**Supplementary Table S2.** Quantifying treatment benefit in marker specific subgroups. Additional examples and clinical interpretation.

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| **Trial 3: PD-L1 status and the treatment effect of combined nivolumab (N) and ipilimumab (I) and nivolumab alone on progression free survival (data from ref.** [**1**](#_ENREF_1)**)** |
| Measure | Marker negative (PD-L1) | Marker positive(PD-L1) | Treatment effect(entire cohort) | Interpretation |
| Hazard ratio for N+I vs I (log scale) | NR | NR | HR=0.42 N + I vs I | The hazard of progressing is 58% (100-42) less in N + I compared to I alone regardless of marker status. No statements can be made about interaction of N + I and PD-L1 over time since the interaction was NR. |
| Hazard ratio for N vs I (log scale) | NR | NR | HR=0.57 N vs I | The hazard of progressing is 43% less in single agent N compared to I regardless of marker status. No statements can be made about interaction of N + I and PD-L1 over time since the interaction was NR. |
| Nivolumab + ipilimumab vs ipilimumab alone |
| At 12 months | Marker negative | Marker positive | Differential treatment benefit |  |
| Ratio of PFS estimates at 12 months | 3.83(46/12) | 2.80(56/20) | 1.37 | At 12 months, both for PD-L1 negative and positive patients, TB is higher with the combination treatment relative to treatment with ipilumumab alone. Compared to PD-L1 positive patients, PD-L1 negative patients had 37% better TB due to combination therapy relative to ipilumumab.  |
| Difference in proportion of patients progression-free at 12 months | 34(46-12) | 36(56-20) | -2 | At 12 months, nivolumab+Ipilimumab benefit is 2% smaller in PD-L1 negative than in PD-L1 positive patients; on the difference scale, greater TB occurs for PD-L1 positive patients. |
| Nivolumab vs ipilimumab alone |
| Ratio of PFS estimates at 12 months | 3(36/12) | 2.80(56/20) | 1.07 | At 12 months, both for PD-L1 negative and positive patients, TB is higher with nivolumab treatment relative to treatment with ipilumumab alone. Nivolumab benefit over ipilimumab for patients with PD-L1 negative is 7% better compared to the benefit in PD-L1 positive patients. |
| Difference in proportion of patients progression-free at 12 months | 24(36-12) | 36(56-20) | -12% | At 12 months, nivolumab benefit over Ipilimumab is 12% smaller in PD-L1 negative than in PD-L1 positive patients. |
| Nivolumab + ipilimumab vs nivolumab |
| Ratio of PFS estimates at 12 months | 1.28(46/36) | 1(56/56) | 1.28 | At 12 months, nivolumab + ipilimumab benefit over nivolumab for patients with PD-L1 negative is 28% better compared to the benefit in PD-L1 positive patients. |
| Difference in proportion of patients progression-free at 12 months | 10 (46-36) | 0 (56-56) | 10% | At 12 months, nivolumab + ipilimumab benefit over nivolumab is 10% larger in PD-L1 negative than in PD-L1 positive patients. |
| **Trial 4: KRAS is predictive of cetuximab benefit in colon patients (2)** |
| Measure | Marker negative (KRAS mutant) | Marker positive(KRAS wildtype) | Differential treatment (Cetuximab)benefit | Interpretation |
| Hazard ratio (log scale); PFS | 0.99 | 0.40 | log(0.99/0.40) (P<0.0001) | Significant interaction of cetuximab treatment and KRAS over time. |
| Ratio of PFS estimates at 2 months | 0.74(26/35) | 1.56(64/41) | 0.48 (\*) | At 2 months, the benefit of cetuximab in patients with KRAS mutations is 52% worse relative to cetuximab benefit in patients with wildtype KRAS. |
| Difference in proportion of patients progression-free at 2 months | -9%(26%-35%) | 23%(64%-41%) | -32% (\*) | At 2 months, cetuximab benefit is 32% smaller in mutant patients than in patients with wildtype KRAS. |

\*Pvalues are not provided in examples where raw data were not available to estimate the variance. NR, not reported; PFS, progression free survival.