Background Anti-PD-1 and CTLA-4 checkpoint inhibitors have shown substantial benefits for certain cancer patients, but their efficacy in thyroid cancer is yet to be established. In this report, we present the latest clinical outcomes and translational analysis of S1609 Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors (DART).

Methods This study is a prospective, open-label, multicenter phase 2 clinical trial of ipilimumab (1 mg/kg intravenously every 6 weeks) plus nivolumab (240 mg intravenously every 2 weeks) in rare tumors. Tumor immunoprofiling on archival specimens (n=13) was conducted using nine markers in two multiplex immunofluorescence (mIF) panels. Gene expression profiling was performed using the PanCancer Immune Profiling panel on the nCounter platform (n=13). Whole exome sequencing data was processed using the CIDC pipeline (n=9).

Results Nineteen patients with papillary (53%, n=10), medullary (21%, n=4), anaplastic (21%, n=4), and Hurthle cell (5%, n=1) histologies were analyzed. ORR was 21% (PR, 21%; n=4; 3/10 papillary, 1/4 anaplastic) and clinical benefit rate 58% (n=11; includes 6 SD>6 months, 4 confirmed PR, 1 unconfirmed PR; 9/10 papillary, 2/4 anaplastic) (figure 1). In the anaplastic cohort (n=4), one achieved a 33+ month PR, while another exhibited 18% regression for a duration of 22 months. 6-month PFS was 57%; median PFS, 9.5 months; 6-month OS, 89%; median OS, 31.5 months (figure 2). Adverse events (AE) occurred in 94.7% of patients (n=18); 57.9% (n=11) experienced a grade 3–5 AE. The most common AE were fatigue (52.6%, n=10), diarrhea and elevated lipase (31.6%, n=6 each).

For translational analysis, seventeen patients [10 responders (3 PR, 1 unconfirmed PR, 6 SD >6 months) and 7 non-responders] were evaluated. Image analysis of the tumor microenvironment using mIF revealed that the presence of PD-1+PD-L1+ tumor-infiltrating lymphocytes (TILs) and PD-1+PD-L1+ cytotoxic T lymphocytes (CTLs) correlated positively with improved PFS and OS (HR=0.19, p=0.01; HR of 0.13, p=0.03 respectively) (figures 3 and 4). Predicted cell scores derived from gene expression profiling did not identify any association with immune cell subsets and outcomes. No association was observed between PD-L1 expression by chromogenic IHC (3/14 ≥1%) along with absolute neutrophil and platelet counts, and either response or survival. Median tumor mutational burden (TMB) and copy number variation (CNV) were not correlated with survival.

Conclusions Combination therapy with ipilimumab plus nivolumab in thyroid cancer resulted in an ORR of 21%, with median duration of response over two years. PD-1+PD-L1+ TIL correlated with favorable PFS and OS.

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Trial Registration NCT02834013

Ethics Approval The study was approved by the NCI Adult Central Institutional Review Board, approval number 02834013.
Abstract 590 Figure 3  Heatmap analysis of the relative contributions of performance status, gender, and immune cell subsets to differential response patterns. Columns represent samples from different patients treated with ipilimumab-nivolumab combination therapy. Patients were further stratified by response defined as resp2.2, which identified 10 responders [3 PR, 1 unconfirmed PR, 6 SD (STA) >6 months] and 7 non-responders. Rows beneath the clinical characteristics display the proportions of immune cells expressing specific markers, with colors signifying either an increase (red), decrease (blue), or no change (gray) in cell-type quantities relative to pre-treatment baseline.

Abstract 590 Figure 4  Progression-free survival and overall survival of PD-1+ PD-L1+ TIL and PD-1+ PD-L1+ CTL patients

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