Identification of symptoms that are associated with irAEs in the I-SPY clinical trial

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Immunotherapy has emerged as an important component of neoadjuvant therapy for some patients with breast cancer (BC). As a result, immune-related adverse events (irAEs) are increasing and have effects on both short and long term symptoms significantly impacting patient quality of life. BC patients may develop new conditions including arthralgias, gastrointestinal issues, endocrinopathies, and fatigue during or after cancer therapy that may be acute or long-lasting in nature. We sought to identify patient demographic characteristics and symptom patterns associated with risk for development of irAEs in the context of a randomized trial for patients with early-stage high-risk breast cancer.

I-SPY2 is a multi-center, phase 2 trial using response-adaptive randomization for high-risk early-stage women with BC. The study population for this analysis includes enrolled patients receiving combinations of experimental immunotherapy and chemotherapy. Groups considered for statistical comparisons included those that developed an irAE versus those that did not develop an irAE up until the surgery timepoint. Hypothyroidism, adrenal insufficiency, and pneumonitis were the irAEs considered in this study. A chi-square test was used to assess associations between race and ethnicity (White, Asian, Black, non-Hispanic) and irAEs. 33 symptoms reported at CTCAE grade 2 or higher were included in the analyses and a symptom burden score was calculated using area under curve (AUC) which combined the duration of each symptom between baseline and week 6 of treatment, and grade of adverse event.

Out of 461 patients, percentages of patients wth irAEs of interest included hypothyroidism (13%), adrenal insufficiency (9%), and pneumonitis (4%). Demographic information was available for 333 patients, of which 270 (81%) were White, 23 (7%) were Asian, 37 (11%) were African American (AA) and 278 (17%) were non-Hispanic. There were proportionately higher number of white patients that developed hypothyroidism than non-white patients (35 of 265 (13%) vs 2 of 63 (3%), $P < 0.04$). Pneumonitis was more common in patients over 50 years old than under 50 years old ($P < 0.02$). Symptoms associated with the development of hypothyroidism included fatigue (15%, mean AUC=11.8 vs 5.8 for those that did not develop irAE), SOB (11%, 4.3 vs 2.8), and blurry vision (1%, 1.0 vs 0.12). Development of adrenal insufficiency was associated with early reports of diarrhea (36%, 19.0 vs 10.5), SOB (11%, 7.8 vs 2.6), joint pain (3%, 2.29 vs 0.58), decreased appetite (3%, 3.55 vs 0.91), and constipation (1%, 3.6 vs 0.02). Our study utilizes an analysis framework that is aimed to determine symptom clusters that predict the development of irAEs. We describe specific symptoms presenting early with the development of hypothyroidism and adrenal insufficiency, in recognition of allowing physicians to be more diligent in active and post treatment monitoring.