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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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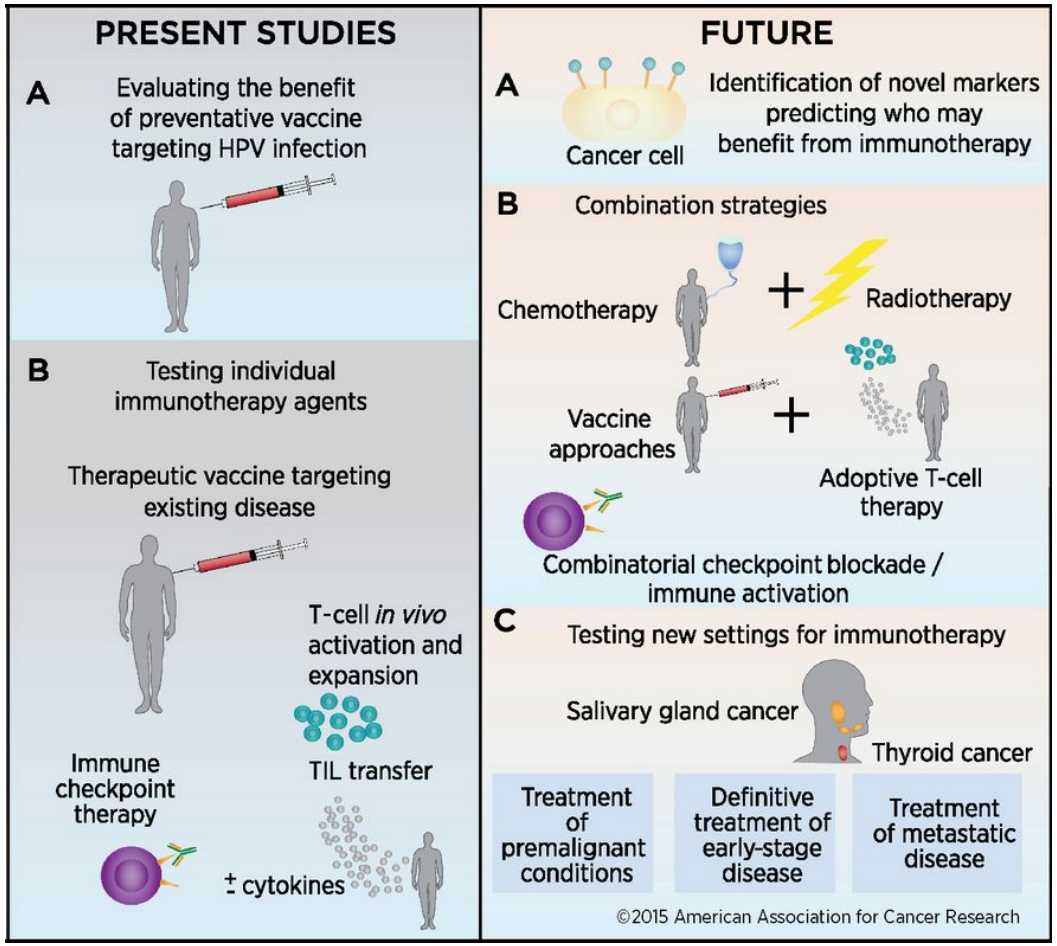
Disclosures

- Consulting Fees: Bayer
- Other (Research Funds): Merck, Astra Zeneca
- Advisory Board Consulting: Rakuten Medical
- 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
  - Preventive vaccination against virally mediated cancers
  - Expression of immunologic markers to guide treatment
  - Therapeutic vaccines for established cancers
  - CAR-T and cell-mediated therapies
  - Combinations with immunotherapies



Schoenfeld, Cancer Immunol Res, 2015

Approved checkpoint inhibitors for 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

•. 2016 Nov 10;34(32):3838-3845.

KEYNOTE-012: Pembrolizumab in R/M HNSCC

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

Patients
- R/M HNSCC
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1
- PD-L1+ (initial cohort)
- PD-L1+ or PD-L1- (expansion cohort)

Initial Cohort

Pembrolizumab 10 mg/kg Q2W
N = 60

Expansion Cohort*

Pembrolizumab 200 mg IV Q3W
N = 132

Continue until:
- 24 months of treatment‡
- Disease progression
- Death
- Withdrawal of consent
- Investigator decision

Combined analyses of Initial and Expansion cohorts

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 §

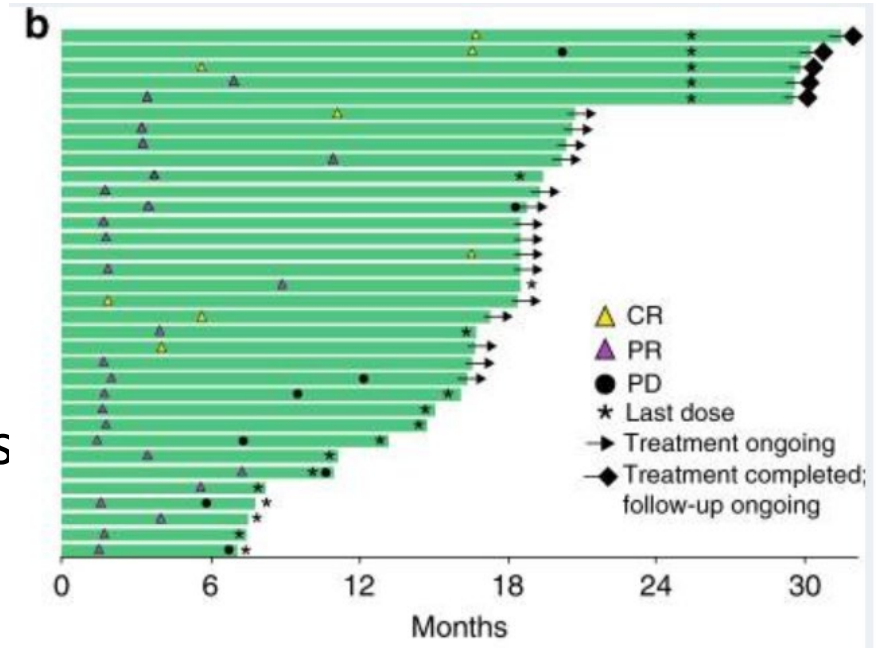
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.

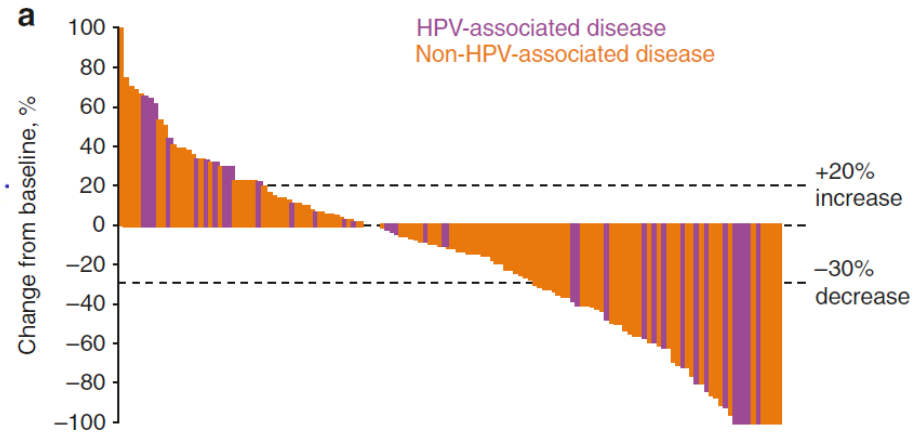
Seiwert et al. Lancet Oncol 2016 Jul: 17(7): 956-965
Chow et al. J Clin Oncol 2016 Nov 10;34(32):3838-3845.

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
- 12m survival 38%

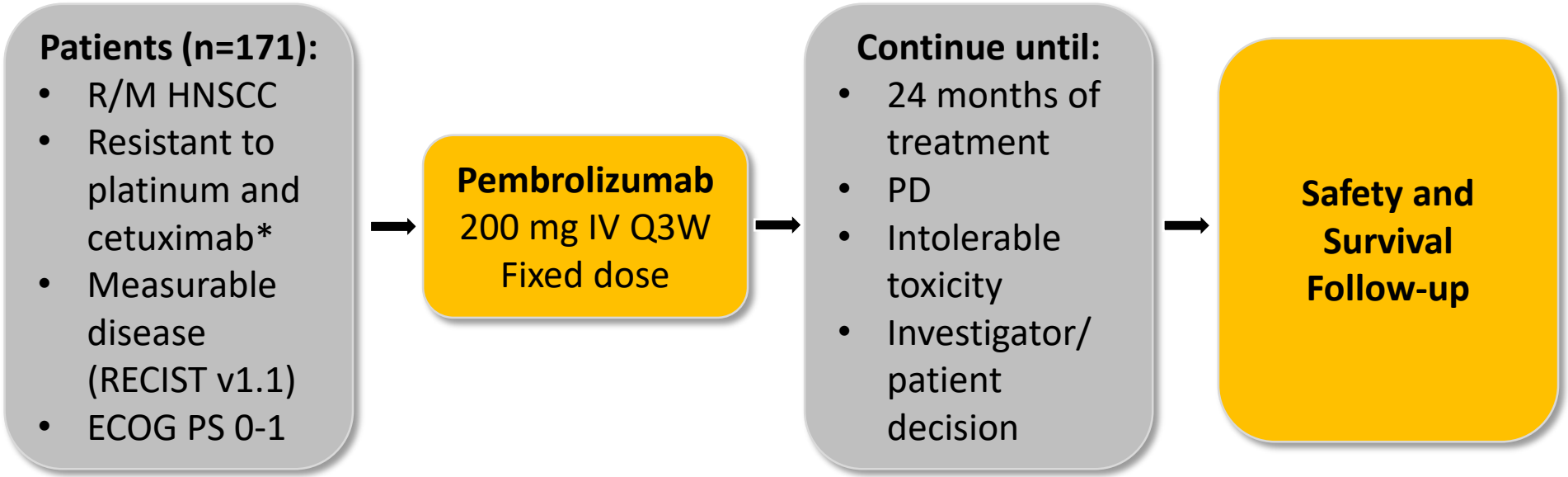




Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

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

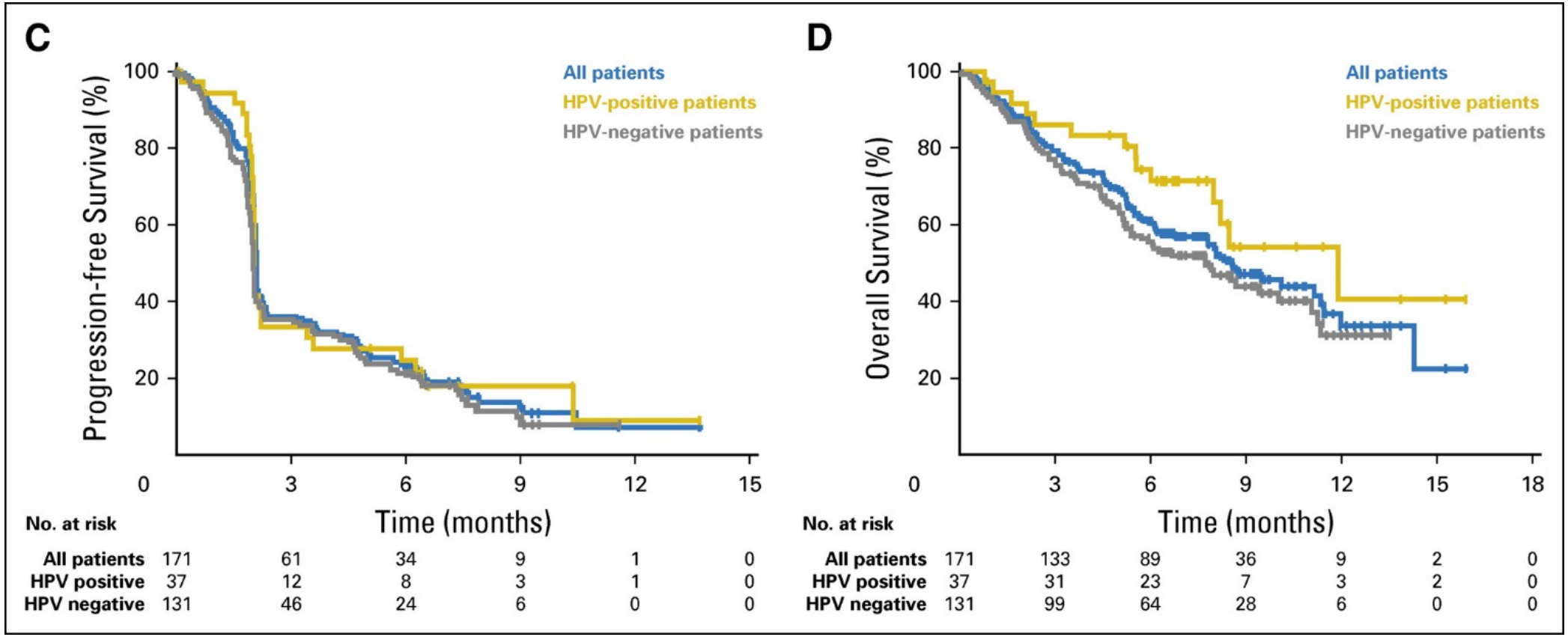
Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*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

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.

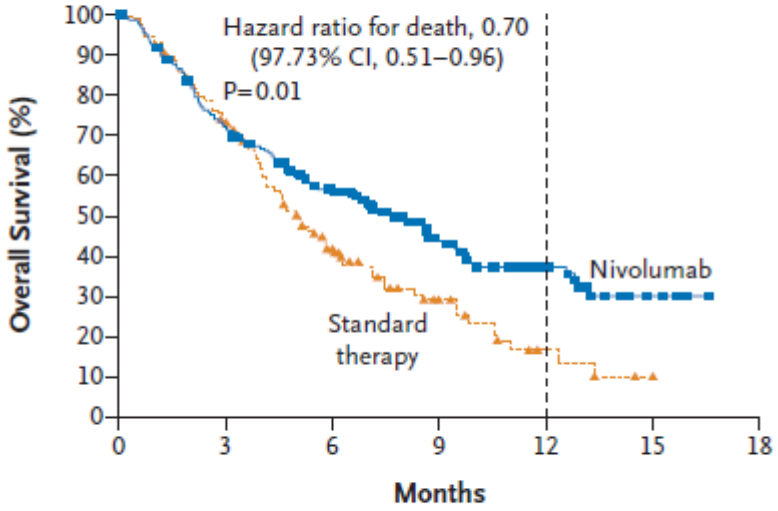
[a]Tissue required for testing

Ferris & Gillison, NEJM 2016.

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

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)

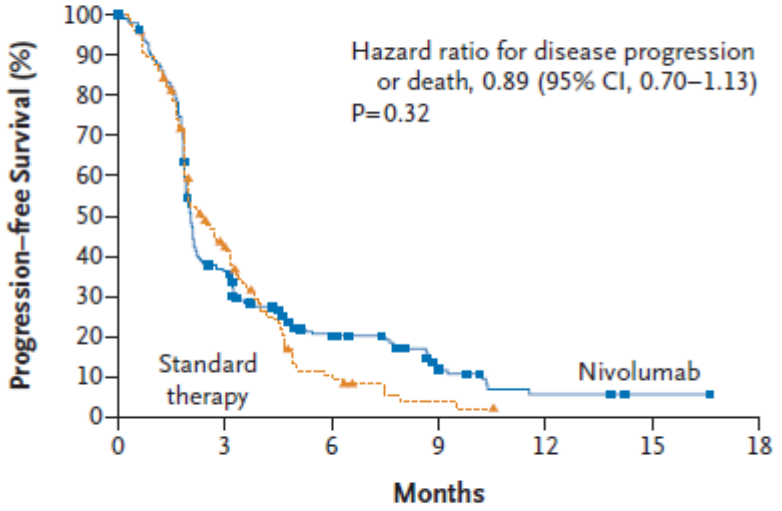


No. at Risk

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

→

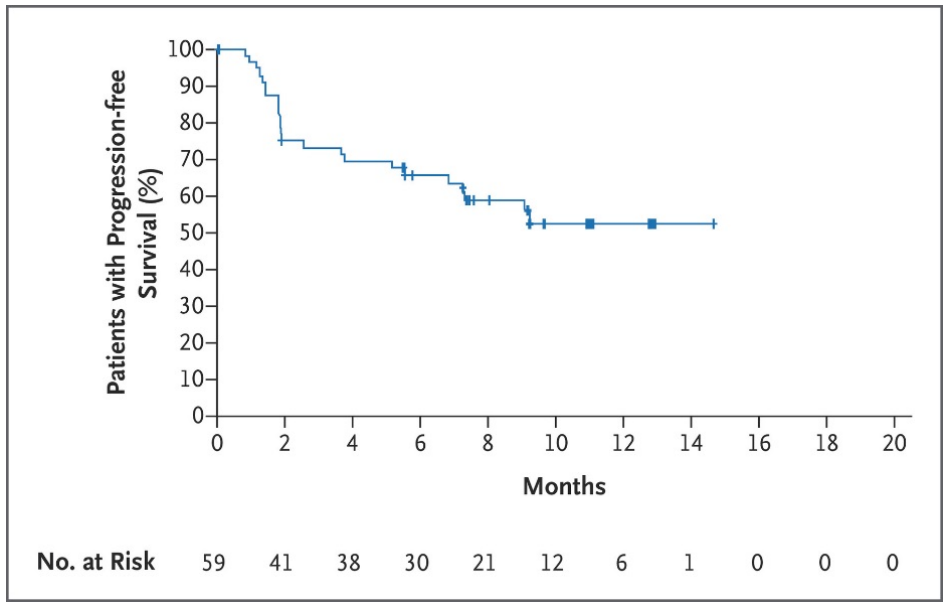
Primary endpoint
- Response rate

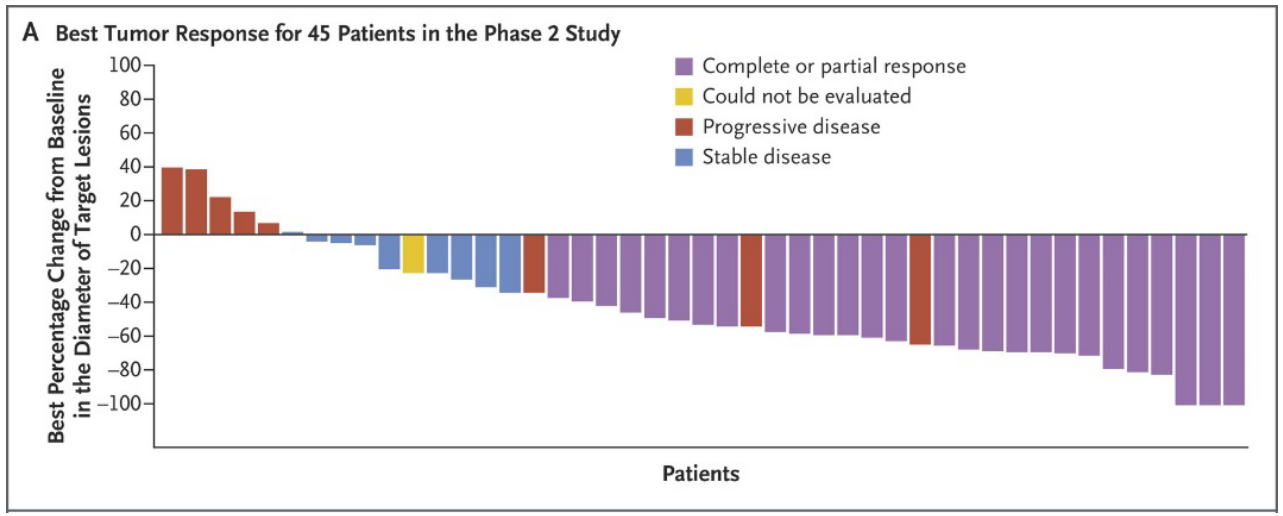
Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

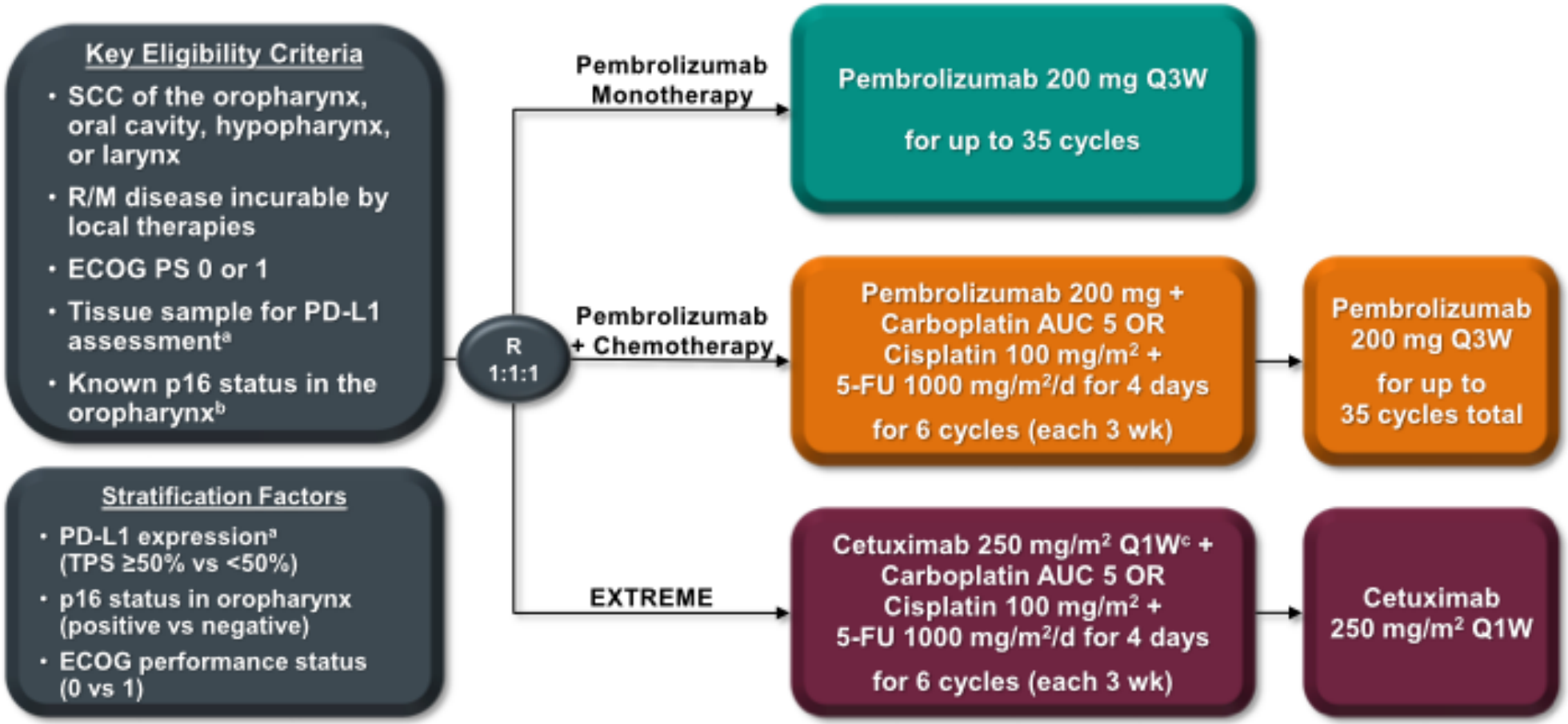
- Cemiplimab 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response





Migden, NEJM 2018.

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

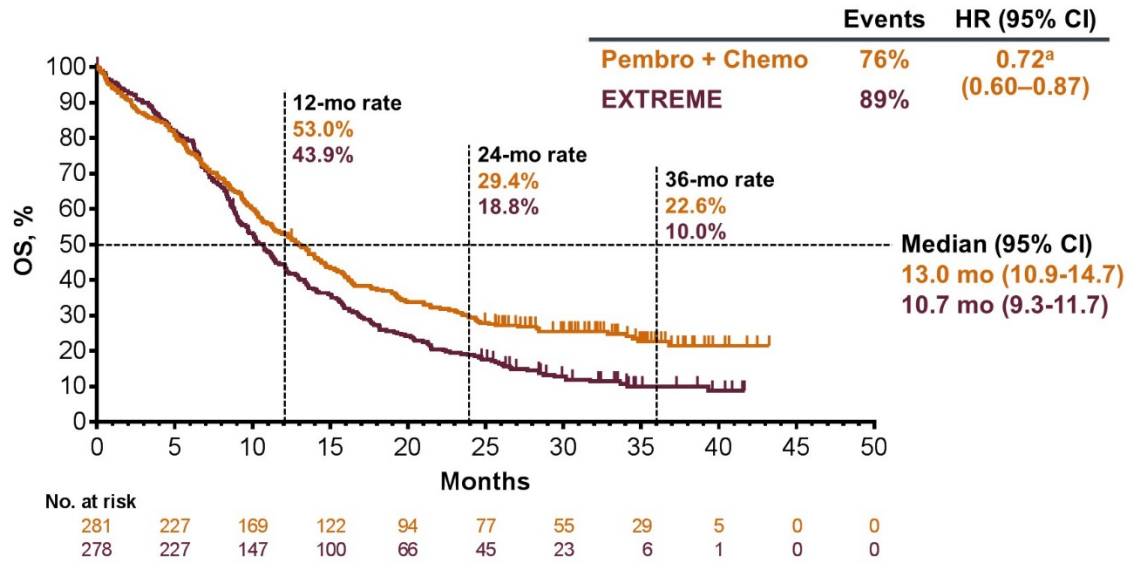


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Burtness Lancet Oncol 2019,
Rischin, ASCO 2019.

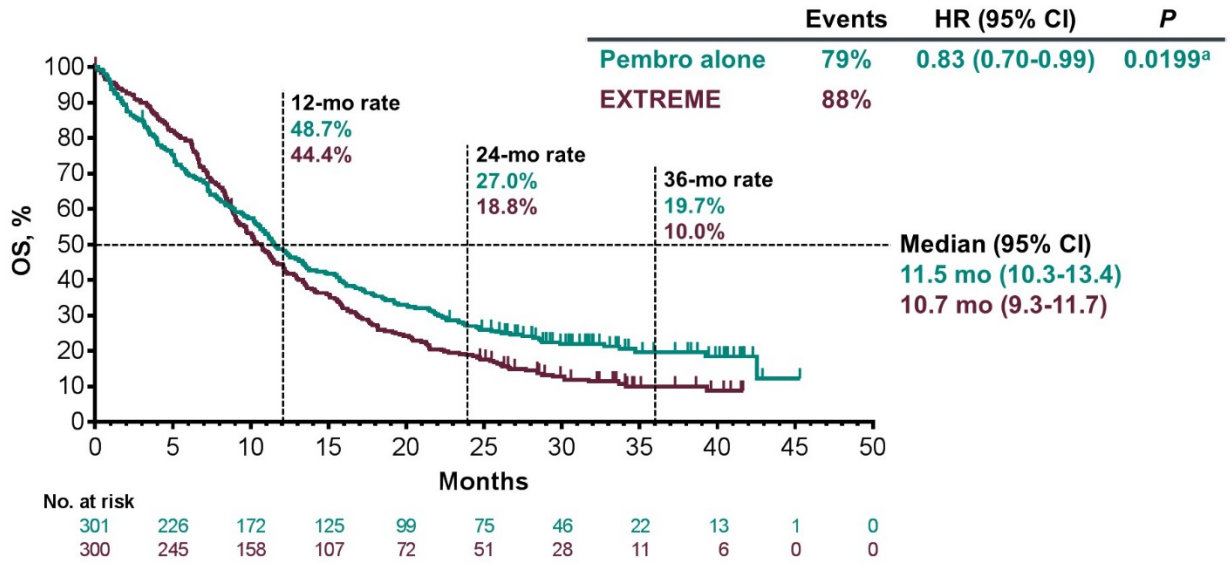
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

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.

KN-048 CPS subset analysis

CPS subgroup	Treatment	Median OS, mo	OS HR	12-mo OS rate, %
<1	Pembrolizumab	7.9	1.51	38.6
<1	EXTREME	11.3	_	48.9
<1	Pembrolizumab + Chemotherapy	11.3	1.21	41.0
<1	EXTREME	10.7	_	46.5
1-19	Pembrolizumab	10.8	0.86	44.0
1-19	EXTREME	10.1	_	42.4
1-19	Pembrolizumab + Chemotherapy	12.7	0.71	52.6
1-19	EXTREME	9.9	_	41.1
≥20	Pembrolizumab	14.8	0.58	56.4
≥20	EXTREME	10.7	_	44.9
≥20	Pembrolizumab + Chemotherapy	14.7	0.60	57.1
≥20	EXTREME	11.0	_	46.1

Burtness AACR 2020

Evaluating Biomarkers in HNSCC

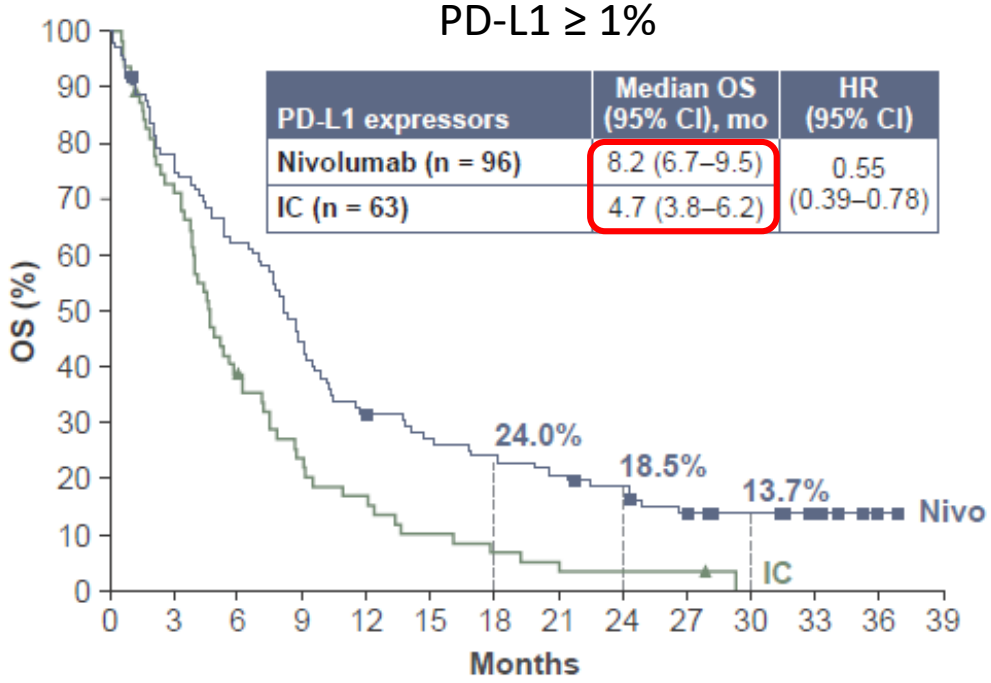
- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit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

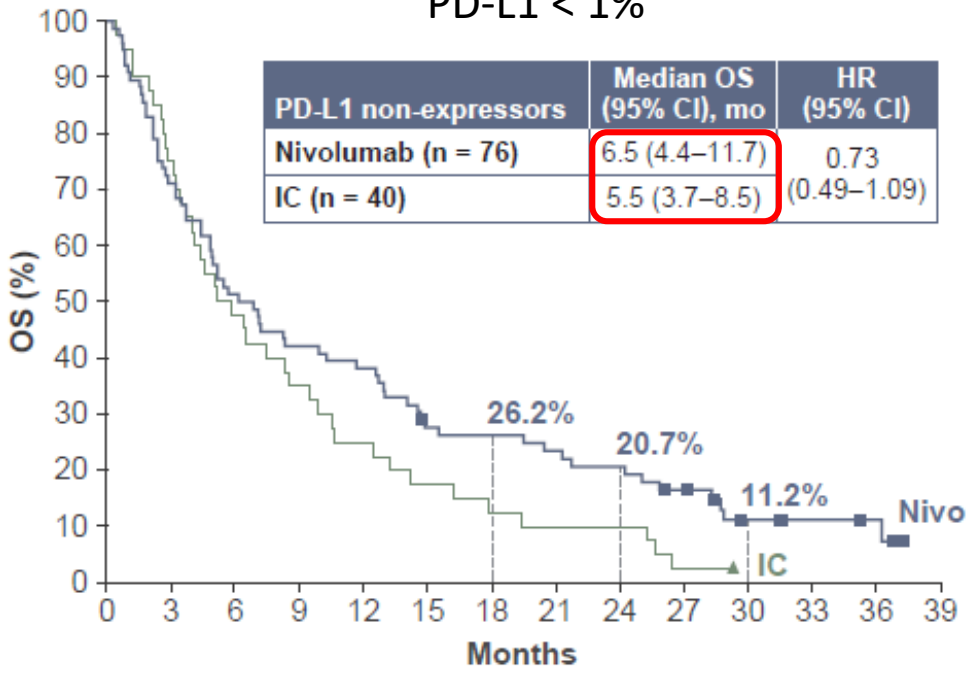


No. at risk

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
- Pembrolizumab/RT (platinum ineligible) – 1 year OS 86%, HPV+ 1 year OS 94%

Leidner, AACR 2019.
Siu, AACR 2018.
Tao, ASCO 2018.
Weiss, AACR/AHNS 2020

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

- Patient AB is a 46 year old man diagnosed with a T3N2M0 squamous cell carcinoma of the oral tongue. Initial treatment included resection followed by reconstruction. The surgical pathology was significant for removal of a moderately differentiated SCC with negative margins. In the neck dissection specimen 1/27 cervical lymph nodes were removed with no evidence of ENE. The patient received adjuvant radiation. 6 months later, on routine imaging, he was noted to have 3 pulmonary nodules. Biopsy confirmed recurrent SCC.

1. The patient presents for medical oncology consultation. What would you do to for treatment planning.
   - A. Option 1: Get tumor mutation burden level (Incorrect as while retrospective data indicates that high TMS tumors are more responsive to IO, it does not guide prospective management at this time.
   - B. PDL1 TPS (Incorrect – This PDL1 biomarker was a stratification factor in Keynote-048 but not the companion biomarker in the final analysis)
   - C. PDL1 CPS (correct – the combined proportion school is the biomarker used in first line treatment selection in KN-048.
   - D. HPV status (incorrect – Oral cavity tongue cancers are not thought to be associated with HPV.

Case Study 1

- The PDL1 CPS was obtained and was greater than 1. The patient is asymptomatic from his disease and a discussion of treatment options included the following.

2. What are appropriate treatments for further care?

A. Extreme – platinum/4FU/cetuximab (incorrect as KN-048 showed an improvement in survival associated with both pembrolizumab monotherapy and pembrolizumab plus chemotherapy over Extreme.

B. Pembrolizumab monotherapy (correct – the patient is asymptomatic, has a low disease burden and has PDL1 expression. This regimen is associated with a survival benefit on KN048

C. Pembrolizumab plus chemotherapy (correct – while the PDL1 expression is positive, this regimen is associated with a survival benefit as well and is a option.

D. B and C (Correct – Both are appropriate treatment options.

Case Study 1

- The patient started on treatment with pembrolizumab monotherapy. After 9 weeks and CT chest showed a response in all of the pulmonary nodules. He continued on therapy. 6 months after the initiation of treatment he noted progressively more symptomatic fatigue which was impacting his quality of life.

  3. What is the next step?

     A. Stop therapy and take a break (Incorrect – it is possible to continue IO while managing toxicity in some instances.

     B. Check TSH, AM cortisol (Correct – endocrinopathies are a common toxicity to IO therapy and hypothyroidism in particular is a risk in someone with prior head and neck RT.

     C. Start steroids (Incorrect – There is no indication for steroids without documentation of a reversible IO toxicity

The patient's TSH was 90 and his was started on thyroid hormone replacement with improvement of symptoms.

Case Study 2

- Patient BI is a 60 year old woman with HPV negative oropharynx cancer. She was diagnosed with T4N2M0 disease and was treated with cisplatin and radiation. 6 months after completing therapy she had a new neck mass which was biopsied and positive for p16- SCC. PDL1 CPS was 0. Further staging showed multiple pulmonary metastases. She has been having increased pain at the site of the locoregional recurrence.

1. What is the next step for treatment?
   - A. Salvage surgery (Incorrect as the patient has metastatic disease
   - B. Nivolumab – (possible as the patient had platinum previously but would likely not select this as the response rate is low and the patient is asymptomatic.
   - C. Pembrolizumab – (possible as the patient had platinum therapy previously, but based on KN-048 would likely not consider this since PDL1 is 0.
   - D. Carboplatin, 5-fluorouracil and pembrolizumab – (Correct. This is the regimen with the best RR and OS in a patient who is symptomatic and with a PDL1 CPS 0.

Case Study 2

- The patient was started on pembrolizumab, carboplatin and 5-Fluorouracil. She had a response to treatment and transitioned to maintenance pembrolizumab after completed combination therapy.