**Supplementary Table 1.** Study drug exposure according to time of data cutoff

|  |  |  |
| --- | --- | --- |
|  | **Data cutoff October 1, 2013** [3] | **Data cutoff May 25, 2018** |
|  | **BRAF inhibitor–naive cohort****n = 63** | **Vemurafenib monotherapy–PD cohort****n = 66** | **BRAF inhibitor–naive cohort****n = 63** | **Vemurafenib monotherapy–PD cohort****n = 66** |
| **Vemurafenib** |  |  |  |  |
| Median duration of exposure, months (range) | 11.9 (1.4–21.9) | 3.1 (0.5–25.8) | 14.7 (1.4–70.7) | 3.3 (0.5–57.0) |
| Median total cumulative dose, g (range) | 534.7 (66.2–1057.9) | 161.9 (25.9–1503.4) | 709.4 (66.2–3133.2) | 162.8 (25.9–2909.5) |
| Mean dose intensity, % (SD) | 86.3 (15.7) | 96.3 (8.0) | 85.1 (15.9) | 96.2 (8.0) |
| **Cobimetinib** |  |  |  |  |
| Median duration of exposure, months (range) | 12.0 (1.4–21.7) | 3.1 (0.5–25.3) | 14.7 (1.4–70.5) | 3.3 (0.5–57.0) |
| Median total cumulative dose, g (range) | 14.3 (2.1–27.5) | 4.2 (0.8–24.9) | 16.6 (2.1–88.1) | 4.5 (0.8–70.6) |
| Mean dose intensity, % (SD) | 88.8 (16.8) | 97.1 (7.7) | 87.9 (17.1) | 97.1 (7.7) |

Abbreviations: PD, progressive disease; SD, standard deviation.

**Supplementary Table 2.** Most common AEs (≥20% in any subgroup), regardless of attribution to study drugs

|  |  |  |
| --- | --- | --- |
| **Most common AEs, n (%)** | **BRAF inhibitor–naive cohort****n = 63** | **Vemurafenib monotherapy–PD cohort****n = 66** |
|  | **Any Grade** | **Grade ≥3** | **Any Grade**  | **Grade ≥3** |
| Diarrhea  | 52 (83) | 6 (10) | 31 (47) | 2 (3) |
| Fatigue  | 46 (73) | 7 (11) | 18 (27) | 1 (2) |
| Photosensitivitya  | 44 (70) | 1 (2) | 12 (18) | 1 (2) |
| Elevations in LFTsa  | 44 (70) | 13 (21) | 22 (33) | 4 (6) |
| Nausea  | 37 (59) | 2 (3) | 23 (35) | 2 (3) |
| Arthralgia  | 31 (49) | 7 (11) | 8 (12) | 1 (2) |
| Vomiting  | 30 (48) | 0 | 14 (21) | 1 (2) |
| CPK level elevation  | 30 (48) | 2 (3) | 10 (15) | 1 (2) |
| Pyrexia  | 28 (44) | 1 (2) | 11 (17) | 1 (2) |
| Peripheral edema  | 27 (43) | 0 | 11 (17) | 0 |
| Anemia  | 23 (37) | 7 (11) | 11 (17) | 5 (8) |
| Blood creatinine increased  | 21 (33) | 1 (2) | 6 (9) | 0 |
| Myalgia  | 20 (32) | 1 (2) | 4 (6) | 0 |
| Headache  | 19 (30) | 2 (3) | 13 (20) | 0 |
| Pruritus  | 19 (30) | 1 (2) | 7 (11) | 0 |
| Hypertension  | 19 (30) | 5 (8) | 6 (9) | 1 (2) |
| Actinic keratosis | 19 (30) | 0 | 3 (5) | 0 |
| Decreased appetite  | 17 (27) | 0 | 14 (21) | 0 |
| Chills  | 17 (27) | 0 | 10 (15) | 0 |
| Dry skin  | 17 (27) | 0 | 2 (3) | 0 |
| Upper respiratory tract infection  | 16 (25) | 0 | 6 (9) | 0 |
| Hypokalemia  | 16 (25) | 3 (5) | 4 (6) | 0 |
| Seborrheic keratosis  | 15 (24) | 1 (2) | 1 (2) | 0 |
| Skin papilloma  | 15 (24) | 0 | 0 | 0 |
| Blurred vision  | 14 (22) | 0 | 2 (3) | 0 |
| Abdominal pain  | 13 (21) | 0 | 10 (15) | 1 (2) |
| Constipation  | 13 (21) | 0 | 10 (15) | 1 (2) |
| Cough  | 13 (21) | 0 | 6 (9) | 0 |
| Hypophosphatemia  | 13 (21) | 6 (10) | 3 (5) | 3 (5) |

Abbreviations: AEs, adverse events; CPK, creatine phosphokinase; cuSCC, cutaneous squamous cell carcinoma; LFTs, liver function tests; PD, progressive disease.

AEs occurring in ≥20% of patients in either cohort are reported.

aGrouped terms.

**Supplementary Table 3.** AEs of special interest

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **AEs of special interest,a n (%)** | **BRAF inhibitor–naive cohort****n = 63****(data cutoff: 2014)** | **Vemurafenib monotherapy–PD cohort****n = 66****(data cutoff: 2014)** | **BRAF inhibitor–naive cohort****(data cutoff: May 25, 2018)** | **Vemurafenib monotherapy–PD cohort****(data cutoff: May 25, 2018)** |
| Retinal detachment/retinopathy | 7 (11) | 0 | 7 (11) | 1 (2)  |
| Grade ≥3 QTc prolongation | 4 (6) | 2 (3) | 4 (6) | 2 (3) |
| cuSCC | 8 (13) | 6 (9) | 8 (13) | 5 (8) |

Abbreviations: AEs, adverse events; cuSCC, cutaneous squamous cell carcinoma; PD, progressive disease; QTc, corrected QT interval.

Increases from the previous analysis [3] in either cohort are reported.

aAEs of special interest were those called out by regulatory authorities based on the prevailing safety data from clinical trials of BRAF and MEK inhibitors.

**Supplementary Table 4.** Summary frequencies of dose modifications or interruption due to AEs

|  |  |  |
| --- | --- | --- |
|  | **BRAF inhibitor–naive cohort****n = 63** | **Vemurafenib monotherapy–PD cohort****n = 66** |
| Dose modificationa because of AEs, n (%)Both drugs Vemurafenib Cobimetinib | 41 (65.1)49 (77.8)43 (68.3) | 13 (19.7)18 (27.3)14 (21.2) |
| Discontinuation because of AEs, n (%)Both drugs VemurafenibCobimetinib | 5 (7.9)7 (11.1)7 (11.1) | 1 (1.5)3 (4.5)1 (1.5) |

Abbreviations: AEs, adverse events; PD, progressive disease.

aDose reductions or interruptions.