**Supplemental Methods**

**Sensitivity analysis 1: Statistical adjustment without inverse probability of treatment weighting (IPTW)**

In the first sensitivity analysis, we performed statistical adjustment on an unweighted population. On the basis of these results (Supplemental Table 1), we concluded that our decision to perform double adjustment with IPTW as a primary analysis had minimal impact on the study results.

**Sensitivity analysis 2: Censoring patients in the practice subanalysis who initiate a therapy off-sequence**

In the second sensitivity analysis, we evaluated whether off-sequence therapy initiation impacted the results of our practice subanalysis. “Off-sequence”, referred to a patient who did not receive their expected 2L drug, e.g., a presumed 1L TT – 2L CPI patient would be considered “off-sequence” if they received chemotherapy in 2L instead of CPI. The hazard ratio (HR) of our IPTW and fully-adjusted outcome model comparing 1L CPI – 2L TT to a reference of 1L TT – 2L CPI was 0.86 (95% confidence interval [CI] 0.49-1.51) in this sensitivity analysis, close to the primary analysis HR of 0.90 (95% CI 0.65-1.26). We conclude that the design decision to keep off-sequence patients in our original analysis did have a major impact on our results.

**Sensitivity analysis 3: Restricting to CPI patients receiving ipilimumab + nivolumab**

Due to potential differences in outcomes among CPI patients treated with dual anti-PD-1 and anti-CTLA-4 therapies compared to CPI patients treated with anti-PD-1 monotherapy, we conducted a third sensitivity analysis in or 1L study cohort in which the CPI population was limited to patients on ipilimumab/nivolumab. As reported in the main text, the results of this sensitivity analysis were qualitatively similar to those of our primary analysis (Supplemental Table 2, Supplemental Figures 1 and 2).

**Supplemental Tables**

**Supplemental Table 1.** Comparison of statistical adjustments with and without inverse probability of treatment weighting (IPTW).

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Hazard ratio (95 % confidence interval)a** | | |
| **Analysis** | **1L CPI vs TT** | **2L CPI vs TT** | **Practice subanalysis** |
| IPTW weighted and adjusted | 0.75 (0.66-0.87) | 1.19 (0.92-1.54) | 0.90 (0.65-1.26) |
| Adjusted only | 0.77 (0.62-0.95) | 1.14 (0.71-1.83) | 0.97 (0.57-1.67) |

Abbreviations: 1L, first-line; 2L, second-line; CPI, checkpoint inhibitors; TT, targeted therapies.

a Hazard ratios refer to the effect of checkpoint inhibitors with targeted therapy as the reference value

**Supplemental Table 2.** Baseline Characteristics of Patients With Advanced *BRAF-*Mt Melanoma by 1L Treatment

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Ipilimumab/ nivolumab**  **(n = 278)** | **TT**  **(n = 357)** | ***P* Value** |
| **Age at diagnosis, n (%)** |  |  |  |
| < 65 years | 181 (65.1) | 208 (58.3) | .094 |
| **Sex, n (%)** |  |  |  |
| Male | 203 (73.0) | 231 (64.7) | .026 |
| **Region, n (%)** |  |  |  |
| Midwest | 33 (11.9) | 68 (19.0) | .001 |
| Northeast | 37 (13.3) | 20 (5.6) |  |
| South | 121 (43.5) | 150 (42.0) |  |
| West | 47 (16.9) | 77 (21.6) |  |
| Unknown | 40 (14.4) | 42 (11.8) |  |
| **Practice type, n (%)** |  |  |  |
| Academic | 37 (13.3) | 34 (9.5) | .162 |
| Community | 241 (86.7) | 323 (90.5) |  |
| **Year of initial diagnosis, n (%)** |  |  |  |
| Before 2010 | 31 (11.2) | 44 (12.3) | .489 |
| 2010-2014 | 51 (18.3) | 77 (21.6) |  |
| 2015-2019 | 196 (70.5) | 236 (66.1) |  |
| **PD-L1, n (%)a** |  |  |  |
| Positive | 19 (6.8) | 14 (3.9) | .257 |
| Negative | 26 (9.4) | 33 (9.2) |  |
| Unknown | 233 (83.8) | 310 (86.8) |  |
| **LDH, n (%)** |  |  |  |
| Normal/low | 123 (44.2) | 97 (27.2) | < .001 |
| Above normal | 43 (15.5) | 73 (20.4) |  |
| Missing | 112 (40.3) | 187 (52.4) |  |
| **ECOG PS, n (%)** |  |  |  |
| 0-1 | 173 (62.2) | 200 (56.0) | .014 |
| 2+ | 15 (5.4) | 43 (12.0) |  |
| Unknown | 90 (32.4) | 114 (31.9) |  |
| **Albumin, mean (SD)** | 40.1 (6.4) | 37.6 (5.7) | < .001 |
| **Metastases, n (%)** |  |  |  |
| < 3 metastases | 172 (61.9) | 205 (57.4) | .293 |
| With liver metastases | 73 (26.3) | 117 (32.8) | .081 |
| With brain/CNS metastases | 95 (34.2) | 108 (30.3) | .304 |
| **Stage at initial diagnosis, n (%)** |  |  |  |
| 0 | NSb | NSb | .038 |
| I | 27 (9.7) | 33 (9.2) |  |
| II | 40 (14.4) | 42 (11.8) |  |
| III | 42 (15.1) | 93 (26.1) |  |
| IV | 112 (40.3) | 121 (33.9) |  |
| Unknown | 56 (20.1) | 66 (18.5) |  |

Abbreviations: 1L, first-line; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NS, not shown; PD-L1, programmed cell death 1 ligand 1; TT, targeted therapies.

a PD-L1 positivity defined as > 1% tumor cells staining positively with ≥ 1+ intensity using Dako 22C3 and Ventana SP142 platforms.

b Value suppressed to minimize the risk of patient reidentification from cells with small counts