

**Supplemental Figure 1:** Consolidated Standards of Reporting Trials (CONSORT) diagram demonstrates the flow of 1638 patients who consented for the study. \*Ten patients of the original 161 were not included in the outcome analysis for the following reasons: lost to follow up prior to first assessment (n=4); received concomitant targeted therapy (n=3); only received one dose of immunotherapy then switched to targeted therapy (n=2); received immunotherapy as adjuvant therapy (n=1).



**Supplemental Figure 2:** **Kaplan Meier curves for PFS and OS (for patients treated with anti-PD-1/PD-L1 monotherapy**)**.** Tick marks represent patients at the time of censoring, and P values were calculated using log-rank (Mantel-Cox) test.For a similar analysis by TMB low vs. intermediate to high, see **Figure 2**.

Panel A:PFS for patients with all tumor types excluding melanoma and NSCLC – TMB low vs. intermediate to high [P = <0.0001, HR = 0.33 (95% CI 0.17 to 0.65)].

Panel B: PFS for patients with all tumor types including melanoma and NSCLC – TMB low vs. intermediate to high [P = <0.0001, HR = 0.38 (95% CI 0.24 to 0.61)].

Panel C: PFS for patients with melanoma or NSCLC – TMB low vs. intermediate to high [P = 0.0023, HR = 0.40 (95% CI 10.20 to 0.80)].

Panel D: OS for patients with all tumor types excluding melanoma and NSCLC – TMB low vs. intermediate to high for all tumor types excluding melanoma and NSCLC [P = 0.0782, HR = 0.50 (95% CI 0.23 to 1.13)].

Panel E:OS forpatients with all tumor types including melanoma and NSCLC – TMB low vs. intermediate to high [P = 0.0103, HR = 0.48 (95% CI 0.26 to 0.86)].

Panel F: OS forpatients with melanoma or NSCLC – TMB low vs. intermediate to high [P = 0.0791, HR = 0.46 (95% CI 0.19 to 1.13)].

**Abbreviations:** CI = confidence interval; HR = hazard ratio; NSCLC = non-small cell lung cancer; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 = programmed death receptor-ligand 1; PFS = progression free survival; NSCLC = non-small cell lung cancer; TMB = tumor mutational burden



A

B

C

D

**Supplemental Figure 3: Kaplan Meier curves for patients with melanoma (Panels A and B) and NSCLC (Panels C and D) for treated with anti-PD-1/PD-L1 monotherapy.** Tick marks represent patients at the time of censoring, and P values were calculated using log-rank (Mantel-Cox) test.

Panel A:PFS for patients with melanoma – TMB low to intermediate vs. high [P = 0.7982 (HR = 0.81, 95% CI 0.17-3.95)].

Panel B: PFS for patients with melanoma– TMB low vs. intermediate to high [P = 0.2075 (HR = 0.38, 95% CI 0.04-3.38)].

Panel C: PFS for patients with NSCLC – TMB low to intermediate vs. high [P = 0.0817 (HR = 0.32, 95% CI 0.13-0.81)].

Panel D: PFS for patients with NSCLC – TMB low vs. intermediate to high [P = 0.0549 (HR = 0.53, 95% CI 0.26-1.07)].

**Abbreviations:** CI = confidence interval; HR = hazard ratio; NSCLC = non-small cell lung cancer; PD-1 = programmed death

**Supplemental Table 1:** Number of patients who received more than one line of treatment with immunotherapy\*.

|  |  |  |
| --- | --- | --- |
| Histology | Number of Patients with >1 treatment line with immunotherapy (N = 37) | Range |
| Melanoma | 28 | 2-5 |
| NSCLC | 3 | 2 |
| Head and neck | 3 | 2-3 |
| Cutaneous SCC | 1 | 2 |
| Kidney | 1 | 2 |
| Sarcoma | 1 | 2 |

\*Immunotherapy agents included anti-PD-1/PD-L1, anti-CTLA4, combination anti-CTLA4/anti-PD-1/PD-L1, high dose IL2, and other agents (see **Table 1**).

Abbreviations: NSCLC = non-small cell lung cancer; SCC = squamous cell carcinoma

**Supplemental** **Table 2**: **Patient Demographics by TMB low vs. Intermediate or High (N = 151)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | Number for all patients (%) | TMB low  N = 65 (%) | TMB intermediate to high  N = 86 (%) | P-value1 |
| Age | <60 years | 78 (52%) | 38 (58%) | 40 (47%) | 0.1833 |
| >60 years | 73 (48%) | 27 (42%) | 46 (53%) |
| Sex | Men | 93 (62%) | 37 (57%) | 56 (65%) | 0.3164 |
| Women | 58 (38%) | 28 (43%) | 30 (35%) |
| Ethnicity | Caucasian | 111 (74%) | 42 (65%) | 69 (80%) | **0.0405** |
| Hispanic | 18 (12%) | 12 (18%) | 6 (7%) | **0.0419** |
| Asian | 9 (6%) | 5 (8%) | 4 (5%) | 0.4999 |
| African American | 9 (6%) | 3 (5%) | 6 (7%) | 0.7327 |
| Other | 4 (3%) | 3 (5%) | 1 (1%) | 0.3151 |
| Tumor type | Melanoma | 52 (34%) | 19 (29%) | 33 (38%) | 0.2999 |
| NSCLC2 | 36 (24%) | 20 (31%) | 16 (19%) | 0.0874 |
| Other tumors3 | 63 (42%) | 26 (40%) | 37 (43%) | 0.7412 |
| Type of Immunotherapy | Anti-PD-1/PD-L1 alone | 102 (68%) | 46 (71%) | 56 (65%) | 0.4877 |
| Anti-CTLA4 alone | 15 (10%) | 6 (9%) | 9 (10%) | 1.0000 |
| High dose IL2 | 9 (6%) | 6 (9%) | 3 (3%) | 0.1743 |
| Anti-CTLA4/Anti-PD-1/PD-L1 | 17 (11%) | 5 (8%) | 12 (14%) | 0.3013 |
| Other immunotherapy4 | 8 (5%) | 2 (3%) | 6 (7%) | 0.4670 |
| Response | CR/PR | 45 (30%) | 8 (12%) | 37 (43%) | **0.0001** (OR = 5.38, 95% CI 2.37-11.94)5 |
| SD or PD | 106 (70%) | 57 (88%) | 49 (57%) | **0.0001** (OR = 0.19, 95% CI 0.08-0.42)5 |
| PFS | Median (months) | 4.6 | 2.5 (2.2) | 6.8 | **<0.0001** (HR = 0.45, 95% CI 0.30-0.67)5 |
| OS | Median (months) | 25.4 | 15.7 (1.87) | Not reached (median f/u of 7.5 mos) | **0.0157** (HR = 0.54, 95% CI 0.32-0.91)5 |

\*See **Table 1** for patient demographics by TMB low to. intermediate versus high.

1Calculated using Fisher's exact test and log-rank (Mantel-Cox) test where appropriate.

2Histologies included: adenocarcinoma (N=30) and squamous cell carcinoma (N=6)

3Tumors included: Adrenal carcinoma (n=1), appendix adenocarcinoma (n=1), basal cell carcinoma (n=2), bladder transitional cell carcinoma (n=4), breast cancer (n=3), cervical cancer (n=2), colon adenocarcinoma (n=5), cutaneous squamous cell carcinoma (n=8), hepatocellular carcinoma (n=3), head and neck (n=13), Merkel cell carcinoma (n=2), ovarian carcinoma (n=2), pleural mesothelioma (n=1), prostate cancer (n=1), renal cell carcinoma (n=6), sarcoma (n=3), thyroid cancer (n=3), unknown primary squamous cell carcinoma (n=2), and urethral squamous cell carcinoma (n=1)

4Other immunotherapy: OX40 (n=3), anti-CD73 (n=1), Talimogene laherparepvec (n=2), OX40+anti-PD-L1 (n=1), and IDO+anti-PD-1/PD-L1 (n=1)

5Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB intermediate to high versus TMB low.

**Abbreviations:** CI = confidence interval; CR = complete response; CTLA4 = cytotoxic T-lymphocyte associated protein 4; HR = hazard ratio; IL2 = interleukin 2; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 3**: **Median TMB for patients treated with immunotherapy agents: responders vs. non-responders**

|  |  |  |  |
| --- | --- | --- | --- |
| All tumor types including melanoma and NSCLC (n = 151) | | | |
| Best response | Number of patients | Median TMB (mutations/mb) (Range) | P-value1 |
| SD/PD | 106 | 5 (1-115) | <0.0001 |
| CR/PR | 45 | 19 (1-347) |
| All tumor types excluding melanoma and NSCLC (n = 63) | | | |
| Best response | Number of patients | Median TMB (mutations/mb) (Range) | P-value1 |
| SD/PD | 51 | 6 (1-115) | 0.0001 |
| CR/PR | 12 | 32 (1-347) |
| Patients with melanoma and NSCLC (n = 88) | | | |
| Best response | Number of patients | Median TMB (mutations/mb) (Range) | P-value1 |
| SD/PD | 55 | 5 (1-92) | 0.0003 |
| CR/PR | 33 | 16 (1-133) |

1Calculated using unpaired Student’s t-test

Abbreviations: CR = complete response; mb = megabase; NSCLC = non-small cell lung cancer; PR = partial response; PD = progressive disease; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 4: Univariate and multivariate analysis of factors affecting outcome for all patients treated with immunotherapy agents (TMB low vs. intermediate or high) (N = 151)\***

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Group  (N) | PR/CR N (%) | OR (95% CI)1 | P–value univariate (PR/CR)2 | P-value multivariate (PR/CR) | Median  PFS  (mos)3 | HR  (95% CI)  (PFS)1 | P-value univariate (PFS)4 | P-value multivariate (PFS) | Median OS  (mos)3 | HR  (95% CI)  (OS)1 | P-value univariate (OS)4 | P-value multivariate (OS) |
| Age | ≤60 years  (N = 78) | 20 (26%) | 0.66 (0.32 -1.33) | 0.2873 |  | 4.0 | 1.12 (0.77-1.63) | 0.5396 |  | 28.4 | 1.03 (0.61-1.72) | 0.9165 |  |
| >60 years  (N = 73) | 25 (34%) | 1.51 (0.75-3.14) | 5.7 | 0.89 (0.61-1.29) | 25.4 | 0.97 (0.58-1.63) |
| Gender | Men  (N = 93) | 33 (36%) | 2.11 (0.97-4.57) | **0.0675** | 0.235 | 5.8 | 0.70 (0.47-1.03) | **0.0572** | 0.362 | 28.4 | 0.88 ().51-1.50) | 0.6204 |  |
| Women  (N = 58) | 12 (21%) | 0.47 (0.22-1.03) | 3.6 | 1.44 (0.97-2.12) | 16.3 | 1.14 (0.67-1.95) |  |
| Ethnicity | Caucasian  (N = 111) | 38 (34%) | 2.45 (0.99-6.29) | **0.0685** | 0.604 | 5.9 | 0.58 (0.36-0.92) | **0.0066** | 0.983 | 28.4 | 0.65 (0.35-1.20) | 0.1192 |  |
| Hispanic  (N = 18) | 3 (17%) | 0.43 (0.13-1.57) | 0.2745 |  | 2.6 | 1.38 (0.73-2.61) | 0.2543 |  | 15.6 | 1.46 (0.64-3.30) | 0.2927 |  |
| Asian  (N = 9) | 1 (11%) | 0.28 (0.02-1.94) | 0.2808 |  | 2.0 | 2.61 (0.86-7.90) | **0.0063** | 0.083 | Not reached (median f/u 3.4 mos) | 1.84 (0.49-7.01) | 0.2265 |  |
| African American  (N = 9) | 3 (33%) | 1.19 (0.31-4.45) | 1.0000 |  | 3.9 | 1.30 (0.55-3.07) | 0.5002 |  | Not reached (median f/u 6.5 mos) | 1.26 (0.35-4.60) | 0.6916 |  |
| Other  (N = 4) | 0 (9%) | 0 (0-2.40) | 0.3181 |  | 4.1 | 1.54 (0.45-5.23) | 0.3902 |  | 38.3 | 1.02 (0.25-4.27) | 0.9730 |  |
| Tumor Type | Melanoma  (N = 52) | 26 (50%) | 3.68 (1.71-7.82) | **0.0007** | 0.562 | 9.3 | 0.36 (0.25-0.51) | **<0.0001** | **0.035** | Not reached (median f/u of 15.6 mos) | 0.26 (0.16-0.43) | **<0.0001** | **0.008** |
| NSCLC  (N = 36) | 7 (19%) | 0.49 (0.19-1.23) | 0.1460 |  | 2.8 | 2.00 (1.21-3.27) | **0.0007** | 0.992 | 8.0 | 1.90 (0.97-3.72) | **0.0213** | 0.928 |
| Other tumors5  (N = 63) | 12 (19%) | 0.39 (0.18-5.51) | **0.0187** | 0.301 | 2.9 | 1.67 (1.12-2.50) | **0.0056** | 0.992 | 11.2 | 2.13 (1.23-3.69) | **0.0022** | 0.928 |
| TMB | Low  (N = 65) | 8 (12%) | 0.19 (0.08-0.42) | **0.0001** | **0.001** | 2.5 | 2.21 (1.49-3.29) | **<0.0001** | **<0.001** | 15.7 | 1.87 (1.10-3.16) | **0.0157** | **0.033** |
| Intermediate to high  (N = 86) | 37 (43%) | 5.38 (2.37-11.94) | 6.8 | 0.45 (0.30-0.67) | Not reached (median f/u of 7.5 mos) | 0.54 (0.32-0.91) |
| Type of immunotherapy | Anti-PD-1/PD-L1 monotherapy  (N = 102) | 21 (21%) | 0.27 (0.13-0.58) | **0.0006** | 0.743 | 3.3 | 2.41 (1.65-3.50) | **<0.0001** | 0.588 | 15.7 | 2.74 (1.63-4.59) | **0.0005** | 0.988 |
| Anti-CTLA4 alone  (N = 15) | 2 (13%) | 0.33 (0.07-1.40) | 0.2329 |  | 4.7 | 1.08 (0.58-2.01) | 0.7957 |  | 28.4 | 0.87 (0.39-1.95) | 0.7529 |  |
| High dose IL2  (N = 9) | 5 (56%) | 3.19 (0.88-10.72) | 0.1270 |  | 37.0 | 0.40 (0.23-0.71) | **0.0146** | 0.070 | Not reached (median f/u of 34.6 mos) | 0.37 (0.17-0.80) | **0.0614** | 0.221 |
| Anti-CTLA4/Anti-PD-1/PD-L1  (N = 17) | 13 (77%) | 10.36 (3.05-30.18) | **<0.0001** | **0.004** | Not reached (median f/u 9.2 mos) | 0.27 (0.16-0.44) | **0.0006** | **0.024** | Not reached (median f/u of 16.3 mos) | 0.20 (0.10-0.40) | **0.0107** | 0.257 |
| Other immunotherapy6  (N = 8) | 4 (50%) | 2.49 (0.69-8.82) | 0.2392 |  | 8.9 | 0.77 (0.32-1.87) | 0.6044 |  | Not reached (median f/u of 5.5 mos) | 0.81 (0.23-2.92) | 0.7694 |  |

\*All univariate P values of <0.1 were included in the multivariate analysis. For a similar analysis by TMB low to intermediate vs. high, see **Table 2**.

1Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death.

2Calculated using Fisher's exact test

3All medians for PFS and OS calculated by Kaplan Meier

4Calculated using log-rank (Mantel-Cox) test

5Other tumors: Adrenal carcinoma (n=1), appendix adenocarcinoma (n=1), basal cell carcinoma (n=2), bladder transitional cell carcinoma (n=4), breast cancer (n=3), cervical cancer (n=2), colon adenocarcinoma (n=5), cutaneous squamous cell carcinoma (n=8), hepatocellular carcinoma (n=3), head and neck (n=13), Merkel cell carcinoma (n=2), ovarian carcinoma (n=2), pleural mesothelioma (n=1), prostate cancer (n=1), renal cell carcinoma (n=6), sarcoma (n=3), thyroid cancer (n=3), unknown primary squamous cell carcinoma (n=2), and urethral squamous cell carcinoma (n=1)

6Other immunotherapy: OX40 (n=3), anti-CD73 (n=1), Talimogene laherparepvec (n=2), OX40+anti-PD-L1 (n=1), and IDO+anti-PD-1/PD-L1 (n=1)

**Abbreviations**: CI = confidence interval; CR = complete response; CTLA4 = cytotoxic T-lymphocyte associated protein 4; HR = hazard ratio; IL2 = interleukin 2; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; TMB = tumor mutational burden

**Supplemental** **Table 5: Univariate and multivariate analysis of factors affecting outcome for patients with all tumor types excluding melanoma and NSCLC treated with immunotherapy agents (TMB low vs. intermediate or high)(N = 63)\***

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Group  (N) | PR/CR N (%) | OR (95% CI)1 | P–value univariate (PR/CR)2 | P-value multivariate (PR/CR) | Median  PFS  (mos)3 | HR  (95% CI)  (PFS)1 | P-value univariate (PFS)4 | p-value multivariate (PFS) | Median OS  (mos)3 | HR  (95% CI)  (OS)1 | P-value univariate (OS)4 | P-value multivariate (OS) |
| Age | ≤60 years (N = 33) | 4 (12%) | 0.38 (0.12-1.35) | 0.2017 |  | 3.4 | 1.44 (0.82-2.54) | 0.2033 |  | 11.1 | 1.25 (0.60-2.65) | 0.5449 |  |
| >60 years (N = 30) | 8 (27%) | 2.64 (0.74-8.55) | 2.7 | 0.69 (0.39-1.22) | 11.2 | 0.80 (0.39-1.66) |
| Gender | Men (N = 41) | 11 (27%) | 7.7 (1.11-86.57) | **0.0433** | 0.219 | 2.9 | 0.70 (0.38-1.29) | 0.2128 |  | 11.1 | 1.23 (0.56-2.69) | 0.6085 |  |
| Women (N = 22) | 1 (5%) | 0.13 (0.01-0.90) | 3.5 | 1.43 (0.78-2.63) | Not reached (median f/u of 5.4 mos) | 0.81 (0.37-1.77) |
| Ethnicity | Caucasian (N = 40) | 10 (25%) | 3.50 (0.77-17.00) | 0.1830 | 0.254 | 3.6 | 0.64 (0.35-1.18) | 0.1179 | 0.613 | 11.2 | 0.63 (0.29-1.38) | 0.2047 |  |
| Hispanic (N = 7) | 0 (0%) | 0 (0-2.58) | 0.3292 |  | 1.9 | 1.38 (0.52-3.65) | 0.4515 |  | 3.1 | 2.82 (0.76-10.44) | **0.0168** | **0.038** |
| Asian (N = 7) | 1 (14%) | 0.68 (0.05-5.40) | 1.0000 |  | 2.0 | 1.62 (0.57-4.56) | 0.2597 |  | Not reached (median f/u of 3.7 mos) | 1.15 (0.32-4.07) | 0.8179 |  |
| African American (N = 6) | 1 (17%) | 0.70 (0.06-5.51) | 1.0000 |  | 5.0 | 1.047 (0.41-2.69) | 0.9212 |  | Not reached (median f/u of 6.0 mos) | 0.80 (0.22-2.97) | 0.7625 |  |
| Other (N = 3) | 0 (0%) | 0 (0-4.99) | 1.0000 |  | 3.6 | 1.66 (0.38-7.21) | 0.3849 |  | Not reached (median f/u of 8.6 mos) | 0.72 (0.13-4.05) | 0.7491 |  |
| TMB | Low (N = 26) | 1 (4%) | 0.095 (0.01-0.65) | **0.0105** | **0.006** | 2.0 | 2.95 (1.56-5.58) | **<0.0001** | **<0.001** | 6.2 | 1.69 (0.81-3.54) | 0.1425 | 0.230 |
| Intermediate to high (N = 37) | 11 (30%) | 10.58 (1.53-118.10) | 6.2 | 0.34 (0.18-0.64) | 21.0 | 0.59 (0.28-1.24) |
| Type of immunotherapy | Anti-PD-1/PD-L1 monotherapy (N = 55) | 9 (16%) | 0.33 (0.06-1.43) | 0.1700 | 0.120 | 2.9 | 0.97 (0.38-2.48) | 0.9477 |  | 11.2 | 1.23 (0.46-3.28) | 0.6633 |  |
| Other immunotherapy5 (N = 8) | 3 (38%) | 3.07 (0.70-15.99) | 2.6 | 1.03 (0.40-2.63) | 25.4 | 0.81 (0.31-2.17) |

\*All univariate P values of <0.2 were included in the multivariate analysis. For a similar analysis by TMB low vs. intermediate to high, see **Table 3**. Tumors included: Adrenal carcinoma (n=1), appendix adenocarcinoma (n=1), basal cell carcinoma (n=2), bladder transitional cell carcinoma (n=4), breast cancer (n=3), cervical cancer (n=2), colon adenocarcinoma (n=5), cutaneous squamous cell carcinoma (n=8), hepatocellular carcinoma (n=3), head and neck (n=13), Merkel cell carcinoma (n=2), ovarian carcinoma (n=2), pleural mesothelioma (n=1), prostate cancer (n=1), renal cell carcinoma (n=6), sarcoma (n=3), thyroid cancer (n=3), unknown primary squamous cell carcinoma (n=2), and urethral squamous cell carcinoma (n=1)

1Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death.

2Calculated using Fisher's exact test

3All medians for PFS and OS calculated by Kaplan Meier

4Calculated using log-rank (Mantel-Cox) test

5Other immunotherapy: OX40 (n=2), anti-CD73 (n=1), anti-CTLA4 (n=2), OX40+anti-PD-L1 (n=1), anti-CTLA4/anti-PD-1/PD-L1 (n=1), and IDO+anti-PD-1/PD-L1 (n=1)

**Abbreviations**: CI = confidence interval; CR = complete response; CTLA4 = cytotoxic T-lymphocyte associated protein 4; HR = hazard ratio; IL2 = interleukin 2; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; TMB = tumor mutational burden

**Supplemental** **Table 6: Univariate and multivariate analysis of factors affecting outcome for patients with melanoma or NSCLC treated with immunotherapy agents (TMB low or intermediate vs. high)(N = 88)\***

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Group  (N) | PR/CR N (%) | OR (95% CI)1 | P–value univariate (PR/CR)2 | P-value multivariate (PR/CR) | Median  PFS  (mos)3 | HR  (95% CI)  (PFS)1 | P-value univariate (PFS)4 | P-value multivariate (PFS) | Median OS  (mos)3 | HR  (95% CI)  (OS)1 | P-value univariate (OS)4 | P-value multivariate (OS) |
| Age | ≤60 years (N = 45) | 16 (36%) | 0.84 (0.35-3.04) | 0.8261 |  | 5.8 | 0.98 (0.59-1.62) | 0.9265 |  | 34.6 | 0.91 (0.44-1.89) | 0.8015 |  |
| >60 years (N = 43) | 17 (40%) | 1.19 (0.49-2.89) | 7.9 | 1.02 (0.62-1.69) | Not reached (median f/u of 8.4 mos) | 1.10 (0.53-2.28) |
| Gender | Men (N = 52) ) | 22 (42%) | 1.67 (0.67-4.13) | 0.3706 |  | 7.9 | 0.62 (0.36-1.04) | **0.0720** | 0.250 | Not reached (median f/u of 10.7 mos) | 0.57 (0.27-1.21) | 0.1241 |  |
| Women (N = 36) | 11 (31%) | 0.60 (0.24-1.49) | 3.9 | 1.62 (0.96-2.74) | 24.0 | 1.75 (0.83-3.71) |
| Ethnicity | Caucasian (N = 71) | 28 (39%) | 1.56 (0.53-4.34) | 0.5801 |  | 6.8 | 0.49 (0.23-1.04) | **0.0641** | 0.376 | 34.6 | 0.83 (0.32-2.16) | 0.6899 |  |
| Hispanic (N = 11) | 3 (27%) | 0.59 (0.16-2.21) | 0.5256 |  | 3.1 | 1.59 (0.65-3.87) | 0.2109 |  | 15.7 | 0.84 (0.28-2.57) | 0.7731 |  |
| Other (N = 6)5 | 2 (33%) | 0.83 (0.15-3.71) | 1.0000 |  | 2.8 | 1.81 (0.55-5.91) | 0.1957 |  | 38.3 | 2.32 (0.48-11.14) | 0.2916 |  |
| Tumor type | Melanoma (N = 52) | 26 (50%) | 4.14 (1.50-10.31) | **0.0040** | 0.258 | 9.3 | 0.31 (0.17-0.56) | **<0.0001** | 0.063 | Not reached (median f/u of 15.6 mos) | 0.25 (0.11-0.57) | **<0.0001** | 0.078 |
| NSCLC (N = 36) | 7 (19%) | 0.24 (0.01-0.67) | 2.8 | 3.20 (1.79-5.75) | 8.0 | 3.99 (1.75-9.14) |
| TMB | Low to intermediate (N = 67) | 19 (28%) | 0.20 (0.08-0.58) | **0.0037** | **0.018** | 4.2 | 2.97 (1.75-5.04) | **0.0012** | **0.015** | 28.4 | 5.59 (2.51-12.45) | **0.0076** | 0.055 |
| High (N = 21) | 14 (67%) | 5.05 (1.73-13.19) | 15.2 | 0.34 (0.20-0.57) | Not reached (median f/u for 14.0 mos) | 0.18 (0.08-0.40) |
| Type of immunotherapy | Anti-PD-1/PD-L1 alone (N = 47) | 12 (26%) | 0.33 (0.13-0.80) | **0.0161** | 0.633 | 3.5 | 2.67 (1.59-4.47) | **<0.0001** | 0.621 | 16.3 | 3.19 (1.52-6.69) | **0.0016** | 0.879 |
| Anti-CTLA4 alone (N = 13) | 2 (15%) | 0.26 (0.05-1.25) | 0.1193 |  | 5.5 | 1.19 (0.58-2.43) | 0.6201 |  | 28.4 | 0.94 (0.33-2.62) | 0.9011 |  |
| High dose IL2 (N = 9) | 5 (56%) | 2.28 (0.60-7.83) | 0.2865 |  | 36.97 | 0.46 (0.24-0.87) | **0.0432** | 0.059 | Not reached (median f/u of 34.6 mos) | 0.48 (0.19-1.19) | 0.1844 |  |
| Anti-CTLA4/Anti-PD-1/PD-L1 (N = 16) | 12 (75%) | 7.29 (2.18-21.96) | **0.0012** | **0.019** | Not reached (median f/u of 9.3 mos) | 0.33 (0.18-0.59) | **0.0055** | **0.042** | Not reached (median f/u of 16.7 mos) | 0.26 (0.11-0.63) | **0.0468** | 0.356 |
| Other immunotherapy (N = 3)6 | 2 (67%) | 3.48 (0.39-51.27) | 0.5534 |  | 8.9 | 0.47 (0.12-1.85) | 0.4368 |  | Not reached (median f/u of 5.8 mos) | 07 | 0.3620 |  |

\*All univariate P values of <0.1 were included in the multivariate analysis. For a similar analysis by TMB low vs. intermediate to high, see **Supplemental Table 7**.

1Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death.

2Calculated using Fisher's exact test

3All medians for PFS and OS calculated by Kaplan Meier

4Calculated using log-rank (Mantel-Cox) test

5Other ethnicities: African American (n=3), Asian (n=2), and unspecified (n=1)

6Other immunotherapy: OX40 (n=1) and Talimogene laherparepvec (n=2)

795% CI could not be calculated because the HR was 0.

**Abbreviations**: CI = confidence interval; CR = complete response; CTLA4 = cytotoxic T-lymphocyte associated protein 4; HR = hazard ratio; IL2 = interleukin 2; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; TMB = tumor mutational burden

**Supplemental** **Table 7: Univariate and multivariate analysis of factors affecting outcome for patients with melanoma or NSCLC treated with immunotherapy agents (TMB low vs. intermediate or high)(N = 88)\***

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | Group  (N) | PR/CR N (%) | OR (95% CI)1 | P–value univariate (PR/CR)2 | P-value multivariate (PR/CR) | Median  PFS  (mos)3 | HR  (95% CI)  (PFS)1 | P-value univariate (PFS)4 | P-value multivariate (PFS) | Median OS  (mos)3 | HR  (95% CI)  (OS)1 | P-value univariate (OS)4 | P-value multivariate (OS) |
| Age | ≤60 years (N = 45) | 16 (36%) | 0.84 (0.35-3.04) | 0.8261 |  | 5.8 | 0.98 (0.59-1.62) | 0.9265 |  | 34.6 | 0.91 (0.44-1.89) | 0.8015 |  |
| >60 years (N = 43) | 17 (40%) | 1.19 (0.49-2.89) | 7.9 | 1.02 (0.62-1.69) | Not reached (median f/u of 8.4 mos) | 1.10 (0.53-2.28) |
| Gender | Men (N = 52) ) | 22 (42%) | 1.67 (0.67-4.13) | 0.3706 |  | 7.9 | 0.62 (0.36-1.04) | **0.0720** | 0.250 | Not reached (median f/u of 10.7 mos) | 0.57 (0.27-1.21) | 0.1241 |  |
| Women (N = 36) | 11 (31%) | 0.60 (0.24-1.49) | 3.9 | 1.62 (0.96-2.74) | 24.0 | 1.75 (0.83-3.71) |
| Ethnicity | Caucasian (N = 71) | 28 (39%) | 1.56 (0.53-4.34) | 0.5801 |  | 6.8 | 0.49 (0.23-1.04) | **0.0641** | 0.376 | 34.6 | 0.83 (0.32-2.16) | 0.6899 |  |
| Hispanic (N = 11) | 3 (27%) | 0.59 (0.16-2.21) | 0.5256 |  | 3.1 | 1.59 (0.65-3.87) | 0.2109 |  | 15.7 | 0.84 (0.28-2.57) | 0.7731 |  |
| Other (N = 6)5 | 2 (33%) | 0.83 (0.15-3.71) | 1.0000 |  | 2.8 | 1.81 (0.55-5.91) | 0.1957 |  | 38.3 | 2.32 (0.48-11.14) | 0.2916 |  |
| Tumor type | Melanoma (N = 52) | 26 (50%) | 4.14 (1.50-10.31) | **0.0040** | 0.258 | 9.3 | 0.31 (0.17-0.56) | **<0.0001** | 0.063 | Not reached (median f/u of 15.6 mos) | 0.25 (0.11-0.57) | **<0.0001** | 0.071 |
| NSCLC (N = 36) | 7 (19%) | 0.24 (0.01-0.67) | 2.8 | 3.20 (1.79-5.75) | 8.0 | 3.99 (1.75-9.14) |
| TMB | Low (N = 39) | 7 (18%) | 0.19 (0.08-0.54) | **0.0009** | **0.004** | 3.3 | 2.07 (1.22-3.49) | **0.0030** | **0.003** | 24.0 | 1.86 (0.88-3.91) | **0.0889** | 0.256 |
| Intermediate to high (N = 49) | 26 (53%) | 5.17 (1.87-12.82) | 11.9 | 0.48 (0.29-0.81) | Not reached (median f/u of 12.6 mos) | 0.54 (0.26-1.13) |
| Type of immunotherapy | Anti-PD-1/PD-L1 alone (N = 47) | 12 (26%) | 0.33 (0.13-0.80) | **0.0161** | 0.633 | 3.5 | 2.67 (1.59-4.47) | **<0.0001** | 0.621 | 16.3 | 3.19 (1.52-6.69) | **0.0016** | 0.672 |
| Anti-CTLA4 alone (N = 13) | 2 (15%) | 0.26 (0.05-1.25) | 0.1193 |  | 5.5 | 1.19 (0.58-2.43) | 0.6201 |  | 28.4 | 0.94 (0.33-2.62) | 0.9011 |  |
| High dose IL2 (N = 9) | 5 (56%) | 2.28 (0.60-7.83) | 0.2865 |  | 36.97 | 0.46 (0.24-0.87) | **0.0432** | 0.059 | Not reached (median f/u of 34.6 mos) | 0.48 (0.19-1.19) | 0.1844 |  |
| Anti-CTLA4/Anti-PD-1/PD-L1 (N = 16) | 12 (75%) | 7.29 (2.18-21.96) | **0.0012** | **0.019** | Not reached (median f/u of 9.3 mos) | 0.33 (0.18-0.59) | **0.0055** | **0.042** | Not reached (median f/u of 16.7 mos) | 0.26 (0.11-0.63) | **0.0468** | 0.515 |
| Other immunotherapy (N = 3)6 | 2 (67%) | 3.48 (0.39-51.27) | 0.5534 |  | 8.9 | 0.47 (0.12-1.85) | 0.4368 |  | Not reached (median f/u of 5.8 mos) | 0 | 0.3620 |  |

\*All univariate P values of <0.1 were included in the multivariate analysis. For a similar analysis by TMB low vs. intermediate to high, see **Supplemental Table 6**.

1Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death.

2Calculated using Fisher's exact test

3All medians for PFS and OS calculated by Kaplan Meier

4Calculated using log-rank (Mantel-Cox) test

5Other ethnicities: African American (n=3), Asian (n=2), and unspecified (n=1)

6Other immunotherapy: OX40 (n=1) and Talimogene laherparepvec (n=2)

**Abbreviations**: CI = confidence interval; CR = complete response; CTLA4 = cytotoxic T-lymphocyte associated protein 4; HR = hazard ratio; IL2 = interleukin 2; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; TMB = tumor mutational burden**Supplemental Table 8**: **All tumor types including melanoma and NSCLC treated with anti-PD-1/PD-L1 monotherapy – TMB low or intermediate vs. high (N = 102)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 102 | TMB low to intermediate  N = 80 (%) | TMB high  N = 22 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 49 | 42 (53%) | 7 (32%) | 0.0974 |
| >60 years | 53 | 38 (47%) | 15 (68%) |
| Sex | Men | 60 | 43 (54%) | 17 (77%) | 0.0539 |
| Women | 42 | 37 (46%) | 5 (23%) |
| Tumor | Melanoma | 11 | 7 (9%) | 4 (18%) | 0.2454 |
| NSCLC | 36 | 33 (41%) | 3 (14%) | **0.0222** |
| Head and neck squamous | 10 | 9 (11%) | 1 (5%) | 0.6856 |
| Cutaneous squamous cell | 8 | 1 (1%) | 7 (32%) | **<0.0001** |
| Renal cell cancer | 6 | 6 (8%) | 0 (0%) | 0.3359 |
| Colorectal | 3 | 1 (1%) | 2 (9%) | 0.1166 |
| Bladder Transitional Cell | 2 | 1 (1%) | 1 (5%) | 0.3865 |
| Hepatocellular | 3 | 3 (4%) | 0 (0%) | 1.0000 |
| Thyroid cancer | 3 | 3 (4%) | 0 (0%) | 1.0000 |
| Breast cancer | 3 | 3 (4%) | 0 (0%) | 1.0000 |
| Basal cell cancer | 2 | 0 (0%) | 2 (9%) | **0.0448** |
| Ovarian | 2 | 2 (3%) | 0 (0%) | 1.0000 |
| Cervical | 2 | 1 (1%) | 1 (5%) | 0.3865 |
| Merkel cell carcinoma | 2 | 2 (3%) | 0 (0%) | 1.0000 |
| Soft tissue sarcoma | 3 | 3 (4%) | 0 (0%) | 1.0000 |
| Unknown primary | 2 | 1 (1%) | 1 (5%) | 0.3865 |
| Appendicle adenocarcinoma | 1 | 1 (1%) | 0 (0%) | 1.0000 |
| Adrenocortical carcinoma | 1 | 1 (1%) | 0 (0%) | 1.0000 |
| Urethral SCC | 1 | 1 (1%) | 0 (0%) | 1.0000 |
| Pleural mesothelioma | 1 | 1 (1%) | 0 (0%) | 1.0000 |
| TMB | Median (range) per megabase | 6 (1-347) | 5 (1-19) | 53 (20-347) | **<0.0001** |
| Response | CR/PR | 21 | 11 (14%) | 10 (46%) | **0.0025** (OR = 5.23, 95% CI 1.87-14.90)3 |
| SD or PD | 81 | 69 (86%) | 12 (54%) | **0.0025** (OR = 0.19, 95% CI 0.07-0.53)3 |
| PFS2 | Median (months) | 3.3 | 2.2 | 10 | **0.0005** (HR = 0.36, 95% CI 0.23-0.58)3 |
| OS2 | Median (months) | 15.7 | 11.1 | Not reached (median f/u of 8.6 mos) | 0.0557 (HR = 0.44, 95% CI 0.23-0.87)3 |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB high versus TMB low to intermediate.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SCC = squamous cell carcinoma; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 9**: **All tumor types including melanoma and NSCLC treated with anti-PD-1/PD-L1 monotherapy – TMB low vs. intermediate or high (N = 102)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 102 | TMB low  N = 46 (%) | TMB intermediate to high N = 56 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 49 | 24 (52%) | 25 (45%) | 0.5508 |
| >60 years | 53 | 22 (48%) | 31 (55%) |
| Sex | Men | 60 | 26 (57%) | 34 (61%) | 0.6907 |
| Women | 42 | 20 (43%) | 22 (39%) |
| Tumor | Melanoma | 11 | 2 (4%) | 9 (16%) | 0.1055 |
| NSCLC | 36 | 20 (43%) | 16 (29%) | 0.1464 |
| Head and neck squamous | 10 | 5 (11%) | 5 (9%) | 0.7513 |
| Cutaneous squamous cell | 8 | 0 (0%) | 8 (14%) | **0.0077** |
| Renal cell cancer | 6 | 5 (11%) | 1 (2%) | 0.0881 |
| Colorectal | 3 | 0 (0%) | 3 (5%) | 0.2499 |
| Bladder Transitional Cell | 2 | 0 (0%) | 2 (4%) | 0.4999 |
| Hepatocellular | 3 | 2 (4%) | 1 (2%) | 0.5874 |
| Thyroid cancer | 3 | 3 (7%) | 0 (0%) | 0.0884 |
| Breast cancer | 3 | 1 (2%) | 2 (4%) | 1.0000 |
| Basal cell cancer | 2 | 0 (0%) | 2 (4%) | 0.4999 |
| Ovarian | 2 | 1 (2%) | 1 (2%) | 1.0000 |
| Cervical | 2 | 0 (0%) | 2 (4%) | 0.4999 |
| Merkel cell carcinoma | 2 | 2 (4%) | 0 (0%) | 0.2009 |
| Soft tissue sarcoma | 3 | 1 (2%) | 2 (4%) | 1.0000 |
| Unknown primary | 2 | 1 (2%) | 1 (2%) | 1.0000 |
| Appendicle adenocarcinoma | 1 | 1 (2%) | 0 (0%) | 0.4510 |
| Adrenocortical carcinoma | 1 | 1 (2%) | 0 (0%) | 0.4510 |
| Urethral SCC | 1 | 0 (0%) | 1 (2%) | 1.0000 |
| Pleural mesothelioma | 1 | 1 (2%) | 0 (0%) | 0.4510 |
| TMB | Median (range) per megabase | 6 (1-347) | 3 (1-5) | 14 (6-347) | **0.0001** |
| Response | CR/PR | 21 | 2 (4%) | 19 (34%) | **0.0002** (OR = 11.3, 95% CI = 2.82-50.68)3 |
| SD or PD | 81 | 44 (96%) | 37 (66%) | **0.0002** (OR = 0.09, 95% CI 0.02-0.36)3 |
| PFS2 | Median (months) | 3.3 | 2.0 | 6.1 | **<0.0001** (HR = 0.38, 95% CI 0.24-0.61)3 |
| OS2 | Median (months) | 15.7 | 8.0 | 21.0 | **0.0103** (HR = 0.48, 95% CI 0.26-0.86)3 |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB intermediate to high versus TMB low.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SCC = squamous cell carcinoma; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 10:** CR/PR rate depending on TMB cutoff for patients treated with anti-PD-1/PD-L1 monotherapy (N = 102)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| TMB cutoff | CR/PR TMB ≤ cutoff (%) | CR/PR rate TMB > cutoff (%) | P-value1 | OR2 | 95% CI |
| 1 | 1/11 (9%) | 20/91 (22%) | 0.4524 | 2.82 | 0.41-32.03 |
| 2 | 1/13 (8%) | 20/89 (22%) | 0.2937 | 3.478 | 0.54-39.00 |
| 3 | 1/25 (4%) | 20/77 (26%) | 0.0211 | 8.421 | 1.27-91.07 |
| 4 | 1/31 (3%) | 20/71 (28%) | 0.0031 | 11.76 | 1.82-126.30 |
| 5 | 2/46 (4%) | 19/56 (34%) | 0.0002 | 11.3 | 2.82-50.68 |
| 6 | 2/56 (4%) | 19/46 (41%) | <0.0001 | 21.28 | 5.15-95.18 |
| 7 | 3/60 (5%) | 18/42 (43%) | <0.0001 | 14.25 | 3.78-47.77 |
| 8 | 4/63 (6%) | 17/39 (44%) | <0.0001 | 11.4 | 3.42-33.06 |
| 9 | 5/64 (8%) | 16/38 (42%) | <0.0001 | 8.58 | 2.80-22.82 |
| 11 | 6/66 (9%) | 15/36 (42%) | 0.0002 | 7.14 | 2.45-21.20 |
| 12 | 6/69 (9%) | 15/33 (45%) | <0.0001 | 8.75 | 2.92-26.55 |
| 13 | 6/70 (4%) | 15/32 (47%) | <0.0001 | 9.41 | 3.11-28.84 |
| 14 | 8/75 (10%) | 13/27 (35%) | 0.0001 | 7.78 | 2.59-20.69 |
| 15 | 9/76 (12%) | 12/26 (46%) | 0.0005 | 6.38 | 2.13-18.47 |
| 16 | 10/77 (13%) | 11/25 (44%) | 0.0030 | 5.26 | 1.95-14.57 |
| 18 | 11/79 (14%) | 10/23 (43%) | 0.0062 | 4.76 | 1.73-13.15 |
| 19 | 11/80 (14%) | 10/22 (45%) | 0.0025 | 5.23 | 1.87-14.9 |
| 20 | 11/82 (13%) | 10/20 (50%) | 0.0009 | 6.46 | 2.21-20.04 |
| 23 | 11/83 (13%) | 10/19 (53%) | 0.0005 | 7.27 | 2.42-19.88 |
| 26 | 11/84 (13%) | 10/18 (56%) | 0.0003 | 8.30 | 2.67-23.58 |
| 29 | 12/85 (14%) | 9/17 (53%) | 0.0011 | 6.84 | 2.10-19.43 |
| 35 | 12/86 (14%) | 9/16 (56%) | 0.0006 | 7.93 | 2.33-24.8 |
| 36 | 12/87 (14%) | 9/15 (60%) | 0.0003 | 9.38 | 2.61-29.05 |
| 39 | 12/88 (14%) | 9/14 (64%) | 0.0001 | 11.4 | 3.36-36.50 |
| 41 | 13/89 (15%) | 8/13 (62%) | 0.0006 | 9.35 | 2.81-30.32 |
| 50 | 13/90 (14%) | 8/12 (67%) | 0.0003 | 11.85 | 3.24-38.03 |
| 53 | 14/92 (15%) | 7/10 (70%) | 0.0005 | 13.0 | 2.86-48.65 |
| 57 | 15/93 (16%) | 6/9 (67%) | 0.0022 | 10.4 | 2.66-39.85 |
| 67 | 16/94 (17%) | 5/8 (63%) | 0.0088 | 8.13 | 1.79-32.17 |
| 75 | 16/95 (17%) | 5/7 (71%) | 0.0038 | 12.34 | 2.21-63.91 |
| 90 | 16/96 (17%) | 5/6 (83%) | 0.0013 | 25.00 | 2.88-296.7 |
| 104 | 18/98 (18%) | 3/4 (75%) | 0.0268 | 13.33 | 1.83-174.6 |
| 115 | 18/99 (18%) | 3/3 (100%) | 0.0077 | Infinity | 3.57-infinity |
| 131 | 19/100 (19%) | 2/2 (100%) | 0.0408 | Infinity | 1.83-infinity |
| 182 | 20/101 (20%) | 1/1 (100%) | 0.1721 | Infinity | 0.53-infinity |
| 347 | 21/102 (21%) | 0/102 (0%) | 1.0000 | N/A | N/A |

1Calculated using Fisher's exact test

2Odds Ratio (OR) >1.0 implies higher chance of response. The OR was calculated by comparing RR above and below the cut-off for each value. See **Figure** **3** for graphic.

**Abbreviations:** CI = confidence interval; CR = complete response; NR = not reached; OR = odds ratio; PR = partial response; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; TMB = tumor mutational burden

**Supplemental Table 11:** PFS and OS depending on TMB cutoff for patients treated with anti-PD-1/PD-L1 monotherapy (N = 102)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TMB cutoff | Median PFS (months) ≤ cutoff 1 | Median PFS  (months) >cutoff 1 | P-value2 | HR3 | 95% CI | Median OS (months) ≤ cutoff 1 | Median OS  (months) >cutoff 1 | P-value2 | HR3 | 95% CI |
| 1 | 3.1 | 3.5 | 0.6673 | 0.86 | 0.41-1.80 | 8.0 | 16.3 | 0.7053 | 0.85 | 0.34-2.12 |
| 2 | 3 | 3.5 | 0.4607 | 0.78 | 0.38-1.62 | 8.0 | 16.3 | 0.2559 | 0.65 | 0.26-1.57 |
| 3 | 2 | 4 | 0.0023 | 0.39 | 0.21-0.72 | 8.0 | 21.0 | 0.0098 | 0.46 | 0.22-0.95 |
| 4 | 2 | 4.5 | 0.0002 | 0.35 | 0.20-0.61 | 7.6 | 21.0 | 0.0157 | 0.49 | 0.25-0.96 |
| 5 | 2 | 6.1 | <0.0001 | 0.38 | 0.23-0.61 | 7.1 | 21.0 | 0.0360 | 0.48 | 0.26-0.86 |
| 6 | 2 | 6.2 | <0.0001 | 0.41 | 0.26-0.64 | 11.1 | NR | 0.0487 | 0.55 | 0.31-0.99 |
| 7 | 2 | 6.2 | <0.0001 | 0.39 | 0.26-0.63 | 11.1 | NR | 0.0658 | 0.57 | 0.32-1.02 |
| 8 | 2.1 | 6.5 | <0.0001 | 0.38 | 0.24-0.60 | 8.2 | NR | 0.0334 | 0.51 | 0.28-0.92 |
| 9 | 2.1 | 6.5 | <0.0001 | 0.41 | 0.26-0.63 | 8.2 | NR | 0.0211 | 0.47 | 0.26-0.85 |
| 11 | 2.1 | 6.5 | 0.0001 | 0.42 | 0.27-0.65 | 8.2 | NR | 0.0386 | 0.51 | 0.28-0.92 |
| 12 | 2.1 | 6.8 | <0.0001 | 0.39 | 0.25-0.59 | 11.1 | NR | 0.0332 | 0.49 | 0.27-0.89 |
| 13 | 2.1 | 10 | <0.0001 | 0.37 | 0.24-0.56 | 8.2 | NR | 0.0165 | 0.44 | 0.24-0.80 |
| 14 | 2.2 | 10 | <0.0001 | 0.36 | 0.23-0.56 | 11.1 | NR | 0.0372 | 0.46 | 0.24-0.85 |
| 15 | 2.2 | 10 | 0.0003 | 0.38 | 0.24-0.59 | 11.1 | NR | 0.0753 | 0.51 | 0.27-0.96 |
| 16 | 2.2 | 6.5 | 0.002 | 0.43 | 0.27-0.68 | 11.1 | NR | 0.1401 | 0.57 | 0.30-1.10 |
| 18 | 2.4 | 10 | 0.0011 | 0.39 | 0.25-0.63 | 11.1 | NR | 0.1066 | 0.52 | 0.27-1.02 |
| 19 | 2.2 | 10 | 0.0005 | 0.36 | 0.23-0.58 | 11.1 | NR | 0.0557 | 0.44 | 0.23-0.87 |
| 20 | 2.2 | 12.5 | 0.0003 | 0.32 | 0.20-0.52 | 11.1 | NR | 0.0926 | 0.49 | 0.25-0.97 |
| 23 | 2.4 | 12.8 | 0.0005 | 0.32 | 0.20-0.52 | 15.7 | NR | 0.1372 | 0.53 | 0.26-1.06 |
| 26 | 2.4 | 12.8 | 0.0003 | 0.29 | 0.18-0.48 | 15.7 | NR | 0.2883 | 0.57 | 0.28-1.16 |
| 29 | 2.5 | NR | 0.0006 | 0.29 | 0.18-0.48 | 15.7 | NR | 0.3259 | 0.65 | 0.31-1.37 |
| 35 | 2.4 | NR | 0.0003 | 0.25 | 0.15-0.42 | 15.7 | NR | 0.2028 | 0.55 | 0.26-1.17 |
| 36 | 2.5 | NR | 0.0003 | 0.22 | 0.13-0.37 | 15.7 | NR | 0.1265 | 0.46 | 0.21-0.99 |
| 39 | 2.5 | NR | 0.0001 | 0.18 | 0.11-0.31 | 15.7 | NR | 0.1677 | 0.49 | 0.22-1.09 |
| 41 | 2.9 | NR | 0.0007 | 0.21 | 0.12-0.37 | 15.7 | NR | 0.2457 | 0.55 | 0.24-1.25 |
| 50 | 2.9 | NR | 0.0009 | 0.18 | 0.10-0.32 | 11.2 | NR | 0.1724 | 0.45 | 0.19-1.06 |
| 53 | 2.8 | NR | 0.0009 | 0.14 | 0.07-0.25 | 11.2 | NR | 0.1095 | 0.33 | 0.14-0.81 |
| 57 | 3.1 | NR | 0.0038 | 0.17 | 0.09-0.32 | 11.2 | NR | 0.1677 | 0.38 | 0.15-0.98 |
| 67 | 3.1 | NR | 0.0074 | 0.19 | 0.09-0.36 | 15.7 | NR | 0.3219 | 0.50 | 0.18-1.41 |
| 75 | 3.1 | NR | 0.0037 | 0.1 | 0.05-0.20 | 15.7 | NR | 0.4202 | 0.56 | 0.19-1.70 |
| 90 | 3.2 | NR | 0.0019 | 0.32 | 0.15-0.65 | 15.7 | NR | 0.2231 | 0.31 | 0.10-1.00 |
| 104 | 3.1 | NR | 0.02 | 0.34 | 0.14-0.84 | 15.7 | NR | 0.5224 | 0.53 | 0.12-2.31 |
| 115 | 3.1 | NR | 0.0284 | 0.34 | 0.13-0.89 | 15.7 | NR | 0.1985 | N/A | N/A |
| 131 | 3.2 | NR | 0.0746 | 0.35 | 0.11-1.11 | 15.7 | NR | 0.3027 | N/A | N/A |
| 182 | 3.2 | NR | 0.1941 | 0.36 | 0.07-1.69 | 15.7 | NR | 0.4544 | N/A | N/A |

1All medians for PFS and OS calculated by Kaplan Meier

2Calculated using log-rank (Mantel-Cox) test

3Hazard Ratio (HR) <1.0 implies less chance of progression or death. The HR was evaluated by comparing PFS or OS above and below the cut-off for each value. See **Figure 3** for graphic.

**Abbreviations:** CI = confidence interval; HR = hazard ratio; NR = not reached; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PFS = progression free survival; TMB = tumor mutational burden**Supplemental Table 12: All tumor types excluding melanoma and NSCLC treated with anti-PD-1/PD-L1 monotherapy – TMB low or intermediate vs. high (N = 55)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 55 | TMB low to intermediate  N = 40 (%) | TMB high N = 15 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 31 | 26 (65%) | 5 (33%) | 0.0651 |
| >60 years | 24 | 14 (35%) | 10 (67%) |
| Sex | Men | 35 | 23 (58%) | 12 (80%) | 0.2076 |
| Women | 20 | 17 (42%) | 3 (20%) |
| Tumor | Head and neck squamous | 10 | 9 (23%) | 1 (7%) | 0.2548 |
| Cutaneous squamous cell | 8 | 1 (3%) | 7 (47%) | **0.0002** |
| Renal cell cancer | 6 | 6 (15%) | 0 (0%) | 0.1734 |
| Colorectal | 3 | 1 (3%) | 2 (13%) | 0.1174 |
| Bladder Transitional Cell | 2 | 1 (3%) | 1 (7%) | 0.4747 |
| Hepatocellular | 3 | 3 (8%) | 0 (0%) | 0.5540 |
| Thyroid cancer | 3 | 3 (8%) | 0 (0%) | 0.5540 |
| Breast cancer | 3 | 3 (8%) | 0 (0%) | 0.5540 |
| Basal cell cancer | 2 | 0 (0%) | 2 (13%) | 0.0707 |
| Ovarian | 2 | 2 (5%) | 0 (0%) | 1.0000 |
| Cervical | 2 | 1 (3%) | 1 (7%) | 0.4747 |
| Merkel cell carcinoma | 2 | 2 (5%) | 0 (0%) | 1.0000 |
| Soft tissue sarcoma | 3 | 3 (8%) | 0 (0%) | 0.5540 |
| Unknown primary | 2 | 1 (3%) | 1 (7%) | 0.4747 |
| Appendicle adenocarcinoma | 1 | 1 (3%) | 0 (0%) | 1.0000 |
| Adrenocortical carcinoma | 1 | 1 (3%) | 0 (0%) | 1.0000 |
| Urethral SCC | 1 | 1 (3%) | 0 (0%) | 1.0000 |
| Pleural mesothelioma | 1 | 1 (3%) | 0 (0%) | 1.0000 |
| TMB | Median (range) per megabase | 6 (1-347) | 5 (1-14) | 53 (20-347) | **<0.0001** |
| Response | CR/PR | 9 | 3 (8%) | 6 (40%) | **0.0086** (OR = 8.22, 95% CI 1.88-32.86)3 |
| SD or PD | 46 | 37 (92%) | 9 (60%) | **0.0086** (OR 0.12, 95% CI 0.03-0.53)3 |
| PFS2 | Median (months) | 2.9 | 2.1 | 10.0 | **0.0033** (HR = 0.35, 95% CI 0.19-0.64)3 |
| OS2 | Median (months) | 11.2 | 11.1 | 11.2 | 0.2836 (HR = 0.59, 95% CI 0.25-1.40)3 |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB high versus TMB low to intermediate.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SCC = squamous cell carcinoma; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 13**: **All tumor types excluding melanoma and NSCLC treated with anti-PD-1/PD-L1 monotherapy – TMB low vs. intermediate or high (N = 55)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 55 | TMB low  N = 24 (%) | TMB intermediate to high N = 31 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 31 | 15 (63%) | 16 (52%) | 0.5841 |
| >60 years | 24 | 9 (47%) | 15 (48%) |
| Sex | Men | 35 | 14 (58%) | 21 (67%) | 0.5753 |
| Women | 20 | 10 (42%) | 10 (33%) |
| Tumor | Head and neck squamous | 10 | 5 (21%) | 5 (16%) | 0.7325 |
| Cutaneous squamous cell | 8 | 0 (0%) | 8 (26%) | **0.0071** |
| Renal cell cancer | 6 | 5 (21%) | 1 (3%) | 0.0755 |
| Colorectal | 3 | 0 (0%) | 3 (10%) | 0.2485 |
| Bladder Transitional Cell | 2 | 0 (0%) | 2 (6%) | 0.4990 |
| Hepatocellular | 3 | 2 (8%) | 1 (3%) | 0.5746 |
| Thyroid cancer | 3 | 3 (13%) | 0 (0%) | 0.0771 |
| Breast cancer | 3 | 1 (4%) | 2 (6%) | 1.0000 |
| Basal cell cancer | 2 | 0 (0%) | 2 (6%) | 0.4990 |
| Ovarian | 2 | 1 (4%) | 1 (3%) | 1.0000 |
| Cervical | 2 | 0 (0%) | 2 (6%) | 0.4990 |
| Merkel cell carcinoma | 2 | 2 (8%) | 0 (0%) | 0.1859 |
| Soft tissue sarcoma | 3 | 1 (4%) | 2 (6%) | 1.0000 |
| Unknown primary | 2 | 1 (4%) | 1 (3%) | 1.0000 |
| Appendicle adenocarcinoma | 1 | 1 (4%) | 0 (0%) | 0.4364 |
| Adrenocortical carcinoma | 1 | 1 (4%) | 0 (0%) | 0.4364 |
| Urethral SCC | 1 | 0 (0%) | 1 (3%) | 1.0000 |
| Pleural mesothelioma | 1 | 1 (4%) | 0 (0%) | 0.4364 |
| TMB | Median (range) per megabase | 6 (1-347) | 3.5 (1-5) | 14 (6-347) | **0.0041** |
| Response | CR/PR | 9 | 1 (4%) | 8 (26%) | 0.0620 (OR = 8.00, 95% CI = 1.26-92.11)3 |
| SD or PD | 46 | 23 (96%) | 23 (74%) | 0.0620 (OR = 0.13, 95% CI = 0.01-0.79)3 |
| PFS2 | Median (months) | 2.9 | 2.0 | 6.2 | **<0.0001** (HR = 0.33, 95% CI 0.17-0.65)3 |
| OS2 | Median (months) | 11.2 | 6.2 | 21.0 | 0.0782 (HR = 0.50, 95% CI 0.23-1.13)3 |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB intermediate to high versus TMB low.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SCC = squamous cell carcinoma; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 14: Patients with melanoma and NSCLC treated with anti-PD-1/PD-L1 monotherapy – TMB low or intermediate vs. high (N = 47)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 47 | TMB low to intermediate  N = 40 (%) | TMB high N 7 = (%) | P-value1 |
| Age at diagnosis | ≤60 years | 18 | 16 (40%) | 2 (29%) | 0.6918 |
| >60 years | 29 | 24 (60%) | 5 (71%) |
| Sex | Men | 25 | 20 (50%) | 5 (71%) | 0.4227 |
| Women | 22 | 20 (50%) | 2 (29%) |
| Tumor | Melanoma | 11 | 7 (18%) | 4 (57%) | **0.0424** |
| NSCLC | 36 | 33 (82%) | 3 (43%) |
| TMB | Median (range) per megabase | 6 (1-104) | 5 (1-19) | 39 (23-104) | **<0.0001** |
| Response | CR/PR | 12 | 8 (20%) | 4 (57%) | 0.0595 (OR = 5.33, 95% CI 1.18-23.51)3 |
| SD or PD | 35 | 32 (80%) | 3 (43%) | 0.0595 (OR = 0.19, 95% CI 0.04-0.85)3 |
| PFS2 | Median (months) | 3.5 | 3.1 | 12.5 | **0.0402** (HR = 0.36, 95% CI 0.17-0.77)3 |
| OS2 | Median (months) | 16.3 | 15.7 | Not reached (median f/u of 13.3 mos) | 0.0926 (HR = 0.21, 95% CI 0.07-0.63)3 |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB high versus TMB low to intermediate.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 15: Patients with melanoma and NSCLC treated with anti-PD-1/PD-L1 monotherapy – TMB low vs. intermediate or high (N = 47)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 47 | TMB low  N = 22 (%) | TMB intermediate to high N = 25 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 18 | 9 (41%) | 9 (36%) | 0.7712 |
| >60 years | 29 | 13 (59)% | 16 (64%) |
| Sex | Men | 25 | 12 (55%) | 13 (52%) | 1.0000 |
| Women | 22 | 10 (45%) | 12 (48)% |
| Tumor | Melanoma | 11 | 2 (9%) | 9 (36%) | **0.0410** |
| NSCLC | 36 | 20 (91%) | 16 (64%) |
| TMB | Median (range) per megabase | 6 (1-104) | 3 (1-5) | 14 (6-104) | **0.0002** |
| Response | CR/PR | 12 | 1 (5%) | 11 (44%) | **0.0023** (OR = 16.5, 95% CI 2.13-185)3 |
| SD or PD | 35 | 21 (95%) | 14 (56%) | **0.0023** (OR = 0.06, 95% CI 0.01-0.47)3 |
| PFS2 | Median (months) | 3.5 | 1.9 | 5.7 | **0.0023** (HR = 0.40, 95% CI 0.20-0.80)3 |
| OS2 | Median (months) | 16.3 | 8.0 | Not reached (median f/u of 7.4 mos) | 0.0791 (HR = 0.46, 95% CI 0.19-1.13)3 |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB intermediate to high versus TMB low.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 16**: **Median TMB for patients treated with anti-PD-1/PD-L1 monotherapy: responders vs. non-responders**

|  |  |  |  |
| --- | --- | --- | --- |
| All tumor types including melanoma and NSCLC (n = 102) | | | |
| Best response1 | Number of patients | Median TMB (mutations/mb) (Range) | P-value1 |
| SD/PD | 81 | 5 (1-115) | <0.0001 |
| CR/PR | 21 | 18 (1-37) |
| All tumor types excluding melanoma and NSCLC (n = 55) | | | |
| Best response | Number of patients | Median TMB (mutations/mb) (Range) | P-value1 |
| SD/PD | 46 | 5.5 (1-115) | <0.0001 |
| CR/PR | 9 | 53 (1-347) |
| Patients with melanoma and NSCLC (n = 47) | | | |
| Best response | Number of patients | Median TMB (mutations/mb) (Range) | P-value1 |
| SD/PD | 35 | 5 (1-39) | 0.0005 |
| CR/PR | 12 | 15.5 (5-104) |

1Calculated using unpaired Student’s t-test

Abbreviations: CR = complete response; mb = megabase; NSCLC = non-small cell lung cancer; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 17: Total treatments for all tumors\***

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Immunotherapy | Median TMB for non-responders (mutations/mb) (range) | Median TMB for responders (mutations/mb) (range) | P-value1 | Median PFS for TMB low to intermediate (months)2 | Median PFS for TMB high (months)2 | P-value3 | HR (95% CI)4 |
| Anti-PD-1/PD-L1 monotherapy (N = 112) | 5 (1-115) | 18 (1-347) | **<0.0001** | 2.3 | 10.0 | **0.0003** | 0.38 (0.25-0.58) |
| Anti-CTLA4 monotherapy (N =29) | 8 (1-92) | 20.5 (16-68) | 0.2430 | 2.7 | 6.4 | **0.0144** | 0.38 (0.17-0.81) |
| Anti-CTLA4/Anti-PD-1/PD-L1 (N = 27) | 6 (1-83) | 9.5 (1-133) | 0.4061 | 9.2 | Not reached (median f/u 9.3 mos) | 0.3055 | 0.47 (0.14-1.60) |
| High-dose IL2 (N = 22) | 5 (1-16) | 16 (1-58) | 0.0565 | 4.2 | 38.95 | 0.1069 | 0.08-0.77 |

\*This data is compiled for total treatments with immunotherapy. Some patients (mainly with melanoma) received multiple lines of immunotherapy. (Data in other Tables/Figures compiled for immunotherapy with longest PFS in each patient) .

1Calculated using unpaired Students t-test

2All medians for PFS and OS calculated by Kaplan Meier

3Calculated using log-rank (Mantel-Cox) test

4Hazard ratio (HR) <1.0 implies less chance of progression or death

5Only 2 patients with TMB high were treated with high dose IL2

**Abbreviations**: CI = confidence interval; CTLA4 = cytotoxic T-lymphocyte associated protein 4; HR = hazard ratio;

mb = megabase; IL2 = interleukin 2; PFS = progression free survival; PD-1 = programmed death receptor-1;

PD-L1 programmed death receptor-ligand 1; TMB = tumor mutational burden

**Supplemental Table 18:** **Review of published abstracts and manuscripts utilizing TMB as a predictor of response to treatment with anti-PD-1/PD-L1 agents**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Tumor type(s) | Number of patients | Calculation methodology for TMB | Results | Reference |
| Analysis of TMB to identify novel non-coding *PMS2* promoter mutations associated with increased TMB | Multiple histologies | >51,000 | CGP (Foundation Medicine) | * **Did not assess response to immunotherapy** * *PMS2* promoter mutations were found in 7.5% of melanoma specimens (n = 101/1,348) and 17% of cutaneous squamous cell carcinomas (n = 30/175) * In both tumor types, *PMS2* promoter mutations were the most significant genomic correlate of TMB | Abstract *(21)* |
| Assessment of TMB using comprehensive genomic profiling. | >400 cancer types | >60,000 | CGP (Foundation Medicine) | * **Did not assess response to immunotherapy** * Lower grade malignancies have the lowest TMB (< 1 mut/Mb) * Epithelial cancers, associated with environmental DNA damage, were most highly mutated ( > 10 mut/Mb) * Mutations in mismatch-repair genes (and *TP53BP1* were associated with > 2x increases in TMB | Abstract *(22)* |
| Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma | Urothelial carcinoma | 150 | CGP (Foundation Medicine) | * The median TMB was significantly increased in responders (12.4 per Mb) compared with non-responders (6.4 per Mb) | Manuscript *(28)* |
| TMB metastatic breast cancer | Breast cancer | 6,751 | CGP (Foundation Medicine) | * **Did not asses response to immunotherapy** * High TMB, defined as greater than the top quartile across all indications, was found in 1,351 of 6,643 (20%) mBC cases | Abstract *(23)* |
| Comprehensive cancer-gene panels used to estimate TMB and predict clinical benefit to PD-1 blockade | Melanoma  NSCLC | 64 | CGP (Foundation Medicine) | * **TMB was calculated using just mutated genes present in cancer gene panel** * 69% of patients with high cancer gene panel-mutational load experienced durable clinical benefit to PD-1 blockade, as compared to 20% of patients with low mutational load (*P*=0.01). | Manuscript *(26)* |
| MSI in diverse solid tumors using CGP | Multiple solid tumors | 11,573 | CGP (Foundation Medicine) | * **Did not asses response to immunotherapy** * Histone methyltransferase *MLL2/3* and chromatin remodeling *ARID1A* mutations were enriched in MSI-H, while *TP53* mutations were depleted (p < 0.0001) | Abstract *(35)* |
| High TMB in melanoma is a marker of response to anti-PD-1/PD-L1 agents | Melanoma | 65 | CGP (Foundation Medicine) | * Responders to anti-PD1 had higher TMB compared to non-responders in discovery (median 45.6 vs. 3.9 mutations/MB; p = 0.003) * RR was superior in TMB high patients compared to intermediate/low * PFS (median not reached vs. 89 days vs. 86 days, p<0.001) * OS (median not reached vs. 300 days vs. 375 days, p<0.001). | Manuscript *(19)* |
| TMB in endometrial adenocarcinoma | Endometrial | 717 | CGP (Foundation Medicine) | * **Did not asses response to immunotherapy** * MSI status by CGP identified three times as many potentially immunotherapy relevant cases. * TMB identified an additional 35% of MMR proficient endometrial cancer patients. | Abstract *(24)* |
| Mutational landscape determines sensitivity to PD-1 blockade in NSCLC | NSCLC | 34 | WES | * Higher somatic nonsynonymous mutation burden was associated with clinical efficacy of pembrolizumab | Manuscript *(18)* |
| PD-1 blockade in tumors with MMR deficiency | CRC  Endometrial  Cholagiocarcinoma  Small bowel  Gastric | 41 | Multiplex PCR for MSS stability (not TMB (Promega) | * **Did not look at TMB.** * The immune-related objective response and PFS were 40% and 78%, respectively, for MMR-deficient CRCs and 0% and 11% for MMR–proficient CRCs. | Manuscript *(30)* |
| TMB as an independent predictor of response to atezolizumab | Urothelial carcinoma | 195 | CGP (Foundation Medicine) | * Median TMB was significantly increased in responders (12.4/Mb) vs non-responders (6.4/Mb; *P*< 0.0001) and correlated with both PFS (*P* = 0.003) and OS (*P* = 0.014) | Abstract *(29)* |
| TMB in CRC | CRC | 2013 | CGP (Foundation Medicine) | * **Did not assess response to immunotherapy** * MSI-high cases were TMB high (range 16.8-72.7 mutations/Mb) and 1510 of 1934 (78.1%) MSI-stable cases were TMB low (range 0.0-8.0 mutations/Mb). * 424 of 1934 (21.9%) MSI-stable cases were confirmed as TMB high (range 8.8-43.1 mutations/Mb). | Abstract *(25)* |
| TMB predicts response to atezolizumab in NSCLC | NSCLC | 454 | CGP (Foundation Medicine) | * OS, PFS, and RR were improved in patients with increased TMB treated with atezolizumab in both unselected and selected patients | Abstract *(27)* |

Abbreviations: CGP = comprehensive genomic profiling; CRC = colorectal cancer; GBM = glioblastoma multiforme; Mb = megabase; MSI = microsatellite instability; MMR = mismatch repair; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; PD-1 = programmed death receptor-1; PD-L1 = programmed death receptor-ligand 1; PFS = progression free survival; RR = response rate; SCLC = small cell lung cancer; TMB = tumor mutational burden; WES = whole exome sequencing

**Supplemental Table 19: Histology, TMB, treatment, are response characteristics for all patients.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Histology | Mutations per megabase | TMB level | Treatment | PFS | Best response |
| Adrenal carcinoma | 4.00 | low | Anti-PD-1 | 1.4 | PD |
| Appendix adenocarcinoma | 3.00 | low | Anti-PD-1 | 0.9 | PD |
| Basal cell carcinoma | 104.00 | high | Anti-PD-1 | 12.0+ | PR |
| Basal cell carcinoma | 90.00 | high | Anti-PD-1 | 3.8 | SD |
| Bladder-TCC | 11.00 | intermediate | Anti-PD-1 | 6.2 | SD |
| Bladder-TCC | 21.00 | high | OX40 + anti-PD-L1 | 5.6+ | PR |
| Bladder-TCC | 20.00 | high | Anti-PD-L1 | 1.9 | PD |
| Bladder-TCC | 23.00 | high | IDO + anti-PD-1 | 5.4+ | PR |
| Breast ductal adenocarcinoma-ER-/PR-,Her2+ | 5.00 | low | Anti-PD-1 | 1.9 | PD |
| Breast ductal adenocarcinoma-ER-/PR+,Her2- | 14.00 | intermediate | Anti-PD-1 | 6.1 | PD |
| Breast ductal adenocarcinoma-triple negative | 6.00 | intermediate | Anti-PD-1 | 1.2 | PD |
| Cervix neuroendocrine carcinoma | 53 | high | Anti-PD-1 | 8.5+ | PR |
| Cervix-SCC | 6.00 | intermediate | Anti-PD-1 | 4.2+ | SD |
| Colon cancer | 8.00 | intermediate | Anti-PD-1 | 1.9 | PD |
| Colon cancer | 131.00 | high | Anti-PD-1 | 8.6+ | PR |
| Colon cancer | 35.00 | high | Anti-PD-1 | 2 | PD |
| Colon cancer | 5.00 | low | OX40 | 3.4 | SD |
| Cutaneous SCC | 115.00 | high | Anti-PD-1 | 2.3+ | SD |
| Cutaneous SCC | 12.00 | intermediate | Anti-PD-1 | 3.5 | PD |
| Cutaneous SCC | 347.00 | high | Anti-PD-1 | 10.4+ | PR |
| Cutaneous SCC | 75 | high | Anti-PD-1 | 2.9 | PD |
| Cutaneous SCC | 50 | high | Anti-PD-1 | 10 | SD |
| Cutaneous SCC | 26.00 | high | Anti-PD-1 | 3.6 | PD |
| Cutaneous SCC | 182.00 | high | Anti-PD-1 | 7.6+ | CR |
| Cutaneous SCC | 41.00 | high | Anti-PD-1 | 13.5+ | PR |
| Endometrial stromal sarcoma | 3.00 | Low | Anti-PD-1 | 1.5 | PD |
| Extraskeletal mesenchymal chondrosarcoma | 6.00 | intermediate | Anti-PD-1 | 5 | SD |
| HCC | 7.00 | intermediate | Anti-PD-1 | 1 | PD |
| HCC | 5.00 | low | Anti-PD-1 | 1.8 | PD |
| HCC-fibrolamellar variant | 2.50 | low | Anti-PD-1 | 1.9 | PD |
| Head and Neck-SCC | 4.00 | low | Anti-PD-1 | 5.9 | SD |
| Head and Neck-SCC | 3.00 | low | Anti-PD-1 | 2.2 | PD |
| Head and Neck-SCC | 6.00 | intermediate | Anti-PD-1 | 6.5 | SD |
| Head and Neck-SCC | 7.00 | intermediate | OX40 | 1.4 | PD |
| Head and Neck-SCC | 20.00 | high | Anti-PD-1 | 6.5 | SD |
| Head and Neck-SCC | 9.00 | intermediate | Anti-PD-1 | 7.1 | PR |
| Head and Neck-SCC | 4.00 | low | Anti-PD-1 | 0.9 | PD |
| Head and Neck-SCC | 6.00 | intermediate | Anti-PD-1 | 17.0+ | SD |
| Head and Neck-SCC | 9.00 | intermediate | Anti-CTLA4/anti-PD-1/PD-L1 | 5.5+ | PR |
| Head and Neck-SCC | 7.00 | intermediate | Anti-PD-1 | 3.8+ | SD |
| Head and Neck-SCC | 10.00 | intermediate | Anti-CTLA4 | 1.8 | PD |
| Melanoma | 16 | intermediate | Anti-PD-1 | 24.0+ | CR |
| Melanoma | 10 | intermediate | Anti-CTLA4/anti-PD-1/PD-L1 | 14.0+ | CR |
| Melanoma | 2 | low | Anti-CTLA4 | 5.5 | SD |
| Melanoma | 4 | low | High dose IL2 | 3.9 | SD |
| Melanoma | 50 | high | Anti-CTLA4 | 6.4 | SD |
| Melanoma | 19 | intermediate | Anti-CTLA4/anti-PD-1/PD-L1 | 21.8+ | CR |
| Melanoma | 6 | intermediate | Anti-PD-1 | 1.4+ | SD |
| Melanoma | 9 | intermediate | High dose IL2 | 9.3 | SD |
| Melanoma | 16 | intermediate | Anti-CTLA4/anti-PD-1/PD-L1 | 7.9+ | CR |
| Melanoma | 21 | high | Anti-CTLA4/anti-PD-1/PD-L1 | 21.1+ | CR |
| Melanoma | 1.00 | low | High dose IL2 | 4.6 | SD |
| Melanoma | 3 | low | Anti-CTLA4/anti-PD-1/PD-L1 | 21.2+ | CR |
| Melanoma | 58 | high | High dose IL2 | 40 | CR |
| Melanoma | 14 | intermediate | Anti-PD-1 | 6.8 | SD |
| Melanoma | 6 | intermediate | Anti-CTLA4/anti-PD-1/PD-L1 | 19.2+ | PR |
| Melanoma | 11 | intermediate | Anti-CTLA4 | 5.8 | SD |
| Melanoma | 10 | intermediate | Anti-CTLA4 | 3.9 | PD |
| Melanoma | 8 | intermediate | Anti-CTLA4 | 2.6 | PD |
| Melanoma | 1.00 | low | High dose IL2 | 54.7 | PR |
| Melanoma | 1.00 | low | Anti-CTLA4/anti-PD-1/PD-L1 | 2.5 | PD |
| Melanoma | 3 | low | OX40 | 8.9 | SD |
| Melanoma | 4 | low | High dose IL2 | 10.7+ | CR |
| Melanoma | 6 | intermediate | Anti-CTLA4/anti-PD-1/PD-L1 | 2.3 | PD |
| Melanoma | 14 | intermediate | Talimogene laherparepvec | 5.8+ | PR |
| Melanoma | 5 | low | Anti-CTLA4/anti-PD-1/PD-L1 | 6.8 | PR |
| Melanoma | 13 | intermediate | Anti-PD-1 | 1.4 | PD |
| Melanoma | 133 | high | Anti-CTLA4/anti-PD-1/PD-L1 | 5.6+ | CR |
| Melanoma | 3 | low | High dose IL2 | 24.2+ | CR |
| Melanoma | 20 | high | Anti-CTLA4 | 29.6+ | CR |
| Melanoma | 32 | high | Anti-CTLA4/anti-PD-1/PD-L1 | 14.0+ | CR |
| Melanoma | 38 | high | High dose IL2 | 40.9+ | CR |
| Melanoma | 29 | high | Anti-PD-1 | 12.8 | PR |
| Melanoma | 4 | low | Anti-CTLA4 | 4.7 | SD |
| Melanoma | 67 | high | Anti-PD-1 | 5.4+ | CR |
| Melanoma | 92 | high | Anti-CTLA4 | 1.4 | PD |
| Melanoma | 68 | high | Anti-CTLA4 | 3.7+ | PR |
| Melanoma | 14 | intermediate | Anti-PD-1 | 15 | PR |
| Melanoma | 83 | high | Anti-CTLA4/anti-PD-1/PD-L1 | 7.4+ | SD |
| Melanoma | 57 | high | Talimogene laherparepvec | 4.8+ | CR |
| Melanoma | 94 | high | Anti-CTLA4/anti-PD-1/PD-L1 | 16.3+ | CR |
| Melanoma | 104 | high | Anti-PD-1 | 10.6+ | PR |
| Melanoma | 101 | high | Anti-CTLA4/anti-PD-1/PD-L1 | 9.3 | CR |
| Melanoma | 21 | high | Anti-CTLA4 | 15.2 | SD |
| Melanoma | 5 | low | Anti-PD-1 | 7.9 | PD |
| Melanoma | 36 | high | Anti-PD-1 | 5.7 | SD |
| Melanoma-Occular | 1.00 | low | Anti-CTLA4 | 14.7+ | SD |
| Melanoma-Occular | 3 | low | Anti-CTLA4/anti-PD-1/PD-L1 | 2.8 | PD |
| Melanoma-Occular | 1.00 | low | Anti-CTLA4 | 3.2 | PD |
| Melanoma-Occular | 1.00 | low | Anti-PD-1 | 3.3 | PD |
| Melanoma-Occular | 3 | low | Anti-CTLA4 | 2.6 | PD |
| Melanoma-Vaginal | 1.00 | low | Anti-CTLA4/anti-PD-1/PD-L1 | 9.2 | CR |
| Melanoma-Vulva | 2 | low | High dose IL2 | 11.6 | SD |
| Merkel cell carcinoma | 1.00 | low | Anti-PD-1 | 9.1+ | PR |
| Merkel cell carcinoma | 3.00 | low | Anti-PD-1 | 2.1 | PD |
| Nasopharyngeal carcinoma | 3.00 | low | Anti-PD-1 | 2 | PD |
| NSCLC-adenocarcinoma | 4 | low | Anti-PD-1 | 2.5 | PD |
| NSCLC-adenocarcinoma | 1 | low | Anti-PD-1 | 1.6 | PD |
| NSCLC-adenocarcinoma | 8 | intermediate | Anti-PD-1 | 4.2 | SD |
| NSCLC-adenocarcinoma | 2 | low | Anti-PD-1 | 1.1 | PD |
| NSCLC-adenocarcinoma | 5 | low | Anti-PD-1 | 0.3 | PD |
| NSCLC-adenocarcinoma | 5 | low | Anti-PD-1 | 1.1 | PD |
| NSCLC-adenocarcinoma | 5 | low | Anti-PD-1 | 2.1 | PD |
| NSCLC-adenocarcinoma | 1 | low | Anti-PD-1 | 0.2 | PD |
| NSCLC-adenocarcinoma | 39 | high | Anti-PD-1 | 3.2 | PD |
| NSCLC-adenocarcinoma | 7 | intermediate | Anti-PD-1 | 3,5 | PR |
| NSCLC-adenocarcinoma | 18 | intermediate | Anti-PD-1 | 4 | PR |
| NSCLC-adenocarcinoma | 23 | high | Anti-PD-1 | 12.5 | SD |
| NSCLC-adenocarcinoma | 57 | high | Anti-PD-1 | 13.3+ | PR |
| NSCLC-adenocarcinoma | 4 | low | Anti-PD-1 | 1 | PD |
| NSCLC-adenocarcinoma | 18 | intermediate | Anti-PD-1 | 3.1 | SD |
| NSCLC-adenocarcinoma | 1 | low | Anti-PD-1 | 5.1+ | SD |
| NSCLC-adenocarcinoma | 15 | intermediate | Anti-PD-1 | 14.7 | PR |
| NSCLC-adenocarcinoma | 11 | intermediate | Anti-PD-L1 | 2.8+ | PR |
| NSCLC-adenocarcinoma | 3 | low | Anti-PD-1 | 1.8 | PD |
| NSCLC-adenocarcinoma | 1 | low | anti PD-L1 (atezolizumab) | 3.1 | PD |
| NSCLC-adenocarcinoma | 6 | intermediate | Anti-PD-1 | 1.6 | PD |
| NSCLC-adenocarcinoma | 3 | low | Anti-PD-1 | 0.5 | PD |
| NSCLC-adenocarcinoma | 5 | low | Anti-PD-1 | 0.9 | PD |
| NSCLC-adenocarcinoma | 1 | low | Anti-PD-1 | 2 | PD |
| NSCLC-adenocarcinoma | 5 | low | Anti-PD-1 | 1.7 | PD |
| NSCLC-adenocarcinoma | 3 | low | Anti-PD-1 | 1.1 | PD |
| NSCLC-adenocarcinoma | 1 | low | Anti-PD-1 | 6.6 | SD |
| NSCLC-adenocarcinoma | 6 | intermediate | Anti-PD-1 | 5.6 | SD |
| NSCLC-adenocarcinoma | 14 | intermediate | Anti-PD-1 | 11.9 | PR |
| NSCLC-adenocarcinoma | 12 | intermediate | Anti-PD-1 | 0.6 | PD |
| NSCLC-SCC | 1 | low | Anti-PD-1 | 4.7 | SD |
| NSCLC-SCC | 5 | low | Anti-PD-1 | 10.8+ | PR |
| NSCLC-SCC | 14 | intermediate | Anti-PD-1 | 1 | PD |
| NSCLC-SCC | 19 | intermediate | Anti-PD-1 | 1.3 | PD |
| NSCLC-SCC | 12 | intermediate | Anti-PD-1 | 5.9 | SD |
| NSCLC-SCC | 3 | low | Anti-PD-1 | 8.8 | SD |
| Ovarian-serous | 5.00 | low | Anti-PD-1 | 3.6 | PD |
| Ovarian-serous | 6.00 | intermediate | Anti-PD-1 | 1.8 | PD |
| Parotid myoepithelial carcinoma | 5.00 | low | Anti-PD-1 | 2.1 | PD |
| Pleural mesothelioma | 3.00 | low | Anti-PD-1 | 1.2 | PD |
| Prostate adenocarcinoma | 3.00 | low | Anti-CTLA4 | 1.3 | PD |
| RCC-clear cell | 6.00 | intermediate | Anti-PD-1 | 0.6 | PD |
| RCC-clear cell | 1.00 | low | Anti-PD-1 | 2.9 | PD |
| RCC-clear cell | 5.00 | low | Anti-PD-1 | 2.4 | PD |
| RCC-collecting duct | 3.00 | low | Anti-PD-1 | 0.6 | PD |
| RCC-papillary | 3.00 | low | Anti-PD-1 | 2.2 | PD |
| RCC-translocation type | 4.00 | low | Anti-PD-1 | 3.9 | PD |
| Rectal cancer | 8.00 | intermediate | Anti-CD73 | 1.8 | PD |
| Soft tissue sarcoma-undifferentiated pleomorphic | 8.00 | intermediate | Anti-PD-1 | 2.8+ | PR |
| Thyroid cancer (NOS) | 5.00 | low | Anti-PD-1 | 4.5 | PD |
| Thyroid cancer-DTC | 5.00 | low | Anti-PD-1 | 1.8 | PD |
| Thyroid cancer-Medullary | 1.00 | low | Anti-PD-1 | 2 | PD |
| Unknown primary-SCC | 5.00 | low | Anti-PD-1 | 0.4 | PD |
| Unknown primary-SCC | 53.00 | high | Anti-PD-1 | 0.7 | PD |
| Urethral SCC | 7.00 | intermediate | Anti-PD-1 | 9.3 | SD |

Abbreviations: CR = complete response; CTLA4 = cytotoxic T-lymphocyte associated protein 4; DTC = differentiated thyroid cancer; HCC = hepatocellular carcinoma; IL2 = interleukin 2; NOS = not otherwise specified; NSCLC = non=small cell carcinoma; PR = partial response; PD = progressive disease; PFS = progression free survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; SD = stable disease; TCC = transitional cell carcinoma; TMB = tumor mutational burden

**Supplemental Table 20**: **Melanoma patients treated with anti-PD-1/PD-L1 monotherapy – TMB low or intermediate vs. high (N = 11)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 11 | TMB low to intermediate  N = 7 (%) | TMB high  N = 4 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 4 | 4 (57%) | 0 (0%) | 0.1939 |
| >60 years | 7 | 3 (43%) | 4 (100%) |
| Sex | Men | 8 | 4 (57%) | 4 (100%) | 0.2364 |
| Women | 3 | 3 (43%) | 0 (0%) |
| TMB | Median (range) per megabase | 14 (1-104) | 13 (1-16) | 51.5 (29-104) | **0.0039** |
| Response | CR/PR | 5 | 2 (29%) | 3 (75%) | 0.2424 (OR = 7.5, 95% CI 0.60-113.1) |
| SD or PD | 6 | 5 (71%) | 1 (25%) | 0.2424 (OR = 0.13, 95% CI 0.01-1.67) |
| PFS2 | Median (months) | 7.9 | 7.9 | 12.8 | 0.7982 (HR = 0.81, 95% CI 0.17-3.95) |
| OS2 | Median (months) | Not reached (median f/u of 12.4 mos) | Not reached (median f/u of 12.4 mos) | Not reached (median f/u of 20.3 mos) | 0.8061 (HR = 0.75, 95% CI 0.07-7.45) |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB high versus TMB low to intermediate.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 21**: **Melanoma patients treated with anti-PD-1/PD-L1 monotherapy – TMB low vs. intermediate or high (N = 11)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 11 | TMB low  N = 2 (%) | TMB intermediate to high  N = 9 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 4 | 0 (0%) | 4 (44%) | 0.4909 |
| >60 years | 7 | 2 (100%) | 5 (56%) |
| Sex | Men | 8 | 1 (50%) | 7 (78%) | 0.4909 |
| Women | 3 | 1 (50%) | 2 (22%) |
| TMB | Median (range) per megabase | 14 (1-104) | 3 (1-5) | 15 (6-104) | 0.2367 |
| Response | CR/PR | 5 | 0 (0%) | 5 (56%) | 0.4545 (undefined, 0.41-undefined) |
| SD or PD | 6 | 2 (100%) | 4 (44%) | 0.4545 (0, 0-2.47) |
| PFS2 | Median (months) | 7.9 | 5.6 | 12.8 | 0.2075 (HR = 0.38, 95% CI 0.04-3.38) |
| OS2 | Median (months) | Not reached (median f/u of 12.4 mos) | Not reached (median f/u of 19.8 mos) | Not reached (median f/u 16.3 mos) | 0.4762 (HR = 3.51, 95% CI = 0.11-111.3) |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB intermediate to high versus TMB low.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 22**: **NSCLC patients treated with anti-PD-1/PD-L1 monotherapy – TMB low or intermediate vs. high (N = 36)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 36 | TMB low to intermediate  N = 33 (%) | TMB high  N = 3 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 14 | 12 (36%) | 2 (67%) | 0.5471 |
| >60 years | 22 | 21 (63%) | 1 (33%) |
| Sex | Men | 17 | 15 (45%) | 2 (67%) | 0.5929 |
| Women | 19 | 18 (55%) | 1 (33%) |
| TMB | Median (range) per megabase | 5 (1-57) | 5 (1-19) | 39 (23-57) | **<0.0001** |
| Response | CR/PR | 7 | 6 (18%) | 1 (33%) | 0.4882 (OR = 2.25, 95% CI 0.13-21.29) |
| SD or PD | 29 | 27 (82%) | 2 (67%) | 0.4882 (OR = 0.44, 95% CI 0.05-7.43) |
| PFS2 | Median (months) | 2.8 | 2.1 | 12.5 | 0.0817 (HR = 0.32, 95% CI 0.13-0.81) |
| OS2 | Median (months) | 8.0 | 7.6 | Not reached (median f/u of 13.3 mos) | 0.1488 (HR = 0.32, 95% CI 0.07-1.50) |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB high versus TMB low to intermediate.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SD = stable disease; TMB = tumor mutational burden

**Supplemental Table 23**: **NSCLC patients treated with anti-PD-1/PD-L1 monotherapy – TMB low vs. intermediate or high (N = 36)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Group | All patients N = 36 | TMB low  N = 20 (%) | TMB intermediate to high  N = 16 (%) | P-value1 |
| Age at diagnosis | ≤60 years | 14 | 9 (45%) | 5 (31%) | 0.5007 |
| >60 years | 22 | 11 (55%) | 11 (69%) |
| Sex | Men | 17 | 11 (55%) | 6 (38%) | 0.3351 |
| Women | 19 | 9 (45%) | 10 (62%) |
| TMB | Median (range) per megabase | 5 (1-57) | 3 (1-5) | 14 (6-57) | **<0.0001** |
| Response | CR/PR | 7 | 1 (5%) | 6 (38%) | **0.0298** (OR = 11.4, 95% CI 1.31-136.3) |
| SD or PD | 29 | 19 (95%) | 10 (62%) | **0.0298** (OR = 0.09, 95% CI 0.01-0.76) |
| PFS2 | Median (months) | 2.8 | 1.8 | 4.0 | 0.0549 (HR = 0.53, 95% CI 0.26-1.07) |
| OS2 | Median (months) | 8.0 | 7.6 | Not reached (median f/u of 6.9 mos) | 0.1540 (HR = 0.48, 95% CI 0.18-1.24) |

1Calculated using Fischer’s exact test, log-rank (Mantel-Cox) test, and Student’s t-test where applicable

2All medians for PFS and OS calculated by Kaplan Meier

3Odds Ratio (OR) >1.0 implies higher chance of response; Hazard ratio (HR) <1.0 implies less chance of progression or death; OR and HR refer to TMB intermediate to high versus TMB low.

**Abbreviations:** CI = confidence interval; CR = complete response; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 programmed death receptor-ligand 1; PD = progressive disease: PFS = progression free survival; PR = partial response; SD = stable disease; TMB = tumor mutational burden