**Table S1. Demographic and clinical characteristics and outcomes of patients with malignant pleural mesothelioma**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristic | Cyclophosphamide  (n=23) | Cyclophosphamide without Pembrolizumab (n=5) | Cyclophosphamide and Pembrolizumaba  (n=18) | Not treated  (n=28)b |
| Age, years | 70 (53–77) | 70 (55–73) | 70 (53–77) | 70.5 (35–80) |
| Sex |  |  |  |  |
| Male | 20 (87) | 5 (100) | 15 (83) | 18 (64) |
| Female | 3 (13) | 0 (0) | 3 (17) | 10 (36) |
| ECOG status |  |  |  |  |
| 0 | 15 (65) | 4 (80) | 11 (61) | 13 (46) |
| 1 | 8 (35) | 1 (20) | 7 (39) | 12 (43) |
| 2 | 0 (0) | 0 (0) | 0 (0) | 3 (11) |
| Body mass index, kg/m2 | 27.5 (19.9–40.9) | 26.0 (19.9–28.1) | 27.8 (22.6–40.9) | 26.2 (19.1–37.2) |
| Mesothelioma histological subtype |  |  |  |  |
| Epithelioid | 21 (91) | 4 (80) | 17 (94) | 25 (89) |
| Biphasic | 2 (9) | 1 (20) | 1 (6) | 3 (11) |
| Clinical stage |  |  |  |  |
| 2 | 1 (4) | 0 (0) | 1 (6) | 1 (4) |
| 3 to 4 | 16 (70) | 3 (60) | 13 (72) | 20 (71) |
| Relapse | 6 (26) | 2 (40) | 4 (22) | 7 (25) |
| Prior anticancer regimens | 1 (1–13) | 4 (1–13) | 1 (1–6) | 2.5 (0–8) |
| Serum SMRP level, nm | 2.7 (0.9–17.5) | 3.3 (1.2–17.5) | 2.4 (0.9–11.8) | 3.1 (0.5–27)c |
| Tumor mesothelin expression, % | 100 (25–100)d | 100 (99–100)l | 100 (25–100)e | 100 (5–100)f |
| Tumor mutational burden, mt/Mb | 2.6 (0–4.9)g | 2.6 (2.6–3.0)l | 1.9 (0–4.9)h | 1.8 (0–2.6)i |
| PD-L1, % | 0 (0–80)j | 0 (0–30) | 0 (0–80)d | 0 (0–80)k |
| Time diagnosis to T-cell infusion,   months | 6.1 (2.9–73.3) | 18.5 (2.9–73.3) | 5.9 (4–52.1) | — |
| Overall survival (95% CI) since  T-cell infusion, months | 17.7 (13.2–NE) | 6.1 (4.6–NE) | 23.9 (14.7–NE) | — |

Data are median (range) or no. (%), unless otherwise noted. No significant differences between groups were observed. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NE, not estimable; PD-L1, programmed death ligand 1; SMRP, soluble mesothelin-related peptide.

aPatients received at least 3 doses of pembrolizumab and had at least 3 months of follow-up after the third dose of pembrolizumab.

bN=28. Stage 2 to 4 epithelioid or biphasic malignant pleural mesothelioma.

cN=27

dN=21

eN=17

fN=13

gN=20

hN=16

iN=11

jN=22

kN=15

lN=4

**Table S2. Adverse events that occurred in ≥15% of the cohort (N=27)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | | | |
| Adverse Event | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Any | 27 (100) | 27 (100) | 23 (85) | 15 (56) |
| Cardiovascular |  |  |  |  |
| Hypotension | 1 (4) | 3 (11) | 0 | 0 |
| Constitutional |  |  |  |  |
| Chills | 4 (15) | 0 | 0 | 0 |
| Fatigue | 12 (44) | 2 (7) | 0 | 0 |
| Fever | 9 (33) | 5 (19) | 0 | 0 |
| Malaise | 5 (19) | 0 | 0 | 0 |
| Pain | 8 (30) | 5 (19) | 0 | 0 |
| CRS |  |  |  |  |
| Cytokine release syndrome | 5 (19) | 2 (7) | 0 | 0 |
| Gastrointestinal |  |  |  |  |
| Constipation | 2 (7) | 1 (4) | 2 (7) | 0 |
| Nausea | 3 (11) | 1 (4) | 0 | 0 |
| Respiratory |  |  |  |  |
| Cough | 8 (30) | 0 | 0 | 0 |
| Dyspnea | 5 (19) | 2 (7) | 1 (4) | 0 |
| Hematologic |  |  |  |  |
| aPTT prolonged | 8 (30) | 3 (11) | 0 | 0 |
| Anemia | 24 (89) | 15 (56) | 6 (22) | 0 |
| INR increased | 12 (44) | 1 (4) | 0 | 0 |
| Lymphocyte count decreased | 11 (41) | 15 (56) | 16 (59) | 6 (22) |
| Neutrophil count decreased | 0 | 10 (37) | 15 (56) | 11 (52) |
| Platelet count decreased | 13 (48) | 0 | 0 | 0 |
| White blood cell decreased | 19 (70) | 16 (59) | 13 (48) | 9 (33) |
| Lab abnormality |  |  |  |  |
| ALT increased | 9 (33) | 0 | 0 | 0 |
| Alkaline phosphatase increased | 8 (30) | 2 (7) | 0 | 0 |
| AST increased | 7 (26) | 0 | 0 | 0 |
| Blood bilirubin increased | 7 (26) | 3 (11) | 0 | 0 |
| Creatinine increased | 4 (15) | 1 (4) | 0 | 0 |
| Hyperglycemia | 27 (100) | 12 (44) | 3 (11) | 0 |
| Hypoalbuminemia | 25 (93) | 8 (30) | 0 | 0 |
| Hypocalcemia | 23 (85) | 9 (33) | 0 | 0 |
| Hypoglycemia | 4 (15) | 0 | 0 | 0 |
| Hypokalemia | 6 (22) | 0 | 0 | 0 |
| Hypomagnesemia | 21 (78) | 1 (4) | 0 | 0 |
| Hyponatremia | 7 (26) | 0 | 2 (7) | 0 |
| Hypophosphatemia | 0 | 14 (52) | 3 (11) | 0 |

Data are no. (%). Shown are adverse events that occurred in ≥15% of the study population; there were no grade 5 events.; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRS, cytokine release syndrome; INR, international normalized ratio.

**Table S3. All adverse events in all patients treated (N=27)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Adverse event | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Any | 27 (100) | 27 (100) | 23 (85) | 15 (56) |
| Cardiovascular |  |  |  |  |
| Atrial fibrillation | 1 (4) | 0 | 0 | 0 |
| Hypertension | 1 (4) | 2 (7) | 0 | 0 |
| Hypotension | 1 (4) | 3 (11) | 0 | 0 |
| Pericardial effusion | 0 | 1 (4) | 0 | 0 |
| Constitutional |  |  |  |  |
| Anorexia | 1 (4) | 0 | 0 | 0 |
| Chills | 4 (15) | 0 | 0 | 0 |
| Fatigue | 12 (44) | 2 (7) | 0 | 0 |
| Fever | 9 (33) | 5 (19) | 0 | 0 |
| Malaise | 5 (19) | 0 | 0 | 0 |
| Pain | 8 (30) | 5 (19) | 0 | 0 |
| Weight gain | 1 (4) | 0 | 0 | 0 |
| Weight loss | 3 (11) | 0 | 0 | 0 |
| Cytokine release syndrome | 5 (19) | 2 (7) | 0 | 0 |
| Gastrointestinal |  |  |  |  |
| Abdominal distension | 1 (4) | 0 | 0 | 0 |
| Abdominal pain | 1 (4) | 1 (4) | 0 | 0 |
| Colitis | 1 (4) | 0 | 0 | 0 |
| Constipation | 2 (7) | 1 (4) | 2 (7) | 0 |
| Diarrhea | 3 (11) | 0 | 0 | 0 |
| Dysphagia | 0 | 0 | 1 (4) | 0 |
| Nausea | 3 (11) | 1 (4) | 0 | 0 |
| Hematological |  |  |  |  |
| aPTT prolonged | 8 (30) | 3 (11) | 0 | 0 |
| Anemia | 24 (89) | 15 (56) | 6 (22) | 0 |
| Febrile neutropenia | 0 | 0 | 1 (4) | 0 |
| INR increased | 12 (44) | 1 (4) | 0 | 0 |
| Lymphocyte count decreased | 11 (41) | 15 (56) | 16 (59) | 6 (22) |
| Neutropenia | 1 (4) | 0 | 0 | 0 |
| Neutrophil count decreased | 0 | 10 (37) | 15 (56) | 11 (41) |
| Platelet count decreased | 13 (48) | 0 | 0 | 0 |
| Thromboembolic event | 0 | 1 (4) | 1 (4) | 0 |
| White blood cell decreased | 19 (70) | 16 (59) | 13 (48) | 9 (33) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Lab abnormality |  |  |  |  |
| ALT increased | 9 (33) | 0 | 0 | 0 |
| Alkaline phosphatase increased | 8 (30) | 2 (7) | 0 | 0 |
| AST increased | 7 (26) | 0 | 0 | 0 |
| Blood bilirubin increased | 7 (26) | 3 (11) | 0 | 0 |
| Creatinine increased | 4 (15) | 1 (4) | 0 | 0 |
| Hypercalcemia | 1 (4) | 0 | 0 | 0 |
| Hyperglycemia | 27 (100) | 12 (44) | 3 (11) | 0 |
| Hyperkalemia | 3 (11) | 0 | 0 | 0 |
| Hypermagnesemia | 1 (4) | 0 | 0 | 0 |
| Hypernatremia | 1 (4) | 1 (4) | 0 | 0 |
| Hypoalbuminemia | 25 (93) | 8 (30) | 0 | 0 |
| Hypocalcemia | 23 (85) | 9 (33) | 0 | 0 |
| Hypoglycemia | 4 (15) | 0 | 0 | 0 |
| Hypokalemia | 6 (22) | 0 | 0 | 0 |
| Hypomagnesemia | 21 (78) | 1 (4) | 0 | 0 |
| Hyponatremia | 7 (26) | 0 | 2 (7) | 0 |
| Hypophosphatemia | 0 | 14 (52) | 3 (11) | 0 |
| Neurological |  |  |  |  |
| Confusion | 1 (4) | 1 (4) | 0 | 0 |
| Delirium | 1 (4) | 0 | 0 | 0 |
| Headache | 2 (7) | 1 (4) | 0 | 0 |
| Tremor | 1 (4) | 0 | 0 | 0 |
| Other |  |  |  |  |
| Acute kidney injury | 0 | 1 (4) | 0 | 0 |
| Alopecia | 2 (7) | 0 | 0 | 0 |
| Anxiety | 3 (11) | 0 | 0 | 0 |
| Arthritis | 1 (4) | 0 | 0 | 0 |
| Fall | 1 (4) | 0 | 0 | 0 |
| Mucositis oral | 1 (4) | 0 | 0 | 0 |
| Myalgia | 1 (4) | 0 | 0 | 0 |
| Noncardiac chest pain | 3 (11) | 0 | 0 | 0 |
| Respiratory |  |  |  |  |
| Bronchopulmonary hemorrhage | 1 (4) | 0 | 0 | 0 |
| Bronchospasm | 1 (4) | 0 | 0 | 0 |
| Cough | 8 (30) | 0 | 0 | 0 |
| Dyspnea | 5 (19) | 2 (7) | 1 (4) | 0 |
| Epistaxis | 1 (4) | 0 | 0 | 0 |
| Lung infection | 0 | 1 (4) | 0 | 0 |
| Nasal congestion | 0 | 1 (4) | 0 | 0 |
| Pleural effusion | 2 (7) | 1 (4) | 0 | 0 |
| Pleuritic pain | 2 (7) | 0 | 0 | 0 |
| Sinusitis | 0 | 2 (7) | 0 | 0 |
| Skin |  |  |  |  |
| Pruritus | 1 (4) | 0 | 0 | 0 |
| Urticaria | 0 | 1 (4) | 0 | 0 |

Data are no. (%). Shown are all adverse events that occurred in the study population; there were no grade 5 events. ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; INR, international normalized ratio.

**Table S4. Adverse events in the population that received combination immunotherapy (n=18)**

|  |  |  |  |
| --- | --- | --- | --- |
| Adverse Event | Grade 1 | Grade 2 | Grade 3 |
| Any | 15 (83) | 7 (39) | 2 (11) |
| Cardiovascular |  |  |  |
| Hypotension | 1 (6) | 0 | 0 |
| Constitutional |  |  |  |
| Chills | 1 (6) | 0 | 0 |
| Fatigue | 6 (33) | 0 | 0 |
| Fever | 1 (6) | 0 | 0 |
| Pain | 0 | 1 (6) | 0 |
| Hematological |  |  |  |
| Thromboembolic event | 0 | 0 | 1 (6) |
| Lab abnormality |  |  |  |
| Hyponatremia | 0 | 0 | 1 (6) |
| Other |  |  |  |
| Anxiety | 3 (17) | 0 | 0 |
| Arthritis | 2 (11) | 0 | 0 |
| Chest wall pain | 5 (28) | 2 (11) | 0 |
| Dry eye | 1 (6) | 0 | 0 |
| Esophagitis | 0 | 1 (6) | 0 |
| Flank pain | 1 (6) | 0 | 0 |
| Foot pain | 1 (6) | 0 | 0 |
| Hypothyroidism | 0 | 1 (6) | 0 |
| Myalgia | 1 (6) | 0 | 0 |
| Neuralgia | 1 (6) | 0 | 0 |
| Urinary tract infection | 0 | 1 (6) | 0 |
| Respiratory |  |  |  |
| Cough | 4 (22) | 1 (6) | 0 |
| Dyspnea | 1 (6) | 2 (11) | 0 |
| Hoarseness | 2 (11) | 0 | 0 |
| Pleural effusion | 0 | 1 (6) | 0 |
| Sore throat | 1 (6) | 0 | 0 |
| Skin |  |  |  |
| Rash | 1 (6) | 0 | 0 |

Data are no. (%). Shown are clinical adverse events that occurred 6 months after CAR T-cell treatment in the combination immunotherapy study population; there were no grade 4 or grade 5 events reported.

**Table S5.** **Clinical trials investigating immune checkpoint inhibitor agents in patients with malignant pleural mesothelioma**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Year**  **Journal/Meeting**  **NCT#** | **Phase/**  **Agent** | **Trial** | **No.** | **CR** | **PR** | **SD** | **Objective**  **Response** | **Median Duration of Response** | **Disease Control Rate** | **Median Duration of Follow-Up** | **Median PFS** | **Median OS** |
| 2021  *Lancet*  NCT02899299 | III  Nivolumab and Ipilimumab | CheckMate 743 | 303 | — | — | — | — | — | — | 29.7 | — | 18.1 |
| Chemotherapy | 302 | — | — | — | — | — | — | 14.1 |
| 2020  *Ann Oncol.*  NCT02991482 | III  Pembrolizumab | PROMISE-MESO | 142 | 0% | 22% | 23% | 22% | 4.6 | — | 11.8 | 2.5 | 10.7  6 mo: 69% |
|  | Single-agent chemotherapy |  |  | 0% | 6% | 32% | 6% | 11.2 | — |  | 3.4 | 11.7  6 mo: 73% |
| 2019  *JAMA Oncol*  NCT01772004 | IB  Avelumab | JAVELIN | 53 | 2% | 8% | 49% | 9% | 15.2 | 58% | 24.8 | 4.1 | 10.7  6 mo: 69%  12 mo: 44% |
| 2019  *Clin Cancer Res.* | II  Nivolumab | MERIT | 34 | 0% | 29% | 38% | 29%e | 11.1 | 68%f | 16.8 | 6.1g | 17.3h  6 mo: 85%  12 mo: 59% |
| 2019  *Lancet Oncol.*  NCT02716272 | II  Nivolumab | MAPS2 | 125 | — | — | — | 19% | 7.4 | 40%l | 20.1 | 4 | 11.9  12 mo: 49% |
| Nivolumab + Ipilimumab | — | — | — | 28% | 8.3 | 52%l | 5.6 | 15.9  12 mo: 58% |
| 2019  *Lancet Respir.*  NCT03048474 | II  Nivolumab + Ipilimumab | INITIATE | 34 | 0% | 29% | 38% | 38%m | 14.3 | 68%n | 14.3 | 6.2 | — |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 2018  *Lancet Respir.*  NCT02588131 | II  Tremelimumab + durvalumab | NIBIT-MESO | 40 | 0% | — | — | 28%o | 16.1p | 63% | 19.2 | 5.7 | 16.6 |
| 2017  *Lancet Oncol.*  NCT02054806 | IB  Pembrolizumab | KEYNOTE-028 | 25 | 0% | 20% | 52% | 20%a | 12b | — | 18.7 | 5.4c | 18d  6 mo: 84%  12 mo: 63% |
| 2017  *Lancet Oncol.*  NCT01843374 | IIB  Tremelimumab | DETERMINE | 571 | 0% | 4% | 27% | 4.5% | 4.8 | 27.7%i | — | 2.8j | 7.7k |
|  | Placebo |  |  | 0% | 1% | 22% | 1.1% | 5.6 | 21.7%i | — | 2.7j | 7.3k |

CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease. Median duration of response, median duration of follow-up, median PFS, and median OS are presented in months.

aDefined as % of evaluable patients with CR and PR by RECIST v1.1.

bDefined as the time from first evidence of response by RECIST v1.1 to disease progression in patients who achieve PR or CR.

cDefined as the time from allocation to treatment to the first documented disease progression by RECIST v1.1 or death due to any cause, whichever occurred first.

dDefined as the time from allocation to treatment to death due to any cause.

eDefined as the proportion of patients with a best overall response of CR or PR by mRECIST.

fDefined as the % of patients with a best overall response of CR, PR, or SD by mRECIST.

gDefined as the time from first nivolumab dose to progression of disease or death from any cause.

hDefined as the time from first nivolumab dose to death from any cause.

iDefined as the proportion of patients with a best response of CR, PR, or SD for at least 12 weeks from the date of randomization by mRECIST for pleura mesothelioma and RECIST v1.0 for peritoneal mesothelioma.

jDefined as the time from randomization to the first record of disease progression or death from any cause.

kDefined as the time from randomization to death from any cause.

lDefined as the proportion of patients with CR, PR, or SD at 12 weeks after randomization by mRECIST.

mDefined as CR or PR at 6 months by mRECIST.

nDefined as CR, PR, or SD by mRECIST at 12 weeks after the start of nivolumab + ipiliumab treatment.

oDefined by immune-related objective response.

pDefined by immune-related duration of response.

**Table S6. Subsequent next treatments received after CAR T cells**

|  |  |
| --- | --- |
| **Patient #** | **Next Treatment** |
| 1 | Chemotherapy |
| 3 | Chemotherapy |
| 5 | Radiation |
| 7 | Surgery |
| 8 | Chemotherapy |
| 9 | Chemotherapy |
| 12 | Chemotherapy |
| 15 | Radiation |
| 16 | Chemotherapy |
| 17 | Chemotherapy |
| 18 | Radiation |
| 20 | Chemotherapy |
| 22 | Surgery |
| 23 | Chemotherapy |