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 6/1/20, 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.

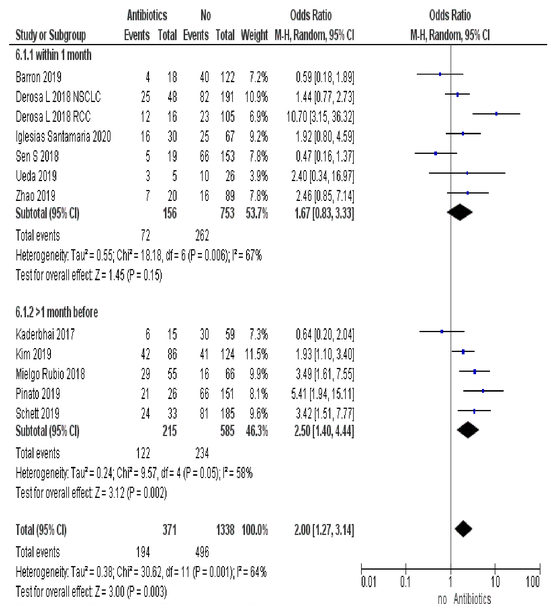

Figure 2. Impact of antibiotics on disease progression-with subgroups based on timing of antibiotics.

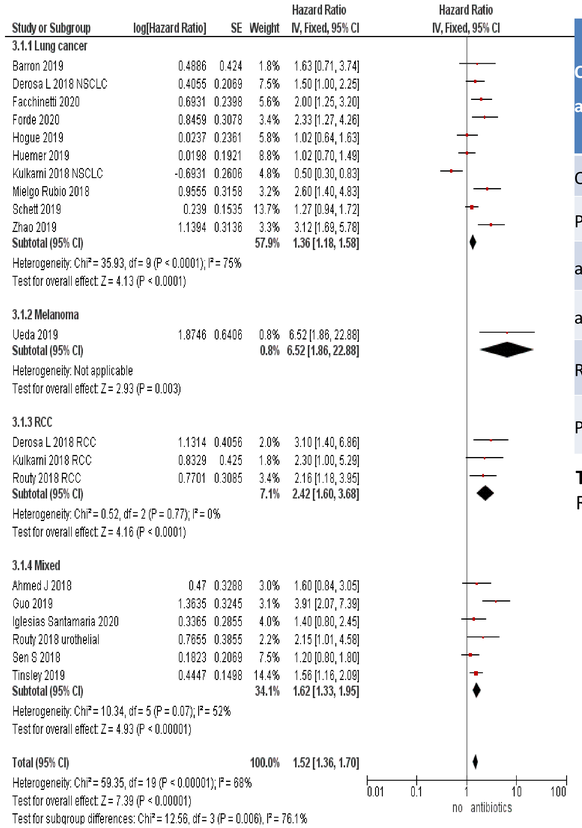

Figure 1. Impact of antibiotics on progression free survival-with subgroups based on cancer type.

Outcome with antibiotic use	Number of studies	(adj.) HR (95%CI) for progression/ Death	OR (95%CI)	*P*	I^2 (%)
OS	27	1.87(1.55-2.25)		<0.001	89%
PFS	20	1.52(1.36-1.70)		<0.001	68%
adj. OS	22	1.88(1.59-2.22)		0.002	50%
adj. PFS	17	1.93(1.59-2.36)		0.006	53%
RR	18		0.54(0.34-0.86)	<0.001	62%
PD	12		2.00(1.27-3.14)	0.001	64%

Table 1. Meta-analysis results. OS=overall survival, PFS=progression-free survival, RR=response rate, PD=progressive disease rate, HR=hazard ratio, OR=Odds-ratio.

Conclusions

- 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

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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.