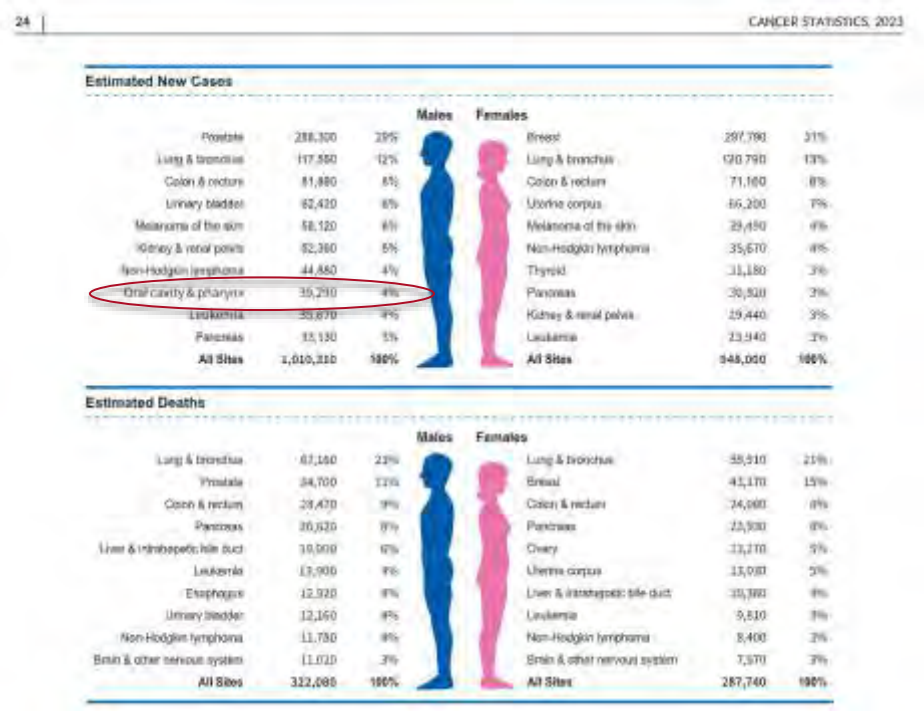
Systemic Therapy in Recurrent and Metastatic Head and Neck Cancer

Omar K. Abughanimeh, MBBS

Assistant professor of Medicine, Department of Internal Medicine/
Division of Hematology and Oncology

University of Nebraska Medical Center

Epidemiology



24 | CANCER STATISTICS, 2023

Estimated New Cases

	Males		Females		
Prostate	288,300	29%	Breast	297,790	31%
Lung & bronchus	117,550	12%	Lung & bronchus	120,790	13%
Colon & rectum	81,680	8%	Colon & rectum	71,160	8%
Urinary bladder	62,420	6%	Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%	Melanoma of the skin	29,490	4%
Kidney & renal pelvis	52,360	5%	Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,860	4%	Thyroid	31,180	3%
Oral cavity & pharynx	35,290	4%	Pancreas	30,520	3%
Leukemia	33,670	4%	Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%	Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**	**All Sites**	**948,000**	**100%**

Estimated Deaths

	Males		Females		
Lung & bronchus	67,160	23%	Lung & bronchus	55,910	21%
Prostate	34,700	12%	Breast	43,170	15%
Colon & rectum	28,470	9%	Colon & rectum	24,080	8%
Pancreas	26,620	8%	Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%	Ovary	13,270	5%
Leukemia	13,900	5%	Uterine corpus	13,030	5%
Esophagus	12,920	4%	Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%	Leukemia	9,610	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,010	3%	Brain & other nervous system	7,570	3%
All Sites	**322,080**	**100%**	**All Sites**	**287,740**	**100%**

- Treatable and curable but:
  - 10% of the cases presents as metastatic disease
  - Around 20-30% develop metastases during the course of the disease.
  - Lungs account for up to 70% to 85% of metastases

Cancer statistics 2023
Acta Otorhinolaryngol Ital. 2020 Apr;40(SUPPL. 1):S1-S86.

Treatment options in metastatic disease

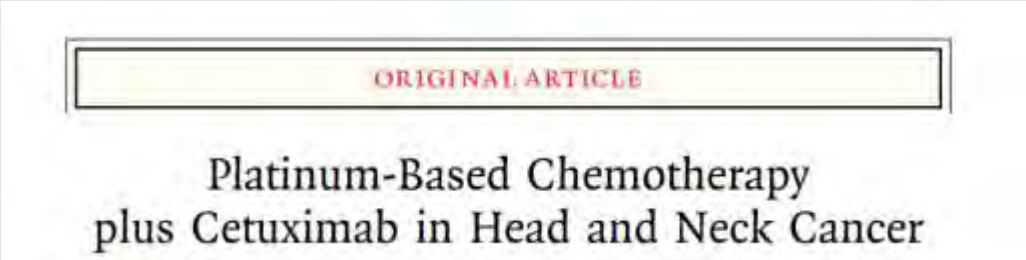
- Systemic therapy is the corner stone:
  - Chemotherapy
  - Immunotherapy
  - Molecular targeted therapy (mainly EGFR)

- Which one to pick?
  - Patient performance status and health
  - Pathologic markers (PD-L1)
  - Prior therapy
  - Extent of disease (local recurrence vs oligometastatic vs widespread disease)
  - Primary site of the tumor (non-nasopharyngeal vs nasopharyngeal vs salivary gland)

https://www.nccn.org

NON-NASOPHARYNGEAL CANCERS

EXTREME trial

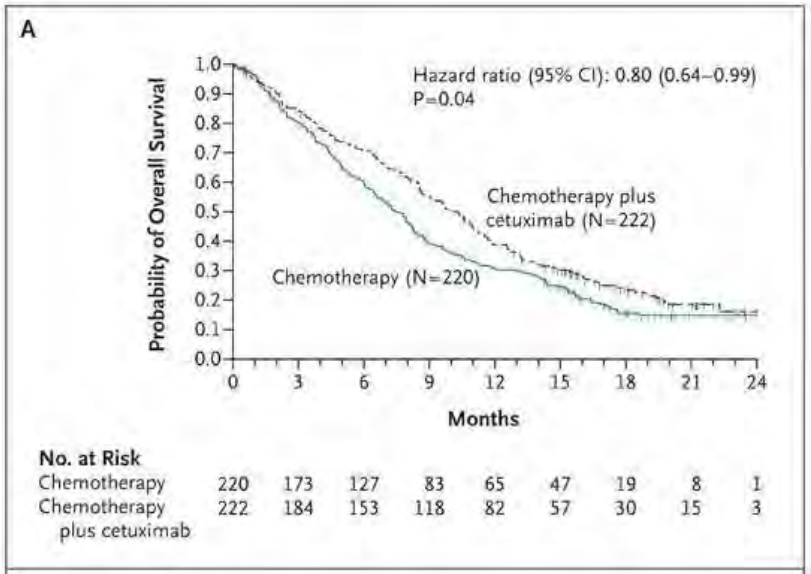

ORIGINAL ARTICLE

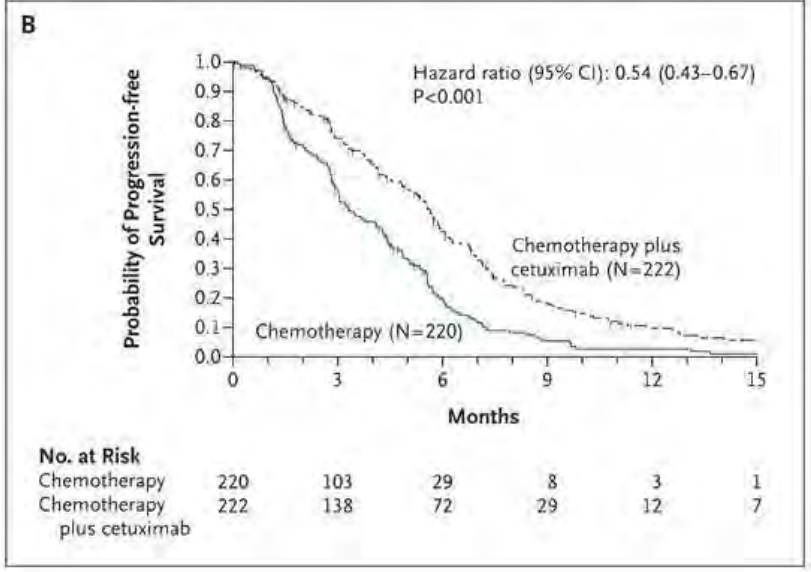
Platinum-Based Chemotherapy
plus Cetuximab in Head and Neck Cancer

- Phase III trial performed during 2004-2005, enrolled 442 patients which were randomized in 2 groups:
  - Platinum and 5FU for 6 cycles
  - Cetuximab with platinum and 5FU for 6 cycles, followed by cetuximab maintenance

N Engl J Med 2008; 359:1116-1127

EXTREME trial





- Adding cetuximab resulted in improving median overall survival from 7.4 months to 10.1 months (HR, 0.80; 95% CI, 0.64 to 0.99; P=0.04).
- The addition of cetuximab prolonged the median progression-free survival time from 3.3 to 5.6 months (HR 0.54; P<0.001)

N Engl J Med 2008; 359:1116-1127

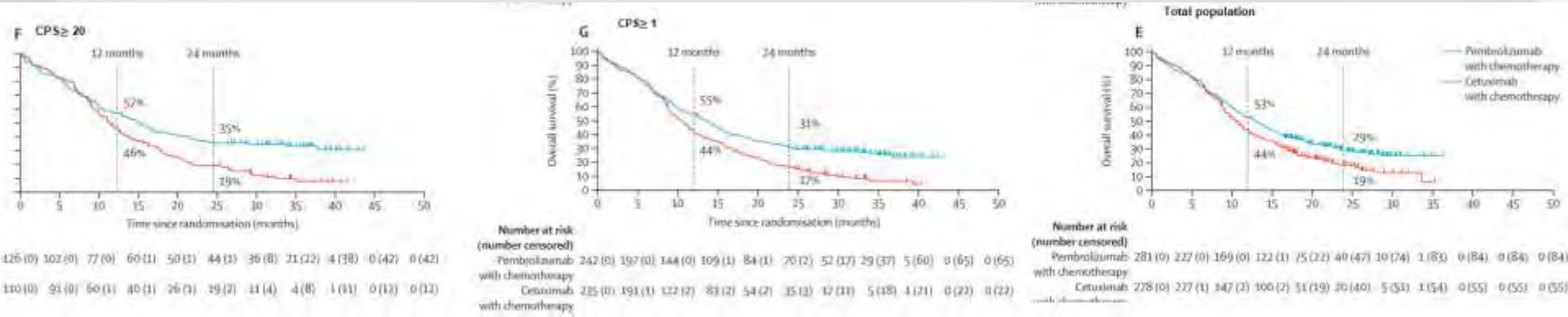
KEYNOTE-048

Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study

- Phase III study performed during 2015-2017, enrolled 882 patients which were randomized in 3 groups:
  - Pembrolizumab alone
  - Pembrolizumab with platinum and 5FU
  - Cetuximab with platinum and 5FU (EXTREME ARM)

Lancet. 2019;394(10212):1915-1928.

Pembrolizumab + chemo vs extreme

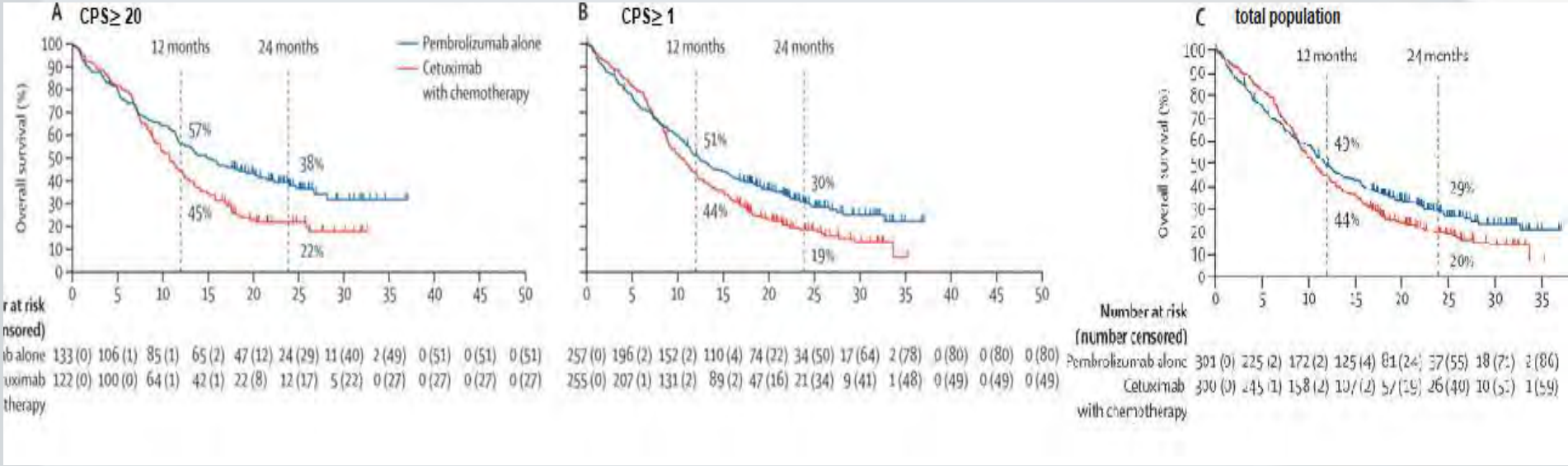


- Improved overall survival in all populations:
  - Total population→ 13m vs. 10.7m (HR, 0.77; 95% [CI, 0.63–0.93]; P = .003).
  - CPS ≥ 20→ 14·7m vs 11·0m (HR 0·60 ; 95% CI [0·45–0·82], p=0·0004)
  - CPS ≥ 1→ 13·6m vs 10·4m (HR 0·65; 95% CI [0·53–0·80], p<0·0001)

- It was also associated with a longer duration of response, and had a comparable safety profile versus cetuximab with chemotherapy.

Lancet 2019; 394: 1915–28

Pembrolizumab vs Extreme

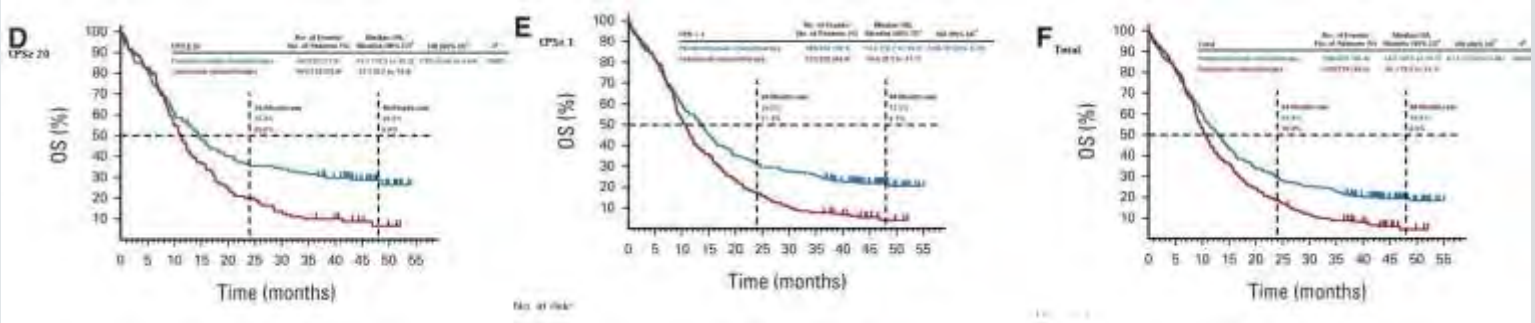


- Improved overall survival in CPS ≥20 and ≥1
  - Total population→ non inferior (11·6m vs 10·7m ,HR 0·85; 95% CI [0·71–1·03]
  - CPS ≥ 20→ 14·9 m vs 10·7m, HR 0·61 [95% CI 0·45–0·83], p=0·0007
  - CPS ≥ 1→ 12·3 m vs 10·3m , HR 0·78; 95% CI [0·64–0·96], p=0·0086

- It was associated with a substantially longer duration of response in all populations, and had a favorable safety profile compared with Extreme

Lancet 2019; 394: 1915–28

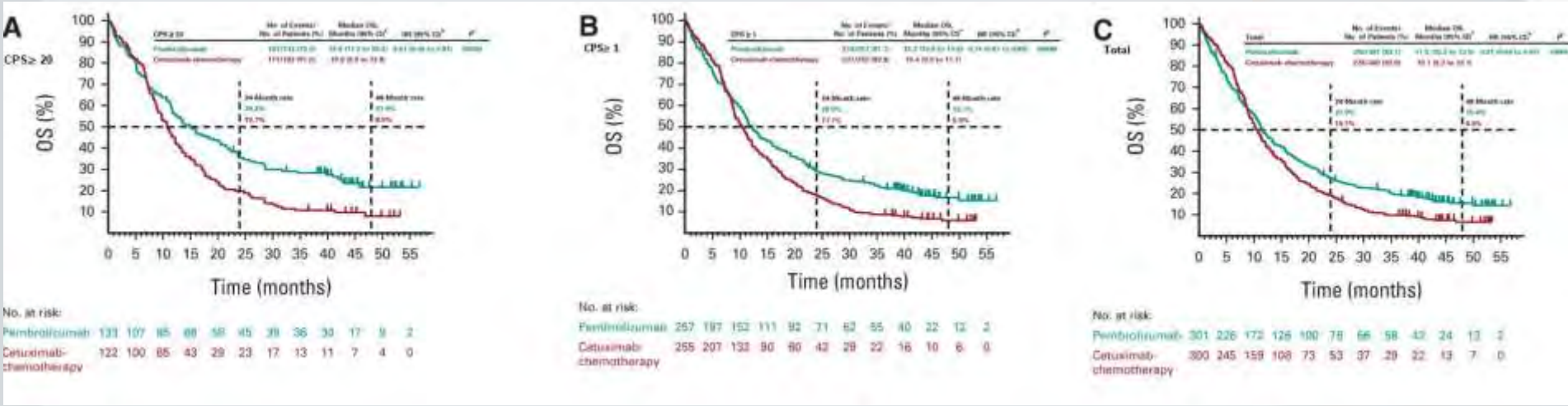
KEYNOTE-048, updated 2023



OS improved with pembrolizumab-chemotherapy in the PD-L1 CPS ≥ 20, CPS ≥ 1, and total populations.

Journal of Clinical Oncology 41, no. 4 (February 01, 2023) 790-802.

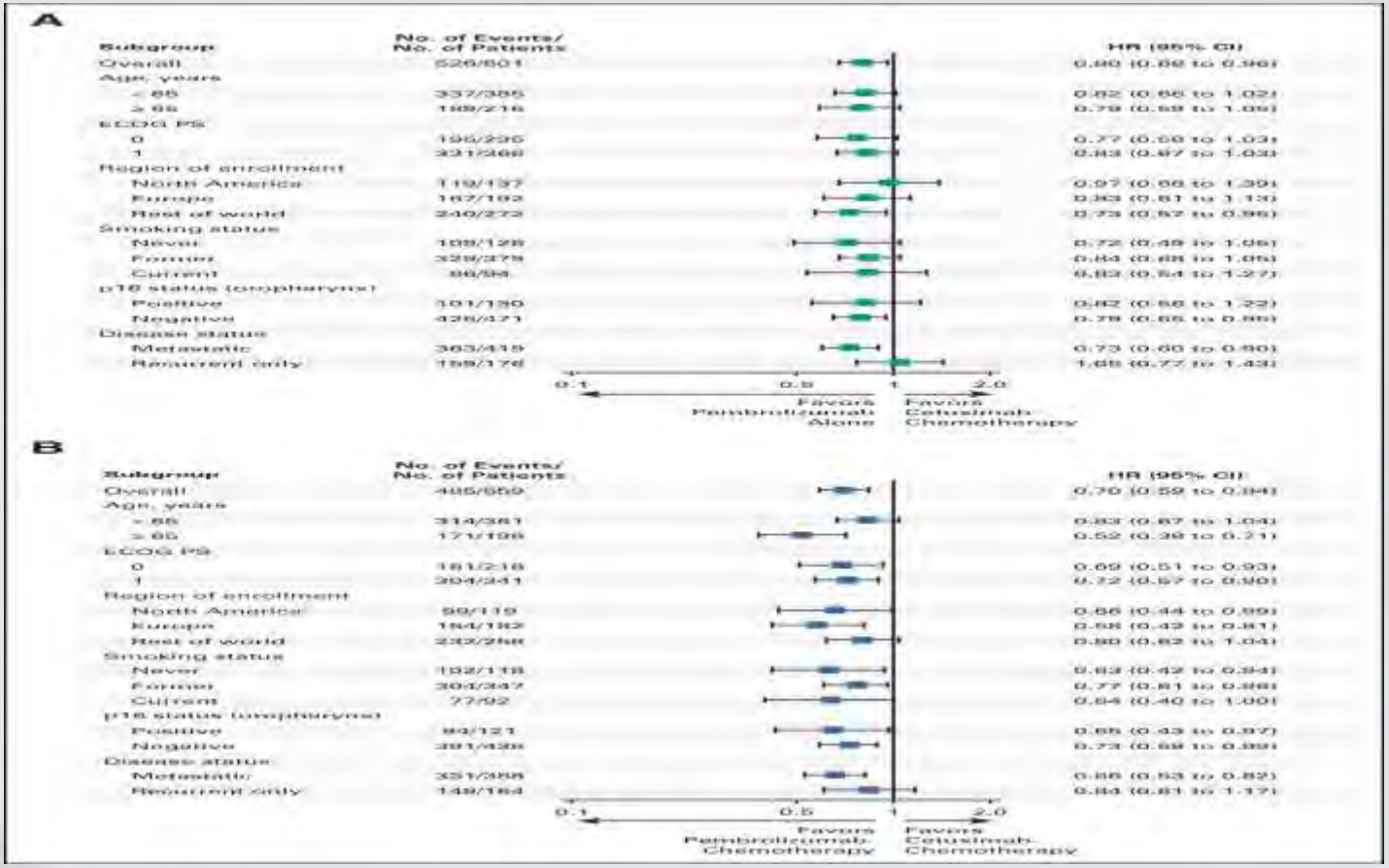
Pembrolizumab alone



- OS improved in the PD-L1 CPS ≥ 20 and CPS ≥ 1
  - It was noninferior in the total population

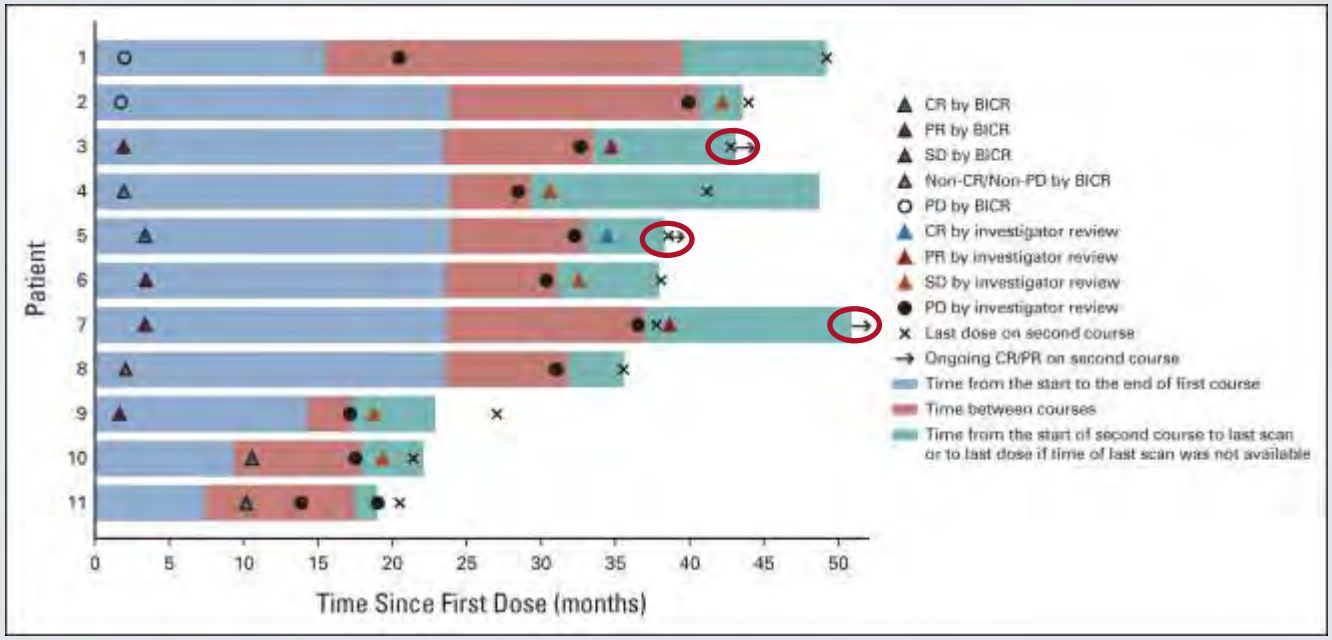
Journal of Clinical Oncology 41, no. 4 (February 01, 2023) 790-802.

KEYNOTE-048, updated 2023



Journal of Clinical Oncology 41, no. 4 (February 01, 2023) 790-802.

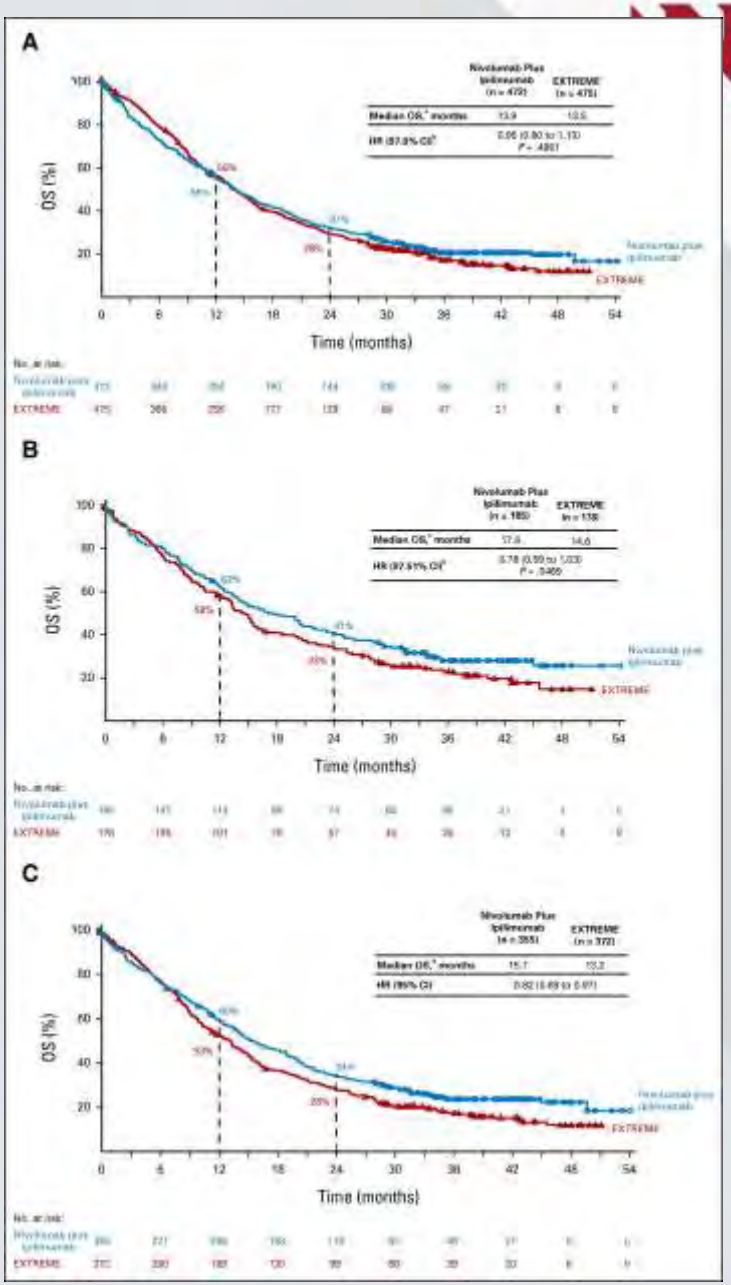
Retreatment



Journal of Clinical Oncology 41, no. 4 (February 01, 2023) 790-802.

Nivolumab Plus Ipilimumab Versus EXTREME Regimen as First-Line Treatment for Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck: The Final Results of CheckMate 651

- Evaluated first-line nivolumab plus ipilimumab versus EXTREME in recurrent/metastatic squamous cell carcinoma of the head and neck.
- There was no difference in OS in all groups including CPS ≥ 20.
- Favorable safety profile compared to chemotherapy.



Journal of Clinical Oncology 41, no. 12 (April 20, 2023) 2166-2180.

Second line therapy

- Depends on what was used in first line:
  - No prior IO or recurrence within 6 months of platinum-containing chemoradiation→ Pembrolizumab or nivolumab.
  - Prior IO in the first line→ Chemotherapy

First and second line treatments

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Head and Neck Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR NON-NASOPHARYNGEAL CANCERS
(Oral Cavity [including mucosal lip], Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, and Occult Primary)

- **The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).**

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

Preferred Regimens

First-Line[c]
- Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU (category 1)[c,30]
- Pembrolizumab (for tumors that express PD-L1 with CPS ≥1)[c,30] (category 1)

Subsequent-Line (if not previously used)
- Nivolumab[31] (if disease progression on or after platinum therapy) (category 1)
- Pembrolizumab[32-34] (if disease progression on or after platinum therapy) (category 1)

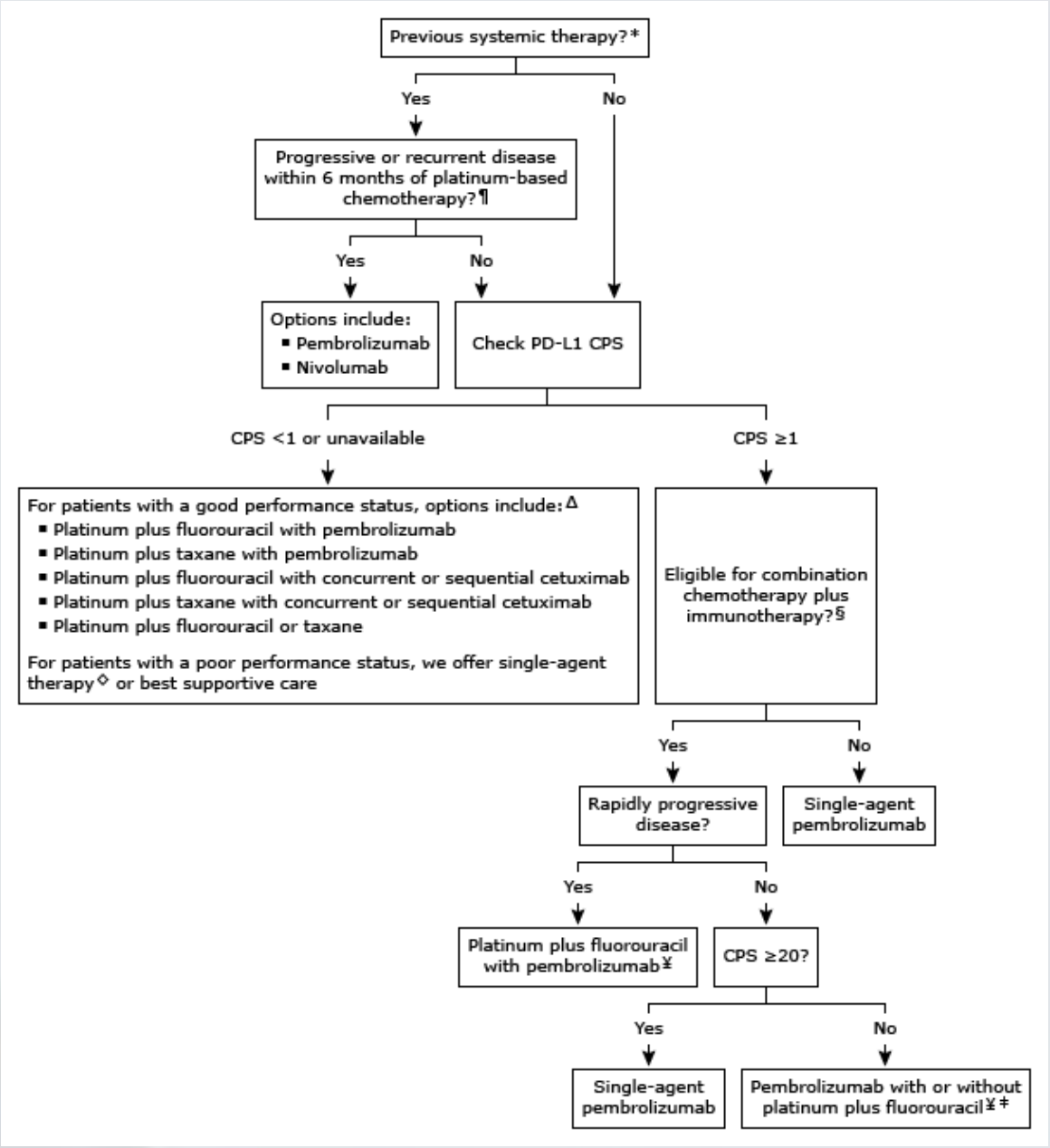
Other Recommended Regimens
(First- and Subsequent-Line)

Combination Regimens
- Cetuximab/platinum (cisplatin or carboplatin)/5-FU[35] (category 1)
- Cisplatin/cetuximab[36]
- Cisplatin or carboplatin/docetaxel[37] or paclitaxel[38]
- Cisplatin/5-FU[38,39]
- Cisplatin or carboplatin/docetaxel/cetuximab[40]
- Cisplatin or carboplatin/paclitaxel/cetuximab[41]
- Pembrolizumab/platinum (cisplatin or carboplatin)/docetaxel[30,37]
- Pembrolizumab/platinum (cisplatin or carboplatin)/paclitaxel (category 2B)[30,38]

Single Agents
- Cisplatin[36,42]
- Carboplatin[43]
- Paclitaxel[44]
- Docetaxel[45,46]
- 5-FU[42]
- Methotrexate[39,47]
- Cetuximab[48,49]
- Capecitabine[50]
- Afatinib[51] (subsequent-line only, if disease progression on or after platinum therapy) (category 2B)

Useful in Certain Circumstances
(First- and Subsequent-Line)
- Squamous cell carcinoma
  - Cetuximab/nivolumab[52]
  - Cetuximab/pembrolizumab (category 2B)[53]
- For select ethmoid/maxillary sinus cancers (ie, small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features):
  - Cisplatin/etoposide or carboplatin/etoposide[14]
  - Cyclophosphamide/doxorubicin/vincristine (category 2B)[15]
- Pembrolizumab (for MSI-H, dMMR, or TMB-H [≥10 mut/Mb] tumors)[54]
- Cisplatin/pemetrexed (for PS 0-1) (category 2B)[55]
- Gemcitabine/paclitaxel (category 2B)[56]

https://www.nccn.org



Uptodate.com

Oligometastatic disease

- Most defined it as the presence of one to five metastatic lesions and represents an intermediate stage between locoregional disease and widespread metastasis

- May benefit from aggressive approach with ablative treatment : Surgery or RT

The Expert Consensus Task Force on Pulmonary Metastasectomy

- They reviewed data from different studies for different cancers with pulmonary metastasis:

Table 5. Survival After Pulmonary Metastasectomy in Head and Neck Cancer

First Author [Reference]	Year	Patients (No.)	Median Survival (months)	Overall Survival (%)	
				3-Year	5-Year
Yotsukura [132]	2015	34	77	NA	NA
Miyazaki [134]	2013	24	NA	68	NA
Haro [130]	2010	21	NA	53.3	NA
Daiko [139]	2010	33	21	43	NA
Winter [133]	2008	67	19.4	NA	20.9
Shiono [19]	2009	114	26	NA	26.5
Chen [137]	2008	20	NA	NA	59.4
Nibu [140]	1997	32	NA	NA	32

NA = not available.

- For head and neck squamous cell carcinoma that underwent pulmonary metastetectomy the OS was 18% at 13 years

Ann Thorac Surg. 2019;107(2):631.

Experts recommendation

- Pulmonary metastatectomy in management of primary head and neck cancer can be considered in the context of disease free interval exceeding 12 months, ability to completely resection, and absence of LN metastases.
  - Strongly Agree: 42%
  - Agree: 42%
  - Neutral: 8%
  - Disagree: 8%
  - Strongly Disagree: 0%

Stereotactic Ablative Radiotherapy

SABR-COMET trial:

- Phase II randomized Trial

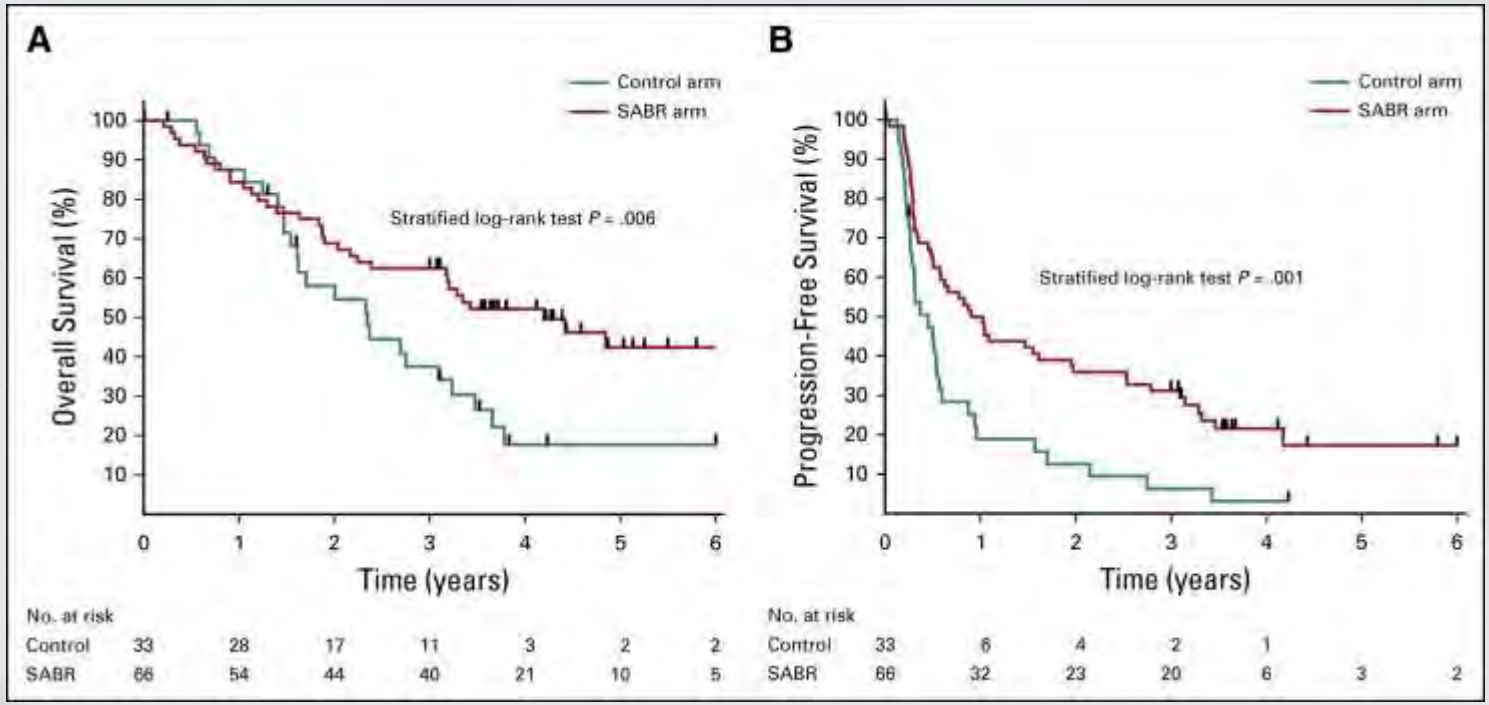
- It enrolled patients with a controlled primary malignancy and 1-5 metastatic lesions, all lesions should be amenable for SABR.

- Patients randomized in a 1:2 ratio between:
  - Palliative standard-of-care treatments
  - Standard-of-care treatment + SABR

Journal of Clinical Oncology 38, no. 25 (September 01, 2020) 2830-2838.

SABR-COMET

- 99 enrolled → MC cancers were breast, lung, colorectal and prostate.



- Using SABR has resulted in improvement of 5-year OS rate (42.3% vs 17.7%) *P* = .006.

Journal of Clinical Oncology 38, no. 25 (September 01, 2020) 2830-2838.

Primary site is important!!

- Different studies showed that the aggressive approach in oligometastatic disease has different outcomes according to primary site

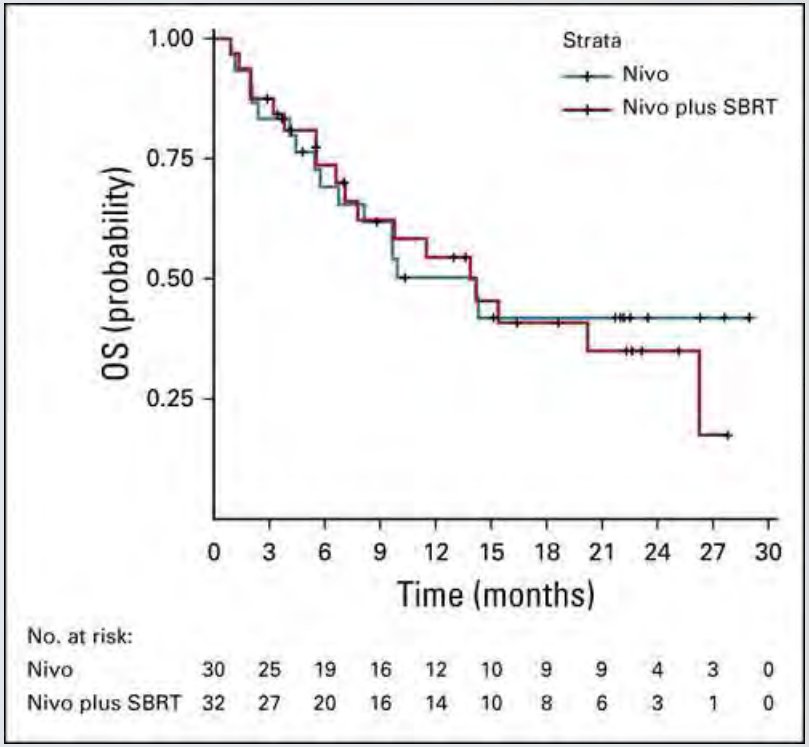
- Most studies showed that primary oral cavity SCC has worse OS compared to other head and neck SCC treated with aggressive approach

Ann Surg Oncol. 1999;6(6):572.
Ann Thorac Surg. 2009;88(3):856.
Interact Cardiovasc Thorac Surg. 2010;11(1):56.

Combining systemic therapy and radiation

- This concept was studied in a phase II trial which compared Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

- There was no statistically significant OS, ORR, PFS, or toxcicity.



Journal of Clinical Oncology 39, no. 1 (January 01, 2021) 30-37.

Targeted Therapy

TABLE 3. Novel Immunotherapies and Immunotherapy Combinations for HNSCC

Class	Drug or Molecule	Key Findings
Targeted Agents		
HRAS	Tipifarnib	Phase II study (30 pts.), ORR 55%; median PFS 5.4 months; OS 15.4 months
EGFR	Cetuximab/pembrolizumab	Phase II study, ORR 45%, median OS 18 months
	Cetuximab/avelumab	Phase II study, ORR 50%
	Afatinib/pembrolizumab	Phase II study, ORR 41%; median PFS and OS 4.1 and 8.4 months, respectively
VEGF	Lenvatinib/cetuximab	Phase I/Ib study (9/12 pts.); ORR 67%; PFS 3.6 months
	Lenvatinib/pembrolizumab	Phase I/Ib study (22 pts.); ORR 46%; median PFS 4.7 months
STAT3	Danvatirsen/durvalumab	Phase Ib/II study (38 pts.), ORR 26%
PI3K	Buparlisib vs. placebo + paclitaxel	Phase II study (158 pts.); ORR 31%; median OS and PFS 10.4 and 4.5 months, respectively, in buparlisib arm
Other Immune Checkpoint Inhibitor Combinations		
IDO	Epacadostat/pembrolizumab	Phase II study, ORR 34%, DCR 61%
	Epacadostat/nivolumab	Phase II study, ORR 23%, DCR 61%
Costimulatory agents	GSK609 (ICOS agonist)/pembrolizumab	Phase I study (34 pts.); ORR 26%, median PFS 5.6 months
B7-H3	Enoblituzumab/pembrolizumab	Phase I study (19 pts.); ORR 33%
NK2GA	Monalizumab/cetuximab	Phase II study; ORR 36% in immunotherapy naive, 17% in immunotherapy pretreated
	Monalizumab/cetuximab/durvalumab	Phase II study cohort 3; ORR 33%, median OS 15 months
T-cell exhaustion (LAG-3)	Eftilagimod alpha/pembrolizumab	Phase II study (36 pts.); ORR 36%
TLR-9	Intratumoral SD-101/pembrolizumab	Phase Ib/II study; ORR 22%, DCR 48%
TGF-β	Bintrafusp alfa	Phase I study (32 pts.); ORR 22% (75 had more than two prior lines of therapy), HPV+ group ORR 50%
Cellular Therapy		
TIL	LN-145/pembrolizumab	Phase II study (18 pts.); ORR 38.9%; DCR 88.9%
Vaccines		
Peptide/protein-based vaccines	ISA101b/nivolumab	Phase II study, ORR 33% in HPV+ oropharyngeal squamous cell carcinoma
Nucleic acid–based vaccines	MEDI0457/durvalumab	Phase II study, ORR 22.2%
Oncolytic Virus	Intratumoral talimogene laherparepvec /pembrolizumab	Phase Ib study; confirmed partial response 14%; median OS and PFS were 5.8 and 3 months, respectively

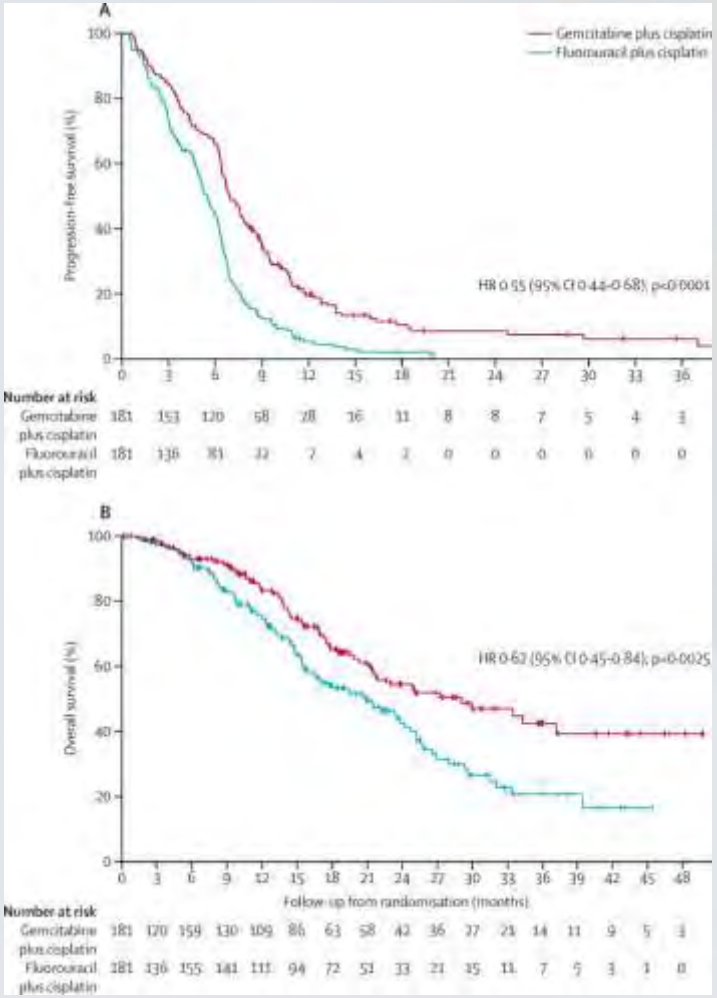
Abbreviations: HNSCC, head and neck squamous cell carcinoma; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; DCR, disease control rate; TIL, tumor-infiltrating lymphocyte.

American Society of Clinical Oncology Educational Book 42 (April 29, 2022) 527-540.

NASOPHARYNGEAL CANCERS

Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial

- Phase III, compared gemcitabine + cisplatin vs fluorouracil + cisplatin



Lancet 2016; 388: 1883–92

Role of Immunotherapy

- Currently under investigation pending OS data.
- Several phase III trials showed addition of CPI such as toripalimab, camrelizumab, or tislelizumab to gem/cis improved PFS.
- Still not in the NCCN panel recommendations

Lancet Oncol. 2021;22(8):1162. Epub 2021 Jun 23.

Nat Med. 2021;27(9):1536. Epub 2021 Aug 2.

J Clin Oncol. 2022;40; 36S

JUPITER-02

- Phase III, compared gem/cis+ toripalimab to gem/cis + placebo
- It showed significant improvement in median PFS 11.7m vs. 8.0m , HR = 0.52 [95% CI: 0.36-0.74] ,p = 0.0003).
- The improvement in PFS was observed across relevant subgroups, including all PD-L1 subgroups.
- OS is not mature

Journal of Clinical Oncology 39, no. 18_suppl

SYSTEMIC THERAPY FOR NASOPHARYNGEAL CANCERS[a]

• **The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).**

Induction[b]/Sequential Systemic Therapy

Preferred Regimens

- Gemcitabine/cisplatin (category 1 for EBV-associated disease, category 2A for non–EBV-associated disease)[1]
- Docetaxel/cisplatin/5-FU (dose-adjusted) (category 1 for EBV-associated disease, category 2A for non–EBV-associated disease)[2-4]

Other Recommended Regimens

- Cisplatin/5-FU[5]
- Docetaxel/cisplatin (category 2B)[6]
- Following induction, agents used with concurrent systemic therapy/RT typically include weekly cisplatin[7] or carboplatin[8]

Systemic Therapy/RT Followed by Adjuvant Chemotherapy

Preferred Regimens

- Cisplatin + RT followed by cisplatin/5-FU[7,9]

Other Recommended Regimens

- Cisplatin + RT followed by carboplatin/5-FU[10]
- Cisplatin + RT without adjuvant chemotherapy[c,11]
- Cisplatin + RT followed by capecitabine (for T4,N1–3 or any T,N2–3) (category 2B)[12]

Useful in Certain Circumstances

- If cisplatin ineligible or intolerant, carboplatin may be used as an alternative:
  - Carboplatin + RT followed by carboplatin/5-FU[8,13]

Reirradiation + Concurrent Systemic Therapy

- Platinum-based regimens (eg, cisplatin, or carboplatin only if cisplatin ineligible/intolerant)[14,15]

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

Preferred Regimens

First-Line[d]

- Cisplatin/gemcitabine (category 1)[16,17]

Other Recommended Regimens

First-Line[d]

- Combination Therapy
  - Cisplatin/5-FU[18,19]
  - Cisplatin or carboplatin/docetaxel[20] or paclitaxel[18]
  - Carboplatin/cetuximab[21]
  - Gemcitabine/carboplatin[1]
  - Cisplatin/gemcitabine + PD-1 inhibitor (eg, pembrolizumab or nivolumab)[22,23]
- Single Agents
  - Cisplatin[24,25]
  - Carboplatin[26]
  - Paclitaxel[27]
  - Docetaxel[28,29]
  - 5-FU[25]
  - Methotrexate[21,30]
  - Gemcitabine[31]
  - Capecitabine[32]

Subsequent-Line

- Immunotherapy
  - Nivolumab if previously treated, recurrent or metastatic non-keratinizing disease (category 2B)[33,34]
  - Pembrolizumab if previously treated, PD-L1–positive, recurrent or metastatic disease (category 2B)[35]

Useful in Certain Circumstances

Subsequent-Line

- Pembrolizumab (for tumor mutational burden-high [TMB-H] tumors [≥10 mut/Mb])[36]

[a] The recommendations are based on clinical trial data for those with EBV-associated nasopharynx cancer.

[b] The categories of evidence and consensus for induction therapy vary depending on site. (See disease-specific site in the Head and Neck Table of Contents)

[c] Use of cisplatin + RT without adjuvant chemotherapy is a category 2B recommendation for stage T3–4,N1–3,M0 or any T,N2–3,M0 disease; it is a category 2A recommendation for all other stages when indicated.

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

Conclusion

- Treatment of metastatic head and neck SCC is mainly done by systemic therapy.
- Treatment depends on the primary site.
  - Non-nasopharyngeal
  - Nasopharyngeal
  - Salivary gland tumors
- The role of immunotherapy is established in non-nasopharyngeal cancers , currently under investigation in nasopharyngeal cancers with promising results


University of
Nebraska
Medical Center