Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

# Immunotherapy for the Treatment of Head and Neck Cancer

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ACCC Association of Community Cancer Centers

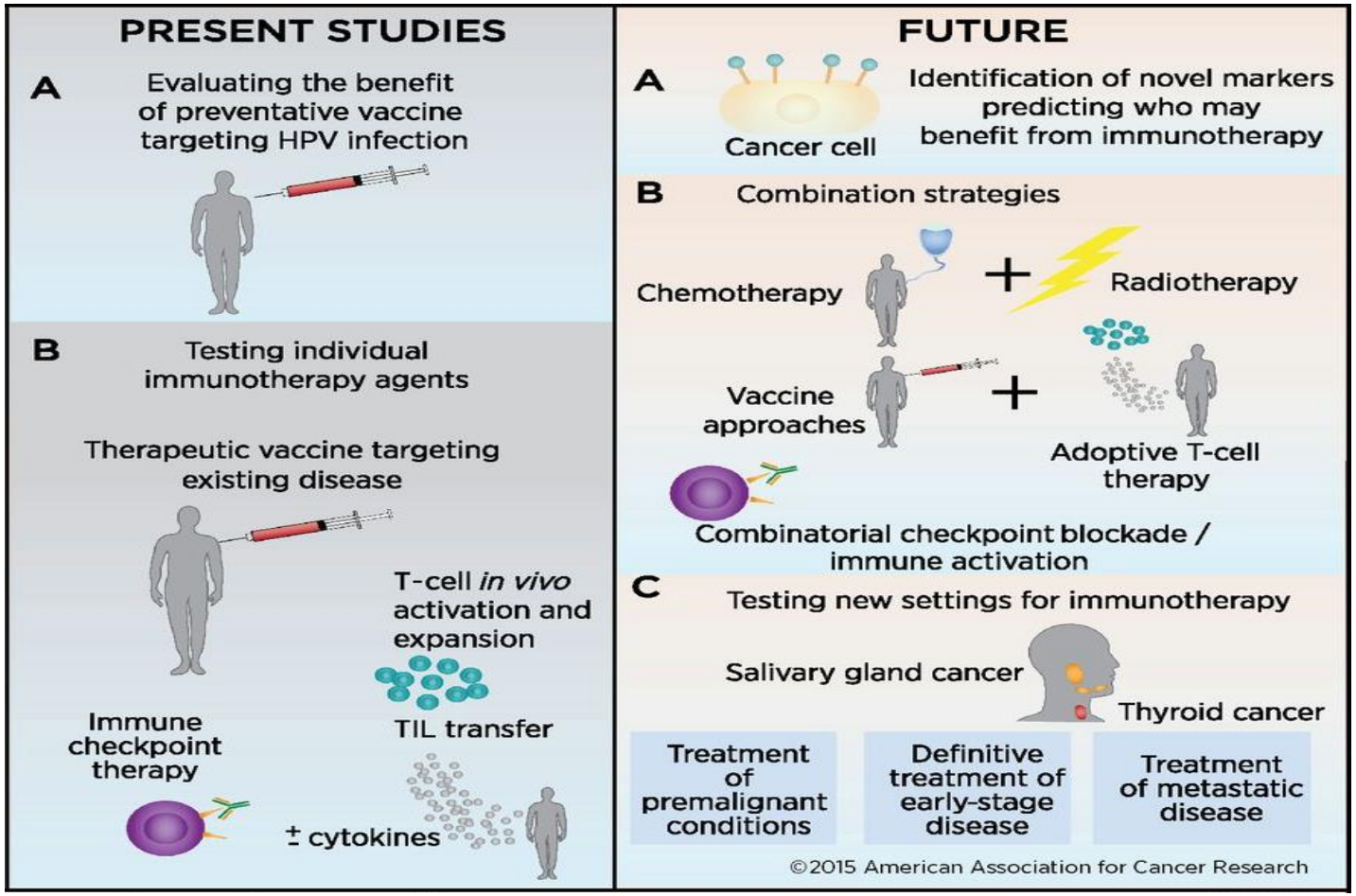
Society for Immunotherapy of Cancer

# Disclosures

- I have served on advisory boards for Dynavax, Merck, Takeda, and Genentech.
- These relationships will not impact my ability to present an unbiased presentation.
- I will not be discussing non-FDA approved indications during my presentation.

# Immunotherapy for the Treatment of Head and Neck Cancers

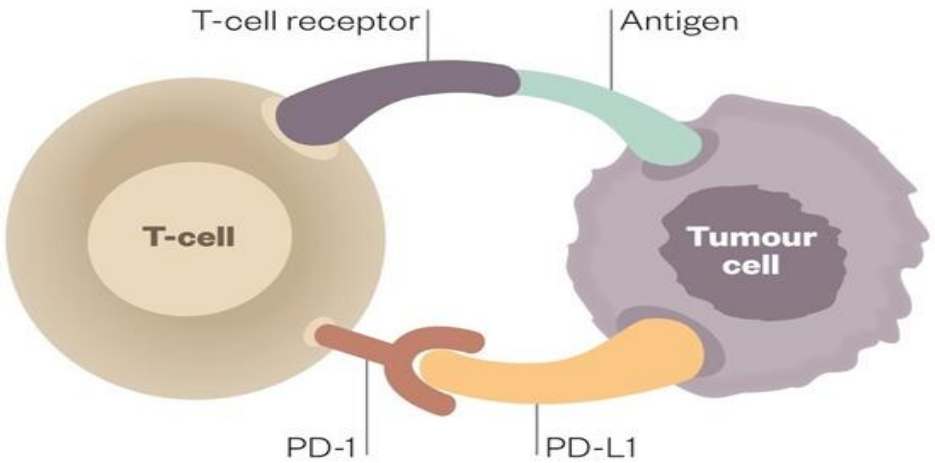
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Expression of immunologic markers to guide treatment
  - Preventive vaccination against virally mediated cancers
  - PD-1 checkpoint inhibitors for the treatment of metastatic disease



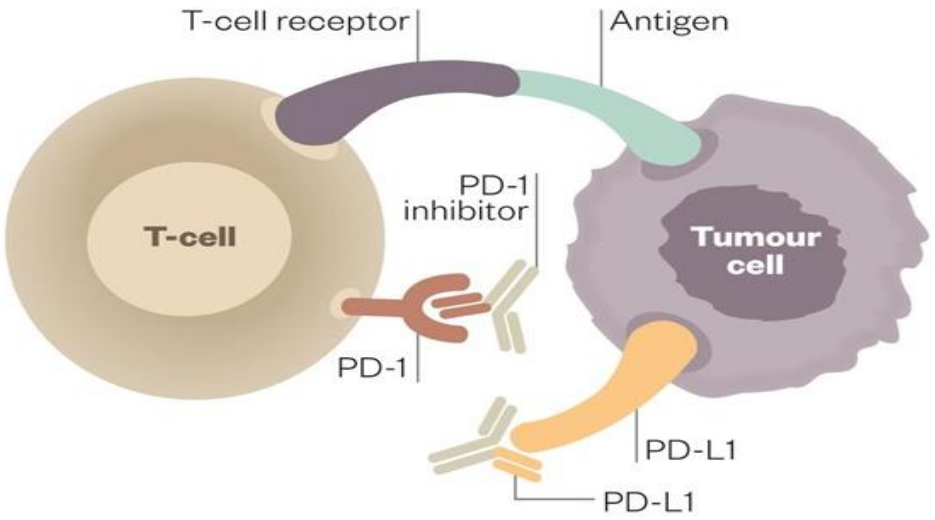

Schoenfeld JD, Cancer Immunol Res, 2015

# Immunotherapy for the Treatment of Head and Neck Cancers

## Immune Checkpoint Inhibitors (ICI)




PD-1 acts as “off-switch” for T cells, allowing cancer cells to evade immune attack




Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells

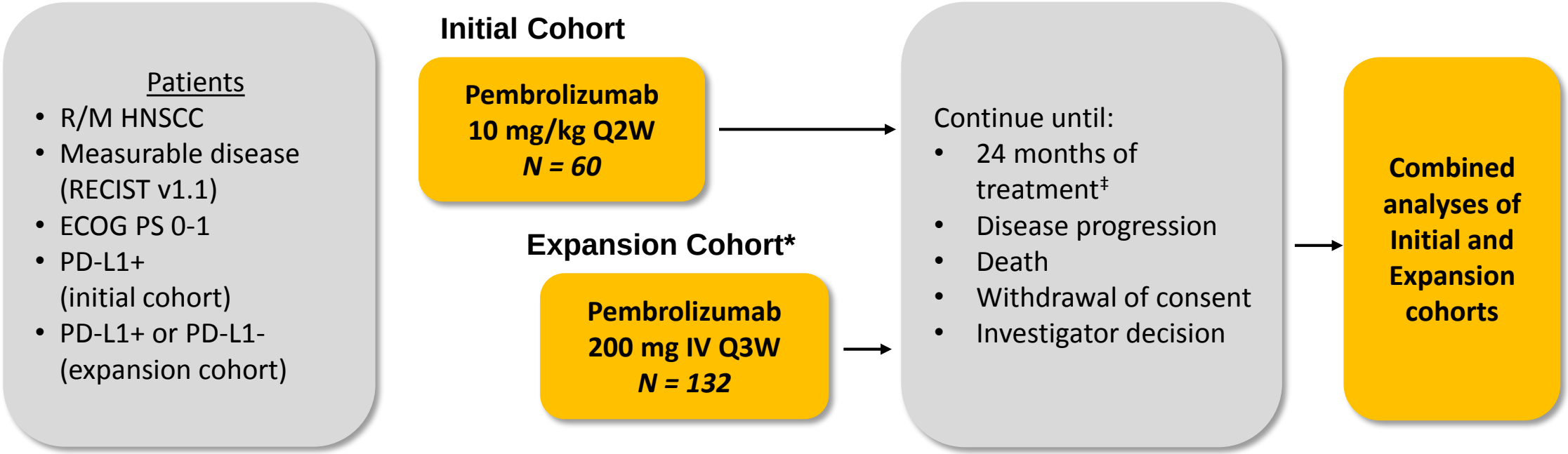
# FDA-approved Checkpoint Inhibitors for Use in Head and Neck Cancers

- Pembrolizumab 200 mg IV Q3W (anti-PD-1)
  - KEYNOTE – 012/055:  Patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (HNSCC) with disease progression on or after platinum-containing chemotherapy
  - Accelerated Approval by FDA – August 5, 2016

- Nivolumab 240 mg IV Q2W or 480 mg IV Q4W (anti-PD-1)
  - CheckMate – 141: Patients with R/M HNSCC with disease progression on or after a platinum-based therapy
  - Breakthrough Therapy Designation by FDA – April, 2016
  - Approval – November 10, 2016

# 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

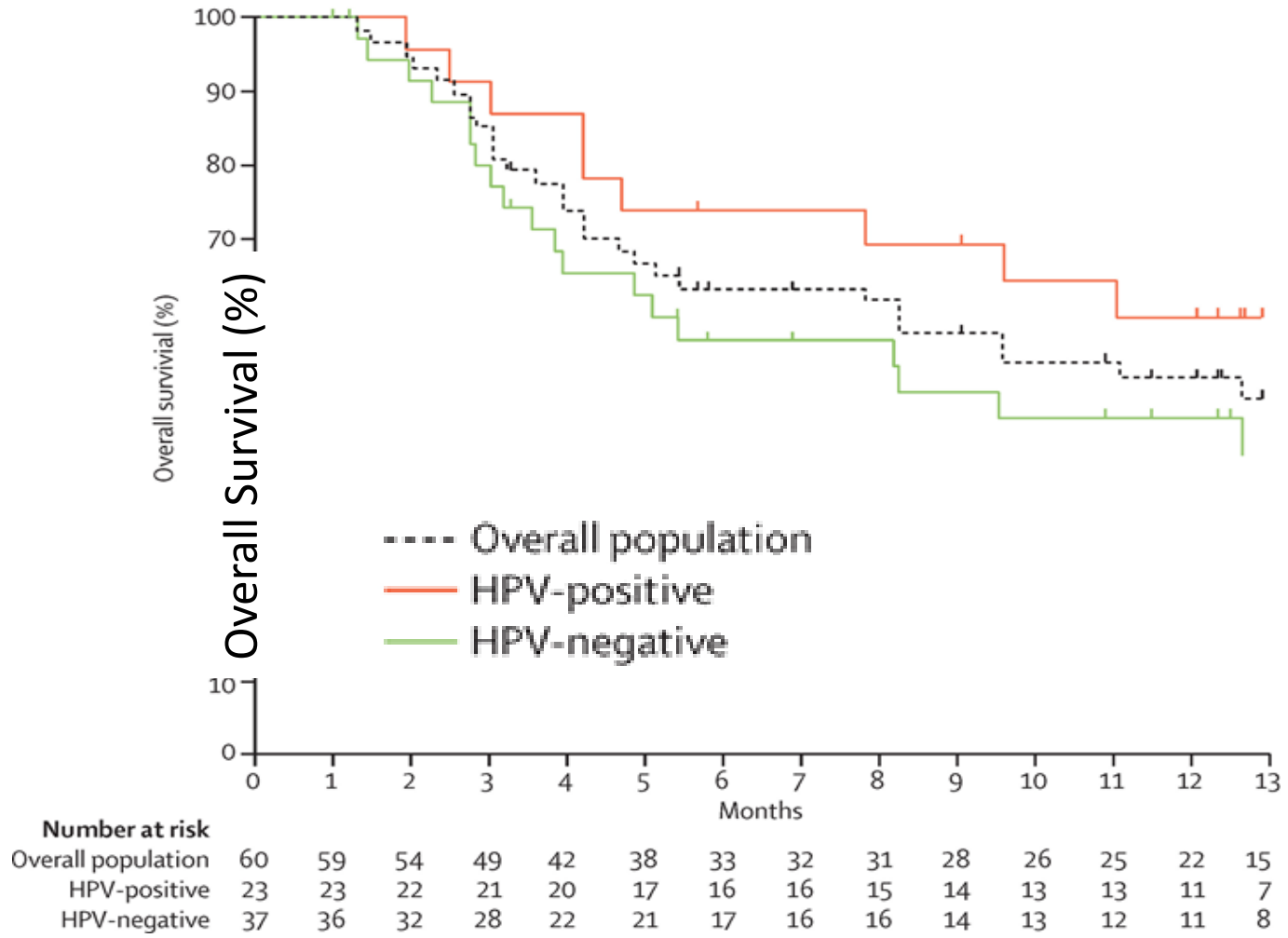
**Secondary end points:** ORR (investigator), PFS, OS, duration of response (DOR), ORR in HPV+ patients§

†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.

Chow, L et al. JCO November 2016

# KEYNOTE-012: Pembrolizumab in R/M HNSCC

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



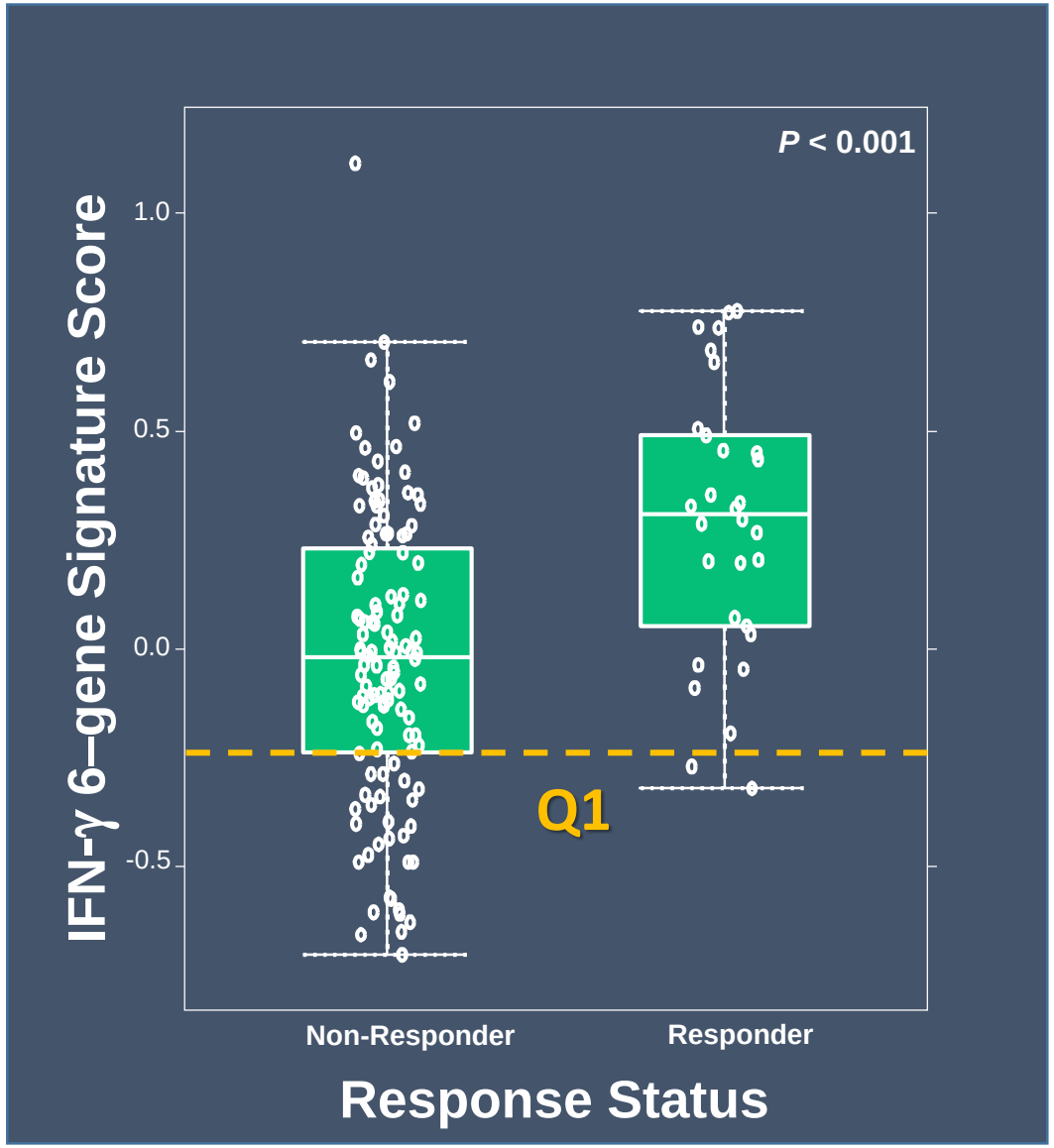

- ORR = 18%
  - CR = 4%
  - PR = 14%
- mOS = 8.0 months
- mPFS = 2.2 months

# KEYNOTE-012 Phase Ib Trial HNSCC Cohorts Overall Response by PD-L1 Status

| | PD-L1 Status | Non-responders n | Responders n | ORR % (95% CI) | P-value |
|---|---|---|---|---|---|
| **TPS (tumor cells)** | **PD-L1+** | 101 | 22 | **18 (12–26)** | 0.461 |
| | **PD-L1–** | 53 | 12 | **19 (10–30)** | |
| **CPS (tumor and inflammatory cells)** | **PD-L1+** | 120 | 32 | **21 (15–28)** | 0.023 |
| | **PD-L1–** | 34 | 2 | **6 (1–19)** | |

**Incorporation of inflammatory cells improves ability to detect responders**

# KEYNOTE-012 Phase Ib Trial HNSCC Cohorts Overall Response by IFN-γ 6-gene Signature Score




- **Score significantly associated with response†**
- **No difference in score by HPV status‡**

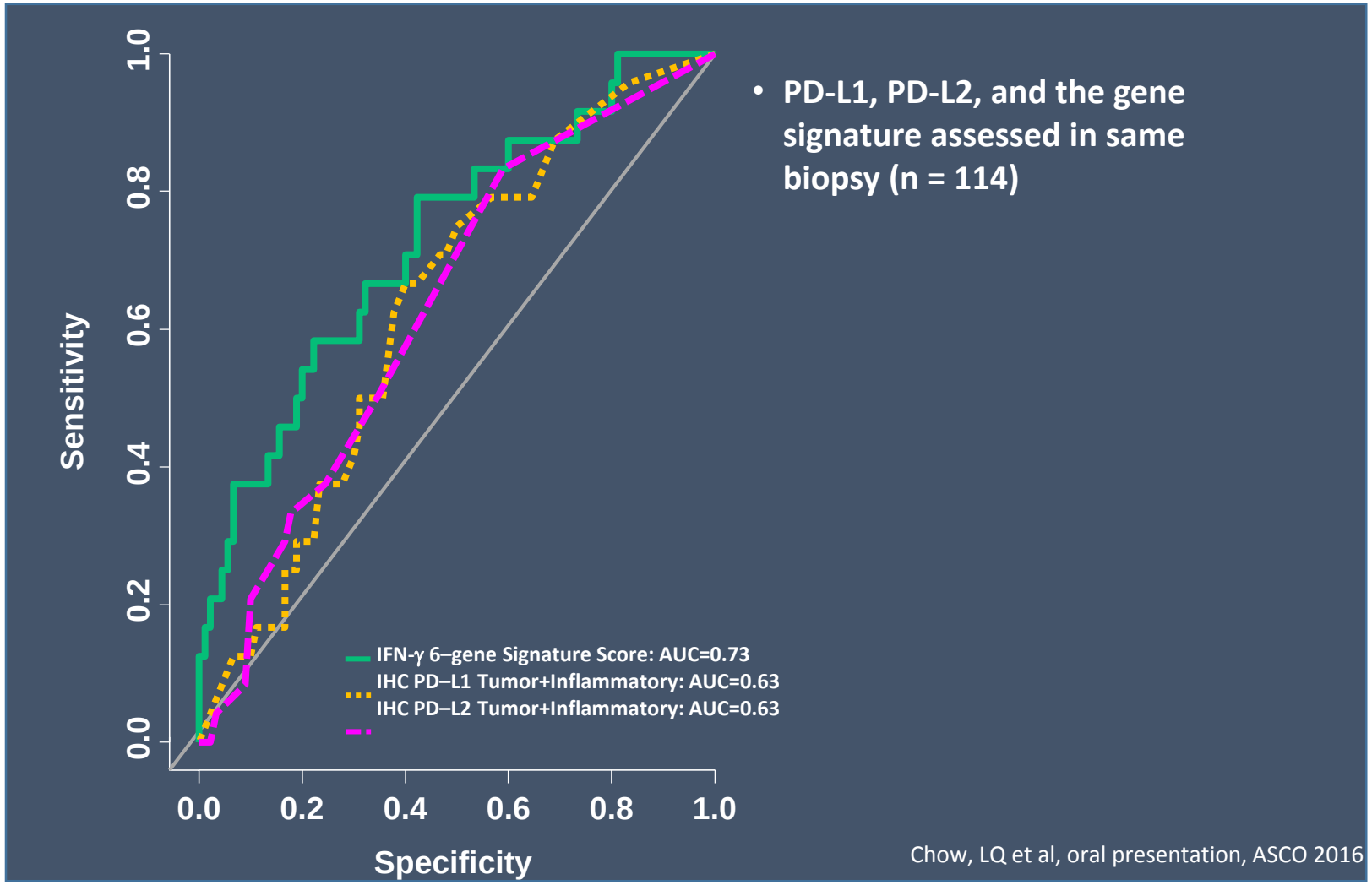
P-values based on logistic regression one-sided testing.

†n = 150

‡ HPV status was assessed at the local institution by p16 immunohistochemistry; n = 93.

Chow, LQ et al, oral presentation, ASCO 2016

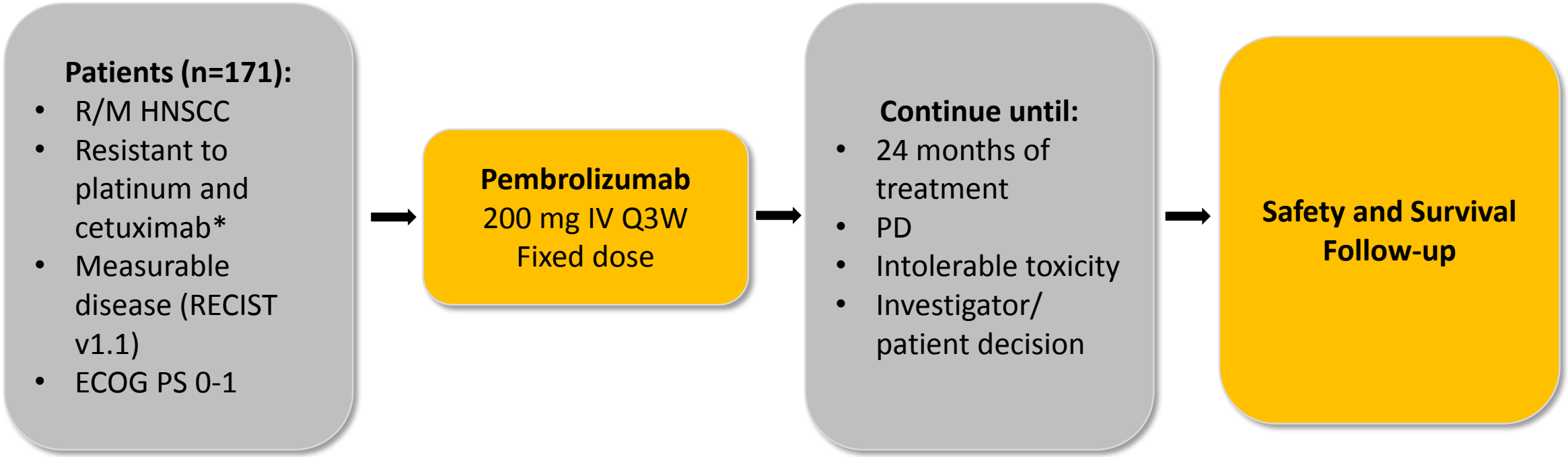
# KEYNOTE-012 Phase Ib Trial HNSCC Cohorts PD-L1, PD-L2, and IFN-γ 6-gene Signature ROC Curves for Overall Response




- **PD-L1, PD-L2, and the gene signature assessed in same biopsy (n = 114)**

Chow, LQ et al, oral presentation, ASCO 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)

Bauml J JCO 2017

**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

# KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab Phase II Trial, Single Arm

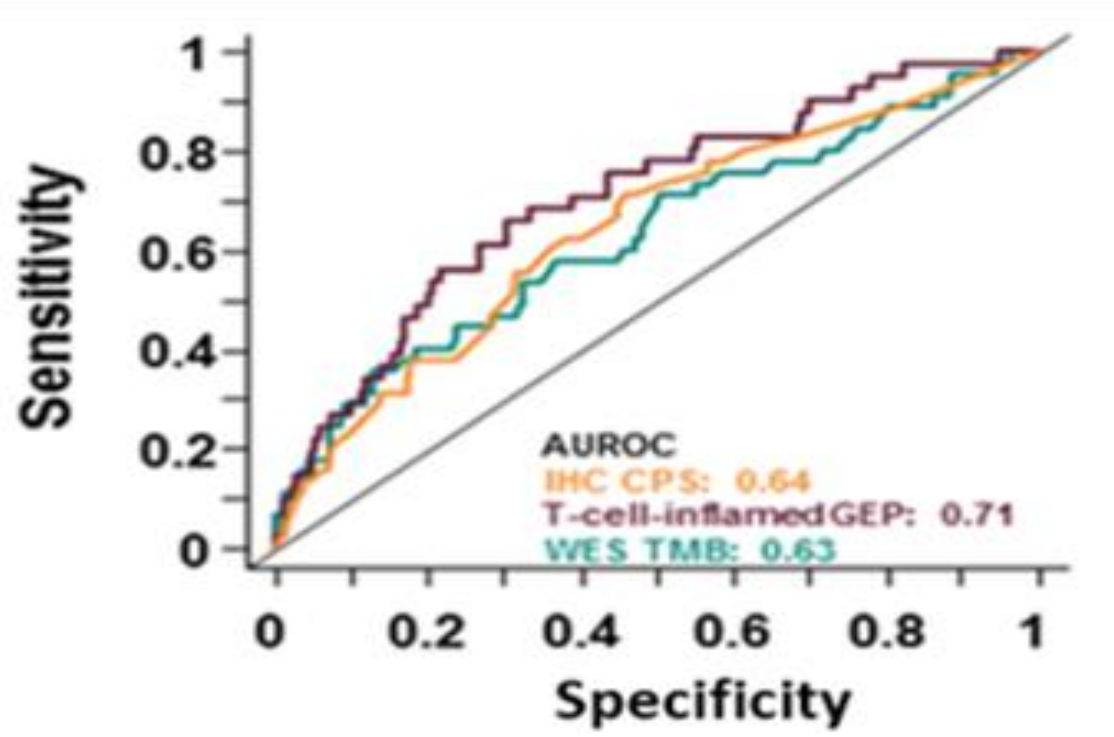
| Outcome | All Patients N=171 | HPV Status Positive n=37 | HPV Status Negative n=131 | PD-L1 Status ≥1% n=140 | PD-L1 Status <1% n=26 | PD-L1 Status ≥50% n=48 |
|---|---|---|---|---|---|---|
| ORR, % | 16 | 16 | 15 | 18 | 12 | 27 |
| mPFS, mo | 2.1 | | | | | |
| 6-mo PFS,% | 23 | 25 | 21 | 24 | 20 | 31 |
| 6-mo OS, % | 59 | 72 | 55 | 59 | 56 | 60 |

- Neither tumor PD-L1 expression or HPV status are sufficiently robust in guiding the use of pembrolizumab at this time.

Bauml J, et al, J Clin Oncol. 2017

# Combined biomarker data from Keynote 012 and Keynote 055 Studies

- First reported biomarker relationships in head and neck cancer:
  - AUROC curves for the relationship of PDL1 immunohistochemistry combined proportional score (IHC CPS), Gene expression profiling (GEP) and tumor mutational burden (TMB)




Siewert T et al. and Chow LQM. AACR 2018

# 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. Clinicaltrials.gov NCT02105636.

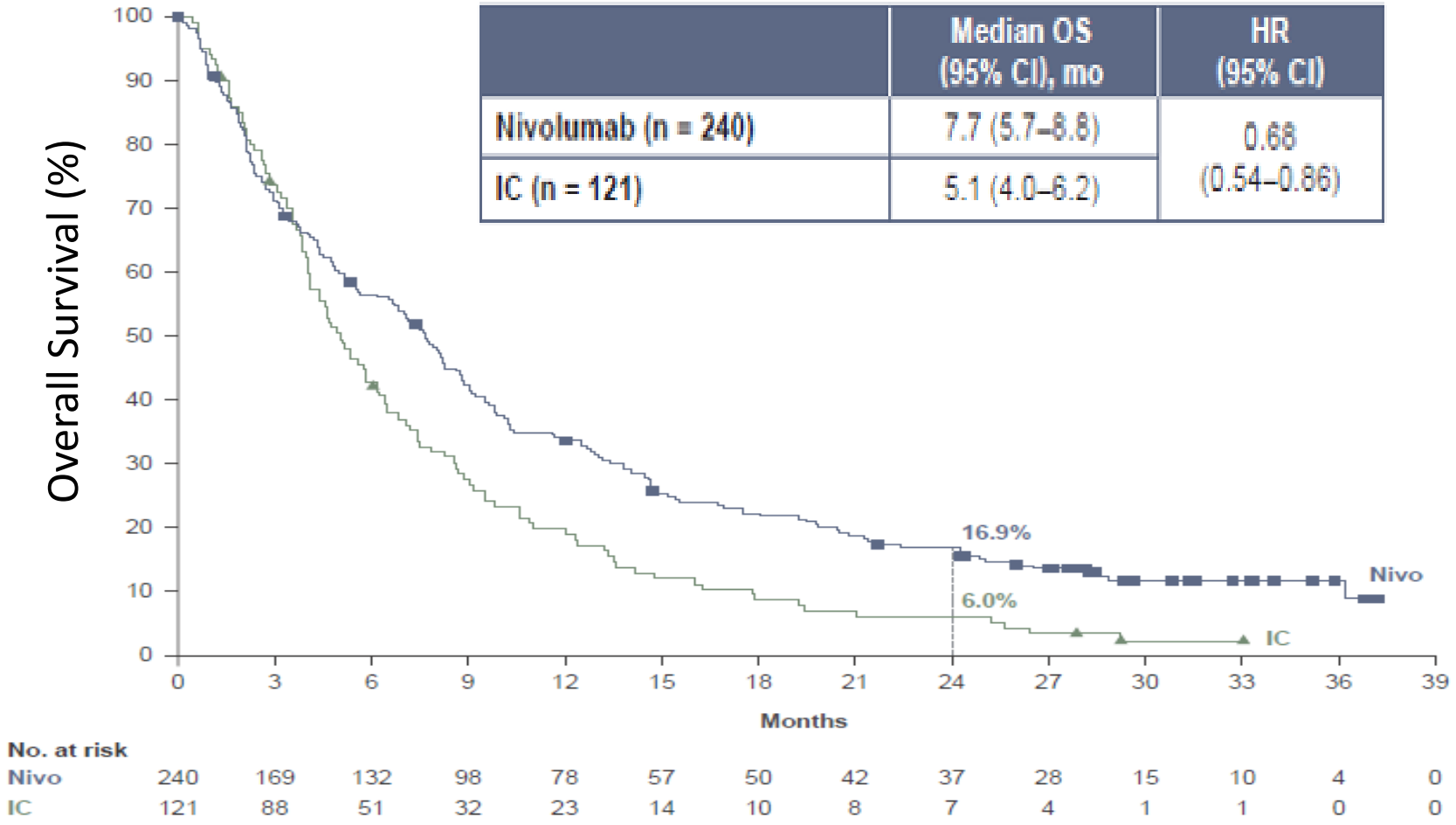
[a]Tissue required for testing

Ferris & Gillison, NEJM, 2016

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

## Overall Survival: 2 year report

| | Median OS (95% CI), mo | HR (95% CI) |
|---|---|---|
| Nivolumab (n = 240) | 7.7 (5.7–8.8) | 0.68 (0.54–0.86) |
| IC (n = 121) | 5.1 (4.0–6.2) | |

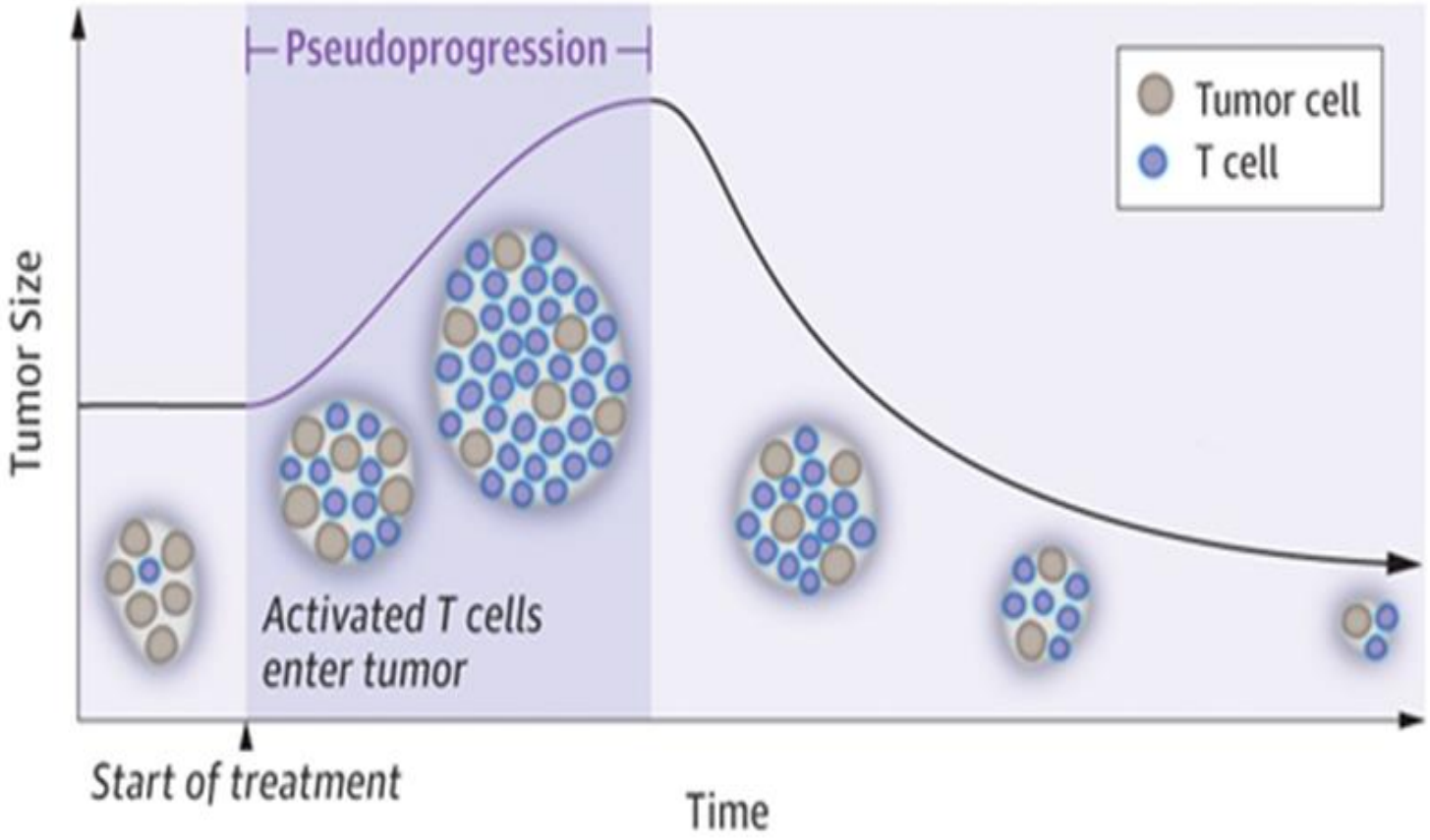



Ferris RL. Oral Oncology, 2018

# Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

## Pseudoprogression

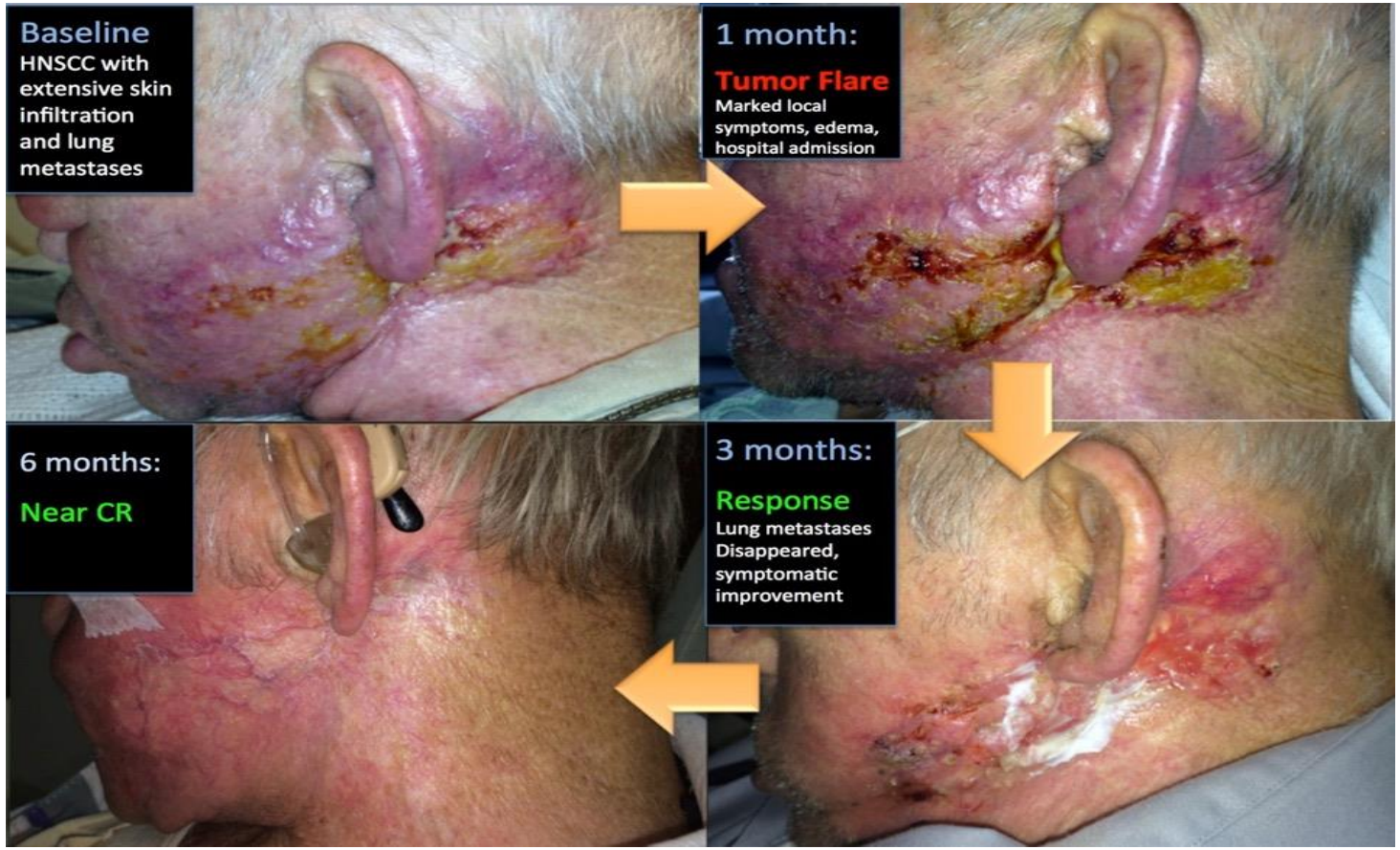
- Early appearance of an increase in tumor burden, subsequently followed by tumor regression
- Initially recognized in the melanoma trials, with incidence up to 10%




Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

# Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

## Case Report – KEYNOTE-012




- Both KEYNOTE-012 and CheckMate 141 trials showed an exceedingly rare rate of pseudoprogression with pembrolizumab and nivolumab, respectively.

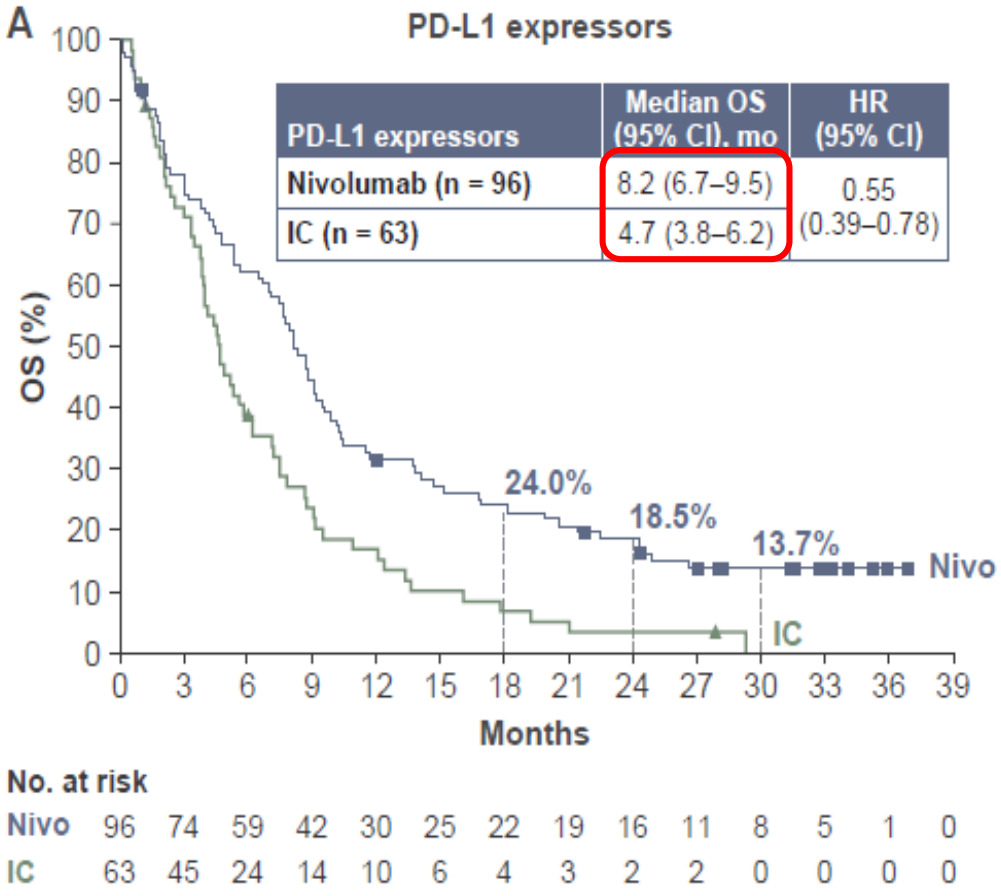
Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

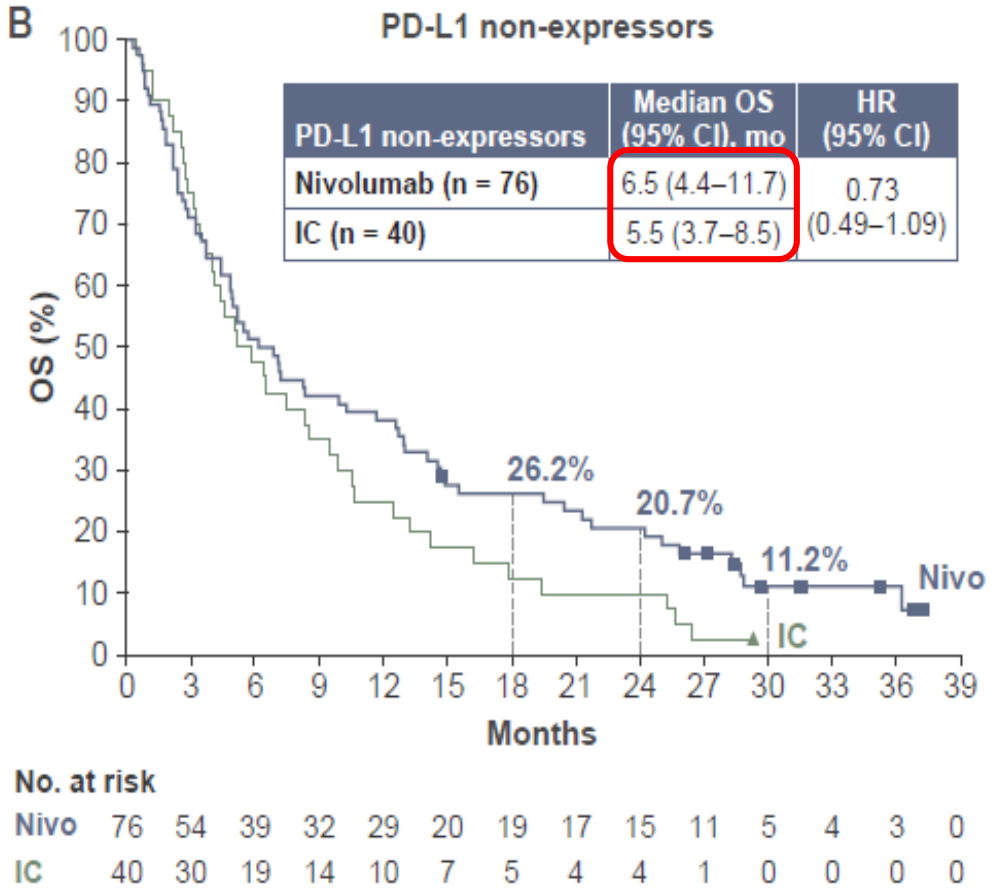
# Evaluating Biomarkers in HNSCC

- Current FDA approvals of pembrolizumab and nivolumab are NOT contingent upon tumor PD-L1 status
  - KEYNOTE - 012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - KEYNOTE - 040: Phase III pembrolizumab vs. investigator's choice chemotherapy
    - Did not meet survival endpoints in total population but improved outcomes in patients with PD-L1 expressing tumor
  - CheckMate 141: Most benefit was seen in PD-L1-positive tumors

# Evaluating Biomarkers in HNSCC

## CheckMate 141: 2 year update



# Immune-related Adverse Events

## KEYNOTE 012

**Table 2.** Treatment-Related Adverse Events by Grade Severity (all-patients-as-treated population; N = 132)

| Treatment-Related Adverse Event | Grade 1 or 2 (≥ 10% of patients), No. (%) | Grade 3 (any occurrence), No. (%) | Grade 4 (any occurrence), No. (%) |
|---|---|---|---|
| Patients with ≥ 1 event | 70 (53) | 8 (6) | 4 (3) |
| Hypothyroidism | 14 (11) | 0 | 0 |
| Immune thrombocytopenic purpura | 0 | 0 | 1 (1) |
| Abdominal pain | 1 (1) | 1 (1) | 0 |
| Colitis | 0 | 1 (1) | 0 |
| Dysphagia | 1 (1) | 1 (1) | 0 |
| Nausea | 6 (5) | 1 (1) | 0 |
| Stomatitis | 1 (1) | 1 (1) | 0 |
| Facial edema | 0 | 1 (1) | 0 |
| Fatigue | 28 (21) | 0 | 0 |
| Localized edema | 0 | 1 (1) | 0 |
| Infection | 0 | 1 (1) | 0 |
| Decreased appetite | 9 (7) | 2 (2) | 0 |
| Dehydration | 0 | 1 (1) | 0 |
| Diabetic ketoacidosis | 0 | 0 | 1 (1) |
| Hyperglycemia | 1 (1) | 0 | 1 (1) |
| Type I diabetes mellitus | 0 | 1 (1) | 0 |
| Laryngeal edema | 0 | 0 | 1 (1) |
| Pneumonitis | 2 (2) | 2 (2) | 0 |
| Respiratory distress | 0 | 1 (1) | 0 |
| Facial swelling | 3 (2) | 1 (1) | 1 (1) |

## CheckMate 141

| Event | Nivolumab (N=236) | |
|---|---|---|
| | Any Grade | Grade 3 or 4 |
| Any event | 139 (58.9)* | 31 (13.1) |
| Fatigue | 33 (14.0) | 5 (2.1) |
| Nausea | 20 (8.5) | 0 |
| Rash | 18 (7.6) | 0 |
| Decreased appetite | 17 (7.2) | 0 |
| Pruritus | 17 (7.2) | 0 |
| Diarrhea | 16 (6.8) | 0 |
| Anemia | 12 (5.1) | 3 (1.3) |
| Asthenia | 10 (4.2) | 1 (0.4) |
| Vomiting | 8 (3.4) | 0 |
| Dry skin | 7 (3.0) | 0 |
| Stomatitis | 5 (2.1) | 1 (0.4) |
| Weight loss | 4 (1.7) | 0 |
| Mucosal inflammation | 3 (1.3) | 0 |
| Peripheral neuropathy | 1 (0.4) | 0 |
| Alopecia | 0 | 0 |
| Neutropenia | 0 | 0 |

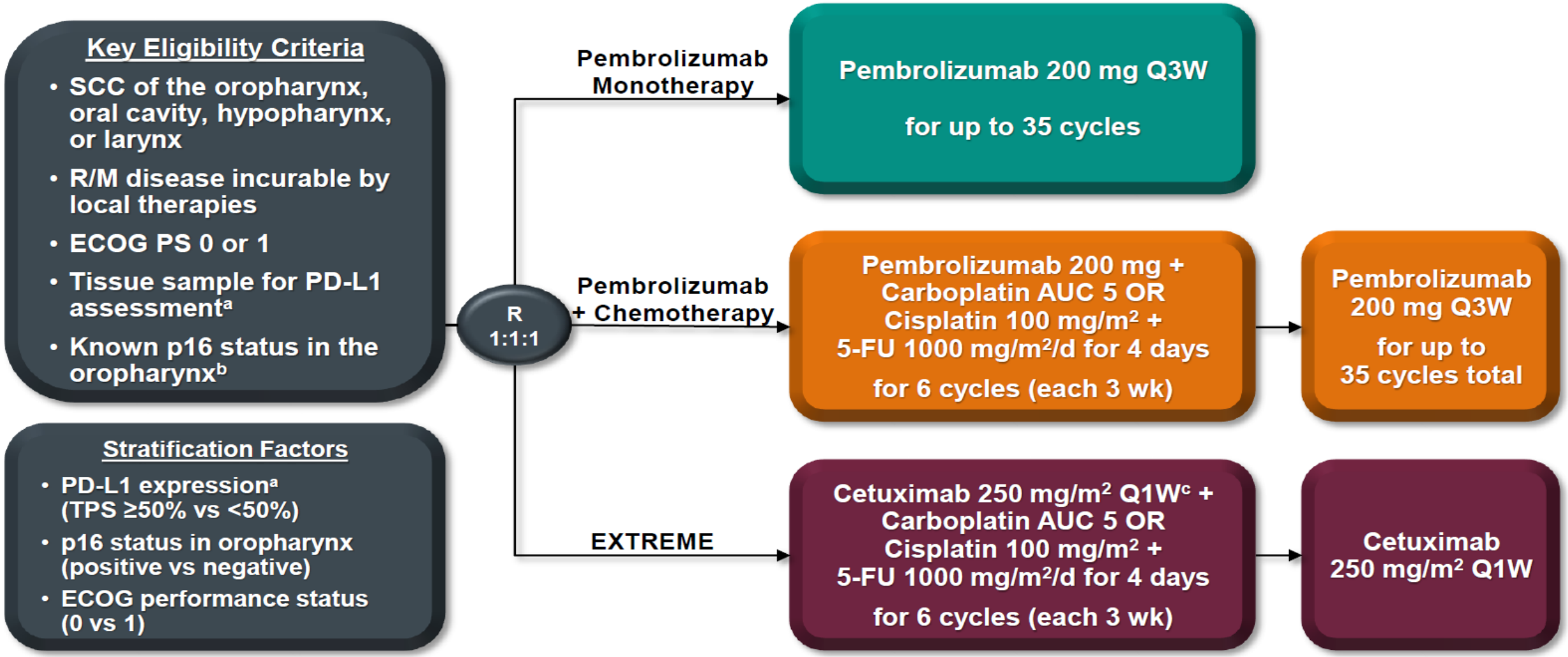
# Immune-related Adverse Events

**Table 2** General guidance for corticosteroid management of immune-related adverse events

| Grade of immune-related AE (CTCAE/equivalent) | Corticosteroid management | Additional notes |
|---|---|---|
| 1 | • Corticosteroids not usually indicated | • Continue immunotherapy |
| 2 | • If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication.<br>• If IV required, start methylprednisolone 0.5-1 mg/kg/day IV<br>• If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day<br>• Once improved to ≤grade 1 AE, start 4–6 week steroid taper | • Hold immunotherapy during corticosteroid use<br>• Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids<br>• Start proton pump inhibitor for GI prophylaxis |
| 3 | • Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone)<br>• If no improvement in 2–3 days, add additional/alternative immune suppressant<br>• Once improved to ≤ grade 1, start 4–6-week steroid taper<br>• Provide supportive treatment as needed | • Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy<br>• Consider intravenous corticosteroids<br>• Start proton pump inhibitor for GI prophylaxis<br>• Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day) |
| 4 | • Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone)<br>• If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab<br>• Provide supportive care as needed | • Discontinue immunotherapy<br>• Continue intravenous corticosteroids<br>• Start proton pump inhibitor for GI prophylaxis<br>• Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day) |

Puzanov Journal for ImmunoTherapy of Cancer 2017

# Keynote-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (NCT02358031)




[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 B et al. ESMO Munich 2018

# Keynote-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

(NCT02358031 Burtness B et al. ESMO Munich 2018

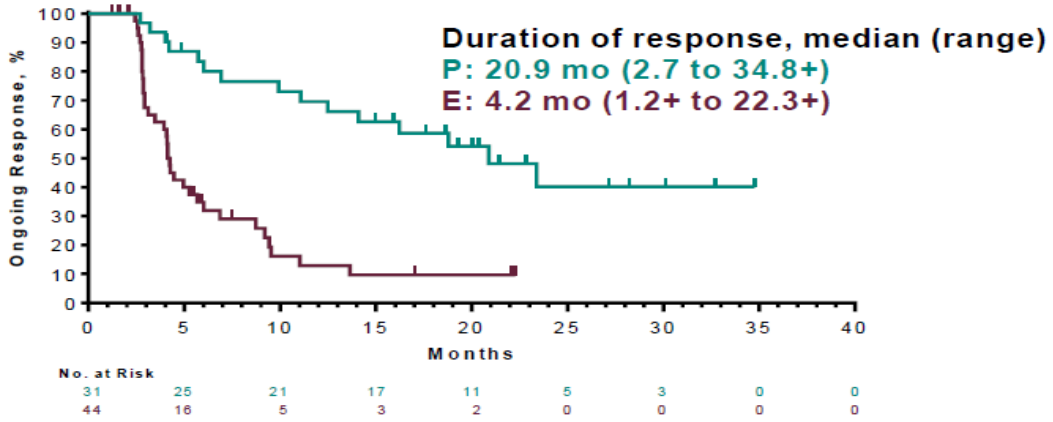
## Response Summary, P vs E

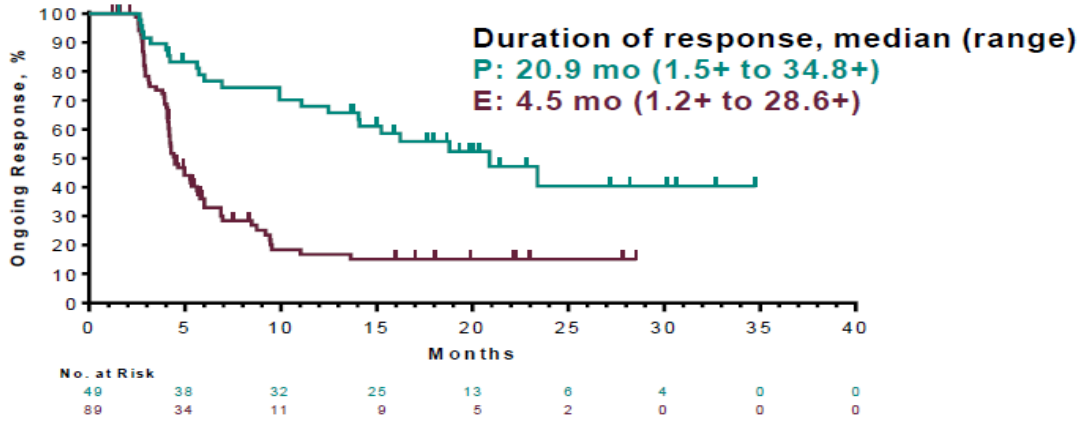
### CPS ≥20

| Confirmed Response, n (%) | Pembro N = 133 | EXTREME N = 122 |
|---|---|---|
| **ORR** | **31 (23.3)** | **44 (36.1)** |
| CR | 10 (7.5) | 4 (3.3) |
| PR | 21 (15.8) | 40 (32.8) |
| SD | 40 (30.1) | 42 (34.4) |
| PD | 42 (31.6) | 13 (10.7) |
| Non-CR/non-PD[a] | 8 (6.0) | 6 (4.9) |
| Not evaluable or assessed[b] | 12 (9.0) | 17 (13.9) |

### CPS ≥1

| Confirmed Response, n (%) | Pembro N = 257 | EXTREME N = 255 |
|---|---|---|
| **ORR** | **49 (19.1)** | **89 (34.9)** |
| CR | 14 (5.4) | 7 (2.7) |
| PR | 35 (13.6) | 82 (32.2) |
| SD | 72 (28.0) | 83 (32.5) |
| PD | 100 (38.9) | 34 (13.3) |
| Non-CR/non-PD[a] | 11 (4.3) | 11 (4.3) |
| Not evaluable or assessed[b] | 25 (9.7) | 38 (14.9) |



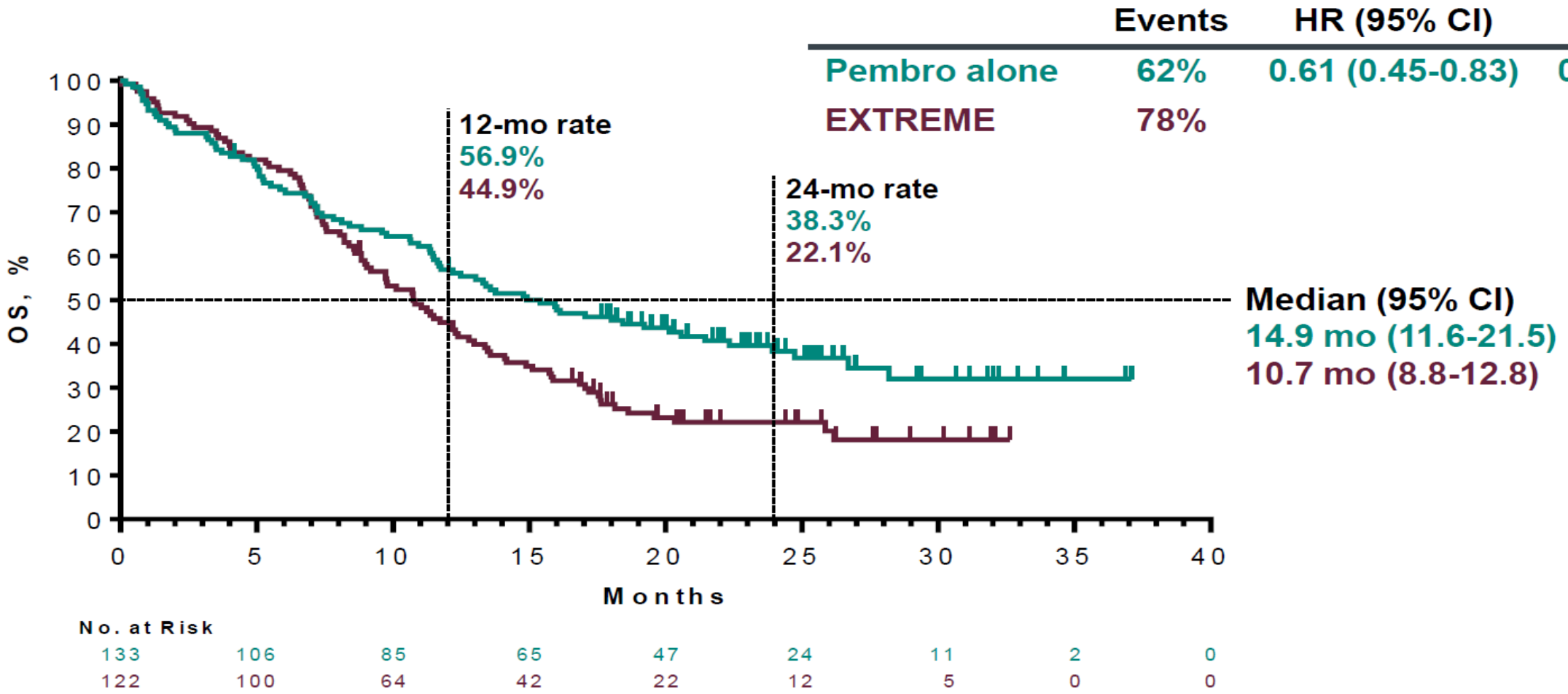




[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cutoff date: Jun 13, 2018.

# Keynote-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (NCT02358031)

Burtness B et al. ESMO Munich 2018

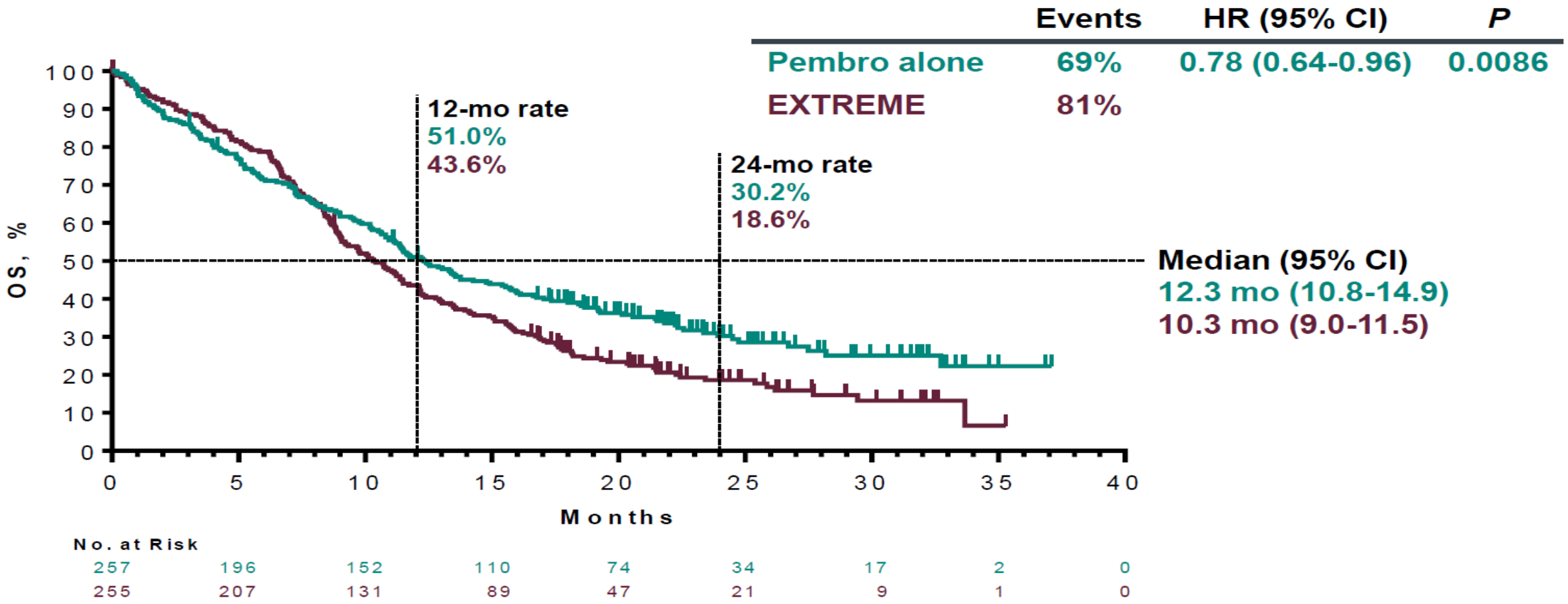
## Overall Survival: P vs E, CPS ≥20 Population



# Keynote-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (NCT02358031)

Burtness B et al. ESMO Munich 2018

## Overall Survival: P vs E, CPS ≥1 Population

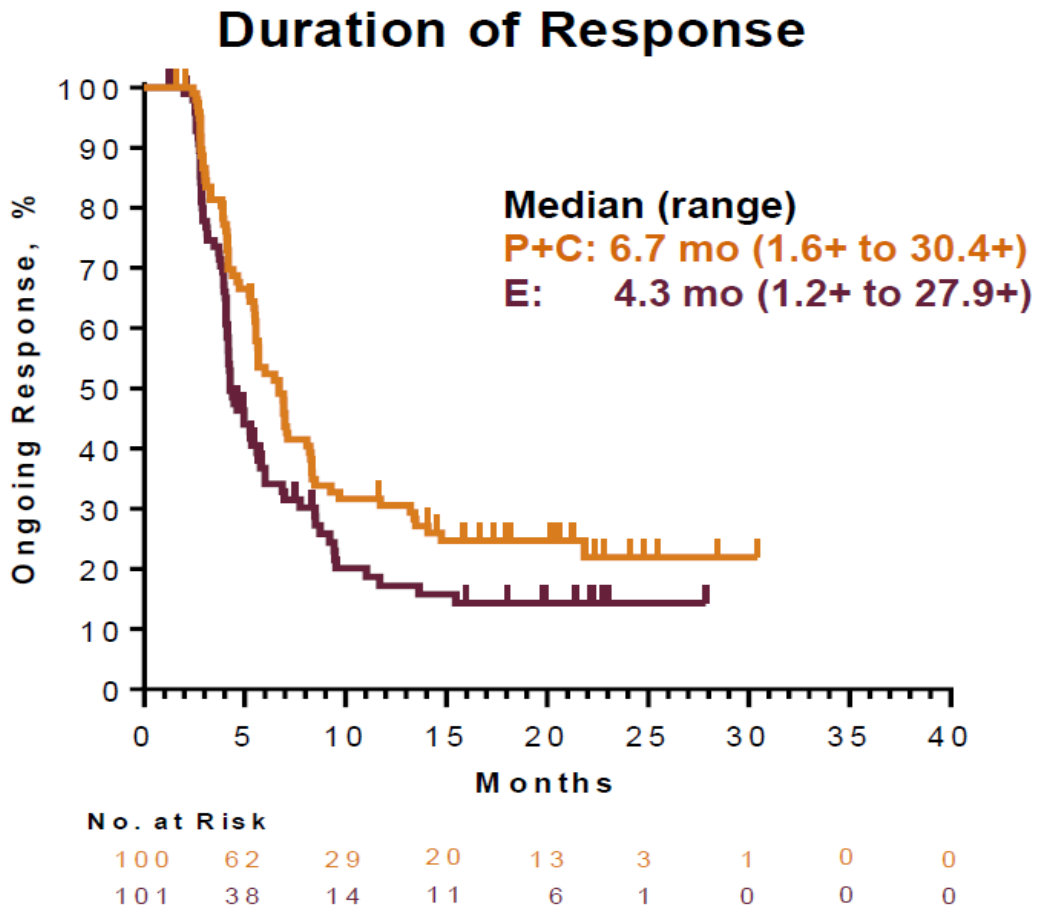


# Keynote-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

(NCT02358031 Burtness B et al. ESMO Munich 2018

## Response Summary, P+C vs E, Total Population

| Confirmed Response, n (%) | Pembro + Chemo N = 281 | EXTREME N = 278 |
|---|---|---|
| **ORR** | **100 (35.6)** | **101 (36.3)** |
| CR | 17 (6.0) | 8 (2.9) |
| PR | 83 (29.5) | 93 (33.5) |
| SD | 78 (27.8) | 94 (33.8) |
| PD | 48 (17.1) | 34 (12.2) |
| Non-CR/non-PD[a] | 13 (4.6) | 9 (3.2) |
| Not evaluable or assessed[b] | 42 (14.9) | 40 (14.4) |

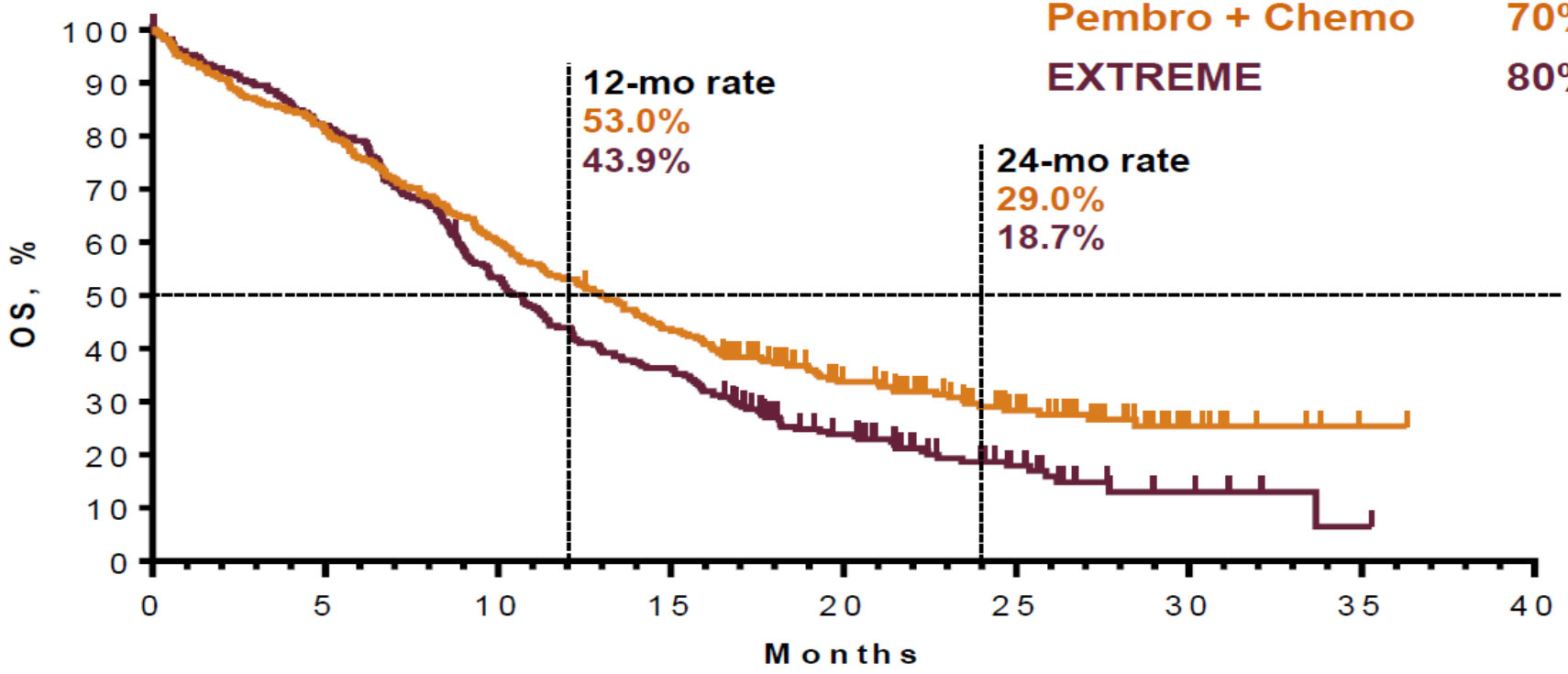


# Keynote-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

(NCT02358( Burtness B et al. ESMO Munich 2018

## Overall Survival: P+C vs E, Total Population

| | Events | HR (95% CI) | *P* |
|---|---|---|---|
| Pembro + Chemo | 70% | 0.77 (0.63-0.93) | 0.0034 |
| EXTREME | 80% | | |

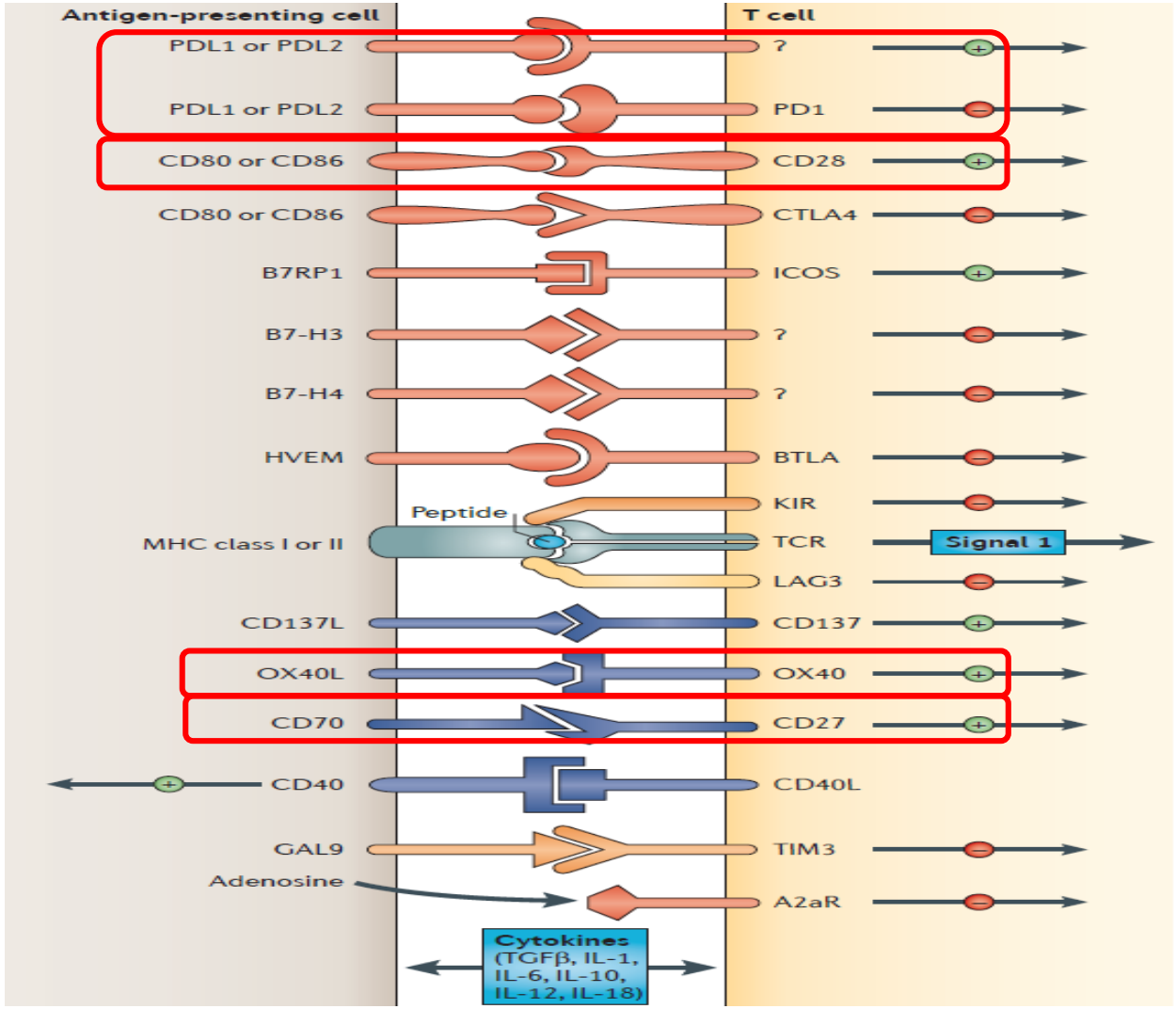



Median (95% CI)
13.0 mo (10.9-14.7)
10.7 mo (9.3-11.7)

No. at Risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 281 | 227 | 169 | 122 | 75 | 40 | 10 | 1 | 0 |
| 278 | 227 | 147 | 100 | 51 | 20 | 5 | 1 | 0 |

# Developmental Immunotherapies for HNSCC




- Durvalumab, atezolizumab, avelumab, CK-301 (anti-PD-L1)
- Cemiplimab (anti-PD-1)
- Ipilimumab, tremelimumab (anti-CTLA-4)
- Varlilumab (anti-CD27)
- PF-04518600, tavolimab (anti-OX40)

Pardoll DM Nature 2012

# Developmental Immunotherapies for HNSCC: MASTERKEY 232/KEYNOTE 137

- Talimogene laherparepvec (T-Vec)
  - Genetically engineered herpes virus
- 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

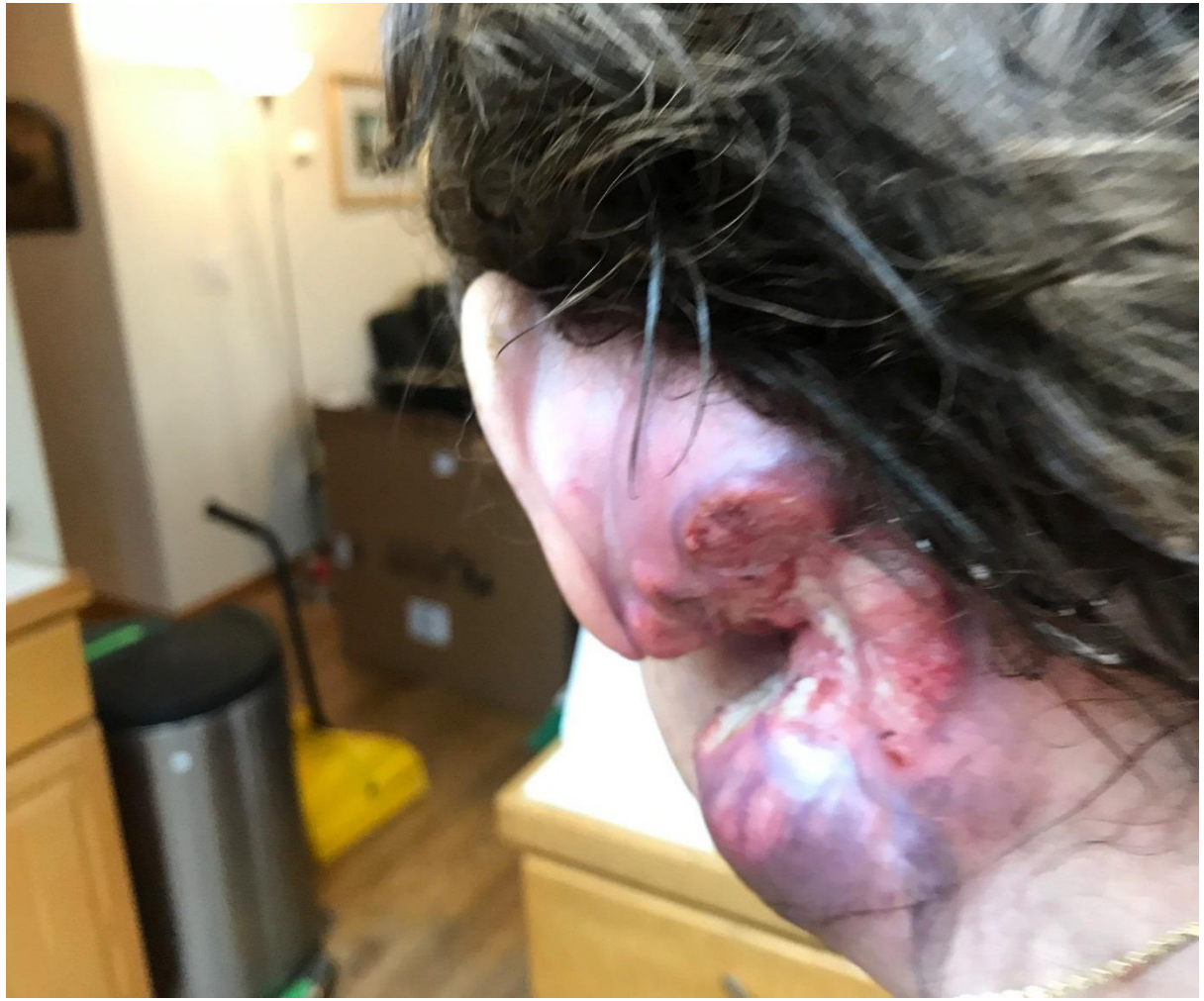
# Patient Case Study 1

59 year old female – original diagnosis stage III T2N2M0 squamous cell carcinoma of the supraglottic larynx 2012

- Treated with radiation 75Gy in 35 fractions with concurrent cisplatin completed 2/2012
- Recurrence submandibular region – resected 5/2014
- Neck recurrence - treated with neck dissection, radiation 60Gy in 30 fractions with concurrent Cetuximab 8/2014
- Local parotid recurrence, treated with Carboplatin + Taxol, 7/2015- 11/2015 with subsequent progression.
- Next options?

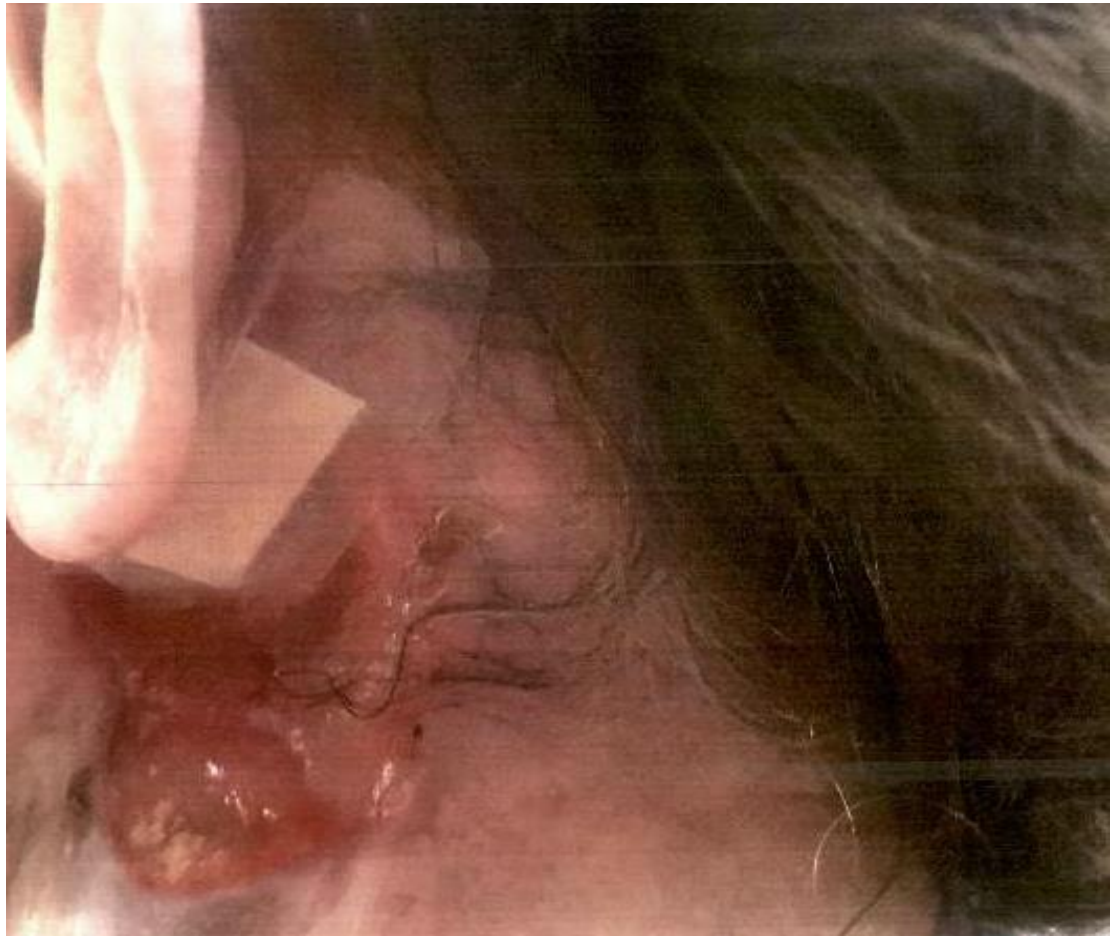
# Patient Case Study 1: July 2017

- Initial enlargement then rapid decrease and resolution with nivolumab on clinical trial x 6 months in 2016
- Subsequent progression - enrolled on two immunotherapy combination trials without benefit and continued progression in late 2016 and early 2017
- 07/2017 - Recurrence with increasing pain, lesion in her left neck area increased 40% with protrusion from left ear, headaches
- ECOG 1 and no signs metastatic spread
- Next steps?



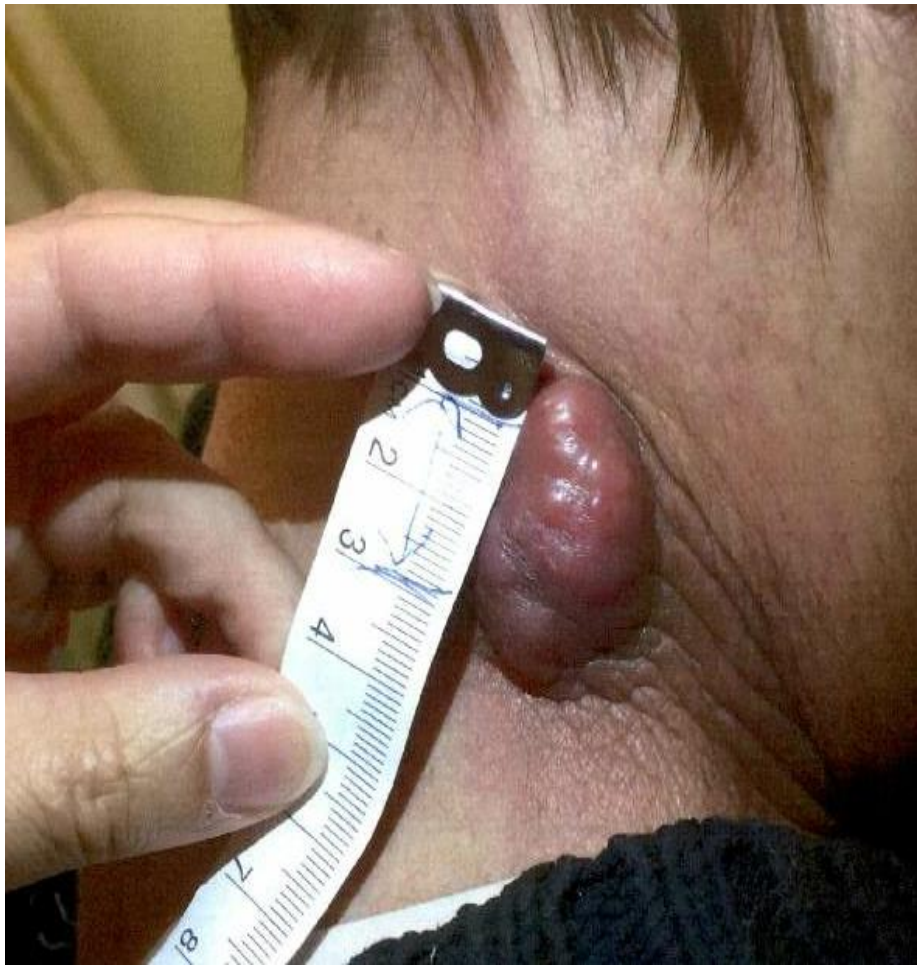
# Patient Case Study 1

- Re-treatment with chemotherapy – carboplatin and taxol weekly with complete response
- Durable to present



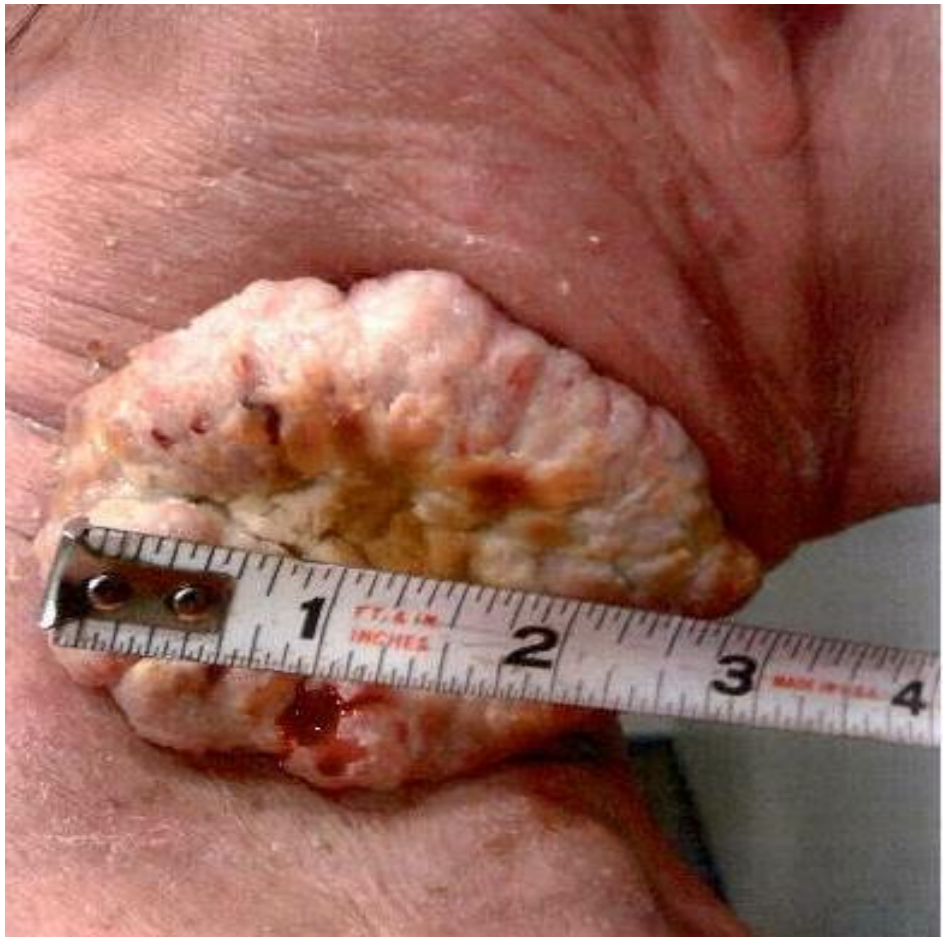
# Patient Case Study 2

- 59-y/o woman with with stage IVB of the right tonsillar base of tongue, p16 negative, prior smoker
  - Treated with docetaxel, cisplatin and 5-FU x 2 cycles with partial response followed by  weekly cetuximab with radiation 7000 gy over 35 fractions, with partial response followed by two subsequent cycles of paclitaxel, carboplatin and cetuximab x2 cycles completed January 2014.
  - Developed metastatic squamous cell carcinoma involving mediastinal lymph nodes and multiple lung metastases in August 2014
  - Started on pembrolizumab on Keynote 012 study August 2014 with near complete response in lymph nodes and lungs after 6 months of therapy
  - Developed localized neck recurrence with biopsy proven disease in summer 2015
  - Next steps?



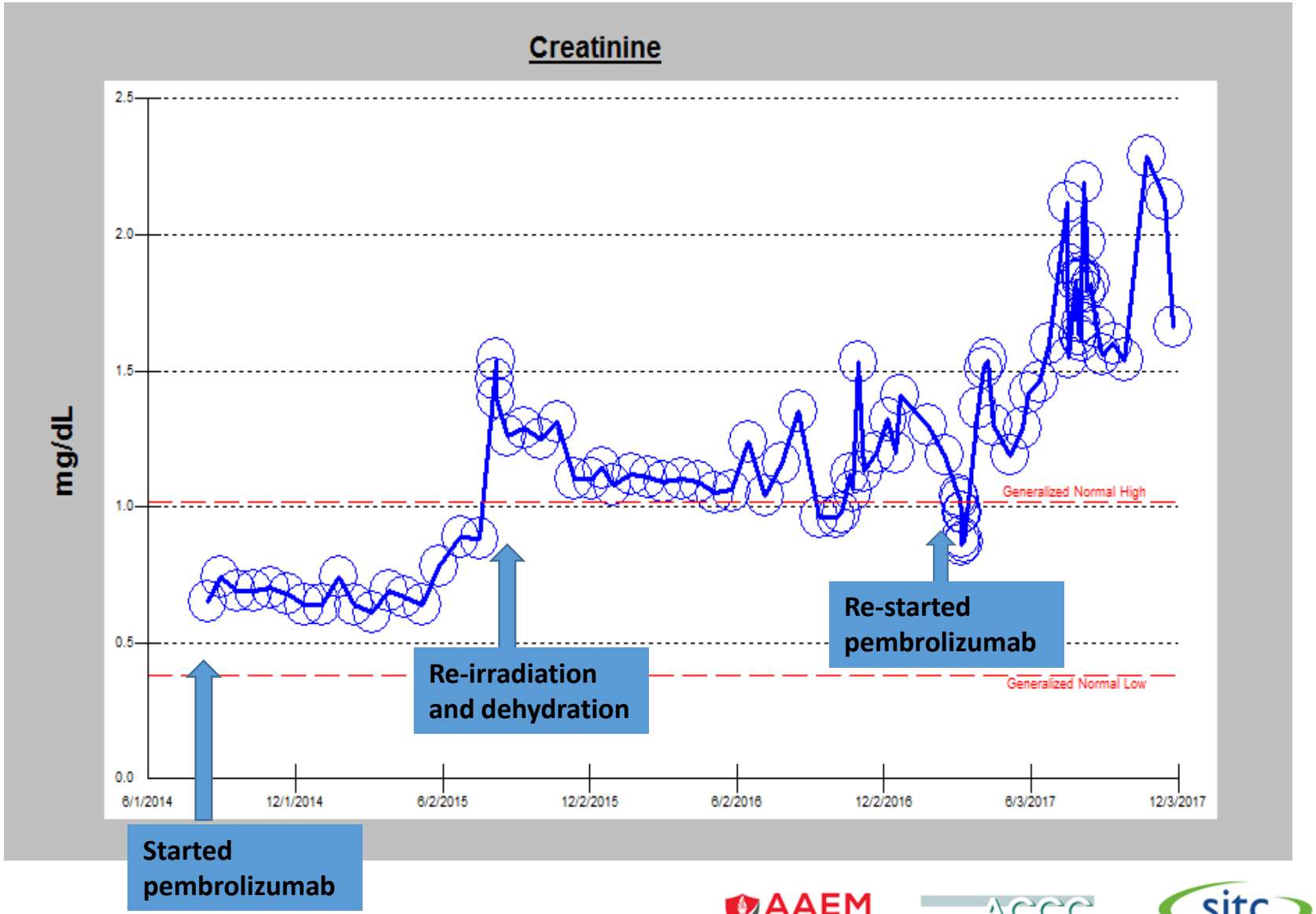
# Patient Case Study 2

- Repeat neck irradiation of 30Gy in 10 fractions complicated by mucositis and dehydration and renal insufficiency from which she recovered from.
- Continued on pembrolizumab on clinical trial until required discontinuation after 2 years of therapy
- Received first dose FDA approved pembrolizumab September 2016 with rapid progression of right neck lymph node
- Subsequently pursued two clinical trials of combination immunotherapy with continued progression
- Surgically resected/debulked disease in 2017
- Resumed pembrolizumab immunotherapy post surgery with no recurrence x 6 months



# Patient Case Study 2

- Fall of 2017 developed slight persistent elevation of creatinine to 1.5 to 1.8 mg/dl range with disease recurrence in surgical site
- Referral to nephrology – renal biopsy shows acute interstitial nephritis
- Patient passed in January 2018



# Conclusions

1. Chemotherapy offers short survival with many side effects
2. PD-1 antibodies nivolumab and pembrolizumab are approved in *platinum-refractory* recurrent / metastatic HNSCC.
3. Most patients have fewer side effects on PD-1 Abs than on chemotherapy
4. Clinical trials are underway to improve immunotherapy response rates and testing immunotherapy in other settings