POLE/POLD1 Mutations as Predictive Biomarkers for Immunotherapy Response: Insights from a Pan-cancer Real-World Dataset

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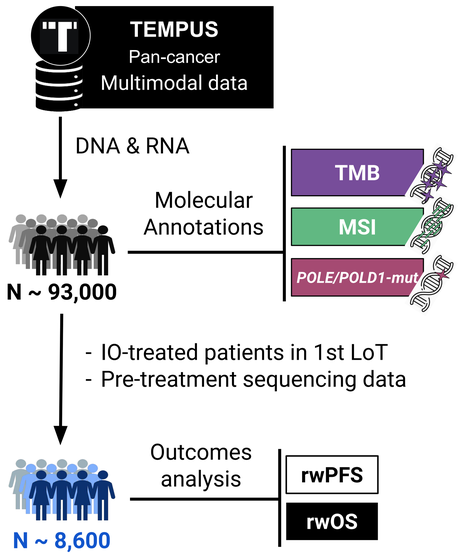
Poster/Abstract #166

INTRODUCTION

- Mutations in DNA polymerases *POLE* and *POLD1* are associated with tumor development and certain hereditary cancers characterized by hyper-mutated genomic phenotypes, leading to high DNA tumor mutation burden (TMB).
- Similar to mismatch repair instability (MSI), increased TMB confers significant prognostic benefits to immunotherapy due to higher immune tumor microenvironment activation.
- The current study utilizes Tempus' multimodal, real-world database, encompassing molecular and clinical de-identified records, to evaluate the prevalence of *POLE/POLD1* mutations and their predictive significance in immunotherapy response, providing a unique perspective for pre-clinical and clinical discovery.

METHODS

- Approximately 93,000 de-identified records with available DNA and RNA sequencing were included in the study.
- The study cohort included molecular and clinical annotations such as mismatch repair immunohistochemistry (IHC), microsatellite instability status (MSI), tumor mutational burden (TMB), and mutations in the *POLE* or *POLD1* genes.
- Outcomes analyses were performed on a subset of patients who received immune checkpoint inhibitor (IO) treatment as their first line of therapy and had sequencing data available prior to receiving immunotherapy.



SUMMARY

- Across solid cancers, 8.83% (N=8,206) of patients harbored mutations (1.84% P/LP and 98.15% VUS) in *POLE* or *POLD1* genes.
- Patients with *POLE/POLD1* mutations (P/LP or VUS) showed improved real-world PFS and OS when treated with immunotherapy, especially among patients with TMB-High or MSI-High.
- Mutations in *POLE/POLD1* as a DNA biomarker may help increase patient inclusion for available IO treatment combinations beyond TMB-High and MSI-High.

RESULTS

In a pan-cancer cohort, 8.83% of patients showed P/LP or VUS *POLE/POLD1* mutations

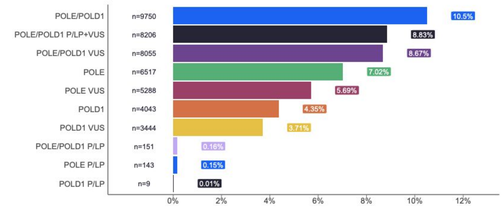


Figure 1. *POLE* or *POLD1* mutation prevalence in a large solid pan-cancer cohort (N~93,000). Bars illustrates the number and percentage of patients with detected germline or somatic mutations overall (benign, P, LP or VUS) and within each variant classification subgroup.

POLE/POLD1-mut show higher levels of TMB, even in TMB-High/MSI-High or TMB-Low/MSI-Stable populations

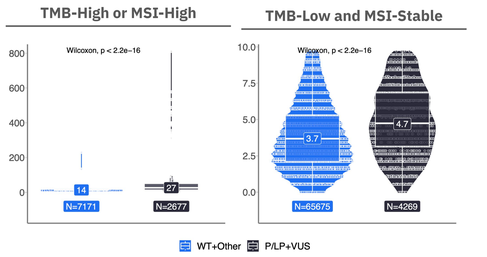
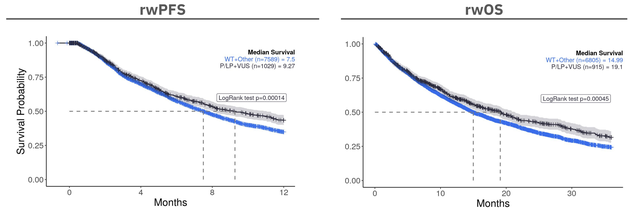


Figure 2. Box and violin plots showing TMB levels between wild-type (WT) and *POLE/POLD1*-mutated (P/LP+VUS) patients in two groups: TMB-High or MSI-High (left panel) and TMB-Low and MSI-Stable (right panel). The numbers within the plots represent the median TMB values for each group, with sample sizes indicated below. Wilcoxon rank sum test p-value is provided.

Abbreviations: pathogenic or likely-pathogenic mutations (P/LP); variants of uncertain significance (VUS); real-world progression-free survival (rwPFS); real-world overall survival (rwOS); immunotherapy (IO); chemotherapy (chemo); line-of-treatment (LoT); Kaplan-Meier (KM).

POLE/POLD1-mut patients exhibit better outcomes after IO therapy in a 1L setting



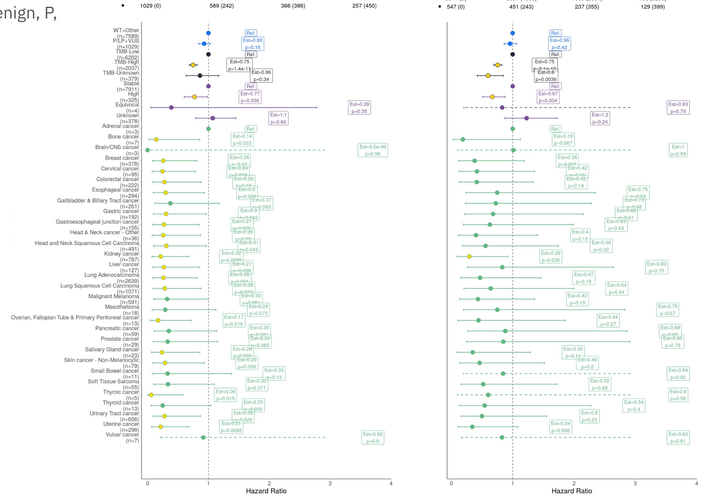
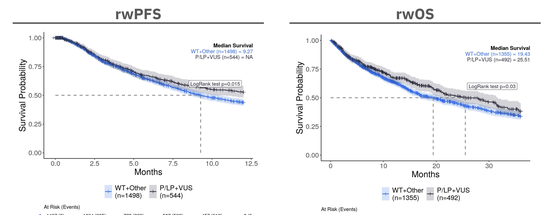


Figure 3. KM survival curves (top panels) and multivariate CoxPH model forest plots (bottom panels) illustrate the outcomes (rwPFS on the left, and rwOS on the right) of *POLE/POLD1*-mutated patients treated with immunotherapy (IO), and a combination of chemotherapy and IO(chemo + IO), against patients with no mutation (WT) or other mutations in *POLE/POLD1* genes (Other). Median survival times and number of patients at risk over time are specified in KM plots. The forest plots present hazard ratios (HR) from multivariate CoxPH models, with 95% confidence intervals for all covariates (*POLE/POLD1* mutations, TMB, MSI status and indication), indicating the relative risk of progression or death.

Increased survival benefit to 1L IO therapy observed for TMB-High or MSI-High patients with *POLE/POLD1* mutations



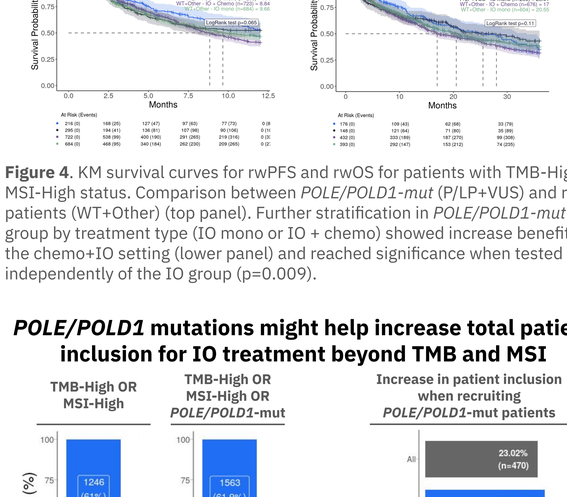


Figure 4. KM survival curves for rwPFS and rwOS for patients with TMB-High or MSI-High status. Comparison between *POLE/POLD1-mut* (P/LP+VUS) and rest of patients (WT+Other) (top panel). Further stratification in *POLE/POLD1-mut* group by treatment type (IO mono or IO + chemo) showed increase benefit in the chemo+IO setting (lower panel) and reached significance when tested independently of the IO group (p=0.009).

POLE/POLD1 mutations might help increase total patient inclusion for IO treatment beyond TMB and MSI

Figure 5. Bar charts depicting responders and non-responders (based on rwPFS median survival time [7.63 months]) when selecting patients with TMB-High or MSI-High status (left panel) and those with TMB-High, MSI-High, or *POLE/POLD1* mutations (middle panel). The right panel shows the difference in patient inclusion between left-panel and middle panel.

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