Novel Therapeutics for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

Assuntina G. Sacco M.D.

Associate Professor of Internal Medicine - Division of Hematology/Oncology

Co-Director, Mark and Hanna Gleiberman Head and Neck Center

Disease Team Leader - Head and Neck, UCSD Moores Cancer Center

UC San Diego Health System

Disclosures

- *Merck*: research support
- *Bicara:* advisory board; research support
- *Merus:* research support
- *AstraZeneca:* research support
- *Genentech Roche:* research support
- *ALX Oncology:* research support
- *iTeos*: research support
- *Seagen:* research support
- *Toragen:* research support
- *Infinity Pharmaceuticals:* research support
- *i3 Health:* honoraria for lecture series

Learning Objectives

- Review current best practices for management of R/M HNSCC
- Develop awareness of clinical trials and emerging therapies for R/M HNSCC

NCCN Guidelines version 3.2024

Recurrent, Unresectable, or Metastatic Disease (with no surgery or RT option)

Preferred Regimens	Other Recommended Regimens (First- and Subsequent-Line)	Useful in Certain Circumstances (First- and Subsequent-Line)
First-Line[c] • Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU (category 1)[c,32] • Pembrolizumab (for tumors that express PD-L1 with CPS ≥1)[c,32] (category 1) **Subsequent-Line (if not previously used)** • Nivolumab[33] (if disease progression on or after platinum therapy) (category 1) • Pembrolizumab[34-36] (if disease progression on or after platinum therapy) (category 1)	**Combination Regimens** • Cetuximab/platinum (cisplatin or carboplatin)/5-FU[37] (category 1) • Cisplatin/cetuximab[38] • Cisplatin or carboplatin/docetaxel[39] or paclitaxel[40] • Cisplatin/5-FU[40,41] • Cisplatin or carboplatin/docetaxel/cetuximab[42] • Cisplatin or carboplatin/paclitaxel/cetuximab[43] • Pembrolizumab/platinum (cisplatin or carboplatin)/docetaxel[32,39] • Pembrolizumab/platinum (cisplatin or carboplatin)/paclitaxel[32,40,44] **Single Agents** • Cisplatin[38,45] • Carboplatin[46] • Paclitaxel[47] • Docetaxel[48,49] • 5-FU[45] • Methotrexate[41,50] • Cetuximab[51,52] • Capecitabine[53] • Afatinib[54](subsequent-line only, if disease progression on or after platinum therapy) (category 2B)	• Squamous cell carcinoma ▸ Cetuximab/nivolumab[55] ▸ Cetuximab/pembrolizumab[56] • For select ethmoid/maxillary sinus cancers (ie, small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features): ▸ Cisplatin/etoposide or carboplatin/etoposide[15] ▸ Cyclophosphamide/doxorubicin/vincristine (category 2B)[16] • Paclitaxel/cetuximab[57] • Docetaxel/cetuximab (category 2B)[42] • Pembrolizumab (for MSI-H, dMMR, or TMB-H [≥10 mut/Mb] tumors)[58] • Cisplatin/pemetrexed (for PS 0–1) (category 2B)[59] • Gemcitabine/paclitaxel (category 2B)[60] • Nivolumab/ipilimumab (CPS ≥20 and first-line only) (category 2B)[61]

Accessed 4/9/24

[c] If not previously used, these regimens may be considered in subsequent-line therapy as other recommended regimens.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

SYST-A
2 OF 4

KEYNOTE-048 Study Schema

Key Eligibility Criteria

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapy
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment
- Known p16 status in the oropharynx

Stratification Factors

- PD-L1 expression (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG PS 0 vs 1

RANDOMIZATION 1:1:1

Pembro → Pembrolizumab 200 mg Q3W for up to 35 cycles

Pembro plus chemo → Pembrolizumab 200 mg plus carboplatin AUC 5 mg/m^2 or cisplatin 100 mg/m^2 plus 5-FU 1,000 mg/m^2/d for 4 days for 6 cycles (every 3 weeks) → Pembrolizumab 200 mg Q3W for up to 35 cycles total

EXTREME → Cetuximab 400 mg/m^2 loading dose, 250 mg/m^2 Q1W plus carboplatin AUC 5 mg/m^2 or cisplatin 100 mg/m^2 plus 5-FU 1,000 mg/m^2/d for 4 days for 6 cycles → Cetuximab 250 mg/m^2 Q1W

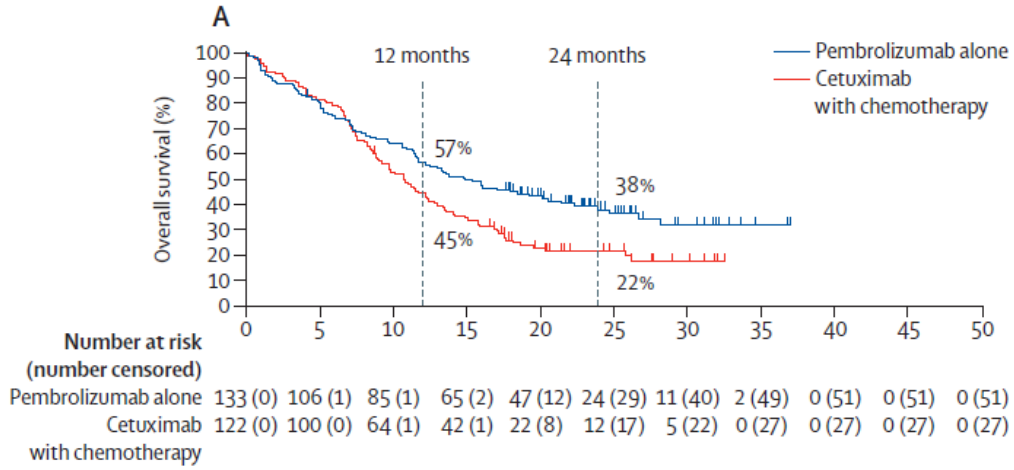
Primary end points: overall survival, PFS
Secondary end points: safety, tolerability, objective response, QOL

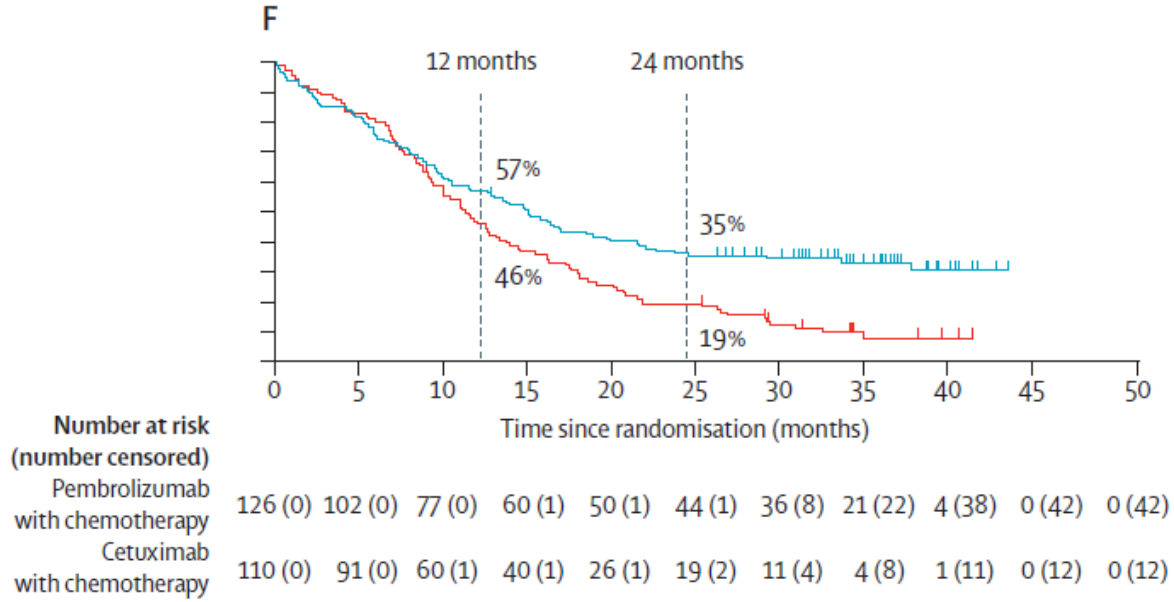
UC San Diego Health

Burtness et al, 2019

Keynote 048: Overall Survival CPS ≥20

- 43% of patients in this category
- With pembro vs EXTREME:
  - Improved OS: 14.9 vs 10.7 months
  - Lower RR: 23% vs 36%
  - More durable responses with pembro
  - Better safety profile with pembro
- With pembro/chemo vs EXTREME:
  - Improved OS: 14.7 vs 11.0 months
  - Similar RR: 43% vs 38%
  - More durable responses with pembro/chemo
  - Comparable safety profiles





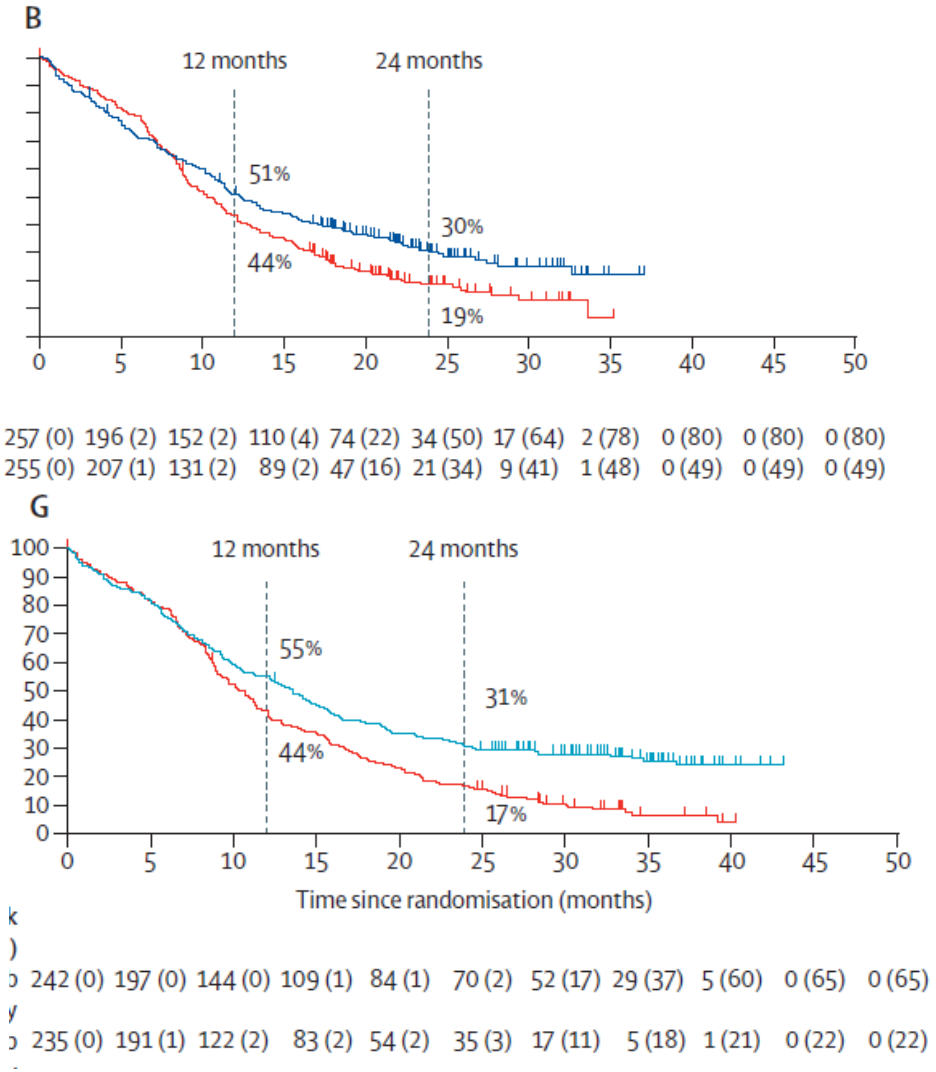
Burtness et al, 2019

Keynote 048: Overall Survival CPS ≥1

- 85% of patients in this category

- With pembro vs EXTREME:
  - Improved OS: 12.3 vs 10.3 months
  - Lower RR: 19% vs 35%
  - More durable responses with pembro
  - Better safety profile with pembro

- With pembro/chemo vs EXTREME:
  - Improved OS: 13.6 vs 10.4 months
  - Same RR: 36%
  - More durable responses with pembro/chemo
  - Comparable safety profiles



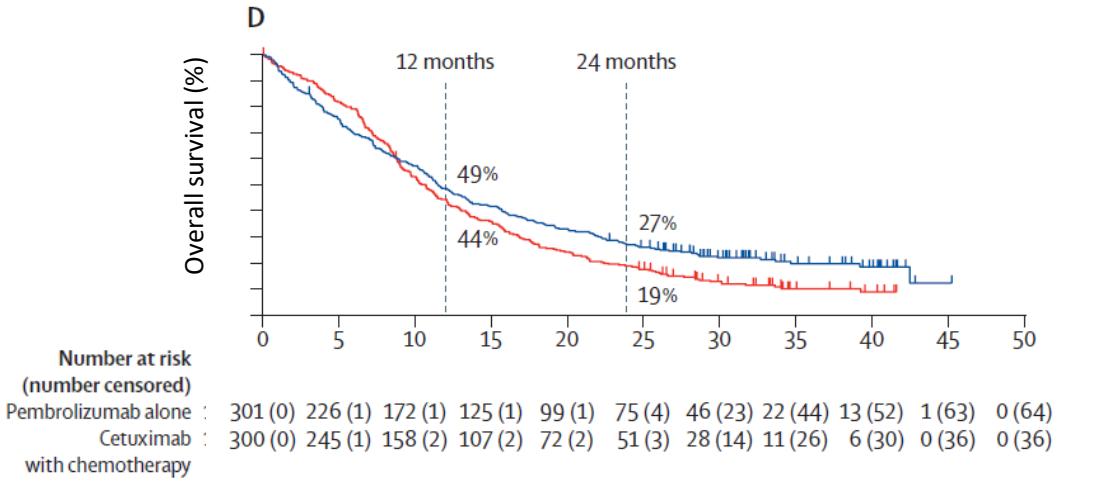
UC San Diego Health

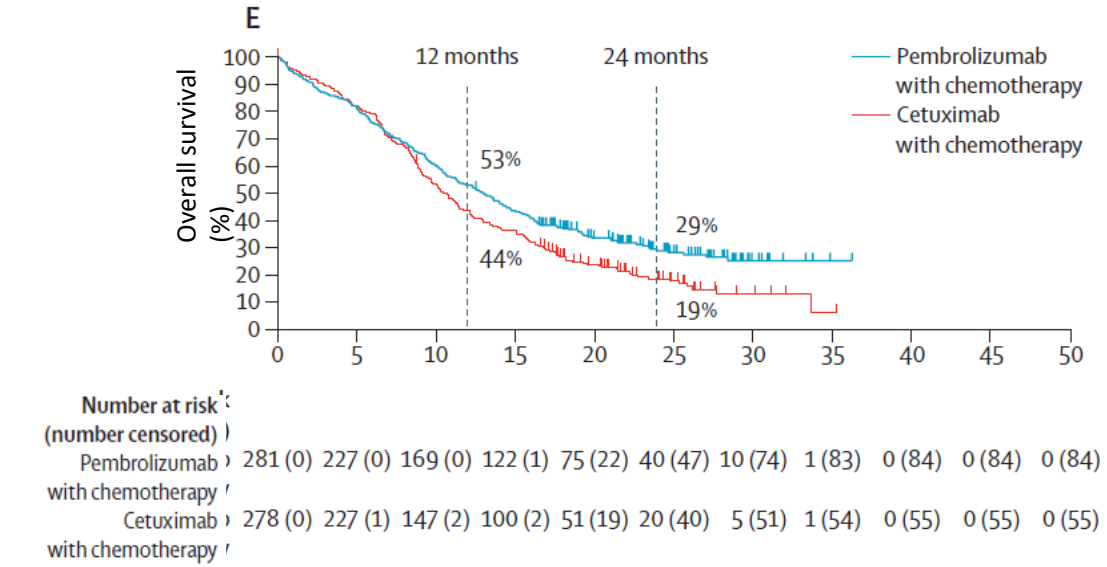
Burtness et al, 2019

Keynote 048: Overall Survival Total Population

- With pembro vs EXTREME:
  - Similar OS: 11.6 vs 10.7 months
  - Lower RR: 17% vs 36%

- With pembro/chemo vs EXTREME:
  - Improved OS: 13.0 vs 10.7 months
  - Same RR: 36%
  - More durable responses with pembro/chemo
  - Comparable safety profiles





Burtness et al, 2019

UC San Diego Health

Rationale for a Taxane Rather than 5-FU

- KEYNOTE-048 supporting platinum + anti–PD-1 as backbone
- E1395 phase 3 randomized cooperative group trial showing no statistically significant difference in response or survival with cisplatin/paclitaxel vs cisplatin/5-FU (Gibson et al, *JCO* 2005)
- SWOG phase 2 study showing activity/safety of carboplatin/docetaxel (Samlowski et al, *Cancer Invest* 2007)
- Phase 4 KEYNOTE-B10 trial (ESMO 2022, proffered paper)

Burtness et al, 2019; Gibson et al, 2005; Samlowski et al, 2007; Dizenis et al, 2022.

Keynote B10: Carboplatin/Paclitaxel/Pembrolizumab

Phase 4 Trial

Key Eligibility Criteria

- Previously untreated R/M HNSCC of oral cavity, oropharynx, larynx, hypopharynx
- PD-L1–agnostic
- ECOG 0-1
- Stage IVc or M1

Pembrolizumab
200 mg IV Q3W

Paclitaxel
(investigator's choice)
for 6 cycles

Carboplatin AUC 5 Q3W
for 6 cycles

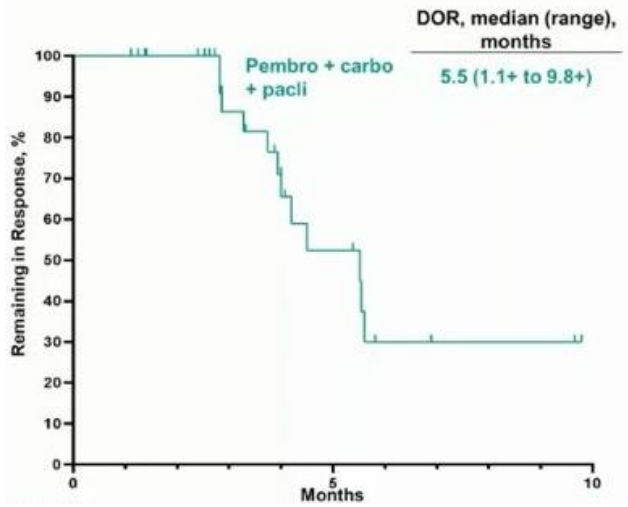
Primary end point

- Overall response rate

Secondary end points

- Duration of response (DOR)
- Progression-free survival
- Overall survival
- Safety

	n=82
ORR, % (95% CI)	42.7 (31.8-54.1)
Best objective response, n (%)	
CR	4 (4.9%)
PR	31 (37.8%)
SD	24 (29.3%)
PD	15 (18.3%)
No assessment	8 (9.8%)
TTR, median (range), months	1.5 (1.1-4.2)
DCR, % (95% CI)	58.5 (47.1-69.3)

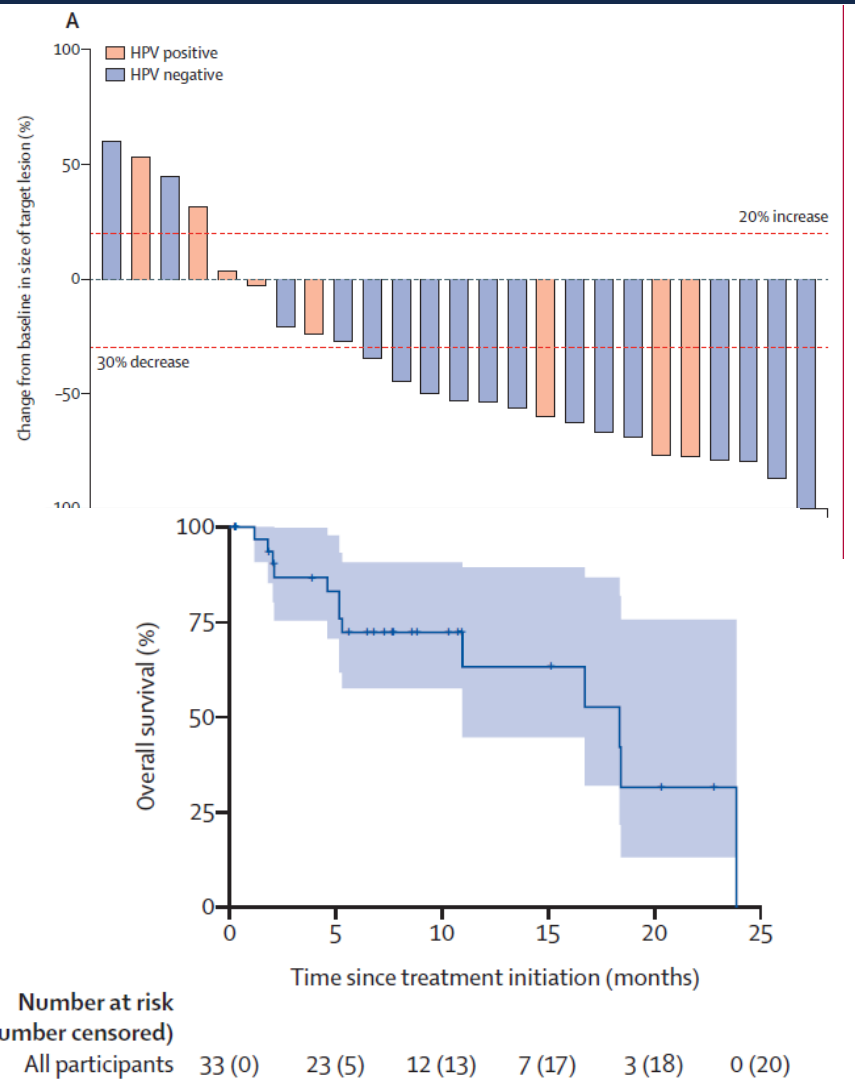


Haddad et al, JCO 2023

UC San Diego Health

Pembrolizumab and Cetuximab

- Phase 2 study
  - 33 pts with platinum refractory or platinum ineligible disease, immunotherapy naïve
- Results:
  - RR 45%
  - Median PFS 6.5 months
  - Median OS 18.4 months



UC San Diego Health

Sacco AG et al, Lancet Oncol, 2021

Nivolumab and Cetuximab

N=95

Key Eligibility Criteria

- SCC of oral cavity, oropharynx, paranasal sinuses, nasal cavity, larynx, hypopharynx
- HPV p16-positive unknown primary in cervical node
- Incurable R/M HNSCC

→

Nivolumab
240 mg Q2W

Cetuximab
500 mg/m^2 Q2W

Lead in cetuximab cycle followed by 24 Cycles

Primary end point

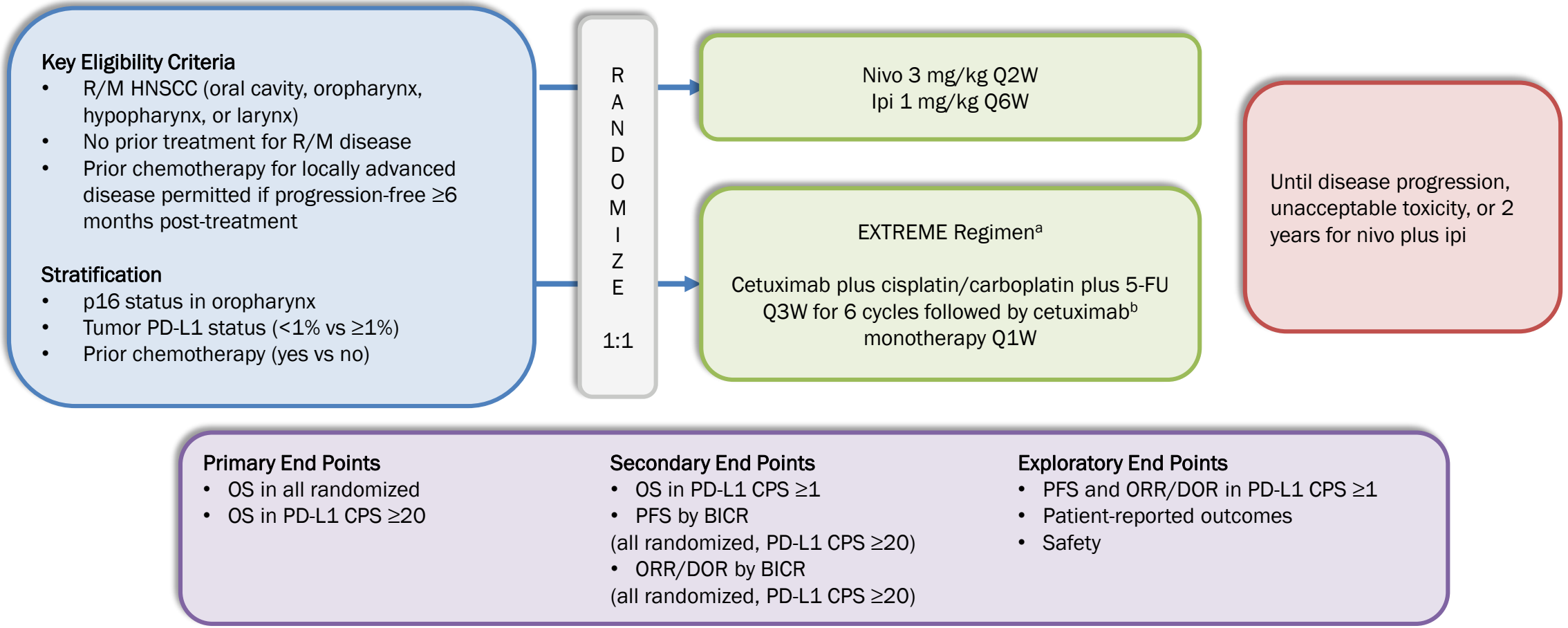
- Overall response rate

- Median OS in previously treated R/M HNSCC = 11.4 months, with 1-year OS 50%
- Median OS in first-line R/M HNSCC = 20.2 months, with 1-year OS 66%
- In the total population:
  - p16-negative patients had higher response rate but no survival advantage
  - Higher PD-L1 score was associated with higher response rate and longer OS
- p16-positive patients with lower median TTMV DNA counts had higher RR and longer OS

UC San Diego Health

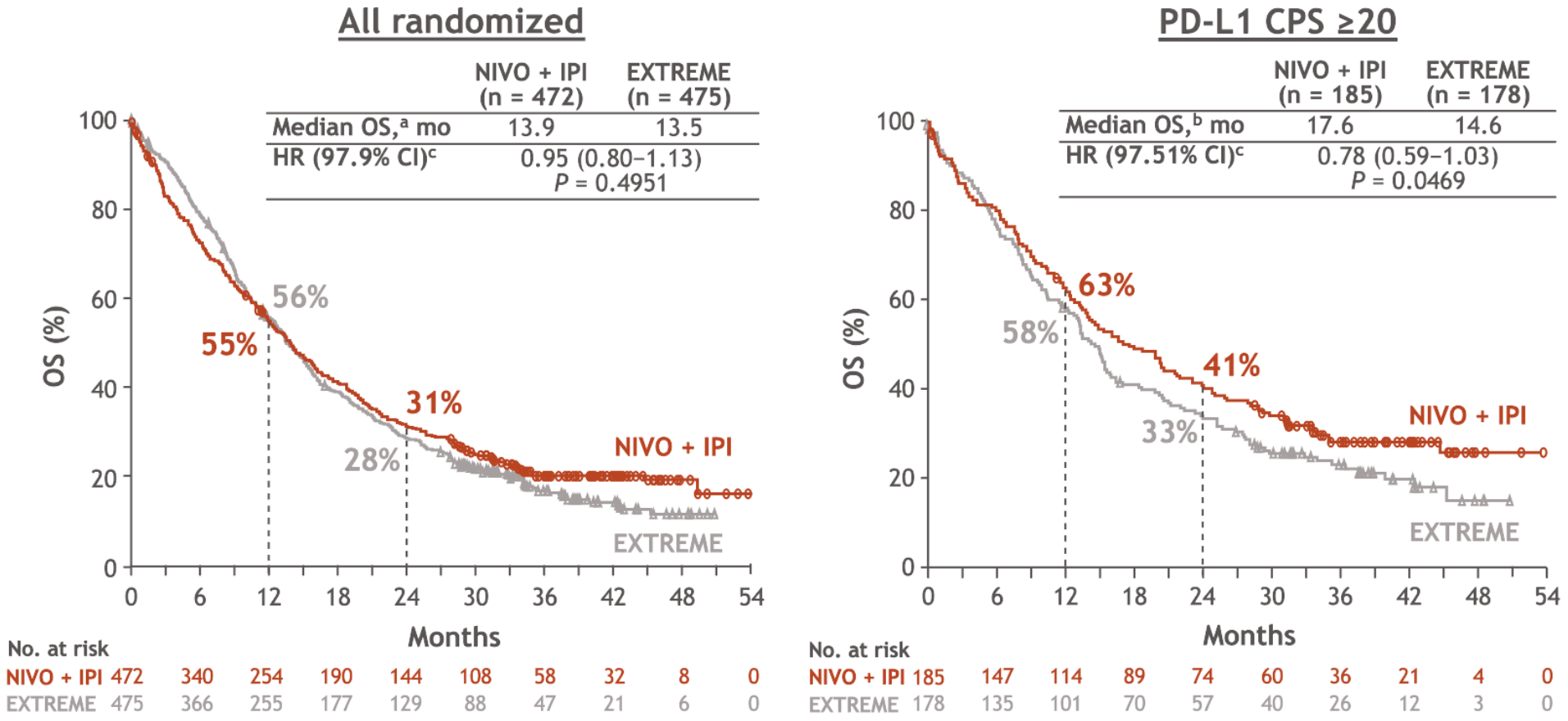
Chung C et al 2022

CheckMate 651: Ipi/Nivo vs EXTREME



Haddad et al, 2023.

CheckMate 651: Ipi/Nivo vs EXTREME



Minimum follow-up: 27.3 months

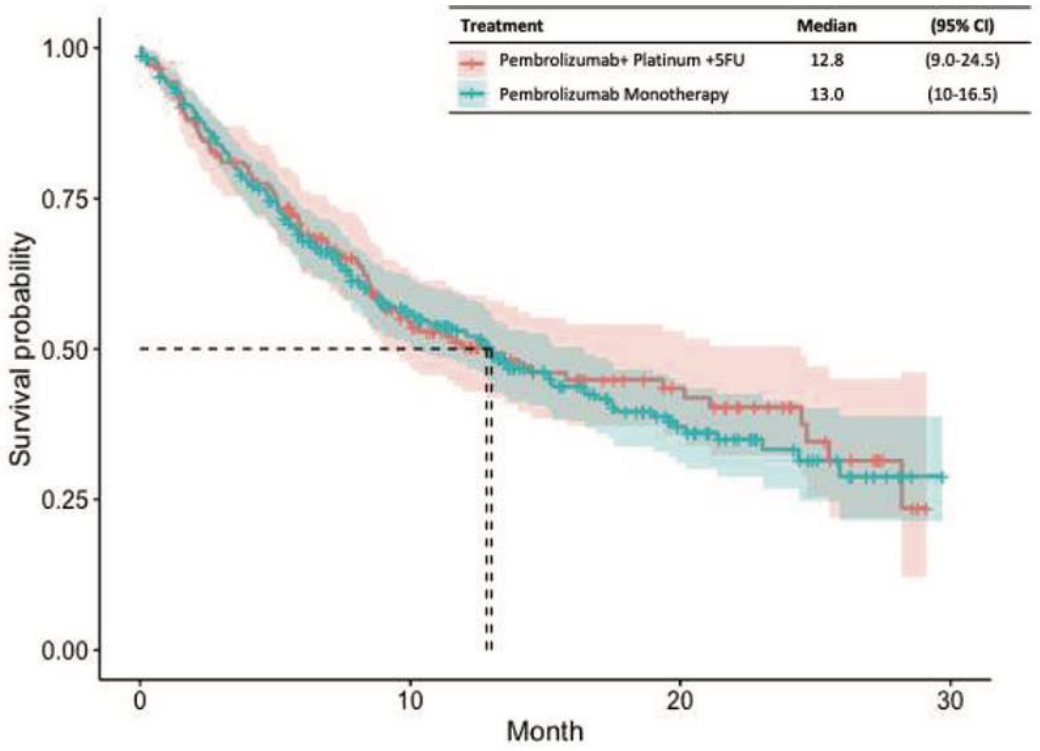
- [a]95% CI: 12.1-15.8 (nivo + ipi) and 12.6-15.2 (EXTREME).
- [b]95% CI: 13.8-22.0 (nivo + ipi) and 12.3-16.0 (EXTREME).
- [c]Confidence intervals are adjusted based on the final α levels for each primary end point.

UC San Diego Health

Haddad et al, 2023

Real World Evidence of 1st Line Pembrolizumab

- Retrospective cohort (Flatiron database in the US) from 2019-2021 of R/M HNSCC patients receiving first-line therapy
- Pembro monotherapy: n= 337
- Pembro + chemo: n=176
- Median rwOS consistent with KEYNOTE-048
- Higher survival rates at 24 months compared with KEYNOTE-048
- Age and ECOG were independent predictors
- In a secondary analysis, comparable treatment duration noted when trial-matched for ECOG PS 0-1



UC San Diego Health

rwOS = real-world OS; Black et al, 2022

Real World Evidence of 2nd Line Nivolumab

Study	Sample size	Response rate (%)	Median PFS in months (95% CI)	Median OS in months (95% CI)	1-year OS (%)
India (Platinum-refractory)[13]	20	15	2 (1.38-2.62)	5 (4.52-5.48)	-
FLATIRON (Post-platinum)[14]	368	-	-	8.1 (7.0-9.8)	40 (SE, 3%)
Japan (Platinum-refractory)[15]	130	16.2 (95% CI, 10.3–23.6)	2 (1.7-2.6)	9.1 (6.9-11.9)	39.5
Present study (Platinum-refractory)[12]	41	19.5	2.27 (1.51-4.14)	5.29 (3.78-11.67)	33.6 (95% CI, 19.5-48.4)
Indian (40 mg flat dose nivolumab, platinum-refractory)[16]	42	23.1	2.3 (0.6-4.02)	6.7 (3.4-8.8)	-

Despite fairly comparable outcomes to clinical trials (cannot make direct comparisons given nuances of the patient populations), global access to immunotherapy remains problematic

In India, only 0.25% of the patient population had access in 2016 compared with 7.3% in 2019

Rajappa et al, 2022

MCLA-158/Petosemtamab

Bispecific antibody targeting EGFR and LGR5

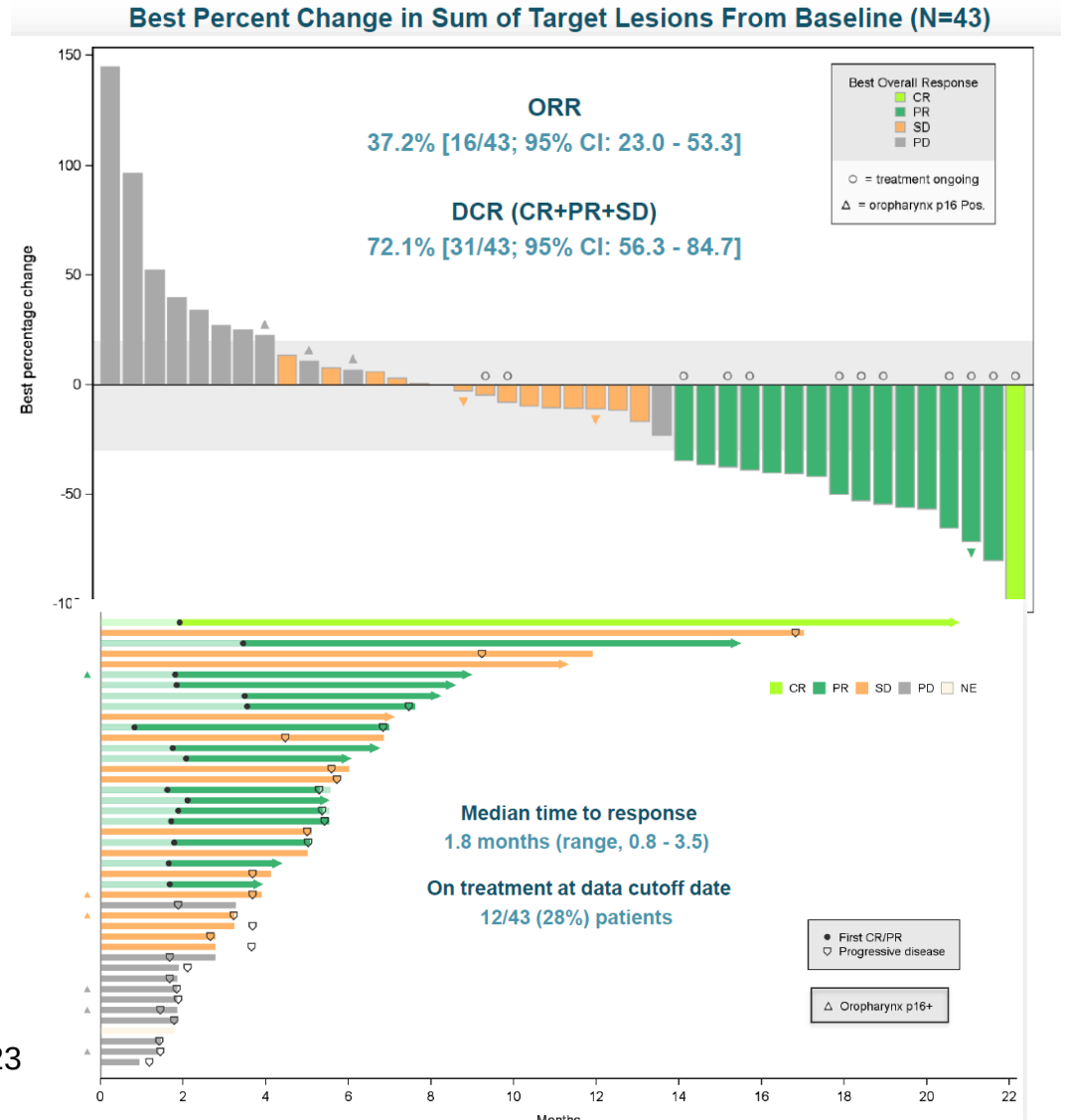
- LGR5 expressed in >50% of HNSCC
- Administered IV every 2 weeks

Results reported from H&N expansion cohort (n=37)

- Progression on or intolerance to platinum and CPI
- Median 2 prior lines systemic therapy
- **ORR 37%, median DOR 6 months, DCR 72%**

Development of petosemtemab ongoing (NCT03526835)

- First-line with pembro fully accrued
- Subsequent line monotherapy fully accrued



UC San Diego Health

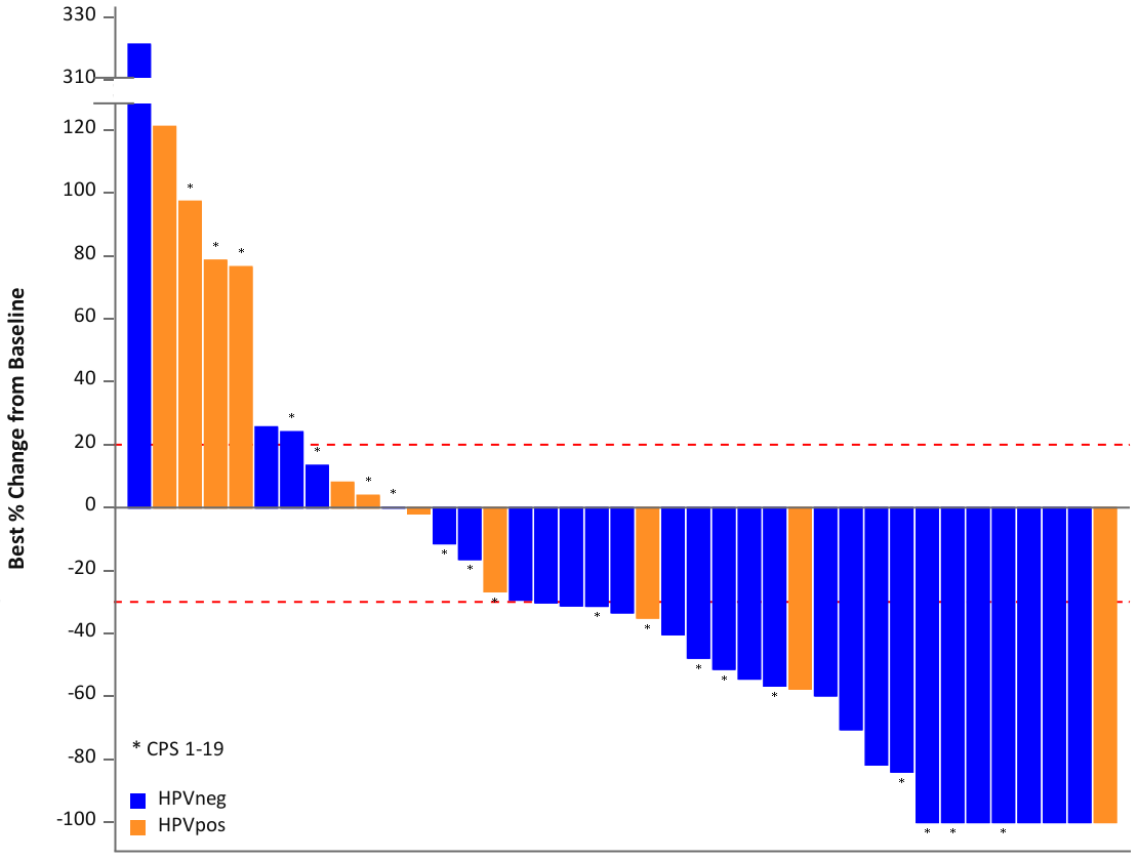
Cohen EE et al, AACR 2023

BCA-101 (Bifunctional EGFR/TGF-beta inhibitor)

Bispecific antibody targeting EGFR and TGF-beta
- Localizes TGF-beta inhibition to TME, preventing EGFR resistance
- Administered IV once weekly (also q2 weeks)

Updated results from H&N expansion cohort
- First-line setting for R/M disease, n=63
- **ORR 54%** total population, **64% in HPV-negative** patients
- Median PFS for HPV-negative not reached, 57% of pts w/PFS>6 mo
- Among HPV-negative patients, responses across all subsites and CPS 1-19 and ≥20

Development of BCA-101 ongoing (NCT04429542)
- Actively enrolling



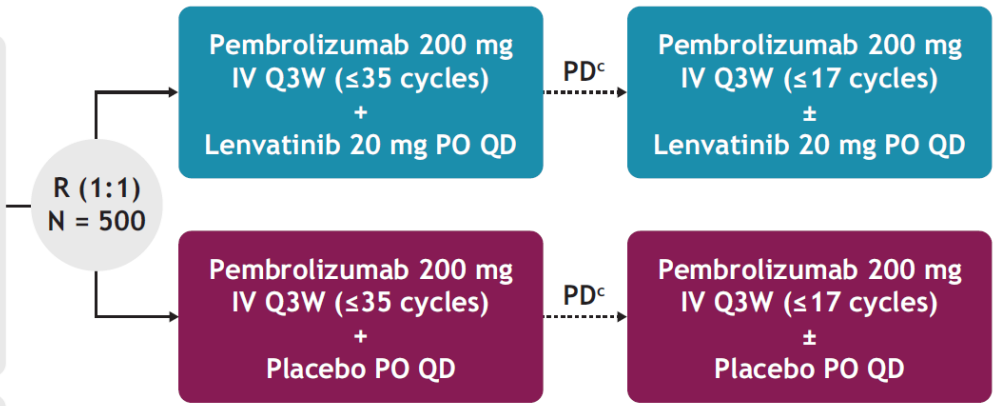
UC San Diego Health

Hanna G et al, MDHNCS 2024

Phase 3 LEAP-010 Trial (NCT04199104) NEGATIVE

Key Eligibility Criteria
- Adults with histologically confirmed R/M HNSCC with no curative treatment
- Measurable disease by RECIST v1.1
- No progression within 6 months of completion of prior CCRT
- PD-L1 CPS ≥1[a]
- Known p16 status in the oropharynx[b]
- ECOG PS 0 or 1

Stratification Factors
- PD-L1 expression (TPS <50% vs ≥50%[a])
- p16 status[b] (positive vs negative)
- ECOG PS (0 vs 1)



Primary End Points
- ORR (blinded independent central review [BICR] per RECIST v1.1)
- PFS (BICR per RECIST v1.1)
- Overall survival

Secondary End Points
- Duration of response (BICR per RECIST v1.1)
- Safety and tolerability

Despite significantly improved ORR and PFS in Lenvatinib group, NO overall survival benefit

- Second interim median OS analysis:
  - Lenvatinib + pembro: 15 months (95% CI 13.2-17.0); 1y and 2y OS rates 59% and 36%
  - Placebo + pembro: 17.9 months (95% CI 13.8-21.6); 1y and 2y OS rates 59% and 40%

UC San Diego Health

Licitra et al, MDHNCS 2024

Evorpacept Fast Track Designation: ASPEN-03 and -04

Evorpacept is a CD47 inhibitor (high affinity binding domain blocks the “don’t eat me” signal)

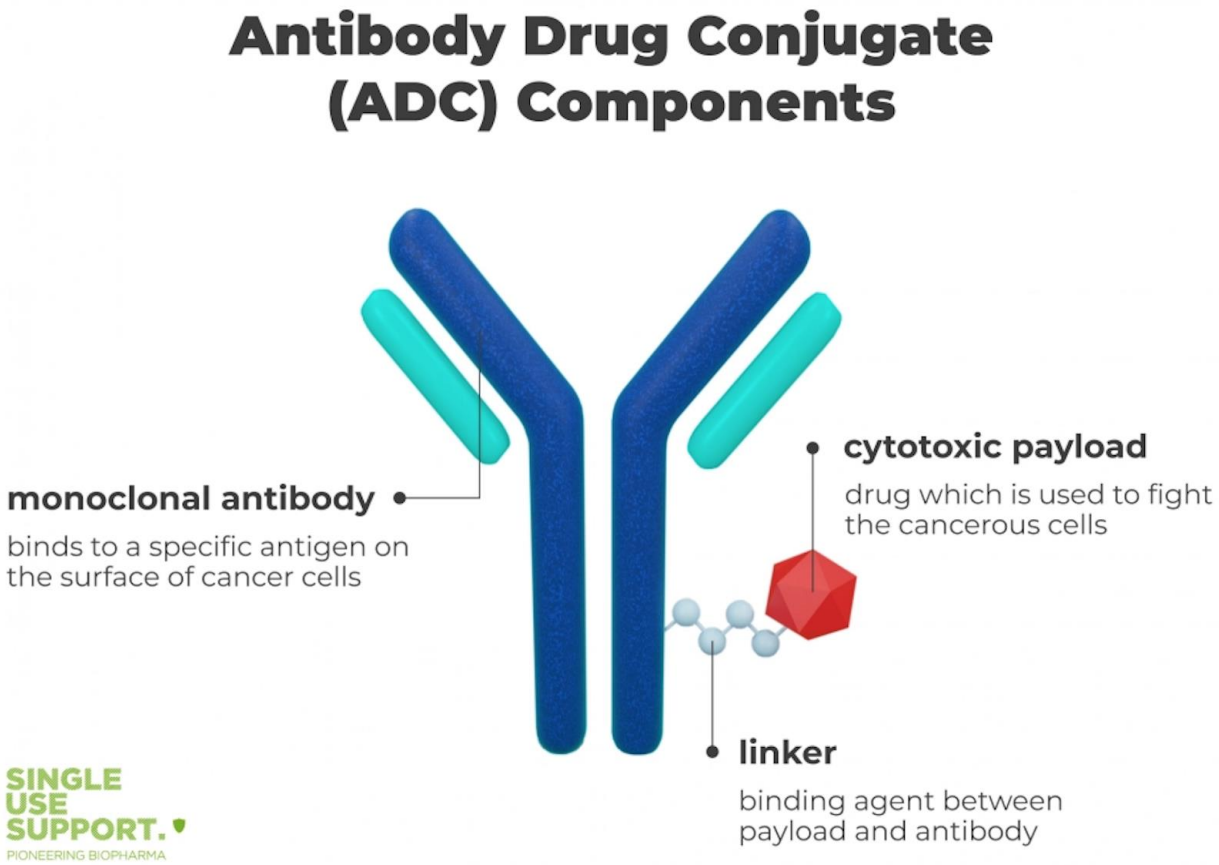
Two 1st-Line Trials in R/M HNSCC based on CPS

ASPEN-03 (NCT04675294): Phase 2 RCT of pembro +/- evorpacept for CPS ≥ 1

ASPEN-04 (NCT04675333): Phase 2 RCT of platinum/5-FU/pembro +/- evorpacept for any CPS

Both studies nearing accrual completion, open slots at UCSD

The ADCs Have Arrived



Multiple ADCs with FDA approvals for various tumor types

1. Gemtuzumab ozogamicin (Pfizer/Wyeth)
2. Brentuximab vedotin (Seattle Genetics, Millenium/Takeda)
3. Trastuzumab emtansine, KADCYLA® (Genentech, Roche)
4. Inotuzumab ozogamicin (Pfizer/Wyeth)
5. Polatuzumab vedotin (Genentech, Roche)
6. Enfortumab vedotin (Astellas/Seagan)
7. Trastuzumab deruxtecan (AstraZeneca/Daiichi Sankyo)
8. Sacituzumab govitecan (Immunomedics)
9. Belantamab mafodotin (GlaxoSmithKline)
10. Moxetumomab pasudotox (AstraZeneca)
11. Loncastuximab tesirine (ADC Therapeutics)
12. Tisotumab vedotin-tftv (Seagen Inc)

ADC for R/M HNSCC (Clinicaltrials.gov)

NCT Number	Study Title	Study Status	Interventions	Sponsor	Phases	Enrollment
NCT06007729	ARTEMIS-006: HS-20093 in Patients With Head and Neck Squamous Cell Carcinoma and Other Solid Tumors	RECRUITING	DRUG: HS-20093	Hansoh BioMedical R&D Company	PHASE2	170
NCT05751512	A Study to Evaluate MRG003 vs Cetuximab/Methotrexate in in the Treatment of Patients With RM-SCCHN	NOT_YET_RECRUITING	DRUG: MRG003|DRUG: Cetuximab injection|DRUG: Methotrexate Injection	Shanghai Miracogen Inc.	PHASE3	180
NCT05271604	A Phase 2 Open Label Study of BA3021 in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck	RECRUITING	BIOLOGICAL: Ozuriftamab Vedotin|BIOLOGICAL: PD-1 inhibitor	BioAtla, Inc.	PHASE2	80
NCT02565758	ABBV-085, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors	COMPLETED	DRUG: ABBV-085	AbbVie	PHASE1	85
NCT06147037	A Phase 1, Dose-escalation Study of [225Ac]-FPI-2068 in Adult Patients With Advanced Solid Tumours	RECRUITING	DRUG: FPI-2053|DRUG: [111In]-FPI-2107|DRUG: [225Ac]-FPI-2068	Fusion Pharmaceuticals Inc.	PHASE1	110
NCT06003231	A Study of Disitamab Vedotin in Previously Treated Solid Tumors That Express HER2	RECRUITING	DRUG: disitamab vedotin	Seagen Inc.	PHASE2	160
NCT01631552	Study of Sacituzumab Govitecan-hziy (IMMU-132) in Adults With Epithelial Cancer	COMPLETED	DRUG: Sacituzumab Govitecan-hziy (SG)	Gilead Sciences	PHASE1|PHASE2	515
NCT06238479	A Study of LY4101174 in Participants With Recurrent, Advanced or Metastatic Solid Tumors	RECRUITING	DRUG: LY4101174	Eli Lilly and Company	PHASE1	280
NCT04152499	Phase I-II, FIH, TROP2 ADC, Advanced Unresectable/Metastatic Solid Tumors, Refractory to Standard Therapies	RECRUITING	DRUG: SKB264	Klus Pharma Inc.	PHASE1|PHASE2	430
NCT02001623	Tisotumab Vedotin (HuMax¬Æ-TF-ADC) Safety Study in Patients With Solid Tumors	COMPLETED	DRUG: Tisotumab Vedotin (HuMax-TF-ADC)	Seagen Inc.	PHASE1|PHASE2	195
NCT06084481	Study to Assess Adverse Events and Change in Disease Activity in Adult Participants With Select Advanced Solid Tumor Indications Receiving Intravenous (IV) ABBV-400	RECRUITING	DRUG: ABBV-400	AbbVie	PHASE1	220

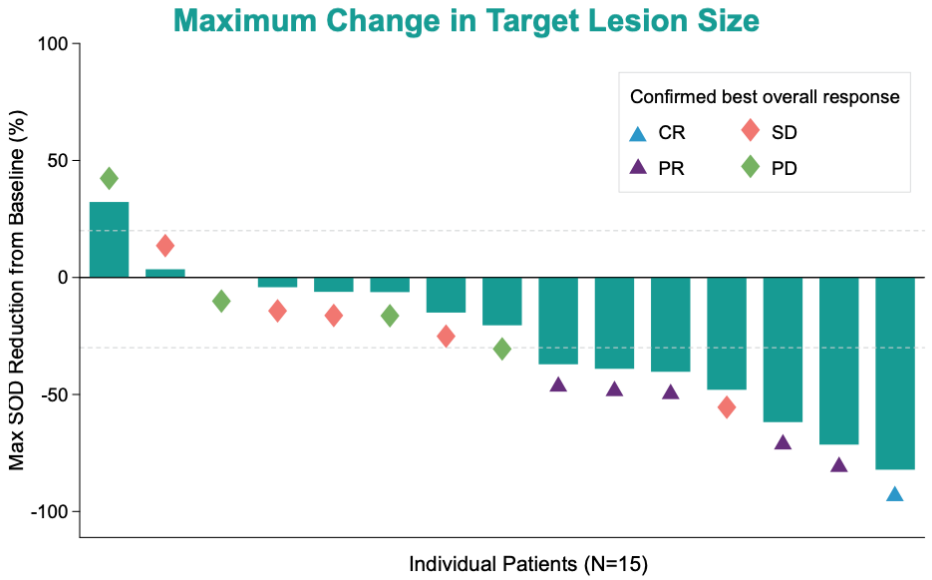
Tisotumab Vedotin in SCCHN: Interim Analysis From InnovaTV 207 (NCT03485209)

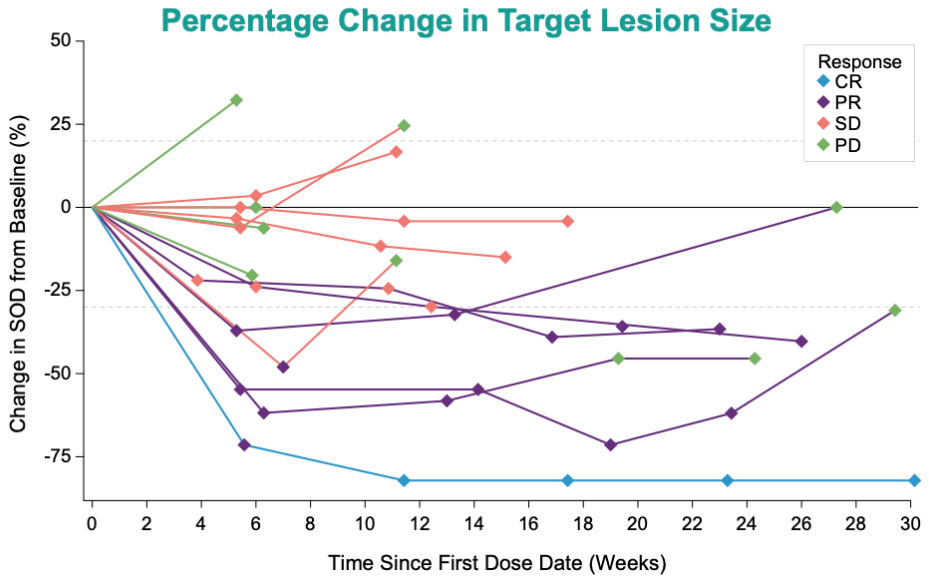
Tisotumab vedotin targets tissue factor, which is expressed in 63-100% of HNSCC

Part C interim analysis involving 15 pts with R/M HNSCC with median of 2 prior lines of therapy

Antitumor Activity in Patients with SCCHN

- Confirmed ORR is 40% (95% CI, 16.3-67.7), with 1 CR and 5 PRs
- DCR (proportion of patients with confirmed CR or PR, or SD) is 60% (95% CI, 32.3-83.7)
- Median PFS, as evaluated per investigator, is 4.4 months (95% CI, 1.4-6.8)





1st and 2nd line cohorts in combination with CPI opening soon at UCSD

Cirauqui et al, AACR 2023

Adding Tools to the Tool Box

- Consider clinical trial opportunities with any line of therapy
- Current 1st line SOC is pembrolizumab +/- cytotoxic chemotherapy
- Subsequent lines may include PD1 + EGFR inhibition, cytotoxic chemotherapy or single-agent PD1 inhibitors if not used in the prior line
- EGFR inhibition has been reinvigorated with emerging bifunctional antibodies being tested in first and subsequent lines (+LGR5, +TGF-beta)
- Multiple immune targets being studied, some key ones include LAG3, TIM, CD47, STING, CD226 axis (TIGIT, PVRIG)
- Antibody drug conjugates are an active area of investigation
- Please partner with us to offer your patients clinical trial opportunities

Thank You

Questions?

Patient referral?

Please contact me:

Assuntina Sacco MD

agsacco@health.ucsd.edu

Cell: 586-260-9288