Supplementary Table 1. Summary of clinical characteristics, CIP onset, and treatment history

of patient groups included in scRNA-seq analysis, Related to Fig. 1b.

|  |  |  |  |
| --- | --- | --- | --- |
|  | CIP (n=6) | No CIP (n=3) | Control (n=3) |
| Age | 53 (52-69) | 63 (59-64) | 24 (22-38) |
| M:F | 6:0 | 2:1 | 2:1 |
| Tumor histology |  |  |  |
|  lung adenocarcinoma  | 2 | 2 | 0 |
|  lung squamous carcinoma | 4 | 1 | 0 |
| Stage |  |  |  |
|  advanced | 6 | 3 | NA |
|  recurrence | 0 | 0 | NA |
| ICI agent |  |  |  |
|  Pembrolizumab | 4 | 2 | NA |
|  Durvalumab | 2 | 1 | NA |
| Average ICI Treatment Cycles (mean +/- sd) | 10.83 +/- 4.75 | 11 +/- 7.94 | NA |
| Time from first treatmentto CIP onset (days)(mean +/- sd) | 361.33 +/- 158.84 | 0 | NA |
| Time from last cycle to CIP onset (days) (mean +/- sd) | 87 +/- 61.8 | 0 | NA |
| Time from CIPonset to bronchoscopy(days) (mean +/- sd) | 3.67 +/- 2.58 | 0 | NA |
| CTCAE Grade |  |  |  |
|  grade1 | 1 | NA | NA |
|  grade2 | 5 | NA | NA |
| Response tocorticosteroids | 5/6 | NA | NA |
| Received Tocilizumab | 2/6 | NA | NA |
| Additional irAE | 2/6 | 0 | NA |

Supplementary Table 2. CIP treatment history for each patient included in scRNA-seq studies, Related to Fig. 1b.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Patient ID | Treatment | Age | Sex | Tumor histology | Stage | Prior Treatment | Time from last Treatment (days) |
| P1 | pembrolizumab | 58 | M |  lung squamous carcinoma | 4 | none | 31 |
| P2 | pembrolizumab | 53 | M |  lung adenocarcinoma | 4 | none | 70 |
| P3 | Durvalumab | 52 | M |  lung squamous carcinoma | 4 | chemotherapy+thoracic radiotherapy | 13 |
| P4 | pembrolizumab | 53 | M |  lung adenocarcinoma | 4 | none | 125 |
| P5 | pembrolizumab | 69 | M |  lung squamous carcinoma | 4 | none | 179 |
| P6 | Durvalumab | 52 | M |  lung squamous carcinoma | 4 | chemotherapy+thoracic radiotherapy | 104 |
| C1 | pembrolizumab | 63 | M |  lung adenocarcinoma | 4 | none | NA |
| C2 | Durvalumab | 59 | M |  lung squamous carcinoma | 4 | none | NA |
| C3 | pembrolizumab | 64 | F |  lung adenocarcinoma | 4 | none | NA |
| H1 | NA | 38 | F |  |  |  |  |
| H2 | NA | 24 | M |  |  |  |  |
| H3 | NA | 22 | M |  |  |  |  |

CIP(+):P1-P6; CIP(-):C1-C3; Healthy:H1-H3

Supplementary Table 3. Characteristics of CIP development and clinical management for each patient included in scRNA-seq studies, Related to Fig. 1b.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Diagnosis | Grade(CTCAE) | Time from firsttreatment to CIP onset (days) | Time from mostlast Treatment toCIP onset (days) | Time from CIP onset to bronchoscopy (days) | Totaltreatmentcycles | Steroidsprior tobronchoscopy | TocilizumabRequired forTreatment |
| P1 | CIP(+) | 2 | 553 | 31 | 4 | 19 | no | no |
| P2 | CIP(+) | 2 | 298 | 70 | 2 | 7 | no | no |
| P3 | CIP(+) | 2 | 163 | 13 | 2 | 9 | no | no |
| P4 | CIP(+) | 2 | 353 | 125 | 1 | 7 | no | yes |
| P5 | CIP(+) | 1 | 547 | 179 | 5 | 14 | no | no |
| P6 | CIP(+) | 2 | 254 | 104 | 8 | 9 | no | yes |
| C1 | CIP(-) | 0 | NA | NA | NA | 14 | no | NA |
| C2 | CIP(-) | 0 | NA | NA | NA | 2 | no | NA |
| C3 | CIP(-) | 0 | NA | NA | NA | 17 | no | NA |
| H1 | normal | 0 | NA | NA | NA | NA | NA | NA |
| H2 | normal | 0 | NA | NA | NA | NA | NA | NA |
| H3 | normal | 0 | NA | NA | NA | NA | NA | NA |

CIP(+):P1-P6; CIP(-):C1-C3; Healthy:H1-H3

Supplementary Table 4. Summary of clinical characteristics, CIP onset, and treatment

history of patient groups included in flow cytometry analysis, related to Fig. 1i.

|  |  |  |
| --- | --- | --- |
|  | CIP (n=5) | No CIP (n=4) |
| Age | 57 (55-79) | 65.5 (25-70) |
| M:F | 5:0 | 3:1 |
| Tumor histology |  |  |
| lung adenocarcinoma  | 1 | 1 |
|  lung squamous carcinoma | 1 | 0 |
|  small cell lung cancer | 2 | 2 |
|  bladder cancer | 1 | 0 |
|  hodgkin lymphomas | 0 | 1 |
| Stage |  |  |
| advanced | 4 | 4 |
|  recurrence | 1 | 0 |
| ICI agent |  |  |
|  Pembrolizumab | 5 | 3 |
|  Durvalumab | 0 | 1 |
| Average ICI Treatment Cycles (mean +/- sd) | 6 +/- 3.08 | 15.25 +/- 11.7 |
| Time from first treatment to CIP onset (days) (mean +/- sd) | 178.6 +/- 78.51 | 0 |
| Time from last cycle to CIP onset (days) (mean +/- sd) | 37.6 +/- 22.23 | 0 |
| Time from CIP onset to bronchoscopy (days) (mean +/- sd) | 3.2 +/- 3.19 | 0 |
| CTCAE Grade |  |  |
|  grade1 | 1 | NA |
|  grade2 | 2 | NA |
|  grade3 | 2 |  |
| Response to corticosteroids | 2/5 | NA |
| Received Tocilizumab | 2/5 | NA |
| Additional irAE | 0 | 0 |

Supplementary Table 5. Clinical characteristics of each patient included in flow cytometry analysis, related to Fig. 1i.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient ID | Age | Sex | Tumor histology | Stage | ICI agent | Treatment Cycles | Time from first treatment to CIP onset (days) | Time from most last Treatment to CIP onset (days) | Time from CIP onset to bronchoscopy (days) | CTCAE Grade | Response tocorticosteroids | Received Tocilizumab | Additional irAE |
| P7 | 68 | M | lungsquamous carcinoma | advanced | Pembrolizumab | 2 | 101 | 21 | 1 | 3 | 0 | 1 | 0 |
| P8 | 79 | M | bladder cancer | recurrence | Pembrolizumab | 4 | 98 | 22 | 5 | 2 | 1 | 0 | 0 |
| P9 | 57 | M | small cell lung cancer | advanced | Pembrolizumab | 9 | 229 | 26 | 1 | 2 | 1 | 0 | 0 |
| P10 | 57 | M | small cell lung cancer | advanced | Pembrolizumab | 9 | 276 | 73 | 1 | 1 | NA | 0 | 0 |
| P11 | 55 | M | lung adenocarcinoma | advanced | Pembrolizumab | 6 | 189 | 46 | 8 | 3 | 0 | 1 | 0 |
| C4 | 68 | M | small cell lung cancer | advanced | Pembrolizumab | 4 |  |  |  |  |  |  |  |
| C5 | 63 | M | lung adenocarcinoma | advanced | Pembrolizumab | 19 |  |  |  |  |  |  |  |
| C6 | 70 | M | small cell lung cancer | advanced | Durvalumab | 8 |  |  |  |  |  |  |  |
| C7 | 25 | F | hodgkin lymphomas | advanced | Pembrolizumab | 30 |  |  |  |  |  |  |  |

CIP(+):P7-P11; CIP(-):C4-C7

Supplementary Table 6, myeloid cells signature, related to Fig. 5f.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **M1** | **M2** | **Angiogenesis** | **Phagocytosis** | **Activated DC** | **Migratory DC** |
| IL23  | IL4R  | CCND2  | MRC1  | FSCN1  | GAL3ST  |
| TNF  | CCL4  | CCNE1  | CD163  | BIRC3  | NUDT17  |
| CXCL9  | CCL13  | CD44  | MERTK  | LAMP3  | ITGB8  |
| CXCL10  | CCL20  | CXCR4  | C1QB  | CCL19  | ADCY6  |
| CXCL11  | CCL17  | E2F3  |  | LAD1  | ENO2  |
| CD86  | CCL18  | EDN1  |  | MARCKS  | IL15RA  |
| IL1A  | CCL22  | EZH2  |  | TNFAIP2  | SOCS2  |
| IL1B  | CCL24  | FGF18  |  | CCR7  | IL15  |
| IL6  | LYVE1  | FGFR1  |  | CCL22  | STAP2  |
| CCL5  | VEGFA  | FYN  |  | MARCKSL1  | PHF24  |
| IRF5  | VEGFB  | HEY1  |  | EBI3  | ANKRD33B  |
| IRF1  | VEGFC  | ITGAV  |  | TNFRSF11B  | INSM1  |
| CD40  | VEGFD  | JAG1  |  | NUB1  | ANXA3  |
| IDO1  | EGF  | JAG2  |  | INSM1  | ARHGAP28  |
| KYNU  | CTSA  | MMP9  |  | RAB9A  | RNF115  |
| CCR7  | CTSB  | NOTCH1  |  | LY75  | ADORA2A  |
|  | CTSC  | PDGFA  |  | SIAH2  | EXTL1  |
|  | CTSD  | PTK2  |  | POGLUT1  | SPSB  |
|  | TGFB1  | SPP1  |  | KDM2B  | SLC22A23  |
|  | TGFB2  | STC1  |  | MGLL  | RABGAP1  |
|  | TGFB3  | TNFAIP6  |  | TXN  | GYG1  |
|  | MMP14  | TYMP  |  | MLLT6  | DAP  |
|  | MMP19  | VAV2  |  | KIF2A  | OGFR  |
|  | MMP9  | VCAN  |  | GRSF1  | GYG2  |
|  | CLEC7A  | VEGFA  |  | FAM49A  | CCSER2  |
|  | WNT7B  |  |  | PLEKHG1  | TMEM123  |
|  | FASL  |  |  | SOCS2  | NET1  |
|  | TNFSF12  |  |  | RFTN1  | GPR52  |
|  | TNFSF8  |  |  | AC009812.4  | SLCO5A1  |
|  | CD276  |  |  | BMP2K  | FAH  |
|  | VTCN1  |  |  | NAV1  | CLU  |
|  | MSR1  |  |  | IL7R  | PCGF5  |
|  | FN1  |  |  | ID2  | SAMSN1  |
|  | IRF4  |  |  | CCL17  | CDKN2B  |
|  |  |  |  | PPP1R9B  | BMP2K  |
|  |  |  |  | NRP2  | ZC2HC1A  |
|  |  |  |  | TUBB6  | SERINC5  |
|  |  |  |  | ARNTL2  | HIVEP1  |
|  |  |  |  | UVRAG  | CNR1  |
|  |  |  |  | TXNDC11  | CNR2  |
|  |  |  |  | MREG  |  |
|  |  |  |  | BTG1  |  |
|  |  |  |  | NDE1  |  |
|  |  |  |  | SPG11  |  |
|  |  |  |  | IL32  |  |
|  |  |  |  | ERICH1  |  |
|  |  |  |  | TBC1D4  |  |
|  |  |  |  | NFKB1  |  |
|  |  |  |  | GCSAM  |  |
|  |  |  |  | BZW1  |  |

Supplementary Table 7, Cytokine assay for examination of BALF in CIP(+) and CIP(-) samples, related to Supplementary Fig. 3d and Supplementary Fig. 3e.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | CCL21 | CXCL13 | CCL27 | CXCL5 | CCL11 | CCL24 | CCL26 | CX3CL1 | CXCL6 | GM\_CSF |
| CIP(+)1 | 800.88 | 1.44 | 4.68 | 1262.48 | 8.43 | 25.97 | 18.03 | 35.18 | 747.36 | 2.64 |
| CIP(+)2 | 6684.63 | 139.82 | 8.99 | 953.44 | 10.23 | 23.8 | 23.67 | 27.7 | 869.75 | 4.67 |
| CIP(+)3 | 572.62 | 128.72 | 2.28 | 595.7 | 6.61 | 14.26 | 16.76 | 29.45 | 656.41 | 1.71 |
| CIP(+)4 | 2543.37 | 140.01 | 3.88 | 700.16 | 8.2 | 19.73 | 12.63 | 23.12 | 663.36 | 1.16 |
| CIP(+)5 | 15631.33 | 56.48 | 20.5 | 1130.46 | 12.35 | 158.36 | 31.32 | 76.82 | 2969.68 | 6.18 |
| CIP(+)6 | 1106.57 | 25.98 | 4.94 | 1281 | 5.7 | 28.14 | 13.65 | 45.46 | 561.03 | 3.32 |
| CIP(+)7 | 511.49 | 73.81 | 3.62 | 209.67 | 2.73 | 7.72 | 6.04 | 6.35 | 68.4 | 2.5 |
| CIP(+)8 | 29060.76 | 235.74 | 11.19 | 997.57 | 18.62 | 6.66 | 29.5 | 57.88 | 588.79 | 4.48 |
| CIP(-)1 | 919.45 | 0.82 | 2.55 | 355.88 | 4.01 | 5.42 | 3.55 | 20.61 | 646.7 | 1.16 |
| CIP(-)2 | 336.01 | 1.13 | 2.82 | 288.55 | 3.71 | 9.34 | 5.31 | 14.22 | 293.34 | 2 |
| CIP(-)3 | 495.57 | 9.59 | 4.81 | 339.44 | 3.39 | 12.64 | 5.85 | 18.43 | 481.63 | 0.64 |
| CIP(-)4 | 1268.33 | 1.75 | 4.41 | 595.7 | 5.7 | 8.33 | 8.29 | 23.18 | 432.24 | 2 |
| CIP(-)5 | 420.04 | 0.34 | 2.01 | 445.19 | 3.07 | 3.33 | 4.24 | 10.42 | 367.07 | 1.47 |
|  |  |  |  |  |  |  |  |  |  |  |
|  | CXCL1 | CXCL2 | CCL1 | IFN\_γ | IL\_1β | IL\_2 | IL\_4 | IL\_6 | CXCL8 | IL\_10 |
| CIP(+)1 | 2826.74 | 57.2 | 21.3 | 2.4 | 3.56 | 1.66 | 5.74 | 8.64 | 730.86 | 5.72 |
| CIP(+)2 | 2027.84 | 97.18 | 34.35 | 14.62 | 4.18 | 2.85 | 7.5 | 764.26 | 134.64 | 3.96 |
| CIP(+)3 | 2375.3 | 20.54 | 28.8 | 2.62 | 0.86 | 1.02 | 5.13 | 21 | 75.2 | 1.9 |
| CIP(+)4 | 1327.77 | 45.85 | 28.56 | 4.43 | 1.53 | 1.44 | 5.57 | 21.93 | 52.86 | 0.93 |
| CIP(+)5 | 6019.77 | 81.7 | 34.03 | 11.17 | 3.52 | 3.84 | 13.3 | 31.48 | 570.18 | 8.1 |
| CIP(+)6 | 2919.2 | 22.02 | 20.13 | 7.8 | 4.91 | 1.77 | 4.86 | 6.21 | 902.25 | 6.72 |
| CIP(+)7 | 45.98 | 15.67 | 14.82 | 2.22 | 0.37 | 0.38 | 2.05 | 5.34 | 38.53 | 1.38 |
| CIP(+)8 | 3326.57 | 58.26 | 34.35 | 26.96 | 3.11 | 2.52 | 7.34 | 9.54 | 411.34 | 4.78 |
| CIP(-)1 | 2603.46 | 12.9 | 10.38 | 0.99 | 0.57 | 0.49 | 2.05 | 2.09 | 62.75 | 1.81 |
| CIP(-)2 | 1805.1 | 11.89 | 11.55 | 0.99 | 0.96 | 0.18 | 2.32 | 0.91 | 83.38 | 2.39 |
| CIP(-)3 | 960.15 | 10.84 | 11.55 | 1.73 | 0.62 | 0.38 | 2.93 | 1.67 | 34.6 | 0.54 |
| CIP(-)4 | 2468.45 | 35.79 | 15.73 | 3.68 | 1.55 | 1.02 | 3.27 | 5.12 | 115.06 | 2.19 |
| CIP(-)5 | 3524.4 | 12.9 | 9.1 | 0.57 | 0.74 | 0.18 | 2.05 | 1.21 | 104.41 | 2.68 |
|  |  |  |  |  |  |  |  |  |  |  |
|  | IL\_16 | CXCL10 | CXCL11 | CCL2 | CCL8 | CCL7 | CCL13 | CCL22 | MIF | CXCL9 |
| CIP(+)1 | 200.15 | 210.18 | 3.52 | 17.26 | 1.18 | 111.37 | 30.29 | 5.06 | 21740.73 | 51.69 |
| CIP(+)2 | 65.42 | 3753.94 | 31.75 | 153.39 | 63.72 | 251.79 | 62.32 | 35.09 | 6349.72 | 438.09 |
| CIP(+)3 | 82.01 | 1699.26 | 24.11 | 43.77 | 52.22 | 156.14 | 17.78 | 14.48 | 5960.37 | 160.21 |
| CIP(+)4 | 30.04 | 1060.3 | 8.41 | 32.16 | 4 | 115.84 | 31.71 | 6.54 | 4584.11 | 204.64 |
| CIP(+)5 | 273.1 | 364.76 | 2.38 | 158.79 | 9.69 | 191.95 | 69.84 | 121.46 | 18045.38 | 197.47 |
| CIP(+)6 | 355.85 | 586.87 | 11.29 | 188.28 | 17.02 | 56.57 | 31.03 | 11.81 | 37103.86 | 146.83 |
| CIP(+)7 | 63.77 | 58.29 | 0.61 | 14.17 | 2.47 | 28.2 | 2.51 | 4.86 | 8323.64 | 28 |
| CIP(+)8 | 257.93 | 23713.3 | 227.23 | 211.21 | 106.83 | 328.65 | 46.02 | 19.88 | 13251.76 | 885.96 |
| CIP(-)1 | 168.98 | 81.27 | 2.76 | 14.61 | 1.16 | 26.06 | 10.68 | 2.77 | 21397.44 | 52.2 |
| CIP(-)2 | 301.34 | 27.15 | 0.49 | 31.44 | 1.25 | 12.49 | 12.33 | 8.45 | 28440.6 | 11.53 |
| CIP(-)3 | 77.36 | 246.14 | 1.74 | 21.9 | 1.95 | 26.06 | 16.96 | 5.44 | 6496.79 | 25.01 |
| CIP(-)4 | 81.7 | 77.99 | 0.93 | 83.71 | 2.52 | 46.72 | 21.3 | 11.03 | 9533.43 | 100.07 |
| CIP(-)5 | 139.41 | 86.15 | 2.58 | 10.53 | 1.76 | 12.49 | 23.14 | 3.65 | 20790.41 | 35.38 |
|  |  |  |  |  |  |  |  |  |  |  |
|  | CCL3 | CCL15 | CCL20 | CCL19 | CCL23 | CXCL16 | CXCL12 | CCL17 | CCL25 | TNFa |
| CIP(+)1 | 10.23 | 629.99 | 16.98 | 374.43 | 30.98 | 95.79 | 144.29 | 5.63 | 601.78 | 0.95 |
| CIP(+)2 | 11.9 | 325.87 | 9.23 | 444.91 | 430.56 | 102.22 | 270.65 | 7.12 | 399.59 | 7.21 |
| CIP(+)3 | 4.55 | 210.71 | 8.12 | 248.51 | 26.01 | 30.97 | 220.88 | 3.4 | 259.46 | 3.33 |
| CIP(+)4 | 2.42 | 292.39 | 3.05 | 234.94 | 130.11 | 103.43 | 113.91 | 2.21 | 259.46 | 3.39 |
| CIP(+)5 | 18.64 | 2568.48 | 47 | 331.35 | 10.44 | 248.78 | 327.26 | 16.42 | 837.14 | 5.63 |
| CIP(+)6 | 9.02 | 408.95 | 6.85 | 226.85 | 12.2 | 272.02 | 122.38 | 7.49 | 645.54 | 2.27 |
| CIP(+)7 | 3.79 | 204.62 | 3 | 110.35 | 7.45 | 105.69 | 39.26 | 1.79 | 140.63 | 0.7 |
| CIP(+)8 | 11.66 | 802.19 | 50.26 | 611.58 | 14.55 | 113.32 | 454.52 | 5.4 | 518.32 | 9.83 |
| CIP(-)1 | 2.01 | 297.61 | 1.75 | 113.25 | 20.59 | 459.12 | 34.48 | 4.07 | 293.57 | 0.21 |
| CIP(-)2 | 1.97 | 144.21 | 0.22 | 65.97 | 9.72 | 604.92 | 24.22 | 7.12 | 357.08 | 0.28 |
| CIP(-)3 | 1.79 | 290.87 | 1.78 | 123.97 | 20.49 | 316.73 | 52.79 | 3.75 | 178.21 | 0.21 |
| CIP(-)4 | 3.37 | 805.95 | 4.33 | 149.61 | 1.26 | 448.76 | 76.04 | 4.37 | 262.71 | 0.95 |
| CIP(-)5 | 1.94 | 217.81 | 1.93 | 69.22 | 8.73 | 150.69 | 26.24 | 2.21 | 329.37 | 0.46 |