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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

- Royalty: Up To Date
- Consulting Fees: Amgen
- Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents: BMS

- I will be discussing non-FDA approved indications during my presentation.

# Summary/Introduction

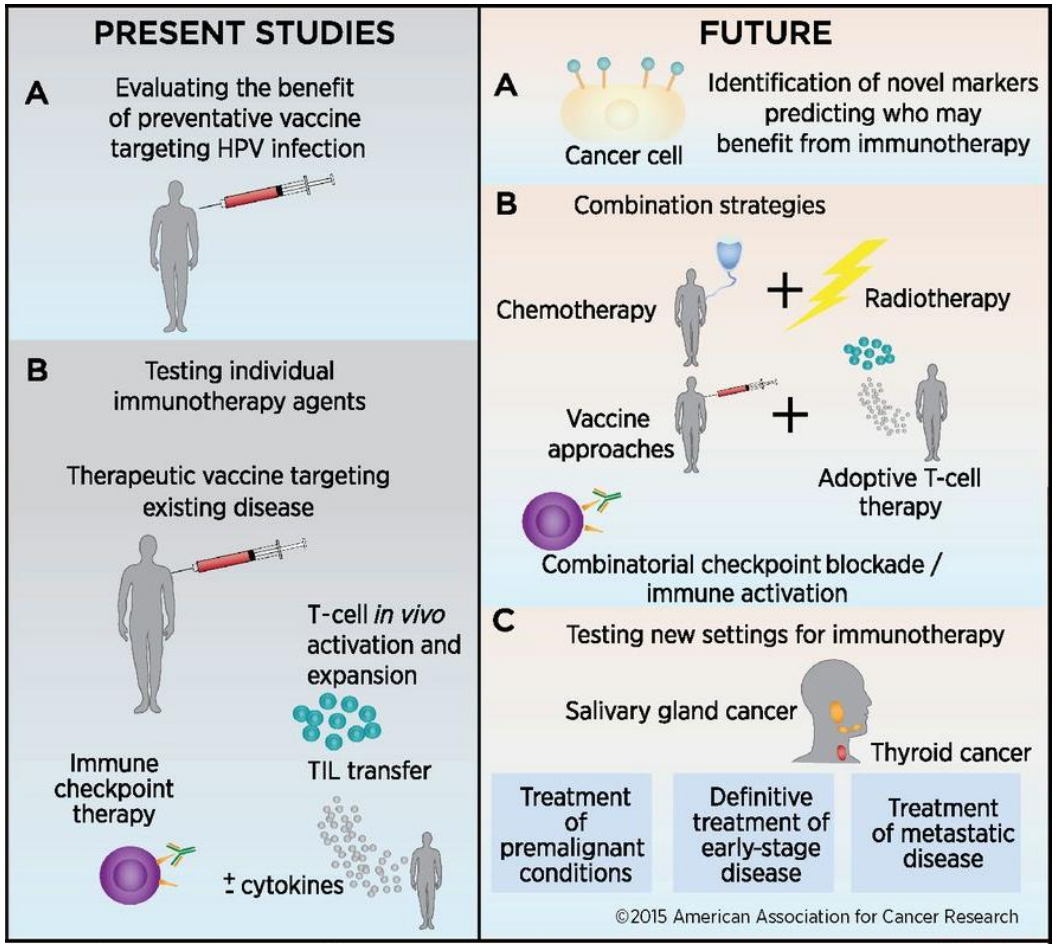
- Overview of I/O treatment approaches for head and neck cancer.
- Timeline for development of PD-1 checkpoint inhibition—nivolumab and pembrolizumab.
- Review of data that led to approval of these drugs for treatment of recurrent/metastatic disease—1st and 2nd line. Phase 1b, II and III trials.
- Future directions.

# Common Themes

- All drugs target the PD-1 receptor.
- Prognosis based on markers:  PD-L1 and p16.
- Selection based on markers: PD-L1.  KEYNOTE 048 only.
- Duration of response.
- Similar outcomes shared in 2nd line trials.
- Immune-related adverse events.

# 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



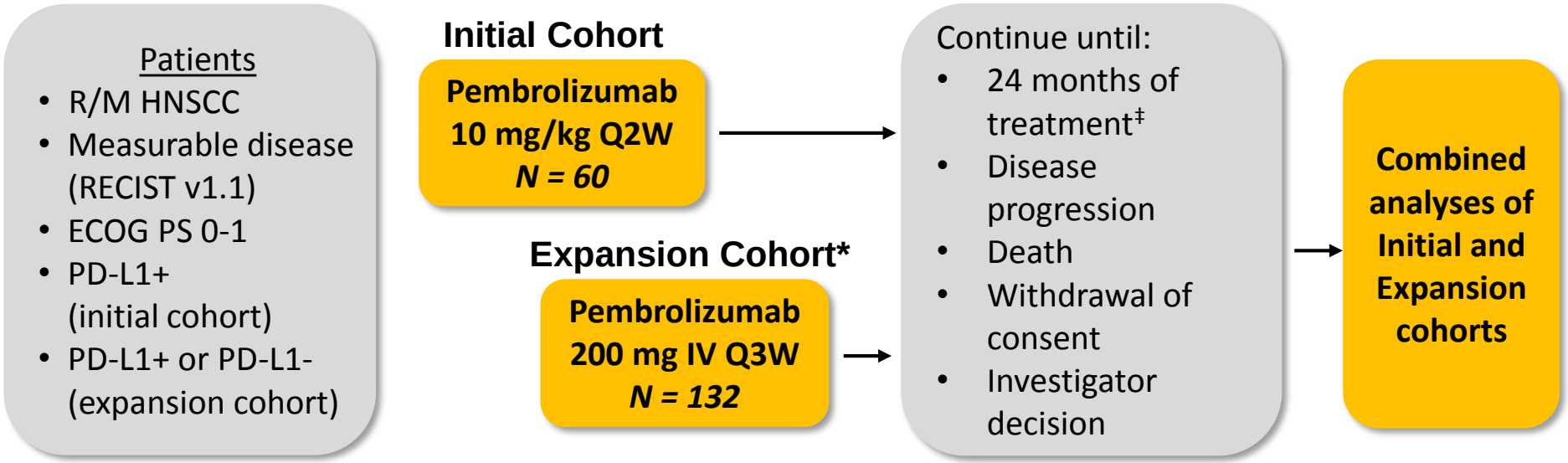

Schoenfeld, Cancer Immunol Res, 2015

# 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<br>or<br>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




**50% > 3 lines of therapy; 23% HPV positive**

**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 §

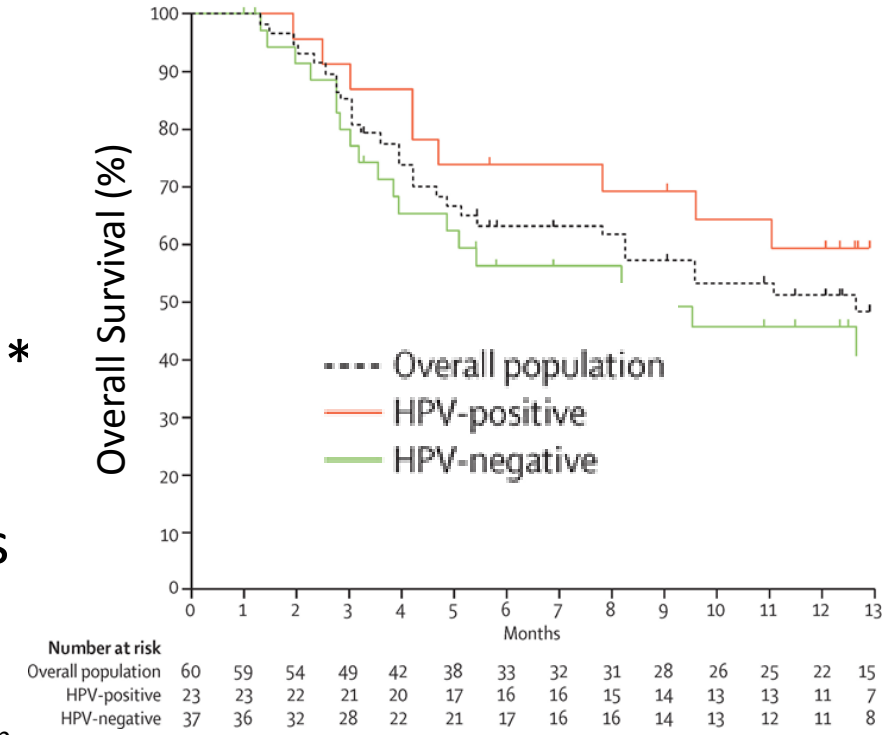
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

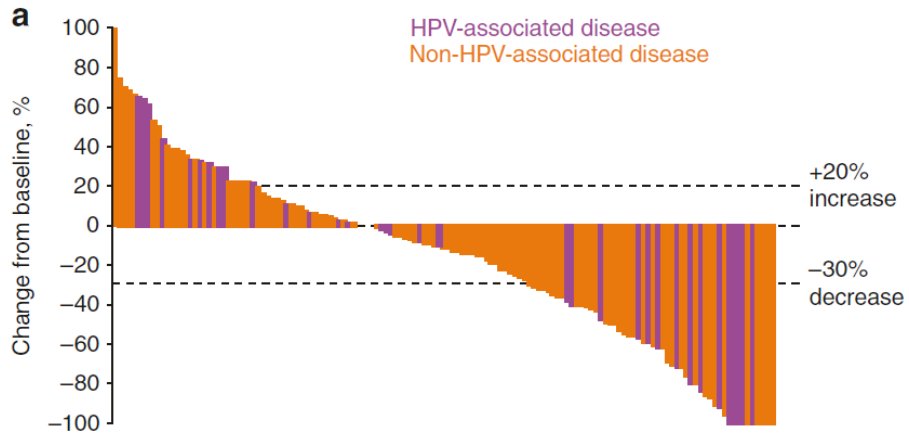
Seiwert, ASCO 2017.

# 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



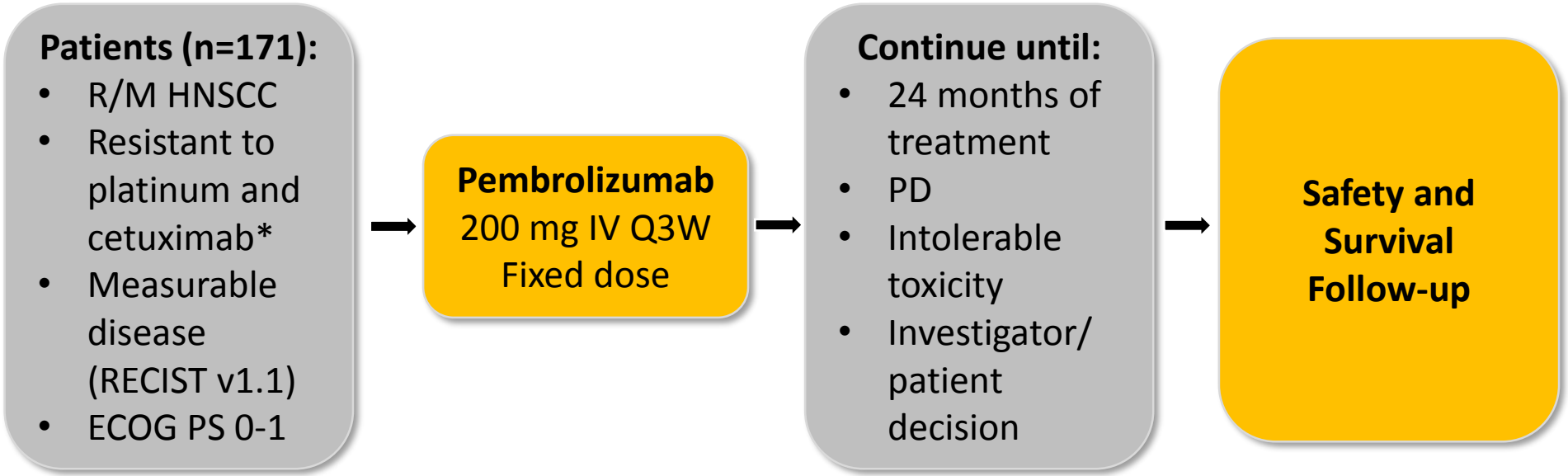




Higher response rates were observed in patients with PD-L1 expression using CPS (21 vs. 6%; one-sided P=0.023),

Seiwert, ASCO 2017. *Taxane in Checkmate 141 ~5 mos; 2nd line.
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; 22% p16+**

Bauml, J Clin Oncol 2017.

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

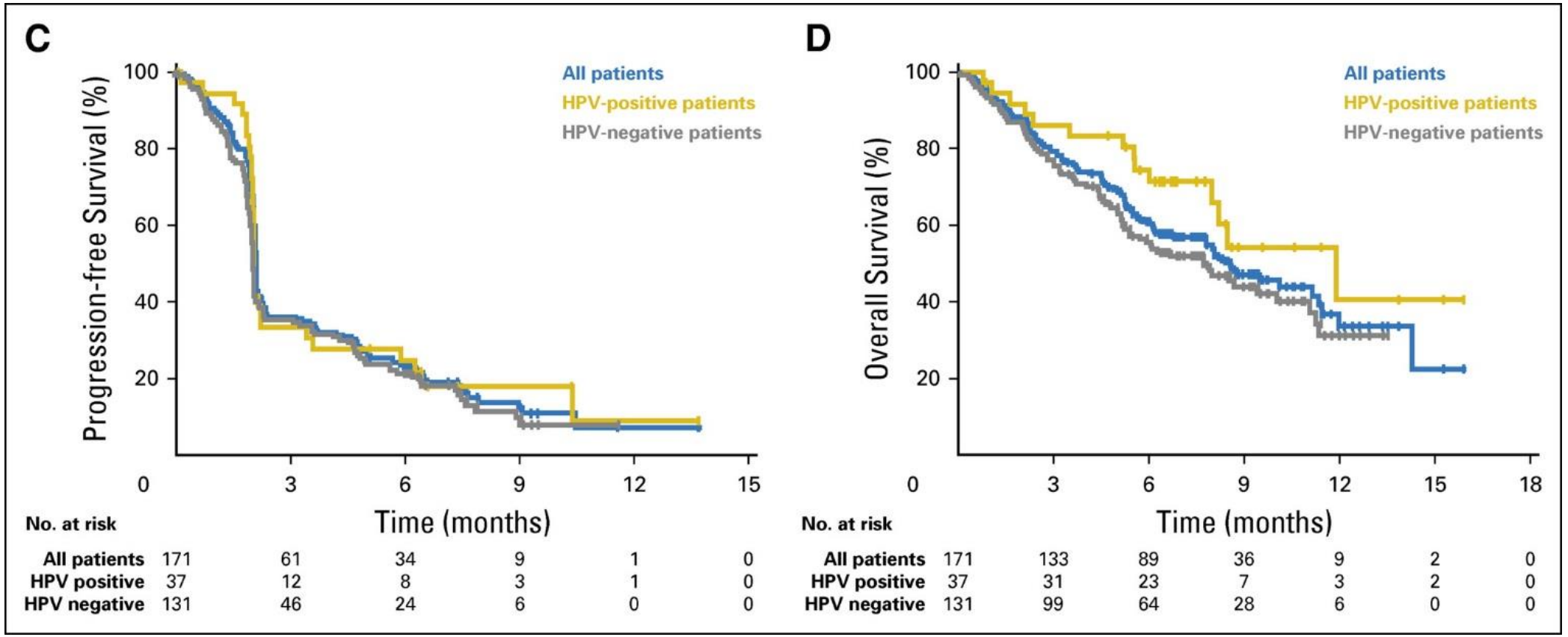
## Phase II Trial, Single Arm

mOS 8 mos

mPFS 2 mos

ORR 16%

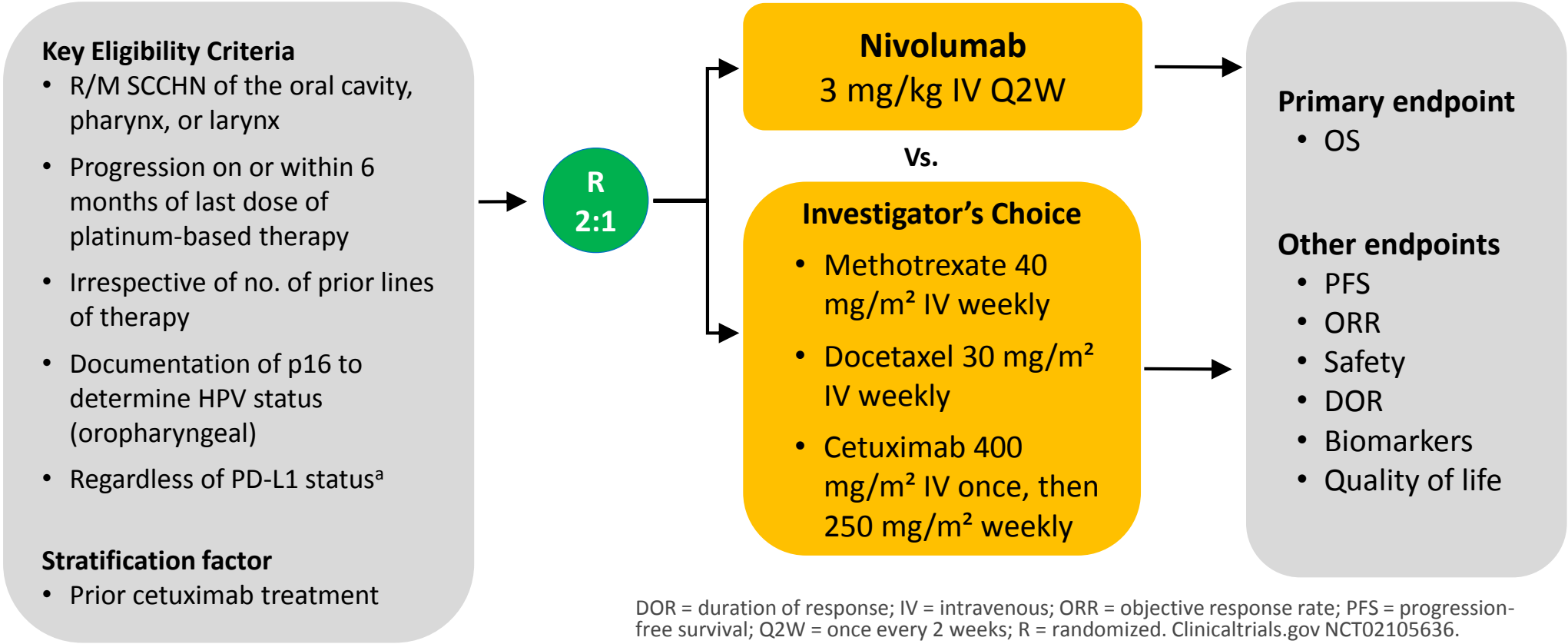
Similar to 012




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

mOS 7.5 mos

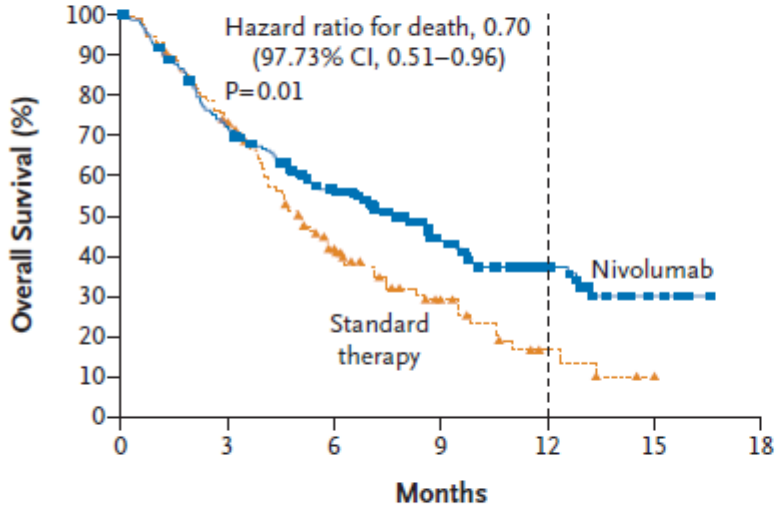
mPFS 2 mos

ORR 13.3%

Similar to 012 and 055

**A Overall Survival**

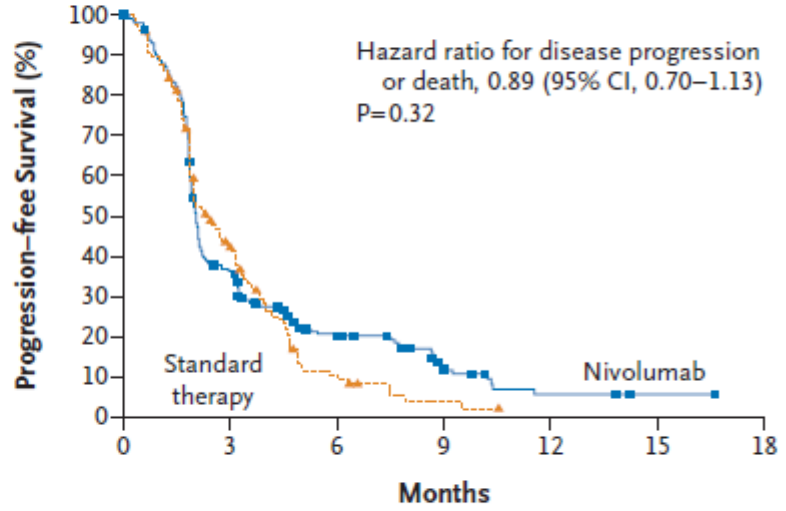
| | No. of Patients | No. of Deaths | 1–Yr Overall Survival Rate % (95% CI) | Median Overall Survival mo (95% CI) |
|---|---|---|---|---|
| Nivolumab | 240 | 133 | 36.0 (28.5–43.4) | 7.5 (5.5–9.1) |
| Standard Therapy | 121 | 85 | 16.6 (8.6–26.8) | 5.1 (4.0–6.0) |




| 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—phase I/II study.

**Key Eligibility Criteria**

- Advanced cutaneous squamous-cell carcinoma (any site)
- Not eligible for surgery
- ECOG 0-1
- ≥1 assessable lesion
- 44% no prior chemo.

→ **Cemiplimab**
3 mg/kg IV Q2W →

**Primary endpoint**

- Response rate

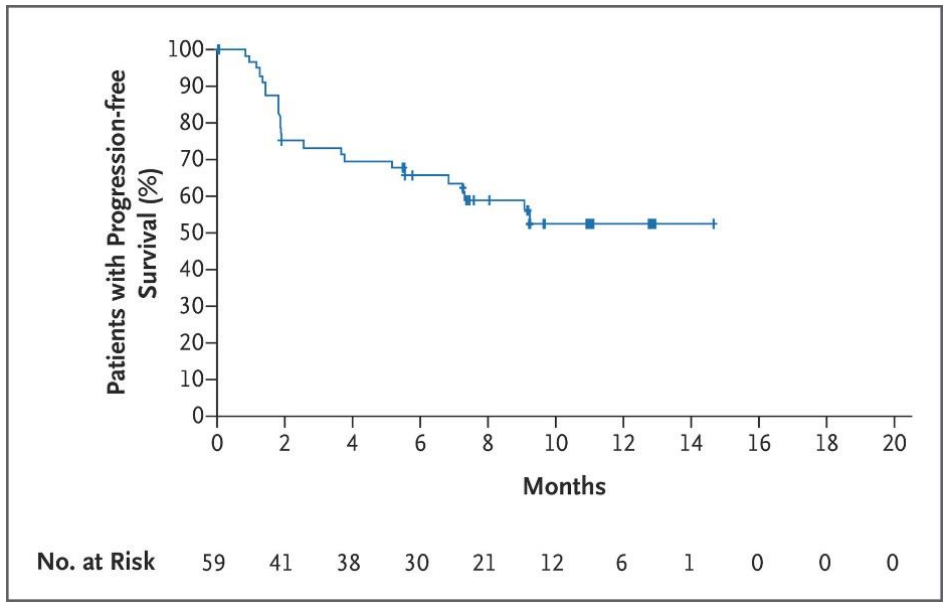
**Other endpoints**

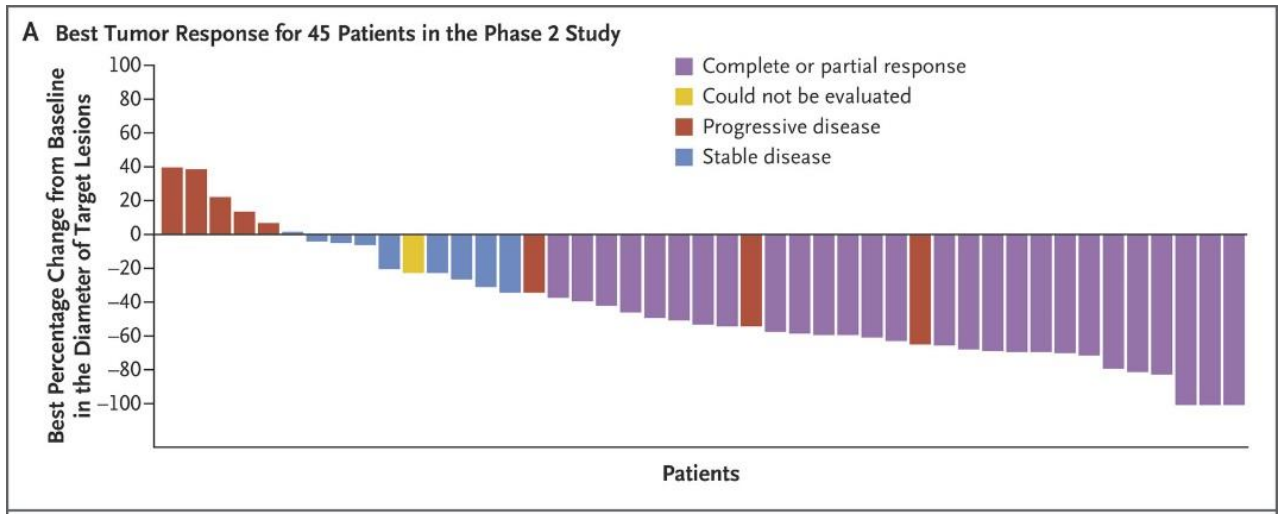
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

# Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma (phase I/II)

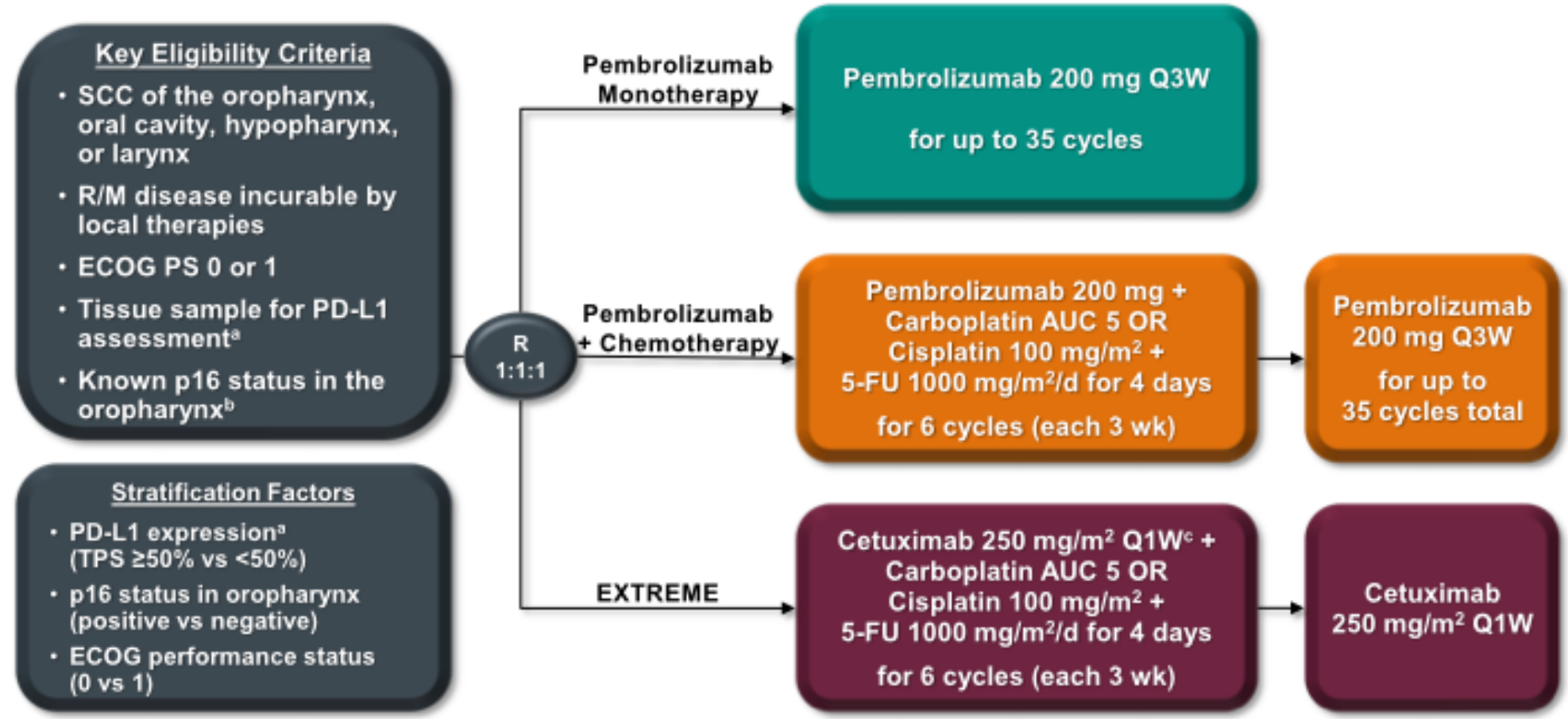
- Cemiplimab 3 mg/kg Q2W; 44% no prior chemotherapy
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response




Migden, NEJM 2018.

# KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC—First Line

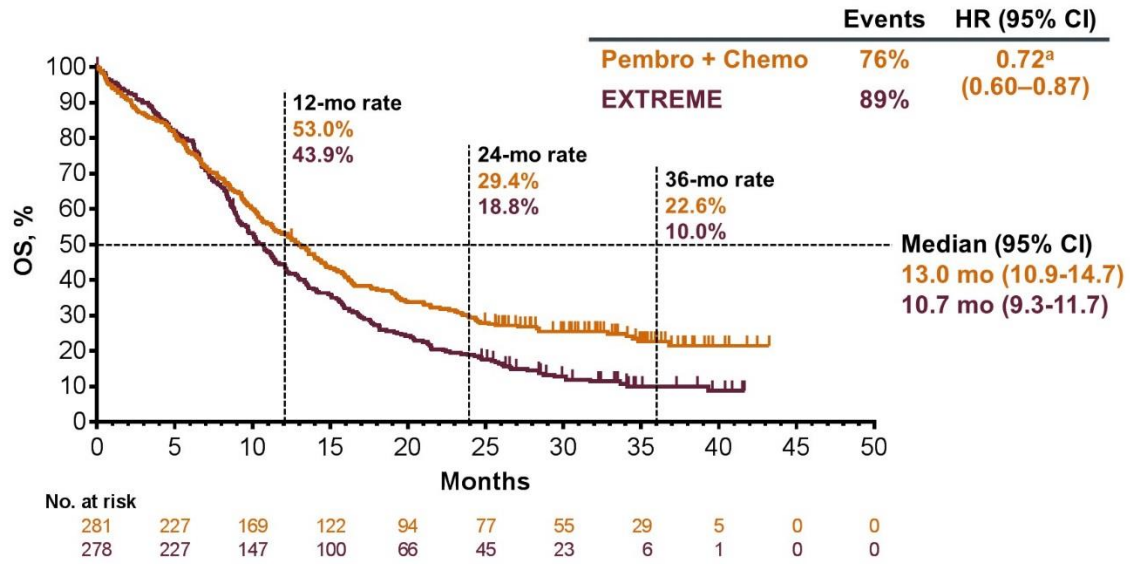



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

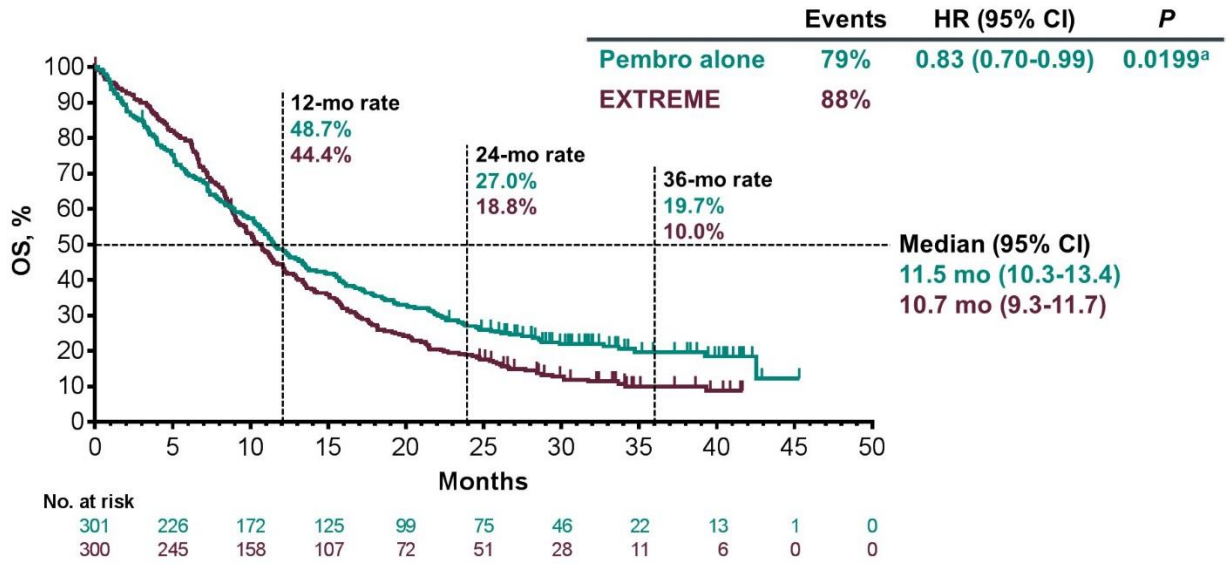
# KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

## 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

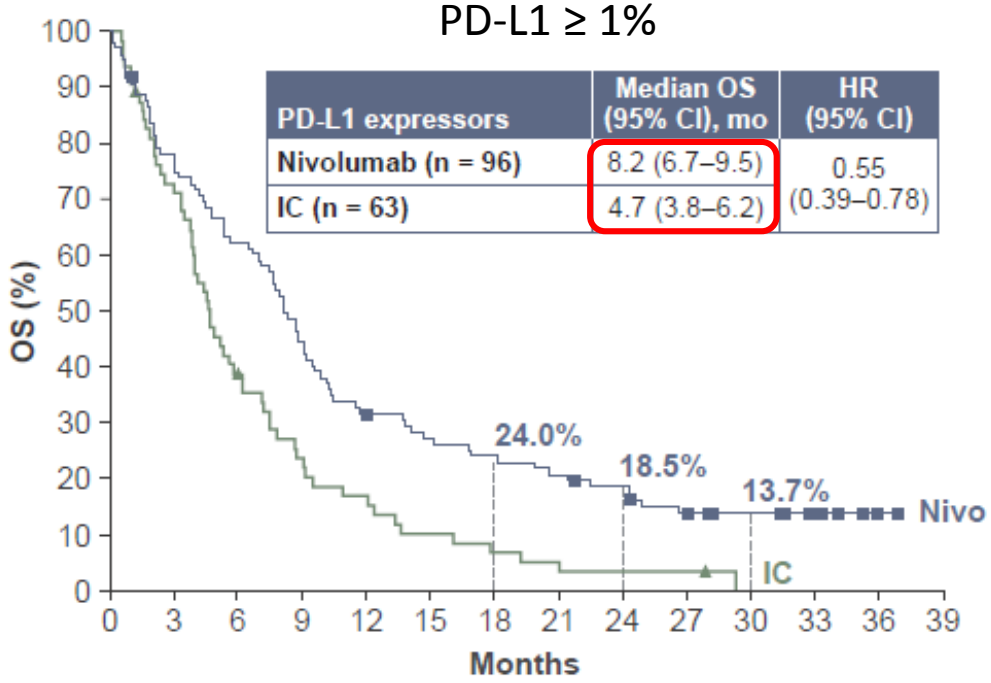
- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit 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) | |

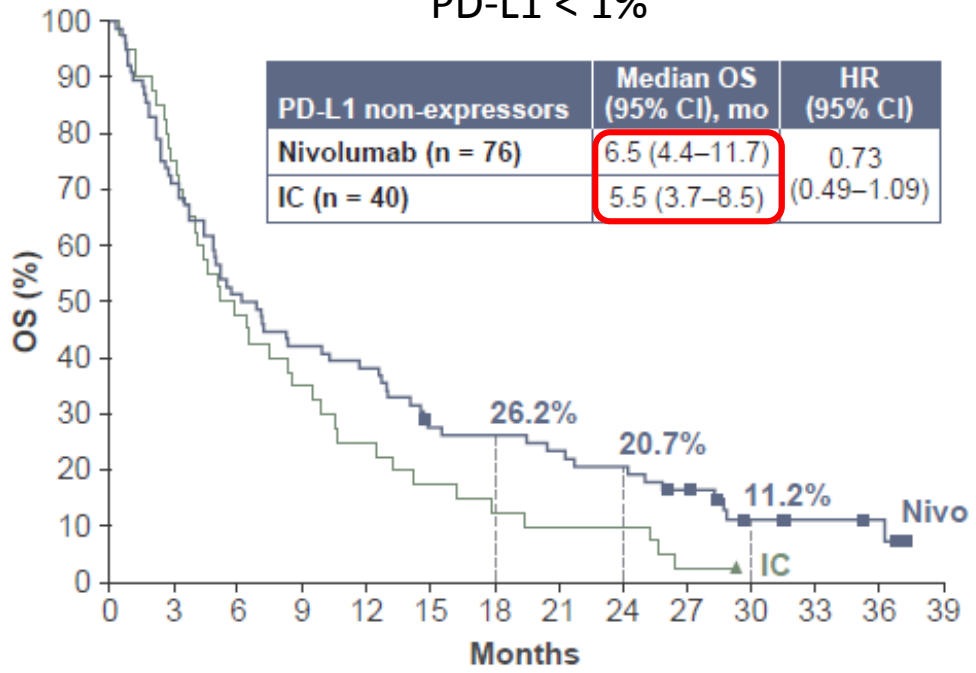



No. at risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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

- STING agonist + pembrolizumab (Innate Immunity)
- NCT03247712: neoadjuvant nivolumab + SBRT (Abscopal)
  - Decreased tumor size prior to surgery; high pathologic CR rate
- KEYNOTE-412: pembrolizumab + chemoradiation (Radiosensitization)
  - Safety confirmed
- REACH: avelumab + cetuximab + radiation (Dual Biotherapy)
  - 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 Study

# Case Study

A 75-year-old man with no history of autoimmune disease was diagnosed with stage IVA, T1N2cM0, p16-negative HNSCC of the right buccal mucosa. He underwent surgical excision of the buccal lesion with bilateral neck dissection and was found to have in-transit soft tissue metastases with positive margins and bilateral lymph nodes with extracapsular invasion. He received adjuvant radiation to 64 gray (Gy) with concurrent weekly cisplatin (40 mg/m2).

Approximately 14 months later, he had tumor recurrence in his right chin with a lymph node metastasis to the right parotid gland. He underwent salvage right superficial parotidectomy and composite resection of the right chin. Pathology revealed extensive angiolymphatic invasion and tumor infiltration into surrounding tissues. He subsequently received re-irradiation with protons to 60 Gy concurrent with weekly paclitaxel.

# Case Study

Three months after re-irradiation, a new submental dermal metastasis was discovered. The patient received nivolumab dosed at 3 mg/kg intravenously (295 mg)—one dose.

Three weeks after the initial infusion, he presented with severe malaise and progressive, diffuse limb weakness. Abnormalities on cranial nerve examination included recent onset of asymmetric bilateral ptosis and longstanding lower facial asymmetry from tumor resections. Manual muscle testing showed mild weakness with elbow extension and more significant weakness in the proximal lower extremities, scoring on the Medical Research Council (MRC) scale as 5−/5 in bilateral elbow extension, 4+/5 in bilateral hipflexion,5−/5 in bilateral knee flexion and knee extension, and 5/5 in distal muscle strength in both hands and feet.

# Case Study

What would you do next?

1. MRI of head/face.
2. Additional lab tests such as creatine kinase.
3. Consult neurology team.
4. All of the above.

# Case Study

New data and clinical situation:

CK = 2593 (0-325).

MRI:  evidence of prior surgeries but no NRO findings.

Neurology: ordered EMG: Electromyogram (EMG) revealed myopathic motor units in the right vastus medialis muscle, supporting a process affecting underlying skeletal muscle, most consistent with **myositis.**

Further neuromuscular testing showed elevated acetylcholine re-ceptor (AChR) binding antibodies at 22.4 nmol/L (0.0–0.4), elevated AChR blocking antibodies at 63% (0–26), and elevated anti-striated muscle antibodies at a titer of 1:320 (< 1:40), supporting a possible concurrent **myesthenia gravis**.

# Case Study

Treatment and Outcome:

Intravenous methylprednisolone 80 mg daily which was then transitioned to oral prednisone 100 mg daily after three weeks.

Five plasmapheresis treatments and a trial of pyridostigmine (60 mg oral), although the latter was ineffective and associated with side effects and thus discontinued.

The patient's CK level normalized at eight days, but there was minimal improvement in fatigue and muscle weakness over the next two months.

The dermal metastases resolved.

PS never recovered and he died of respiratory failure and bacteremia.