



Immunotherapy for the Treatment of Head and Neck Cancer

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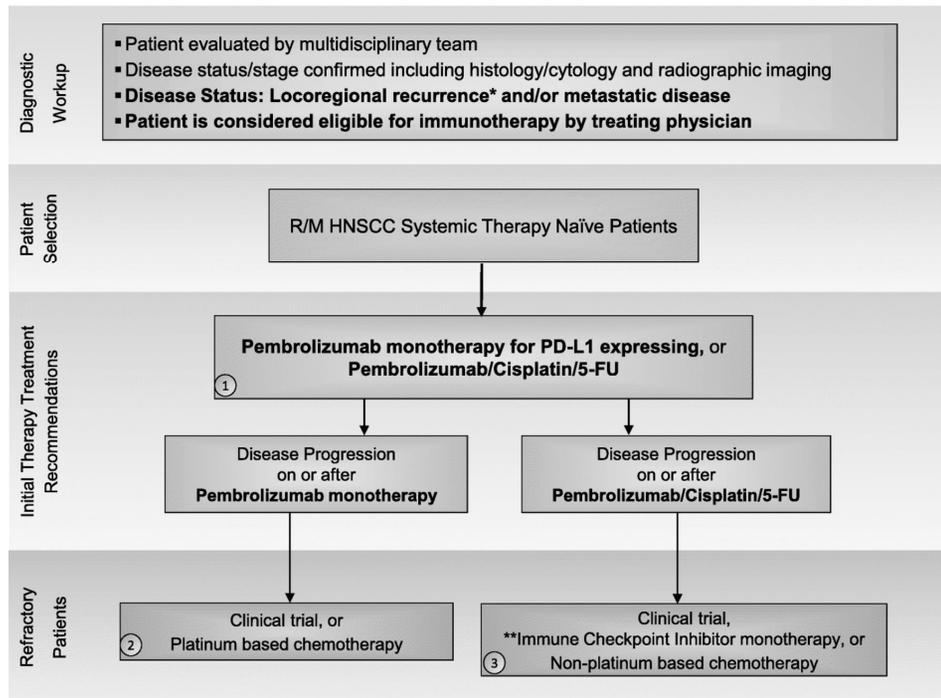
Disclosures

- Consulting Fees: Astra Zeneca, Curio Science
- Contracted Research: Merck, Astra Zeneca, Bristol Myers Squibb
- I will be discussing non-FDA approved indications during my presentation.

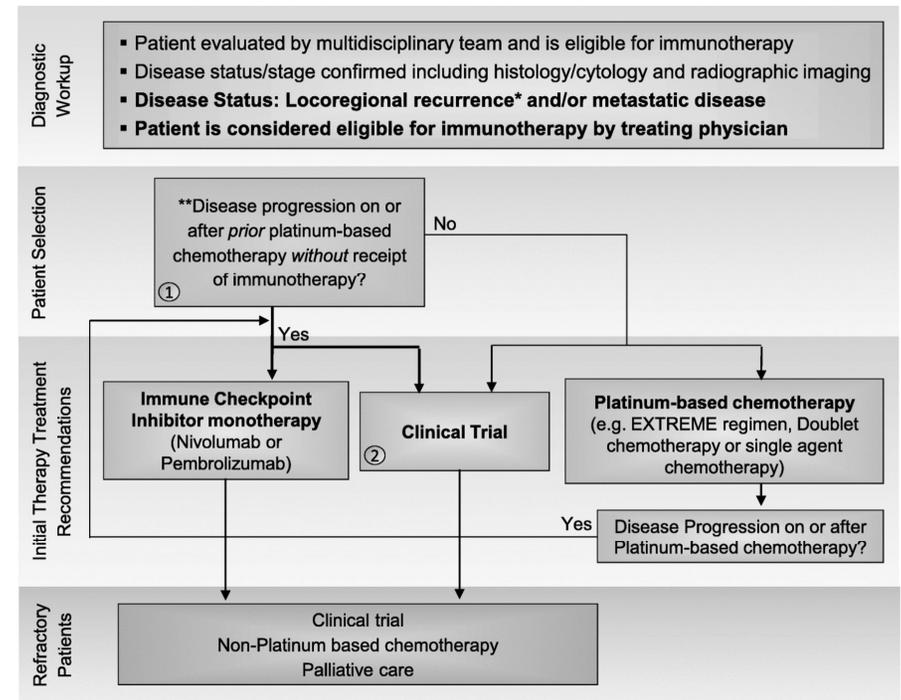
Outline

- Approved immunotherapies in head and neck cancers
- Biomarkers and immunotherapy responsiveness
- Unique considerations for head and neck cancers
- Future directions

Immunotherapy in head and neck cancer treatment



*Locoregional recurrence without salvage surgical or radiation option or declines local therapies
 **Refer to Figure 2. Initial Therapy Treatment Recommendations: Immune Checkpoint Inhibitor monotherapy (nivolumab or pembrolizumab)



*Locoregional recurrence without salvage surgical or radiation option or declines local therapies
 **Disease Progression on or after Platinum-Based Therapy: Disease progression on or after platinum-based therapy including within 6 months of platinum-based CRT given in the locally advanced setting. Patients that receive but cannot tolerate platinum-based chemotherapy would also be included in this category.
 HNSCC: head and neck squamous cell carcinoma

Approved checkpoint inhibitors in head and neck cancers

Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W or 400 mg Q6W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Pembrolizumab + platinum + fluorouracil	2019	Recurrent/metastatic HNSCC 1 st line – all patients	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1 st line – PD-L1 CPS \geq 1	200 mg Q3W or 400 mg Q6W

Clinical trials in HNSCC

Trial	Patient selection criteria	Treatment arm(s)	N	ORR	Median PFS (months)	Median OS (months)
KEYNOTE-048	Untreated R/M HNSCC (total population)	Pembrolizumab	301	16.9%	2.3	11.5
		Pembrolizumab + chemo	281	36%	4.9	13.0
		Cetuximab + chemo	300	36%	5.2	10.7
KEYNOTE-012	R/M HNSCC	Pembrolizumab	192	18% (PD-L1+: 21%, PD-L1-: 6%)	2.1	8
CheckMate 141	R/M HNSCC with progression on platinum	Nivolumab	240	13.1% (PD-L1+: 17.7%, PD-L1-: 11.8%)	2.0	7.7
		Investigator's choice	121	5.8%	2.3	5.1
KEYNOTE-040	R/M HNSCC with progression on platinum	Pembrolizumab	247	14.6%	2.1	8.4
		Investigator's choice	248	10.1%	2.3	6.9

Mehra, Br J Cancer 2018; Ferris, Oral Oncol 2018; Cohen, Lancet 2018; Burtneiss, Lancet 2019.

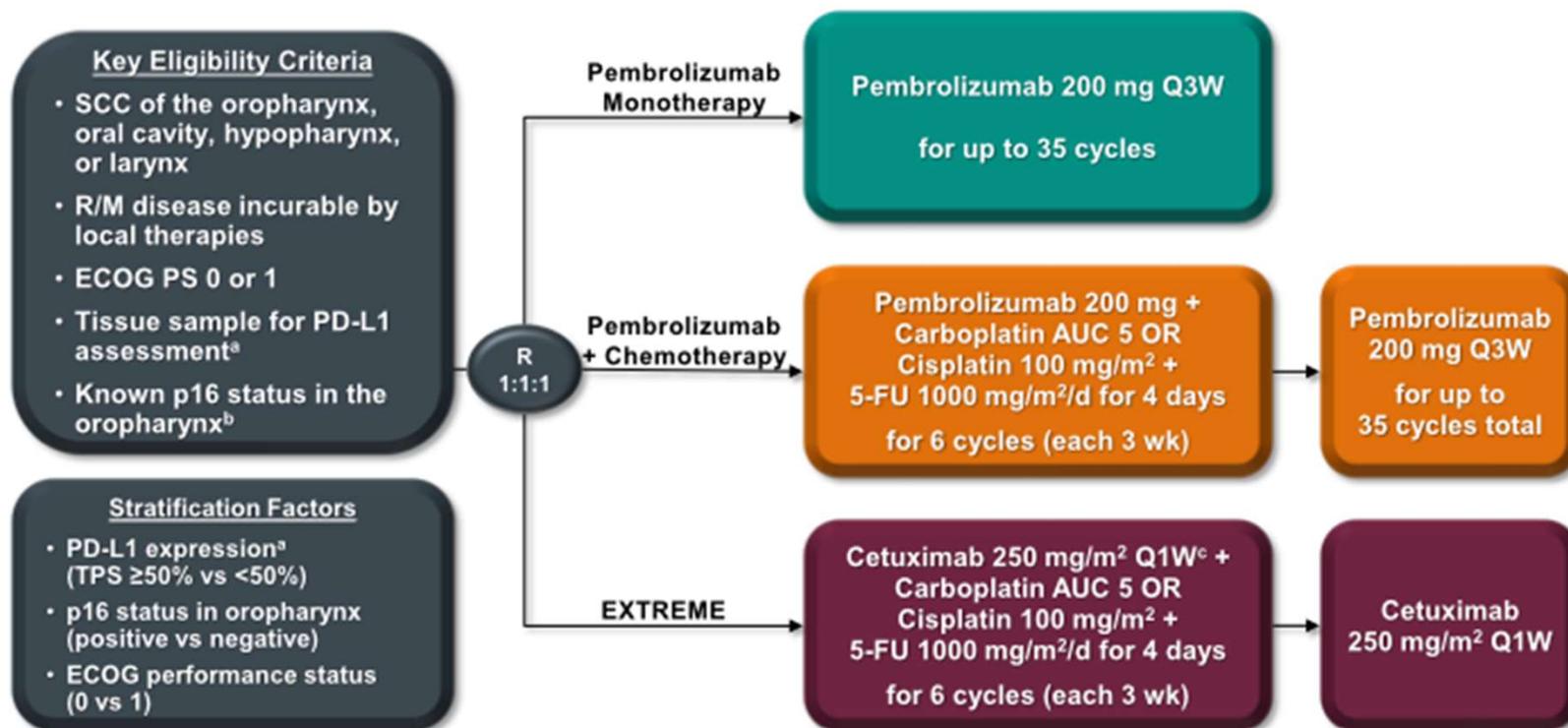
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Slide 6

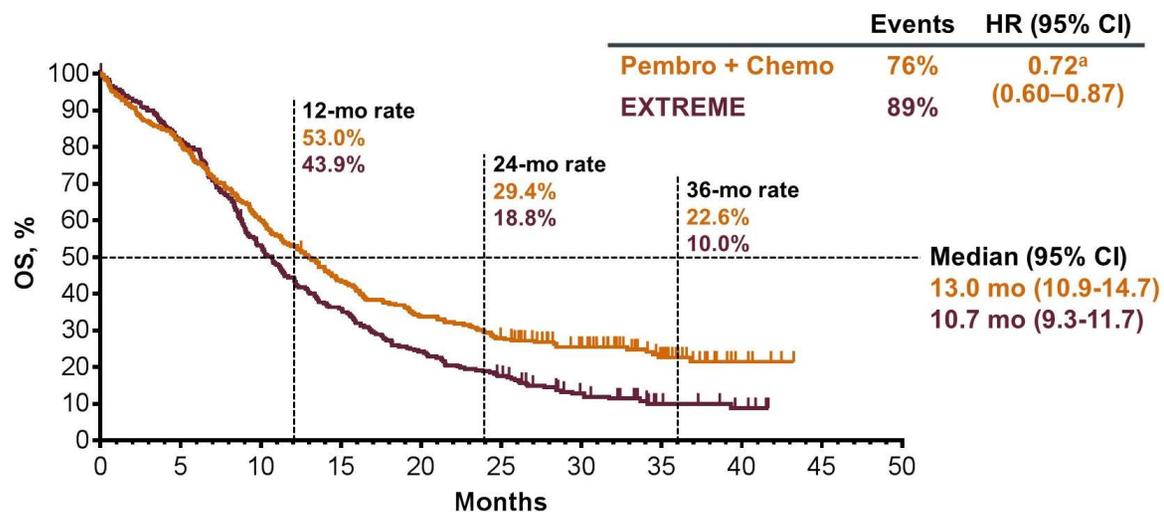
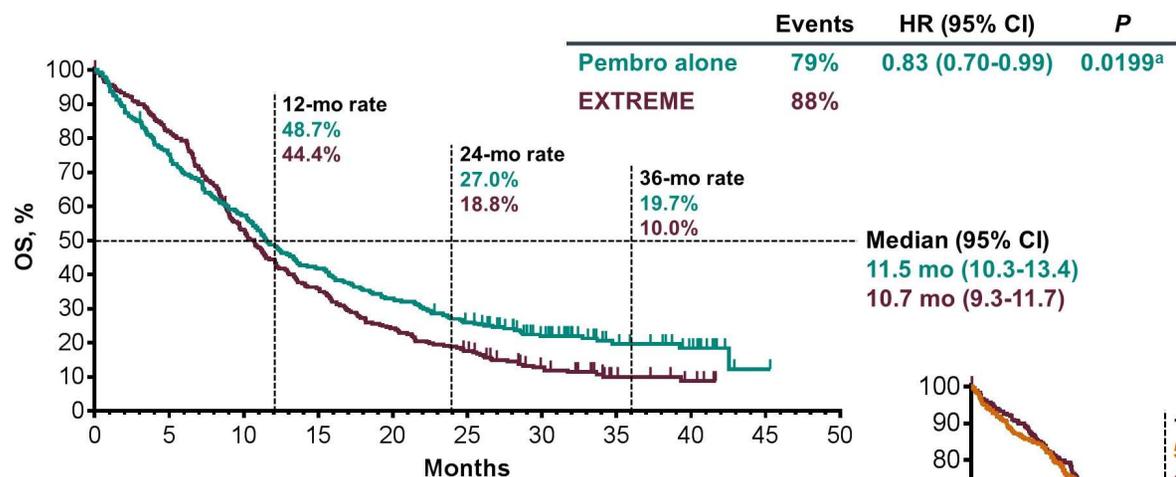
EE13 I cannot access the full KEYNOTE-048 paper - can you add in the response rate for pembro+chemo in the total population?
Emily Ehlerding, 8/31/2020

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC



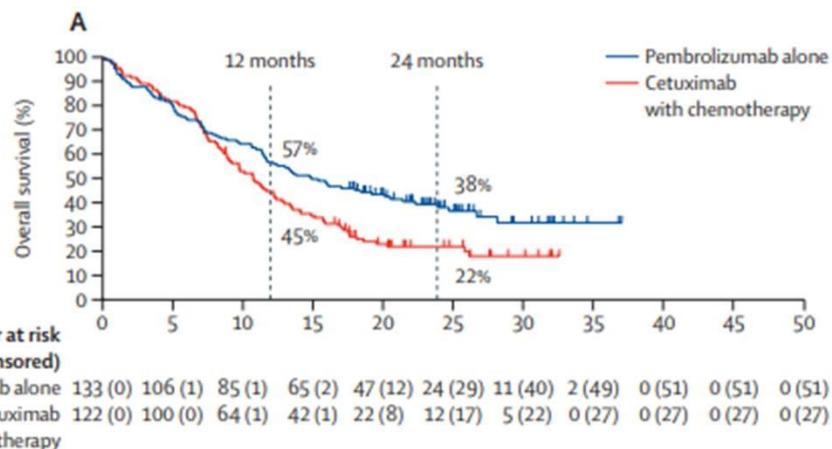
^aAssessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. ^bAssessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. ^cFollowing a loading dose of 400 mg/m².

KEYNOTE-048: Overall survival in the total population

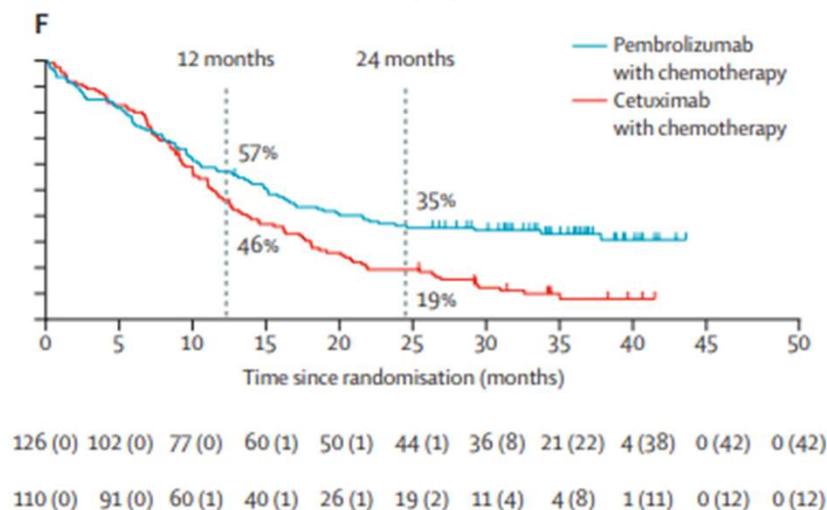


KEYNOTE-048: Overall survival in the PD-L1 positive population

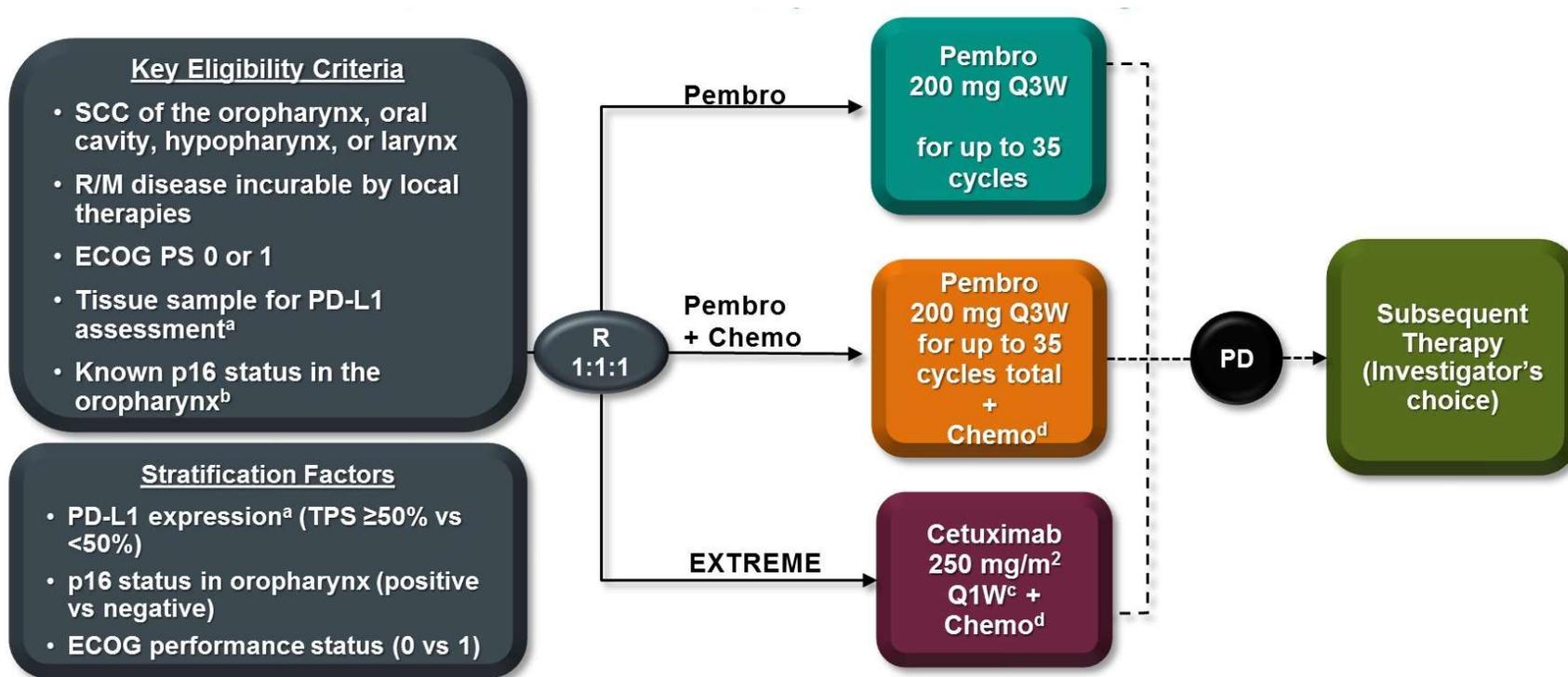
PD-L1 CPS ≥1



PD-L1 CPS ≥1



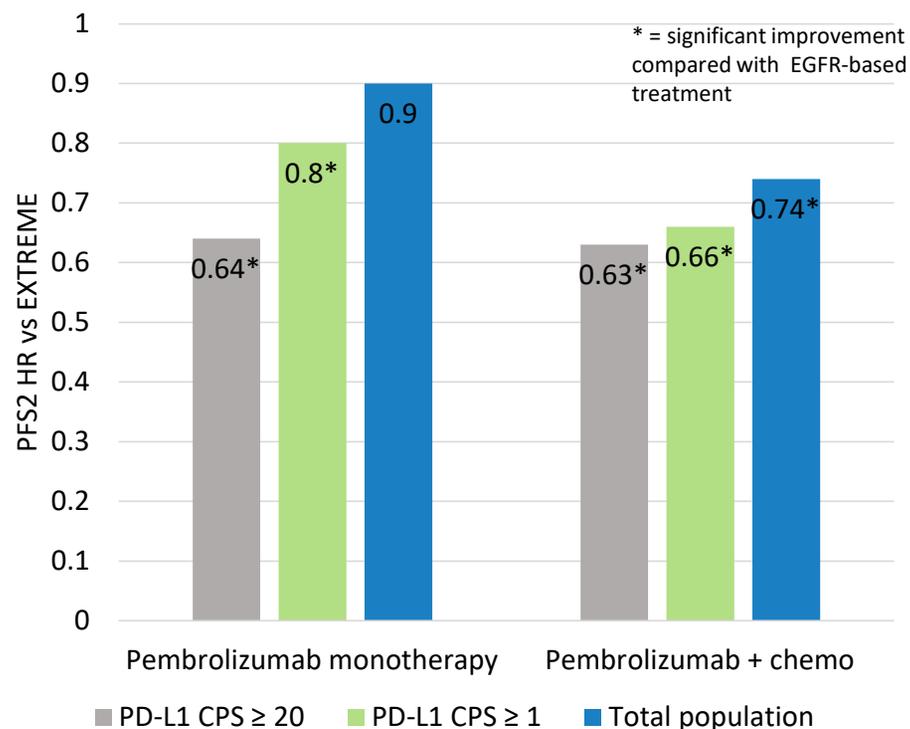
KEYNOTE-048: Outcomes on subsequent therapy



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KEYNOTE-048: Outcomes on subsequent therapy

- After progression, most common next treatment was a chemotherapy regimen
- PFS2: Progression-free survival on second treatment (after progression on KEYNOTE-048 treatment)
- Benefits seen for patients who received pembrolizumab regimens up-front
- Provides support to use of immunotherapy in front-line setting



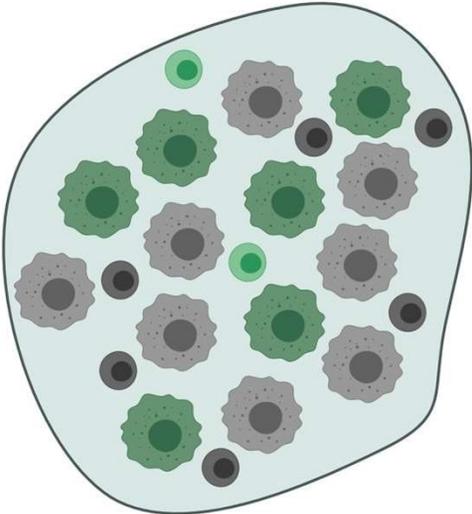
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PD-L1: TPS vs CPS

$$TPS = \frac{\# \text{ of PD-L1 positive tumor cells}}{\text{number of viable tumor cells}} \times 100$$

$$CPS = \frac{\# \text{ of PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{total number of tumor and immune cells}} \times 100$$



-  PD-L1-positive immune cell
-  PD-L1-negative immune cell
-  PD-L1-positive tumor cell
-  PD-L1-negative tumor cell

$$TPS = \frac{6 \text{ positive tumor cells}}{14 \text{ total tumor cells}} \times 100 = 43$$

$$CPS = \frac{6 \text{ positive tumor cells} + 2 \text{ positive immune cells}}{22 \text{ total cells}} \times 100 = 36$$

Impact of PD-L1 in HNSCC

PD-L1 CPS

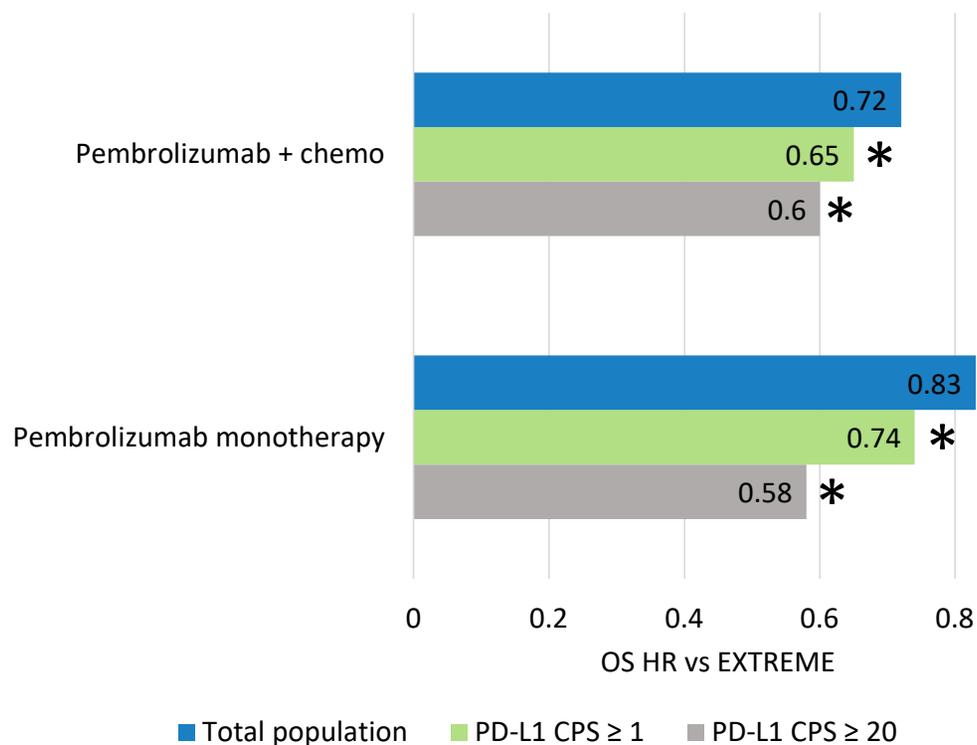
- KEYNOTE-048
 - First-line treatment
 - Approval of pembrolizumab monotherapy: CPS \geq 1
- KEYNOTE-040
 - After platinum
 - Improved outcomes in PD-L1-positive patients (by CPS \geq 1), no significance in total population

PD-L1 TPS

- CheckMate 141
 - After platinum
 - Greatest benefit seen for PD-L1-positive tumors (TPS \geq 1%), but benefit regardless
- KEYNOTE-012
 - Second-line treatment
 - Higher response rate with PD-L1 CPS-positive tumors
 - No difference for PD-L1-positive tumors by TPS

KEYNOTE-048: Outcomes by PD-L1 status

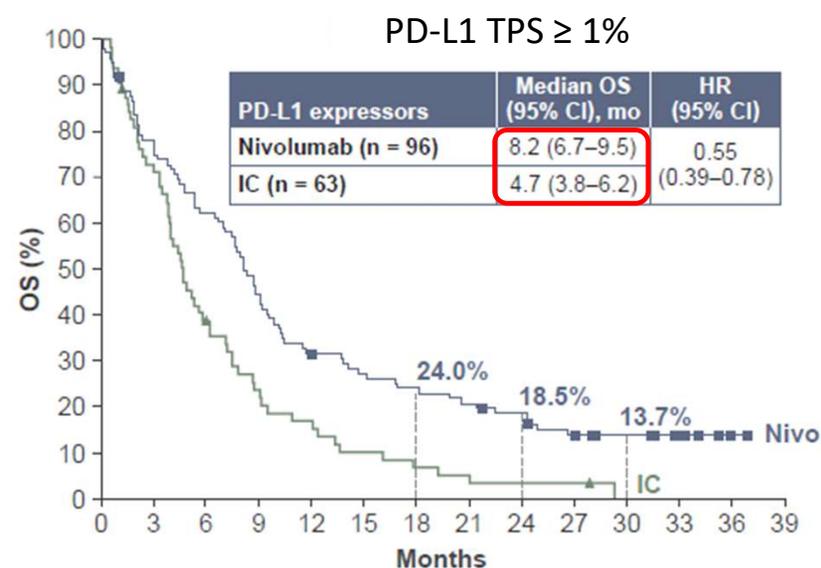
- Greatest benefits seen in tumors with highest PD-L1 expression
- Approval requires PD-L1 expression (CPS) only for monotherapy
- For PD-L1 negative, only pembrolizumab + chemotherapy should be considered, not monotherapy



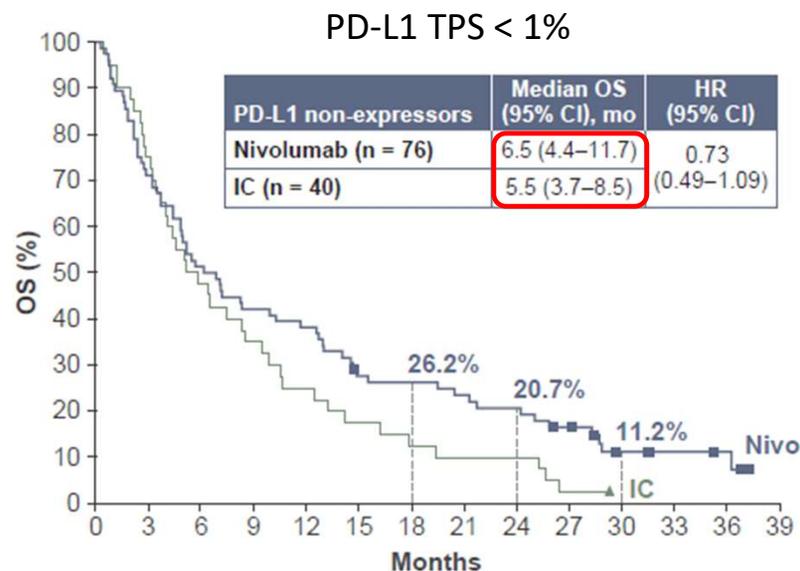
*superiority statistically demonstrated at interim or final analysis

CheckMate 141: Outcomes by PD-L1 status

CheckMate 141: 2 year update



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Nivo	96	74	59	42	30	25	22	19	16	11	8	5	1	0
IC	63	45	24	14	10	6	4	3	2	2	0	0	0	0



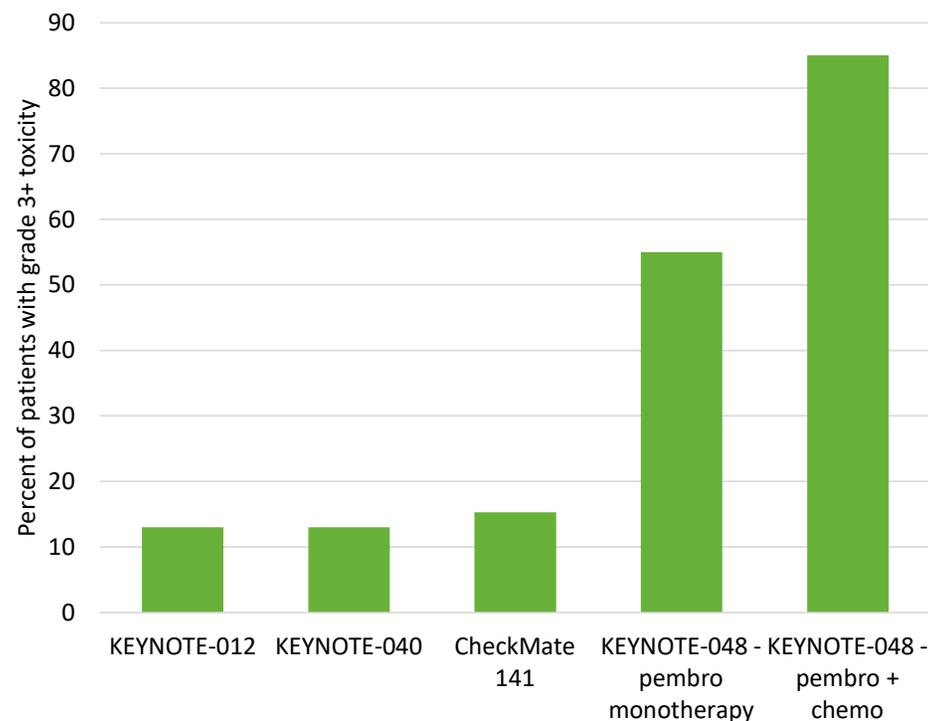
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

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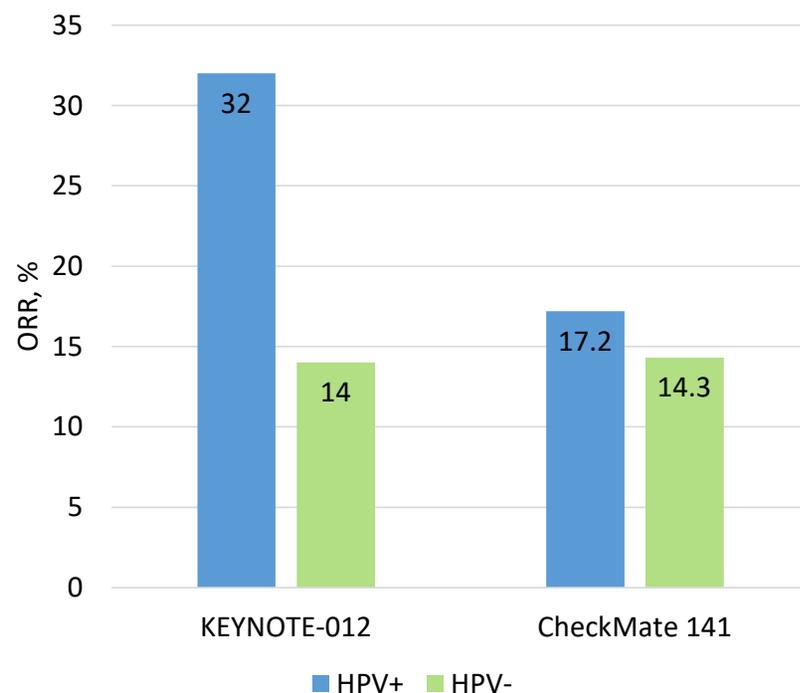
Toxicities in head and neck cancer patients

- Patients typically receive aggressive radiation treatment, with accompanying side effects
- Radiation in combination with chemotherapy, immunotherapy and/or surgery can further complicate toxicity profiles
- While combinations may have higher response rates, also have higher toxicity rates



Viral infections in HNSCC

- Virally-associated cancers are biologically and clinically distinct
 - Human papillomavirus associated with oropharynx cancer
 - Epstein Barr virus associated with nasopharyngeal cancer
- Evidence that HPV+ tumors may perform better, but there is benefit with immunotherapy regardless of HPV status



Combination immune checkpoint inhibition in HNSCC – *limited success to date*

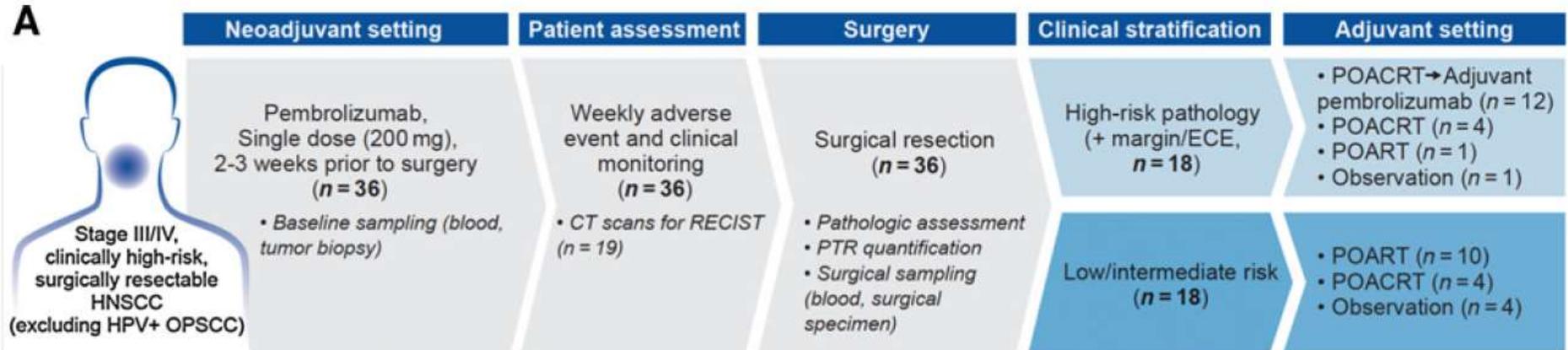
Trial	Patient population	Treatment arms	ORR	Median OS (months)	Landmark OS
EAGLE	R/M HNSCC after platinum	Durvalumab	17.9%	7.6	24-months: 18.4%
		Durvalumab + tremelimumab	18.2%	6.5	24-months: 13.3%
		SoC	17.3%	8.3	24-months: 10.3%

Trial	Patient population	Treatment arms	Expected study completion
KESTREL	Untreated HNSCC	Durvalumab	February 2021
		Durvalumab + tremelimumab	
		SoC	
CheckMate 714	Platinum-refractory HNSCC	Nivolumab + ipilimumab	January 2024
		Nivolumab	
CheckMate 651	Untreated HNSCC	Nivolumab + ipilimumab	February 2026
		EXTREME regimen	

Outline

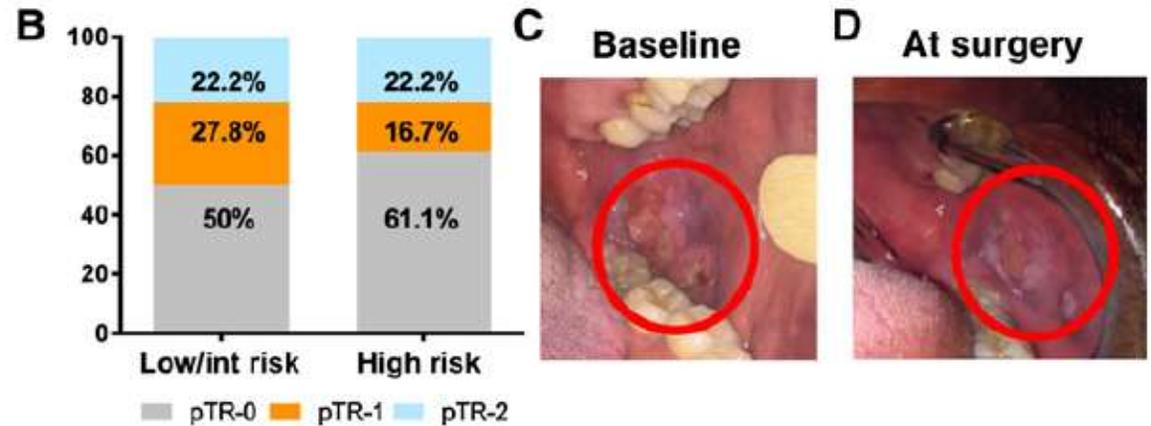
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In development: Oral cavity cancer



In development: Oral cavity cancer

- No serious AEs or unexpected surgical complications/delays
- pTR-2: 22%
- pTR-1: 22%
- pTR-0: 50%
- 1-year relapse rate: 16.7%



In development: Checkpoint inhibitors + radiotherapy as primary therapy

- NCT03247712: neoadjuvant nivolumab + SBRT
 - Phase I
 - Decreased tumor size prior to surgery; high pathologic CR rate
- KEYNOTE-412: pembrolizumab + chemoradiation
 - Phase III
 - Safety confirmed, estimated completion 2021
- JAVELIN Head and Neck 100: avelumab + chemoradiation
 - Phase III trial terminated in early 2020, due to likelihood of limited efficacy
- REACH: avelumab + cetuximab + radiotherapy
 - Phase III
 - Safety confirmed, estimated completion 2027

In development: cetuximab + pembrolizumab for recurrent metastatic disease

- Cetuximab and pembrolizumab are both approved as monotherapies for HNSCC
- Phase II trial testing cetuximab + pembrolizumab:
 - Platinum refractory or ineligible disease
 - ORR: 45%
 - Median OS: 18.4 months
 - Safety profile consistent with individual drugs

In development: Selected ongoing combination trials

Trial	Patient population	Treatment arms	Targets	Expected study completion
LEAP-010	Untreated recurrent/metastatic PD-L1+ HNSCC (CPS \geq 1)	Pembrolizumab + lenvatinib	PD-1 + multikinase inhibitor	April 2024
		Pembrolizumab	PD-1	
INDUCE-3	Untreated recurrent/metastatic PD-L1+ HNSCC (CPS \geq 1)	Pembrolizumab + GSK609	PD-1 + ICOS	July 2023
		Pembrolizumab	PD-1	
NCT02643550	HNSCC after 1-2 therapies, including progression on Pt	Monalizumab + cetuximab	NKG2A + EGFR	Phase 1/2: 2021 Phase 3: planned

Conclusions

- Cytotoxic chemotherapy achieves limited survival in HNSCC with unfavorable side effects.
- Checkpoint inhibitors that target the PD-1 axis, nivolumab and pembrolizumab, are approved in platinum-refractory/exposed recurrent/metastatic HNSCC.
- Nivolumab and pembrolizumab are in general better tolerated than cytotoxic chemotherapy.
- Ongoing areas of research include combinations of immunotherapy with radiation and/or other drugs and development of predictive biomarkers.

Cohen et al. *Journal for Immunotherapy of Cancer* (2019) 7:184
<https://doi.org/10.1186/s40425-019-0662-5>

Journal for Immunotherapy
of Cancer

POSITION ARTICLE AND GUIDELINES

Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC)



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Case Studies



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Case #1

- 64 y.o. WM with hx of tobacco use and HTN initially presented with SqCC of the Left Tonsil (HPV +, T4N2M0)
- Treated with concurrent chemoradiation in 2018 and f/u PET shows a complete response
- Recently, patient presents with new left neck mass and imaging shows metastatic disease to the left neck, 4 small lung nodules, and several asymptomatic bony metastases → biopsy shows SqCC (PD-L1 10%)

Case #1

- What would be the best initial treatment option?
 - a. Pembrolizumab alone
 - b. Pembrolizumab + Carboplatin/5FU
 - c. Pembrolizumab + Carboplatin/Paclitaxel
 - d. Cetuximab + Carboplatin/5FU

Case #1

- The patient is started on Pembrolizumab alone
- He had a partial response that lasted for 8 months and then imaging showed evidence of mixed response with near resolution of lung nodules but new bony metastases and a single liver nodule

Case #1

- What would be the next best option for treatment?
 - a. Cetuximab alone
 - b. Platinum doublet chemotherapy + Pembrolizumab
 - c. Platinum doublet chemotherapy alone
 - d. Gemcitabine alone

Case #1

- The patient was continued on Pembrolizumab and Carboplatin and Paclitaxel were added
- He had a renewed response with the addition of chemotherapy x 4 cycles and then went back on Pembrolizumab maintenance
- He ultimately progressed 9 months later and went on to Gemcitabine and then a clinical trial before opting for hospice care

Case #2

- This is a 49 y.o. male with history of heavy tobacco and ETOH abuse who presented with a T2N2 SqCC of the oral cavity
- Initially treated with surgical resection with flap reconstruction and adjuvant XRT in 2019
- Now presents with painful bony metastases, 3 liver metastases, local recurrence at the flap margin, and thoracic/cervical lymphadenopathy
- Biopsy by ENT shows SqCC with a PD-L1 CPS of 30%

Case #2

- What would be the best initial treatment option?
 - a. Pembrolizumab alone
 - b. Pembrolizumab + Carboplatin/5FU
 - c. Pembrolizumab + Carboplatin/Paclitaxel
 - d. Cetuximab + Carboplatin/5FU

Case #2

- The patient was started on Carbo/5FU + Pembrolizumab
- He has a partial response with improvement in his pain symptoms that lasts for 6 months, but now he develops new lung and liver nodules and progressive bony metastases

Case #2

- What would be the next best option for treatment?
 - a. Cetuximab
 - b. Gemcitabine
 - c. Docetaxel
 - d. Afatinib
 - e. Capecitabine

Case #2

- The patient was started on Capecitabine 800mg/m² and had a brief partial response
- He was then trialed on Cetuximab alone because of declining performance status and ultimately opted for hospice a few months later



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Questions?



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