# Update of Systematic Reviews and Meta-Analyses Studying the Association Between Antibiotic Use and Clinical Outcomes of Cancer Patients Treated with Immune Checkpoint Inhibitors

**50P** 

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# BACKGROUND

- Experimental studies involving mouse models and fecal microbiota tumor transplant from cancer patients have suggested that intestinal dysbiosis impacts the response to anti-PD(L1) mAb<sup>1,2,3</sup>.
- Prior clinical research has strongly suggested that systemic antibiotic (ABX) exposure impacts the intestinal microbiota and may result in suboptimal immune inhibitor (ICI) checkpoint treatment outcomes.
- In 2020, our team published a systematic review and meta-analysis<sup>4</sup> showing that ABX use was associated with a decrease of the survival of patients diagnosed with non-small-cell lung cancer (NSCLC) and treated with ICI.
- Since then, a number of publications including patients with other cancer types were published. We decided to conduct a new systematic review and meta-analysis on the impact of ABX on the efficacy of ICI in all types of cancer.

#### 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 ICI.
- Studies were deemed eligible for inclusion when they mentioned a hazard ratio (HR) or Kaplan–Meier curves for overall survival (OS) or for progression-free survival (PFS) based on antibiotic exposure.
- Pooled HR for OS and PFS were calculated according to cancer types and according to time windows of ABX exposure

### RESULTS

65 studies reported data for OS (23,146 patients) and 45 for PFS (14,689 patients). The overall pooled HR was 1.65 (95% confidence interval [CI]: 1.46-1.87) for OS and 1.44 (95% CI: 1.27-1.64) for PFS, confirming a significantly reduced survival in cancer patients treated with ICI and exposed to ABX. The detailed analysis in subgroups according to cancer type (Figure 1) demonstrates a decreased survival for most cancers.

#### Study

**Cancer = NSCLC** Bagley 2019 Chalabi 2020 Clark 2020 - TW [-30;0] Clark 2020 - TW [0;+∞[ Derosa 2018 Facchinetti 2020 Fidler 2019 - TW [-90;0] Fidler 2019 - TW [0;+∞[ Galli 2018 Hakozaki 2018 Huemer 2019 Kim 2020 Kulkarni 2020 Metges 2018 - Lung cancer Mielgo Rubio 2019 Mielgo Rubio 2018 Ouaknine 2019 Pinato 2019 - Lung cancer Riudavets 2019 Rounis 2020 Ruiz-Patino 2020 chett 2019 - TW [-60;0] chett 2019 - TW [0;+∞[ pakowicz 2020 Svaton 2020 Thompson 2017 Tien Phu Doc 2018 - Lung cancer Zhang 2020 Zhao 2019

#### **Random effects model** Heterogeneity: $I^2 = 77\%$ , $\tau^2 = 0.2896$ , p < 0.01

Cancer = Urothelial carcinoma Agarwal 2019 offman-Censits 2020 Khan M. 2020 Spakowicz 2020 - Bladder cancer Veinstock 2020 **Random effects model** Heterogeneity:  $I^2 = 76\%$ ,  $\tau^2 = 0.1060$ , p < 0.01

#### Cancer = Melanoma

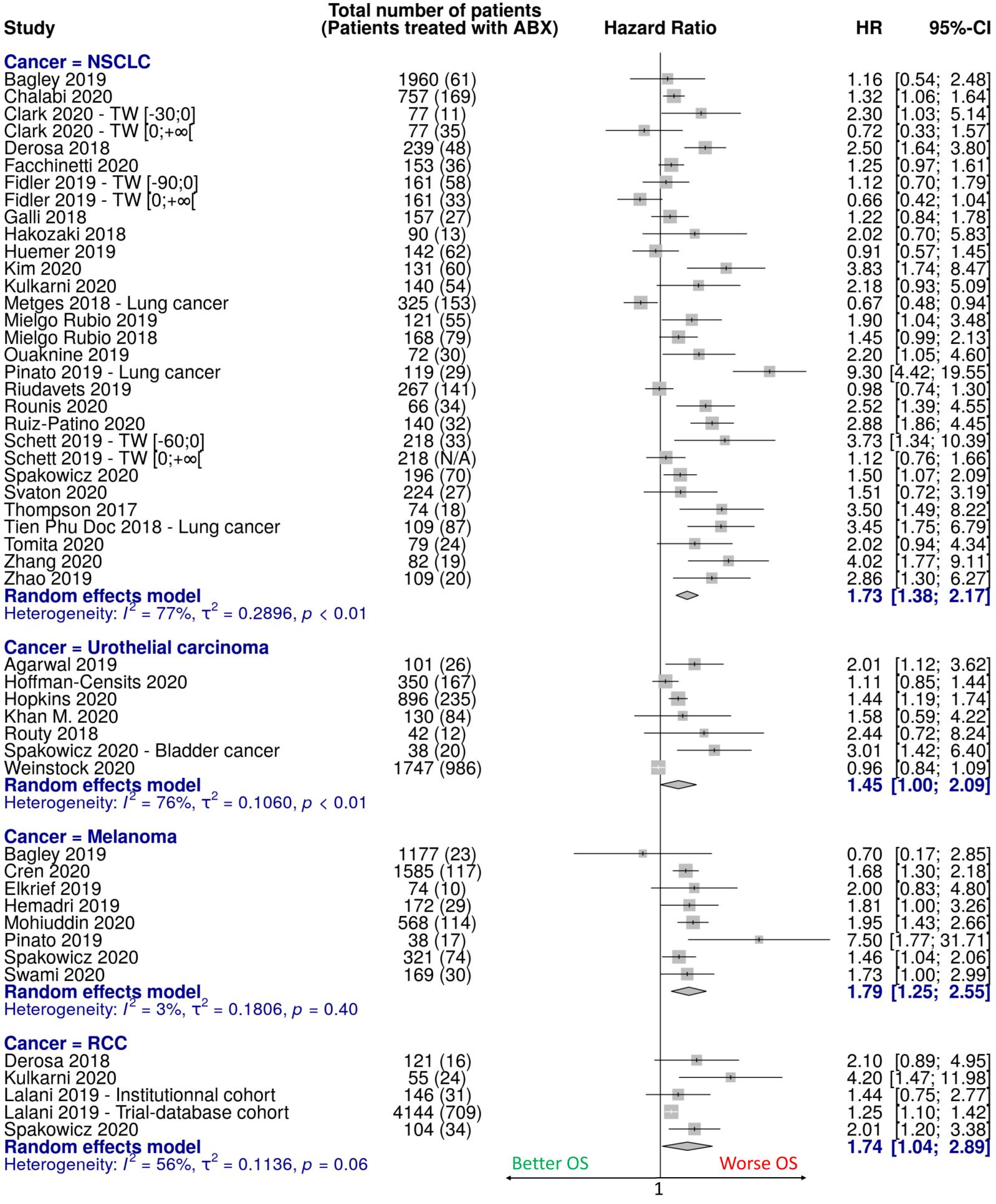
Bagley 2019 Cren 2020 Elkrief 2019 Hemadri 2019 Mohiuddin 2020 Pinato 2019 Spakowicz 2020 Swami 2020 Random effects model Heterogeneity:  $I^2 = 3\%$ ,  $\tau^2 = 0.1806$ , p = 0.40

Cancer = RCC Derosa 2018 Kulkarni 2020 Lalani 2019 - Institutionnal cohort Lalani 2019 - Trial-database cohort Spakowicz 2020 **Random effects model** 

#### Figure 1: Forest plots of hazard ratios for OS of cancer patients exposed or not to antibiotics, according to cancer type

ABX, Antibiotic; HR, Hazard Ratio; CI, Confidence Interval; TW Time Window; RCC, Renal Cell Carcinoma

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%-CI		Total number of patients Patients treated with ABX)	Hazard Ratio	HR 95	%-CI
2.48 1.64 5.14 1.57 3.80 1.61 1.79 1.04 1.78 5.83 1.45 8.47	<b>Cancer = Other</b> Plana 2020 - Head & Neck cancer Spakowicz 2019 - Head & Neck cancer Vellanki 2020 - Head & Neck cancer Greally 2019 - Esophagogastric cancer Guo 2020 - Esophagogastric cancer Hwang 2020 - TW [-90;0] - Hodgkin lymp Hwang 2020 - TW [0;+ $\infty$ [ - Hodgkin lymp Jun 2020 - Hepatocellular carcinoma Spakowicz 2020 - Sarcoma <b>Random effects model</b> Heterogeneity: $I^2$ = 55%, $\tau^2$ = 0.2106, $p$ = 0	homa 62 (21) 95 (25) 45 (14)		$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2.75 2.03 1.82 3.55 2.55 7.18 3.34 2.82
8.47 5.09 0.94 3.48 2.13 4.60 9.55 1.30 4.55 4.45 0.39 1.66 2.09 3.19 8.22 6.79	Cancer = Aggregated Kapoor 2020 Cortellini 2020 - ABX taken for prophylax Cortellini 2020 - ABX taken for infection Abu-Sheih 2019 Iglesias-Santamaria 2019 Masini 2019 Perez-Ruiz 2020 Sen 2018 Spakowicz 2020 Tinsley 2019 Random effects model Heterogeneity: $I^2$ = 91%, $\tau^2$ = 0.1673, $p < 0$	1012 (48) 826 (569) 102 (60) 169 (59) 253 (53) 172 (19) 225 (89) 291 (92)	1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2.98 .75 2.87 .68 .94 3.13 3.32 2.97 2.10

The detailed analysis in subgroups according to time windows of ABX exposure (Table 1) suggests that the deleterious effect of ABX is stronger when the exposure happens shortly before and after the start of the ICI treatment.

Time Window of Exposure to ABX in Relation to ICI Treatment Initiation (Days)									HR OS [95% CI] N studies (N patients)	HR PFS [95% CI] N studies (N patients)	
-∞	-90	-60	-30	0	30	60	90	120	+∞	1.35 [0.85-2.14] 4 (1,141)	1.03 [0.99-1.07] 2 (511)
-∞	-90	-60	-30	0	30	60	90	120	+∞	1.85 [1.26-2.73] 7 (975)	1.74 [0.93-3.24] 6 (880)
-∞	-90	-60	-30	0	30	60	90	120	+∞	2.32 [1.61-3.34] 12 (2,326)	1.55 [1.19-2.02] 10 (2,123)
-∞	-90	-60	-30	0	30	60	90	120	+∞	2.12 [0.80-5.65] 3 (278)	1.81 [1.30-2.51] 6 (460)
-∞	-90	-60	-30	0	30	60	90	120	+∞	1.63 [1.43-1.86] 27 (15,798)	1.52 [1.23-1.86] 17 (9,867)
-∞	-90	-60	-30	0	30	60	90	120	+∞	1.81 [1.23-2.68] 7 (1,800)	1.67 [0.93-3.01] 4 (552)
-∞	-90	-60	-30	0	30	60	90	120	+∞	1.47 [0.89-2.44] 11 (1,616)	1.13 [0.66-1.91] 6 (1,123)

Statistically significant. Non statistically significant

Table 1: Hazard ratios for OS and PFS of cancer patients exposed to ABX versus not exposed to ABX, according to the ABX exposure time window

# **CONCLUSION & PERSPECTIVES**

The meta-analysis confirms the previously reported deleterious effect of ABX on outcomes of ICItreated cancer patients.

The impact of ABX exposure seems stronger for melanoma and NSCLC and when the exposure to ABX happens shortly before and after the initiation of the ICI treatment. Later ABX use during ICI treatment course does not seem to alter survival or to a lesser extent. The topic deserves further research to uncover if the effect will stand with 1<sup>st</sup> line use of ICI together with chemotherapies, elucidate the mechanisms at stake and improve the care of patients.

### **CONFLICTS OF INTEREST**

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### CONTACTS

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