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A Review of Meta-Analyses on the Impact of Antibiotics on the Efficacy of Immune Checkpoint Inhibitors and Cancer Patients' Survival

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BACKGROUND

- Prior research has strongly suggested that systemic antibiotic (ABX) exposure impacts the intestinal microbiota and may result in suboptimal immune checkpoint inhibitor (ICI) treatment outcomes.
- The magnitude of the observed effect seems to depend on cancer type and on the window of exposure to ABX relatively to the initiation of the ICI treatment.
- Several independently-developed meta-analyses studying this phenomenon have been published in the past 24 months.

METHODS

Medline (through PubMed), the Cochrane Library and major oncology conferences proceedings were systematically searched to identify abstracts, posters, articles, systematic reviews and meta-analyses studying the impact of ABX use on the clinical outcomes of cancer patients treated with ICIs. The meta-analyses were compared and the publications that were not included in any of the meta-analyses as of 25th of August 2020 were listed.

CONFLICT OF INTEREST

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RESULTS

6 independently-developed meta-analyses (published in 2019 and 2020) studying the progression-free survival (PFS) and overall survival (OS) of cancer patients treated with ICIs (mainly anti-PD(L)1 antibodies as monotherapy or combined with other anticancer drugs) and exposed to ABX were identified and compared.

Table 1: Comparison of meta-analyses studying the impact of ABX exposure on the clinical outcomes of cancer patients treated with ICI

1st Author Publication Date	Journal	HR PFS [95% CI] p-value N Studies	HR OS [95% CI] p-value N Studies	HR PFS [95% CI], p-value, N studies Depending on Main Cancer Types				HR OS [95% CI], p-value, N studies Depending on Main Cancer Types			
				Lung	Melanoma	Urothelial Carcinoma	Renal Cell Carcinoma	Lung	Melanoma	Urothelial Carcinoma	Renal Cell Carcinoma
Huang. 2019[1]	OncoImmunology	1.84 [1.49-2.26] p < 0.001 N = 15	2.37 [2.05-2.75] p < 0.001 N = 17	1.79 [1.29-2.49] p < 0.001 N = 9	Not Available (NA)	NA	2.12 [1.51-2.96] p < 0.001 N = 2	2.68 [2.19-3.28] p < 0.001 N = 10	NA	2.01 [1.23-3.29] p = 0.0054 N = 2	1.68 [1.00-2.83] p = 0.052 N = 2
Wilson. 2019[2]	Cancer Immunology, Immunotherapy	1.65 [1.30-2.10] p < 0.001 N = 14	1.92 [1.37-2.68] p < 0.001 N = 18	1.64 [1.07-2.52] p = 0.023 N = 7	1.54 [0.33-7.12] p = 0.59 N = 2	2.13 [1.54-2.93] p < 0.001 N = 4		2.00 [1.23-3.25] p = 0.0052 N = 11	1.08 [0.40-2.92] p = 0.89 N = 2	1.86 [1.16-2.98] p = 0.0099 N = 3	
Xu. 2020[3]	Critical Reviews in Oncology/Hematology	1.53 [1.30-1.79] p < 0.001 N = 15	1.90 [1.55-2.34] p < 0.001 N = 19	1.39 [1.16-1.67] p < 0.001 N = 8	2.76 [2.12-3.59] p < 0.001 N = 1	NA	2.47 [1.52-3.99] p < 0.001 N = 2	1.73 [1.26-2.38] p < 0.001 N = 12	3.70 [1.06-12.89] p = 0.040 N = 1	NA	1.84 [0.81-4.16] p = 0.14 N = 2
Petrelli. 2020[4]	Journal of Clinical Medicine	1.53 [1.22-1.93] p < 0.001 N = 13	2.01 [1.48-2.74] p < 0.001 N = 14	NA	NA	NA	NA	NA	NA	NA	NA
Lurienne. 2020[5]	Journal of Thoracic Oncology	1.47 [1.13-1.90] p = 0.0037 N = 17	1.69 [1.25-2.29] p < 0.001 N = 21	1.47 [1.13-1.90] p = 0.0037 N = 17	NA	NA	NA	1.69 [1.25-2.29] p < 0.001 N = 21	NA	NA	NA
Yang. 2020[6]	International Immunopharmacology	1.76 [1.47-2.12] p < 0.001 N = 29	1.76 [1.41-2.19] p < 0.001 N = 29	1.70 [1.27-2.27] p < 0.001 N = 13	NA	NA	2.29 [1.68-3.12] p < 0.001 N = 5	1.80 [1.28-2.55] p < 0.001 N = 16	NA	NA	1.97 [0.86-4.54] p = 0.11 N = 2

Statistically significant. Non statistically significant.

Table 2: Reported hazard ratios for PFS and OS depending on the time window of exposure to ABX

1st Author & Publication Date	Time Window of Exposure to ABX in Relation to ICI Treatment Initiation (Days)	HR PFS [95% CI], p-value, N Studies	HR OS [95% CI], p-value, N Studies
Huang. 2019[1]	-90 -60 -30 0 30 60 90 ∞	1.70 [1.43-2.02], p < 0.001, N = 8	2.29 [1.92-2.73], p < 0.001, N = 10
	-90 -60 -30 0 30 60 90 ∞	NA	2.23 [1.82-2.74], p < 0.001, N = 7
	-90 -60 -30 0 30 60 90 ∞	NA	1.97 [1.49-2.59], p < 0.001, N = 2
	-90 -60 -30 0 30 60 90 ∞	1.91 [1.31-2.78], p < 0.001, N = 8	2.56 [1.96-3.36], p < 0.001, N = 7
Wilson. 2019[2]	-90 -60 -30 0 30 60 90 ∞	2.10 [1.44-3.06], p < 0.001, N = 6	3.43 [2.29-5.14], p < 0.001, N = 7
	-90 -60 -30 0 30 60 90 ∞	1.66 [1.40-1.96], p < 0.001, N = 7	1.81 [1.29-2.54], p < 0.001, N = 10
	-90 -60 -30 0 30 60 90 ∞	0.88 [0.42-1.86], p = 0.75, N = 3	0.89 [0.42-1.90], p = 0.77, N = 4
Xu. 2020[3]	-90 -60 -30 0 30 60 90 ∞	NA	1.81 [0.91-3.63], p = 0.092, N = 3
	-90 -60 -30 0 30 60 90 ∞	NA	2.09 [1.31-2.32], p < 0.001, N = 7
Petrelli. 2020[4]	-90 -60 -30 0 30 60 90 ∞	NA	2.33 [1.33-2.34], p < 0.001, N = 2
	-90 -60 -30 0 30 60 90 ∞	NA	Not Significant N = 1
Lurienne. 2020[5]	-90 -60 -30 0 30 60 90 ∞	1.56 [0.78-3.13], p = 0.21, N = 4	2.49 [0.95-6.51], p = 0.063, N = 5
	-90 -60 -30 0 30 60 90 ∞	1.72 [1.30-2.27], p < 0.001, N = 12	2.04 [1.49-2.79], p < 0.001, N = 14
	-90 -60 -30 0 30 60 90 ∞	2.00 [1.34-2.99], p < 0.001, N = 3	2.94 [1.60-5.40], p < 0.001, N = 3
	-90 -60 -30 0 30 60 90 ∞	0.97 [0.44-2.17], p = 0.95, N = 5	1.24 [0.56-2.76], p = 0.61, N = 7
Yang. 2020[6]	-90 -60 -30 0 30 60 90 ∞	1.88 [1.47-2.41], p < 0.001, N = 8	2.58 [1.94-3.43], p < 0.001, N = 8
	-90 -60 -30 0 30 60 90 ∞	2.01 [1.55-2.61], p < 0.001, N = 12	1.64 [1.20-2.24], p = 0.0019, N = 12
	-90 -60 -30 0 30 60 90 ∞	1.29 [0.77-2.17], p = 0.34, N = 7	1.38 [0.89-2.15], p = 0.15, N = 9

Note: the time windows of exposure to ABX in relation to ICI treatment initiation were adjusted, when possible and relevant, to match the time windows used in the studies referenced in each meta-analysis

Statistically significant. Non statistically significant.

CONCLUSION & PERSPECTIVES

The independently-developed meta-analyses vary in the scope of studies included and their methodology but they all conclude on a significant deleterious effect of ABX use on the survival of patients treated with ICIs, regardless of cancer type. They also concur that the impact of ABX exposure on the clinical outcomes of cancer patients treated with ICIs is stronger when the exposition happens shortly before and after the initiation of the ICI treatment, whereas ABX use later during ICI treatment course does not seem to alter survival or to a lesser extent. Given that many of the studies included in these meta-analyses overlap, quite logically, their results and conclusions cannot be considered as being completely independent. The topic deserves further research to uncover if the effect will stand with 1st line use of ICIs together with chemotherapies and/or other approved combinations, elucidate the mechanisms at stake and improve the care of patients. 21 new studies identified, not included in any of the compared meta-analyses, are eligible for inclusion in a future updated meta-analysis.

REFERENCES

1. Huang XZ, Gao P, Song YX, et al. Antibiotic use and the efficacy of immune checkpoint inhibitors in cancer patients: a pooled analysis of 2740 cancer patients. Oncoimmunology. 2019;8(12):e1665973.
2. Wilson, B.E., Routy, B., Nagrial, A. et al. The effect of antibiotics on clinical outcomes in immune-checkpoint blockade: a systematic review and meta-analysis of observational studies. Cancer Immunol Immunother 2019;69, 343–354.
3. Xu H, Xu X, Wang H, et al. The association between antibiotics use and outcome of cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology. 2020 May;149:102909.
4. Petrelli F, Iaculli A, Signorelli D, et al. Survival of Patients Treated with Antibiotics and Immunotherapy for Cancer: A Systematic Review and Meta-Analysis. JCM. 2020 May 13;9(5):1458.
5. Lurienne L, Cervesi J, Duhalde L, et al. NSCLC Immunotherapy Efficacy and Antibiotic Use: A Systematic Review and Meta-Analysis. Journal of Thoracic Oncology. 2020 Jul;15(7):1147–59.
6. Yang M, Wang Y, Yuan M, et al. 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. International Immunopharmacology. 2020 Nov;88:106876.