Characterizing the Genomic Landscape of *POLE/POLD1*-Mutated Colorectal Adenocarcinoma

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INTRODUCTION

Pathogenic mutations in *POLE/POLD1* lead to decreased fidelity of DNA replication, resulting in a high tumor mutational burden (TMB-H) independent of deficient mismatch repair (dMMR) and high microsatellite instability (MSI-H). Studies have shown associations between this hypermutated phenotype and susceptibility to immune checkpoint inhibition.

Here, we characterized *POLE/POLD1* alterations in a large, real-world cohort of patients with colorectal cancer (CRC).

METHODS

- De-identified records of primary CRC patients profiled with the Tempus xT assay (DNA-seq of 595-648 genes at 500x) were identified from the Tempus Database.
- Immunological markers analyzed included TMB, MSI, and dMMR.
- MSI-H was determined by the assay through assessment of 239 loci. dMMR was determined by immunohistochemistry.

Cohort Overview by *POLE/POLD1* Status

Characteristic	Overall, N=9,136[1]	POLE/POLD1 wild-type, n=8,919[1]	*POLE/POLD1* mutant, n=217[1]	p-value[2]
Age at Diagnosis	59 (50, 69)	59 (50, 69)	58 (49, 66)	**0.15**
Gender				**0.7**
Male	5,112 (56%)	4,987 (56%)	125 (58%)	
Female	3,993 (44%)	3,901 (44%)	92 (42%)	
Race/Ethnicity				
White	3,907 (76%)	3,823 (76%)	84 (71%)	
Black/African American	703 (14%)	680 (14%)	23 (19%)	
Asian	216 (4.2%)	212 (4.2%)	4 (3.4%)	
Hispanic/Latino	531 (18%)	515 (18%)	16 (22%)	
Stage				**0.010**
I-II	567 (7%)	557 (7%)	10 (5.1%)	
III-IV	7,701 (93%)	7,516 (93%)	185 (95%)	
dMMR	240 (6.8%)	236 (6.8%)	4 (5.3%)	

[1] Median (IQR); n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

RESULTS

POLE/POLD1 Alterations

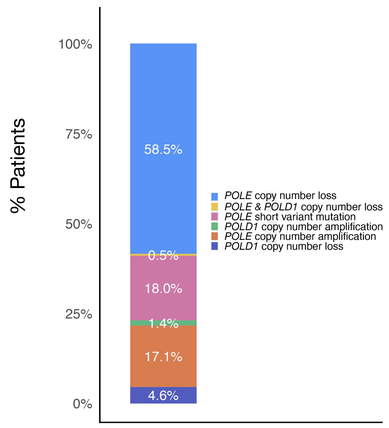

Figure 1. Among the *POLE/POLD1*-mutant cohort (n=203 *POLE*, n=13 *POLD1*, n=1 both; 0 germline), *POLE* copy number losses accounted for most mutations (n=127), followed by *POLE* short variants and copy number amplifications (n=76). The remaining tumors exhibited *POLD1* CNVs (n=14), including one with both *POLE* and *POLD1* CNVs.

MSI-H by *POLE/POLD1* Status

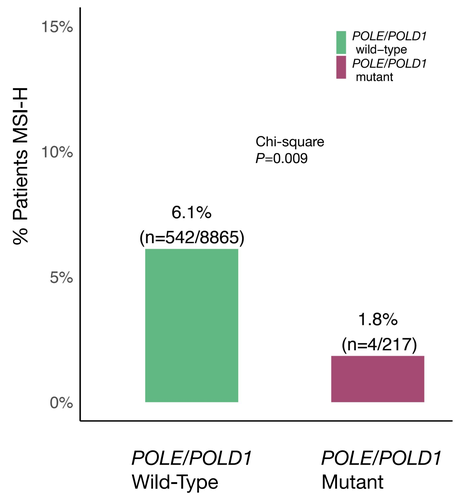

Figure 2. *POLE/POLD1*-mutated tumors presented with a lower frequency of MSI-H compared to wild-type (1.8% vs 6.1%, Chi-square *P*=0.009).

TMB by *POLE/POLD1* Status

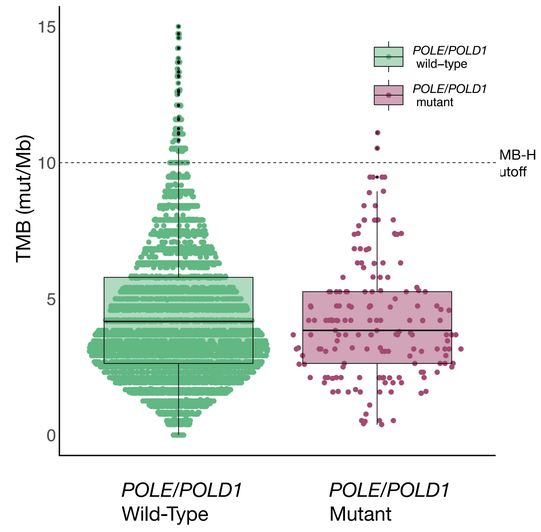

Figure 3. There was a higher frequency of TMB-H cases (>10 mut/Mb, dotted line) for P*OLE/POLD1*- mutated compared to wild-type tumors (22% vs 9.9%, Wilcoxon *P*=0.005).

POLE/POLD1 Co-mutations

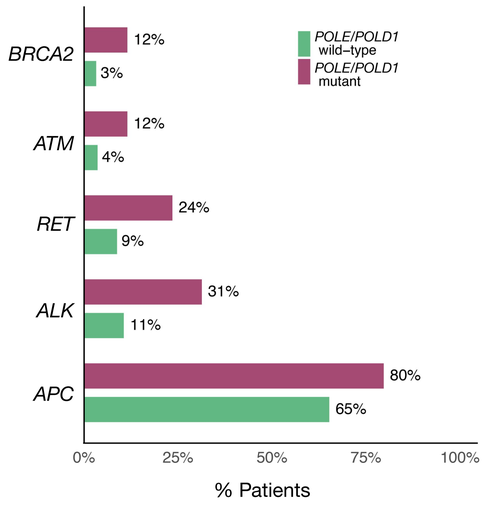

Figure 4. Differences between *POLE/POLD1*-mutated and wild-type tumors were observed among many co-mutated genes, including *APC* (80% vs 65%, *P*<0.001), *ALK* (31% vs 11%, *P*<0.001), *ATM* (12% vs 3.6%, *P*<0.001), *BRCA2* (12% vs. 3.2%), and *RET* (24% vs 8.9%, *P*<0.001).

CONCLUSIONS

- Patients with *POLE/POLD1* mutations exhibited significant differences across immunological markers and molecular co-alterations. These results have identified *POLE/POLD1*-mutated tumors as a unique genomic subpopulation.
- While *POLE/POLD1*-mutated CRCs have previously been associated with a hypermutated phenotype, only 22% of this cohort was considered hypermutated (defined as TMB >10).

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