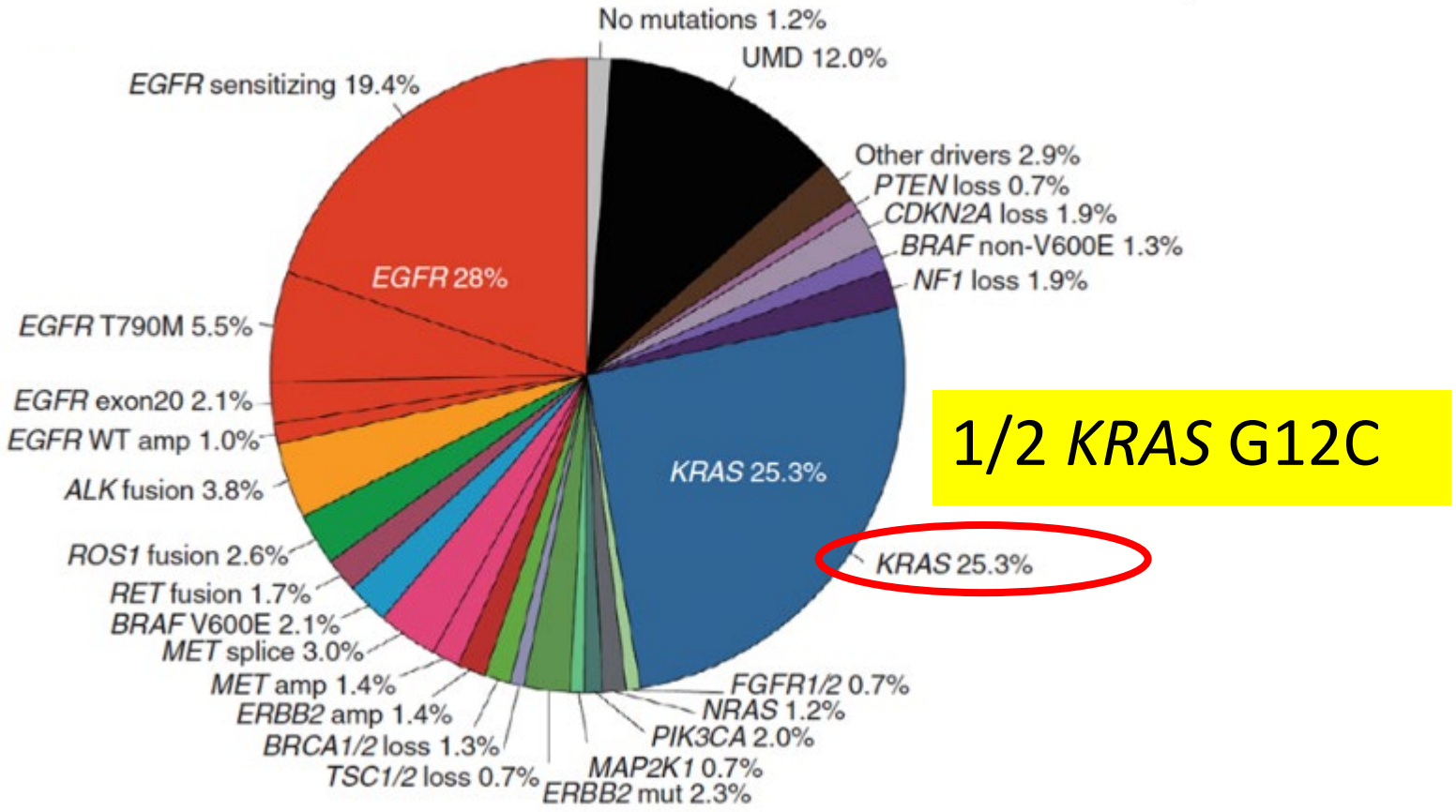


Entrectinib

Big Question in *NTRK*

- Will I ever find a patient?

KRAS



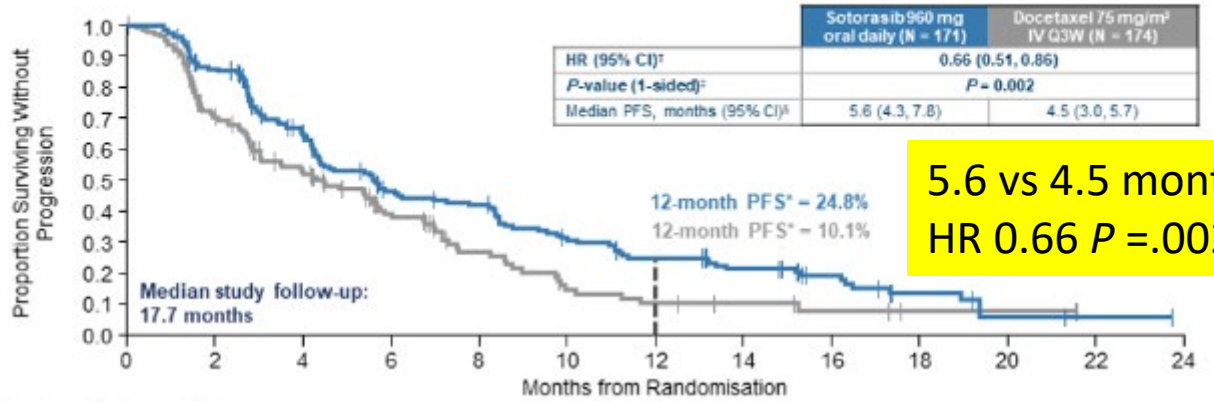
1/2 *KRAS* G12C

Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

ESMO 2022: Presidential Symposium

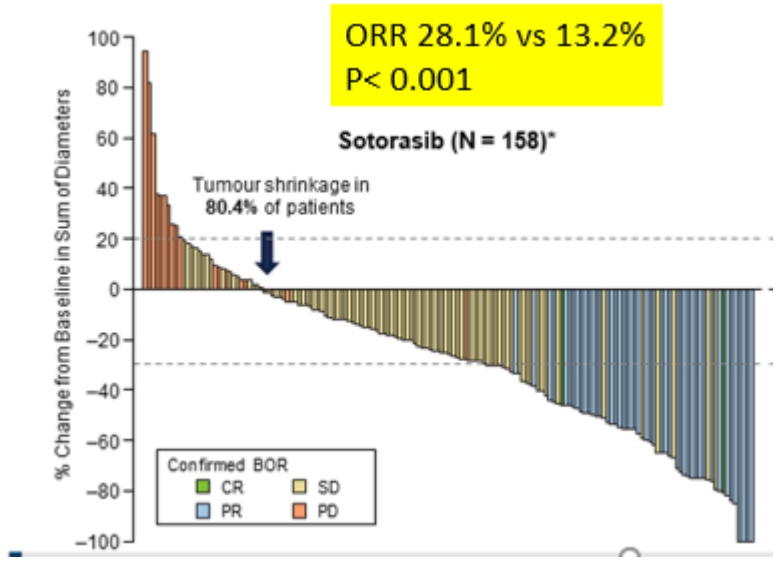
Sotorasib versus docetaxel for previously treated non-small cell lung cancer with *KRAS* G12C mutation: CodeBreaK 200 Phase 3 study

Primary Endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

5.6 vs 4.5 months
HR 0.66 *P* =.002



ORR 28.1% vs 13.2%
P< 0.001

KRAS G12C Inhibitors in Clinical Development

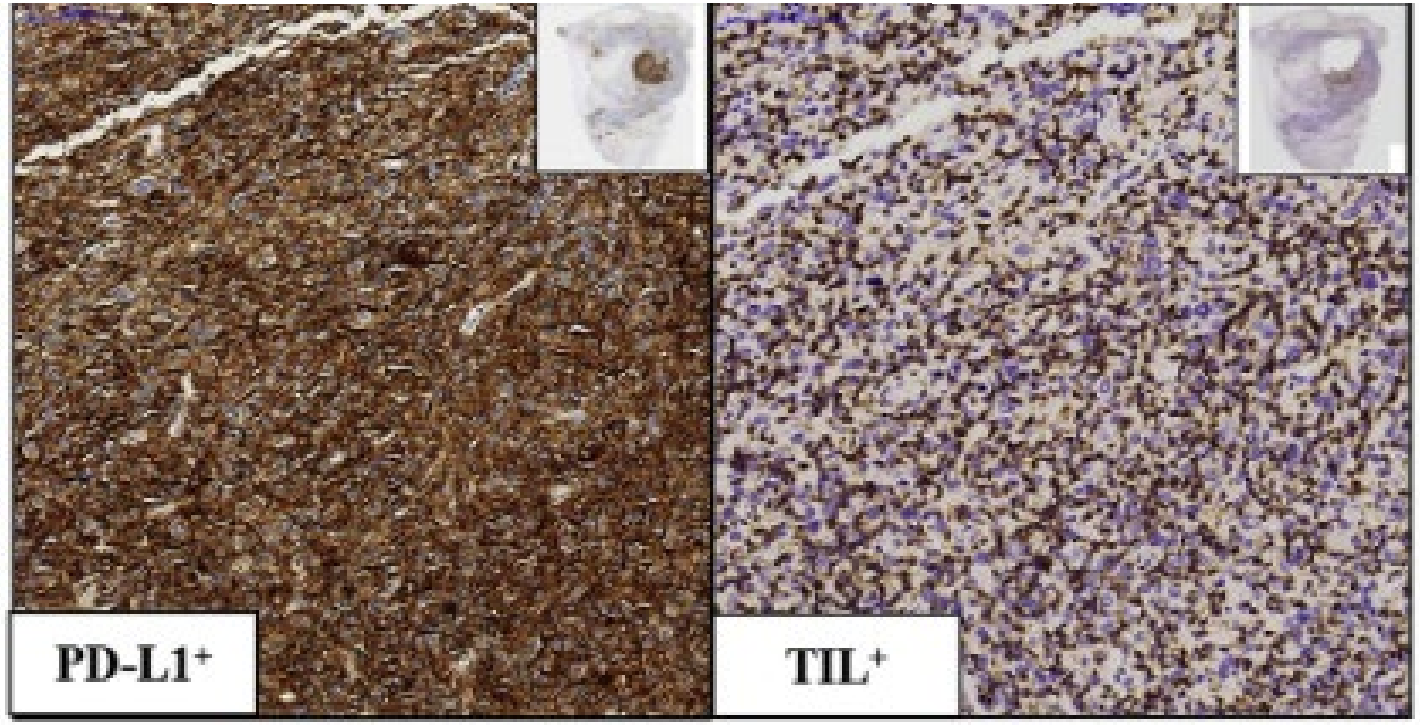
Drug	Sponsor	Stage	NCT #
Sotorasib	Amgen	Phase I-III	NCT04185883
Adagrasib	Mirati	Phase I-III	NCT03785249
GDC-6036	Genentech/Roche	Phase I	NCT04449874
JNJ-74699157	Janssen	Phase I	NCT04006301
D-1553	Inventis Bio	Phase I	NCT04585035

Several others in preclinical development……

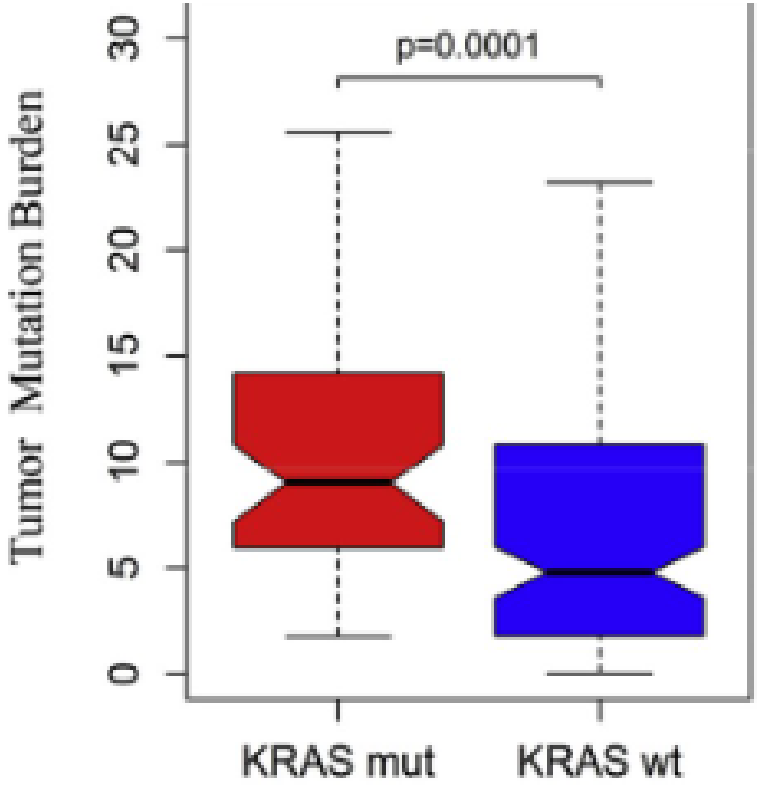
KRAS 12C Have High PD-L1/TIL and High TMB

PD-L1

TIL



TMB



Liu C, et al. *Cancer Lett.* 2020;470:95-105.

Big Question in *KRAS* 12C

- Should sotorasib be used in the first line?
- Single agent or with IO?

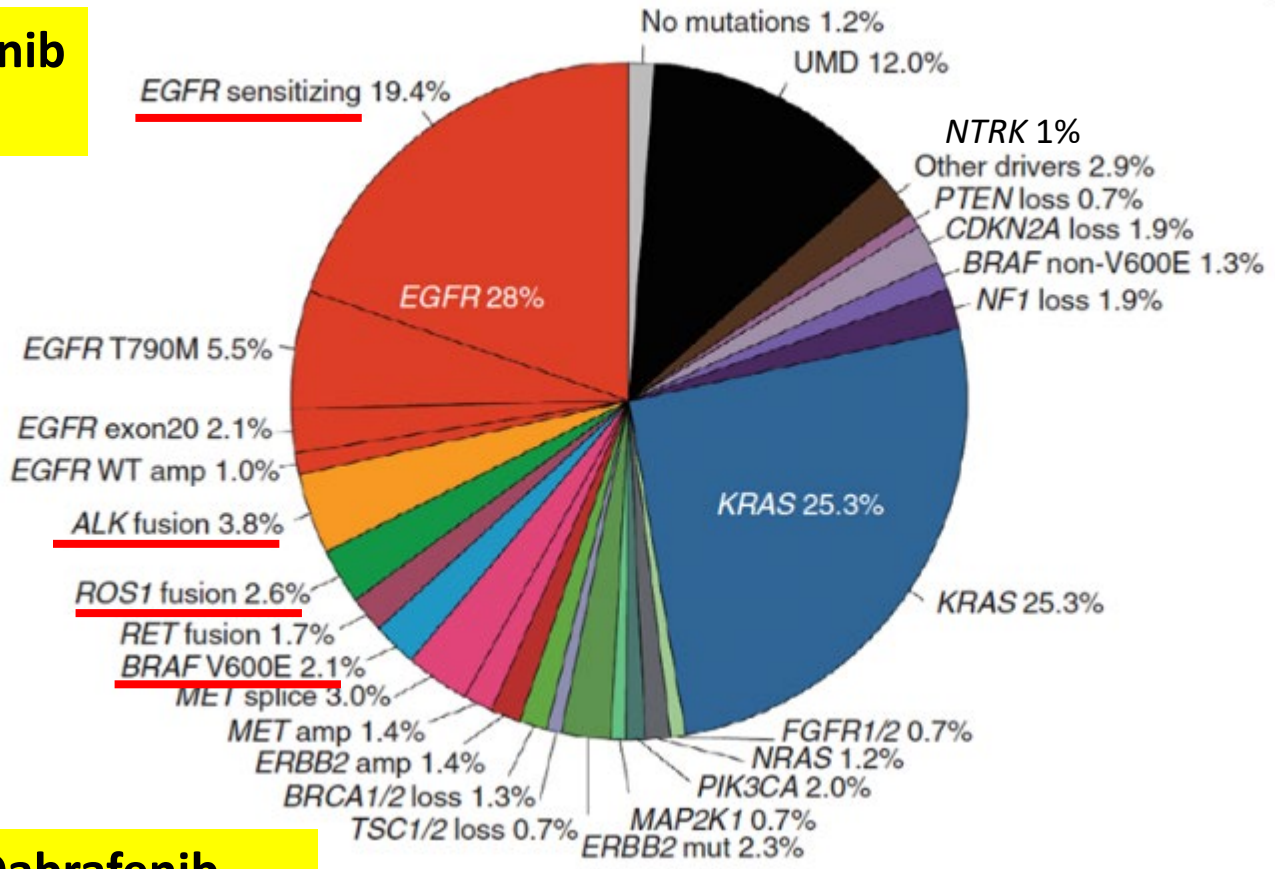
Conclusion

Osimertinib
Afatinib

Alectinib
Brigatinib
Lorlatinib

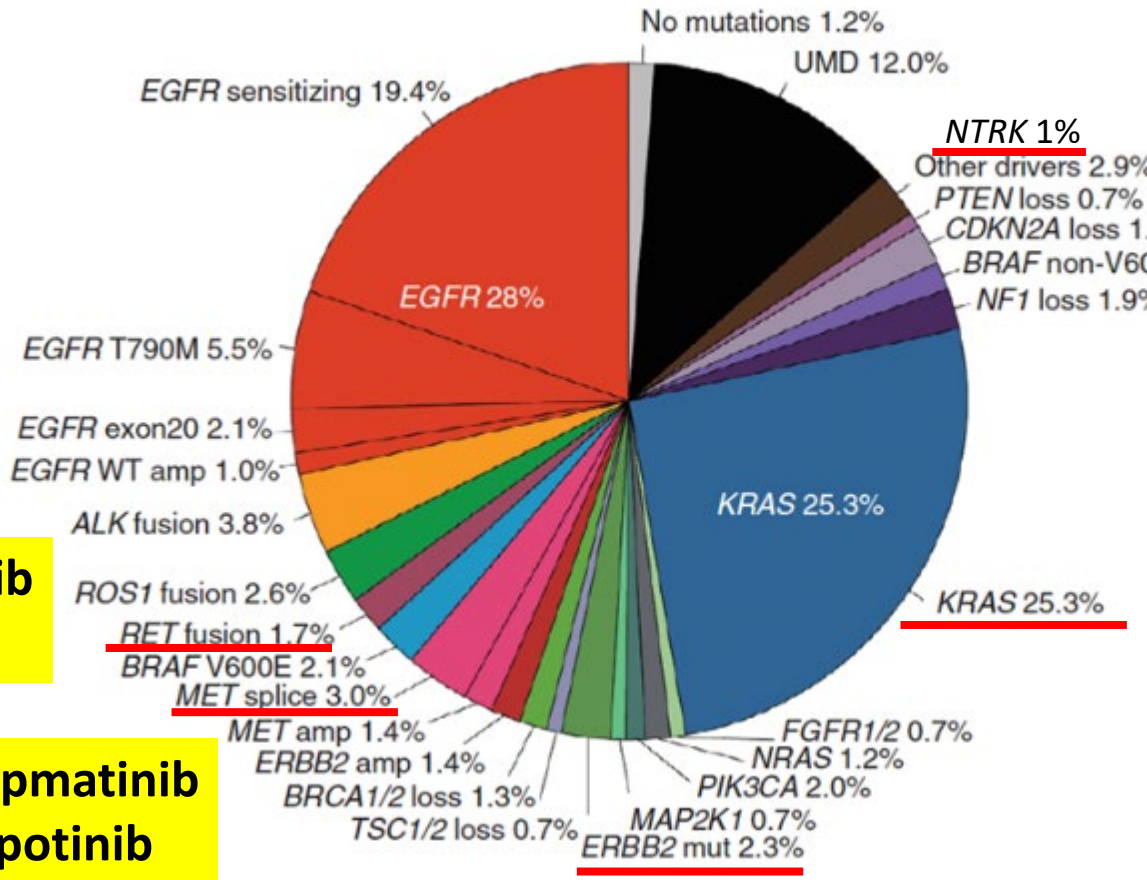
Crizotinib
Entrectinib

Dabrafenib
Trametinib



Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

Conclusion



Entrectinib
Larotrectinib

Sotorasib

Selpercatinib
Pralsetinib

Capmatinib
Tepotinib

T-DXd

Travis WD, et al. *J Thorac Oncol.* 2015;10:1243-1260; Jordan EJ, et al. *Cancer Discov.* 2017;7:596-609.

Thank You

Global Lung Cancer Academy

Immunotherapy Approaches for Advanced NSCLC

Edgardo S. Santos, MD

Immunotherapy Approaches for Advanced NSCLC

Edgardo S. Santos, M.D., FACP
Genesis Care US
Medical Director of Research Services/GC Hematology-Oncology
Thoracic Oncology
Clinical Associate Professor
Charles E. Schmidt School of Medicine/Florida Atlantic University
Treasurer, FLASCO & President, FLASCO Foundation

October 21, 2022

GenesisCare

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

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OLA
Oncology Latin American Association

Global Lung Cancer Academy

SAVE THE DATE

Sharing Best Practices to Optimize Patient Care in Lung Cancer

October 21 and 24, 2022

VIRTUAL MEETING

Friday, October 21, 2022
4.00 PM – 8.00 PM EDT

Monday, October 24, 2022
4.00 PM – 7.00 PM EDT

CHAIR
Corey J. Langer, MD, FACP
University of Pennsylvania Perelman School of Medicine, USA

CO-CHAIR
Carlos H. Barrios, MD
Oncology Research Center Hospital São Lucas, PUCRS, Brazil

Outline

- Predictive biomarkers
- Mechanism of resistance
- Monotherapy vs combination therapy strategies
- Rechallenge

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- **Predictive biomarkers and mechanism of resistance to IO**

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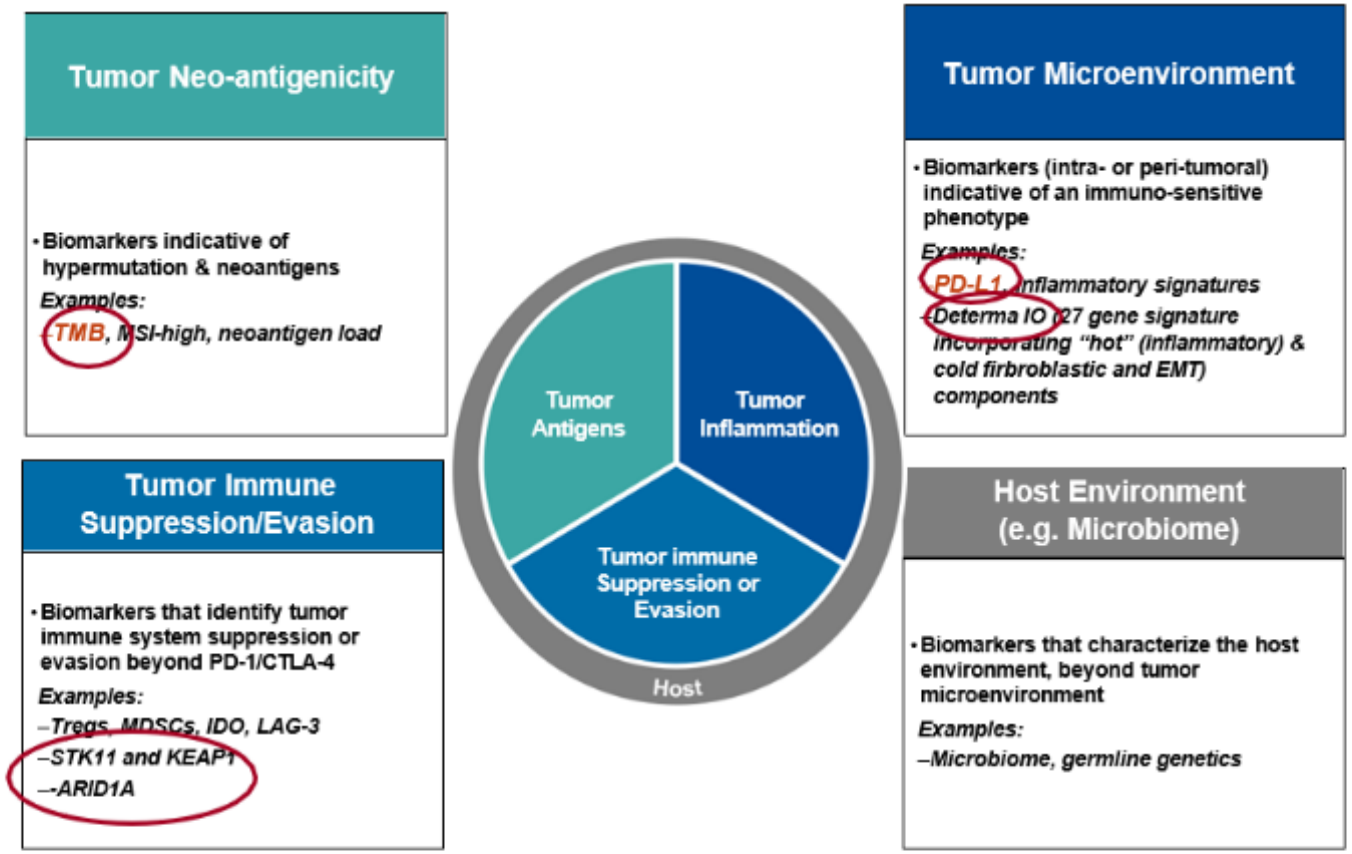
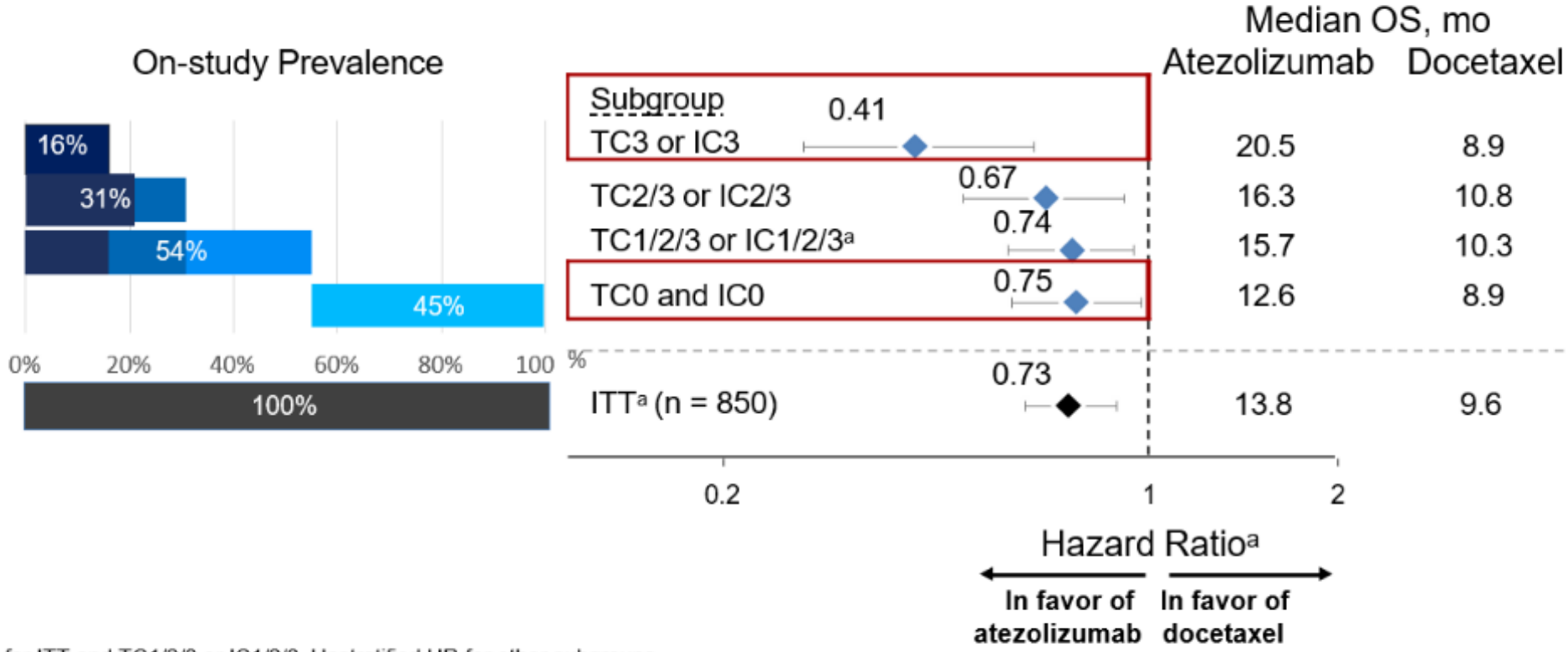
Immune Phenotype as potential Predictive Biomarkers for benefit from Checkpoint Immunotherapy



Adapted from Blank CU, et al. Science 2016;352:658–60.

OAK (Atezolizumab vs Docetaxel) in 2nd line+ Advanced NSCLC: OS by PD-L1 Expression



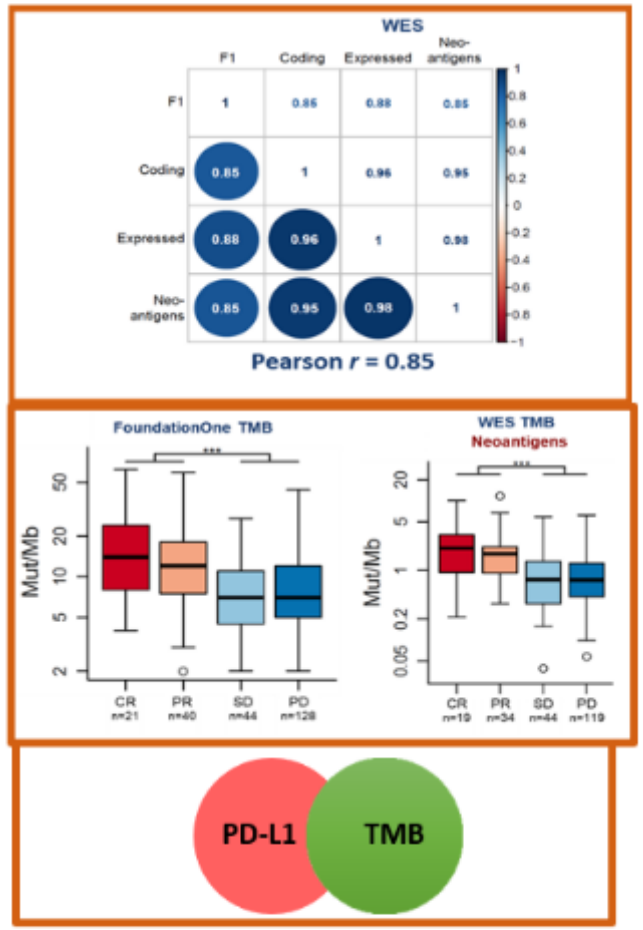
aStratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for other subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

Rittmeyer. Gandara et al. Lancet. 2017;389:255-65.

TMB as a Candidate Predictive Biomarker for Cancer Immunotherapy

- **Somatic mutations in cancers** produce **neoantigens** that induce anti- tumor immune responses
- **TMB is an emerging predictive biomarker** for cancer checkpoint immunotherapy (CIT)
- TMB can be estimated using whole-exome sequencing **(WES)** or comprehensive genomic profiling by NGS **(e.g., FoundationOne & FACT in blood[bTMB]) . MSK-IMPACT. Guardant OMNI** in blood[1-8]
  - Studies show that TMB either by WES or CGP correlate with each other & with efficacy of CPI therapy in multiple cancer types[1-3]
- **Predicted neoantigen load (NAL),** a component of TMB most closely linked to immune response, correlates with F1 TMB & OMNI[4,5,7,8]
- **TMB identifies a distinct patient population** not currently captured by PD-L1 IHC or other immune biomarkers[5,6]

IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden.
1. Yarchoan M, et al. *N Engl J Med*. 2017; 2. Chalmers ZR, et al. *Genome Med*. 2017; 3. Goodman AM, et al. *Mol Cancer Ther*. 2017; 4. Efremova M, et al. *Front Immunol*. 2017; 5. Topalian SL, et al. *Nat Rev Cancer*. 2016; 6. Kowanetz M, et al. WCLC 2017. 7. Mariathansan, et al. Nature 2018. 8. Rizvi et al: ESMO IO 2018.



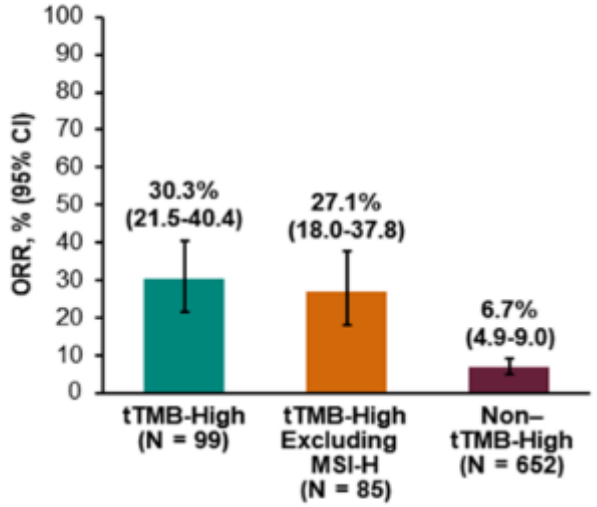
From Gandara, LeGrand et al: ASCO 2018

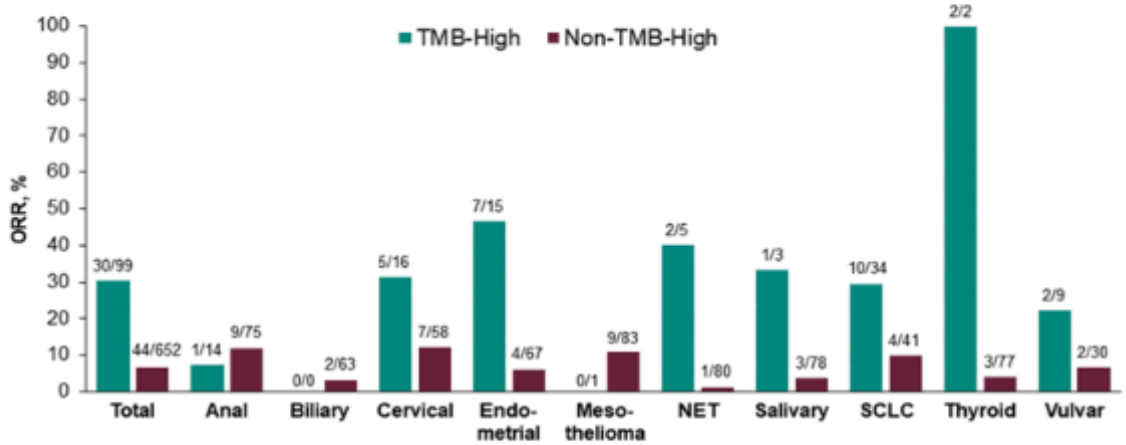
Pembrolizumab Approved for Patients with Tumor Mutational Burden-High (TMB-H) [≥10 Mutations/Megabase] Solid Tumors, as determined by an FDA-Approved Test, that Have Progressed Following Prior Treatment & Who Have No Satisfactory Alternative Treatment Options

KEYNOTE-158 (NCT02628067):
Phase 2 Multicohort Study of Pembrolizumab for Select Previously Treated Advanced Solid Tumors

Patients
- Unresectable and/or metastatic cancer
- Progression on or intolerance to standard therapy
- ECOG PS 0 or 1
- ≥1 measurable lesion
- Evaluable tumor sample for biomarker assessment

→ **Pembrolizumab 200 mg IV Q3W** for 2 years or until PD, intolerable toxicity, or withdrawal[a]

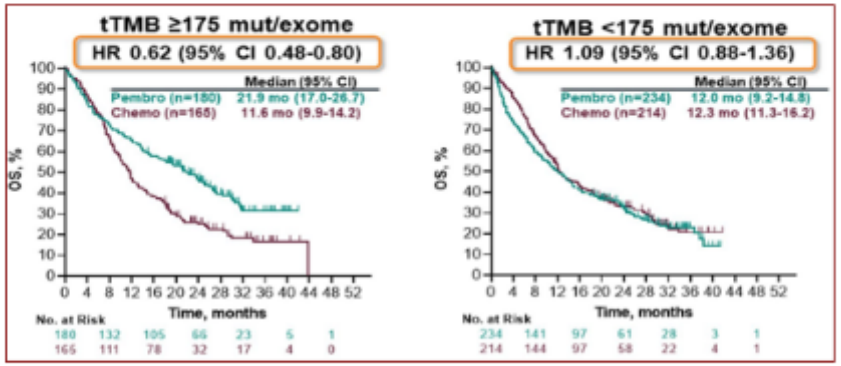




TMB in CPI Monotherapy vs CPI + Chemo Trials in NSCLC

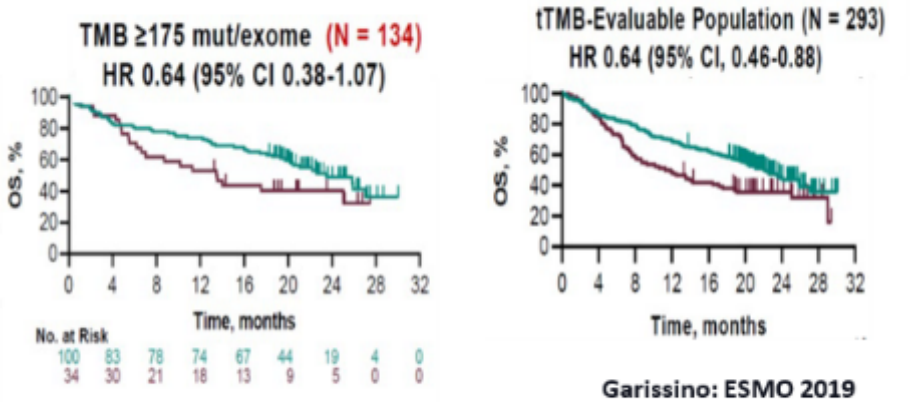
Phase III Trials	Mono- or Combination	TMB	PFS	OS
KN-010	Pembro Mono	WES-tissue	√	√
KN-042	Pembro Mono	WES-tissue	√	√
KN-189	Pembro + Chemo	WES-tissue	No	No
KN-407	Pembro + Chemo	WES-tissue	No	No

KN-042: Pembro vs Chemo: tTMB by WES



Herbst: ESMO 2019

KN-189: Pembro+Chemo vs Chemo (Non-Squamous): tTMB by WES



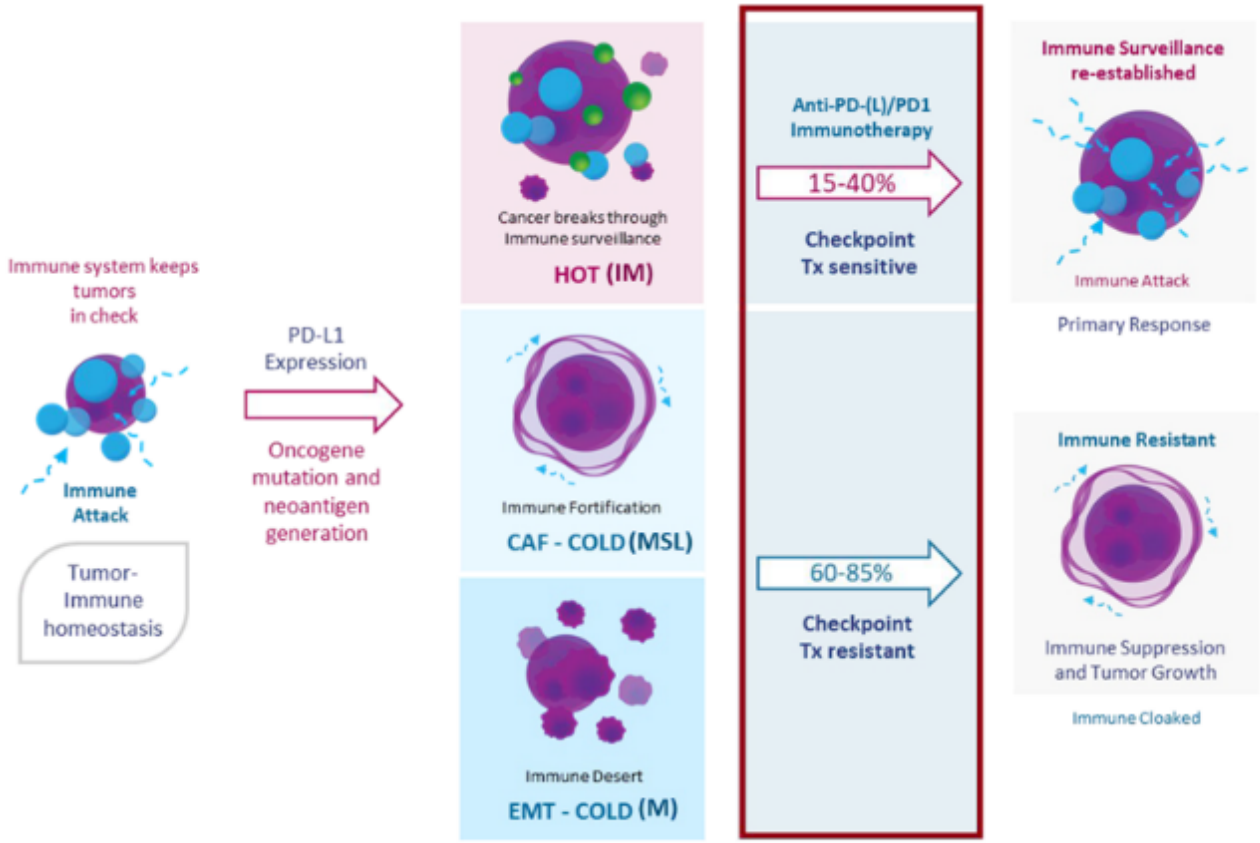
Garissino: ESMO 2019

from Gandara: Master Lecture Series 2020

27 gene assay for Immunoreactivity (Determa-IO) reflecting both "Hot" and "Cold" components of the Immune microenvironment

- Determa –IO: run as an algorithm on whole transcriptome RNAseq data
- Translated into an RTPCR assay for clinical use
- Measures 3 distinct components of the tumor immune microenvironment:
  1. Immune infiltrates (IM) ("Hot")
  2. Fibroblast/ECM component (MSL) ("Cold")
  3. Epithelial-Mesenchymal Transition (M) ("Cold")
- Specimen Requirements
  - FFPE tissue block or 5 slides (5 µm)
  - 20% tumor purity
  - Turn-around time: 5 days

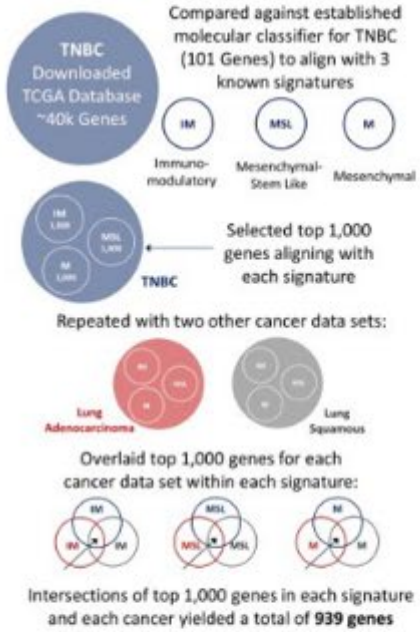
Nielsen et al Cell/Heliyon 2021.

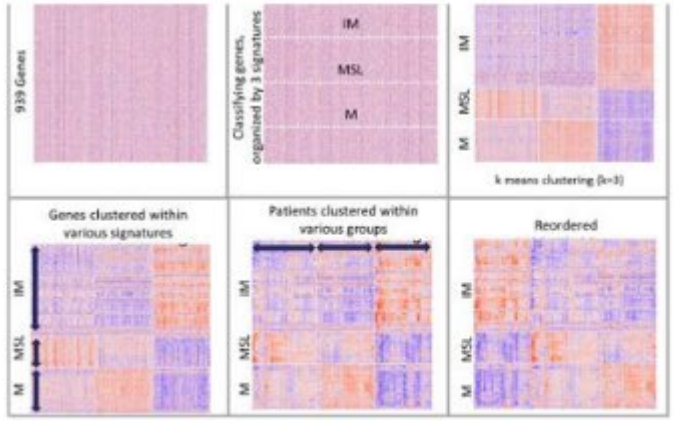


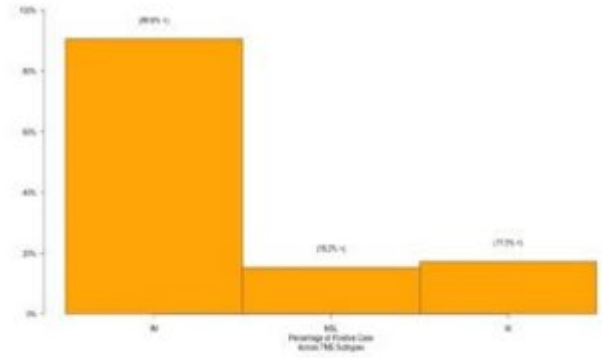
Seitz et al. AACR 2021

Applying Determa IO Across Cancer Types

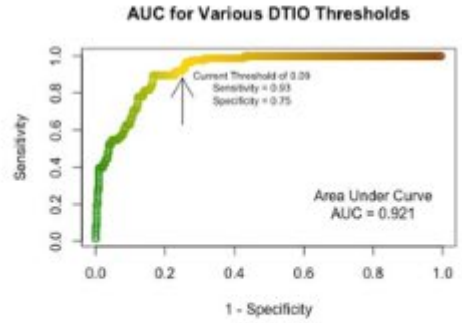
Pathway modeling shows consistent IO gene expression patterns across several solid tumor types



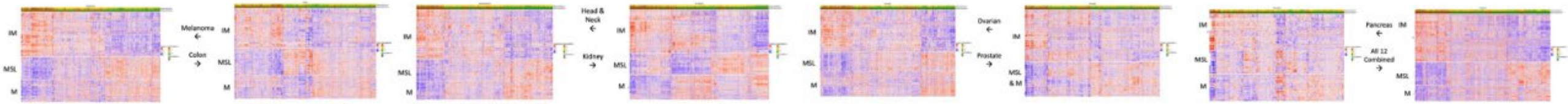




- **(Above Left)** The combined 939-gene set representing the known IM, MSL, and M signatures were clustered by gene and patient
- **(Above Right)** The 27-gene predictor was then calculated for the 406 patients and overlaid on the Heatmap (top bar, right) showi clear association with left side ("Immune Hot") portion of the map.



Similar patterns have been shown in 10+ tumor types to date:



Seitz et al. AACR 2021

Determa-IO Clinical Validation

Clinical validation data presented in multiple tumor types to date

- Non-Small Cell Lung Cancer (NSCLC)
- Triple Negative Breast Cancer (TNBC)
- Metastatic Urothelial Cancer
- Renal Cell Carcinoma
- Colorectal Cancer

- ❑ Over 1,000 patients tested across these tumor types.
- ❑ Studies involving all 4 of the FDA approved checkpoint inhibitors.
- ❑ Multiple additional studies in these and other tumor types are ongoing.

Determa IO Analysis: NSCLC Checkpoint Inhibitor Therapy

Advanced NSCLC Patients Treated with Pembrolizumab or Nivolumab

- N=71
- Histology: 18 squamous, 39 adeno, 12 other
- All patients had completed eight weeks of treatment
- 58 received ICI monotherapy
- 13 received ICI + chemotherapy

- Primary Endpoint: PFS

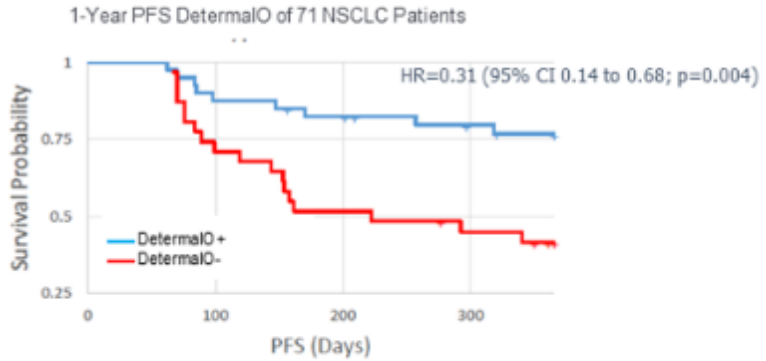
NSCLC (N=71)

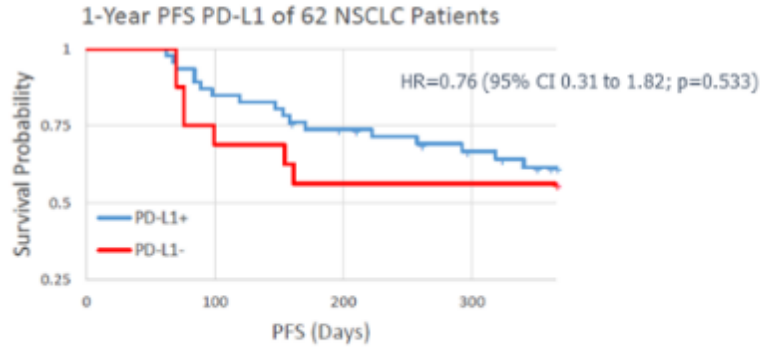
Marker	Cases	Neg.	Pos.	Percent Positive	
DetermaIO (-/+)	71	32	39	55%	
PD-L1	66	19	47	71%	1% threshold
TMB	41*	17	24	59%	>10 mutations/MgB

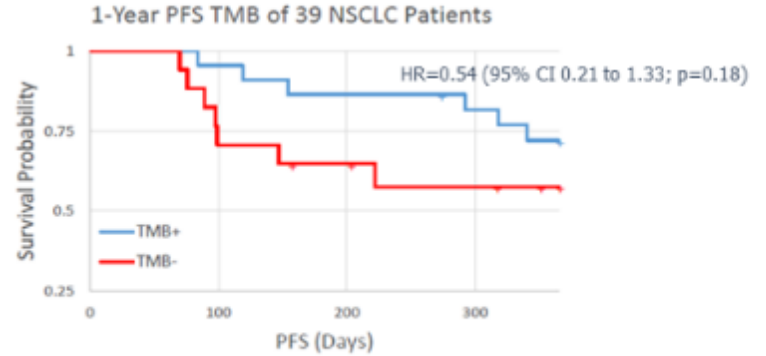
Ranganath et al. BMC Cancer 2022

DetermaIO predictive of Immunotherapy outcome independent of PD-L1 or TMB scores, demonstrating superiority to both biomarkers

Progression-free survival comparing DetermaIO to PD-L1 and TMB analysis







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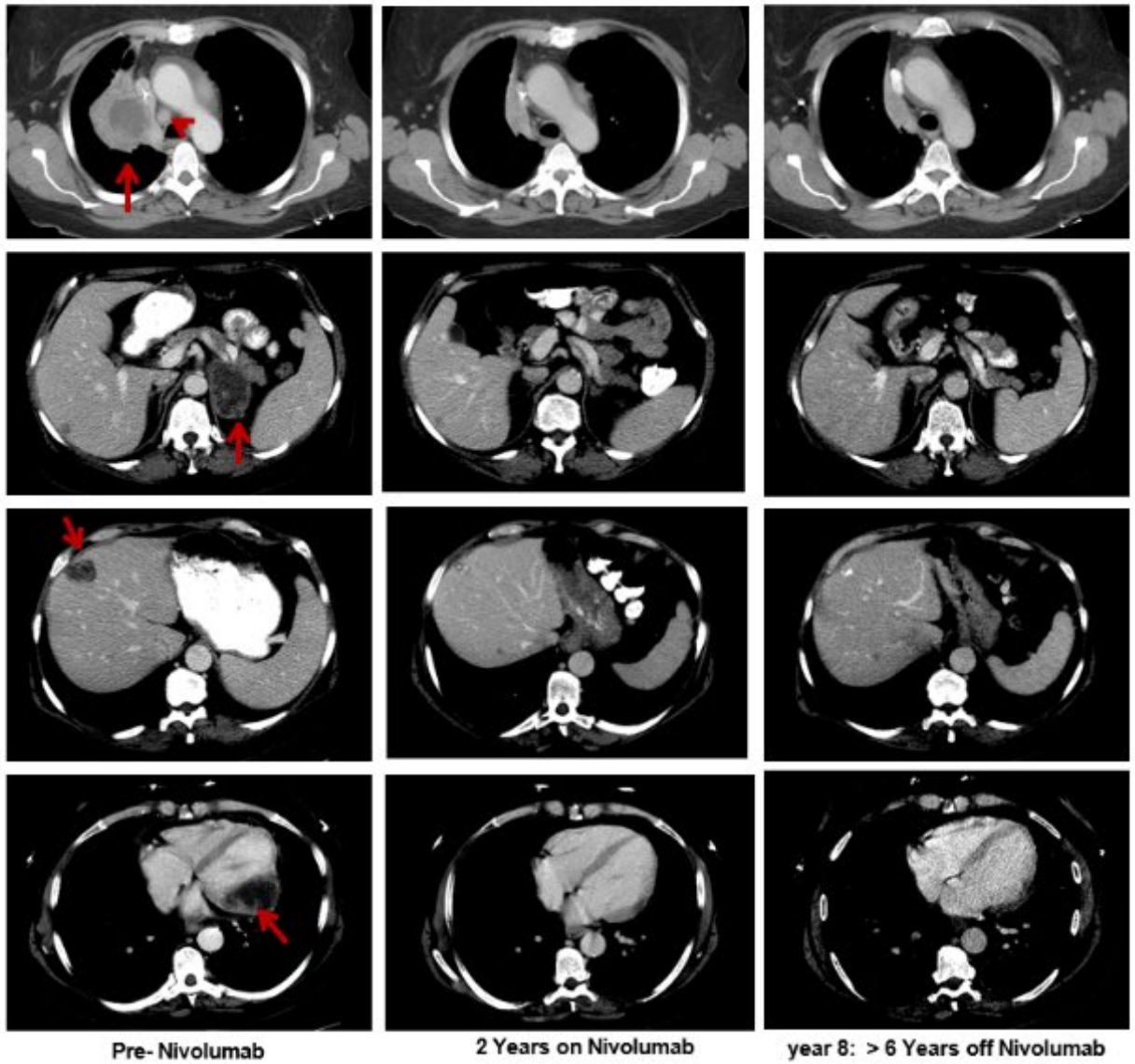
Conclusions

- Although PD-L1 and TMB are approved biomarkers for checkpoint immunotherapy, each has significant limitations at present.
- Composite IO signatures incorporating genomic markers may yield increased predictive value.
- Integrating components of the **TME** into a biomarker strategy is another approach to to improve predictive value.
- Determa IO is an analytically validated gene signature incorporating both "hot" and "cold" components of the **TME**.

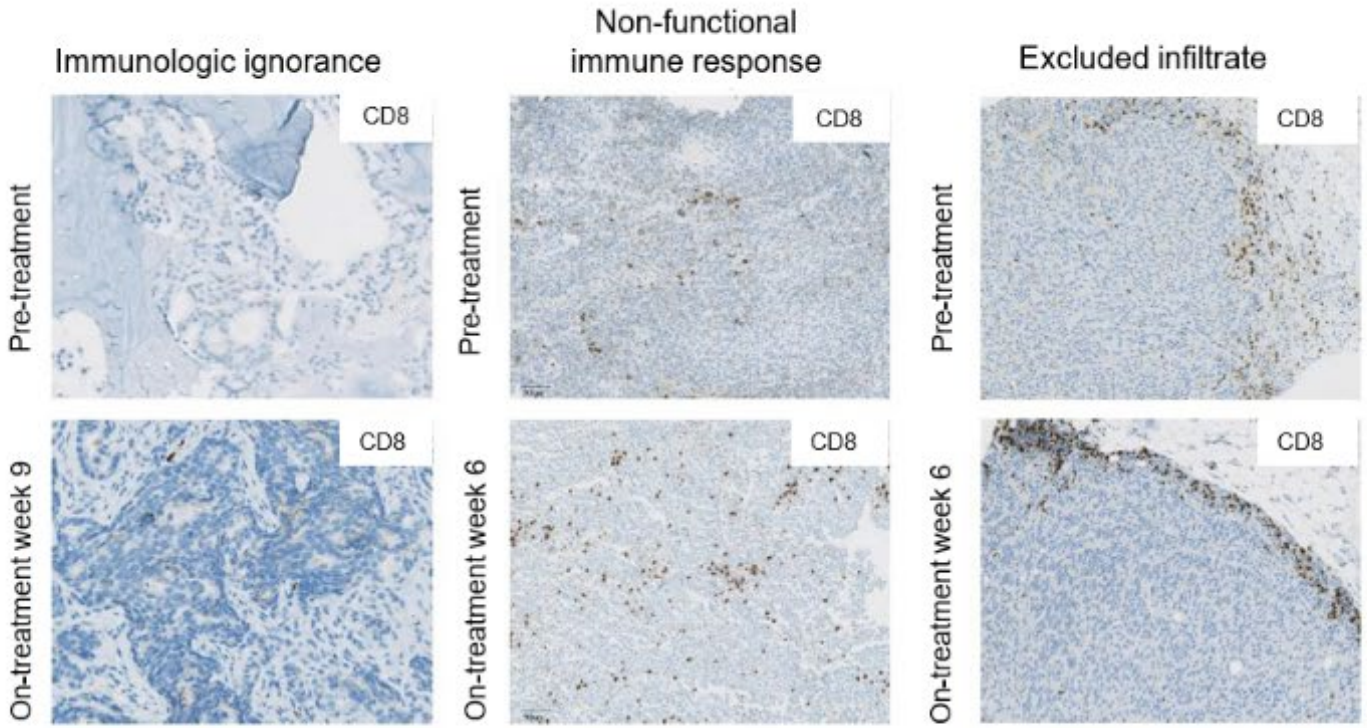


Courtesy of Scott Gettinger, Yale Centerpoint

One of the very first lung patients
on MDX-1106 (Nivolumab)
3X Chemo-Refractory
Squamous Cell NSCLC
June 2010

Biomarker Analyses
Defining the Profile of Non-responders

Immune Desert

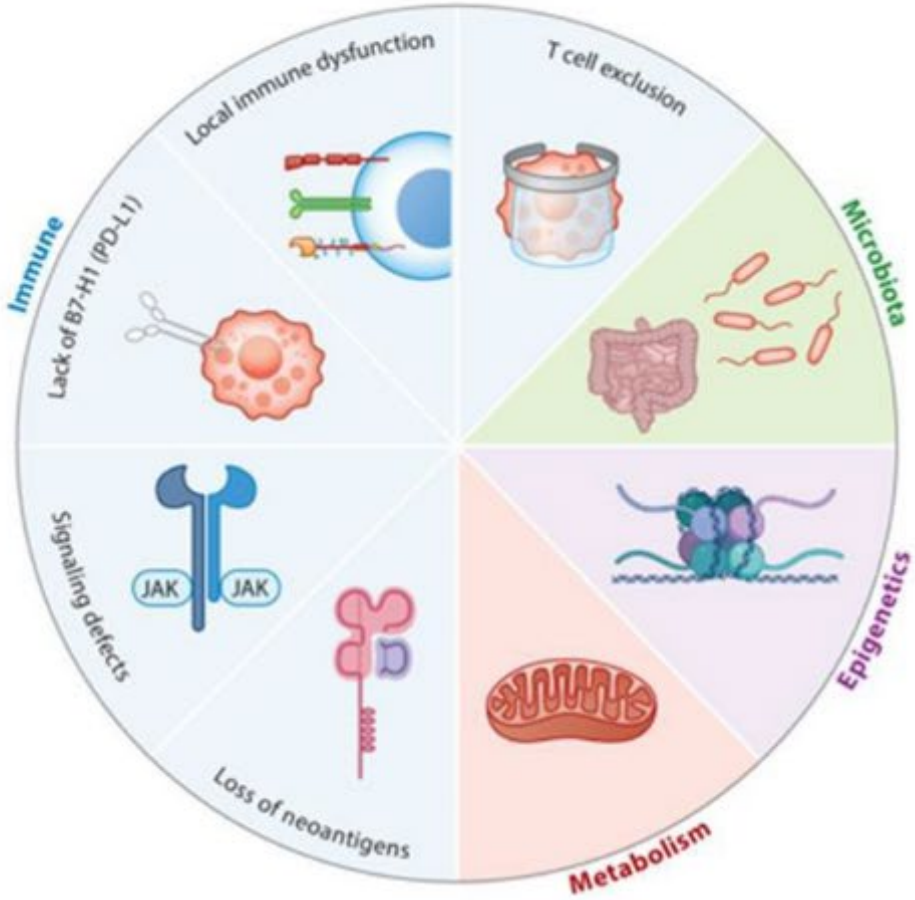


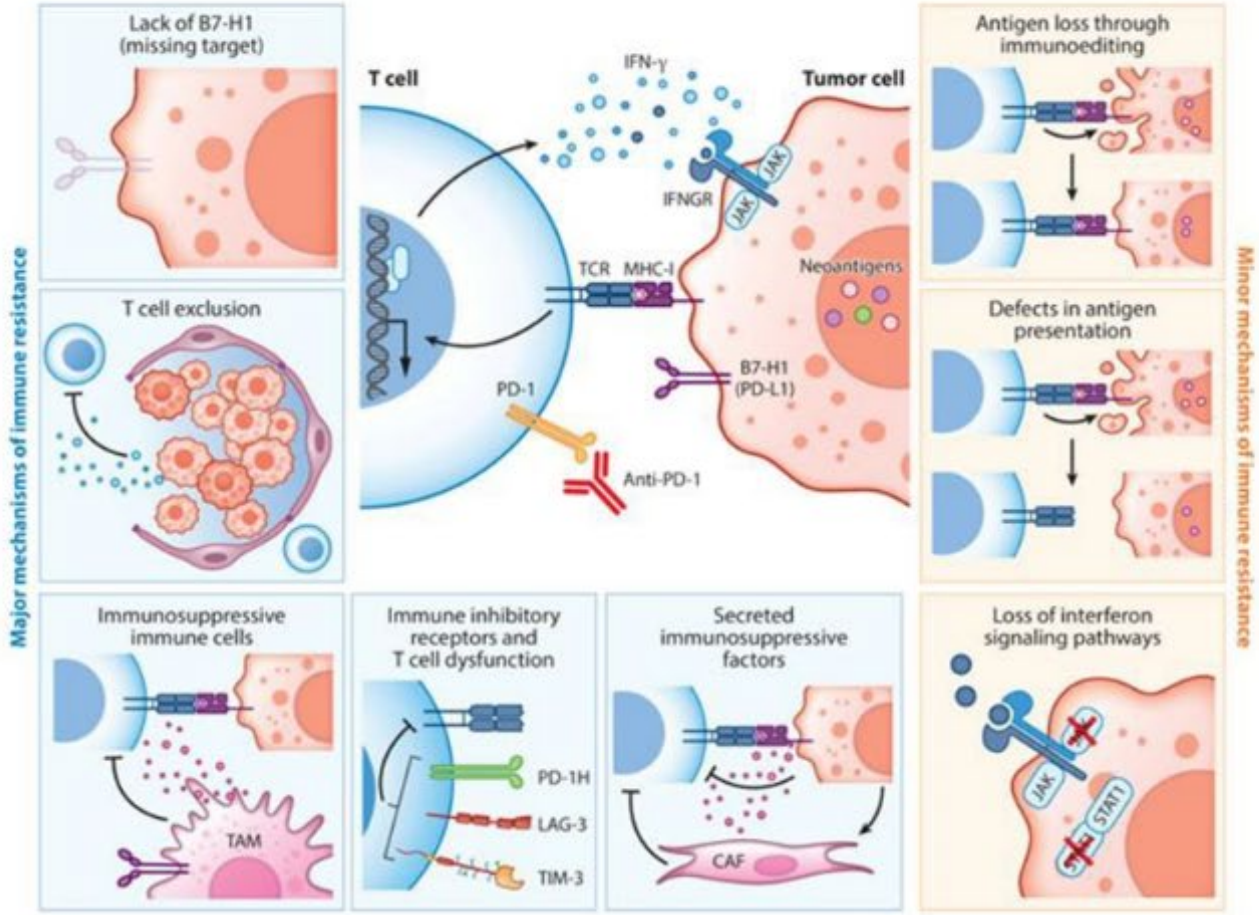
Immune Excluded

- Three distinct patterns of nonresponse were observed
- Most patients who progressed failed to show up-regulation of PD-L1 or evidence of activated T cells
- These results provide evidence for the "inflamed tumor" hypothesis

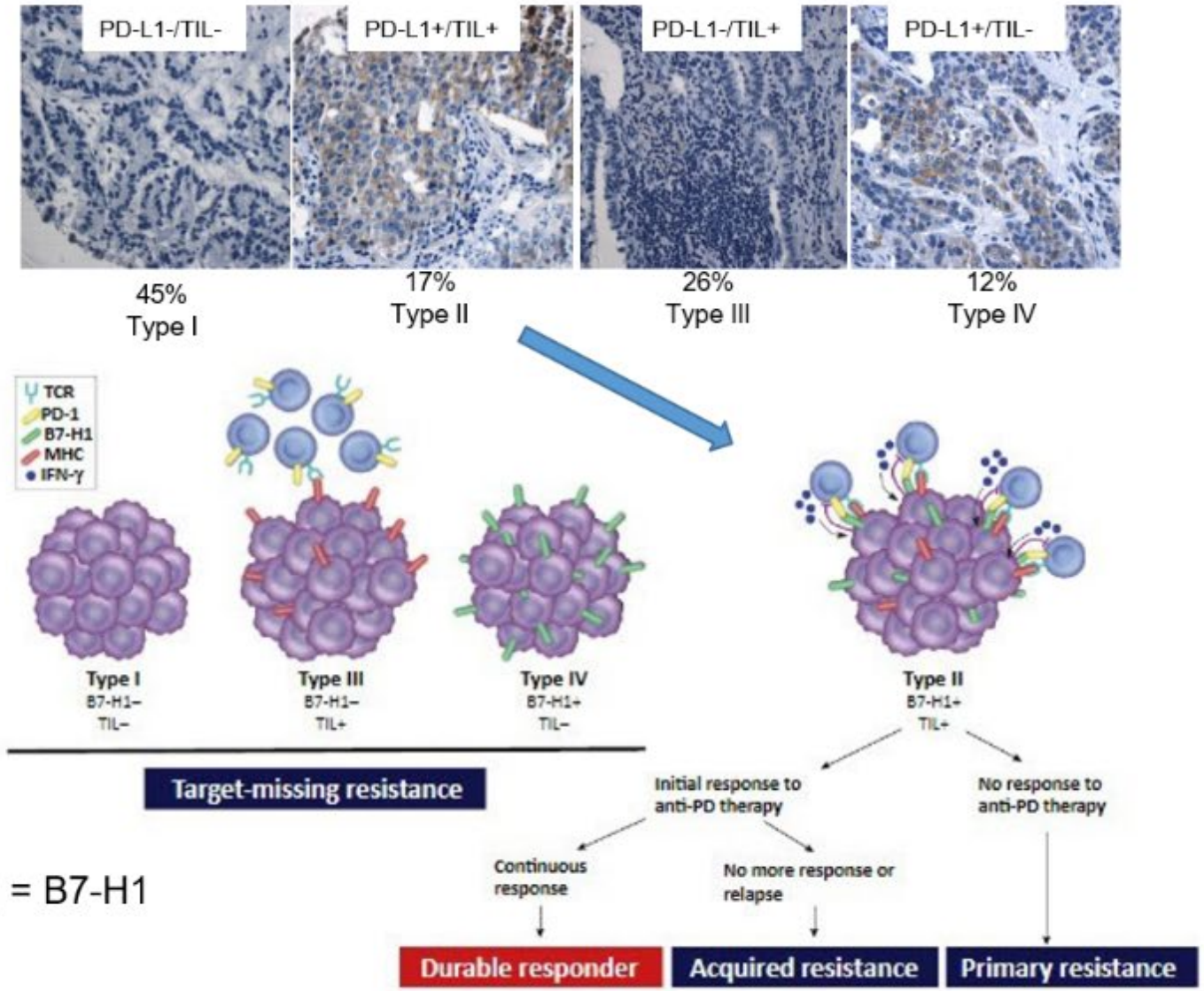
Herbst RS et al. Nature 2014;515: 563-7.

Mechanisms of Resistance to ICIs





Four Categories of Tumors
Based on Presence of PD-L1 and TILS



450 samples analyzed PD-L1 = B7-H1

Velcheti (Rimm) et al. *Lab Invest*. 2014 Jan;94(1):107-16.; Chen L. Cell; Kim et al. *Trends in Immunology* 2018

Global Lung Cancer Academy

SAVE THE DATE

Sharing Best Practices to Optimize Patient Care in Lung Cancer

October 21 and 24, 2022

VIRTUAL MEETING

Friday, October 21, 2022
4.00 PM – 8.00 PM EDT

Monday, October 24, 2022
4.00 PM – 7.00 PM EDT

CHAIR
Corey J. Langer, MD, FACP
University of Pennsylvania Perelman School of Medicine, USA

CO-CHAIR
Carlos H. Barrios, MD
Oncology Research Center Hospital São Lucas, PUCRS, Brazil

- **Monotherapy vs combination therapy strategies**

GenesisCare

OLA

FLASCO

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

Clinical case.

60-yr-old female patient heavy smoker in the past (25 py) presented with sudden SOB and pleuritic pain. Work up at the ER (CTA chest) revealed bilateral pulmonary embolism and incidentally a 4.2 cm in LUL as well as bilateral mediastinal adenopathy. Patient is placed on heparin drip and sent for CT guided biopsy. Tissue biopsy revealed adenocarcinoma (TTF-1, Napsin A +; CK20 neg); and TMP is requested. Patient is discharged in stable condition on apixaban. TMP revealed EGFR/ALK/ROS1/BRAF/RET/MET/KRAS/NTRK/HER2 negative, STK11 +, PD-L1 80%. Staging w/u showed no brain metastases and single lesion in L adrenal gland 1.4 cm (SUV 13).

What therapeutic options are considered category 1 by the NCCN?

1. Carbo/Pemetrexed/Pembrolizumab
2. Carbo/Paclitaxel/Bevacizumab/Atezolizumab
3. Cemiplimab
4. Nivolumab/Ipilimumab
5. Carbo/nab-paclitaxel/atezolizumab
6. Carbo/pemetrexed/nivolumab/ipilimumab
7. 2,3,4
8. 4,5,6
9. 1,2,3,4,6
10. 1,2,3,6
11. 1,2,3

For PD-L1 ≥ 50% & no actionable mutation & PS 0-2

Preferred
- **Pembrolizumab (category 1) or**
- **(Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1) or**
- **Atezolizumab (category 1) or**
- **Cemiplimab-rwlc (category 1)**

Other Recommended
- **Carboplatin + paclitaxel + bevacizumab[rr,ss] + atezolizumab (category 1) or**
- **Carboplatin + albumin-bound paclitaxel + atezolizumab or**
- **Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)**

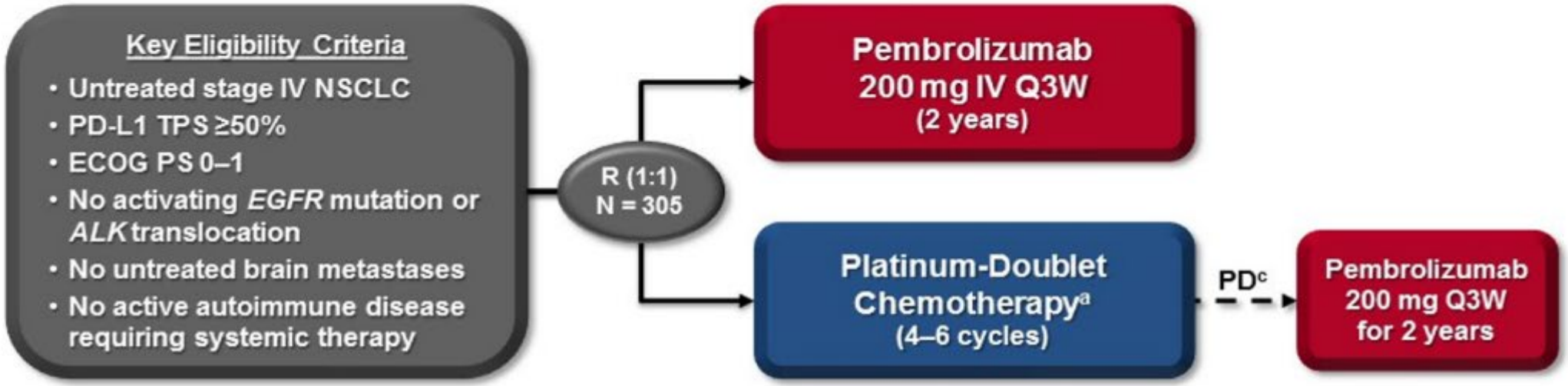
Useful in Certain Circumstances
- **Nivolumab + ipilimumab (category 1)**

NCCN v5.2022, 09/26/2022

Answer: 9

Mono IO

KEYNOTE-024 Study Design (NCT02142738)



End Points

Primary:	PFS (RECIST v1.1, blinded independent central review)
Key secondary:	OS
Secondary:	ORR, safety
Exploratory:	DOR

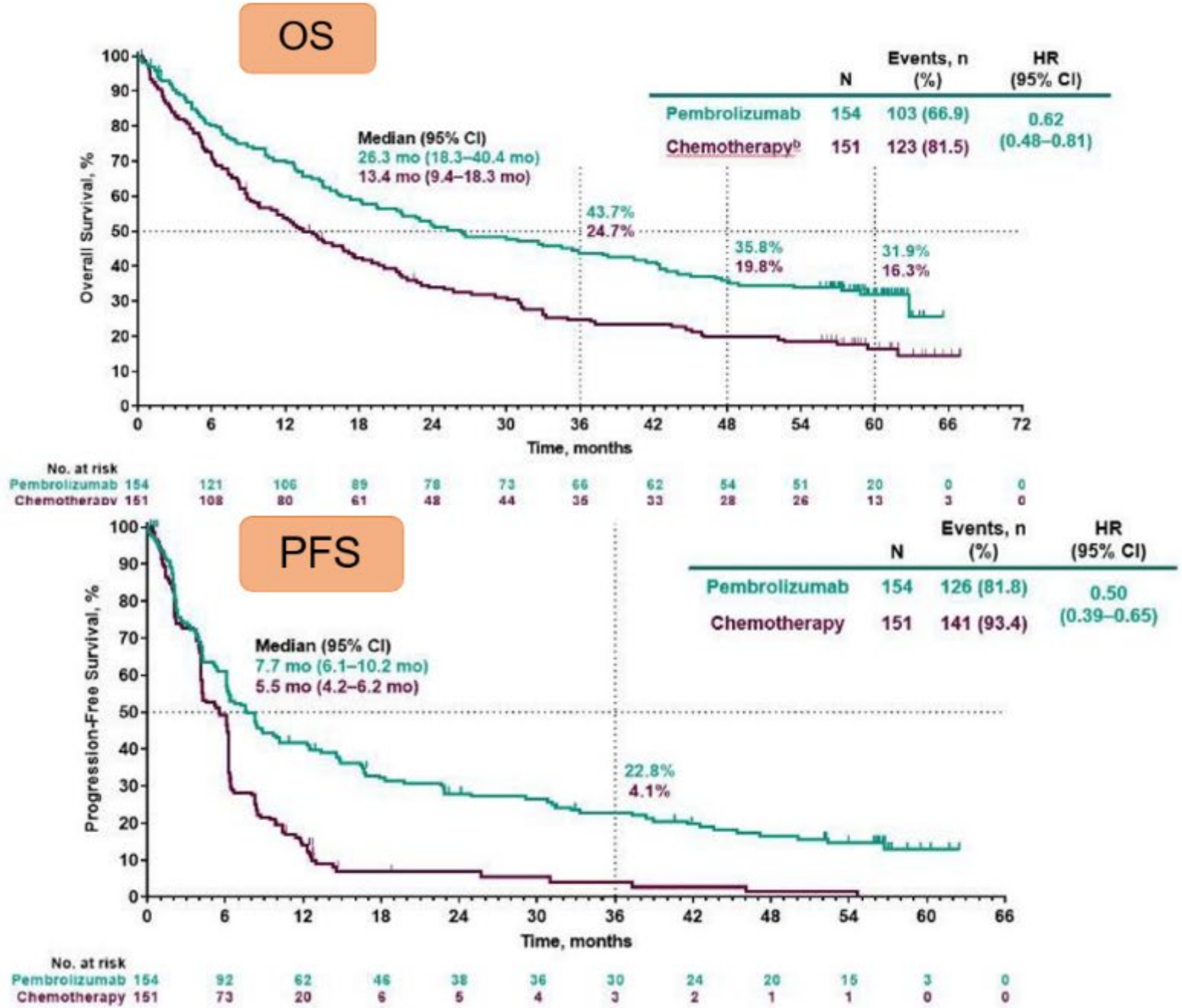
[a]Optional pemetrexed maintenance therapy for nonsquamous disease. [b]Permitted for nonsquamous disease only.
[c]Prior to the DMC recommendation and amendment 6, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent central radiology review.

5 Year OS:
Median
26.3 mo (18.3-40.4 mo) 31.9% vs.
13.4 mo (94-18.3 mo) 16.3%
HR: 0.62 (0.48-0.81)

3 Year PFS:
Median
7.7 mo (6.1-10.2 mos) 22.8% vs.
5.5 mo (4.2-6.2 mo) 4.1%
HR: 0.50 (0.39-0.65)

Overall Response Rate:
46.1% vs. 31.1%
Partial Response:
41.6% vs. 31.1%
Complete Response:
4.5% vs. 0

J.R. Brahmer KEYNOTE-024 *ESMO 2020: LBA 51*



KEYNOTE-042 Study Design

B Cho. WCLC Jan 2021

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥1%[a]
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- No untreated or unstable central nervous system metastases
- No history of pneumonitis that required systemic corticosteroids

N = 637

Pembrolizumab 200 mg Q3W for up to 35 cycles[b]

Second-Course Pembrolizumab[b]

Pembrolizumab 200 mg Q3W 17 cycles (1 year)

R 1:1

N = 637

Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W[c] OR Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W[c] for up to 6 cycles

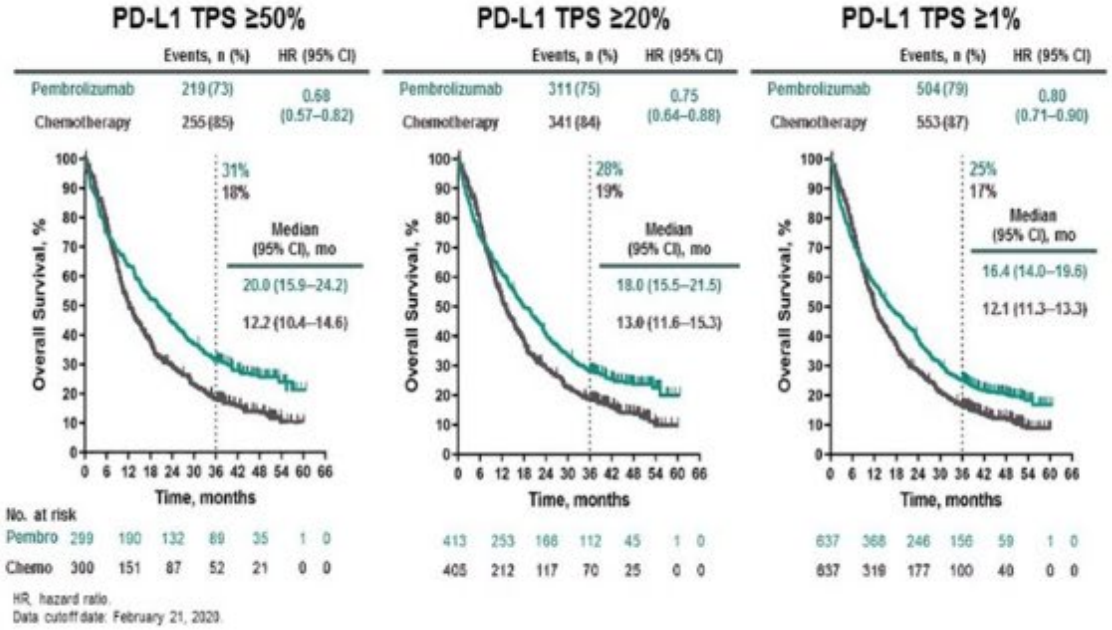
Stratification Factors

- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS (≥50% vs 1%–49%)

Endpoints

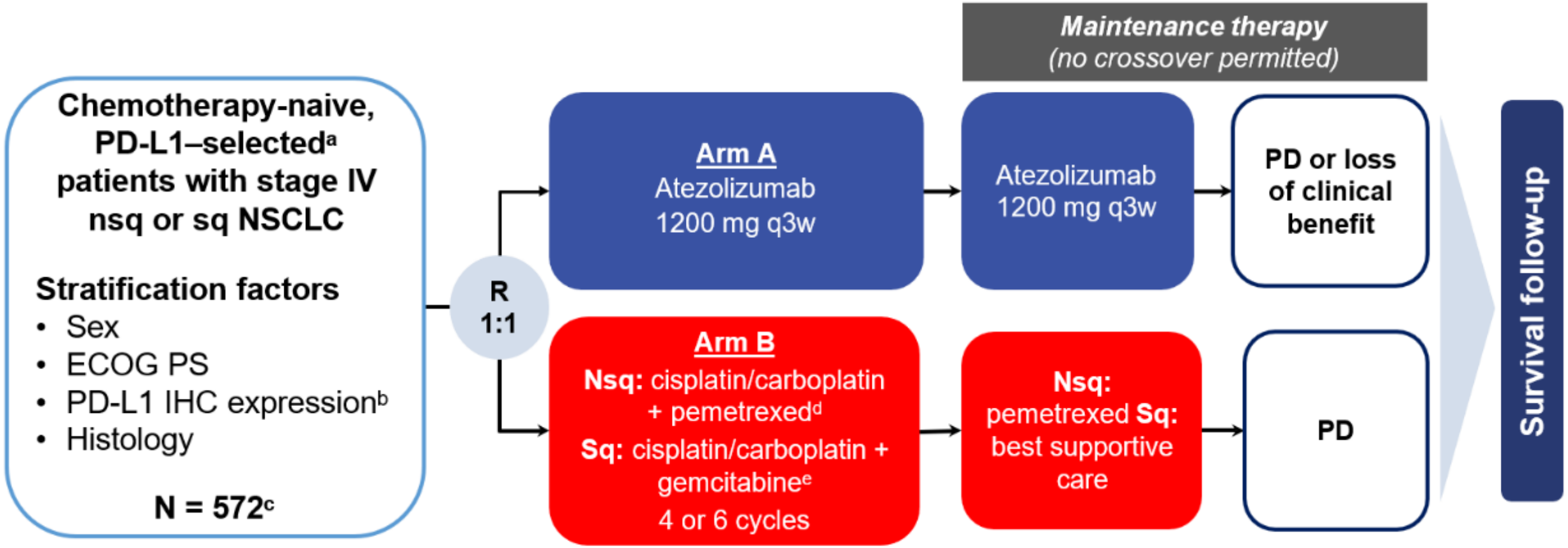
- Primary: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- Secondary: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%
- Exploratory: DOR, PFS2[d]

AUC, area under the curve.DOR, duration of response.
[a]Assessed in formalin-fixed tumor samples using PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA), with expression measured using TPS (defined as the percentage of tumor cells with membranous PD-L1 staining). [b]Patients randomized to pembrolizumab who completed 35 treatment cycles with SD or better or stopped treatment after confirmed CR could receive second-course pembrolizumab after disease progression if eligibility criteria were met. [c]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology. [d]PFS2 was defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer treatment or death from any cause, whichever occurred first.



HR, hazard ratio.
Data cutoff date: February 21, 2020.

IMpower 110 Study Design



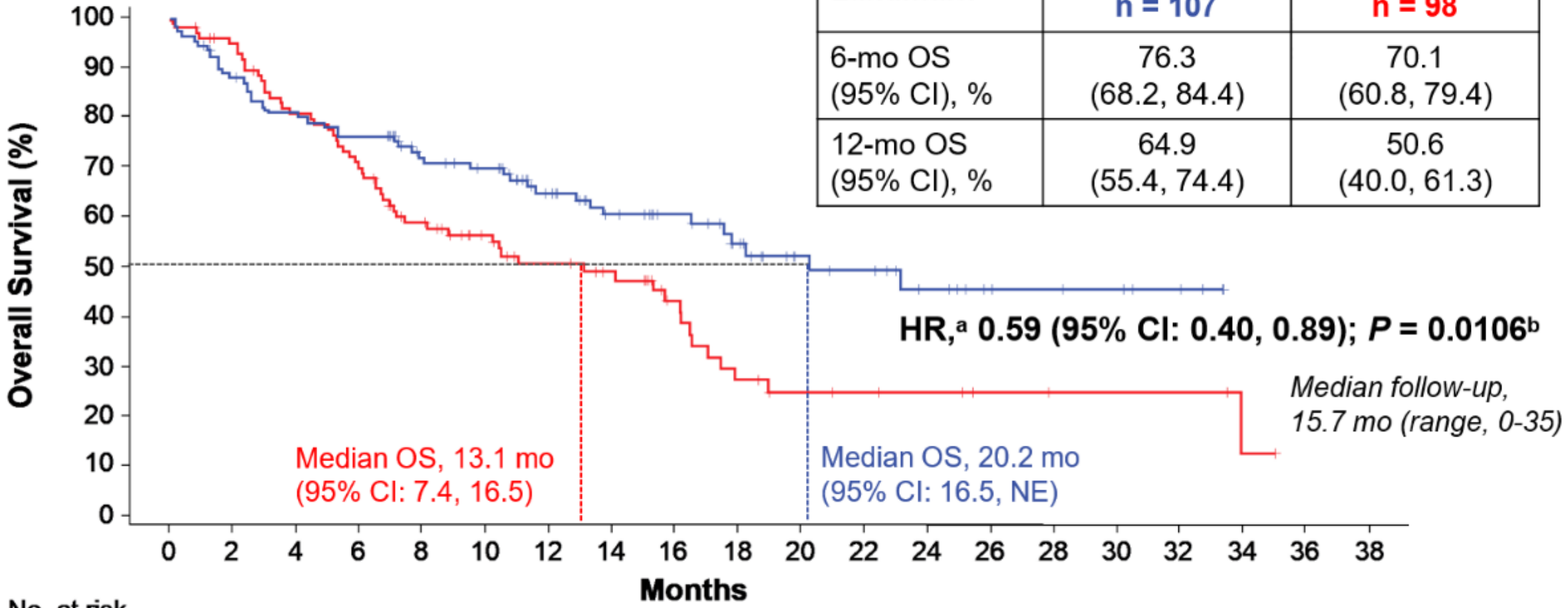
- Primary endpoint: OS in WT population[f]
- Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST version 1.1)

IC, tumour-infiltrating immune cells; IHC, immunohistochemistry; nsq, non-squamous; PD, progressive disease; q3w, every 3 weeks; R, randomised; sq, squamous; TC, tumour cells; WT, wild-type. [a] PD-L1 expression (VENTANA SP142 IHC assay) ≥ 1% on TC or IC. [b] TC1/2/3 and any IC vs TC0 and IC1/2/3. [c] 554 patients in the WT population. [d] Cisplatin 75 mg/m² or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m² IV q3w. [e] Cisplatin 75 mg/m² + gemcitabine 1250 mg/m² or carboplatin AUC 5 + gemcitabine 1000 mg/m² IV q3w. [f] WT population excludes patients with *EGFR*+ and/or *ALK*+ NSCLC.

OS: TC3 or IC3 WT (IMpower110 Study Design)

High PD-L1 expression WT

Landmark	Arm A (atezo) n = 107	Arm B (chemo) n = 98
6-mo OS (95% CI), %	76.3 (68.2, 84.4)	70.1 (60.8, 79.4)
12-mo OS (95% CI), %	64.9 (55.4, 74.4)	50.6 (40.0, 61.3)



No. at risk

Atezolizumab	107	94	85	80	66	61	48	40	34	25	18	16	11	7	6	5	2	
Chemotherapy	98	89	75	65	50	40	33	28	19	12	9	7	6	4	3	3	3	1

NE, not estimable. [a] Stratified. [b] Stratified log-rank.
Data cutoff: 10 September 2018.

Herbst et al, NEJM 2021

EMPOWER-Lung 1 Study Design (NCT03088540)

Key Eligibility Criteria
- Treatment-naïve advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK* or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification Factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW)

N=710

Five interim analyses were prespecified per protocol

Second interim analysis (1 March 2020) presented here

R 1:1

Arm A
Cemiplimab monotherapy IV
350 mg Q3W
Treat until PD or 108 weeks

PD → **Optional continuation of cemiplimab + 4 cycles of chemotherapy**

Arm B
4–6 cycles of investigator's choice chemotherapy

PD → **Optional crossover to cemiplimab monotherapy**

Follow-up

Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

ALK, anaplastic lymphoma kinase; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomised; ROS1, c-ros oncogene 1; ROW, rest of the world.

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Baseline Characteristics

	Cemiplimab	Chemotherapy	Cemiplimab	Chemotherapy
n (%), unless stated	ITT (n=356)	ITT (n=354)	PD-L1 ≥50% ITT (n=283)	PD-L1 ≥50% ITT (n=280)
Median age (range), year	63.0 (31.0–79.0)	64.0 (40.0–84.0)	63.0 (31.0–79.0)	64.0 (40.0–84.0)
≥65 year	156 (43.8)	164 (46.3)	126 (44.5)	133 (47.5)
Male	312 (87.6)	294 (83.1)	248 (87.6)	231 (82.5)
Region on enrolment				
Europe	275 (77.2)	278 (78.5)	215 (76.0)	216 (77.1)
Asia	39 (11.0)	38 (10.7)	31 (11.0)	29 (10.4)
Rest of the world	42 (11.8)	38 (10.7)	37 (13.1)	35 (12.5)
ECOG PS 0; 1	96 (27.0); 260 (73.0)	96 (27.1); 258 (72.9)	77 (27.2); 206 (72.8)	75 (26.8); 205 (73.2)
Histology				
Non-squamous	197 (55.3)	202 (57.1)	161 (56.9)	159 (56.8)
Squamous	159 (44.7)	152 (42.9)	122 (43.1)	121 (43.2)
Brain metastases	44 (12.4)	39 (11.0)	34 (12.0)	34 (12.1)
Cancer stage at screening				
Metastatic	293 (82.3)	302 (85.3)	238 (84.1)	238 (85.0)
Locally advanced	63 (17.7)	52 (14.7)	45 (15.9)	42 (15.0)
Prior systemic therapy				
Neoadjuvant	4 (1.1)	7 (2.0)	3 (1.1)	4 (1.4)
Adjuvant	9 (2.5)	15 (4.2)	5 (1.8)	12 (4.3)

ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; PD-L1, programmed cell death-ligand 1.

Data cut-off date: 1 March 2020 (interim analysis #2)

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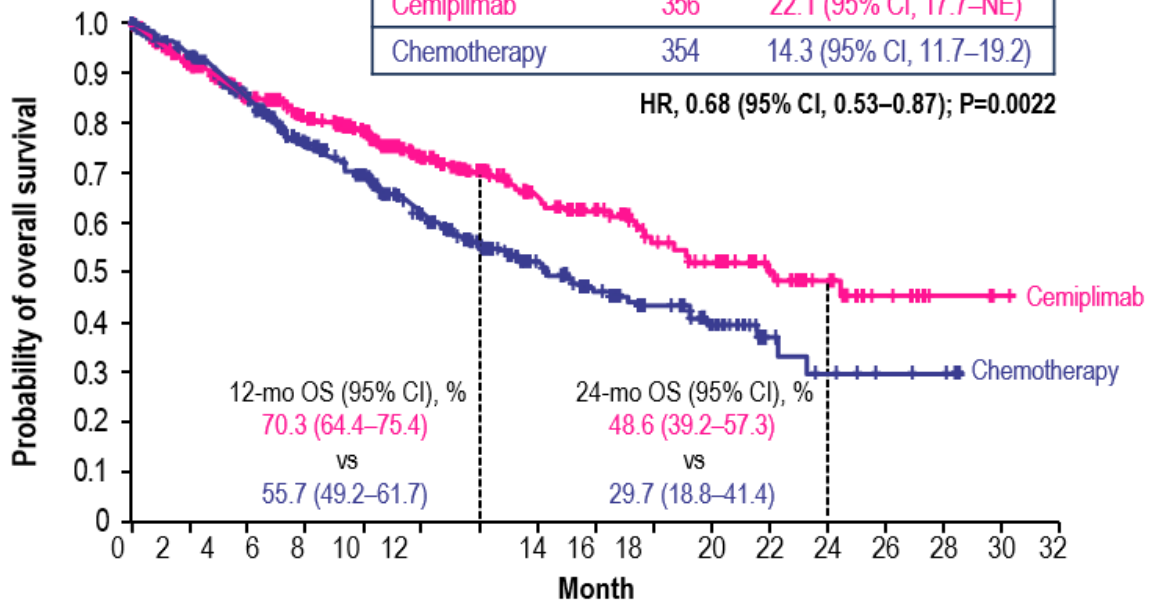
Overall Survival

ITT

	No. of Patients	Median OS (95% CI) *mo*
Cemiplimab	356	22.1 (95% CI, 17.7–NE)
Chemotherapy	354	14.3 (95% CI, 11.7–19.2)

HR, 0.68 (95% CI, 0.53–0.87); P=0.0022



No. at risk

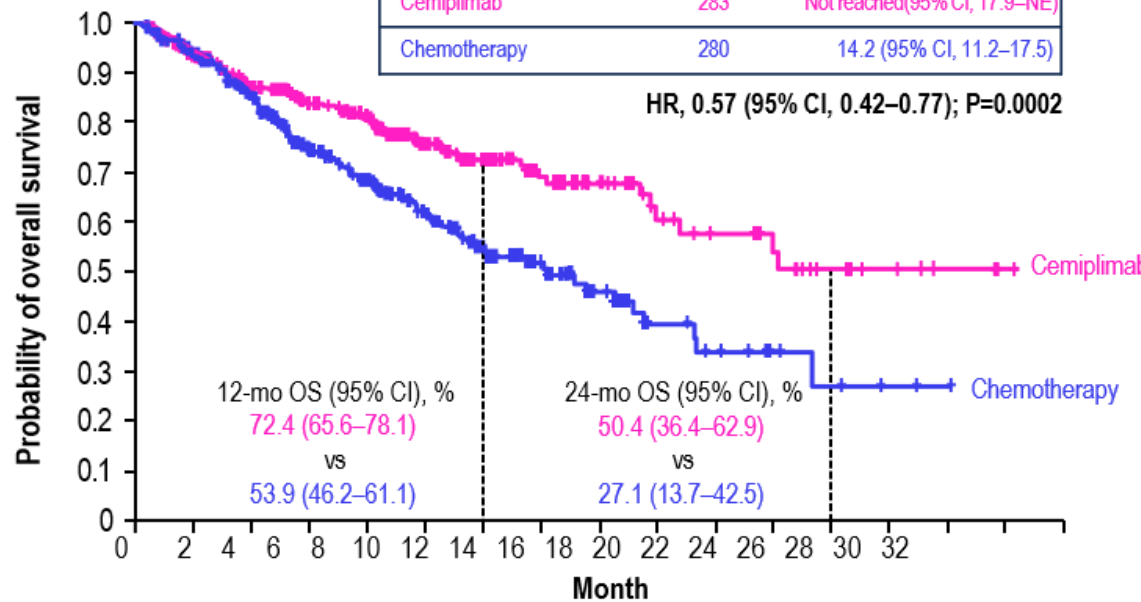
Cemiplimab	356	304	254	223	198	147	120	87	71	48	37	27	18	8	3	1	0
Chemotherapy	354	303	254	205	172	126	93	73	52	41	27	12	7	4	3	0	0

Median duration of follow-up:
Cemiplimab → 13.1 months (range: 0.1–31.9)
Chemotherapy → 13.1 months (range: 0.2–32.4)

PD-L1 ≥ 50% ITT

	No. of Patients	Median OS (95% CI) *mo*
Cemiplimab	283	Not reached(95% CI, 17.9–NE)
Chemotherapy	280	14.2 (95% CI, 11.2–17.5)

HR, 0.57 (95% CI, 0.42–0.77); P=0.0002



No. at risk

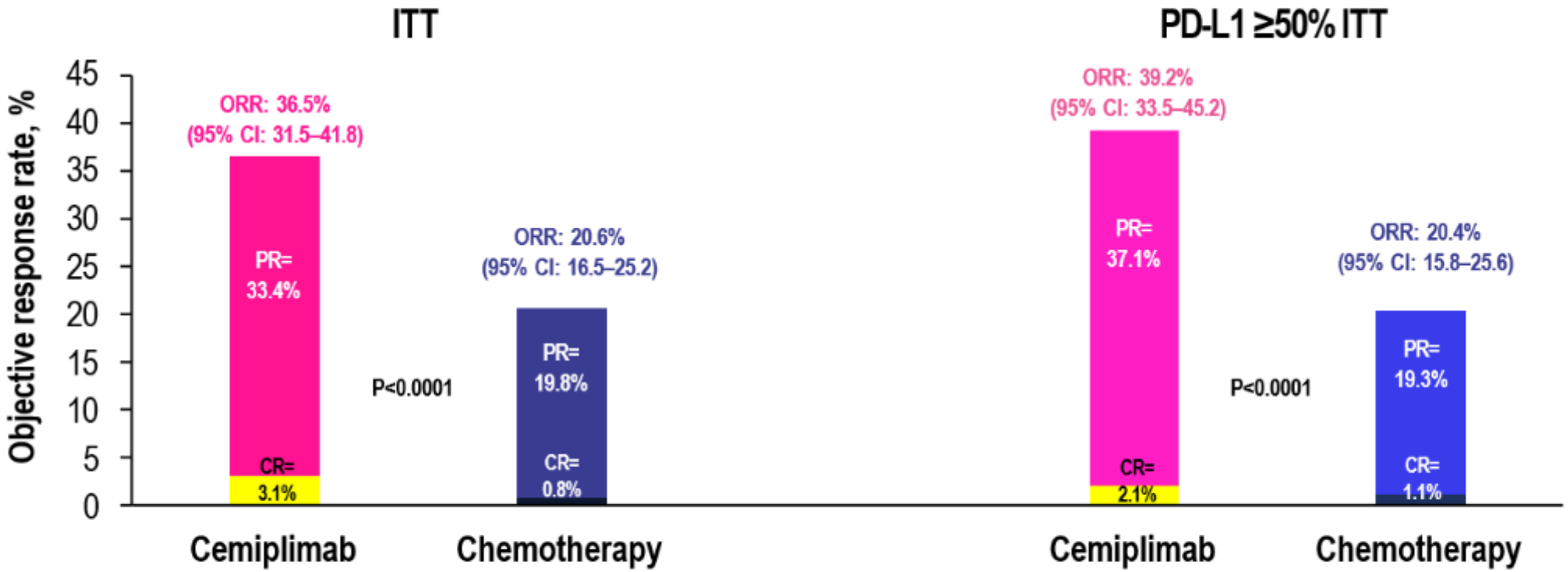
Cemiplimab	283	244	203	177	154	108	83	55	42	24	18	15	10	6	3	1	0
Chemotherapy	280	239	198	153	125	87	57	41	25	15	11	6	4	2	1	0	0

Median duration of follow-up:
Cemiplimab → 10.8 months (range: 0.1–31.9)
Chemotherapy → 10.2 months (range: 0.2–29.5)

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mo, month; NE, not evaluable; OS, overall survival; PD-L1, programmed cell death-ligand 1.

Data cut-off date: 1 March 2020 (interim analysis #2)

Tumour Response and DOR

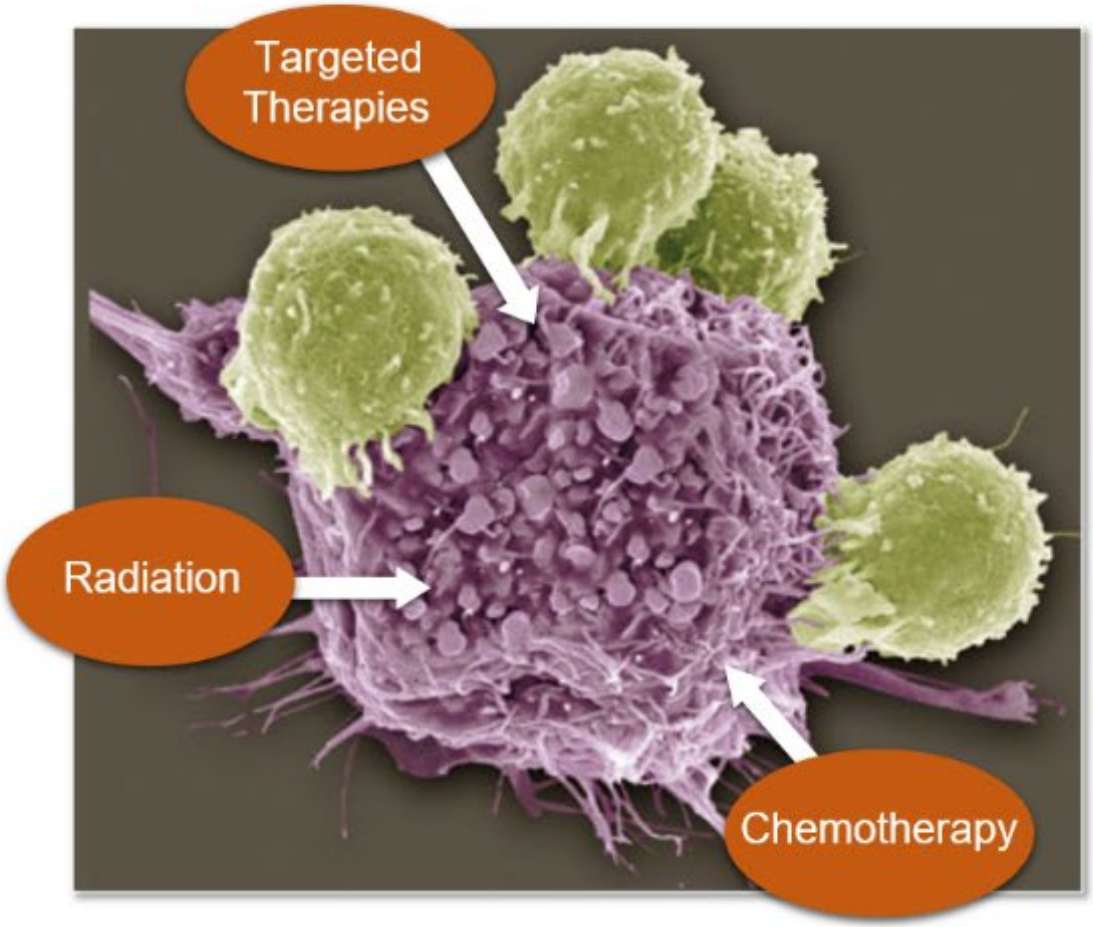


	Cemiplimab	Chemotherapy	Cemiplimab	Chemotherapy
n (%), unless stated	ITT (n=356)	ITT (n=354)	PD-L1 ≥50% ITT (n=283)	PD-L1 ≥50% ITT (n=280)
Median DOR, months (95% CI)	21.0 (14.9–NE)	6.0 (4.3–6.4)	16.7 (12.5–22.8)	6.0 (4.3–6.5)
Median observed time to response, months (range)	2.1 (1.4–10.4)	2.1 (1.4–6.7)	2.1 (1.4–10.4)	2.1 (1.4–6.3)

CI, confidence interval; CR, complete response; DOR, duration of response; ITT, intention-to-treat; NE, not evaluable; ORR, objective response rate; PD-L1, programmed cell death-ligand 1; PR, partial response.

Data cut-off date: 1 March 2020 (interim analysis #2)

Rationale for Combination Therapy: Chemo-IO

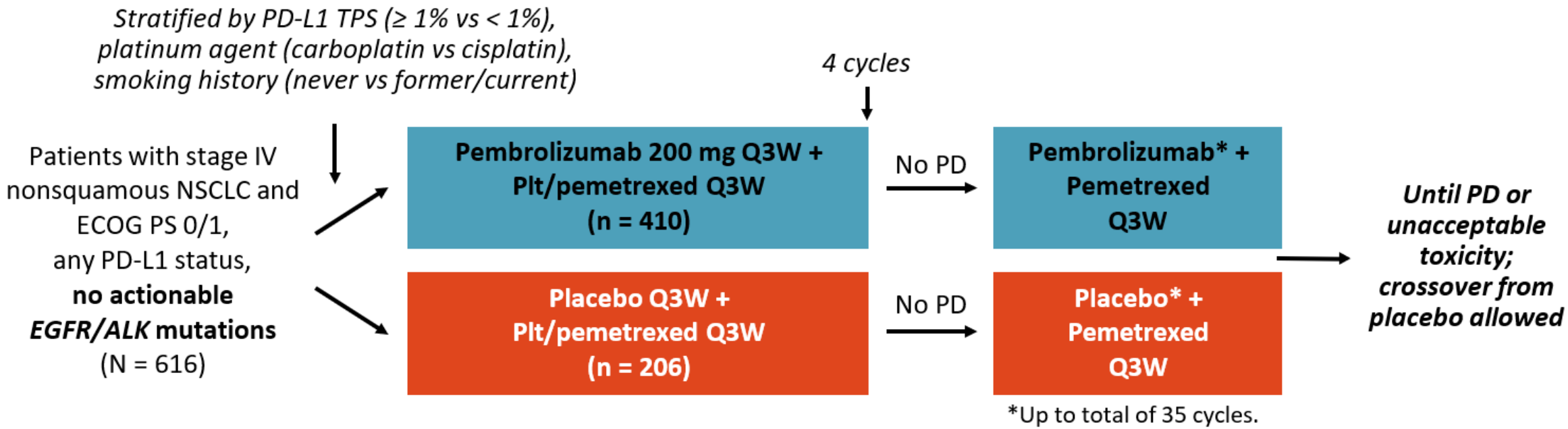


Adapted from M. Sznol, Yale Cancer Center

- **Reduces tumor bulk** – Improves T-cell: tumor target ratio.
- **Separate mechanism of kill** – 'synergize' with T-cell mechanism of killing.
- **Reduces T-cell inhibitory substances** produced by tumor.
- Alters tumor barriers (vasculature/pressure) to T-cell penetration.
- Kills tumor cells in a manner that increases their recognition by T-cells and APC (vaccination).
- Alters T-cell signaling/gene expression to produce T-cell attractants.

KEYNOTE-189: First-line Pembrolizumab + CT vs Placebo + CT in Stage IV Nonsquamous NSCLC

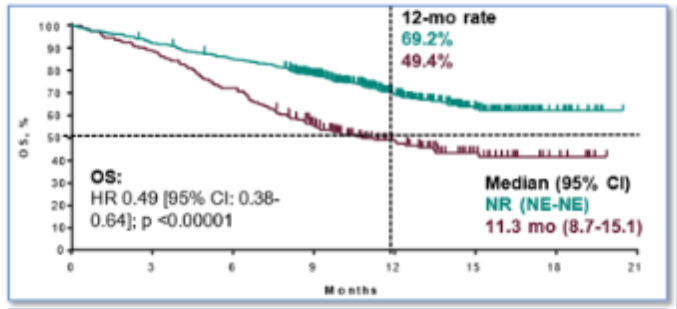
- Randomized, double-blind, international phase III study

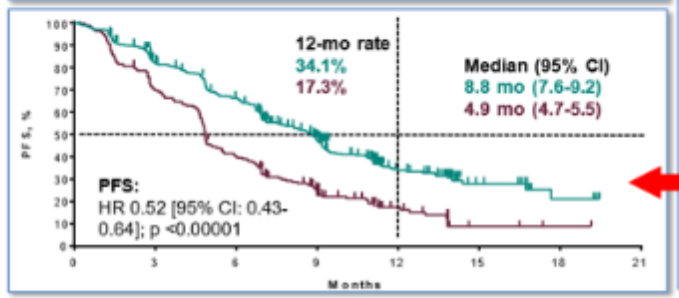


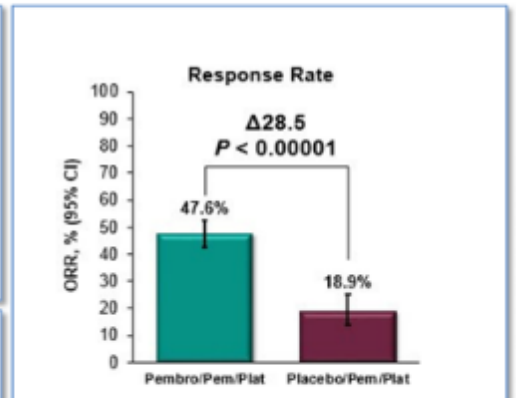
- ❑ Primary endpoints: OS, PFS by BICR
- ❑ Secondary endpoints: ORR, DoR, safety

Gandhi L, et al. N Engl J Med. 2018;[Epub ahead of print]. ClinicalTrials.gov. NCT02578680.

KEYNOTE 189: Pembrolizumab (PD1 plus Chemotherapy)
Met All Primary Endpoints





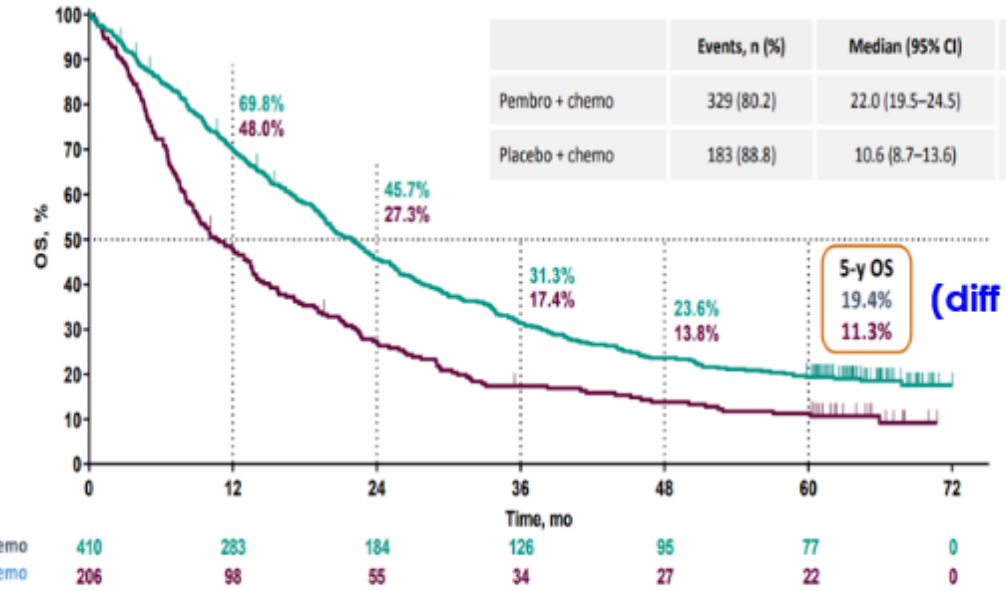


Subgroup Analyses
OS: Positive across all subgroups
PFS: Positive across all subgroups except for PD-L1 TPS <1%

Gandhi et al, *N Engl J Med* 2018; 378:2078-2092

2022 ESMO Congress

OS: KN 189 – no plateau, few % loss every year
PDL1 subgroups – early sep



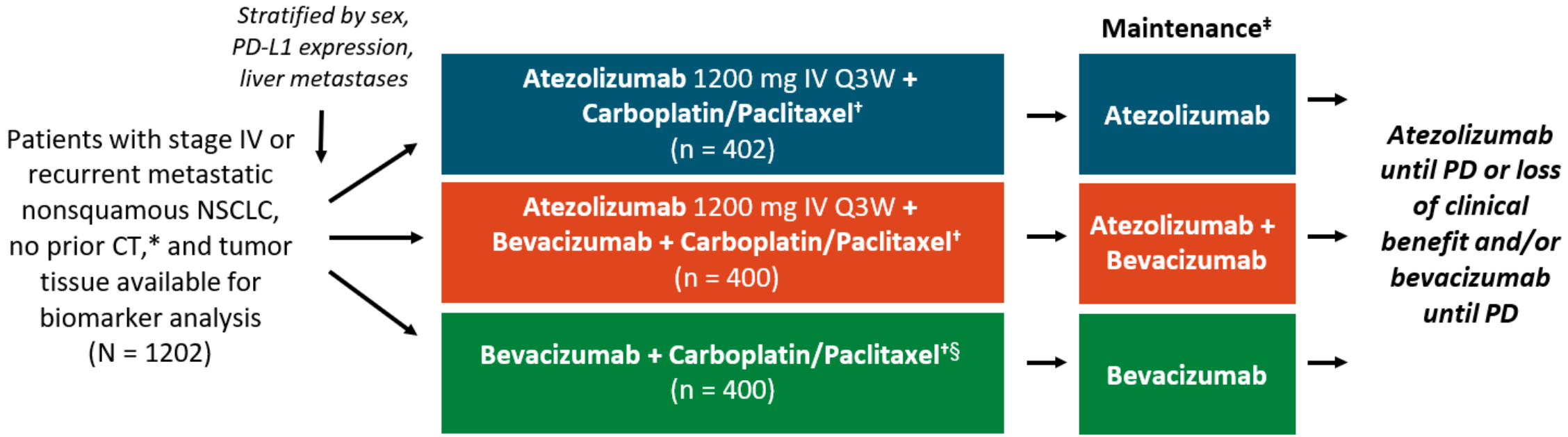
	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

(diff 8.1%)

M. Garassino. 2022 ESMO Congress. KN189 5-year update.

IMpower 150: Study Design

- Multicenter, open-label, randomized phase III trial (data cutoff: January 22, 2018)

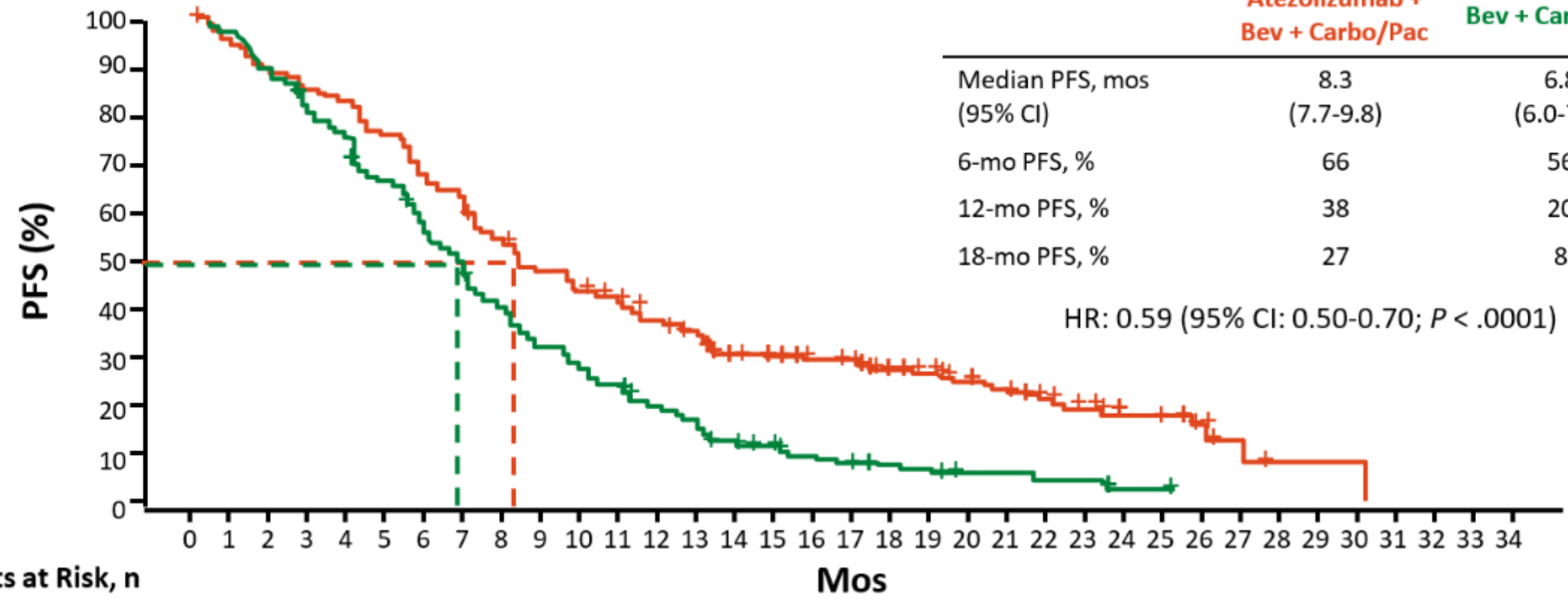


*If sensitizing *EGFR* mutation or *ALK* translocation present, must have PD on or intolerance to ≥ 1 approved targeted therapy. †Bevacizumab 15 mg/kg; carboplatin AUC 6; paclitaxel 200 mg/m^2; all given IV Q3W for 4 or 6 cycles. ‡No crossover permitted. §Control arm.

- ❑ Coprimary endpoints: investigator-assessed PFS in ITT WT, Teff-high WT; OS in ITT WT.
- ❑ Secondary endpoints: investigator-assessed PFS, OS in ITT; investigator-assessed PFS in PD-L1 subgroups; IRF-assessed PFS; ORR, DoR per RECIST v1.1; safety in ITT

Socinski MA, et al. ASCO 2018. Abstract 9002. Socinski MA, et al. N Engl J Med. 2018; 378:2288-2301.

IMpower 150: Updated PFS in ITT WT Population* (Coprimary Endpoint)



	Atezolizumab + Bev + Carbo/Pac	Bev + Carbo/Pac
Median PFS, mos (95% CI)	8.3 (7.7-9.8)	6.8 (6.0-7.1)
6-mo PFS, %	66	56
12-mo PFS, %	38	20
18-mo PFS, %	27	8

HR: 0.59 (95% CI: 0.50-0.70; $P < .0001$)

Patients at Risk, n

Atezolizumab + Bev + Carbo/Pac	359	336	315	301	293	267	234	213	190	168	154	146	125	112	85	80	69	68	53	50	37	33	24	20	12	11	6	3	1	1	1
Bev + Carbo/Pac	337	323	294	263	244	215	180	148	127	103	89	78	61	50	35	29	21	18	14	13	6	6	5	5	1	1					

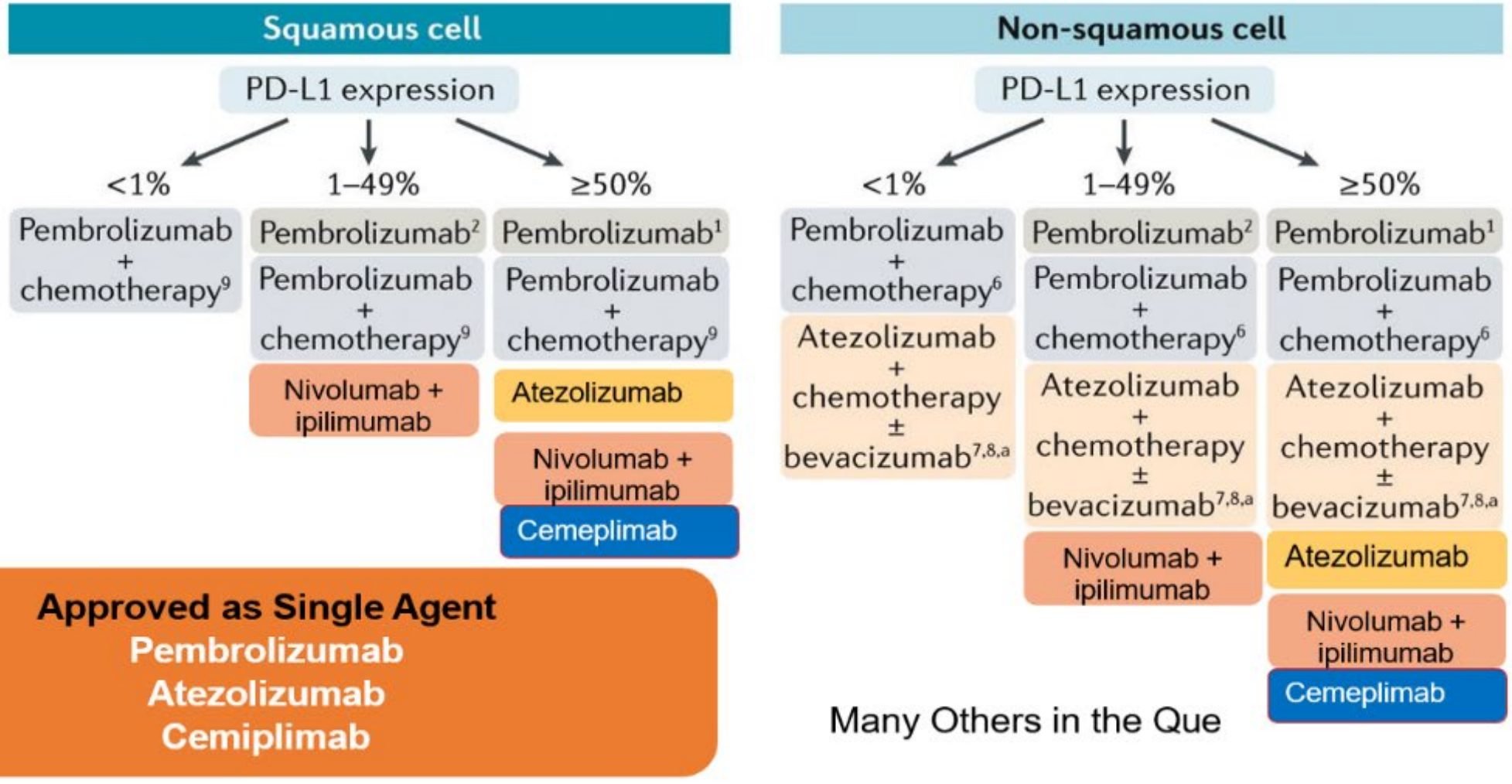
*ITT WT: patients without *EGFR* or *ALK* genetic alterations; 87% of randomized patients.

Median follow-up: ~ 20 mos.

Socinski MA, et al. ASCO 2018. Abstract 9002.

A Current First Line Treatment Algorithm

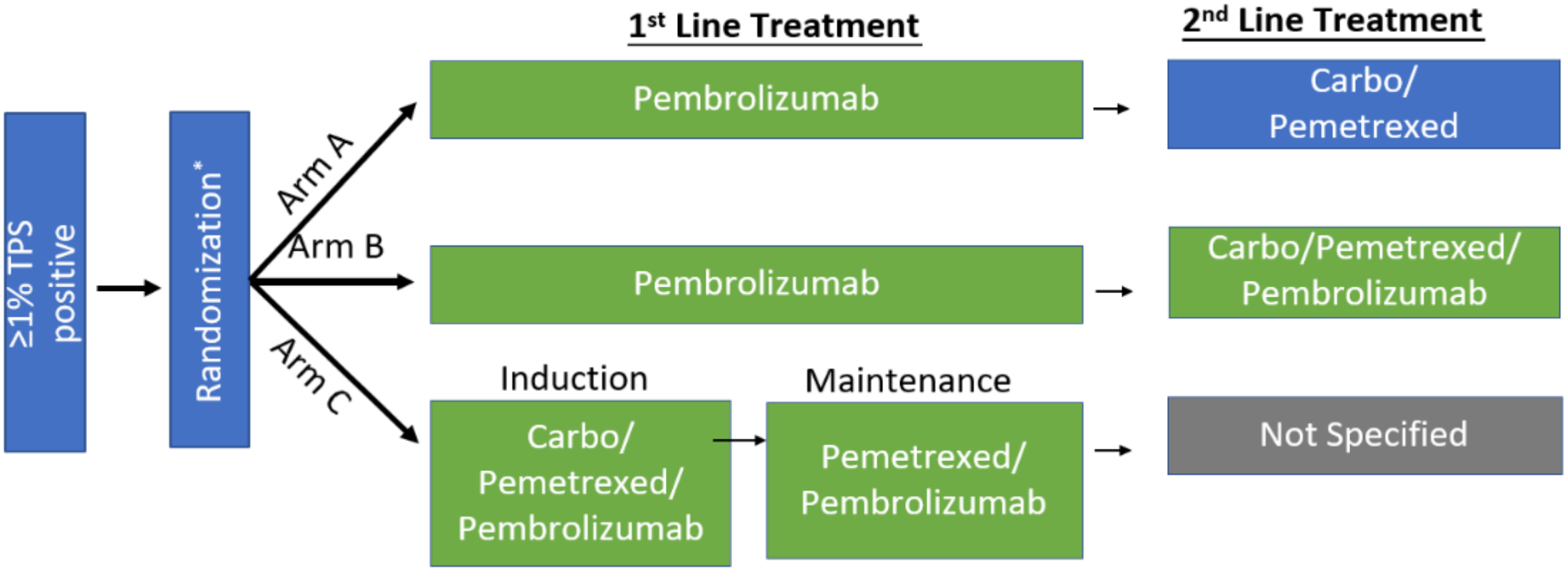
For advanced-stage non-small-cell lung cancer without targetable driver mutations



Nature Reviews Clinical Oncology 2020: Frontline Immunotherapy for NSCLC – the tale of the tail. (Chiang, AC & Herbst, RS)

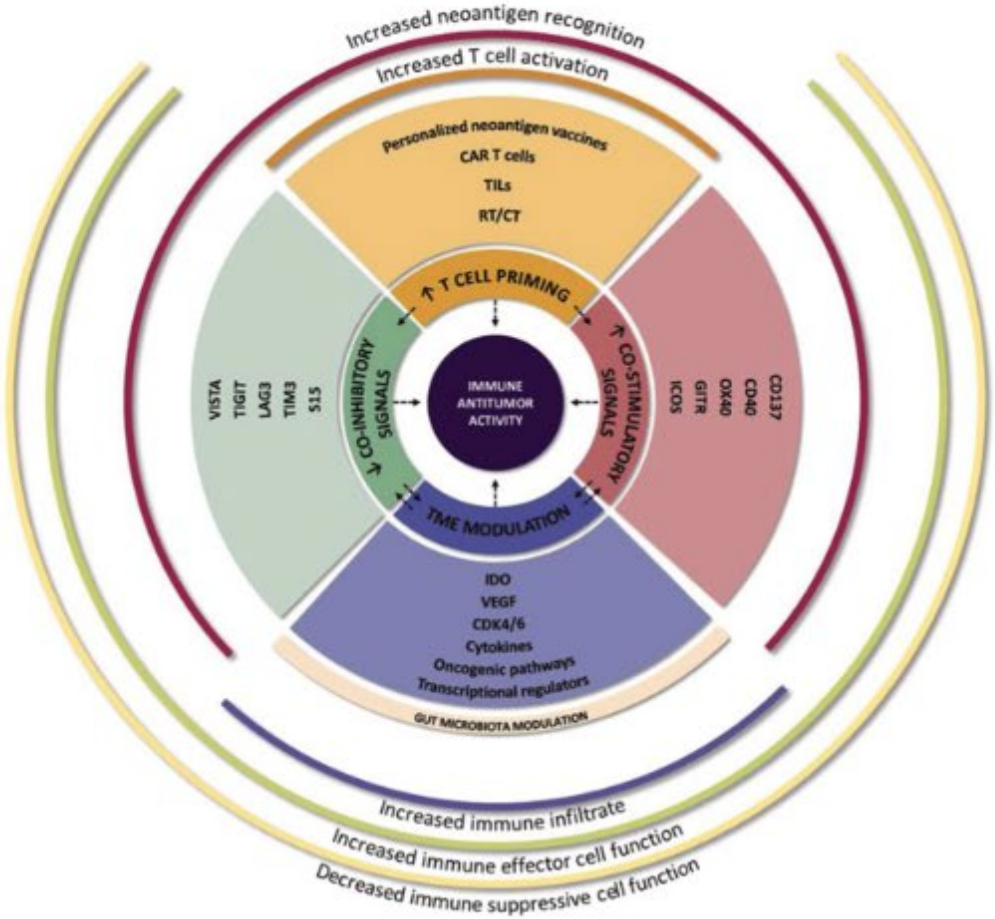
Combining Immunotherapy with Chemo

INSIGNA: A Randomized, Phase III Study of Firstline **I**mmunotherapy alone or in Combination with Chemotherapy in Induction/Maintenance or Post-progression in Advanced **N**onsquamous Non-Small Cell Lung Cancer (NSCLC) with Immunobiomarker **SIGN**ature-driven **A**nalysis



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

Immunotherapy Combinations



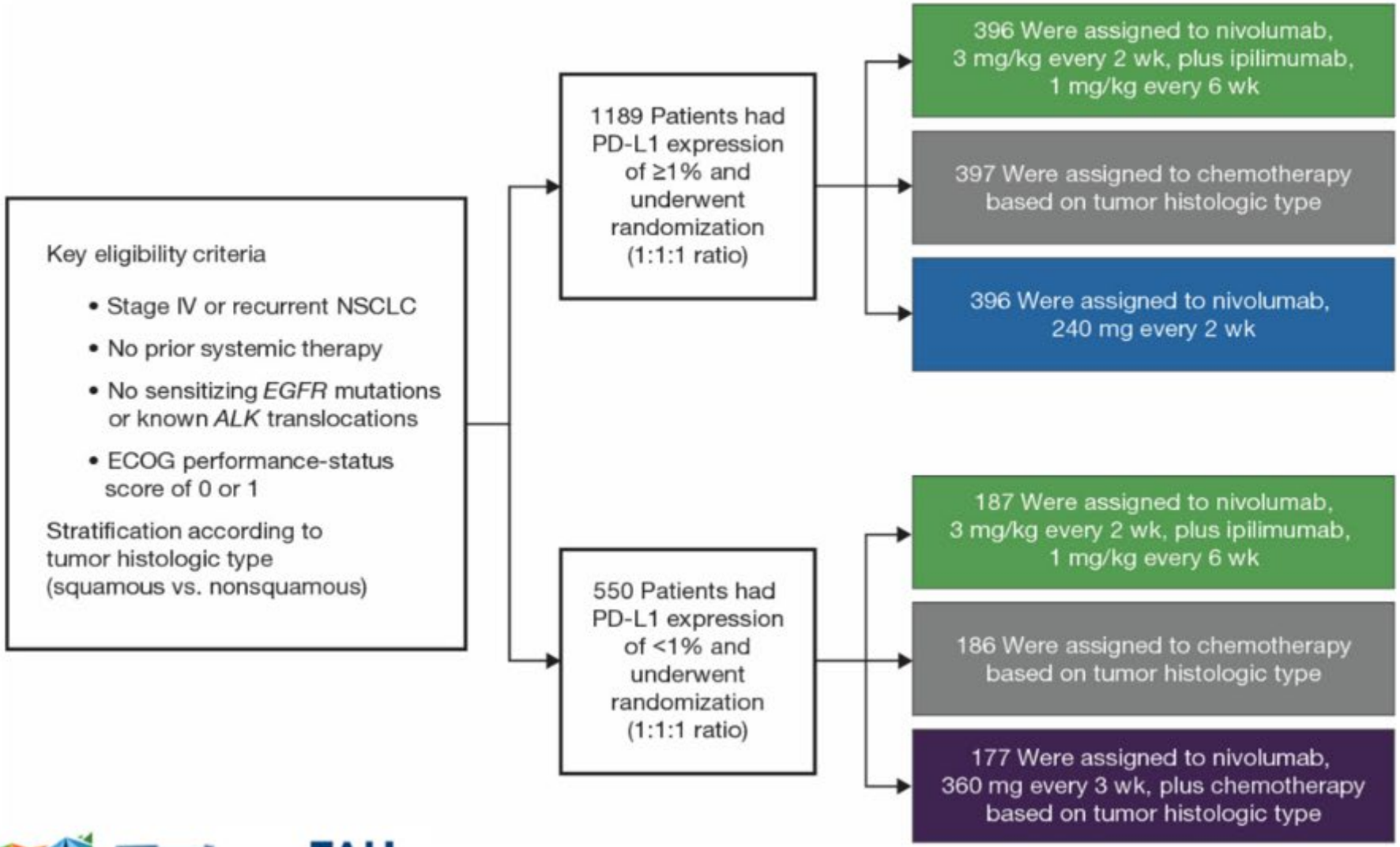
Attilli I, Lung Cancer 2021

Receptor and ligands	Mechanism of action	Current status	Examples of agents
Co-inhibitory receptors			
CTLA4 — CD80/86	Limits initial T cell activation and proliferation	FDA-approved	Ipilimumab, tremelimumab
PD1 — PD-L1	Inhibits the activity of effector T cells	FDA-approved	Nivolumab, pembrolizumab, durvalumab, atezolizumab
LAG3 — MHC II	Inhibits the activity of effector T cells via the KIEELE motif, which is functionally linked with T_{reg} cell-mediated immunosuppression	Phase III trial ongoing	Relatlimab
TIM-3 — Galectin-9, CEACAM1	Triggers $CD8^+$ T cell apoptosis and/or exhaustion	Phase II trials ongoing	Cobolimab, sabatolimab
TIGIT — CD155, CD112	Downregulation of T cell and NK cell function	Phase II trials ongoing	Tiragolumab
BTLA — HVEM	Suppression of downstream activation of TCR signalling via SH2	Phase I trials ongoing	Icatolimab
Co-stimulatory receptors			
GITR — GITRL	Promotes activation and proliferation of effector T cells and a reduction in T_{reg} cells	Phase II trials ongoing	TRX518, BMS-986156
OX40 — OX40L	Promotes survival, but not priming, of both effector and memory T cells	Phase II trials ongoing	GSK3174998, MEDI6469, PF-04518600
4-1BB — 4-1BBL	Promotes T cell proliferation and mitochondrial function and biogenesis	Phase I trials ongoing	Utomilumab, urelumab
ICOS — ICOSL	Promotes TCR co-stimulation and T_{reg} cell stimulation	Phase I trials ongoing	Vopratelimab, KY1044, GSK3359609

Kraehenbuehl L, Nature Rev Clin Oncol 2022

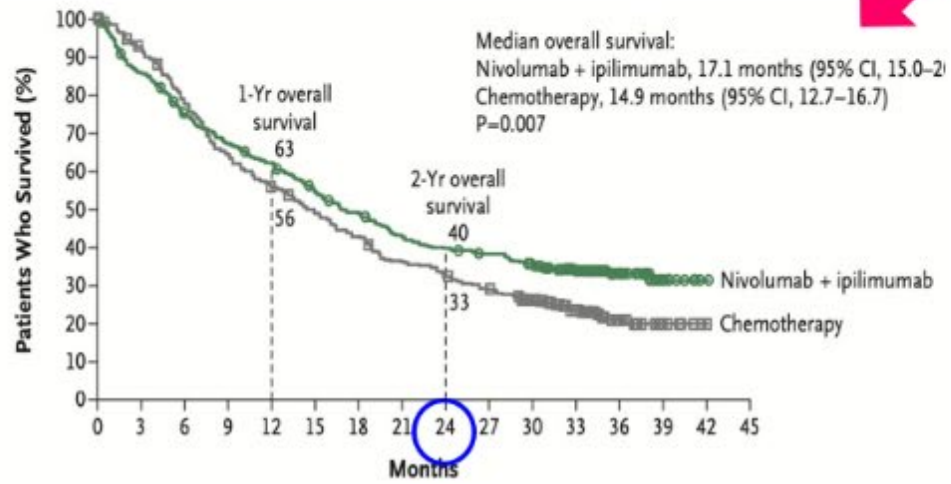
GenesisCare OLA FLASCO FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

CheckMate 227



Hellmann, MD, N Engl J Med 2019

Outcomes… PD-L1 ≥ 1%

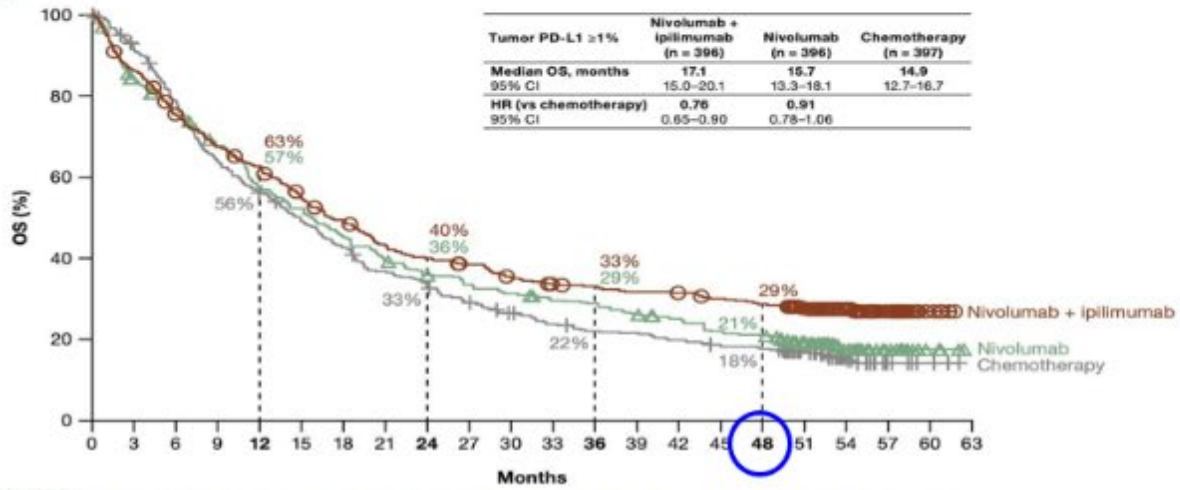


No. at Risk

Nivolumab + ipilimumab	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
Chemotherapy	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

Hellmann, MD, N Engl J Med 2019

Updated OS PD-L1 ≥ 1%:



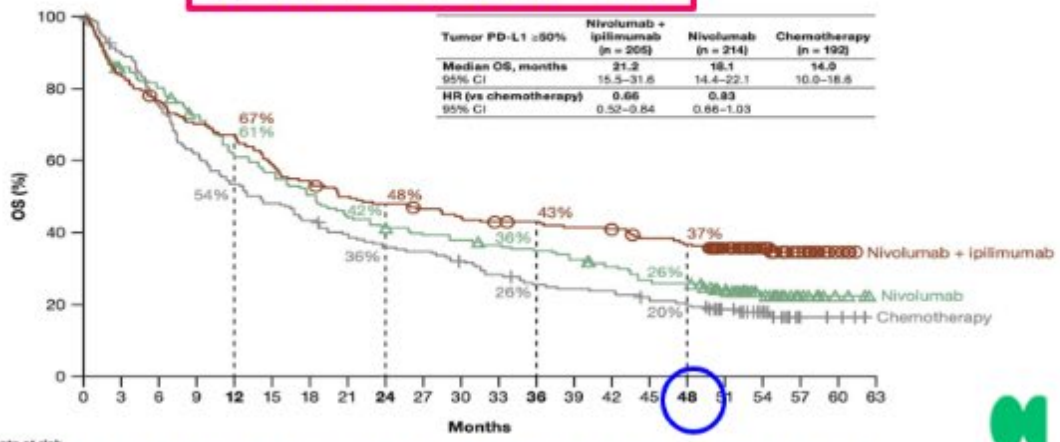
Tumor PD-L1 ≥1%	Nivolumab + ipilimumab (n = 396)	Nivolumab (n = 396)	Chemotherapy (n = 397)
Median OS, months	17.1	15.7	14.9
95% CI	15.0–20.1	13.3–18.1	12.7–16.7
HR (vs chemotherapy)	0.76	0.91	
95% CI	0.65–0.90	0.78–1.06	

Number of patients at risk

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

Paz-Ares LG, J Thorac Oncol 2022

Updated OS PD-L1 ≥ 50%:



Tumor PD-L1 ≥50%	Nivolumab + ipilimumab (n = 205)	Nivolumab (n = 214)	Chemotherapy (n = 192)
Median OS, months	21.2	18.1	14.9
95% CI	15.5–31.6	14.4–22.1	10.0–18.6
HR (vs chemotherapy)	0.66	0.83	
95% CI	0.52–0.84	0.66–1.03	

Number of patients at risk

Nivolumab + ipilimumab	205	172	156	143	137	120	111	101	97	93	88	85	84	81	79	73	70	55	38	15	4	0
Nivolumab	214	161	169	151	127	116	104	92	87	81	78	74	72	66	60	52	51	41	20	9	3	0
Chemotherapy	192	169	142	116	101	91	82	74	67	65	59	52	46	44	43	38	35	25	16	4	3	0

Paz-Ares LG, J Thorac Oncol 2022

Summary & after more mature data…

OS at around 3+yrs – combo chemo IO v chemo

	n	FU	IO	control	diff
KN 189 2:1*adeno	616	64.6m	19.4%	11.3%	8.1%
KN 407 1:1**sq	559	56.9m	18.4%	9.7%	8.7%
Adeno and Sq:					
Poseidon T+D+C v C	1013	46.5m	20.5%	8.3%	12.2%
CM 9LA [2]	719	36m	27%	19%	8%
CM 227 >1% [1]	792	61.3m	24%	14%	10%
<1%	373	61.3m	19%	7%	12%
Impower 150 ***[3]	1202	39m (final)	30% v 20%		

*116/202 crossover – 57.5%
** 143/281 crossover – 51.1%
*** adeno + mut, 4 v 3 drugs

1. Brahmer, Poster ASCO 2022
2. Paz Ayers, LBA, ASCO 2022
3. Socinski et al, JTO Vol. 16 No. 11: 1909–1924

OS HR + CI – combo chemo IO v chemo

	HR	CI
KN 189 2:1*adeno	0.6	0.50-0.72
KN 407 1:1**sq	0.71	0.59-0.85
KN 024	0.62	0.48-0.81
KN 042	0.68	0.57-0.82
Poseidon T+D+C v C	0.75	0.63-0.88
CM 9LA	0.72	0.61-0.86
CM 227 >1%	0.76	0.65-0.90
<1%	0.64	0.51-0.81
Impower 130 (nab)	0.79	0.64-0.98
Impower 110	0.76	0.54-1.09
Impower 131 (n + pac)	0.88	0.73-1.03
Impower 132 (pem)	0.86	0.71-1.06

PD-L1 ≥ 50% chemoIO or IO?

	N	FU	IO	control	diff
KN 024 >50%	305	60m	31.9%	16.3%	15.6%
KN 189 >50%	202	64.6	29.6%	21.4%	8.2%
KN 407 >50%	146	56.9m	23.3%	8.3%	15%

M. O'Brien. 2022 ESMO Congress.

Conclusion

- Chemo IO or IO+IO – gives around 10% survival gain across the board at 3-5yrs FU.
- KN-407 best squamous data we have.
- For 5-yr OS single agent IO for PD-L1 $\geq$ 50% is holding up and equivalent to combo.

M. O'Brien. 2022 ESMO Congress.

Global Lung Cancer Academy

SAVE THE DATE

Sharing Best Practices to Optimize Patient Care in Lung Cancer

October 21 and 24, 2022

VIRTUAL MEETING

Friday, October 21, 2022
4.00 PM – 8.00 PM EDT

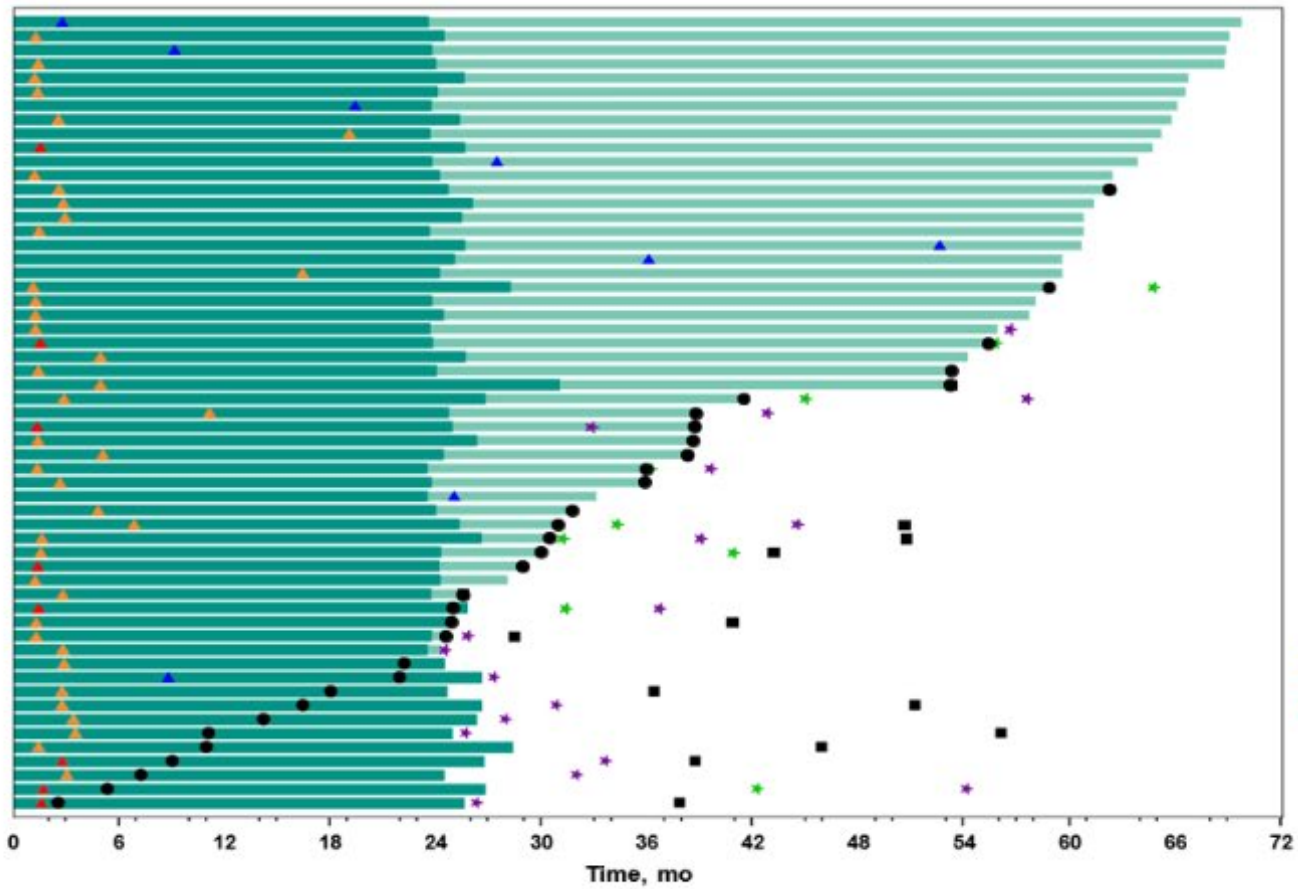
Monday, October 24, 2022
4.00 PM – 7.00 PM EDT

CHAIR
Corey J. Langer, MD, FACP
University of Pennsylvania Perelman School of Medicine, USA

CO-CHAIR
Carlos H. Barrios, MD
Oncology Research Center Hospital São Lucas, PUCRS, Brazil

- Rechallenge

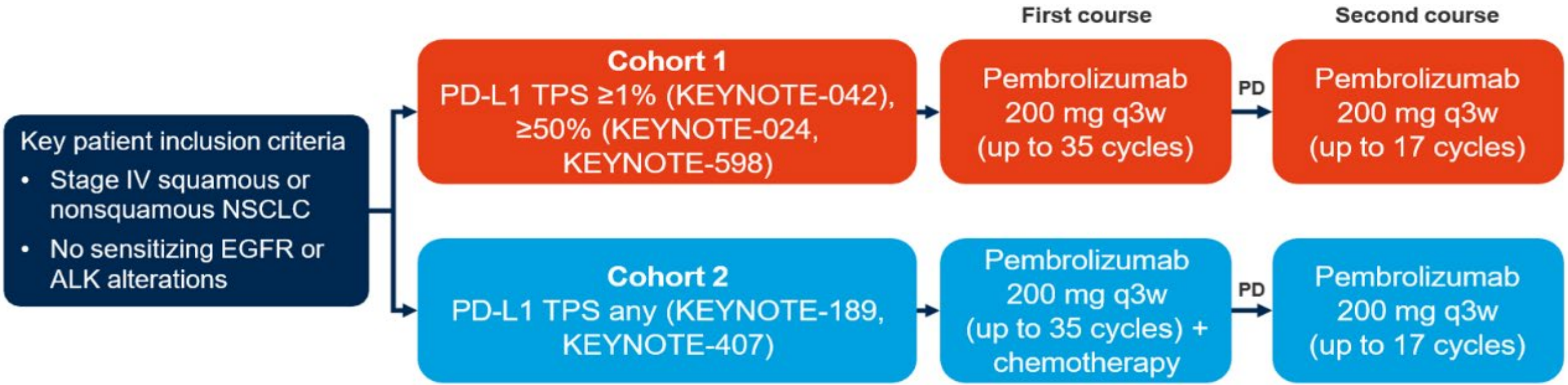
KN189: 19% OS at 5 yrs (n=77). Completed 35 Cycles of Pembrolizumab – 57/410 – 14%, 23/410 (who completed 35 cycles) + 54/410 (less than 35 cycles) alive with/without PD =19%.



	n = 57
ORR (95% CI),[a] %	86.0 (74.2–93.7)
Best overall response, n (%)	
CR	8 (14.0)
PR	41 (71.9)
Median DOR (range),[b] mo	57.7 (4.2 to 68.3+)
3-y OS rate after completing 35 cycles[c]	71.9%
Alive without PD or subsequent therapy, n (%)	23 (40.4)

M. O'Brien. 2022 ESMO Congress.

Pooled Analysis of Outcomes With Second-Course Pembrolizumab Across 5 Phase 3 Studies of Non-Small-Cell Lung Cancer – Rodriguez-Abreu D, et al

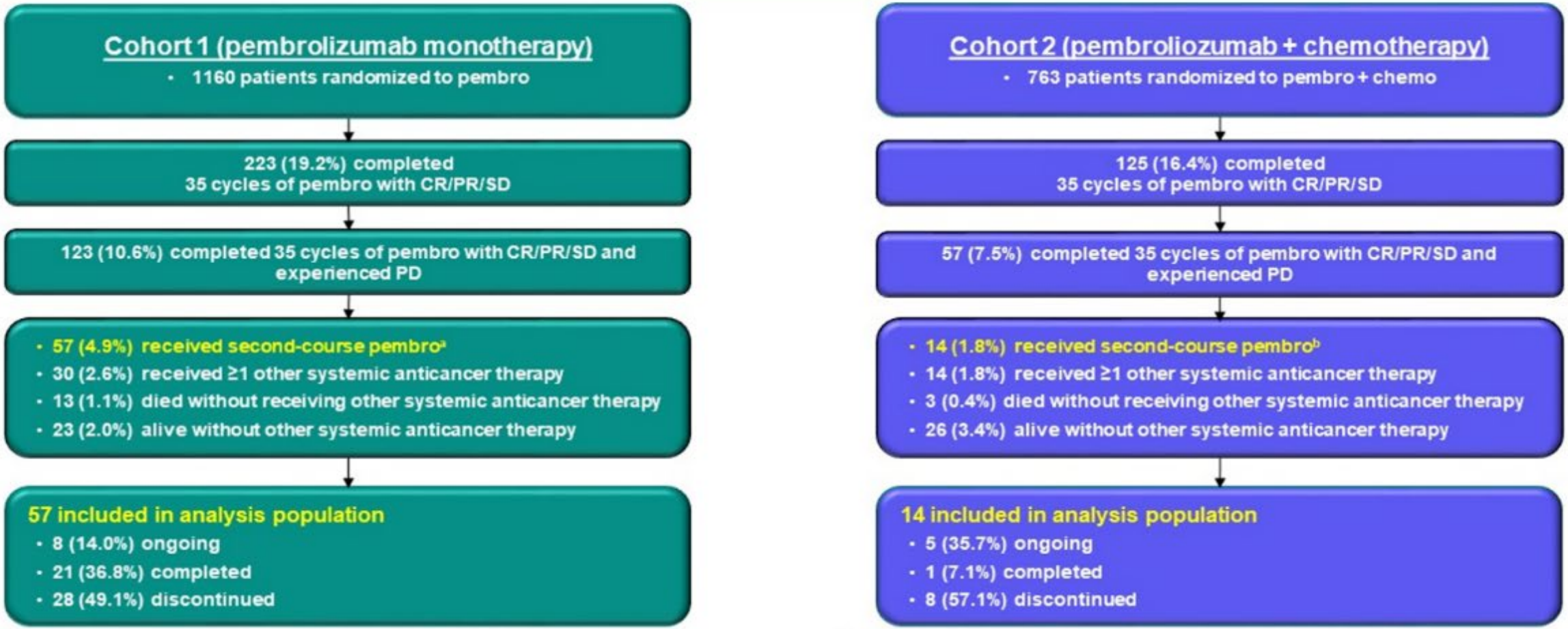


Endpoints

- ORR, DCR, DoR, OS, PFS, safety

Rodriguez-Abreu D, et al. J Thorac Oncol 2022;17(suppl):Abstr OA15.06

Patient Disposition



- **Median duration on second course:** 8.3 mo (95% CI, 5.6–NR)
- **Remaining on second-course pembro at 6 mo:** 62.8% (95% CI, 48.5%–74.2%)

- **Median duration on second course:** 7.6 mo (95% CI, 1.4–NR)
- **Remaining on second course pembro at 6 mo:** 55.0% (95% CI, 25.8%–76.8%)

[a]1 patient completed 35 cycles after assessment of PD by BICR but PR per investigator; 1 patient did not complete 35 cycles because of CR assessment.
[b]2 patients did not complete 35 cycles but did receive 2 years of treatment.
Database cutoff dates: Jun 1, 2020 (KN024); Apr 28, 2021 (KN042); Oct 1, 2021 (KN598); Aug 28, 2020 (KN189); Sep 30, 2020 (KN407).

D Rodriguez-Abreu. 2022 WCLC.

Conclusion

2 yrs of treatment is a very good standard. *Only 5% overall had rechallenge* – particularly if treated with IO alone initially and >1% PDL1

Around 10%, with 35 cycles and LESS are alive without disease - ?cure.

Ongoing Trials in 2L in NSCLC Patients *Pretreated* with IO

LEAP-008
NCT03976375 (Ph III)
Pembro + Lenvatinib

CINC280D2201
NCT03647488 (phII)
Capmatinib + Spartalizumab

CONTACT-01
NCT04471428 (phIII)
Atezo + cabozantinib

MK-7684A-003
NCT04725188 (PhII)
Vibo/Pembro Cof or Vibo/Pembro Cof + Doce vs. Doce

ATALANTE-1
NCT02654587 (phIII)
Tedopi (OSE2101) (HLA-A2+)

SAPPHIRE
NCT03906071 (PhIII)
Nivo + Sitravatinib (non-sq)

21-x066
NCT04791839 (PhII)
Zimbe + Domva + Etruma

Atezo = Atezolizumab, Tira = Tiragolumab (anti-TIGIT), non-sq = non-sqamous, sq = sqamous, Bev = bevacizumab, carbopac = Carboplatin + Paclitaxel, Pem = Pemetrexed, Plat Chemo = Platinum-based Doublet Chemotherapy, Nivo = Nivolumab, EGFR-mut = Epidermal Growth Factor Receptor (EGFR)- mutated, Durva = Durvalumab, Treme = Tremelimumab, Zimbe = Zimberelimab (anti-PD-1); Domva = Domvanalimab (anti-TIGIT), Etruma = Etrumadenant (A2aR and A2bR antagonist), Vibo =Vibostolimab (anti-TIGIT), Cemiplimab (anti-TIGIT); Tedopi OSE2101 = immunotherapeutic vaccine

Edgardo S. Santos, MD, FACP; Genesis Care US/Florida Atlantic University, USA. @EdgardoSantosMD

Global Lung Cancer Academy

De Novo—or at Relapse—Oligometastatic NSCLC: Management of Local and Systemic Disease

Narjust Florez, MD

De Novo—or at Relapse—Oligometastatic NSCLC: Management of Local and Systemic Disease

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October 2022

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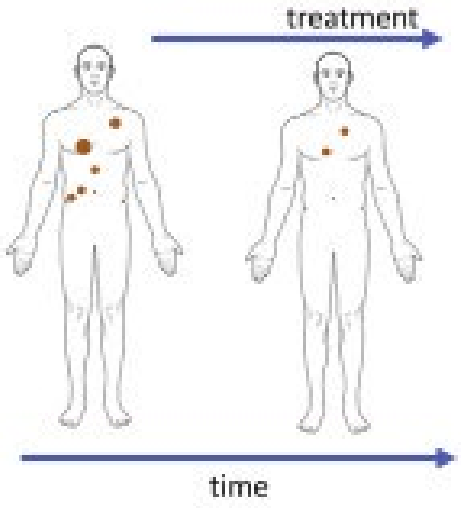
Disclosures

Advisory/Consulting: NeoGenomics, Pfizer, Janssen, BMS, Merck, DSI, and AstraZeneca

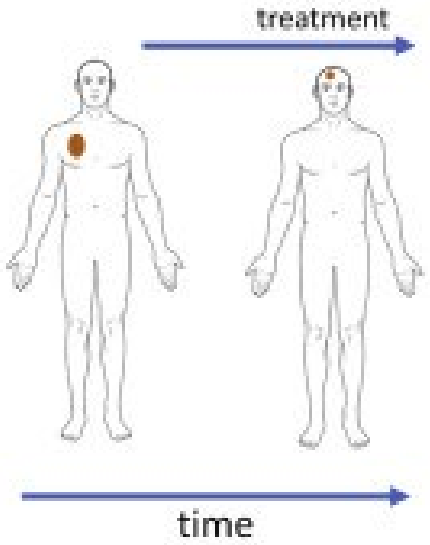
Speakers Engagement: Clinical Care Options (CCO), OncLive, and Physician Education Resource (PER)

De novo synchronous oligometastastic disease

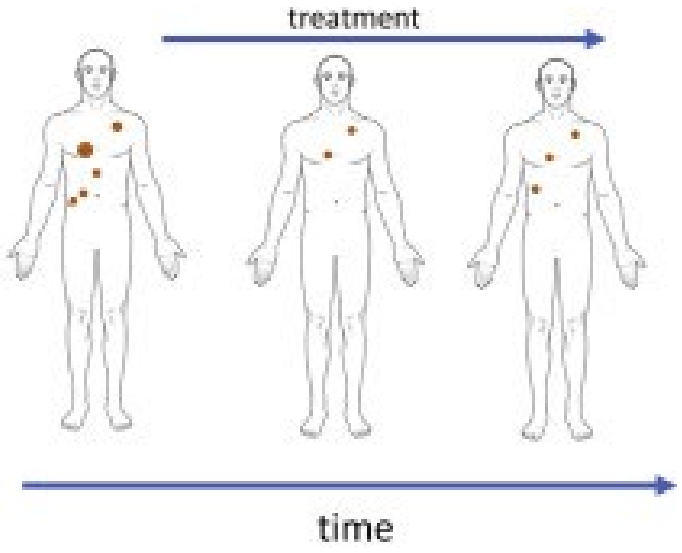
Oligopersistent disease



De novo metachronous oligometastastic disease



Oligoprogression



Patients with few metastases at diagnosis are described as having de novo oligometastases, whereas patients who are widely metastatic but become oligometastatic after systemic therapy are referred to as having induced oligometastases.

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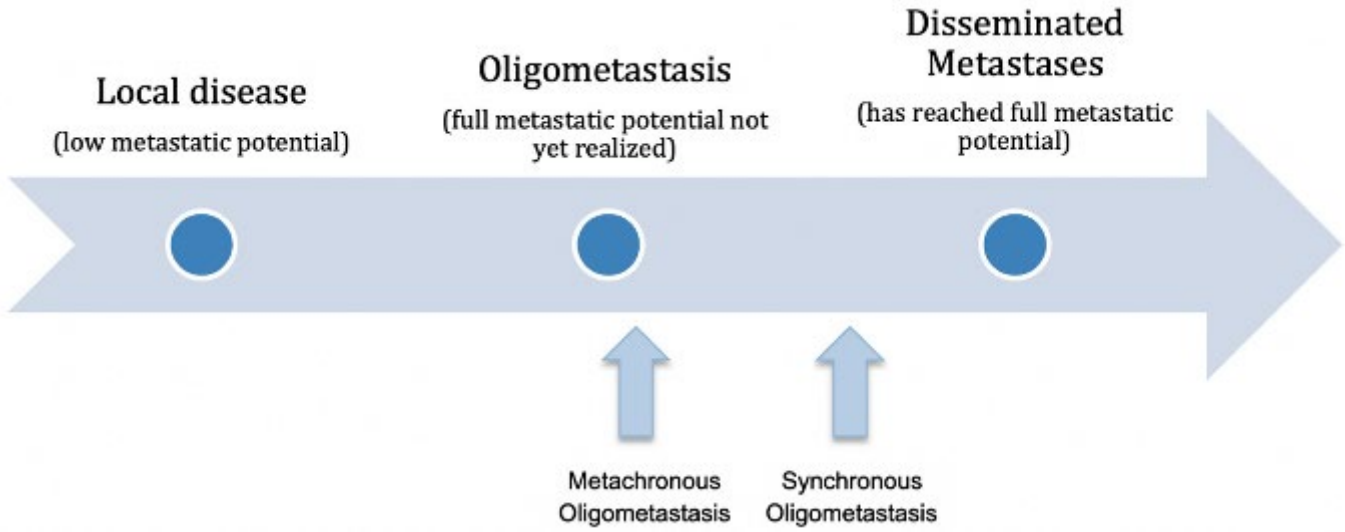
Stephens SJ, et al. *J Oncol Pract*. 2018;14:23-31.

Oligometastatic NSCLC

- Evidence from preclinical and retrospective studies suggest that some patients with metastatic NSCLC may have a less aggressive or “limited metastatic” phenotype and may benefit from more aggressive therapy; this is known as “oligometastatic disease”
- Patients with oligometastases in NSCLC seem to be common (up to 50%) and have improved outcomes compared with those with more widespread disease



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Gomez DR, et al. ASCO 2016. Abstract 9004;
Stephens SJ, et al. *J Oncol Pract.* 2018;14:23-31.

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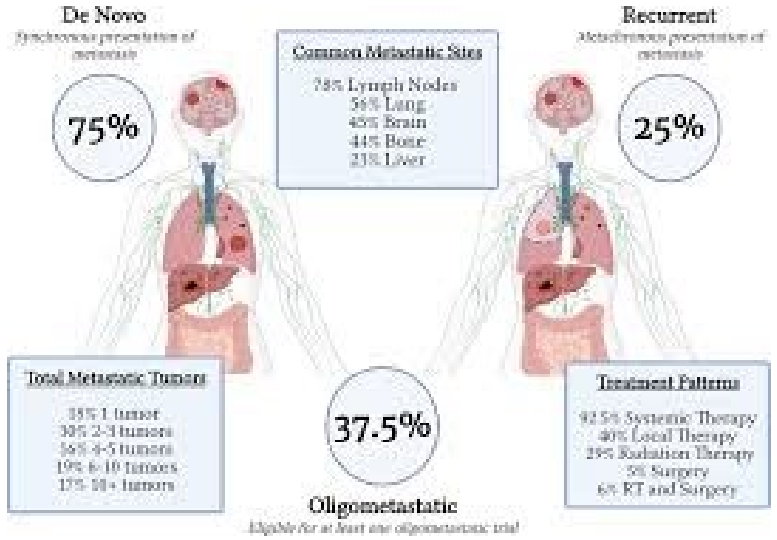
So, What Defines Oligometastatic Disease in NSCLC?

- Oligometastases means limited or few metastases and is rarely defined further. Although most studies have limited their focus to patients with **5 or fewer metastases,** some studies have defined it as up to 8 metastases

- But the location of the metastases also matters, eg, same organ, contralateral lung

Characterization of Metastatic Non-small Cell Lung Cancer and Oligometastatic Incidence in an Era of Changing Treatment Paradigms

- 37.5% of patients were classified as oligometastatic, 28.3% meeting criteria for the MD Anderson Cancer Center trial
- Of those tumors identified as oligometastatic, 44.4% received local therapy and 28.9% underwent ablative therapy to all sites
- There was a trend toward greater overall survival (44.4 vs 24.9 months; *P* = .055) and progression-free survival (8.0 vs 5.4 months; *P* = .06) in patients meeting eligibility for at least 1 oligometastatic trial



Joshua, et al. RED, ASTRO. 2022.

Does the Site of Disease Matter?

- Historically, the greatest experience—and perhaps greatest benefit—with local treatment in oligometastatic NSCLC has been observed with brain metastases—particularly with solitary brain metastasis

- For patients on molecularly targeted therapies, because oligoprogression in the brain is likely to represent pharmacokinetic failure rather than molecular evolution, continuation of the original targeted therapy after local treatment may result in prolonged disease control

- Bone metastases can also be easily controlled with local therapy in the oligometastatic setting

- Liver lesions with ablation has also been successfully treated (ablation)

Tanvetyanon T, et al. *J Clin Oncol.* 2008;26:1142-1147;
Grommes C, et al. *Neuro Oncol.* 2011;13:1364-1369;
Weickhardt AJ, et al. *J Thorac Oncol.* 2012;7:1807-1814.

We NEED Systemic Control of the Disease First

- Patients with oligometastases cannot be selected solely by the number of metastases and/or the number of organs involved

- Only 20%–25% of patients with limited metastases have favorable outcomes with either no further progression or limited progression

- Ideally, patients with oligometastases can be identified early on the basis to response to therapy

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Stephens SJ, et al. *J Oncol Pract.* 2018;14:23-31;
Joshua, et al. RED, ASTRO. 2022.

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Does the Biomarker Status Matter?

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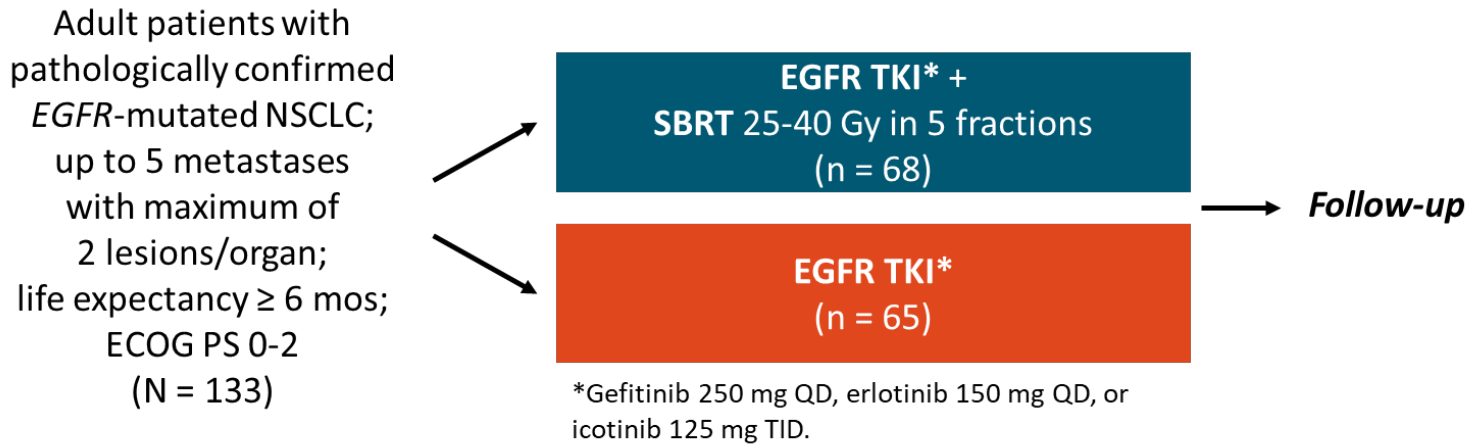
Phase III SINDAS: Interim Analysis of First-Line EGFR TKI With vs Without SBRT in Patients With *EGFR*-Mutated Oligometastatic NSCLC

SINDAS: Study Design

- Multicenter, open-label, randomized phase III trial in China (January 2016 - June 2019)



- Primary endpoint: PFS
- Secondary endpoint: OS
- Other endpoint: safety

Wang. ASCO 2020. Abstr 9508.

Wang X, et al. ASCO 2020. Abstract 9508.

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Phase III SINDAS Trial

Median Outcome, Mo	EGFR TKI + SBRT (n = 68)	EGFR TKI Only (n = 65)	HR
PFS (primary endpoint)	20.2	12.5	0.618 (95% CI: 0.394–0.969; log-rank *P* <.001)
OS (secondary endpoint)	25.5	17.4	0.682 (95% CI: 0.456–1.001; log-rank *P* <.001)

- After median follow-up of 19.6 mo, EGFR TKI + SBRT significantly prolonged PFS and OS vs EGFR TKI only

Wang X, et al. ASCO 2020. Abstract 9508.

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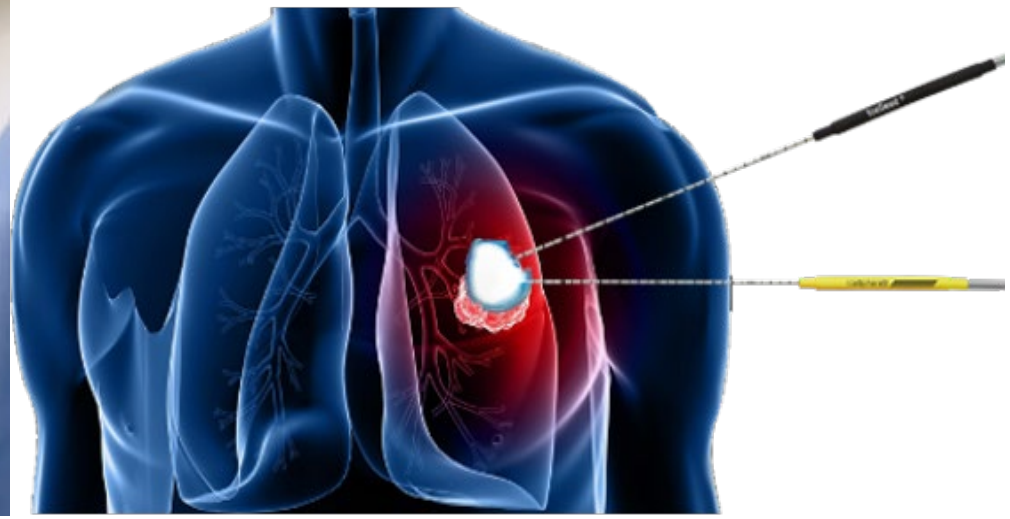
SINDAS Interim Analysis: Safety

Grade 3 AE, n	EGFR TKI + SBRT	EGFR TKI Only	*P* Value
All	20	13	
Skin rash	10	8	.423
Pneumonitis	6	2	.338
Esophagitis	3	2	.976
Pathological rib fracture	1	0	.413
Severe liver injury	0	1	.208

- No significant differences observed in distribution of types of grade 3 AEs between arms
- No grade 5 AEs or treatment-related deaths

Wang X, et al. ASCO 2020. Abstract 9508.

How Have These Patients Been Treated?



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Joshua, et al. RED, ASTRO. 2022.

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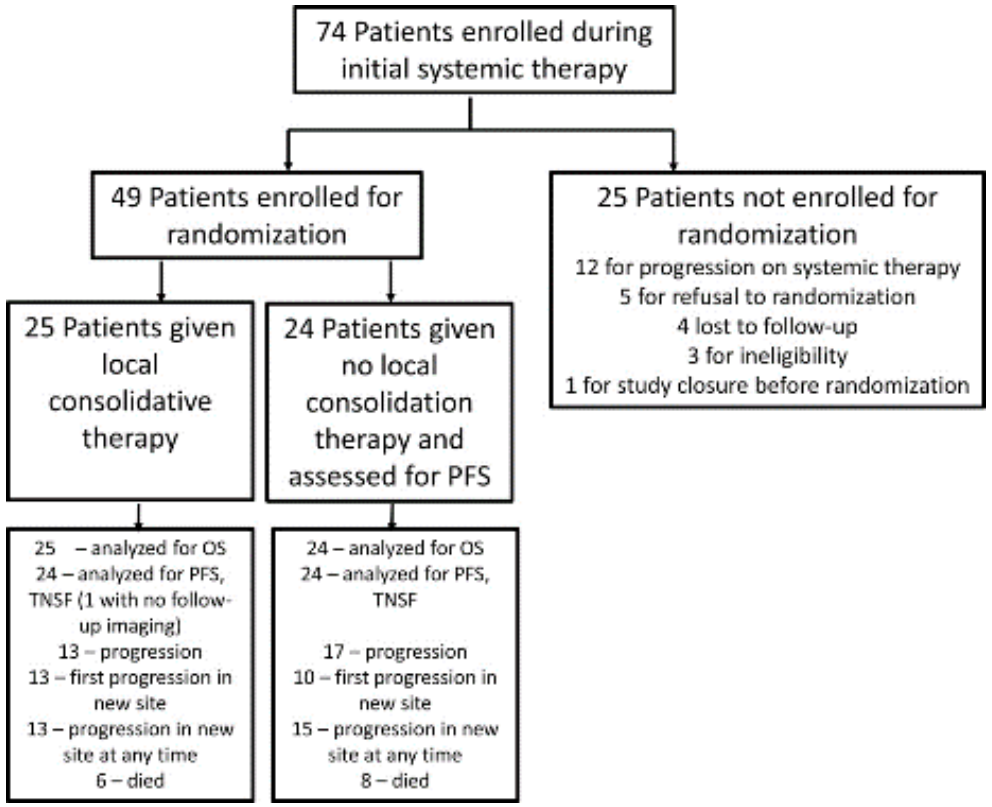
Any Survival Benefit?

- In a randomized phase II study, local consolidative therapy + SOC maintenance treatment, including observation, significantly prolonged PFS vs maintenance alone in patients with NSCLC and 1–3 oligometastases after first-line systemic therapy
  - Median PFS: 11.9 vs 3.9 mo (HR: 0.35; *P* = .005)
  - Adding LCT also delayed the appearance of new lesions, implying that the benefit of consolidation may extend beyond known sites of disease



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Gomez DR, et al. *Lancet Oncol.* 2016;17:1672-1682.

Table 2. **Completed Randomized Phase 2/3 Trials of LAT in Patients With OM-NSCLC**

Study	N	Setting	OMD definition and evaluation			Brain metastases	Timing of LAT	Systemic therapy	Dose and number of fractions	Toxicity
			Number of lesions	Primary tumor	Lymph nodes[a]					
SABR-COMET 2019, 2020[8,26]	99 (NSCLC, n = 18)	M: 100%	▪ ≤5 per protocol ▪ 1: 42% ▪ 2-3: 51% ▪ 4-5: 7%	▪ Not treated ▪ Required controlled primary tumor for 3 months	▪ Excluded per protocol ▪ 3% of patients had a lymph node as SBRT target (protocol violation)	▪ Included in OMD count ▪ 4% of patients affected	After registration	NR	▪ Lung: 54-60 Gy in 3-8 fractions ▪ Bone: 35 Gy in 5 fractions ▪ Vertebrae: 16-20 Gy in 1 fraction or 30 Gy in 3 fractions. ▪ Liver: 45-60 Gy in 3-8 fractions ▪ Adrenal: 60 Gy in 8 fractions	▪ Grade ≥2: 29% vs 9% ▪ Grade 5: 5% (2 pulmonary, 1 gastrointestinal) vs 0%
Iyengar 2018[6]	29	NR	▪ ≤6 prior to induction per protocol ▪ Number of lesions NR	Included in OMD count	▪ Included in OMD count but did not specify how ▪ 17.2% had involved N1 nodes ▪ 50% had involved N2 or N3 nodes	▪ Not included in A ▪ Required treatment prior to enrollment	After 4-6 cycles of CMT	Cytotoxic CMT, bevacizumab, or erlotinib	▪ 21-27 Gy in 1 fraction ▪ 26.5-33.0 Gy in 3 fractions ▪ 30.0-37.5 Gy in 5 fractions ▪ 45 Gy in 15 fractions (for bulky lymphadenopathy)	Grade ≥3: 0% vs 0%
Gomez 2016, 2019[16,27]	49	S: 94% M: 6%	▪ ≤3 post induction, per protocol ▪ 1: 6.1% ▪ 2-3: 93.9%	Included in OMD count	▪ Included in OMD count. Each level (N1-N3) counted as a site of OMD ▪ Involved N1 nodes: 24.5% ▪ Involved N2/3 nodes: 53%	▪ Included in OMD count ▪ 27% of patients affected	▪ After 4-6 cycles of CMT ▪ LAT could be surgery or radiotherapy	Cytotoxic CMT, bevacizumab, or erlotinib	▪ Brain: 15-20 Gy in 1 fraction ▪ Lung: variety of SBRT, hypofractionated, and conventional regimens ▪ Bone: 18-45 Gy in 1-15 fractions ▪ Adrenal: 60 Gy in 8 fractions	▪ Grade 3: 20% vs 8.3% ▪ Grade 4/5: 0%
SINDAS 2020[50]	133 (*EGFR*-mutant)	S: 100%	▪ ≤5 per protocol ▪ 1-2: 48.6% ▪ 3-4: 28.6% ▪ 5: 12.8%	Included in OMD count	▪ Included in OMD count. Each involved node counted separately ▪ Number of patients with involved nodes NR	Brain metastases excluded	After registration	Erlotinib, gefitinib, or icotinib	25-40 Gy in 5 fractions	▪ Grade 3/4 pneumonitis (7.3% vs 2.9%) ▪ Grade 3/4 esophagitis (4.4% vs 3.0%)

CMT, chemotherapy; LAT, local ablative therapy; M, metachronous disease presentation; NR, not reported; NSCLC, non–small cell lung cancer; OM-NSCLC, oligometastatic NSCLC; OMD, oligometastatic disease; S, synchronous disease presentation; SBRT, stereotactic body radiotherapy.

[a]N1, N2, and N3 refer to nodal group staging as defined by the American Joint Committee on Cancer, 8th edition.

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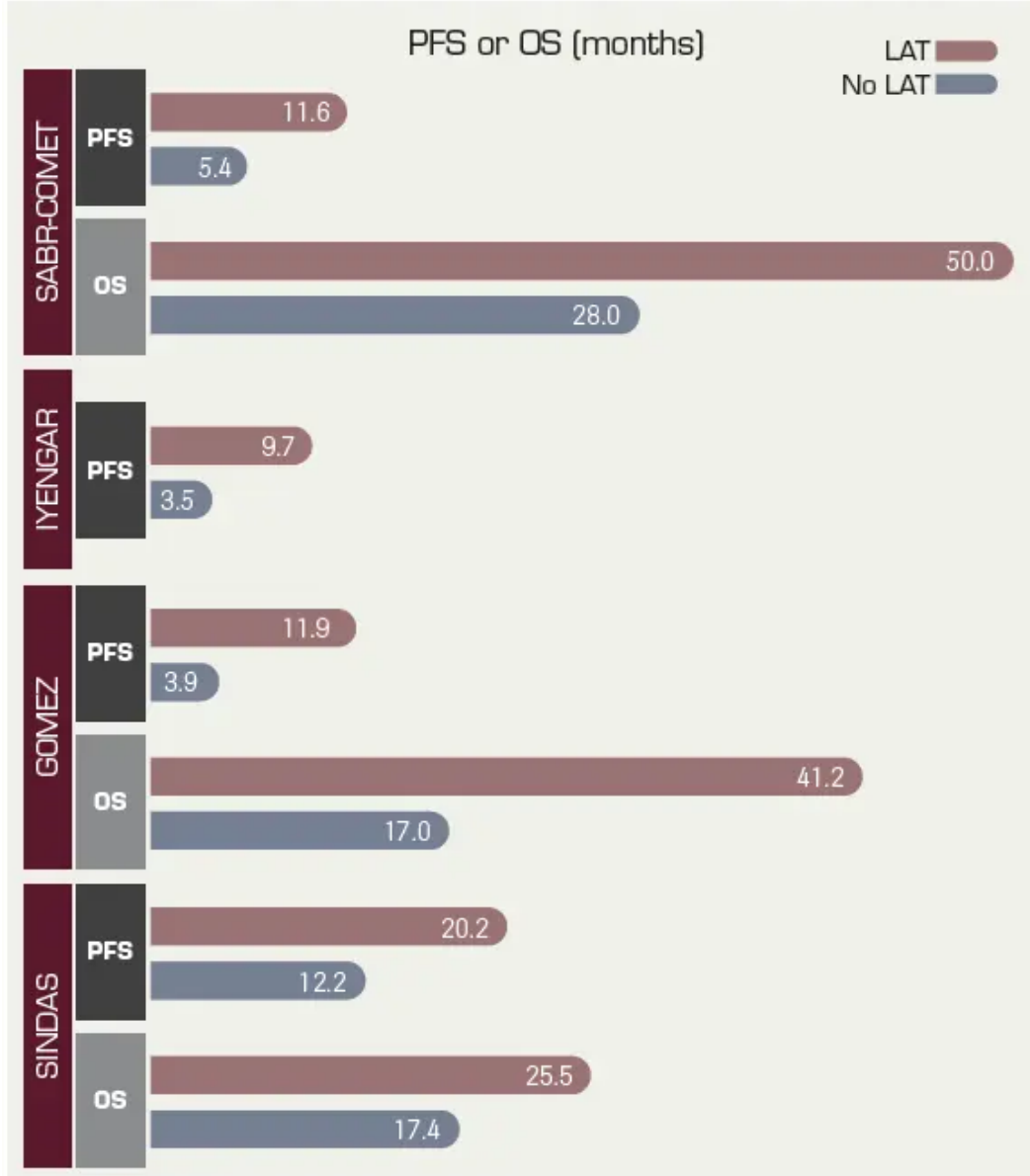
Figure. **Outcomes of Completed Phase 2/3 Trials of LAT in OM-NSCLC[a]**



LAT, local ablative therapy; OM-NSCLC, oligometastatic non–small cell lung cancer; OS, overall survival; PFS, progression-free survival.

[a]PFS and OS are plotted for each of the 4 trials involving LAT. Of note, values plotted in the SABR-COMET trial reflect the entire cohort (N = 99) rather than those with OM-NSCLC; N = 18. OS in the Iyengar trial was not reached and is therefore not shown.

NRG-LU002

- RG-LU002, comparing local consolidative therapy (LCT) and maintenance systemic therapy to maintenance systemic therapy alone for limited-metastatic non-small cell lung cancer (NSCLC)

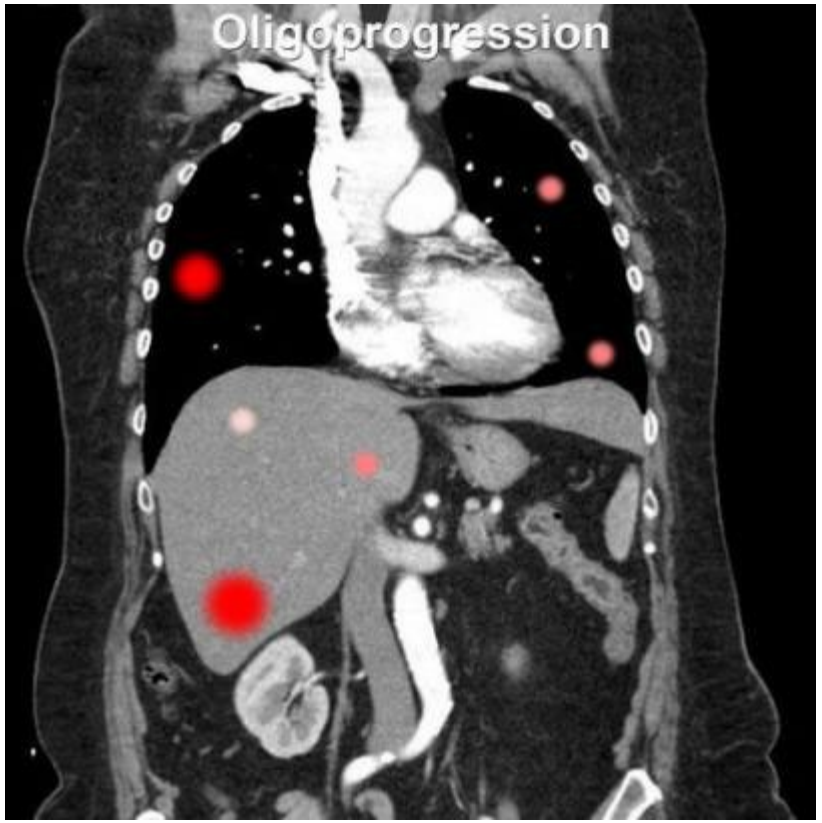
- Patients with limited metastatic NSCLC who had completed at least 4 cycles of first-line systemic therapy and had displayed no signs of progression. Patients were randomly assigned to receive either maintenance systemic therapy alone, or LCT

- Phase II suspended for interim monitoring, July 2022

Oligoprogressive disease is a relatively new clinical concept describing progression at only a few sites of metastasis in patients with otherwise controlled widespread disease.

The origin of oligoprogressive disease is considered complex and has numerous parameters, including

1. Molecular evolution of cancer cells
2. Changes in the tumor microenvironment
3. Hemodynamic parameters
4. Previous application of local therapies
5. Unique disease characteristics



In the Era of Well-tolerated Targeted Treatments, Resistance Inevitably Occurs, and Overcoming This Is a Challenge

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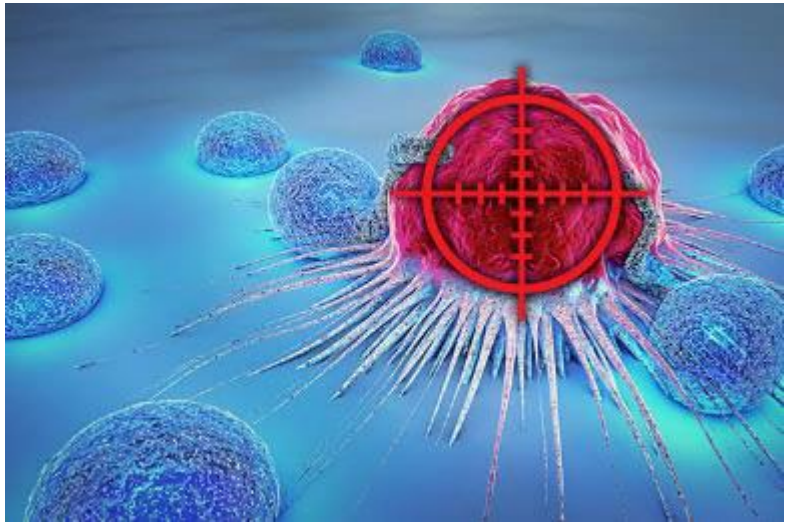
Notwithstanding, from a therapeutic point of view, oligo-progression carries a very simple and important implication: **the opportunity to regain control of disseminated tumors by use of local treatments**, which can thereby prolong benefit from systemic therapies and patient survival



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1. Presence of symptoms and sites of disease progression

2. Available resources (at institution) and r/o disease transformation

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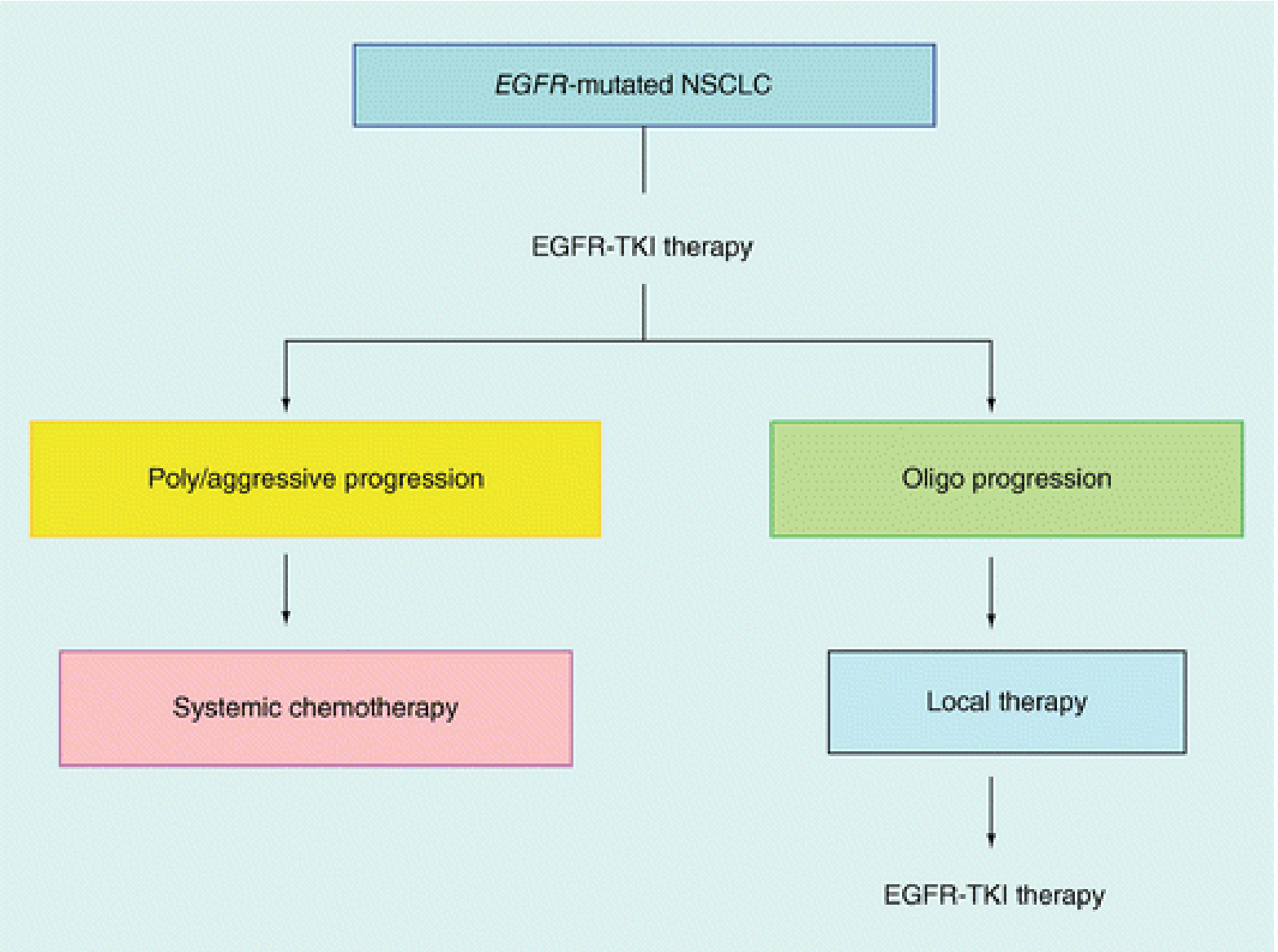
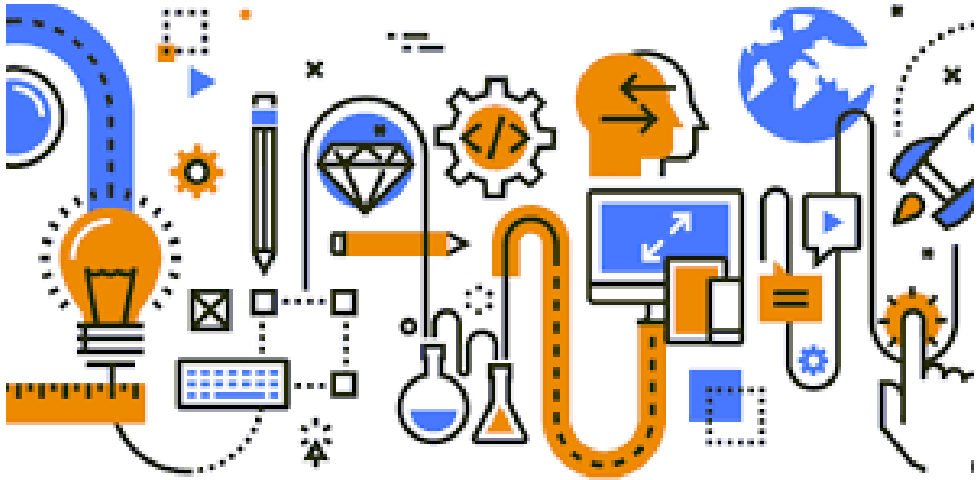
Second-Line Therapy Tailored to Each Patient

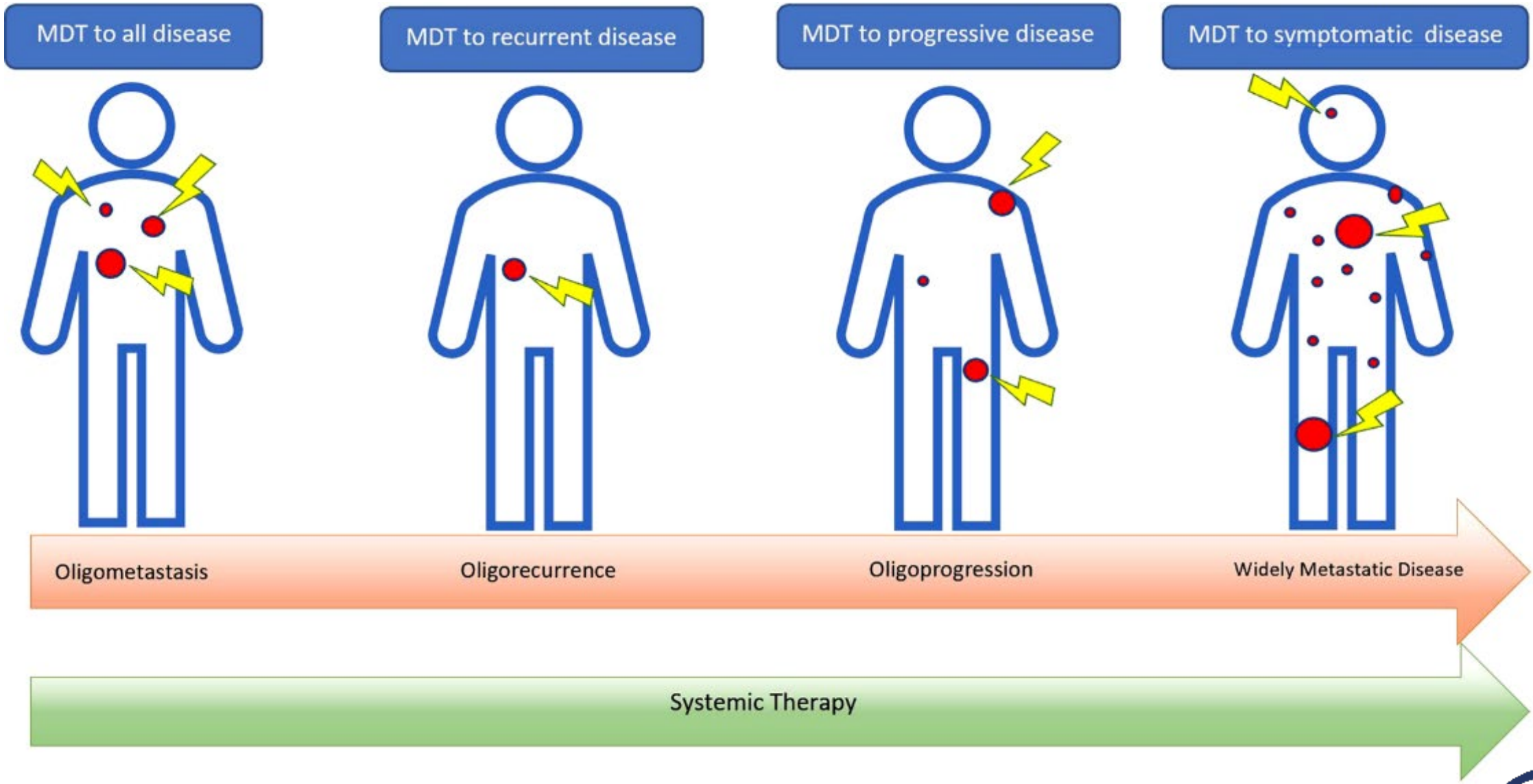
Choice of second-line therapy will vary on the basis of

- Molecular subtype
- Details of the first-line regimen
  - Specific regimen, degree of benefit received, tolerability
- Circumstances of resistance
  - Timing, location
- Patient comorbidities
- Patient choices and values
- Performance status at the time of disease progression


EGFR-mutated NSCLC
EGFR-TKI therapy
Poly/aggressive progression
Oligo progression
Systemic chemotherapy
Local therapy
EGFR-TKI therapy

Role of the Multidisciplinary Care Team





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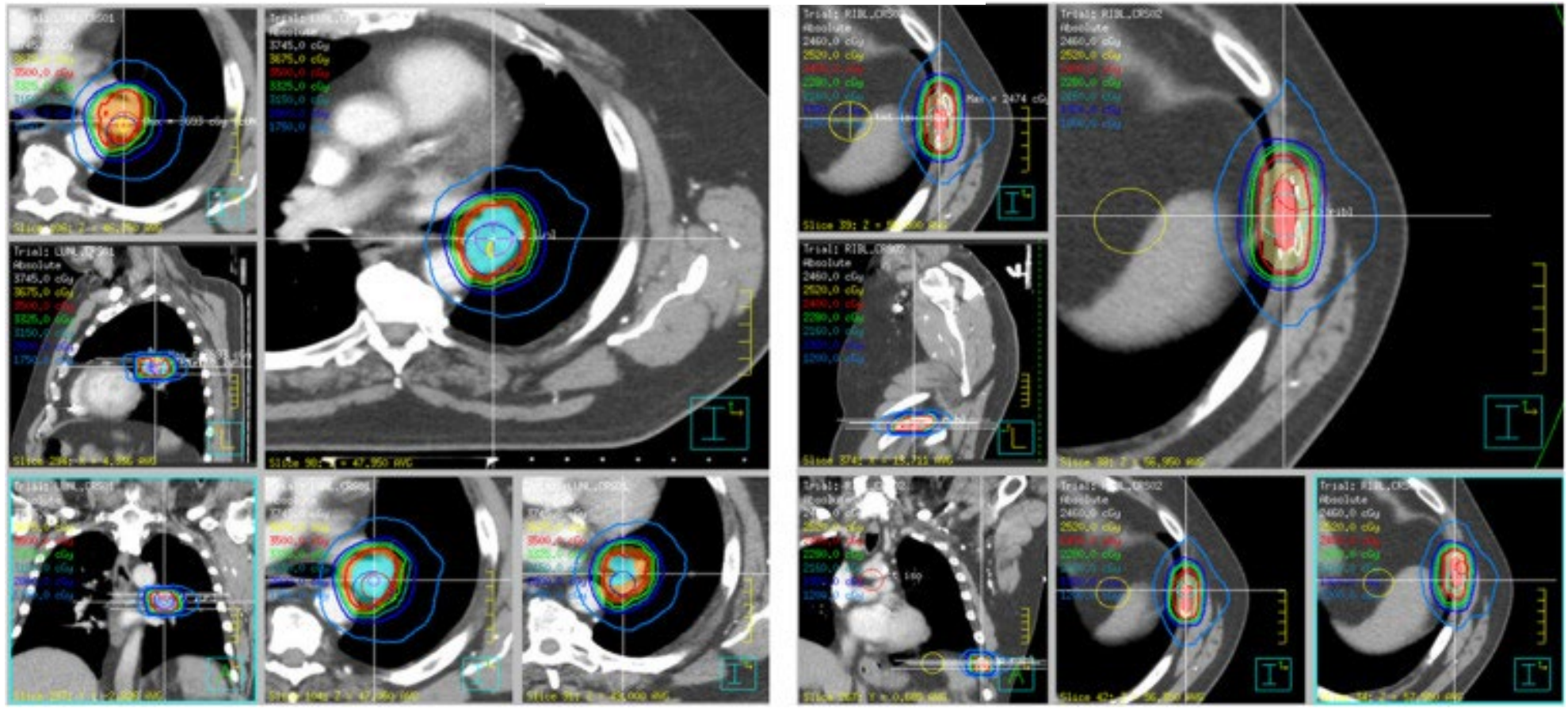
EXAMPLE



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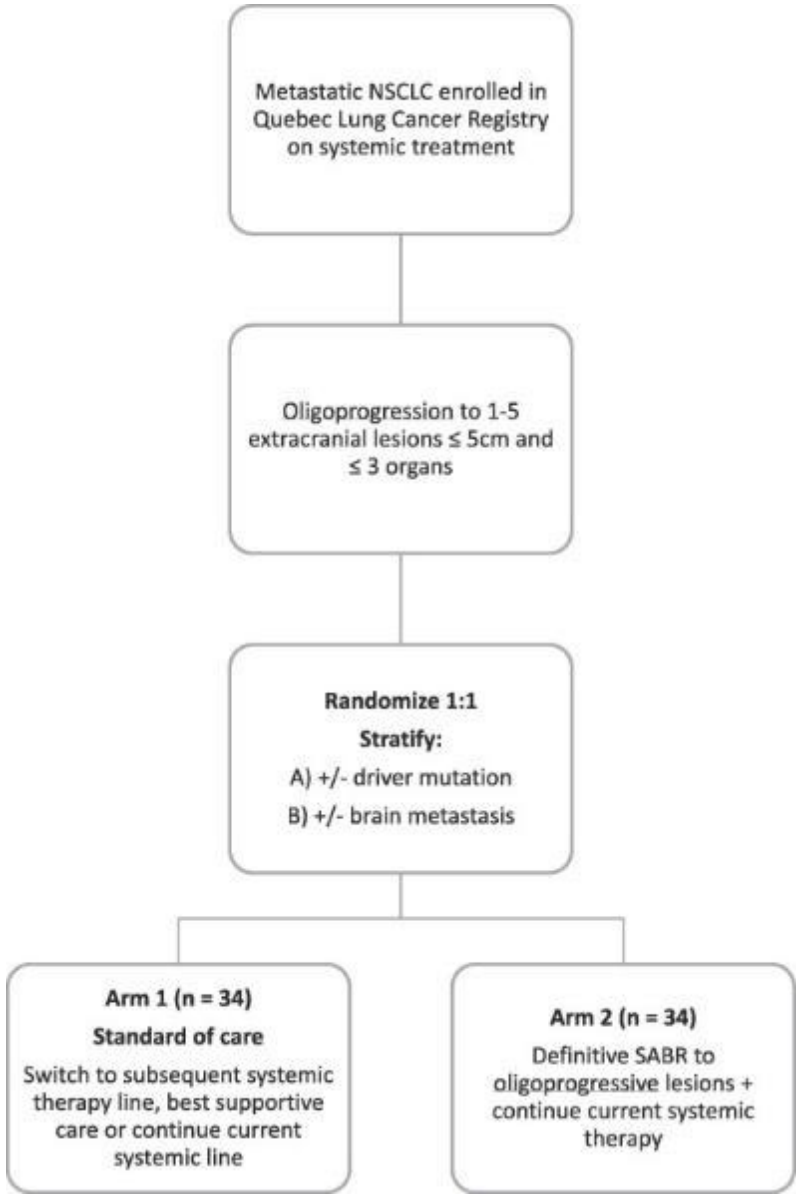

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Bahig H, et al. *Clin Transl Radiat Oncol*. 2022;33:115-119.

The Many Faces of Lung Cancer

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Remaining Challenges

Targeted vs chemotherapy

Evolving definitions

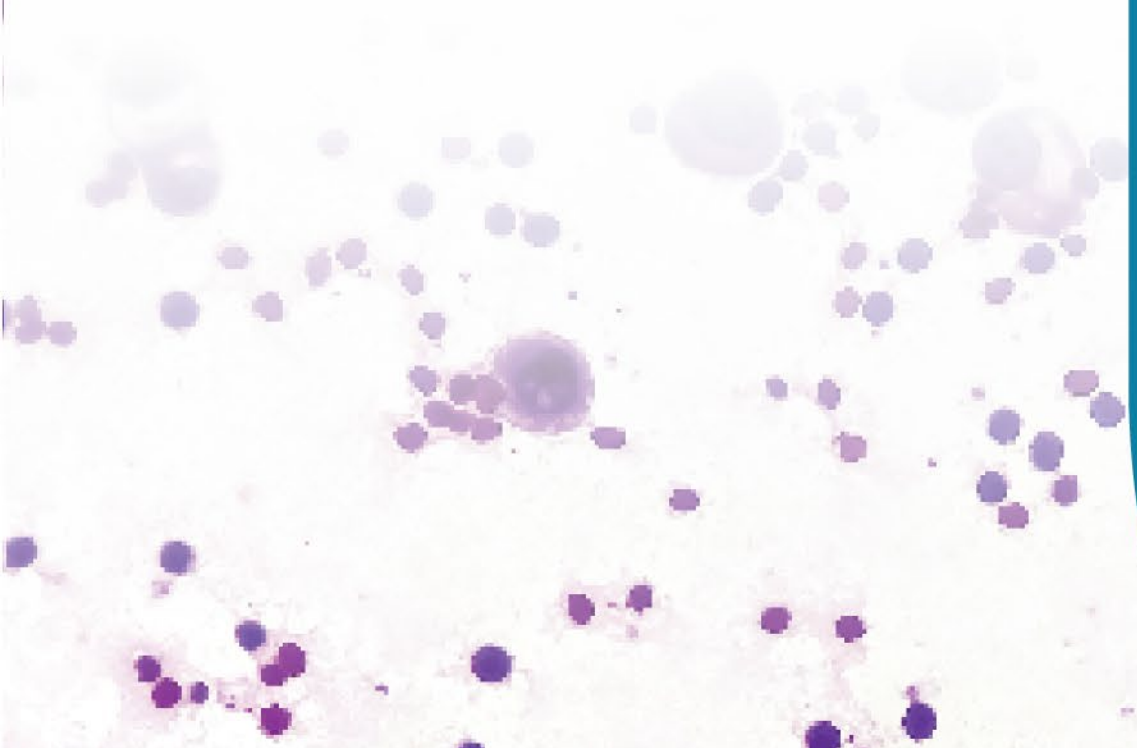
SBRT access

Shared decision-making

Local therapies: #?

Q&A

Global Lung Cancer Academy



Tumor Board Discussion

Moderator: Corey Langer, MD, FACP

Case presenters: Vinícius Lorandi, MD, and Barbara Melosky, MD, FRCP

Global Lung Cancer Academy

Patient case 1

Vinícius Lorandi, MD

Clinical Case

NSCLC Stage III

Vinícius Lorandi, MD
Medical Oncologist

Conflicts of Interest

Category	Company
Transport, congress, or educational support	**Roche, AstraZeneca, Novartis, BMS, MSD, Lilly, Daiichi Sankyo**
Clinical studies	**-**
Conference talks	**Foundation Medicine, Servier, BMS, Ipsen**
Scientific text writing	**Novartis**
Stock Market	**-**

Male, 44 Years Old, No Comorbidities

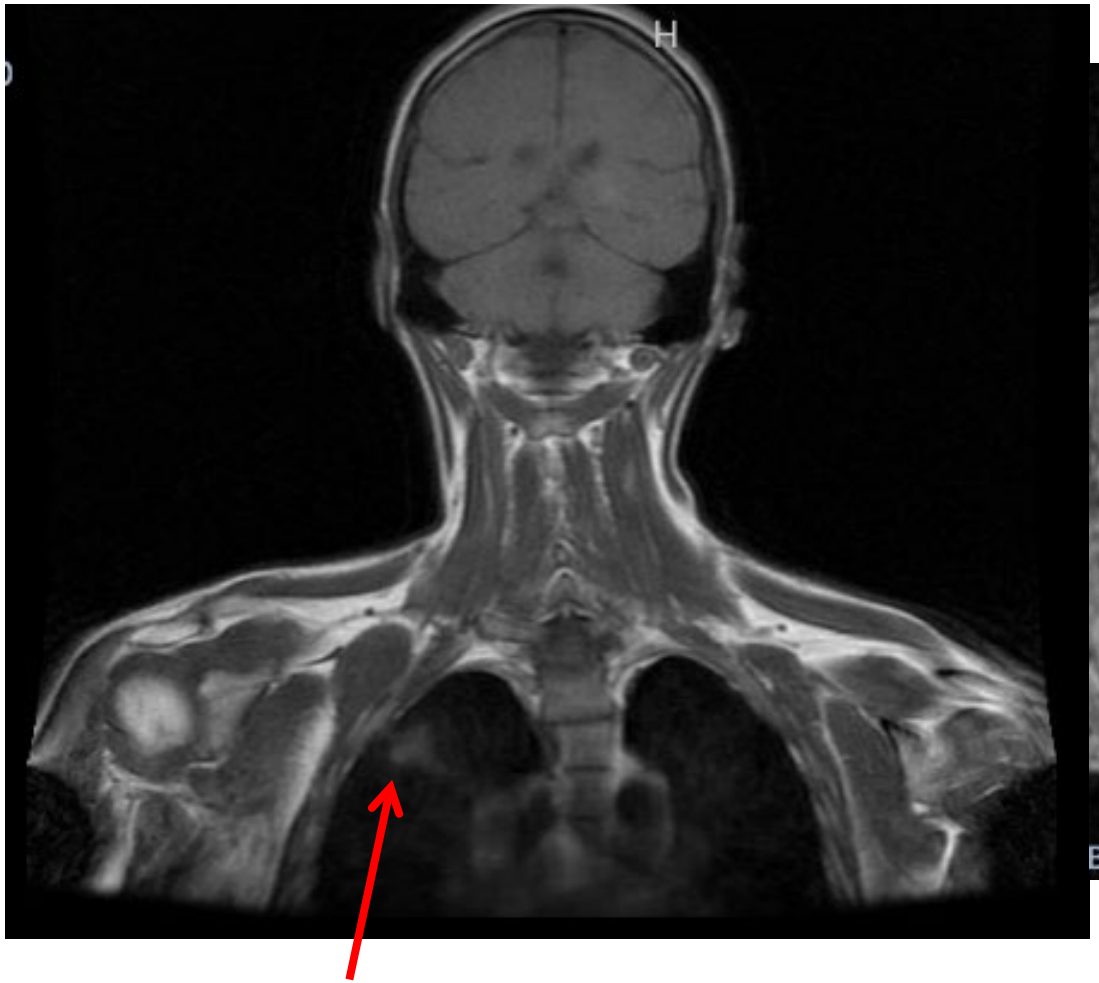
- Asymptomatic
- Not on any medication
- Never smoker
- Occasional drinker
- Lives in London with wife and 18-month-old boy
- Currently unemployed/works in risk management

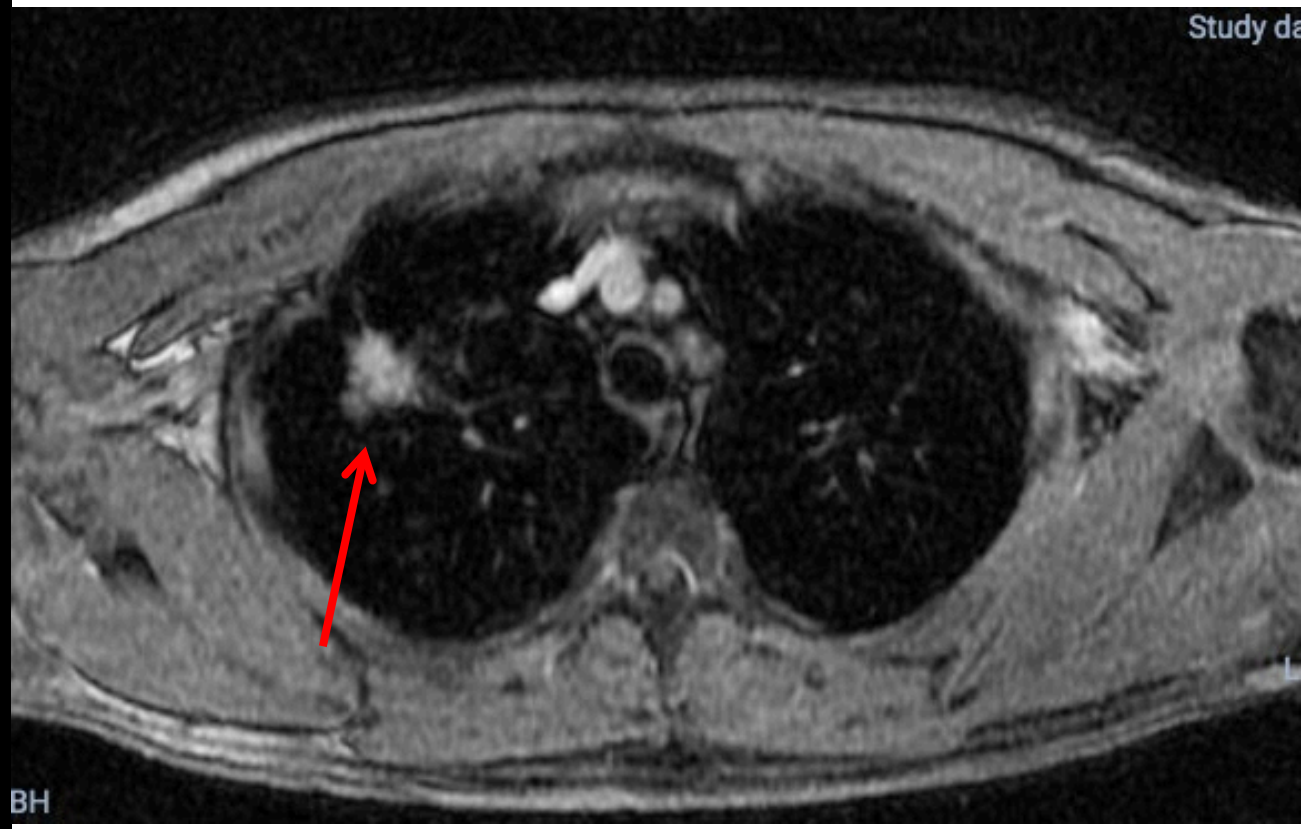
Family history

- Mom diagnosed with breast cancer at 45 and died later of a retroperitoneal sarcoma
- Brother diagnosed with a metastatic salivary gland adenocarcinoma
- Brother goes for genetic counseling and tested positive for m*TP53* (R337H) – Li-Fraumeni syndrome
- Patient also tests positive for a germline *TP53* mutation

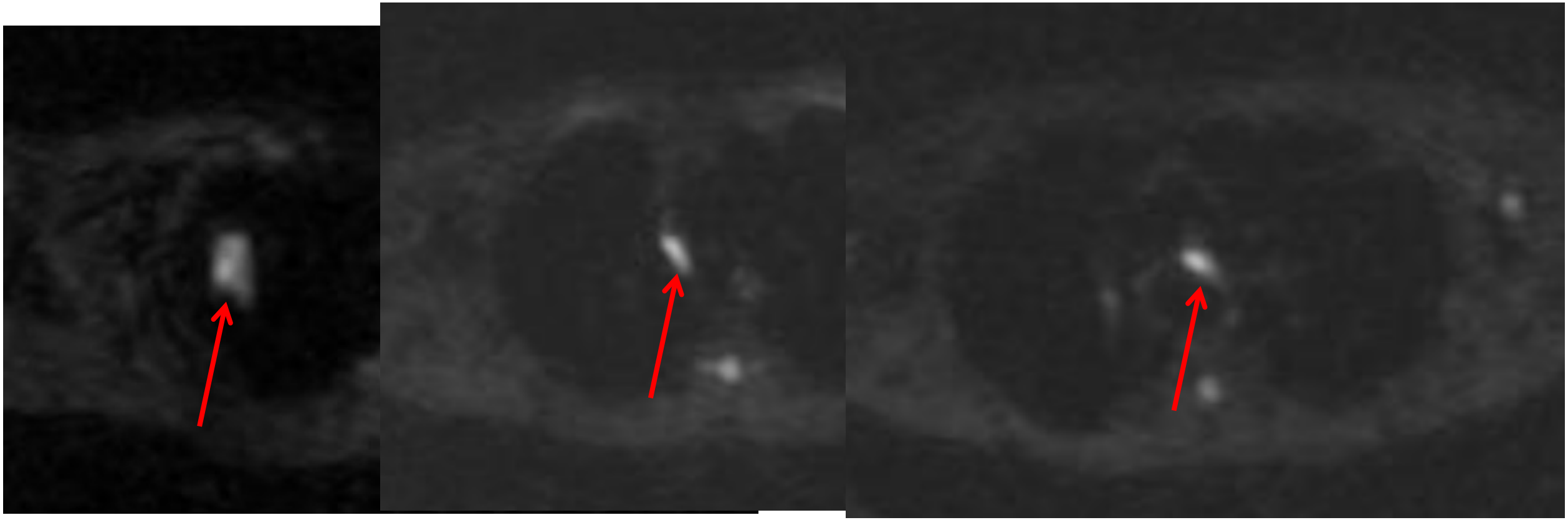
During a short visit to Brazil, patient decides to see his brother's geneticist and to perform his first-ever screening whole-body MRI. He tried to get this in the UK but was told he had no coverage since the test is not cost-effective.

Male, 44 Years Old, Asymptomatic, Li-Fraumeni: WB-MRI

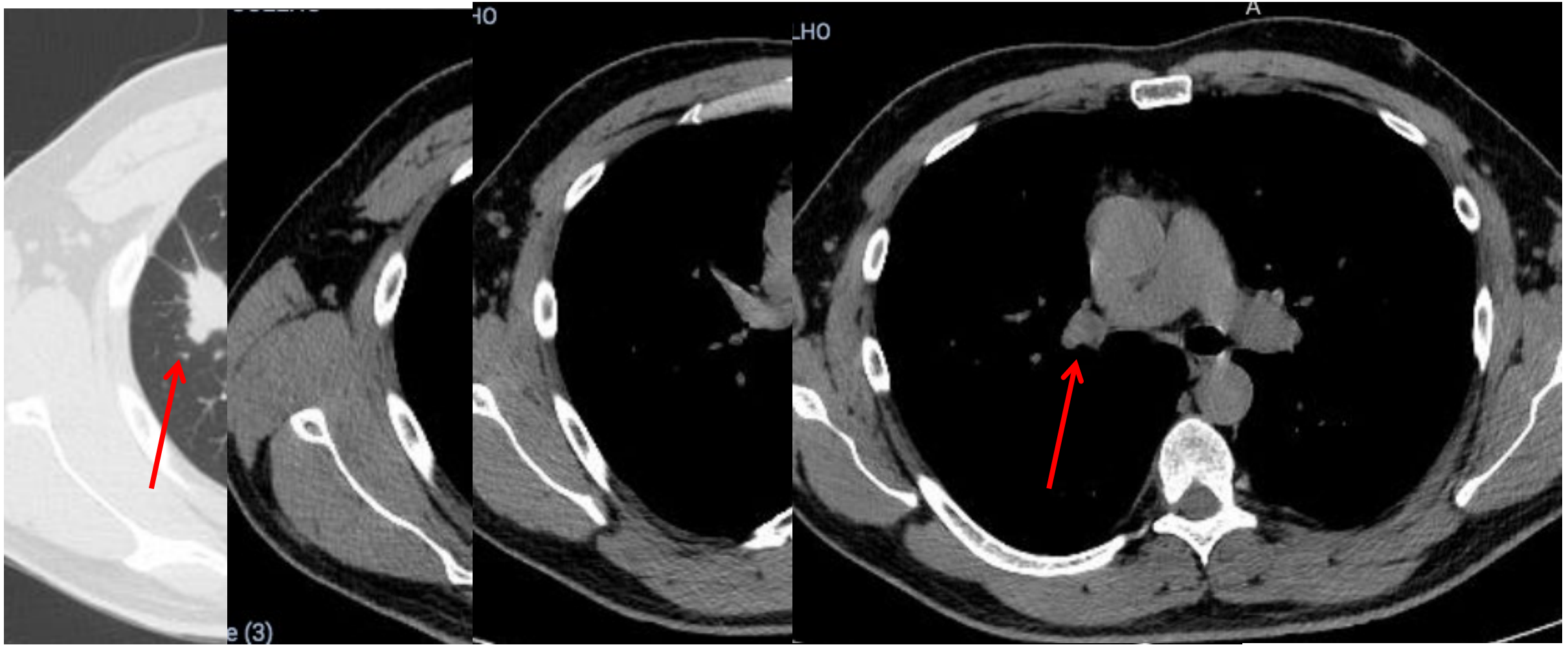


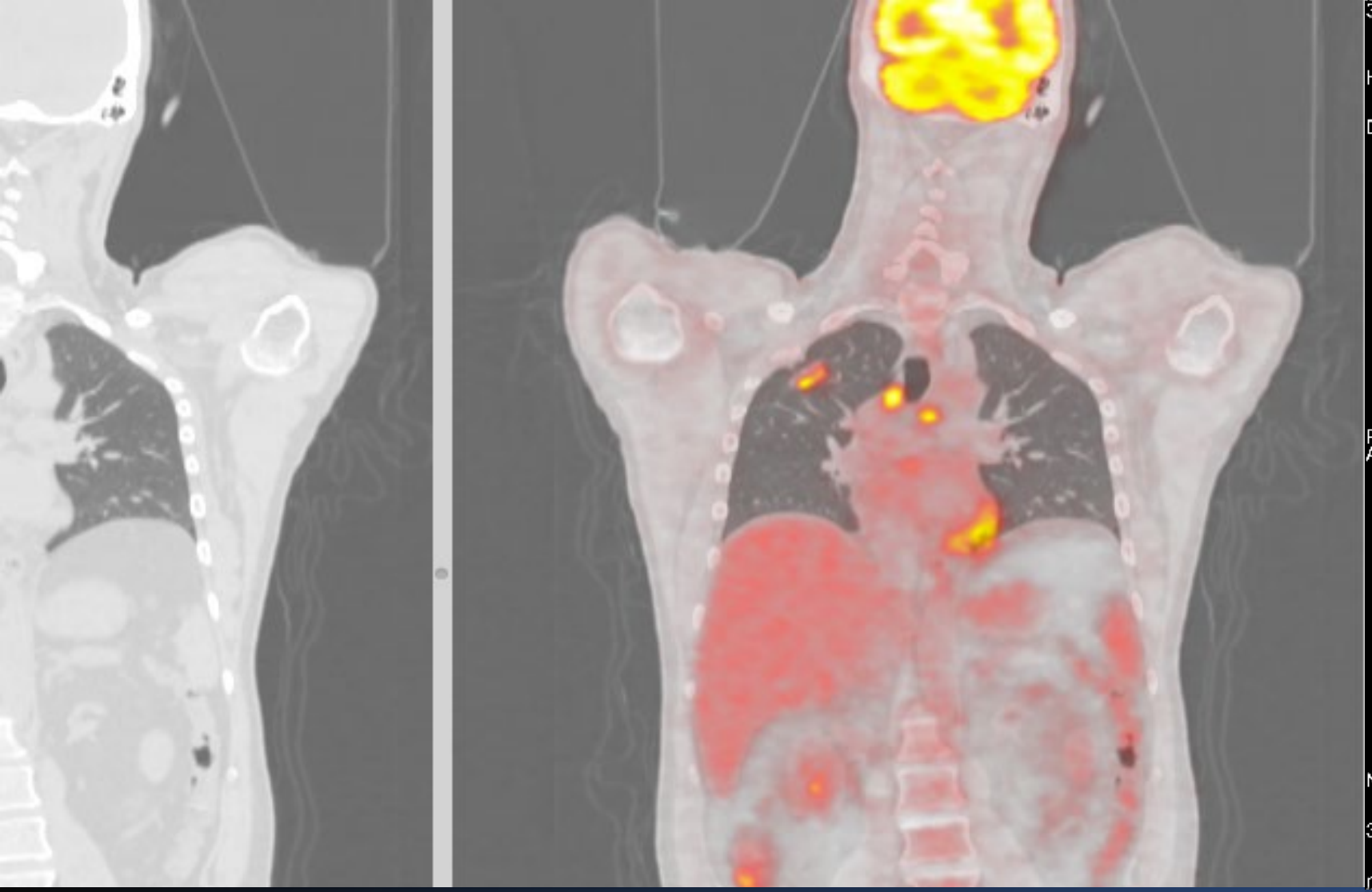


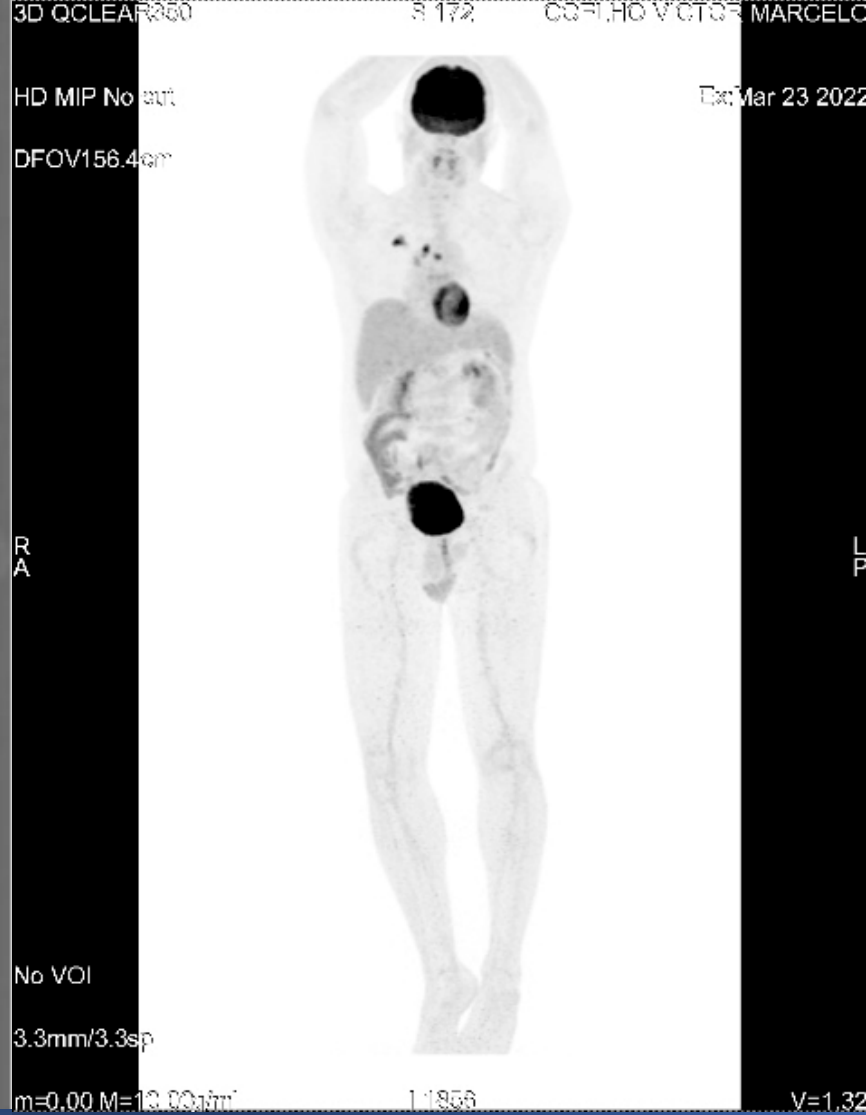
Male, 44 Years Old, Asymptomatic, Li-Fraumeni: WB-MRI



Male, 44 Years Old, Asymptomatic, Li-Fraumeni Chest-CT







Male, 44 Years Old, Asymptomatic, Li-Fraumeni: PET-CT

Male, 44 Years Old, Li-Fraumeni, ECOG 0, Lung Mass – cT1N3M0 – IIIC

- **EBUS**: carcinoma positive in mediastinal 4L and 4R
- **Lung function:** FEV1/FVC = 3.8/5.6 (94% and 106% of predicted), TLCOc 95%

EXAME ANATOMOPATOLOGICO
ANATOMOPATOLOGICO TRANSOPERATÓRIO

MATERIAL: A- LINFONODO MEDIASTINAL; NÍVEL 4L (FRASCO 1).
B- LINFONODO MEDIASTINAL; NÍVEL 4L (FRASCO 2).
C- LINFONODO MEDIASTINAL; NÍVEL 4R (LÂMINAS).

MACROSCOPIA: A- Recebidos, fixados em formalina, escassos fragmentos irregulares de tecido, friáveis e de aspecto hemorrágico, pesando em conjunto menos de 1,0 g. 3xnfit

B- Recebidos, fixados em formalina, escassos fragmentos irregulares de tecido, friáveis e de aspecto hemorrágico, pesando em conjunto menos de 1,0 g. 6xnfit LZ/mgc

Diagnóstico transoperatório por congelação:

A e C- POSITIVO PARA CÉLULAS MALIGNAS.

Dra. Mariana Guimarães Coelho
CRMRS 33902

DIAGNÓSTICO: A e B- NEOPLASIA MALIGNA INDIFERENCIADA EM MEIO A LINFÓCITOS E COÁGULOS HEMÁTICOS. PROVÁVEL CARCINOMA.

EXAME IMUNOHISTOQUIMICO

MATERIAL: LINFONODO MEDIASTINAL (NÍVEL 4L).

CONCLUSÃO: - PERFIL COMPATÍVEL COM ADENOCARCINOMA POUCO DIFERENCIADO PULMONAR.

NOTA: **necessária estreita correlação clínica e radiológica.**

NÚMERO ORIGINAL: 263632, fração 4/9.

RESUMO DA TÉCNICA: Cortes histológicos em lâminas silanizadas, com recuperação antigênica em instrumento DAKO modelo PT Link e processamento final realizado em plataforma automatizada DAKO modelo Autostainer Link 48.

ANTICORPOS E CLONES UTILIZADOS:

- Citoqueratina 7 (clone OV-TL12/30 - DAKO): POSITIVO.
- CDX-2 (clone DAK-CDX-2 - DAKO): NEGATIVO.
- TTF-1 (clone 8G7G3/1 - DAKO): POSITIVO.
- PAX-8 (clone MRQ-50): NEGATIVO.
- p63 (clone DO-7 - DAKO): POSITIVO FRACO E FOCAL.

Male, 44 Years Old, Li-Fraumeni, ECOG 0, Lung Adenocarcinoma – cT1 pN3 – CS IIIC

What other information would you seek in order to make a treatment decision? *(Please select all that apply.)*

1. *EGFR* mutation status
2. PD-L1 expression level
3. *BRAF*
4. *KRAS*
5. *ALK*
6. Other
7. None

Male, 44 Years Old, Li-Fraumeni, ECOG 0, Lung Adenocarcinoma – cT1 pN3 – CS IIIC

Report

MOLECULAR PATHOLOGY SUPPLEMENTARY REPORT

Results:

Histology block:	22H00015459 block A1
Tissue adequacy:	20% tumour cells (without macrodissection)
Analysis method:	COBAS 480
Target(s):	EGFR (Exons 18-21)
Reference cDNA sequence:	NM_005228.3 (EGFR)
Result:	Mutation detected
Details:	c.2573T>G or c.2573_2574TG>GT p.Leu858Arg (L858R)

Interpretation:

The specimen was suitable for molecular analysis, based on tumour cellularity.

An EGFR mutation (L858R) was detected in this sample. This is consistent with a mutant EGFR tumour and this patient may benefit from EGFR-inhibitor therapy.

Male, 44 Years Old, Li-Fraumeni, ECOG 0, Lung Adenocarcinoma – cT1 pN3 – CS IIIC *EGFR*m – L858R

How would you treat him?

1. Encourage the patient to have CRT alone
2. Encourage the patient to have CRT + durvalumab
3. Neoadjuvant (+/- IO) CT followed by surgery (+/- osimertinib)
4. Resection upfront and adjuvant osimertinib
5. Immunotherapy
6. Neoadjuvant/palliative osimertinib
7. Other

Male, 44 Years Old, Li-Fraumeni, ECOG 0, Lung Adenocarcinoma – cT1 pN3 – CS IIIC *EGFR*m – L858R

- ✓ Patient declined radiotherapy
- ✓ Demanded to be considered for surgery

Male, 44 Years Old, Li-Fraumeni, ECOG 0, Lung Adenocarcinoma – cT1 pN3 – CS IIIC *EGFR*m – L858R Declined RxT

April 26, 2022:
Started on neoadjuvant osimertinib 80 mg qid (off-label)

May 5, 2022:
PET-CT already showing decrease in size of both the lung tumor and mediastinal LNs

- Male, 44 years old, Li-Fraumeni, ECOG 0, lung adenocarcinoma – cT1 pN3 – CS IIIC *EGFR*m – **L858R**
- **Neoadjuvant *(off-label)* osimertinib April 2022**
- 4 months → PET-CT shows **no mediastinal uptake + reduced size in lung**
- Right upper lobectomy + radical LN dissection in **August 2022**

SITE OF SPECIMEN:

A) Right upper lobe.
B) Station 2 to 4 en bloc in packet.
C) Station 7.
D) Station 8.
E) Station 9.
F) Station 10.
G) Station 11.
H) Station 11 lower.
J) N3 node.

A) Pot labelled right upper lobe.
A lobe of lung measuring 90x75x65mm. The bronchial margin is stapled. There is a 29mm subpleural tumour which is well away from the trimmed bronchial margin. There is adjacent inflammatory change which may represent regression. The background lung is otherwise unremarkable.

B) The station 2-4 lymph nodes show evidence of previous tumour involvement, including fibrosis and collections of foamy macrophages. There is no residual viable tumour present.

C-H) These lymph nodes do not show any evidence of tumour involvement.

J) The N3 lymph node contains areas of fibrosis which would be consistent with previous tumour involvement. No residual viable tumour is present.

Histological type		: Adenocarcunoma
Maximum tumour diameter		: 7mm
Maximum invasive tumour diameter (non-mucinous adenocarcinoma)	: 7mm	
Visceral Pleural Invasion (VPI)		: Absent (PL0)
Vascular invasion		: Absent
Resection margins:		
- Bronchial		: Clear
- Vascular		: Clear
Lymph node metastases		: Absent
TNM stage (8th edition, 2017)		: ypT1a, ypN0

Planned for 3 years of adjuvant osimertinib

Global Lung Cancer Academy

Patient case 2

Barbara Melosky, MD, FRCP

“Ms SC”

Presentation

- 71-year-old female Asian never smoker
- 2-month history of hemoptysis, fevers 38.5°
- Bitemporal headaches
- 6-pound weight loss

Investigations

CT chest on Feb 18, 2022

- RUL 6.3 × 6.0 × 5.2-cm mass
- Adjacent pleural thickening and abutting horizontal fissure

PET CT on March 5, 2022

Intensely FDG-avid mass within the RUL (SUV 24)

No direct chest wall involvement

No FDG-avid distant metastatic disease is demonstrated

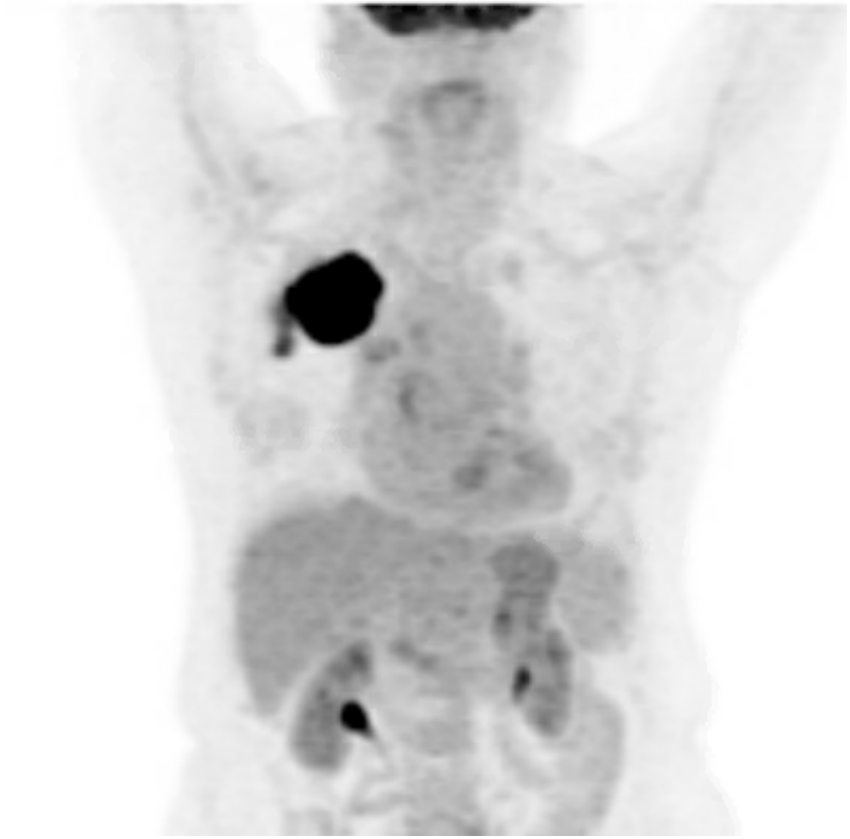
Pathology

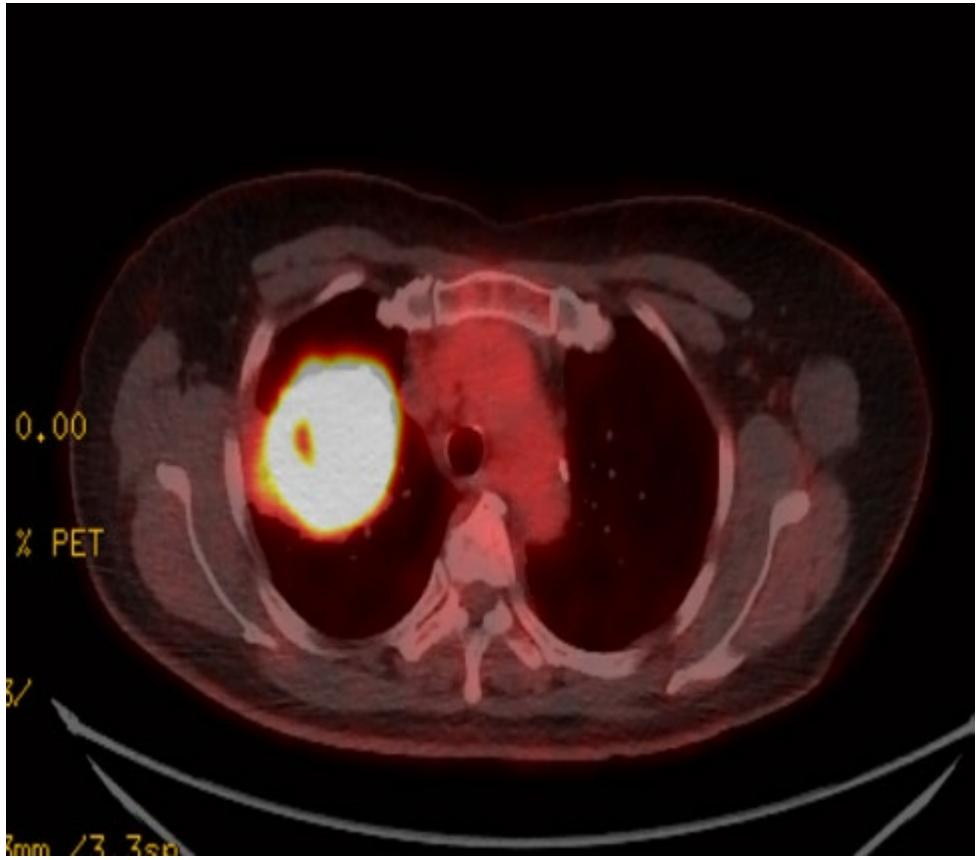
- EBUS on Feb 25, 2022
  - RUL: moderately differentiated squamous cell carcinoma
  - LN 11R, 11N, 7, 4R negative

EGFR M+ 19 deletion

--- TIER I: VARIANTS OF STRONG CLINICAL SIGNIFICANCE ---
EGFR:c.2240_2257del, p.Leu747_Pro753delinsSer (VAF:51.5%)
This exon 19 in-frame deletion results in activation of the receptor and constitutive EGFR pathway signaling. In non-small cell lung cancer, this mutation is predictive of sensitivity to anti-EGFR TKI therapies. First- to third-generation anti-EGFR TKIs are approved by the FDA and Health Canada for first-line treatment of non-small cell lung cancers carrying activating EGFR mutations.

PET Scan





Pathology

RUL Lobectomy on March 14

1. Adenosquamous carcinoma, 7.7 cm
2. All margins clear
3. Early visceral pleural invasion but not into chest wall
4. Bronchial resection margins negative
5. All nodes negative

Question 1

What stage is this patient?

1. Stage lllA
2. Stage lllB
3. Stage ll
4. Stage lV

T4N0M0

Stage IIIA

Lung Cancer Staging Updates

Stage IIIA

Lung Cancer Stage Grouping (7th Edition)[2]

Anatomic Stage/Prognostic Groups			
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0

Anatomic Stage/Prognostic Groups			
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Stage IIIA

Lung Cancer Stage Grouping (8th Edition)[1,3]

Anatomic Stage/Prognostic Groups			
Stage IA1	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0

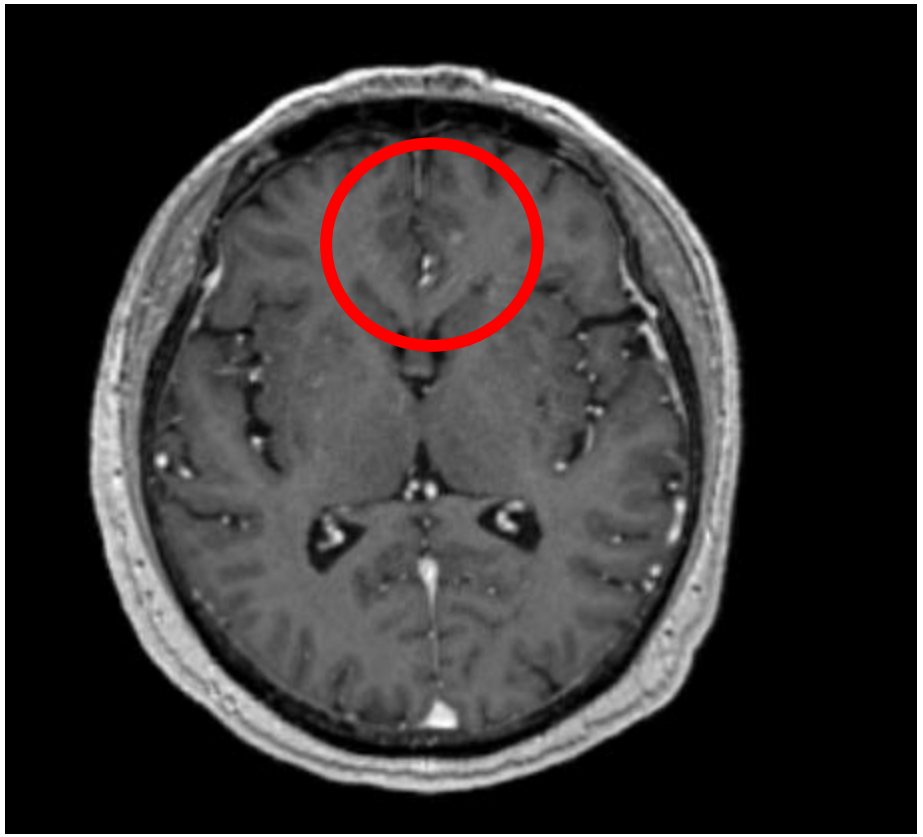
Anatomic Stage/Prognostic Groups			
Stage IIIA (cont)	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

1. Detterbeck FC, et al. *Chest*. 2017;151:193-203; 2. American Joint Committee on Cancer (AJCC). 2012. 1-2; 3. Kay FU, et al. *World J Radiol.* 2017;9:269-279.

Question

- MRI 3-mm lesion L frontal lobe
- What do you do about it?

April 5 Postoperative



Question 2

What is her benefit of chemotherapy?

1. 0%
2. 5%
3. 15%
4. 25%

2004

Canadian Cancer Trials Group BR.10 – Study Design

T2N0
T1–2N1

N = 482

STRATIFIED
Nodal
N0 N1

No Chemotherapy

Chemotherapy
VbP* × 4 cycles

*Cisplatin 50 mg/m2 day 1, 8 q4w
Vinorelbine 25 mg/m2 weekly × 16

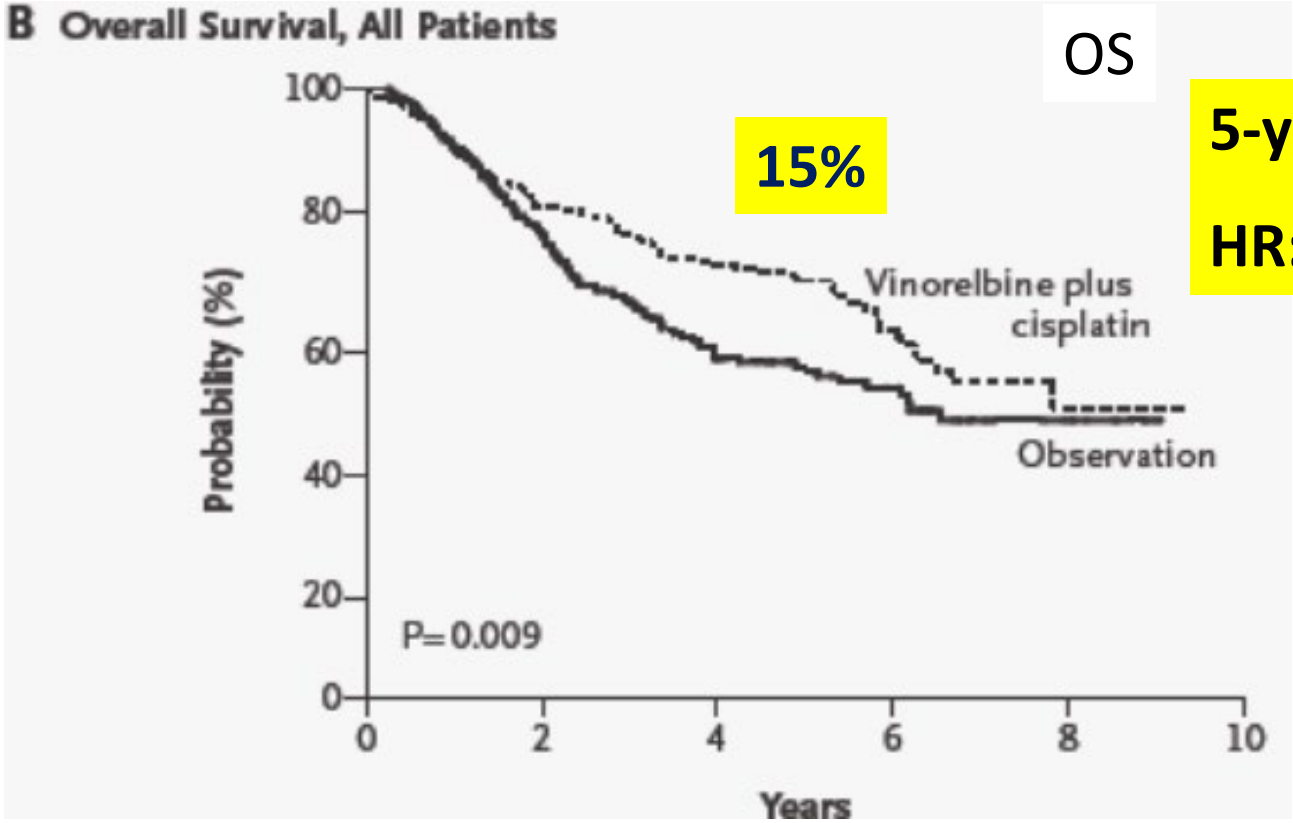
Winton T, et al ASCO 2004. Abstract 7018.

2004

Canadian Cancer Trials Group BR.10

Stage IB, II

Cisplatin-vinorelbine 4 cycles vs no treatment



5-yr: 69% vs 54%

HR: 0.69 *P* = .009

Winton T, et al ASCO 2004. Abstract 7018.

6th Edition 2002–2009

Table 1

AJCC TNM staging system for lung cancer (6th edition, 2002)

Primary tumor (T)	
T1	Tumor ≤3 cm diameter without invasion more proximal than lobar bronchus
T2	Tumor >3 cm diameter; tumor with pleural invasion; partial lung atelectasis; proximal extent ≥2 cm from the carina
T3	Tumor of any size with: chest wall invasion; diaphragm, pericardium, or diaphragm involvement; complete lung atelectasis; proximal extent <2 cm from the carina
T4	Tumor of any size with: mediastinal, great vessel, trachea, esophageal, carinal or vertebral body invasion; malignant pleural or pericardial effusion; same lobe satellite nodule(s)
Nodal involvement (N)	
N0	No regional lymph node involvement
N1	Ipsilateral hilar and/or ipsilateral peribronchial nodal involvement
N2	Ipsilateral mediastinal and/or subcarinal nodal involvement
N3	Contralateral mediastinal or hilar nodal involvement; supraclavicular nodal involvement
Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis; metastatic tumor nodules in different lobes from the primary tumor

JBR.10: Survival by Stage

Winton, et al

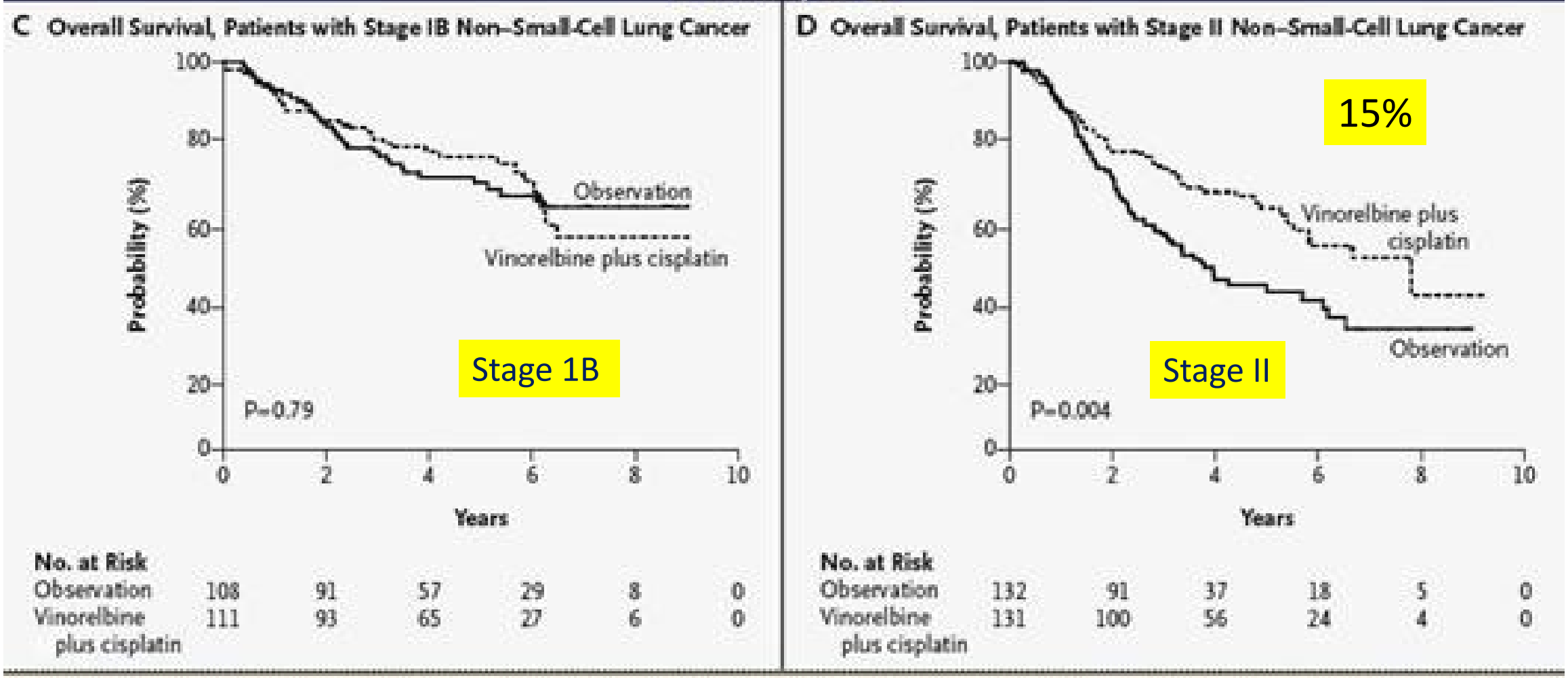


Figure 1. Kaplan–Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone.

P values are based on two-sided statistical analyses of differences between treatment groups after randomization.

Plan

- Cisplatin-vinorelbine 4 cycles followed by 1 year of osimertinib

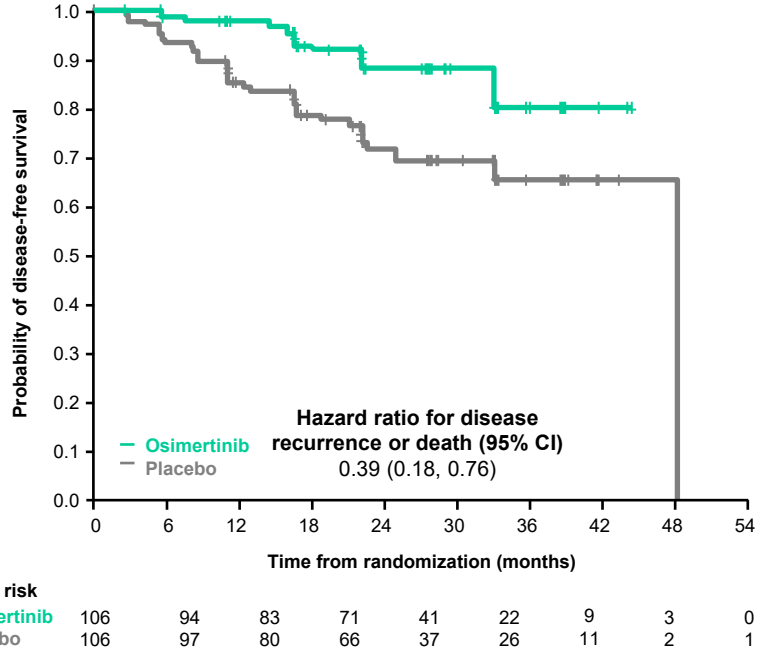
Question

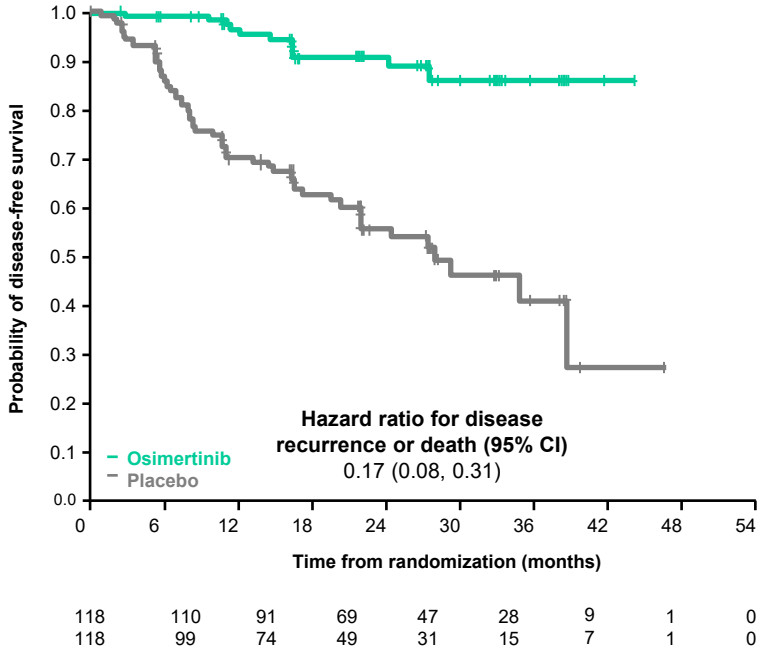
- What is her benefit from osimertinib?

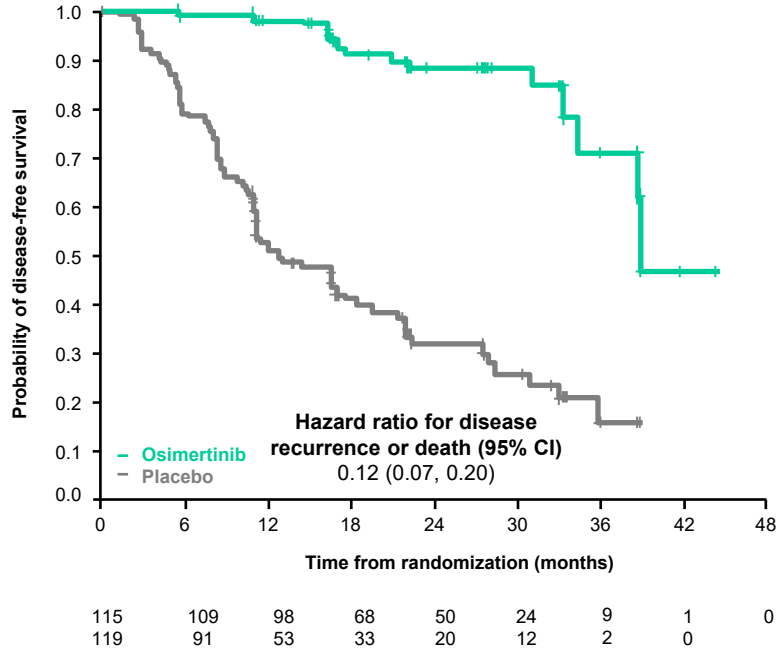
ESMO 2020

ADAURA: DFS by Stage

	Stage IB	Stage II	Stage IIIA
2-year DFS rate, % (95% CI)			
– Osimertinib	88 (78, 94)	91 (82, 95)	88 (79, 94)
– Placebo	71 (60, 80)	56 (45, 65)	32 (23, 41)
Overall HR (95% CI)	**0.39 (0.18–0.76)**	**0.17 (0.08–0.31)**	**0.12 (0.07–0.20)**

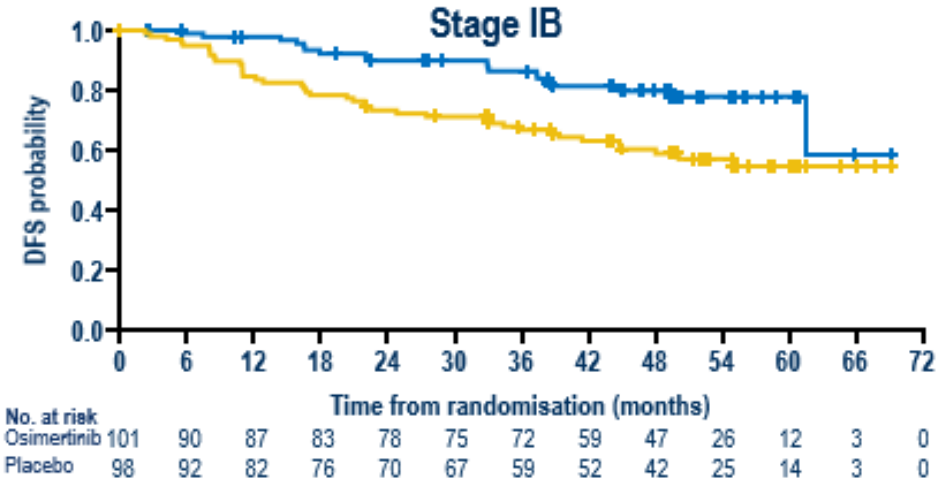




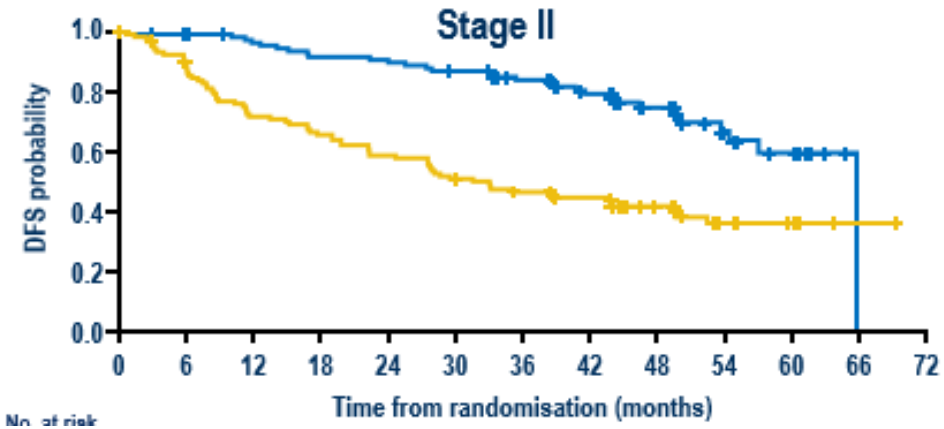


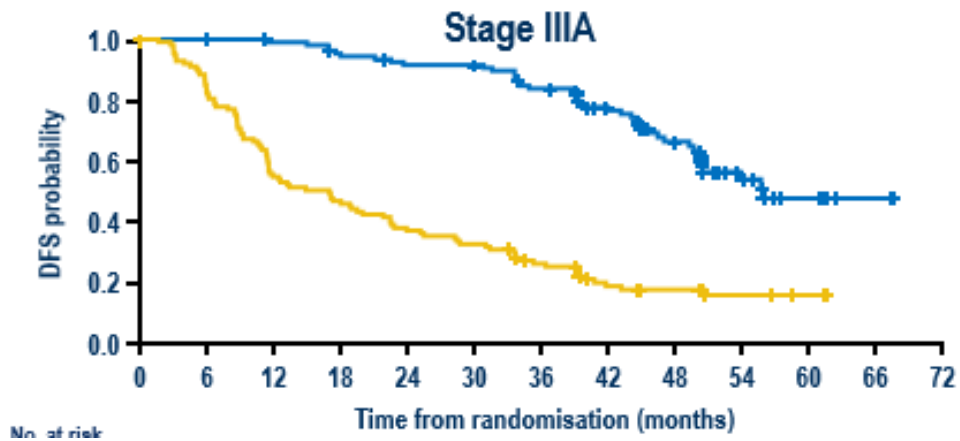
ESMO 2022

UPDATED DFS BY STAGE (AJCC / UICC 8TH EDITION*)



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





Course

- Adjuvant cisplatin-vinorelbine, June–August 2022
- Osimertinib, September 2022–ongoing
- No side effects

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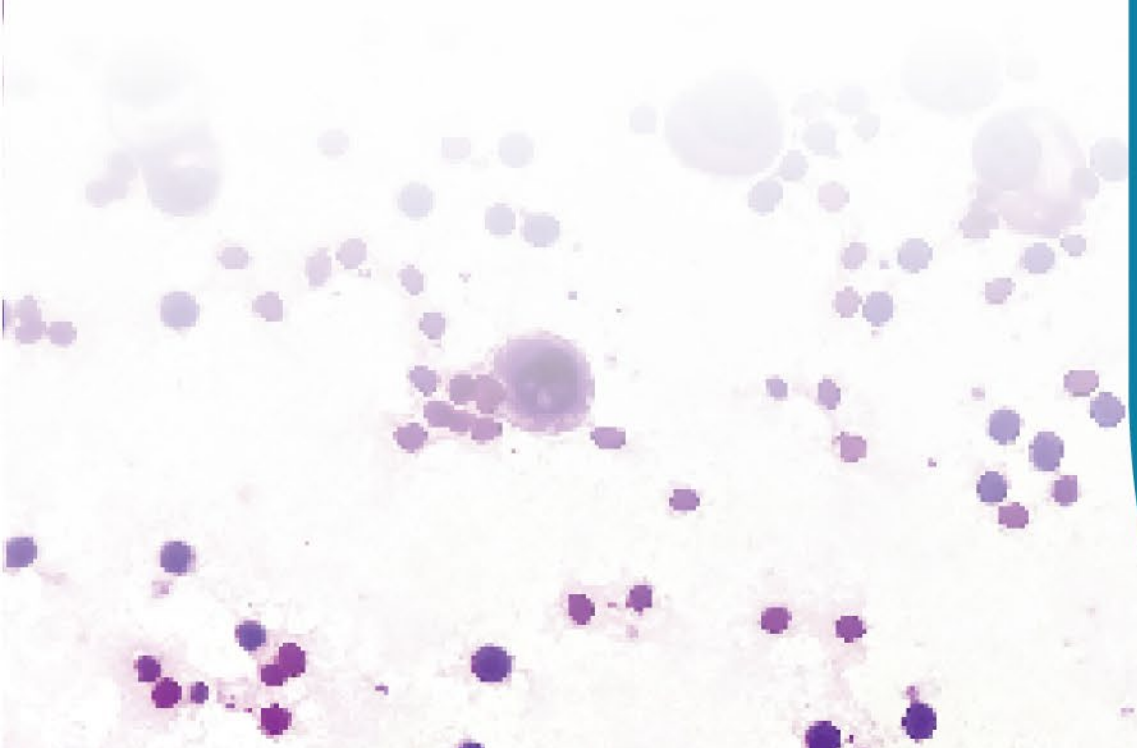

Tumor Board Discussion

Moderator: Corey Langer, MD, FACP

All faculty

Global Lung Cancer Academy

Session Close

Corey Langer, MD

Meeting evaluation

> Please complete the **evaluation link** that will be sent to you via chat

Question 1

In the EMPOWER-Lung 1 trial, cemiplimab showed improvement over chemotherapy in:

1. PFS only
2. OS only
3. PFS and OS
4. Neither

Day 2: Plenary Sessions

Monday, 24 October 2022 from 4.00 PM – 7.00 PM EDT

Time (EDT)	Title	Speaker
4.00 PM – 4.10 PM (10 min)	**Session Open** • ARS questions	Corey Langer and Carlos Barrios
4.10 PM – 4.40 PM (30 min)	**Interactive Discussion: Regional Challenges in NSCLC Management** • Interactive discussion and Q&A (15 min)	Moderator: Carlos Barrios All faculty
4.40 PM – 5.00 PM (20 min)	**Current Diagnostic Options and Initial Management of Early-Stage NSCLC in Latin America** • Overview of currently available diagnostic methods and treatment options for early-stage NSCLC (resectable vs unresectable)	William William
5.00 PM – 5.20 PM (20 min)	**Current Treatment Options for Metastatic NSCLC in Latin America** • Overview of currently available treatment options for metastatic NSCLC	Carlos Barrios
5.20 PM – 5.50 PM (30 min)	**Tumor Board Discussion** • Patient case 1 (10 min) • Patient case 2 (10 min) • Discussion and Q&A (10 min)	Moderator: Carlos Barrios Caio Abner Leite Alvaro Guimaraes Paula All faculty
5.50 PM – 6.00 PM (10 min)	***Break***	
6.00 PM – 6.20 PM (20 min)	**Monitoring and Managing Immunotherapy-Related AEs** • Optimal monitoring and managing of the most common AEs associated with immunotherapy	Edgardo S. Santos
6.20 PM – 6.50 PM (30 min)	**Tumor Board Discussion** • Patient case (10 min) • Discussion and Q&A (20 min)	Moderator: Corey Langer Barbara Melosky All faculty
6.50 PM – 7.00 PM (10 min)	**Session Close** • ARS questions	Carlos Barrios

Thank you!

- Thank you to our sponsor, expert presenters, and to you for your participation
- Please complete the **evaluation link** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the globallungcanceracademy.com website within a few weeks
- If you have a question for any of our experts that was not answered today, you can submit it through the GLCA website in our Ask the Experts section

THANK YOU!

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Sharing Best Practices to Optimize Patient Care

SEE YOU MONDAY!

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