Two-Year Checkpoint Inhibitor Therapy: Is It Enough for Advanced NSCLC?

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> The optimal duration of immune checkpoint inhibitor (ICI) therapy for advanced or metastatic non-small cell lung cancer (amNSCLC) has been an area of ongoing clinical debate. While many trials have continued ICI indefinitely, others have explored fixed-duration regimens, often stopping at two years. This systematic review synthesizes current evidence to address whether a two-year fixed duration of ICI therapy is non-inferior to continuous treatment.

KEY TAKEAWAYS

- The Pivot: Discontinuing ICI therapy at two years in amNSCLC may yield similar long-term survival outcomes compared to continuous treatment.
- The Data: Five-year overall survival rates for two-year fixed cohorts ranged from 69% to 83%, comparable to continuous therapy cohorts.
- The Action: A fixed two-year duration of ICI therapy could be a viable option for amNSCLC patients, potentially mitigating the accumulation of immune-related adverse events.

Uncertainty in Treatment Duration for Advanced NSCLC

Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape for advanced or metastatic non-small cell lung cancer (amNSCLC). However, a significant clinical question remains regarding the optimal duration of this therapy. Previous clinical trials have largely adopted two main approaches: either continuing ICI therapy indefinitely until disease progression or unacceptable toxicity, or implementing a fixed-duration strategy, typically stopping at two years in patients without progressive disease or limiting immune-related adverse events (irAEs)1.

Systematic Review Design and Methodology

To address this unresolved question, a systematic review was conducted, encompassing randomized controlled trials (RCTs) and real-world evidence studies (RWEs) involving adults with amNSCLC treated with ICI therapy. The search for relevant studies was performed up to August 24, 2024. Patients included in the review were categorized into two cohorts: a 'two-year fixed cohort,' where ICI therapy was discontinued after two years, and a 'continuous therapy cohort,' where ICI therapy extended beyond two years1.

Comparative Survival Outcomes

The systematic review included a total of 20 studies, comprising data from 5027 patients. A key finding was the comparability of survival outcomes between the two cohorts. Specifically, the 5-year overall survival (OS) rates for patients in the two-year fixed cohorts ranged from 69% to 83% across the included studies. These rates were found to be

similar to those observed in the continuous therapy cohorts. Four RWEs directly compared survival outcomes between the two-year fixed and continuous cohorts and reported no significant difference in survival1.

Immune-Related Adverse Events Profile

The incidence of immune-related adverse events (irAEs) also showed distinct patterns. Patients who completed two years of therapy in RCTs tended to experience higher rates of irAEs compared to the overall baseline RCT population. Furthermore, three RWEs specifically reported higher rates of irAEs in the continuous therapy cohorts when compared to the two-year fixed cohorts. This suggests a potential accumulation of irAEs over time with prolonged ICI exposure1.

Disease Progression and Practice Patterns

Interestingly, the review noted that many patients who developed progressive disease (PD) after the two-year mark in both the fixed and continuous cohorts remained alive at the data cutoff. This observation suggests that even after two years, patients may continue to derive benefit or have a more indolent disease course. The study also highlighted differences in clinical practice, with larger academic centers showing a preference for the two-year fixed therapy approach, in contrast to community centers1.

Clinical Implications and Future Directions

The findings of this systematic review suggest that for patients with advanced or metastatic non-small cell lung cancer, discontinuing immune checkpoint inhibitor therapy after two years may offer survival outcomes comparable to those achieved with continuous therapy. This has significant implications for patient management, particularly concerning the potential reduction of long-term immune-related adverse events, which tend to accumulate with prolonged treatment. The data indicate that a fixed two-year duration could be a reasonable and effective treatment strategy, potentially improving patient quality of life by minimizing chronic toxicities without compromising efficacy.

Why this matters for clinical practice today: This evidence provides valuable support for clinicians considering a fixed-duration approach to ICI therapy in amNSCLC. Given the potential for cumulative toxicities with continuous treatment, a two-year fixed regimen could offer a more favorable risk-benefit profile for many patients. It encourages a re-evaluation of current practice, especially in patients who have achieved a durable response, and may facilitate shared decision-making discussions regarding treatment cessation. While individual patient factors and disease characteristics will always guide treatment decisions, these findings offer a robust basis for discussing a finite treatment course.

Limitations and Next Steps

While this systematic review provides important insights, it is essential to acknowledge its limitations. The included studies varied in design and patient populations, which can introduce heterogeneity. The reliance on real-world evidence, while valuable, can also be subject to confounding factors not present in controlled trials. Future research should focus on prospective studies specifically designed to compare fixed-duration versus continuous ICI therapy, with detailed analyses of long-term survival, quality of life, and the full spectrum of immune-related adverse events. Further investigation into biomarkers that could predict which patients benefit most from a fixed duration versus continuous therapy would also be beneficial1.

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REFERENCES

1. 1. Pandey T, Bhatti SA. Efficacy and safety of two-year fixed versus continuous immune checkpoint inhibitor therapy in advanced or metastatic non-small cell lung cancer: a systematic review. Cancer Immunol Immunother. 2025;74(10):317. doi:10.1007/s00262-025-04143-8

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