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

Fessas et al.

**Contents**

**Supplementary Table 1 Page 2**

Geographical Origin of HCC patients treated with ICI.

**Supplementary Table 2** **Page 3**

Detailed indications for ATB administration in the pATB and eATB groups.

**Supplementary Table 3**   **Page 4**

Detailed ATB types in the pATB and eATB groups.

**Supplementary Table 4**  **Page 5**

Additional PFS and OS univariable analyses.

**Supplementary Table 5**  **Page 6**

30-days landmark analysis illustrating the relationship between early ATB exposure (EIOP) and key efficacy outcomes in patients with HCC treated with immunotherapy.

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

|  |  |
| --- | --- |
| **Region. Institution** | **Patients (%)** |
| **Europe**  Humanitas Cancer Center. Italy  Imperial College London. United Kingdom  Freiburg University. Germany  Medical University Vienna. Austria | 109 (25)  59 (14)  5 (1)  3 (1)  42 (9) |
| **North America**  Mount Sinai. New York. USA  MD Anderson Cancer Center. Texas. USA  Kansas University Medical Center. Kansas. USA  Weill Cornell Medical Center. New York. USA  University of Chicago. Illinois. USA  East 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. Taiwan  Kindai 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-lactams  Quinolones  Others single agent ATB  ATB combinations | 0.77 (0.54-1.10); p = 0.1580  0.56 (0.34-0.91); p = 0.0217  0.95 (0.65-1.37); p = 0.7877  0.72 (0.51-1.03); p = 0.0735 | 0.89 (0.59-1.34); p = 0.5937  0.56 (0.29-1.07); p = 0.0816  1.03 (0.64-1.07); p = 0.8902  1.16 (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 |