

COMMENTARY

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Antibiotic therapy and outcome from immune-checkpoint inhibitors

David J. Pinato^{1,2*} , Daria Gramenitskaya¹, Daniel M. Altmann³, Rosemary J. Boyton^{4,5}, Benjamin H. Mullish¹, Julian R. Marchesi¹ and Mark Bower⁶

Abstract

Sensitivity to immune checkpoint inhibitor (ICPI) therapy is governed by a complex interplay of tumor and host-related determinants. Epidemiological studies have highlighted that exposure to antibiotic therapy influences the probability of response to ICPI and predict for shorter patient survival across malignancies. Whilst a number of studies have reproducibly documented the detrimental effect of broad-spectrum antibiotics, the immune-biologic mechanisms underlying the association with outcome are poorly understood. Perturbation of the gut microbiota, an increasingly well-characterized factor capable of influencing ICPI-mediated immune reconstitution, has been indicated as a putative mechanism to explain the adverse effects attributed to antibiotic exposure in the context of ICPI therapy. Prospective studies are required to validate antibiotic-mediated gut perturbations as a mechanism of ICPI refractoriness and guide the development of strategies to overcome this barrier to an effective delivery of anti-cancer immunotherapy.

Keywords: Antibiotics, Immune checkpoint inhibitors, Survival

Introduction

Antibiotic therapy has produced unquestionable advances in the management of patients with cancer, a population with intrinsically higher risk of bacterial infection as a result of malignancy or treatment-related immune suppression.

While antimicrobial therapy has markedly reduced morbidity and mortality stemming from infection, the effects of broad-spectrum antibiotics on commensal, non-pathogenic bacterial species have remained for a long time an under-appreciated effect of this therapeutic class of drugs.

The gut microbiota, source of over 100 trillion bacteria, exists in a condition of mutually beneficial relationship with the host. Commensal bacteria are provided with a niche to colonise the host in return for their participation in the digestion of nutrients and xenobiotics, protection from pathogens and shaping of the host's immune system subsets. Derangement of this delicate relationship has

been increasingly well-characterised in the context of tumour-specific immune tolerogenesis [1].

Multiple levels of evidence now support the link between sensitivity to immunotherapy, taxonomic diversity and enrichment in specific gut bacterial taxa, suggesting that some species or species consortia provide intrinsic immunomodulating properties. The landmark study by Gopalakrishnan [2] demonstrated how broader stool bacterial diversity and higher representation of *Ruminococcaceae* communities including *Faecalibacterium* positively influences patients' survival following ICPI by promoting a strongly immune-reactive microenvironment and lower systemic release of pro-inflammatory cytokines [3]. Many other commensal bacteria have subsequently been recognised to play a similar role including *Bifidobacteria* spp., a saccharolytic Gram-positive genus highly represented within the gut that facilitates dendritic cell maturation and increased accumulation of antigen-specific T-cells within the tumour microenvironment [4]. Similarly, the presence of the anaerobic commensal *Akkermansia Muciniphila* is more common in responders to ICPI, who display higher peripheral CD4 and CD8 memory T-cell responses to this bacterium [5].

Antibiotic (ATB) therapy imposes profound and protracted changes to the taxonomic diversity of the host

* Correspondence: david.pinato@imperial.ac.uk

¹Department of Surgery and Cancer, Imperial College London, Faculty of Medicine, Hammersmith Hospital, Du Cane Road, London W120NN, UK

²Imperial College London Hammersmith Campus, Du Cane Road, London W12 0HS, UK

Full list of author information is available at the end of the article



microbial ecosystem, affecting the composition of up to 30% of the bacterial species in the gut microbiome [6], consequently leading to loss of microbial functions that are protective for the host. Such changes in gut microbial communities are rapid and pervasive, occurring within days from the first antibiotic dose [7] and persisting for up to several months after completion of therapy [8].

Mounting evidence from epidemiological studies has underscored the detrimental role of antibiotics in ICPI outcome, with exposure to antibiotics having been linked to shortened progression-free, overall survival and reduced response rates in patients receiving ICPI as part of clinical trials and in routine practice (Table 1). In a previous study, we demonstrated time-dependence of antibiotics exposure as a strong, tumour-agnostic determinant of outcome in ICPI recipients, confirming prior, but not concurrent antibiotic therapy as doubling the risk of primary progression to immunotherapy and leading to a > 20-months shortening in patients' survival independent of established prognostic factors and corticosteroid use [10]. Whilst mirroring pre-clinical evidence, where antibiotic pre-conditioning ahead of tumour implantation leads to impaired responses to ICPI in mice [26, 27], the expanding body of clinical studies has so far painted an incomplete picture as to the mechanistic foundations underlying the relationship between ATB and immunotherapy, a point of greater consequence given the potential practice-influencing implications of ATB prescribing in the clinic.

Most of the studies highlighting the importance of a healthy gut microbial environment as a pre-requisite for ICPI response were unfortunately characterised by insufficient data on preceding or concomitant antibiotic exposure, making it impossible to disentangle the role of antibiotic-induced perturbation of the gut ecosystem in influencing clinically meaningful outcomes in these patients [3].

Mechanistically, the breadth and depth of downstream effects produced by antibiotics within the cancer-immune synapse are an important challenge in studying this prognostically adverse relationship. On one hand, the direct bacteriostatic/bactericidal effect of antibiotics can cause selective pressure within the host microbial ecosystem and instigate an alternative microbiota state characterised, amongst other traits, by downregulation of major histocompatibility complex (MHC) class I/II genes and impaired effector T-cell responses, immunologic traits implicated in reduced responsiveness to ICPI [28].

ATB-induced depletion of gut bacteria can also shift the repertoire of microbial-associated molecular patterns (MAMPS). These molecules signal through mucosal innate immune cells primarily via toll-like receptors (TLRs) and NOD1 [29] to influence neutrophil priming, reduce local cytokine release and prime adaptive

immunity by influencing the expression of MHC genes within the intestinal mucosa and reduce immunoglobulin secretion [30]. Antibiotic treatment impairs TH₁/TH₁₇ responses in tumour-bearing mice through direct pre-conditioning of the gut microbiota, reducing the efficacy of cyclophosphamide-mediated immune-rejection of the tumour [31]. In addition, antibiotics can also reduce the capacity of adoptively transferred CD8⁺ T-cells to mediate a tumour-specific response through altered LPS/TLR4 signaling in lymphodepleted mice [32].

By disrupting the gut ecosystem, antibiotics instigate downstream metabolic alterations within the microenvironment with complex repercussions to the tumour-host-microbe interface. Amongst them, changes in the availability of short-chain fatty acids produced by *Akkermansia*, *Faecalibacteria* and *Enterococcus* from the catabolism of non-digestible carbohydrates and the conversion of primary bile acids to secondary bile acids (including deoxycholate) mediated by *Clostridiales* can significantly alter gut homeostasis and lead to profound and clinically meaningful immunomodulatory consequences [33]. The immune-metabolic repercussions secondary to gut dysbiosis, potentially reversible by oral *Akkermansia* supplementation [34], might explain the influence of body mass index in determining response to ICPI [35, 36].

With improved characterization of immune-microbiologic underpinning of the relationship between antibiotics and ICPI outcome, a key question now is whether disruption of a well-equilibrated gut bacterial ecosystem is truly causal in this relationship, and thus whether reversal of antibiotic-mediated gut dysbiosis might prove beneficial in restoring full sensitivity to ICPI. Whether a favourable gut microbiota is a reflection of an otherwise healthy host rather than the *primum movens* of clinically meaningful anti-cancer immune responses is still the subject of intense debate [13]. To this end, appreciating how antibiotics might dynamically affect such a strong immune-microbiologic correlate of response to checkpoint inhibition is of key importance to pave the way for strategies that could restore or protect the integrity of this important phenotypic correlate of response. To address the multiplicity of mechanisms that are likely to underscore this complex and bi-directional relationship, the coordinated study of a number of fundamental pathophysiologic processes including bacterial translocation, immune-modulation, an altered metabolome, enzymatic degradation and reduced diversity of the gut microbiome has been proposed as an overarching framework [37].

Gaining sufficient insight as to the mode of action by which bacteria might work as biotherapeutic agents is not just important for patient prognostication, but is in fact key to a successful, rational development of microbiome-modulating therapies which improve patient's outcome with ICPI. With antibiotic use now having been validated as an important and dynamic factor influencing outcome from

Table 1 The relationship between antibiotic exposure and outcomes from immune checkpoint inhibitor therapy

Study	Tumour Sites	ICPI (n, %)	ATB exposure	ATB Duration	ATB Type	Administration route	Response	Survival	Notes
Derosa L et al. [9]	NSCLC (239)	PD-L1 (205, 86%) PD-L1/CTLA-4 (34, 14%)	pATB (within 30 days) (48, 20%) No ATB (191, 80%)	≤ 7 days (35, 73%) > 7 days (13, 27%)	Beta-lactam (15, 32%) Quinolones (14, 29%) Macrolides (4, 8%) Sulfonamides (12, 25%) Tetracyclines (1, 2%) Nitromidazole (1, 2%) Others (1, 2%)	Oral (42, 87%) IM/ IV (5, 11%) Unreported (1, 2%)	PD in 52% exposed vs in 43% unexposed, <i>P</i> = 0.26	ATB vs no ATB median OS: 7.9 months vs 24.6 months, HR 4.4, 95% CI 2.6–7.7, <i>P</i> < 0.001 median PFS: 1.9 months vs 3.8 months, HR 1.5, 95% CI 1.0–2.2, <i>P</i> = 0.03	Significant impact supported by multivariate analysis
			RCC (121)	pATB (within 30 days) (16, 13%) No ATB (105, 87%) Bevacizumab (5, 4%)	≤ 7 days (8, 50%) > 7 days (8, 50%)	Beta-lactam (13, 82%) Quinolones (1, 6%) Tetracyclines (1, 6%) Aminoglycosides (1, 6%)	Oral (15, 94%) IV/ IM (1, 6%)	PD in 75% exposed vs in 22% unexposed, <i>P</i> < 0.01	ATB vs no ATB median OS: 17.3 months vs 30.6 months, HR 3.5, 95% CI 1.1–10.8, <i>P</i> = 0.03 median PFS: 1.9 months vs 7.4 months, HR 3.1, 95% CI 1.4–6.9, <i>P</i> < 0.01
Pinato DJ et al. [10]	NSCLC (119, 60%) Melanoma (38, 20%) Renal (27, 14%) Head & neck (10, 5%) Total <i>n</i> = 196	PD-1/PD-L1 (189, 96%)	pATB (29, 15%) (within 30 days) cATB (during ICPI therapy until cessation) (68, 35%) no ATB (99, 50%)	pATB (≤ 7 days (26, 90%) > 7 days (3, 10%) cATB (≤ 7 days (39, 88%)	Beta-lactam (22, 75%) cATB (3, 10%) Beta-lactam in 49, 72%	-	pATB: PD in 80% exposed vs 44% unexposed, <i>P</i> < 0.001 cATB: PD in 50% exposed vs 49% unexposed, <i>p</i> = 0.87	pATB (<i>p</i> < 0.001) but not cATB (<i>p</i> = 0.76) predicted worse OS (26 vs 2 months, HR 7.4, 95% CI 4.2–12.9) Multivariate analysis confirmed pATB as a predictor of OS (HR 3.4, 95%CI 1.9–6.1 <i>p</i> < 0.001)	ICI-refractory in 81% pATB vs 44% no pATB, <i>p</i> < 0.001
			NSCLC (90)	pATB (13, 14%) (30 days before ICPI initiation) no pATB (77, 86%)	≤ 7 days (1, 8%) > 7 days (12, 92%)	Beta-lactam (8, 61%) Sulfonamides (4, 31%) Quinolones (1, 8%)	Oral (10, 77%) IV (3, 23%)	-	pATB vs no ATB median PFS: 1.2 [95% CI, 0.5–5.8] vs 4.4 months [95% CI, 2.5–7.4], <i>P</i> = 0.04 median OS: 8.8 months vs not reached, <i>P</i> = 0.037
Galli G et al. [12]	NSCLC (157)	PD-1 (98, 62.4%) PD-L1 (52, 33%) CTLA4 (1, 0.6%) PD-L1/CTLA4	ATB: in EIOP (27, 17%) in WIOIP (46, 29%) No ATB (111, 71%)	Median duration 7.0 days (50–33.0)	Quinolone (33, 72%) Macrolide (8, 17%) Beta-lactam (14, 30%) Rifaximin (4, 8.7%)	Oral (44, 98%) IM (3, 6.5%) IV (2, 4.4%)	Exposed in EIOP RR: 11.1% vs 24.6%, <i>p</i> = 0.20; DCR: 51.9% vs 56.2%, <i>p</i> = 0.8319.	Exposed vs unexposed in EIOP median PFS: 2.2 [95% CI, 1.8–3.2] vs 3.3 months [95% CI, 2.6–4.8] <i>P</i> = 0.1772 median OS: 11.9 [95% CI, 9.2–15.6] vs 5.9	

Table 1 The relationship between antibiotic exposure and outcomes from immune checkpoint inhibitor therapy (Continued)

Study	Tumour Sites	ICPI (n, %)	ATB exposure	ATB Duration	ATB Type	Administration route	Response	Survival	Notes
Ahmed J et al. [13]	NSCLC (34, 57%) Renal (4, 7%) HCC (5, 8%) Urothelial (5, 8%) Other (12, 20%) Total n = 60	(6, 4%) ICPI with chemotherapy (8, 13%) PD-1 (49, 82%) PD-L1 (3, 5%)	High AIER 23 (15%) Low AIER (134, 85%)	8–14 days	Beta-lactam (14, 82%) Quinolone (5, 29%) Vancomycin (7, 41%) Daptomycin (1, 6%) Linezolid (2, 12%) Meropenem (3, 18%) Tetracyclines (2, 12%) Bactrim (1, 6%) Azithromycin (1, 6%) Nitrofurantoin (1, 6%)	-	AIER (high vs low) RR: 8.7%, vs 26.6%, <i>p</i> = 0.11 DCR: 47.8% vs 56.0%, <i>p</i> = 0.50, RR: 29.4% in exposed vs 62.8% in unexposed, <i>p</i> = 0.024	Decreased PFS with ATB HR 1.6; 95% CI: 0.84–3.03, <i>p</i> = 0.048 Median OS: 24 in exposed vs 89 months in unexposed <i>p</i> = 0.003	months [95% CI, 4.5–22.5] <i>p</i> = 0.2492 Significant impact supported by multivariate analysis Narrow-spectrum ATB alone did not affect the RR, but broad-spectrum ATB decreased RR (<i>p</i> = 0.02) and PFS (<i>p</i> = 0.012). Multivariate analysis found that only ATB decreased RR (<i>p</i> = 0.0038) and PFS (<i>p</i> = 0.01)
Tinsley N et al. [14]	Melanoma (206, 66%) NSCLC (56, 18%) Renal (46, 15%) Total n = 303	-	pATB or cATB (2 weeks before or 6 weeks after ICPI initiation) (94,31%)	-	The commonest ATBs: beta-lactam and macrolides	-	ATB vs no ATB PFS 97 (95% CI 84–122) vs 178 days (95% CI 155–304) <i>p</i> = 0.049 OS 317 days (95% CI 221–584) vs 651 days (95% CI 477–998) <i>p</i> = 0.001.	Cumulative ATB (> 10 days, multiple concurrent/successive courses) further shortened PFS to 87 days (95% CI 83–122) <i>p</i> = 0.0093 and OS to 193 days (95% CI 96–355) <i>p</i> = 0.00021 pATB exposed had shorter PFS and OS than cATB exposed (HR 1.37, <i>p</i> = 0.29 and HR 1.72, <i>p</i> = 0.08)	
Khan U et al. [15]	Lung (111, 46%) Bladder (36, 15%) Renal (35, 14%) GI (16, 7%) Other (44, 18%) Total n = 242	PD-1 (189, 78%) PD-L1 (52, 21%)	75, 46 and 32% received ATBs within 6 months, 60 days and 30 days of starting ICPIs	-	-	-	cATB use in the first 30- or 60-days of ICPI therapy associated with inferior ORR (OR 0.40, <i>p</i> = 0.01 and OR 0.42, <i>p</i> = 0.005, respectively)	pATB or cATB use in the first 6 months of ICPI use had no impact	
Routy B et al. [5]	NSCLC (140, 56%), RCC (67, 27%)	PD-1/PD-L1 (249, 100%)	pATB or cATB (2 months before or 1 month after	-	β-lactam+/- inhibitors, fluoroquinolonesor macrolides	Mostly oral	-	ATB vs no ATB For all groups combined median PFS: 3.5 vs 4.1 months	Univariate and multivariate Cox regression analyses confirmed the negative impact of ATB, independent from other factors

Table 1 The relationship between antibiotic exposure and outcomes from immune checkpoint inhibitor therapy (Continued)

Study	Tumour Sites	ICPI (n, %)	ATB exposure	ATB Duration	ATB Type	Administration route	Response	Survival	Notes
Mielgo-Rubio X et al. [16]	urothelial carcinoma (42, 17%) Total n = 249	PD-1 (168, 100%)	ICPI initiation) (69, 28%) no ATB (180, 72%)	-	-	Oral (70%) IV (30%)	-	<i>p</i> = 0.017 median OS: 11.5 vs 20.6 months <i>p</i> < 0.001 For individual cancer groups, PFS and/or OS were also shorter in ATB group	IV ATB had a more negative impact than oral ATB OS: 2.9 (95%CI, 1.6–4.1) vs 14.2 months (95%CI, 7.9–20.6) <i>p</i> = 0.0001 PFS: 5 (95%CI 3.1–6.9) vs 7.3 months (95%CI 2–12) <i>p</i> = 0.028
Quaknine J et al. [17]	NSCLC (72)	PD-1 (72, 100%)	pATB or cATB (2 months before or 1 month after ICPI initiation) (47.9%) No ATB (52.1%)	Median duration (IQR 7–14)	The commonest ATBs: β-lactam and vancomycin	Mostly oral (65%)	ATB vs no pATB ORR 37% vs 24% <i>p</i> = 0.276 Clinical benefit rate 27% vs 29% <i>p</i> = 0.859	ATB vs no ATB median OS: 5.1 (IQR 3.4–not reached) vs 13.4 months (IQR 10.6–not reached) <i>p</i> = 0.03 median PFS: 2.8 (IQR 1.4–5.1) vs 3.3 months (IQR 1.8–7.3) <i>p</i> = 0.249	-
Kaderbhai C et al. [18]	NSCLC (74)	PD-1 (74, 100%)	pATB (within 3 months) (15, 20%) No ATB (59, 80%)	-	-	-	No difference in ORR <i>p</i> = 0.75	No difference in PFS and <i>p</i> = 0.72,	-
Zhao S et al. [19]	NSCLC (109)	PD-1 (57, 52%) PD-1/ chemotherapy (33, 30%) PD-1/apatinib or bevacizumab (19, 18%)	pATB or cATB (1 month before or after ICPI initiation) (20, 18%) No ATB (89, 82%)	-	The commonest ATBs: β-lactam inhibitors and fluoroquinolones	-	Higher PD rates in ATB-treated group (<i>p</i> = 0.092)	ATB decreased PFS and OS , <i>p</i> = 0.0021	In multivariable analysis, ATB was associated with shorter PFS (HR = 0.29, 95%CI 0.15–0.56, <i>p</i> < 0.0001) and OS (HR = 0.35, 95%CI 0.16–0.77, <i>p</i> = 0.009)
Thompson et al. [20]	NSCLC (74)	PD-1 (74, 100%)	pATB (within 6 weeks) (18, 24%) No ATB (56, 76%)	-	Mostly fluoroquinolones (50%)	-	ORR in ATB vs no ATB groups 25% vs 23% (adjusted OR 1.2, <i>p</i> = 0.20).	ATB vs no ATB PFS 2.0 vs 3.8 months <i>p</i> < 0.001 OS 4.0 vs 12.6 months, <i>p</i> = 0.005	The impact of ATB on PFS and OS was independent of other factors (HR 2.5, <i>p</i> = 0.02), (HR 3.5, <i>p</i> = 0.004), respectively

Table 1 The relationship between antibiotic exposure and outcomes from immune checkpoint inhibitor therapy (Continued)

Study	Tumour Sites	ICPI (n, %)	ATB exposure	ATB Duration	ATB Type	Administration route	Response	Survival	Notes
Derosa L et al. [21]	RCC (80)	PD-1/PD-L1 (67, 84%), PD-1/CTLA-4 (10, 12%), PD-L1/bevacizumab (3, 4%)	pATB (within 1 month) (16, 20%) No ATB (64, 80%)	-	Mostly β -lactam and fluoroquinolones	-	Lower ORR in ATB group vs no ATB $p < 0.002$	ATB vs no ATB PFS 2.3 vs. 8.1 months, $p < 0.001$	Confirmed by multivariate analysis
Do TP et al. [22]	Lung (109)	PD-1 (109, 100%)	pATB or cATB (1 month before ICPI or concurrently) (87, 80%) No ATB (22, 20%)	-	β -lactam (12, 13.8%) quinolones (11, 12.6%) other (7, 8.1%) multiple antibiotics (57, 65.5%)	-	-	ATB vs no ATB OS 5.4 vs 17.2 months (HR 0.29, 95% CI 0.15–0.58 $p = 0.0004$)	
Elkrief A et al. [23]	Melanoma (74)	PD-1 (54, 73%), CTLA-4 (5, 6.8%), CTLA-4/carboplatin/paclitaxel (15, 20%)	pATB (within 1 month) (10, 13.5%) No ATB (64, 86.5%)	> 7 days (7, 70%) < 7 days (3, 30%)	Mostly β -lactams \pm inhibitors	Oral (40%) IV (60%)	ORR ATB vs no ATB 0% vs 34%	ATB vs no ATB median PFS 2.4 vs 7.3 months (HR 0.28, 95% CI 0.10–0.76 $p = 0.01$) median OS 10.7 vs 18.3 months (HR: 0.52, 95% CI 0.21–1.32 $p = 0.117$)	The multivariate analysis supported the impact of ATB on PFS (HR 0.32 (0.13–0.83) 95% CI, $p = 0.02$).
Huemer F et al. [24]	NSCLC (30)	PD-1 (30, 100%)	pATB or cATB (1 month before or 1 month after ICPI initiation) (11, 37%) No ATB (19, 63%)	-	β -lactam (7, 64%), fluoroquinolones (4, 36%) and carbapenems (2, 18%)	-	-	ATB vs no ATB median PFS 3.1 vs 2.9 months, (HR = 0.46 95%CI: 0.12–0.90 $p = 0.031$), median OS 15.1 vs 7.5 months (HR = 0.31 95%CI: 0.02–0.78 $p = 0.026$).	The multivariate analysis supported the impact of ATB on PFS ($p = 0.028$) and OS ($p = 0.026$).
Lalani A et al. [25]	RCC (146)	PD-1/PD-L1 (146, 100%)	pATB or cATB (2 months before or 1 month after ICPI initiation) (31, 21%) No ATB (115, 79%)	-	-	-	ATB vs no ATB ORR 12.9 vs 34.8% $p = 0.026$	ATB vs no ATB 2.6 (1.7–5.3) vs 8.1 (5.6–10.9) months $p = 0.008$	-

Abbreviations: *EIOP* (Early immunotherapy Period); antibiotics given between 1 month before and 3 months after starting immunotherapy; *WOP* (Whole immunotherapy Period); antibiotics given throughout immunotherapy, cumulative exposure to antibiotics; *AIER* defined as "days of antibiotic therapy/days of immunotherapy"; *AIER* stratified over the median (4.2%) into high and low *AIER* groups, *RR* Response rate, *DCR* Disease control rate, *GI* Gastrointestinal, *ORR* Overall response rate, *IV* Intravenous, *IM* Intramuscular

immunotherapy, concerted efforts should be aimed at characterizing the candidate taxonomic features in the gut microbiota that are associated with worse outcome from ICPI in the context of preceding and concomitant antibiotic exposure and evaluate them in conjunction with the concomitant prescription of proton pump inhibitors, corticosteroids and vaccines, all of which have been postulated to influence ICPI response [38].

Recognising these changes is expected to facilitate the clinical development of diverse biotherapeutic approaches to induce microbiome reprogramming including dietary interventions with pre-biotics, therapeutic administration of single or multiple types of bacterial species or their metabolites, selective antibiotic therapy or faecal microbial transplantation, all of which are currently at the focus of intense clinical research efforts [26].

Abbreviations

ATB: Antibiotic; cATB: Concurrent antibiotic treatment; CD: Cluster of Differentiation; CTLA-4: Cytotoxic T-Lymphocyte Associated Protein 4; DCR: Disease control rate; EIO: Early Immunotherapy Period; GI: Gastrointestinal; HR: Hazard Ratio; ICPI: Immune-checkpoint inhibitors; LPS: Lipopolysaccharide; MHC: Major Histocompatibility Complex; NOD1: Nucleotide-binding oligomerization domain-containing protein 1; NSCLC: Non-small Cell Lung Cancer; ORR: Overall response rate; OS: Overall Survival; pATB: Prior antibiotic treatment; PD: Progressive Disease; PD-1: Programmed Cell-Death 1; PD-L1: Programmed Cell-Death Ligand 1; PFS: Progression-free survival; RCC: Renal Cell Carcinoma; RR: Response rate; TH: T-Helper cell; TLR: Toll-like receptors; WIO: Whole immunotherapy Period

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Author details

¹Department of Surgery and Cancer, Imperial College London, Faculty of Medicine, Hammersmith Hospital, Du Cane Road, London W120NN, UK. ²Imperial College London Hammersmith Campus, Du Cane Road, London W12 0HS, UK. ³Department of Immunology and Inflammation, Faculty of Medicine, Imperial College London, London W12 0NN, UK. ⁴Lung Immunology Group, Department of Infectious Disease, Faculty of Medicine, Imperial College London, London W12 0NN, UK. ⁵Department of Respiratory Medicine, Royal Brompton & Harefield NHS Foundation Trust, London SW3 6NP, UK. ⁶National Centre for HIV Malignancy, Department of Oncology, Chelsea & Westminster Hospital, Fulham Road, London SW10 9NH, UK.

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References

- Zitvogel L, Galluzzi L, Viaud S, Vetizou M, Daillere R, Merad M, et al. Cancer and the gut microbiota: an unexpected link. *Sci Transl Med*. 2015;7(271):271ps1.
- Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinetz TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science*. 2018;359(6371):97–103.
- Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol*. 2017;28(6):1368–79.
- Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015;350(6264):1084–9.
- Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillere R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science*. 2018;359(6371):91–7.
- Francino MP. Antibiotics and the human gut microbiome: Dysbioses and accumulation of resistances. *Front Microbiol*. 2015;6:1543.
- Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A*. 2011;108(Suppl 1):4554–61.
- Yoon MY, Yoon SS. Disruption of the gut ecosystem by antibiotics. *Yonsei Med J*. 2018;59(1):4–12.
- Derosa L, Hellmann M, Spaziano M, Halpenny D, Fidelle M, Rizvi H 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*. 2018;29(6):1437–1444.
- Pinato DJ, Howlett S, Ottaviani D, Urus H, Patel A, Mineo T, et al. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. *JAMA Oncol*. 2019. <https://doi.org/10.1001/jamaoncol.2019.2785>.
- Hakozaki T, Okuma Y, Omori M, Hosomi Y. Impact of prior antibiotic use on the efficacy of nivolumab for non-small cell lung cancer. *Oncol Lett*. 2019; 17(3):2946–2952. <https://doi.org/10.3892/ol.2019.9899>. Epub 2019 Jan 8.
- Galli G, Triulzi T, Proto C, Signorelli D, Imbimbo M, Poggi M et al. Association between antibiotic-immunotherapy exposure ratio and outcome in metastatic non small cell lung cancer. *Lung Cancer*. 2019;132: 72–78. <https://doi.org/10.1016/j.lungcan.2019.04.008>.
- Ahmed J, Kumar A, Parikh K, Anwar A, Knoll B, Puccio C et al. Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors. *Oncol Immunology*. 2018;7(11):e1507670. <https://doi.org/10.1080/2162402X.2018.1507670>
- Tinsley N, Zhou C, Villa S, Tan G, Lorigan P, Blackhall F et al. Cumulative antibiotic use and efficacy of immune checkpoint inhibitors in patients with advanced cancer. *J Clin Oncol*. 2018;36(15_suppl):3010–3010.
- Khan U, Peña C, Brouwer J, Hoffman K, Choudhury A, Zhang C et al. Impact of antibiotic use on response to treatment with immune checkpoint inhibitors. *J Clin Oncol*. 2019;37(4_suppl):143–143.
- Mielgo-Rubio X, Chara L, Sotelo-Lezama M, Lopez Castro R, Rubio-Martínez J, Velastegui A 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*. 2018;13(10):S389.
- Quaknine Krief J, Helly de Tauriers P, Dumenil C, Neveux N, Dumoulin J, Giraud V 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*. 2019;7(1):176. <https://doi.org/10.1186/s40425-019-0658-1>.
18. Kaderbhai C, Richard C, Fumet JD, Aarnink A, Foucher P, Coudert B, Favier L, Lagrange A, L E, Boidot R, Ghiringhelli F. Antibiotic Use Does Not Appear to Influence Response to Nivolumab. *Anticancer Res*. 2017;37(6):3195-3200.
 19. Zhao S, Gao G, Li W, Li X, Zhao C, Jiang T 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*. 2019;130:10-17. <https://doi.org/10.1016/j.lungcan.2019.01.017>. Epub 2019 Jan 31.
 20. Thompson J, Szabo A, Arce-Lara C, 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*. 2017;12(11):S1998.
 21. Derosa L, Routy B, Enot D, Baciarello G, Massard C, Loriot Y et al. Impact of antibiotics on outcome in patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors. *J Thorac Oncol*. 2017;35(6_suppl):462-462.
 22. Do T, Hegde A, Cherry C, Stroud C, Sharma N, Cherukuri S et al. Antibiotic use and overall survival in lung cancer patients receiving nivolumab. *J Clin Oncol*. 2018;36(15_suppl):e15109-e15109.
 23. Elkrief A, El Raichani L, Richard C, Messaoudene M, Belkaid W, Malo J et al. Antibiotics are associated with decreased progression-free survival of advanced melanoma patients treated with immune checkpoint inhibitors. *Oncol Immunology*. 2019 Feb 18;8(4):e1568812. <https://doi.org/10.1080/2162402X.2019.1568812>.
 24. Huemer F, Rinnerthaler G, Westphal T, Hackl H, Hutarew G, Gampenrieder S et al. Impact of antibiotic treatment on immune-checkpoint blockade efficacy in advanced non-squamous non-small cell lung cancer. *Oncotarget*. 2018;9(23):16512-16520. <https://doi.org/10.18632/oncotarget.24751>.
 25. Lalani A, Xie W, Lin X, Steinharter J, Martini D, Duquette A et al. Antibiotic use and outcomes with systemic therapy in metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2018;36(6_suppl):607-607.
 26. Routy B, Gopalakrishnan V, Daillere R, Zitvogel L, Wargo JA, Kroemer G. The gut microbiota influences anticancer immunosurveillance and general health. *Nat Rev Clin Oncol*. 2018;15(6):382-96.
 27. Vezizou M, Pitt JM, Daillere R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science*. 2015;350(6264):1079-84.
 28. Cianci R, Franza L, Schinzari G, Rossi E, Ianaro G, Tortora G, et al. The interplay between immunity and microbiota at intestinal immunological niche: The case of cancer. *Int J Mol Sci*. 2019;20(3). <https://doi.org/10.3390/ijms20030501>.
 29. Ubeda C, Pamer EG. Antibiotics, microbiota, and immune defense. *Trends Immunol*. 2012;33(9):459-66.
 30. Dufour V, Millon L, Faucher JF, Bard E, Robinet E, Piarroux R, et al. Effects of a short-course of amoxicillin/clavulanic acid on systemic and mucosal immunity in healthy adult humans. *Int Immunopharmacol*. 2005;5(5):917-28.
 31. Viaud S, Saccheri F, Mignot G, Yamazaki T, Daillere R, Hannani D, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science*. 2013;342(6161):971-6.
 32. Paulos CM, Wrzesinski C, Kaiser A, Hinrichs CS, Chieppa M, Cassard L, et al. Microbial translocation augments the function of adoptively transferred self/tumor-specific CD8+ T cells via TLR4 signaling. *J Clin Invest*. 2007;117(8):2197-204.
 33. Maslowski KM. Metabolism at the Centre of the host-microbe relationship. *Clin Exp Immunol*. 2019;197(2):193-204. <https://doi.org/10.1111/cei.13329>.
 34. Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, et al. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat Med*. 2019; 25(7):1096-103.
 35. Cortellini A, Bersanelli M, Buti S, Cannita K, Santini D, Perrone F, et al. A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favorable. *J Immunother Cancer*. 2019;7(1):57.
 36. Xu H, Cao D, He A, Ge W. The prognostic role of obesity is independent of sex in cancer patients treated with immune checkpoint inhibitors: a pooled analysis of 4090 cancer patients. *Int Immunopharmacol*. 2019;74:105745.
 37. Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK, Kinross JM. Gut microbiota modulation of chemotherapy efficacy and toxicity. *Nat Rev Gastroenterol Hepatol*. 2017;14(6):356-65.
 38. Rossi G, Pezzuto A, Sini C, Tuzi A, Citarella F, McCusker MG, et al. Concomitant medications during immune checkpoint blockage in cancer patients: novel insights in this emerging clinical scenario. *Crit Rev Oncol Hematol*. 2019;142:26-34.

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