https://doi.org/10.1038/s41591-026-04554-9

# Oncology must confront hidden side effects



**As a new generation of cancer drugs continues to extend the lives of people with cancer, strategies for recording and managing their toxicity and long-term effects will need innovation too.**

Recent breakthroughs in cancer therapy, including immunotherapies, antibody–drug conjugates and bispecific antibodies, have transformed oncology care. Cancer therapy has become more targeted to the patients' tumors, and patients' overall survival is becoming longer. However, those who survive cancer can face lifelong challenges because of treatment-induced toxicities with short- and long-term effects. While innovations have rapidly changed the cancer therapy landscape, approaches to recording and managing treatment-induced toxicities have not evolved at the same pace, and their impact on the quality of life of those who survive cancer is unclear.

Those who survive cancer must live with the consequences of therapy-induced toxicities and may have to remain on treatment for the rest of their lives. Even low-grade adverse effects such as rash and diarrhea can become functionally and psychologically devastating when experienced over a long period of time. Immune-related adverse events in patients treated with immune checkpoint inhibitors can be chronic and persist for years or be irreversible[1]. However, the duration of adverse events is not factored into the existing common terminology criteria for adverse events (CTCAE) for acute toxicities[2].

The problem is that what is deemed manageable according to current criteria might be unacceptable to patients. Moreover, quality-of-life data are commonly reported years after the primary clinical report has been published and the drug has been approved, so these data are not available to new patients. Patient questionnaires to assess quality-of-life data may be outdated and patients' issues potentially may not be accurately presented.

The latest breakthrough therapy in oncology, the pan-RAS inhibitor daraxonrasib, doubled the survival of patients with aggressive *RAS* oncogene-driven advanced pancreatic cancer, which had thus far had very limited treatment options. Most patients experienced acneiform rash and, although less common, diarrhea and stomatitis as low-grade therapy-related adverse events[3]. Full quality-of-life data, which would include data on daily functioning and emotional well-being, have not yet been disclosed, owing to short follow-up. As functional and psychological disruptions to patients are also not factored into CTCAE[2], this means that non-CTCAE toxicities, such as impaired daily functioning and emotional well-being, are hidden from prescribing clinicians in the first years after roll-out of a therapy. Patients may be less accepting of new agents when expected toxicities, short or long term, cannot be disclosed because they are unknown or underappreciated or their severity is underestimated. If toxicities cannot be disclosed, obtaining actual informed consent for treatment with new agents in clinical practice is not possible. New toxicity reporting guidelines need to be developed, and patient questionnaires need to be frequently updated, together with and based on input from patients, so that their needs are accurately reflected in the development of drugs.

Toxicity profiles of novel drugs can differ depending on the targets and mechanisms of action of the respective therapies, and on the individual patient's genetic background and physical condition, such as the existence of other long-term conditions. For patients who have been historically excluded from trials on the basis of these factors, only real-world data or appropriately designed trials bring to light the toxicities they can expect from novel treatments. It is important to include populations at risk in the adaptation of current toxicity and quality-of-life reporting, because disparities exist in the severity of treatment-related adverse events across malignancies and therapeutic modalities, including gender disparities in adverse events induced by immunotherapy[4] and racial disparities in those induced by chimeric antigen receptor T cell therapy[5].

Real-world experiences with the bispecific antibody amivantamab in lung cancer have shown that the full extent and severity of skin toxicities can come to light only when a broader patient population has been exposed to the respective drug. In addition, because of historical siloing of disciplines, knowledge transfer may be limited in how to detect, monitor and manage therapy-induced toxicities, such as cytokine-release-syndrome in the case of chimeric antigen receptor T cell therapy, or immune system-related adverse events in the case of immune checkpoint inhibition. Such silos need to be removed so that patients' needs can be met across disease settings. In addition, after broader implementation of therapies across cancer types, the detection of rare treatment-induced syndromes may become more likely, and coordinated research into the mechanisms of toxicities can help mitigate risks and aid in the development of more targeted treatments.

Global and interdisciplinary efforts to detect and manage novel treatment-related adverse events are required when tissue-agnostic drugs and specific drug classes across cancer types are approved for clinical practice. Examples of important steps in this direction are the existence of cross-disciplinary working groups that, for example, provide guidelines for identifying and treating a rare syndrome associated with immune effector cell-based therapies[6] and monitoring immune-related side effects at Side Effect Registry Immuno-Oncology.

This is a time of unprecedented pace in oncology drug development and clinical translation. The opportunity to reconsider current approaches to recording and managing treatment-related toxicities and to involving patients' perspectives early on during clinical development cannot be missed.

Published online: 8 July 2026

## References

1. Barron, C. C. et al. *J. Immunother. Cancer* **11**, e006500 (2023).
2. Gyawali, B. et al. *Lancet Oncol.* **26**, e80–e89 (2025).
3. O'Reilly, E. M. et al. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2605555 (2026).
4. Unger, J. M. et al. *J. Clin. Oncol.* **40**, 1474–1486 (2022).
5. Rayapureddy, A. K. et al. *J. Clin. Oncol.* **44**, e18576 (2026).
6. Hines, M. R. et al. *Transplant. Cell. Ther.* **29**, 438.e1–438.e16 (2023).