1

Disclosures

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

2

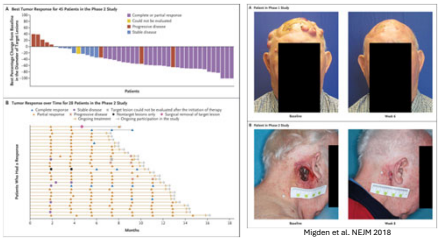
Overview

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

3

Immunotherapy in Advanced cSCC

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

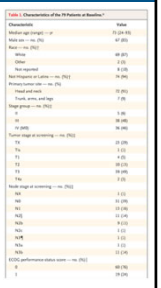


Migden et al. NEJM 2018

4

Neoadjuvant Cemiplimab

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



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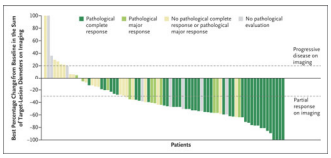
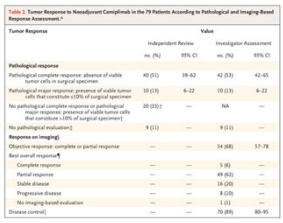
Neoadjuvant Cemiplimab Results

- 51% CR rate





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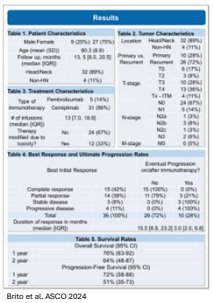
Primary immunotherapy monotherapy (PRIMO)

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

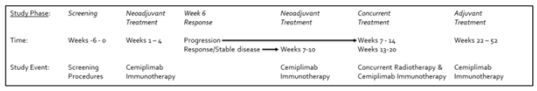


Brito et al. ASCO 2024

7

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 ImmunoTRherapy for locally Advanced, Unresectable Cutaneous Squamous cell Carcinoma
  - Primary endpoint disease free survival at 18 months
  - ORR secondary endpoint



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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

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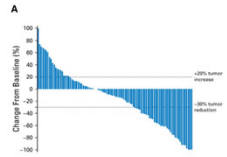
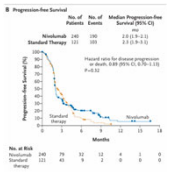
Immunotherapy in HNSCC

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



Chow et al. JCO 2018



Ferris et al. NEJM 2016

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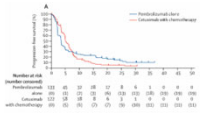
Immunotherapy in first line HNSCC

- 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

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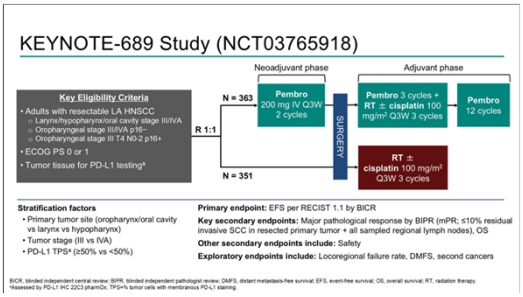
Keynote 689 – Neoadjuvant pembrolizumab



Adkins et al ASCO 2025

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Keynote 689 – Neoadjuvant pembrolizumab

Baseline Characteristics

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

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Keynote 689 – Neoadjuvant pembrolizumab

Treatment Disposition

ITT Population

		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 (%)	322 (88.7)	308 (87.7)
	Completed surgery	321 (88.4)	308 (87.7)
	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 BIPR, n (%)		
	High-risk features present	118 (32.5)	156 (44.4)
	Low risk (no high-risk features present)	196 (54.0)	148 (42.2)
	Missing	49 (13.5)	47 (13.4)
Adjuvant therapy	Received ≥1 dose of adjuvant therapy after surgery, n (%)	267 (73.6)[b]	267 (76.1)[b]
	Started radiotherapy	266 (73.3)	267 (76.1)
	Started pembrolizumab	248 (68.3)	0
	Started cisplatin	100 (27.5)	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]6 additional pts in each group received definitive therapy without surgery.

Data cutoff date: 25 July 2024

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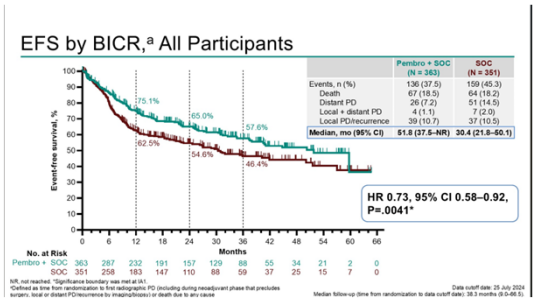
Keynote 689 – EFS



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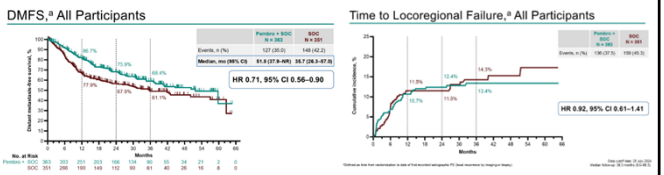
Keynote 689 – DM prevention driving benefit



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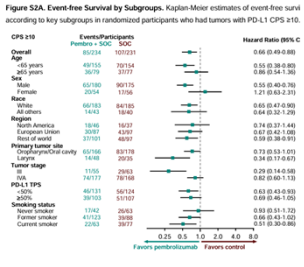
Keynote 689 – Who benefits most?

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



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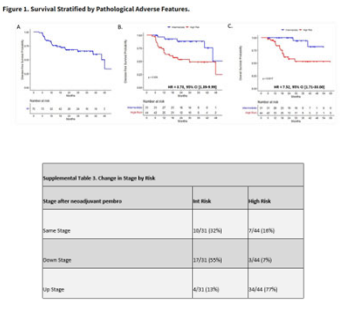
Phase 2 study Wise Draper

- 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)



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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 = 336	Pembro + SOC N = 363	SOC N = 361
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)	

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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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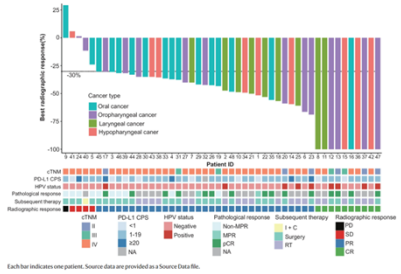
Chemo-IO associated with good tumor control

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 pilot phase II trial



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

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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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