BRAF-V600E Papillary Thyroid Cancer: Updated Analysis of Real-world Patient Data

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Background

- Papillary thyroid cancer (PTC) usually carries a good prognosis after surgery +/- radioactive iodine therapy (RAI).
- 5-15% of patients become RAI refractory, and some require systemic therapy.
- BRAF-V600E, the most common mutation in PTC, is associated with poor outcomes.
- The effectiveness of TKI compared to BRAF-targeted therapy (BRAF/MEKi) and immunotherapy (IO) remains unclear in the BRAF-V600E mutant (BRAF-m) population.

Research Questions

- To investigate molecular/transcriptional signatures in BRAF-m versus (vs) BRAF-wildtype (WT) PTC.
- To investigate rwOS (real-world OS) in BRAF-m vs BRAF-WT.
- To explore differences in rwOS in BRAF-m PTC according to treatment received.

Methods

DNA/RNA Next-Gen Sequencing Algorithm

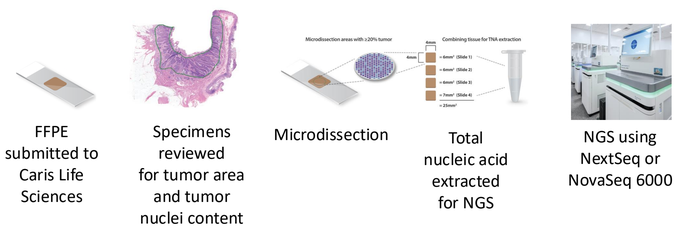

Fig. 1 Next-Gen Sequencing (NGS) was performed on genomic DNA isolated from formalin-fixed paraffin-embedded (FFPE) tumor samples using the NextSeq or NovaSeq 6000 platforms (Illumina, Inc., San Diego, CA). For NextSeq sequenced tumors, a custom-designed SureSelect XT assay was used to enrich 592 whole-gene targets (Agilent Technologies, Santa Clara, CA). For NovaSeq sequenced tumors, more than 700 clinically relevant genes at high coverage and high read-depth was used, along with another panel designed to enrich for an additional >20,000 genes at lower depth.

Summary

BRAF-m PTC was associated with a more pro-inflammatory TME milieu compared to BRAF-WT PTC. In this limited data set, treatment with mTKI vs BRAF-targeted therapy was not associated with differences in overall survival in BRAF-m PTC.

Results

- 1,102 patients with PTC were identified. The majority (95%) were naïve to TKI or BRAF/MEKi. BRAF-V600E mutations were present in 68%.

Genomic alteration landscape: BRAF-m vs BRAF-WT PTC

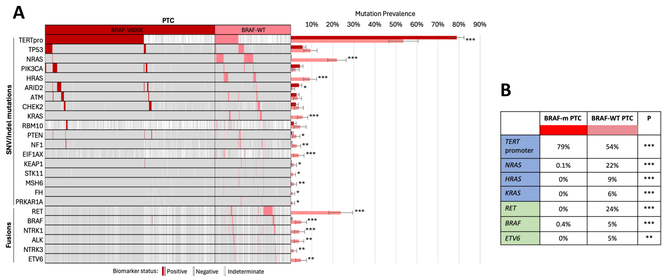

Fig. 2 **A** Oncoprint of single-nucleotide variants/insertion-deletion (SNV/Indel) mutations and gene fusions significantly associated with BRAF mutation status in PTC. *P<0.05, **P<0.01, ***P<0.001 reflect Chi-squared or Fisher's exact test, where appropriate, with Benjamini-Hochberg procedure applied to adjust p-values for multiple comparisons. **B** Summary of the most prevalent mutations (in blue) and gene fusions (in green) in BRAF-m vs BRAF-WT PTC.

BRAF-m PTC has a pro-inflammatory TME

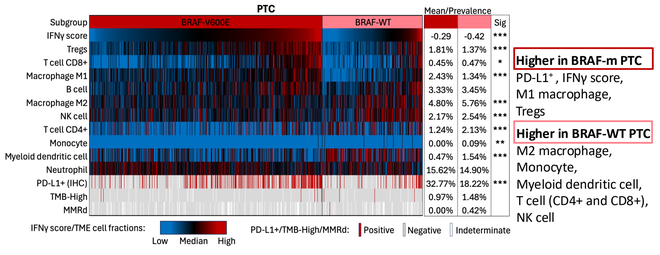

Fig. 4 Heatmap of BRAF-m and BRAF-WT subgroups sorted by the IFNγ score along with tumor microenvironment (TME) cell fractions estimated by deconvolution of bulk tumor RNA expression. *P<0.05, **P<0.01, ***P<0.001. Statistical significance was determined using Mann-Whitney U test for continuous variables and Chi-squared or Fisher's exact test for categorical variables, where appropriate.

Differentially expressed genes: BRAF-m vs BRAF-WT PTC

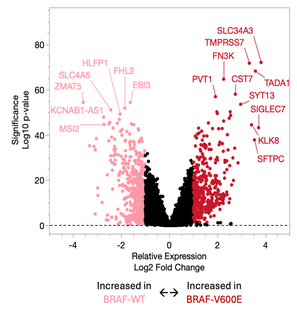

Fig. 3 Volcano plots of differentially expressed genes between BRAF-m and BRAF-WT subgroups in PTC. Dark red data points represent genes with significantly (adjusted p-value<0.05) increased expression in BRAF-m (log2FC > 1), whereas pink data points represent genes with significantly (adjusted p-value<0.05) increased expression in BRAF-WT (log2FC < -1) tumors. P-values reflect Mann-Whitney U test, with Benjamini-Hochberg procedure applied to adjust p-values for multiple comparisons. The largest fold changes were observed for *SLC34A3* in BRAF-m and *ZMAT5* in BRAF-WT PTC.

No difference in rwOS in BRAF-m vs BRAF-WT PTC

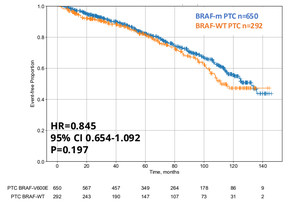

Fig. 5 Insurance claims data was used to infer rwOS from the time of initial diagnosis to death/last contact for BRAF-m and BRAF-WT subgroups. Hazard ratios and p-values were calculated using the Cox proportional hazards model and log-rank test, respectively.

Treatment choice is not associated with differences in rwOS in BRAF-m PTC

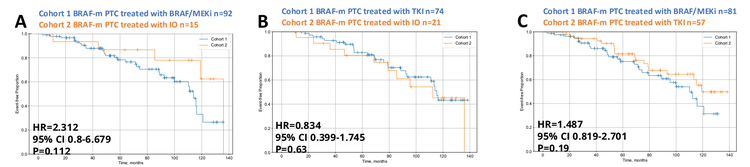

Fig. 6 rwOS calculated from the initial diagnosis date to the last contact/death for BRAF-m PTC patients treated with BRAF/MEKi vs IO **(A)**, TKI vs IO **(B)** and BRAF/MEKi vs TKI **(C).** Hazard ratios and p-values were calculated using the Cox proportional hazards model and log-rank test, respectively.

Future directions

- Compare the transcriptomic signatures of differentiated vs non differentiated thyroid cancers.
- Investigate factors that can predict response to BRAF/MEKi treatment in BRAF-m PTC.

Acknowledgments

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Please contact Martina Chirra at chirrama@ucmail.uc.edu for any questions