Journal of Immunology and Infectious Diseases
Volume 9 | Issue 1
ISSN: 2394-6512

Research Article Open Access

Anti-Infectives do not Impact Treatment Response to Immune Checkpoint Inhibitors: a Single Center Retrospective Analysis

Krystal Garrovillo[1,2,*], John Garrett[1,2], Kathryn Bollin[3], Samantha R. Spierling Bagsic[4], Harminder Sikand[1]

[1]Department of Pharmacy, Scripps Mercy Hospital, San Diego, CA, USA
[2]Department of Pharmacy, Scripps MD Anderson, San Diego, CA, USA
[3]Hematology/Oncology, Scripps MD Anderson, San Diego, CA USA
[4]Scripps Health, San Diego, CA, USA

[*]**Corresponding author:** Krystal Garrovillo, Department of Pharmacy, Scripps Mercy Hospital, San Diego, CA, USA Tel: 858-554-8788 E-mail: Garrovillo.KrystalAshley@ScrippsHealth.org

Citation: Krystal Garrovillo, John Garrett, Kathryn Bollin, Samantha Spierling Bagsic, Harminder Sikand (2022) Anti-Infectives do not Impact Treatment Response to Immune Checkpoint Inhibitors: a Single Center Retrospective Analysis. J Immunol Infect Dis 9(1): 102

Abstract

Background and Purpose: Immune-checkpoint inhibitors (ICI) have provided groundbreaking advancements for a variety of malignancies. It has been of recent interest to identify predictive indicators of response to improve cancer management using immunotherapy. The intestinal microbiome has been recognized as a potential predictor of ICI anti-tumor activity. Antibiotics reduce diversity the overall composition of the gut microbiota, with effects seen as quickly as in a single day. Post-antibiotic dysbiosis recovery varies depending on type and duration of exposure. Preclinical studies in mice with advanced cancer treated with broad spectrum antibiotics have been associated with resistance to ICI treatment.

Materials and Methods: A retrospective analysis of 241 cancer patients receiving ICI treatment between 2017 and 2020 was conducted. Patients were classified as having received anti-infective (AI) therapy within 30 days of ICI initiation or during ICI treatment or no anti-infective (no-AI) treatment. Progression-free survival (PFS), overall survival (OS), and objective response rates (ORR) were measured at 6-months.

Results: 120 patients were included in the AI group and 121 patients in the no-AI group. There was no difference in PFS or OS between patients who received AI versus no-AI (50% vs 59%, p=0.40), (74% vs 79%, p=0.42). Multivariate analysis showed performance status and use of beta-lactam antibiotics significantly impacted OS while only performance status impacted PFS. AI use 30 days prior to ICI initiation showed a trend towards inferior OS. No significant difference was noted between ORR (19% vs 24%, p=0.57).

Conclusions: In the current study, anti-infective therapy does not appear to affect efficacy of immune-checkpoint inhibitors in patients with cancer. Further prospective research is needed to confirm the effect of specific anti-infective agents and temporal proximity of anti-infective onset on checkpoint blockade survival outcomes.

Keywords: Immune checkpoint inhibitors; immunotherapy; antibiotics; anti-infectives; gut microbiota

Abbreviations: Immune checkpoint inhibitor (ICI), anti-infective (AI), Eastern Cooperative Oncology Group performance status (ECOG PS), progression-free survival (PFS), overall survival (OS), objective response rates (ORR), complete response (CR), progressive disease (PD)

Introduction

ICI have revolutionized the management of several malignancies, with improvements in ORR, PFS, and OS in comparison to cytotoxic chemotherapy alone. ICI are the backbone of several treatment recommendations for various malignancies including advanced non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and melanoma. Despite their promising outcomes, there continues to be a significant number of treatment non-responders, classified as having stable or progressive disease (SD, PD) [1-3]. The gut microbiome has been identified as a potential predictor of response to immunotherapy. Commensal bacteria play a crucial role in maintaining the gastrointestinal barrier and have been shown to regulate host immune responses. Antibiotics can affect gut microbiota by decreasing diversity and abundancy. These effects can be seen as quickly as in a single day with varied dysbiosis recovery depending on the type of agent and duration of exposure [4,5]. Altered immune responses are evident when the gut microbiota is dysregulated, illustrated in chronic inflammatory and autoimmune disorders [6-8].

Several preclinical studies have shown that alterations in the intestinal microbiome impact immunotherapy efficacy in mice. Germ-free and antibiotic-treated mice with induced NSCLC, RCC, and melanoma treated with ICI targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and/or programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PDL-1) were shown to have poor outcomes, demonstrating less effective ICI anti-tumor activity in settings of dysbiosis [9-11]. Further confirming the importance of the intestinal microbiome in ICI efficacy, fecal microbiota transplants from responder and non-responder patients with NSCLC and metastatic RCC to cancer-bearing germ-free and antibiotic-treated mice seemed to restore ICI response. The mice subsequently showed significantly reduced tumor size, slowed tumor growth, and improved PFS [10-12]. Microbiome profiling was performed on the stool samples of these patients, finding differences in gut microbiota composition between immunotherapy responders and non-responders. Antibiotics and lack of commensal diversity, therefore, may affect the outcomes of patients treated with ICI.

Several clinical studies have paralleled the outcomes of preclinical studies. The largest study to date examined patients with advanced NSCLC and RCC receiving antibiotics within 30 days before initiation of ICI emphasized an increased risk of PD (75 vs 22%, $p<0.01$) with shorter PFS (1.9 vs 7.4 months, HR 3.1, 95% CI 1.4-6.9, $p<0.01$) and shorter OS (17.3 vs 30.6 months, HR 3.5, 95% CI 1.1-10.8, $p=0.03$) [13]. Several smaller studies investigated antibiotic use in close proximity to ICI initiation in NSCLC, RCC, and melanoma patients also found negative impacts on PD, PFS, and OS [10, 14-18]. Extension of Derosa's analysis to antibiotic use within 60 days before ICI initiation found antibiotic use associated with less marked effect on ICI efficacy, although still statistically significant for worse PD and PFS, suggesting that time-dependent recovery of the intestinal microbiome reverses negative impacts on immunotherapy [13].

In contrast, Kulkarni *et al.* produced results in their NSCLC population where antibiotic exposure was associated with improved PFS, OS, and ORR [19]. Similarly, Hogue *et al.* found that antibiotic use was associated with improved PFS but did not detect a difference in OS in RCC and NSCLC patients [20]. Administration of antibiotics within 90 days of ICI initiation did not affect OS, contrary to the findings previously mentioned. Other studies did not find that antibiotic use impacted ICI outcomes [21-24]

Published data describing the association between antibiotics and effects on ICI treatment outcomes are conflicting, so we looked to build upon existing data and examine the effect of anti-infective agents in temporal proximity to initiation of or during ICI therapy for treatment of cancer patients within Scripps Health.

Materials and Methods

From April 1, 2017 to April 1, 2020, patients ≥18 years old, diagnosed with cancer and receiving treatment with an immune-checkpoint inhibitor: pembrolizumab, nivolumab alone or in combination with ipilimumab, or atezolizumab within Scripps Health were evaluated for the study. Patients were classified as having received AI therapy if prescribed oral or intravenous antibiotics, antifungals, or antivirals within 30 days prior to initiation of ICI or anytime during ICI therapy. Patients who did not receive anti-infectives during this period were classified in the no-AI group. Patients were excluded if they previously received ICI therapy in combination with oral or intravenous cytotoxic chemotherapy, had a formal indication for immunosuppressive therapy, chronic use of systemic corticosteroids, had a history of recurrent Clostridium difficile colitis, or documented daily use of probiotics or yogurt.

Patient information was retrospectively collected via chart review including age, gender, primary tumor type, prior lines of systemic treatment, metastatic tumor burden, Eastern Cooperative Oncology Group (ECOG) performance status score, list of comorbidities, PD-L1 status, mismatch repair status, ICI start date, and ICI drug name.

Antibiotic, antifungal, or antiviral use, indication, classification, and duration was collected from all patients in the AI group.

Tumor response was evaluated with the modified Response Evaluation Criteria in Solid Tumours for immune-based therapeutics (iRECIST) [25].

Patient characteristics were compared using the Fisher's exact test or Chi-squared test for categorical data and t-test for continuous data. Differences in the proportion of patients who were progression-free at 6 months, those who survived at 6 months, and between ORR (CR, PR, SD, and PD) were compared using a Chi-squared test. PFS and OS analyses were performed using the Kaplan-Meier method. Multivariate analyses for PFS and OS were conducted using the Cox-regression model considering age, ECOG performance status, time elapsed since initiation of ICI therapy and type of AI therapy. Based on published rates of PFS in this population of patients, we estimate that a total sample size of 181 subjects with 157 subjects with no-AI therapy and 24 subjects with AI therapy would provide the study with 80% power, at a two-sided alpha level of 0.05.

The primary efficacy outcome of this study is 6-month PFS when AI agents (antibiotics, antifungals, and antivirals) are prescribed in close temporal proximity to the first dose of ICI or during ICI therapy compared to no AI agents. The primary safety outcome is rates of adverse effects of skin rash, pruritus, diarrhea, colitis, hepatotoxicity, and endocrine related (hypophysitis, thyroiditis, adrenal insufficiency). Secondary outcomes consist of ORR and OS at 6 months.

Results

Baseline Characteristics: Between April 1, 2017 and April 1, 2020, a total of 241 patients with cancer treated with ICI across Scripps Health were identified. Of these 241 patients, 120 patients received AI therapy within 30 days of ICI initiation or during ICI therapy and 121 patients did not receive AI therapy. The baseline characteristics were similar between the two groups (Table 1). In the overall population, the median age was 72 years and 43% of the patients were female, 73% of all patients were designated as having an ECOG performance status of 0 or 1, 84% of patients were diagnosed with metastatic disease at the time of ICI initiation, 53% of patients received ICI as first-line therapy, and 38% of patients had received 1 prior line of therapy. Pembrolizumab was the most common ICI, used in 62% of all patients. Ninety- one percent of patients received treatment with palliative intent. Melanoma, lung, urothelial carcinoma, and head and neck squamous cell carcinoma were the most frequent primary tumor types among the AI and no-AI groups (Figure 1). The type of AI used were predominantly antibiotics (88%), consisting of beta-lactam antibiotics (43%), fluoroquinolones (17%), sulfonamides (11%), macrolides (10%), and tetracyclines (7%). Antivirals were used in 8% of patients, most commonly valacyclovir (6%). Antifungals were used in 4% of patients, most commonly fluconazole (3%).

Table 1: Baseline Characteristics

Characteristic	**AI** (n=120)	**No AI** (n=121)	**p-value**
Age – years, median (range)	72 (33-95)	71 (31-99)	0.99
Female	44%	42%	0.75
White	83%	85%	0.70
Comorbidities			
HLD	45%	36%	0.16
HTN	40%	41%	0.94
CAD	25%	27%	0.72
ECOG PS			0.44
0-1	68%	77%	
2	22%	17%	
3	4.2%	1.7%	
4	0.8%	0%	
Not reported	5%	4.3%	
Metastatic (%)	82%	79%	0.75
PDL1 Status - Positive (%)	18% n=22*	24% n=30*	0.22
MSI Status - High (%)	4.2% n=5*	2.5% n=3*	0.71
Number of Prior Lines of Therapy			0.64
0	50%	55%	
1	39%	36%	
≥2	11%	8.2%	
Treatment			0.29
Pembrolizumab	69%	57%	
Nivolumab	20%	25%	
Ipilimumab/nivolumab	8%	16%	
Treatment Intent			0.83
Palliative	92%	91%	
Curative	8%	9%	
Duration of ICI Treatment, months (median)	4.4	3.5	0.60
Subsequent Change in Therapy	27%	36%	0.14

HLD – hyperlipidemia, HTN – hypertension, CAD – coronary artery disease, ECOG PS – European Cooperative Oncology Group performance status, PDL1 – programmed death ligand-1, MSI – microsatellite instability

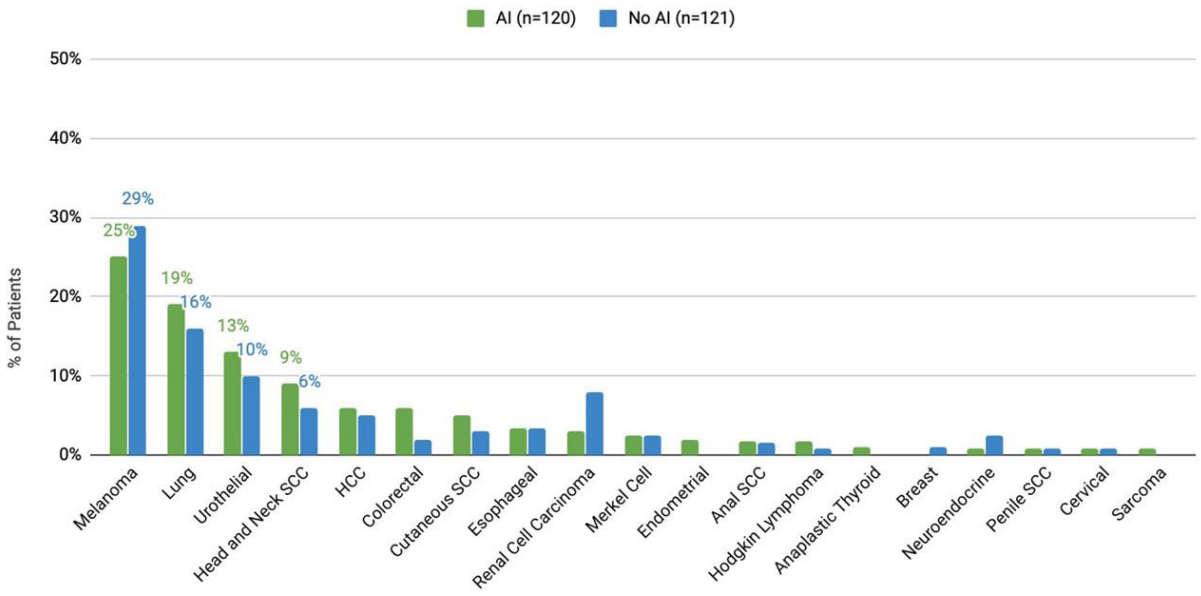

Figure 1: Primary tumor types of represented patients

6-Month Progression-Free Survival: There was no difference in PFS between patients who receive AI versus no-AI (50% vs 59%, p=0.40, Figure 2). Median PFS was not reached. The multivariate analysis of the effect of AI administration considering age, ECOG performance status, time elapsed since initiation of ICI therapy and type of AI therapy further supported that AI use did not influence PFS (HR 1.01, 95% CI 0.81-1.22, p=0.93). ECOG performance status was identified as an independent risk factor for worsening PFS using Cox regression analysis (Table 2) and was the only predictive factor for PFS in the multivariate analysis (HR 1.9, 95% CI 1.77-2.06, p<0.01, Table 3).

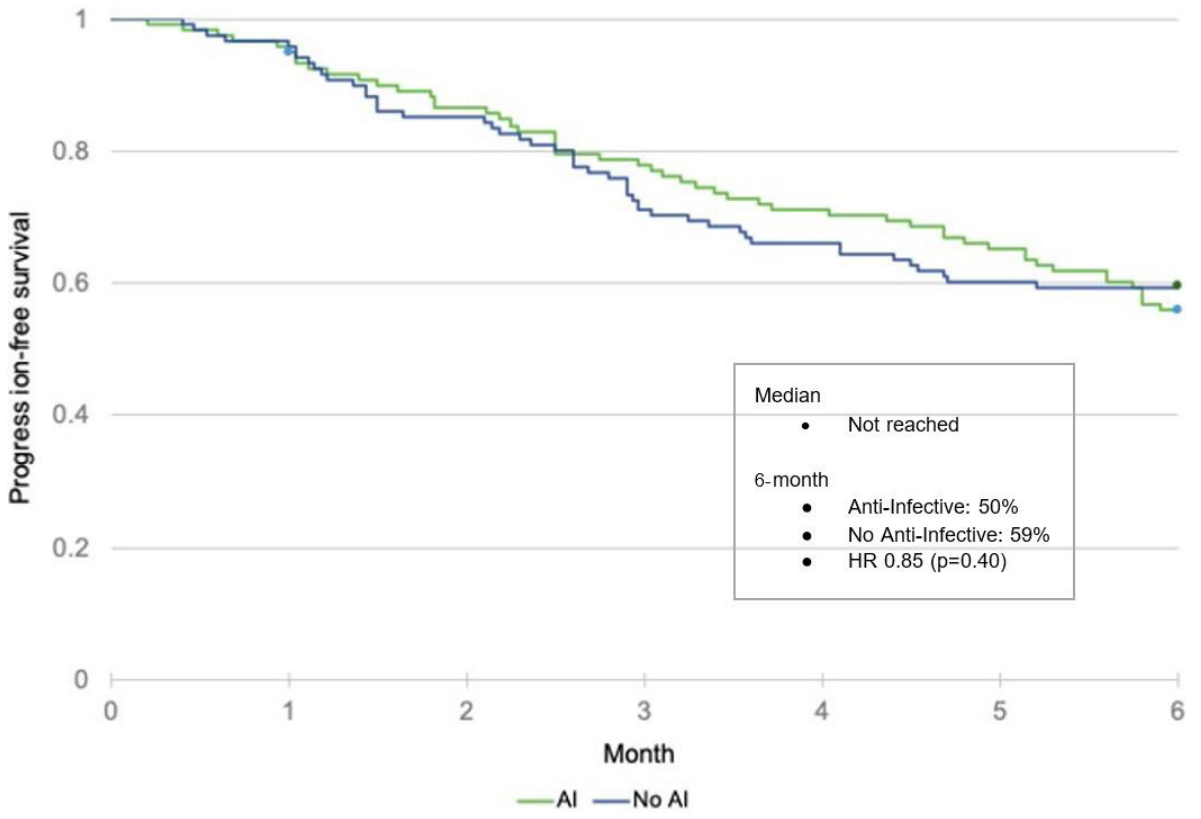

Figure 2: Kaplan-Meier curves of 6-month progression-free survival in all patients treated with immune checkpoint inhibitors based on anti-infective treatment status

Table 2: Univariate Analysis

PFS			
Variable	**Hazard Ratio**	**95% CI**	**p-value**
Anti-infective (Yes vs No)	1.10	0.91 – 1.30	0.61
Age	0.99	0.98 – 1.00	0.14
ECOG PS	1.92	1.77 – 2.07	**<0.01**
Beta-Lactam Antibiotic	1.56	1.32 – 1.79	0.06
Antifungal	1.29	0.69 – 1.88	0.67
Antiviral	0.42	-0.30 – 1.15	0.23
AI -30 to -1 days prior to ICI	1.31	1.01 – 1.60	0.36
AI after 0 to 30 days	1.12	0.86 – 1.39	0.66
AI after 31-60 days	1.69	1.39 – 2.00	0.08
AI after 61-90 days	0.24	-0.77 – 1.26	0.16
AI after 91-180 days	0.61	0.14 – 1.08	0.29

OS			
Variable	**Hazard Ratio**	**95% CI**	**p-value**
Anti-infective (Yes vs No)	1.24	0.98 – 1.51	0.41
Age	1.01	1.00 – 1.02	0.59
ECOG PS	2.51	2.33 – 2.70	**<0.01**
Beta-Lactam Antibiotic	2.20	1.90 – 2.48	**<0.01**
Antifungal	Not Reported	Not Reported	Not Reported
Antiviral	Not Reported	Not Reported	Not Reported
AI -30 to -1 days prior to ICI	1.96	1.61 – 2.31	0.05
AI after 0 to 30 days	1.65	1.32 – 1.98	0.13
AI after 31-60 days	0.87	0.33 – 1.40	0.79
AI after 61-90 days	0.54	-0.48 – 1.56	0.54
AI after 91-180 days	Not Reported	Not Reported	Not Reported

ECOG, PS – European Cooperative Oncology Group performance status

Table 3: Multivariate Analysis

PFS			
Variable	**Hazard Ratio**	**95% CI**	**p-value**
Anti-infective (Yes vs No)	1.01	0.81 – 1.22	0.93
ECOG PS	1.9	1.77 – 2.06	**<0.01**

OS			
Variable	**Hazard Ratio**	**95% CI**	**p-value**
Anti-infective (Yes vs No)	1.02	0.74 – 1.29	0.95
ECOG PS	2.51	2.32 – 2.70	**<0.01**
Beta-Lactam Antibiotic	3.33	2.95 – 3.72	**<0.01**
AI -30 to -1 days prior to ICI	1.96	1.61 – 2.31	0.05

ECOG, PS – European Cooperative Oncology performance status

6-Month Overall Survival: There was no difference in OS between patients who received AI versus no-AI (74% vs 79%, p=0.42, Figure 3). A multivariate analysis for OS was also performed, considering the same factors in the above model for PFS. AI use did not influence OS (HR 1.02, 95% CI 0.74-1.29, p=0.95). Cox regression analysis identified ECOG performance status, and use of beta-lactam antibiotic as independent risk factors for worsening OS (Table 2). These factors remained significant in the multivariate analysis (Table 3). There was a trend for inferior OS in patients with AI use within 30 days prior to ICI initiation, but this did not reach statistical significance.

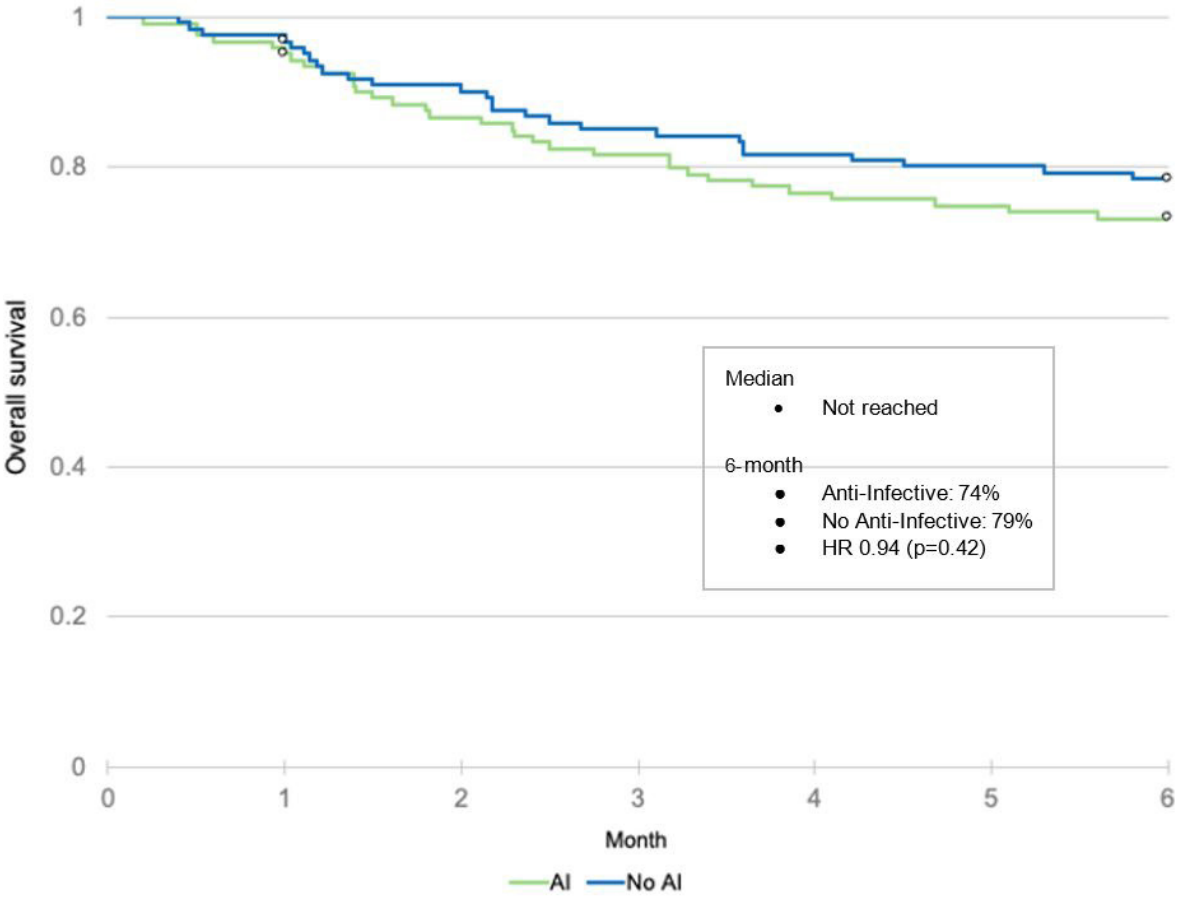

Figure 3: Kaplan-Meier curves of 6-month overall survival in all patients treated with immune checkpoint inhibitors based on anti-infective treatment status

Objective Response Rates: There was no difference between rates of complete response (CR) (11% vs 17%, p=0.20), partial response (PR) (8% vs 7%, p=0.79), stable disease (SD) (32% vs 25%, p=0.61), and progressive disease (PD) (48% vs 40%, p=0.35) between patients who received AI versus no-AI (Table 4).

Table 4: Objective Response Rate

	AI (n=120)	**No-AI** (n=121)	**p-value**
Objective Response			0.57
Complete Response (CR)	11%	17%	
Partial Response (PR)	7.5%	7.4%	
Stable Disease (SD)	32%	35%	
Progressive Disease (PD)	48%	40%	

Adverse Events

There was no difference in the incidence of immune-related toxicities between patients who received AI versus no-AI (Table 5).

Table 5: Adverse Events

	AI (n=120)	**No-AI** (n=121)	**p-value**
Skin rash, dermatitis, pruritus	11%	13%	0.57
Diarrhea, colitis	7%	7%	0.98
Hepatotoxicity	3%	7%	0.24
Endocrine Related	3%	4%	0.48
Myopathy, arthralgias	3%	3%	0.99
Pneumonitis	3%	4%	0.48
Neurotoxicity	1%	1%	0.99

Discussion

In this study, we found no statistically significant association between survival and AI use within 30 days of ICI initiation or during ICI therapy, although a trend towards worse outcomes in the AI group was noted. Lower rates of CR and higher rates of SD and PD were observed in AI patients compared to those with no-AI. These results may be influenced by use of beta-lactam antibiotics and ECOG performance status, which were found to negatively impact OS, while PFS was only affected by performance status in multivariate analysis. We also noted use of AI within 30 days prior to ICI therapy produced shorter OS, though not statistically significant.

Beta-lactams and fluoroquinolones were among the most used AIs in this study and utility was a prognostic factor for inferior OS in our analysis. These are broad spectrum antibiotics that alter and disrupt the composition of gut microbiota, including favorable bacteria. It has been previously reported that Bacteroides spp., Bifidobacterium spp., Faecalibacterium, Ruminococcaeceae, and Akkermansia muciniphila presence in gut microbiota is associated with response to ICIs [11,12]. Lack of these beneficial species secondary to antibiotic-related gut dysbiosis may have downstream detrimental effects with antigen presentation and T-cell function associated with anti-tumor response [26]. It is of note that this effect was not found to be true for narrow spectrum antibiotics [16]. There is limited data regarding altered gut microbiota with valacyclovir, though there is data suggesting that acyclovir therapy in hematopoietic stem cell transplant patients may cause gut dysbiosis [27]. Antifungal agents can also cause dysbiosis of commensal intestinal fungi but the effect of specific agents on the human immune system is yet to be elucidated [28]. Unfortunately, our sample of patients who received antivirals and antifungals are too small to draw meaningful conclusions from.

Overall, our findings support those of Kaderbhai *et al.* showing similar response rates and PFS between 74 patients with NCSLC treated with nivolumab, with no impact of antibiotic use within the 3 months prior to nivolumab initiation [21]. Nevertheless, we observed a trend towards shortened OS in patients who received AI when we used a more narrow time frame from the start of ICI treatment. Other studies define the time window of antibiotic onset in relation to start of ICI therapy differently, which may contribute to differing results in the literature [20, 22-24]. Wilson *et al.* suggests that a broad definition of 60 days before and any time after ICI initiation eliminates the negative effects of antibiotics on OS, consistent with the results of our overall population, though our time window is slightly shorter and includes only 30 days before and any time during ICI treatment [29]. When we examined a narrower time frame of 30 days prior to start of ICI, we noticed a trend towards inferior OS which is consistent with that of several other reports [29-32]. In a large retrospective study of 140 NSCLC, 67 RCC and 32 urothelial carcinoma patients, antibiotic use 2 months before or 1 month after ICI initiation was associated with significantly shorter PFS and OS [10]. Another large retrospective study of 249 NSCLC and 121 RCC patients demonstrated that antibiotic use within 1 month prior to ICI therapy was associated with significantly shorter PFS and OS [13]. Similarly, Elkrief *et al.* noted significantly shorter PFS and decreased response rates when treated with

antibiotics 1 month prior to ICI initiation in 74 melanoma patients [18]. Ahmed *et al.* focused on a shorter time period of antibiotics prescribed 14 days before or 14 days after ICI initiation, again finding decreased response rates and shorter PFS in 60 patients with various cancers [16]. Several other studies have illustrated similar detrimental effects of antibiotics on clinical outcomes in patients receiving ICI therapy [33-36]. Our results build on existing data that suggests antibiotic exposure in close temporal proximity to ICI initiation may negatively affect overall survival outcomes with ICI therapy.

There is an abundance of evidence which suggests antibiotic-induced dysregulation of gut microbiota is associated with reduced ICI efficacy [37,38]. However, this association can also be partially explained by alternative patient characteristics. As seen in our multivariate models, poorer ECOG performance status is associated with worse outcomes, in which age, stage of cancer, time since cancer diagnosis, number of prior lines of therapy and recent hospitalizations may play a role. Additionally, requiring treatment with anti-infectives may represent an intrinsically less healthy subgroup of patients. Moreover, cancer type, comorbid conditions, and baseline intestinal microbiota composition may be other confounding variables.

Our study is not without limitations, which includes lack of adequate power as we were only able to enroll 121 patients in the no-AI arm rather than the projected 157. The retrospective nature of the data from a single institution and small sample size makes our results difficult to generalize to the population at large. We were unable to directly examine the composition of gut microbiota as stool samples were not available for assessment. We also did not consider other factors that can potentially influence gut microbiota such as other medications, diet, or geographic location of origin. Additionally, several of our patients received multiple treatments with various antibiotics throughout treatment with their ICI and only the earliest prescription was used in our analysis. Furthermore, our patients consisted of a diverse category of cancer diagnoses, different treatment intents, and a variety of anti-infectives used for numerous types of indications with each population being too small to carry out statistical analysis.

Conclusion

AI therapy does not appear to affect efficacy of immune-checkpoint inhibitors in patients with cancer. Though our study is limited by its retrospective nature and small sample size, we did appreciate that patients with poorer performance status, use of beta-lactam antibiotics, and AI use 30 days prior to ICI initiation can impact OS. In view of these results, caution should be taken to minimize empiric use of AI to situations of clear or high suspicion of infectious indications. Further prospective research with larger cohorts is needed to better evaluate the association of AI use with ICI efficacy.

References

1. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, et al (2015) Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373(17): 1627-39. https://doi.org/10.1056/nejmoa1507643

2. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, et al (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366: 2443-54. https://doi.org/10.1056/nejmoa1200690

3. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, et al (2015) Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 373: 1803-13. https://doi.org/10.1056/nejmoa1510665

4. Lange K, Buerger M, Stallmach A, Bruns T (2016) Effects of Antibiotics on Gut Microbiota. Digestive Diseases 34(3): 260-8. https://doi.org/10.1159/000443360

5. Manichanch C, Reeder J, Gibert P, Varela E, Llopis M, et al (2010) Reshaping the gut microbiome with bacterial transplantation and antibiotic intake. Genome Res 20(10): 1411-1419. https://doi.org/10.1101%2Fgr.107987.110

6. Ida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, et al (2013) Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 342(6161): 967-70. https://doi.org/10.1126/science.1240527

7. Tlaskalova-Hogenova H, Stepankova R, Hudcovic T, Tuckova L, Cukrowska B, et al (2004) Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. Immunol Lett 93: 97–108. https://doi.org/10.1016/j.imlet.2004.02.005

8. Neish AS (2009) Microbes in gastrointestinal health and disease. Gastroenterology 136(1): 65-80. https://doi.org/10.1053%2Fj.gastro.2008.10.080

9. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, et al (2015) Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 350: 1084-9. https://doi.org/10.1126/science.aac4255

10. Routy B, Le Chatelier E, Derosa L, Duong CP, Alou MT, et al (2018) Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359(6371): 91-7. https://doi.org/10.1126/science.aan3706

11. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, et al (2018) The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 359: 104-8. https://doi.org/10.1126/science.aao3290

12. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, et al (2017) Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 359(6371): 97-103. https://doi.org/10.1126/science.aan4236

13. Derosa L, Hellmann MD, Spaziano M, Halpenny D, Fidelle M, et al (2018) Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol 29(6): 1437-44. https://doi.org/10.1093/annonc/mdy103

14. Derosa L, Routy B, Enot D, Baciarello G, Massard C, et al (2017) Impact of antibiotics on outcome in patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors. Journal of Clinical Oncology 35(6_suppl): 462. DOI: 10.1200/JCO.2017.35.6_suppl.462

15. Huemer F, Rinnerthaler G, Westphal T, Hackl H, Hutarew G, et al (2018) Impact of antibiotic treatment on immune checkpoint blockade efficacy in advanced non-squamous non-small cell lung cancer. Oncotarget 9: 16512-20. https://doi.org/10.18632/oncotarget.24751

16. Ahmed J, Kumar A, Parikh K, Anwar A, Knoll BM, et al. (2018) Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors. OncoImmunology 7(11): e1507670. https://doi.org/10.1080/2162402x.2018.1507670

17. Khan U, Pena C, Brouwer J, Hoffman K, Roy A, et al (2019) Impact of antibiotic use on response to treatment with immune checkpoint inhibitors. Journal of Clinical Oncology 37(4_suppl): 143. DOI: 10.1200/JCO.2019.37.4_suppl.143

18. Elkrief A, El Raichani L, Richard C, Messaoudene M, Belkaid W, et al (2019) Antibiotics are associated with decreased progression-free survival of advanced melanoma patients treated with immune checkpoint inhibitors, OncoImmunology 8: 4. https://doi.org/10.1080/2162402X.2019.1568812

19. Kulkarni A, Kumar M, Pease DF, Wang Y, DeFor TE, et al (2019) Impact of antibiotics and proton pump inhibitors on clinical outcomes of immune check point blockers in advanced non-small cell lung cancers and metastatic renal cell cancer. Journal of Clinical Oncology 37(15_suppl): e20520. DOI: 10.1200/JCO.2019.37.15_suppl.e20520

20. Hogue C, Kuzel T, Borgia J, Marwaha G, Bonomi P, et al (2019) Impact of antibiotic usage on survival during checkpoint inhibitor treatment of non-small cell lung cancer (NSCLC). J Thorac Oncol 14(10): S735. https://doi.org/10.1016/j.jtho.2019.08.1574

21. Kaderbhai C, Richard C, Fumet JD, Aarnink A, Foucher P, et al (2017) Antibiotic Use Does Not Appear to Influence Response to Nivolumab. Anticancer Res 37: 3195-200. https://doi.org/10.21873/anticanres.11680

22. Huemer F, Lang D, Westphal T, Gampenrieder SP, Hutarew G, et al (2019) Baseline absolute lymphocyte count and ECOG performance score are associated with survival in advanced non-small cell lung cancer undergoing PD-1/PD-L1 blockade. J Clin Med 8(7): 1014. doi: 10.3390/jcm8071014.

23. Iglesias-Santamaria A. (2020) Impact of antibiotic use and other concomitant medications on the efficacy of immune checkpoint inhibitors in patients with advanced cancer. Clin Transl Oncol 22: 1481-1490. https://doi.org/10.1007/s12094-019-02282-w

24. Svaton M, Zemanova M, Zemanova P, Kultan J, Fischer O, et al (2020) Impact of concomitant medication administered at the time of initiation of nivolumab therapy on outcome in non-small cell lung cancer. Anticancer Res 40(4): 2209-17. doi: 10.21873/anticanres.14182.

25. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, et al (2017) iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 18(3): e143-52. https://doi.org/10.1016/s1470-2045(17)30074-8

26. Naqash AR, Kihn-Alarcon AJ, Stavraka C, Kerrigan K, Vareki SM, et al (2021) The role of gut microbiome in modulating response to immune checkpoint inhibitor therapy in cancer. Ann Transl Med 9(12): 1034. doi: 10.21037/atm-20-6427

27. Ramakrishna C, Mendonca S, Ruegger PM, Kim JH, Borneman J, et al (2020) Herpes simplex virus infection, acyclovir and IVIG treatment all independently cause gut dysbiosis. PLoS ONE 15(8): e0237189. https://doi.org/10.1371/journal.pone.0237189

28. Iliev ID, Cadwell K (2021) Effects of intestinal fungi and viruses on immune responses and inflammatory bowel diseases. 160(4): 1050-1066. doi: 10.1053/j.gastro.2020.06.100

29. Wilson BE, Routy B, Nagrial A, Chin VT (2020) The effect of antibiotics on clinical outcomes in immune checkpoint blockade: a systematic review and meta-analysis of observational studies. Cancer Immunol Immunother 69: 343-54. doi: 10.1007/s00262-019-02453-2.

30. Sen S, Pestana RC, Hess K, Viola GM, Subbiah V. (2018) Impact of antibiotic use on survival in patients with advanced cancers treated on immune checkpoint inhibitor phase I clinical trial. Ann Oncol 29(12): 2396-2398. doi: 10.1093/annonc/mdy453.

31. Pinato DJ, Howlett S, Ottaviani D, Urus H, Patel A, et al (2019) Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. JAMA Oncol 5(12): 1774-1778. doi: 10.1001/jamaoncol.2019.2785.

32. Huang L, Chen X, Zhou L, Xu Q, Xie J, et al (2021) Antibiotic exposure windows and the efficacy of immune checkpoint blockers in patients with cancer: a meta-analysis. Ann Palliat Med 10(3): 2709-2722. doi: 10.21037/apm-20-2076

33. Tinsley N, Zhou C, Villa S, Tan G, Lorigan P, et al (2018) Cumulative antibiotic use and efficacy of immune checkpoint inhibitors in patients with advanced cancer. Journal of Clinical Oncology 36(15_suppl): 3010. DOI: 10.1200/JCO.2018.36.15_suppl.3010

34. Do TP, Hegde AM, Cherry CR, Stroud CRG, Sharma N, et al (2018) Antibiotic use and overall survival in lung cancer patients receiving nivolumab. Journal of Clinical Oncology 36(15_suppl): e15109. DOI: 10.1200/JCO.2018.36.15_suppl.e15109

35. Mielgo-Rubio X, Chara L, Sotelo-Lezama M, Castro RL, Rubio-Martinez J, et al (2018) MA10.01 Antibiotic Use and PD-1 Inhibitors: Shorter Survival in Lung Cancer, Especially When Given Intravenously. Type of Infection Also Matters. Journal of Thoracic Oncology 13(10): S389. https://doi.org/10.1016/j.jtho.2018.08.395

36. Ouaknine J, Helly De Tauriers P, Dumenil C, Neveux N, Dumoulin J, et al (2018) MA10.03 Plasmatic Evaluation of the Intestinal Barrier and Blood Microbiota, and Antibiotic Use in Non-Small Cell Lung Cancer Patients Treated with Nivolumab. Journal of Thoracic Oncology 13(10): S389-S390. https://doi.org/10.1016/j.jtho.2018.08.397

37. Tsikala-Vafea M, Belani N, Vieira K, Khan H, Farmakiotis D (2021) 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 106: 142-154. doi: 10.1016/j.ijid.2021.03.063

38. Jiang S, Geng S, Chen Q, Zhang C, Cheng M, et al (2022) Effects of concomitant antibiotics use on immune checkpoint inhibitor efficacy in cancer patients. Front Oncol 12: 823705. doi: 10.3389/fonc.2022.823705