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

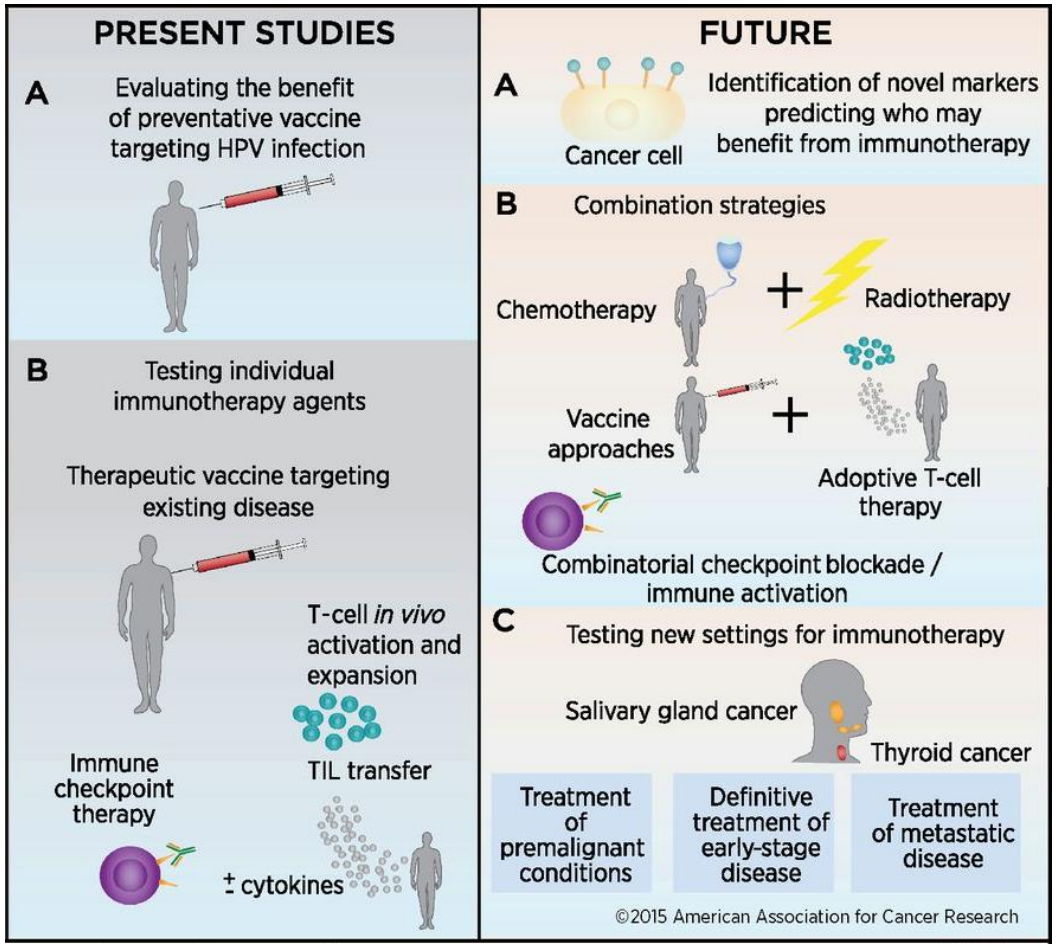
Disclosures

- Advisory boards: AstraZeneca, Rakuten, Klus Pharma
- Research support: Pharmacyclics, Pfizer, BerGenBio

- 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



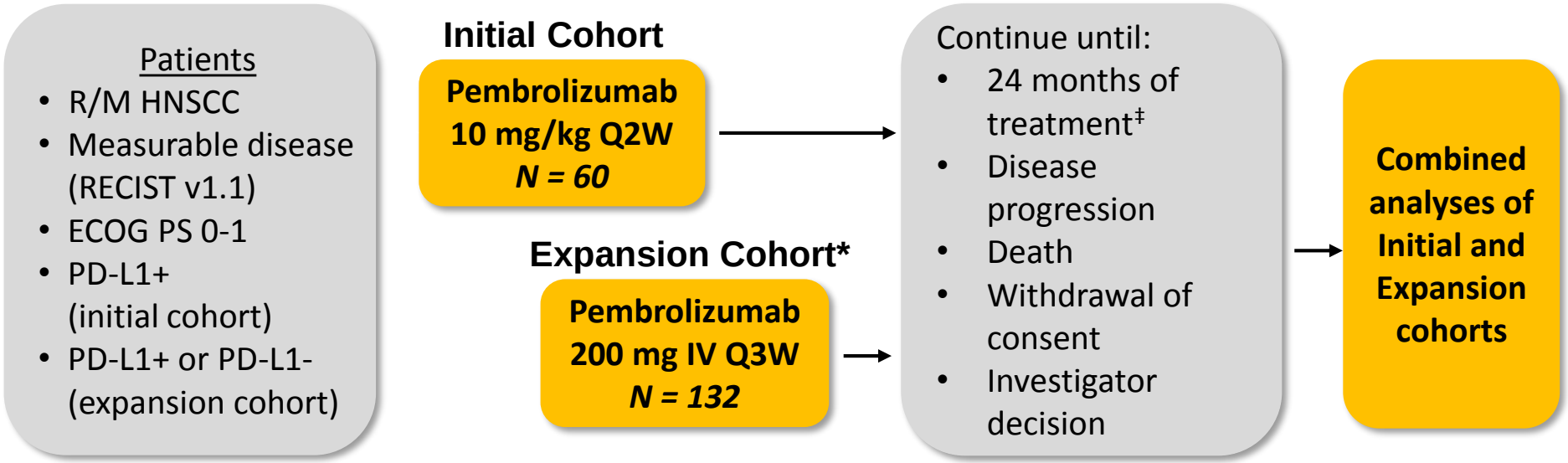
Schoenfeld, Cancer Immunol Res, 2015

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 §

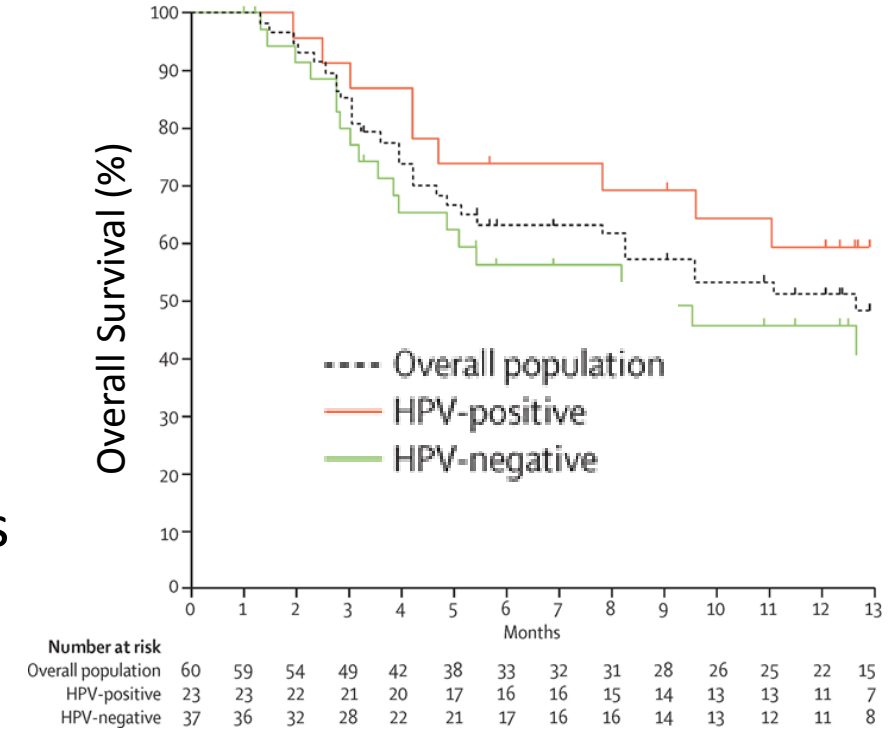
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

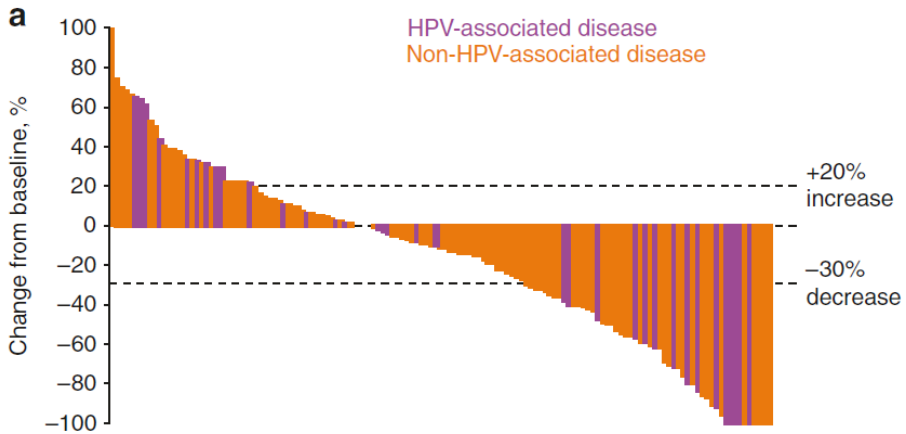
Seiwert, ASCO 2017.

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

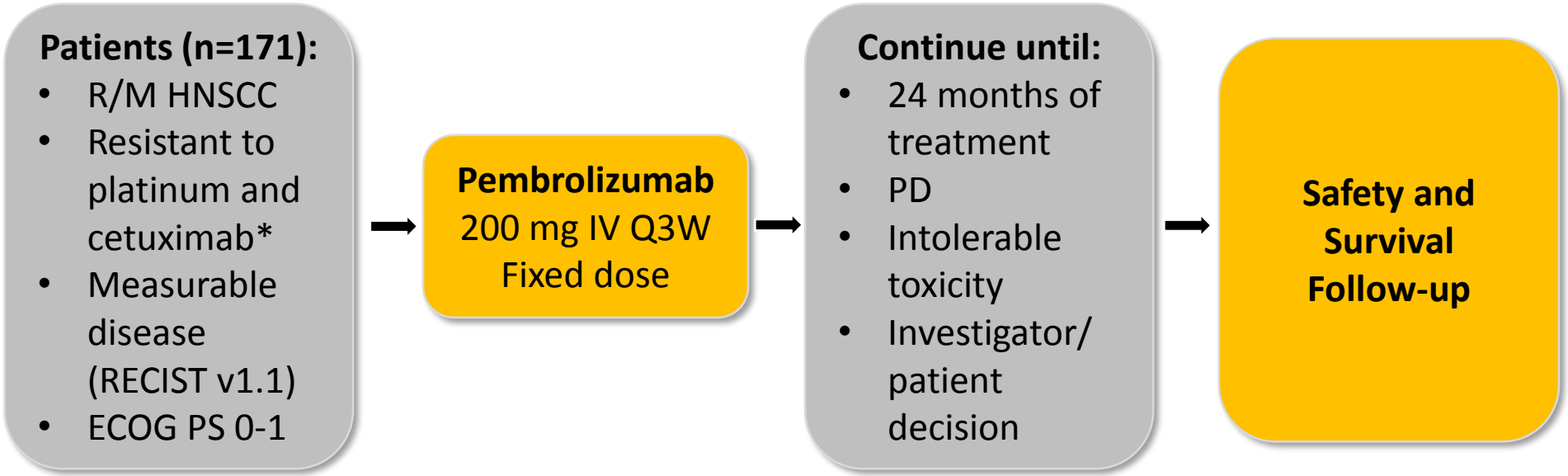




Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

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

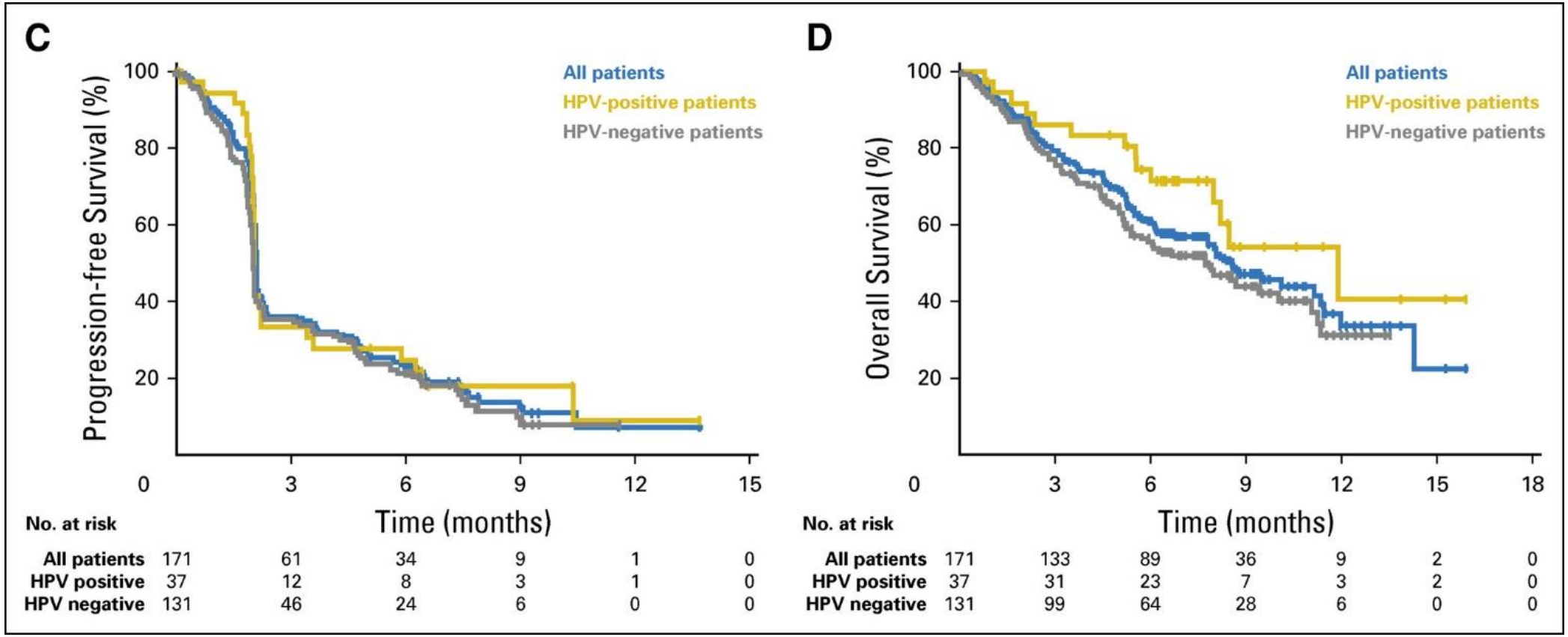
Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*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

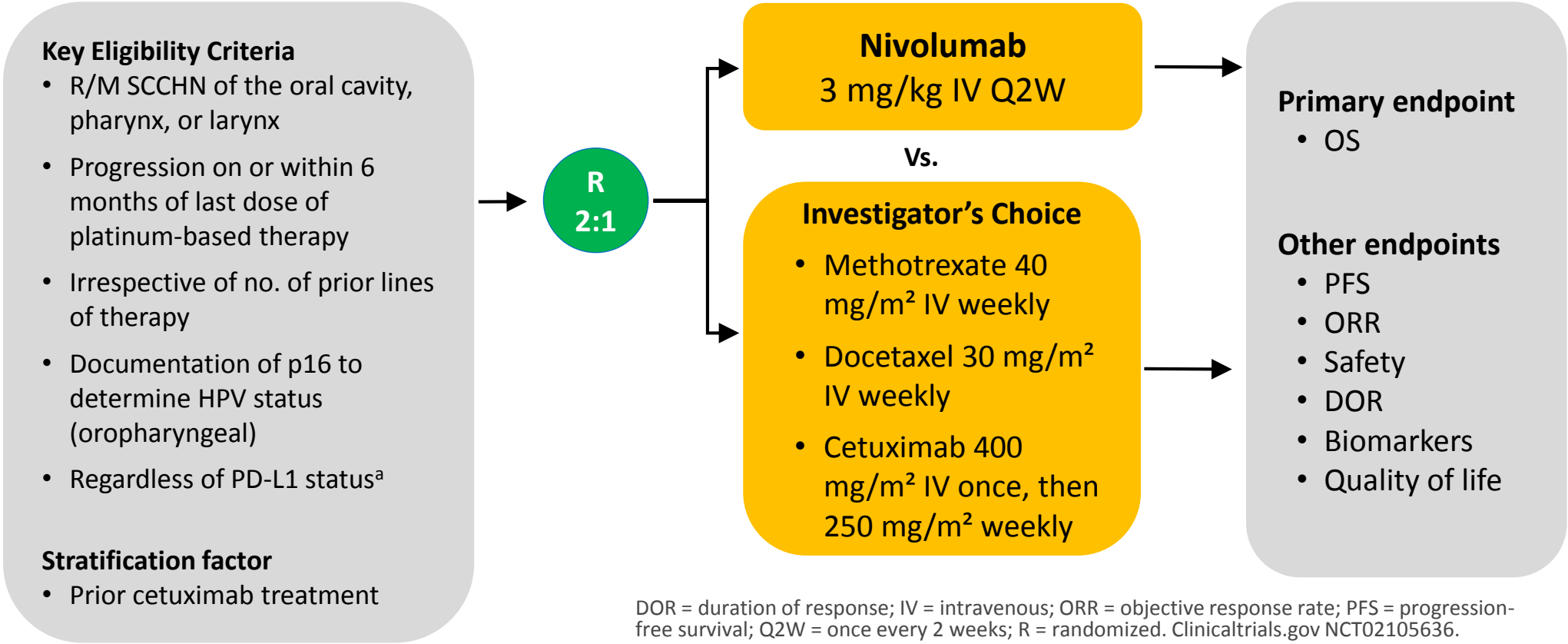
Phase II Trial, Single Arm



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.

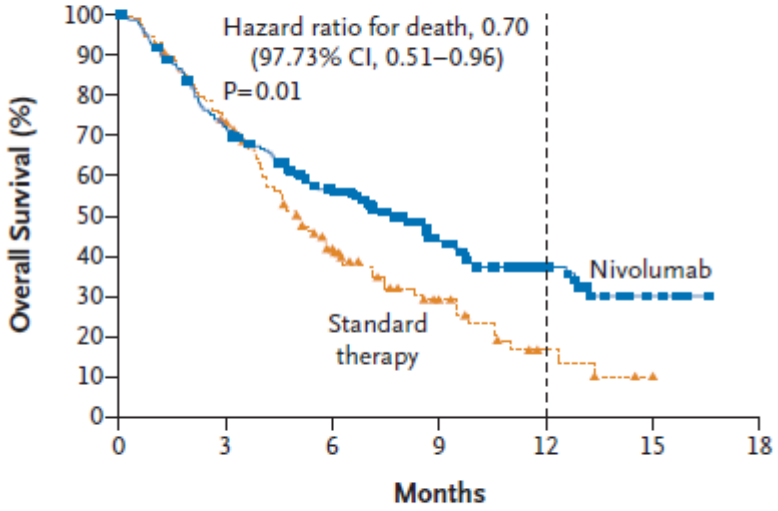
[a]Tissue required for testing

Ferris & Gillison, NEJM 2016.

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

A Overall Survival

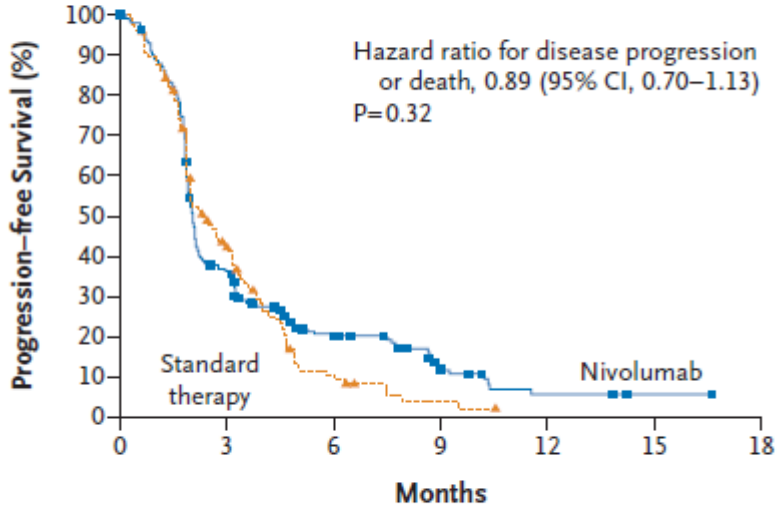
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



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

→

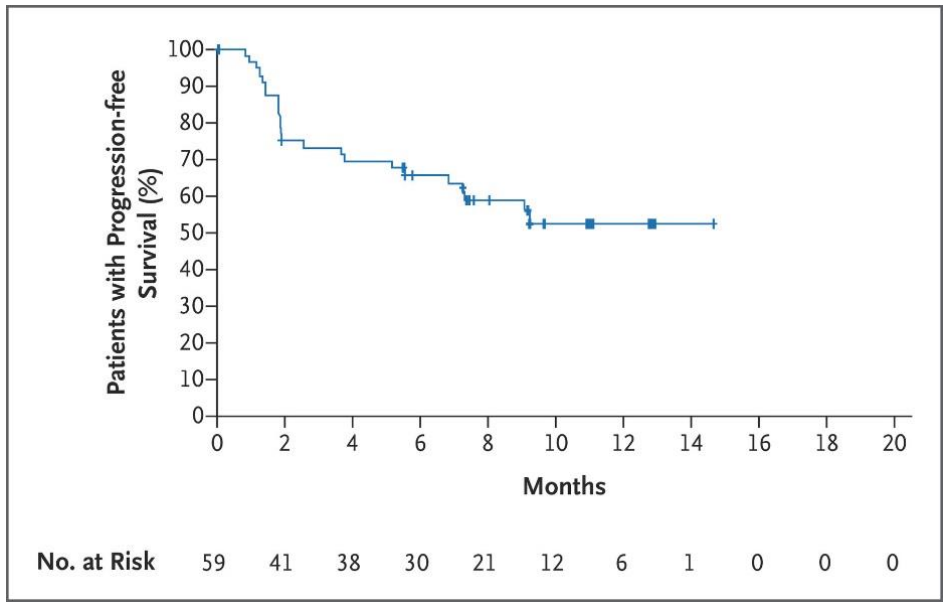
Primary endpoint
- Response rate

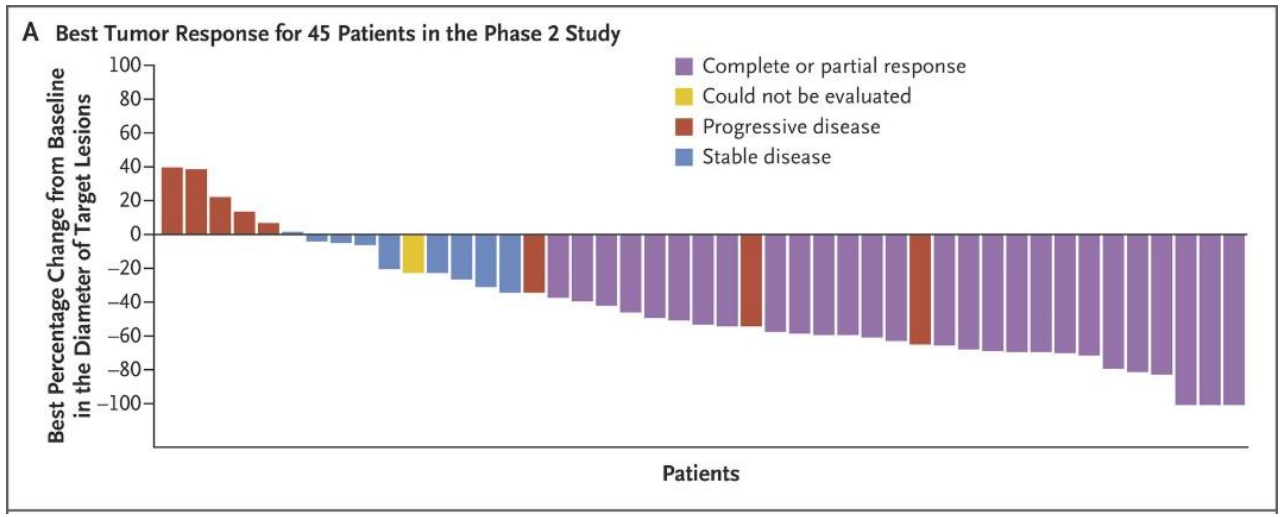
Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

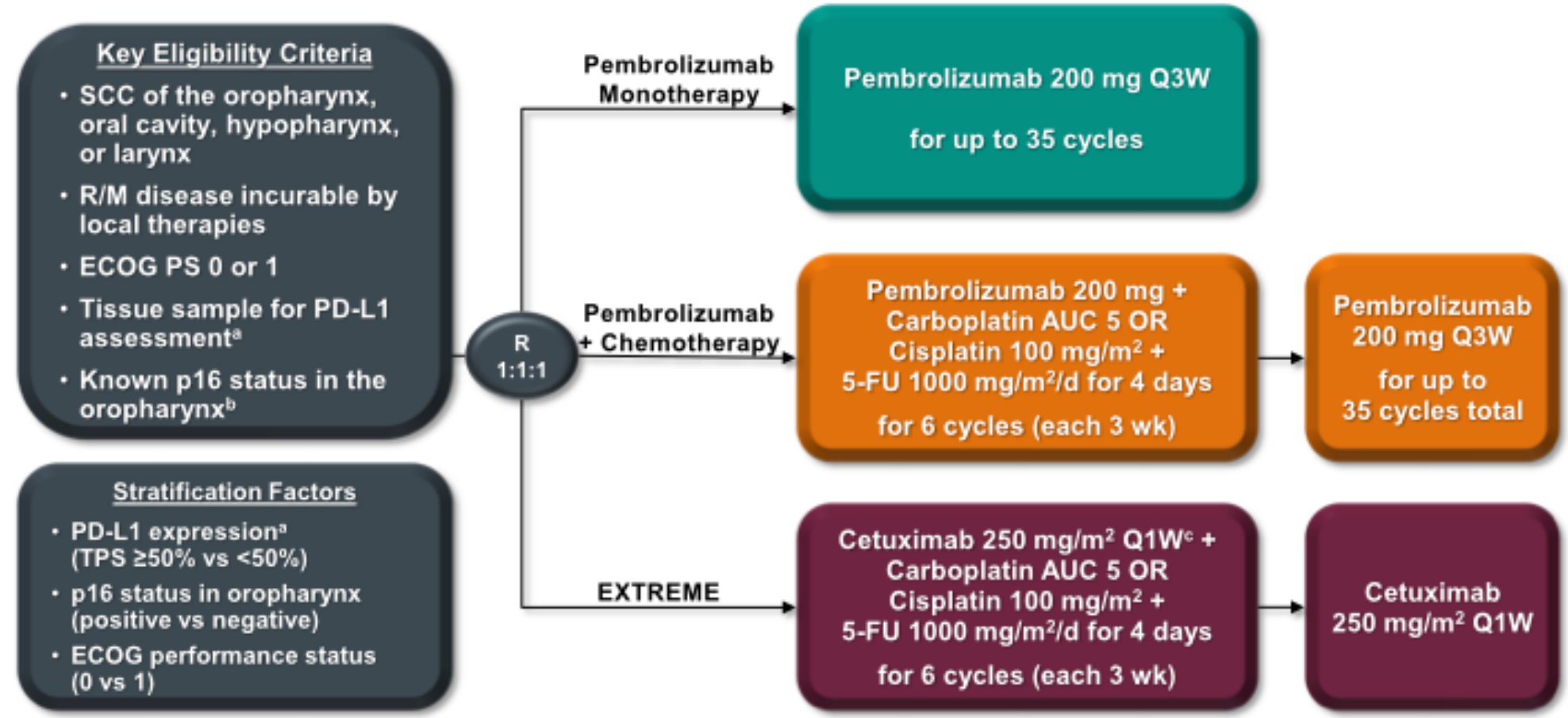
- Cemiplimab 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response





Migden, NEJM 2018.

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

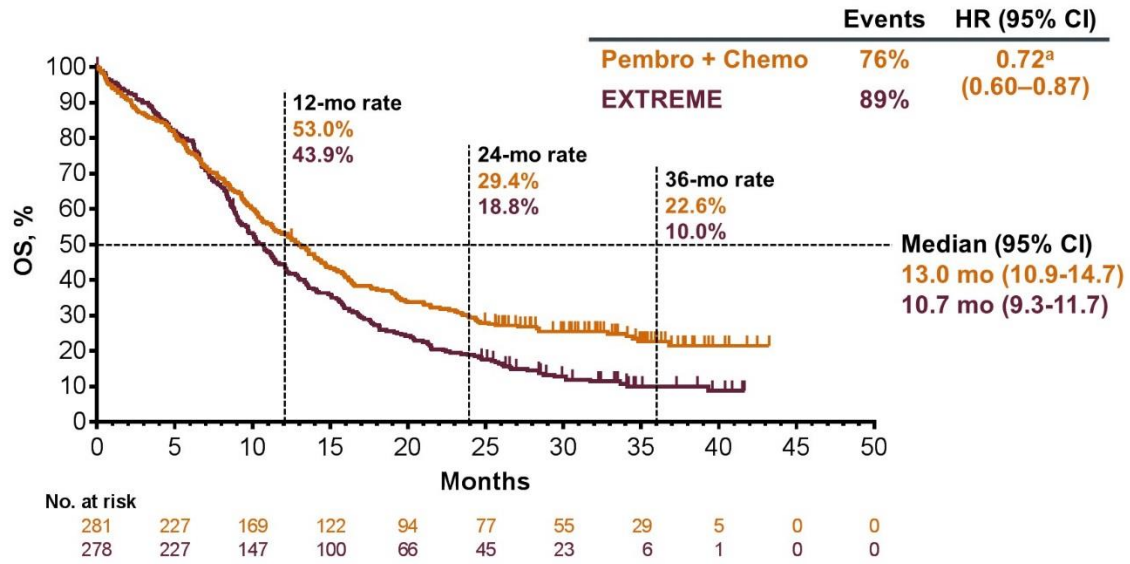


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

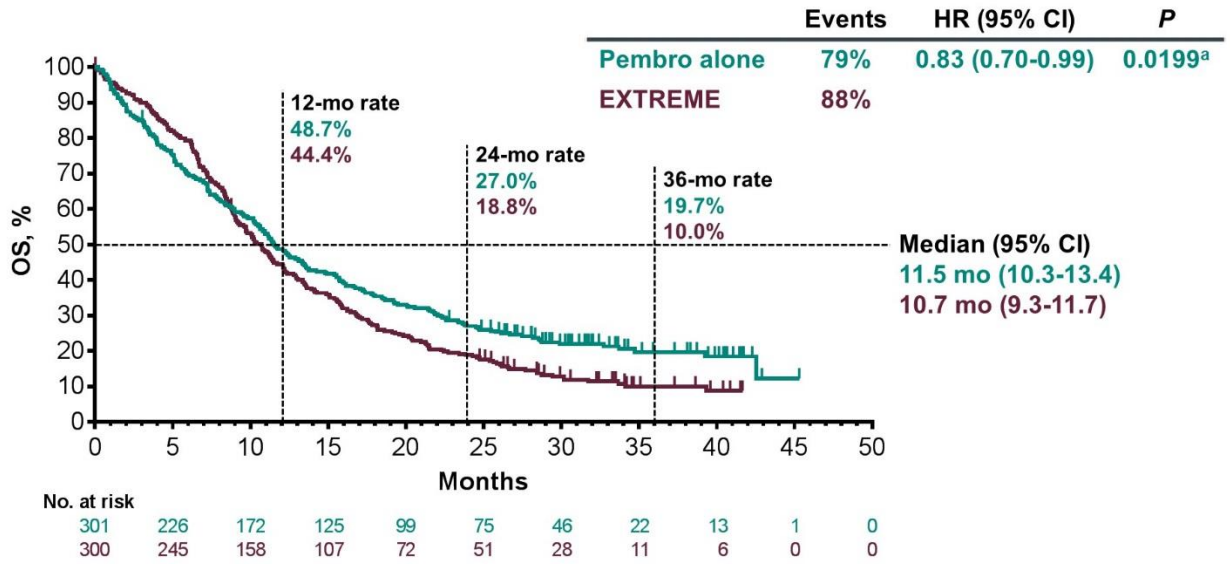
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

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

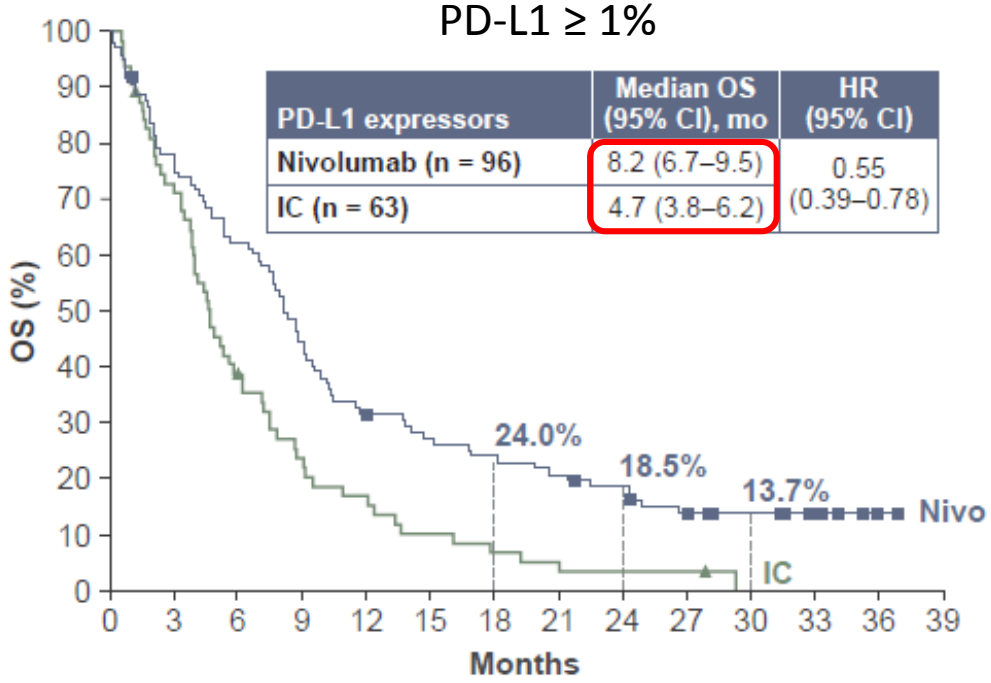
- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit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

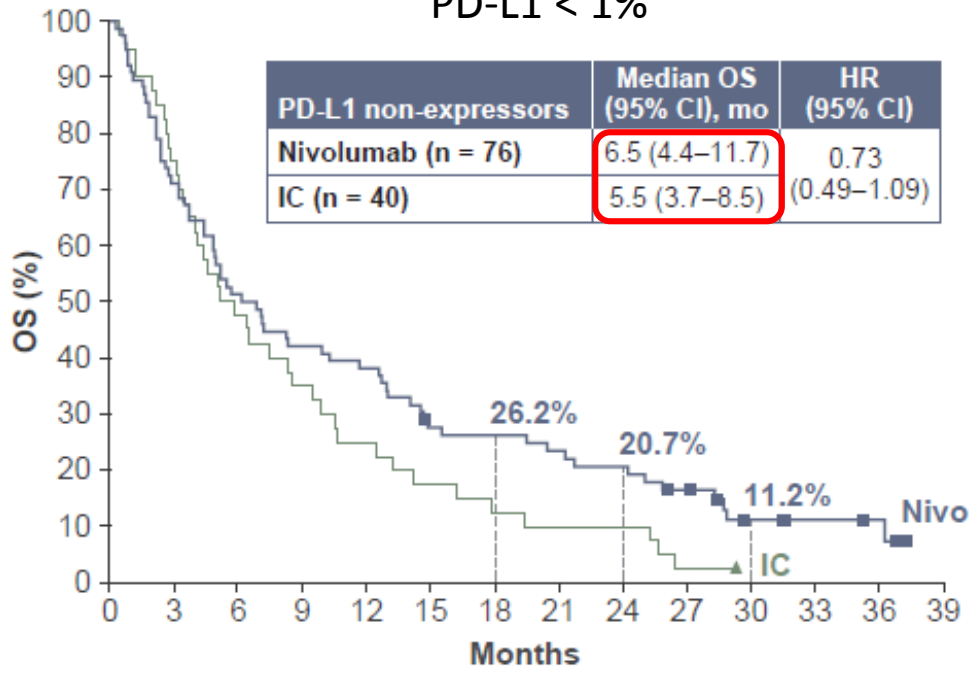


No. at risk

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 Study 1

Mr. Smith is a 60 yo otherwise healthy, non-smoking male with p16 positive squamous cell carcinoma of the tonsil. He was diagnosed 2 years ago with locally advanced disease (T2N1M0 by AJCC 8th edition) and received chemoradiation with high dose cisplatin. He initially had a complete response but recently scans showed bilateral lung nodules, with the largest about 3 cm. Biopsy of one of the lung nodules shows squamous cell carcinoma, p16 positive. PD-L1 CPS 25.

He is asymptomatic. ECOG PS 0. Exam is notable for post radiation changes of the neck without palpable adenopathy. Lungs are clear.

Case Study 1

He presents to your clinic to discuss treatment options. What would you recommend?

1. Carboplatin/5FU/Cetuximab (EXTREME regimen)
2. Pembrolizumab
3. Carboplatin/5FU/Pembrolizumab
4. Cetuximab

Case Study 1

He presents to your clinic to discuss treatment options. What would you recommend?

1. Carboplatin/5FU/Cetuximab (EXTREME regimen)
2. Carboplatin/5FU/Pembrolizumab
3. Cetuximab
4. Pembrolizumab

Case Study 1

He presents to your clinic to discuss treatment options. What would you recommend?

1. Carboplatin/5FU/Cetuximab (EXTREME regimen)
2. **Carboplatin/5FU/Pembrolizumab**
3. Cetuximab
4. **Pembrolizumab**

Case Study 1

- For patients with CPS>1 – chemo plus pembro and pembro alone are both superior to the EXTREME regimen
- No direct comparisons between chemo plus pembro vs pembro alone
- Consider pros and cons for each patient:
  - Bulky vs non-bulky
  - Performance status
  - Tolerance of prior chemo
  - PD-L1 level
  - Patient preference

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Head and Neck Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

- The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).

Non-Nasopharyngeal

Recurrent, Unresectable, or Metastatic (with no surgery or RT option):

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
First-Line	• Cisplatin/5-FU/cetuximab[c,36] (category 1) • Carboplatin/5-FU/cetuximab[c,36] (category 1) Immunotherapy • Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU[c,37] • Pembrolizumab (for PD-L1 positive tumors)[52,53]	Combination Therapy • Cisplatin/cetuximab[38] • Cisplatin or carboplatin/docetaxel[39] or paclitaxel[40] • Cisplatin/5-FU[40,41] • Cisplatin or carboplatin/docetaxel/cetuximab[42] • Cisplatin or carboplatin/paclitaxel/cetuximab[43] Single Agents • Cisplatin[38,44] • Carboplatin[45] • Paclitaxel[46] • Docetaxel[47,48] • 5-FU[44] • Methotrexate[41,49] • Cetuximab[50] • Capecitabine[51]	• For select ethmoid/maxillary sinus cancers (small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features): ‣ Cisplatin/etoposide or carboplatin/etoposide[35] ‣ Cyclophosphamide/doxorubicin/vincristine (category 2B)
Subsequent Line	Immunotherapy • Nivolumab[54] if disease progression on or after platinum therapy (category 1) • Pembrolizumab[55-57] if disease progression on or after platinum therapy (category 1)	Combination Therapy or Single Agents • See options listed above for first-line therapy Targeted Therapy • Afatinib[58] if disease progression on or after platinum therapy (category 2B)	• For select ethmoid/maxillary sinus cancers (small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features): ‣ Cisplatin/etoposide or carboplatin/etoposide[35] ‣ Cyclophosphamide/doxorubicin/vincristine (category 2B)

[c] Data suggest an overall survival advantage for patients treated with pembrolizumab/platinum/5-FU when compared to cetuximab/platinum/5-FU for first-line treatment of recurrent/metastatic head and neck squamous cell carcinoma. (Rischin D, Harrington KJ, Greil R, et al. Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma. ASCO 2019.)

See References

Case Study 1 (Continued)

Mr. Smith received treatment prior to the presentation of results of KEYNOTE-048, and was treated with 4 cycles of carboplatin/5FU/cetuximab followed by 2 months of cetuximab maintenance, with initial response and then progression. Performance status remains excellent. What treatment would you recommend now?

1. Docetaxel
2. Nivolumab
3. Pembrolizumab
4. Methotrexate

Case Study 1 (Continued)

Mr. Smith received treatment prior to the presentation of results of KEYNOTE-048, and was treated with 4 cycles of carboplatin/5FU/cetuximab followed by 2 months of cetuximab maintenance, with initial response and then progression. Performance status remains excellent. What treatment would you recommend now?

1. Docetaxel
2. **Nivolumab**
3. **Pembrolizumab**
4. Methotrexate

Based on the results of CheckMate 141 and KEYNOTE-040 – either nivo or pembro are preferred options after progression on platinum based therapy

Case Study 2

Ms Brown is 70 year old female with a history of tobacco use with p16 negative squamous cell carcinoma of the hypopharynx with recurrent and metastatic disease 4 months after completing chemoradiation with weekly cisplatin. Scans reveal recurrent disease in the neck as well as in the lungs. PD-L1 10%. She initiates therapy with nivolumab.

12 weeks after initiating therapy, scans show a good partial response, with resolution of lung nodules and improvement in cervical lymphadenopathy. However, she reports new diarrhea with 10+ bowel movements per day. She feels dehydrated and labs show newly elevated creatinine and hypokalemia.

Case Study 2

She is hospitalized and receives IV fluids. What additional work-up and treatment do you pursue?

1. Evaluation for possible infectious causes of diarrhea
2. CT abdomen/pelvis
3. IV steroids
4. All of the above

Case Study 2

She is hospitalized and receives IV fluids. What additional work-up and treatment do you pursue?

1. Evaluation for possible infectious causes of diarrhea
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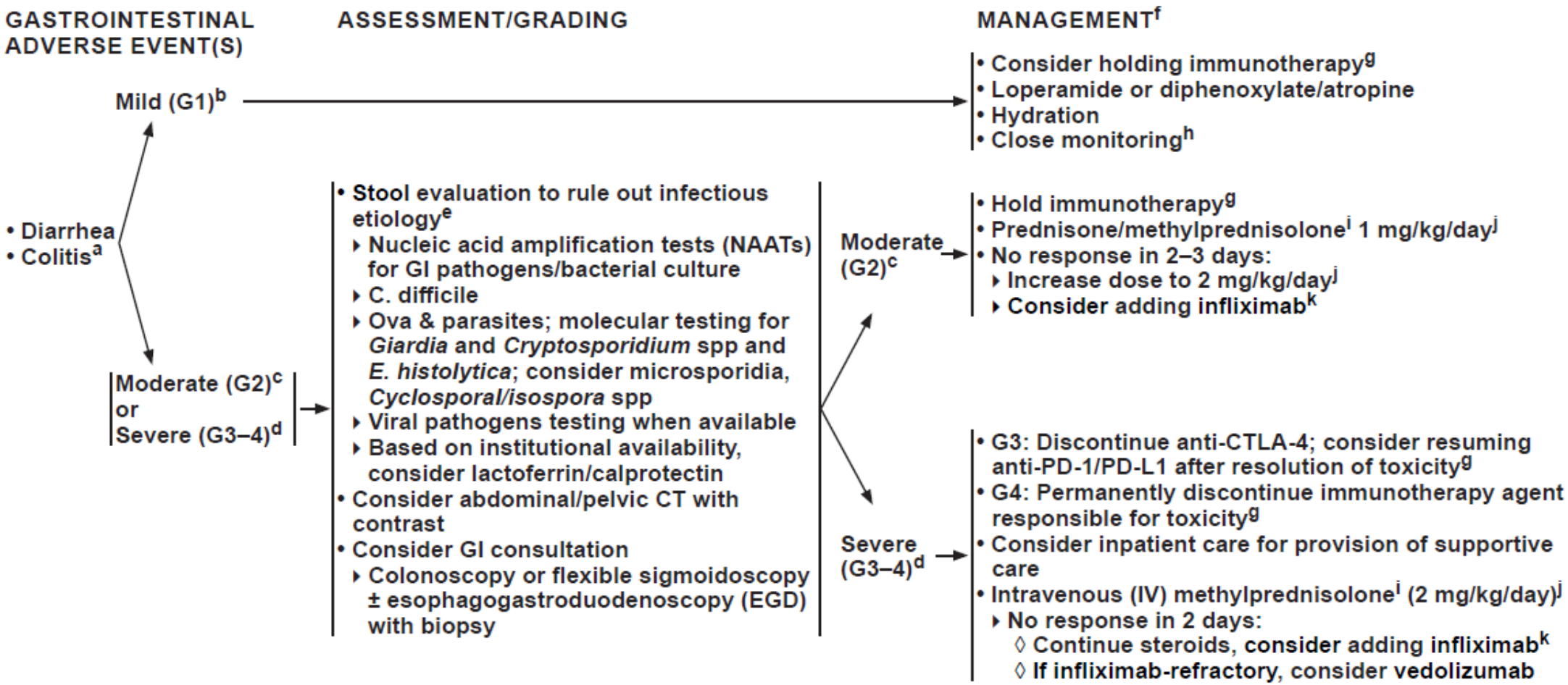
3. IV steroids
4. **All of the above**

Case Study 2



NCCN Guidelines Accessed 6/15/19

Case Study 2

She receives IV solumedrol (2 mg/kg/day) and IV fluids. Infectious work-up is negative. Her symptoms improve within 48 hours of starting treatment, and she completes a four week taper of oral steroids.

She returns to your office to discuss further management. Currently she feels well and is having one formed bowel movement daily. Scans are stable from one month prior, with maintained response to immunotherapy.

Would you restart immunotherapy now?

1. Yes
2. No