460 EFFICACY OF ADDING ANTI-PD1 IMMUNOTHERAPY TO DABRAFENIB + TRAMETINIB (DT) AT PROGRESSION IN BRAFV600E MUTATED ANAPLASTIC THYROID CARCINOMA (BRAFM-ATC)

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Background Although the FDA approved BRAF/MEK inhibitor combination DT has revolutionized the treatment of BRAFm-ATC, most patients eventually acquire resistance and progress. Given high immunogenicity and PD-L1 expression, immune checkpoint inhibitors have been studied in ATC. Single-agent anti-PD1 spartalizumab showed limited response rate of 19%. We studied the efficacy of addition of pembrolizumab at progression on DT compared to stopping DT or switching to a multikinase inhibitor (MKI) alone, and to upfront DT plus pembrolizumab (DTP), in locally advanced or metastatic BRAFm-ATC.

Methods Retrospective cohort study of patients with BRAFm-ATC treated with DT or DTP as initial systemic therapy, between 1/2014–3/2023 (outside of trial or on reported clinical trial). Patients treated with neoadjuvant approach were excluded. Primary endpoint was median overall survival (mOS) with pembrolizumab added to DT at progression (DT+Pprog) vs if DT stopped at progression or replaced by a MKI (DTstop) vs upfront DTP. Best response was assessed using RECISTv1.1; survival by Kaplan-Meier method.

Results 71/135 BRAFm-ATCs were included: n=14 in DT +Pprog, n=6 in DTstop and n=34 in DTP. All evaluable specimens (31/48) in pembrolizumab-treated patients had a PDL1 score >1%. Median follow-up was 58.0 months (range:3–58) in DT+Pprog arm, 4.0months in DTstop (range:1–9) and 18.0months (range:3 -63) in upfront DTP. Median duration on DT alone was 5.5months in DT+Pprog and 3.5 months in DTstop. mOS was significantly longer when pembrolizumab was added to DT at progression (16.0months; 95%CI,6.2–25.8) compared to stopping DT or switching to a MKI (4.0months; 95%CI,0.40–7.6); p=0.003. mOS from progression was also significantly longer in DT +Pprog arm (3.0months; range,0.67 to 55) compared to DTstop arm (0.47months; range, 0.33 to 2.0); p< 0.001. Interestingly, there was no significant difference in mOS between upfront DTP (17.0months [95% CI,11.8–22.2]) and DT+Pprog arms; p=0.554. Mutation status at progression on DT was available for only 4 patients. Identified emergent mutations included: GNAS, TSC1, HRAS and CDK4. No grade 5 adverse events occurred.

Conclusions Our results suggest that in locally advanced or metastatic BRAFm-ATC, addition of pembrolizumab to DT, either as initial treatment or at progression on DT, provides a significant survival benefit compared to current standard of care DT alone. However, conclusions are limited by the retrospective nature of the study and small number of patients in DTPprog group. Additional prospective data are needed to confirm this observation.

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