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# Impact of the Timing of Immune Checkpoint Inhibitor Initiation in Neoadjuvant Therapy

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# AI Use Disclosure

- No generative AI tools were used in the preparation of this poster.



# Background and Objective

- In the CheckMate 816 trial, neoadjuvant therapy with an immune checkpoint inhibitor (ICI) and chemotherapy was shown to improve patient outcomes compared with neoadjuvant chemotherapy alone for the patients with resectable NSCLC.

*N Engl J Med. 2022;386:1973–1985.*

- Although based on a retrospective study, the timing of ICI initiation in combination with chemotherapy for metastatic NSCLC has been reported to potentially affect treatment efficacy, with better clinical outcomes observed in patients receiving treatment earlier in the day.

*EBioMedicine. 2025 Mar;113:105607.*

- This study aimed to evaluate the association between ICI initiation time and pathological response and long-term outcomes in patients with NSCLC receiving neoadjuvant therapy.





# Patient Flowchart

## All cases (n = 59)

- In 2018-2026, NSCLC patients who received at least one course of neoadjuvant ICIs therapy were included.



## Cases for analysis (n = 46)

- Patients who were still receiving neoadjuvant therapy were excluded.



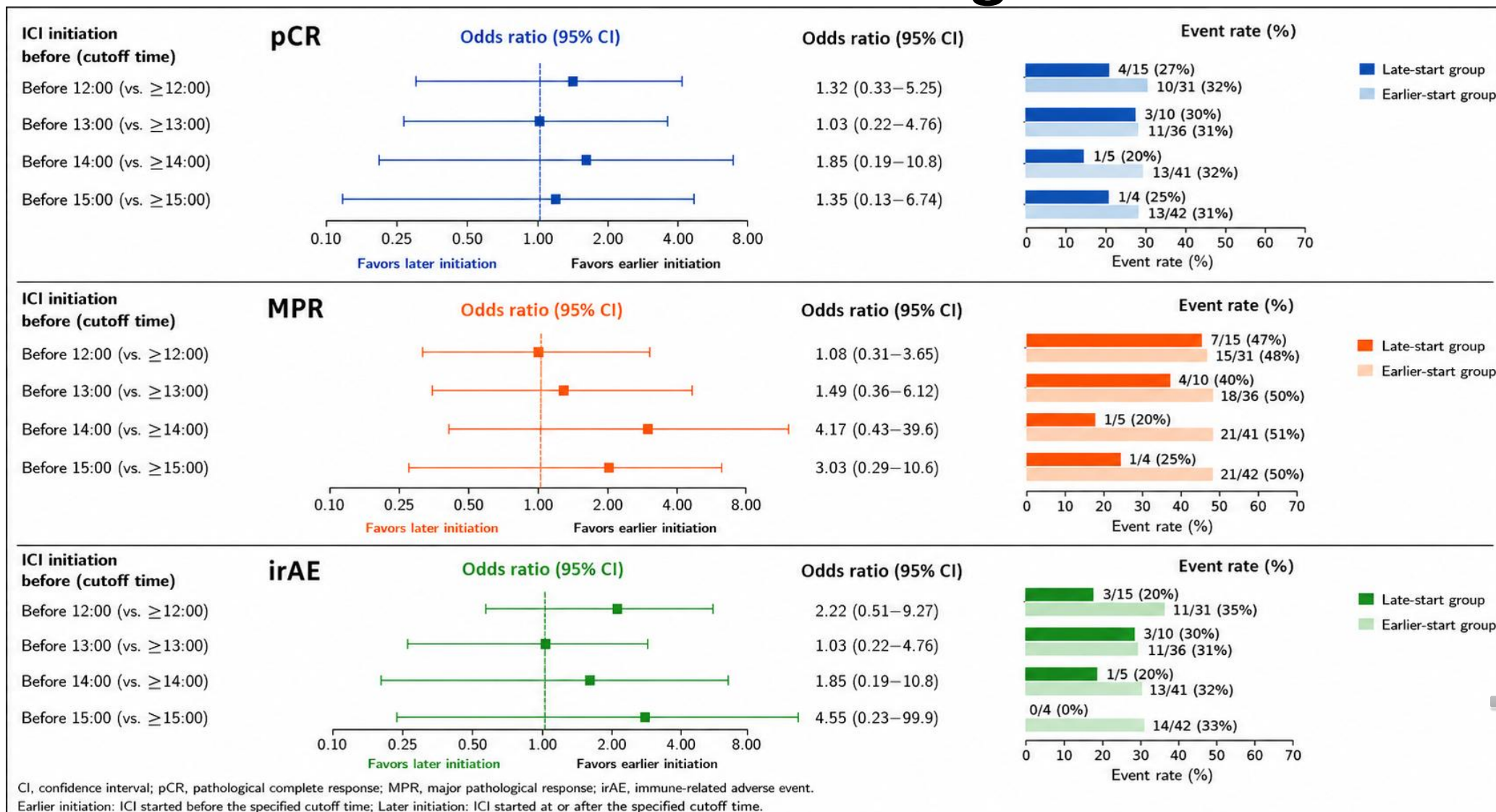
# Patient Characteristics

| Characteristic                 | All (n=46) |
|--------------------------------|------------|
| Age                            |            |
| median (IQR) -- yr             | 71 (62-77) |
| Sex -- n. (%)                  |            |
| male                           | 36 (78)    |
| Smoking -- n. (%)              |            |
| yes                            | 44 (96)    |
| Performance status             |            |
| 1                              | 10 (22)    |
| Clinical stage -- n. (%)       |            |
| III                            | 35 (76)    |
| Histology-- n. (%)             |            |
| SQ                             | 23 (50)    |
| PD-L1 status -- n. (%)         |            |
| <1%                            | 8 (17)     |
| 1-49%                          | 14 (30)    |
| ≥50%                           | 17 (37)    |
| Unknown                        | 7 (15)     |
| Driver gene mutation -- n. (%) |            |
| yes                            | 16 (35)    |
| Surgical procedure -- n. (%)   |            |
| Lobectomy                      | 28 (61)    |
| Segmentectomy                  | 13 (28)    |
| Exploratory thoracotomy        | 1 (2)      |
| Cancelled definitive surgery   | 4 (9)      |

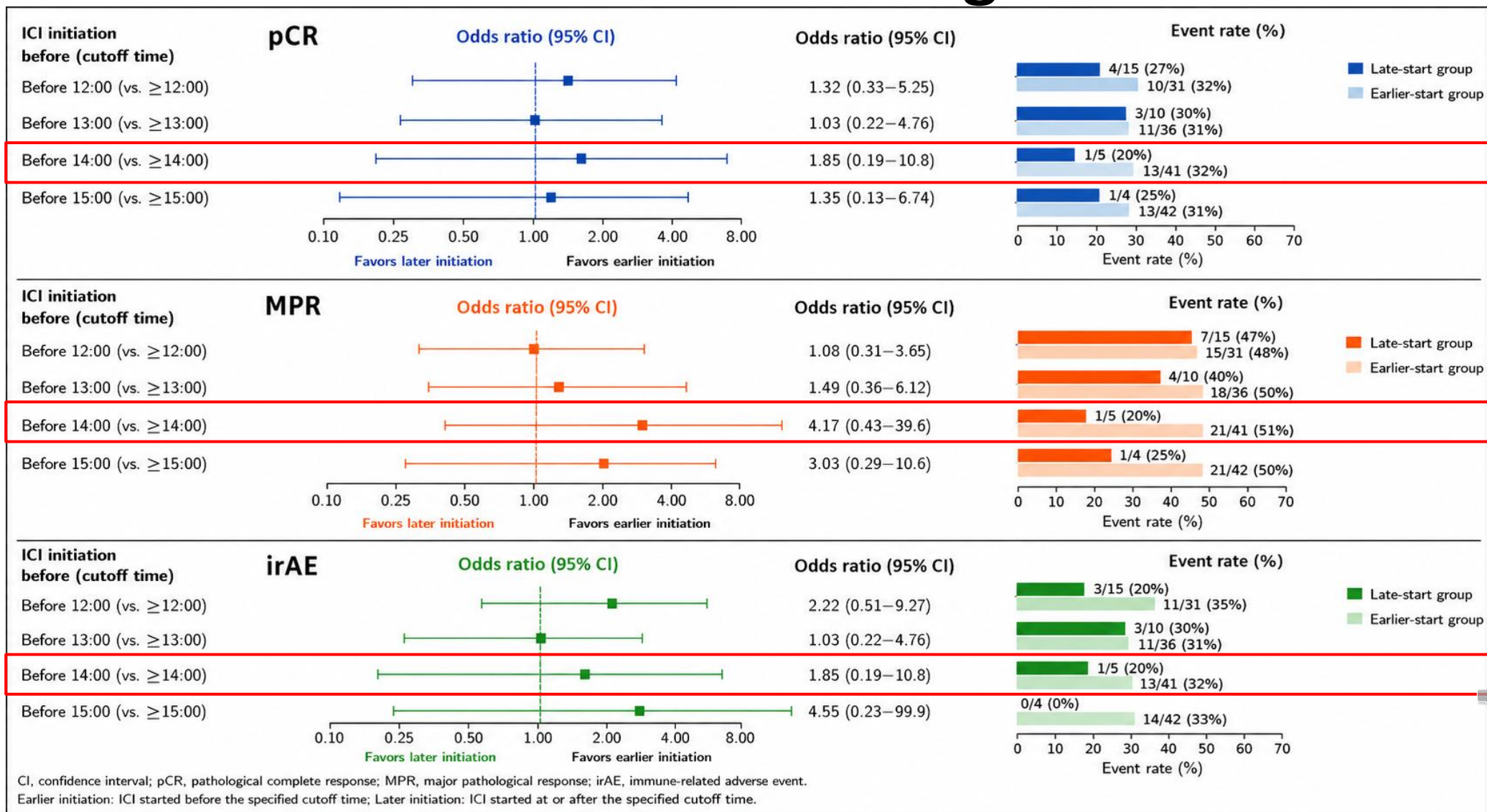
| n=46 | n. (%)  |
|------|---------|
| pCR  | 14 (30) |
| MPR  | 22 (48) |
| irAE | 14 (30) |



# Effect of ICI Initiation Time on Pathological Outcomes



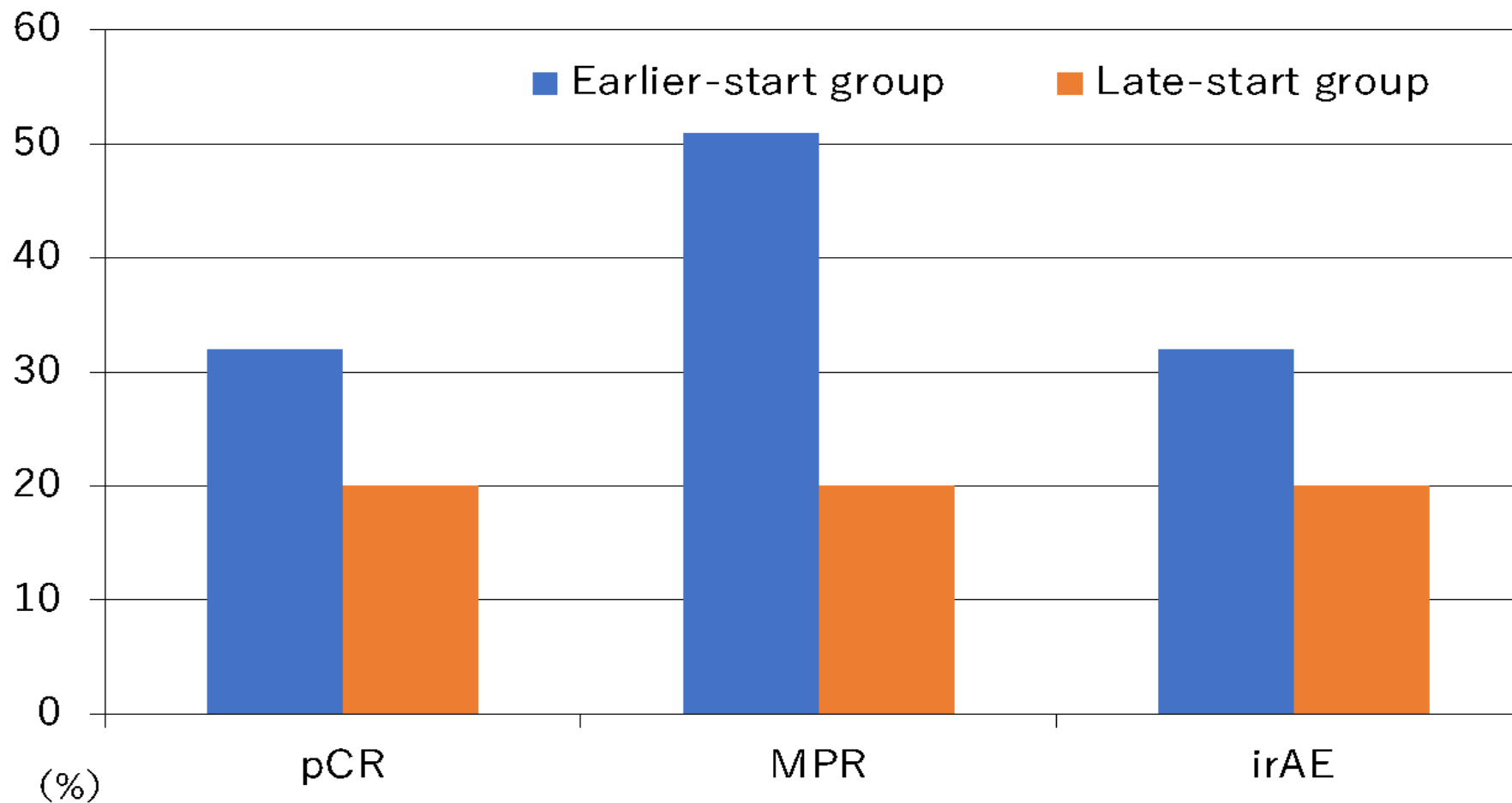
# Effect of ICI Initiation Time on Pathological Outcomes



# Patient Characteristics

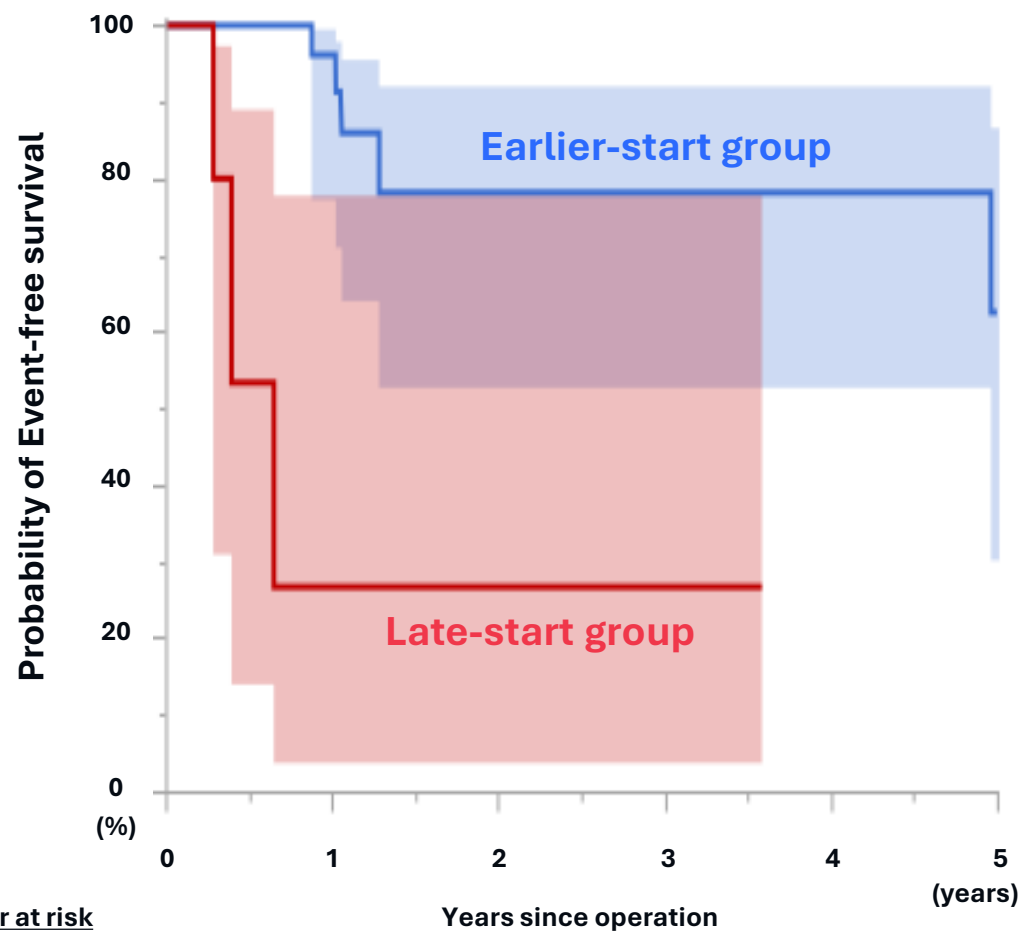
| Characteristic                        | Late-start group<br>(n=5) | Earlier-start group<br>(n=41) | p value |
|---------------------------------------|---------------------------|-------------------------------|---------|
| <b>Age</b>                            |                           |                               |         |
| median (IQR) -- yr                    | 70 (56-82)                | 71 (63-77)                    | 0.900   |
| <b>Sex -- n. (%)</b>                  |                           |                               |         |
| male                                  | 3 (60)                    | 33 (80)                       | 0.295   |
| <b>Smoking -- n. (%)</b>              |                           |                               |         |
| yes                                   | 5 (100)                   | 39 (95)                       | >0.999  |
| <b>Performance status</b>             |                           |                               |         |
| 1                                     | 2 (40)                    | 8 (20)                        | 0.295   |
| <b>Clinical stage -- n. (%)</b>       |                           |                               |         |
| III                                   | 4 (80)                    | 31 (76)                       | >0.999  |
| <b>Histology-- n. (%)</b>             |                           |                               |         |
| SQ                                    | 2 (40)                    | 21 (51)                       | >0.999  |
| <b>PD-L1 status -- n. (%)</b>         |                           |                               |         |
| <1%                                   | 0 (0)                     | 8 (20)                        |         |
| 1-49%                                 | 1 (20)                    | 13 (32)                       |         |
| ≥50%                                  | 4 (80)                    | 13 (32)                       |         |
| Unknown                               | 0 (0)                     | 7 (16)                        | 0.184   |
| <b>Driver gene mutation -- n. (%)</b> |                           |                               |         |
| yes                                   | 2 (40)                    | 14 (34)                       | >0.999  |
| <b>Surgical procedure -- n. (%)</b>   |                           |                               |         |
| Lobectomy                             | 3 (60)                    | 25 (61)                       |         |
| Segmentectomy                         | 0 (0)                     | 13 (32)                       |         |
| Exploratory thoracotomy               | 1 (20)                    | 0 (0)                         | 0.014   |
| Cancelled definitive surgery          | 1 (20)                    | 3 (7)                         | 0.379   |

# Event Rates - 2:00 PM Cutoff



→The earlier-start group showed higher rates of pCR, MPR, and irAE than the late-start group.

# Event-Free Survival (EFS)



✓ 2-year Event-free survival rate

Earlier-start group : 78%

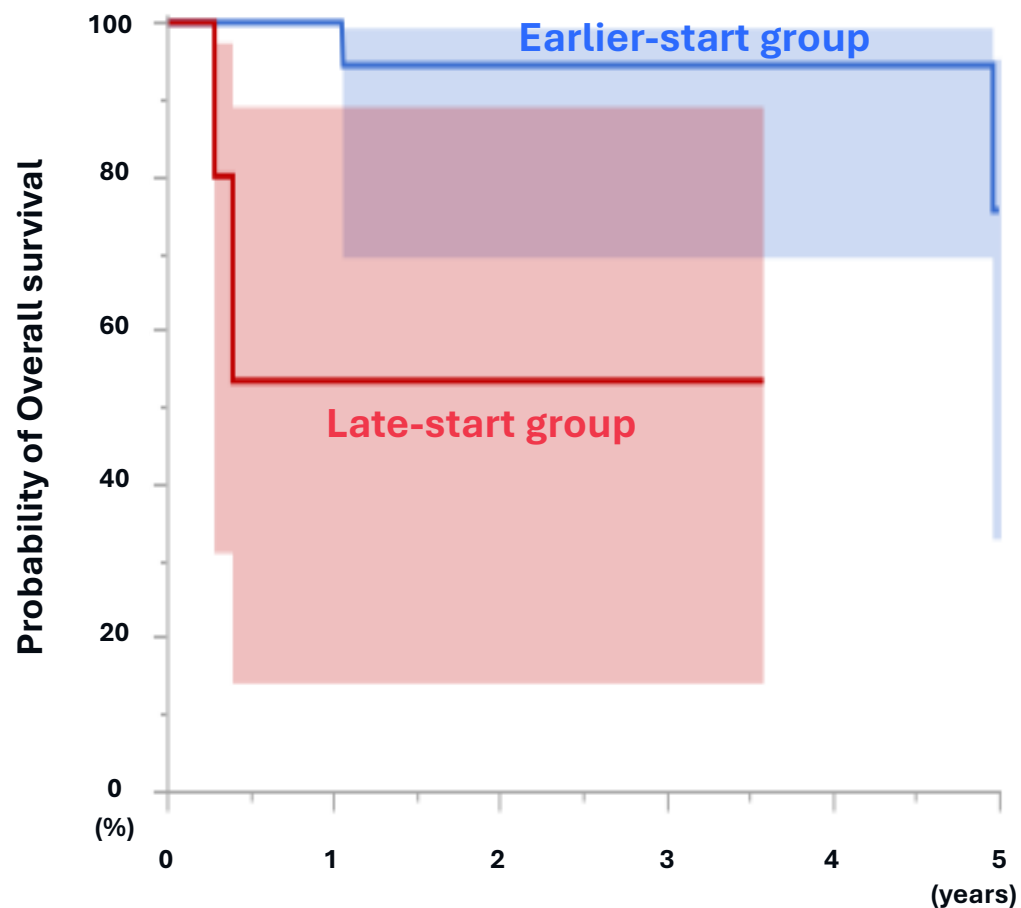
Late-start group : 27%

✓ Log-rank  $p < 0.001$

✓ HR (95%CI) : 10.92 (2.39-49.92)



# Overall Survival (OS)



|                     | Number at risk |    |   |   |   |   |
|---------------------|----------------|----|---|---|---|---|
|                     | 0              | 1  | 2 | 3 | 4 | 5 |
| Late-start group    | 5              | 3  | 2 | 2 | 1 | 1 |
| Earlier-start group | 41             | 23 | 9 | 6 | 6 | 5 |

✓ 2-year Overall Survival rate

Earlier-start group : 94%

Late-start group : 53%

✓ Log-rank  $p < 0.001$

✓ HR (95%CI) : 19.48 (1.75-216.61)





# Multivariable Analysis for EFS

| Variables                                | Univariate         |         | Multivariate        |         |
|------------------------------------------|--------------------|---------|---------------------|---------|
|                                          | HR (95%CI)         | P Value | HR (95%CI)          | P Value |
| Age ( $\geq 70$ vs. $<70$ )              | 2.41 (0.59-9.89)   | 0.221   |                     |         |
| Sex (male vs. female)                    | 0.65 (0.16-2.61)   | 0.546   |                     |         |
| Smoking (yes vs. no)                     | 0.23 (0.03-2.11)   | 0.195   | 0.13 (0.01-1.84)    | 0.132   |
| Performance status (1 vs. 0)             | 3.30 (0.72-15.11)  | 0.124   | 3.20 (0.47-21.92)   | 0.236   |
| Clinical stage (III vs. II)              | 0.64 (0.15-2.70)   | 0.540   |                     |         |
| Histology (SQ vs. Non-SQ)                | 1.52 (0.41-5.71)   | 0.533   |                     |         |
| PD-L1 status ( $\geq 50\%$ vs. $<50\%$ ) | 0.62 (0.12-3.21)   | 0.567   | 0.25 (0.03-1.99)    | 0.189   |
| Driver gene mutation (yes vs. no)        | 1.99(0.52-7.59)    | 0.315   |                     |         |
| ICI administration (Late vs. Earlier)    | 10.92 (2.39-49.92) | 0.002   | 19.46 (2.62-144.66) | 0.004   |





# Multivariable Analysis for OS

| Variables                                | Univariate          |          | Multivariate       |         |
|------------------------------------------|---------------------|----------|--------------------|---------|
|                                          | HR (95%CI)          | P Value  | HR (95%CI)         | P Value |
| Age ( $\geq 70$ vs. $<70$ )              | 3.24 (0.33-31.62)   | 0.311    |                    |         |
| Sex (male vs. female)                    | 0.86 (0.09-8.30)    | 0.897    |                    |         |
| Smoking (yes vs. no)                     | 26072572.00 (0-NA)  | $>0.999$ |                    |         |
| Performance status (1 vs. 0)             | 7.35 (0.67-81.18)   | 0.104    | 4.19 (0.34-51.80)  | 0.265   |
| Clinical stage (III vs. II)              | 0.95 (0.10-9.20)    | 0.967    |                    |         |
| Histology (SQ vs. Non-SQ)                | 0.37 (0.04-3.63)    | 0.397    |                    |         |
| PD-L1 status ( $\geq 50\%$ vs. $<50\%$ ) | 2.93 (0.27-32.40)   | 0.380    | 2.59 (0.20-32.96)  | 0.463   |
| Driver gene mutation (yes vs. no)        | 0.80 (0.08-7.82)    | 0.849    |                    |         |
| ICI administration (Late vs. Earlier)    | 19.48 (1.75-216.61) | 0.016    | 9.74 (0.86-110.61) | 0.066   |



# Why Does the Timing of ICI Administration Matter?

## → Circadian Rhythm and Immunity

- The human body has an approximately 24-hour circadian rhythm.
- Immune cell functions also exhibit diurnal variations.

### Morning☀

- ↑ CD8<sup>+</sup> T-cell activity
- ↑ Antigen-presenting capacity of dendritic cells
- ↑ Production of inflammatory cytokines
- ↑ PD-1 expression (*circadian variation*)

### Evening🌙

- ↓ Early T-cell activation
- ↓ Antitumor immunity

➔ Antitumor immunity may be stronger in the morning.

# Hypothesis for Neoadjuvant ICI Therapy

ICI administration earlier in the day



Enhanced immune activation ↑

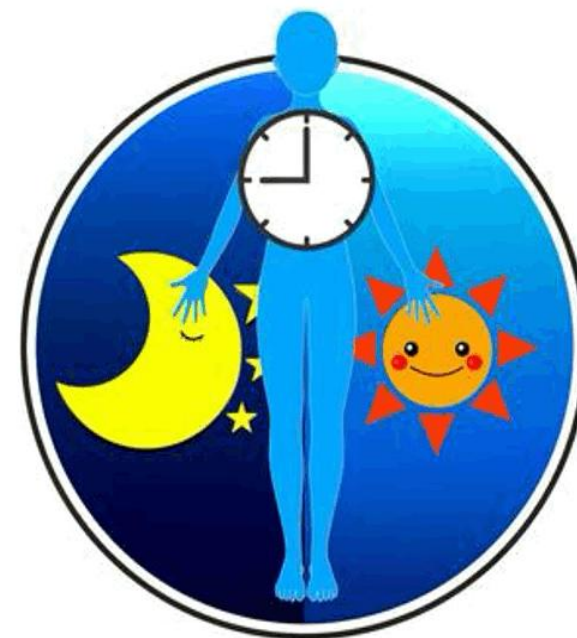


Increased tumor cell killing



Improved pathological response (pCR / MPR)

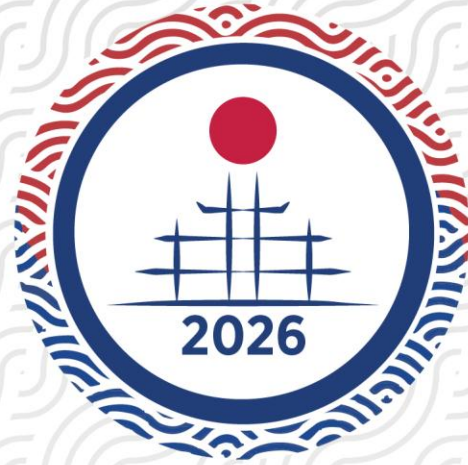
Prolonged EFS and OS



# Conclusion

- In neoadjuvant therapy with ICIs, initiating ICI treatment earlier in the day was associated with better pathological response and prolonged EFS and OS, suggesting a potential improvement in prognosis.
- However, as this was a single-center retrospective study, further validation in larger cohorts and accumulation of additional cases are warranted.





# Thank You.

