ORAL PRESENTATIONS - PROFFERED ABSTRACTS | MAY 22 2025

Abstract CT001: Neoadjuvant and adjuvant pembrolizumab plus standard of care (SOC) in resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC): Phase 3 KEYNOTE-689 study FREE

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Cancer Res (2025) 85 (8_Supplement_2): CT001.

https://doi.org/10.1158/1538-7445.AM2025-CT001

Abstract

Background:

Neoadjuvant and adjuvant immune checkpoint inhibitors added to SOC (surgery + postoperative radiotherapy [PORT] ± concurrent chemotherapy) yielded promising efficacy results in participants (pts) with LA HNSCC in early phase studies. The randomized, open-label, phase 3 KEYNOTE-689 study (NCT03765918) evaluates neoadjuvant and adjuvant pembrolizumab + SOC vs SOC in this population.

Methods:

Adults with newly diagnosed resectable LA HNSCC (larynx/hypopharynx/oral cavity stage III/IVA; oropharyngeal stage III/IVA p16− or stage III T4 N0-2 p16+) were randomized 1:1 to 2 cycles neoadjuvant and 3 cycles concurrent (during PORT) and 12 cycles adjuvant pembrolizumab 200 mg IV Q3W + SOC vs SOC. SOC included surgery for all pts + PORT 60 Gy in 30 fractions for low-risk, PORT 66 Gy in 33 fractions + 3 cycles concurrent cisplatin 100 mg/m^2 Q3W for high-risk, and PORT 70 Gy in 35 fractions + cisplatin for gross residual disease. The primary endpoint is event-free survival (EFS) per RECIST 1.1 by blinded independent central review. Key secondary endpoints are major pathological response (mPR; ≤10% invasive SCC) by blinded independent pathologist review and overall survival (OS). Efficacy endpoints are sequentially assessed in 3 populations: pts with tumors with PD-L1 combined positive score (CPS) ≥10, CPS ≥1, and all pts. Treatment-related adverse events (TRAEs) are graded per CTCAE v4.03.

Results:

Skip to Main Content

From December 2018 to October 2023, 363 pts were randomized to pembrolizumab + SOC and 351 to SOC. As of 25 July 2024 (first interim analysis), median follow-up was 38.3 months (range, 9.0-66.5). Baseline demographics were balanced between arms. The CPS ≥10 population included 234 pts in the pembrolizumab + SOC arm and 231 in the SOC arm; the CPS ≥1 population included 347 and 335 pts, respectively. EFS (CPS ≥10: median 59.7 vs 26.9 months, HR 0.66, 95% CI 0.49-0.88, *P*=.00217; CPS ≥1: 59.7 vs 29.6 months, HR 0.70, 95% CI 0.55-0.89, *P*=.00140; all pts: 51.8 vs 30.4 months, HR 0.73, 95% CI 0.58-0.92, *P*=.00411) and mPR rate difference (CPS ≥10: 13.7%, 95% CI 9.7-18.7, *P*<.00001; CPS ≥1: 9.8%, 95% CI 7.0-13.3, *P*<.00001; all pts: 9.3%, 95% CI 6.7-12.8, *P*<.00001) analyses were statistically significant with pembrolizumab + SOC vs SOC in all prespecified populations. Additional follow-up for OS is ongoing. Grade ≥3 TRAE frequency was similar (44.6% with pembrolizumab + SOC vs 42.9% with SOC); 4 and 1 deaths occurred due to TRAE, respectively. Immune-mediated AEs occurred in 43.2% of pts with pembrolizumab + SOC, most commonly hypothyroidism (24.7%).

Conclusions:

Adding neoadjuvant and adjuvant pembrolizumab to SOC significantly improved EFS and mPR rate difference in pts with resectable LA HNSCC independent of CPS. The safety profile of pembrolizumab was consistent with expectations.

Citation Format:

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Online ISSN 1538-7445 **Print ISSN** 0008-5472

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