Early antibiotic exposure is associated with greater therapeutic benefit from immunotherapy in hepatocellular carcinoma.

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**Supplementary Table 1.** Geographical Origin of HCC patients treated with ICI.

|  |  |
| --- | --- |
| **Region. Institution** | **Patients (%)** |
| **Europe**Humanitas Cancer Center. ItalyImperial College London. United KingdomFreiburg University. GermanyMedical University Vienna. Austria | 109 (25)59 (14)5 (1)3 (1)42 (9) |
| **North America**Mount Sinai. New York. USAMD Anderson Cancer Center. Texas. USAKansas University Medical Center. Kansas. USAWeill Cornell Medical Center. New York. USAUniversity of Chicago. Illinois. USAEast Carolina Medical Centre. North Carolina. USA | 250 (55)92 (21)69 (15)32 (7)20 (4)34 (8)3 (1) |
| **Asia**Taipei Veterans General Hospital. TaiwanKindai University. Osaka. Japan | 91 (20)42 (9)49 (10) |

**Supplementary Table 2.** Detailed indications for ATB administration in the pATB and eATB groups.

|  |  |  |
| --- | --- | --- |
| **INDICATIONS** | **pATB n** | **eATB n** |
| Pneumonia | 3 (3,7%) | 15 (11,7%) |
| Urinary tract infections | 3 (3,7%) | 14 (10,9%) |
| Gastro-intestinal infections | 6 (7,3%) | 11 (8,6%) |
| Skin infections | 3 (3,7%) | 3 (2,3%) |
| Empirical – unclear source | 49 (59,8%) | 63 (49,2%) |
| ENT infections | 2 (2,4%) | 9 (7,0%) |
| Dental infections | 2 (2,4%) | 4 (3,1%) |
| Encephalopaty | 7 (8,5%) | 7 (5,5%) |
| Blood borne/septicaemia | 1 (1,2%) | 2 (1,6%) |
| Pre-TACE prophylaxis | 6 (7,3%) | - |
| **Total** | **82** | **128** |

**Supplementary Table 3.** Detailed ATB types in the pATB and eATB groups**.**

|  |  |  |
| --- | --- | --- |
| **ATB class** | **pATB**  | **eATB**  |
| Beta-lactams | 34 (41,4%) | 87 (67,9%) |
| Quinolones | 28 (34,1%) | 45 (35,1%) |
| Macrolides | 6 (7,3%) | 14 (10.9%) |
| Sulfonamides | 1 (1,2%) | 1 (0,8%) |
| Aminoglycosides | 1 (1,2%) | - |
| Tetracyclines | 3 (3,7%) | 5 (3,9%) |
| Carbapenems | 2 (2,4%) | 3 (3,1%) |
| Cephalosporins | 18 (21,9%) | 41 (32%) |
| Nitroimidazole | 7 (8.5%) | 8 (6,2%) |
| Trimethoprim | 4 (4,8%) | 2 (1,5%) |
| Glycopeptides | 2 (2,4%) | 14 (10,9%) |
| Rifampicin  | 7 (8.5%) | 11 (8,6%) |
| **Total** | **82** | **128** |

|  |  |  |
| --- | --- | --- |
| ***Variable******(Control)*** | ***Progression Free Survival (PFS)*** | ***Overall Survival (OS)*** |
| *HR (95% CI); p-value* | *HR (95% CI); p-value* |
| **EIOP ATB therapy**(NO)Beta-lactamsQuinolonesOthers single agent ATBATB combinations | 0.77 (0.54-1.10); p = 0.15800.56 (0.34-0.91); p = 0.02170.95 (0.65-1.37); p = 0.78770.72 (0.51-1.03); p = 0.0735 | 0.89 (0.59-1.34); p = 0.59370.56 (0.29-1.07); p = 0.08161.03 (0.64-1.07); p = 0.89021.16 (0.78-1.71); p = 0.4502 |

**Supplementary Table 4.** Additional progression Free Survival and Overall Survival univariable analyses according to different EIOP ATB types.

**Supplementary Table 5.** Four-weeks landmark analysis illustrating the relationship between early ATB exposure (EIOP) and key efficacy outcomes in patients with HCC treated with immunotherapy. DCR and ORR analyses: 386 patients included. PFS and OS analyses: 397 patients included.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Variable*** | ***Objective Response Rate (ORR)*** | ***Disease Control Rate (DCR)*** | ***Progression Free Survival (PFS)*** | ***Overall Survival (OS)*** |
| *Multivariable**OR (95% CI); p-value* | *Multivariable**OR (95% CI); p-value* | *Multivariable**HR (95% CI); p-value* | *Multivariable**HR (95% CI); p-value* |
| **EIOP***Yes vs No* | 1.29 (0.77-2.17); p = 0.3242 | 1.49 (0.96-2.32); p = 0.0714 | 0.73 (0.57-0.93); p = 0.0130 | 1.01 (0.75-1.34); p = 0.9524 |
| **Gender**Male vs Female | 0.79 (0.40-1.55); p = 0.4955 | 0.81 (0.47-1.40); p = 0.4597 | 1.00 (0.74-1.34); p = 0.9976 | 0.85 (0.59-1.22); p = 0.3872 |
| **Age**<70 vs >70 years | 0.94 (0.55-1.59); p = 0.8280 | 1.21 (0.78-1.88); p = 0.3720 | 0.90 (0.70-1.14); p = 0.4023 | 1.16 (0.86-1.54); p = 0.3138 |
| **Viral aetiology**Yes vs No | 1.19 (0.69-2.05); p = 0.5268 | 0.90 (0.58-1.41); p = 0.6707 | 0.98 (0.77-1.24); p = 0.8803 | 0.82 (0.61-1.09); p = 0.1782 |
| **Child-Turcotte****Pugh class**B vs A | 1.18 (0.66-2.13); p = 0.5652 | 0.98 (0.60-1.61); p = 0.9565 | 1.17 (0.90-1.52); p = 0.2292 | 1.53 (1.12-2.09); p = 0.0069 |
| **BCLC Stage**C vs A/B | 1.31 (0.69-2.49); p = 0.4035 | 0.68 (0.40-1.14); p = 0.1499 | 1.04 (0.78-1.39); p = 0.7685 | 1.09 (0.77-1.55); p = 0.5885 |
| **ICI treatment***PD-(L)1 Monotherapy vs Others* | 0.70 (0.34-1.44); p = 0.3436 | 0.40 (0.20-0.81); p = 0.0105 | 1.25 (0.89-1.75); p = 0.1882 | 1.20 (0.78-1.85); p = 0.3958 |
| **Treatment line***>1L vs 1L* | 0.94 (0.55-1.59); p = 0.8298 | 0.95 (0.61-1.48); p = 0.8423 | 1.44 (1.13-1.83); p = 0.0030 | 1.27 (0.94-1.70); p = 0.1066 |
| **AFP (ng/ml)**≥400 vs < 400 | 1.36 (0.80-2.31); p = 0.2427 | 0.64 (0.41-0.99); p = 0.0462 | 1.22 (0.96-1.55); p = 0.0897 | 1.82 (1.37-2.42); p < 0.0001 |