Supplemental Table 1: Genes analyzed which are known to be involved in melanoma pathogenesis (Online Only)

|  |  |  |  |
| --- | --- | --- | --- |
| *BRAF* | *RAC1* | *CDKN2A* | *MAP2K2* |
| *AKT1* | *HRAS* | *MDM4* | *CDK4* |
| *PTEN* | *TERT* | *NF1* | *CCND1* |
| *AKT3* | *MYC* | *PPP6C* | *TP53* |
| *MET* | *RAF1* | *MITF* | *MAP2K1* |
| *RB1* | *MDM2* | *NRAS* | *NOTCH2* |
| *KRAS* | *KIT* |  |  |

# Supplemental Table 2: Patient demographics and disease characteristics (Online Only)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | E2603 total sample | |  | | P value |  | | 119 patients with CNV data | | P value |
|  | Patients excluded from the CNV study (n=704) | | Patients included in the CNV study (n=119) | |  | CP arm (n=53) | | SCP arm (n=66) | |  |
|  | n | % | n | % |  | n | % | n | % |  |
| Age (mean, SD) | 58.9 | 12.8 | 57.7 | 12.2 | 0.341 | 58.1 | 11.7 | 57.3 | 12.6 | 0.733 |
| Gender |  |  |  |  | 0.337 |  |  |  |  | 0.301 |
| Male | 441 | 62.6 | 80 | 67.2 |  | 33 | 62.3 | 47 | 71.2 |  |
| Female | 263 | 37.4 | 39 | 32.8 |  | 20 | 37.7 | 19 | 28.8 |  |
| Race |  |  |  |  | 0.424 |  |  |  |  | 0.835 |
| White | 684 | 97.2 | 114 | 95.8 |  | 51 | 96.2 | 63 | 95.5 |  |
| Other | 20 | 2.8 | 5 | 4.2 |  | 2 | 3.8 | 3 | 4.6 |  |
| AJCC stage |  |  |  |  | 0.003 |  |  |  |  | 0.322 |
| Unresectable Stage III | 51 | 7.2 | 20 | 16.8 |  | 9 | 17.0 | 11 | 16.7 |  |
| M1a/M1b | 246 | 34.9 | 35 | 29.4 |  | 12 | 22.6 | 23 | 34.9 |  |
| M1c | 407 | 57.8 | 64 | 53.8 |  | 32 | 60.4 | 32 | 48.5 |  |
| ECOG performance status |  |  |  |  | 0.997 |  |  |  |  | 0.187 |
| 0 | 432 | 61.4 | 73 | 61.3 |  | 36 | 67.9 | 37 | 56.1 |  |
| 1 | 272 | 38.6 | 46 | 38.7 |  | 17 | 32.1 | 29 | 43.9 |  |
| Prior therapy |  |  |  |  | 0.104 |  |  |  |  | 0.069 |
| None | 418 | 59.4 | 61 | 51.3 |  | 23 | 43.4 | 38 | 57.6 |  |
| IFN/IL-2/GM-CSF | 256 | 36.4 | 55 | 46.2 |  | 27 | 50.9 | 28 | 42.4 |  |
| One investigational therapy | 30 | 4.3 | 3 | 2.5 |  | 3 | 5.7 | 0 | 0.0 |  |
| Number of organs involved |  |  |  |  | 0.955 |  |  |  |  | 0.638 |
| 1 | 148 | 21.1 | 26 | 21.9 |  | 10 | 18.9 | 16 | 24.2 |  |
| 2-3 | 388 | 55.3 | 64 | 53.8 |  | 31 | 58.5 | 33 | 50.0 |  |
| >=4 | 166 | 23.7 | 29 | 24.4 |  | 12 | 22.6 | 17 | 25.8 |  |
| LDH |  |  |  |  | 0.701 |  |  |  |  | 0.080 |
| Normal | 393 | 58.3 | 66 | 56.4 |  | 34 | 65.4 | 32 | 49.2 |  |
| Above normal | 281 | 41.7 | 51 | 43.6 |  | 18 | 34.6 | 33 | 50.8 |  |
| Status of primary tumor |  |  |  |  | 0.134 |  |  |  |  | 0.871 |
| Unresected | 131 | 18.6 | 14 | 11.8 |  | 7 | 13.2 | 7 | 10.6 |  |
| Recurrent | 83 | 11.8 | 12 | 10.1 |  | 6 | 11.3 | 6 | 9.1 |  |
| Not recurrent, resected | 100 | 14.2 | 17 | 14.3 |  | 7 | 13.2 | 10 | 15.2 |  |
| Not recurrent, resected, residual tumor | 173 | 24.6 | 43 | 36.1 |  | 19 | 35.9 | 24 | 36.4 |  |
| Primary tumor is unknown | 6 | 0.9 | 1 | 0.8 |  | 1 | 1.9 | 0 | 0.0 |  |
|  | 210 | 29.9 | 32 | 26.9 |  | 13 | 24.5 | 19 | 28.8 |  |

# Supplemental Table 3: Clinical outcomes (Online Only)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | E2603 total sample | |  | 119 patients with CNV data | |  |
| Endpoints | Patients excluded from the CNV study (n=704) | Patients included in the CNV study (n=119) | P value | CP arm (n=53) | SCP arm (n=66) | P value |
| ORR (95% CI) | 19.5% (16.6-22.6) | 18.5% (12.0-26.6) | 0.80 | 17.0 (8.1-29.8) | 19.7 (10.9-31.3) | 0.70 |
| OS (median, 95%CI) | 11.4 (10.6-12.3) | 9.3 (8.1-11.0) | 0.22 | 10.4 (7.2-14.7) | 8.8 (7.3-10.4) | 0.95 |
| PFS (median, 95%CI) | 4.7 (4.3-5.1) | 4.4 (3.0-5.8) | 0.94 | 3.9 (1.9-5.8) | 5.0 (3.0-6.0) | 0.63 |

**Supplemental Table 4: *BRAF* gene amplification is associated with *BRAF* somatic mutations (Online Only)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | *BRAF* | | *NRAS* | | WT | |  |
| CNV | N | % | N | % | N | % | P-value |
| *BRAF* |  |  |  |  |  |  | 0.0011 |
| Diploid | 10 | 18.50% | 10 | 35.70% | 22 | 55.00% |  |
| Gain | 44 | 81.50% | 18 | 64.30% | 18 | 45.00% |  |

**Supplemental Table 5: RAF1 gene amplification is associated with worse PS (Online Only)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *RAF1* | Diploid | | Gain | | Loss | |  |
| Variable | N | % | N | % | N | % | P-value |
| ECOG PS |  |  |  |  |  |  | 0.002 |
| 0 | 55 | 73.33% | 15 | 44.12% | 3 | 30% |  |
| 1 | 20 | 26.67% | 19 | 55.88% | 7 | 70% |  |

FIGURE LEGENDS:

Supplemental Figure 1. Frequency plot of copy gains and losses in somatic mutation cohorts across the whole genome. (Online Only)

Aggregate frequency plots for *BRAF*, *NRAS* and WT somatic cohorts. Frequency of copy number is on the Y-axis, where frequencies greater that 0% (blue) denote copy gains and frequencies less than 0% (red) denote copy losses. Some areas of copy gains or losses that appear to be different between the somatic mutation cohorts are circled. Genomic location of selected genes (*BRAF*, *MET*, *NRAS*, and *RAF1*) has been identified with arrows.

Supplemental Figure 2. Kaplan-Meier curves demonstrating no association between *RAF1* amplification and *NRAS* somatic mutations on PFS or OS (Online Only)

Kaplan-Meier curves evaluating the conjoined analysis of *RAF1* copy gain, *NRAS* somatic mutations, both, or neither on effect of PFS (A) and OS (B).

Supplemental Figure 3. *BRAF* and *MET* gene amplifications are associated with *BRAF* V600K mutation cohort (Online Only)

A. *BRAF* copy number in designated somatic mutation cohorts. Y-axis, average *BRAF* probe median (log2 scale).

B. *MET* copy number in designates somatic mutation cohorts. Y-axis, average *MET* probe median (log2 scale).

N=9 for V600K and N=38 for V600E samples.