
# Challenges and Controversies in Perioperative Immunotherapy in Early-Stage NSCLC : *Pessimistic Aspect*

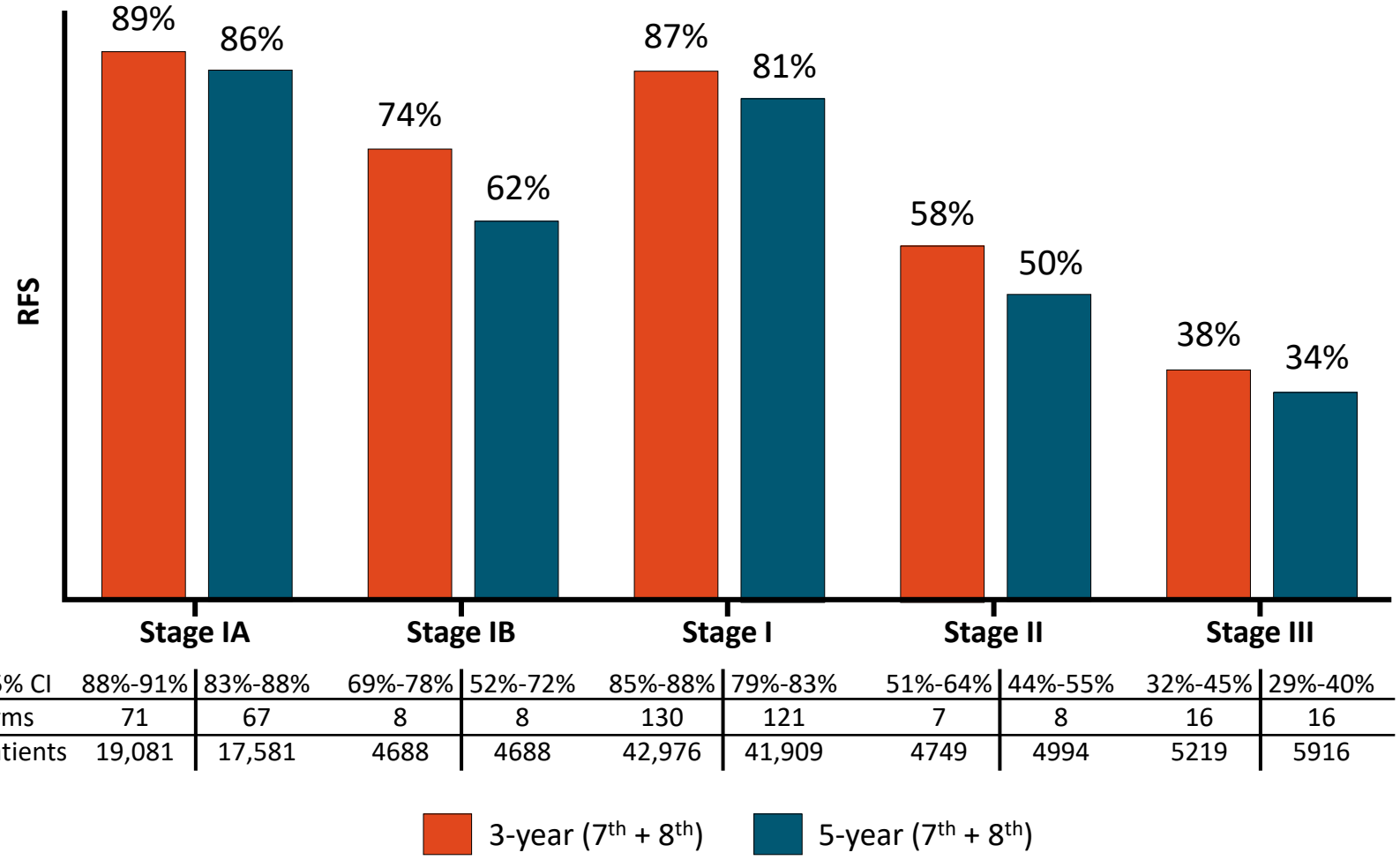
**In-Jae Oh, MD, PhD**

Lung Cancer Center, Chonnam National University Medical School and Hwasun Hospital, Republic of Korea

# Contents

1. What we know from recent RCT data: benefits and risks
2. Biomarkers such as pathologic response and ctDNA
3. My conclusion

# RFS Rates After Surgery for NSCLC By Stage




| | Stage IA | | Stage IB | | Stage I | | Stage II | | Stage III | |
|---|---|---|---|---|---|---|---|---|---|---|
| 95% CI | 88%-91% | 83%-88% | 69%-78% | 52%-72% | 85%-88% | 79%-83% | 51%-64% | 44%-55% | 32%-45% | 29%-40% |
| Arms | 71 | 67 | 8 | 8 | 130 | 121 | 7 | 8 | 16 | 16 |
| Patients | 19,081 | 17,581 | 4688 | 4688 | 42,976 | 41,909 | 4749 | 4994 | 5219 | 5916 |

**Recurrence rates for stage II NSCLC**

- 3-yr: 42%
- 5-yr: 50%

**Recurrence rates for stage III NSCLC**

- 3-yr: 62%
- 5-yr: 66%

Ravi. Chest. 2024;165:1260.

**TABLE 2.** Ongoing and Completed Trials With Neoadjuvant and Adjuvant Immunotherapy in Resectable NSCLC

| ICI | Trial | Treatment Setting | Stage | Primary End Points | Primary Efficacy Results: EFS, DFS, OS: HR (95% CI) pCR/MPR: % | Regulatory Status |
|---|---|---|---|---|---|---|
| Atezolizumab | IMpower030 (NCT03456063) | Neoadjuvant + adjuvant | II to IIIB (AJCC8) | EFS | NA | Ongoing |
| | IMpower010 (NCT02486718) | Adjuvant | II to IIIA (AJCC7) | DFS[a] | 0.66 (0.50 to 0.88)[b] | FDA-approved[b,c] |
| Durvalumab | AEGEAN (NCT03800134) | Neoadjuvant + adjuvant | IIA to IIIB (AJCC8) | EFS, pCR | 0.68 (0.53 to 0.88)<br>17.2% *v* 4.3% | Ongoing |
| | MERMAID-I (NCT04385368) | Adjuvant | II to III (AJCC7) | DFS[a] | NA | Ongoing |
| | BR.31 (NCT02273375) | Adjuvant | IB to IIIA (AJCC7) | DFS[a] | NA | Ongoing |
| Nivolumab | CheckMate-816 (NCT02998528) | Neoadjuvant | IB to IIIA (AJCC7) | EFS, pCR[a] | 0.63 (0.43 to 0.91)<br>24.0% *v* 2.2% | FDA-approved |
| | CheckMate-77T (NCT04025879) | Neoadjuvant + adjuvant | IIA to IIIB (AJCC8) | EFS[a] | NA | Ongoing |
| | ANVIL (NCT02595944) | Adjuvant | IB to IIIA (AJCC7) | DFS, OS | NA | Ongoing |
| Pembrolizumab | KEYNOTE-671 (NCT03425643) | Neoadjuvant + adjuvant | II to IIIB (AJCC8) | EFS, OS | 0.58 (0.46 to 0.72)<br>18.1% *v* 4.0% | FDA-approved |
| | KEYNOTE-091/PEARLS (NCT02504372) | Adjuvant | II to IIIA (AJCC7) | DFS[a] | 0.76 (0.63 to 0.91) | FDA-approved[c] |
| | NCI ACCIO (NCT04267848) | Adjuvant | II to IIIB (AJCC8) | DFS | NA | Ongoing |
| | BTCRC-LUN18-153 (NCT04317534) | Adjuvant | I (AJCC8) | DFS | NA | Ongoing |
| Adebrelimab | NCT04316364 (China-only) | Neoadjuvant + adjuvant | II to IIIB (AJCC8) | EFS, MPR | NA | Ongoing |
| Sintilimab | NCT05116462 (China-only) | Neoadjuvant + adjuvant | IIB to IIIB (AJCC8) | EFS, pCR | NA | Ongoing |
| Tislelizumab | RATIONALE 315 (NCT04379635 China-only) | Neoadjuvant + adjuvant | II to IIIA | EFS, MPR | NA | Ongoing |
| Toripalimab | NEOTORCH (NCT04158440; China-only) | Neoadjuvant + adjuvant | II toIIIB (AJCC8) | EFS, MPR[a] | 0.40 (0.28 to 0.57)<br>48.5% *v* 8.4% | Ongoing |

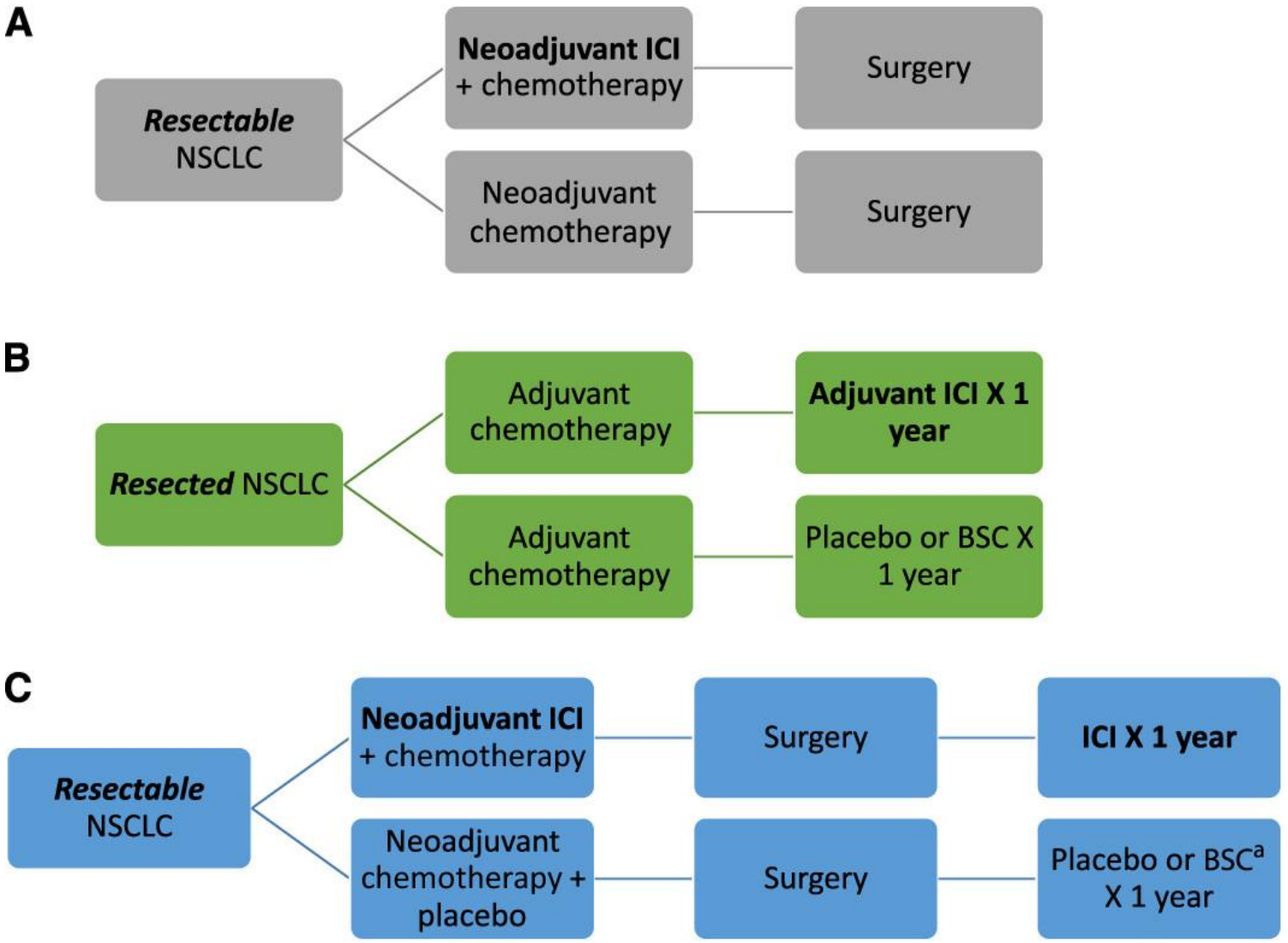
Abbreviations: AJCC, American Joint Committee on Cancer staging edition; DFS, disease-free survival; EFS, event-free survival; FDA, US Food and Drug Administration; HR, hazard ratio; ICI, immune checkpoint inhibitor; MPR, major pathologic response; NA, not applicable; NSCLC, non–small cell lung cancer; OS, overall survival; pCR, pathologic complete response.

[a]Overall survival included in the protocol-prespecified statistical testing strategy to control overall type I error.

[b]Results and approval pertain to patients with NSCLC and PD-L1 expression of 1% or greater.

[c]Approved for patients who received previous adjuvant platinum-based chemotherapy.

# Current designs of trials evaluating perioperative IO




*Am Soc Clin Oncol Educ Book 2024 Jun;44(3):e432500.*

# Phase III Adjuvant Immunotherapy Trials

## IMpower010[1-3]

**Chemotherapy mandatory**

*Stratification by sex, stage, histology, PD-L1 status*

Adults with completely resected stage IB-IIIA NSCLC per UICC/AJCC v7 (includes tumors ≥4 cm) (N = 1280)

→ **Adjuvant cisplatin-based CT*** for 4 cycles

- → **Atezolizumab** 1200 mg IV Q3W x 16
- → **Best supportive care**

*Cisplatin + pemetrexed (nonsquamous), gemcitabine, docetaxel, or vinorelbine.

- **Primary endpoint:** DFS by investigator among 3 populations: stage II-IIIA with PD-L1 TC ≥1%, all stage II-IIIA, and ITT population (randomized stage IB-IIIA)

## PEARLS/KEYNOTE-091[4-6]

**Chemotherapy not mandatory**

*Stratified by stage, PD-L1 status, prior adjuvant CT, geographic location*

Adults with stage IB-IIIA NSCLC (includes tumors ≥4 cm); complete surgical resection with disease-free margins (R0); with or without adjuvant CT (N = 1177)

- → **Pembrolizumab** 200 mg IV Q3W x ~1 yr
- → **Placebo** IV Q3W x ~1 yr

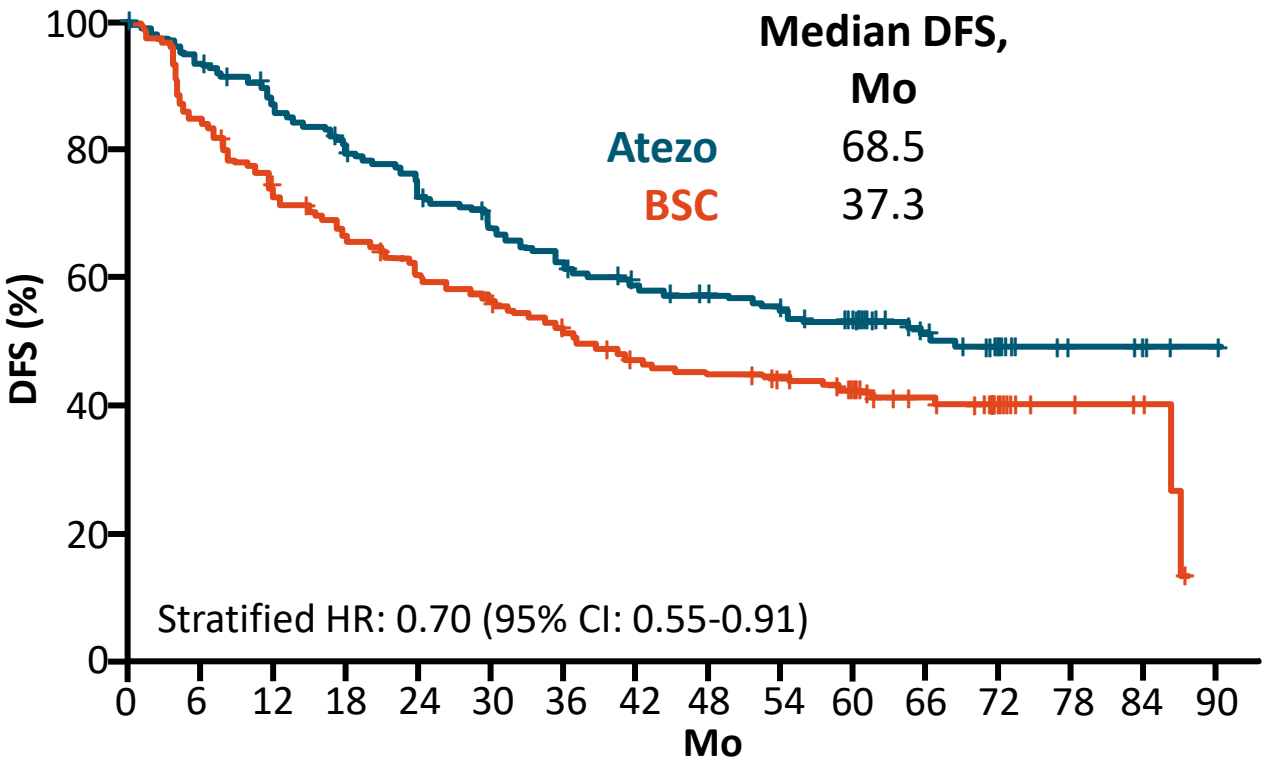
- **Primary endpoint:** DFS in overall and PD-L1 TPS ≥50% population

**NOTE: Cross-trial comparisons have significant limitations.**
This information is presented to generate discussion, not to make direct comparisons between study results.

1. NCT02486718. 2. Felip. Lancet. 2021;398:1344. 3. Felip. WCLC 2022. Abstr PL03.09.
4. NCT02504372. 5. O'Brien. Lancet Oncol.2022;23:1274. 6. Pas-Arez. ESMO 2022. Abstr VP3-2022.

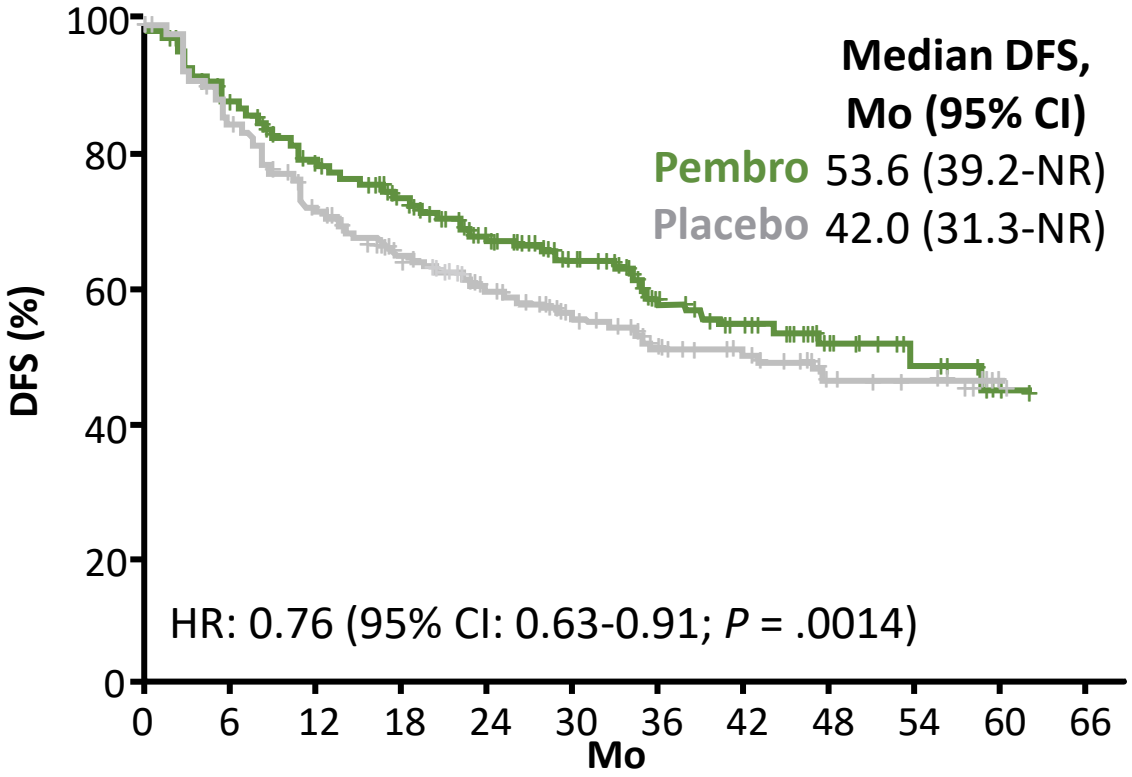
# Adjuvant IO Trials: DFS

## IMpower 010: Stage II-IIIA NSCLC With PD-L1 TC ≥1%




FDA approved in October 2021 as adjuvant treatment following resection and platinum-based CT for adults with stage II-IIIA NSCLC and **PD-L1 expression on ≥1% of tumor cells**[3]

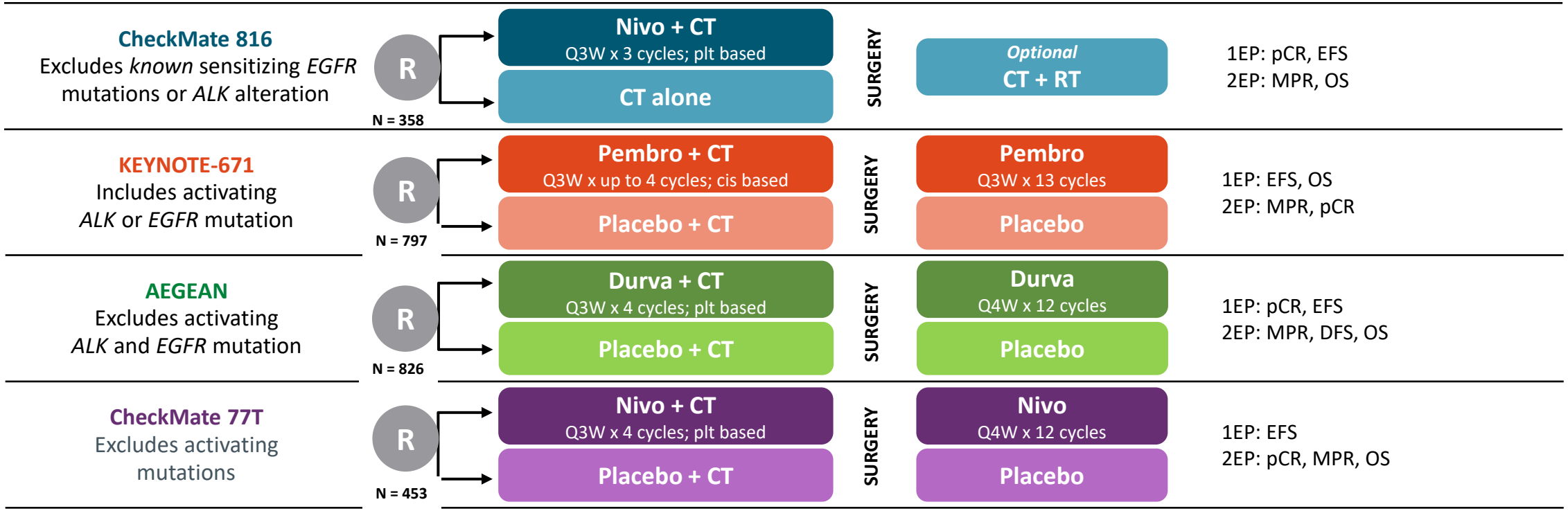
## PEARLS/KEYNOTE-091: Overall Population[4,5]




FDA approved in January 2023 as adjuvant treatment following resection and platinum-based CT for adult patients with stage IB-IIIA, including T2a ≥4 cm, NSCLC[6]

1. Felip. Lancet. 2021;398:1344. 2. Wakelee. ASCO 2024. Abstr LBA8035. 3. Atezolizumab PI. 4. Paz-Ares. ESMO Virtual 2022. Abstr VP3-2022. 5. O'Brien. Lancet Oncol. 2022;23:1274. 6. Pembrolizumab PI.

# Key Trials With Neoadjuvant Chemotherapy Plus Immunotherapy



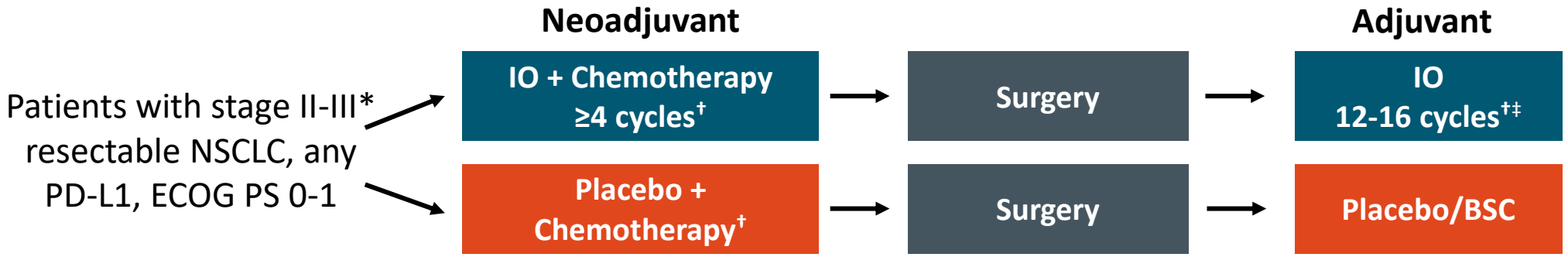

Forde. NEJM. 2022;386:1973. Wakelee. NEJM. 2023;389:491. Heymach. NEJM. 2023;389:1672. Cascone. NEJM. 2024;390:1756.

# Neoadjuvant and Perioperative IO Trials

| Trial | CheckMate 816[1,2] | | KEYNOTE-671[3-5] | | AEGEAN[6,7] | | CheckMate 77T[8,9] | |
|---|---|---|---|---|---|---|---|---|
| Neoadjuvant therapy | Nivo + CT, 3 cycles | CT alone, 3 cycles | Pembro + CT, 4 cycles | Placebo + CT, 4 cycles | Durva + CT, 4 cycles | Placebo + CT, 4 cycles | Nivo + CT, 4 cycles | Placebo + CT, 4 cycles |
| Adjuvant therapy | Optional CT, 4 cycles | Optional CT, 4 cycles | Pembro, 13 cycles | Placebo, 13 cycles | Durva, 12 cycles | Placebo, 12 cycles | Nivo, 12 cycles, Q4W | Placebo, 12 cycles, Q4W |
| CT regimens | Carboplatin or cisplatin; Cisplatin in CT-only arm | | Cisplatin | | Cisplatin or carboplatin | | Cisplatin or carboplatin | |
| Nodal status: N0/N1/N2, % | Not reported | | 37.3/20.4/42.3 | 35.5/17.8/46.8 | 30.1/20.5/49.5 | 27.3/23.3/49.5 | Not reported | |
| **pCR, %** | **24.0** | **2.2** | **18.1** | **4.0** | **17.2** | **4.3** | **25.3** | **4.7** |
| Completed surgery | 83.2 | 75.4 | 82.1 | 79.4 | 77.6 | 76.7 | 77.7 | 76.7 |
| R0 resection | 83.2 | 77.8 | 92.0 | 84.2 | 94.7 | 91.3 | 89.3 | 90.4 |
| Median f/u, mo | 57.6 | | 36.6 (range: 18.8-62.0) | | 25.9 (range: 0-56.6) | | 33.3 (range: 23.6-52.1) | |
| **mEFS, mo (95% CI)** | **43.8** | **18.4** | **47.2 (32.9-NR)** | **18.3 (14.8-22.1)** | **NR (42.3-NR)** | **30.0 (20.6-NR)** | **40.1 (33.7-NR)** | **17.0 (13.6-28.1)** |
| HR for mEFS | 0.66 (0.49-0.90) | | 0.59 (0.48-0.72) | | 0.69 (0.53-0.88) | | 0.59 (0.45-0.79) | |
| **mOS, mo (95% CI)** | **NR** | **NR** | **NR (NR-NR)** | **52.4 (45.7-NR)** | **NR** | **53.2 (44.3-NR)** | **Not yet tested** | |
| HR for mOS | 0.71 (98.36% CI, 0.47-1.07) | | 0.72 (0.56-0.93) | | 0.89 (0.70-1.14) | | N/A | |

1. Forde. NEJM. 2022;386:1973. 2. Spicer. ASCO 2024. Abstr LBA8010. 3. Wakelee. ASCO 2023. Abstr LBA100. 4. Wakelee. NEJM. 2023;389:491. 5. Spicer. ESMO 2023. Abstr LBA56. 6. Heymach. WCLC 2024. Abstr OA13.03. 7. Heymach. NEJM. 2023;389:1672. 8. Spicer. ESMO 2024. Abstr LBA50. 9. Cascone. NEJM. 2024;390:1756.

# Ongoing Phase III Perioperative Studies in Resectable NSCLC




| | KEYNOTE-671[1,2] | AEGEAN[3,4] | CheckMate 77T[5,6] | IMpower030[7,8] |
|---|---|---|---|---|
| IO agent | Pembrolizumab | Durvalumab | Nivolumab | Atezolizumab |
| Primary endpoint(s) | EFS, OS | pCR, EFS | EFS | EFS |
| Disease stage (TNM 8th ed.) | II-IIIB§ | IIA-IIIB§ | II-IIIB§ | II-IIIB§ |
| N | 797 | 826 | 482 | 453 |
| *EGFR* or *ALK* mut allowed | Yes | Amended to exclude | No | No |
| Chemotherapy backbone | ≥4 cycles of cis/(gem or pemetrexed) | 4 cycles of carbo/pac, carbo/pemetrexed, cis/gem, or cis/pemetrexed | ≥4 cycles carbo/pac, cis/doc, carbo/pemetrexed, cis/pemetrexed, or carbo/pac | 4 cycles of carbo/pemetrexed, carbo/*nab*-pac, cis/pemetrexed, or cis/gem |

*Stages included differ between trials. †Dosage, timing, duration, and chemotherapy backbones differ between trials. ‡In contrast, CheckMate 816 allowed optional adjuvant CT ± RT. §Includes stages IIIB patients with N2 disease that is considered resectable. Cross trial comparisons are not intended. ‖Molecular testing no mandated

1. Spicer. ESMO 2023. Abstr LBA56. 2. NCT03425643. 3. Heymach. NEJM. 2023;389:1672. 4. NCT03800134.
5. Cascone. ESMO 2023. Abstr LBA1. 6. NCT04025879 7. Peters. Annal Oncol. 2019;30:Suppl 2. 8. NCT03456063.

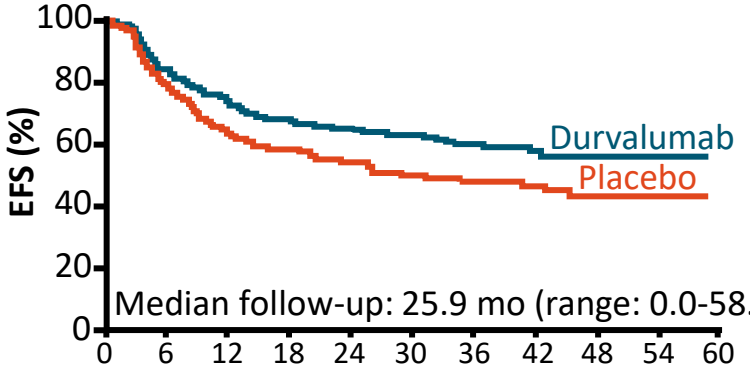
# Phase III Perioperative Studies in Resectable NSCLC: pCR and EFS

**pCR Rate, %**

| Trial | IO + CT | Pbo + CT |
|---|---|---|
| **AEGEAN** (durvalumab) | 17.2 | 4.3 |
| **CheckMate 77T** (nivolumab) | 25.3 | 4.7 |
| **KEYNOTE-671** (pembrolizumab) | 18.1 | 4.0 |

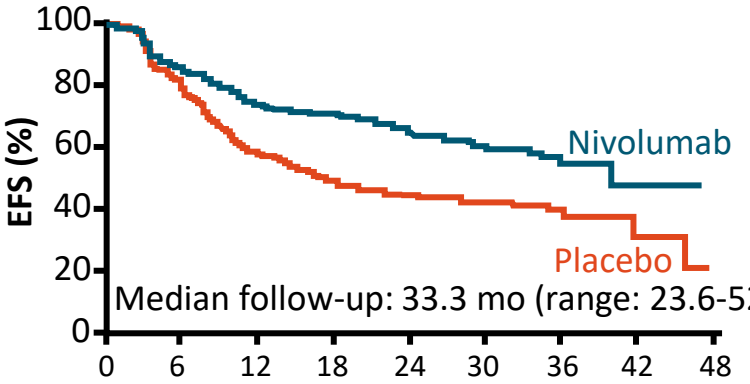
**mEFS (HR)**

**AEGEAN**



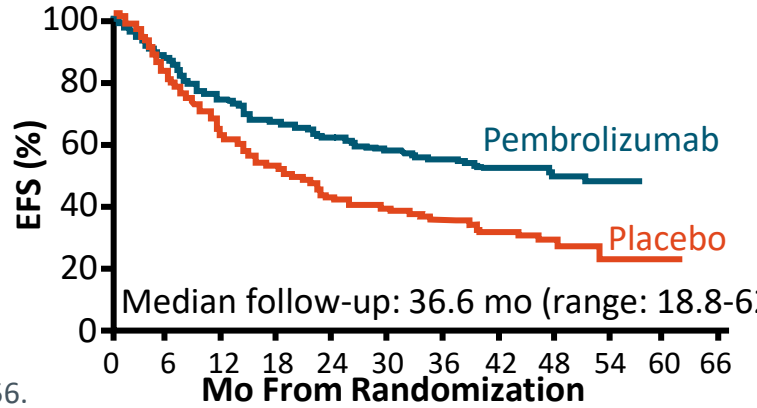

NR vs 30.0 mo (0.69)

**CheckMate 77T**




40.1 vs 17.0 mo (0.59)

**KEYNOTE-671**




47.2 vs 18.3 mo (0.59)

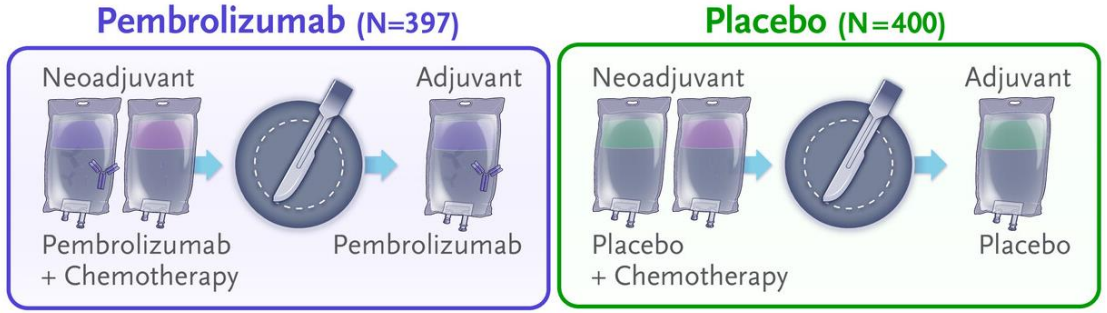
Wakelee. ASCO 2023. Abstr LBA100. Wakelee. NEJM. 2023;389:491. Spicer. ESMO 2023. Abstr LBA56. Cascone. NEJM. 2024;390:1756. Cascone. ESMO 2023. Abstr LBA1. Spicer. ESMO 2024. Abstr LBA50. Heymach. AACR 2023. Abstr CT005. Heymach. NEJM. 2023;389:1672. Heymach. WCLC 2024. Abstr OA13.03.

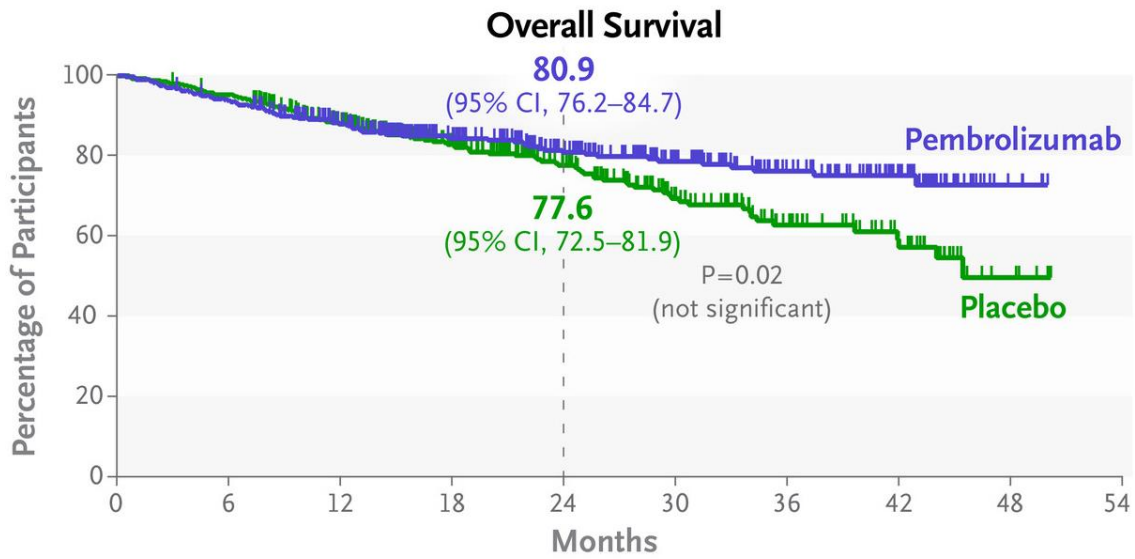
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

# Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

Wakelee H et al. DOI: 10.1056/NEJMoa2302983

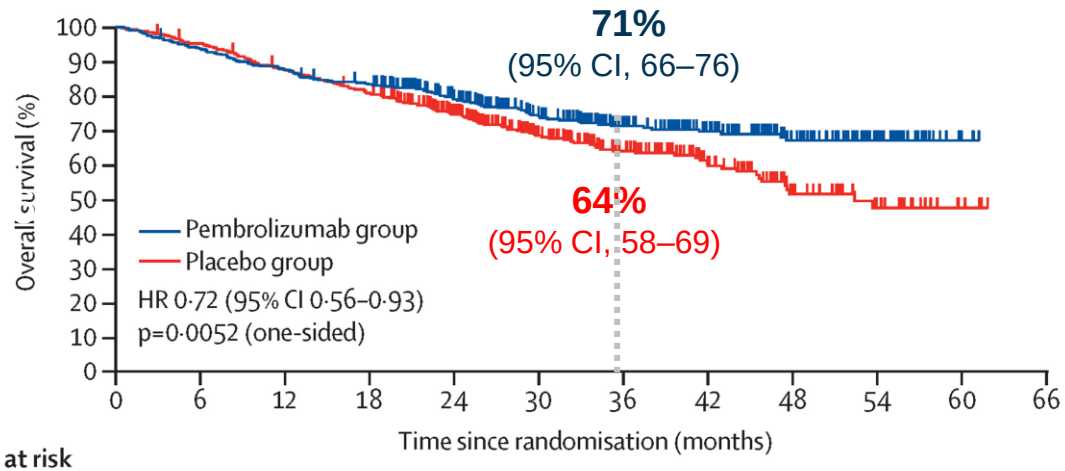



N Engl J Med 2023;389:491-503.

# Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in patients with early-stage non-small-cell lung cancer (KEYNOTE-671): a randomised, double-blind, placebo-controlled, phase 3 trial

A




| Number at risk (number censored) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab group | 397 (0) | 371 (1) | 347 (1) | 327 (4) | 277 (38) | 205 (95) | 148 (145) | 108 (182) | 69 (218) | 32 (255) | 4 (283) | 0 (287) |
| Placebo group | 400 (0) | 379 (2) | 347 (4) | 319 (5) | 256 (45) | 176 (106) | 125 (147) | 77 (190) | 39 (219) | 20 (236) | 4 (252) | 0 (256) |

Lancet 2024;404(10459): 1240-1252.

# Immunotherapy Approvals for Neoadjuvant and Adjuvant Therapies in Early-Stage NSCLC

| Neoadjuvant | Perioperative | Adjuvant |
|---|---|---|
| **Nivolumab:** combined with plt-based CT, adults with resectable NSCLC (CheckMate 816 trial) | **Durvalumab:** for resectable NSCLC (tumors ≥4 cm or node positive) combined with plt-based CT; continued as single agent after surgery (AEGEAN trial)<br><br>**Pembrolizumab**: for resectable NSCLC (tumors ≥4 cm or node positive) combined with plt-based CT; continued as single agent after surgery (KEYNOTE-671 trial)<br><br>**Nivolumab**: for resectable (tumors ≥4 cm and/or node positive) NSCLC combined with plt-doublet CT; continued as single agent after surgery (Checkmate 77T trial) | **Atezolizumab:** following resection and plt-based CT, adults with stage II-IIIA and PD-L1 ≥1% of tumor cells (IMpower010 trial)<br><br>**Pembrolizumab:** Following resection and plt-based CT, adults with stage IB-IIIA (KEYNOTE-091 trial) |

Atezolizumab PI. Durvalumab PI. Nivolumab PI. Pembrolizumab PI.

# Real-world challenging clinical cases

Case 1: Limited radiographic response with pCR

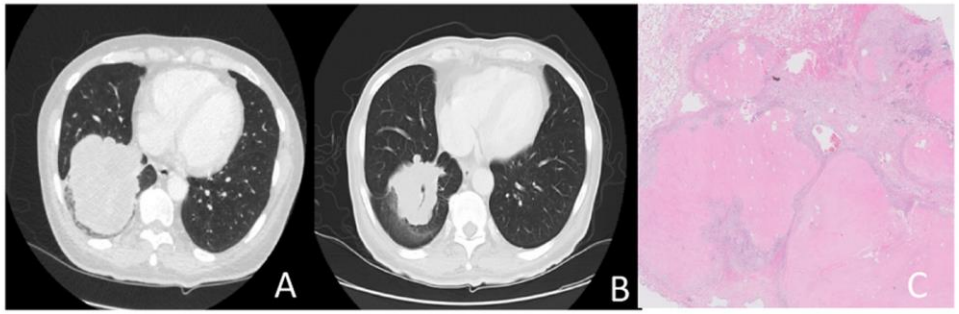



Figure 1. Imaging and pathologic response in a patient with Stage IIIA (T4N0) NSCLC (PD-L1 TPS 75%) treated with neoadjuvant chemoimmunotherapy per Keynote 671 regimen. (A) Baseline scan. (B) Posttreatment scan following four cycles chemoimmunotherapy shows limited response but persistent disease. (C) Resected tumor bed with no viable tumor but occupied by necrosis and fibrosis, consistent with pCR.

Case 2: Nodal flare

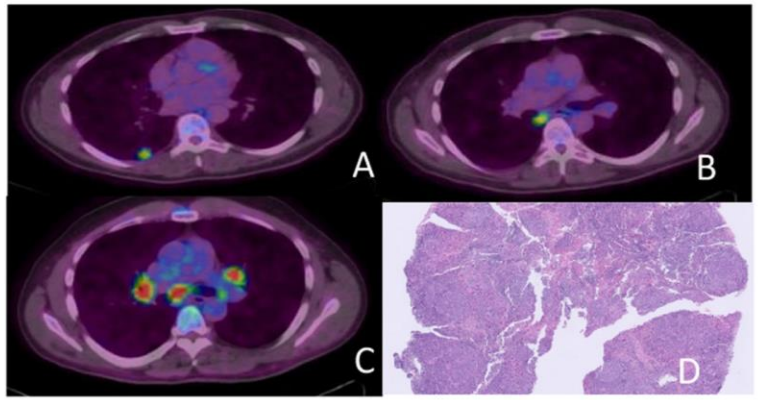



Figure 2. Nodal flare in a patient with Stage IIIA (T1N2) NSCLC (PD-L1 TPS 5%) treated with neoadjuvant chemoimmunotherapy. (A) Pre-treatment PET/CT scan shows primary tumor and (B) N2 disease. (C) Post-treatment PET/CT with lower SUV uptake in primary tumor and higher uptake in multiple nodes. (D) Right level 4 lymph node dissection with benign lymph node tissue showing reactive germinal centers.

Case 3: Progression on neoadjuvant therapy

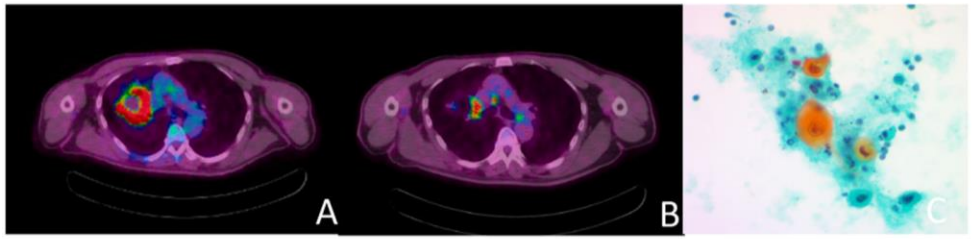



Figure 3. Patient with Stage IIIA (T4N0) NSCLC (PD-L1 TPS 5%) with progression of disease on neoadjuvant chemoimmunotherapy per Checkmate 816. (A) Pre-treatment imaging PET/CT. (B) Post-treatment PET/CT with worsening mediastinal LN following three cycles of neoadjuvant chemoimmunotherapy. (C) LN biopsy showing keratinized squamous cell carcinoma

Case 4: Incomplete pathologic response following neoadjuvant chemoimmunotherapy

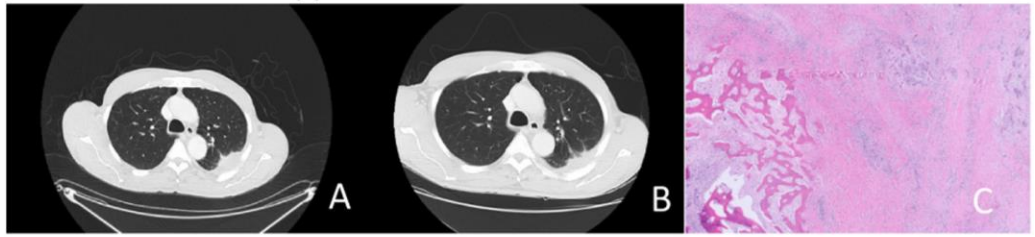


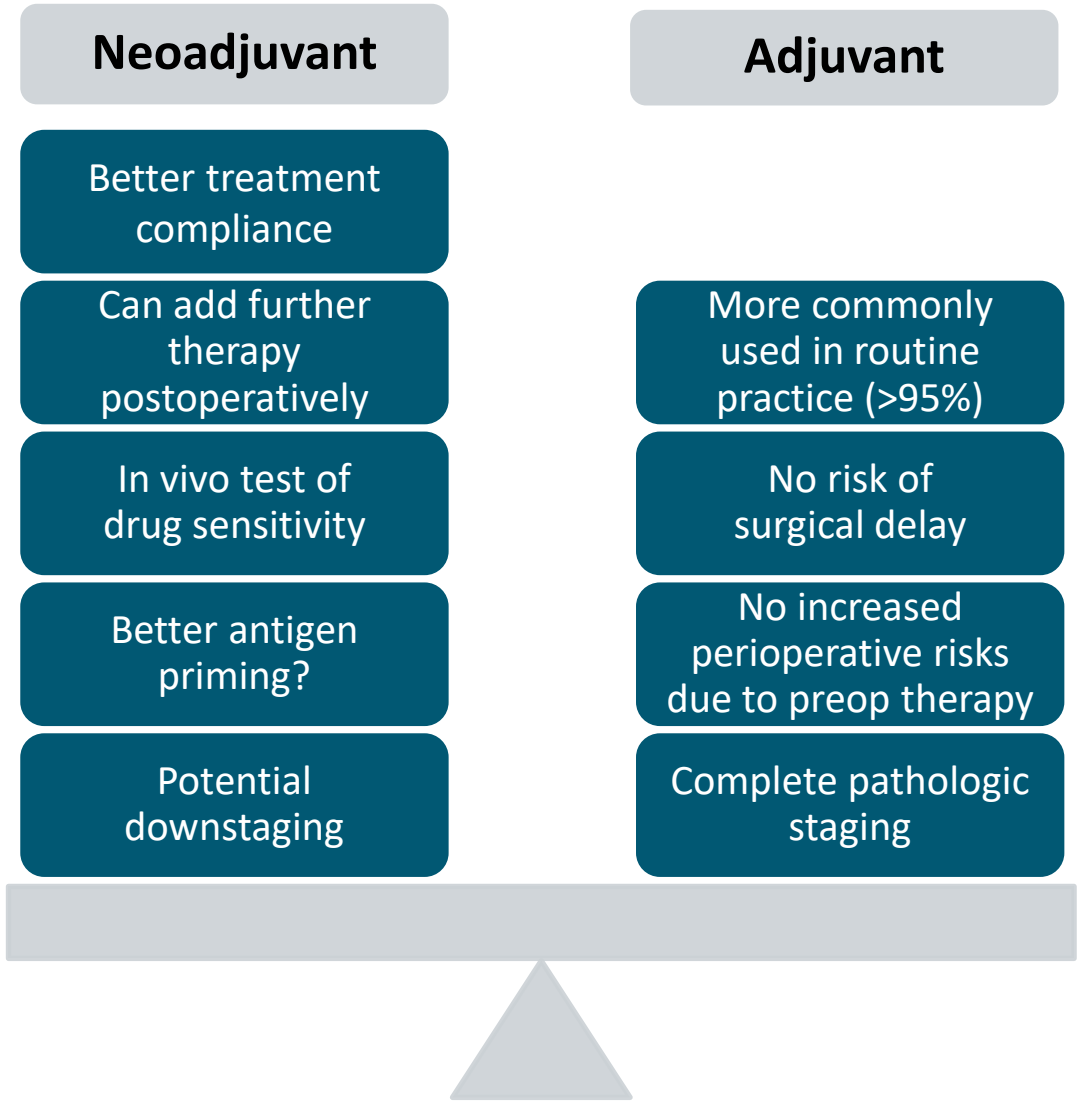

Figure 4. Patient with Stage IIB (T3N0) NSCLC (PD-L1 TPS 60-70%) treated with neoadjuvant chemoimmunotherapy per CM816 with incomplete pathologic response transitioned to adjuvant atezolizumab per IMPOWER010.(A) Pre-treatment imaging. (B) Post-treatment imaging. (C ) Resected tumor bed with extensive fibrosis, with small clusters of residual adenocarcinoma (approximately 10% residual tumor) involving chest wall

*Clin Lung Cancer 2024;25(3):197-214.*

# How Is the Decision Made?

Neoadjuvant approaches provide rich research opportunities:

- **Rapid assessment of response to novel therapies within tumors and surrounding tissue, LNs**
- Platform for biomarker development




**Multidisciplinary and Patient Discussion**

# CASE(1): 49/M, ADC,LUL IIIA(cT1bN2M0)

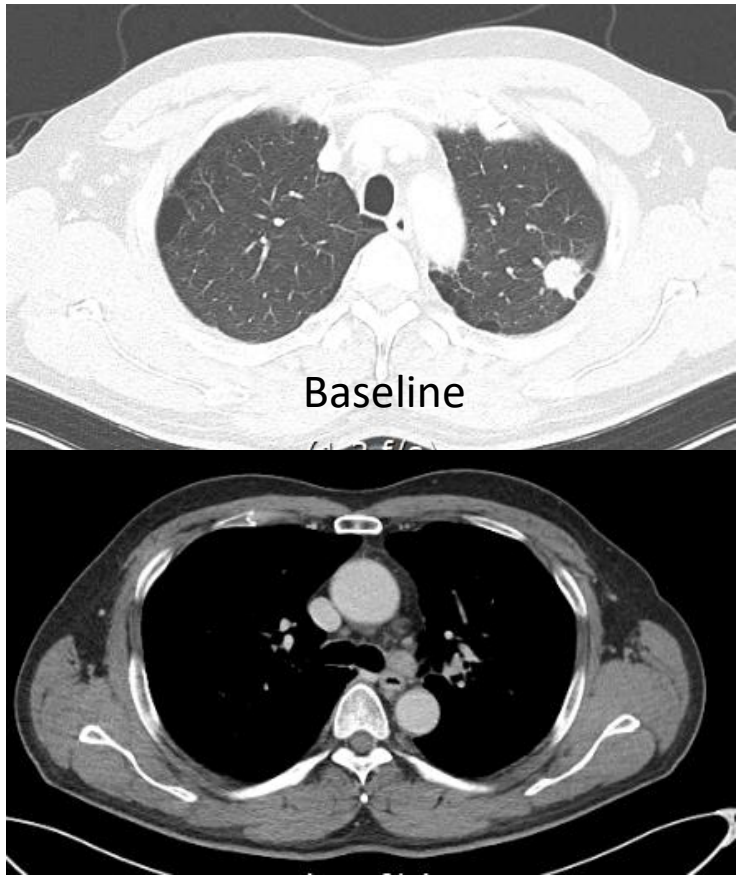
30 PYS, Current smoker
P/H: HNP op

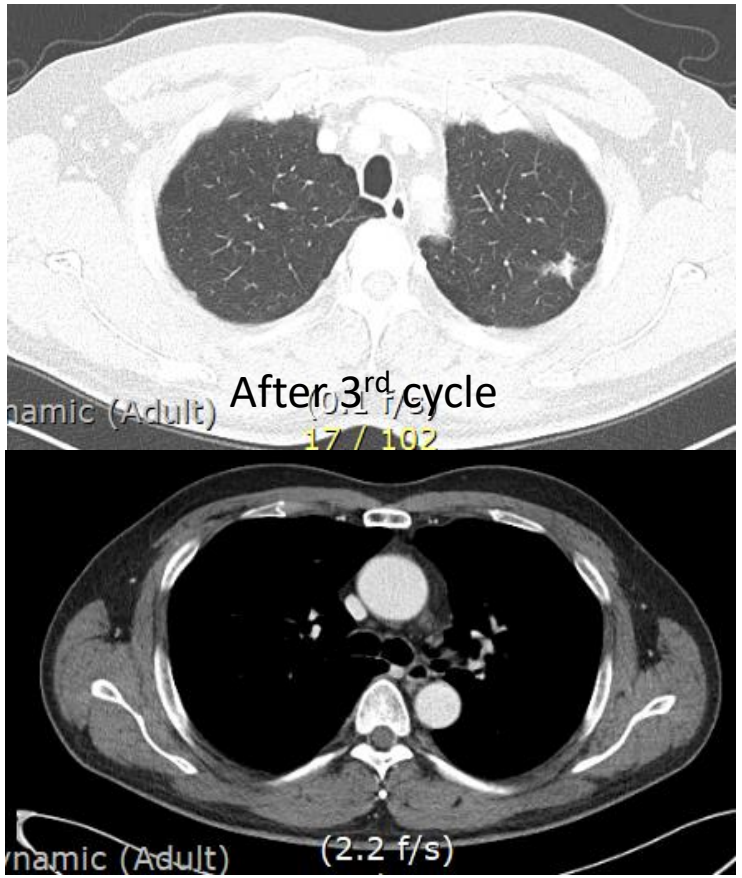
- Bx: ADC, G3
- EGFR/ALK/ROS1(-), PDL1[sp263,22C3]:100%

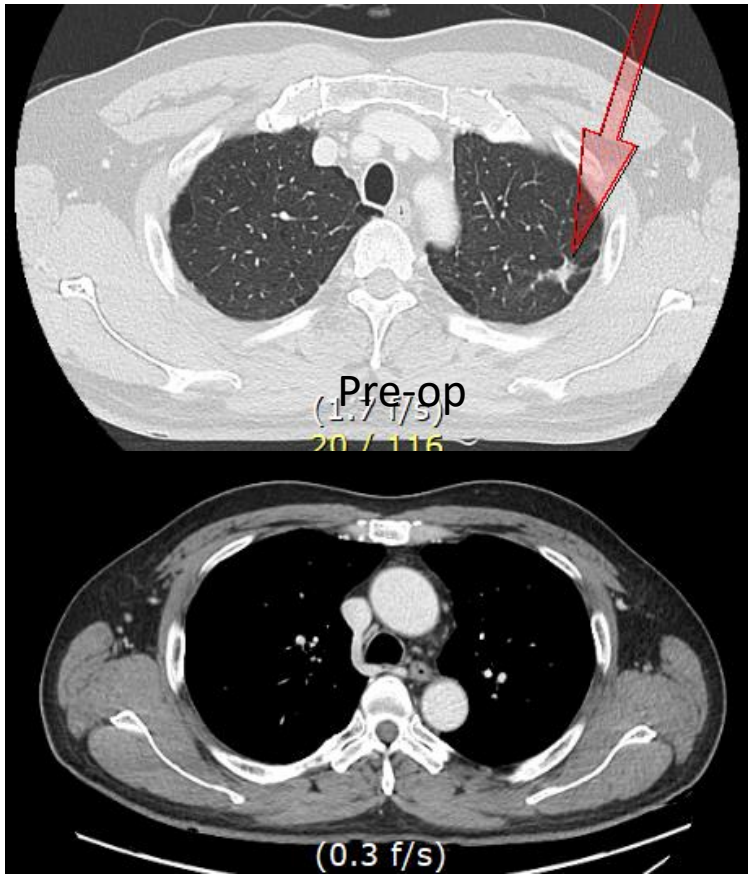
- **Nivo** + Pemetrexed/cisplatin #3: 2024.1.12 ~ 2.23 *PR
- VATS LUL lobectomy c MLND: 2024.4.4

**Next ?**
*Adjuvant chemo
*Adjuvant IO

- Bx: **pCR**

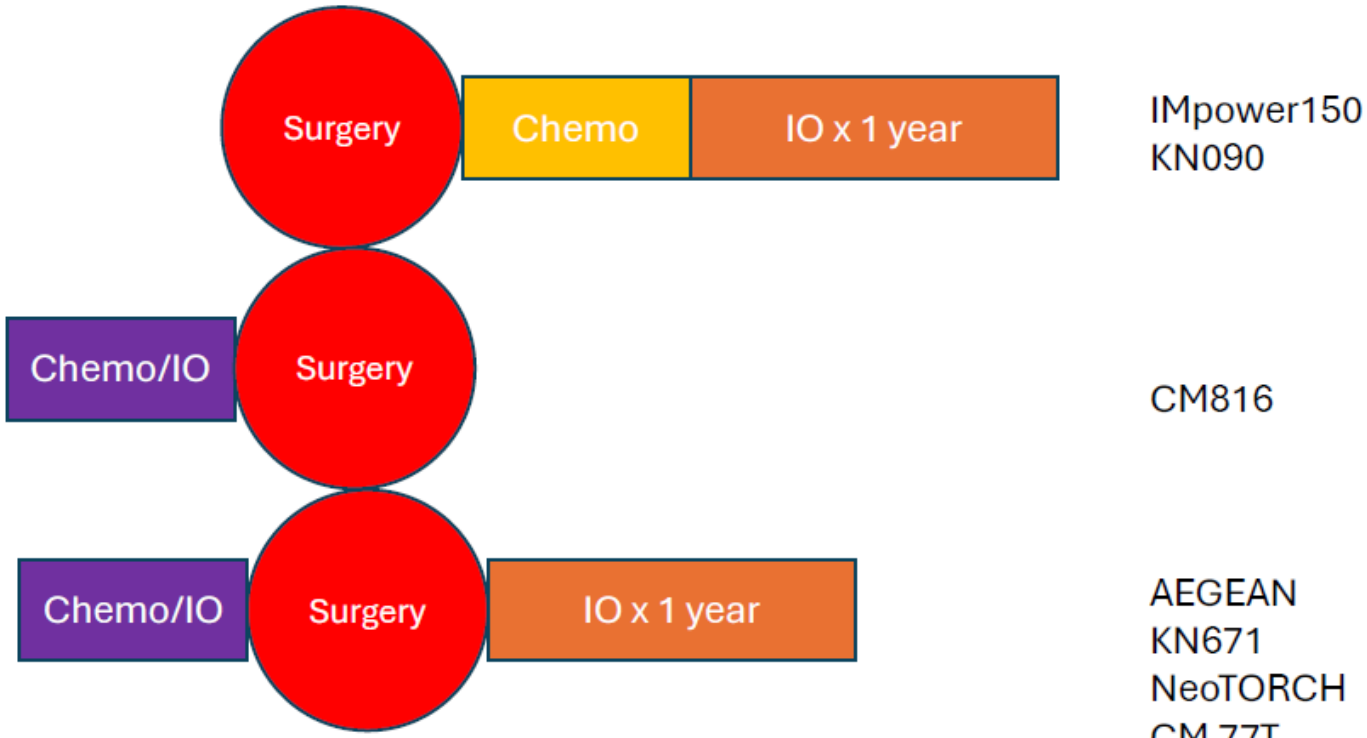


# Pathological response may contribute to the decision for adjuvant Tx?

- **pCR**: With excellent survival outcome from CM816, these patient may not need further adjuvant IO
- **MPR**: Unclear if adjuvant IO provide additional benefit
- **Less than MPR**: KN671 suggested improvement of survival with neo-adjuvant IO followed by IO



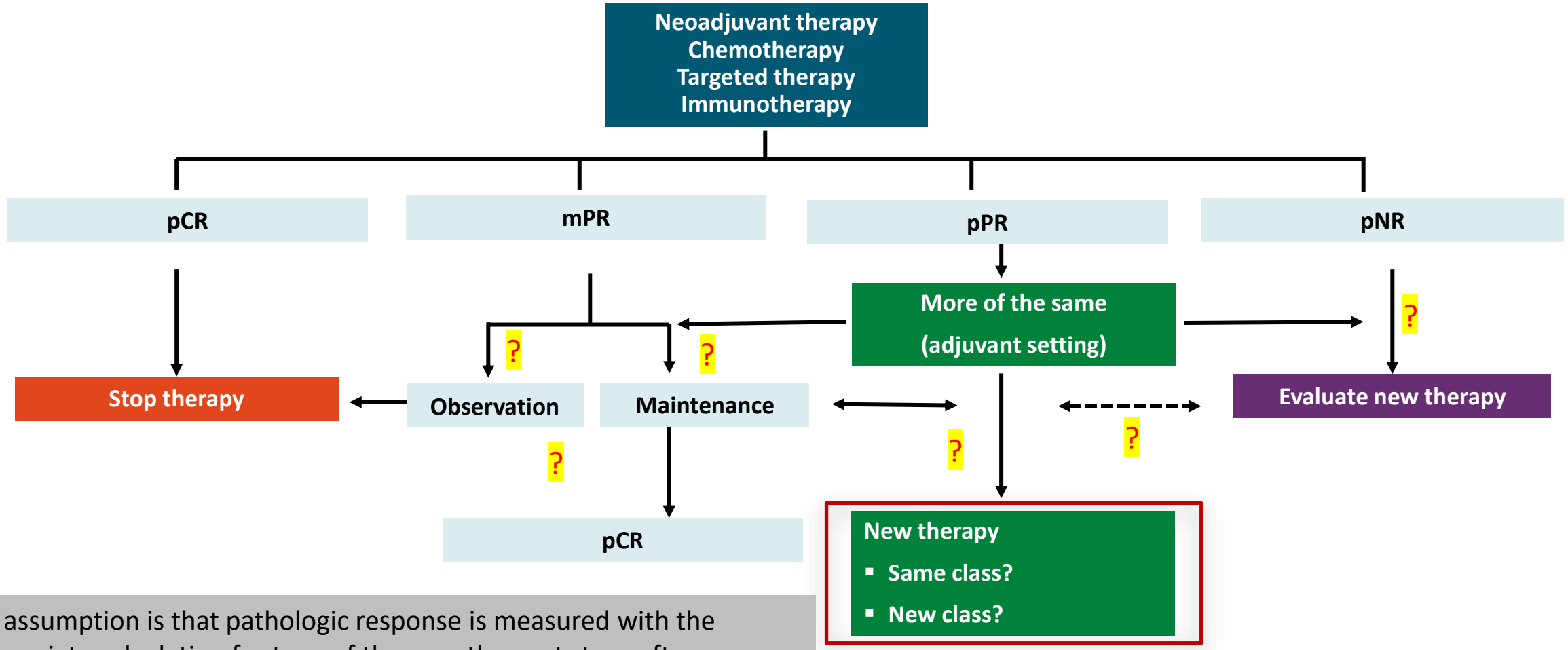

IMpower150
KN090

CM816

AEGEAN
KN671
NeoTORCH
CM 77T

Courtesy of Tony M.

# Questions Remain in the Management of Patients Who Receive Neoadjuvant Immunotherapy

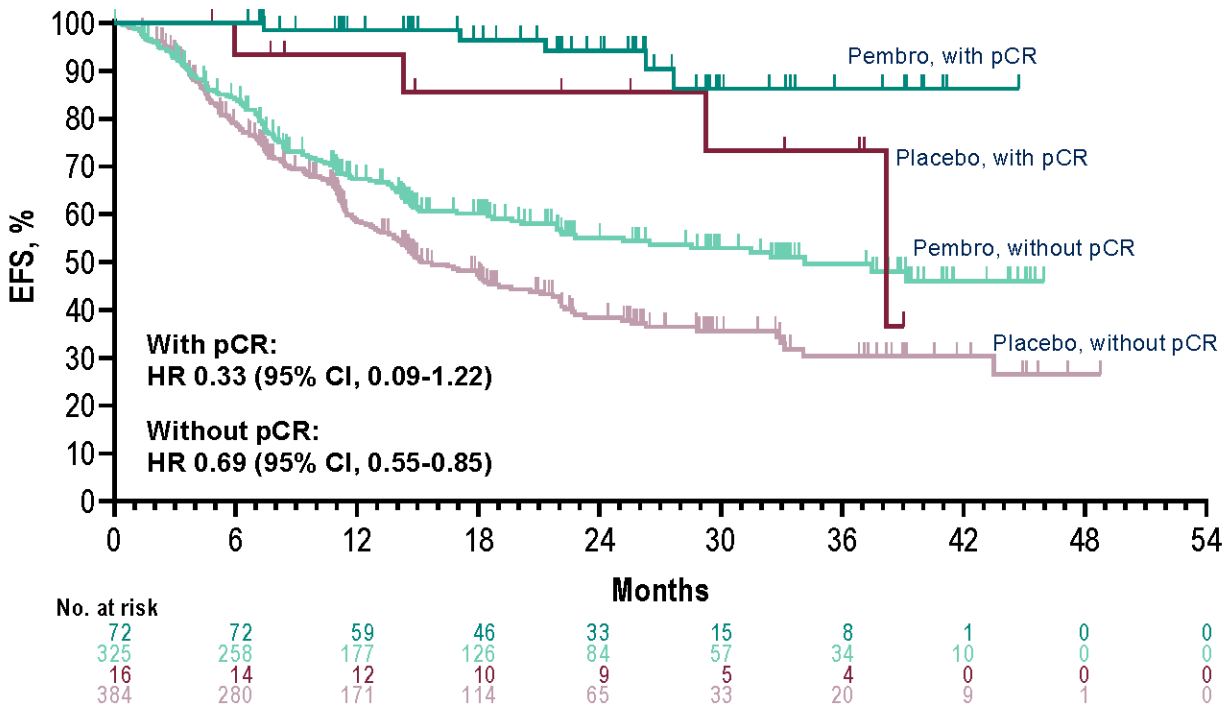



The assumption is that pathologic response is measured with the appropriate calculation for type of therapy; the next steps after response may somewhat be influenced by the type of therapy received.

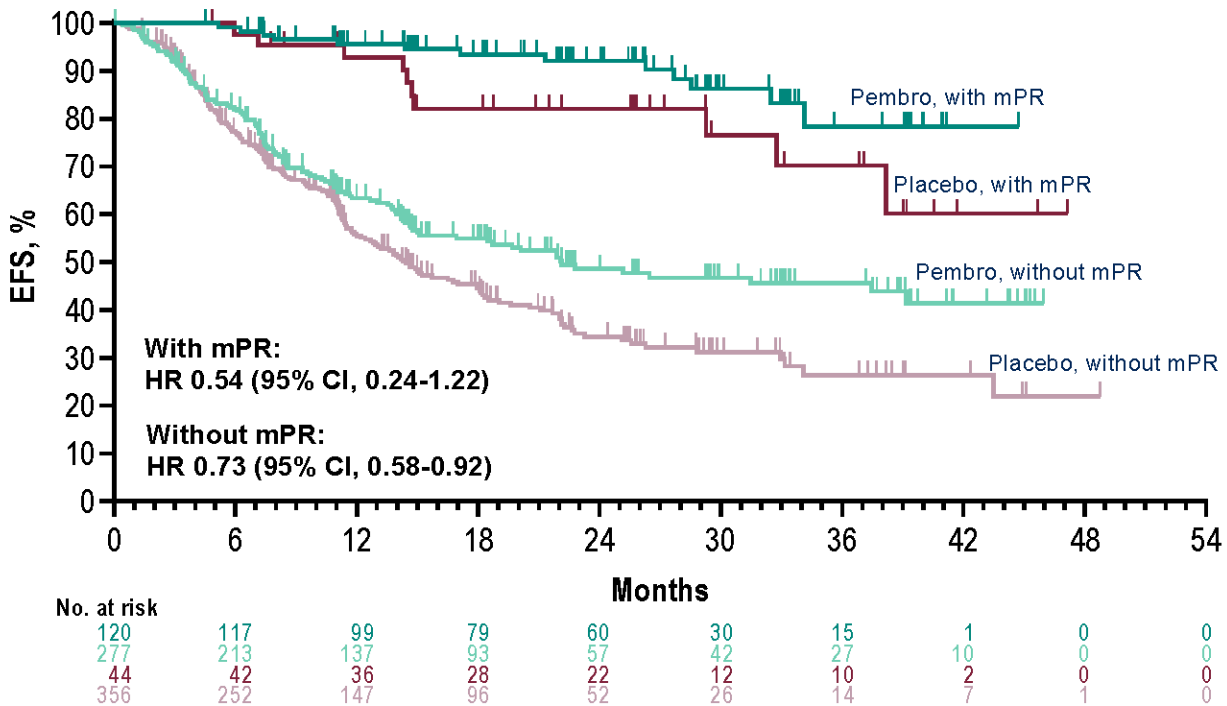
Slide credit: clinicaloptions.com

# Event-Free Survival Among Patients With pCR or mPR[a,1]

## pCR




## mPR



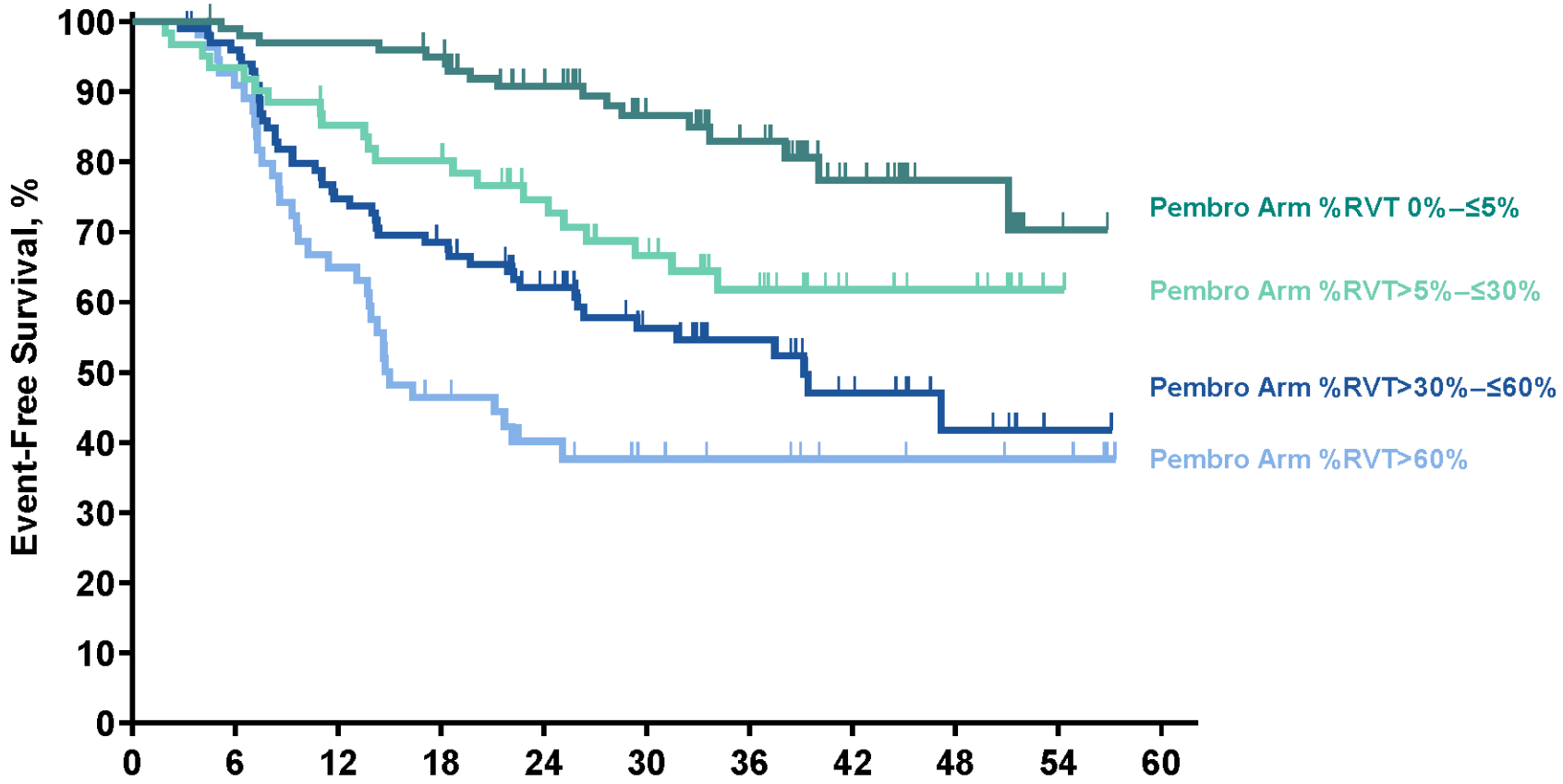

**Objective of this analysis was to evaluate efficacy of perioperative pembrolizumab across different RVT cutpoints, beyond pCR and mPR**

[1]Wakelee H et al. *N Engl J Med* 2023;389:491–503.

[a]Exploratory analysis. pCR defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). [b]mPR defined as ≤10% viable tumor cells in resected primary tumor and lymph nodes. EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022.

# Event-Free Survival

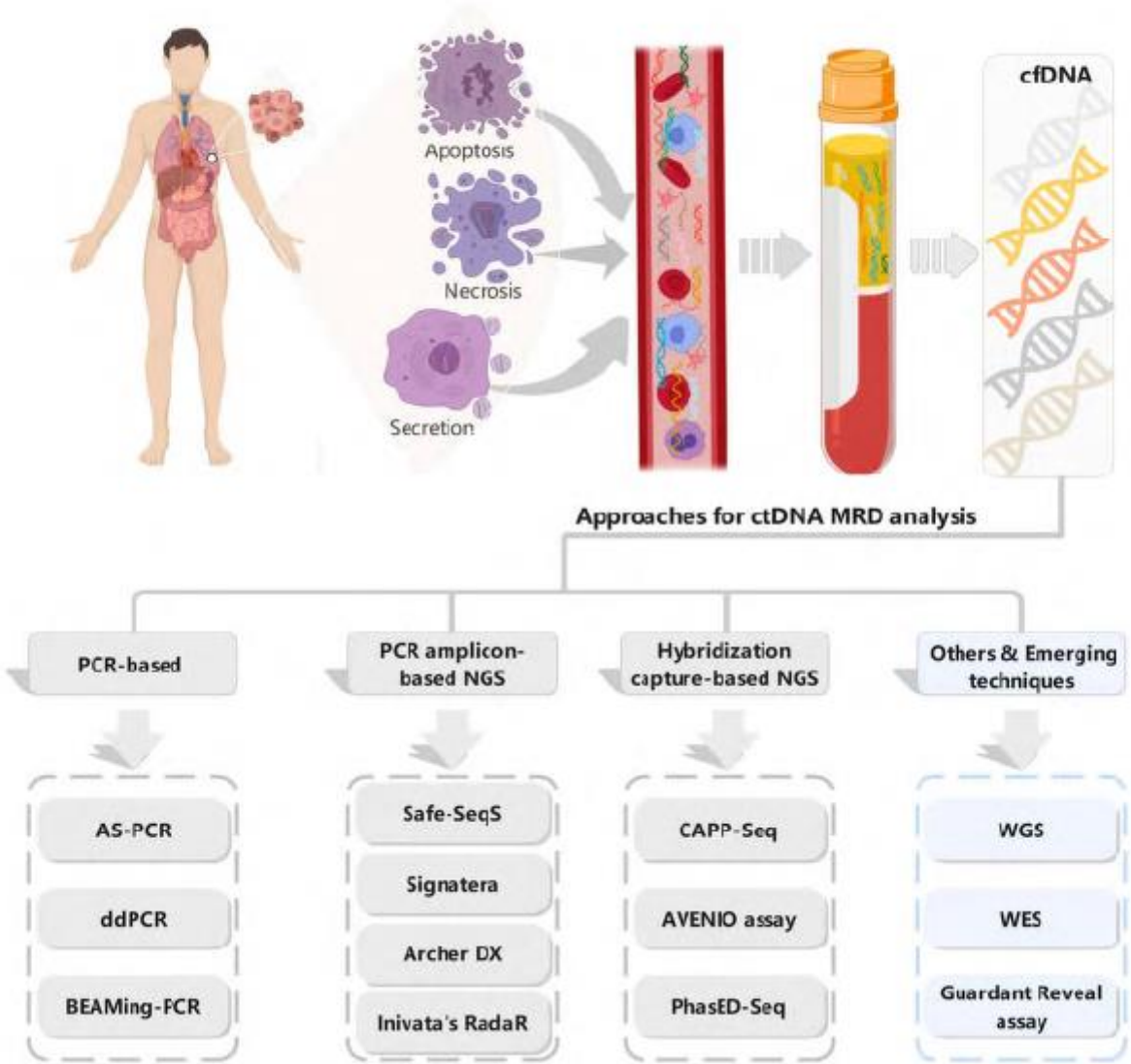
## According to %RVT Categorization in the Pembrolizumab Arm



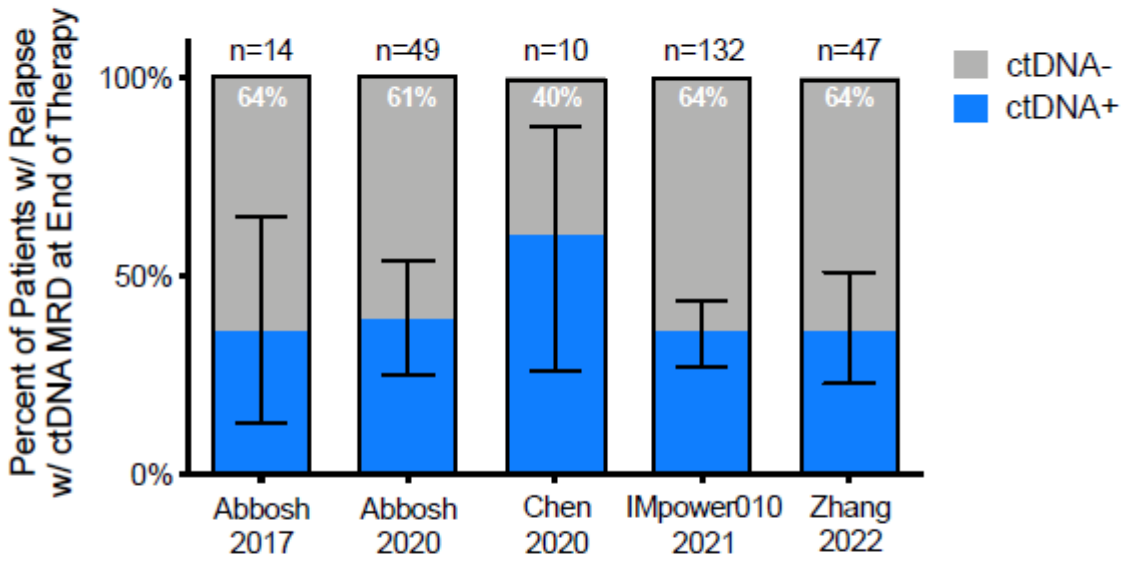

| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| %RVT 0%–≤5% | 102 | 100 | 98 | 94 | 77 | 54 | 39 | 21 | 11 | 2 | 0 |
| %RVT >5%–≤30% | 61 | 57 | 51 | 48 | 38 | 32 | 23 | 13 | 11 | 1 | 0 |
| %RVT >30%–≤60% | 101 | 95 | 73 | 66 | 52 | 34 | 24 | 16 | 8 | 2 | 0 |
| %RVT >60% | 56 | 50 | 35 | 24 | 16 | 12 | 10 | 7 | 6 | 5 | 0 |

Data cutoff date: July 10, 2023.

# ctDNA MRD assays are constantly evolving



# Existing ctDNA MRD assays are insufficiently sensitive and have significant false negative rates

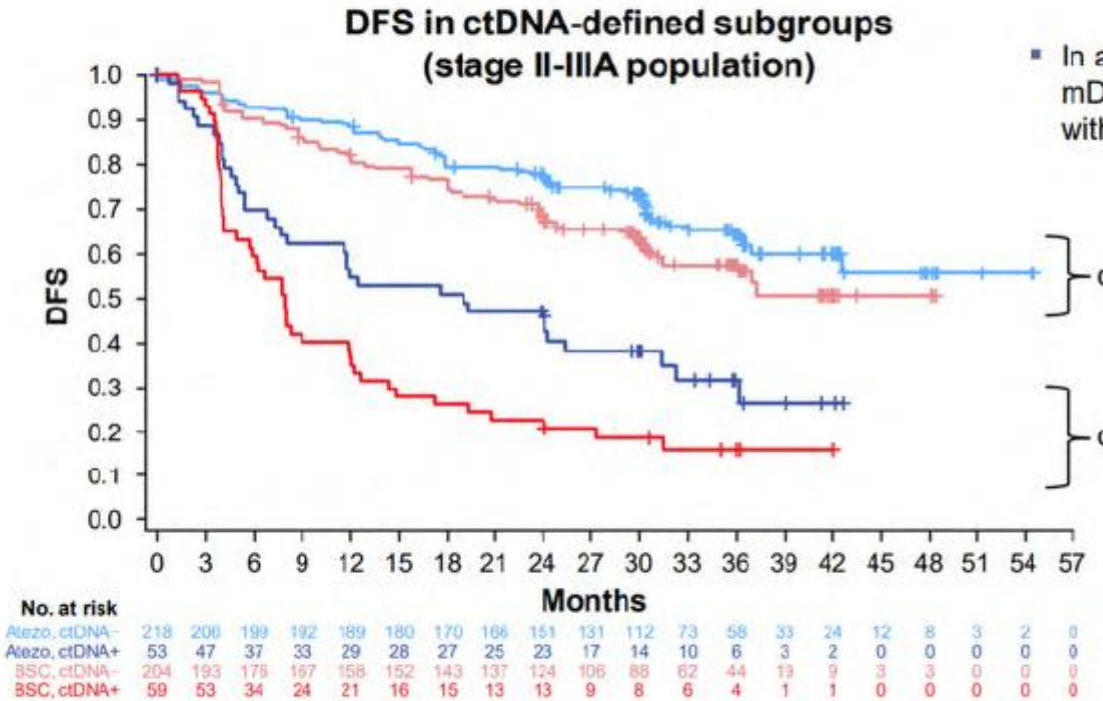



1st generation ctDNA MRD assays have high false negative rates

| Updated_NSCLC_Prognostic_Studies_Table | | | | |
|---|---|---|---|---|
| **Study** | **N** | **Stage** | **Treatment(s)** | **Tumor informed ctDNA MRD assay** |
| Chaudhuri Cancer Discov 2017 | 37 | IB-IIIB | RT and/or surgery +/- chemo | CAPP-Seq |
| Abbosh Nature 2017 | 24 | IA-IIIB | Surgery +/- chemo | Natera |
| Chen CCR 2019 | 25 | I-III | Surgery +/- chemo | cSMART |
| Moding Cancer Discov 2020 | 48 | IIB-IIIB | chemoRT +/- IO | CAPP-Seq |
| Zviran Nat Med 2020 | 22 | I-III | Surgery +/- chemo | MRDdetect |
| Waldeck Mol Oncol 2021 | 16 | IA-IIIB | Surgery +/- chemo, RT | Custom NGS |
| Xia CCR 2021 | 329 | I-III | Surgery +/- chemo | Custom NGS |
| Zhou ESMO I-O 2021 | 600 | IB-IIIA | Surgery + chemo +/- IO | Natera |
| Gale Ann Oncol 2022 | 59 | I-III | RT and/or surgery +/- chemo | Inivata |
| Zhang Cancer Discov 2022 | 245 | I-III | Surgery +/- chemo, IO, TKI | Custom NGS |
| Abbosh Nature 2023 | 197 | I-III | Surgery +/- chemo | Invitae |
| Waldeck Mol Oncol 2021 | 16 | IA-IIIB | Surgery +/- chemo, RT | Custom NGS |
| Xia CCR 2021 | 329 | I-III | Surgery +/- chemo | Custom NGS |
| Zhou ESMO I-O 2021 | 600 | IB-IIIA | Surgery + chemo +/- IO | Natera |
| Gale Ann Oncol 2022 | 59 | I-III | RT and/or surgery +/- chemo | Inivata |
| Zhang Cancer Discov 2022 | 245 | I-III | Surgery +/- chemo, IO, TKI | Custom NGS |
| Abbosh Nature 2023 | 197 | I-III | Surgery +/- chemo | Invitae |

Modified from Diehn, ESMO 22; Abbosh et al. *Nature* 2017; Abbosh et al. *AACR Annual Mtg* 2020; Chen et al. *Clin Cancer Res* 2019; Zhang et al. *Cancer Discovery* 2022; Girard AACR 2022, Diehn, HKIOS

# IMpower-010: MRD post-surgery is prognostic but neither predictive nor sufficiently sensitive for de-escalation decisions




- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

| ctDNA− | Atezo (n=218) | BSC (n=204) |
|---|---|---|
| mDFS, mo | NR | NR |
| HR (95% CI) | 0.72 (0.52, 1.00) | |

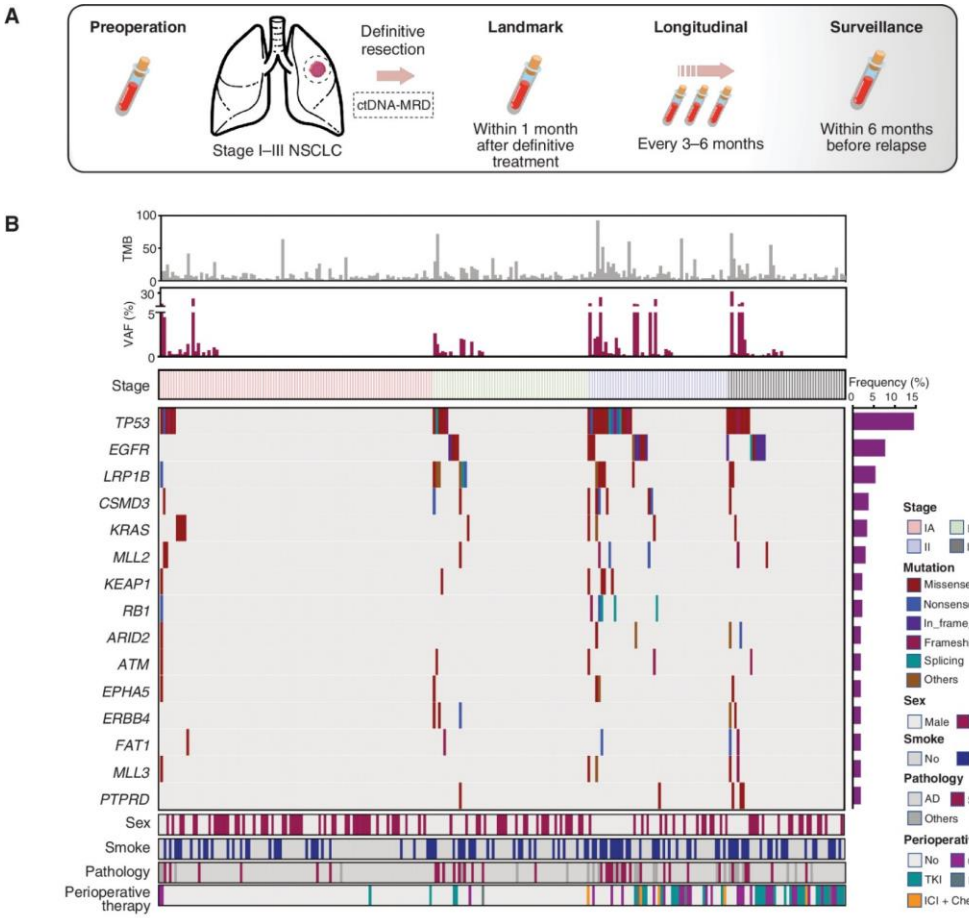
| ctDNA+ | Atezo (n=53) | BSC (n=59) |
|---|---|---|
| mDFS, mo | 19.1 | 7.9 |
| HR (95% CI) | 0.61 (0.39, 0.94) | |

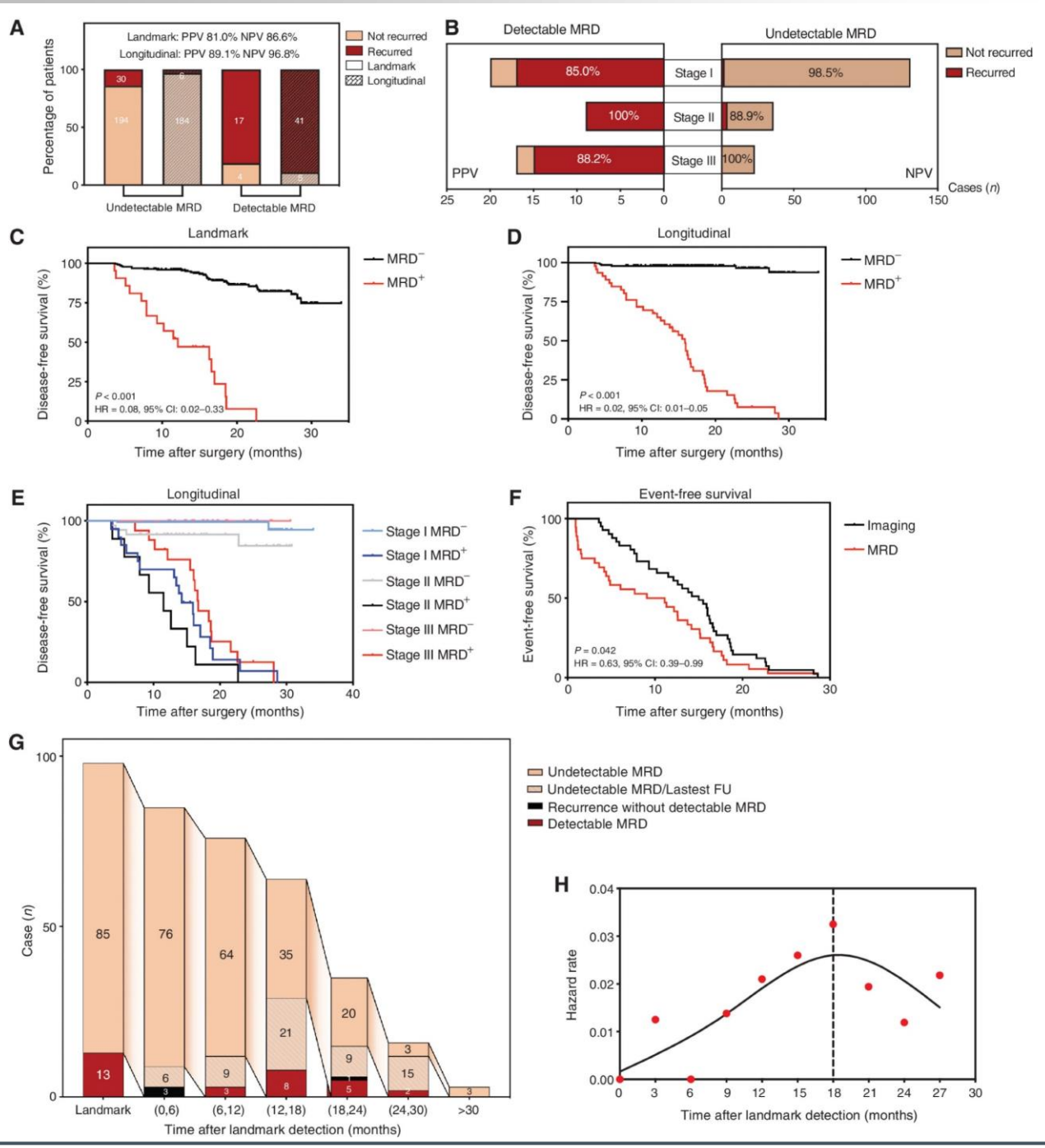
Signatera can detect VAF down to 0.01%. It is tumor-informed

Zhang, Cancer Disc 2022

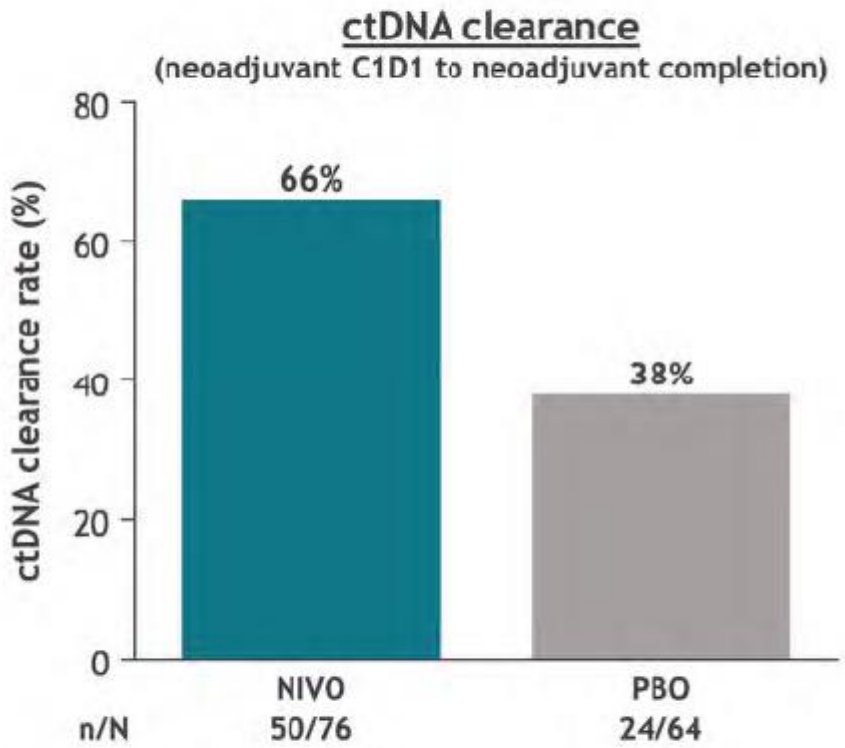
RESEARCH ARTICLE Cancer Discov 2022;12(7):1690–1701.

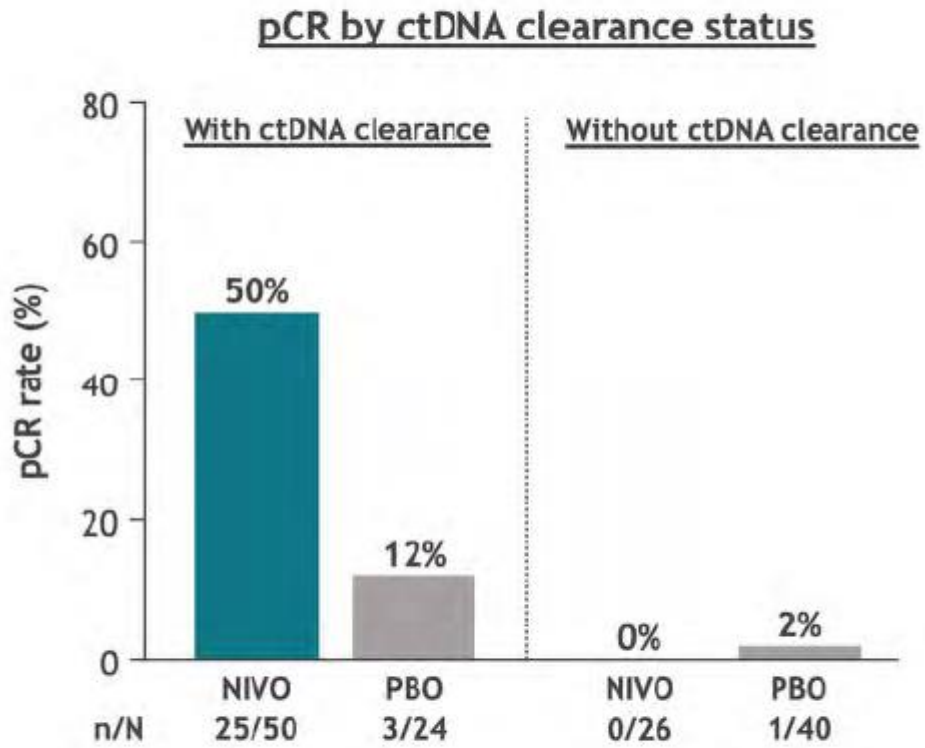
# Longitudinal Undetectable Molecular Residual Disease Defines Potentially Cured Population in Localized Non–Small Cell Lung Cancer



# 50% of ctDNA clearance is seen in absence of pCR in CM77T



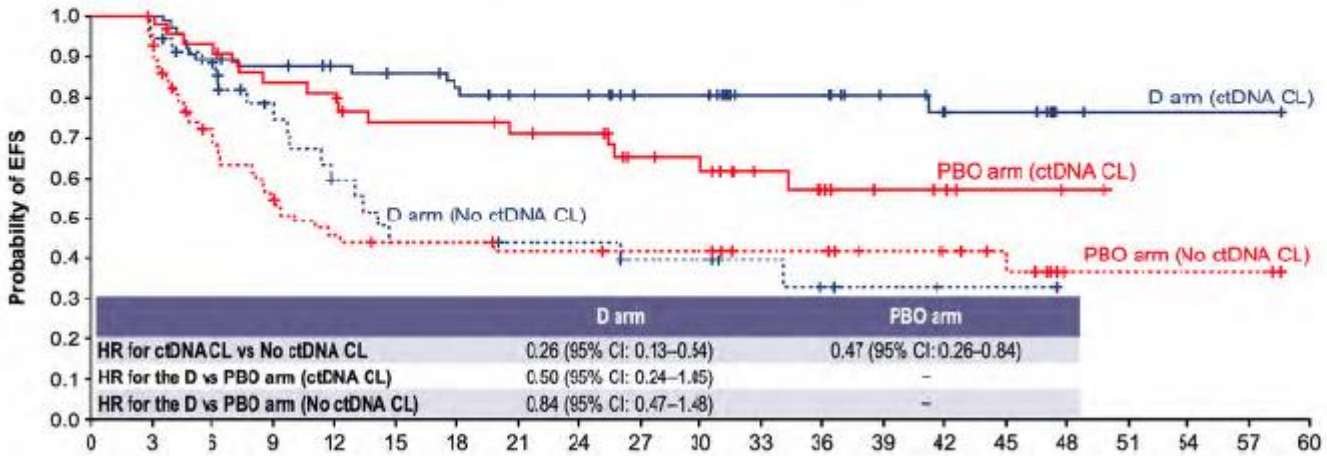

- CtDNA clearance evaluated at the end of neoadjuvant treatment or prior to definitive surgery
- ctDNA (used for MRD assessment) has a strong PPV - not NPV

Invitae Personalized Cancer Monitoring (tumor-informed) assay

Provencio, ESMO 2024

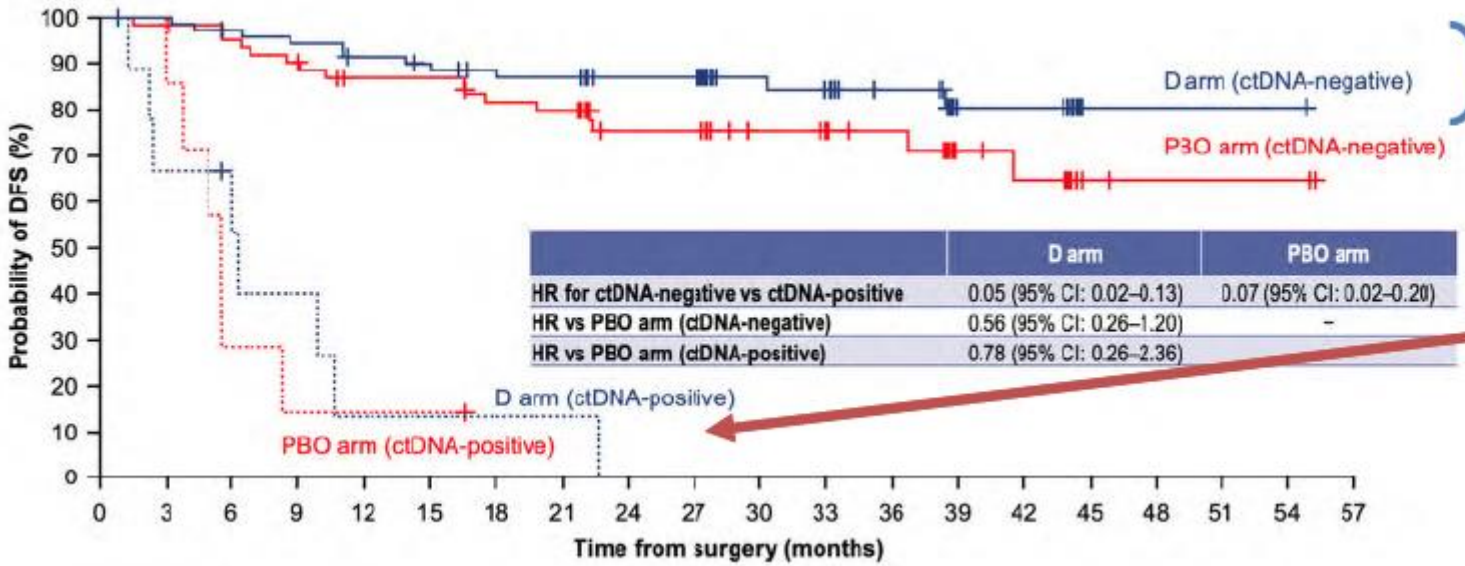
# ctDNA negative or cleared are certainly NOT cured

## And ctDNA positive urgently need intensification strategies!




20% relapse

Pre-surgery ctDNA




20% relapse

**Escalation needed**

Post-surgery ctDNA

Reck, ESMO 2024

# CASE(2): 65/M, SQC,RLL IIA(cT2bN0M0)

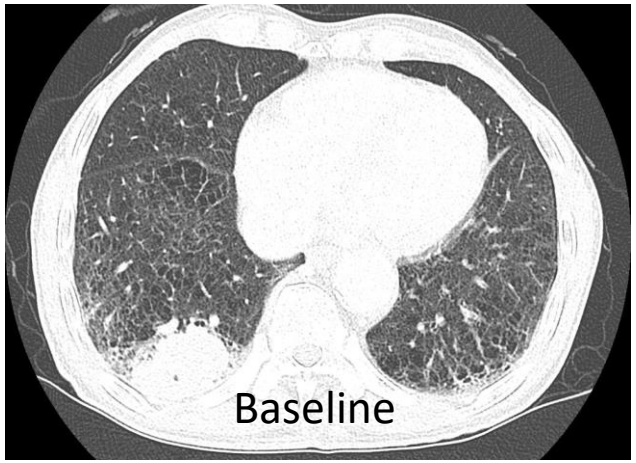
68 PYS, Current smoker
Daily drinker

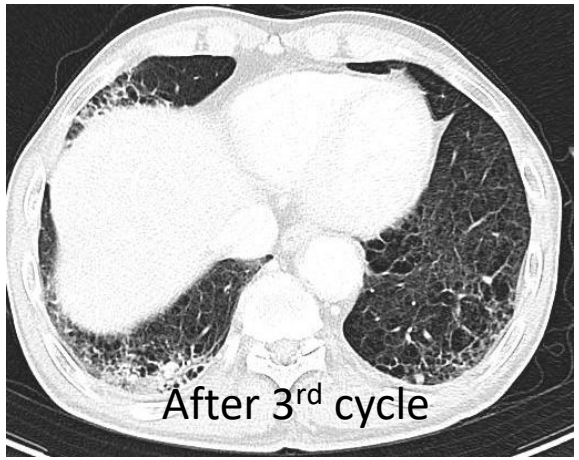
- Bx: SQC, G1
- PDL1[sp263]:0%, [22C3]:1%

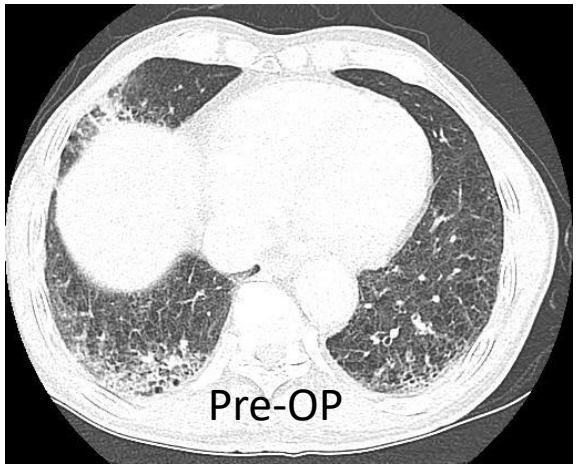
- **Nivo** + Paclitaxel/carboplatin #3: 2024.8.28 ~ 10.10 *PR
- Robotic VATS RLL lobectomy c MLND: 2024.11.26 ***pCR**

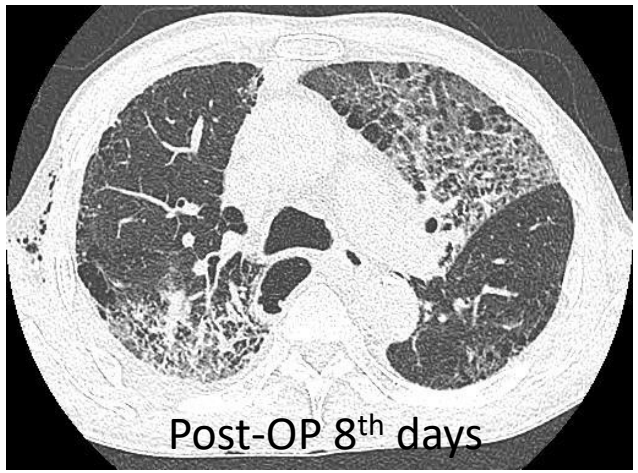
❖ **Additional surgeries for BPF**

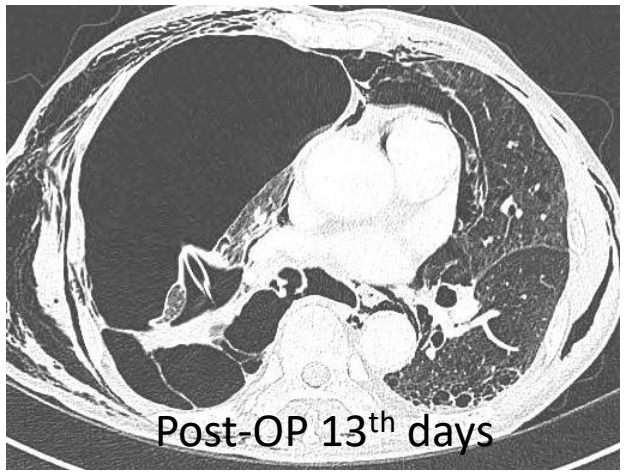
- VATS Rt. exploration & Repair of BPF via thoracotomy: 2024.12.9
- Thoracotomic RML completion lobectomy d/t recurred BPF: 2024.12.13

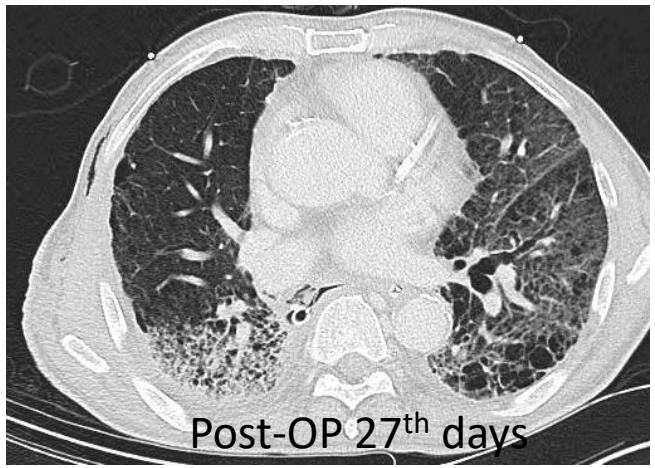


# Neoadjuvant Chemoimmunotherapy Complicates Subsequent Surgical Resection and Adjuvant Immunotherapy Is Preferable From the Surgical Standpoint



IASLC

CONTROVERSIES IN THORACIC ONCOLOGY

# The Surgical Resection Difficulty From Neoadjuvant Chemoimmunotherapy Is Minimal and Neoadjuvant Therapy Should Be the Standard



**Table 3. Comparison of NI, NC, and S**

| Characteristics | NI | S | NC |
|---|---|---|---|
| n | 37 | 37 | 37 |
| Open procedures, % | 70.3 | 51.4 | 83.8 |
| Number of lymph nodes dissected | 9 | 19 | 24 |
| Length of stay (d) | 7 | 6 | 7 |
| Postoperative complications, % | 37.8 | 10.8 | 16.2 |
| 30-d mortality, % | 5.4 | 0 | 0 |

Modified from Zhang et al.[9]
NC, neoadjuvant chemotherapy, NI, neoadjuvant immunotherapy; S, immediate/upfront surgery.

**Table 1. Summary of Clinical Results for the Main Phase 3 Trials for Neoadjuvant Chemoimmunotherapy**

| Specific Item | CheckMate- 816[1] | Keynote-671[4] | Aegean[2] | Neotorch[3] | CheckMate-77T[a] | Rationale-315[b] |
|---|---|---|---|---|---|---|
| NSCLC stage | IB-II 36<br>IIIA 63 | II 30<br>IIIA-B 70 | II 29<br>III 71 | IIIA 67<br>IIIB 33 | IIA-B 35<br>IIIA-B 64 | II 42<br>IIIA 58 |
| Cancelled surgery | 16 | 18 | 23 | 18 | 22 | 20 |
| Pneumonectomy | 17 | 11 | - | 9 | - | 9 |
| R0 resection | 83 | 92 | 95 | 96 | 70 | 89 |
| Adverse events (grade 3-4) | 33 | 45 | 42 | 22 | 63 | 47 |
| 90-day surgical mortality | 1 | 3 | 6 | - | - | 2 |

**Table 2. Reasons for Cancelled Surgery After Neoadjuvant Chemoimmunotherapy**

| Surgery Cancellation | CheckMate 816[1] | Keynote-671 trial[4] | Aegean[2] | Neotorch[3] |
|---|---|---|---|---|
| Resection cancelled after neoadjuvant chemoimmunotherapy | 15.6 | 17.9 | 22.5 | 17.8 |
| Reason for Cancellation | | | | |
| Disease progression | 6.7 | 4.1 | 8.8 | 2.5 |
| AEs | 1.1 | 6.3 | 1.8 | 3.0 |
| Other[a] | 7.8 | 7.5 | 12.3 | 12.4 |

*J Thorac Oncol 2024;19(6):858-865.*

# Comparison of surgical difficulty in patients with resectable non-small cell lung cancer under different neoadjuvant treatment modes: a retrospective cohort study

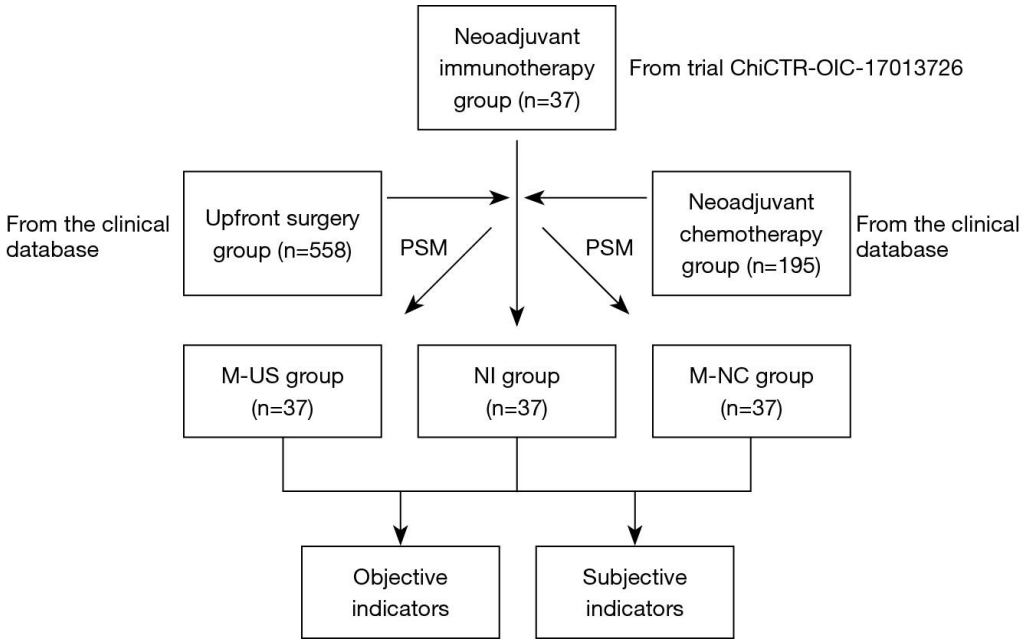



**Table 3** Detailed complications after surgery in the three groups

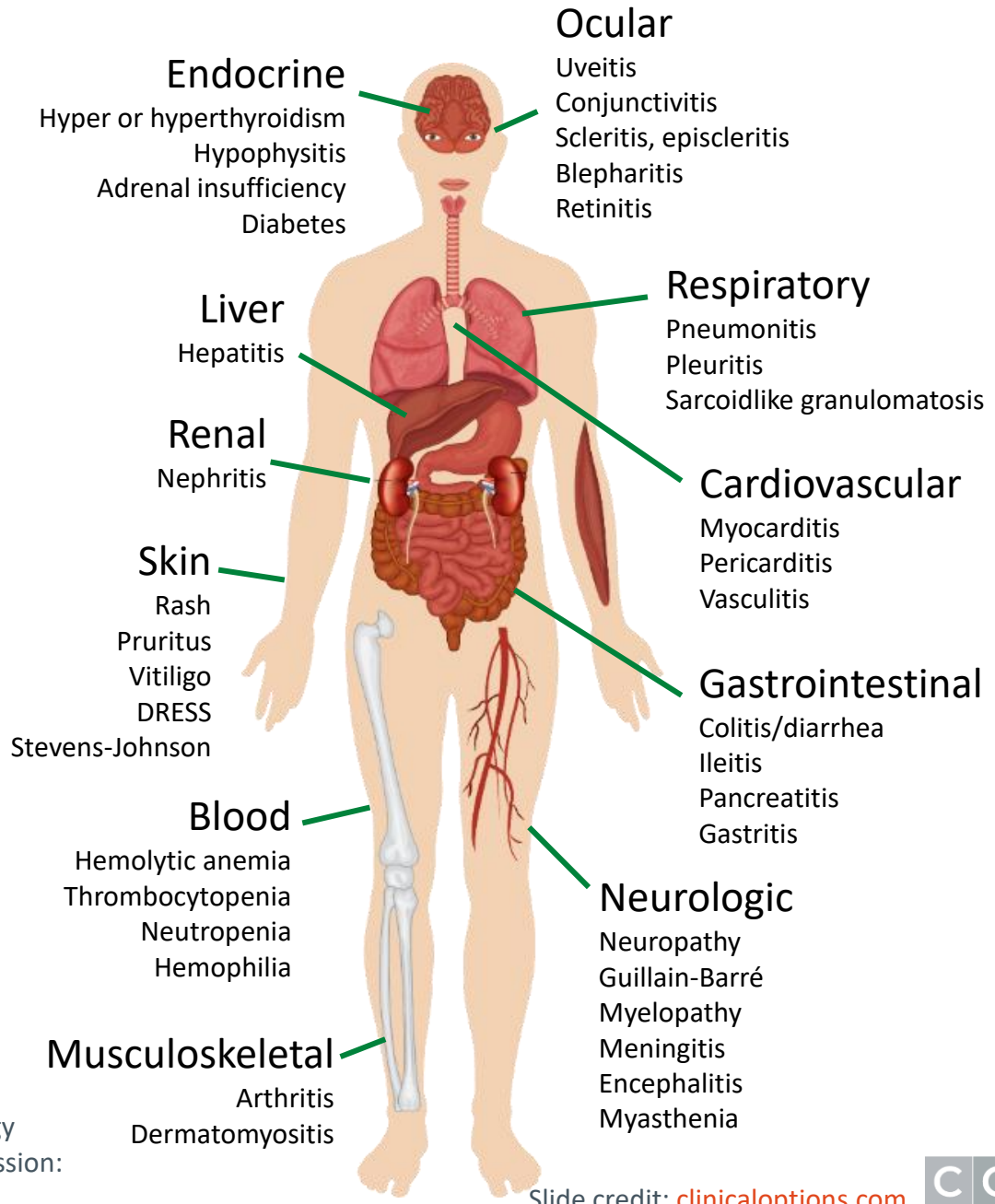
| Variables | NI group (n=37) | | M-US group (n=37) | | M-NC group (n=37) | |
|---|---|---|---|---|---|---|
| | All grades, n (%) | Grade 3–4, n (%) | All grades, n (%) | Grade 3–4, n (%) | All grades, n (%) | Grade 3–4, n (%) |
| Prolonged air leak | 1 (2.7) | 0 (0.0) | 1 (2.7) | 1 (2.7) | 2 (5.4) | 0 (0.0) |
| Subcutaneous emphysema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) | 1 (2.7) |
| Hemoptysis | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Atelectasis | 0 (0.0) | 0 (0.0) | 2 (5.4) | 0 (0.0) | 2 (5.4) | 0 (0.0) |
| Intrathoracic bleeding | 3 (8.1) | 2 (5.4) | 1 (2.7) | 1 (2.7) | 0 (0.0) | 0 (0.0) |
| Subcutaneous ecchymosis | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Chylothorax | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) | 1 (2.7) |
| Pneumonia | 2 (5.4) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Fever | 6 (16.2) | 2 (5.4) | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Disturbance of consciousness | 1 (2.7) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Diabetes insipidus | 1 (2.7) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Hyponatremia | 1 (2.7) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Incision infection | 1 (2.7) | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| High blood pressure | 2 (5.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) | 0 (0.0) |
| Atrial fibrillation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (5.4) | 1 (2.7) |
| Total (events) | 22 (59.5) | 10 (27.0) | 6 (16.2) | 2 (5.4) | 9 (24.3) | 3 (8.1) |
| Total (patients) | 14 (37.8) | 6 (16.2) | 4 (10.8) | 2 (5.4) | 6 (16.2) | 3 (8.1) |

Categorical data are presented as count or percentage (%). All complications are classified according to CTCAE 5.0. NI group: neoadjuvant immunotherapy group; M-US group: matched upfront surgery group; M-NC group: matched neoadjuvant chemotherapy group. CTCAE 5.0, Common Terminology Criteria for Adverse Events version 5.0.

*J Thorac Dis 2021;13(10):5604-5616.*

# Spectrum of Immune-Related AEs

- irAEs can affect **any** organ of the body
- Onset varies
  - Usually 2-3 mo after starting tx
  - Up to 2 yr after tx completion
- Maintain high level of suspicion for irAEs when new symptoms develop
- If irAEs are suspected, conduct a complete workup, including lab tests, to rule out other causes




Schneider. JCO. 2021;39:4073. Zimmerman. Am Soc Clin Oncol Educ Book. 2018;38:682. Champiat. Ann Oncol. 2016;27:559. Michot. Eur J Cancer. 2016;54:139. Steven. Rheumatology (Oxford). 2019;58:vii29. Winer. J Thorac Dis. 2018;10:S480. Robert. ASCO 2017. Education session: checkpoint inhibitor immunotherapy.

Slide credit: clinicaloptions.com

# Differences in AEs Between Chemotherapy and ICI

- Counsel patients: “Report all your symptoms and let the provider figure out what’s causing it”
- Management depends on determining cause of AE → **timing is critical!**

| | Chemotherapy | ICI |
|---|---|---|
| **Incidence of moderate/severe AEs** | **Almost all patients** | **Majority without** |
| **Safety profile** | **Well described** | **Variable** |
| **Affected systems/organs** | **Few organs affected** | **Any organ** |
| **Time course** | **Well established** | **Variable (even after end of tx)** |
| | **Predictable** | **Relatively unpredictable** |

| Parameter | CT | ICI |
|---|---|---|
| **Typical timing/pattern** | ▪ Rapid onset after administration<br>▪ Cyclical onset and recovery | ▪ Onset after several cycles<br>▪ Persists or worsens over time |
| **General management strategies** | | |
| ▪ Hold dose | **Yes** | **Yes** |
| ▪ Reduce dose | **Yes** | **No** |
| ▪ Switch to less toxic agent | **Yes** | **No** |
| ▪ Steroids | **Rarely (depends on toxicity)** | **Yes** |
| ▪ Permanently discontinue | **Yes (if severe)** | **Yes (if severe)** |

Hoffner. Cancer Treat Rev. 2020;85:101979. Madden. Clin J Oncol Nurs. 2017;21:30.

# You can’t walk properly in either case

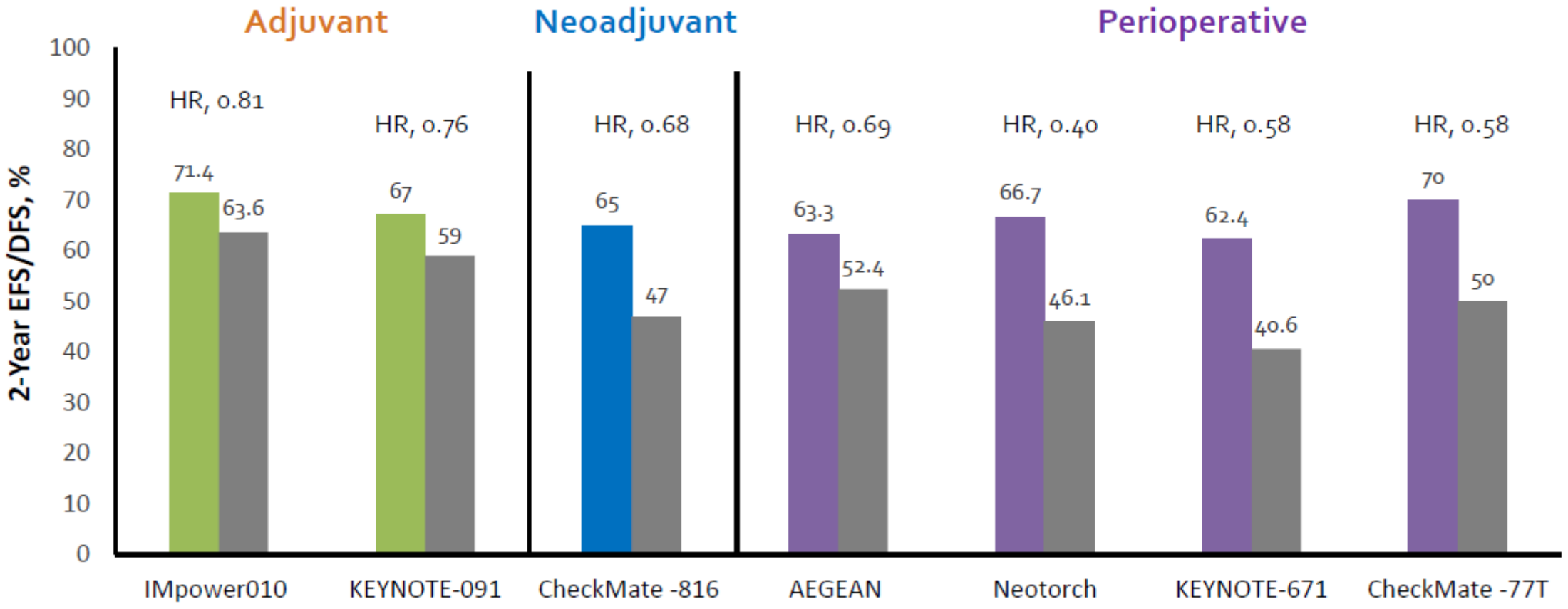
Small feet in big shoes

Big feet in small shoes

Giving too much therapy for those who don’t need it!
Giving not enough therapy for those who need more!

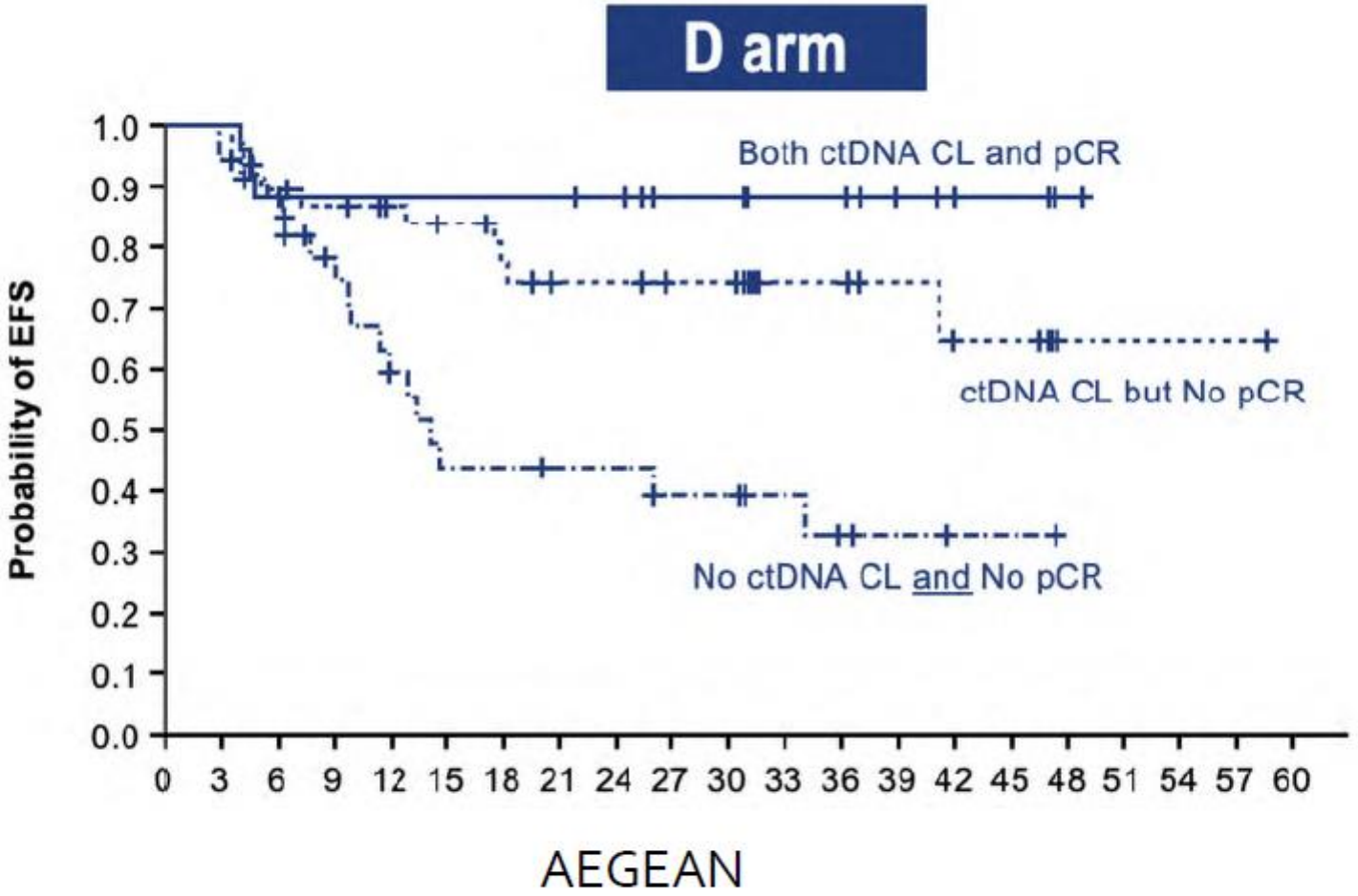
Courtesy of Tony M.

# There is room for IO across schedules



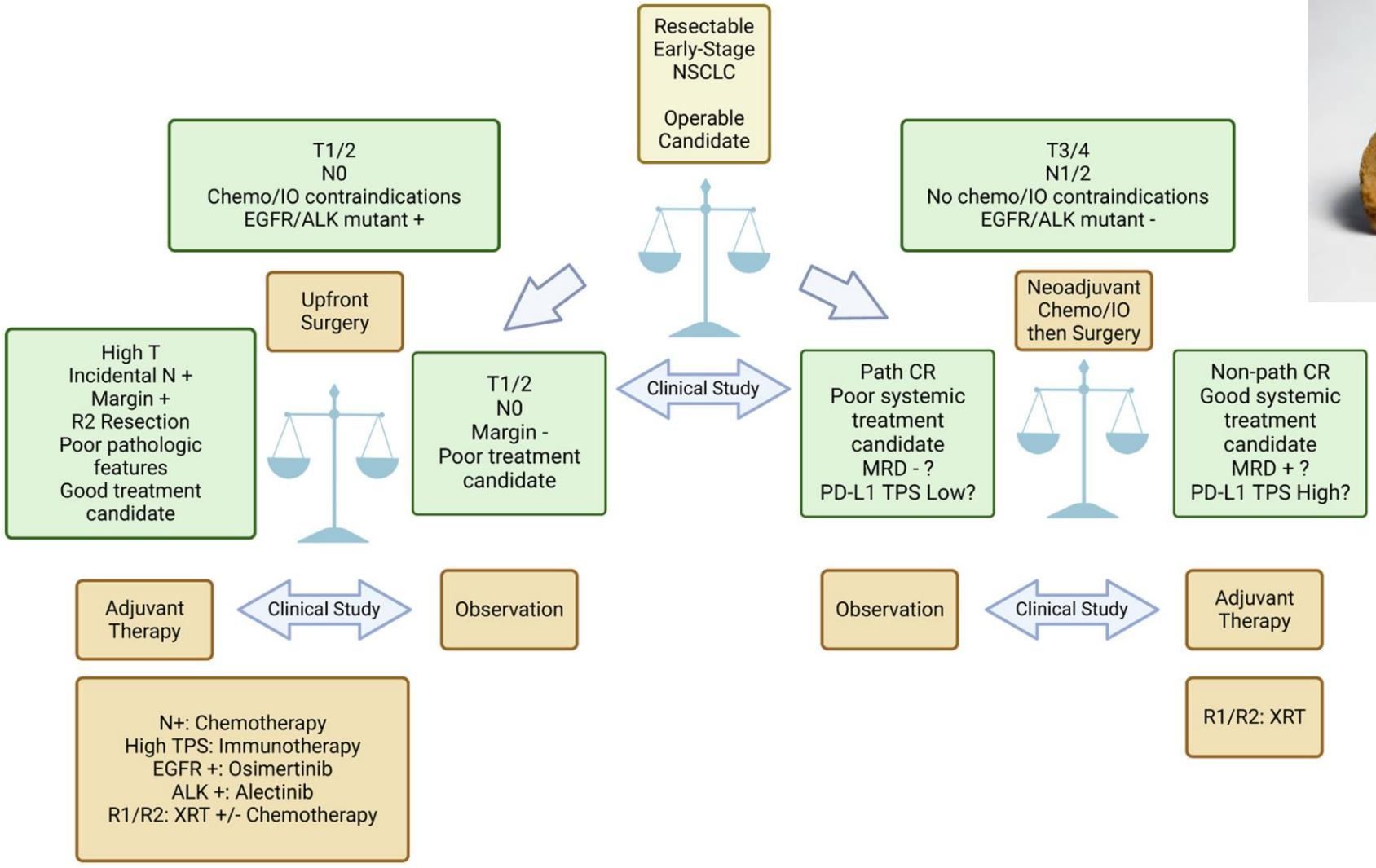

1. Felipe E et al. *Lancet*. 2021;398:1344-1357. 2. O'Brien M et al. *Lancet Oncol*. 2022;23:1274-1286. 3. Forde P et al. ELCC 2023. Abstract 840. 4. Heymach J et al. AACR 2023. Abstract CT005. 5. Lu S et al. ASCO 2023. Abstract 8501. 6. Wakelee H et al. *N Engl J Med*. 2023;389:491-503. 7. Cascone T et al. ESMO 2023. Abstract LBA1.

# We need to learn how to escalate/intensify Tx and when




In both Tx arms, patients with no ctDNA clearance at pre-Sx and no pCR had the poorest EFS outcomes

# Practical implementation and patient navigation for perioperative IO in NSCLC




*Clin Lung Cancer 2024;25(3):197-214.*

# Challenges and Controversies in Perioperative IO : My conclusion

- ***I question whether we are at prime time*** for the standardized adoption of perioperative chemoimmunotherapy
  - Immunotherapy may change the default treatment strategy for patients with resectable NSCLC
  - However, the benefits and risks (e.g., adverse events) associated with immunotherapy must be weighed up
  - Moreover, additional clinical evidence is needed to further optimize the protocol (e.g., composition, dosage, and timing) of ICI regimens