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Survival of patients treated with antibiotics and immunotherapy for cancer: A systematic review and meta-analysis

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Antibiotics and immune checkpoint inhibitors

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Abstract

Antibiotics (ABs) are common medications used for treating infections. In cancer patients treated with immune checkpoint inhibitors (ICIs), concomitant exposure to ABs may impair the efficacy of ICIs and lead to a poorer outcome compared to AB non-users. We report here the results of a meta-analysis evaluating the effects of ABs on the outcome of patients with solid tumors treated with ICIs. PubMed, the Cochrane Library, and Embase were searched from inception until September 2019 for observational or prospective studies reporting prognosis of adult patients with cancer treated with ICIs and with or without ABs. Overall survival (OS) was the primary endpoint, and progression-free survival (PFS) was the secondary endpoint. The effect size was reported as hazard ratios (HRs) with a 95% confidence interval (CI), and an HR > 1 associated with a worse outcome in ABs users compared to no-ABs users. Fifteen publications were retrieved for a total of 2363 patients. In the main analysis (n = 15 studies reporting data), OS was reduced in patients exposed to ABs before or during treatment with ICIs (HR = 2.07, 95%CI 1.51–2.84; P<.01). Similarly, PFS was inferior in ABs users in n = 13 studies with data available (HR = 1.53, 95%CI 1.22–1.93; p<.01). In cancer patients treated with ICIs, AB use significantly reduces OS and PFS. Short duration/course of ABs may be considered in clinical situations in which they are strictly needed.

Keywords: cancer, immune checkpoint inhibitors, survival, antibiotic, meta-analysis

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Introduction

Cancer immunotherapy with immune checkpoint inhibitors (ICIs) has demonstrated efficacy among several tumor types [1]. However, a non-negligible percentage of patients do not derive any benefit from ICIs, and the research for predictive factors may help to refine patients' selection and improve treatment efficacy.

Preclinical studies on murine models have demonstrated that gut microbiota may act as a key modulator of efficacy and toxicity of ICIs [2,3]. Thus, it has been supposed that response to ICIs in humans could be affected by conditions that alter the composition of gut microbiota, including dysbiosis, due to the administration of antibiotics (ABs). In fact, retrospective studies reported worse outcomes for patients treated with ICIs that received ABs as compared with those not receiving Abs [4-6].

The present meta-analysis evaluated the association between AB use and outcomes in patients with solid tumors treated with ICIs.

Results

Among the publications retrieved using electronic search, 15 studies were eligible for quantitative analysis, for a total of 2,363 patients [4-18] (Fig. 1).

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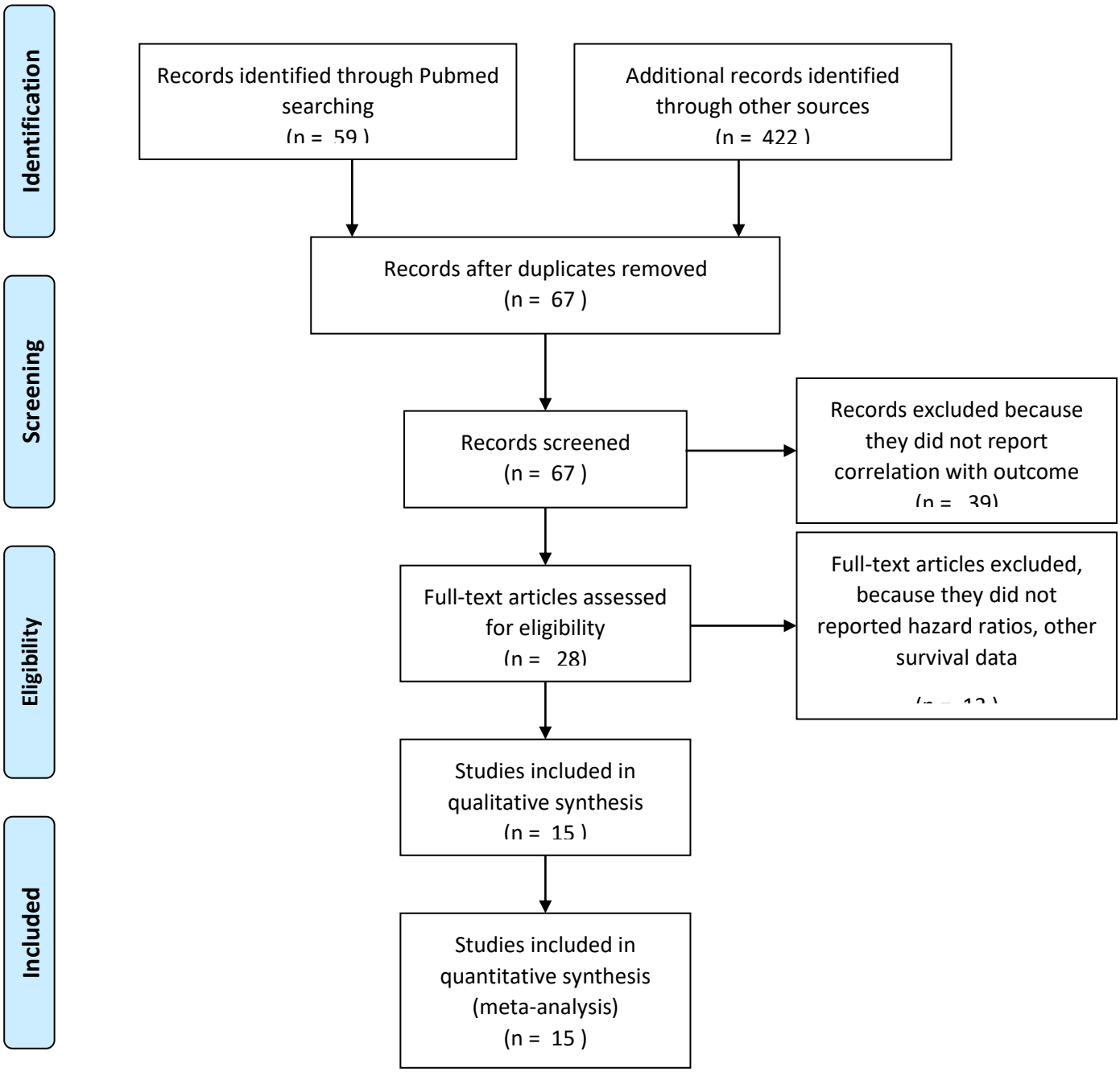

Fig.1 Flow diagram of included studies

Baseline characteristics of the included studies and treatments received are presented in Table 1. Thirteen were retrospective series, and two were prospective studies.

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Tab. 1 Characteristics of included studies

Author/ year	Type of study	N° of patients	Treatment received (%)	Median age (years)	Ab% /timing	Med FUP (mos)	Type of analysis	Covariates of MVA for OS	Quality (NOS score)
Abu-Sbeih/ 2019	retrospective	826 (various)	anti-PD(L)1 (51.6), anti-CTLA4 (32), combo (16.5)	62	68.9 /before or after start (47.5%), both (52.5%)	NR	MVA	ICI type, Stage IV cancer, IMDC, anaerobic ab use	6
Ahmed/ 2018	retrospective	60 (various)	anti-PD1 (81.7), anti-PDL1 (5), ICI + CT (13.3)	59	28 /2w before and/or after start	NR	MVA	broad spectrum ab use, age	5
Derosa/ 2018	retrospective	36 (RCC, NSCLC)	RCC: anti-PD(L)1 (88), anti-PD(L)1 + anti-CTLA4 (8), anti-PD(L)1 + BEVA (4) NSCLC: anti-PD(L)1 (86), anti-PD(L)1 + anti-CTLA4 (14)	64	21.5 /1 mos prior start	NR	MVA	RCC: ab 30-0 days/no ab IMDC risk, tumor burden NSCLC: ab 30-0 days/no ab, PS, clinical trial Y/N, prior regimens>/< 3	5
Elkrief/ 2019	retrospective	59 (melanoma)*	NIVO/PEMBRO/IPI (100)	64.5	13.5° /1 month prior	NR	MVA	age, PS, gender, ab use, LDH, BRAF, line of tx, type of ICI	5
Galli/ 2019	retrospective	157 (NSCLC)	anti-PD(L)1 (95.6), anti-CTLA4 o combo (4.4)	66.7	17.2 /during ICI period	28.6	MVA	high ab/immunotherapy exposure ratio in whole ICI period	8

Guo/ 2019	retrospective	49 (esophageal)	anti-PD(L1) alone (61), combo (39)	56.7	43/2 mos prior or 1 month after	16.4	MVA	PS, treatment, n° of metastatic sites, NLR, antibiotic use	7
Hakozaki/ 2019	retrospective	90 (NSCLC)	NIVO (100)	68	14.4/1 month prior start	NR	MVA	driver mutations	6
Huemer / 2018	retrospective	30 (NSCLC)	NIVO (83), PEMBRO (17)	NR	37/1 month before/after start	NR	MVA	sex, antibiotic use, ICI, EGFR/ALK mutations, line of tx, PDL1 status, immune-related adverse events	5
Huemer / 2019	retrospective	142 (NSCLC)	NIVO, PEMBRO or ATEZO (100)	66	44/1 months prior or after start	13.3	UVA	NR	7
Kaderbhai/ 2017	retrospective	74 (NSCLC)	NIVO (100)	67.5	20.3/3 months prior or concurrent	NR	UVA (PFS)	NR	5
Krief/ 2019	prospective cohort	72 (NSCLC)	NIVO (100)	68.8	42/2 months before or 1 month after start	16.6	MVA	Ab use; KRAS mutations, gemmatimonadaceae on blood microbiome at baseline	7

Pinato/ 2019	prospective cohort	196 (various)	anti-PD(L)1 (96)	68	29/1 month prior or concurrent	NR	MVA	response to ICI, ab 0-30 days before ICI	6
Sen/ 2018	retrospective	172 (various)	anti-CTLA4 (61), anti-PD1 (39)	60	33/during and up to 2 mos before	NR	UVA	NR	5
Tinsley/ 2019	retrospective	291 (melanoma, RCC, NSCLC)	NR	66	32/2w before up to 6w after start	NR	MVA	ab use, comorbilities, metastatic sites > 3, PS > 0	6
Zhao/ 2019	retrospective	109 (NSCLC)	anti-PD1 (52.3), anti-PD1 + CT (30.3), anti-PD1 + antiangiogenic (17.4)	62	18.3/1 mos prior or after start	NR	MVA	ab use, PS	6

*only immunotherapy without chemotherapy; °, all patients; ab: antibiotic; mos: months; RCC, renal cell carcinoma; NSCLC, non-small-cell lung cancer; PD1, programmed death 1; PDL1, programmed death-ligand 1; ICI, immune checkpoint inhibitors; CT, chemotherapy; CTLA4, Cytotoxic T-lymphocyte antigen 4; BEVA, bevacizumab; NIVO, nivolumab; PEMBRO, pembrolizumab; IPI, ipilimumab; ATEZO, atezolizumab; MVA, multivariate analysis; UVA, univariate analysis; PFS, progression-free survival; IMDC, international metastatic RCC database consortium; PS ECOG, performance status; tx, therapy; NLR, neutrophile to lymphocyte ratio; NR, not reported

The median age was 64 years. Antibiotics were assumed by 29% of patients.

Progression-free survival was reduced in those who take antibiotics (HR = 1.53, 95% CI 1.22–1.93; p <. 01; Fig. 2).

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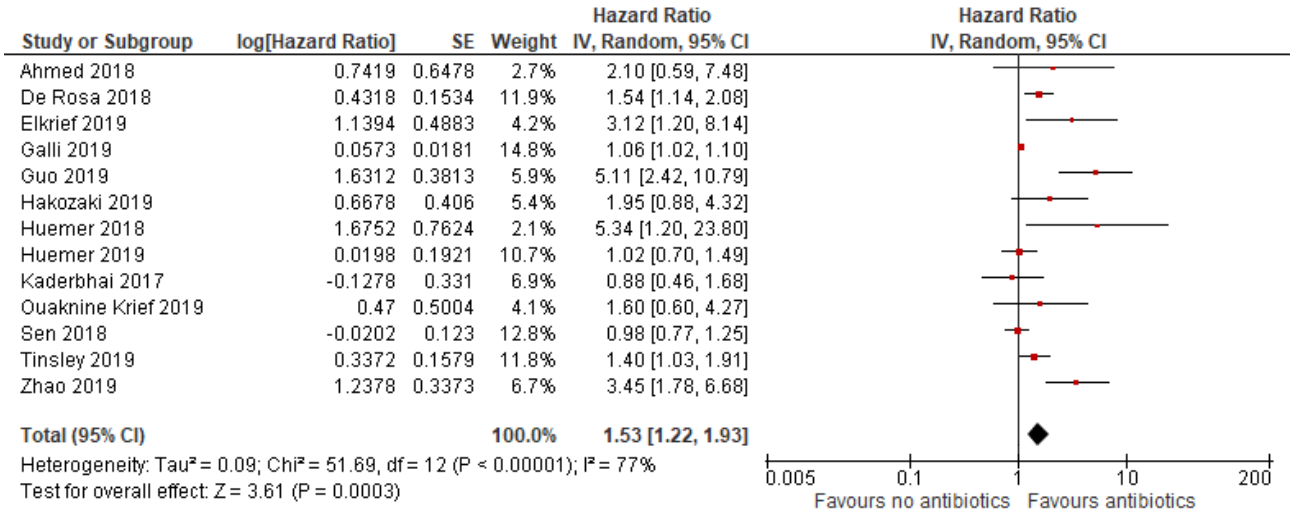

Fig.2 Forrest plot for progression-free survival in patients assuming antibiotics pre/during immunotherapy

The analysis included nine studies, and due to high heterogeneity (I^2 = 77%), a random effect model was adopted.

In the primary analysis, use of antibiotics was associated with an increased risk of death (HR = 2.07, 95% CI 1.51–2.84; p < .01; Fig. 3).

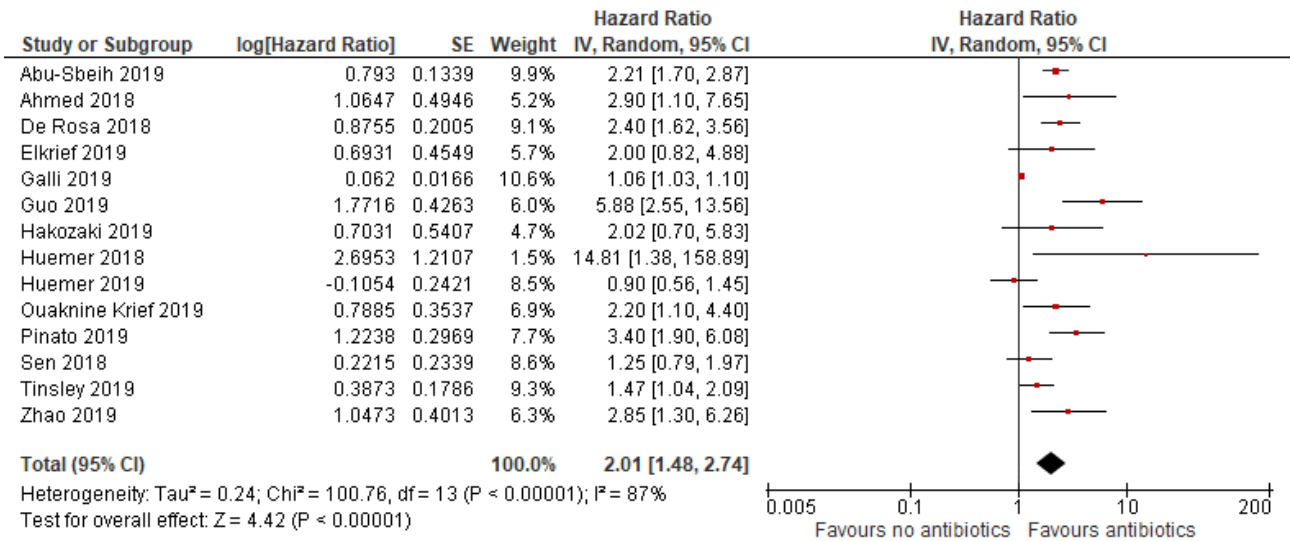

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Fig.3 Forrest plot for overall survival in patients assuming antibiotics pre/during immunotherapy

The analysis included 14 studies, and due to high heterogeneity (I^2 = 87%), a random effect model was adopted.

Risk of bias through Begg's funnel plot was not significant for the OS analysis (Fig. 4). Conversely, Egger's test showed evidence of bias (p < .01).

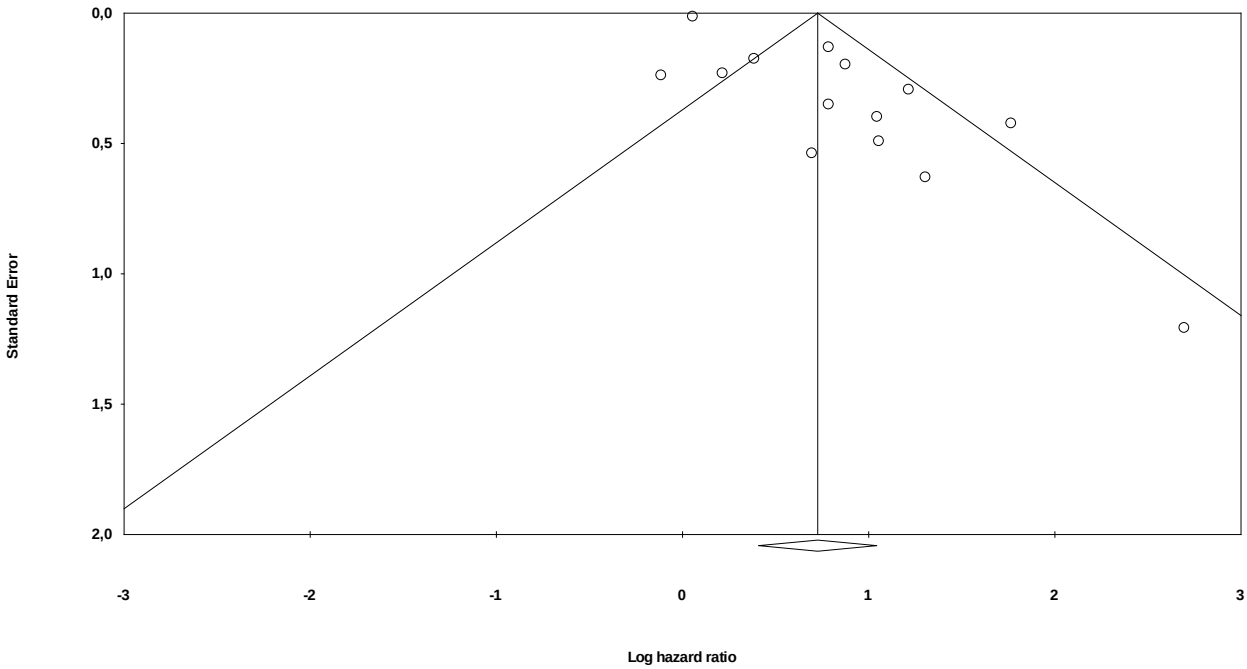

Fig.4 Funnel plot for publication bias

Discussion

In the past years, it has been reported that changes in the gut microbiota of individuals with cancer who received antibiotics, may reduce outcome when treated with ICIs. We performed a systematic review and meta-analysis of observational evidence reporting the

outcome of patients treated with ICIs for advanced cancers according to AB exposure, and we found that use of ABs reduces OS and PFS.

In a seminal paper published in *Science* in 2018, Routy et al. [19] showed that AB consumption is associated with reduced response to anti-PD-(L)1 blockade. Samples attained from patients with lung and kidney cancer showed that non-responding patients had low levels of the bacterium Akkermansia muciniphila. Oral bacterium supplementation in antibiotic-treated mice instead, restored the response to immunotherapy. Gopalakrishnan et al. and Matson et al. [20,21] evaluated fecal samples from melanoma patients receiving anti-PD-(L)1 blockade and found that those who failed immunotherapy had an imbalance in commensal bacteria composition, which was linked with impaired activity of immune cells. Other authors found that fecal Bifidobacterium was associated with the antitumor effects of ICIs[3]. Oral administration of Bifidobacterium alone also improved tumor control to the same magnitude as anti-PD-(L)1 therapy, and combination treatment nearly abolished tumor outgrowth. Increased dendritic cell function with a consensual enhanced cluster of differentiation 8 (CD8)+ T cell priming/accumulation in the tumor microenvironment mediated the observed effect. Similarly, even the antitumor effect of Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) blockade seems to depend on distinct Bacteroides species, as found in mouse models by Vétizou et al. [22] Lack of response was overcome by B. fragilis, by immunization with B. fragilis polysaccharides, or by adoptive transfer of B. fragilis-specific T cells; conversely, ABs-treated mice did not respond to CTLA-4 blockade.

In clinical settings, several authors reported a possible detrimental association between timing of/exposure to ABs and survival with ICIs. Particularly, Galli et al.[5] found that an elevated ratio between days of antibiotics and days of immunotherapy is more harmful than the use of ABs itself. In a similar study, Tinsley et al. [23] observed that a single course of ABs is associated with a better OS than that observed with multiple/prolonged

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courses of ABs. Although these observations are consistent with a possible detrimental effect of ABs, it cannot be excluded that AB use may identify a group of patients with poor prognosis due to concomitant severe infections or comorbidities, rather than ABs themselves affecting the outcome of patients treated with ICIs.

Our meta-analysis has some limitations. First, this is a meta-analysis of retrospective series with heterogeneous populations and obvious diversity in tumor stages/types and patient characteristics. Also, AB type and duration, as well as the indication of AB use, were only partially reported. Finally, patients treated with anticancer therapy other than ICIs were not included. However, this pooled analysis of real-life experiences seems to confirm the hypothesis that AB-associated dysbiosis might be detrimental in patients treated with ICIs. A recent published paper by Huang and colleagues had the same goal of the present meta-analysis, but has a less updated literature search, and included about half of papers as congress abstract forms, come to a similar conclusions [24].

Material and Methods

Search strategy and inclusion criteria

The present review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations[25]. Electronic searches were performed using Embase, PubMed, SCOPUS, and the Cochrane Library. The studies were searched up to September 2019, using the terms *antibiotics AND (PD-1 or PD-L1 or "immune checkpoint inhibitors" or CTLA-4) AND survival*. All the identified articles were then systematically and independently assessed for inclusion and exclusion criteria by two investigators (Alessandro Inno and Fausto Petrelli).

The inclusion criteria used to screen articles were: 1) adult patients with solid tumors and treated with ICIs, 2) evaluation of survival (OS and/or PFS) according to intake of ABs (yes versus no), 3) a hazard ratio (HR) statistic accompanied by 95% confidence interval (CI)

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from univariate or adjusted Cox multivariate analysis, and 4) cohorts of adult patients. The exclusion criteria were: 1) phase I studies and 2) patients treated with ICIs and other (non-immunotherapy) drugs. When institutions published duplicate studies involving overlapping patients or increased lengths of follow-up, the most updated reports were included for quantitative assessment. Only studies involving human subjects and published in English were considered.

Data extraction

Two investigators (Alessandro Inno and Fausto Petrelli) independently extracted data of interest (author and year of publication, number of patients, type of study, treatment received, timing of AB therapy, median follow-up, and type of analysis). The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS)[26].

Statistical analysis

The outcome of interest was the prognostic effect of AB intake and reported as HR and its respective 95% CI. Overall survival was the primary endpoint, and PFS was the secondary endpoint. The HRs of each selected study were pooled together to provide the overall estimate. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity. A random-effect model was tested, and in the case of $I^2 < 50\%$, a fixed-effect model was also considered [27]. Publication bias was assessed through the generation of funnel plots for OS and analyzed for asymmetry using Begg's and Egger's test. All *p* values were two-sided with significance set at $p < 0.05$. Statistical analyses were conducted with the Review Manager computer program, Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Conclusions

An intact gut microbiota is needed to elicit the immune system and provide ICI benefits to cancer patients. Strategies to modulate the microbiome with the aim to improve ICI efficacy should be actively investigated.

Author contributions

Conceptualization, F.P., A.Z., ; Methodology, F.P., A.Z.; Software, F.P.; Validation. S.G.; Formal Analysis, F.P.; Investigation, F.P.; Resources, F.P., A.Z, ; Data Curation, F.P., M.G.; Writing – Original Draft Preparation, F.P. .A.I.; Writing – Review & Editing, A.I., D.S., A.G., L.D., G.P.; Visualization, M.G., ; Supervision, A.Z., S.G. ; Project Administration, F.P., A.I.; Funding Acquisition, A.Z.".

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