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Association Between Antibiotic Exposure and Survival Among Patients Diagnosed With Advanced Melanoma or Advanced Non-Small Cell Lung Cancer (NSCLC) Treated With Immune Checkpoint Inhibitor (ICI) Therapy

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Background

- Gut microbiota play a key role in immune modulation, and disruption to the gut microbiome by antibiotics can suppress host immune response against cancer cells.[1]
- Among patients with cancer who are treated with ICI, previous studies suggest worse outcomes for those exposed to antibiotics.[2]
- This study investigates the association between antibiotic exposure and survival among patients diagnosed with advanced melanoma (aMel) or advanced NSCLC (aNSCLC) receiving ICI therapy in an electronic health records (EHR)-claims linked dataset.

Methods

- The Flatiron Health Research Database (FHRD) is a nationwide EHR-derived longitudinal database comprised of de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. During the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care).[3,4] Komodo Health is healthcare technology company and its Healthcare Map™ consists of proprietary real-time commercial claims activity data on 330 million US patients and their interactions with the US healthcare system.
- Retrospective longitudinal clinical data were derived from EHR data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to closed claims coverage within the Komodo Healthcare Map using a third-party linking software to probabilistically match patients.
- Patients with aMel or advanced aNSCLC diagnosed between 2013 and 2021 treated with ICI from the FHRD linked with Komodo Claims Health Database (KCHD) were selected. Patients were required to have continuous medical (Mx) and prescription drug (Rx) coverage in KHCD for 42 days before and up to 28 days after their first ICI start date. Patients were included if they were treated with ICI during any oncologist-defined, rule-based Lines of Therapy (LOT); however patients were excluded if LOT rules indicated they were treated with ICI in the adjuvant or neoadjuvant setting. Additionally, patients were excluded if they had documented diagnosis of both aMel and aNSCLC.
- National Drug Code (NDC), International Classification of Disease (ICD), and Healthcare Common Procedure Coding System (HCPCS) codes were identified through administrative claims data to derive systemic antibiotic use (oral and intravenous).
- The patient cohort was dichotomized into exposure groups based on presence or absence of at least one systemic antibiotic use claim within a window of 42 days before to 28 days after the ICI start date.
- Patient characteristics, ICI treatment, and outcomes were identified through EHR.
- Cox proportional hazards models were used to compare real-world overall survival (rwOS) and real-world progression-free survival (rwPFS) across exposure groups. Outcomes were adjusted for cancer diagnosis, gender, age at diagnosis, ethnicity/race, region, practice type and ECOG PS at ICI start. Inverse probability of treatment weighting (IPTW) matching was used to account for non-random selection into the exposure group.

Results

Table 1: Baseline Characteristics

Characteristic	Overall, N = 3,271	Antibiotic Exposure N = 1,350 (41.3%)	No Antibiotic Exposure N = 1,921 (58.7%)
Age - Median (p25, p75)	65 (59, 73)	64 (58, 72)	66 (59, 74)
Diagnosis			
Advanced Melanoma	521 (16%)	179 (13%)	342 (18%)
Advanced NSCLC	2,750 (84%)	1,171 (87%)	1,579 (82%)
Gender			
Female	1,532 (47%)	655 (49%)	877 (46%)
Male	1,739 (53%)	695 (51%)	1,044 (54%)
Race			
Asian	85 (2.6%)	28 (2.1%)	57 (3.0%)
Black or African American	303 (9.3%)	120 (8.9%)	183 (9.5%)
Other Race	367 (11%)	162 (12%)	205 (11%)
Unknown	301 (9.2%)	138 (10%)	163 (8.5%)
White	2,215 (68%)	902 (67%)	1,313 (68%)
Ethnicity			
Hispanic or Latino	111 (3.4%)	50 (3.7%)	61 (3.2%)
Unknown	3,160 (97%)	1,300 (96%)	1,860 (97%)
Practice Type			
Academic	421 (13%)	130 (9.6%)	291 (15%)
Community	2,831 (87%)	1,216 (90%)	1,615 (84%)
Both	19 (0.6%)	4 (0.3%)	15 (0.8%)
ECOG PS			
0	901 (28%)	329 (24%)	572 (30%)
1	1,267 (39%)	553 (41%)	714 (37%)
2+	596 (18%)	266 (20%)	330 (17%)
Unknown	507 (15%)	202 (15%)	305 (16%)
First ICI Line Number			
1	2,254 (69%)	970 (72%)	1,284 (67%)
2	747 (23%)	261 (19%)	486 (25%)
3	188 (5.7%)	87 (6.4%)	101 (5.3%)
4+	82 (2.5%)	32 (2.4%)	50 (2.6%)
ICI Treatment ❖			
Atezolizumab	124 (3.8%)	56 (4.1%)	68 (3.5%)
Cemiplimab	1 (<0.1%)	1 (<0.1%)	0 (0%)
Durvalumab	63 (1.9%)	27 (2.0%)	36 (1.9%)
Ipilimumab	305 (9.3%)	125 (9.3%)	180 (9.4%)
Nivolumab	835 (26%)	323 (24%)	512 (27%)
Pembrolizumab	1,943 (59%)	818 (61%)	1,125 (59%)

❖ ICI used were assigned according to line of therapy components and using this order of precedence: pembrolizumab, ipilimumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab.

Figure 1: Cohort Selection

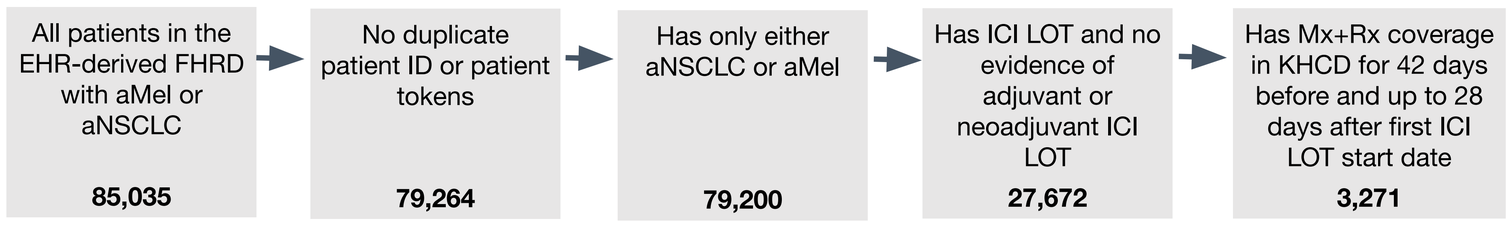


Figure 2: Real-world Overall Survival of Patients with aMel and aNSCLC Treated with ICI by Antibiotic Exposure

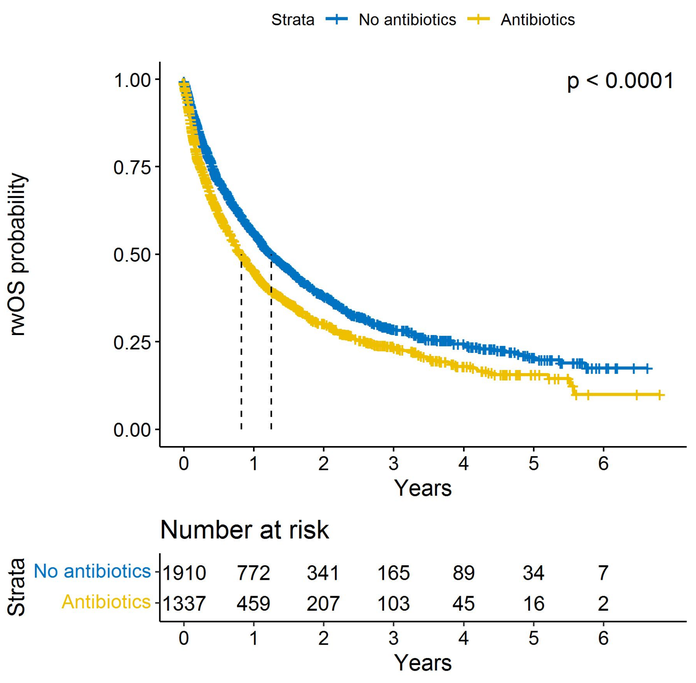
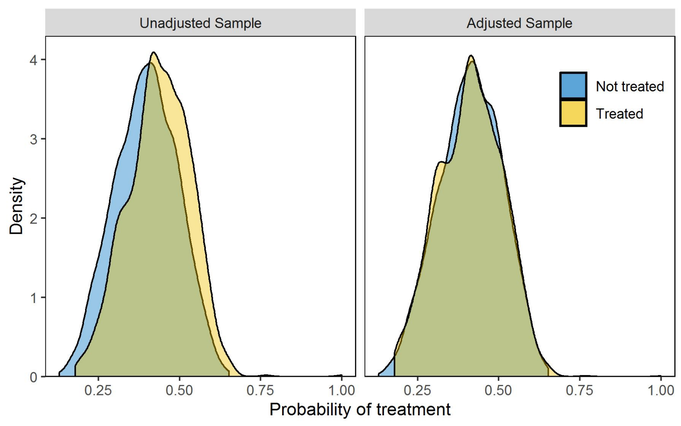


Table 2: Hazard ratios of real-world mortality[5], progression or mortality by antibiotic exposure and disease

Disease	Model	Outcome	Hazard Ratio (95% CI)	P value
aNSCLC (n=2750)	Unadjusted	rwPFS	1.13 (1.04 - 1.23)	0.0054
		rwOS	1.27 (1.15 - 1.4)	< 0.001
	Adjusted	rwPFS	1.11 (1.01 - 1.12)	0.0027
		rwOS	1.26 (1.14 - 1.39)	< 0.001
aMel (n=521)	Unadjusted	rwPFS	1.17 (0.93 - 1.47)	0.1736
		rwOS	1.32 (1.01 - 1.72)	0.0425
	Adjusted	rwPFS	1.21 (0.95 - 1.54)	0.1146
		rwOS	1.32 (1 - 1.75)	0.0481

Figure 4: Propensity Score Distributions



Covariates used for propensity score model development included the following: age at index, line number, gender, practice type, ECOG PS, region, and ethnicity/race.

Table 3: Median rwPFS and rwOS in days

Outcome	No Antibiotic Exposure median (95% CI)	Antibiotic Exposure median (95% CI)
rwPFS (unweighted)	98 (91-108)	86 (81-93)
rwOS (unweighted)	457 (413-510)	300 (270-335)
rwPFS (weighted)	98 (91-107)	86 (81-94)
rwOS (weighted)	445 (408-499)	313 (276-346)
Median follow-up time was 702 days (95% CI: 653-751)		

Table 4: Hazard ratios of real-world mortality[5], progression or mortality by antibiotic exposure

Model	Outcome	Hazard Ratio (95% CI)	P value
Unadjusted	rwPFS	1.13 (1.05 - 1.23)	0.00242
	rwOS	1.31 (1.2 - 1.43)	< 0.001
Adjusted	rwPFS	1.12 (1.03 - 1.22)	0.0076
	rwOS	1.26 (1.15 - 1.38)	< 0.001
Adjusted Weighted	rwPFS	1.12 (1.03 - 1.22)	0.005
	rwOS	1.26 (1.15 - 1.38)	< 0.001

Conclusions and Limitations

- Similar to previously published literature, our study demonstrated that antibiotic exposure around ICI initiation is associated with worse rwOS and rwPFS among patients with aMel or aNSCLC.
- This study included a large patient cohort to investigate the association. We used a novel EHR-claims linked data set to identify drug exposure. Integrated claims and oncology EHR-derived data enable investigation of associations between non-oncology drug exposure and oncology outcomes.
- Some limitations of our analysis are that we did not account for indication for antibiotics, antibiotic class, or duration of antibiotic exposure; confounding by indication cannot be excluded. Additionally, there may be misalignment between Rx claims billing date and the date antibiotic treatment was initiated and hence some patients may be misclassified with respect to exposure status. We also excluded patients who received ICI in the adjuvant and neoadjuvant setting per LOT rules. Although we adjusted for many patient characteristics, we did not adjust for stage at initial diagnosis or for comorbidities, which may confound results.

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Disclosures: At the time of the study, all authors report employment at Flatiron Health, Inc., which is an independent subsidiary of the Roche Group, and stock ownership in Roche.

References

1. Li X, Zhang S, Guo G, Han J, Yu J. Gut microbiome in modulating immune checkpoint inhibitors. EBioMedicine. 2022;82:104163. doi:10.1016/j.ebiom.2022.104163
2. Tsikala-Vafea M, Belani N, Vieira K, Khan H, Farmakiotis D. Use of antibiotics is associated with worse clinical outcomes in patients with cancer treated with immune checkpoint inhibitors: A systematic review and meta-analysis. Int J Infect Dis. 2021 May;106:142-154.
3. Ma, Xinran & Long, Lura & Moon, Sharon & Adamson, Blythe & Baxi, Shrujal. (2020). Comparison of Population Characteristics in Real-World Clinical Oncology Databases in the US: Flatiron Health, SEER, and NPCR. 10.1101/2020.03.16.20037143
4. Birnbaum, Benjamin & Nussbaum, Nathan & Seidl-Rathkopf, Katharina & Agrawal, Monica & Estevez, Melissa & Estola, Evan & Haimson, Joshua & He, Lucy & Larson, Peter & Richardson, Paul. (2020). Model-assisted cohort selection with bias analysis for generating large-scale cohorts from the EHR for oncology research..
5. Zhang Q, Gossai A, Monroe S, Nussbaum NC, Parrinello CM. Validation analysis of a composite real-world mortality endpoint for patients with cancer in the United States. Health Serv Res. 2021;56(6):1281-1287. doi:10.1111/1475-6773.13669