

Description of Additional Supplementary Files

Supplementary Data 1

Description: Prevalence of tissue-agnostic alterations in 295,316 tumors. TMB-High and MSI-High/MMRd alterations are associated with pembrolizumab; BRAFV600E mutations with dabrafenib+trametinib, NTKR1/2/3 fusions with entrectinib or Larotrectinib, and RET fusions with selpercatinib. Pan-tumor cohort sizes that were investigated were as follows: TMB-High (N=262,429), MSI-High/MMRd (N=251,968), BRAFV600E (N=248,181), NTRK1/2/3 or RET fusions (N=226,566), and any positive (N=181,463).

Supplementary Data 2

Description: Age and sex in patients carrying “Any Positive” tissue agnostic alteration compared to those without any alterations. Statistical significance was determined by Chi-square test (no multiple comparison testing).

Supplementary Data 3

Description: Race and ethnicity in patients carrying “Any Positive” tissue agnostic alteration compared to those without any alterations. Statistical significance was determined by Chi-square test (no multiple comparison testing).

Supplementary Data 4

Description: Time-on-treatment (TOT) with pembrolizumab in tumor mutational burden (TMB)-High tumors. Excluded = excluded from Figure 3A due to small N. Included = included in Figure 3A. HRs were computed utilizing the Cox proportional hazards model.

Supplementary Data 5

Description: Overall survival (OS) from start of pembrolizumab in tumor mutational burden (TMB)-High tumors. Excluded = excluded from Figure 3B due to small N. Included = included in Figure 3B. HRs were computed utilizing the Cox proportional hazards model.

Supplementary Data 6

Description: Time-on-treatment (TOT) with pembrolizumab in microsatellite instability (MSI)-High/mismatch repair deficient (MMRd) tumors. Excluded = excluded from Figure 3C due to small N. Included = included in Figure 3C. HRs were computed utilizing the Cox proportional hazards model.

Supplementary Data 7

Description: Overall survival (OS) from start of pembrolizumab in microsatellite instability (MSI)-High/mismatch repair deficient (MMRd) tumors. Excluded = excluded from Figure 3D due to small N. Included = included in Figure 3D. HRs were computed utilizing the Cox proportional hazards model.

Supplementary Data 8

Description: Time on treatment (TOT) with pembrolizumab in microsatellite stable (MSS)/mismatch repair proficient (MMRp) tumors. Excluded = excluded from Figure 3E due to small N. Included = included in Figure 3E. HRs were computed utilizing the Cox proportional hazards model.

Supplementary Data 9

Description: Overall survival (OS) from start of pembrolizumab in microsatellite stable (MSS)/mismatch repair proficient (MMRp) tumors. Excluded = excluded from Figure 3F due to small N. Included = included in Figure 3F. HRs were computed utilizing the Cox proportional hazards model.

Supplementary Data 10

Description: Association of MSI-High/MMRd with pembrolizumab and nivolumab across various cancer types. HR = hazard ratio; CI = confidence interval. HRs were computed utilizing the Cox proportional hazards model, and P values were assessed by 2-sided log-rank test (no multiple comparison testing).

Supplementary Data 11

Description: Association of TMB-High and time-on-treatment (TOT) of additional immune checkpoint inhibitors across various cancer types. Hazard ratios (HRs) indicate comparison of TMB-High to TMB-Low. CI = confidence interval. HRs were computed utilizing the Cox proportional hazards model, and P values were assessed by 2-sided log-rank test (no multiple comparison testing).

Supplementary Data 12

Description: Association of MSI-High/MMRd and time-on-treatment (TOT) of additional immune checkpoint inhibitors across various cancer types. Hazard ratios (HRs) indicate comparison of MSI-High to MSS. CI = confidence interval. HRs were computed utilizing the Cox proportional hazards model, and P values were assessed by 2-sided log-rank test (no multiple comparison testing).

Supplementary Data 13

Description: Association of TMB and MSI-High/MMRd with overall survival (OS) from start of pembrolizumab. Cox-Proportional Hazard multivariate model was run on post-pembrolizumab OS with MSI-High/MMRd input as categorical variable and TMB input as a continuous variable (mt/MB). Hazard ratio (HR) is shown for each unit of TMB increase. Only cancer types with $n > 5$ are shown. CI = confidence interval. P values were determined by 2-sided log-rank test.

* OS significantly associated with MSI-High/MMRd after adjusting for TMB.

** OS significantly associated with increased TMB after adjusting for MSI-High/MMRd.

*** Both increased TMB and MSI-High/MMRd status are associated with OS after adjusting for the other variant.