**Figure Legends**

**Fig 1. TsMHCII is decreased in PTCs with BRAFV600E mutation.** A) Flow chart of iTRAQ-labeling LC-MS/MS analyses. B) A Volcano plot highlighting differentially expressed proteins (DEPs). 4,722 peptides were identified with greater than 1.2-fold change in BRAFV600E relative to BRAF wildtype samples and plotted as red (down-regulation) or green (up-regulation), respectively. C) Proteins with significant expression changes were plotted in the heatmap. D) KEGG analysis of total identified DEPs. Proteins of the antigen processing and presentation related pathways had the greatest degree of up-regulation while proteins involved in metabolic pathways had the greatest degree of down-regulation between BRAFV600E and wildtype BRAF samples. E) Heatmap of MHCI and MHCII proteins identified by iTRAQ. F) Representative immunohistochemical staining of tsMHCII in PTC specimens. G) Percentage of samples with varying expression levels of tsMHCII in 185 PTC samples. H) Stacked histogram of tsMHCII staining levels in PTC samples. PTC samples with BRAFV600E mutation showed a signiﬁcantly lower rate of tsMHCII expression than BRAF wildtype tumors.

**Fig 2. Constitutive activation of BRAF-MAPK pathway down-regulated tsMHCII expression in PTC.** A) Real-time PCR detection of CIITA and tsMHCII genes (HLA-DQA1, HLA-DRA, and HLA-DPA1) expression in PTC cell lines normalized to that in an immortalized thyroid cell line Nthy-ori-3-1 (TT). B) Flow-cytometric analyses of tsMHCII in BCPAP and K1 cells with (PLX4032) and without (Ctrl) treatment with BRAF inhibitor PLX4032 (10 µM) for 72 h. C) Protein expression of tsMHCII in BCPAP and K1 cells with (U0126) and without (Ctrl) treatment with MEK inhibitor U0126 for 72 h. D) Western blot analysis of BRAF expression in doxycycline (DOX)-inducible BRAFV600E over-expressing TPC1 cells. E) Flow-cytometric analysis of tsMHCII in BRAFV600E over-expressing TPC1 cells compared to control cells.

**Fig 3. BRAFV600E downregulated tsMHCII expression through TGF-β1/SMAD3 pathway.** A) Real-time PCR detection of CIITA and tsMHCII mRNAs in BCPAP and K1 cells after treatment with inhibitors for various signaling pathways (DAPT at 25 µM for NOTCH, IWR1 at 10 µM for Wnt, SB431542 at 10 µM for TGF-β1, and Cyclopamine at 20 µM for Hedgehog pathway) or additional medium (Ctrl) for 48 h. Results presented as a heatmap. SB431542 inhibition significantly decreased transcript levels of MCHII genes in BCPAP and K1 PTC cell lines. B) Correlation analysis of TGF-β1 and CIITA gene expression levels in all PTCs or in PTCs with BRAFV600E mutation according to expression data in the TCGA database. C) Flow-cytometric analyses of tsMHCII in BCPAP and K1 cells after treatment with exogenous TGF-β1 (10 ng/ml) for 72 h. D) Flow-cytometric analysestsMHCII in BCPAP and K1 cells after treatment by PLX4032 with or without with TGF-β1. E) Correlation analysis of SMAD3 expression and BRAF mutation status according to information in the TCGA database. F) Representative IHC staining of phosphorylated SMAD3 in PTC specimens. Tumors with BRAFV600E mutation showed a signiﬁcantly higher rate of p-SMAD3 expression than BRAF wildtype tumors. G) Correlation analysis between SMAD3 and CIITA in all PTCs or in PTCs with BRAFV600E mutation according to information in the TCGA database. H) Flow-cytometric analyses of tsMHCII in BCPAP and K1 cells after treatment with SMAD3 inhibitor SIS3 (10 µM) for 72 h. I) Western blot analysis in doxycycline-inducible BRAFV600E over-expressing TPC1 cells. J) Flow-cytometric analyses oftsMHCII in BRAFV600E over-expressing TPC1 cells treated with SIS3.

**Fig 4. TsMHCII increased the elimination effect of immune cells in vitro, and increased expression of tsMHCII correlated with good prognosis in patients with PTC.** B). Western blot analysis of tsMHCII in BCPAP and K1 cells after transfection with siCIITA. C) Real-time PCR analysis of CIITA in BCPAP and K1 cells after transfection with siCIITA. A) In vitro cytotoxicity assays of peripheral blood leukocytes (PBL) to BCPAP and K1 cells after pre-treatment with PLX4032 or combined with siCIITA transfection. D) Extracellular INF-γ produced by CD4+ T-cells in co-culture with BCPAP or K1 cells pre-treated with PLX4032 or combined with siCIITA transfection. E) *In vitro* cytotoxicity assays of PBL against TPC1 cells overexpressing BRAFV600E with corresponding response in F) INF-γ produced by CD4+ T-cells. G) Representative immunohistochemical staining of tsMHCII and CD4 in PTC specimens. The expression of tsMHCII was remarkably associated with high CD4 T-cell infiltration. H) Kaplan-Meier analyses of patients with PTC according to staining status of tsMHCII. Association analysis of tsMHCII expression by immune cell type with the TIMER web tool analysis revealed I) a positive association between tsMHCII and CD4+ T-cell, CD8+ T-cell, and B-cell infiltration and J) survival in patients with thyroid carcinoma.

**Fig 5. PLX4032 combined with anti-PD-1 treatment offers durable therapeutic response.** A) *In vitro* cytotoxicity assays of PBL to BCPAP and K1 cells after pre-treatment with PLX4032, anti-PD-1 antibody (Nivolunab, 20 µg/ml), or combination PLX4032 and Nivolunab for X hours . B) INF-γ produced by CD4+ T-cells were analyzed after co-culture with BCPAP or K1 cells that have been treated with PLX4032, Nivolunab, or combination treatment of PLX4032 with Nivolunab. C) Therapy protocol for spontaneous thyroid cancer generated in transgenic mice. D) Representative images of dissected mouse thyroid tumors after different therapies. E) Tumor weight of each group. F) Tumor immune profiles after single and combined therapy regimens in transgenic mice depicted by heatmap of fold-changes compared to vehicle+α-IgG treatment (control). G) Representative hematoxylin and eosin staining and IHC staining of tsMHCII expression in mouse tumor specimens.

**Fig 6. Schematic model of oncogenic BRAF-dependent regulation of tsMHCII.** Our data show that BRAFV600E downregulates tsMHCII expression via the TGF-β1/SMAD3 pathway in PTCs. BRAF inhibitor treatment up-regulates tsMHCII level to increase tumor cell elimination by the immune system and enhance the response to anti-PD-1 antibody treatment.