

Decision Letter (JCQ-2025-0001)**From:**

To: la6322@gmail.com

CC: la6322@gmail.com

BCC:**Subject:** Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0001**Body:** 10-Feb-2025

Dear Dr Uzair:

Manuscript ID JCQ-2025-0001 entitled "Efficacy and Safety of Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials" 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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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,

Professor EIC JCQ

Editor in Chief, Journal of Clinical Question

jqeic@gleampub.com

[Editor's Comments]

Associate Editor

Comments to the Author:

(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author

The authors should be congratulated for their work. They relied on PRISMA methodology enrolling 7 RCTs with 2,529 patients. The conclusions that they pointed out are however superficial. They cannot say only "GC-D demonstrates superior pCR rates and comparable safety, establishing it as a promising NAC option for MIBC.". They did not take into account ICIs neoadjuvant therapy (which has a proven efficacy for MIBC) PMID 34440975, 33269713, 30343614, 34008425. Moreover, they did not rely on important outcomes such as overall survival or cancer-specific survival. The pathologic response is an important outcome, but it should not be the only element that may drive the choice of a molecule over another. Moreover, the introduction section should be improved with novel papers on neoadjuvant settings in MIBC (PMID 39424431, 39160435, 38972785).

Reviewer: 2

Comments to the Author

The manuscript is well-structured and follows rigorous scientific methodology, but there are areas that could be improved for clarity, impact, and coherence. Here are my detailed recommendations:

1. Title & Abstract

Title: The title is clear but could be slightly refined for better readability. Example: "Efficacy and Safety of Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis of RCTs". The term "randomized controlled trials" could be abbreviated as RCTs since the audience will be familiar with it.

Abstract:

The background is well-defined, but the rationale behind choosing GC-D as the focus regimen could be more explicit.

The results section is detailed but could be more structured. Consider separating key outcomes (pCR, OS, AEs) with clearer transitions.

The conclusion should highlight implications for clinical practice more explicitly.

2. Introduction

- Presenting data-driven context upfront (e.g., global prevalence statistics in the first few lines).

- Adding a more explicit research gap before introducing the study objectives.

3. Methods

- Study Selection: Clearly structured, but the inclusion/exclusion criteria should explicitly mention the criteria for quality assessment beyond PRISMA adherence.

- Data Extraction & Bias Assessment: Well-documented, but the statistical software used should be stated earlier.

- Statistical Analysis: The method of network meta-analysis (NMA) is well-detailed, but it should clarify if there was a hierarchy of evidence strength when interpreting direct vs. indirect comparisons.

- Subgroup analysis criteria should be better justified in terms of clinical significance.

5. Discussion

- The discussion acknowledges heterogeneity but does not sufficiently propose ways to address this in future studies.

- The lack of standardization in chemotherapy cycles is an important limitation. It would help to propose how this could be resolved in future trial designs.

- The findings should be contextualized in current clinical practice guidelines (e.g., how does this impact NCCN or EAU guidelines?).

- Potential biomarkers for predicting response to GC-D should be mentioned if available.

6. Conclusion

- The conclusion is well-stated but could be more forward-looking by explicitly outlining the next steps in research or clinical trials.

Date Sent: 10-Feb-2025

Author's Response to Decision Letter for (JCQ-2025-0001)**Efficacy and Safety of Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials**

Response Letter

Dear Reviewer,

We sincerely appreciate your thorough review and valuable feedback on our manuscript. Your insightful comments have significantly contributed to improving the clarity and quality of our work. Below, we provide detailed responses to each of your comments and outline the corresponding revisions made to the manuscript.

Reviewer: 1

Major comment 1: They cannot say only "GC-D demonstrates superior pCR rates and comparable safety, establishing it as a promising NAC option for MIBC." They did not take into account ICIs neoadjuvant therapy (which has a proven efficacy for MIBC) PMID 34440975, 33269713, 30343614, 34008425.

Response: Thank you for your insightful comment. We acknowledge that our statement regarding GC-D as a promising neoadjuvant chemotherapy (NAC) option for MIBC did not account for the role of immune checkpoint inhibitors (ICIs) in the neoadjuvant setting. As these studies were not randomized controlled trials (RCTs) and followed a single-arm design, they were not suitable for inclusion in a network meta-analysis. We have incorporated this information into the discussion section as follows:

"Preliminary studies and ongoing trials, such as the PURE-01 and NABUCCO studies, have demonstrated the potential of ICI-based regimens to improve pCR rates and enhance immune responses against residual tumor cells.^{1,2} Similarly, other studies have discussed pembrolizumab's and nivolumab's efficacy as neoadjuvant MIBC therapies.³⁻⁵ However, the absence of a controlled arm precludes their inclusion in a meta-analysis. The results of ongoing phase 3 trials are eagerly awaited."

Comment 2: They did not rely on important outcomes such as overall survival or cancer-specific survival. The pathologic response is an important outcome, but it should not be the only element that may drive the choice of a molecule over another.

Response: Thank you for your insightful comment. We acknowledge that overall survival and cancer-specific survival are critical endpoints in evaluating treatment efficacy. While pathologic response serves as an important surrogate marker, it should not be the sole factor in treatment selection. However, long-term survival data from neoadjuvant ICI trials remain limited, with only a few studies reporting 3-year OS data. Consequently, our discussion primarily focused on pathologic response outcomes. To address this limitation, we have revised the discussion section to emphasize the need for longer follow-up and comprehensive survival analyses, as follows: "OS calculations were based on a three-year follow-up period, which is shorter than that used in most RCTs. This limited follow-up duration may impact the comprehensiveness of survival outcome evaluation, underscoring the necessity for long-term data to fully assess treatment efficacy."

Comment 3: The introduction section should be improved with novel papers on neoadjuvant settings in MIBC (PMID 39424431, 39160435, 38972785).

Response: Thank you for your valuable suggestion. We appreciate the recommendation to strengthen the introduction section by incorporating recent studies on neoadjuvant therapy in MIBC. In response, we have integrated discussions on these updated insights and revised the text as follows: "Although questions remain regarding the choice between NAC and adjuvant chemotherapy, particularly in specific racial groups,^{6,7} NAC has shown a survival advantage over RC alone, enhancing cancer-specific outcomes in both localized and advanced stages.⁸"

Reviewer 2:

Comment 1: Title: The title is clear but could be slightly refined for better readability. Example: "Efficacy and Safety of Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer: A Systematic Review and Network Meta-Analysis of RCTs". The term "randomized controlled trials" could be abbreviated as RCTs since the audience will be familiar with it.

Response: We appreciate the reviewer's insightful suggestion. We have modified the title accordingly, replacing "randomized controlled trials" with "RCTs" for clarity and conciseness.

Comment 2.1: Abstract: The background is well-defined, but the rationale behind choosing GC-D as the focus regimen could be more explicit.

Response: We appreciate the reviewer's comment on this point. We have added the following contents in introduction section to focus the GC-D regimen as follows: "Among these, durvalumab in combination with gemcitabine and cisplatin (GC-D) has gained attention for its potential efficacy in MIBC. However, its comparative effectiveness and safety relative to other NAC regimens remain unclear."

Comment 2.2 The results section is detailed but could be more structured. Consider separating key outcomes (pCR, OS, AEs) with clearer transitions.

Response: We appreciate the reviewer's comment on this point. We have added information about the outcomes in the Methods section and used abbreviations of pCR, OS, and AEs in the Results section to improve clarity.

Comment 2.3 The conclusion should highlight implications for clinical practice more explicitly.

Response: We appreciate the reviewer's insightful comment. To better emphasize the clinical implications, we have revised the conclusion to highlight the potential impact of GC-D on treatment decisions and its role in optimizing NAC strategies for MIBC. Accordingly, we have modified the conclusion as follows: "GC-D demonstrates superior pCR rates and overall survival (OS) while maintaining comparable safety to other NAC regimens, establishing it as a promising treatment option for MIBC. However, alternative regimens remain essential for patients in whom GC-D is not applicable."

Comment 3.1 Presenting data-driven context upfront (e.g., global prevalence statistics in the first few lines).

Response: We appreciate the reviewer's comment on this point. We have added data-driven context as follows: "In 2022, bladder cancer was diagnosed in over 600,000 individuals globally, leading to more than 220,000 related deaths.⁹"

Comment 3.2 Adding a more explicit research gap before introducing the study objectives.

Response: We appreciate the reviewer's comment. To explicitly highlight the research gap, we have added the following discussion: "Despite numerous clinical trials highlighting the potential of combining ICIs with GC and other regimens, a comprehensive analysis of their efficacy and safety remains limited. This gap is particularly evident in the context of recent study evaluating GC with durvalumab (GC-D), which have shown promising outcomes but require further validation through robust comparative analyses."

Comment 4.1 Study Selection: Clearly structured, but the inclusion/exclusion criteria should explicitly mention the criteria for quality assessment beyond PRISMA adherence.

Response: We appreciate the reviewer's suggestion. In addition to adhering to PRISMA guidelines, we ensured methodological rigor by incorporating quality assessment criteria. Specifically, we included only RCTs that were applicable for risk of bias assessment using the Cochrane Risk of Bias tool. The inclusion and exclusion criteria have been revised accordingly for clarity. "This study included RCTs that evaluated the efficacy and safety of NAC for MIBC. Eligible studies met the following criteria: (1) enrolled patients had histologically confirmed MIBC without metastatic disease, (2) NAC was administered prior to RC or definitive treatments, (3) reported survival outcomes such as pCR, overall survival (OS), or AEs, and (4) underwent quality assessment using the Cochrane Risk of Bias tool was applicable. Studies were excluded if they met any of the following criteria: (1) not an RCT, (2) published only as abstracts or preclinical data, and (3) lacked sufficient data for analysis. Only peer-reviewed journal articles were considered, with no language restrictions."

Comment 4.2: Data Extraction & Bias Assessment: Well-documented, but the statistical software used should be stated earlier.

Response: We appreciate the reviewer's suggestion. To enhance clarity, we have stated the statistical software used earlier in the manuscript as follows: "All statistical analyses were conducted using R (Version 4.4, R Foundation for Statistical Computing, Vienna, Austria)"

Comment 4.3 Statistical Analysis: The method of network meta-analysis (NMA) is well-detailed, but it should clarify if there was a hierarchy of evidence strength when interpreting direct vs. indirect comparisons.

Response: We appreciate the reviewer's comment. In our NMA, we accounted for the hierarchy of evidence strength when interpreting direct and indirect comparisons. Specifically, direct comparisons from head-to-head RCTs were prioritized over indirect comparisons, as they provide higher certainty in effect estimates. When only indirect evidence was available, we ensured consistency by evaluating the transitivity assumption and coherence between direct and indirect estimates. We have clarified this aspect in the statistical analysis section accordingly.

Comment 4.4 Subgroup analysis criteria should be better justified in terms of clinical significance.

Thank you for your insightful comment. We recognize the importance of clearly justifying the criteria for subgroup analysis in terms of clinical significance. However, due to the limited number of enrolled studies, subgroup analysis was feasible only for AE outcomes, as presented in Figure 2. We have clarified this limitation in the manuscript to ensure transparency regarding the scope of our analysis.

Comment 5. 1 The discussion acknowledges heterogeneity but does not sufficiently propose ways to address this in future studies.

Response: We appreciate this insightful suggestion and have revised the manuscript accordingly. We have added the following contents in discussion as follows: "High heterogeneity was observed in AEs, which can be attributed in part to differences in regimen compositions. Standardizing treatment protocols and incorporating a common add-on therapy in future studies may help reduce this heterogeneity."

Comment 5.2 The lack of standardization in chemotherapy cycles is an important limitation. It would help to propose how this could be resolved in future trial designs.

Thank you for highlighting this important limitation. We acknowledge that the lack of standardization in chemotherapy cycles introduces variability, which may affect the interpretation of treatment outcomes. To address this, we have revised the discussion section and added, "The variability in chemotherapy cycles across studies remains a significant limitation, potentially contributing to inconsistencies in treatment efficacy and adverse event profiles. Future clinical trials should aim to standardize the number and duration of chemotherapy cycles to improve comparability."

Comment 5.3 The findings should be contextualized in current clinical practice guidelines (e.g., how does this impact NCCN or EAU guidelines?).

Response: Thank you for your insightful comment. We acknowledge the importance of contextualizing our findings within current clinical practice guidelines to enhance their clinical relevance. We have revised the discussion section and added, "The National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines currently recommend cisplatin-based neoadjuvant chemotherapy as the standard of care.^{10,11} However, our results suggest that GC-D may offer an alternative option with comparable efficacy and safety profiles."

Comment 5.4 Potential biomarkers for predicting response to GC-D should be mentioned if available.

Response: We appreciate the reviewer's suggestion. We acknowledge the relevance of biomarkers in predicting treatment response. "Evidence suggests that PD-L1 expression, tumor mutational burden, and DNA damage response gene mutations may influence GC-D response.¹² However, variability in biomarker assessment and limited standardized data precluded a comprehensive analysis." We have incorporated this discussion accordingly.

Comment 6: The conclusion is well-stated but could be more forward-looking by explicitly outlining the next steps in research or clinical trials.

We appreciate the reviewer's comment on this point. To explicitly outline the next steps, we have added the following statement to the conclusion: "Further research is warranted to refine patient selection criteria and optimize NAC strategies to maximize clinical benefits."

Once again, we thank you for your time and constructive feedback. We believe that the revisions have strengthened the manuscript, and we hope that our responses sufficiently address your concerns. Please let us know if further clarifications or modifications are required.

Sincerely,
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References

1. Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study. *Journal of Clinical Oncology*. 2018;36(34):3353-3360. doi:10.1200/jco.2018.01148
2. van Dijk N, Gil-Jimenez A, Silina K, et al. Preoperative ipilimumab plus nivolumab in locoregionally advanced urothelial cancer: the NABUCCO trial. *Nature Medicine*. 2020;12/01 2020;26(12):1839-1844. doi:10.1038/s41591-020-1085-z
3. Peyrottes A, Ouzaid I, Califano G, Hermieu JF, Xylinas E. Neoadjuvant Immunotherapy for Muscle-Invasive Bladder Cancer. *Medicina (Kaunas)*. Jul 29 2021;57(8)doi:10.3390/medicina57080769
4. Califano G, Ouzaid I, Verze P, Stivalet N, Hermieu JF, Xylinas E. New immunotherapy treatments in non-muscle invasive bladder cancer. *Arch Esp Urol*. Dec 2020;73(10):945-953. Nuevos tratamientos de inmunoterapia en cáncer de vejiga no musculoinvasivo.
5. Galsky MD, Holmes CJ, Necchi A, et al. Perioperative pembrolizumab therapy in muscle-invasive bladder cancer: Phase III KEYNOTE-866 and KEYNOTE-905/EV-303. *Future Oncol*. Aug 2021;17(24):3137-3150. doi:10.2217/fon-2021-0273
6. de Angelis M, Siech C, Jannello LMI, et al. Neoadjuvant Versus Adjuvant Chemotherapy in Non-Metastatic Locally-Advanced Stage Radical Cystectomy Candidates. *Clin Genitourin Cancer*. Oct 2024;22(5):102132. doi:10.1016/j.clgc.2024.102132
7. de Angelis M, Jannello LMI, Siech C, et al. Race/Ethnicity Affects Access and Survival Differences After Neoadjuvant or Adjuvant Chemotherapy at Radical Cystectomy in Urothelial Carcinoma Patients. *J Racial Ethn Health Disparities*. Aug 19 2024;doi:10.1007/s40615-024-02131-9
8. de Angelis M, Jannello LMI, Siech C, et al. Neoadjuvant chemotherapy before radical cystectomy in patients with organ-confined and non-organ-confined urothelial carcinoma. *Urol Oncol*. Jan 2025;43(1):62.e1-62.e6. doi:10.1016/j.urolonc.2024.09.015
9. International Agency for Research on Cancer. Bladder cancer. https://www.iarc.who.int/cancer-type/bladder-cancer/?utm_source=chatgptcom (Published in 2022, Accessed on February 14, 2025).
10. The National Comprehensive Cancer Network. NCCN Guidelines Bladder Cancer Version 6.2024. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417&utm_source=chatgptcom (Published in 2024, Accessed on February 14, 2025).
11. European Association of Urology. Muscle-invasive and Metastatic Bladder Cancer. https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer/?utm_source=chatgptcom (Published in 2024, Accessed on February 14, 2025).
12. Labriola MK, Zhu J, Gupta RT, et al. Characterization of tumor mutation burden, PD-L1 and DNA repair genes to assess relationship to immune checkpoint inhibitors response in metastatic renal cell carcinoma. *J Immunother Cancer*. Mar 2020;8(1)doi:10.1136/jitc-2019-000319

1. [Response Letter.pdf](#) [PDF](#)

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