

# 28750

## Pembrolizumab or placebo plus concurrent definitive chemoradiotherapy in esophageal and gastroesophageal junction (GEJ) cancer: The phase 3 randomized KEYNOTE-975 study

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### Background

The role of immunotherapy in participants (pts) with locally advanced, esophageal cancer (EC) treated with definitive chemoradiotherapy (dCRT) is not established. KEYNOTE-975 (NCT04210115) is an international phase 3, randomized, double-blind, placebo (pbo) controlled multicenter study that examines dCRT ± pembro in pts with previously untreated locally advanced unresectable esophageal and GEJ cancer. We report results from the second interim analysis (IA2).

### Methods

Eligible pts with histologically confirmed cTX N+ M0 or cT2-T4a NX M0 esophageal squamous cell cancer (ESCC) or adenocarcinoma (EAC) or GEJ cancer, or cTX N+ M1 cervical or upper thoracic EC with supraclavicular lymph node metastases only, ECOG PS 0-1, and who were ineligible for curative surgery but suitable for dCRT, were randomized 1:1 to 200 mg pembro or pbo Q3W for 8 cycles then 400 mg pembro or pbo Q6W for 5 cycles + site choice of dCRT (5-fluorouracil + cisplatin [FP] with radiotherapy [RT] 50 Gy or 60 Gy, or FOLFOX with RT 50 Gy). Dual-primary endpoints were event-free survival (EFS) by investigator and OS in pts with PD-L1 combined positive score (CPS) ≥10, CPS ≥1, and all pts. Data cut-off was Jan 21, 2026.

### Results

A total of 703 pts were randomized (349 pembro + dCRT; 354 pbo + dCRT). Median follow-up was 47.1 mo (range, 21.7-70.2) in all pts. At IA2, in pts with PD-L1 CPS ≥10, EFS was not improved with pembro + dCRT vs pbo + dCRT (median 15.2 vs 14.7 mo; HR 0.97; 95% CI, 0.77-1.23 [P=0.3994; P-value boundary for significance 0.0193]). In pts with PD-L1 CPS ≥10, median OS was 32.2 mo vs 35.0 mo (HR 1.00; 95% CI, 0.77-1.30 [nominal P-value 0.5003]). As EFS was not positive in PD-L1 CPS ≥10, EFS in PD-L1 CPS ≥1 and all pts, and OS were not tested for statistical significance, and the study was stopped. Grade ≥3 AEs occurred in 100% of pts in each arm, with grade 5 AEs in 44 (13%) vs 37 (10%) pts. Discontinuation due to any AE occurred in 117 (34%) vs 97 (27%) pts.

### Conclusions

Pembrolizumab + dCRT vs pbo + dCRT did not significantly improve EFS in untreated unresectable esophageal or GEJ cancer with PD-L1 CPS ≥10. No new safety signals were observed.

### Clinical trial identification

NCT04210115.

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**Legal entity responsible for the study**

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