Decision Letter (JCQ-2026-0024)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0024

Body: 25-Jul-2026

Dear Dr Nagai:

Manuscript ID JCQ-2026-0024 entitled "Cell Therapy for Solid Tumours: From an Exceptional iNKT-Cell Response to a Testable Therapeutic Platform" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
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5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author

I have critically evaluated the short communication titled "Cell Therapy for Solid Tumours: From an Exceptional INKT Cell Response to a Testable Therapeutic Platform" authored by Hisashi Nagai. This manuscript, submitted to the Journal of Clinical Question, serves as a timely commentary on a clinical case report by Cheng and colleagues. The commented case report documented a complete remission lasting over six years in an HIV positive patient with recurrent EGFR L858R mutated lung adenocarcinoma who received allogeneic invariant natural killer T cells combined with dendritic cells. The author notes that the patient remained free from documented disease progression after four treatment cycles and treatment discontinuation, experiencing only grade 1 to 2 adverse events. In my assessment, discussing the clinical implications of this exceptional response is highly pertinent, as achieving long term disease control in advanced solid tumors remains a major therapeutic hurdle in medical oncology. As the author rightly points out, while a single case cannot establish causality or define therapeutic efficacy, this prolonged remission represents a clinically important observation that invites careful consideration of invariant natural killer T cell therapy and the broader potential of cellular immunotherapy in solid tumors.

In my evaluation, the primary strength of this commentary lies in its comprehensive contextualization of the case report within the rapidly evolving field of cellular immunotherapy for solid tumors. The author effectively synthesizes recent landmark clinical milestones, including a randomized phase III trial by Rohaan and colleagues demonstrating that tumor infiltrating lymphocyte therapy improved progression free survival compared with ipilimumab in patients with advanced melanoma. The commentary also highlights the subsequent accelerated approval of lifileucel for unresectable or metastatic melanoma as validation of cellular therapy for selected solid tumors. Furthermore, the manuscript accurately references neoantigen specific T cell receptor gene therapy targeting KRAS G12D in metastatic pancreatic cancer reported by Leidner and colleagues, which resulted in substantial regression of visceral metastases in a treatment refractory malignancy. Another notable strength is the author's clear articulation of the microenvironmental barriers in solid tumors, accurately cataloging obstacles such as heterogeneous antigen expression, impaired antigen presentation, dense stromal architecture, abnormal vasculature, hypoxia, nutrient deprivation, regulatory T cells, myeloid derived suppressor cells, tumor associated macrophages, inhibitory cytokines, and checkpoint pathways. I also commend the author for emphasizing the clinical relevance of the patient's HIV positive status, correctly pointing out that people living with HIV have historically been underrepresented in immunotherapy and cell therapy trials despite improved viral suppression and immune restoration achieved with modern antiretroviral therapy.

Despite these conceptual strengths, I identified several significant opportunities for improvement that should be addressed to enhance the scholarly depth and immunological rigor of this commentary. First, while the author contrasts the limitations of autologous cell therapies against scalable off the shelf allogeneic approaches derived from healthy donors or induced pluripotent stem cells, the manuscript lacks an in depth mechanistic exploration of how invariant natural killer T cells specifically function within the tumor microenvironment. Because invariant natural killer T cells recognize glycolipid antigens presented by monomorphic CD1d molecules rather than classical peptide antigens presented by polymorphic major histocompatibility complex molecules, explicitly detailing this HLA independent recognition pathway would provide a stronger scientific explanation for why this cellular subset might succeed where conventional T cell therapies face resistance. Second, although the commentary references a phase I study by Iinuma and colleagues evaluating allogeneic induced pluripotent stem cell derived invariant natural killer T cells in recurrent head and neck cancer to support platform feasibility, it omits a critical appraisal of the biological synergy between invariant natural killer T cells and dendritic cells. Since the therapeutic regimen reported by Cheng and colleagues utilized a combination of both invariant natural killer T cells and dendritic cells, the author should elucidate the reciprocal activation mechanisms between these two cell types. Specifically, discussing how invariant natural killer T cell activation induces dendritic cell maturation and subsequent cross priming of host CD8 positive cytotoxic T lymphocytes would significantly enrich the translational value of the article.

Another opportunity for refinement involves the discussion of immune competence and safety in HIV positive cancer patients receiving allogeneic cell therapy. While the author appropriately recommends that future reports include detailed longitudinal immune profiling, viral load tracking, CD4 and CD8 T cell counts, antiretroviral treatment details, and opportunistic infection history, the commentary would benefit from exploring the pharmacological interactions between antiretroviral regimens and adoptive cell infusions. Furthermore, when addressing the risks associated with allogeneic cell platforms, the author notes the need to evaluate persistence, host versus graft rejection, alloimmunization, cytokine mediated toxicity, and long term safety. However, a critical omission is the specific discussion of graft versus host disease. In allogeneic cellular immunotherapy, graft versus host disease is a primary safety concern, yet invariant natural killer T cells are biologically distinct in that their invariant T cell receptor repertoire confers a minimal risk of inducing graft versus host disease compared to conventional allogeneic alpha beta T cells. Incorporating this immunological distinction would provide a compelling mechanistic justification for why allogeneic invariant natural killer T cells represent an attractive off the shelf platform for solid tumors.

In conclusion, this short communication provides a timely and well structured commentary on an exceptional clinical response. By expanding upon the unique biology of CD1d restricted lipid recognition, detailing the adjuvant role of dendritic cell co administration, and addressing graft versus host disease dynamics in allogeneic settings, the author can transform this overview into an authoritative perspective on invariant natural killer T cell therapy in solid oncology.

In your commentary, you highlight the six year complete remission reported by Cheng and colleagues in an HIV positive patient with recurrent EGFR L858R mutated lung adenocarcinoma who received allogeneic invariant natural killer T cells combined with dendritic cells. Given that invariant natural killer T cells recognize glycolipid antigens presented by monomorphic CD1d molecules rather than peptide antigens, what proportion of this clinical benefit do you attribute to the evasion of classical human leukocyte antigen downregulation on tumor cells versus the enhanced antigen presentation provided by the co administered dendritic cells? You accurately describe the hostile microenvironment of solid tumors, noting that regulatory T cells, myeloid derived suppressor cells, tumor associated macrophages, hypoxia, and inhibitory cytokines restrict cellular trafficking and effector function. What specific biological mechanisms allow invariant natural killer T cells to resist immune exhaustion within this immunosuppressive

contexture more effectively than conventional tumor infiltrating lymphocytes or chimeric antigen receptor T cells? When discussing the clinical translation of allogeneic off the shelf cellular platforms derived from healthy donors or induced pluripotent stem cells, you emphasize the need to evaluate persistence, host versus graft rejection, alloimmunization, and cytokine mediated toxicity. Why does your commentary omit a detailed appraisal of graft versus host disease, considering that the restricted T cell receptor diversity of invariant natural killer T cells theoretically minimizes this risk compared to conventional allogeneic alpha beta T cells? You cite the phase I trial by Iinuma and colleagues evaluating allogeneic induced pluripotent stem cell derived invariant natural killer T cells in recurrent head and neck cancer as evidence of platform feasibility. Since the therapeutic success reported by Cheng and colleagues relied on a dual infusion of invariant natural killer T cells and dendritic cells, do you anticipate that invariant natural killer T cell monotherapy can achieve comparable long term efficacy in solid tumors, or is the co administration of dendritic cells essential for sustained antitumour immunity? You emphasize that people living with HIV have historically been underrepresented in immunotherapy trials and recommend that future case reports capture longitudinal immune profiling, CD4 and CD8 T cell counts, and antiretroviral treatment details. In your opinion, how might specific classes of antiretroviral agents directly influence the in vivo persistence, proliferation, or cytotoxic signaling of infused allogeneic immune cells in this patient population? The case report under discussion involved a patient with an EGFR L858R mutated lung adenocarcinoma. How might underlying oncogenic driver mutations such as EGFR L858R alter the expression of CD1d lipid presentation molecules on lung cancer cells or modulate the chemokine gradients necessary for invariant natural killer T cell infiltration into the tumor bed? Your manuscript synthesizes important clinical progress in cell therapy, including the progression free survival benefit of tumor infiltrating lymphocytes reported by Rohaan and colleagues in advanced melanoma and the neoantigen specific T cell receptor gene therapy reported by Leidner and colleagues in pancreatic cancer. How do you compare the therapeutic potential of these peptide dependent autologous platforms against glycolipid targeting invariant natural killer T cells in solid tumors with low tumor mutational burdens? You note that autologous cellular therapies are constrained by manufacturing time, cost, patient specific variability, and treatment related lymphocyte dysfunction. What specific ex vivo expansion and differentiation hurdles must be overcome during the manufacturing of induced pluripotent stem cell derived invariant natural killer T cells to prevent phenotypic exhaustion and ensure product consistency across diverse patient cohorts? In the commented case, the patient experienced no documented progression after four treatment cycles and treatment discontinuation, with only grade 1 to 2 adverse events reported. From a clinical monitoring perspective, what specific circulating cytokine panels or host versus graft cellular biomarkers should be serialized during repetitive allogeneic infusions to detect early immunological rejection or subclinical alloimmunization? Invariant natural killer T cells are known to rapidly secrete both pro inflammatory Th1 cytokines such as interferon gamma and immunomodulatory Th2 cytokines such as interleukin 4 upon activation. How can future clinical protocols or genetic engineering strategies be designed to selectively bias allogeneic invariant natural killer T cells toward a Th1 antitumour phenotype while suppressing Th2 mediated immunosuppression within the solid tumor microenvironment?

Reviewer: 2

Comments to the Author
Nagai provides a timely commentary on the exceptional case reported by Cheng et al., in which an HIV-positive patient with recurrent EGFR L858R-mutated lung adenocarcinoma experienced a complete remission lasting more than six years following treatment with allogeneic invariant natural killer T (iNKT) cells in combination with dendritic cells. The manuscript appropriately places this observation within the broader development of cellular immunotherapy for solid tumors and highlights the potential relevance of allogeneic platforms in immunologically complex patient populations. The topic is clinically interesting, and the commentary is generally clear and balanced. However, several minor revisions would improve its precision, focus, and translational relevance.
The patient received both allogeneic iNKT cells and dendritic cells. Therefore, the clinical outcome cannot be attributed specifically to the iNKT-cell component. The commentary should briefly acknowledge the potential contribution of the dendritic-cell treatment and describe the intervention consistently as a combination therapy throughout the manuscript.
The broad overview of TILs, TCR-engineered T cells, CAR-T cells, NK cells, γδ T cells, and other cellular platforms is informative but occupies a substantial portion of this short commentary. Some of this material could be condensed to allow greater emphasis on the biological and translational rationale for iNKT-cell therapy. In particular, the authors could expand on the suitability of iNKT cells for allogeneic use, their endogenous CD1d-restricted recognition, their immunoregulatory functions, and the distinction between graft-versus-host disease and host-versus-graft rejection. The discussion should also acknowledge emerging stem cell-derived allogeneic iNKT-cell platforms, including the clinically guided generation of CAR-NKT cells from hematopoietic stem and progenitor cells reported by Li et al. (Nat Biotechnol. 2025;43:329–344).
The discussion currently ends with the section on HIV-positive populations and then proceeds directly to the declarations. A concise concluding paragraph would strengthen the commentary by emphasizing that this single case is hypothesis-generating rather than definitive evidence of efficacy. The authors should also briefly identify the next steps required for prospective evaluation, including validation in larger cohorts, clarification of the contribution of each treatment component, and assessment of durability, safety, and reproducibility.

Date Sent: 25-Jul-2026

Journal of Clinical Question

Author's Response to Decision Letter for (JCQ-2026-0024)

Cell Therapy for Solid Tumours: From an Exceptional iNKT-Cell Response to a Testable Therapeutic Platform

Response Letter

Response to Reviwer 1
We sincerely thank the reviewer for the careful and comprehensive evaluation of our commentary and for recognizing its clinical relevance, particularly its contextualization of the exceptional response reported by Cheng and colleagues within the broader development of cellular immunotherapy for solid tumors. We also appreciate the reviewer's positive assessment of the discussion of recent advances in TIL and T-cell receptor therapies, the barriers imposed by the solid-tumor microenvironment, and the clinical importance of considering people living with HIV in future cellular-therapy studies.
The reviewer has identified several important areas in which the immunological and translational discussion could be strengthened. In response, we have expanded the commentary to clarify the biological significance of CD1d-restricted glycolipid recognition, the potential reciprocal interaction between iNKT cells and dendritic cells, the theoretical influence of antiretroviral therapy on adoptive cellular treatment, and the comparatively low but not absent risk of graft-versus-host disease associated with allogeneic iNKT-cell products. Because this article is a commentary on a single exceptional case, these mechanisms are presented as biologically plausible interpretations and priorities for future investigation rather than as mechanisms established in the reported patient.

In your commentary, you highlight the six year complete remission reported by Cheng and colleagues in an HIV positive patient with recurrent EGFR L858R mutated lung adenocarcinoma who received allogeneic invariant natural killer T cells combined with dendritic cells. Given that invariant natural killer T cells recognize glycolipid antigens presented by monomorphic CD1d molecules rather than peptide antigens, what proportion of this clinical benefit do you attribute to the evasion of classical human leukocyte antigen downregulation on tumor cells versus the enhanced antigen presentation provided by the co administered dendritic cells?
Response: We appreciate this insightful question. It is not possible to determine the relative contribution of evasion of classical HLA downregulation versus dendritic-cell-mediated immune activation from this single case. CD1d-restricted recognition may allow iNKT cells to bypass some forms of peptide–HLA immune escape; however, the intervention also included dendritic cells, which may have enhanced glycolipid presentation, co-stimulation, cytokine production, and activation of endogenous NK and T cells. The clinical outcome should therefore be interpreted as arising from a combination strategy rather than being attributed specifically to the iNKT-cell component. We have clarified this point throughout the commentary.

You accurately describe the hostile microenvironment of solid tumors, noting that regulatory T cells, myeloid derived suppressor cells, tumor associated macrophages, hypoxia, and inhibitory cytokines restrict cellular trafficking and effector function. What specific biological mechanisms allow invariant natural killer T cells to resist immune exhaustion within this immunosuppressive contexture more effectively than conventional tumor infiltrating lymphocytes or chimeric antigen receptor T cells?
Response: We thank the reviewer for raising this important mechanistic consideration. The available evidence does not demonstrate that iNKT cells are intrinsically more resistant to exhaustion than TILs or CAR-T cells. Their potential advantages include rapid cytokine secretion, reduced dependence on classical HLA-restricted recognition, direct cytotoxicity, and the ability to activate other innate and adaptive immune cells. Nevertheless, iNKT cells may also develop anergy or functional impairment under chronic antigenic stimulation, hypoxia, inhibitory cytokines, and checkpoint signaling. We have therefore framed these characteristics as distinct functional properties rather than established resistance to exhaustion.

When discussing the clinical translation of allogeneic off the shelf cellular platforms derived from healthy donors or induced pluripotent stem cells, you emphasize the need to evaluate persistence, host versus graft rejection, alloimmunization, and cytokine mediated toxicity. Why does your commentary omit a detailed appraisal of graft versus host disease, considering that the restricted T cell receptor diversity of invariant natural killer T cells theoretically minimizes this risk compared to conventional allogeneic alpha beta T cells?
Response: We appreciate this important observation. The invariant T-cell receptor and CD1d restriction of iNKT cells theoretically reduce the risk of graft-versus-host disease compared with conventional allogeneic αβ T cells because their recognition is less dependent on polymorphic HLA molecules. However, this risk cannot be assumed to be absent, particularly in the presence of product heterogeneity, contaminating conventional T cells, genetic modification, or prolonged cellular persistence. We agree that graft-versus-host disease warrants explicit consideration and have incorporated it into the discussion of allogeneic-platform safety.

You cite the phase I trial by Iinuma and colleagues evaluating allogeneic induced pluripotent stem cell derived invariant natural killer T cells in recurrent head and neck cancer as evidence of platform feasibility. Since the therapeutic success reported by Cheng and colleagues relied on a dual infusion of invariant natural killer T cells and dendritic cells, do you anticipate that invariant natural killer T cell monotherapy can achieve comparable long term efficacy in solid tumors, or is the co administration of dendritic cells essential for sustained antitumour immunity?
Response: We thank the reviewer for this clinically relevant question. Current evidence is insufficient to determine whether iNKT-cell monotherapy can achieve efficacy comparable to that observed in the reported combination-treatment case. Dendritic cells may provide important antigen-presenting and co-stimulatory functions and may facilitate broader endogenous antitumor immunity. Conversely, early studies of iPSC-derived iNKT-cell monotherapy suggest that biological activity may occur without co-administered dendritic cells. Comparative clinical studies will therefore be necessary to determine whether dendritic-cell administration is essential, selectively beneficial, or replaceable by alternative activation strategies.

You emphasize that people living with HIV have historically been underrepresented in immunotherapy trials and recommend that future case reports capture longitudinal immune profiling, CD4 and CD8 T cell counts, and antiretroviral treatment details. In your opinion, how might specific classes of antiretroviral agents directly influence the in vivo persistence, proliferation, or cytotoxic signaling of infused allogeneic immune cells in this patient population?
Response: We appreciate this thoughtful question. Direct effects of individual antiretroviral classes on the persistence, proliferation, or cytotoxic signaling of infused allogeneic immune cells remain poorly defined. Effective antiretroviral therapy may indirectly support cellular immunotherapy by suppressing viral replication, reducing chronic immune activation, and promoting immune reconstitution. In contrast, mitochondrial toxicity, metabolic effects, organ dysfunction, or drug–drug interactions associated with some antiretroviral agents could theoretically influence cellular fitness or treatment tolerability. Future reports should therefore document the precise antiretroviral regimen, HIV viral load, CD4 and CD8 counts, organ function, concomitant medications, and cellular pharmacokinetics.

The case report under discussion involved a patient with an EGFR L858R mutated lung adenocarcinoma. How might underlying oncogenic driver mutations such as EGFR L858R alter the expression of CD1d lipid presentation molecules on lung cancer cells or modulate the chemokine gradients necessary for invariant natural killer T cell infiltration into the tumor bed?
Response: We thank the reviewer for highlighting this area of uncertainty. A direct relationship between EGFR L858R and CD1d expression or lipid-antigen presentation has not been established. Nevertheless, oncogenic EGFR signaling may contribute to an immunologically less inflamed tumor microenvironment through altered chemokine production, reduced lymphocyte recruitment, and modulation of immune-regulatory pathways. Whether these changes specifically affect iNKT-cell trafficking or CD1d-mediated recognition remains unknown. We have therefore presented this as an important question for future studies rather than as an established mechanism.

Your manuscript synthesizes important clinical progress in cell therapy, including the progression free survival benefit of tumor infiltrating lymphocytes reported by Rohaan and colleagues in advanced melanoma and the neoantigen specific T cell receptor gene therapy reported by Leidner and colleagues in pancreatic cancer. How do you compare the therapeutic potential of these peptide dependent autologous platforms against glycolipid targeting invariant natural killer T cells in solid tumors with low tumor mutational burdens?
Response: We appreciate this thoughtful comparison. TIL and neoantigen-specific T-cell receptor therapies can generate highly specific antitumor responses but generally depend on immunogenic peptide antigens, intact HLA expression, identifiable tumor-reactive clones, and individualized manufacturing. These requirements may limit their applicability in tumors with low mutational burden or impaired HLA expression. iNKT cells, by contrast, recognize glycolipid antigens through CD1d and may recruit broader innate and adaptive immune responses. However, their clinical development remains limited by variable CD1d expression, incompletely characterized tumor-associated lipid antigens, and insufficient evidence of durable efficacy. These platforms are therefore better regarded as complementary rather than directly competing approaches.

You note that autologous cellular therapies are constrained by manufacturing time, cost, patient specific variability, and treatment related lymphocyte dysfunction. What specific ex vivo expansion and differentiation hurdles must be overcome during the manufacturing of induced pluripotent stem cell derived invariant natural killer T cells to prevent phenotypic exhaustion and ensure product consistency across diverse patient cohorts?
Response: We thank the reviewer for raising this important translational issue. Major challenges include maintaining genomic stability, eliminating residual undifferentiated cells, achieving reproducible lineage differentiation, preserving the invariant T-cell receptor phenotype, and avoiding excessive stimulation that may induce anergy or terminal differentiation. Additional priorities include GMP-compatible culture systems, consistent post-thaw viability, preserved cytotoxic activity, and robust lot-to-lot reproducibility. Product characterization should therefore include identity, purity, genomic integrity, proliferative capacity, cytokine production, metabolic fitness, cytotoxic function, and markers of differentiation or exhaustion.

In the commented case, the patient experienced no documented progression after four treatment cycles and treatment discontinuation, with only grade 1 to 2 adverse events reported. From a clinical monitoring perspective, what specific circulating cytokine panels or host versus graft cellular biomarkers should be serialized during repetitive allogeneic infusions to detect early immunological rejection or subclinical alloimmunization?

Response: We appreciate this clinically important suggestion. Serial monitoring should ideally integrate inflammatory, cellular, and humoral assessments. Relevant measurements may include IFN-γ, IL-6, TNF, IL-2, IL-4, IL-10, IL-15, CXCL9, and CXCL10, together with C-reactive protein, ferritin, blood counts, liver function, and coagulation parameters. Donor-cell persistence may be assessed using donor-specific HLA markers, short-tandem-repeat analysis, digital polymerase chain reaction, or product-specific molecular tracking. Host-versus-graft immunity may be evaluated through donor-specific anti-HLA antibodies, panel-reactive antibodies, recipient cellular responses, and serial changes in activated host CD8-positive T cells and NK cells.

Invariant natural killer T cells are known to rapidly secrete both pro inflammatory Th1 cytokines such as interferon gamma and immunomodulatory Th2 cytokines such as interleukin 4 upon activation. How can future clinical protocols or genetic engineering strategies be designed to selectively bias allogeneic invariant natural killer T cells toward a Th1 antitumour phenotype while suppressing Th2 mediated immunosuppression within the solid tumor microenvironment?
Response: We thank the reviewer for this constructive question. Future protocols may seek to enrich NKT1-like populations characterized by high T-bet and Eomes expression, strong IFN-γ production, preserved cytotoxicity, and limited IL-4 or IL-13 secretion. Potential approaches include optimized cytokine conditions during manufacturing, Th1-biased glycolipid agonists, IL-15 support, tumor-directed activation, resistance to TGF-β signaling, and genetic enhancement of type 1 transcriptional programs. Functional release criteria could include the IFN-γ-to-IL-4 ratio in addition to conventional cytotoxicity assays. However, excessive Th1 polarization may increase systemic inflammation, and any such strategy would require careful preclinical and clinical safety evaluation.
We again thank the reviewer for these thoughtful and academically stimulating comments. The revised manuscript now provides a more focused discussion of the biological mechanisms, safety considerations, and translational uncertainties surrounding allogeneic iNKT-cell and dendritic-cell combination therapy. We believe these revisions have strengthened the scientific depth of the commentary while maintaining an appropriately cautious interpretation of this exceptional single case.

Response to Reviewer 2
We sincerely thank Reviewer 2 for the careful and constructive evaluation of our commentary. We appreciate the reviewer's recognition of the clinical relevance of the case and the balanced discussion of cellular immunotherapy in solid tumors. The suggested revisions have helped us improve the precision, focus, and translational relevance of the manuscript.
The patient received both allogeneic iNKT cells and dendritic cells. Therefore, the clinical outcome cannot be attributed specifically to the iNKT-cell component. The commentary should briefly acknowledge the potential contribution of the dendritic-cell treatment and describe the intervention consistently as a combination therapy throughout the manuscript.
Response: We agree that the prolonged complete remission cannot be attributed specifically to the iNKT-cell component because the patient received allogeneic iNKT cells in combination with dendritic cells. The dendritic-cell treatment may have contributed through glycolipid presentation, co-stimulation, cytokine production, and activation of endogenous NK and T-cell responses. We have therefore revised the manuscript to describe the intervention consistently as an allogeneic iNKT-cell and dendritic-cell combination therapy and have explicitly acknowledged that the relative contribution of each component cannot be determined from this single case.

The broad overview of TILs, TCR-engineered T cells, CAR-T cells, NK cells, γδ T cells, and other cellular platforms is informative but occupies a substantial portion of this short commentary. Some of this material could be condensed to allow greater emphasis on the biological and translational rationale for iNKT-cell therapy.
Response: We appreciate this important suggestion. The overview of other cellular platforms has been condensed to allow greater emphasis on the biological and translational rationale for iNKT-cell therapy. The revised discussion now highlights the endogenous CD1d-restricted recognition of glycolipid antigens, reduced dependence on polymorphic HLA molecules, rapid cytokine secretion, direct cytotoxicity, and the capacity of iNKT cells to activate dendritic cells, NK cells, and conventional T cells. We have also clarified that the restricted T-cell receptor repertoire of iNKT cells may reduce the risk of graft-versus-host disease compared with conventional allogeneic αβ T cells, whereas host-versus-graft rejection remains an important limitation to persistence. In addition, we have incorporated emerging stem cell-derived allogeneic iNKT-cell approaches, including the clinically guided generation of CAR-NKT cells from hematopoietic stem and progenitor cells reported by Li et al. in Nature Biotechnology.

In particular, the authors could expand on the suitability of iNKT cells for allogeneic use, their endogenous CD1d-restricted recognition, their immunoregulatory functions, and the distinction between graft-versus-host disease and host-versus-graft rejection. The discussion should also acknowledge emerging stem cell-derived allogeneic iNKT-cell platforms, including the clinically guided generation of CAR-NKT cells from hematopoietic stem and progenitor cells reported by Li et al. (Nat Biotechnol. 2025;43:329–344).
Response: We agree that these two immunological processes should be distinguished more clearly. Graft-versus-host disease results from donor immune cells attacking recipient tissues and is expected to be less frequent with iNKT-cell products because of their restricted invariant T-cell receptor and CD1d-dependent recognition. In contrast, host-versus-graft rejection reflects recipient immune responses against the infused allogeneic cells and may limit their persistence and repeated administration. The manuscript has been revised to clarify this distinction and to identify both processes as relevant, but biologically different, considerations in the clinical development of off-the-shelf iNKT-cell platforms.

The discussion currently ends with the section on HIV-positive populations and then proceeds directly to the declarations. A concise concluding paragraph would strengthen the commentary by emphasizing that

this single case is hypothesis-generating rather than definitive evidence of efficacy. The authors should also briefly identify the next steps required for prospective evaluation, including validation in larger cohorts, clarification of the contribution of each treatment component, and assessment of durability, safety, and reproducibility.
Response: We thank the reviewer for this helpful recommendation. A concise concluding paragraph has been added to emphasize that the reported case is hypothesis-generating and should not be regarded as definitive evidence of efficacy. The revised conclusion identifies the principal next steps for prospective evaluation, including validation in larger patient cohorts, clarification of the respective contributions of iNKT cells and dendritic cells, characterization of cellular persistence and host immune responses, and assessment of the durability, safety, and reproducibility of treatment outcomes.
We again thank Reviewer 2 for the careful and constructive assessment of our manuscript. The suggested revisions have improved the precision, focus, and translational relevance of the commentary, particularly regarding the contribution of dendritic cells, the biological rationale for allogeneic iNKT-cell platforms, and the distinction between graft-versus-host disease and host-versus-graft rejection. We believe the revised conclusion also more clearly defines this case as hypothesis-generating and outlines the priorities for future prospective evaluation.

Best Regards
Hisashi Nagai
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