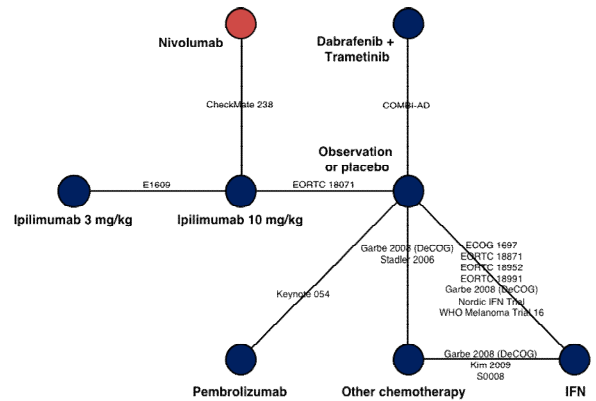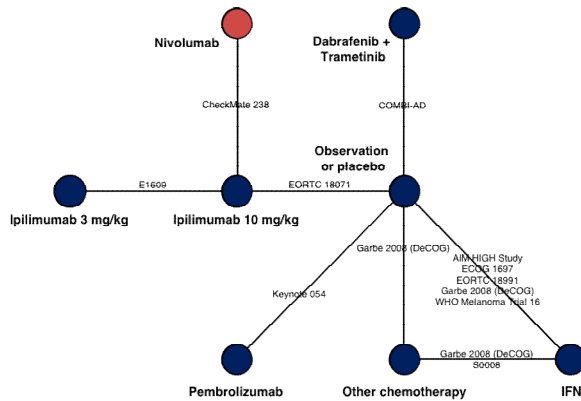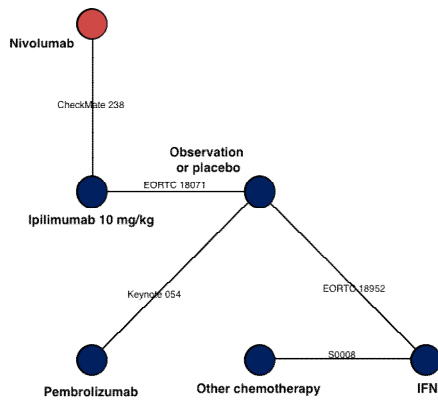**Appendix D: Safety analyses**

**Figure D.1**

Network diagrams of randomized controlled trials for subgroup analysis of safety outcomes

**A.** Stage II/III/IV population – grade 3/4 adverse events

**B.** Stage II/III/IV population – discontinuations due to adverse events



**C.** Stage III/IV subgroup population – discontinuations



Notes: Trial names in red font indicate stage III subgroup data was used to inform comparison; other chemotherapy includes various combinations of cisplatin, vinblastine, dacarbazine, interleukin-2, temozolomide, and IFN-alfa-2b. IFN: interferon.

**Table D.1**

Odds ratio estimates[a] from a fixed-effects network meta-analysis of grade 3/4 adverse events in patients with stage II-IV melanoma.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Observation or placebo | 1.08 (0.73, 1.60) | **0.23 (0.16, 0.32)** | **0.30 (0.23, 0.39)** | **0.50 (0.34, 0.72)** | **0.05 (0.03, 0.08)** | **0.09 (0.07, 0.11)** | **0.49 (0.37, 0.66)** |
| 0.92 (0.63, 1.37) | Nivolumab | **0.21 (0.13, 0.36)** | **0.28 (0.21, 0.36)** | **0.46 (0.32, 0.66)** | **0.05 (0.03, 0.08)** | **0.08 (0.05, 0.13)** | **0.45 (0.28, 0.74)** |
| **4.32 (3.12, 6.06)** | **4.68 (2.79, 7.86)** | Dabrafenib + trametinib | 1.30 (0.84, 1.99) | **2.15 (1.31, 3.54)** | **0.21 (0.12, 0.37)** | **0.40 (0.27, 0.59)** | **2.13 (1.37, 3.30)** |
| **3.34 (2.55, 4.41)** | **3.62 (2.74, 4.79)** | 0.77 (0.50, 1.18) | Ipilimumab 10 mg/kg | **1.66 (1.29, 2.13)** | **0.16 (0.10, 0.27)** | **0.31 (0.22, 0.43)** | **1.64 (1.10, 2.46)** |
| **2.01 (1.40, 2.92)** | **2.18 (1.50, 3.17)** | **0.47 (0.28, 0.76)** | **0.60 (0.47, 0.77)** | Ipilimumab 3 mg/kg | **0.10 (0.06, 0.17)** | **0.18 (0.12, 0.28)** | 0.99 (0.62, 1.59) |
| **20.46 (13.30, 31.55)** | **22.15 (12.44, 39.52)** | **4.73 (2.72, 8.13)** | **6.12 (3.69, 10.18)** | **10.16 (5.74, 17.93)** | Other chemotherapy | **1.88 (1.28, 2.75)** | **10.05 (5.97, 17.04)** |
| **10.91 (8.90, 13.40)** | **11.81 (7.61, 18.32)** | **2.52 (1.70, 3.69)** | **3.26 (2.33, 4.57)** | **5.41 (3.56, 8.23)** | **0.53 (0.36, 0.78)** | IFN | **5.36 (3.75, 7.66)** |
| **2.03 (1.52, 2.73)** | **2.20 (1.34, 3.59)** | **0.47 (0.30, 0.73)** | **0.61 (0.41, 0.91)** | 1.01 (0.63, 1.62) | **0.10 (0.06, 0.17)** | **0.19 (0.13, 0.27)** | Pembrolizumab |

[a]The value in each cell represents the hazard ratio (95% credible interval) for the comparison of the treatment indicated in that row versus the treatment indicated in that column; bolded values are statistically significant at the 0.05 significance level.

IFN: interferon.

**Table D.2**

Odds ratio estimates[a] from a fixed-effects network meta-analysis of discontinuations due to adverse events in patients with stage II-IV melanoma.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Observation or placebo | **0.28 (0.15, 0.51)** | **0.08 (0.04, 0.14)** | **0.04 (0.02, 0.07)** | **0.09 (0.05, 0.15)** | **0.07 (0.04, 0.10)** | **0.04 (0.03, 0.06)** | **0.14 (0.07, 0.25)** |
| **3.52 (1.95, 6.48)** | Nivolumab | **0.28 (0.11, 0.65)** | **0.14 (0.10, 0.21)** | **0.31 (0.20, 0.49)** | **0.23 (0.11, 0.49)** | **0.15 (0.08, 0.30)** | 0.48 (0.19, 1.15) |
| **12.65 (7.16, 24.76)** | **3.62 (1.53, 8.82)** | Dabrafenib + trametinib | 0.52 (0.24, 1.18) | 1.12 (0.50, 2.67) | 0.83 (0.39, 1.83) | 0.55 (0.29, 1.12) | 1.72 (0.70, 4.26) |
| **24.49 (15.38, 40.49)** | **6.96 (4.86, 10.08)** | 1.93 (0.85, 4.15) | Ipilimumab 10 mg/kg | **2.17 (1.68, 2.80)** | 1.60 (0.85, 3.09) | 1.06 (0.62, 1.86) | **3.31 (1.45, 7.41)** |
| **11.25 (6.65, 19.84)** | **3.21 (2.06, 4.97)** | 0.89 (0.37, 2.00) | **0.46 (0.36, 0.59)** | Ipilimumab 3 mg/kg | 0.74 (0.37, 1.49) | **0.49 (0.27, 0.90)** | 1.52 (0.65, 3.55) |
| **15.38 (9.78, 23.67)** | **4.36 (2.04, 9.08)** | 1.20 (0.55, 2.54) | 0.63 (0.32, 1.18) | 1.36 (0.67, 2.70) | Other chemotherapy | **0.66 (0.45, 0.96)** | 2.08 (0.89, 4.50) |
| **23.25 (17.61, 29.80)** | **6.57 (3.36, 12.56)** | 1.83 (0.89, 3.47) | 0.94 (0.54, 1.61) | **2.05 (1.11, 3.69)** | **1.51 (1.04, 2.21)** | IFN pooled | **3.15 (1.45, 6.20)** |
| **7.37 (3.95, 14.93)** | 2.10 (0.87, 5.15) | 0.58 (0.23, 1.44) | **0.30 (0.14, 0.69)** | 0.66 (0.28, 1.55) | 0.48 (0.22, 1.12) | **0.32 (0.16, 0.69)** | Pembrolizumab |

[a]The value in each cell represents the hazard ratio (95% credible interval) for the comparison of the treatment indicated in that row versus the treatment indicated in that column; bolded values are statistically significant at the 0.05 significance level.

IFN: interferon.

**Table D.3**

Odds ratio estimates[a] from a fixed-effects network meta-analysis of discontinuation in patients with stage II-IV melanoma.

| | | | | | |
|---|---|---|---|---|---|
| Observation or placebo | 1.46 (0.82, 2.56) | **0.35 (0.21, 0.56)** | 1.79 (0.92, 3.58) | **0.32 (0.20, 0.53)** | 0.97 (0.76, 1.25) |
| 0.68 (0.39, 1.22) | Nivolumab | **0.24 (0.18, 0.31)** | 1.23 (0.52, 3.01) | **0.22 (0.11, 0.48)** | 0.67 (0.36, 1.25) |
| **2.89 (1.78, 4.84)** | **4.23 (3.20, 5.61)** | Ipilimumab 10 mg/kg | **5.20 (2.29, 12.20)** | 0.93 (0.47, 1.92) | **2.81 (1.64, 4.97)** |
| 0.56 (0.28, 1.09) | 0.81 (0.33, 1.94) | **0.19 (0.08, 0.44)** | Other chemotherapy | **0.18 (0.11, 0.29)** | 0.54 (0.26, 1.11) |
| **3.11 (1.88, 5.08)** | **4.54 (2.08, 9.52)** | 1.07 (0.52, 2.11) | **5.56 (3.51, 9.02)** | IFN pooled | **3.02 (1.73, 5.22)** |
| 1.03 (0.80, 1.32) | 1.50 (0.80, 2.77) | **0.36 (0.20, 0.61)** | 1.84 (0.90, 3.82) | **0.33 (0.19, 0.58)** | Pembrolizumab |

[a]The value in each cell represents the hazard ratio (95% credible interval) for the comparison of the treatment indicated in that row versus the treatment indicated in that column; bolded values are statistically significant at the 0.05 significance level.

IFN: interferon.