Background Tumors with high tumor mutational burden (TMB) or defects in mismatch repair (dMMR) respond well to immune checkpoint inhibitors (ICIs). TMB and DNA repair gene mutations including dMMR are closely related to the increase of neoantigens, which are recognized by immune cells to trigger an immune response. Although not a standard of care in thyroid cancer treatment, there are ongoing clinical trials for ICI use in differentiated thyroid carcinoma. However, not much has been explored concerning the neoantigen landscape and its association with immune traits in papillary thyroid cancer (PTC). We aim to analyze the immune landscape of PTC in association with neoantigen burden, TMB, and DNA repair gene mutations.

Methods We used the PTC cohort data from The Cancer Genome Atlas (TCGA). The mutation counts and data for neoantigen prediction were acquired from TCGA mutation calling. CloudNeo pipeline was used for neoantigen prediction. TMB was calculated as the sum of missense and indel mutation counts per megabase pairs covered by whole-exome sequencing. Tumor-infiltrating immune cells were estimated using CIBERSORT.

Results Out of the 496 PTC patients from cBioPortal, a subset of 400 patients with available mutation counts and predicted neoantigen burden was included in the study. Immune cell infiltration estimated by CIBERSORT showed macrophage M2 as the most abundant, followed by macrophage M0 and other T cells (figure 1). The TMB ranged from 0.03 to 2.05 with a median value of 0.2. Neoantigen burden ranged from 0 to 18 with a median value of 1, which is relatively low compared to the median value of 18 in non-small cell lung cancer (NSCLC) (figure 2). One or more DNA repair gene mutations were discovered in 32 patients (8%). The mutation status of repair genes was not related to TMB or neoantigen burden. TMB or neoantigen burden was not related to immune traits such as infiltration of CD8+ T cells or regulatory T cells, cytolytic activity score, and PD-L1 expression.

Conclusions This is the first study to report the immune landscape of PTC in the context of neoantigen. The lack of association between TMB or neoantigen burden with immune traits may be due to the relatively low number of neoantigens in PTC compared to other immunogenic cancers such as NSCLC. Our results suggest that mutations in DNA repair genes or TMB are likely to have limited value in predicting response to ICI treatment in PTC.

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treatment ICM in newly diagnosed BC patients (pts) and compare them to healthy controls.

Methods Soluble forms of ICM, as well as cytokines and chemokines, were measured using Multiplex® bead array and ELISA technologies. Plasma samples from 98 BC pts and 45 healthy controls were analyzed for each protein. Data was prospectively obtained. Measured levels were compared between BC pts and healthy controls using a non-parametric test (Mann-Whitney).

Results Soluble stimulatory molecules GITR (p < 0.000002), GITRL (p < 0.007), CD27 (p < 0.002), CD28 (p < 0.003), CD40 (p < 0.003), CD80 (p < 0.009), ICOS (p < 0.0006) as well as inhibitory molecules PD-L1 (p < 0.0000001), CTLA-4 (p < 0.005), TIM-3 (p < 0.000006), HVEM (p < 0.000002) and TLR-2 (p < 0.05) levels were significantly lower in early BC pts compared to healthy controls. When analyzed according to BC characteristics (TNBC vs. non-TNBC, tumor size, stage, nodal status and age) no significant difference was detected between the soluble levels of these ICM and between the different subsets. Additionally, serum levels of CXCL5 (p < 0.000001), CCL23 (p < 0.04), IL-16 (p < 0.00005), interferon-a (p < 0.03) and IL1-RA (p < 0.03) were significantly lower compared to healthy controls. Serum CX3Cl1 or fractalkine (p < 0.024465) was significantly higher compared to healthy controls.

Conclusions In the current study, we identified low levels of both stimulatory and inhibitory soluble immune checkpoint molecules in newly diagnosed, non-metastatic BC pts compared to healthy controls. These results indicate that early BC is associated with a down-regulation of both soluble stimulatory and inhibitory immune-checkpoint pathways. Newly diagnosed early BC pts have a generalized immune-suppression independent of subtype and stage, which, to our knowledge, is the first study to describe soluble immune checkpoints in early BC pts.

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Trial Registration N/A

Ethics Approval The study was approved by The Research Ethics Committee, Faculty Health Sciences, University of Pretoria, approval number 517/2017.

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