# Supplementary Material

**Supplemental Table 1. Treatment Patterns after Index Line for the Anti-programmed Cell Death-1-treated Patients with Advanced Melanoma Treated with a *BRAF* Therapy in the Index Line or Prior to Index**

|  |  |
| --- | --- |
| **Treatment Patterns** | ***BRAF*mt (N=78)** |
| **Subsequent treatment** |
|     Yes | 34 (43.6%) |
|     No | 44 (56.4%) |
| **Patients with a subsequent treatment** |
|     Follow-up duration (months) |
|         Mean (SD) | 12.2 (12.1) |
|         Median (IQR) | 7.9 (3.6–16.1) |
|     Follow-up ended at death |
|         Yes | 24/34 (70.6%) |
|         No (censored) | 10/34 (29.4%) |
| **Patients without a subsequent treatment** |
|     Follow-up duration (months) |
|         Mean (SD) | 8.3 (11.3) |
|         Median (IQR) | 2.3 (1.1–13.6) |
|     Follow-up ended at death |
|         Yes | 32/44 (72.7%) |
|         No (censored) | 12/44 (27.3%) |

Abbreviations: *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; IQR = interquartile range; mt = mutation; SD = standard deviation

Note: Cell entries show n (%), unless otherwise specified.

**Supplemental Table 2. Baseline Demographic Characteristics for Patients with Advanced Melanoma, Died on Index, by *BRAF* Status**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Overall (N=308)** | ***BRAF*mt (N=114)** | ***BRAF*wt (N=194)** |
| **Age (years) at index date** |
|     Mean (SD) | 71.1 (11.7) | 65.7 (13.7) | 73.3 (9.6) |
|     Median (IQR) | 74 (65–81) | 68 (58–77) | 76 (68–81) |
| **Age (years) at index date categories** |
|     18–29 | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
|     30–39 | 7 (2.0%) | 5 (4.4%) | 2 (1.0%) |
|     40–49 | 11 (3.1%) | 9 (7.9%) | 1 (0.5%) |
|     50–59 | 37 (10.4%) | 19 (16.7%) | 15 (7.7%) |
|     60–69 | 73 (20.5%) | 28 (24.6%) | 36 (18.6%) |
|     70–79 | 114 (32.0%) | 31 (27.2%) | 73 (37.6%) |
|     ≥80 | 113 (31.7%) | 21 (18.4%) | 67 (34.5%) |
| **Sex** |
|     Male | 246 (69.1%) | 76 (66.7%) | 135 (69.6%) |
|     Female | 110 (30.9%) | 38 (33.3%) | 59 (30.4%) |
| **Race** |
|     White | 289 (81.2%) | 93 (81.6%) | 152 (78.4%) |
|     Black or African American | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Asian | 1 (0.3%) | 0 (0.0%) | 1 (0.5%) |
|     Other | 27 (7.6%) | 9 (7.9%) | 18 (9.3%) |
|     Unknown | 39 (11.0%) | 12 (10.5%) | 23 (11.9%) |
| **Practice type** |
|     Academic | 19 (5.3%) | 9 (7.9%) | 9 (4.6%) |
|     Community | 337 (94.7%) | 105 (92.1%) | 185 (95.4%) |
| **Index year** |
|     2015 | 25 (7.0%) | 7 (6.1%) | 14 (7.2%) |
|     2016 | 54 (15.2%) | 20 (17.5%) | 26 (13.4%) |
|     2017 | 84 (23.6%) | 19 (16.7%) | 55 (28.4%) |
|     2018 | 87 (24.4%) | 32 (28.1%) | 44 (22.7%) |
|     2019 | 106 (29.8%) | 36 (31.6%) | 55 (28.4%) |

Abbreviations: *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; IQR = interquartile range; mt = mutation; SD = standard deviation; wt = wild type

Notes: Cell entries show n (%), unless otherwise specified; patients with unknown *BRAF* status are excluded from the *BRAF*-stratified columns.

**Supplemental Table 3. Baseline Clinical Characteristics for Patients with Advanced Melanoma, Died on Index, by *BRAF* Status**

| **Characteristics** | **Overall (N=308)** | ***BRAF*mt (N=114)** | ***BRAF*wt (N=194)** |
| --- | --- | --- | --- |
| **Time (months) from diagnosis to index date** |
|     From initial melanoma diagnosis |
|         Mean (SD) | 33.9 (44.8) | 29.9 (39.2) | 33.6 (41.1) |
|         Median (IQR) | 20.4 (5.3–43.8) | 17.0 (6.1–36.4) | 22.3 (4.4–45.5) |
|     From first diagnosis of advanced melanoma |
|         Mean (SD) | 10.6 (11.0) | 12.5 (11.9) | 9.8 (10.5) |
|         Median (IQR) | 5.5 (2.9–15.1) | 8.5 (4.4–17.0) | 4.8 (2.8–13.9) |
| **Stage at initial melanoma diagnosis** |
|     0 | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
|     I | 19 (5.3%) | 5 (4.4%) | 13 (6.7%) |
|     II | 76 (21.3%) | 20 (17.5%) | 40 (20.6%) |
|     III | 45 (12.6%) | 20 (17.5%) | 19 (9.8%) |
|     IV | 136 (38.2%) | 48 (42.1%) | 77 (39.7%) |
|     Unknown | 79 (22.2%) | 20 (17.5%) | 45 (23.2%) |
| **Evidence of progression on index date** |
|     Radiographic evidence | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Pathologic evidence | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Radiographic or pathologic evidence | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Physical exam/clinical assessment only | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
| **Presence of visceral metastases on or prior to index date** |
|     Yes | 312 (87.6%) | 101 (88.6%) | 171 (88.1%) |
|     No/unknown | 44 (12.4%) | 13 (11.4%) | 23 (11.9%) |
| **Presence of non-visceral metastases on or prior to index date** |
|     Yes | 164 (46.1%) | 63 (55.3%) | 79 (40.7%) |
|     No/unknown | 192 (53.9%) | 51 (44.7%) | 115 (59.3%) |
| **Presence of brain metastases on or prior to index date\*** |
|     Yes | 81 (22.8%) | 36 (31.6%) | 39 (20.1%) |
|     No/unknown | 275 (77.2%) | 78 (68.4%) | 155 (79.9%) |
| **BMI (kg/m2); measurement on the index date or closest within 6 months prior** |
|     Underweight (<18.5) | 15 (4.2%) | 6 (5.3%) | 8 (4.1%) |
|     Normal (18.5 to <25) | 103 (28.9%) | 37 (32.5%) | 46 (23.7%) |
|     Overweight (25 to <30) | 116 (32.6%) | 32 (28.1%) | 70 (36.1%) |
|     Obese (≥30) | 95 (26.7%) | 34 (29.8%) | 52 (26.8%) |
|     Unknown | 27 (7.6%) | 5 (4.4%) | 18 (9.3%) |
| **ECOG performance status; measurement on the index date or closest within 6 months prior** |
|     0 | 44 (12.4%) | 13 (11.4%) | 22 (11.3%) |
|     1 | 86 (24.2%) | 29 (25.4%) | 44 (22.7%) |
|     2 | 67 (18.8%) | 24 (21.1%) | 37 (19.1%) |
|     3 | 53 (14.9%) | 11 (9.6%) | 31 (16.0%) |
|     4 | 8 (2.2%) | 4 (3.5%) | 4 (2.1%) |
|     Unknown | 98 (27.5%) | 33 (28.9%) | 56 (28.9%) |

Abbreviations: BMI = body mass index; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; mt = mutation; SD = standard deviation; wt = wild type

Notes: Cell entries show n (%), unless otherwise specified; patients with unknown *BRAF* status are excluded from the *BRAF*-stratified columns.

\*Presence of brain metastases may be under-reported.

**Supplemental Table 4. Treatment Characteristics in Baseline, Died on Index, by *BRAF* Status**

| **Characteristics** | **Overall (N=308)** | ***BRAF*mt (N=114)** | ***BRAF*wt (N=194)** |
| --- | --- | --- | --- |
| **Number of LOT prior to index LOT for advanced melanoma** |
|     0 | 295 (82.9%) | 65 (57.0%) | 185 (95.4%) |
|     1 | 50 (14.0%) | 40 (35.1%) | 8 (4.1%) |
|     2 | 10 (2.8%) | 8 (7.0%) | 1 (0.5%) |
|     3 | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
| **Drug categories received in any line prior to index LOT** |
|     BRAF ± MEK | 45 (12.6%) | 45 (39.5%) | 0 (0.0%) |
|     BRAF ± MEK + IO | 2 (0.6%) | 2 (1.8%) | 0 (0.0%) |
|     MEK monotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     MEK + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-PD-1 alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-CTLA-4 alone | 16 (4.5%) | 5 (4.4%) | 9 (4.6%) |
|     Anti CTLA4 + anti PD-1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Chemotherapy alone | 3 (0.8%) | 2 (1.8%) | 1 (0.5%) |
|     Chemotherapy + IO | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
|     Clinical study drug, alone or in combination | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic + chemotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Other | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) |
|     No treatment | 295 (82.9%) | 65 (57.0%) | 185 (95.4%) |
| **Drug categories received in LOT immediately prior to index LOT** |
|     BRAF ± MEK | 44 (12.4%) | 44 (38.6%) | 0 (0.0%) |
|     BRAF ± MEK + IO | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
|     MEK monotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     MEK + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-PD-1 alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-CTLA-4 alone | 13 (3.7%) | 3 (2.6%) | 8 (4.1%) |
|     Anti-CTLA-4 + anti-PD-1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Chemotherapy alone | 2 (0.6%) | 1 (0.9%) | 1 (0.5%) |
|     Chemotherapy + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Clinical study drug, alone or in combination | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic + chemotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Other | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) |
|     No treatment | 295 (82.9%) | 65 (57.0%) | 185 (95.4%) |
| **Drug categories, second line prior to index LOT** |
|     BRAF ± MEK | 4 (1.1%) | 4 (3.5%) | 0 (0.0%) |
|     BRAF ± MEK + IO | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
|     MEK monotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     MEK + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-PD-1 alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-CTLA-4 alone | 3 (0.8%) | 2 (1.8%) | 1 (0.5%) |
|     Anti-CTLA-4 + anti-PD-1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Chemotherapy alone | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
|     Chemotherapy + IO | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
|     Clinical study drug, alone or in combination | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic + chemotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Other | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) |
|     No treatment | 345 (96.9%) | 105 (92.1%) | 193 (99.5%) |
| **Drug categories, third line prior to index LOT** |
|     BRAF ± MEK | 1 (0.3%) | 1 (0.9%) | 0 (0.0%) |
|     BRAF ± MEK + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     MEK monotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     MEK + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-PD-1 alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-CTLA-4 alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-CTLA-4 + anti-PD-1 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Chemotherapy alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Chemotherapy + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Clinical study drug, alone or in combination | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic alone | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic + chemotherapy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Anti-angiogenic + IO | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     Other | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|     No treatment | 355 (99.7%) | 113 (99.1%) | 194 (100.0%) |

Abbreviations: *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; CTLA = cytotoxic T lymphocyte-associated antigen; IO = immunotherapy; IQR = interquartile range; LOT = line of therapy; MEK = mitogen-activated protein kinase/extra-cellular signal-regulated kinase; mt = mutation; PD-1 = programmed cell death-1; wt = wild type

Notes: Cell entries show n (%), unless otherwise specified; patients with unknown *BRAF* status are excluded from the *BRAF*-stratified columns. *BRAF* inhibitors include vemurafenib, dabrafenib, and encorafenib; patients with multiple baseline LOTs may contribute to more than one category.

**Supplemental Table 5. *BRAF*mt and *BRAF*wt Overall Survival from the Index Date, Stratified by Receipt of Index Anti-PD-1 After Progression**

|  | **OS (Months)** |
| --- | --- |
| **Stratifications** | **N** | **Censored (%)** | **KM Median (95% CI)** |
| Received at least one dose of the index anti-PD-1 after progression |
| ***BRAF*mt** |  |  |  |
|     No | 142 | 39 (27.5%) | 8.0 (5.3-10.7) |
|     Yes | 133 | 73 (54.9%) | 24.6 (16.5-NA) |
| ***BRAF*wt** |  |  |  |
|     No | 158 | 48 (30.4%) | 5.8 (3.8-7.9) |
|     Yes | 216 | 89 (41.2%) | 13.5 (11.1-18.0) |

Abbreviations: BRAF = B-Raf proto-oncogene, serine/threonine kinase; CI = confidence interval; KM = Kaplan-Meier; mt = mutation; OS = overall survival; PD-1 = programmed cell death protein 1; wt = wild type