MUSC
Medical University of South Carolina

Hollings Cancer Center
An NCI-Designated Cancer Center

Neoadjuvant Immunotherapy: cSCC to HNSCC

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Disclosures

- Consulting/Advisory: Bicara Therapeutics, Regeneron, PDS Biosciences

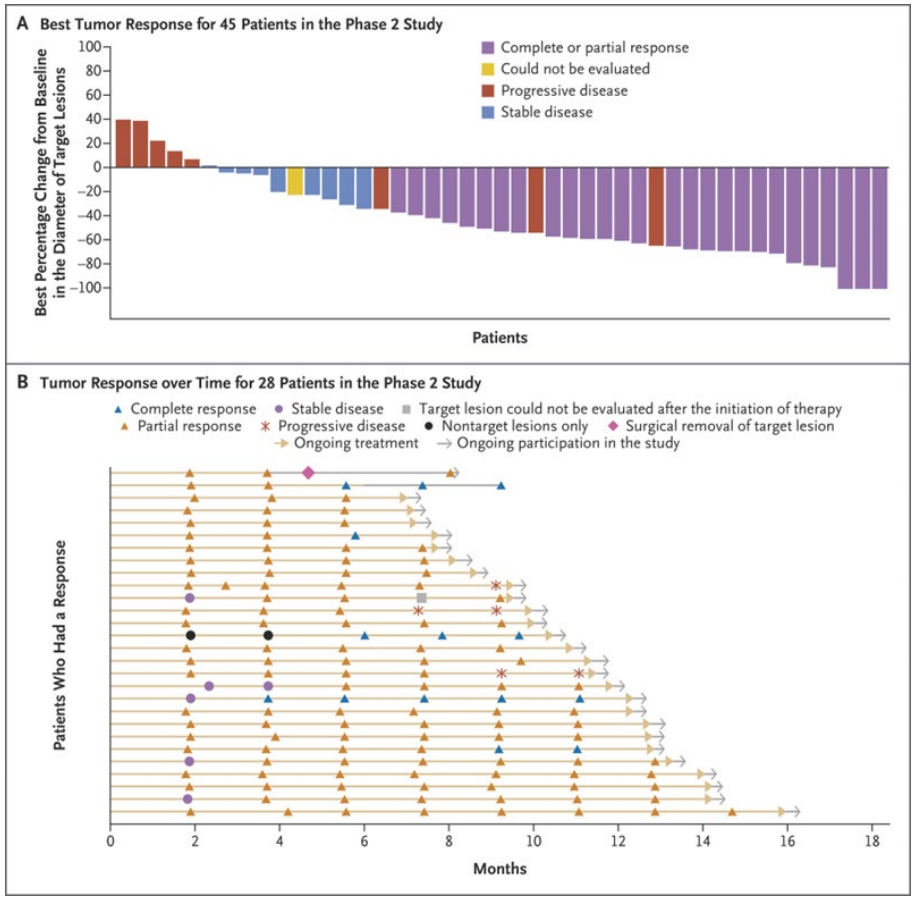
- Nonfinancial: I have no relevant nonfinancial relationship to disclose.

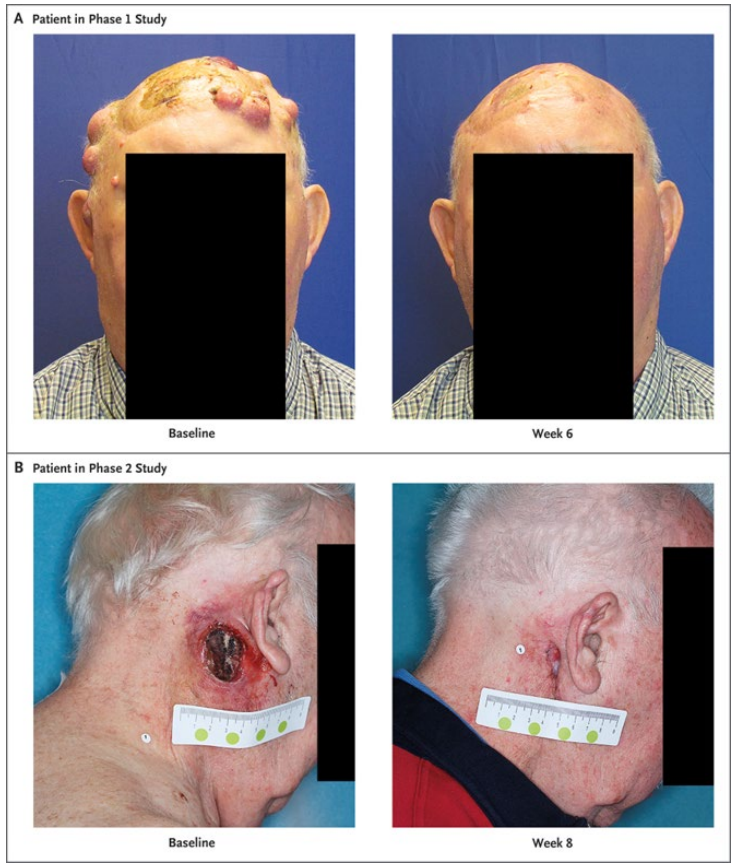
Overview

- Immunotherapy in cSCC
  - R/M
  - Neoadjuvant
  - Future state/controversies
- Immunotherapy in HNSCC
  - R/M
  - Neoadjuvant
  - Future state/controversies

Immunotherapy in Advanced cSCC

- Cemiplimab (anti-PD1)
  - First FDA approved agent to treat cSCC (2018!)
- Pembrolizumab approved shortly thereafter





Migden et al. NEJM 2018

Neoadjuvant Cemiplimab

- Phase 2 study
  - 95% III/IV (M0)
  - 4 neoadjuvant cycles
  - Protocol allowed for adjuvant treatment at investigator discretion

Table 1. Characteristics of the 79 Patients at Baseline.*

Characteristic	Value
Median age (range) — yr	73 (24–93)
Male sex — no. (%)	67 (85)
Race — no. (%)†	
White	69 (87)
Other	2 (3)
Not reported	8 (10)
Not Hispanic or Latinx — no. (%)†	74 (94)
Primary tumor site — no. (%)	
Head and neck	72 (91)
Trunk, arms, and legs	7 (9)
Stage group — no. (%)‡	
II	5 (6)
III	38 (48)
IV (M0)	36 (46)
Tumor stage at screening — no. (%)‡	
TX	23 (29)
Tis	1 (1)
T1	4 (5)
T2	10 (13)
T3	39 (49)
T4a	2 (3)
Node stage at screening — no. (%)‡	
NX	1 (1)
N0	31 (39)
N1	13 (16)
N2§	11 (14)
N2b	9 (11)
N2c	1 (1)
N3¶	1 (1)
N3a	1 (1)
N3b	11 (14)
ECOG performance-status score — no. (%)‖	
0	60 (76)
1	19 (24)

Neoadjuvant Cemiplimab Results

- 51% CR rate

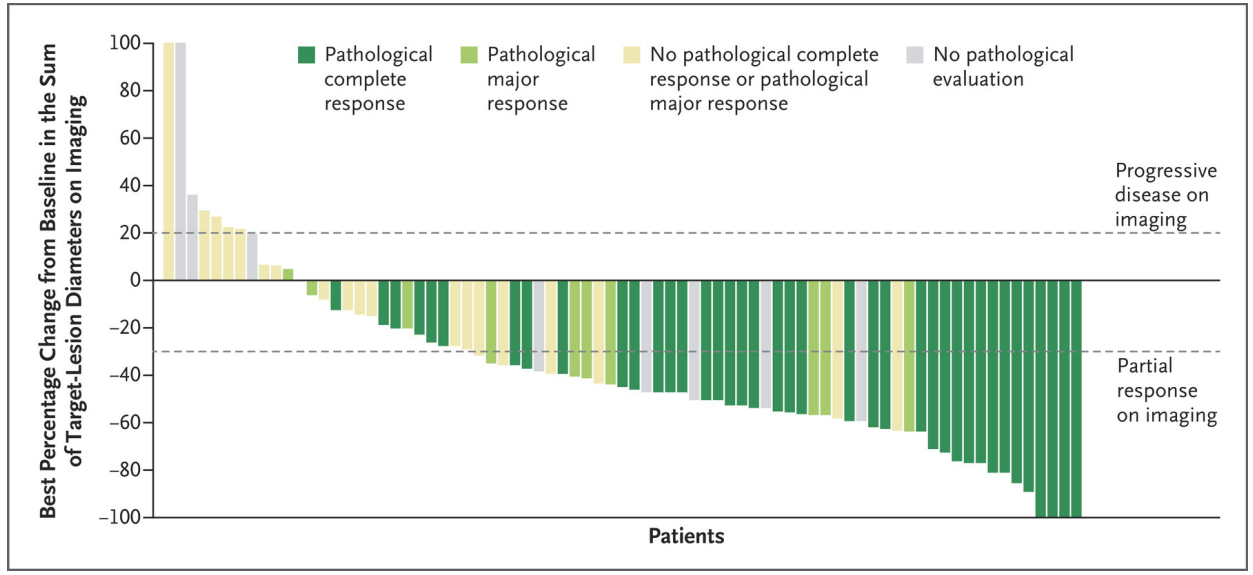


Table 2. Tumor Response to Neoadjuvant Cemiplimab in the 79 Patients According to Pathological and Imaging-Based Response Assessment.*

Tumor Response	Value			
	Independent Review		Investigator Assessment	
	no. (%)	*95% CI*	*no. (%)*	*95% CI*
Pathological response				
Pathological complete response: absence of viable tumor cells in surgical specimen	40 (51)	39–62	42 (53)	42–65
Pathological major response: presence of viable tumor cells that constitute ≤10% of surgical specimen	10 (13)	6–22	10 (13)	6–22
No pathological complete response or pathological major response: presence of viable tumor cells that constitute >10% of surgical specimen†	20 (25)†	—	NA	—
No pathological evaluation‡	9 (11)	—	9 (11)	—
Response on imaging§				
Objective response: complete or partial response	—	—	54 (68)	57–78
Best overall response¶				
Complete response	—	—	5 (6)	—
Partial response	—	—	49 (62)	—
Stable disease	—	—	16 (20)	—
Progressive disease	—	—	8 (10)	—
No imaging-based evaluation	—	—	1 (1)	—
Disease control‖	—	—	70 (89)	80–95

Primary immunotherapy monotherapy (PRIMO)

- “Definitive” immunotherapy
- Mean age 80
- Patients with CR/PR rarely suffered PD
- Reserve surgery and radiation for PD

Results

Table 1. Patient Characteristics

Male:Female	9 (25%): 27 (75%)
Age (mean (SD))	80.3 (8.9)
Follow up, months (median [IQR])	13. 5 [8.0, 20.5]
Head/Neck	32 (89%)
Non-HN	4 (11%)

Table 2. Tumor Characteristics

Location	Head/Neck	32 (89%)
	Non-HN	4 (11%)
Primary vs. Recurrent	Primary	10 (28%)
	Recurrent	26 (72%)
T-stage	T0	6 (17%)
	T2	3 (8%)
	T3	10 (28%)
	T4	13 (36%)
	Tx - ITM	4 (11%)
N-stage	N0	24 (67%)
	N1	5 (14%)
	N2a	1 (3%)
	N2b	3 (8%)
	N2c	1 (3%)
	N3	2 (6%)
M-stage	M0	0 (0%)

Table 3. Treatment Characteristics

Type of immunotherapy	Pembrolizumab	5 (14%)
	Cemiplimab	31 (86%)
# of infusions (median [IQR])	13 [7.0, 18.8]	
Therapy modified due to toxicity?	No	24 (67%)
	Yes	12 (33%)

Table 4. Best Response and Ultimate Progression Rates

Best Initial Response		Eventual Progression on/after immunotherapy?	
		No	Yes
Complete response	15 (42%)	15 (100%)	0 (0%)
Partial response	14 (39%)	11 (79%)	3 (21%)
Stable disease	3 (8%)	0 (0%)	3 (100%)
Progressive disease	4 (11%)	0 (0%)	4 (100%)
Total	36 (100%)	26 (72%)	10 (28%)
Duration of response in months (median [IQR])		15.5 [8.8, 23.2]	3.0 [2.0, 6.8]

Table 5. Survival Rates

	Overall Survival (95% CI)
1 year	76% (63-92)
2 year	64% (48-87)
	Progression-Free Survival (95% CI)
1 year	72% (58-88)
2 year	51% (35-73)

Brito et al. ASCO 2024

RAMPART

- Unresectable cSCC
  - A Phase II, Multicenter, Single-Arm Clnical Trial of Defintiive **R**adiotherapy **A**nd Ce**M**i**P**lim**A**b-wlc Immuno**T**Rherapy for locally Advanced, Unresectable Cutaneous Squamous cell Carcinoma
  - Primary endpoint disease free survival at 18 months
  - ORR secondary endpoint

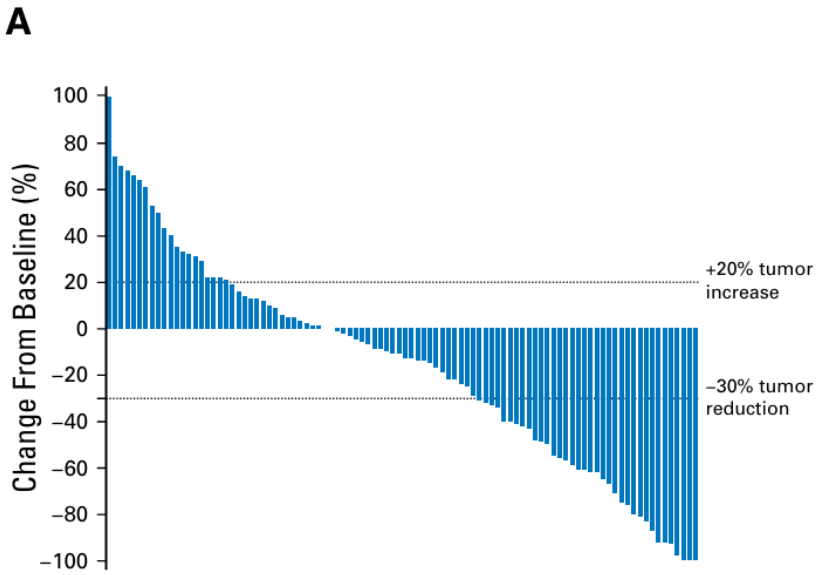
Study Phase:	*Screening*	*Neoadjuvant Treatment*	*Week 6 Response*	*Neoadjuvant Treatment*	*Concurrent Treatment*	*Adjuvant Treatment*
Time:	Weeks -6 - 0	Weeks 1 – 4	Progression →		Weeks 7 - 14	Weeks 22 – 52
			Response/Stable disease →	Weeks 7-10	Weeks 13-20	
Study Event:	Screening Procedures	Cemiplimab Immunotherapy		Cemiplimab Immunotherapy	Concurrent Radiotherapy & Cemiplimab Immunotherapy	Cemiplimab Immunotherapy

cSCC conclusion

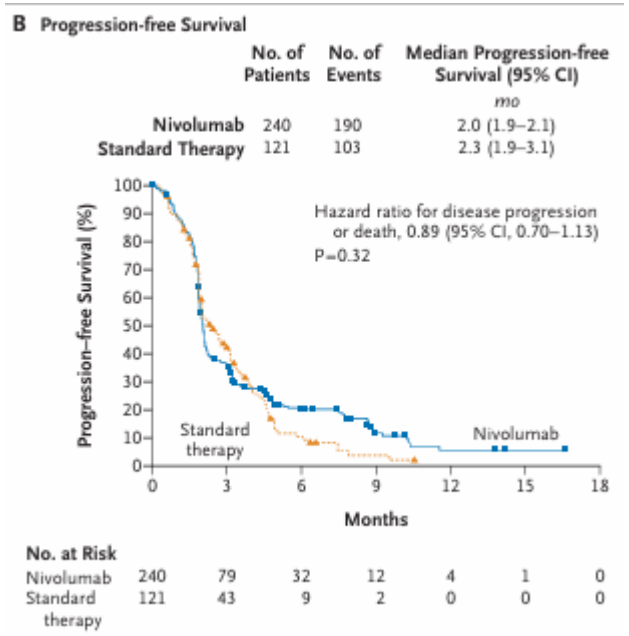
- Lots of good options for patients
- The best treatment algorithm is _____ (???)
- HN 014
  - Testing the Addition of an Immunotherapy Drug, Cemiplimab (REGN2810), Plus Surgery to the Usual Surgery Alone for Treating Advanced Skin Cancer
  - Phase 3 to confirm neoadjuvant is superior to soc
  - **C-POST data imperils this study**
- Future directions/Needs
  - Add LAG3 and other agents to neoadjuvant
  - Determine who needs more than single agent

Immunotherapy in HNSCC

- Checkmate 141 Nivolumab 2016 approved 2nd line
- Keynote 012 supports pembrolizumab



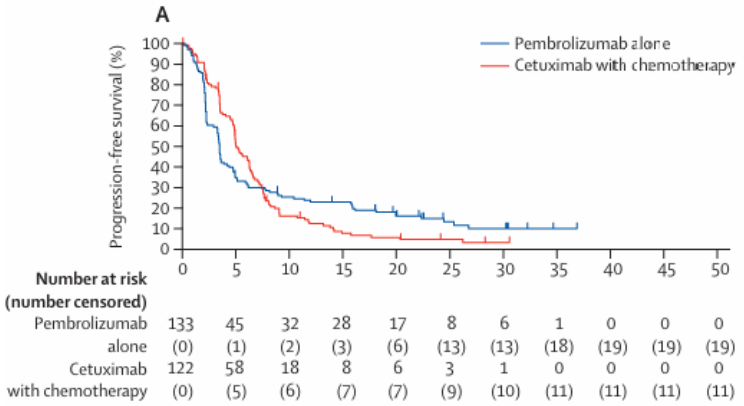
Chow et al. JCO 2018



Ferris et al. NEJM 2016

Immunotherapy in first line HNSCC

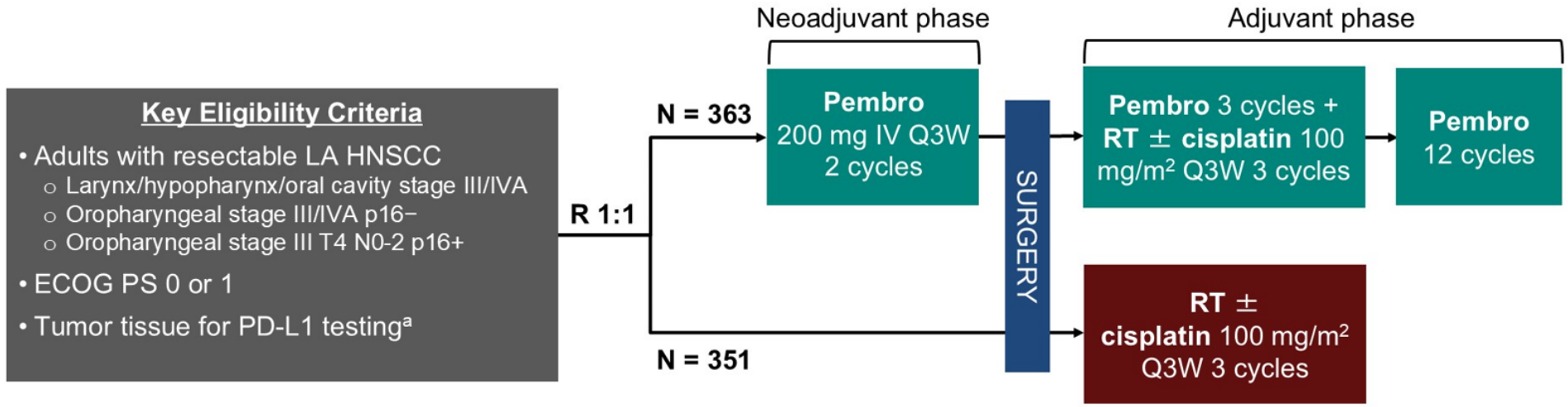
- Keynote 048 supports first line pembrolizumab (CPS >=1) or pembrolizumab + chemotherapy (any CPS)
- Keynote B10 supports paclitaxel substitution
- PFS for single agent pembrolizumab 2-3 months



Burtness et al. Lancet 2019

Keynote 689 – Neoadjuvant pembrolizumab

KEYNOTE-689 Study (NCT03765918)



Stratification factors

- Primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx)
- Tumor stage (III vs IVA)
- PD-L1 TPS[a] (≥50% vs <50%)

Primary endpoint: EFS per RECIST 1.1 by BICR

Key secondary endpoints: Major pathological response by BIPR (mPR; ≤10% residual invasive SCC in resected primary tumor + all sampled regional lymph nodes), OS

Other secondary endpoints include: Safety

Exploratory endpoints include: Locoregional failure rate, DMFS, second cancers

BICR, blinded independent central review; BIPR, blinded independent pathologist review; DMFS, distant metastasis-free survival; EFS, event-free survival; OS, overall survival; RT, radiation therapy.
[a]Assessed by PD-L1 IHC 22C3 pharmDx; TPS=% tumor cells with membranous PD-L1 staining.

Adkins et al ASCO 2025

Keynote 689 – Neoadjuvant pembrolizumab

Uppaluri KN689 AACR 2025

Baseline Characteristics

AACR American Association for Cancer Research ANNUAL MEETING 2025 CHICAGO
APRIL 25–30 | AACR.ORG/AACR2025 | #AACR25

Characteristic	Pembro + SOC (N = 363)	SOC (N = 351)
Median age (range), years	60.0 (29–82)	61.0 (22–87)
Male, n (%)	286 (78.8)	277 (78.9)
Current/former smoker, n (%)[a]	293 (80.7)	267 (76.1)
Alcohol use–yes, n (%)[a]	250 (68.9)	238 (67.8)
Primary tumor site, n (%)		
Oral cavity	219 (60.3)	213 (60.7)
Larynx	81 (22.3)	73 (20.8)
Hypopharynx	28 (7.7)	26 (7.4)
Oropharynx	35 (9.6)	38 (10.8)
Missing	0	1 (0.3)
Positive HPV status, n (%)[b]	12 (3.3)	15 (4.3)
PD-L1 CPS ≥10, n (%)	234 (64.5)	231 (65.8)
PD-L1 CPS ≥1, n (%)	347 (95.6)	335 (95.4)

[a]6 pts in the pembro + SOC group and 3 pts in the SOC group had unknown smoking and alcohol use status. [b]HPV (human papillomavirus) status was determined by local testing for pts with oropharyngeal cancer per p16 IHC. 1 pt in the SOC group had unknown HPV status.

Data cutoff date: 25 July 2024

Keynote 689 – Neoadjuvant pembrolizumab

Uppaluri KN689 AACR 2025

Treatment Disposition

ITT Population

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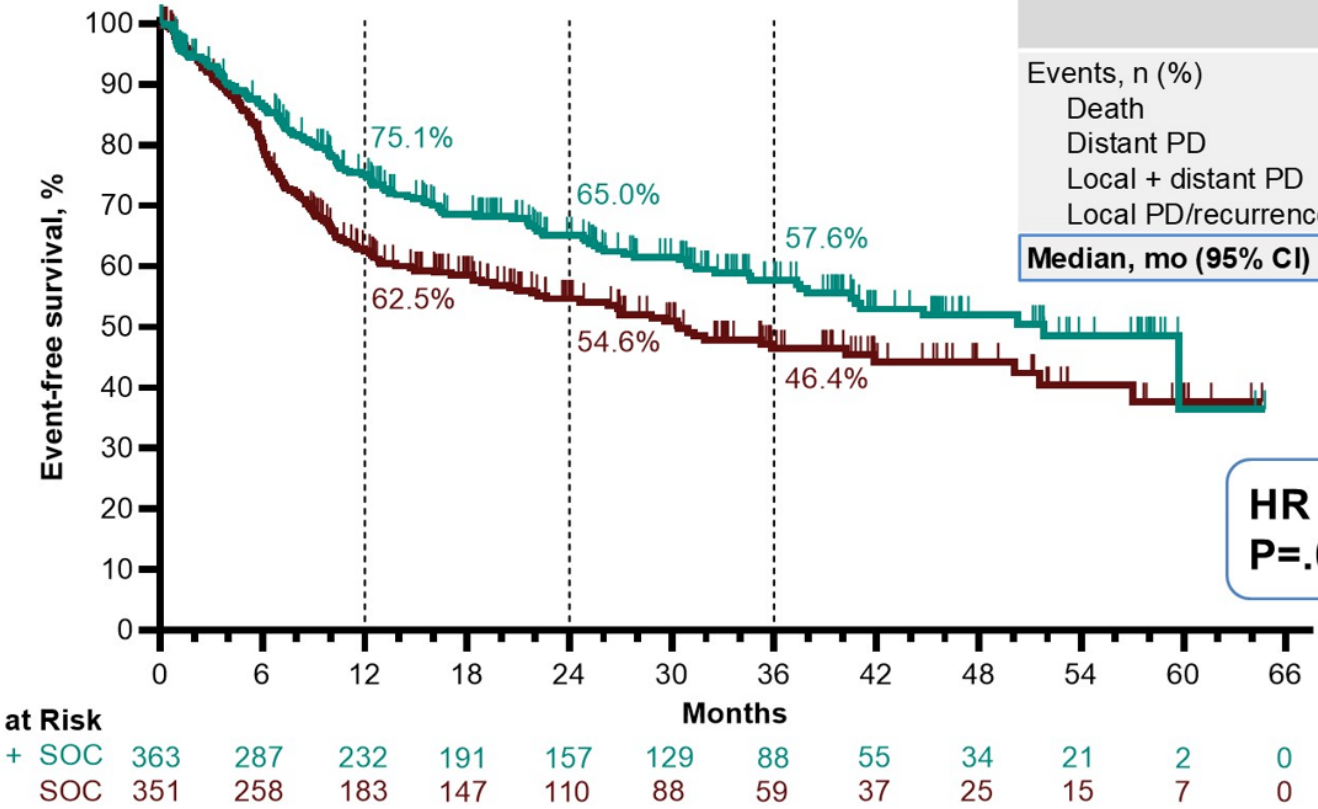
		Pembro + SOC	SOC
Study start	Participants randomized (Dec 2018-Oct 2023), N	363	351
Neoadjuvant therapy	Received ≥1 dose of neoadjuvant pembrolizumab, n (%)	360 (99.2)	2[a] (0.6)
	Completed 2 cycles of pembrolizumab, n (%)	341 (93.9)	1 (0.3)
	Permanently discontinued all study therapy at this phase, n (%)	30 (8.3)	0
In-study surgery	Underwent surgery, n (%) Completed surgery Tumor found to be surgically unresectable	322 (88.7) 321 (88.4) 1 (0.3)	308 (87.7) 308 (87.7) 0
	Permanently discontinued all study therapy at this phase, n (%)	55 (15.2)	41 (11.7)
	Postoperative risk assessment by BIPR, n (%) High-risk features present Low risk (no high-risk features present)	 118 (32.5) 196 (54.0)	 156 (44.4) 148 (42.2)
	Missing	49 (13.5)	47 (13.4)
Adjuvant therapy	Received ≥1 dose of adjuvant therapy after surgery, n (%) Started radiotherapy Started pembrolizumab Started cisplatin	267 (73.6)[b] 266 (73.3) 248 (68.3) 100 (27.5)	267 (76.1)[b] 267 (76.1) 0 132 (37.6)
	Permanently discontinued all study therapy at this phase, n (%)	109 (30.0)	14 (4.0)
All study treatment	Completed all study treatment, n (%)	155 (42.7)	261 (74.4)
	Treatment ongoing, n (%)	11 (3.0)	0

[a]2 pts in the SOC group received neoadjuvant pembro in error (protocol deviations). [b]8 additional pts in each group received definitive therapy without surgery.

Data cutoff date: 25 July 2024

Keynote 689 – EFS

EFS by BICR,[a] All Participants



	Pembro + SOC (N = 363)	SOC (N = 351)
Events, n (%)	136 (37.5)	159 (45.3)
Death	67 (18.5)	64 (18.2)
Distant PD	26 (7.2)	51 (14.5)
Local + distant PD	4 (1.1)	7 (2.0)
Local PD/recurrence	39 (10.7)	37 (10.5)
Median, mo (95% CI)	**51.8 (37.5–NR)**	**30.4 (21.8–50.1)**

HR 0.73, 95% CI 0.58–0.92, P=.0041*

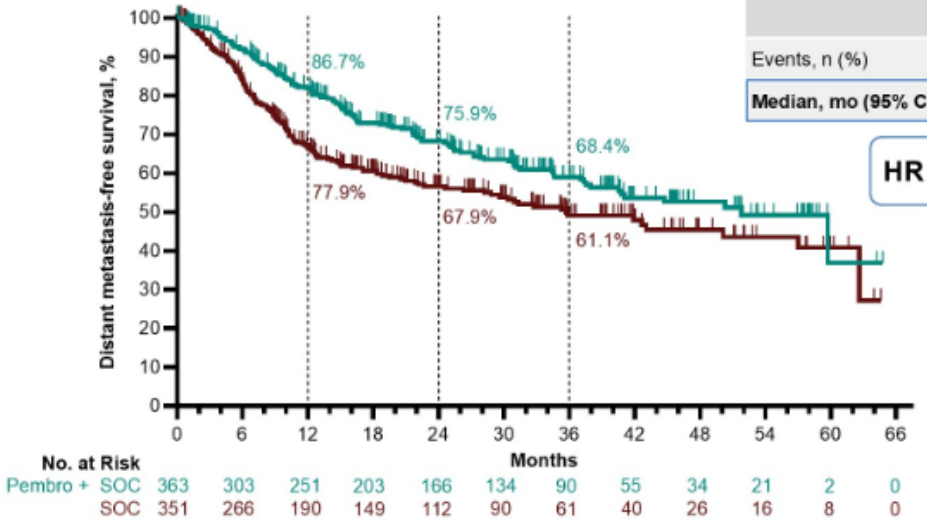
No. at Risk												
Pembro + SOC	363	287	232	191	157	129	88	55	34	21	2	0
SOC	351	258	183	147	110	88	59	37	25	15	7	0

NR, not reached. *Significance boundary was met at IA1.
[a]Defined as time from randomization to first radiographic PD (including during neoadjuvant phase that precludes surgery, local or distant PD/recurrence by imaging/biopsy) or death due to any cause

Data cutoff date: 25 July 2024
Median follow-up (time from randomization to data cutoff date): 38.3 months (9.0–66.5).

Keynote 689 – DM prevention driving benefit

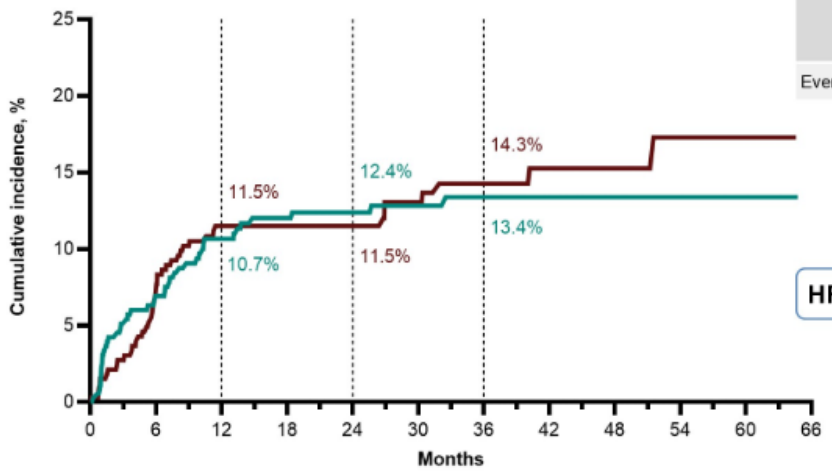
DMFS,[a] All Participants



	Pembro + SOC N = 363	SOC N = 351
Events, n (%)	127 (35.0)	148 (42.2)
Median, mo (95% CI)	**51.8 (37.9–NR)**	**35.7 (26.3–57.0)**

HR 0.71, 95% CI 0.56–0.90

Time to Locoregional Failure,[a] All Participants



	Pembro + SOC N = 363	SOC N = 351
Events, n (%)	136 (37.5)	159 (45.3)

HR 0.92, 95% CI 0.61–1.41

[a]Defined as time from randomization to date of first recorded radiographic PD (local recurrence by imaging or biopsy).

Data cutoff date: 25 July 2024
Median follow-up: 38.3 months (9.0–66.5).

Keynote 689 – Who benefits most?

- III with marked benefit
- IVA no benefit?
- Non-smokers ?benefit
- Older patients ?benefit
- PDL1 higher more benefit

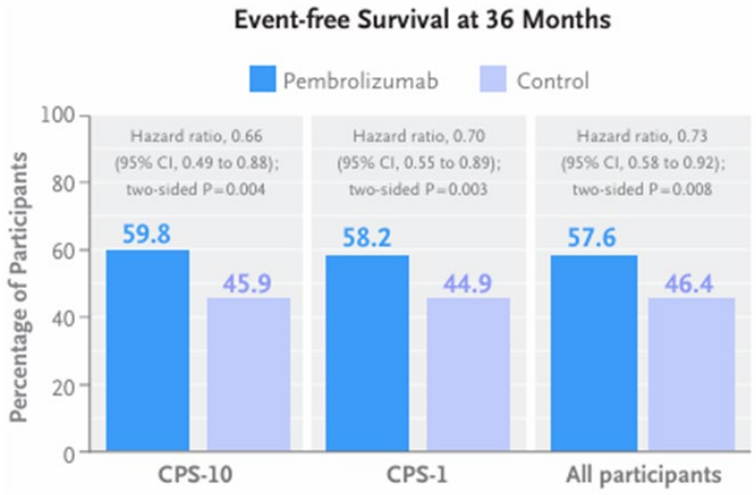
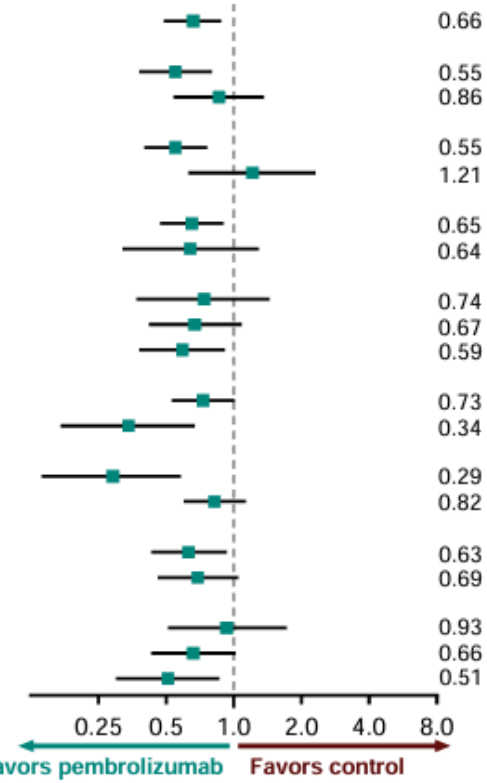


Figure S2A. Event-free Survival by Subgroups. Kaplan-Meier estimates of event-free survi
according to key subgroups in randomized participants who had tumors with PD-L1 CPS ≥10.

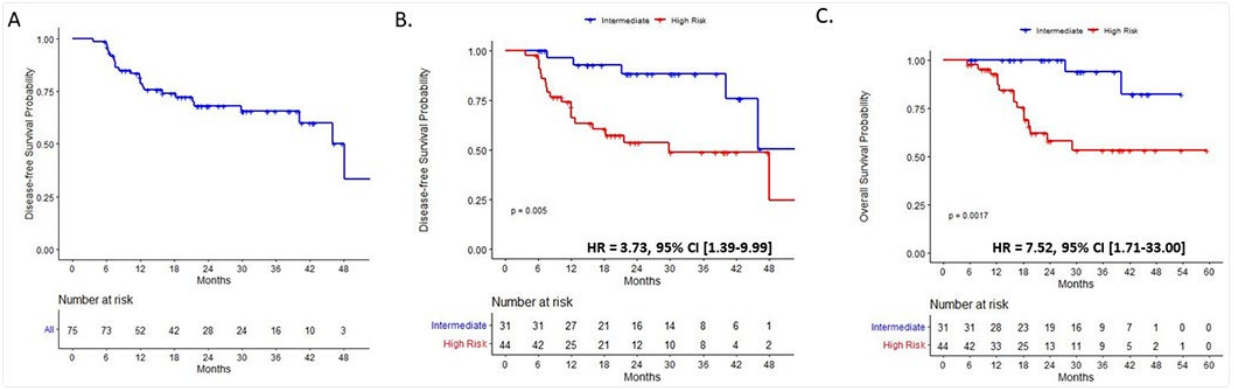
CPS ≥10	Events/Participants Pembro + SOC	Events/Participants SOC	Hazard Ratio (95% C
Overall	85/234	107/231	0.66 (0.49-0.88)
Age			
<65 years	49/155	70/154	0.55 (0.38-0.80)
≥65 years	36/79	37/77	0.86 (0.54-1.36)
Sex			
Male	65/180	90/175	0.55 (0.40-0.76)
Female	20/54	17/56	1.21 (0.63-2.31)
Race			
White	66/183	84/185	0.65 (0.47-0.90)
All others	14/43	18/40	0.64 (0.32-1.29)
Region			
North America	18/46	16/37	0.74 (0.37-1.44)
European Union	30/87	43/97	0.67 (0.42-1.08)
Rest of world	37/101	48/97	0.59 (0.38-0.91)
Primary tumor site			
Oropharynx/Oral cavity	65/166	83/178	0.73 (0.53-1.01)
Larynx	14/48	20/35	0.34 (0.17-0.67)
Tumor stage			
III	11/55	29/63	0.29 (0.14-0.58)
IVA	74/177	78/168	0.82 (0.60-1.13)
PD-L1 TPS			
<50%	46/131	56/124	0.63 (0.43-0.93)
≥50%	39/103	51/107	0.69 (0.46-1.05)
Smoking status			
Never smoker	17/42	26/63	0.93 (0.51-1.72)
Former smoker	41/123	39/88	0.66 (0.43-1.02)
Current smoker	22/63	39/77	0.51 (0.30-0.86)



Phase 2 study Wise Draper

- Similar*ish* design
  - 1 cycle neoadjuvant 1-3 weeks prior to surgery
  - Concurrent/adjuvant pembrolizumab for 18 weeks
  - 1 year DFS 97% (intermediate risk) vs. 66% (high risk)

Figure 1. Survival Stratified by Pathological Adverse Features.



Supplemental Table 3. Change in Stage by Risk		
Stage after neoadjuvant pembro	**Int Risk**	**High Risk**
Same Stage	10/31 (32%)	7/44 (16%)
Down Stage	17/31 (55%)	3/44 (7%)
Up Stage	4/31 (13%)	34/44 (77%)

Keynote 689 – Pathological Response

- pCR and mPR rates low
- pCR rate could be a surrogate marker for OS

	CPS ≥10 Population		CPS ≥1 Population		All Participants	
	Pembro + SOC n = 234	SOC n = 231	Pembro + SOC n = 347	SOC n = 335	Pembro + SOC N = 363	SOC N = 351
mPR, n (%)	32 (13.7)	0	34 (9.8)	0	34 (9.4)	0
Estimated difference (95% CI)	13.7 (9.7–18.7)		9.8 (7.0–13.3)		9.3 (6.7–12.8)	
P value	<0.00001*		<0.00001*		<0.00001*	
pCR, n (%)	10 (4.3)	0	11 (3.2)	0	11 (3.0)	0
Estimated difference (95% CI)	4.2 (2.1–7.6)		3.1 (1.6–5.6)		3.0 (1.5–5.3)	

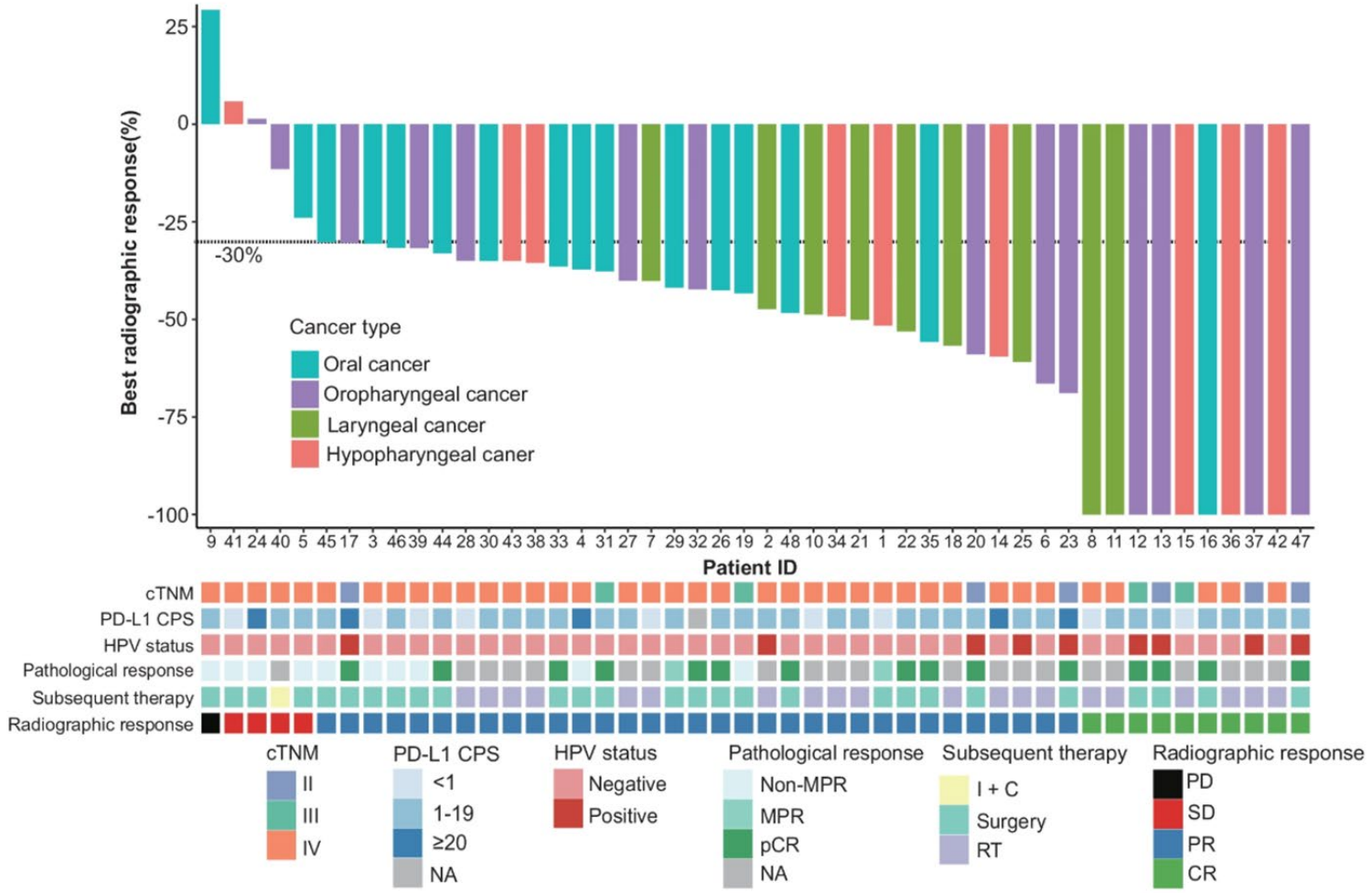
Chemo+IO better?

- ~25% pCR in NSCLC
- Two small phase 2 studies in Asia utilizing **cisplatin + nab-paclitaxel + camrelizumab** in locally advanced (III-IVB
  - Zhang et al → 27 patients (all went to surgery) – no oral cavity!
    - ORR 97%
    - pCR 37%, MPR 74.1
  - Wu et al → 48 patients including oropharynx, larynx, hypopharynx, and oral cavity → 27 treated with surgery, 21 non-surgical (CRT)
    - ORR 89.6% (48 patients)
    - pCR 55.6%, MPR 63%

Chemo-IO associated with good tumor control

Fig. 2: The waterfall plot of best radiographic response by RECIST 1.1 (n = 48).

From: Neoadjuvant chemo-immunotherapy with camrelizumab plus nab-paclitaxel and cisplatin in resectable locally advanced squamous cell carcinoma of the head and neck: a pilot phase II trial



Each bar indicates one patient. Source data are provided as a Source Data file.

HNSCC Conclusion/Future directions

- Pembrolizumab improves EFS
  - DMFS seems to be driver
- Benefit may be uneven
- How much does adjuvant immunotherapy drive EFS and potentially OS?
- Intensification of neoadjuvant for IVA and greater patients?