

# Response to the Article on Antibiotics and Immune Checkpoint Inhibitors by Lin et al.

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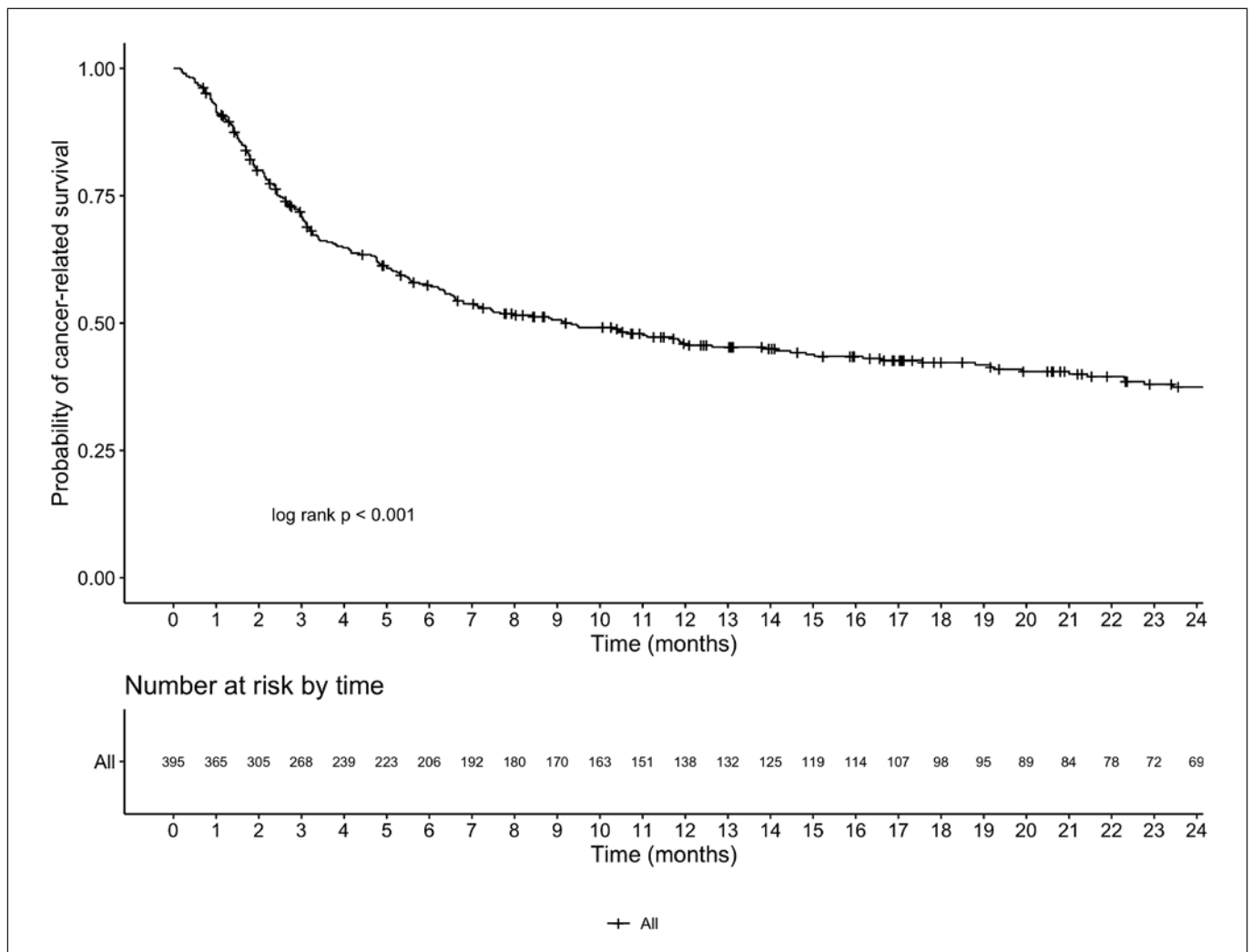
We thank Lin et al. [1] for their comments on our manuscript entitled “Use of antibiotics during immune checkpoint inhibitors associates with lower survival in hepatocellular carcinoma” [2]. Several issues were raised in the letter including the start time for survival analysis, the details of survival time with Kaplan-Meier curve, and definition of cancer-related death.

We would like to first highlight that a corrigendum has been made concerning the follow-up time [3]. The median follow-up should be 6.6 months (IQR: 2.3–17.8) with 4,810 person-months. The median time from receiving the first ICI to cancer-related and all-cause mortality should be 3.1 months (IQR: 1.6–6.7) and 3.2 months (IQR: 1.7–8.2), respectively.

In the “Outcome definition” paragraph of our manuscript, it was mentioned that patients were observed from the start date of first immune checkpoint inhibitor as the index date till the occurrence of the outcome of interest or end of study. In the same paragraph, we have defined the primary outcome of cancer-related mortality as “liver cancer specified as the cause of death in the database” by the diagnosis codes.

In the whole cohort, the 3-month, 6-month, 1-year, and 2-year probability of cancer-related survival was 70.7% (95% CI: 66.3–75.4%), 57.4% (95% CI: 52.6–62.6%), 45.9% (95% CI: 41.1–51.4%), and 37.4% (32.4–43.3%), respectively. Figure 1 shows the Kaplan-Meier survival plot of the whole cohort.

Among the antibiotic users, the 3-month, 6-month, 1-year, and 2-year probability of cancer-related survival was 50.9% (95% CI: 42.0–61.7%), 35.3% (95% CI: 26.9–46.4%), 26.8% (95% CI: 19.1–37.7%), and 19.3% (12.0–31.1%), respectively. For antibiotic nonusers, the 3-month, 6-month, 1-year, and 2-year probability of cancer-related survival was 77.8% (95% CI: 73.1–82.8%), 64.7% (95% CI: 59.4–70.6%), 52.2% (95% CI: 46.5–58.5%), and 43.6% (37.7–50.5%), respectively. There was significant difference in cancer-related survival between the two groups (log-rank  $p < 0.001$ ). Figure 2 shows the Kaplan-Meier survival plot according to antibiotic use.



**Fig. 1.** Kaplan-Meier plot for cancer-related survival of the whole cohort.

### Conflict of Interest Statement

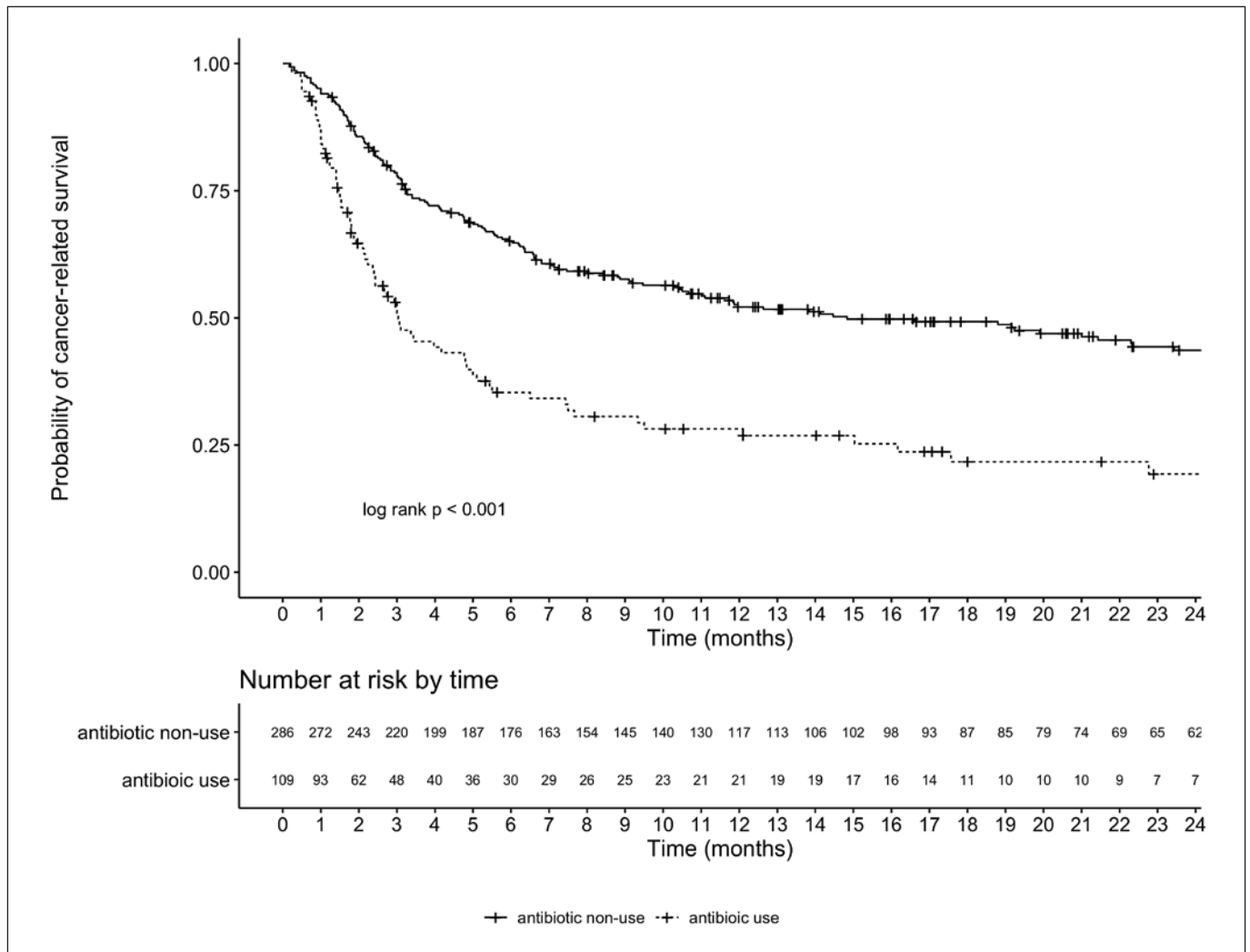
The authors have no conflicts of interest to declare.

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### Author Contributions

Dr. Ka Shing Cheung was involved with study concept and design, literature search, analysis and interpretation of data, drafting of manuscript, and approval of the final version of the manuscript. Professor Wai K. Leung was involved with the study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision; and approval of the final version of the manuscript.



**Fig. 2.** Kaplan-Meier plot for cancer-related survival according to antibiotic use.

## References

- 1 Lin KY, Tang SC, Zhang CW, Zeng YY, Yang T. Impact of antibiotics use on cancer-related and all-cause mortality among patients receiving immunotherapy for advanced hepatocellular carcinoma. *Liver Cancer*. 2022; doi: 10.1159/000525028.
- 2 Cheung KS, Lam LK, Seto WK, Leung WK. Use of antibiotics during immune checkpoint inhibitor treatment is associated with lower survival in hepatocellular carcinoma. *Liver Cancer*. 2021;10(6):606–14.
- 3 Erratum. *Liver Cancer* 2022;11:397.