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

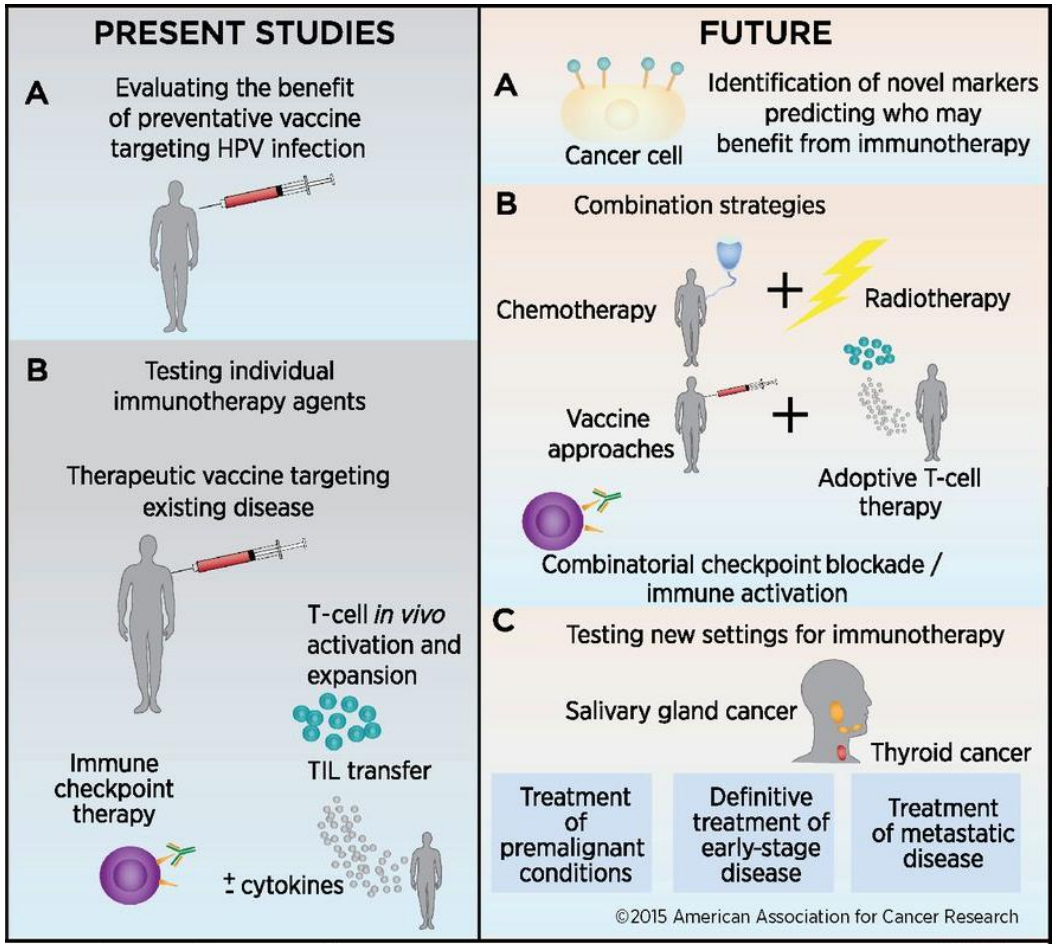
Society for Immunotherapy of Cancer

Disclosures

- Contracted Research: Aeglea Biotherapeutics, Astra-Zeneca, GlaxoSmithKline, Loxo, Merck, Pfizer
- 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



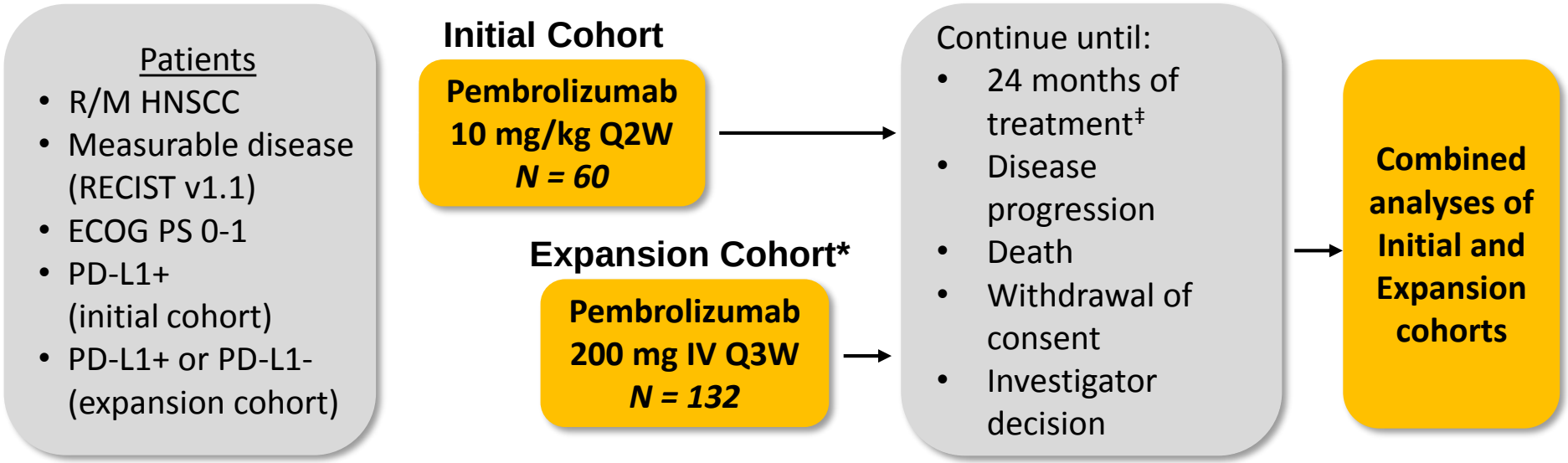
Schoenfeld, Cancer Immunol Res, 2015

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 §

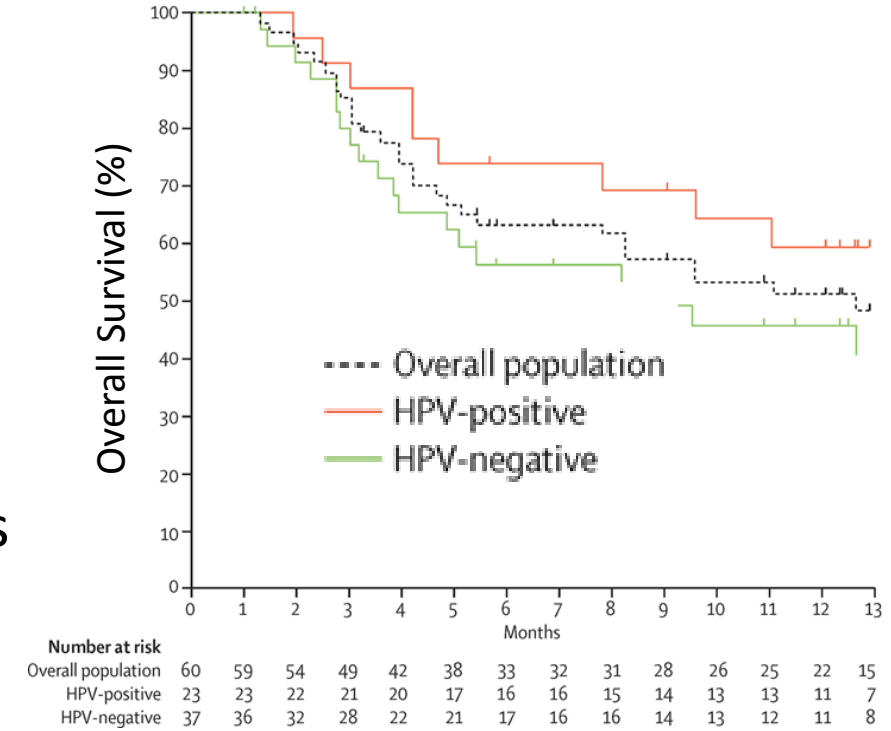
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

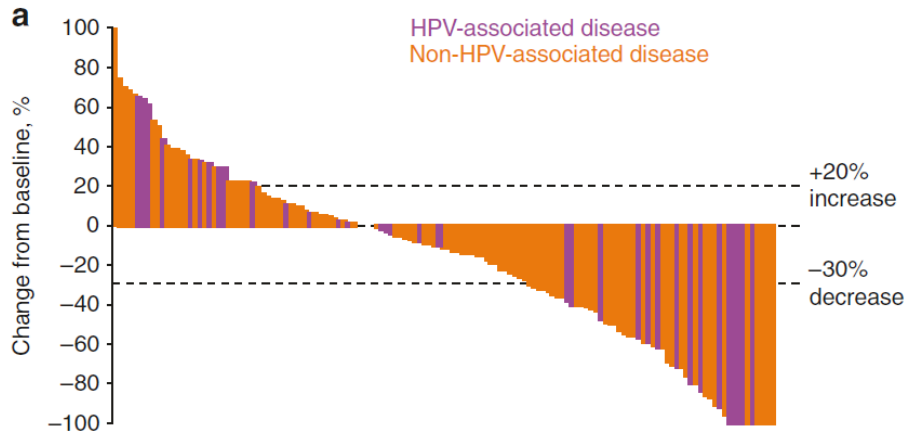
Seiwert, ASCO 2017.

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

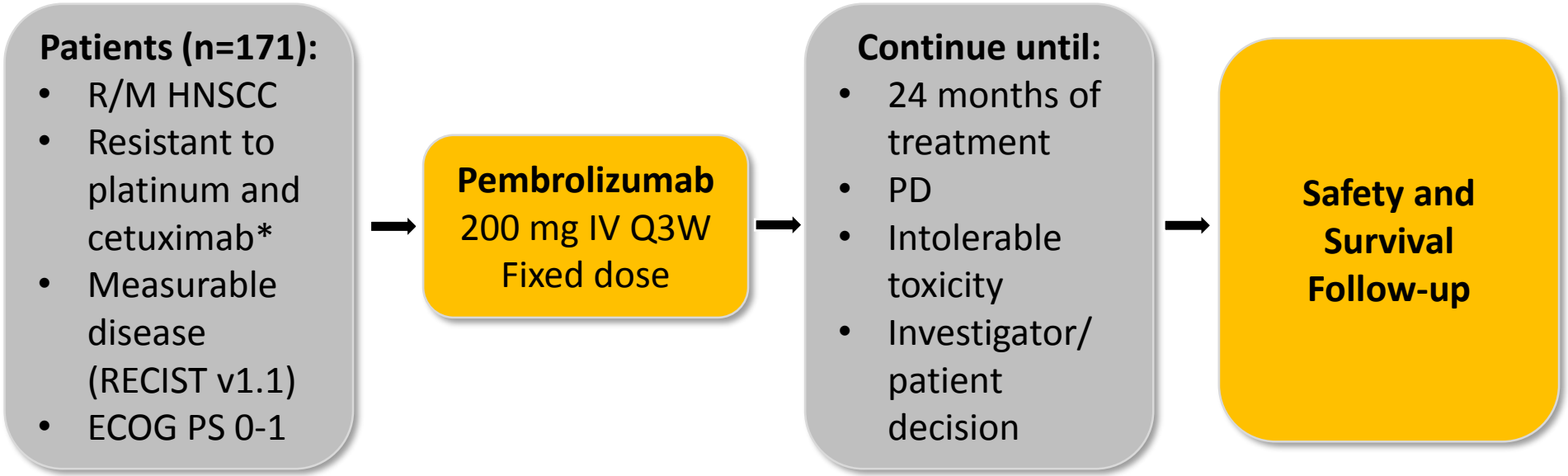




Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

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

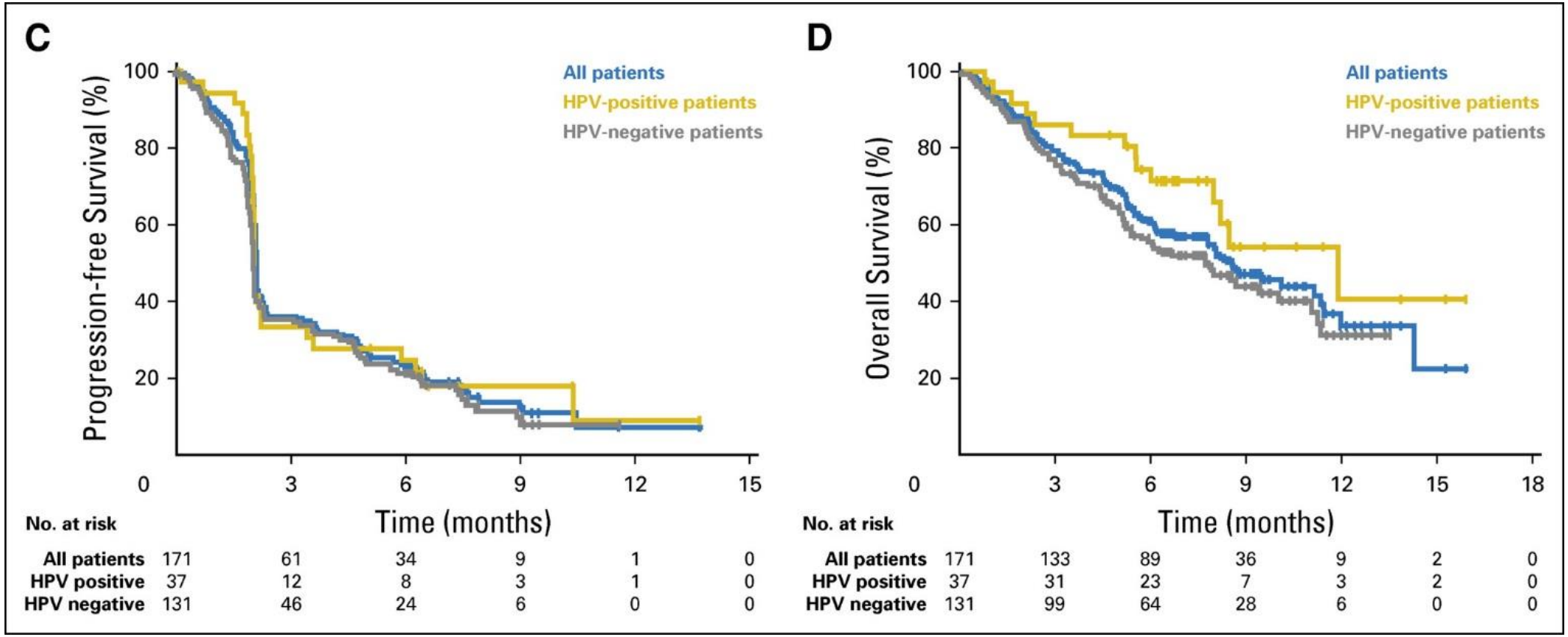
Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*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

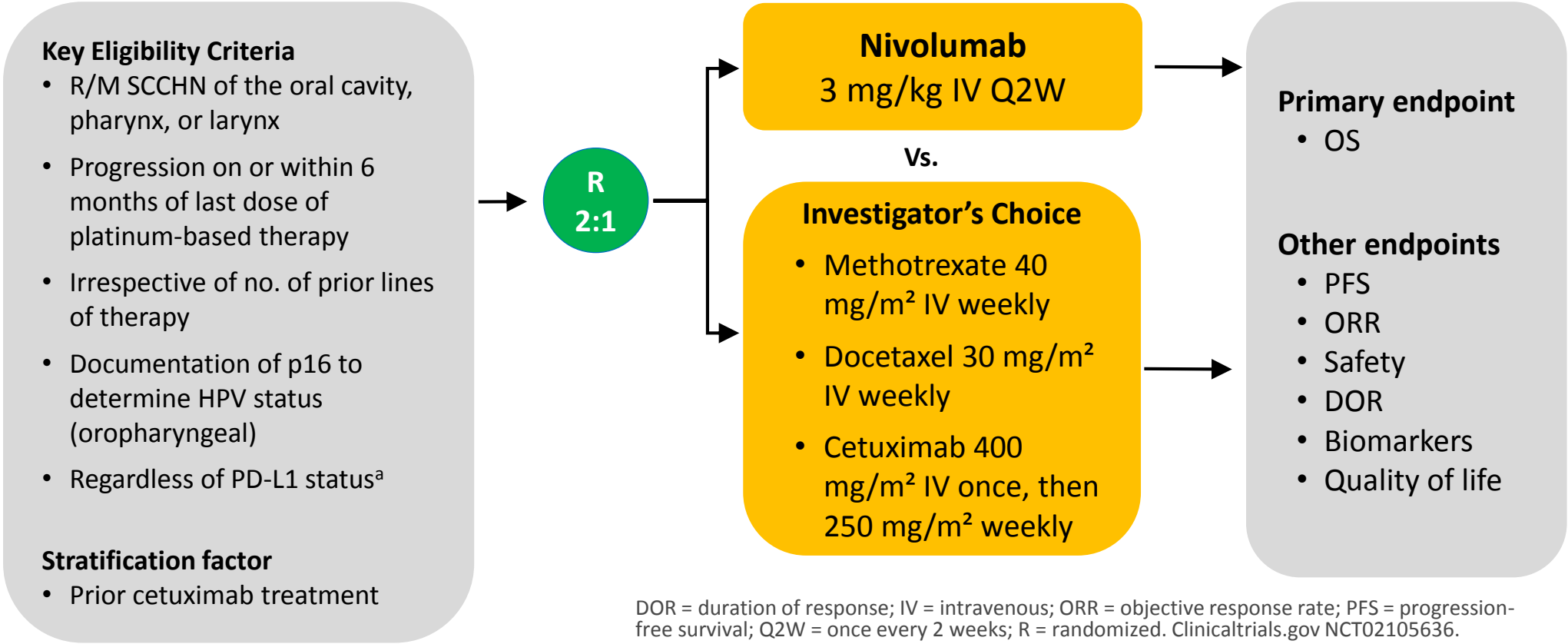
Phase II Trial, Single Arm



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.

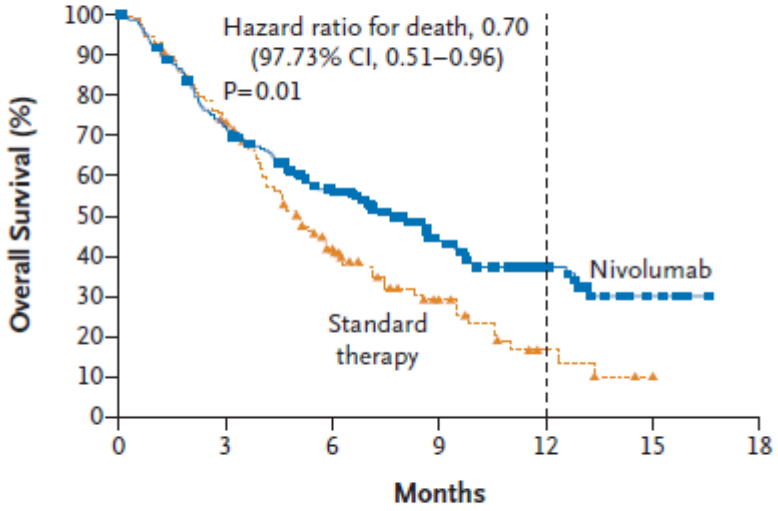
[a]Tissue required for testing

Ferris & Gillison, NEJM 2016.

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

A Overall Survival

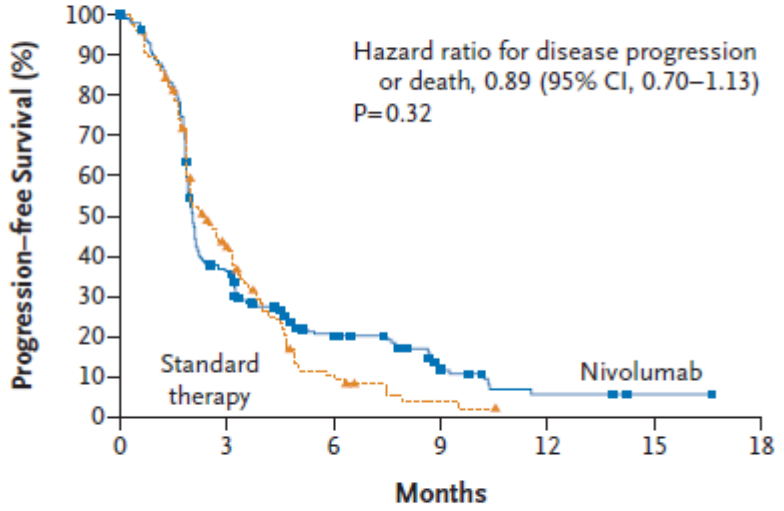
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



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

→

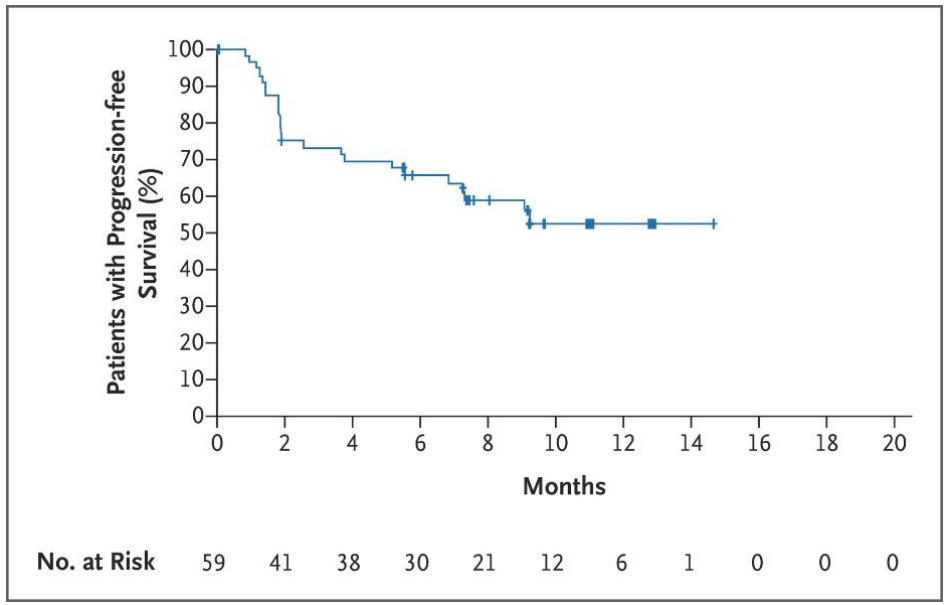
Primary endpoint
- Response rate

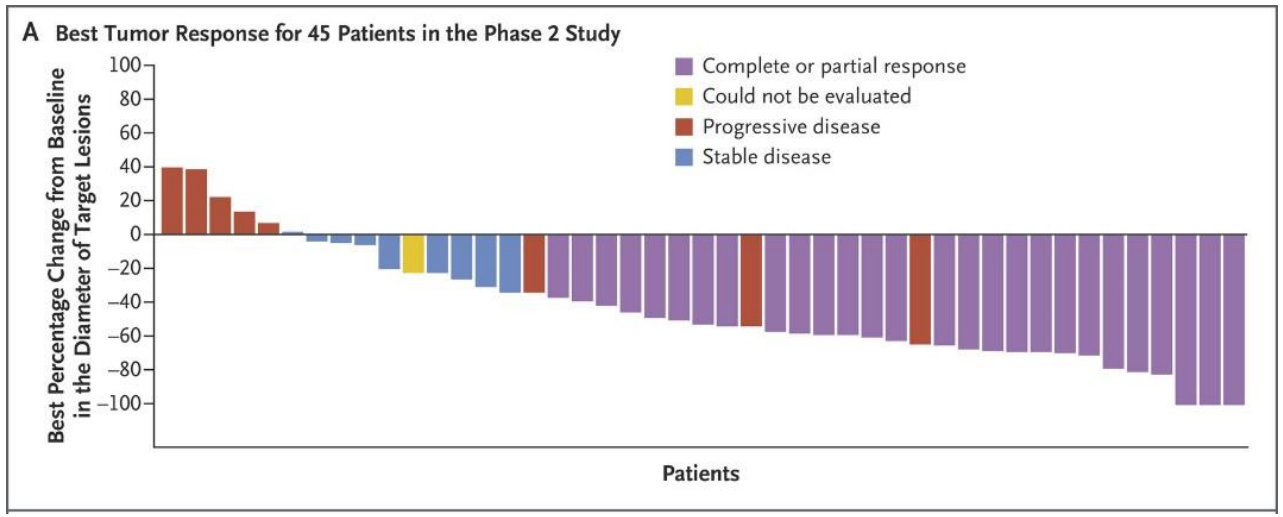
Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

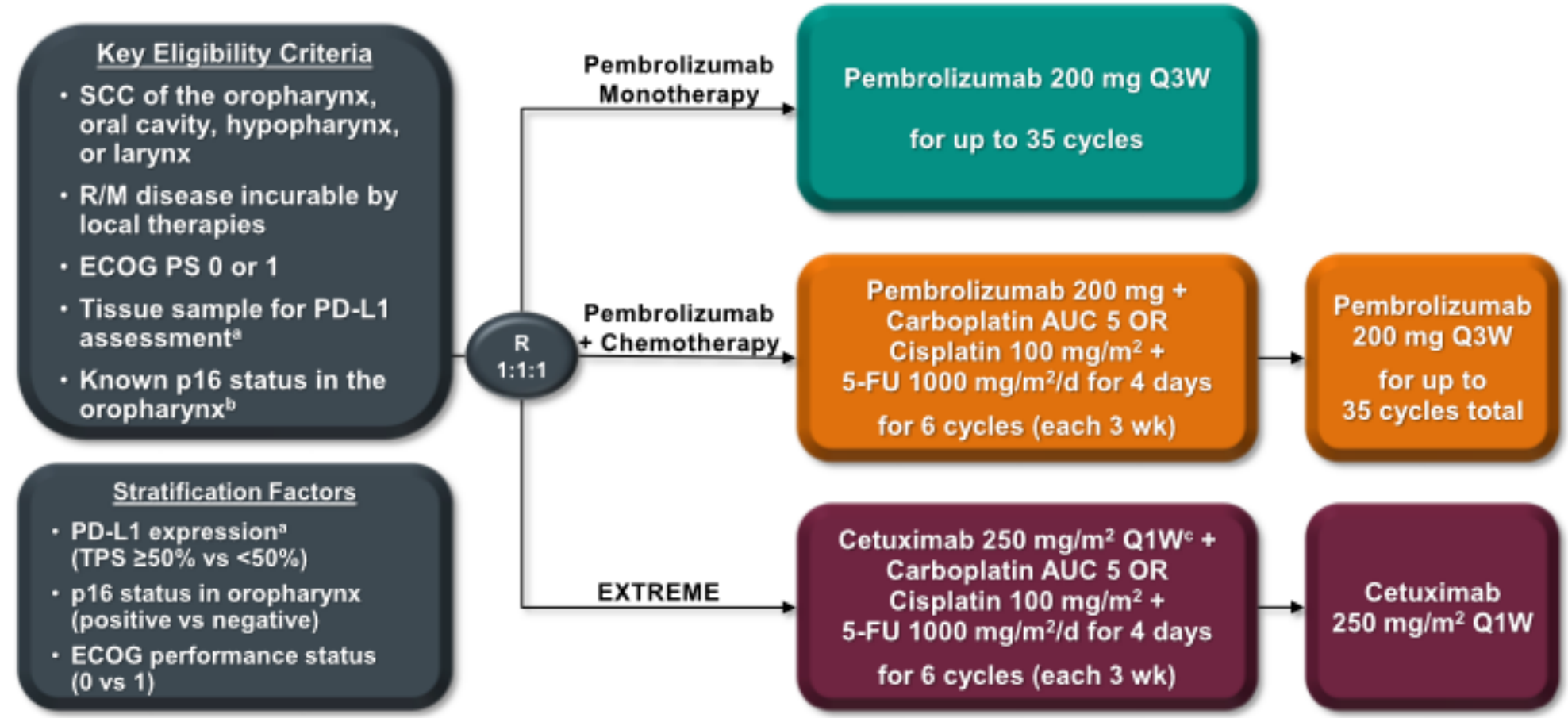
- Cemiplimab 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response





Migden, NEJM 2018.

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

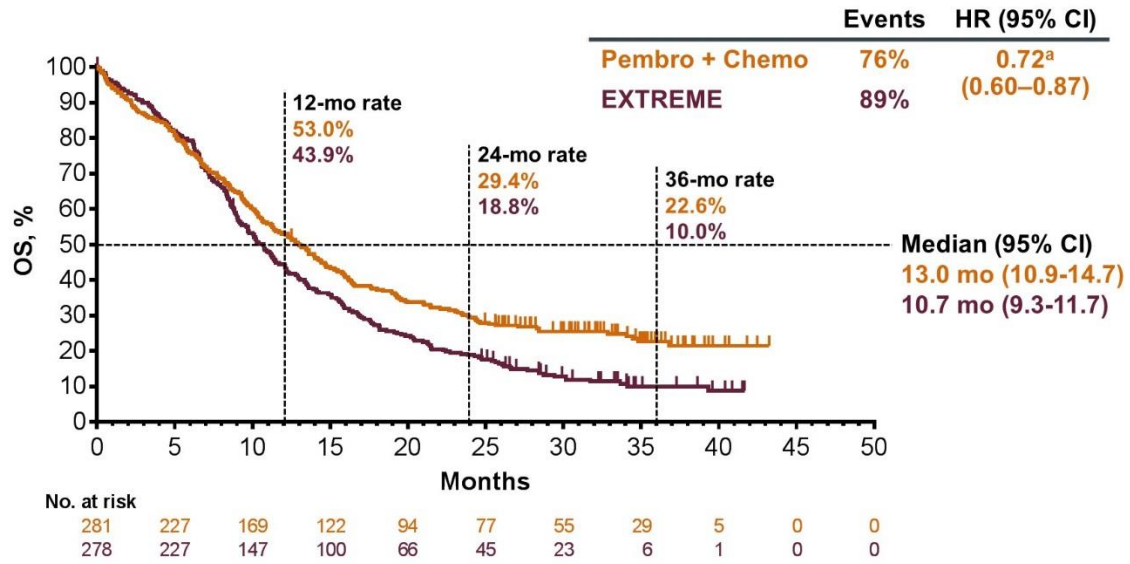


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

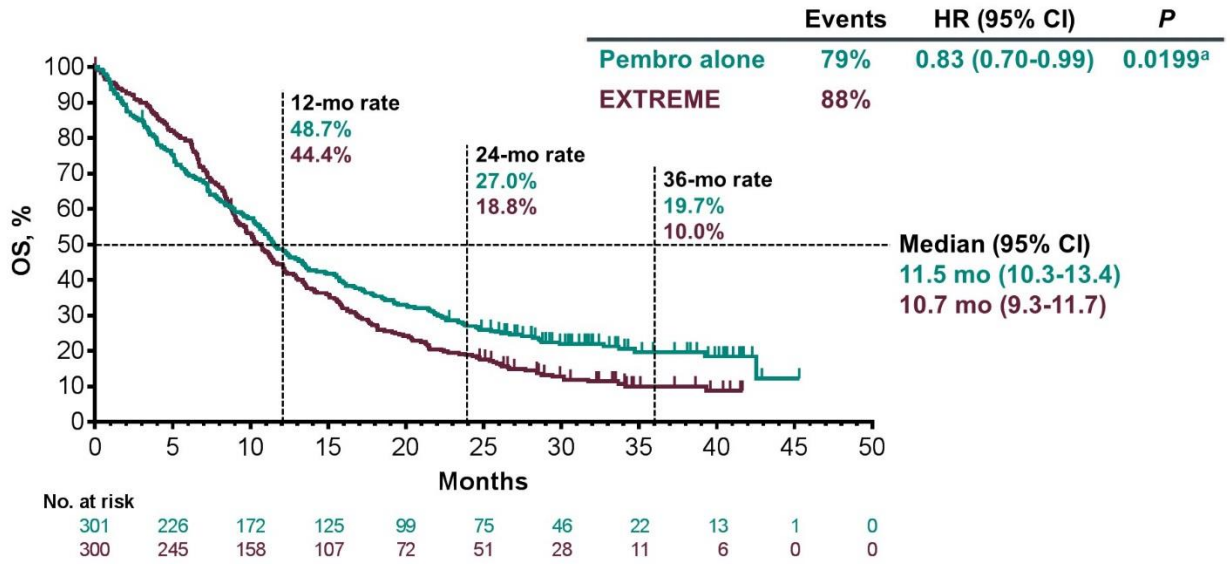
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

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.

PD-L1: TPS vs CPS

- TPS = Tumor Proportion Score
  - TPS (%) =

    (# of PD-L1 Stained Tumor Cells/total number of viable tumor cells) * 100
- CPS = Combined Positive Score
  - CPS (%) =

    (# of PD-L1 stained cells^)/total number of viable tumor cells) * 100

    ^tumor cells, lymphocytes and macrophages

- Math: If TPS is positive then CPS is positive but if TPS is negative then CPS could still be Positive (≥1%)

Kulangara K, Zhang N, Corigliano E, et al. Clinical Utility of the Combined Positive Score for Programmed Death Ligand-1 Expression and the Approval of Pembrolizumab for Treatment of Gastric Cancer *Arch Pathol Lab Med* 2019;143:330-337.

Evaluating Biomarkers in HNSCC

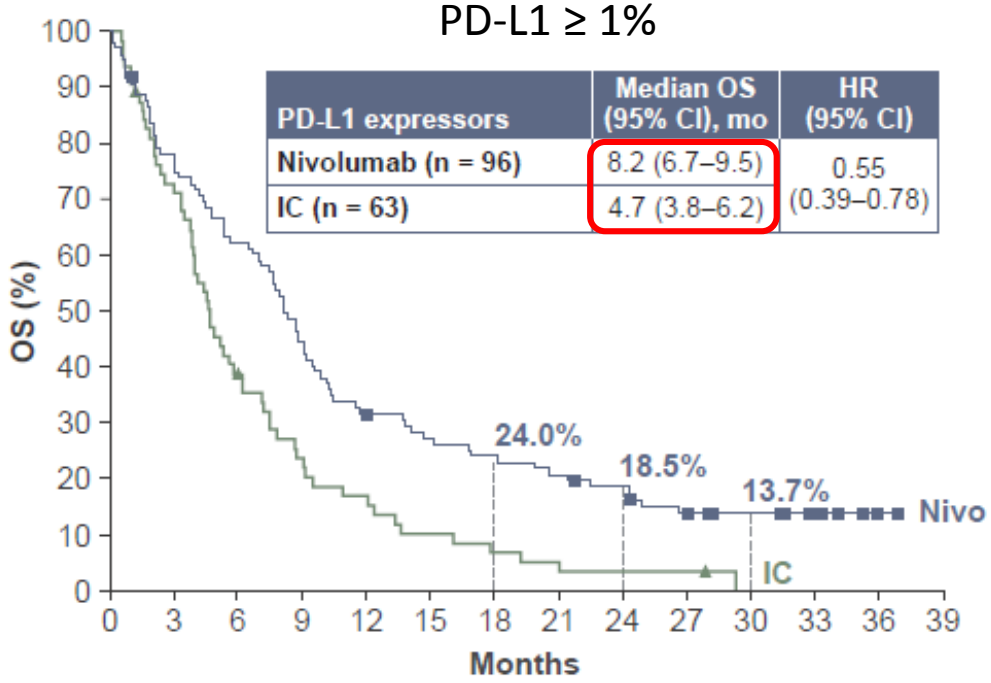
- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit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

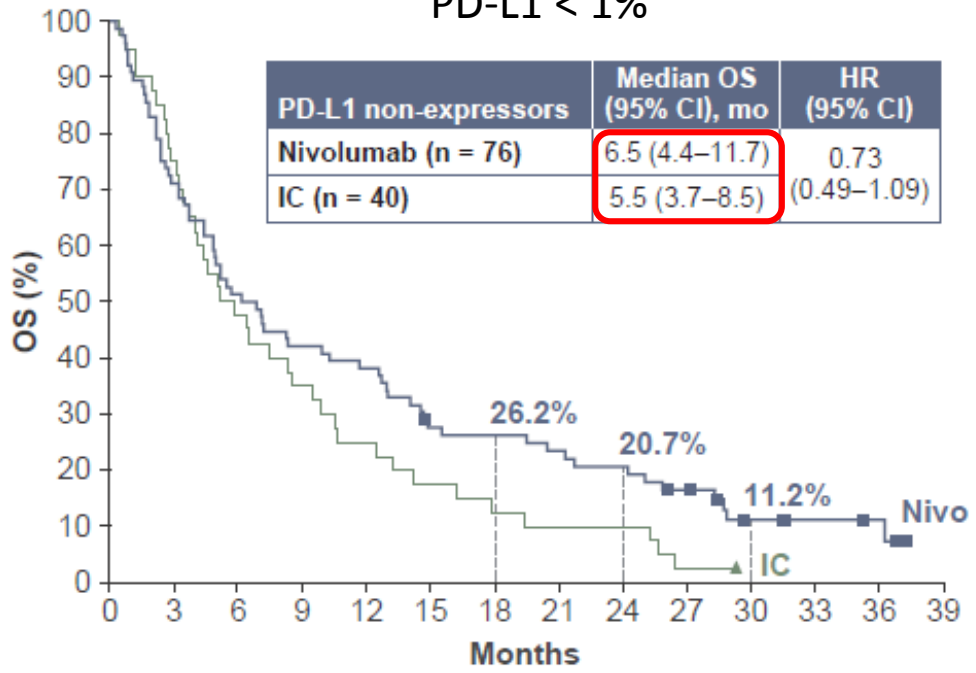


No. at risk

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*]

Case Studies

Case Study 1

- 50 yo female presents to office after being referred by ENT
  - 3 months of progressive dysphagia/odynophagia
  - Left tonsillar mass on flexible fiberoptic visualization
  - FNA of left cervical lymph node
    - Squamous cell carcinoma – P40 positive
    - P16 negative
  - PET scan shows no evidence of disease outside the head and neck
  - PMHx: Only Tobacco and ETOH Abuse
  - SHx: 80 oz beer daily but quit at cancer diagnosis (no DTs); current smoker with 10 pack year history (1 pack every 3 days)
  - Exam: benign except for mild submental lymphedema, no palpable lymphadenopathy or visible oropharyngeal mass

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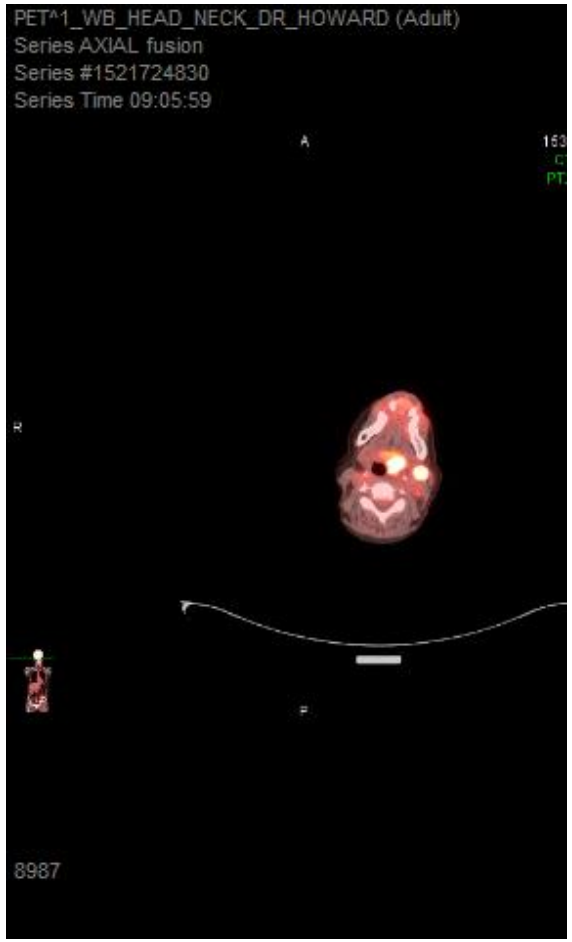
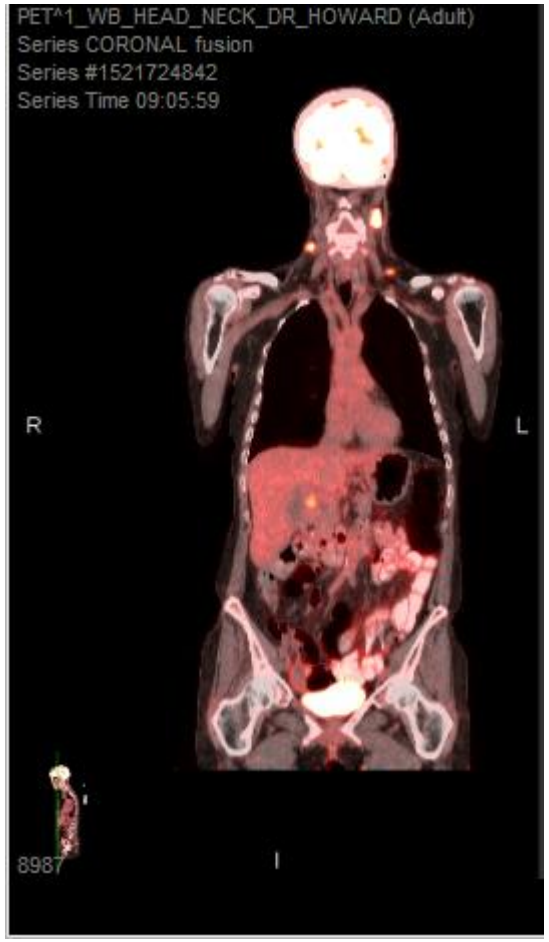
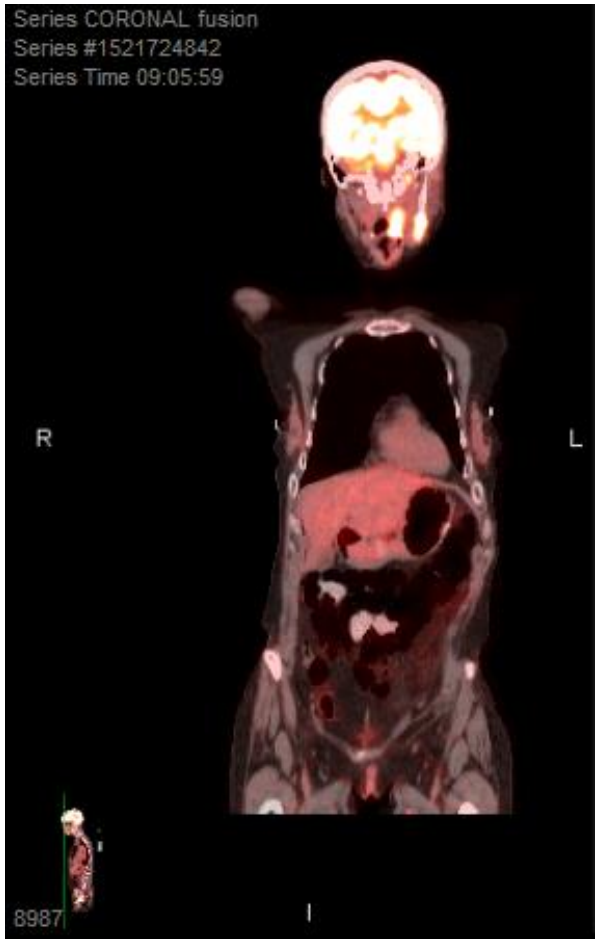
Case Study 1







Case Study 1

- What would be your expected treatment plan?
  - Referral for TransOral Robotic Surgery
    - Incorrect: Though on NCCN as an option, patient has high risk of Extranodal extension and would likely need trimodality therapy that will have greater risk of morbidity
  - Induction chemotherapy
    - Incorrect: Category 3 on NCCN as there is no survival benefit and no indication per LCI guidelines (bulky cervical lymphadenopathy, inability to start radiation in a timely manner)
  - Concurrent chemoradiation with Cisplatin
    - Correct: Personal preference of Bolus Cisplatin (100mg/m2 q3wks * 3) as she is a young patient with no hearing or renal issues but weekly cisplatin (40mg/m2) is also an option
  - Clinical Trial
    - Correct: always on option but patient was not interested in research

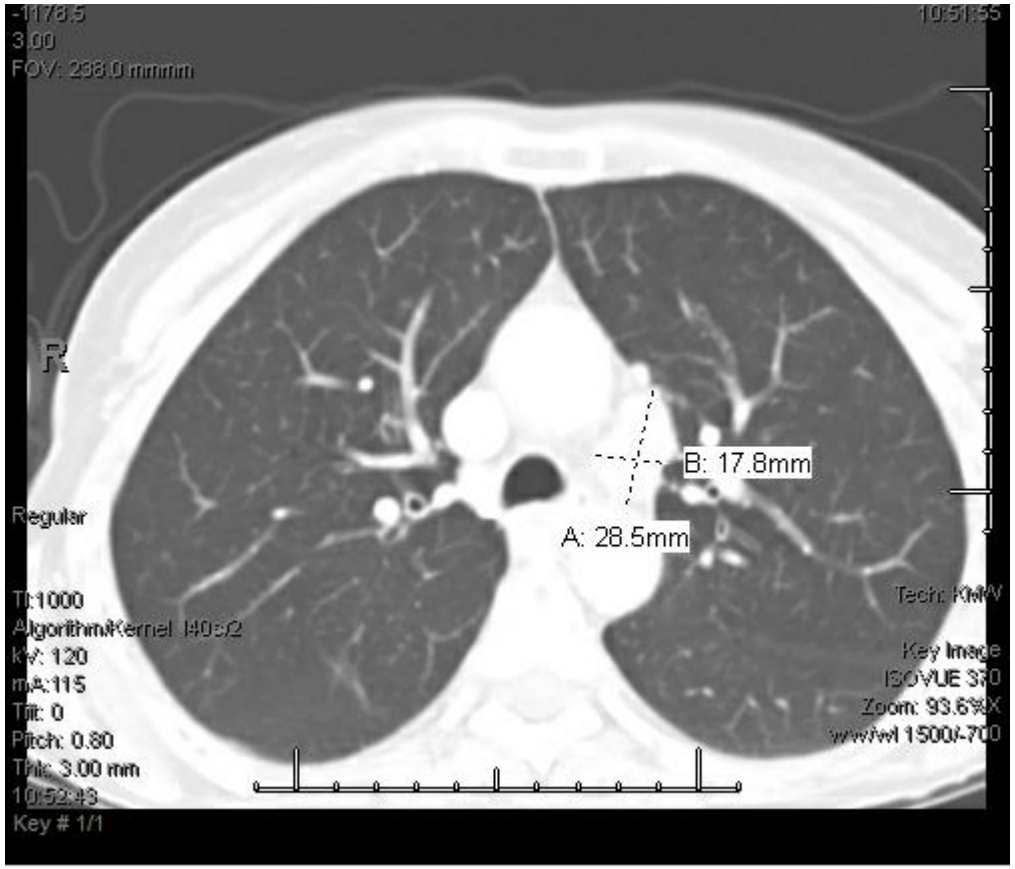
Case Study 1

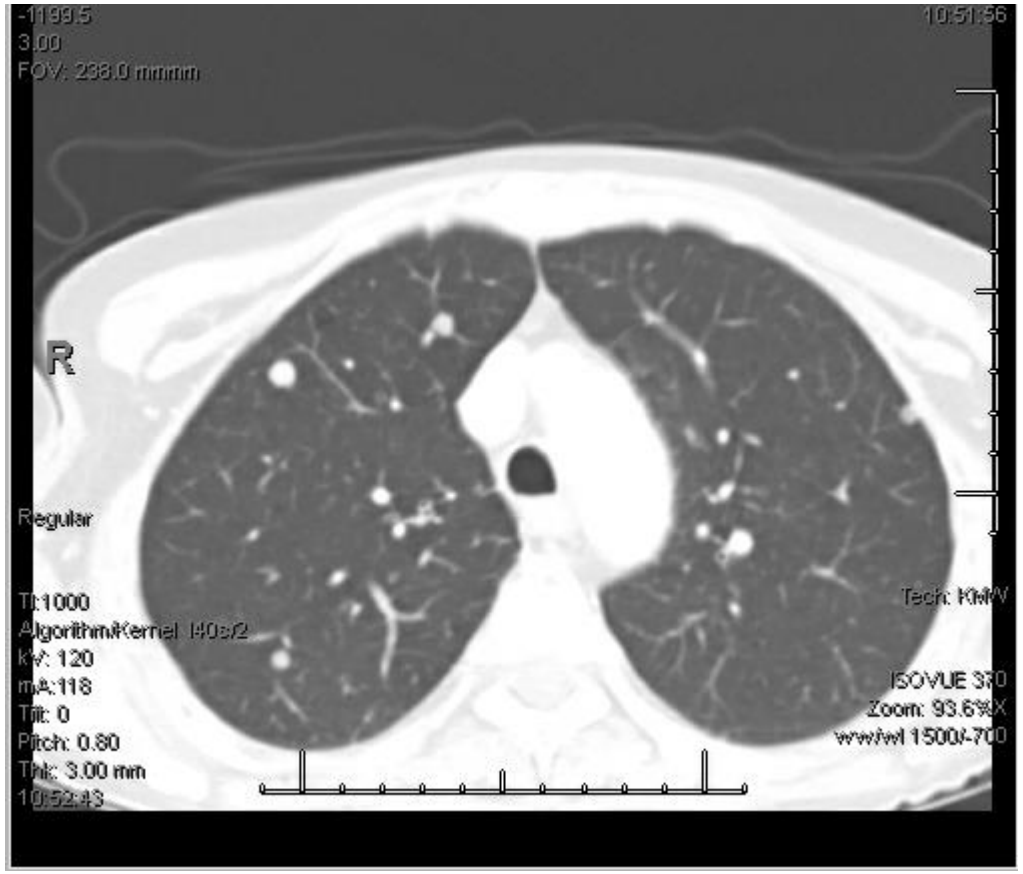
- Treated with Bolus Cisplatin (100mg/m2) with concurrent radiation
  - Received all three cycles with no delay or dose reduction
  - No renal dysfunction or clinical hearing loss or tinnitus
- PET Scan 3 months following completion of radiation
  - Complete Response (CR) with no residual tonsillar mass or lymphadenopathy

Case Study 1

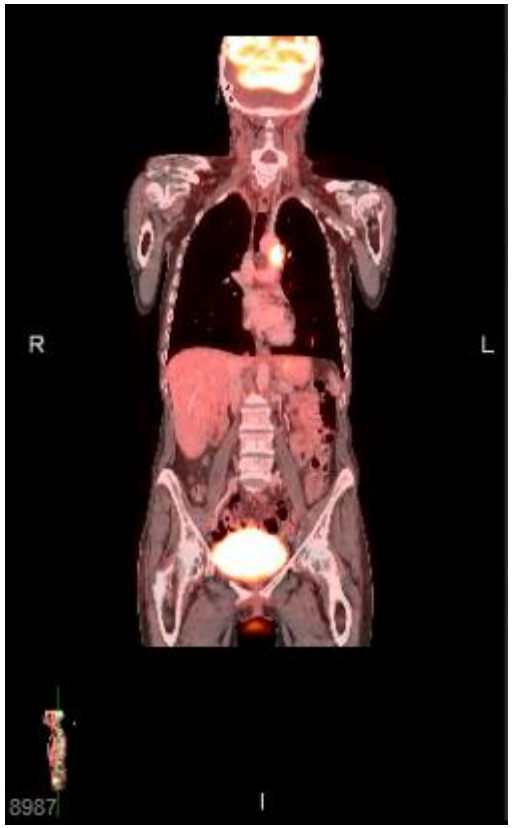
- Coming in for 6 month follow-up
- Has been “not feeling well like when I was diagnosed with cancer”
- Lost 8 lbs without intent
- No clinical lymphadenopathy and no lesion on direct visualization of the tonsil
- CT Scan of neck ordered:

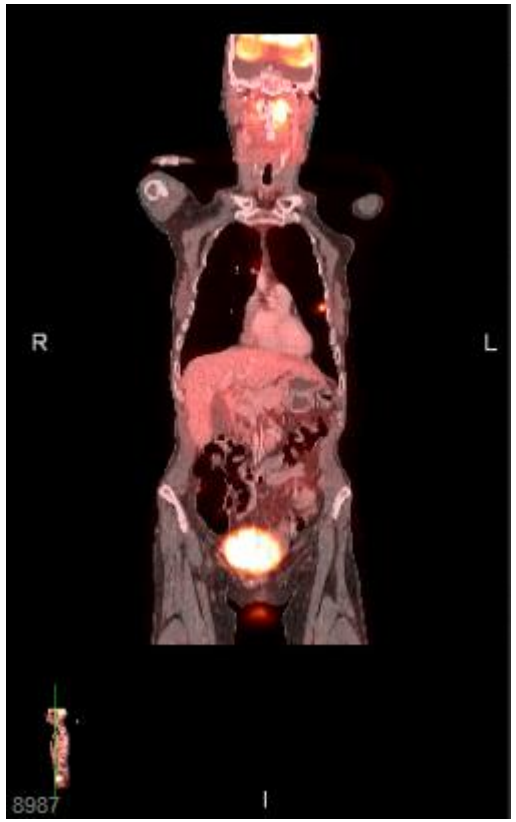
Case Study 1

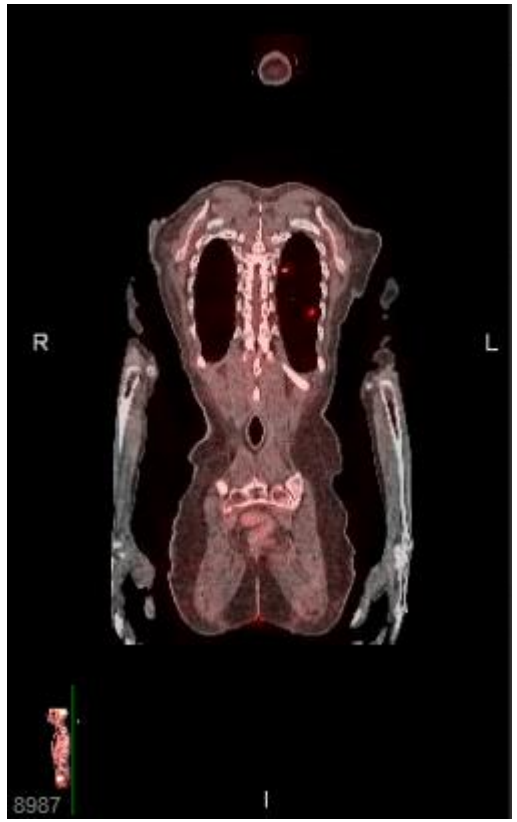




Case Study 1







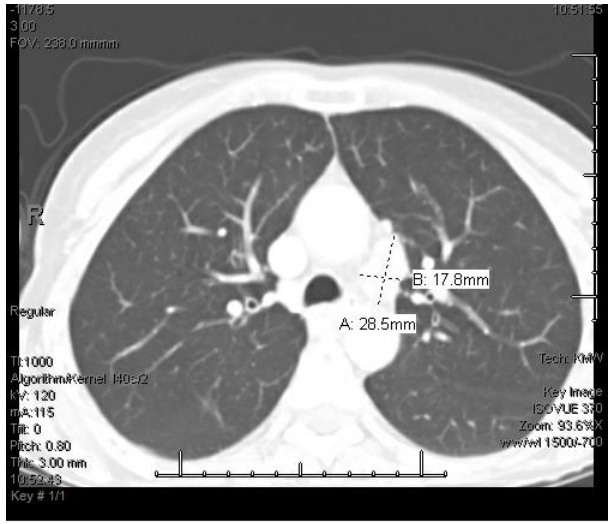
Case Study 1

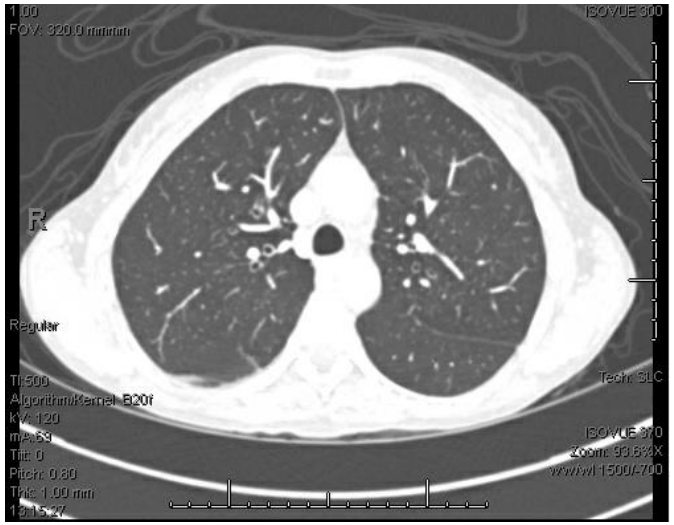
- What would you do now?
  - Biopsy to document recurrence and check PD-L1
    - Correct: PD-L1 would guide treatment therapy and prove recurrence in smoker
  - Empirically treat with Extreme Regimen (Platinum/Cetuximab/5-FU)
    - Incorrect: Keynote 048 would favor either pembrolizumab (CPS≥1) or chemoimmunotherapy (platinum/5-FU/pembrolizumab for any or unknown CPS)
  - Treat with Pembrolizumab
    - Correct if PD-L1 (CPS) ≥ 1; Incorrect if CPS of 0
  - Treat with Platinum/5-FU/Pembrolizumab
    - Correct: Option available without knowing CPS or if patient needs immediate response or if there is a concern that they are progressing rapidly

Case Study 1

- Patient underwent biopsy:
  - CT-guided core showed squamous cell carcinoma c/w known disease
    - CPS 25%

- Started on Pembrolizumab alone w/ CR after 3 doses





Case Study 2

- 77 yo female with a past medical history of Diabetes Mellitus, hypertension and R MCA CVA and recurrent TIAs presents in follow-up
  - Patient treated 6 years prior for squamous cell carcinoma of the Right Upper lobe and NED
    - Resected (T2aN0M0) with lobectomy
    - Adjuvant chemotherapy (carboplatin/paclitaxel * 4)
  - Diagnosed with Right Squamous Cell Carinoma of the Pinna/Conchal Bowl 1 year ago and s/p MOHS surgery
    - Margins negative
  - Presents with enlarging mass in Right Neck
- MEDS: Clopidogrel, ASA, Insulin, Carvedilol, Losartan, Ezetimibe, Tramadol
- PMHx: DM, HTN, R MCA CVA (mild left-sided deficits), recurrent TIAs, MI (s/p drug eluding stent), GERD, hypercholesterolemia,COPD

Case Study 2

- PE
  - Right ear with scarring and no lesion
  - Right Neck: 2 firm, mildly tender, immobile 2cm lesions inferior to right mastoid
  - Chest CTA
  - CV: irregularly irregular

Case Study 2

- What would you do now?
  - CT Scan of the Neck/PET Scan
    - Correct: low-density enhancing lesion inferior to right ear lobe between tail of parotid and mastoid (2.3*1.4cm), 2 Level 2A necrotic lymph nodes (1.8*1.6cm and 1.4*1cm), small lymph nodes in superior mediastinum with low density concerning for mets.
    - Correct: Above lesions are all FDG avid, No hilar lymphadenopathy, no other FDG-avid lesions.
  - Biopsy Lesion or cervical lymph node
    - Correct: Right FNA with malignant cells, poorly-differentiated c/w squamous cell carcinoma.
  - Refer to Surgery
    - Correct: Patient is not a surgical candidate due to comorbidites
  - Refer to Hospice as no treatment available for metastatic cutaneous squamous cell carcinoma
    - Incorrect: If patient is not a surgical candidate, could consider radiation or systemic therapy

Case Study 2

- Patient not a surgical candidate due to comorbidities and could not come off of Plavix
- Patient saw radiation oncology and refused radiation (family member had bad experience)
- No history of autoimmune disease
- ECOG 1

Case Study 2

- What would you do now?
  - Refer to Hospice as patient refused radiation
    - Incorrect: see below
  - Extreme Chemotherapy (carboplatin/cetuximab/5-FU)
    - Incorrect: No data in cutaneous squamous cell carcinoma of the head and neck
  - Cemiplimab-rwlc
    - Correct: Patient has no contraindication to PD-L1 blockade, higher response rates than chemotherapy or biologics
  - Cetuximab
    - Incorrect: As patient is a candidate for immunotherapy, would favor immunotherapy and this could be considered if ineligible for immune checkpoint inhibition or clinical trials.
  - Refer for Clinical Trial
    - Always correct

Case Study 2

- Patient started Cemiplimab and had partial response after 3 cycles.
  - Pain had resolved and she was feeling well/hopeful
- Unfortunately, she had two more cycles with clinical improvement and then had a large hemorrhagic stroke leading to functional decline and death within a few weeks.