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DEBATES AND DIDACTICS in Hematology and Oncology

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Adding Without Subtracting: Preserving Adjuvant Intensity in the Era of Neoadjuvant Immunotherapy

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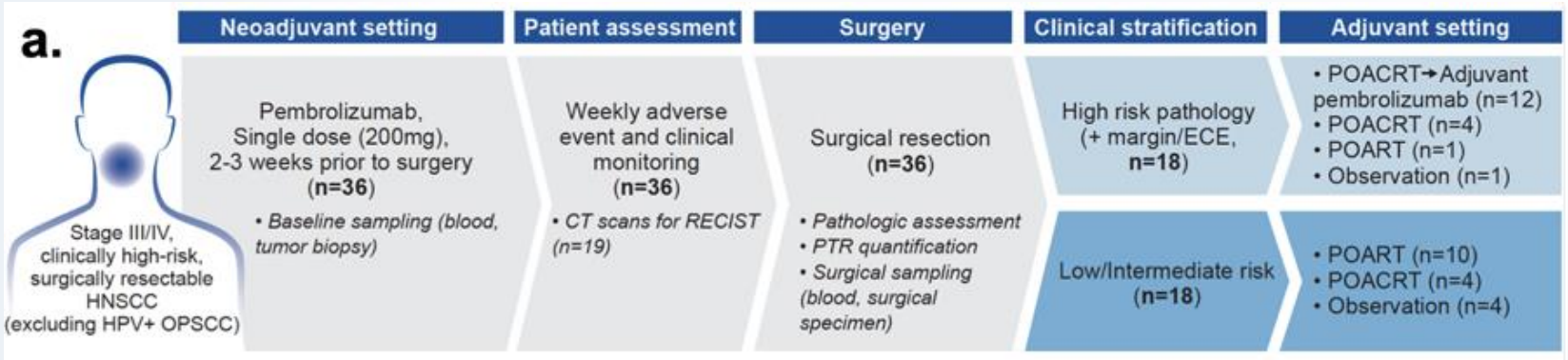
THE UNMET NEED: A 20-Year Plateau in Outcomes

- Patients with locally advanced resectable head and neck squamous cell carcinoma (HNSCC) have suboptimal outcomes
  - Standard of care postoperative chemoradiation (CRT) associated with 40-50% relapse (RTOG 9501, EORTC 22931
  - Survival is 50% at 5 years
- For two decades there has been no meaningful improvement in disease outcomes for this patient cohort
- Emergence of immunotherapy has transformed treatment landscape of HNSCC in recurrent/metastatic HNSCC
  - KEYNOTE 040, CheckMate 141
- Trials in locally advanced HNSCC have largely failed
  - JAVELIN Head and Neck 100, KEYNOTE412

Uppaluri et al, 2021 (Neoadjuvant in HPV- HNSCC)

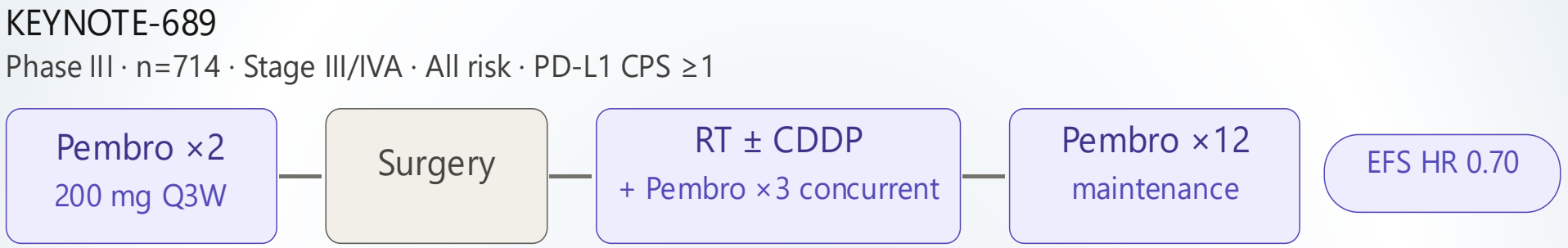


Results:

- pTR-2 (≥50% pathological response) occurred in 22% of patients
- pTR-1 (10-49% pathological response) occurred in 22% of patients
- Any pathological response occurred in 44% of patients
- One year relapse rate among high-risk patients was 17%

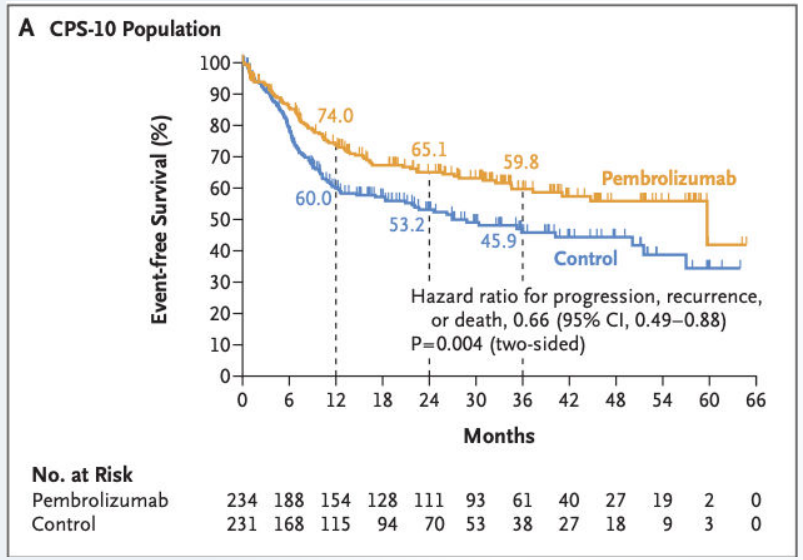
Uppaluri et al., 2020 Clinical Cancer Research

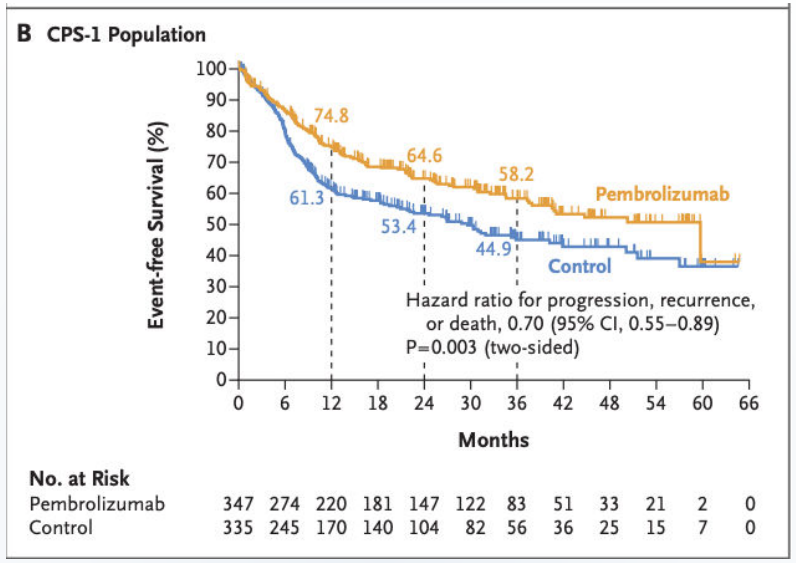
KEYNOTE-689: Phase III Trial Design and Key Results

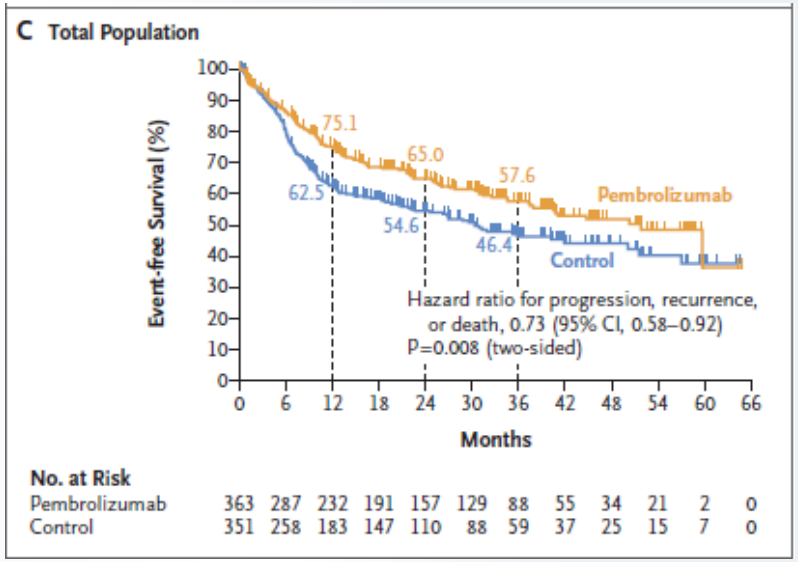


- Resectable Stage III/IV LA-HNSCC (n=714)
  - P16+ Stage III oropharyngeal with T4 and N0-N2, p16- Stage III-IVA oropharyngeal, Stage III/IVA laryngeal, hypopharyngeal or oral cavity
  - Pembro arm: 2 cycles neoadjuvant pembro ⟶ surgery ⟶ PORT ± cisplatin + 15 cycles adjuvant pembro
  - Control arm: Control arm: surgery ⟶ PORT ± cisplatin (SOC)

Results







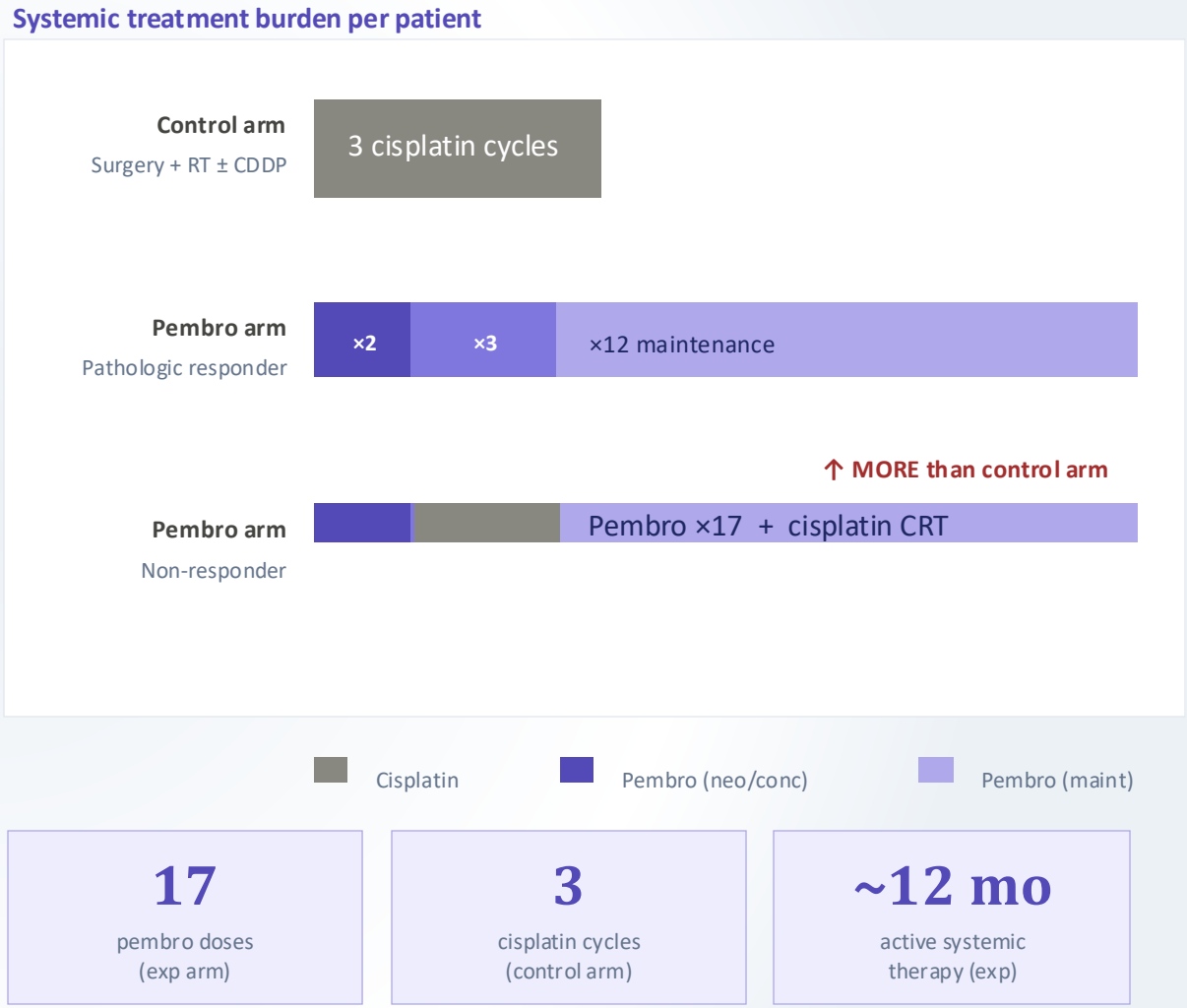
- Postoperative Treatment was not de-escalated in the studies
  - 66 Gy for high-risk disease in both studies
  - High dose Cisplatin (100 mg/m2 q 3 weeks)
  - RT targets based on pre-treatment imaging
  - Surgical resection guided by initial pre-treatment tumor extent
  - Outcomes are still suboptimal;
  - This is not favorable risk HPV associated OPSCC

Never let your foot off the gas!

"De-escalation of chemotherapy ≠ de-intensification of treatment"

KEYNOTE-689 • Systemic treatment burden in the pembrolizumab arm

- **Pembrolizumab is given for a long time.** Patients avoiding cisplatin received 17 doses of pembro spanning ~12 months of active systemic therapy.
- **Distinct, clinically significant toxicity.** Hypothyroidism, pneumonitis, colitis, hepatitis, and immune-mediated dermatitis are all documented — irAEs are not trivial.
  - iRAE in 43.2% of patients in pembro arm
  - iRAE $\geq Grade\ 3$ in 10% of patients in pembro arm
- **Prolonged cumulative exposure.** The 12-cycle maintenance phase spans ~9 months of continuous immunotherapy with no treatment-free interval.



Uppaluri R, et al. N Engl J Med 2025;393:37-50. Supplementary Appendix: Figure S1, Tables S5B and S5C.

The Pathologic Response Argument: Response ≠ Cure

De-intensification argument: neoadjuvant ICI induces pathologic response → less residual disease → less adjuvant therapy needed. This reasoning is flawed for multiple reasons:

01

pCR Rate is Low (3%) in KEYNOTE-689

Major pathologic response (≤10% viable tumor) occurred in only 9.4%, and complete pCR in 3.0%. The vast majority of patients — even responders — retained viable tumor cells after neoadjuvant pembro.

02

Microscopic Residual Disease is Invisible

Pathologic staging cannot detect micrometastatic deposits or margin-proximate cells. Full-dose RT and cisplatin serve to sterilize these occult deposits, which is unchanged by neoadjuvant immune priming.

03

pCR-to-EFS Surrogacy Not Validated in HNSCC

Unlike some breast cancer subtypes, pathologic response has not been prospectively validated as a surrogate for EFS or OS in HNSCC.

04

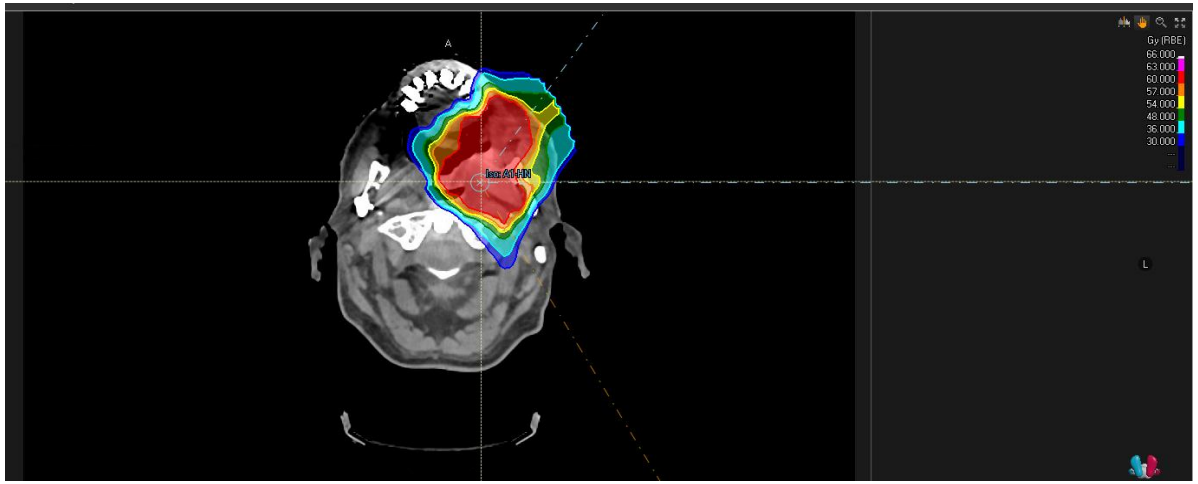
Risk Classification Persists Pathologically

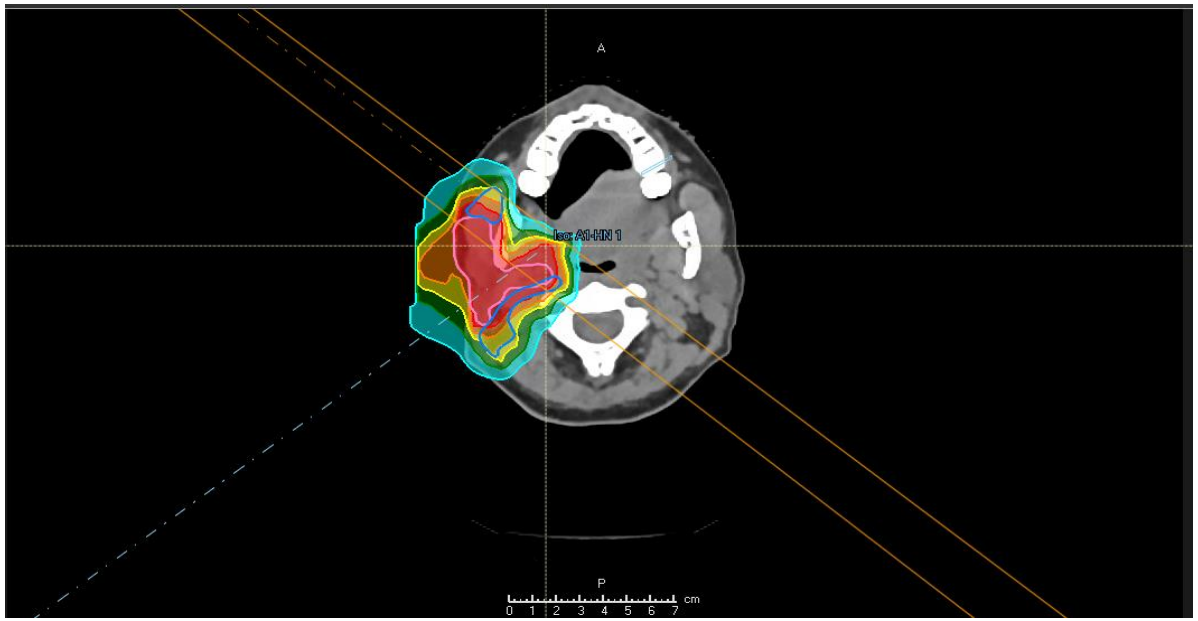
Extranodal extension and positive margins — the key high-risk features driving need for full-dose CRT — were present post-surgery in 33% of KEYNOTE-689 patients.

Pathologic complete response with neoadjuvant immunotherapy

Trial (year)	Phase	N	Neoadjuvant regimen	Site / population	MPR	pCR
Checkpoint inhibitor monotherapy						
Uppaluri (2020)	II	36	Pembrolizumab ×1	HPV− oral cavity / OPC / larynx	—	**0%**
CheckMate 358, Ferris (2021)	I/II	52	Nivolumab ×2	HPV± mucosal HNSCC	5.9% (HPV+)	**~0%[1]**
Dual checkpoint blockade						
IMCISION, Vos (2021)	Ib/IIa	23	Nivolumab + ipilimumab	Oral cavity / oropharynx	35%	**3.1%**
Schoenfeld (2020)	II	29	Nivolumab ± ipilimumab	Oral cavity	NR	**8%**
CIAO, Ferrarotto (2021)	II	28	Durvalumab ± tremelimumab	Oropharynx	29%	**NR**
Chemoimmunotherapy						
Zhang (2022)	II	30	Camrelizumab + nab-paclitaxel + cisplatin	LA HNSCC	74%	**37%**
Pooled meta-analysis (2025)	—	2,021[2]	Chemotherapy + PD-1/PD-L1 ICI	LA HNSCC (28 trials)	—	**~33%**
Perioperative ICI + standard of care (Phase 3)						
KEYNOTE-689 (2025)	III	363	Perioperative pembrolizumab + SOC	Stage III/IVA mucosal	9.4%	**3.0%**

Same team. Same goal: less toxicity, not less therapy





Conclusions

- In KEYNOTE-689, perioperative pembrolizumab improved event-free survival (HR 0.73) by adding to full standard-of-care surgery and radiotherapy.
- Pathologic response to neoadjuvant immunotherapy is low (pCR ~3%, MPR ~9%)
- Extranodal extension and positive margins still drive locoregional recurrence, so adequate surgery and adjuvant (chemo)radiation remain essential.
- Immunotherapy discontinuation was high on this trial. Adjuvant RT with or without chemotherapy may act as a safety measure to eradicate loco-regional disease.
- Focus on strategies to minimize normal tissue injury such as the use of novel radiation techniques
  - Proton beam therapy

Q&A