|  | Year 2012 (n = 241) | Year 2014 (n = 284) | Year 2016 (n = 313) | Year 2018 (n = 325) | p-value1 | q-value2 |
| --- | --- | --- | --- | --- | --- | --- |
| **Gender, n (%)** |  |  |  |  | 0.320 | 0.391 |
| *M* | 143 (59) | 165 (58) | 171 (55) | 201 (62) |  |  |
| *F* | 98 (41) | 119 (42) | 142 (45) | 124 (38) |  |  |
| **Age at 1st Treatment, Median (IQR)** | 68 (56 – 76) | 68 (59 – 77) | 70 (59 – 78) | 71 (60 – 77) |  |  |
| **BRAF status, n (%)** |  |  |  |  | 0.188 | 0.295 |
| *Wild-type* | 88 (55) | 152 (56) | 164 (54) | 151 (48) |  |  |
| *Mutant* | 73 (45) | 120 (44) | 140 (46) | 166 (52) |  |  |
| *Not reported* | 80 | 12 | 9 | 8 |  |  |
| **First-line treatments, n (%)** |  |  |  |  |  |  |
| *No treatment* | 73 (30) | 62 (22) | 68 (22) | 34 (10) |  |  |
| *Anti-CTLA-4* | 26 (11) | 136 (48) | 1 (0.3) | 1 (0.3) |  |  |
| *Anti-PD-1* | 0 (0) | 1 (0.4) | 149 (48) | 157 (48) |  |  |
| *Anti-PD-1 plus Anti-CTLA-4* | 0 (0) | 1 (0.4) | 11 (3.5) | 79 (24) |  |  |
| *BRAFi* | 14 (5.8) | 44 (15) | 67 (21) | 49 (15) |  |  |
| *Experimental Treatments* | 0 (0) | 1 (0.4) | 8 (2.6) | 4 (1.2) |  |  |
| *IFN/IL2* | 58 (24) | 1 (0.4) | 1 (0.3) | 0 (0) |  |  |
| *IL2 intralesional* | 0 (0) | 0 (0) | 0 (0) | 1 (0.3) |  |  |
| *Temozolomid* | 70 (29) | 38 (13) | 8 (2.6) | 0 (0) |  |  |
| **Brain metastases, n (%)** | 68 (28) | 68 (24) | 85 (27) | 68 (21) | 0.157 | 0.288 |
| **Disease stage, n (%)** |  |  |  |  | 0.036 \* | 0.132 |
| *M1c/M1d* | 165 (68) | 196 (69) | 213 (68) | 193 (59) |  |  |
| *III/M1a/M1b* | 76 (32) | 88 (31) | 100 (32) | 132 (41) |  |  |
| **LDH level, n (%)** |  |  |  |  | 0.423 | 0.423 |
| *>= ULN* | 96 (47) | 124 (47) | 121 (42) | 124 (41) |  |  |
| *< ULN* | 110 (53) | 142 (53) | 167 (58) | 178 (59) |  |  |
| *Not reported* | 35 | 18 | 25 | 23 |  |  |
| **Performance status, n (%)** |  |  |  |  | 0.051 | 0.132 |
| *0/1* | 155 (65) | 196 (69) | 216 (71) | 243 (76) |  |  |
| *2/3/4* | 83 (35) | 87 (31) | 90 (29) | 78 (24) |  |  |
| *Not reported* | 3 | 1 | 7 | 4 |  |  |
| **Steroids, n (%)** | 56 (23) | 50 (18) | 66 (21) | 46 (14) | 0.027 \* | 0.132 |
| **Comorbidities, n (%)** | 29 (12) | 58 (20) | 50 (16) | 46 (14) | 0.060 | 0.132 |
| *Not reported* | 4 | 1 | 0 | 0 |  |  |
| **Autoimmunity, n (%)** | 10 (4.1) | 13 (4.6) | 26 (8.3) | 29 (8.9) | 0.037 \* | 0.132 |
| **Other malignancies, n (%)** | 17 (7.1) | 20 (7.1) | 33 (11) | 31 (9.5) | 0.362 | 0.398 |
| *Not reported* | 2 | 3 | 0 | 0 |  |  |
| **eligible, n (%)** |  |  |  |  | 0.223 | 0.307 |
| *trial-like* | 96 (40) | 131 (46) | 128 (41) | 152 (47) |  |  |
| *trial-excluded* | 145 (60) | 153 (54) | 185 (59) | 173 (53) |  |  |
| 1\*p<0.05; \*\*p<0.01; \*\*\*p<0.001 | | | | | | |
| 2False discovery rate correction for multiple testing | | | | | | |