

Disclosures

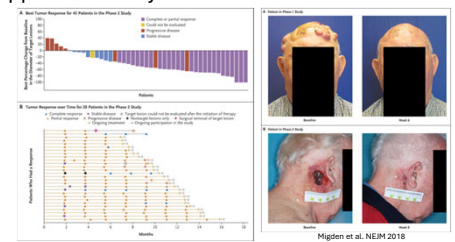
- **Consulting/Advisory:** Bicara Therapeutics, Regeneron, PDS Biosciences
- **Nonfinancial:** I have no relevant nonfinancial relationship to disclose.

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



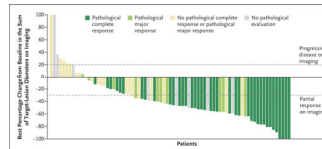
Neoadjuvant Cemiplimab

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

Table 1. Characterization of the 76 Patients at Baseline ^a	Value
Median age (range)	71 (24-83)
Male (n, %)	47 (62)
Race	
White	48 (63)
Other	28 (37)
Non-exposed	8 (10)
Not registered in trial (n, %)	10 (13)
Primary tumor site (n, %)	76 (100)
Head and neck	33 (43)
Pituitary, skin, and lung	3 (4)
Other	40 (53)
Stage group (n, %)	76 (100)
I	36 (47)
II	36 (47)
III	4 (5)
IV	1 (1)
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Neoadjuvant Cemiplimab Results

- 51% CR rate



Tumor Response	Value	
	Independent Review (n (%))	Investigator Assessment (n (%))
Pathological response		
Pathological complete response: absence of viable tumor cells	40 (51)	39–42 (50)
Pathological complete response: presence of viable tumor cells	39 (50)	39–42 (50)
Pathological partial response: presence of viable tumor cells	19 (24)	6–22 (8)
No pathological response	20 (25)	NA
No pathological evaluation†	9 (11)	9 (11)
Response on imaging‡		
Objective response rate: complete or partial response		54 (68), 57–58
Best overall response		
Complete response		5 (6)
Partial response		49 (62)
Stable disease		19 (24)
Progressive disease		3 (4)
No imaging-based evaluation		1 (1)
		79 (100), 80–79

Primary immunotherapy monotherapy (PRIMO)

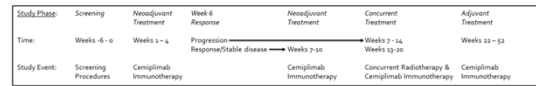
- “Definitive” immunotherapy
- Mean age 80
- Patients with CR/PR rarely suffered PD
- Reserve surgery and radiation for PD

Results	
Table 1. Patient Characteristics	Table 2. Tumor Characteristics
Mean (range)	Median
Age (years) (SD)	80.3 (8.6)
Female:male	15:55 (26.5%)
Primary vs. recurrent	Primary: 10 (28%) Recurrent: 26 (72%)
Head/neck	73 (20%)
Non-HNS	12 (3%)
Table 3. Treatment Characteristics	Table 4. Best Response and Ultimate Progression Rates
Type of treatment	Progression-free survival (95% CI)
Immunotherapy	Complete response: 15 (42%) Partial response: 14 (39%) Stable disease: 2 (5%) Progressive disease: 4 (11%) Total: 35 (100%)
Therapy	Median progression-free survival (months) (95% CI)
Immunotherapy	15.5 (9.8, 22.2)
Immunotherapy + surgery	15.5 (9.8, 22.2)
Immunotherapy + radiation	15.5 (9.8, 22.2)
Immunotherapy + surgery + radiation	15.5 (9.8, 22.2)
Immunotherapy + surgery + radiation + chemotherapy	15.5 (9.8, 22.2)
Immunotherapy + surgery + radiation + chemotherapy + immunotherapy	15.5 (9.8, 22.2)

Britto et al. ASCO 2024

RAMPART

- Unresectable cSCC
 - A Phase II, Multicenter, Single-Arm Clinical Trial of Definitive Radiotherapy And CemiplimAb-w/ Immunotherapy for locally Advanced, Unresectable Cutaneous Squamous cell Carcinoma
 - Primary endpoint disease free survival at 18 months
 - ORR secondary endpoint

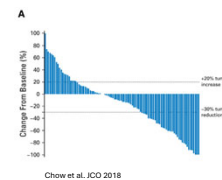


cSCC conclusion

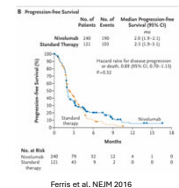
- Lots of good options for patients
- The best treatment algorithm is _____ (???)
- HN 014
 - Testing the Addition of an Immunotherapy Drug, Cemiplimab (REGN2810), Plus Surgery to the Usual Surgery Alone for Treating Advanced Skin Cancer
 - Phase 3 to confirm neoadjuvant is superior to soc
 - C-POST 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



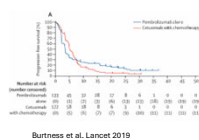
Chow et al. JCO 2016



Ferris et al. NEJM 2016

Immunotherapy in first line HNSCC

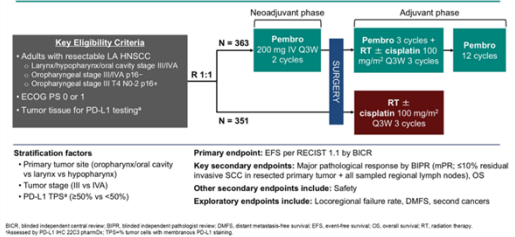
- Keynote 048 supports first line pembrolizumab (CPS ≥1) or pembrolizumab + chemotherapy (any CPS)
- Keynote B10 supports paclitaxel substitution
- PFS for single agent pembrolizumab 2-3 months



Burtness et al. Lancet 2019

Keynote 689 – Neoadjuvant pembrolizumab

KEYNOTE-689 Study (NCT03765918)



Adkins et al. ASCO 2025

Keynote 689 – Neoadjuvant pembrolizumab

Baseline Characteristics

Update: KPS99 AACR 2022
AACR 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)
Dropharynx	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 16 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.

Date cutoff date: 25 July 2022

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Keynote 689 – Neoadjuvant pembrolizumab

Treatment Disposition

ITT Population

Update: KPS99 AACR 2022
AACR ANNUAL MEETING 2025 CHICAGO
APRIL 25-30 | AACR.ORG/AACR2025 | AACR25

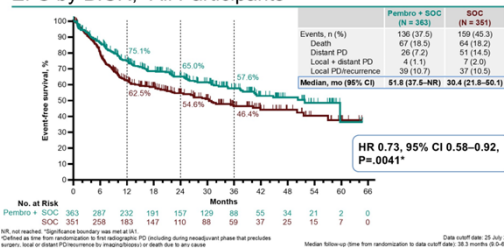
		Pembro + SOC	SOC
Study start	Participants randomized (Dec 2018-Oct 2022), N	363	351
Neoadjuvant therapy	Received ≥1 dose of neoadjuvant pembrolizumab, n (%)	360 (99.2)	2* (0.6)
	Completed 2 cycles of pembrolizumab, n (%)	341 (93.9)	1 (0.3)
	Permanently discontinued all study therapy at this phase, n (%)	30 (8.3)	0
	Underwent surgery, n (%)	322 (88.7)	308 (87.7)
	Completed surgery, n (%)	321 (88.4)	308 (87.7)
In-study surgery	Tumor found to be surgically unresectable	1 (0.3)	0
	Permanently discontinued all study therapy at this phase, n (%)	55 (15.2)	41 (11.7)
	Postoperative risk assessment by BPIR, n (%)		
	High-risk features present	118 (25.5)	156 (44.4)
	Low risk (no high-risk features present)	186 (51.0)	182 (52.2)
Adjuvant therapy	Missing	49 (13.5)	41 (11.7)
	Received ≥1 dose of adjuvant therapy after surgery, n (%)	267 (73.6) ^a	267 (76.1) ^a
	Started radiotherapy	268 (73.3)	267 (76.1)
	Started pembrolizumab	268 (73.3)	267 (76.1)
	Started cisplatin	100 (27.5)	132 (37.6)
All study treatment	Permanently discontinued all study therapy at this phase, n (%)	109 (30.0)	14 (4.0)
	Completed all study treatment, n (%)	155 (42.7)	281 (80.0)
	Treatment ongoing, n (%)	11 (3.0)	0

^a 12 pts in the SOC group received neoadjuvant pembro in error (protocol deviations). ^b 16 additional pts in each group received definitive therapy without surgery.

Date cutoff date: 25 July 2022

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Keynote 689 – EFS

EFS by BICR, ^a All Participants

^a HR not reported. ^b Significant between-group difference at 66 months.

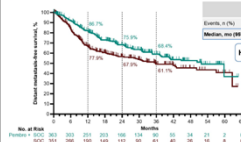
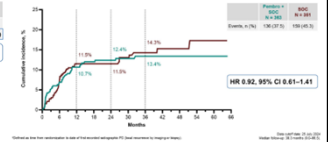
^c Defined as time from randomization to first subsequent PD (including during neoadjuvant phase that precedes surgery), local or distant PD recurrence, or death due to any cause.

Median follow-up time from randomization to date cutoff date: 38.1 months (5.46–65.5)

Date cutoff date: 25 July 2022

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Keynote 689 – DM prevention driving benefit

DMFS, ^a All ParticipantsTime to Locoregional Failure, ^a All Participants

^a HR not reported. ^b Significant between-group difference at 66 months.

^c Defined as time from randomization to first subsequent PD (including during neoadjuvant phase that precedes surgery), local or distant PD recurrence, or death due to any cause.

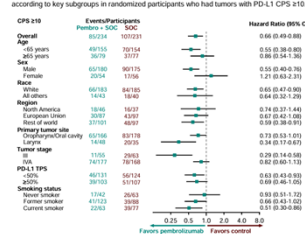
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Keynote 689 – Who benefits most?

- Ill 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 survival according to key subgroups in randomized participants who had tumors with PD-L1 CPS ≥10.



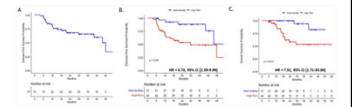
Favors pembrolizumab

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Phase 2 study Wise Draper

- Similarish 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 Pathologic Adverse Features.



Supplemental Table 3. Change in Stage by Risk		
Stage after neoadjuvant pembrolizumab	Low Risk	High Risk
Same Stage	10/70 (14%)	7/44 (16%)
Down Stage	13/70 (19%)	16/44 (36%)
Up Stage	4/70 (6%)	16/44 (36%)

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Keynote 68g – Pathological Response

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

	CPS 310 Population		CPS 311 Population		All Participants	
	Pembrolizumab + SOC n = 224	SOC n = 231	Pembrolizumab + SOC n = 247	SOC n = 238	Pembrolizumab + SOC n = 351	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 (7.5–13.3)		9.3 (6.7–12.8)	
P value	<0.0001*		<0.0001*		<0.0001*	
pCR, n (%)	19 (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)	

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Chemo+IO better?

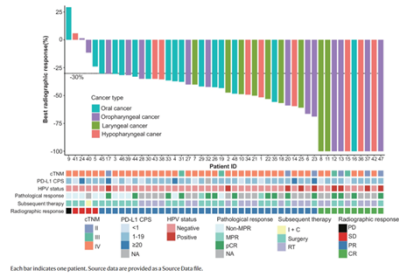
- ~25% pCR in NSCLC
- Two small phase 2 studies in Asia utilizing **cisplatin + nab-paclitaxel + camrelizumab** in locally advanced (III-IVB)
 - Zhang et al → 27 patients (all went to surgery) – no oral cavity!
 - ORR 97%
 - pCR 37%, MPR 74.1
 - Wu et al → 48 patients including oropharynx, larynx, hypopharynx,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

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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 phase II trial



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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?

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