sitc 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

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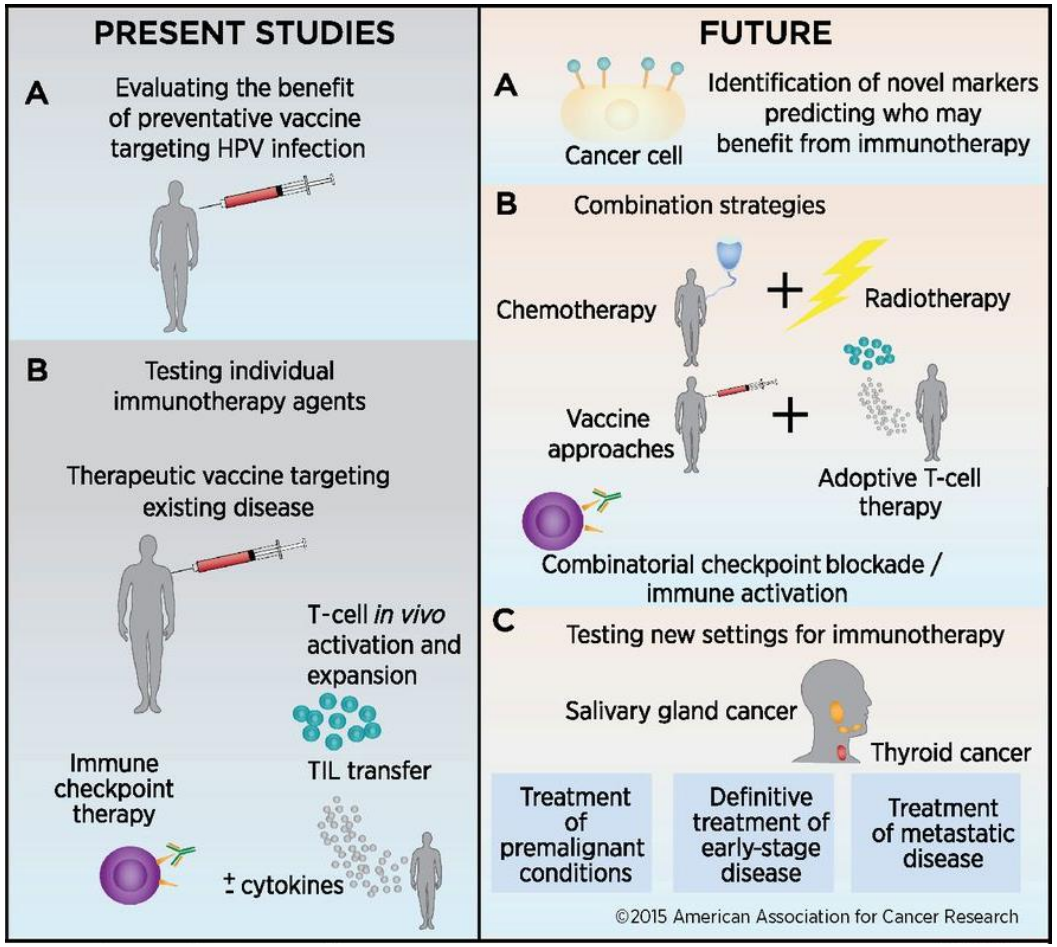
Disclosures

- Consulting Fees:
  - Regeneron, Sanofi, BMS, Maverick, Merck, Kura
- Contracted Research:
  - BMS, Exicure, GSK, Altor BioScience, Kite, Regeneron, Sanofi, Kartos, ASCO/CCF, V Foundation
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Head and Neck Cancers

- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Expression of immunologic markers to guide treatment
  - Preventive vaccination against virally mediated cancers
  - Therapeutic vaccines for established cancers
  - CAR-T and cell-mediated therapies
  - Combinations with immunotherapies



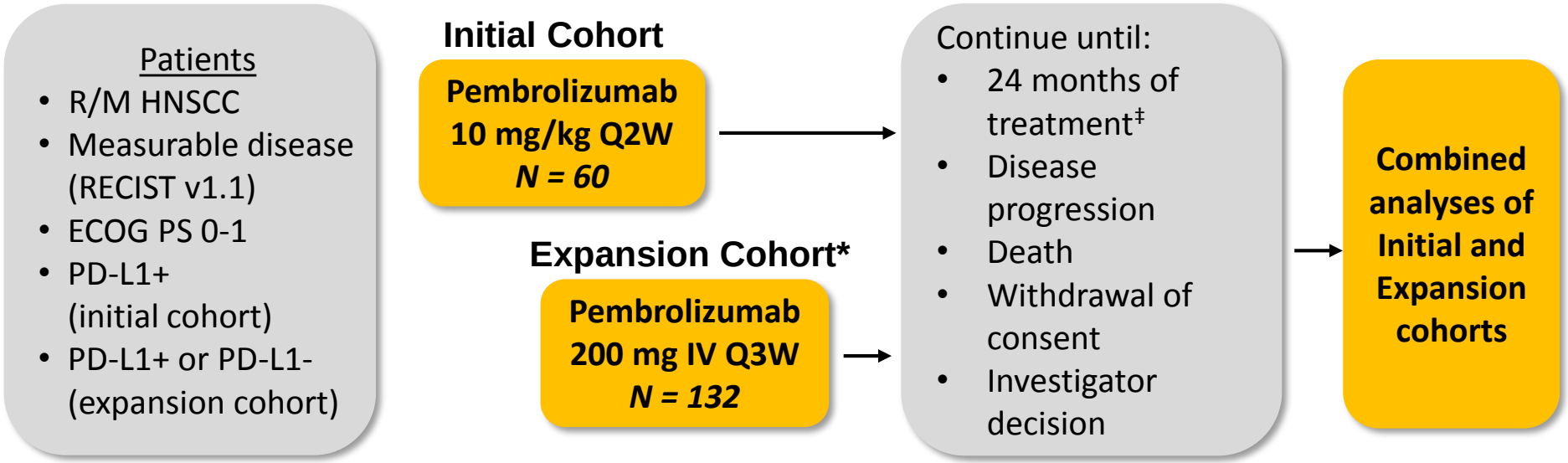
Schoenfeld, Cancer Immunol Res, 2015

Approved checkpoint inhibitors in Head and Neck Cancers

Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Cemiplimab-rwlc	2018	Metastatic cutaneous squamous cell carcinoma, 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	2019	Recurrent locally advanced/metastatic squamous cell carcinoma of esophagus (PD-L1 CPS ≥ 10)	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 §

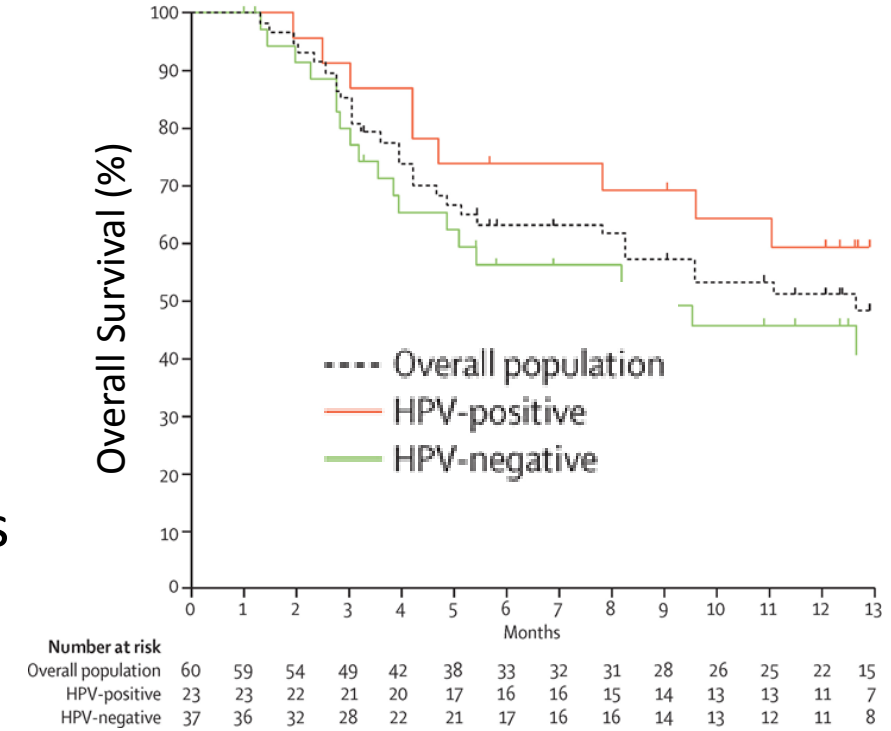
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

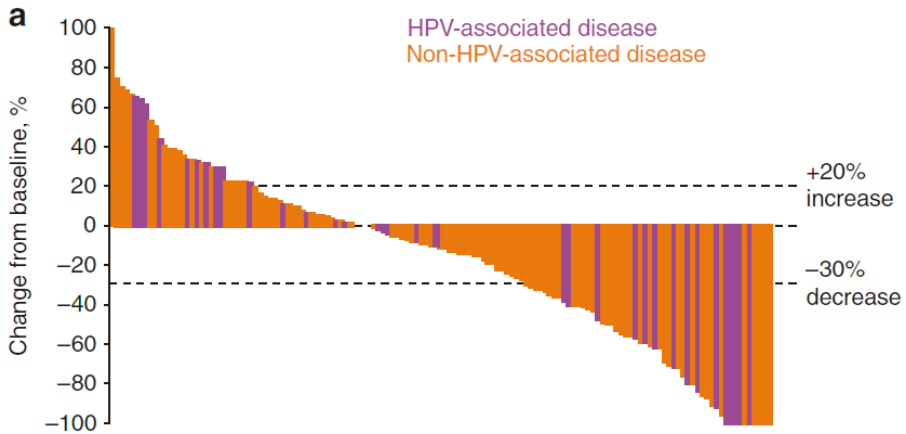
Seiwert, ASCO 2017.

KEYNOTE-012: Pembrolizumab in R/M HNSCC

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

- ORR = 18%
  - CR = 4%
  - PR = 14%
- mOS = 8.0 months
- mPFS = 2.1 months

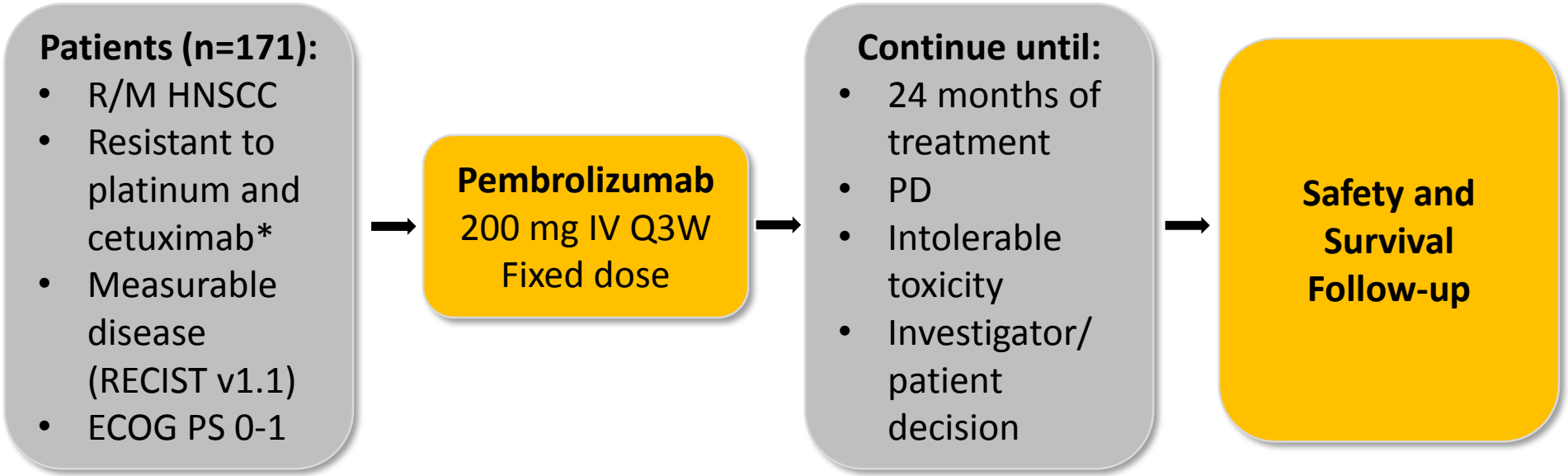




Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

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

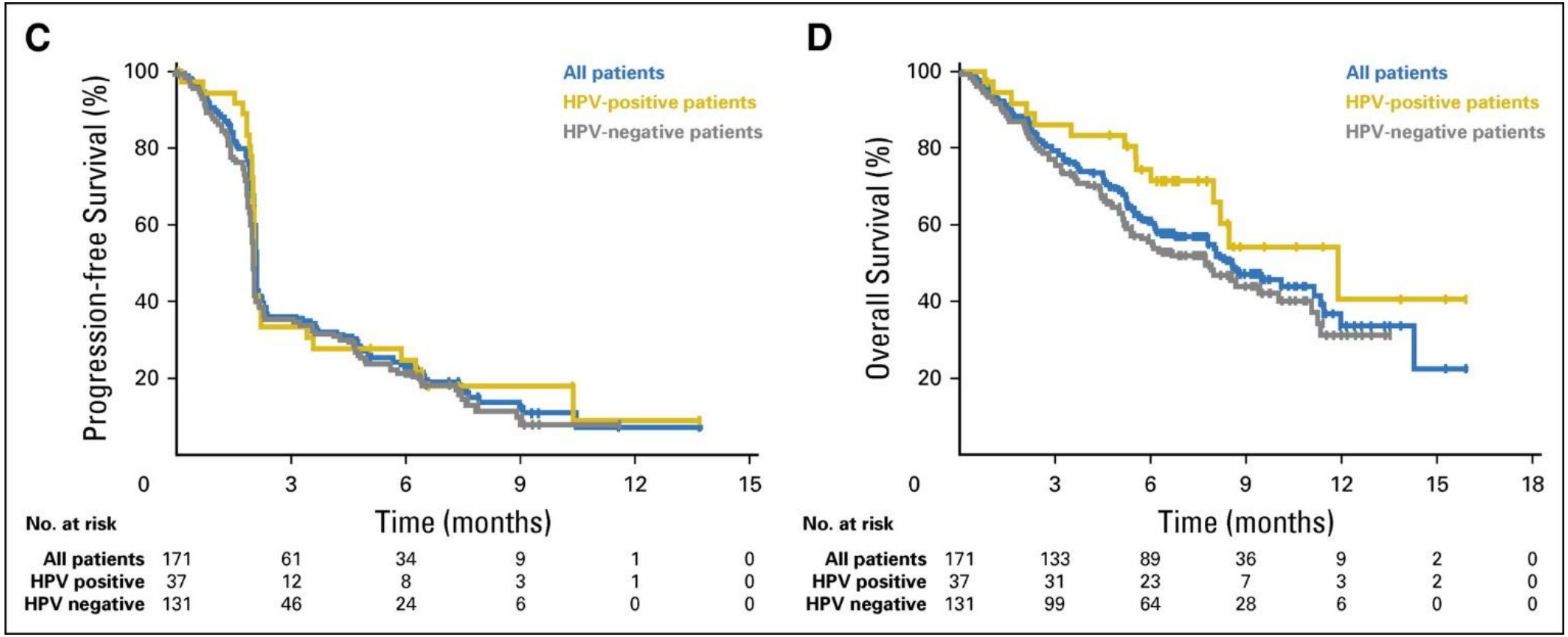
Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*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

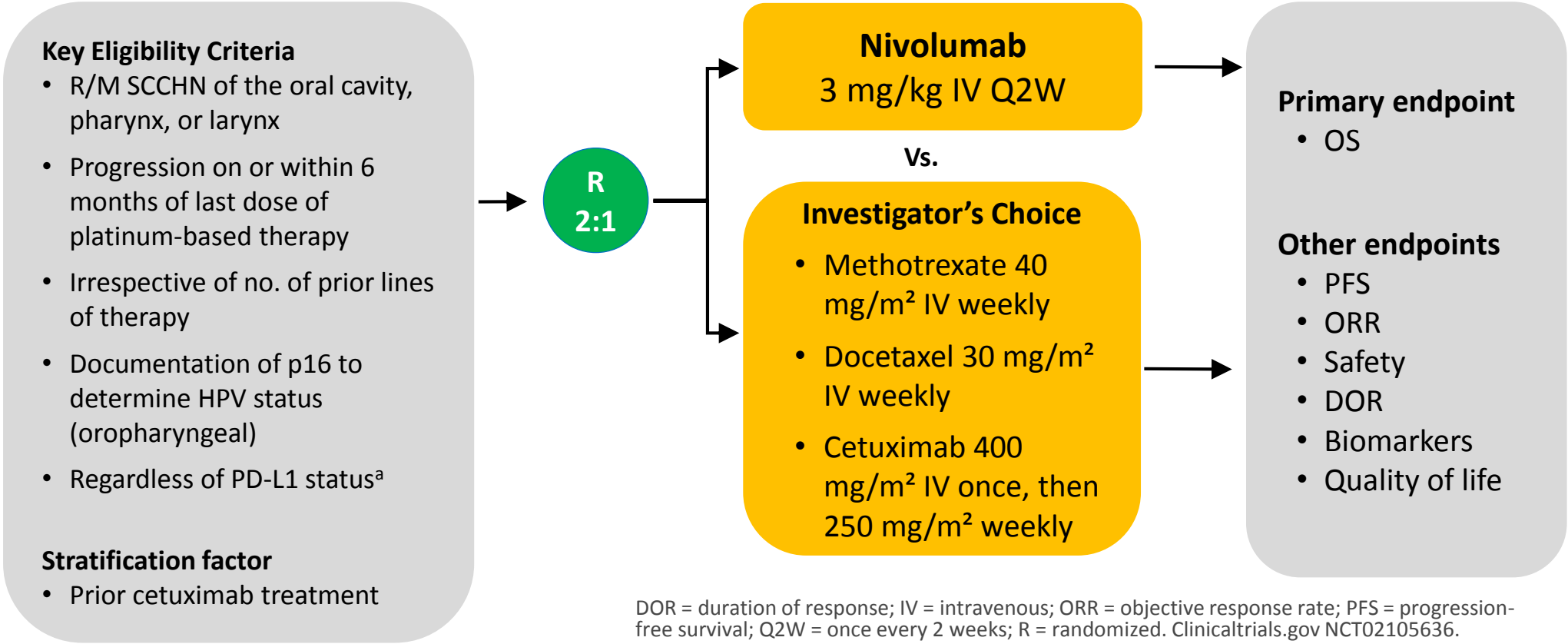
Phase II Trial, Single Arm



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



DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

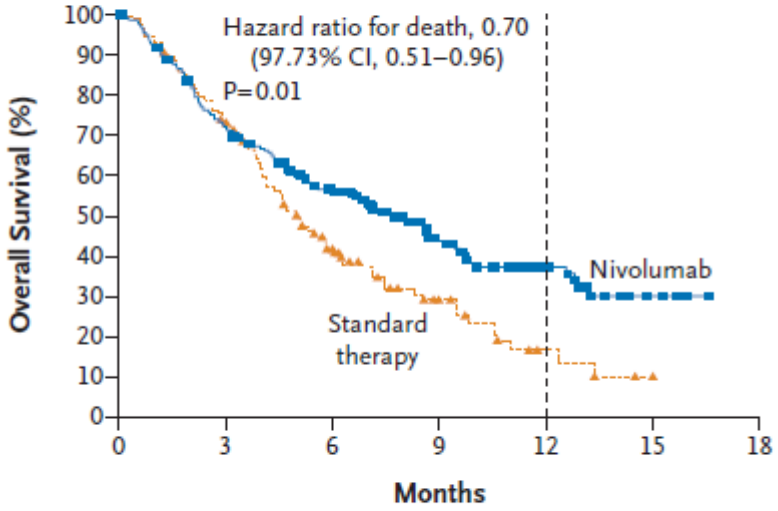
[a]Tissue required for testing

Ferris & Gillison, NEJM 2016.

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

A Overall Survival

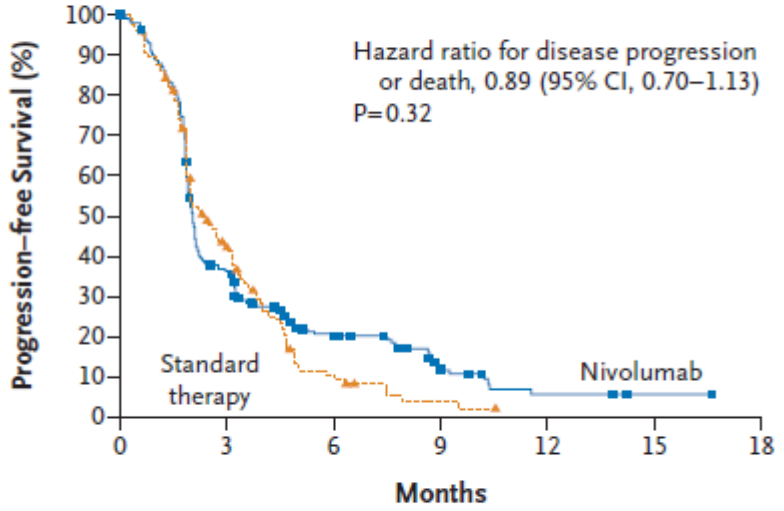
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



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

B Progression-free Survival

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Nivolumab	240	190	2.0 (1.9–2.1)
Standard Therapy	121	103	2.3 (1.9–3.1)



No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Standard therapy	121	43	9	2	0	0	0

Ferris & Gillison, NEJM 2016.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

Key Eligibility Criteria
- Advanced cutaneous squamous-cell carcinoma (any site)
- Not eligible for surgery
- ECOG 0-1
- ≥1 assessable lesion

→

Cemiplimab
3 mg/kg IV Q2W

→

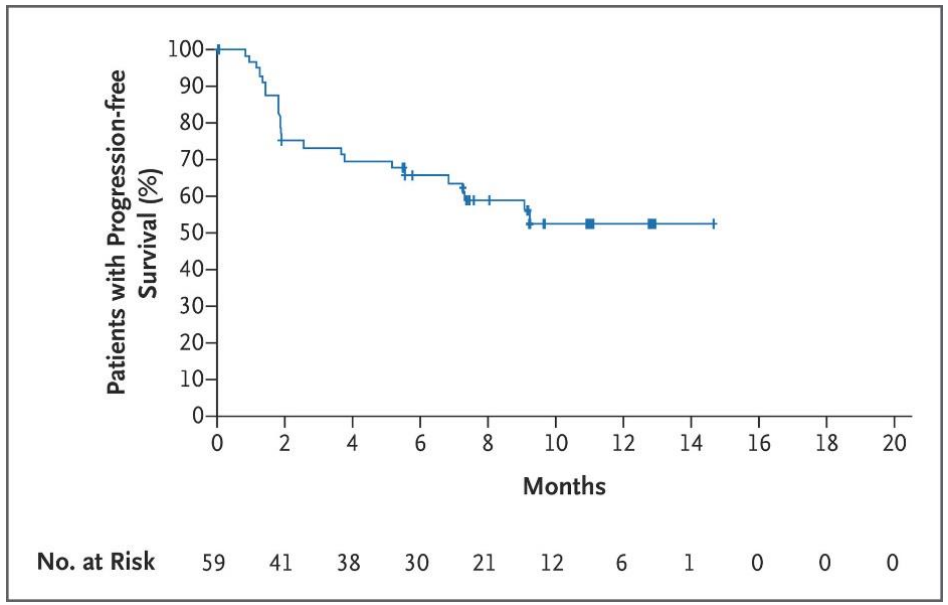
Primary endpoint
- Response rate

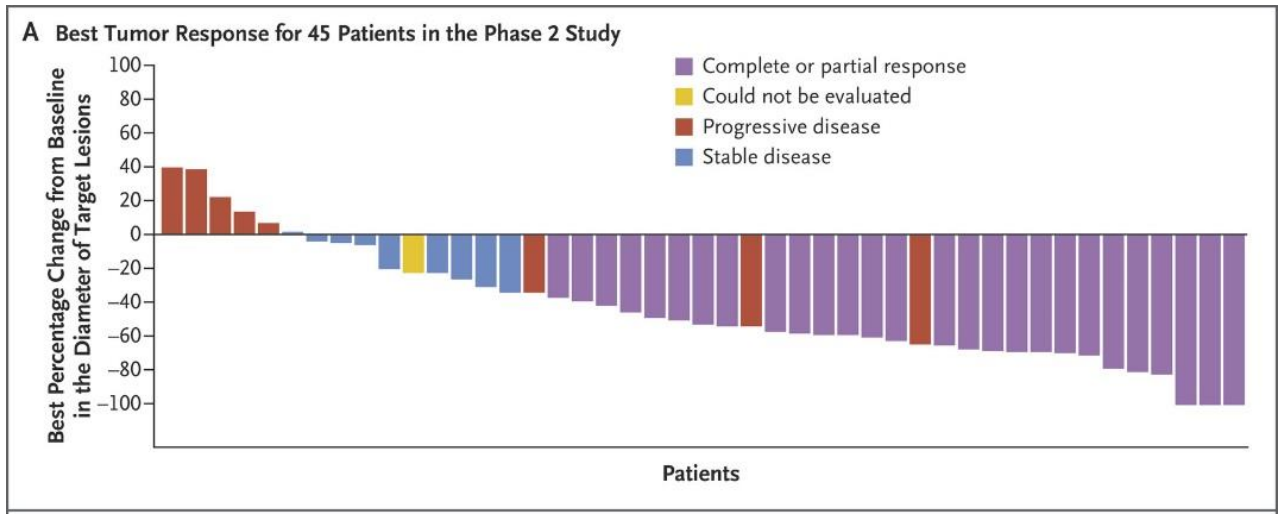
Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

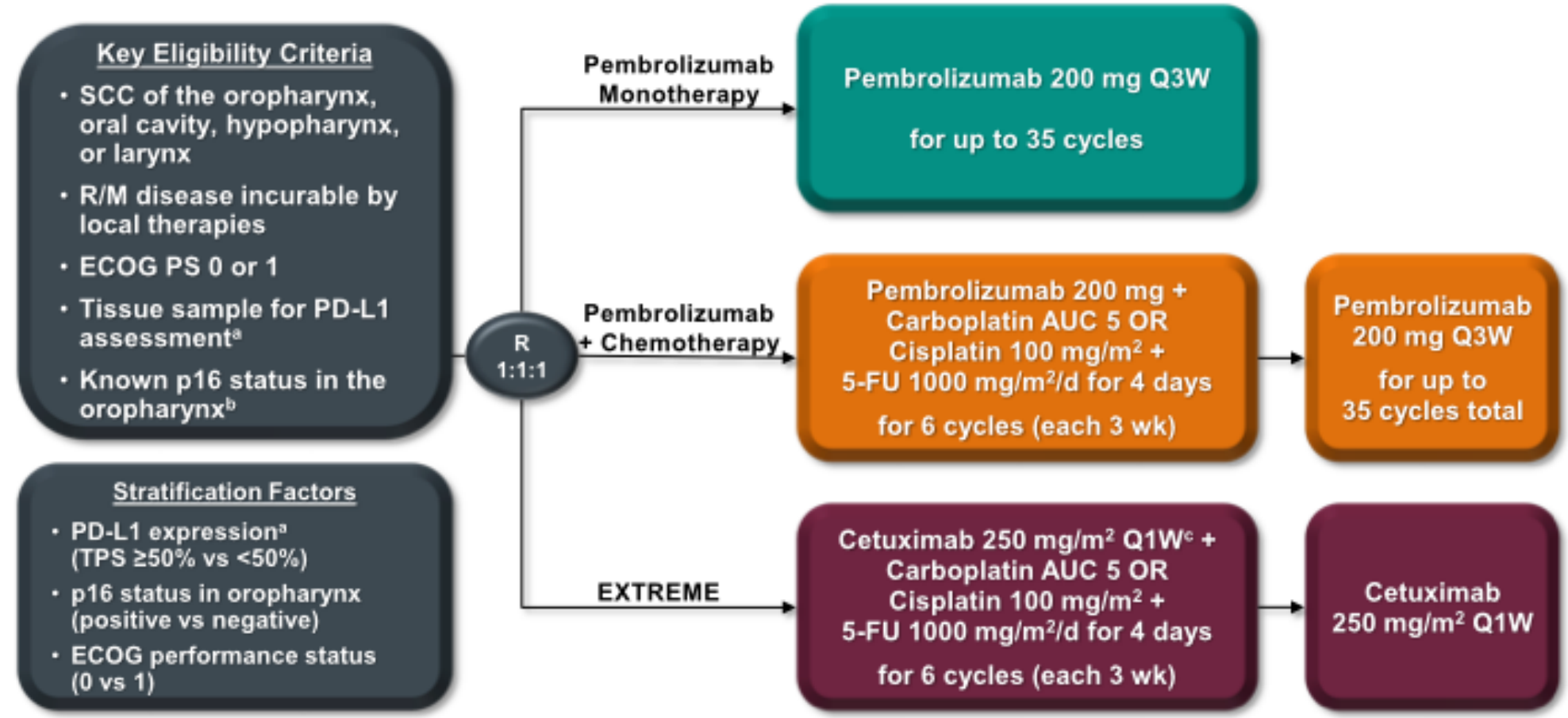
- Cemiplimab 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response





Migden, NEJM 2018.

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

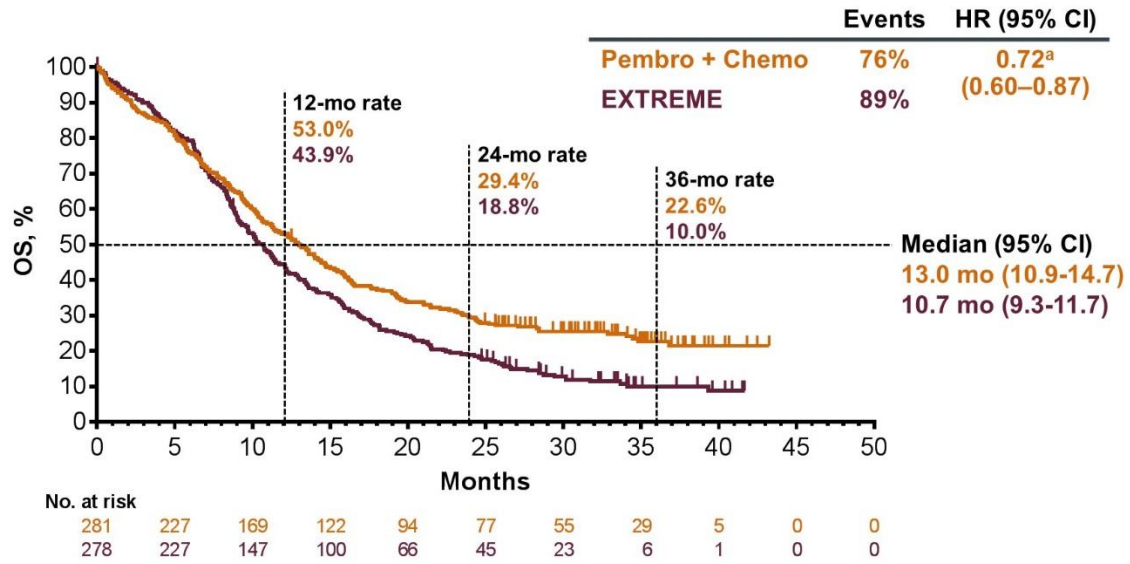


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

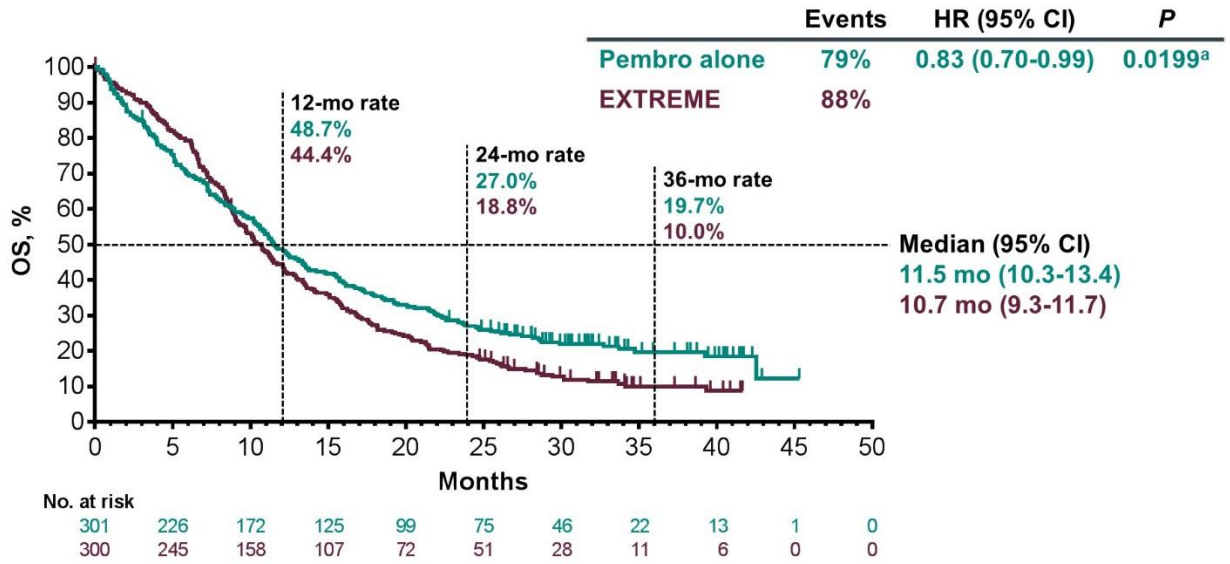
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

OS, P+C vs E, Total Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, Total Population



[a]Not statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

Rischin, ASCO 2019.

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]

[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.

Rischin, ASCO 2019.

Evaluating Biomarkers in HNSCC

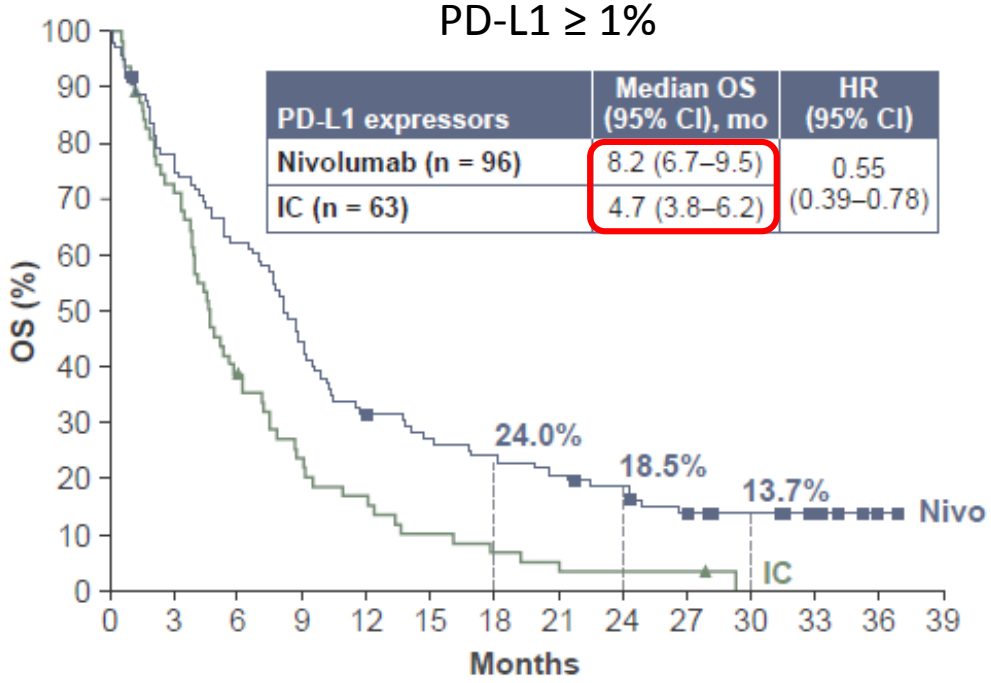
- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit seen in PD-L1 positive tumors
  - KEYNOTE-040: pembrolizumab vs investigator's choice chemotherapy – did not meet survival endpoints in total population but improved outcomes in PD-L1-expressors

Evaluating Biomarkers in HNSCC

CheckMate 141: 2 year update

PD-L1 ≥ 1%

PD-L1 expressors	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 96)	8.2 (6.7–9.5)	0.55 (0.39–0.78)
IC (n = 63)	4.7 (3.8–6.2)	

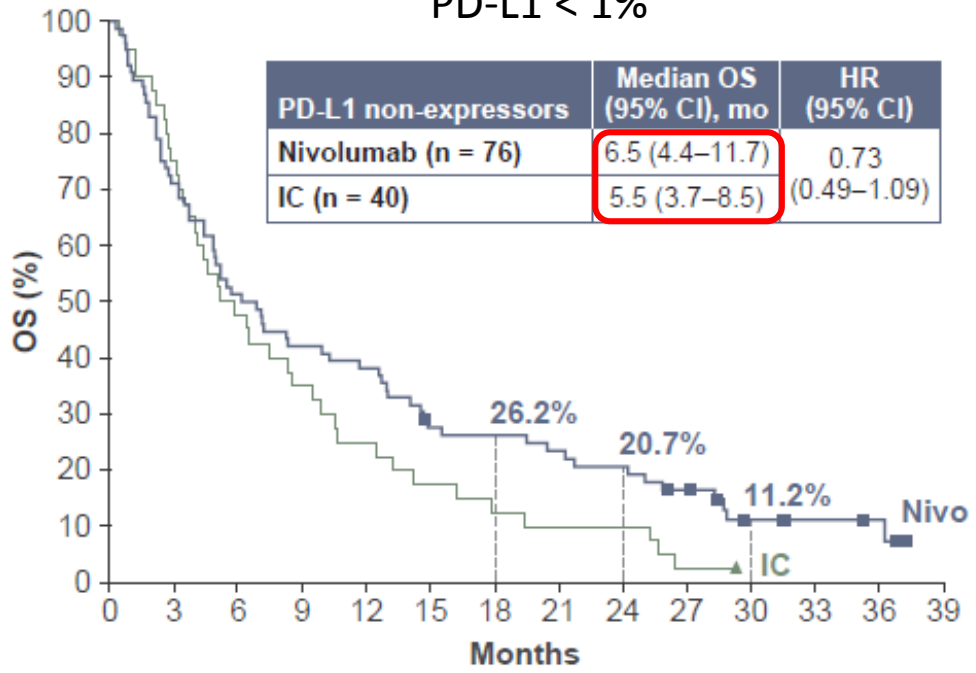


No. at risk

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

PD-L1 < 1%

PD-L1 non-expressors	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 76)	6.5 (4.4–11.7)	0.73 (0.49–1.09)
IC (n = 40)	5.5 (3.7–8.5)	



No. at risk

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

Ferris, Oral Oncol 2018.

In development:
T-VEC + pembrolizumab
KEYNOTE-137

- T-Vec 10^6 PFU/mL intratumoral injection followed by 10^8 PFU/mL Q3W
- Pembrolizumab 200 mg IV Q3W
- Eligibility:
  - R/M HNSCC not suitable for curative therapy
  - Progressed after platinum treatment
  - At least 1 injectable cutaneous, subcutaneous, or nodal tumor ≥ 10 mm in longest diameter
- ORR: 16.7%

Harrington, ASCO 2018.

In development: Checkpoint inhibitors + radiotherapy

- NCT03247712: neoadjuvant nivolumab + SBRT
  - Decreased tumor size prior to surgery; high pathologic CR rate
- KEYNOTE-412: pembrolizumab + chemoradiation
  - Safety confirmed
- REACH: avelumab + cetuximab + radiation
  - Safety confirmed

Leidner, AACR 2019.
Siu, AACR 2018.
Tao, ASCO 2018.

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 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
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)

Ezra E. W. Cohen[1], R. Bryan Bell[2], Carlo B. Bifulco[2], Barbara Burtness[3], Maura L. Gillison[4], Kevin J. Harrington[5], Quynh-Thu Le[6], Nancy Y. Lee[7], Rom Leidner[2], Rebecca L. Lewis[8], Lisa Licitra[9], Hisham Mehanna[10], Loren K. Mell[1], Adam Raben[11], Andrew G. Sikora[12], Ravindra Uppaluri[13], Fernanda Whitworth[14], Dan P. Zandberg[8] and Robert L. Ferris[8*]

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Case Studies

Case 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

Case 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

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 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?

Case 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:

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

Case 1

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

<u>Therapeutic options</u>:

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

Case 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

Case 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

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

Case 2

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

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

Case 2

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

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

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)

Case 2

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

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)

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

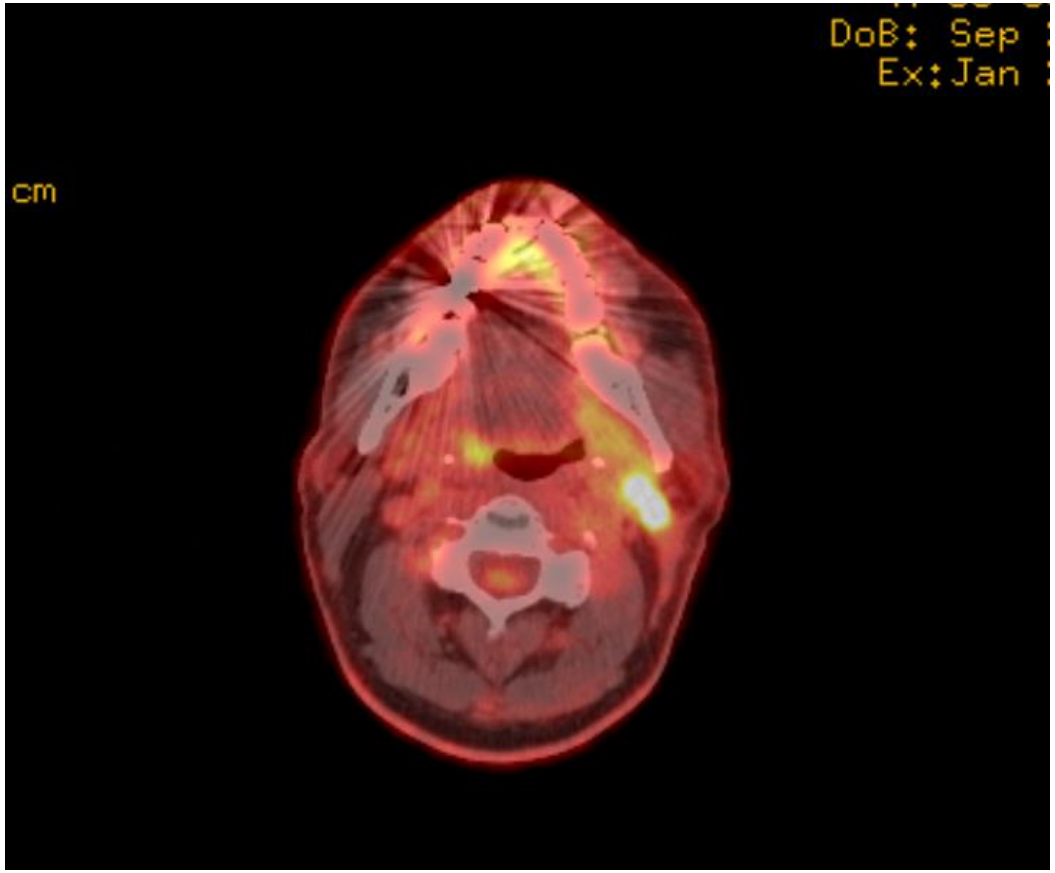
Case 2

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



Case 2

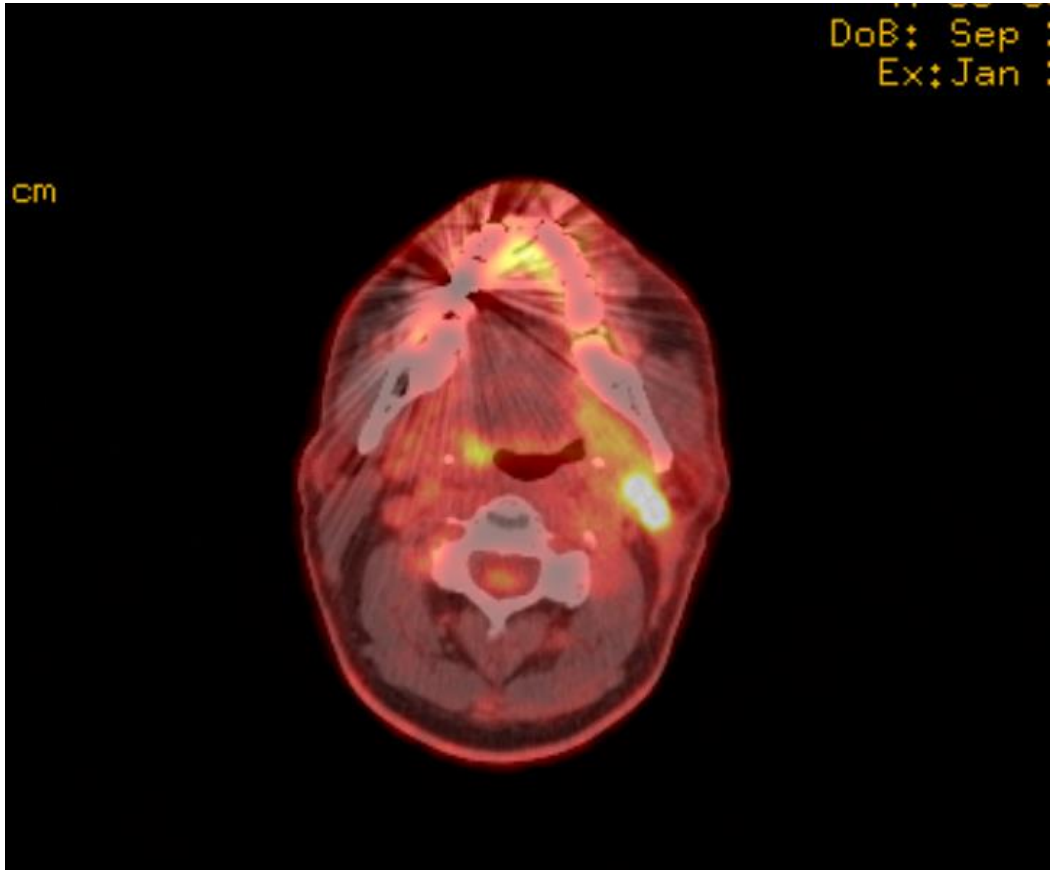
What would be your best next step?

A. US-guided left neck biopsy

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

C. Consider palliative radiation

- 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 2

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

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

In January 2018 imaging shows focal regional node progression and he receives SBRT

He has continued on nivolumab with no further disease progression

Case 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 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 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

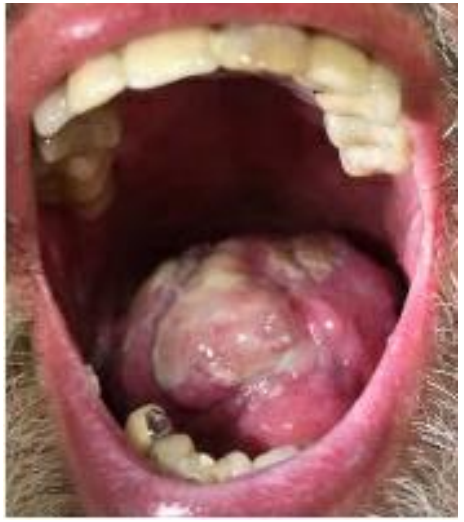
Event: in **August 2019** calls with mucositis, oral pain with difficulty swallowing, skin rash…

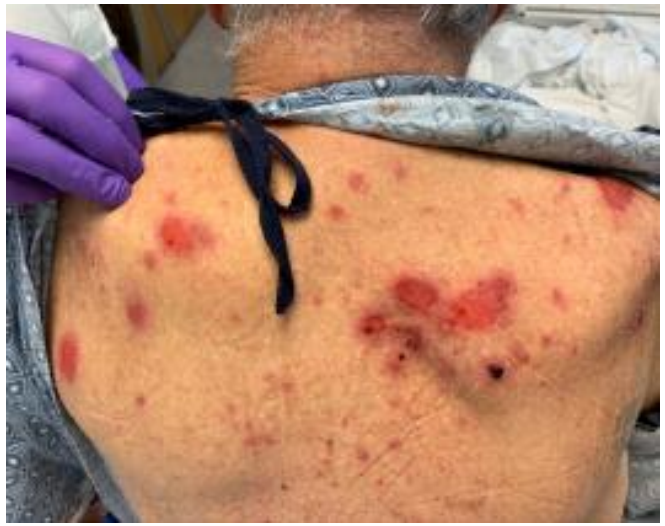
Case 3

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

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…





Case 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