222-N ANALYSIS OF PATHOLOGIC FEATURES AND EFFICACY OUTCOMES WITH NEOADJUVANT NIVOLUMAB PLUS PLATINUM-DOUBLET CHEMOTHERAPY FOR RESECTABLE NON-SMALL CELL LUNG CANCER IN CHECKMATE 816

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Background Pathologic response assessment after neoadjuvant treatment is the potential analog to radiographic response for advanced disease, with regard to study design, clinical care, and accelerated regulatory approvals. A standardized system for assessing degree of pathologic response in the primary tumor (PT) and lymph nodes (LNs) as a survival surrogate is an unmet need. It is also a prerequisite for determining whether patients with versus without LN involvement benefit from neoadjuvant therapy. Here, in a pre-specified exploratory analysis from CheckMate 816, we report the first in-depth assessment of the full spectrum of percent residual viable tumor (RVT; beyond pathologic complete response) in both the PT and LNs and its association with event-free survival (EFS). This study represents the first prospective use of such a pan-tumor scoring system in a phase 3 registrational trial.

Methods Pathologic response was prospectively assessed in the randomized phase 3 study of neoadjuvant nivolumab plus chemotherapy versus chemotherapy alone in patients with resectable non-small cell lung carcinoma. Percentages of RVT, regression, and necrosis were quantified (0%-100%) in the PT and LNs using pan-tumor immune-related pathologic response criteria (irPRC). Pathologic features scored using this system were tested for association with EFS. An exploratory comparison between pathologic response, radiographic response, and circulating tumor DNA (ctDNA) clearance was performed.

Results In both treatment arms and regardless of pathologic evidence of LN involvement, EFS was improved in patients with 0% versus >0% RVT-PT (HR=0.18). RVT-PT predicted EFS for nivolumab plus chemotherapy (AUC=0.74); 2-year EFS rates were 90%, 60%, 57%, and 39% for patients with 0%-5%, >5%-30%, >30%-80%, and >80% RVT, respectively. Each 1% increase in RVT associated with a 0.017 increase in HR for EFS. Combining pathologic response from PT+LNs helped differentiate outcomes. An increase in% necrosis was not observed in paired pre- and on-treatment specimens in either treatment arm. Further, necrosis within the on-treatment specimens was associated with lower EFS rates, arguing against necrosis as a histologic feature of treatment effect. When pathologic response was compared to radiographic response and ctDNA clearance, pathologic response best approximated EFS.

Conclusions Percent RVT associates with improved EFS, supporting pathologic response as an emerging survival surrogate. Given the prognostic value of%RVT, its assessment using routine surgical pathology workflows, and a scoring system generalizable to any solid tumor type, it is also anticipated to become a biomarker for guiding subsequent adjuvant therapy. Further assessment of clinically-relevant%RVT cutoffs in PT +LN is warranted.

Acknowledgements Funding for this study was provided by Bristol Myers Squibb and Ono Pharmaceutical Company Ltd.
Trial Registration NCT02998528
Ethics Approval This study was approved by the Johns Hopkins University Institutional Review Board.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0222-N