# The impact of antibiotic use on clinical outcomes in cancer patients treated with immune checkpoint inhibitors: a meta-analysis

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## Background

Observational studies and experimental models suggest that use of antibiotics close to the administration of immune checkpoint inhibitors (ICI) can negatively affect tumor response and patient survival. This observation may be attributed to microbiome dysbiosis and the resultant suppression of host immune response against neoplastic cells (1-2).

## Materials/methods

- Systematic search of Pubmed and Embase databases and references of articles retrieved.
- Inclusion criteria: studies published between 1/1/17 and which evaluated the association between antibiotic use and clinical outcomes in cancer patients treated with ICI.
- Primary endpoints: overall survival (OS), progression free survival (PFS), response rate (RR) and progressive disease (PD) rate.
- Primary analysis: study-level random-effects meta-analysis with pooling of hazards ratios (HR) for OS, PFS, and odds ratios (OR) for RR and PD (PROSPERO ID: CRD42020166473), using RevMan 5.3.
- Secondary analysis: subgroup analyses: cancer type [lung, melanoma, renal cell carcinoma (RCC), mixed] and timing of antibiotic administration (within one month before ICI start versus within more than one month).

#### Results

- Among 2,462 articles, 48 studies fulfilled our criteria and were included in our analysis.
- Antibiotics were associated with worse overall survival and progression-free survival after pooling of HRs and adjusted HRs (Table 1).

## Results(cont'd)

- Antibiotics were also associated with reduced response rate and increased disease progression (Table 1).
- Subgroup analysis revealed a stronger association of antibiotics with progression-free survival in patients with RCC or melanoma, than in lung cancer patients (Figure 1).
- After subgroup analysis, only patients receiving antibiotics within more than 1 month of ICI administration were associated with increased disease progression (Figure 2).
- Heterogeneity was substantial in all outcomes.

	Antibiotics		No		Odds Ratio		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI				
6.1.1 within 1 month											
Barron 2019	4	18	40	122	7.2%	0.59 [0.18, 1.89]					
Derosa L 2018 NSCLC	25	48	82	191	10.9%	1.44 [0.77, 2.73]	+				
Derosa L 2018 RCC	12	16	23	105	6.9%	10.70 [3.15, 36.32]					
Iglesias Santamaria 2020	16	30	25	67	9.2%	1.92 [0.80, 4.59]	<del>  •</del>				
Sen S 2018	5	19	66	153	7.8%	0.47 [0.16, 1.37]					
Ueda 2019	3	5	10	26	3.9%	2.40 [0.34, 16.97]	-				
Zhao 2019	7	20	16	89	7.8%	2.46 [0.85, 7.14]					
Subtotal (95% CI)		156		753	<b>53.7</b> %	1.67 [0.83, 3.33]	•				
Total events	72		262								
Heterogeneity: Tau <sup>2</sup> = 0.55; Chi <sup>2</sup> = 18.18, df = 6 (P = 0.006); $I^2$ = 67%											
Test for overall effect: Z = 1.4	5 (P = 0.1	5)									
6.1.2 >1 month before											
Kaderbhai 2017	6	15	30	59	7.3%	0.64 [0.20, 2.04]					
Kim 2019	42	86	41	124	11.5%	1.93 [1.10, 3.40]					
Mielgo Rubio 2018	29	55	16	66	9.9%	3.49 [1.61, 7.55]	<del></del>				
Pinato 2019	21	26	66	151	8.1%	5.41 [1.94, 15.11]					
Schett 2019	24	33	81	185	9.6%	3.42 [1.51, 7.77]					
Subtotal (95% CI)		215		585	46.3%	2.50 [1.40, 4.44]	•				
Total events	122		234								
Heterogeneity: Tau <sup>2</sup> = 0.24; (	Chi <b>²</b> = 9.5	7, df = 4	I (P = 0.0	5);   <b>2</b> = :	58%						
Test for overall effect: Z = 3.1	2 (P = 0.0	)02)									
Total (95% CI)		371		1338	100.0%	2.00 [1.27, 3.14]	•				
Total events	194		496								
Heterogeneity: Tau <sup>2</sup> = 0.38; Chi <sup>2</sup> = 30.62, df = 11 (P = 0.001); $I^2$ = 64%											
Test for overall effect: Z = 3.0	i0 (P = 0.0	0.01 0.1 1 10 100 no Antibiotics									
Test for subgroup differences: Chi <sup>2</sup> = 0.77, df = 1 (P = 0.38), $I^2$ = 0%											

Figure 2. Impact of antibiotics on disease progression-with subgroups based on timing of antibiotics.





		Hazard Ratio	Hazard Ratio						
Study or Subgroup	log[Hazard Ratio] SE Weigh	t IV, Fixed, 95% CI	IV, Fixed, 95% CI	_		(adj.) HR			
3.1.1 Lung cancer									
Barron 2019	0.4886 0.424 1.8%	• ' •		Outcome with		(95%CI)			
Derosa L 2018 NSCLC Facchinetti 2020	0.4055 0.2069 7.5% 0.6931 0.2398 5.6%		·		Number of		OR (95%CI)	P	l <sup>2</sup> (%)
Forde 2020	0.8459 0.3078 3.4%	• • •		antibiotic use	studies	for progression/			
Hogue 2019	0.0237 0.2361 5.8%					Death			
Huemer 2019	0.0198 0.1921 8.8%	• • •	+			Death			
Kulkarni 2018 NSCLC	-0.6931 0.2606 4.8%			OS	27	1.87(1.55-2.25)		<0.001	89%
Mielgo Rubio 2018	0.9555 0.3158 3.2%	% 2.60 [1.40 <sub>1</sub> 4.83]	<del></del>	03	_,	1.07 (1.33 2.23)		10.002	3370
Schett 2019	0.239 0.1535 13.7%	% 1.27 [0.94, 1.72]	<del>  •  </del>	DEC	20	1 52/1 26 1 70\		<0.001	68%
Zhao 2019	1.1394 0.3136 3.3%			PFS	20	1.52(1.36-1.70)		<0.001	00%
Subtotal (95% CI)	57.9%	% 1.36 [1.18, 1.58]	♥						
<del>-</del> · · ·	df= 9 (P < 0.0001); I <sup>2</sup> = 75%			adj. OS	22	1.88(1.59-2.22)		0.002	50%
Test for overall effect: $Z = 4.7$	3 (P < 0.0001)								
3.1.2 Melanoma				adj. PFS	17	1.93(1.59-2.36)		0.006	53%
Ueda 2019 Subtotal (95% CI)		% 6.52 [1.86, 22.88] % 6.52 [4.96, 22.99]							
		% 6.52 [1.86, 22.88]		DD	18		0.54(0.34-0.86)	<0.001	62%
Heterogeneity: Not applicab Test for overall effect: Z = 2.9				RR	10		0.54(0.54-0.80)	<b>\0.001</b>	0270
1631 IOI OVERAII EIIGUL Z — 2.3	oo (r  — 0.000)								
3.1.3 RCC				PD	12		2.00(1.27-3.14)	0.001	64%
Derosa L 2018 RCC	1.1314 0.4056 2.0%	% 3.10 [1.40, 6.86]		10	12		2.00(1.27 3.11)	0.001	0 170
Kulkarni 2018 RCC	0.8329 0.425 1.8%		•						
Routy 2018 RCC	0.7701 0.3085 3.4%	% 2.16 [1.18, 3.95]	<del></del>	<b>Table 1</b> . Met	a-analysis res	ults. OS=overal	l survival, PFS=	progression-free	survival,
Subtotal (95% CI)	7.1%	% 2.42 [1.60, 3.68]	•	RR=response r	ate PD=progre	essive disease ra	te, HR=hazard ra	tio OR=Odds-rat	io
Heterogeneity: Chi²= 0.52, (				Titt response i	acc, i b progre	coord alocase ra	cc, iiit iiazaia ia	cio, or odds ide	10.
Test for overall effect: $Z = 4.6$	6 (P < 0.0001)								
3.1.4 Mixed				Conclusi	ons				
J. 1.4 MIACU				Conclusi					

- Overall survival and progression-free survival are significantly shorter in cancer patients who are treated with ICI and receive antibiotics.
- Also these patients experience a lower response rate to treatment and greater disease progression rate.
- Further studies are needed to better characterize this complex relationship and determine the potential benefits of antimicrobial stewardship in this population.

### References

Ahmed J 2018

Tinsley 2019

Iglesias Santamaria 2020

Heterogeneity:  $Chi^2 = 10.34$ , df = 5 (P = 0.07);  $I^2 = 52\%$ 

Heterogeneity:  $Chi^2 = 59.35$ , df = 19 (P < 0.00001);  $i^2 = 68\%$ 

subgroups based on cancer type.

Test for subgroup differences:  $Chi^2 = 12.56$ , df = 3 (P = 0.006),  $I^2 = 76.1\%$ 

Test for overall effect: Z = 4.93 (P < 0.00001)

Test for overall effect: Z = 7.39 (P < 0.00001)

Routy 2018 urothelial

0.47 0.3288 3.0% 1.60 [0.84, 3.05]

4.0% 1.40 [0.80, 2.45]

34.1% 1.62 [1.33, 1.95]

100.0% 1.52 [1.36, 1.70]

Figure 1. Impact of antibiotics on progression free survival-with

no antibiotics

1.3635 0.3245 3.1% 3.91 [2.07, 7.39]

0.7655 0.3855 2.2% 2.15 [1.01, 4.58]

0.1823 0.2069 7.5% 1.20 [0.80, 1.80]

0.4447 0.1498 14.4% 1.56 [1.16, 2.09]

- 1. B. Routy et al., "Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors," Science (80-.)., vol. 359, no. 6371, pp. 91–97, 2018, doi: 10.1126/science.aan3706.
- 2. R. B. Derosa L 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., vol. 26, no. 9, pp. 1437–1444, 2018, doi: 10.1093/annonc/mdy103.