6012 Rapid Oral Abstract Session

Neoadjuvant and adjuvant pembrolizumab plus standard of care (SOC) in resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC): Exploratory efficacy analyses of the phase 3 KEYNOTE-689 study.

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Background: The addition of immune checkpoint inhibitors to neoadjuvant/adjuvant SOC has led to efficacy benefits across multiple tumor types. The randomized phase 3 KEYNOTE-689 study (NCT03765918) showed significantly improved event-free survival (EFS) with neoadjuvant/adjuvant pembrolizumab + SOC vs SOC alone for participants (pts) with resectable LA HNSCC independent of PD-L1 combined positive score (CPS ≥10 population: HR 0.66, 95% CI 0.49–0.88, *P*=.00217; CPS ≥1 population: HR 0.70, 95% CI 0.55–0.89, *P*=.00140; all pts: HR 0.73, 95% CI 0.58–0.92, *P*=.00411). We present exploratory efficacy endpoints for the intention-to-treat population of the study. **Methods:** Adults with SCC of the larynx/hypopharynx/oral cavity (stage III/IVA) or oropharynx (stage III/IVA p16− or stage III T4 N0-2 p16+) were randomized 1:1 to SOC (consisting of surgery + postoperative radiotherapy [PORT] ± concurrent cisplatin 100 mg/m^2 Q3W) with or without 2 cycles of neoadjuvant pembrolizumab, 3 cycles of pembrolizumab concurrent with PORT ± cisplatin and 12 cycles of adjuvant pembrolizumab (200 mg IV Q3W). The primary endpoint is EFS per RECIST 1.1 by blinded independent central review. Safety is a secondary endpoint. Prespecified exploratory efficacy endpoints include locoregional control (time from randomization to first locoregional radiographic progression or recurrence by imaging or biopsy), distant metastases-free survival (DMFS; time from randomization to first distant metastasis or death), and incidence of second head and neck or other cancers. **Results:** A total of 714 pts were randomized (363 to pembrolizumab + SOC, 351 to SOC). At first interim analysis (data cutoff date 25 Jul 2024), median follow-up was 38.3 mo (range, 9.0–66.5). In all pts, cumulative incidence of locoregional progression or recurrence at 36 mo was 13.4% with pembrolizumab + SOC and 14.3% with SOC. The HR for risk of a locoregional failure event with pembrolizumab + SOC vs SOC was 0.92 (95% CI 0.61–1.41). Median DMFS was 51.8 mo with pembrolizumab + SOC vs 35.7 mo with SOC (HR 0.71, 95% CI 0.56–0.90). Estimated DMFS rate at 36 mo was 59.1% vs 49.0%, respectively. Second head and neck or other cancers occurred in 9 (2.5%) and 18 pts (5.1%), respectively. Incidence of treatment-related adverse events was similar with pembrolizumab + SOC and SOC (any grade, 81.4% vs 81.9%; grade ≥3, 44.6% vs 42.9%). **Conclusions:** Among all pts with resectable LA HNSCC in KEYNOTE-689, DMFS results and incidence of second cancers favored the addition of neoadjuvant/adjuvant pembrolizumab to SOC surgery and (chemo)radiotherapy, consistent with the primary EFS results of the study. Locoregional control was similar between arms. No new safety signals for pembrolizumab were observed. Clinical trial information: NCT03765918. Research Sponsor: This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.