# Immunotherapy Integration in Thoracic Surgery: Recent Progress and Essential Perspectives - Lung cancer

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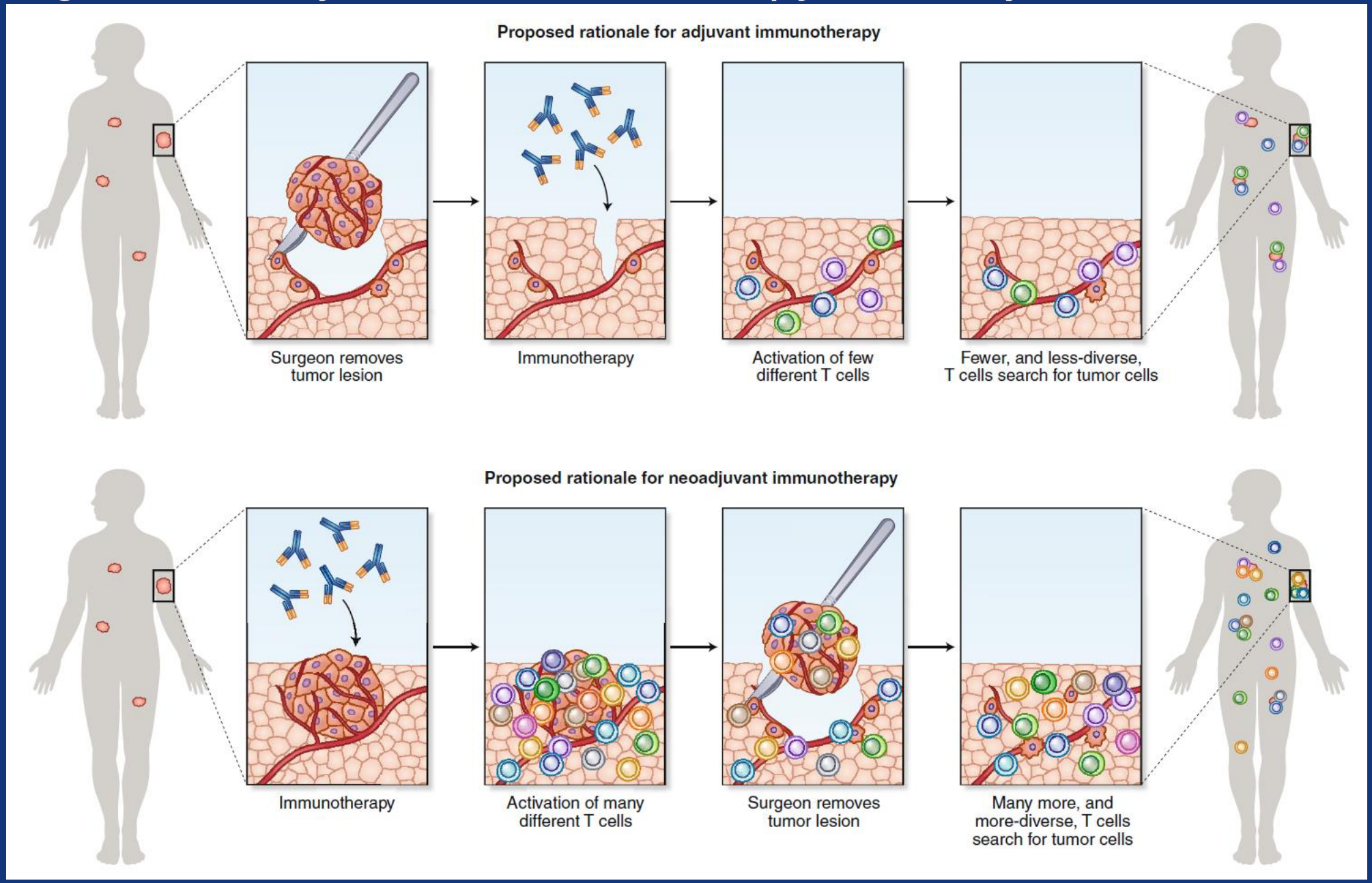
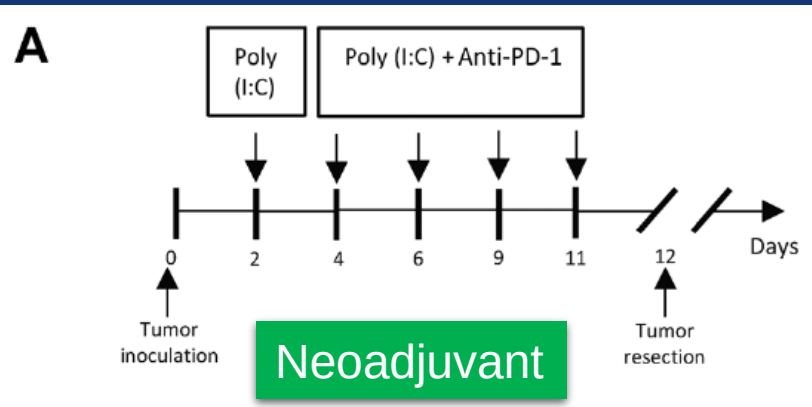
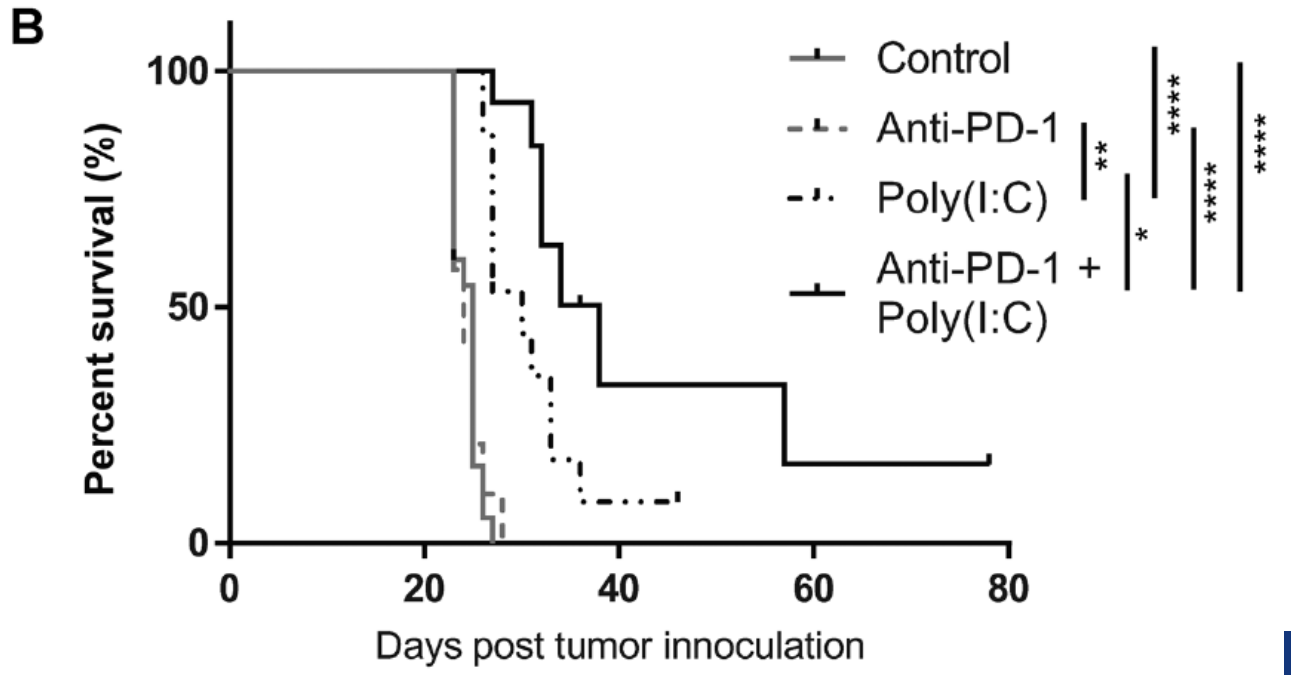
# Advantage of neoadjuvant immunotherapy over adjuvant immunotherapy

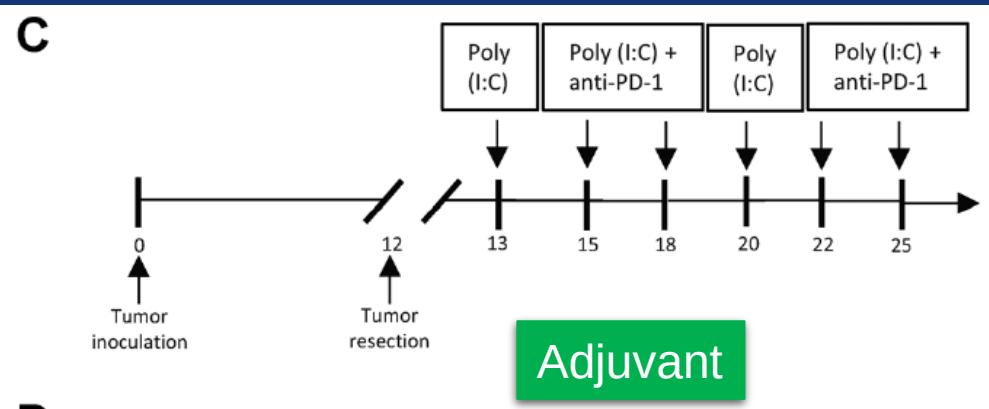


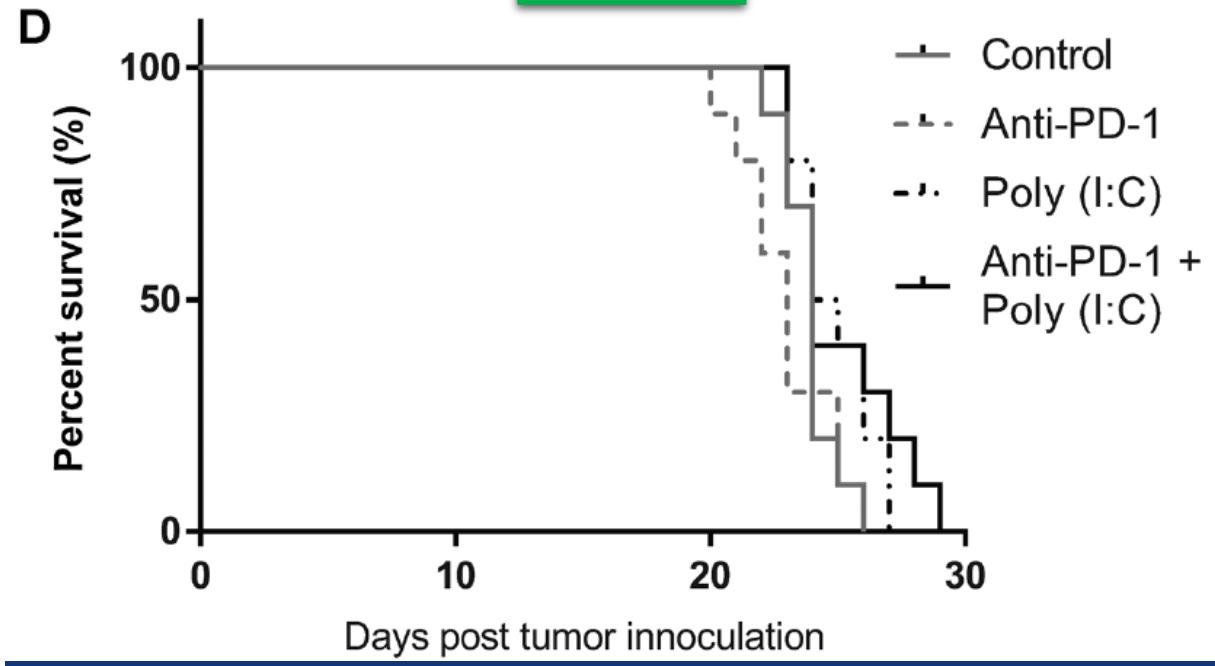

Nat Med. 2020 Apr;26(4):475-484.

# Improved efficacy of neoadjuvant over adjuvant setting



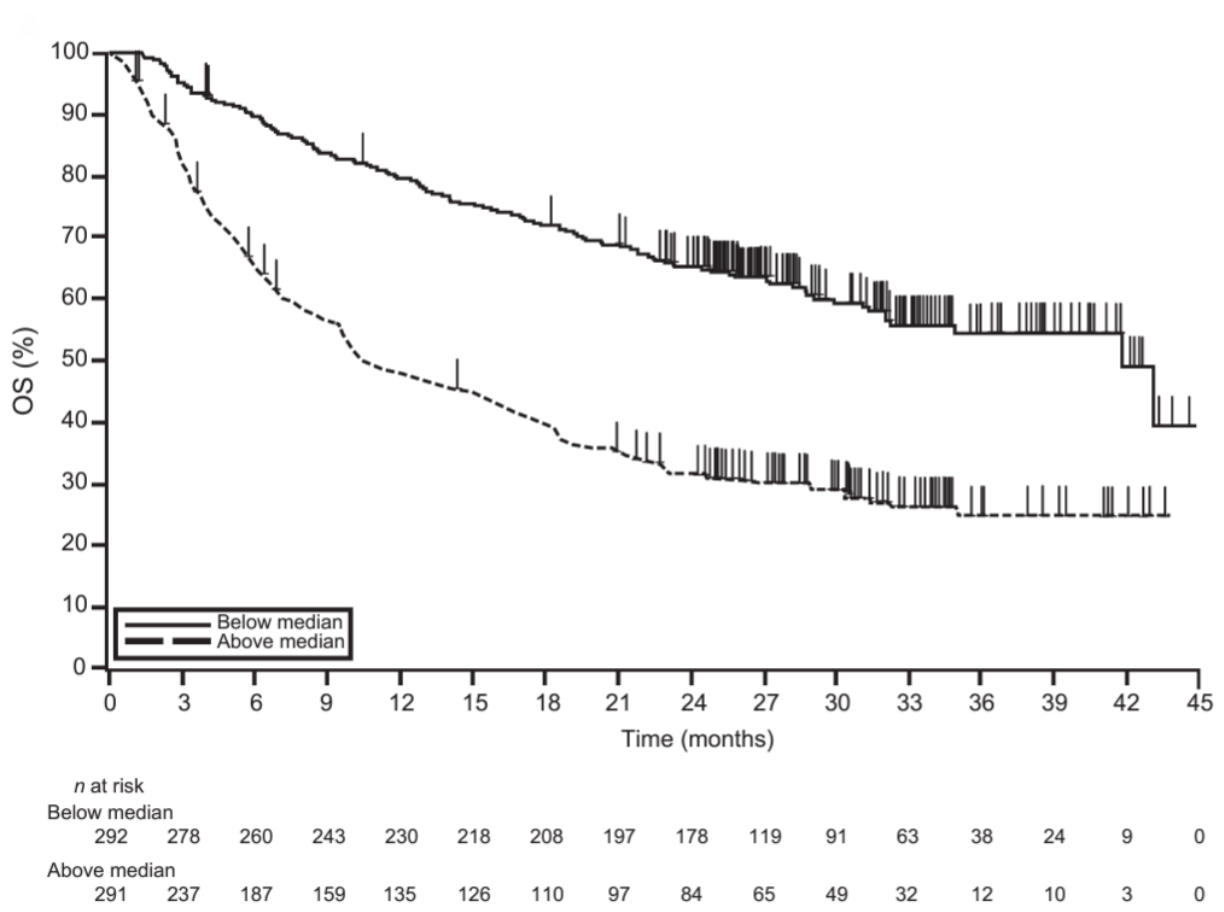



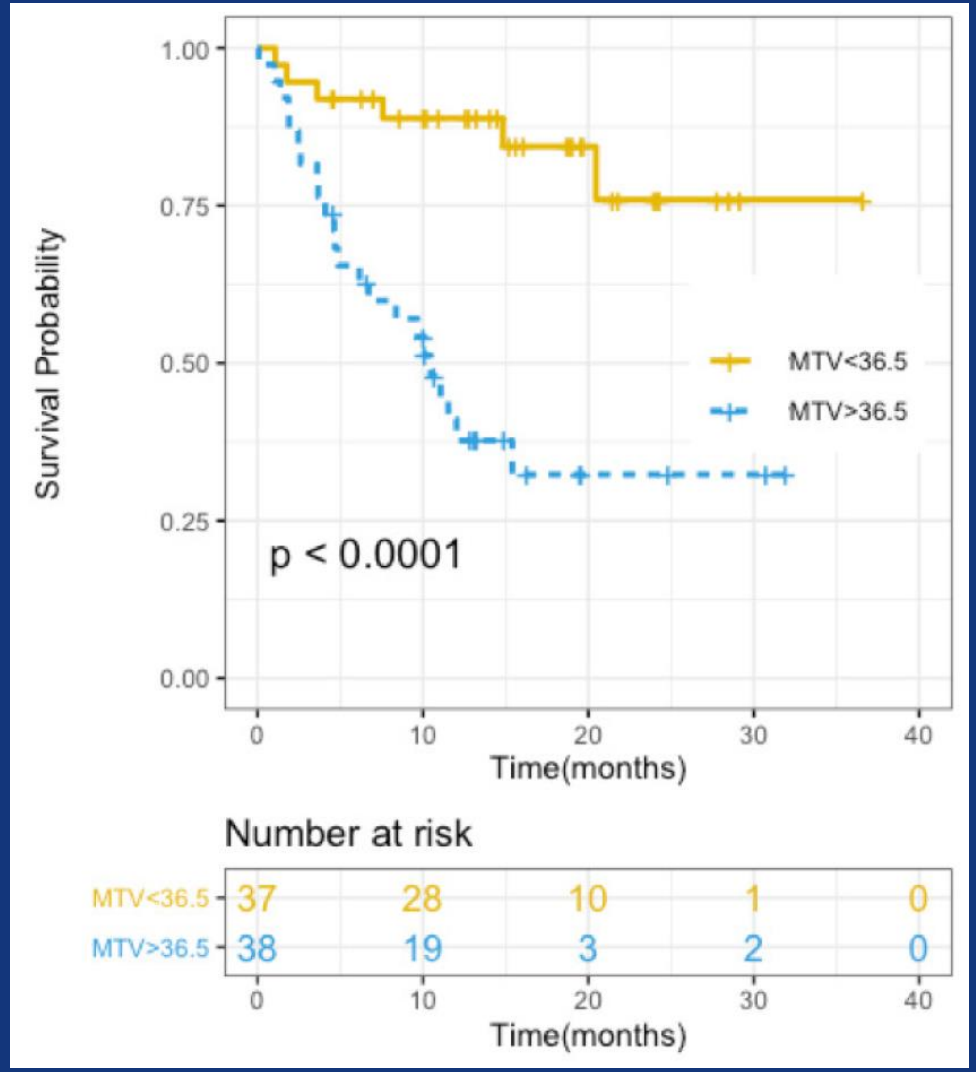

Highly metastatic 4T1.2-luc2 cell line (TNBC) injected to BALB/c mice
median OS: 25 days even after primary surgery
No difference in adjuvant setting between control and immunotherapy

Cancer Immunol Res. 2017 Oct;5(10):871-884.

# Baseline tumor burden and efficacy of immunotherapy in the clinic




Melanoma treated with keytruda




NSCLC treated with various PD-1 inhibitors

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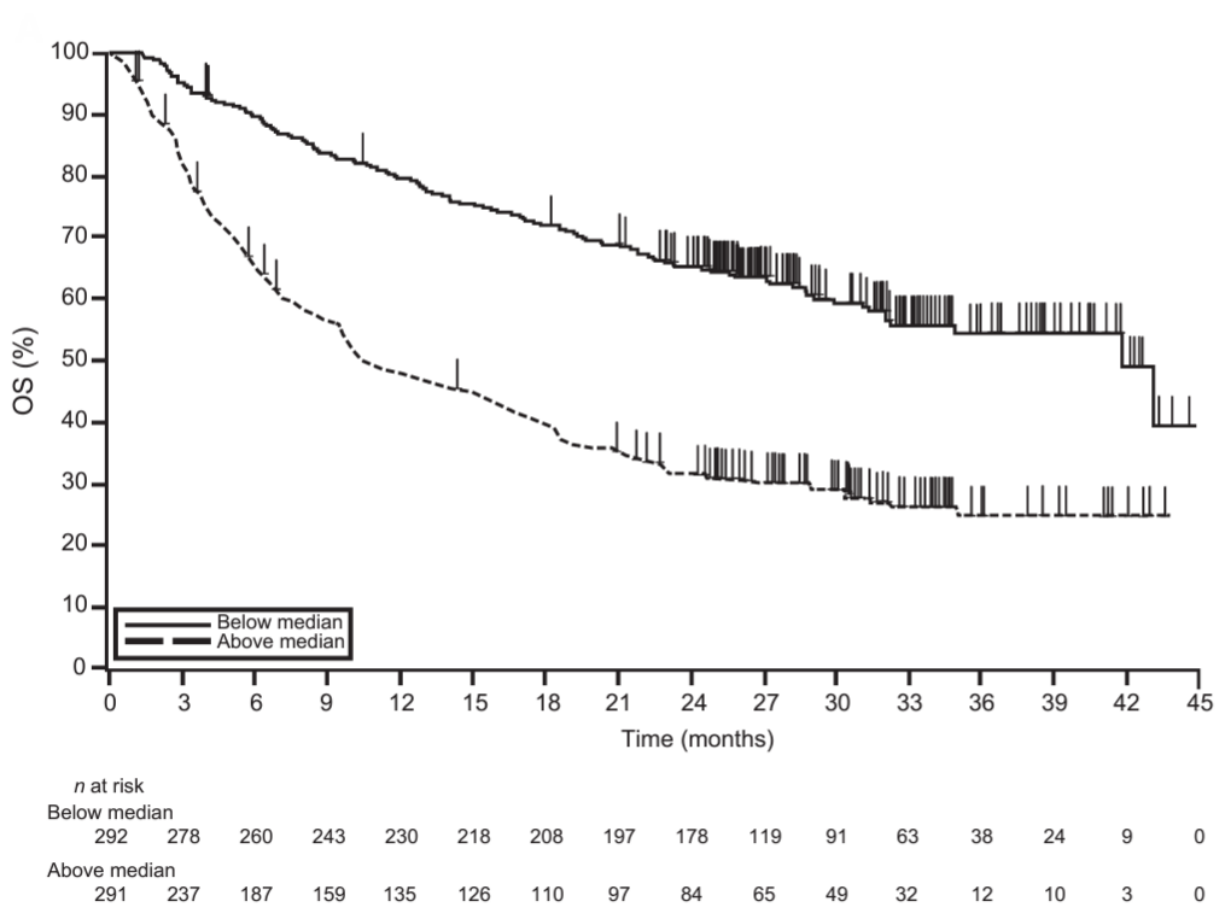
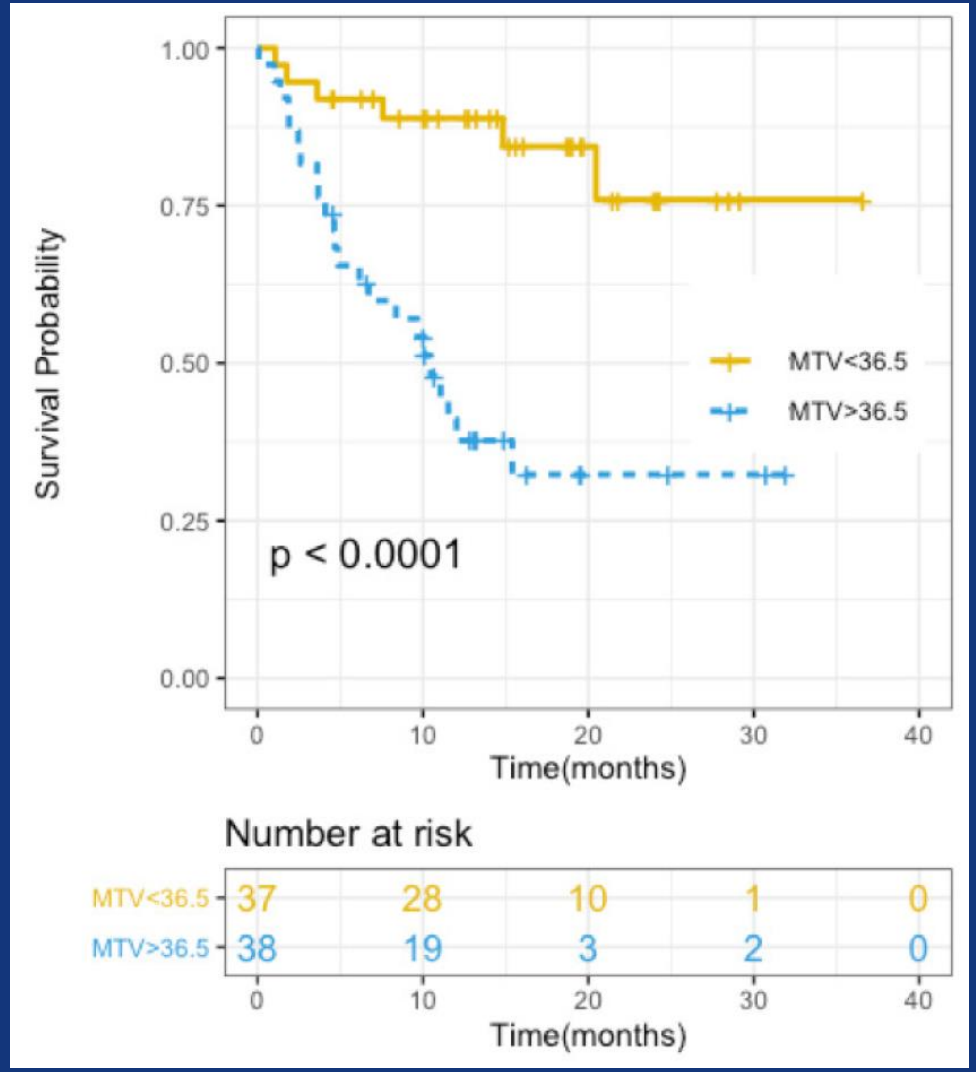
Clin Cancer Res. 2018 Dec 1;24(23):6098, J Immunother Cancer. 2020 Jul;8(2):e000645.

# Baseline tumor burden and efficacy of immunotherapy in the clinic



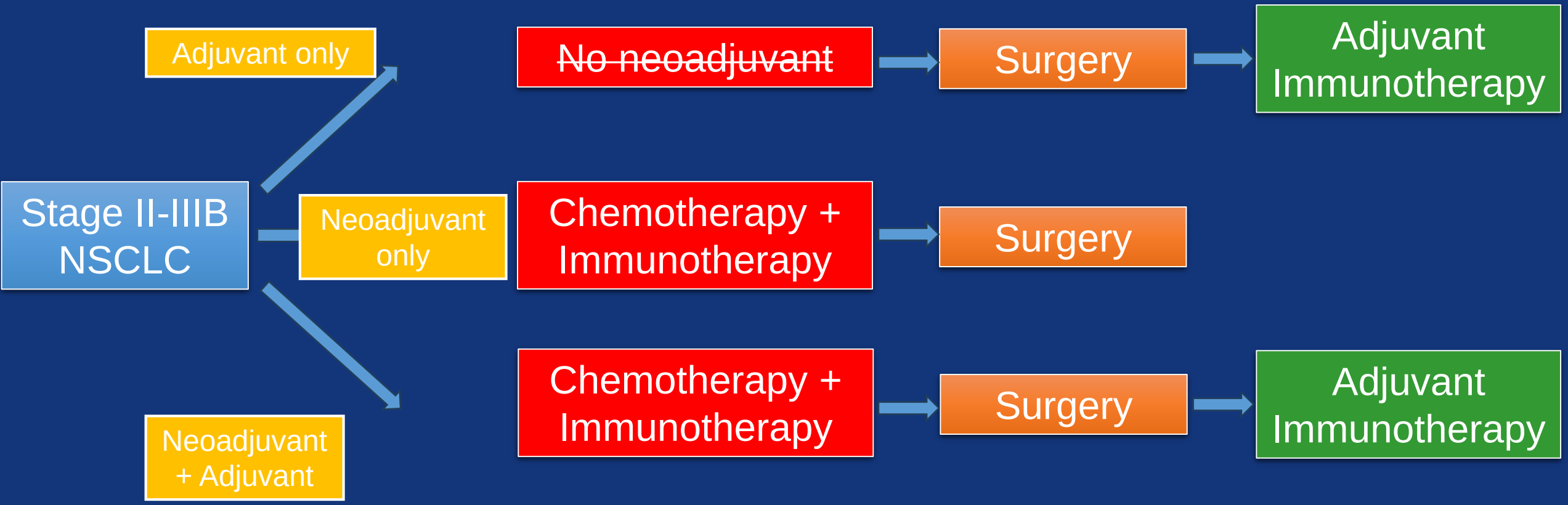

Activity of immunotherapy?
- Presence of tumor > Absence of tumor
- Small tumor volume > Large tumor volume

→ These findings support the advantage of ICI in preoperative setting.

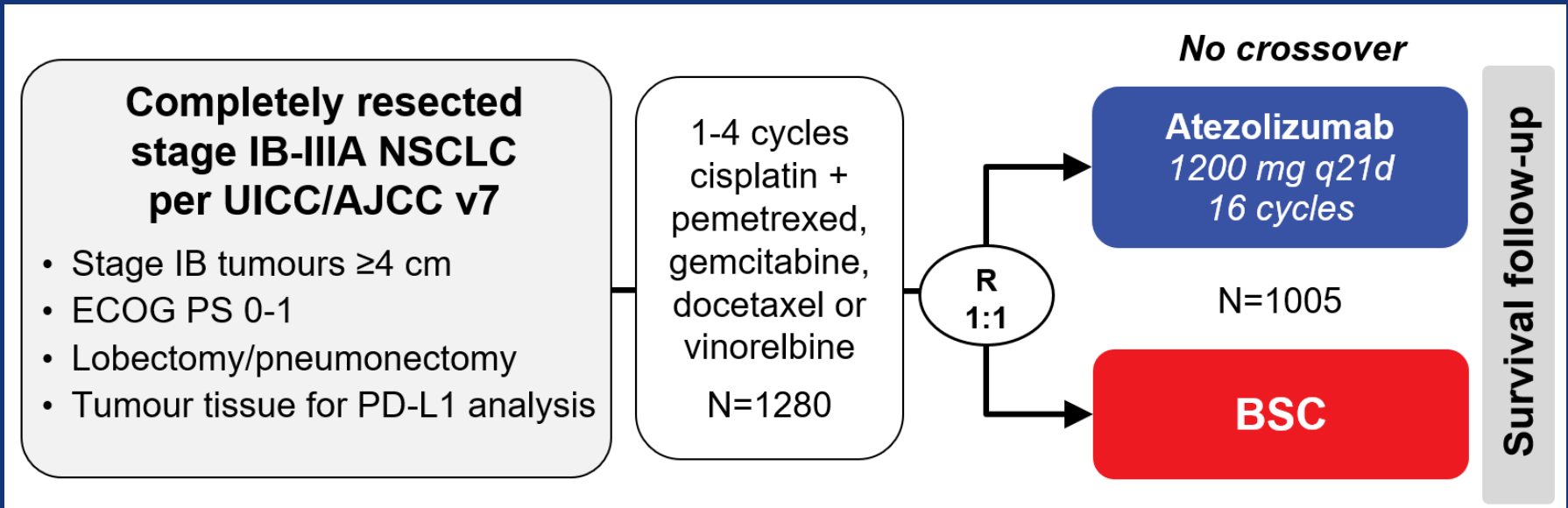
LC treated with various PD-1 inhibitors

Clin Cancer Res. 2018 Dec 1;24(23):6098, J Immunother Cancer. 2020 Jul;8(2):e000645.

# Potential perioperative strategy with immunotherapy in NSCLC



# IMpower010 study design

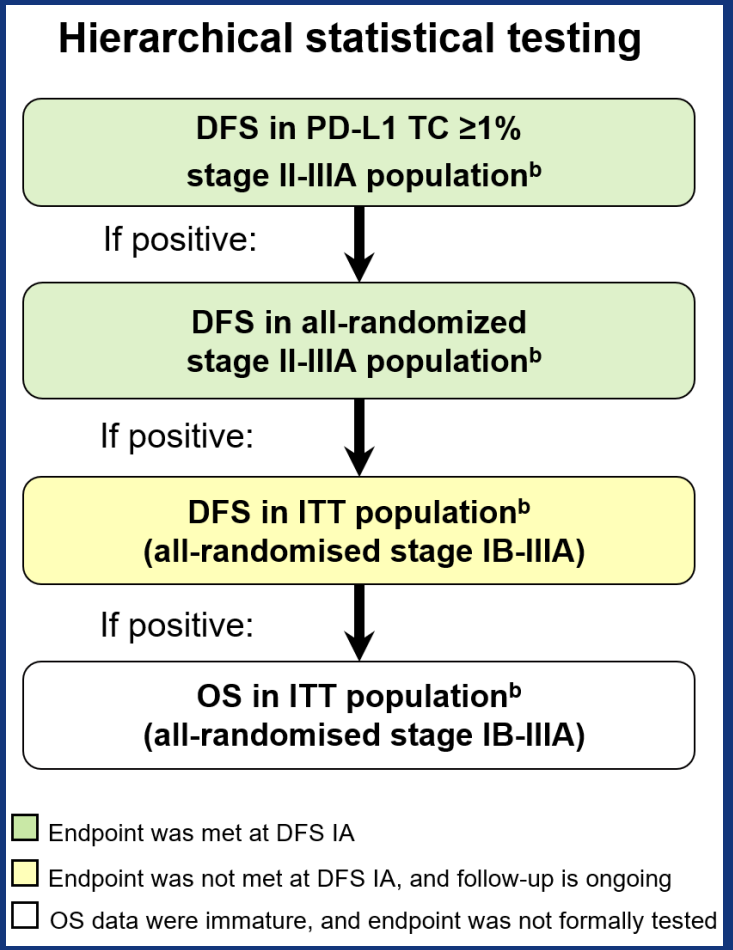



**Stratification factors**

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

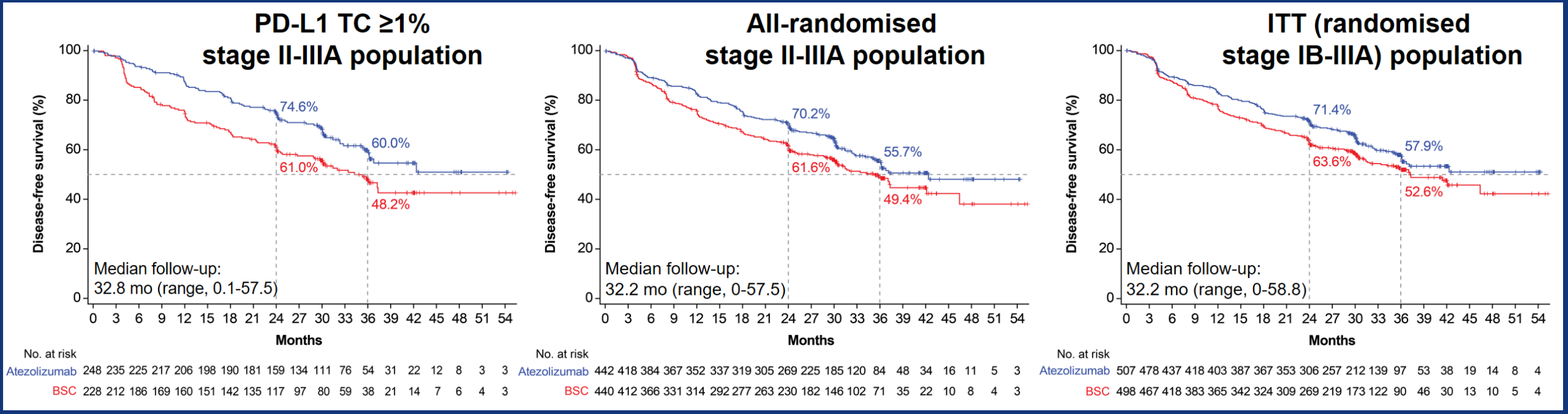
**Primary endpoints**

- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (SP263) stage II-IIIA population
  - All-randomised stage II-IIIA population
  - ITT (all-randomised stage IB-IIIA) population
- **Key secondary endpoints**
  - OS in ITT (all-randomised stage IB-IIIA) population
  - DFS in PD-L1 TC ≥50% (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.
IC, tumour-infiltrating immune cells. [a] Per SP142 assay. [b] Two-sided α=0.05.

# DFS in the PD-L1 TC ≥1% stage II-IIIA, all-randomised stage II-IIIA and ITT populations (primary endpoint)[1]




| | Atezolizumab (n=248) | BSC (n=228) |
|---|---|---|
| Median DFS (95% CI), mo | NE (36.1, NE) | 35.3 (29.0, NE) |
| Stratified HR (95% CI) | 0.66 (0.50, 0.88) | |
| *P* value[b] | 0.004[c] | |

| | 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[b] | 0.02[c] | |

| | 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[b] | 0.04[d] | |

Clinical cutoff: 21 January 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS. [d] The statistical significance boundary for DFS was not crossed. 1. Wakelee H, et al. J Clin Oncol. 2021;39(suppl 15):8500.

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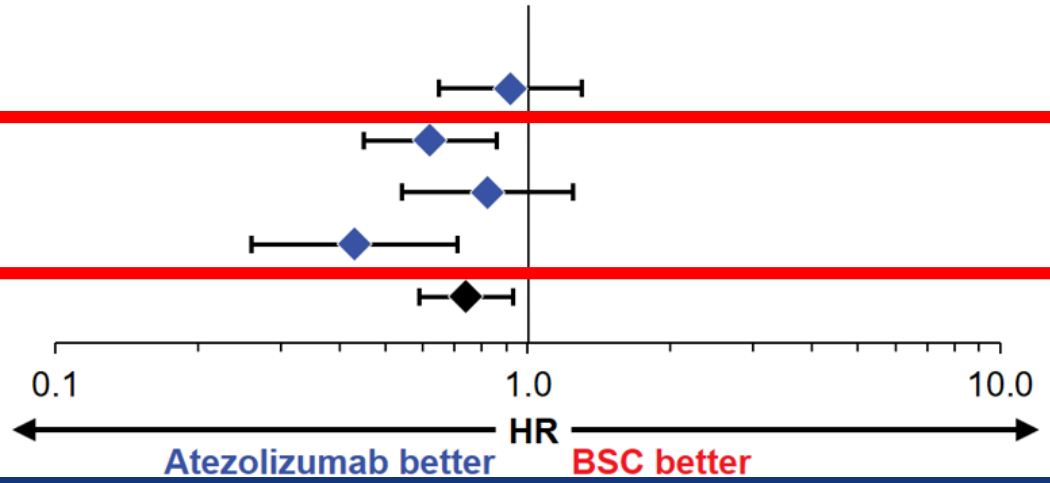
# DFS by PD-L1 status[a]
# All-randomised stage II-IIIA population (with and without known EGFR/ALK+ disease)

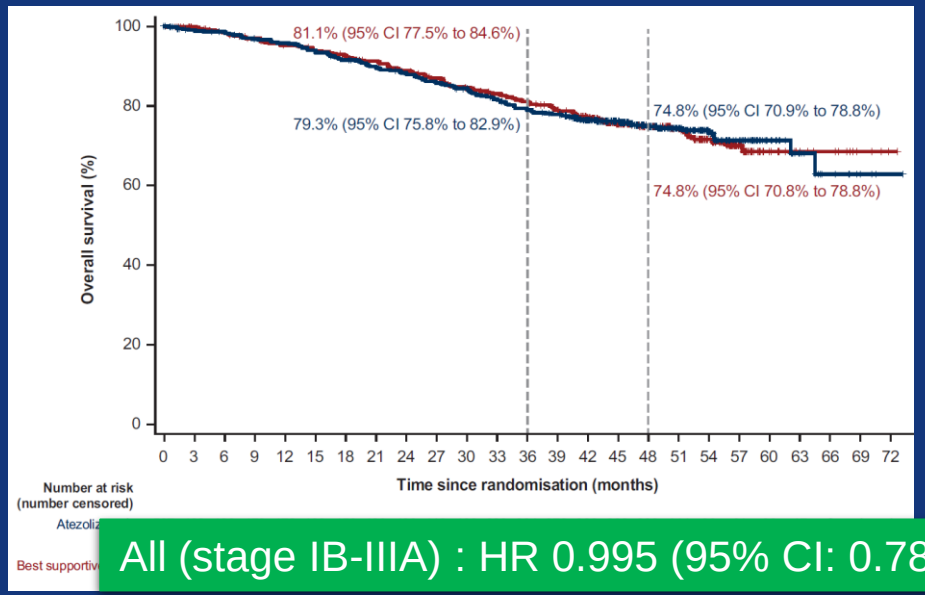
| Subgroup *(excluding EGFR/ALK+)*[e] | n | HR (95% CI)[f,g] |
|---|---|---|
| **PD-L1 status by SP263** | | |
| TC <1% | 312 | 0.92 (0.65, 1.30) |
| TC ≥1% | 410 | 0.62 (0.45, 0.86) |
| TC 1-49% | 201 | 0.82 (0.54, 1.25) |
| TC ≥50% | 209 | 0.43 (0.26, 0.71) |
| **All patients**[h] | 743 | 0.74 (0.59,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



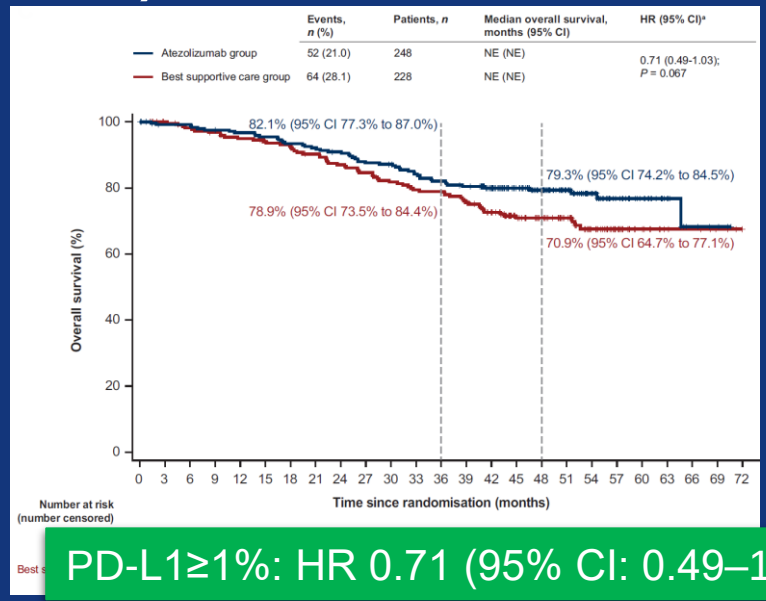

While there is no significant effect in the TC 1-49% group, the pronounced effect in the TC ≥50% group makes it seem as though the TC ≥1% group is benefiting overall.

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

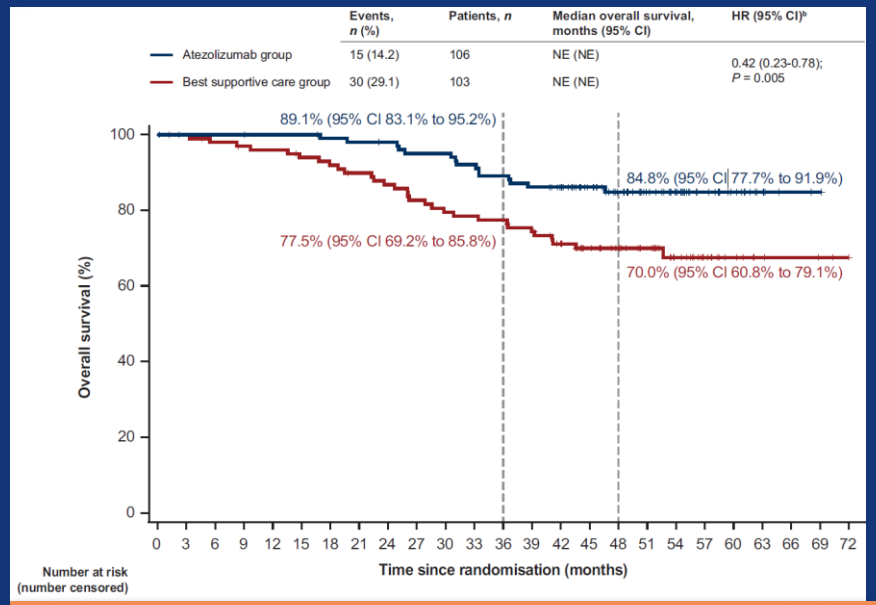
# IMpower010-OS data (median f/u of 45.3 m)



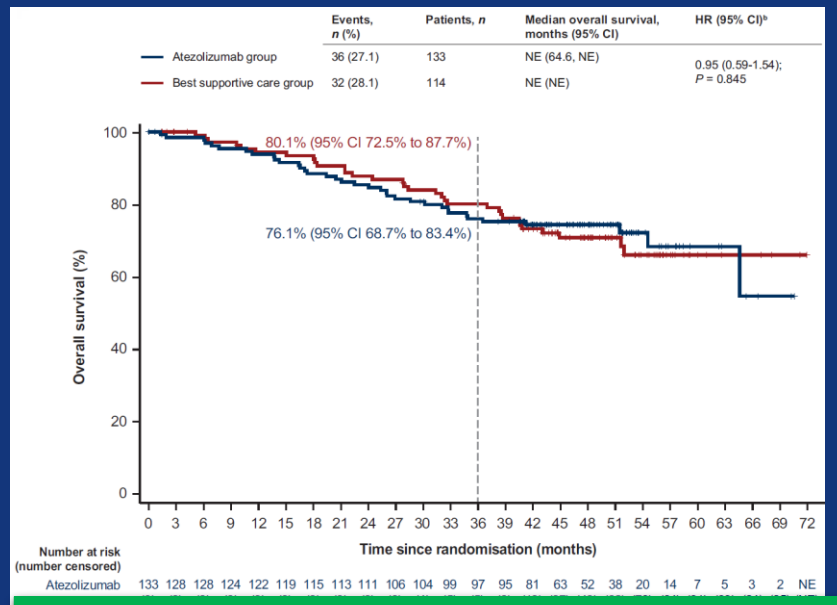

All (stage IB-IIIA) : HR 0.995 (95% CI: 0.78-1.28)




PD-L1≥1%: HR 0.71 (95% CI: 0.49–1.03)



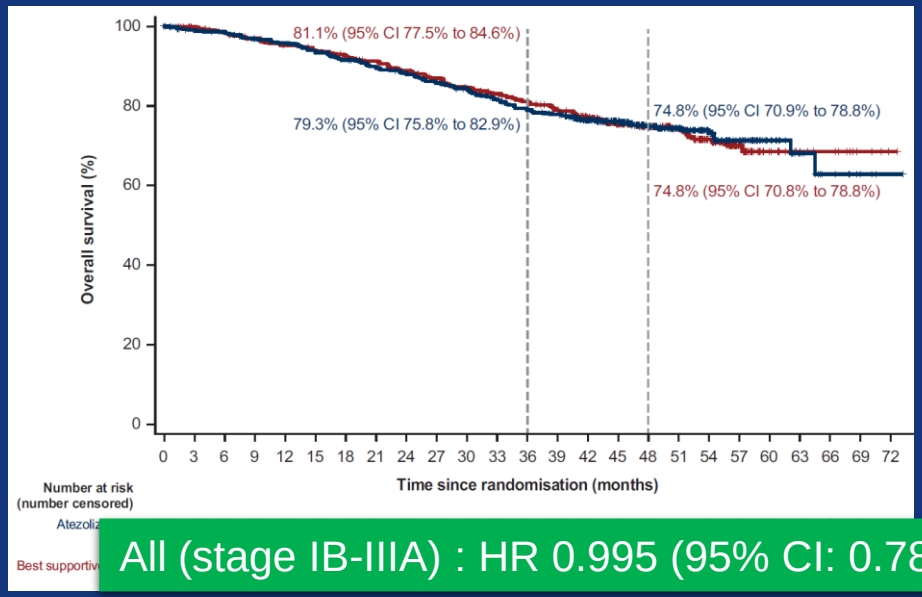

PD-L1 ≥ 50% wo EGFR/ALK: HR 0.42 (95% CI 0.23-0.78)




PD-L1 1-49%: HR 0.95 (95% CI 0.59-0.1.54)

Ann Oncol. 2023 Oct;34(10):907-919.

# IMpower010-OS data (median f/u of 45.3 m)

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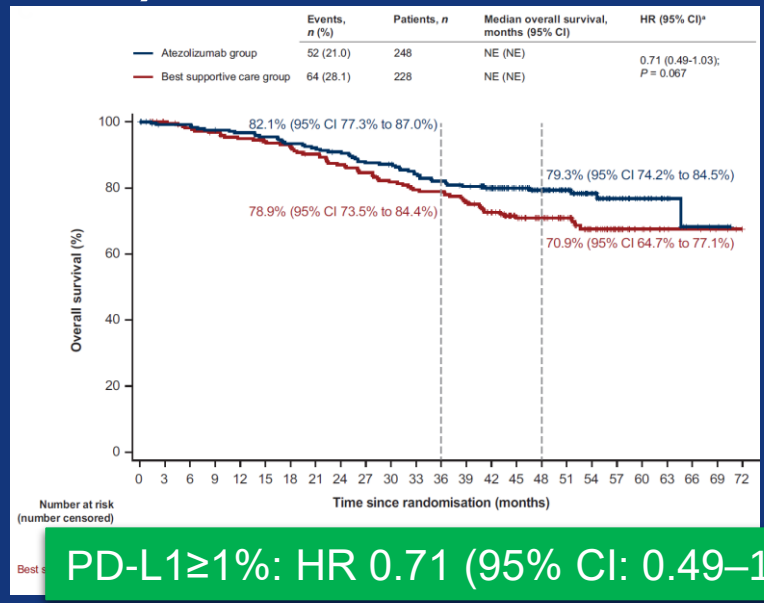


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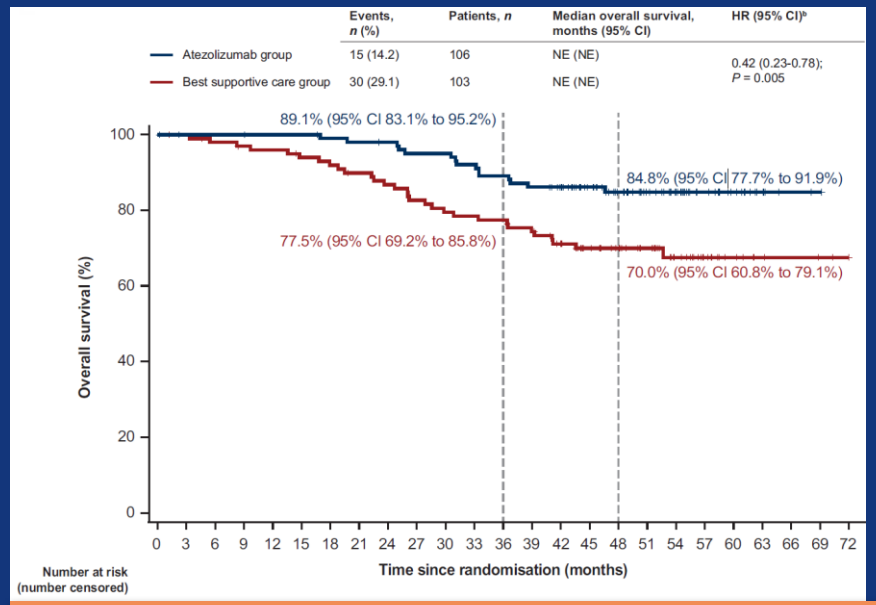


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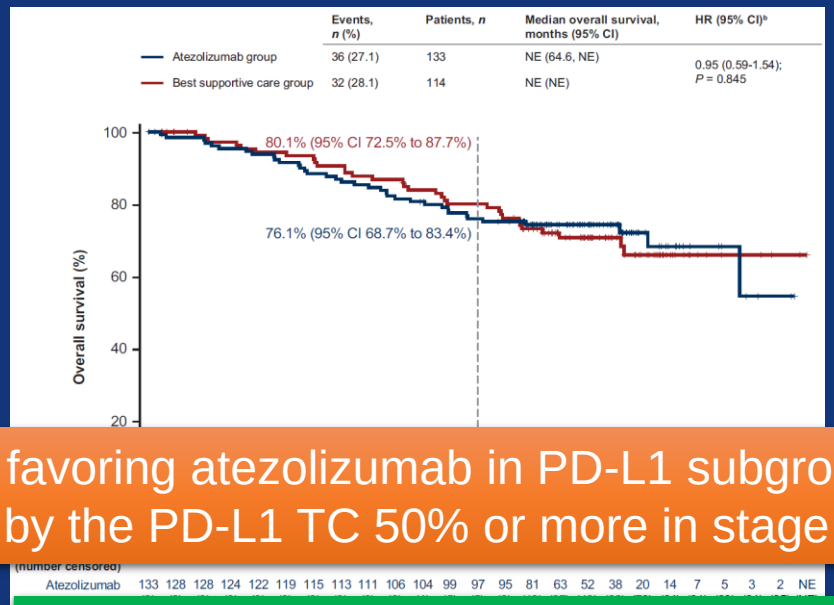



PD-L1 1-49%: HR 0.95 (95% CI 0.59-0.1.54)

A positive trend favoring atezolizumab in PD-L1 subgroup analyses, primarily driven by the PD-L1 TC 50% or more in stage II-IIIA subgroup

Ann Oncol. 2023 Oct;34(10):907-919.

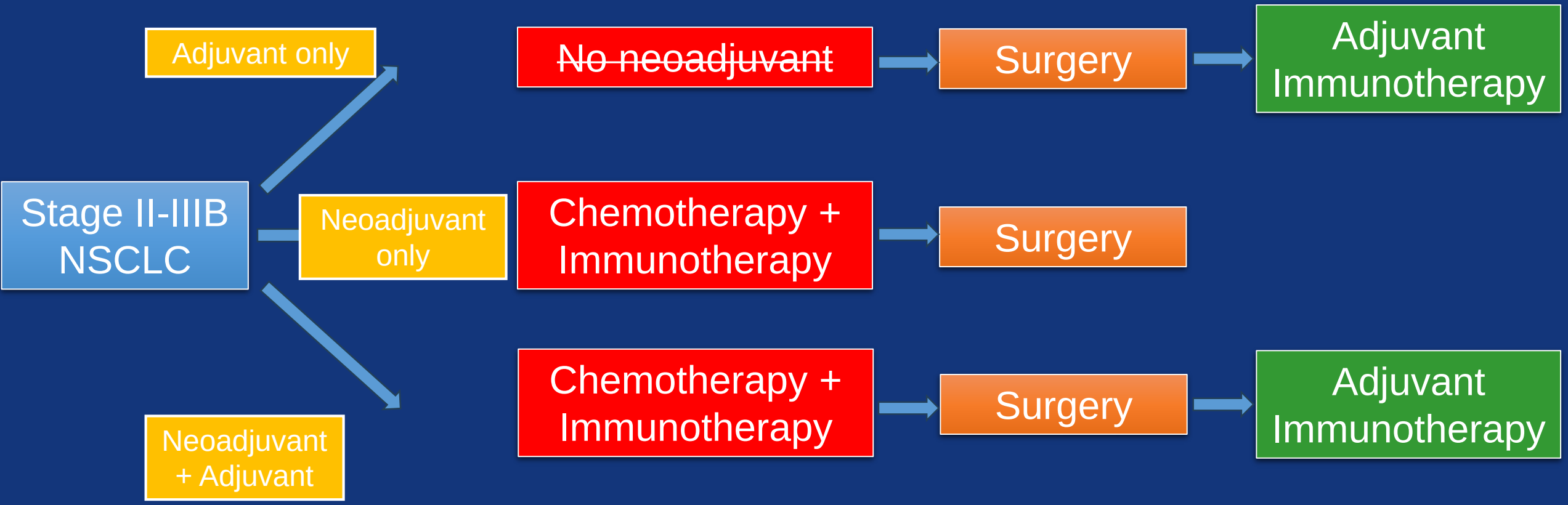
# FDA, EMA, KFDA indication on adjuvant atezolizumab

- FDA – 2021/Oct
  - Approved for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA non–small cell lung cancer (NSCLC) with PD-L1 expression on ≥ 1% of tumor cells, as determined by a U.S. Food and Drug Administration (FDA)-approved test. (Regardless of EGFR and ALK status)

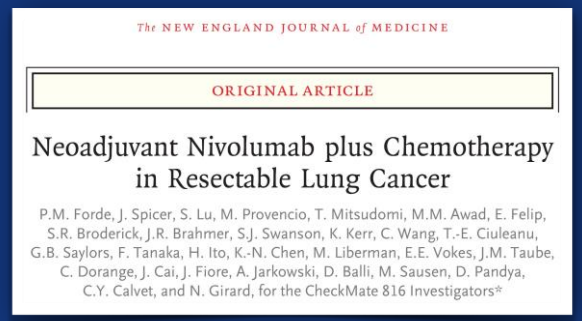
- EMA – 2022/June
  - Approved as an adjuvant treatment, following complete resection and platinum-based chemotherapy, for adults with non-small cell lung cancer (NSCLC) with a high risk of recurrence* whose tumors express PD-L1≥50% and who do not have EGFR mutant or ALK-positive NSCLC.
- KFDA – 2023
  - Approved as an adjuvant treatment, following complete resection and platinum-based chemotherapy, for adults with non-small cell lung cancer (NSCLC) with a high risk of recurrence* whose tumors express PD-L1≥50% (regardless of EGFR mutant or ALK-positive NSCLC).

→ IMpower010 is the first adjuvant immunotherapy trial in NSCLC which met its primary endpoint and got a regulatory approval.

# Potential perioperative strategy with immunotherapy in NSCLC



# 4 key phase III neoadjuvant RCTs in NSCLC

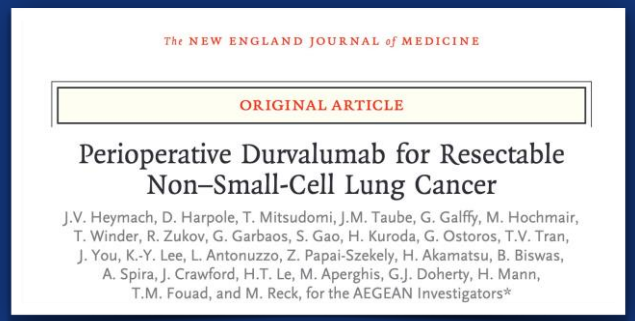

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

CM-816

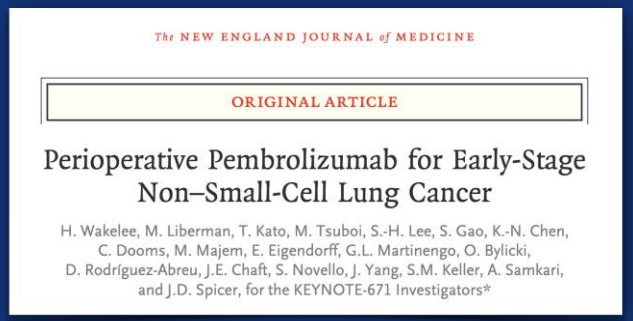

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer

J.V. Heymach, D. Harpole, T. Mitsudomi, J.M. Taube, G. Galffy, M. Hochmair, T. Winder, R. Zukov, G. Garbaos, S. Gao, H. Kuroda, G. Ostoros, T.V. Tran, J. You, K.-Y. Lee, L. Antonuzzo, Z. Papai-Szekely, H. Akamatsu, B. Biswas, A. Spira, J. Crawford, H.T. Le, M. Aperghis, G.J. Doherty, H. Mann, T.M. Fouad, and M. Reck, for the AEGEAN Investigators*

AEGEAN

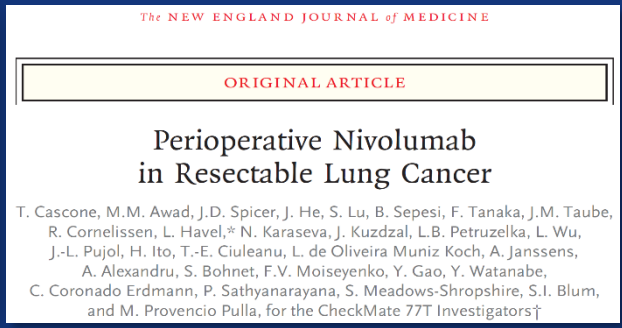

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

H. Wakelee, M. Liberman, T. Kato, M. Tsuboi, S.-H. Lee, S. Gao, K.-N. Chen, C. Dooms, M. Majem, E. Eigendorff, G.L. Martinengo, O. Bylicki, D. Rodríguez-Abreu, J.E. Chaft, S. Novello, J. Yang, S.M. Keller, A. Samkari, and J.D. Spicer, for the KEYNOTE-671 Investigators*

KN-671


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Nivolumab in Resectable Lung Cancer

T. Cascone, M.M. Awad, J.D. Spicer, J. He, S. Lu, B. Sepesi, F. Tanaka, J.M. Taube, R. Cornelissen, L. Havel,* N. Karaseva, J. Kuzdzal, L.B. Petruzelka, L. Wu, J.-L. Pujol, H. Ito, T.-E. Ciuleanu, L. de Oliveira Muniz Koch, A. Janssens, A. Alexandru, S. Bohnet, F.V. Moiseyenko, Y. Gao, Y. Watanabe, C. Coronado Erdmann, P. Sathyanarayana, S. Meadows-Shropshire, S.I. Blum, and M. Provencio Pulla, for the CheckMate 77T Investigators†

CM-77T

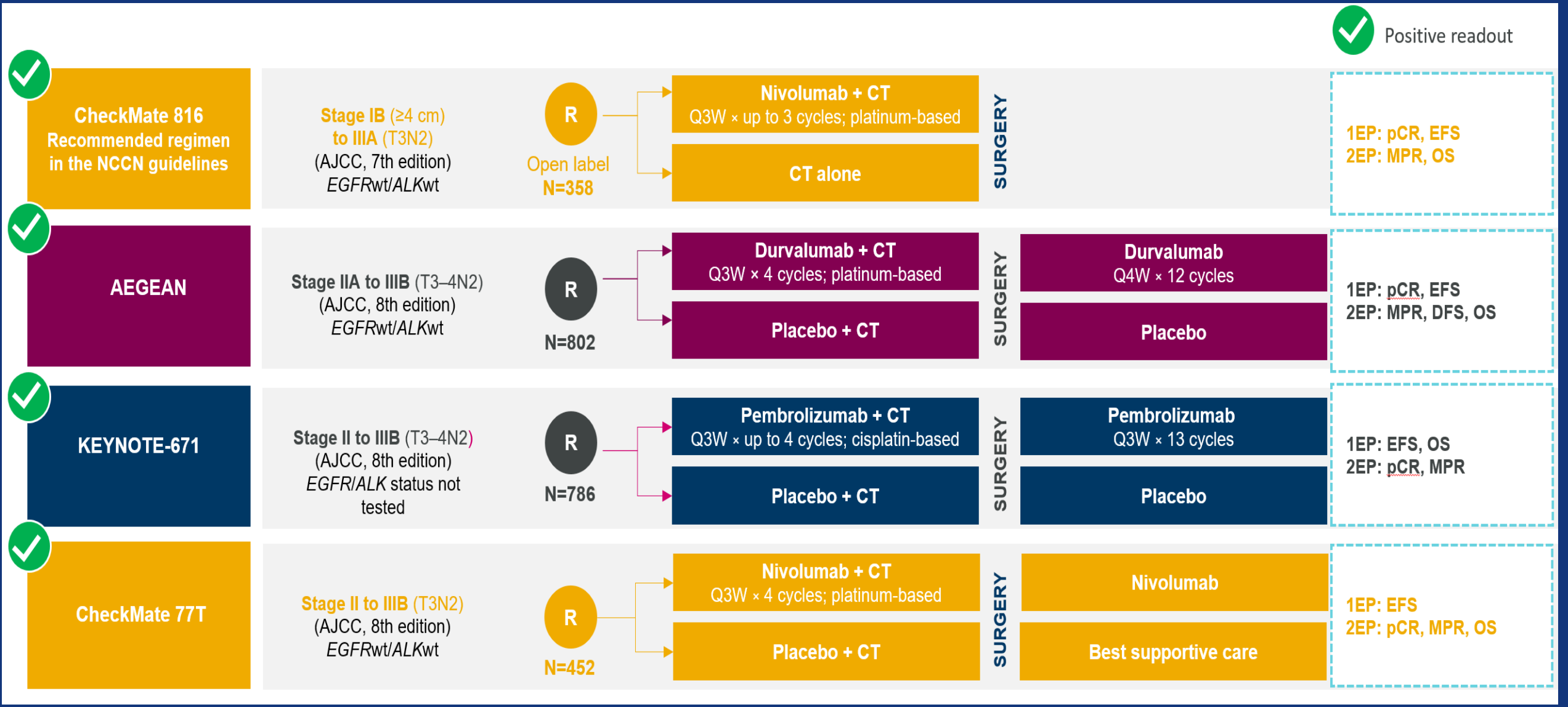


N Engl J Med 2022;386:1973-85., N Engl J Med. 2023 Nov 2;389(18):1672-1684.N Engl J Med. 2023 Aug 10;389(6):491-503.N Engl J Med. 2024 May 16;390(19):1756-1769.

# What is the GOAL of perioperative therapy for LA-NSCLC?

| Safety & Tolerability | Short-term efficacy | Long-term survival |
| --- | --- | --- |
| • High neoadjuvant completion rate<br>• High surgical completion rate | • High MPR, pCR | • Long EFS,DFS,OS |

# Trial Design




***KN671 regimen Pembrolizumab** 200 mg Q3W **+ cisplatin** 75 mg/m$^2$ **+ pemetrexed**[b] 500 mg/m$^2$ OR **gemcitabine**[c] 1,000 mg/m$^2$ 4 cycles



Heymach JV, et al. Clin Lung Cancer 2022;23:e247–e251; Forde PM, et al. N Engl J Med 2022;386:1973–1985; Tsuboi M, et al. Ann Oncol 2020;31:S801–S802; Peters S, et al. Ann Oncol 2019;30:ii30; Cascone T, et al. J Clin Oncol 2019;38:TPS9076; Gray J, et al. Poster presentation at FLASCO 2021, Spring Session (Abstract BR-04396).

# Baseline Characteristics

| Characteristics | | CheckMate 816[1] | | AEGEAN[2] | | KEYNOTE-671[3] | | CheckMate-77T[4] | |
|---|---|---|---|---|---|---|---|---|---|
| | | Nivolumab | CTx | Durvalumab | Placebo | Pembrolizumab | Placebo | Nivolumab | Placebo |
| n | | 179 | 179 | 366 | 374 | 397 | 400 | 229 | 232 |
| Age | Median (range), years | 64 (41–82) | 65 (34–84) | 65.0 (30–88) | 65.0 (39–85) | 63 (26–83) | 64 (35–81) | 66 (37–83) | 66 (35–86) |
| Sex, % | Male | 71.5 | 70.9 | 68.9 | 74.3 | 70.3 | 71.0 | 73.0 | 69.0 |
| | Female | 28.5 | 29.1 | 31.1 | 25.7 | 29.7 | 29.0 | 27.0 | 31.0 |
| ECOG PS, % | 0 | 69.3 | 65.4 | 68.6 | 68.2 | 63.7 | 61.5 | 64.0 | 61.0 |
| | 1 | 30.7 | 34.6 | 31.4 | 31.8 | 36.3 | 38.5 | 36.0 | 39.0 |
| Region, % | Asia | 47.5 | 51.4 | 38.8 | 43.6 | 31.0† | 30.3† | 28.0 | 22.0 |
| | Europe | 22.9 | 14.0 | 38.5 | 37.4 | - | - | 54.0 | 55.0 |
| | North America | 22.9 | 27.9 | 11.7 | 11.5 | - | - | 10.0 | 9.0 |
| | Rest of World* | 6.7 | 6.7 | 10.9 | 7.5 | 69.0 | 69.8 | 8.0 | 15.0 |
| Smoking status, % | Current / former | 89.4 | 88.3‡ | 86.1 | 85.0 | 86.4 | 88.3 | 93.0 | 88.0 |
| | Never | 10.6 | 11.2‡ | 13.9 | 15.0 | 13.6 | 11.8 | 7.0 | 12.0 |
| Disease stage (AJCC 8th edition),§ % | II | 36.3¶ | 34.6¶ | 28.4 | 29.4 | 29.7 | 30.3 | 35.0 | 35.0 |
| | IIIA | 63.1 | 64.2 | 47.3 | 44.1 | 54.7 | 56.3 | 45.0 | 49.0 |
| | IIIB | 0 | 0 | 24.0 | 26.2 | 15.6 | 13.5 | 19.0 | 15.0 |
| Histology, % | Squamous | 48.6 | 53.1 | 46.2 | 51.1 | 43.1 | 43.3 | 51.0 | 51.0 |
| | Non-squamous | 51.4 | 46.9 | 53.6 | 47.9 | 56.9 | 56.8 | 49.0 | 49.0 |
| PD-L1 expression,‖ % | TC <1% | 43.6 | 43.0 | 33.3 | 33.4 | 34.8 | 37.8 | 41.0 | 40.0 |
| | TC 1–49% | 28.5 | 26.3 | 36.9 | 38.0 | 32.0 | 28.8 | 36.0 | 33.0 |
| | TC ≥50% | 21.2 | 23.5 | 29.8 | 28.6 | 33.2 | 33.5 | 20.0 | 22.0 |
| Planned neoadjuvant platinum agent, % | Cisplatin | 69.3 | 74.9 | 27.3 | 25.7 | 100 | 100 | 24.0 | 18.0 |
| | Carboplatin | 21.8 | 18.4 | 72.7 | 74.3 | 0 | 0 | 73.0 | 78.0 |

*CheckMate 816: Argentina and Turkey, AEGEAN: South America, KEYNOTE-671: regions outside of East Asia, CheckMate 77-T: includes only Argentina, Australia, Brazil and Mexico; †East Asia; ‡1 patient in the CTx arm had unknown smoking status; §CheckMate 816: 1 patient in the chemotherapy-alone group had Stage IA disease, and 1 patient in each group had Stage IV disease[1]; AEGEAN: 0.3% and 0% of patients had Stage IV disease in the durvalumab and placebo arms, respectively[2]; ¶Including Stage IB; ‖KEYNOTE-671: PD-L1 expression assessed using TPS <1%, TPS 1–49% and TPS ≥50%

1. Forde PM, et al. N Engl J Med 2022;386:1973–85; 2. Heymach J et al. Oral presentation at AACR 2023 (Abstract CT005); 3. Wakelee HA, et al. Oral presentation at ASCO 2023 (Abstract LBA100); 4. Cascone T, et al. Oral presentation at ESMO 2023 (Abstract LBA1); 5. Provencio M, et al. N Engl J Med 2023;389:504–513.

# What is the GOAL of perioperative therapy for LA-NSCLC?

## Safety & Tolerability

- High neoadjuvant completion rate
- High surgical completion rate

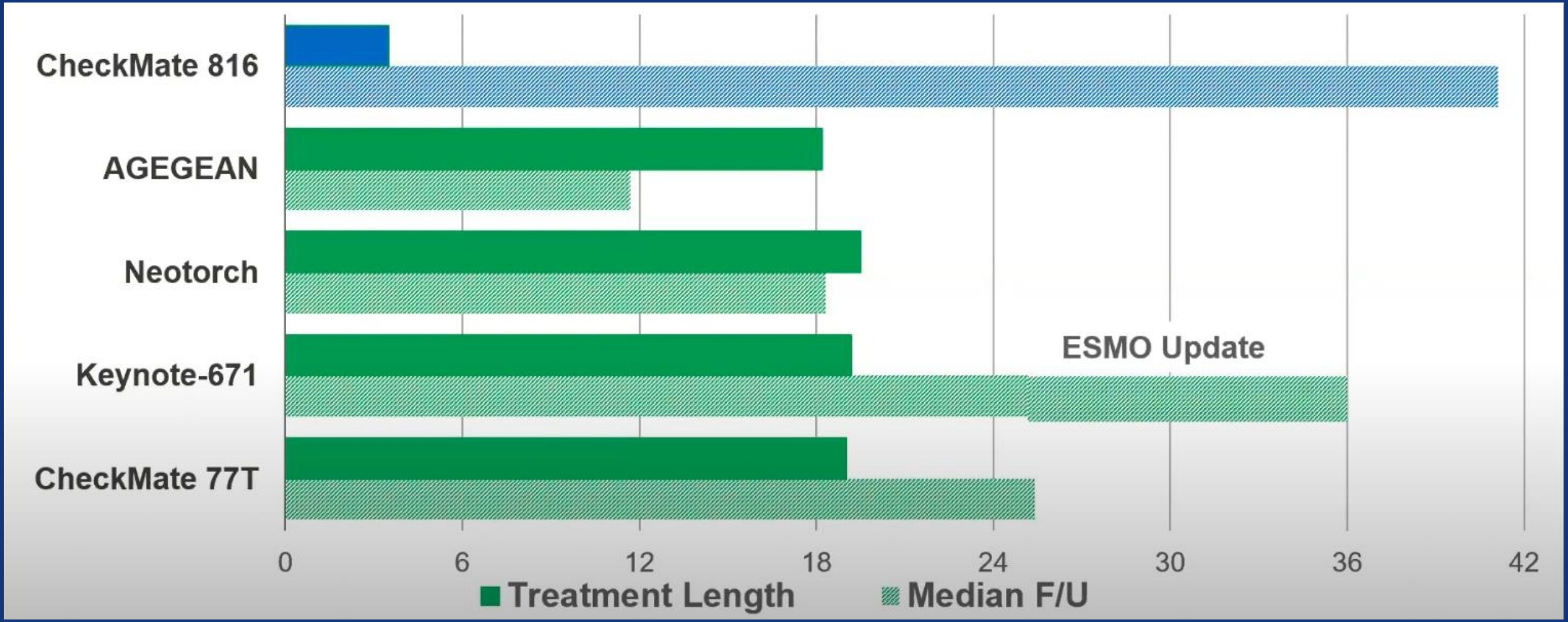
## Short-term efficacy

- High MPR, pCR

## Long-term survival

- Long EFS,DFS,OS

# 4 key phase III neoadjuvant RCTs in NSCLC (As of May/2024)






N Engl J Med 2022;386:1973-85., N Engl J Med. 2023 Nov 2;389(18):1672-1684.N Engl J Med. 2023 Aug 10;389(6):491-503. ,Youtube: https://www.youtube.com/watch?v=w1zyDe8fv-8

# 4 key phase III neoadjuvant RCTs in NSCLC

| | CM-816 | AEGEAN | KN-671 | CM-77T |
|---|---|---|---|---|
| Completed neoTx (≥ 3cycles) | 94% vs 85% | 87% vs 89% | 87% vs 87% | 85% vs 89% |
| Canceled surgery | 16% vs 21% | 19% vs 19% | 18% vs 21% | 22% vs 23% |
| d/t PD | 7% vs 9% | 6.8% vs 7.5% | 4.1% vs 6.7% | 6% vs 10% |
| d/t Tx-related toxicity (or adverse event) | 1% vs 1% | 1.8% vs 1.2% | 6.3% vs 4.2% | 3% vs 2% |
| Delayed surgery | 21% vs 18% | 15% vs 17% | NR | NR |

| | |
|---|---|
| Completed Neoadjuvant IO + CT | 85 ~ 95% |
| Rate of surgery | 78 ~ 83% |
| Completion of adjuvant (immature) | 41 ~ 66% |

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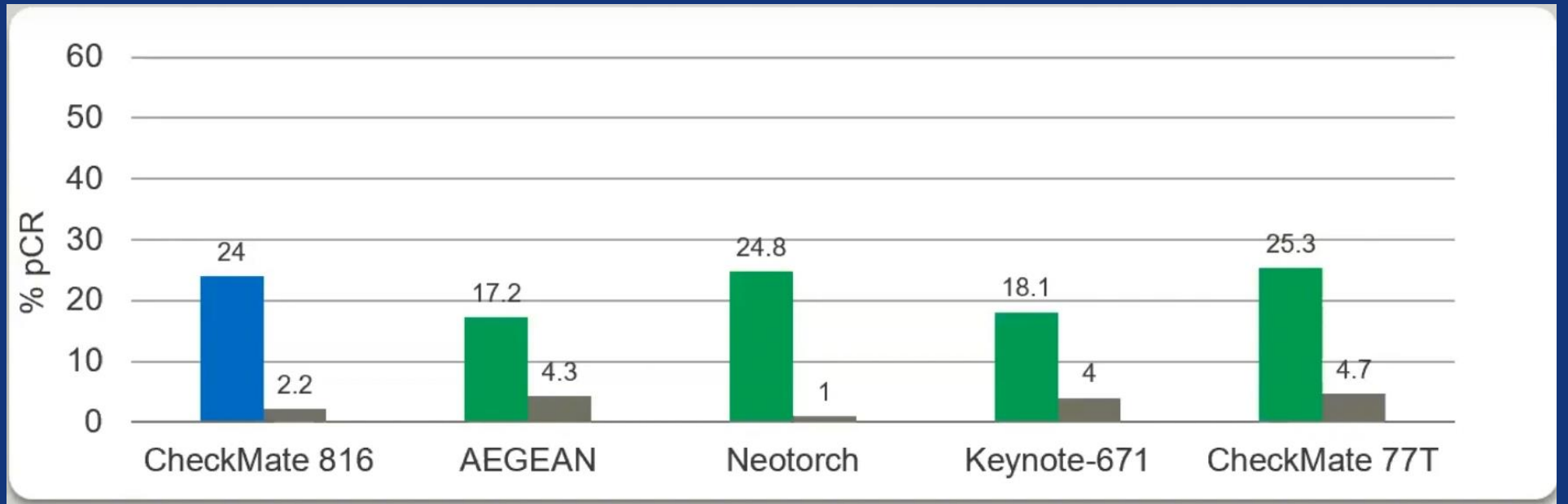
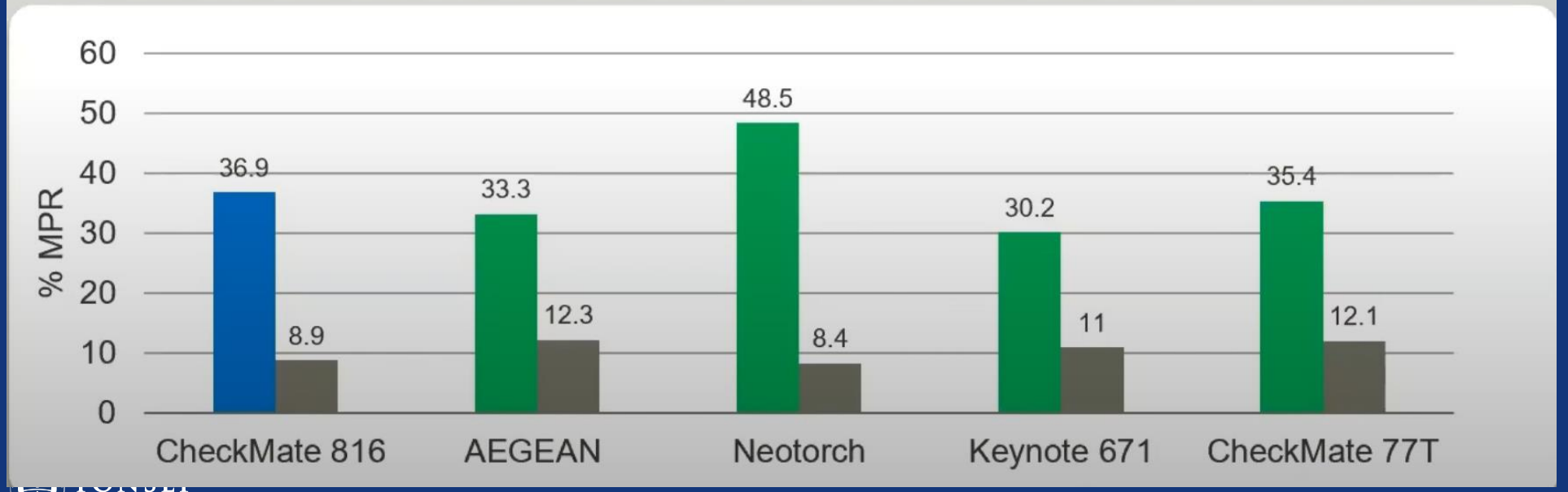
# What is the GOAL of perioperative therapy for LA-NSCLC?

| Safety & Tolerability | Short-term efficacy | Long-term survival |
| --- | --- | --- |
| • High neoadjuvant completion rate<br>• High surgical completion rate | • High MPR, pCR | • Long EFS,DFS,OS |

# % pCR and % MPR in major perioperative ICI trials



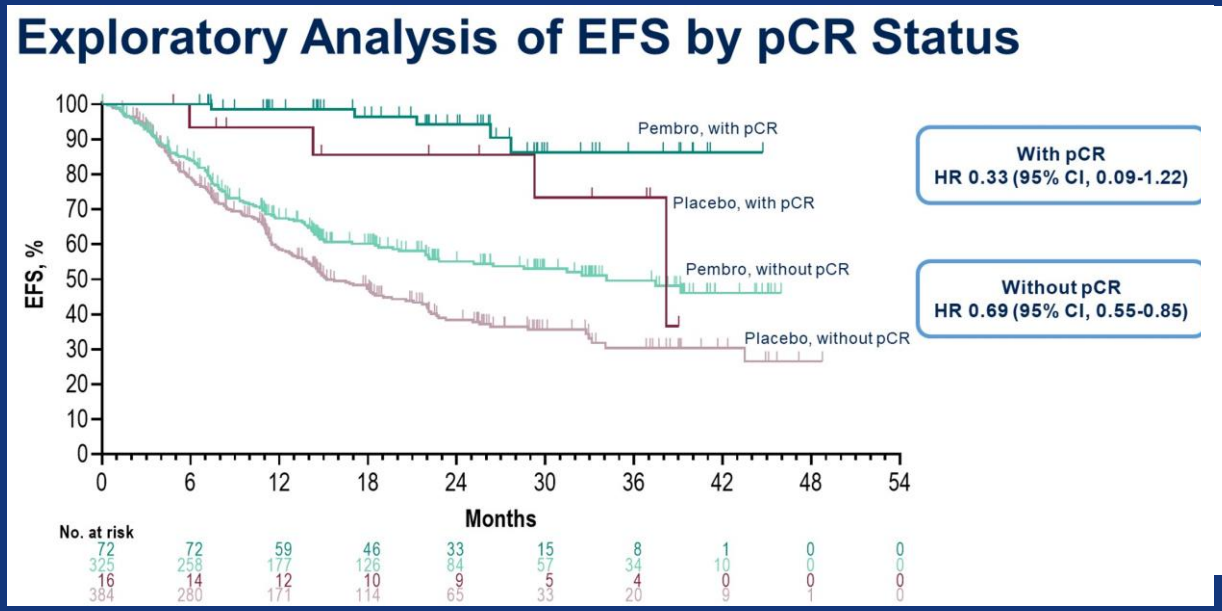


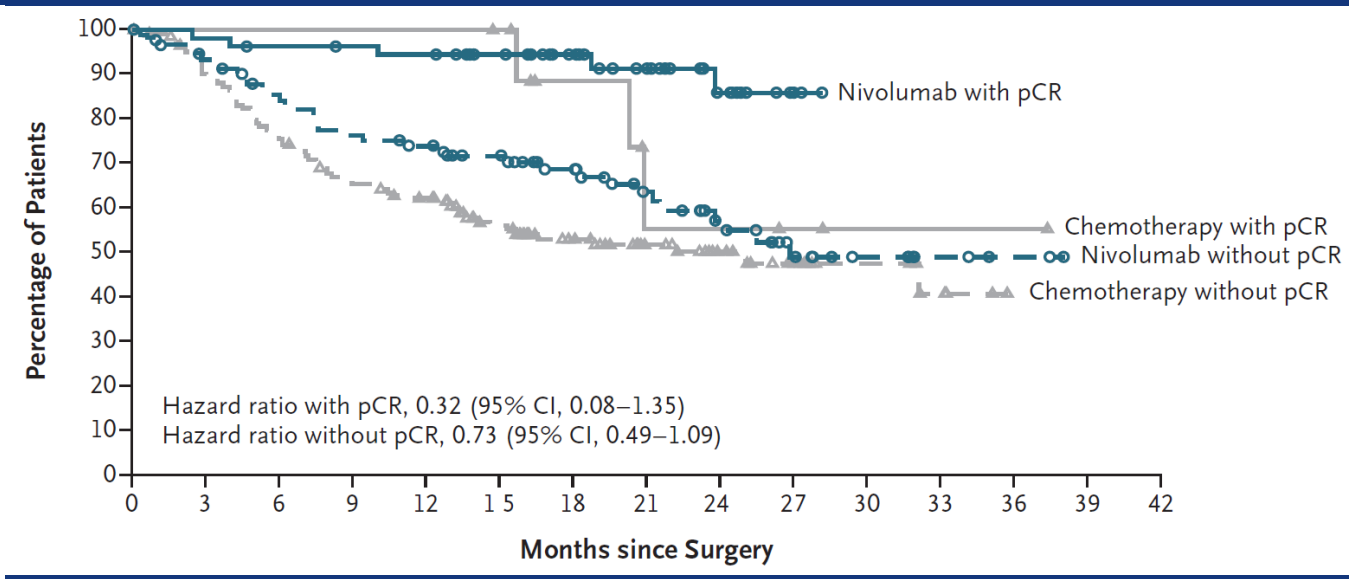

N Engl J Med 2022;386:1973-85., N Engl J Med. 2023 Nov 2;389(18):1672-1684.N Engl J Med. 2023 Aug 10;389(6):491-503. ,Youtube: https://www.youtube.com/watch?v=w1zyDe8fv-8

# What is the GOAL of perioperative therapy for LA-NSCLC?

| Safety & Tolerability | Short-term efficacy | Long-term survival |
| --- | --- | --- |
| • High neoadjuvant completion rate<br>• High surgical completion rate | • High MPR, pCR | • Long EFS,DFS,OS |

# Does long-term survival correlate with pathologic response in ICI trials?

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N Engl J Med. 2023 Aug 10;389(6):491-503.N Engl J Med. 2024 May 16;390(19):1756-1769.

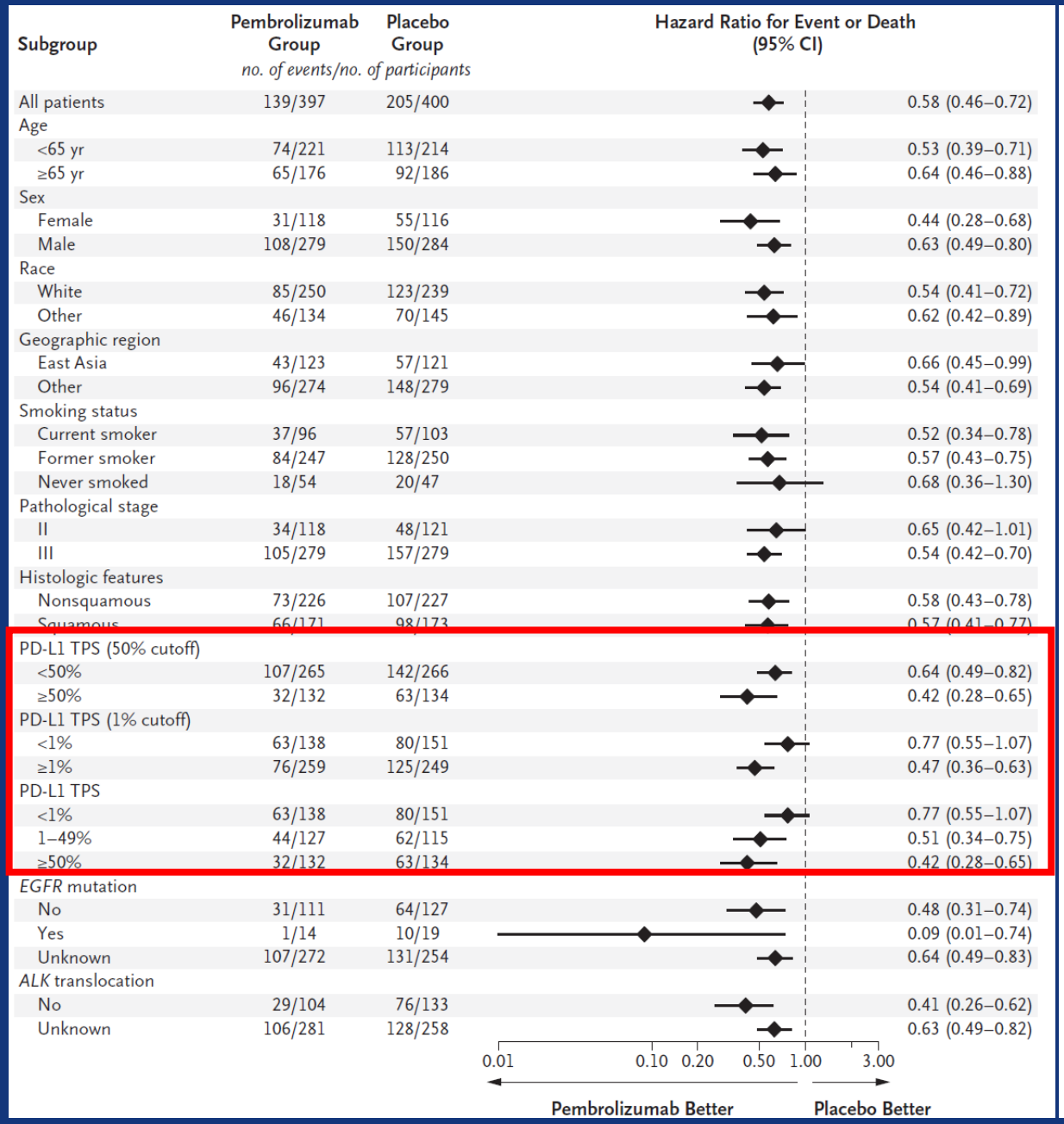
# 4 key phase III neoadjuvant RCTs in NSCLC (As of May/2024)

| | CM-816 | AEGEAN | KN-671 | CM-77T |
|---|---|---|---|---|
| Median f/u (mon) | 41.4 | 11.7 | 36.6 | 25.4 |
| Stage II (%) | 35% | 29% | 30% | 35% |
| NSQ, SQ | 50%, 50% | 50%, 50% | 56%, 43% | 50%, 50% |
| PD-L1 ≥1%, ≥50% | 50%, 22%<br>(28-8 pharmDx) | 66%, 29%<br>(SP263) | 65%, 33.2%<br>(22C3 pharmDx) | 56%, 20%<br>(28-8 pharmDx) |
| MPR | 36.9%, 8.9% | 33.3%, 12.3% | 30.2%, 11.0% | 35.4%, 12.1% |
| pCR | 24.0%, 2.2% | 17.2%, 4.3% | 18.1%, 4.0% | 25.3%, 4.7% |
| EFS HR | 0.68 [0.49-0.93]<br>(NR – 21.1mo) | 0.68 [0.53-0.88]<br>(NR vs 25.9 mo) | 0.59 [0.48-0.72]<br>(47.2 vs 18.3 mo) | 0.58 [0.42-0.81)<br>(NR vs 18.4) |
| EFS rate, 2yr | 65% | 63% | 62% | 70% (1.5yr) |
| OS HR | 0.62 (mOS: NR) | NA | 0.72 (mOS: NR) | NA |
| OS rate, 2yr | 83% (2yr) | NA | 80.9% | NA |



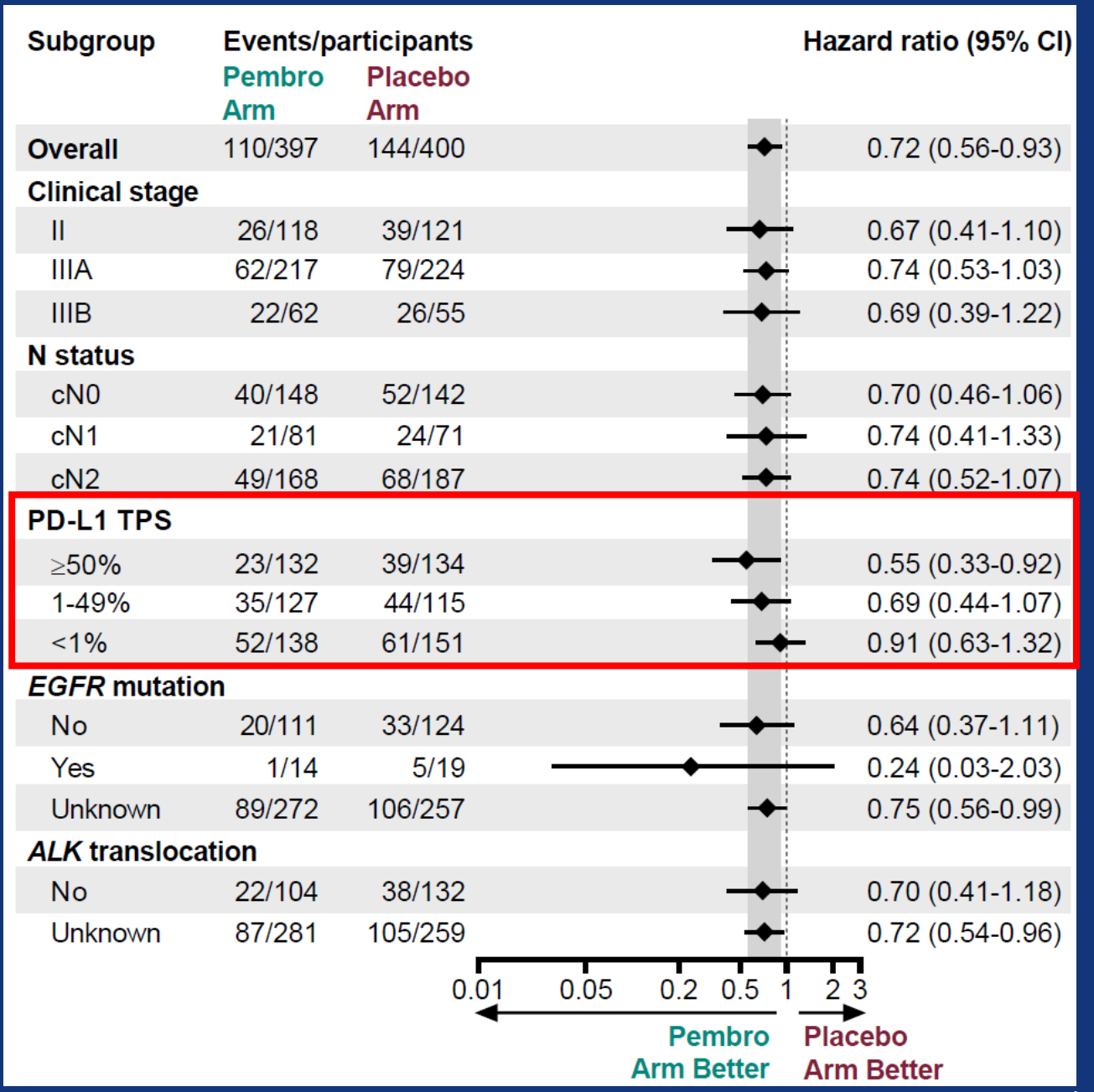
N Engl J Med 2022;386:1973-85., N Engl J Med. 2023 Nov 2;389(18):1672-1684.N Engl J Med. 2023 Aug 10;389(6):491-503.N Engl J Med. 2024 May 16;390(19):1756-1769.

# Keynote-671 data (EFS & OS)



| Subgroup | Pembrolizumab Group | Placebo Group | Hazard Ratio for Event or Death (95% CI) |
|---|---|---|---|
| | *no. of events/no. of participants* | | |
| All patients | 139/397 | 205/400 | 0.58 (0.46–0.72) |
| Age | | | |
| <65 yr | 74/221 | 113/214 | 0.53 (0.39–0.71) |
| ≥65 yr | 65/176 | 92/186 | 0.64 (0.46–0.88) |
| Sex | | | |
| Female | 31/118 | 55/116 | 0.44 (0.28–0.68) |
| Male | 108/279 | 150/284 | 0.63 (0.49–0.80) |
| Race | | | |
| White | 85/250 | 123/239 | 0.54 (0.41–0.72) |
| Other | 46/134 | 70/145 | 0.62 (0.42–0.89) |
| Geographic region | | | |
| East Asia | 43/123 | 57/121 | 0.66 (0.45–0.99) |
| Other | 96/274 | 148/279 | 0.54 (0.41–0.69) |
| Smoking status | | | |
| Current smoker | 37/96 | 57/103 | 0.52 (0.34–0.78) |
| Former smoker | 84/247 | 128/250 | 0.57 (0.43–0.75) |
| Never smoked | 18/54 | 20/47 | 0.68 (0.36–1.30) |
| Pathological stage | | | |
| II | 34/118 | 48/121 | 0.65 (0.42–1.01) |
| III | 105/279 | 157/279 | 0.54 (0.42–0.70) |
| Histologic features | | | |
| Nonsquamous | 73/226 | 107/227 | 0.58 (0.43–0.78) |
| Squamous | 66/171 | 98/173 | 0.57 (0.41–0.77) |
| PD-L1 TPS (50% cutoff) | | | |
| <50% | 107/265 | 142/266 | 0.64 (0.49–0.82) |
| ≥50% | 32/132 | 63/134 | 0.42 (0.28–0.65) |
| PD-L1 TPS (1% cutoff) | | | |
| <1% | 63/138 | 80/151 | 0.77 (0.55–1.07) |
| ≥1% | 76/259 | 125/249 | 0.47 (0.36–0.63) |
| PD-L1 TPS | | | |
| <1% | 63/138 | 80/151 | 0.77 (0.55–1.07) |
| 1–49% | 44/127 | 62/115 | 0.51 (0.34–0.75) |
| ≥50% | 32/132 | 63/134 | 0.42 (0.28–0.65) |
| *EGFR* mutation | | | |
| No | 31/111 | 64/127 | 0.48 (0.31–0.74) |
| Yes | 1/14 | 10/19 | 0.09 (0.01–0.74) |
| Unknown | 107/272 | 131/254 | 0.64 (0.49–0.83) |
| *ALK* translocation | | | |
| No | 29/104 | 76/133 | 0.41 (0.26–0.62) |
| Unknown | 106/281 | 128/258 | 0.63 (0.49–0.82) |





| Subgroup | Events/participants Pembro Arm | Events/participants Placebo Arm | Hazard ratio (95% CI) |
|---|---|---|---|
| **Overall** | 110/397 | 144/400 | 0.72 (0.56-0.93) |
| **Clinical stage** | | | |
| II | 26/118 | 39/121 | 0.67 (0.41-1.10) |
| IIIA | 62/217 | 79/224 | 0.74 (0.53-1.03) |
| IIIB | 22/62 | 26/55 | 0.69 (0.39-1.22) |
| **N status** | | | |
| cN0 | 40/148 | 52/142 | 0.70 (0.46-1.06) |
| cN1 | 21/81 | 24/71 | 0.74 (0.41-1.33) |
| cN2 | 49/168 | 68/187 | 0.74 (0.52-1.07) |
| **PD-L1 TPS** | | | |
| ≥50% | 23/132 | 39/134 | 0.55 (0.33-0.92) |
| 1-49% | 35/127 | 44/115 | 0.69 (0.44-1.07) |
| <1% | 52/138 | 61/151 | 0.91 (0.63-1.32) |
| ***EGFR* mutation** | | | |
| No | 20/111 | 33/124 | 0.64 (0.37-1.11) |
| Yes | 1/14 | 5/19 | 0.24 (0.03-2.03) |
| Unknown | 89/272 | 106/257 | 0.75 (0.56-0.99) |
| ***ALK* translocation** | | | |
| No | 22/104 | 38/132 | 0.70 (0.41-1.18) |
| Unknown | 87/281 | 105/259 | 0.72 (0.54-0.96) |

# Efficacy Regarding PD-L1 expression

| | Neoadjuvant | | Peri-operative | | | | | |
|---|---|---|---|---|---|---|---|---|
| Trial Name | CheckMate 816 | | AEGEAN | | KEYNOTE-671 | | CheckMate 77T | |
| Arm | Nivo arm (n=179) | Chemo (n=179) | Durva arm (n=366) | Placebo arm (n=374) | Pembro arm (n=397) | Placebo arm (n=400) | Nivo arm (n=229) | Chemo (n=232) |
| EFS | NR | 21.1m | NR | 25.9m | 47.2m | 18.3m | NR | 18.4m |
| OS | NR | NR | Not reported | | NR | 52.4m | Not reported | |
| pCR | 24% | 2.2% | 17.2% | 4.3% | 18.1% | 4.0% | 25.3% | 4.7% |
| **PD-L1 status, %** | | | | | | | | |
| ≥50% | 21.2 | 23.5 | 29.8 | 28.6 | 32.2 | 33.5 | 20 | 22 |
| 1-49% | 28.5 | 26.3 | 36.9 | 38.0 | 32.0 | 28.8 | 36 | 33 |
| <1% | 43.6 | 43.0 | 33.3 | 33.4 | 34.8 | 37.8 | 41 | 40 |
| **OS, HR (95% CI)** | 3yr update | | | | | | | |
| ≥50% | Not reported | | Not reported | | 0.55 (0.33-0.92) | | Not reported | |
| 1-49% | Not reported | | | | 0.69 (0.44-1.07) | | | |
| <1% | 0.81 (0.48-1.36) | | | | 0.91 (0.63-1.32) | | | |
| ≥1% | 0.37 (0.20-0.71) | | | | | | | |
| **EFS, HR (95% CI)** | 3yr update | | | | | | | |
| ≥50% | 0.29 | | 0.60 (0.35-1.01) | | 0.48 (0.33-0.71) | | 0.26 (0.12-0.55) | |
| 1-49% | 0.63 | | 0.70 (0.46-1.05) | | 0.52 (0.36-0.73) | | 0.76 (0.46-1.25) | |
| <1% | 0.87(0.57-1.35) | | 0.76 (0.49-1.17) | | 0.75 (0.56-1.01) | | 0.73 (0.47-1.15) | |
| ≥1% | 0.46(0.28-0.77) | | | | | | 0.52 (0.35-0.78) | |
| **pCR, Diff. (95% CI)** | 3yr update | | | | | | | |
| ≥50% | 40.0 (21.7-55.9) | | 22.9 (13.7-32.5) | | Not reported | | 45.3 (28.1-59.8) | |
| 1-49% | 23.5 (11.4-36.8) | | 11.4 (4.3-19.1) | | | | 22.6 (11.7-33.3) | |
| <1% | 14.1 (4.8-24.0) | | 5.8 (-0.2-12.7) | | | | 8.6 (0.4-17.3) | |
| ≥1% | 30.3 (19.9-40.7) | | | | | | 30.5 (21.2-39.4) | |

1. Forde PM, et al. N Engl J Med 2022;386:1973–85; 2. Heymach J et al. Oral presentation at AACR 2023 (Abstract CT005); 3. Wakelee HA, et al. Oral presentation at ASCO 2023 (Abstract LBA100); 4. Cascone T, et al. Oral presentation at ESMO 2023 (Abstract LBA1)

# Efficacy Regarding Stage & Histology

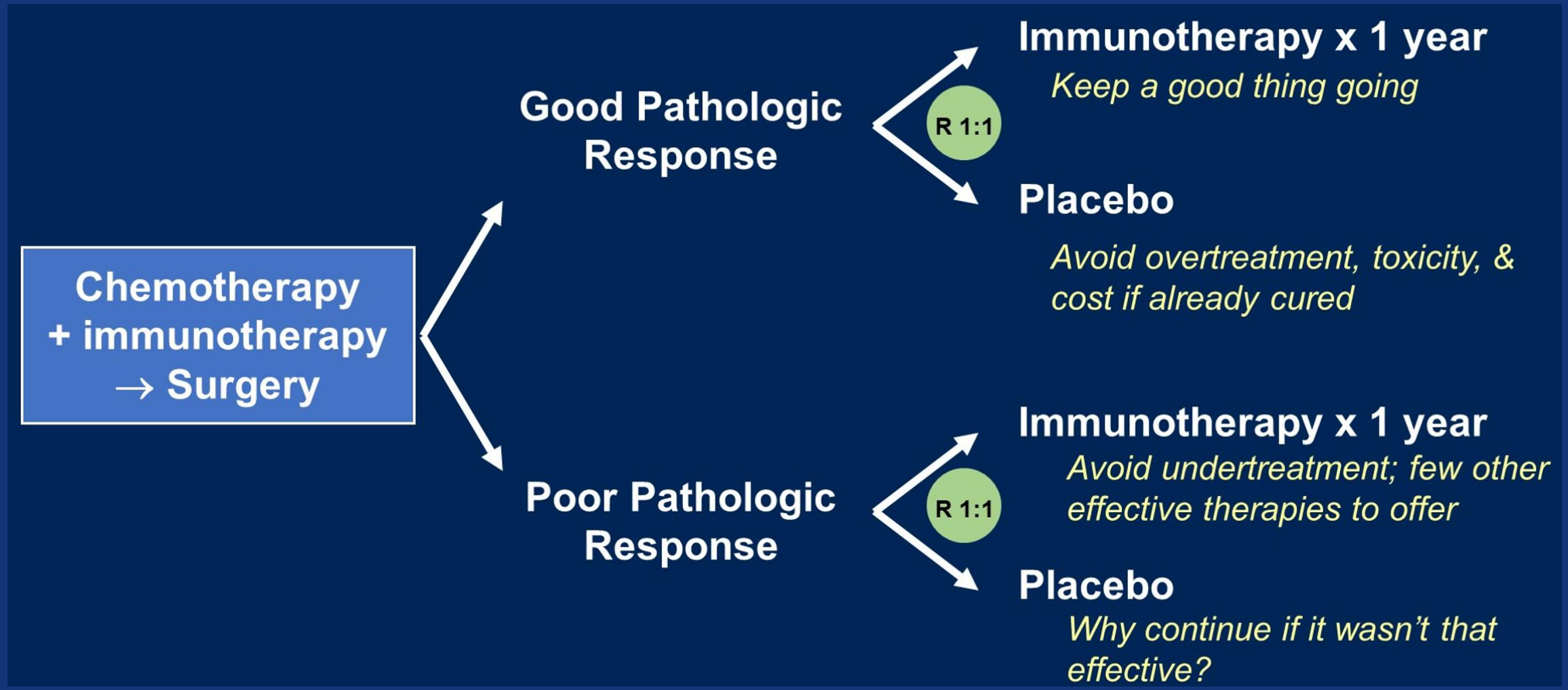
| | Neoadjuvant | | Peri-operative | | | | | |
|---|---|---|---|---|---|---|---|---|
| Trial Name | CheckMate 816 | | AEGEAN | | KEYNOTE-671 | | CheckMate 77T | |
| Arm | Nivo arm (n=179) | Chemo (n=179) | Durva arm (n=366) | Placebo arm (n=374) | Pembro arm (n=397) | Placebo arm (n=400) | Nivo arm (n=229) | Chemo (n=232) |
| **OS, HR (95% CI)**<br>Stage II<br>Stage IIIA<br>Stage IIIB | Not reported | | Not reported | | 0.67 (0.41-1.10)<br>0.74 (0.53-1.03)<br>0.69 (0.39-1.22) | | Not reported | |
| **EFS, HR (95% CI)**<br>Stage II<br>Stage IIIA<br>Stage IIIB | 3yr update<br>0.94 *Stage IB-II<br>0.57 *Stage III | | 0.76 (0.43-1.34)<br>0.57 (0.39-0.83)<br>0.83 (0.52-1.32) | | 0.59 (0.40-0.88)<br>0.57 (0.44-0.74)<br>0.57 (0.36-0.90) | | 0.81 (0.46-1.43) *Stage II<br>0.51 (0.36-0.72) *Stage III | |
| **pCR, Diff. (95% CI)**<br>Stage II<br>Stage IIIA<br>Stage IIIB | Initial analysis<br>21 *Stage IB-II<br>22 *Stage III | | 16.6 (8.1-26.0)<br>13.6 (7.1-20.7)<br>7.2 (0.1-15.7) | | Not reported | | 25.9 (14.9-36.9) *Stage II<br>17.7 (10.0-25.5) *Stage III | |
| **OS, HR (95% CI)**<br>Squamous<br>Nonsquamous | Not reported | | Not reported | | 0.71 (0.51-0.99)<br>0.73 (0.50-1.06) | | Not reported | |
| **EFS, HR (95% CI)**<br>Squamous<br>Nonsquamous | 3yr update<br>0.82<br>0.52 | | 0.71 (0.49-1.03)<br>0.69 (0.48-0.99) | | 0.51 (0.38-0.69)<br>0.66 (0.51-0.86) | | 0.46 (0.30-0.72)<br>0.72 (0.49-1.07) | |
| **pCR, Diff. (95% CI)**<br>Squamous<br>Nonsquamous | Initial analysis<br>21<br>23 | | 16.1 (9.3-23.4)<br>9.9 (4.6-15.8) | | Not reported | | 22.5 (13.1-31.8)<br>18.6 (10.2-27.4) | |



1. Forde PM, et al. N Engl J Med 2022;386:1973–85; 2. Heymach J et al. Oral presentation at AACR 2023 (Abstract CT005); 3. Wakelee HA, et al. Oral presentation at ASCO 2023 (Abstract LBA100); 4. Cascone T, et al. Oral presentation at ESMO 2023 (Abstract LBA1)

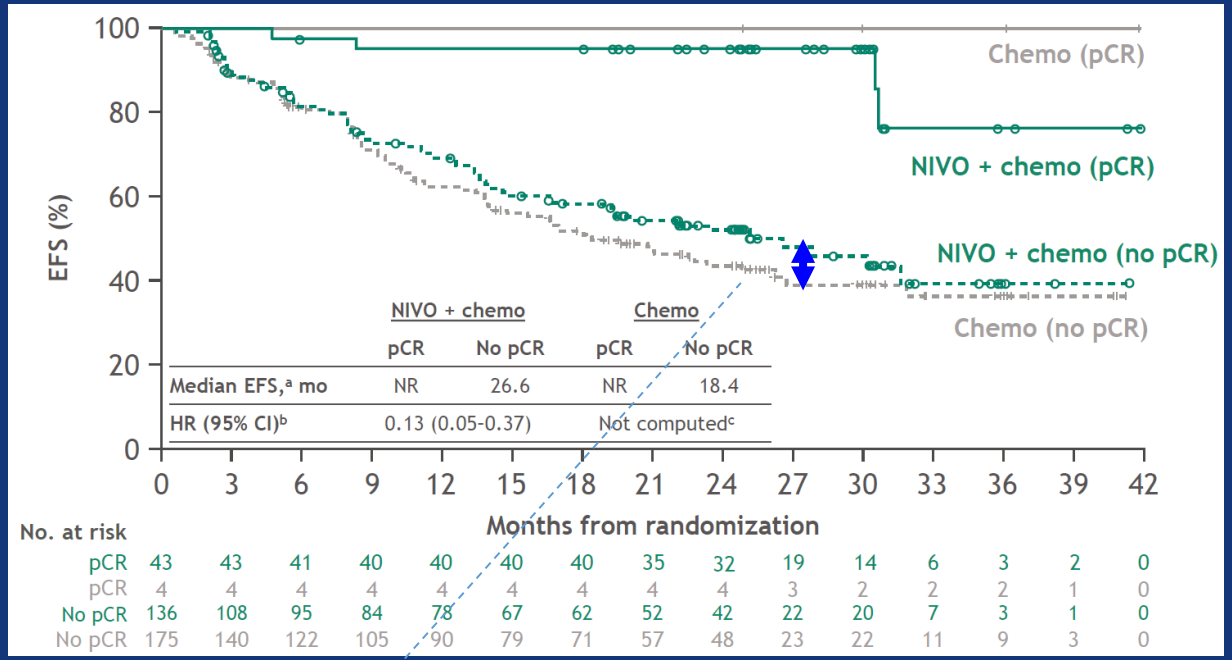
# Q1. Neoadjuvant only versus perioperative (neo+adjuvant) IO?

Role of adjuvant IO after neoadjuvant IO?
Do we need adjuvant IO after neoadjuvant IO + CTx?



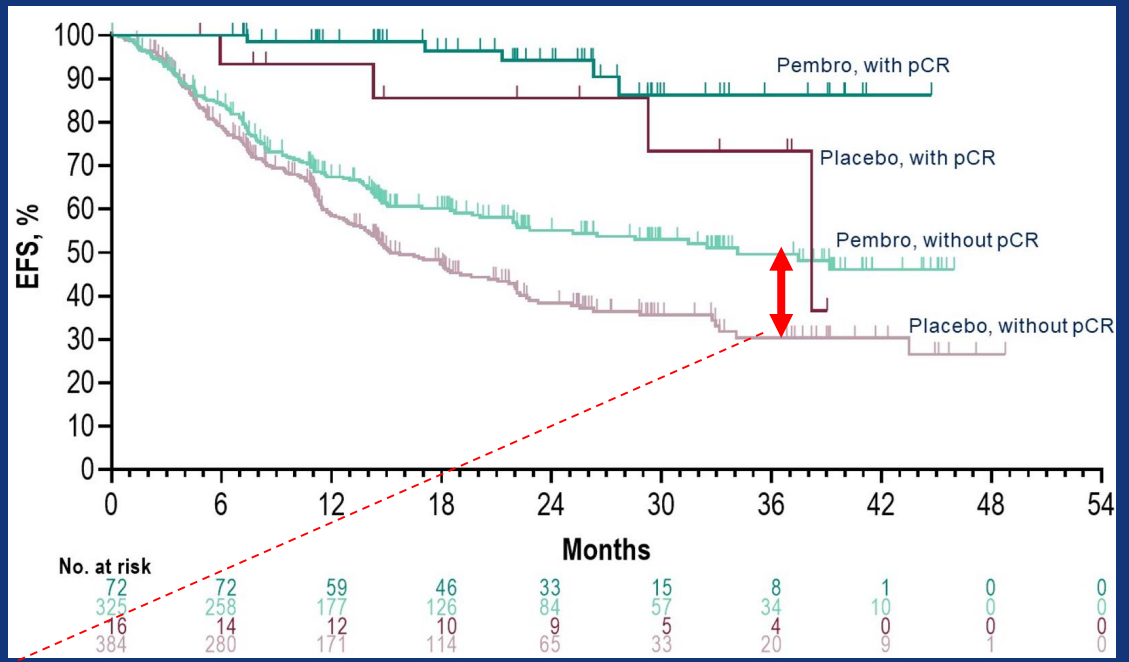
# Q1. Do we need adjuvant IO after neoadjuvant IO+CTx then surgery?

## Checkmate-816 (neo-IO+CTx +S)




| | NIVO + chemo | | Chemo | |
|---|---|---|---|---|
| | pCR | No pCR | pCR | No pCR |
| Median EFS,[a] mo | NR | 26.6 | NR | 18.4 |
| HR (95% CI)[b] | 0.13 (0.05-0.37) | | Not computed[c] | |

## Keynote-617 (neo-IO+CTx +S + adj IO)




-No separation of EFS curves of pts without pCR in CM-816 (neoadj. only)

-Prominent separation of EFS curves of pts without pCR in KN-617 (neoadj + adj.)

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Lancet 2021;398:1344-57. Lancet Oncol 2022;23:1274-86.N Engl J Med 2022;386:1973-85., N Engl J Med. 2023 Nov 2;389(18):1672-1684.N Engl J Med. 2023 Aug 10;389(6):491-503..

# Neoadjuvant VS Perioperative: Checkmate-816 vs Checkmate-77T

| | Neoadjuvant | Perioperative |
|---|---|---|
| Study | Checkmate-816 | CheckMate 77T |
| Regimen | chemoIOx3 | chemoIOx4 --> IOx12 (4wks) |
| Duration | 5개월 | 14개월 |
| Phase | III (open-labelled) | III (double-blinded) |
| No. | 358 | 461 |
| Asian | 47.5% | 24.9% |
| cStage | IB-IIIA (7th); IIIA (63.1%) | II-IIIA, IIIB (N2) (8th); III (64%) |
| SQCC | 50.80% | 51% |
| PDL1 ≥50% | 22.30% | 21% |
| Median EFS | 31.6 vs. 20.8 months | NR vs. 18.4 months |
| Hazard ratio | 0.63 (95% CI, 0.43-0.91) | 0.58 (95% CI, 0.42-0.81) |
| pCR | 24.0% vs. 2.2% | 25.3% vs. 4.7% |
| stage II | NR vs. NR; 0.87 (0.48-1.56) | NR vs. NR; 0.81 (0.46-1.43) |
| stage III | 31.6 vs. 15.7; 0.54 (0.37-0.80) | 31.2 vs. 13.4; 0.51 (0.36-0.72) |
| SQCC | 30.6 vs. 22.7; 0.77 (0.49-1.22) | NR vs. 17.0: 0.46 (0.30-0.72) |
| nonSQCC | NR vs. 19.6; 0.50 (0.32-0.79) | 28.9 vs. 18.4; 0.72 (0.49-1.07) |
| PDL1 <1% | 25.1 vs. 18.4; 0.85 (0.54-1.32) | 29.0 vs. 19.8; 0.73 (0.47-1.15) |
| PDL1 ≥1% | NR vs. 21.1; 0.41 (0.24-0.70) | NR vs. 15.8; 0.52 (0.35-0.78) |
| PDL1 ≥50% | NR vs. 19.6; 0.24 (0.10-0.61) | NR vs. 8.0; 0.26 (0.12-0.55) |
| Asia | NR vs. 16.5; 0.45 (0.29-0.71) | NR vs. 13.9; 0.47 (0.26-0.86) |

| | | Neoadjuvant | Peri-operative |
|---|---|---|---|
| Trial Name | | CheckMate 816 | CheckMate 77T |
| Response | pCR | 24.0% | 25.3% |
| | MPR | 36.9% | 35.4% |
| EFS | EFS/DFS | NR (HR=0.68): ITT | NR (HR=0.58): ITT |
| | EFS HR with pCR pts | - | 0.33 (0.08-1.37): ITT |
| | EFS HR without pCR pts | 0.89 (0.64-1.22) | 0.79 (0.58-1.06): ITT |
| | EFS HR with MPR pts | - | 0.40 (0.16-0.99) |
| | EFS HR without MPR pts | - | 0.85 (0.62-1.15) |
| OS | OS | NR (HR=0.62) | - |
| | OS HR without pCR pts | 0.77 (0.52-1.14) | - |
| Received Surgery | | 85% | 78% |
| R0 resection rate | | 83% | 89% |

# Adjuvant VS Perioperative
# Totally different group

| STUDY | PD-L1 ≥50% | PD-L1 1-49% | PD-L1 ≤1% | ALL |
|---|---|---|---|---|
| CheckMate 816[1] HR for EFS | 0.29 | 0.63 | 0.87 | 0.68 |
| AEGEAN[2] HR for EFS | 0.60 | 0.70 | 0.76 | 0.68 |
| KN671[3] HR for EFS | 0.42 | 0.51 | 0.59 | 0.58 |
| NEOTORCH[4] HR for EFS | 0.31 | 0.31 | 0.59 | 0.50 |
| CheckMate 77T[5] HR for EFS | 0.26 | 0.76 | 0.73 | 0.58 |
| PEARLS[6] HR for DFS | 0.82???? | 0.67 | 0.78 | 0.76 |
| IMpower 010[7] HR for DFS | 0.43 | 0.87 | 0.97 | 0.79 |

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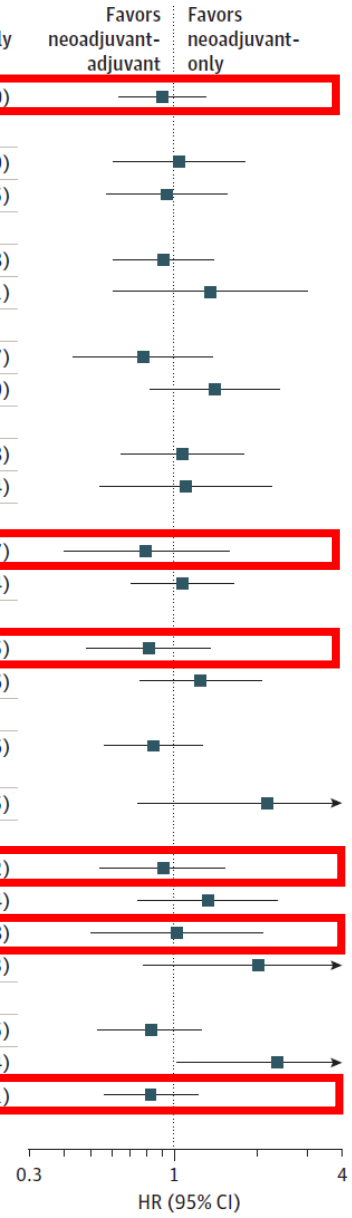
1. Forde PM, et al. Abstract 84O. Presented at the European Lung Cancer Congress 2023, 29 March-1 April 2023, Copenhagen, Denmark.; 2. Heymach J, et al. Abstract CT005. Presented at the American Association for Cancer Research Annual Meeting, 14-19 April 2023, Orlando, FL, United States.; 3. Wakelee H, et al. Abstract LBA100. Presented at the American Society of Clinical Oncology Annual Meeting, 2-6 June 2023, Chicago, IL, United States; 4. Lu S, et al. Abstract 425126. Presented at the American Society of Clinical Oncology Plenary Series, 20 April 2023.; 5. Cascone T, et al. Abstract LBA1. Presented at the European Society for Medical Oncology Congress, 20-24 October 2023, Madrid, Spain.; 6. O'Brien M, et al. Lancet Oncol. 2022;23(10):1274-1286.; 7. Felip E, et al. Presented at the World Conference on Lung Cancer, 6-9 August 2022, Vienna, Austria.

# Meta-analysis of 5 major trials

| Trial name | Adjuvant immunotherapy duration, y | Stage[a] | Primary end point |
|---|---|---|---|
| CheckMate 816,[5] 2022 | Neoadjuvant only | II-III[b] | EFS and pCR |
| KEYNOTE-671,[15] 2023 | 1 | II-III | EFS and OS |
| Neotorch,[16] 2023 | 1 | II-III | EFS and MPR |
| AEGEAN,[17] 2023 | 1 | II-III | EFS and pCR |
| NADIM II,[18] 2023 | 0.5 | III | pCR |

| Subgroup | Patients, No. | | Direct meta-analysis | | Indirect meta-analysis, HR for neoadjuvant-adjuvant vs neoadjuvant-only (95% CI) | *P* value | *P* value for interaction |
|---|---|---|---|---|---|---|---|
| | Neoadjuvant-adjuvant treatment | Neoadjuvant-only treatment | HR for neoadjuvant-adjuvant vs control (95% CI) | HR for neoadjuvant-only vs control (95% CI) | | | |
| Overall | 2027 | 358 | 0.57 (0.49-0.66) | 0.63 (0.45-0.87) | 0.90 (0.63-1.30) | .59 | |
| Age, y | | | | | | | |
| <65 | 793 | 176 | 0.59 (0.46-0.75) | 0.57 (0.35-0.93) | 1.04 (0.60-1.79) | .90 | .79 |
| ≥65 | 744 | 182 | 0.66 (0.52-0.84) | 0.70 (0.45-1.08) | 0.94 (0.57-1.55) | .82 | |
| Sex | | | | | | | |
| Male | 1093 | 255 | 0.62 (0.51-0.75) | 0.68 (0.47-0.98) | 0.91 (0.60-1.38) | .66 | .34 |
| Female | 444 | 103 | 0.62 (0.45-0.86) | 0.46 (0.22-0.96) | 1.35 (0.60-3.01) | .47 | |
| Region | | | | | | | |
| Non-Asia | 986 | 157 | 0.61 (0.50-0.75) | 0.79 (0.46-1.35) | 0.77 (0.43-1.37) | .38 | .14 |
| Asia | 551 | 177 | 0.63 (0.47-0.84) | 0.45 (0.29-0.71) | 1.40 (0.82-2.39) | .22 | |
| ECOG PS | | | | | | | |
| 0 | 506 | 241 | 0.65 (0.47-0.89) | 0.61 (0.41-0.91) | 1.07 (0.64-1.78) | .81 | .95 |
| 1 | 234 | 117 | 0.78 (0.49-1.23) | 0.71 (0.41-1.21) | 1.10 (0.54-2.24) | .80 | |
| Disease stage | | | | | | | |
| II | 453 | 127 | 0.69 (0.49-0.98) | 0.87 (0.48-1.56) | 0.79 (0.40-1.57) | .51 | .46 |
| III | 1572 | 228 | 0.58 (0.48-0.69) | 0.54 (0.37-0.80) | 1.07 (0.70-1.64) | .74 | |
| Histologic characteristics | | | | | | | |
| Squamous | 704 | 182 | 0.62 (0.49-0.79) | 0.77 (0.49-1.22) | 0.81 (0.48-1.35) | .41 | .25 |
| Nonsquamous | 828 | 176 | 0.62 (0.49-0.78) | 0.50 (0.32-0.79) | 1.24 (0.75-2.06) | .41 | |
| Smoking status | | | | | | | |
| Current or former smoker | 1329 | 318 | 0.57 (0.46-0.70) | 0.68 (0.48-0.96) | 0.84 (0.56-1.26) | .39 | .11 |
| Never smoked | 208 | 39 | 0.71 (0.44-1.16) | 0.33 (0.13-0.87) | 2.15 (0.74-6.25) | .16 | |
| PD-L1 expression, % | | | | | | | |
| <1 | 536 | 155 | 0.77 (0.59-0.99) | 0.85 (0.54-1.32) | 0.91 (0.54-1.52) | .71 | .50 |
| ≥1 | 1001 | 178 | 0.54 (0.44-0.67) | 0.41 (0.24-0.70) | 1.32 (0.74-2.34) | .35 | |
| 1-49 | 519 | 98 | 0.59 (0.45-0.79) | 0.58 (0.30-1.12) | 1.02 (0.50-2.08) | .96 | |
| ≥50 | 482 | 80 | 0.48 (0.35-0.67) | 0.24 (0.10-0.61) | 2.00 (0.77-5.23) | .16 | |
| Type of platinum | | | | | | | |
| Cisplatin | 993 | 258 | 0.58 (0.47-0.71) | 0.71 (0.49-1.03) | 0.82 (0.53-1.25) | .35 | .03 |
| Carboplatin | 544 | 72 | 0.73 (0.54-0.98) | 0.31 (0.14-0.67) | 2.35 (1.02-5.44) | .045 | |
| Without pCR | 633 | 311 | 0.69 (0.56-0.86) | 0.84 (0.61-1.17) | 0.82 (0.56-1.21) | .32 | |

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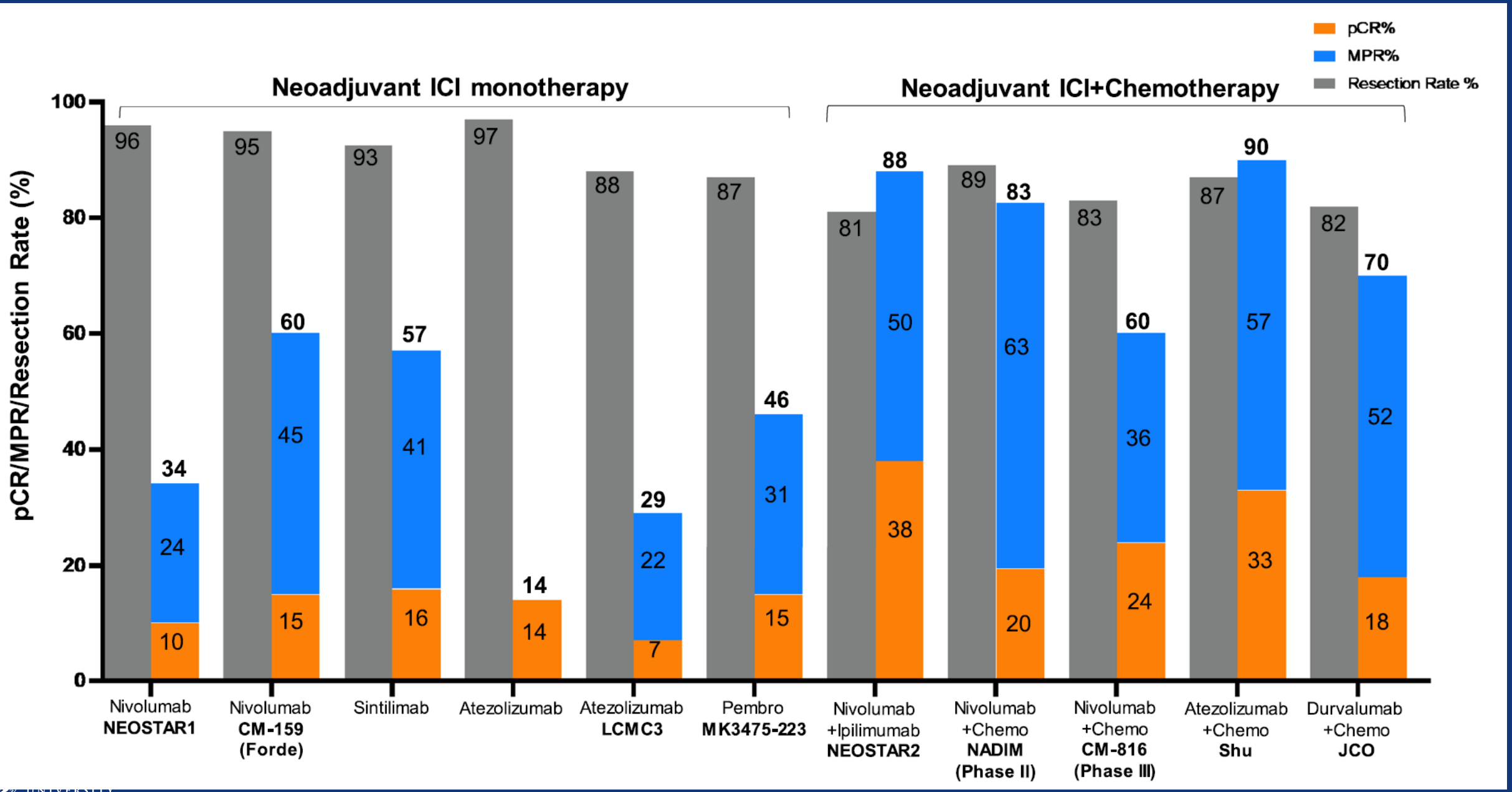
JAMA Netw Open. 2024 Mar 4;7(3):e241285.

# Q2. Neoadjuvant IO alone?




Biomark Res. 2023 Jan 18;11(1):7. doi: 10.1186/s40364-022-00444-7.

# Q3. Role of PD-L1?

| EFS | CM-816 | AEGEAN | KN-671 | CM-77T |
|---|---|---|---|---|
| **PD-L1** | | | | |
| **≥ 50%** | HR 0.24 (0.10-0.61) | HR 0.60 (0.35-1.01) | HR 0.48 (0.33-0.71) | HR 0.26 (0.12-0.55) |
| **1 - 49%** | HR 0.58 (0.30-1.12) | HR 0.70 (0.46-1.05) | HR 0.52 (0.36-0.73) | HR 0.76 (0.46-1.25) |
| **< 1%** | HR 0.85 (0.54-1.32) | HR 0.76 (0.49-1.17) | HR 0.75 (0.56-1.01) | HR 0.73 (0.47-1.15) |

Trend of better survival in higher PD-L1 expression!

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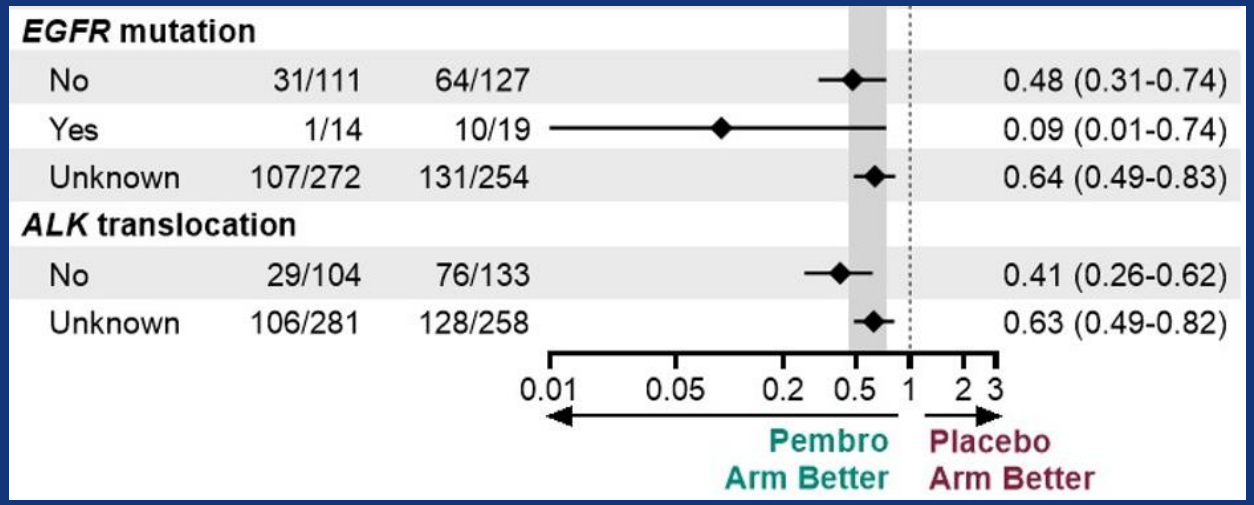
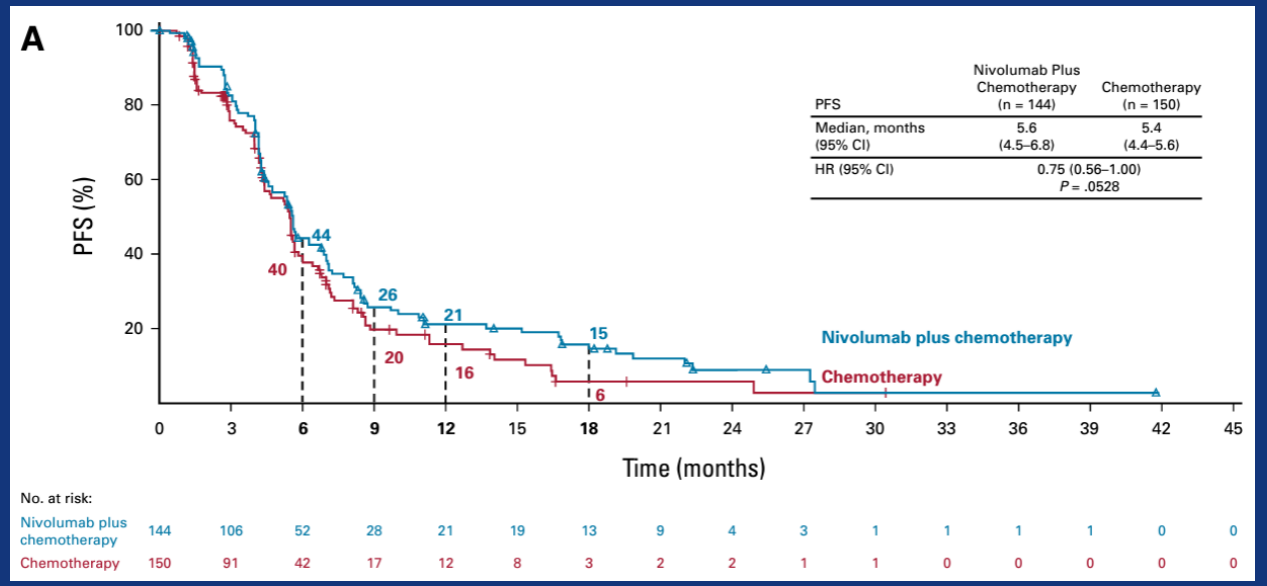
The data presented here is for updated scientific information exchange. MSD does not encourage any off-label prescription. Please prescribe the drug or medicine based on your country's prescribing information. This table is not intended for direct trial comparison; it is only for educational purposes. In the absence of head-to-head trials, cross-trial comparison cannot be made as trials differ in design, size, time period of recruitment, location of study sites, etc.

Lancet 2021;398:1344-57. Lancet Oncol 2022;23:1274-86.N Engl J Med 2022;386:1973-85., N Engl J Med. 2023 Nov 2;389(18):1672-1684.N Engl J Med. 2023 Aug 10;389(6):491-503..

# Q4. In patients with AGA such as EGFR+ or ALK+?

- Only Keynote-671 permitted these subgroup.




Number of EGFR/ALK+ is small.

Checkmate-722 of platinum + pemetrexed +- nivolumab after progression on EGFR-TKI did not meet endpoint.

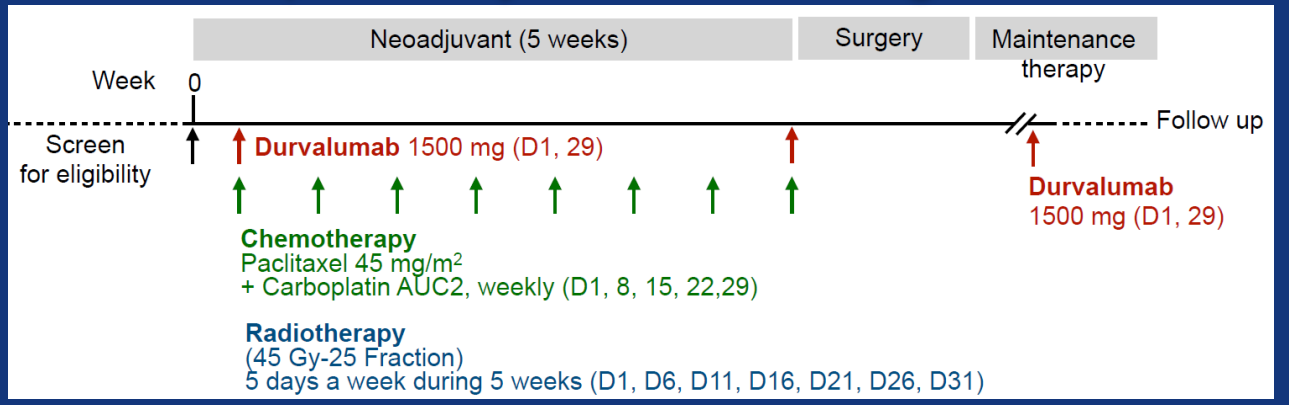


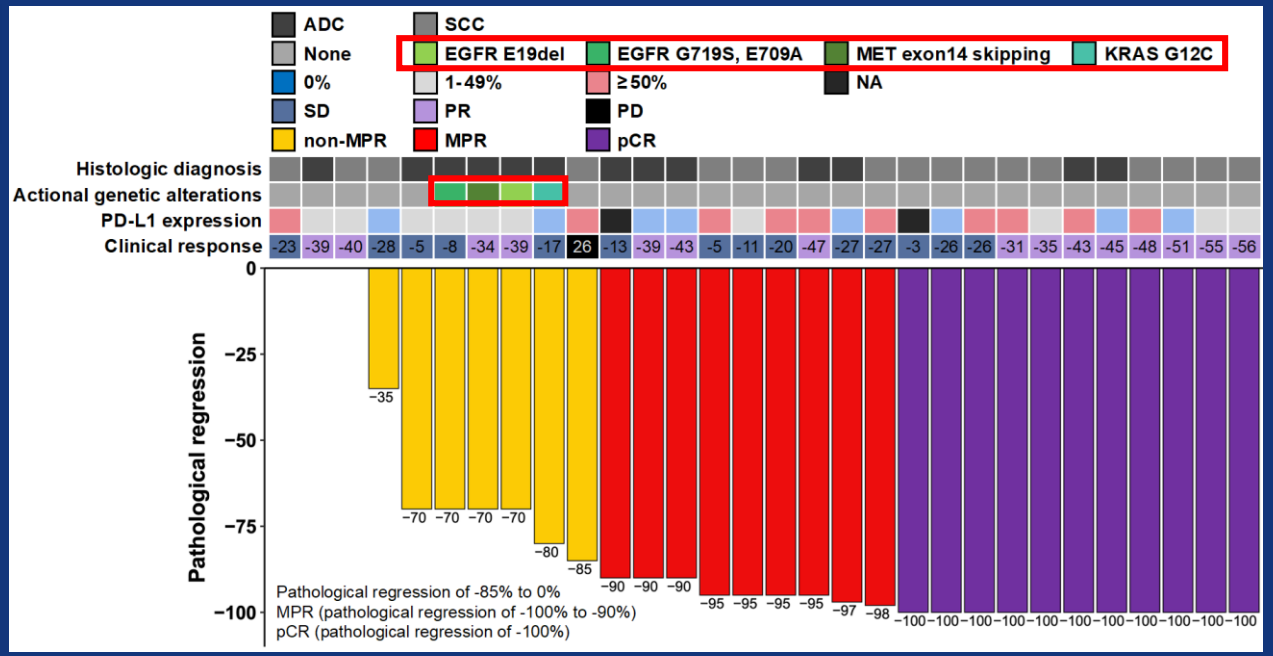
N Engl J Med. 2023 Aug 10;389(6):491-503, J Clin Oncol. 2024 Jan 22:JCO2301017.

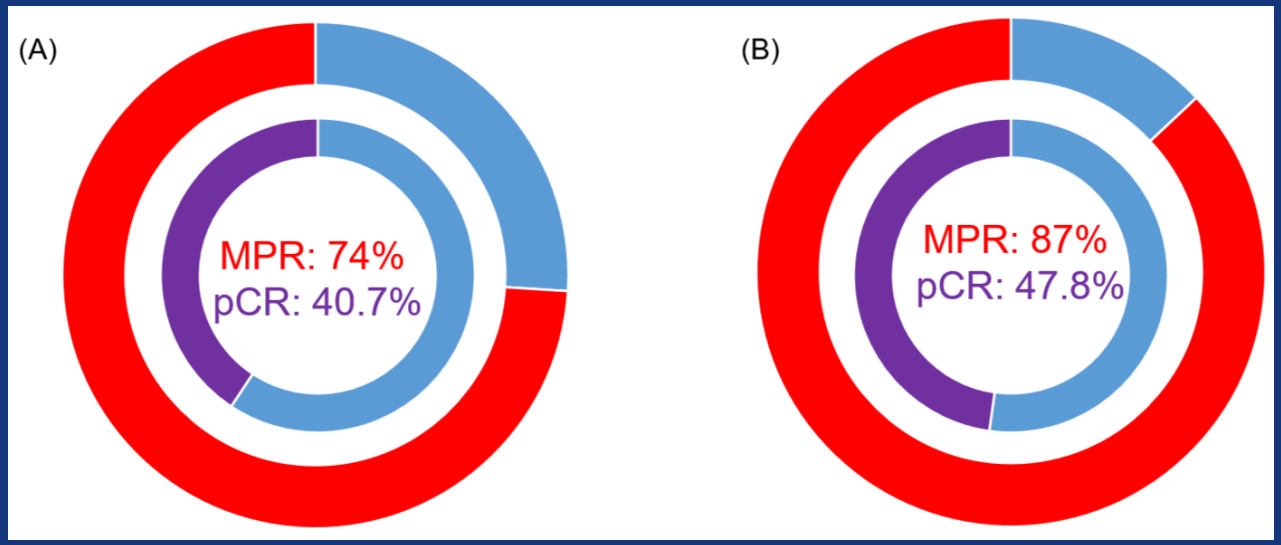
# Q5. What about adding radiation?

## Neoadjuvant IO+CTx + S followed by adjuvant IO trial – (NCT03694236)

### Inclusion: potentially resectable cStage III NSCLC




(A) All resected patients (n=27),
(B) Without actionable mutation (n=23)

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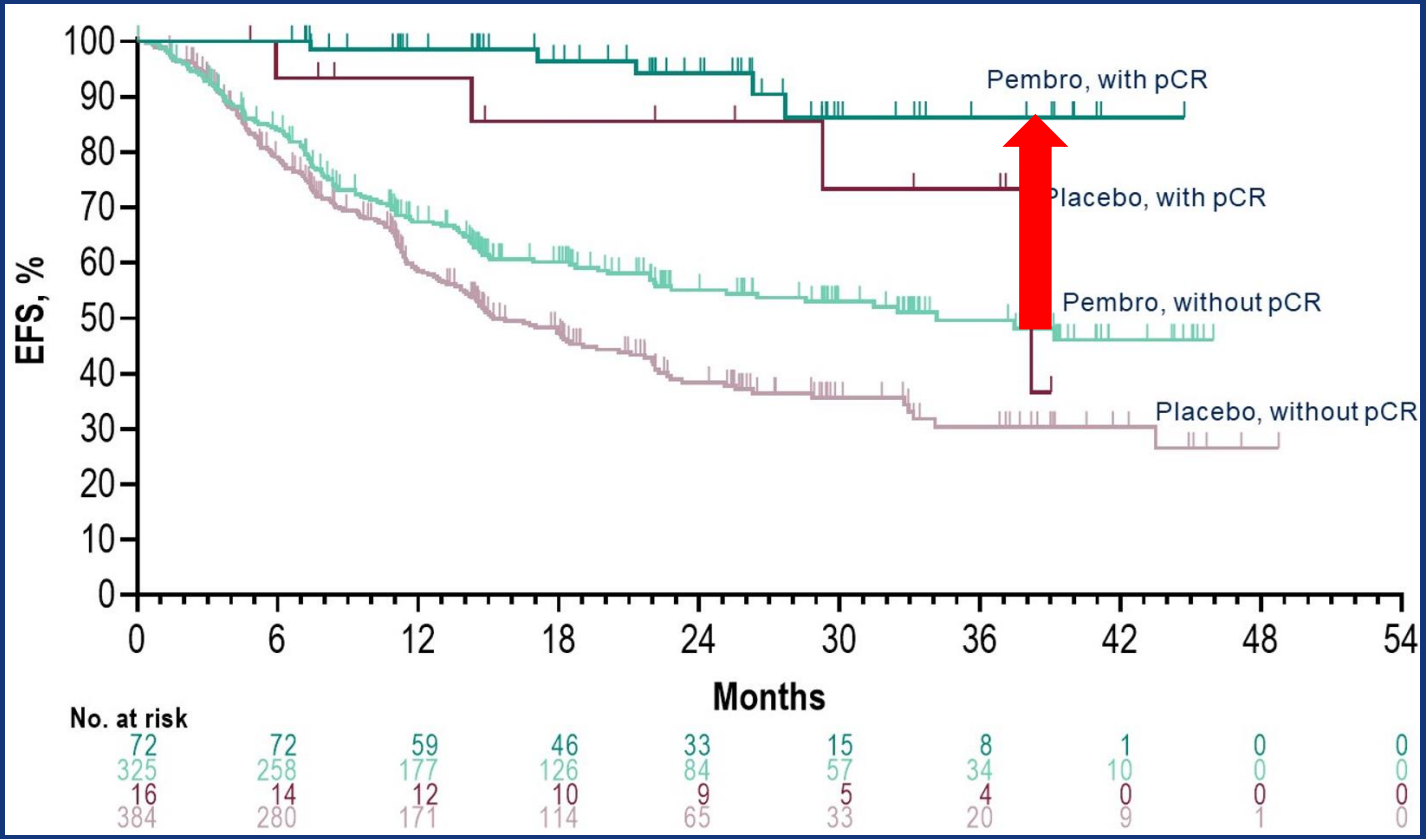
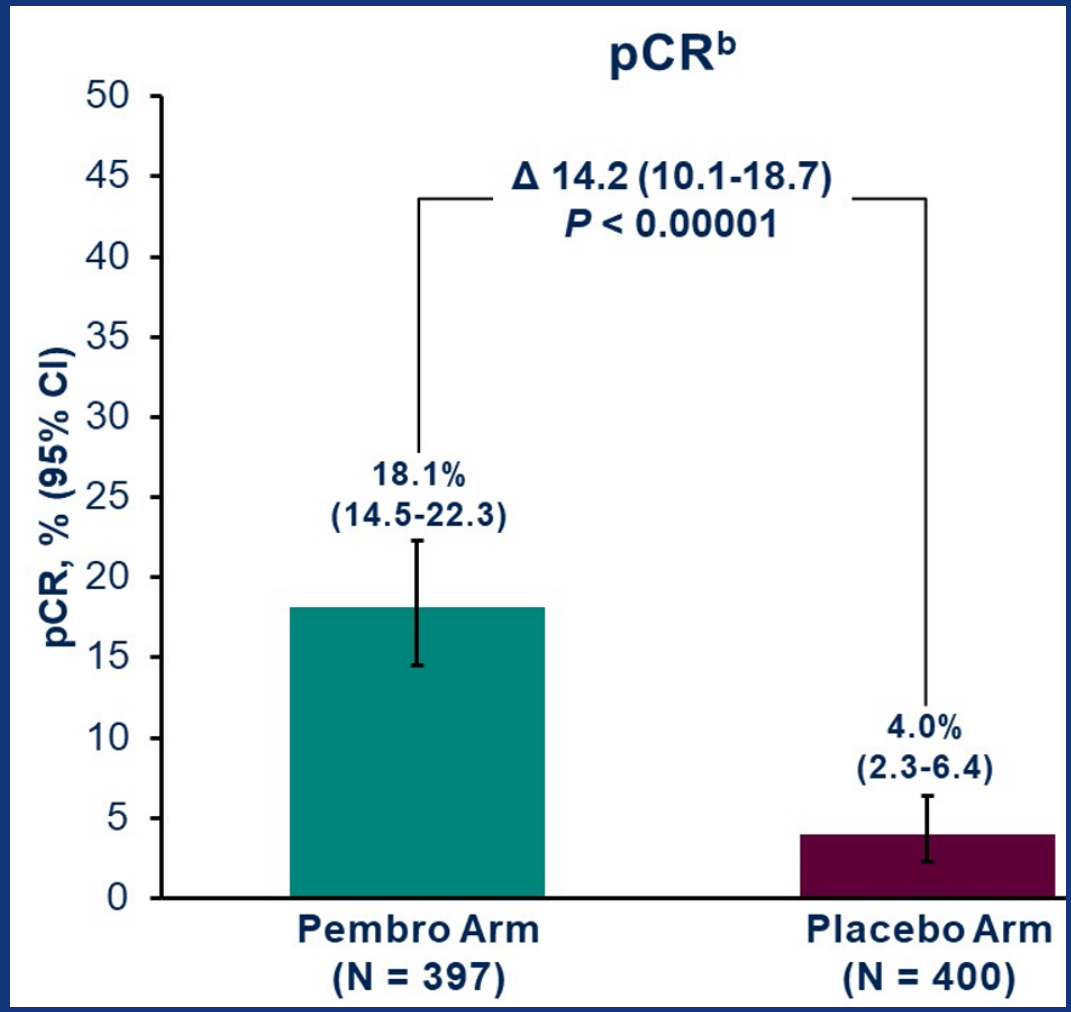
# Future direction

## Keynote-671 (neo-IO+CTx +S + adj IO)






N Engl J Med. 2023 Aug 10;389(6):491-503.

# Summary

- The standard of care in patients with early-stage NSCLC had been surgery followed by adjuvant chemotherapy despite modest improvements in survival and high rates of disease recurrence.
- Recently, perioperative IO combined with chemotherapy has demonstrated high pathologic response rate, survival benefit with good tolerability profile in large phase III randomized clinical trials, and has become **a standard of care**.
- Like the outcome in metastatic NSCLC trials, patients with high PD-L1 benefit in neoadjuvant IO trials.
- Neoadjuvant IO+ chemotherapy seems to result in better survival benefit than adjuvant IO monotherapy.
- While the benefit of adding adjuvant IO after completion of neoadjuvant IO + chemotherapy is not definite, it appears that there may be an advantage for subgroup of non-pCR, squamous cell histology, low PD-L1 expression, and stage II disease.
- Neoadjuvant IO is promising strategy. However, considering pCR rate of approximately 20%, there is still a long way to go.


Severance
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