sitc 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

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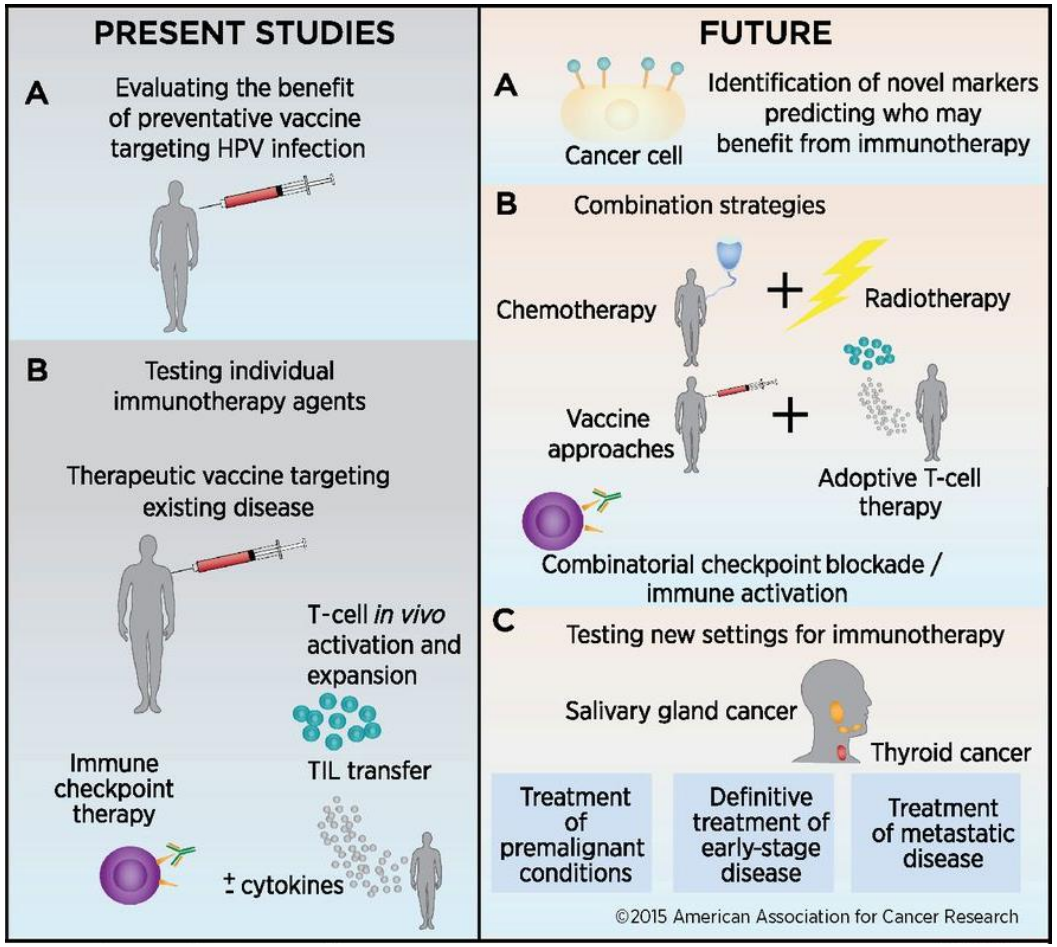
Disclosures

- Principle investigator of IIT funded by Bristol Myers Squibb
- 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



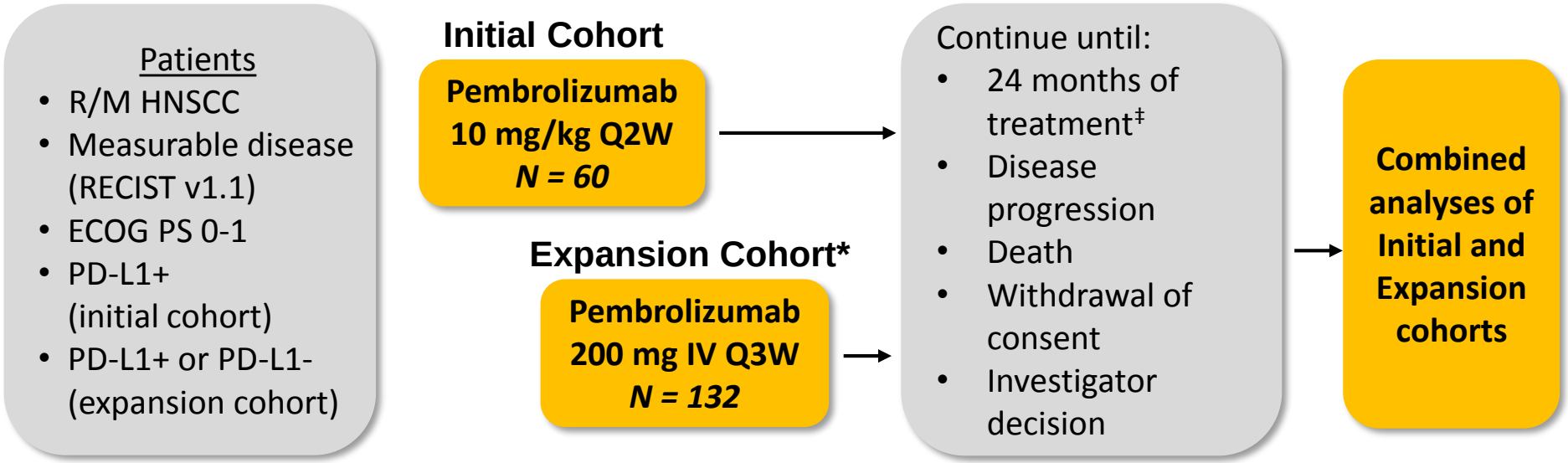
Schoenfeld, Cancer Immunol Res, 2015

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 §

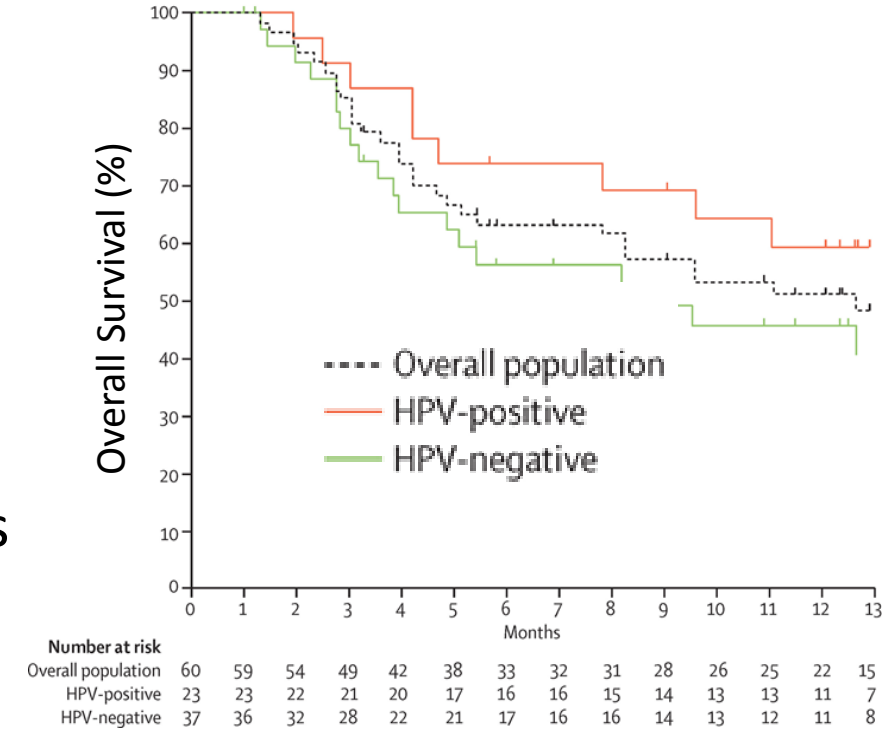
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

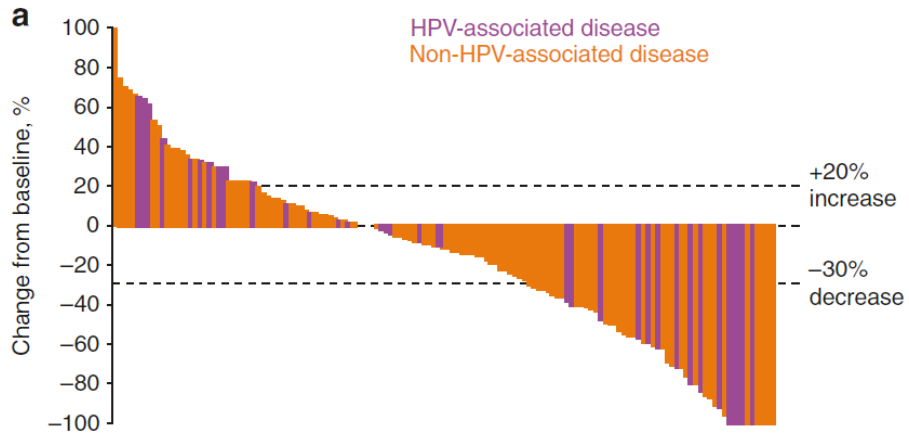
Seiwert, ASCO 2017.

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

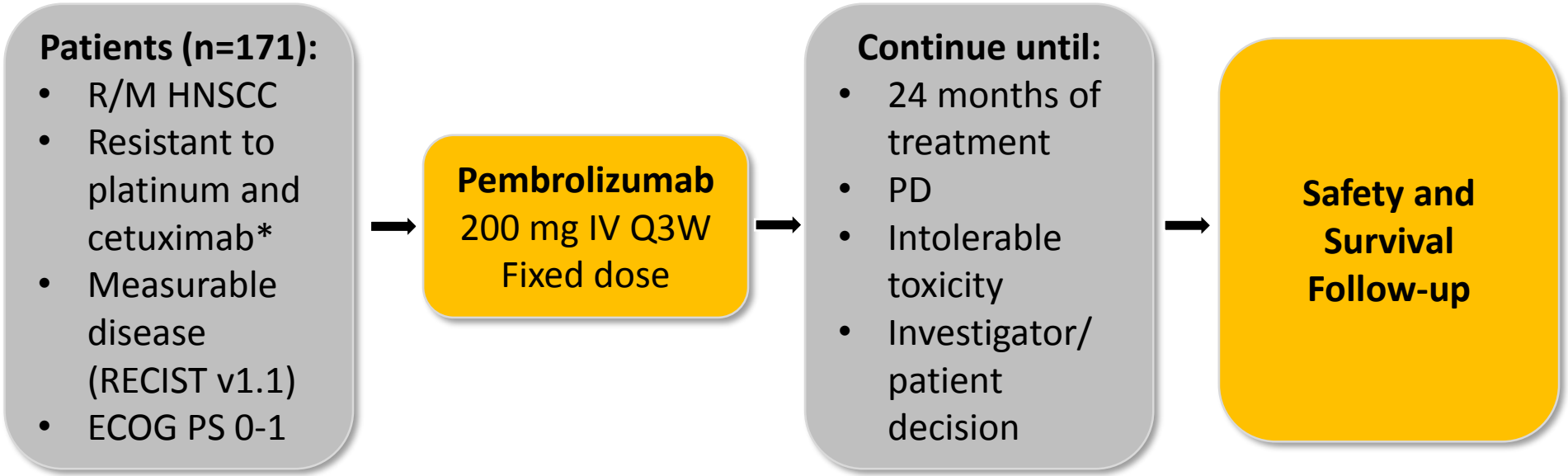




Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

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

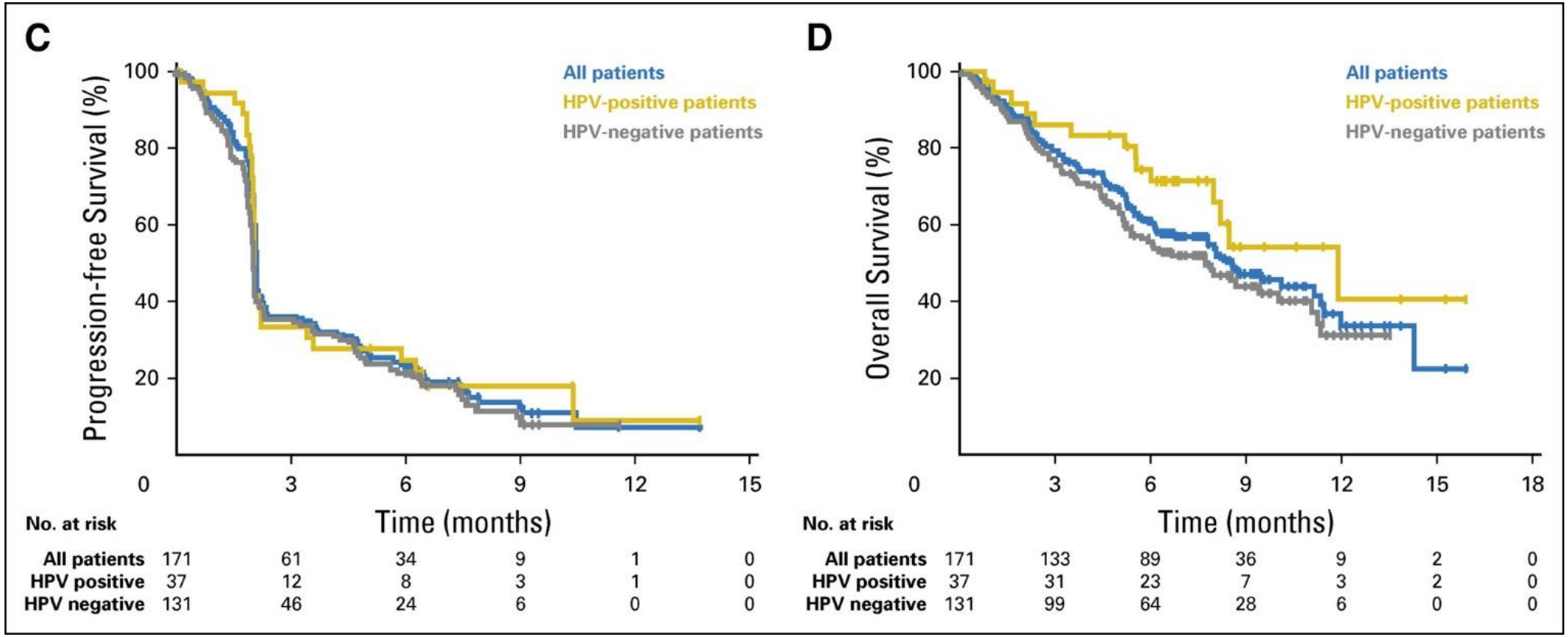
Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*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

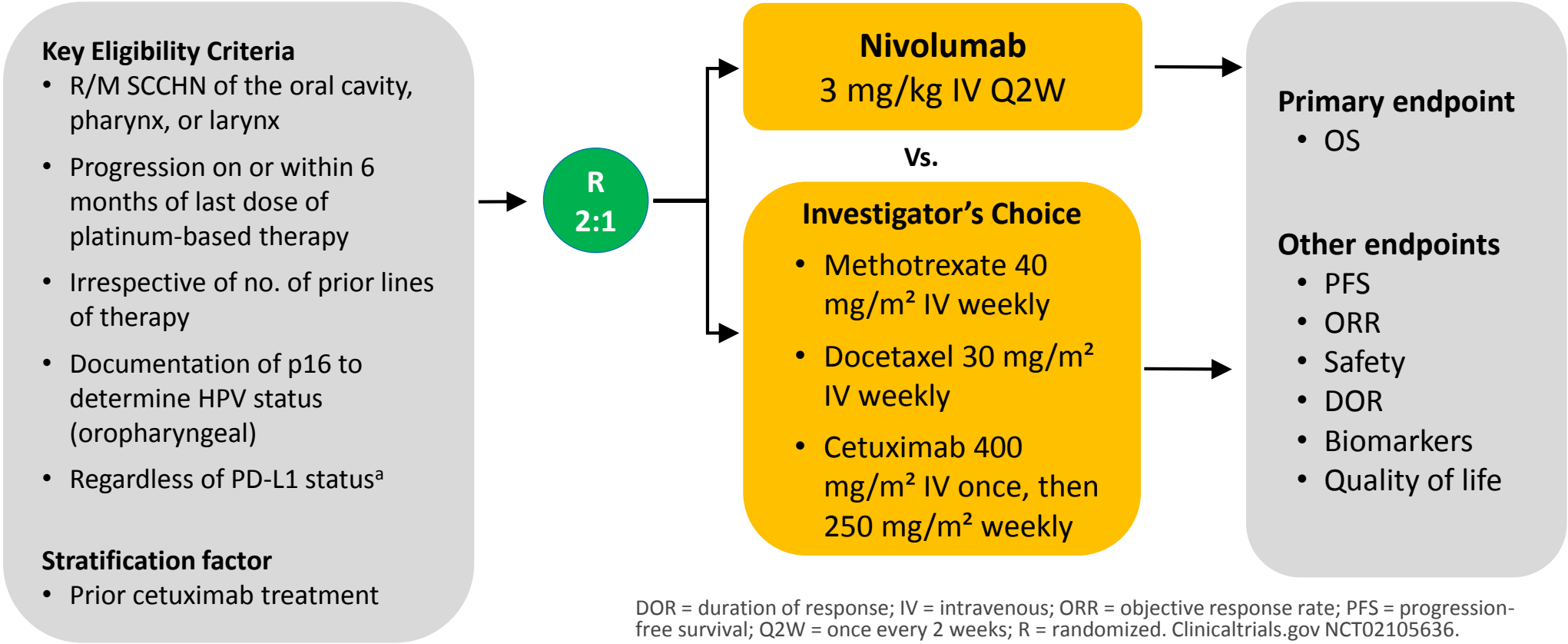
Phase II Trial, Single Arm



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.

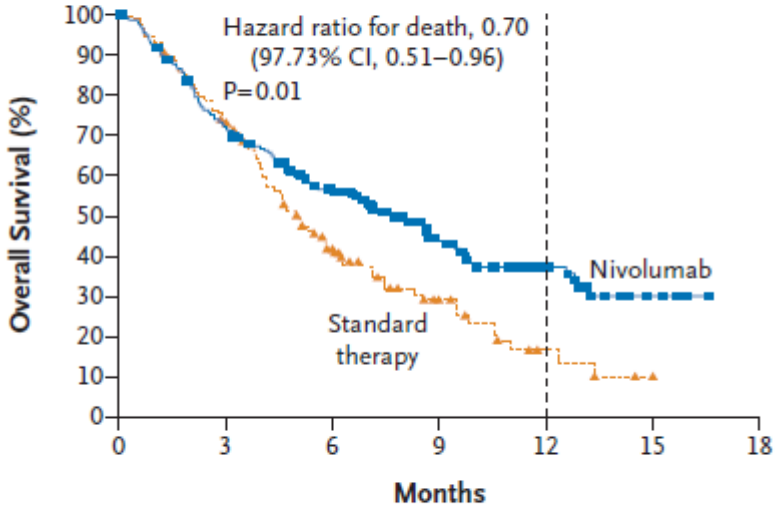
[a]Tissue required for testing

Ferris & Gillison, NEJM 2016.

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

A Overall Survival

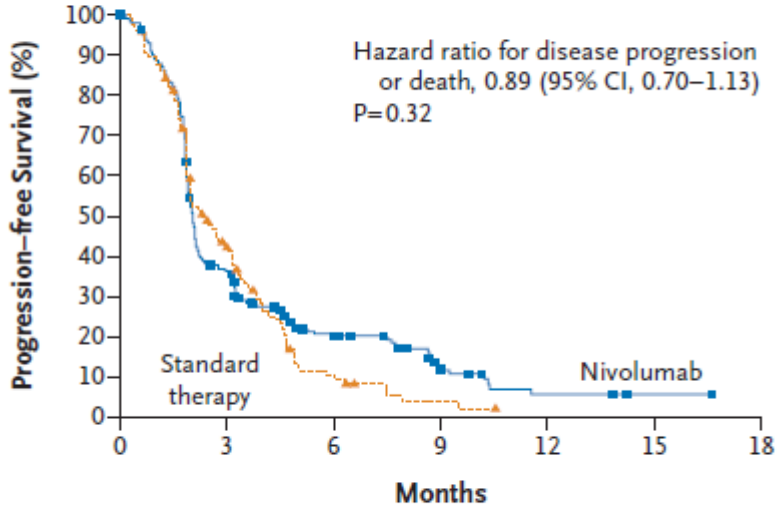
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



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

→

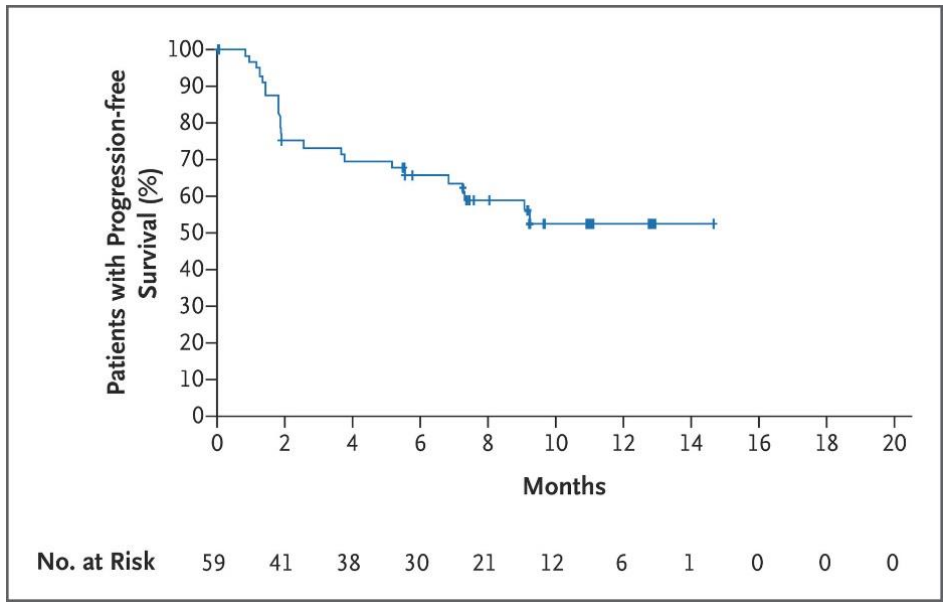
Primary endpoint
- Response rate

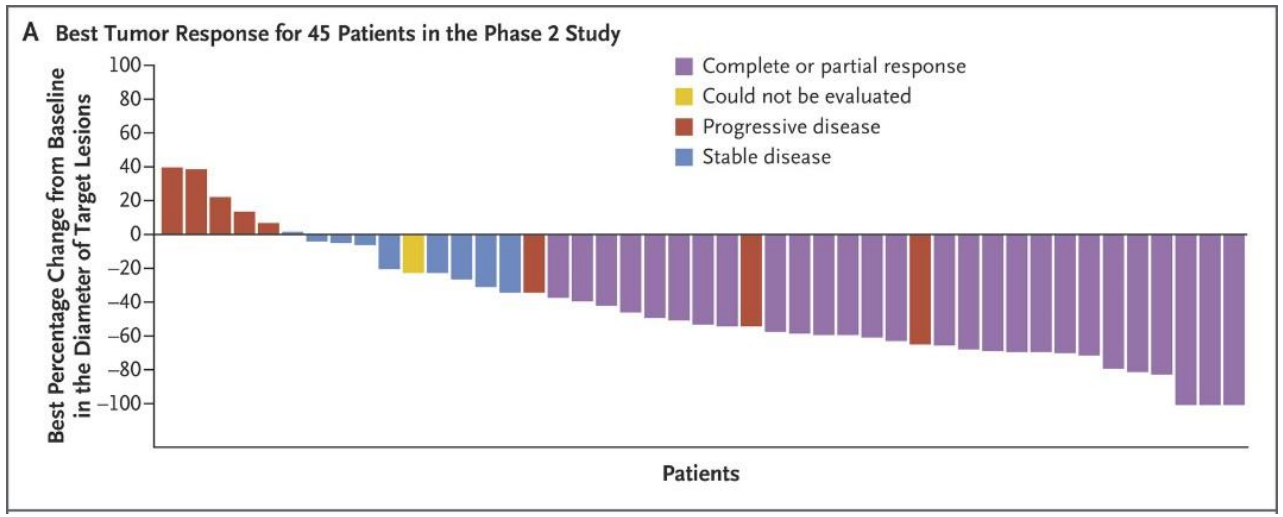
Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

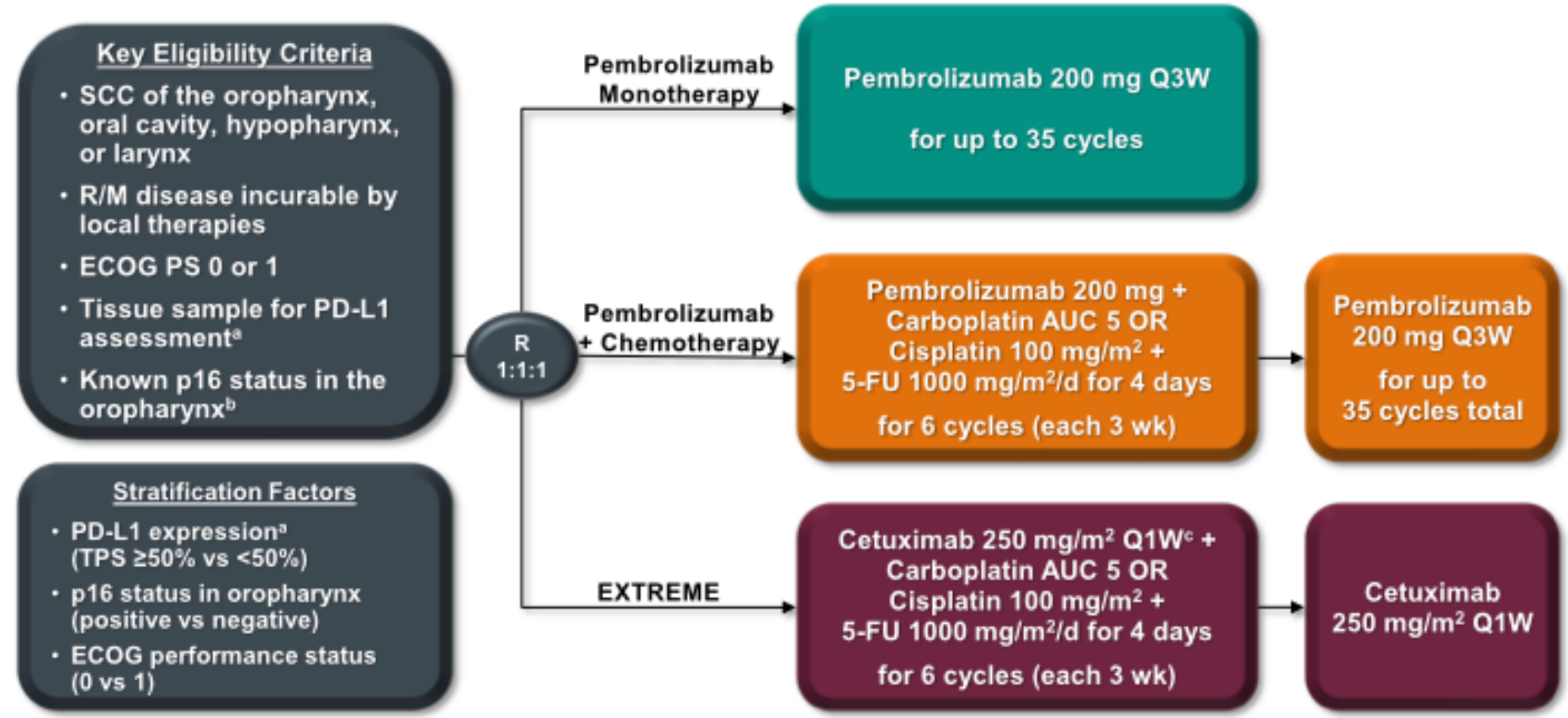
- Cemiplimab 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response





Migden, NEJM 2018.

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

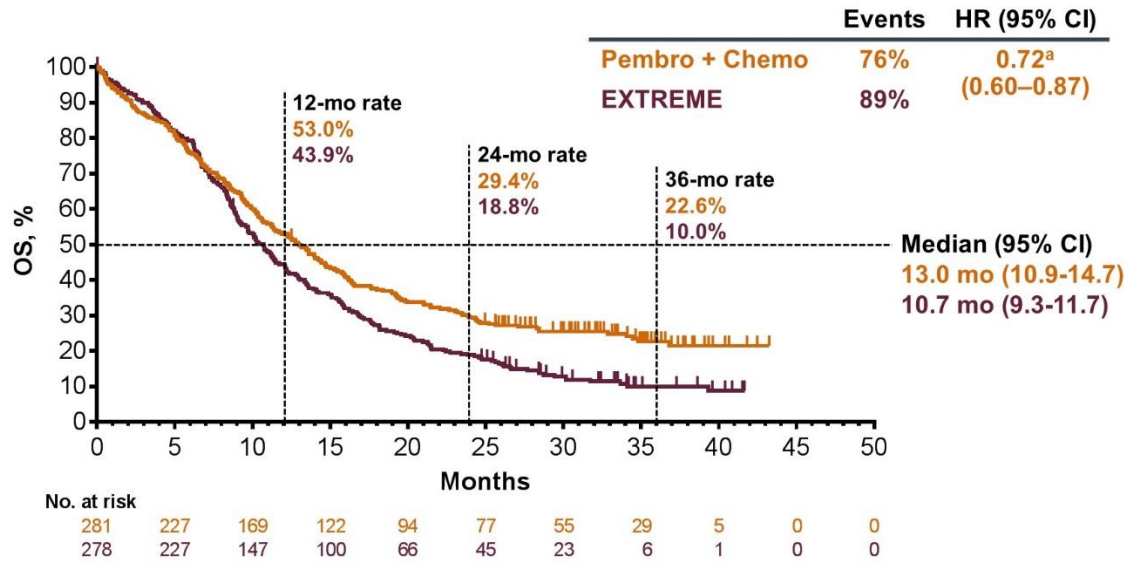


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

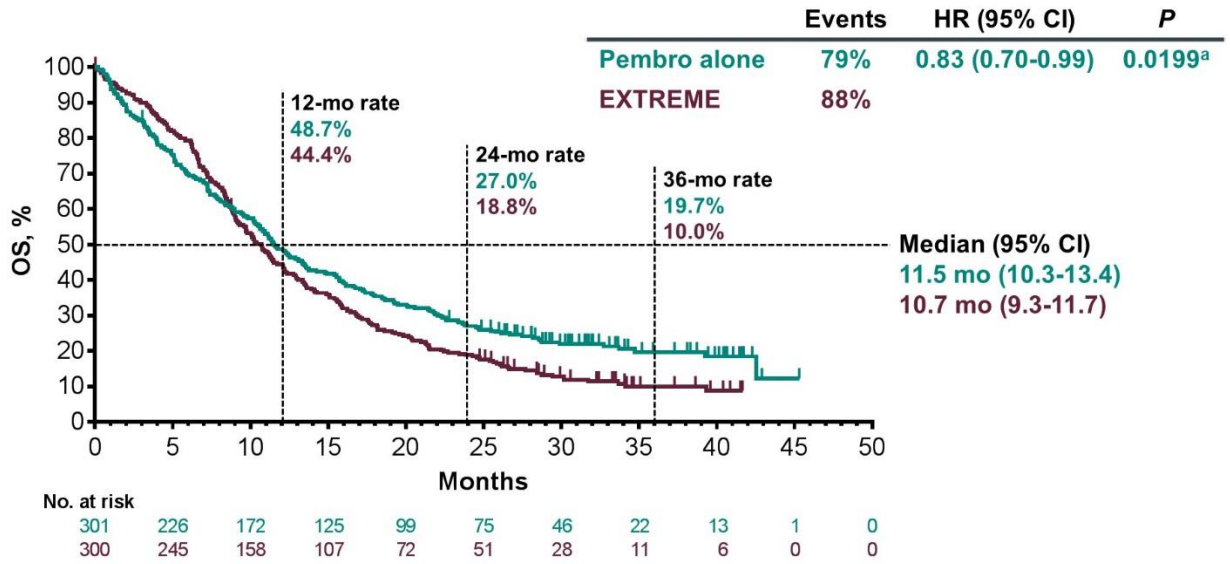
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

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

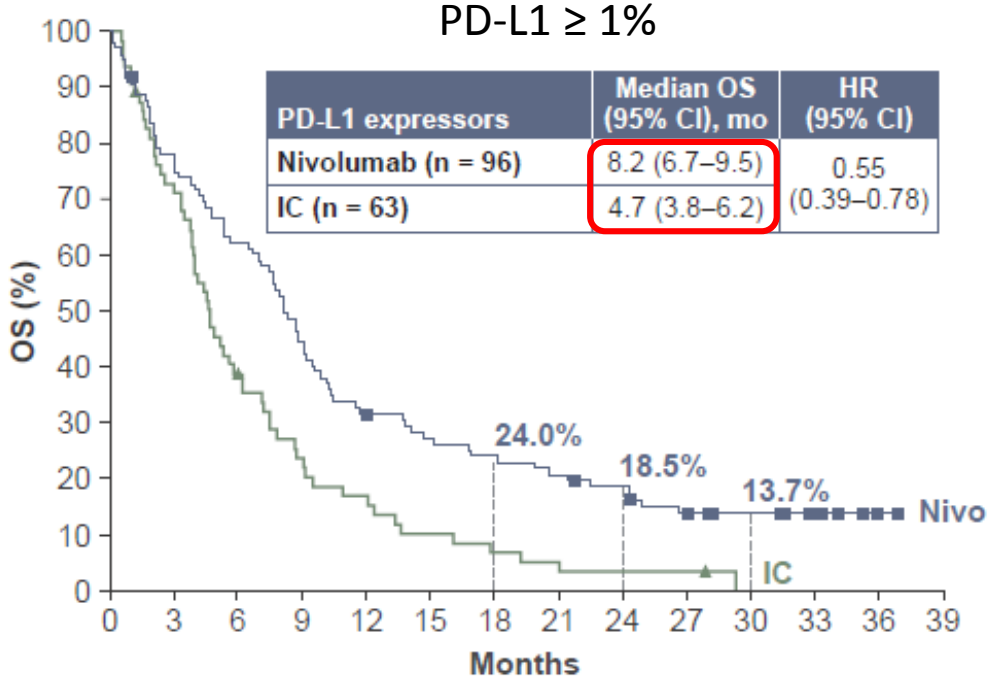
- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit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

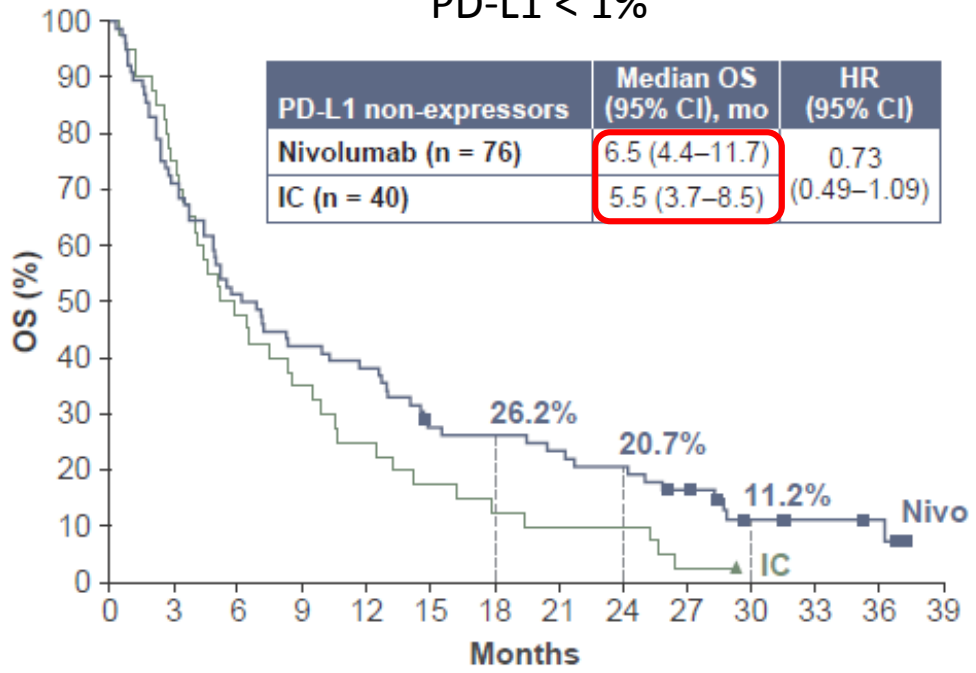


No. at risk

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

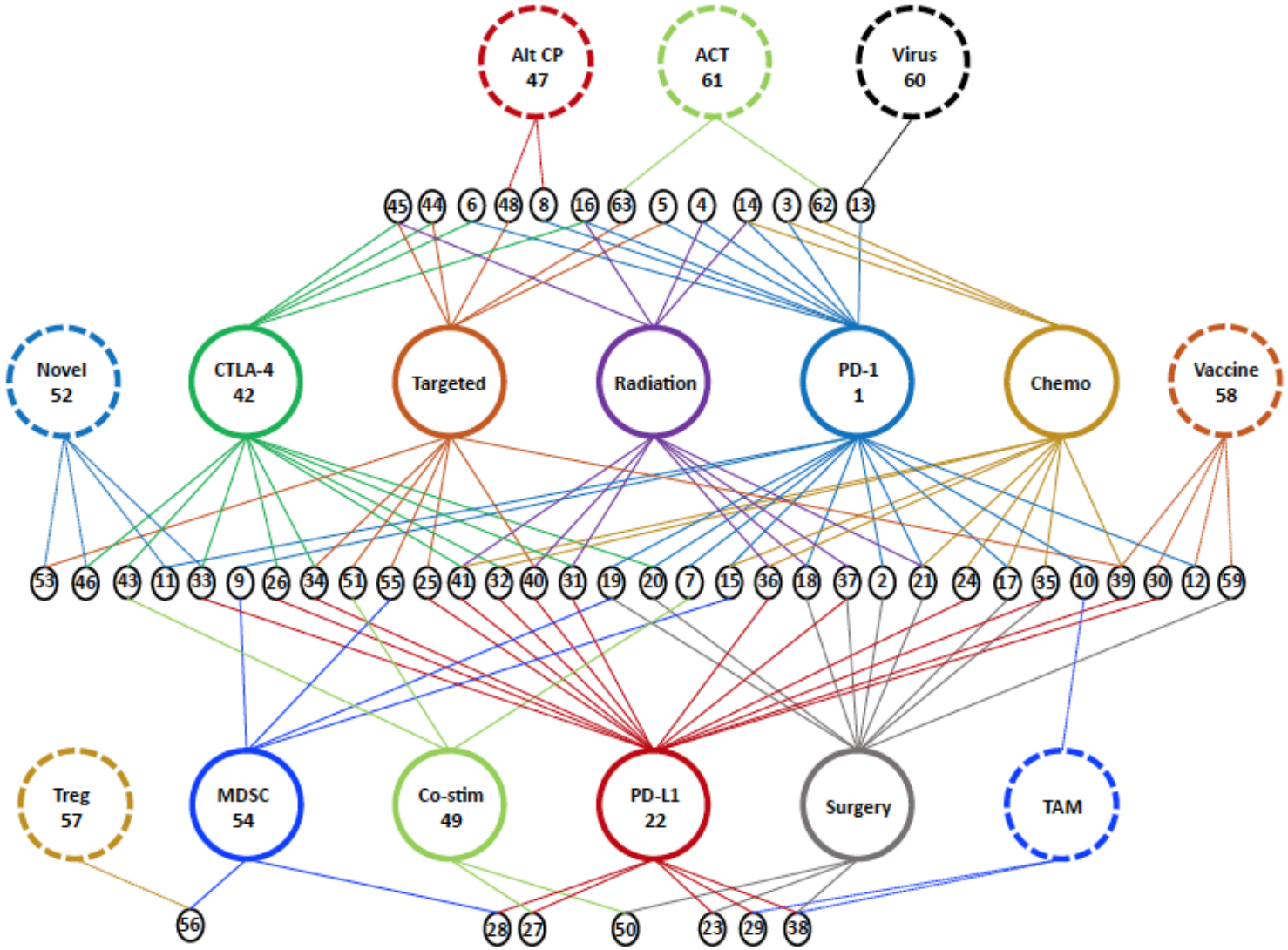
- T-Vec 10^6 PFU/mL intratumoral injection followed by 10^8 PFU/mL Q3W
- Pembrolizumab 200 mg IV Q3W
- Eligibility:
  - R/M HNSCC not suitable for curative therapy
  - Progressed after platinum treatment
  - At least 1 injectable cutaneous, subcutaneous, or nodal tumor ≥ 10 mm in longest diameter
- ORR: 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.



Trends in Cancer

 Horton et al. Trends in Cancer 2019

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*]

Case Studies

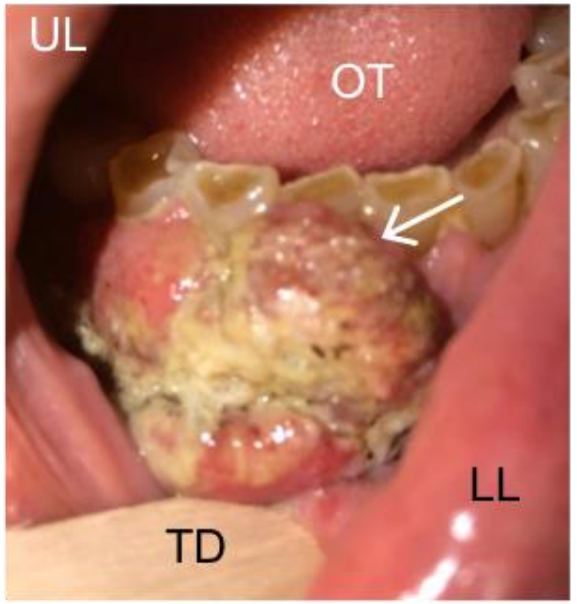
- 63 year old male presents with cT4acN1cM0 squamous cell carcinoma of the oral cavity.

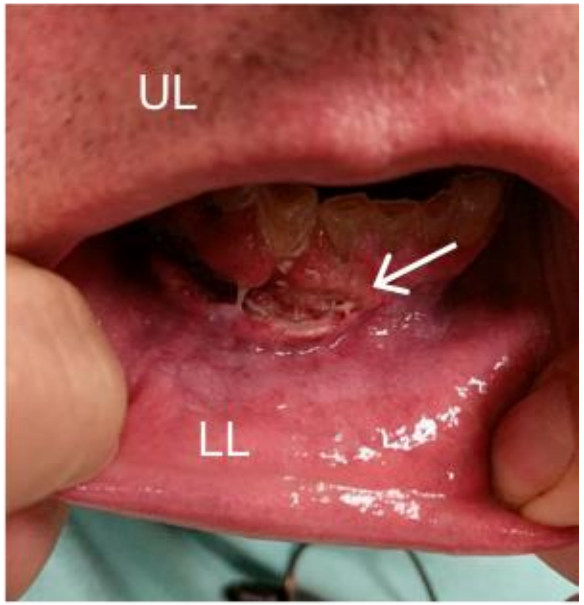
  After discussion about treatment options patient was enrolled in NCT03021993, Phase II Trial of Nivolumab as a Novel Neoadjuvant Pre-Surgical Therapy for Locally Advanced Oral Cavity Cancer.

  He received 4 doses of nivolumab (3mg/kg q2 weeks) and had a partial response

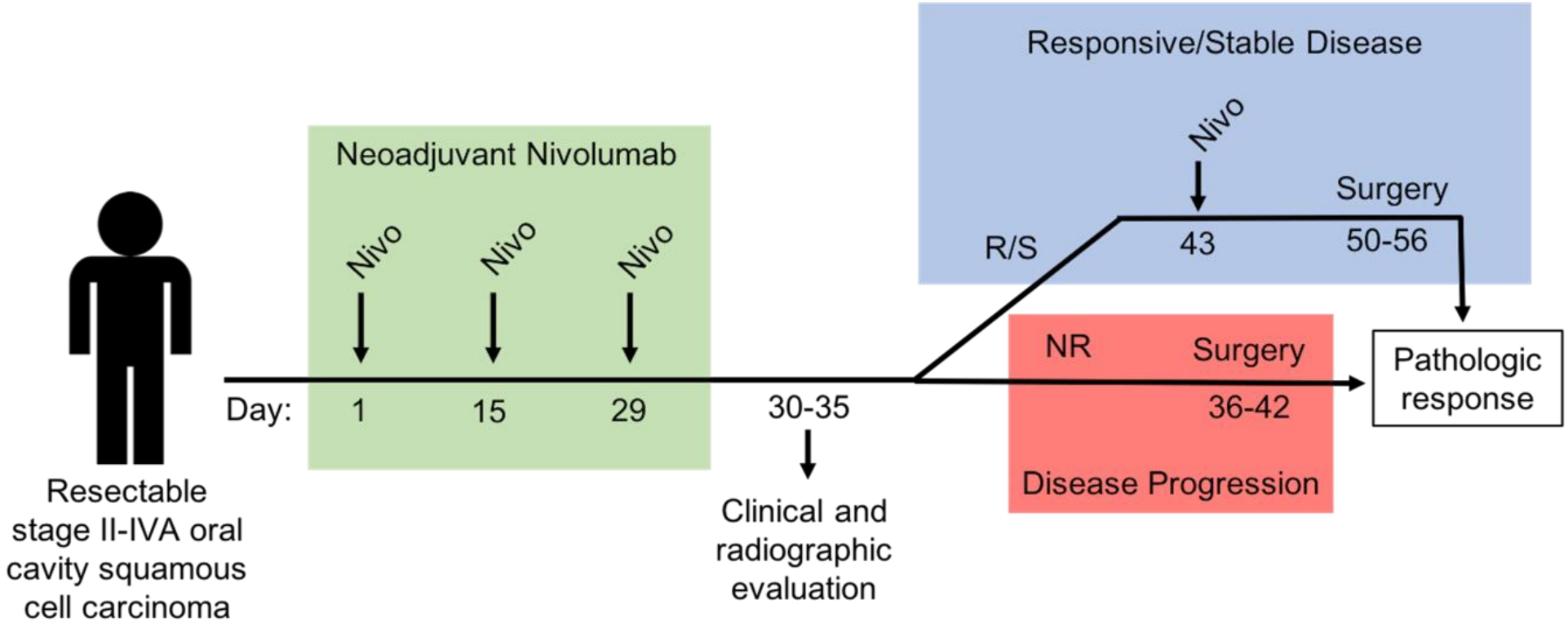
  Underwent surgical resection which revealed ypT2N0 with 30% reduction in tumor size.

  Completed adjuvant radiation is currently without evidence of disease at 18 months.



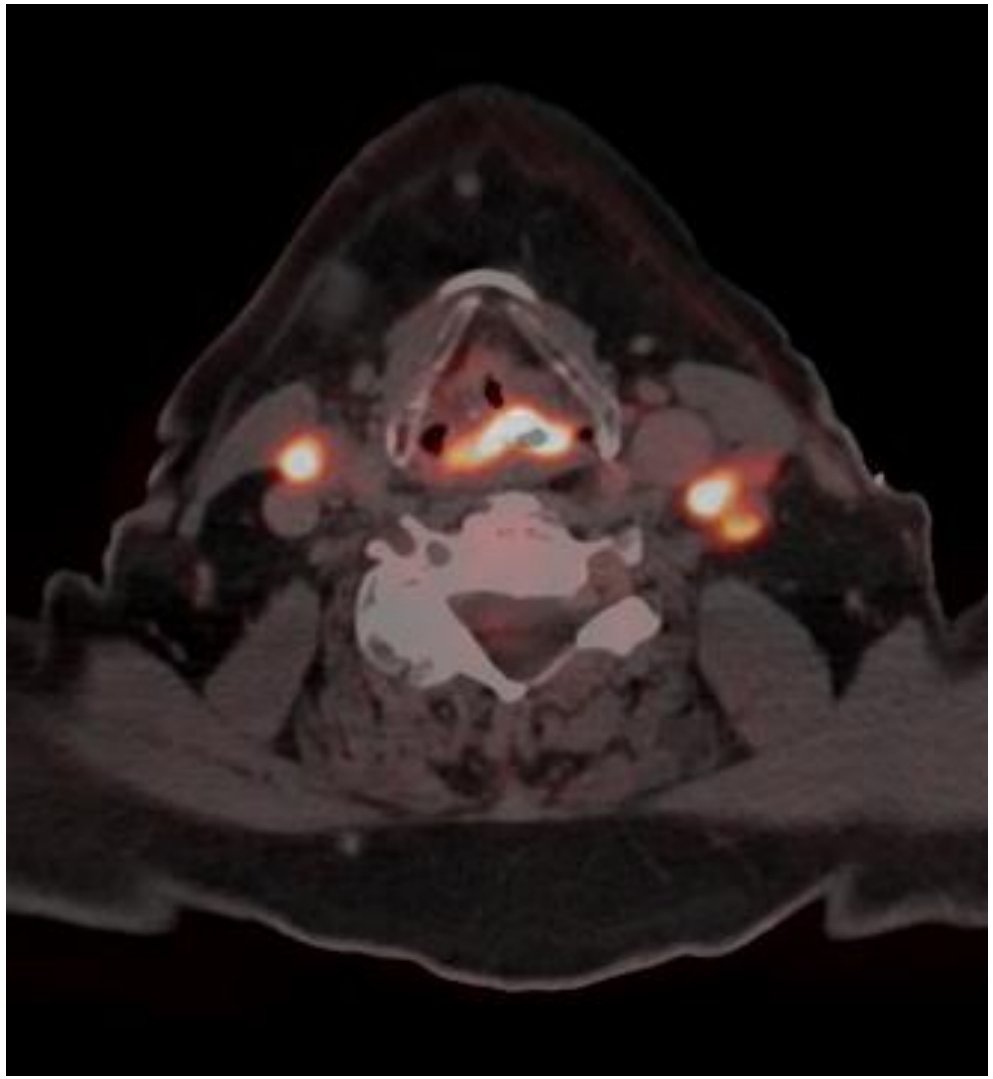


Phase II Trial of Nivolumab as a Novel Neoadjuvant Pre-Surgical Therapy for Locally Advanced Oral Cavity Cancer (NCT03021993) .



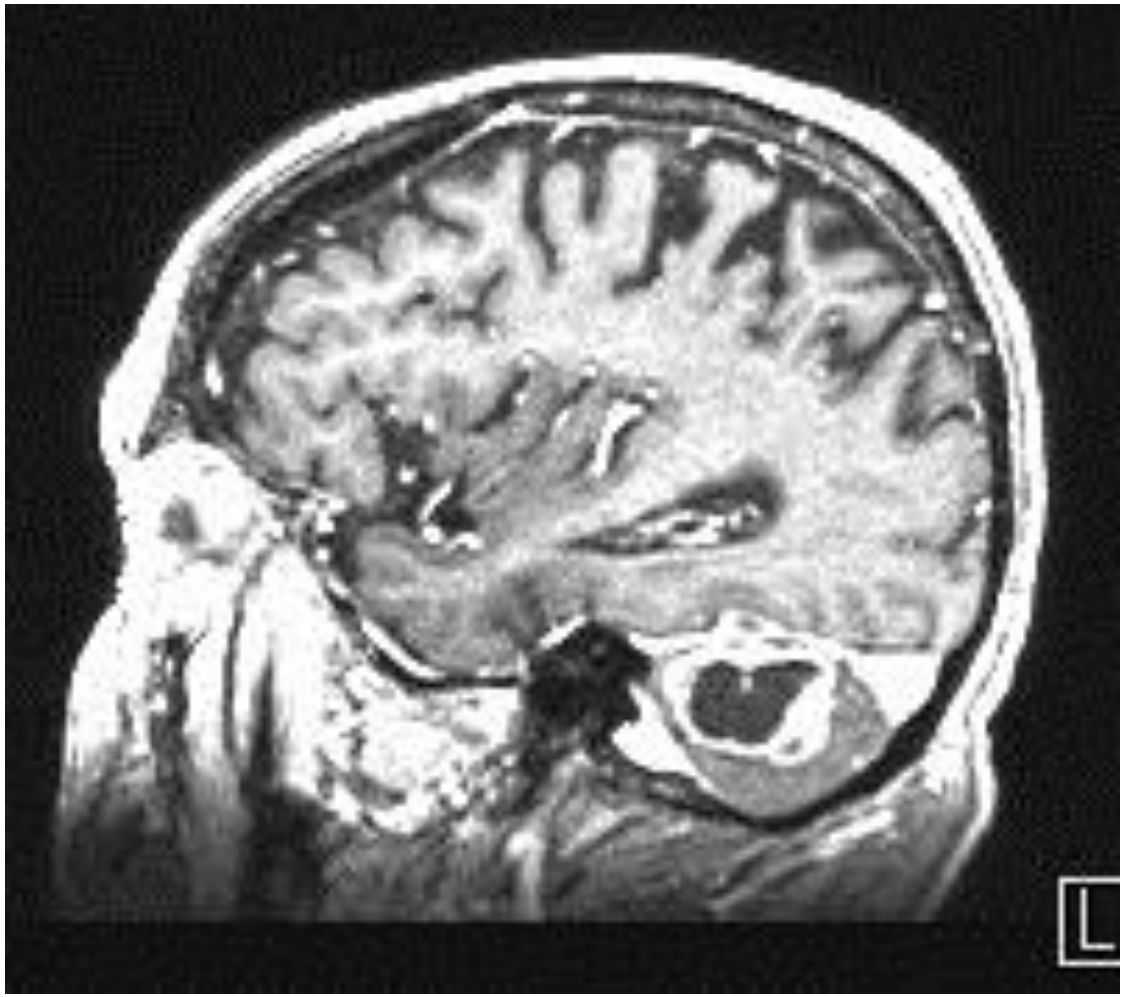
Case Study 2

- 74 year old male presented with one year history of throat pain and dysphagia
- Was ultimately diagnosed with squamous cell carcinoma of the hypopharynx cT2cN2cM0
- He was enrolled in JAVELIN Head and Neck 100: a Phase III trial of avelumab and chemoradiation for locally advanced head and neck cancer (NCT02952586).



Case Study 2

- 3 weeks after completing maintenance therapy biopsy of mediastinal node was positive for squamous cell carcinoma for which he received palliative radiation.
- 6 months later he developed a cerebellar mass with associated edema and mass effect on fourth ventricle and underwent surgical resection of cerebellar metastasis with pathology consistent with squamous cell carcinoma.
- He ultimately died of disease 8 months later.



JAVELIN Head and Neck 100

- A randomized double-blind phase 3 study of avelumab in combination with standard of care chemoradiotherapy (cisplatin plus definitive radiation therapy) versus standard of care chemoradiotherapy in the front-line treatment of patients with locally advanced squamous cell carcinoma of the head and neck
- Enrollment n=697
- Primary endpoint: Progression free survival at 48 months
- Experimental arm: Avelumab + SOC Chemoradiation Therapy and Q2W for 12 months during the Maintenance Phase
- Placebo Comparator: Placebo + SOC Chemoradiation Therapy and Placebo IV matching avelumab and Q2W for 12 months during the Maintenance Phase