



# Early antibiotic exposure delays disease progression following immune checkpoint inhibitor therapy for hepatocellular carcinoma: Evidence from an observational study.

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## INTRODUCTION

- Immune checkpoint inhibition (ICI) is an expanding option in hepatocellular carcinoma (HCC).
- Antibiotics (ATB) have been shown to reduce response and survival after ICI in other cancers.

## AIM

- Investigate the relationship between antibiotic exposure and response to ICI in a large HCC cohort.

## METHOD

- Efficacy of ICI is described in patients from 11 centres (246 USA, 100 Asia, 68 Europe).
- Median overall (OS), progression-free survival (PFS) and best response were compared between patients with and without ATB exposure in the early immunotherapy period (EIOP) of 30 days before and after ICI initiation.
- Landmark selection analysis was repeated, only including patients with a minimum follow-up for PFS of 30 days, to overcome possible bias introduced by misclassification of patients that received antibiotics but discontinued immunotherapy within 30 days of immunotherapy initiation.

Characteristic	Overall N=449 (%)	Non-EIOP N=279 (%)	EIOP N=170 (%)	Chi-square
Age, median (range) $\geq 70$ years	65 (15-89) 119 (26.5)	65 (18-89) 74 (26.5)	65 (15-87) 45 (26.5)	P = 0.8333
Male	355 (79.1)	223 (79.9)	132 (77.6)	P = 0.5648
Female	94 (20.9)	56 (20.1)	38 (22.4)	
ECOG-PS				P = 0.2230*
0	178 (39.6)	110 (39.4)	68 (40.0)	
1	177 (39.4)	115 (41.2)	115 (41.2)	
2	18 (4.0)	8 (2.9)	8 (2.9)	
Unknown	76 (16.9)	46 (16.5)	30 (17.6)	
Cirrhosis				P = 0.5929
Absent	120 (26.7)	77 (27.6)	43 (25.3)	
Present	329 (73.3)	202 (72.4)	127 (74.7)	
Risk factor for Liver Disease				P = 0.0954
Non-viral HCC	178 (39.6)	119 (42.7)	59 (34.7)	
HBV and/or HBV infection	271 (60.4)	160 (57.3)	111 (65.3)	
Child-Turcotte Pugh Class				P = 0.5697
A	332 (73.9)	209 (74.)	123 (72.4)	
B	117 (26.1)	70 (25.1)	47 (27.6)	
BCLC stage				P = 0.9841
A	15 (3.3)	9 (3.2)	6 (3.5)	
B	109 (24.3)	68 (24.4)	41 (24.1)	
C	325 (72.4)	202 (72.4)	123 (72.4)	
AFP (ng/ml), <400 IU/mL	266 (59.2)	166 (59.5)	100 (58.8)	P = 0.5968*
>400 IU/mL	172 (38.3)	103 (36.9)	69 (40.6)	

Table 1 – Baseline characteristics of patients. Early immunotherapy period antibiotics, EIOP

## RESULTS

- International HCC cohort (n=449) with median age of 65, majority male (79.1%), cirrhotic (73.3%) due to viral hepatitis (60.4%), with Child-Pugh class A (73.9%), BCLC stage C (72.4%) and ECOG-PS 0-1 (79.0%) (Table 1).
- Antibiotics in the EIOP were not associated with objective response rate (EIOP+: 20.2% [95%CI: 14.0–28.2], EIOP-: 16.1% [95%CI: 11.6–21.8]; p=0.2808) or disease control rate (EIOP+: 63.1% [95%CI: 51.6–76.3], EIOP-: 55.4% [95%CI: 46.7–65.4]; p=0.1144).
- Median OS was not significantly different between the groups (EIOP+: 15.3 months [95%CI: 11.1–52.5; 88 events], EIOP-: 15.4 months [95%CI: 11.3–17.6; 153 events], p=0.6275; HR 0.93 [95%CI: 0.72-1.21], **Figure 1A**),
- Median PFS was significantly reduced in EIOP+ patients: 6.1 months (95%CI: 4.3–8.0; 128 events) for EIOP+ patients, and 3.7 months (95%CI: 3.3–4.3; 228 events) for EIOP-ones (log-rank: p=0.0086; HR 0.74 [95%CI: 0.60-0.93], **Figure 1B**).
- Re-analysis after a 30-day minimum follow up landmark selection (n=402) confirmed the above findings (**Figure 1C-D**).

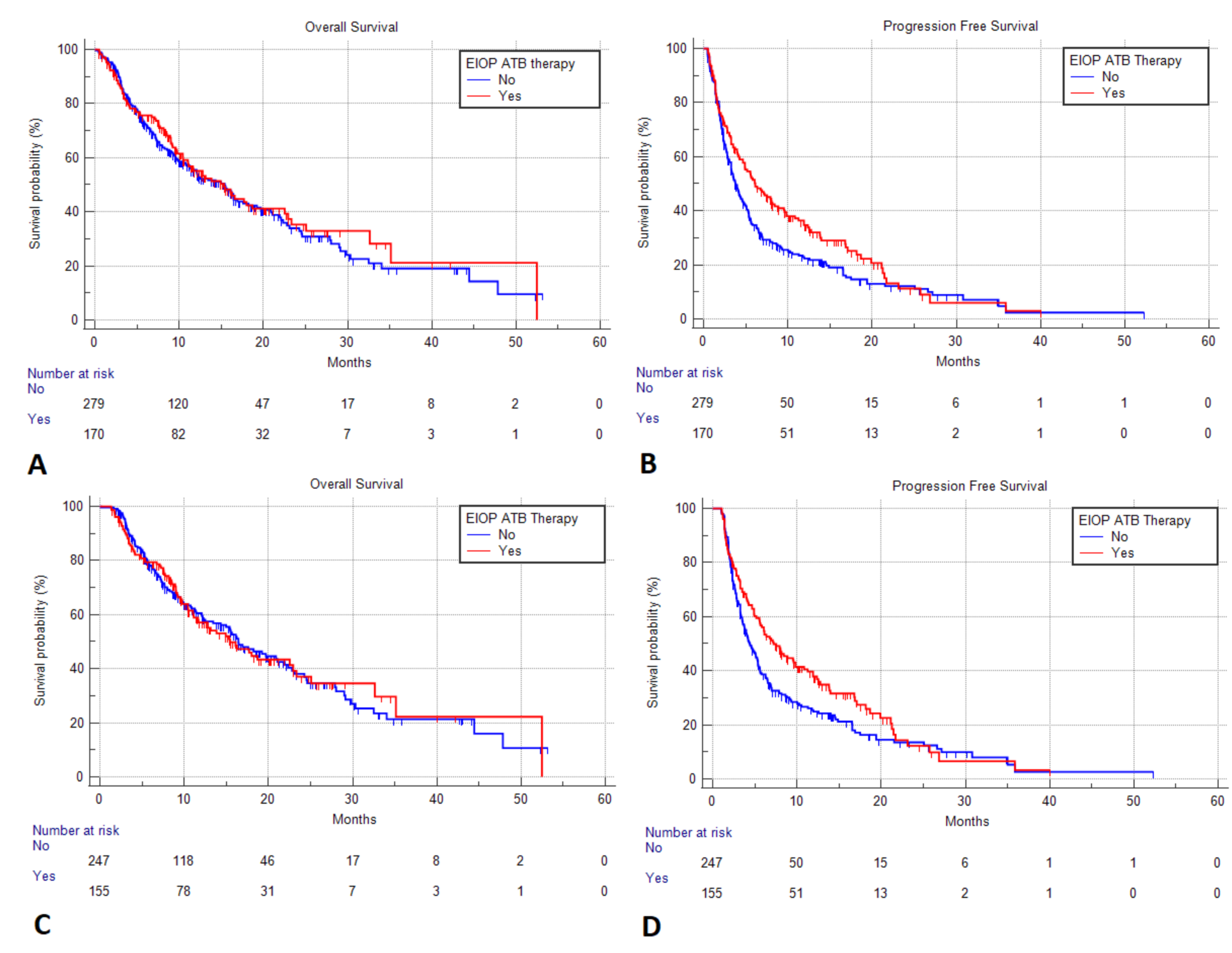


Figure 1 – Overall survival and progression-free survival according to antibiotic exposure.

## CONCLUSIONS

- Antibiotic exposure in the 30 days before or after immune checkpoint initiation (ICI) in hepatocellular carcinoma (HCC) is associated with prolonged PFS.
- Evaluation of the immune-microbiologic determinants of response to ICI in HCC a key research question.

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