# The Great Adjuvant Debate — Exploring the Role of Novel Therapies in the Management of Localized Cancer

**Monday, February 28, 2022**

**5:00 PM – 6:00 PM ET**

## Faculty

**Roy S Herbst, MD, PhD**
**Sara M Tolaney, MD, MPH**
**Jeffrey S Weber, MD, PhD**

## Moderator

**Neil Love, MD**

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# Faculty

## Melanoma

**Jeffrey S Weber, MD, PhD**
Deputy Director
Laura and Isaac Perlmutter Cancer Center
(NCI-Funded Comprehensive Cancer Center)
Professor of Medicine
NYU Grossman School of Medicine
New York, New York

## Lung Cancer

**Roy S Herbst, MD, PhD**
Ensign Professor of Medicine (Medical Oncology)
Professor of Pharmacology
Assistant Dean for Translational Research
Chief of Medical Oncology
Deputy Director, Clinical Affairs
Director, Center for Thoracic Cancers
Associate Cancer Center Director, Translational Science
Yale Comprehensive Cancer Center
Yale School of Medicine
New Haven, Connecticut

## Breast Cancer

**Sara M Tolaney, MD, MPH**
Chief, Division of Breast Oncology
Associate Director, Susan F Smith Center for Women's Cancers
Senior Physician
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

## Moderator

**Neil Love, MD**
Research To Practice
Miami, Florida

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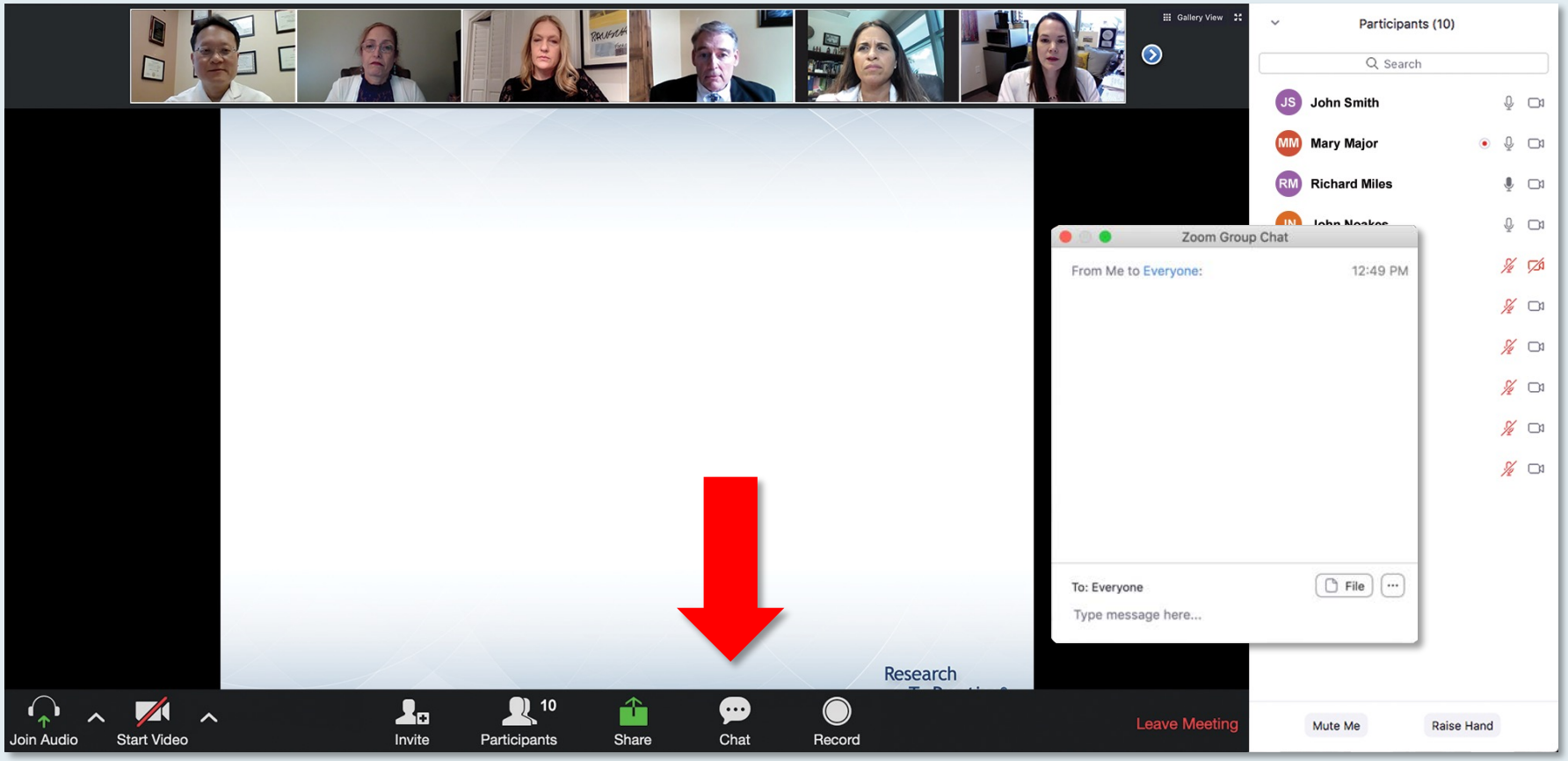


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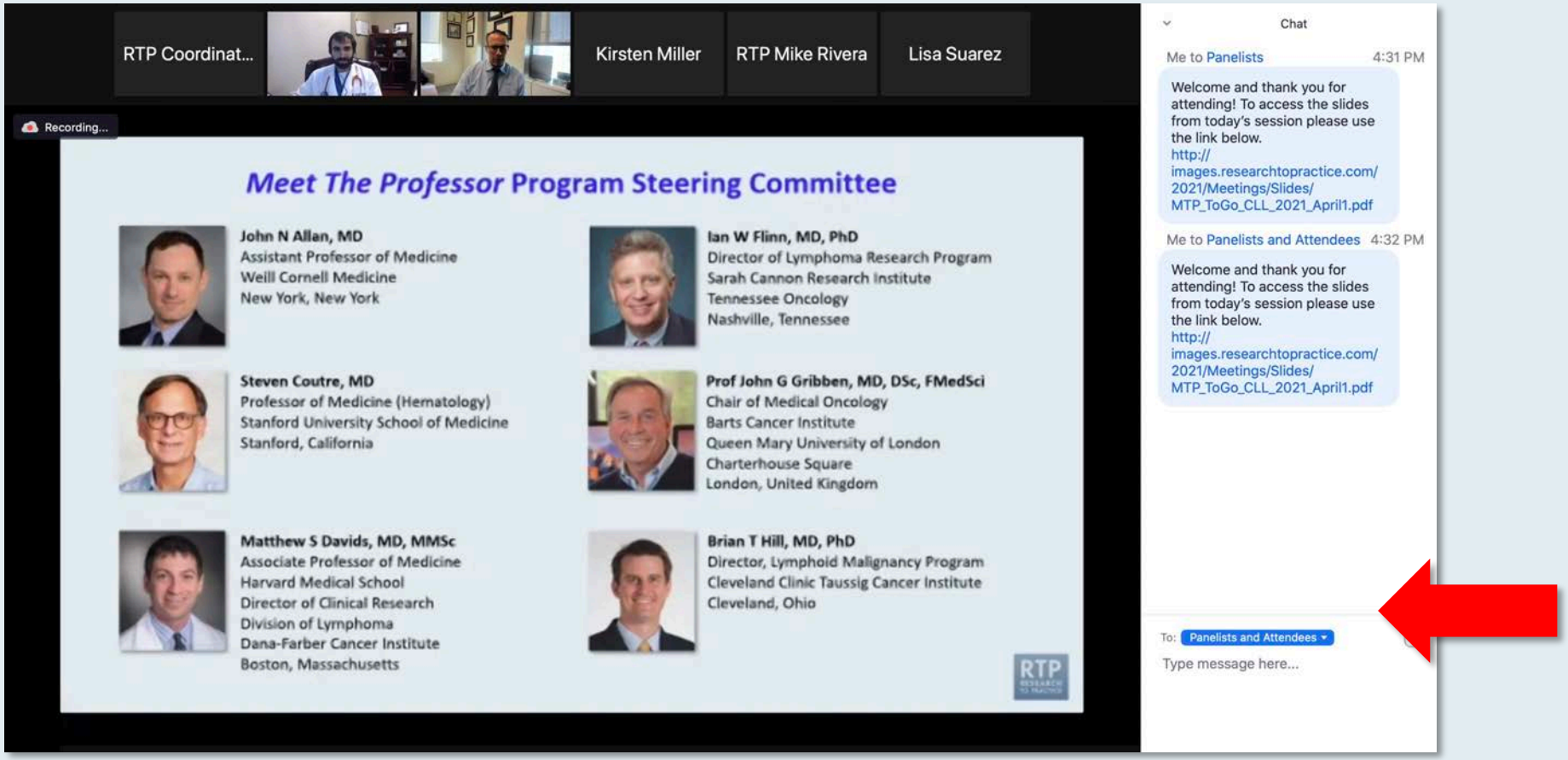
## Expand chat submission box




**Drag the white line above the submission box up to create more space for your message.**

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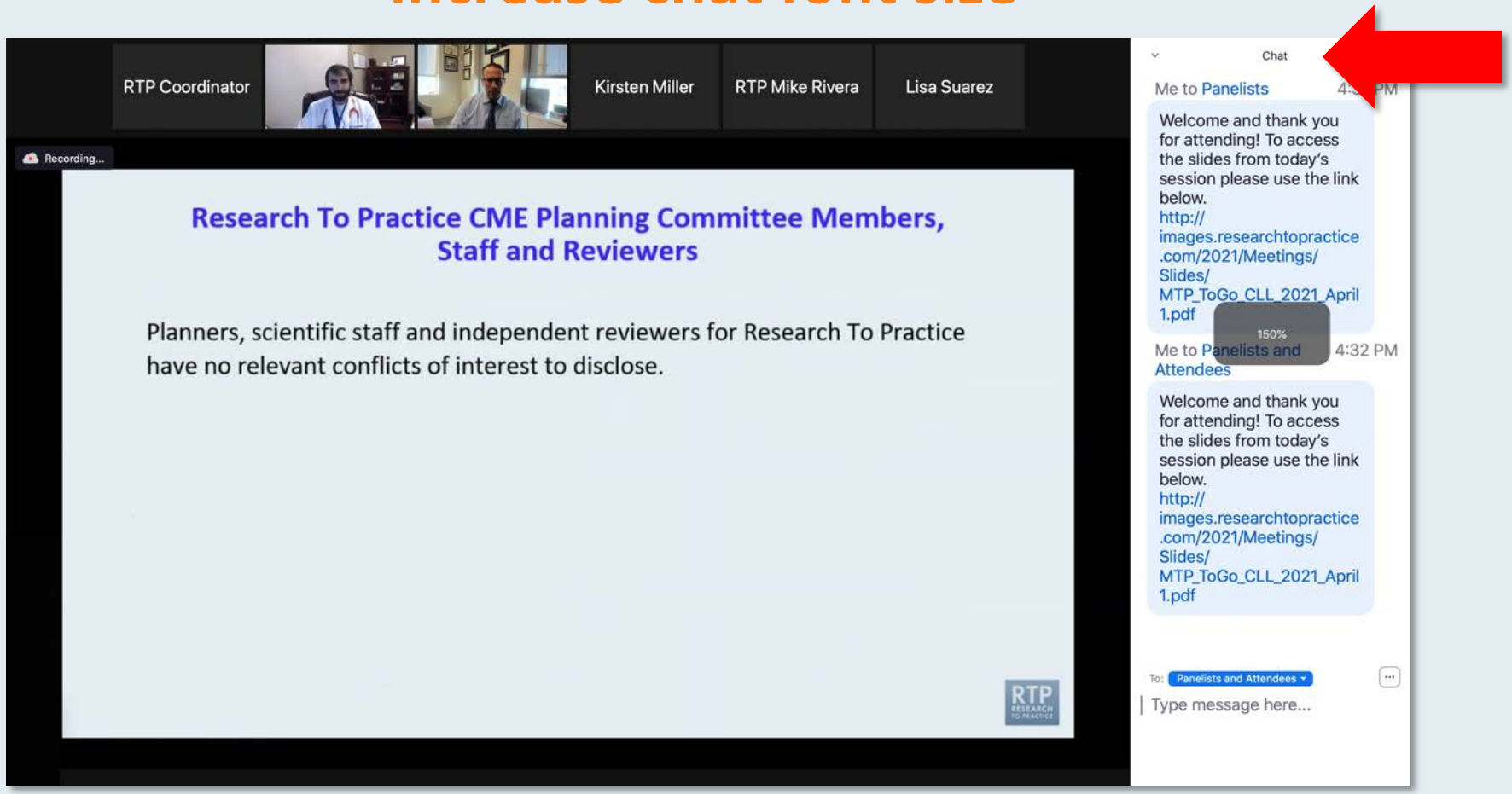
## Increase chat font size




**Press Command (for Mac) or Control (for PC) and the + symbol.**
**You may do this as many times as you need for readability.**

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WITH DR NEIL LOVE

# NSCLC with EGFR Exon 20 Insertion Mutations

DR GREGORY RIELY
MEMORIAL SLOAN KETTERING CANCER CENTER

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# *Meet The Professor*

# Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

**Tuesday, March 1, 2022**
**5:00 PM – 6:00 PM ET**

## Faculty

**Michael E Williams, MD, ScM**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*

## Optimizing the Management of Metastatic Castration-Resistant Prostate Cancer

**Wednesday, March 2, 2022**
**5:00 PM – 6:00 PM ET**

### Faculty

**Andrew J Armstrong, MD, ScM**

### Moderator

**Neil Love, MD**

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# *Meet The Professor*

# Current and Future Management of Chronic Lymphocytic Leukemia

**Thursday, March 3, 2022**
**5:00 PM – 6:00 PM ET**

## Faculty

**William G Wierda, MD, PhD**

## Moderator

**Neil Love, MD**

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## Current and Future Role of Immunotherapy in the Management of Lung Cancer

**Monday, March 7, 2022**
**5:00 PM – 6:00 PM ET**

### Faculty

**Charu Aggarwal, MD**

### Moderator

**Neil Love, MD**

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# Year in Review:
## Kidney and Bladder Cancer

**Tuesday, March 8, 2022**
**5:00 PM – 6:00 PM ET**

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**Elizabeth R Plimack, MD, MS**

**Thomas Powles, MBBS, MRCP, MD**

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RTP Year in Review 2022

# *Meet The Professor*

## Optimizing the Management of Acute Myeloid Leukemia

**Wednesday, March 9, 2022**
**5:00 PM – 6:00 PM ET**

### Faculty

**Rebecca L Olin, MD, MSCE**

### Moderator

**Neil Love, MD**

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# *Meet The Professor*

## Current and Future Management of Myelofibrosis

**Thursday, March 10, 2022**
**5:00 PM – 6:00 PM ET**

### Faculty

**Srdan Verstovsek, MD, PhD**

### Moderator

**Neil Love, MD**

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*Thank you for joining us!*

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

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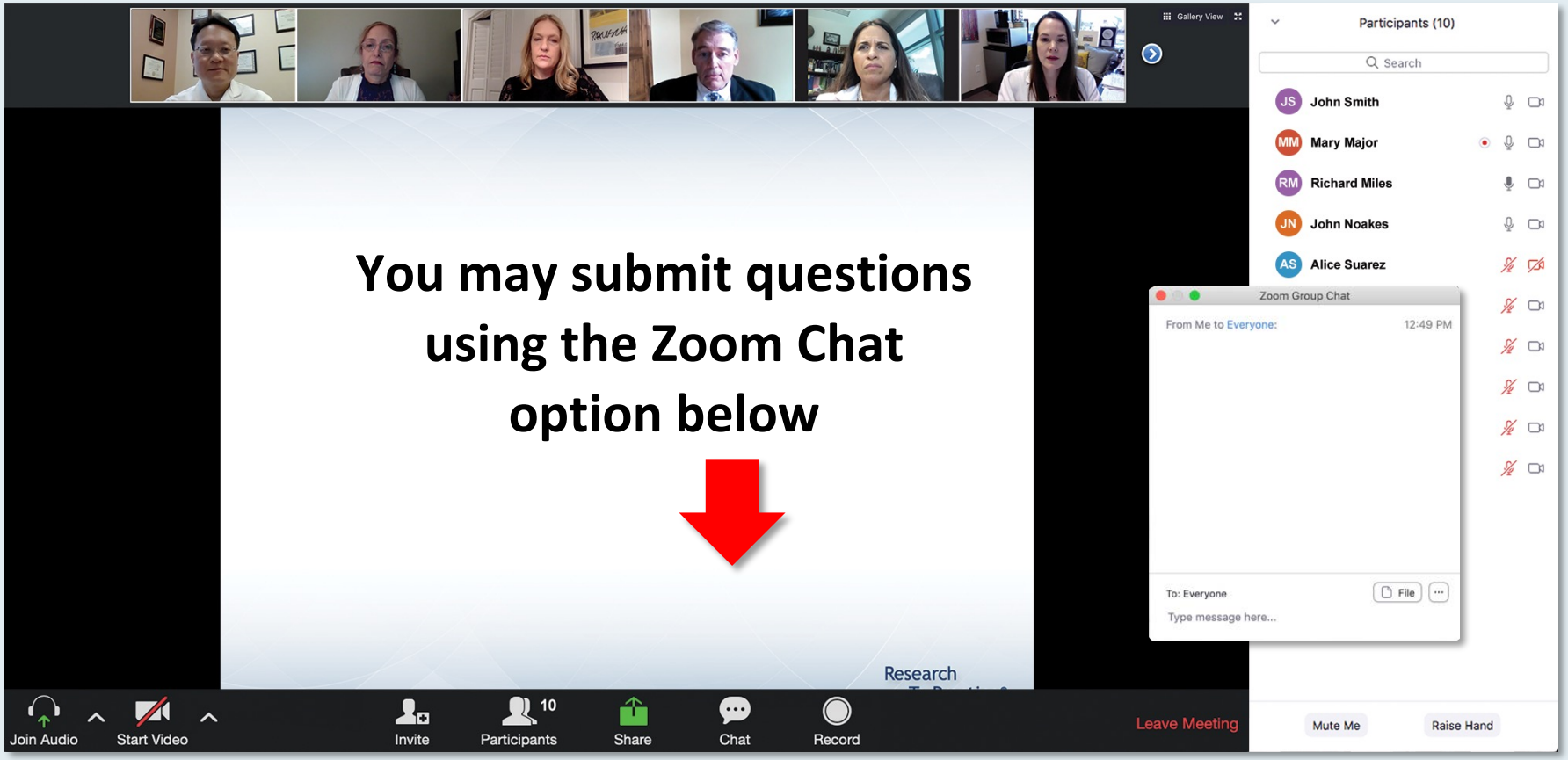


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# Optimal Integration of Novel Therapies in the Management of Early-Stage Breast Cancer

Sara M. Tolaney, MD, MPH

HARVARD MEDICAL SCHOOL

Dana-Farber Cancer Institute

# Adjuvant Approaches to Early Stage NSCLC

February 2022
RTP

**Roy S. Herbst**
Ensign Professor of Medicine
Professor of Pharmacology
Chief of Medical Oncology
Director, Thoracic Oncology Research Program
Associate Cancer Center Director for Translational Research

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Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

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## *The Great Adjuvant Debate — Exploring the Role of Novel Therapies in the Management of Localized Cancer: Melanoma*

Jeffrey S Weber MD PhD
Laura and Isaac Perlmutter Cancer Center
NYU Langone Health
New York, NY

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# Agenda

**Module 1: Snapshot of Key Trials/Interdisciplinary Impact**

**Module 2: Estimates of Benefit with Adjuvant Treatment**

**Module 3: Risks of Adjuvant Therapies**

**Module 4: Adjuvant Therapy Decision-Making**

**Module 5: Future Directions**

# Agenda

**Module 1: Snapshot of Key Trials/Interdisciplinary Impact**

**Module 2: Estimates of Benefit with Adjuvant Treatment**

**Module 3: Risks of Adjuvant Therapies**

**Module 4: Adjuvant Therapy Decision-Making**

**Module 5: Future Directions**

# Areas of Interest

**Non-Small Cell Lung Cancer**

**Breast Cancer**

**Melanoma**

**Others:**

- Urothelial bladder cancer
- Renal cell carcinoma
- Esophageal cancer
- Ovarian cancer

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# The Great Adjuvant Debate

Sir Richard Peto, FRS (Oxford, England)

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**How have recent adjuvant trials affected your approach to biomarker assessment in the adjuvant and neoadjuvant settings?**

**What are some of the common challenging clinical scenarios in your interdisciplinary meetings and tumor boards?**

**What are the advantages and disadvantages of neoadjuvant versus adjuvant immunotherapy?**

**Is there a role for a postneoadjuvant "KATHERINE" strategy in NSCLC?**

# Is there likely a future role for MRD cell-free DNA assays and adjuvant and neoadjuvant therapy?

# The Great Adjuvant Debate 1
# Non-Small Cell Lung Cancer (NSCLC)

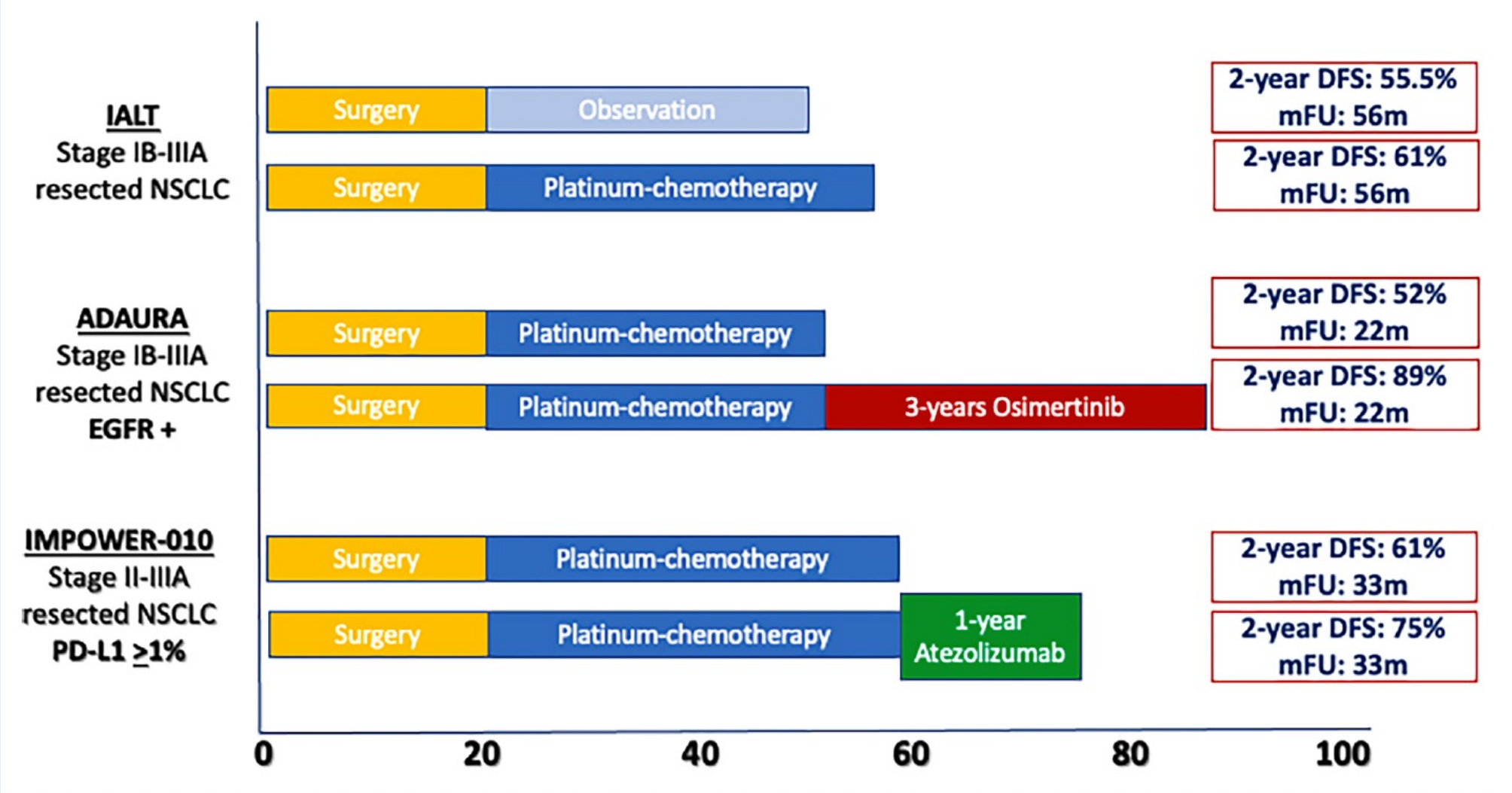
**Scenario 1 – NSCLC with EGFR Mutation**

- Key trial: ADAURA
- Key agents: Osimertinib, other EGFR tyrosine kinase inhibitors

**Scenario 2 – PD-L1-Positive NSCLC**

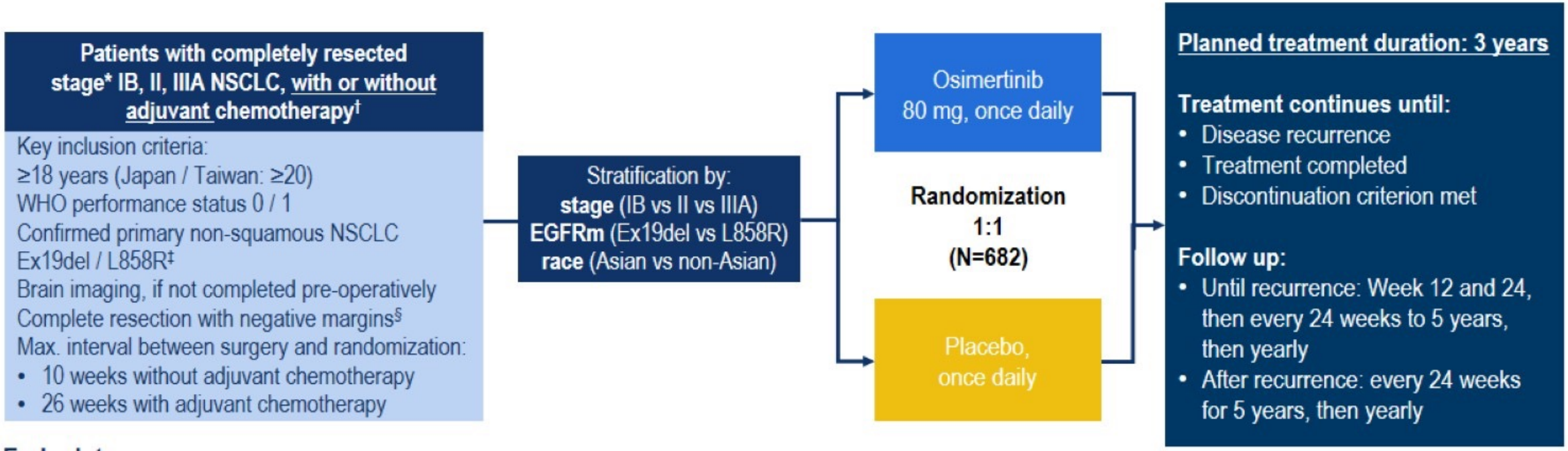
- Key trials: IMpower010, CheckMate 816, (PACIFIC)
- Key agents: Atezolizumab, nivolumab, (durvalumab)

# Adjuvant Treatment Strategies for Surgically Resected NSCLC




Passiglia F et al. *Cancer Treat Rev* 2021;1010:102308.

# ADAURA Phase III double-blind study design




## 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

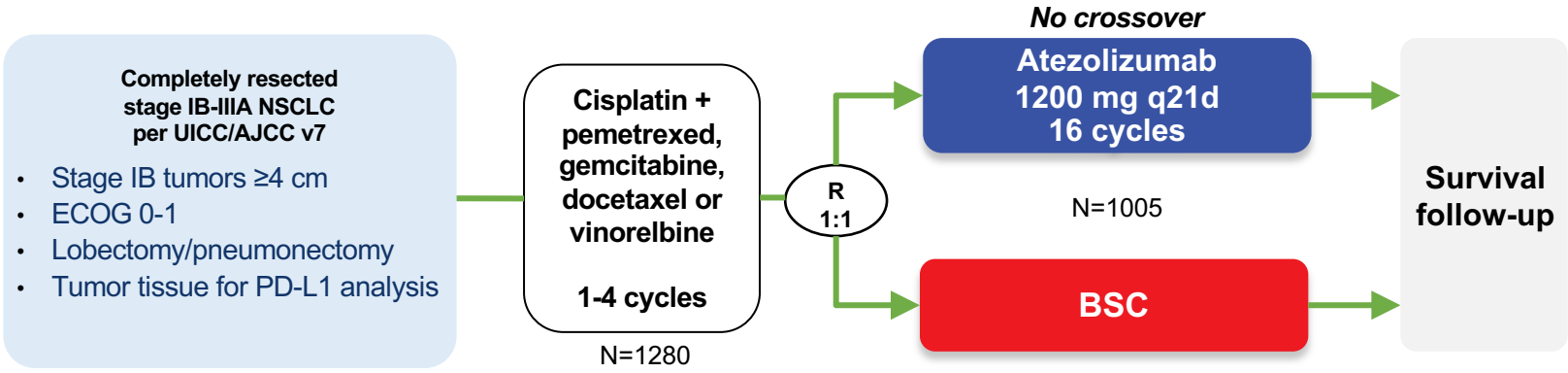
- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

DFS: Disease Free Survival, OS: Overall Survival

Wu, Herbst, et al. NEJM Sept 2020 DOI: 10.1056/NEJMoa2027071

Courtesy of Roy S Herbst, MD, PhD

# IMpower010: study design




**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

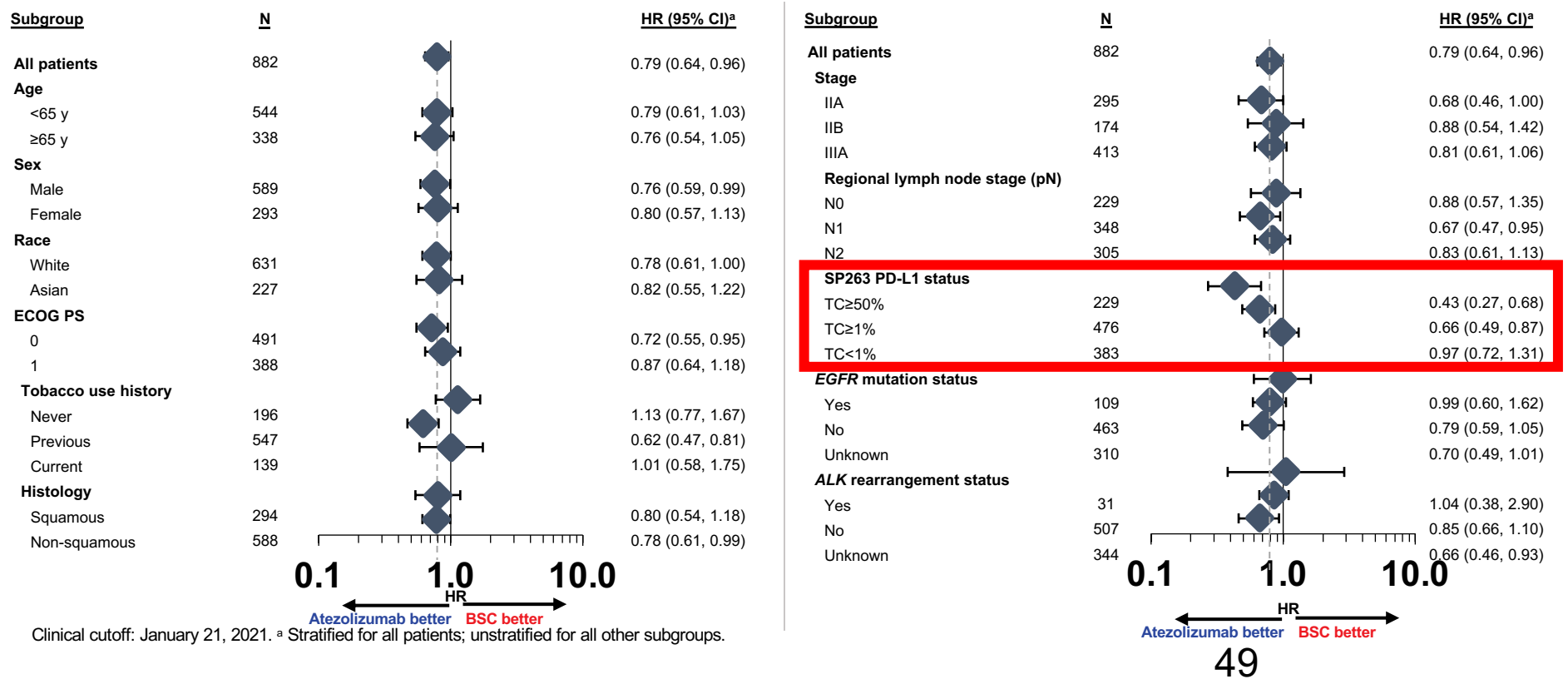
**Primary endpoints**
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

**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

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

Dr. Heather A. Wakelee ASCO 2021
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

# IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population




Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

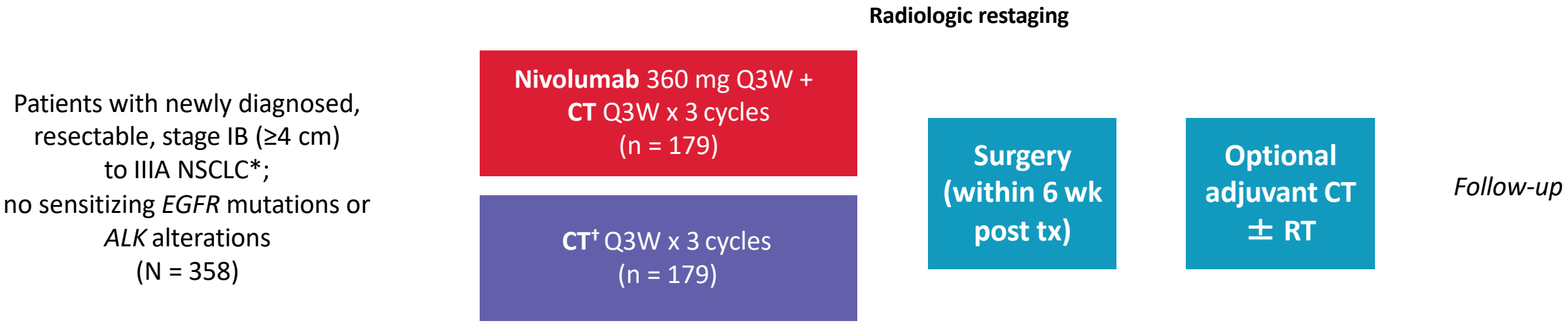


Dr. Heather A. Wakelee ASCO 2021, abstr 8500
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

Courtesy of Roy S Herbst, MD, PhD

# CheckMate 816: Neoadjuvant Nivolumab + Platinum Chemotherapy for Resectable Stage IB-IIIA NSCLC

**Randomized, open-label phase III trial (data cutoff: September 16, 2020; min f/u: 7.6 mo)**




*By TNM 7th edition. †PD-L1 28-8 pharmDx IHC assay.
Arm evaluating nivolumab (3 mg/kg for 3 cycles) + ipilimumab (1 mg/kg for 1 cycle) not shown.

- Primary endpoints: pCR (by BIPR), EFS (by BICR)
- Key secondary endpoints: OS, MPR (by BIPR), time to death or distant metastasis
- Key exploratory endpoints: ORR (by BICR), surgery feasibility, peri/postoperative surgery-related AEs

Forde. AACR 2021. Abstr CT003. Spicer. ASCO 2021. Abstr 8503. NCT02998528.

Courtesy of Roy S Herbst, MD, PhD

original reports

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

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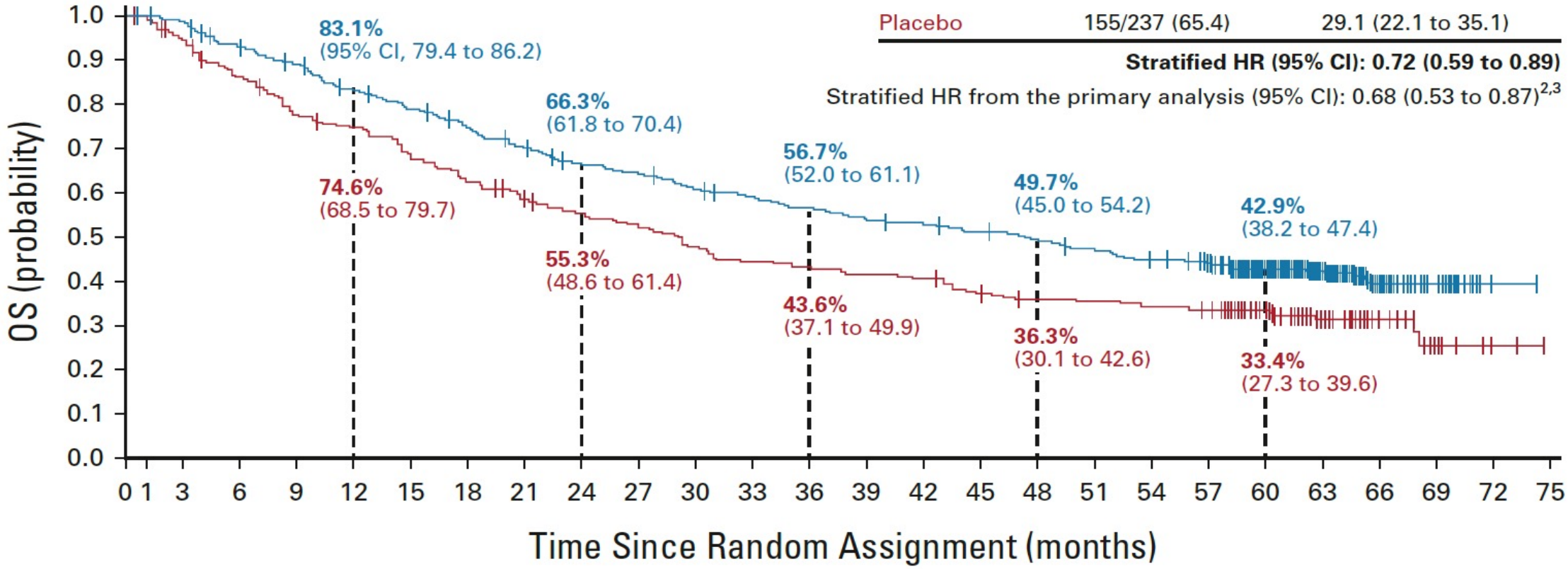
*J Clin Oncol* 2022;[Online ahead of print].

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

| Arm | No. of Events/ Total No. of Patients (%) | Median OS (95% CI), Months |
|---|---|---|
| Durvalumab | 264/476 (55.5) | 47.5 (38.1 to 52.9) |
| Placebo | 155/237 (65.4) | 29.1 (22.1 to 35.1) |

**Stratified HR (95% CI): 0.72 (0.59 to 0.89)**

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]




Spigel DR et al. *J Clin Oncol* 2022;[Online ahead of print].

# The Great Adjuvant Debate 1
# Breast Cancer

**Scenario 3 – HER2-Positive Breast Cancer**

- Key trials: KATHERINE, DESTINY-Breast03
- Key agents: Antibody-drug conjugates

**Scenario 4 – ER-positive, HER2-Negative Breast Cancer**

- Key trials: monarchE, (RxPONDER)
- Key agents: Abemaciclib, (21-gene RS assay)

**Scenario 5 – BRCA/Homologous Recombination Deficiency (HRD)**

- Key trial: OlympiA
- Key agents: Olaparib,

**Scenario 6 – PD-L1-Positive Triple-Negative Breast Cancer**

- Key trial: KEYNOTE 522
- Key agents: Pembrolizumab

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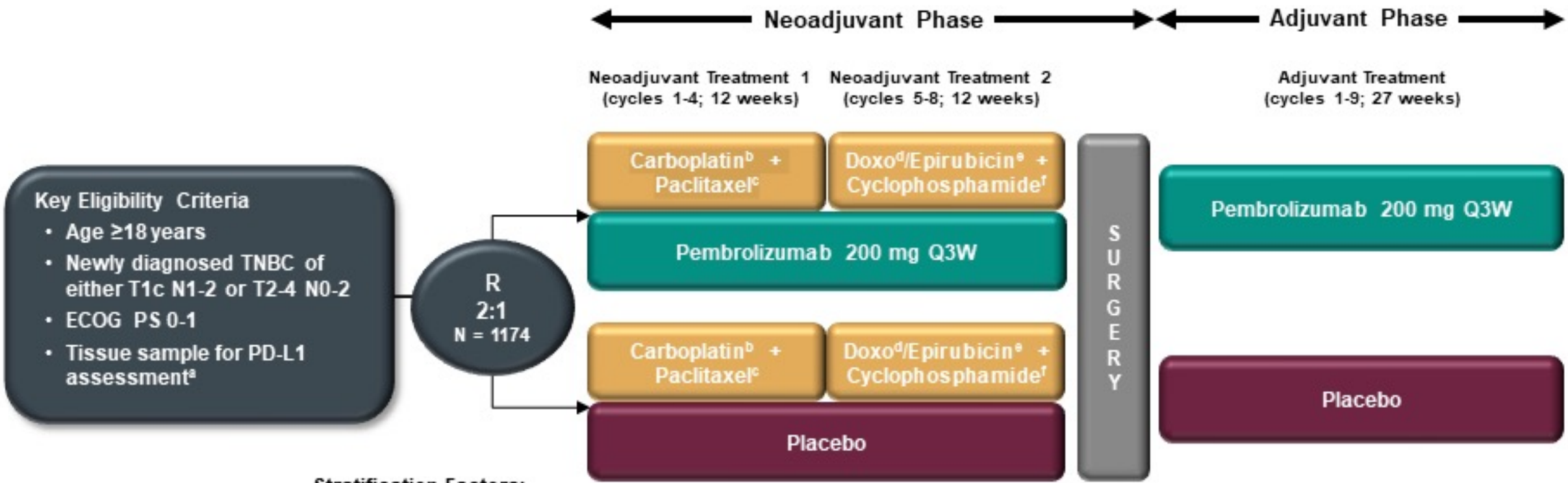
# KEYNOTE-522 Study Design (NCT03036488)




**Stratification Factors:**
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

**Neoadjuvant phase:** starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

**Adjuvant phase:** starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

Courtesy of Sara M Tolaney, MD, MPH

# OlympiA: Trial schema

- Local genetic testing or on-study central screening
  (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

**Neoadjuvant Group**
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

**≥ 6 cycles Neoadjuvant Chemotherapy** → **Surgery** → **+/- Radiotherapy**

**Adjuvant Group**
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

**Surgery** → **≥ 6 cycles Adjuvant Chemotherapy** → **+/- Radiotherapy**

**1:1 Randomization N=1836**

**Olaparib** 300 mg twice daily for 1 year

**Placebo** twice daily for 1 year

**Primary End Point**
- Invasive disease-free survival (IDFS) by STEEP system[1]

**Secondary End Points**
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

**Stratification Factors**
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

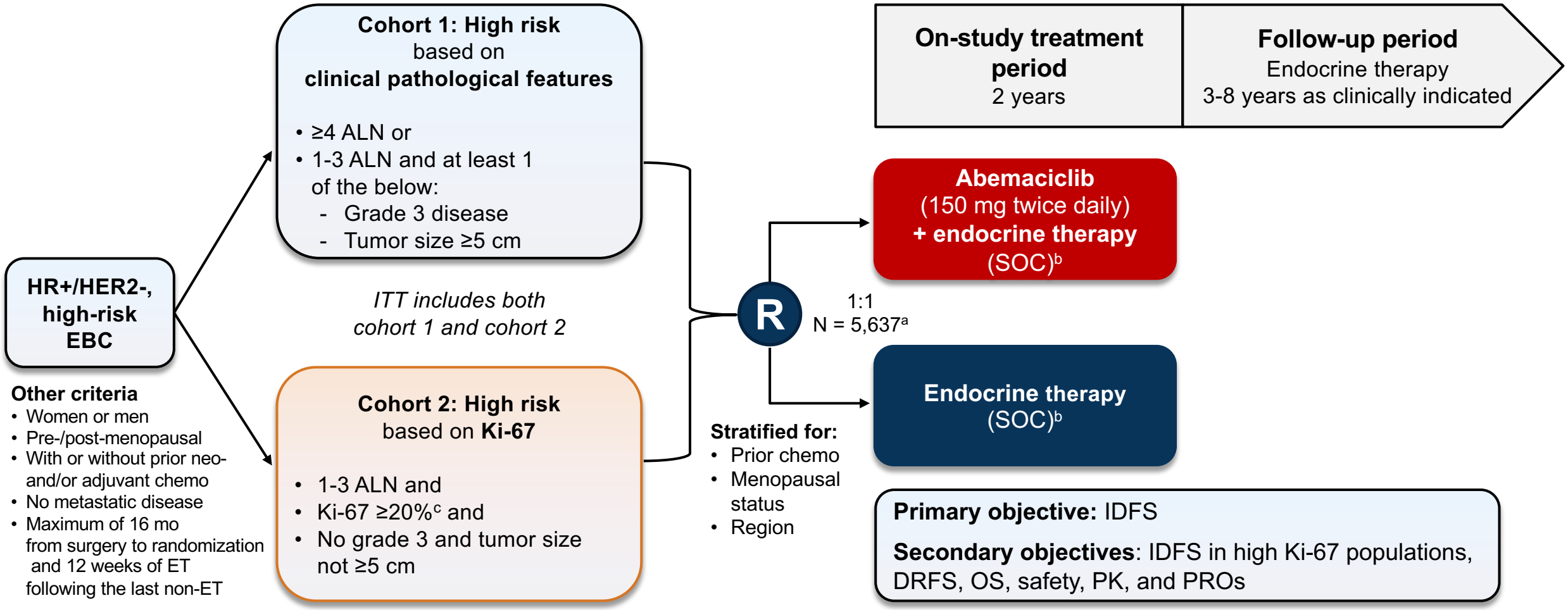
**Concurrent Adjuvant Therapy**
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Sara M Tolaney, MD, MPH

# monarchE Study Design




[a] Recruitment from July 2017 to August 2019. [b] Endocrine therapy of physician's choice (eg, aromatase inhibitors, tamoxifen, LHRH agonist). [c] Ki-67 expression centrally assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry.

1. O'Shaughnessy et al. ESMO 2021. Abstract VP8-2021. 2. Harbeck N et al. Ann Oncol. 2021;S0923-7534(21)04494-X.

Courtesy of Sara M Tolaney, MD, MPH

# The Great Adjuvant Debate 1
# Melanoma

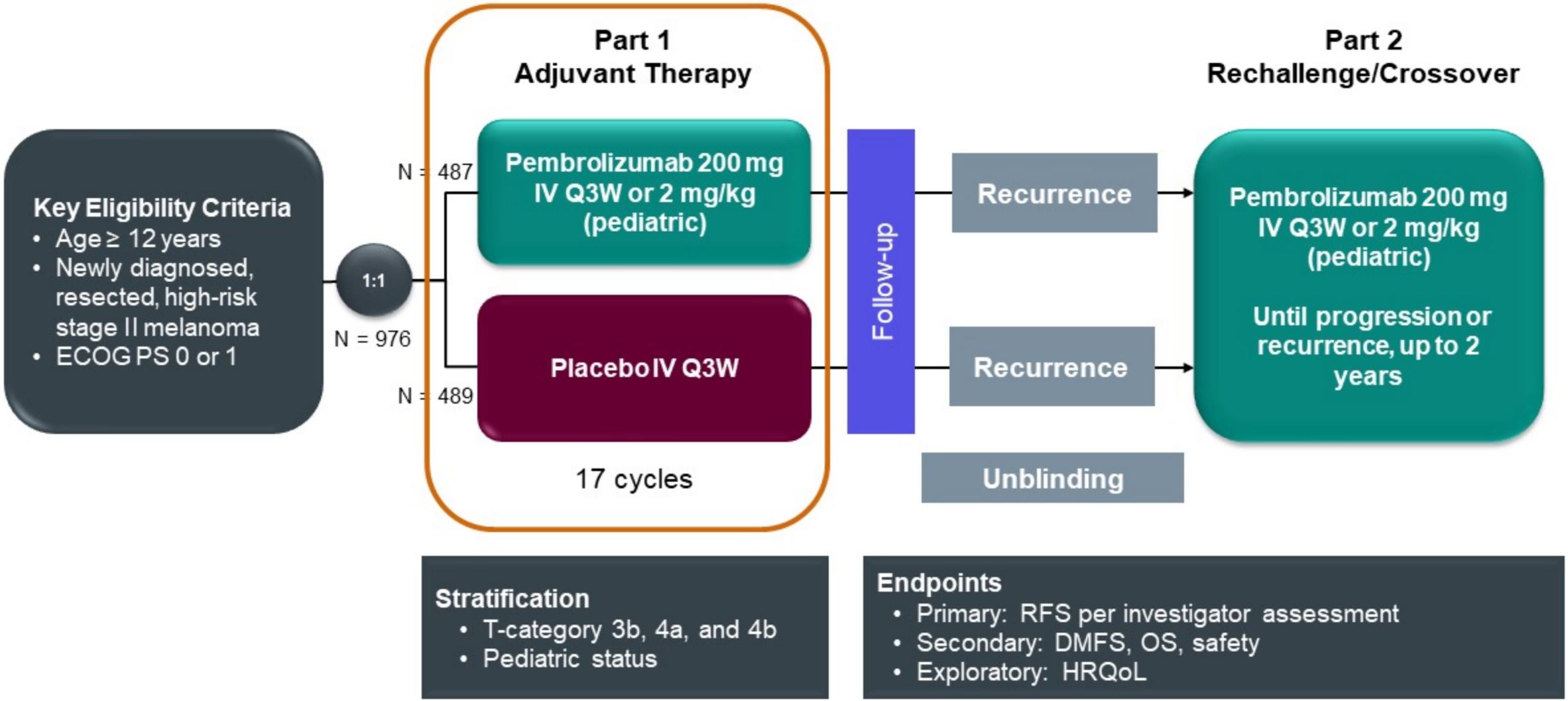
## Scenario 7 – Melanoma with BRAF Mutation

- Key trials: COMBI-AD, KEYNOTE-716, CheckMate 238, EORTC-1325/KEYNOTE-54
- Key agents: Anti-BRAF-MEK inhibition (dabrafenib/trametinib); IO (pembrolizumab, nivolumab)

## Scenario 8 – BRAF Wild-Type Melanoma

- KEYNOTE-716, CheckMate 238, EORTC-1325/KEYNOTE-54
- Key agents: Pembrolizumab, nivolumab

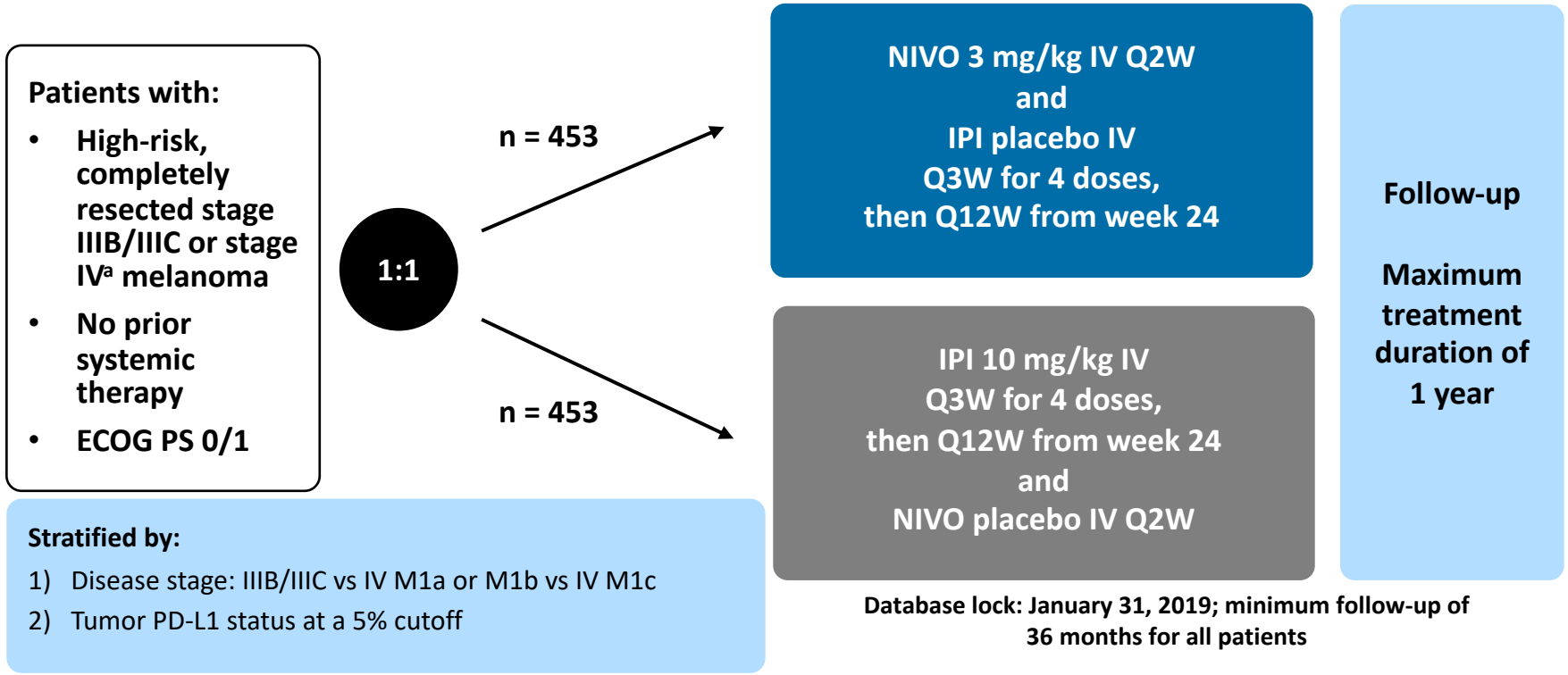
# KEYNOTE-716 Study Design
## (NCT03553836)




Courtesy of Jeffrey S Weber, MD, PhD

HRQoL, health related quality of life; OS, overall survival; Q3W, every 3 weeks; RFS, time from randomization to recurrence of melanoma at any site (skin, regional lymph nodes or distant) or death from any cause, whichever occurred first.

# Adjuvant CheckMate 238 Study: Nivolumab vs Ipilimumab

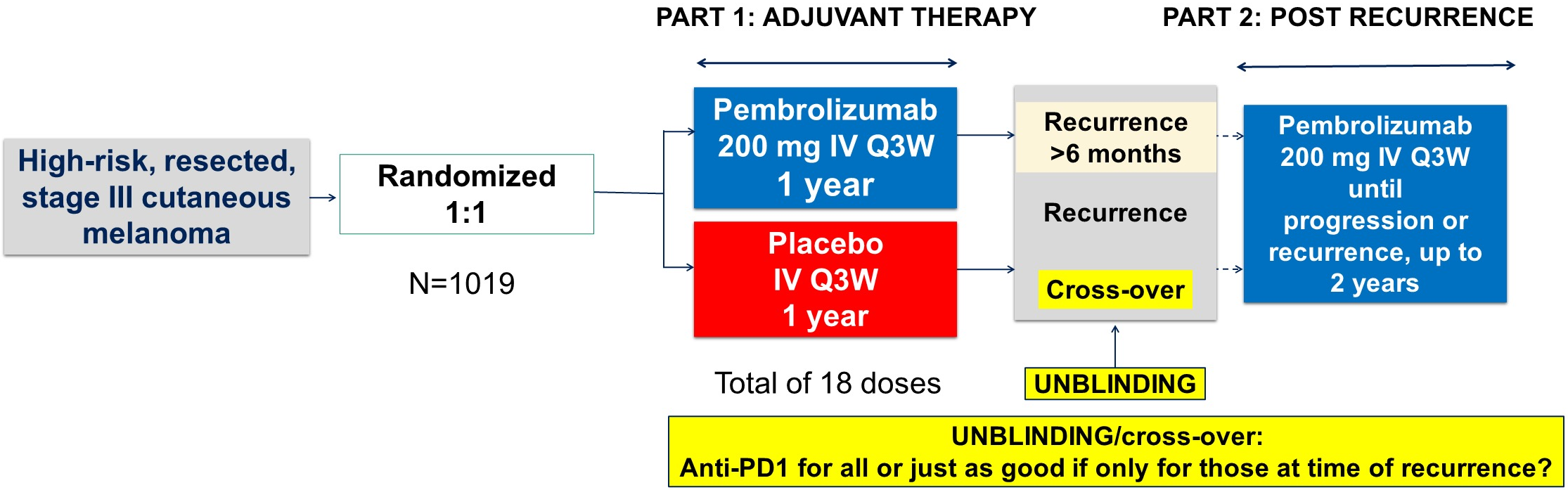



NCT02388906.[a]Per American Joint Committee on Cancer (AJCC) Cancer Staging Manual, seventh edition.

Weber J et al. *N Engl J Med.* 2017;377(19):1824-1835; SMR 2021

Courtesy of Jeffrey S Weber, MD, PhD

# EORTC 1325/KEYNOTE-54 Study Design




**Stratification factors:**

✓**AJCC-7 Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes

✓**Region**: North America, European countries, Australia/New Zealand, other countries

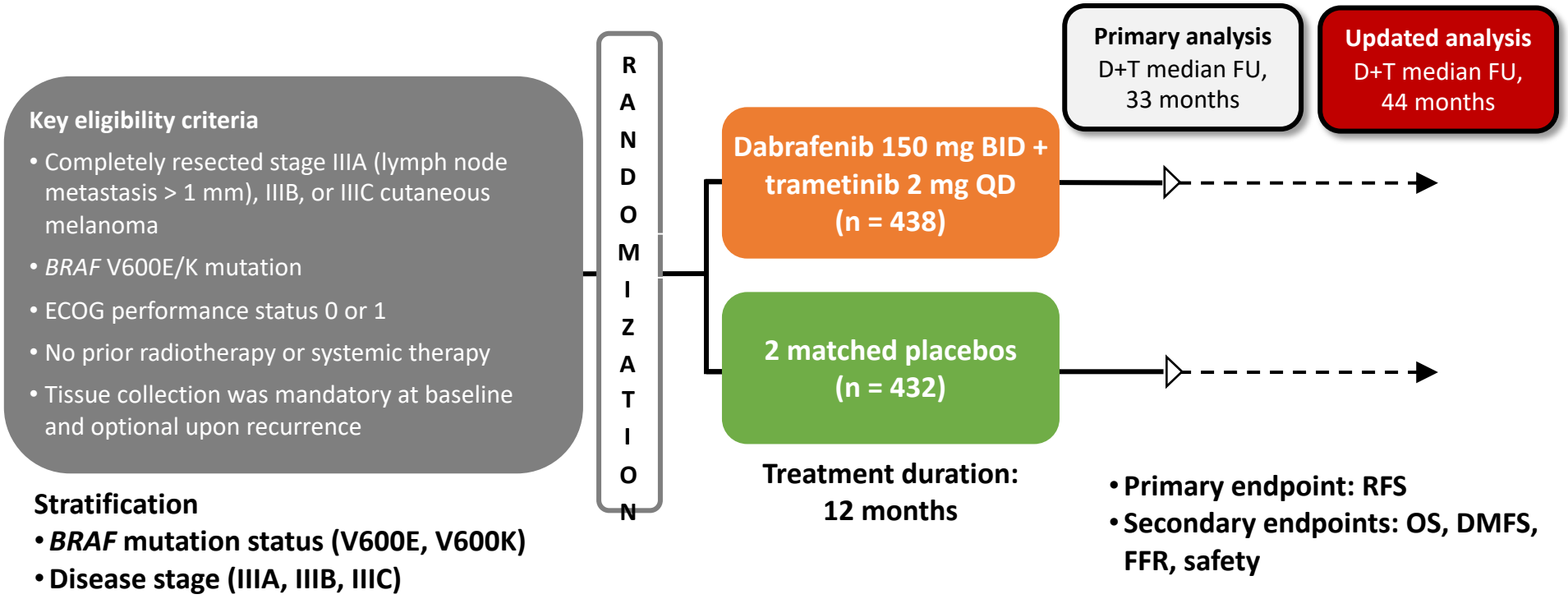
**Primary Endpoints:**

- **RFS (per investigator) in overall ITT population,** and **in patients with PD-L1-positive tumors**

**Secondary Endpoints:**

- **DMFS and OS** in these 2 populations; **Safety, Health-related quality of life**

# COMBI-AD Adjuvant Study Design— Extended Follow-up Analysis




BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

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**Long GV, et al. *N Engl J Med*. 2017;377:1813-1823, Hauschild, A et al ASCO 2020, Dummer, R et al NEJM 2020**

Courtesy of Jeffrey S Weber, MD, PhD

# Agenda

Module 1: Snapshot of Key Trials/Interdisciplinary Impact

**Module 2: Estimates of Benefit with Adjuvant Treatment**

Module 3: Risks of Adjuvant Therapies

Module 4: Adjuvant Therapy Decision-Making

Module 5: Future Directions

**How would you describe to an interested patient the potential benefits of adjuvant therapy for the key scenarios being discussed today?**

**How would you respond to a patient interested in quantitative estimates of benefit?**

**How should relative and absolute benefits be explained?**

**How do you assess the value of disease-free compared to overall survival in adjuvant trials?**

# Agenda

**Module 1: Snapshot of Key Trials/Interdisciplinary Impact**

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**Module 5: Future Directions**

**How would you describe to an interested patient the risks of adjuvant immune checkpoint inhibitors and other targeted adjuvant therapies (ie, CDK4/6, BRAF, PARPi, EGFR TKIs)?**

# Agenda

**Module 1: Snapshot of Key Trials/Interdisciplinary Impact**

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**Putting aside cost and access issues, for which patients do you strongly recommend adjuvant treatment in these scenarios, and in which scenarios do you present treatment as an option but usually not encourage its use?**

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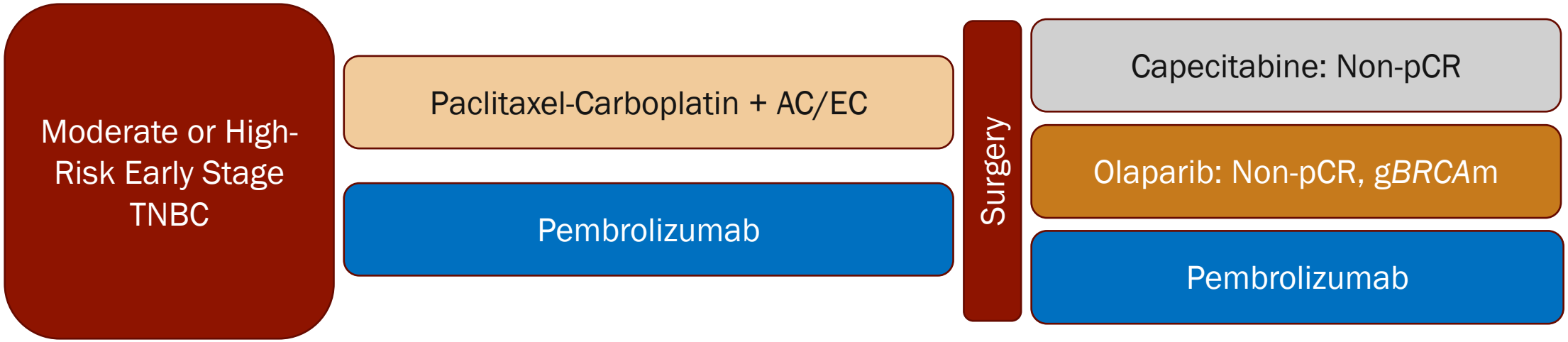
# SHOULD PARP + CHECKPOINT INHIBITION BE GIVEN TO PATIENTS WITH TNBC AND RESIDUAL DISEASE AFTER PREOPERATIVE CHECKPOINT INHIBITION?

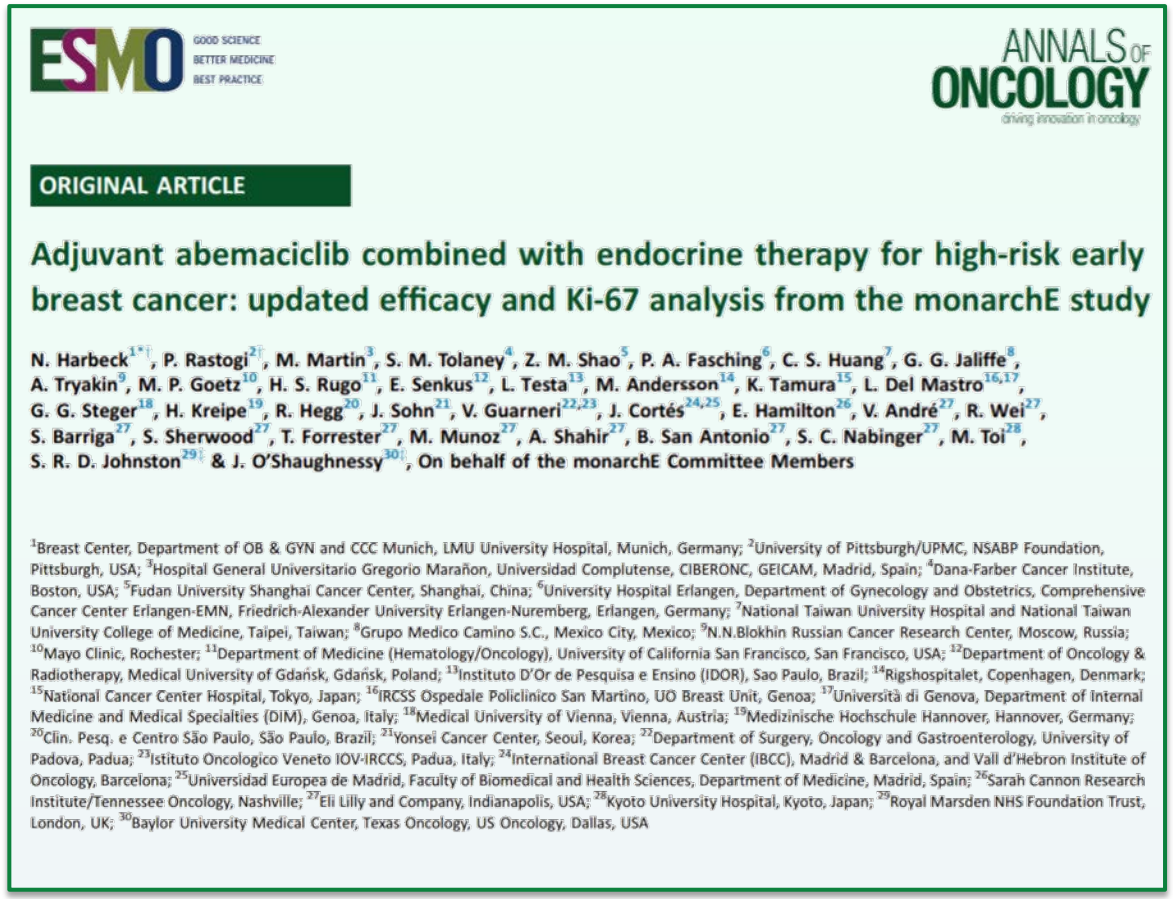
Courtesy of Sara M Tolaney, MD, MPH

# How Do We Integrate Adjuvant Therapy in the Management of Early Stage TNBC?




Courtesy of Sara M Tolaney, MD, MPH

# Adjuvant Abemaciclib for High-Risk, HR+/HER2-, Early Breast Cancer



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

**Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study**

N. Harbeck[1*†], P. Rastogi[2†], M. Martin[3], S. M. Tolaney[4], Z. M. Shao[5], P. A. Fasching[6], C. S. Huang[7], G. G. Jaliffe[8], A. Tryakin[9], M. P. Goetz[10], H. S. Rugo[11], E. Senkus[12], L. Testa[13], M. Andersson[14], K. Tamura[15], L. Del Mastro[16,17], G. G. Steger[18], H. Kreipe[19], R. Hegg[20], J. Sohn[21], V. Guarneri[22,23], J. Cortés[24,25], E. Hamilton[26], V. André[27], R. Wei[27], S. Barriga[27], S. Sherwood[27], T. Forrester[27], M. Munoz[27], A. Shahir[27], B. San Antonio[27], S. C. Nabinger[27], M. Toi[28], S. R. D. Johnston[29‡] & J. O'Shaughnessy[30‡], On behalf of the monarchE Committee Members

[1]Breast Center, Department of OB & GYN and CCC Munich, LMU University Hospital, Munich, Germany; [2]University of Pittsburgh/UPMC, NSABP Foundation, Pittsburgh, USA; [3]Hospital General Universitario Gregorio Marañon, Universidad Complutense, CIBERONC, GEICAM, Madrid, Spain; [4]Dana-Farber Cancer Institute, Boston, USA; [5]Fudan University Shanghai Cancer Center, Shanghai, China; [6]University Hospital Erlangen, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [7]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [8]Grupo Medico Camino S.C., Mexico City, Mexico; [9]N.N.Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Mayo Clinic, Rochester; [11]Department of Medicine (Hematology/Oncology), University of California San Francisco, San Francisco, USA; [12]Department of Oncology & Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland; [13]Instituto D'Or de Pesquisa e Ensino (IDOR), Sao Paulo, Brazil; [14]Rigshospitalet, Copenhagen, Denmark; [15]National Cancer Center Hospital, Tokyo, Japan; [16]IRCSS Ospedale Policlinico San Martino, UO Breast Unit, Genoa; [17]Università di Genova, Department of Internal Medicine and Medical Specialties (DIM), Genoa, Italy; [18]Medical University of Vienna, Vienna, Austria; [19]Medizinische Hochschule Hannover, Hannover, Germany; [20]Clin. Pesq. e Centro São Paulo, São Paulo, Brazil; [21]Yonsei Cancer Center, Seoul, Korea; [22]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua; [23]Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; [24]International Breast Cancer Center (IBCC), Madrid & Barcelona, and Vall d'Hebron Institute of Oncology, Barcelona; [25]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [26]Sarah Cannon Research Institute/Tennessee Oncology, Nashville; [27]Eli Lilly and Company, Indianapolis, USA; [28]Kyoto University Hospital, Kyoto, Japan; [29]Royal Marsden NHS Foundation Trust, London, UK; [30]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, USA


On October 12, 2021, the FDA approved abemaciclib for adjuvant treatment of adult patients with HR+/HER2-, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test

The FDA also approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay as a companion diagnostic for selecting patients for this indication

1. Harbeck N et al. *Ann Oncol*. 2021;S0923-7534(21)04494-X.
2. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

Courtesy of Sara M Tolaney, MD, MPH

# FDA Benefit-Risk Assessment for Abemaciclib Approval

| Dimension | Evidence and Uncertainties | Conclusion and Reasons |
|---|---|---|
| Analysis of condition | Approximately 70% of breast cancers are HR+, HER2–<br>Early-stage, HR+, HER2– breast cancer is potentially curable; however, approximately 30% of patients relapse with local and metastatic disease and metastatic disease is incurable<br>High-risk features include size, grade, and number of involved lymph nodes, as well as Ki-67. | High-risk, early-stage, HR+, HER2– breast cancer is a serious and life-threatening condition. |
| Current treatment options | Standard-of-care treatment of early-stage, HR+, HER2– breast cancer includes surgery ± radiation therapy ± adjuvant chemotherapy, followed by at least 5 years of adjuvant ET (aromatase inhibitor or tamoxifen, with or without GnRH agonist). | There is an unmet medical need to improve upon long-term outcomes such as IDFS and OS. |
| Benefit | Statistically significant improvement in IDFS for patients with HR+, HER2–, node-positive EBC at high risk of recurrence (cohort 1) with Ki-67 score ≥ 20% at the final IDFS analysis with an HR of 0.643 (95% CI, 0.475 to 0.872; $P = .0042$).<br>In the ITT population, abemaciclib plus ET demonstrated a statistically significant improvement in IDFS; however, the immature OS analysis showed a nonsignificant HR > 1 showing a potential detriment with abemaciclib plus ET in the ITT population.<br>OS data for the indicated population remain immature and are not statistically significant; however, the point estimate numerically favors the abemaciclib plus ET arm (HR = 0.767; 95% CI, 0.511 to 1.512) and do not indicate a detrimental effect of treatment with adjuvant abemaciclib plus ET. | Although the benefit:risk profile was favorable for the indicated subpopulation, given the immaturity and potential OS detriment, it was not favorable for the ITT population. |
| Risk and risk management | No new safety signals were observed compared with the known safety profiles of abemaciclib in combination with ET. However, increased rates of grade 3-4 AEs, serious AEs, and discontinuations were seen in the abemaciclib arm. | The safety profile of adjuvant abemaciclib is acceptable for the indicated patient population and the package insert adequately informs prescribers regarding safe usage. |

Courtesy of Sara M Tolaney, MD, MPH

Royce M et al, JCO 2022

# Agenda

**Module 1: Snapshot of Key Trials/Interdisciplinary Impact**

**Module 2: Estimates of Benefit with Adjuvant Treatment**

**Module 3: Risks of Adjuvant Therapies**

**Module 4: Adjuvant Therapy Decision-Making**

**Module 5: Future Directions**

**What are some of the current ongoing clinical trials and trial concepts in these areas that you think are most likely to have important clinical sequelae?**

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# Trastuzumab Deruxtecan Significantly Improved Both Progression-Free and Overall Survival in DESTINTY-Breast04 Trial for Patients with HER2-Low Metastatic Breast Cancer

## Press Release: February 21, 2022

"Positive high-level results from the pivotal DESTINY-Breast04 Phase III trial showed fam-trastuzumab deruxtecan-nxki demonstrated a statistically significant and clinically meaningful improvement in both progression-free survival (PFS) and overall survival (OS) in patients with HER2-low unresectable and/or metastatic breast cancer regardless of hormone receptor (HR) status versus physician's choice of chemotherapy.

Up to 55% of all patients with breast cancer have tumors with an HER2 IHC score of 1+, or 2+ in combination with a negative ISH test, a level of HER2 expression not currently eligible for HER2-targeted therapy. HER2-low expression occurs in both HR-positive and HR-negative disease.

Currently, chemotherapy remains the only treatment option both for patients with HR-positive tumors following progression on endocrine (hormone) therapy, and for those who are HR-negative."

https://finance.yahoo.com/news/enhertu-fam-trastuzumab-deruxtecan-nxki-161500917.html

RTP RESEARCH TO PRACTICE

# ONGOING PHASE 3 ADJUVANT TRIALS OF CHECKPOINT INHIBITION

## SWOG S1418/NRG BR006
## Ph 3 Pembrolizumab for Residual TNBC post NAC

TNBC with >/=1 cm residual invasive breast cancer or any + LN after neoadjuvant chemotherapy N=1000

1:1

- Pembrolizumab 200 mg IV q 3 weeks x 1y
- Observation

- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

PIs: Pusztai/Mamounas

## A-BRAVE
## Ph 3 Adjuvant Avelumab vs Observation for TNBC

EUDRACT: 2016-000189-45
NCT02926196

A-BRAVE-TRIAL

Sponsor: University of Padova
PI: Pierfranco Conte

HIGH RISK PRIMARY TNBC PTS WHO COMPLETED TREATMENT WITH CURATIVE INTENT INCLUDING SURGERY, CHEMOTHERAPY AND RADIOTHERAPY (if indicated)

Stratum A: Adjuvant
Stratum B: Post-neoadjuvant

R

- Avelumab for 1 year
- Observation

Randomization 1:1 balanced for adjuvant and post-neoadjuvant patients.

**Co-primary endpoints**: 1. DFS in all-comers;
2. DFS in Stratum B post-neoadjuvant
**Secondary endpoints:** OS, DFS in PD-L1+, Safety, Biomarkers
**Sample size = 474 patients**

## THESE STUDIES DO NOT ADDRESS QUESTION OF CONTINUATION OF ADJUVANT PEMBRO AFTER PREOP PEMBRO IN PTS WITH RESIDUAL DISEASE

Courtesy of Sara M Tolaney, MD, MPH

# Next Steps: Osimertinib in Non-Small Cell Lung Cancer

- NeoAdaura (Neoadjuvant)
- Laura (Stage III)
- Combo studies
- Other Agents



1. Herbst et al. J Clin Oncol.2020;38:18_suppl.LBA5.
ADAURA data cut-off: 17 January, 2020

Courtesy of Roy S Herbst, MD, PhD

# NSCLC Phase III adjuvant trials:

**Primary endpoint(s)**

| Trial | Inclusion criteria | Treatment arms | Primary endpoint(s) |
|---|---|---|---|
| **IMpower010** | Resected stage IB (≥4 cm)-IIIA<br>≤ 4 cycles Adj CT<br>N=1280 | Atezolizumab (1 yr) *vs*<br>BSC | DFS |
| **ANVIL** | Resected stage IB (≥4 cm)-IIIA<br>Adj CT optional<br>N=903 | Nivolumab (1 yr) *vs*<br>Observation | DFS and OS |
| **PEARLS/ KEYNOTE-091** | Resected stage IB (≥4 cm)-IIIA<br>Adj CT optional<br>N=1177 | Pembrolizumab (1 yr) *vs*<br>placebo | DFS |
| **BR31** | Resected stage IB (≥4 cm)-IIIA<br>Adj CT optional<br>N=1360 | Durvalumab (1 yr) *vs*<br>placebo | DFS |
| **ALCHEMIST Chemo-IO** | Resected stage IB (≥4 cm)-IIIA<br>No prior CT (adj or neoadj)<br>N=1263 | CT+pembrolizumab (4C) followed by pembro (1 yr)<br>vs<br>CT (4C) followed by pembro (1 yr) *vs*<br>CT (4C) followed by observation | DFS and OS |
| **MERMAID-1** | Resected stage II-IIIA<br>No prior CT<br>N=332 | Durvalumab+CT *vs*<br>CT+placebo | DFS in MRD+ |



Courtesy of Roy S Herbst, MD, PhD

# NSCLC Neoadjuvant Phase 3 Clinical Trials

| Study* | CheckMate 816[1] CT + nivolumab | KEYNOTE-617[2] CT+ pembrolizumab | IMpower030[3] CT + Atezolizumab | AEGEAN[4] CT + Durvalumab | CheckMate 77T[5] |
|---|---|---|---|---|---|
| **Stage** | IB–IIIA | II–IIIB (T3-4N2) | II–IIIB (cT3N2) | IIA–IIIB | IIA–IIIB (T3N2) |
| **Patients, No.** | 350 | 786 | 374 | 300 | 452 |
| **Study arms** | CT + nivolumab (360 mg) × 3 cycles → S vs. CT × 3 cycles → S | CT + pembrolizumab (200 mg)/placebo × 4 cycles → S →pem/placebo × 13 cycles | CT + atezolizumab (1200 mg)/placebo × 4 cycles → S → atezo/placebo × 16 cycles | CT + durvalumab (1500 mg)/placebo × 3 cycles → S → durvalumab/placebo × 12 cycles | CT + nivolumab (360 mg)/placebo × 3 cycles → S → nivolumab/placebo |
| **Key inclusion criteria** | ▪ Early stage IB-IIIA, operable NSCLC, confirmed in tissue<br>▪ Lung function capacity tolerating the surgery<br>▪ Available tissue of primary tumor | ▪ Confirmed resectable Stage II, IIIA, or IIB (N2) NSCLC<br>▪ Eligible for protocol therapy, including surgery<br>▪ Tissue sample available | ▪ Confirmed resectable Stage II, IIIA, IIIB (T3N2) NSCLC<br>▪ Eligible for R0 resection<br>▪ Measurable disease by RECIST v1.1<br>▪ Negative HIV, HBV, HCV | ▪ Confirmed resectable Stage II, IIIA, IIIB (N2) NSCLC<br>▪ ≥1 lesion, no prior irradiation, qualifying as a RECIST 1.1 target lesion<br>▪ No prior IO | ▪ Confirmed resectable Stage II, IIIA, IIIB (T3N2) NSCLC<br>▪ ≥1 lesion, no prior irradiation, qualifying as a RECIST 1.1 target lesion<br>▪ No prior IO |
| **Primary Endpoints** | ▪ EFS, pCR, MPR | ▪ EFS, OS | ▪ EFS | ▪ MPR | ▪ EFS |
| **ORR, %** | ▪ 31 v 24%<br>▪ pCR 24 v 2%<br>▪ MPR 36.9 v 8.9% | ▪ N/A | ▪ N/A | ▪ N/A | ▪ N/A |
| **Median EFS, mo** | ▪ EFS endpoint met | ▪ N/A | ▪ N/A | ▪ N/A | ▪ N/A |
| **Median OS, mo** | ▪ N/A | ▪ N/A | ▪ N/A | ▪ N/A | ▪ N/A |

**No head-to-head studies have been conducted and direct comparisons cannot be made between these studies**

Courtesy of Roy S Herbst, MD, PhD

1. ClinicalTrials.gov. NCT02998528. Accessed April 8th, 2021. 2. ClinicalTrials.gov. NCT03425643. Accessed April 8th, 2021. 3. ClinicalTrials.gov. NCT03456063. Accessed April 8th, 2021. 4. ClinicalTrials.gov. NCT03800134. Accessed April 8th, 2021. 5. ClinicalTrials.gov. NCT04351555. Accessed April 8th, 2021. 6. Cascone T et al J Clin Oncol 2020 TPS 9076

# Background: Tiragolumab, an Anti-TIGIT Antibody

- Tiragolumab is a fully human IgG1/kappa anti-TIGIT monoclonal antibody with an intact Fc region that blocks the binding of TIGIT to its receptor PVR

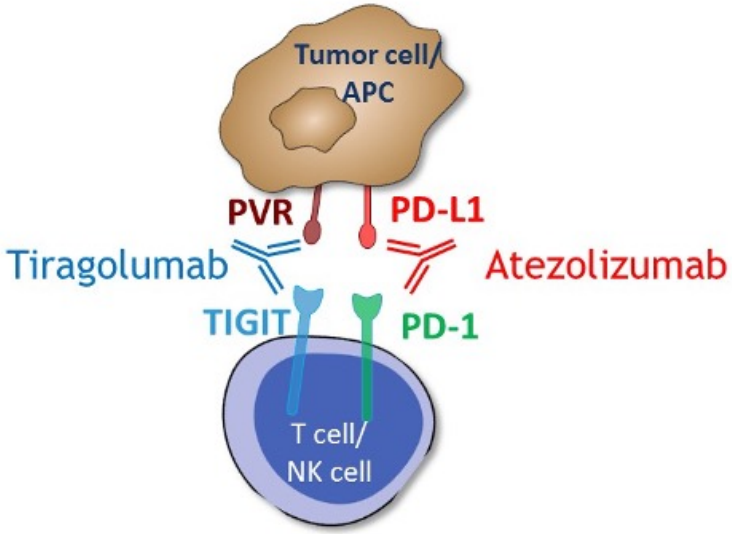
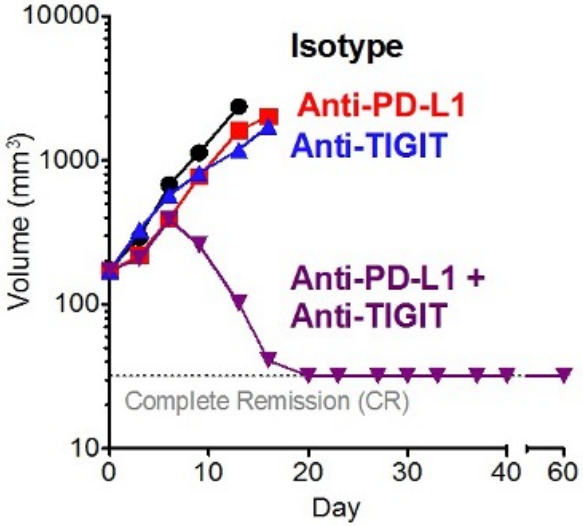



Figure adapted from Manieri et al. *Trends Immunology* 2017

- In preclinical models, combination treatment with anti-TIGIT and anti-PD-L1 antibodies synergistically improves tumor control and prolongs survival in mice[1]



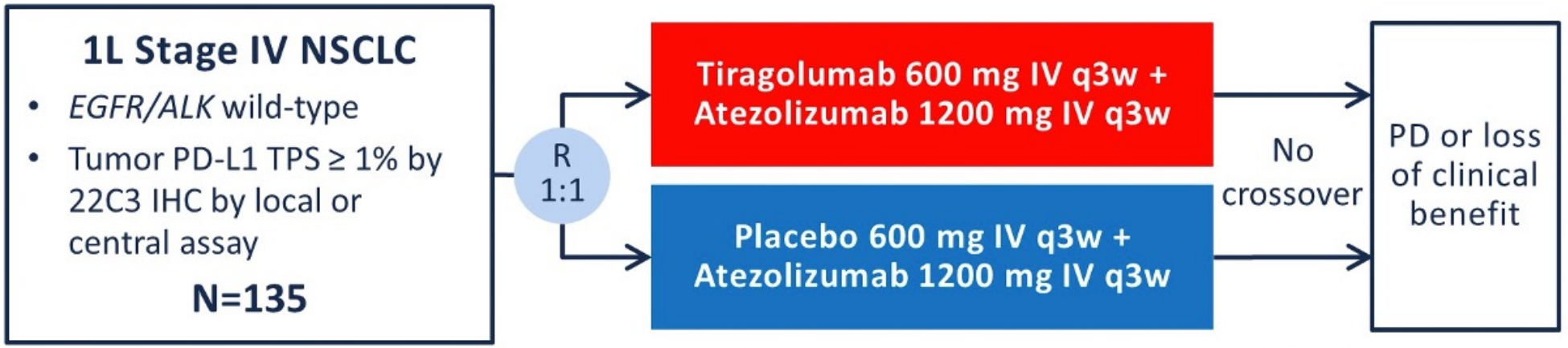

[1] Johnston et al. *Cancer Cell* 2014





Rodriguez-Abreu D et al. ASCO 2020;Abstract 9503.

# CITYSCAPE Study Design




**Stratification Factors:**

- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety**, DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

DOR = duration of response; IHC = immunohistochemistry; ORR = confirmed overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival ; q3w = every 3 weeks; R = randomized; TPS = tumor proportion score

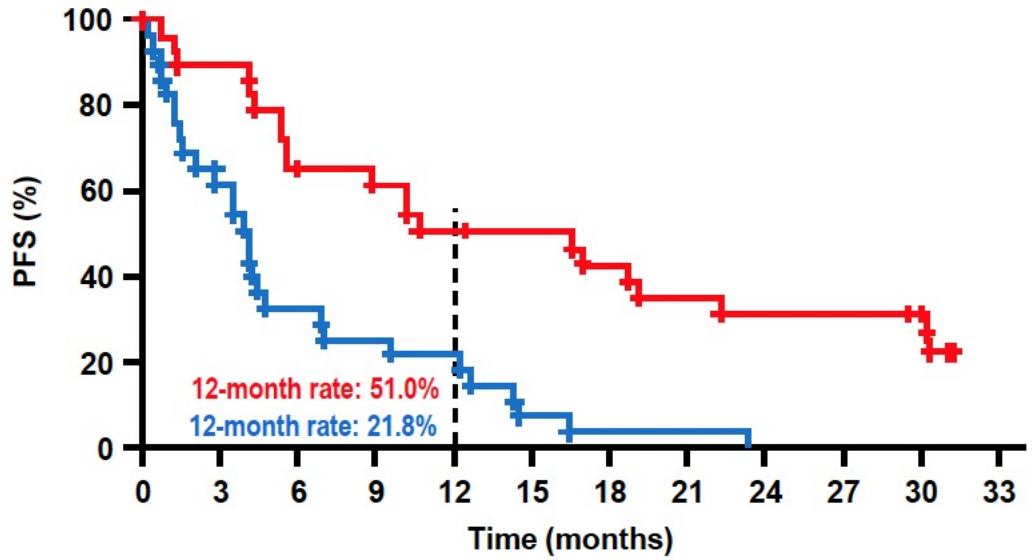


Rodriguez-Abreu D et al. ASCO 2020;Abstract 9503.

# CITYSCAPE: PFS by PD-L1 Subgroup

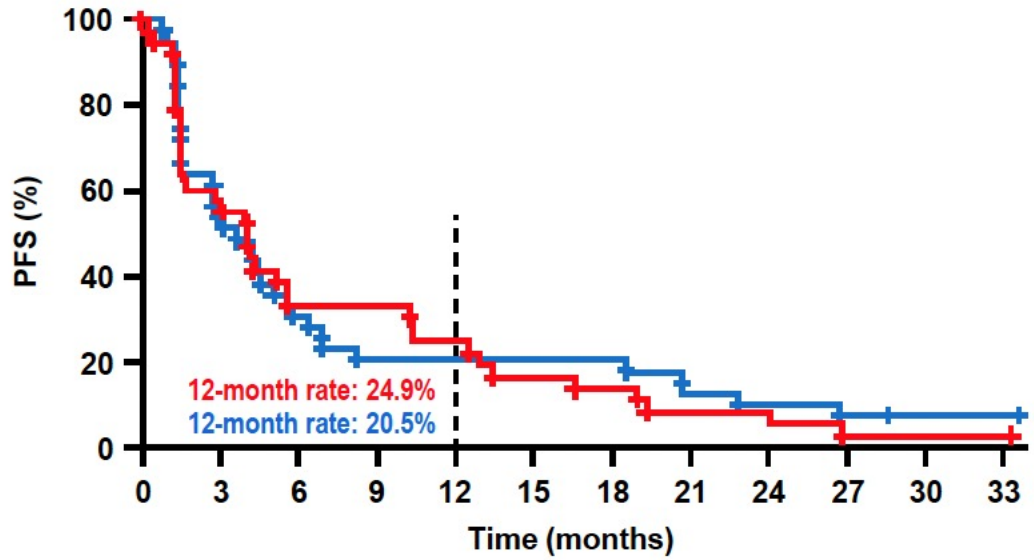
## PD-L1 TPS ≥50% (n=58)

| | Events n (%) | Median PFS, months (95% CI) | PFS HR (95% CI) | ORR, % | Median DOR, months (95% CI) |
|---|---|---|---|---|---|
| Tira + atezo | 21 (72.4) | 16.6 (5.5–22.3) | 0.29* (0.15–0.53) | 69.0 | 15.7 (9.1–NE) |
| Placebo + atezo | 28 (96.6) | 4.1 (2.1–6.8) | | 24.1 | 8.2 (5.6–10.4) |




## PD-L1 TPS 1–49% (n=77)

| | Events n (%) | Median PFS, months (95% CI) | PFS HR (95% CI) | ORR, % | Median DOR, months (95% CI) |
|---|---|---|---|---|---|
| Tira + atezo | 36 (94.7) | 4.0 (1.6–5.6) | 1.07* (0.67–1.71) | 15.8 | 17.8 (8.3–24.2) |
| Placebo + atezo | 36 (92.3) | 3.6 (1.4–5.5) | | 17.9 | 18.8 (15.9–22.8) |



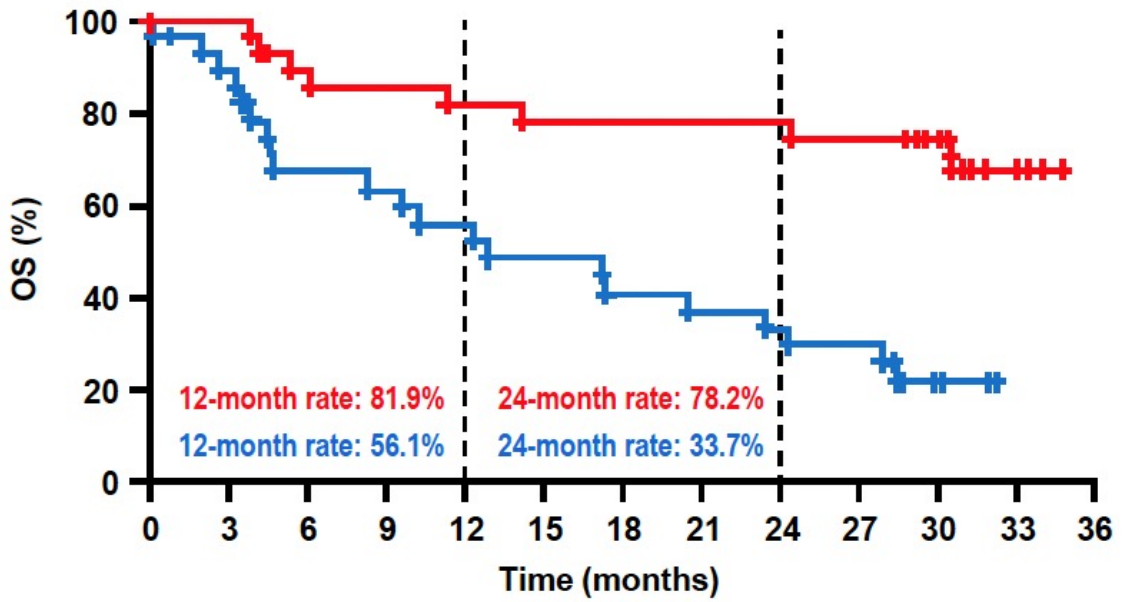

Cho BC et al. ESMO Immuno-Oncology 2021;Abstract LBA2.

RTP RESEARCH TO PRACTICE

# CITYSCAPE: OS by PD-L1 Subgroup

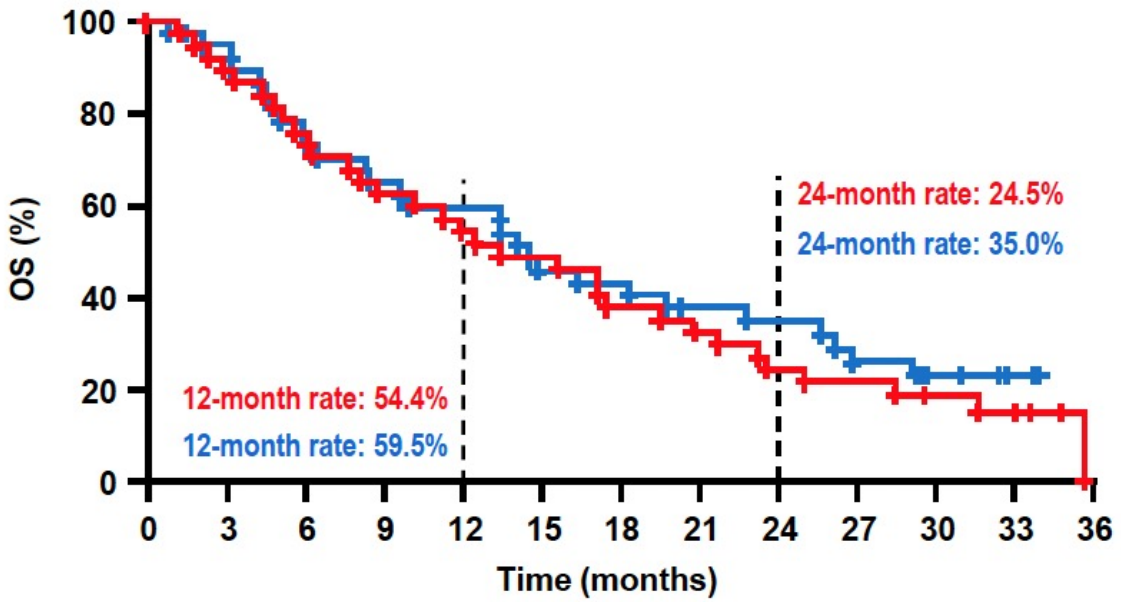
## PD-L1 TPS ≥50% (n=58)

| | Events n (%) | Median OS, months (95% CI) | HR (95% CI) |
|---|---|---|---|
| Tira + atezo | 8 (27.6) | NE (30.3–NE) | 0.23* (0.10–0.53) |
| Placebo + atezo | 21 (72.4) | 12.8 (4.7–24.2) | |




## PD-L1 TPS 1–49% (n=77)

| | Events n (%) | Median OS, months (95% CI) | HR (95% CI) |
|---|---|---|---|
| Tira + atezo | 32 (84.2) | 13.3 (8.0–20.7) | 1.16* (0.70–1.94) |
| Placebo + atezo | 28 (71.8) | 14.5 (8.3–25.6) | |




Cho BC et al. ESMO Immuno-Oncology 2021;Abstract LBA2.

RTP RESEARCH TO PRACTICE

# Appendix
# Key Recent Data Sets

# Trastuzumab Deruxtecan Significantly Improved Both Progression-Free and Overall Survival in DESTINTY-Breast04 Trial for Patients with HER2-Low Metastatic Breast Cancer

## Press Release: February 21, 2022

"Positive high-level results from the pivotal DESTINY-Breast04 Phase III trial showed fam-trastuzumab deruxtecan-nxki demonstrated a statistically significant and clinically meaningful improvement in both progression-free survival (PFS) and overall survival (OS) in patients with HER2-low unresectable and/or metastatic breast cancer regardless of hormone receptor (HR) status versus physician's choice of chemotherapy.

Up to 55% of all patients with breast cancer have tumors with an HER2 IHC score of 1+, or 2+ in combination with a negative ISH test, a level of HER2 expression not currently eligible for HER2-targeted therapy. HER2-low expression occurs in both HR-positive and HR-negative disease.

Currently, chemotherapy remains the only treatment option both for patients with HR-positive tumors following progression on endocrine (hormone) therapy, and for those who are HR-negative."

https://finance.yahoo.com/news/enhertu-fam-trastuzumab-deruxtecan-nxki-161500917.html

RTP RESEARCH TO PRACTICE

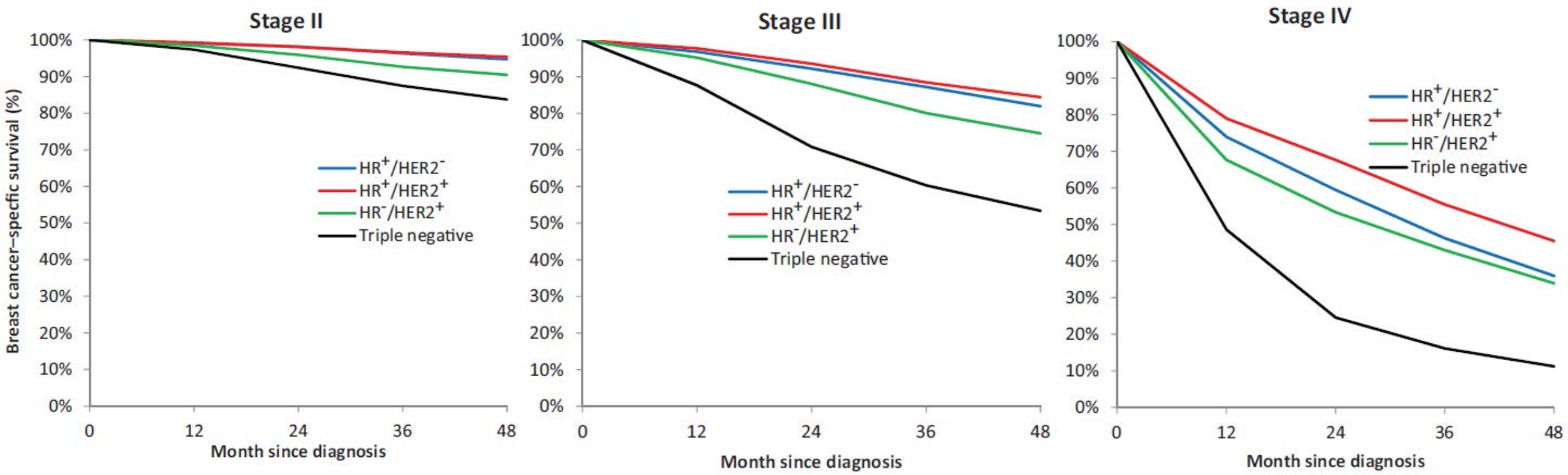
# Optimal Integration of Novel Therapies in the Management of Early-Stage Breast Cancer

Sara M. Tolaney, MD, MPH

HARVARD MEDICAL SCHOOL

Dana-Farber Cancer Institute

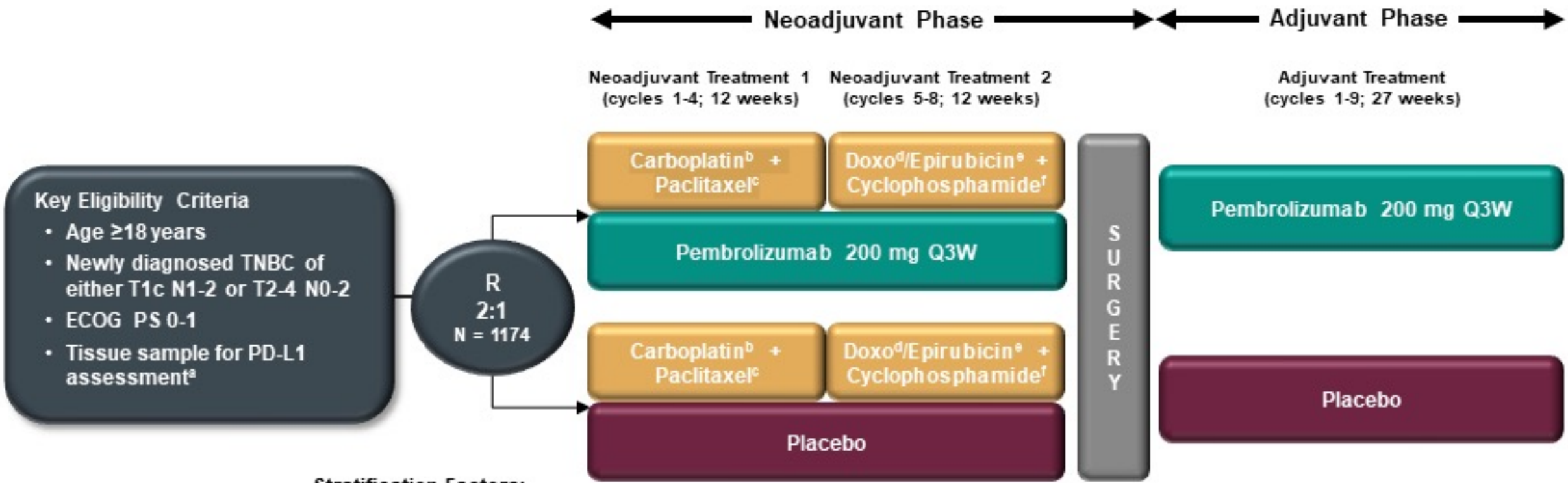
# TNBC IS ASSOCIATED WITH SHORTER OVERALL SURVIVAL COMPARED WITH OTHER SUBTYPES DESPITE ANTHRACYCLINE + TAXANE THERAPY




Howlader N, et al. *Cancer Epidemiol Biomarkers Prev. 2018*;27(6):1–8.
Bauer KR, et al. *Cancer*. 2007 May 1;109(9):1721-1728.

Courtesy of Sara M Tolaney, MD, MPH

# KEYNOTE-522 Study Design (NCT03036488)




**Stratification Factors:**
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

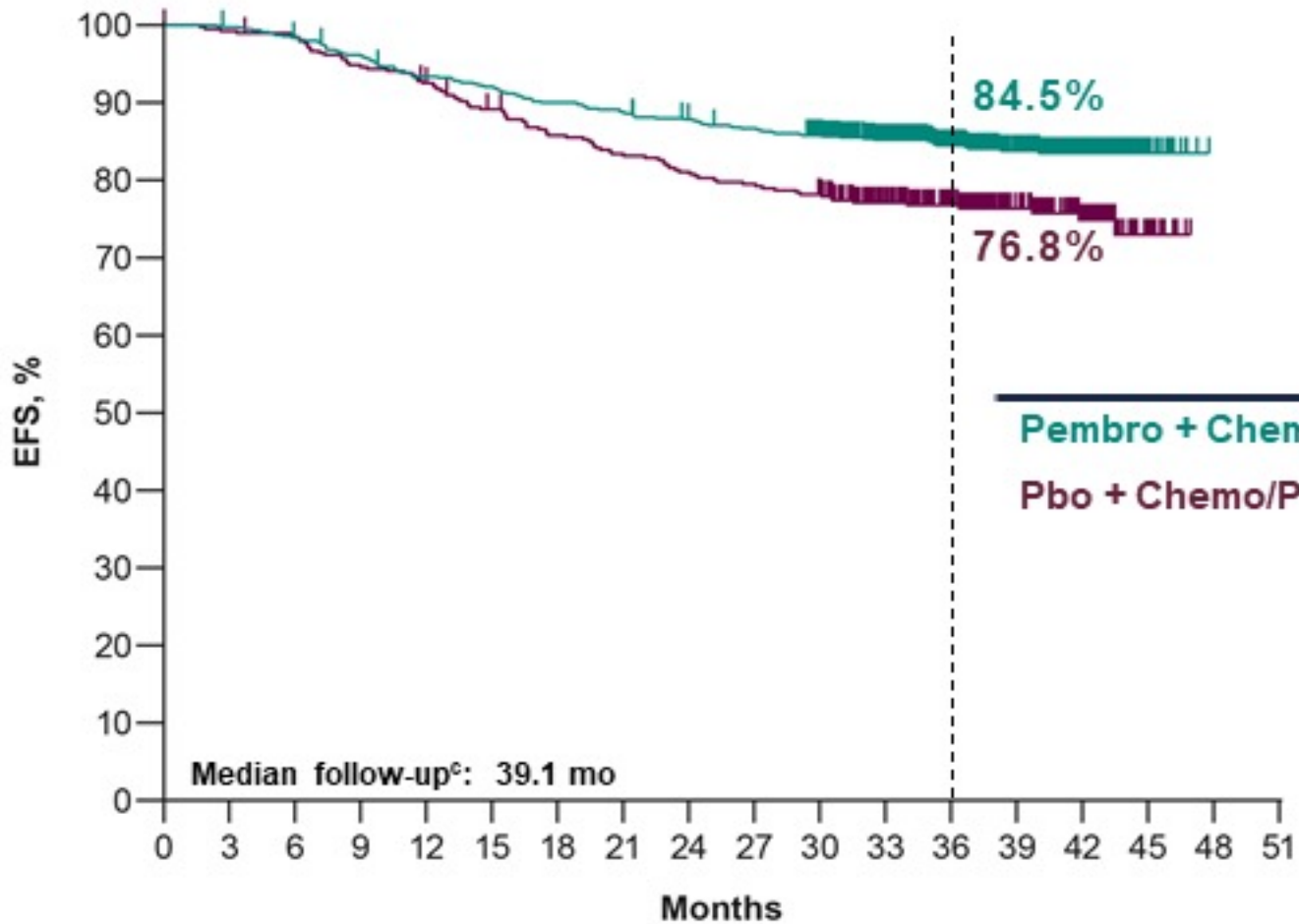
**Neoadjuvant phase:** starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

**Adjuvant phase:** starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

Courtesy of Sara M Tolaney, MD, MPH

# Statistically Significant and Clinically Meaningful EFS at IA4




| | Events | HR (95% CI) | *P*-value |
|---|---|---|---|
| Pembro + Chemo/Pembro | 15.7% | 0.63[a] (0.48-0.82) | 0.00031[b] |
| Pbo + Chemo/Pbo | 23.8% | | |

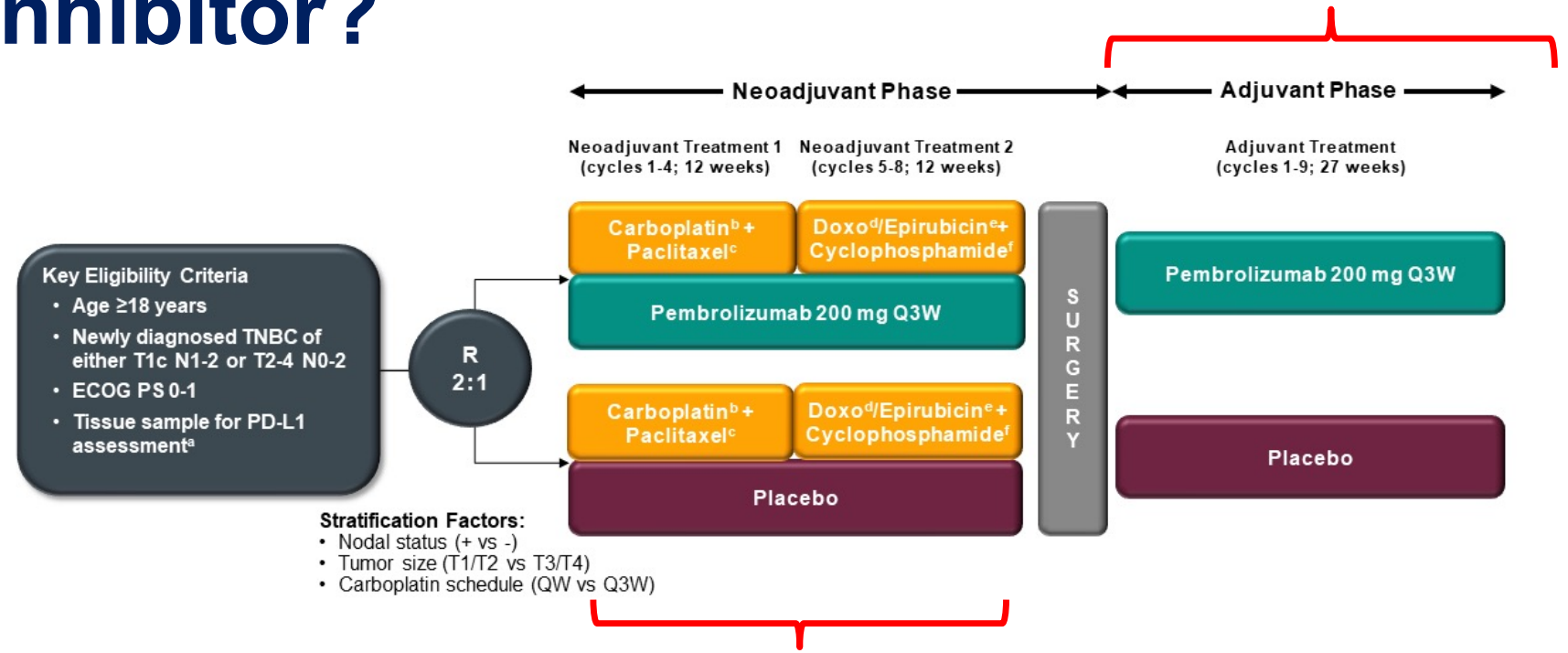
No. at Risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembro + Chemo/Pembro | 784 | 781 | 769 | 751 | 728 | 718 | 702 | 692 | 681 | 671 | 652 | 551 | 433 | 303 | 165 | 28 | 0 | 0 |
| Pbo + Chemo/Pbo | 390 | 386 | 382 | 368 | 358 | 342 | 328 | 319 | 310 | 304 | 297 | 250 | 195 | 140 | 83 | 17 | 0 | 0 |

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Courtesy of Sara M Tolaney, MD, MPH

# Do patients need adjuvant checkpoint inhibition after surgery if they received a preoperative checkpoint inhibitor?

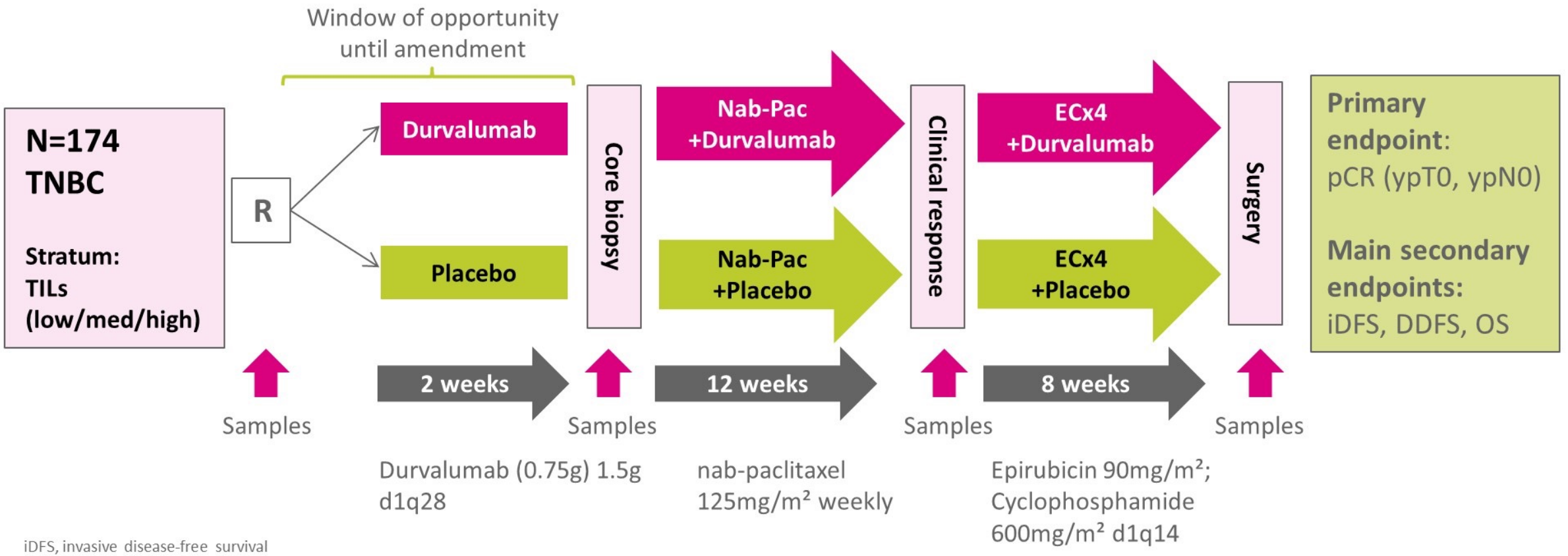



- Is there an ideal chemotherapy backbone? Anthracycline?
- Which patients really need a checkpoint inhibitor added? Which can get away with chemo alone?
- Biomarker of benefit??

- What is the optimal duration?
- Should additional adjuvant chemotherapy be given to pts after preop checkpoint? If so, is it capecitabine with checkpoint or capecitabine alone?
- In patients who have a pCR, is more checkpoint needed?
- For patients who fail to achieve a pCR, will more help?

Courtesy of Sara M Tolaney, MD, MPH

# Study Design




iDFS, invasive disease-free survival
DDFS, distance disease-free survival
OS, overall survival

Loibl S, et al. Ann Oncol 2019

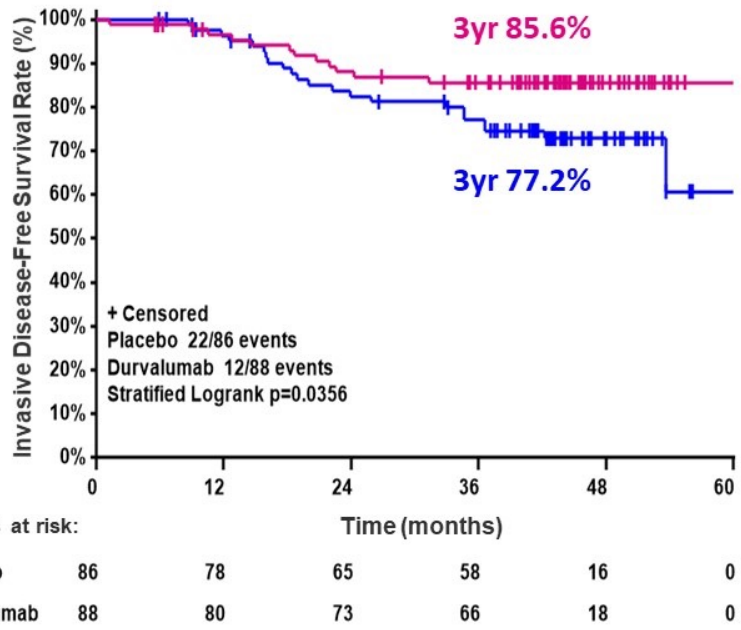




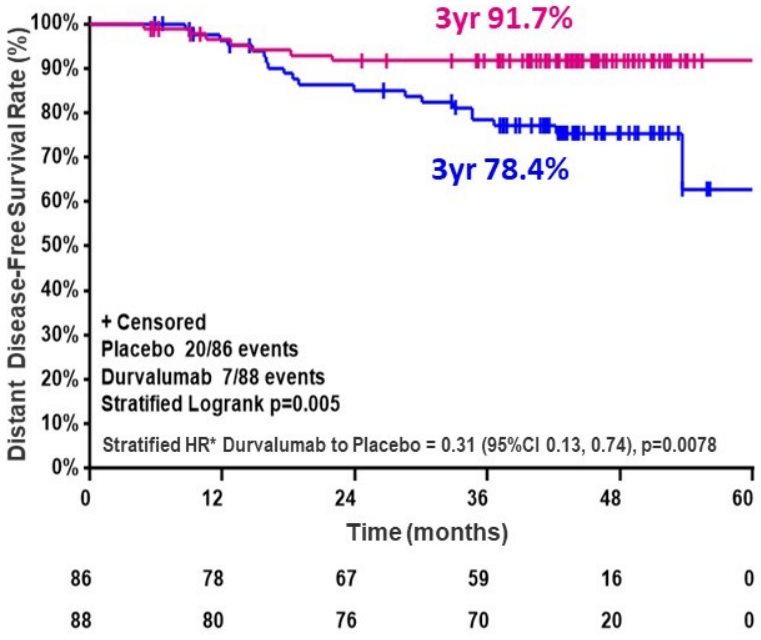
Courtesy of Sara M Tolaney, MD, MPH

# iDFS, DDFS and OS Between Treatment Arms

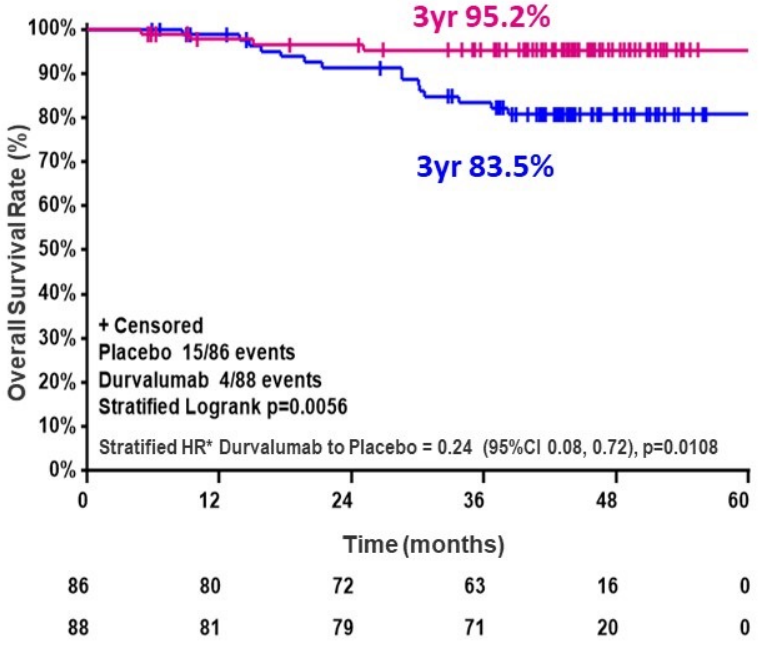
## iDFS




## DDFS




## OS




| Patients at risk: | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 86 | 78 | 65 | 58 | 16 | 0 |
| Durvalumab | 88 | 80 | 73 | 66 | 18 | 0 |

| Patients at risk: | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 86 | 78 | 67 | 59 | 16 | 0 |
| Durvalumab | 88 | 80 | 76 | 70 | 20 | 0 |

| Patients at risk: | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 86 | 80 | 72 | 63 | 16 | 0 |
| Durvalumab | 88 | 81 | 79 | 71 | 20 | 0 |

* Stratified by sTILs





Courtesy of Sara M Tolaney, MD, MPH

# ONGOING PHASE 3 ADJUVANT TRIALS OF CHECKPOINT INHIBITION

## SWOG S1418/NRG BR006
## Ph 3 Pembrolizumab for Residual TNBC post NAC

TNBC with >/=1 cm residual invasive breast cancer or any + LN after neoadjuvant chemotherapy N=1000

1:1

- Pembrolizumab 200 mg IV q 3 weeks x 1y
- Observation

- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

PIs: Pusztai/Mamounas

## A-BRAVE
## Ph 3 Adjuvant Avelumab vs Observation for TNBC

EUDRACT: 2016-000189-45
NCT02926196

A-BRAVE-TRIAL

Sponsor: University of Padova
PI: Pierfranco Conte

HIGH RISK PRIMARY TNBC PTS WHO COMPLETED TREATMENT WITH CURATIVE INTENT INCLUDING SURGERY, CHEMOTHERAPY AND RADIOTHERAPY (if indicated)

Stratum A: Adjuvant
Stratum B: Post-neoadjuvant

R

- Avelumab for 1 year
- Observation

Randomization 1:1 balanced for adjuvant and post-neoadjuvant patients.

**Co-primary endpoints**: 1. DFS in all-comers;
2. DFS in Stratum B post-neoadjuvant
**Secondary endpoints:** OS, DFS in PD-L1+, Safety, Biomarkers
**Sample size = 474 patients**

## THESE STUDIES DO NOT ADDRESS QUESTION OF CONTINUATION OF ADJUVANT PEMBRO AFTER PREOP PEMBRO IN PTS WITH RESIDUAL DISEASE

Courtesy of Sara M Tolaney, MD, MPH

# OlympiA: Trial schema

- Local genetic testing or on-study central screening
  (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

**Neoadjuvant Group**
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

**≥ 6 cycles Neoadjuvant Chemotherapy** → **Surgery** → **+/- Radiotherapy**

**Adjuvant Group**
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

**Surgery** → **≥ 6 cycles Adjuvant Chemotherapy** → **+/- Radiotherapy**

**1:1 Randomization N=1836**

**Olaparib** 300 mg twice daily for 1 year

**Placebo** twice daily for 1 year

**Primary End Point**
- Invasive disease-free survival (IDFS) by STEEP system[1]

**Secondary End Points**
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

**Stratification Factors**
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

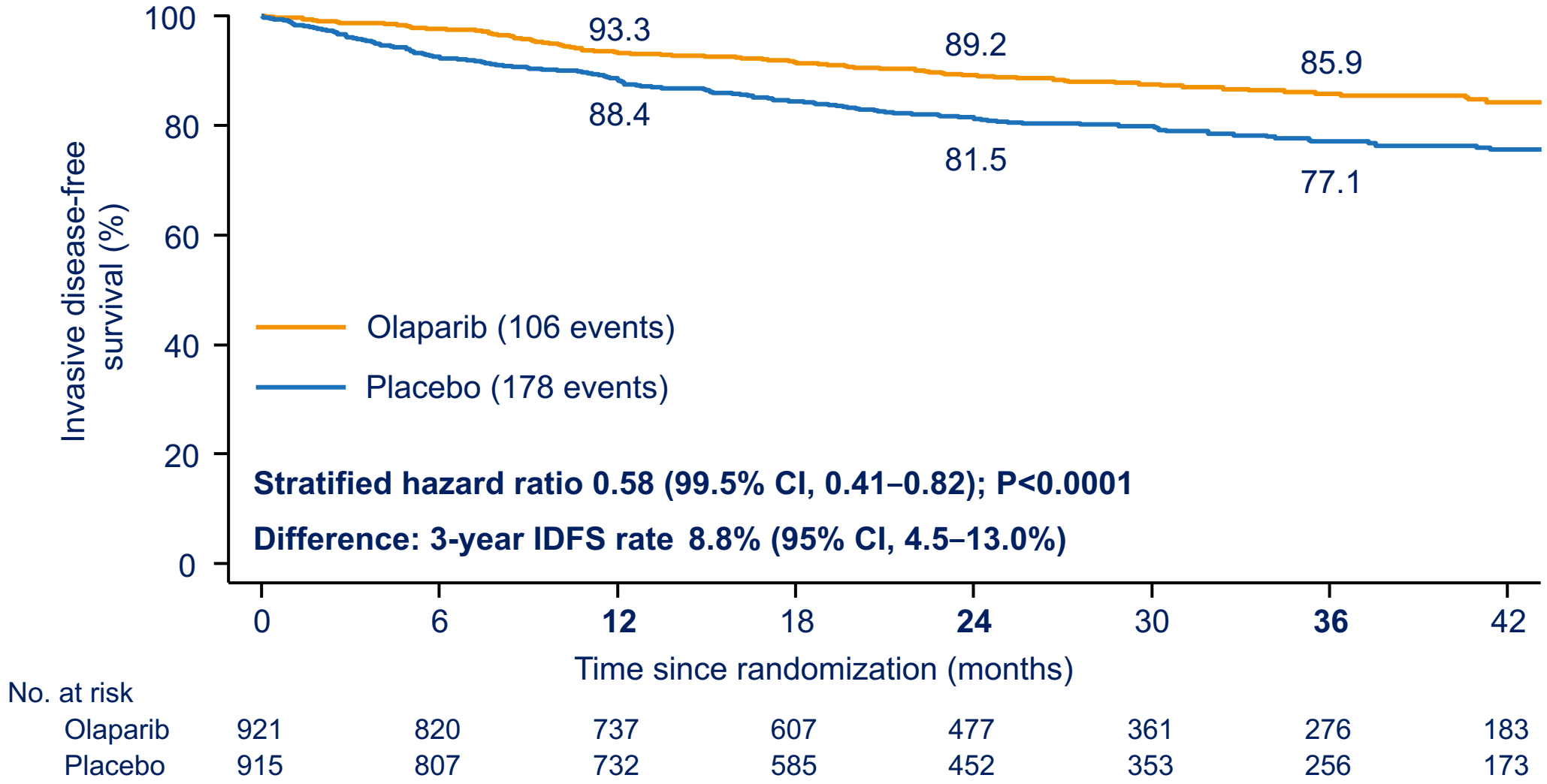
**Concurrent Adjuvant Therapy**
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Sara M Tolaney, MD, MPH

# OlympiA: Invasive disease-free survival (ITT)



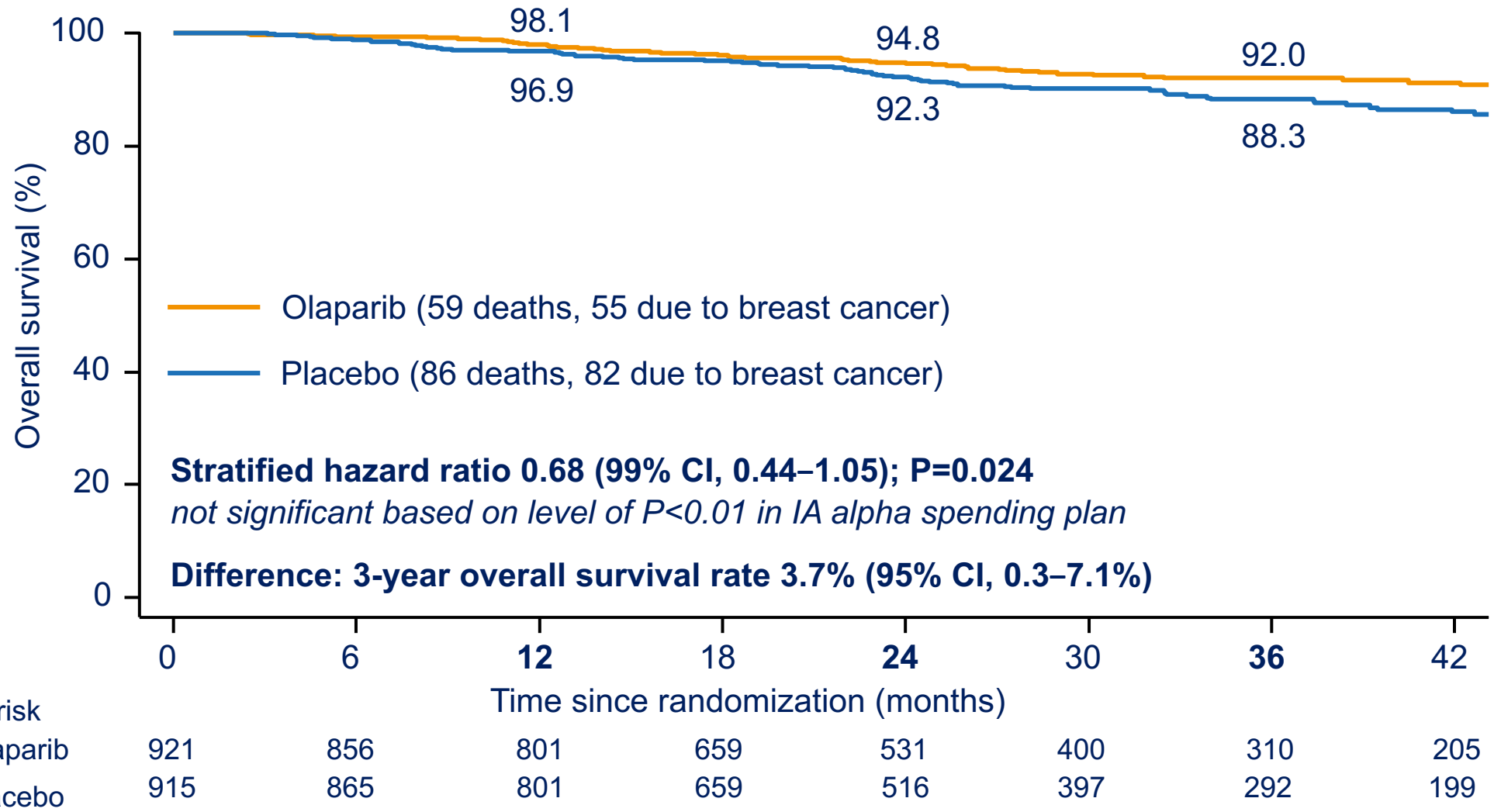

No. at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Olaparib | 921 | 820 | 737 | 607 | 477 | 361 | 276 | 183 |
| Placebo | 915 | 807 | 732 | 585 | 452 | 353 | 256 | 173 |

Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Sara M Tolaney, MD, MPH

# OlympiA: Overall survival




No. at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Olaparib | 921 | 856 | 801 | 659 | 531 | 400 | 310 | 205 |
| Placebo | 915 | 865 | 801 | 659 | 516 | 397 | 292 | 199 |

Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Sara M Tolaney, MD, MPH

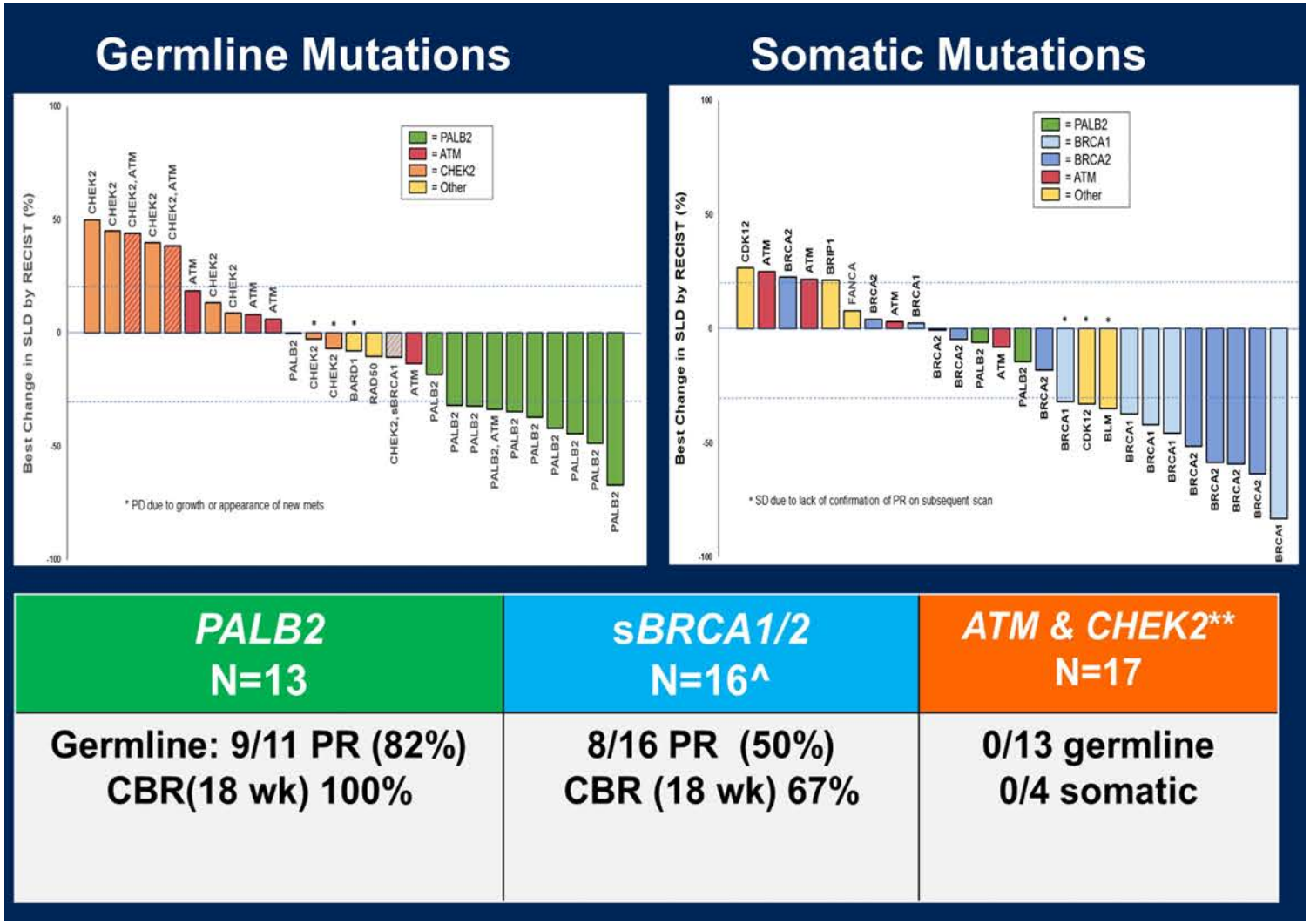
# WHO SHOULD GET GENETIC TESTING?

Courtesy of Sara M Tolaney, MD, MPH

# What about PARPi for other breast cancer with homologous recombination deficiency (HRD)?

- gPALB2: 82% ORR
- sBRCA: 50% ORR

- Not unreasonable to consider PARPi in these populations




Courtesy of Sara M Tolaney, MD, MPH

# SHOULD PARP + CHECKPOINT INHIBITION BE GIVEN TO PATIENTS WITH TNBC AND RESIDUAL DISEASE AFTER PREOPERATIVE CHECKPOINT INHIBITION?

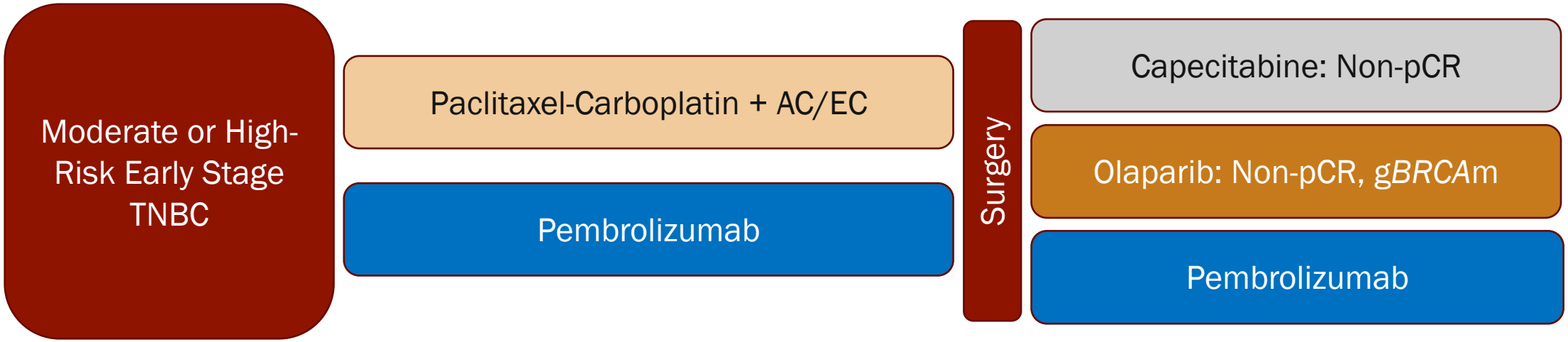
Courtesy of Sara M Tolaney, MD, MPH

# PARP + Checkpoint?

- No randomized data yet suggesting immunotherapy adds to PARPi
  - Ongoing ETCTN trial will address this (Olaparib +/- Atezolizumab)
- Safety data from TOPACIO and MEDIOLA
- Possible synergistic activity
- Could consider combination olaparib + pembrolizumab in BRCAm patients with RD after preop pembrolizumab

Courtesy of Sara M Tolaney, MD, MPH

# How Do We Integrate Adjuvant Therapy in the Management of Early Stage TNBC?

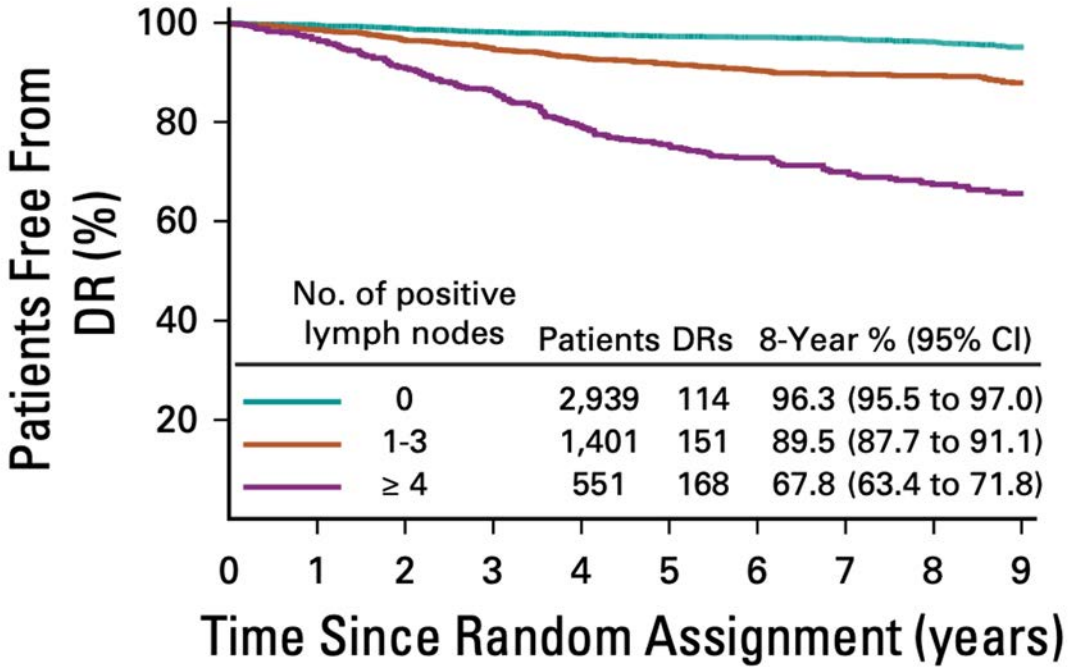



Courtesy of Sara M Tolaney, MD, MPH

# Early Stage HR+ Breast Cancer: Assessing Risk

- Clinical + pathologic features
- 10-y estimated risk of relapse with current therapies:
  - > 30% (ALN ≥ 4)
  - > 20% (ALN 1-3 + another poor prognostic factor)

HR+/HER2– Operable BC

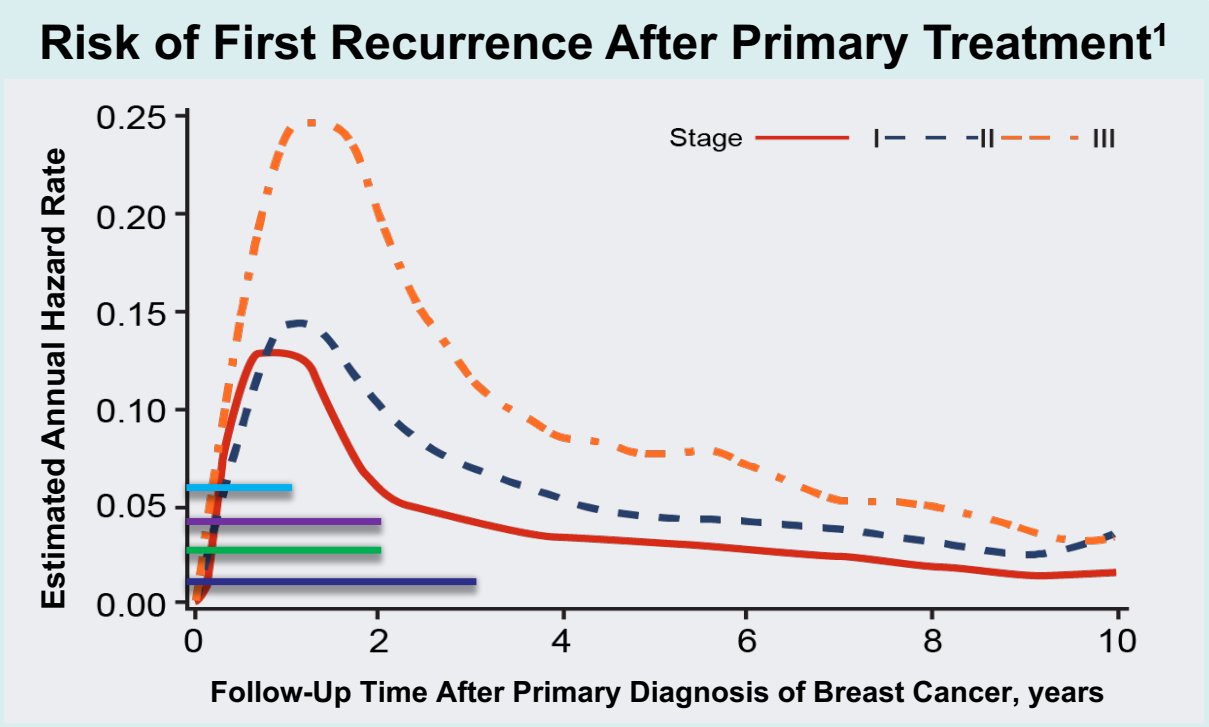



ALN, axillary lymph node.

Pagani O, et al. J Clin Oncol. 2020;38:1293-1303.

Courtesy of Sara M Tolaney, MD, MPH

# CDK 4/6 INHIBITORS FOR EARLY STAGE HR+ BREAST CANCER




PENELOPE-B
palbociclib
(after neoadjuvant, high risk)

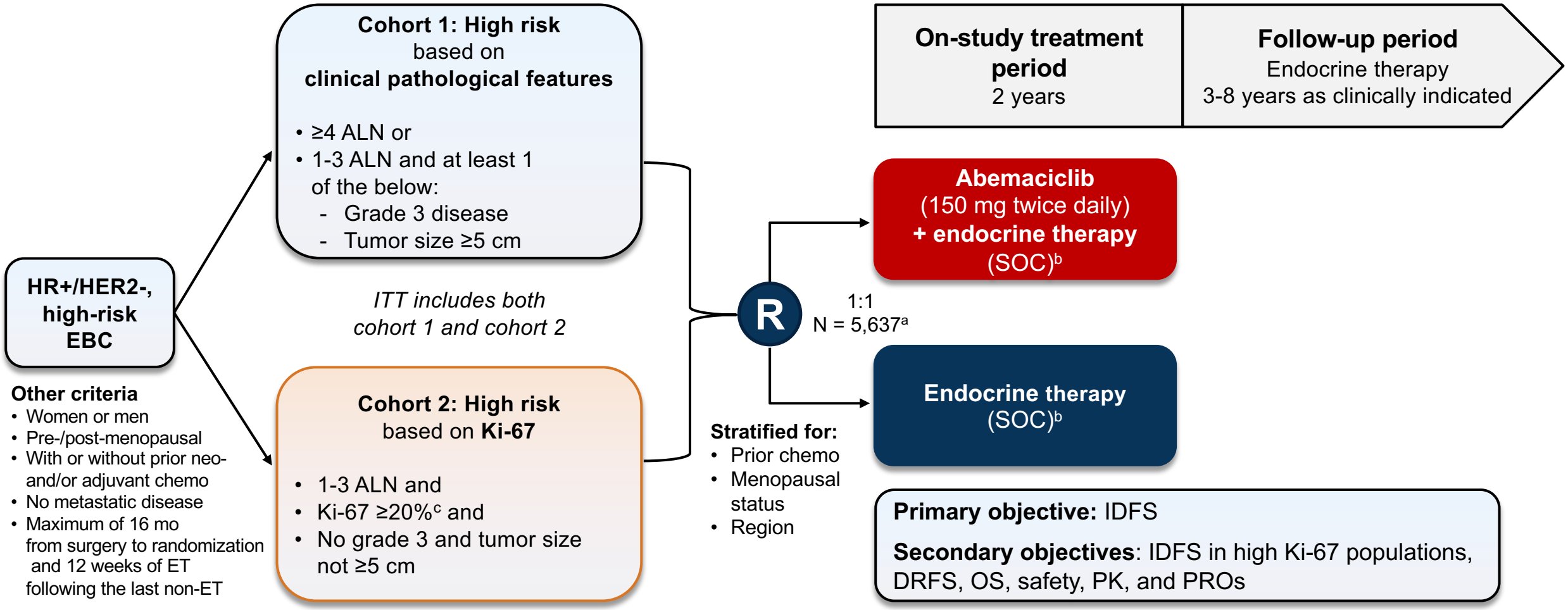
monarchE
abemaciclib
High risk CPR factors, Ki-67

PALLAS
palbociclib
Stage II, III

NATALEE
ribociclib
Stage II, III

Courtesy of Sara M Tolaney, MD, MPH

# monarchE Study Design

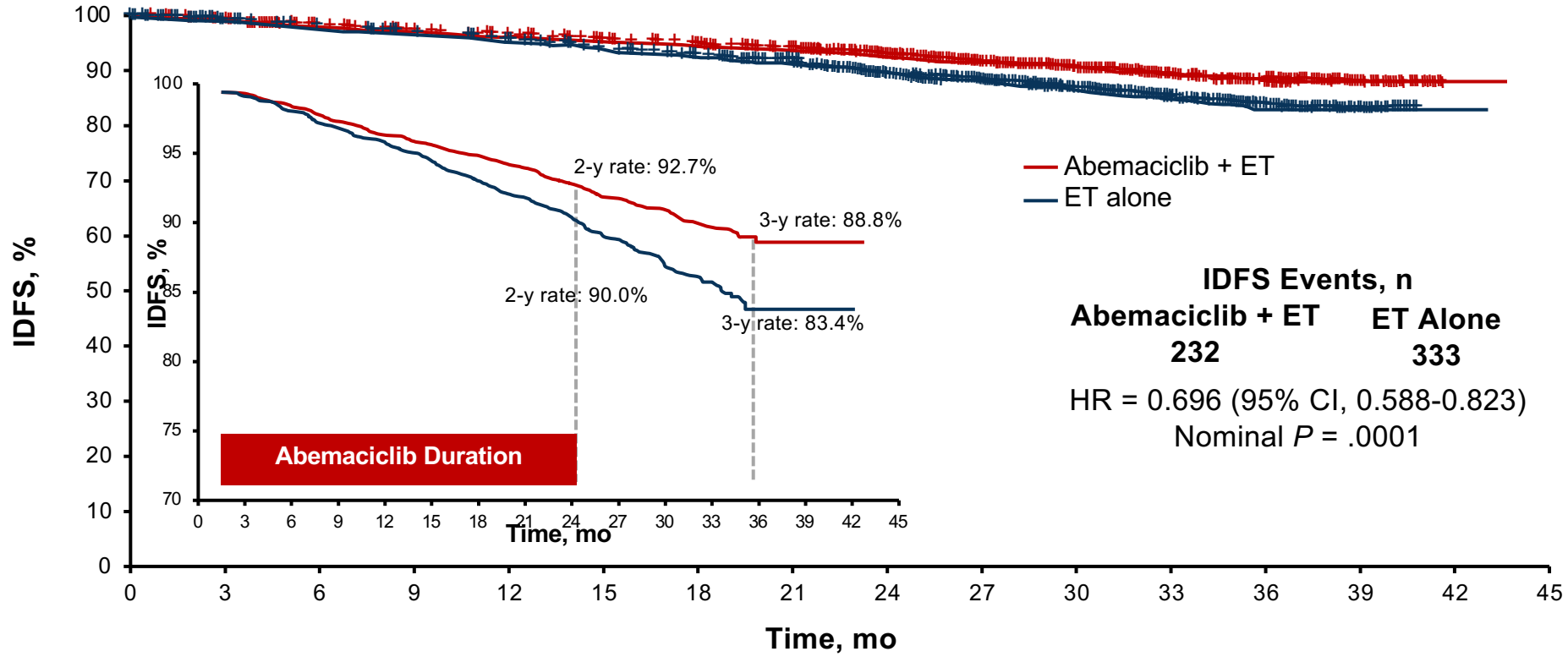



[a] Recruitment from July 2017 to August 2019. [b] Endocrine therapy of physician's choice (eg, aromatase inhibitors, tamoxifen, LHRH agonist). [c] Ki-67 expression centrally assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry.

1. O'Shaughnessy et al. ESMO 2021. Abstract VP8-2021. 2. Harbeck N et al. Ann Oncol. 2021;S0923-7534(21)04494-X.

Courtesy of Sara M Tolaney, MD, MPH

# monarchE: IDFS Benefit Maintained With Additional Follow-Up in ITT Population




**No. at Risk**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abemaciclib + ET | 2,808 | 2,680 | 2,621 | 2,579 | 2,547 | 2,508 | 2,47 | 2,430 | 1,970 | 1,287 | 919 | 522 | 275 | 67 | 8 | 0 |
| ET alone | 2,829 | 2,700 | 2,652 | 2,608 | 2,572 | 2,513 | 2,472 | 2,400 | 1,930 | 1,261 | 906 | 528 | 281 | 64 | 10 | 0 |

**30.4% reduction in the risk of developing an IDFS event**
**The absolute difference in IDFS rates between arms was 5.4% at 3 years**

1. O'Shaughnessy et al. ESMO 2021. Abstract VP8-2021. 2. Harbeck N et al. Ann Oncol. 2021;S0923-7534(21)04494-X.

Courtesy of Sara M Tolaney, MD, MPH

# monarchE: Abemaciclib Treatment Effect Over Time

| Analysis Landmark | IDFS | | | DRFS | | |
|---|---|---|---|---|---|---|
| | Events | | Piecewise HR[a] (95% CI[b]) | Events | | Piecewise HR[a] (95% CI[b]) |
| | Abemaciclib + ET | ET Alone | | Abemaciclib + ET | ET Alone | |
| Year 0-1 | 93 | 116 | 0.795 (0.589-1.033) | 67 | 91 | 0.732 (0.520-0.987) |
| Year 1-2 | 98 | 146 | 0.681 (0.523-0.869) | 85 | 129 | 0.675 (0.507-0.875) |
| Year 2+ | 41 | 71 | 0.596 (0.397-0.855) | 39 | 58 | 0.692 (0.448-1.032) |

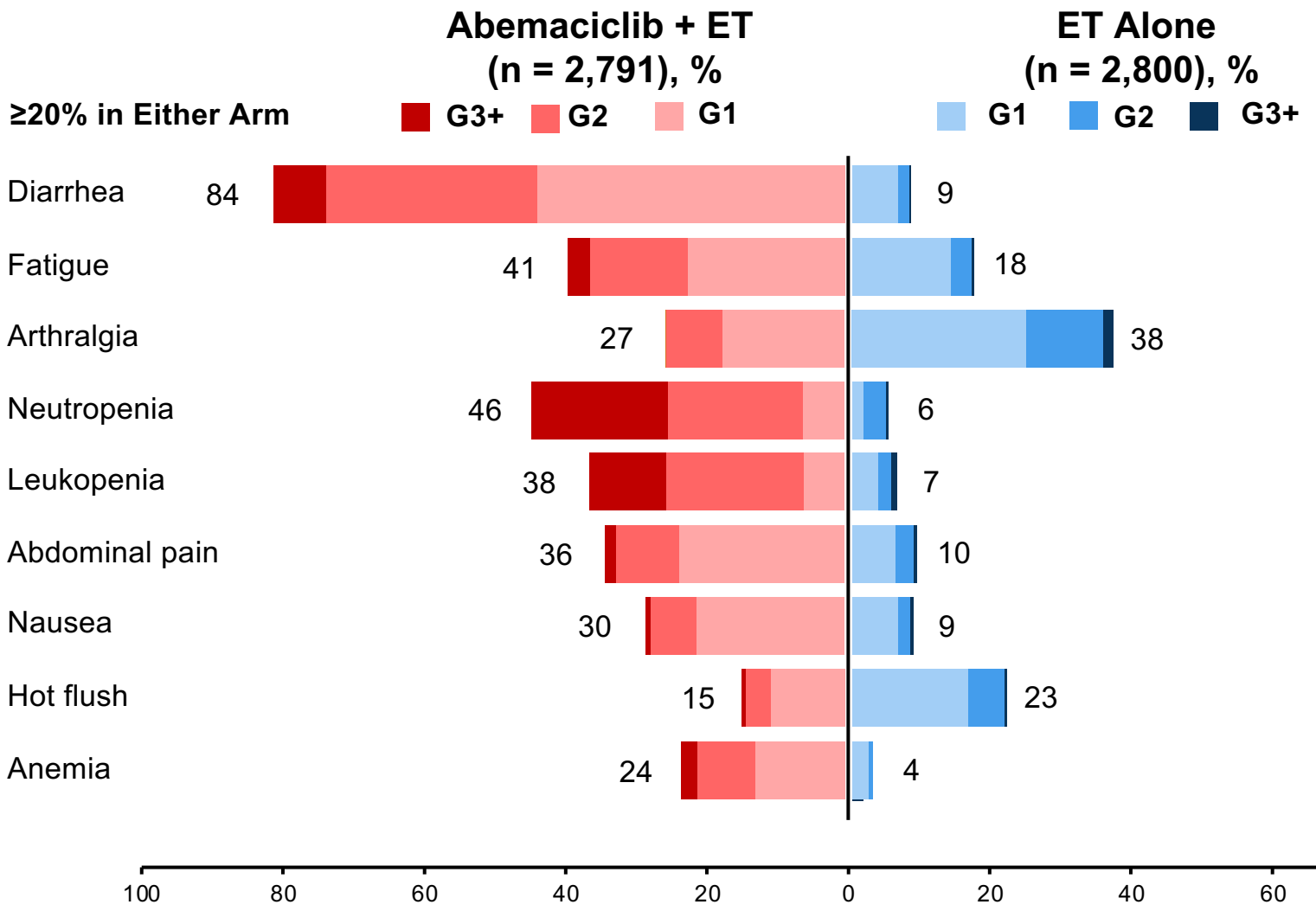
**Increasing magnitude of IDFS and DRFS effect size from the first year to the second year, with maintained treatment benefit beyond the 2-year study treatment period**

[a] Piecewise hazard ratio was estimated using piecewise exponential model to assess the yearly treatment effect size.
[b] 95% credible intervals were calculated by equal tails in the posterior samples of Bayesian exponential models

1. O'Shaughnessy et al. ESMO 2021. Abstract VP8-2021. 2. Harbeck N et al. Ann Oncol. 2021;S0923-7534(21)04494-X.

Courtesy of Sara M Tolaney, MD, MPH

# Mature Safety Findings Consistent With Previous Analyses




*Median duration of abemaciclib: 23.7 mo*

| | | |
|---|---|---|
| VTE | 2.5 | 0.6 |
| PE | 1.0 | 0.1 |
| ILD | 3.2 | 1.3 |

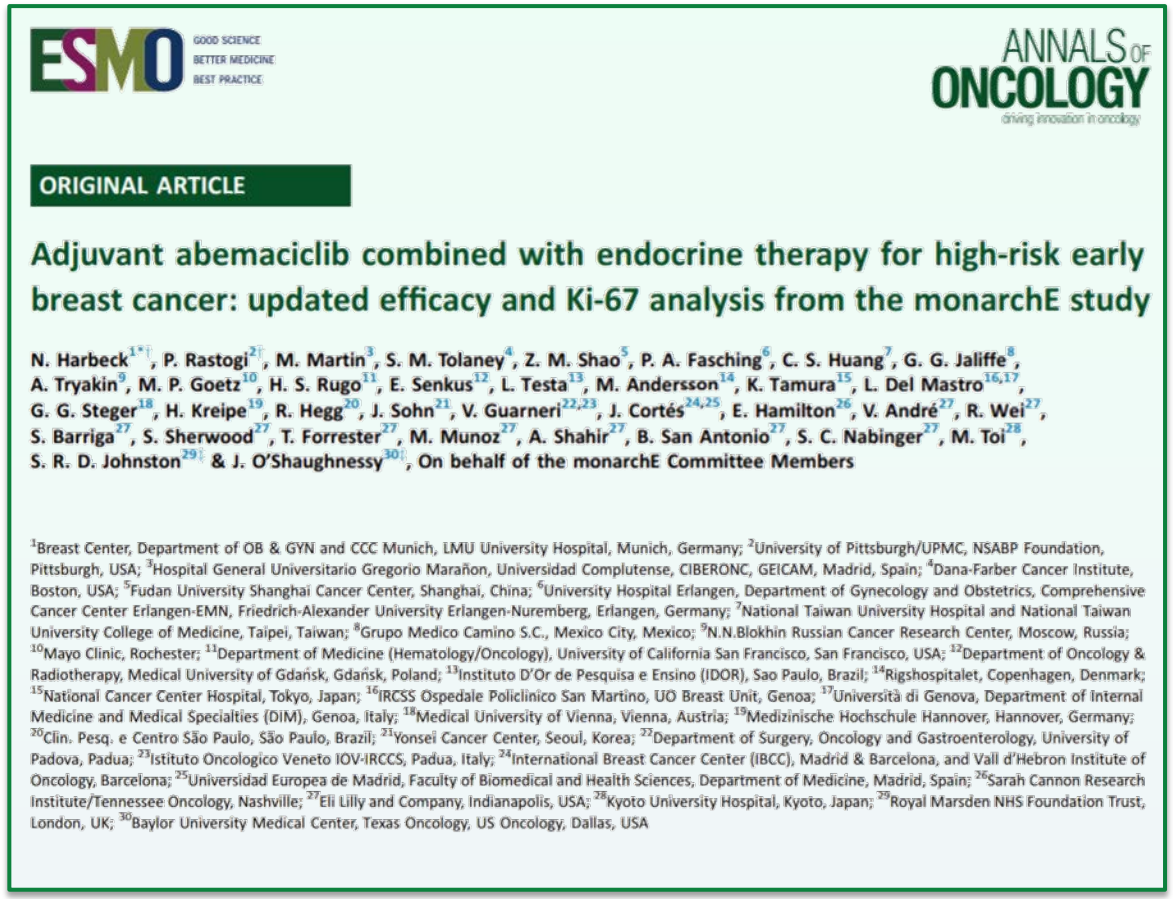
| | |
|---|---|
| Dose-reduction due to AE | 1,187 (42.5%) |
| Dose hold due to AE | 1,661 (59.5%) |

[a] All patients who received at least one dose of study treatment were included in the safety population.

1. O'Shaughnessy et al. ESMO 2021. Abstract VP8-2021.

Courtesy of Sara M Tolaney, MD, MPH

# Adjuvant Abemaciclib for High-Risk, HR+/HER2-, Early Breast Cancer



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

**Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study**

N. Harbeck[1*†], P. Rastogi[2†], M. Martin[3], S. M. Tolaney[4], Z. M. Shao[5], P. A. Fasching[6], C. S. Huang[7], G. G. Jaliffe[8], A. Tryakin[9], M. P. Goetz[10], H. S. Rugo[11], E. Senkus[12], L. Testa[13], M. Andersson[14], K. Tamura[15], L. Del Mastro[16,17], G. G. Steger[18], H. Kreipe[19], R. Hegg[20], J. Sohn[21], V. Guarneri[22,23], J. Cortés[24,25], E. Hamilton[26], V. André[27], R. Wei[27], S. Barriga[27], S. Sherwood[27], T. Forrester[27], M. Munoz[27], A. Shahir[27], B. San Antonio[27], S. C. Nabinger[27], M. Toi[28], S. R. D. Johnston[29‡] & J. O'Shaughnessy[30‡], On behalf of the monarchE Committee Members

[1]Breast Center, Department of OB & GYN and CCC Munich, LMU University Hospital, Munich, Germany; [2]University of Pittsburgh/UPMC, NSABP Foundation, Pittsburgh, USA; [3]Hospital General Universitario Gregorio Marañon, Universidad Complutense, CIBERONC, GEICAM, Madrid, Spain; [4]Dana-Farber Cancer Institute, Boston, USA; [5]Fudan University Shanghai Cancer Center, Shanghai, China; [6]University Hospital Erlangen, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [7]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [8]Grupo Medico Camino S.C., Mexico City, Mexico; [9]N.N.Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Mayo Clinic, Rochester; [11]Department of Medicine (Hematology/Oncology), University of California San Francisco, San Francisco, USA; [12]Department of Oncology & Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland; [13]Instituto D'Or de Pesquisa e Ensino (IDOR), Sao Paulo, Brazil; [14]Rigshospitalet, Copenhagen, Denmark; [15]National Cancer Center Hospital, Tokyo, Japan; [16]IRCSS Ospedale Policlinico San Martino, UO Breast Unit, Genoa; [17]Università di Genova, Department of Internal Medicine and Medical Specialties (DIM), Genoa, Italy; [18]Medical University of Vienna, Vienna, Austria; [19]Medizinische Hochschule Hannover, Hannover, Germany; [20]Clin. Pesq. e Centro São Paulo, São Paulo, Brazil; [21]Yonsei Cancer Center, Seoul, Korea; [22]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua; [23]Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy; [24]International Breast Cancer Center (IBCC), Madrid & Barcelona, and Vall d'Hebron Institute of Oncology, Barcelona; [25]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [26]Sarah Cannon Research Institute/Tennessee Oncology, Nashville; [27]Eli Lilly and Company, Indianapolis, USA; [28]Kyoto University Hospital, Kyoto, Japan; [29]Royal Marsden NHS Foundation Trust, London, UK; [30]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, USA


On October 12, 2021, the FDA approved abemaciclib for adjuvant treatment of adult patients with HR+/HER2-, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test

The FDA also approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay as a companion diagnostic for selecting patients for this indication

1. Harbeck N et al. *Ann Oncol*. 2021;S0923-7534(21)04494-X.
2. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

Courtesy of Sara M Tolaney, MD, MPH

# FDA Benefit-Risk Assessment for Abemaciclib Approval

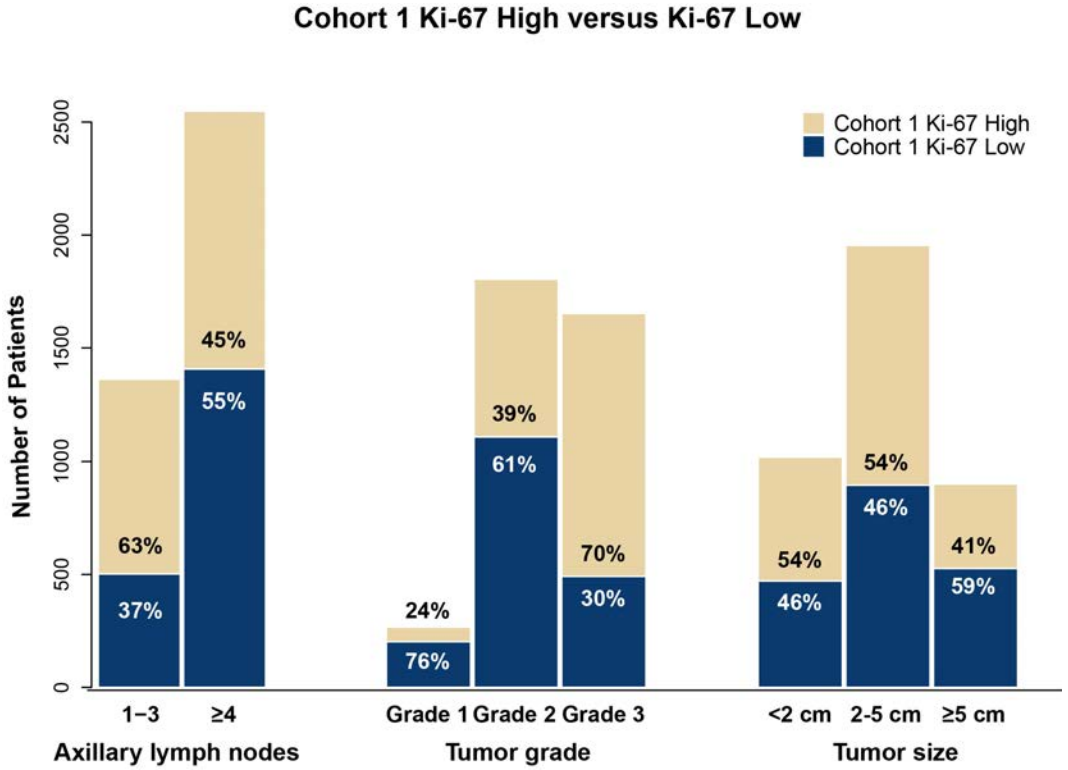
| Dimension | Evidence and Uncertainties | Conclusion and Reasons |
|---|---|---|
| Analysis of condition | Approximately 70% of breast cancers are HR+, HER2–<br>Early-stage, HR+, HER2– breast cancer is potentially curable; however, approximately 30% of patients relapse with local and metastatic disease and metastatic disease is incurable<br>High-risk features include size, grade, and number of involved lymph nodes, as well as Ki-67. | High-risk, early-stage, HR+, HER2– breast cancer is a serious and life-threatening condition. |
| Current treatment options | Standard-of-care treatment of early-stage, HR+, HER2– breast cancer includes surgery ± radiation therapy ± adjuvant chemotherapy, followed by at least 5 years of adjuvant ET (aromatase inhibitor or tamoxifen, with or without GnRH agonist). | There is an unmet medical need to improve upon long-term outcomes such as IDFS and OS. |
| Benefit | Statistically significant improvement in IDFS for patients with HR+, HER2–, node-positive EBC at high risk of recurrence (cohort 1) with Ki-67 score ≥ 20% at the final IDFS analysis with an HR of 0.643 (95% CI, 0.475 to 0.872; $P = .0042$).<br>In the ITT population, abemaciclib plus ET demonstrated a statistically significant improvement in IDFS; however, the immature OS analysis showed a nonsignificant HR > 1 showing a potential detriment with abemaciclib plus ET in the ITT population.<br>OS data for the indicated population remain immature and are not statistically significant; however, the point estimate numerically favors the abemaciclib plus ET arm (HR = 0.767; 95% CI, 0.511 to 1.512) and do not indicate a detrimental effect of treatment with adjuvant abemaciclib plus ET. | Although the benefit:risk profile was favorable for the indicated subpopulation, given the immaturity and potential OS detriment, it was not favorable for the ITT population. |
| Risk and risk management | No new safety signals were observed compared with the known safety profiles of abemaciclib in combination with ET. However, increased rates of grade 3-4 AEs, serious AEs, and discontinuations were seen in the abemaciclib arm. | The safety profile of adjuvant abemaciclib is acceptable for the indicated patient population and the package insert adequately informs prescribers regarding safe usage. |

Courtesy of Sara M Tolaney, MD, MPH

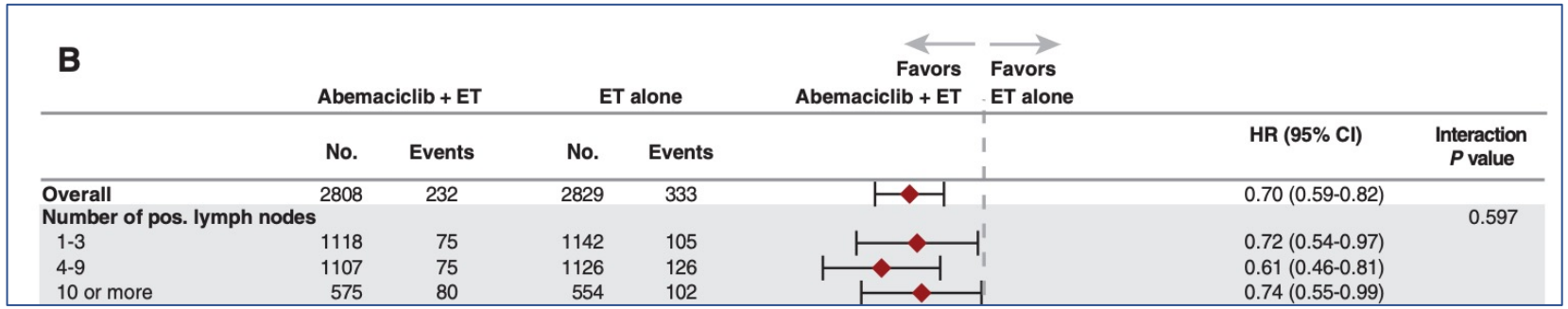
Royce M et al, JCO 2022

# Most patients with ≥4 ALN were Ki-67 low

- 55% of patients with ≥ 4 ALN involved in the trial were Ki-67 low
- This population, despite a very high risk of recurrence, would currently be excluded based on the FDA indication from treatment with abemaciclib




**iDFS HR in patients with 4-9 ALN: 0.61**




1. O'Shaughnessy et al. ESMO 2021. Abstract VP8-2021. 2. Harbeck N et al. Ann Oncol. 2021;S0923-7534(21)04494-X.

Courtesy of Sara M Tolaney, MD, MPH

# Ki-67 has low analytical validity

| Question | Subquestion | Consensus conclusions |
|---|---|---|
| Analytical validity for Ki67? | Specimen handling, staining, and scoring | Recommendations are listed in Table 1 |
| | Cutoffs | Depends on intended use<br>Prognosis: ≤5%, ≥30% acceptable; >5% to <30% not acceptable<br>Prediction chemotherapy efficacy: Insufficient evidence<br>Serial monitoring: Variable:<br>▪ Decline below absolute level<br>▪ Decline by specified percent<br>▪ Values may be artifactually low due to reduction in cellular content |
| Clinical utility? | | |
| Prognosis to decide chemotherapy or not | ER negative | Insufficient evidence |
| | ER positive | • Evidence suggestive but analytical validity issues limit decisions based on Ki67<br>• Acceptable if Ki67 index ≤5% (no chemotherapy) or ≥30% (chemotherapy indicated)<br>• For cases >5 to <30%, recommend multi-parameter gene expression assays per ASCO[8] |
| Prediction to decide efficacy of chemotherapy | Insufficient evidence; not indicated for this use | |

A recent consensus by the International Ki67 BC Working Group has convened on the unacceptable analytical validity of Ki-67, particularly for thresholds in the range of 5-30%

Courtesy of Sara M Tolaney, MD, MPH

Nielsen et al. JNCI 2021

# ASCO Recommendation Update on the Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for EBC

- Based on a secondary pre-defined analysis conducted by the FDA, two years of abemaciclib (150 mg twice daily) plus ET may be offered to patients with HR-positive, HER2-negative, node-positive early breast cancer with a high risk of recurrence and a Ki-67 score of ≥ 20% as determined by an FDA-approved test

- The Panel also recommends, based on analyses reported by Harbeck et al, that abemaciclib for two years plus ET for ≥ 5 years may be offered to the broader intent-to-treat population of patients with resected, HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence, defined as having ≥ 4 positive axillary lymph nodes, or as having 1-3 positive axillary lymph nodes and one or more of the following features: histologic grade 3 disease, tumor size ≥ 5 cm, or Ki-67 index ≥ 20%

Qualifying statements

- Although exploratory analyses suggested similar HRs in favor of abemaciclib regardless of Ki-67 status, there were relatively few Ki-67 low tumors in monarchE
- When discussing treatment options with patients, the potential benefits (improved IDFS) should be weighed against the potential harms (treatment toxicity, financial cost)

Courtesy of Sara M Tolaney, MD, MPH

# Which patients should receive adjuvant abemaciclib?

Patient with surgically resected early-stage, HR+ breast cancer

| | |
|---|---|
| **≥4 ALN** | Offer adjuvant abemaciclib for up to two years, regardless of Ki-67 score |
| **1-3 ALN** *AND* **T≥5 cm or G3** | Offer adjuvant abemaciclib for up to two years, regardless of Ki-67 score |

Courtesy of Sara M Tolaney, MD, MPH

# Who are the patients eligible for monarchE?

- 4,496 HR+ HER2- patients treated at Dana-Farber Cancer Institute (2016-2021)
  - 11.1% eligible for monarchE based on ASCO/NCCN guidelines
- Patients eligible for abemaciclib were more likely:
  - Premenopausal (52% vs 30%)
  - BRCA2 mutation carriers (11% vs 3%)
  - Lobular tumors (21% vs 14%)
  - High Onco*type* DX RS (31% vs 14%)

Courtesy of Sara M Tolaney, MD, MPH

# Summary: Novel Therapies for Early Stage Breast Cancer

- Preoperative pembrolizumab + chemotherapy is now a standard treatment for patients with stage 2/3 TNBC
    - Lots of questions remain regarding optimal chemotherapy backbone, duration of checkpoint inhibition, and optimal therapy post-surgery
- Adjuvant olaparib for one year is standard adjuvant therapy for high risk gBRCAm early stage breast cancer
    - Genetic testing is critical to identify patients who may benefit from therapy
- Adjuvant abemaciclib for 2 yrs reduces risk of recurrence by 30% for patients with high risk HR+ breast cancer

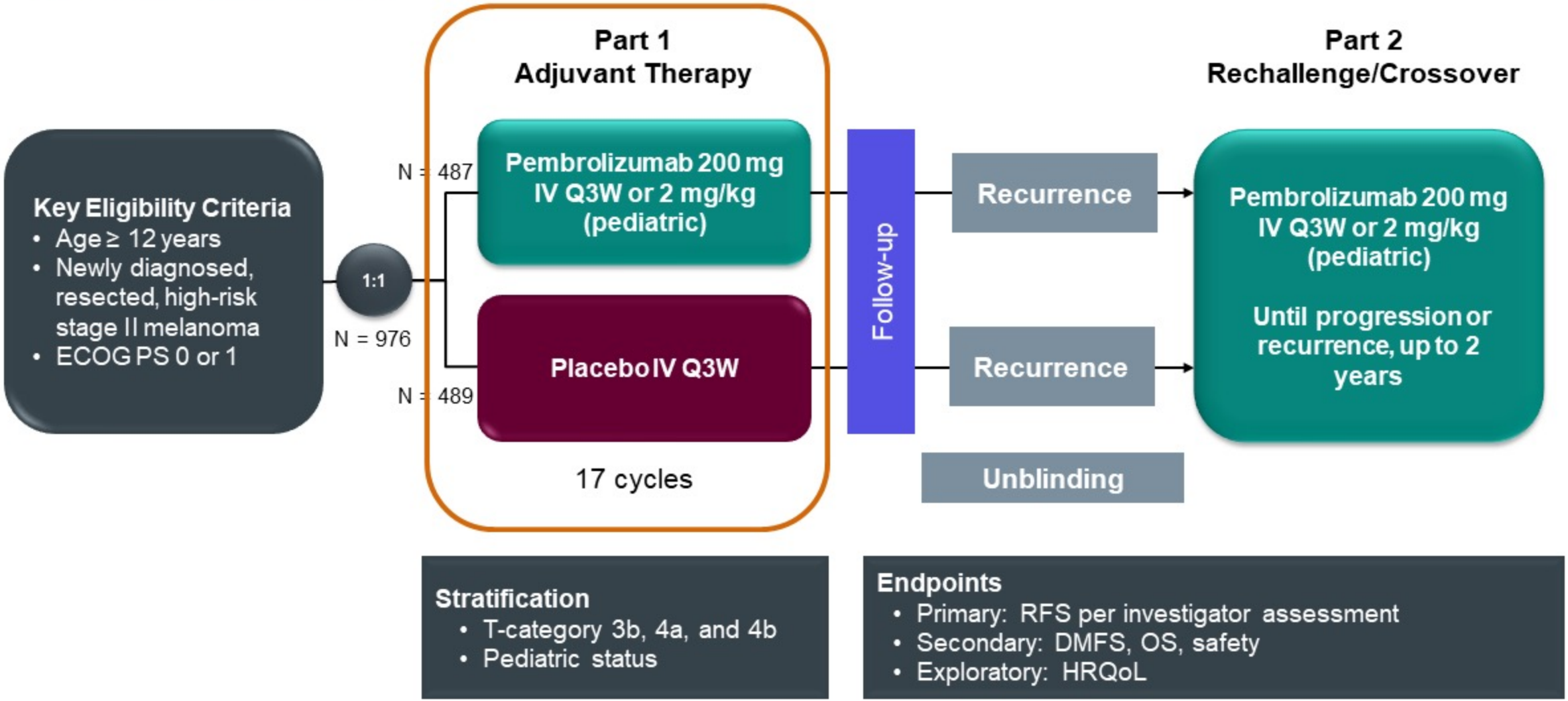
Courtesy of Sara M Tolaney, MD, MPH

# Research To Practice

## *The Great Adjuvant Debate — Exploring the Role of Novel Therapies in the Management of Localized Cancer: Melanoma*

Jeffrey S Weber MD PhD
Laura and Isaac Perlmutter Cancer Center
NYU Langone Health
New York, NY

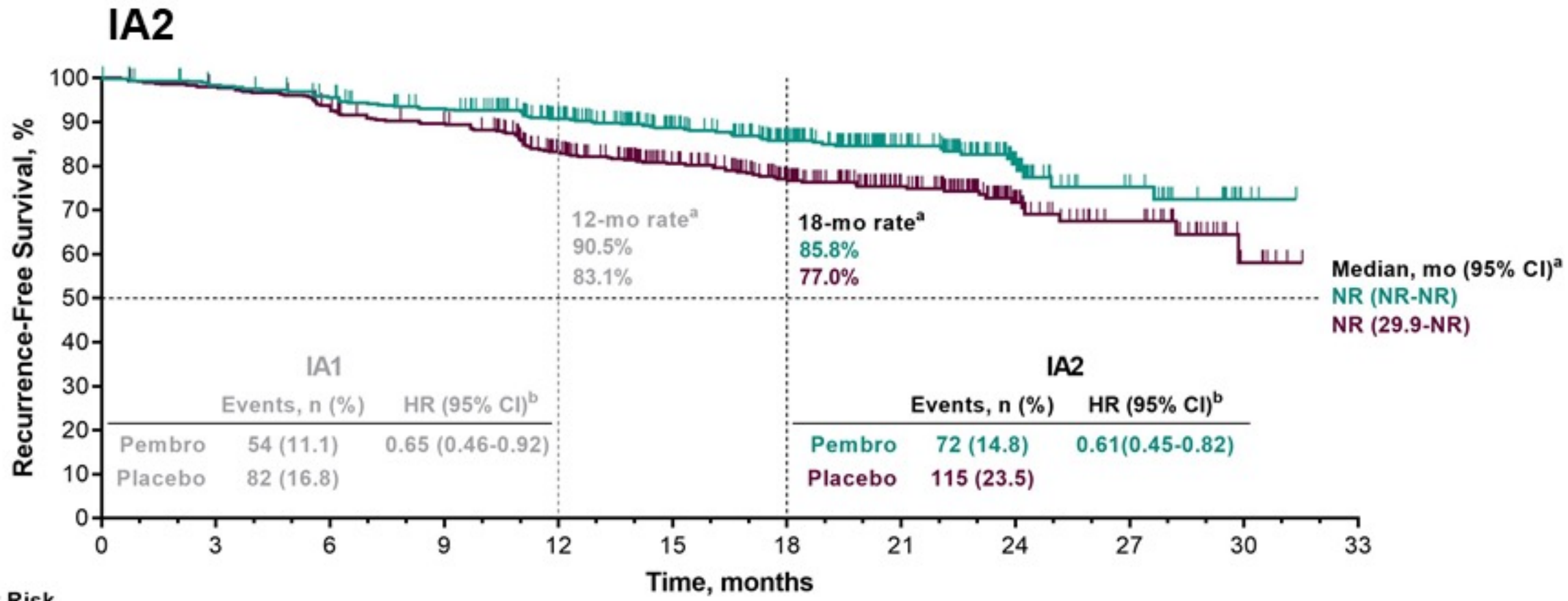
# KEYNOTE-716 Study Design
## (NCT03553836)




Courtesy of Jeffrey S Weber, MD, PhD

HRQoL, health related quality of life; OS, overall survival; Q3W, every 3 weeks; RFS, time from randomization to recurrence of melanoma at any site (skin, regional lymph nodes or distant) or death from any cause, whichever occurred first.

# Recurrence-Free Survival



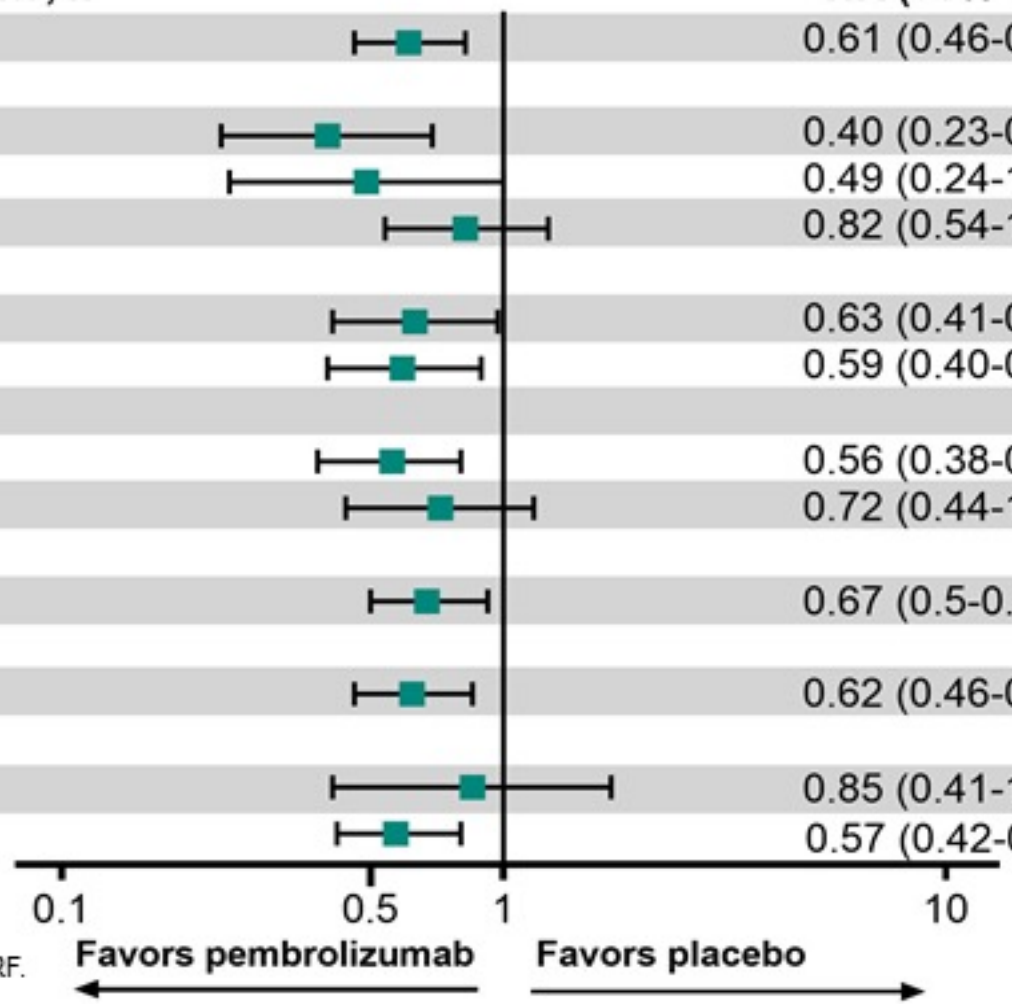

| No. at Risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 487 | 471 | 454 | 432 | 369 | 300 | 229 | 149 | 60 | 28 | 3 | 0 |
| Placebo | 489 | 476 | 451 | 425 | 352 | 273 | 213 | 151 | 63 | 34 | 6 | 0 |

Courtesy of Jeffrey S Weber, MD, PhD

[a]From product-limit (Kaplan-Meier) method for censored data. [b]Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T category (T3b vs T4a vs T4b). IA1 data cutoff: December 04, 2020. IA2 data cutoff: June 21, 2021.

# Recurrence-Free Survival: Subgroup Analysis

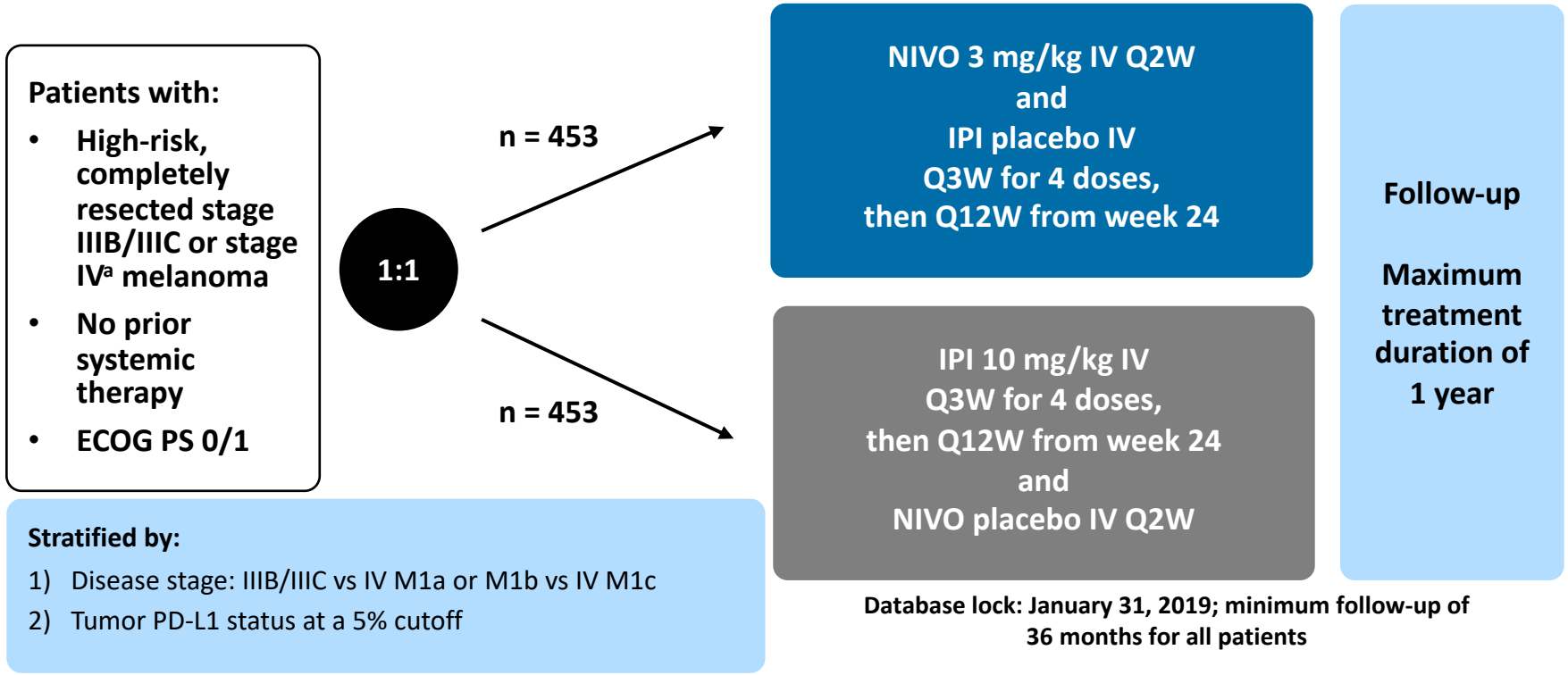
| Subgroup | Events/Patients, n | HR (95% CI) |
|---|---|---|
| **Overall** | 187/976 | 0.61 (0.46-0.82) |
| **T category**[a] | | |
| T3b | 62/400 | 0.40 (0.23-0.69) |
| T4a | 35/225 | 0.49 (0.24-1.00) |
| T4b | 84/340 | 0.82 (0.54-1.26) |
| **Age, years** | | |
| <65 | 87/598 | 0.63 (0.41-0.97) |
| ≥65 | 100/378 | 0.59 (0.40-0.89) |
| **Gender** | | |
| Male | 119/589 | 0.56 (0.38-0.80) |
| Female | 68/387 | 0.72 (0.44-1.17) |
| **Race** | | |
| White | 169/874 | 0.67 (0.5-0.92) |
| **ECOG status** | | |
| 0 | 166/906 | 0.62 (0.46-0.85) |
| **Geographic region** | | |
| US | 29/175 | 0.85 (0.41-1.75) |
| Non-US | 158/801 | 0.57 (0.42-0.80) |




[a]Based on actual baseline tumor stages IIB and IIC collected on eCRF.
Data cutoff: June 21, 2021.

Courtesy of Jeffrey S Weber, MD, PhD

# Adjuvant CheckMate 238 Study: Nivolumab vs Ipilimumab

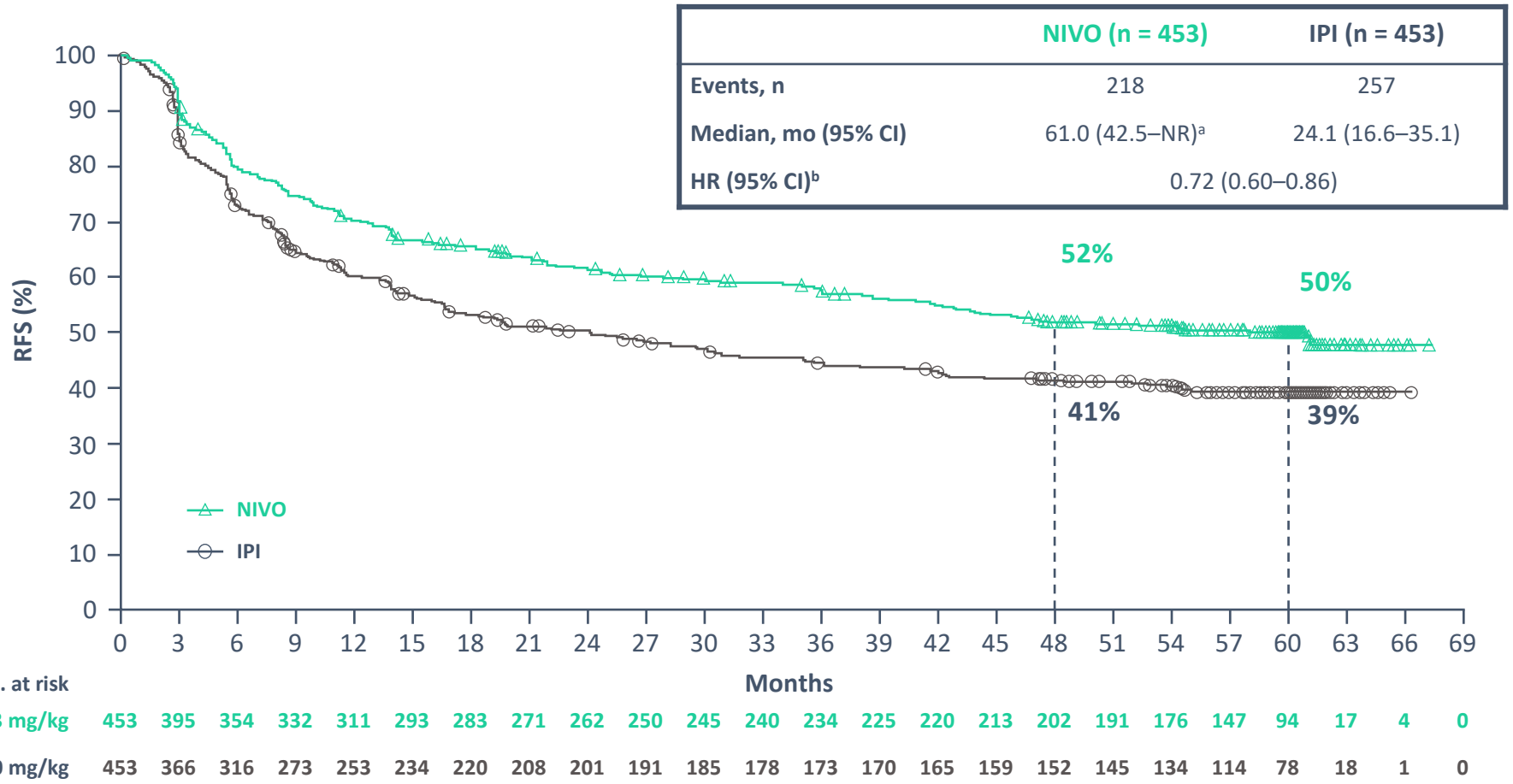



NCT02388906.[a]Per American Joint Committee on Cancer (AJCC) Cancer Staging Manual, seventh edition.

Weber J et al. *N Engl J Med.* 2017;377(19):1824-1835; SMR 2021

Courtesy of Jeffrey S Weber, MD, PhD

# Primary endpoint: 60-month RFS update in all patients




| | NIVO (n = 453) | IPI (n = 453) |
|---|---|---|
| Events, n | 218 | 257 |
| Median, mo (95% CI) | 61.0 (42.5–NR)[a] | 24.1 (16.6–35.1) |
| HR (95% CI)[b] | 0.72 (0.60–0.86) | |

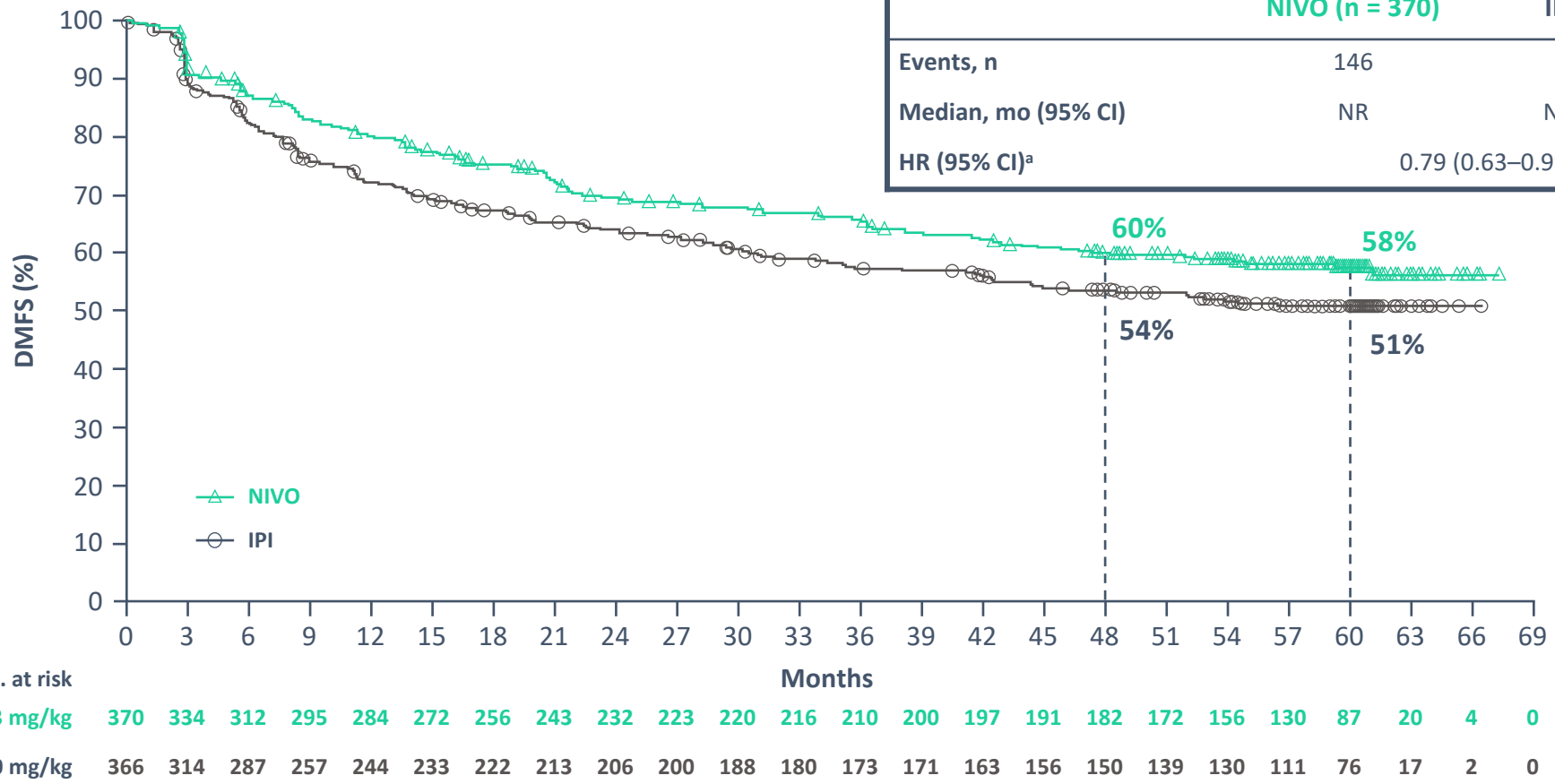
- New events since 4-year database lock: 6 (NIVO – 4 regional, 2 distant) and 4 (IPI – 1 each of local, distant, new primary, and death)

[a]Median not stable. [b]Stratified. Mo, month; NR, not reached. **Weber J et al SMR 2021**

Courtesy of Jeffrey S Weber, MD, PhD

# Exploratory endpoint: 60-month DMFS update in stage IIIB–C patients

| | NIVO (n = 370) | IPI (n = 366) |
|---|---|---|
| Events, n | 146 | 164 |
| Median, mo (95% CI) | NR | NR (42.4–NR) |
| HR (95% CI)[a] | 0.79 (0.63–0.99) | |

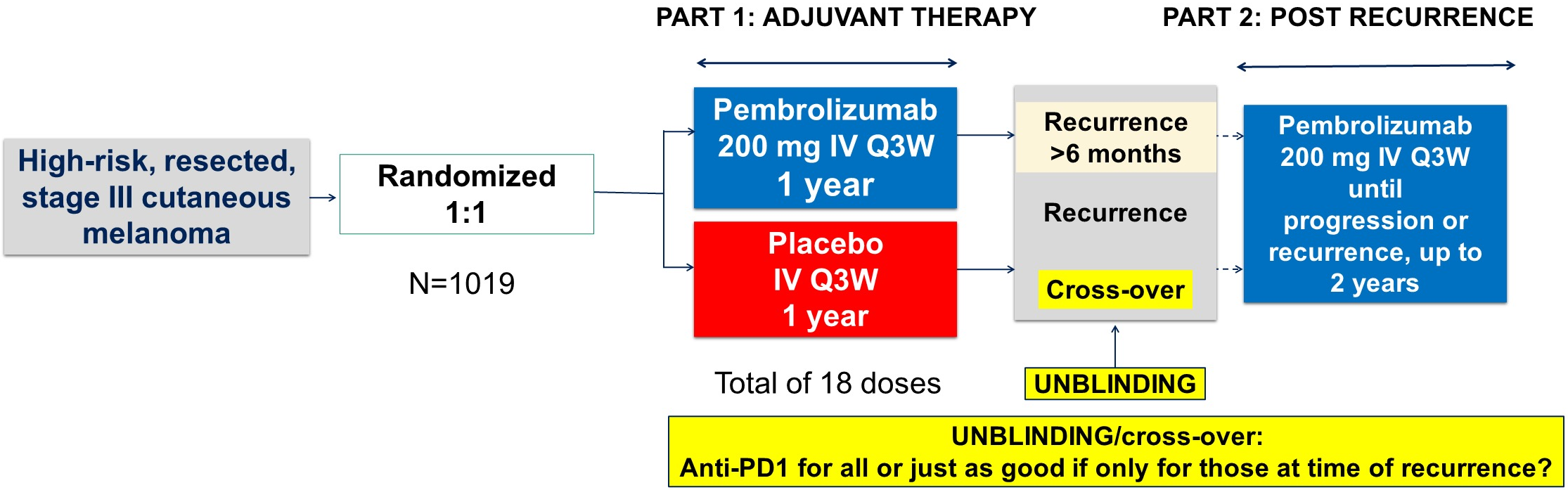



| No. at risk | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO 3 mg/kg | 370 | 334 | 312 | 295 | 284 | 272 | 256 | 243 | 232 | 223 | 220 | 216 | 210 | 200 | 197 | 191 | 182 | 172 | 156 | 130 | 87 | 20 | 4 | 0 |
| IPI 10 mg/kg | 366 | 314 | 287 | 257 | 244 | 233 | 222 | 213 | 206 | 200 | 188 | 180 | 173 | 171 | 163 | 156 | 150 | 139 | 130 | 111 | 76 | 17 | 2 | 0 |

[a]Stratified. NR, not reached. **Weber, J et al SMR 2021**

Courtesy of Jeffrey S Weber, MD, PhD

# EORTC 1325/KEYNOTE-54 Study Design




**Stratification factors:**

✓**AJCC-7 Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes

✓**Region**: North America, European countries, Australia/New Zealand, other countries

**Primary Endpoints:**

- **RFS (per investigator) in overall ITT population,** and **in patients with PD-L1-positive tumors**

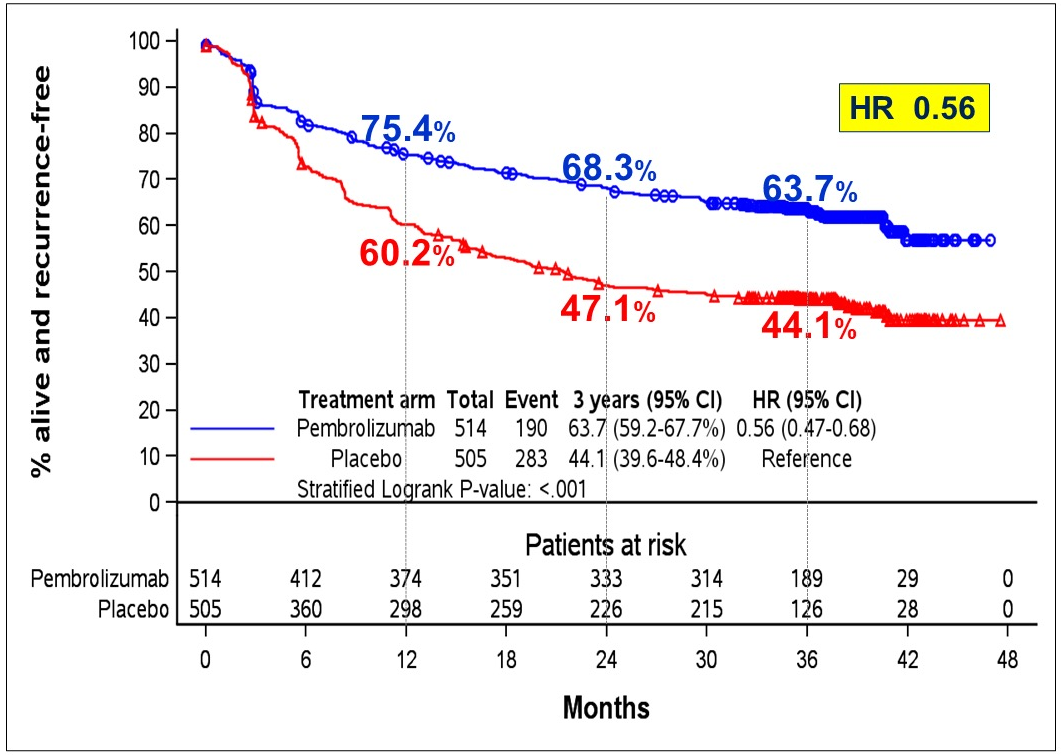
**Secondary Endpoints:**

- **DMFS and OS** in these 2 populations; **Safety, Health-related quality of life**

# EORTC 1325/KEYNOTE-54: RFS (ASCO 2020) and DMFS (ESMO 2020)

## RFS updated analysis @ 3YR (ASCO 2020)[1]

- ***Cut-off date*** (30-Sep-2019); median follow-up: **3** years; **473 RFS events**

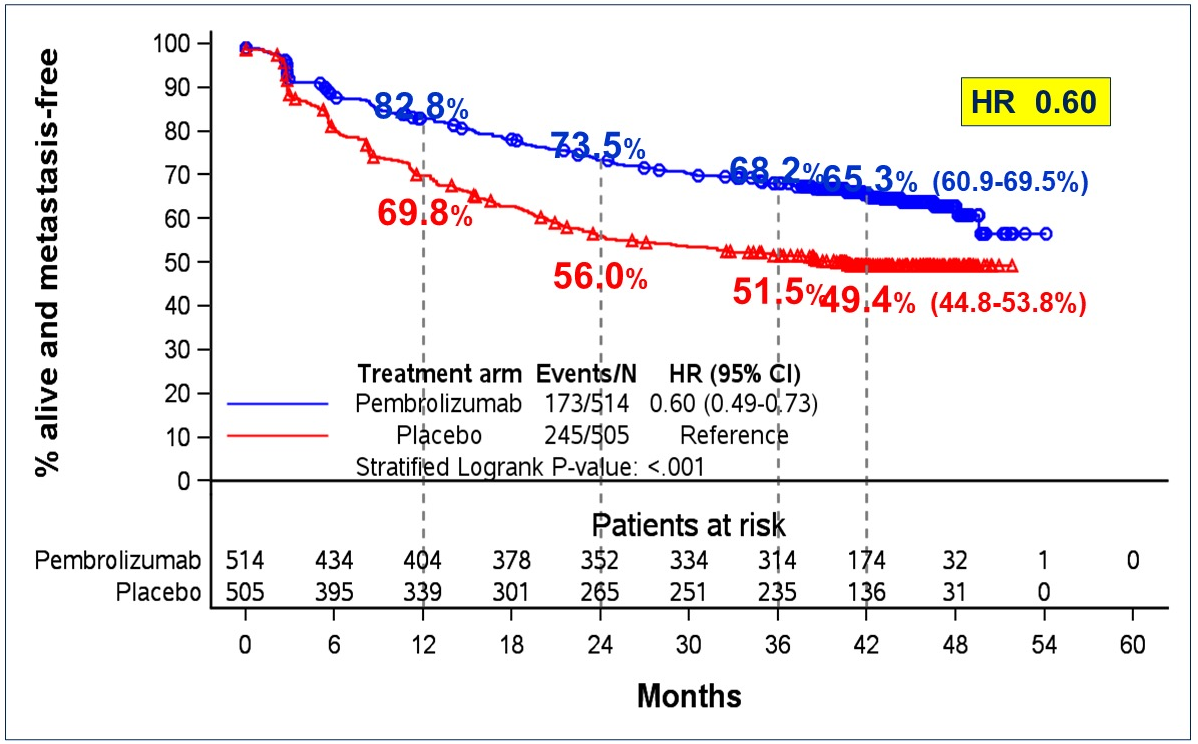



irAE: grade 1-5 (38%); grade 3-5 (7%)

[1]Eggermont AMM, et al. *J Clin Oncol* 2020;38:3925-36

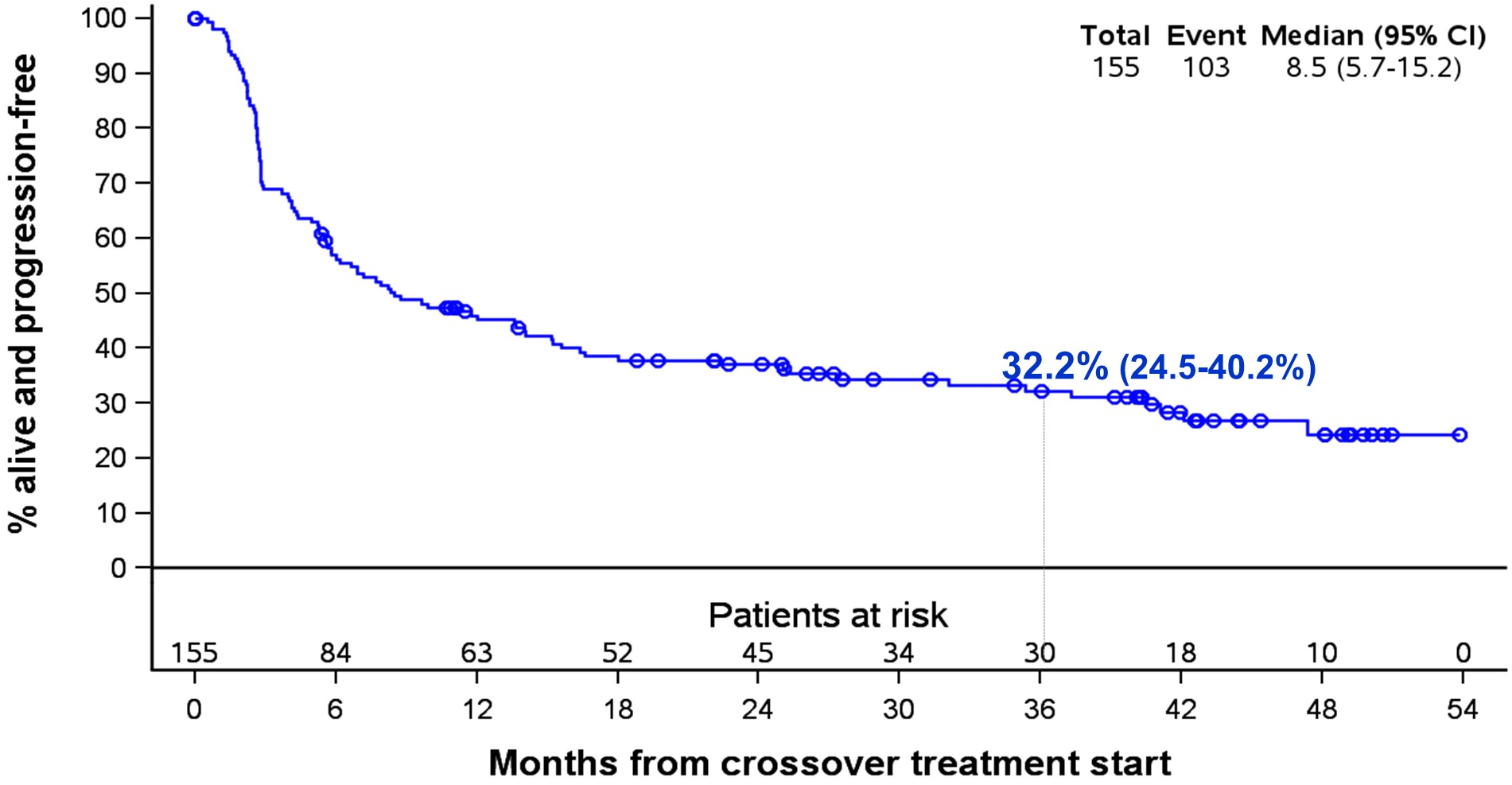
## DMFS final analysis @ 3.5 YR (ESMO 2020)[2]

- ***Cut-off date*** (3-Apr-2020); median follow-up: **3.5** years; **418 DMFS events** (423 planned: ~87% power HR=0.725)

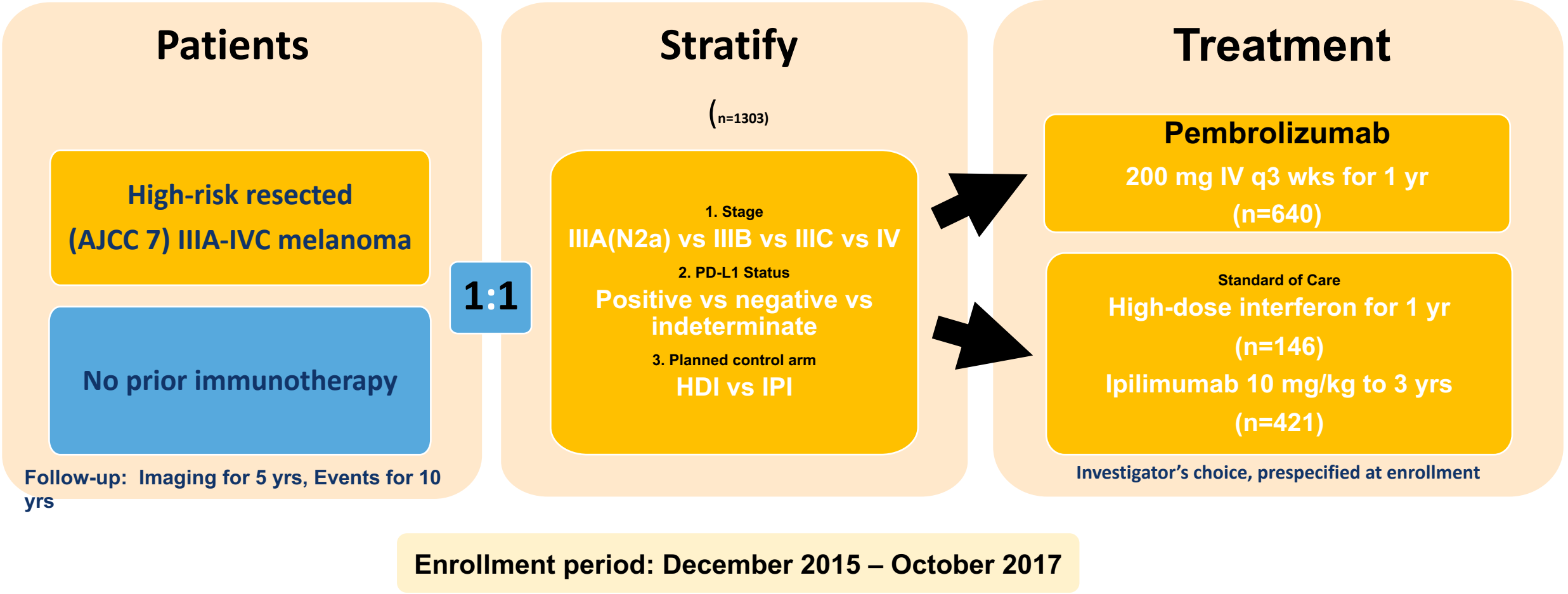



[2]Eggermont AMM, et al. *Lancet Oncol.* 2021;22:643-654

# EORTC 1325/KEYNOTE-54
## Crossover patients: Recurrence/Progression-free survival



# Study Design: S1404 Adjuvant Protocol

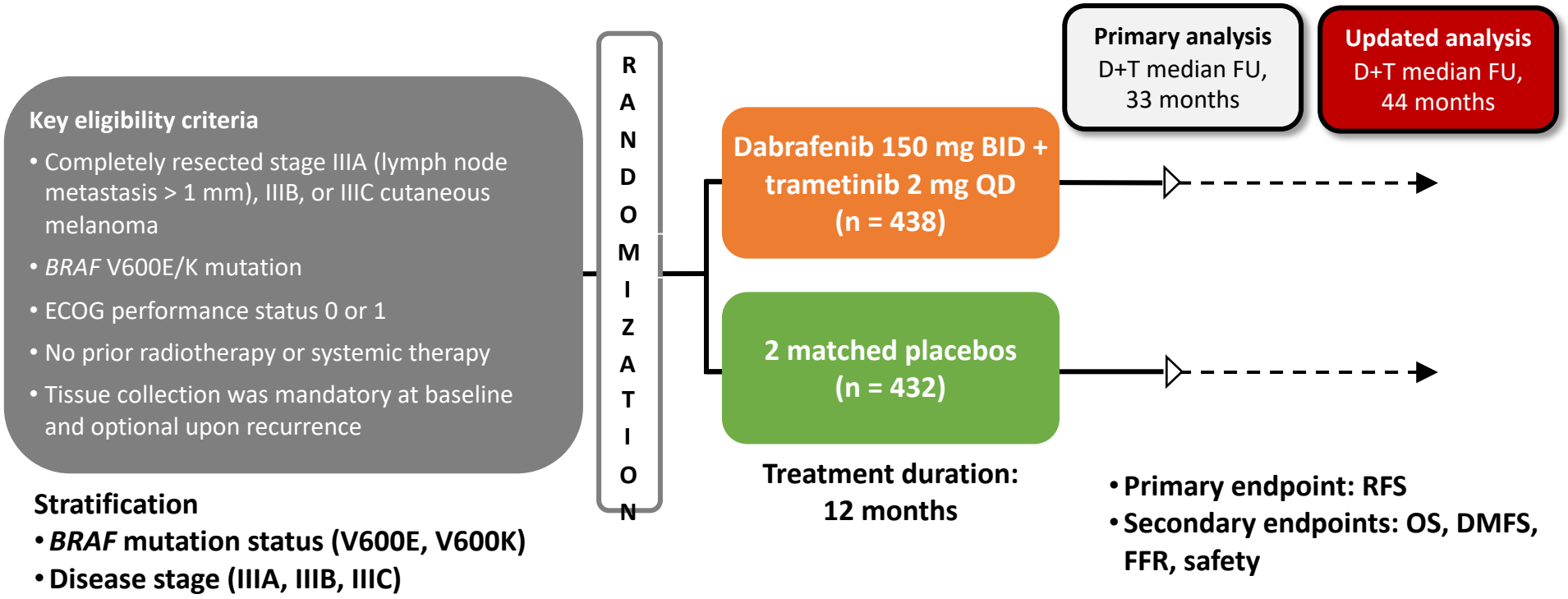



**Enrollment period: December 2015 – October 2017**

Kenneth F. Grossmann, M.D., Ph.D. ASCO 2021

Courtesy of Jeffrey S Weber, MD, PhD

# COMBI-AD Adjuvant Study Design— Extended Follow-up Analysis



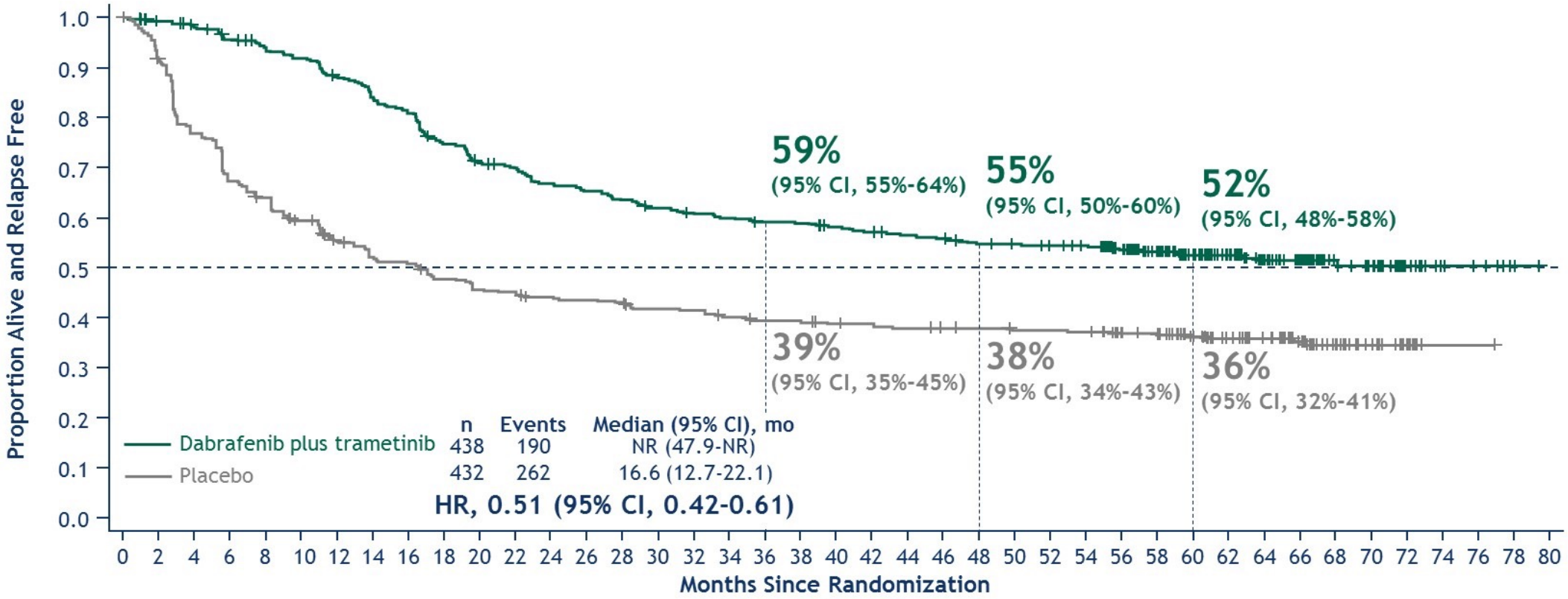

BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

.

**Long GV, et al. *N Engl J Med*. 2017;377:1813-1823, Hauschild, A et al ASCO 2020, Dummer, R et al NEJM 2020**

Courtesy of Jeffrey S Weber, MD, PhD

# Relapse-Free Survival ASCO 2020 5-year follow-up




No. at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dabrafenib plus trametinib | 438 | 413 | 405 | 391 | 381 | 372 | 354 | 335 | 324 | 298 | 281 | 275 | 262 | 256 | 249 | 242 | 236 | 233 | 229 | 228 | 221 | 217 | 213 | 210 | 204 | 202 | 199 | 195 | 176 | 156 | 133 | 109 | 92 | 80 | 45 | 38 | 17 | 8 | 6 | 2 | 0 |
| Placebo | 432 | 387 | 322 | 280 | 263 | 243 | 219 | 204 | 199 | 185 | 178 | 175 | 168 | 166 | 164 | 158 | 157 | 151 | 147 | 146 | 143 | 140 | 139 | 137 | 136 | 133 | 133 | 132 | 121 | 115 | 99 | 80 | 69 | 56 | 35 | 26 | 13 | 1 | 1 | 0 | 0 |

Dummer, R et al NEJM 2020.

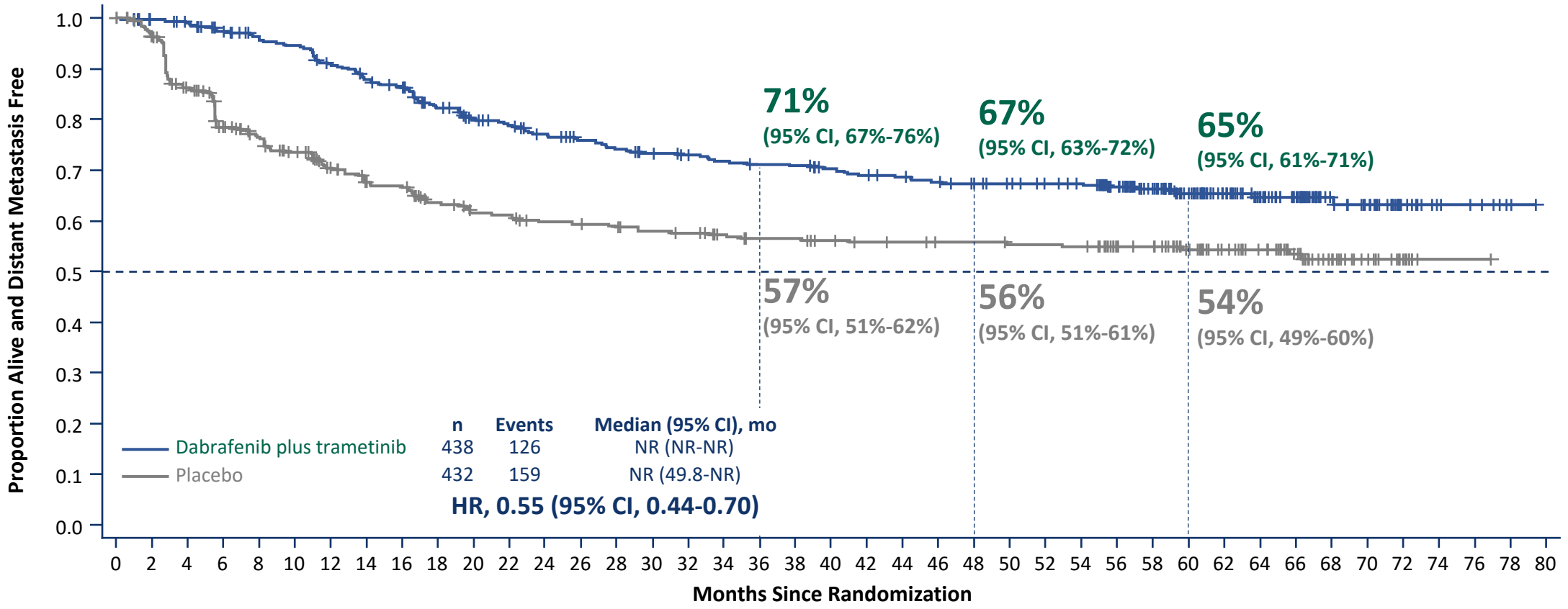
HR, hazard ratio; NR, not reached.





Courtesy of Jeffrey S Weber, MD, PhD

# COMBI-A/D 5-Yr Distant Metastasis-Free Survival




**No. at risk**

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dabrafenib plus trametinib | 438 | 413 | 407 | 390 | 380 | 373 | 352 | 336 | 327 | 301 | 285 | 278 | 265 | 257 | 251 | 243 | 238 | 234 | 231 | 230 | 223 | 219 | 216 | 212 | 208 | 205 | 201 | 197 | 179 | 158 | 135 | 110 | 93 | 80 | 45 | 38 | 17 | 8 | 6 | 2 | 0 |
| Placebo | 432 | 393 | 329 | 284 | 266 | 247 | 221 | 206 | 202 | 186 | 179 | 176 | 169 | 168 | 165 | 161 | 159 | 153 | 149 | 148 | 145 | 141 | 140 | 138 | 138 | 135 | 135 | 134 | 121 | 116 | 100 | 80 | 69 | 56 | 35 | 26 | 13 | 1 | 1 | 0 | 0 |

[a] Due to informative censoring, patients who had a local or regional first recurrence may not be represented in this analysis. Per protocol, patients with a first relapse at a locoregional site were not required to continue follow-up for distant metastases and were censored at the time of locoregional recurrence if follow-up was not complete.

Hauschild A, et al. Presented at ASCO 2020. Abstract 10001; Dummer, R et al NEJM 2020.

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# Conclusions:

- Adjuvant PEMBRO for stage IIB/C resected melanoma prolonged RFS with a HR of 0.66 and no significant decrease in quality of life
- Adjuvant therapy with PD-1 blockade using NIVO or PEMBRO in resected stage III melanoma is very effective, with a HR of 0.5 to 0.6 for RFS versus no therapy
- There was no OS advantage in Checkmate-238 for NIVO versus IPI
- Only 30% of patients that were on the placebo arm of Keynote-054 and crossed over to PEMBRO were progression-free at 3 years; in comparison, 60% of patients that received PEMBRO were without relapse at 3 years in the treatment arm
- Adjuvant DAB + TREM remains an excellent adjuvant choice with a RFS plateau at 5 years
- IPI + NIVO adjuvant therapy was not more effective than NIVO alone for patients with PD-L1+ tumors, or for those with stage IIIB/C versus IV, but was considerably more toxic
- Neoadjuvant therapy with IPI/NIVO or RELA/NIVO induces high rates of pCR or near pCR associated with prolonged RFS, but only randomized studies will show if this is just selection

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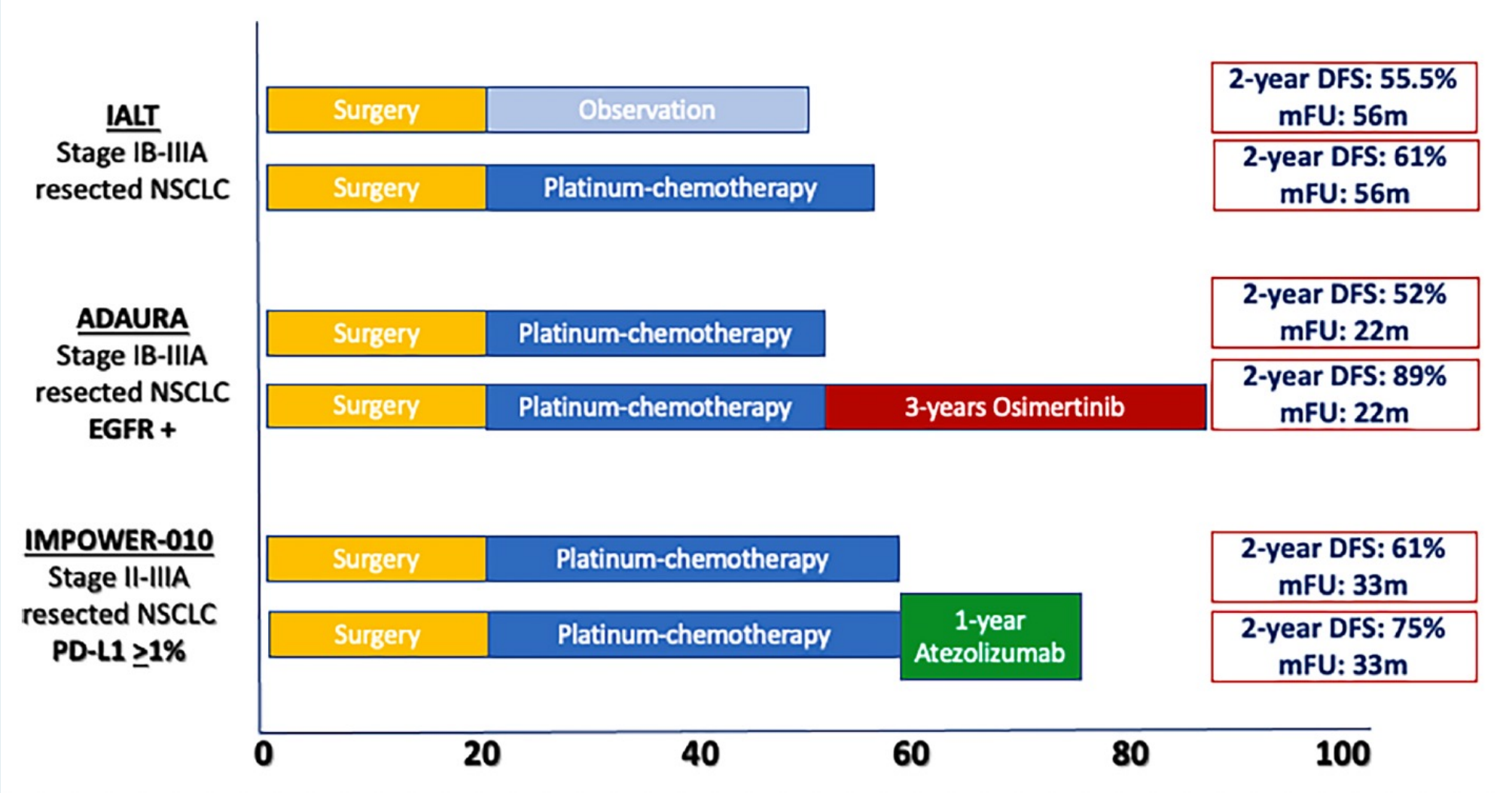
# Adjuvant Treatment Strategies for Surgically Resected NSCLC




Passiglia F et al. *Cancer Treat Rev* 2021;1010:102308.

# Adjuvant Approaches to Early Stage NSCLC

February 2022
RTP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# Based on a limited number of studies, the prevalence of EGFR mutations appears broadly similar across disease stages

## Overall estimated prevalence[1]

**Asian:**
**30–40%**

**Caucasian:**
**10–20%**

## Prevalence estimates for each stage:[a]

| Disease stage | Asia | US[b] | Europe |
|---|---|---|---|
| Stage I | 34.4–54.8 | 19.0–40.5 | 11.5–26.5 |
| Stage II | 24.5–47.6 | 14.9–33.3 | 4.4–11.1 |
| Stage III | 27.8–47.3 | 17.4–42.9 | 12.0[c] |
| Stage IV | 33.3–48.9 | 35.6–40.0 | 21.7[c] |

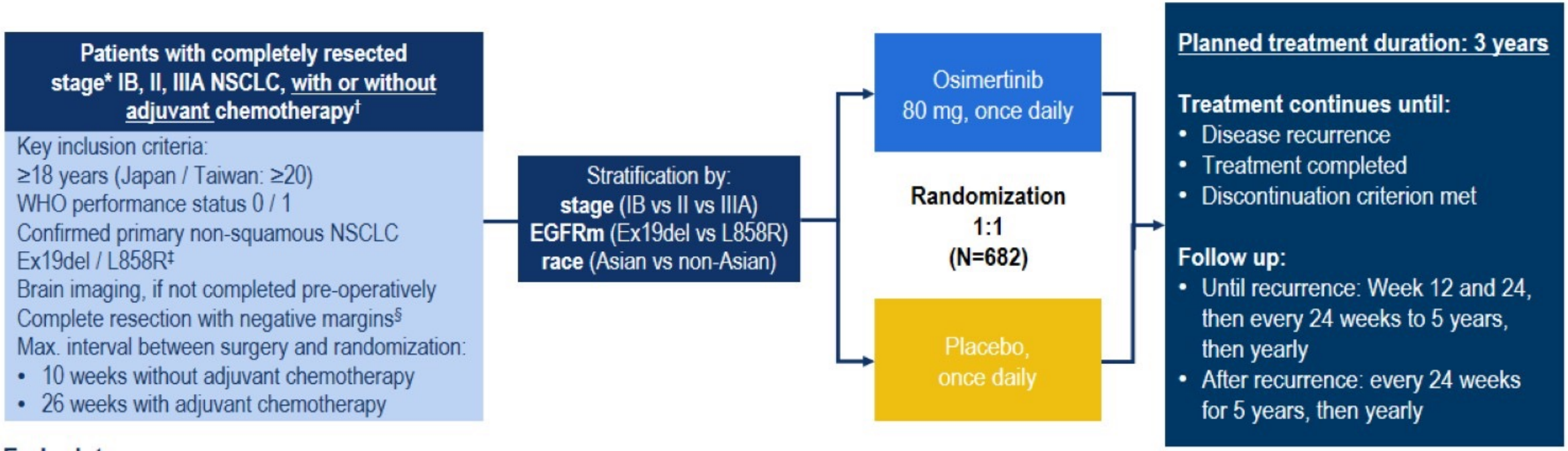
**If EGFR-TKIs were available in the resectable setting, a similar proportion of patients may be able to benefit compared to the advanced setting**

[a]References for calculations of prevalence estimates for each disease stage are listed in the slide notes; [b]US studies are adenocarcinoma histology only;
[c]Based on a single study

Note that prevalence in resectable disease is not fully verified, the increased prevalence of EGFR mutations in the metastatic dataset may partially reflect referral bias, and differences between sequencing platforms and mutation calling algorithms may further account for variation in prevalence estimates

1. Li T, et al. *J Clin Oncol* 2013;31:1039–1049

# ADAURA Phase III double-blind study design




## 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**

DFS: Disease Free Survival, OS: Overall Survival

Wu, Herbst, et al. NEJM Sept 2020 DOI: 10.1056/NEJMoa2027071

Courtesy of Roy S Herbst, MD, PhD

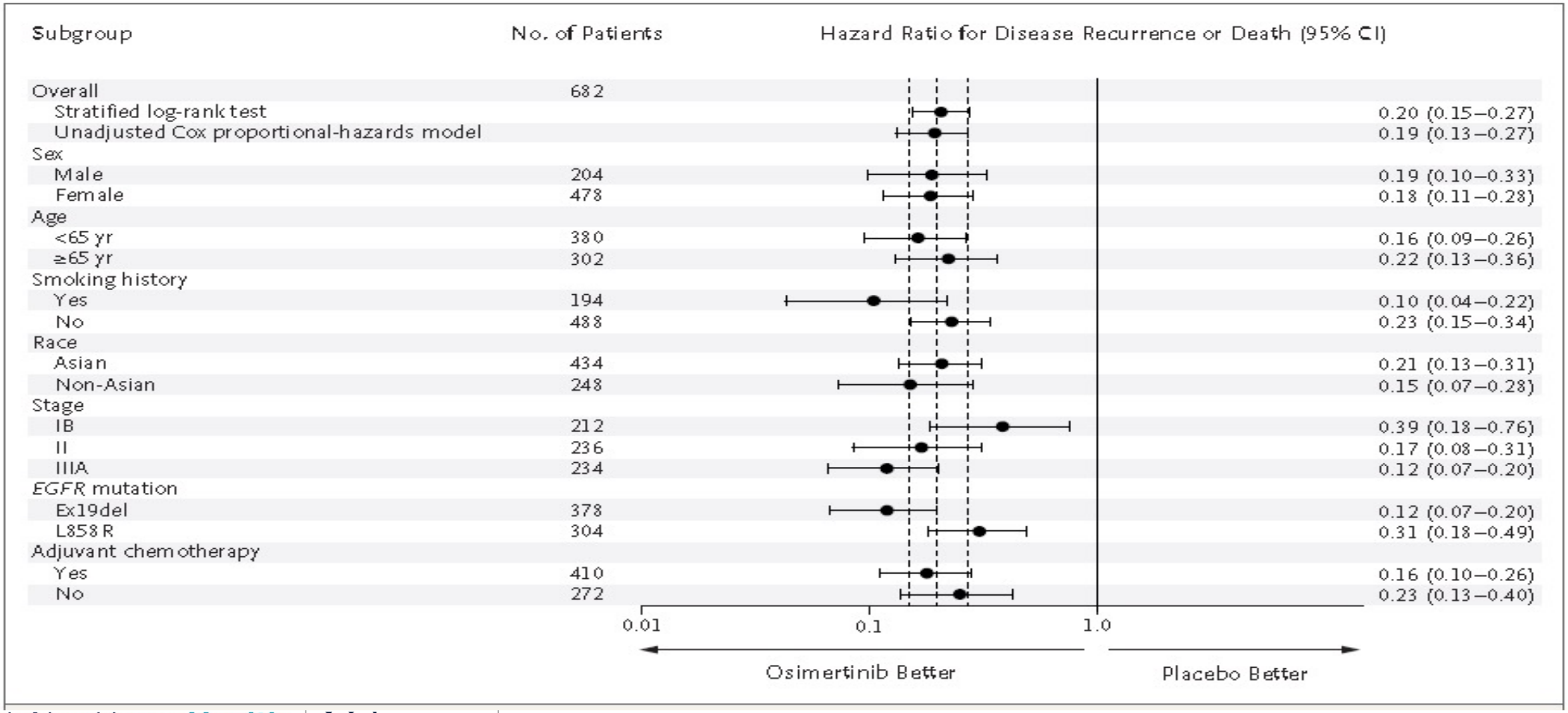
# ADAURA: Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
| --- | --- |
| Adults ≥18 years (≥20 years in patients from Japan and Taiwan) | Previous randomization and treatment in the present study |
| Primary non-squamous NSCLC,<br>**post-operatively staged as IB–IIIA** | Prior treatment with:<br>- pre- or post-operative **radiotherapy**,<br>- **pre-operative chemotherapy**,<br>- EGFR-TKIs,<br>- CYP3A4 inhibitors (≤ 3 weeks prior), |
| **Central confirmation** of Ex19del or L858R EGFR mutation | Time between surgery and randomization:<br>- 10 (if **no** adjuvant chemotherapy was used) or<br>- 26 weeks (if adjuvant chemotherapy was used) |
| Standard **post-operative adjuvant chemotherapy**, consisting of a platinum-based doublet for 4 cycles maximum, is **allowed but not mandatory** | Patients who have had only **segmentectomies or wedge resections** |
| **Complete surgical resection** of the primary NSCLC and recovery from resection surgery; treatment to start no earlier than 4 weeks following surgery | Cardiac criteria including factors that could increase the risk of QTc prolongation or any arrhythmic events |
| **An MRI or CT scan** of the brain prior to surgery | Any evidence of severe or uncontrolled systemic diseases; |
| WHO Performance Status of 0 to 1 | Medical history of ILD or any other malignancies |

Courtesy of Roy S Herbst, MD, PhD

Wu, Herbst, et al. NEJM Sept 2020 DOI: 10.1056/NEJMoa2027071

# Subgroup Analysis of Disease Recurrence or Death, According to Investigator Assessment

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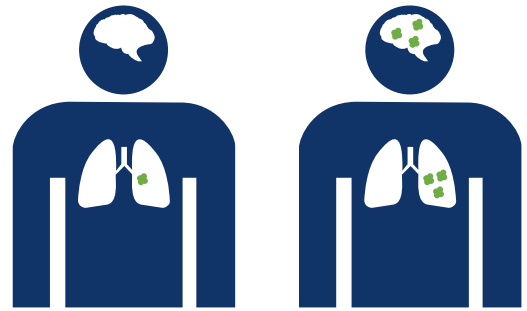
Wu, Herbst, et al. NEJM Sept 2020 DOI: 10.1056/NEJMoa2027071

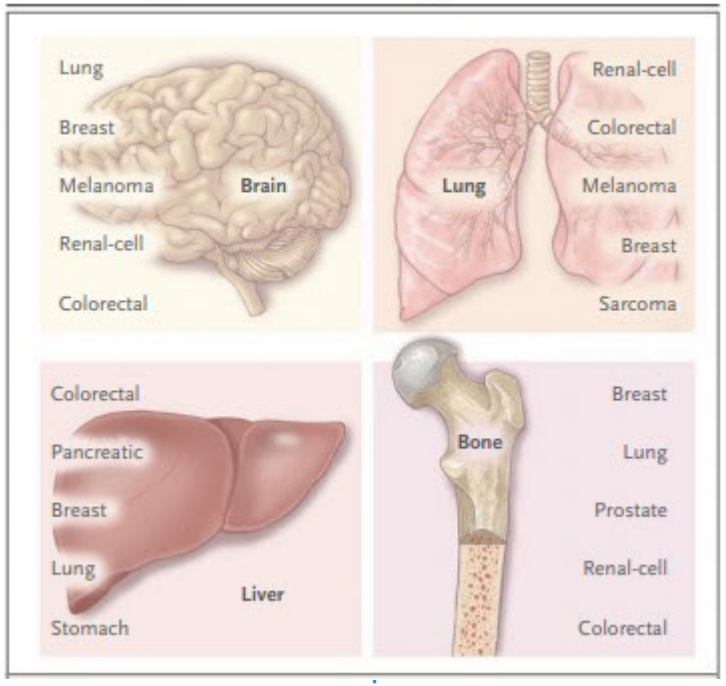
Courtesy of Roy S Herbst, MD, PhD

# Additional Considerations

1

## Local versus distant recurrence






2

3

## Subsequent therapies

## Quality of life

4

A. Chiang and J. Massague. N Engl J Med. 2008 Dec 25; 359(26): 2814–2823.

CNS, central nervous system.

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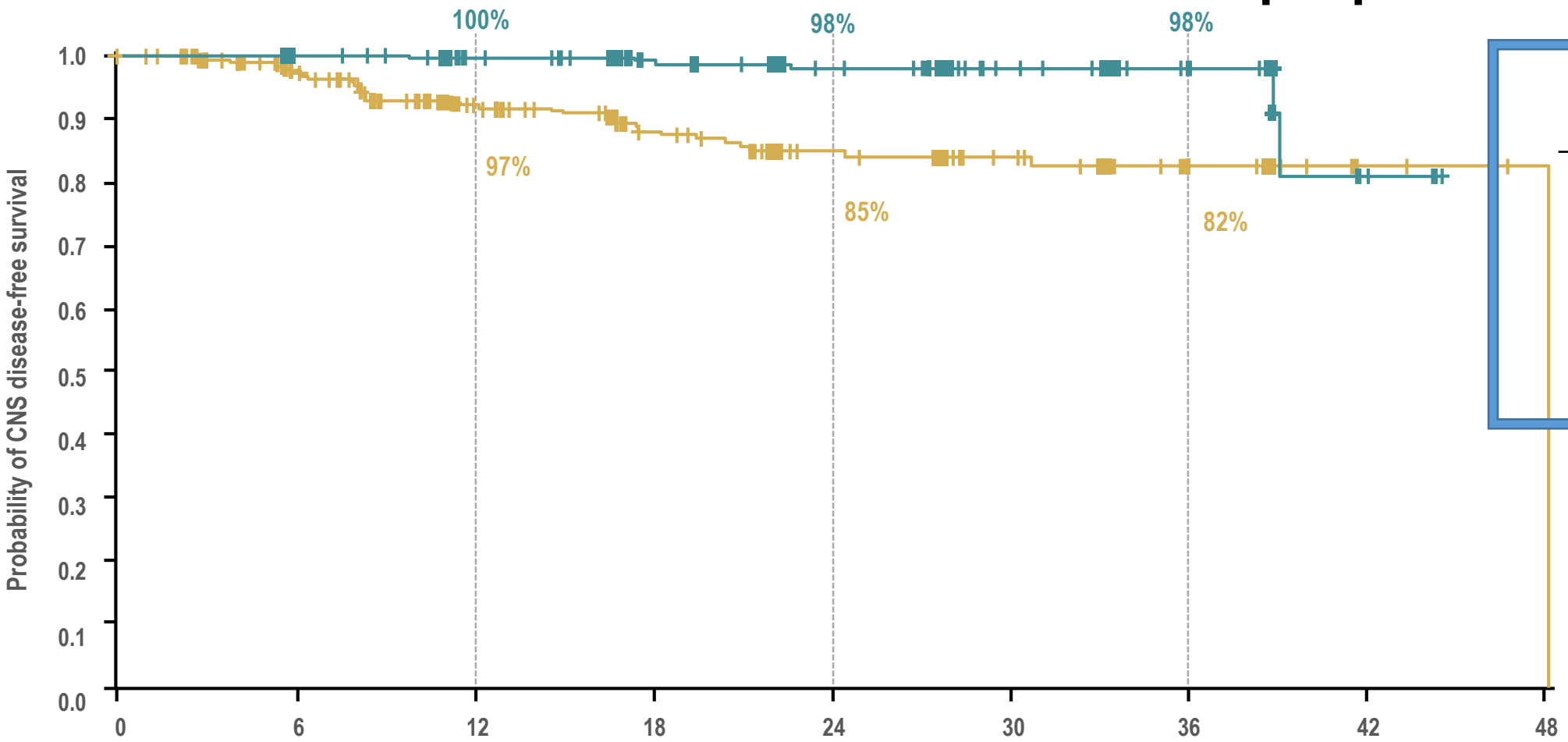
Courtesy of Roy S Herbst, MD, PhD

# ADAURA :CNS DFS in the overall population




| No at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 339 | 313 | 272 | 209 | 138 | 74 | 28 | 5 | 0 |
| Placebo | 343 | 288 | 208 | 149 | 88 | 53 | 20 | 3 | 1 |

| Median CNS DFS, months (95% CI) | |
|---|---|
| Osimertinib | NR (39, NC) |
| Placebo | 48.2 (NC, NC) |
| HR* (95% CI) | 0.18 (0.10, 0.33); p<0.0001 |

Maturity 7%:
osimertinib 2%, placebo 11%

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

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Wu, Herbst, et al. NEJM Sept 2020 DOI: 10.1056/NEJMoa2027071

Courtesy of Roy S Herbst, MD, PhD

# Adjuvant chemotherapy use

- Overall, 410 / 682 (60%) patients received adjuvant chemotherapy, for a median duration of 4.0 (Q1: 4.0, Q3: 4.0) cycles, consistent across treatment arms
- The majority of patients (409 / 410)* received platinum-based† chemotherapy, most with stage II / IIIA disease (76%), and fewer with stage IB disease (26%)
- Adjuvant chemotherapy use was more frequent in patients aged <70 years and in patients enrolled in Asia, and was not influenced by WHO PS (0 or 1)

| Characteristic | Patients, n | Received adjuvant chemotherapy |
|---|---|---|
| Stage IB | 216 | 26%‡ |
| Stage II | 231 | 71%‡ |
| Stage IIIA | 235 | 80%‡ |
| Aged <70 years | 509 | 66% |
| Aged ≥70 years | 173 | 42% |
| WHO PS 0 | 434 | 60% |
| WHO PS 1 | 248 | 60% |
| Enrolled in Asia¶ | 414 | 65%§ |
| Enrolled outside of Asia# | 268 | 53% |

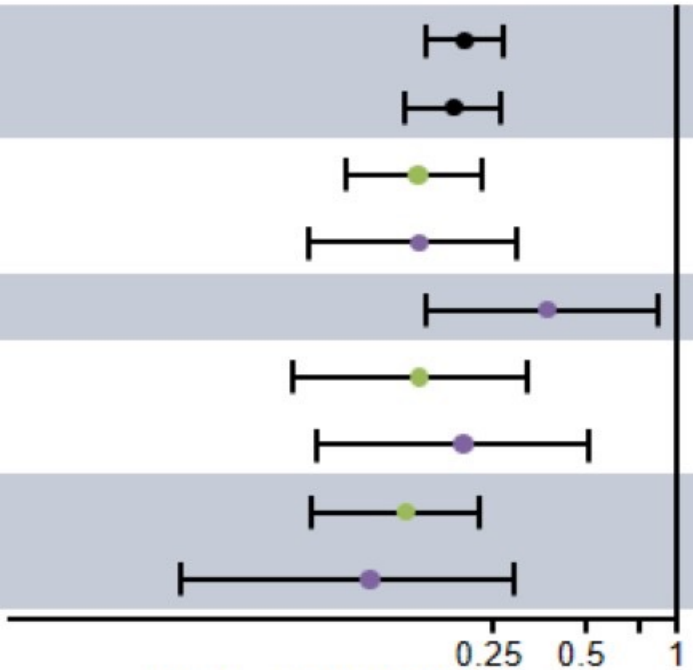
ADAURA data cut-off: January 17, 2020.
*One patient received only single-agent non-platinum chemotherapy (pemetrexed) as adjuvant treatment with an adjunct traditional Chinese medicine (protocol deviation); †Predominantly cisplatin- or carboplatin-based (cisplatin: n=275; carboplatin: n=139); ‡Includes only patients who received platinum-based chemotherapy (n=409); ¶No Japan patients with stage IB disease; §Japan: n=71; China: n=106; Asia non-Japan, non-China: n=91); #Enrolled in Europe, Australia, United States, Canada or Brazil.



Courtesy of Roy S Herbst, MD, PhD

# DFS in patients with and without adjuvant chemotherapy, by disease stage

| Subgroup | | HR | 95% CI |
|---|---|---|---|
| Overall (N=682) | Stratified log-rank | 0.20 | 0.15, 0.27 |
| | Unadjusted Cox PH | 0.19 | 0.13, 0.27 |
| Stage II / IIIA | With adjuvant chemotherapy (n=352) | 0.14 | 0.08, 0.23 |
| | Without adjuvant chemotherapy (n=118) | 0.15 | 0.06, 0.30 |
| Stage IB* | Without adjuvant chemotherapy (n=154) | 0.38 | 0.15, 0.88 |
| Stage II | With adjuvant chemotherapy (n=166) | 0.15 | 0.06, 0.32 |
| | Without adjuvant chemotherapy (n=70) | 0.20 | 0.07, 0.52 |
| Stage IIIA | With adjuvant chemotherapy (n=186) | 0.13 | 0.06, 0.23 |
| | Without adjuvant chemotherapy (n=48) | 0.10 | 0.02, 0.29 |




- Overall population
- Patients with adjuvant chemotherapy
- Patients without adjuvant chemotherapy

ADAURA data cut-off: January 17, 2020.
Performed using a Cox proportional hazards model including treatment, subgroup and a treatment-by-subgroup interaction term.
*Subgroup categories with less than 20 events, such as patients with stage IB disease with adjuvant chemotherapy, were excluded from the analysis. A HR of less than 1 favors osimertinib.



Courtesy of Roy S Herbst, MD, PhD

# ADAURA: Summary

- A clinically meaningful DFS benefit with osimertinib was observed in patients **with or without adjuvant chemotherapy (DFS HR of 0.16 and 0.23 respectively)** regardless of disease state.

- Higher disease recurrence rates observed among patients in placebo arm who received adjuvant chemotherapy compared to those who didn't were likely driven by the large proportion of patients with stage II/IIIA, as disease stage is a prognostic factor for disease outcome.

- **Overall HRQoL was maintained** with adjuvant osimertinib treatment with no clinically meaningful differences vs placebo despite prolonged treatment.

**Adjuvant osimertinib will provide a highly effective, practice changing treatment for patients with stage IB / II / IIIA *EGFR*m NSCLC after complete tumor resection.**



Courtesy of Roy S Herbst, MD, PhD

# Next Steps

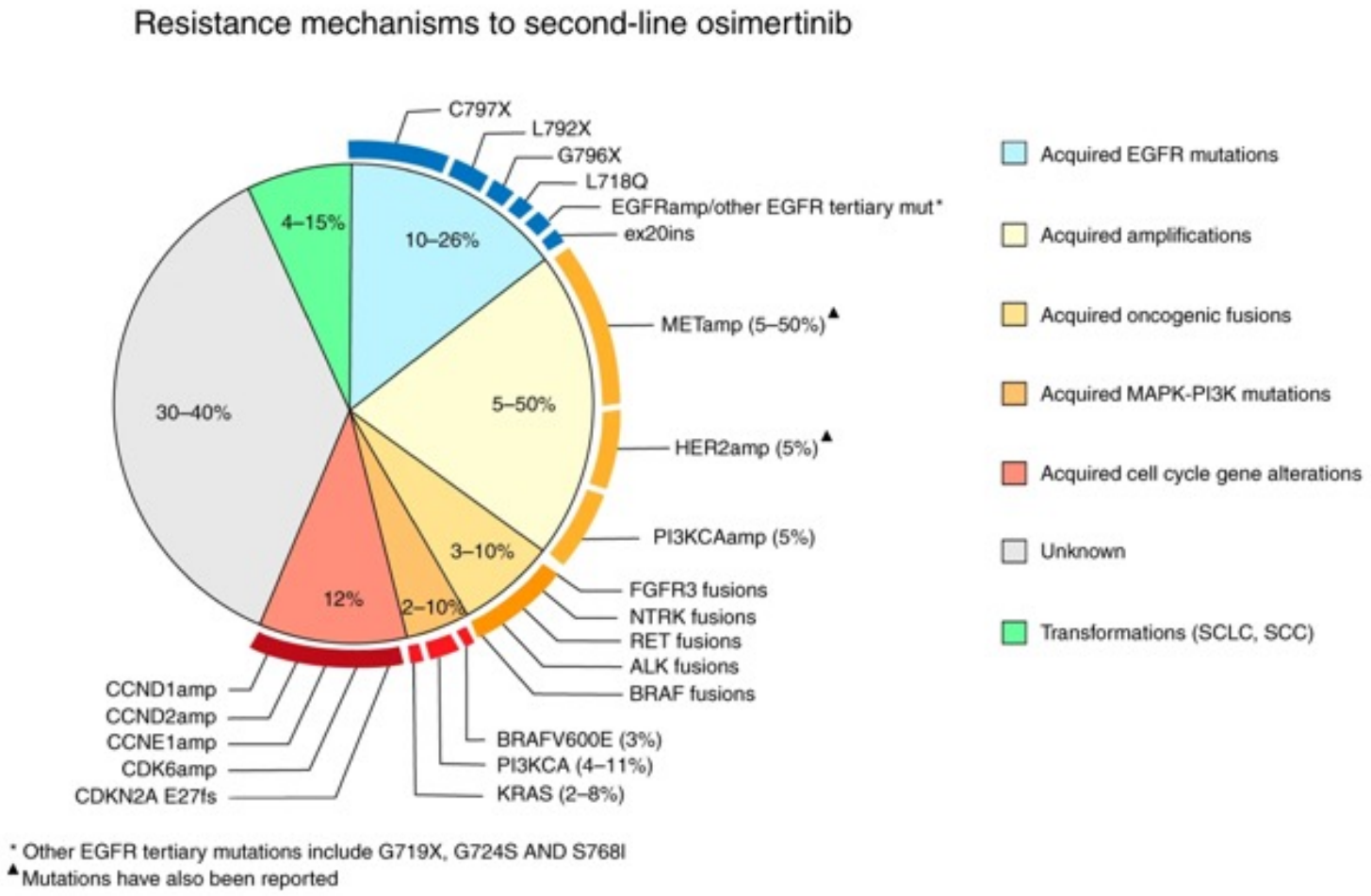
- NeoAdaura (Neoadjuvant)
- Laura (Stage III)
- Combo studies
- Other Agents

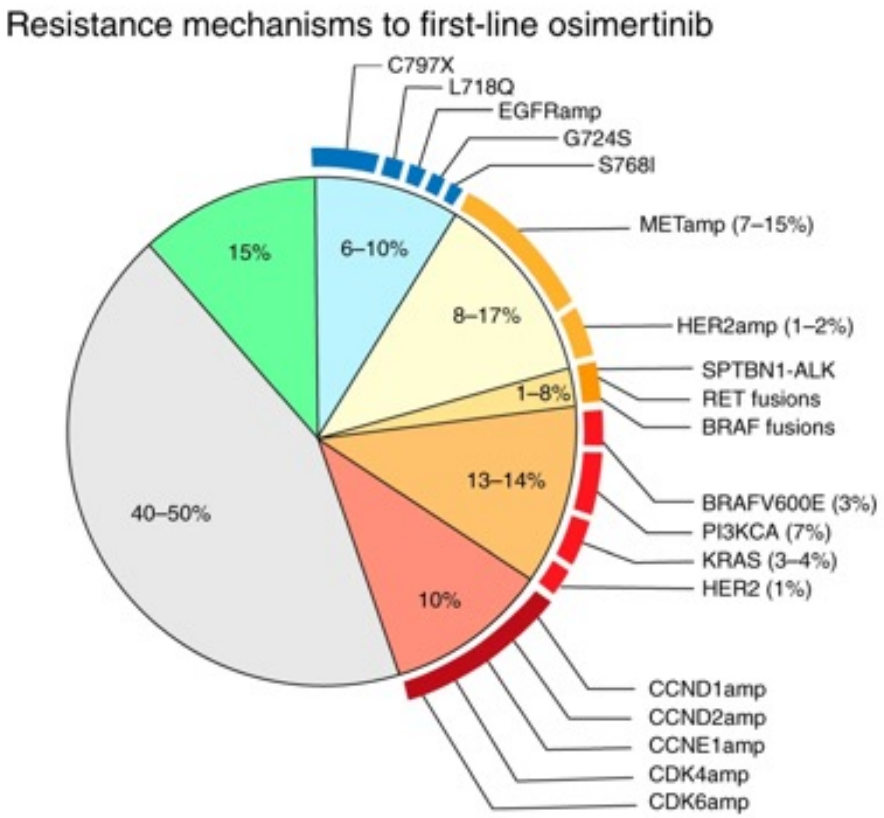


1. Herbst et al. J Clin Oncol.2020;38:18_suppl.LBA5.
ADAURA data cut-off: 17 January, 2020

Courtesy of Roy S Herbst, MD, PhD

# Resistance mechanisms to osimertinib



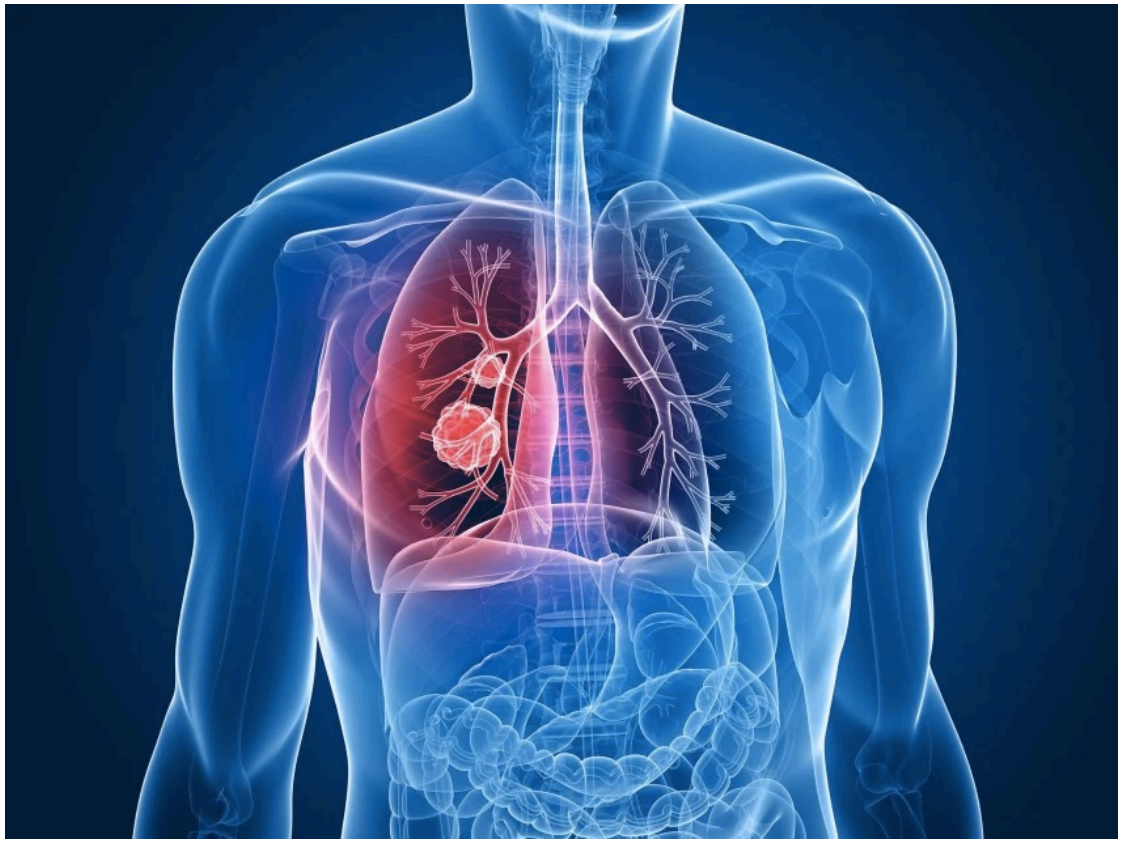




Leonetti A, et al. BJC 2019

Courtesy of Roy S Herbst, MD, PhD

# Can We Bring Our Best Agents from the Metastatic Setting Earlier?

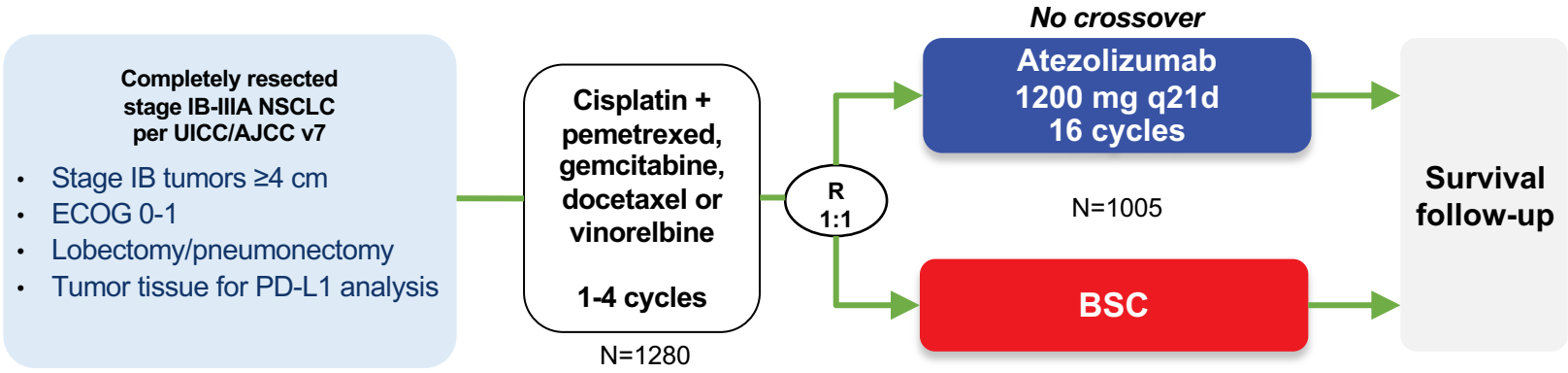
Immunotherapy





Courtesy of Roy S Herbst, MD, PhD

# IMpower010: study design




**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

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

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IMpower010 Interim Analysis
https://bit.ly/33t6JJP

# IMpower010: baseline characteristics

| Characteristic | All patients (N=1005) | PD-L1 TC ≥1% (SP263) (stage II-IIIA) | | All randomized (stage II-IIIA) | | ITT (stage IB-IIIA) | |
|---|---|---|---|---|---|---|---|
| | | Atezolizumab (n=248) | BSC (n=228) | Atezolizumab (n=442) | BSC (n=440) | Atezolizumab (n=507) | BSC (n=498) |
| Median (range) age, y | **62 (26-84)** | 61 (34–82) | 62 (26–84) | 62 (33–82) | 62 (26–84) | 62 (33–83) | 62 (26–84) |
| Age ≥65 y, n (%) | **382 (38.0)** | 92 (37.1) | 97 (42.5) | 161 (36.4) | 177 (40.2) | 184 (36.3) | 198 (39.8) |
| Sex, male, n (%) | **672 (66.9)** | 171 (69.0) | 147 (64.5) | 295 (66.7) | 294 (66.8) | 337 (66.5) | 335 (67.3) |
| Race, n (%) | | | | | | | |
| White | **738 (73.4)** | 162 (65.3) | 166 (72.8) | 307 (69.5) | 324 (73.6) | 362 (71.4) | 376 (75.5) |
| Asian | **242 (24.1)** | 78 (31.5) | 56 (24.6) | 121 (27.4) | 106 (24.1) | 130 (25.6) | 112 (22.5) |
| Other | **25 (2.5)** | 8 (3.2) | 6 (2.6) | 14 (3.2) | 10 (2.3) | 15 (3.0) | 10 (2.0) |
| ECOG PS, n (%) | | | | | | | |
| 0 | **556 (55.3)** | 140 (56.5) | 125 (54.8) | 239 (54.1) | 252 (57.3) | 273 (53.8) | 283 (56.8) |
| 1 | **446 (44.4)** | 107 (43.1) | 102 (44.7) | 201 (45.5) | 187 (42.5) | 232 (45.8) | 214 (43.0) |
| Histology, non-squamous, n (%) | **659 (65.6)** | 152 (61.3) | 143 (62.7) | 292 (66.1) | 296 (67.3) | 328 (64.7) | 331 (66.5) |
| Stage, n (%) | | | | | | | |
| IB | **123 (12.2)** | – | – | – | – | 65 (12.8) | 58 (11.6) |
| IIA | **295 (29.4)** | 85 (34.3) | 76 (33.3) | 147 (33.3) | 148 (33.6) | 147 (29.0) | 148 (29.7) |
| IIB | **174 (17.3)** | 46 (18.5) | 37 (16.2) | 90 (20.4) | 84 (19.1) | 90 (17.8) | 84 (16.9) |
| IIIA | **413 (41.1)** | 117 (47.2) | 115 (50.4) | 205 (46.4) | 208 (47.3) | 205 (40.4) | 208 (41.8) |
| Tobacco use history, n (%) | | | | | | | |
| Never | **222 (22.1)** | 51 (20.6) | 41 (18.0) | 100 (22.6) | 96 (21.8) | 114 (22.5) | 108 (21.7) |
| Current/previous | **783 (77.9)** | 197 (79.4) | 187 (82.0) | 342 (77.4) | 344 (78.2) | 393 (77.5) | 390 (78.3) |
| PD-L1 by SP263, TC≥1%, n (%)[a] | **535 (54.6)** | 248 (100) | 228 (100) | 248 (57.8) | 228 (53.0) | 283 (57.4) | 252 (51.9) |
| *EGFR* mutation status, n (%)[b] | | | | | | | |
| Positive | **117 (11.6)** | 23 (9.3) | 20 (8.8) | 49 (11.1) | 60 (13.6) | 53 (10.5) | 64 (12.9) |
| Negative | **527 (52.4)** | 123 (49.6) | 125 (54.8) | 229 (51.8) | 234 (53.2) | 261 (51.5) | 266 (53.4) |
| Unknown[c] | **361 (35.9)** | 102 (41.1) | 83 (36.4) | 164 (37.1) | 146 (33.2) | 193 (38.1) | 168 (33.7) |
| *ALK* rearrangement status, n (%)[b] | | | | | | | |
| Positive | **33 (3.3)** | 12 (4.8) | 11 (4.8) | 14 (3.2) | 17 (3.9) | 15 (3.0) | 18 (3.6) |
| Negative | **574 (57.1)** | 133 (53.6) | 121 (53.1) | 251 (56.8) | 256 (58.2) | 280 (55.2) | 294 (59.0) |
| Unknown[c] | **398 (39.6)** | 103 (41.5) | 96 (42.1) | 177 (40.0) | 167 (38.0) | 212 (41.8) | 186 (37.3) |

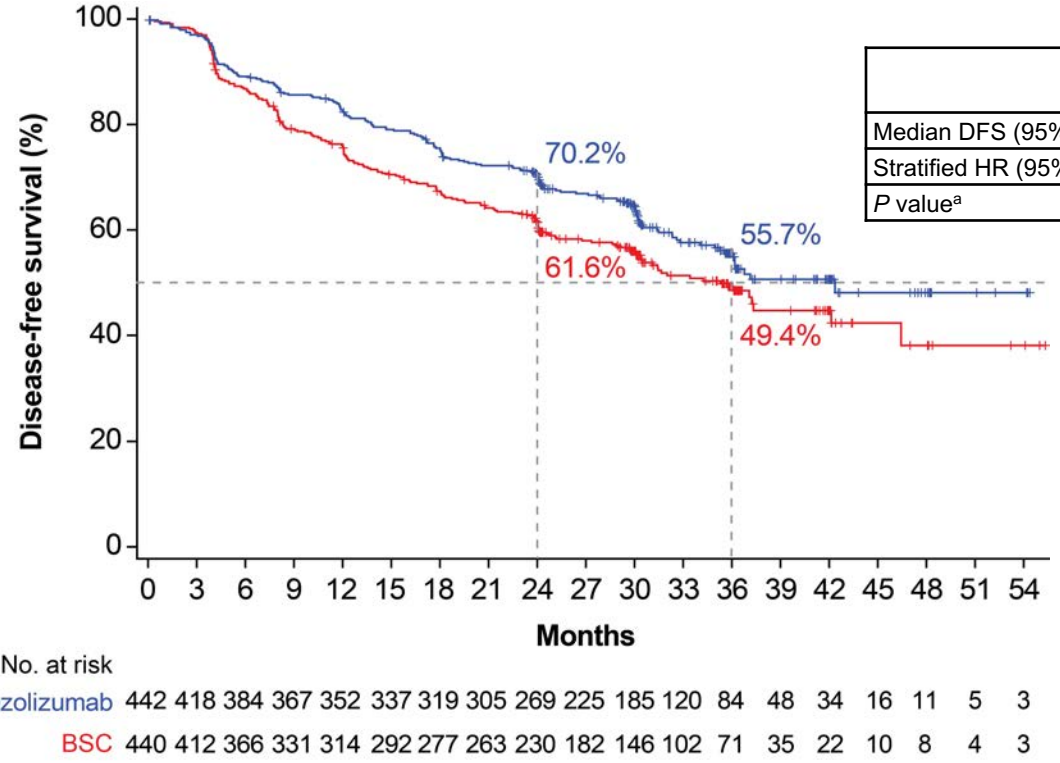
Clinical cutoff: January 21, 2021. [a] 26 patients in the ITT population had unknown PD-L1 status as assessed by SP263. [b] For patients with non-squamous NSCLC, *EGFR/ALK* status was assessed locally or centrally. [c] 89.2% of patients with unknown *EGFR* status and 80.7% of patients with unknown *ALK* status in the ITT population had squamous NSCLC and were not required to undergo local or central testing.

Dr. Heather A. Wakelee ASCO 2021, abstr 8500
IMpower010 Interim Analysis
https://bit.ly/33t6JJP



Courtesy of Roy S Herbst, MD, PhD

# IMpower010: DFS in the all-randomized stage II-IIIA population (primary endpoint)




| | Atezolizumab (n=442) | BSC (n=440) |
|---|---|---|
| Median DFS (95% CI), mo | 42.3 (36.0, NE) | 35.3 (30.4, 46.4) |
| Stratified HR (95% CI) | 0.79 (0.64, 0.96) | |
| *P* value[a] | 0.02[b] | |

*Median follow-up: 32.2 mo (range, 0-57.5)*

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

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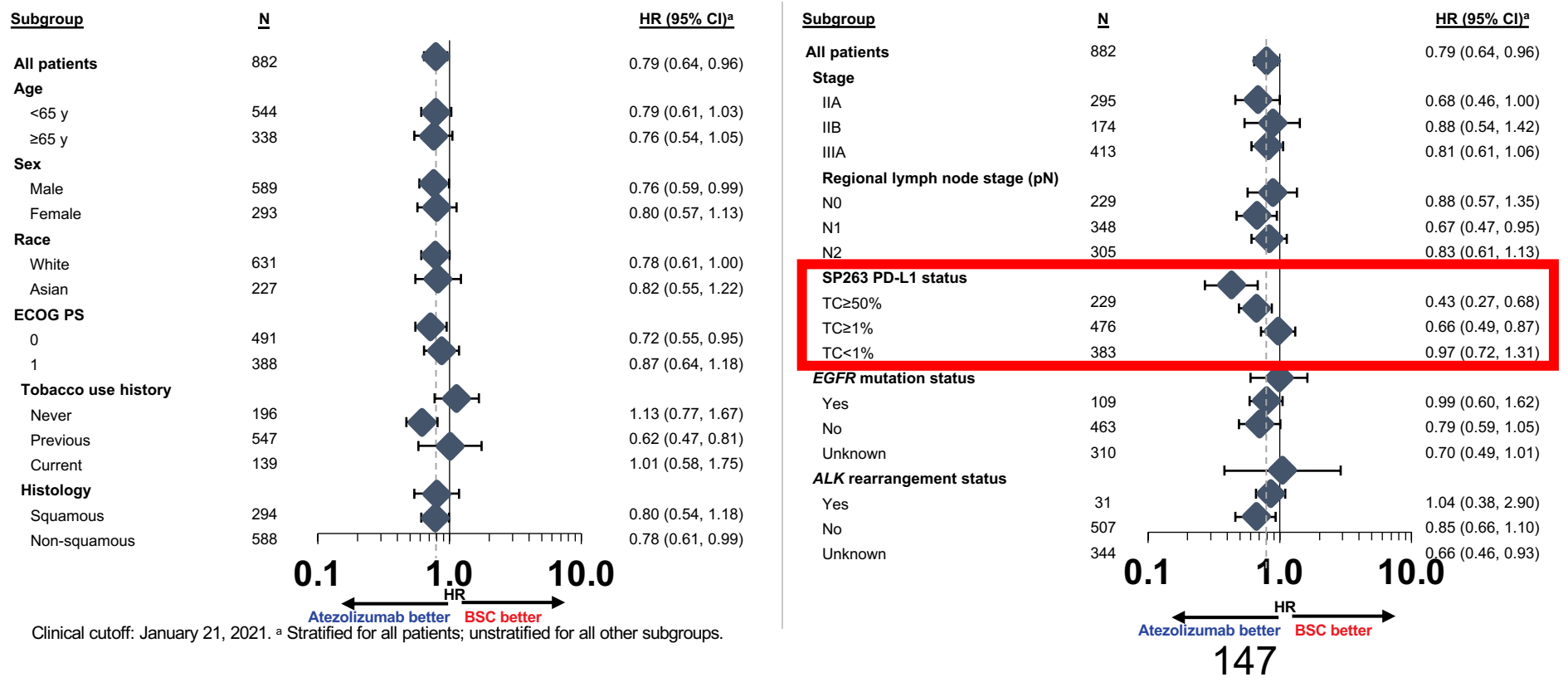
# IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population




Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

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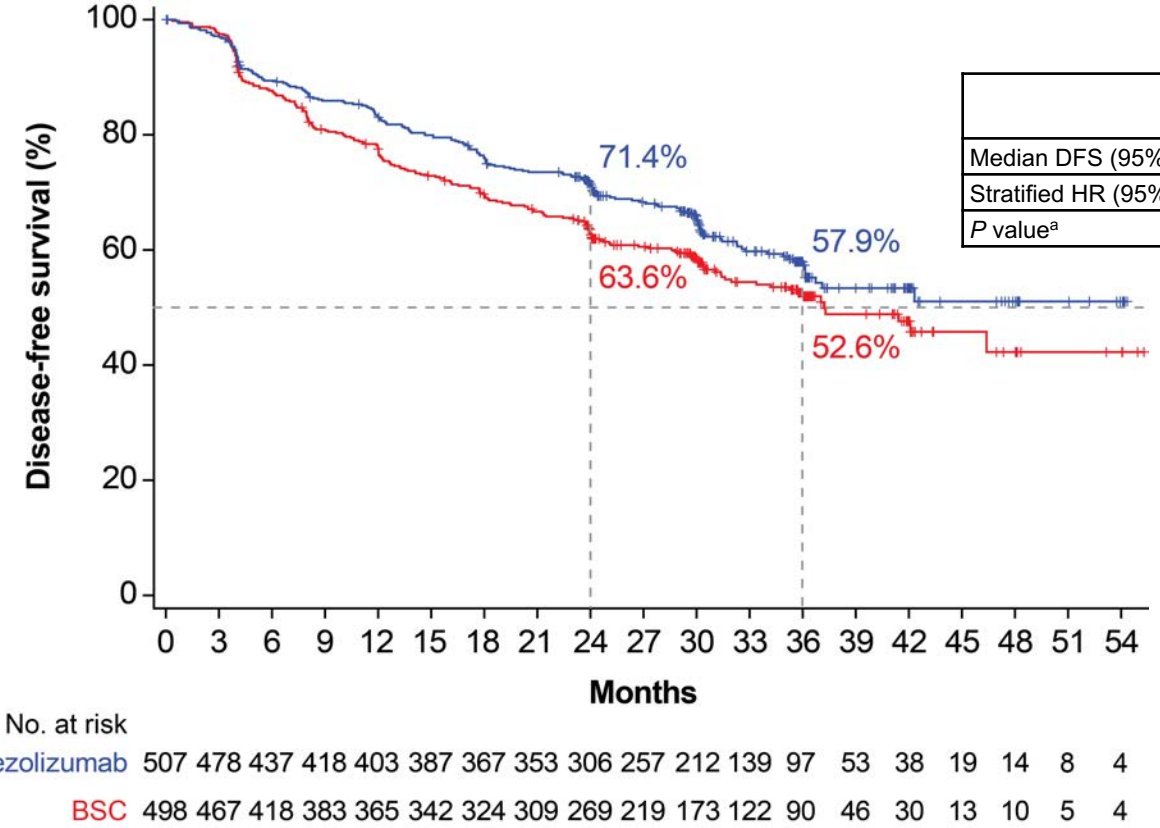
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

Courtesy of Roy S Herbst, MD, PhD

# IMpower010: DFS in the ITT population- Exploratory (stage IB-IIIA; primary endpoint)




| | 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

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] The statistical significance boundary for DFS was not crossed.

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IMpower010 Interim Analysis
https://bit.ly/33t6JJP

# IMpower010: safety summary[a]

| n (%) | Atezolizumab (n=495) | BSC (n=495) |
|---|---|---|
| Any-cause AE | 459 (92.7) | 350 (70.7) |
| Treatment-related AE | 335 (67.7) | – |
| Grade 3-4 AE | 108 (21.8) | 57 (11.5) |
| Treatment-related grade 3-4 AE | 53 (10.7) | – |
| Serious AE | 87 (17.6) | 42 (8.5) |
| Treatment-related serious AE | 37 (7.5) | – |
| Grade 5 AE | 8 (1.6)[b] | 3 (0.6)[c] |
| Treatment-related grade 5 AE | 4 (0.8) | – |
| AE leading to dose interruption of atezolizumab | 142 (28.7) | – |
| AE leading to atezolizumab discontinuation | 90 (18.2) | – |
| Immune-mediated AEs | 256 (51.7) | 47 (9.5) |
| Grade 3-4 immune-mediated AEs | 39 (7.9) | 3 (0.6) |
| Immune-mediated AEs requiring the use of systemic corticosteroids | 60 (12.1) | 4 (0.8) |

Clinical cutoff: January 21, 2021. AE, adverse event; [a] Data are from the safety population (all randomized patients who received ≥1 atezolizumab dose or for BSC, had ≥1 post-baseline assessment). [b] Interstitial lung disease*; pneumothorax; multiple organ dysfunction syndrome*; cerebrovascular accident; arrhythmia; myocarditis*; acute myeloid leukemia*; acute cardiac failure. [c] Pneumonia; pulmonary embolism; cardiac tamponade and septic shock in the same patient. *, Treatment related per investigator.



Dr. Heather A. Wakelee ASCO 2021, abstr 8500
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

Courtesy of Roy S Herbst, MD, PhD

# IMpower010: conclusions

- IMpower010 is the first Phase III study of cancer immunotherapy to demonstrate DFS improvement in the adjuvant NSCLC setting after platinum-based chemotherapy
  - Adjuvant atezolizumab following complete resection and adjuvant chemotherapy showed statistically significant DFS benefit in the PD-L1 TC ≥1% stage II-IIIA (HR, 0.66; 95% CI: 0.50, 0.88) and all-randomized stage II-IIIA (HR, 0.79; 95% CI: 0.64, 0.96) populations, with enriched clinical
    benefit in patients whose tumors express PD-L1
- IMpower010 will continue for DFS and OS analyses in the ITT population
  - DFS in the ITT population, including patients with stage IB disease, did not cross the significance boundary at this interim DFS analysis
  - At this pre-planned interim DFS analysis, OS data were immature and not formally tested
- The safety profile of atezolizumab was consistent with prior experience of atezolizumab monotherapy across indications and lines of therapy
- Atezolizumab may be considered a practice-changing adjuvant treatment option for patients with PD-L1 TC ≥1% stage II-IIIA NSCLC

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IMpower010 Interim Analysis
https://bit.ly/33t6JJP



Courtesy of Roy S Herbst, MD, PhD

# Phase III adjuvant trials: Primary endpoint(s)

| Trial | Inclusion criteria | Treatment arms | Primary endpoint(s) |
|---|---|---|---|
| **IMpower010** | Resected stage IB (≥4 cm)-IIIA<br>≤ 4 cycles Adj CT<br>N=1280 | Atezolizumab (1 yr) *vs*<br>BSC | DFS |
| **ANVIL** | Resected stage IB (≥4 cm)-IIIA<br>Adj CT optional<br>N=903 | Nivolumab (1 yr) *vs*<br>Observation | DFS and OS |
| **PEARLS/ KEYNOTE-091** | Resected stage IB (≥4 cm)-IIIA<br>Adj CT optional<br>N=1177 | Pembrolizumab (1 yr) *vs*<br>placebo | DFS |
| **BR31** | Resected stage IB (≥4 cm)-IIIA<br>Adj CT optional<br>N=1360 | Durvalumab (1 yr) *vs*<br>placebo | DFS |
| **ALCHEMIST Chemo-IO** | Resected stage IB (≥4 cm)-IIIA<br>No prior CT (adj or neoadj)<br>N=1263 | CT+pembrolizumab (4C) followed by pembro (1 yr)<br>vs<br>CT (4C) followed by pembro (1 yr) *vs*<br>CT (4C) followed by observation | DFS and OS |
| **MERMAID-1** | Resected stage II-IIIA<br>No prior CT<br>N=332 | Durvalumab+CT *vs*<br>CT+placebo | DFS in MRD+ |



Courtesy of Roy S Herbst, MD, PhD

original reports

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

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

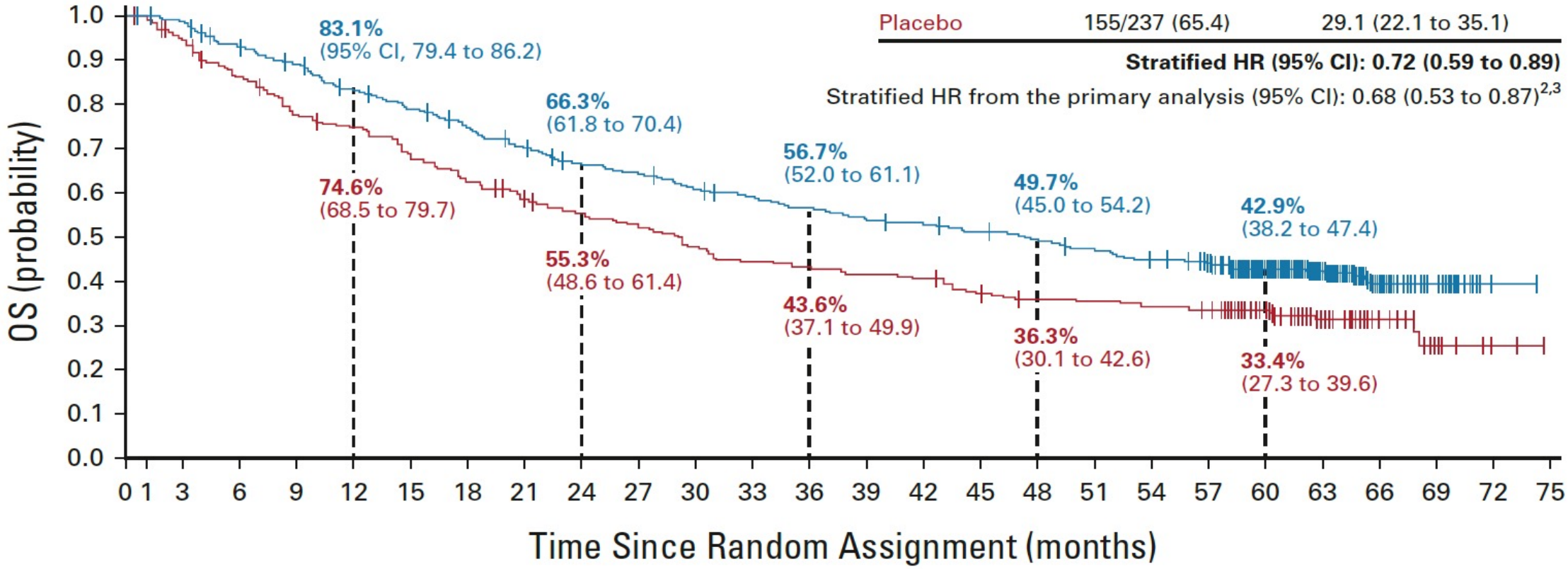
*J Clin Oncol* 2022;[Online ahead of print].

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

| Arm | No. of Events/ Total No. of Patients (%) | Median OS (95% CI), Months |
|---|---|---|
| Durvalumab | 264/476 (55.5) | 47.5 (38.1 to 52.9) |
| Placebo | 155/237 (65.4) | 29.1 (22.1 to 35.1) |

**Stratified HR (95% CI): 0.72 (0.59 to 0.89)**

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



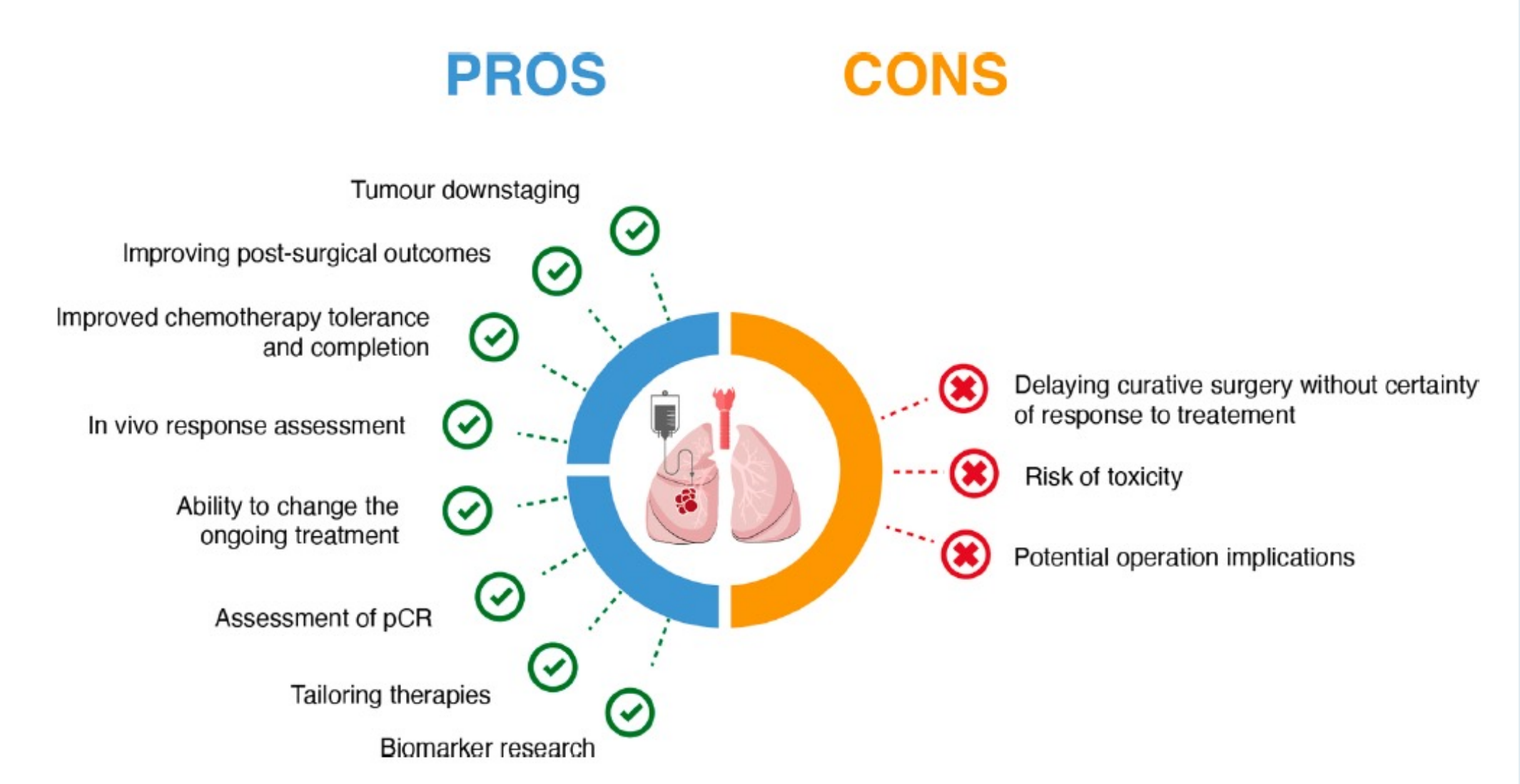

Spigel DR et al. *J Clin Oncol* 2022;[Online ahead of print].

# Neoadjuvant Approaches



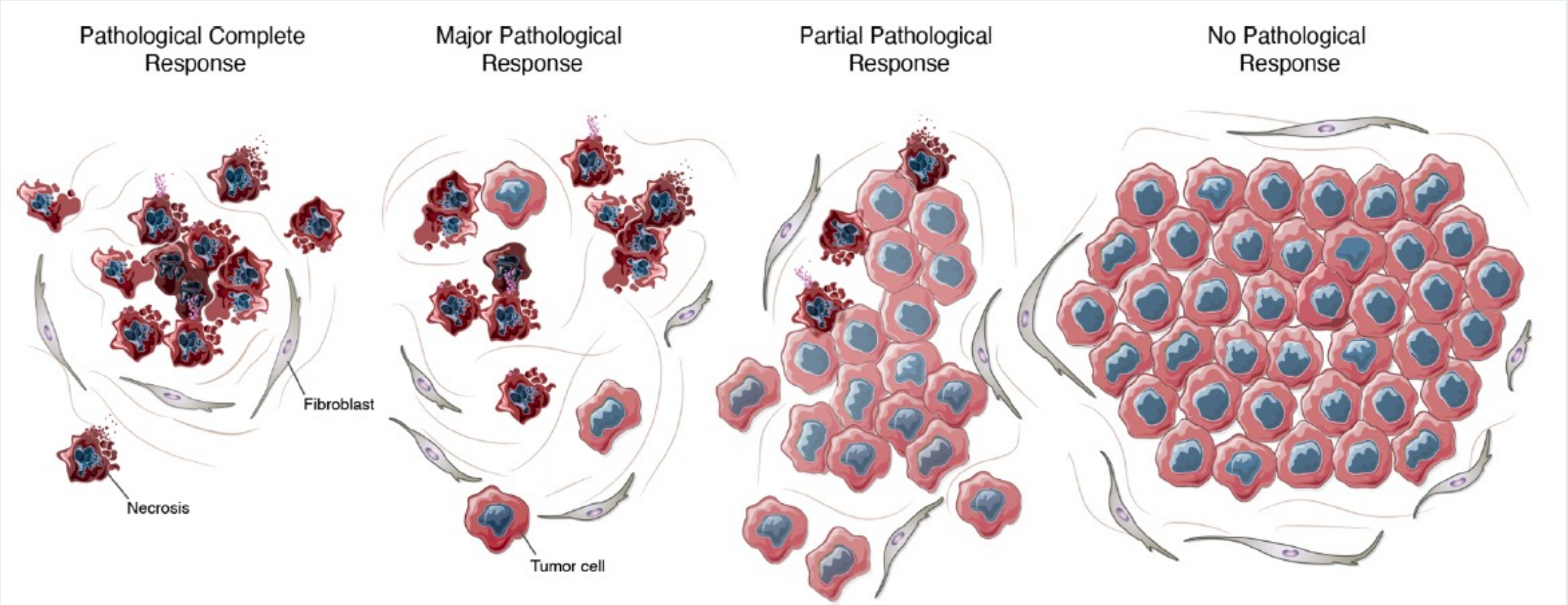
Courtesy of Roy S Herbst, MD, PhD

# Potential Pros and Cons of Neoadjuvant Therapy in NSCLC




Friedlaender A et al. *Cancer Treat Rev* 2022;[Online ahead of print].

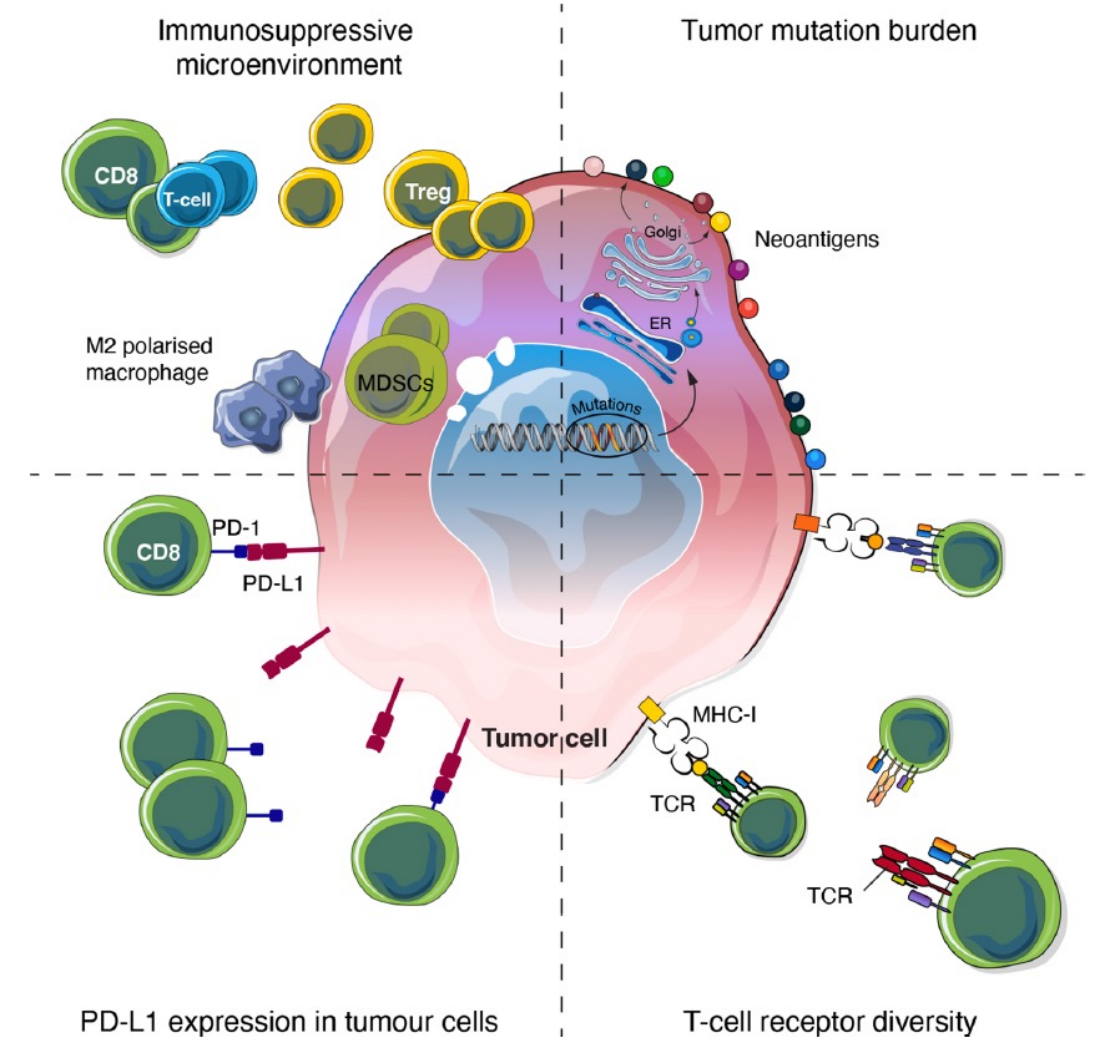
# Depth of Pathologic Response to Neoadjuvant Therapy




Friedlaender A et al. *Cancer Treat Rev* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

# Potential Predictive Biomarkers of Response to Neoadjuvant Immunotherapy

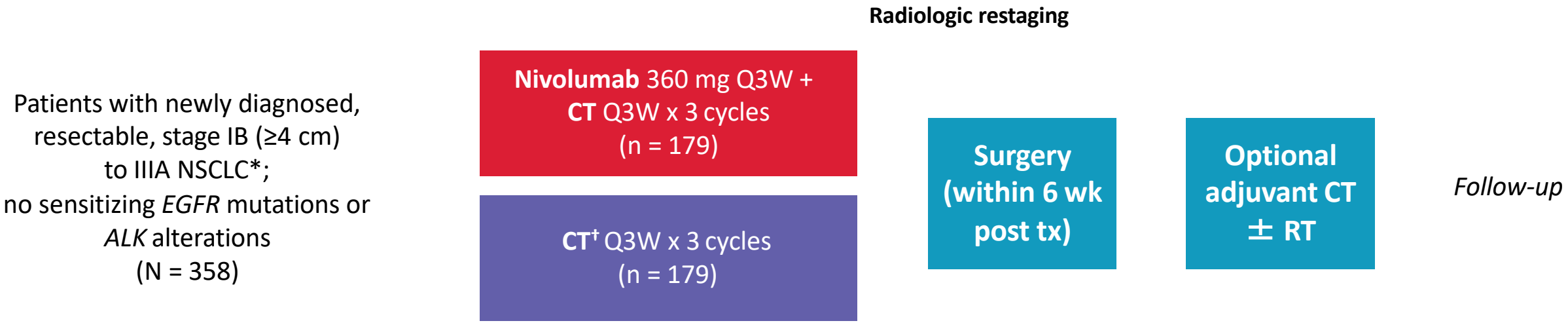



Friedlaender A et al. *Cancer Treat Rev* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

# CheckMate 816: Neoadjuvant Nivolumab + Platinum Chemotherapy for Resectable Stage IB-IIIA NSCLC

**Randomized, open-label phase III trial (data cutoff: September 16, 2020; min f/u: 7.6 mo)**



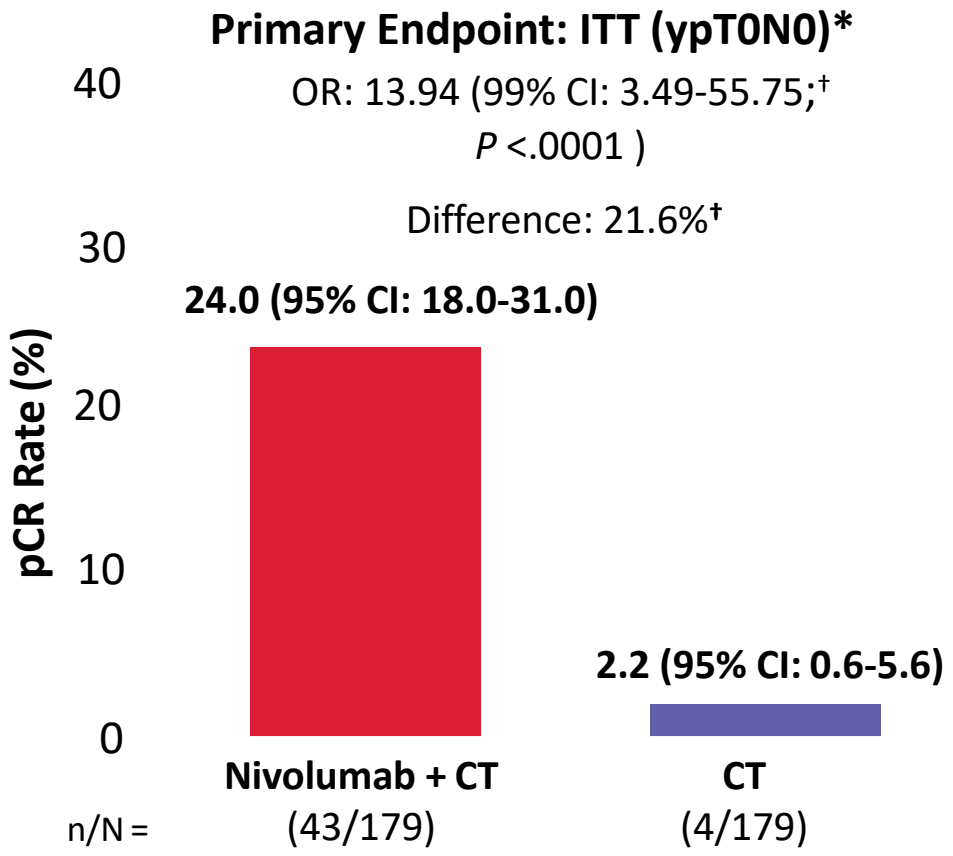

*By TNM 7th edition. †PD-L1 28-8 pharmDx IHC assay.
Arm evaluating nivolumab (3 mg/kg for 3 cycles) + ipilimumab (1 mg/kg for 1 cycle) not shown.

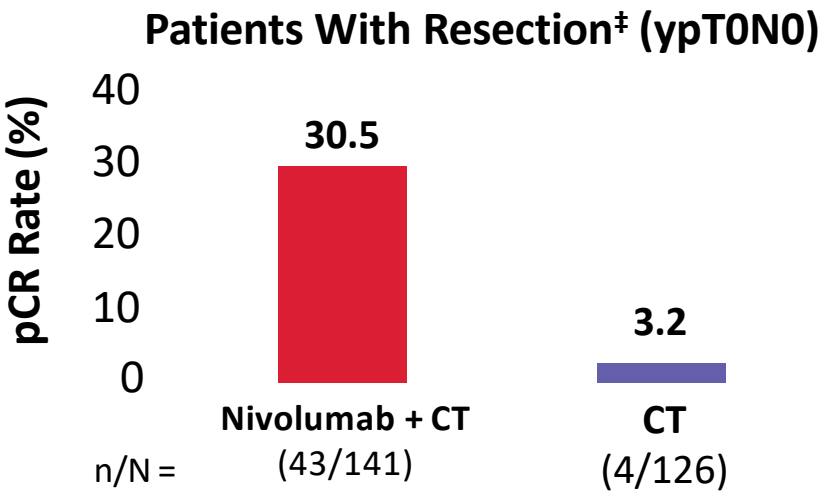
- Primary endpoints: pCR (by BIPR), EFS (by BICR)
- Key secondary endpoints: OS, MPR (by BIPR), time to death or distant metastasis
- Key exploratory endpoints: ORR (by BICR), surgery feasibility, peri/postoperative surgery-related AEs

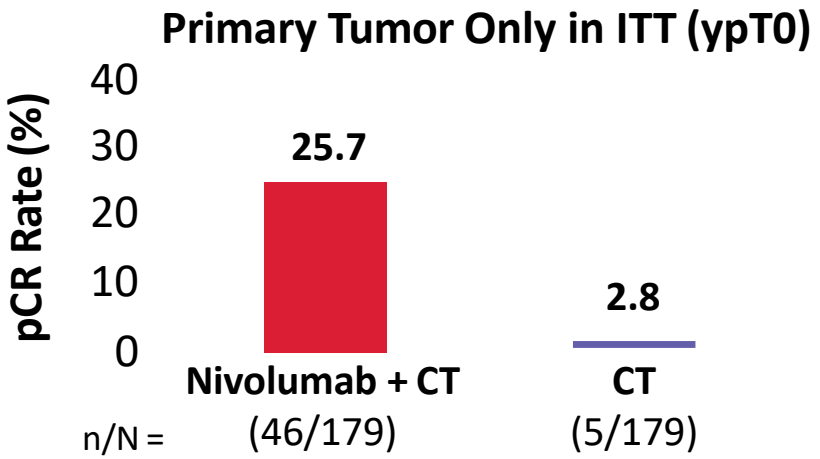
Forde. AACR 2021. Abstr CT003. Spicer. ASCO 2021. Abstr 8503. NCT02998528.

Courtesy of Roy S Herbst, MD, PhD

# CheckMate 816: pCR Rate per BIPR (Primary Endpoint)



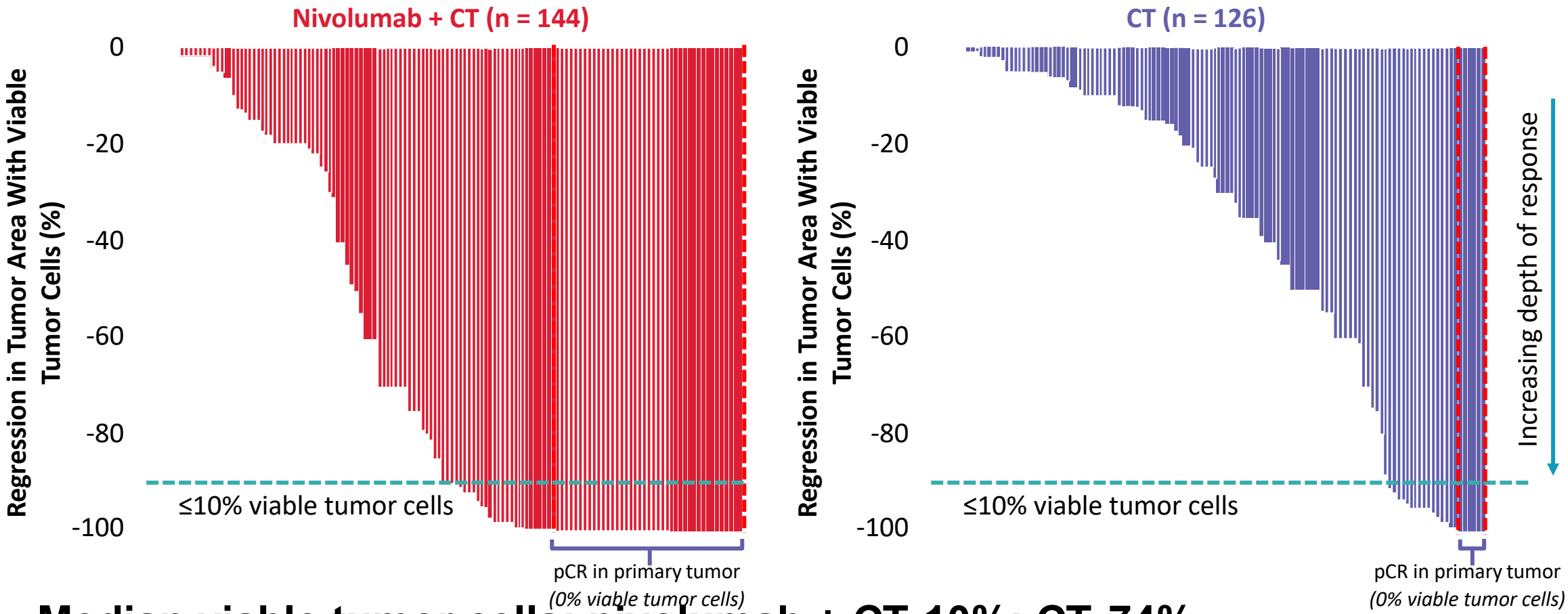

**pCR rate in exploratory nivolumab + ipilimumab arm (ITT): 20.4% (95% CI: 13.4% to 29.0%)**

pCR defined as 0% residual viable tumor cells in primary lung tumor and sampled LNs. *In ITT population, those who did not undergo surgery categorized as nonresponders in primary analysis. †Calculated using stratified Cochran–Mantel–Haenszel method. ‡Patients who underwent definitive surgery with evaluable pathology sample.

Forde. AACR 2021. Abstr CT003.

Courtesy of Roy S Herbst, MD, PhD

# CheckMate 816: Depth of Pathologic Regression in Primary Tumor




**Median viable tumor cells: nivolumab + CT, 10%; CT, 74%**

Forde. AACR 2021. Abstr CT003.

Courtesy of Roy S Herbst, MD, PhD

# CheckMate 816: Impact of Neoadjuvant Immunotherapy on Surgery

## Neoadjuvant immunotherapy did not negatively affect surgery outcomes

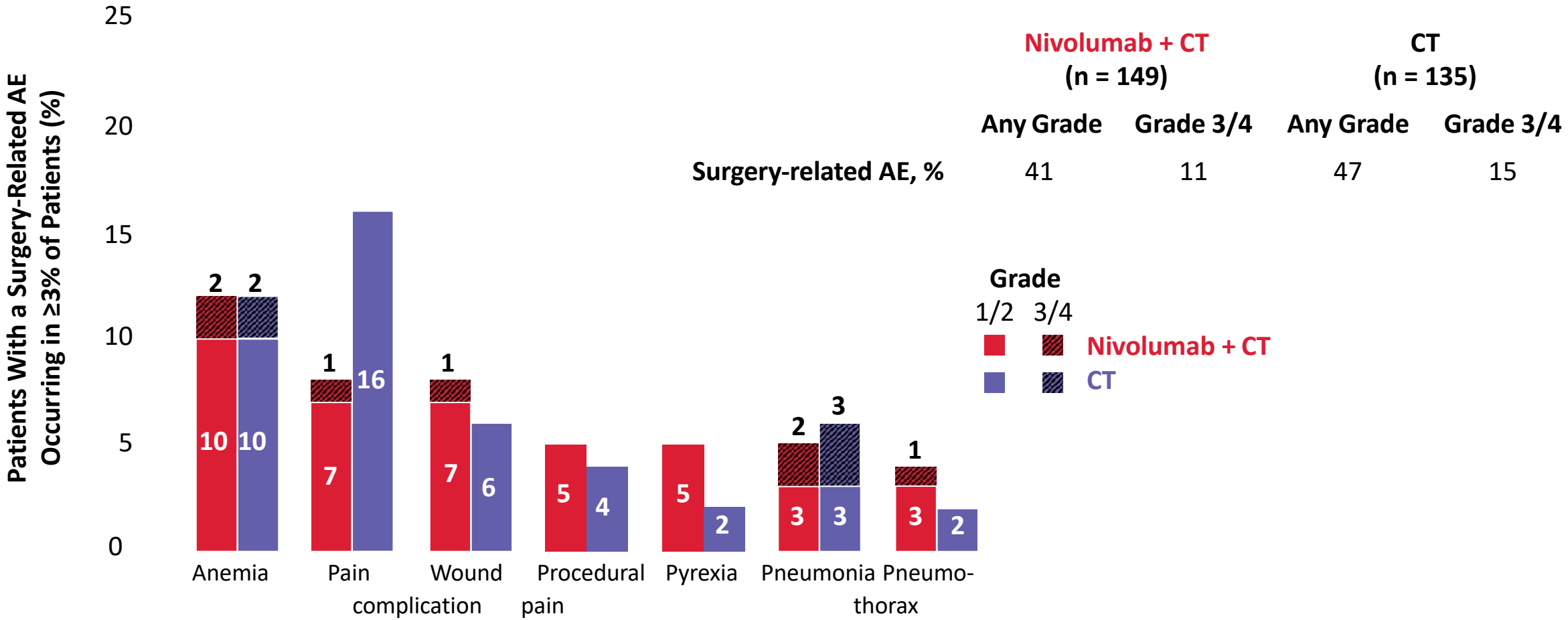
| Surgery-Related Parameter in All Randomized Patients | Nivolumab + CT (n = 179) | CT (n = 179) |
|---|---|---|
| Surgery received/cancelled, % | 83/16 | 75/21 |
| | 184 (130-252)* | 217 (150-283)† |
| Surgery approach, % | | |
| ▪ Thoracotomy | 59‡ | 63§ |
| ▪ Minimally invasive | 30‡ | 22§ |
| ▪ Minimally invasive → open | 11‡ | 16§ |
| Type of surgery, %# | | |
| ▪ Lobectomy | 77‡ | 61§ |
| ▪ Pneumonectomy | 17‡ | 25§ |
| Complete resection (R0), % | 83 | 78 |

*n = 122. †n = 121. ‡n = 149. §n = 135. #Calculated from patients who received definitive surgery. Patients may have had ≥1 surgery type. Patients who received other types of surgery (eg, sleeve lobectomy, bilobectomy) not shown.

Courtesy of Roy S Herbst, MD, PhD

Spicer. ASCO 2021. Abstr 8503.

# CheckMate 816: Surgery-Related Complications up to 90 Days After Definitive Surgery




**Surgery-related AEs not shown: subcutaneous emphysema, atrial fibrillation, cough, pleural effusion, nausea, dyspnea, pulmonary fistula, non-cardiac chest pain. n = 2 grade 5 surgery-related AEs (pulmonary embolism, aortic rupture) in nivolumab + CT arm considered unrelated to study drug by investigator. n = 2 intraoperative complications (intraoperative hemorrhage, aortic rupture) in nivolumab + CT arm deemed not related to study drug.**

Spicer. ASCO 2021. Abstr 8503.

Courtesy of Roy S Herbst, MD, PhD

# CheckMate 816: Safety Summary

| AE, % | Nivolumab + Chemotherapy (n = 176) | | Chemotherapy (n = 176) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Any AE | 92 | 41 | 97 | 44 |
| Treatment-related AE* | 82 | 34 | 89 | 37 |
| Any AE leading to d/c | 10 | 6 | 11 | 4 |
| Treatment-related AE leading to d/c | 10 | 6 | 10 | 3 |
| Any serious AE | 16 | 11 | 14 | 10 |
| Treatment-related serious AE | 12 | 8 | 10 | 8 |
| Surgery-related AEs† | 41 | 11 | 47 | 15 |
| Treatment-related deaths | 0 | | 3‡ | |

*Treatment-related AEs in 15% of patients: nausea, anemia, constipation, decreased appetite, neutropenia, decreased neutrophil count. †Reported within 90 days of definitive surgery. Grade 5 surgery-related AEs in 2 patients with nivolumab + chemotherapy deemed not related to study drug. ‡n = 1 each: enterocolitis, pneumonia, pancytopenia.

Immune-mediated AEs with nivolumab + chemotherapy included rash, hyperthyroidism, hypothyroidism/thyroiditis, diabetes mellitus, hypophysitis, adrenal insufficiency, pneumonitis, hypersensitivity/IRR, but not hepatitis, diarrhea/colitis, and nephritis/renal dysfunction

Forde. AACR 2021. Abstr CT003.

Courtesy of Roy S Herbst, MD, PhD

# Neoadjuvant Phase 3 Clinical Trials

| Study* | CheckMate 816[1] CT + nivolumab | KEYNOTE-617[2] CT+ pembrolizumab | IMpower030[3] CT + Atezolizumab | AEGEAN[4] CT + Durvalumab | CheckMate 77T[5] |
|---|---|---|---|---|---|
| **Stage** | IB–IIIA | II–IIIB (T3-4N2) | II–IIIB (cT3N2) | IIA–IIIB | IIA–IIIB (T3N2) |
| **Patients, No.** | 350 | 786 | 374 | 300 | 452 |
| **Study arms** | CT + nivolumab (360 mg) × 3 cycles → S vs. CT × 3 cycles → S | CT + pembrolizumab (200 mg)/placebo × 4 cycles → S →pem/placebo × 13 cycles | CT + atezolizumab (1200 mg)/placebo × 4 cycles → S → atezo/placebo × 16 cycles | CT + durvalumab (1500 mg)/placebo × 3 cycles → S → durvalumab/placebo × 12 cycles | CT + nivolumab (360 mg)/placebo × 3 cycles → S → nivolumab/placebo |
| **Key inclusion criteria** | ▪ Early stage IB-IIIA, operable NSCLC, confirmed in tissue<br>▪ Lung function capacity tolerating the surgery<br>▪ Available tissue of primary tumor | ▪ Confirmed resectable Stage II, IIIA, or IIB (N2) NSCLC<br>▪ Eligible for protocol therapy, including surgery<br>▪ Tissue sample available | ▪ Confirmed resectable Stage II, IIIA, IIIB (T3N2) NSCLC<br>▪ Eligible for R0 resection<br>▪ Measurable disease by RECIST v1.1<br>▪ Negative HIV, HBV, HCV | ▪ Confirmed resectable Stage II, IIIA, IIIB (N2) NSCLC<br>▪ ≥1 lesion, no prior irradiation, qualifying as a RECIST 1.1 target lesion<br>▪ No prior IO | ▪ Confirmed resectable Stage II, IIIA, IIIB (T3N2) NSCLC<br>▪ ≥1 lesion, no prior irradiation, qualifying as a RECIST 1.1 target lesion<br>▪ No prior IO |
| **Primary Endpoints** | ▪ EFS, pCR, MPR | ▪ EFS, OS | ▪ EFS | ▪ MPR | ▪ EFS |
| **ORR, %** | ▪ 31 v 24%<br>▪ pCR 24 v 2%<br>▪ MPR 36.9 v 8.9% | ▪ N/A | ▪ N/A | ▪ N/A | ▪ N/A |
| **Median EFS, mo** | ▪ EFS endpoint met | ▪ N/A | ▪ N/A | ▪ N/A | ▪ N/A |
| **Median OS, mo** | ▪ N/A | ▪ N/A | ▪ N/A | ▪ N/A | ▪ N/A |

**No head-to-head studies have been conducted and direct comparisons cannot be made between these studies**

Courtesy of Roy S Herbst, MD, PhD

1. ClinicalTrials.gov. NCT02998528. Accessed April 8th, 2021. 2. ClinicalTrials.gov. NCT03425643. Accessed April 8th, 2021. 3. ClinicalTrials.gov. NCT03456063. Accessed April 8th, 2021. 4. ClinicalTrials.gov. NCT03800134. Accessed April 8th, 2021. 5. ClinicalTrials.gov. NCT04351555. Accessed April 8th, 2021. 6. Cascone T et al J Clin Oncol 2020 TPS 9076

# Advances in Early-Stage NSCLC: Conclusions

- Immune checkpoint inhibitors and targeted therapies are now being moved earlier in the disease course of NSCLC
- IMpower010 established that adjuvant atezolizumab prolongs DFS in patients with stage II-III NSCLC
  - Benefit is most concentrated in PD-L1 ≥1%, in particular PD-L1 ≥50%

**Press release 11/8/2021**

**…the Phase 3 CheckMate -816 trial met the primary endpoint of improved event-free survival (EFS) in patients with resectable stage IB to IIIA non-small cell lung cancer (NSCLC). In a prespecified interim analysis, nivolumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in EFS compared to chemotherapy alone when given before surgery.**

Courtesy of Roy S Herbst, MD, PhD

**What are we waiting for?**

**Time for more targeted immunotherapy!**

YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Yale SCHOOL

Courtesy of Roy S Herbst, MD, PhD

# *Meet The Professor*

# Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

**Tuesday, March 1, 2022**
**5:00 PM – 6:00 PM ET**

## Faculty

**Michael E Williams, MD, ScM**

## Moderator

**Neil Love, MD**

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*Thank you for joining us!*

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