Updates to Treatment of Recurrent/ Metastatic Head and Neck Cancers

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March 19th, 2025

Outline

1. Introduction
2. Chemotherapy
3. Targeted therapy
4. Immunotherapy Advances
5. Novel Therapeutic Approaches
6. Future Directions and Conclusion

Introduction

- Head and neck cancer (HNC) is the seventh most common cancer worldwide.
- Recurrent/metastatic (R/M) HNC has a poor prognosis.
- Median survival in most series is 6 to 15 months depending on patient- and disease-related factors.
- Need for more effective therapeutic strategies

Current treatment

- Immune checkpoint inhibitors (ICIs)
- Conventional cytotoxic chemotherapy
- Molecularly targeted agents (eg, epidermal growth factor receptor [EGFR] inhibitors)

Good Prognostic Factor

- Ambulatory performance status (ECOG 0 or 1)
- Prior response to chemotherapy
- Longer time since completion of definitive therapy
- HPV associated oropharyngeal cancers
- Tumor PD-L1 expression status based on combined positive score (CPS), a predictive marker for response to anti-programmed cell death protein 1 (PD-1)

Poor Prognostic Factor

- Weight loss
- Poor performance status
- Prior radiation therapy
- Active smoking
- Significant comorbidity

Oligometastatic HNSCC

- Defined as 5 or fewer sites of metastasis
- The most extensive data come from small series of patients with oligometastatic disease in the lungs, in whom disease in the primary site and regional lymph nodes has been completely controlled
- Oral cavity SCC with oligometastatic disease had worst prognosis
- Surgical resection, SBRT

Platinum-based chemotherapy

- Cisplatin and Carboplatin
- Carboplatin: less neurotoxicity, nephrotoxicity, ototoxicity, N/V
- ->but may cause more myelosuppression
- Cisplatin/Carboplatin+ 5-FU+ cetuximab: no apparent difference in progression-free survival(PFS)

ORIGINAL ARTICLE

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

Authors: Jan B. Vermorken, M.D., Ph.D., Ricard Mesia, M.D., Fernando Rivera, M.D., Ph.D., Eva Remenar, M.D., Andrzej Kawecki, M.D., Ph.D., Sylvie Rottey, M.D., Ph.D., Jozsef Erfan, M.D., +10, and Ricardo Hitt, M.D., Ph.D. Author Info & Affiliations

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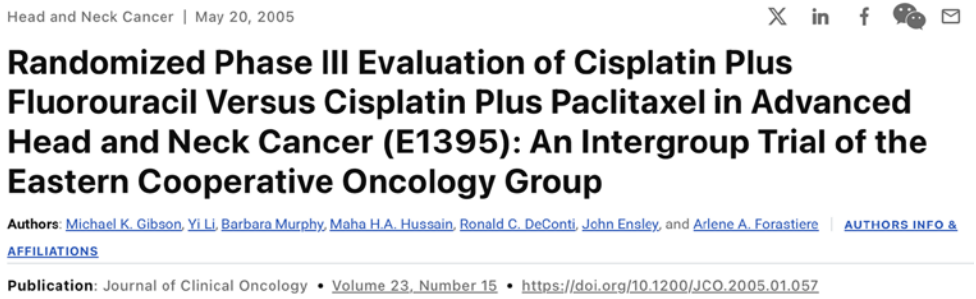
Combined chemotherapy

- Cisplatin/Carboplatin+ 5FU
- Cisplatin/Carboplatin+ paclitaxel/docetaxel
- Cisplatin+5-FU V.S Cisplatin + paclitaxel

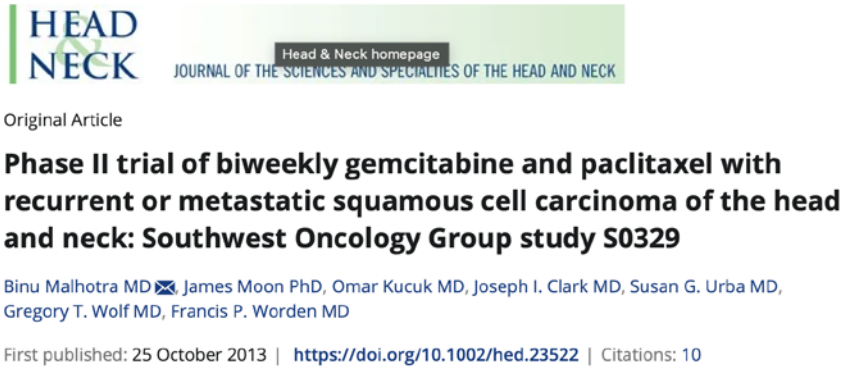
No significant difference in OS or objective response rate

Cisplatin+5-FU: more GI and Hematologic toxicities



Non-platinum-based chemotherapy

- Gemcitabine+ paclitaxel
- 28% objective response rate
- Median PFS: 4months
- Median OS: 8 months



HEAD & NECK

Head & Neck homepage

JOURNAL OF THE SCIENCES AND SPECIALTIES OF THE HEAD AND NECK

Original Article

Phase II trial of biweekly gemcitabine and paclitaxel with recurrent or metastatic squamous cell carcinoma of the head and neck: Southwest Oncology Group study S0329

Binu Malhotra MD, James Moon PhD, Omar Kucuk MD, Joseph I. Clark MD, Susan G. Urba MD, Gregory T. Wolf MD, Francis P. Worden MD

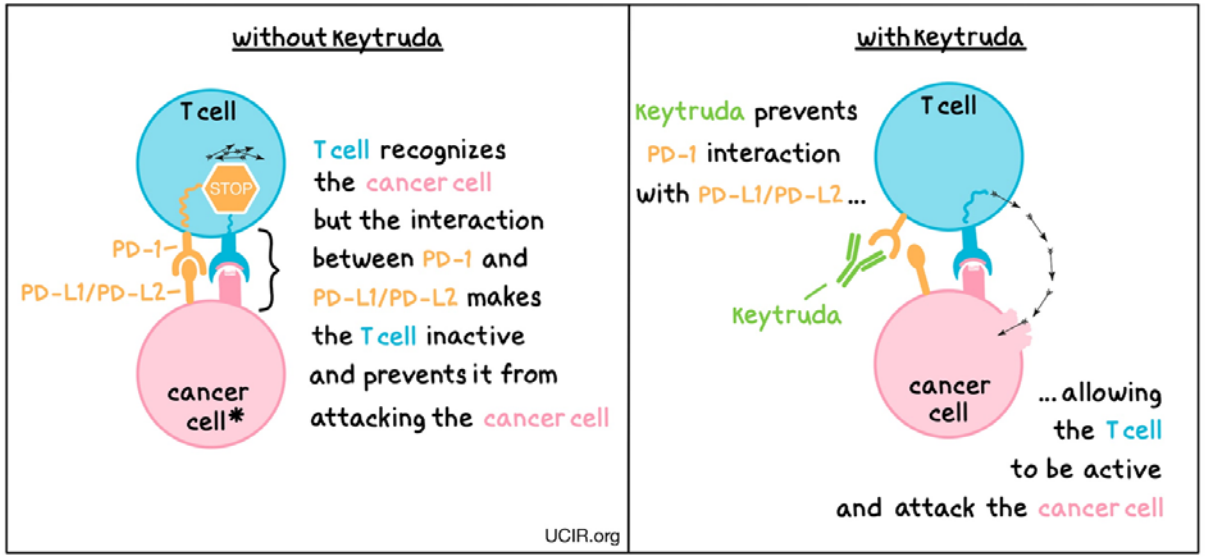
First published: 25 October 2013 | https://doi.org/10.1002/hed.23522 | Citations: 10

Targeted Therapy

- Cetuximab: Epidermal growth factor receptor [EGFR] inhibitors
- ~~Sorafenib(Nexavar)~~
- ~~Everolimus~~
- ~~Palbociclib~~
- ~~Panitumumab~~
- ~~Bevacizumab~~

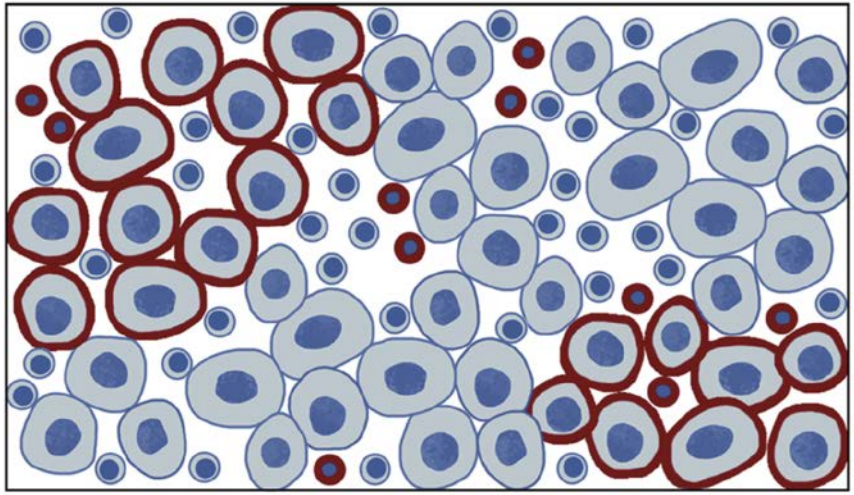
Immunotherapy

- Pembrolizumab(anti-PD-1): checkpoint inhibitor of programmed cell death protein 1



*other cells within the tumor mass or elsewhere can also display PD-L1/PD-L2 on their surface and make T cells inactive

Combined Positive Score



$$\text{TPS} = \frac{\text{No. PD-L1 positive tumor cells}}{\text{Total No. of viable tumor cells}} \times 100$$

$$\text{CPS} = \frac{\text{No. PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study

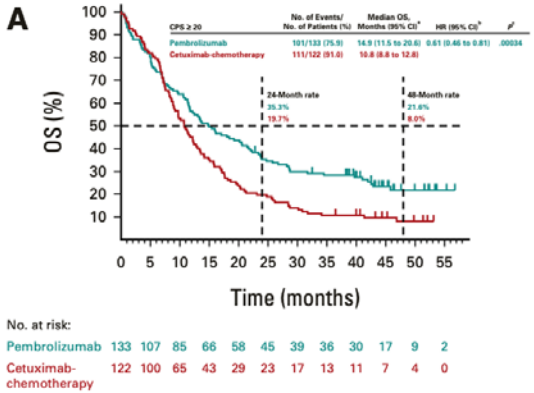
Kevin J. Harrington, PhD[1]; Barbara Burtness, MD[2]; Richard Greil, MD[3,4]; Denis Soulières, MD[5]; Makoto Tahara, MD[6]; Gilberto de Castro Jr, MD[7]; Amanda Psyrri, MD[8]; Irene Brana, MD[9]; Neus Basté, MD[9]; Prakash Neupane, MD[10]; Åse Bratland, PhD[11]; Thorsten Fuereder, MD[12]; Brett G.M. Hughes, MBBS[13]; Ricard Mesia, PhD[14]; Nuttapong Ngamphaiboon, MD[15]; Tamara Rordorf, MD[16]; Wan Zamaniah Wan Ishak, MD[17]; Jianxin Lin, MS[18]; Burak Gumuscu, MD[18]; Ramona F. Swaby, MD[18]; and Danny Rischin, MD[19,20]

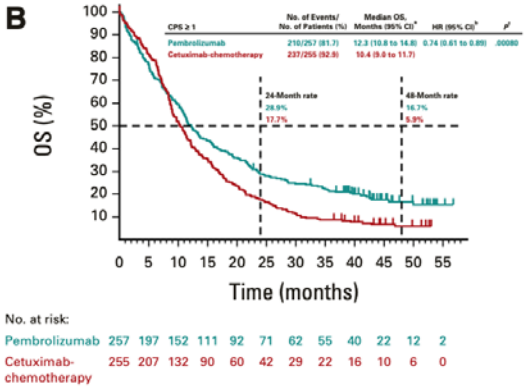
Study Design & Methodology

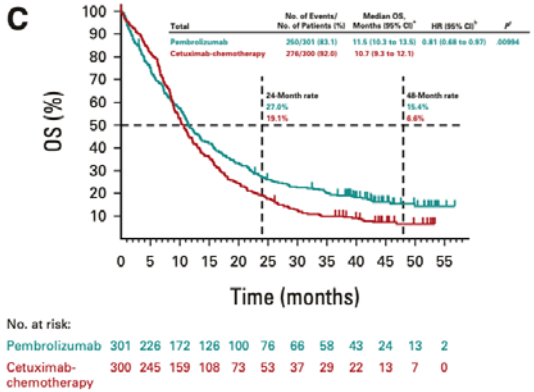
- Phase III, randomized, open-label trial
- 882 patients with R/M HNSCC(without previous ST)
- Three groups:

1. Pembrolizumab alone
2. Pembrolizumab + chemotherapy
3. Cetuximab + chemotherapy (control)

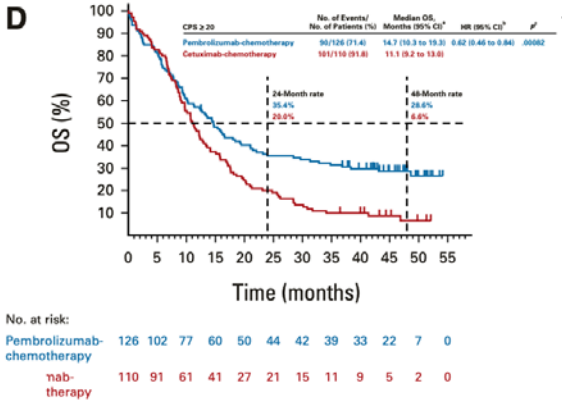
Key Results: Overall Survival

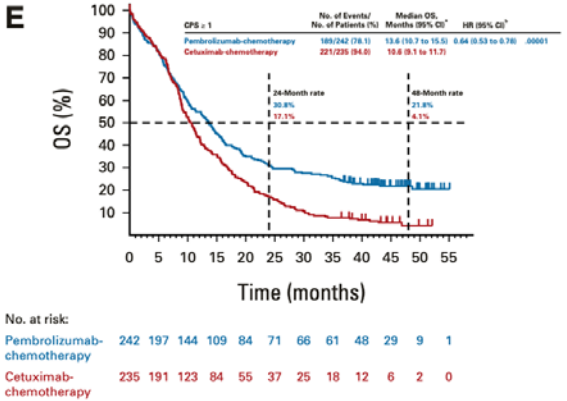


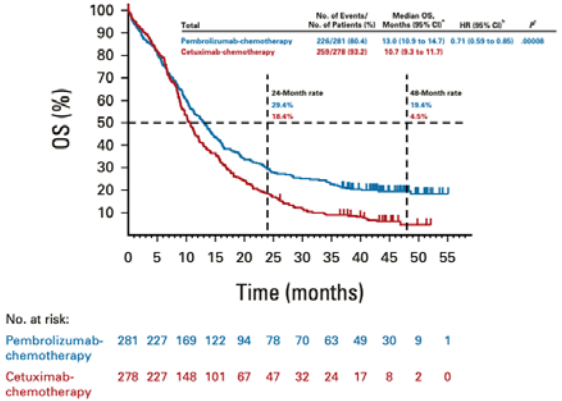




Key Results: Overall Survival







Key Results: Overall Survival

- Pembrolizumab alone improved OS:

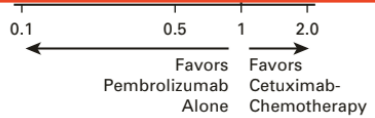
- CPS ≥ 20: HR 0.61
- CPS ≥ 1: HR 0.74
- Total population: HR 0.81

- Pembrolizumab + chemo improved OS in all groups

Overall Survival Subgroup analysis-I

A

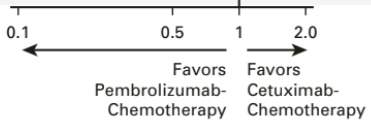
Subgroup	No. of Events/ No. of Patients	HR (95% CI)
Overall	526/601	0.80 (0.68 to 0.96)
Age, years		
< 65	337/385	0.82 (0.66 to 1.02)
≥ 65	189/216	0.79 (0.59 to 1.05)
ECOG PS		
0	195/235	0.77 (0.58 to 1.03)
1	331/366	0.83 (0.67 to 1.03)
Region of enrollment		
North America	119/137	0.97 (0.68 to 1.39)
Europe	167/192	0.83 (0.61 to 1.13)
Rest of world	240/272	0.73 (0.57 to 0.95)
Smoking status		
Never	109/126	0.72 (0.49 to 1.05)
Former	329/379	0.84 (0.68 to 1.05)
Current	86/94	0.83 (0.54 to 1.27)
p16 status (oropharynx)		
Positive	101/130	0.82 (0.56 to 1.22)
Negative	425/471	0.79 (0.65 to 0.95)
Disease status		
Metastatic	363/419	0.73 (0.60 to 0.90)
Recurrent only	159/176	1.05 (0.77 to 1.43)



Overall Survival Subgroup analysis-II

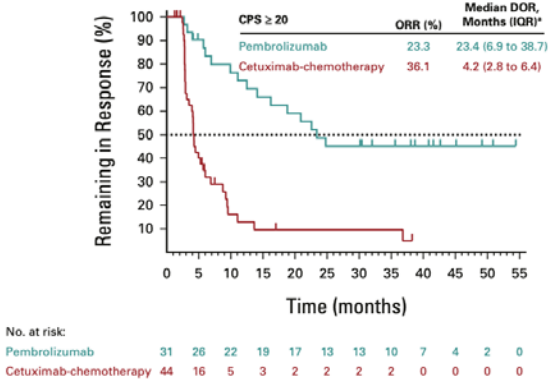
B

Subgroup	No. of Events/ No. of Patients	HR (95% CI)
Overall	485/559	0.70 (0.59 to 0.84)
Age, years		
< 65	314/361	0.83 (0.67 to 1.04)
≥ 65	171/198	0.52 (0.38 to 0.71)
ECOG PS		
0	181/218	0.69 (0.51 to 0.93)
1	304/341	0.72 (0.57 to 0.90)
Region of enrollment		
North America	99/119	0.66 (0.44 to 0.99)
Europe	154/182	0.58 (0.42 to 0.81)
Rest of world	232/258	0.80 (0.62 to 1.04)
Smoking status		
Never	102/118	0.63 (0.42 to 0.94)
Former	304/347	0.77 (0.61 to 0.96)
Current	77/92	0.64 (0.40 to 1.00)
p16 status (oropharynx)		
Positive	94/121	0.65 (0.43 to 0.97)
Negative	391/438	0.73 (0.59 to 0.89)
Disease status		
Metastatic	331/388	0.66 (0.53 to 0.82)
Recurrent only	149/164	0.84 (0.61 to 1.17)

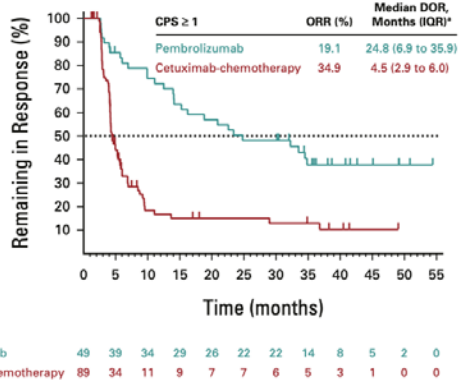


Duration of Response-I

A



B



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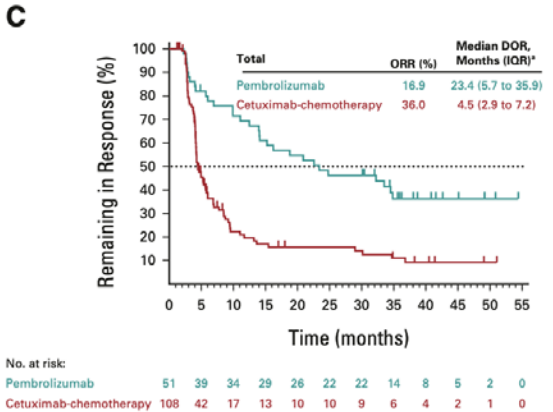
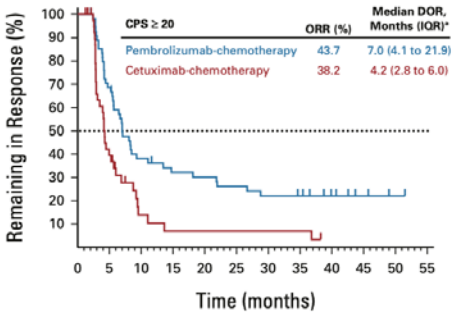


Duration of Response-II

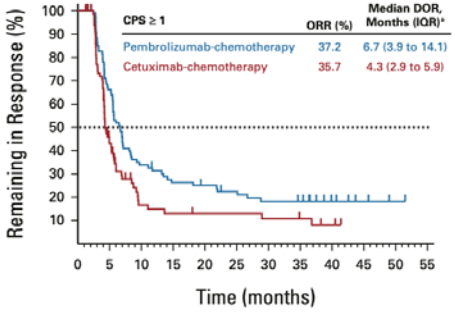
D



No. at risk:

Pembrolizumab-chemotherapy	55	37	20	16	15	13	11	10	6	3	1	0
Cetuximab-chemotherapy	42	15	4	2	2	2	2	2	0	0	0	0

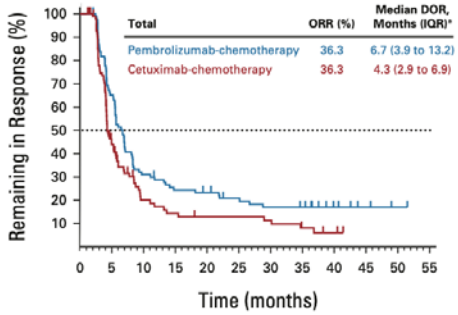
E



No. at risk:

Pembrolizumab-chemotherapy	90	56	28	21	19	16	13	12	6	3	1	0
Cetuximab-chemotherapy	84	31	9	7	6	6	5	4	2	0	0	0

F



No. at risk:

Pembrolizumab-chemotherapy	102	62	29	22	20	16	13	12	6	3	1	0
Cetuximab-chemotherapy	101	38	14	10	8	8	7	4	2	0	0	0

Adverse Effect

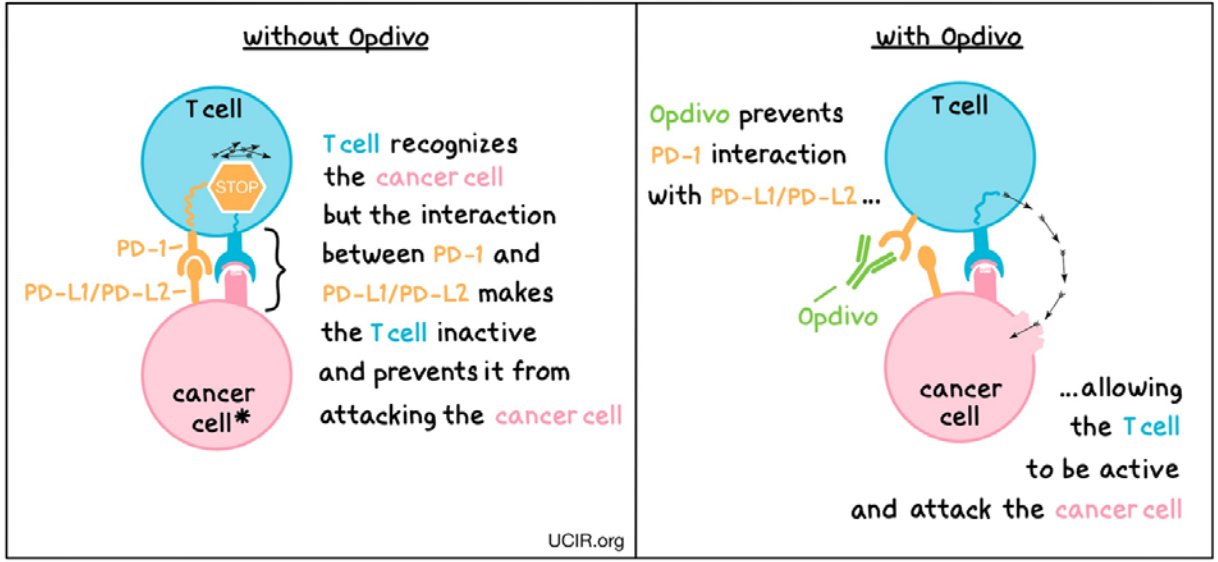
- Any-grade treatment-related AEs occurred
- ✓ pembrolizumab-alone : 58.3%(n=175)
- ✓ pembrolizumab-chemotherapy: 95.7% (n=264)
- ✓ cetuximab-chemotherapy: 96.9% (n=278) (Data Supplement).
- > Grade 3 treatment-related AEs reported in 17.0% (n=51), 71.7% (n=198), and 69.3%, (n=199) of patients

Conclusion

- KEYNOTE-048 confirms pembrolizumab as a superior first-line therapy for R/M HNSCC.
    - Improved OS and PFS
    - Better response durability
    - Safe and effective

Immunotherapy

- Nivolumab(anti-PD-1): checkpoint inhibitor of programmed cell death protein 1



*other cells within the tumor mass or elsewhere can also display PD-L1/PD-L2 on their surface and make T cells inactive

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L. Gillison

Checkmate-141

- 361 patients with platinum-refractory, recurrent or metastatic disease were randomly assigned to either nivolumab (3 mg/kg every two weeks) or a single-agent investigator's choice of therapy (methotrexate, docetaxel, or cetuximab)

Result

- OS for the entire study population was longer in patients treated with nivolumab (median 7.7 versus 5.1 months, one-year survival rate 34 versus 19.7 percent, HR 0.71, 95% CI 0.55-0.9)
- OS was increased with nivolumab in patients with PD-L1 expression ≥1 percent (8.7 versus 4.6 months, HR 0.55, 95% CI 0.36-0.83).

Selection of therapy

- Previously untreated patients
- ❖ Rapidly progressive disease: pembrolizumab+ platinum+ 5-FU/taxane
- ❖ Without rapidly progressive disease:

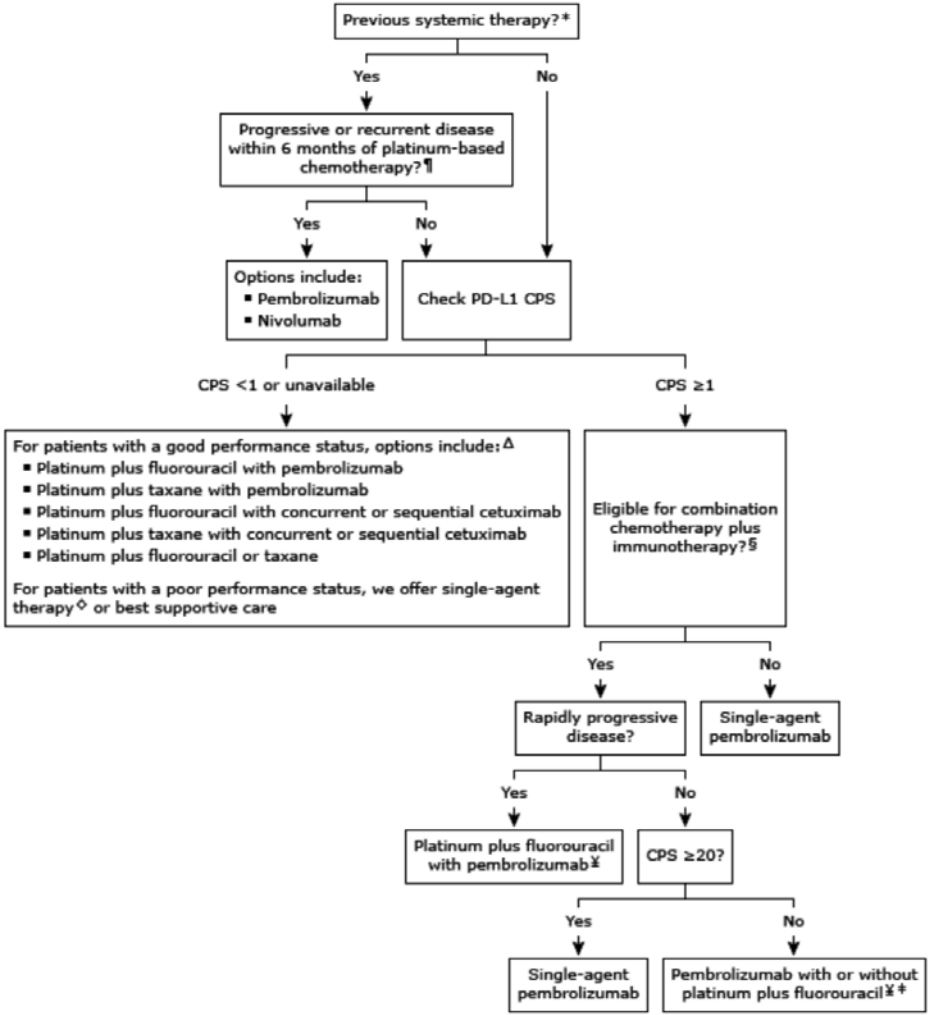
CPS ≥20 : pembrolizumab monotherapy

CPS ≥1 and <20: pembrolizumab+ platinum+ 5-FU/taxane

CPS <1 or unavailable: platinum-based chemotherapy, +/- pembrolizumab

Selection of therapy

- Previously treated patients
- Original chemotherapy exposure and drugs (either concurrent or induction)
- Response to the initial chemotherapy or chemoradiation regimen
- Interval between initial treatment and disease progression
- Patient performance status and comorbidities
- Exposure to immunotherapy


Previous systemic therapy?*
Yes
No
Progressive or recurrent disease within 6 months of platinum-based chemotherapy?¶
Yes
No
Options include:
▪ Pembrolizumab
▪ Nivolumab
Check PD-L1 CPS
CPS <1 or unavailable
CPS ≥1
For patients with a good performance status, options include:Δ
▪ Platinum plus fluorouracil with pembrolizumab
▪ Platinum plus taxane with pembrolizumab
▪ Platinum plus fluorouracil with concurrent or sequential cetuximab
▪ Platinum plus taxane with concurrent or sequential cetuximab
▪ Platinum plus fluorouracil or taxane
For patients with a poor performance status, we offer single-agent therapy◇ or best supportive care
Eligible for combination chemotherapy plus immunotherapy?§
Yes
No
Rapidly progressive disease?
Single-agent pembrolizumab
Yes
No
Platinum plus fluorouracil with pembrolizumab¥
CPS ≥20?
Yes
No
Single-agent pembrolizumab
Pembrolizumab with or without platinum plus fluorouracil¥‡

健保給付規定(112/12/1)

I.先前未曾接受全身性治療且無法手術切除之復發性或轉移性(第三期或第四期)頭頸部鱗狀細胞癌成人患者。（112/12/1)

II.先前已使用過platinum類化學治療失敗後，又有疾病惡化的復發性或轉移性(第三期或第四期)頭頸部鱗狀細胞癌成人患者。

III.本類藥品與cetuximab僅能擇一使用，且治療失敗時不可互換。

健保給付規定(112/12/1)

- 病人身體狀況良好(ECOG≦1)。
- 病人之心肺與肝腎功能須符合下列所有條件：

❑ NYHA (the New York Heart Association) Functional Class I或II

❑ GOT<60U/L及GPT<60U/L，且T-bilirubin<1.5mg/dL (晚期肝細胞癌病人可免除此條件)

❑ Creatinine<1.5mg/dL且eGFR>60mL/min/1.73m2 (晚期腎細胞癌病人可免除此條件)

健保給付規定(112/12/1)

給付範圍	pembrolizumab （略）	nivolumab （略）	atezolizumab （略）	avelumab （略）
（略）	（略）	（略）	（略）	（略）
頭頸部鱗狀細胞癌第一線用藥	CPS≧20	本藥品尚未給付於此適應症	本藥品尚未給付於此適應症	本藥品尚未給付於此適應症
頭頸部鱗狀細胞癌第二線用藥	TPS≧50%	TC≧10%	本藥品尚未給付於此適應症	本藥品尚未給付於此適應症

Novel Therapeutic Approaches

Head and Neck Cancer

Breaking Ground in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Novel Therapies Beyond PD-L1 Immunotherapy

Ari J. Rosenberg, MD[1]; Cesar A. Perez, MD[2]; Wenji Guo, MD[1]; Jose Monteiro de Oliveira Novaes, MD[3]; Kamilla F. Oliveira da Silva Reis, MD[4]; Patrick W. McGarrah, MD[5]; and Katharine A.R. Price, MD[5]

DOI https://doi.org/10.1200/EDBK_433330

Therapeutic Vaccines

- Investigating vaccines as monotherapy or in combination with PD-1 inhibitors:
- HPV-directed: ISA101, PDS0101, BNT113…
- Non-HPV-directed:

➢ UV1: Human telomerase reverse transcriptase (hTERT) is a ribonucleoprotein enzyme that can extend telomeres

➢ personalized neoantigen vaccines: phase I/II

Bispecific Antibodies.Fusion Proteins. Multikinase inhibitor

TABLE 1. Novel Bispecifics, Fusion Proteins, and Multikinase Inhibitors Under Active Evaluation in Patients With Recurrent and/or Metastatic HNSCC

Trial	Phase	Agents	Key Eligibility	Primary End Point	Results (if available)
Bispecifics and fusion proteins					
NCT03526835	I/II	MCLA-158 (petosemtamab): IgG1-bispecific antibody targeting EGFR and LGR5	Progression on or intolerant to anti–PD-(L)1 and platinum-based therapy in incurable recurrent or metastatic disease	ORR	ORR 37% (95% CI, 23 to 53)
NCT04429542	I	BCA101 (bifunctional EGFR/TGF-β fusion protein) monotherapy and in combination with pembrolizumab	PD-L1 CPS ≥1. No previous systemic therapy for recurrent/metastatic disease. Primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx. Participants might not have a primary tumor site of nasopharynx (any histology)	Safety and tolerability of BCA101 alone and in combination with pembrolizumab	ORR of 46%
NCT06129864	III	Volrustomig (MEDI5752; bispecific antibody targeting PD-1 and CTLA-4)	Unresectable locoregionally advanced HNSCC stage III or IVa/b after completion of definitive chemoradiation	Progression-free survival in participants with unresected locoregionally advanced HNSCC with PD-L1–expressing tumors	Ongoing
Multikinase inhibitors					
NCT04199104 (LEAP-010)	III	Lenvatinib + pembrolizumab *v* pembrolizumab alone as first-line treatment in the recurrent/metastatic setting	PD-L1 CPS ≥1	ORR, PFS, OS	The ORR was 46.1% for lenvatinib + pembrolizumab *v* 25.4% for placebo + pembrolizumab. The median PFS was 6.2 months for lenvatinib + pembrolizumab *v* 2.8 months for pembrolizumab + placebo. The median OS was 15.0 months for pembrolizumab + lenvatinib *v* 17.9 months for pembrolizumab + placebo
NCT04428151 (LEAP-009)	II	Lenvatinib + pembrolizumab *v* lenvatinib monotherapy *v* standard-of-care chemotherapy (docetaxel, paclitaxel, cetuximab, or capecitabine)	Disease progression after platinum-based chemotherapy and a PD-1/PD-L1 inhibitor	ORR	Ongoing
NCT03468218	II	Cabozantinib + pembrolizumab	No previous exposure to immune checkpoint inhibitors and PD-L1 CPS ≥1	ORR	ORR of 52%
NCT06082167 (STELLAR-305)	II/III	Zanzalintinib + pembrolizumab *v* pembrolizumab	PD-L1 CPS equal to or >1. No previous systemic therapy in the recurrent or metastatic setting	PFS, OS	Ongoing

Antibody-Drug Conjugates (ADCs)

✔ Monoclonal Antibody (mAb)
- Targets a specific antigen on cancer cells (e.g., HER2, Trop-2, CD30, CD79b).
- Ensures selective binding to tumor cells while sparing normal cells.

✔ Linker: Connects the cytotoxic drug to the antibody.
- Cleavable linkers: Release the drug under specific conditions (e.g., acidic pH, enzyme activity).
- Non-cleavable linkers: Require antibody degradation inside the cell to release the drug.

✔ Cytotoxic Payload

Highly potent chemotherapy, often 100-1000 times stronger than traditional chemo.
- Microtubule inhibitors (e.g., MMAE, MMAF, DM1, DM4) – block cell division
- DNA-damaging agents (e.g., Calicheamicin, PBD) – induce cell death.

Antibody-Drug Conjugates (ADCs)

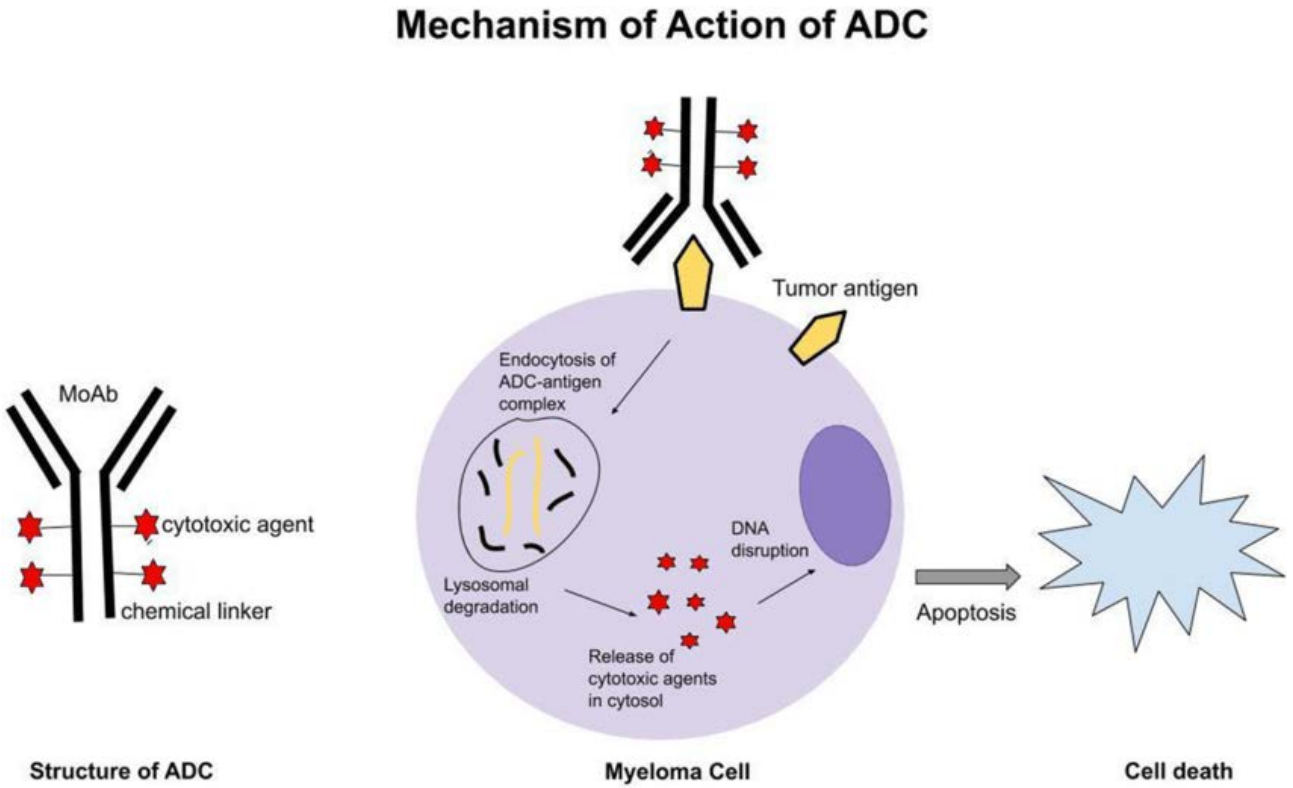


TABLE 2. Current Antibody-Drug Conjugates Under Active Evaluation in Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma

ADC	Target Antigen	Payload	Linker	No.	ORR	DCR	Common Toxicities
Bivatuzumab mertansine	CD44v6	DM1	Cleavable disulfide	31	10%	NA	80% of dermatologic AEs
Tisotumab vedotin	Tissue factor (CD142)	MMAE	Cleavable (Val-Cit)	31	16%-40%	78%	Ocular, peripheral neuropathy, anemia, pneumonia
SGN-B6A	Integrin beta-6	MMAE	Cleavable	56	23%	61% (35/56)	Fatigue, neutropenia, peripheral sensory neuropathy, pneumonia
Enfortumab vedotin	Nectin-4	MMAE	Protease-cleavable peptide linker: Maleimidocaproyl-valine-citrulline-p-aminobenzoyloxy-carbonyl linker (MC-VC-PABC)	46	23.9%	56.5%	Peripheral neuropathy, dermatologic AEs, hyperglycemia
Sacituzumab govitecan	TROP-2	SN-38 (active metabolite of irinotecan)	Hydrolyzable CL2A linker	43	16%	65%	Gastrointestinal AEs, cytopenias

Future Direction and Conclusion

- Trends

  Personalized medicine.

  AI-driven treatment selection.

- Clinical Decision-Making

  Optimizing therapy based on biomarkers.

- Next Steps in Research & Clinical Trials

Take home massage

- Anti-PD-1 have demonstrated significant survival benefits, particularly in PD-L1 positive patients.
- Combination therapy (Anti-PD-1 + chemotherapy) offers improved outcomes for select patients.
- Antibody-drug conjugates (ADCs), bispecific antibodies, and therapeutic vaccines are promising future directions.

Thanks for your attention!