**Appendix 1.** Patient and Health System characteristics. First-line ipilimumab stratified by receipt of <60 days of chemotherapy prior to ipilimumab start.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** |  | **Type Of Systemic Treatment** | | |
|  | **Total** | **First-line dacarbazine  in 2007-2009** | **First-line ipilimumab (excluding <60 days chemo) in 2010-2015** | **Ipilimumab with <60 days chemo in 2010-2015** |
|  | N=464 | N=175 | N=172 | N=117 |
| **Age (categorized) at first systemic therapy** |  |  |  |  |
| 20-39 | 34 (7.33%) | 15 (8.57%) | 9 (5.23%) | 10 (8.55%) |
| 40-49 | 48 (10.34%) | 23 (13.14%) | 18 (10.47%) | 7 (5.98%) |
| 50-59 | 104 (22.41%) | 44 (25.14%) | 39 (22.67%) | 21 (17.95%) |
| 60-69 | 136 (29.31%) | 39 (22.29%) | 56 (32.56%) | 41 (35.04%) |
| 70-79 | 106 (22.84%) | 42 (24.00%) | 35 (20.35%) | 29 (24.79%) |
| 80+ | 36 (7.76%) | 12 (6.86%) | 15 (8.72%) | 9 (7.69%) |
| **Age** |  |  |  |  |
| Median (IQR) | 63 (53-72) | 62 (51-73) | 63 (54-72) | 65 (57-71) |
| **Sex** |  |  |  |  |
| F | 185 (39.87%) | 71 (40.57%) | 70 (40.70%) | 44 (37.61%) |
| M | 279 (60.13%) | 104 (59.43%) | 102 (59.30%) | 73 (62.39%) |
| **Elixhauser comorbidity index** | |  |  |  |
| 0 | 306 (65.95%) | 117 (66.86%) | 113 (65.70%) | 76 (64.96%) |
| 1 | 90 (19.40%) | 34 (19.43%) | 33 (19.19%) | 23 (19.66%) |
| 2 | 32 (6.90%) | 10 (5.71%) | 11 (6.40%) | 11 (9.40%) |
| 3+ | 36 (7.76%) | 14 (8.00%) | 15 (8.72%) | 7 (5.98%) |
| **Neighbourhood income quintile** | |  |  |  |
| 1 (lowest) | 65 (14.01%) | 33 (18.86%) | 15 (8.72%) | 16 (13.68%) |
| 2 | 87 (18.75%) | 29 (16.57%) | 38 (22.09%) | 20 (17.09%) |
| 3 | 87 (18.75%) | 25 (14.29%) | 34 (19.77%) | 28 (23.93%) |
| 4 | 96 (20.69%) | 41 (23.43%) | 30 (17.44%) | 25 (21.37%) |
| 5\* (highest) | 129 (27.80%) | 47 (26.86%) | 55 (31.98%) | 28 (23.93%) |
| **Place of residence** | |  |  |  |
| Southwestern Ontario | 82 (17.67%) | 37 (21.14%) | 25 (14.53%) | 20 (17.09%) |
| GTA/Central Ontario | 275 (59.27%) | 100 (57.14%) | 114 (66.28%) | 61 (52.14%) |
| Eastern Ontario | 77 (16.59%) | 28 (16.00%) | 25 (14.53%) | 24 (20.51%) |
| Northern Ontario | 30 (6.47%) | 10 (5.71%) | 8 (4.65%) | 12 (10.26%) |
| **Developed environment** |  |  |  |  |
| Urban (RIO<10)\* | 288 (62.07%) | 115 (65.71%) | 105 (61.05%) | 68 (58.12%) |
| Suburban (10≤RIO<40) | 121 (26.08%) | 48 (27.43%) | 42 (24.42%) | 31 (26.50%) |
| Rural (40≤RIO) | 55 (11.85%) | 12 (6.86%) | 25 (14.53%) | 18 (15.38%) |

\*There were <6 patients whose status was unknown. Due to privacy regulations, they were aggregated with the noted category

**Appendix 2.** Disease and Prior Treatment Characteristics. First-line ipilimumab stratified by receipt of <60 days of chemotherapy prior to ipilimumab start.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Type of Systemic Treatment** | | |
|  | **Total** | **First-line dacarbazine  in 2007-2009** | **First-line ipilimumab (excluding <60 days chemo) in 2010-2015** | **ipilimumab with <60 days chemo in 2010-2015** |
|  | N=464 | N=175 | N=172 | N=117 |
| **Topography of first melanoma diagnosis** |  |  |  |  |
| Scalp, neck, ear and other parts of face | 82 (17.67%) | 29 (16.57%) | 27 (15.70%) | 26 (22.22%) |
| Upper limb and shoulder | 78 (16.81%) | 23 (13.14%) | 37 (21.51%) | 18 (15.38%) |
| Trunk | 116 (25.00%) | 47 (26.86%) | 43 (25.00%) | 26 (22.22%) |
| Lower limb and hip | 71 (15.30%) | 31 (17.71%) | 28 (16.28%) | 12 (10.26%) |
| GI, gyne, head and neck mucosal, uveal, or other | 46 (9.91%) | 8 (4.57%) | 21 (12.21%) | 17 (14.53%) |
| Malignant neoplasm of skin, site unspecified or multiple | 71 (15.30%) | 37 (21.14%) | 16 (9.30%) | 18 (15.38%) |
| **Prior adjuvant interferon** |  |  |  |  |
| Yes | 86 (18.53%) | 46 (26.29%) | 24 (13.95%) | 16 (13.68%) |
| **Time from first (any stage) melanoma diagnosis**  **to first palliative systemic treatment (days)** | |  |  |  |
| Median (IQR) | 674 (246-1,846) | 591 (222-1,621) | 752 (317-2,188) | 621 (223-1,503) |
| **Prior palliative radiotherapy** |  |  |  |  |
| Brain radiotherapy | 49 (10.56%) | 9 (5.14%) | 24 (13.95%) | 16 (13.68%) |
| Non-brain radiotherapy | 61 (13.15%) | 28 (16.00%) | 15 (8.72%) | 18 (15.38%) |
| **Prior metastasis surgery** |  |  |  |  |
| Intracranial tumor surgery | 7 (1.51%) | 0 (0.00%) | <7 (<4.07%) | <7 (<5.98%) |
| Spinal cord compression surgery | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Thoracic tumor surgery | <25\* (<5.39%) | <6 (<3.43%) | 11 (6.40%) | 8 (6.84%) |
| Liver tumor surgery | <6\* (<1.29%) | 0 (0.00%) | <6 (<3.49%) | <6 (<5.13%) |

\*Totals for full cohort could not be displayed given privacy regulations regarding re-identification of patients in groups of <6.

**Appendix 3.** Treatment and Hospital Utilization Characteristics following start of first-line systemic therapy. First-line ipilimumab stratified by receipt of <60 days of chemotherapy prior to ipilimumab start.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Type of Systemic Treatment** | | |
|  | **Total** | **First-line dacarbazine  in 2007-2009** | **First-line ipilimumab (excluding <60 days chemo) in 2010-2015** | **ipilimumab with <60 days chemo in 2010-2015** |
|  | N=464 | N=175 | N=172 | N=117 |
| **Subsequent systemic therapy after first-line treatment** |  |  |  |  |
| Dacarbazine\* | <6\* (<1.29%) | <6 (<3.43%) | 0 (0.00%) | 0 (0.00%) |
| Carbo-Taxol, Temozolomide or other chemo | 52 (11.21%) | 37 (21.14%) | 6 (3.49%) | 9 (7.69%) |
| BRAF and/or MEK | 7 (1.51%) | <7 (<4.00%) | <7 (<4.07%) | <7 (<5.98%) |
| CTLA4 | 15 (3.23%) | 15 (8.57%) | 0 (0.00%) | 0 (0.00%) |
| PD-1 | 50 (10.78%) | 0 (0.00%) | 26 (15.12%) | 24 (20.51%) |
| New drug- other | 8 (1.72%) | <8 (<4.57%) | <8 (<4.65%) | 0 (0.00%) |
| Billing for unnamed systemic therapy\*\* | 95 (20.47%) | 9 (5.14%) | 66 (38.37%) | 20 (17.09%) |
| **Subsequent palliative radiotherapy** |  |  |  |  |
| Brain radiotherapy | 97 (20.91%) | 39 (22.29%) | 18 (10.47%) | 40 (34.19%) |
| Non-brain radiotherapy | 116 (25.00%) | 58 (33.14%) | 21 (12.21%) | 37 (31.62%) |
| **Subsequent metastasis surgery** | |  |  |  |
| Intracranial tumor surgery | <16\* (<3.45%) | <6 (<3.43%) | <10 (<5.81%) | <10 (<8.54%) |
| Spinal cord compression surgery | <6\* (<1.29%) | 0 (0.00%) | <6 (<3.49%) | 0 (0.00%) |
| Thoracic tumor surgery | <6\* (<1.29%) | 0 (0.00%) | <6 (<3.49%) | 0 (0.00%) |
| Liver tumor surgery | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| **Hospitalizations within 3 months after first systemic treatment** |  |  |  |  |
| 0 | 281 (60.56%) | 107 (61.14%) | 110 (63.95%) | 64 (54.70%) |
| 1 | 130 (28.02%) | 52 (29.71%) | 48 (27.91%) | 30 (25.64%) |
| 2+ | 53 (11.42%) | 16 (9.14%) | 14 (8.14%) | 23 (19.66%) |
| **ED-only visits within 3 months after first systemic treatment** |  |  |  |  |
| 0 | 308 (66.38%) | 115 (65.71%) | 116 (67.44%) | 77 (65.81%) |
| 1 | 99 (21.34%) | 37 (21.14%) | 44 (25.58%) | 18 (15.38%) |
| 2+ | 57 (12.28%) | 23 (13.14%) | 12 (6.98%) | 22 (18.80%) |

\*Totals for full cohort could not be displayed given privacy regulations regarding re-identification of patients in groups of <6.

\*\* Latest systemic therapy billing in specified time frame that is more than 8 weeks after last named systemic therapy

**Appendix 4:**  Multivariable model for first-line ipilimumab for overall survival

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | | | | |
|  |  |  | **Characteristics** | **Estimate** | **95% LCL** | **95% UCL** | **p-value** |
|  |  |  |  |  |  |  |  |
|  |  |  | Ipilimumab (Yes vs. No) | 0.629 | 0.471 | 0.840 | 0.0017 |
|  |  |  | Temozolomide (Yes vs. No) | 3.614 | 1.692 | 7.721 | 0.0009 |
|  |  |  | Unnamed systemic therapy billing (Yes vs. No) | 0.555 | 0.363 | 0.847 | 0.0064 |
|  |  |  | Radiotherapy dose (Per 1-Gy increase) | 0.958 | 0.928 | 0.989 | 0.0085 |
|  |  |  | Brain radiotherapy (Yes vs. No) | 4.085 | 2.684 | 6.219 | <0.0001 |
|  |  |  | Non-brain radiotherapy (Yes vs. No) | 2.651 | 1.773 | 3.963 | <0.0001 |
|  |  |  | Prior Interferon use (Yes vs. No) | 1.367 | 1.030 | 1.813 | 0.0302 |
|  |  |  | Neighbourhood income quintiles (Per 1-unit increase) | 1.026 | 0.908 | 1.160 | 0.6795 |
|  |  |  | Place of residence (Region 1 vs. Other) | 1.329 | 0.896 | 1.972 | 0.1574 |
|  |  |  | RIO score (Per 1-unit increase) | 1.001 | 0.988 | 1.014 | 0.8901 |
|  |  |  | Age (60-69 years vs. Other) | 1.094 | 0.857 | 1.397 | 0.4692 |
|  |  |  | Age (80+ years vs. Other) | 1.758 | 1.178 | 2.622 | 0.0057 |
|  |  |  | Stage (IV vs. Other) | 0.900 | 0.592 | 1.368 | 0.6217 |
|  |  |  | Elixhauser comorbidity index score (1 vs. Other) | 1.646 | 1.243 | 2.179 | 0.0005 |
|  |  |  | Elixhauser comorbidity index (Diabetes, uncomplicated vs. Other) | 1.099 | 0.750 | 1.610 | 0.6292 |
|  |  |  | Elixhauser comorbidity index (Solid tumor without metastasis vs. Other)\* | 1.258 | 0.959 | 1.648 | 0.0971 |
|  |  |  | Place of residence (LHIN H vs. Other) | 1.221 | 0.742 | 2.009 | 0.4311 |
|  |  |  | Place of residence (LHIN I vs. Other) | 1.319 | 0.921 | 1.889 | 0.1314 |
|  |  |  | Place of residence (LHIN K vs. Other) | 0.800 | 0.497 | 1.288 | 0.3579 |
|  |  |  | Place of residence (LHIN L vs. Other) | 0.818 | 0.477 | 1.404 | 0.4658 |
|  |  |  | Topography of first melanoma diagnosis (Malignant neoplasm of skin, site unspecified vs. Other) | 1.229 | 0.884 | 1.708 | 0.2209 |
|  |  |  | RIO score quintiles (5 vs. Other) | 1.125 | 0.621 | 2.038 | 0.6965 |
|  |  |  | Quintiles of duration between first palliative and systemic treatment (4 vs. Other) | 1.496 | 1.113 | 2.010 | 0.0076 |
|  |  |  | Neighbourhood income quintiles (5 vs. Other) | 0.698 | 0.483 | 1.009 | 0.0559 |
|  |  |  | Square root of duration between first palliative and systemic treatment (Per 1-unit increase) | 1.019 | 0.996 | 1.043 | 0.1016 |
|  |  |  | Squared duration between first palliative and systemic treatment (Per 1-unit increase) | 1.000 | 1.000 | 1.000 | 0.1133 |
|  |  |  | \*Solid tumor without metastasis was used as an adjusting variable,  but was not included in the derived comorbidity index score | |  |  |  |

**Appendix 5.** Results stratified by first-line ipilimumab subgroup (no prior chemotherapy vs <60 days prior chemotherapy) for overall survival

1. Results of multivariable model for first-line ipilimumab with no prior chemotherapy

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **First-line ipilimumab with no prior chemotherapy** | | | | |
|  |  |  | **Characteristics** | **Estimate** | **95% LCL** | **95% UCL** | **p-value** |
|  |  |  |  |  |  |  |  |
|  |  |  | Ipilimumab (Yes vs. No) | 0.630 | 0.440 | 0.904 | 0.0121 |
|  |  |  | Temozolomide (Yes vs. No) | 3.761 | 1.608 | 8.800 | 0.0023 |
|  |  |  | Unnamed systemic therapy billing (Yes vs. No) | 0.502 | 0.301 | 0.837 | 0.0083 |
|  |  |  | Radiotherapy dose (Per 1-Gy increase) | 0.974 | 0.942 | 1.007 | 0.1224 |
|  |  |  | Brain radiotherapy (Yes vs. No) | 5.523 | 3.604 | 8.465 | <0.0001 |
|  |  |  | Non-brain radiotherapy (Yes vs. No) | 2.478 | 1.568 | 3.916 | 0.0001 |
|  |  |  | Prior Interferon use (Yes vs. No) | 1.203 | 0.875 | 1.653 | 0.2557 |
|  |  |  | Place of residence (Region 1 vs. Other) | 1.470 | 1.048 | 2.063 | 0.0256 |
|  |  |  | RIO score (Per 1-unit increase) | 0.995 | 0.981 | 1.010 | 0.5182 |
|  |  |  | Age (60-69 years vs. Other) | 1.106 | 0.830 | 1.473 | 0.4912 |
|  |  |  | Stage (IV vs. Other) | 1.267 | 0.816 | 1.969 | 0.2922 |
|  |  |  | Stage (Unknown vs. Other) | 1.063 | 0.798 | 1.417 | 0.6761 |
|  |  |  | Duration between first palliative and systemic treatment (Per 1-day increase) | 0.997 | 0.990 | 1.003 | 0.3259 |
|  |  |  | Type of institution performing first melanoma diagnosis (Private lab vs. Other) | 1.296 | 0.924 | 1.817 | 0.1326 |
|  |  |  | Place of residence (LHIN J vs. Other) | 0.912 | 0.556 | 1.495 | 0.7140 |
|  |  |  | Place of residence (LHIN D vs. Other) | 0.474 | 0.237 | 0.947 | 0.0346 |
|  |  |  | Place of residence (LHIN L vs. Other) | 0.673 | 0.365 | 1.241 | 0.2045 |
|  |  |  | Topography of first melanoma diagnosis (Malignant neoplasm of skin, site unspecified vs. Other) | 1.111 | 0.768 | 1.608 | 0.5770 |
|  |  |  | Topography (Upper limb and shoulder vs. Other) | 1.046 | 0.697 | 1.570 | 0.8292 |
|  |  |  | RIO score quintiles (5 vs. Other) | 1.415 | 0.743 | 2.693 | 0.2910 |
|  |  |  | Quintiles of duration between first palliative and systemic treatment (4 vs. Other) | 1.546 | 1.086 | 2.201 | 0.0155 |
|  |  |  | Neighbourhood income quintiles (2 vs. Other) | 0.770 | 0.533 | 1.112 | 0.1627 |
|  |  |  | Square root of duration between first palliative and systemic treatment (Per 1-unit increase) | 1.061 | 0.973 | 1.157 | 0.1827 |
|  |  |  | Squared duration between first palliative and systemic treatment (Per 1-unit increase) | 1.000 | 1.000 | 1.000 | 0.5806 |

1. Results of multivariable model for ipilimumab with <60 days prior chemotherapy

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Ipilimumab with <60 days prior chemotherapy** | | | | |
|  |  |  | **Characteristics** | **Estimate** | **95% LCL** | **95% UCL** | **p-value** |
|  |  |  |  |  |  |  |  |
|  |  |  | Ipilimumab (Yes vs. No) | 0.676 | 0.471 | 0.971 | 0.0342 |
|  |  |  | Temozolomide (Yes vs. No) | 5.268 | 3.050 | 9.099 | <0.0001 |
|  |  |  | Unnamed systemic therapy billing (Yes vs. No) | 0.698 | 0.409 | 1.191 | 0.1874 |
|  |  |  | Radiotherapy dose (Per 1-Gy increase) | 0.959 | 0.922 | 0.996 | 0.0325 |
|  |  |  | Brain radiotherapy (Yes vs. No) | 4.024 | 2.568 | 6.306 | <0.0001 |
|  |  |  | Non-brain radiotherapy (Yes vs. No) | 2.760 | 1.806 | 4.217 | <0.0001 |
|  |  |  | Prior Interferon use (Yes vs. No) | 1.480 | 1.091 | 2.007 | 0.0116 |
|  |  |  | Place of residence (Region 1 vs. Other) | 1.260 | 0.855 | 1.856 | 0.2433 |
|  |  |  | Age (60-69 years vs. Other) | 0.990 | 0.756 | 1.295 | 0.9404 |
|  |  |  | Age (80+ years vs. Other) | 1.938 | 1.292 | 2.909 | 0.0014 |
|  |  |  | Stage (IV vs. Other) | 0.849 | 0.549 | 1.314 | 0.4640 |
|  |  |  | Elixhauser comorbidity index score (1 vs. Other) | 1.707 | 1.258 | 2.315 | 0.0006 |
|  |  |  | Elixhauser comorbidity index (Solid tumor without metastasis vs. Other)\* | 1.405 | 1.052 | 1.875 | 0.0212 |
|  |  |  | Place of residence (LHIN H vs. Other) | 1.542 | 0.904 | 2.632 | 0.1123 |
|  |  |  | Place of residence (LHIN K vs. Other) | 0.621 | 0.360 | 1.070 | 0.0863 |
|  |  |  | Place of residence (LHIN F vs. Other) | 0.946 | 0.635 | 1.408 | 0.7827 |
|  |  |  | RIO score quintiles (5 vs. Other) | 1.206 | 0.865 | 1.682 | 0.2697 |
|  |  |  | Quintiles of duration between first melanoma diagnosis and palliative treatment (3 vs. Other) | 1.336 | 0.983 | 1.816 | 0.0640 |
|  |  |  | Neighbourhood income quintiles (3 vs. Other) | 0.950 | 0.667 | 1.354 | 0.7769 |
|  |  |  | \*Solid tumor without metastasis was used as an adjusting  variable, but was not included in the derived comorbidity index score | |  |  |  |
|  |  |  |  |  |  |  |  |