Enhanced pathologic tumor response with two cycles of neoadjuvant pembrolizumab in surgically resectable, locally advanced HPV-negative head and neck squamous cell carcinoma (HNSCC).

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Background: We reported that one cycle of neoadjuvant pembrolizumab induced pathologic tumor response in >10% (pTR-any) and in >50% (pTR-2) of the resection bed in 44% and 22% of patients (pts) with surgically resectable HPV-negative, Stage III/IV HNSCC (Clin Cancer Res 2020). We hypothesized that two cycles of neoadjuvant pembrolizumab would induce pTR-2 in 50% of pts. Increasing the pathologic response rate may favorably impact clinical outcomes. Methods: Multi-institutional phase 2 trial where pts with locally advanced, HPV-negative HNSCC received two cycles of pembrolizumab (200 mg), given 42 and 21 days prior to surgery. Resected tumor was analyzed by two independent pathologists for pTR (tumor necrosis and/or giant cell/histiocytic reaction to keratinous debris) in the resection bed (primary tumor and/or lymph nodes). Additional definitions: pTR-1 (>10-49%) and major pathologic response (>90%). The primary endpoint was pTR-2. A sample size of 26 pts was needed to detect a significantly higher pTR-2 rate of 50%, with 80% power using a one-sided alpha level of 0.05. Pts were followed for serious adverse events (AEs) for 30 days after surgery and for AEs of clinical interest for 90 days following the last dose of pembrolizumab. Pts underwent baseline blood collection and tumor biopsies to match with blood and surgical specimens obtained post-pembrolizumab. Planned correlatives included PD-L1 expression, immune function, and molecular signatures of activation in the pre- and post-treatment blood and tumor tissue. Results: Characteristics of 29 enrolled and treated pts were median age 62 (30-82) yrs, smoking history 62% (18 pts); clinical stage T2 (n = 6), T3 (n = 5), T4 (n = 18) and N0/1 (n = 17), N2 (n = 12). All treated patients received two cycles of neoadjuvant pembrolizumab, which was tolerated well with only one (3%) grade 3 AE (rash) and no grade 4 AEs. The primary endpoint was evaluable in 25 pts, and not evaluable in 4 pts (one pt withdrew before surgery and in three pts, pTR review was pending). pTR-2 occurred in 44% (11 of 25 pts), and 4 (16%) of these pts had a major pathologic response including 1 (4%) pathologic CR at the primary site. Conclusions: Two (vs one) cycles of neoadjuvant pembrolizumab resulted in a two-fold increase in the frequency of pTR-2 (44% vs 22%). These data imply that the frequency of pTR to neoadjuvant pembrolizumab can be improved by increasing the number of cycles and the treatment interval. Clinical trial information: NCT02296684. Research Sponsor: Merck Inc.