Using the unique somatic mutation profile of POLE loss of proof-reading mutation helps in selection of patients who may benefit from immunotherapy

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Methods

A curated list of 19 known loss of proof-reading (LOP) POLE mutations was used to identify 66 tumors with POLE LOP mutation from which we extracted somatic mutational signatures from WES data. These averaged together, defined a positive control POLE LOP signature. POLE mutant tumors with mutational signatures that highly correlated with the positive control (>0.75) were determined to be LOP.

An exploratory cohort included WES data (SignateraTM assay, Natera, Inc.) from a pancreatic cancer cohort of 46332 patients collected from Natera and a validation cohort with 69223 from cBioportal were evaluated for POLE mutations and tested against the positive control. A clinical cohort of forty-one metastatic CRC patients with POLE mutations, treated with IO at MDACC were explored to evaluate IO predictive value of LOP POLE mutations. Survival analysis was estimated with Kaplan Meier and compared with log-rank test.

Results - updated

A total of 2581 POLE mutations were identified from 46332 tumors in the exploratory cohort as previously defined. Correlation with the positive control POLE LOP signature identified 31 variants with hypermutated phenotype. A comprehensive list was made and consistent high TMB value was observed for LOP compared to non-LOP POLE mut.

Data were confirmed in cBioportal validation cohort. Endometrial and colorectal cancer were confirmed to be the cancers with the high incidence of LOP mutations within the overall POLE mutations (28.69% and 18.15%, respectively).

Conclusions

For Non-LOP POLE mut cohort, disease progression was detected with a median PFS of 3.7 months (log-rank <0.0001) with both an increase in known lesions and appearance of new nodes. OS was significantly shorter as well for this subgroup of pts (p=0.0009).

As a clinical validation for the predictive role, we selected a cohort of pts with POLE mutant mCRC treated with immunotherapy (IO) (n=41).

Approximately 66% of the population was male, 46.35 had a right primary tumor location and the median age at diagnosis was 55 y. Nine pts were identified as carrying POLE LOP and they all achieved clinical benefit (ORR 88.9%, DCR 100%) from IO, with mPFS and mOS not reached after 48 months. In contrast, none of the 9 MSS pts with Non-LOP POLE mut achieved an objective response to IO therapy.

References


Presenter has no COI to declare.
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