Response for Comments

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| No | Questions/Comments | Response |
| 1. | **Prof. Hu:**"For comparison table, please add the conclusions of these two papers. Do you believe the conclusions?" | Thank you for the comment, Professor Hu. I will add the conclusions of these two papers.Regarding the conclusion of the first study, it examined the effectiveness of bedaquiline use beyond six months in patients with MDR-TB using a target trial emulation approach. I believe this study design is particularly robust, as it employed data cloning to prevent immortal time bias and applied IPTW (Inverse Probability of Treatment Weighting) to adjust for potential confounding. Therefore, I consider the findings to be reliable. Moreover, the study also compared its results with those from a naïve analysis, further strengthening the credibility of its conclusions. |
| 2.  | Chiu- Wen Chang : In this study, it estimated a small decrease in the probability of successful **treatment for 7–11 months** compared with 6 months of BDQ. Do you think there is **misclassification** of treatment? How do you explain the impact? (Paper 1) | I agree that misclassification and immortal time bias is a potential issue in this study. **With an 89% adherence rate, around 11%** of patients did not fully comply with the treatment protocol, which could lead to misclassification bias. However, the study try to avoid immortal time bias by using statistical approach such as **cloning and censoring,** to provide more accurate comparison between treatment durations. As a result, the potential impact of misclassification **is minimized,** reducing its influence on the study’s overall conclusions |
| 3. | The characteristics of participants, there are 80%(n=1,181) of previous TB treatment with second-line drugs. Could it influence the results? (Paper 1) | The high proportion of previously treated patients could influence the results, particularly by lowering success rates due to resistance and disease severity. However, the study applied statistical **adjustments (IP Weighting) to control for confounding.** I believe it will reduce this potential bias and minimize the effect to outcome |
| 4. | There are 10%(n=149) of missing with extensive disease. Could it influence the results? (Paper 1) | The 10% missing data on extensive disease could influence the results, particularly by underestimating disease severity and potentially biasing BDQ duration comparisons.However, in this study the authors have adjusted this problem using IP weighting to control confounding and make it balance comparison between three group. So, the impact to outcome will be minimial. |
| 5. | **Takeshi:** Low coverage in the U.K.Why is the coverage in the U.K. so low (10%) compared to other countries/regions, which reported data for 80–100% of patients treated with bedaquiline and delamanid? Does the value of including U.K. data outweigh the potential risk of bias (though could be small due to small *n*) in the overall results? | The low UK data coverage (10%) may introduce bias due to underrepresentation, with only four cases enrolled, limiting statistical power. However, since this is a **descriptive study**, the researchers included UK data for geographic diversity and healthcare insights. Given the large cohort from 29 countries, the impact of this bias is minimal, with limited influence on overall conclusions. |
| 6. | Patient-centred outcomesThe study reports on clinical outcomes such as culture conversion and treatment success, but how might the use of bedaquiline-containing regimens impact patients’ quality of life and adherence to treatment? What additional patient-centred outcomes should be considered in future studies? | * The impact of bedaquiline-containing regimens on patients’ quality of life and adherence is truly important. Bedaquiline offers an all-oral, less toxic regimen, shorter duration treatment, potentially improving treatment adherence.
* However, prolonged BDQ use may also lead to adverse events like QT prolongation, (not frequent) which could impact patient well-being and willingness to continue treatment.
* Additional patient center we can consider: **quality of life, treatment adherence, incidence of adverse effect.**
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