**Supplementary Table S1. Patient characteristics by cohort**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Dose Level** | **Age**a | **Baseline PSA**b  **(ng/ml)** | **LDH**c  **(U/L)** | **EGOG**  **(n)** | **Gleason score**  **(n)** |
| 1  (0.5 mg/kg x 4) | 76  (69 – 77) | 20.80  (20.10 - 35.90) | 188  (151 – 242) | 0 (3)  1 (0) | ≤6 (1)  7 (1)  ≥8 (1) |
| 2  (0.5 mg/kg x 3,  1.5 mg/kg x 1) | 69  (47 - 75) | 35.30  (6.72 – 262.20) | 185  (136 – 356) | 0 (6)  1 (1) | ≤6 (3)  7 (2)  ≥8 (2) |
| 3  (1.5 mg/kg x 4) | 72  (61 – 82) | 45.70  (12.10 – 435.10) | 214  (146 – 234) | 0 (3)  1 (2) | ≤6 (0)  7 (0)  ≥8 (5) |
| 4  (1.5 mg/kg x 3,  3 mg/kg x 1) | 73  (71 – 78) | 36.90  (14.62 – 128.70) | 157  (139 – 165) | 0 (3)  1 (0) | ≤6 (1)  7 (2)  ≥8 (0) |
| 5  (3 mg/kg x 4) | 61.5  (51 – 82) | 31.21  (12.50 – 68.00) | 201  (140 – 381) | 0 (5)  1 (1) | ≤6 (0)  7 (3)  ≥8 (3) |
| 6  (5 mg/kg x 4) | 73  (60 – 77) | 43.75  (12.44 – 359.40) | 167.5  (138 – 425) | 0 (4)  1 (2) | ≤6 (1)  7 (0)  ≥8 (5) |
| 7  (10 mg/kg x 4) | 70.5  (65 – 82) | 64.74  (15.60 – 321.10) | 231  (156 – 557) | 0 (3)  1 (3) | ≤6 (0)  7 (3)  ≥8 (1)  NA (2) |
| 5A  (3 mg/kg x 4) | 72  (60 – 79) | 133.90  (7.20 – 366.60) | 162  (143 – 297) | 0 (4)  1 (2) | ≤6 (2)  7 (1)  ≥8 (3) |
| Cumulative | 70.5  (47 – 82) | 37.45  (6.72 – 435.10) | 172  (136 – 557) | 0 (31)  1 (11) | ≤6 (8)  7 (12)  ≥8 (20)  NA (2) |

**a,b,c**, Patients’ characteristics by cohort are presented as median with range in brackets (); ECOG, Eastern Cooperative Oncology group; LDH, lactate dehydrogenase; n, numbers; U/L, Units per liter.

**Supplementary Table S2. Treatment-related toxicity**

|  |  |  |
| --- | --- | --- |
| **Dose Level** | **All adverse events**a | **Dose-Limiting Toxicities** |
| 1 | 1/3  grade 1: nausea (1) | 0/3 |
| 2 | 1/7  grade 3: CVA (1) | 1/7  grade 3: CVA |
| 3 | 2/5  grade 3: fatigue (1), **rash (1)** | 1/5  grade 3: **rash** requiring steroids |
| 4 | 0/3 | 0/3 |
| 5 | 4/6  grade 2: muscle spasms (1)  grade 3: angina (1), **temporal arteritis (1)**, **diarrhea (1)**, **panhypopituitarism (1)**  grade 4: CVA (1) | 1/6  grade 4: CVA |
| 6 | 5/6  grade 1: fatigue (1), muscle spasms (1), **diarrhea (2)**  grade 2: wheezing (1), hot flashes (1), fatigue (1), pruritus (2), **rash** (3)  grade 3: fatigue (1), atrial fibrillation (1)  grade 5: PE (1) | 1/6  grade 5: PE |
| 7 | 6/6  grade 1: **diarrhea (1), rash (1)**  grade 2: vomiting (1), dehydration (1), pruritus (3), fatigue (1), erythema (1), **adrenal insufficiency (2)**  grade 3: fatigue (2), **diarrhea (2)**, **rash (3)**  grade 4: elevated troponin (1) | 1/6  grade 3: **rash** requiring steroids |
| 5A**b** | 4/4  grade 1: increased LFT (1)  grade 2: **adrenal insufficiency (1)**, **pneumonitis** (1)  grade 3: atrial fibrillation (1), DVT (1), **diarrhea (1)**  grade 4: fatigue (1) | 1/4  grade 3: **diarrhea** requiring steroids |

**a**, Immune-related adverse events are in bold. The fraction of patients with any adverse event is presented per cohort. The number of patients with each adverse event is listed in brackets (). As a patient might have experienced more than one adverse event, the sum of all adverse events may be greater than the number of patients in each cohort; **b**, Information for adverse events was available only for four out of six patients in this cohort; CVA, cerebrovascular accidents; DVT, deep venous thrombosis; LFT, liver function test; PE, pulmonary embolism.

**Supplementary table S3. Individual clinical response of patients treated with ipilimumab at ≥ 3mg/kg/dose**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient ID** | **Dose level**  **mg/kg** | **Total number of cycle of treatment** | **Months on study** | **Toxicity profile** | **Best PSA decline**a  **%** | **Clinical response** | **Additional therapies off treatment** | **Pre-treatment**  **%**  **PD-1+ CD4 Teff cells** | **Cycle 1**  **%**  **PD-1+ CD4 Teff cells** | **Cycle 2**  **%**  **PD-1+ CD4 Teff cells** | **OS Mths** | |
| 19 | 3 | 4 | 5.5 | Gr3 panhypopituitarism, Gr4 stroke | -95.2 | ≥ 50% PSA decline; Objective tumor response | No | 10.9 |  | 18.3 | 100 | |
| 20 | 3 | 4 | 27.04 | none | -78.5 | ≥ 50% PSA decline | No |  | 7.12 |  | 56 | |
| 21 | 3 | 4 | 4.1 | Gr2 muscle spasms | 103.7 |  | No | 12.8 | 21.7 | 23.9 | 14 | |
| 22 | 3 | 4 | 8.0 | none | -23.7 |  | Yes | 9.23 | 13.4 |  | 56 | |
| 23 | 3 | 4 | 4.5 | Gr3 temporal arteritis | -31.4 |  | Yes | 8.66 |  |  | 60 | |
| 24 | 3 | 4 | 6.7 | Gr3 diarrhea | -97.2 | ≥ 50% PSA decline; Objective tumor response | Yes |  |  | 14.6 | 48 | |
| 25 | 5 | 3 | 2.1 | Gr2 wheezing, Gr3 fatigue, Gr5 PE | -27.2 |  | No | 14.2 | 28.1 |  | 2 | |
| 26 | 5 | 4 | 3.8 | none | 1214.5 |  | No | 26.9 | 37.5 |  | 13 | |
| 27 | 5 | 4 | 3.8 | Gr2 hot flashes, Gr2 fatigue | -5.9 |  | No | 8.91 | 18.8 | 19 | 29 | |
| 28 | 10 | 6 | 7.4 | Gr2 pruritus, Gr2 erythema, Gr3 total body rash | -29.2 |  | Unknown | 5.39 | 11.9 | 8.9 | 44 | |
| 29 | 10 | 4 | 4.0 | Gr2 temporal arteritis | 138 |  | No | 13.6 | 32.4 | 35.4 | 16 | |
| 30 | 5 | 5 | 5.0 | Gr1 diarrhea, Gr1 fatigue, Gr1 muscle spasms,  Gr2 pruritus, Gr2 rash | -7.5 |  | Yes | 17.5 | 25.4 | 33 | 13 | |
| 31 | 5 | 6 | 6.0 | Gr1 diarrhea, Gr2 rash,  Gr2 pruritus | -13.2 |  | No | 14.1 | 22 |  | 86 | |
| 33 | 10 | 2 | 3.0 | Gr2 adrenal insufficiency, Gr2 pruritus,  Gr3 diarrhea, Gr3 fatigue | -50 | ≥ 50% PSA decline | No | 14.5 | 35.4 | 34.5 | 25 |
| 34 | 10 | 3 | 2.7 | Gr2 vomiting, Gr2 dehydration, Gr3 total body rash | 76.4 |  | No | 28.1 | 37.7 | 35.9 | 10 |
| 35 | 10 | 3 | 5.2 | Gr1 diarrhea, Gr2 fatigue, Gr3 rash, Gr2 pruritus | 129.4 |  | Yes | 13.1 | 13.6 | 17.2 | 22 |
| 36 | 10 | 2 | 15.0 | Gr2 adrenal insufficiency, Gr3 fatigue, Gr3 diarrhea, Gr3 rash, Gr4 elevated troponin | -79.8 | ≥ 50% PSA decline | No | 22 | 25.6 | 22.7 | 14 |
| 37 | 3 | 4 | 4.0 | Gr3 DVT | 30.9 |  | No | 28.6 |  |  | 7 |
| 38 | 3 | 4 | 4.1 | Gr1 increased LFT | 330.6 |  | Yes |  | 27.9 | 32.1 | 40 |
| 39 | 3 | 3 | 3.0 | Gr2 pneumonitis, Gr2 adrenal insufficiency, Gr3 diarrhea, Gr4 fatigue | -49 |  | Yes | 11.2 |  | 15.7 | 57 |
| 40 | 3 | 4 | 4.0 | Gr3 atrial fibrillation | -8.2 |  | Yes | 42.3 |  | 51.2 | 15 |
| 41 | 3 | 4 | 4.3 | NA | 293.6 |  | No | 39.1 | 49.5 |  | 22 |
| 42 | 3 | 3 | 2.9 | NA | 663.4 |  | No | 21.9 |  | 29.2 | 18 |

**a**, PSA response refers to decline in PSA levels of ≥50% from baseline; DVT, deep venous thrombosis; Gr, grade; LFT, liver function test; NA, not available; PE, pulmonary embolism.

**Supplementary Table S4. Comparison of absolute counts of T cell subsets between LTS and STS**

|  |  |  |  |
| --- | --- | --- | --- |
| **T cell subsets**a | **LTS**b  **Median**c **(Range**d**)** | **STS**b  **Median**c **(Range**d**)** | **p-value**e |
| **Week 0 (pre-treatment)**  Total CD4 T cells (CD4+CD3+)  CD4 Teff cells (CD4+CD3+FoxP3-)  PD-1+ (PD-1+CD4+CD3+FoxP3-)  Treg (CD4+CD3+FoxP3+CD127-CD25+)  Total CD8 T cells (CD4-CD3+)  PD-1+ (PD-1+CD4-CD3+)  **Week 4 (cycle 1)**  Total CD4 T cells (CD4+CD3+)  CD4 Teff cells (CD4+CD3+FoxP3-)  PD-1+ (PD-1+CD4+CD3+FoxP3-)  Treg (CD4+CD3+FoxP3+CD127-CD25+)  Total CD8 T cells (CD4-CD3+)  PD-1+ (PD-1+CD4-CD3+)  **Week 8 (cycle 2)**  Total CD4 T cells (CD4+CD3+)  CD4 Teff cells (CD4+CD3+FoxP3-)  PD-1+ (PD-1+CD4+CD3+FoxP3-)  Treg (CD4+CD3+FoxP3+CD127-CD25+)  Total CD8 T cells (CD4-CD3+)  PD-1+ (PD-1+CD4-CD3+) | 0.80 (0.48 – 0.99)  0.74 (0.45 – 0.91)  0.07 (0.04 – 0.10)  0.02 (0.02 – 0.05)  0.44 (0.05 – 0.79)  0.05 (0.01 – 0.10)  0.95 (0.72 – 1.54)  0.86 (0.65 – 1.41)  0.17 (0.10 – 0.23)  0.05 (0.04 - 0.07)  0.33 (0.06 – 1.10)  0.04 (0.02 – 0.11)  0.94 (0.41 – 1.71)  0.86 (0.39 – 1.53)  0.22 (0.06 – 0.28)  0.05 (0.02 – 0.10)  0.31 (0.07 – 1.17)  0.06 (0.02 – 0.10) | 0.64 (0.33 – 1.15)  0.61 (0.27 – 1.07)  0.12 (0.07 – 0.30)  0.03 (0.02 – 0.06)  0.22 (0.09 – 1.17)  0.03 (0.02 – 0.37)  0.90 (0.34 – 1.65)  0.83 (0.26 – 1.53)  0.24 (0.13 – 0.39)  0.05 (0.03 – 0.07)  0.30 (0.12 – 0.55)  0.06 (0.05 – 0.15)  0.80 (0.62 – 1.53)  0.73 (0.55 – 1.44)  0.24 (0.16 – 0.40)  0.05 (0.04 – 0.08)  0.31 (0.21 – 1.32)  0.08 (0.04 – 0.41) | 0.841  0.841  **0.003**  0.504  0.304  >0.999  0.745  0.745  0.090  0.348  0.670  0.206  0.845  0.845  0.150  0.752  0.835  0.072 |

**a**, T cell subsets are defined by immune markers as indicated in the table; **b**, Not all 23 patients have PBMC available at all time points. Pre-treatment, n = 8 for LTS and n = 12 for STS; cycle 1, n = 7 for LTS and n = 9 for STS; cycle 2, n = 7 for LTS and n = 8 for STS; **c**, Median absolute counts of T cell subsets; **d**, Values in brackets () are range of each data set; **e**, Mann-Whitney test; **Bold-faced** characters highlight p-value ≤ 0.05; LTS, long-term survivors; STS, short-term survivors.