|  | trial-like | | | | | | trial-excluded | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Year 2012 (n = 96) | Year 2014 (n = 131) | Year 2016 (n = 128) | Year 2018 (n = 152) | p-value1 | q-value2 | Year 2012 (n = 145) | Year 2014 (n = 153) | Year 2016 (n = 185) | Year 2018 (n = 173) | p-value1 | q-value2 |
| **Gender, n (%)** |  |  |  |  | 0.002 \*\* | **0.016 \*** |  |  |  |  | 0.197 | 0.281 |
| *M* | 46 (48) | 81 (62) | 55 (43) | 95 (62) |  |  | 97 (67) | 84 (55) | 116 (63) | 106 (61) |  |  |
| *F* | 50 (52) | 50 (38) | 73 (57) | 57 (38) |  |  | 48 (33) | 69 (45) | 69 (37) | 67 (39) |  |  |
| **Age at 1st Treatment, Median (IQR)** | 65 (53 – 71) | 66 (55 – 72) | 69 (58 – 76) | 67 (55 – 76) |  |  | 71 (60 – 79) | 71 (61 – 79) | 73 (61 – 79) | 73 (64 – 78) |  |  |
| **BRAF status, n (%)** |  |  |  |  | 0.995 | >0.999 |  |  |  |  | 0.045 \* | 0.149 |
| *Wild-type* | 41 (53) | 67 (52) | 65 (51) | 76 (51) |  |  | 47 (57) | 85 (60) | 99 (56) | 75 (45) |  |  |
| *Mutant* | 37 (47) | 63 (48) | 63 (49) | 74 (49) |  |  | 36 (43) | 57 (40) | 77 (44) | 92 (55) |  |  |
| *Not reported* | 18 | 1 | 0 | 2 |  |  | 62 | 11 | 9 | 6 |  |  |
| **First-line treatments, n (%)** |  |  |  |  |  |  |  |  |  |  |  |  |
| *No treatment* | 5 (5.2) | 3 (2.3) | 4 (3.1) | 3 (2.0) |  |  | 68 (47) | 59 (39) | 64 (35) | 31 (18) |  |  |
| *Anti-CTLA-4* | 22 (23) | 105 (80) | 1 (0.8) | 0 (0) |  |  | 4 (2.8) | 31 (20) | 0 (0) | 1 (0.6) |  |  |
| *Anti-PD-1* | 0 (0) | 1 (0.8) | 89 (70) | 87 (57) |  |  | 0 (0) | 0 (0) | 60 (32) | 70 (40) |  |  |
| *Anti-PD-1 plus Anti-CTLA-4* | 0 (0) | 1 (0.8) | 11 (8.6) | 52 (34) |  |  | 0 (0) | 0 (0) | 0 (0) | 27 (16) |  |  |
| *BRAFi* | 7 (7.3) | 10 (7.6) | 14 (11) | 6 (3.9) |  |  | 7 (4.8) | 34 (22) | 53 (29) | 43 (25) |  |  |
| *Experimental Treatments* | 0 (0) | 0 (0) | 8 (6.2) | 4 (2.6) |  |  | 0 (0) | 1 (0.7) | 0 (0) | 0 (0) |  |  |
| *IFN/IL2* | 49 (51) | 1 (0.8) | 1 (0.8) | 0 (0) |  |  | 9 (6.2) | 0 (0) | 0 (0) | 0 (0) |  |  |
| *IL2 intralesional* | 0 (0) | 0 (0) | 0 (0) | 0 (0) |  |  | 0 (0) | 0 (0) | 0 (0) | 1 (0.6) |  |  |
| *Temozolomid* | 13 (14) | 10 (7.6) | 0 (0) | 0 (0) |  |  | 57 (39) | 28 (18) | 8 (4.3) | 0 (0) |  |  |
| **Brain metastases, n (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | >0.999 | >0.999 | 68 (47) | 68 (44) | 85 (46) | 68 (39) | 0.505 | 0.505 |
| **Disease stage, n (%)** |  |  |  |  | 0.531 | >0.999 |  |  |  |  | 0.114 | 0.192 |
| *M1c/M1d* | 49 (51) | 70 (53) | 67 (52) | 69 (45) |  |  | 116 (80) | 126 (82) | 146 (79) | 124 (72) |  |  |
| *III/M1a/M1b* | 47 (49) | 61 (47) | 61 (48) | 83 (55) |  |  | 29 (20) | 27 (18) | 39 (21) | 49 (28) |  |  |
| **LDH level, n (%)** |  |  |  |  | 0.408 | >0.999 |  |  |  |  | 0.441 | 0.489 |
| *>= ULN* | 38 (41) | 46 (36) | 45 (35) | 44 (31) |  |  | 58 (51) | 78 (57) | 76 (48) | 80 (51) |  |  |
| *< ULN* | 54 (59) | 83 (64) | 83 (65) | 100 (69) |  |  | 56 (49) | 59 (43) | 84 (52) | 78 (49) |  |  |
| *Not reported* | 4 | 2 | 0 | 8 |  |  | 31 | 16 | 25 | 15 |  |  |
| **Performance status, n (%)** |  |  |  |  | >0.999 | >0.999 |  |  |  |  | 0.072 | 0.181 |
| *0/1* | 95 (100) | 131 (100) | 127 (100) | 149 (100) |  |  | 60 (42) | 65 (43) | 89 (50) | 94 (55) |  |  |
| *2/3/4* | 0 (0) | 0 (0) | 0 (0) | 0 (0) |  |  | 83 (58) | 87 (57) | 90 (50) | 78 (45) |  |  |
| *Not reported* | 1 | 0 | 1 | 3 |  |  | 2 | 1 | 6 | 1 |  |  |
| **Steroids, n (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | >0.999 | >0.999 | 56 (39) | 50 (33) | 66 (36) | 46 (27) | 0.115 | 0.192 |
| **Comorbidities, n (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | >0.999 | >0.999 | 29 (20) | 58 (38) | 50 (27) | 46 (27) | 0.008 \*\* | 0.080 |
| *Not reported* | 1 | 0 | 0 | 0 |  |  | 3 | 1 | 0 | 0 |  |  |
| **Autoimmunity, n (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | >0.999 | >0.999 | 10 (6.9) | 13 (8.5) | 26 (14) | 29 (17) | 0.019 \* | 0.096 |
| **Other malignancies, n (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | >0.999 | >0.999 | 17 (12) | 20 (13) | 33 (18) | 31 (18) | 0.321 | 0.402 |
| *Not reported* |  |  |  |  |  |  | 2 | 3 | 0 | 0 |  |  |
| 1Fisher's exact test | | | | | | | | | | | | |
| 2False discovery rate correction for multiple testing | | | | | | | | | | | | |