

Immune effector cell-associated neurotoxicity syndrome (ICANS) during tebentafusp in metastatic uveal melanoma

Laura Schreieder¹  | Laura Jockel² | Veronika Zenderowski¹ | Ralf A. Linker² | Sebastian Haferkamp¹ | Elisabeth Bumès^{2,3} | Peter Hau^{2,3} | Konstantin Drexler¹

¹Department of Dermatology, Regensburg University Hospital, Regensburg, Germany

²Department of Neurology, Regensburg University Hospital, Regensburg, Germany

³Wilhelm Sander-NeuroOncology Unit, Regensburg University Hospital, Regensburg, Germany

Correspondence

Laura Schreieder, Department of Dermatology, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany.

Email: laura.schreieder@ukr.de

Dear Editors,

A 78-year-old male was diagnosed with ciliary body melanoma in June 2019 and treated with stereotactic radiotherapy (CyberKnife®). He remained under routine surveillance for 4.5 years until hepatic metastases were detected and confirmed histopathologically. Selective internal radiation therapy (SIRT) of the right hepatic lobe was performed. However, 3 months later, disease progressed with multiple new liver metastases and bilateral adrenal metastases.

Given stage IV disease and confirmed HLA-A*02:01 positivity, systemic immunotherapy with tebentafusp was initiated after a second SIRT procedure. After treatment initiation, the patient developed grade 1 cytokine release syndrome (CRS) with fever and a maculopapular exanthema, managed with paracetamol and topical corticosteroids. At treatment initiation, the patient already had thrombocytopenia (81/nl; reference range, 150–370/nl). After six doses of tebentafusp, he reported headache, progressive imbalance and intermittent vertigo without nausea, triggered by movement or standing up. Otorhinolaryngological as well as cardiac evaluations were unremarkable.

A month later, the patient was admitted due to worsening cerebellar symptoms. Neurological examination revealed a broad-based gait with instability on turning, a positive Romberg test with omnidirectional swaying, left-dominant distal hypesthesia of hands, feet and lower legs, mild dysarthria, and altered handwriting. Occupational therapy assessment demonstrated a change in handwriting compared with his premorbid state, corroborated by

the patient's wife, as well as objectively reduced writing fluency. The *Montreal Cognitive Assessment* (MoCA) yielded a score of 18/30, indicating mild cognitive impairment. Therapy-associated immune-mediated neurotoxicity was suspected.

A comprehensive diagnostic work-up (Table 1), including cranial and spinal MRI (online supplementary Figure S1), repeated cerebrospinal fluid analyses, extended autoantibody and paraneoplastic antibody panels, nerve conduction studies, somatosensory evoked potentials, and laboratory screening for infectious, vascular, and autoimmune etiologies, was unremarkable, apart from a positive ANA titer (1:1280; AC-5 coarse speckled nuclear pattern; positive SS-B antibodies), findings deemed clinically irrelevant. No evidence of CNS metastasis or meningeosis, paraneoplastic disease including paraneoplastic cerebellar degeneration, paraneoplastic cerebellitis, and paraneoplastic subacute sensory neuronopathy (ganglionopathy), infection, inflammation, or other neurological differential diagnoses was found.

To assess neurotoxicity in the context of a suspected immune effector cell-associated neurotoxicity syndrome (ICANS), grading was performed according to the American Society for Transplantation and Cellular Therapy (ASTCT) ICANS consensus criteria, yielding a score of 7/10 on the Immune Effector Cell-Associated Encephalopathy (ICE) Score, corresponding to ICANS grade 1 (Table 2).¹

High-dose corticosteroid pulse therapy with a cumulative dose of 5,000 mg methylprednisolone intravenously

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2026 The Author(s). *Journal der Deutschen Dermatologischen Gesellschaft* published by John Wiley & Sons Ltd on behalf of Deutsche Dermatologische Gesellschaft.

TABLE 1 Selected laboratory findings at tebentafusp initiation and at presentation of ICANS neurotoxicity.

Parameter	Reference (range)	At tebentafusp initiation	At ICANS presentation
Platelets (nl ⁻¹)	150–370	81	133
Leukocytes (nl ⁻¹)	4.0–10.0	10.3	5.83
C-reactive protein (mg/l)	< 5	14.7	4.6
LDH (U/l)	< 250	521	229
ANA	Negative	Not recorded	1:1,280 (AC-5 coarse speckled nuclear pattern; positive SS-B antibodies)

Abbr.: ANA, antinuclear antibodies; ICANS, immune effector cell-associated neurotoxicity syndrome; LDH, lactate dehydrogenase

TABLE 2 Cognitive and neurotoxicity assessment results at presentation. The Immune Effector Cell-Associated Encephalopathy (ICE) score was 7/10, corresponding to grade I immune effector cell-associated neurotoxicity syndrome (ICANS) according to ASTCT consensus criteria.

ICE-Score		
Orientation	Year	1/1
	Month	1/1
	City	1/1
	Hospital	0/1
Naming	3 objects	3/3
Follow commands	Able to follow simple command	1/1
Writing	Standard sentence	0/1
Attention	Count backward from 100 by 10's	0/1
Total		7/10
ICANS Grading		
ICE Score	7	
Level of consciousness	Awakens spontaneously	
Seizure	–	
Motor findings	–	
Elevated intracranial pressure/cerebral edema	–	
Grade	I	

Abbr.: ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Immune Effector Cell-Associated Encephalopathy

over 5 days resulted in minor clinical improvement. Subsequently, four cycles of therapeutic plasmapheresis (TPE) were performed, each exchanging approximately 1.2 patient plasma volumes per session, leading to marked symptom resolution. ASTCT ICANS score improved to 0. Upon discharge, oral dexamethasone (4 mg daily) was initiated, leading to complete clinical resolution of the residual gait ataxia and subsequent discontinuation. At 2-month follow-up, neurological remission was sustained. The dermatologic therapy was switched to dual immune checkpoint inhibition with four cycles of ipilimumab and nivolumab, which was well tolerated and subsequently de-escalated to monotherapy with nivolumab as maintenance. The patient died 9 months later from progressive disease under the care of an external medical institution.

Tebentafusp is a bispecific T cell receptor (TCR)-based fusion protein approved for HLA-A*02:01-positive adults with metastatic or unresectable uveal melanoma. It targets glycoprotein 100 (gp100), a melanoma-associated antigen presented in the context of HLA-A*02:01, and simultaneously engages CD3 on T cells via an affinity-enhanced TCR fused to an anti-CD3 single-chain variable fragment.² This dual targeting redirects polyclonal T cells to gp100-expressing melanoma cells, inducing T cell activation, cytokine release, and tumor cell lysis.³

The safety profile is dominated by immune-mediated and cytokine-driven adverse events, particularly rash, pyrexia, hypotension, and CRS, typically grade 1–2 in early treatment cycles.⁴ Neurotoxicity – particularly ICANS – has not been reported in pivotal trials or pharmacovigilance databases to date.

Given tebentafusp's mechanism of action, there are plausible pathophysiological parallels to CAR-T cell therapies, known to cause ICANS via cytokine-mediated endothelial activation and blood-brain barrier dysfunction.^{1,5} Both are capable of inducing broad T cell activation and high-level release of proinflammatory cytokines such as IL-6, IFN- γ , and TNF- α .⁶ Therefore, comparable immune-mediated toxicities such as CRS and ICANS appear biologically plausible. Our case suggests that, despite differing therapeutic platforms, both modalities may trigger similar neuroinflammatory cascades. A high tumor burden as well as thrombocytopenia, both present in our patient, are recognized risk factors for the development of ICANS.^{7,8}

Differential diagnoses of subacute cerebellar dysfunction in combination with distal sensory symptoms were evaluated. Paraneoplastic cerebellar degeneration was considered. Although seronegative cases have been described, absence of MRI abnormalities argued against advanced disease, as well as ischemia. Immune-mediated cerebellar ataxias – post-infectious or autoimmune targeting ion channels, synaptic proteins, neurotransmitter receptors, glial cells, or other CNS antigens – were ruled out by normal cerebrospinal fluid analyses and bloodwork. Examination and electrophysiology did not support peripheral neuropathies. The rapid improvement following corticosteroid therapy and plasmapheresis further supports the diagnosis of a treatment-related immune-mediated pathogenesis.

This case illustrates, for the first time, that TCR-based immunotherapies such as tebentafusp can induce central

neurotoxicity like ICANS. A possible explanation for the absence of previously reported ICANS under tebentafusp may lie in tebentafusp being a soluble fusion protein with transient systemic exposure, potentially reducing the risk of prolonged endothelial dysfunction and blood-brain barrier disruption. Furthermore, tebentafusp is not as widely used in oncology because HLA-A*02:01-positive uveal melanoma is rare, and knowledge of its adverse events is therefore limited. The favorable response to immunomodulatory treatment in our index patient highlights the importance of vigilance for neurological symptoms and timely intervention. Established management strategies for T cell-associated neurotoxicity may be applicable in this context. Prospective data collection and heightened awareness of neurotoxicity are needed to define the neurological safety profile of tebentafusp and optimize patient care.

The case has been reported to Immunocore's European Team Lead Regional Account Manager.

ACKNOWLEDGMENT

This work was performed in the framework of the Bavarian Center for Cancer Research (BZKF).

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

L.S. has received honoraria and travel support from BMS, MSD, Novartis, SunPharma, and Pierre Fabre. V.Z. has received honoraria and travel support from BMS, MSD, Novartis, SunPharma, and Pierre Fabre. R.L. has received honoraria and research support from Alexion, Merck, Novartis, and Sanofi. S.H. has received honoraria and travel support from BMS, MSD, Novartis, SunPharma, Immunocore, and Pierre Fabre. P.H. has received honoraria and has served on the speakers' bureaus of Novocure, Servier, and

BMS. K.D. has received honoraria and travel support from BMS, MSD, Novartis, SunPharma, Immunocore, and Pierre Fabre. L.J. and E.B. declare no conflicts of interest.

ORCID

Laura Schreieder  <https://orcid.org/0009-0006-4198-0836>

REFERENCES

1. Lee DW, Santomaso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.
2. Chen LN, Rao DA. Tebentafusp for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. *Expert Rev Anticancer Ther*. 2022;22(10):1017-1027.
3. Carvajal RD, Nathan P, Sacco JJ, et al. Phase I study of safety, tolerability, and efficacy of tebentafusp using a step-up dosing regimen and expansion in patients with metastatic uveal melanoma. *J Clin Oncol*. 2022;40(17):1939-1948.
4. Hassel JC, Berking C, Forschner A, et al. Practical guidelines for the management of adverse events of the T cell engager bispecific tebentafusp. *Eur J Cancer*. 2023;191:112986.
5. Rees JH. Management of immune effector cell-associated neurotoxicity syndrome (ICANS). In: Kröger N, Gribben J, Chabannon C, Yakoub-Agha I, Einsele H, eds: *The EBMT/EHA CAR-T Cell Handbook*. Cham: Springer International Publishing; 2022:141-145.
6. Gust J, Hay KA, Hanafi LA, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov*. 2017;7(12):1404-1419.
7. Brudno JN, Kochenderfer JN. Current understanding and management of CAR T cell-associated toxicities. *Nat Rev Clin Oncol*. 2024;21(7):501-521.
8. Santomaso BD, Park JH, Salloum D, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov*. 2018;8(8):958-971.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.