Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancer

Jessica L. Geiger, MD
Associate Staff, Medical Oncology
Assistant Professor, Lerner College of Medicine of Case Western Reserve University

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

sitc Society for Immunotherapy of Cancer

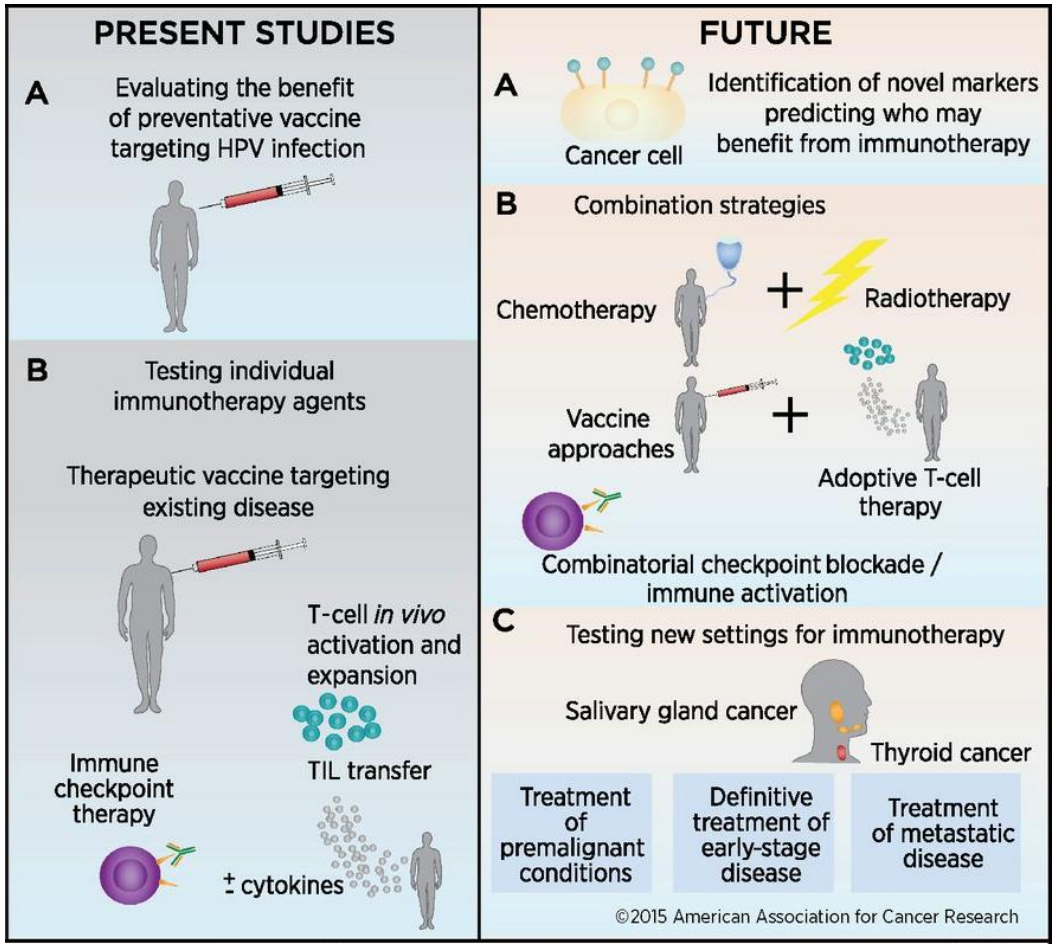
Disclosures

- Regeneron (research funding, advisory board)
- Genentech (research funding)

- 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
  - Therapeutic vaccines for established cancers
  - CAR-T and cell-mediated therapies
  - Combinations with immunotherapies



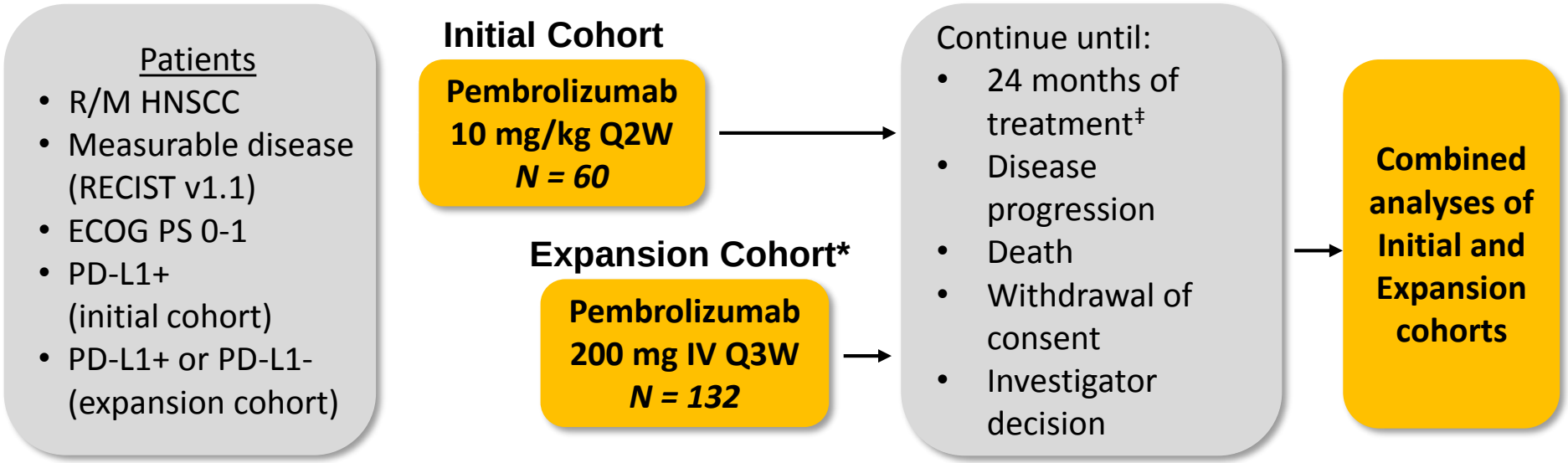
Schoenfeld, Cancer Immunol Res, 2015

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

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 §

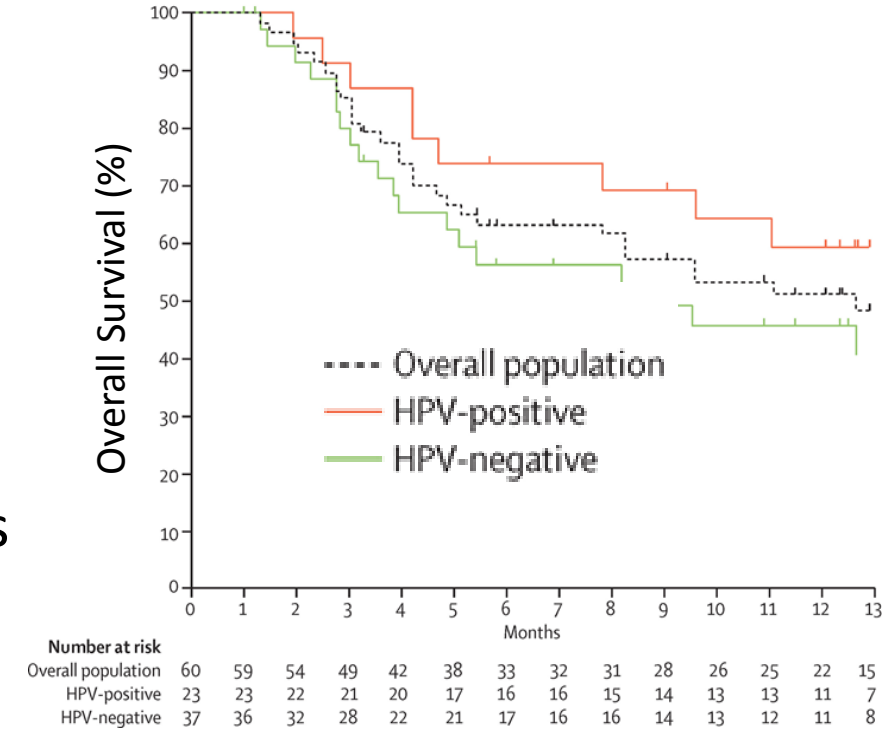
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

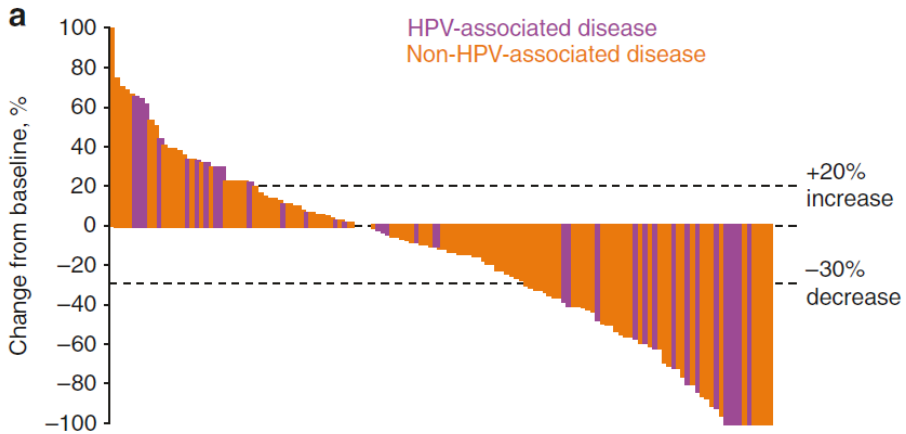
Seiwert, ASCO 2017.

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

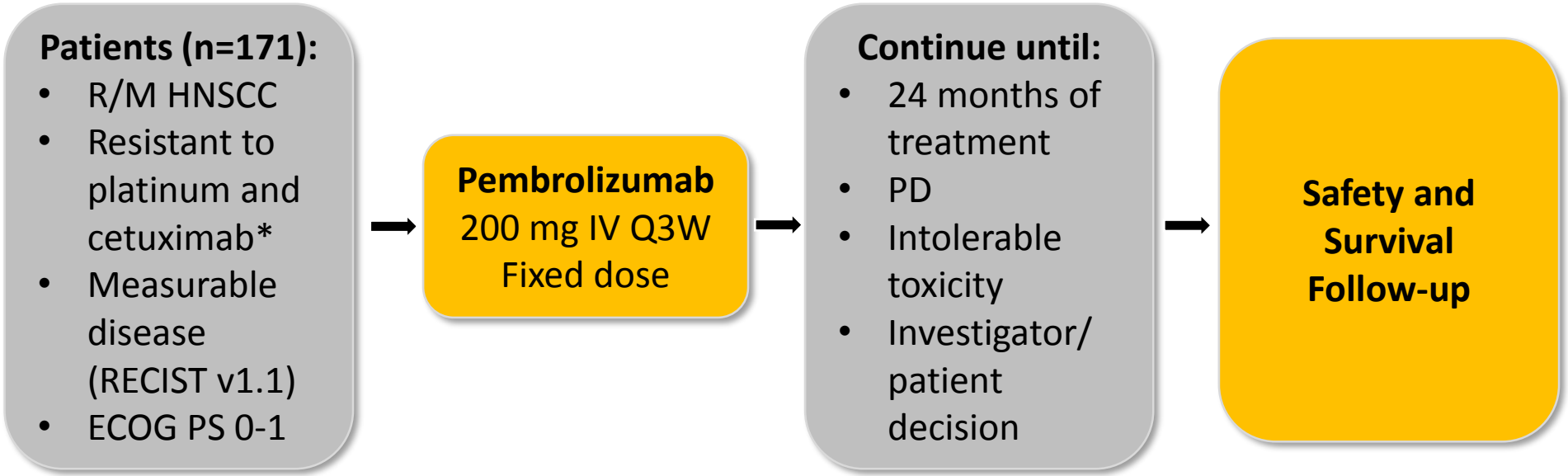




Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

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

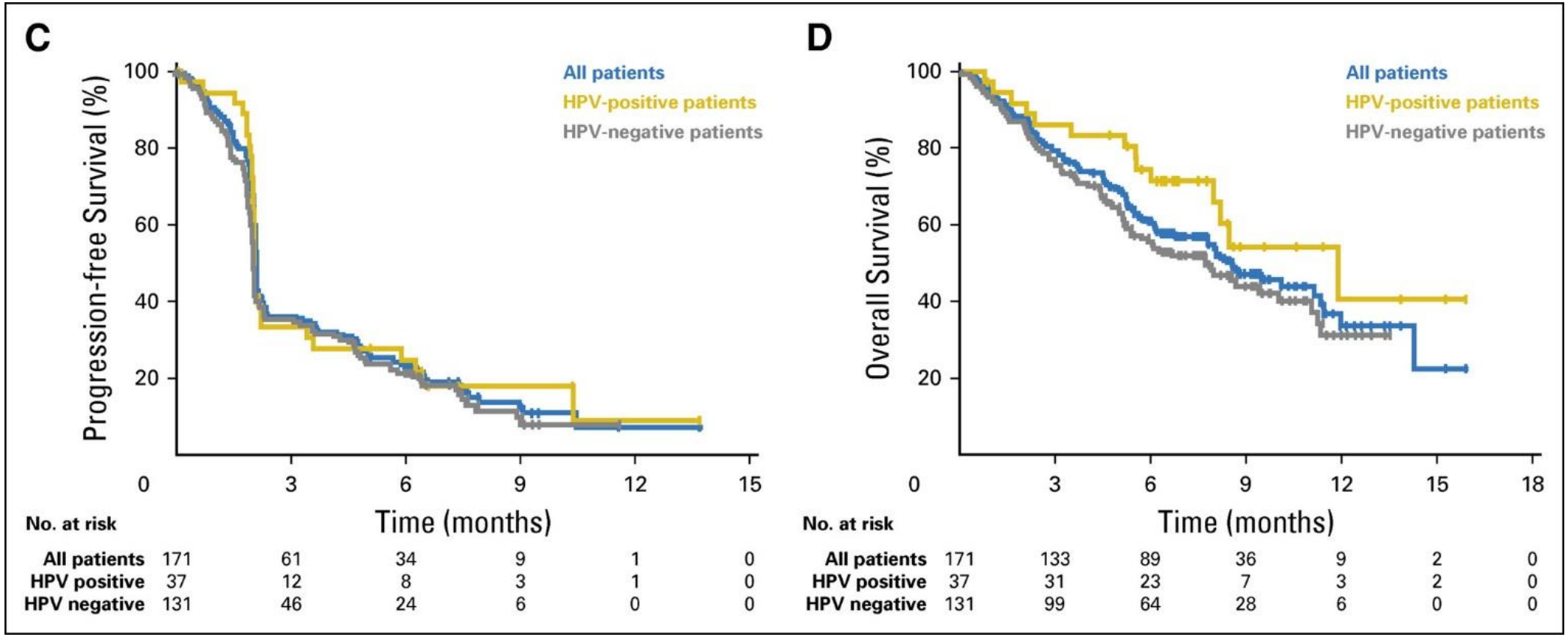
Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*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

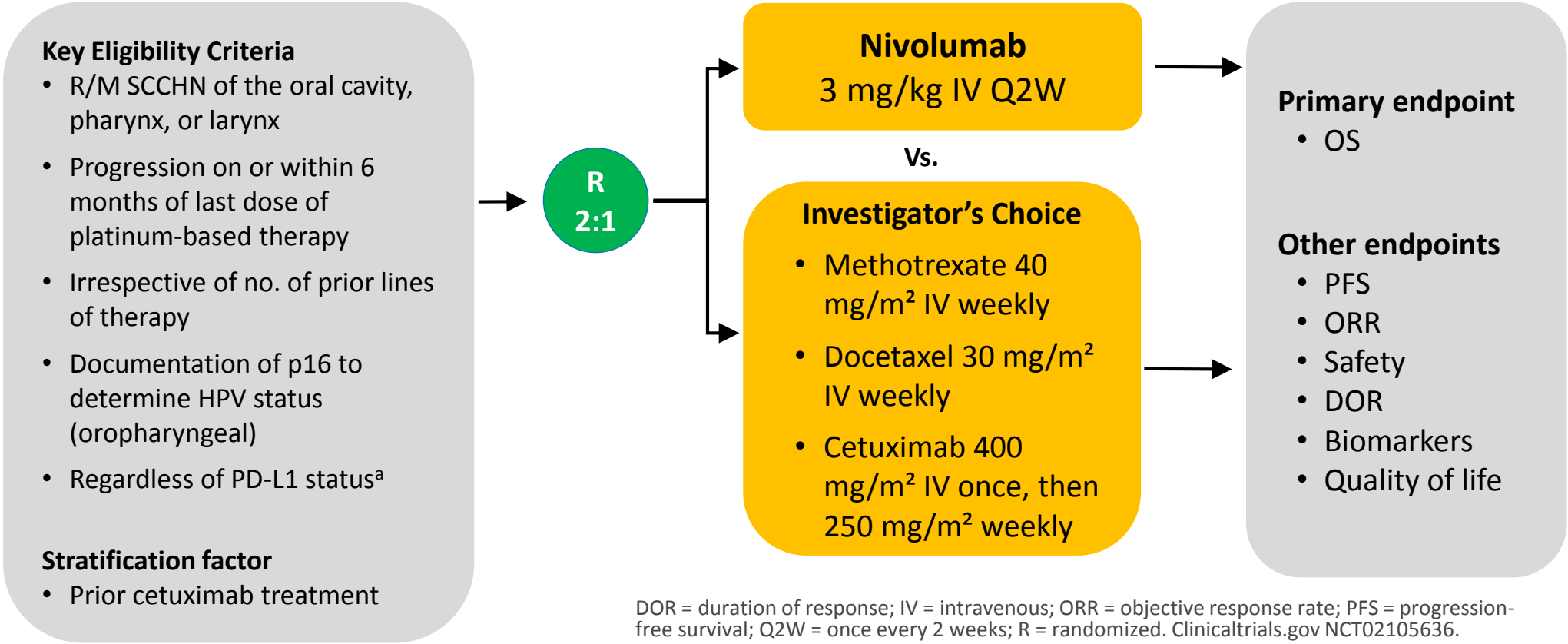
Phase II Trial, Single Arm



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.

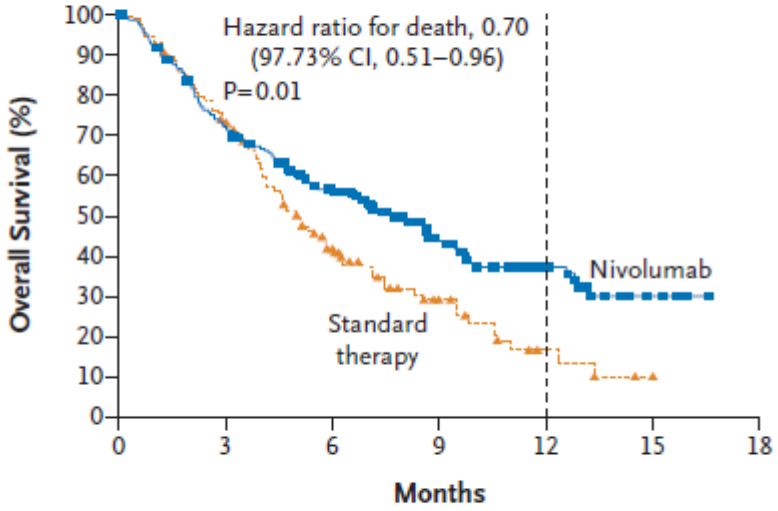
[a]Tissue required for testing

Ferris & Gillison, NEJM 2016.

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

A Overall Survival

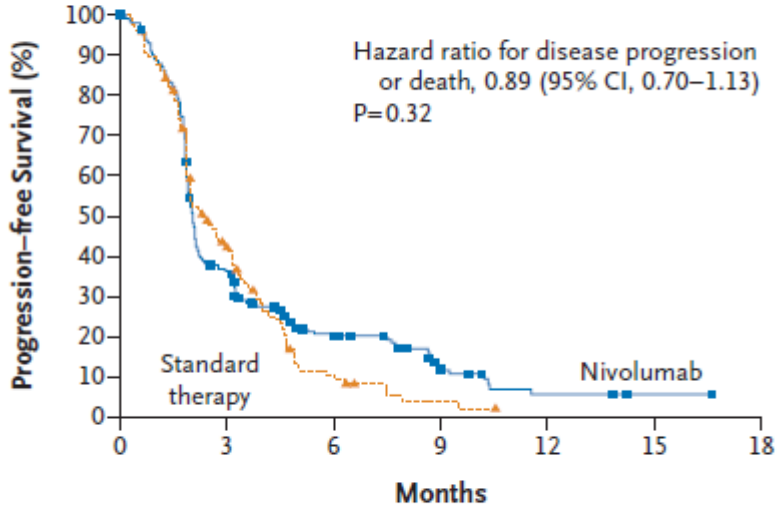
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



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

→

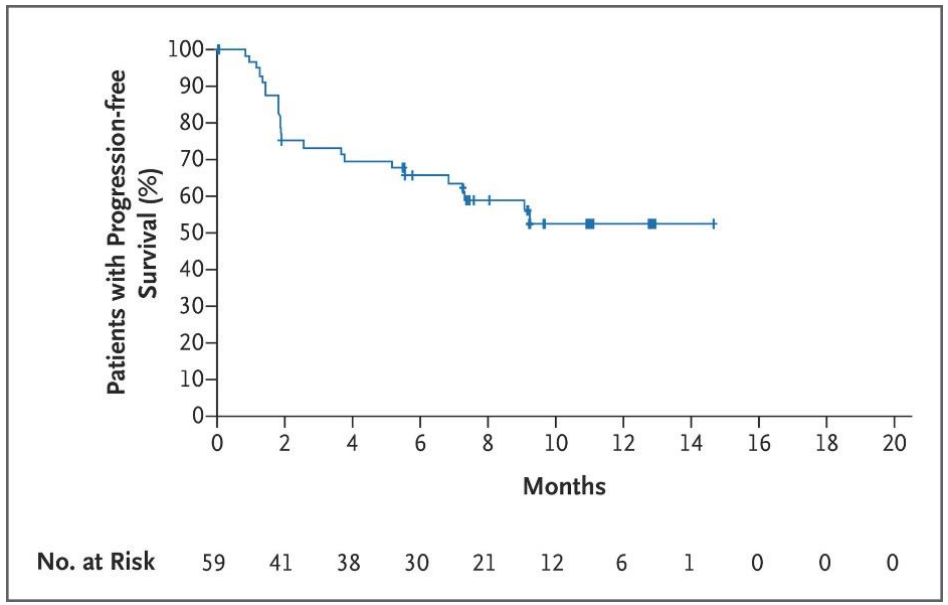
Primary endpoint
- Response rate

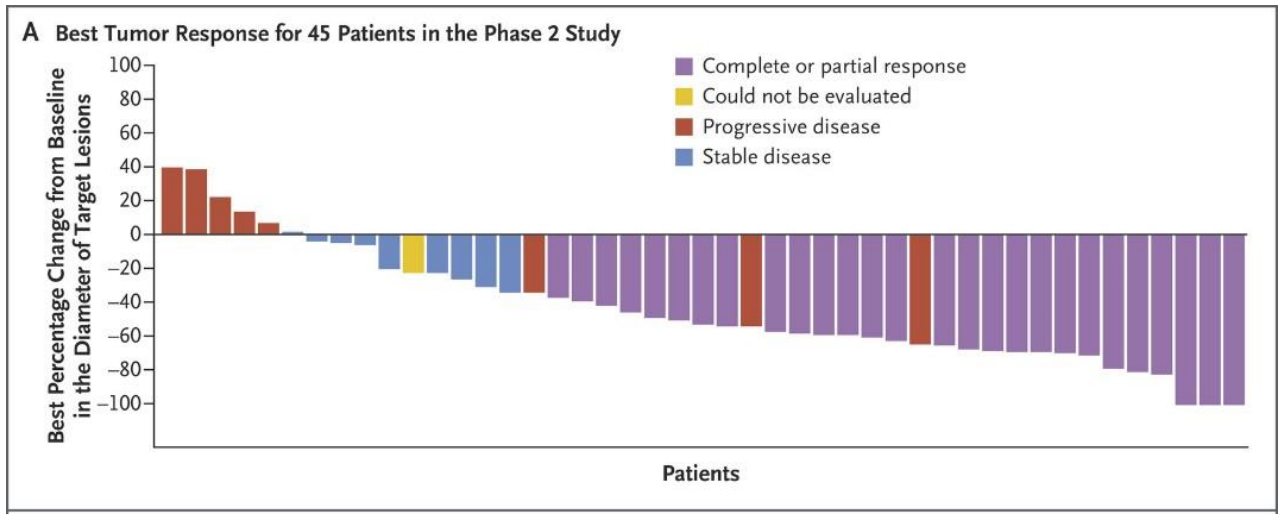
Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

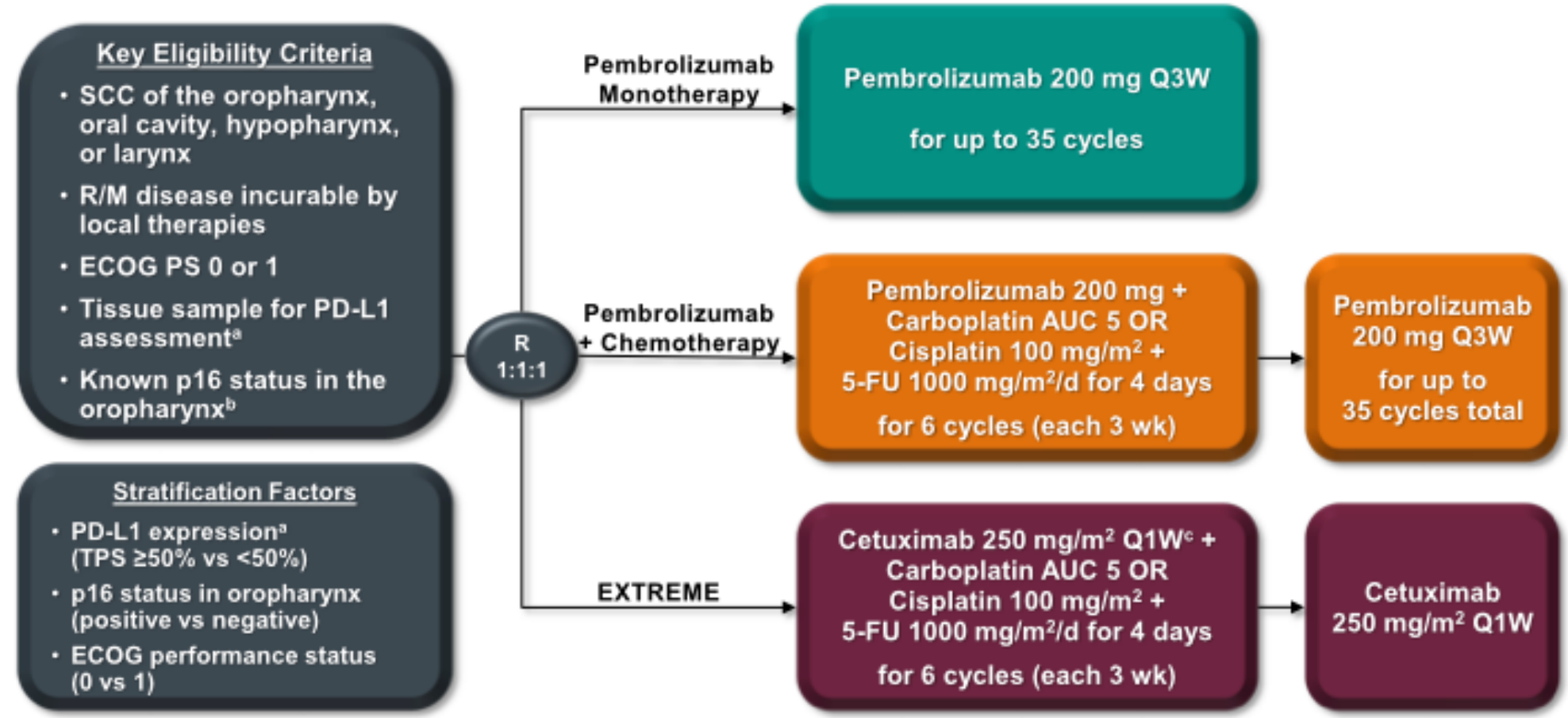
- Cemiplimab (anti-PD-1) 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response





Migden, NEJM 2018.

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

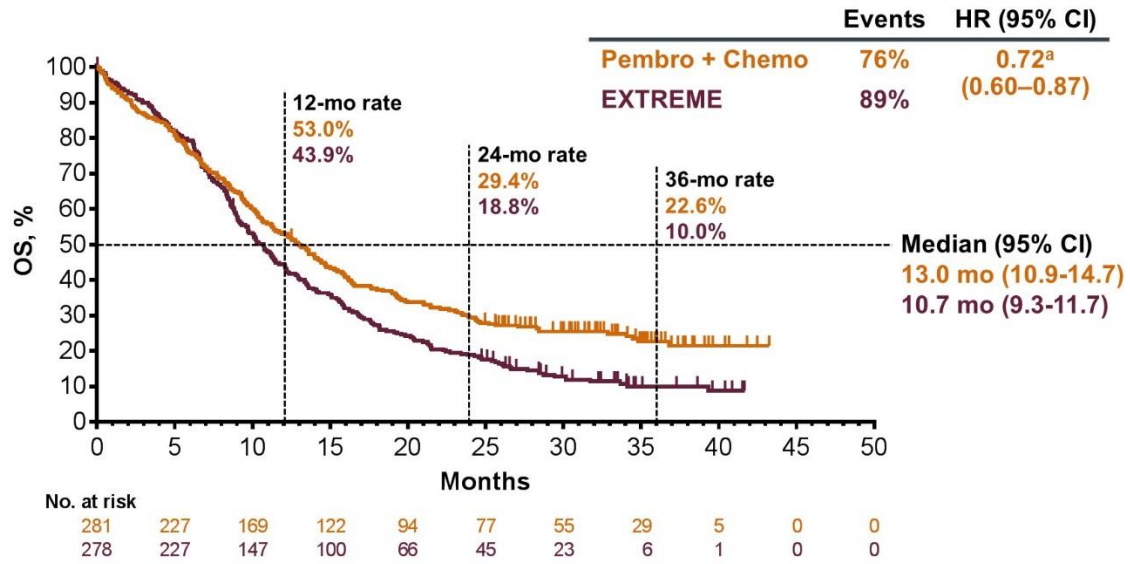


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

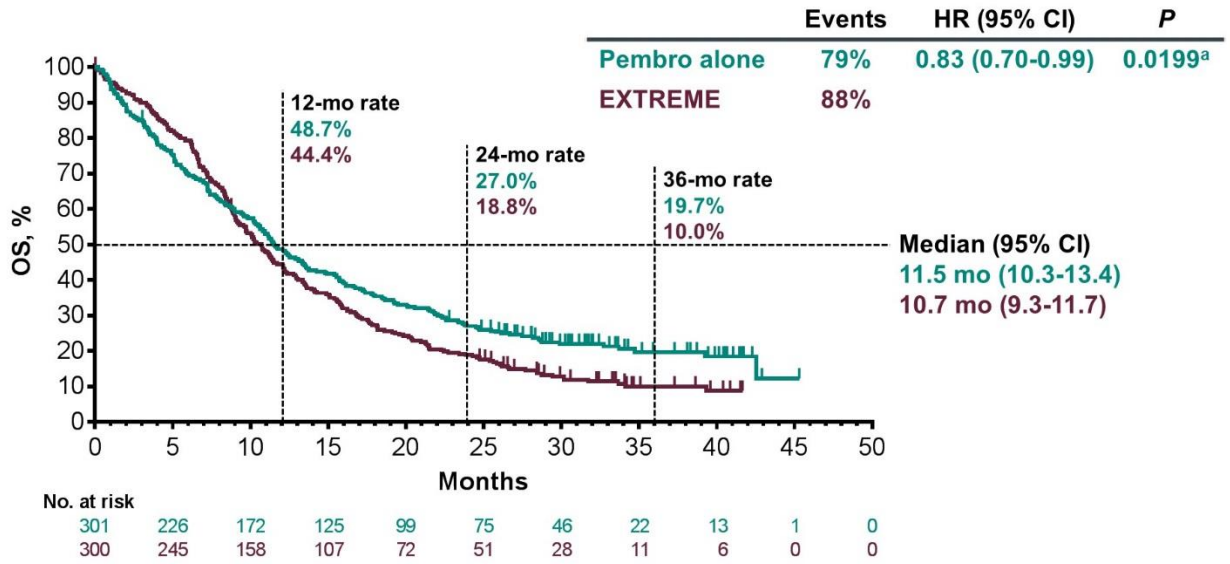
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

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.

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

Evaluating Biomarkers in HNSCC

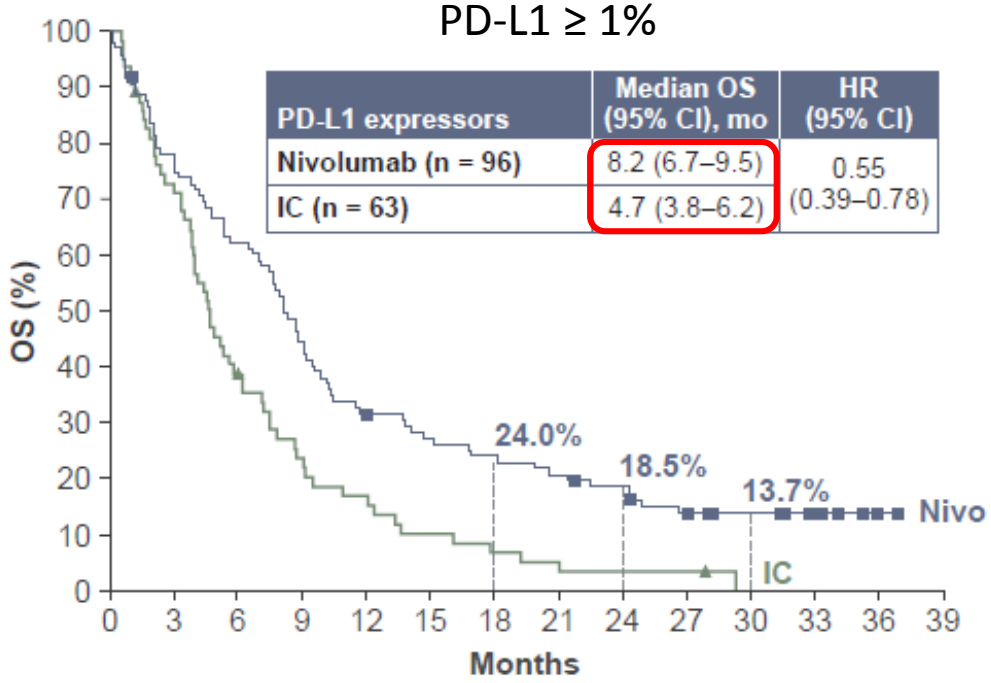
- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit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

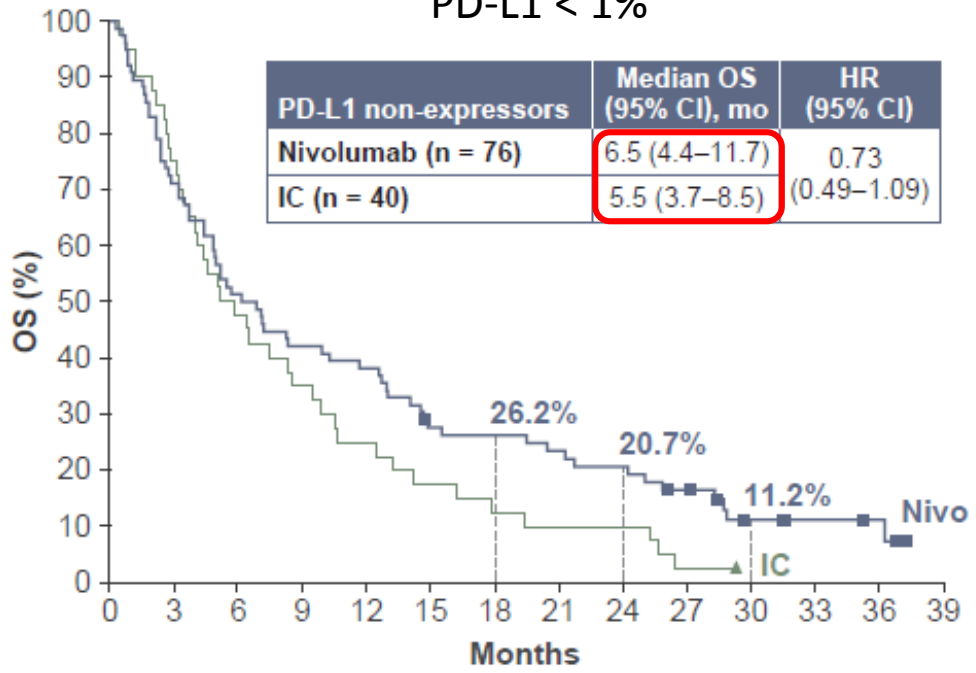


No. at risk

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*]

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

Case Study 1

- A 59 year old male was diagnosed with T1 N1 (multiple cervical LN, <3 cm) SCC of the left base of tongue, p16+ (Stage I, AJCC 8th edition; Stage IVA, AJCC 7th edition)
- Completed definitive CRT with weekly cisplatin and post-treatment imaging confirms complete response with no evidence of disease
- Approximately 2 years later, the patient presents with new cough. CT chest reveals new bilateral pulmonary nodules
- CT guided biopsy of lung nodule: poorly differentiated SCC, non-keratinizing, p16+

Case Study 1

- **What is the next step in management?**
- A. Treat with EXTREME chemotherapy regimen
- B. Treat with PD-1 inhibitor
- C. Continue to monitor given low tumor burden
- D. Treat with combination chemotherapy plus PD-1 inhibitor
- E. Request PD-L1 CPS testing on biopsy specimen to guide therapy

Case Study 1

- A. Treat with EXTREME chemotherapy
  - Incorrect – while this may be an option, the patient may also be considered for immunotherapy incorporated into treatment, either single-agent or in combination with chemotherapy, based on CPS score
- B. Treat with PD-1 inhibitor
  - Incorrect – while single-agent pembrolizumab or nivolumab are approved in the second line of treatment following platinum, single agent pembrolizumab is also approved frontline in patients with CPS≥1. This may or may not be an option in this patient.
- C. Continue to monitor
  - Incorrect – would not wait for further progression to initiate systemic therapy
- D. Treat with combination chemotherapy plus PD-1 inhibitor
  - Incorrect – this may be a correct answer as pembrolizumab is approved in combination with platinum/5-FU chemotherapy in the frontline setting regardless of PD-L1 expression; however, we should first obtain PD-L1 information
- B. Request PD-L1 CPS testing on tissue
  - Correct – PD-L1 expression will help guide the most appropriate therapy for this patient

Case Study 1

- The patient's PD-L1 CPS≥1. What are the treatment options for this patient?
- A. Pembrolizumab
- B. Nivolumab
- C. EXTREME regimen
- D. cisplatin + 5-FU + pembrolizumab
- E. A and B
- F. A and D
- G. A, C, and D
- H. A, B, C, and D

Case Study 1

- A. Pembrolizumab
- B. Nivolumab
- C. EXTREME regimen
- D. cisplatin + 5-FU + pembrolizumab
- E. A and B
- F. A and D
- G. A, C, and D
- H. A, B, C, and D

- As the patient demonstrates a positive CPS, his frontline therapeutic options include:
  - Single-agent pembrolizumab (KN048 for CPS≥1)
  - Pembrolizumab + platinum/5-FU (KN048, regardless of PD-L1 expression)
  - EXTREME chemotherapy

Case Study 1

- A 62 year old gentleman presents with a neck mass and odynophagia. He is found to have a 2.5 cm left tonsillar lesion and left-sided cervical lymphadenopathy. FNA of the neck mass reveals squamous cell carcinoma. IHC for p16 is strongly and diffusely positive. He is an active smoker with a history of 2 ppd x 40 years. PET/CT is negative for distant metastatic disease, and the patient is clinically staged as T2 N1 (Stage I, AJCC 8th edition) with multiple ipsilateral cervical lymph nodes involved. The patient declines primary surgery and wishes to proceed with definitive CRT.

Case Study 1

- What do you recommend for this patient?
- A. Concurrent chemoradiation with cisplatin
- B. Cisplatin, pembrolizumab, and RT

Case Study 2

- What do you recommend for this patient?
- Option A (cisplatin + RT) is currently the standard of care for definitive treatment of advanced HNSCC.
- The addition of immunotherapy to the backbone of chemoradiation is under investigation but should not be utilized outside of a clinical trial.

Case Study 2

- The patient completes treatment, receiving a total of 70 Gy of radiation to the left tonsil and left neck in addition to a total of 200 mg/m2 cisplatin chemotherapy administered concurrently.

- Post-treatment PET/CT imaging demonstrates complete anatomic and metabolic response to treatment.

- The patient continues with oncologic surveillance with annual chest imaging given smoking history. One year later, imaging reveals multiple bilateral lung nodules.

Case Study 2

- What do you recommend for this patient?
- A. Proceed with frontline therapy in the metastatic setting.
- B. Proceed with biopsy to confirm metastatic disease.

Case Study 2

- What do you recommend for this patient?

- Option B is the appropriate answer – to confirm metastatic disease but also to evaluate for PD-L1 expression, as this may influence recommendations for treatment frontline.

Case Study 2

- The patient undergoes CT-guided biopsy of a lung nodule, confirming metastatic disease.
- PD-L1 testing is negative (CPS<1).
- The patient maintains an excellent performance status and has no risk factors precluding use of immunotherapy.

Case Study 2

- What do you recommend for this patient?
- A. Pembrolizumab or nivolumab single-agent therapy
- B. Chemotherapy + pembrolizumab

Case Study 2

- Option B is the appropriate answer (chemotherapy + pembrolizumab). This combination is approved in all patients regardless of PD-L1 expression as per Keynote 048.

- Single-agent pembrolizumab is approved in the frontline R/M setting only in CPS≥1 patients, as per Keynote 048.

- Nivolumab as a single agent is not approved as frontline therapy in R/M HNSCC.