Decision Letter (JCQ-2026-0016)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0016

Body: 1-May-2026

Dear Dr Xu:

Manuscript ID JCQ-2026-0016 entitled "Complete Remission Lasting Over 6 Years After Allogeneic iNKT Cell Immunotherapy in an HIV-Positive Patient With Lung Adenocarcinoma: A Case Report" 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.

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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
In this study, the authors report a clinical case demonstrating complete remission lasting over 6 years following allogeneic invariant natural killer T (iNKT) cell immunotherapy in an HIV-positive patient with recurrent lung adenocarcinoma. The patient received four cycles of allogeneic iNKT cells combined with dendritic cells, resulting in durable complete tumor remission that persisted for more than 6 years after treatment discontinuation. This study provides important clinical evidence supporting the safety and therapeutic potential of allogeneic iNKT cell–based immunotherapy for cancer treatment, particularly in selected HIV-positive patients.
I have the following comments and questions:
1. The allogeneic iNKT cells were generated from the patient's son. Please provide additional characterization of the infused iNKT cell product, including cell yield, purity, CD4/CD8 subset distribution, and phenotypic features. For example, analysis of markers such as CD45RO and CD62L would help define the differentiation and memory status of the expanded iNKT cells.
2. Please provide the HLA typing information for both the patient and the donor (son). Did they share highly similar HLA alleles? Additional discussion regarding the potential impact of HLA compatibility on iNKT cell persistence, engraftment, and antitumor efficacy would strengthen the manuscript.
3. The mechanism of tumor targeting remains unclear. Did the lung tumor cells express CD1d? If not, how do the infused iNKT cells mediate tumor killing? Alternatively, do iNKT cells exert indirect antitumor effects through activation of endogenous NK cells and $CD8^+$ T cells? Additional discussion regarding the mechanism of action (MOA) would be valuable.
4. Please clarify the rationale for administering four cycles of iNKT cells. Was repeated administration necessary due to limited in vivo persistence of transferred cells? If available, pharmacokinetic/pharmacodynamic (PK/PD) data or information regarding iNKT cell persistence would further strengthen the study.
5. As allogeneic iNKT cell immunotherapy is an emerging field, the Discussion section would benefit from a broader comparison with other allogeneic iNKT and CAR-iNKT cell therapy studies, including both preclinical and clinical reports. The authors should discuss key parameters such as cell source, manufacturing strategy, expansion yield, purity, functionality, efficacy, and safety. In particular, the following studies should be included and discussed: PMID: 34841295, 38744947, and 39893165.

Reviewer: 2

Comments to the Author
This manuscript presents a highly interesting and potentially important case of durable remission in an HIV-positive patient with recurrent EGFR-mutated lung adenocarcinoma treated with allogeneic iNKT cell immunotherapy. The exceptionally long follow-up period of more than six years after treatment discontinuation is a major strength and adds novelty to the report. The manuscript is generally well written and clinically relevant, particularly given the limited data available for iNKT cell-based immunotherapy approaches in HIV-associated malignancies. However, several areas require clarification and further detail to strengthen the scientific rigor of the report, particularly regarding disease characterization, attribution of therapeutic benefit, immune monitoring, and interpretation of mechanistic conclusions.

1. The authors should clarify how the postoperative lesion in the anterior segment of the left upper lobe was determined to represent recurrent disease rather than synchronous multifocal primary adenocarcinoma or residual disease after surgery. The manuscript states that the lesion shared the same EGFR exon 21 L858R mutation and was therefore considered highly suggestive of recurrence, but this evidence alone may not be sufficient because EGFR mutations are common in lung adenocarcinoma. Additional information regarding pathological comparison, radiographic progression, molecular clonality analysis, or multidisciplinary assessment would help justify the diagnosis and better define the actual disease stage at the start of iNKT therapy.

2. The discussion should more carefully address the possibility that surgery itself contributed substantially to the long-term favorable outcome. The patient initially had stage IA EGFR-mutated disease, which can sometimes have prolonged survival after resection alone. Because the manuscript attributes the durable remission largely to iNKT immunotherapy, the authors should provide a more balanced discussion of alternative explanations, including whether complete surgical resection was achieved, whether the postoperative lesion was definitively progressive before immunotherapy, and why the observed clinical course is unlikely to represent the natural history of limited-volume disease. This is especially important in a single-case report where causality cannot be established conclusively.

3. The immune monitoring data remain relatively limited for a manuscript proposing a novel immunologic mechanism of durable tumor control. The authors report stable HIV suppression, preserved CD4 counts, increased CD8+ T-cell populations, and normalization of the CD4/CD8 ratio, but additional longitudinal immune profiling would greatly strengthen the study. Specifically, it would be valuable to include serial immune cell counts, cytokine data, iNKT persistence or chimerism analyses, and any available markers of immune activation or exhaustion. If such data are unavailable, this limitation should be acknowledged explicitly in the Discussion section.

4. More methodological detail is needed regarding the allogeneic donor and safety monitoring procedures. The manuscript notes that the patient received iNKT cells from her son, but important immunologic details are lacking, including the degree of HLA matching, donor infectious disease screening, donor HIV status, and whether donor-specific antibodies or microchimerism were evaluated. Since the manuscript emphasizes the absence of GVHD and the feasibility of allogeneic iNKT therapy, these details are important for readers to interpret both safety and potential reproducibility.

5. The rationale for discontinuing therapy after four cycles should be explained more clearly. The manuscript emphasizes durable remission after treatment interruption, yet it remains unclear whether therapy cessation was protocol-defined, based on patient preference, due to toxicity, logistical considerations, or because clinicians believed maximal benefit had already been achieved. Clarifying this issue would help readers better understand the treatment strategy and the significance of the sustained remission observed after discontinuation.

6. The manuscript would benefit from a dedicated paragraph discussing the limitations of this report. Important limitations include the single-patient design, inability to establish causality, potential confounding effects of surgery and brief EGFR-targeted therapy, limited translational immune analyses, and uncertain generalizability to broader HIV-positive populations with lung cancer. Explicitly acknowledging these limitations would strengthen the credibility of the manuscript and help appropriately contextualize the findings for readers.

7. The authors report the development and clinical promise of allogeneic iNKT cell therapy, which represents a highly important and rapidly evolving field, particularly in the context of iNKT- and CAR-engineered cellular therapies. Accumulating evidence has demonstrated that these cells possess potent antitumor activity in multiple solid tumor models, with favorable tumor infiltration capacity and an encouraging safety profile. In the Discussion section, the authors should more comprehensively review the current landscape of allogeneic iNKT cell therapy in solid tumors, including recent studies in ovarian cancer (PMID: 40803321), breast cancer (PMID: 41077583), and pancreatic cancer (PMID: 41269799). These studies are highly relevant to the present report and would help better contextualize the translational significance and broader therapeutic potential of allogeneic iNKT-based immunotherapy.

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Author's Response to Decision Letter for (JCQ-2026-0016)

Complete Remission Lasting Over 6 Years After Allogeneic iNKT Cell Immunotherapy in an HIV-Positive Patient With Lung Adenocarcinoma: A Case Report

Dear Editor and Reviewers,
We sincerely thank the reviewers for their careful evaluation of our manuscript and for their constructive comments. We are encouraged that both reviewers recognized the potential clinical importance of this case, particularly the durable complete remission observed in an HIV-positive patient with recurrent EGFR-mutated lung adenocarcinoma following allogeneic iNKT cell-based immunotherapy. We have revised the manuscript to address the reviewers' concerns, including additional methodological details, a more balanced discussion of alternative explanations, expanded mechanistic interpretation, and broader contextualization of allogeneic iNKT and CAR-iNKT cell therapy. Our point-by-point responses are provided below.

Reviewer: 1
Comment 1. The allogeneic iNKT cells were generated from the patient's son. Please provide additional characterization of the infused iNKT cell product, including cell yield, purity, CD4/CD8 subset distribution, and phenotypic features. For example, analysis of markers such as CD45RO and CD62L would help define the differentiation and memory status of the expanded iNKT cells.
Response: We thank the reviewer for this important and constructive suggestion. We agree that additional characterization of the infused iNKT cell product is essential for improving the reproducibility and interpretation of this therapeutic intervention. In the present study, the allogeneic iNKT cells were generated from the patient's son, with an infused iNKT cell dose ranging from 1×109 - 5×109cells. The viability of the infused cell product was higher than 80%.
However, because this was an exploratory treatment performed according to a previously designed protocol, detailed subset and memory-phenotype analyses, including CD4/CD8 distribution and expression of CD45RO and CD62L, were not included in the original flow-cytometry panel. Therefore, these parameters could not be retrospectively assessed for the infused product. We have clarified this limitation in the revised manuscript. We also acknowledge that comprehensive phenotypic characterization, including CD4/CD8 subsets and differentiation/memory markers such as CD45RO and CD62L, should be incorporated into future iNKT-cell product evaluation to better define product composition and support reproducibility across studies.

Comment 2. Please provide the HLA typing information for both the patient and the donor (son). Did they share highly similar HLA alleles? Additional discussion regarding the potential impact of HLA compatibility on iNKT cell persistence, engraftment, and antitumor efficacy would strengthen the manuscript.
Response: We thank the reviewer for this important suggestion. We agree that HLA typing of both the patient and donor would have been useful for assessing donor–recipient compatibility. However, HLA typing was not performed in this case because it was not required for donor selection in the original protocol, which was based on the CD1d-restricted, non-classical HLA-restricted biology of iNKT cells. We have clarified this point in the revised manuscript and acknowledged it as a limitation. Although iNKT cells are expected to have lower HLA-driven alloreactivity than conventional allogeneic T cells, HLA compatibility may still indirectly influence host-versus-graft responses, infused-cell persistence, engraftment, and antitumor activity. Because HLA typing was not performed, we cannot determine the degree of donor–recipient HLA similarity or its potential impact on clinical outcome.
"Although HLA typing was not performed in this case, donor–recipient HLA compatibility may still be relevant to the interpretation of allogeneic iNKT-cell therapy. HLA disparity could theoretically promote host-versus-graft immune responses, potentially limiting the persistence, engraftment, or functional duration of infused donor-derived iNKT cells. Conversely, greater donor–recipient HLA similarity may reduce immune-mediated rejection and support longer persistence or antitumor activity. Therefore, the absence of HLA typing, donor-specific antibody assessment, and longitudinal iNKT-cell persistence monitoring represents an important limitation of this report. Future studies should incorporate donor–recipient HLA typing together with immune monitoring and persistence/chimerism analyses to clarify how HLA compatibility influences the safety and efficacy of allogeneic iNKT-cell therapy."

Comment 3. The mechanism of tumor targeting remains unclear. Did the lung tumor cells express CD1d? If not, how do the infused iNKT cells mediate tumor killing? Alternatively, do iNKT cells exert indirect antitumor effects through activation of endogenous NK cells and $CD8^+$ T cells? Additional discussion regarding the mechanism of action (MOA) would be valuable.
Response: We thank the reviewer for this insightful comment. We agree that the mechanism of action should be discussed more clearly. In this case, CD1d expression on the lung tumor cells was not assessed; therefore, we cannot determine whether the infused iNKT cells directly recognized and killed tumor cells through a CD1d-dependent mechanism. We have revised the Discussion to present a more balanced interpretation. While iNKT cells may directly kill CD1d-expressing tumor cells, they can also exert indirect

antitumor effects by producing cytokines such as IFN-γ and activating dendritic cells, endogenous NK cells, and $CD8^+$ T cells. Thus, the observed clinical effect may have involved broader immune activation rather than direct CD1d-restricted tumor recognition alone.
"This case supports the hypothesis that iNKT-cell therapy may contribute to tumor control through both direct and indirect immune mechanisms. However, because CD1d expression on the lung tumor cells was not assessed, direct CD1d-dependent tumor recognition cannot be confirmed. Beyond possible direct cytotoxicity against CD1d-expressing tumor cells, iNKT cells may promote antitumor immunity by producing IFN-γ, activating dendritic cells, and enhancing endogenous NK-cell and $CD8^+$ T-cell responses. These effects may help restore systemic immune surveillance and support durable tumor suppression, particularly in the setting of controlled HIV infection. Nevertheless, the precise mechanism remains uncertain because cytokine dynamics, iNKT-cell persistence, and immune activation markers were not systematically evaluated."

Comment 4. Please clarify the rationale for administering four cycles of iNKT cells. Was repeated administration necessary due to limited in vivo persistence of transferred cells? If available, pharmacokinetic/pharmacodynamic (PK/PD) data or information regarding iNKT cell persistence would further strengthen the study.
Response: We thank the reviewer for this helpful comment. We have clarified in the Case Presentation that the four-cycle schedule followed the original treatment plan and was selected based on clinical feasibility and prior experience with repeated NKT/iNKT-cell–based immunotherapy protocols, rather than patient-specific PK/PD data. Dedicated PK/PD analyses and longitudinal monitoring of infused donor-derived iNKT-cell persistence were not performed in this case. Therefore, we cannot determine whether repeated administration was required because of limited in vivo persistence or define the relationship between iNKT-cell persistence and clinical efficacy. We have added this limitation to the revised Discussion.
"Dedicated PK/PD analyses were also unavailable, limiting assessment of the relationship among repeated administration, in vivo persistence, immune remodeling, and clinical efficacy."

Comment 5. As allogeneic iNKT cell immunotherapy is an emerging field, the Discussion section would benefit from a broader comparison with other allogeneic iNKT and CAR-iNKT cell therapy studies, including both preclinical and clinical reports. The authors should discuss key parameters such as cell source, manufacturing strategy, expansion yield, purity, functionality, efficacy, and safety. In particular, the following studies should be included and discussed: PMID: 34841295, 38744947, and 39893165.
Response We thank the reviewer for this constructive suggestion. We have expanded the Discussion to compare our donor-derived non-CAR iNKT-cell approach with recent allogeneic iNKT and CAR-iNKT/CAR-NKT studies, including PMID 34841295, 38744947, and 39893165. We now discuss that HSC/HSPC-derived allogeneic iNKT or CAR-NKT cells can be generated as scalable off-the-shelf products with high expansion capacity, high purity, preserved iNKT functionality, and low alloreactivity/GVHD potential, with demonstrated antitumor activity including in AML/MDS models. We also clarify that, unlike these engineered platforms, our study used non-CAR donor-derived iNKT cells, which is less complex but may have limitations in scalability, antigen specificity, persistence, and standardized characterization. Future studies should systematically assess cell source, manufacturing strategy, expansion yield, purity, functionality, efficacy, persistence, and safety.
"iNKT- and CAR-iNKT/CAR-NKT–based therapies may provide a complementary immunotherapeutic strategy. Recent studies have shown that allogeneic HSC/HSPC-derived iNKT or CAR-NKT cells can be generated as scalable off-the-shelf products with high expansion capacity, preserved iNKT-cell functionality, and low alloreactivity/GVHD potential1,2. These platforms have demonstrated antitumor activity in hematologic malignancy models, including AML/MDS, and in multiple solid tumor models, including ovarian cancer, triple-negative breast cancer, and pancreatic cancer3-5. Importantly, allogeneic CAR-NKT cells may retain endogenous iNKT-cell properties, including tumor infiltration, cytokine secretion, NK-like cytotoxicity, and modulation of the tumor immune microenvironment, while also gaining CAR-mediated antigen specificity5,6. These findings support the broader translational potential of allogeneic iNKT-based immunotherapy, although its clinical efficacy, persistence, and safety in HIV-positive patients with lung cancer remain to be defined."

Reviewer: 2
Comment 1. The authors should clarify how the postoperative lesion in the anterior segment of the left upper lobe was determined to represent recurrent disease rather than synchronous multifocal primary adenocarcinoma or residual disease after surgery. The manuscript states that the lesion shared the same EGFR exon 21 L858R mutation and was therefore considered highly suggestive of recurrence, but this evidence alone may not be sufficient because EGFR mutations are common in lung adenocarcinoma. Additional information regarding pathological comparison, radiographic progression, molecular clonality analysis, or multidisciplinary assessment would help justify the diagnosis and better define the actual disease stage at the start of iNKT therapy.
Response: We thank the reviewer for this important comment. We agree that the shared EGFR exon 21 L858R mutation alone is insufficient to definitively establish recurrence, as this mutation is relatively common in lung adenocarcinoma. In the revised manuscript, we have clarified that the postoperative lesion in the anterior segment of the left upper lobe was considered highly suspicious for recurrence because biopsy showed histopathological similarity to the initial surgical specimen and the same EGFR exon 21 L858R mutation, together supporting recurrence of the primary lung cancer. We have also acknowledged that, because comprehensive molecular clonality analysis was not performed, synchronous multifocal primary adenocarcinoma or residual disease could not be completely excluded.
"Postoperative evaluation revealed a new nodule in the anterior segment of the left upper lobe. Biopsy showed histopathological similarity to the initial surgical specimen and the same EGFR exon 21 L858R mutation, supporting recurrence of the primary lung cancer. However, because molecular clonality analysis

was not performed, synchronous multifocal primary adenocarcinoma or residual disease could not be completely excluded."

Comment 2. The discussion should more carefully address the possibility that surgery itself contributed substantially to the long-term favorable outcome. The patient initially had stage IA EGFR-mutated disease, which can sometimes have prolonged survival after resection alone. Because the manuscript attributes the durable remission largely to iNKT immunotherapy, the authors should provide a more balanced discussion of alternative explanations, including whether complete surgical resection was achieved, whether the postoperative lesion was definitively progressive before immunotherapy, and why the observed clinical course is unlikely to represent the natural history of limited-volume disease. This is especially important in a single-case report where causality cannot be established conclusively.

Response: We thank the reviewer for this important comment. We agree that causality cannot be established in a single-case report and that the favorable long-term outcome cannot be attributed solely to iNKT-cell immunotherapy. In the revised Discussion, we provide a more balanced interpretation by noting that complete resection of the initial stage IA EGFR-mutated lung adenocarcinoma may have substantially contributed to disease control, and that synchronous multifocal primary adenocarcinoma or residual postoperative disease could not be definitively excluded because comprehensive molecular clonality analysis was not performed. Accordingly, we now describe iNKT-cell therapy as a potential contributing factor rather than the definitive cause of durable remission and have added this issue as a key limitation.

"As a single-case report, this study cannot establish a causal relationship between iNKT-cell therapy and the patient's long-term favorable outcome. Complete surgical resection of stage IA EGFR-mutated lung adenocarcinoma may have substantially contributed to disease control, and the absence of comprehensive molecular clonality analysis precludes definitive exclusion of synchronous multifocal primary adenocarcinoma or residual postoperative disease. Therefore, the durable remission observed in this case should be interpreted cautiously, and prospective studies with appropriate controls, standardized disease monitoring, and immune correlates are needed to clarify the therapeutic contribution of iNKT-cell therapy."

Comment 3. The immune monitoring data remain relatively limited for a manuscript proposing a novel immunologic mechanism of durable tumor control. The authors report stable HIV suppression, preserved CD4 counts, increased CD8+ T-cell populations, and normalization of the CD4/CD8 ratio, but additional longitudinal immune profiling would greatly strengthen the study. Specifically, it would be valuable to include serial immune cell counts, cytokine data, iNKT persistence or chimerism analyses, and any available markers of immune activation or exhaustion. If such data are unavailable, this limitation should be acknowledged explicitly in the Discussion section.

Response: We thank the reviewer for this important comment. We agree that more comprehensive longitudinal immune monitoring would have strengthened the mechanistic interpretation of this case. In the revised Discussion, we have clarified that immune monitoring was limited to routine clinical parameters, including HIV viral load, CD4 counts, $CD8^+$ T-cell populations, and CD4/CD8 ratio. Cytokine profiling, iNKT-cell persistence or chimerism analysis, and immune activation/exhaustion markers were not included in the original protocol and were not performed. We have acknowledged this as a limitation and revised the mechanistic interpretation more cautiously.

"Second, immune monitoring was limited to routine clinical parameters; comprehensive longitudinal analyses, including cytokine profiling, iNKT-cell persistence or chimerism assessment, and immune activation/exhaustion markers, were not performed."

Comment 4. More methodological detail is needed regarding the allogeneic donor and safety monitoring procedures. The manuscript notes that the patient received iNKT cells from her son, but important immunologic details are lacking, including the degree of HLA matching, donor infectious disease screening, donor HIV status, and whether donor-specific antibodies or microchimerism were evaluated. Since the manuscript emphasizes the absence of GVHD and the feasibility of allogeneic iNKT therapy, these details are important for readers to interpret both safety and potential reproducibility.

Response: We thank the reviewer for this important comment. We have clarified that the donor was the patient's son and that donor infectious disease screening, including HIV testing and screening for other transmissible infections, was performed before cell collection; the donor was HIV-negative. The patient was monitored after infusion for infusion-related reactions, fever, organ toxicity, infection, and clinical signs of GVHD. We also clarified that HLA typing, donor-specific antibody assessment, and microchimerism/persistence analyses were not performed. Because donor–recipient HLA compatibility may influence host-versus-graft responses, iNKT-cell persistence, engraftment, and antitumor activity, we have acknowledged this as an important limitation and noted that future studies should include HLA typing, immune monitoring, and persistence/chimerism analyses.

"HLA typing was not performed in this case, donor–recipient HLA compatibility may still be relevant to the interpretation of allogeneic iNKT-cell therapy. HLA disparity could theoretically promote host-versus-graft immune responses, potentially limiting the persistence, engraftment, or functional duration of infused donor-derived iNKT cells. Conversely, greater donor–recipient HLA similarity may reduce immune-mediated rejection and support longer persistence or antitumor activity. Therefore, the absence of HLA typing, donor-specific antibody assessment, and longitudinal iNKT-cell persistence monitoring represents an important limitation of this report. Future studies should incorporate donor–recipient HLA typing together with immune monitoring and persistence/chimerism analyses to clarify how HLA compatibility influences the safety and efficacy of allogeneic iNKT-cell therapy."

Comment 5. The rationale for discontinuing therapy after four cycles should be explained more clearly. The manuscript emphasizes durable remission after treatment interruption, yet it remains unclear whether therapy cessation was protocol-defined, based on patient preference, due to toxicity, logistical considerations, or because clinicians believed maximal benefit had already been achieved. Clarifying this issue would help readers better understand the treatment strategy and the significance of the sustained

remission observed after discontinuation.
Response: We thank the reviewer for this helpful comment. We have clarified in the revised manuscript that iNKT-cell therapy was discontinued after completion of the planned four-cycle treatment course according to the original treatment plan. Treatment cessation was not due to toxicity, GVHD, disease progression, patient preference, or the clinical judgment that maximal benefit had been achieved. We also clarified that the durable remission observed after treatment discontinuation should be interpreted cautiously, as this single case cannot determine whether additional cycles would have provided further benefit or define the optimal treatment duration. This point has been added to the Discussion as a limitation.
"The four-cycle schedule followed the original treatment plan and was selected based on clinical feasibility and prior experience with repeated NKT/iNKT-cell–based immunotherapy protocols, rather than patient-specific PK/PD data7,8."
"Third, the durable remission observed in this case should be interpreted cautiously, and prospective studies with appropriate controls, standardized disease monitoring, predefined immune correlates, and persistence analyses are needed to clarify the therapeutic contribution of iNKT-cell therapy."

Comment 6. The manuscript would benefit from a dedicated paragraph discussing the limitations of this report. Important limitations include the single-patient design, inability to establish causality, potential confounding effects of surgery and brief EGFR-targeted therapy, limited translational immune analyses, and uncertain generalizability to broader HIV-positive populations with lung cancer. Explicitly acknowledging these limitations would strengthen the credibility of the manuscript and help appropriately contextualize the findings for readers.
Response: We thank the reviewer for this important suggestion. We have added a dedicated limitations paragraph to the Discussion. We now explicitly acknowledge the single-patient design, the inability to establish causality, and the possibility that the favorable outcome may have been influenced by complete surgical resection, brief EGFR-targeted therapy, or the natural history of limited-volume disease. We also note the lack of comprehensive molecular clonality analysis, limited translational immune analyses, and uncertain generalizability to broader HIV-positive populations with lung cancer. These revisions help contextualize the findings more cautiously.
"First, as a single-patient observation, this report cannot establish a causal relationship between iNKT-cell therapy and the patient's long-term favorable outcome. Complete surgical resection of stage IA EGFR-mutated lung adenocarcinoma, brief EGFR-targeted therapy, and the natural history of limited-volume disease may have contributed to disease control. In addition, the lack of comprehensive molecular clonality analysis prevents definitive exclusion of synchronous multifocal primary adenocarcinoma or residual postoperative disease."

Comment 7. The authors report the development and clinical promise of allogeneic iNKT cell therapy, which represents a highly important and rapidly evolving field, particularly in the context of iNKT- and CAR-engineered cellular therapies. Accumulating evidence has demonstrated that these cells possess potent antitumor activity in multiple solid tumor models, with favorable tumor infiltration capacity and an encouraging safety profile. In the Discussion section, the authors should more comprehensively review the current landscape of allogeneic iNKT cell therapy in solid tumors, including recent studies in ovarian cancer (PMID: 40803321), breast cancer (PMID: 41077583), and pancreatic cancer (PMID: 41269799). These studies are highly relevant to the present report and would help better contextualize the translational significance and broader therapeutic potential of allogeneic iNKT-based immunotherapy.
Response: We thank the reviewer for this helpful suggestion. We have expanded the Discussion to include recent allogeneic iNKT/CAR-NKT studies in ovarian cancer, breast cancer/triple-negative breast cancer, and pancreatic cancer, including the reviewer-suggested reports. We now discuss that allogeneic HSC/HSPC-derived iNKT or CAR-NKT cells can be generated as scalable off-the-shelf products with preserved functionality and low alloreactivity/GVHD potential. We also highlight their antitumor activity in hematologic and solid tumor models, including ovarian cancer, triple-negative breast cancer, and pancreatic cancer. These additions better contextualize the translational potential of allogeneic iNKT-based immunotherapy, while noting that its clinical efficacy, persistence, and safety in HIV-positive patients with lung cancer remain to be defined.
"iNKT- and CAR-iNKT/CAR-NKT–based therapies may provide a complementary immunotherapeutic strategy. Recent studies have shown that allogeneic HSC/HSPC-derived iNKT or CAR-NKT cells can be generated as scalable off-the-shelf products with high expansion capacity, preserved iNKT-cell functionality, and low alloreactivity/GVHD potential1,2. These platforms have demonstrated antitumor activity in hematologic malignancy models, including AML/MDS, and in multiple solid tumor models, including ovarian cancer, triple-negative breast cancer, and pancreatic cancer3-5. Importantly, allogeneic CAR-NKT cells may retain endogenous iNKT-cell properties, including tumor infiltration, cytokine secretion, NK-like cytotoxicity, and modulation of the tumor immune microenvironment, while also gaining CAR-mediated antigen specificity5,6. These findings support the broader translational potential of allogeneic iNKT-based immunotherapy, although its clinical efficacy, persistence, and safety in HIV-positive patients with lung cancer remain to be defined."

We again thank the reviewers for their valuable comments. Their suggestions have helped us substantially improve the methodological clarity, scientific balance, and translational context of the manuscript.

Best Regards
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