Cancer Chemoimmunotherapy: Time Will Tell

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ABSTRACT

Endogenous circadian programs coordinate physiology across tissues, including immune cell trafficking and drug metabolism. Previous retrospective studies suggested that the timing of immune checkpoint inhibitor delivery may be a modifiable determinant of survival in patients with cancer, with earlier infusions often associated with improved outcomes. Recently, the prospective randomized phase III LungTIME-C01 trial reported that earlier time-of-day (before 3:00 pm) administration of chemoimmunotherapy nearly doubled progression-free survival in patients with non–small cell lung cancer. In this commentary, we examine the trial's clinical design and execution, including protocol amendments and safety reporting that warrant clarification. We consider the mechanistic interpretation of the results, highlighting that the observed effects may reflect contributions from cytotoxic chronopharmacology, circadian immune regulation, and healthcare delivery factors rather than immunotherapy timing alone. We outline implications for future trial design, including factorial approaches to disentangle the timing of immunotherapy from chemotherapy and the need for multicenter validation before scheduling recommendations are widely adopted.

Humans anticipate diurnal changes through endogenous circadian programs that coordinate physiology across tissues, including immune cell trafficking and drug metabolism (1). Thus, the timing of anticancer treatment in oncology practice could be a modifiable determinant of benefit irrespective of drug choice and is of considerable interest across cancer types.

As the efficacy of immune checkpoint inhibitors (ICI) depends upon endogenous antitumor immunity, a process under circadian control (2), the timing of immunotherapy delivery has emerged as a modifiable variable of interest. A propensity-matched cohort found that patients with metastatic melanoma who received more than 20% of checkpoint inhibitor infusions after 4:30 pm experienced significantly worse overall survival (OS; ref. 3). Multiple retrospective studies observed similar associations across diverse cancer types including melanoma (4), esophageal cancer (5), renal cancer (6), and non–small cell lung cancer (NSCLC; refs. 7, 8), as well as a pancancer meta-analysis (9). However, these studies mostly derived their optimal cutoff time from the data under analysis rather than specifying it *a priori*, raising the risk that reported thresholds reflect overfitting of the data. Furthermore, these retrospective findings can be confounded by socioeconomic factors that influence both access to scheduling and treatment response, such as travel distance to the clinic (10, 11). This may explain why a *post hoc* analysis of the CheckMate 238 trial found no significant difference in recurrence-free survival or OS between adjuvant nivolumab administered before versus after 1:00 pm (12), and a patient-level meta-analysis of eight prospective lung cancer trials (i-TIMES; $n = 1{,}550$) reported noninferiority of late versus early ICI administration (13). These inconsistent findings highlighted the need for prospective trials.

In the chemoimmunotherapy trials that established the modern first-line standard of care for NSCLC, KEYNOTE-189 (nonsquamous NSCLC; ref. 14) and KEYNOTE-407 (squamous NSCLC; ref. 15), the time of infusion was not specified, and the median progression-free survival (PFS) and OS in the chemoimmunotherapy arms were 9 and 22 months and 8 and 17.2 months, respectively. Huang and colleagues (Nat Med. 2026 10.1038/s41591-025-04181-w) (16) report the prospective randomized phase III LungTIME-C01 trial (NCT05549037), in which 210 treatment-naïve patients with stage IIIC to IV NSCLC without targetable driver alterations were randomized to receive the first four cycles of anti–PD-1–based immunochemotherapy before versus after 3:00 pm. The median start times were 10:55 am (range, 7:34 am–2:00 pm) in the early arm and 3:57 pm (3:00 pm–8:39 pm) in the late arm, with chemotherapy administered approximately 30 minutes after immunotherapy. The reported effect size is significant in favor of the early arm, with a doubling of PFS [11.3 vs. 5.7 months; hazard ratio (HR), 0.40], improved OS (28 vs. 16.8 months; HR, 0.42), and a higher objective response rate (ORR; 69.5% vs. 56.2%). LungTIME-C01 reports no adverse events leading to death or treatment discontinuation.

That giving treatment at different times of the day may have profound beneficial or detrimental effects, exceeding the effect sizes of adding immunotherapy to a chemotherapy backbone, is provocative and could, if validated, represent an important consideration in cancer care. The question is supported by prior retrospective clinical data and robust preclinical evidence for circadian regulation of antitumor immunity. Thus, careful consideration of this study, future

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validation, and continued advancement of the biological understanding are indicated.

Clinical Trial Design and Execution

LungTIME-C01 underwent several amendments from initial protocol registration on September 7, 2022. The primary endpoint evolved from an exploratory analysis with ORR and OS to PFS and OS and ultimately to PFS alone, with duration of response added as a secondary endpoint following the first public disclosure of interim data in May 2025 (17). Most notably, the intervention itself—the time-of-day threshold—was modified from "after 6:00 pm versus 6:00 am" to "after 9:00 am versus after 3:00 pm" and finally to "before 3:00 pm versus after 3:00 pm" in March 2024, approximately 1.5 years after trial initiation and 1 year before data cutoff. Although protocol modifications are expected in pragmatic oncology trials, these are not described or explained in the article, and thus their potential impact on patient accrual, treatment assignment, and outcome ascertainment remains unclear. Neither the article nor the protocol specifies a predefined number of PFS events required to trigger the primary analysis, leaving the statistical maturity of the reported results uncertain. A complete account of all protocol amendments, including their timing, rationale, and any sensitivity analyses addressing their impact, would add to the reported findings and facilitate independent replication. We would further encourage the release of anonymized patient-level data to enable independent validation.

Several features of the trial findings and operations warrant comparison with published clinical experience. The article reports no treatment discontinuations due to adverse events across the entire study population, which is markedly different from the established safety profile of pembrolizumab-based combination chemotherapy. For example, the rates of treatment discontinuation in patients receiving the anti–PD-1 plus chemotherapy triplet in KEYNOTE-189 and KEYNOTE-407 were 13.8% and 13.3%, respectively (14, 15). We note that as a single-center study conducted in China, aspects of care delivery infrastructure, supportive care practices, and staffing models may also differ from the US and European settings in which the reference trials were conducted. Also, no patients in LungTIME-C01 are reported to have crossed over between timing groups during the first four cycles. Although protocol adherence is desirable, perfect compliance is unexpected given the practical realities of chemotherapy scheduling, in which appointment changes due to clinic capacity, patient preference, or toxicity management are routine. We also note that page 35 of the published protocol for LungTIME-C01 (16) specifies that patients who do not receive ICIs at the scheduled times during the initial cycles of treatment should be withdrawn from the study. If so, the analysis would not constitute an intention-to-treat population. Reporting of any patients excluded after randomization, with reasons, and clarification of whether a strict intention-to-treat, modified intention-to-treat, or per-protocol analysis was performed, would help proper interpretation of the reported efficacy estimates and in planning future studies.

Mechanistic Interpretation of LungTIME-C01 Trial Results

The divergence in efficacy between early and late arms (16), in which early timing seems to outperform historical benchmarks whereas late timing seems to underperform, could reflect a true benefit of early infusion, an unrecognized detriment of late infusion, or both. The authors suggest circadian immunology as a mechanistic explanation. Immune effector functions vary across the 24-hour diurnal cycle (18), with circadian rhythms governing dendritic-cell trafficking (19), tumor-infiltrating lymphocyte dynamics (20), and immunotherapy efficacy in preclinical models (21). Notably, peak antitumor immunity in nocturnal mice occurs at the end of the resting phase, the circadian equivalent of morning in diurnal humans (21). These findings lend biological plausibility to the LungTIME-C01 trial's overall premise and could be consistent with the divergent time-dependent peripheral $CD8^+$ trajectories reported in the study (16), although the peripheral T-cell measurements are more characteristic of anti–CTLA-4 than anti–PD-1 therapy (22) and are of uncertain value in predicting cancer immunotherapy responses. The flow cytometry methodology is currently described briefly, with an incomplete gating strategy and a lack of a viability marker, and the denominator used to calculate reported T-cell subset percentages is not specified. Lymphocyte profiling was performed on blood samples collected in a standardized morning window (8:00 am–10:00 am), reducing the likelihood that the observed differences simply reflect diurnal sampling. Yet, peripheral immune phenotypes, particularly in the setting of unequal clinical outcomes, can represent cause or consequence. Without paired on-treatment tumor biopsies, it remains unclear whether time-of-day drives intratumoral immune remodeling or whether improved tumor control in the early arm secondarily preserves systemic immune fitness.

The LungTIME-C01 is a trial of timed combination therapy. Two pharmacologically distinct components are sequentially administered. The pharmacokinetics of anti–PD-1 and cytotoxic agents differ by orders of magnitude. PD-1 antibodies have half-lives measured in weeks (23) and achieve near-complete receptor occupancy early after dosing that persists for months after even a single dose (24), such that a shift of several hours is unlikely to meaningfully alter steady-state systemic exposure after the first cycle. For time-of-day to act through immunotherapy alone, one must therefore invoke a time-restricted "effect window" at treatment initiation, in which only the timing of the first dose of immunotherapy is important, a possible explanation that warrants further research. By contrast, carboplatin, nab-paclitaxel, and pemetrexed have half-lives measured in hours (25) and have well-described diurnal variation in hepatic metabolism (26) and renal clearance (27), DNA damage responses (28), and hematopoietic progenitor cycling (29). Platinum agents, including cisplatin in prior NSCLC studies, show diurnal variation in clearance, and morning administration for cisplatin has been associated with a markedly higher rate of leukopenia in NSCLC (30). Beyond direct cytotoxicity, these agents also have immunomodulatory properties (31). Taxanes and antimetabolites can promote immunogenic cell death (32), whereas pemetrexed has been reported to upregulate PD-L1 and promote checkpoint blockade responsiveness (33). Consistent with a chemotherapy chronotoxicity signal, leukopenia was more frequent in the early arm of LungTIME-C01, whereas immune-related adverse events, established correlates of checkpoint efficacy (34), did not differ between arms. Given that cisplatin can induce immunogenicity in tumors, for example, by neoantigen formation (35, 36), one potential explanation for the observed results is that circadian biology influences outcomes through time-dependent variations in immune competence and cytotoxic efficacy, with potentially favorable pharmacodynamic interactions between them. The implication is not that the authors' circadian immune hypothesis is incorrect, but that the mechanism may be distributed across both components of the regimen.

A further layer is the structure of care delivery. In LungTIME-C01, late infusions began as late as 8:39 pm, with chemotherapy administered after checkpoint inhibitor infusions, plausibly shifting treatment completion into late hours that would usually be met with reduced staffing and monitoring. In many healthcare systems, this period of the day offers patients diminished access to immediate evaluation of infusion reactions, reduced availability of same-day supportive care escalation, and longer turnaround times for decision-making. Even subtle increases in unplanned admissions, dose delays, or dose reductions can affect both PFS and OS (37–39). The absence of AE-related discontinuation in either arm heightens the importance of reporting relative dose intensity, treatment delays, and reasons for dose modification by arm, as these data would help adjudicate whether timing acts directly through biology or indirectly through treatment delivery.

Implications for Future Trial Design

Administration times for therapies are modifiable, and clinical trials in this area are important. Future trial designs will need to disentangle the timing of immunotherapy from the timing of chemotherapy. Factorial approaches, randomizing chemotherapy timing while holding immunotherapy timing constant (or vice versa), would directly test whether the observed benefit reflects immune circadian priming, chemotherapy chronopharmacology, or their interaction. Future studies should also test whether timed administration restricted to cycle 1, day 1 alone is sufficient to recapitulate the observed effect, which would both clarify underlying biology and represent a far more practical intervention to embed within routine care. The inclusion of a cohort of patients with PD-L1 tumor proportion score ≥50% treated with anti–PD-1 monotherapy, a standard of care in this population, would further clarify the degree to which the observed effects are immunotherapy dependent. Such studies should prospectively capture relative dose intensity, supportive care utilization, unplanned admissions, and postprogression therapies, alongside prespecified translational endpoints that include paired blood and tumor sampling. Finally, because time-of-day interventions intersect with real-world capacity constraints, multicenter validation across diverse healthcare settings is essential before scheduling mandates are widely implemented.

In sum, LungTIME-C01 raises the important possibility that the clock hour of chemoimmunotherapy delivery is associated with differences in outcome in advanced NSCLC. This question deserves rigorous investigation through independent validation in prospective, randomized trials with preestablished endpoints and interventions. Moreover, important and interesting questions remain to be addressed about the mechanism by which timing may have an effect on outcome and the relative contributions of immunology, chronopharmacology, and healthcare delivery to outcomes of patients with cancer.

Note Added in Proof

After acceptance of our manuscript, Huang Z, Zeng L, Ruan Z, Zeng Q, Yan H, Jiang W, et al. Time-of-day immunochemotherapy in non-small cell lung cancer: a randomized phase 3 trial. Nat Med 2026;32:1233–40, was formally retracted by the publisher. The retraction note indicates that "due to the amount and nature of the problems identified, the editors no longer have confidence in the integrity of the results."

Authors' Disclosures

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