A Report on "Time-of-Day Immunochemotherapy in Nonsmall Cell Lung Cancer: A Randomized Phase 3 Trial" by Huang et al. (2026)

Reviewer 2

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I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.

Plato, *The Apology of Socrates*, 21d

To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.

Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Huang, Z., Zeng, L., Ruan, Z., Zeng, Q., Yan, H., Jiang, W., Xiong, Y., Zhou, C., Yang, H., Liu, L., Dai, J., Zou, N., Xu, S., Wang, Y., Wang, Z., Deng, J., Chen, X., Wang, J., Xiang, H., Li, X., Duchemann, B., Chen, G., Xia, Y., Mok, T., Scheiermann, C., Lévi, F., Yang, N., & Zhang, Y. (2026). Time-of-Day Immunochemotherapy in Nonsmall Cell Lung Cancer: A Randomized Phase 3 Trial. *Nature Medicine*.

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Abstract Summary: This randomized phase 3 trial evaluated the effect of early versus late time-of-day (ToD) infusion of immunochemotherapy in 210 patients with advanced non-small cell lung cancer (NSCLC), finding that early ToD administration substantially improved progression-free survival and overall survival.

Key Methodology: Prospective, randomized, single-center, open-label phase 3 trial (Lung TIME-CO1) comparing early (before 15 : 00 h) versus late (after 15 : 00 h) immunochemotherapy infusion in 210 NSCLC patients, assessed by a Blinded Independent Review Committee (BIRC), supplemented by flow cytometric analysis of peripheral blood lymphocyte subsets.

Research Question: Does the time-of-day infusion of first-line immunochemotherapy (before or after 15 : 00 h) affect progression-free survival and overall survival in patients with treatment-naive stage IIIC-IV non-small cell lung cancer?

Summary

Is It Credible?

This study presents a randomized Phase 3 trial evaluating the impact of infusion timing on the efficacy of immunochemotherapy in patients with advanced non-small cell lung cancer (NSCLC). The headline claim is substantial: administering the first four cycles of treatment before 15:00 h resulted in a median Progression-Free Survival (PFS) of 11.3 months compared to 5.7 months for late administration, and a median Overall Survival (OS) of 28.0 months versus 16.8 months (p. 1). These differences correspond to hazard ratios of 0.40 and 0.42 respectively, suggesting that early infusion reduces the risk of progression or death by approximately 60% (p. 1). The authors attribute this benefit to circadian modulation of the immune system, supported by exploratory data showing enhanced CD8+ T cell characteristics in the early treatment group (p. 1).

While the randomized design represents a significant advance over previous retrospective work, the credibility of the reported effect size—which rivals or exceeds the benefit of many blockbuster drugs—is tempered by the study's single-center design and the derivation of its central parameter. The cutoff time of 15:00 h was not selected based on an external biological standard but was derived from a retrospective analysis of 447 patients at the same institution, specifically chosen because it yielded the "lowest HR for PFS" in that prior dataset (p. 9; Supplementary Information, p. 55). Testing a hypothesis on a population operationally identical to the one used to optimize that hypothesis introduces a high risk of overfitting. It raises the possibility that the 15:00 h cutoff captures site-specific operational variables—such as shift changes, staffing levels, or pharmacy workflows unique to this hospital—rather than a universal chronobiological threshold.

Furthermore, the study design confounds the timing of immunotherapy with the

timing of chemotherapy. Patients received chemotherapy approximately 30 minutes after immunotherapy (p. 9), meaning the "Late ToD" group received both agents later in the day. Given that chronochemotherapy is an established field, it is difficult to attribute the survival advantage solely to the immune checkpoint inhibitor as the authors imply. Additionally, while the protocol specified timing only for the first four cycles, data indicate that 77.0% of patients in the early group continued to receive early infusions in subsequent cycles, compared to only 38.5% in the late group (p. 2). This sustained divergence in treatment timing complicates the authors' suggestion that the benefit is driven by an initial "immunological imprinting" (pp. 1, 9).

Finally, the mechanistic evidence provided to support the circadian hypothesis is drawn from a small, non-randomized subset of patients ($n = 39$) (p. 6). While the reported increase in activated T cells in the early group is statistically significant, the analysis was exploratory and unadjusted for multiple comparisons. Similarly, while the abstract claims "no significant differences" in immune-related adverse events, the main text reveals that general hematologic toxicities, specifically leukopenia, were significantly more common in the early group (p. 3). This suggests that the physiological impact of the timing intervention is real, but potentially broader and more complex than the immune-specific mechanism proposed.

The Bottom Line

Huang et al. report a remarkably large survival benefit from early-day immunochemotherapy, but the findings should be viewed with caution due to the single-center design and the use of a cutoff time optimized on local retrospective data. The dramatic effect size may reflect site-specific operational factors or the confounding influence of chemotherapy timing rather than a pure circadian immune response. While the results are provocative and the intervention is cost-neutral, multi-center replication is required to establish this as a biological reality rather

than a statistical or operational artifact.

Potential Issues

Hypothesis based on an optimized, single-center retrospective cutoff time: The study's central intervention—a 15:00 h cutoff for treatment administration—was not pre-specified based on an independent biological rationale but was instead selected through a data-mining exercise on a prior dataset. The study protocol reveals that investigators performed a retrospective analysis of 447 patients at the same institution (Hunan Cancer Hospital) and "searched for the most discriminant cutoff time," which was found to be 15:00 h as it yielded the "lowest HR [Hazard Ratio] for PFS" (p. 9; Supplementary Information, pp. 55–56). This process of optimizing a design parameter on a retrospective dataset to maximize a statistical signal, and then testing it prospectively in the same clinical environment, carries a high risk of capitalizing on chance and overfitting to local, unmeasured conditions. This may inflate the probability of a Type I error (a false positive) and raises questions about whether the 15:00 h cutoff is a robust biological time point or a statistical artifact of the initial dataset.

Single-center design and the risk of operational confounding: The trial was conducted at a single hospital in China, which limits the external validity of the findings to other populations and healthcare systems, a point the authors acknowledge (p. 7). More critically, for a study where the intervention is time of day, the single-center design introduces a significant risk of operational confounding that threatens internal validity. Systematic differences between morning and afternoon hospital operations—such as different nursing or pharmacy staff, varying levels of supervision or fatigue, or different patient-to-staff ratios—are inextricably linked with the "early" versus "late" intervention. These logistical factors, rather than a chronobiological mechanism, could provide a plausible alternative explanation for the observed differences in patient outcomes. The manuscript does not report any measures taken to standardize care or staffing across the different time windows.

Causal interpretation confounded by sustained intervention beyond the protocol

period: The trial is framed as testing the effect of infusion timing during only the first four cycles of immunochemotherapy, implying a short-term "immunological imprinting" effect (pp. 1, 9). However, the results demonstrate that the timing difference between the groups was largely maintained long after this mandated period. For cycles 5, 6, and 7, 77.0% of patients in the early group continued to receive infusions before 15:00 h, compared to only 38.5% in the late group (p. 2). The authors rightly concede that "the observed effects of ToD may not be attributable solely to the ToD of the initial four cycles" (p. 6). This discrepancy between the protocol-defined intervention and the actual treatment received means the study cannot distinguish between the effect of a short-term intervention and that of a sustained, long-term difference in administration time. This confounds the causal interpretation and makes the framing of the study, which emphasizes the initial four cycles, potentially misleading.

Confounding of immunotherapy and chemotherapy timing: The study was designed to administer chemotherapy approximately 30 minutes after the immunotherapy infusion in both arms (p. 9). This means the timing of both drug classes was confounded, making it impossible to attribute the observed survival benefit solely to the timing of the anti-PD-1 agent. The effect could be driven partially or entirely by the timing of chemotherapy (chronochemotherapy), a field with established precedents. This possibility is supported by the finding that leukopenia, a classic chemotherapy-related toxicity, was significantly more common in the early group (p. 3). While the authors acknowledge this ambiguity (p. 6), the paper's narrative and title ("Time-of-day immunochemotherapy") often imply the effect is driven by the immunotherapy component, an over-interpretation not supported by the study's design.

Potential for bias in an open-label design: The study was open-label, meaning both clinicians and patients were aware of the treatment allocation (p. 9). While blinding may have been infeasible, this design is susceptible to bias. A key concern is perfor-

mance bias, where clinicians might provide more diligent care, closer monitoring, or more aggressive management of side effects for patients in the "favorable" early group. While the primary endpoint was assessed by a Blinded Independent Review Committee (BIRC) based on a fixed imaging schedule of every two cycles (p. 9), which mitigates some detection bias, unblinded investigators still make crucial decisions about ordering unscheduled scans based on clinical symptoms or managing patients at the margins of progression. These subjective decisions could be influenced by knowledge of the treatment arm, potentially affecting the measured outcomes.

Exceptionally large effect size: The study reports a remarkably large survival benefit, with a hazard ratio of 0.40 for progression-free survival and 0.42 for overall survival (p. 1). This suggests that early infusion reduced the hazard of progression by 60% and the hazard of death by 58%. An effect of this magnitude from a simple logistical change is highly unusual and is larger than the benefit seen from many novel therapeutic agents. While the authors note this is consistent with prior retrospective meta-analyses (p. 2), the sheer size of the effect in a prospective trial, combined with the other methodological concerns, may warrant a degree of caution until the finding is replicated, ideally in a multi-center trial.

Mechanistic claims based on a small and non-random subsample: A central mechanistic claim of the paper, highlighted in the abstract, is that early treatment is "associated with enhanced antitumor CD8+ T cell characteristics" (p. 1). This conclusion is drawn from an exploratory, post-hoc analysis of a small, imbalanced, and non-randomly selected cohort of 39 patients (14 in the early group, 25 in the late group) whose cryopreserved samples were available and of sufficient quality (pp. 3, 9). The authors appropriately acknowledge that the small sample size and potential for bias from prolonged sample storage are significant limitations and that "further studies are warranted" (p. 7). However, the prominence given to this conclusion in the abstract may overstate the strength of evidence provided by such a limited and po-

tentially biased sub-study.

Lack of adjustment for multiple comparisons: The study reports numerous statistical tests, particularly for subgroup analyses and exploratory endpoints like the flow cytometry data, without adjusting for multiple comparisons. This is noted in the figure captions (e.g., pp. 6, 13). This practice increases the risk of Type I errors, meaning some findings reported as statistically significant may have occurred by chance. For example, the objective response rate (ORR), a key secondary endpoint, was found to be significantly different with a p-value of 0.046 (p. 3), a value close to the conventional 0.05 threshold that may not be robust in the context of multiple unadjusted tests. The authors are transparent about this lack of adjustment, but it weakens the statistical evidence for the secondary and exploratory findings.

Transparency in safety reporting: The abstract states that "No significant differences in immune-related adverse events were observed" (p. 1). While this is technically correct, it omits a clinically relevant and statistically significant finding reported in the main text: "Hematologic toxicities of any grade were more common in the early ToD group, with leukopenia (any grade) occurring in 44.8% and 28.6% of patients in the early and late ToD group, respectively ($P = 0.015$)" (p. 3). The decision to exclude this significant difference in treatment-related toxicity from the abstract's safety summary, while technically accurate regarding the definition of "immune-related," may reduce transparency about the overall safety profile of the intervention.

Minor methodological and presentation issues: Several minor issues are present. First, the trial used simple randomization "without stratification" for key prognostic factors like PD-L1 status (p. 9). While the groups were ultimately well-balanced, this is a deviation from best practice for a Phase 3 trial and introduced an unnecessary risk of chance imbalance. Second, the CONSORT diagram shows that a large number of screened patients (84 of 228 not allocated) refused to accept the timing stipulations (p. 2), suggesting the enrolled population is highly selected and may not be representative of the general NSCLC population, potentially limiting generaliz-

ability. Finally, the supplementary Reporting Summary contains several significant data discrepancies compared to the main text—for instance, reporting that 72.4% of patients had high baseline LDH versus 27.6% in the main text (pp. 2, 22). While these appear to be clerical errors in a supplementary document, they represent significant data discrepancies that raise concerns about the rigor of the final document preparation.

Future Research

Multi-center validation: Future trials must be conducted across multiple institutions with diverse operational environments to rule out the possibility that the observed benefits are due to site-specific factors, such as staffing patterns or fatigue during afternoon shifts at the original study site. This would test the external validity of the 15:00 h cutoff.

Isolation of immunotherapy effects: To disentangle the effects of chronochemotherapy from chronoimmunotherapy, future study designs should evaluate the timing of immune checkpoint inhibitors in patients receiving immunotherapy monotherapy, or use a factorial design where chemotherapy timing is fixed while immunotherapy timing varies.

Operational confounding controls: Subsequent research should explicitly record and adjust for operational variables that differ by time of day, such as nurse-to-patient ratios, wait times, and the use of supportive care medications. This would help distinguish between biological circadian effects and healthcare system factors.

Prospective mechanistic cohorts: To validate the proposed immunological mechanism, future trials should include a pre-specified, adequately powered translational cohort with standardized sample collection times to assess peripheral blood lymphocyte subsets, avoiding the limitations of small, post-hoc subgroups.

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