International Immunopharmacology 88 (2020) 106876

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Antibiotic administration shortly before or after immunotherapy initiation is correlated with poor prognosis in solid cancer patients: An up-to-date systematic review and meta-analysis

Mengxue Yang[a,1], Ying Wang[a,1], Man Yuan[a,1], Mingyang Tao[a,1], Cheng Kong[b,d], Hao Li[c,d], Jiandong Tong[a,*], Huiyuan Zhu[e,*], Xuebing Yan[a,*]

[a] Department of Oncology, the Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China
[b] Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA
[c] Department of Biomedical Engineering, University of Houston, Houston, TX, USA
[d] Institute of Intestinal Diseases, Tongji University School of Medicine, Shanghai, China
[e] Department of Pathology, Shanghai Tenth People's Hospital Affiliated to Tongji University, Shanghai, China

ARTICLE INFO

Keywords:
Immunotherapy
Immune checkpoint inhibitors
Antibiotic
Prognosis
Meta-analysis

ABSTRACT

Objective: Immune checkpoint inhibitors (ICIs) have recently achieved inspiring performance in improving the prognosis of various solid tumors. Gut microbiome plays a crucial modulatory role in the efficacy of ICIs, which can be influenced by antibiotic (ATB) administration. In this meta-analysis, we aimed to clarify the correlations of ATB administration with the prognosis of solid cancer patients receiving ICI treatment.

Method: The eligible literatures were searched using PubMed, Cochrane Library, Web of Science, and Clinical trials.gov databases before 29 February 2020. The correlations of ATB administration with overall survival (OS) and progression-free survival (PFS) were determined using Hazard ratios (HRs) coupled with 95% confidence intervals (CIs).

Results: A total of 33 studies enrolling 5565 solid cancer patients receiving ICI treatment were included in this meta-analysis. As a whole, ATB administration was significantly correlated worse OS (HR = 1.76, 95%CI = 1.41–2.19, $P < 0.00001$) and PFS (HR = 1.76, 95%CI = 1.47–2.12, $P < 0.00001$). This significant association was then observed in the subgroup analysis based on region (except for OS in Europe), sample size, age, therapeutic strategy and ICI type. The similar results were also found in subgroup analysis for lung, renal cell (except for OS) and other cancers (such as melanoma) but not for mixed cancers. In addition, the ICI efficacy was more likely to be diminished by ATB administration within a time frame from 60 days before to 60 days after ICI initiation.

Conclusion: ATBs should be used cautiously in solid cancer patients receiving ICIs. However, further validations are still essential due to existing publication bias.

1. Introduction

The cancer immunotherapy targeting immune checkpoints has resulted in significant improvement of patient prognosis in various cancers in the past few years, with its representative drugs including Programmed cell death 1(PD-1)/Programmed cell death-Ligand 1(PDL-1) inhibitors and Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibodies [1]. However, numerous challenging problems remain to be unsolved such as identifying dominant therapy related factors and maximizing personalized management [2]. Recently, emerging evidences have suggested that gut microbiota plays a crucial role in modulating the efficacy and toxicity of cancer immunotherapy [3,4]. For instance, *Bifidobacterium*, *Akkermansia muciniphila* and *Ruminococcaceae* are found to correlate with clinical benefits of anti-PD-1/PD-L1 therapy, while *B. fragilis*, *B. thetaiotaomicron* and *Burkholderiales* are for that of anti-CTLA-4 therapy [5]. Furthermore, the animal experiment demonstrated that fecal microbiota transplantation (FMT) from responding patients into germ-free mice reinforced the anti-tumor efficacy of PD-1 inhibitor [6]. It is well-established that gut microbiota can be clinically manipulated using antibiotics (ATBs), probiotics and

* Corresponding authors.
E-mail addresses: tongjiandong@csco.ac.cn (J. Tong), zhy_pfmy@163.com (H. Zhu), yyxxbb8904@163.com (X. Yan).
[1] These authors contributed equally to the manuscript writing.

https://doi.org/10.1016/j.intimp.2020.106876
Received 5 April 2020; Received in revised form 16 July 2020; Accepted 3 August 2020

FMT. Therefore, it is of great practical significance to investigate the potential impact of these interventions on cancer immunotherapy.

The association of ATB administration with cancer treatment has already been widely investigated in the past decades, especially in its unquestionable preventive role in perioperative infection and chemoradiotherapy-induced immunosuppression related infection [7]. With regard to its role in cancer immunotherapy, related investigations are just beginning and their conclusions seem to be inconsistent. For instance, in a recent single-site retrospective study enrolling 291 advanced cancer cases, Tinsley et al found ATB administration was an unfavourable independent prognostic factor affecting the progression-free survival (PFS) and overall survival (OS) of patients receiving ICI treatment, and the subgroup analysis further revealed patients with cumulative ATB administration had the worst clinical outcome than others [8]. Similarly, Hakozaki et al found prior ATB administration was negatively correlated with the PFS and OS of non-small cell lung cancer (NSCLC) patients treated with nivolumab [9]. However, Kaderbhai et al found ATB administration in or before nivolumab therapy was not significantly correlated with the response rate and PFS of NSCLC patients [10]. Sen et al found ATB administration in or before ICI was not associated with the PFS of patients with advanced cancers and only ATB administration within 30 days of ICI was negatively correlated with OS [11]. Therefore, the prognostic role of ATB administration in ICI treatment remains inconclusive and should be evaluated comprehensively and objectively. To achieve this goal, a meta-analysis of 33 studies enrolling 5565 ICI treated cancer patients was performed. Our findings will help improve the individualized clinical management during cancer immunotherapy and contribute to benefiting patient prognosis.

2. Materials and methods

2.1. Search strategy

As shown in Fig. 1, the systematic review was performed according to the PRISMA guidelines. Relevant studies regarding the association between ATB administration and cancer immunotherapy were searched using the PubMed, Cochrane Library, Web of Science, and Clinical trials.gov (up to February 29th, 2020). The search key words were used as follows: “antibiotic”, “ATB”, “antibacterial”, “broad-spectrum antibiotic”, “narrow-spectrum antibiotic”, “Immunotherapy”, “Programmed cell death (Ligand) 1”, “PD-1(PD-L1)”, “cytotoxic T lymphocyte antigen 4”, “CTLA-4”, “immune checkpoint inhibitor”, “ICI”, “immune checkpoint blocking agent”, “cancer”, “tumor”, “malignancy” and “neoplasm”. Moreover, reference lists of identified original articles and reviews (including supplementary issues) were also carefully screened to identify additional eligible studies, which might be missed by electronic search strategies.

2.2. Inclusion and exclusion criteria

Inclusion criteria are as follows: (1) The literatures were focusing on the effects of ATBs in cancer patients treated with ICIs; (2) Patients were diagnosed with solid cancer and treated with ICIs, regardless of alone or combined with other anti-cancer treatments; (3) ATBs were administered before and/or during the ICI treatment, irrespective of the administration duration and dosage; (4) The control group were defined as those without ATB treatment in defined time frames; (5) The results include OS and/or PFS. Exclusion criteria are as follows: (1) Duplicated publications or data; (2) Animal or cell experiments; (3) Reviews and comments without original data; (4) Literatures were published in non-English languages. Furthermore, if there were several eligible duplicated studies identified, the most recent study was selected for the meta-analysis.

2.3. Data extraction

The following data from the full texts of selected studies were extracted: the first author, publication year, region, cancer type, the number of cases, type of ICI, ATB exposure, ATB type, ATB duration, age, Hazard ratios (HRs) for OS and PFS. If the HRs for OS or PFS were calculated using both univariate and multivariate analyses, the latter was preferentially selected because of confounding factor adjustment. In addition, in case where the study was unable to provide the 95% CIs, we estimated the data according to the method described by Altman et al. [12]. The data extraction was performed by two independent researchers and the divergences was solved through discussion or the assessment of the third researcher.

2.4. Quality assessment

The quality of the selected literatures was independently assessed based on the Newcastle-Ottawa Scale(NOS) score [13]. In the NOS system, literatures with a score ≥ 6 were considered as high-quality ones.

2.5. Statistical analysis

All the statistical analysis were performed using Stata SE14.0 and RevMan5.3 software. Cochrane Q-test and I^2 statistics were utilized to determine the heterogeneity among all the studies. In case where $P > 0.05$ and $I^2 < 50\%$, no heterogeneity exist among studies and their results were analyzed using a fixed-effect model. Contrarily, heterogeneity was determined among studies and their results were analyzed using a random-effect model. The sensitivity analysis was used for assessing the stability of results. The Begg’s and Egger’s test were used for assessing publication bias. An observed HR > 1 indicated ATB administration was negatively correlated with OS or PFS, while an observed 95% CI > 1 indicated the correlation was statistically significant. For all the analysis, a P value < 0.05 is considered to be statistically significant.

3. Results

3.1. Characteristics of the included studies

The systematical literature search was shown in Fig. 1. A total of 1064 candidate articles were selected from the electronic databases using our search strategy and 13 additional articles were identified through other sources. After removing the duplications, 978 articles were preserved. Then, articles were removed due to irrelevant topics (n = 907), reviews or meta-analysis (n = 24), no human researches (n = 8), no solid tumors (n = 2), repeated study cohort (n = 1) and no available results (n = 3). Finally, a total of 33 articles were determined to be eligible for the meta-analysis [6,8–11,14–41].

The general clinical characteristics of the included studies were summarized in Table 1. All the studies were published between January 2017 and February 2020. 5 of the included studies were performed on Asian patients, while the rest were performed on patients mainly from Europe and North America. The enrolled patients were most commonly diagnosed as lung and renal cell carcinoma (RCC). The treatment contains immunotherapy alone or combined with chemotherapy/targeted therapy, and the immunotherapy drugs include PD-1/PD-L1 inhibitor and CTLA-4 antibody. The majority of patients received ATB before and/or within immunotherapy, and the most frequently used ATB drug was β- lactam. The available timing of ATB exposure from the included studies was provided in Fig. 2.

The prognostic information and quality assessment of included studies were summarized in Table 2. Only two studies were prospective, while the rest were retrospective. A total of 14 studies reported both OS and PFS with complete HR values that were calculated using

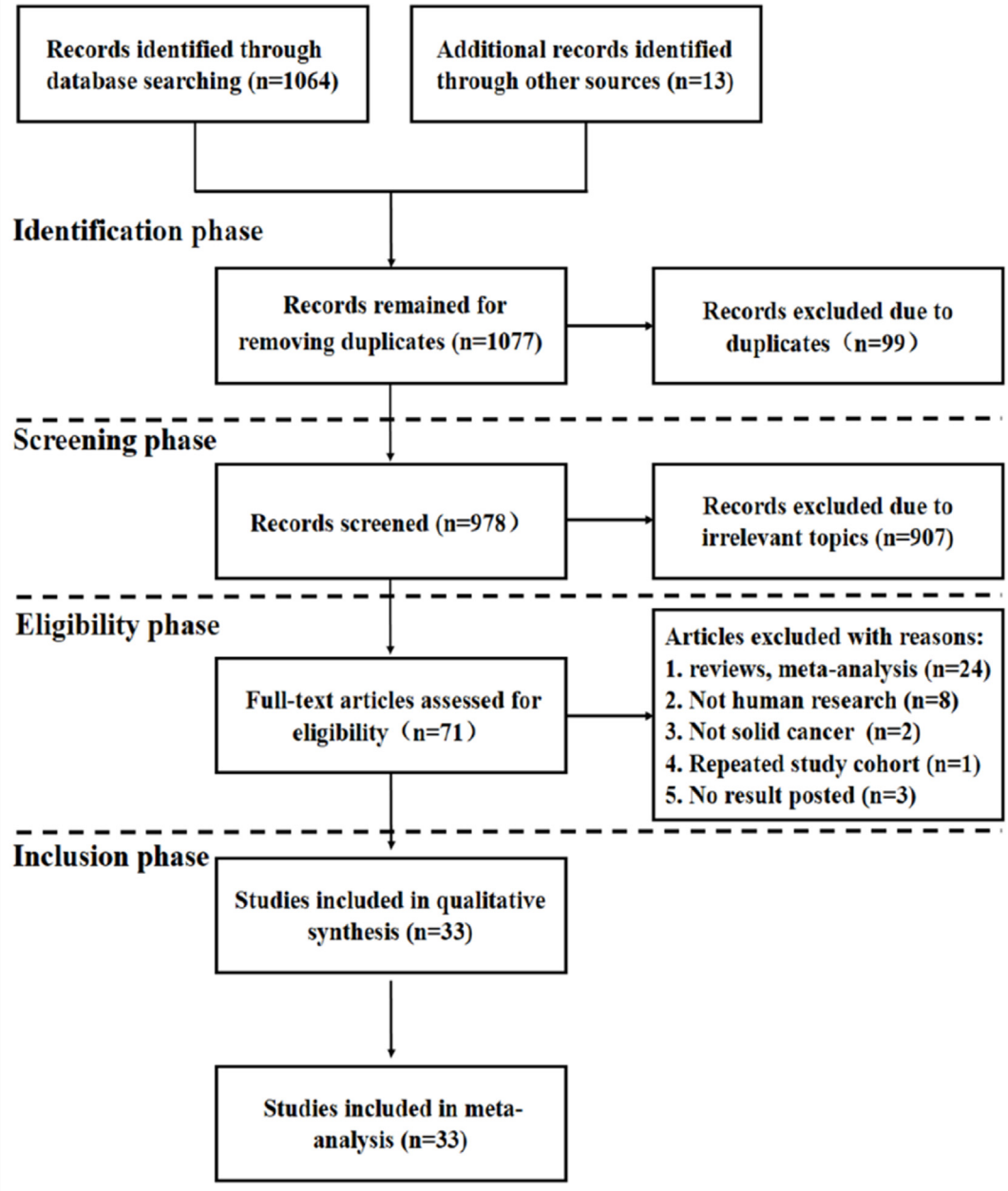

Fig. 1. Flowchart of the literature search process.

multivariable or univariate analysis. Nine studies were found to have a NOS score of five, while all of the rest had NOS scores no less than six.

3.2. Prognostic significance of ATB administration in the entire cancer patients treated with ICIs

As shown in Fig. 3A, using a random-effect model (I^2 = 79%, P < 0.00001), we found ATB administration was significantly correlated with a worse OS in cancer patients treated with ICIs (HR = 1.76(1.41–2.19), P < 0.00001). Using the same model (I^2 = 72%, P < 0.00001), we found ATB administration was also significantly correlated with a worse PFS in cancer patients treated with ICIs (HR = 1.76(1.47–2.12), P < 0.00001, Fig. 3B).

3.3. Subgroup analysis for the prognostic significance of ATB administration

For further investigating the prognostic impact of ATB administration in various defined patients, the subgroup analysis were performed according to region, cancer type, sample size, age, therapeutic strategy, ICI drugs and ATB exposure timing. As shown in Tables 3 and 4, we firstly observed that ATB administration was significantly associated with both worse OS and PFS in patients from Asia (OS: HR = 2.64(1.53, 4.58); PFS: HR = 2.85(1.79, 4.52)) and North America (OS: HR = 1.93 (1.30, 2.88); PFS: HR = 1.59(1.10, 2.28)). For European patients, this association was only significant in PFS (HR = 1.65(1.21, 2.25)) instead of OS (HR = 1.41(0.98, 2.02), *P* = 0.06). In cancer type, ATB administration was significantly associated with worse OS in lung cancer (HR = 1.80(1.28, 2.55)) and other cancers (HR = 2.08(1.27, 3.42)), while this association with worse PFS was significant in lung cancer (HR = 1.70(1.27, 2.27)), RCC (HR = 2.29 (1.68, 3.12)) and other cancers (HR = 2.56(1.29, 5.10)). In lung cancer, a further analysis revealed the negative impact of ATB administration on OS was significant in studies with squamous cell proportions more than 25.8% (HR = 2.28 [1.56, 3.34]), while it was

Table 1
General information of included studies.

Author, year	Country	Cancer type(s)	No. of patients	Treatment	ATB exposure	ATB Duration	Age (years)	ATB Type
Ahmed 2018	USA	MIX	60	PD-(L)1 alone or with chemotherapy	Prior, within	8–14 days	52	β-lactam, Quinolones, Vancomycin, Daptomycin, Linezolid, Meropenem, Tetracyclines, Azithromycin, Nitrofurantoin
Agarwal 2019	USA	UC	101	PD-(L)1	Prior, Within	NA	NA	NA
Chalabi 2020	Multicenter	NSCLC	757	PD-1	Prior, Within	NA	NA	Quinolone, Penicillins, Cephalosporin, Macrolide, Carbapenem, Glycopeptide, Lincomycin, Oxazolidinone
Derosa 2018	USA	NSCLC	239	PD-(L)1 alone or with CTLA-4	Prior	≤ 7 days > 7 days	66	β-lactam (± other), Quinolones (± other), Macrolides, Sulfonamides, Tetracyclines, Nitromidazole
Derosa 2018	France	RCC	121	PD-(L)1 alone or in with CTLA-4 or bevacizumab	Prior	≤7 days (n = 8) > 7 days (n = 8)	61	β-lactam (± other), Quinolones (± other), Tetracyclines, Aminoglycosides
Do 2018	USA	Lung cancer	109	PD-1	Prior, Within	NA	NA	Penicillins, Quinolones, Other antibiotics
Elkrief 2019	Canada	Melanoma	74	PD-1 or CTLA-4 alone or with chemotherapy	Prior	< 7 days (n = 3) > 7 days (n = 7)	58	Doxycycline, Vancomycin, Clarithromycin Piperacillin/Tazobactam, Amoxicillin/ Clavulanic acid, Cefazolin, Ertapenem, Levofloxacin
Galli 2019	Italy	NSCLC	157	PD-(L)1 alone or with CTLA-4	Prior, Within	Median 7.0 days	66.7	Levofloxacin, Amoxicillin/Clavulanate, Claritromicin, Ceftriaxon, Rifaximin, Ciprofloxacin, Azitromicin
Greally 2019	USA	ESCC	161	PD-(L)1 alone or with CTLA-4	Prior, Within	NA	62	β-lactam, Quinolones, Vancomycin, Macrolides, Sulfonamides
Guo 2019	China	esophagogastric cancer	49	PD-(L)1 alone or combination	Prior, Within	Median 10.0 days	56.7	Mostly β-lactam
Hakozaki 2019	Japan	NSCLC	90	PD-1	Prior	≤ 7 days (n = 1) > 7 days (n = 12)	67	Trimethoprim/Sulfamethoxazole, Amoxicillin/Clavulanate, Ceftriaxone, Meropenem, Piperacillin/Tazobactam, Ampicillin/Sulbactam, Cefazolin, Levofloxacin
Hemadri 2019	USA	Melanoma	172	PD-1	Within	NA	NA	NA
Huemer 2018	Austria	NSCLC	30	PD-(L)1	Prior, Within	NA	NA	Mostly Penicillins, Fluoroquinolones, Carbapenems
Huemer-Linz 2019	Austria	NSCLC	53	PD-(L)1	Prior, Within	NA	66	Penicillin, Fluoroquinolone, Cephalosporin, Macrolide, Clindamycin, Metronidazole
Huemer-Salzburg -Linz 2019	Austria	NSCLC	96	PD(L)1 alone or combination	Prior, Within	NA	NA	NA
Iglesias-Santamaría 2020	Spain	MIX	102	PD-(L)1/CTLA-4	Prior, Within	NA	66	β-lactams, Fluoroquinolones, Cephalosporins, Macrolides, Sulphonamides
Kaderbhai 2017	France	NSCLC	74	PD-1	Prior, Within	≤7 days (n = 7) > 7 days (n = 8)	69	NA
Khan 2019	NA	MIX	242	PD-(L)1	Prior, Within	NA	NA	NA
Kim 2019	Korea	MIX	234	PD-(L)1/CTLA4 alone or with chemotherapy	Prior	≤7 days (n = 25) > 7 days (n = 83)	NA	Fluoroquinolones, β-lactam, Carbapenem, Glycopeptides, Macrolides, etc
Kulkarni 2019	USA	NSCLC	148	PD-(L)1	Prior, Within	NA	NA	NA
Kulkarni 2019	USA	RCC	55	PD-(L)1	Prior, Within	NA	NA	NA
Lalani 2019	USA	RCC	146	PD-(L)1 alone or combination	Prior, Within	NA	61	β-lactams, Fluoroquinolones, Macrolide, Tetracycline

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Cancer type(s)	No. of patients	Treatment	ATB exposure	ATB Duration	Age (years)	ATB Type
Masini 2019	Italy	MIX	169	PD-(L)1,CTLA-4	Within	NA	NA	NA
Mielgo-Rubio 2018	Spain	NSCLC	168	PD-1	Prior, Within	NA	65	NA
Ouaknine 2019	France	NSCLC	72	PD-1	Prior, Within	Median 9.5 days	67.8	β-lactams, Vancomycin, Amoxicillin/Clavulanic acid, etc
Pinato 2019	Multicenter	MIX	196	PD-(L)1 alone or PD-(L)1/ CTLA-4 combination	Prior	≤7 days (n = 26) > 7 days (n = 3)	68	β-lactam (± other), Quinolones (± other), Macrolides Sulfonamides, Tetracyclines, Aminoglycosides, Nitromidazole
Rounis 2019	Greece	NSCLC	44	ICI	Prior, Within	NA	69	NA
Routy 2018	France	NSCLC	140	PD-(L)1	Prior, Within	NA	65	β-lactam, Quinolones, Macrolides, Sulfonamides, Tetracyclines, Streptogramins, β-lactam + Quinolone + Streptogramin, etc
Routy 2018	Multicenter	RCC	67	PD-(L)1	Prior, Within	NA	62	β-lactam, Quinolones, Tetracyclines, Aminoglycosides, Nitrofurans, etc
Routy 2018	Multicenter	UC	42	PD-(L)1	Prior, Within	NA	66	β-lactam, Quinolones, Macrolides, etc
Schett 2020	Switzerland	NSCLC	218	PD(L)1 alone or combination	Prior, Within	NA	61	β-lactam, Quinolones, Macrolides, Sulfonamides, Nitro-imidazoles, Tetracyclines
Sen 2018	USA	MIX	172	PD-1 or CTLA-4 alone or combination	Prior	NA	60	β-lactam, Quinolones, Tetracyclines
Swami 2018	USA	Melanoma	199	PD-1	Prior, Within	NA	63	NA
Thompson 2017	USA	NSCLC	74	PD-1	Prior	NA	66	NA
Tinsley 2018	British	MIX	303	ICI	Prior, Within	NA	NA	β-lactam, Macrolides
Tinsley 2020	British	MIX	291	PD-(L)1,CTLA-4	Prior, Within	NA	66	NA
Ueda 2019	Japan	RCC	31	PD-(L)1, CTLA-4	Prior	NA	67	β-lactams
Zhao 2019	China	NSCLC	109	PD-(L)1 alone or combination	Prior, Within	NA	57.5	β-lactam, Fluoroquinolones

Abbreviations: NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma; ICI, immune checkpoint inhibitor, CTLA-4, cytotoxic T-Lymphocyte-associated Antigen 4, PD-1, programmed cell death protein-1; PD-L1, programmed cell Death-Ligand 1; NA, not available; ESCC, esophageal squamous cell carcinoma.

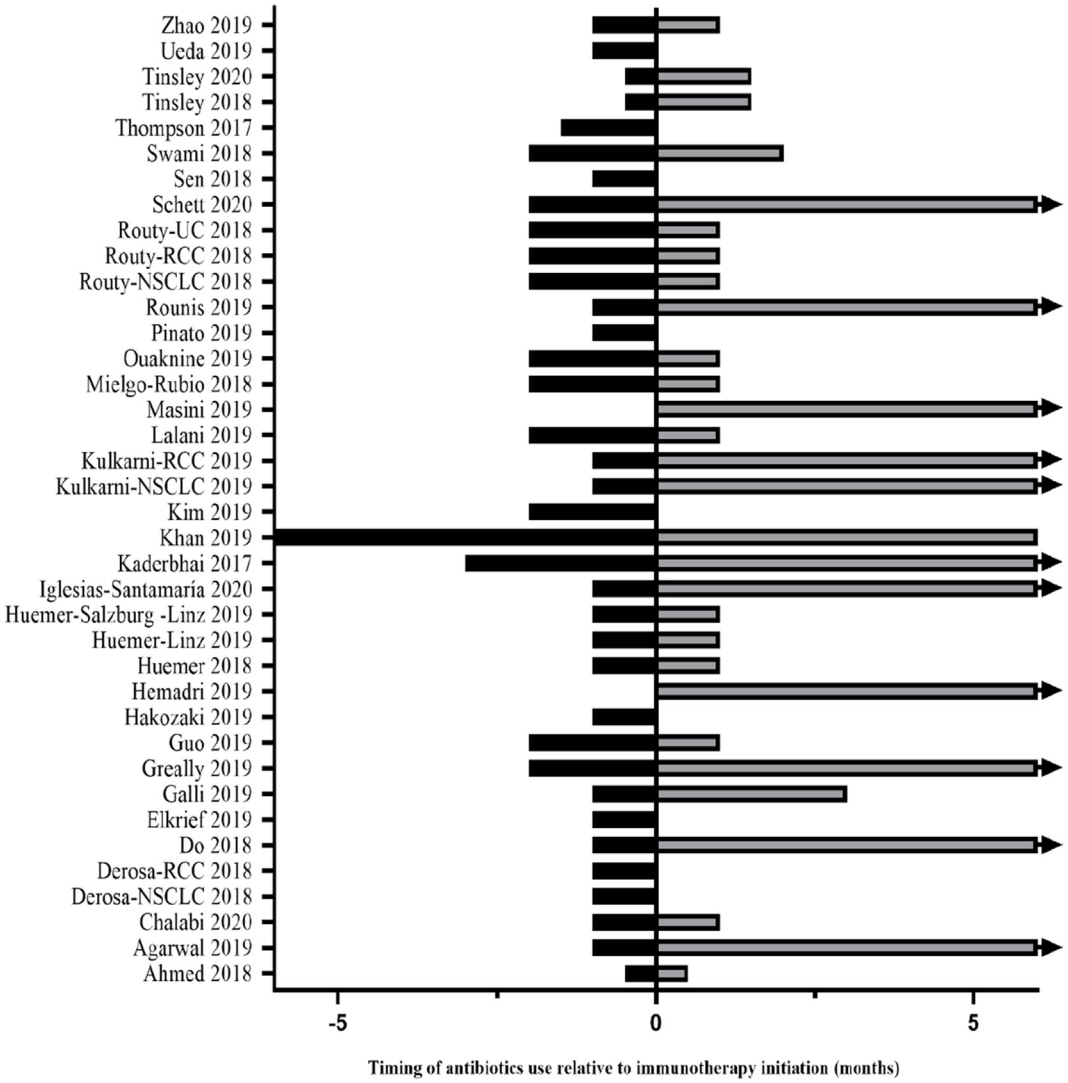

Fig. 2. . Summary graph of the timing for antibiotic administration in included studies.

significant for PFS in studies with squamous cell proportions both less and more than 25.8% (≤25.8%: HR = 1.93 [1.41, 2.64]; > 25.8%: HR = 1.77 [1.23, 2.55]). The negative association of ATB administration with OS and PFS remained significant regardless of sample size (OS: ≤100: HR = 2.19(1.19, 4.05), > 100: HR = 1.64(1.30, 2.07); PFS: ≤100: HR = 2.27(1.80, 2.86), > 100: HR = 1.51(1.21, 1.89)) and age (OS: ≤65 years: HR = 2.09 (1.59, 2.74), > 65 years: HR = 1.82(1.14, 2.92); PFS: ≤65 years: HR = 2.20(1.65, 2.92), > 65 years: HR = 1.59(1.21, 2.08)). With regard to therapeutic strategy, the similar result was observed both in patients treated with immunotherapy alone (OS: HR = 1.52 (1.15, 2.01); PFS: HR = 1.56(1.26, 1.94)) and combined anti-cancer treatment (OS: HR = 2.25(1.64, 3.09); PFS: HR = 2.28 (1.69, 3.08)). Consistently, ATB administration was significantly correlated with poor outcome in patients receiving PD-1/PD-L1 inhibitor alone (OS: HR = 1.78(1.31, 2.42); PFS: HR = 1.96(1.50, 2.57)) or PD-1/PD-L1 inhibitor ± CTLA-4 antibody (OS: HR = 1.74(1.25, 2.43); PFS: HR = 1.53(1.19, 1.96)). Finally, we focused on the timing frames of ATB administration and found its negative association with prognosis was significant in patients receiving ATB within 60 days before ICI initiation (-60–0: OS: HR = 2.58(1.94, 3.43); PFS: HR = 1.88(1.47, 2.41) and from 60 days before ICI to 60 days after ICI initiation (-60–60: OS: HR = 1.64(1.20, 2.24); PFS: HR = 2.01(1.55, 2.61). However, for patients receiving ICI from 60 days before ICI to any timing after ICI initiation (-60-∞), the association was not statistically significant (OS: HR = 1.38(0.89, 2.15), P = 0.15; PFS: HR = 1.29(0.77, 2.17), P = 0.33).

3.4. Sensitivity analysis and publication bias

As shown in Fig. 4A-B, a sensitivity analysis was performed to evaluate the bias caused by limited included studies and the result demonstrated no single study was able to significantly influence the pooled HRs of OS and PFS, validating the reliability of our results. In addition, the Begg's (Fig. 4C-D) and Egger's test were used to evaluate the publication bias and the result test suggested there was significant publication bias in our analysis regarding the association of ATB administration with PFS (Begg's test: P = 0.002; Egger's test: P = 0.003) instead of OS (Begg's test: P = 0.053; Egger's test: P = 0.082). However, the following trim and fill method (Fig. 4E) indicated the publication bias was unable to significantly affect the result trend of PFS (HR = 1.48(1.23–1.77), P < 0.00001).

4. Discussion

With the increasing popularity of immunotherapy in cancer treatment, enormous efforts have been made to identify potential factors that influences its efficacy. Among these identified factors, a considerable amount of evidences have pointed to a crucial role of gut

Table 2
Prognostic information and quality assessment of included studies.

Author, year	Method	Outcome	PFS Hazard ratios (95% CI)	OS Hazard ratios (95% CI)	Analysis	NOS score
Ahmed 2018	RE	PFS/OS	1.6 (0.84–3.03)	2.9 (1.1–8.1)	NA	7
Agarwal 2019	RE	OS	NA	1.93 (1.93–3.42)	NA	5
Chalabi 2020	RE	PFS/OS	1.17 (0.97–1.40)	1.32 (1.06–1.63)	NA	6
Derosa NSCLC 2018	RE	PFS/OS	1.5 (1.0–2.2)	4.4 (2.6–7.7)	NA	7
Derosa RCC 2018	RE	PFS/OS	3.1 (1.4–6.9)	3.5 (1.1–10.8)	NA	7
Do 2018	RE	OS	NA	3.45 (1.72–6.67)	NA	5
Elkrief 2019	RE	PFS/OS	3.13 (1.20–7.69)	2 (0.83–4.76)	M	7
Galli 2019	RE	PFS/OS	1.5 (1.01–2.23)	1.23 (0.79–1.92)	NA	6
Greally 2019	RE	PFS/OS	1.1 (0.78–1.55)	1.26 (0.87–1.81)	U	6
Guo 2019	RE	PFS/OS	5.11 (2.42–10.82)	5.88 (2.55–13.55)	M	7
Hakozaki 2019	RE	PFS/OS	2.56 (1.28–5.15)	2.02 (0.70–5.83)	M	6
Hemadri 2019	RE	PFS/OS	NA	NA	NA	5
Huemer 2018	RE	PFS/OS	5.34 (1.11–27.11)	14.81 (1.35–164.02)	M	6
Huemer -Linz 2019	RE	OS	NA	0.33 (0.16–0.76)	NA	5
Huemer -Salzburg -Linz 2019	RE	OS	NA	0.84 (0.48–1.47)	NA	6
Iglesias-Santamaría 2020	RE	PFS/OS	0.47 (0.25–0.91)	0.73 (0.43–1.54)	M	7
Kaderbhai 2017	RE	PFS/OS	1.07 (0.53–2.17)	NA	NA	7
Khan 2019	RE	PFS	1.98 (1.31–2.99)	NA	NA	5
Kim 2019	RE	PFS/OS	1.715 (1.264–2.326)	1.785 (1.265–2.519)	M	7
Kulkarni-NSCLC 2019	RE	PFS/OS	0.5 (0.3–0.7)	0.5 (0.3–0.8)	NA	5
Kulkarni-RCC 2019	RE	PFS/OS	2.3 (1.0–5.0)	NA	NA	5
Lalani 2019	RE	PFS/OS	1.96 (1.20–3.20)	1.44 (0.75–2.77)	M	7
Masini 2019	RE	OS	NA	0.59 (0.37–0.94)	NA	5
Mielgo-Rubio 2018	RE	PFS/OS	1.77 (1.26–2.46)	1.45 (0.97–2.1)	NA	6
Ouaknine 2019	RE	PFS/OS	1.6 (0.6–2.2)	2.2 (1.1–4.8)	M	7
Pinato 2019	PRO	OS	NA	3.4 (1.9–6.1)	M	7
Rounis 2019	PRO	PFS/OS	2.76 (1.8–6.4)	4.6 (1.7–12)	M	6
Routy-NSCLC 2018	RE	PFS/OS	NA	2.21 (1.30–3.74)	M	7
Routy-RCC 2018	RE	PFS/OS	2.12 (1.11–4.05)	NA	M	7
Routy-UC 2018	RE	PFS/OS	1.96 (0.91–4.23)	NA	M	7
Schett 2020	RE	PFS/OS	3.45 (1.44–8.29)	3.73 (1.34–10.4)	M	6
Sen 2018	RE	PFS/OS	1.2 (0.8–2.1)	2.0 (1.2–3.3)	NA	6
Swami 2018	RE	PFS	4.06 (1.78–9.25)	NA	NA	5
Thompson 2017	RE	PFS/OS	2.5 (1.11–5.47)	3.5 (1.65–8.17)	M	6
Tinsley 2018	RE	PFS/OS	NA	NA	M	6
Tinsley 2020	RE	PFS/OS	1.401 (1.028–1.920)	1.473 (1.038–2.107)	M	7
Ueda 2019	RE	PFS/OS	3.830 (1.086–12.717)	NA	M	6
Zhao 2019	RE	PFS/OS	3.45 (1.79–6.67)	2.86 (1.30–6.25)	M	6

Abbreviations: RE, retrospective; PRO, prospective; PFS, progression-free survival; OS, overall survival; NA, not available; U, univariate; M, multivariate.

microbiota [42]. ATBs are commonly used for interfering gut microbiota in clinical practice and its association with immunotherapy efficacy has been raising heated discussion recently [43–45]. Some retrospective clinical studies have found that ATB administration diminished the efficacy of cancer immunotherapy, while some failed to acquire the similar result [8,10]. During the preparation of our manuscript, we noted that two meta-analysis have already performed to investigate the impact of antibiotic administration on the efficacy of cancer immunotherapy last year [46,47]. The first research by Huang et al includes 19 studies enrolling 2740 cancer patients and demonstrates a negative association of ATB administration with immunotherapy efficacy [46]. The other research by Wilson et al includes 18 studies enrolling 2889 cancer patients and shows the similar result [47]. Compared with them, our present study has included much more studies (n = 33) as well as patients (n = 5565), especially containing several latest studies reporting negative results [19,23]. Therefore, our study may provide some novel insights into the role of ATB administration in cancer immunotherapy.

Firstly, using a random-effect model, we found ATB administration was significantly associated with worse OS and PFS in the entire patients receiving ICI, which is generally in accordance with previous findings by Huang et al and Wilson et al. [46,47]. The following analysis of sensitivity and publication bias confirmed the reliability of our results. To our knowledge, the most likely explanation for this finding is the fact that the administration of broad-spectrum ATBs dramatically impairs the diversity and abundance of host microbiome. Using 16S rRNA gene and metagenome sequencing, Peters et al found the diversity and richness of gut microbiota was positively correlated with prolonged PFS in melanoma patients treated with immunotherapy [48]. The mechanism investigation has preliminarily revealed that favorable gut microbiota contributes to anti-tumor immune response through promoting antigen presentation and effector T cell function [49]. Dubin et al even found the bacteria of bacteroidetes phylum could decrease the risk of immunotherapy induced colitis, supporting the necessity of maintaining gut microbiota [50]. In addition, despite of limited evidences, urinary and lung microbiome have been recently speculated to participate in the modulation of host immunity as well as tumor response to immunotherapy and related clinical investigation are ongoing, implying the potential impact of local microbiome in immunotherapy [51–53]. Therefore, it seems that increasing studies have collectively highlighted the crucial role of host microbiome that should be prevented from disruption by ATBs. However, there are some studies reporting no or even positive association of ATB administration with immunotherapy efficacy [10,23,38]. For instance, in a clinical investigation enrolling 169 advanced cancer patients, Masini et al found ATB administration during immunotherapy was significantly correlated with prolonged OS (HR = 0.59, 95%CI = 0.37–0.94) [38]. Furthermore, considering clinical heterogeneity among various cancers and individuals, we are unable to clearly determine the negative impact of ATBs on immunotherapy efficacy simply based on our integral analysis of the entire included cancers and further subgroup investigations are needed.

For further clarifying the prognostic impact of ATBs on cancer patients receiving immunotherapy, subgroup analysis were performed

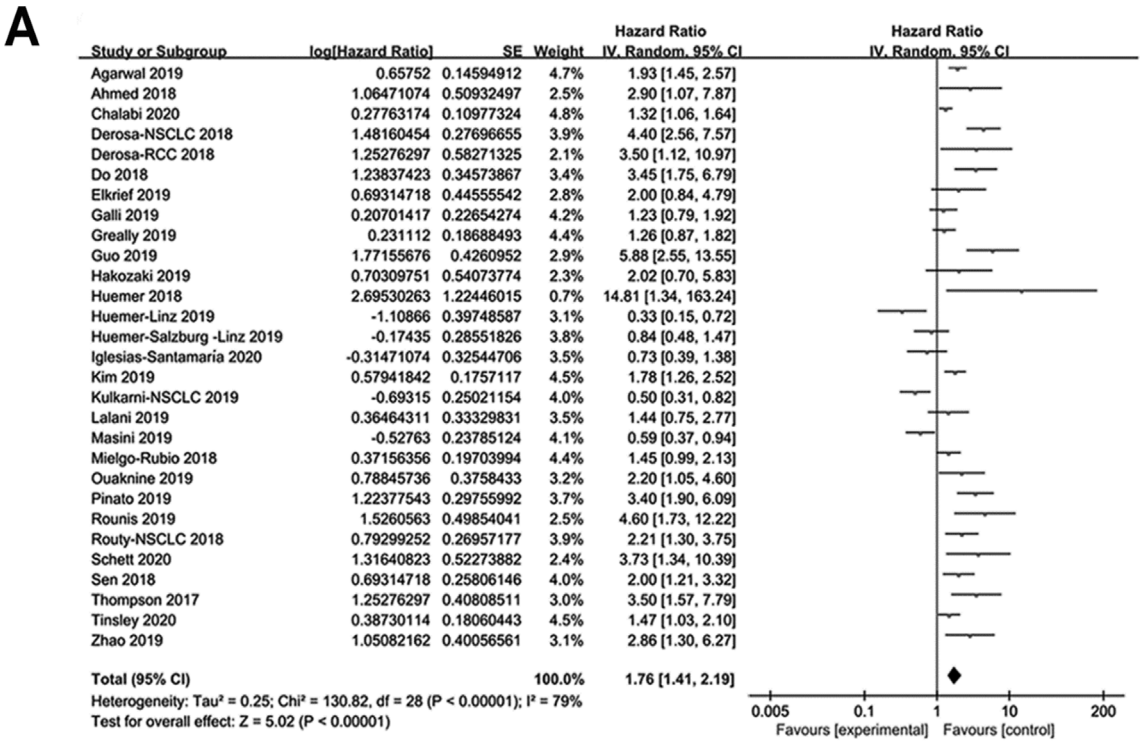

Fig. 3. Forest plots of HRs for correlations of antibiotic administration with overall survival (A) and progression-free survival (B).

according to region, cancer type, sample size, age, therapeutic strategy, immunotherapy drug and the timing of ATB administration. Firstly, except for OS in European group (HR = 1.41(0.98, 2.02), $P = 0.06$), we found ATB administration was significantly correlated with poor outcome in patients from Asia, North America and Europe, suggesting that the unfavorable prognostic impact of ATBs might be uncorrelated with regional difference that potentially results in diverse genetic backgrounds and microbiota compositions. Then, we analyzed the prognostic impact of ATBs in various cancer types and found it significantly correlated with poor efficacy of immunotherapy in NSCLC, RCC and other cancer types, although the OS result of RCC had no statistical significance largely due to limited studies (n = 2, HR = 1.97(0.86, 4.54), P = 0.11). Meanwhile, we speculated the negative observation in the PFS of mixed cancers was probably caused by

Table 3
Subgroup analysis for the association of antibiotic administration with overall survival.

Subgroup	No. of studies	OS Hazard ratios	*P* value	Heterogeneity		Publication bias
		(95%CI)		*P* -value	I^2	Begg's test Egg's test
Region						
Asian	4	2.64 [1.53, 4.58]	0.0005	0.07	58%	0.497 0.315
North America	10	1.93 [1.30, 2.88]	0.001	< 0.00001	81%	0.421 0.459
Europe	13	1.41 [0.98, 2.02]	0.06	< 0.00001	77%	0.393 0.260
Cancer Type						
Lung cancer	16	1.80 [1.28, 2.55]	0.0008	< 0.00001	82%	0.126 0.148
Squamous cell proportion						
≤25.8	8	1.70 [0.91, 3.17]	0.10	< 0.00001	83%	0.621 0.625
> 25.8	7	2.28 [1.56, 3.34]	< 0.0001	0.002	71%	0.099 < 0.00001
RCC	2	1.97 [0.86, 4.54]	0.11	0.19	43%	0.317 /
Others	4	2.08 [1.27, 3.42]	0.004	0.009	74%	1.000 0.462
MIX	7	1.51 [0.98, 2.33]	0.06	< 0.0001	81%	0.652 0.848
Sample Size						
≤100	10	2.19 [1.19, 4.05]	0.01	< 0.00001	79%	0.421 0.115
> 100	19	1.64 [1.30, 2.07]	< 0.0001	< 0.00001	79%	0.132 0.261
Age						
≤65	11	2.09 [1.59, 2.74]	< 0.00001	0.04	48%	0.016 0.003
> 65	10	1.82 [1.14, 2.92]	0.01	< 0.00001	82%	0.929 0.696
Therapeutic strategy						
ICI Alone	18	1.52 [1.15, 2.01]	0.003	< 0.00001	82%	0.306 0.463
Combined Therapy	11	2.25 [1.64, 3.09]	< 0.00001	0.008	58%	0.102 0.136
Immunotherapy Drug						
PD-(L)1	17	1.78 [1.31, 2.42]	0.0002	< 0.00001	79%	0.084 0.200
PD-(L)1, CTLA-4	12	1.74 [1.25, 2.43]	0.001	< 0.00001	80%	0.337 0.265
ATB Exposure (days)						
−60–0	8	2.58 [1.94, 3.43]	< 0.00001	0.14	36%	0.621 0.313
−60–60	12	1.64 [1.20, 2.24]	0.002	< 0.0001	73%	0.075 0.232
−60-∞	9	1.38 [0.89, 2.15]	0.15	< 0.00001	85%	0.835 0.756

Abbreviations: RCC, renal cell carcinoma; CTLA-4, cytotoxic T-Lymphocyte-associated Antigen 4; ICI, immune Checkpoint Inhibitors; PD-1, programmed cell death protein-1; PD-L1, programmed cell Death-Ligand 1; OS, overall survival.

Table 4
Subgroup analysis for the association of antibiotic administration with progression-free survival.

Subgroup	No. of studies	PFS Hazard ratios	*P* value	Heterogeneity		Publication bias
		(95% CI)		*P* -value	I^2	Begg's test Egg's test
Country						
Asian	5	2.85 [1.79, 4.52]	< 0.00001	0.04	60%	0.327 0.059
North America	10	1.59 [1.10, 2.28]	0.01	< 0.00001	77%	0.016 0.035
Europe	10	1.65 [1.21, 2.25]	0.002	0.002	66%	0.325 0.452
Cancer Type						
Lung cancer	13	1.70 [1.27, 2.27]	0.0004	< 0.00001	77%	0.180 0.056
Squamous cell proportion						
≤25.8	6	1.93 [1.41, 2.64]	< 0.0001	0.14	40%	0.039 0.056
> 25.8	6	1.77 [1.23, 2.55]	0.002	0.005	70%	0.348 0.074
RCC	5	2.29 [1.68, 3.12]	< 0.00001	0.80	0%	0.050 0.038
Others	5	2.56 [1.29, 5.10]	0.007	0.0004	80%	0.624 0.041
MIX	6	1.35 [0.98, 1.84]	0.06	0.008	68%	0.188 0.250
Sample Size						
≤100	13	2.27 [1.80, 2.86]	< 0.00001	0.29	15%	0.067 0.099
> 100	16	1.51 [1.21, 1.89]	0.0003	< 0.00001	78%	0.072 0.175
Age						
≤65	12	2.20 [1.65, 2.92]	< 0.00001	0.001	65%	0.020 0.003
> 65	11	1.59 [1.21, 2.08]	0.0008	0.009	58%	0.139 0.397
Therapeutic strategy						
ICI Alone	20	1.56 [1.26, 1.94]	< 0.0001	< 0.00001	73%	0.027 0.049
Combined Therapy	9	2.28 [1.69, 3.08]	< 0.00001	0.02	55%	0.095 0.042
Immunotherapy Drug						
PD-(L)1	18	1.96 [1.50, 2.57]	< 0.00001	< 0.00001	76%	0.045 0.007
PD-(L)1, CTLA-4	11	1.53 [1.19, 1.96]	0.0009	0.002	65%	0.484 0.323
ATB Exposure (days)						
−60–0	8	1.88 [1.47, 2.41]	< 0.00001	0.20	29%	0.048 0.028
−60–60	12	2.01 [1.55, 2.61]	< 0.00001	0.0002	69%	0.028 < 0.00001
−60-∞	7	1.29 [0.77, 2.17]	0.33	< 0.00001	85%	0.293 0.389

Abbreviations: RCC, renal cell carcinoma; CTLA-4, cytotoxic T-Lymphocyte-associated Antigen 4; ICI, immune Checkpoint Inhibitors; PD-1, programmed cell death protein-1; PD-L1, programmed cell Death-Ligand 1; PFS, progression-free survival.

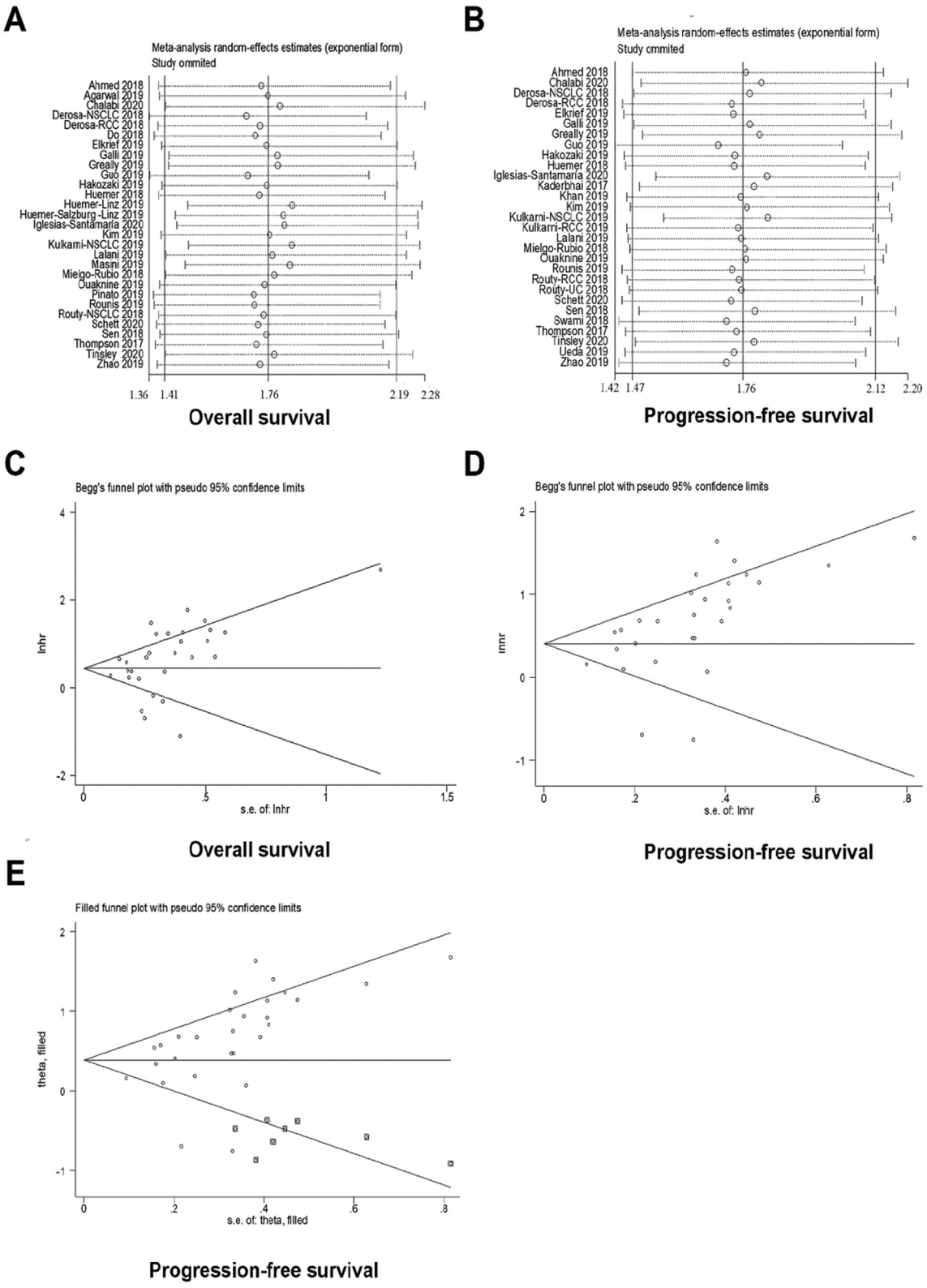

Fig. 4. Sensitivity analysis and publication bias. (A) Sensitivity analysis of the studies assessing overall survival (OS). (B) Sensitivity analysis of the studies assessing progression-free survival (PFS). (C) Begg's funnel plots for evaluating publication bias of OS. (D) Begg's funnel plots for evaluating publication bias of PFS. (E) Trim and fill method for evaluating publication bias of PFS.

the complicated interactions between microbiome and host immunity in some rarely studied cancers such as sarcoma and gastrointestinal cancers [11]. Furthermore, we classified the studies regarding lung cancer based on the median proportion of squamous-cell carcinoma and found the negative prognostic impact of ATBs on PFS was still significant in both the groups, implying this impact may be uncorrelated with histopathological phenotypes in lung cancer. Next, we found ATB administration was significantly correlated with poor OS and PFS

regardless of sample size, however, clinical validations based on large samples are still essential due to the some uncertainties (such as hyperprogression) of ICIs as novel drugs [54]. Previous studies have found that ICIs equivalently improved the overall prognosis in both elderly and young cancer patients [55]. It is worth noting that our present result demonstrated ATB administration diminished the efficacy of ICIs significantly both in elderly and young patients, strongly supporting that cautious administration of ATBs should be advocated regardless of age. With regard to therapeutic strategy, we observed similar results not only in cancer patients receiving ICIs alone, but also in those receiving ICIs combined with other therapies such as chemotherapy and targeted therapy. In fact, the negative association of ATB administration with chemotherapy efficacy has already been observed in several clinical studies. For instance, using clinical trial datasets, a recent study found ATB administration before first-line chemotherapy was significantly correlated with worse OS and PFS in metastatic colorectal cancer [56]. Another study found the similar correlation in hepatocellular carcinoma (HCC) patients and the sequencing analysis of fecal microbiota revealed ATB administration reduced the abundance of intestinal anaerobic bacteria (such as Blautia) that were associated with a favourable clinical outcome in HCC [57]. Therefore, considering its extra unfavorable impact on traditional anti-cancer therapies, ATBs should be used more cautiously before or during ICI-based combined therapies. Furthermore, we found the negative association of ATB administration with poor prognosis was significant not only in patients receiving PD-1/PDL-1 inhibitor alone, but also in those receiving PD(L)-1 inhibitor/CTLA-4 antibody alone or both combined, further highlighting the critical role of microbiome in ICI efficacy. Finally, since previous studies have proposed the controversy about the timing frames of ATB administration in ICI treatment, we therefore stratified the subgroups according to the timing before and/or after ICI initiation [11,22,23,27]. As a result, we found the adverse prognostic impact of ATBs was significant in patients receiving ATB within 60 days before ICI initiation as well as from 60 days before ICI to 60 days after ICI initiation. Meanwhile, we observed ATB administration was uncorrelated with OS and PFS in patients receiving ATB from 60 days before ICI to any timing after ICI initiation, implying that the detrimental role of ATB administration may be correlated with the limited timing frame shortly before and after ICI initiation. This hypothesis is in accordance with a recent comprehensive investigation regarding lung cancer [58]. However, on the other hand, we also noted a recent opinion that the prognostic effect of ATBs was probably dependent on the cumulative ATB exposure ratio rather than some defined time frames, which still needs further validations in future [18,23].

It is worth mentioning that there are several inherent limitations in our study. Firstly, our study was essentially a meta-analysis depending on the available data from published literatures. Although we have made enormous efforts to collect the information as much as possible, many important details of included studies were incomplete such as the timing or duration of ATB administration, the type of ATBs and ICIs, partly limiting our further analysis and affecting our results. Furthermore, we failed to discuss the microbiome change in patients receiving ATBs before and/or within ICI treatment due to rare sequencing evidences, which are expected to be solved by following metagenomic analysis based on sufficient samples. Secondly, we noted the potential publication bias in our study, although we confirmed it was unable to significantly affect our conclusion. We attributed this limitation to two reasons: 1) we inevitably included many more studies with positive results than those with negative/opposite results; 2) we focused on the literatures published in English, potentially omitting eligible ones published in other languages. Thirdly, the study heterogeneity was affected by various inherent factors in retrospective analysis such as patient selection, therapeutic methods, drug type/dose. This limitation is expected to be improved by stricter inclusion based on upon sufficient literatures. Fourthly, we failed to investigate the correlation between ATB administration and ICI induced adverse events, which should be emphasized in our following work. Finally, in terms of cancer type, our present study mainly focused on lung and renal cell carcinoma, and therefore more attention should be paid in other solid tumors such as gastrointestinal or esophageal tumors in future.

In summary, our study indicated that ATB administration was significantly associated with worse outcome in solid cancer patients receiving ICI treatment. In addition, the subgroup analysis revealed this significant association was independent of sample size, age, therapeutic strategy and ICI type. The detrimental impact of ATB administration on ICI efficacy was significant in patients with lung, renal cell and other cancers (such as melanoma). The ICI efficacy was more likely to be diminished by ATB administration within a time frame from 60 days before to 60 days after ICI initiation. These findings collectively suggest that ATB administration should be cautiously considered in solid cancer patients receiving ICI treatment. More clinical validations based on large samples are necessary and meanwhile experimental efforts should be made to further clarify the underlying mechanism of ATB induced detrimental effect on cancer immunotherapy.

CRediT authorship contribution statement

Mengxue Yang: Writing - original draft. **Ying Wang:** Writing - original draft. **Man Yuan:** Writing - original draft. **Mingyang Tao:** Writing - original draft. **Cheng Kong:** Writing - review & editing. **Hao Li:** Writing - review & editing. **Jiandong Tong:** Conceptualization, Methodology. **Huiyuan Zhu:** Conceptualization, Methodology. **Xuebing Yan:** Conceptualization, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This research was financially supported by the China National Natural Science Foundation (No. 81902422) and Lijieshou Intestinal Barrier Foundation (No. LJS-201701). Pandeng Research Foundation of Shanghai Tenth People's Hospital (No. 2018SYPDRC008).

References

[1] A. Ribas, J.D. Wolchok, Cancer immunotherapy using checkpoint blockade, Science 359 (6382) (2018) 1350–1355, https://doi.org/10.1126/science.aar4060.
[2] P.S. Hegde, D.S. Chen, Top 10 challenges in cancer immunotherapy, Immunity 52 (1) (2020) 17–35, https://doi.org/10.1016/j.immuni.2019.12.011.
[3] L. Shui, X. Yang, J. Li, C. Yi, Q. Sun, H. Zhu, Gut microbiome as a potential factor for modulating resistance to cancer immunotherapy, Front. Immunol 10 (2020) 2989, https://doi.org/10.3389/fimmu.2019.02989.
[4] V. Gopalakrishnan, B.A. Helmink, C.N. Spencer, A. Reuben, J.A. Wargo, The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy, Cancer Cell 33 (4) (2018) 570–580, https://doi.org/10.1016/j.ccell.2018.03.015.
[5] S. Temraz, F. Nassar, R. Nasr, M. Charafeddine, D. Mukherji, A. Shamseddine, Gut microbiome: a promising biomarker for immunotherapy in colorectal cancer, Int. J. Mol. Sci. 20 (17) (2019) 4155, https://doi.org/10.3390/ijms20174155.
[6] B. Routy, E. Le Chatelier, L. Derosa, C.P.M. Duong, M.T. Alou, R. Daillère, A. Fluckiger, M. Messaoudene, C. Rauber, M.P. Roberti, et al., Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors, Science 359 (6371) (2018) 91–97, https://doi.org/10.1126/science.aan3706.
[7] A. Teillant, S. Gandra, D. Barter, D.J. Morgan, R. Laxminarayan, Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study, Lancet Infect. Dis. 15 (12) (2015) 1429–1437, https://doi.org/10.1016/s1473-3099(15)00270-4.
[8] N. Tinsley, C. Zhou, G. Tan, S. Rack, P. Lorigan, F. Blackhall, M. Krebs, L. Carter, F. Thistlethwaite, D. Graham, et al., Cumulative antibiotic use significantly decreases efficacy of checkpoint inhibitors in patients with advanced cancer, Oncologist. 25 (1) (2020) 55–63, https://doi.org/10.1634/theoncologist.2019-0160.
[9] T. Hakozaki, Y. Okuma, M. Omori, Y. Hosomi, Impact of prior antibiotic use on the efficacy of nivolumab for non-small cell lung cancer, Oncol. Lett. 17 (3) (2019) 2946–2952, https://doi.org/10.3892/ol.2019.9899.

[10] C. Kaderbhai, C. Richard, J.D. Fumet, A. Aarnink, P. Foucher, B. Coudert, L. Favier, A. Lagrange, E. Limagne, R. Boidot, et al., Antibiotic use does not appear to influence response to nivolumab, Anticancer Res. 37 (6) (2017) 3195–3200, https://doi.org/10.21873/anticanres.11680.

[11] S. Sen, R.C. Pestana, K. Hess, G.M. Viola, V. Subbiah, Impact of antibiotic use on survival in patients with advanced cancers treated on immune checkpoint inhibitor phase I clinical trials, Ann. Oncol. 29 (12) (2018) 2396–2398, https://doi.org/10.1093/annonc/mdy453.

[12] D.G. Altman, J.M. Bland, How to obtain the confidence interval from a P value, BMJ 343 (2011) d2090, , https://doi.org/10.1136/bmj.d2090.

[13] H. Yu, S. Li, S.X. Wu, S. Huang, S. Li, L. Ye, The prognostic value of long non-coding RNA H19 in various cancers: a meta-analysis based on 15 studies with 1584 patients and the Cancer Genome Atlas data, Medicine 99 (2) (2020) e18533, , https://doi.org/10.1097/md.0000000000018533.

[14] J. Ahmed, A. Kumar, K. Parikh, A. Anwar, B.M. Knoll, C. Puccio, H. Chun, M. Fanucchi, S.H. Lim, Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors, Oncoimmunology 7 (11) (2018) e1507670, , https://doi.org/10.1080/2162402x.2018.1507670.

[15] M. Chalabi, A. Cardona, D.R. Nagarkar, A. Dhawahir Scala, D.R. Gandara, A. Rittmeyer, M.L. Albert, T. Powles, M. Kok, F.G. Herrera, Efficacy of chemotherapy and atezolizumab in patients with non-small-cell lung cancer receiving antibiotics and proton pump inhibitors: pooled post hoc analyses of the OAK and POPLAR trials, Ann. Oncol. 31 (4) (2020) 525–531, https://doi.org/10.1016/j.annonc.2020.01.006.

[16] L. Derosa, M.D. Hellmann, M. Spaziano, D. Halpenny, M. Fidelle, H. Rizvi, N. Long, A.J. Plodkowski, K.C. Arbour, J.E. Chaft, et al., 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) (2018) 1437–1444, https://doi.org/10.1093/annonc/mdy103.

[17] A. Elkrief, L. El Raichani, C. Richard, M. Messaoudene, W. Belkaid, J. Malo, K. Belanger, W. Miller, R. Jamal, N. Letarte, et al., Antibiotics are associated with decreased progression-free survival of advanced melanoma patients treated with immune checkpoint inhibitors, Oncoimmunology. 8 (4) (2019) e1568812, , https://doi.org/10.1080/2162402x.2019.1568812.

[18] G. Galli, T. Triulzi, C. Proto, D. Signorelli, M. Imbimbo, M. Poggi, G. Fucà, M. Ganzinelli, M. Vitali, D. Palmieri, et al., Association between antibiotic-immunotherapy exposure ratio and outcome in metastatic non small cell lung cancer, Lung Cancer. 132 (2019) 72–78, https://doi.org/10.1016/j.lungcan.2019.04.008.

[19] M. Greally, J.F. Chou, W.K. Chatila, M. Margolis, M. Capanu, J.F. Hechtman, Y. Tuvy, R. Kundra, F. Daian, M. Ladanyi, et al., Clinical and molecular predictors of response to immune checkpoint inhibitors in patients with advanced esophagogastric cancer, Clin. Cancer Res. 25 (20) (2019) 6160–6169, https://doi.org/10.1158/1078-0432.ccr-18-3603.

[20] J.C. Guo, C.C. Lin, C.Y. Lin, M.S. Hsieh, H.Y. Kuo, M.Y. Lien, Y.Y. Shao, T.C. Huang, C.H. Hsu, Neutrophil-to-lymphocyte ratio and use of antibiotics associated with prognosis in esophageal squamous cell carcinoma patients receiving immune checkpoint inhibitors, Anticancer Res. 39 (10) (2019) 5675–5682, https://doi.org/10.21873/anticanres.13765.

[21] F. Huemer, G. Rinnerthaler, T. Westphal, H. Hackl, G. Hutarew, S.P. Gampenrieder, L. Weiss, R. Greil, Impact of antibiotic treatment on immune-checkpoint blockade efficacy in advanced non-squamous non-small cell lung cancer, Oncotarget. 9 (23) (2018) 16512–16520, https://doi.org/10.18632/oncotarget.24751.

[22] F. Huemer, G. Rinnerthaler, D. Lang, H. Hackl, B. Lamprecht, R. Greil, Association between antibiotics use and outcome in patients with NSCLC treated with immunotherapeutics, Ann. Oncol. 30 (4) (2019) 652–653, https://doi.org/10.1093/annonc/mdz021.

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

[24] H. Kim, J.E. Lee, S.H. Hong, M.A. Lee, J.H. Kang, I.H. Kim, The effect of antibiotics on the clinical outcomes of patients with solid cancers undergoing immune checkpoint inhibitor treatment: a retrospective study, BMC Cancer. 19 (1) (2019) 1100, https://doi.org/10.1186/s12885-019-6267-z.

[25] A.A. Lalani, W. Xie, D.A. Braun, M. Kaymakcalan, D. Bosse, J.A. Steinharter, D.J. Martini, R. Simantov, X. Lin, X.X. Wei, et al., Effect of antibiotic use on outcomes with systemic therapies in metastatic renal cell carcinoma, Eur. Urol. Oncol. (2019), https://doi.org/10.1016/j.euo.2019.09.001.

[26] J. Ouaknine Krief, P. Helly de Tauriers, C. Dumenil, N. Neveux, J. Dumoulin, V. Giraud, S. Labrune, J. Tisserand, C. Julie, J.F. Emile, et al., Role of antibiotic use, plasma citrulline and blood microbiome in advanced non-small cell lung cancer patients treated with nivolumab, J. Immunother Cancer. 7 (1) (2019) 176, https://doi.org/10.1186/s40425-019-0658-1.

[27] D.J. Pinato, S. Howlett, D. Ottaviani, H. Urus, A. Patel, T. Mineo, C. Brock, D. Power, O. Hatcher, A. Falconer, et al., Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer, JAMA Oncol. 5 (12) (2019) 1774–1778, https://doi.org/10.1001/jamaoncol.2019.2785.

[28] K. Ueda, S. Yonekura, N. Ogasawara, Y. Matsunaga, R. Hoshino, H. Kurose, K. Chikui, K. Uemura, M. Nakiri, K. Nishihara, et al., The Impact of antibiotics on prognosis of metastatic renal cell carcinoma in Japanese patients treated with immune checkpoint inhibitors, Anticancer Res. 39 (11) (2019) 6265–6271, https://doi.org/10.21873/anticanres.13836.

[29] S. Zhao, G. Gao, W. Li, X. Li, C. Zhao, T. Jiang, Y. Jia, Y. He, A. Li, C. Su, et al., Antibiotics are associated with attenuated efficacy of anti-PD-1/PD-L1 therapies in Chinese patients with advanced non-small cell lung cancer, Lung Cancer. 130 (2019) 10–17, https://doi.org/10.1016/j.lungcan.2019.01.017.

[30] K. Rounis, C. Papadaki, D. Makrakis, A. Monastirioti, L. Vamvakas, K. Kalbakis, D. Mavroudis, S. Aggelaki, Correlation of various clinical, imaging and laboratory parameters with outcome in patients with metastatic non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs): Results from a prospective, observational, single institution study, Ann. Oncol. 30 Suppl 2 (2019) ii61, https://doi.org/10.1093/annonc/mdz063.064.

[31] A. Schett, S.I. Rothschild, A. Curioni-Fontecedro, S. Krahenbuhl, M. Fruh, S. Schmid, C. Driessen, M. Joerger, Predictive impact of antibiotics in patients with advanced non small-cell lung cancer receiving immune checkpoint inhibitors: Antibiotics immune checkpoint inhibitors in advanced NSCLC, Cancer Chemother. Pharmacol. 85 (1) (2020) 121–131, https://doi.org/10.1007/s00280-019-03993-1.

[32] J. Thompson, A. Szabo, C. Arce-Lara, S. Menon, S. P1.07-008 Microbiome & Immunotherapy: Antibiotic Use Is Associated with Inferior Survival for Lung Cancer Patients Receiving PD-1 Inhibitors, J. Thorac. Oncol. 12 (11) (2017) S1998. https://doi.org/10.1016/j.jtho.2017.09.926.

[33] U. Swami, V. Monga, T. Knutson, A.D. Bossler, Y. Zakharia, M.M. Milhem, Prognostic markers for progression free survival (PFS) to anti PD-1 therapies in metastatic melanoma, J. Clin. Oncol. 36 (15_suppl) (2018) e21527, , https://doi.org/10.1200/JCO.2018.36.15_suppl.e21527.

[34] X. Mielgo-Rubio, L. Chara, M. Sotelo-Lezama, R. Lopez Castro, J. Rubio-Martínez, A. Velastegui, C. Olier-Garate, S. Falagan, I. Gómez-Barreda, P. Bautista-Sanz, et al., MA10.01 antibiotic use and PD-1 inhibitors: shorter survival in lung cancer, especially when given intravenously. Type of infection also matters, J. Thorac. Oncol. 13 (10) (2018) S389, https://doi.org/10.1016/j.jtho.2018.08.395.

[35] A. Agarwal, G.R. Pond, C. Curran, A. Nassar, P.V. Nuzzo, V. Kumar, B.A. McGregor, X.X. Wei, L.C. Harshman, T.K. Choueiri, et al., Impact of concurrent medications on outcomes with PD1/PD-L1 inhibitors for metastatic urothelial carcinoma, J. Clin. Oncol. 37 (7_suppl) (2019) 435, https://doi.org/10.1200/JCO.2019.37.7_suppl.435.

[36] N. Tinsley, C. Zhou, S. Villa, G. Tan, P. Lorigan, F.H. Blackhall, T. Elliott, M. Krebs, L. Carter, F. Thistlethwaite, et al., Cumulative antibiotic use and efficacy of immune checkpoint inhibitors in patients with advanced cancer, J. Clin. Oncol. 36 (15_suppl) (2018) 3010, https://doi.org/10.1200/JCO.2018.36.15_suppl.3010.

[37] T.P. Do, A.M. Hegde, C.R. Cherry, C.R.G. Stroud, N. Sharma, S.D. Cherukuri, M. Bowling, P.R. Walker, Antibiotic use and overall survival in lung cancer patients receiving nivolumab, J. Clin. Oncol. 36 (15_suppl) (2018) e15109, , https://doi.org/10.1200/JCO.2018.36.15_suppl.e15109.

[38] C. Masini, A. Berselli, A. Romagnani, C. Bonelli, E. Fantinel, M. Pagano, M. Banzi, G. Prati, E. Gasparini, G. Moretti, et al., Results of an Italian CORE-IMMUNO study: Safety and clinical-related biomarkers as predictors of immunotherapy (IT) benefit in real-world treatment of various advanced tumors (ATs), J. Clin. Oncol. 37 (15_suppl) (2019) e14156, , https://doi.org/10.1200/JCO.2019.37.15_suppl.e14156.

[39] A. Hemadri, H. Lin, Y. Lin, A. Rose, C. Sander, Y. Najjar, H.M. Zarour, J.M. Kirkwood, D. Davar, Association of medication (Med) and antibiotic (Abx) use with response and survival in advanced melanoma (MEL) receiving PD-1 inhibitors, J. Clin. Oncol. 37 (15_suppl) (2019) 9572, https://doi.org/10.1200/JCO.2019.37.15_suppl.9572.

[40] U. Khan, C. Peña, J. Brouwer, K. Hoffman, A.R. Choudhury, C. Zhang, P. Thakkar, D. Betel, S. Sarkar, G. Sonnenberg, et al., Impact of antibiotic use on response to treatment with immune checkpoint inhibitors, J. Clin. Oncol. 37 (4_suppl) (2019) 143, https://doi.org/10.1200/JCO.2019.37.4_suppl.143.

[41] A. Kulkarni, M. Kumar, D.F. Pease, Y. Wang, T.E. DeFor, M. Patel, 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, J. Clin. Oncol. 37 (15_suppl) (2019) e20520, , https://doi.org/10.1200/JCO.2019.37.15_suppl.e20520.

[42] T. Christofi, S. Baritaki, L. Falzone, M. Libra, A. Zaravinos, Current Perspectives in Cancer Immunotherapy, Cancers. 11 (10) (2019), https://doi.org/10.3390/cancers11101472.

[43] J.P. Reed, S. Devkota, R.A. Figlin, Gut microbiome, antibiotic use, and immunotherapy responsiveness in cancer, Ann. Transl. Med. 7 (Suppl 8) (2019) S309, https://doi.org/10.21037/atm.2019.10.27.

[44] C. Yan, X.X. Tu, W. Wu, Z. Tong, L.L. Liu, Y. Zheng, W.Q. Jiang, P. Zhao, W.J. Fang, H.Y. Zhang, Antibiotics and immunotherapy in gastrointestinal tumors: Friend or foe? World J. Clin. Cases. 7 (11) (2019) 1253–1261, https://doi.org/10.12998/wjcc.v7.i11.1253.

[45] D.J. Pinato, D. Gramenitskaya, D.M. Altmann, R.J. Boyton, B.H. Mullish, J.R. Marchesi, M. Bower, Antibiotic therapy and outcome from immune-checkpoint inhibitors, J. Immunother. Cancer. 7 (1) (2019) 287, https://doi.org/10.1186/s40425-019-0775-x.

[46] X.Z. Huang, P. Gao, Y.X. Song, Y. Xu, J.X. Sun, X.W. Chen, J.H. Zhao, Z.N. Wang, Antibiotic use and the efficacy of immune checkpoint inhibitors in cancer patients: a pooled analysis of 2740 cancer patients, Oncoimmunology. 8 (12) (2019) e1665973, , https://doi.org/10.1080/2162402x.2019.1665973.

[47] B.E. Wilson, B. Routy, A. Nagrial, V.T. Chin, The effect of antibiotics on clinical outcomes in immune-checkpoint blockade: a systematic review and meta-analysis of observational studies, Cancer Immunol. Immunother. 69 (3) (2020) 343–354, https://doi.org/10.1007/s00262-019-02453-2.

[48] B.A. Peters, M. Wilson, U. Moran, A. Pavlick, A. Izsak, T. Wechter, J.S. Weber, I. Osman, J. Ahn, Relating the gut metagenome and metatranscriptome to immunotherapy responses in melanoma patients, Genome Med. 11 (1) (2019) 61, https://doi.org/10.1186/s13073-019-0672-4.

[49] V. Gopalakrishnan, C.N. Spencer, L. Nezi, A. Reuben, M.C. Andrews, T.V. Karpinets, P.A. Prieto, D. Vicente, K. Hoffman, S.C. Wei, et al., Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients, Science 359 (6371)

(2018) 97–103, https://doi.org/10.1126/science.aan4236.
[50] K. Dubin, M.K. Callahan, B. Ren, R. Khanin, A. Viale, L. Ling, D. No, A. Gobourne, E. Littmann, C. Huttenhower, et al., Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis, Nat. Commun. 7 (2016) 10391, https://doi.org/10.1038/ncomms10391.
[51] M. Bersanelli, M. Santoni, A. Ticinesi, S. Buti, The urinary microbiome and anticancer immunotherapy: the potentially hidden role of unculturable microbes, Target. Oncol. 14 (3) (2019) 247–252, https://doi.org/10.1007/s11523-019-00643-7.
[52] A.G. Ramírez-Labrada, D. Isla, A. Artal, M. Arias, A. Rezusta, J. Pardo, E.M. Gálvez, The influence of lung microbiota on lung carcinogenesis, immunity, and immunotherapy, Trends Cancer 6 (2) (2020) 86–97, https://doi.org/10.1016/j.trecan.2019.12.007.
[53] C. Carbone, G. Piro, V. Di Noia, E. D'Argento, E. Vita, M.G. Ferrara, S. Pilotto, M. Milella, G. Cammarota, A. Gasbarrini, et al., Lung and gut microbiota as potential hidden driver of immunotherapy efficacy in lung cancer, Mediators Inflamm. 2019 (2019) 7652014, https://doi.org/10.1155/2019/7652014.
[54] J.J. Adashek, S. Kato, R. Ferrara, G. Lo Russo, R. Kurzrock, Hyperprogression and immune checkpoint inhibitors: hype or progress? Oncologist. 25 (2) (2020) 94–98, https://doi.org/10.1634/theoncologist.2019-0636.
[55] C. Ciccarese, R. Iacovelli, E. Bria, A. Palazzo, B.A. Maiorano, C. Mosillo, C. Carbone, G. Piro, G. Tortora, The anticancer efficacy of immune checkpoint inhibitors according to patients' age: a systematic review and meta-analysis, J. Immunother. 43 (3) (2020) 95–103, https://doi.org/10.1097/cji.0000000000000312.
[56] O. Abdel-Rahman, S. Ghosh, J. Walker, Outcomes of metastatic colorectal cancer patients in relationship to prior and concurrent antibiotics use; individual patient data analysis of three clinical trials, Clin. Transl. Oncol. (2020), https://doi.org/10.1007/s12094-020-02301-1.
[57] N. Iida, E. Mizukoshi, T. Yamashita, T. Terashima, K. Arai, J. Seishima, S. Kaneko, Overuse of antianaerobic drug is associated with poor postchemotherapy prognosis of patients with hepatocellular carcinoma, Int. J. Cancer. 145 (10) (2019) 2701–2711, https://doi.org/10.1002/ijc.32339.
[58] L. Lurienne, J. Cervesi, L. Duhalde, J. de Gunzburg, A. Andremont, G. Zalcman, R. Buffet, P.A. Bandinelli, Non-small-cell lung cancer immunotherapy efficacy and antibiotic use: a systematic review and meta-analysis, J. Thorac. Oncol. (2020), https://doi.org/10.1016/j.jtho.2020.03.002.