Global Lung Cancer Academy

Global Lung Cancer Academy

Sharing Best Practices to Optimize Patient Care

7 November 2022

Sponsor: Sanofi Oncology & Regeneron

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Global Lung Cancer Academy

Welcome and Meeting Overview

Solange Peters, MD

Meet the faculty

CO-CHAIRS

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

Solange Peters, MD
University Hospital of Lausanne
Lausanne, Switzerland

FACULTY

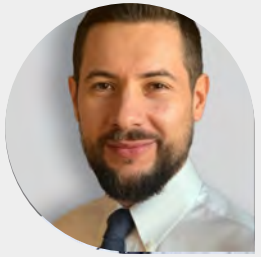
Benjamin Besse, MD, PhD
Institute Gustave Roussy
Villejuif, France

Federico Cappuzzo, MD, PhD
AUSL della Romagna
Ravenna, Italy

Anne-Marie Dingemans, MD, PhD
Erasmus Medical Center
Rotterdam, the Netherlands

Enriqueta Felip, MD, PhD
Vall d'Hebron University Hospital
Barcelona, Spain

Umberto Malapelle, PhD
University of Naples Federico II
Naples, Italy



Antonio Passaro, MD, PhD
European Institue of Oncology
Milan, Italy

Johan Vansteenkiste, MD, PhD
University Hospital KU Leuven
Leuven, Belgium

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 Europe

Day 1: Plenary Sessions

Monday, 7 November 2022 from 15.00 – 19.00 CET

Time	Title	Speaker
15.00 – 15.10 (10 min)	**Welcome and Meeting Overview** • Introduction to audience response system (ARS)	Solange Peters
15.10 – 15.40 (30 min)	**Recent Developments in NSCLC – What is New in Research and Management?** • Overview of recently presented data in NSCLC	Corey Langer
15.40 – 16.00 (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	Umberto Malapelle
16.00 – 16.20 (20 min)	**Targeted Therapies for Early-Stage NSCLC – Evidence-Based Data and Perspectives** • Summary of targeted therapies for different NSCLC genotypes	Enriqueta Felip
16.20 – 16.40 (20 min)	**Adjuvant Therapy in Resectable NSCLC** • Current standard practices and ongoing studies	Benjamin Besse
16.40 – 17.10 (30 min)	**Tumor Board Discussion** • Case 1 (10 min) • Case 2 (10 min) • Discussion and Q&A (10 min)	Moderator: Solange Peters Johan Vansteenkiste Daphne Dumoulin All faculty
17.10 – 17.20 (10 min)	***Break***	
17.20 – 17.40 (20 min)	**Neoadjuvant Therapy for NSCLC – Is It Ready for Prime Time?** • Current state of neoadjuvant therapy in resectable NSCLC	Anne-Marie Dingemans
17.40 – 18.00 (20 min)	**Locally Advanced Unresectable NSCLC – What Are the Options?** • Current standard practices and ongoing studies	Antonio Passaro
18.00 – 18.30 (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 Johan Vansteenkiste Benjamin Besse All faculty
18.30 – 18.50 (20 min)	**Options After Early-Stage Relapse** • Current and emerging treatment options after early-stage relapse	Federico Cappuzzo
18.50 – 19.00 (10 min)	**Session Close** • ARS questions	Corey Langer

Day 2: Plenary Sessions

Monday, 14 November 2022 from 16.00 – 19.15 CET

Time	Title	Speaker
16.00 – 16.10 (10 min)	**Session Open** • ARS questions	Corey Langer
16.10 – 16.30 (20 min)	**Optimizing First-Line Therapy in NSCLC – Integration of Immunotherapy Into Frontline Regimens** • Optimal use of immunotherapeutic treatment choices in frontline NSCLC	Luis Paz-Ares
16.30 – 16.50 (20 min)	**Current Immunotherapy Options for Relapsed NSCLC** • Optimal use of immunotherapeutic treatment choices in relapsed NSCLC including considerations for potential rechallenge, and treatment selection mono vs combination therapy	Benjamin Besse
16.50 – 17.25 (35 min)	**Tumor Board Discussion** • Case 1 (10 min) • Case 2 (10 min) • Discussion & Q&A (15 min)	Moderator: Solange Peters Francesca Fusco Luis Angel Leon Mateos All faculty
17.25 – 17.35 (10 min)	***Break***	
17.35 – 17.50 (15 min)	**ALK Inhibitors in NSCLC** • Considerations for optimal use in clinical practice in patients with and without brain metastasis	Enriqueta Felip
17.50 – 18.05 (15 min)	**EGFR Inhibitors in NSCLC** • Considerations for optimal use in clinical practice	Johan Vansteenkiste
18.05 – 18.30 (25 min)	**Other Targets in NSCLC** • Considerations for optimal use of ROS1, NTRK, RET and MET inhibitors in clinical practice	Anne-Marie Dingemans
18.30 – 19.05 (35 min)	**Tumor Board Discussion** • Case 1 (10 min) • Case 2 (10 min) • Discussion & Q&A (30 min)	Moderator: Corey Langer May-Lucie Meyer Xander Verbeke All faculty
19.05 – 19.15 (10 min)	**Session Close** • ARS questions	Solange Peters

Question 1

In which country do you currently practice?

1. Austria
2. France
3. Germany
4. Italy
5. Poland
6. Spain
7. The Netherlands
8. United Kingdom
9. Other country in Europe
10. Outside Europe

Question 2

How would you describe your specialty?

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

Question 3

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 4

70-year-old female, former smoker (25 pk/yrs) presents with stage IIIB NSCLC with LSCN involvement. Cell type is squamous cell carcinoma. PD-L1 level is 60%. Patient completes chemo-XRT with 60 Gy and concurrent weekly paclitaxel/carboplatin with excellent PR on f/u CT imaging, no complications. Which of the following is “approved” consolidation therapy in this setting?

1. Durvalumab
2. Pembrolizumab
3. Atezolizumab
4. Nivolumab

Global Lung Cancer Academy

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

Corey Langer, MD, FACP

Penn Medicine
Abramson Cancer Center

Division of Hematology and Oncology

Recent Advances in Management of Lung Cancer

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Director of Thoracic Oncology
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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

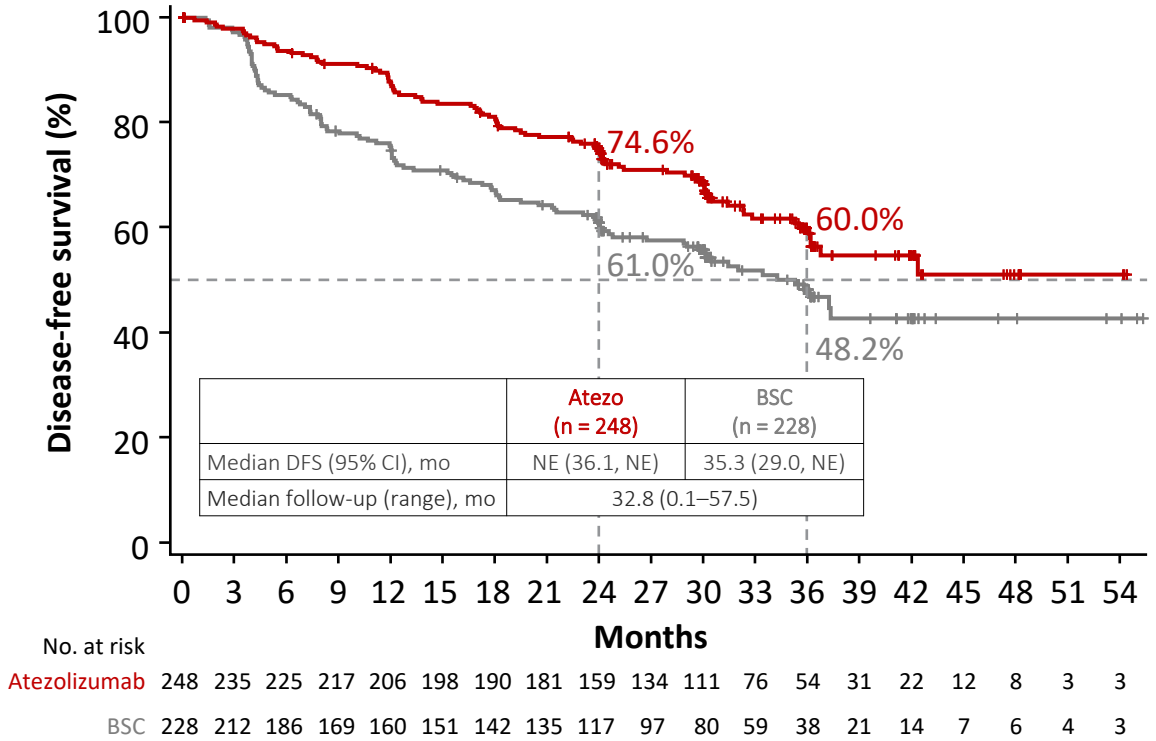
Curable NSCLC: Can We Isolate the Role of Immunotherapy in the Neoadjuvant and Combined Modality Arena?

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

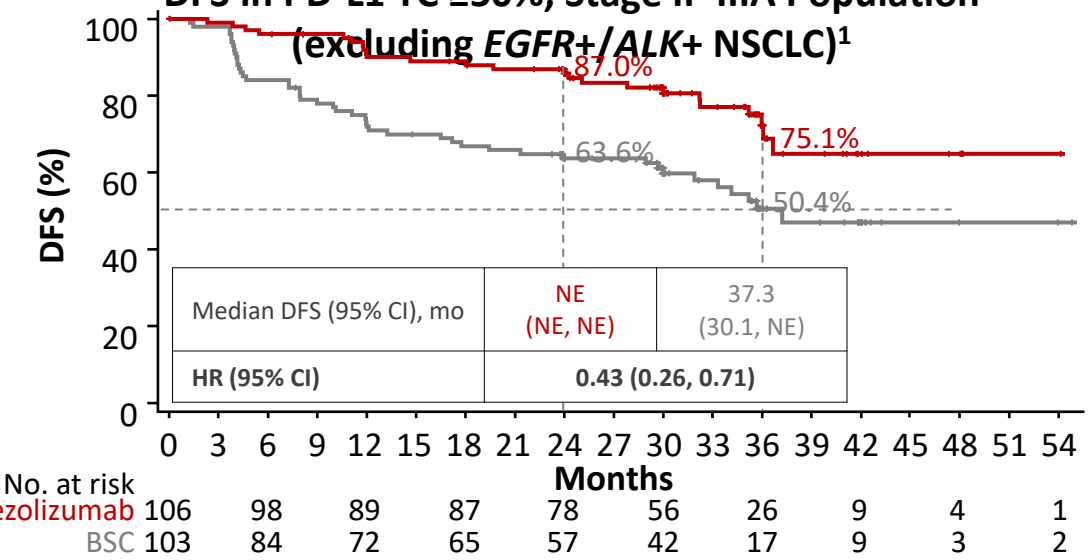
Endpoint was not met at DFS IA, and follow-up is ongoing

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

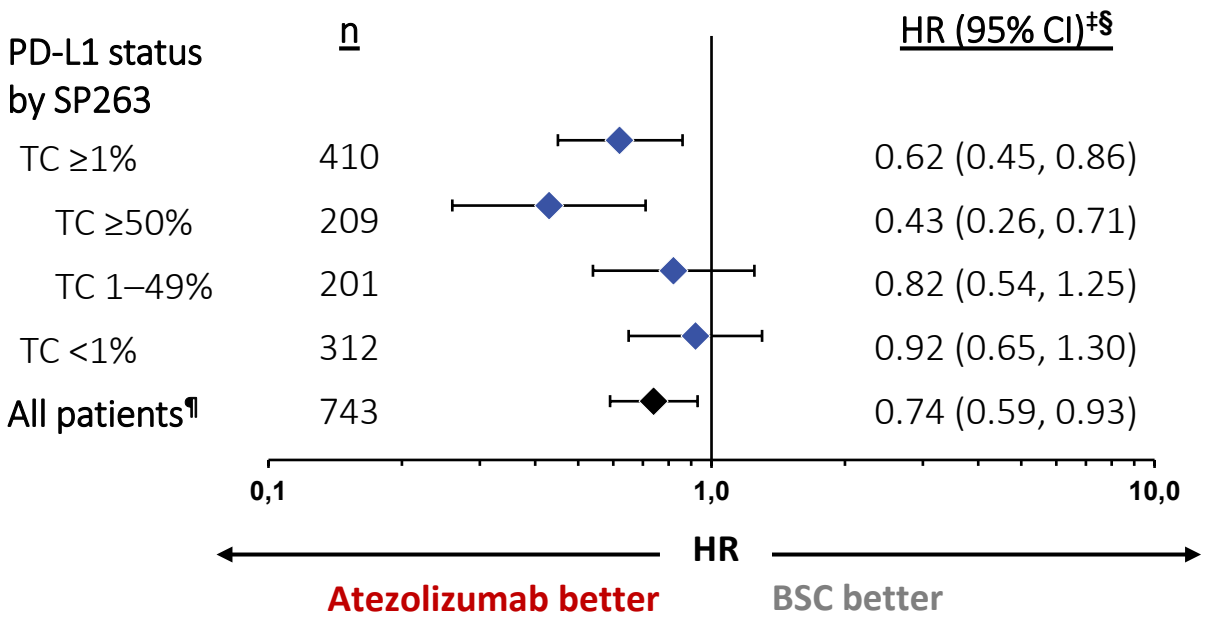
Wakelee H, et al. ASCO 2021. Abstract 8500; Felip E, et al. *Lancet.* 2021;398:1344-1357.

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]



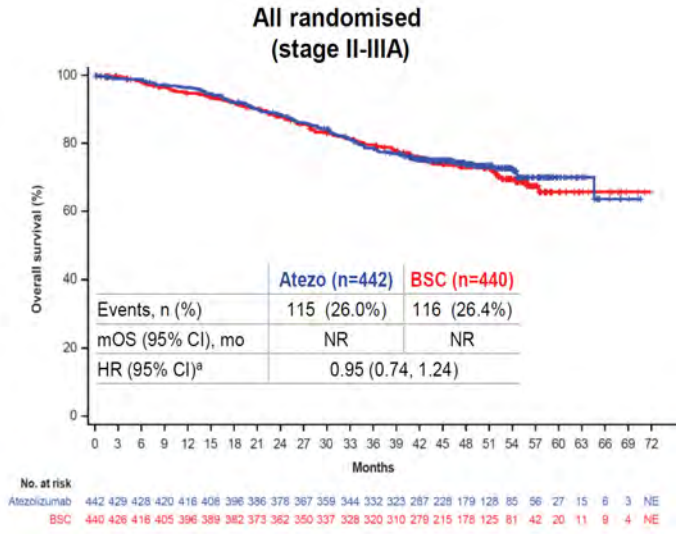
Clinical cut-off: 21 January 2021.

*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.

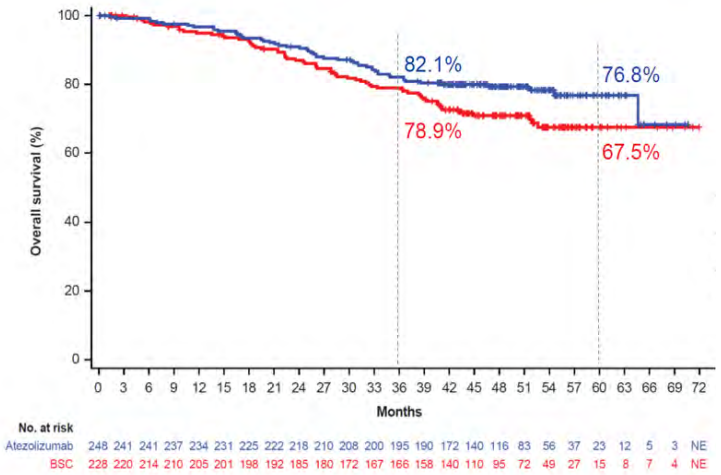
IMpower010: OS Trend of Atezolizumab in PD-L1 ≥1% Stage II–IIIA (interim OS analysis)

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)	

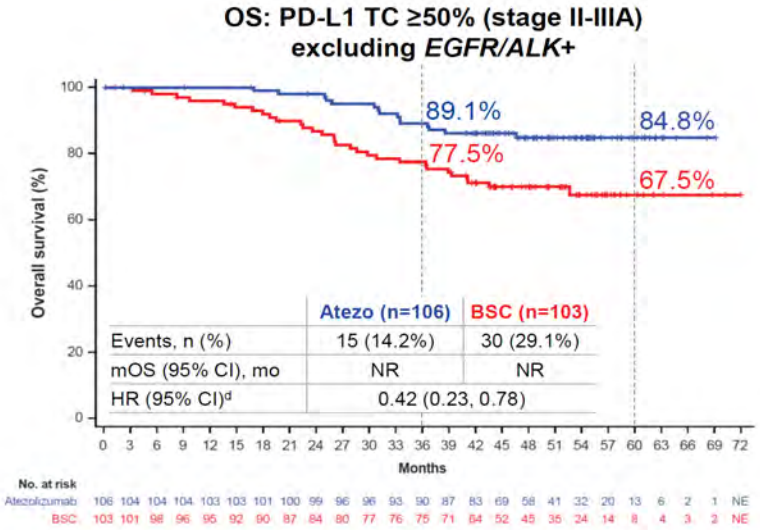
OS Interim Analysis in PD-L1 TC ≥1% (stage II–IIIA)



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.

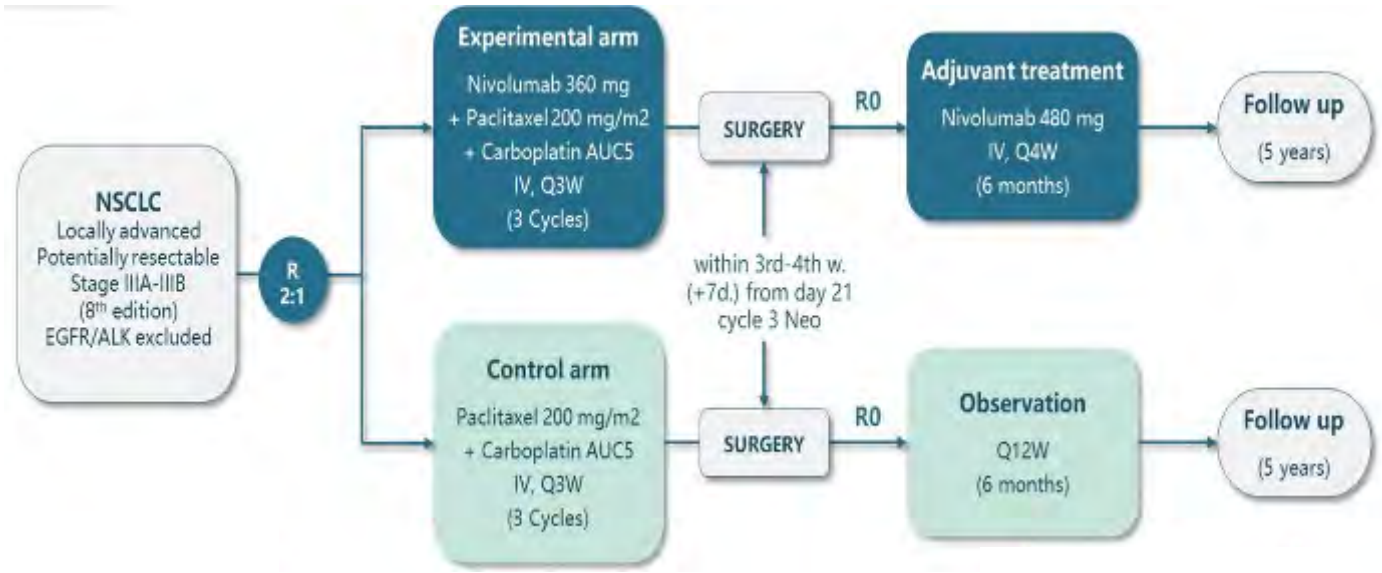
Neoadjuvant Nivolumab: CheckMate 816 and NADIM II

CheckMate 816

Primary Endpoints

- pCR by BICR
- EFS by BICR

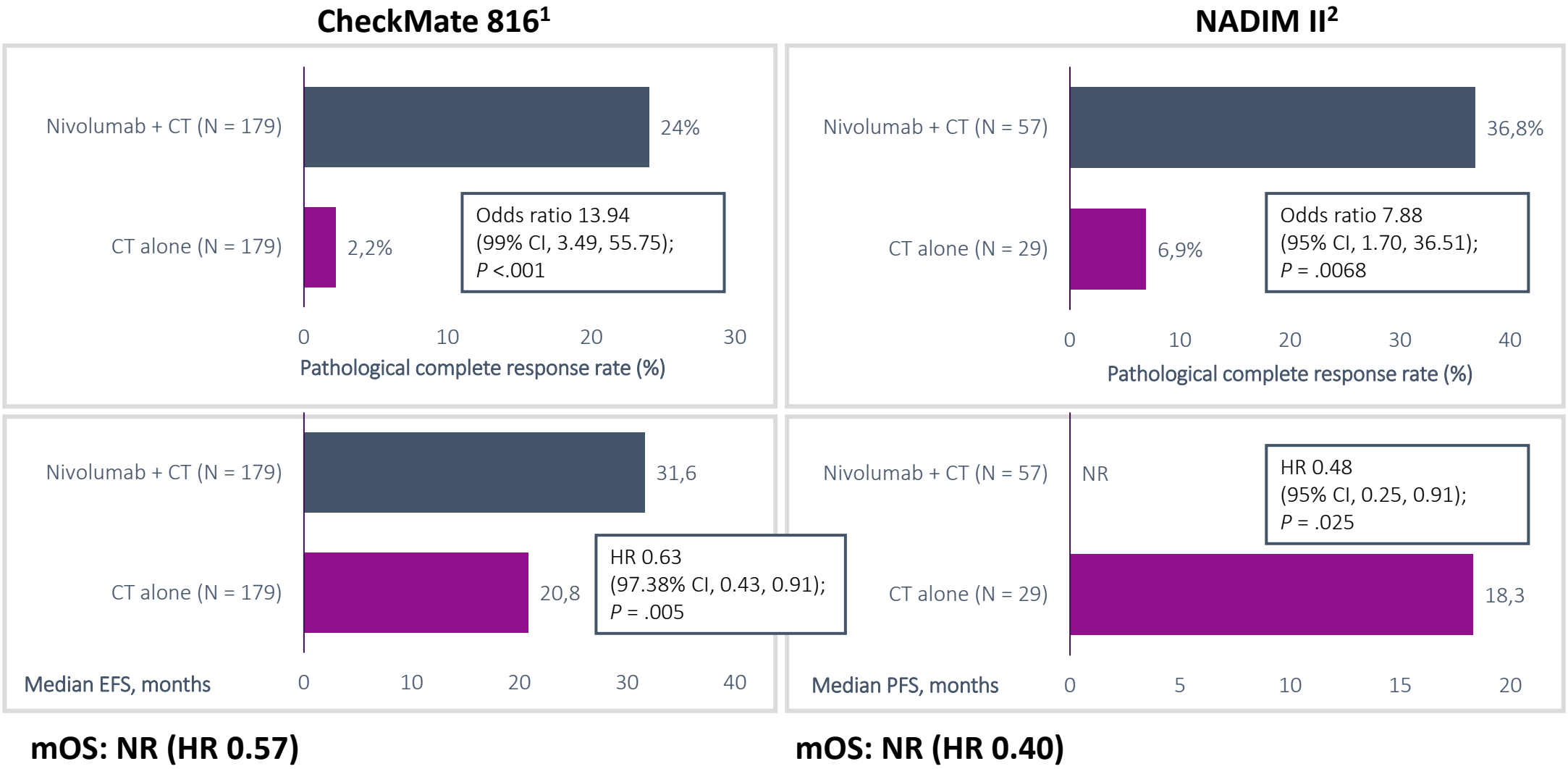
NADIM II



Primary Endpoint

- pCR

Neoadjuvant Nivolumab: Odds Ratio and EFS



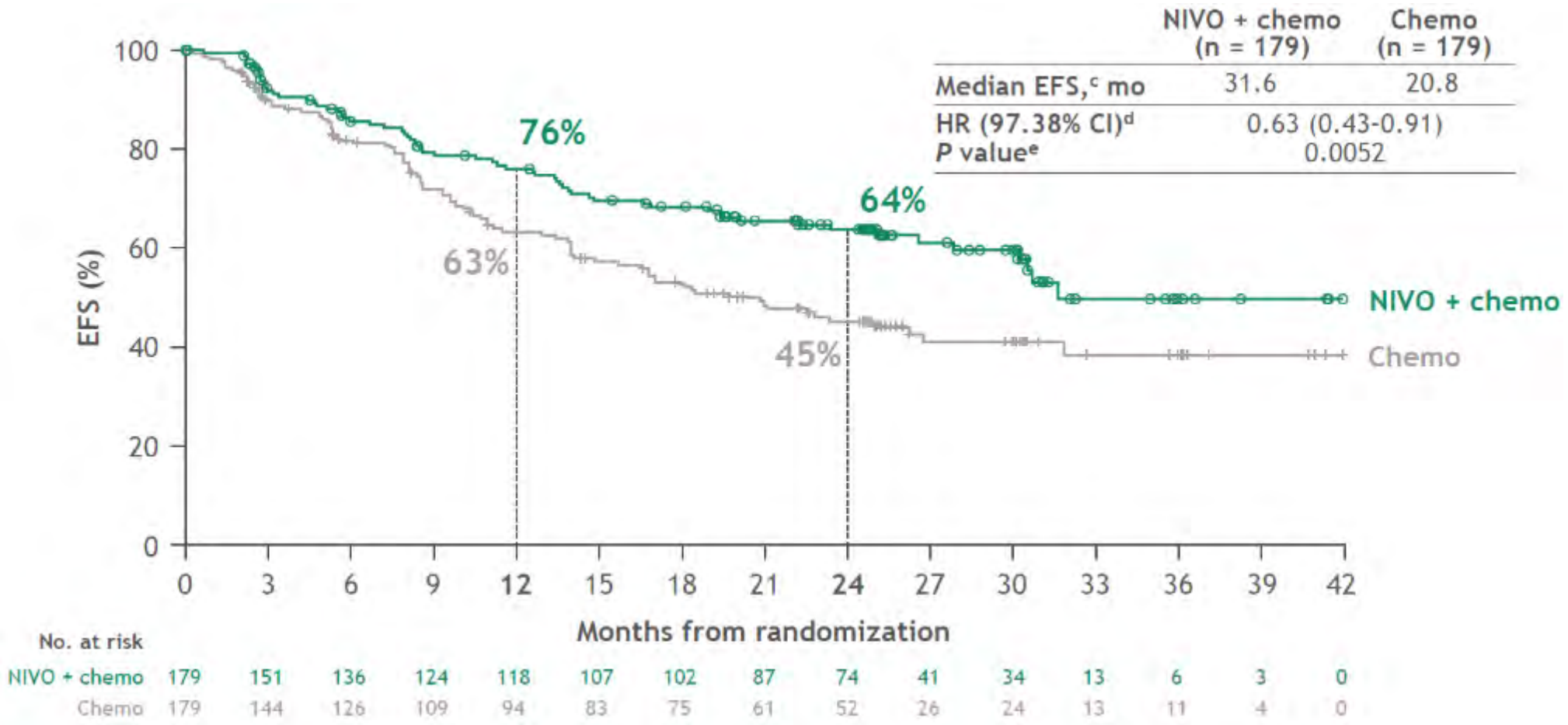
mOS: NR (HR 0.57)

mOS: NR (HR 0.40)

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

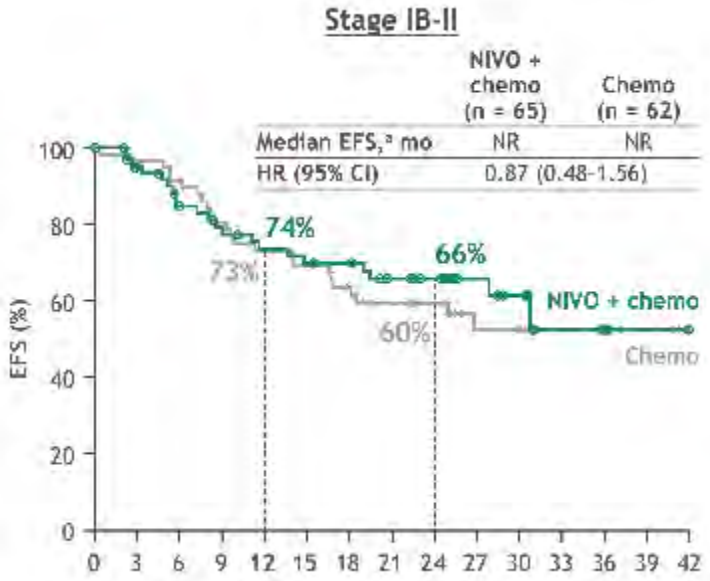
1. Forde PM, et al. *N Engl J Med.* 2018;378:1976-86; 2. Provencio M, et al. ASCO 2022. Abstract 8501.

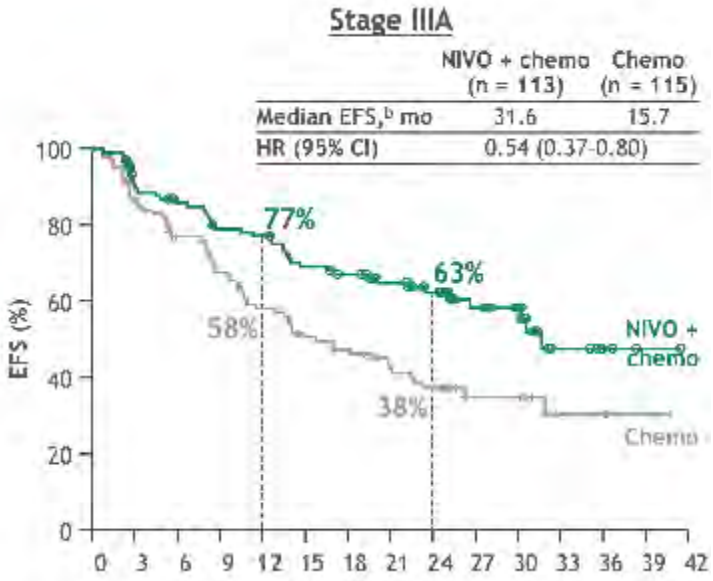
CheckMate 816: Neoadjuvant Nivolumab + Chemotherapy Improved EFS Compared With Chemotherapy Alone

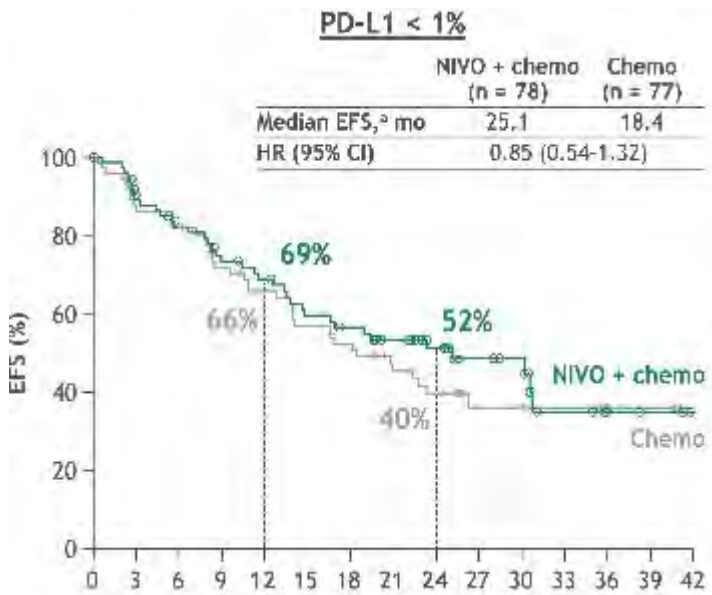


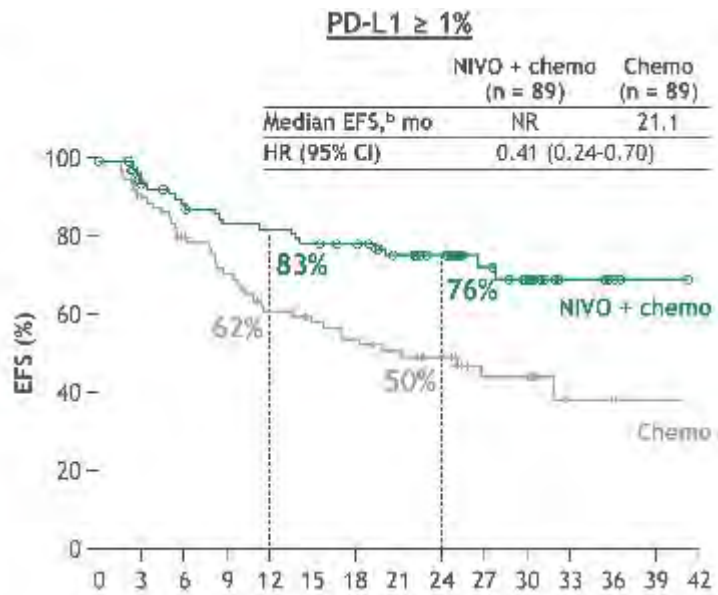
Girard, et al. AACR 2022. Abstract CT012; Forde PM, et al. *N Engl J Med.* 2022;386:1973-1985.

CheckMate 816: An EFS by Stage and PD-L1

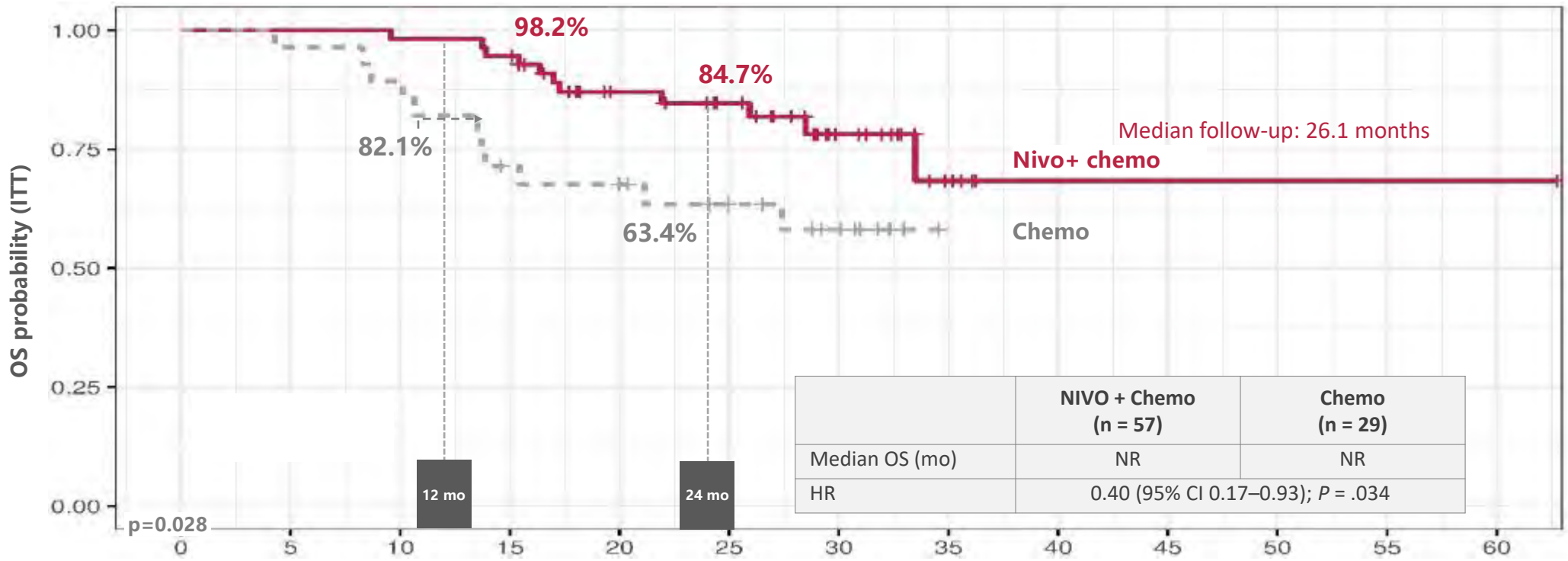








NADIM: Secondary Endpoints – Overall Survival



	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

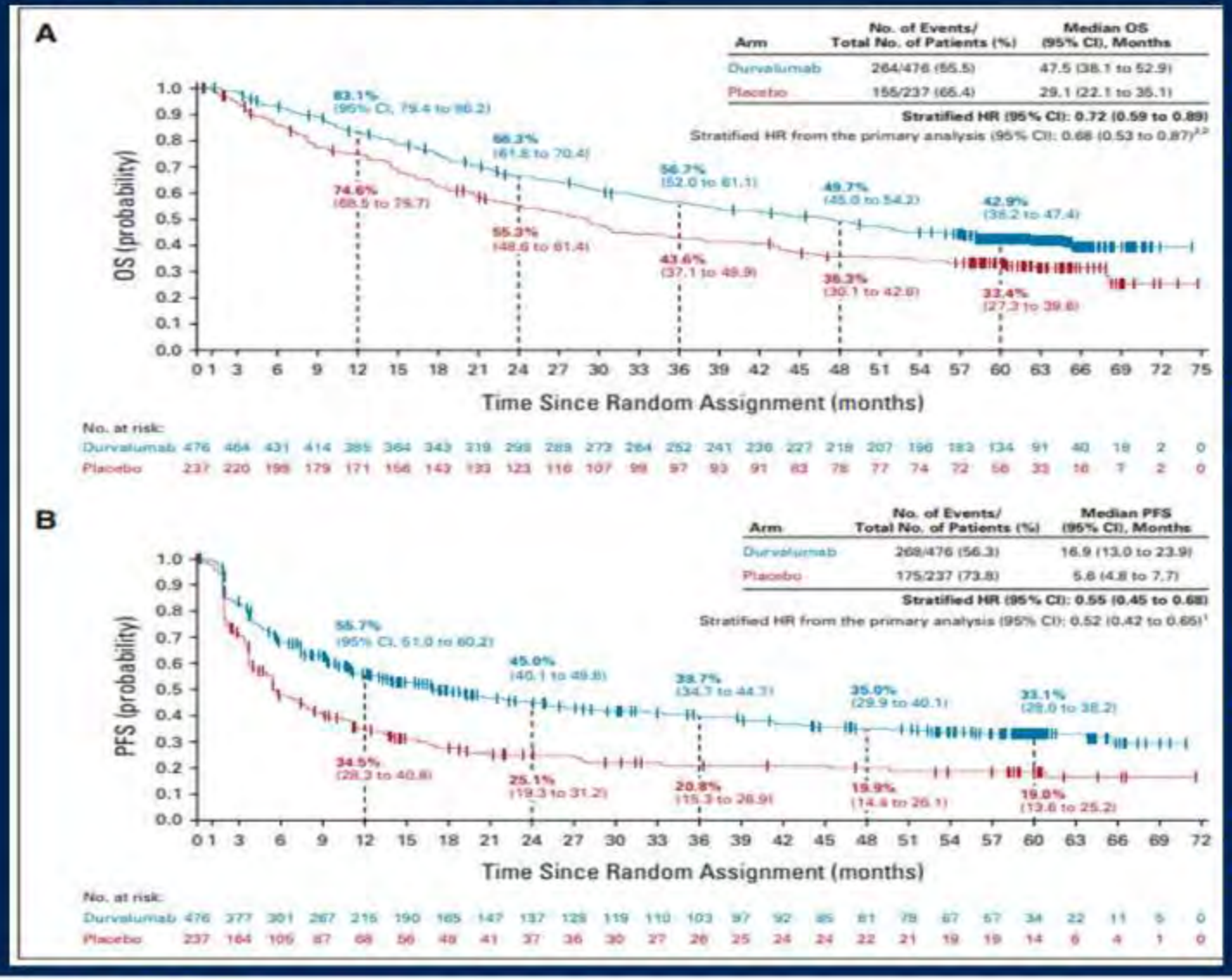
Overall survival was defined as the time from randomization to death. OS was censored on the last date a participant was known to be alive.

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

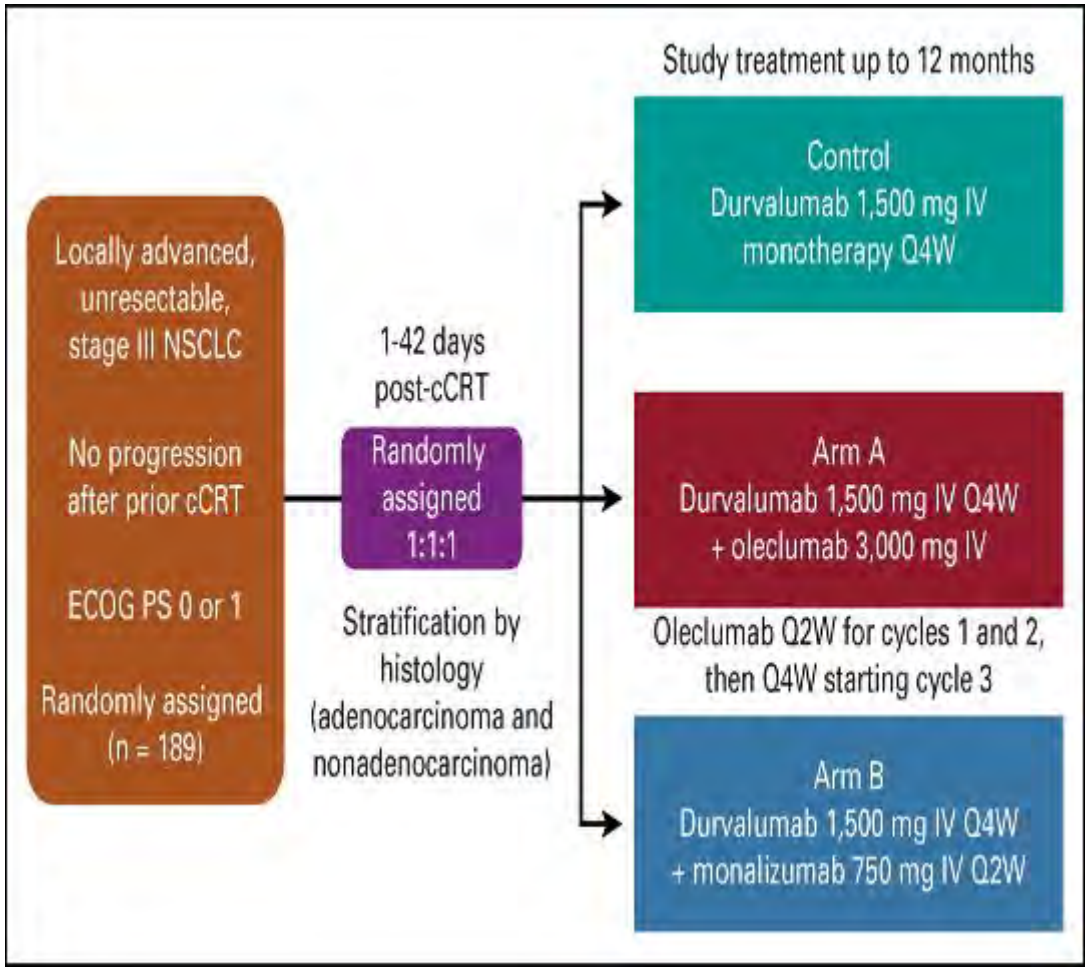
PACIFIC

- 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

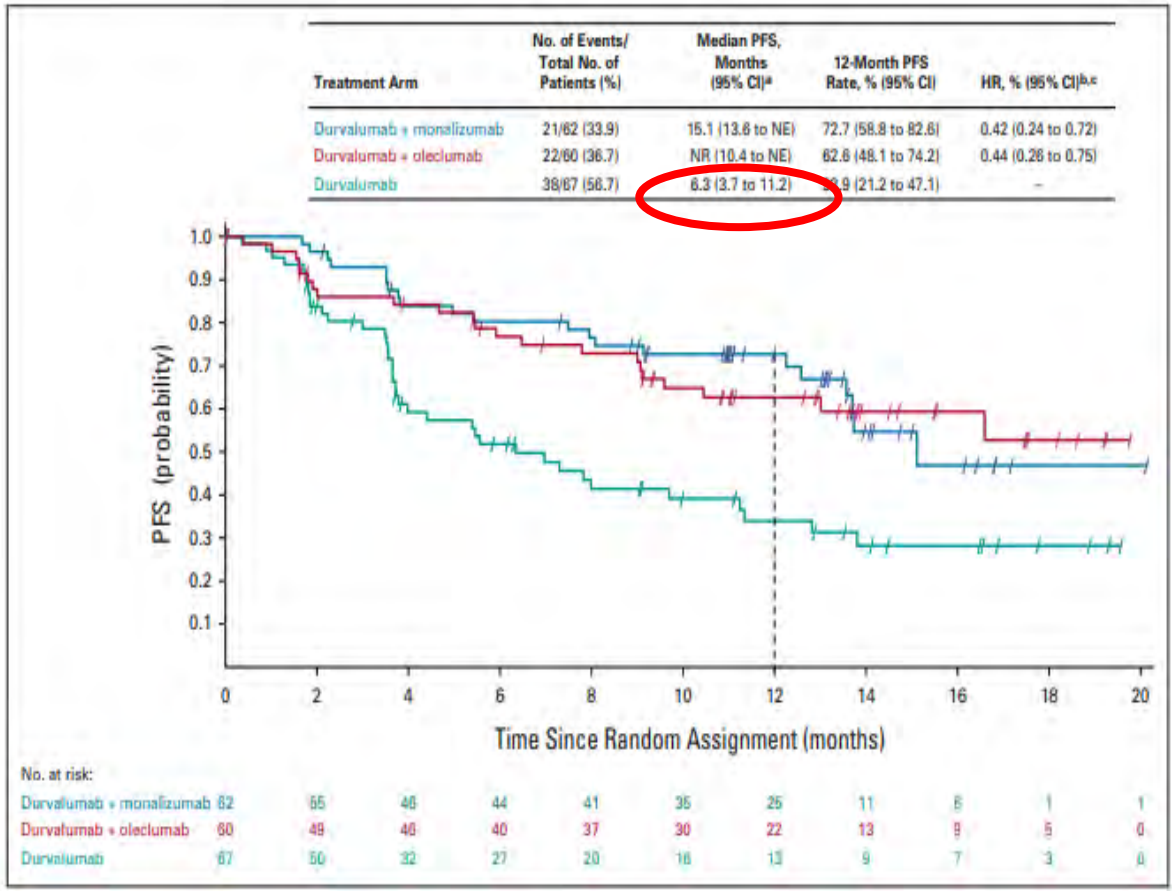


ORR

18%

36%

30%

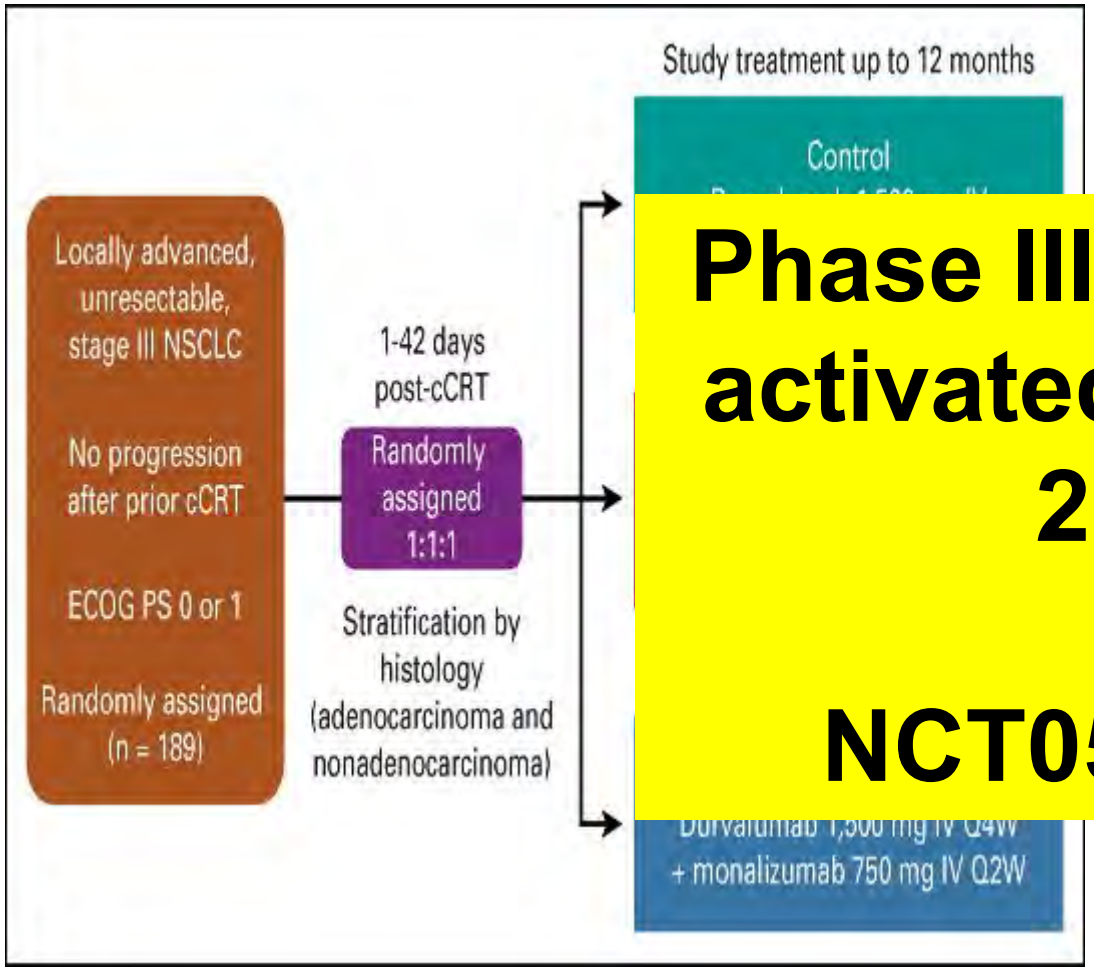


Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.8 to NE)	72.7 (58.8 to 82.8)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.8 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	36.9 (21.2 to 47.1)	–

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

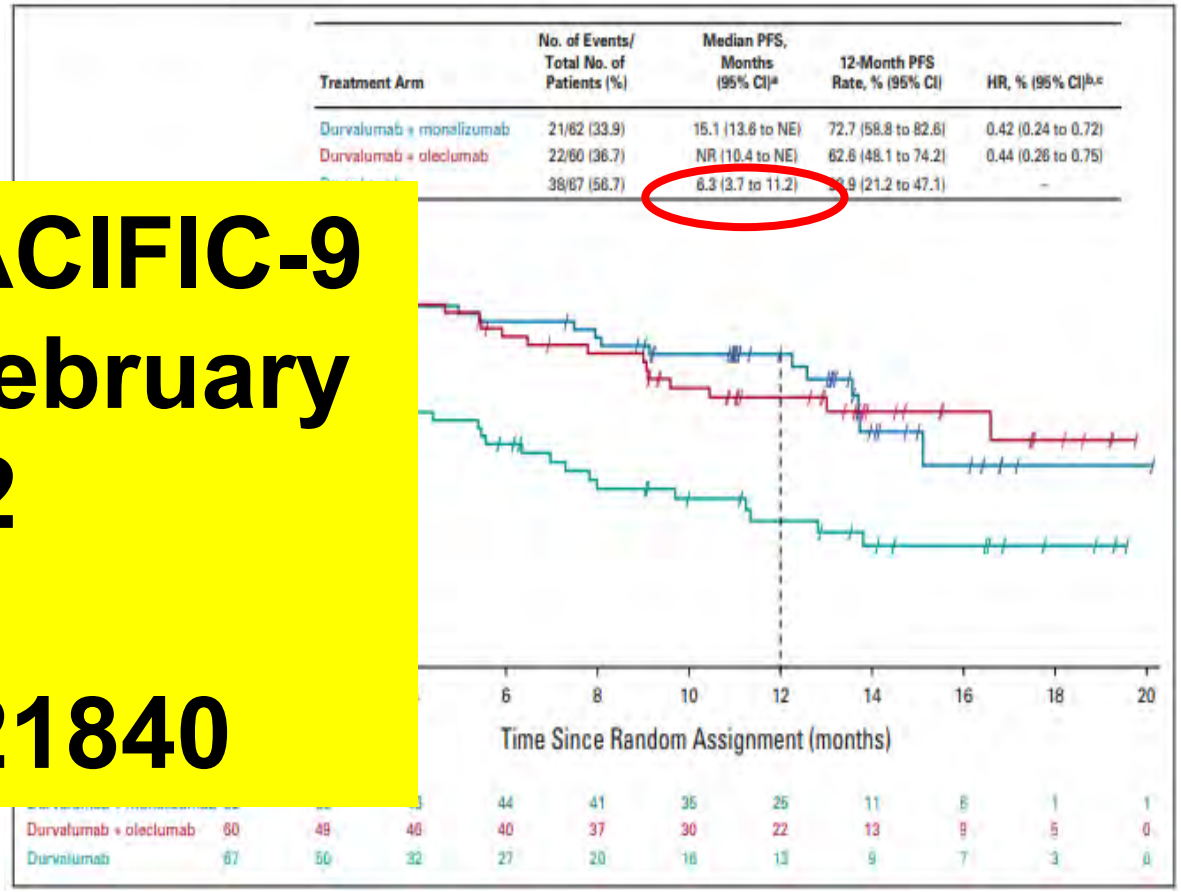


ORR

30%

Phase III PACIFIC-9 activated February 2022

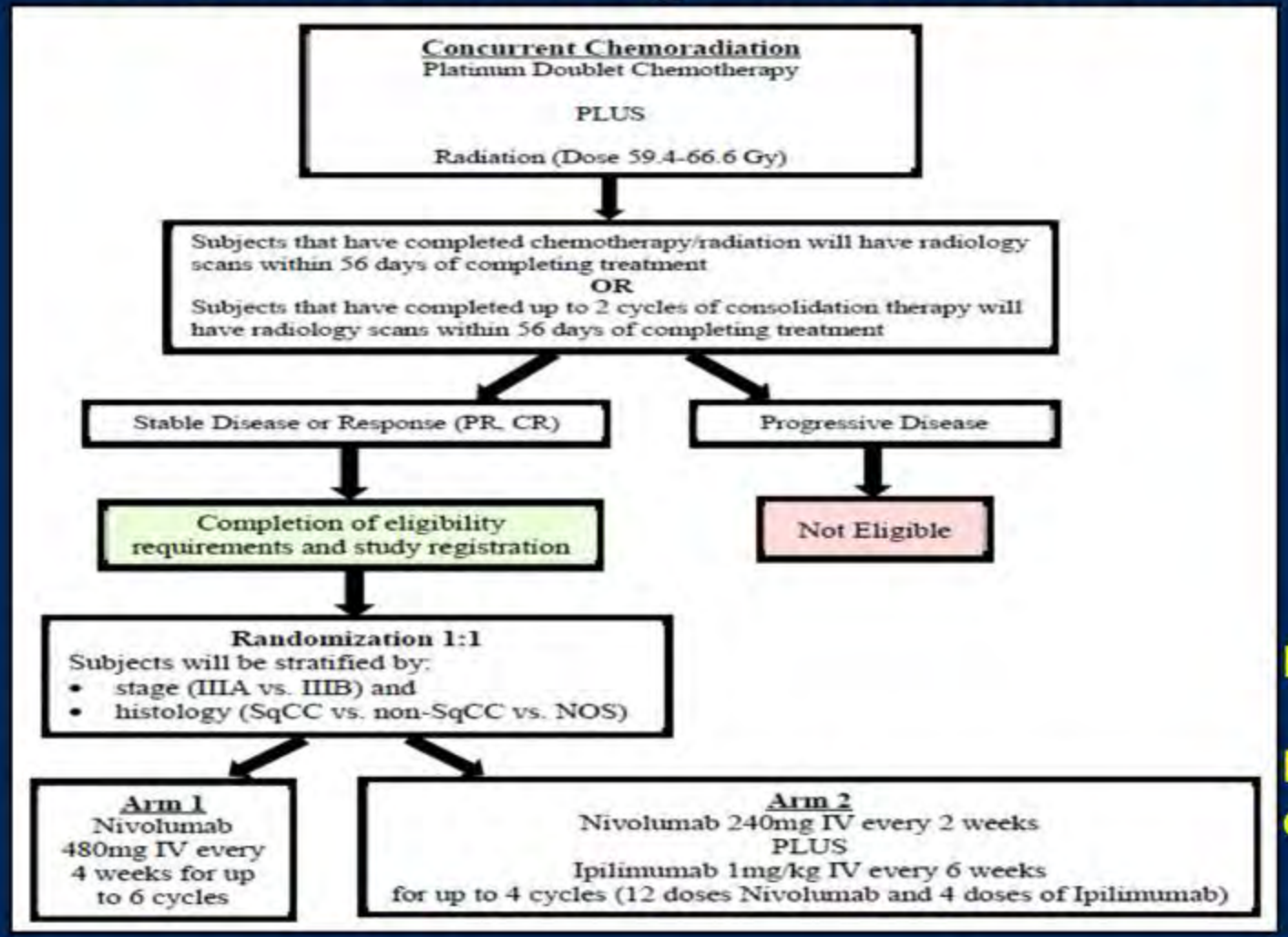
NCT05221840



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**

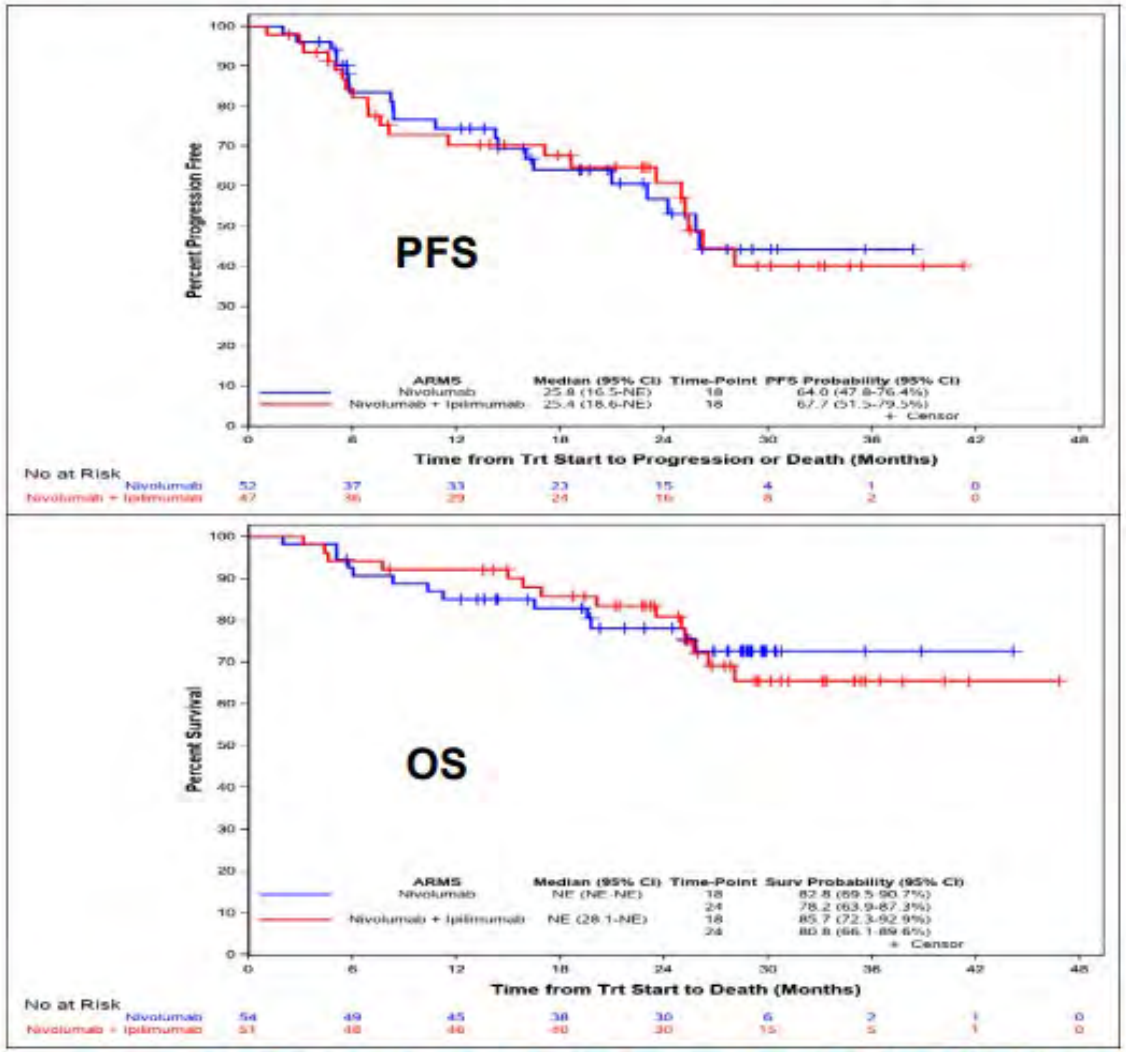
Big question-

Is 6 months of consolidative immunotherapy enough?

Abstract 8509

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

Results

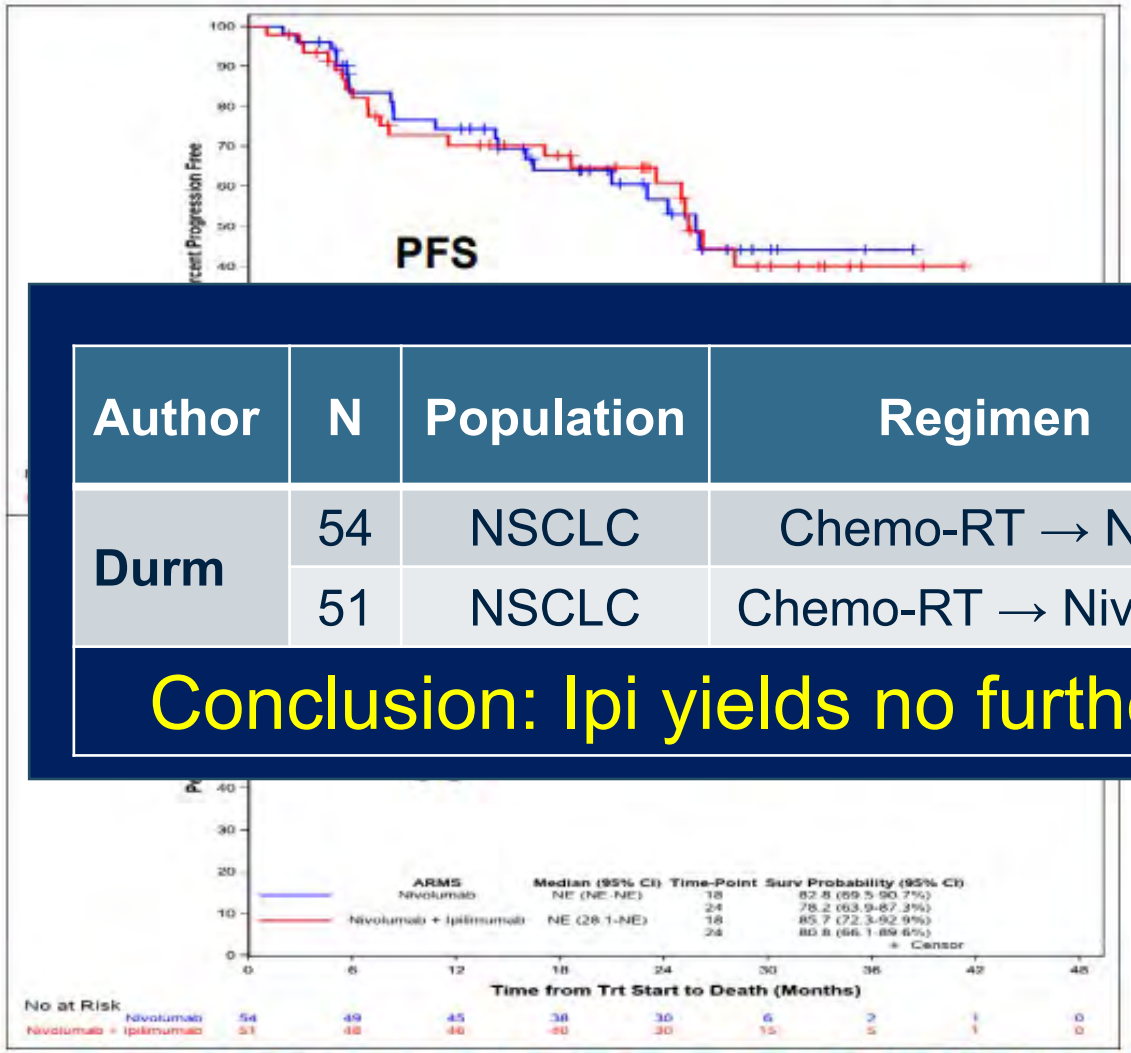


	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	28.5 (2-44.2)	29.4 (3.2-46.8)
Progression Free Survival*		
18- Month (95% CI)	64.0 (53.8-72.6)	67.7 (57.6-75.9)
P-value	<0.1	<0.1
Median, months (95% CI)	25.8 (23.0-NR)	25.4 (25.0-NR)
Overall Survival		
18- Month (95% CI)	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)

IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Results

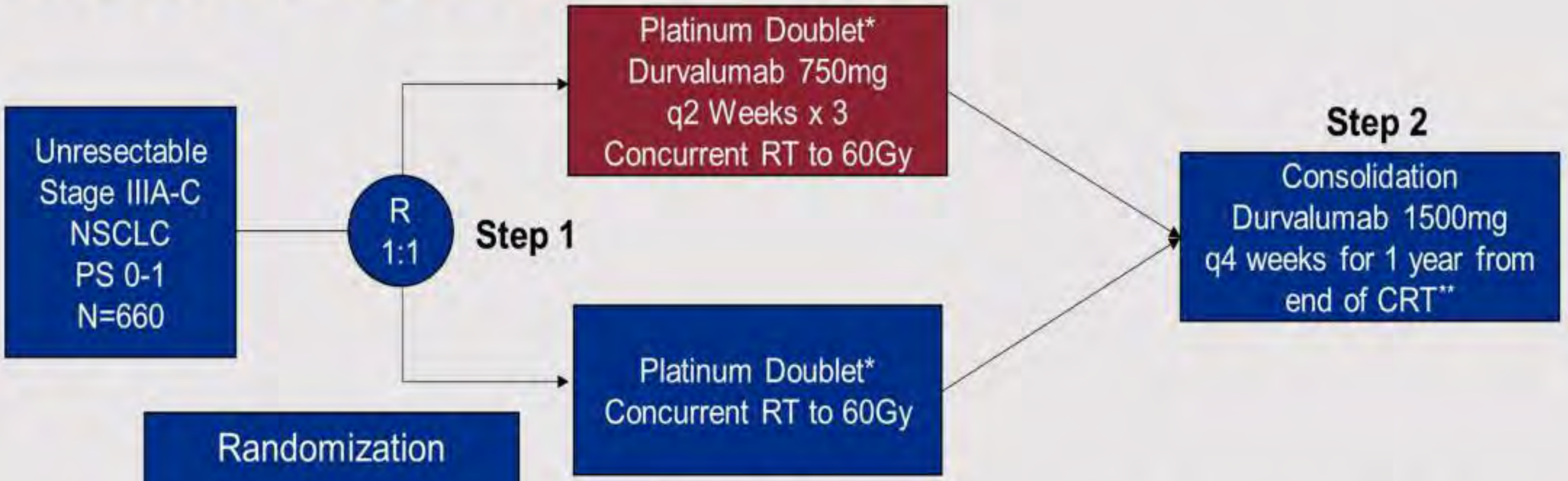


	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	28.5 (2-44.2)	29.4 (3.2-46.8)
Progression Free Survival*		
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

Author	N	Population	Regimen	ORR (%)	PFS, med (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

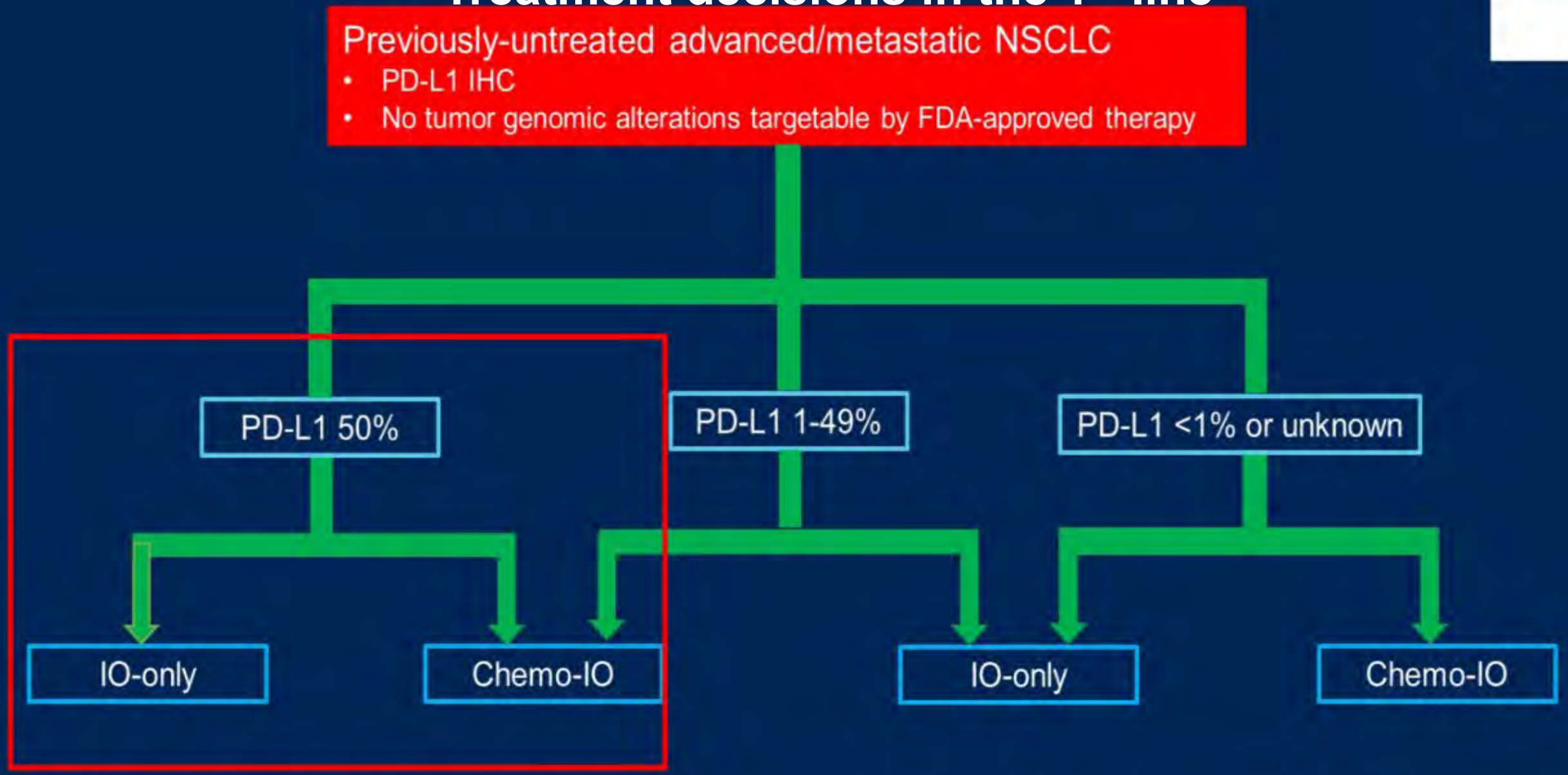
Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

[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

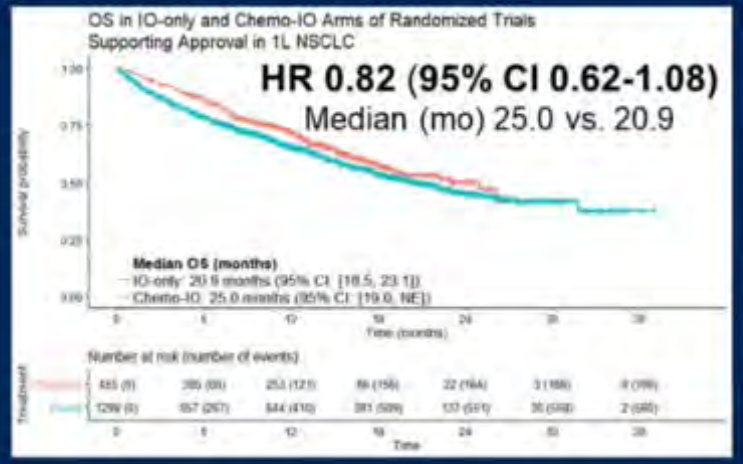


Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; IO=immunotherapy; NSCLC=non-small-cell lung cancer; PD-L1=programmed death ligand-1.

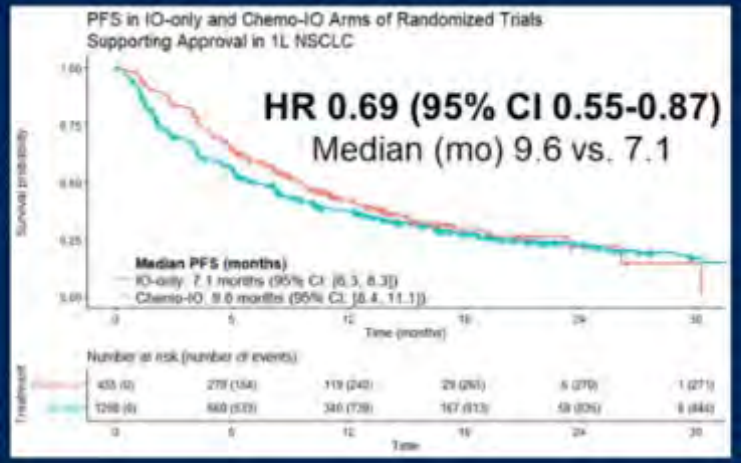
IO vs Chemo-IO in PD-L1 ≥50%

- **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)	

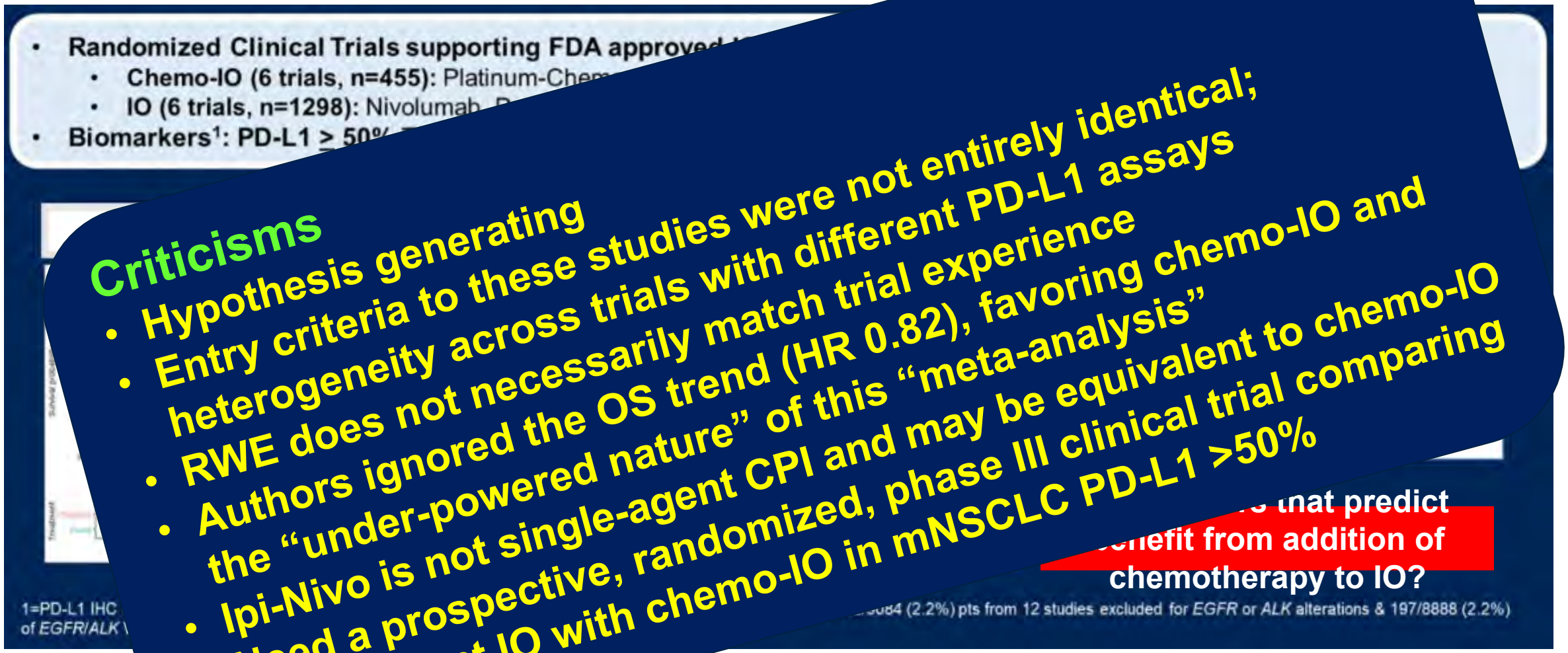
Risk factors that predict benefit from addition of chemotherapy to IO?

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%

…that predict …benefit from addition of chemotherapy to IO?

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

Sequential vs Combination Therapy: INSIGNA

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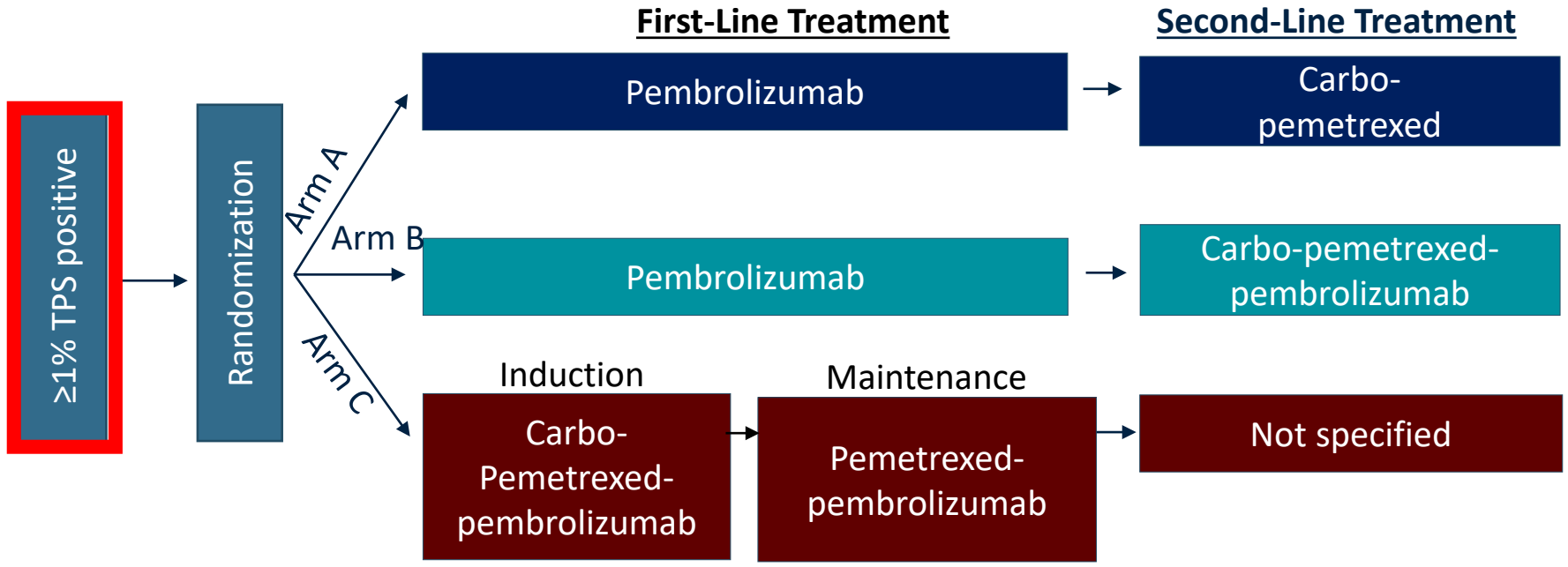
And the Landscape Is Changing

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;

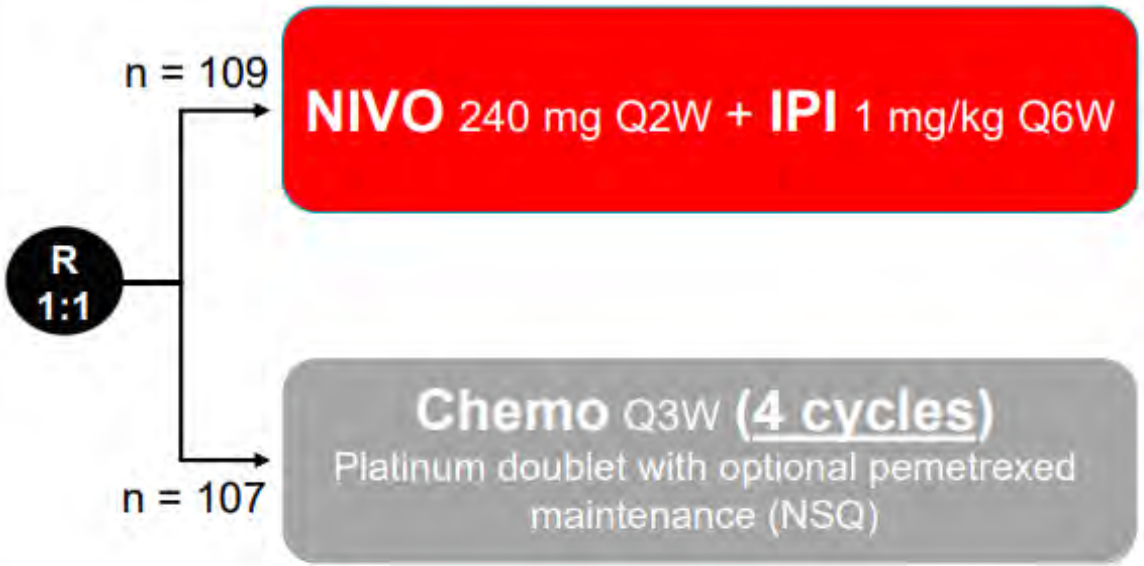
1 CHU, Rennes, France; 2 Pneumologie, CHI Creteil, Creteil, France; 3 HIA Desgenettes, Ampuis, France; 4 Orientation Oncologique, Hôpital Sainte-Musse, Toulon, France; 5 Pneumologie, Hopital Nord Ouest Villefranche Sur Saone, Villefranche Sur Saone, France; 6 Unite d'Oncologie Thoracique, Limoges, France; 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

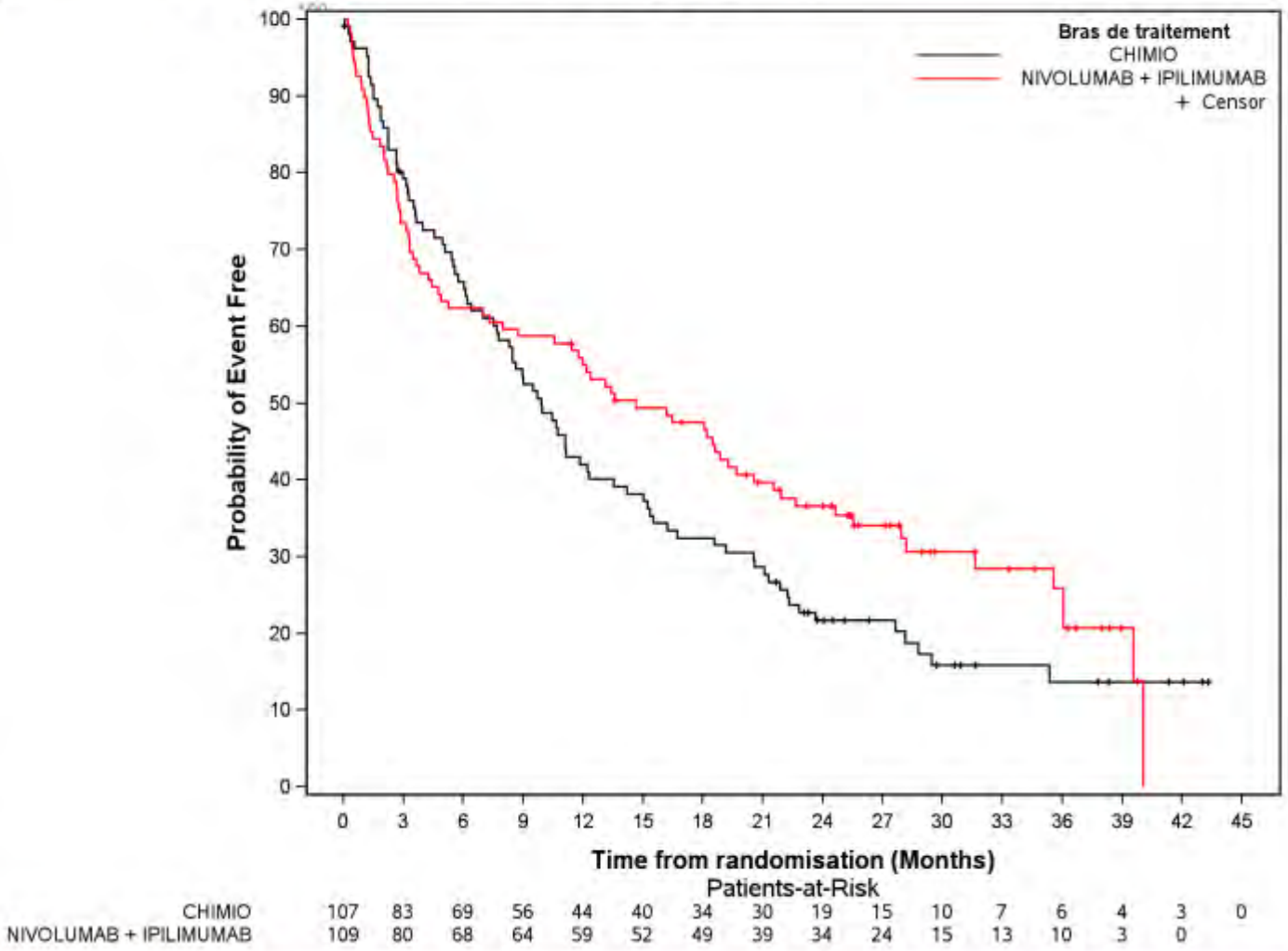
- 242 patients had to be randomized with 199 events to detect a treatment effect hazard ratio (HR) of 0.65 with 85% power, translating in an improvement of 1-year OS rate from 40% (control arm) to 55% (NIVO-IPI), and using a log-rank test at a 2-sided alpha level of 5%.
- One preplanned interim analysis 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

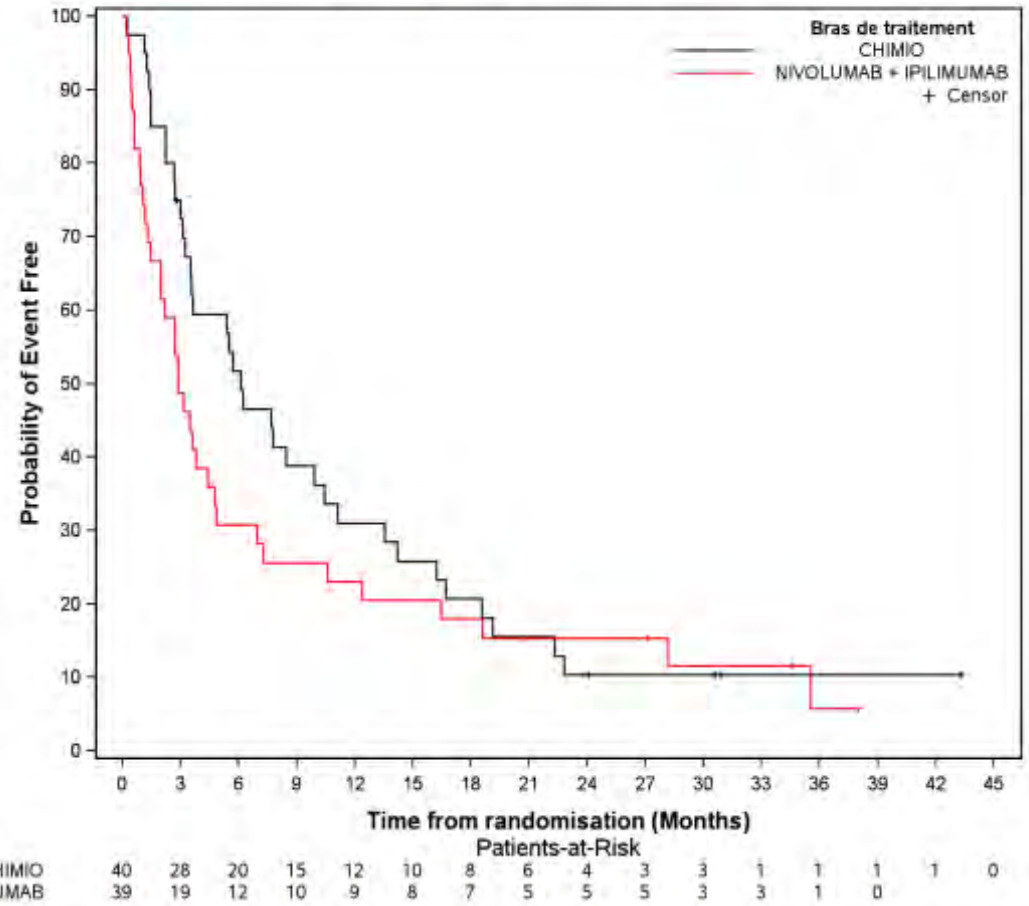
Overall survival whole population



	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%

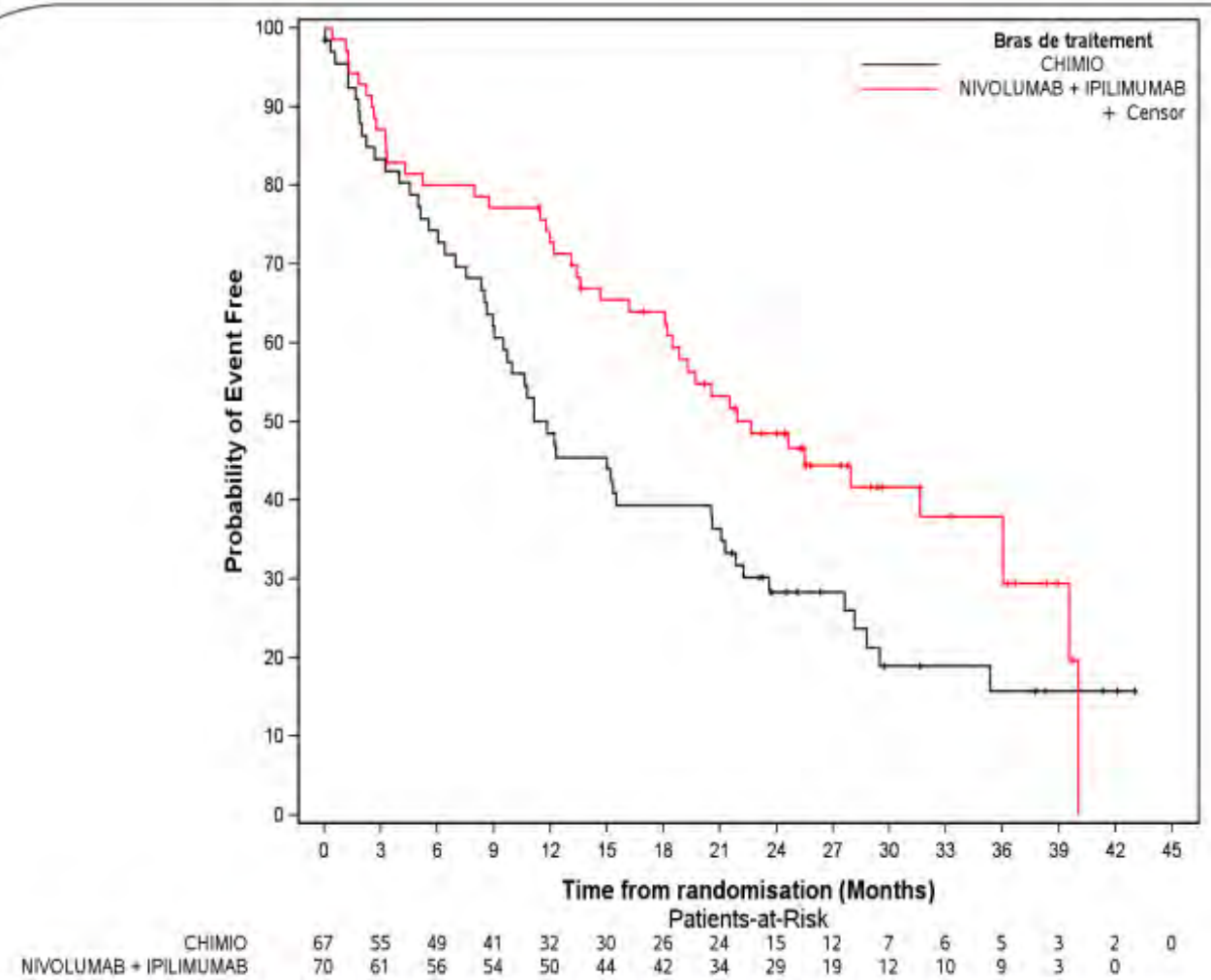
Overall survival PS 2 patients

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

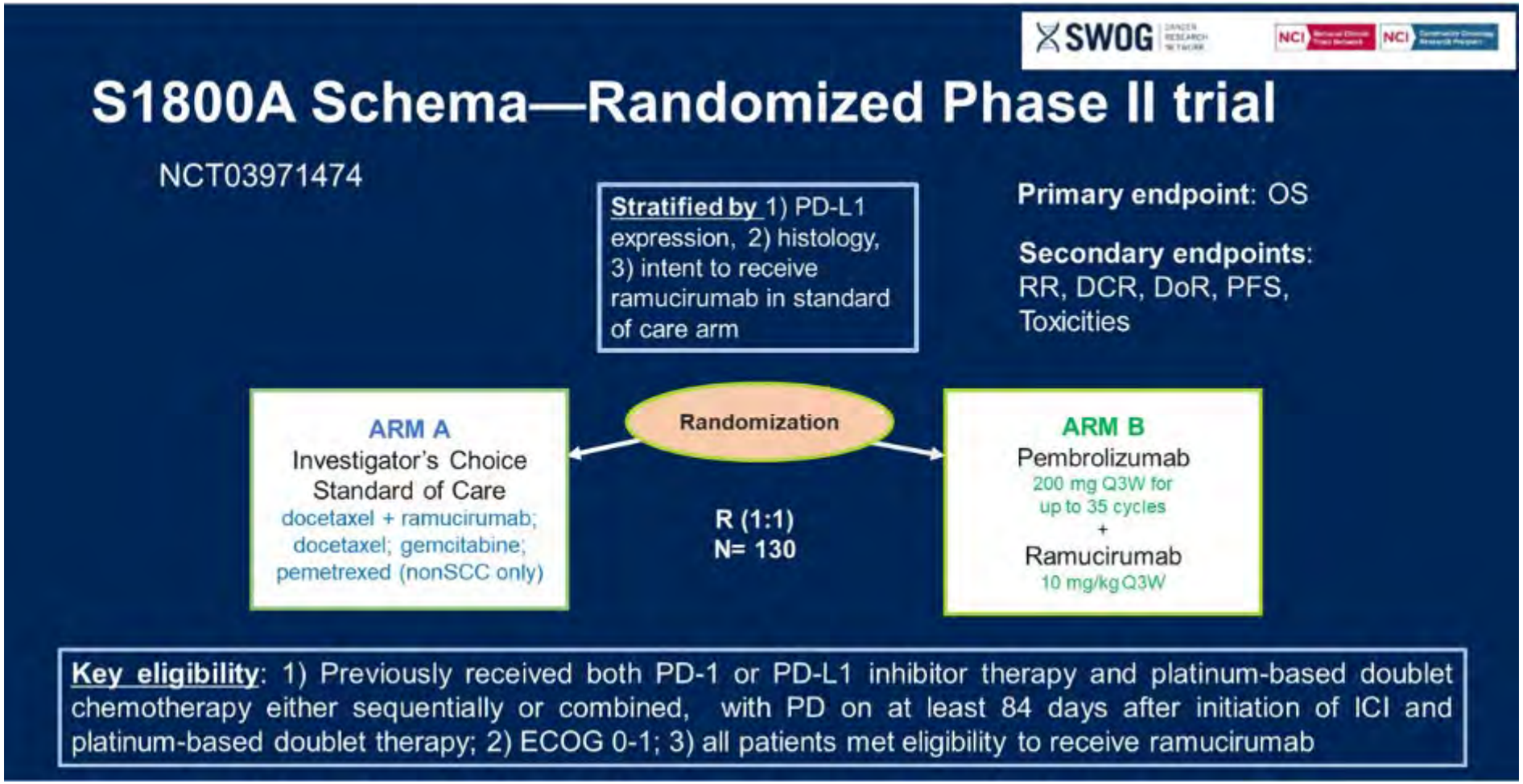
SWOG CANCER RESEARCH NETWORK | NCI National Clinical Trials Network | NCI Community Oncology Research Program

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

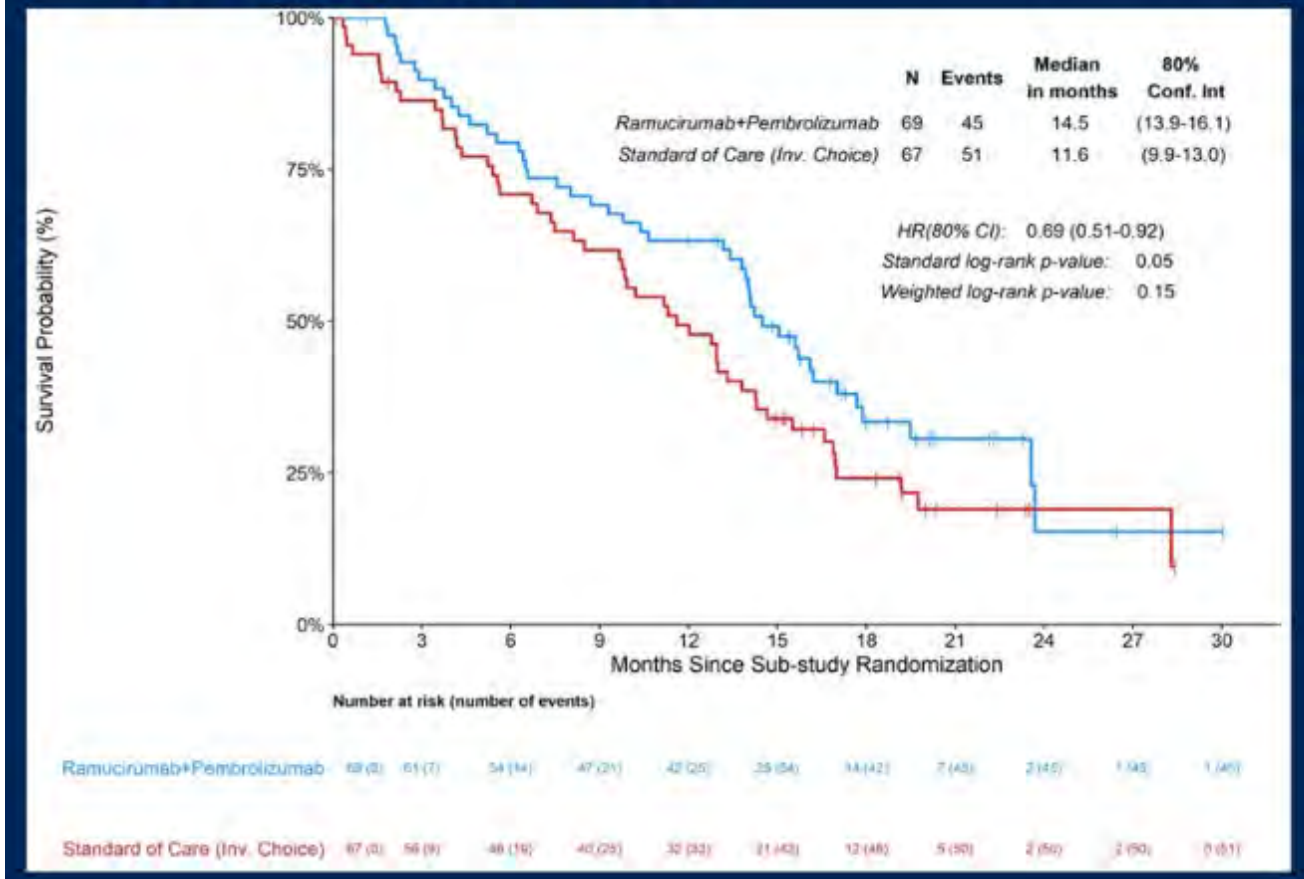
What Is the Best Second-Line Treatment After Chemotherapy and Immunotherapy?

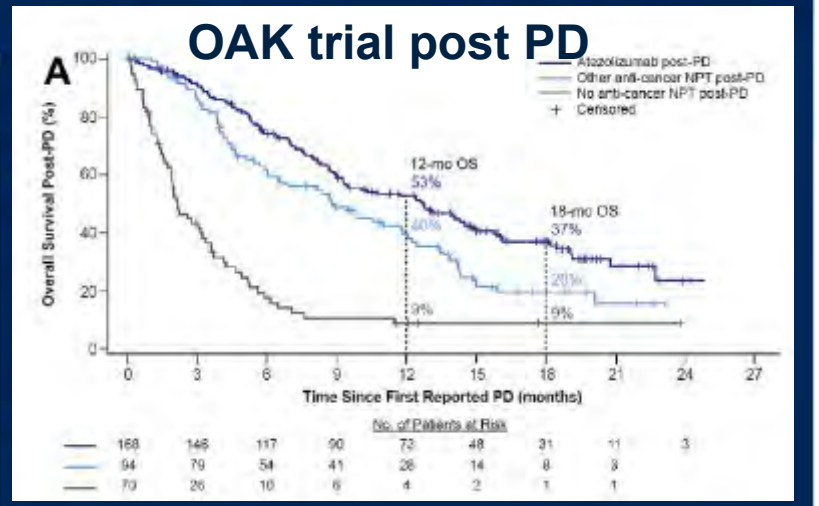


Adapted from ASCO 2022 presentation by Karen Reckamp.

Improved OS for Ramucirumab-Pembrolizumab

Overall survival





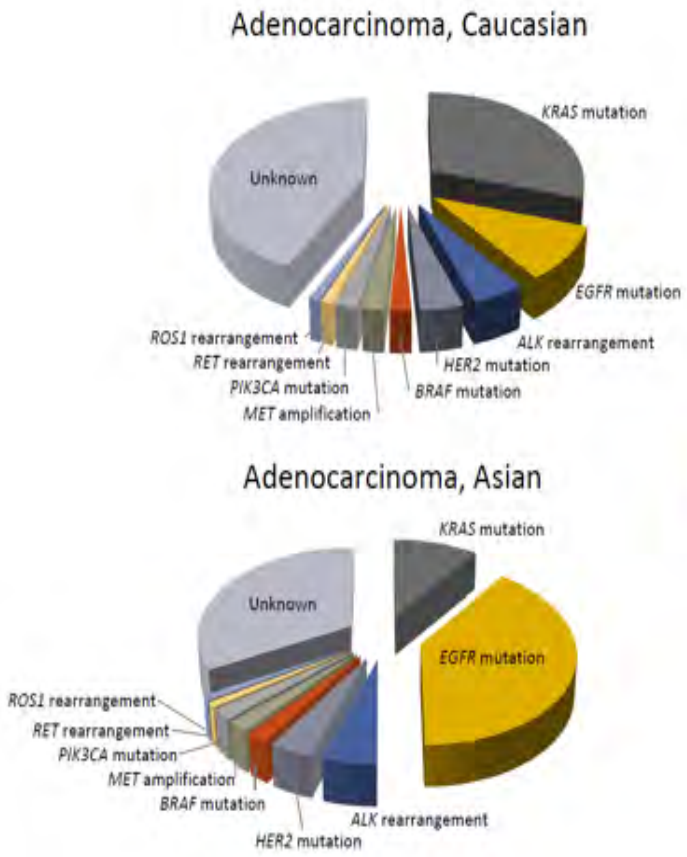
Standard of care therapy received:

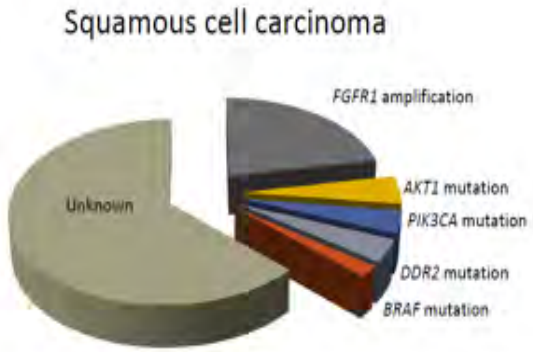
- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

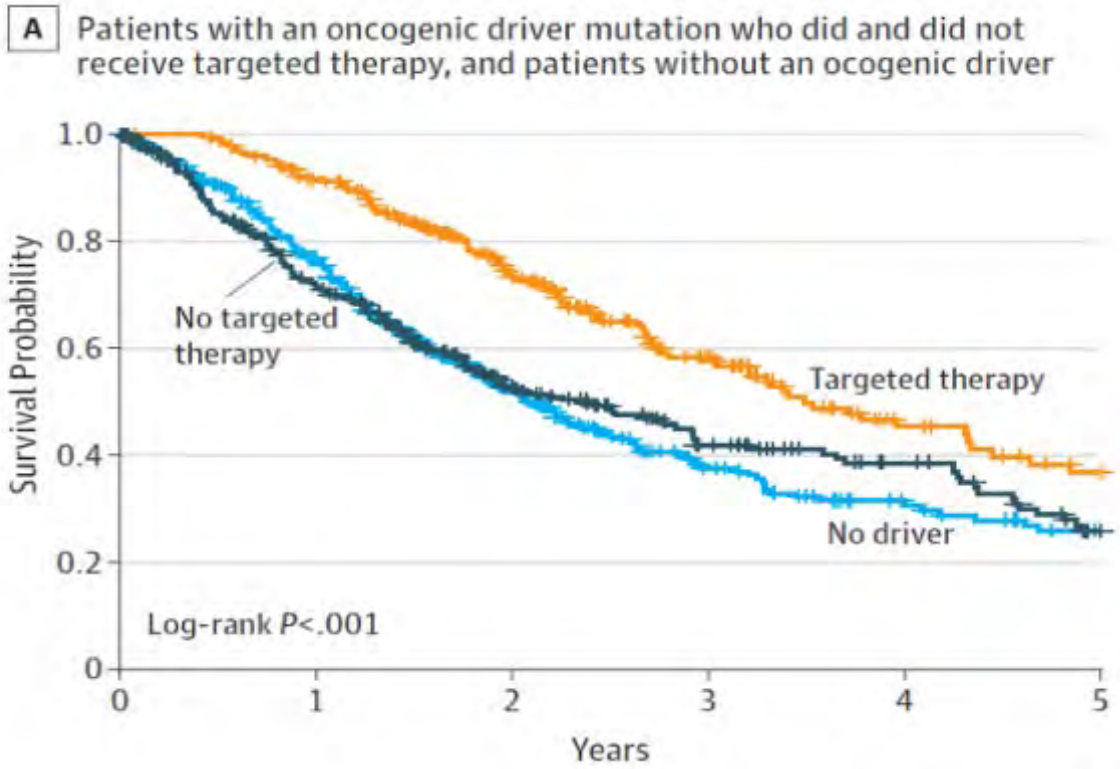
Adapted from ASCO 2022 presentation by Karen Reckamp; Gandara DR, et al. *J Thorac Oncol.* 2018;13:1906-1918.

Penn Medicine Abramson Cancer Center

Target Directed Therapy Improves OS





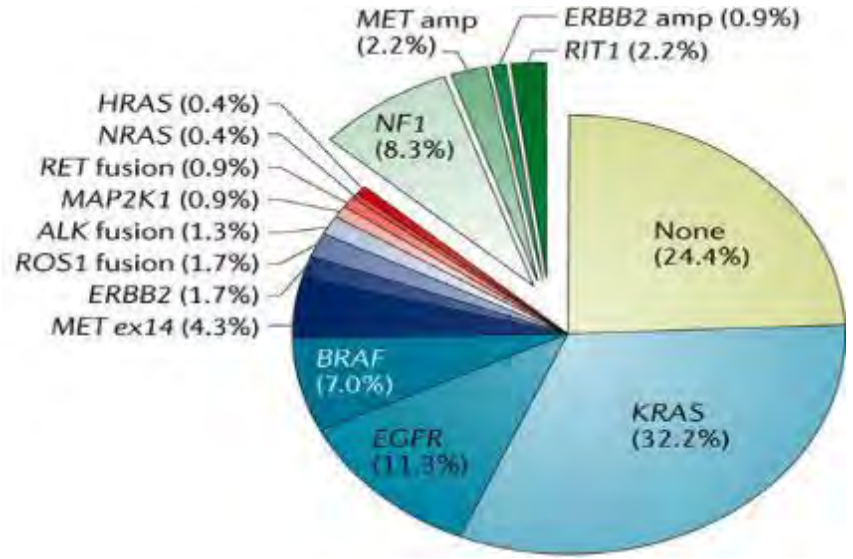


Kris MG, et al. *JAMA.* 2014;21;311:1998-2006.

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

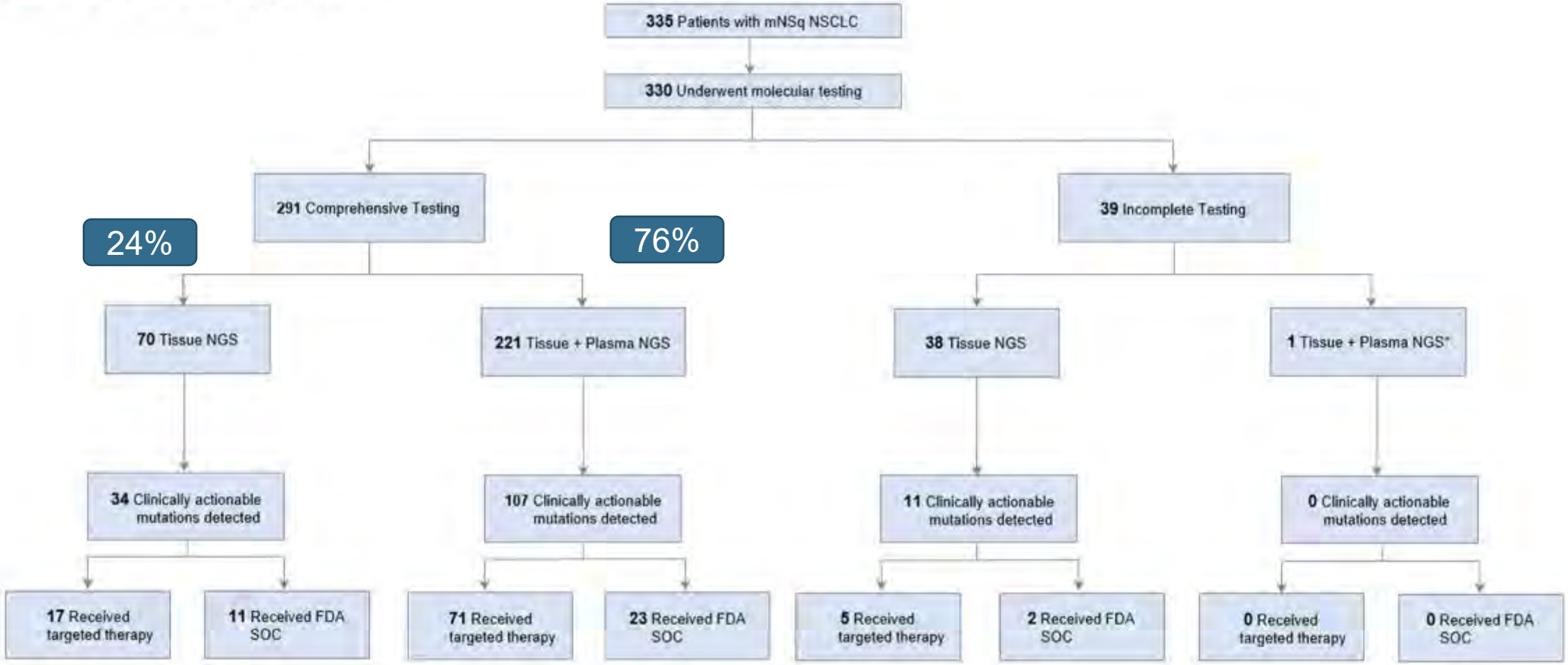


Fig 1.
Flowchart summarizes the overall patient enrollment and the number of clinically actionable mutations detected (*EGFR, ALK, BRAF, ROS1, MET, RET, NTRK1,2* and *3, KRAS* G12C, and *ErbB2)* on Tissue vs. Tissue + Plasma NGS for patients with comprehensive testing as well as for those with incomplete/no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

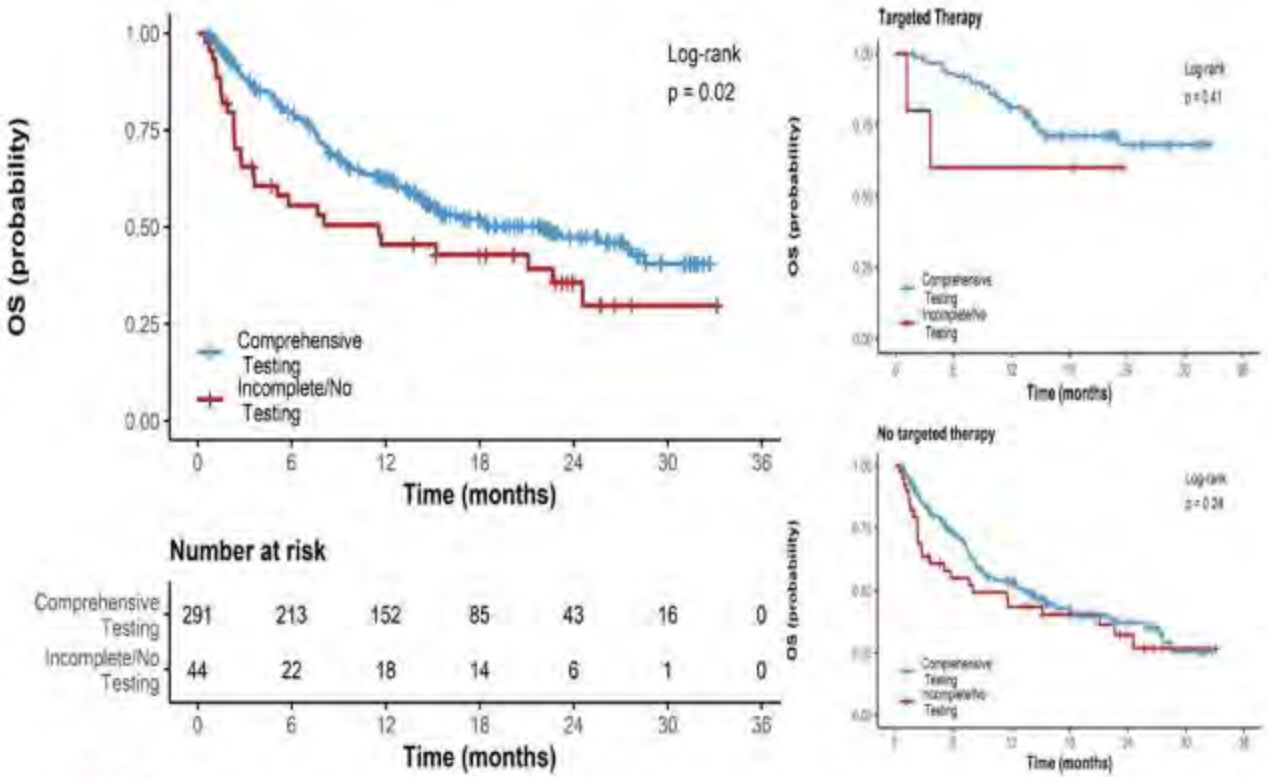


Fig 1.
Kaplan-Meier curve for OS of patients with comprehensive testing compared to patients with incomplete/no testing.

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

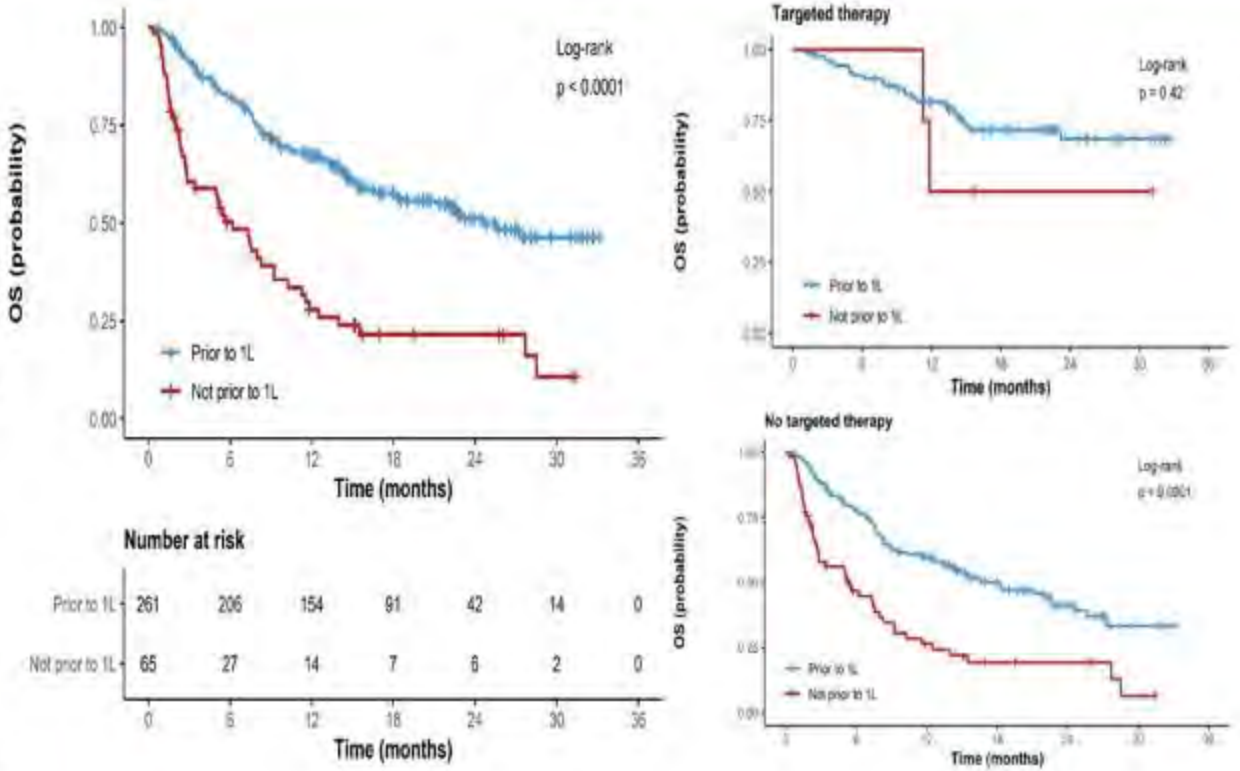


Fig 2.
Kaplan-Meier curve for OS of patients with comprehensive testing back prior to first line treatment compared to patients with results not back prior to first line treatment.

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

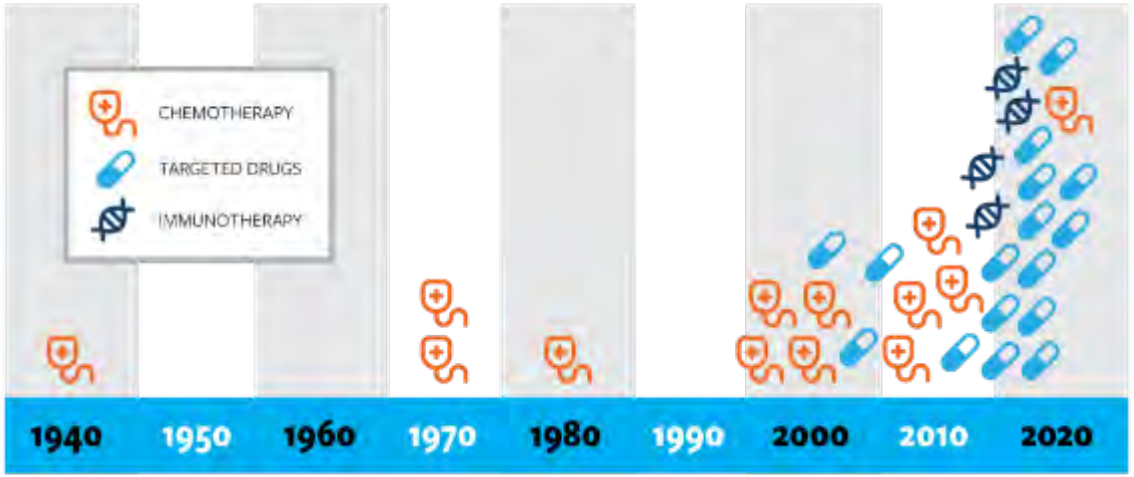
Liquid biopsy for NGS testing

- 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

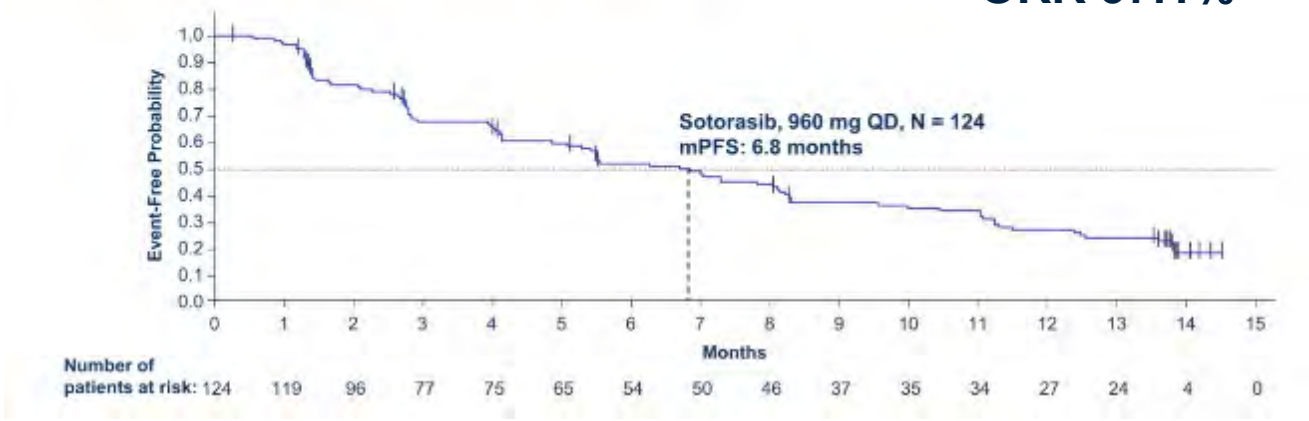
2020
Pralsetinib – *RET*
Brigatinib – *ALK* 1L
Capmatinib – *MET* exon 14 skipping
Selpercatinib – *RET*

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.

Penn Medicine Abramson Cancer Center

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.

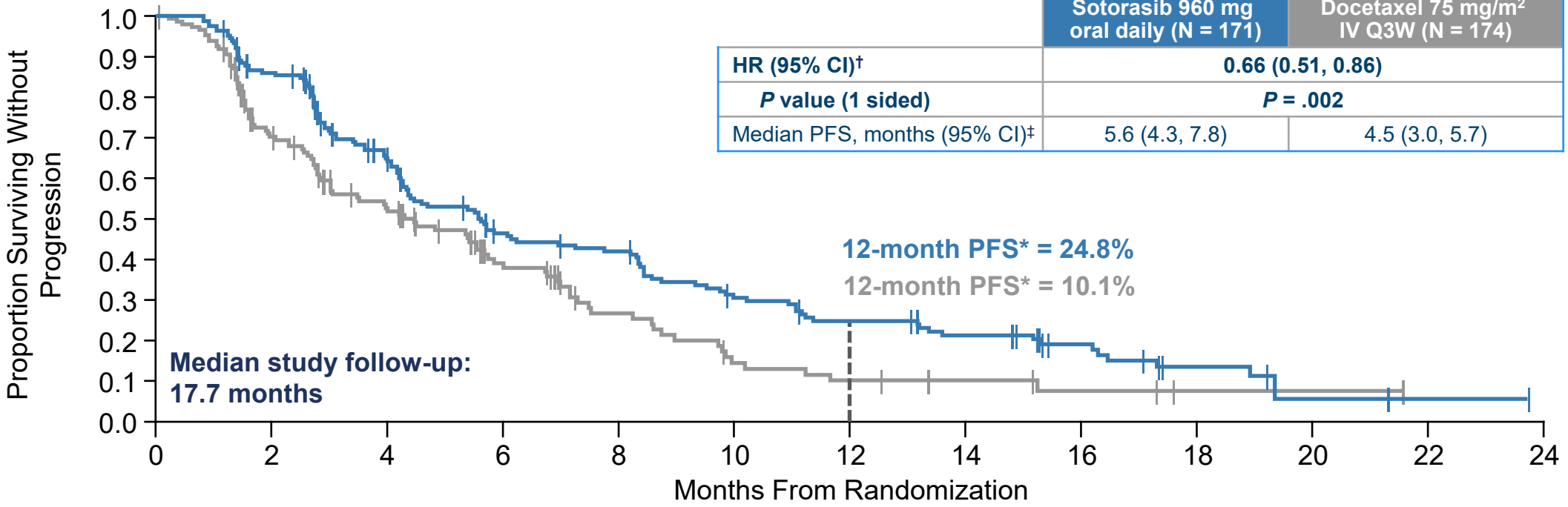
*Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval.

†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!

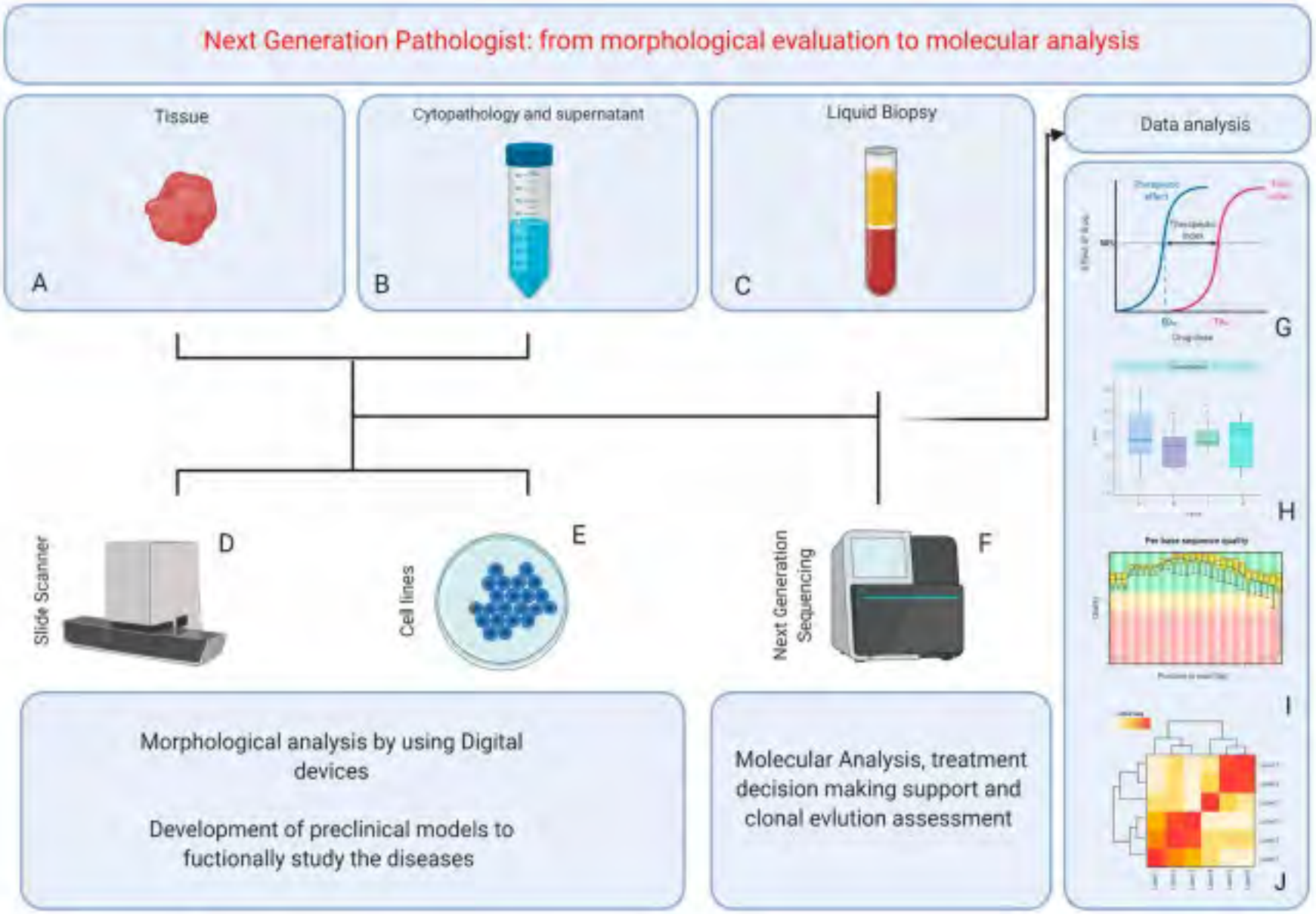
Penn Medicine
Abramson Cancer Center

Global Lung Cancer Academy

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

Umberto Malapelle, PhD

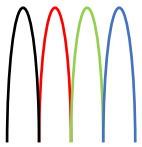
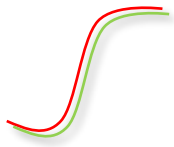
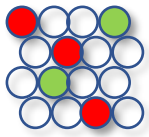
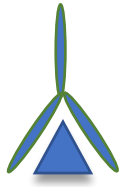
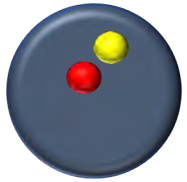
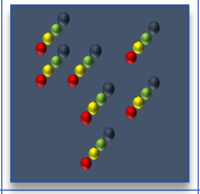
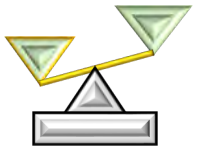
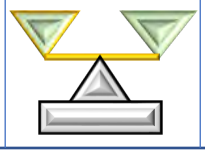
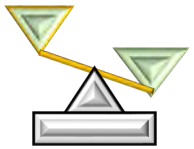
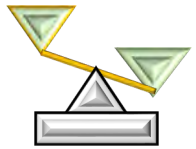
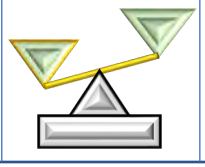
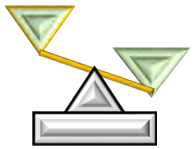
Ineligible Company (formerly: commercial interest)	**Relationship(s)**
Boehringer Ingelheim	Speaker bureau/advisory role; research grant (institution)
AstraZeneca	Speaker bureau/advisory role; research grant (institution)
Roche	Speaker bureau/advisory role
MSD	Speaker bureau/advisory role
Amgen	Speaker bureau/advisory role; research grant (institution)
Merck	Speaker bureau/advisory role
Diatech	Speaker bureau/advisory role
Biocartis	Speaker bureau/advisory role; research grant (institution)
BMS	Speaker bureau/advisory role
Eli Lilly	Speaker bureau/advisory role
Thermo Fisher	Speaker bureau/advisory role; research grant (institution)
Janssen	Speaker bureau/advisory role
Hedera	Advisory role

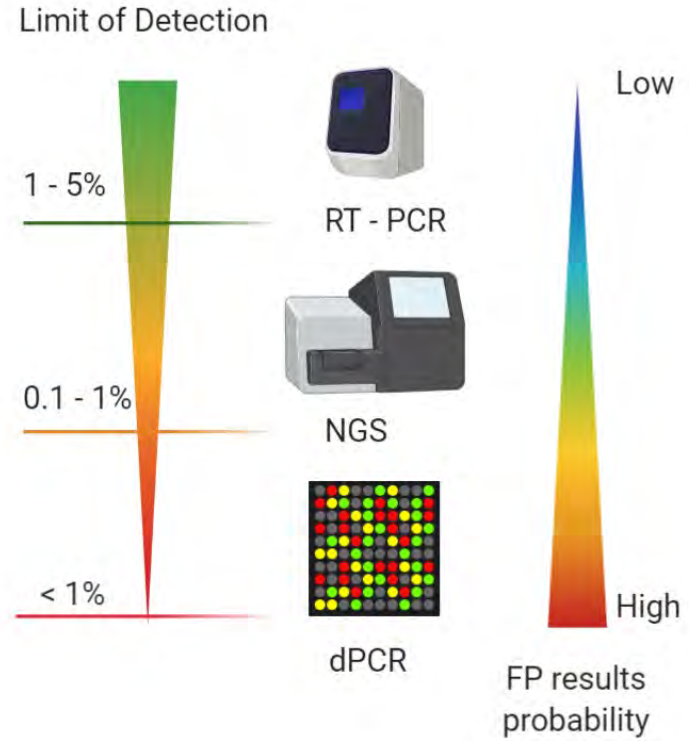


Angerilli V, et al. *Diagnostics (Basel)*. 2021;11:339.

Point Mutations and Indels

Protein Expression and Gene Fusions

	Sanger sequencing	Real-time PCR	Digital PCR	Next-generation sequencing	Immuno-histochemistry	Fluorescent in situ hybridization	Multiplex digital color-coded barcode	Next-generation sequencing
								
Limit of detection	10%–20%	1%–5%	0.1%–1%	0.01%–5%	Tissue-based technique (protein)	Tissue-based technique (DNA)	5%–10%	0.01%– 5%
Reference Range	All the mutations present in the analyzed gene regions	Only hot spot mutations (probe based)	Only hot spot mutations (probe based)	All the mutations present in the analyzed gene regions	All the fusions protein (antibody based)	Only specific fusions (probe based)	All the fusions present in the analyzed gene regions	All the fusions present in the analyzed gene regions
	FP FN	FP FN	FP FN	FP FN	FP FN	FP FN	FP FN	FP FN
								



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Review

The evolving landscape of biomarker testing for non-small cell lung cancer in Europe

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Oncogenic driver mutations
NSCLC

ABSTRACT

The discovery of oncogenic driver mutations rendering non-small cell lung cancer (NSCLC) targetable by small-molecule inhibitors, and the development of immunotherapies, have revolutionised NSCLC treatment. Today, instead of non-selective chemotherapies, all patients with advanced NSCLC eligible for treatment (and increasing numbers with earlier, less extensive disease) require fast and comp treatment.

The discovery of oncogenic driver mutations rendering non-small cell lung cancer (NSCLC) targetable by small-molecule inhibitors, and the development of immunotherapies, have revolutionised NSCLC treatment. Today, instead of non-selective chemotherapies, all patients with advanced NSCLC eligible for treatment (and increasing numbers with earlier, less extensive disease) require fast and comprehensive screening of biomarkers for first-line patient selection for targeted therapy, chemotherapy, or immunotherapy (with or without chemotherapy). To avoid unnecessary re-biopsies, biomarker screening before first-line treatment should also include markers that are actionable from second-line onwards; PD-L1 expression testing is also mandatory before initiating treatment.

Population differences exist in the frequency of oncogenic driver mutations: *EGFR* mutations are more frequent in Asia than Europe, whereas the converse is true for *KRAS* mutations. In addition to approved first-line

Abbreviations: ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; BRAF, B-Raf proto-oncogene; CAP, College of American Pathologists; ctDNA, circulating tumour cell DNA; ddPCR, digital droplet PCR; EGFR, epidermal growth factor receptor; EMQN, European Molecular Genetic Quality Network; EQA, external quality assessment; ERBB2, Erb-B2 receptor tyrosine kinase 2; ESCAT, ESMO Scale of Clinical Actionability of Molecular Targets; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; FISH, fluorescence *in situ* hybridisation; FNA, fine needle aspiration; HER, human epidermal growth factor receptor; IASLC, International Association for the Study of Lung Cancer; ICC, immunocytochemistry; IHC, immunohistochemistry; ISH, *in situ* hybridisation; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase kinase; MET, hepatocyte growth factor receptor; MTB, molecular tumour board; NCCN, National Comprehensive Cancer Network; NEQAS, National External Quality Assessment Service; NGS, next generation sequencing; NRG1, neuregulin 1; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; OncoKB, Oncology Knowledge Base; PCR, polymerase chain reaction; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; qPCR, quantitative PCR; QuIP, Quality Initiative for Pathology; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1; ROSE, rapid on-site evaluation; RT-PCR, real-time polymerase chain reaction; SGT, single-gene testing; SOC, standard of care; SOP, standard operating procedures; TAT, turnaround time; TMB, tumour mutational burden; VAF, variant allele frequency.

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[1] Employed by Amgen at initiation of the manuscript.

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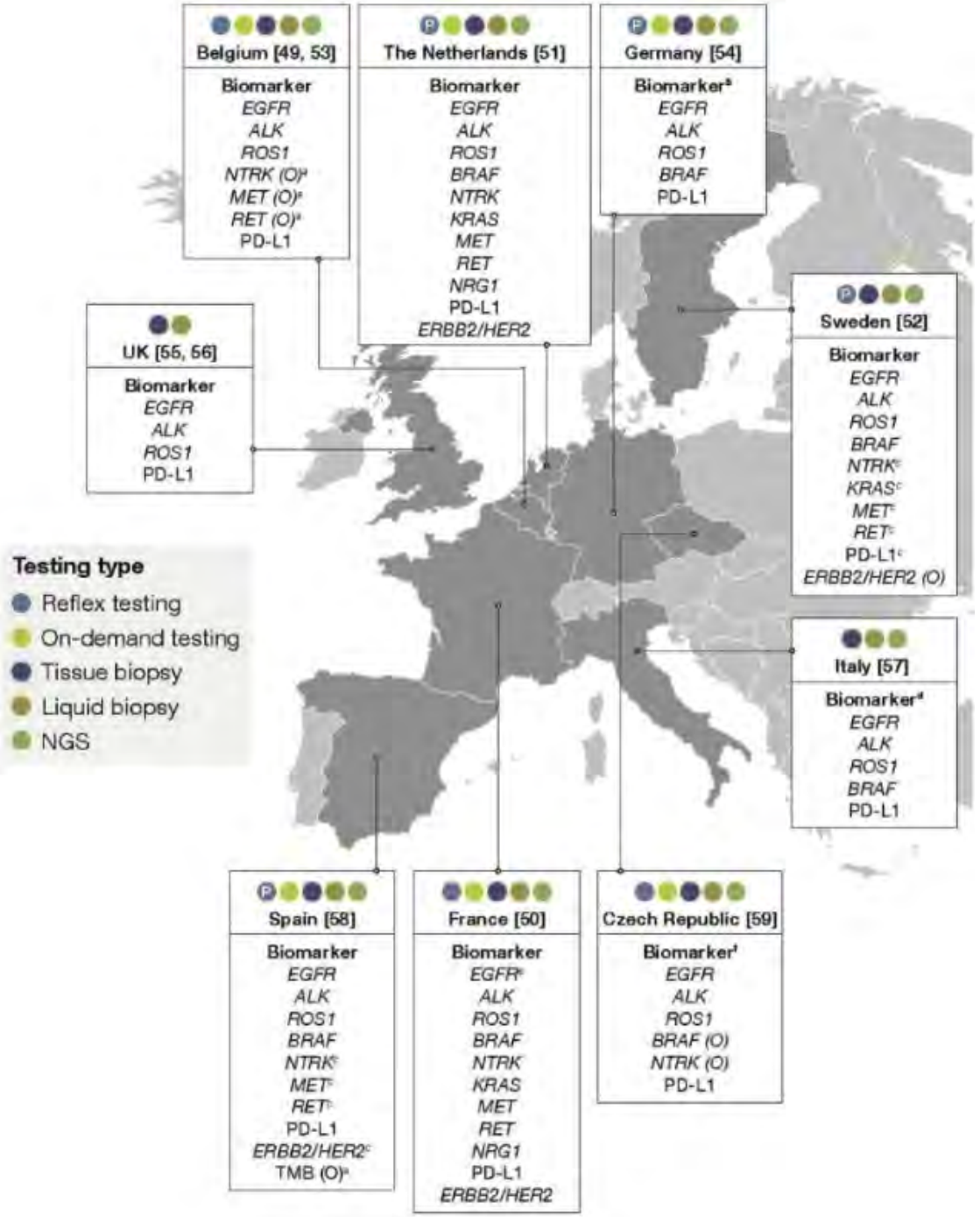
Available online 22 February 2021



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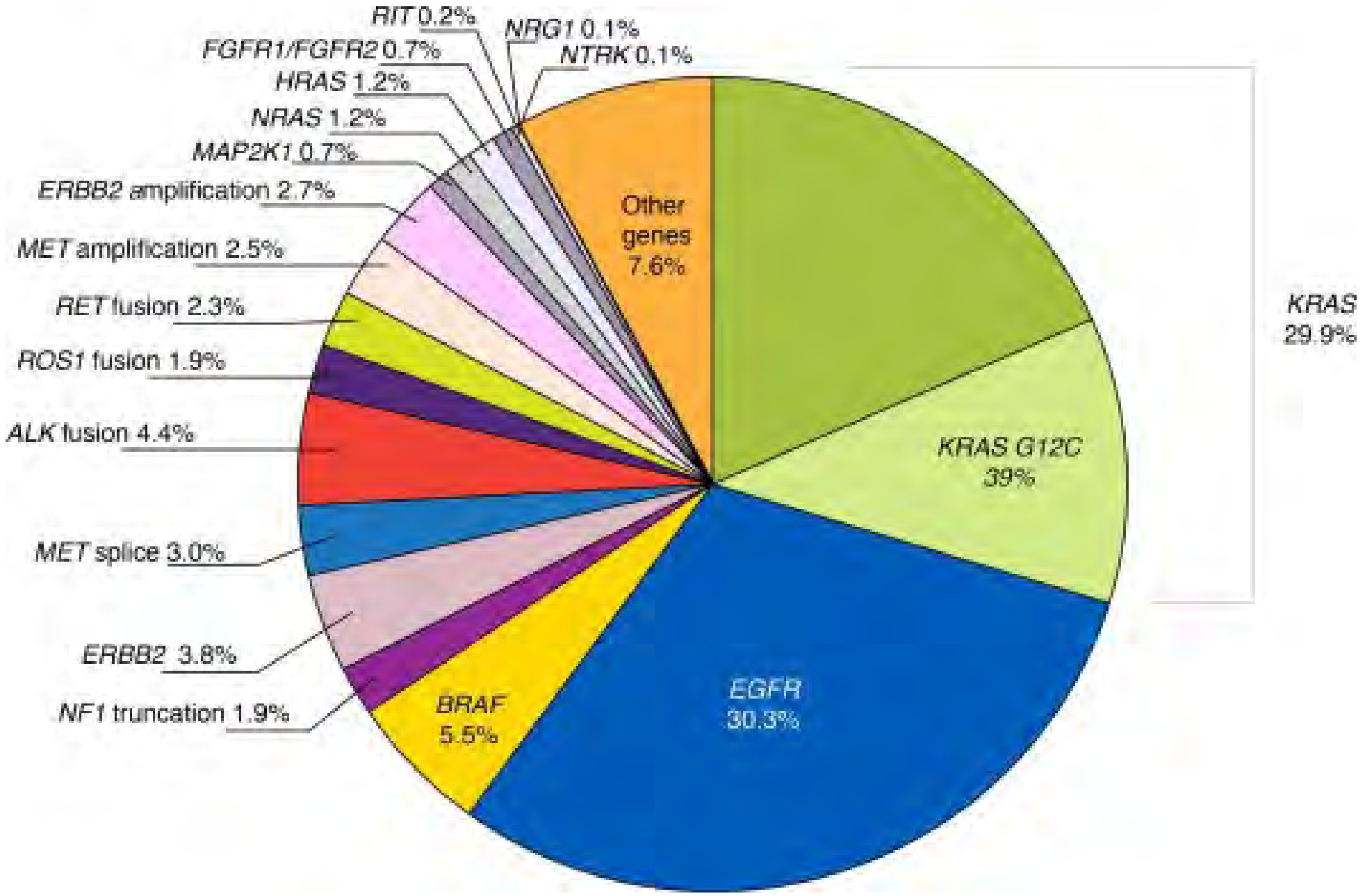

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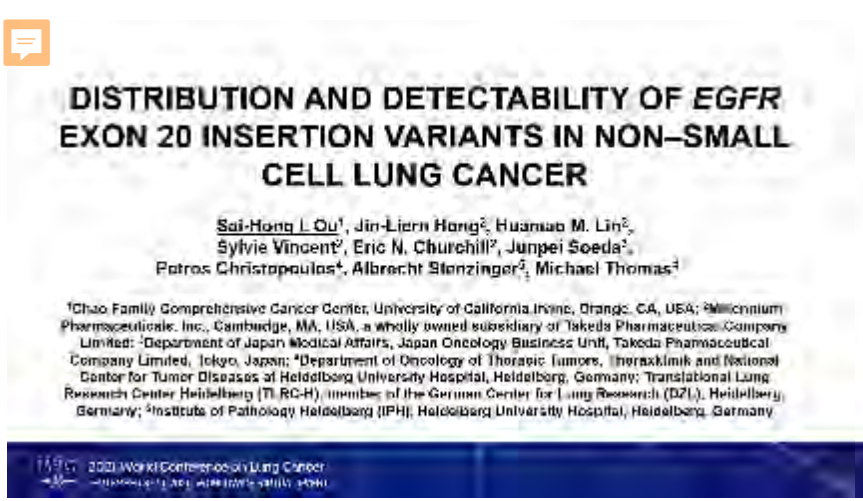
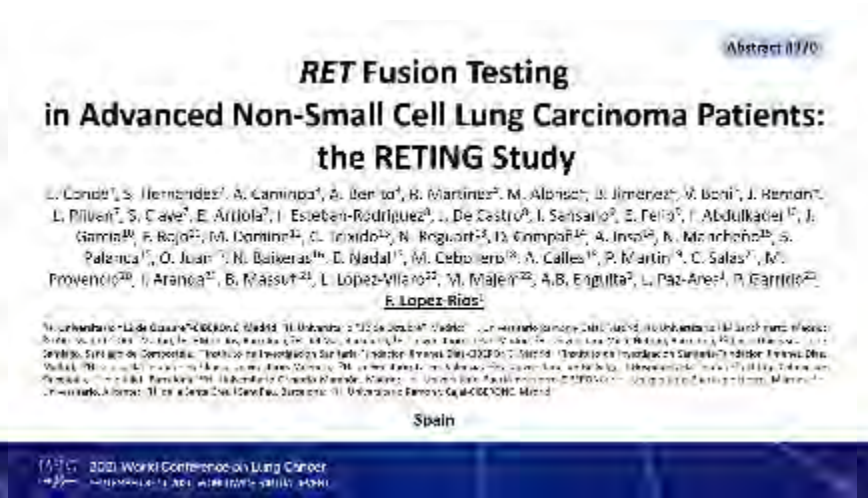

DISTRIBUTION AND DETECTABILITY OF *EGFR* EXON 20 INSERTION VARIANTS IN NON–SMALL CELL LUNG CANCER

Sai-Hong I. Ou[1], Jin-Liern Hong[2], Huaibao M. Lin[2], Sylvie Vincent[2], Eric N. Churchill[2], Junpei Soeda[2], Petros Christopoulos[4], Albrecht Stenzinger[5], Michael Thomas[3]

[1]Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA, USA; [2]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [3]Department of Japan Medical Affairs, Japan Oncology Business Unit, Takeda Pharmaceutical Company Limited, Tokyo, Japan; [4]Department of Oncology of Thoracic Tumors, Thoraxklinik and National Center for Tumor Diseases at Heidelberg University Hospital, Heidelberg, Germany; Translational Lung Research Center Heidelberg (TLRC-H), member of the German Center for Lung Research (DZL), Heidelberg, Germany; [5]Institute of Pathology Heidelberg (IPH), Heidelberg University Hospital, Heidelberg, Germany


Abstract 1170

RET Fusion Testing in Advanced Non-Small Cell Lung Carcinoma Patients: the RETING Study

E. Conde[1], S. Hernandez[2], A. Caminoa[3], A. Benito[4], R. Martinez[5], M. Alonso[6], B. Jimenez[7], V. Boni[8], J. Rendon[9], L. Pliven[10], S. Cave[11], E. Artiola[12], I. Esteban-Rodriguez[13], L. De Castro[14], I. Sansano[15], E. Ferro[16], F. Abdulkadel[17], J. Garcia[18], F. Rojo[19], M. Domine[20], C. Teixido[21], N. Reguart[22], D. Compan[23], A. Insa[24], R. Manchoño[25], S. Palenca[26], O. Juan[27], N. Baikeras[28], D. Nadal[29], M. Cebollero[30], A. Calles[31], P. Martin[32], C. Salas[33], M. Provencio[34], I. Aranda[35], B. Massuti[36], L. Lopez-Villaro[37], M. Majem[38], A.B. Enguita[39], L. Paz-Ares[40], P. Garrido[41], F. Lopez-Rios[1]

Spain


Genomic profiles and potential determinants of response and resistance in *KRAS* p.G12C-mutated NSCLC treated with sotorasib

Ferdinandos Skoulidis, MD, PhD

Department of Thoracic and Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center, USA

Conclusion 1: NGS is the way

Conclusion 2: ~~1 gene – 1 biomarker~~
1 mutation – 1 biomarker [considering the specific and dynamic genomic landscape]

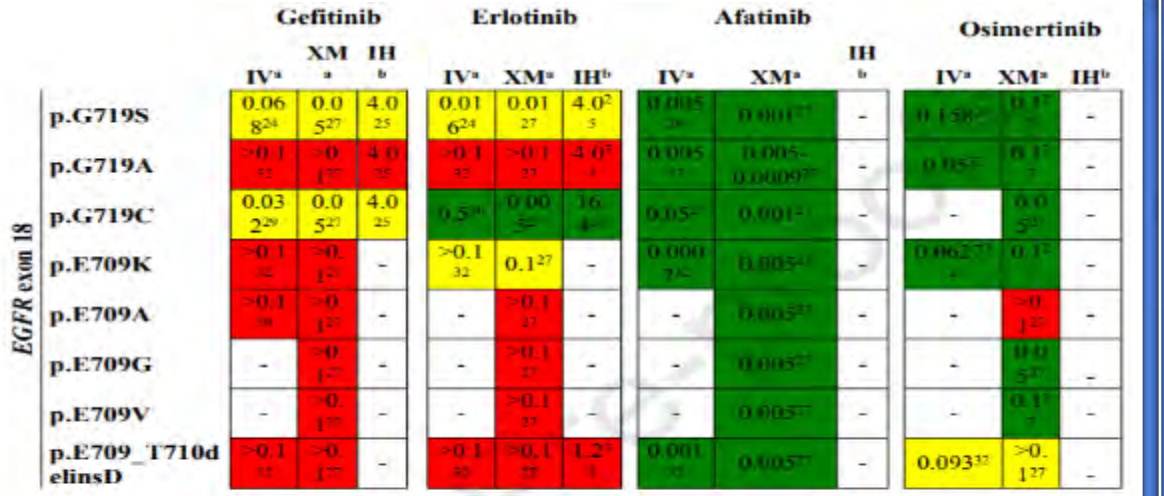


Figure 2. Overview and assessment of EGFR TKIs activity in cell lines (IV), xenograft models (XM) and patients (IH) harboring exon 18 mutations [[a]expressed in term of micromolar (μM) concentration, [b]expressed in term of median months of progression-free survival (PFS)]. The drug sensitivity was color-coded according to the scheme indicated at the top right and was categorized as sensitive, resistant, controversial or not available based on literature data.

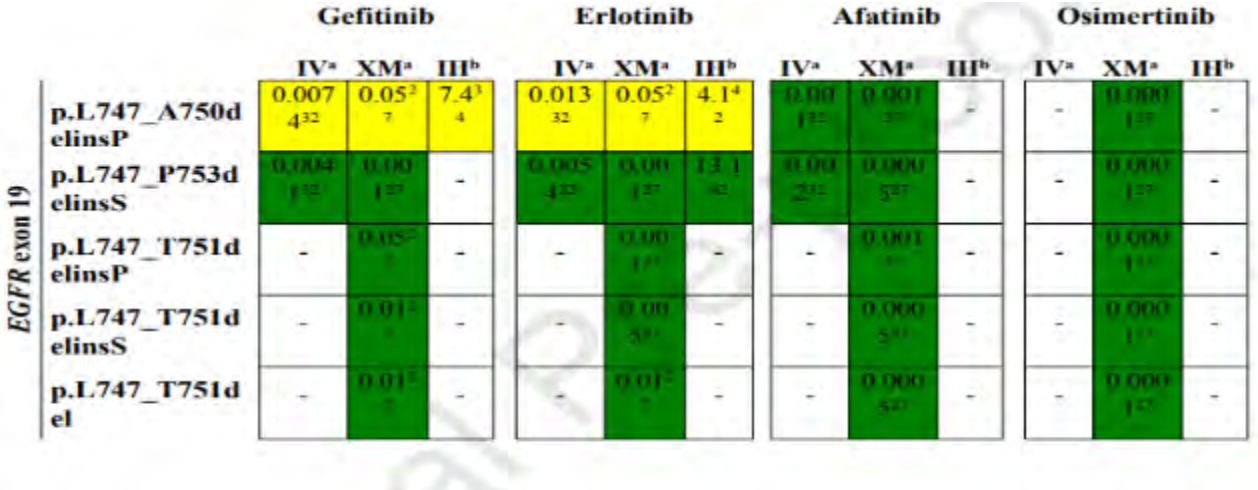


Figure 3. Overview and assessment of EGFR TKIs activity in cell lines (IV), xenograft models (XM) and patients (IH) harboring exon 19 mutations [[a]expressed in term of micromolar (μM) concentration, [b]expressed in term of median months of progression-free survival (PFS)]. The drug sensitivity was color-coded according to the scheme indicated at the top right and was categorized as sensitive, controversial or not available based on literature data.

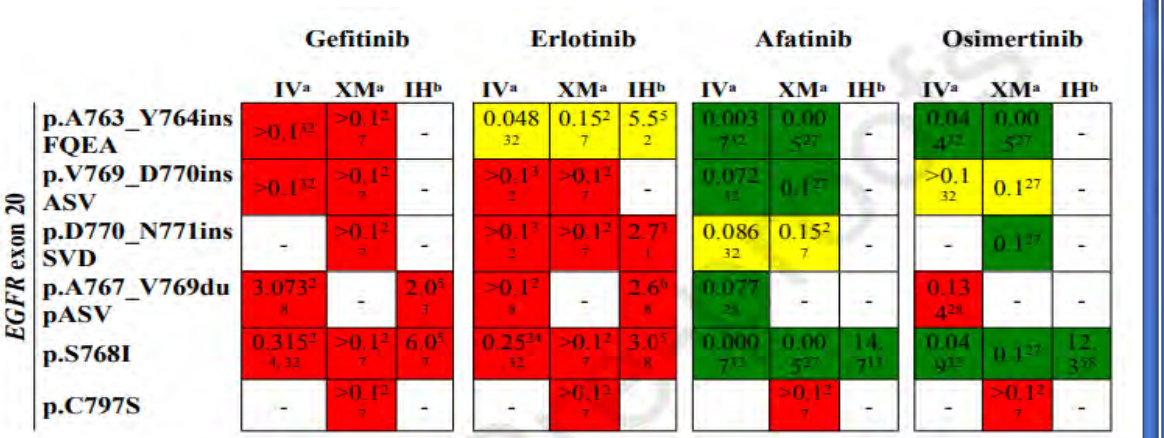


Figure 4. Overview and assessment of EGFR TKIs activity in cell lines (IV), xenograft models (XM) and patients (IH) harboring exon 20 mutations [[a]expressed in term of micromolar (μM) concentration, [b]expressed in term of median months of progression-free survival (PFS)]. The drug sensitivity was color-coded according to the scheme indicated at the top right and was categorized as sensitive, resistant, controversial or not available based on literature data.

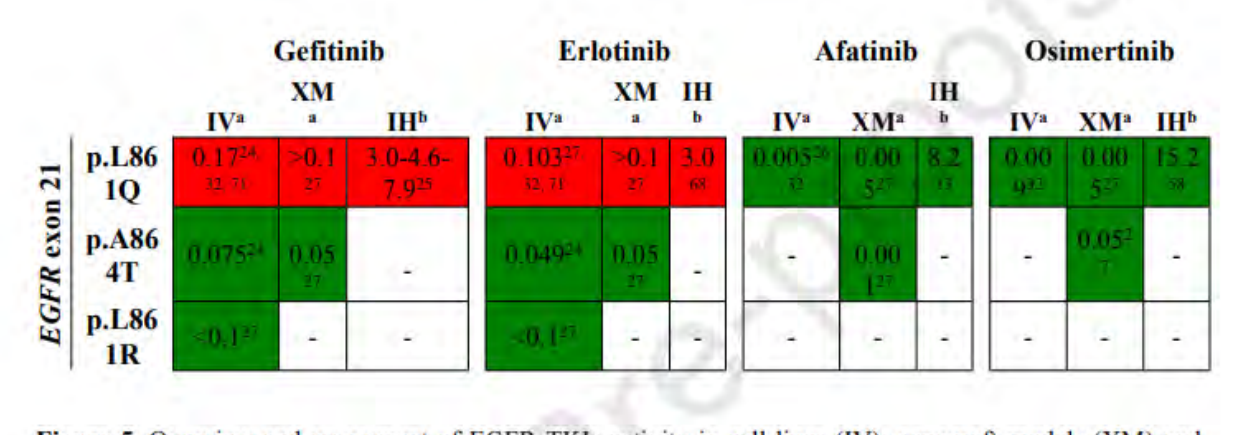
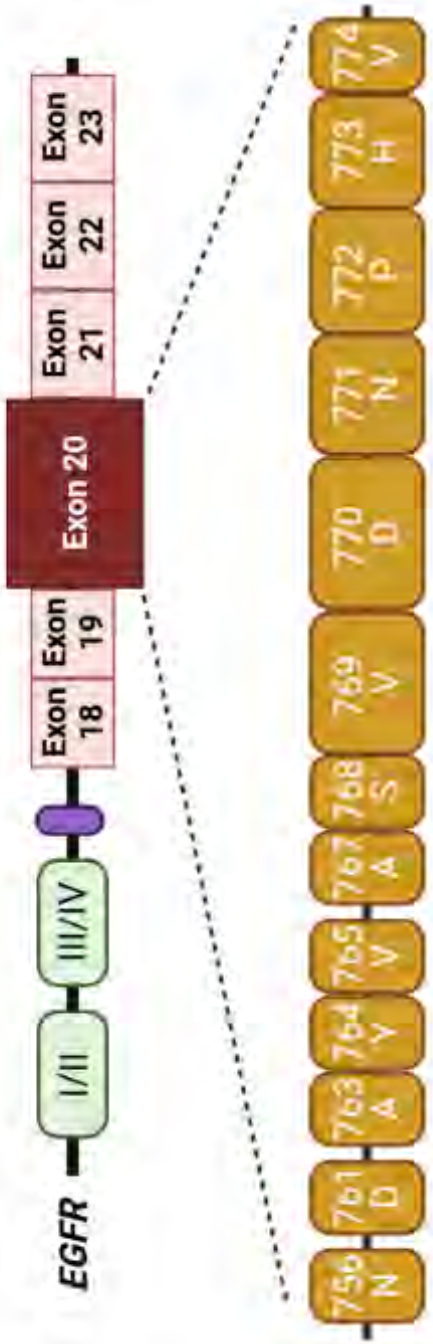


Figure 5. Overview and assessment of EGFR TKIs activity in cell lines (IV), xenograft models (XM) and patients (IH) harboring exon 21 mutations [[a]expressed in term of micromolar (μM) concentration, [b]expressed in term of median months of progression-free survival (PFS)]. The drug sensitivity was color-coded according to the scheme indicated at the top right and was categorized as sensitive, resistant, controversial or not available based on literature data.



p.V774_C775insHV	p.V774_C775insPHV	p.V774_C775insPR	
p.H773_V774dup	p.H773_V774insGH	p.H773_V774insNPH	p.H773_V774insQ
p.H773_V774insAH	p.H773_V774insGNPH	p.H773_V774insNPHT	p.H773_V774insTQPP
p.H773_V774insG	p.H773_V774insH	p.H773_V774insPH	p.H773dup
p.P772_H773dup	p.P772_H773insNP	p.P772_H773insQV	p.P772_H773insVDN
p.P772_H773ins?	p.P772_H773insPNP	p.P772_H773insTHP	p.P772_H773insX
p.P772_H773insDHP	p.P772_H773insPR	p.P772_H773insV	p.P772_H773insYNP
p.P772_H773insDNP	p.P772_H773insQCP		
p.N771_H773dup	p.N771_P772insH	p.N771_P772insRH	p.N771_P772insV
p.N771_P772ins?	p.N771_P772insHH	p.N771_P772insTQPNP	p.N771dup
p.N771_P772insG	p.N771_P772insN		
p.D770_N771insAPW	p.D770_N771insGF	p.D770_N771insPAW	p.D770_N771insSVQ
p.D770_N771insAWT	p.D770_N771insGL	p.D770_N771insSN	p.D770_N771insVDSVDNP
p.D770_N771insD	p.D770_N771insGT	p.D770_N771insSVD	p.D770_N771insY
p.D770_N771insG	p.D770_N771insH	p.D770_N771insSVE	p.D770_P772dup
p.D770_N771insGD	p.D770_N771insMATP	p.D770_N771insSVP	p.D770Efs*61
p.V769_D770insANV	p.V769_D770insGGTR	p.V769_D770insGV	p.V769_D770insMASVD
p.V769_D770insASV	p.V769_D770insGRV	p.V769_D770insGVG	p.V769_N771dup
p.V769_D770insCV	p.V769_D770insGSV	p.V769_D770insGVV	p.V769dup
p.V769_D770insERG			
p.S768_D770dup	p.S768_V769insAWT	p.S768_V769insVAS	
p.A767_S768insIA	p.A767_V769dup	p.A767_S768insTLA	p.A767_S768insYVM
p.V765_M766insMAS			
p.Y764_V765insHH			
p.A763_Y764insFQEA			
p.D761_E762insEAFQ			
p.N756dup			

Malapelle U, et al. *Crit Rev Oncol Hematol*. 2022;169:103536.

~~A mutation in BRAF~~: The Mutation p.V600E (c.1799T>A) in *BRAF*

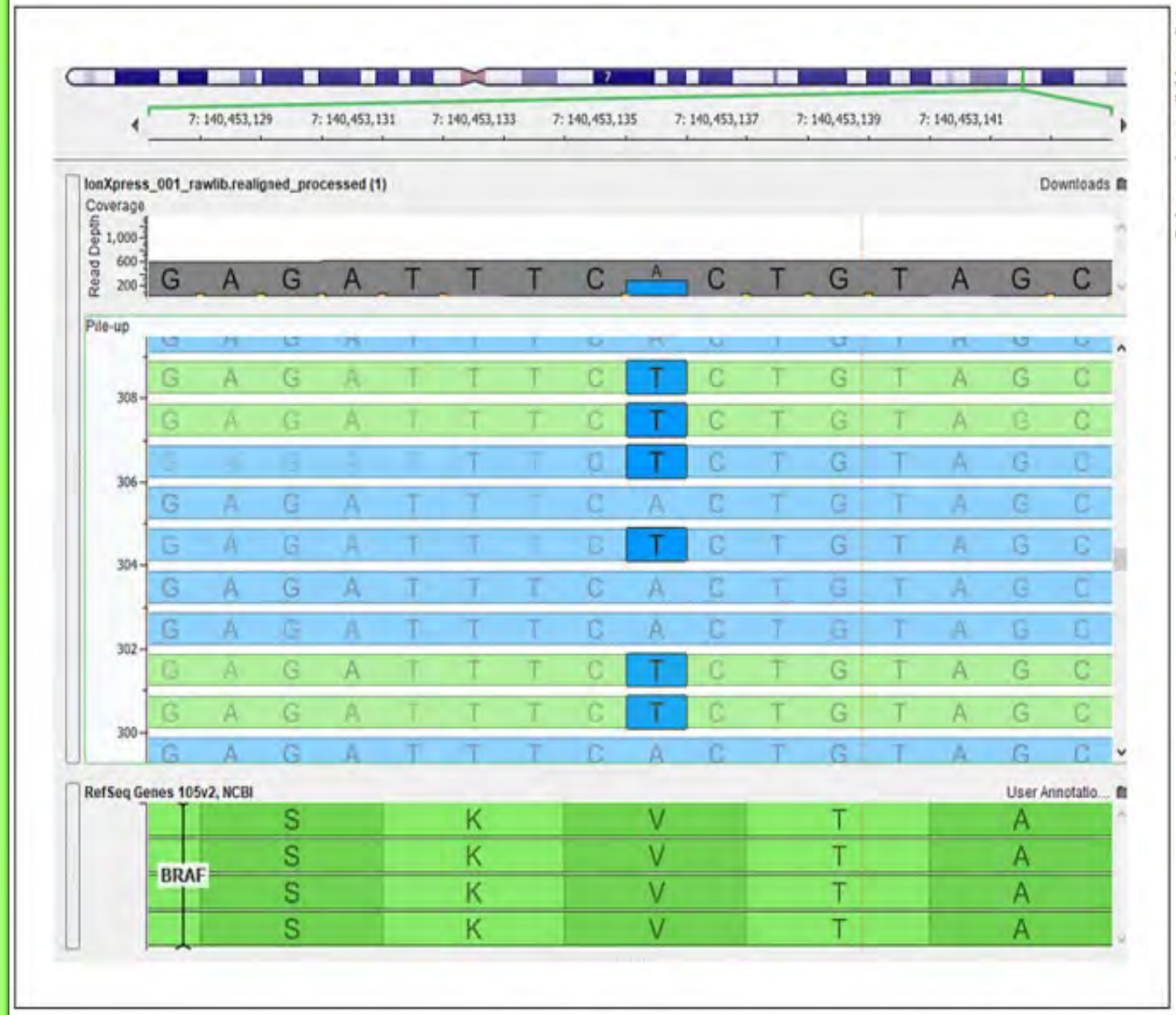


Fig. 1. Next-generation sequencing detection of a *BRAF* p.V600E point mutation with the SiRe® panel on a Personal Genome Machine in case No. 1 (Table 1).

Fig. 2. Next-generation sequencing detection of a *BRAF* non-p.V600E (p.D594G) point mutation with the SiRe® panel on a Personal Genome Machine in case No. 2 (Table 1).

Pisapia P, et al. *Acta Cytol.* 2019;63:247-250.

European Journal of Cancer 137 (2020) 57–68

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journal homepage: www.ejcancer.com

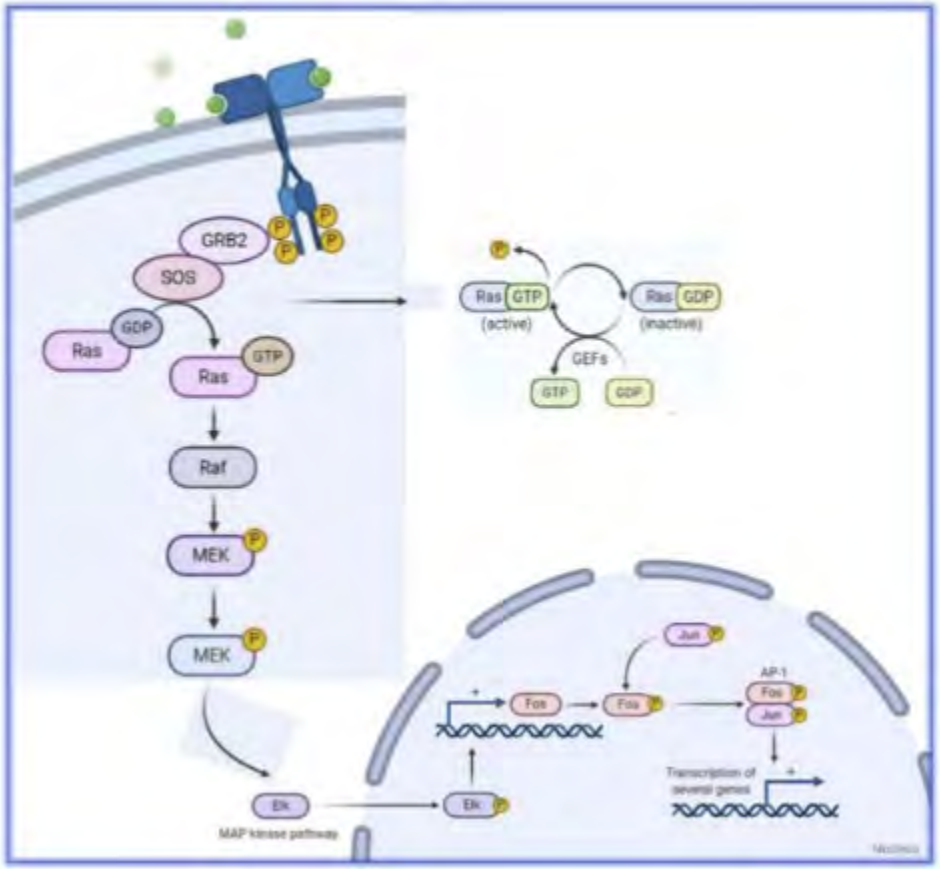
EJC

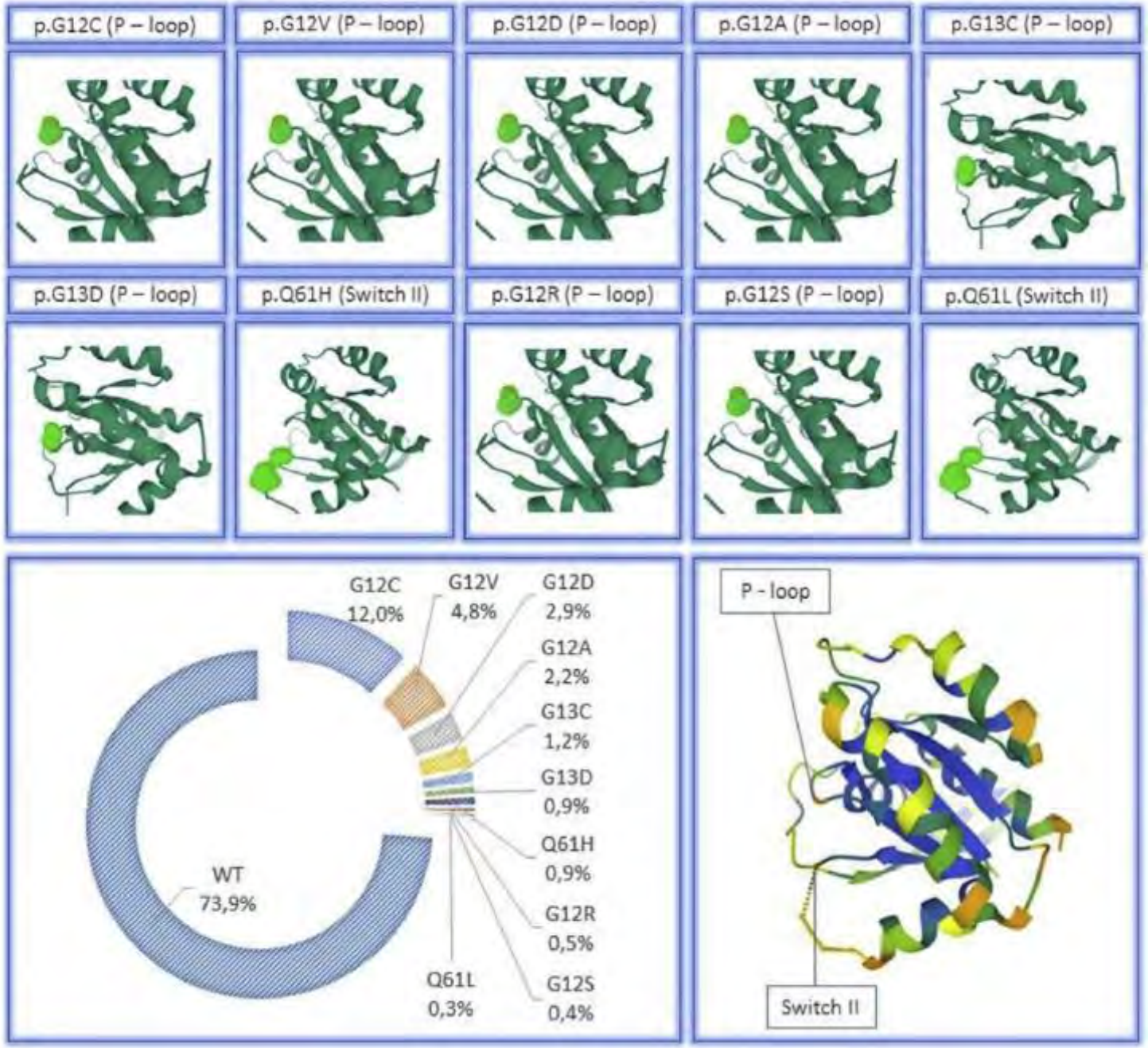
ELSEVIER

Review

KRAS inhibition in non–small cell lung cancer: Past failures, new findings and upcoming challenges

Francesco Passiglia [a,*], Umberto Malapelle [b,f], Marzia Del Re [c,f], Luisella Righi [a], Fabio Pagni [d], Daniela Furlan [e], Romano Danesi [c], Giancarlo Troncone [b], Silvia Novello [a,*]





Passiglia F, et al. *Eur J Cancer*. 2020;137:57-68.

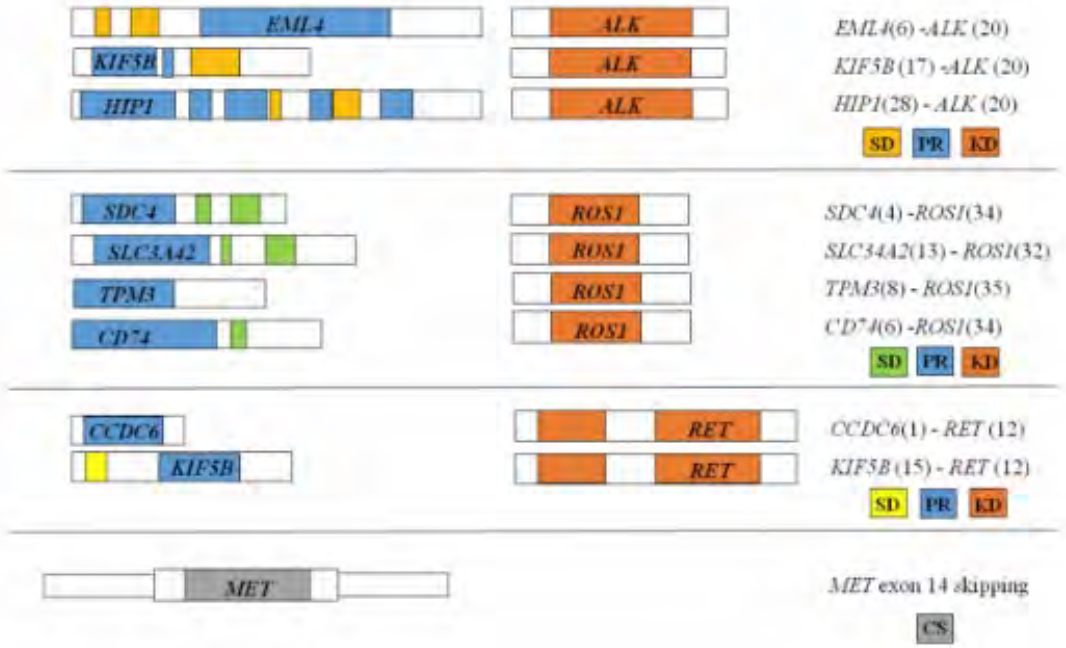
cancers

MDPI

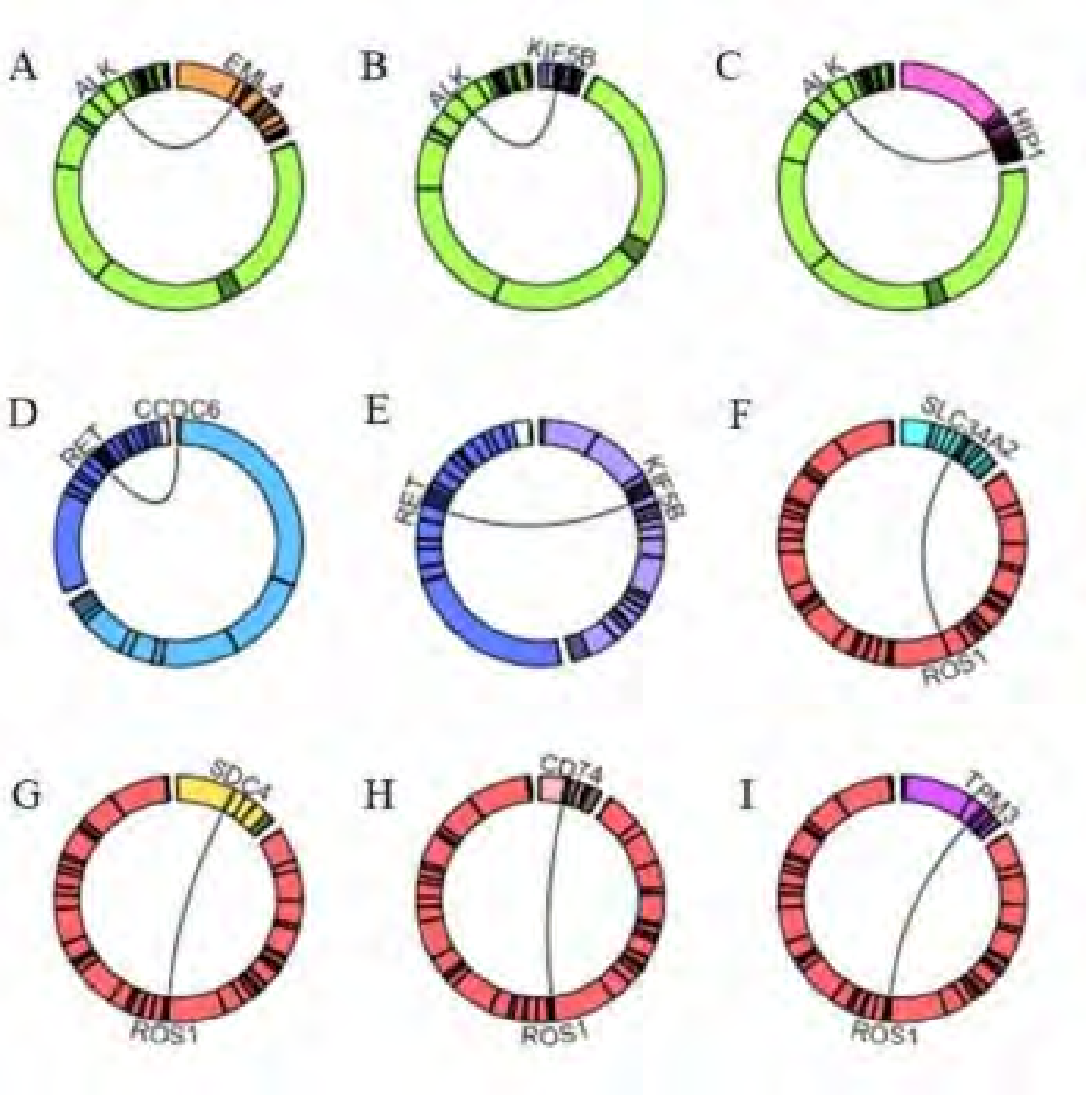
Article

RNA-Based Assay for Next-Generation Sequencing of Clinically Relevant Gene Fusions in Non-Small Cell Lung Cancer

Caterina De Luca [1,†], Francesco Pepe [1,†], Antonino Iaccarino [1,†], Pasquale Pisapia [1], Luisella Righi [2], Angela Listì [2], Lorenza Greco [1], Gianluca Gragnano [1], Severo Campione [3], Gianfranco De Dominicis [3], Fabio Pagni [4], Roberta Sgariglia [1], Mariantonia Nacchio [1], Rossella Tufano [5], Floriana Conticelli [1], Elena Vigliar [1], Claudio Bellevicine [1], Diego Luigi Cortinovis [4], Silvia Novello [3], Miguel Angel Molina-Vila [6], Rafael Rosell [7], Giancarlo Troncone [1,*] and Umberto Malapelle [1]



Open source: "All the panel design files were reported in the Supplementary Material (Supplementary Files S1–S9)."



De Luca C, et al. *Cancers (Basel)*. 2021;13:139.

Tumor Mutational Burden on Cytological Samples: A Pilot Study

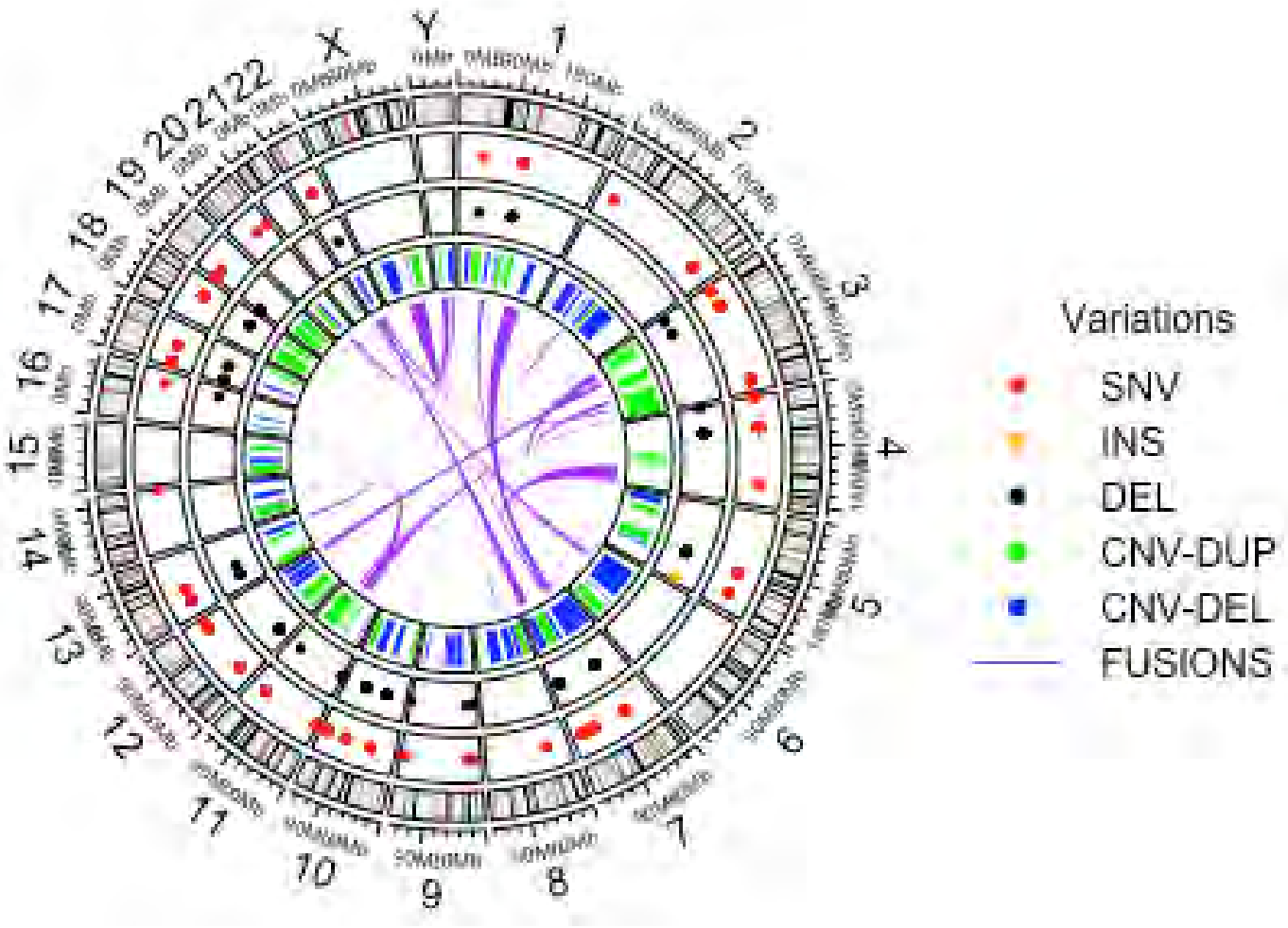
Francesco Pepe, PhD[1]; Pasquale Pisapia, MD[1]; Valerio Gristina, MD[2]; Danilo Rocco, MD[3]; Mariacarolina Micheli, BS[4]; Pietro Micheli, MD[4]; Antonino Iaccarino, PhD[1]; Rossella Tufano, PhD[5]; Gianluca Gragnano, BS[1]; Gianluca Russo, BS[1]; Caterina De Luca, PhD[1]; Roberta Sgariglia, PhD[1]; Mariantonia Nacchio, PhD[1]; Ilaria Girolami, MD[6]; Albino Eccher, MD, PhD[7]; Antonio Russo, MD[2]; Giancarlo Troncone, MD, PhD[1]; and Umberto Malapelle, PhD[1]

BACKGROUND: Immune-checkpoint inhibitors (ICIs) represent an important treatment option for patients who have advanced stage non–small cell lung cancer (NSCLC). Currently, evaluation of the expression level of programmed death-ligand 1 (PD-L1) has proven highly successful as a positive predictive biomarker for ICIs. In addition to PD-L1, other promising predictive biomarkers are emerging, including high tumor mutational burden (TMB-H). However, measuring TMB-H remains challenging for several reasons, among which is the difficulty in obtaining adequate tissue material from NSCLC patients. There are no data in the current literature regarding the possibility of adopting cell blocks (CBs) for TMB evaluation; therefore, our goal was to evaluate the feasibility of analyzing TMB on CBs. **METHODS:** For evaluation of differences in run metric parameters, 8 pairs of histological and CB samples from patients with NSCLC were analyzed using the Oncomine Tumor Mutational Load Assay on Ion Torrent S5 GS next-generation sequencing (NGS) platform. **RESULTS:** Most CBs (6/8, 75.0%) were successfully analyzed by adopting the broad NGS panel approach. CBs provided results similar to those obtained on histological matched specimens in terms of median total reads (7207048.80 vs 7558817.80), median mapped reads (7075753.83 vs 7513822.00), median read lengths (115.50 vs. 113.00), median percentage of reads on-target (97.49% vs 98.45%), median average reads per amplicon (454.67 vs 476.14), and median uniformity of amplicon coverage (83.52% vs 84.13%). **CONCLUSION:** In this pilot study, we demonstrated the technical feasibility of assessing TMB on CBs. ***Cancer Cytopathol* 2020;0:1-8**. © *2020 American Cancer Society*

KEY WORDS: cytology; immunotherapy; lung cancer; next generation sequencing; TMB

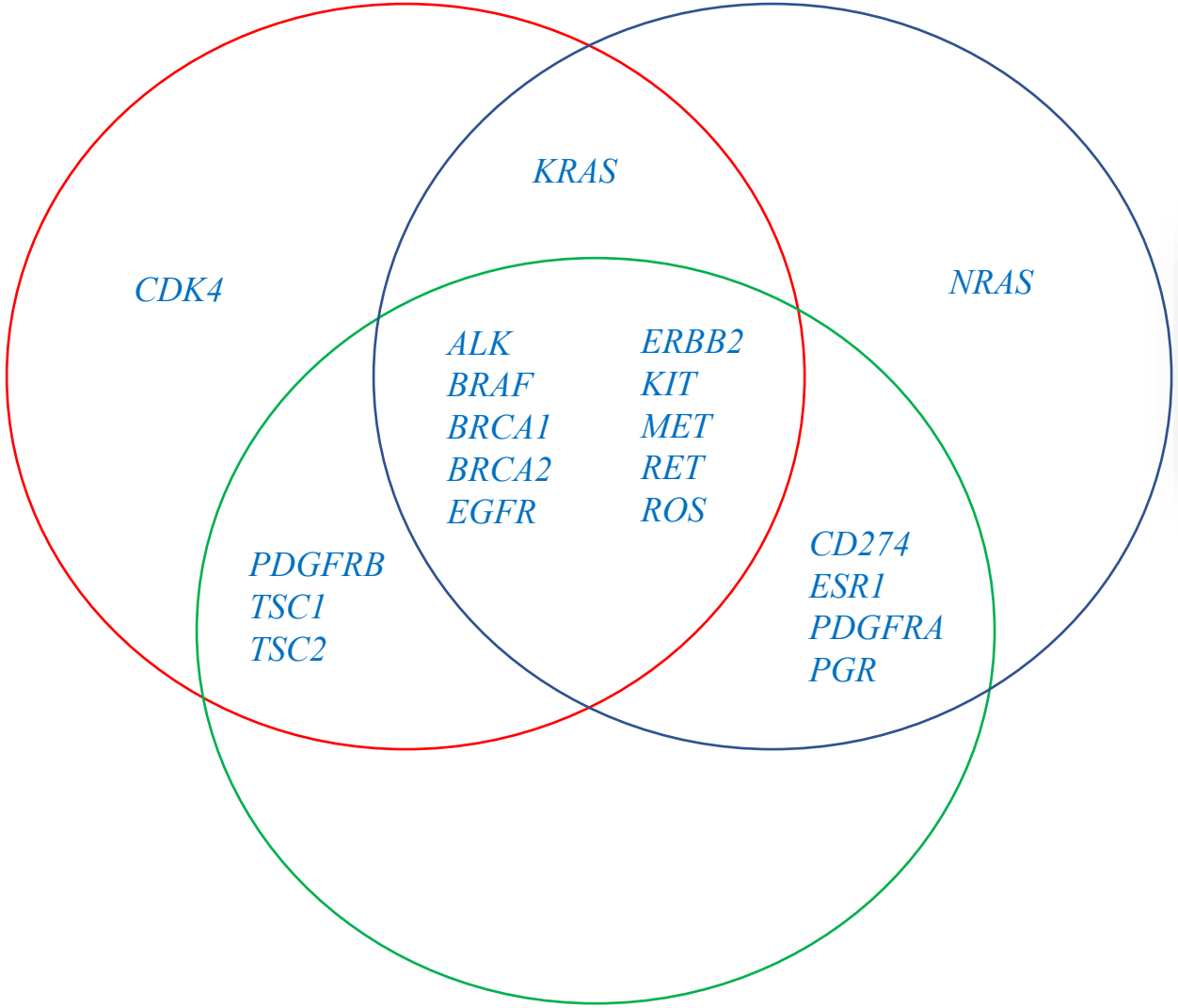
TABLE 2. Total Number of Nonsynonymous Mutations Obtained for Histological and Cytological Paired Samples per Megabases

Patient No.	Histological Sample	Cytological Sample
1	Failed	20.0
2	25.6	77.5
3	25.7	12.4
4	25.4	22.3
5	27.8	17.8
6	38.1	Failed
7	Failed	Failed
8	Failed	7.25



Pepe F, et al. *Cancer Cytopathol*. 2021;129:460-467.

Variations Between Knowledge Bases: Therapeutic Assertions at Level of Biomarker



MD Anderson Cancer Center Personalized Cancer Therapy

ATLAS

HOME CHI SIAMO CONSULTA IL DATABASE

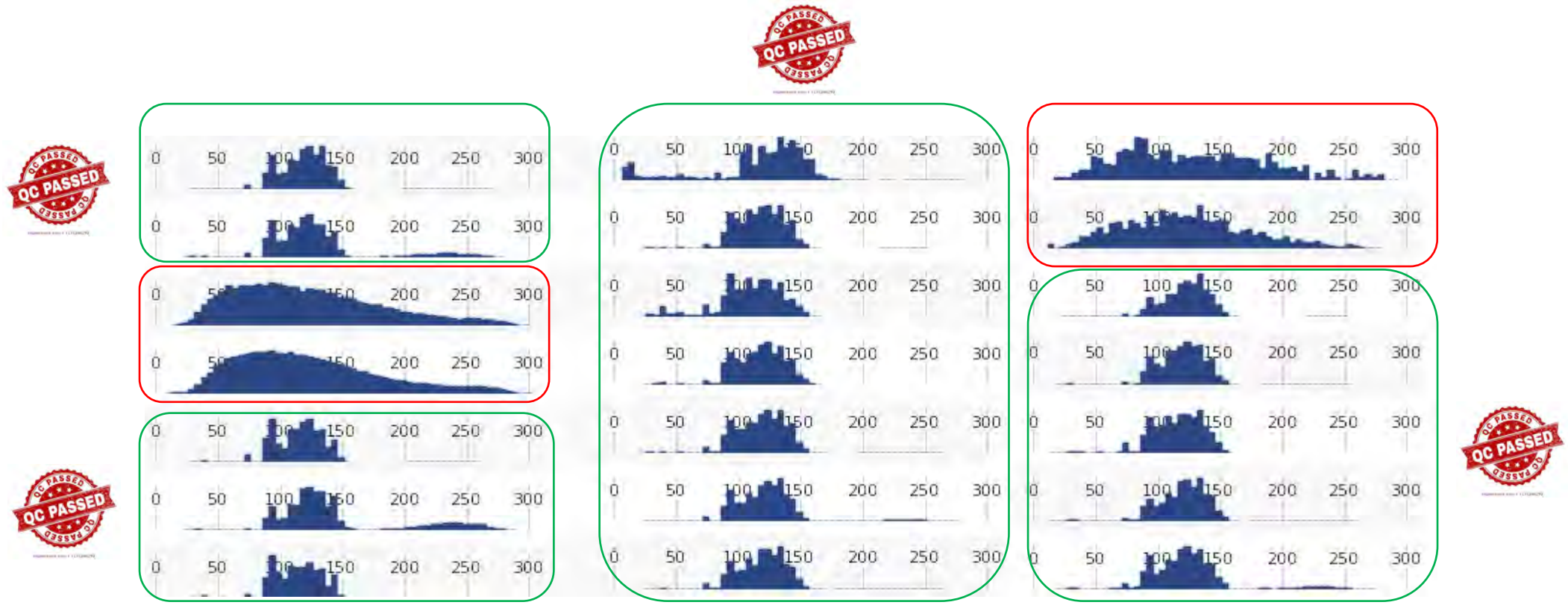
La Piattaforma Database interattiva e sempre aggiornata per lo studio, la caratterizzazione e l'interpretazione delle mutazioni a carico dei geni RAS

Un atlante relativo alle mutazioni a carico dei geni RAS che rappresenta un aiuto nel comprendere il **carattere predittivo** di ogni specifica mutazione. I contenuti sono stati sviluppati e curati da un **gruppo di esperti di oncologia e patologia molecolare predittiva.**

Malapelle U, et al. *Eur J Cancer.* 2021;146:74-83.

Malapelle U, et al. *Crit Rev Oncol Hematol*. 2021;160:103300.

Read Length Histogram: Resections vs Biopsy



Resections

Biopsy

Data from internal archive of Predictive Molecular Pathology Laboratory at Department of Public Health, University Federico II of Naples.

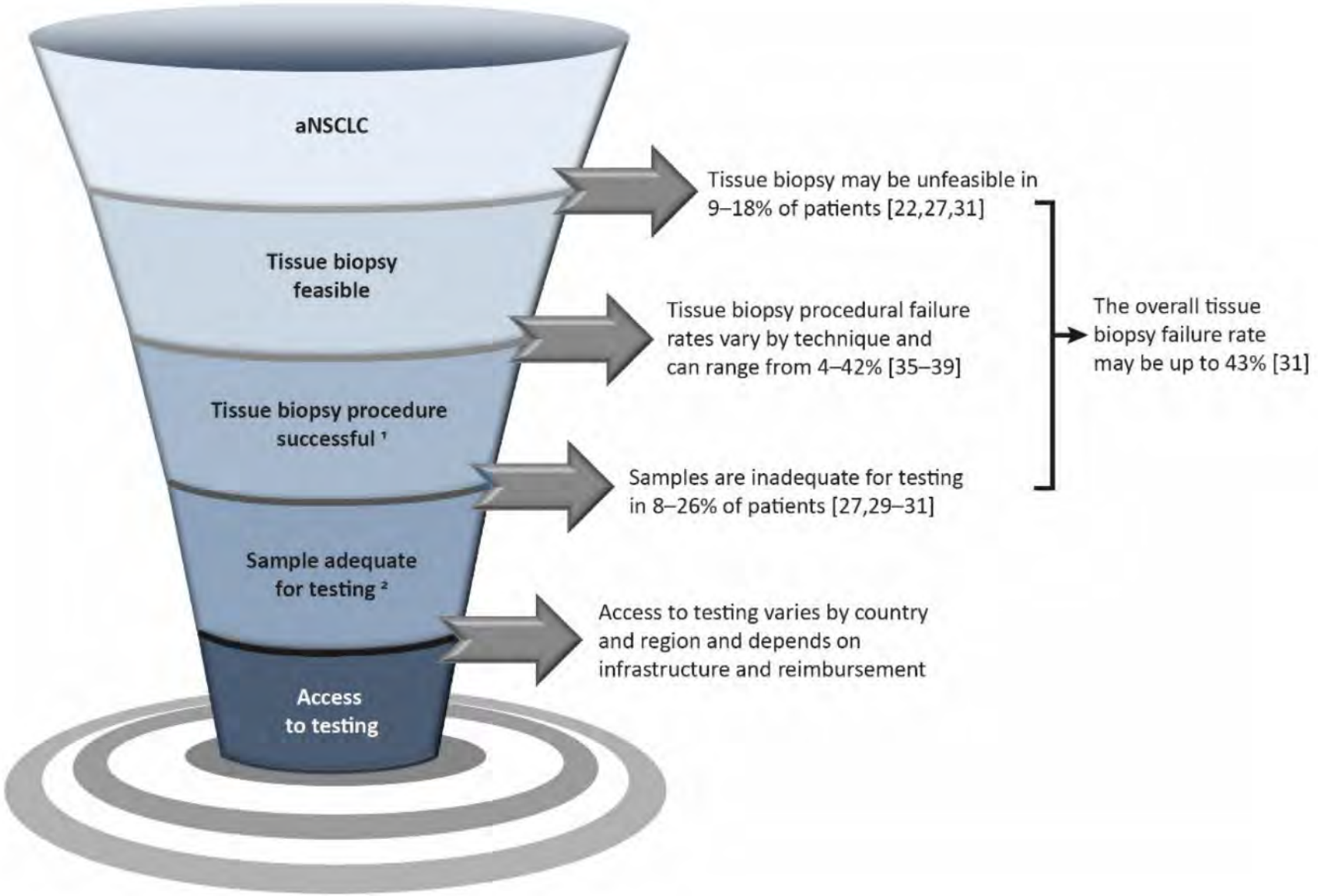
Journal of Molecular Pathology

MDPI

Review

Liquid Biopsy for Biomarker Testing in Non-Small Cell Lung Cancer: A European Perspective

Umberto Malapelle [1], Marcello Tiseo [2], Ana Vivancos [3], Joshua Kapp [4], M. Josè Serrano and Markus Tiemann [8,*]



Journal of Molecular Pathology

MDPI

Review

Liquid Biopsy for Biomarker Testing in Non-Small Cell Lung Cancer: A European Perspective

Umberto Malapelle [1], Marcello Tiseo [2], Ana Vivancos [3], Joshua Kapp [4], M. Josè Serrano [5,6,7] and Markus Tiemann [8,*]

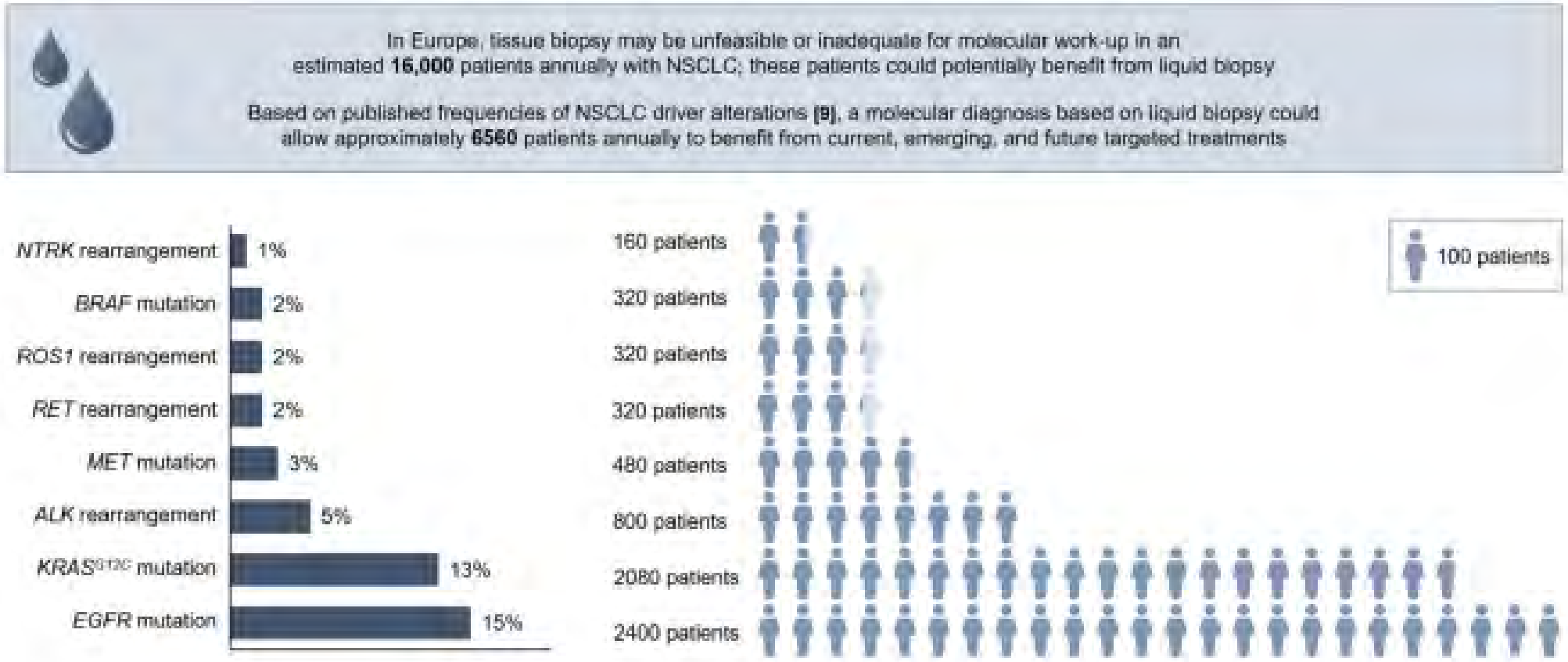
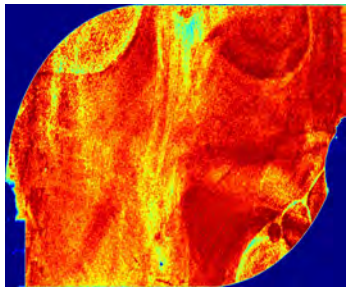


Figure 3. Estimated number of patients in Europe who could potentially benefit from liquid biopsy. Abbreviations: *ALK*, anaplastic lymphoma kinase; *BRAF*, B-Raf proto-oncogene; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *MET*, hepatocyte growth factor receptor; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; *RET*, rearranged during transfection; *ROS1*, ROS proto-oncogene 1.

Example of techniques



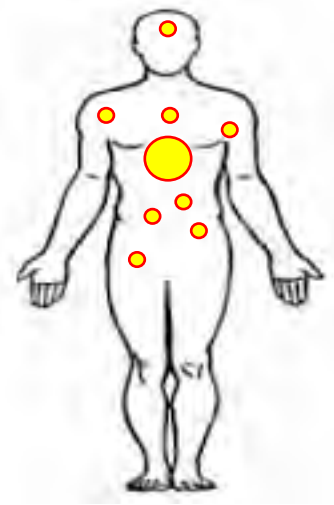
LOD (%)

5
2
1
0.1
0.01

t1
t2
t (day)

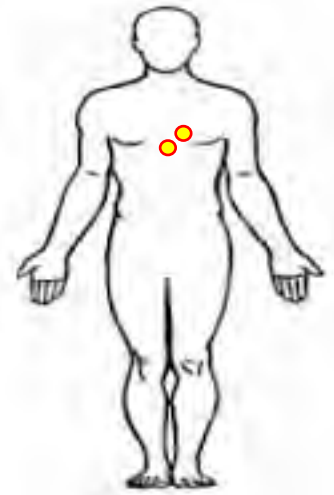
Tumor burden

High



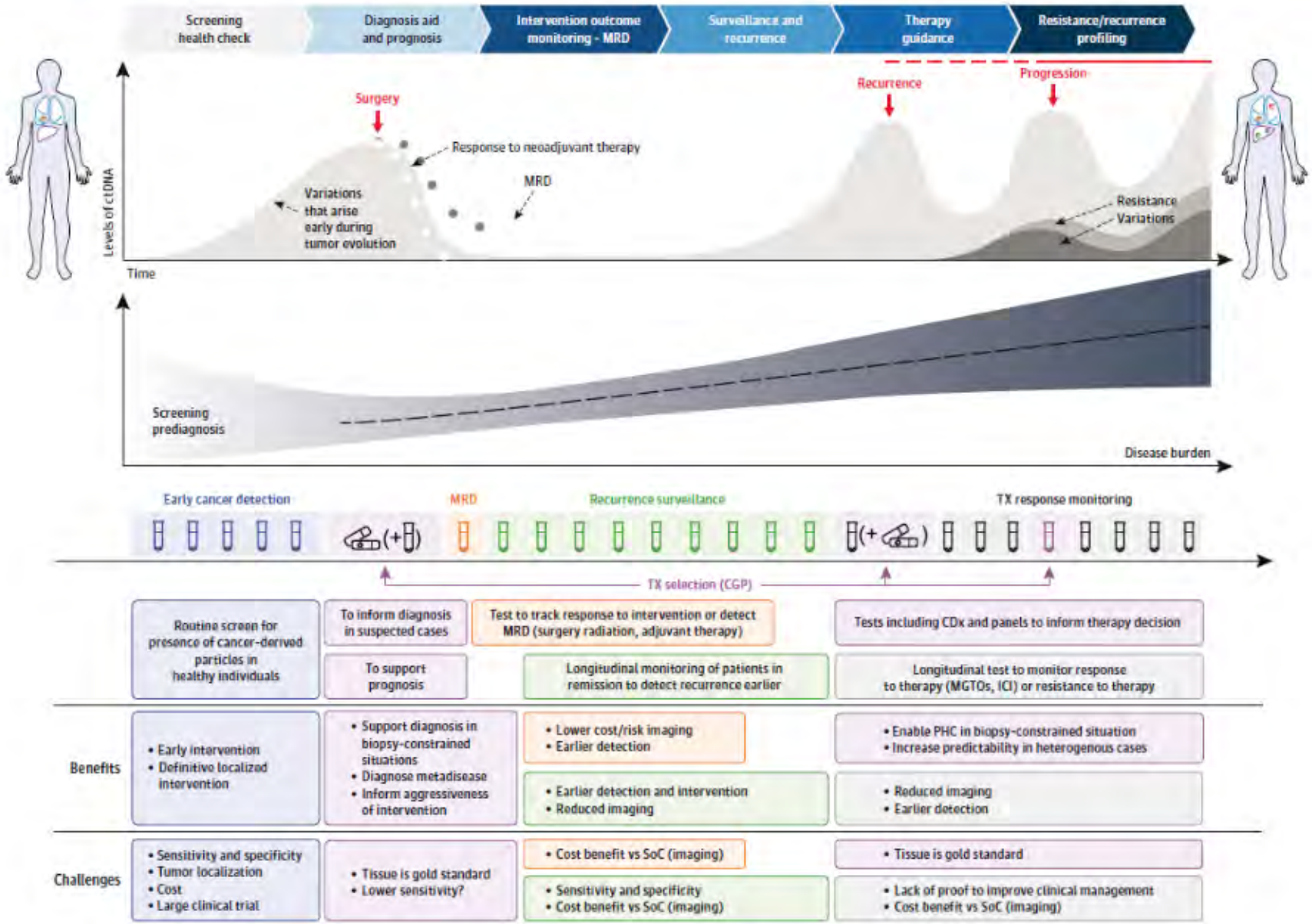
Oligo – progression

Low



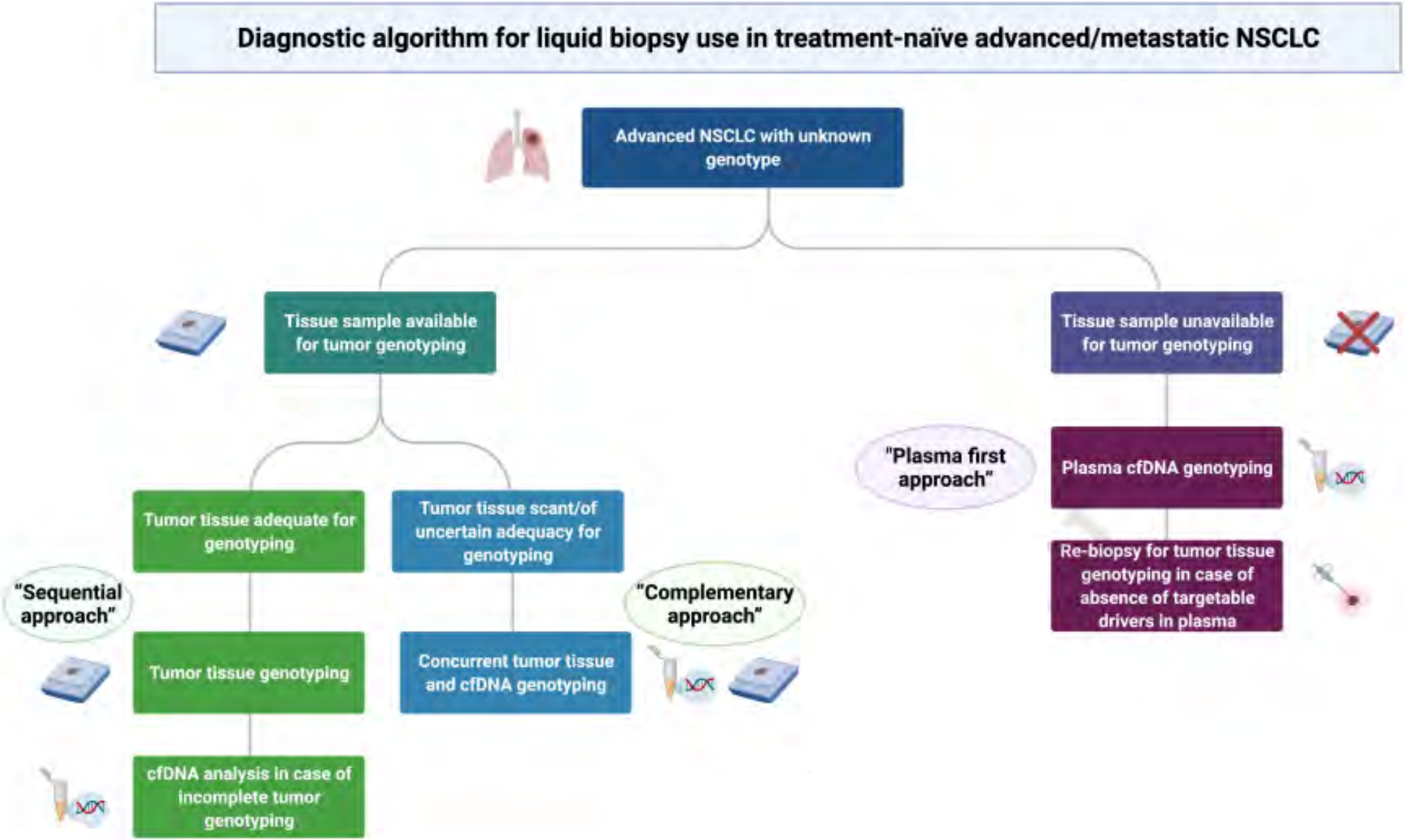
Malapelle U, et al. *Expert Rev Mol Diagn*. 2017;17:209-215.

Figure 1. The Patient Journey Through Oncology Treatment



Abbreviations: CGP, comprehensive genomic profiling; ctDNA, circulating tumor DNA; ICI, immune checkpoint inhibitor; MGTOs, molecularly guided treatment options; MRD, minimal residual disease; PHC, personalized health care; SoC, standard of care; TX, treatment.

Krebs MG, et al. *JAMA Oncol*. 2022;10.1001/jamaoncol.2022.4457.



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

European Journal of Cancer 171 (2022) 44–54

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Up-front cell-free DNA next generation sequencing improves target identification in UK first line advanced non-small cell lung cancer (NSCLC) patients

Wanyuan Cui [a], Charlotte Milner-Watts [a], Hazel O'Sullivan [a], Hannah Lyons [a], Anna Minchom [a], Jaishree Bhosle [a], Michael Davidson [a], Nadia Yousaf [a], Sophie Scott [b], Iris Faull [b], Marina Kushnir [b], Rebecca Nagy [b], Mary O'Brien [a,c], Sanjay Popat [a,c,d,*]

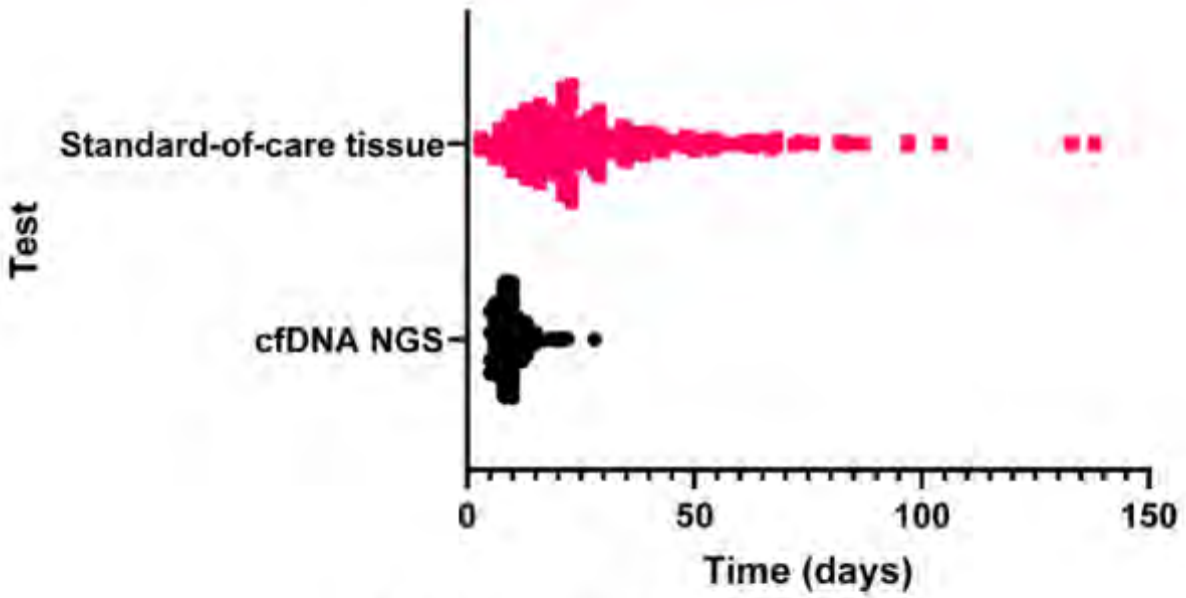


Fig. 4. Test turnaround times (n=243).

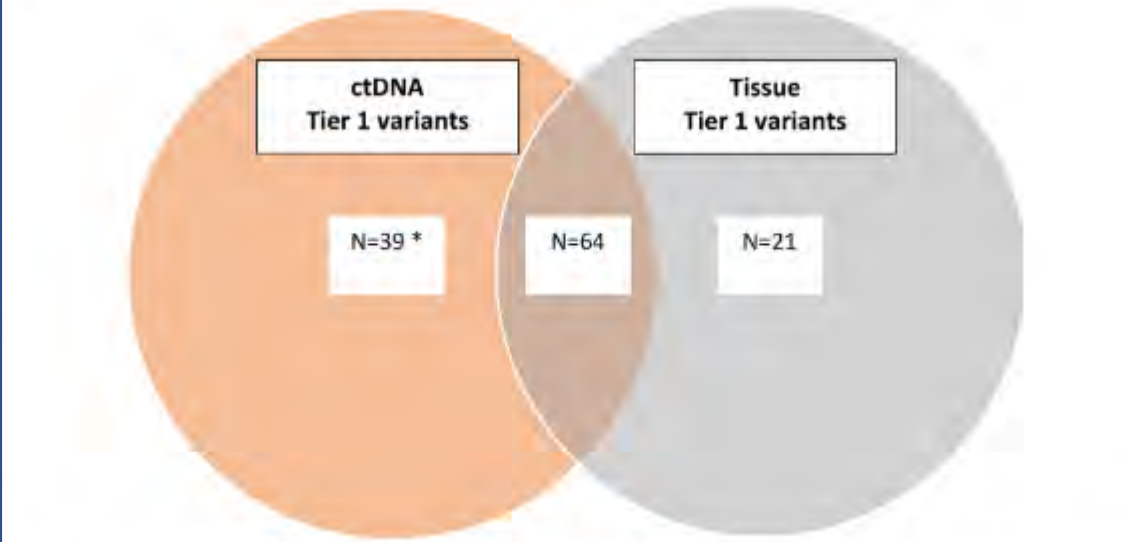
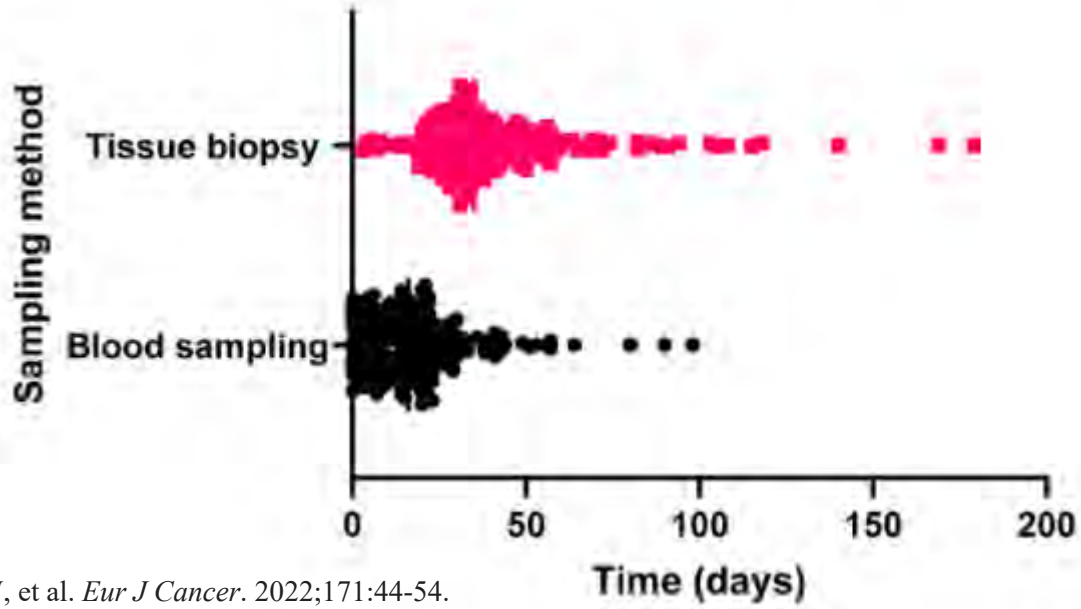
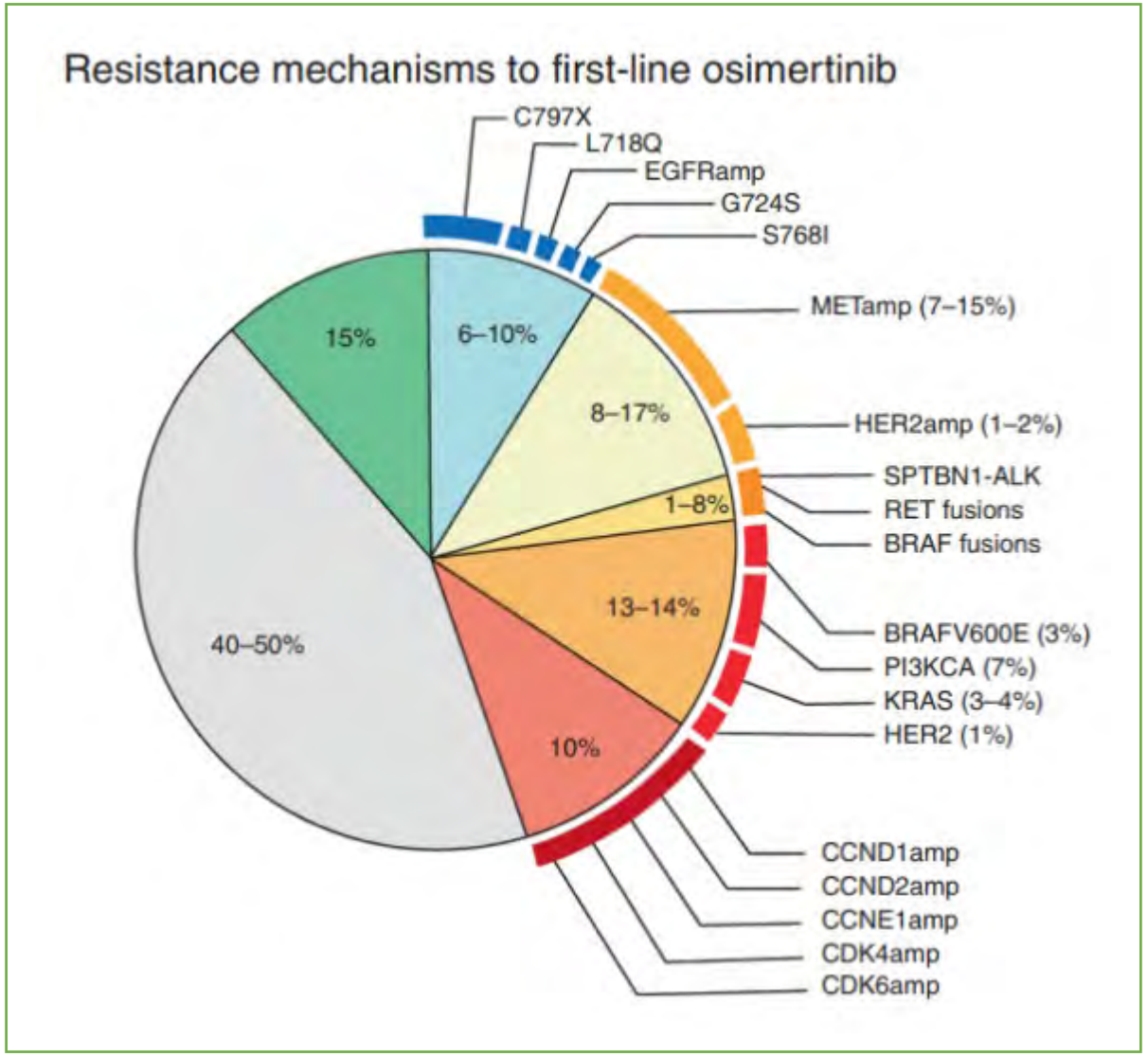


Fig. 3. **Concordance between cfDNA-NGS and all (standard-of-care and non-standard additional) tissue molecular tests in treatment-naïve patients with paired cfDNA and tissue tests.** * Seventeen of the 39 additional variants detected by cfDNA-NGS alone were actionable (*KRAS* G12C [n = 9], *MET* exon 14 skipping [n = 3], *ERBB2* exon 20 insertion [n = 2], *EGFR* exon 20 insertion [n = 2], *EGFR* exon 18 deletion [n = 1]); 22 were not actionable (*KRAS* non-G12C [n = 19], *ERBB2* amplification [n = 2], *MET* amplification [n = 1]).



Cui W, et al. *Eur J Cancer*. 2022;171:44-54.



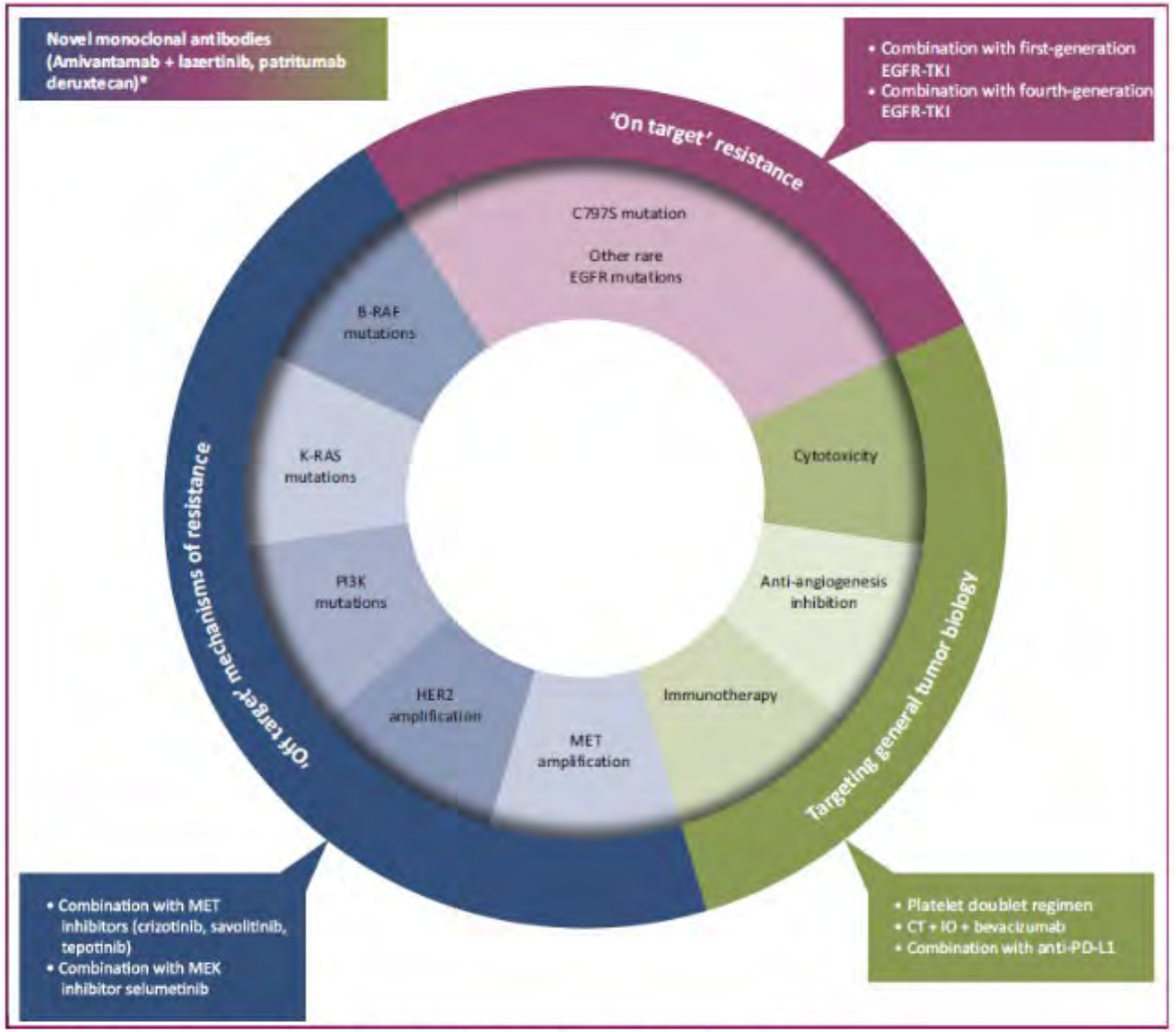
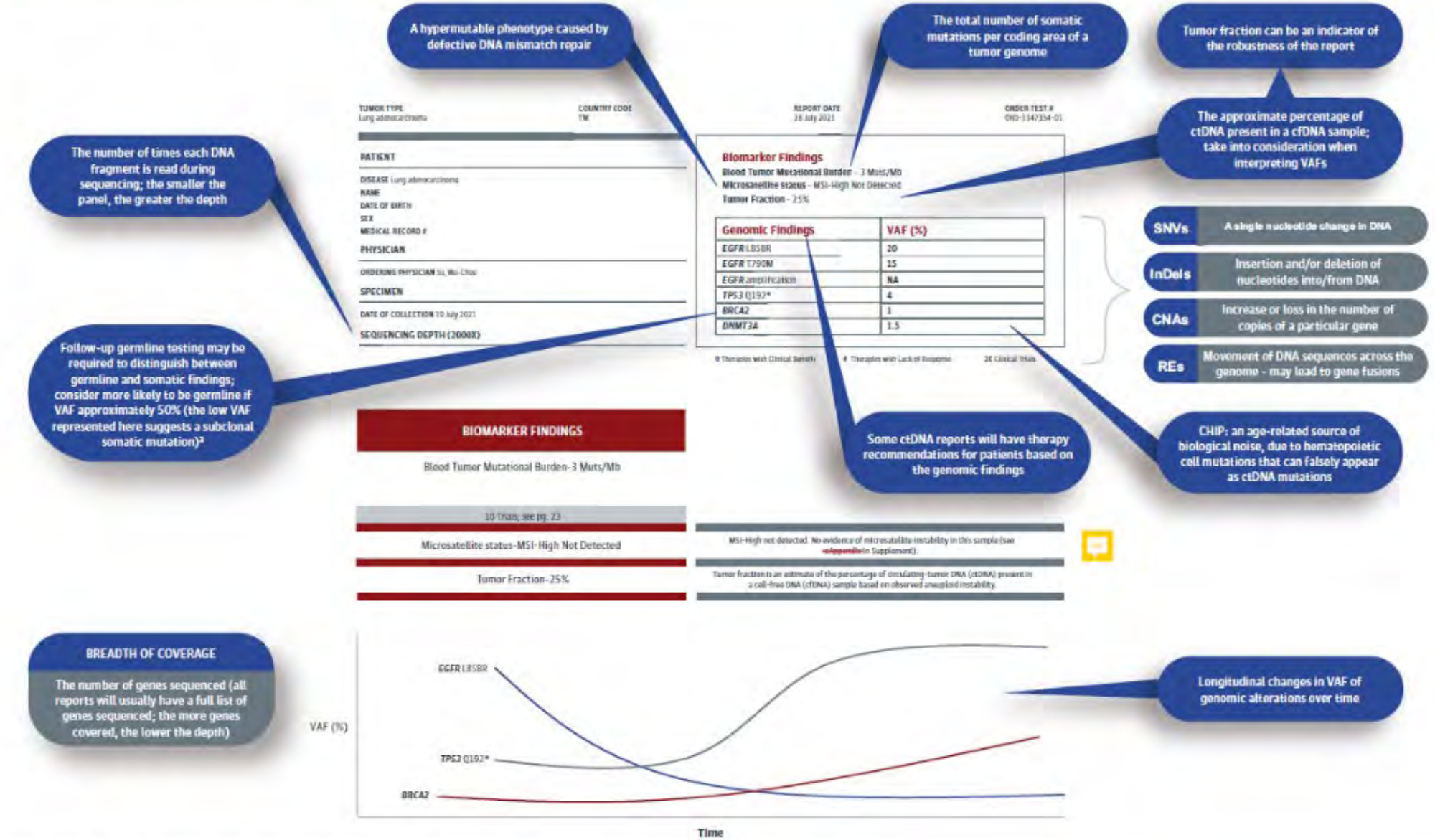


Figure 1. **Mechanisms of resistance to osimetinib and potential strategies of treatments to overcome resistance.**
CT, chemotherapy; IO, immunotherapy.
*Activity demonstrated across resistance mechanisms.

Leonetti A, et al. *Br J Cancer.* 2019; 121:725-737; Di Noia V, et al. *ESMO Open.* 2021;6:100280.

Figure 2. A Sample ctDNA Report With Its Key Elements



Abbreviations: cfDNA, cell-free DNA; CHIP, clonal hematopoiesis of indeterminate potential; CNA, copy number amplifications; ctDNA, circulating tumor DNA; InDels, insertions and deletions; Muts/Mb, mutations per megabase; RE, rearrangement; SNV, single nucleotide variants; VAF, variant allele frequency.

[a] Expert opinion, not formal recommendation.

Krebs MG, et al. *JAMA Oncol*. 2022;10.1001/jamaoncol.2022.4457.

Meeting Abstract | 2019 ASCO Annual Meeting I

LUNG CANCER—NON-SMALL CELL METASTATIC

SAVANNAH: A Phase II trial of osimertinib plus savolitinib for patients (pts) with *EGFR*-mutant, *MET*-driven (*MET*+), locally advanced or metastatic non-small cell lung cancer (NSCLC), following disease progression on osimertinib.

Check for updates

Geoffrey R. Oxnard, Mireille Cantarini, Paul Frewer, George Hawkins, Jane Peters, Paul Howarth, Ghada F. Ahmed, Tarjinder Sahota, Ryan Hartmaier, Xiaocheng Li-Sucholeiki, Myung-Ju Ahn

Dana-Farber Cancer Institute, Boston, MA; AstraZeneca, Cambridge, United Kingdom; Quantitative Clinical Pharmacology, Early Clinical Development, IMED Biotech Unit, AstraZeneca, Cambridge, United Kingdom; AstraZeneca, Waltham, MA; Samsung Medical Center, Seoul, South Korea

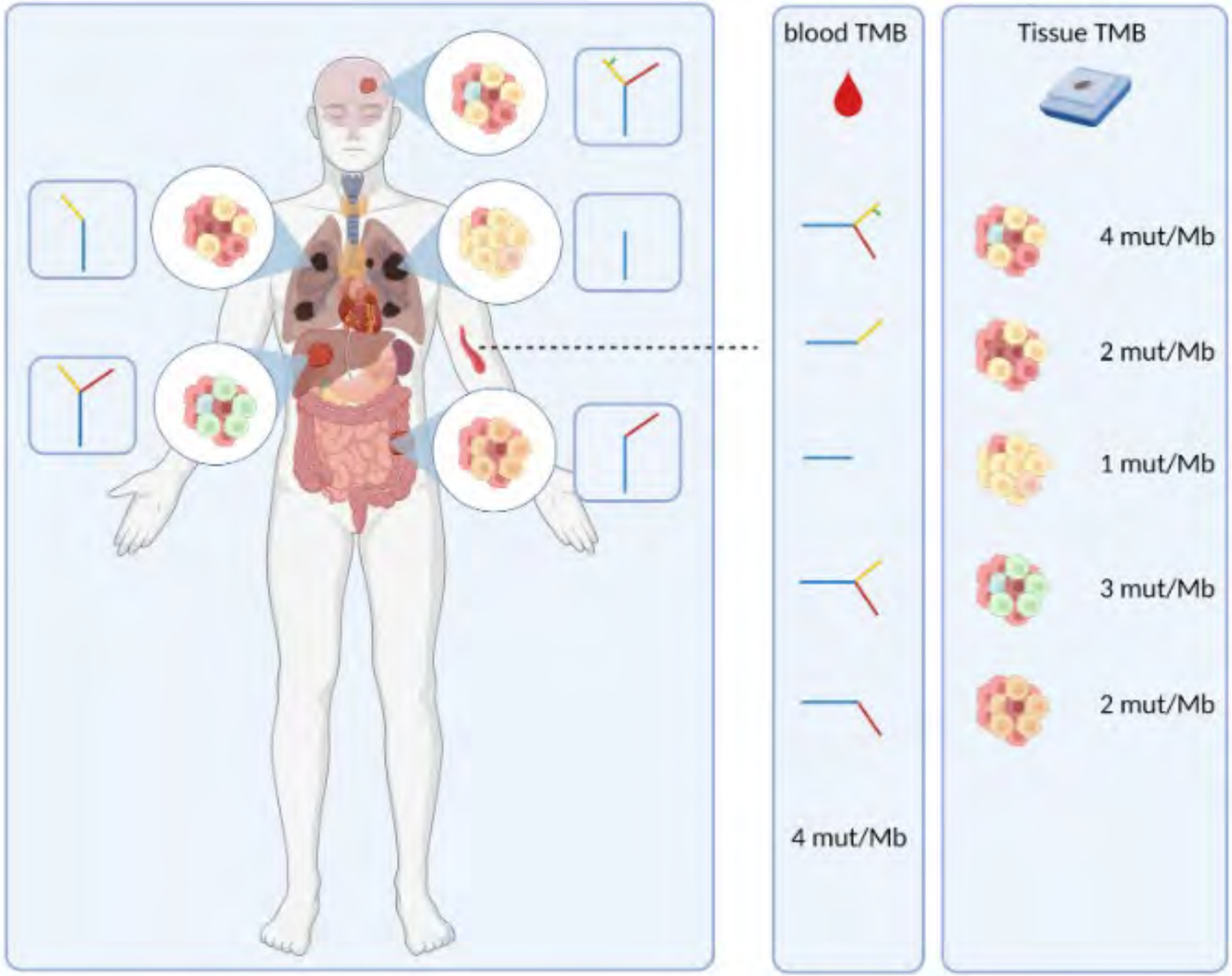
"Eligible patients will have histologically/cytologically confirmed *EGFR*-mutant NSCLC, and *MET*+ disease by central FISH, central IHC, or local NGS (retrospectively confirmed by central FISH/IHC)."

"Combination with a MET inhibitor is an intuitive approach as *MET* amplification was identified as the most common mechanism of resistance to osimertinib in preliminary ctDNA data from the phase III FLAURA (15% of pts) and AURA3 (19% of pts) studies."

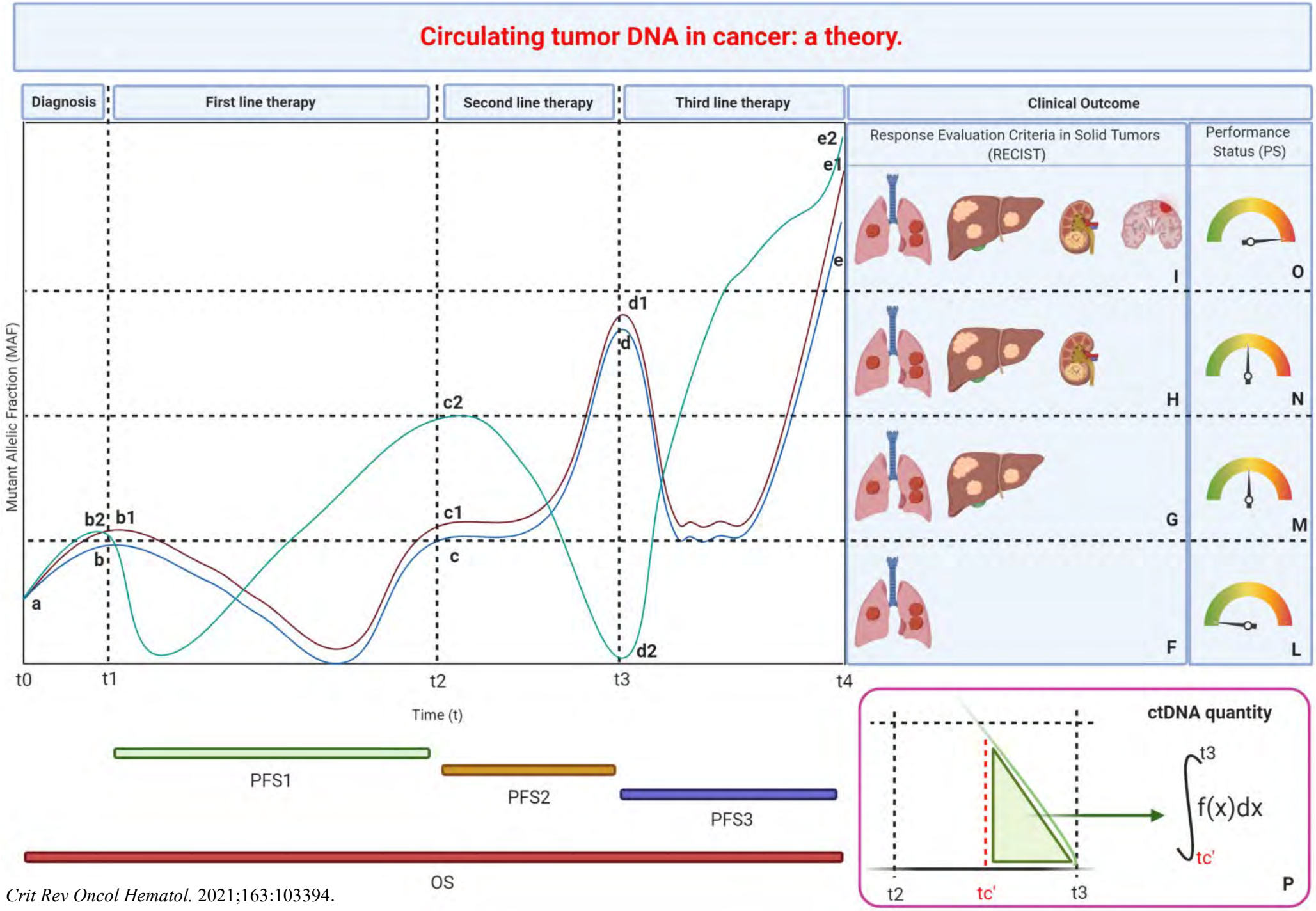
Considering SAVANNAH results

- *MET* amplification, identified by FISH, remains the optimal biomarker to identify suitable candidates for MET TKI therapy
- The prevalence of *MET* overexpression and/or amplification in patients centrally tested for enrolment to SAVANNAH was 34% using the high cutoffs
- High *MET* levels, as detected by IHC and FISH, seem to predict efficacy to osimertinib + savolitinib using SAVANNAH data

Oxnard GR, et al. ASCO 2019. Abstract TPS9119.

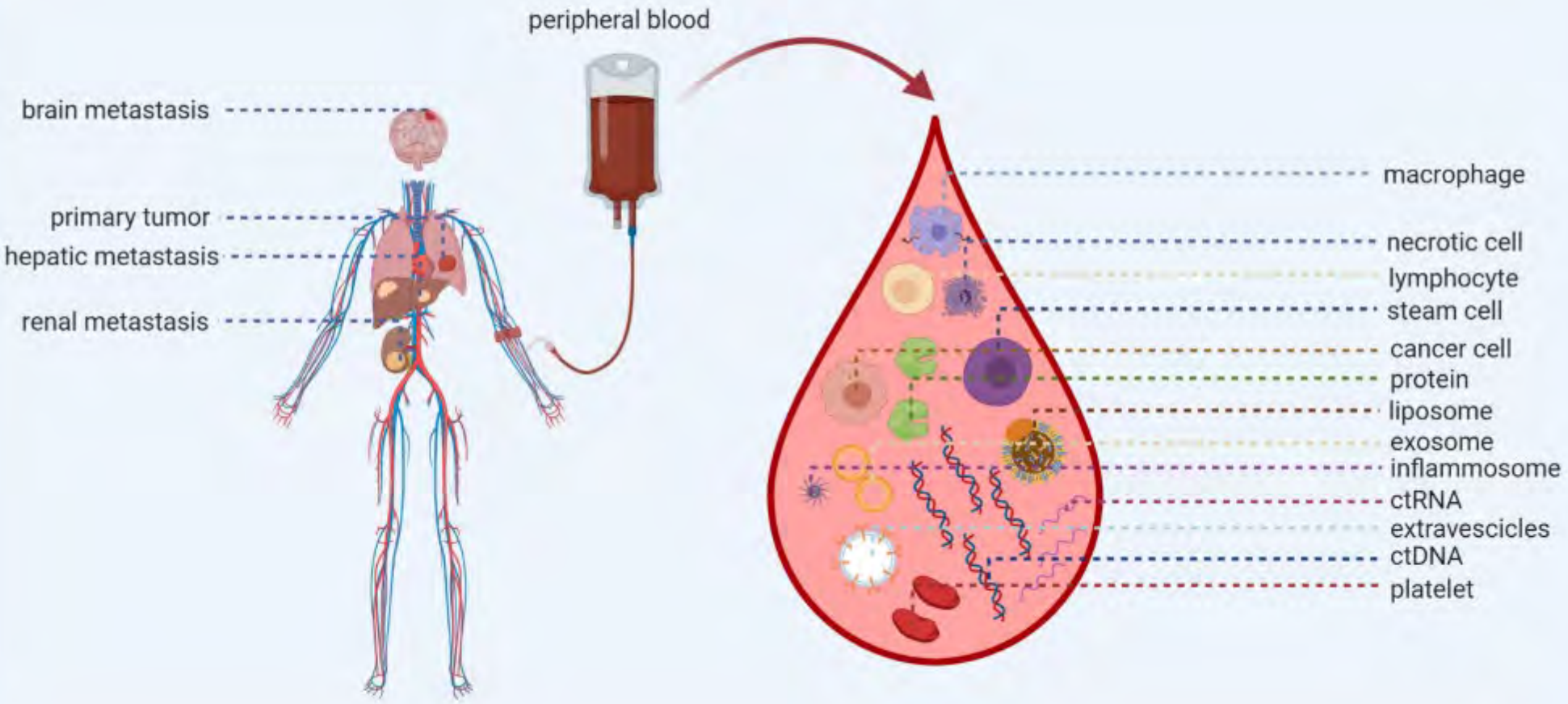


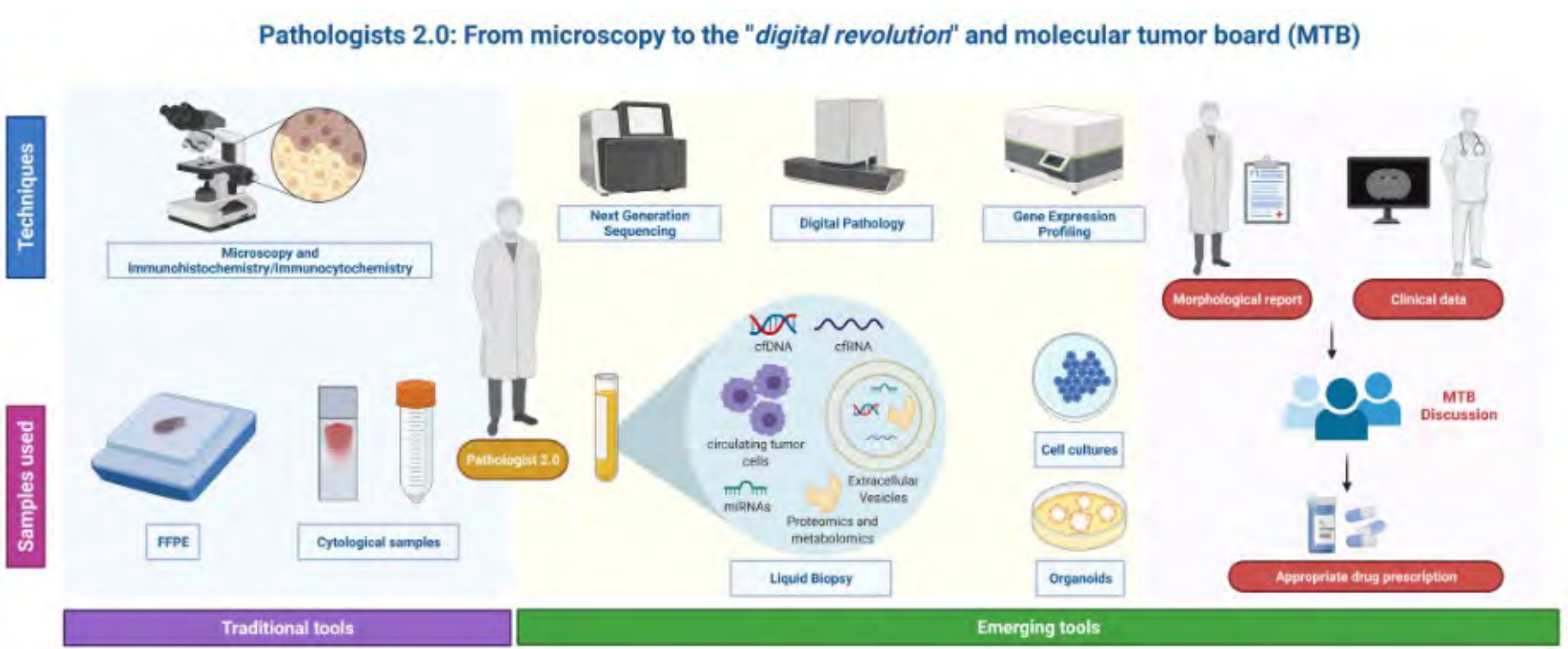
Malapelle U, et al. *Lung Cancer.* 2022;172:53-64.



Malapelle U, et al. *Crit Rev Oncol Hematol.* 2021;163:103394.

The "cancer world" in a drop





Pisapia P, et al. *Crit Rev Oncol Hematol.* 2022; 178:103776.

Grazie

ISLB
INTERNATIONAL SOCIETY
OF LIQUID BIOPSY

Global Lung Cancer Academy

Targeted Therapies for Early-Stage NSCLC – Evidence-Based Data and Perspectives

Enriqueta Felip, MD, PhD

Disclosures

- Dr Enriqueta Felip has the following relationships to disclose
  - Advisory role or speaker's bureau: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, F. Hoffman-La Roche, GlaxoSmithKline, Ipsen, Janssen, Medscape, Merck KGaA, MSD, Novartis, Peptomyc, PeerVoice, Pfizer, Regeneron, Sanofi, Seattle Genetics, Takeda, and Turning Point Therapeutics
  - Independent board member: Grifols
  - Research funding: Fundación Merck Salud, Grant for Oncology Innovation, and Merck Healthcare KGaA

Early-Stage and Locally Advanced (nonmetastatic) NSCLC: ESMO Clinical Practice Guidelines

Adjuvant ChT Recommendations

- Adjuvant ChT should be offered to patients with resected TNM 8th edition stage IIB and III NSCLC [I, A] and can be considered in patients with T2bN0, stage IIA resected primary tumor >4 cm [II, B]
- For adjuvant ChT, a 2-drug combination with cisplatin is preferable [I, A]. In randomized studies, the attempted cumulative cisplatin dose was up to 300 mg/m^2, delivered in 3–4 cycles
- When cisplatin administration is not feasible, carboplatin is an accepted alternative [IV, B]

Postoperative Radiotherapy Recommendations

- PORT in completely resected early-stage I–IIIA NSCLC is not recommended [I, E]

Postmus PE, et al. *Ann Oncol.* 2017;28(suppl_4):iv1-iv21; Remon J, et al. ESMO Clinical Practice Guidelines. 2021. https://www.esmo.org/guidelines/guidelines-by-topic/lung-and-chest-tumours/early-stage-and-locally-advanced-non-metastatic-non-small-cell-lung-cancer/eupdate-early-and-locally-advanced-non-small-cell-lung-cancer-nsclc-treatment-recommendations2 Accessed November 2, 2022.

IMPACT Study

Study design

Completely resected stage II-III NSCLC
Lobectomy or more
EGFR mutation (Ex19-del or L858R)
Without T790M
ECOG PS 0-1 Age ≧20 & <75 years
N=230

R

Gefitinib 250mg/day for 24 months
or until disease progression
or unacceptable toxicity

Cisplatin 80mg/m2 day1
plus vinorelbine 25mg/m2 day1 and 8
every 3 weeks, for 4 cycles

Stratification factors
- institute
- stage II vs. III
  - UICC TNM classification (7th version)
- gender
- age <65 or ≧65

Efficacy assessment schedules
every 6 months :
- contrast chest/abdominal CT

every 12 moths : brain MRI. PET/CT or bone scan

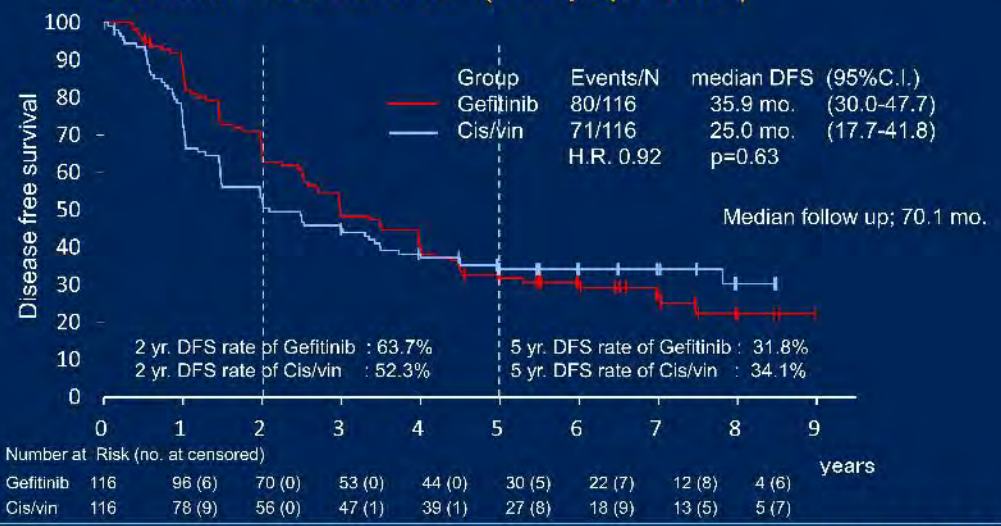
Primary endpoint :
- Disease free survival by BICRC.

Secondary endpoint
- Overall survival
- Safety and tolerability
- Relapse pattern

UMIN000006252

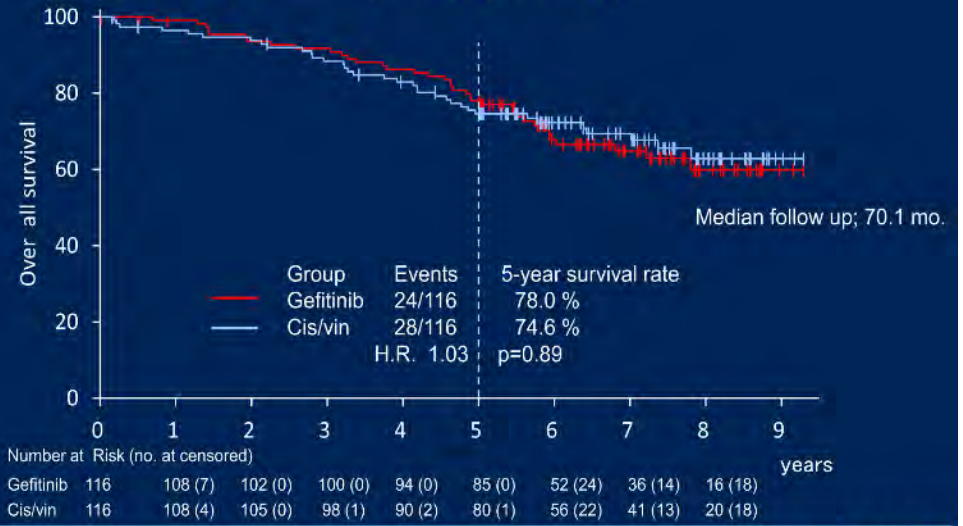
10

Disease Free Survival (ITT population)



12

Overall Survival (ITT population)



Tada H, et al. *J Clin Oncol*. 2022;40:231-241.

ADJUVANT study design (NCT01405079)

Completely resected pathological stage II-IIIA (N1-N2) NSCLC
***EGFR* activating mutation**
(exon 19 deletions or exon 21 L858R)
ECOG PS 0-1
Age ≥18 years & <75 years
n=220

Stratification factors:
- ***EGFR* mutation**
- **N stage**

Efficacy assessment:
- **Every 12 weeks in 3 years**
- **Every 6 months after 3 year**

R 1:1

Gefitinib 250 mg/day for 24 months or until disease progression or unacceptable toxicity

Vinorelbine (25 mg/m² Days 1 & 8) plus cisplatin (75 mg/m² Day 1) every 3 weeks, for up to 4 cycles

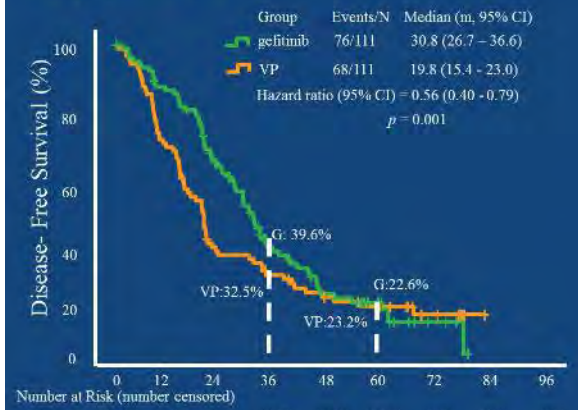
DFS

Primary endpoint:
- **DFS**

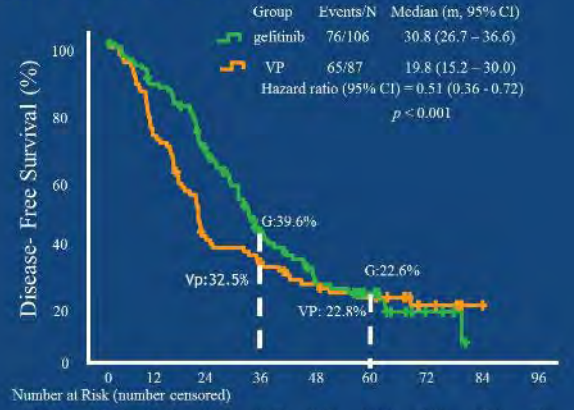
Secondary endpoints:
- **3-year DFS rate, 5-year DFS rate, OS, 5-year OS rate, safety, HRQoL (FACT-L, LCSS, TOI), exploratory biomarker analyses**

Updated 3-year & 5-year DFS rate

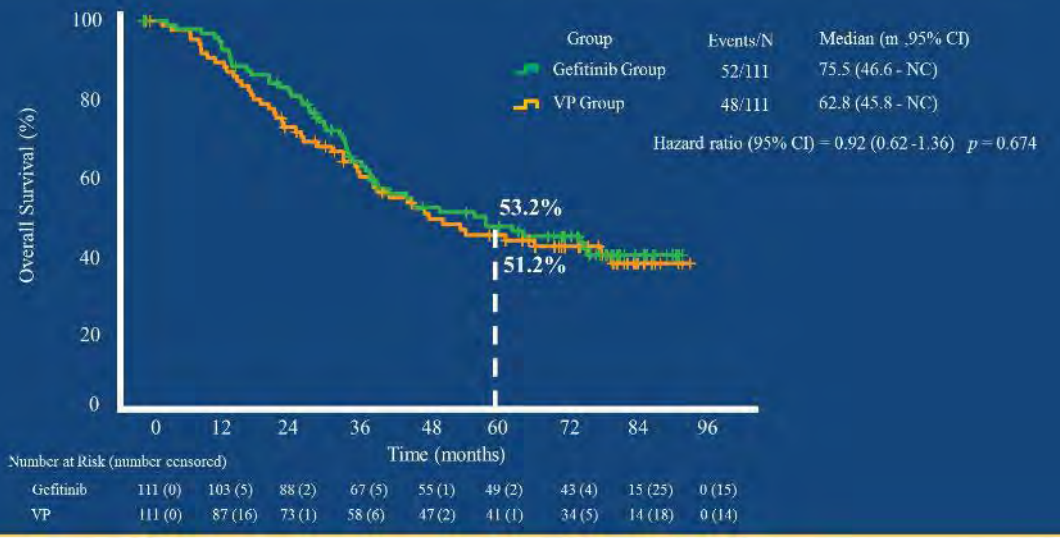
ITT population (n=222)



PP population (n=193)



Overall survival (ITT population)



Zhong WZ, et al. *J Clin Oncol*. 2021;39:713-722.

Icotinib versus chemotherapy as adjuvant treatment for stage II–IIIA EGFR-mutant NSCLC (EVIDENCE): a randomized, open-label, phase 3 study

Dr. Caicun Zhou

Shanghai Pulmonary Hospital & Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China

- Patients with completely resected stage II-IIIA NSCLC
- Primary NSCLC with *EGFR* ex19del or L858R
- Aged ≥ 18 yrs and < 70 yrs
- ECOG PS 0-1
- N=322

1:1

Icotinib 125mg TID for 2 yrs N=161

Stratified by stage (II vs. IIIA), EGFR mutation (ex19del vs. L858R), resection methods (lobectomy vs. pneumonectomy)

NP or PP for 4 cycles* N=161

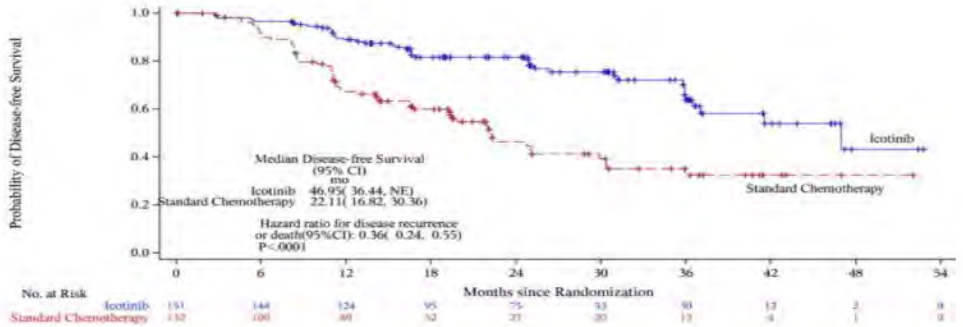
*cisplatin plus vinorelbine for adenocarcinoma or squamous carcinoma, cisplatin plus pemetrexed for non-squamous carcinoma

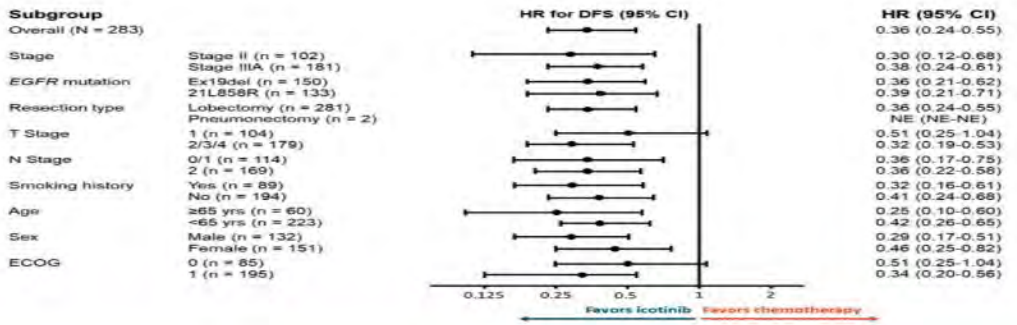
- Primary endpoint: DFS
- Secondary endpoints: DFS rates at Yrs 3, and 5; OS; safety
- Data cutoff: 31st Mar, 2020

- The sample size was determined based on a median DFS of 28 months for standard chemotherapy according to IMPACT (WJOG6410L) trial (UMIN000006252), and median DFS of 43 months for icotinib.
- To achieve 85% power at a two-sided $\alpha = 0.05$ and an anticipated dropout rate of 10%, 320 patients (with 196 events required for the analyses) were needed.
- An interim analysis was planned to perform when 98 (50%) DFS events occurred.
- The overall type I error was controlled at a two-sided α level of 0.003 and 0.049 for the interim and final analyses leveraging the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary.

EVIDENCE: DFS

- Adjuvant icotinib significantly prolonged DFS vs chemo in stage II-IIIA disease ($P < .0001$)





PHASE III ADAURA STUDY DESIGN

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

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

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

→ **Randomisation 1:1 (N=682)**
- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

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

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

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

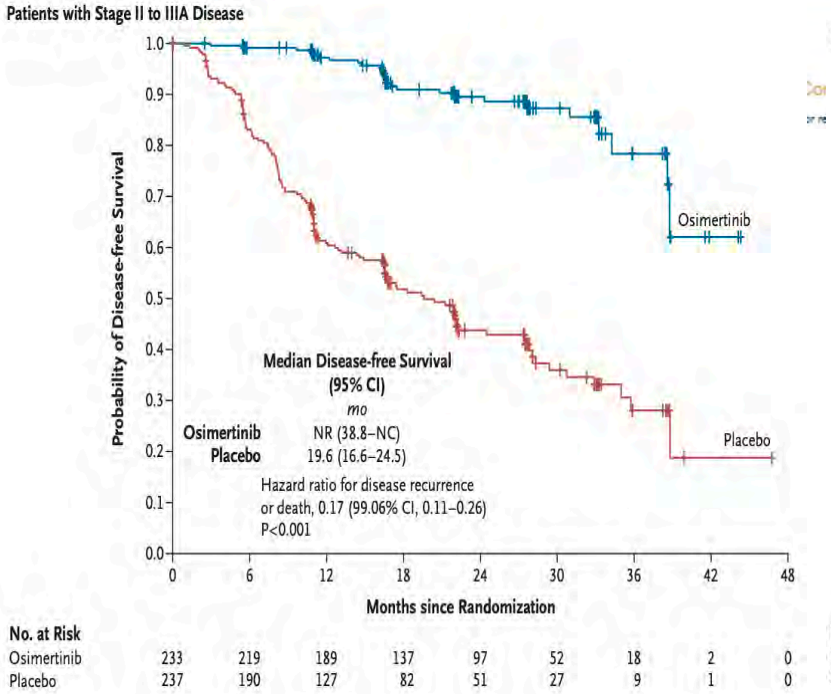
The NEW ENGLAND JOURNAL of MEDICINE

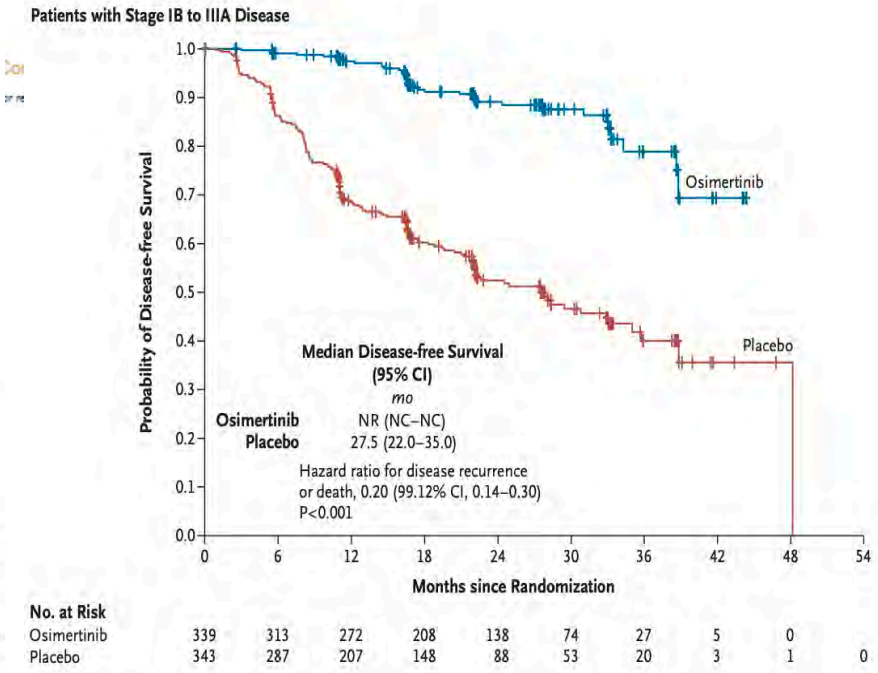
ORIGINAL ARTICLE

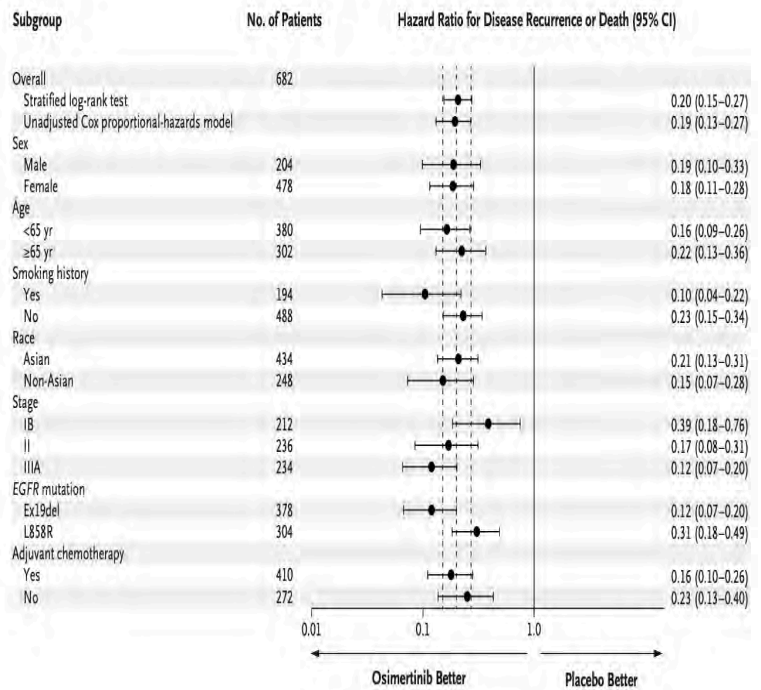
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

2020



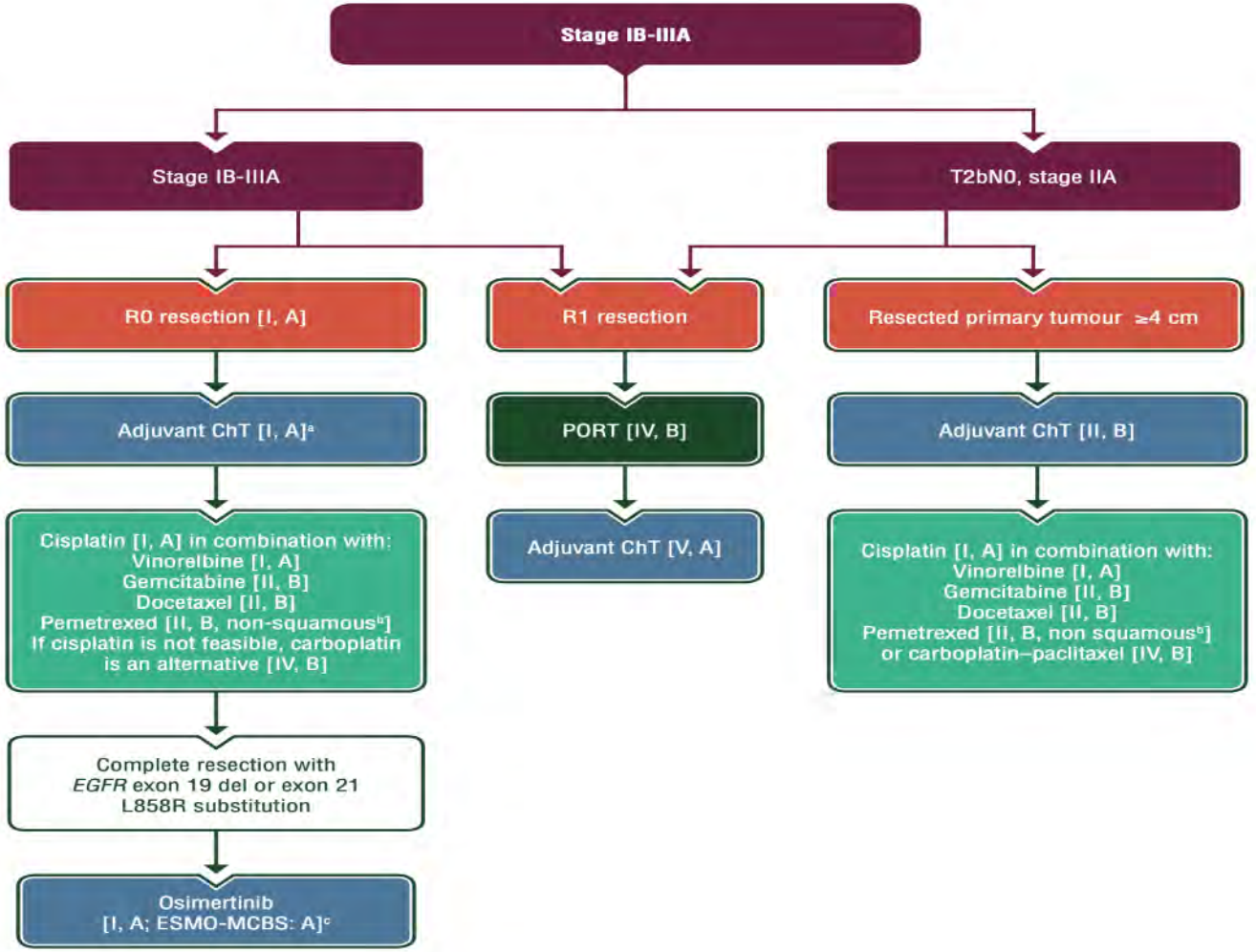




Wu YL, et al. *N Engl J Med*. 2020;383:1711-1723.

Adjuvant Treatment With Targeted Agents

- **Osimertinib is indicated for the adjuvant treatment after complete tumor resection in adult patients with stage IB–IIIA NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 *L858R* substitution mutations [I, A]**



Remon J, et al. ESMO Clinical Practice Guidelines. 2021. https://www.esmo.org/guidelines/guidelines-by-topic/lung-and-chest-tumours/early-stage-and-locally-advanced-non-metastatic-non-small-cell-lung-cancer/eupdate-early-and-locally-advanced-non-small-cell-lung-cancer-nsclc-treatment-recommendations2 Accessed November 2, 2022.

GOOD SCIENCE
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SPECIAL ARTICLE

ESMO expert consensus statements on the management of *EGFR* mutant non-small-cell lung cancer

A. Passaro[1*], N. Leighl[2†], F. Blackhall[3,4†], S. Popat[5,6,7†], K. Kerr[8†], M. J. Ahn[9], M. E. Arcila[10], O. Arrieta[11], D. Planchard[12],

2022

Early and locally advanced disease

1: What is the role of adjuvant osimertinib for common *EGFR*-mutated, stage IB-IIIA R0 resected NSCLC?

STATEMENT: To date, the use of osimertinib for 3 years, is recommended as adjuvant therapy in patients with resected, stage IB-IIIA (7th American Joint Committee on Cancer TNM edition) NSCLC harboring *EGFR* mutations.

The impressive improvement of DFS, including better CNS control, should ideally be supported by OS and/or quality of life benefit upon mature follow up [I,A].

Passaro A, et al. *Ann Oncol*. 2022;33:466-487.

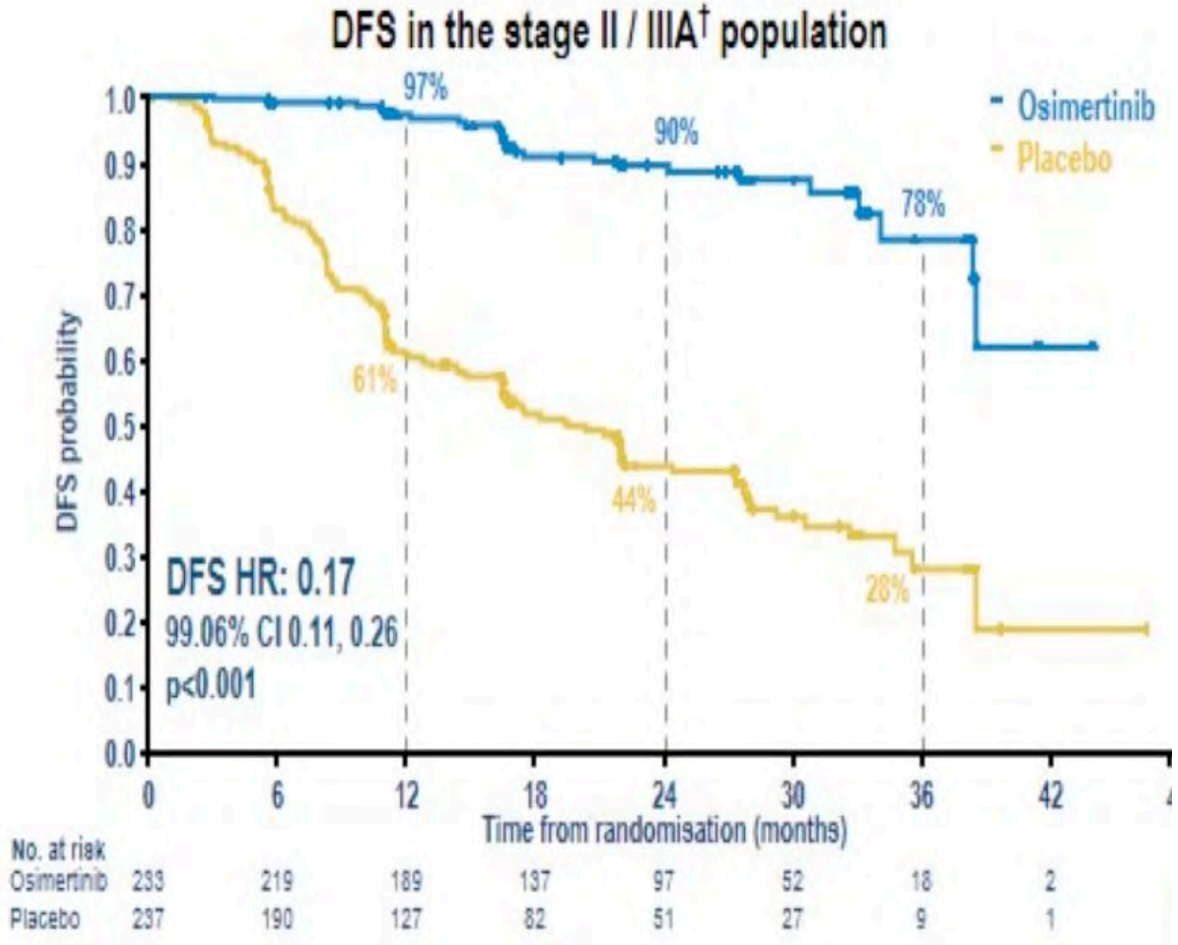
Here we will present an updated analysis of the final DFS data at the protocol-specified maturity of 50%, a pre-specified exploratory analysis of recurrence patterns and updated safety data, after 2 years of further follow up, in which all patients have had the opportunity to receive the full 3 years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

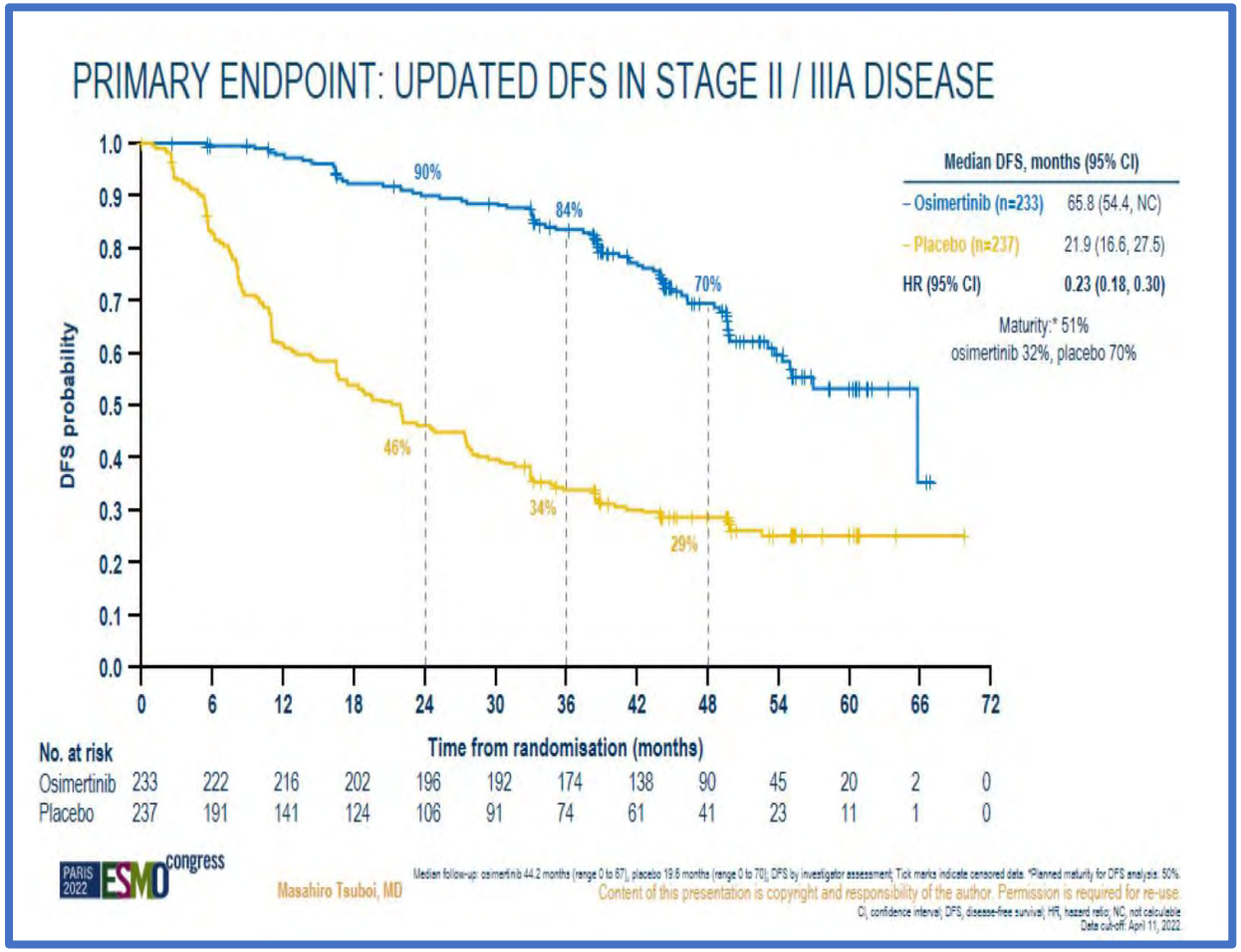
PARIS 2022 ESMO congress

Masahiro Tsuboi, MD

Tick marks indicate censored data. *Reported ~2 years earlier than planned following IDMC recommendation. †AJCC 7th edition staging.
1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38:18_suppl.LBA5.

AJCC, American Joint Committee on Cancer; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IDMC, Independent Data Monitoring Committee
Data cut-off: January 17, 2020.





Tsuboi M, et al. ESMO 2022. Abstract LBA47.

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

PARIS 2022 ESMO congress

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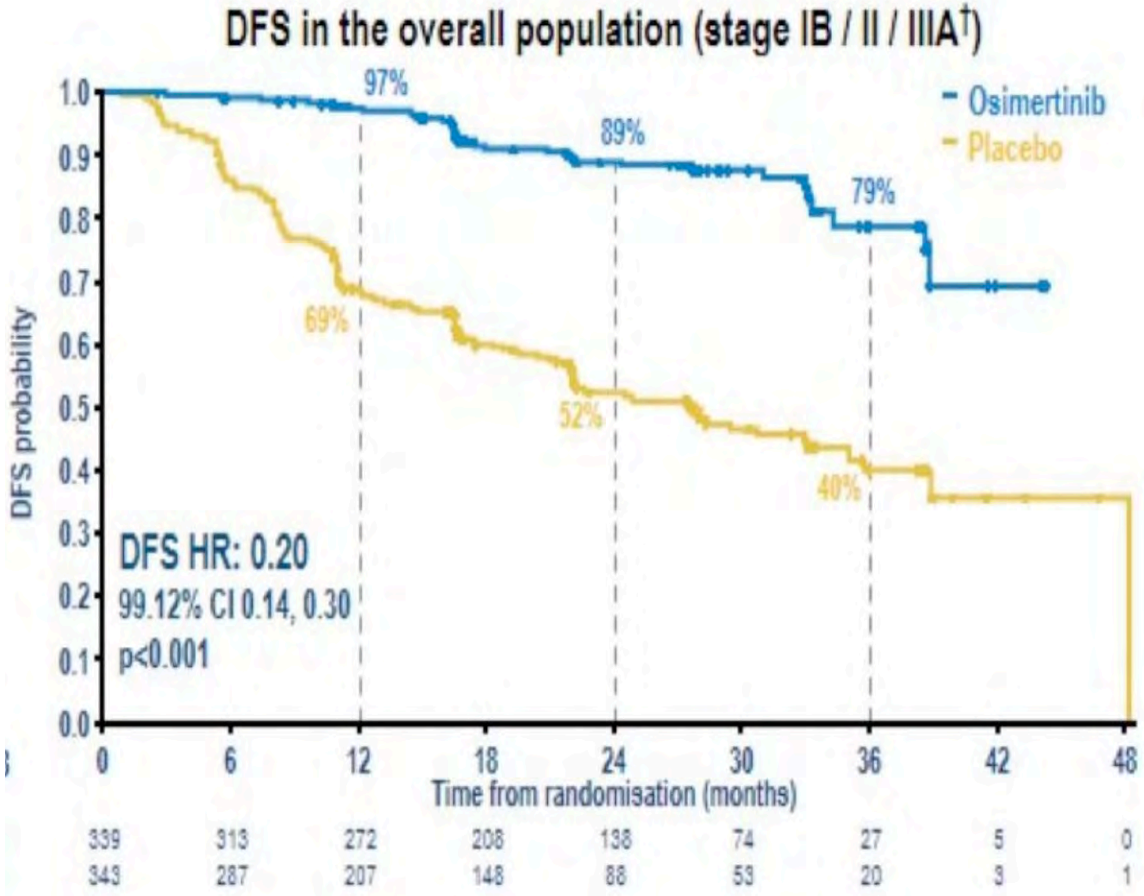
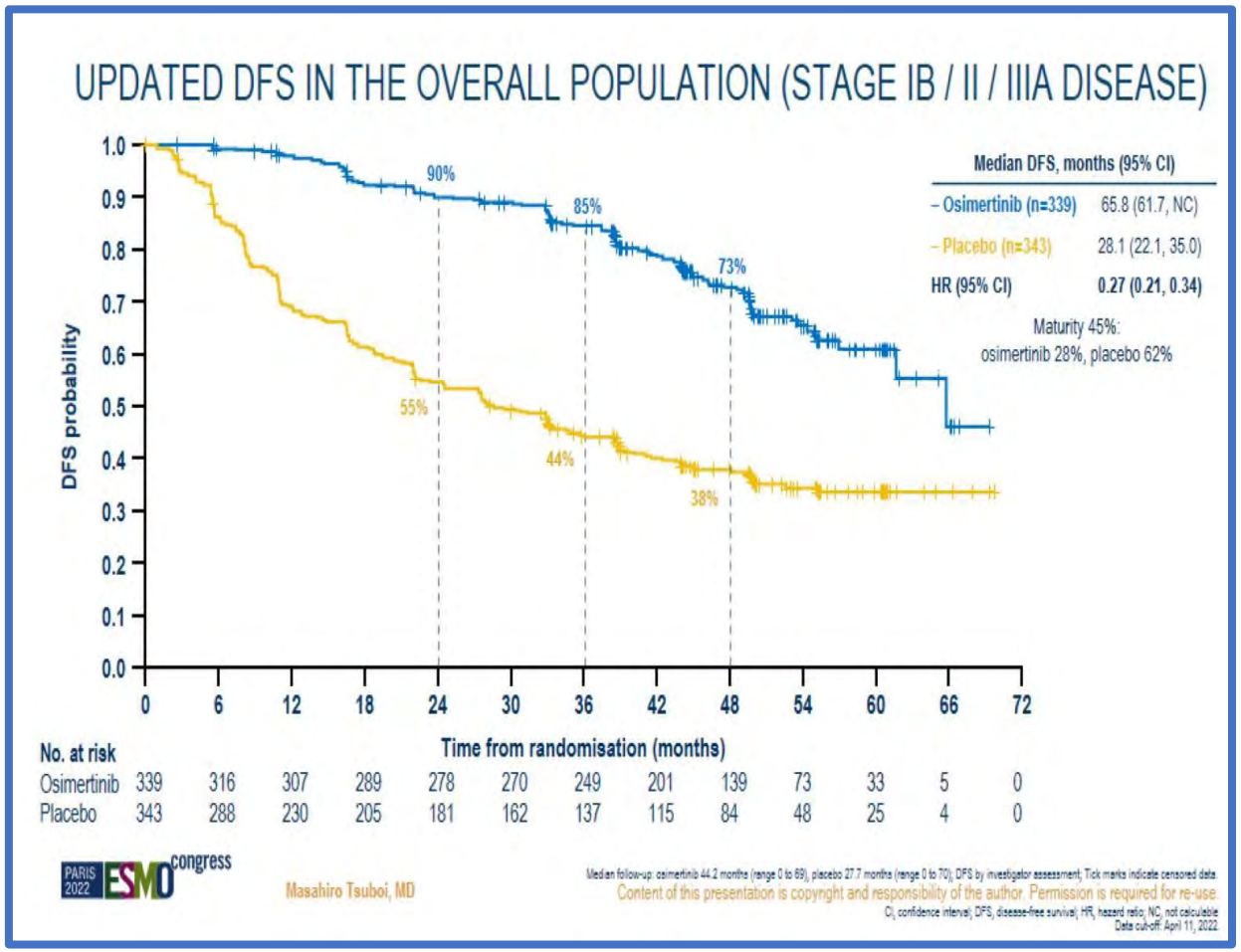
Data cut-off: January 17, 2020.



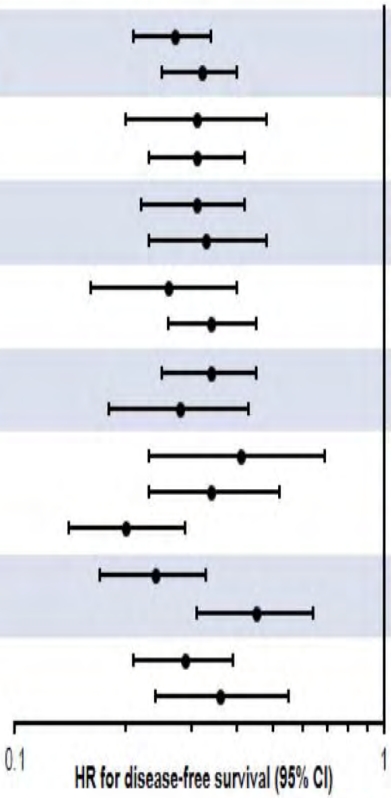


Tsuboi M, et al. ESMO 2022. Abstract LBA47.

UPDATED DFS ACROSS SUBGROUPS IN THE OVERALL POPULATION

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

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



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

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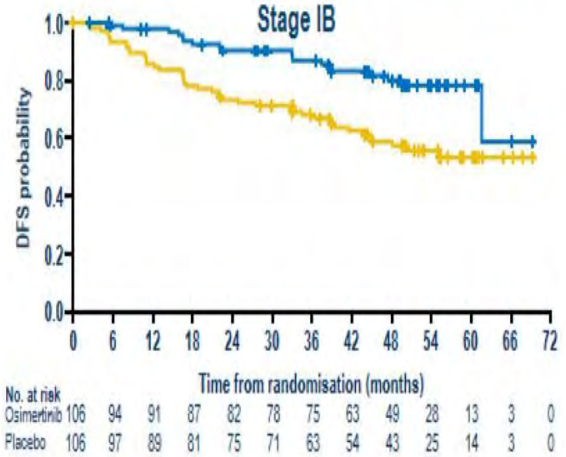
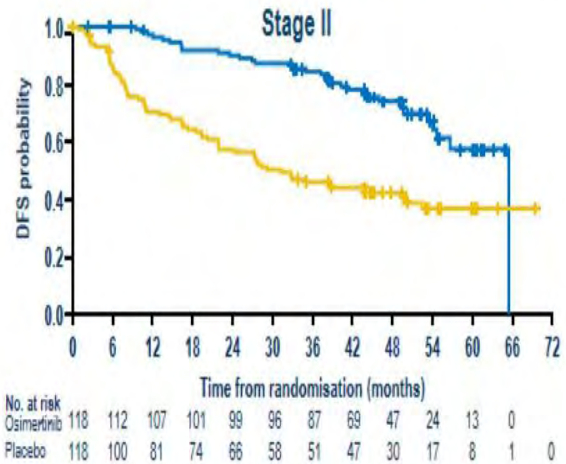
AJCC, American Joint Committee on Cancer; CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio

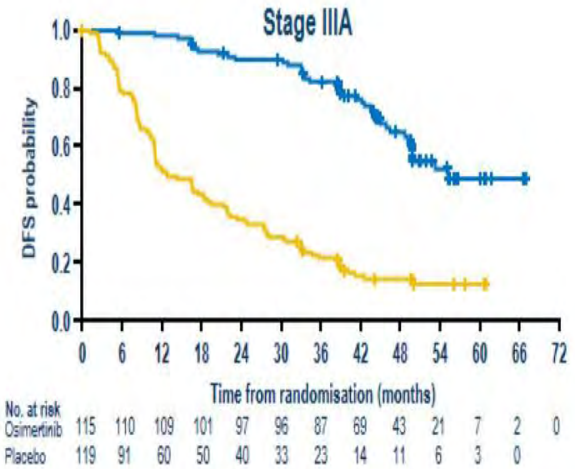
Data cut-off: April 11, 2022

UPDATED DFS BY STAGE (AJCC 7TH EDITION)





	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (70, 87)	74 (64, 82)	65 (54, 74)
– Placebo	59 (48, 68)	42 (33, 51)	14 (8, 22)
Overall HR (95% CI)	0.41 (0.23, 0.69)	0.34 (0.23, 0.52)	0.20 (0.14, 0.29)



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DFS by investigator assessment; Tick marks indicate censored data.

AJCC, American Joint Committee on Cancer; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio

Data cut-off: April 11, 2022

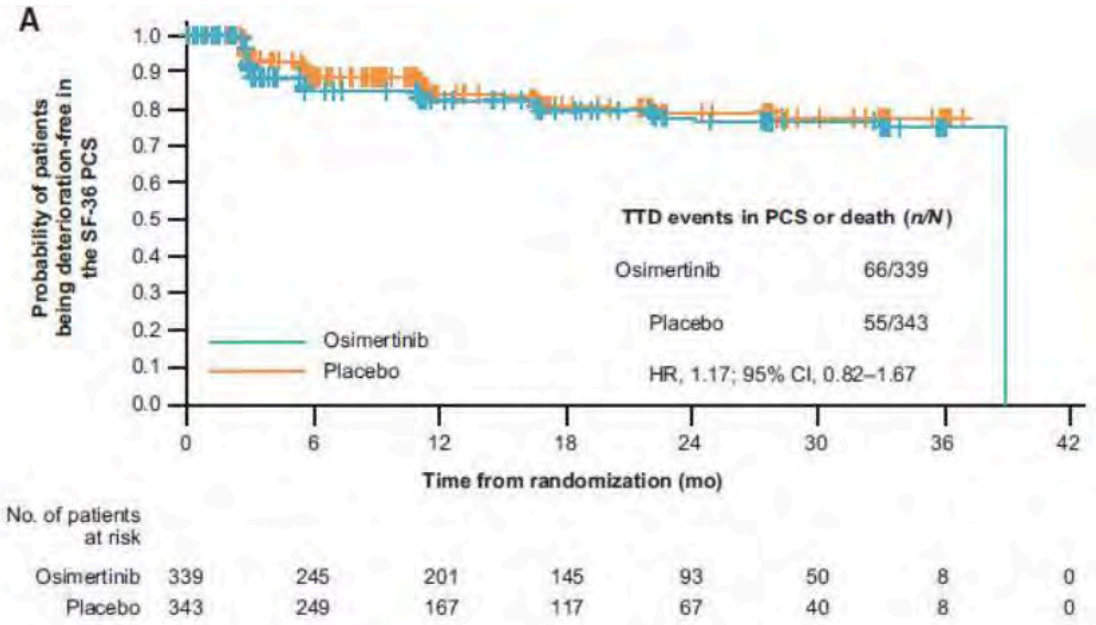
Tsuboi M, et al. ESMO 2022. Abstract LBA47.

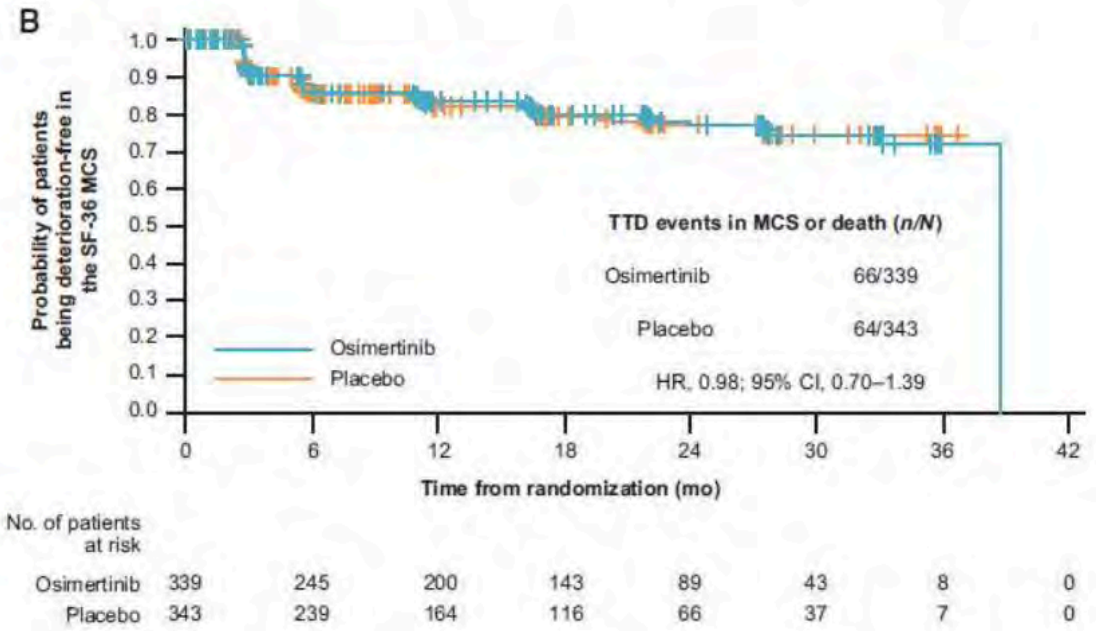
Health-Related Quality of Life Outcomes in Patients with Resected Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer Who Received Adjuvant Osimertinib in the Phase III ADAURA Trial

Margarita Majem[1], Jonathan W. Goldman[2], Thomas John[3], Christian Grohe[4], Konstantin Laktionov[5], Sang-We Kim[6], Terufumi Kato[7], Huu Vinh Vu[8], Shun Lu[9], Shanqing Li[10], Kye Young Lee[11], Charuwan Akewanlop[12], Chong-Jen Yu[13], Filippo de Marinis[14], Laura Bonanno[15], Manuel Domine[16], Frances A. Shepherd[17], Shinji Atagi[18], Lingmin Zeng[19], Dakshayini Kulkarni[20], Nenad Medic[21], Masahiro Tsuboi[22], Roy S. Herbst[23], and Yi-Long Wu[24]

Clin Cancer Res, 2022

"HRQoL was maintained with adjuvant Osimertinib in patients with stage IB–IIIA EGFRm NSCLC, who were disease-free after complete resection, with no clinically meaningful differences versus placebo, further supporting adjuvant osimertinib as a new treatment in this setting"

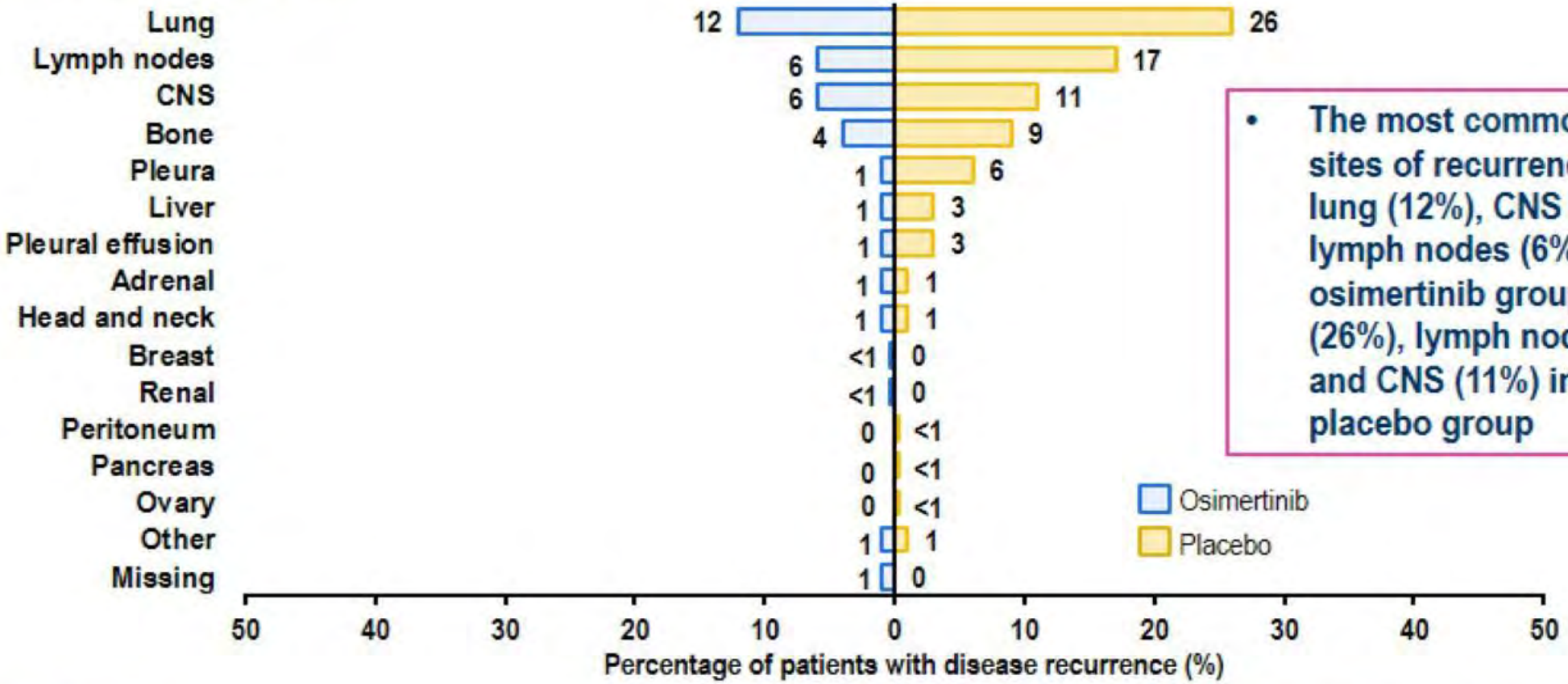




Majem M, et al. *Clin Cancer Res*. 2022;28:2286-2296.

PATTERNS OF DISEASE RECURRENCE (OVERALL POPULATION)

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



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

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

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

Tsuboi M, et al. ESMO 2022. Abstract LBA47.

SAFETY SUMMARY

AE, any cause*, n (%)	Osimertinib (n=337)	Placebo (n=343)
Any AE	330 (98)	309 (90)
Any AE Grade ≥3	79 (23)	48 (14)
Any AE leading to death	1 (<1)	2 (1)
Any serious AE	68 (20)	47 (14)
Any AE leading to discontinuation	43 (13)	9 (3)
Any AE leading to dose reduction	42 (12)	3 (1)
Any AE leading to dose interruption	91 (27)	43 (13)
AE, possibly causally related†, n (%)		
Any AE	308 (91)	199 (58)
Any AE Grade ≥3	36 (11)	7 (2)
Any AE leading to death	0	0
Any serious AE	10 (3)	2 (1)

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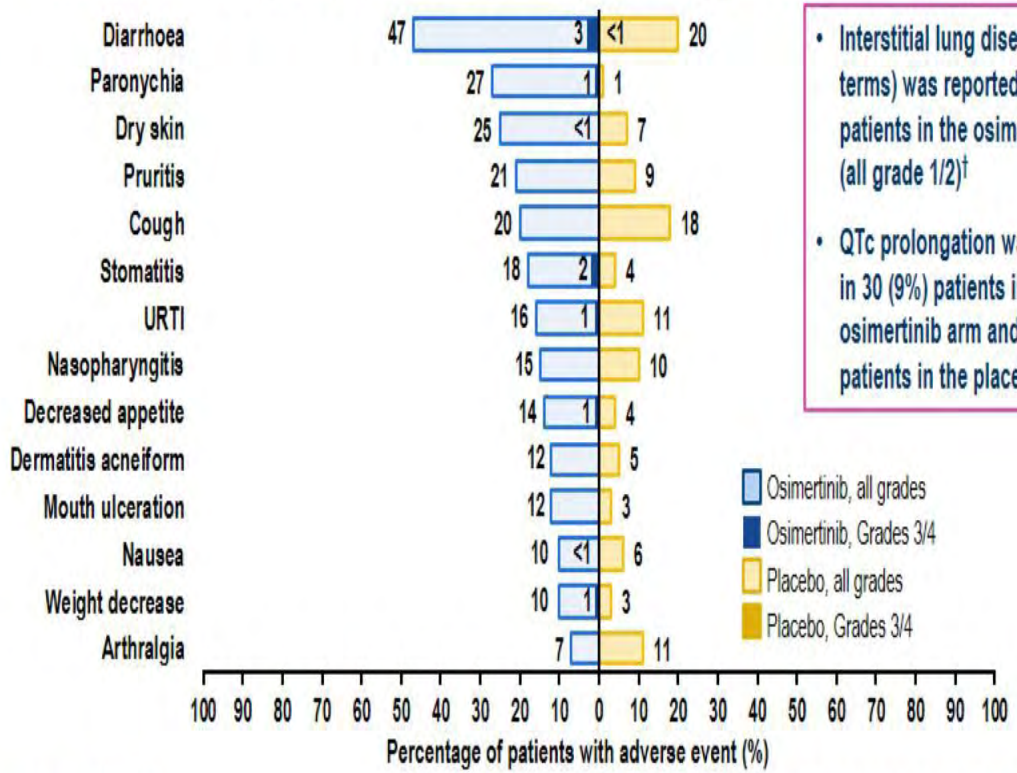
*Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; †As assessed by the investigator, includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy.

AE, adverse event
Data cut-off: April 11, 2022

ALL CAUSALITY ADVERSE EVENTS (≥10% OF PATIENTS)

- Completed planned duration of treatment of 3 years: osimertinib n=222 (66%), placebo n=139 (41%)
- Median total duration of exposure: osimertinib: 35.8 months (range 0 to 38), placebo: 25.1 months (range 0 to 39)



- **Interstitial lung disease (grouped terms) was reported in 11 (3%)* patients in the osimertinib arm (all grade 1/2)†**
- **QTc prolongation was reported in 30 (9%) patients in the osimertinib arm and 8 (2%) patients in the placebo arm‡**

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*Compared with the January 17, 2020 data cut-off, one additional patient reported interstitial lung disease (grouped term): pneumonitis, Grade 2; †Grade 1, n=6; Grade 2, n=5; Grade 3, n=0; ‡Osimertinib: Grade 1, n=16, Grade 2, n=10; Grade 3, n=4; placebo: Grade 1, n=7, Grade 2, n=0; Grade 3, n=1.

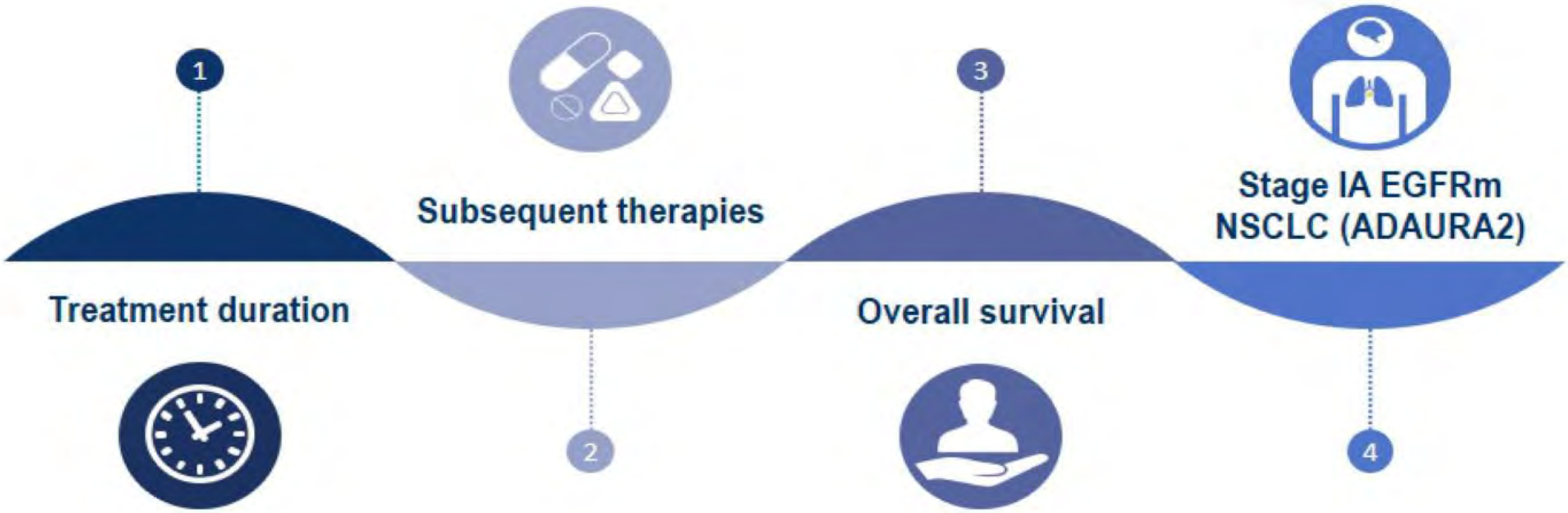
QTc, electrocardiogram QT; URTI, upper respiratory tract infection
Data cut-off: April 11, 2022

Tsuboi M, et al. ESMO 2022. Abstract LBA47.

FUTURE CONSIDERATIONS

Longitudinal assessment of MRD

Acquired resistance mechanisms at relapse



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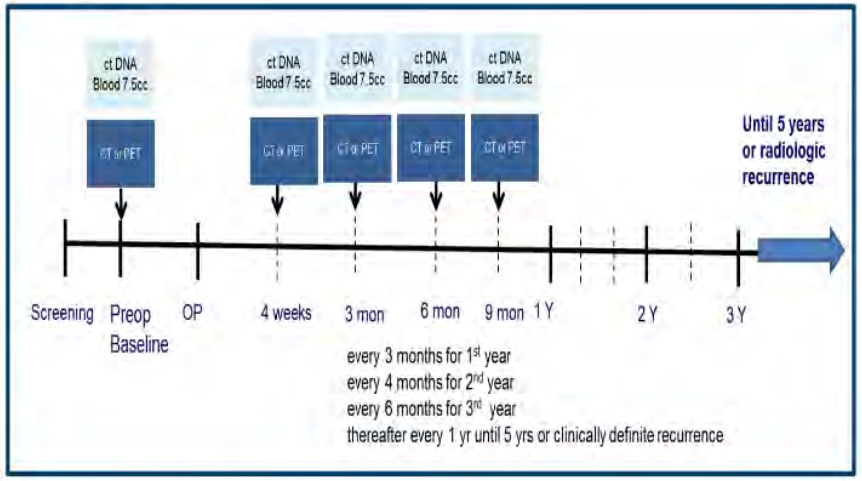
EGFRm, epidermal growth factor receptor-mutated; NSCLC, non-small cell lung cancer

Tsuboi M, et al. ESMO 2022. Abstract LBA47.

Longitudinal Monitoring of Circulating Tumor DNA from Plasma in Patients with Curative Resected Stage IA-IIIA *EGFR* mutant Non-small Cell Lung Cancer

Study population

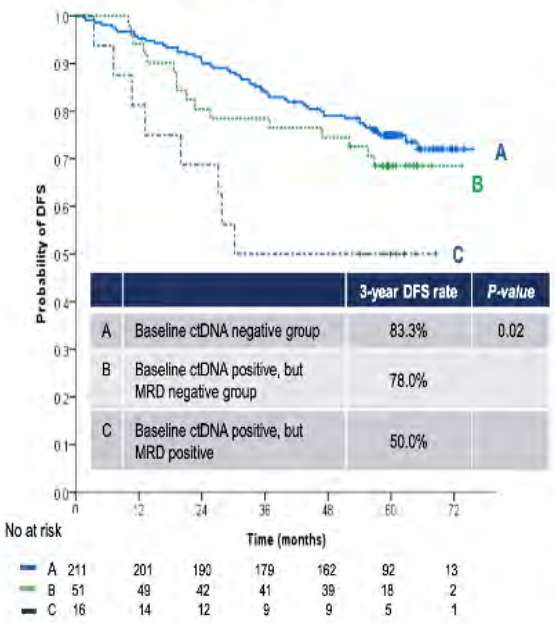
- Between August 2015 and October 2017
- Patients with curative resected stage IA-IIIA (AJCC 7th edition) *EGFR*-M+ (Del 19 or L858R) NSCLC
- Radiological follow-up including chest CT or PET-CT was accompanied with serial longitudinal monitoring of ctDNA using a droplet digital PCR(BioRad)



Myung-Ju Ahn, M.D.

DFS by ctDNA status

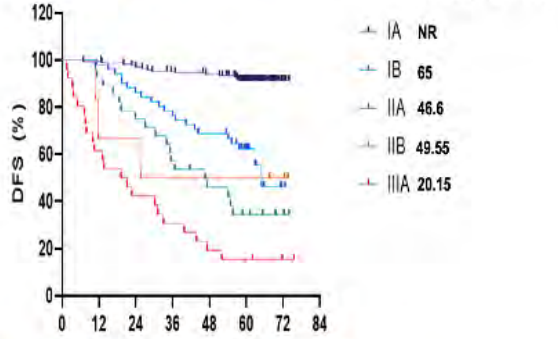
Recurrence 78/278 (28.1%)



		3-year DFS rate	P-value
A	Baseline ctDNA negative group	83.3%	0.02
B	Baseline ctDNA positive, but MRD negative group	78.0%	
C	Baseline ctDNA positive, but MRD positive	50.0%	

Myung-Ju Ahn, M.D.

DFS by Stage



Multivariate Analysis for DFS

Variable	HR (95% CI)	P-value
Sex (Female vs. Male)	0.70 (0.31-1.58)	0.39
Smoking status (Never vs. Ever)	1.55 (0.67-3.55)	0.31
EGFR mutation (Del19 vs. L858R)	0.68 (0.42-1.11)	0.12
ECOG PS (0 vs.1)	0.91 (0.21-4.01)	0.91
Stage (I vs II-III)	3.84 (2.91-5.06)	<0.001
ctDNA group	1.27 (1.03-1.57)	0.03

MRD: minimal residual disease

Ahn A, et al. ESMO 2022. Abstract 933MO.

Stage IA adjuvant phase 3 design: ADAURA2 NCT05120349

Adjuvant osimertinib *vs* placebo in completely resected stage IA EGFRm NSCLC

Study Population

Patients with pStage IA2 or IA3 (8th edition) NSCLC

- ❑ Post complete (R0) resection
- ❑ Exon 19 deletion or L858R EGFR mutation
- ❑ Tumor sample submission for central pathology assessment of:
  - Invasive tumour size
  - Lymphovascular invasion
  - Tumour histology
- ❑ PS 0-1
- ❑ No pre-/post-operative RT or systemic therapy
- ❑ Not eligible for any local SOC treatment

R → 1 → **Arm A** Osimertinib 80 mg PO QD

R → 1 → **Arm B** Placebo PO QD

N=380

Primary: DFS per investigator in high-risk* stratum

Secondary:
DFS in ITT
OS in high-risk stratum
OS in ITT
HRQoL
Safety/tolerabilit
PK
Exploratory: MR

A Study of 5 Years of Adjuvant Osimertinib in Completely Resected Epidermal Growth Factor Receptor Mutation (EGFRm) Non-small Cell Lung Carcinoma (NSCLC) (TARGET)

Study Design

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	180 participants
Allocation:	N/A
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment

ClinicalTrials.gov Identifier: NCT05526755

Durvalumab vs Placebo With Stereotactic Body Radiation Therapy in Early Stage Unresected Non-small Cell Lung Cancer (NSCLC) Patients / Osimertinib Following SBRT in Patients With Early Stage Unresected NSCLC Harboring an EGFR Mutation (PACIFIC-4) NCT03833154

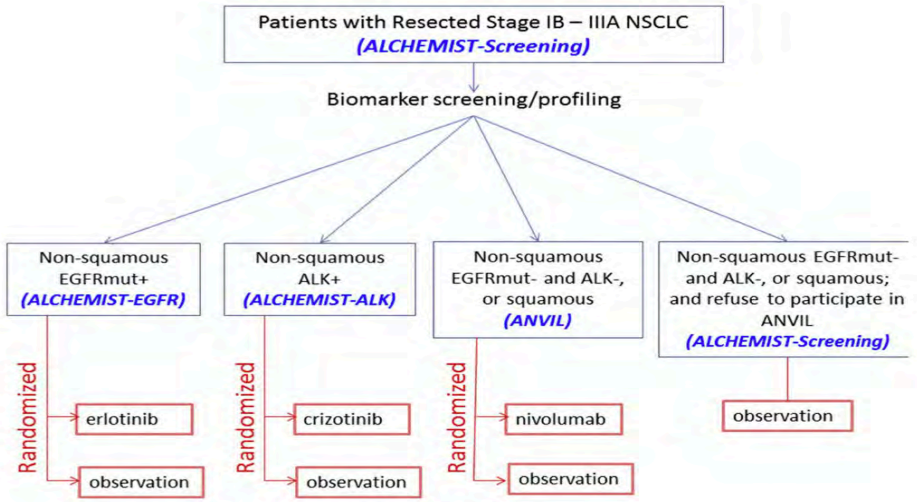
Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	733 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	Double- Blind
Primary Purpose:	Treatment
Official Title:	A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab With Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Patients With Unresected Stage I/II, Lymph-node Negative Non-small Cell Lung Cancer (PACIFIC-4/RTOG-3515) Osimertinib Following SBRT, a Single Arm Cohort for Patients With Unresected Stage I/II, Lymph Node Negative NSCLC Harboring a Sensitizing EGFR Mutation

Adjuvant Use of Genotype-Directed Therapy

ALCHEMIST study

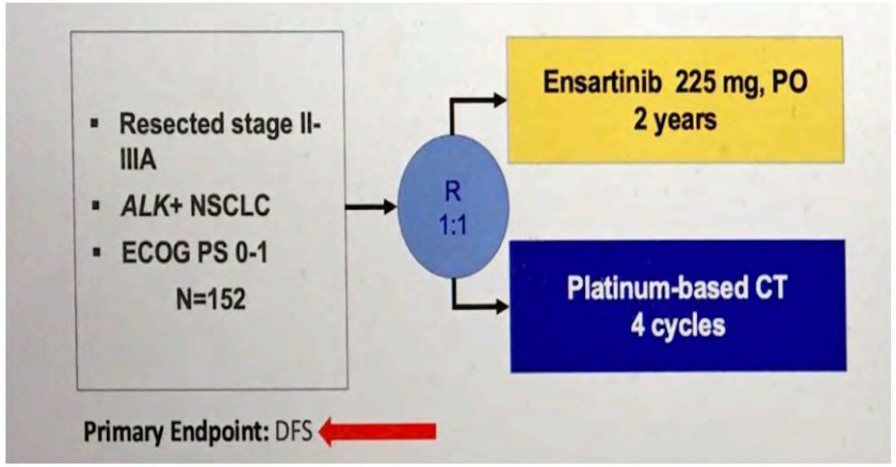


NCT02194738

ALINA study: ALK +

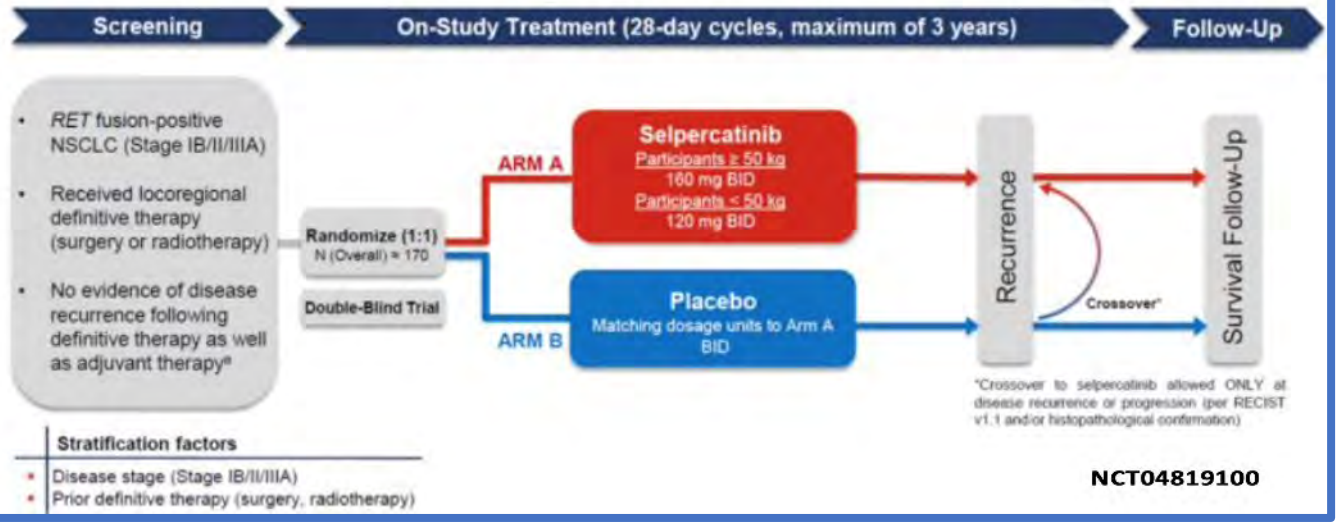
NCT03456076

SICHUAN UNIVERSITY



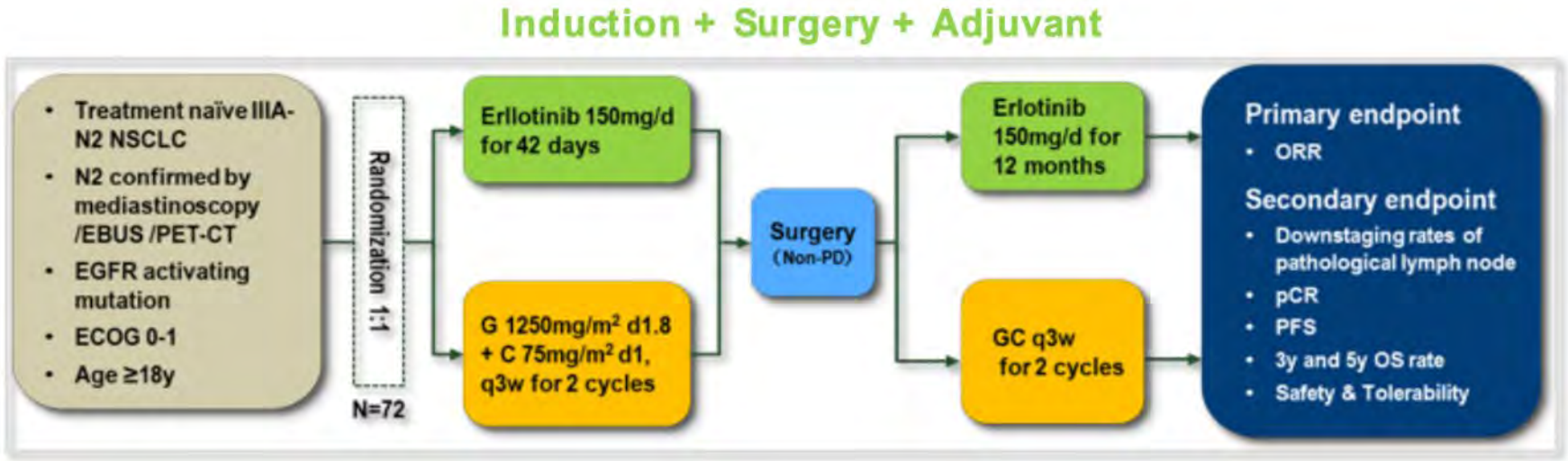
NCT05186506

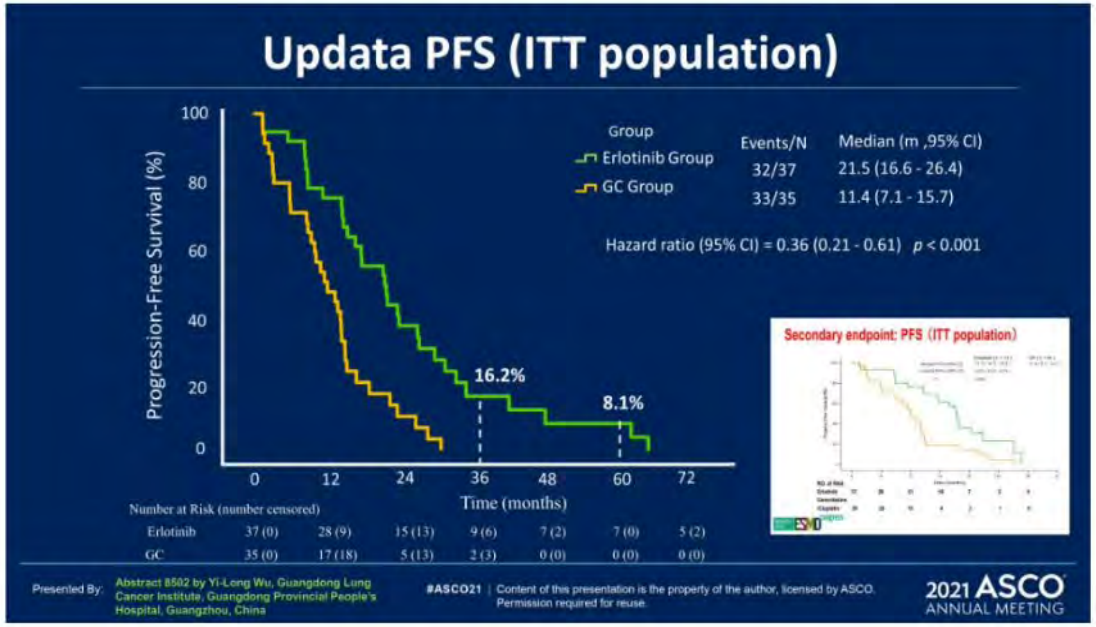
LIBRETTO 432 STUDY

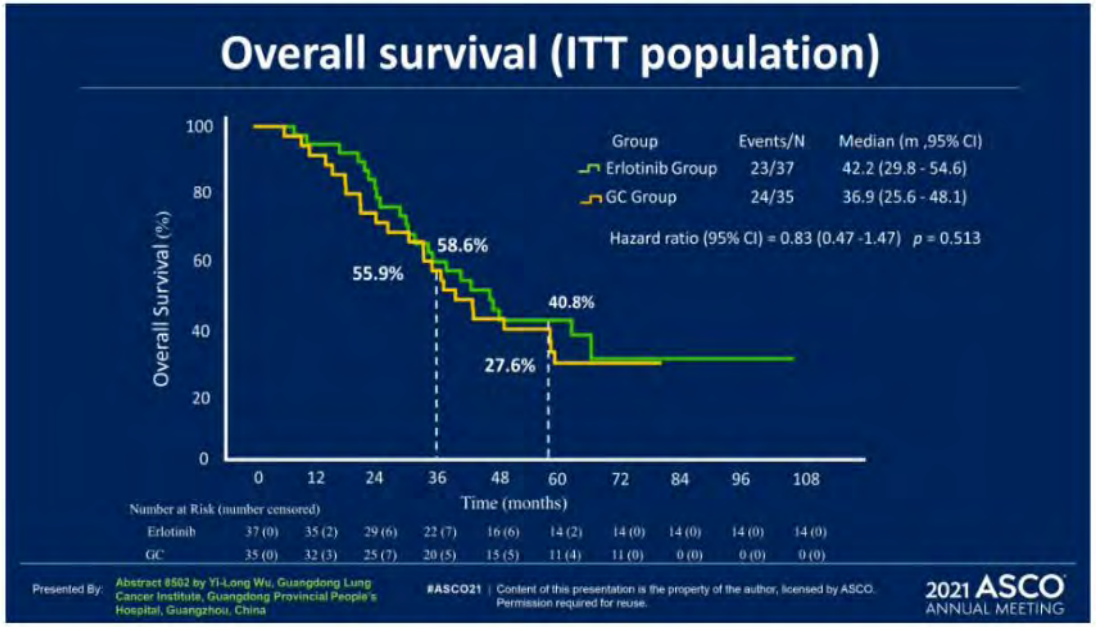


NCT04819100

EMERGING Study





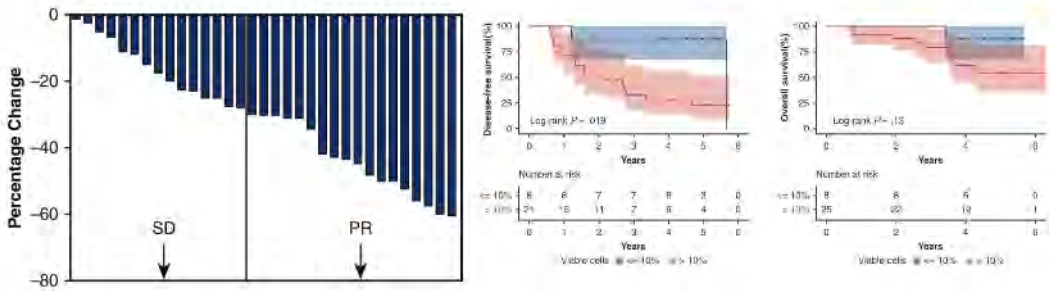


Zhong WZ, et al. *J Clin Oncol*. 2019;37:2235-2245.

Gefitinib in *EGFR*m Stage II–IIIA NSCLC

ORR 54.5% (after 6 wks treatment)

Major Pathologic Response (24.2%)



Zhang et al. J Thorac Cardiovasc Surg . 2021 Feb;161(2):434-442.e2.

NEOS Study: Neoadjuvant Osimertinib

NEOS – Phase II Single-Arm, 6 weeks neoadjuvant osimertinib

Eligibility Criteria
- NSCLC with an EGFR mutation (del19 or L858R)
- Stage II-IIIB

→ **Neoadjuvant**
Osimertinib 6 weeks (n = 40)

→ **Surgical Resection**

Primary Endpoint:
Objective Response Rate

Secondary Endpoints:
R0 rate, MPR rate, pCR rate
N2 downstaging rate, safety

Objective Response Rate 71.1%
MPR Rate 10.7%
pCR Rate: 3.6%

Lyu et al. Annals Oncol. 2022;23(2):571-2.

NeoADAURA Study

NeoADAURA (NCT04351555): Phase III, Randomized, Controlled, Multicenter Study of Neoadjuvant Osimertinib in EGFRm Resectable NSCLC

Resectable
Stage II–IIIB NSCLC
EGFRm NSCLC (Ex19del / L858R)

N=351

R 1:1:1

- **Placebo + Chemotherapy (3 cycles, Q3W)**
- **Osimertinib + Chemotherapy (3 cycles, Q3W)**
- **Osimertinib (9 weeks)**

→ SURGERY → **MPR & pCR** → **Adjuvant: Investigator choice (optimal care)** → **EFS & OS**

Primary endpoints
Major pathological response* defined as ≤10% residual cancer cells in the lung tumor specimen post-surgery,[1] assessed centrally

Stratification:
- Stage II/III
- Non-Asian/Chinese/ other Asian
- Ex19del/L858R

Double-blind treatment arms:
1. Placebo QD + investigator's choice of pemetrexed 500 mg/m² plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m²
2. Osimertinib 80 mg QD + investigator's choice of pemetrexed 500 mg/m² plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m²

Open-label (sponsor-blind) treatment arm:
3. Osimertinib 80 mg QD

Adjuvant therapy and follow-up:
- Patients will be followed up for OS until 5 years from surgery, with evaluation at 12 and 24 weeks post-surgery, then every 24 weeks, until disease recurrence or withdrawal of consent
- Osimertinib will be offered to all patients who complete surgery (+/- post-surgical chemotherapy) for up to 3 years or until disease recurrence

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO expert consensus statements on the management of *EGFR* mutant non-small-cell lung cancer

A. Passaro[1*], N. Leighl[2†], F. Blackhall[3,4†], S. Popat[5,6,7†], K. Kerr[8†], M. J. Ahn[9], M. E. Arcila[10], O. Arrieta[11], D. Planchard[12],

8: What is the role of neoadjuvant EGFR TKIs for patients with operable stage IA-IIIA NSCLC or borderline operable e.g. T3/T4 disease?

STATEMENT: There are currently no data to support neo-adjuvant EGFR TKIs for NSCLC in operable or borderline operable cases [II,C].

Passaro A, et al. *Ann Oncol*. 2022;33:466-487.

ALNEO study NCT05015010

- STAGE III (Any T N2 or T4N0-1)
- ALK +
- PET and Brain MRI
- N=33 p.

1 end point: MPR

Alectinib 8 weeks → SURGERY → Alectinib 2 ys

SOTORASIB + CT phase 2 study NCT05118854 (MD Anderson)

- Surgically resectable stage IIA to select stage IIIB (T3-4N2)
- KRAS G12C-mutant non-squamous
- N=27 p.

1 end point: MPR / safety

Sotorasib + Platinum + Pemetrexed x 4 cycles → SURGERY

NeoAdjuvant KRAS G12C study NCT05472623

Open label randomized phase 2, JHU +14 partner sites PI: Marrone & Scott

Subject eligibility
- Newly diagnosed, treatment-naive NSCLC
- Resectable, stage IB-IIIA
- *KRAS* G12C genotype
- ECOG 0-1

Arm A n=20: Adagrasib 600mg BID

Randomize 1:1

Arm B n=20: Adagrasib 600mg BID + Nivolumab 240mg Q2 weeks x3

6 weeks

Primary endpoint
- Pathologic complete response (pCR)

Secondary endpoints
- Major pathologic response (MPR)
- Event-free survival
- Overall survival
- Safety
- Feasibility

GEOMETRY-N study NCT04926831

- Stage IB-IIIA, N2 and selected IIIB MET positive:
- Cohort a: MET Exon 14 Skipping Mutation
- Cohort b: High MET Amplification
- N=38 p.

1 end point: MPR

Capmatinib 8 weeks → SURGERY → Capmatinib 3 ys

NAUTIKA1 phase II study NCT043022025

Resectable NSCLC

Stage II-IIIA

Test for molecular alteration in a CLIA certified laboratory

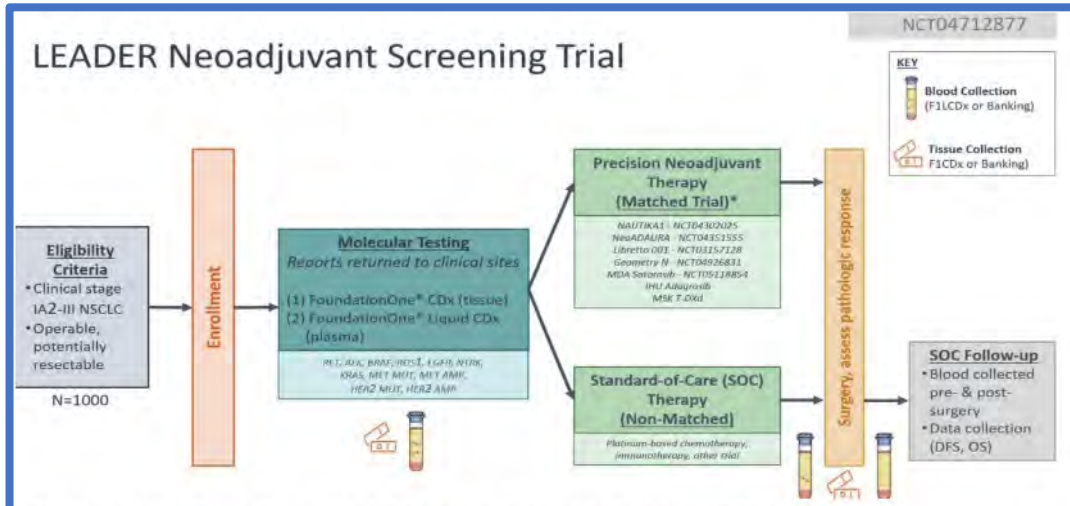
ALK fusion detected by FISH or IHC (tissue) or NGS (tissue / blood)	*ALK*+ cohort	Alectinib	Alectinib
fusion detected by FISH or NGS (tissue / blood)	[illegible]	Entrectinib	Entrectinib
NTRK1/2/3 fusion detected by RT-PCR (tissue) or NGS (tissue / blood)	*NTRK*+ cohort	Entrectinib	Entrectinib
BRAF V600 mut+ detected by RT-PCR or NGS (tissue)	*BRAF* cohort	Vemurafenib Cobimetinb	Vemurafenib Cobimetinb
RET fusion detected by FISH or RT-PCR (tissue) or NGS (tissue / blood)	*RET*+ cohort	Pralsetinib	Pralsetinib

8 weeks: SURGERY

2 years: CT X 4 CYCLES

LEADER Neoadjuvant Screening Trial

NCT04712877



Presented by Boris Sepesi, ASCO Annual Meeting 2022, #TPS8596

Targeted Therapies for Early-Stage NSCLC – Evidence-Based Data and Perspectives: Summary

- Routine assessment of tumor molecular profiling on surgical specimens
- Adjuvant chemotherapy still indicated
- In sensitizing *EGFR* mutant: adjuvant osimertinib SOC in *EGFR* mutant
  - ✓OS?
  - ✓Duration?
  - ✓Role of ctDNA/MRD?
- Other driver mutations: ongoing adjuvant/neoadjuvant trials

Thanks!!!

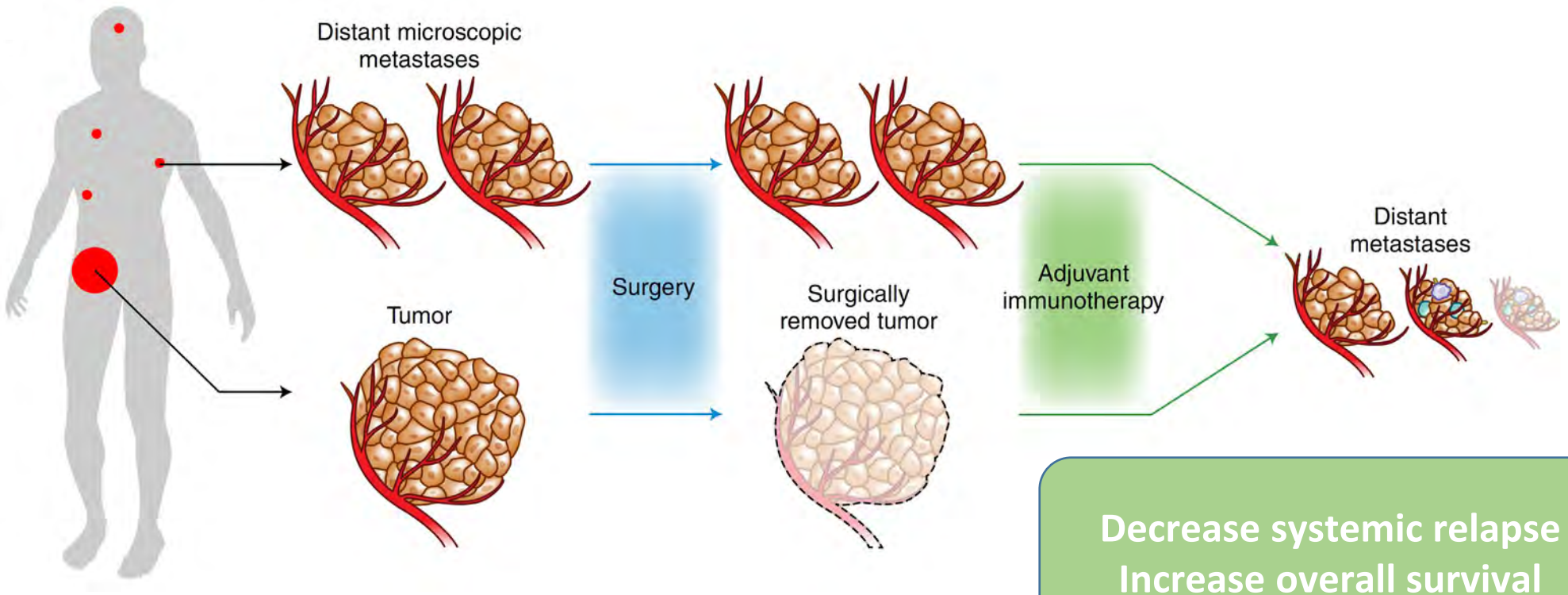
efelip@vhio.net

Global Lung Cancer Academy

Adjuvant Therapy in Resectable NSCLC

Benjamin Besse, MD, PhD

If Surgery Is the Local Treatment



Decrease systemic relapse
Increase overall survival

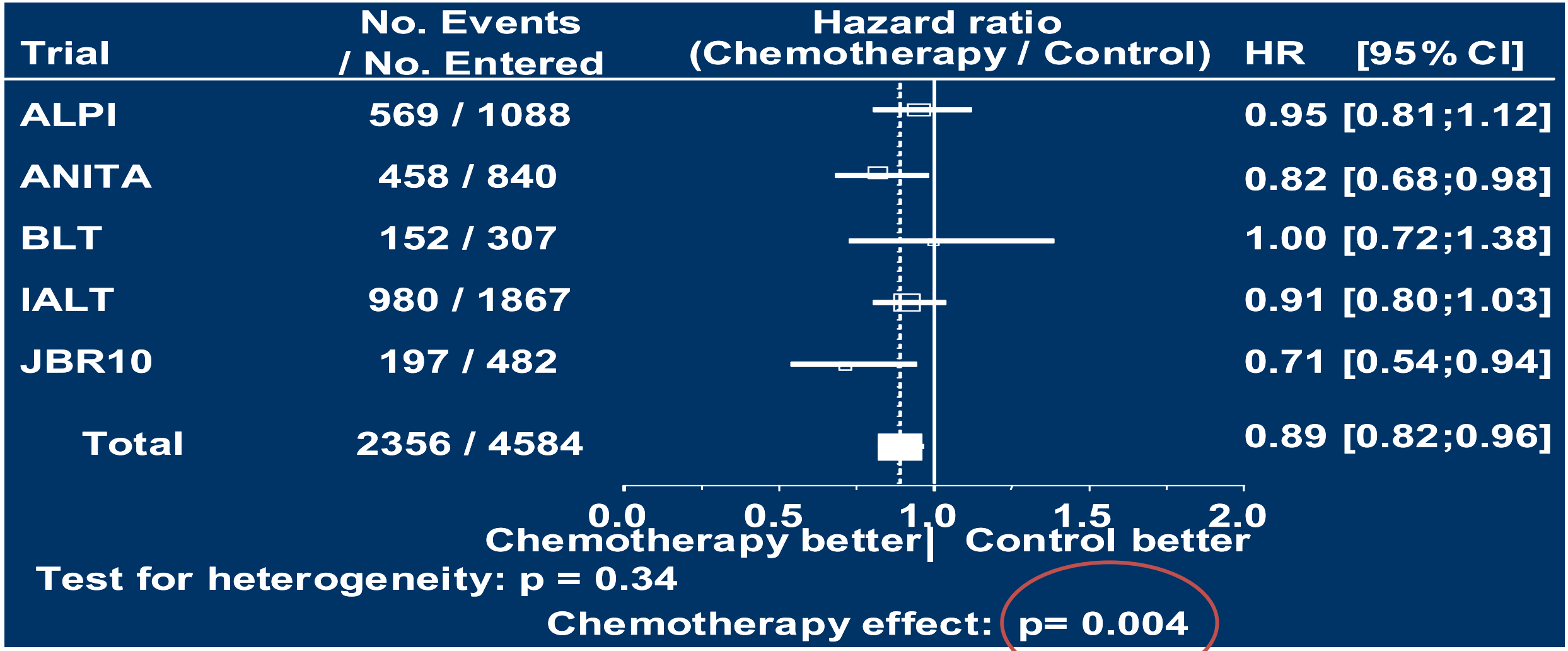
Robert C. *Nat Med*. 2018;24:1645-1648.

Lung Adjuvant Cisplatin Evaluation (LACE)

- 5 randomized trials, n >300
- 4584 patients
- Comparison cisplatin-based CT vs absence of CT
- Median follow-up: 5.1 yr (3.1–5.9)
- Pathologic stage
  IA: 8%, IB: 30%, II: 35%, III: 27%
- 31% pulmonectomy
- Pathology
  - 49% squamous cell carcinoma
  - 39% adenocarcinoma
  - 12% others

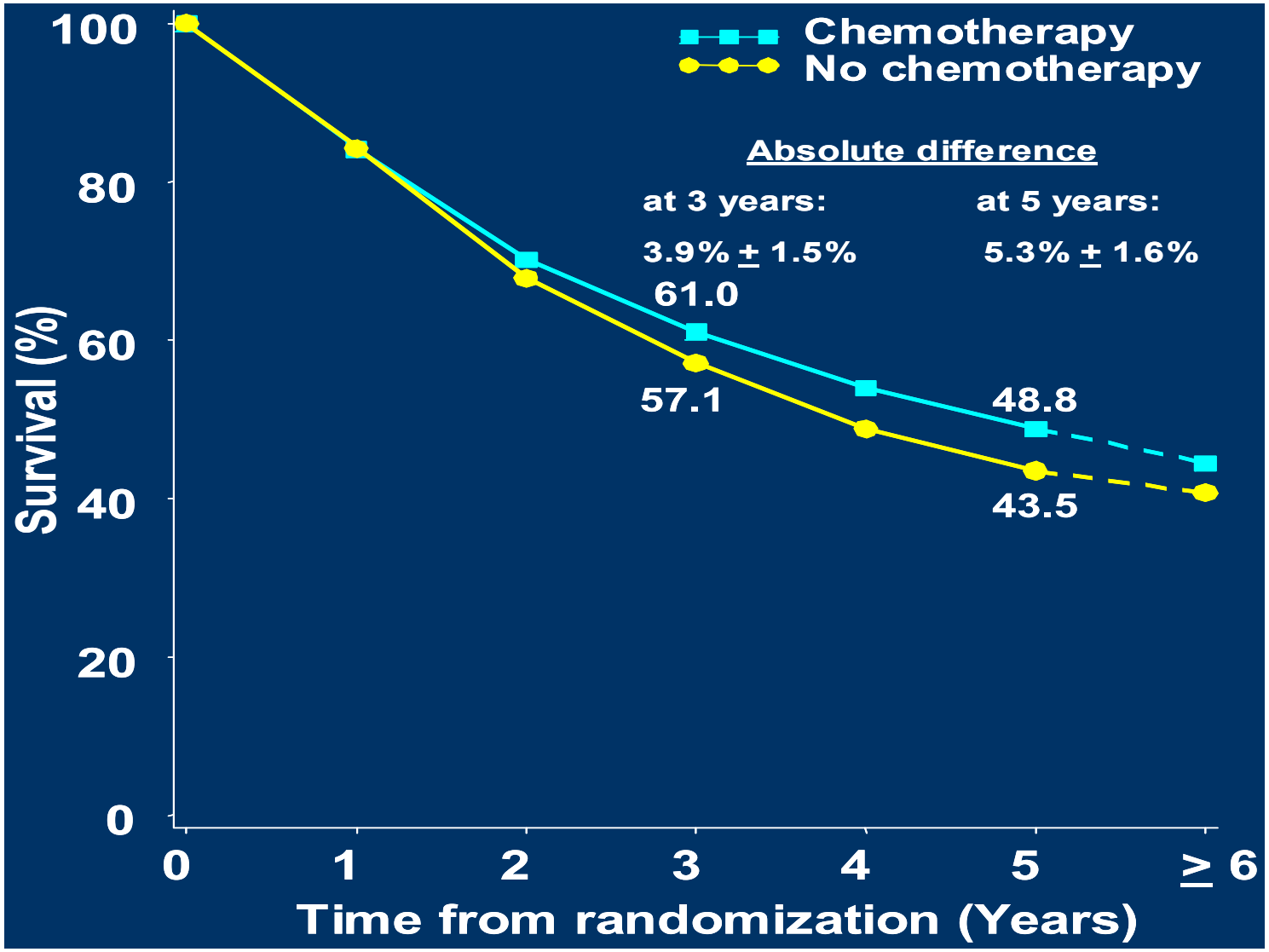
Pignon JP, et al. *J Clin Oncol*. 2008;26:3552-3559.

Overall Survival



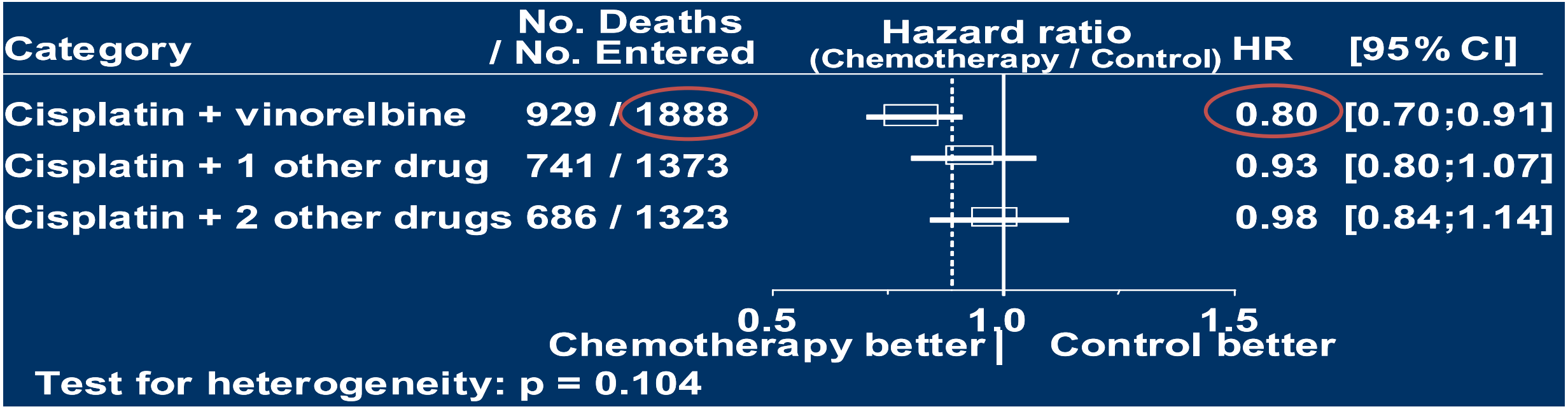
Pignon JP, et al. *J Clin Oncol*. 2008;26:3552-3559.

Overall Survival



Pignon JP, et al. *J Clin Oncol*. 2008;26:3552-3559.

Regimens

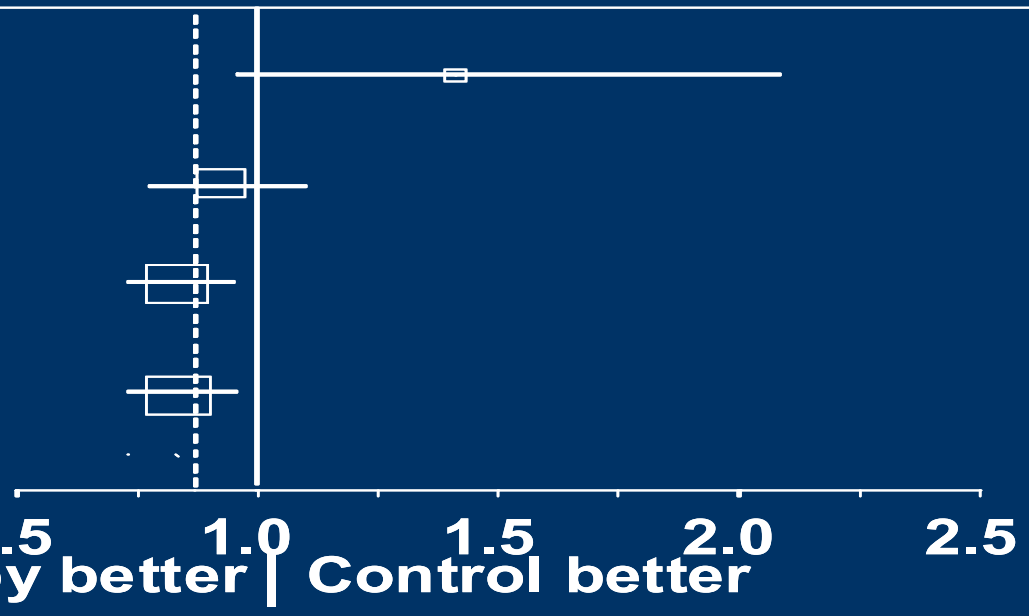


The effect of cisplatin + vinorelbine was marginally better than the effect of other drug combinations. This is significant when the other combinations are pooled (*P* = .04, post hoc analysis).

Pignon JP, et al. *J Clin Oncol*. 2008;26:3552-3559.

Effect Based on Stage

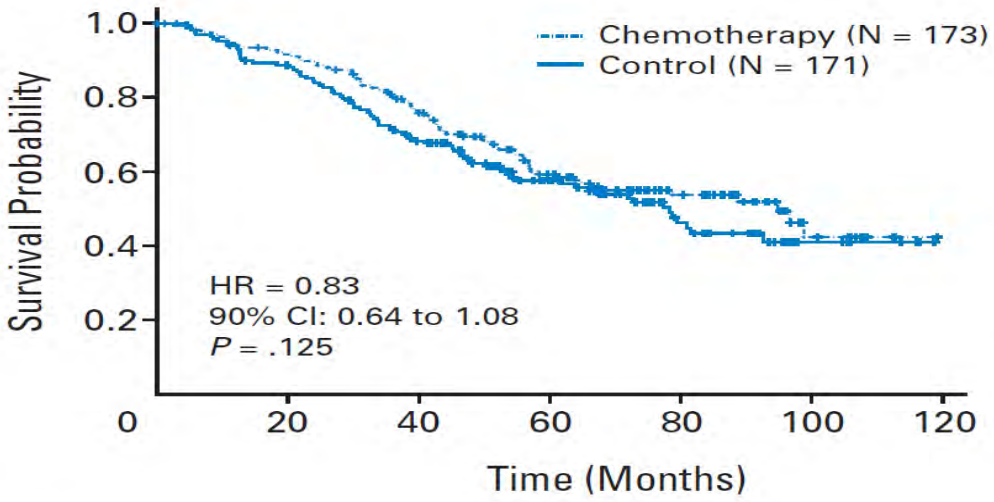
Category	No. Deaths / No. Entered	HR	[95% CI]
Stage IA	102 / 347	1.41	[0.96;2.09]
Stage IB	509 / 1371	0.92	[0.78;1.10]
Stage II	880 / 1616	0.83	[0.73;0.95]
Stage III	865 / 1247	0.83	[0.73;0.95]



Test for trend: p = 0.051

Pignon JP, et al. *J Clin Oncol*. 2008;26:3552-3559.

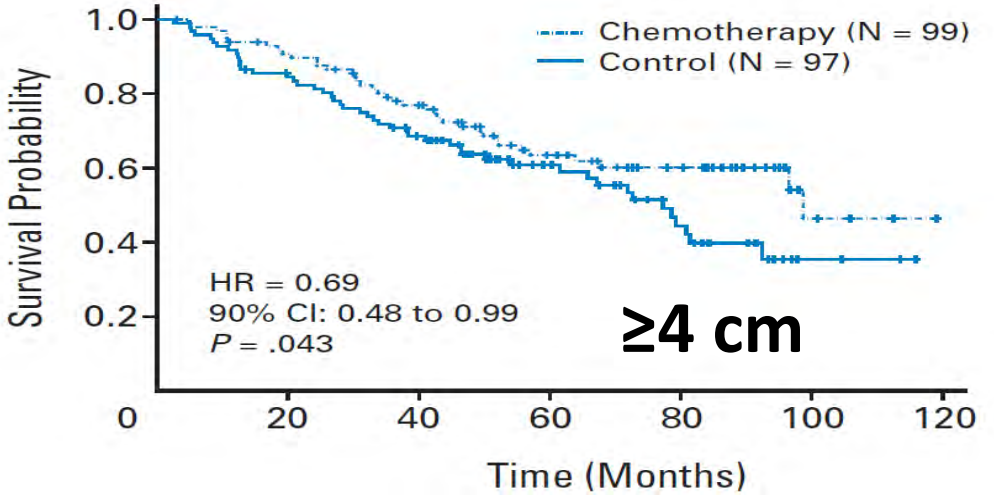
Stage IB?

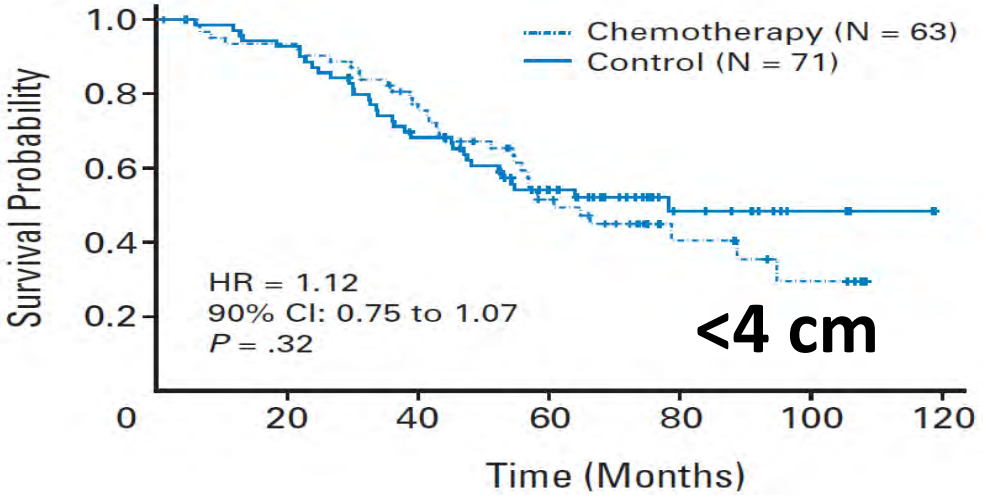


CALGB trial

Limited to stage IB

Paclitaxel + carboplatin
4 cycles

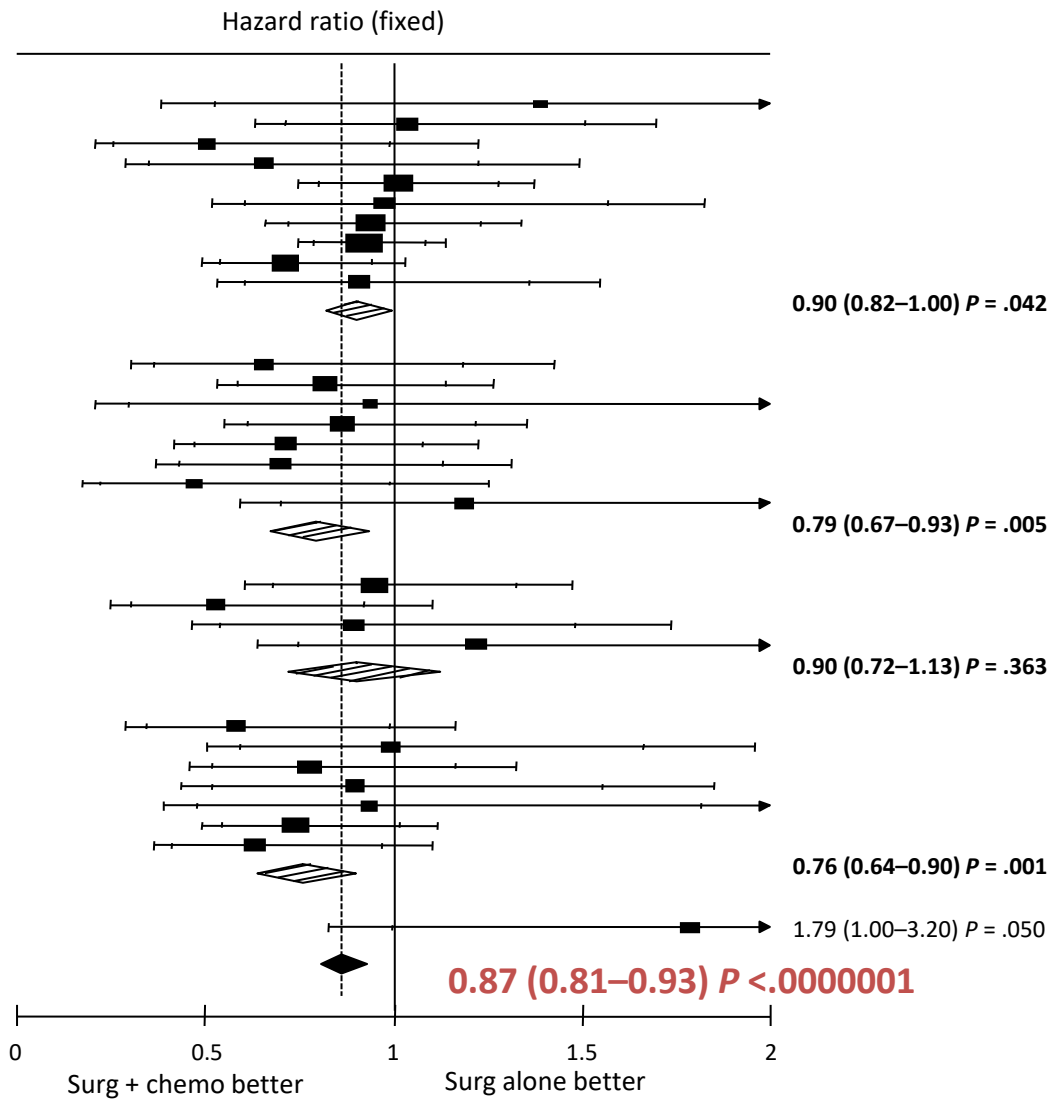




Strauss GM, et al. *J Clin Oncol*. 2008;26:5043-5051.

Meta-analysis IGR-MRC

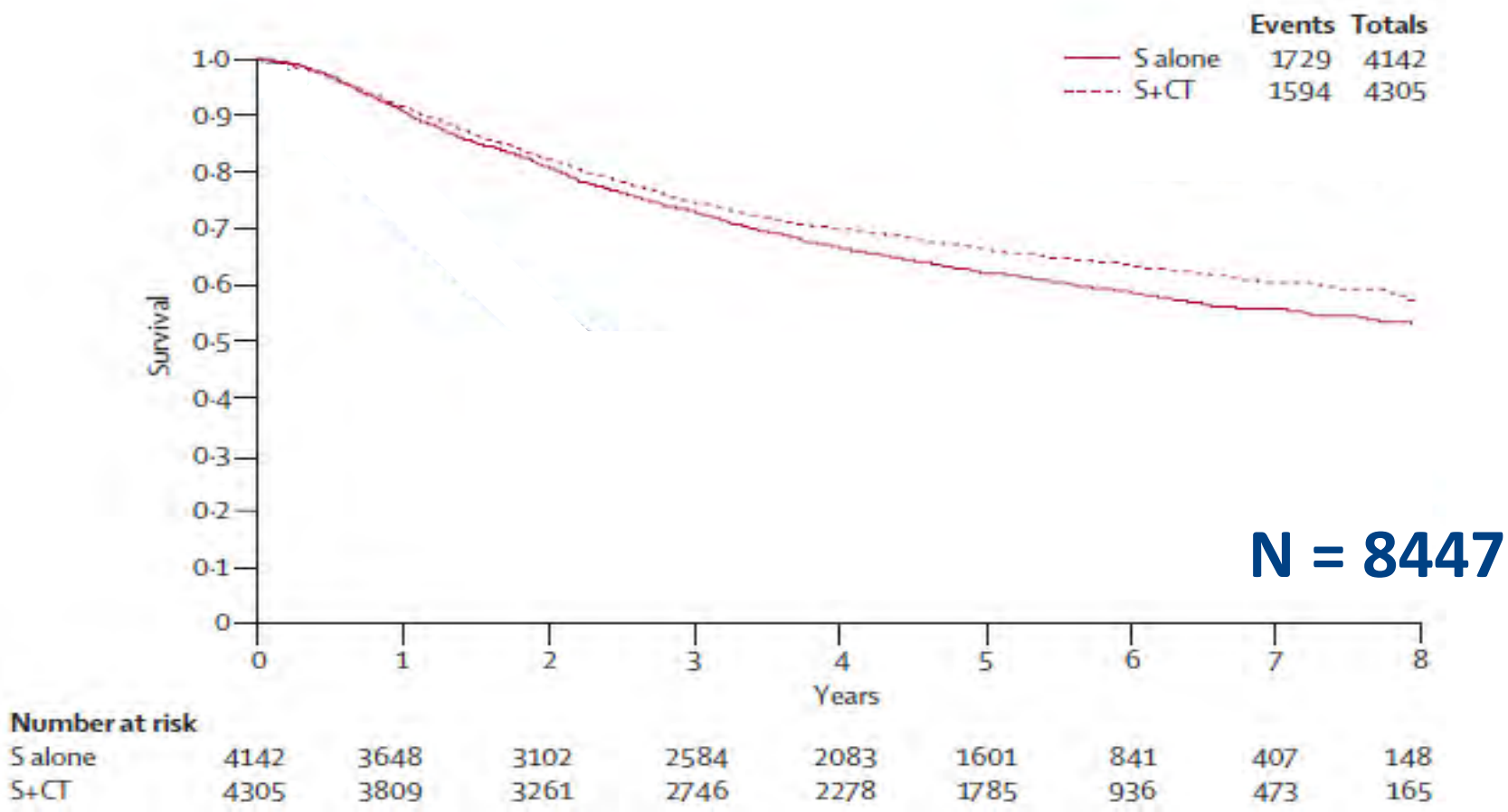
Trial ID	Surg + chemo	Surg alone
	[no. events/no. entered]	
Cisplatin + vinca alkaloid/etoposide		
IPCR CHIBA	11/15	7/14
JLCSSG	59/111	52/98
MINEO	14/33	21/33
PARK	17/59	23/59
ALPI	143/310	144/308
JCOG 9304	33/59	35/60
ANITA	102/231	113/232
IALT	290/648	304/647
BR10	86/242	111/240
BLT1	49/106	47/95
Subtotal	804/1814	857/1786
Cisplatin + antimetabolic agent		
XU	19/35	26/35
SGACLC ACTLC1	68/154	75/152
OLCSG1C	5/12	7/16
SGACLC ACTLC2	64/165	68/167
WJSG2 (1+3)	44/115	49/100
WJSG3	27/109	40/116
ACTLC4A	10/52	18/52
OLCSG2B	28/47	28/48
Subtotal	265/689	311/686
Other cisplatin regimens		
LSCG 801	66/140	71/143
FLCSG1	20/54	30/56
LCSG 853	29/94	32/94
BLT2	34/56	34/62
Subtotal	149/344	167/355
Antimetabolic agent only		
OLCSG2A	20/85	35/87
OLSCG1A	30/163	28/158
WJSG4	38/176	56/191
NJSGLCS	24/109	27/110
ACTLC4B	17/52	18/52
JLCRG	67/498	91/501
WJSG2 (2+3)	38/108	49/100
Subtotal	234/1191	304/1199
Antimetabolic agent + other agent		
OLCSG1B	27/41	21/42
Total	**1479/4079**	**1660/4068**



Heterogeneity: $P = .267$, $I^2 = 12.82\%$

NSCLC Meta-analyses Collaborative Group, Arriagada R, et al. *Lancet*. 2010;375:1267-1277.

Meta-analysis IGR-MRC



N = 8447

HR = 0.87 (0.81–0.93) *P* <.000001

Absolute benefit : 4% at 5 years

NSCLC Meta-analyses Collaborative Group, Arriagada R, et al. *Lancet*. 2010;375:1267-1277.

Adjuvant Chemotherapy 2022

- **Standard: cisplatin-based chemotherapy**
- **Standard: II–IIIA**
- **Option: carboplatin**
- **Criteria: <75 years, within 2 months after surgery, PS 0–1**

Adjuvant Chemotherapy With or Without Bevacizumab: Results of E1505

Key patient inclusion criteria
- Resected
- Stage IB (≥4 cm)–IIIA
- 6–12 weeks postop
- No prior chemotherapy
- ECOG PS 0–1

(n = 1,501)

R
1:1

Stratification
- Cisplatin doublet, stage, histology, gender

Chemotherapy* × 4 cycles
(n = 749)

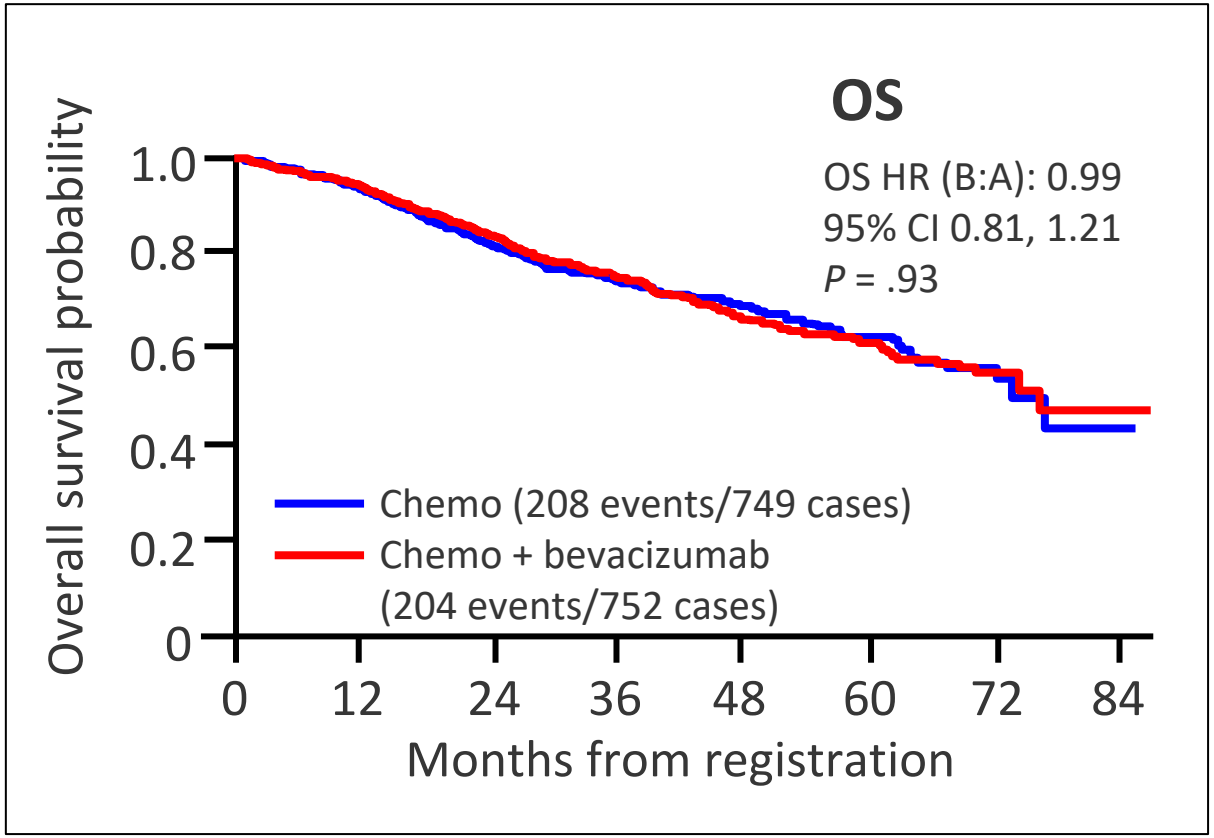
Chemotherapy* × 4 cycles +
bevacizumab 15 mg/kg q3w × 1 yr
(n = 752)

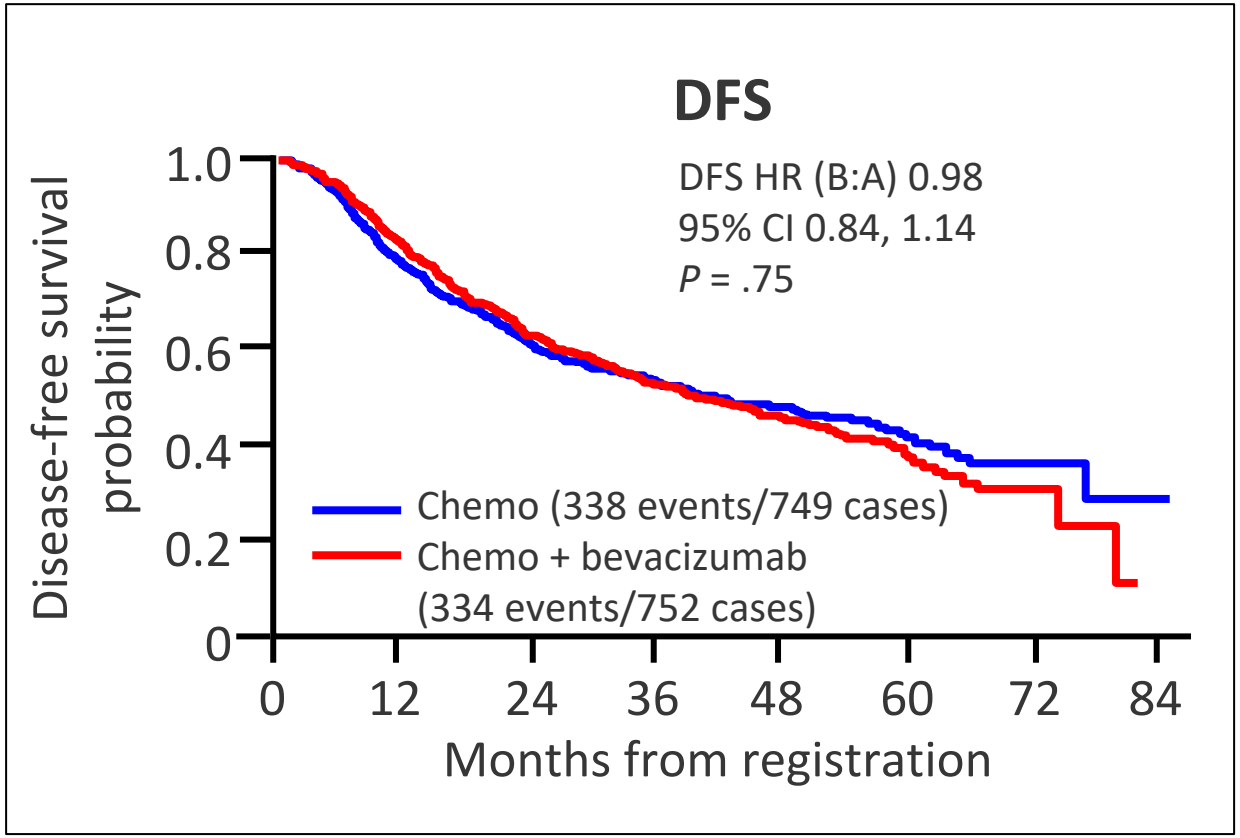
Primary endpoint: OS
Secondary endpoints: DFS, safety

***Chemotherapy regimens q3w.**
Cisplatin 75 mg/m^2 D1 combined with any of the following
- Vinorelbine 30 mg/m^2 D1, 8
- Docetaxel 75 mg/m^2 D1
- Gemcitabine 1200 mg/m^2 D1, 8
- Pemetrexed 500 mg/m^2 D1

Wakelee HA, et al. *Lancet Oncol*. 2017;18:1610-1623.

Adjuvant Chemotherapy With or Without Bevacizumab: Results of E1505





The groups were balanced according stage, gender, age, smoking, histology, surgical procedure, LN dissection procedure, and CT schedule.

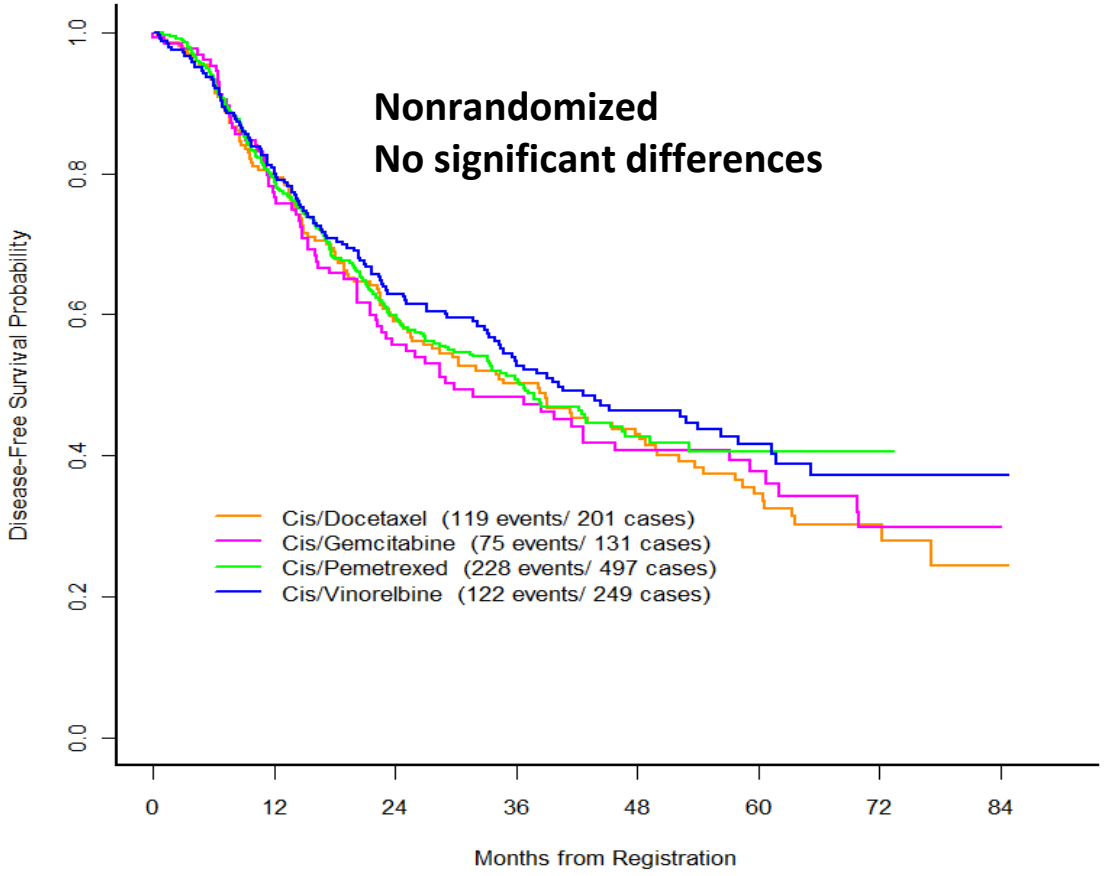
Wakelee HA, et al. *Lancet Oncol*. 2017;18:1610-1623.

Adjuvant Chemotherapy With or Without Bevacizumab: Results of E1505

Pooled Chemo Analysis (all patients regardless of treatment arm)

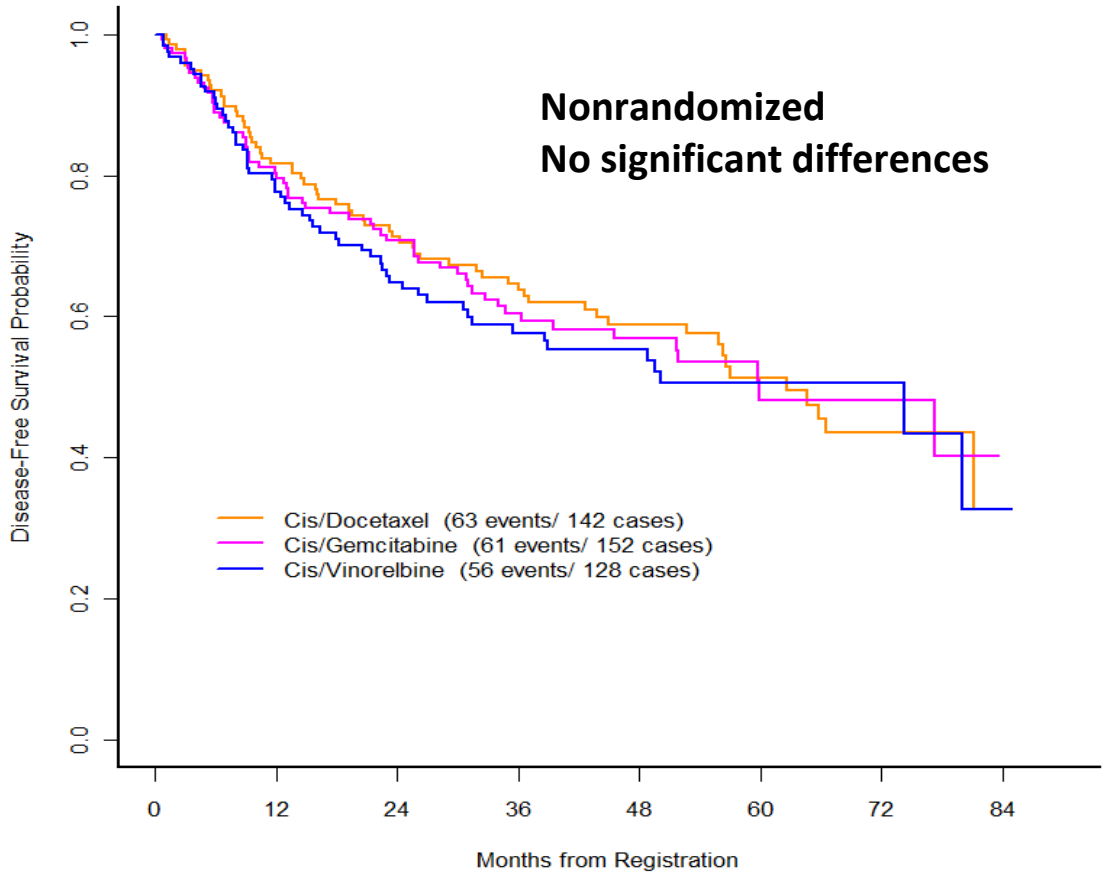
DFS by Chemo Group

Nonsquamous: Log rank *P* = .58



DFS by Chemo Group

Squamous: Log rank *P* = .83



Wakelee H, et al. WCLC 2015. Abstract 8507.

ADAURA Phase III double-blind study design

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

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

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

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

Randomization 1:1 (N=682)

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

Planned treatment duration: 3 years

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

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

Endpoints

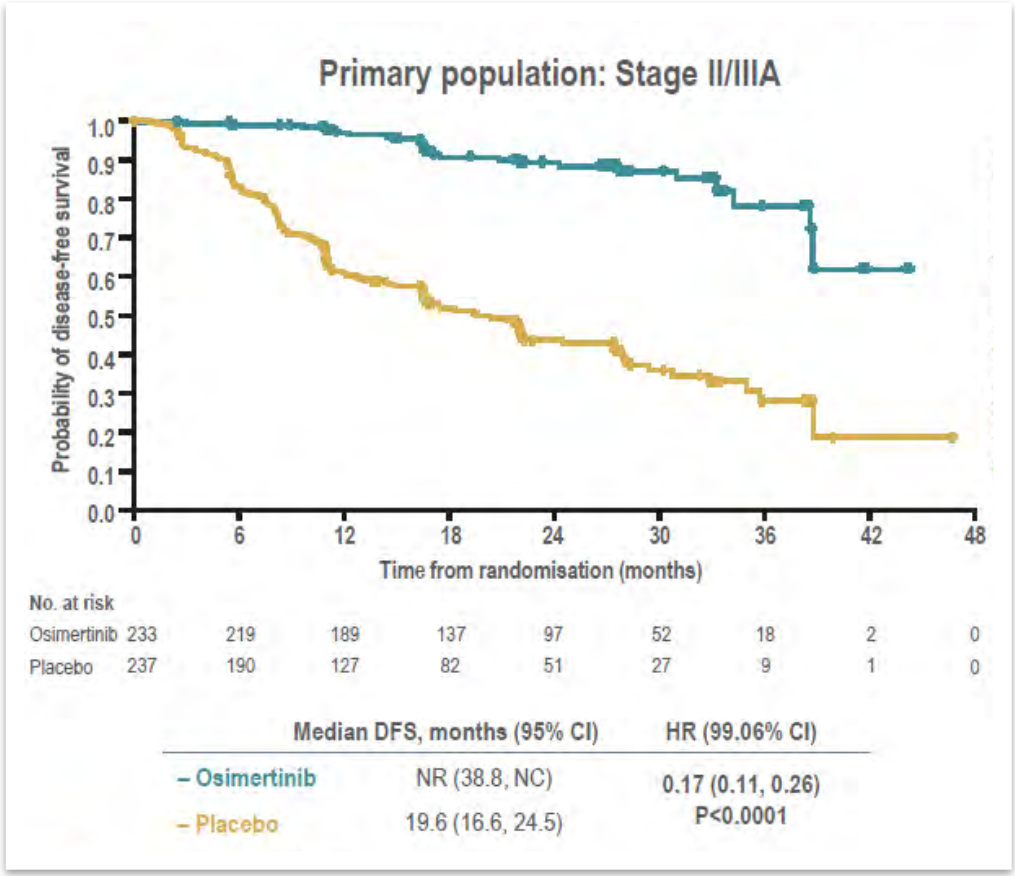
- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

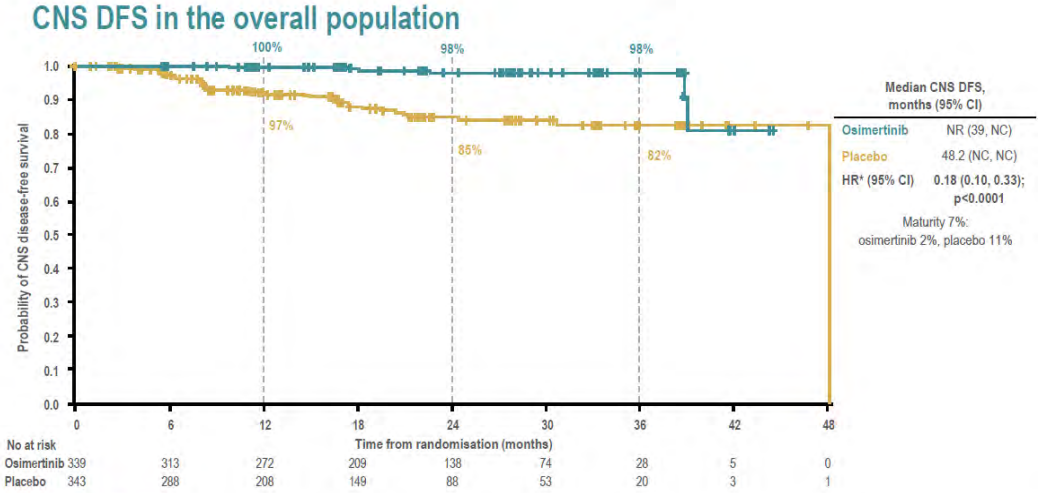
ADAURA

DFS



CNS Mets

Patients, n (%)	Overall population: Osimertinib n=339	Overall population: Placebo n=343
CNS DFS events:	6 (2%)	39 (11%)
CNS recurrence	4 (1%)	33 (10%)
Death†	2 (1%)	6 (2%)



Median follow-up: osimertinib 22.1 months, placebo 16.6 months;
‡A hazard ratio of <1 favours osimertinib.
ADAURA data cut-off: 17 January, 2020

Herbst R, et al. ASCO 2020. Abstract LBA5; Tsuboi M, et al. ESMO 2020. Abstract LBA1.

LUNG ART phase III Trial

(IFCT-0503, UK NCRI, SAKK)

Trial registry: NCT00410683

Study design

Completely resected NSCLC with N2 histo/ cytologically proven nodal involvement

R

1:1 randomization

Pre-op and/or Post-op CT

Control

Conformal PORT (54 Gy/5,5 wks)

Stratification factors : Center, Administration of CT (no CT vs Post-op CT vs pre-op CT alone), Histology (SCC vs other), Extent of mediastinal lymph node involvement (0 vs 1 vs 2+), use of pre-treatment PET-scan (yes/no)

Primary end-point: Disease-free survival

Secondary end-points: Overall survival, patterns of relapse, local failure, second cancers, and treatment-related toxicity

Le Pechoux C, et al. ESMO 2020. Abstract LBA3_PR.

LUNG ART

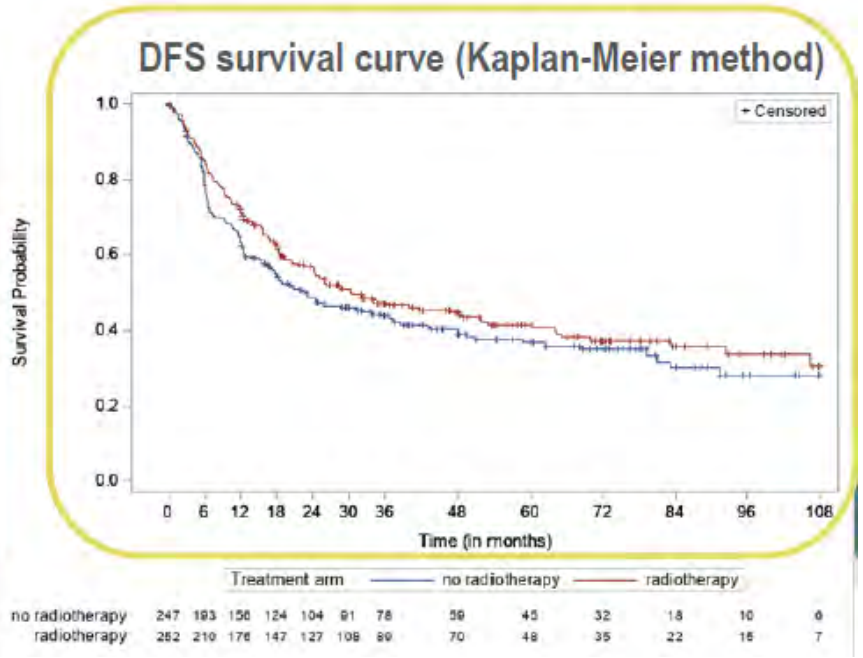
DFS (primary endpoint)

Main analysis (Adjusted Cox Model)

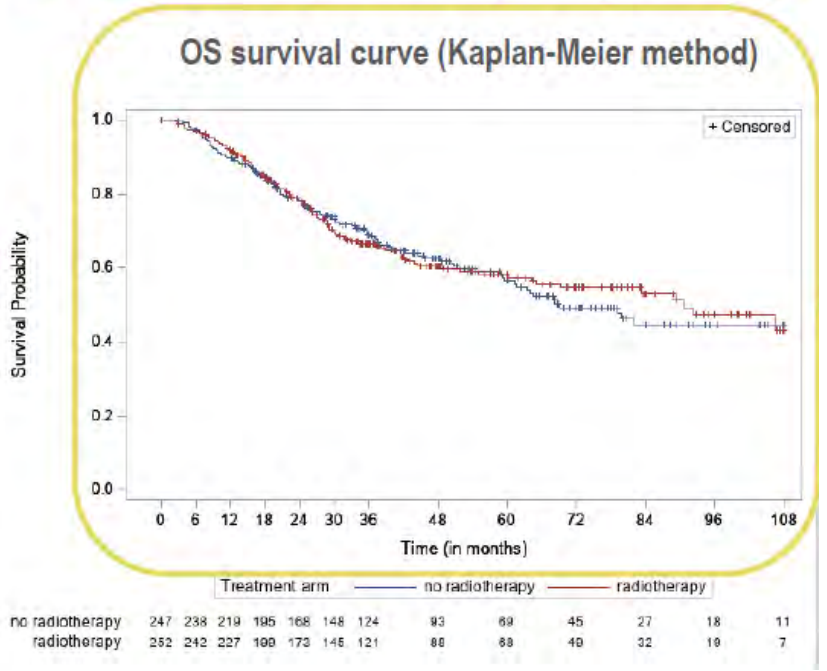
HR = 0.85
95% CI = [0.67;1.07]
p value = 0.16

	Control	PORT
Median DFS	22.8 mo (95% CI = [17;37])	30.5 mo (95% CI = [24;49])
3-yr DFS	43.8% (95% CI = [37;51])	47.1 % (95% CI = [40;54])

95%CI = 95% bilateral Confidence Interval



OS



Le Pechoux C, et al. ESMO 2020. Abstract LBA3_PR.

LUNG ART: Causes of Death

	Control arm (n = 249)	PORT arm (n = 252)
Deaths	102 (41.5%)	99 (39.6%)
Cause of death		
- Progression or recurrence	87 (86.1%)	68 (69.4%)
- Cardio-pulmonary	2 (2.0%)	16 (16.2%)
- Second primary	1 (1.0%)	5 (5.1%)
- RT or CT related toxicity	0 (0%)	3 (3.0%)
- Other	11 (10.9%)	6 (6.1%)
- Unreported	1	1

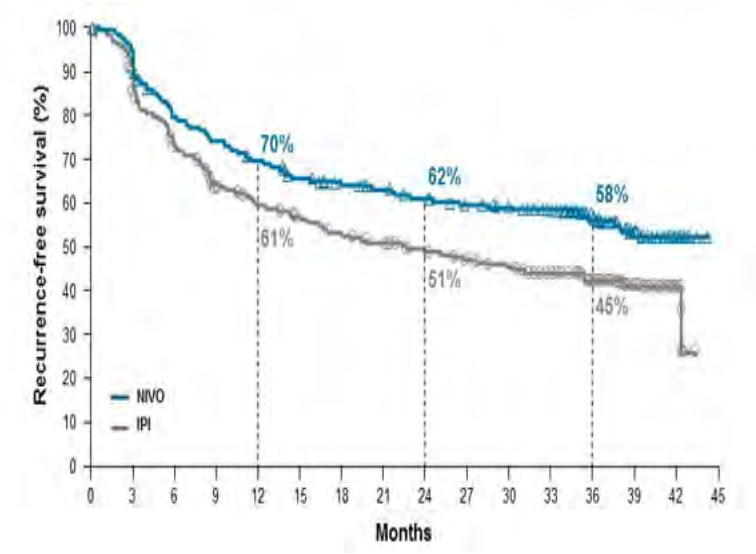
Percents calculated on non missing data

Le Pechoux C, et al. ESMO 2020. Abstract LBA3_PR.

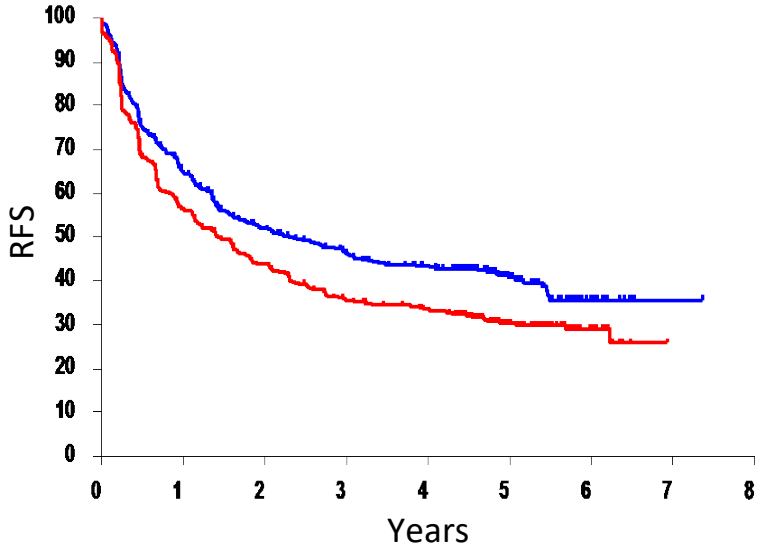
Adjuvant Chemotherapy 2022

- **Standard: cisplatin-based chemotherapy**
- **Standard: II–IIIA**
- **Option: carboplatin**
- **Criteria: <75 years, within 2 months after surgery, PS 0–1**
- **Osimertinib 3 years if *EGFR* mutated**

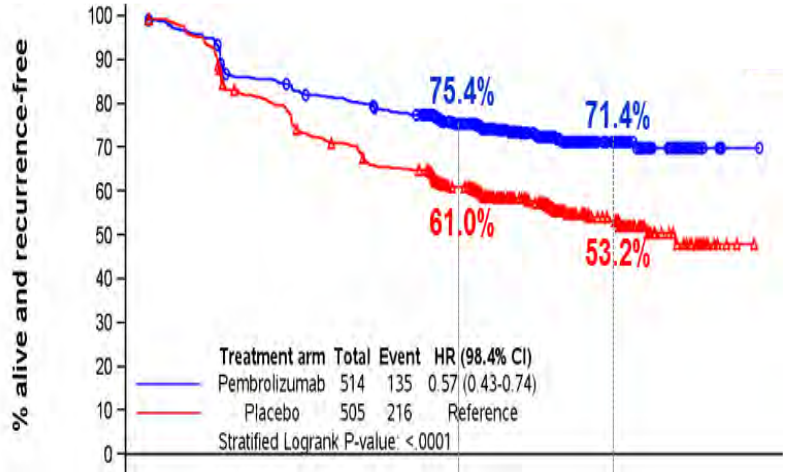
Adjuvant ICI Changing History in LA Melanoma



Ipilimumab 10 mg/kg vs nivolumab
Stage IIIB–C + IV
RFS HR: 0.68



Ipilimumab 10 mg/kg vs placebo
Stage IIIA–C
RFS HR: 0.76
OS HR: 0.72



Pembrolizumab vs placebo
Stage IIIA–C
RFS HR: 0.57

Weber JS, et al. ESMO 2019. Abstract 2801; Long GV, et al. *N Engl J Med.* 2018;378:679-680; Weber J, et al. *N Engl J Med.* 2018;378:680; Eggermont AMM, et al. *N Engl J Med.* 2018;378:1789-1801.

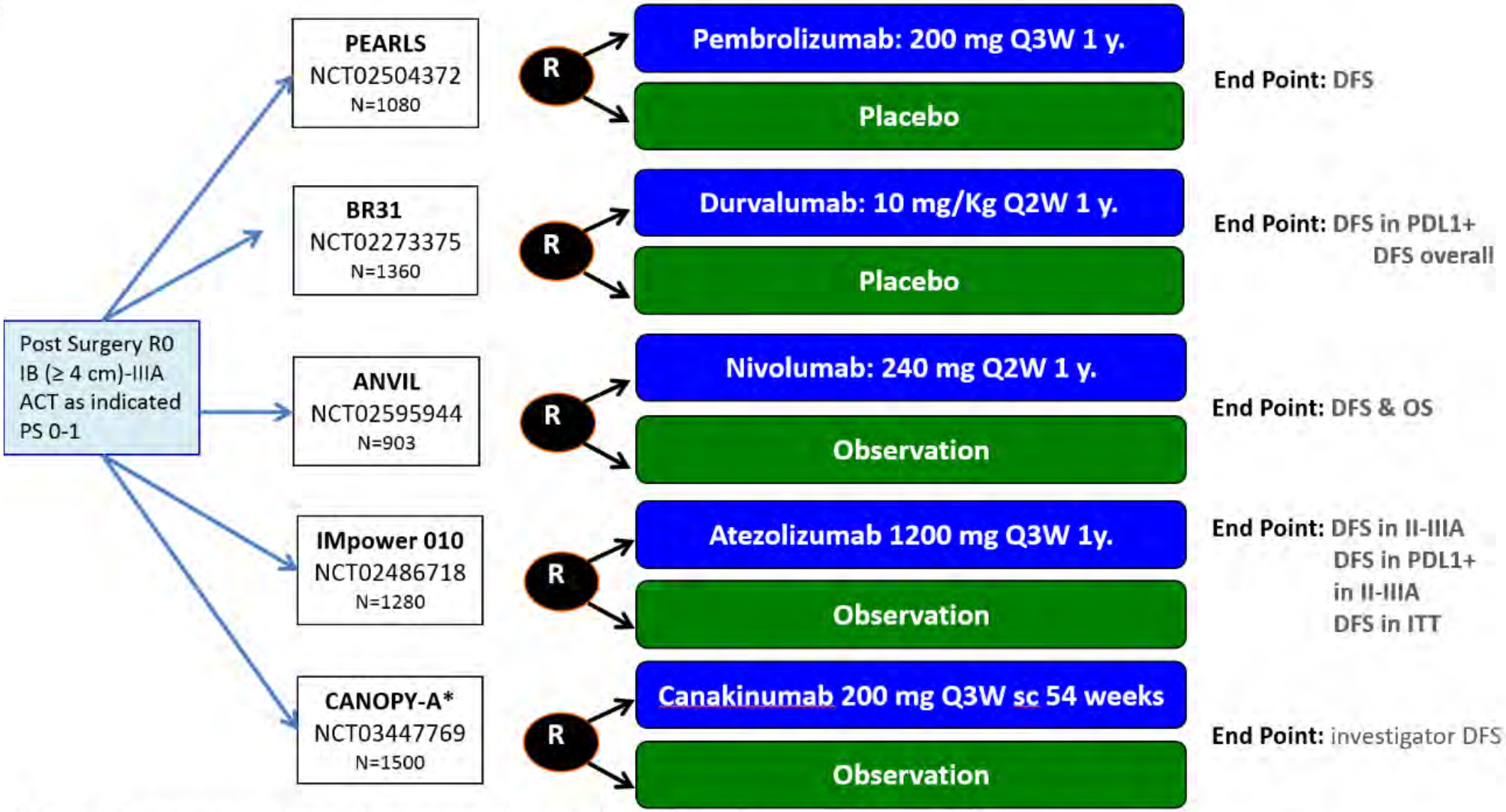


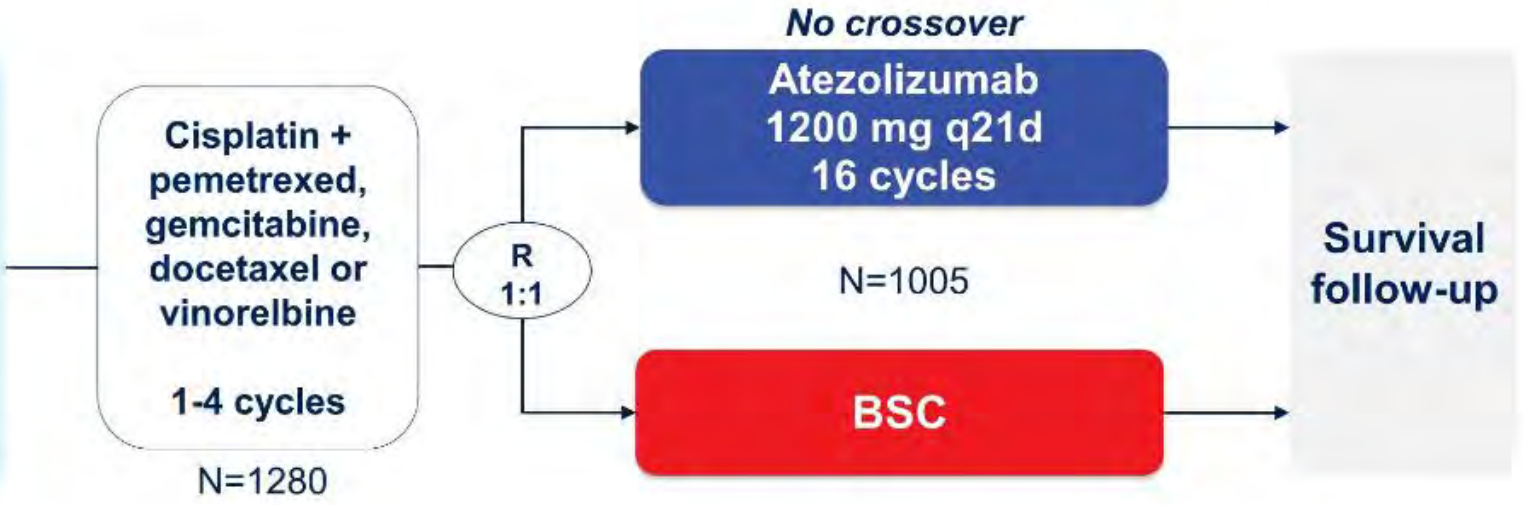
Figure 2. Ongoing phase III trials with adjuvant ICI. * IIA-IIIB (N2 only) according to 8th TNM
ACT: adjuvant chemotherapy. PS: Performance Status. 1y.: 1 year. DFS: disease free survival. OS: Overall Survival. sc: subcutaneous

Courtesy of J. Remon.

Adjuvant: IMpower010

Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7

- Stage IB tumors ≥4 cm
- ECOG 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis



Stratification factors

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

Primary endpoints

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

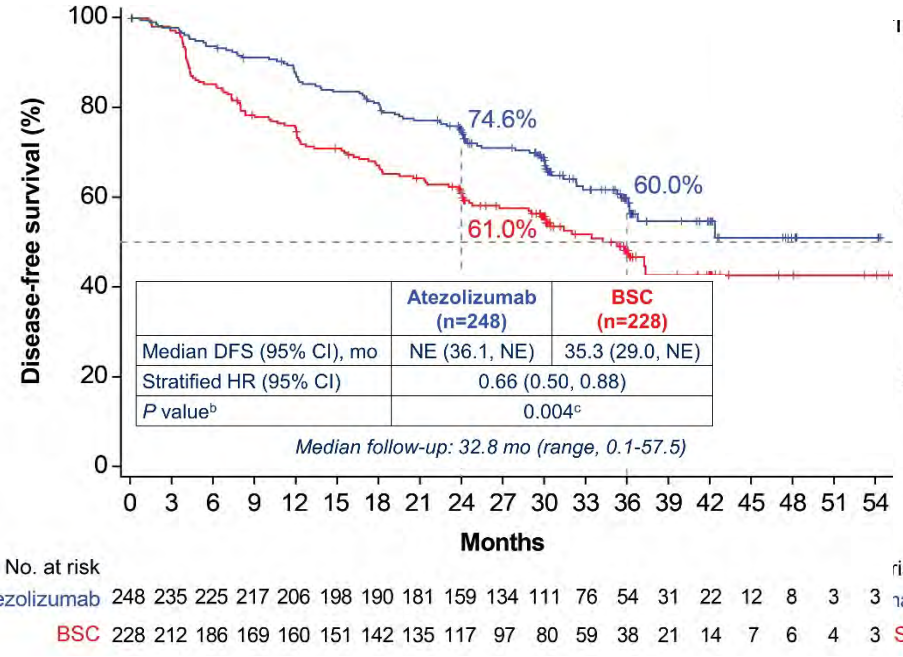
Key secondary endpoints

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

Wakelee HA, et al. ASCO 2021. Abstract 8500.

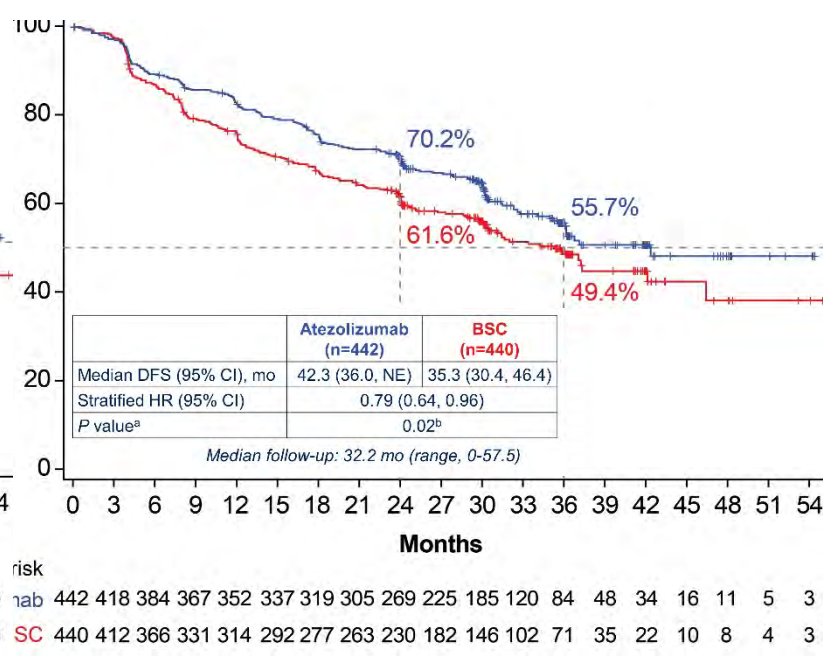
Adjuvant: IMpower010

DFS PD-L1–Positive Stage II–III



HR 0.66 (0.50, 0.88)
***P* = .004**

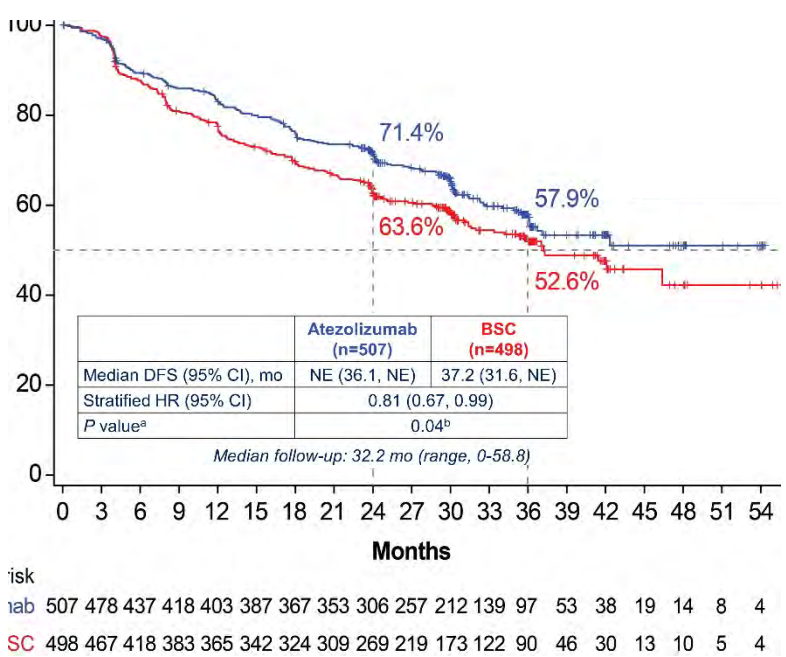
DFS Stage II–III



HR 0.79 (0.64, 0.96)
***P* = .02**

Current/never smoker, N0, *EGFR* positive, *ALK* positive, PD-L1 negative, no benefit

DFS Stage IB–III



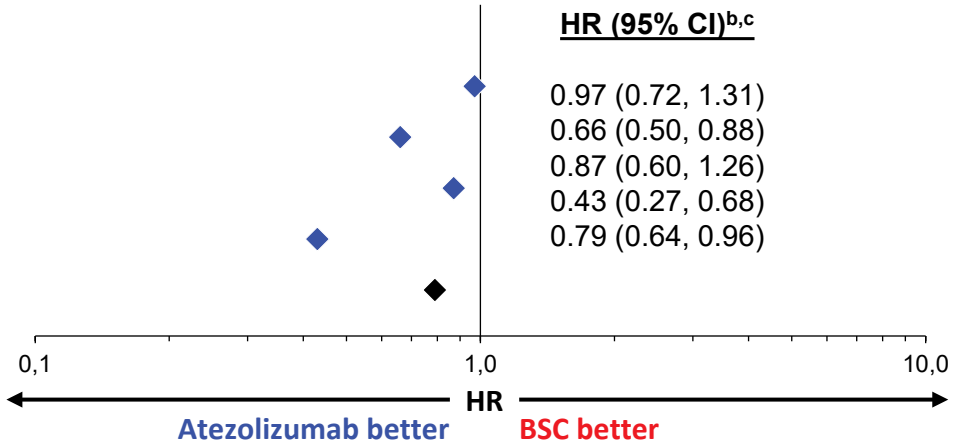
HR 0.81 (0.67, 0.99)
***P* = .04**
NOT SIGNIFICANT

Courtesy L. Hendriks.

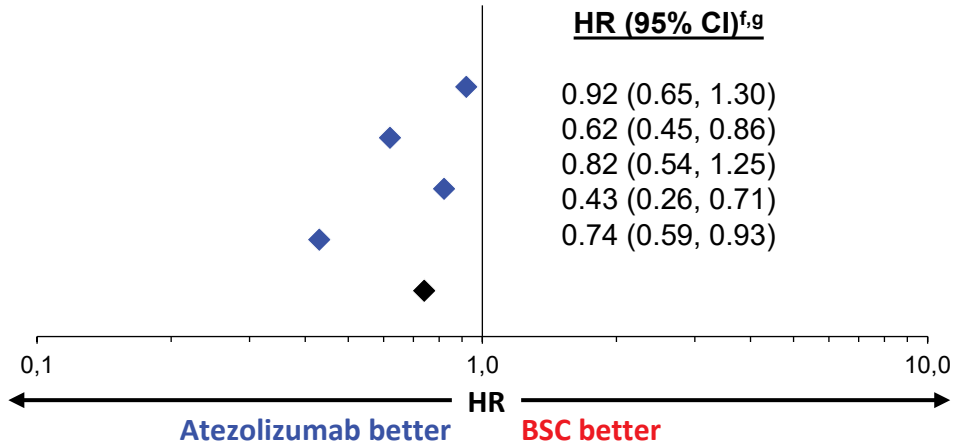
Wakelee HA, et al. ASCO 2021. Abstract 8500.

DFS by PD-L1 Status: All-Randomized Stage II–IIIA Population (with and without known *EGFR/ALK*-positive disease)

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



Subgroup (excluding *EGFR/ALK* positive)[e]	n	HR (95% CI)[f,g]
PD-L1 status by SP263		
TC <1%	312	0.92 (0.65, 1.30)
TC ≥1%	410	0.62 (0.45, 0.86)
TC 1%–49%	201	0.82 (0.54, 1.25)
TC ≥50%	209	0.43 (0.26, 0.71)
All patients[h]	743	0.74 (0.59, 0.93)



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

Felip E, et al. ESMO 2021. Abstract LBA9.

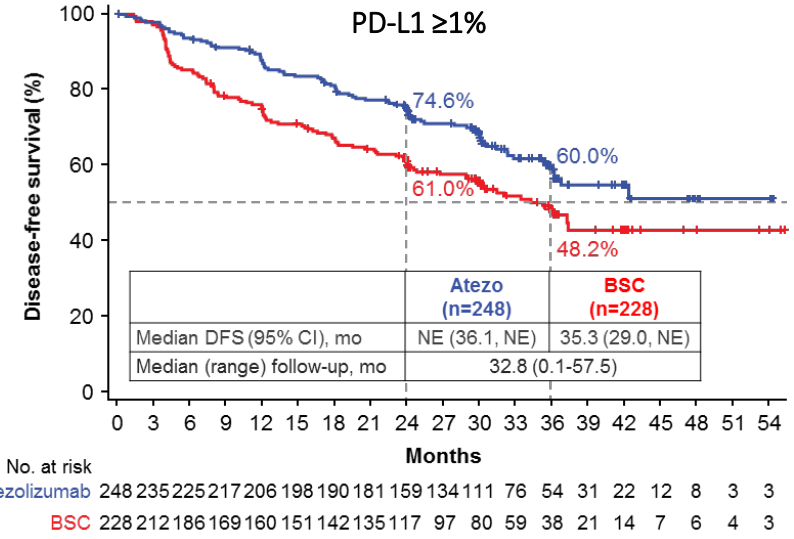
Adjuvant: IMpower010

Summary of Previous Results: DFS in Stage II–IIIA

Population analyzed for DFS	n	HR (95% CI)
PD-L1 TC ≥1%[a] stage II–IIIA	**476**	**0.66 (0.50, 0.88)[b]**
PD-L1 TC 1%–49% stage II–IIIA	247	0.87 (0.60, 1.26)[c]
PD-L1 TC ≥50% stage II–IIIA	**229**	**0.43 (0.27, 0.68)[c]**

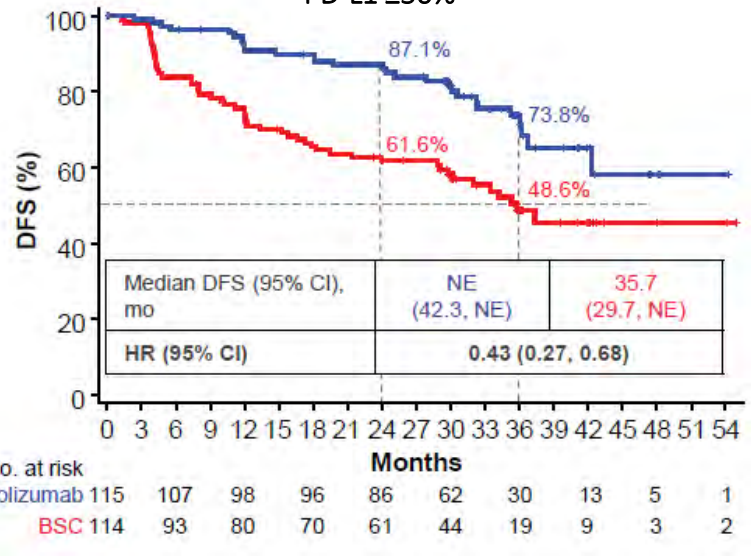
[a]Per SP263 assay. [b]Stratified. [c]Unstratified.

PD-L1 ≥1%



APPROVAL

PD-L1 ≥50%



APPROVAL

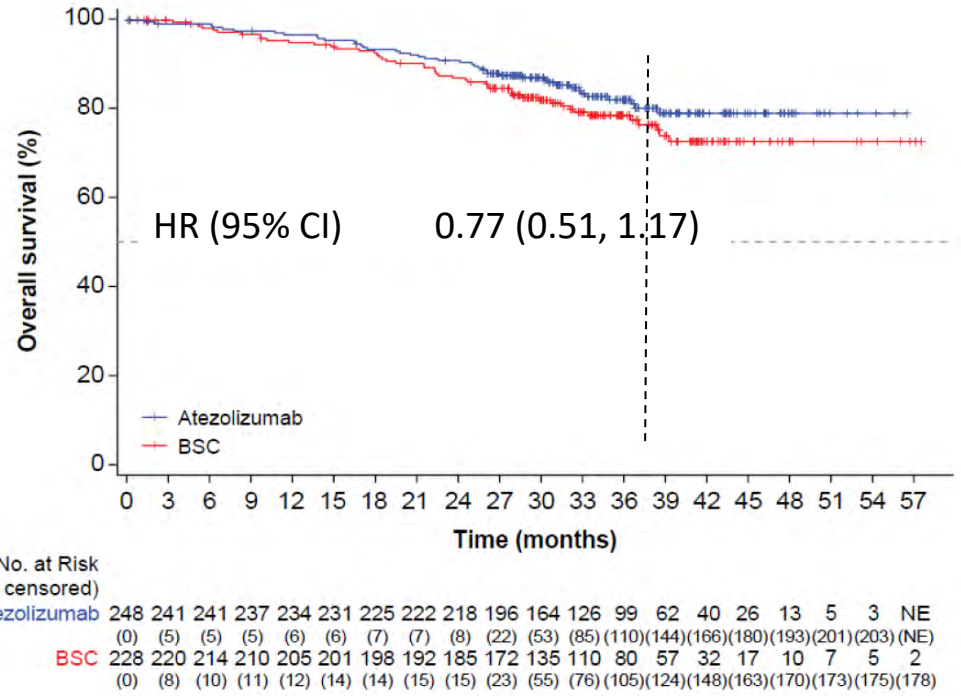
and other countries

Felip E, et al. *Lancet*. 2021;398:1344-1357.

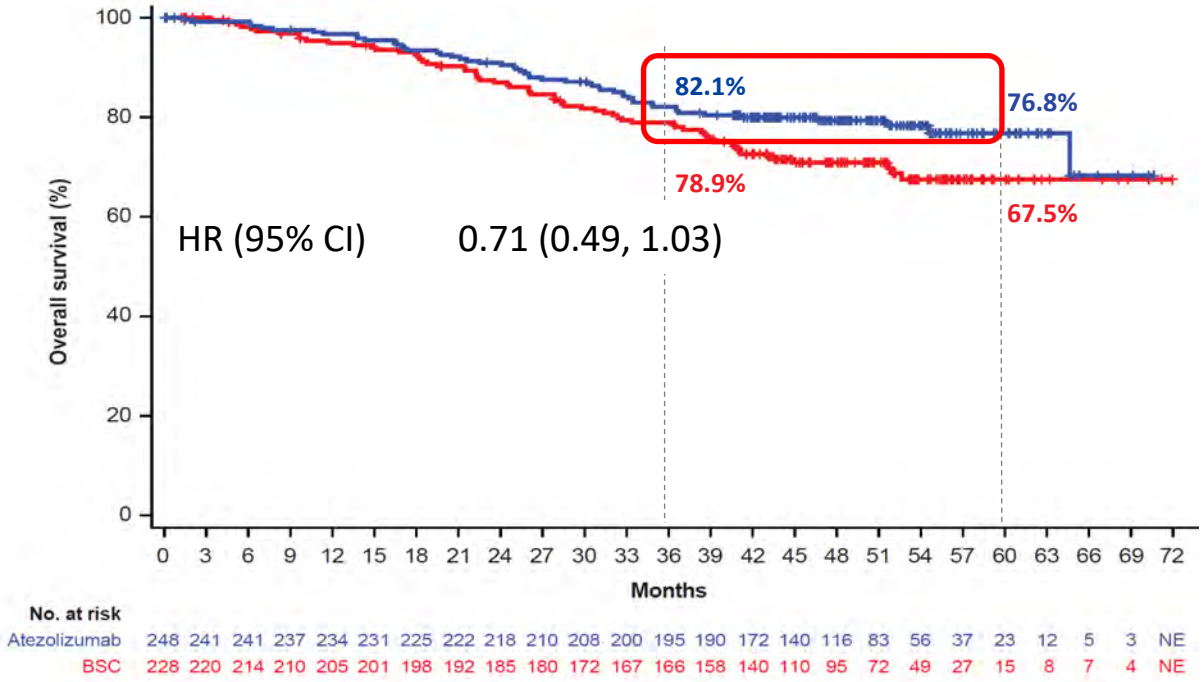
Adjuvant: IMpower010

Overall Survival: PD-L1 TC ≥1% Stage II/IIIA Population

Median Duration of Follow-up 32.8 mo



Median Duration of Follow-up 46 mo

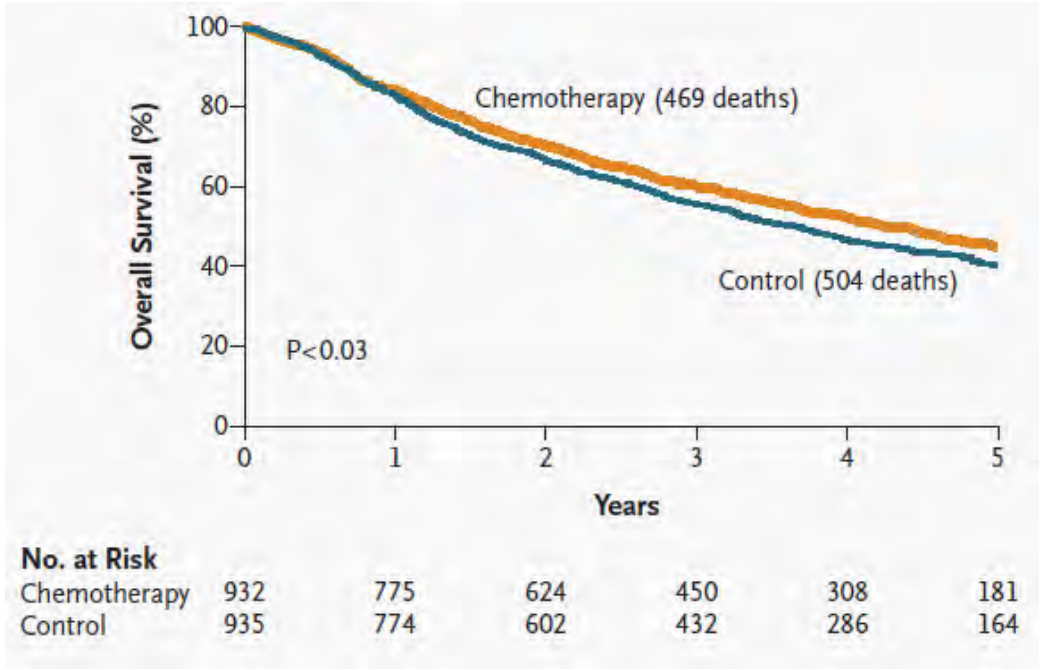


Felip E, et al. *Lancet*. 2021;398:1344-1357; Felip E, et al. WCLC 2022. Abstract PL03.09.

Adjuvant: IMpower010

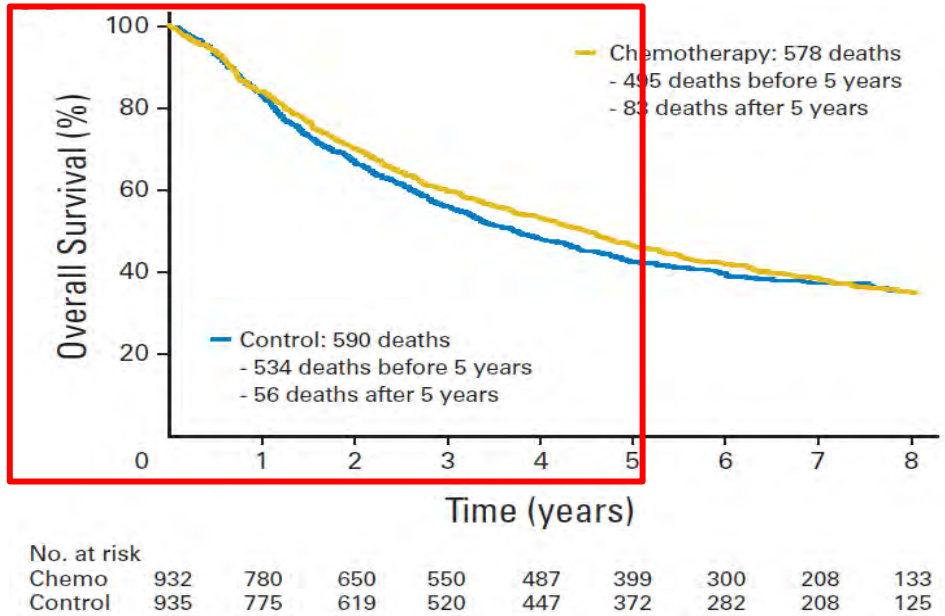
Overall Survival: With Adjuvant Chemotherapy

IALT: 4.6-Yr Follow-up



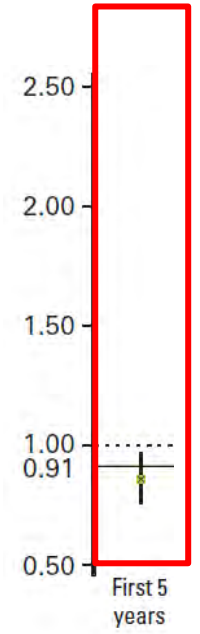
HR 0.86 (95 % CI 0.76–0.98) *P* <.03)

IALT: 7.5-Yr Follow-up



HR 0.91 (95% CI 0.81–1.02) *P* = .10

HR

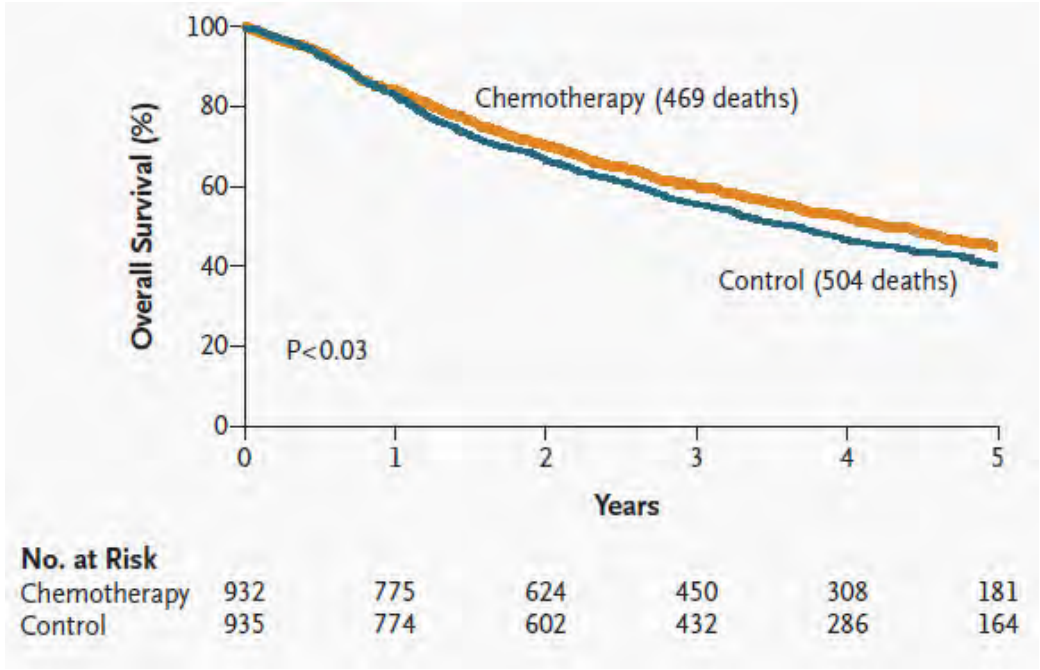


Le Chevalier et al. *N Engl J Med.* 2004; Le Chevalier et al. *J Clin Oncol.* 2009.

Adjuvant: IMpower010

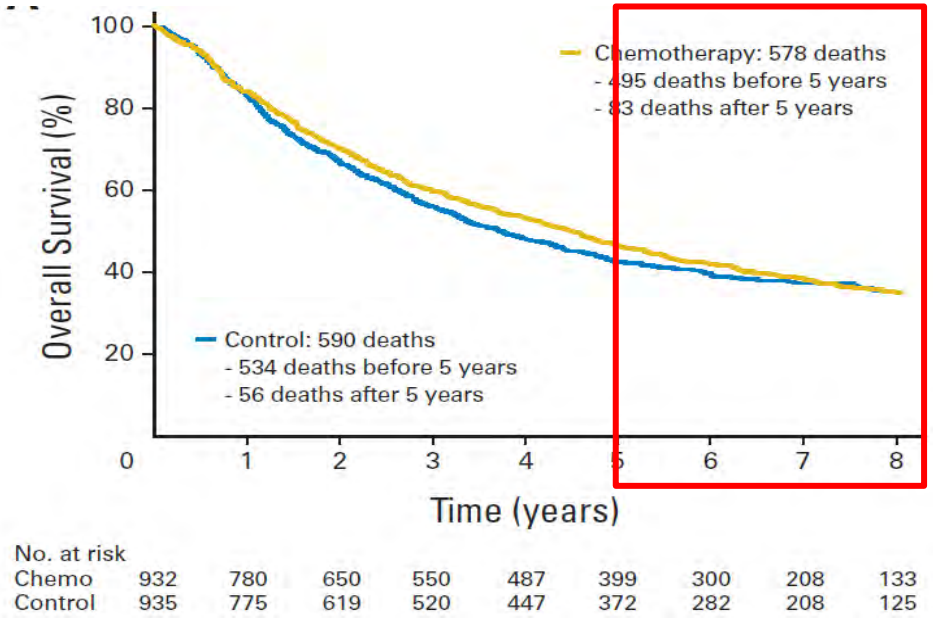
Overall Survival: With Adjuvant Chemotherapy

IALT: 4.6-Yr Follow-up



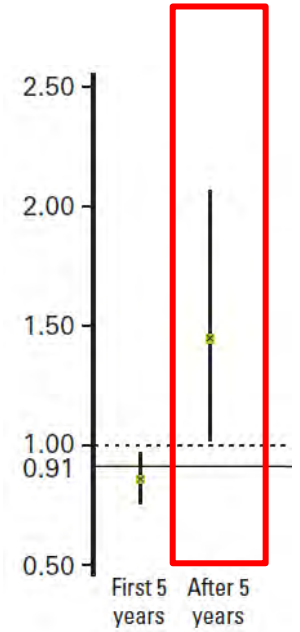
HR 0.86 (95 % CI 0.76–0.98) *P* <.03)

IALT: 7.5-Yr Follow-up



HR 0.91 (95% CI 0.81–1.02) *P* = .10

HR

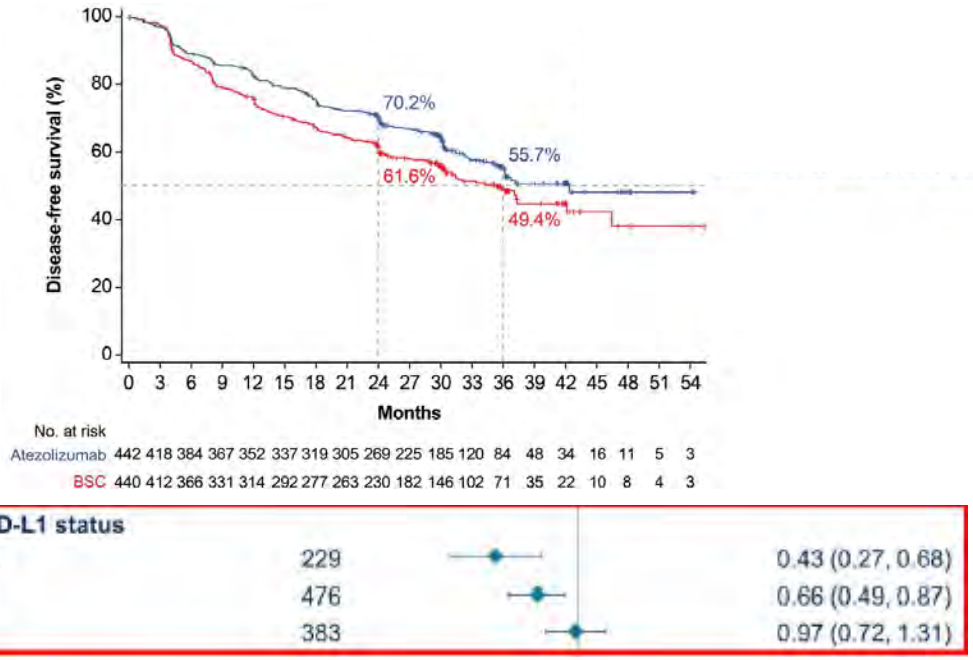


Le Chevalier et al. *N Engl J Med.* 2004; Le Chevalier et al. *J Clin Oncol.* 2009.

Patients Benefit IO Whatever the Line?

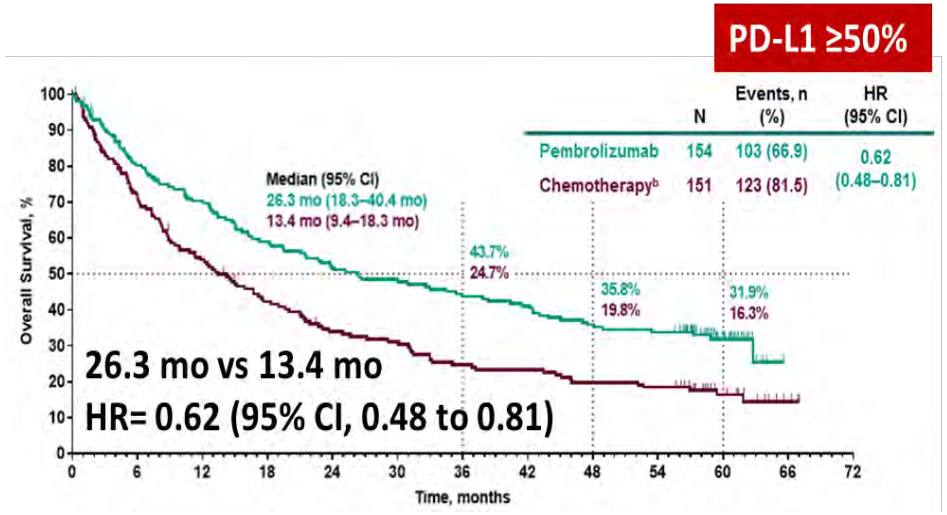
- Is the adjuvant benefit restricted to those who respond to first-line therapy?

IMpower010
Adjuvant Atezolizumab
Stage II–IIIA Population



Curves for PD-L1 ≥50% unseen.

KEYNOTE-024
First-Line Pembrolizumab
Stage IIIB–IV Population



Felip E, et al. ESMO 2021. Abstract LBA9.

PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial

Eligibility for Registration

- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing
done centrally using PD-L1 IHC 22C3 pharmDx

Eligibility for Randomization

- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R 1:1

Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 yr)

Placebo Q3W for ≤18 administrations (~1 yr)

Stratification Factors

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

Dual Primary End Points

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

Secondary End Points

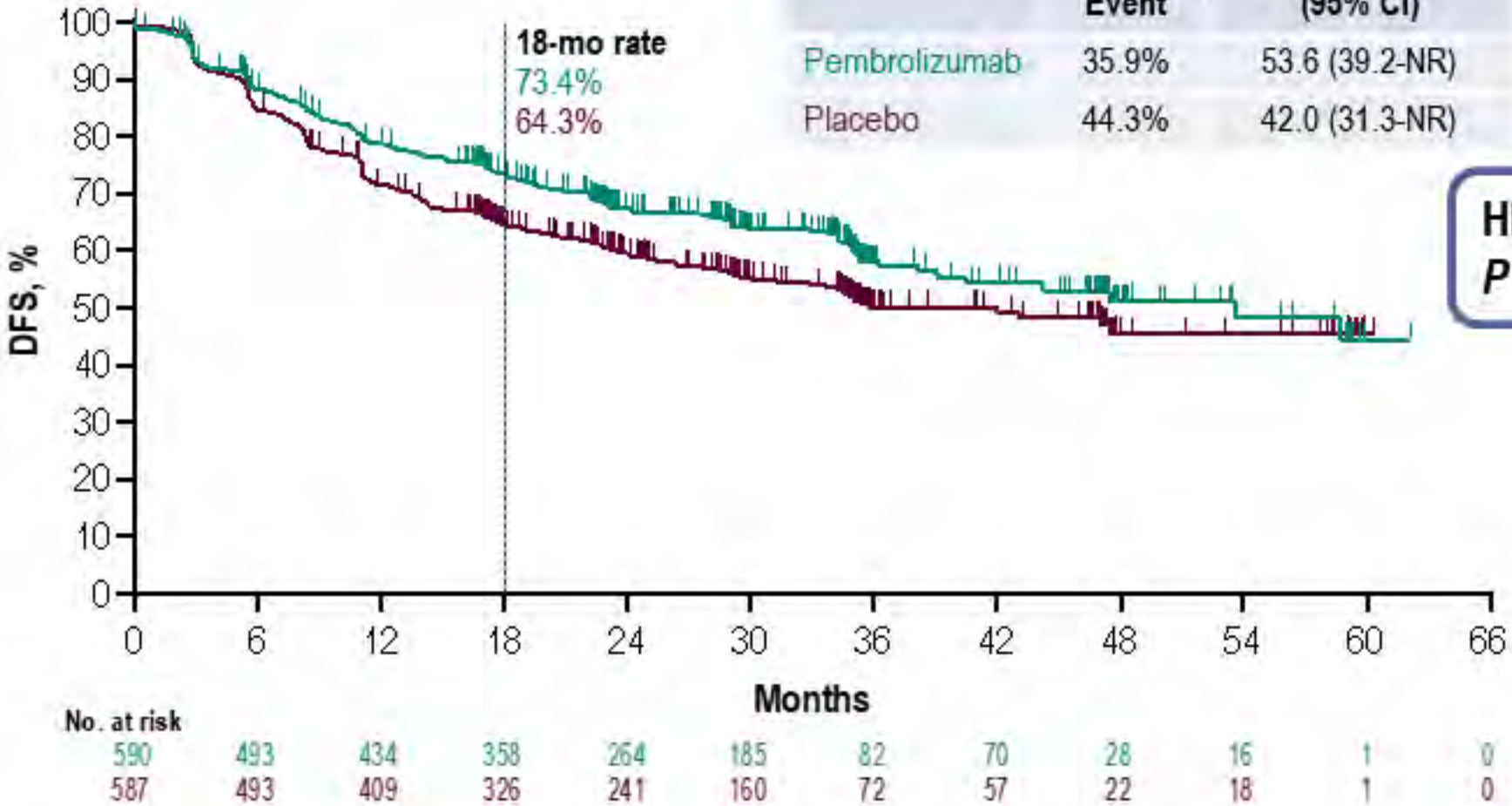
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

ESMO VIRTUAL PLENARY

ClinicalTrials.gov number, NCT02504372.

DFS, Overall Population

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



HR 0.76 (95% CI, 0.63-0.91)
***P* = 0.0014**

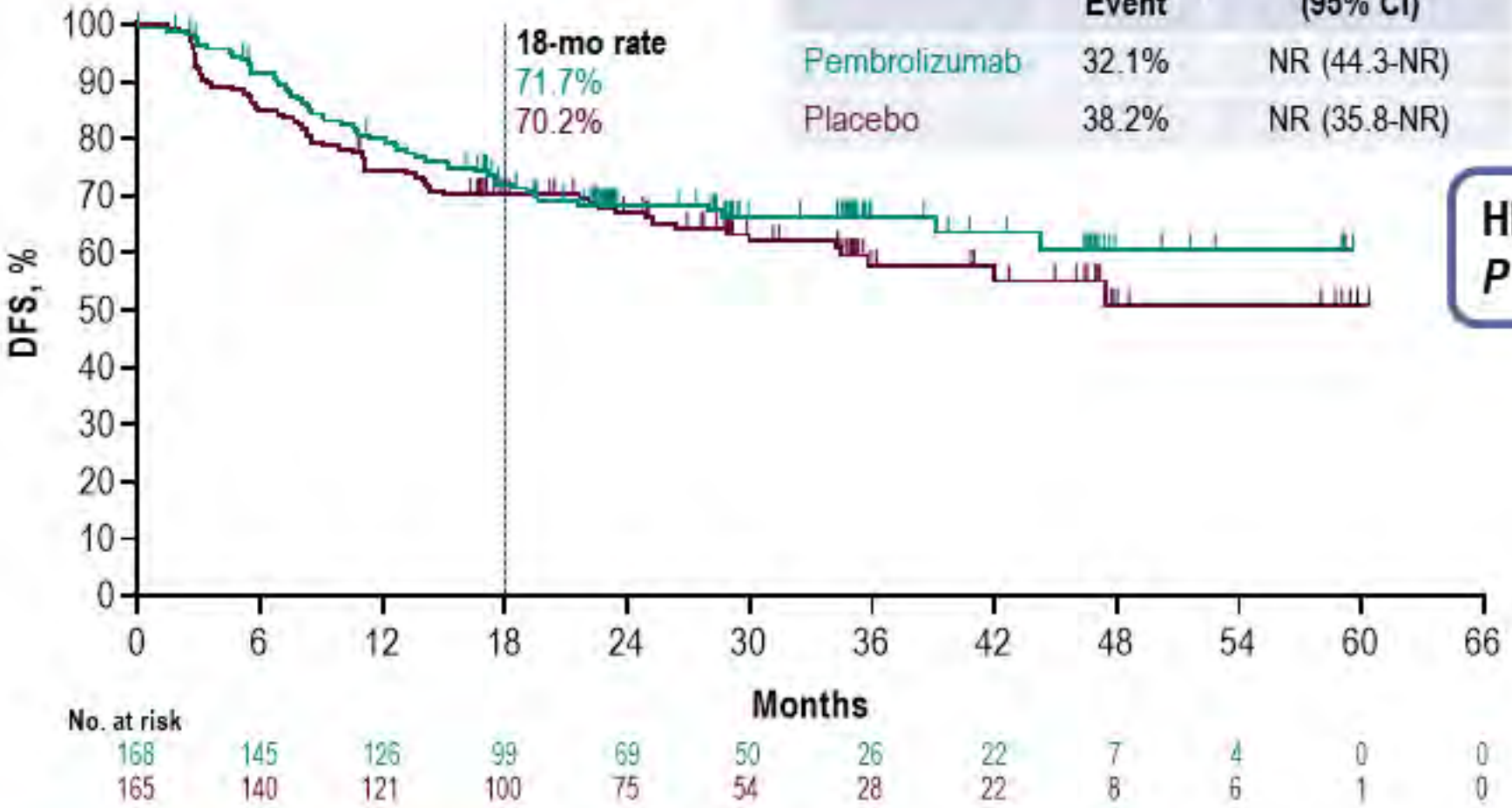
ESMO VIRTUAL PLENARY

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

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

DFS, PD-L1 TPS ≥50% Population

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



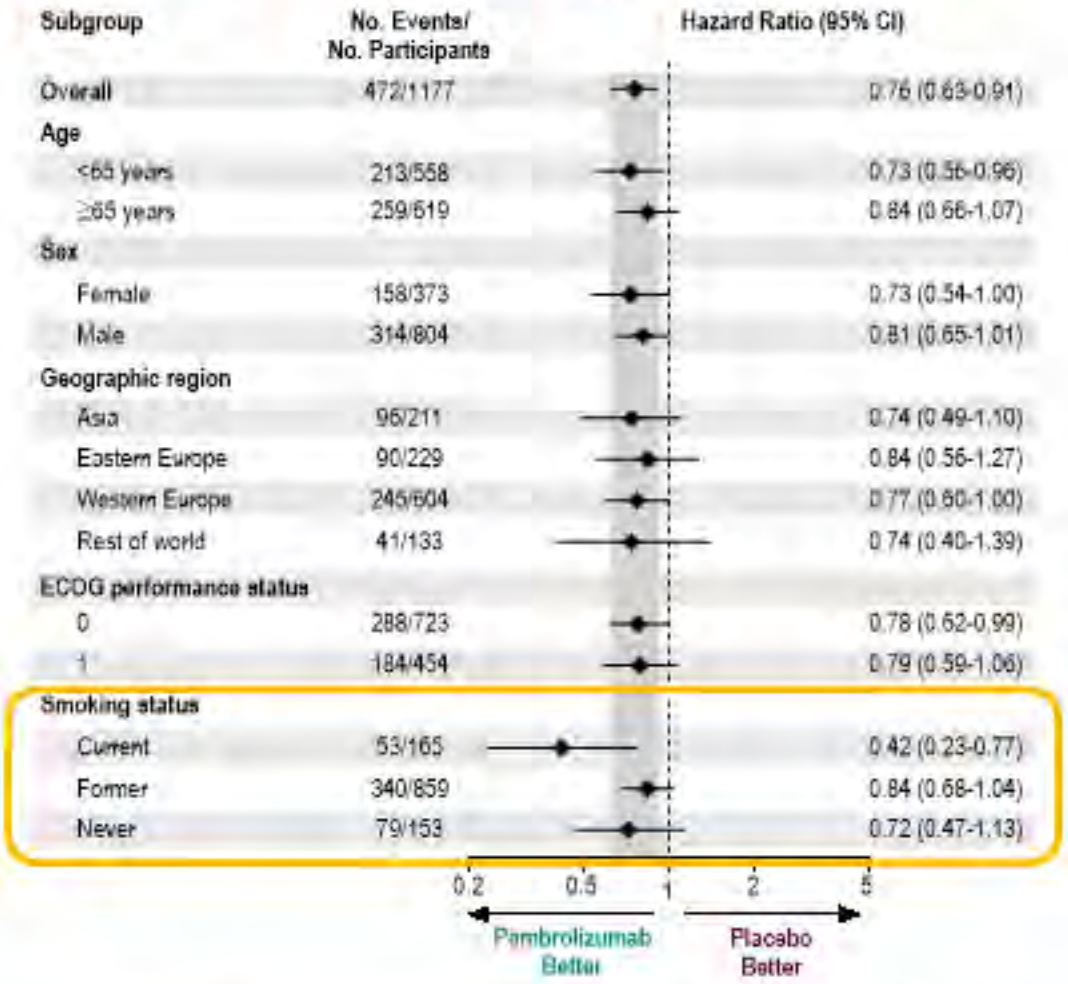
HR 0.82 (95% CI, 0.57-1.18)
***P* = 0.14**

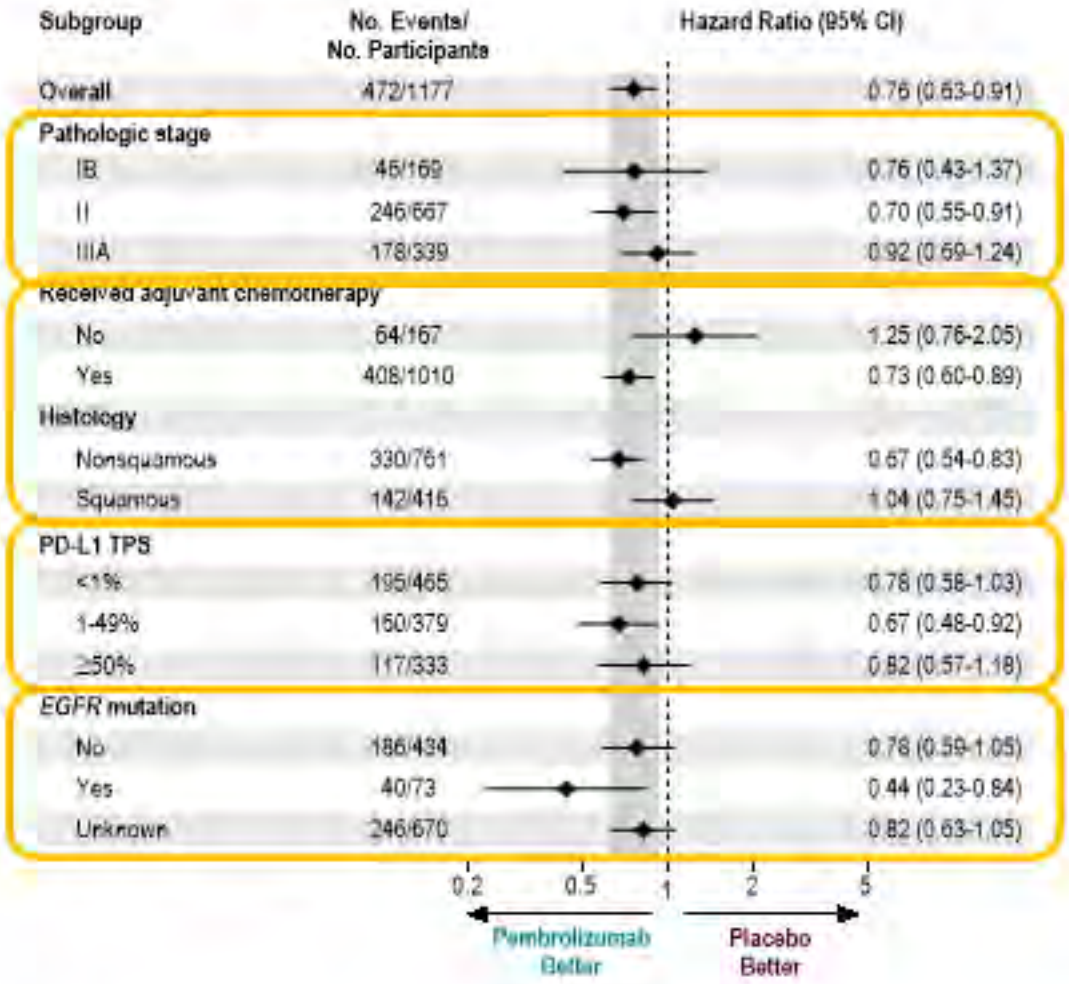
ESMO VIRTUAL PLENARY

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

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

DFS in Key Subgroups, Overall Population





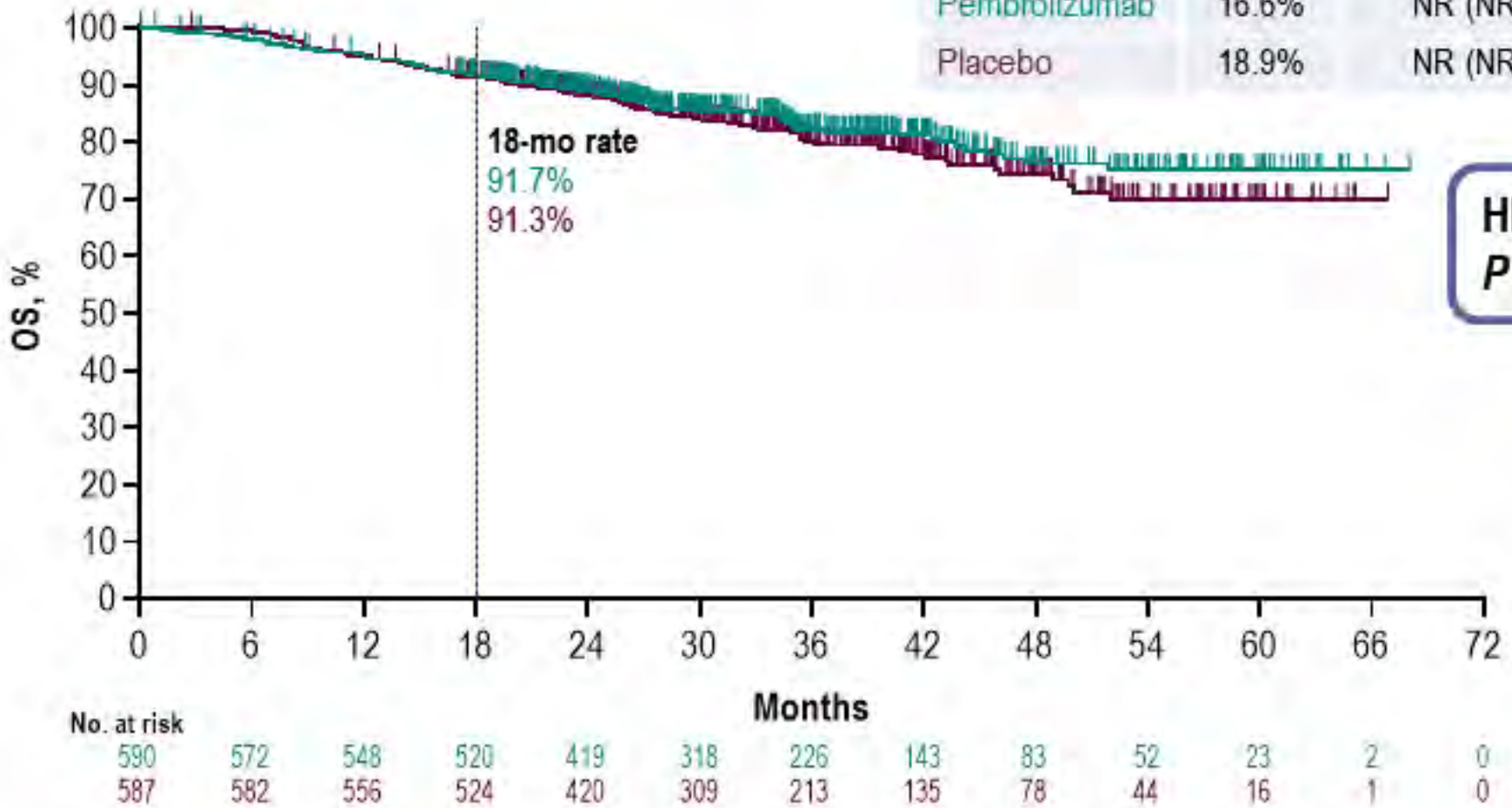
ESMO VIRTUAL PLENARY

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

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

OS, Overall Population

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



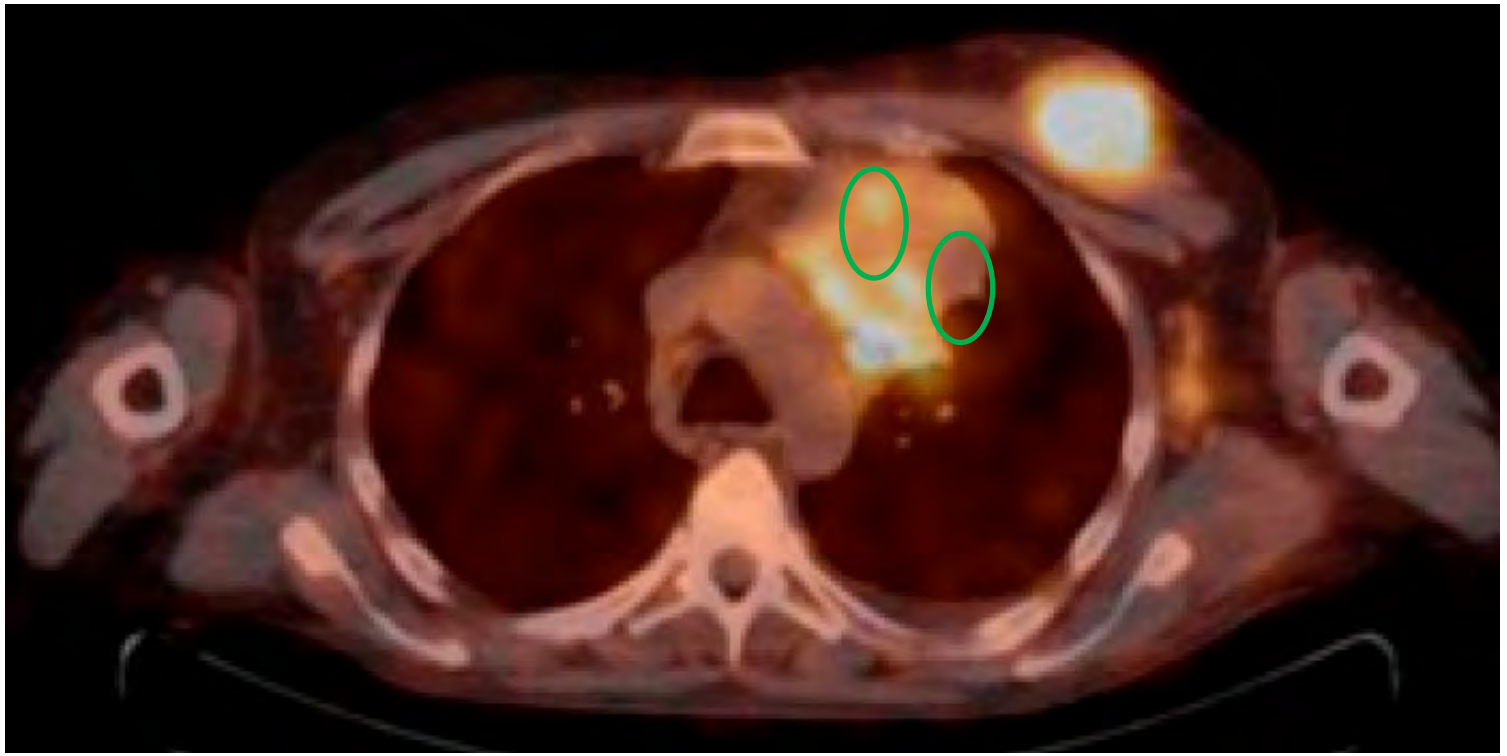
HR 0.87 (95% CI, 0.67-1.15)
***P* = 0.17**

ESMO VIRTUAL PLENARY

Data cutoff date: September 20, 2021

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

^{89}Zr-Pembrolizumab PET/CT: Heterogeneous Uptake



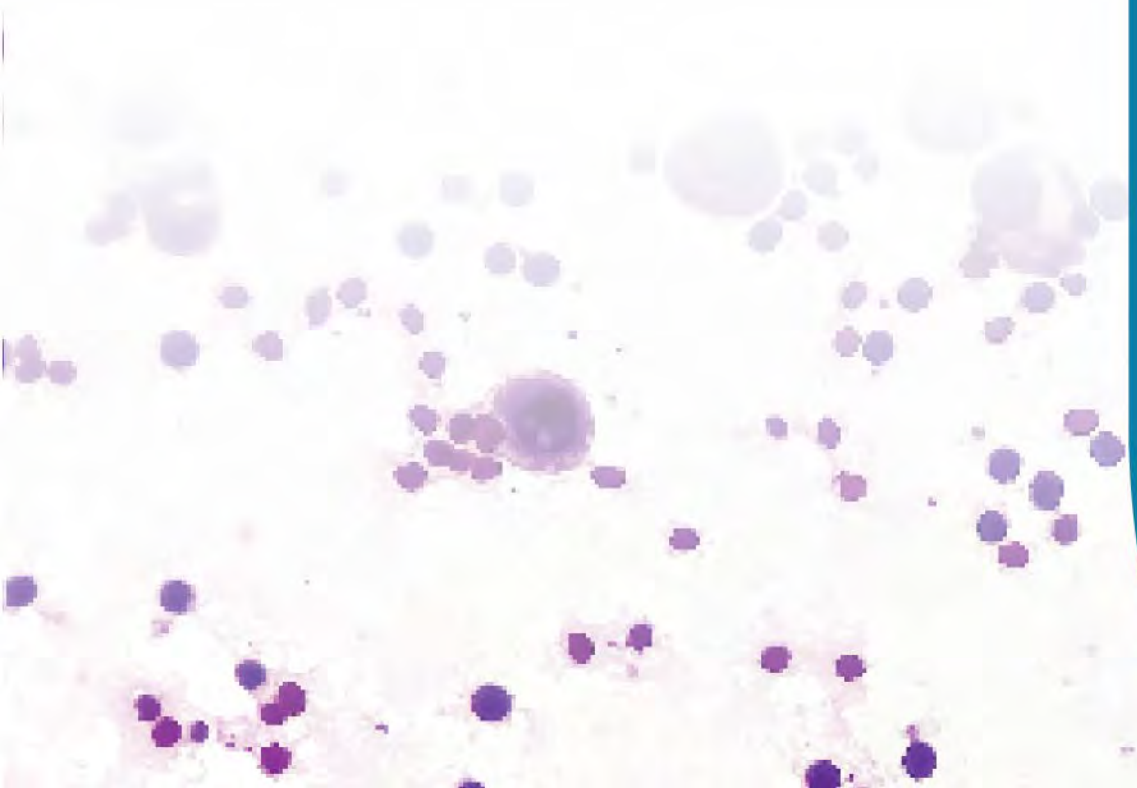
Where PD-L1 is tested?

Niemeijer AN, et al. *J Nucl Med*. 2022;63:362-367.

Adjuvant Chemotherapy 2022

- **Standard: cisplatin-based chemotherapy**
- **Standard: II–IIIA**
- **Option: carboplatin**
- **Criteria: <75 years, within 2 months after surgery, PS 0–1**
- **Osimertinib 3 years if *EGFR* mutated**
- **Atezolizumab 1 year if PD-L1 1%+ or 50%**
- ***Pembrolizumab 1 year all comers?***

Global Lung Cancer Academy



Tumor Board Discussion

Moderator: Solange Peters, MD

Case presenters: Johan Vansteenkiste, MD, PhD, and Daphne Dumoulin, MD

Global Lung Cancer Academy

Patient Case 1

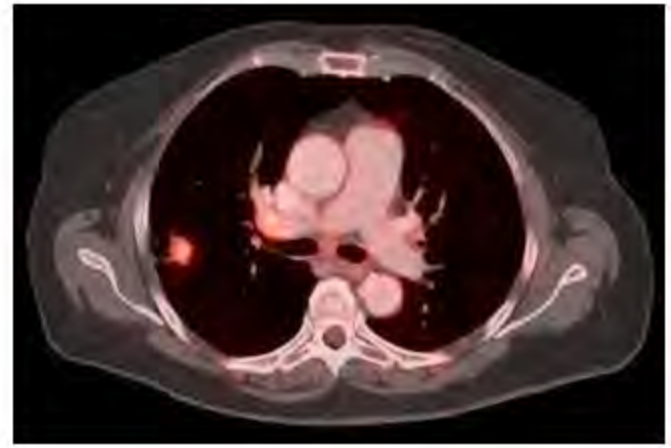
Johan Vansteenkiste, MD, PhD

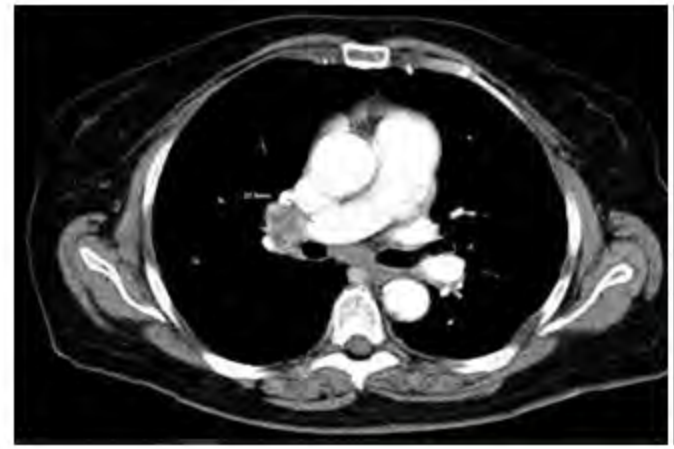
Disclosures [update 09/2022, alphabetical]

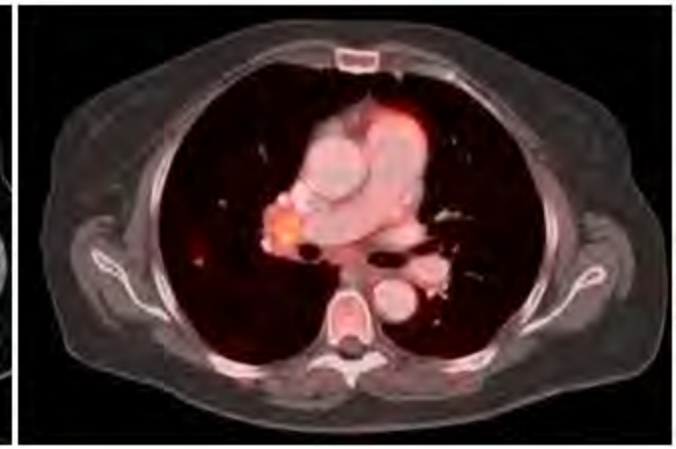
- **Research funding at University Hospitals KU Leuven**
  - **MSD**
- **Advisory functions**
  - **AstraZeneca, BMS, Daiichi-Sankyo, Janssen, Merck, MSD, Novartis, PDCline, Pfizer, Roche, Sanofi**
- **Lectures**
  - **AstraZeneca, BMS, Janssen, Novartis, Roche, Sanofi**
- **Others**
  - **None**

Case study: 64 year old female

- Medical history
  - 35 pack-year smoker
  - 2013: type 2 diabetes – insulin started
  - 2017: rheumatoid arthritis – currently on methotrexate 15 mg weekly
- 01/2020: referral from other hospital
  - Persistent abnormality in R lung after R lung pneumonia
  - Chronic fatigue, no other symptoms
  - FDG PET-CT: R lung lesion 18 mm – major R hilar lymph node disease – no distant lesions
- Bronchoscopy-EBUS
  - Endobronchial normal – EBUS: multiple TBNA samples
  - Pathology:
    - LN 10R: squamous cell carcinoma – PD-L1 10%
    - LN 7, 4R, 4L, 2R: free of tumor







Stage IIb: T1b N1 M0

Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

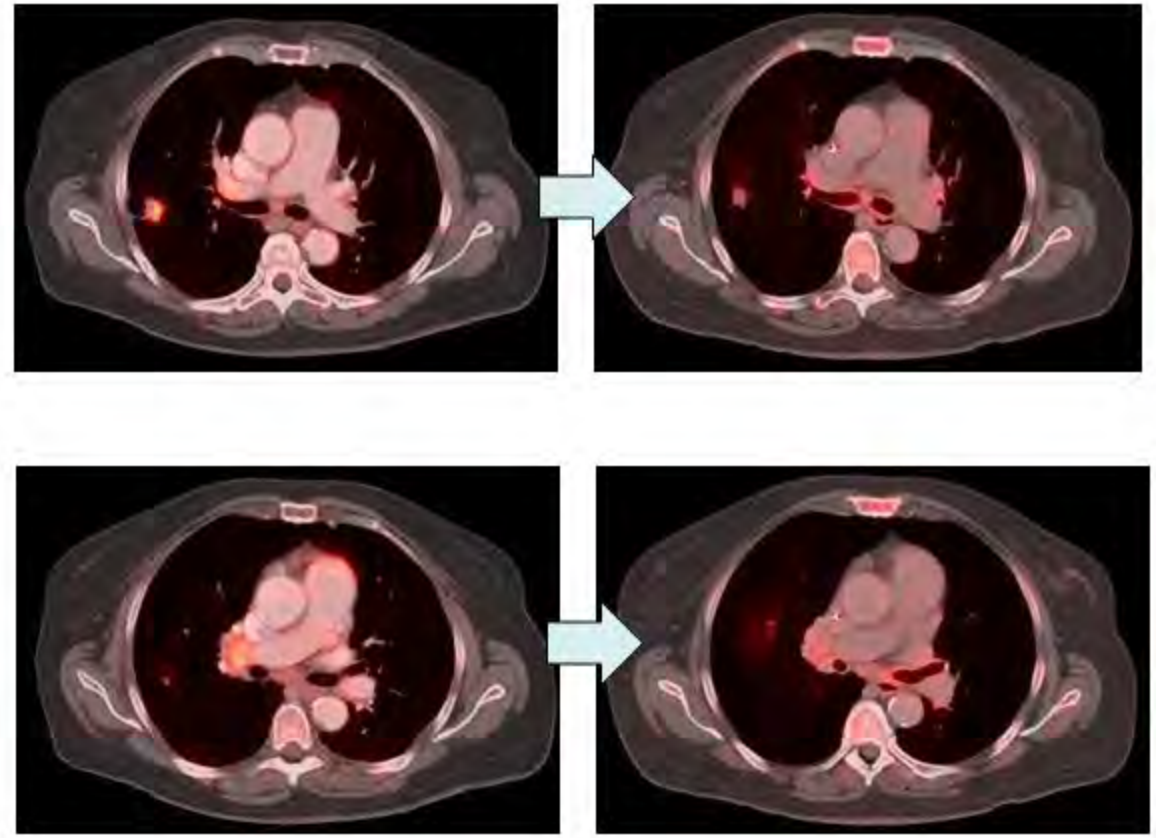
Case study: 64 year old female
> polling question

- **Which of the following options do you prefer?**
  1. **Surgical resection/LN dissection followed by adjuvant chemotherapy**
  2. **Neoadjuvant chemotherapy followed by surgical resection/LN dissection**
  3. **Neoadjuvant chemoradiotherapy followed by surgical resection/LN dissection**
  4. **Trial with neoadjuvant chemo-immunotherapy followed by surgical resection/LN dissection**

Case study: 64 year old female

> multidisciplinary tumor board

- Thoracic surgeon: major hilar N1 disease will most probably lead to pneumonectomy – neoadjuvant approach preferred
- 3 cycles of neoadjuvant therapy -> little volume change, but metabolic response on FDG PET-CT
- Surgery
  - Resection limited to superior bilobectomy
- Pathology: ypT1aN0
  - Few viable tumor cells
  - All lymph nodes free of tumor



Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Case study: 64 year old female

> multidisciplinary tumor board

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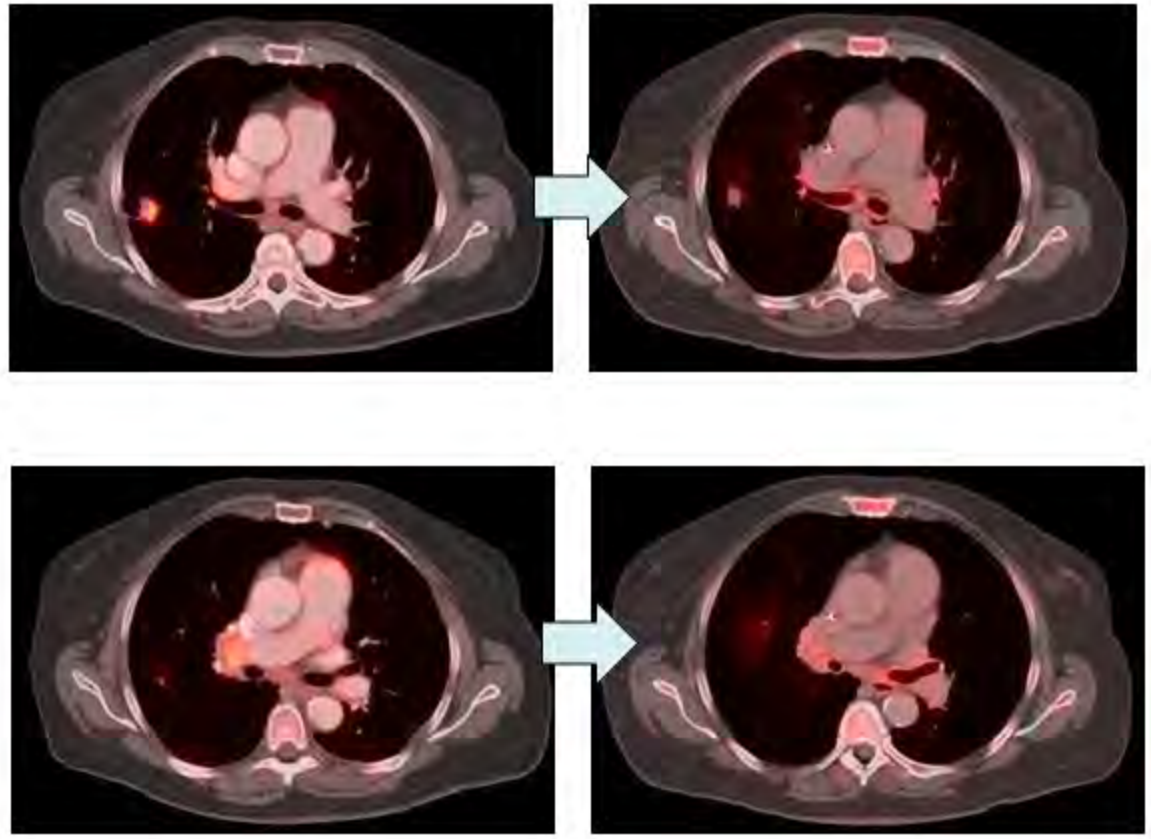


➢ Neoadjuvant therapy was 3 cycles of carboplatin-gemcitabine [non-eligible for Keynote-671 chemo-immuno trial because of poor renal function]

Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Thank you for your kind attention

Respiratory Oncology Unit
Univ. Hospital Leuven
Leuven Lung Cancer Group
http://www.LLCG.be

Global Lung Cancer Academy

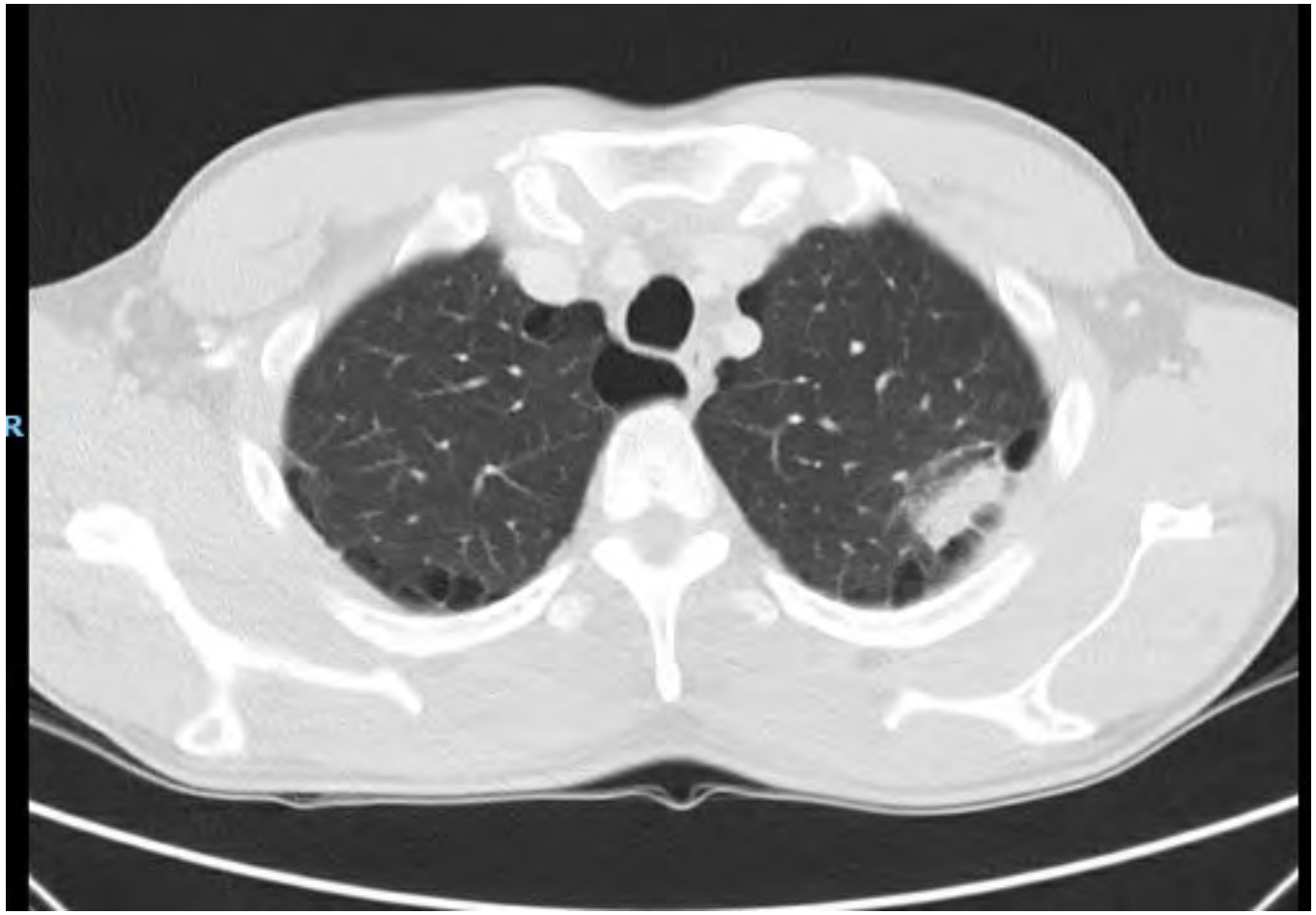
Patient Case 2

Daphne Dumoulin, MD

Case Presentation

March 2020: ~40-year-old man

- Persisting thoracic pain after viral infection
- Former smoker, 10 PY
- No relevant medical history
- Medication: paracetamol, tramadol
- WHO PS 1



CT Feb 2020

CT-guided biopsy: adenocarcinoma

Diagnosis: cT3N0M0 NSCLC LUL

Erasmus MC Cancer Institute

How should we treat this patient?

1. Upfront surgery
2. Neoadjuvant treatment
3. Chemoradiotherapy
4. Other

Tumor Board March 2020

cT3N0M0 NSCLC adenocarcinoma LUL

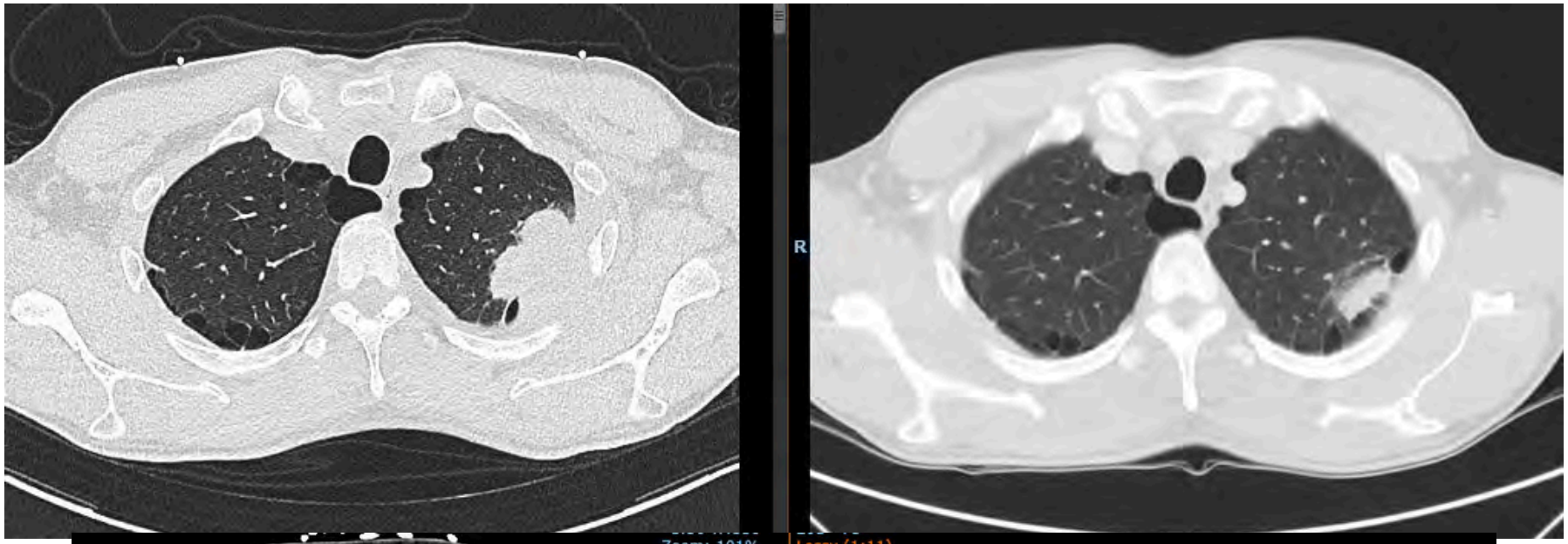
- Involvement chest wall
- CheckMate 77T trial on hold due to COVID-19 circumstances

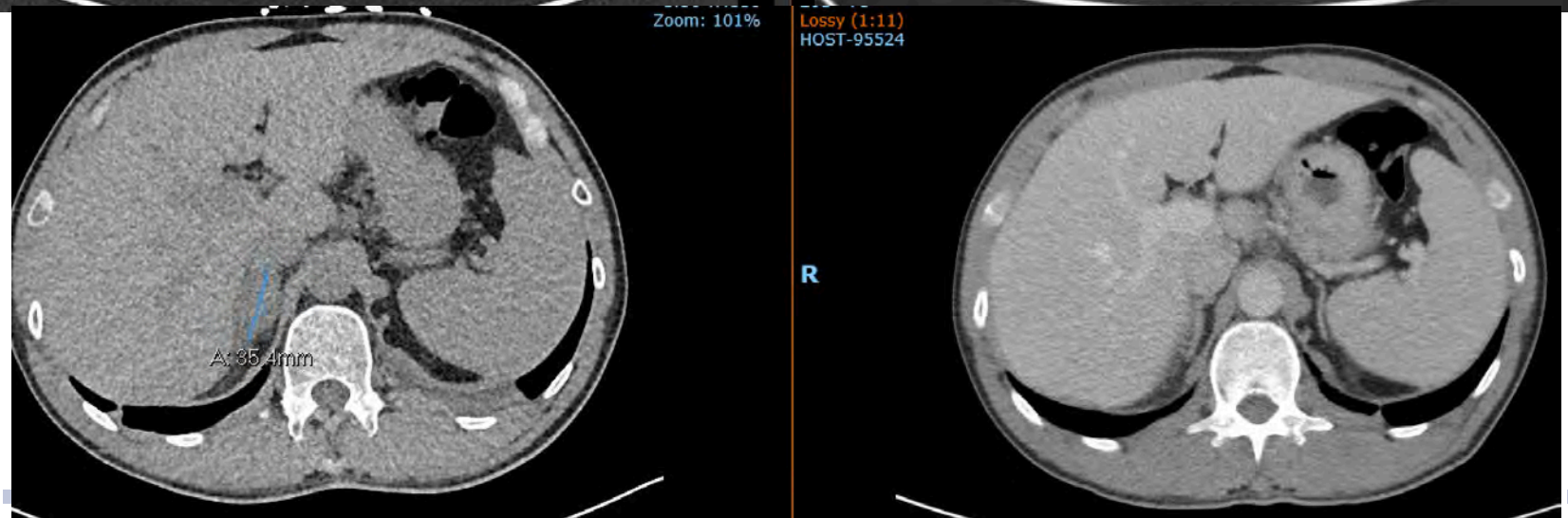
Plan: upfront resection including chest wall

Returning to Case

4 weeks after CT of Feb 2020

Feb 2020





How to Move Further?

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Tumor Board

cT3N0M1a NSCLC adenocarcinoma

Resection canceled

New staging with PET-CT and brain MRI

Revision pathology for NGS and PD-L1

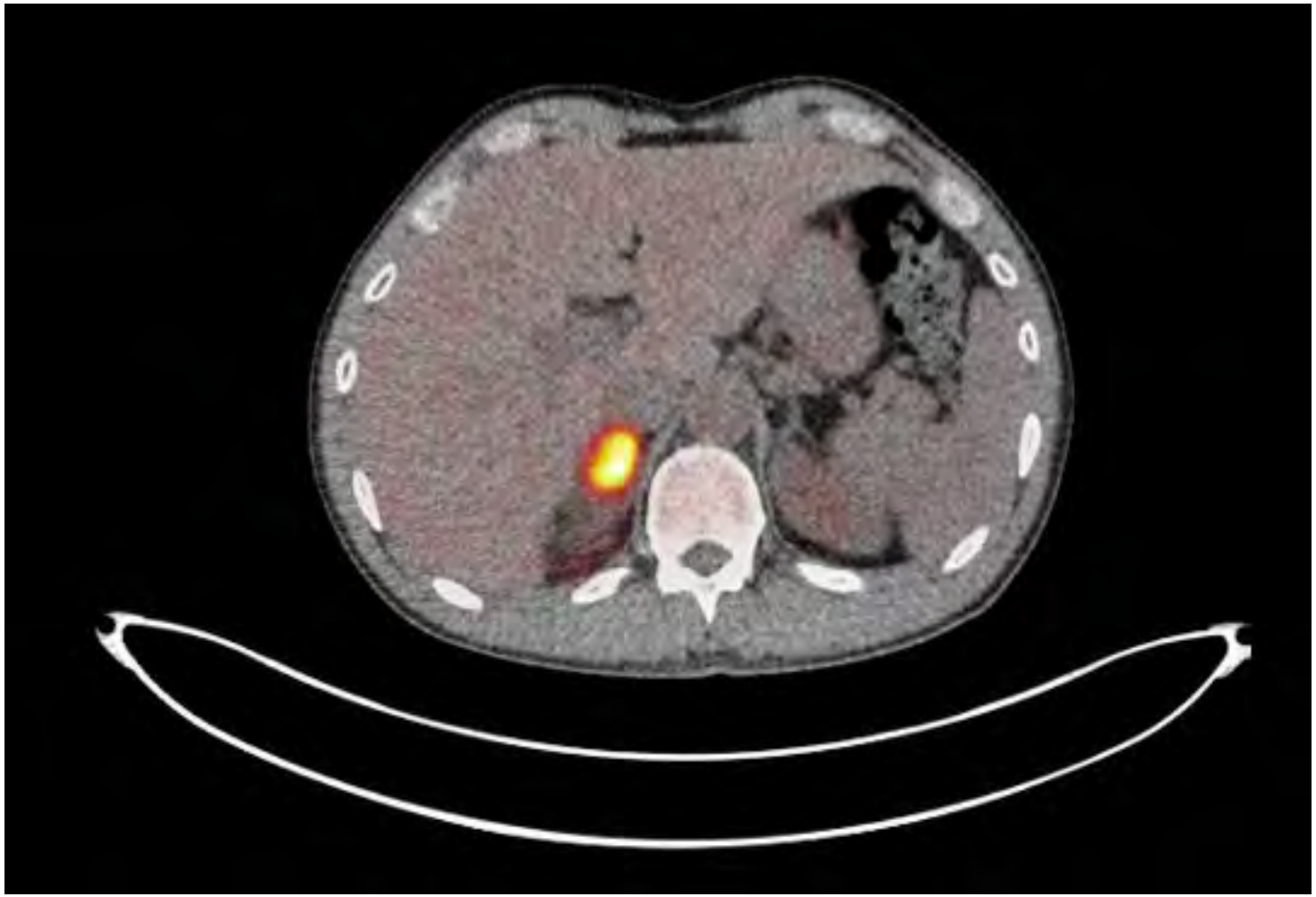
ASAP start chemotherapy: carboplatin + pemetrexed

Evaluation after 2 cycles chemotherapy, for resection of primary tumor and local treatment adrenal gland if no other metastases

New Staging

Erasmus MC Cancer Institute

Apr 2020



Pathology Lung Biopsy Apr 2020

Erasmus MC Cancer Institute

No mutations in *BRAF, EGFR, HER2, KRAS, MET*

Mutation(s) in

- *TP53* exon 5: c.473G>T; p.R158L
- *STK11* exon 3: c.455A>C; p.Q152P

No translocations

After 2 Cycles Chemotherapy

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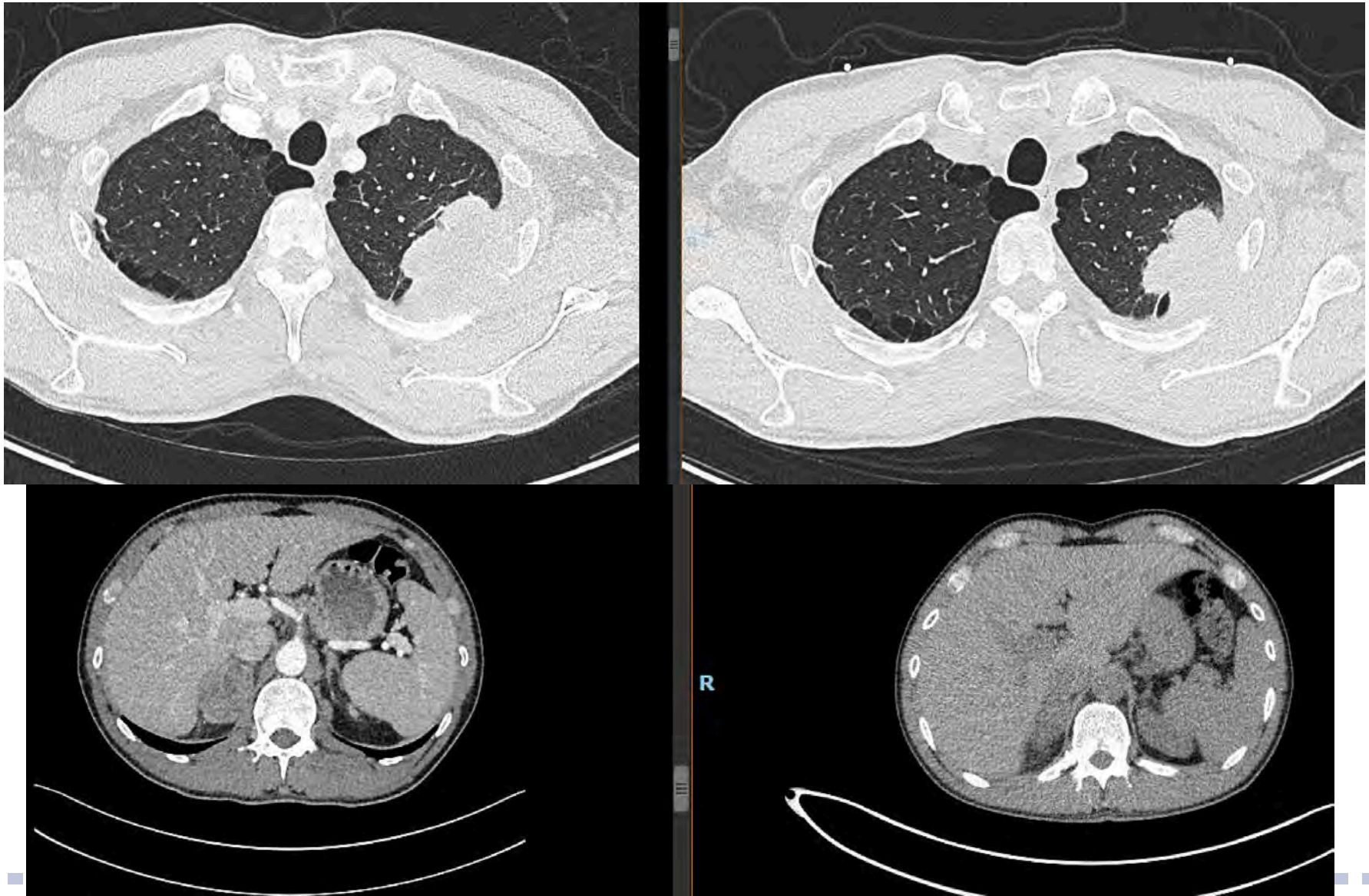
May 2020

Apr 2020



What to Do Now?

Progressive disease after 2 cycles chemotherapy (carboplatin-pemetrexed)

Plan: switch to carboplatin, paclitaxel, bevazicumab, atezolizumab

After 2 Cycles Chemotherapy + IO

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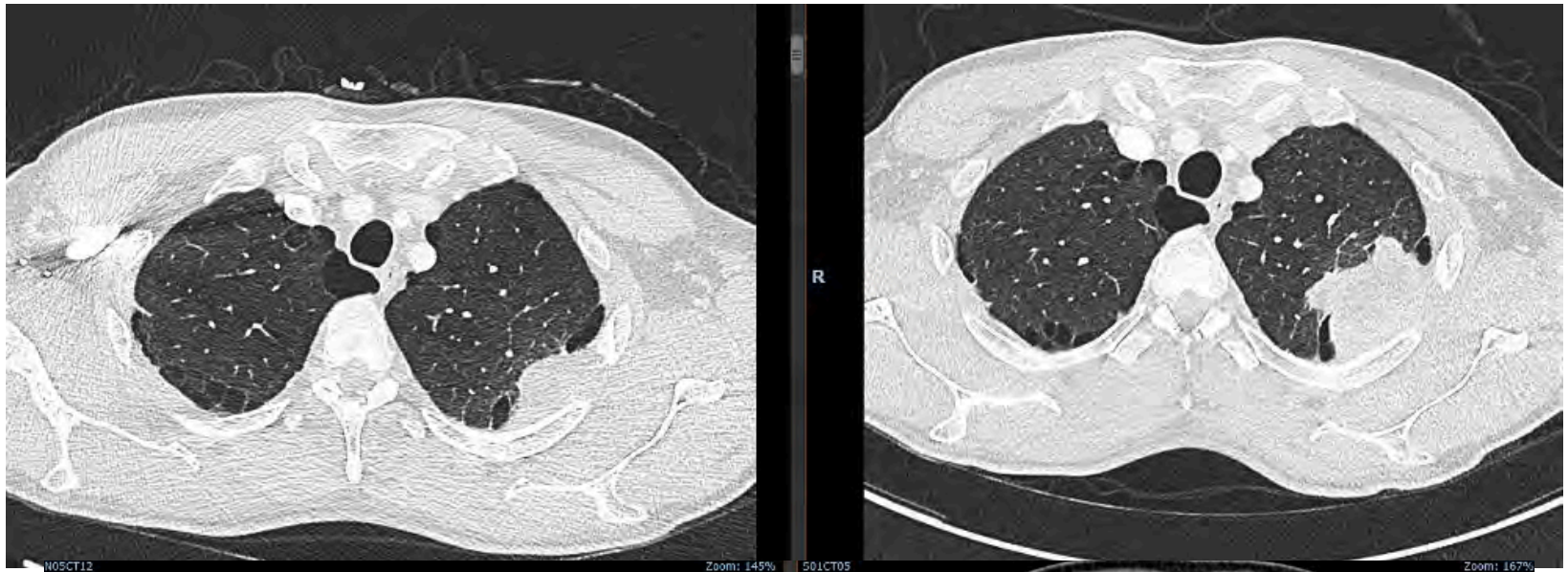
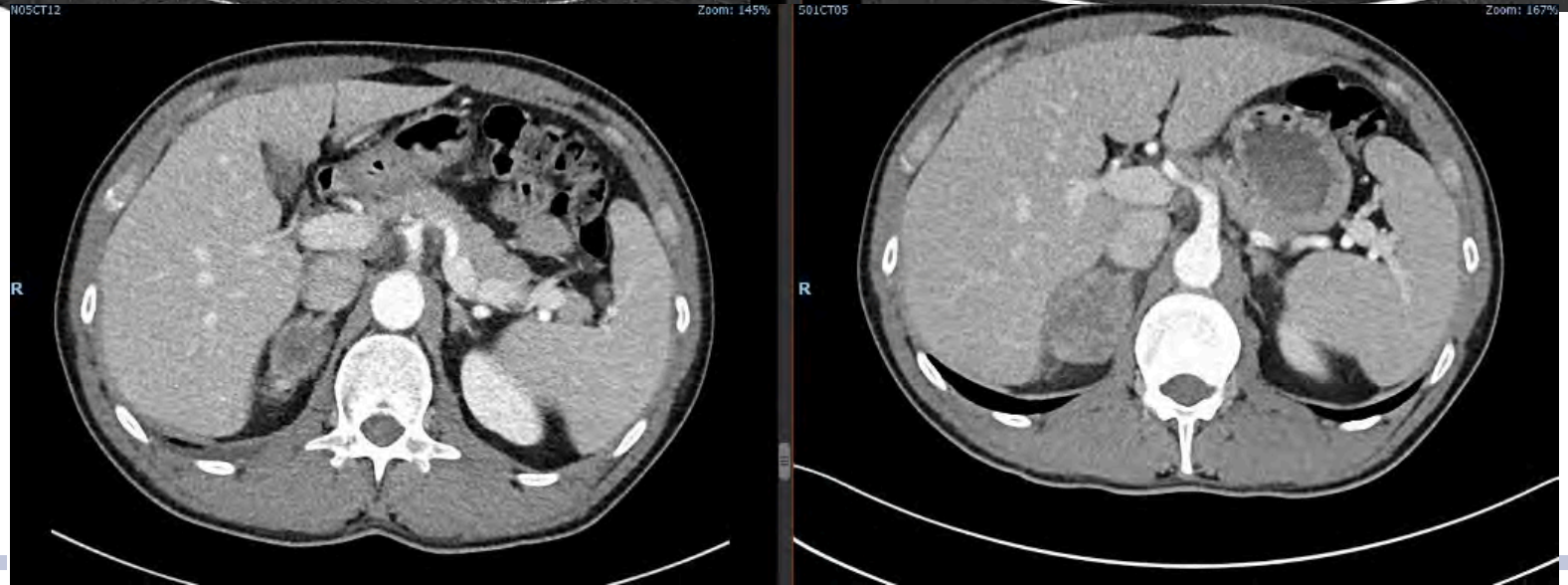
Jul 2020

May 2020



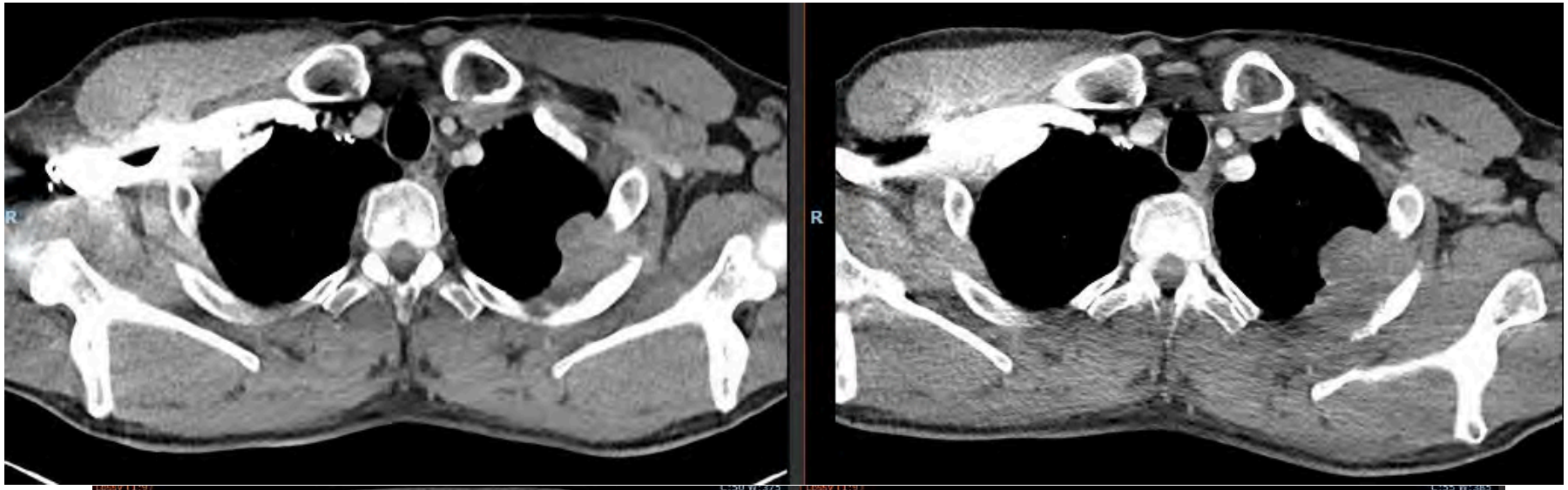


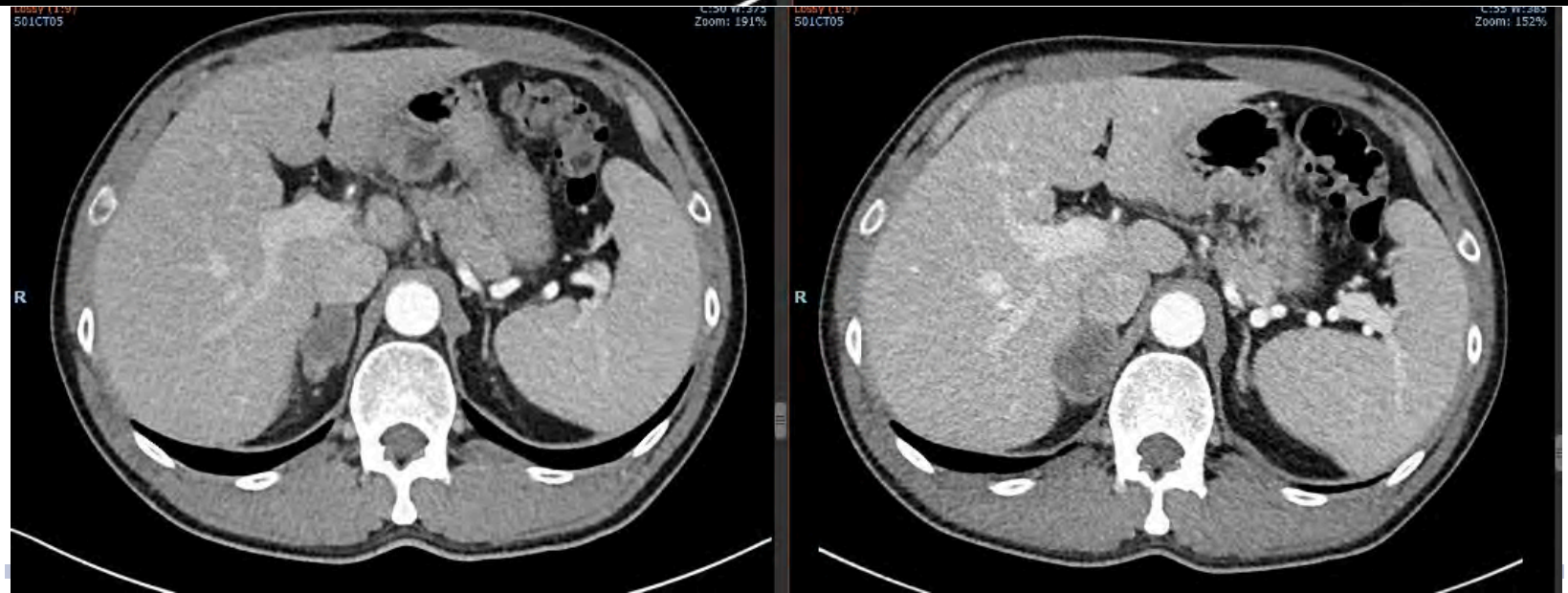
After 4 Cycles Chemotherapy + IO

Erasmus MC Cancer Institute

Aug 2020

Jul 2020





Partial Response After 4 Cycles Carboplatin, Paclitaxel, Bevacizumab, Atezolizumab

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How would you treat this patient now?

1. Maintenance immunotherapy
2. Radiotherapy
3. Resection primary tumor and local treatment adrenal gland
4. Other

Sep 2020: Lobectomy LUL With Lymph Node Dissection

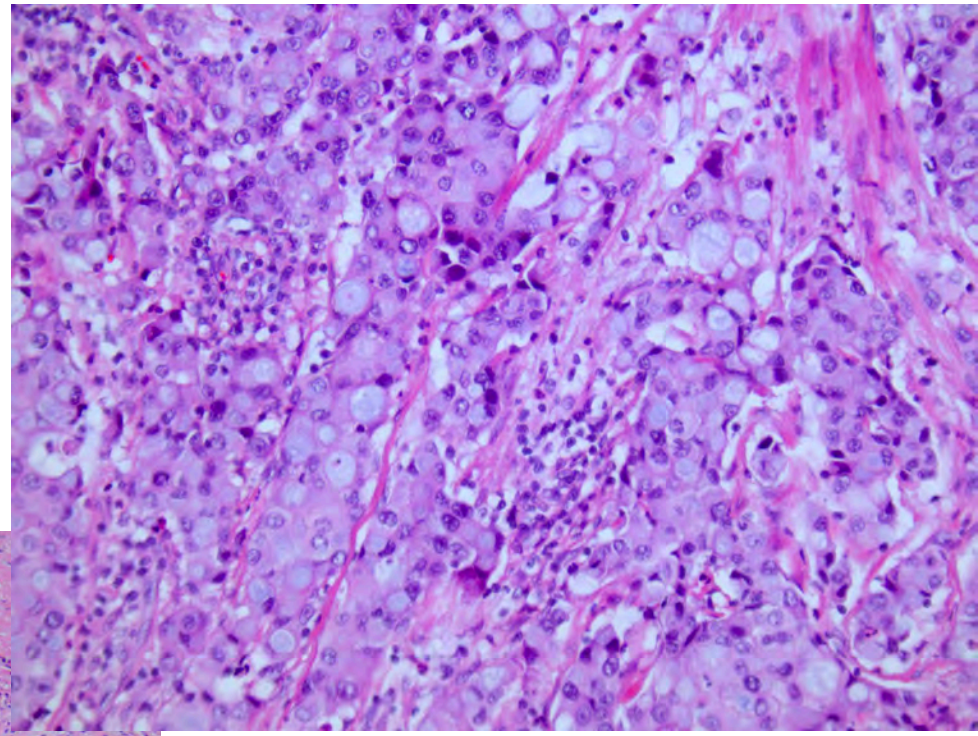
Erasmus MC Cancer Institute

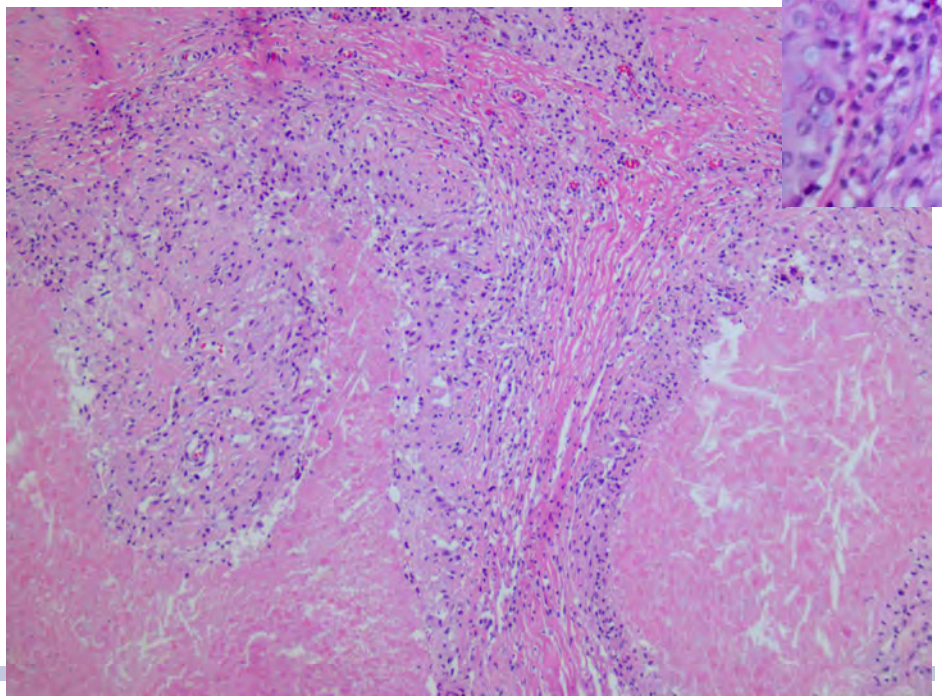
Pathology

Resection LUL: adenocarcinoma with invasion of thoracic wall

Resection lymph nodes N5L, N10L, N11L, N7: no tumor cells

ypT3N0





Tumor Board Sep 2020

TNM 8: ypT3N0PL3

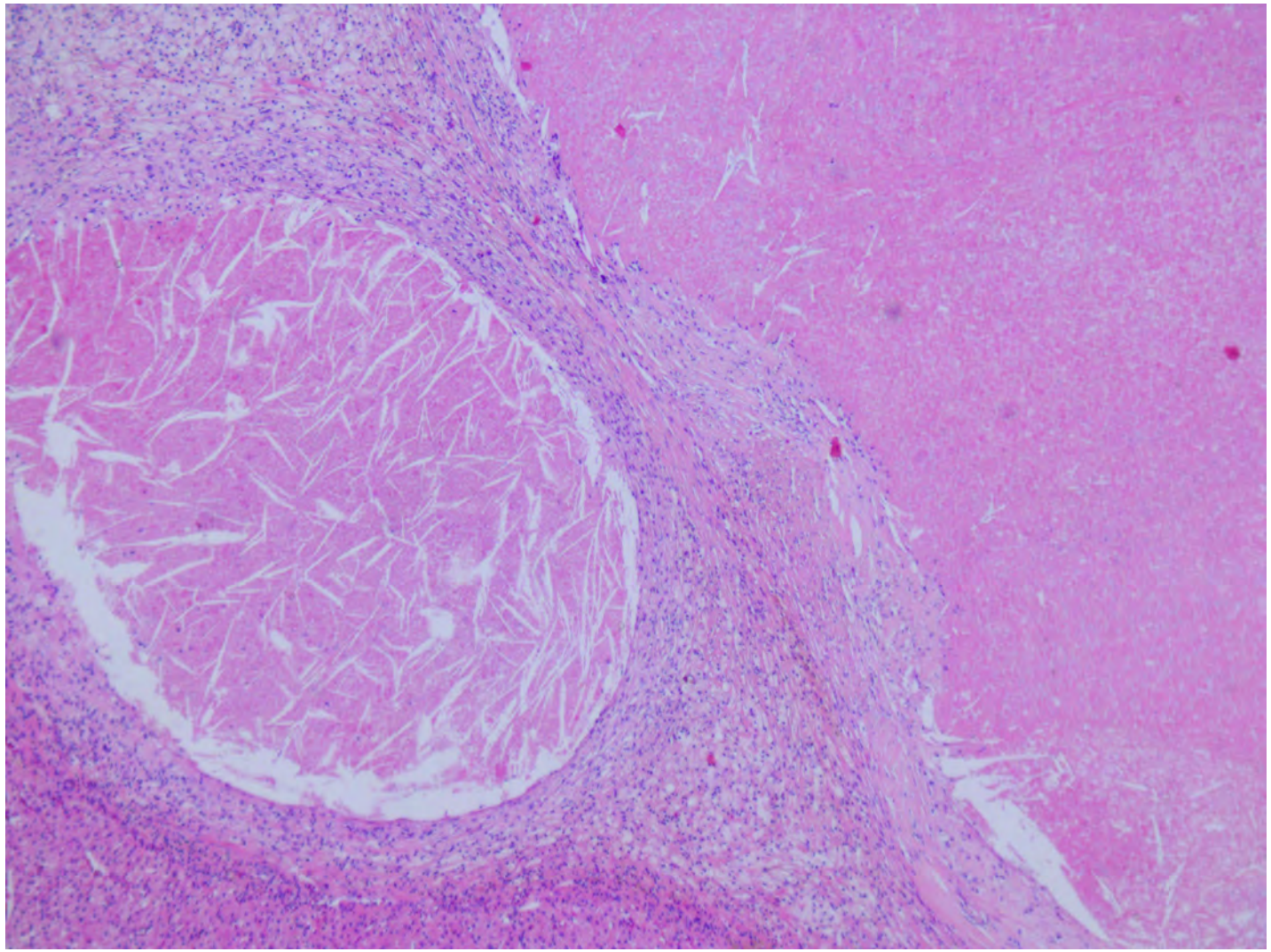
Plan

- PORT 30 × 2 Gy
- Resection adrenal gland

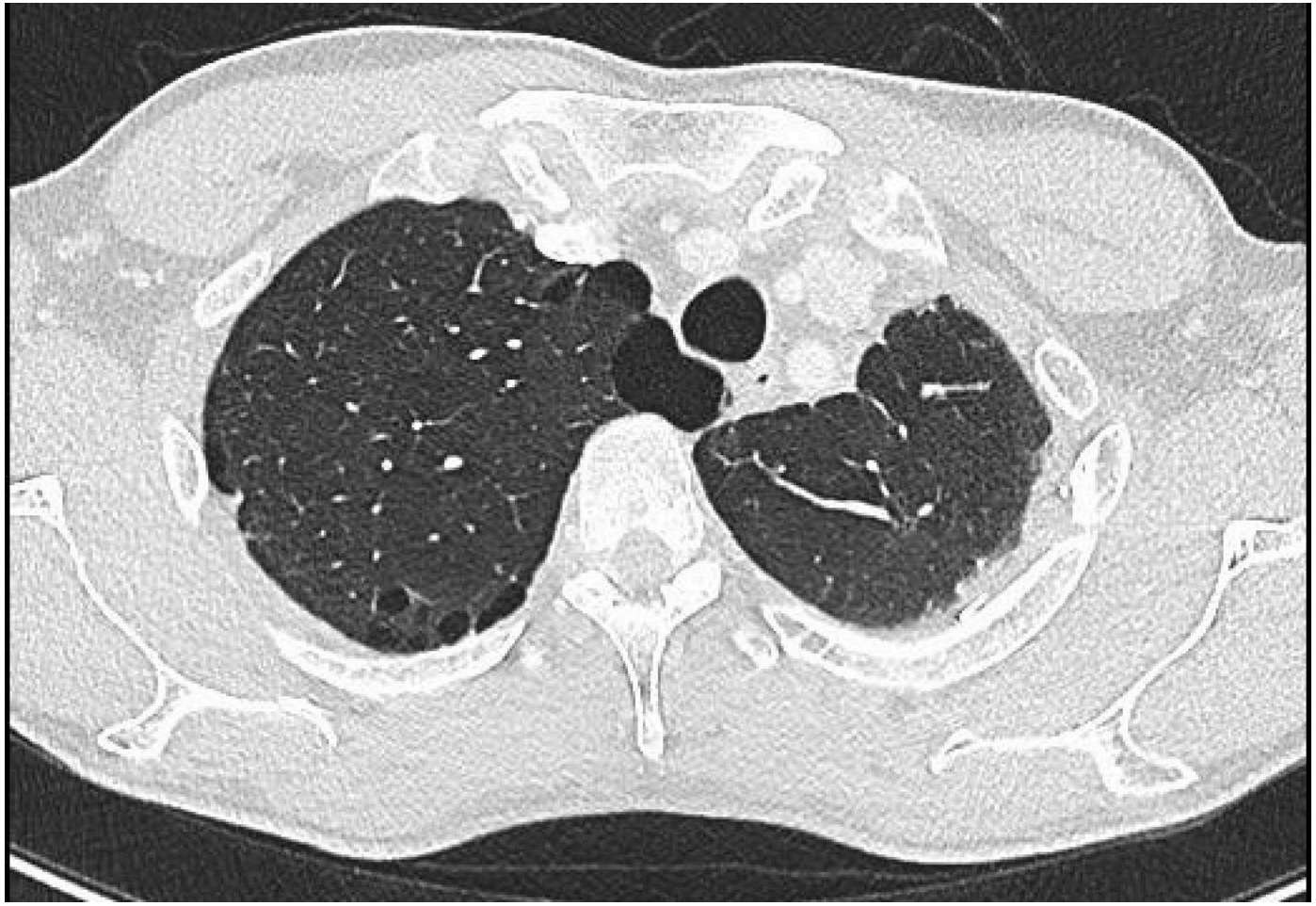
Resection Adrenal Gland

Erasmus MC Cancer Institute

Pathology: 100% necrosis



Last FU Sep 2022: No Recurrence



Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

Thank you for your attention

Daphne Dumoulin

d.dumoulin@erasmusmc.nl

Global Lung Cancer Academy

Tumor Board Discussion

Moderator: Solange Peters, MD

All faculty

Global Lung Cancer Academy

BREAK

Global Lung Cancer Academy

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

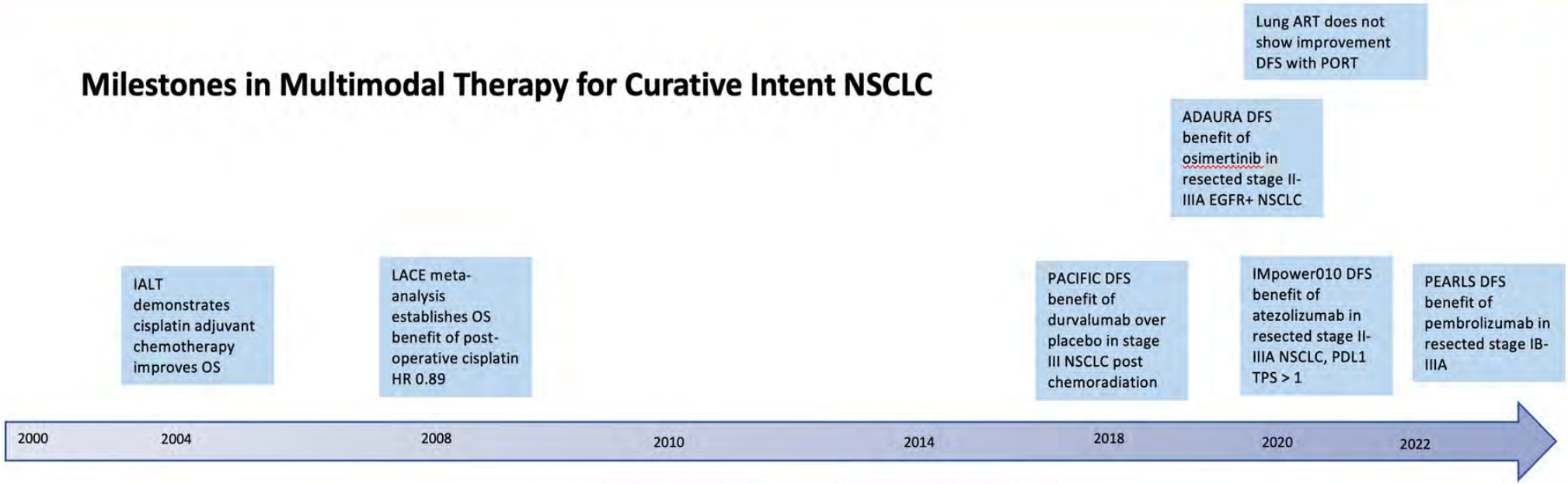
Anne-Marie Dingemans, MD, PhD

Disclosures

Erasmus MC Cancer Institute

Commercial Interest	Relationship(s) – All Paid to Institute
Roche	Advisory Board, Steering Committee
Eli Lilly	Honorarium
Boehringer Ingelheim	Advisory Board
AstraZeneca	Honorarium, Advisory Board
Janssen	Honorarium (industry-sponsored symposium)
Chiesi	Honorarium
Amgen	Advisory Board, Research Support
Pfizer	Honorarium
Bayer	Advisory Board
Takeda	Honorarium
PharmaMar	Advisory Board
Sanofi	Advisory Board

Milestones in Multimodal Therapy for Curative Intent NSCLC

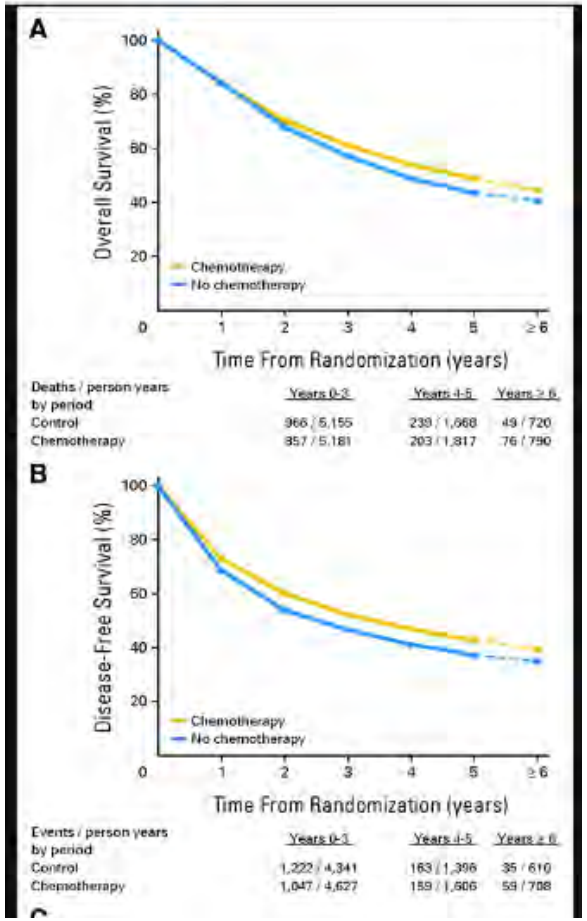


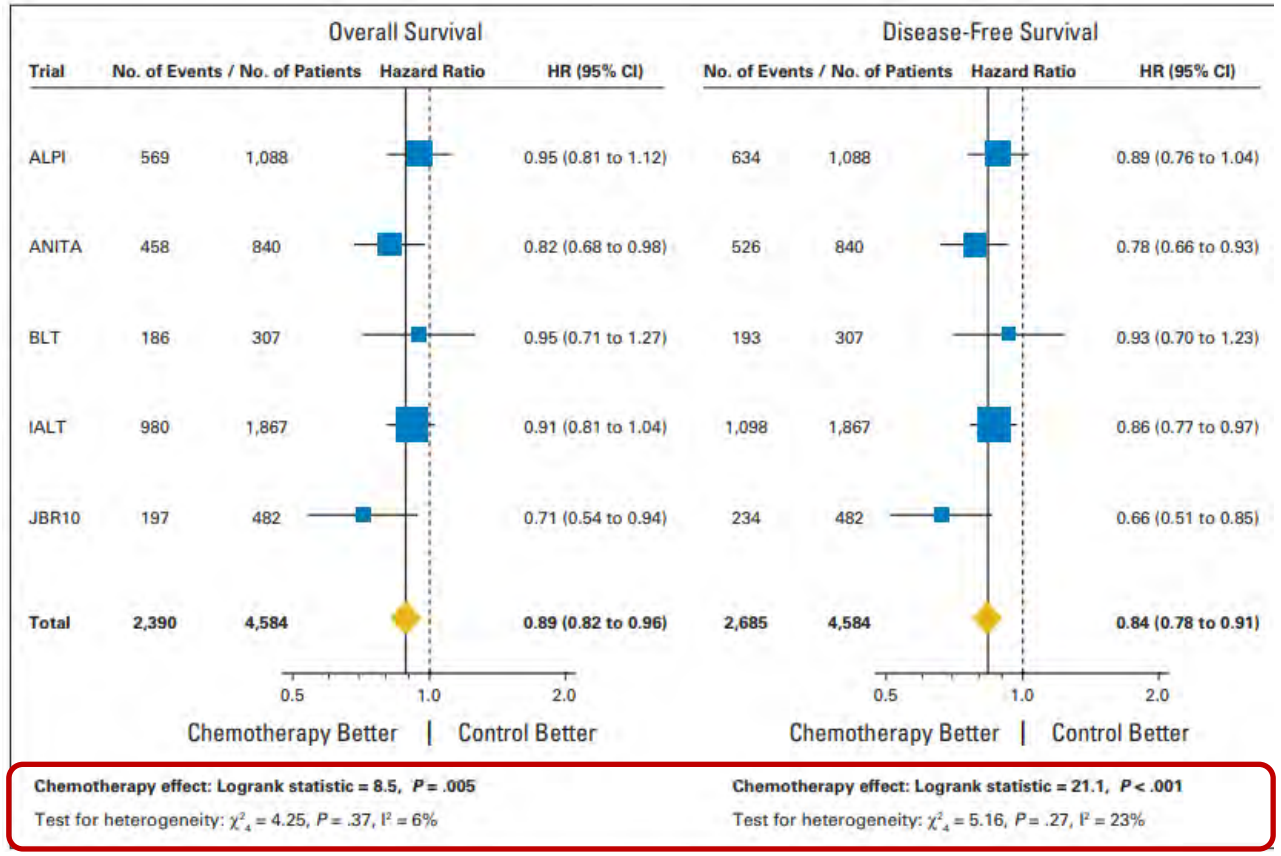
Arriagada, NEJM 2004
Pignon, JCO 2008
Felip, JCO 2010
NSCLC Meta-analysis, Lancet 2014
Antonia, NEJM 2018
Wu, NEJM 2020
Felip, Lancet 2021
Le Pechoux, Lancet 2021
Forde, NEJM 2022
Paz Ares, Proc ESMO, 2022

PRESENTED BY:
Jyoti D. Patel, MD FASCO
Northwestern University

Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group

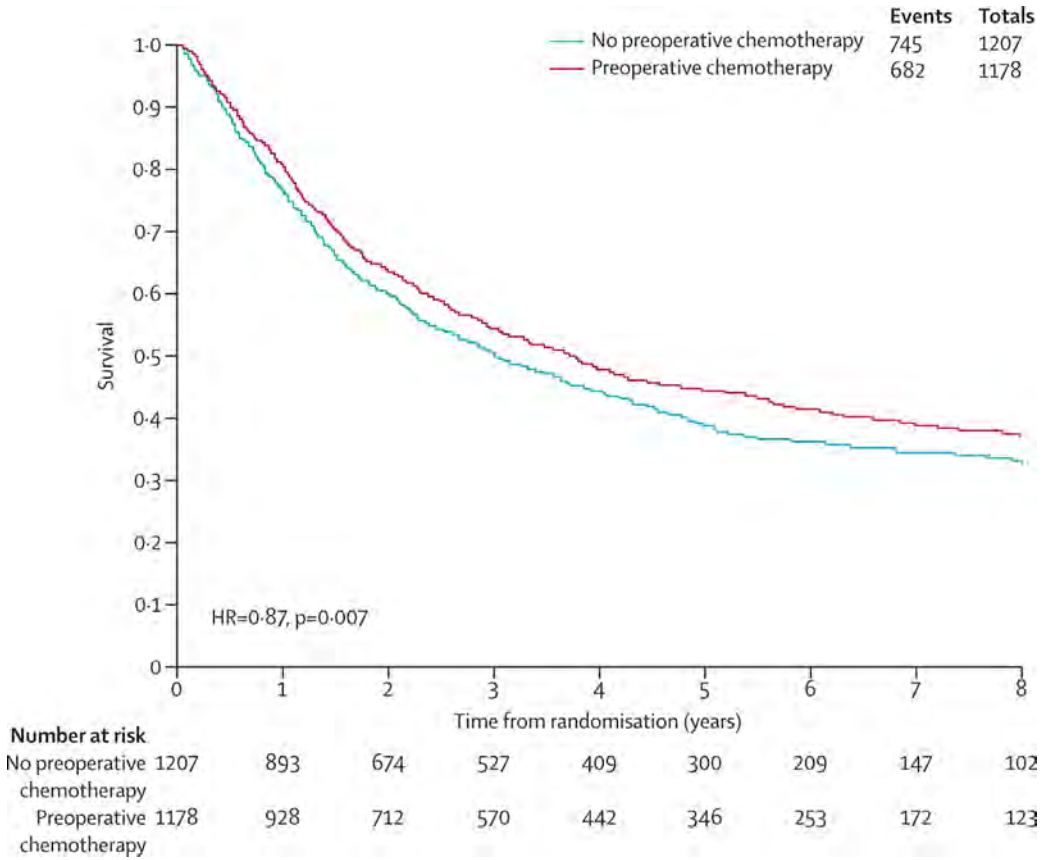
Jean-Pierre Pignon, Hélène Tribodet, Giorgio V. Scagliotti, Jean-Yves Douillard, Frances A. Shepherd, Richard J. Stephens, Ariane Dunant, Valter Torri, Rafael Rosell, Lesley Seymour, Stephen G. Spiro, Estelle Rolland, Roldano Fossati, Delphine Aubert, Keyue Ding, David. Waller, and Thierry Le Chevalier

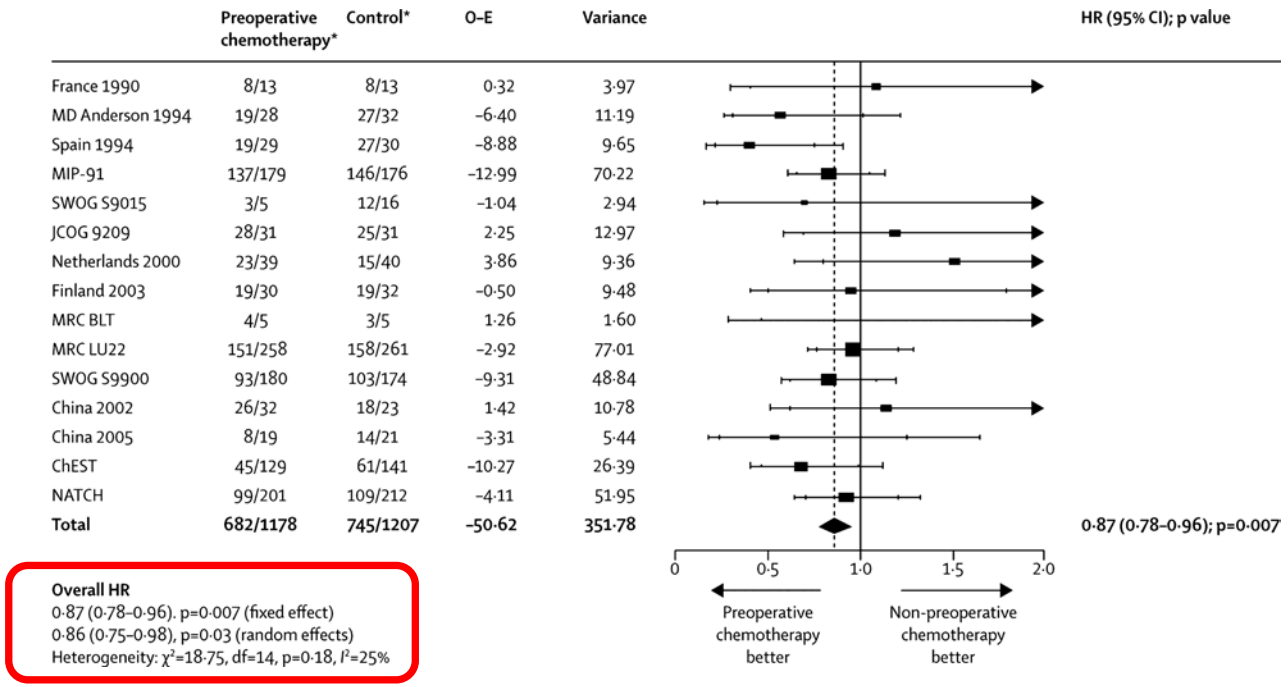




Pignon JP, et al. *J Clin Oncol.* 2008;26:3552-3559.

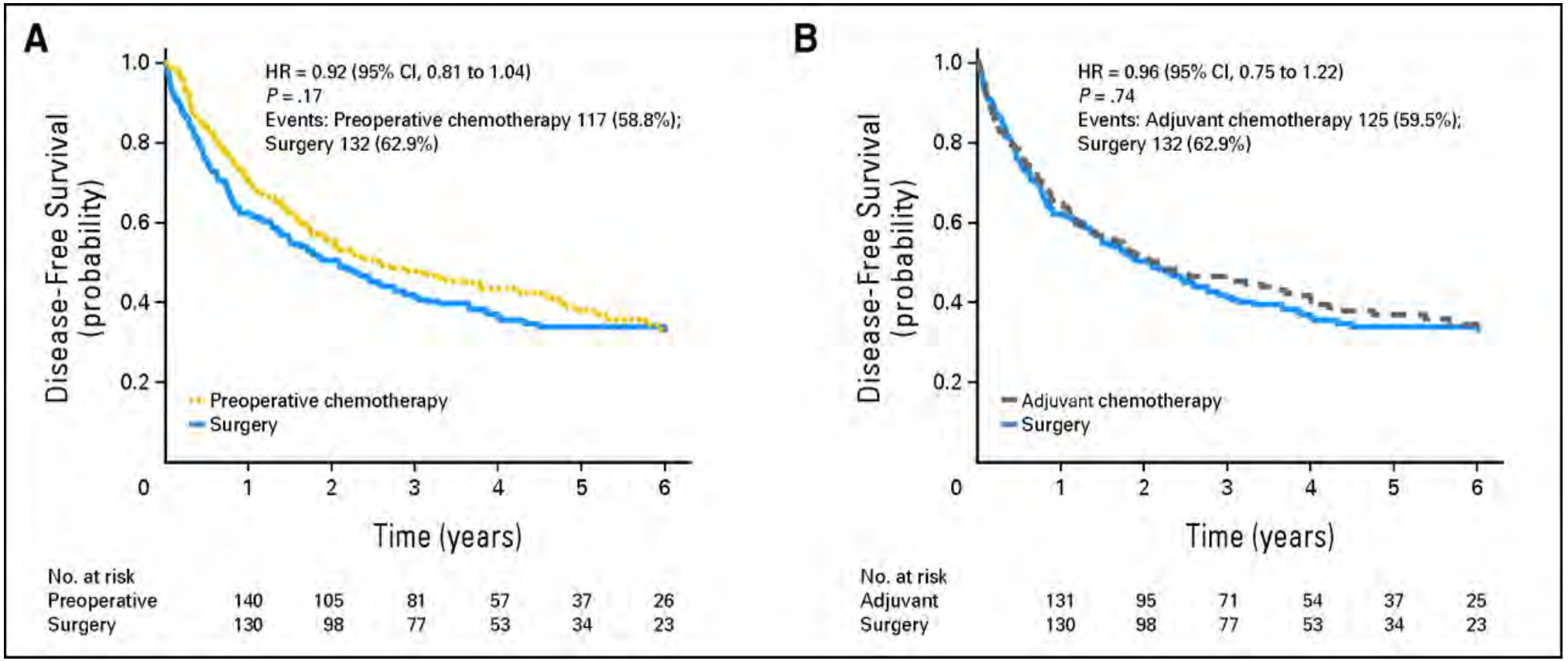
Preoperative Chemotherapy Meta-analysis





NSCLC Meta-analysis Collaborative Group. *Lancet*. 2014;383:1561-1571.

Adjuvant vs Neoadjuvant: The NATCH Trial



Felip E, et al. *J Clin Oncol.* 2010;28:3138-3145.

CheckMate 816: Press Release

Erasmus MC Cancer Institute

Neoadjuvant Nivolumab Plus Chemo Significantly Improves EFS in Resectable NSCLC

November 8, 2021
Kristi Rosa

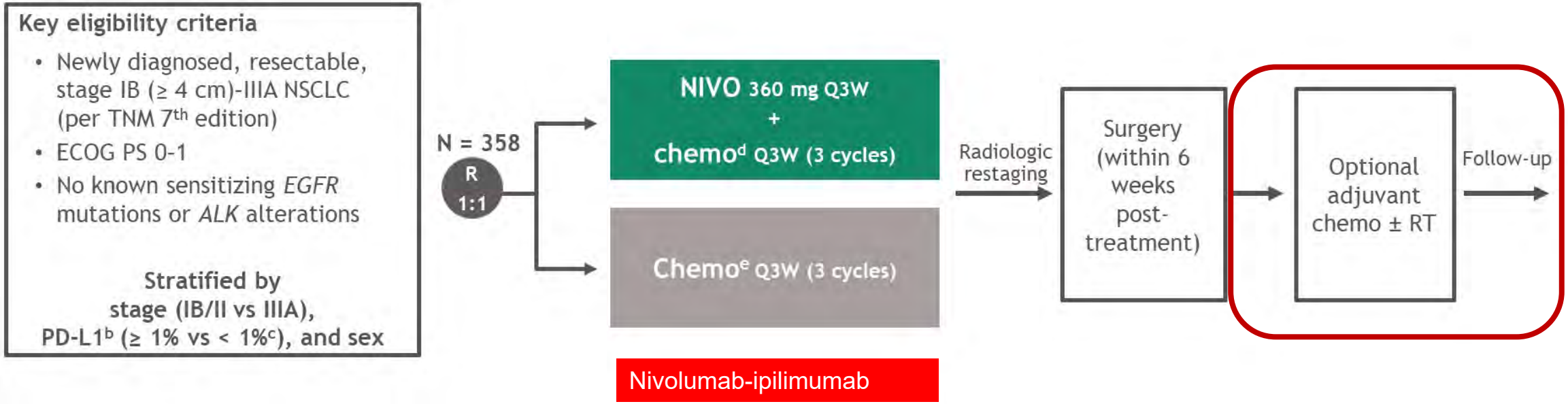
U.S. Food and Drug Administration Approves Opdivo® (nivolumab) with Chemotherapy as Neoadjuvant Treatment for Certain Adult Patients with Resectable Non-Small Cell Lung Cancer

03/04/2022

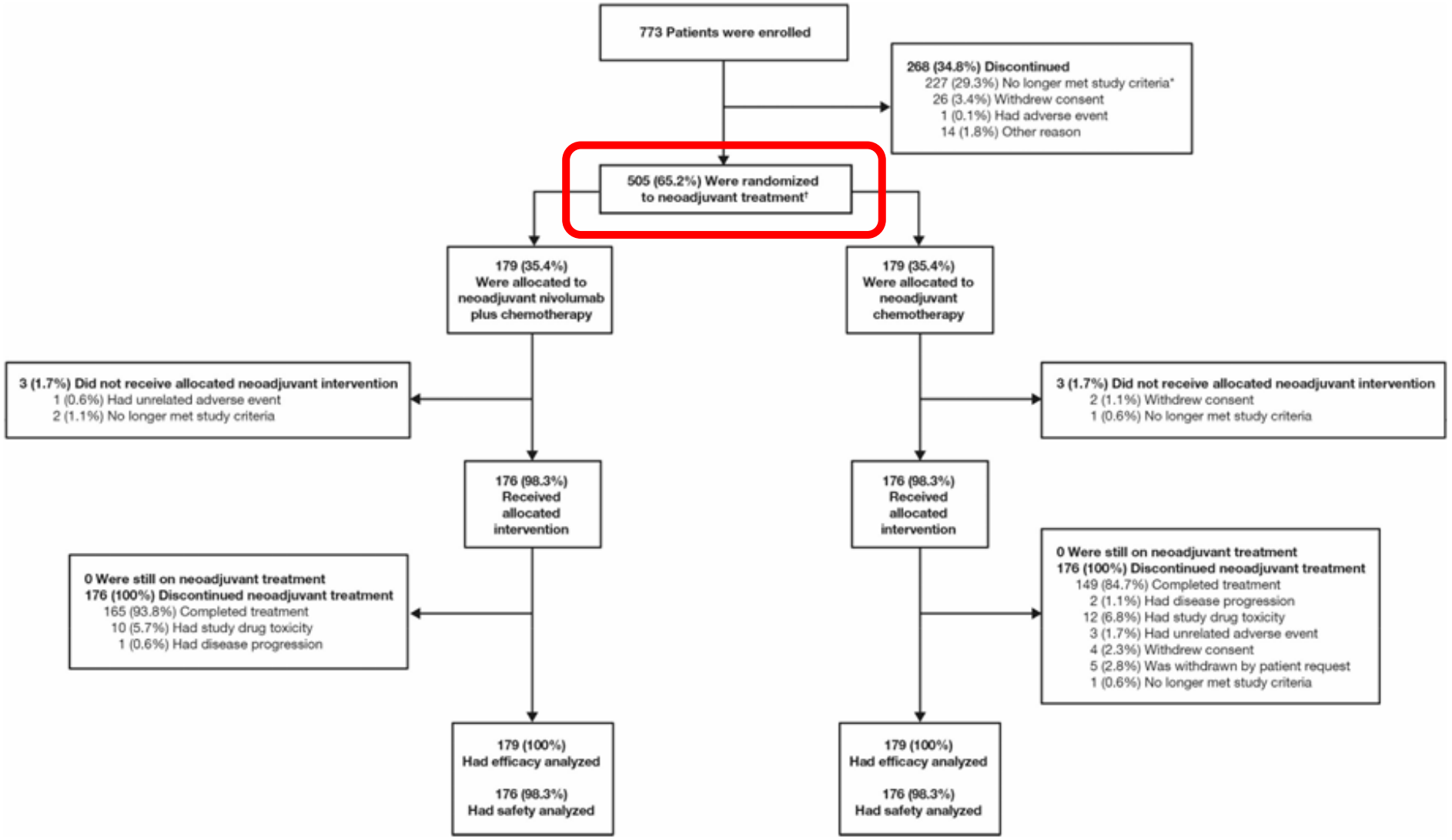
CATEGORY: Corporate/Financial News

OncLive. 2021. https://www.onclive.com/view/neoadjuvant-nivolumab-plus-chemo-significantly-improves-efs-in-resectable-nscl. Accessed November 4, 2022.
Bristol Meyers Squibb. 2022. https://news.bms.com/news/details/2022/U.S.-Food-and-Drug-Administration-Approves-Opdivo-nivolumab-with-Chemotherapy-as-Neoadjuvant-Treatment-for-Certain-Adult-Patients-with-Resectable-Non-Small-Cell-Lung-Cancer/default.aspx. Accessed November 4, 2022.

CheckMate 816: Study Design



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



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

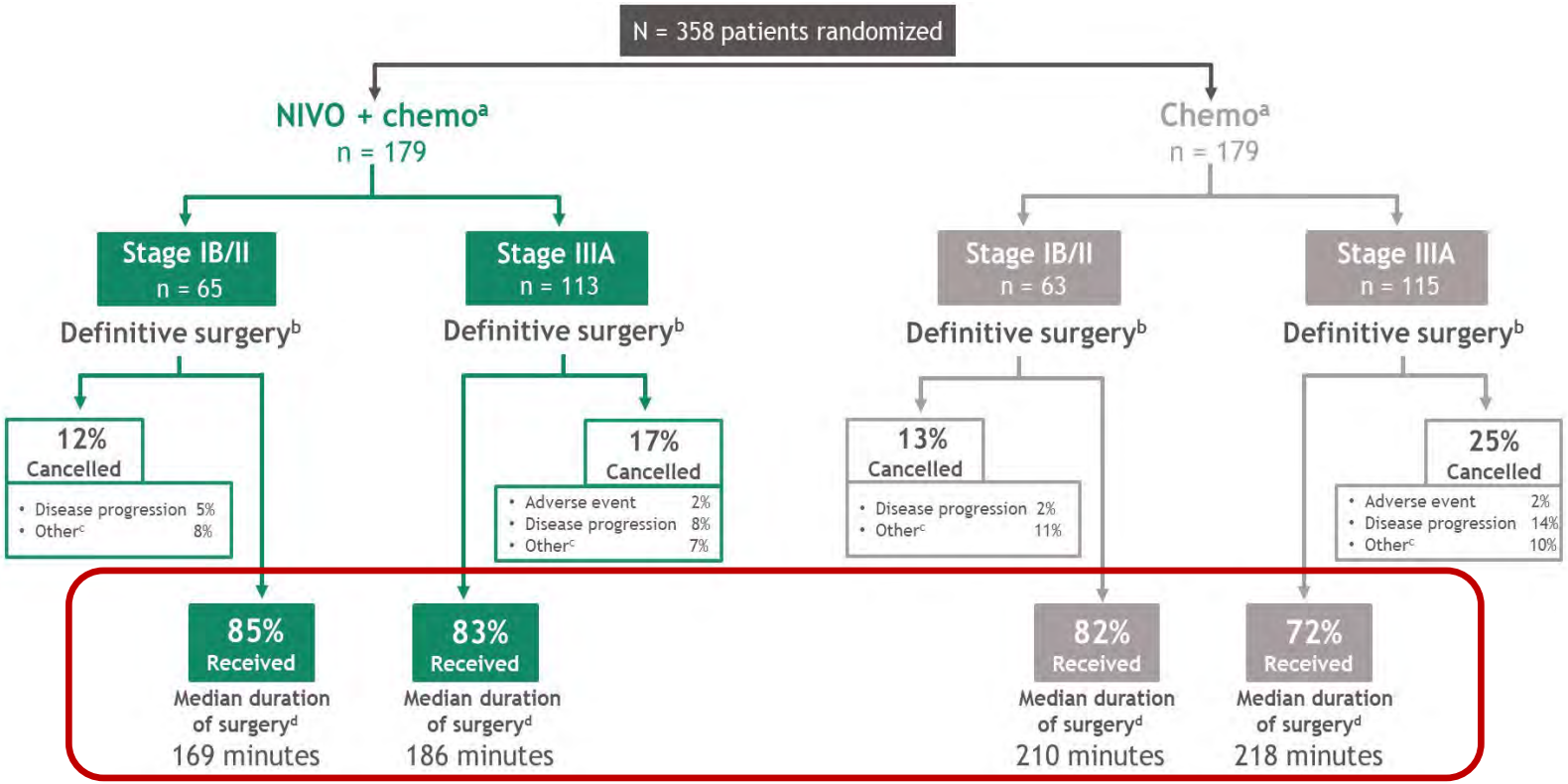
Neo-adjuvant therapy
Rule number 1: Do not harm!

- Progressive disease
- Preoperative toxicity
- Postoperative morbidity

Rule number 1: Do not harm!

Erasmus MC Cancer Institute

CheckMate 816: *Surgery Outcomes*



NIVO+chemo:

More minimally invasive
Less conversions
More lobectomy
more R0

Spicer J, et al. *J Clin Oncol*. 2021;39(suppl 15) abstract 8503.

Preoperative Nivolumab Does Not Increase Surgery-Related AEs

Erasmus MC Cancer Institute

Table 2. Adverse Events.*

Event	Nivolumab plus Chemotherapy (N=176)		Chemotherapy Alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause — no. (%)†				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events — no. (%)†				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death‡	0	—	3 (1.7)	—
Surgery-related adverse events — no./total no. (%)§	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)

* Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 24.0, and were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.
† Included are events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose.
‡ Treatment-related deaths in the chemotherapy-alone group were due to pancytopenia, diarrhea, acute kidney injury (all in one patient), enterocolitis, and pneumonia.
§ The denominators are based on patients who underwent definitive surgery. Included are events reported up to 90 days after definitive surgery. Grade 5 surgery-related adverse events (defined as events that led to death ≤24 hours after the onset of an adverse event) were reported in two patients in the nivolumab-plus-chemotherapy group and were deemed by the investigator to be unrelated to the trial drugs (one each due to pulmonary embolism and aortic rupture).

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

Neo-adjuvant therapy
Rule number 1: Do not harm!

Erasmus MC Cancer Institute

- Progressive disease
- Pre-operative toxicity
- Post-operative morbidity

CheckMate 816:
pCR, MPR, depth of pathologic regression

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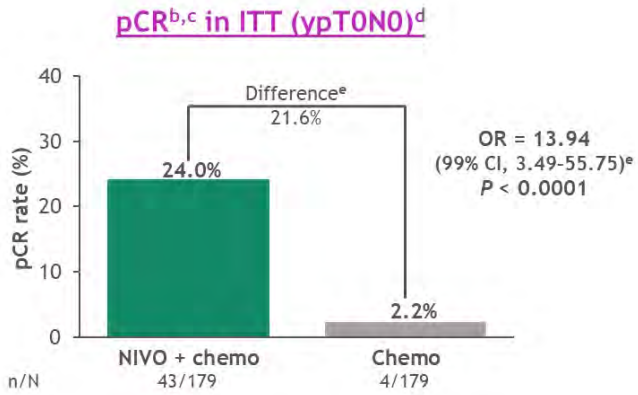
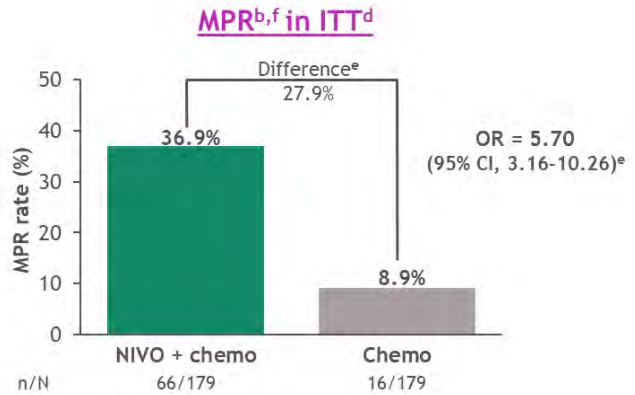
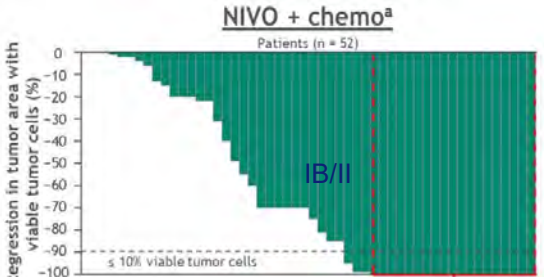
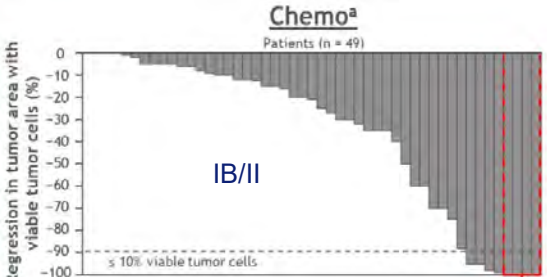
NIVO + chemo

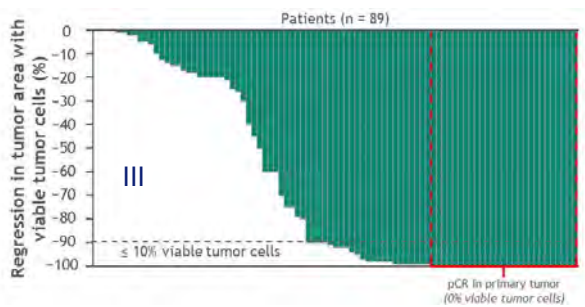
pCR independent of RECIST respons

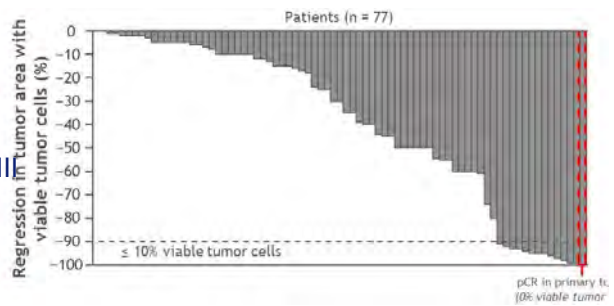






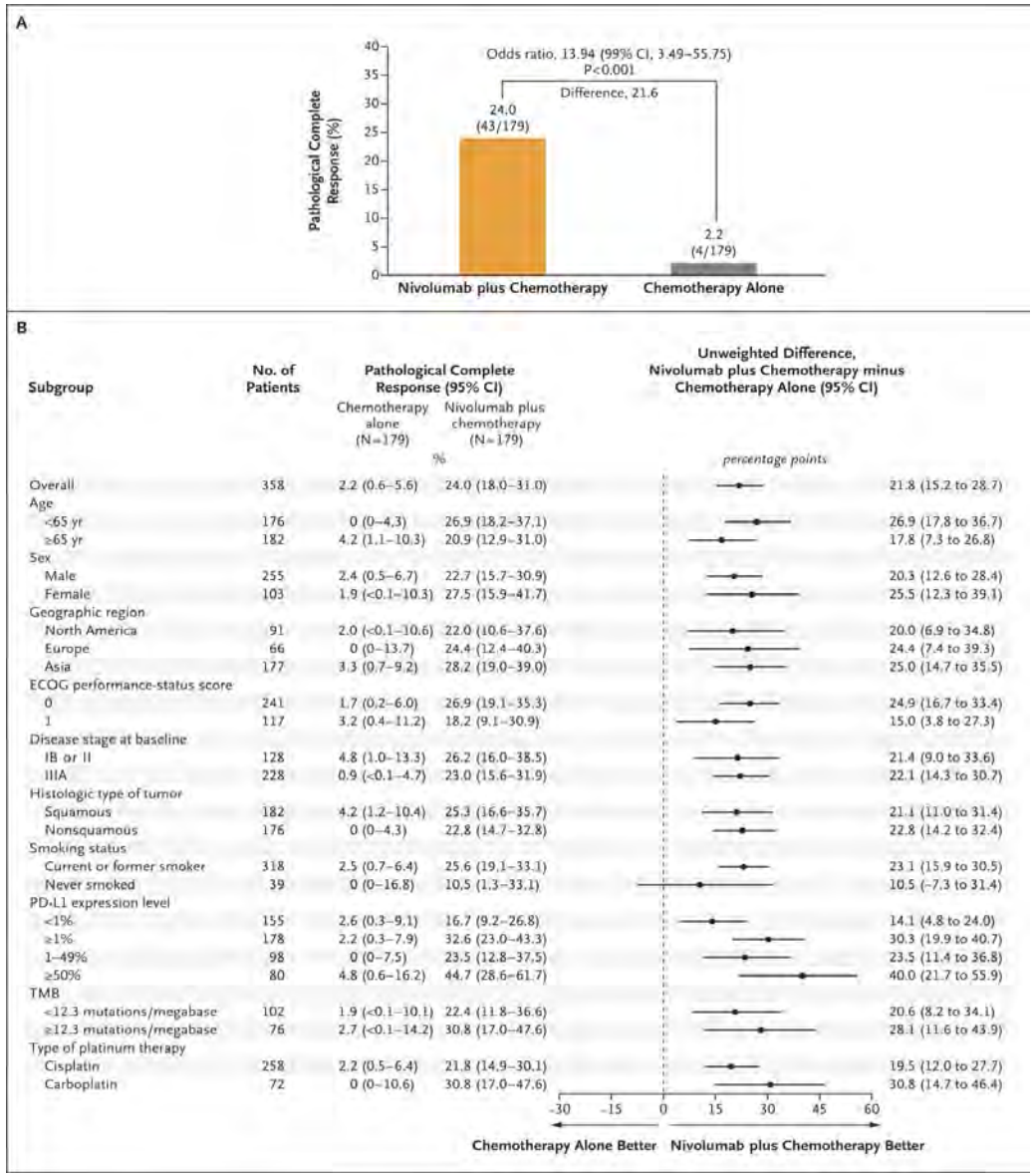






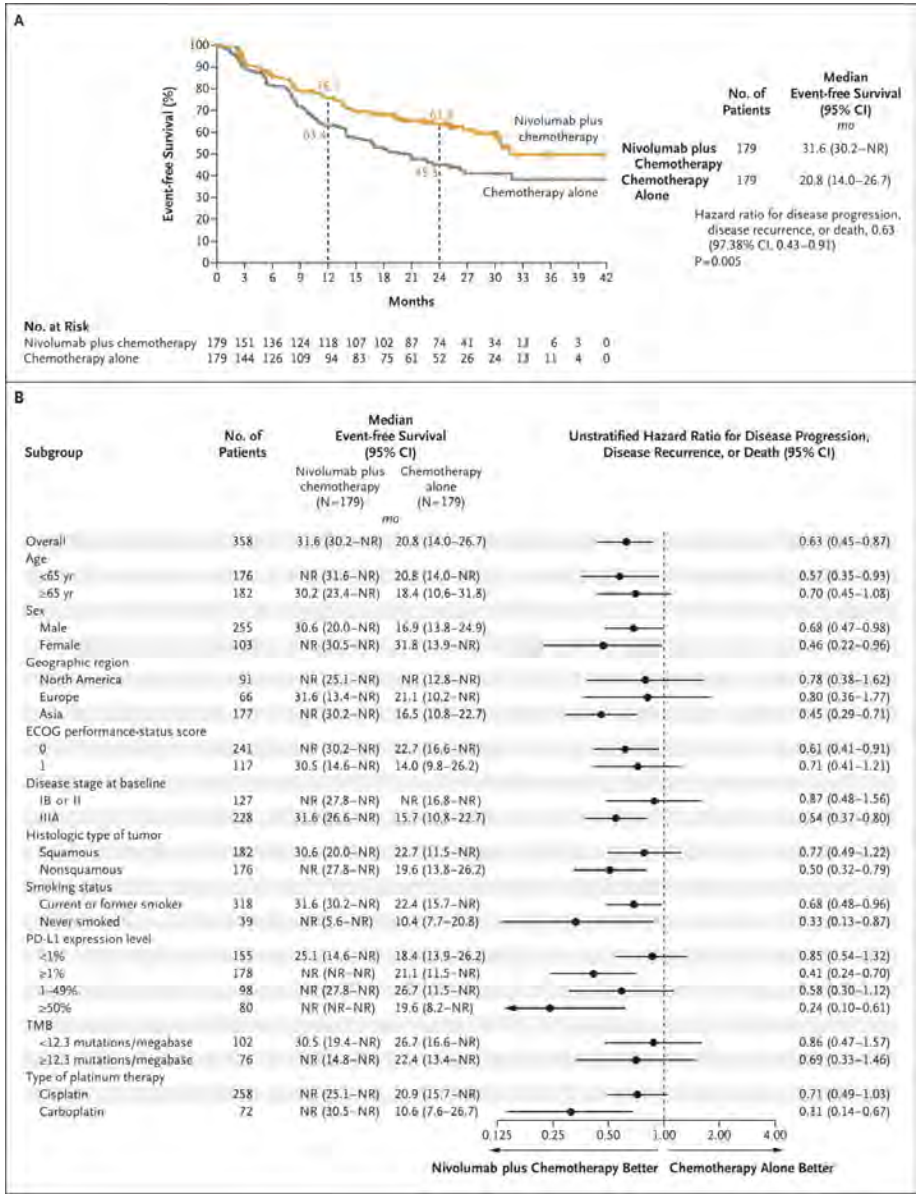
Spicer J, et al. *J Clin Oncol*. 2021;39(suppl 15) abstract 8503.

pCR Rate Driven by PD-L1 Expression



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

Neoadjuvant Chemo-Nivolumab Increases EFS

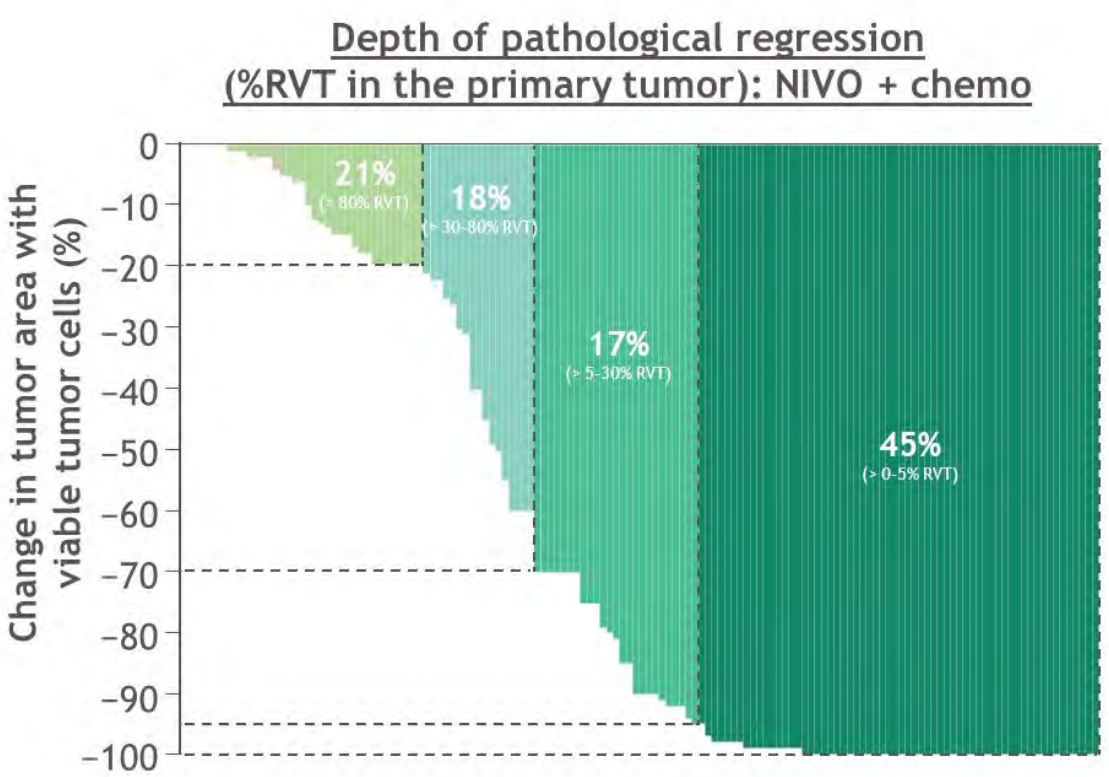


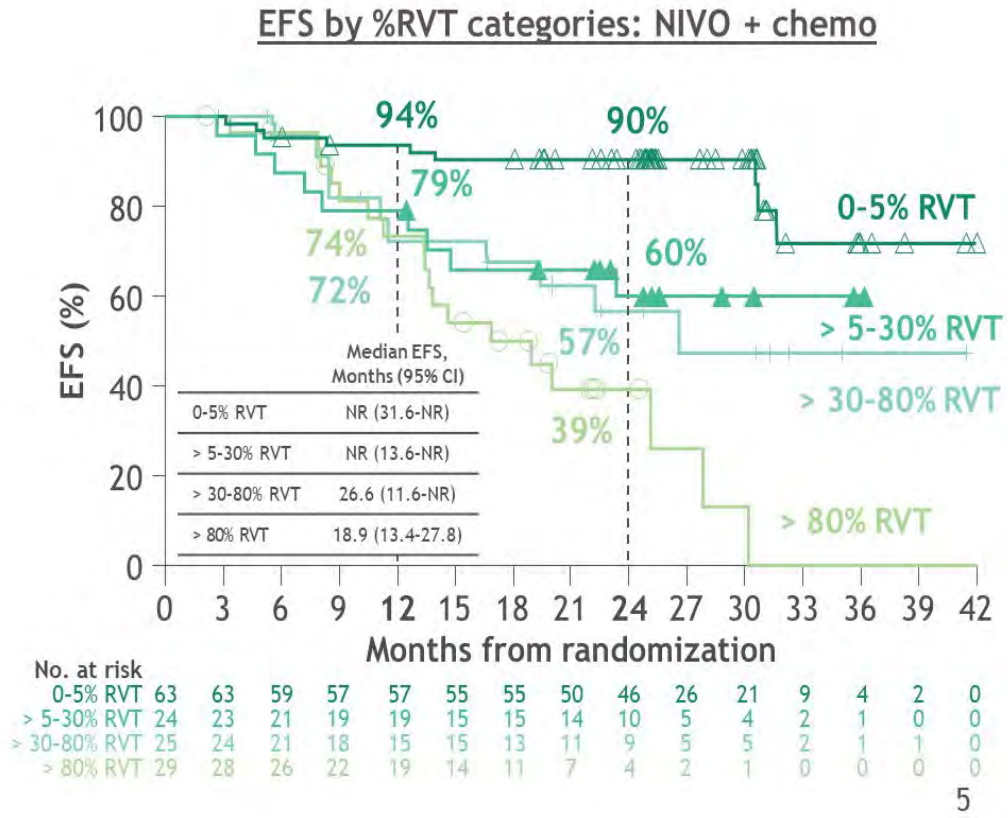
EFS is longer in patients with pCR

In non-pCR, mEFS is 26.6 mo vs 18.4 mo; HR 0.84(95% CI: 0.61–1.17)

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

Neoadjuvant CheckMate 816: EFS vs Pathologic Response

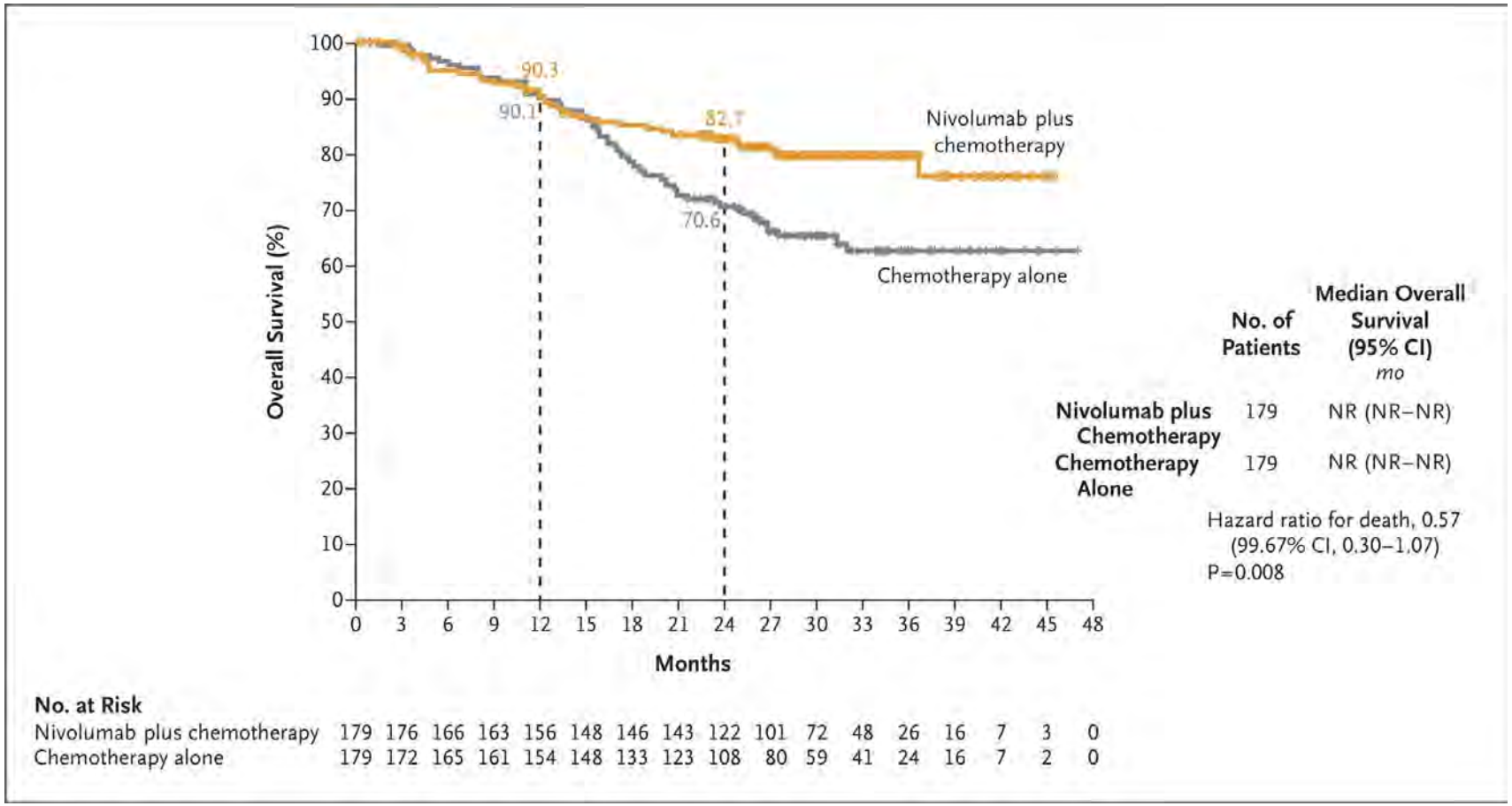




In pCR, EFS benefit independent of PD-L1 or stage

Provencio-Pulla M, et al. *J Clin Oncol*. 2022;40(17 suppl): abstract LBA8511.

Overall Survival: Preoperative Chemo-Nivolumab



OS is key secondary endpoint.

At first planned interim analysis, did not meet criteria for significance

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

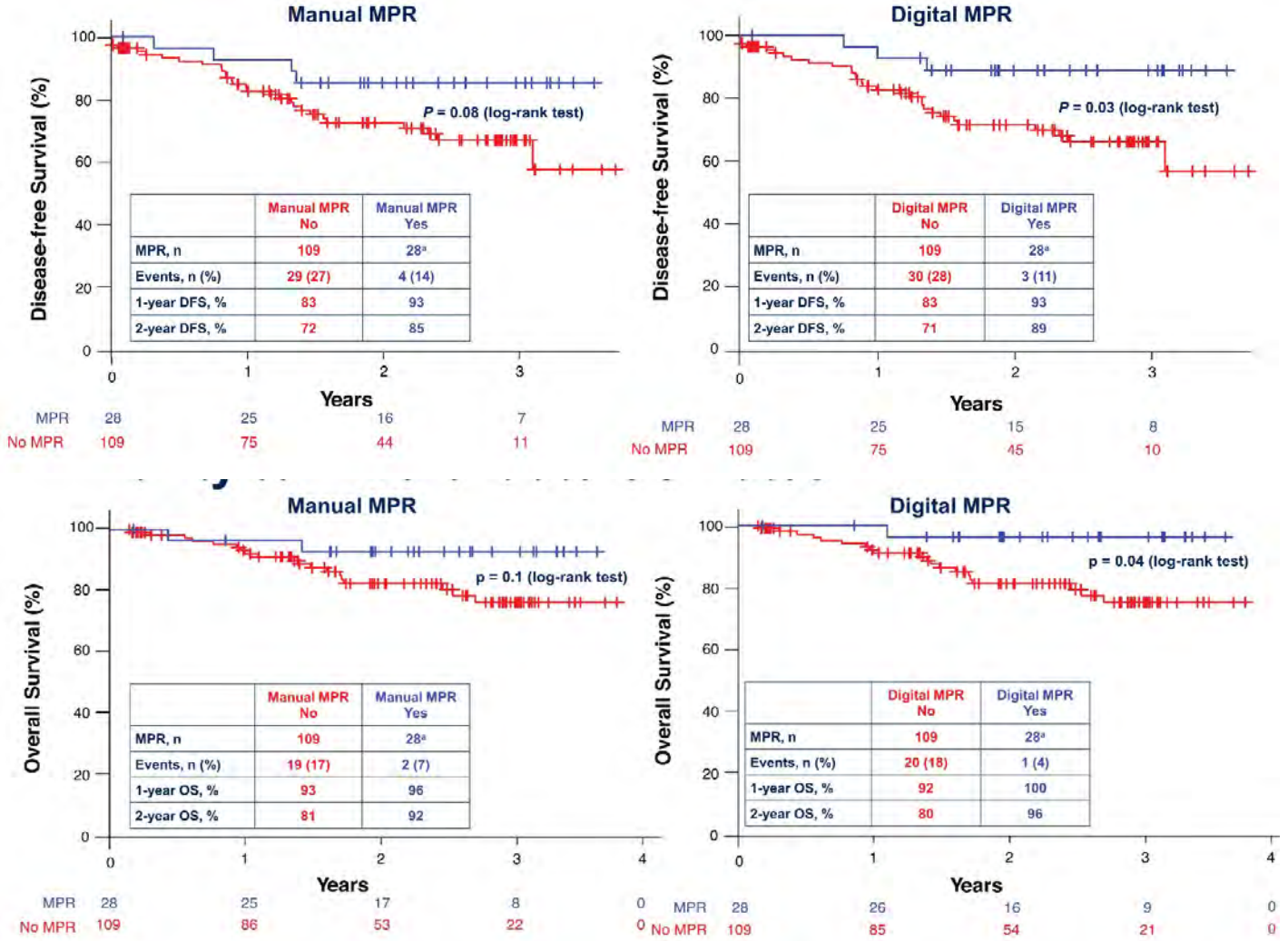
Digital vs Manual MPR in LCMC3

REVIEW ARTICLE

IASLC

IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy

William D. Travis, MD,[a,*] Sanja Dacic, MD,[b] Ignacio Wistuba, MD,[c] Lynette Sholl, MD,[d] Prasad Adusumilli, MD,[e] Lukas Bubendorf, MD,[f] Paul Bunn, MD,[g] Tina Cascone, MD, PhD,[h] Jamie Chaft, MD,[i] Gang Chen, MD,[j] Teh-Ying Chou, MD,[k] Wendy Cooper, MD,[l] Jeremy J. Erasmus, MD,[m] Carlos Gil Ferreira, MD,[n] Jin-Mo Goo, MD,[o] John Heymach, MD, PhD,[h] Fred R. Hirsch, MD,[p] Hidehito Horinouchi, MD,[q] Keith Kerr, MD,[r] Mark Kris, MD,[i] Deepali Jain, MD,[s] Young T. Kim, MD,[t] Fernando Lopez-Rios, MD,[u] Shun Lu, MD,[v]



Travis WD, et al. *J Thorac Oncol*. 2020;15:709-740; Dacic S, et al. ASCO 2021. Abstract 106.

NADIM: Single-Arm Phase II Neoadjuvant Nivolumab + Chemotherapy for Resectable Stage IIIa NSCLC

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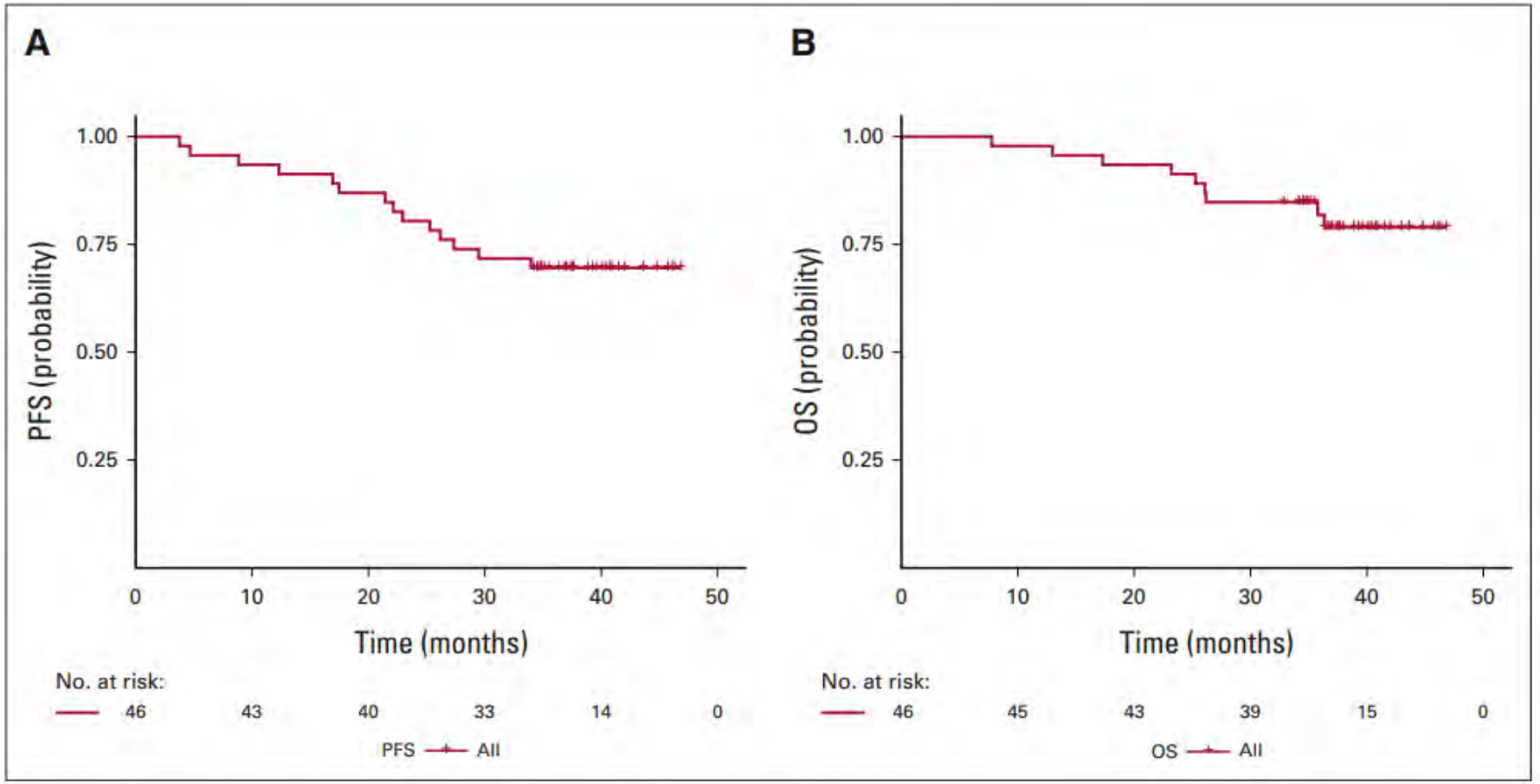
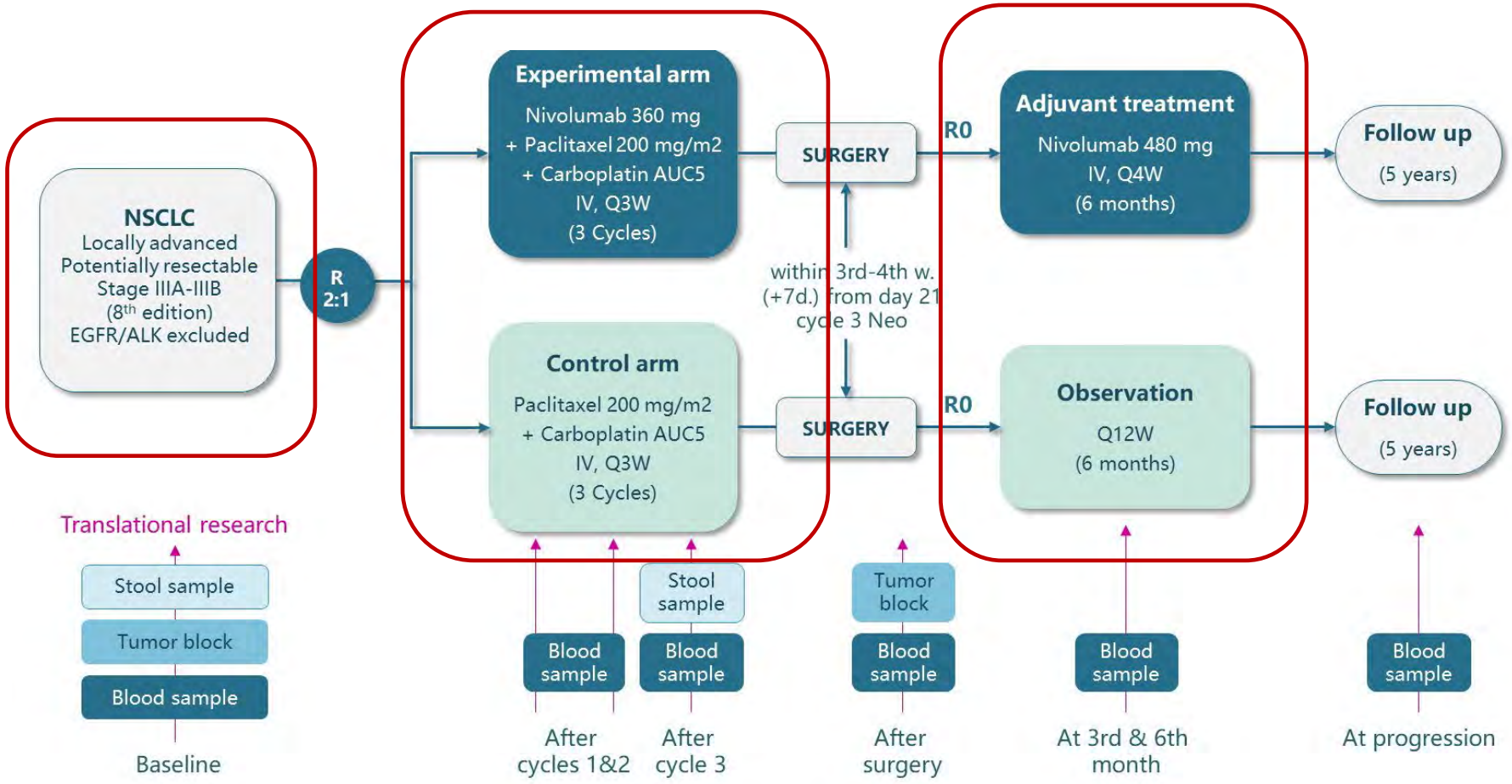


FIG 1. Kaplan-Meier curves for (A) PFS and (B) OS in the ITT population (N = 46). ITT, intention-to-treat; OS, overall survival; PFS, progression-free

3-year OS ~82%

Provencio M, et al. *J Clin Oncol.* 2022;40:2924-2933.

Neoadjuvant NADIM II Phase II RCT



N = 86
Resection: 97% (ICI) vs 69%
Patient characteristics similar
1/3 multistation N2

Primary endpoint: pCR rate

Provencio-Pulla M, et al. *J Clin Oncol*. 2022;40(16 suppl): abstract 8501.

Neoadjuvant ICI: NADIM

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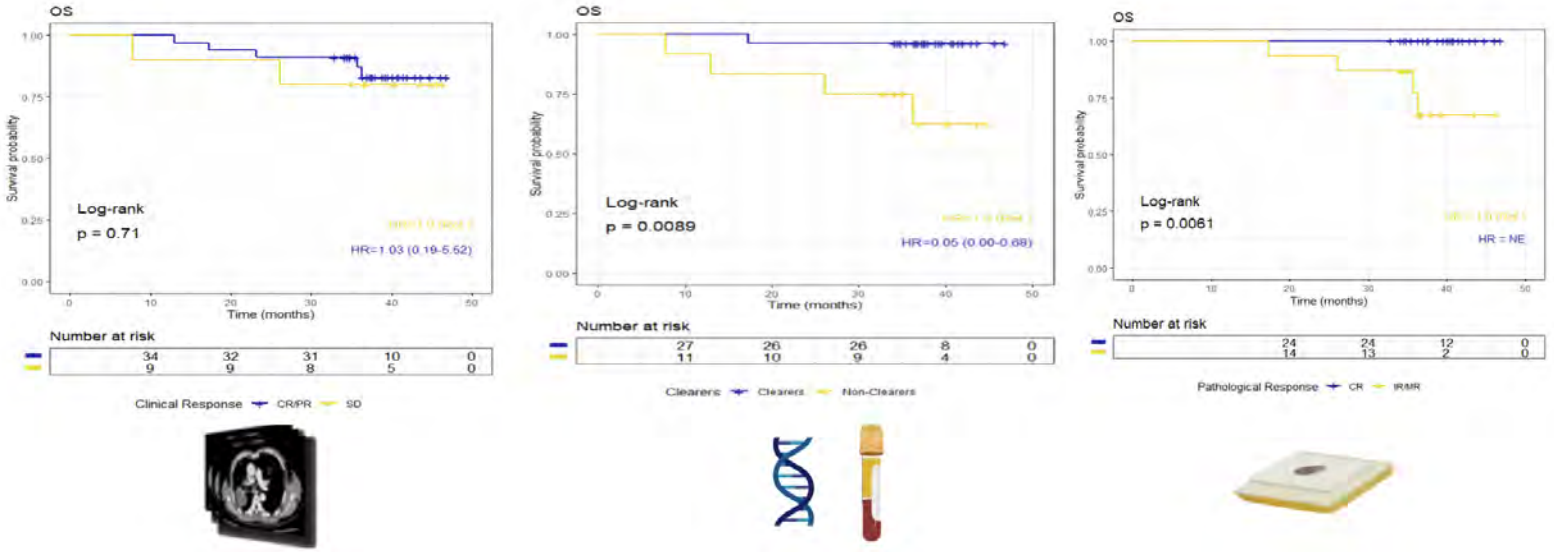
Survival surrogate	HR (PFS)	95% CI	P	Adjusted PFS C-statistic	95% CI	HR (OS)	95% CI	P	Adjusted OS C-statistic	95% CI
Clinical respone (CR+PR vs SD)	0.93	0.24-3.56	0.921	0.61	0.45-0.78	1.03	0.19-5.52	0.974	0.68	0.44-0.93
Pathological response (Complete vs Major+Incomplete)	0.25	0.06-1.00	**0.05**	0.68	0.52-0.84	--	--	--	0.83	0.75-0.91
ctDNA Clearance	0.3	0.08-1.11	**0.072**	0.62	0.43-0.81	0.05	0.00-0.68	**0.024**	0.79	0.55-1.03

MOLECULAR RESPONSE

Clearers

Non-clearers

ctDNA clearance (i.e lack of detectable ctDNA at the end of neoadjuvant tx), **significantly predicted long-term survival.**



Provencio M, et al. WCLC 2021. Abstract OA20.01.

NADIM: High pCR Rate in Line With CM816

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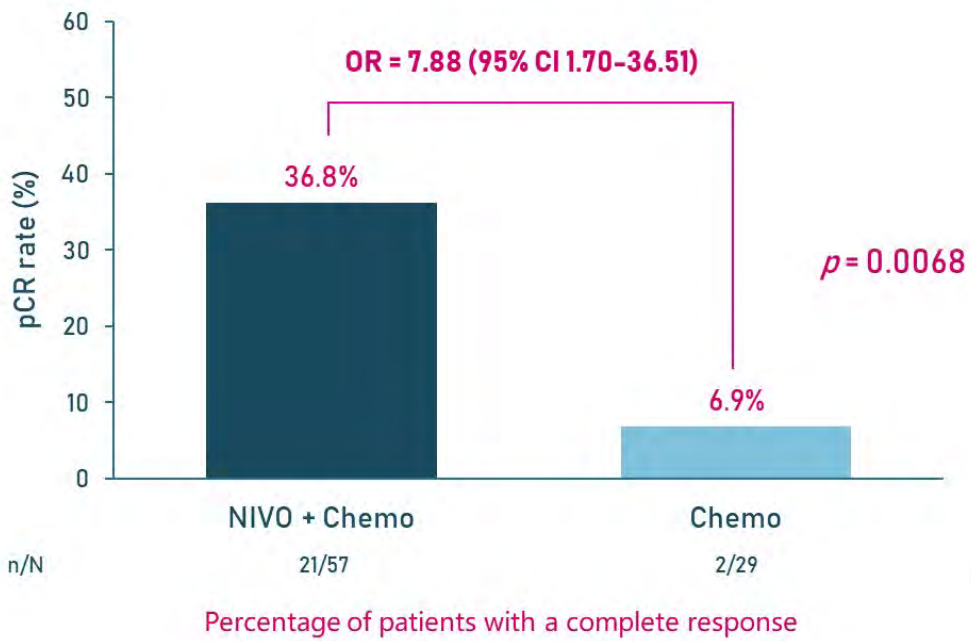
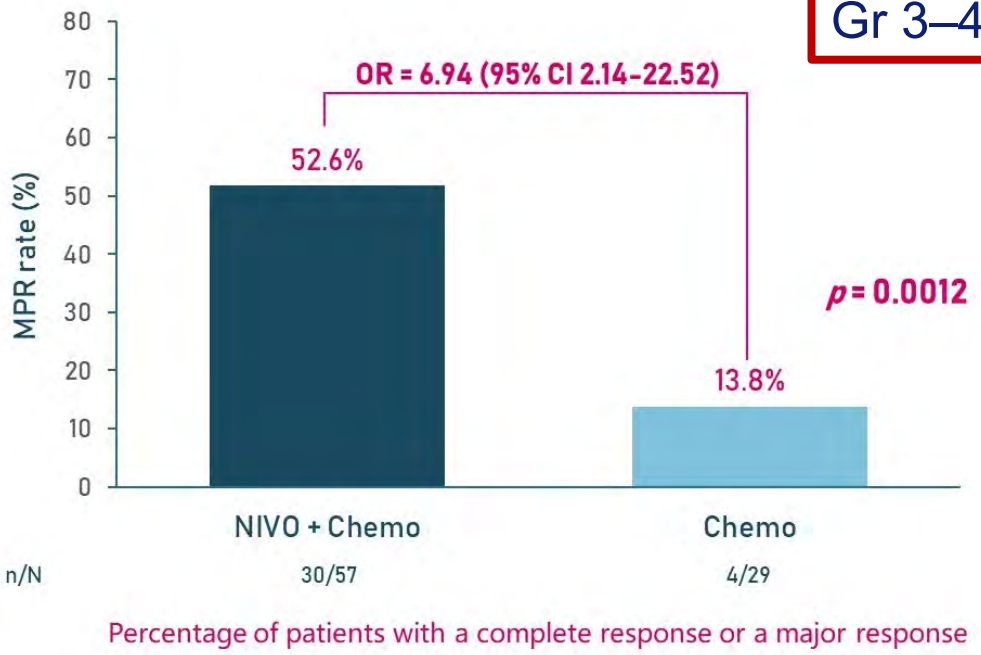
pCR rate



MPR rate

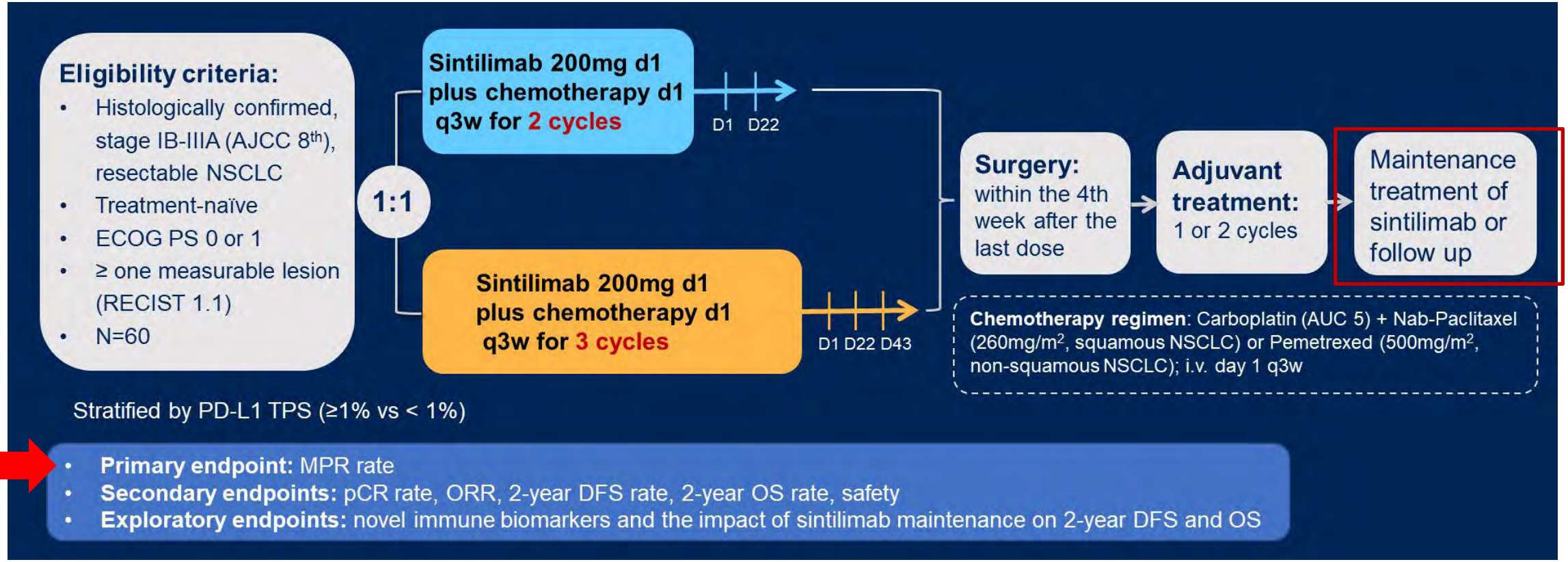


ORR: 75% vs 48%
Gr 3–4 tox: 25% vs 10%

pCR driven by PD-L1

Provencio M, et al. *J Clin Oncol.* 2022;40:2924-2933.

neoSCORE Phase II: 2 or 3 Cycles of Neoadjuvant Treatment



DSMB: unplanned stop of enrollment after N = 60/102
99% on to resection, 1/3 stage IIIA, 1/3 never smoker, 1/2 PD-L1 neg
Tox 3 cycles ~ 2 cycles

Qiu F, et al. *J Clin Oncol.* 2022;40(16 suppl): abstract 8500.

Numerically Higher MPR and pCPR With 3 Cycles, but Also Longer Time Between Cycle 1–2 and Surgery!

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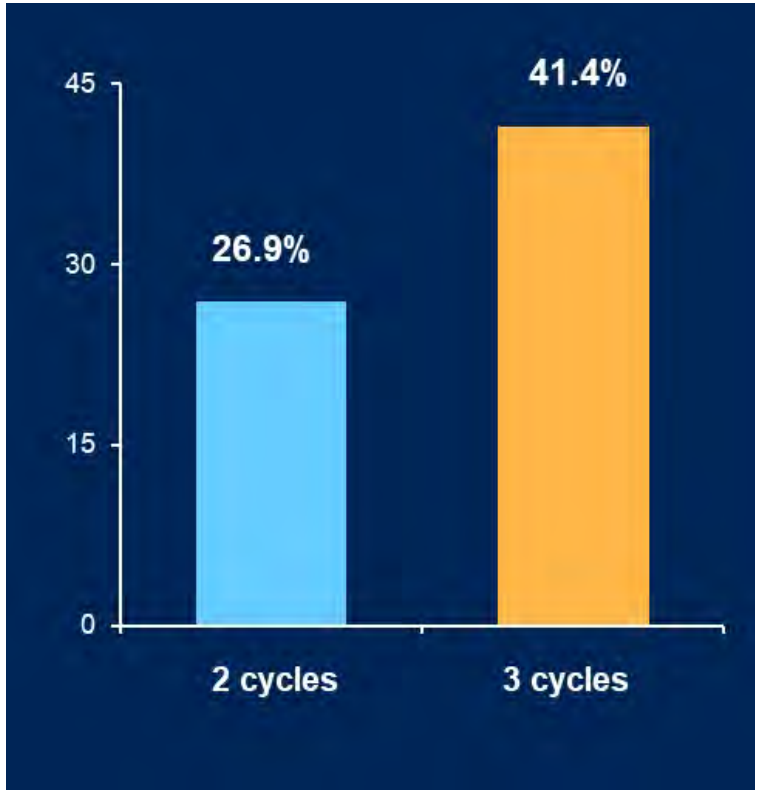
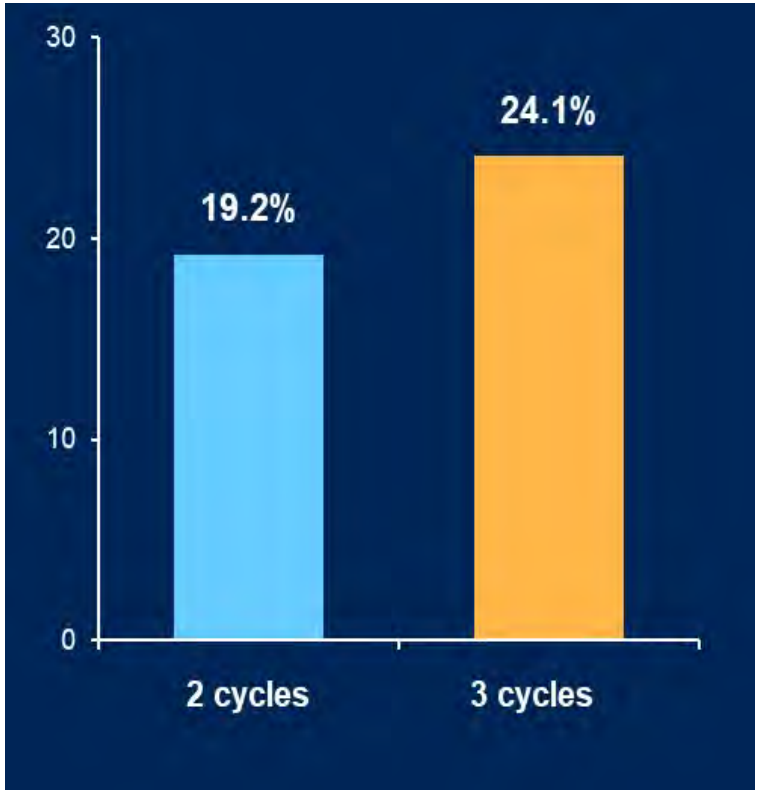
MPR rate

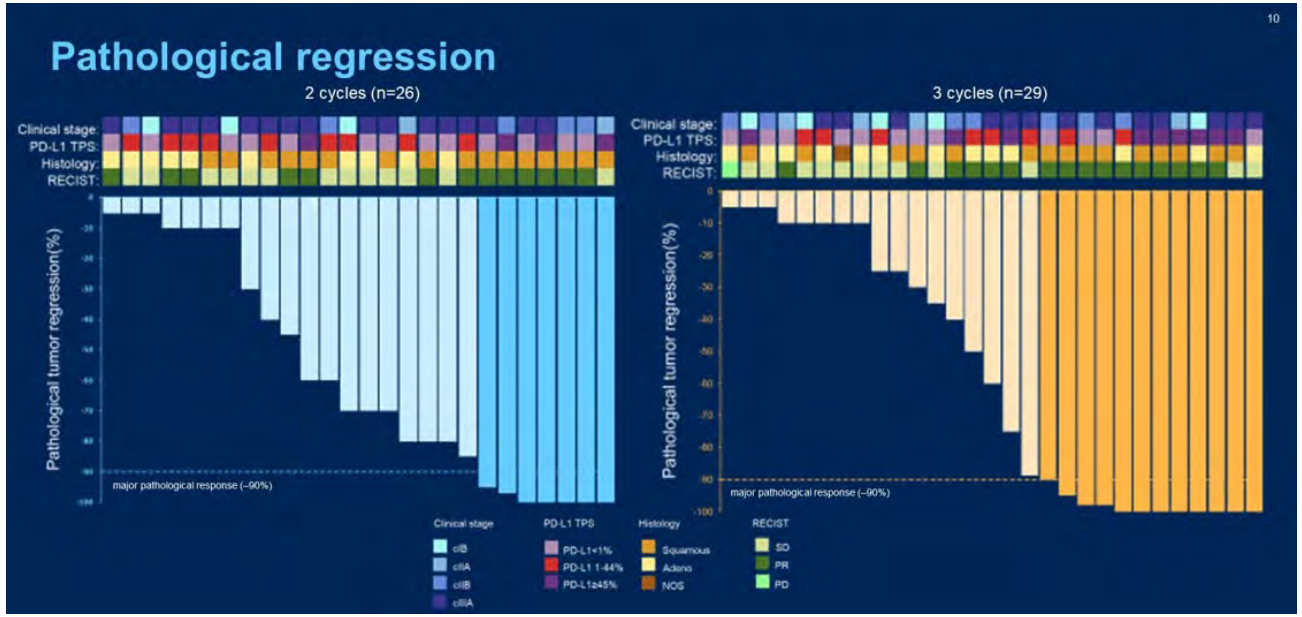


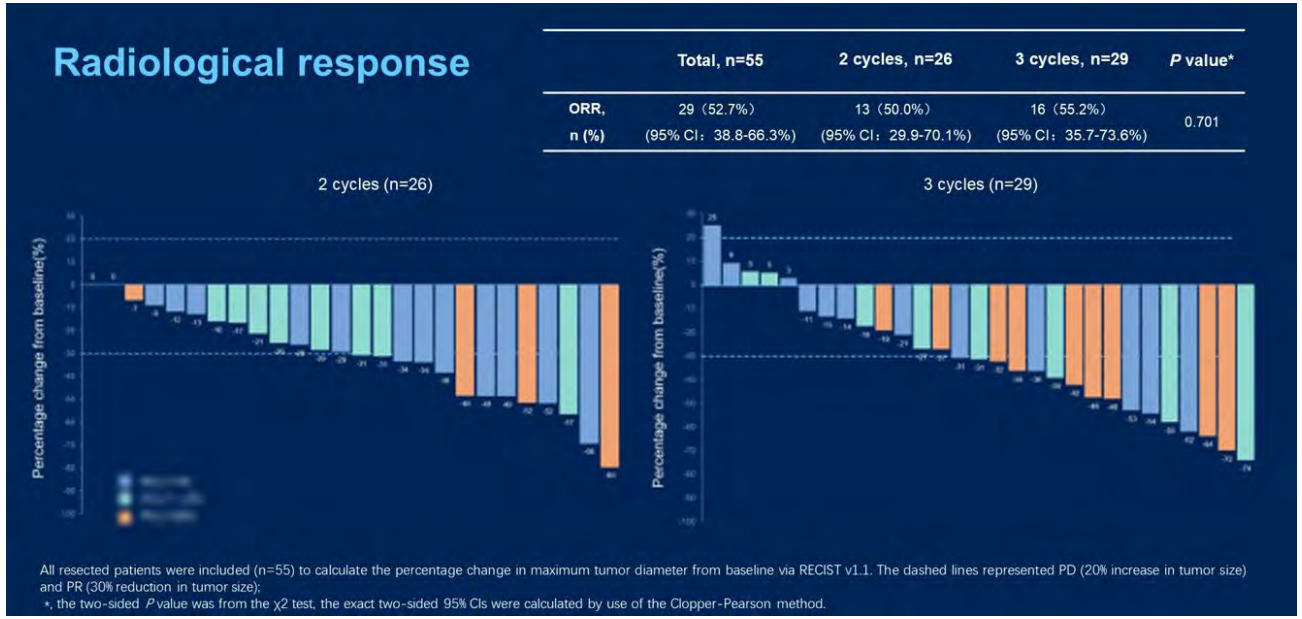
pCR rate



MPR/pCR more frequent in SQ and high PD-L1 (≥45%)

Qiu F, et al. *J Clin Oncol.* 2022;40(16 suppl): abstract 8500.





	Total, n=55	2 cycles, n=26	3 cycles, n=29	*P* value*
ORR, n (%)	29（52.7%）(95% CI：38.8-66.3%)	13（50.0%）(95% CI：29.9-70.1%)	16（55.2%）(95% CI：35.7-73.6%)	0.701

All resected patients were included (n=55) to calculate the percentage change in maximum tumor diameter from baseline via RECIST v1.1. The dashed lines represented PD (20% increase in tumor size) and PR (30% reduction in tumor size);
*, the two-sided *P* value was from the $\chi 2$ test, the exact two-sided 95% CIs were calculated by use of the Clopper-Pearson method.

Radiologic response underestimates pathologic response

Qiu F, et al. *J Clin Oncol.* 2022;40(16 suppl): abstract 8500.

	CheckMate 816		NADIM		neoSCORE	
	NIVO + chemo × 3	Chemo × 3	NIVO + chemo × 3	Chemo × 3	Sintilimab + chemo × 2	Sintilimab + chemo × 3
N	179	179	57	29		
Stage III	63%	64%	100%	100%	62%	45%
Surgery	83%	75%	92%	69%	89%	97%
CPR	24%	2%	37%	7%	19%	24%
MPR	37%	9%	53%	14%	27%	41%

Forde PM, et al. *N Engl J Med*. 2022;386:1973-1985; Provencio M, et al. *J Clin Oncol.* 2022;40:2924-2933; Qiu F, et al. *J Clin Oncol.* 2022;40(16 suppl): abstract 8500.

Conclusions: Neoadjuvant Therapy for Resectable NSCLC

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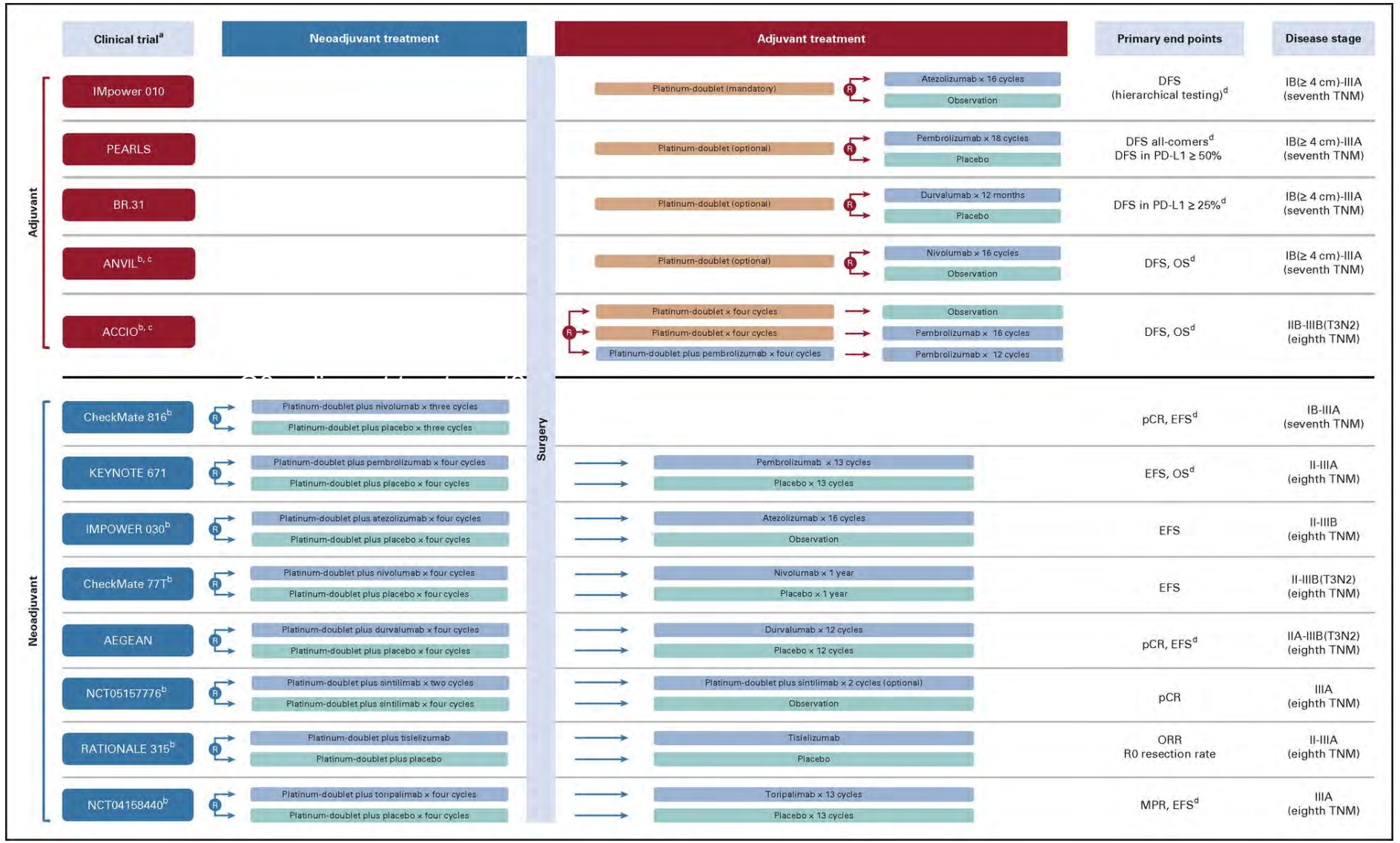
Neoadjuvant chemo-IO

- Feasible
- Impressive pCR ~ DFS ---→ >OS?
- Resectable stage IIIa (~CRT?)

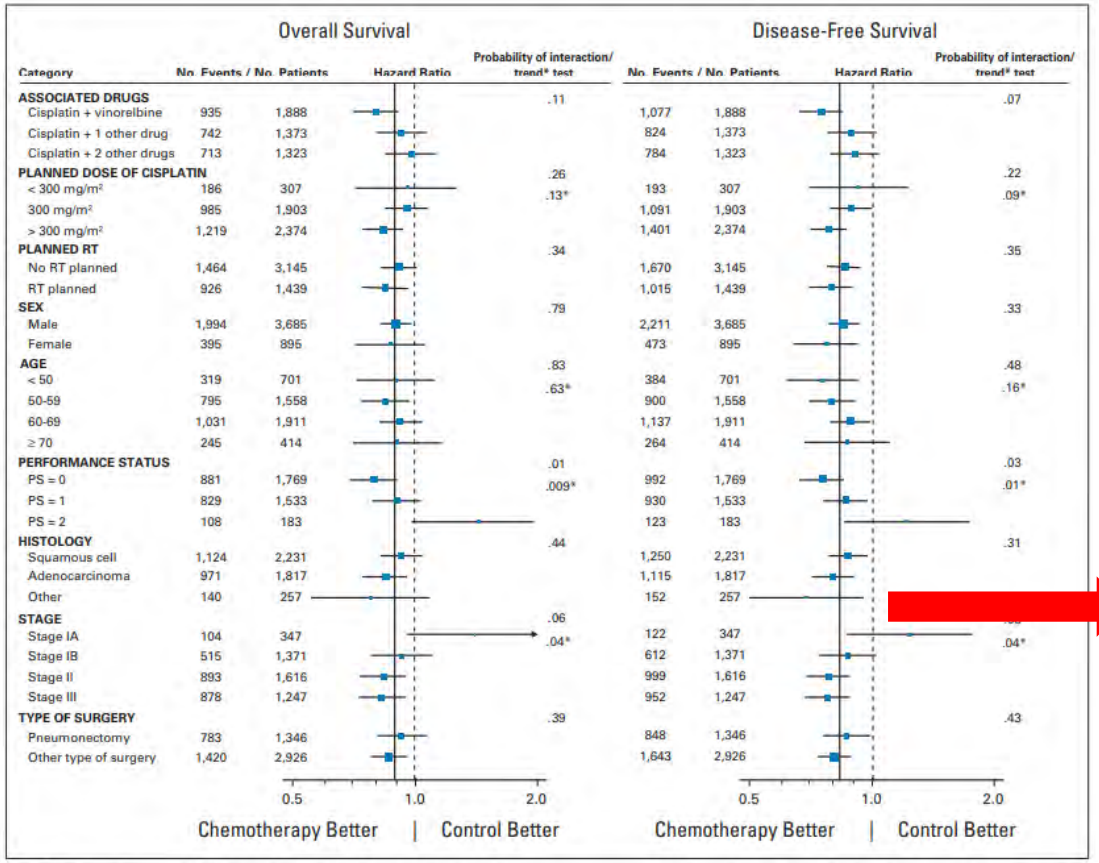
Q1: Adjuvant Treatment?



	Clinical trial[a]	Neoadjuvant treatment		Surgery	Adjuvant treatment		Primary end points	Disease stage
Adjuvant	IMpower 010				Platinum-doublet (mandatory)	Atezolizumab × 16 cycles / Observation	DFS (hierarchical testing)[d]	IB(≥ 4 cm)-IIIA (seventh TNM)
Adjuvant	PEARLS				Platinum-doublet (optional)	Pembrolizumab × 18 cycles / Placebo	DFS all-comers[d] DFS in PD-L1 ≥ 50%	IB(≥ 4 cm)-IIIA (seventh TNM)
Adjuvant	BR.31				Platinum-doublet (optional)	Durvalumab × 12 months / Placebo	DFS in PD-L1 ≥ 25%[d]	IB(≥ 4 cm)-IIIA (seventh TNM)
Adjuvant	ANVIL[b, c]				Platinum-doublet (optional)	Nivolumab × 16 cycles / Observation	DFS, OS[d]	IB(≥ 4 cm)-IIIA (seventh TNM)
Adjuvant	ACCIO[b, c]				Platinum-doublet × four cycles / Platinum-doublet × four cycles / Platinum-doublet plus pembrolizumab × four cycles	Observation / Pembrolizumab × 16 cycles / Pembrolizumab × 12 cycles	DFS, OS[d]	IIB-IIIB(T3N2) (eighth TNM)
Neoadjuvant	CheckMate 816[b]	Platinum-doublet plus nivolumab × three cycles / Platinum-doublet plus placebo × three cycles					pCR, EFS[d]	IB-IIIA (seventh TNM)
Neoadjuvant	KEYNOTE 671	Platinum-doublet plus pembrolizumab × four cycles / Platinum-doublet plus placebo × four cycles			Pembrolizumab × 13 cycles / Placebo × 13 cycles		EFS, OS[d]	II-IIIA (eighth TNM)
Neoadjuvant	IMPOWER 030[b]	Platinum-doublet plus atezolizumab × four cycles / Platinum-doublet plus placebo × four cycles			Atezolizumab × 16 cycles / Observation		EFS	II-IIIB (eighth TNM)
Neoadjuvant	CheckMate 77T[b]	Platinum-doublet plus nivolumab × four cycles / Platinum-doublet plus placebo × four cycles			Nivolumab × 1 year / Placebo × 1 year		EFS	II-IIIB(T3N2) (eighth TNM)
Neoadjuvant	AEGEAN	Platinum-doublet plus durvalumab × four cycles / Platinum-doublet plus placebo × four cycles			Durvalumab × 12 cycles / Placebo × 12 cycles		pCR, EFS[d]	IIA-IIIB(T3N2) (eighth TNM)
Neoadjuvant	NCT05157776[b]	Platinum-doublet plus sintilimab × two cycles / Platinum-doublet plus sintilimab × four cycles			Platinum-doublet plus sintilimab × 2 cycles (optional) / Observation		pCR	IIIA (eighth TNM)
Neoadjuvant	RATIONALE 315[b]	Platinum-doublet plus tislelizumab / Platinum-doublet plus placebo			Tislelizumab / Placebo		ORR R0 resection rate	II-IIIA (eighth TNM)
Neoadjuvant	NCT04158440[b]	Platinum-doublet plus toripalimab × four cycles / Platinum-doublet plus placebo × four cycles			Toripalimab × 13 cycles / Placebo × 13 cycles		MPR, EFS[d]	IIIA (eighth TNM)

Passaro A, et al. *J Clin Oncol*. 2022;40:2871-2877.

Q2: Cisplatin >> Carboplatin



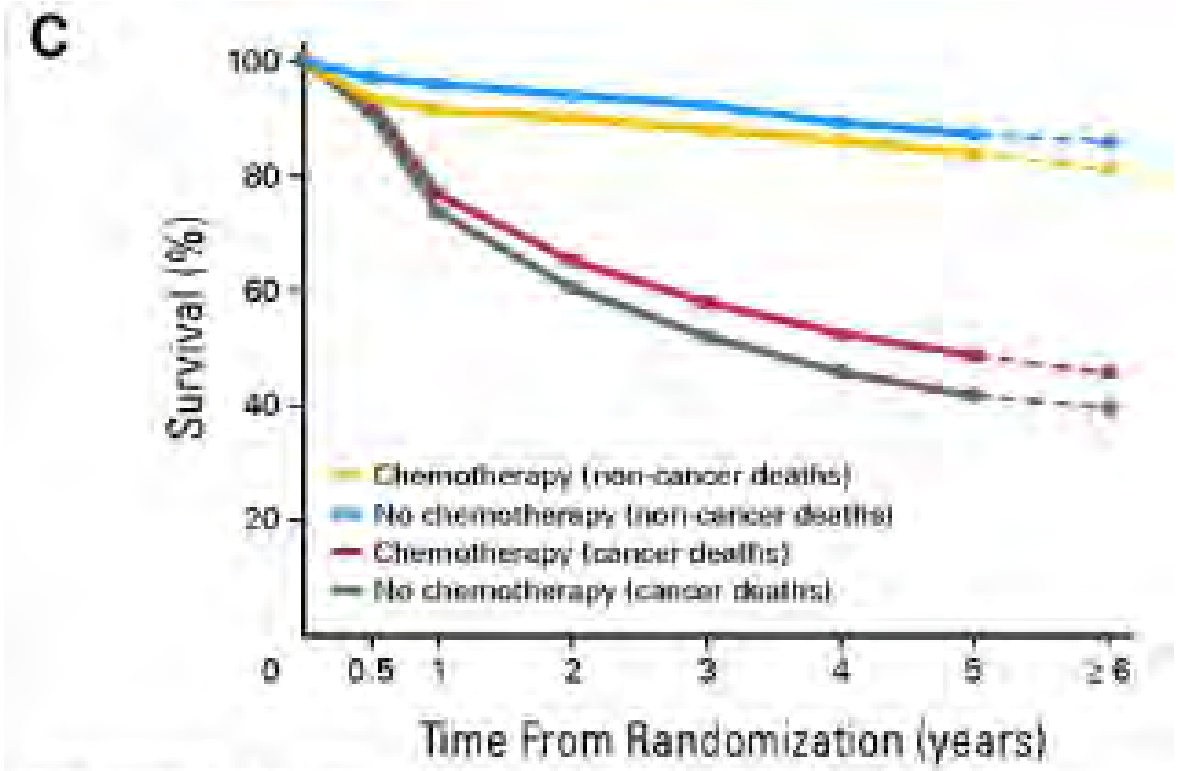
	Number of trials	Number of deaths/ patients	Hazard ratio (95%CI), p value	Hetero-geneity p value	F ratio p value	Interaction p value
Survival by planned chemotherapy schedule (n=15 trials)					0·32	0·23
Preoperative chemotherapy only	10	1045/1883	0·90 (0·80–1·02), 0·09	0·10		
Preoperative and postoperative chemotherapy (to responders)	5	382/502	0·78 (0·64–0·95), 0·02	0·62		
Survival by number of preoperative chemotherapy cycles (n=14 trials)					0·74	0·68
2 cycles	6	418/576	0·89 (0·74–1·08), 0·25	0·39		
3 cycles	8	1002/1799	0·85 (0·75–0·96), 0·01	0·10		
Survival by chemotherapy regimen (n=14 trials)					0·96 (all trials), 0·94 (platinum-only trials)	0·95 (all trials), 0·91 (platinum-only trials)
Platinum plus second generation chemotherapy	7	543/694	0·86 (0·72–1·02), 0·08	0·03		
Platinum plus third generation chemotherapy	6	801/1540	0·85 (0·74–0·97), 0·02	0·57		
Non-platinum chemotherapy	1	38/62	0·95 (0·50–1·79), 0·87	NA		
Survival by the number of chemotherapy agents (n=15 trials)					0·90 (all trials), 0·70 (platinum-only trials)	0·84 (all trials), 0·61 (platinum-only trials)
Non-platinum single agent regimen	1	38/62	0·95 (0·50–1·79), 0·87	NA		
Doublet regimen	9	907/1702	0·88 (0·78–1·01), 0·06	0·42		
Triplet regimen	5	475/611	Fixed effect 0·83 (0·69–1·00), 0·05; random effects 0·79 (0·53–1·18), 0·25	0·01		
Survival by chemotherapy regimen and number of chemotherapy agents (n=14 trials)					0·89 (all trials), 0·95 (platinum-only trials)	0·79 (all trials), 0·62 (platinum-only trials)
Non-platinum single agent regimen	1	38/62	0·95 (0·50–1·79), 0·87	NA		
Platinum second generation, doublet	2	68/83	1·08 (0·68–1·76), 0·76	0·42		
Platinum second generation, triplet	5	475/611	Fixed effect 0·83 (0·69–1·00), 0·05; random effects 0·79 (0·53–1·18), 0·25	0·01		
Platinum third generation, doublet	6	801/1540	0·85 (0·74–0·97), 0·02	0·57		
Survival by cisplatin or carboplatin regimen (n=12 trials)					0·54	0·48
Cisplatin-based	7	830/1289	0·83 (0·72–0·95), 0·01	0·08		
Carboplatin-based	5	492/905	0·90 (0·75–1·07), 0·23	0·88		
Survival by planned postoperative radiotherapy (n=15 trials)					0·64	0·57
No postoperative radiotherapy given	8	431/852	0·83 (0·68–1·01), 0·05	0·40		
Postoperative radiotherapy given	7	996/1533	0·88 (0·78–1·00), 0·05	0·09		
Survival by whether trial stopped early (all trials; n=15 trials)					0·10	0·05
Reached target accrual	3	800/1287	0·90 (0·79–1·04), 0·16	0·66		
Stopped for benefit of chemotherapy	2	92/119	0·48 (0·31–0·74), <0·001	0·43		
Stopped for high progression on chemotherapy arm	1	16/26	1·08 (0·41–2·90), 0·87	NA		
Stopped for poor accrual/positive adjuvant trials	9	519/953	0·88 (0·74–1·05), 0·17	0·31		

NA=not applicable.

Table 3: Effect of preoperative chemotherapy by prespecified trial group

Pignon JP, et al. *J Clin Oncol*. 2008;26:3552-3559; NSCLC Meta-analysis Collaborative Group. *Lancet*. 2014;383:1561-1571.

Q3: Chemo(platinum)-Free Alternatives?

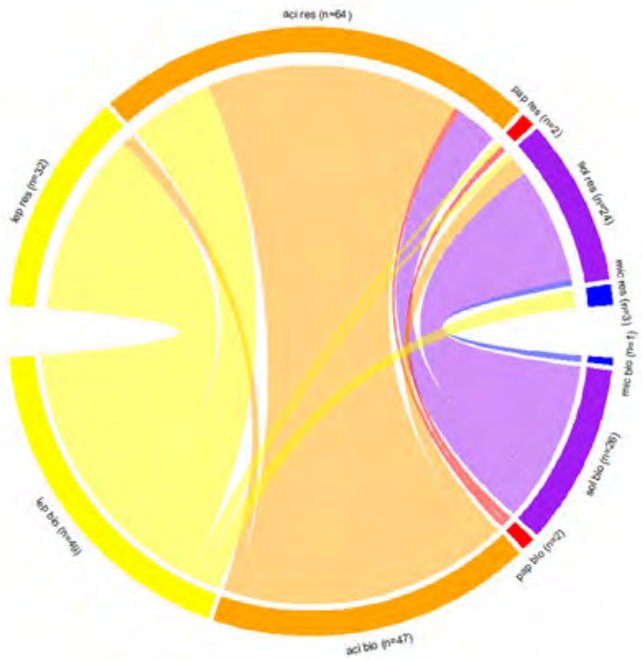


Non-cancer deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	88 / 4,353	42 / 1,389	9 / 611
Chemotherapy	141 / 4,638	38 / 1,611	24 / 708
Cancer deaths by period			
Control	878	197	40
Chemotherapy	716	166	52

More non–cancer-related death after adjuvant chemotherapy?

Pignon JP, et al. *J Clin Oncol.* 2008;26:3552-3559.

Q4: Predictive Value of Adenocarcinoma Growth Pattern

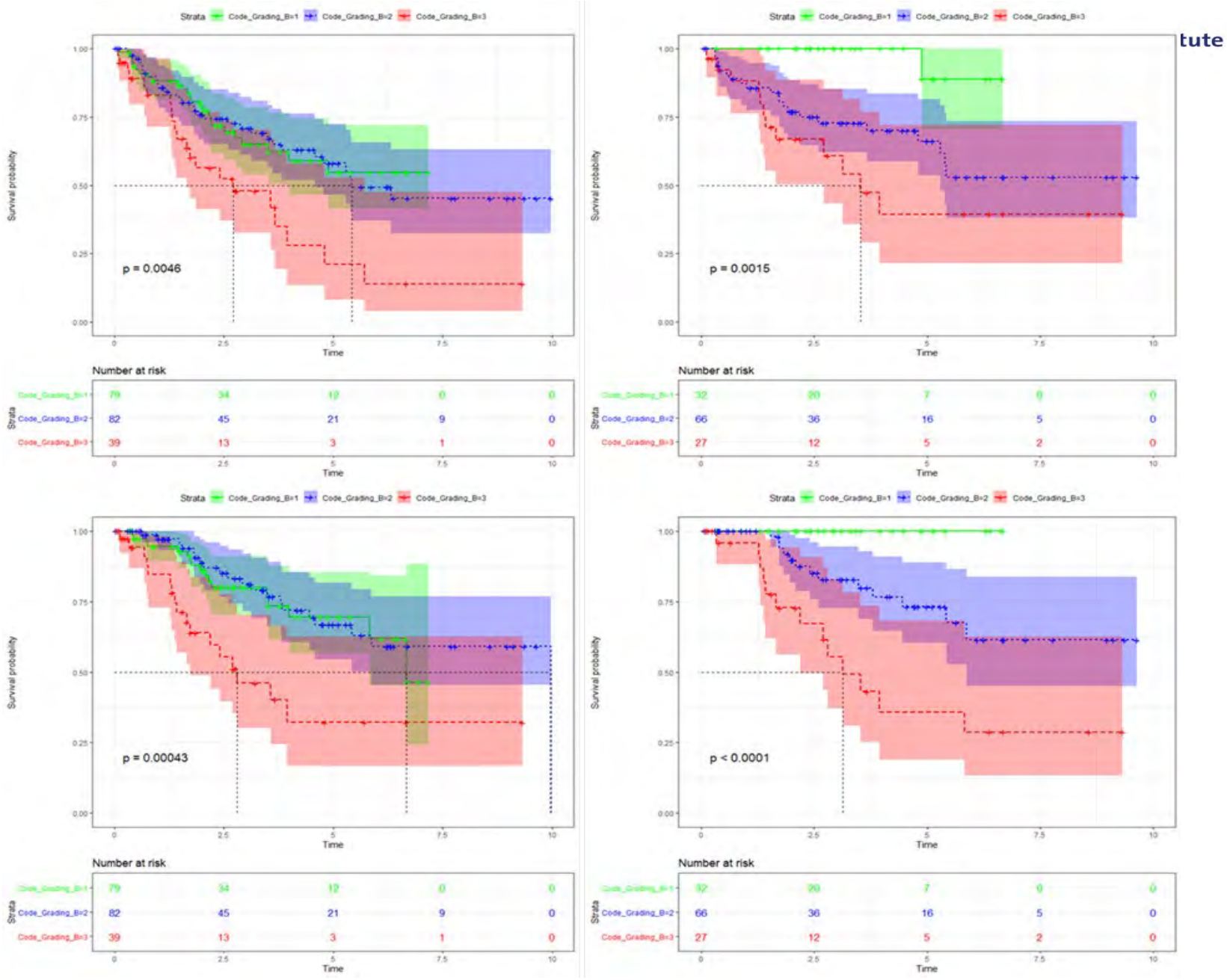


		Dominant growthpattern of biopsy					
		Lepidic	Acinary	Micropapillary	Papillary	Solid	Total
Dominant growthpattern of resection	Lepidic	30 (93.8%); p=0.000*	2 (6.2%); p=0.000*	0 (0.0%); p=1*	0 (0.0%); p=1*	0 (0.0%); p=0.000*	32 (100%)
	Acinary	14 (21.9%); p=0.000	42 (65.6%); p=0.000	0 (0.0%); p=0.488*	1 (1.6%); p=1*	7 (10.9%); p=0.01	64 (100%)
	Micropapillary	3 (100%); p=0.057*	0 (0.0%); p=0.29*	0 (0.0%); p=1*	0 (0.0%); p=1*	0 (0.0%); p=1*	3 (100%)
	Papllary	1 (50%); p=1*	0 (0.0%); p=0.527*	0 (0.0%); p=1*	1 (50%); p=0.031*	0 (0.0%); p=1*	2 (100%)
	Solid	1 (4.2%); p=0.000*	3 (12.5%); p=0.000*	1 (4.2%); p=0.192*	0 (0.0%); p=0.192*	19 (79.2%); p=0.000	24 (100%)
	Total	49 (39.2%)	47 (37.6%)	1 (0.8%)	2 (1.6%)	26 (20.8)	125 (100%)

*Fisher Exact Test

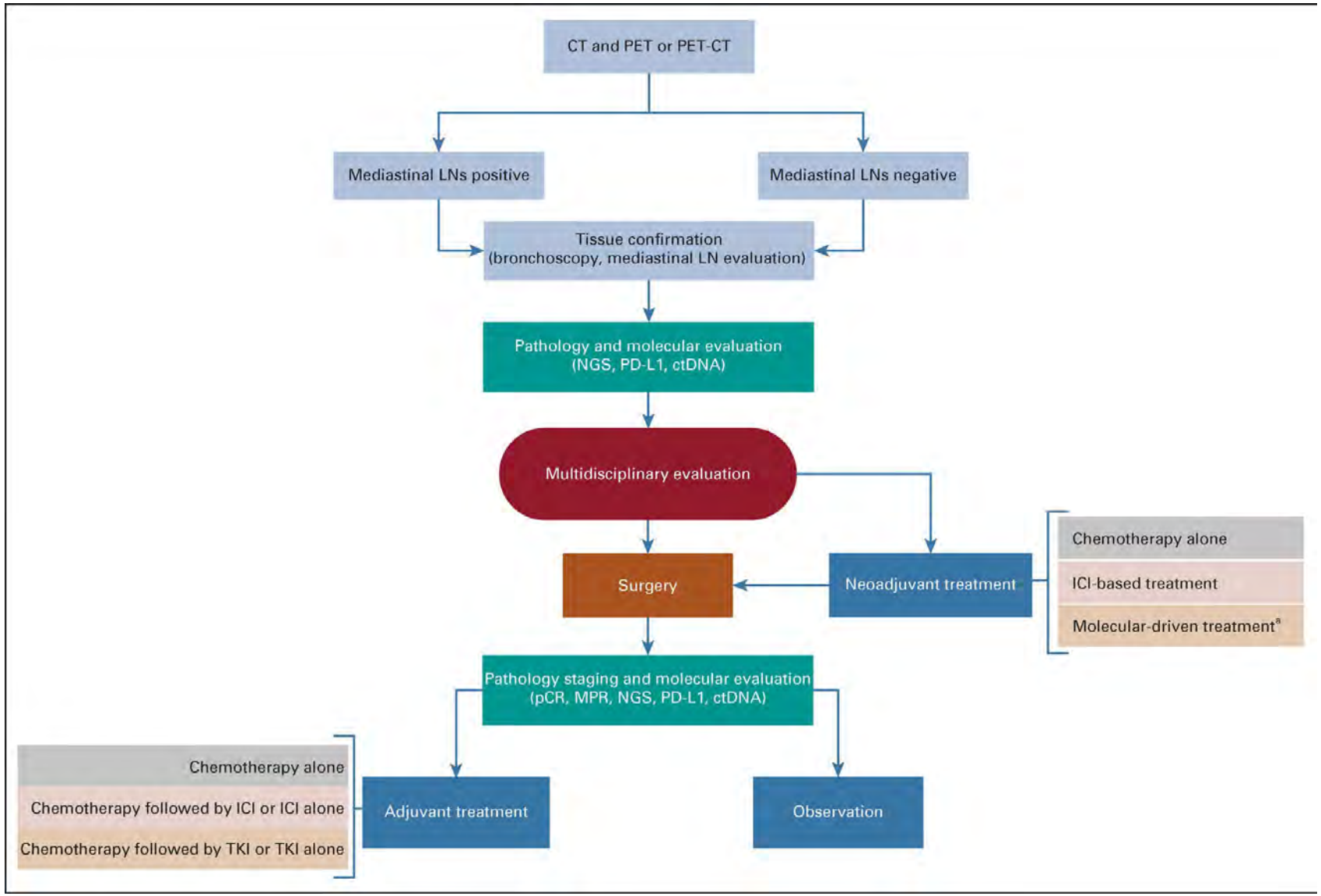
Wolff ESP. 2022. Submitted.

Comparison of OS and PFS between biopsies (right) and resections (left) for the growth pattern



Wolff ESP. 2022. Submitted.

Neoadjuvant Chemo-IO



Passaro A, et al. *J Clin Oncol*. 2022;40:2871-2877.

Conclusion neo-adjuvant therapy for resectable NSCLC

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Neo-adjuvant

- Feasible
- Impressive pCR ~ DFS ---→> OS?
- Resectable stage IIIa (~ CRT?)

- Strategy in case no pCR/MPR / no ctDNA clearance?
- Adjuvant treatment required?

Future:

- Personalized treatment of early stage NSCLC
- MDT including all involved specialists!
- Primary resectability / N2 disease

Different treatment for patients with driver mutations:
NGS – PD-L1 required in all patients before starting treatment!
TISSUE

THANK YOU FOR YOUR ATTENTION!

Erasmus MC Cancer Institute

Global Lung Cancer Academy

Locally Advanced Unresectable NSCLC – What Are the Options?

Antonio Passaro, MD, PhD

Locally Advanced Unresectable NSCLC What Are the Options?

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Declaration of interest

I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom I have received honoraria:

Consultation / Advisory role / Speakers' Bureau:

AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck Sharp and Dohme, Merck Serono, Novartis, Pfizer, Roche/Genentech, MundiPharma, Daiichi Sankyo

Talk in a company's organized public event supported by:

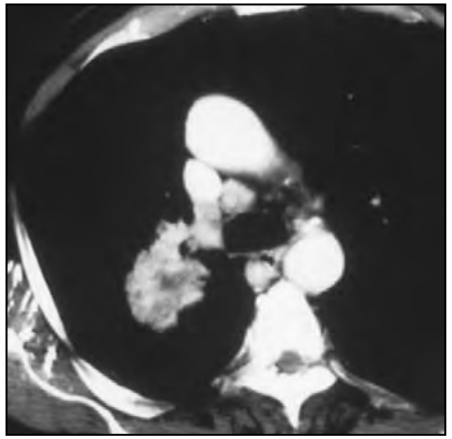
AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, eCancer, Medscape, Takeda, Jansenn , Merck Sharp and Dohme

Receipt of grants/research supports:

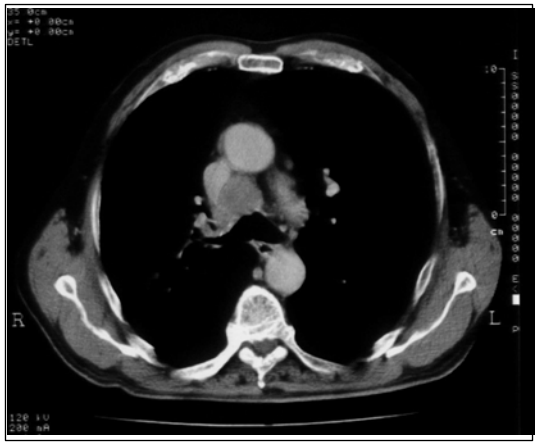
(Sub)investigator in trials (institutional financial support for clinical trials) sponsored by AstraZeneca, Boehringer Ingelheim, Janssen, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck Sharp and Dohme, Merck Serono, Mirati, Pfizer, Roche/Genentech, RMC, Daiichi Sankyo

Member of Steering Committee for trials of: Jansenn & ArriVent Biopharma

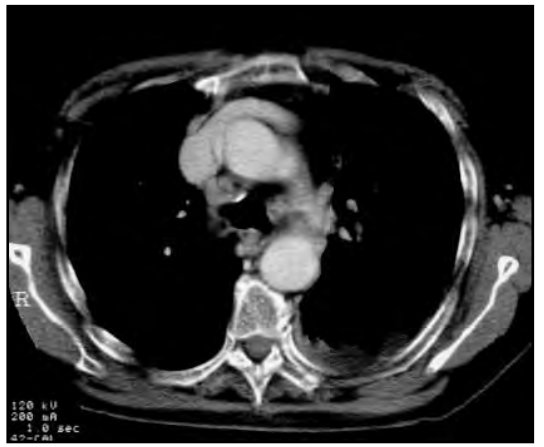
Stage III: many realities (T, N)



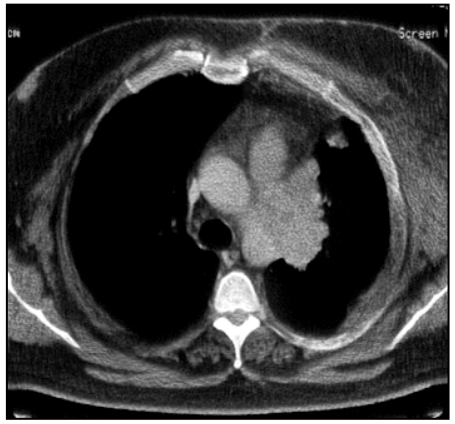
N2 non- bulky (IIIA)



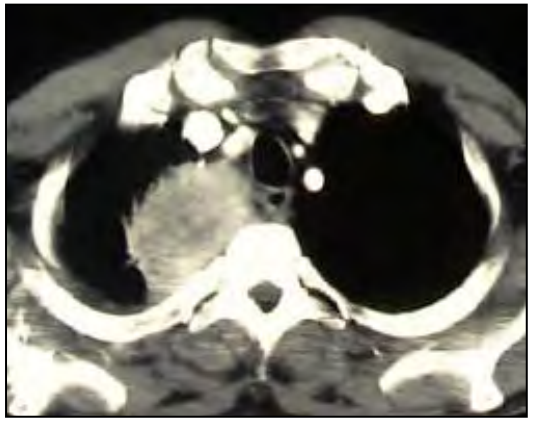
N2 bulky (IIIA)



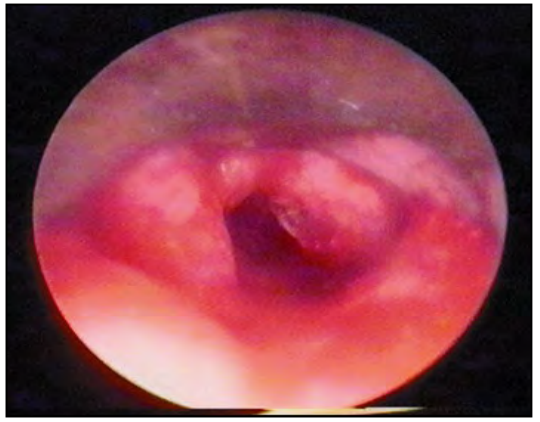
N3 (IIIB)



T4
(mediastinal infiltration)



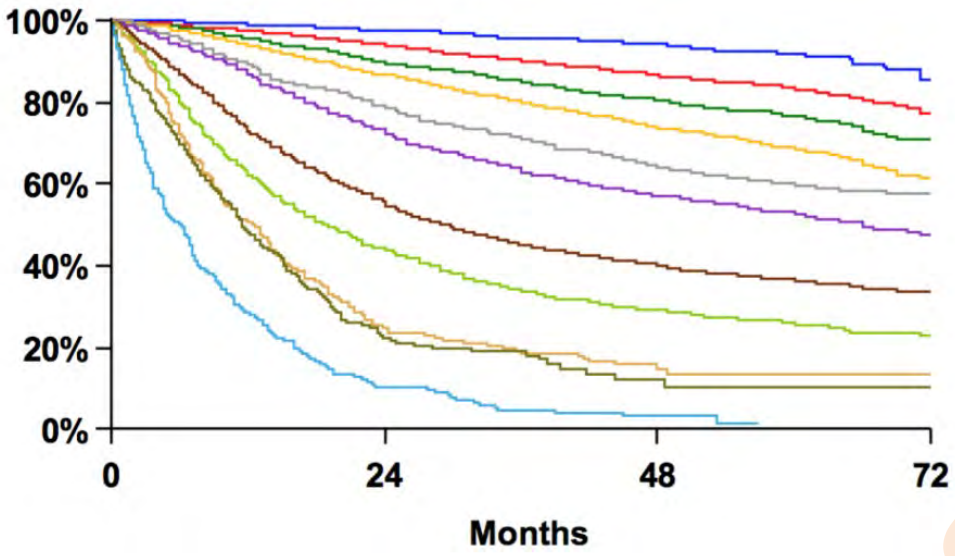
T4
(Chest Wall infiltration)



T4
(tracheal infiltration)

Unresectable stage III NSCLC

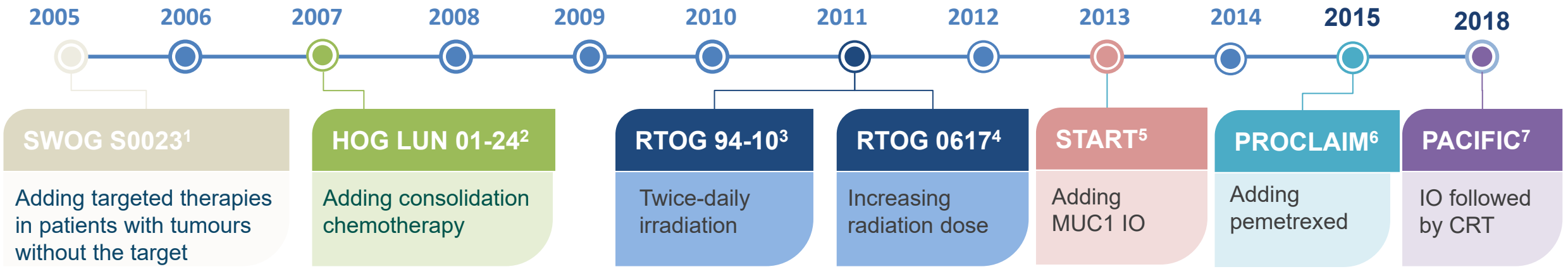
- SoC for patients with unresectable, Stage III NSCLC has been platinum-based CRT[1]
- **However, outcomes have been poor with ~15% to 30% of patients alive at 5 years**[1,2]



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

1. Yoon SM et al. *World J Clin Oncol.* 2017;8:1-20. **2.** Bradley JD et al. *Int J Radiat Oncol Biol Phys.* 2017;99(Suppl):S105..

Treatment Approach for Stage III NSCLC Prior to Immuno-Oncology Over the Past 20 Years Has Remained Unchanged



Concurrent chemoradiation therapy[8,9]

Active surveillance

Patients are routinely monitored for disease progression[9]

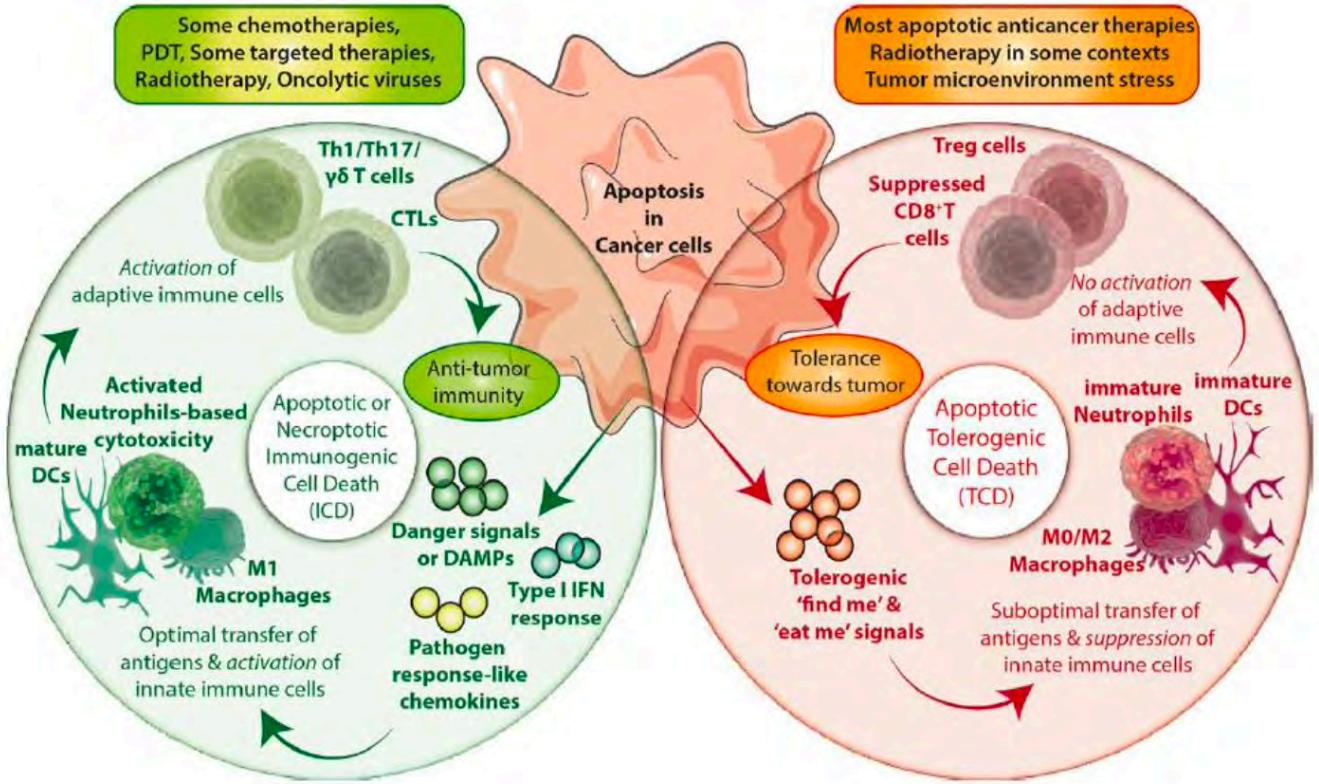
High unmet need

Several phase 3 trials failed in stage III setting prior to PACIFIC[1-4,10]

HOG=Hoosier Oncology Group; RTOG=Radiation Therapy Oncology Group; SWOG=Southwest Oncology Group.

1. Kelly K, et al. J Clin Oncol. 2008;26:2450-2456. 2. Hanna N, et al. J Clin Oncol. 2008;26:5755-5760. 3. Curran WJ, et al. J Natl Cancer Inst. 2011;103:1452-1460. 4. Bradley JD, et al. Lancet Oncol. 2015;16:187-199.
5. Butts C, et al. Lancet Oncol. 2014;15:59-68 and ASCO 2013. 6. Senan S, et al. J Clin Oncol. 2016;34:953-962 and ASCO 2015. 7. IMFINZI Summary of Product Characteristics. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. 8. Aupérin A, et al. J Clin Oncol. 2010;28:2181-2190. 9. Postmus PE, et al. Annal of Oncol. 2017;28(suppl 4):iv1-iv21. 10. Hanna N. Am Soc Clin Oncol Educ Book. 2015:e442-e447.

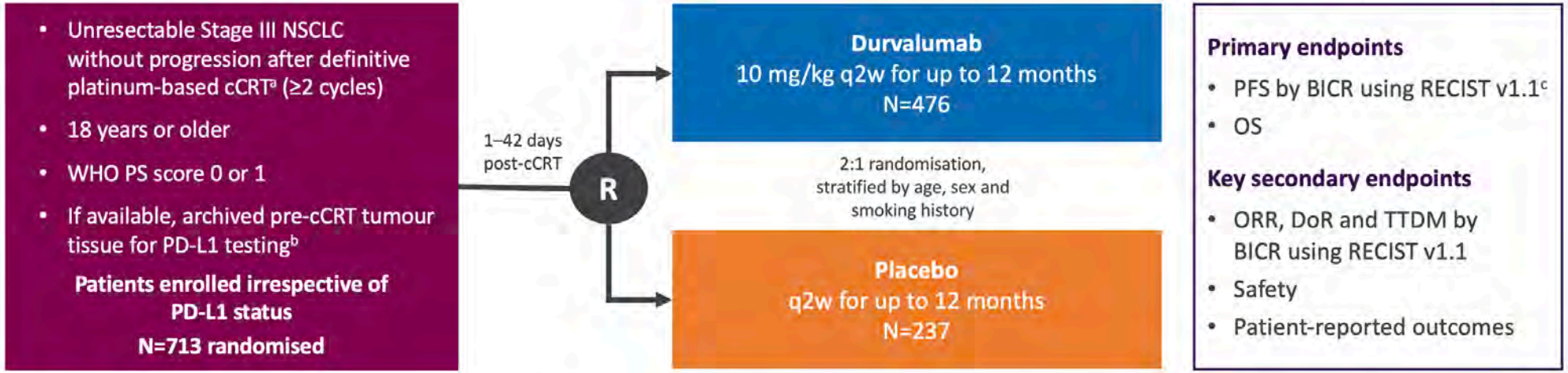
Adding chemo or RT: immunogenic cell death hypothesis



Damage-associated molecular patterns (DAMPs), are **danger signals** that mediate robust immunomodulation and de facto underlie the immunogenicity of cancer cell death

Leisha A. Emens, and Gary Middleton Cancer Immunol Res 2015;3:436-443
Lorenzo Galluzzi et al. Cancer Immunol Res 2016
Peters, ASCO 2017

Pacific phase 3 trial in unresectable NSCLC



Updated analyses of OS and PFS, assessed ~5 years after the last patient was randomised (data cut-off: 11 January 2021; exploratory, post-hoc analysis)

- Treatment effects were estimated using stratified log-rank tests in the ITT population
- Medians and yearly landmark rates were estimated using the Kaplan–Meier method

ClinicalTrials.gov identifier: NCT02125461

[a]Radiation dosage typically 60–66 units of gray in 30–33 fractions; [b]Using the Ventana SP263 immunohistochemistry assay; [c]Defined as the time from randomisation to the date of objective disease progression or death by any cause in the absence of progression

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; ITT, intent-to-treat; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to distant metastasis; WHO, World Health Organization

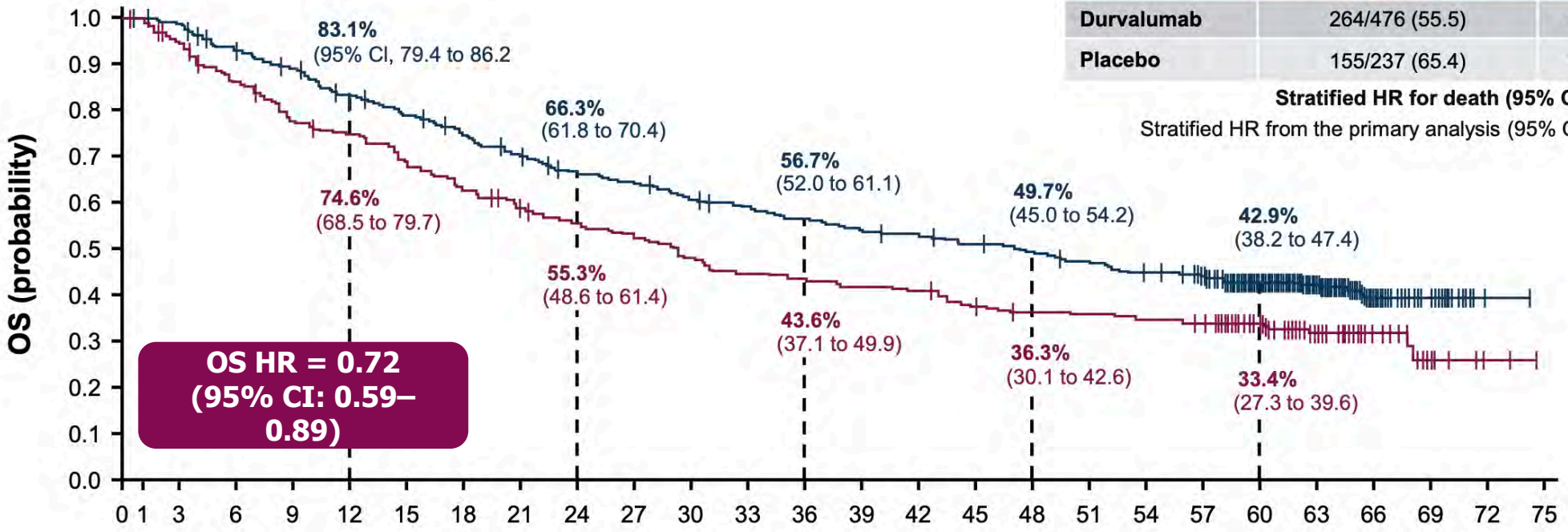
Spigel et al. Presented at ASCO 2021, Poster 8511

Updated OS results of PACIFIC trial

Arm	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)

Stratified HR for death (95% CI): 0.72 (0.59–0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53–0.87)



No. at risk

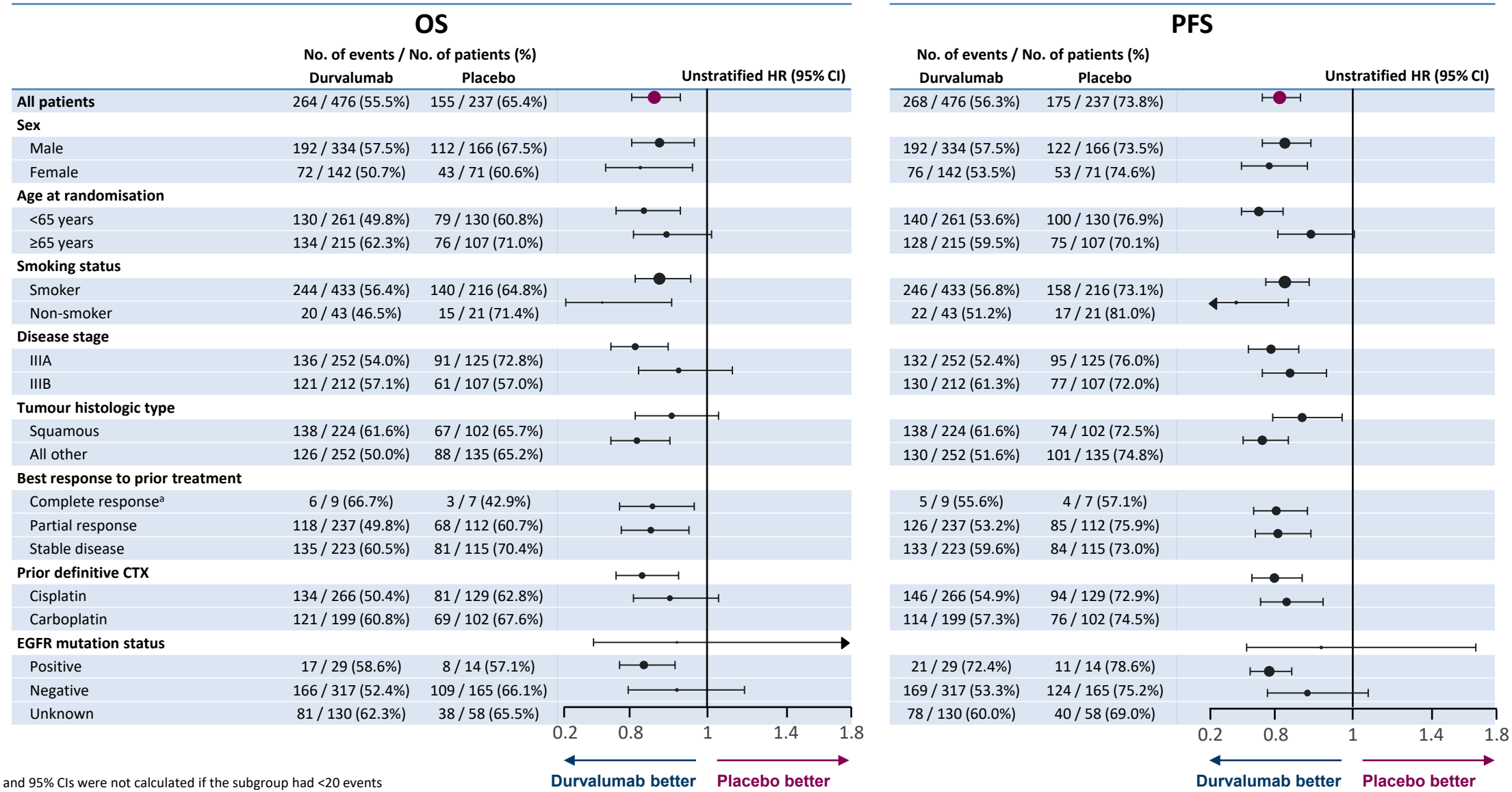
Durva.	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

DCO5: January 11, 2021; median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7].

CI = confidence interval; DCO = data cutoff; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival.

Spigel D et al. Online ahead of print. *J Clin Oncol. 2022.*

Updated OS and PFS in prespecified subgroups



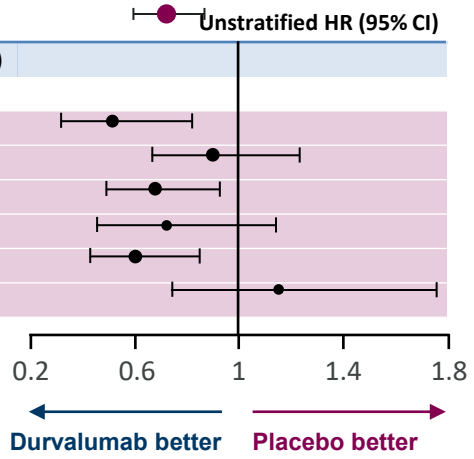
[a]HRs and 95% CIs were not calculated if the subgroup had <20 events

CTX, chemotherapy; EGFR, epidermal growth factor receptor

Updated OS and PFS in PD-L1 subgroups

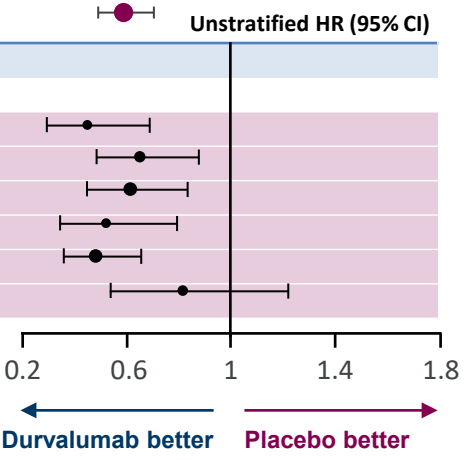
OS

	No. of events / No. of patients (%)	
	Durvalumab	Placebo
All patients	264 / 476 (55.5%)	155 / 237 (65.4%)
PD-L1 expression level		
≥25%	51 / 115 (44.3%)	27 / 44 (61.4%)
<25%	111 / 187 (59.4%)	64 / 105 (61.0%)
Unknown	102 / 174 (58.6%)	64 / 88 (72.7%)
1–24% (post-hoc analysis)	52 / 97 (53.6%)	29 / 47 (61.7%)
≥1% (post-hoc analysis)	103 / 212 (48.6%)	56 / 91 (61.5%)
<1% (post-hoc analysis)	59 / 90 (65.6%)	35 / 58 (60.3%)



PFS

	No. of events / No. of patients (%)	
	Durvalumab	Placebo
264 / 476 (55.5%)	**155 / 237 (65.4%)**	
61 / 115 (53.0%)	33 / 44 (75.0%)	
105 / 187 (56.1%)	77 / 105 (73.3%)	
102 / 174 (58.6%)	65 / 88 (73.9%)	
50 / 97 (51.5)	36 / 47 (76.6%)	
111 / 212 (52.4%)	69 / 91 (75.8%)	
55 / 90 (61.1%)	41 / 58 (70.7%)	

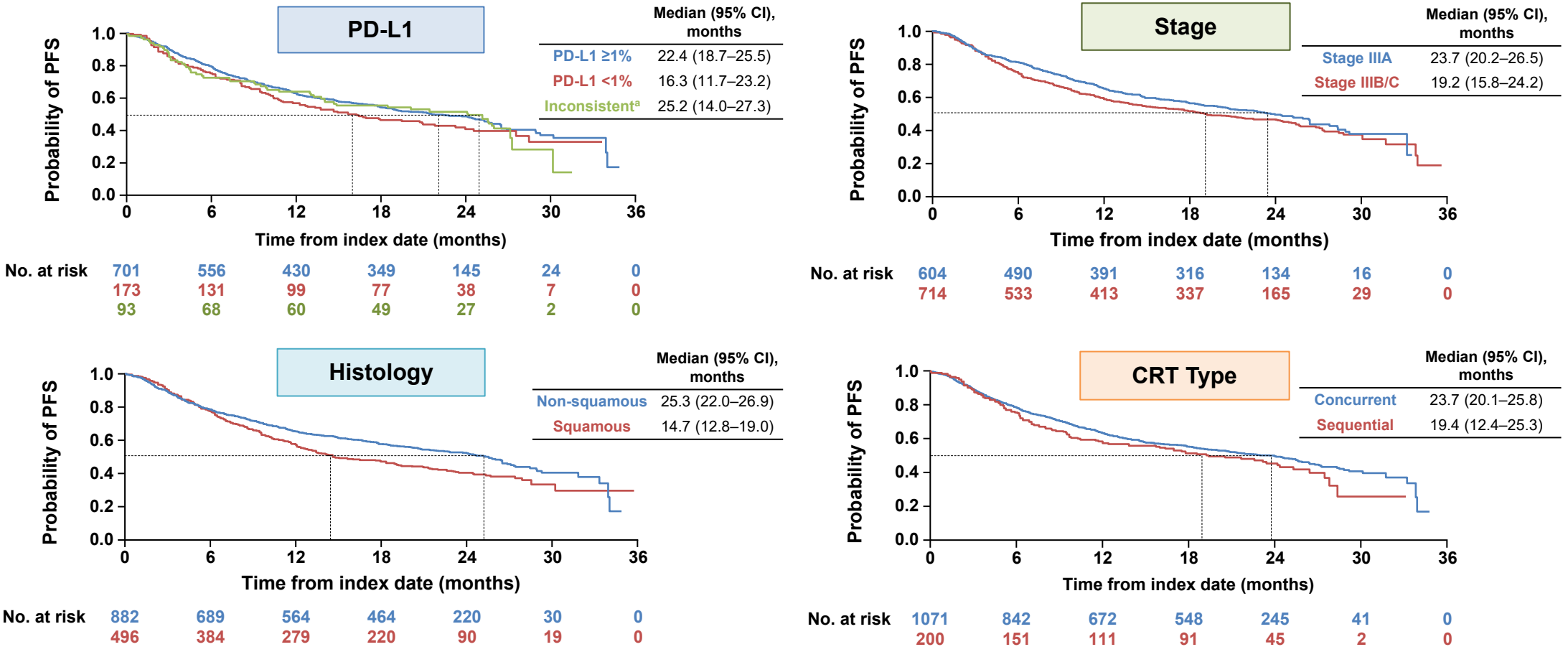


- Updated OS and PFS for subgroups were consistent with the results reported at the time of the primary analyses [1,2]

1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50. 2.Antonia SJ, et al. New Engl J Med 2017;377:1919–29.

PACIFIC-R: Real-world PFS by Subgroup

- The effectiveness of durvalumab after CRT in the analyzed subgroups was generally consistent[1] with previous analyses from the PACIFIC trial[2] including PD-L1 subgroups.[3]



DCO 8 April, 2021.

[a]PD-L1 expression tested but not clearly reported.

CI = confidence interval; CRT = chemoradiotherapy; DCO = data cutoff; PD-L1 = programmed death ligand-1; PFS = progression-free survival.

1. Girard N et al. Presented at: ESMO Congress (virtual); September 16-21, 2021. 2. Antonia SJ, et al. *N Engl J Med* 2017;377:1919-29; 3. Paz-Ares L, et al. *Ann Oncol* 2020;31:798-806.

How to improve the *Pacific* results?

Optimizing the use of IO in stage III?

- Timing of IO + CT/RT
- Duration of IO

New agents?

Evaluation new agents and combination

Identifying predictive biomarkers?

Timing of IO: concurrent IO and CT RT (Ph 2)

Trial	ADK	Stage IIIB/C	PET	PD-L1 <1%	Dose RT	IMRT	Chemo	Conc. ICI	Med. FU	1 y PFS	1 y OS	PNP ⩾ G3	G5 PNP
RTOG 0617[13] (SD arm)	39%	34%	91%	ND	60	59.2%	Carbo Tx	None	5.1 y	49.2%	80%	7%**	1%
KEYNOTE-799[39]	39% (A)	63.4% (A)	ND"	18.8% (A)	60	ND	Carbo Tx (A)	Pembro	1.1 y (A)	67.1% (A)	81.3% (A)	8% (A)	2.3%
	100% (B)	61.8% (B)		27.5% (B)			Cis Pem (B)		1.5 y (B)	76.6% (B)	87% (B)	6.9% (B)	
DETERRED[42] (part 2+)	67%	44%	ND"	8%	66	80%	Carbo Tx	Atezo	1.3 y	52%*	80%*	3%	0%
						20% protons							
NICOLAS[43,44]	59.5%	63.3%	ND"	ND	66	ND	82% Cis-based doublet	Nivo	1.8 y	53.7%	75.7%	11.7%	0%

ADK, adenocarcinomas; atezo, atezolizumab; Carbo, carboplatin; Chemo, chemotherapy; Cis, cisplatin; conc., concurrent; FU, follow-up; G, grade; ICI, immune checkpoint inhibitor; IMRT, intensity-modulated RT; ND, not described; nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; pem, pemetrexed; Pembro, pembrolizumab; PET, whole body positron emission tomography/computed tomography (PET/CT) scan; PFS, progression-free survival; PNP, pneumonitis; RT, radiation therapy; SD, standard dose; Tx, paclitaxel; y, year.
+Concurrent ICI part.
"Inclusion criteria.
*ND, based on curves.
**7.9% (*Three dimensional (3D) conformal radiation therapy* 3DRT) *versus* 3.5% (IMRT) in the whole trial.

J. Remon, TAMO2022

Timing of IO: concurrent plus consolidation

	Investigational arm		
EA 5181	CT-RT + Durvalumab	→	Durvalumab for 1 year
PACIFIC 2	CT-RT + Durvalumab	→	Durvalumab 1500 q4w, until PD
KEYLYNK-012	CT-RT + Pembrolizumab	→	Pembrolizumab for 1 year +/- Olaparib
CheckMate 73L	CT-RT + Nivolumab	→	Nivolumab +. Ipilimumanb for 1 year
		→	Nivolumab for 1 year

How to improve the *Pacific* results?

Optimizing the use of IO in stage III?

Timing of IO + CT/RT

Duration of IO

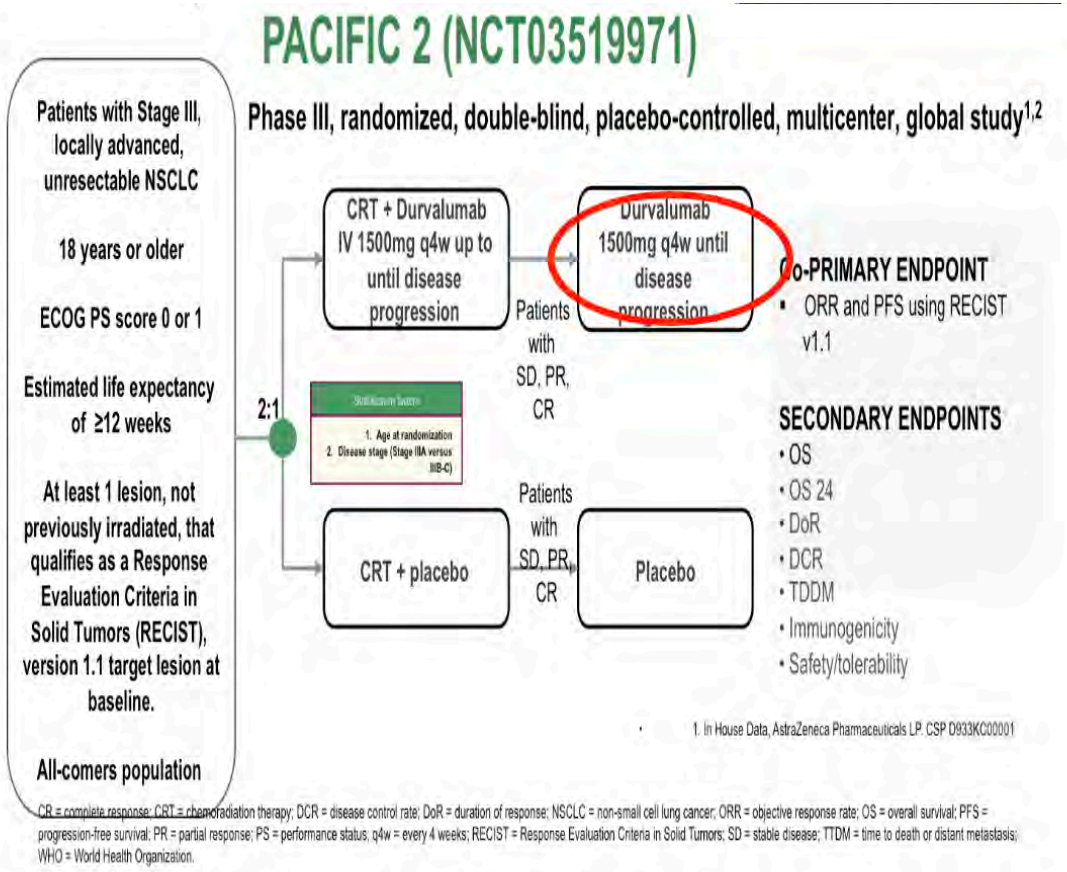
New agents?

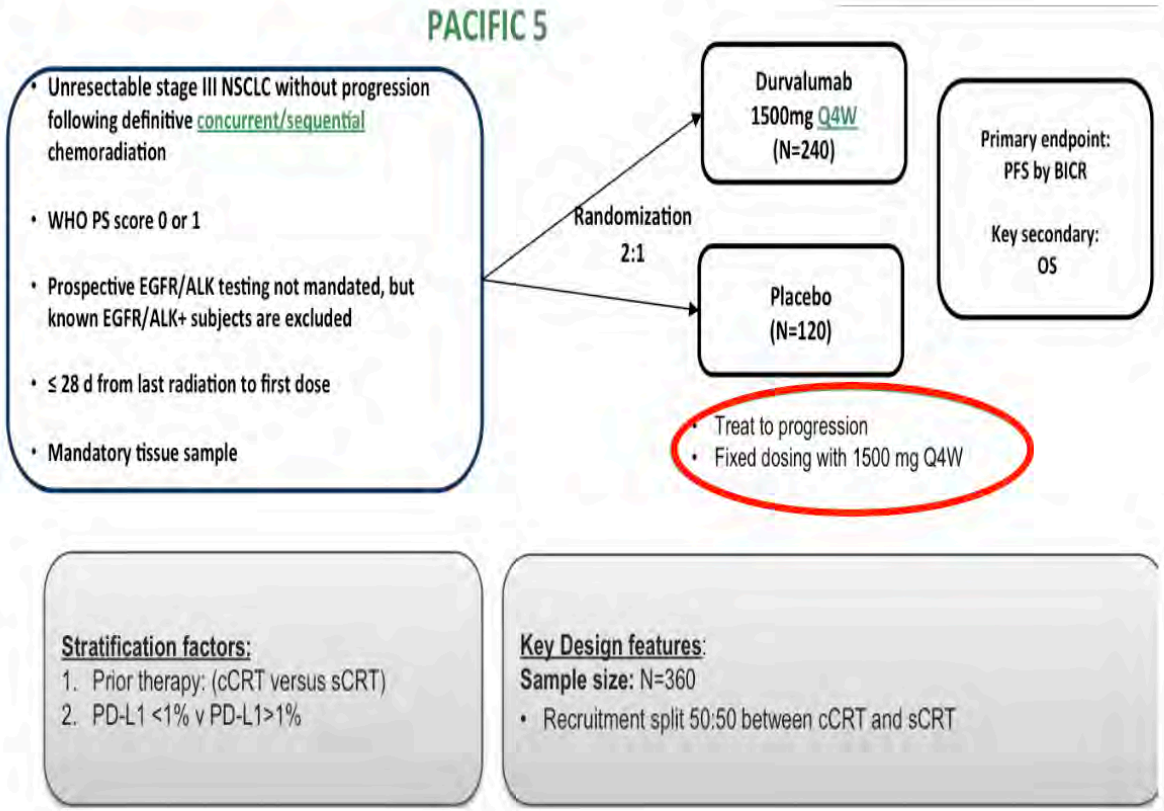
Evaluation new agents and combination

Predictive biomarkers?

Duration of IO: clinical relevant question

not addressed in current & ongoing clinical trial





How to improve the *Pacific* results?

Optimizing the use of IO in stage III?

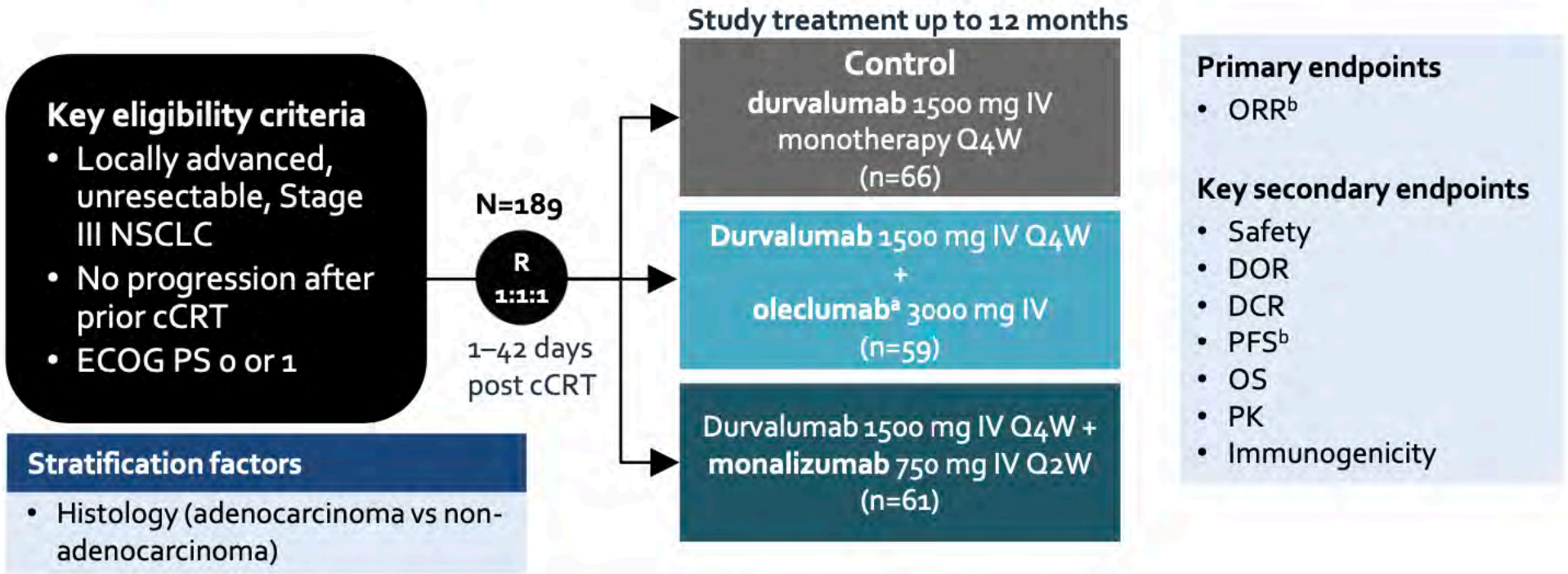
- Timing of IO + CT/RT
- Duration of IO

New agents?

Evaluation new agents and combination

Predictive biomarkers?

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



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

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

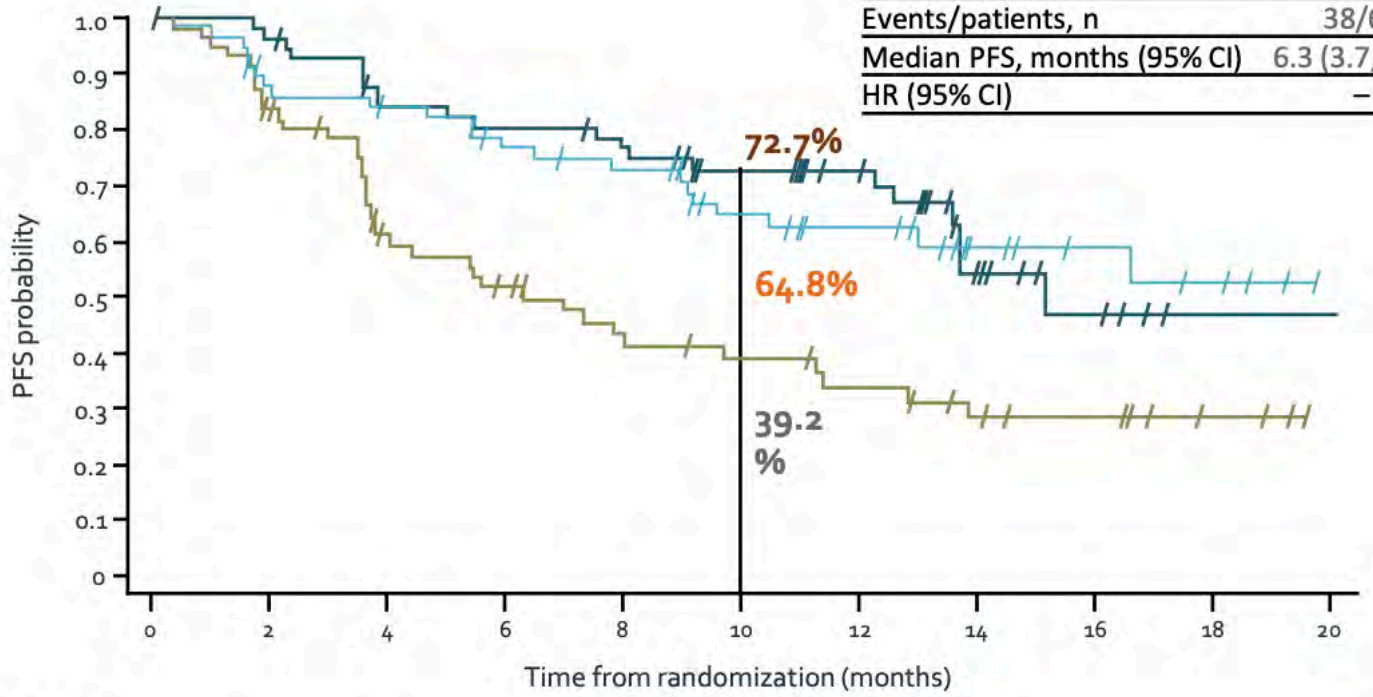
[a]Oleclumab Q2W for cycles 1 and 2 then Q4W; [b]Investigator assessment by RECIST v1.1. cCRT, concurrent chemoradiotherapy; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NK, natural killer; ORR, objective response rate; PK, pharmacokinetics.

Martinez-Marti A, et al. ESMO 2021. Abstract LBA42.

COAST: Investigator assessed PFS

PFS: interim analysis (ITT population)

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



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

ORRs:

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

- ORR and PFS improved with both dual checkpoint inhibitor approaches
- Propensity weighting analysis shows superimposable data to PACIFIC
- Very encouraging data

Martinez-Marti A, et al. ESMO 2021. Abstract LBA42.

GEMSTONE-301 (Phase 3): Sugemalimab in patients with unresectable Stage III NSCLC without progression after chemotherapy

Key eligibility criteria

- Patients with unresectable Stage III NSCLC who have not progressed following cCRT or sCRT
- ECOG PS 0– 1
- No known sensitizing *EGFR*, *ALK*, or *ROS1* genomic alterations

N=368

R 2:1

1–42 days post cCRT/sCRT

Sugemalimab 1200 mg IV Q3W

Placebo IV Q3W

For up to 24 months

Primary endpoints

- PFS

Key secondary endpoints

- PFS
- ORR
- DOR
- Safety
- TTDM
- PK

Stratification factors

- ECOG PS (0 vs 1)
- CRT (cCRT vs sCRT)
- Total RT dose (<60 Gy vs ≥60 Gy)

Statistical considerations

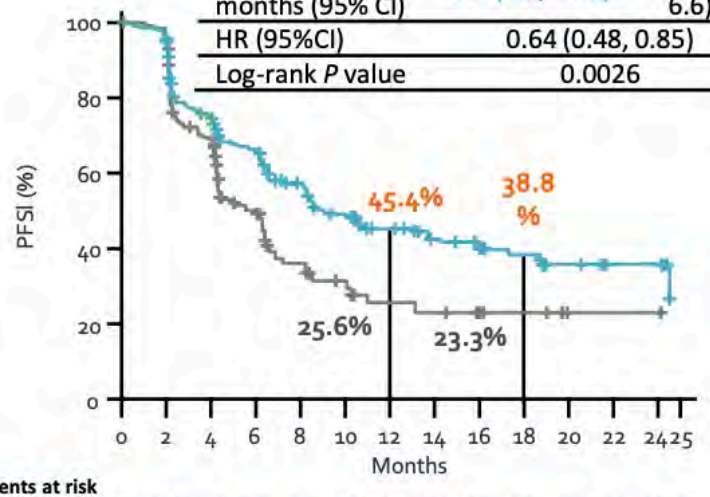
- PFS tested first at a two sided alpha of 0.05; if PFS is significant, then OS would be tested at a two sided alpha of 0.05

Carbone D, et al. WCLC 2021. Abstract OA09.01.

GEMSTONE-301: PFS by BICR and CRT type

PFS by BICR

	Sugemalimab (n=255)	Placebo (n=126)
Median PFS, months (95% CI)	9.0 (8.1, 14.1)	5.8 (4.2, 6.6)
HR (95%CI)	0.64 (0.48, 0.85)	
Log-rank *P* value	0.0026	

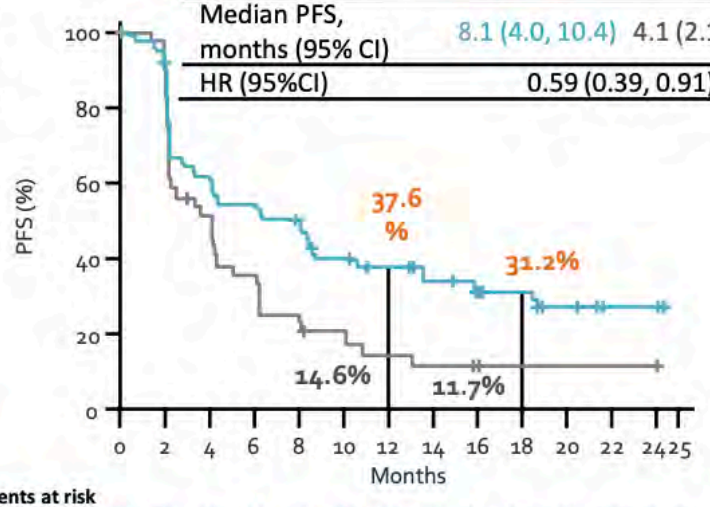


Patients at risk

Sugemalimab	255	225	162	130	96	76	63	48	35	30	20	11	11	0
Placebo	126	115	77	46	25	16	11	10	6	4	1	1	1	0

PFS for patients receiving sCRT

	Sugemalimab (n=86)	Placebo (n=41)
Median PFS, months (95% CI)	8.1 (4.0, 10.4)	4.1 (2.1, 6.1)
HR (95%CI)	0.59 (0.39, 0.91)	

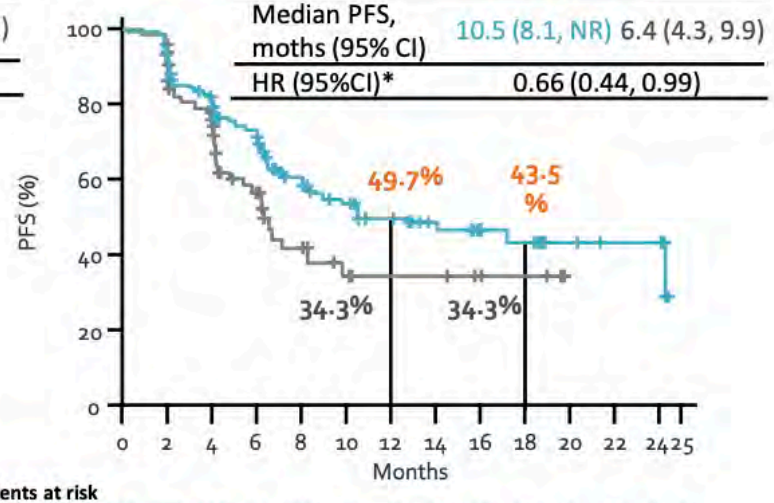


Patients at risk

Sugemalimab	86	73	51	46	41	32	28	22	17	15	11	6	6	0
Placebo	41	37	20	14	10	7	5	4	2	1	1	1	1	0

PFS for patients receiving cCRT

	Sugemalimab (n=169)	Placebo (n=85)
Median PFS, moths (95% CI)	10.5 (8.1, NR)	6.4 (4.3, 9.9)
HR (95%CI)*	0.66 (0.44, 0.99)	



Patients at risk

Sugemalimab	169	152	111	84	55	44	35	25	18	15	9	5	5	0
Placebo	85	78	57	32	15	9	6	6	4	3	0	0	0	0

- Another drug for consolidation therapy post chemo-RT in China (outside of China?)
- First evidence of efficacy post sequential chemo-RT

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; sCRT, sequential chemoradiotherapy.

Carbone D, et al. WCLC 2021. Abstract OA09.01.

SKYSCRAPER-3 (800 patients)

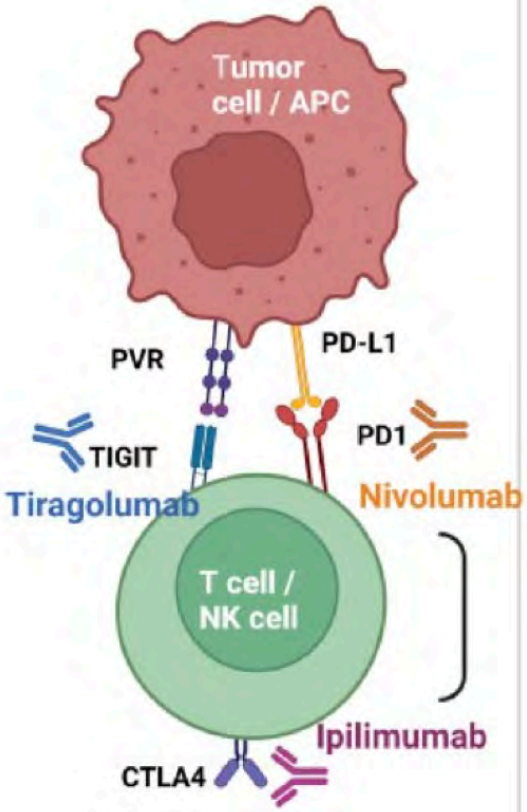
Patient population:
- Locally advanced, unresectable (stage III) NSCLC
- Recived at least 2 cylce of cCRT
- WHO/ECOG performance status 0 or 1

Randomize 1:1

- Atezolizumab and Tiragolumab (Arm A) → **PD**
- Durvalumab consolidation (Arm B) → **PD**

Primary endpoints:
PFS

Key secondary endpoints:
OS



How to improve the *Pacific* results?

Optimizing the use of IO in stage III?

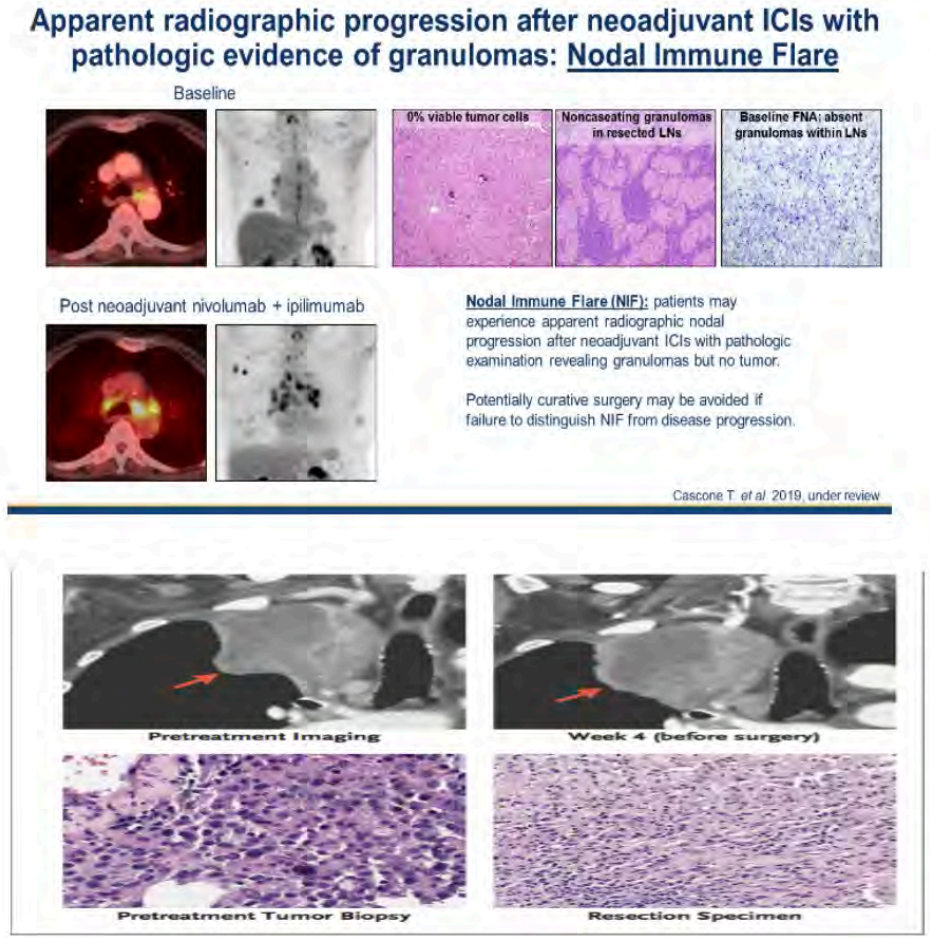
- Timing of IO + CT/RT
- Duration of IO

New agents?

Identifying predictive biomarkers?

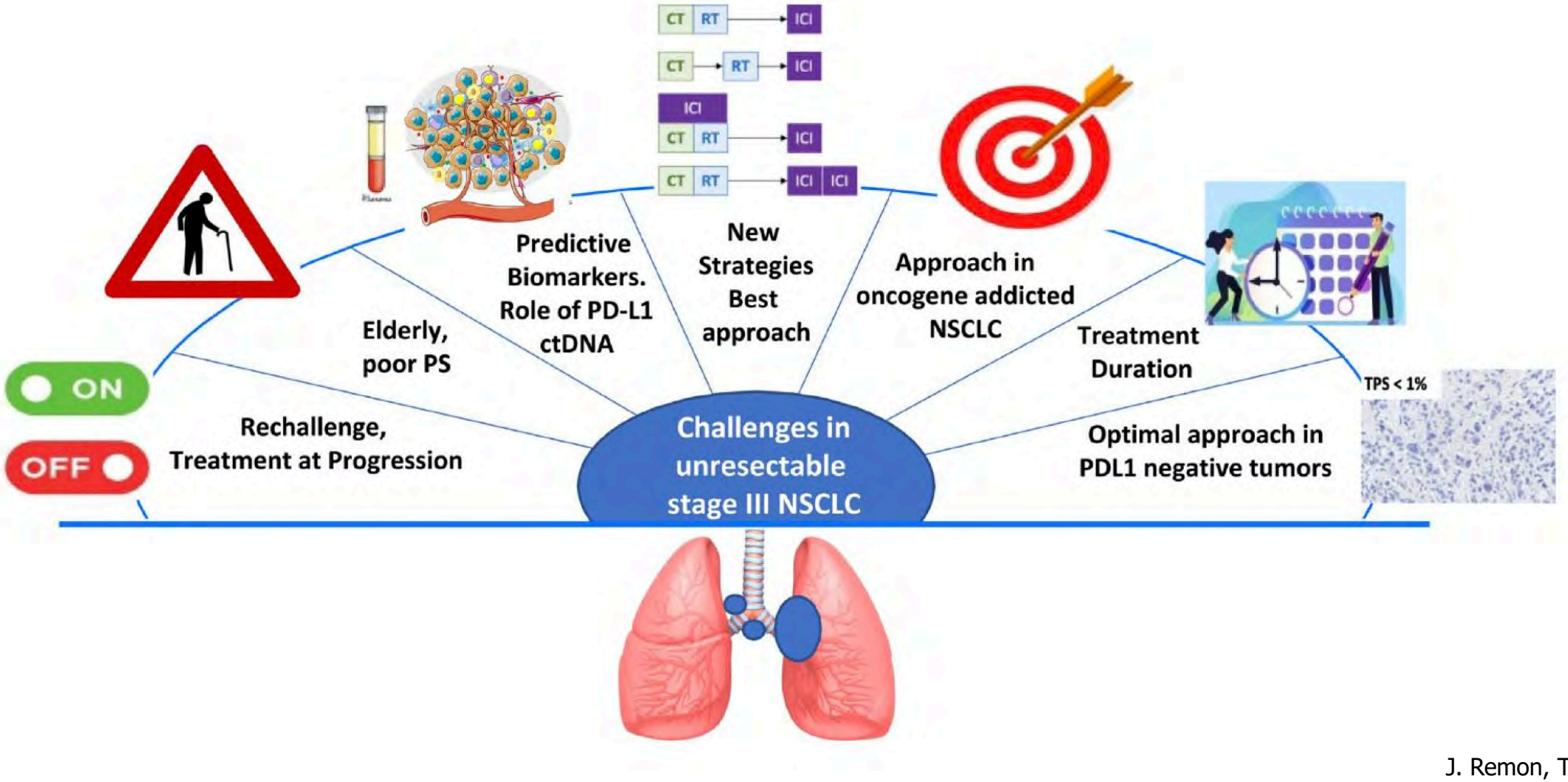
Is clinical response enough to make decision in stage III?

- Different pattern of response under IO:
  - •Pseudo progression, Hyper progression, dissociate responses *(Borcoman E, Ann Oncol 2019)*
  - •Lack of correlation between RECIST and pathologic responses *(Forde, NEJM 2018)*
  - •Nodal Immune Flare? *(Cascone T, ASCO 19)*
- Artificial Intelligence algorithms can automatically quantify radiographic characteristics and may function as non invasive biomarkers for response to IO in advanced NSCLC *(Trebeschi S, Ann Oncol 2019)*
- This research should be expanded to stage III due to the extreme complexity of evaluation of response after CT/RT and IO



P. Garrido, WCLC 2019

Current challenges with ICIs in unresectable stage III NSCLC



J. Remon, TAMO2022

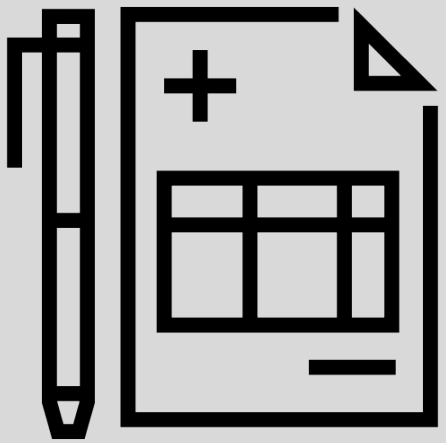
Global Lung Cancer Academy

Debate: Adjuvant vs Neoadjuvant Therapy for NSCLC

Moderator: Corey Langer, MD, FACP

Presenters: Johan Vansteenkiste, MD, PhD, and Benjamin Besse, MD, PhD

Patient case



Patient and disease characteristics

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

Diagnosis

- Stage II NSCLC, lymph-node positive, T2N1M0
- 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

Johan Vansteenkiste, MD, PhD

Perioperative therapy resectable NSCLC

- Neoadjuvant chemo- or chemoradiotherapy?
- Neoadjuvant chemo- or chemo-immunotherapy?
- Patient selection: multidisciplinary tumor board!

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Perioperative therapy resectable NSCLC
> neoadjuvant chemo- or chemoradiotherapy?

ORIGINAL ARTICLE

Survival after Trimodality Treatment for Superior Sulcus and Central T4 Non-small Cell Lung Cancer

Paul De Leyn, MD, PhD, Johan Vansteenkiste, MD, PhD,† Yolande Lievens, MD, PhD,‡ Dirk Van Raemdonck, MD, PhD,* Philippe Nafteux, MD,* Georges Decker, MD,* Willy Coosemans, MD, PhD,* Herbert Decaluwé, MD,* Johny Moons, MScM,* and Tony Lerut, MD, PhD**

- **Principle: "no need for a double local therapy unless the problem is local"**

- **T-factor: chemoradiotherapy useful**
  - **32 consecutive patients with potentially resectable superior sulcus (cT3-T4) or central cT4 NSCLC in prospective database had induction chemoradiotherapy (2 courses of cisplatin-etoposide) + concurrent RT (45 Gy/1.8 Gy)**
  - **Complete resection rate 78% (25/32). In 74% of the resected patients, there was a complete pathologic response or minimal residual microscopic disease**
  - **With a median follow-up of 26.5 months, 5-year OS was 74% in the intent-to-treat population**

- **N-factor: chemotherapy alone is sufficient**

De Leyn et al, J Thorac Oncol 4:62-68, 2009

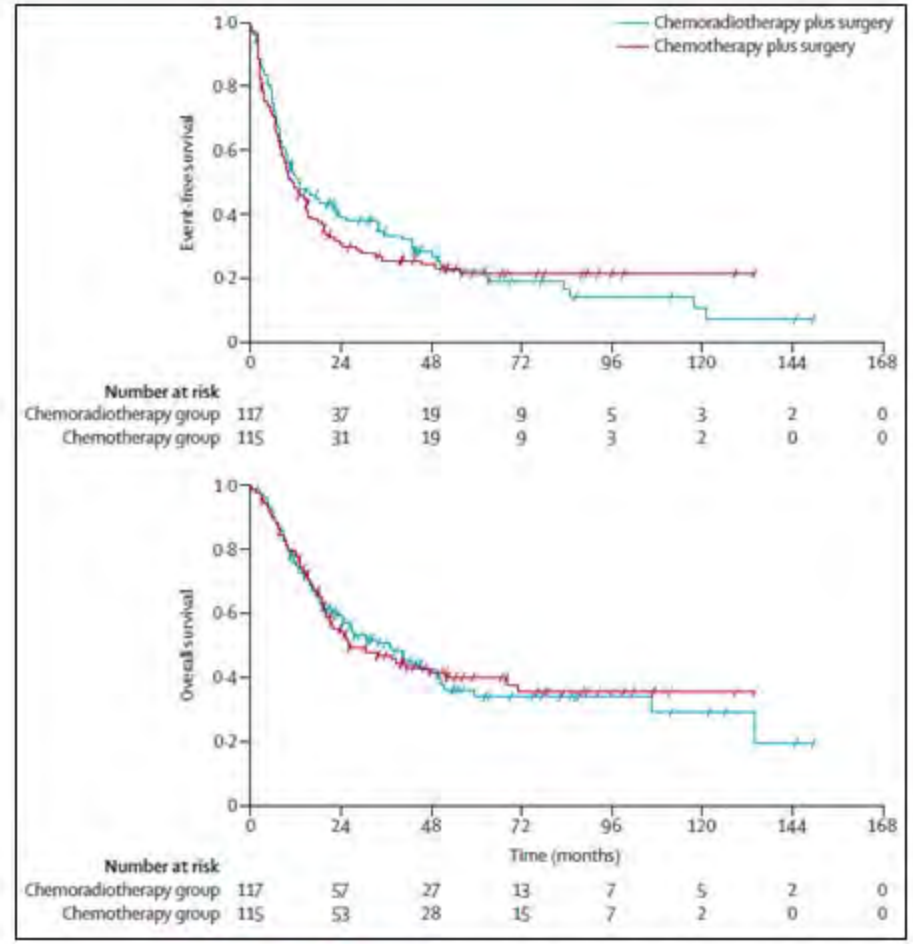
Perioperative therapy resectable NSCLC
> neoadjuvant chemo- or chemoradiotherapy?

- **232 patients with stage pathology proven IIIA/N2 NSCLC**
  - **Experimental: 117 patients: 3 courses of cisplatin-docetaxel + RT (44 Gy/2 Gy)**
  - **Control: 115 patients: 3 courses of cisplatin-docetaxel**
  - **Interpretation: Radiotherapy did not add any benefit to induction chemotherapy followed by surgery. We suggest that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA/N2 NSCLC**

Pless et al, Lancet 386:1049-1056, 2015

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Faith, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group



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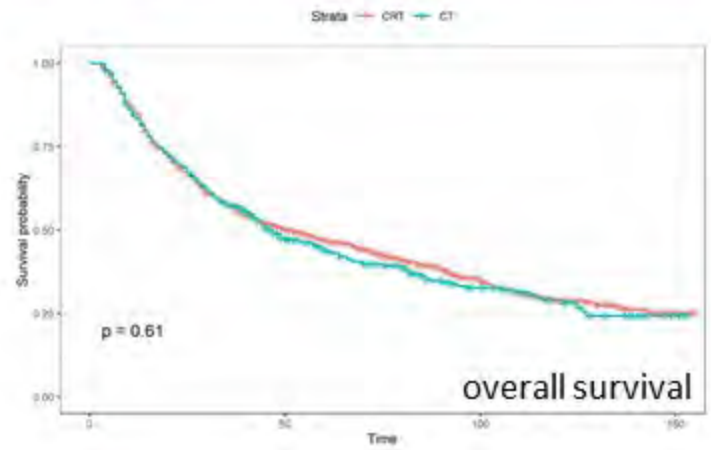
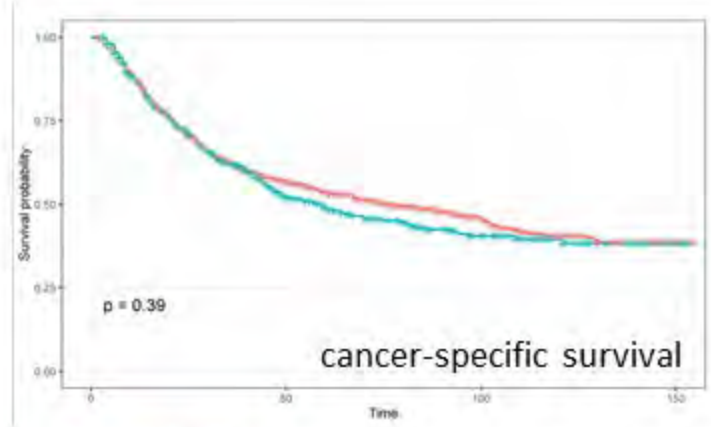
Perioperative therapy resectable NSCLC
> neoadjuvant chemo- or chemoradiotherapy?

Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy for patients with stage III-N2M0 non-small cell lung cancer (NSCLC): A population-based study

Marah Akhdar[1], Sebawe Syaj[1], Osaid Alser, MD, MSc(Oxon)[2], Mohamedraed Elshami, MD, MMSc, [3] and Shadi Hamouri[1] MD, MRCSI, FCCP, FEBTS, FACS

- **SEER database 2004-2015**
  - **1175 patients with stage III NSCLC patients with N2, of any T stage, and no known distant metastasis (M0)**
  - **799 (68.0%) neoadjuvant CRT and 376 (32.0%) neoadjuvant ChT**
- **Results**
  - **HR for OS 1.08, 95%CI: 0.91-1.28**
  - **HR for CSS 1.04, 95%CI: 0.89-1.21**





Akhar et al, ASCO 2022, abstr 8503

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Perioperative therapy resectable NSCLC

- Neoadjuvant chemo- or chemoradiotherapy?
- Neoadjuvant chemo- or chemo-immunotherapy?
- Patient selection: multidisciplinary tumor board!

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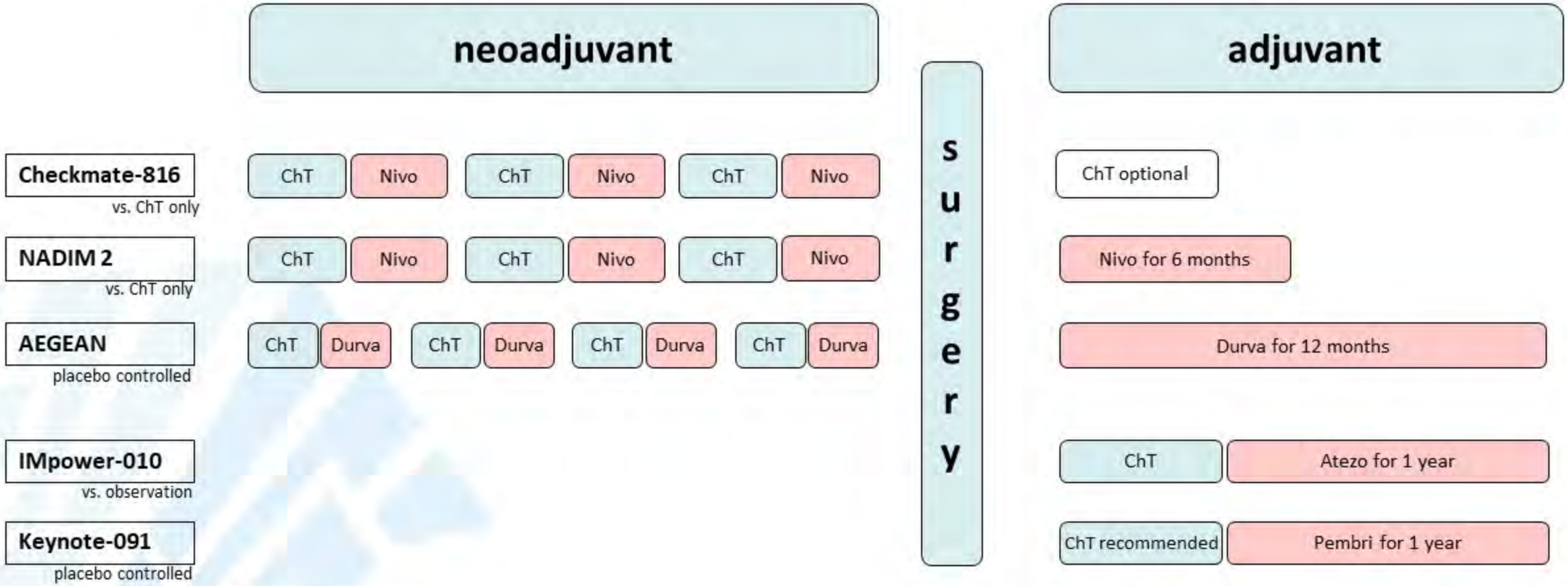
Perioperative therapy resectable NSCLC

> neoadjuvant chemo- or chemo-immunotherapy?



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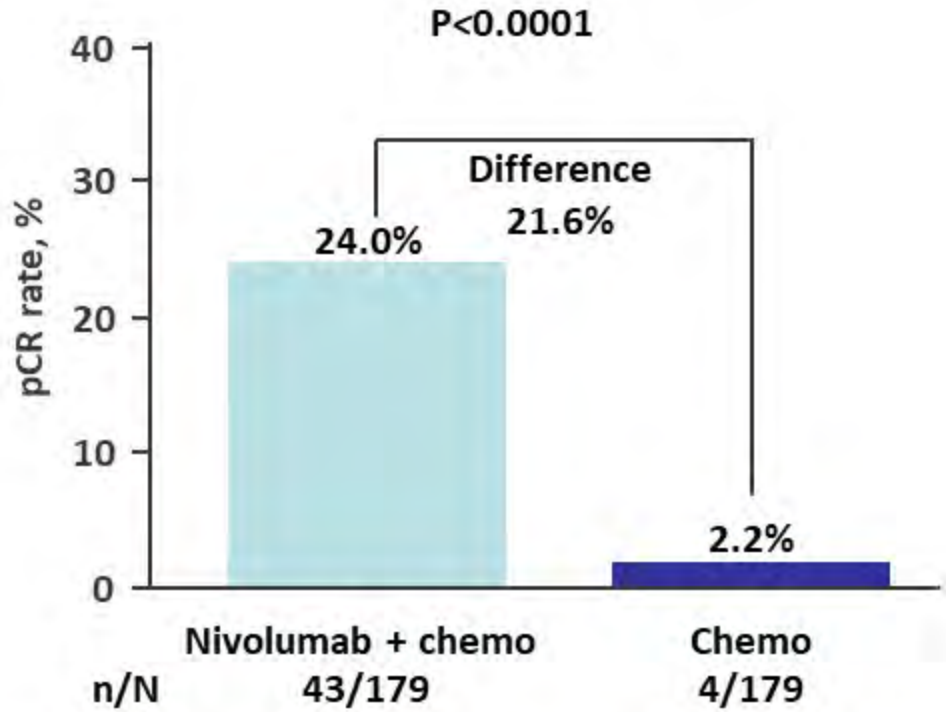
Perioperative therapy resectable NSCLC

> Checkmate-816: chemo- *vs.* chemo-immunotherapy: pCR rates

Minimum follow-up 7.6 mo

pCR (= ypT0N0) in ITT



pCR: PD-L1$_{pos}$ 30% ; PD-L1$_{neg}$ 14%

Forde et al, AACR 2021, abstract CT003

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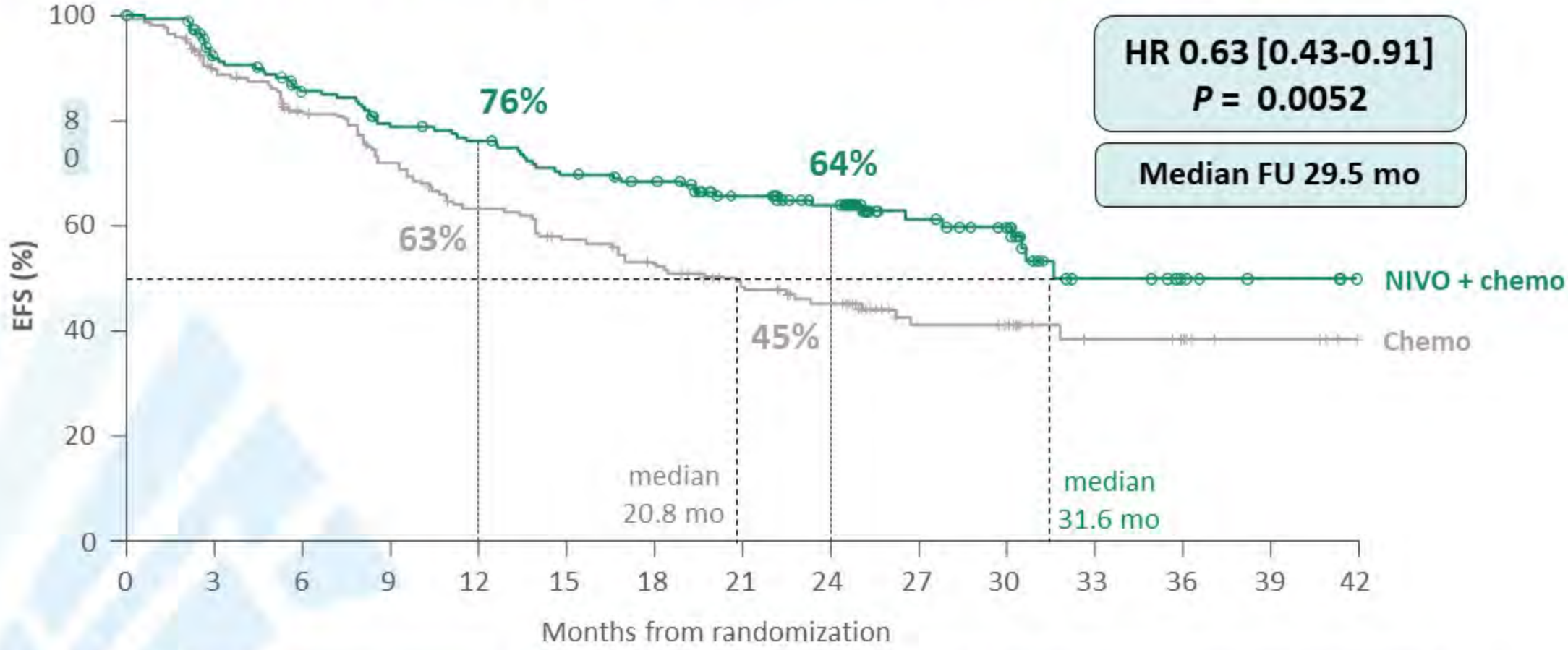
Perioperative therapy resectable NSCLC

> Checkmate-816: chemo- *vs.* chemo-immunotherapy: EFS



PD-L1 <1%: HR 0.85 [0.54-1.32]

PD-L1 1-49%: HR 0.58 [0.30-1.12]

PD-L1 ≥50%: HR 0.24 [0.10-0.61

Girard et al, AACR 2022, abstract CT012

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Perioperative therapy resectable NSCLC

- Neoadjuvant chemo- or chemoradiotherapy?
- Neoadjuvant chemo- or chemo-immunotherapy?
- Patient selection: multidisciplinary tumor board!

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Perioperative therapy resectable NSCLC

> adjuvant or neoadjuvant?

	Adjuvant	Neo-adjuvant
No delay or miss of surgery		
Full pathological TNM		
Large amount of tissue for biomarkers		
Earlier action on micromets *(earlier immune priming)*		
Tolerance/Compliance		
Drug delivery (intact blood vessels) *(intact lymph nodes)*		
Assessment of *patient benefit* (individual level)	None	ORR (repeat imaging)
Early interpretation of *strategy benefit* (clinical trial level)	None	Pathological response

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Perioperative therapy resectable NSCLC
> adjuvant or neoadjuvant?

- **Three types of medically fit patients**
  - **Resectable: most patients with stage I (N0)**
  - **Potentially resectable: most patients with stage II (N1), some with stage IIIA-B (N2)**
  - **Unresectable: most with stage IIIA-B and all with stage IIIC (N3)**

➢ **This judgment is the unique privilege of your multidisciplinary board**

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Perioperative therapy resectable NSCLC
> adjuvant or neoadjuvant?

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

'A state of mind'

First study including exclusively stage III patients
What does potentially resectable mean?
Heterogeneity of stage IIIA/B

Slide courtesy C. Finn

- **SAKK 16/00** [Pless M et al, Lancet 386:1049-1056, 2015]
  - **Primary technical resectability was *assessed by local surgeons* with the aim to achieve complete resection according to the Rami-Porta criteria, and it was *validated by an interdisciplinary tumor board***
- **CheckMate-816** [Forde PM, et al. N Engl J Med. 386:1973-1985. 2022]
  - **Participants with stage IB (≥ 4 cm), II or IIIA (N2), PD-L1+ (≥1%) NSCLC *considered resectable by the local multidisciplinary team***
- **NADIM-2** [Provencio et al, WCLC, abstr PL03.12]
  - **NSCLC of stage IIIA-B (TNM8) that was deemed locally to be *surgically resectable by a multidisciplinary clinical team***

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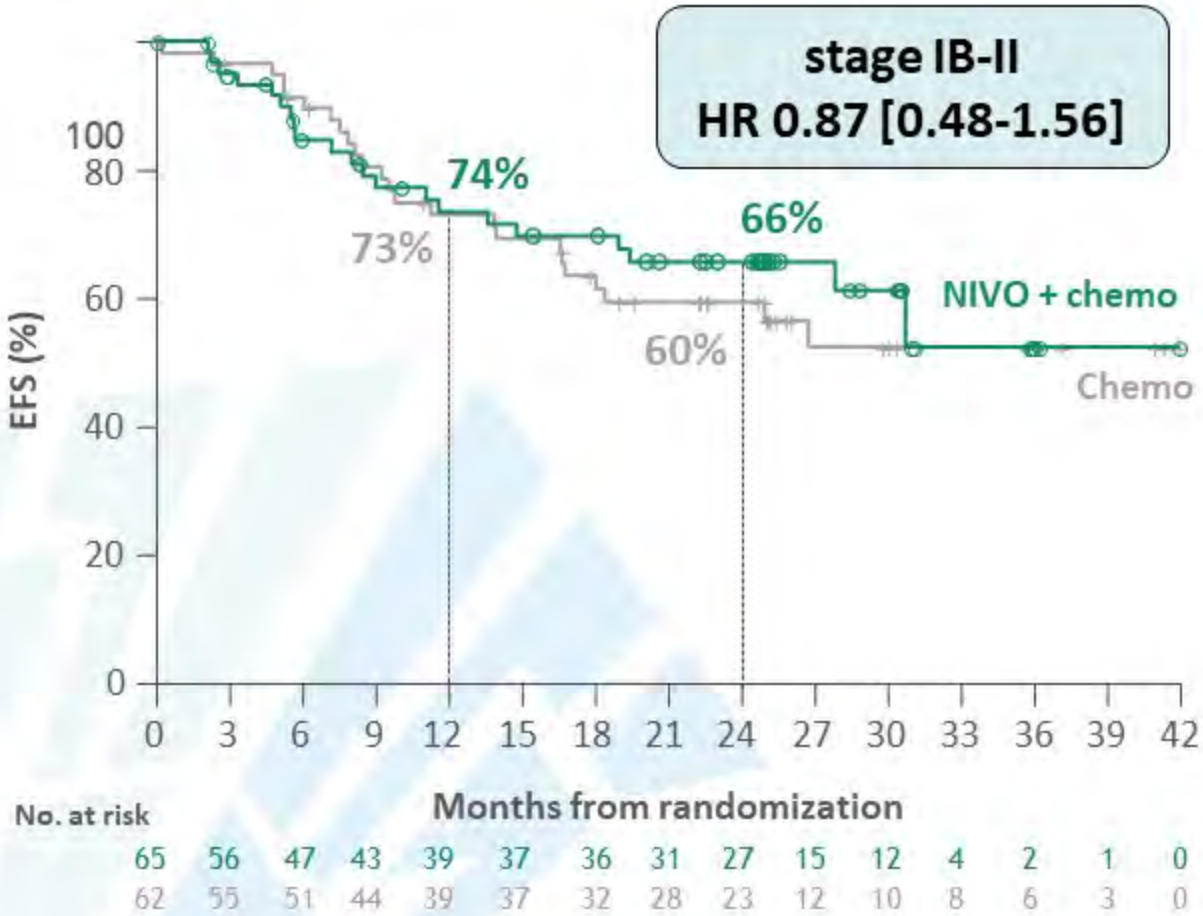
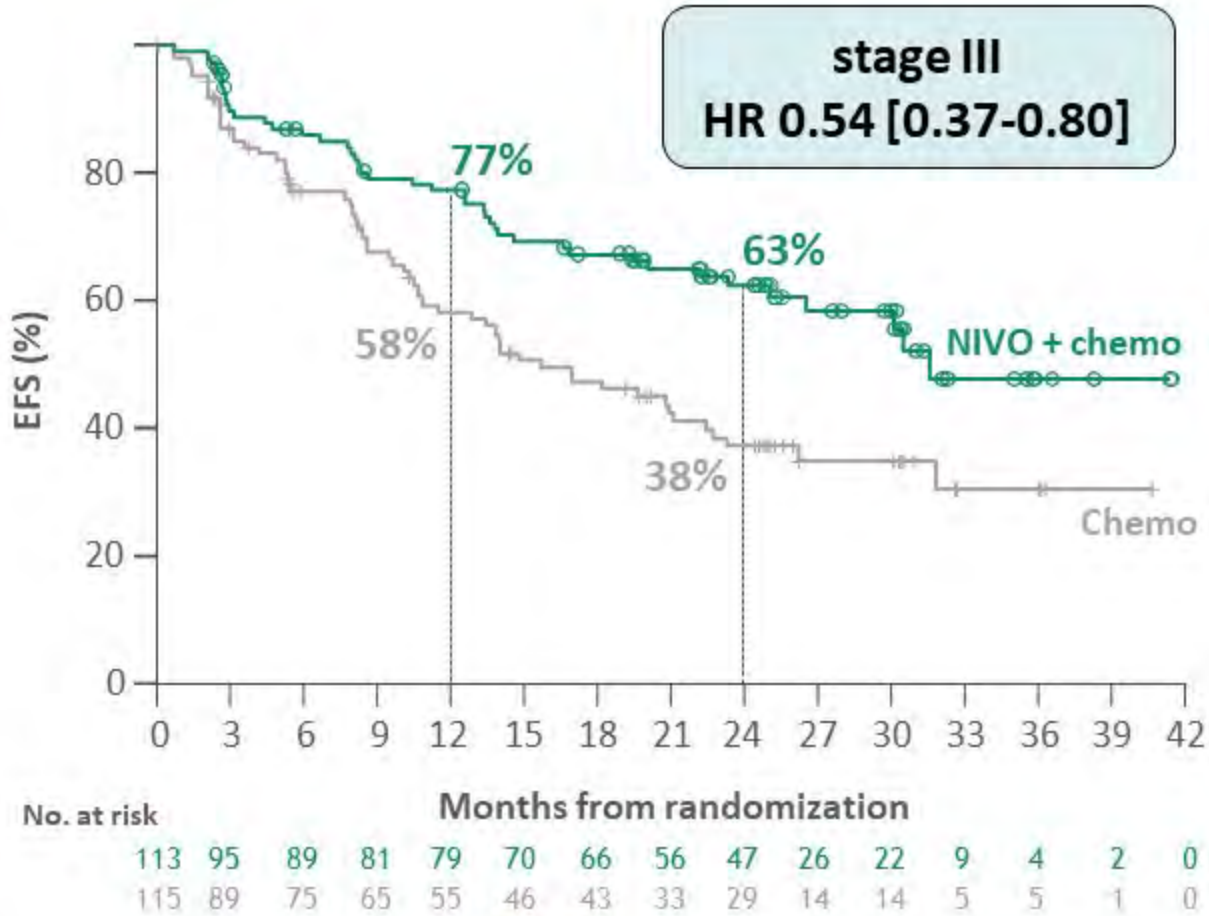
Perioperative therapy resectable NSCLC

> Checkmate-816: chemo- *vs.* chemo-immunotherapy: EFS ≈ stage





Girard et al, AACR 2022, abstract CT012

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Perioperative therapy resectable NSCLC
> adjuvant or neoadjuvant?

- **Three types of medically fit patients -> potential benefit of ICI in all**
  - **Resectable: most patients with stage I (N0)**
    - **Preferred strategy 1 : direct resection. No adj ChT. Adj. ICI to be considered**
  - **Potentially resectable: most patients with stage II (N1), some with stage IIIA-B (N2)**
    - **N1: equipoise between strategy 1 and 2**
    - **N2: preferred strategy 2: neoadjuvant chemo-immuno therapy -> surgery -> consolidation ICI to be considered**
  - **Unresectable: many patients with stage IIIA-B and all with stage IIIC (N3)**
    - **Preferred stratey 3: chemoradiotherapy -> Durvalumab 1 year**
- **This judgement REMAINS the unique privilege of your multidisciplinary board, and should not be influenced by pro-con discussions of pharma**

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Thank you for your kind attention

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Global Lung Cancer Academy

Adjuvant Therapy

Benjamin Besse, MD, PhD

Disclosures

- **No personal financial disclosures**
- **Sponsored research at Gustave Roussy Cancer Center**

  4D Pharma, AbbVie, Amgen, Aptitude Health, AstraZeneca, BeiGene, Blueprint Medicines, Boehringer Ingelheim, Celgene, Cergentis, Chugai pharmaceutical, Cristal Therapeutics, Daiichi-Sankyo, Eli Lilly, EISAI, Genzyme Corporation, GSK, Inivata, IPSEN, Janssen, Onxeo, OSE Immunotherapeutics, Pfizer, Roche-Genentech, Sanofi, Takeda, Tolero Pharmaceuticals, Turning Point Therapeutics

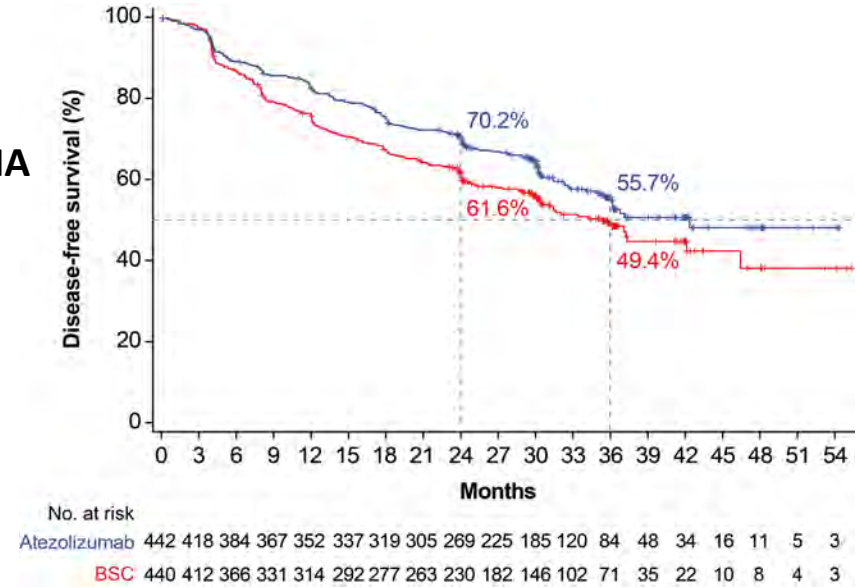
Adjuvant Treatment in 2022

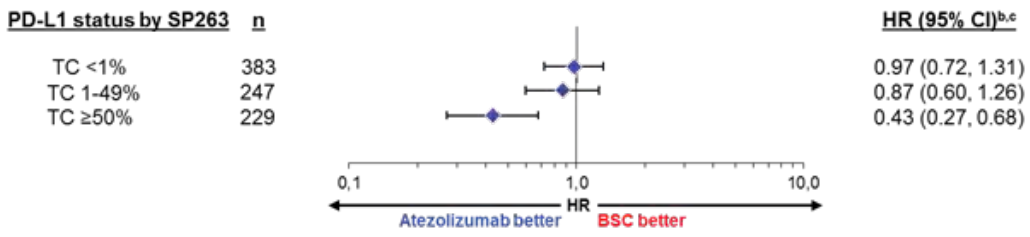
- **Chemotherapy**
  - **Standard: cisplatin-based chemotherapy, 4 cycles**
  - **Standard: stage II–IIIA**
  - **Option: carboplatin**
  - **Indication: <75 years old, within 2 months after surgery, PS 0–1**
- **If *EGFR* mutated**
  - **3 years of osimertinib**

Adjuvant ICI in NSCLC

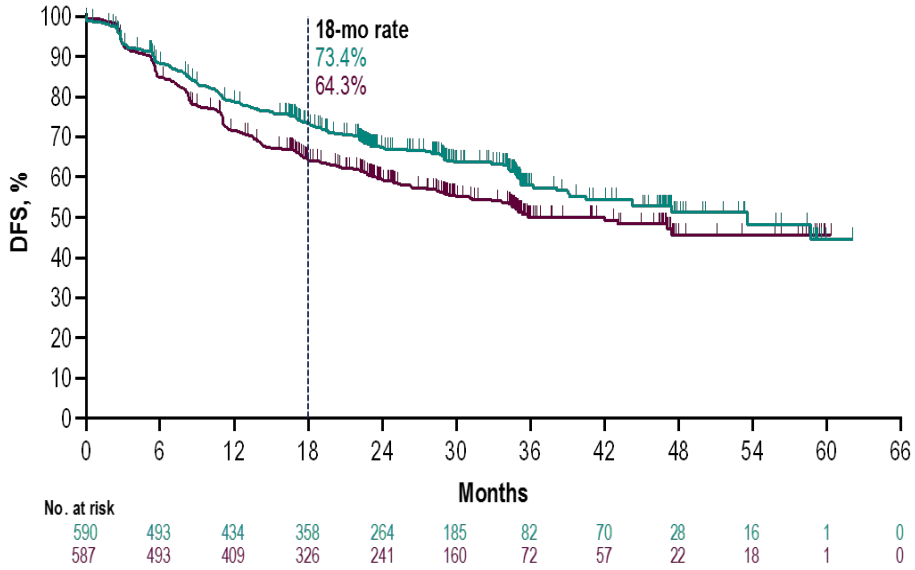
IMpower010
Atezolizumab vs BSC

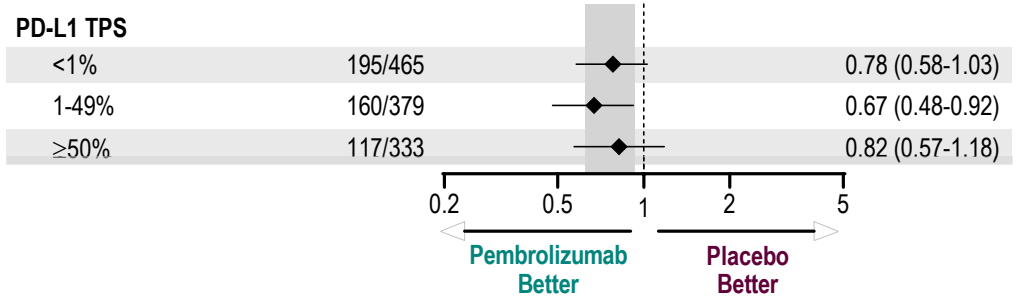
Stage II and IIIA
PD-L1 1%





PEARLS/KEYNOTE-091
Pembrolizumab vs placebo





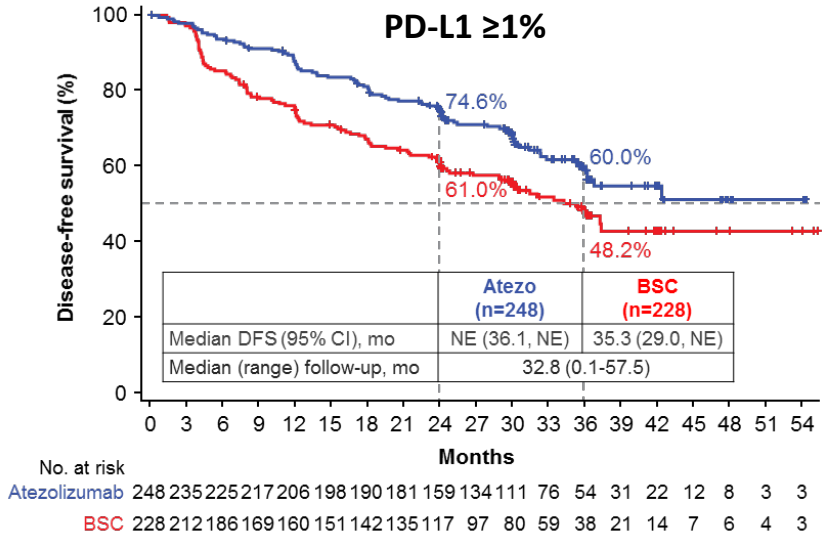
Felip E, et al. WCLC 2022. Abstract PL03.09; Paz-Ares L, et al. ESMO Virtual Plenary 2022. Abstract VP3-2022.

Approval of Adjuvant Atezolizumab

Population analyzed for DFS	n	HR (95% CI)
PD-L1 TC ≥1%[a] stage II–IIIA	**476**	**0.66 (0.50, 0.88)[b]**
PD-L1 TC 1%–49% stage II–IIIA	247	0.87 (0.60, 1.26)[c]
PD-L1 TC ≥50% stage II–IIIA	**229**	**0.43 (0.27, 0.68)[c]**

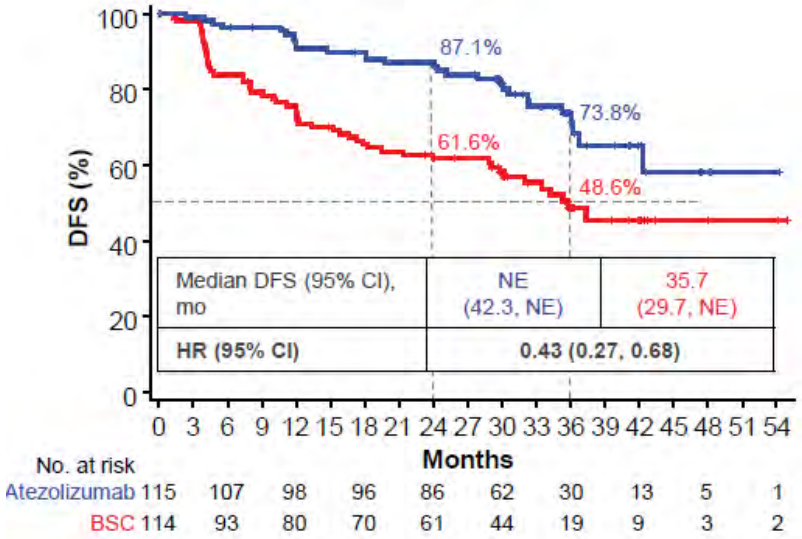
[a]Per SP263 assay. [b]Stratified. [c]Unstratified.

PD-L1 ≥1%



APPROVAL

PD-L1 ≥50%

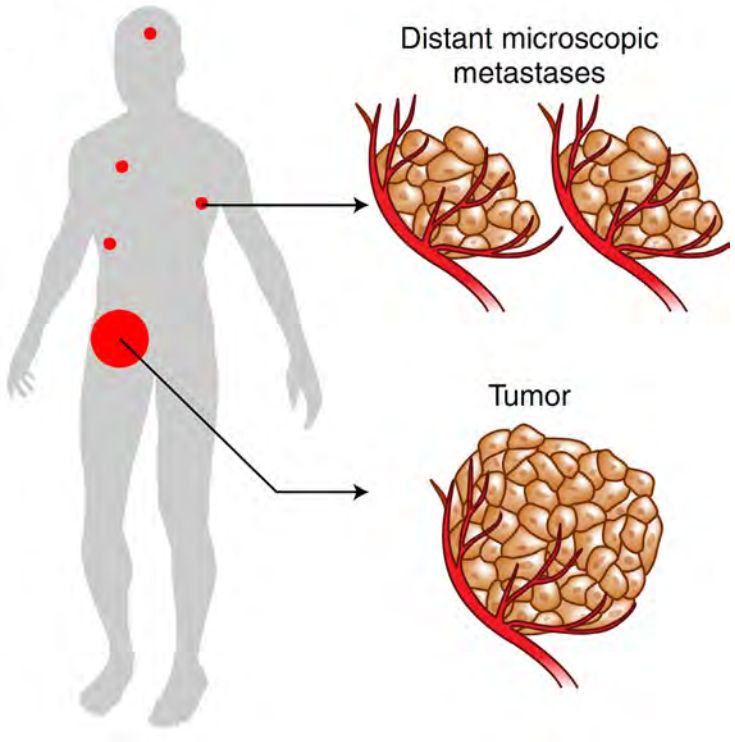


APPROVAL

and other countries

Felip E, et al. *Lancet*. 2021;398:1344-1357.

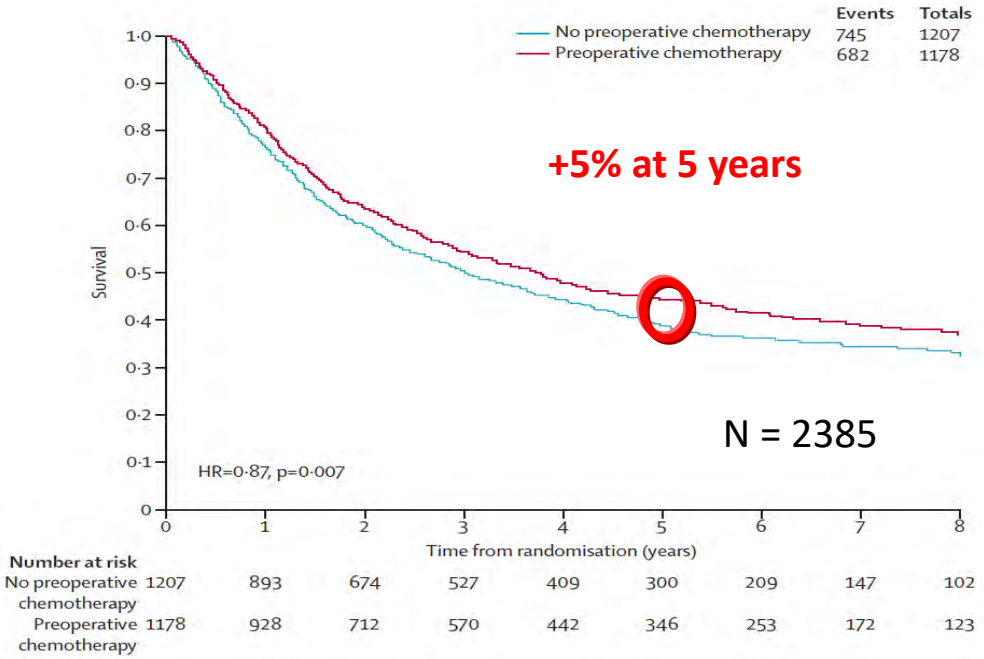
Theoretical Benefits of Induction Treatment



Eradicate micrometastatic disease

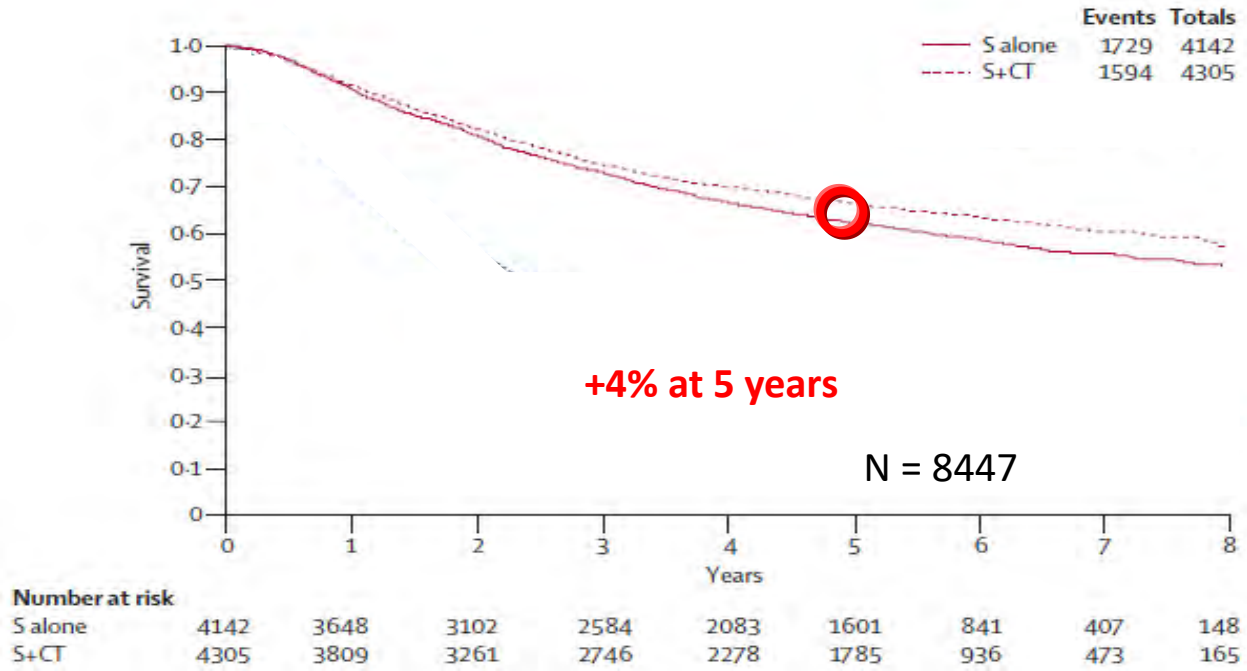
Chemotherapy and Resected NSCLC

Neoadjuvant



HR = 0.87, 95% CI 0.78–0.96, *P* = .007

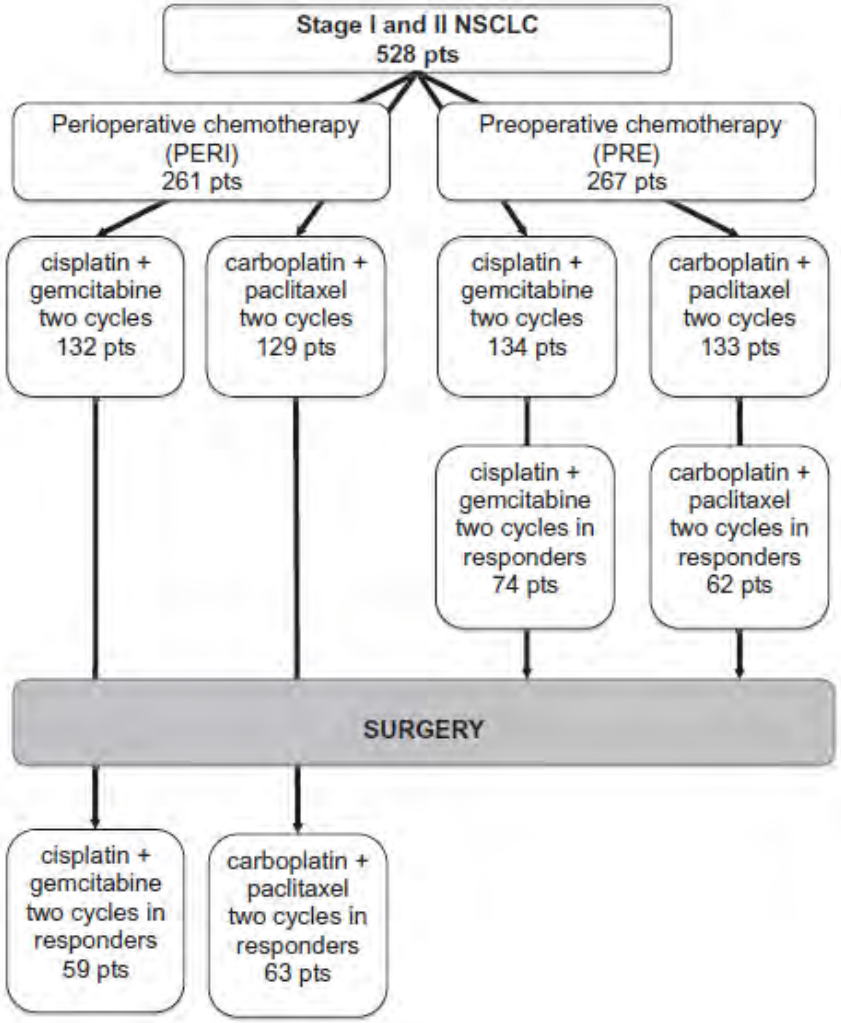
Adjuvant



HR = 0.87 (0.81–0.93) *P* <.000001

NSCLC Meta-analyses Collaborative Group, Arriagada R, et al. *Lancet.* 2010;375:1267-1277; NSCLC Meta-analysis Collaborative Group. *Lancet*. 2014;383:1561-1571.

Pathologic Responses After Chemotherapy

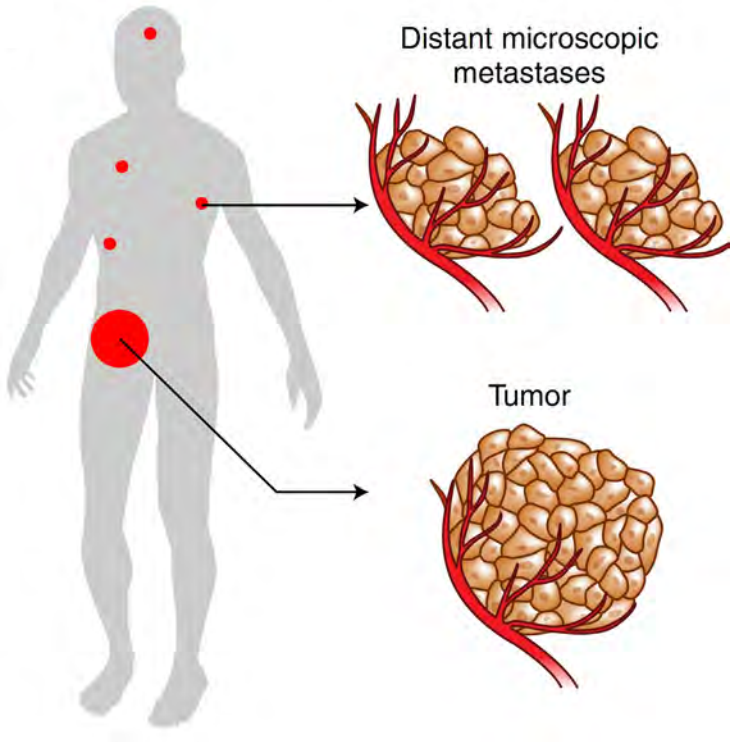


	GP $N = 266$ (%)	TC $N = 262$ (%)
Clinical response[a]		
Objective response	139 (52.3)	129 (49.2)
Complete response	10 (3.8)	4 (1.5)
Partial response	129 (48.5)	125 (47.7)
No change	111 (41.7)	112 (42.7)
Progressive disease	5 (1.9)	12 (4.6)
Not assessable	11 (4.1)	9 (3.4)
Pathological response[b]		
pT0N0	17 (6.4)	21 (8)

GP = gemcitabine plus cisplatin; TC = paclitaxel plus carboplatin.
[a] Evaluated after the first two chemotherapy cycles.
[b] Proportion of patients treated with four cycles: 41.7% in the GP arm, 42.8% in the TC arm.

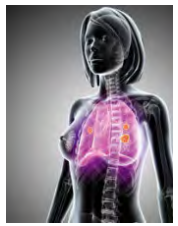
Westeel V, et al. *Eur J Cancer*. 2013;49:2654-2664.

Theoretical Benefits of Induction Treatment



Eradicate micrometastatic disease

Downstaging

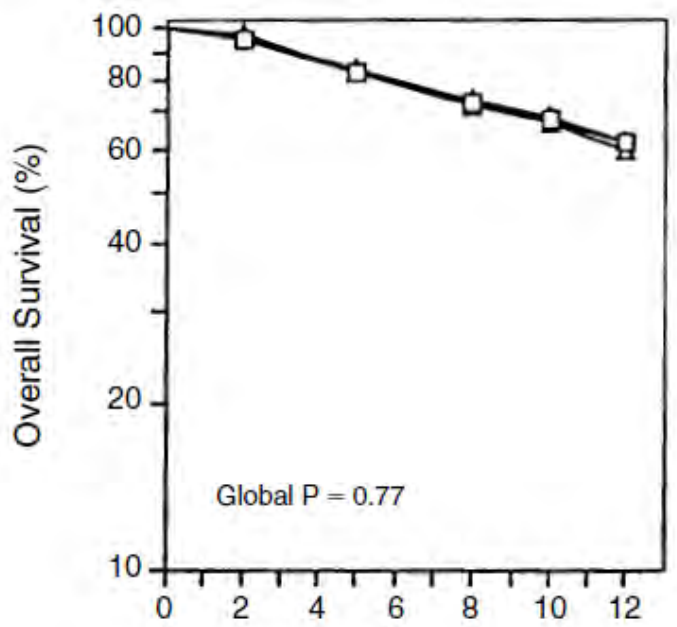


Can avoid mastectomy

Cannot avoid pneumonectomy

Local Treatment for Breast Cancer

Overall Survival (years!)

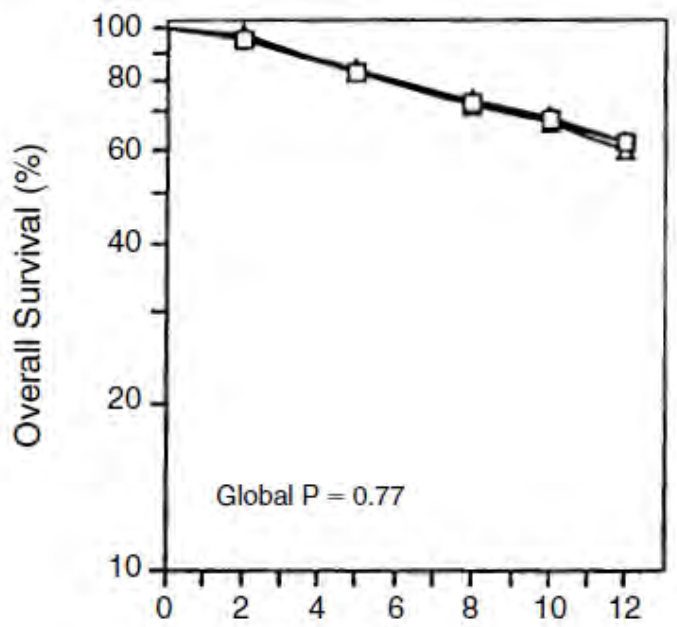


□	Total mastectomy	692/250
△	Lumpectomy	699/270
▲	Lumpectomy + irradiation	714/256
	Total	2105/776

Fisher B, et al. *N Engl J Med*. 1995;333:1456-1461.

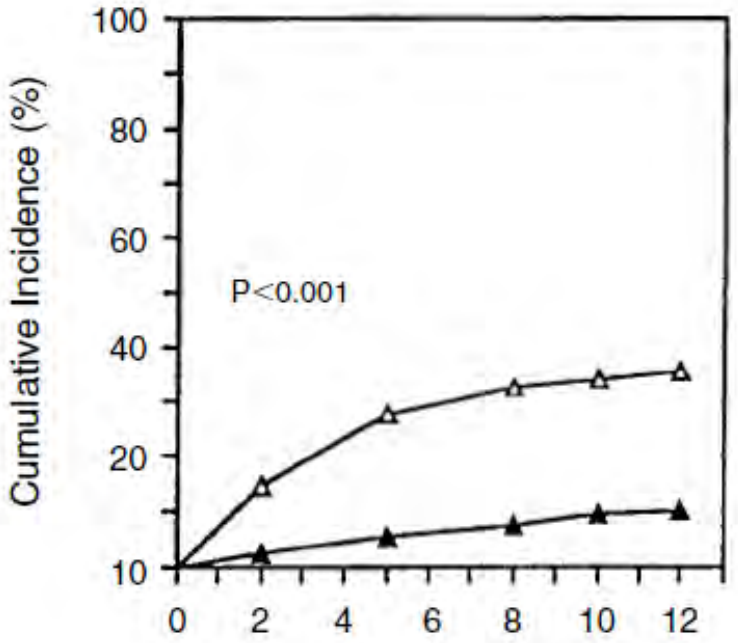
Local Treatment for Breast Cancer

Overall Survival (years!)



□ Total mastectomy	692/250
△ Lumpectomy	699/270
▲ Lumpectomy + irradiation	714/256
Total	2105/776

Recurrence in the Ipsilateral Breast

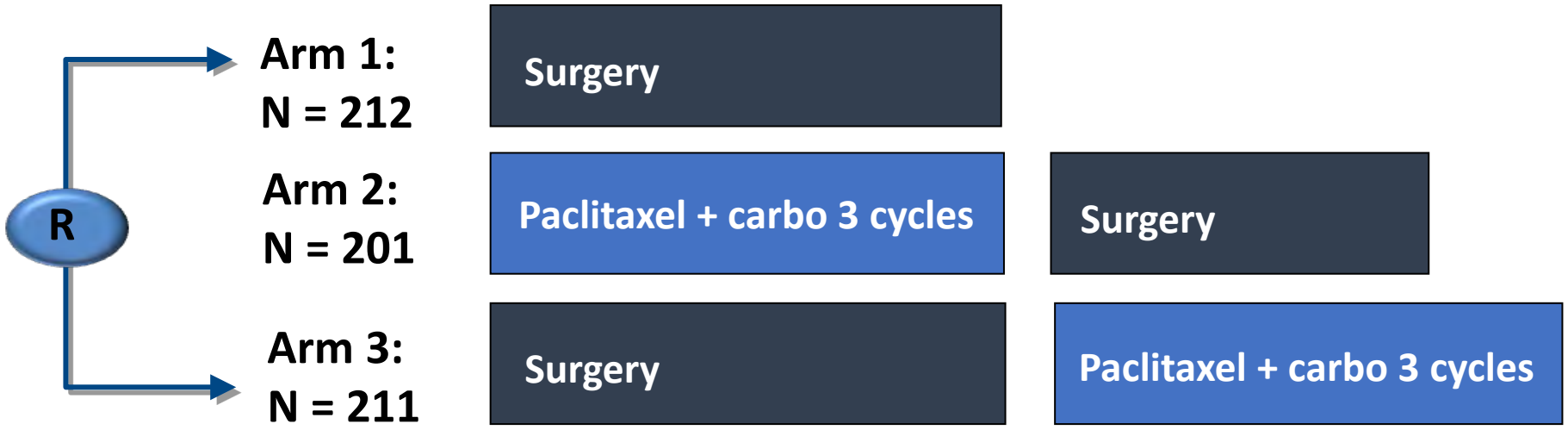


△ Lumpectomy	570/210
▲ Lumpectomy + irradiation	567/62

Fisher B, et al. *N Engl J Med*. 1995;333:1456-1461.

NATCH

Phase III
624 patients
IA (>2 cm), IB, II, T3N1



Paclitaxel 200 mg/m² + carboplatin AUC 6/3w

Felip E, et al. *J Clin Oncol*. 2010;28:3138-3145.

NATCH: Type of Surgery

	Surgery Alone (n = 210)		Preoperative Chemotherapy (n = 199)		Adjuvant Chemotherapy (n = 210)		
Surgery	No.	%	No.	%	No.	%	P*
Surgery, total explored	200	95.2	181	91.0	201	95.7	
Surgical procedures†							.37
Lobectomy/bilobectomy	130	65.0	131	72.3	139	69.2	
Pneumonectomy	52	26.0	42	23.2	49	24.4	
Wedge resection/segmentectomy	7	3.5	1	0.6	2	0.9	
Exploratory thoracotomy	11	5.5	7	3.9	11	5.5	
Postoperative mortality†	11	5.5	9	5.0	15	7.5	.48

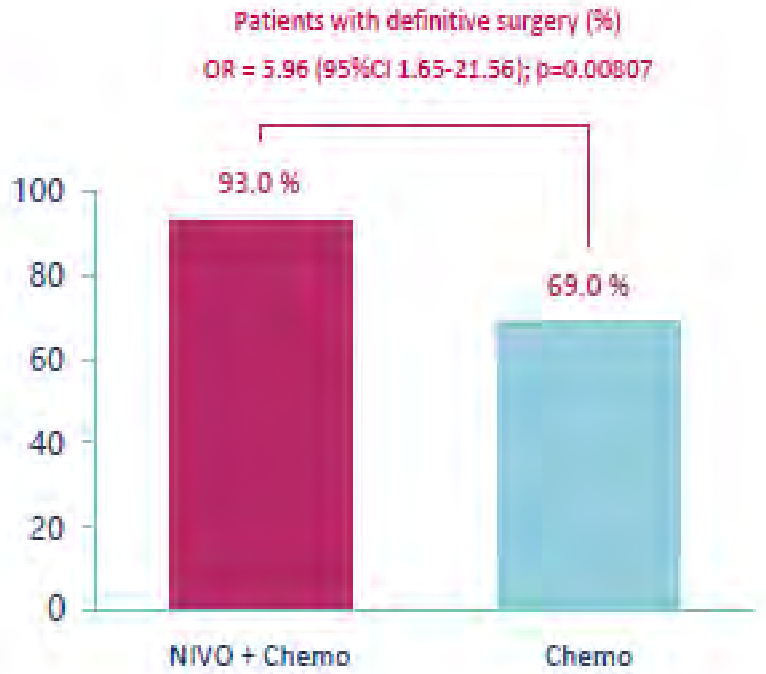
Felip E, et al. *J Clin Oncol*. 2010;28:3138-3145.

NADIM II: Type of Surgery

3 Cycles of Paclitaxel + Carboplatin With or Without Nivolumab in Patients With Potentially Operable Stage IIIA–B

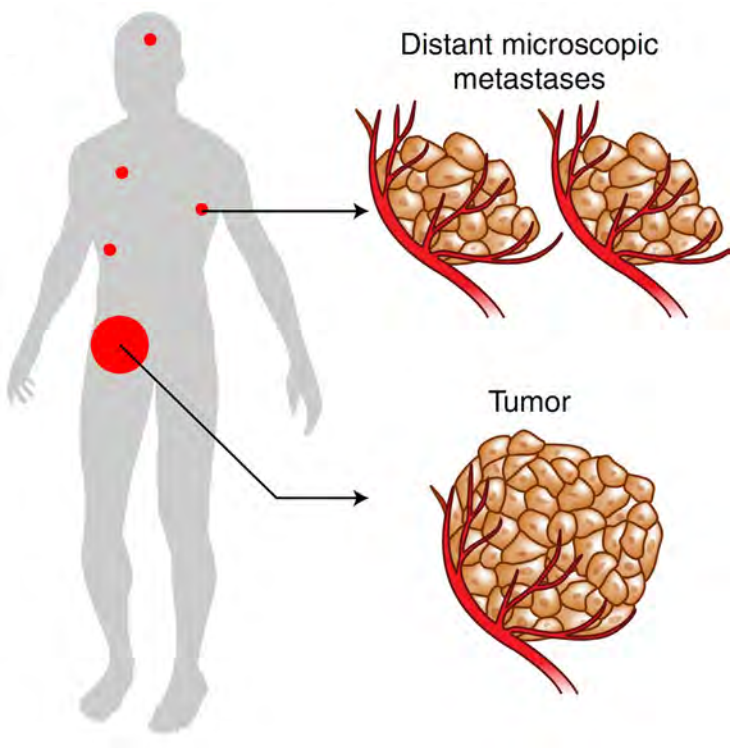
Type of surgery, No. (%)	NIVO + Chemo (n = 53)	Chemo (n = 20)	Total (n = 73)
Pneumonectomy	6 (11.3)	2 (10.0)	8 (11.0)
Lobectomy	40 (75.5)	17 (85.0)	57 (78.1)
Bilobectomy	4 (7.5)	1 (5.0)	5 (6.8)
Segmentectomy	2 (3.8)	0 (0.0)	2 (2.7)
Right Lower Lobectomy + Segmentectomy	1 (1.9)	0 (0.0)	1 (1.4)

Resection degree, No (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)
R0	49 (92.5)	13 (65.0)
Odds Ratio: 6.60 (95% CI 1.67-26.02); p = 0.007		



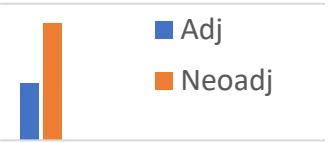
Provencio M, et al. *J Clin Oncol*. 2022;40:2924-2933.

Theoretical Benefits of Induction Treatment

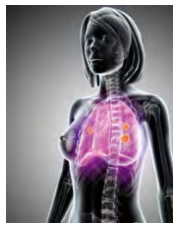


Eradicate micrometastatic disease

Increase compliance and tolerability



Downstaging

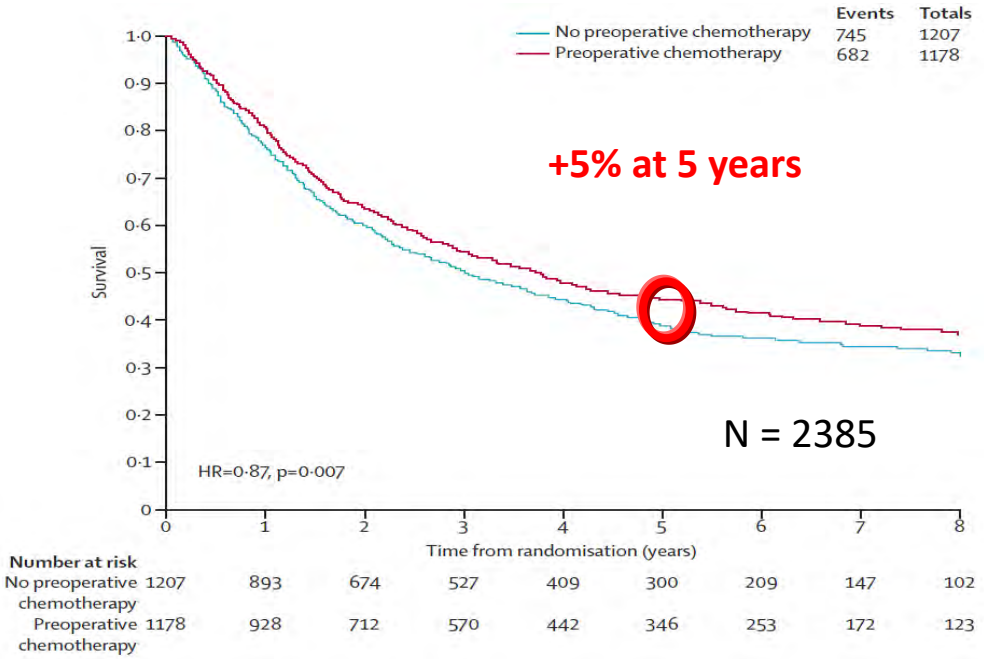


Can avoid mastectomy

Cannot avoid pneumonectomy

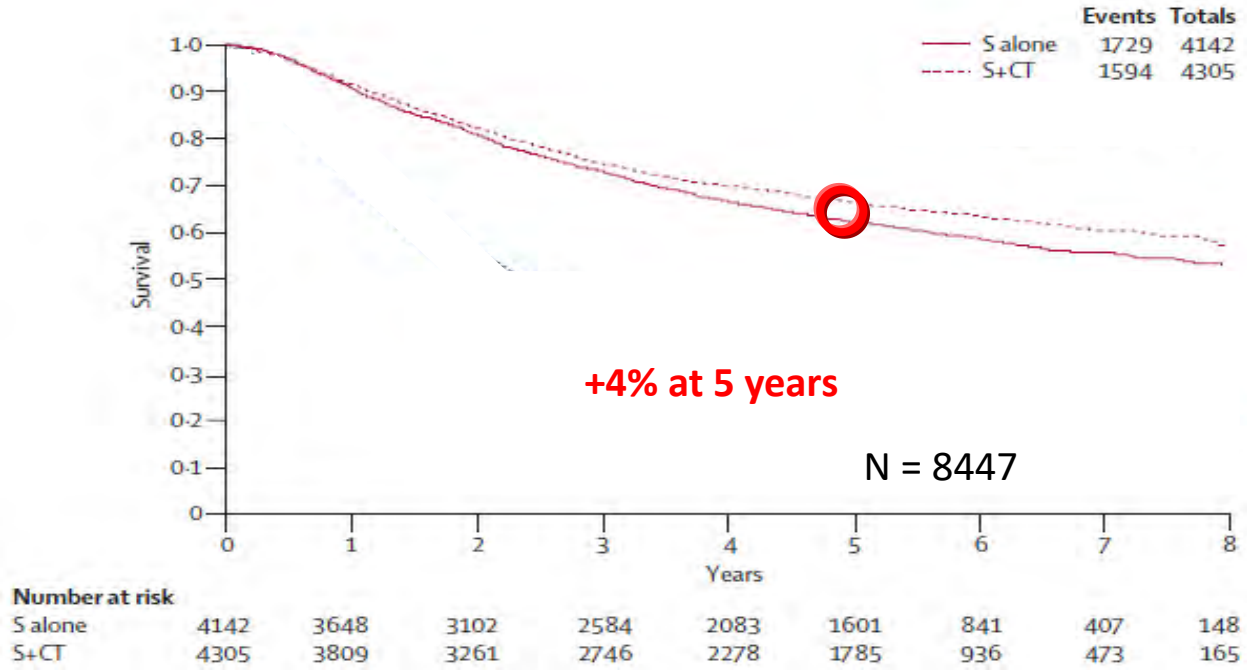
Chemotherapy and Resected NSCLC

Neoadjuvant



HR = 0.87, 95% CI 0.78–0.96, *P* = .007

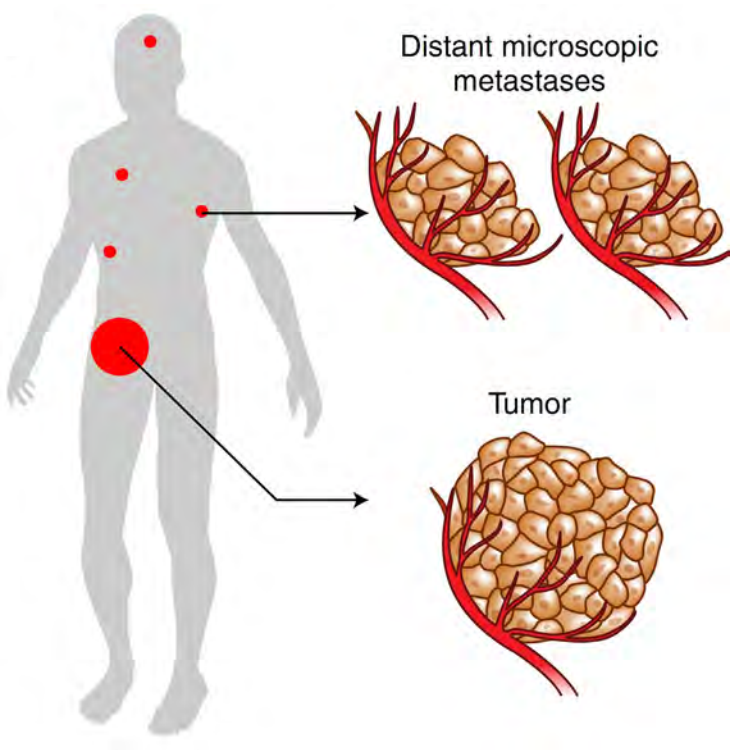
Adjuvant



HR = 0.87 (0.81–0.93) *P* <.000001

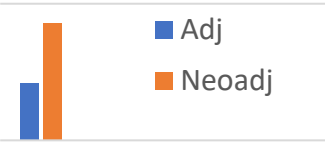
NSCLC Meta-analyses Collaborative Group, Arriagada R, et al. *Lancet.* 2010;375:1267-1277; NSCLC Meta-analysis Collaborative Group. *Lancet*. 2014;383:1561-1571.

Theoretical Benefits of Induction Treatment



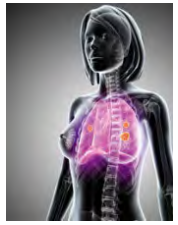
Eradicate micrometastatic disease

Increase compliance and tolerability



Dose intensity

Downstaging

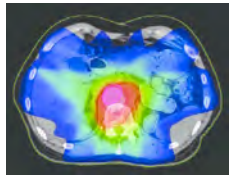


Can avoid mastectomy

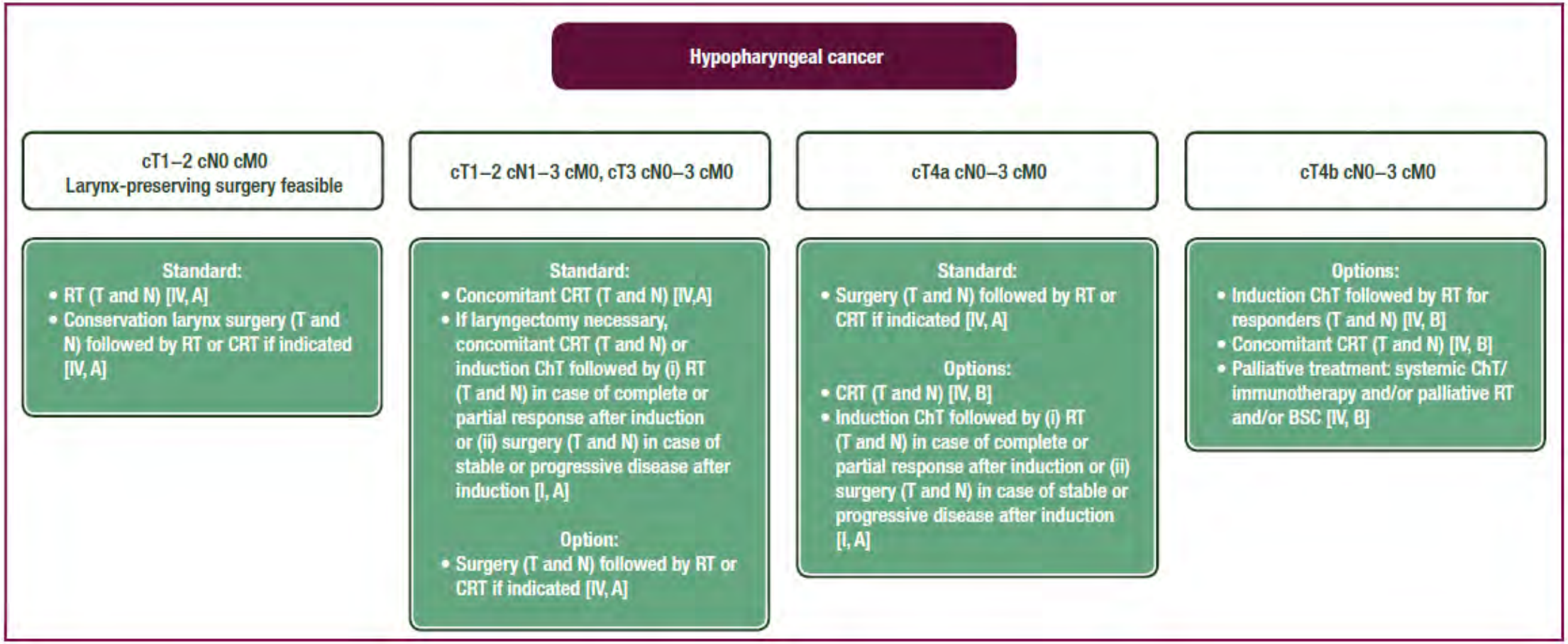
Cannot avoid pneumonectomy

Select local treatment

Partial response?



ESMO Guidelines for Hypopharyngeal Cancer

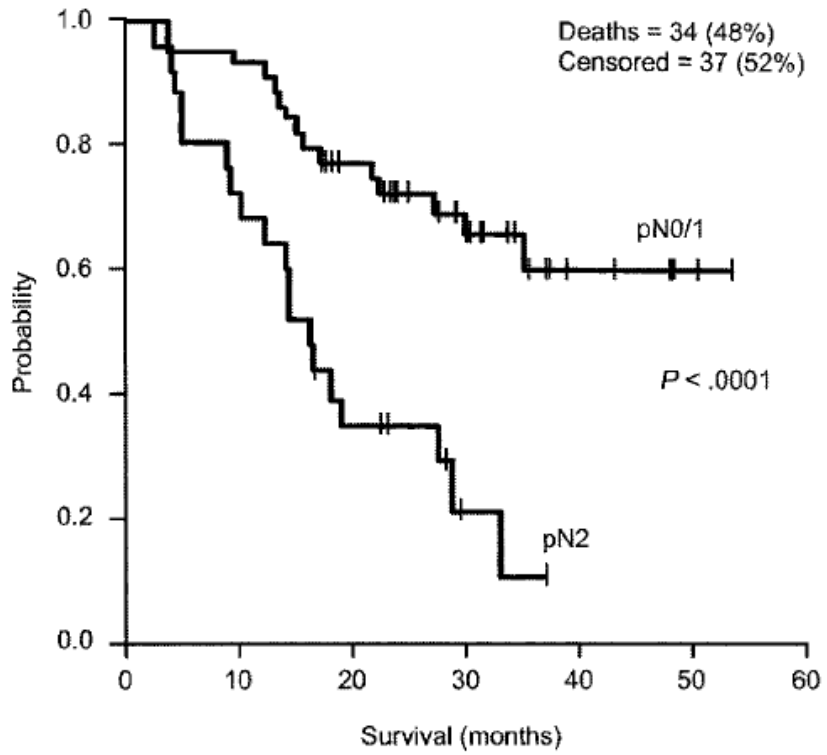


Machiels JP, et al. *Ann Oncol*. 2020;31:1462-1475.

Induction Chemotherapy to Select Candidates for Surgery?

3 Cycles of Docetaxel + Cisplatin in 90 Patients With Potentially Operable Stage IIIA (mediastinoscopy pN2)

Pathologic Downstaging



Betticher DC, et al. *J Clin Oncol*. 2003;21:1752-1759.

Induction Chemotherapy to Select Candidates for Surgery?

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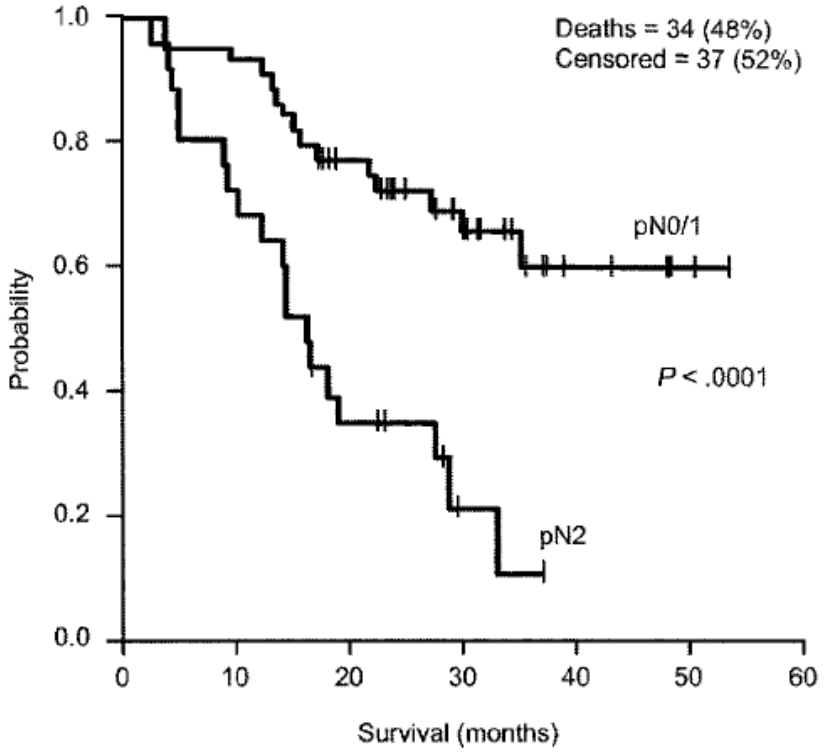
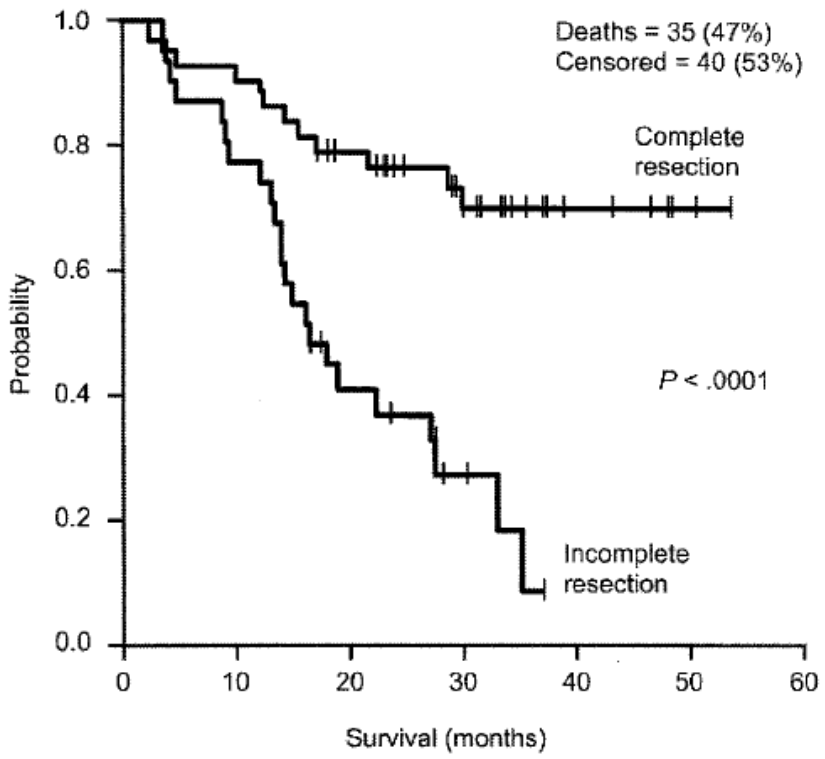


Complete Resection



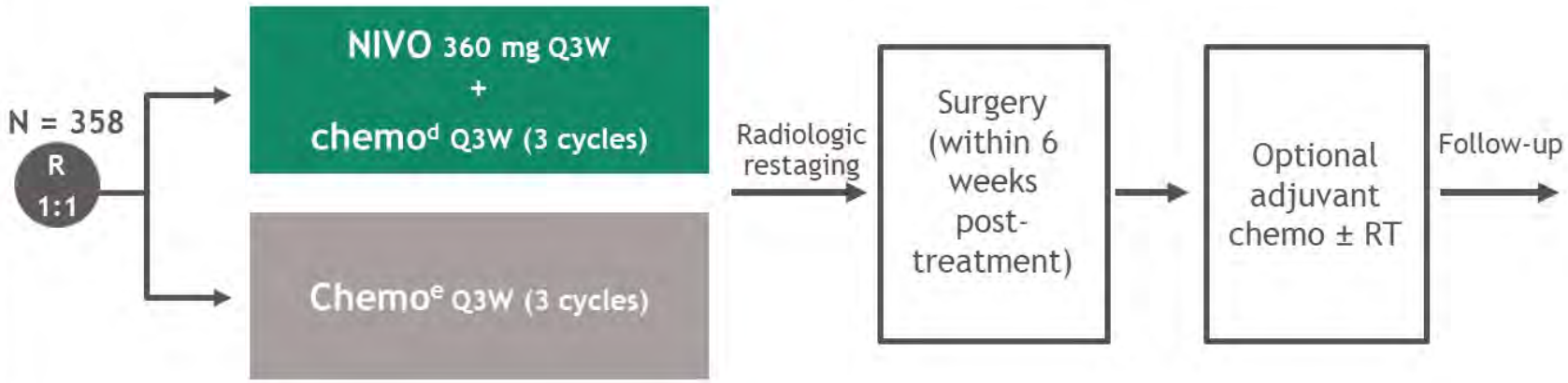
Betticher DC, et al. *J Clin Oncol*. 2003;21:1752-1759.

Neoadjuvant: CheckMate 816

Key eligibility criteria

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

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



Primary endpoints

- pCR by BIPR
- EFS by BICR

Key secondary endpoints

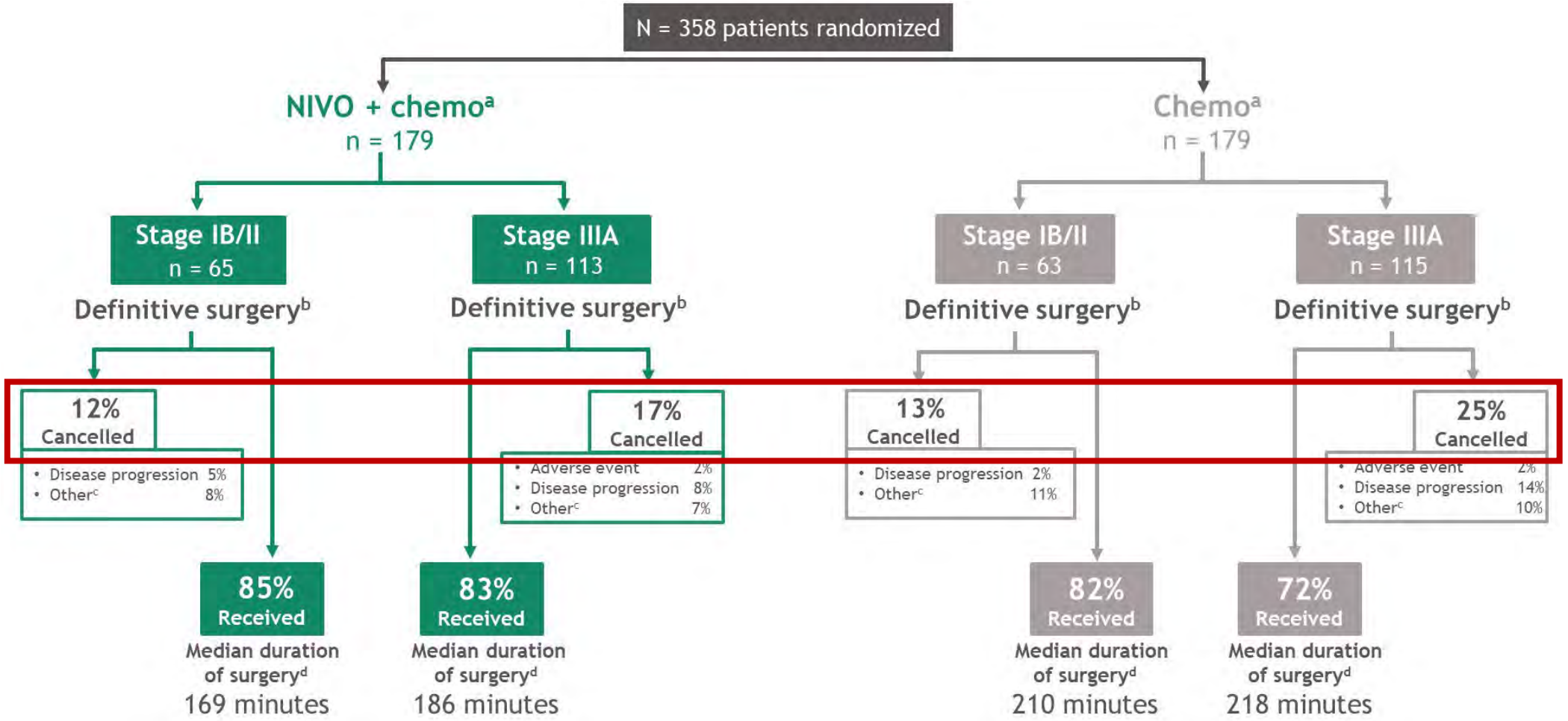
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included

- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

Spicer J, et al. ASCO 2021. Abstract 8503.

Neoadjuvant: CheckMate 816



Spicer J, et al. ASCO 2021. Abstract 8503.

Conclusions

- Systemic benefit of neoadjuvant or adjuvant chemotherapy is similar
- Rate of missed surgery is high with chemoimmunotherapy
- Response does not impact the type of surgery
- Surgery is the curative step!

What would be your treatment approach for this patient?

- Neoadjuvant therapy
- Adjuvant therapy

Global Lung Cancer Academy

Debate: Adjuvant vs Neoadjuvant Therapy for NSCLC

Moderator: Corey Langer, MD, FACP

All faculty

Global Lung Cancer Academy

Options After Early-Stage Relapse

Federico Cappuzzo, MD, PhD

Options After Early-Stage Relapse in NSCLC

Federico Cappuzzo

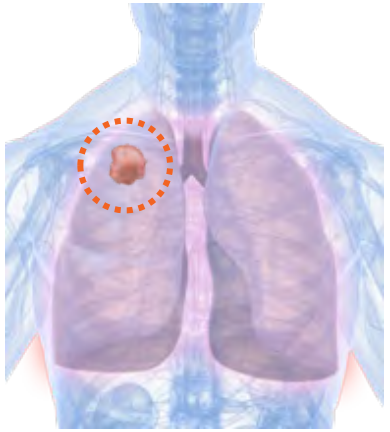
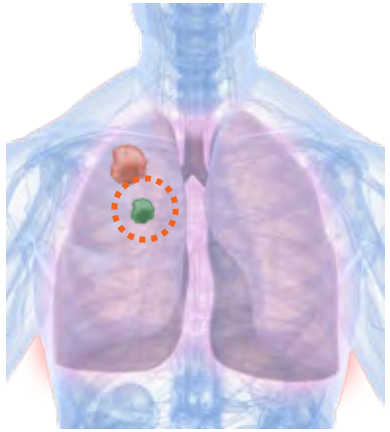
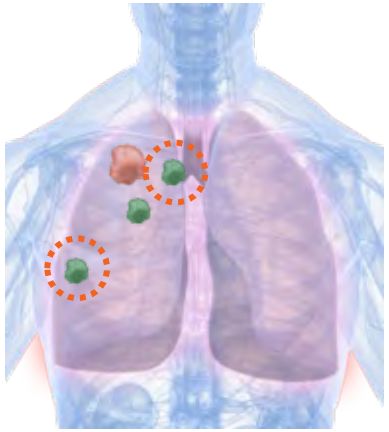
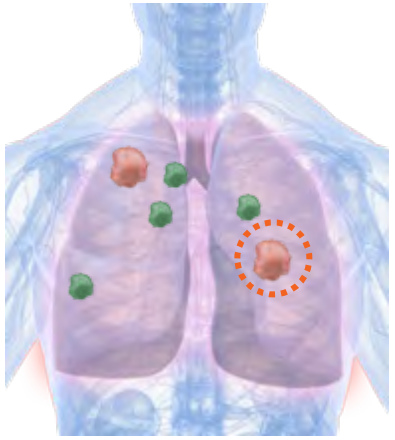
Istituto Nazionale Tumori Regina Elena

Roma

Disclosures

- Dr Cappuzzo discloses the following conflicts of interest
  - Fees for membership of an advisory board or lectures from Roche, AstraZeneca, BMS, Pfizer, Takeda, Lilly, Bayer, Amgen, Sanofi, PharmaMar, Novocure, Mirati, Galecto, OSE, and MSD

Staging of Non-small Cell Lung Cancer

16% of patients		22% of patients	57% of patients
Stage I	**Stage II**	**Stage III**	**Stage IV**
			
Primary tumor	**Lymph node metastasis**	**Lymph node metastases**	**Metastatic tumor**
Cancer is 3–5 cm in the lung and has not spread.	Cancer is 3–5 cm with localized lymph node metastases or is 5–7 cm.	Cancer may have spread to the sternum, lung lining, heart, or major blood vessels.	Cancer may also have spread to distant lymph nodes, the other lung, or to other organs.

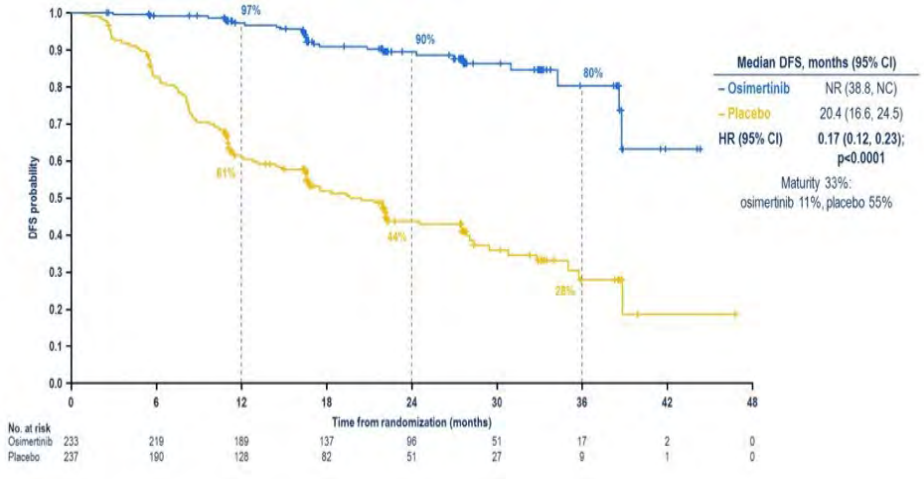
Which option at relapse?

American Cancer Society. Lung Cancer (Non-Small Cell). Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf. Accessed November 1, 2022.

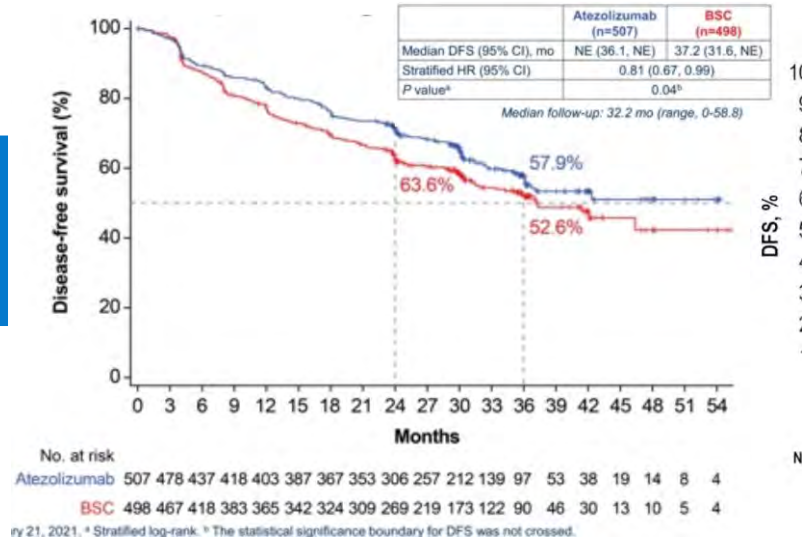
Options for Resected NSCLC in 2022

Stage IA Any EGFR Any PD-L1	Stage Ib EGFR wild-type Any PD-L1	Stage Ib EGFR common Mut+ Any PD-L1	Stage II-IIIA EGFR common Mut+ Any PD-L1+	Stage II-IIIA EGFR wild-type PD-L1+
Follow-up	**Follow-up**	**Osimertinib x 3 years**	**Platinum-based CT or no CT**	**Platinum-based CT**
			↓	↓
			Osimertinib for 3 year	**Atezolizumab for 1 year**

ADAURA

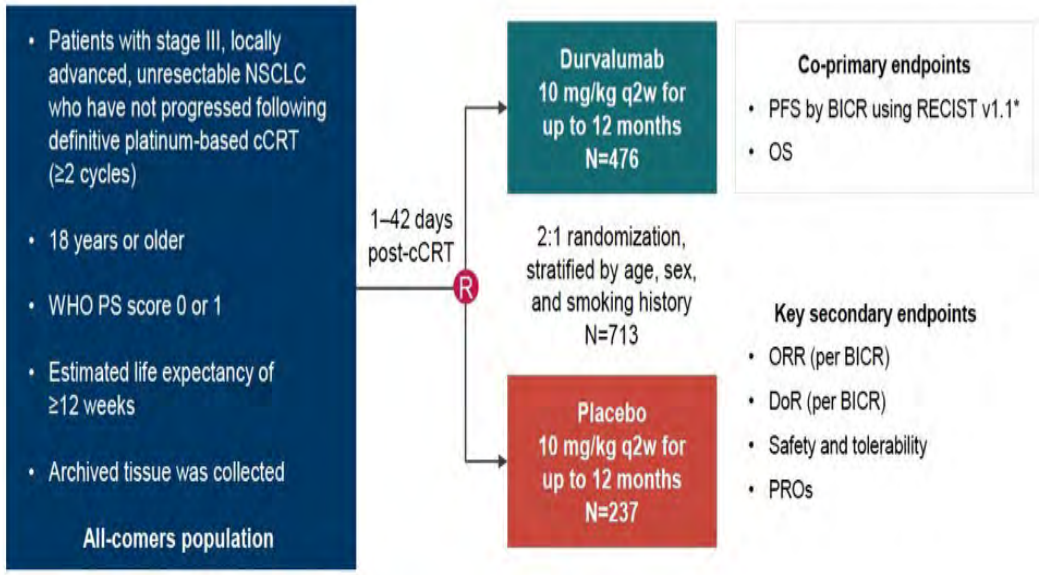


IMpower010

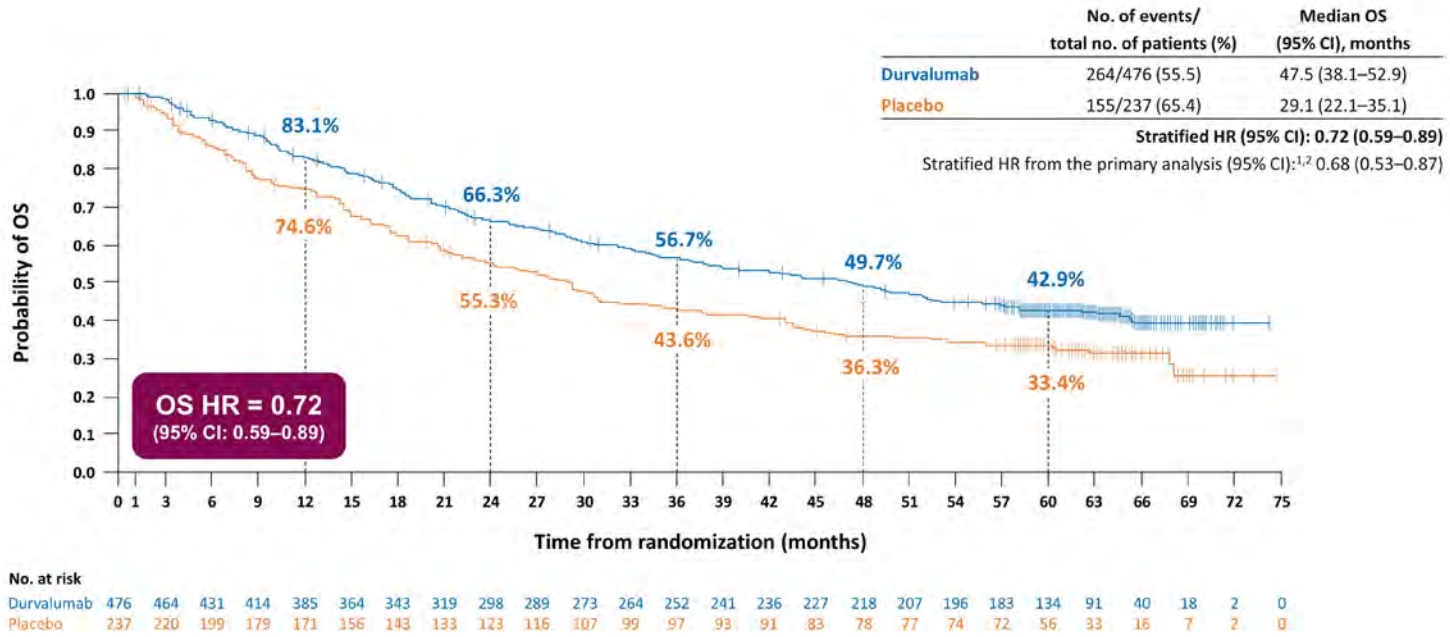


Chemoradiotherapy Followed by Maintenance Durvalumab Is the Standard of Care in Inoperable Stage III NSCLC

PACIFIC trial



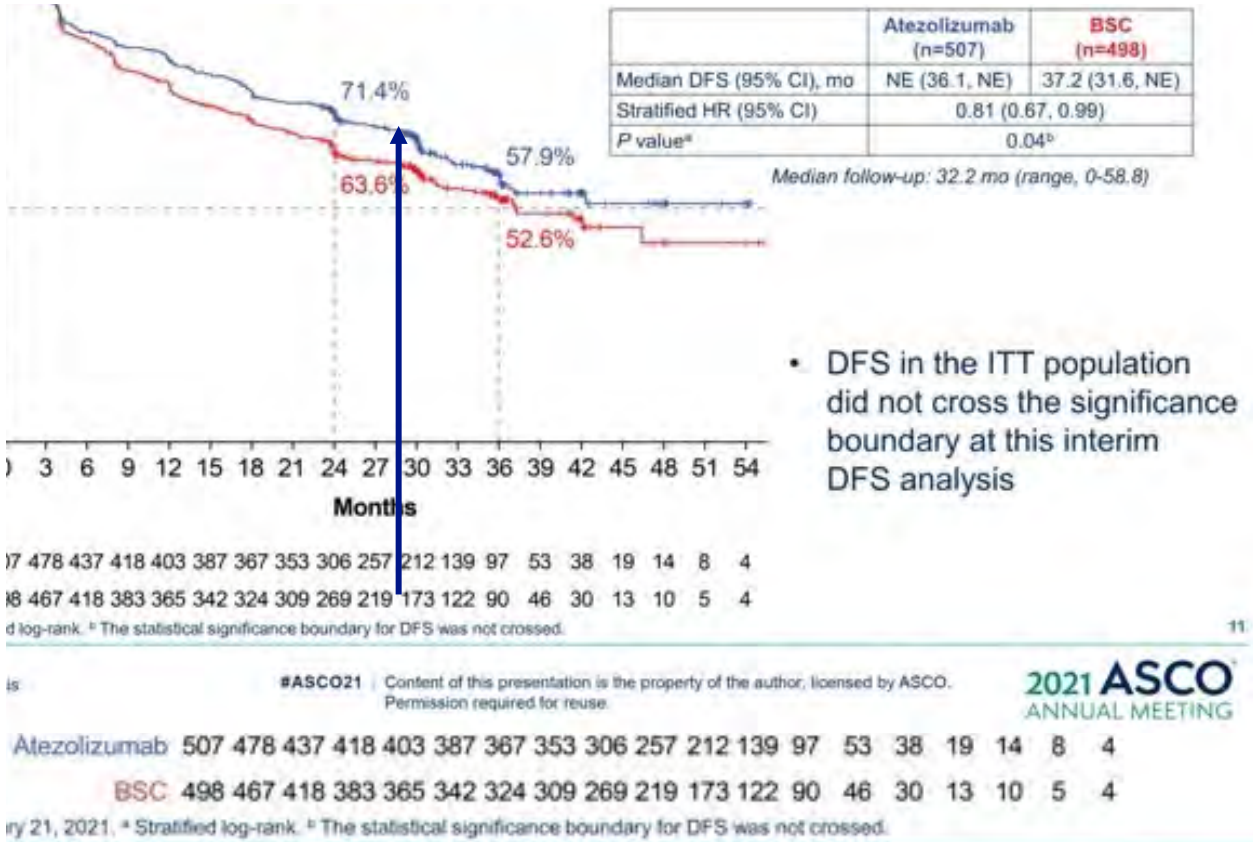
5-year OS



Spigel DR, et al. ASCO 2021. Abstract 8511.

Immunotherapy as Adjuvant Therapy in Surgically Resected NSCLC: 15%–20% of Patients Relapse During Immunotherapy

IMpower010



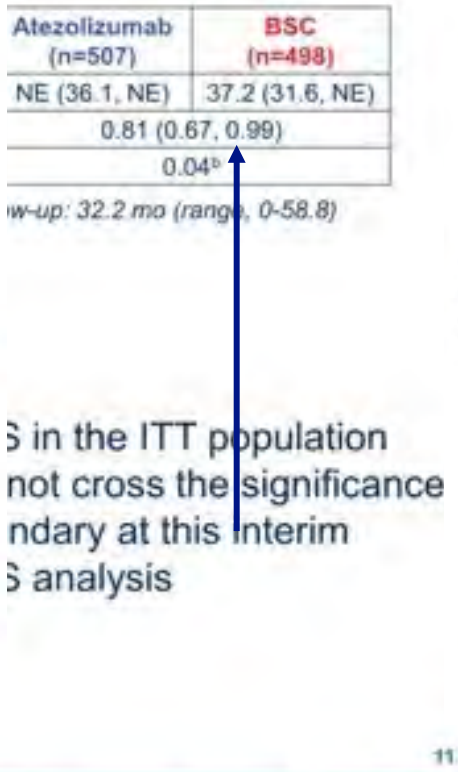
	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[a]	0.04[b]	

Median follow-up: 32.2 mo (range, 0-58.8)

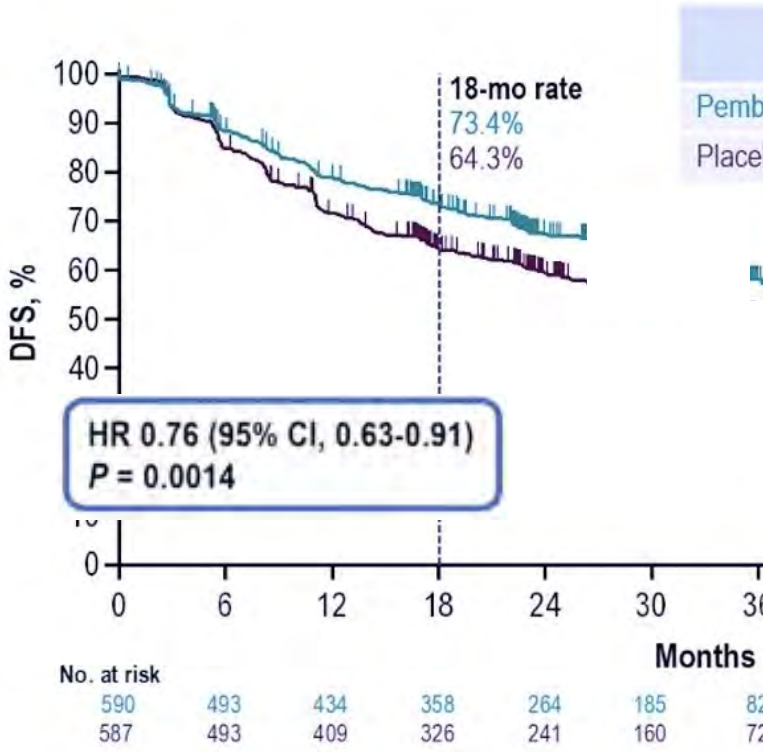
- DFS in the ITT population did not cross the significance boundary at this interim DFS analysis

[a] Stratified log-rank. [b] The statistical significance boundary for DFS was not crossed.

11



KEYNOTE-091



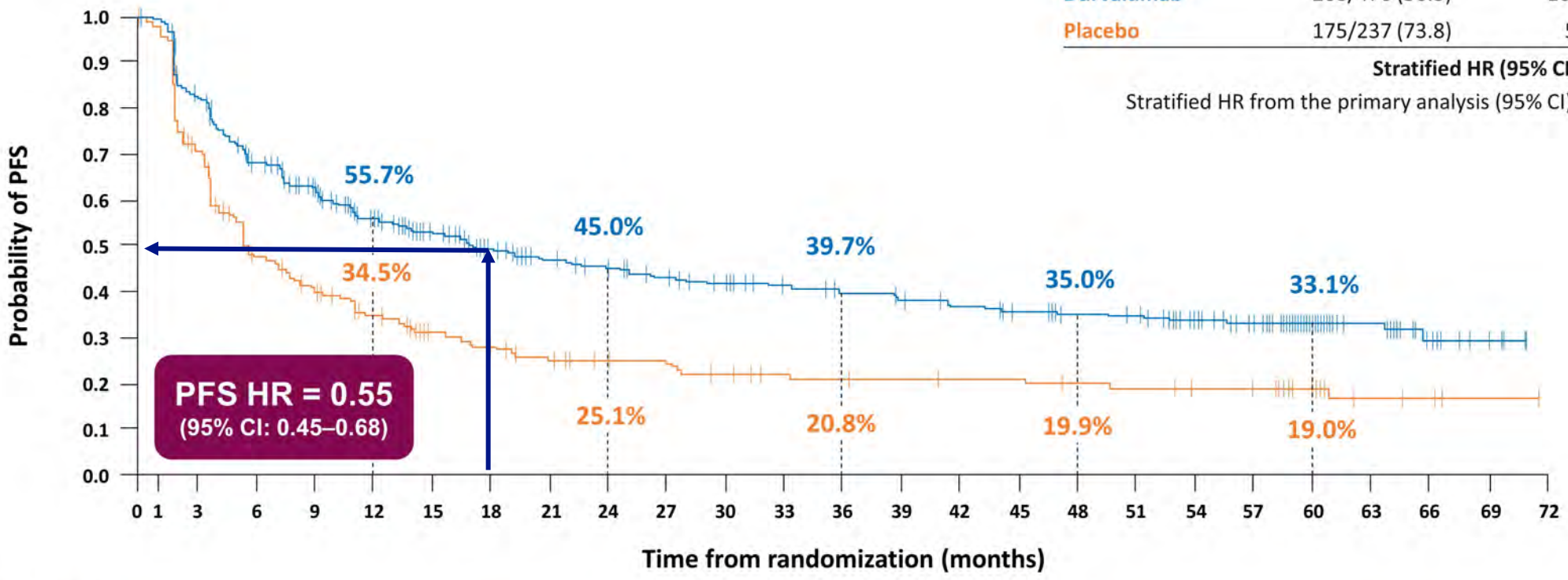
Felip E, et al. ELCC 2022; Paz-Ares L, et al. ESMO virtual 2022. Abstract VP3-2022.

5-Year PFS in PACIFIC: ~50% of Patients Relapse at 12–18 Months

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months
Durvalumab	268/476 (56.3)	16.9 (13.0–23.9)
Placebo	175/237 (73.8)	5.6 (4.8–7.7)

Stratified HR (95% CI): 0.55 (0.45–0.68)

Stratified HR from the primary analysis (95% CI):[1] 0.52 (0.42–0.65)

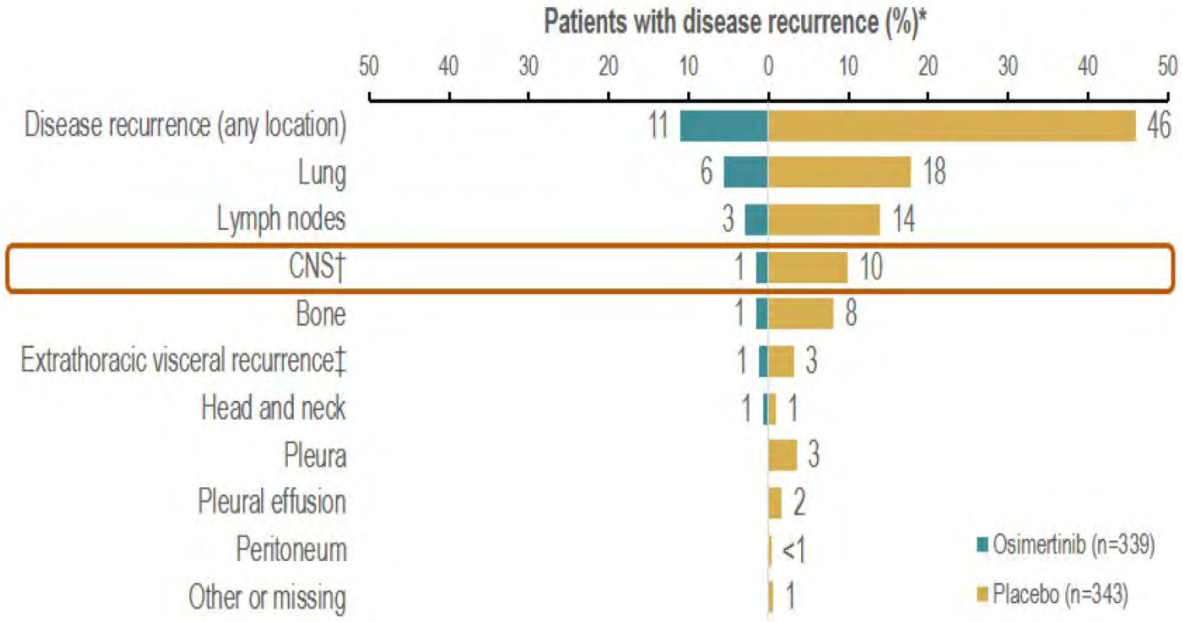


No. at risk																								
Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

Spigel DR, et al. ASCO 2021. Abstract 8511.

Site of Relapse in Early or Locally Advanced NSCLC

ADAURA

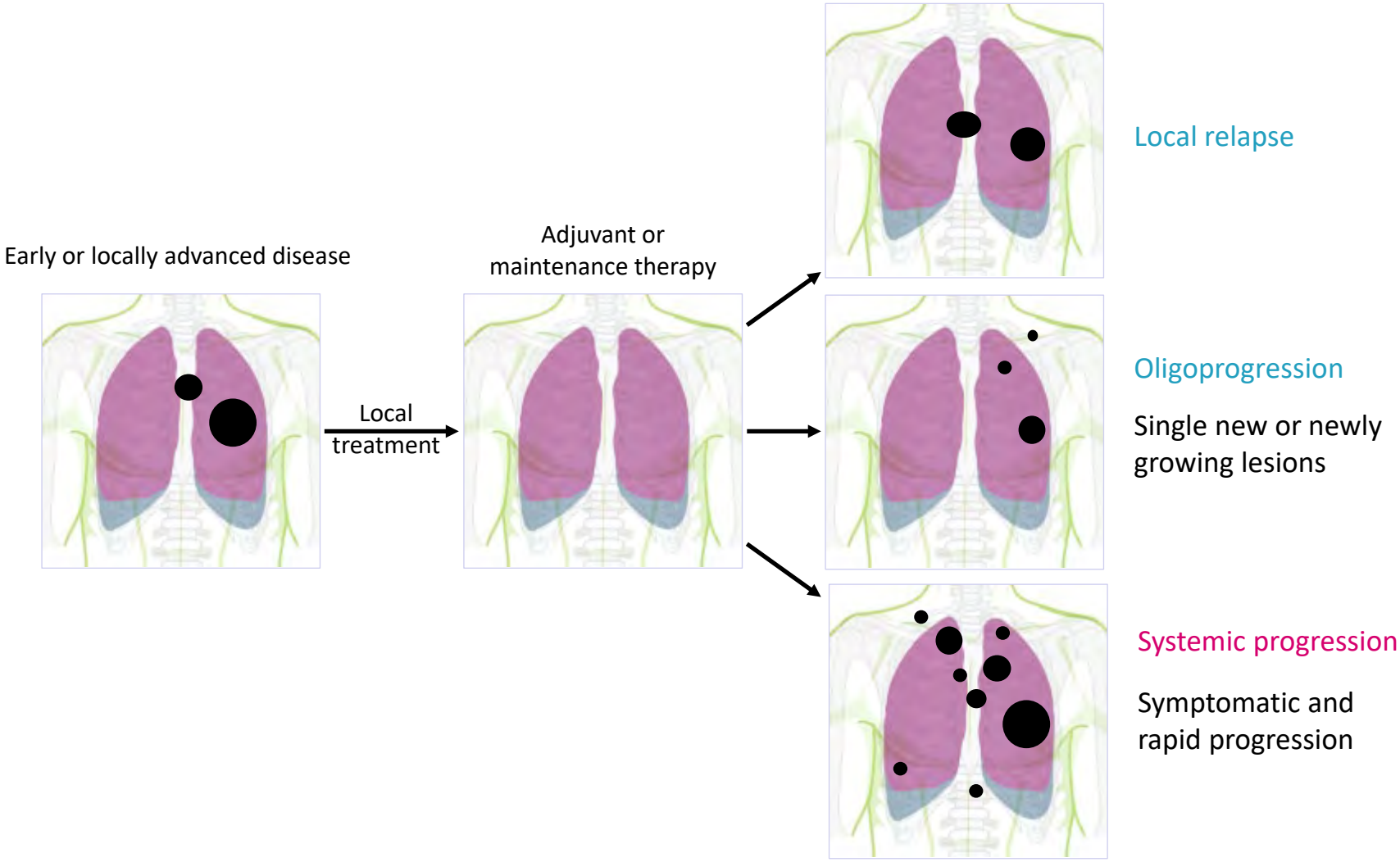


PACIFIC

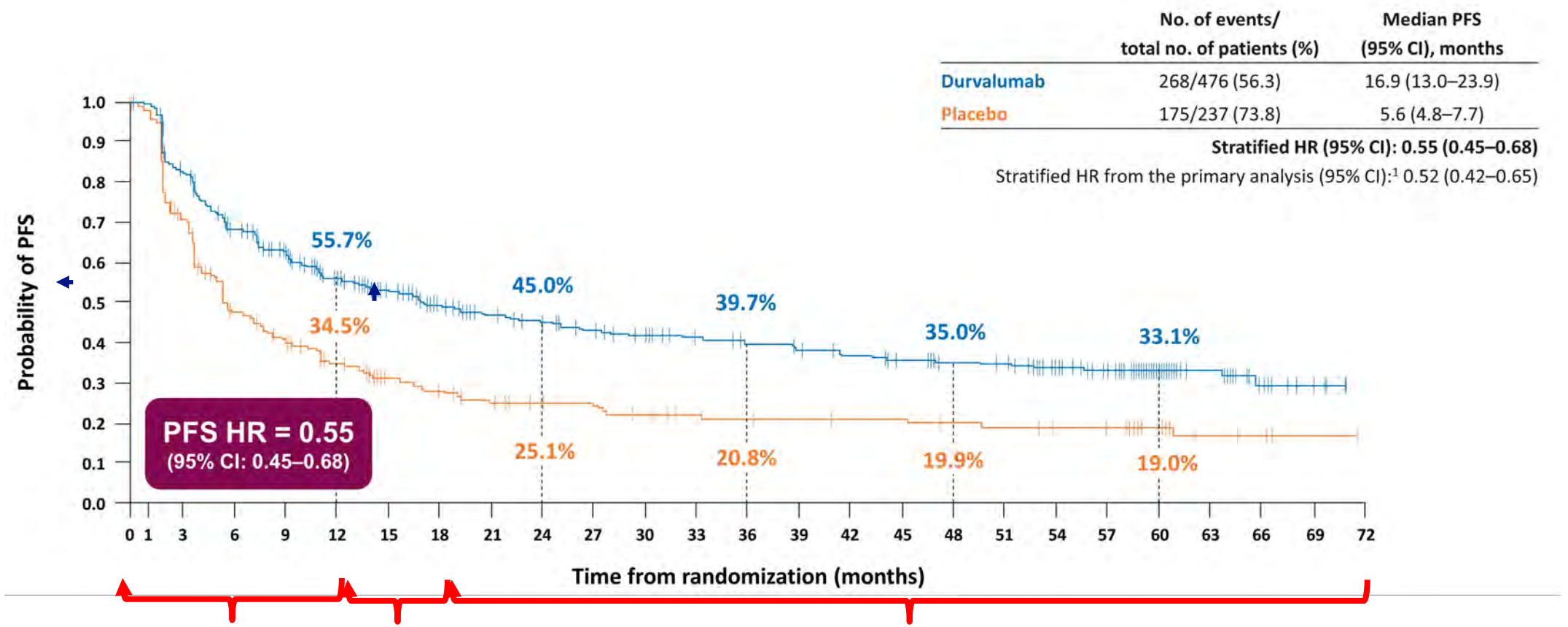
Updated Incidence of New Lesions by BICR* (ITT)

New Lesion Site†	Durvalumab (N=476)	Placebo (N=237)
Patients with any new lesion, n (%)	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

Factors Influencing Therapy Decision:
1. Type of Relapse



Factors Influencing Therapy Decision:
2. Timing of Relapse – PACIFIC as an Example



Early recurrence

During therapy or at therapy stop

Late recurrence

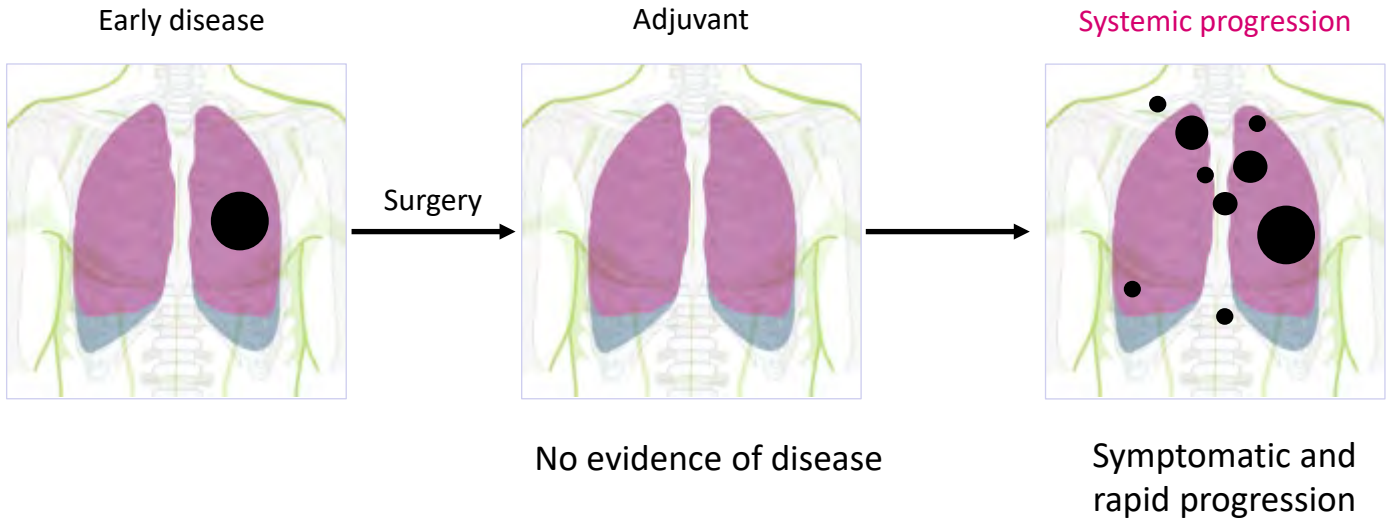
Other Factors Influencing Treatment Decision

1. Potential efficacy of therapies for advanced disease
2. Toxicity of previous therapy
3. Patient characteristics (eg, age, PS, comorbidities)
4. Biologic characteristics (presence of a specific driver, PD-L1)

Potential Clinical Scenarios: Simulated Situations

1. Patient with systemic progression during adjuvant immunotherapy
2. Patient with local relapse after the end of adjuvant immunotherapy
3. Patient with oligoprogression during adjuvant immunotherapy

Case 1: Patient With Systemic Progression During Adjuvant Immunotherapy



Question: What Is the Best Option?

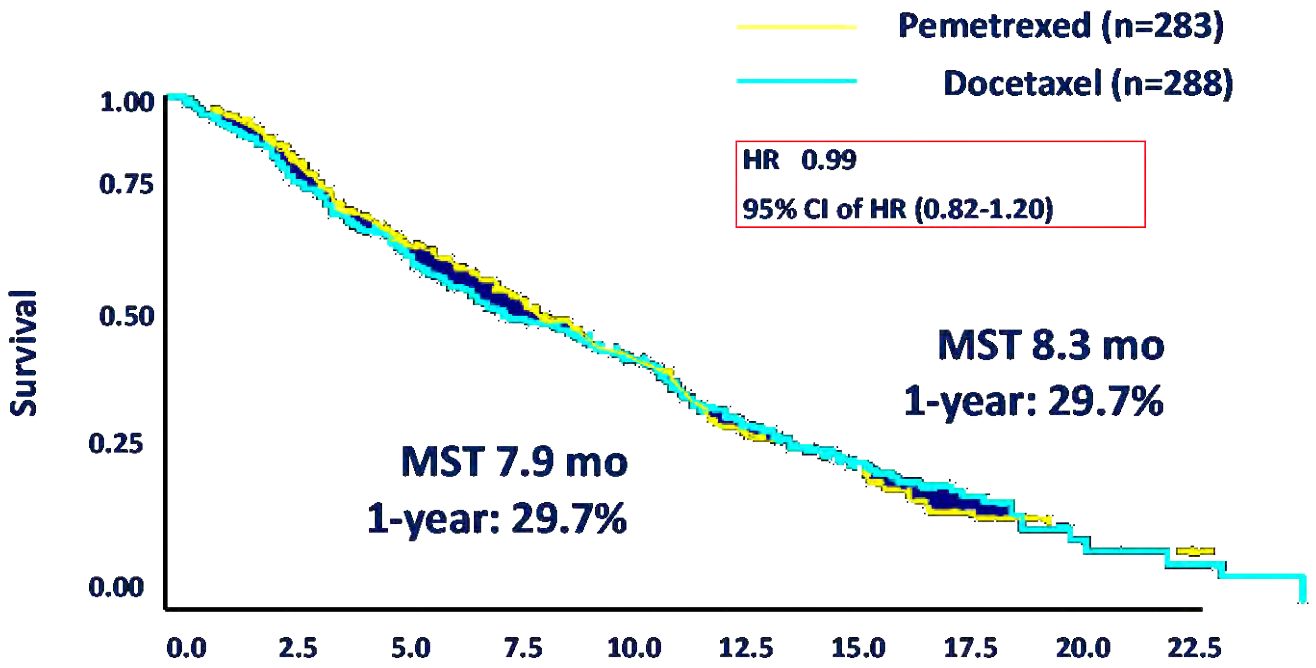
- Standard second-line therapy (ie, docetaxel single agent or in combo with antiangiogenesis agent)
- Platinum-based chemotherapy
- Immunotherapy-based combination
- Targeted therapy

Case 1: Patient With Systemic Progression During Adjuvant Immunotherapy

Efficacy of second-line therapy is modest

Docetaxel, pemetrexed, or docetaxel + nintedanib as potential options

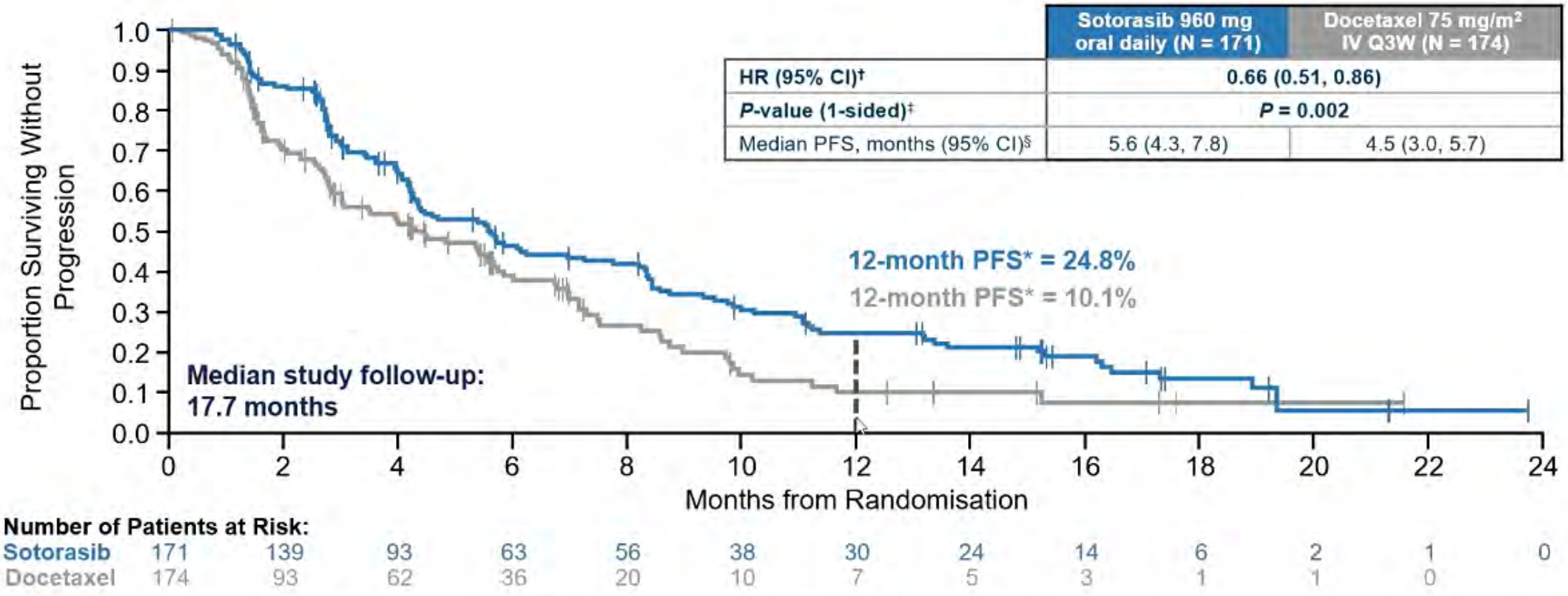
Median PFS: 3–4 months
Median OS: 7–8 months



Toxicity particularly with docetaxel is a clinical issue

Hanna N, et al. *J Clin Oncol*. 2004;22:1589-1597.

Sotorasib Is an Option in *KRAS*$^{G12C+}$: PFS in CodeBreaK 200

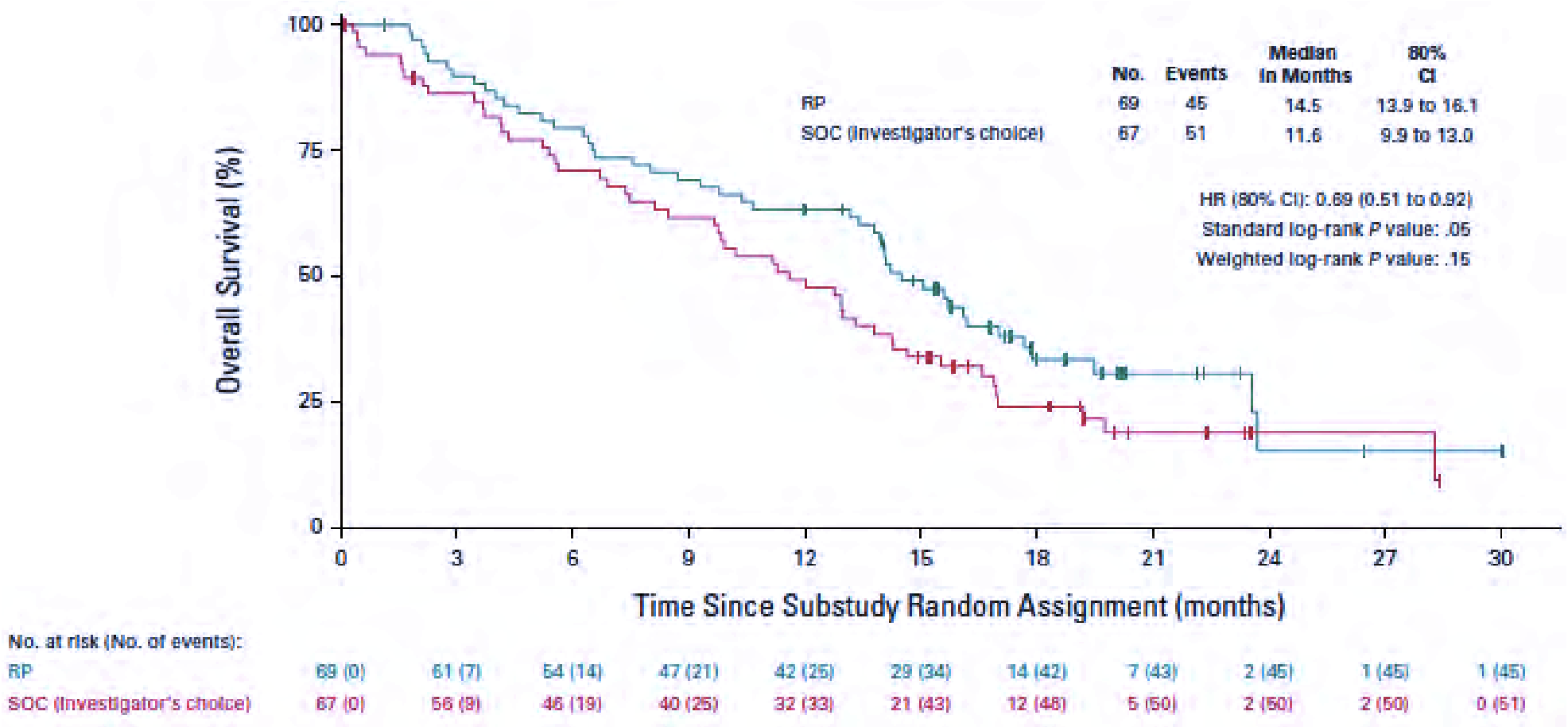


	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

Johnson M, et al. ESMO 2022. Abstract LBA10.

Immunotherapy Rechallenge: OS With Pembro-Ramucirumab in Lung-MAP Trial



Reckamp KL, et al. *J Clin Oncol*. 2022;40:2295-2306.

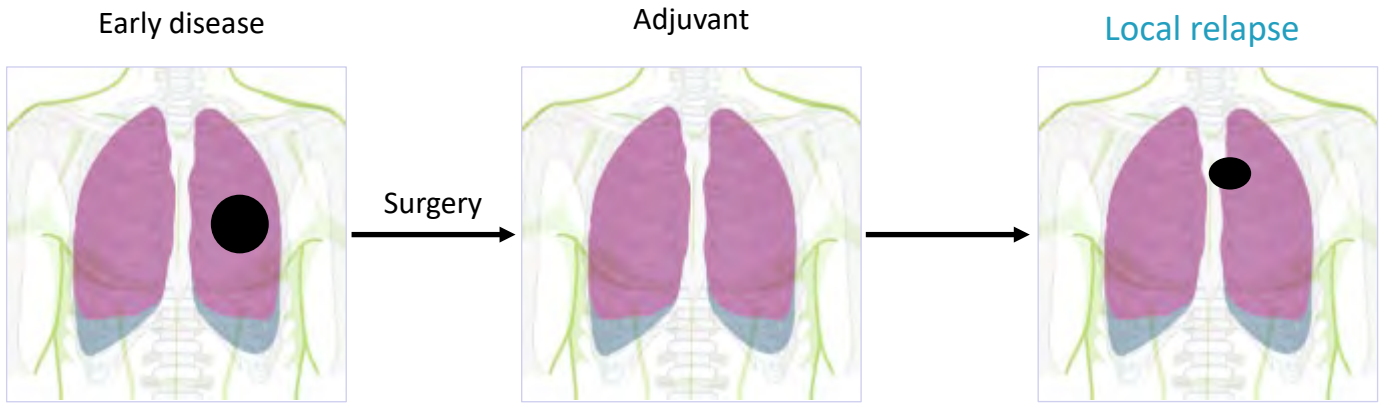
Platinum Rechallenge Is a Potential Option in NSCLC

Clinical trials in patients relapsing after at least 3 months after platinum-based chemotherapy

First author, year [ref.]	Phase	Patients	Arms	PFS months	p-value	OS months	p-value	Response rate %	p-value
Pallis, 2010 [23]	III	132	Docetaxel + carboplatin	3.33	0.012	10.3	0.55	10.4	0.764
			Docetaxel	2.60		7.70		7.7	
Takeda, 2009 [22]	III	130	Docetaxel + gemcitabine	2.8	0.028	10.3	0.36	7.0	0.71
			Docetaxel	2.1		10.1		6.8	
Gebbia, 2009 [5]	III	84	Docetaxel	12.4 weeks	0.44	40 weeks	0.18	6.4	NR
			Docetaxel + vinorelbine or gemcitabine	13.1 weeks	0.60	32.6 weeks	0.90	16.7	
			Docetaxel + capecitabine	11.9 weeks		39.7 weeks		5.3	
Ardizzoni, 2012 [25]	II	479	Pemetrexed + carboplatin	3.9	0.70	8.7	0.316	15	0.062
			Pemetrexed	3.0		8.2		9	
Smit, 2009 [24]	II	240	Pemetrexed + carboplatin	4.2	0.005	8.0	NS	9	NS
			Pemetrexed	2.8		7.6		4	
Pectasides, 2005 [26]	II	130	Docetaxel + irinotecan	5.6	0.065	6.5	0.49	20	0.36
			Docetaxel	4.8		6.4		14	
Wachters, 2005 [27]	II	108	Docetaxel + irinotecan	15 weeks	0.42	27 weeks	0.69	10	NR
			Docetaxel	18 weeks		32 weeks		16	
Georgoulias, 2005 [30]	II	147	Cisplatin + irinotecan	NR	NR	7.8	0.934	22.5	0.012
			Cisplatin			8.8		7	

Platinum rechallenge seems to offer higher ORR and longer PFS than single-agent CT

Case 2: Patient With Local Relapse After the End of Adjuvant Immunotherapy



NCCN guidelines

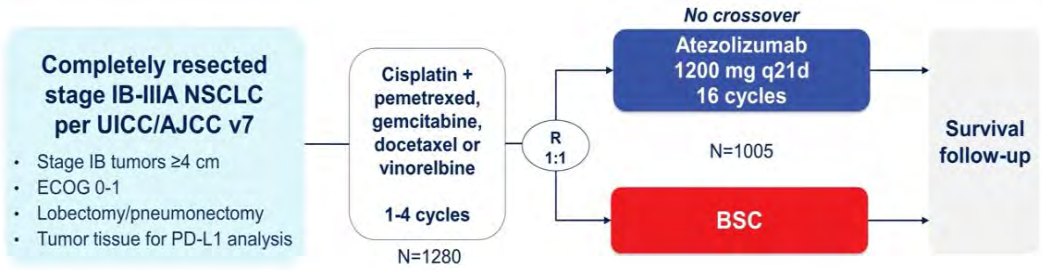
Resectable recurrence: Surgery preferred

Nonresectable recurrence: Chemoradiotherapy preferred

Case 2: Patient With Local Relapse After the End of Adjuvant Immunotherapy

Should we consider a rechallenge with immunotherapy?

IMpower010: Atezolizumab for 1 year



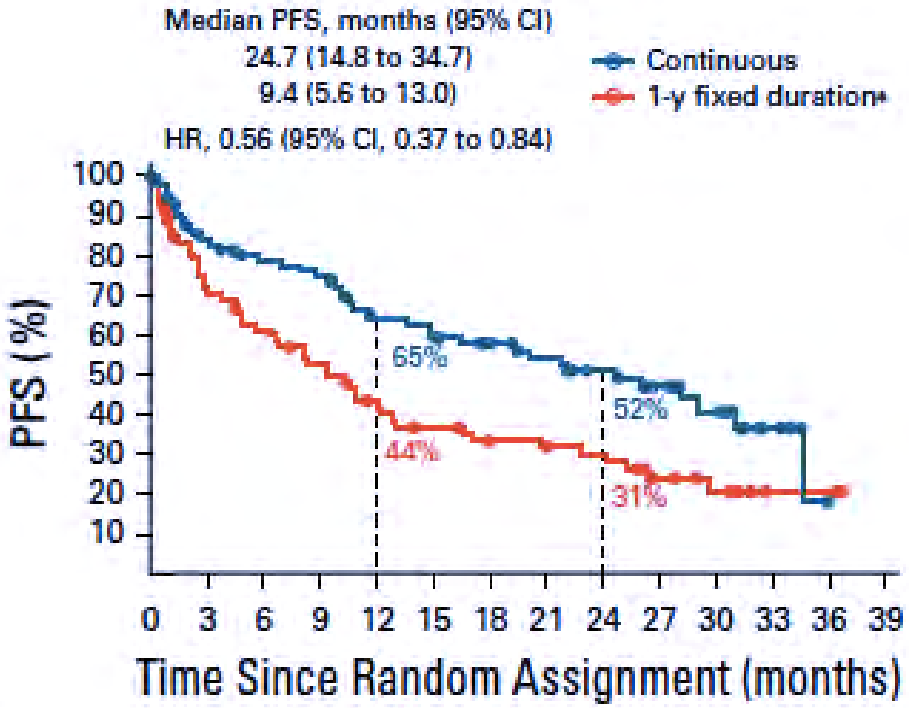
Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

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

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

Felip E et al ELCC 2022

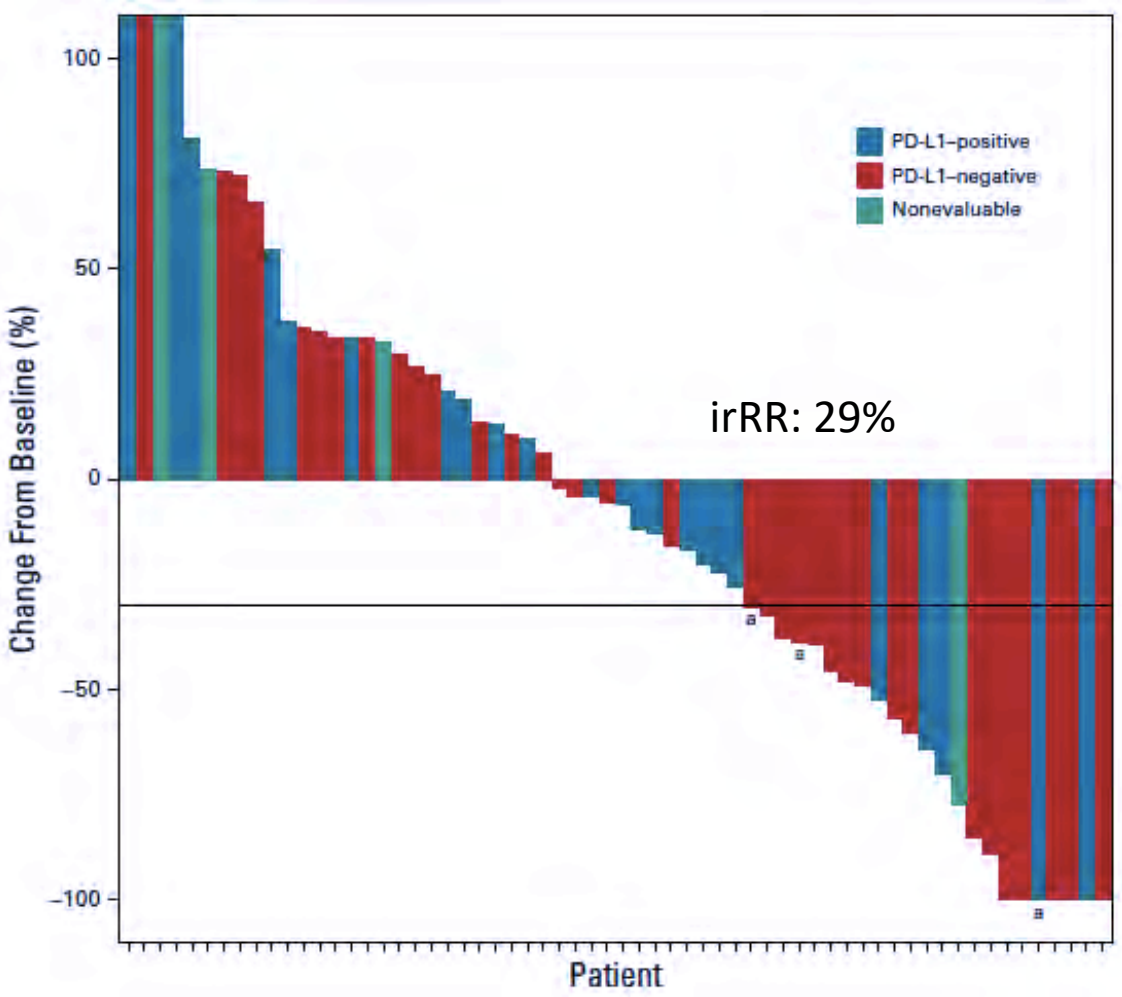
CheckMate 153: Nivolumab continuous vs 1-yr duration

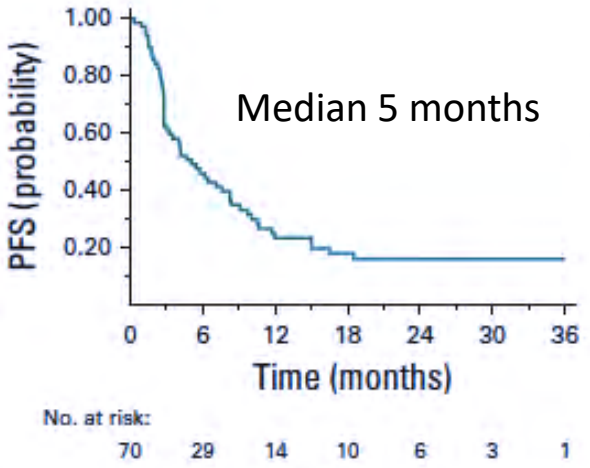


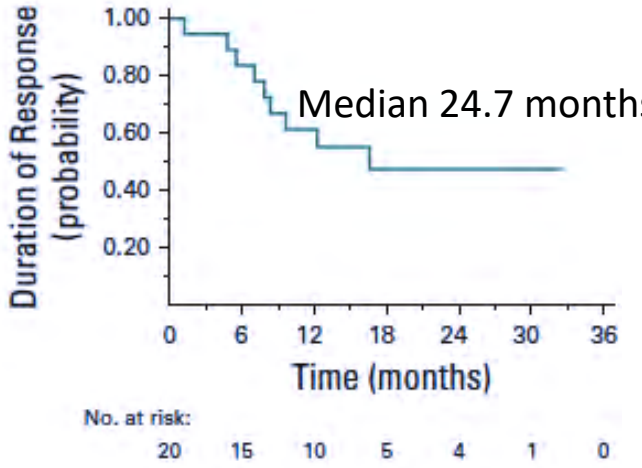
Immunotherapy optimal duration is a relevant issue

Waterhouse DM, et al. *J Clin Oncol*. 2020;38:3863-3873.

IO + IO Combo Could Be Effective in IO-Pretreated Patients: Data With Pembrolizumab + Ipilimumab in Melanoma



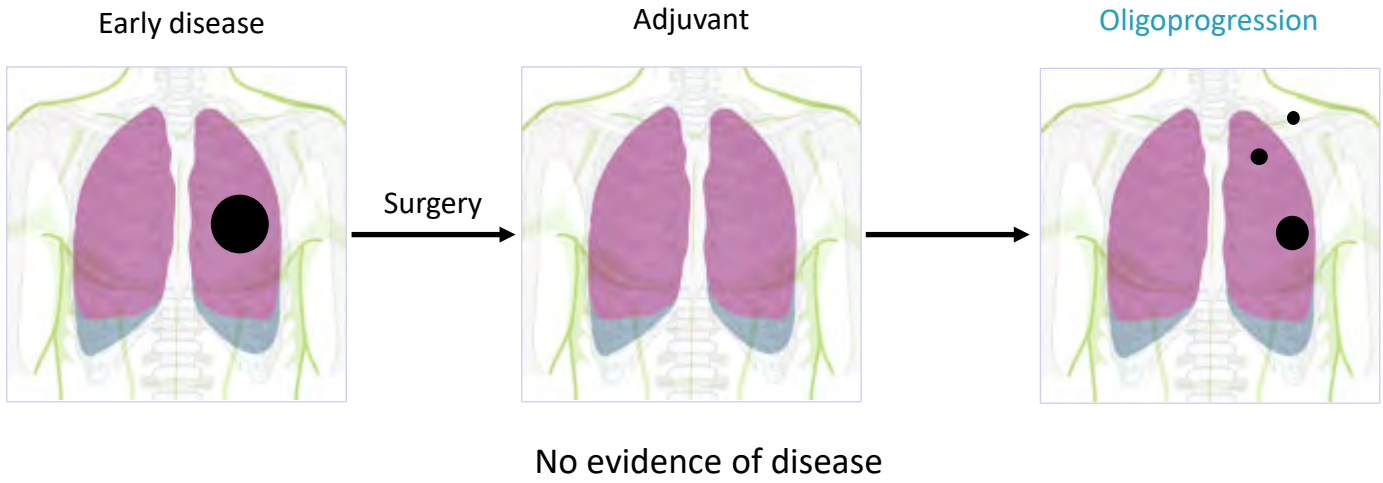




Median DOR: 16.6 months

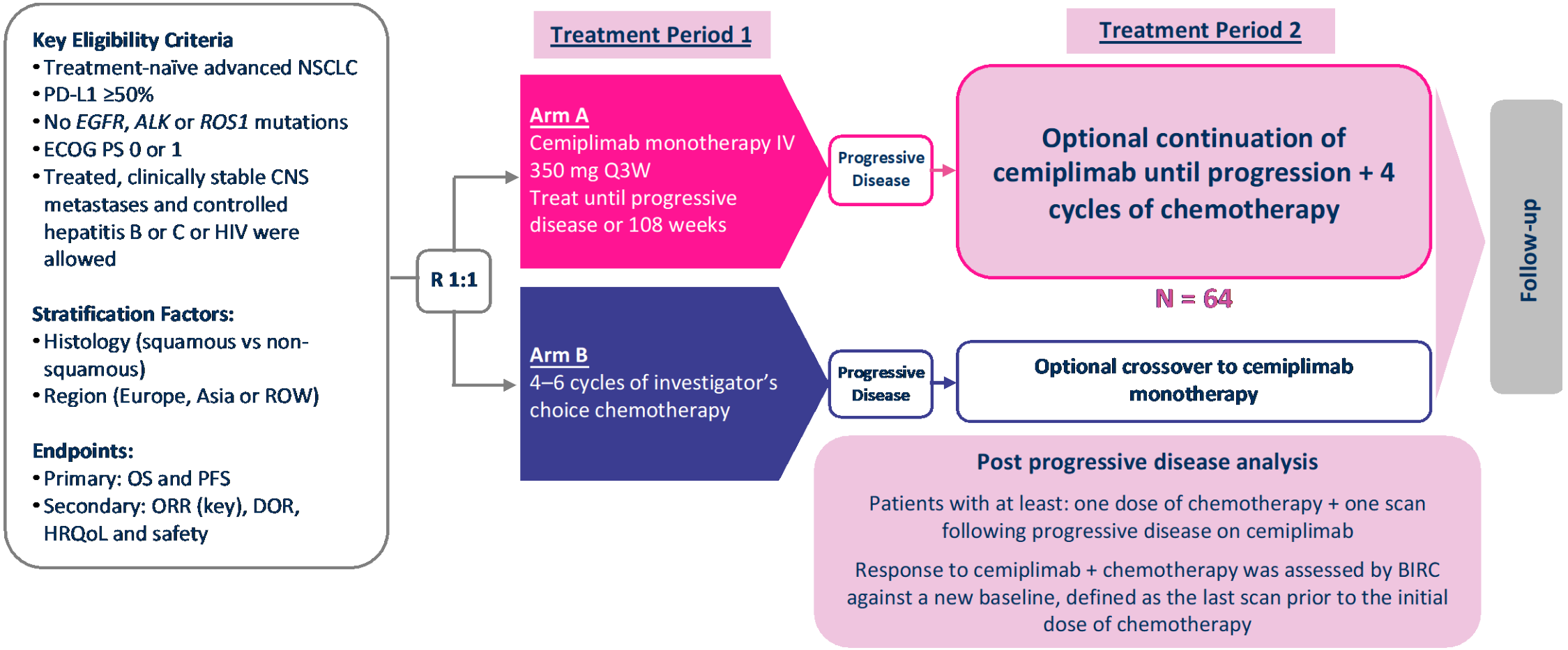
Olson DJ, et al. *J Clin Oncol*. 2021;39:2647-2655.

Case 3: Patient With Oligoprogression During Adjuvant Immunotherapy



Local therapy recommended
Question: Should we continue immunotherapy beyond progression?

Immunotherapy Beyond Progression: Data With Cemiplimab in EMPOWER-Lung 1 Trial



Özgüroğlu M, et al. ESMO 2022. Abstract 112P.

Prolonged Survival in the Second-Line Setting With Cemiplimab Beyond Progression

	Cemiplimab Beyond Progression N=64	
OS	**Period 1+2 Randomization to Death**	**Period 2 Day 1 of Continued Treatment to Death**
Median (95% CI, months)	27.4 (23.0, 31.8)*	15.1 (11.3, 18.7)
Estimated Survival Probability, % (95% CI)		
6 months	100 (NE, NE)	91.9 (81.6, 96.5)
12 months	91.8 (81.4, 96.5)	56.8 (43.0, 68.5)
24 months	60.5 (46.6, 71.8)	26.2 (14.3, 39.8)
36 months	32.3 (20.1, 45.1)	NE (NE, NE)

*Includes the 15.1 months of survival beyond progression; CI, confidence interval; OS, overall survival; NE, non-evaluable.

Data cut-off date: March 4

Continued cemiplimab with addition of chemotherapy beyond progression appears superior to historical data for chemotherapy in the 2nd line setting where median OS is 8.4 months (range: 5.6 - 11.2) (Bersanelli et al., Lung Cancer, 2020)

Özgüroğlu M, et al. ESMO 2022. Abstract 112P.

Conclusions

- Relapse in patients exposed to immunotherapy for early-stage disease treated with curative intent is a relevant unmet need
- Several factors influence therapy decision
  - Type of relapse
  - Timing
  - Patient characteristics
- Few data are currently available with rechallenge or continuation of immunotherapy beyond progression as a potential option
- Clinical trials are urgently needed

Global Lung Cancer Academy

Session Close

Corey Langer, MD, FACP

Meeting evaluation

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

Repeat Question 3

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

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

Repeat Question 4

70-year-old female, former smoker (25 pk/yrs) presents with stage IIIB NSCLC with LSCN involvement. Cell type is squamous cell carcinoma. PD-L1 level is 60%. Patient completes chemo-XRT with 60 Gy and concurrent weekly paclitaxel/carboplatin with excellent PR on f/u CT imaging, no complications. Which of the following is “approve”’ consolidation therapy in this setting?

1. Durvalumab
2. Pembrolizumab
3. Atezolizumab
4. Nivolumab

Day 2: Plenary Sessions

Monday, 14 November 2022 from 16.00 – 19.15 CET

Time	Title	Speaker
16.00 – 16.10 (10 min)	**Session Open** • ARS questions	Corey Langer
16.10 – 16.30 (20 min)	**Optimizing First-Line Therapy in NSCLC – Integration of Immunotherapy Into Frontline Regimens** • Optimal use of immunotherapeutic treatment choices in frontline NSCLC	Luis Paz-Ares
16.30 – 16.50 (20 min)	**Current Immunotherapy Options for Relapsed NSCLC** • Optimal use of immunotherapeutic treatment choices in relapsed NSCLC including considerations for potential rechallenge, and treatment selection mono vs combination therapy	Benjamin Besse
16.50 – 17.25 (35 min)	**Tumor Board Discussion** • Case 1 (10 min) • Case 2 (10 min) • Discussion & Q&A (15 min)	Moderator: Solange Peters Francesca Fusco Luis Angel Leon Mateos All faculty
17.25 – 17.35 (10 min)	***Break***	
17.35 – 17.50 (15 min)	**ALK Inhibitors in NSCLC** • Considerations for optimal use in clinical practice in patients with and without brain metastasis	Enriqueta Felip
17.50 – 18.05 (15 min)	**EGFR Inhibitors in NSCLC** • Considerations for optimal use in clinical practice	Johan Vansteenkiste
18.05 – 18.30 (25 min)	**Other Targets in NSCLC** • Considerations for optimal use of ROS1, NTRK, RET and MET inhibitors in clinical practice	Anne-Marie Dingemans
18.30 – 19.05 (35 min)	**Tumor Board Discussion** • Case 1 (10 min) • Case 2 (10 min) • Discussion & Q&A (30 min)	Moderator: Corey Langer May-Lucie Meyer Xander Verbeke All faculty
19.05 – 19.15 (10 min)	**Session Close** • ARS questions	Solange Peters

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

Global Lung Cancer Academy

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Sharing Best Practices to Optimize Patient Care

SEE YOU NEXT MONDAY!

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