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ATLANTA

LUNG CANCER SYMPOSIUM

# DEBATE: Should Adjuvant IO be Given After Surgery Following Chemo-IO
# NO

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University of Virginia Cancer Center

October 26, 2024

PACE
Partners for Advancing Clinical Education

Bio Ascend™

# Disclosures (3 yrs)

**Research funding** to institution from Pfizer, Tempus, Nalo Therapeutics, Puma, Mirati, Bristol Myers Squibb, Dizal, Chugai, Amgen, AstraZeneca, Janssen, Daiichi Sankyo, Jounce Therapeutics, Takeda, Merck.

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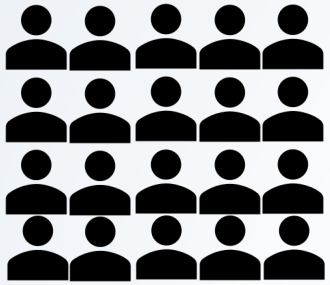
# The Matchup

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

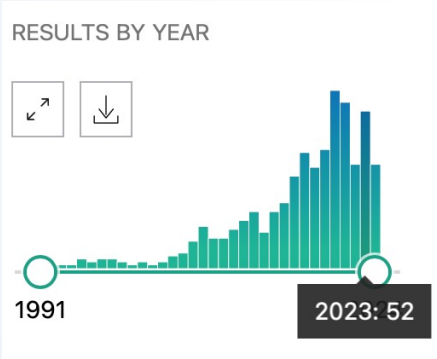
Thoracic Med Onc

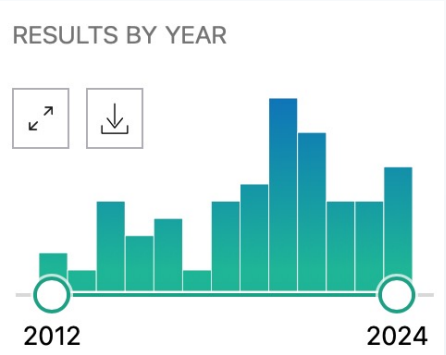



UVA Health
UVA Cancer Center
*An NCI-Designated Comprehensive Cancer Center*

Thoracic Med Onc

PubMed




18th Annual ATLANTA LUNG CANCER SYMPOSIUM

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# Root for the Underdog

Rocky Statue, Philadelphia


Philadelphia Eagles
Super Bowl Champions, 2018


Chris Long, UVA Alum
ESPN Muhammad Ali Sports Humanitarian Award

# Outline

- Current Treatment Paradigms
- Key Questions about adjuvant IO after neoadjuvant (the adjuvant phase)
- Sequencing Scenario – More IO now vs. IO at recurrence
- Estimating the absolute benefit of adjuvant IO
  - Historical data
  - Cross trial comparisons
  - Fancy cross trial comparisons and post-hoc subgroup analyses
- Risks of additional adjuvant IO
- Conclusions

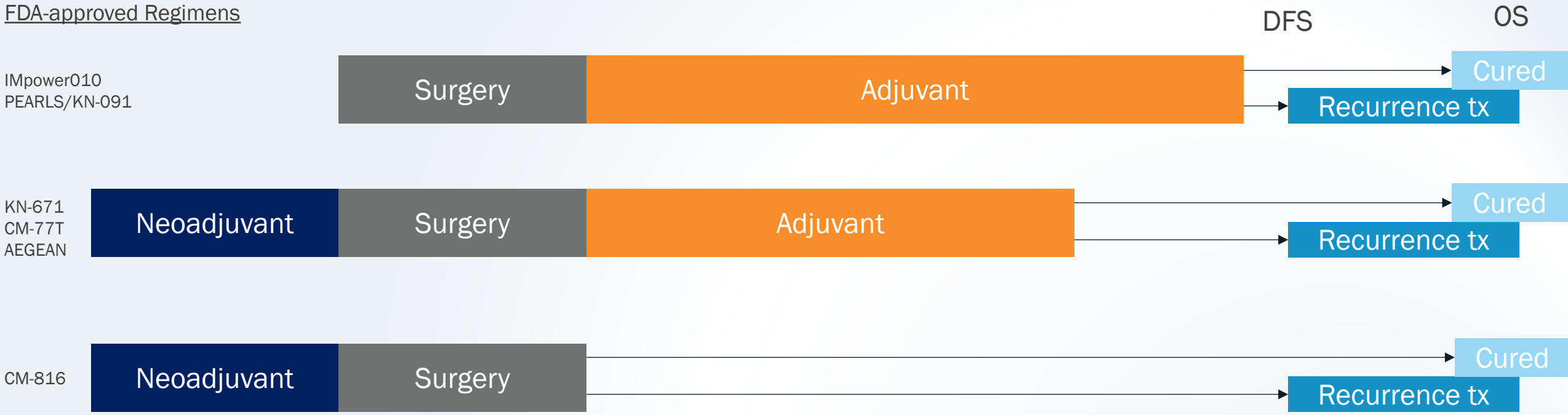
# Anti-PD-(L)1-Based Regimens for Resectable NSCLC

| | Adjuvant Only | | Neoadjuvant Only | Neoadjuvant followed by Adjuvant | | |
|---|---|---|---|---|---|---|
| **ICI** | **Atezolizumab** | **Pembrolizumab** | **Nivolumab** | **Pembrolizumab** | **Durvalumab** | **Nivolumab** |
| **Stage** | II-IIIA | IB[a]-IIIA | IB[a]-IIIA | II-IIIB | II-IIIB | II-IIIB |
| **Pivotal Trial** | IMpower-010 | KEYNOTE-091 | CHECKMATE -816 | KEYNOTE-671 | AEGEAN | CHECK MATE-77T |
| **Primary Endpoint(s)** | DFS | DFS | EFS/pCR | EFS/OS | EFS/pCR | EFS |
| **DFS/EFS HR (95% CI)** | **0.66 (0.50, 0.88)** | **0.73 (0.60, 0.89)** | **0.63 (0.45, 0.87)** | **0.58 (0.46, 0.72)** | **0.68 (0.53, 0.88)** | **0.58 (0.42, 0.81)** |

July 25, 2024 Meeting of the Oncologic Drugs Advisory Committee- FDA Presentations
https://www.fda.gov/advisory-committees/updated-agenda-information-july-25-2024-meeting-oncologic-drugs-advisory-committee-meeting

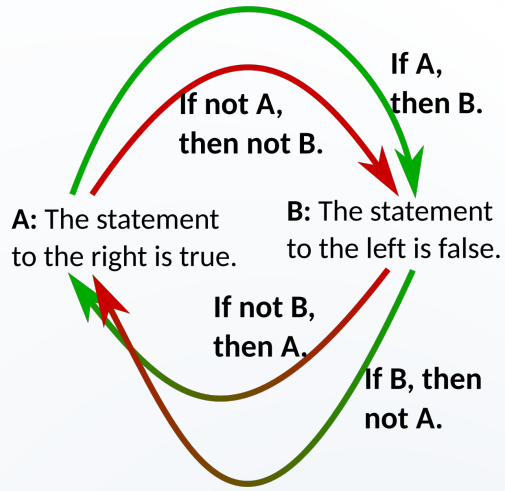
# Treatment Paradigms, Surgically Resectable Stage II-III NSCLC

FDA-approved Regimens



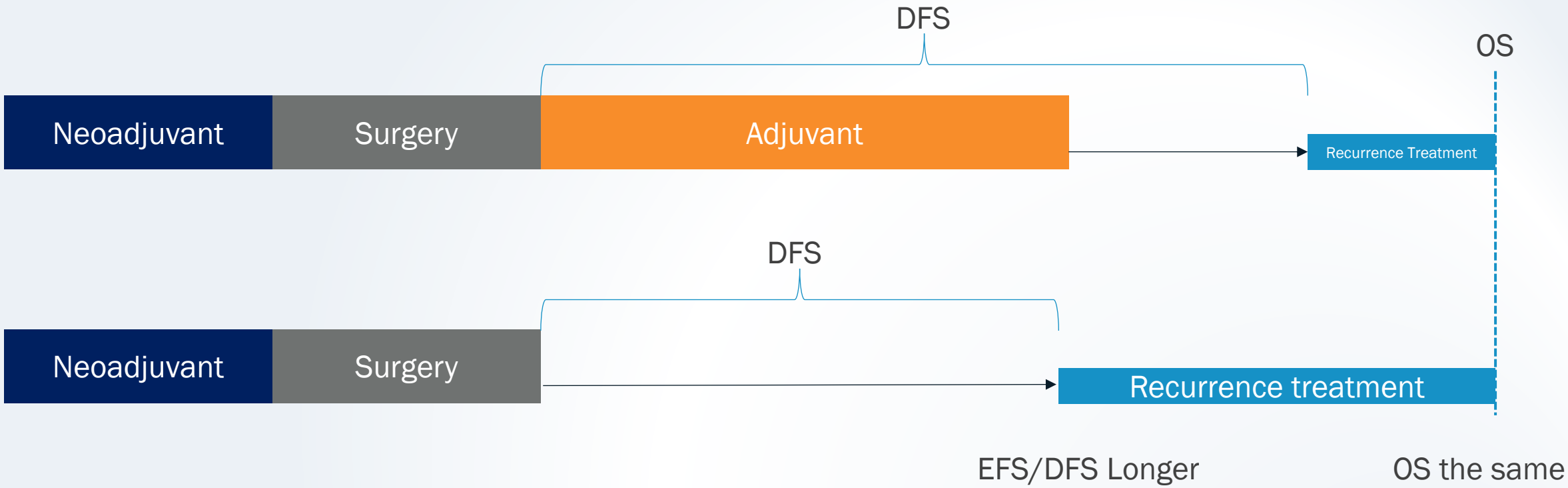
# Adjuvant phase after Neoadjuvant IO - Questions

- How much additional gain from additional IO in adjuvant phase of after neoadjuvant?
  - Duration and optimal timing question
- Relevant Endpoints: DFS/EFS vs. OS
- Patient selection after neoadjuvant: pCR vs. non-pCR?
  - Paradoxical reasoning
    - pCR are the ones where treatment was most effective, more IO is better
    - pCR are lowest risk of recurrence, no need for more treatment
    - Non-pCR: treatment didn't work, no value in giving more
    - Non-pCR: high risk of recurrence, need more treatment



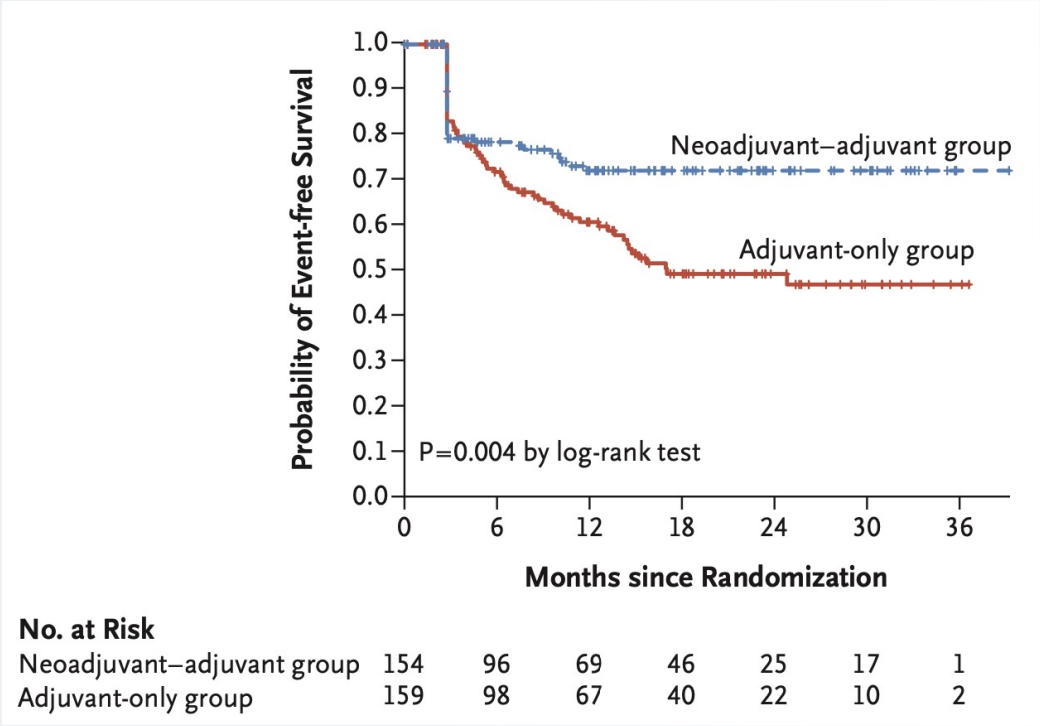

Liars paradox.svg, Creative Commons
"Paradox" Wikipedia.org

# Theoretical EFS/DFS gains without OS difference




How much OS benefit, if any, can we expect from Adjuvant phase IO?

# Melanoma lessons learned – SWOG 1801




Same duration IO exposure

More benefit derived from neoadjuvant phase of pembrolizumab

Patel S, et al. NEJM 2023;288:813-823

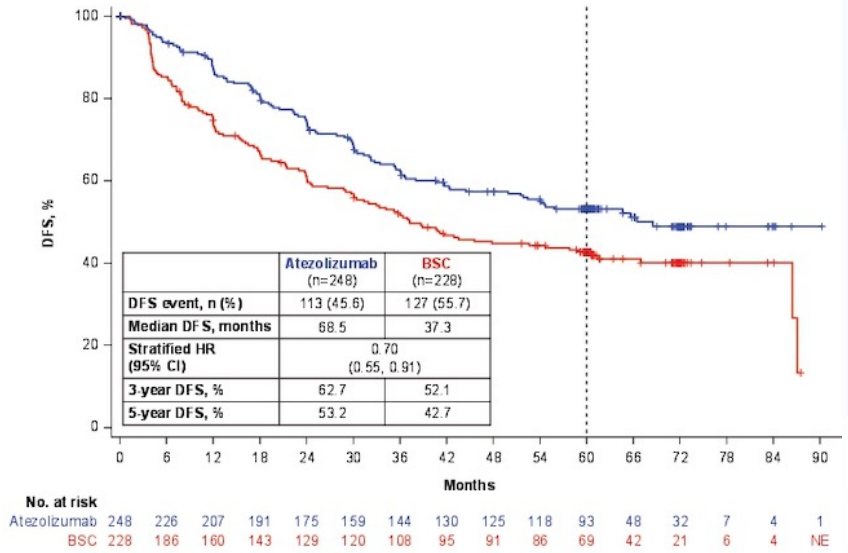
# Adjuvant IO Benefits (No neoadjuvant)

## IMpower 010

~3% absolute OS benefit** @ 3 yrs
~8.5% absolute OS benefit** @ 5 yrs

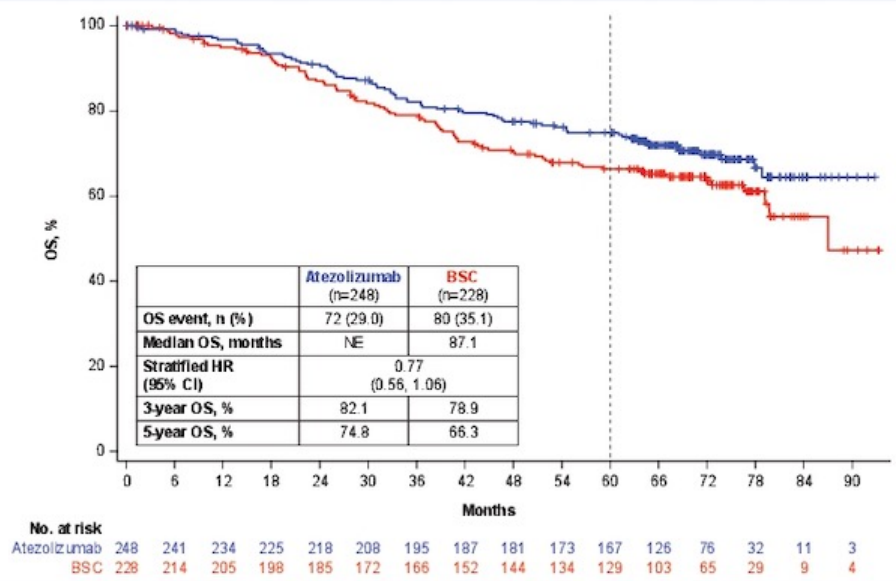
**not-significant, interim analysis

**Figure 2.** DFS in the stage II-IIIA PD-L1 TC ≥1% population




NE, not estimable.

**Figure 4.** OS in the stage II-IIIA PD-L1 TC ≥1% population

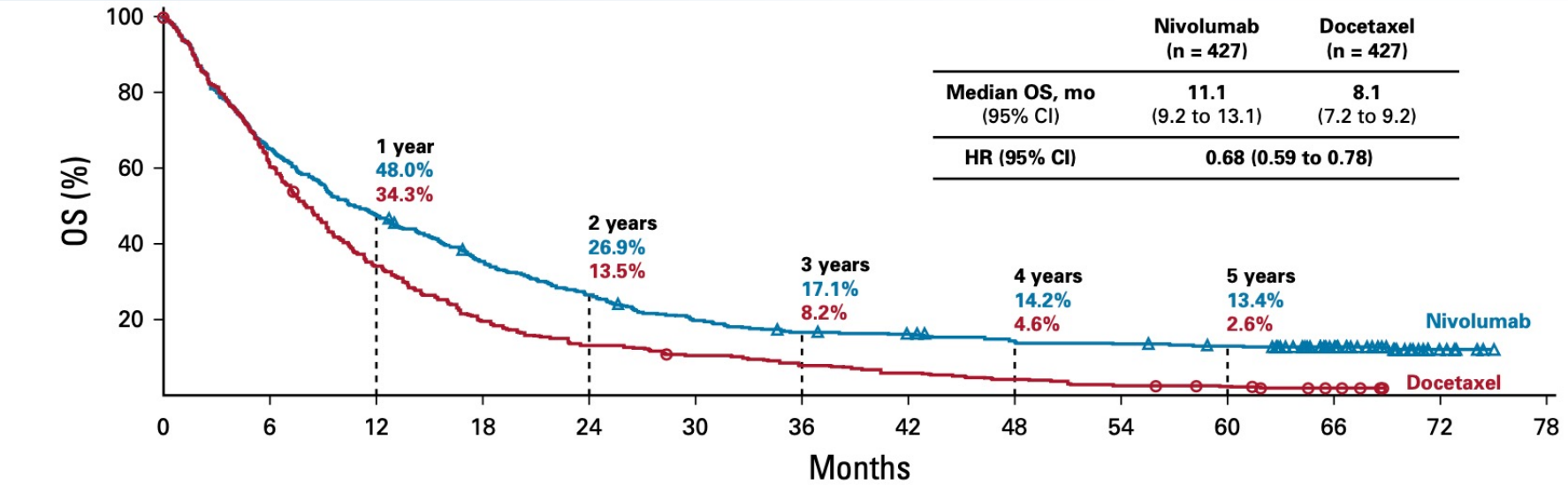



NE, not estimable.

Wakelee H, et al. ASCO 2024;LBA8035

# OS benefit of IO in stage IV NSCLC

## Checkmate 017 and 057: 5-yr outcomes



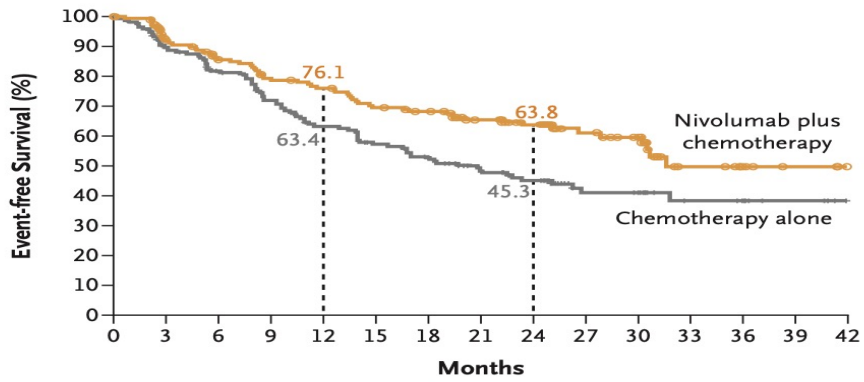

10.8% 5-yr OS improvement

Borghaei H, et al. J Clin Oncol 2021;39:723-733

# Existing data comparing peri-op IO vs. neoadjuvant only IO in NSCLC

# CM816 vs. CM 77T

Checkmate 816

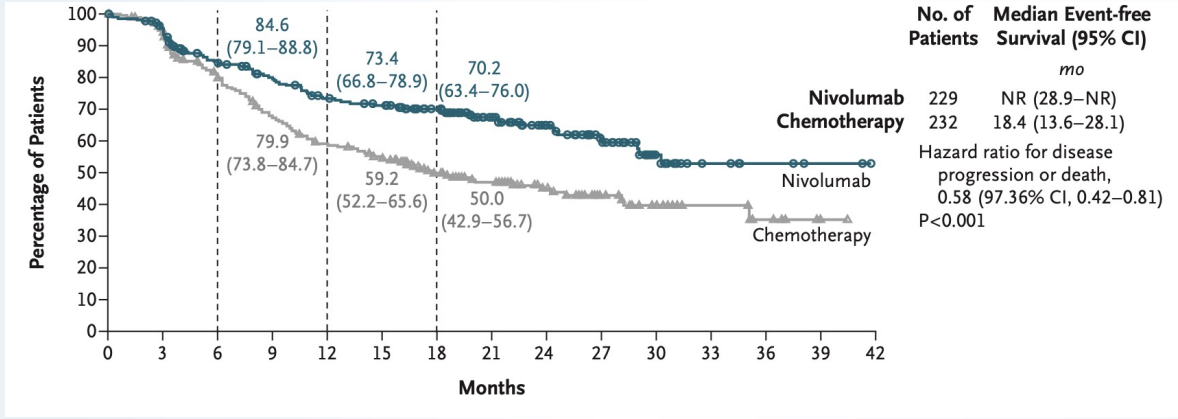



| | No. of Patients | Median Event-free Survival (95% CI) mo |
|---|---|---|
| Nivolumab plus Chemotherapy | 179 | 31.6 (30.2–NR) |
| Chemotherapy Alone | 179 | 20.8 (14.0–26.7) |

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

No adjuvant phase

Checkmate 77T




| | No. of Patients | Median Event-free Survival (95% CI) mo |
|---|---|---|
| Nivolumab | 229 | NR (28.9–NR) |
| Chemotherapy | 232 | 18.4 (13.6–28.1) |

Hazard ratio for disease progression or death, 0.58 (97.36% CI, 0.42–0.81)
P<0.001

Adjuvant Nivo x1 year

Forde PM, et al. NEJM 2022; 386:1973-1985
Cascone T, et al. NEJM 2024;390(19):1756-1769

# FDA ODAC 7/25/24

## AEGEAN: Major Review Issue

**Inability to determine the contribution of effect of each treatment phase (neoadjuvant and adjuvant) to the overall effect of the perioperative regimen**

July 25, 2024 Meeting of the Oncologic Drugs Advisory Committee- FDA Presentations
https://www.fda.gov/advisory-committees/updated-agenda-information-july-25-2024-meeting-oncologic-drugs-advisory-committee-meeting


CHERRY PICKING
If you can't debate your opponents on the substance of the issue, crush them on the minor details.

# Fancy Cross Trial Comparison

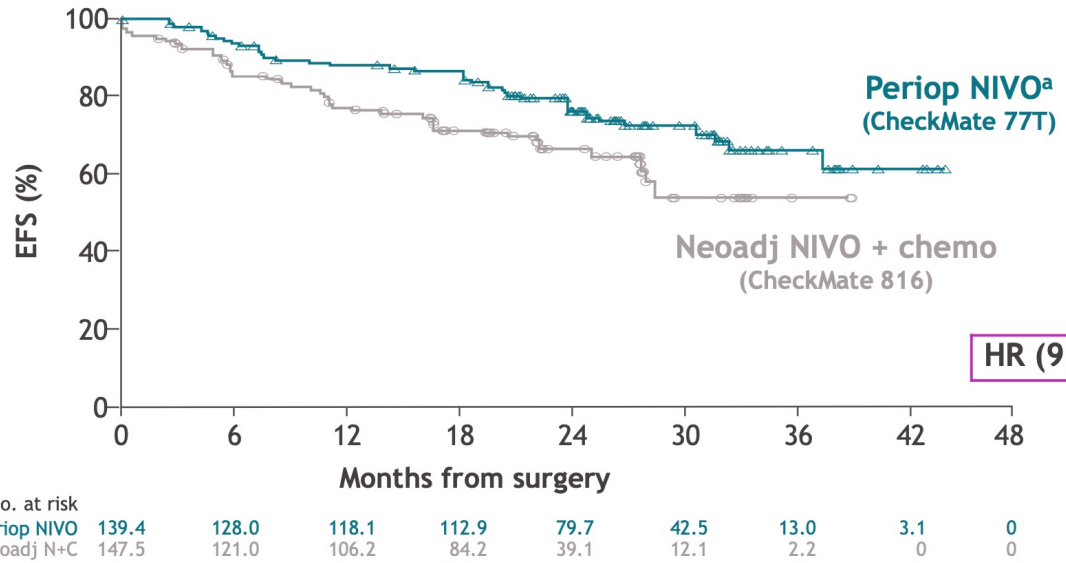

## Perioperative vs neoadjuvant nivolumab for resectable NSCLC: patient-level data analysis of CheckMate 77T vs CheckMate 816

Patrick M. Forde,[1] Solange Peters,[2] Jessica Donington,[3] Stephanie Meadows-Shropshire,[4] Phuong Tran,[4] Stefano Lucherini,[5] Cinthya Coronado Erdmann,[6] Hong Sun,[6] Tina Cascone[7]

Forde PM, et al. WCLC 2024; abst: PL02.08

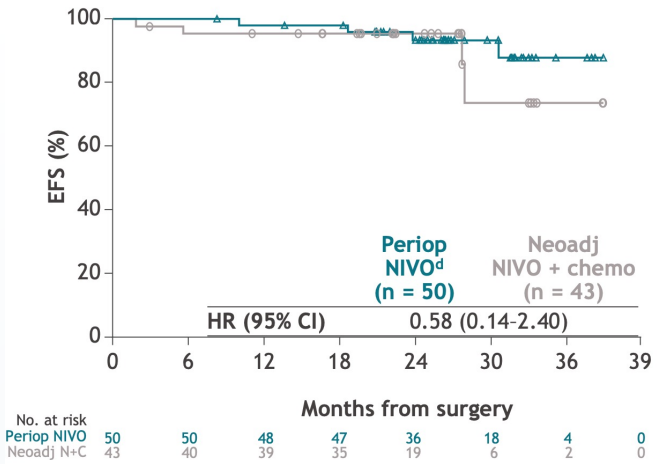
# Checkmate 816 vs. 77T pt-level analysis: results

## Landmark EFS (BICR) from definitive surgery

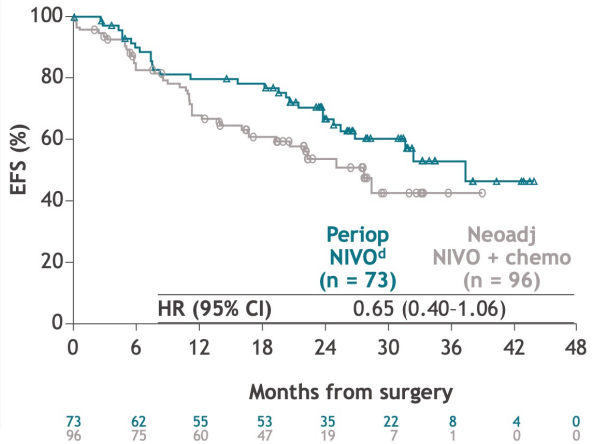



| | Weighted (ATE)[b] | |
|---|---|---|
| | Periop NIVO[a] (n = 139.4[c]) | Neoadj NIVO + chemo (n = 147.5[c]) |
| HR (95% CI) | 0.61 (0.39-0.97) | |

### pCR[c]



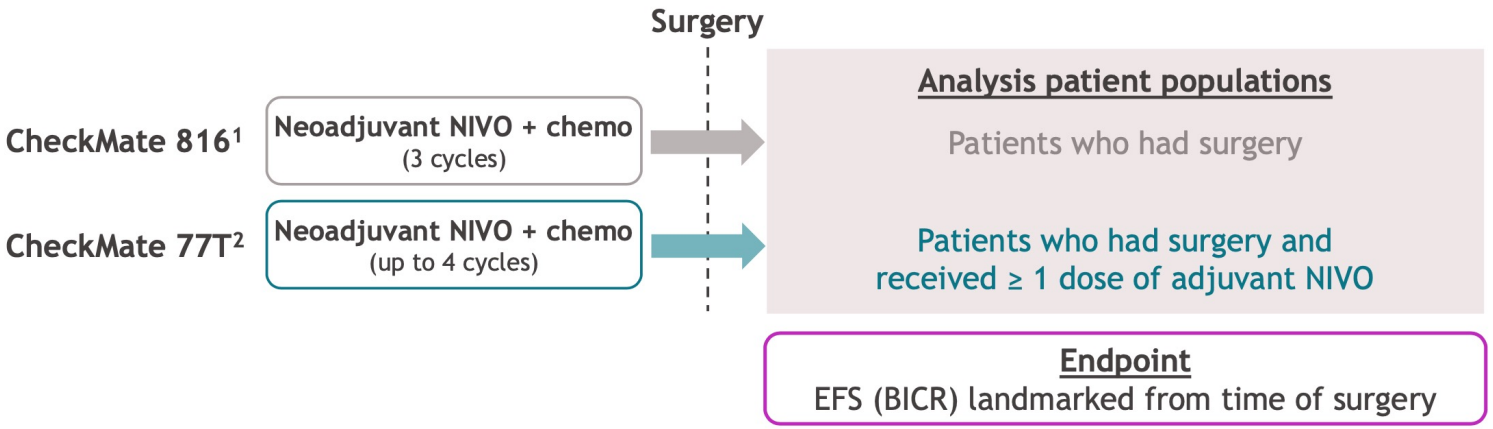

### No pCR




Forde PM, et al. WCLC 2024; abst: PL02.08

# Checkmate 816 vs. 77T pt-level analysis: Methods

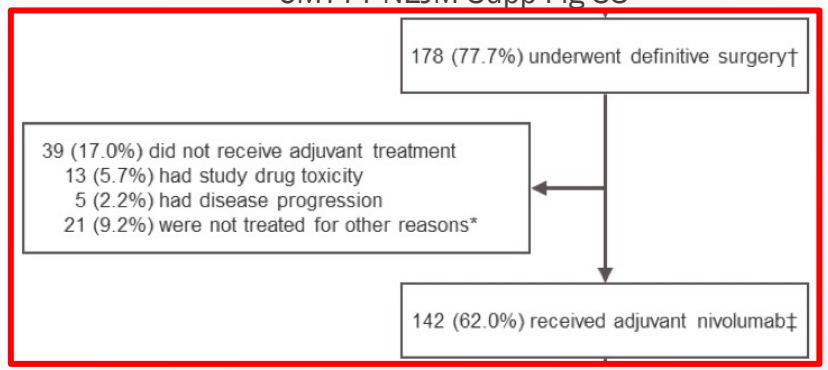
## Methods: perioperative NIVO vs neoadjuvant NIVO + chemo




83.2% of enrolled pts

62% of enrolled pts

CM77T NEJM Supp Fig S3



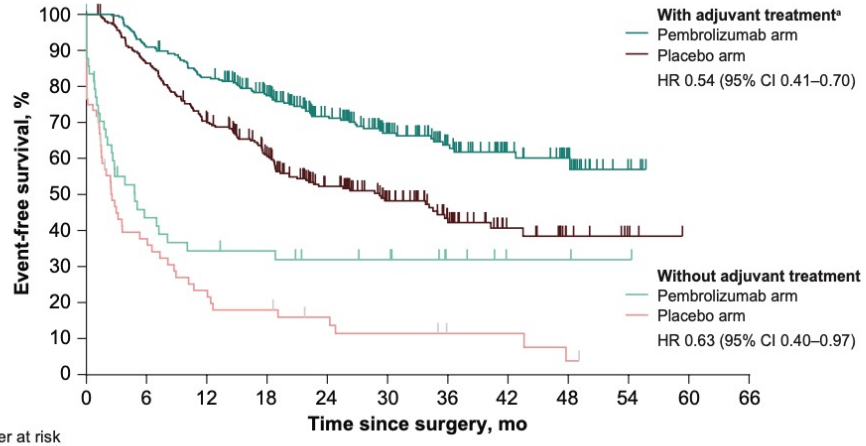

Pts with worse outcomes likely excluded from this analysis in 77T cohort

Forde PM, et al. WCLC 2024; abst: PL02.08

# KEYNOTE-671: Adjuvant Phase Analysis

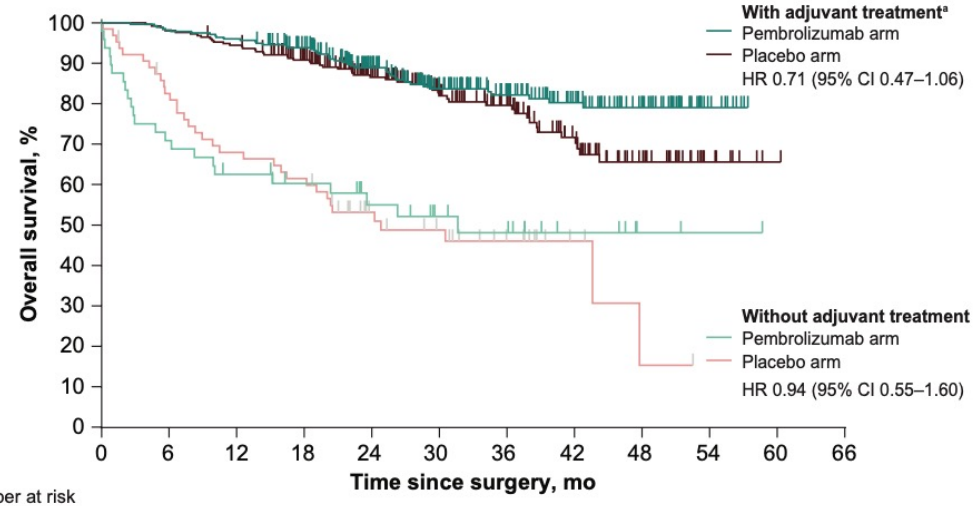
**Figure 3. Kaplan-Meier estimates of (A) EFS per RECIST version 1.1 by investigator review and (B) OS from the time of in-study surgery based on receipt of adjuvant therapy**

**A) EFS in patients who received or did not receive adjuvant therapy**




| | Number at risk (number censored) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| With adjuvant treatment | Pembrolizumab arm | 276 (0) | 250 (1) | 225 (3) | 191 (24) | 139 (63) | 99 (95) | 64 (126) | 38 (150) | 24 (163) | 4 (182) | 0 (186) | 0 (186) |
| | Placebo arm | 253 (0) | 216 (3) | 173 (5) | 136 (21) | 91 (48) | 64 (69) | 39 (89) | 18 (108) | 8 (117) | 3 (122) | 0 (125) | 0 (125) |
| Without adjuvant treatment | Pembrolizumab arm | 49 (0) | 19 (4) | 15 (4) | 14 (5) | 11 (7) | 10 (8) | 5 (13) | 2 (16) | 2 (16) | 1 (17) | 0 (18) | 0 (18) |
| | Placebo arm | 64 (0) | 21 (5) | 13 (5) | 10 (5) | 7 (7) | 5 (7) | 3 (9) | 3 (9) | 1 (9) | 0 (10) | 0 (10) | 0 (10) |

**B) OS in patients who received or did not receive adjuvant therapy**

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| With adjuvant treatment | Pembrolizumab arm | 276 (0) | 271 (0) | 265 (0) | 245 (14) | 183 (64) | 139 (98) | 102 (133) | 71 (162) | 45 (187) | 10 (222) | 0 (232) | 0 (232) |
| | Placebo arm | 253 (0) | 248 (0) | 238 (1) | 212 (18) | 158 (63) | 112 (102) | 85 (126) | 52 (152) | 26 (174) | 8 (192) | 1 (199) | 0 (200) |
| Without adjuvant treatment | Pembrolizumab arm | 49 (0) | 34 (1) | 29 (2) | 25 (5) | 19 (9) | 14 (13) | 12 (14) | 6 (20) | 2 (24) | 1 (25) | 0 (26) | 0 (26) |
| | Placebo arm | 64 (0) | 51 (2) | 42 (2) | 38 (2) | 24 (11) | 18 (15) | 11 (21) | 4 (28) | 1 (29) | 0 (30) | 0 (30) | 0 (30) |

[a]Among patients who started adjuvant therapy, HRs for EFS and OS from the start of adjuvant therapy were 0.55 (95% CI, 0.42–0.72; N = 548) and 0.71 (95% CI, 0.49–1.03; N = 557), respectively.

Garassino MC, et al. ESMO 2024: Abst: 1210P

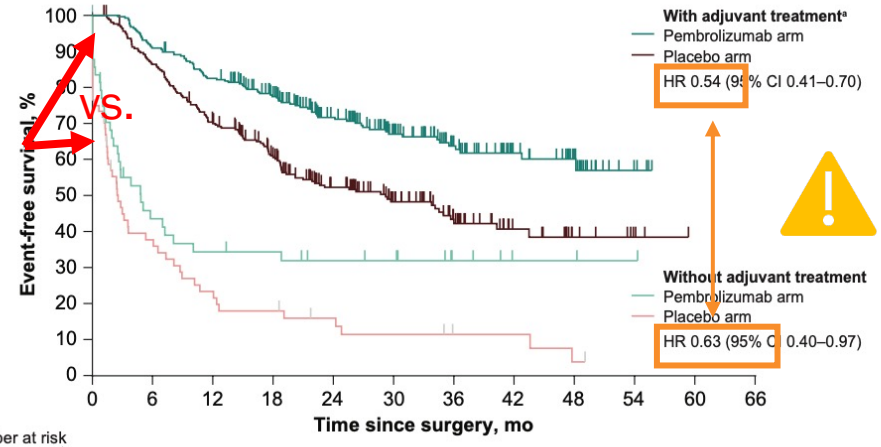
# KEYNOTE-671: Adjuvant Phase Analysis

**Figure 3. Kaplan-Meier estimates of (A) EFS per RECIST version 1.1 by investigator review and (B) OS from the time of in-study surgery based on receipt of adjuvant therapy**

**A) EFS in patients who received or did not receive adjuvant therapy**

Biased populations

vs.

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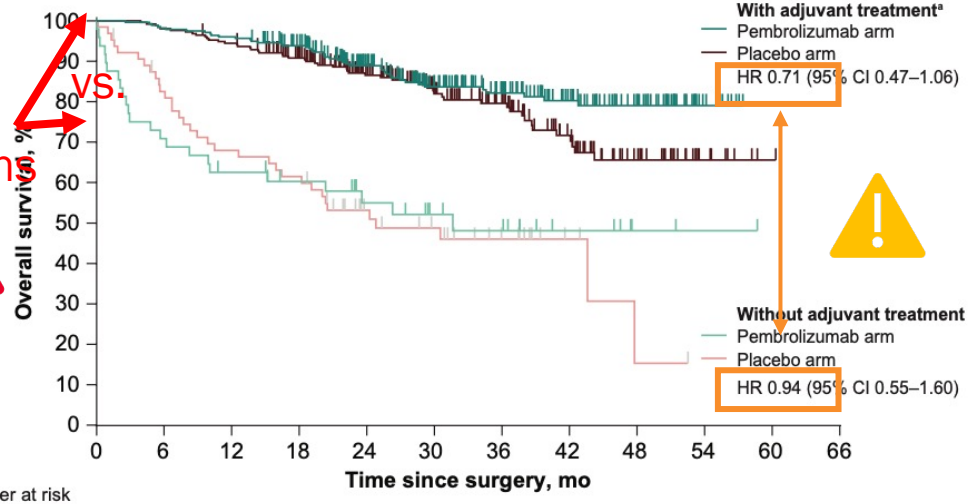
**B) OS in patients who received or did not receive adjuvant therapy**

Biased populations

vs.




| | Number at risk (number censored) | | | | | | | | | | | | |
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| With adjuvant treatment | Pembrolizumab arm | 276 (0) | 271 (0) | 265 (0) | 245 (14) | 183 (64) | 139 (98) | 102 (133) | 71 (162) | 45 (187) | 10 (222) | 0 (232) | 0 (232) |
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Garassino MC, et al. ESMO 2024: Abst: 1210P

# Benefit of additional adjuvant IO

Cloudy view of benefits of adjuvant phase IO

**Gold standard: OS**

EFS ⊘

Cross-trial comparisons ⊘

# Risks of Adjuvant IO

AEGEAN

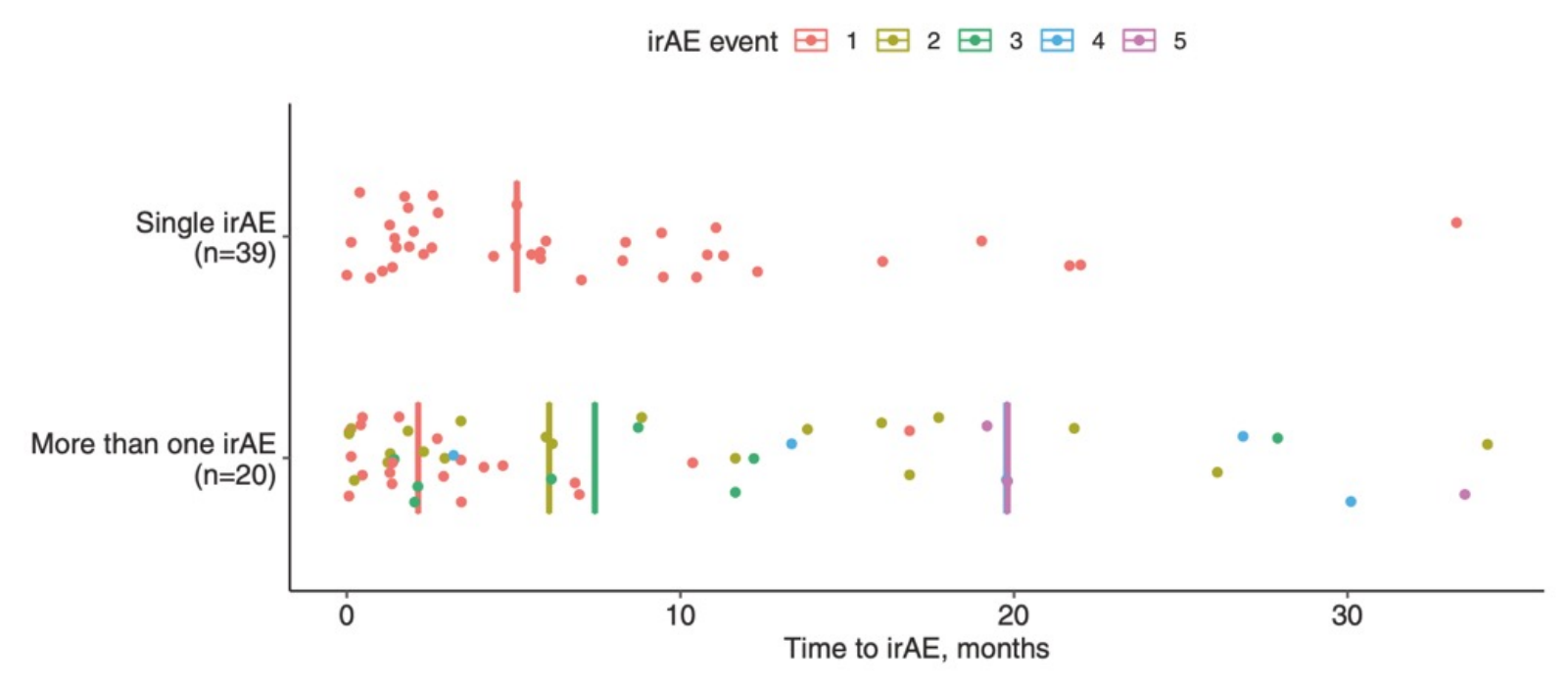
## Immune-related adverse events (IRAEs) during the Adjuvant Phase

| | Durva + Chemo N=265 n (%) | Placebo + Chemo N=254 n (%) |
|---|---|---|
| **All-Grade IRAEs** | 83 (31) | 27 (11) |
| **Grade 3-4 IRAEs** | 10 (3.8) | 5 (2) |
| **Grade 5 (Deaths due to IRAEs)** | 1 (0.4) | 0 (0) |
| **Study drug withdrawn due to IRAEs** | 14 (5) | 3 (1.2) |
| **Study drug interrupted due to IRAEs** | 14 (5) | 3 (1.2) |

July 25, 2024 Meeting of the Oncologic Drugs Advisory Committee- FDA Presentations
https://www.fda.gov/advisory-committees/updated-agenda-information-july-25-2024-meeting-oncologic-drugs-advisory-committee-meeting

# Timing of irAEs

Stage IV NSCLC irAEs




Hsu ML, et al. The Oncologist 2022

# Summary

- Multiple FDA approved regiments including Neoadjuvant alone and Peri-operative
- Contribution of Adjuvant Phase is not known: no prospective randomized data
  - FDA ODAC Agrees with me
- Likelihood of additional benefits of adjuvant phase is low (<10%)
- Cross-trial comparisons suggest similar outcomes
- Per-patient and post-hoc analyses are flawed
- OS needs to be the standard to answer duration and sequencing questions
- irAE risks for patients who are cured after surgery

# Everything is bigger in Texas. Is more always better?


"In my opinion, undertreatment is a greater risk than overtreatment

FDA ODAC 7/25/24

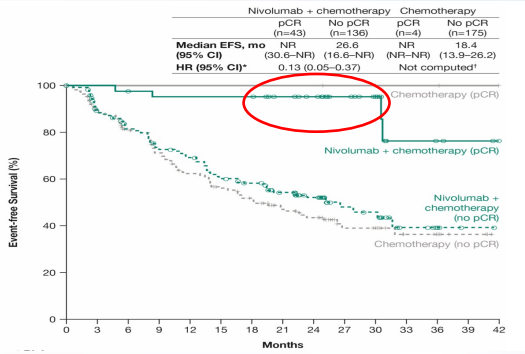

WCLC 2024 OA13.01: AEGEAN Panel Discussion

Heymach: "Patients with a pathCR clearly have better outcomes…This is the group that responded best…The degree of benefit is larger in the pathCR group."

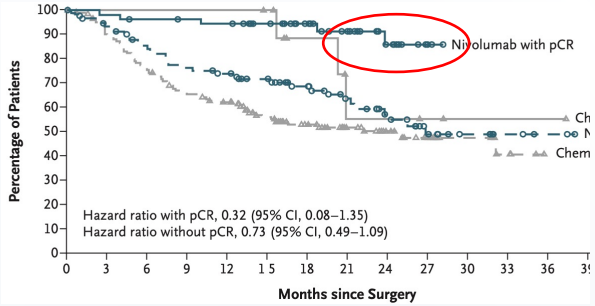
What is the number needed to treat?
10, 100, 1000?

OS NNT???

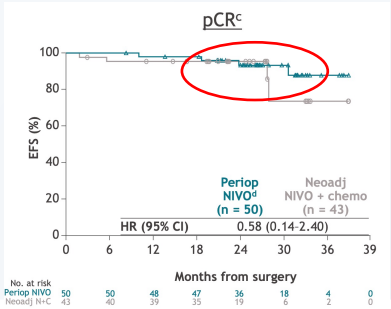
CM 816 pCR




CM 77T pCR




CM 816 vs.77T



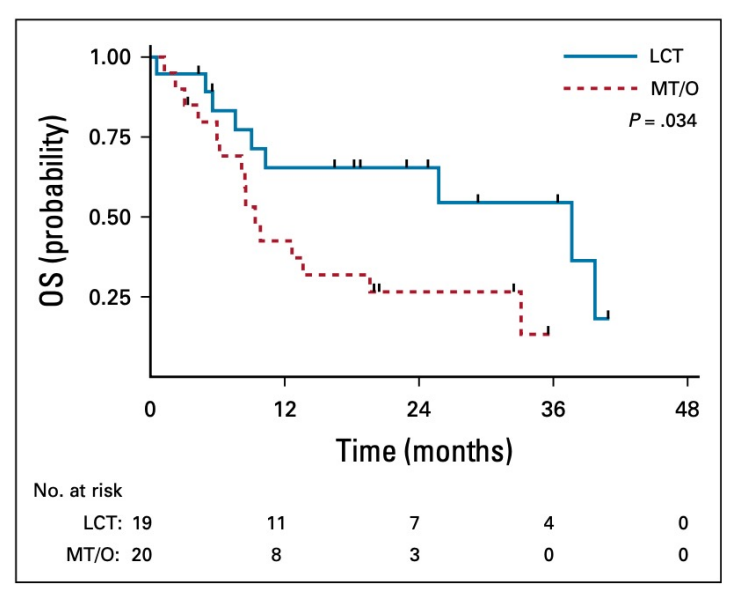

18th Annual ATLANTA LUNG CANCER SYMPOSIUM

PACE Partners for Advancing Clinical Education

Bio Ascend

# MD Anderson ≠ Real world: Local Consolidative Therapy

## MD Anderson




Gomez D, et al. J Clin Oncol 2019

## Real World

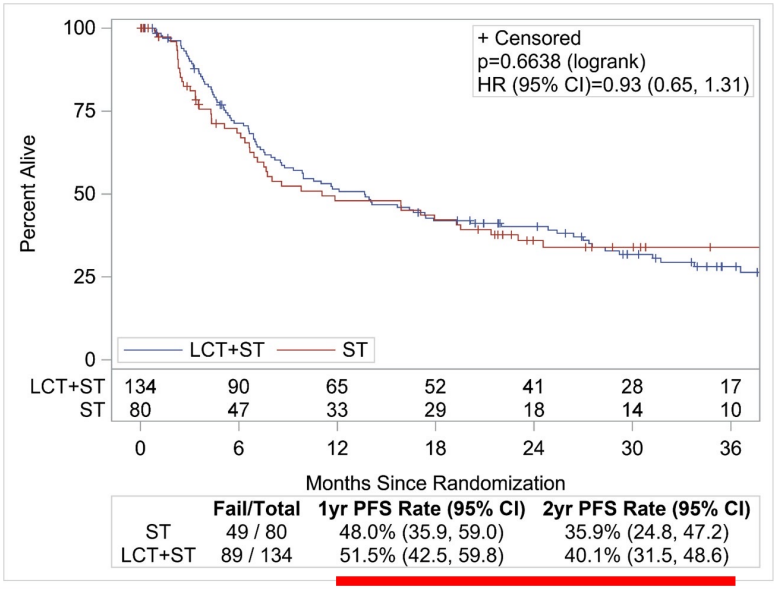
**Results – PFS**

**Median Follow-up:**

**All patients – 21.9 mo**

**Surviving patients – 29.4 mo**

**Of 185/215 patients treated with IO-containing systemic therapy regimens, the PFS HR was 0.90 (95% CI: 0.61, 1.32).**

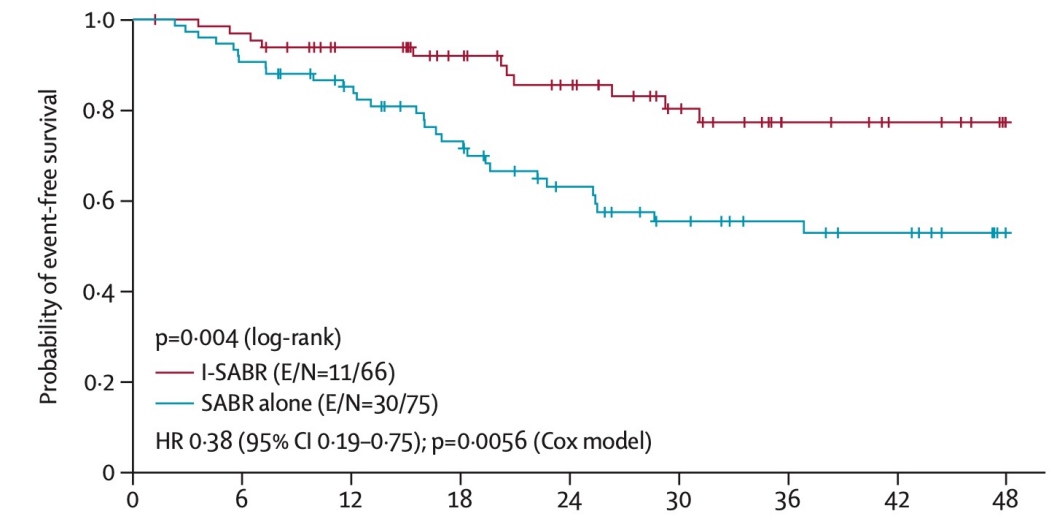



NRG LU002

Iyengar P, et al. ASCO 2024: Abst 8506

# MD Anderson ≠ Real world: SBRT + IO

## MD Anderson




Chang JY, et al. Lancet 2023

## Real World

### Press Release August 29, 2024

### Company Provides Update on Phase 3 KEYNOTE-867

RAHWAY, N.J.--(BUSINESS WIRE)-- Company today provided updates on two Phase 3 trials, KEYNOTE-867 and KEYNOTE-630. Company is **discontinuing the Phase 3 KEYNOTE-867** trial evaluating pembrolizumab, an anti-PD-1 therapy, in combination with stereotactic body radiotherapy (SBRT) for the treatment of patients with stage I or II (stage IIB N0, M0) non-small cell lung cancer (NSCLC), including those who are medically inoperable or have refused surgery. This decision is based on the recommendation of an independent Data Monitoring Committee (DMC), which reviewed data from a planned interim analysis. At the pre-specified interim analysis, pembrolizumab in combination with SBRT **did not demonstrate an improvement in event-free survival (EFS) or overall survival (OS),** the study's primary endpoint and key secondary endpoint, respectively, compared to placebo plus SBRT, and the benefit/risk profile of the combination did not support continuing the trial. Pembrolizumab in combination with SBRT was associated with higher rates of adverse events (AEs), including AEs leading to death, compared with SBRT and placebo.

https://www.merck.com/news/merck-provides-update-on-phase-3-keynote-867-and-keynote-630-trials/

# ODAC Declares Debate Winner

## Question 2: Vote

**Future Perioperative Trial Designs to Support Contribution of Sequence**

Should FDA require that new trial design proposals for perioperative regimens for resectable NSCLC include adequate within trial assessment of contribution of treatment phase?

| | | |
|---|---|---|
| Yes | 11 | 7/25/2024 |
| No | 0 | 1:33:45 PM |
| Abstain | 0 | |
| Non-Vote Member | 0 | |

July 25, 2024 Meeting of the Oncologic Drugs Advisory Committee- FDA Presentations
https://www.fda.gov/advisory-committees/updated-agenda-information-july-25-2024-meeting-oncologic-drugs-advisory-committee-meeting

https://www.youtube.com/watch?v=smUHtK5wdic

# Thank you

UVA Medical Center from Carter Mountain Orchard, September 2024