Big Cancers, Big Hopes: Neoadjuvant Immunotherapy for Cancers of the Mouth, Throat, and Voice Box

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March 27, 2026

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Unmet Need in Resectable Locally Advanced HNSCC

Current Treatment Challenges

Standard surgery and radiotherapy +/- chemotherapy yield 40-50% five-year survival with high recurrence rates within the first year.

Need for Therapeutic Innovation

Long-term outcomes have stagnated for two decades, highlighting urgent need for new curative treatments in HNSCC.

Immunotherapy Advances

PD-1/PD-L1 inhibitors like pembrolizumab improve survival in metastatic HNSCC and prompt investigation in earlier disease stages (1-3).

Rationale for Perioperative Immunotherapy

Administering immunotherapy before and after surgery may prime the immune response and helps eradicate residual disease.

KEYNOTE-689 Trial Design (NEJM)

Patient Population	Adults with resectable, locally advanced head and neck squamous cell carcinoma (Stage III–IVA), treatment-náive
Eligibility Criteria	Resectable LA-HNSCC; PD-L1 assessed (CPS stratification); adequate organ function

Randomized Phase III open-label; 1:1 (N=714)

Perioperative Pembrolizumab Arm N-363

- Neoadjuvant pembrolizumab
- Surgery
- Adjuvant pembrolizumab ± radiotherapy ± cisplatin
- Maintenance pembrolizumab

Standard of Care Arm N=351

- Surgery
- Adjuvant radiotherapy ± cisplatin

Primary End Point

Event-Free Survival

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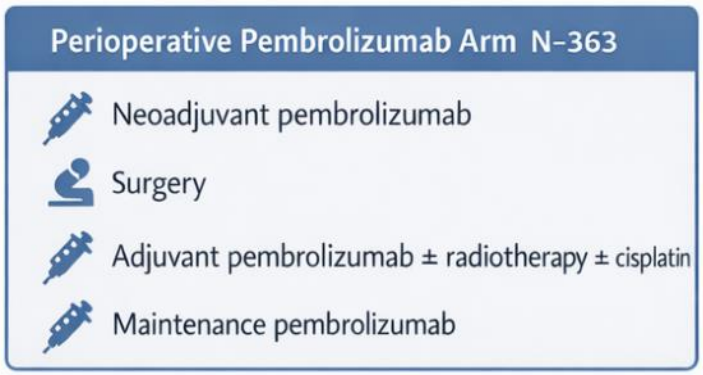
Perioperative Pembrolizumab Versus Standard of Care



Neoadjuvant Pembrolizumab Therapy

Pembrolizumab was given before surgery every three weeks for two cycles, marking a shift from traditional treatment.

Adjuvant Therapy Combination

After surgery, pembrolizumab was combined with radiotherapy and optionally cisplatin for three cycles to address risk factors.

Maintenance Pembrolizumab Monotherapy

Patients received up to twelve cycles of pembrolizumab monotherapy after adjuvant treatment completing the perioperative course.

Standard Care Control Arm

Control patients underwent upfront surgery followed by standard radiotherapy with or without cisplatin, without immunotherapy.

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Event-Free Survival as the Key Measure of Benefit

Population	Pembrolizumab Group	Control Group	Hazard Ratio	P Value
CPS ≥10	**59.8%**	**45.9%**	0.66	0.004
CPS ≥1	**58.2%**	**44.9%**	0.70	0.003
Total Population	**57.6%**	**46.4%**	0.73	0.008

- **Median follow-up:** 38.3 months
- **Primary endpoint:** Event-free survival (EFS)
- **Significance:** All comparisons showed statistically significant improvement in EFS with pembrolizumab

Definition of Event-Free Survival

EFS measures time from randomization to disease progression, recurrence, or death, capturing outcomes throughout treatment years.

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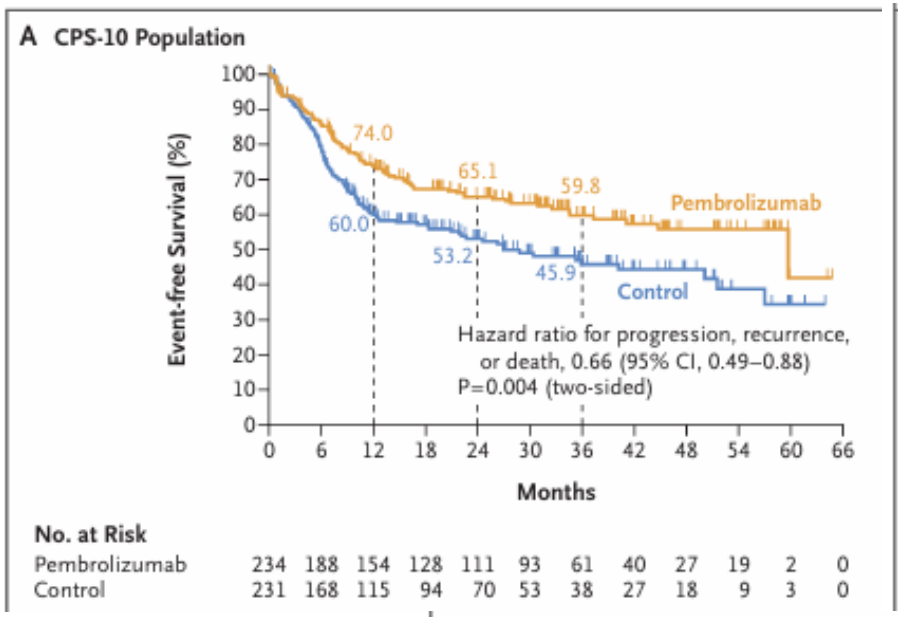

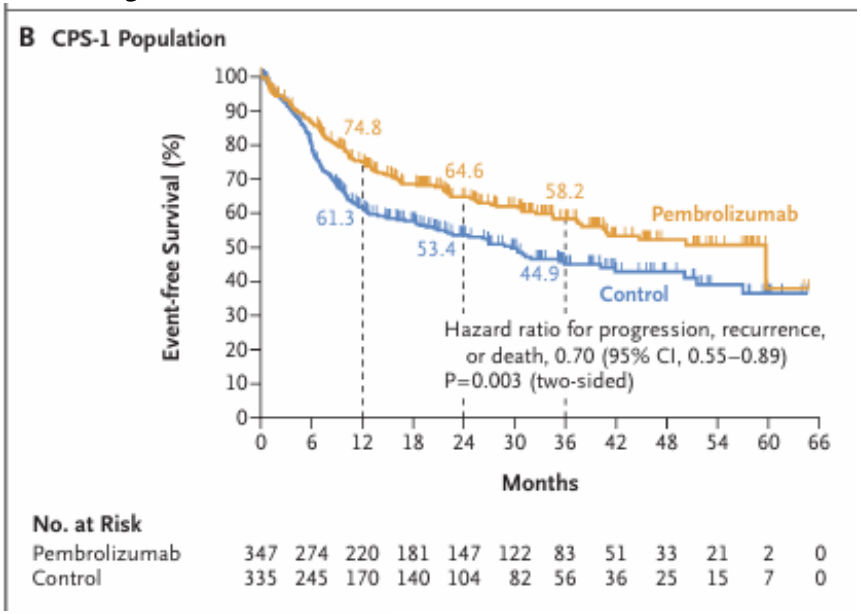

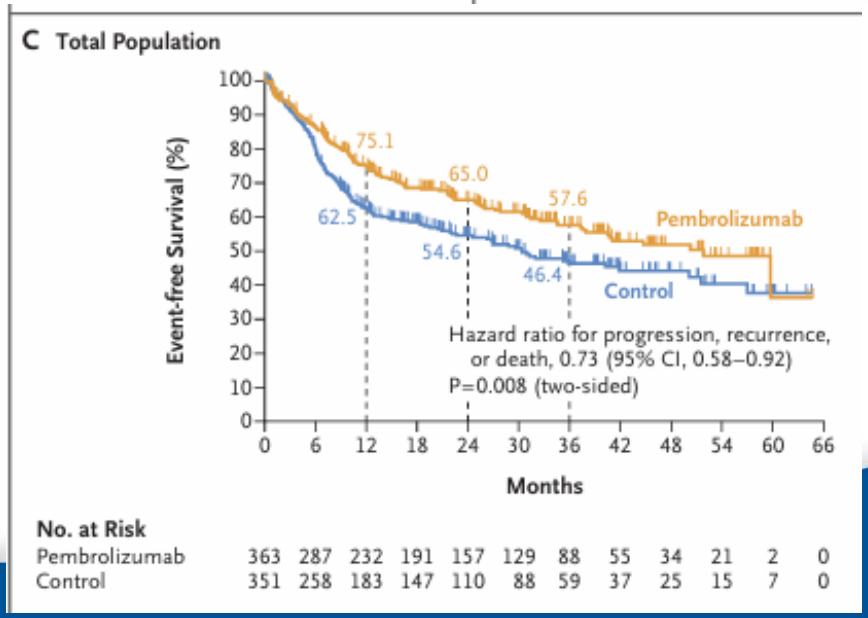

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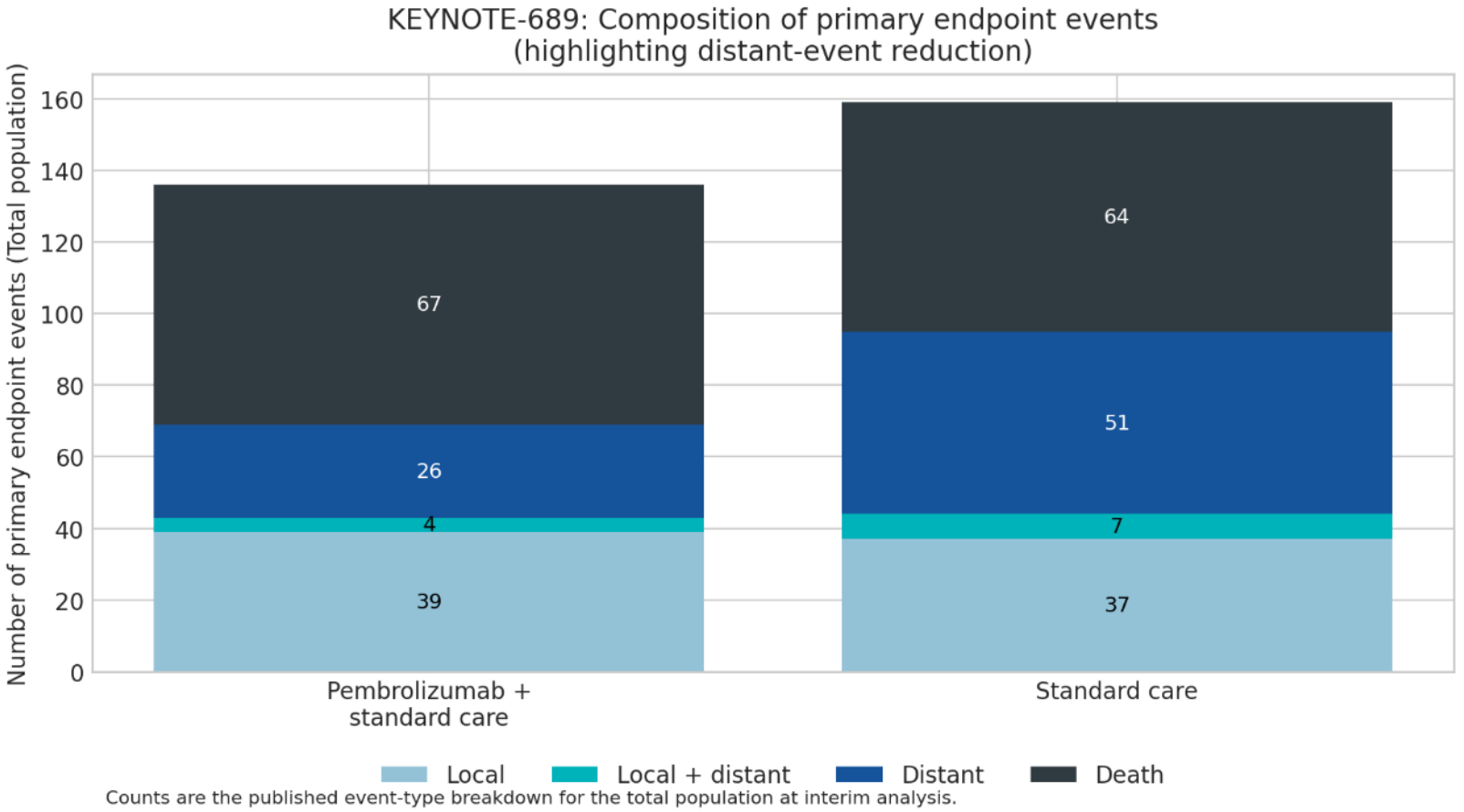

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Secondary Outcomes

- Overall Survival
- Pathologic Response
- Safety

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Interim Overall Survival Findings

Population	Pembrolizumab	Control
CPS ≥10	68.2%	59.2%
CPS ≥1	69.0%	60.2%
Total	68.4%	61.1%

Interim Analysis Status

Interim OS data were immature with about 75% of required events in the PD-L1 CPS ≥1 population recorded.

Future Follow-Up Importance

Longer follow-up and future analyses are critical to confirm OS advantage and characterize long-term survival impact

Pathologic Response

Panel C: Major Pathological Response (≤10% residual tumor)

Population	Pembrolizumab	Control
CPS ≥10	13.7%	0%
CPS ≥1	9.8%	0%
Total Population	9.3%	0%

Panel D: Pathological Complete Response

Population	Pembrolizumab	Control
CPS ≥10	4.2%	0%
CPS ≥1	3.1%	0%
Total Population	3.0%	0%

Not a measured outcome …but interesting

11.6% fewer patients in pembrolizumab group required chemotherapy postoperatively with radiation therapy.

Safety

- Any Adverse Events:
  - Pembrolizumab 81.4%
  - Control 81.9%
- Grade >3
  - Pembrolizumab 44.6%
  - Control 42.9%
- Surgery In-Trial
  - Pembrolizumab 88.4%
  - Control 87.7%

Key Takeaways from KEYNOTE-689

Landmark Clinical Trial

KEYNOTE-689 showed significant event-free survival benefits in head and neck cancer treatment.

Clinical and Patient Impact

The trial highlights early immunotherapy integration and offers hope for improved long-term outcomes.

Future Innovation Foundation

KEYNOTE-689 sets the stage for continued advancements in curative head and neck cancer therapies.

What about the Patient?

- ***So why are we doing this?***

  "We're adding immunotherapy before and after surgery to lower the chance the cancer comes back—especially in other parts of the body."

- ***Will the tumor continue to grow so that I cannot have surgery?***

  "Most people still proceed to surgery on schedule."

- ***What kind of side effects am I likely to experience? Is this the same as traditional chemotherapy?***

  "Side effects are different from chemo—tell us early about breathing changes, diarrhea, rash, or fatigue."

References

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2. Wise-Draper TM, Gulati S, Palackdhar ry S, et al. Phase II clinical trial of neo adjuvant and adjuvant pembrolizumab in resectable local-regionally advanced head and neck squamous cell carcinoma. Clin Cancer Res 2022; 28: 1345-52.
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4. Uppaluri R, Haddad RI, Tao Y, et al. Neoadjuvant and Adjuvant Pembrolizumab in Locally Advanced Head and Neck Cancer. N Engl J Med 2025;393:37–50. DOI: 10.1056/NEJMoa2415434