SYSTEMATIC REVIEW AND META-ANALYSIS EVALUATING THE IMPACT OF ANTIBIOTIC USE ON CLINICAL OUTCOMES OF NON-SMALL-CELL LUNG CANCER PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background In recent years, the gut microbiome has increasingly emerged as influencing the response to immune checkpoint inhibitors (ICIs).¹⁻³ Antibiotic (ABX) exposure, that leads to microbiome dysbiosis, was further shown in numerous studies to adversely influence the clinical outcomes of cancer patients treated with ICIs, especially in non-small-cell lung cancer (NSCLC).⁴⁻⁶ We published in 2020 a meta-analysis confirming that ABX use could hamper survival of NSCLC patients treated with ICIs.⁷ The present study aims at updating this prior work by incorporating studies published until July 2021 and by studying new clinical outcomes.

Methods PubMed and major oncology conferences' proceedings were systematically searched to identify studies assessing the impact of ABX on the clinical outcomes of NSCLC patients treated with ICIs. Studies were included when reporting a hazard ratio (HR) or Kaplan-Meier curves for Overall Survival (OS) or Progression-Free Survival (PFS) based on antibiotic exposure, and/or data on treatment response such as Overall Response Rate (ORR) and Progressive Disease Rate (PD) according to antibiotic exposure. Pooled HRs for OS and PFS and Odds Ratios (OR) for ORR and PD were calculated, as well as HRs for OS and PFS according to different time windows of ABX exposure.

Results Overall, 35 independent cohorts were included for a total of 12,235 patients. The pooled HRs for OS (12,235 patients) and PFS (5,356 patients) were 1.63 [95% Confidence Interval (CI) 1.37–1.94] and 1.49 [95% CI 1.26–1.76], respectively, confirming a significantly reduced survival in patients exposed to ABX. The subgroup analyses of OS and PFS based on the time window of ABX exposure (figures 1 and 2) suggest a harmful effect of ABX when taken around ICI initiation. The pooled OR for ORR (1,992 patients) and PD (1,272 patients) were 0.66 [95% CI 0.44–0.99] and 1.98 [95% CI 1.39–2.8], respectively, reflecting both a decreased odd of treatment response and an almost two-fold increased odd of cancer progression among ABX users (figures 3 and 4). These findings confirm the previously reported deleterious effect of ABX on all clinical outcomes (table 1).

Conclusions Antibiotics were shown to impair clinical outcomes of NSCLC patients treated with ICIs in this study. Two (non mutually exclusive) mechanisms are increasingly discussed in the literature to explain the role of microbiome on immunotherapy response: the immunomodulatory effects of bacterial molecules,⁸ and antigenic mimicry between commensal bacteria and tumor antigens cross reactive for the same antigen specific T cells.^{9,10}

Abstract 278 Figure 1 Forest plot of hazard ratios for overall survival of patients diagnosed with NSCLC and exposed to antibiotics versus not exposed to antibiotics, according to the time window of antibiotic exposure

Abstract 278 Figure 2 Forest plot of hazard ratios for progression-free survival of patients diagnosed with NSCLC and exposed to antibiotics versus not exposed to antibiotics, according to the time window of antibiotic exposure

Abstract 278 Figure 3 Forest plot of odds ratios for overall response rate of patients diagnosed with NSCLC and exposed to antibiotics versus not exposed to antibiotics

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Abstract 278 Figure 4 Forest plot of odds ratios for progressive disease rate of patients diagnosed with NSCLC and exposed to antibiotics versus not exposed to antibiotics

Abstract 278 Table 1 Summary of the impact of antibiotic use on all clinical outcomes

TW of ABX Exposure in Relation to CI Start (Days)	Number of Patients for OS (ABX users)	Pooled HR OS [95% CI]	Number of Patients for PFS (ABX users)	Pooled HR PFS [95% CI]	Number of Patients for ORR (ABX users)	Pooled OR ORR [95% CI]	Number of Patients for PD (ABX users)	Pooled OR PD [95% CI]
All Time Windows Confounded	12,235 (2,939)	1.63 [1.37-1.94]	5,356 (1,346)	1.49 [1.26-1.76]	1,992 (382)	0.66 [0.44-0.99]	1,272 (314)	1.98 [1.39-2.8]
[-60;0]	6,244 (1,307)	2.36 [1.68-3.31]	2,074 (577)	1.75 [1.29-2.37]				
[-60;60]	7,790 (1,745)	1.54 [1.30-1.82]	2,473 (661)	1.65 [1.26-2.17]				
[-90;120]	794 (296)	1.14 [0.82-1.58]	527 (155)	1.20 [0.92-1.56]				
[-any];+any{	1,236 (> 430)	1.32 [0.75-2.31]	725 (> 155)	0.90 [0.57-1.42]				

Statistically significant. Non statistically significant

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