Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancer

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

Consulting Fees: Regeneron, Sanofi Genzyme, BMS, Maverick, Merck, Kura, Bio-Rads, Prelude, Bicara

Speaker's Bureau: none

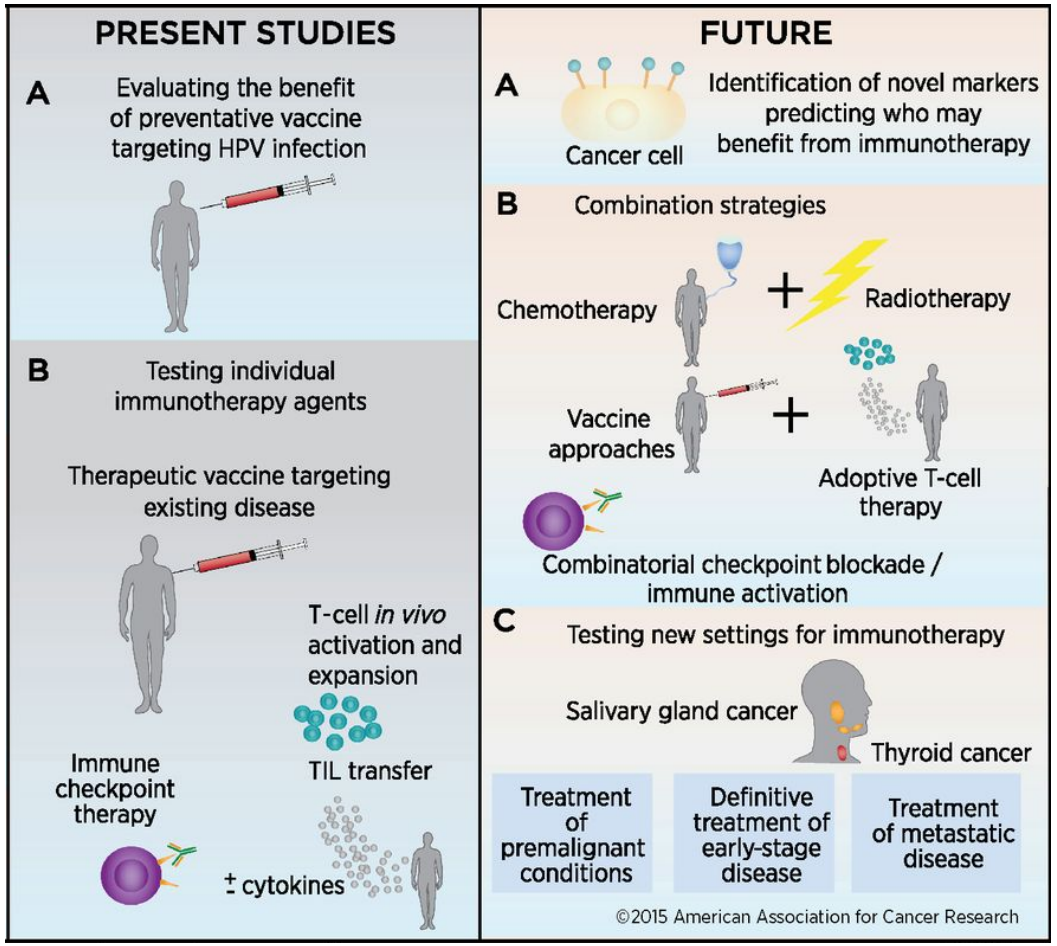
Contracted Research: BMS, Exicure, GSK, NantKWwest, Kite, Regeneron, Sanofi Genzyme, Kartos, Elevar, ASCO/Conquer Cancer Foundation, V Foundation, Gateway for Cancer Research

Major Shareholder: none

I will be discussing off-label or unapproved uses of drugs or medications

Immunotherapy for the Treatment of Head and Neck Cancers

- Immuno-Oncology (I-O) developments in the treatment of head and neck cancers
  - Expression of immunologic and molecular markers to guide treatment
  - Novel immune checkpoint inhibitor combinations
  - IO agents in the definitive and (neo)adjuvant setting
  - Therapeutic vaccination targeting virally mediated cancers
  - Immune effector cell therapies



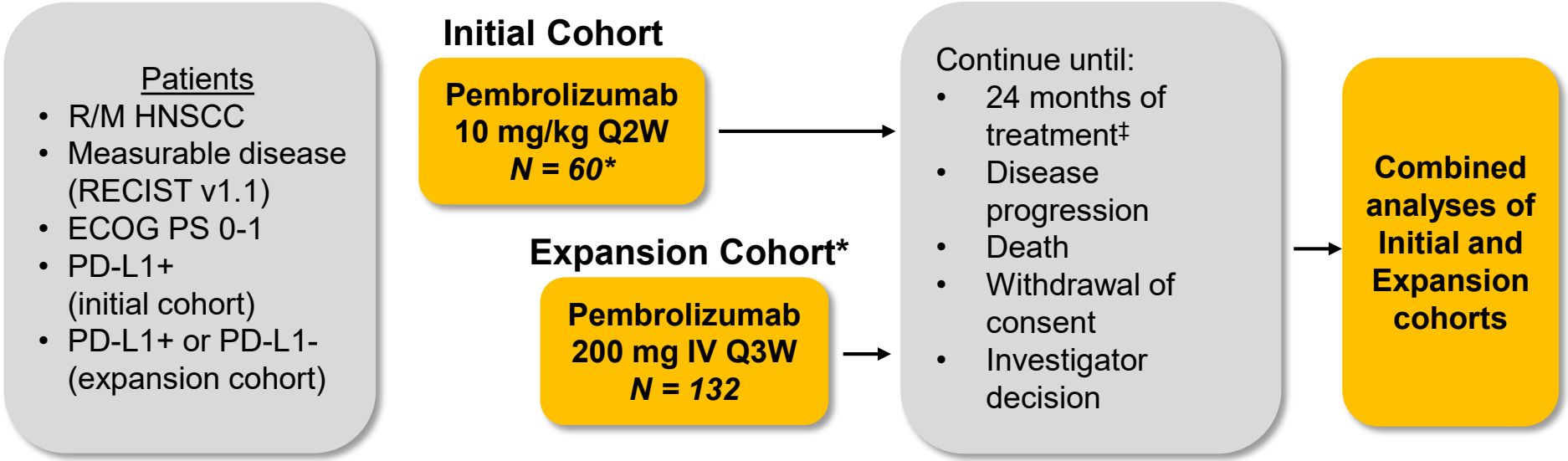
Schoenfeld, Cancer Immunol Res, 2015

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 600 mg Q6W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Cemiplimab-rwlc	2018	Metastatic cSCC, not candidate for curative therapies (any site)	350 mg Q3W
Pembrolizumab + platinum + fluorouracil	2019	Recurrent/metastatic HNSCC 1st line – all patients	200 mg Q3W
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1st line – PD-L1 CPS ≥ 1	200 mg Q3W
Pembrolizumab	2020	Recurrent/metastatic cSCC, not curable by surgery or radiation	200 mg Q3W

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2



Response assessment: Every 8 weeks until disease progression

Primary end points: ORR (RECIST v1.1, central imaging vendor review), safety

Secondary end points: ORR (investigator), PFS, OS, duration of response (DOR), ORR in HPV+ patients §

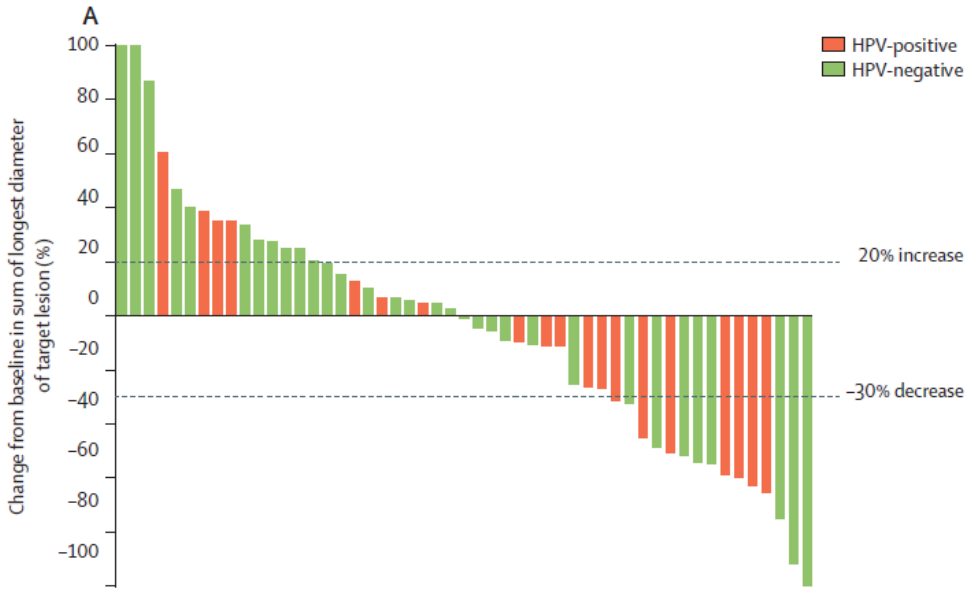
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*PD-L1 positive patients (1% tumor cells or stroma)

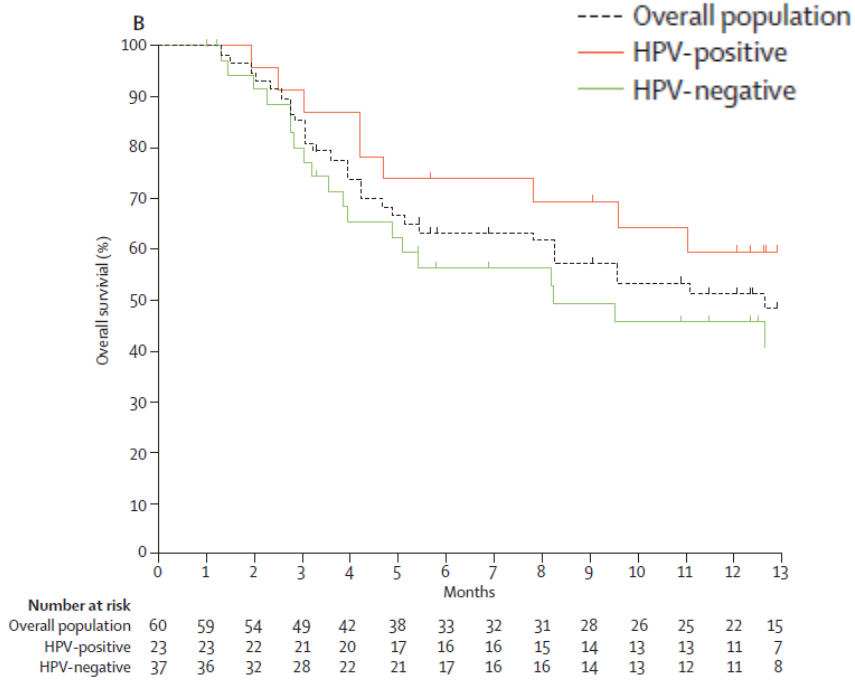
Seiwert, Lancet Oncol 2016.
Chow LQM, J Clin Oncol 2016.

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2

- ORR = 18%
  - CR = 2%
  - PR = 16%
- mOS = 13.0 months
- mPFS = 2.0 months





mOS = NR vs. 8 months

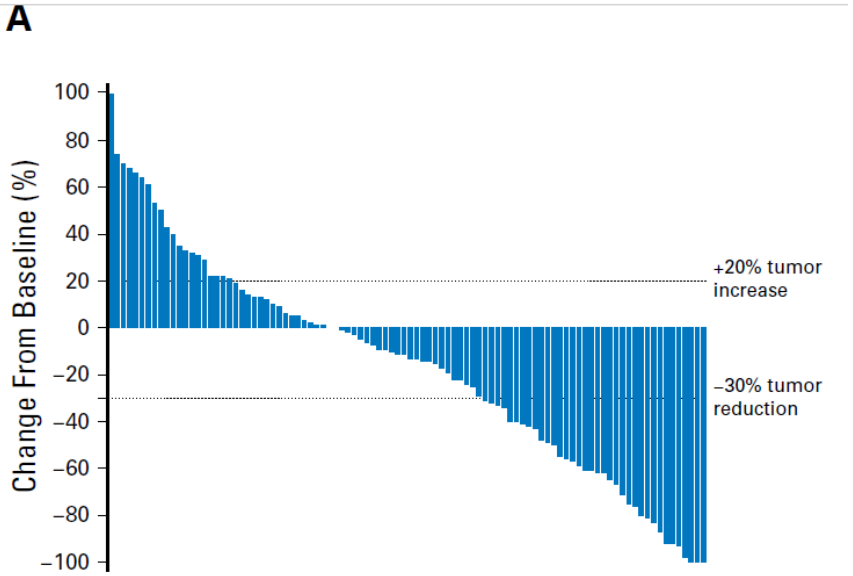
Seiwert, Lancet Oncol 2016.

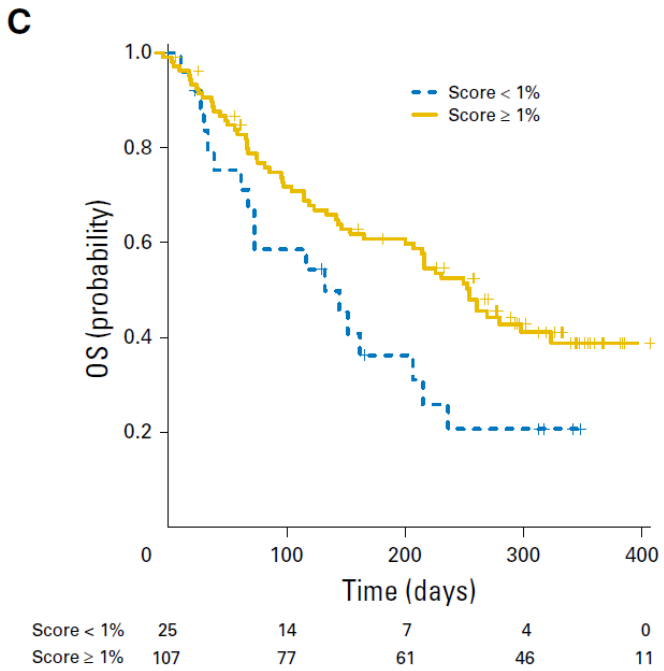
KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2

- ORR = 18%*
  - CR = 3%
  - PR = 15%
- mOS = 8.0 months
- mPFS = 2.0 months

*ORR 32% among HPV+



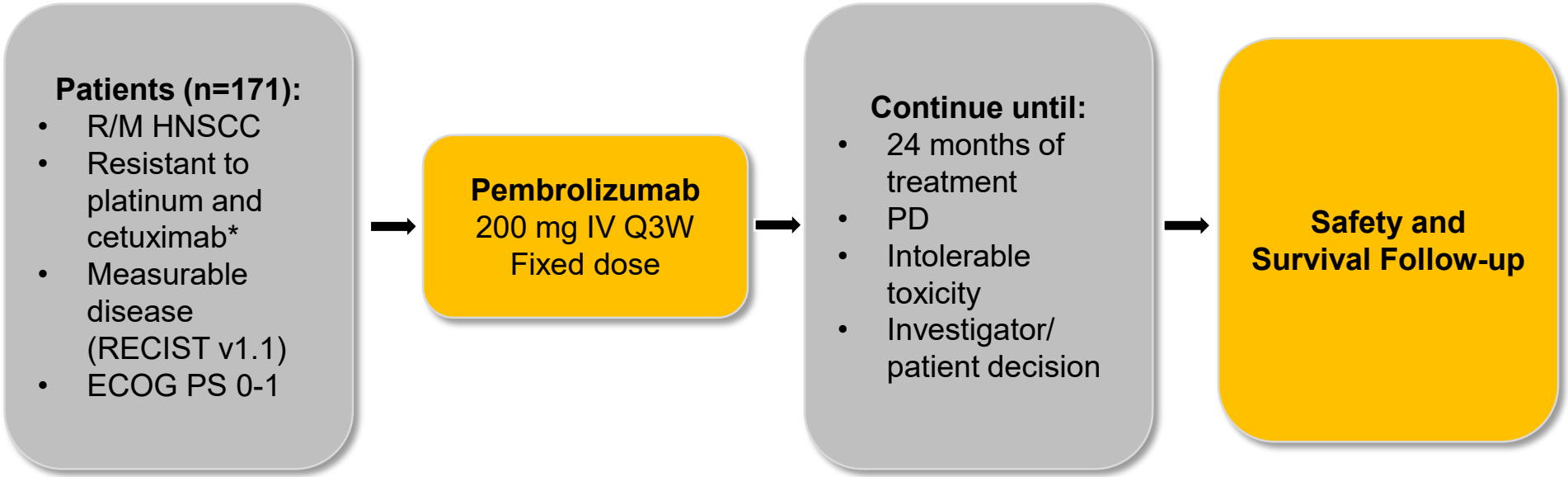


mOS = 303 vs. 151 days

Chow LQM, J Clin Oncol 2016.

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab

Phase II Trial, Single Arm



Response assessment: Imaging every 6 to 9 weeks (central radiology review)

Primary end points: ORR (RECIST v1.1) by Response Evaluation Criteria in Solid Tumors and safety

Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

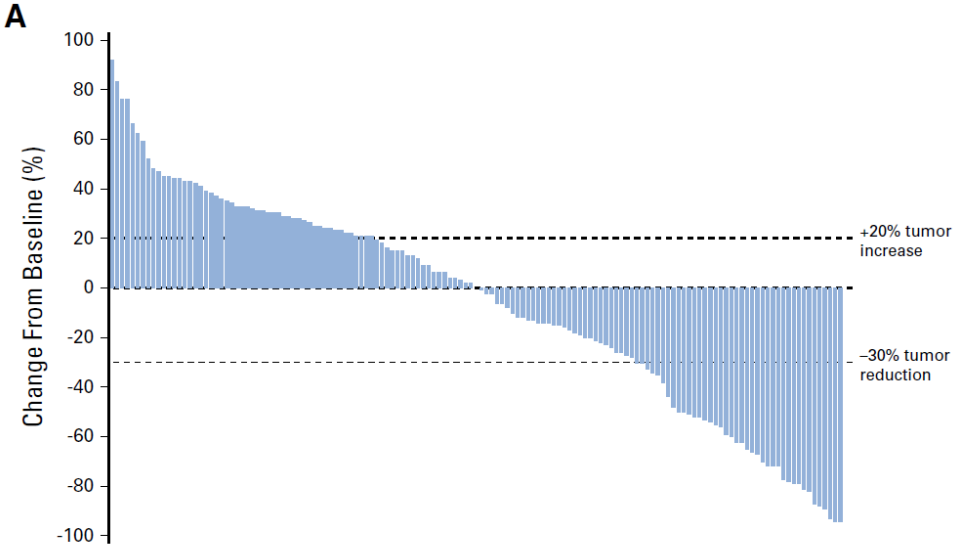
*75% of patients had ≥ 2 prior lines of therapy for metastatic disease

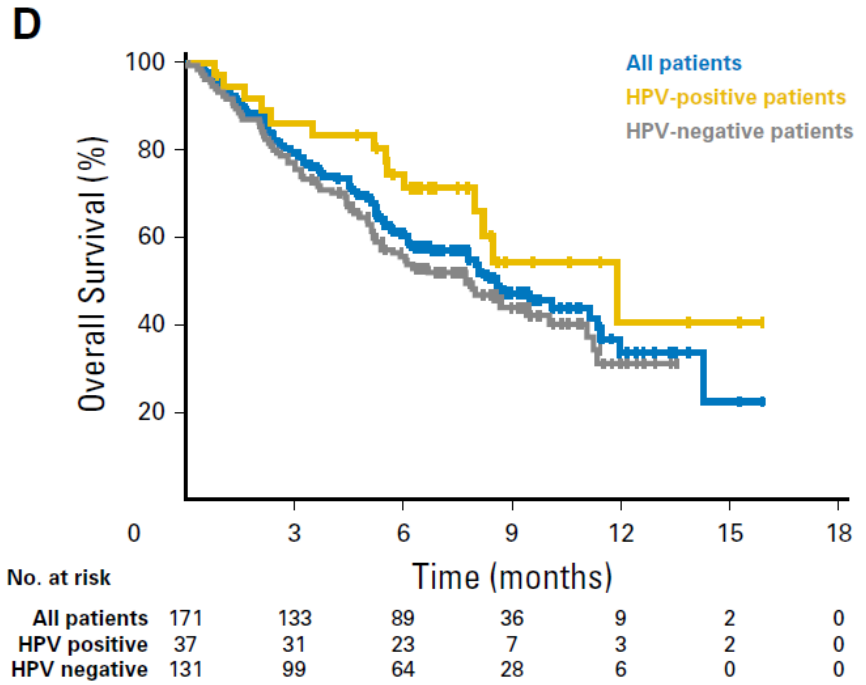
Bauml, J Clin Oncol 2017.

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab

Phase II Trial, Single Arm

- ORR = 16%
  - CR = 1%
  - PR = 15%
- mOS = 8.0 months
- mPFS = 2.1 months





ORR = 18 vs. 12% for PD-L1 CPS 1+

27 vs. 13% for PD-L1 CPS 50+

6m OS = 72 vs. 55%

Bauml, J Clin Oncol 2017.

CheckMate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

Phase III Randomized, Safety and Efficacy Trial

Key Eligibility Criteria
- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status[a]

Stratification factor
- Prior cetuximab treatment

→ **R 2:1**

Nivolumab
3 mg/kg IV Q2W

Vs.

Investigator's Choice
- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized.

[a]Tissue required for testing

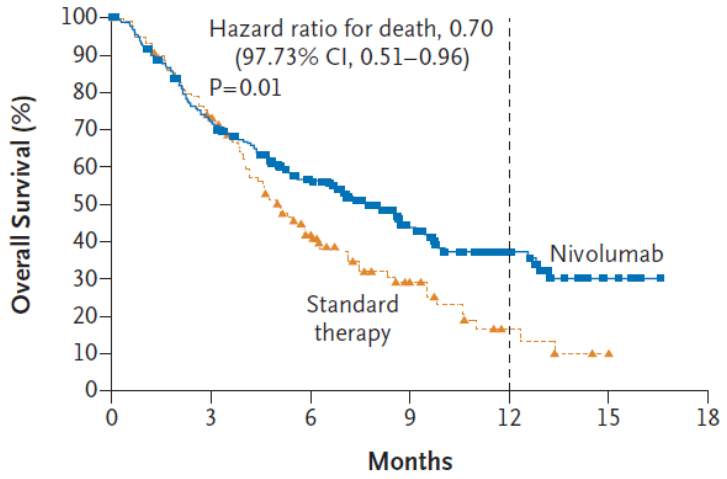
Ferris, NEJM 2016.

Checkmate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

- mOS = 7.5 vs. 5.1 months
- 1y mOS: 36 vs. 16%
- mPFS = 2.3 vs. 2.0 months
- ORR = 13%

A Overall Survival

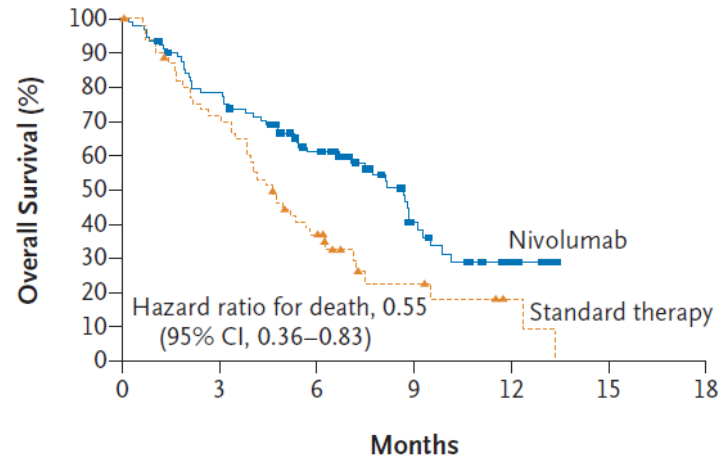
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

A Overall Survival among Patients with Baseline PD-L1 ≥1%

	No. of Patients	No. of Deaths	Median Overall Survival mo (95% CI)
Nivolumab	88	49	8.7 (5.7–9.1)
Standard Therapy	61	45	4.6 (3.8–5.8)



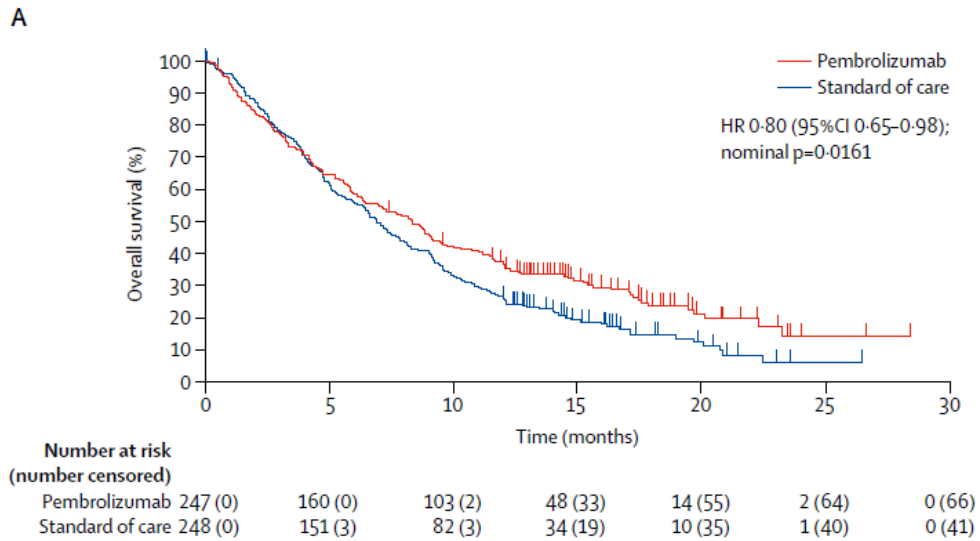
No. at Risk							
Nivolumab	88	67	44	18	6	0	
Standard therapy	61	42	20	6	2	0	

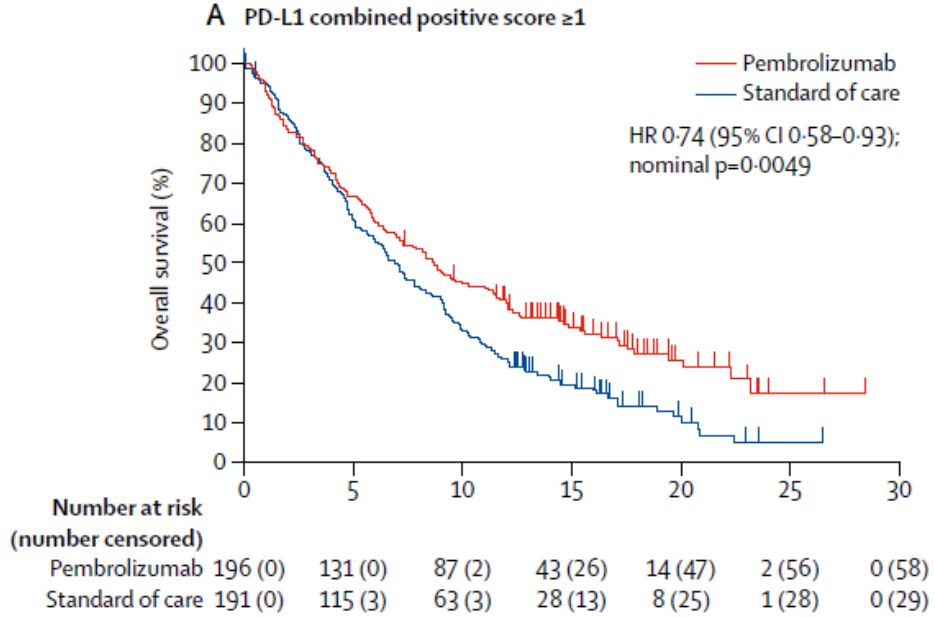
Ferris, NEJM 2016.

KEYNOTE-040: Pembrolizumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

Phase III Randomized, Safety and Efficacy Trial

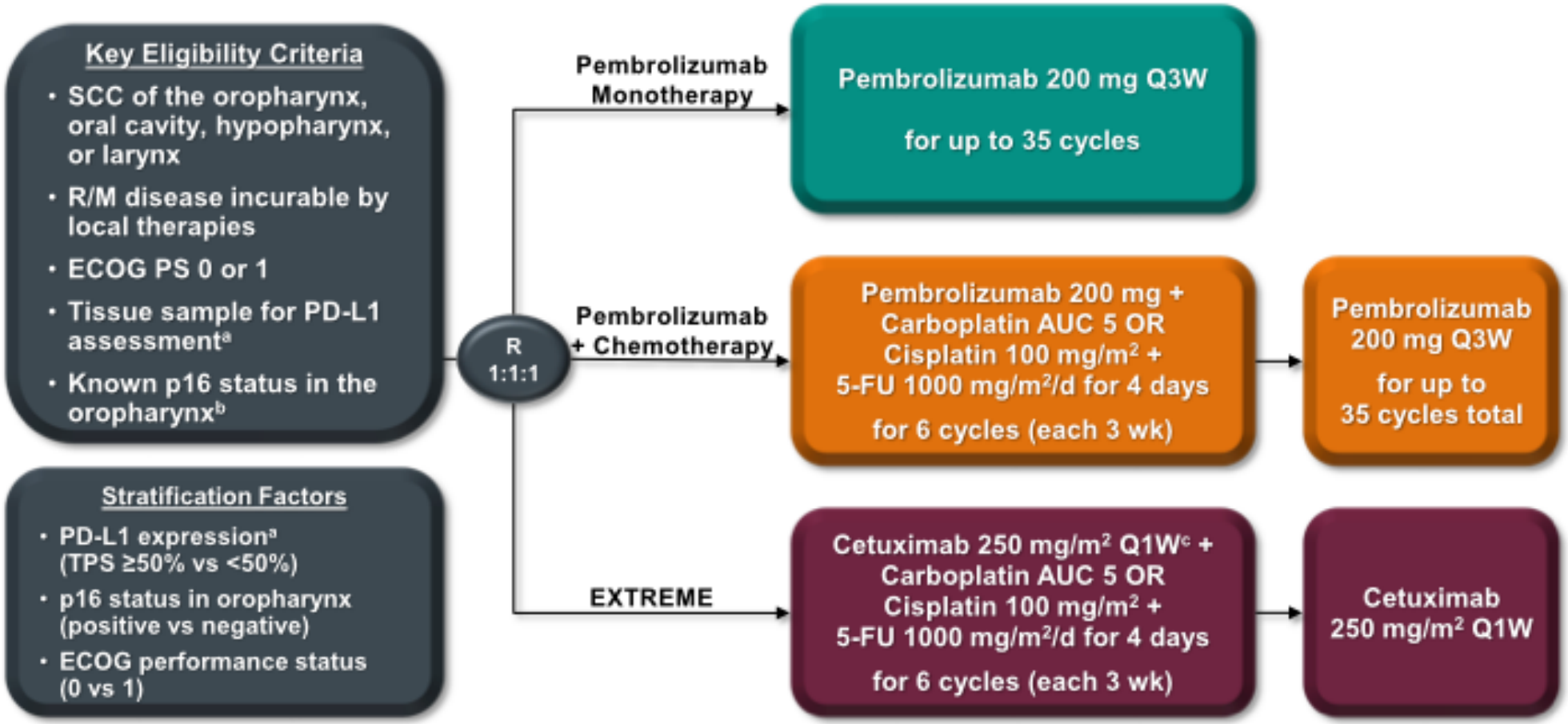
- mOS = 8.4 vs. 6.9 months
- 1y mOS: 37 vs. 26.5%
- mPFS = 2.1 vs. 2.3 months
- ORR = 14.6%





Cohen EEW, Lancet Oncol 2018.

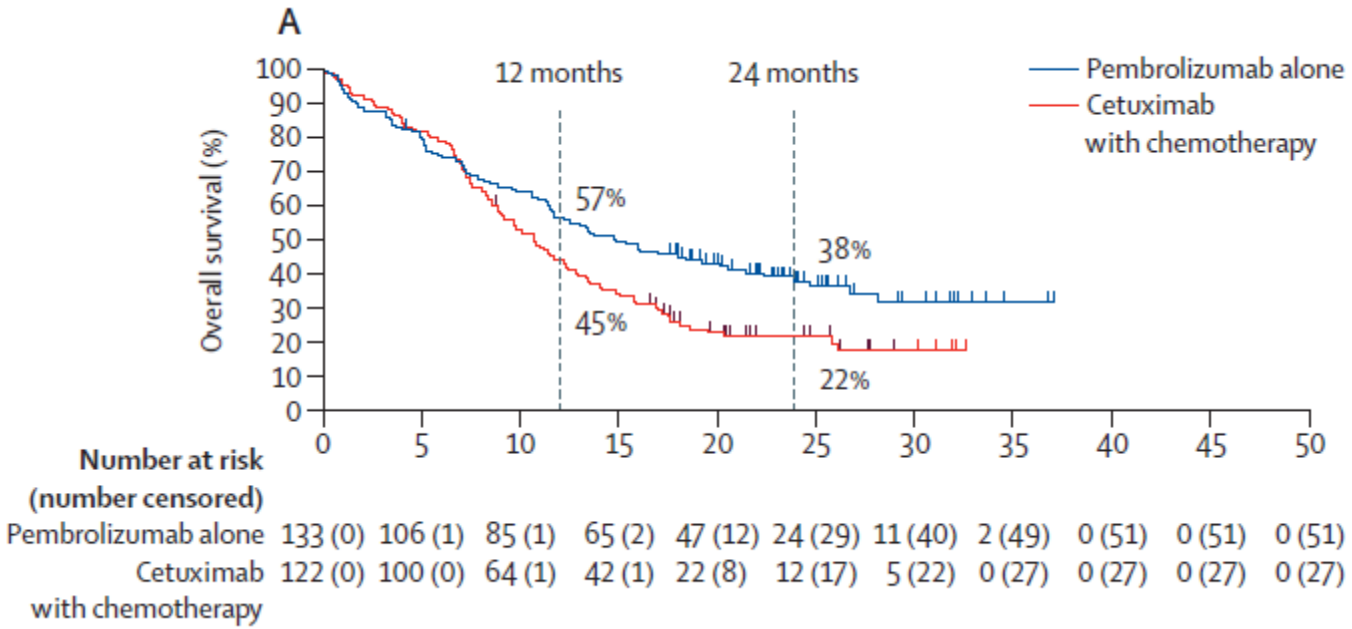
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC



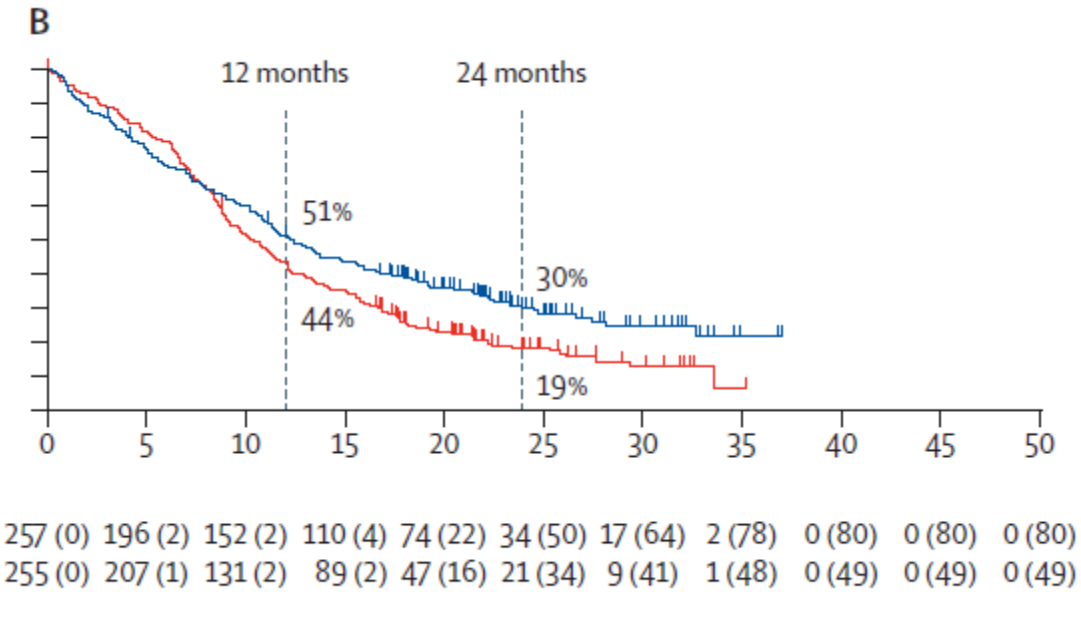
[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Burtness, Lancet 2020.

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



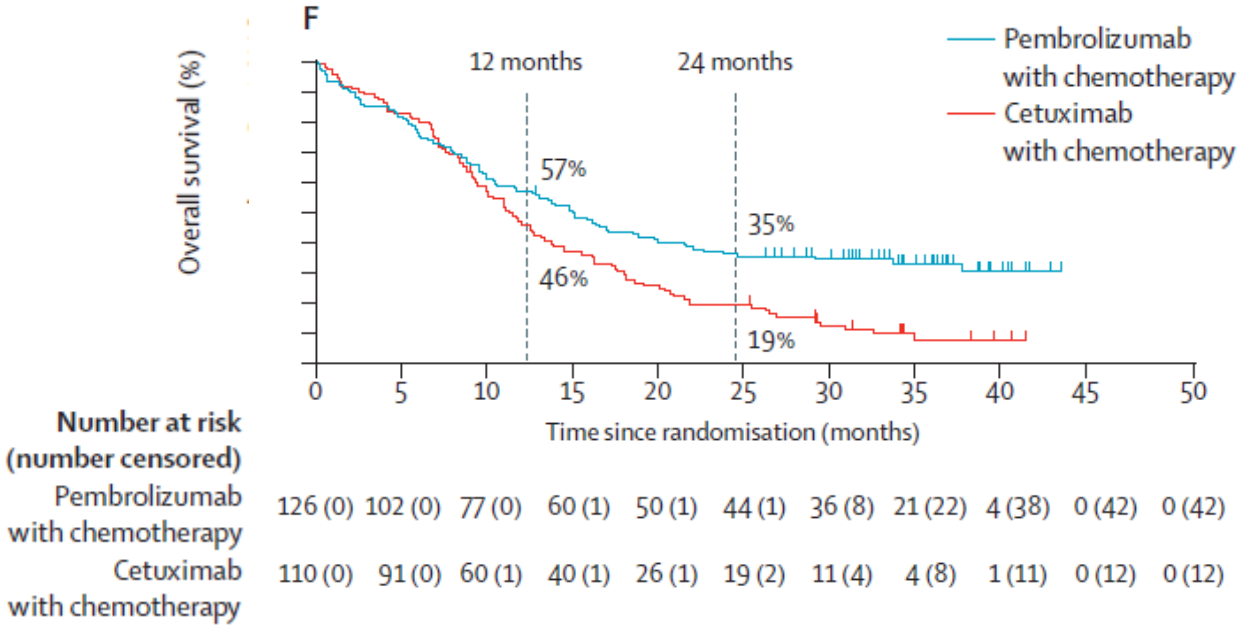
PD-L1 CPS 20+



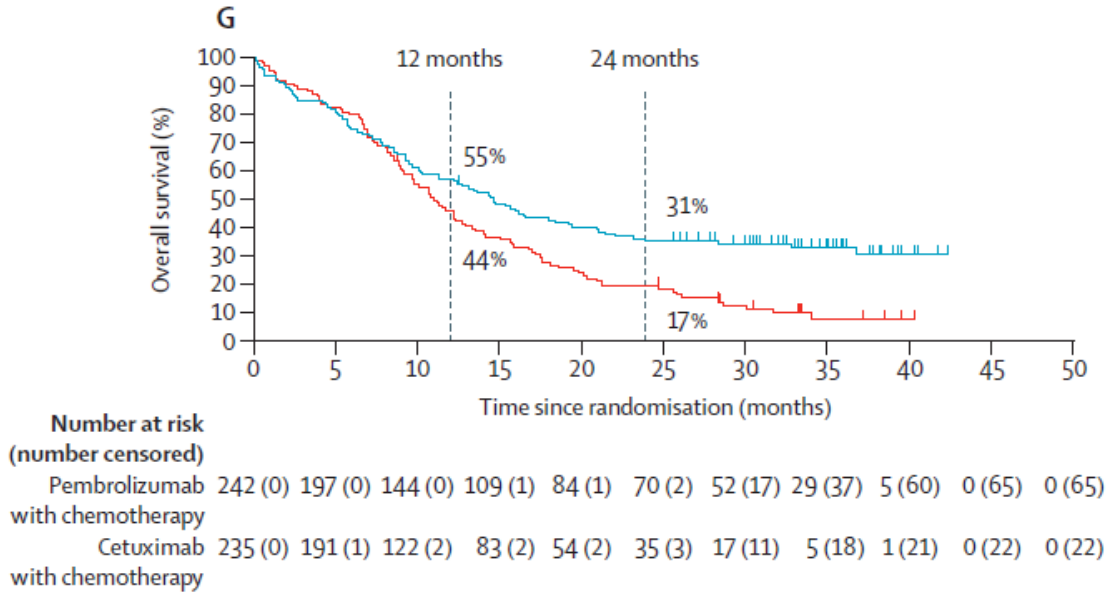
PD-L1 CPS 1+

Burtness, Lancet 2020.

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



PD-L1 CPS 20+



PD-L1 CPS 1+

Burtness, Lancet 2020.

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

Summary of Overall Survival

Population	IA2[1] HR (95% CI)	FA HR (95% CI)
Pembrolizumab monotherapy vs EXTREME		
PD-L1 CPS ≥20	0.61 (0.45–0.83); *P* = 0.0007[a]	0.58 (0.44–0.78)[c]
PD-L1 CPS ≥1	0.78 (0.64–0.96); *P* = 0.0086[a]	0.74 (0.61–0.90)[c]
Total	0.85 (0.71–1.03)[b]	0.83 (0.70–0.99); *P* = 0.0199[d]
Pembrolizumab + chemotherapy vs EXTREME		
PD-L1 CPS ≥20	—	0.60 (0.45–0.82); *P* = 0.0004[a]
PD-L1 CPS ≥1	—	0.65 (0.53–0.80); *P* < 0.0001[a]
Total	0.77 (0.63–0.93); *P* = 0.0034[a,b]	0.72 (0.60–0.87)[c]

Approved for CPS 1+

Approved for all

[a]Superiority demonstrated. [b]Noninferiority demonstrated (boundary of 1.2). [c]No statistical testing performed. [d]Superiority not demonstrated.

1. Burtness B et al. *Ann Oncol* 2018;29(suppl 8):LBA8_PR.

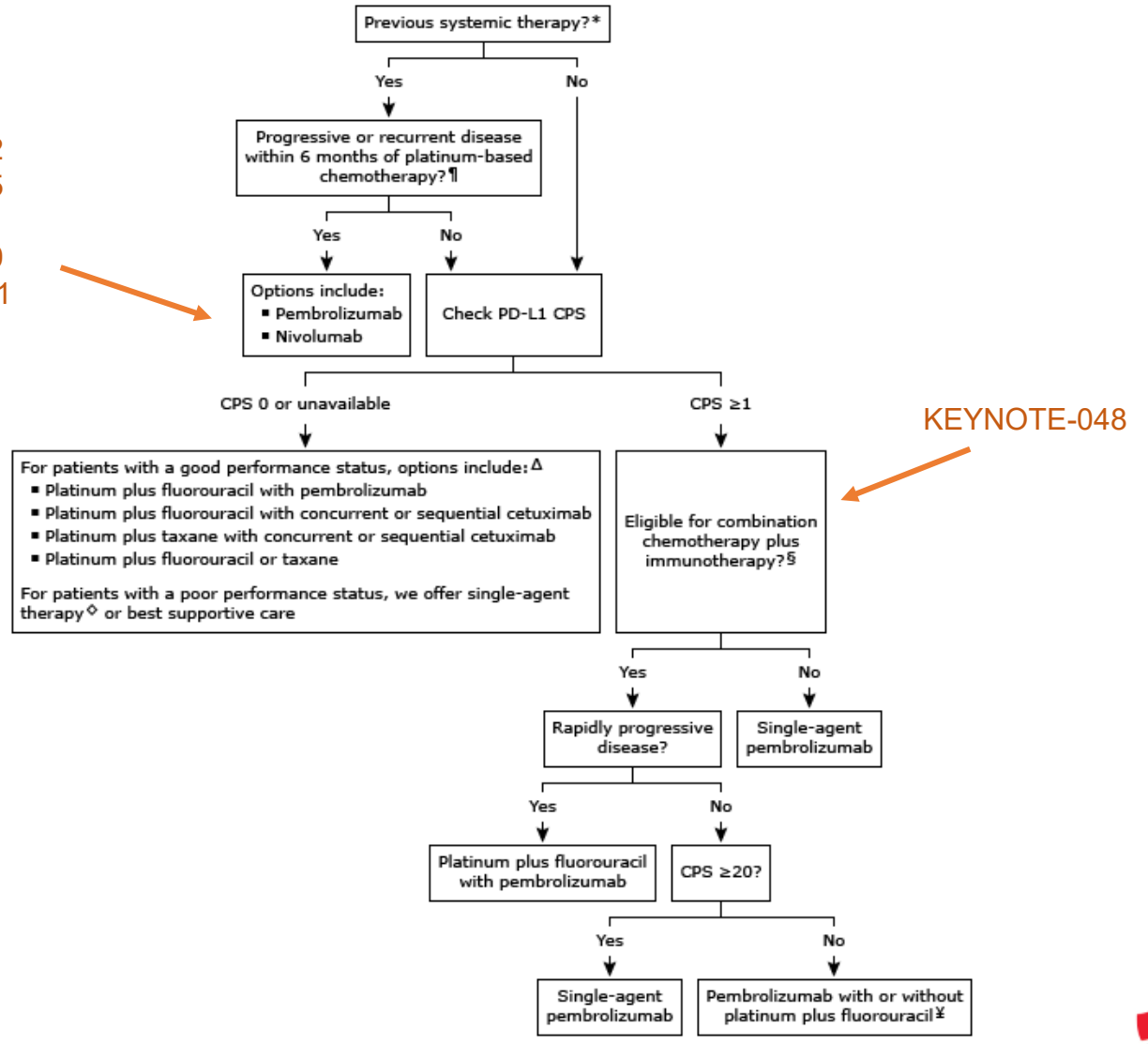
Burtness, Lancet 2020.

Immunotherapy for R/M HNSCC

KEYNOTE-012
KEYNOTE-055

KEYNOTE-040
Checkmate-141

KEYNOTE-048



Up To Date, 2020.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

Key Eligibility Criteria
- Advanced cutaneous squamous-cell carcinoma (any site)
- Locally advanced disease not eligible for surgery, or metastatic
- ECOG 0-1
- ≥1 assessable lesion

→

Cemiplimab
3 mg/kg IV Q2W

→

Primary endpoint
- Response rate

Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

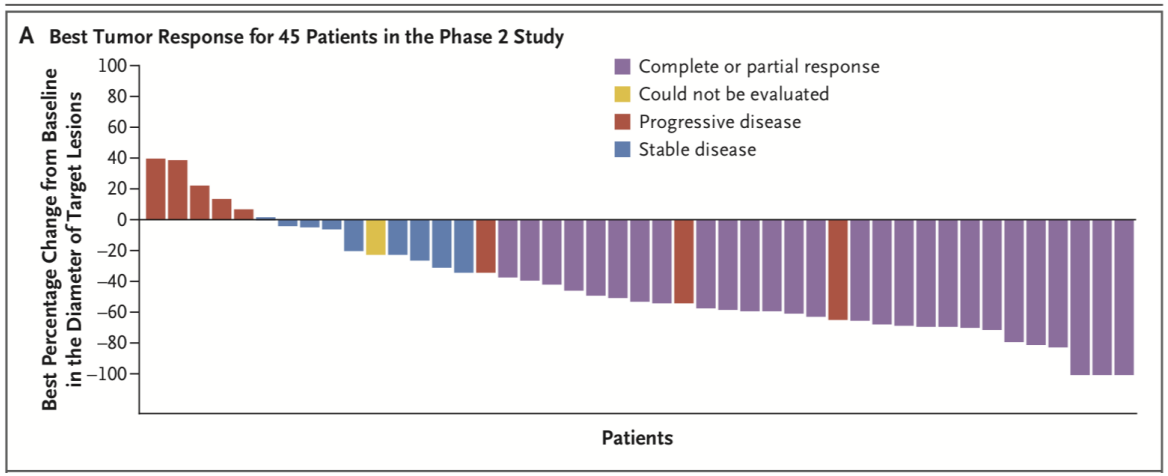
Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

ORR = 47-50%

CR = 7%, PR = 13-24%

mOS not reached (1y OS: 81%)

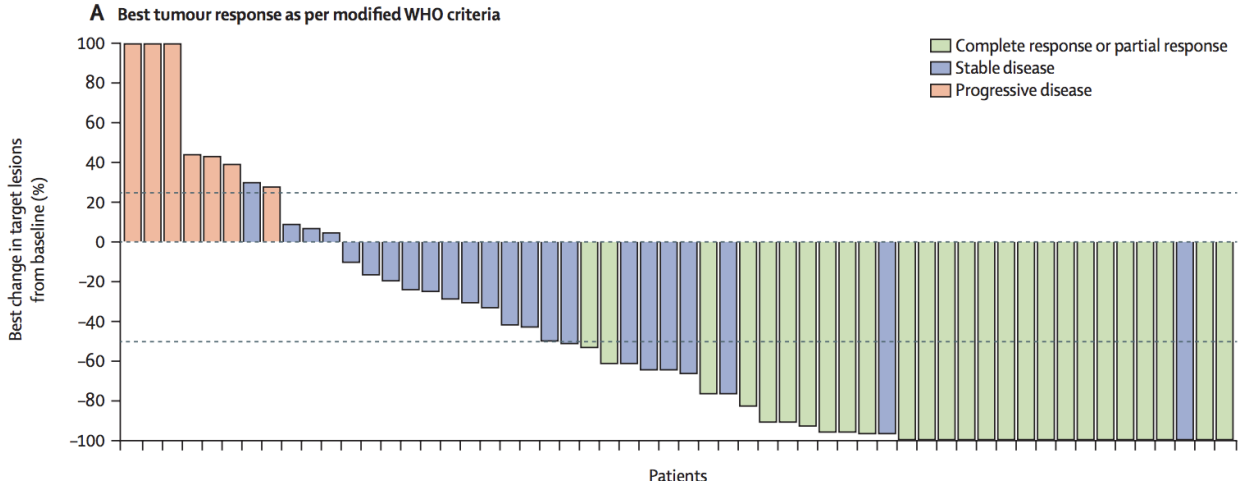


Metastatic>locally advanced

ORR = 34%

CR = 13%, PR = 24%

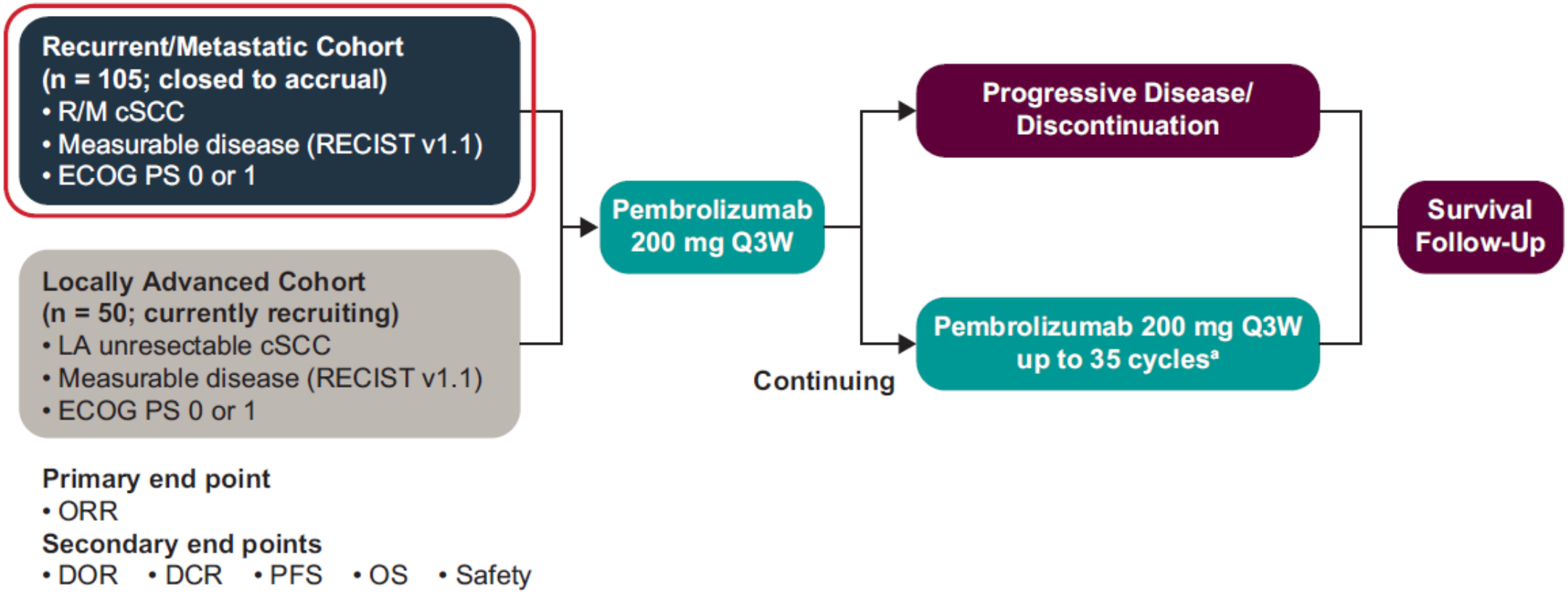
mOS not reached



Locally advanced>metastatic

Migden, NEJM 2018 and Lancet Oncol 2020.

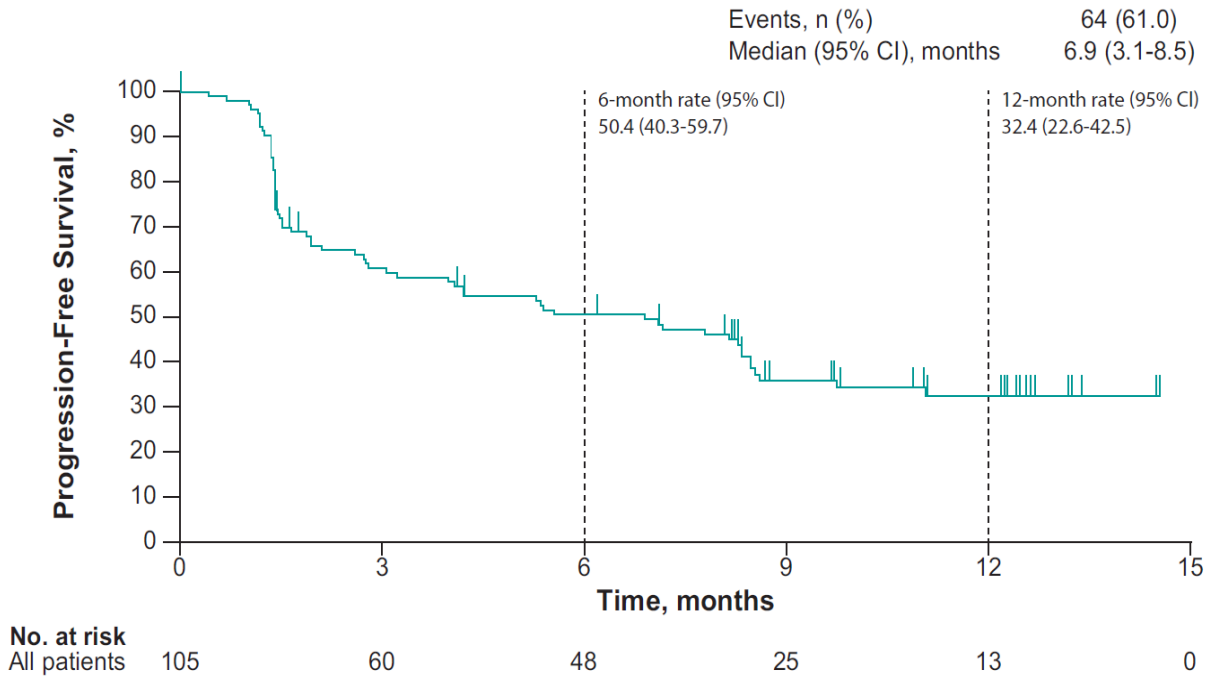
KEYNOTE-629: Pembrolizumab in advanced/metastatic cSCC



Grob, ASCO 2019.

KEYNOTE-629: Pembrolizumab in advanced/metastatic cSCC

	Total n = 105	First Line n = 14	Second Line and Beyond n = 91
Objective response rate, % (95% CI)[a]	34.3 (25-44)	50.0 (23-77)	31.9 (23-43)
Disease control rate, % (95% CI)[b]	52.4 (42-62)	64.3 (35-87)	50.5 (40-61)
Best overall response, n (%)			
Complete response	4 (3.8)	2 (14.3)	2 (2.2)
Partial response	32 (30.5)	5 (35.7)	27 (29.7)
Stable disease	31 (29.5)	3 (21.4)	28 (30.8)
Stable disease ≥12 weeks	19 (18.1)	2 (14.3)	17 (18.7)
Progressive disease	28 (26.7)	4 (28.6)	24 (26.4)
Not evaluable[c]	2 (1.9)	0	2 (2.2)
Not assessed[d]	8 (7.6)	0	8 (8.8)



Similar results to cemiplimab trials

Grob, ASCO 2019.

Evaluating Biomarkers in HNSCC

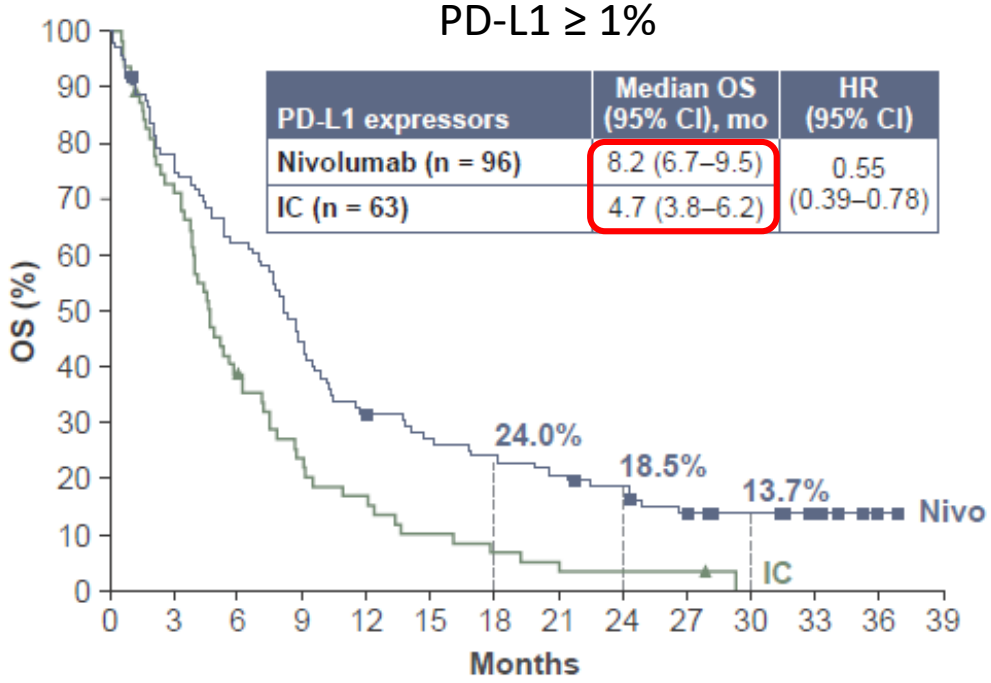
- **Only** indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)

- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate-141: Most benefit seen in PD-L1 positive tumors
  - KEYNOTE-040: improved outcomes in PD-L1-expressors

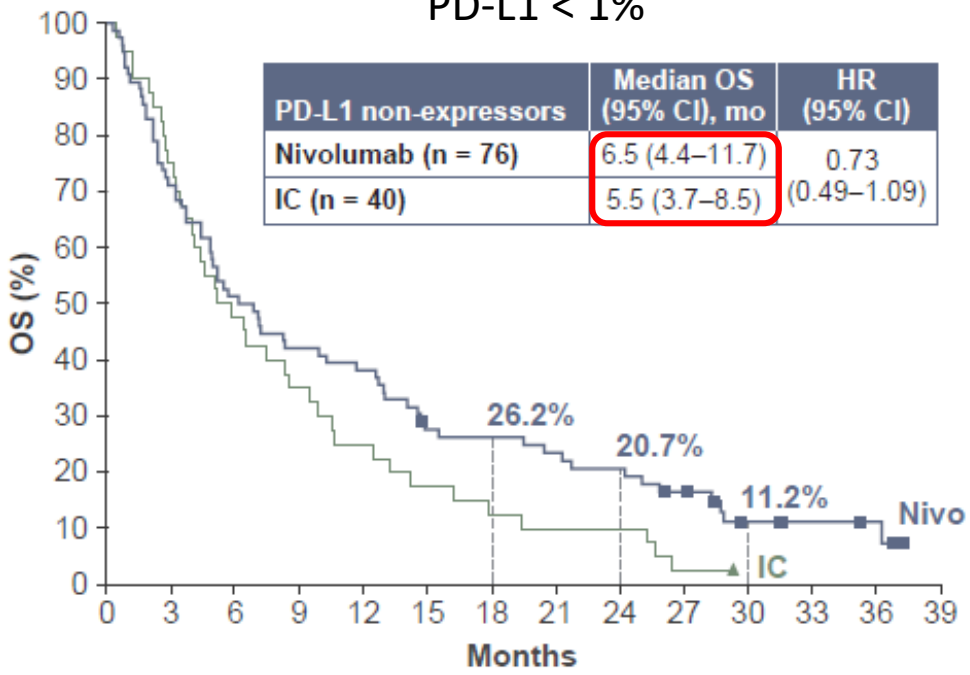
Evaluating Biomarkers in HNSCC

CheckMate-141: 2 year update

PD-L1 ≥ 1%

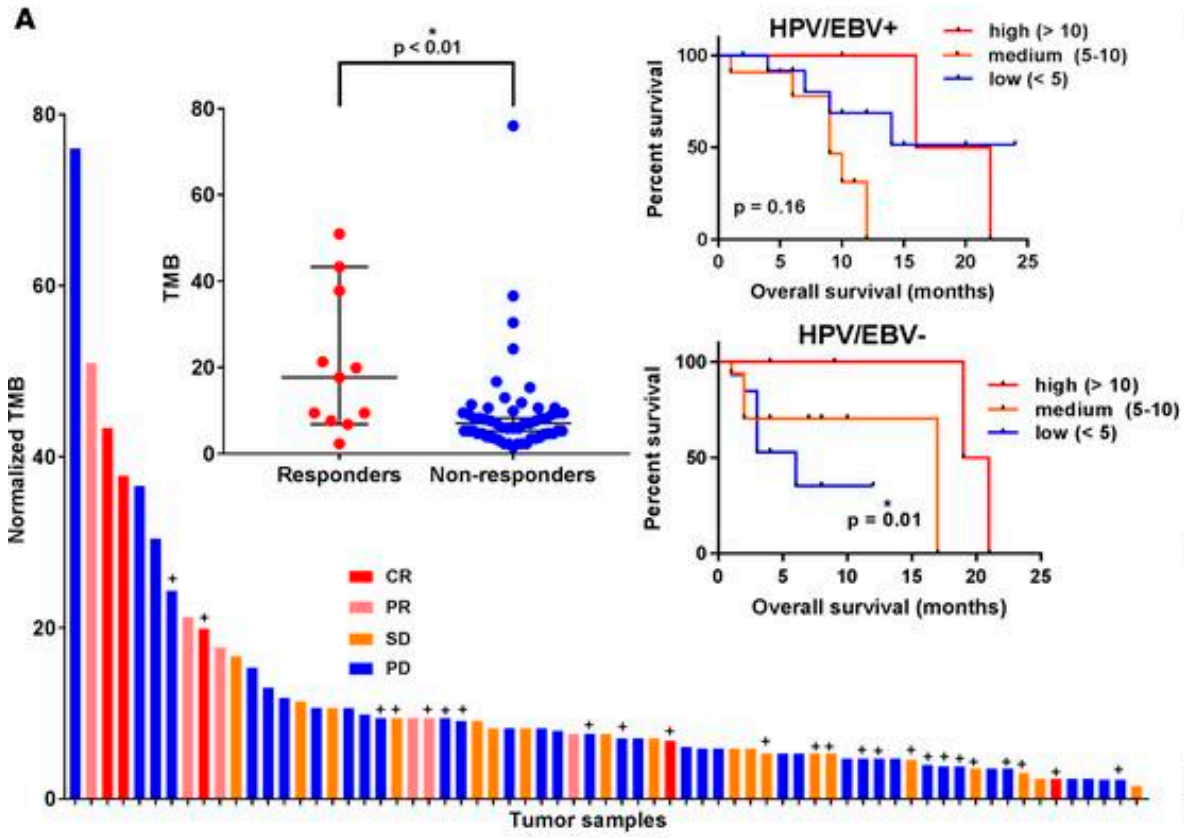


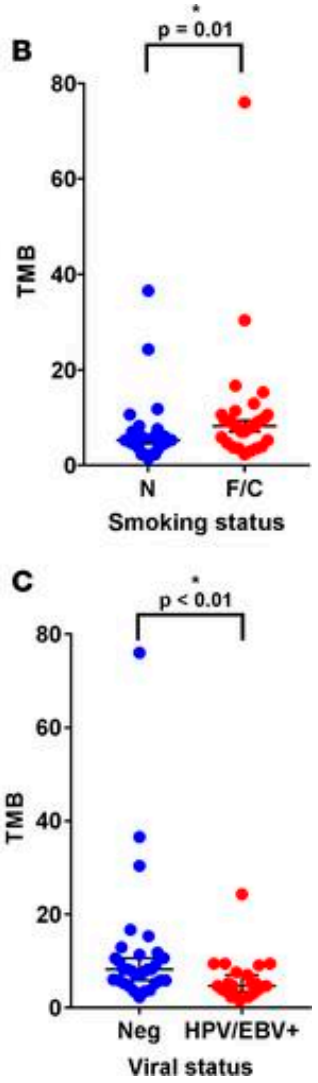
PD-L1 < 1%

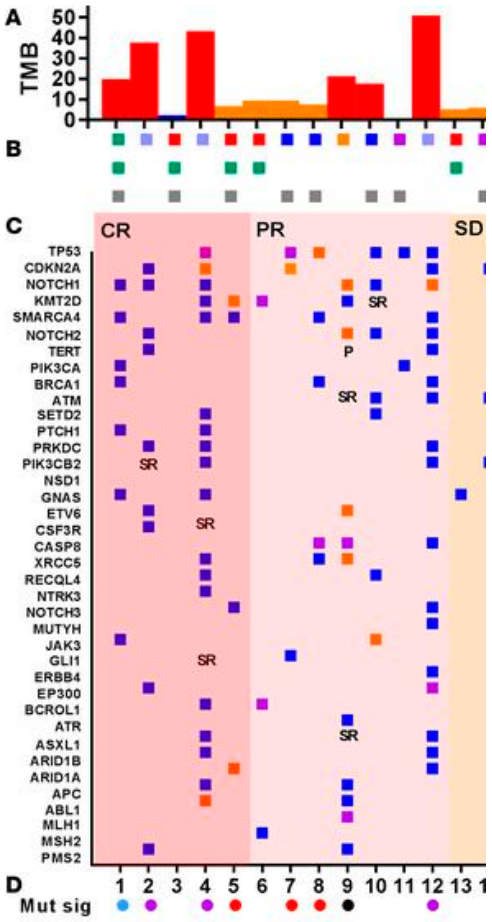


Ferris, Oral Oncol 2018.

Evaluating Biomarkers in HNSCC

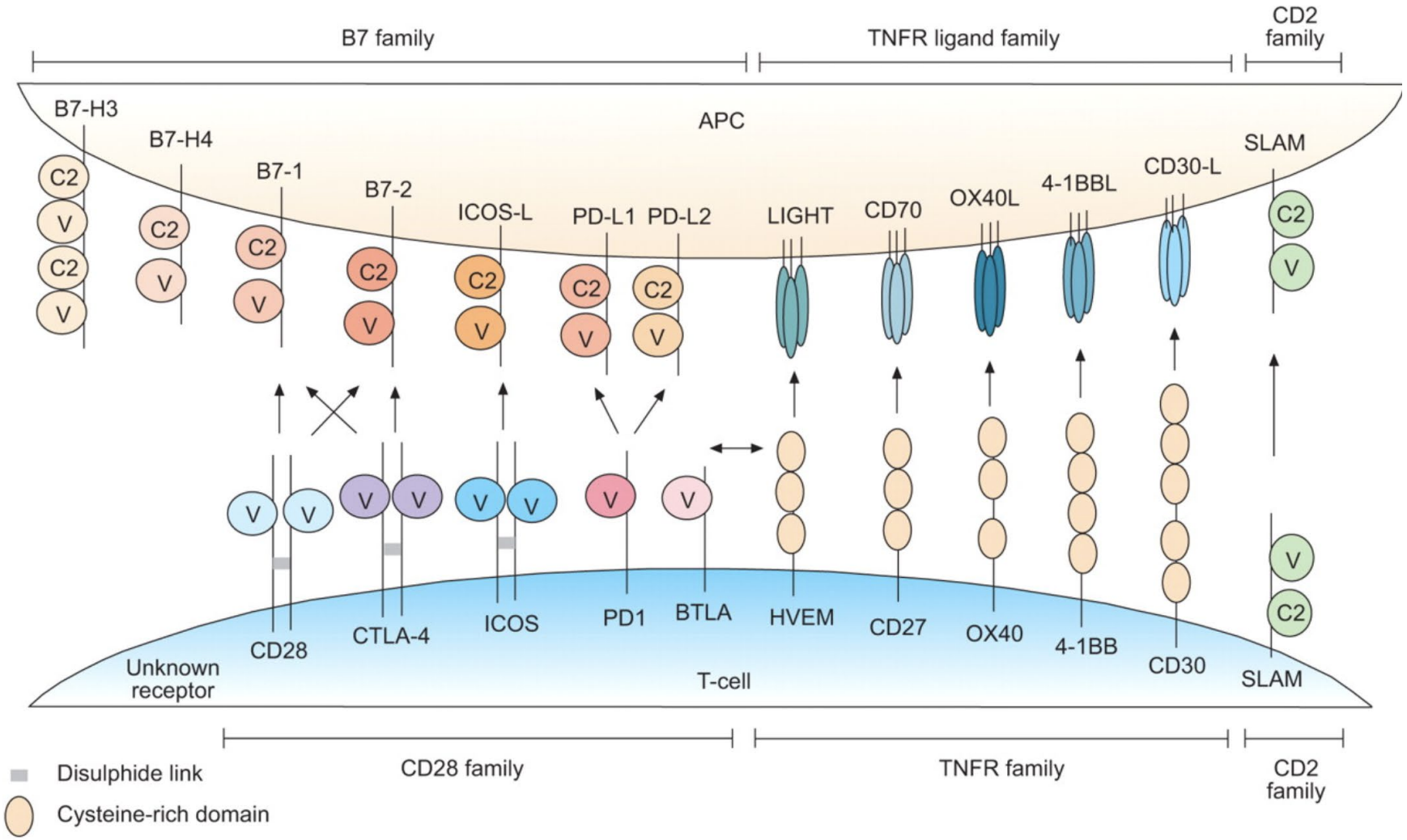






Hanna, JCI Insight 2018.

On the horizon…



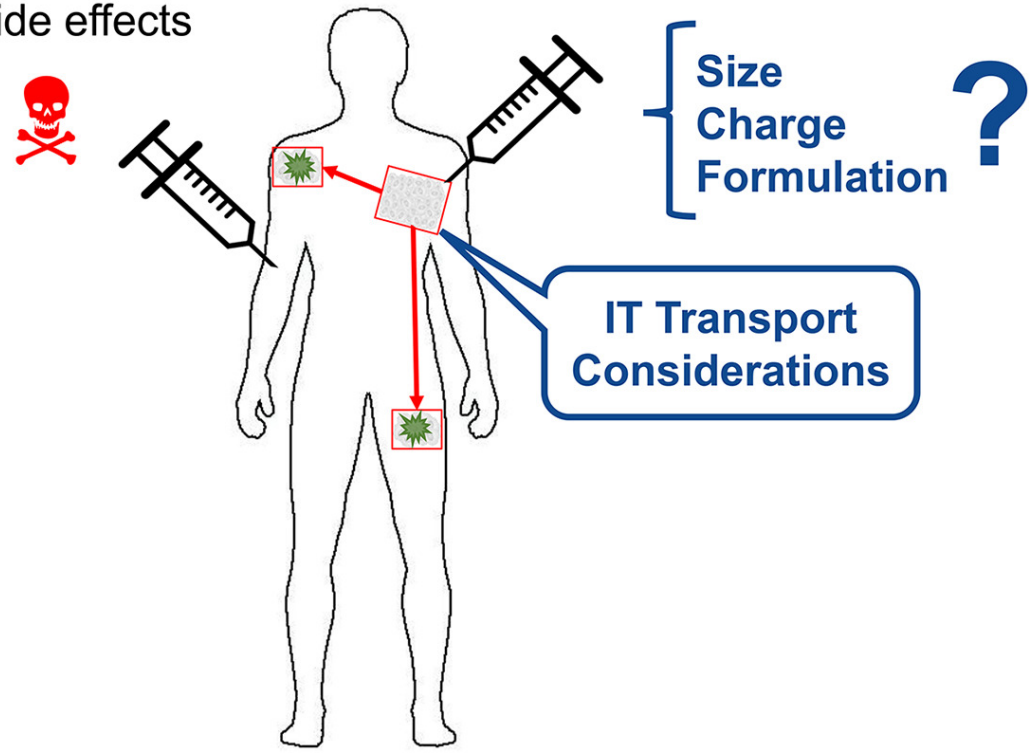
Combinations with newer immune checkpoint inhibitors

Beier, Eur Resp J 2007.

On the horizon…

Intratumoral (IT)
↓ Side effects
↓ Dose required
↑ T-cell priming for antitumor immune response

Systemic delivery
↑ Side effects

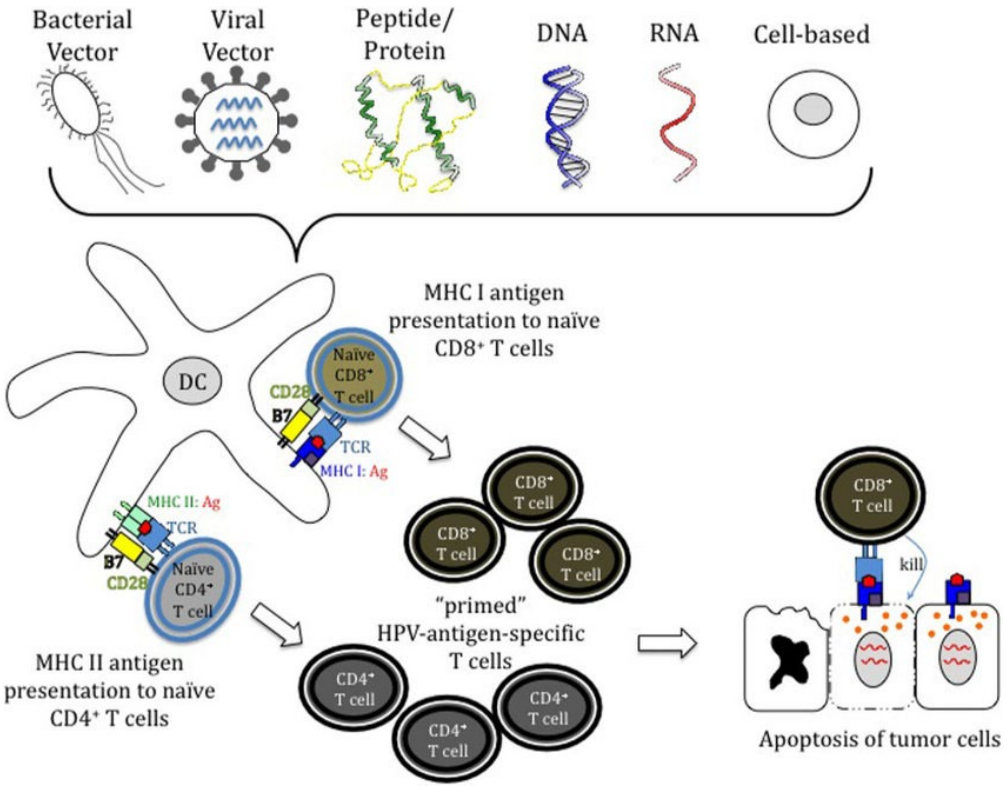


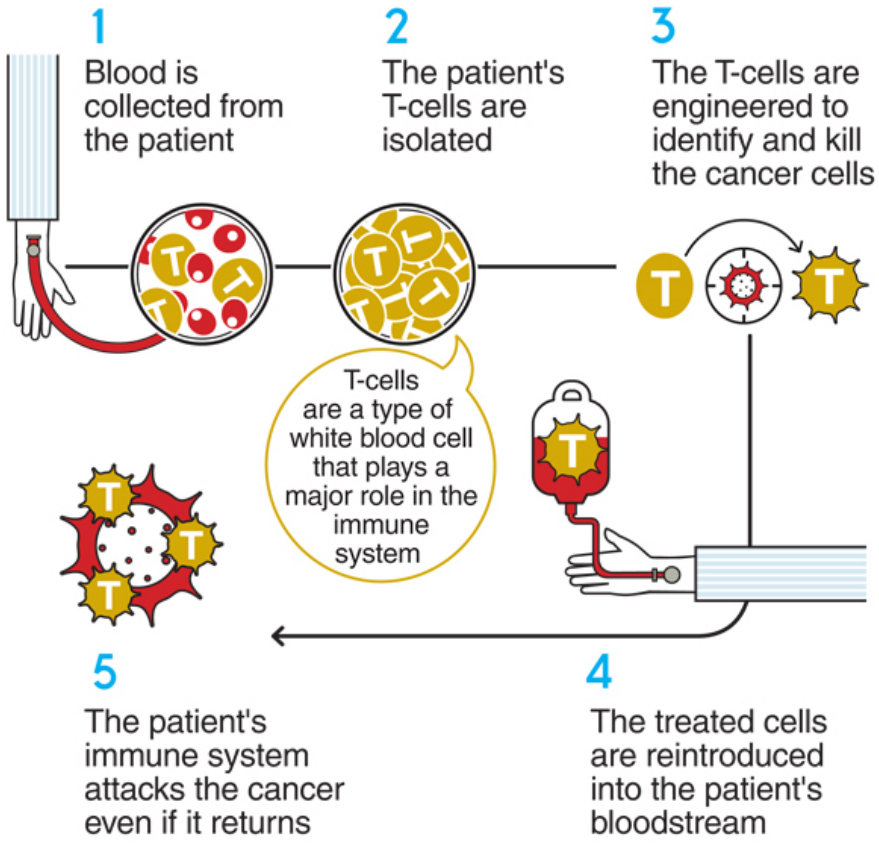
Intratumoral injectables to stimulate a local cytokine response

Huang, J Con Rel 2020.

On the horizon…

Therapeutic vaccines or cell-based therapies aimed at HPV in particular





Lin, J Formos Med Assoc 2010. Gilead/Kite 2020.

Conclusions

- Cytotoxic chemotherapy achieves limited survival with unfavorable side effects.
- Checkpoint inhibitors that target the PD-1 axis, nivolumab and pembrolizumab, are approved in platinum-refractory/exposed and 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, development of predictive biomarkers and approaches to overcoming resistance.

Resources

Cohen *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:184
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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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ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

Case Study 1

55M (former smoker) diagnosed in December 2017 with locoregionally advanced, HPV+ SCC arising from the right tonsil

Staging: cT3N2M0 (**stage II**, AJCC 2017 8th ed)

He received definitive concurrent chemoradiation with bolus cisplatin (35/35 fractions to 70 Gy involving the oropharynx and bilateral necks, 3-cycles cisplatin 100 mg/m^2)

Completed all therapy March 2018

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Completed all therapy March 2018

Clinical evidence of chest wall soft tissue nodule with biopsy-proven HPV+ **metastatic recurrence in August 2019**

NPL shows local recurrence in the right larynx and scans clarify mediastinal adenopathy

Case Study 1

55M (former smoker) with R/M HPV+ SCC arising from the right tonsil. Completed cisplatin-RT in March 2018, with local and distant recurrence in August 2019

NPL shows local recurrence in the right larynx with no stridor but evolving dysphagia and dry cough

Therapeutic options?

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Therapeutic options:

- Clinical trial protocol?
- First-line chemoimmunotherapy (platinum + 5-FU + pembrolizumab) or pembrolizumab alone (CPS PD-L1 testing)?
- Platinum-based chemotherapy with cetuximab?

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Therapeutic options:

- Clinical trial protocol?
- **First-line chemoimmunotherapy (platinum + 5-FU + pembrolizumab) or pembrolizumab alone (CPS PD-L1 testing)?**
- Platinum-based chemotherapy with cetuximab?

Case Study 2

55M (never smoker) initially diagnosed with HPV+ SCC of the left base of tongue with ipsilateral level II/III cervical adenopathy in October 2016

Staging: cT4N1M0 (**stage III**, AJCC 2017 8th ed)

Treatment: definitive concurrent chemoradiation with weekly cisplatin ending February 2017

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Staging: cT4N1M0 (stage III, AJCC 2017 8th ed)

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Restaging: PET-CT in June 2017 shows local residual disease and new lung metastases

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55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

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Started nivolumab (3 mg/kg IV D1, 15) q28d **in July 2017**

Interval scan: in September 2017 his lung lesions had resolved and his local disease showed regression (partial response)

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Interval scan: in September 2017 his lung lesions had resolved and his local disease showed regression (partial response)

In **January 2018** he has new left neck pain and a PET-CT is obtained

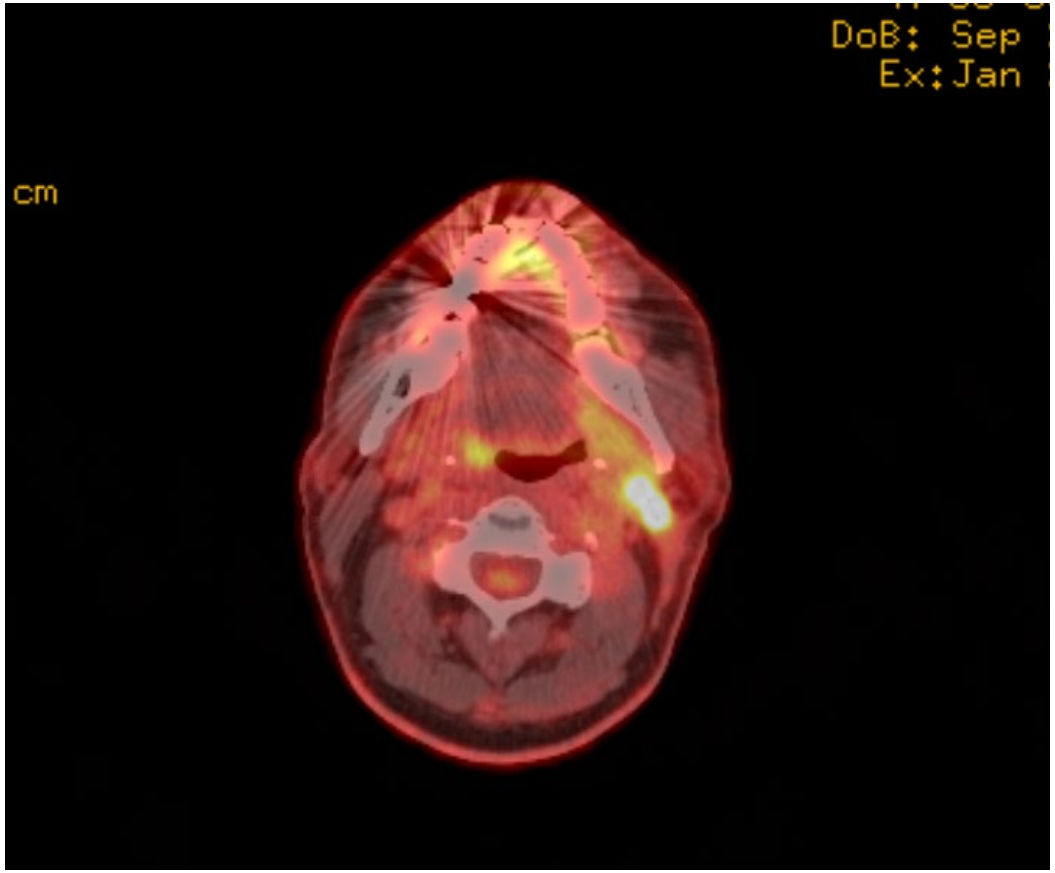
Case Study 2

What would be your best next step?

A. US-guided left neck biopsy

B. Discontinue PD-1 blockade and start second line chemotherapy or clinical trials

C. Consider palliative radiation



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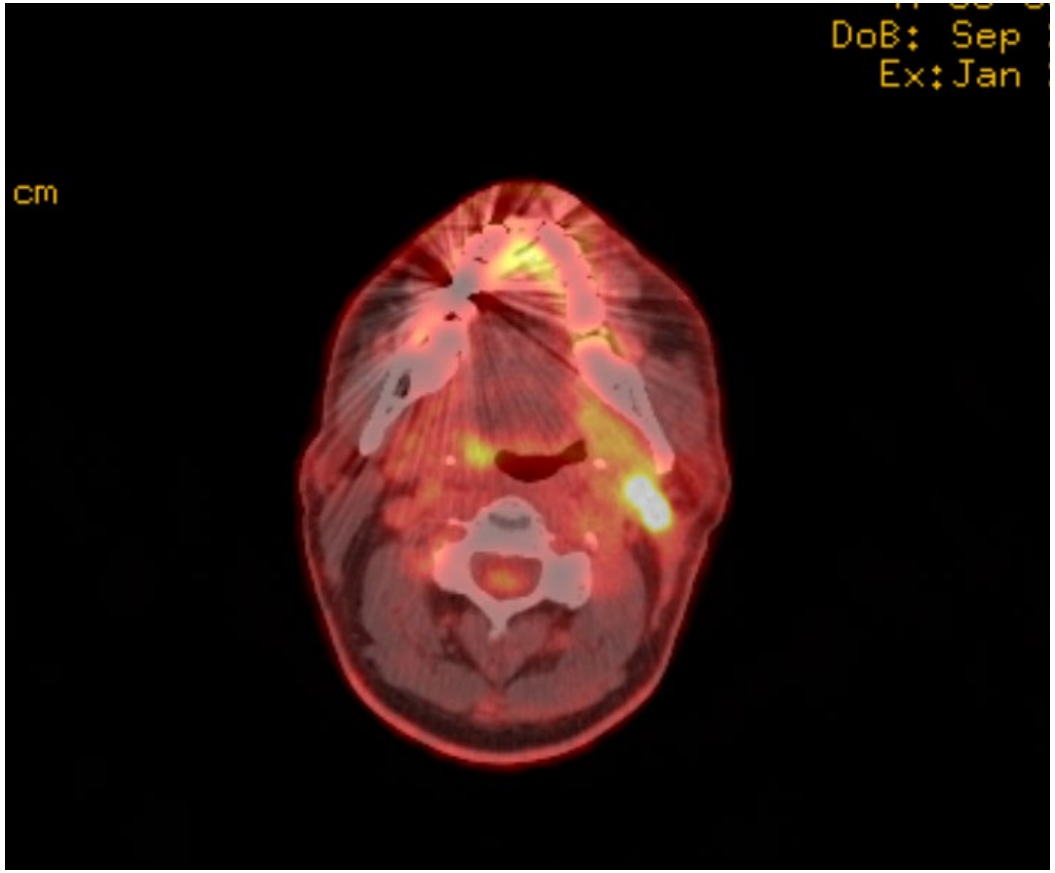
A. US-guided left neck biopsy

B. Discontinue PD-1 blockade and start second line chemotherapy or clinical trials

C. Consider palliative radiation

- Localized disease with slow progression
- Clear clinical benefit from PD-1i at distant site
- Would continue PD-1 blockade during or after SBRT or IMRT



Case Study 3

83M (never smoker) initially diagnosed with SCC of the left ventrolateral oral tongue

Staging: cT3N0M0 (stage III, AJCC 2017 8th ed)

Treatment: he declined surgery and radiation but had oral pain symptoms and elective for palliative therapies; started on pembrolizumab in **January 2019**

Case Study 3

83M (never smoker) initially diagnosed with SCC of the left ventrolateral oral tongue

Staging: cT3N0M0 (stage III, AJCC 2017 8th ed)

Treatment: he declined surgery and radiation but had oral pain symptoms and elective for palliative therapies; started on pembrolizumab in **January 2019**

Develops a clinical response after one dose but then has two episodes of PD-1 induced colitis requiring steroid tapers

Pembrolizumab discontinued in **May 2019**

Case Study 3

83M (never smoker) initially diagnosed with SCC of the left ventrolateral oral tongue

Staging: cT3N0M0 (stage III, AJCC 2017 8th ed)

Treated with pembrolizumab in January to **May 2019**. Develops a clinical response after one dose but then has two episodes of PD-1 induced colitis requiring steroid tapers

Event: in **August 2019** calls with mucositis, oral pain with difficulty swallowing, skin rash…

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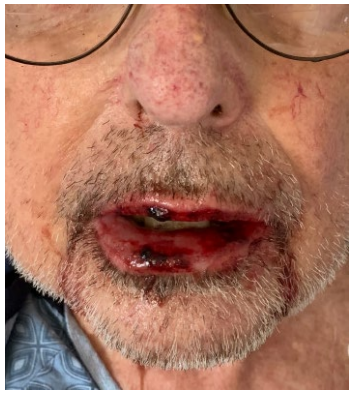

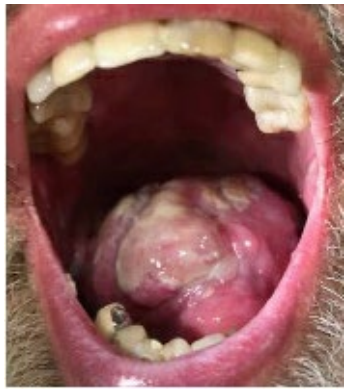

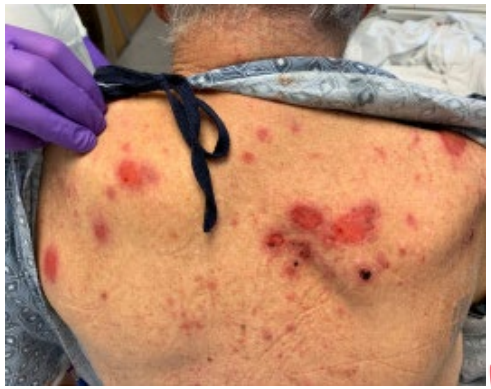

Case Study 3

Pembrolizumab or **PD-1 induced SJS-like reaction or erythema multiforme**

Treatment:

- Urgent dermatologic consultation with biopsy

  negative for immunofluorescence studies (IgA, IgG, IgM, C3, fibrinogen)

- High-dose IV corticosteroids
- Topical immunosuppression to skin and lips
- Oral rinses for pain control; nutritional support
- Permanent PD-1 inhibitor discontinuation