Rechallenging ICI after encephalitis: When the risk is worth taking

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Immune checkpoint inhibitors (ICIs) have transformed oncology, but their efficacy comes tethered to a spectrum of immune-related adverse events (irAEs), some profoundly severe. Among the most concerning is ICI-related encephalitis (ICI-IE), a rare but devastating neurological complication that typically mandates immediate and permanent discontinuation of therapy. The question of rechallenge after such a severe event has long been considered too risky, leaving clinicians with few options for patients whose cancer progresses. But a recent case report in the Journal of Neuroimmunology offers a glimpse into a potential path forward.1

KEY TAKEAWAYS

- The Pivot: Rechallenge with an ICI after a prior severe ICI-related encephalitis is possible, challenging the conventional wisdom of permanent discontinuation.
- The Data: A 66-year-old female with metastatic renal cell carcinoma tolerated nivolumab rechallenge for over 9 months without recurrence of ICI-IE.
- The Action: Consider a multidisciplinary approach for ICI rechallenge in select patients with severe irAEs, particularly when alternative treatments are exhausted and the oncologic benefit is high.

Immune checkpoint inhibitors, specifically PD-1/PD-L1 and CTLA-4 antibodies, have become cornerstones in the treatment of numerous advanced malignancies. They function by unleashing the immune system's inherent ability to target cancer cells, but this mechanism can also lead to immune dysregulation affecting healthy tissues. These irAEs can manifest in virtually any organ system, ranging from mild dermatological reactions to life-threatening myocarditis or encephalitis. ICI-related encephalitis (ICI-IE) is a particularly severe manifestation, characterized by inflammation of the brain parenchyma, often presenting with personality changes, memory loss, seizures, or focal neurological deficits. Its incidence is low, estimated at less than 1% across all ICI-treated patients, but its morbidity and mortality are substantial, frequently necessitating high-dose corticosteroids and other immunosuppressants.1

The standard of care following a severe irAE, especially a grade III or higher event like encephalitis, dictates permanent discontinuation of the offending ICI. This conservative approach prioritizes patient safety, given the unpredictable nature and potential lethality of recurrent irAEs. But this leaves a significant unmet need for patients with aggressive or refractory cancers who initially responded to ICI therapy but then developed a severe irAE. For these individuals, the prospect of effective subsequent treatment can be bleak, forcing a difficult balance between disease control and the risk of life-threatening toxicity. The case presented by Baker and Shah directly addresses this clinical conundrum, offering a rare example of successful rechallenge.1

A Case of Successful Rechallenge

The case involved a 66-year-old female diagnosed with localized renal cell carcinoma. Her initial treatment regimen included combination immunotherapy with ipilimumab and nivolumab. After only the second cycle of this combination, she developed subacute progressive personality changes, memory loss, and encephalopathy. Clinicians diagnosed her with CTCAE grade III immune-related limbic encephalitis. This severe adverse event prompted immediate discontinuation of both ipilimumab and nivolumab. She received seven days of intravenous solumedrol, followed by a prolonged oral steroid taper, which resolved her neurological symptoms.1

Four years later, the patient experienced recurrent metastatic disease. This recurrence presented a significant therapeutic challenge, particularly given her history of severe ICI-IE. The decision to pursue further immunotherapy was complex, balancing the potential for oncologic benefit against the high risk of recurrent encephalitis. The treating team opted for palliative immunotherapy, initiating cabozantinib and, for the patient's survival, rechallenging with nivolumab. This decision involved a multidisciplinary consultation with neuroimmunology, highlighting the careful consideration of risks and benefits.1

The patient tolerated the rechallenge with nivolumab for over 9 months without any recurrence of immune-related adverse events. This outcome is significant because it demonstrates that ICI rechallenge, even after a severe, life-threatening irAE like encephalitis, is not universally contraindicated and can be successful in carefully selected patients. The choice to rechallenge with a single agent (nivolumab) rather than the original combination (ipilimumab/nivolumab) likely played a role in mitigating risk, as combination ICI regimens are known to carry a higher incidence and severity of irAEs compared to monotherapy.1

Weighing the Decision to Rechallenge

The decision to rechallenge with an ICI after a severe irAE is fraught with uncertainty. The primary concern is the risk of recurrence of the same or a different severe irAE, which could be more aggressive or even fatal upon re-exposure. Factors influencing this decision include the severity and type of the initial irAE, the time elapsed since the initial event, the patient's overall health status, the availability of alternative effective therapies, and the prognosis of the underlying malignancy. In this specific case, the patient's recurrent metastatic renal cell carcinoma, a disease where ICIs have demonstrated significant efficacy, likely tipped the balance towards rechallenge, especially given the lack of other viable palliative options.1

The mechanism of ICI-IE is not fully understood, but it is thought to involve T-cell mediated inflammation targeting neuronal antigens. The fact that the patient in this report did not experience a recurrence of encephalitis suggests several possibilities. It could be that the initial irAE was idiosyncratic, or that the prolonged interval of four years allowed for immune system recalibration. But it is also possible that nivolumab monotherapy carries a lower risk of neurotoxicity compared to the ipilimumab/nivolumab combination, which is known to be more immunogenic. Understanding the specific mechanisms of immune-related adverse events remains a critical area of research.1

This case report, while compelling, represents a single patient experience. It does not provide definitive evidence for the safety or efficacy of ICI rechallenge in a broader population. The absence of recurrence in one patient does not guarantee similar outcomes in others. But it does provide a proof-of-concept that challenges existing dogma and opens the door for further investigation. The authors rightly emphasize the imperative for a multidisciplinary approach, involving oncologists, neurologists, and neuroimmunologists, to carefully assess the risks and benefits for each individual patient.

This collaborative model is essential for navigating such complex clinical scenarios, particularly when considering managing severe adverse events from novel cancer therapies.1

The Broader Context of irAE Management

The management of irAEs has evolved significantly as ICI use has expanded. Guidelines from major oncology societies now provide detailed recommendations for grading and treating irAEs, emphasizing early recognition and prompt intervention. For severe irAEs, high-dose corticosteroids are the mainstay of treatment, often followed by a prolonged taper. In refractory cases, other immunosuppressive agents such as infliximab, mycophenolate mofetil, or intravenous immunoglobulin may be employed. But even with aggressive management, some irAEs can lead to permanent organ damage or be fatal. The details of drug dosing and adverse effects are critical for all clinicians.1

The question of rechallenge extends beyond encephalitis to other severe irAEs, such as myocarditis, pneumonitis, or colitis. While data remain scarce, a growing body of case reports and small retrospective studies suggests that rechallenge may be feasible in highly selected patients, particularly those with a strong initial response to ICI and limited alternative treatment options. The type of ICI used for rechallenge (same agent, different agent, or combination), the dose, and the duration of the initial irAE-free interval are all factors that warrant careful consideration. This case report adds to the sparse literature supporting cautious rechallenge in specific, high-stakes situations. Clinicians can find comprehensive guidance on managing such complex cases in resources like the Oxford Handbook of Oncology.1

Still, the open-label nature of a single case report is the obvious caveat. This patient's experience, while positive, does not constitute robust evidence. There is no control group, no randomization, and no statistical power to draw generalizable conclusions. The absence of recurrence could be due to factors specific to this patient, the specific ICI chosen for rechallenge, or simply chance. But the fact that a patient with a history of grade III ICI-IE tolerated rechallenge for over 9 months without recurrence provides a compelling data point that warrants further exploration in larger cohorts or registries. The inherent risks of ICI rechallenge mean that any such decision must be made with extreme caution and thorough patient education regarding potential outcomes.1

CLINICAL IMPLICATIONS

This case report, while a single data point, forces a re-evaluation of the absolute contraindication against ICI rechallenge after severe irAEs. For patients with aggressive, metastatic cancers who have exhausted other options, the prospect of resuming an effective therapy, even with known risks, offers a lifeline. The conventional wisdom of permanent discontinuation, while safe, can condemn patients to disease progression when ICIs are their best hope.

Clinicians managing these complex cases must now consider a more individualized approach. A multidisciplinary team, including oncologists, neurologists, and immunologists, becomes indispensable. This collaborative model allows for a thorough assessment of individual patient factors, the specific irAE, and the oncologic imperative, moving beyond a blanket prohibition to a risk-stratified decision-making process.

The industry must also recognize this evolving clinical landscape. While large randomized controlled trials for ICI rechallenge after severe irAEs are unlikely due to ethical and logistical challenges, real-world data registries and carefully designed prospective observational studies are essential. These efforts could help identify patient subgroups most likely to benefit from rechallenge and define optimal strategies, such as

> monotherapy versus combination, or different ICI agents.
> The unanswered question remains: how many patients like this one exist, and under what precise conditions can rechallenge be safely and effectively implemented? This single success story is a beacon, but it is not a map. Future research needs to delineate predictive biomarkers for irAE recurrence and response to rechallenge, providing clinicians with better tools to navigate these high-stakes decisions.

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REFERENCES

1. 1. Baker V, Shah S. Re-challenge of immune checkpoint inhibitor after ICI-encephalitis: A case report. J Neuroimmunol. 2026;420:577770. doi:10.1016/j.jneuroim.2026.577770

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