Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancer

Ezra Cohen, MD

University of California San Diego

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

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Disclosure Information

Consulting Fees: ALX Oncology, Ascendis Pharma, Bayer, BioLineRx, Bristol Myers Squibb, Debiopharm, Dynavax Technologies, Merck KGaA, Merck & Co., Regeneron Pharmaceuticals, and Sanofi

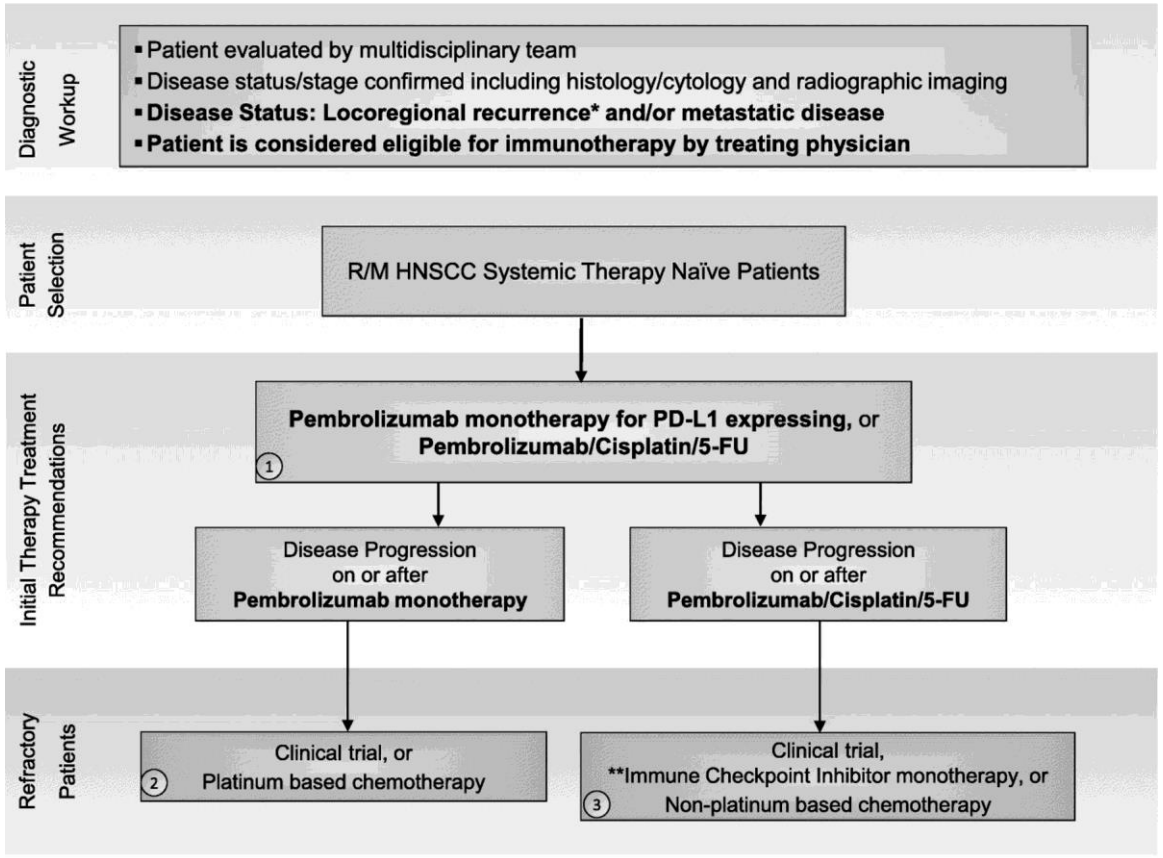
Ownership Interest (<5%): Kinnate Biopharma

I will be discussing non-FDA approved indications during my presentation.

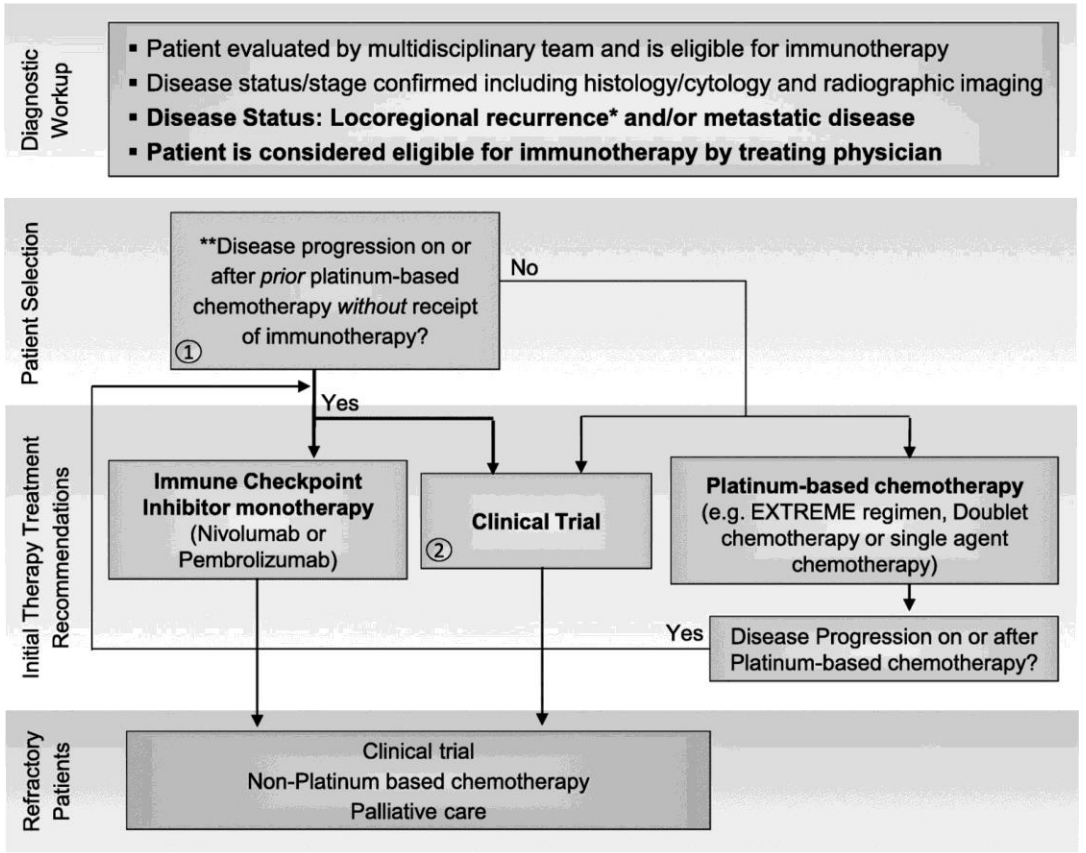
Outline

- Approved immunotherapies in head and neck cancers
- Biomarkers and immunotherapy responsiveness
- Unique considerations for head and neck cancers
- Future directions

Immunotherapy in head and neck cancer treatment



*Locoregional recurrence without salvage surgical or radiation option or declines local therapies
**Refer to Figure 2. Initial Therapy Treatment Recommendations: Immune Checkpoint Inhibitor monotherapy (nivolumab or pembrolizumab)



*Locoregional recurrence without salvage surgical or radiation option or declines local therapies
**Disease Progression on or after Platinum-Based Therapy: Disease progression on or after platinum-based therapy including within 6 months of platinum-based CRT given in the locally advanced setting. Patients that receive but cannot tolerate platinum-based chemotherapy would also be included in this category.
HNSCC: head and neck squamous cell carcinoma

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Approved checkpoint inhibitors in head and neck cancers

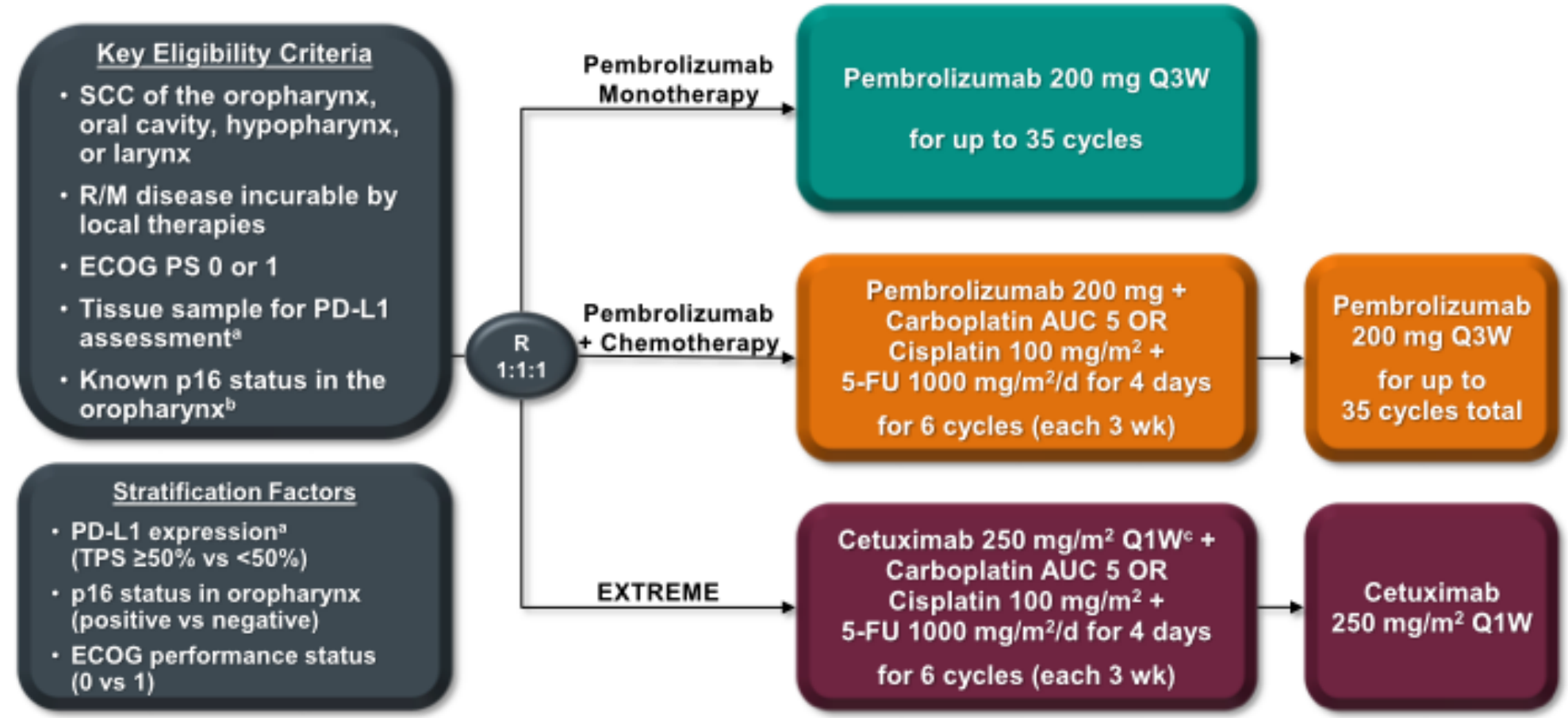
Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W or 400 mg Q6W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Pembrolizumab + platinum + fluorouracil	2019	Recurrent/metastatic HNSCC 1st line – all patients	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1st line – PD-L1 CPS ≥ 1	200 mg Q3W or 400 mg Q6W

Clinical trials in HNSCC

Trial	Patient selection criteria	Treatment arm(s)	N	ORR	Median PFS (months)	Median OS (months)
KEYNOTE-048	**Untreated** R/M HNSCC (total population)	Pembrolizumab	301	16.9%	2.3	11.5
		Pembrolizumab + chemo	281			13.0
		Cetuximab + chemo	300	36.0%	5.2	10.7
KEYNOTE-012	R/M HNSCC	Pembrolizumab	192	18% (PD-L1+: 21%, PD-L1-: 6%)	2.1	8
CheckMate 141	R/M HNSCC with **progression on platinum**	Nivolumab	240	13.1% (PD-L1+: 17.7%, PD-L1-: 11.8%)	2.0	7.7
		Investigator's choice	121	5.8%	2.3	5.1
KEYNOTE-040	R/M HNSCC with **progression on platinum**	Pembrolizumab	247	14.6%	2.1	8.4
		Investigator's choice	248	10.1%	2.3	6.9

Mehra, Br J Cancer 2018; Ferris, Oral Oncol 2018; Cohen, Lancet 2018; Burtness, Lancet 2019.

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

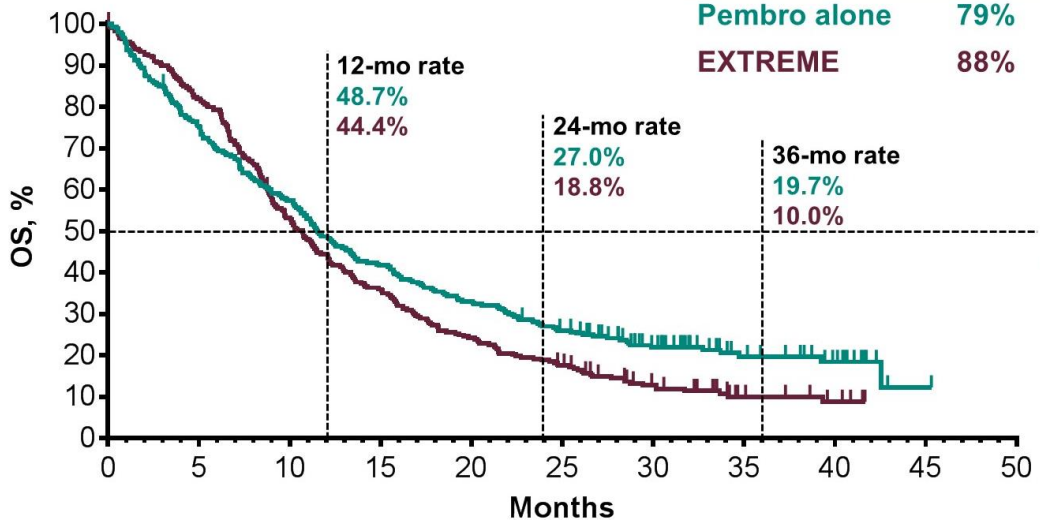


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

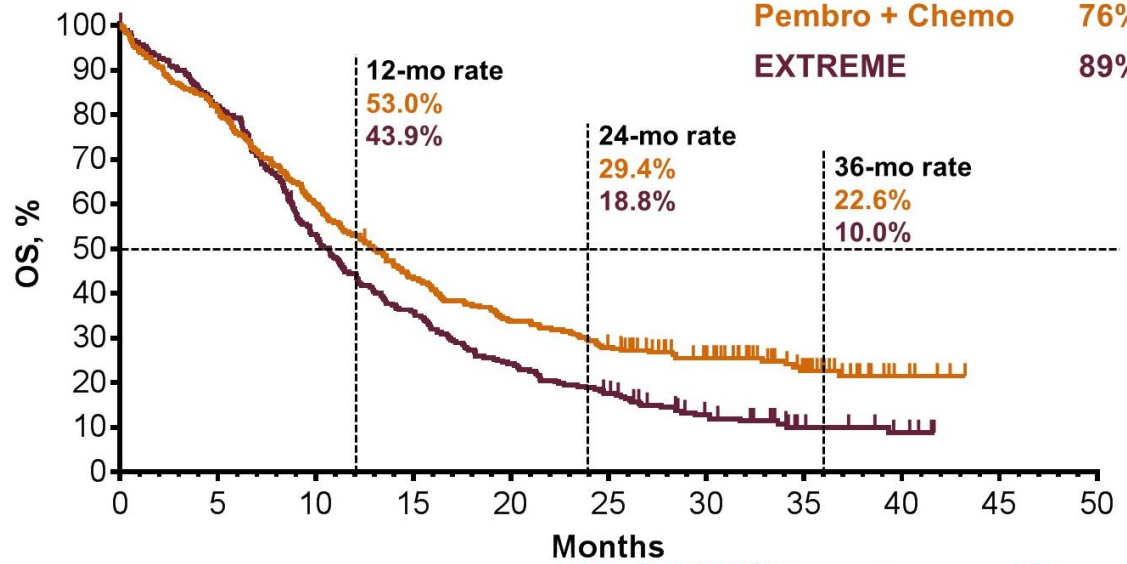
Rischin, ASCO 2019.

KEYNOTE-048: Overall survival in the total population

	Events	HR (95% CI)	*P*
Pembro alone	79%	0.83 (0.70-0.99)	0.0199[a]
EXTREME	88%		



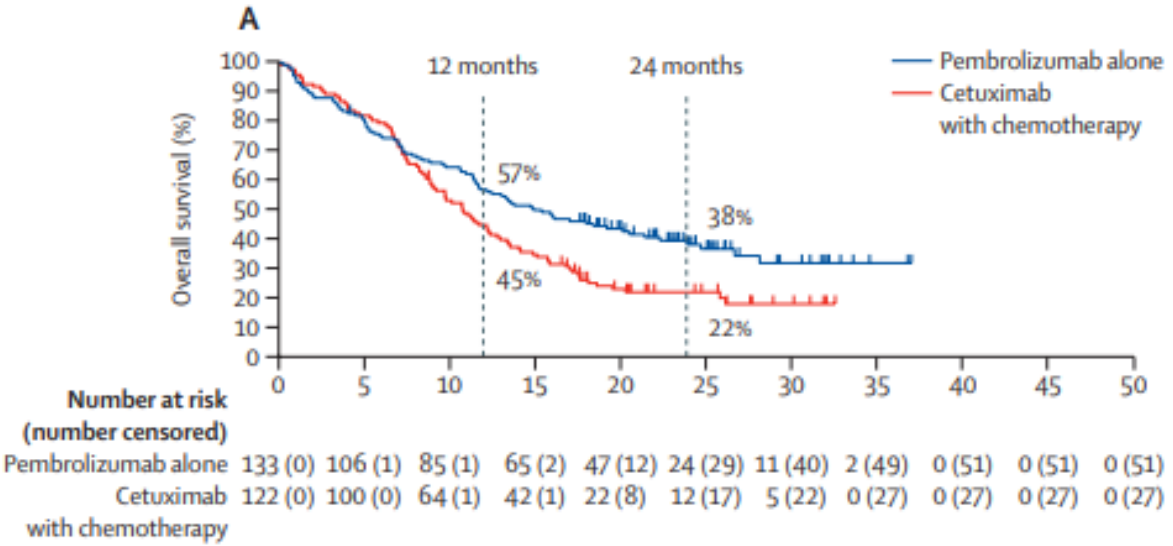
	Events	HR (95% CI)
Pembro + Chemo	76%	0.72[a] (0.60–0.87)
EXTREME	89%	



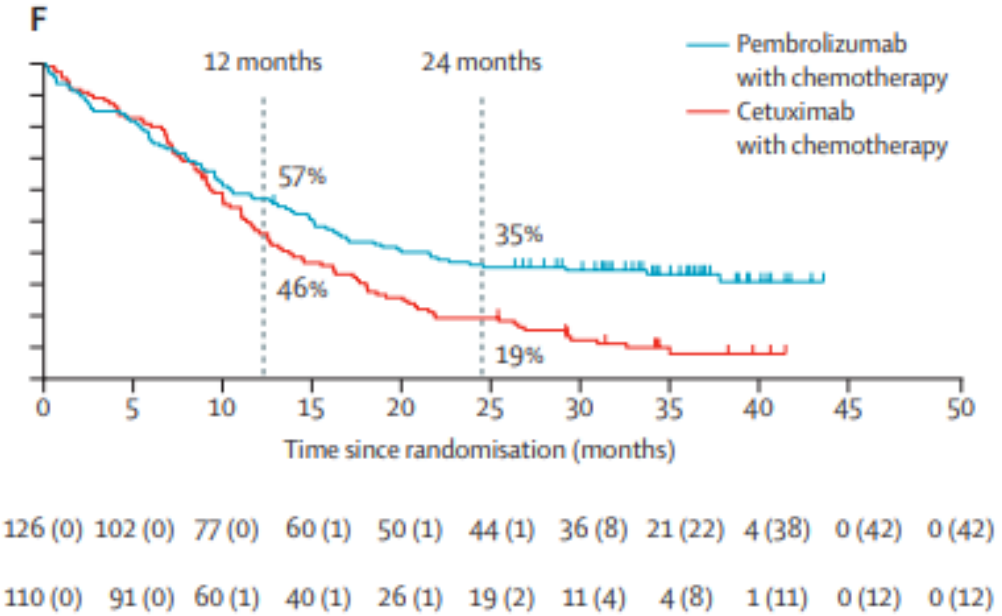
Rischin, ASCO 2019

KEYNOTE-048: Overall survival in the PD-L1 positive population

PD-L1 CPS ≥1



PD-L1 CPS ≥1



Burtness, Lancet 2019

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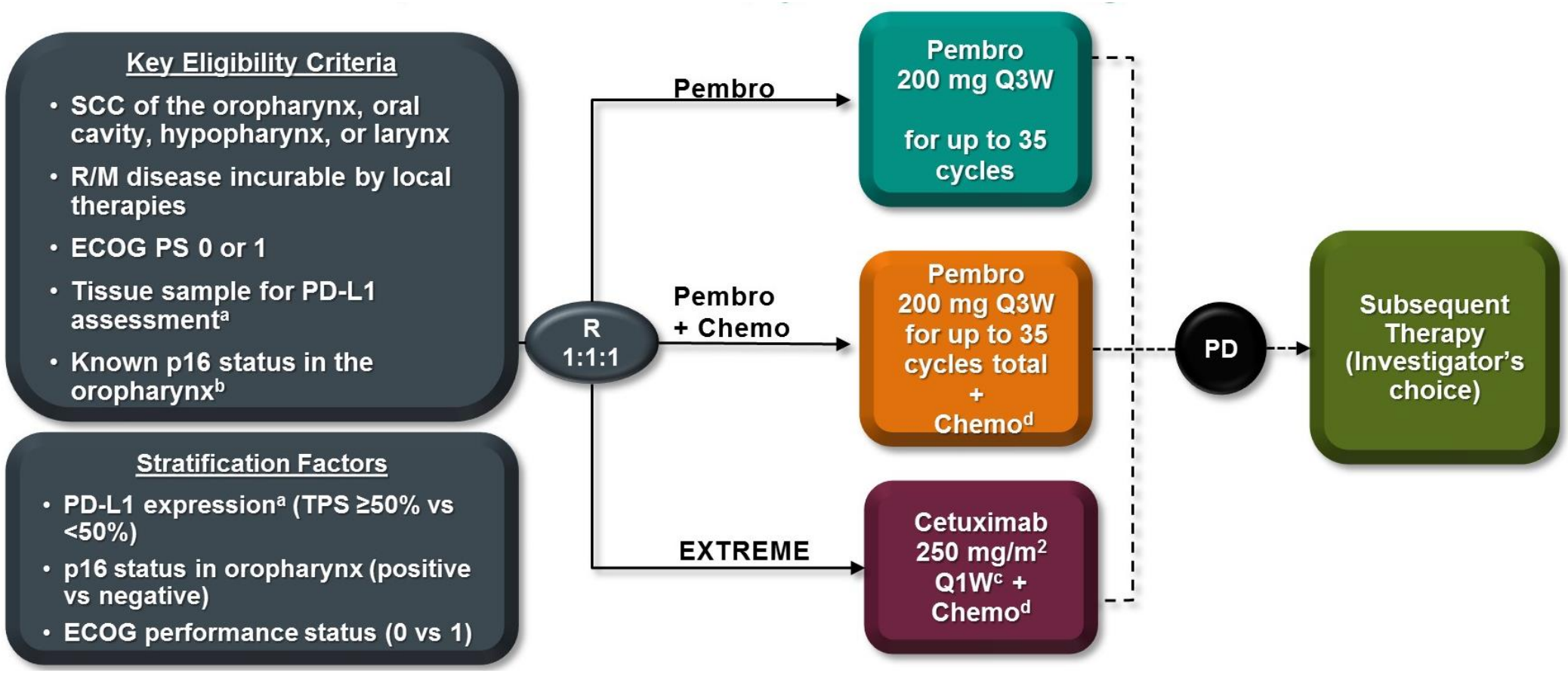
KEYNOTE-048: Outcomes on subsequent therapy



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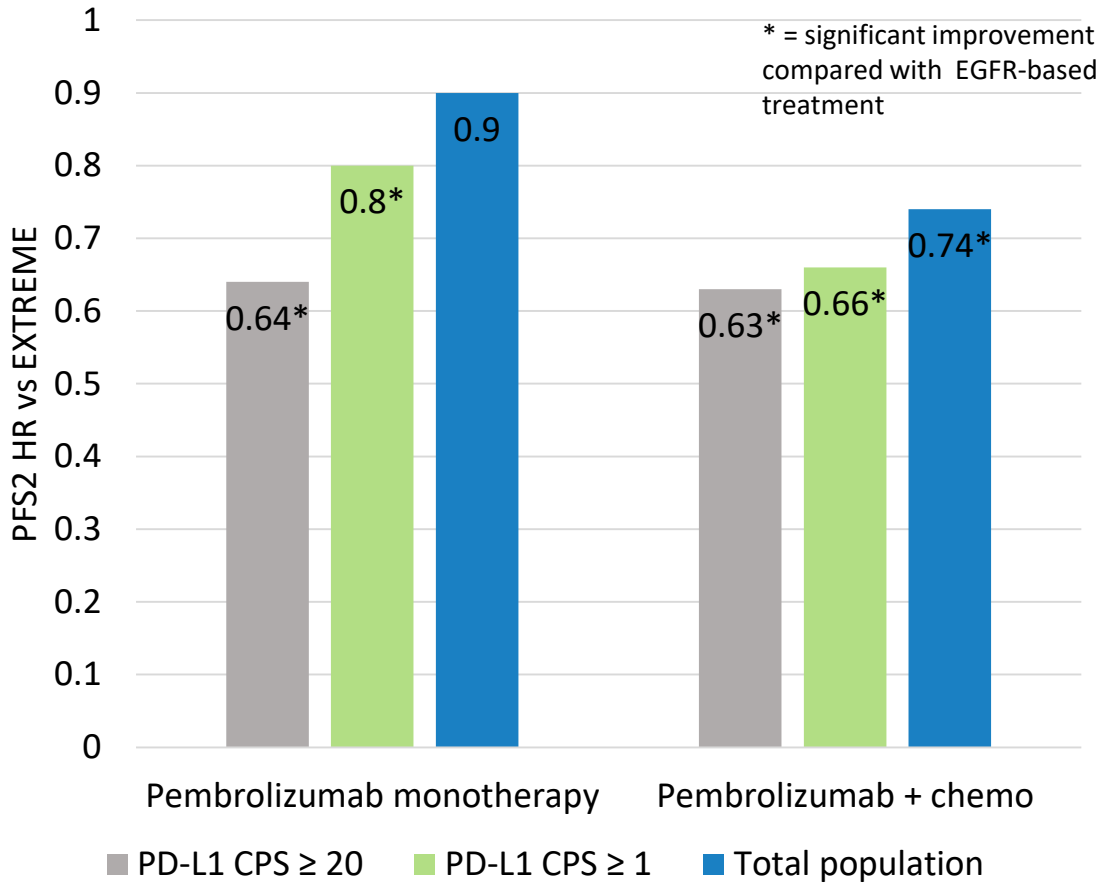
KEYNOTE-048: Outcomes on subsequent therapy

- After progression, most common next treatment was a chemotherapy regimen
- PFS2: Progression-free survival on second treatment (after progression on KEYNOTE-048 treatment)
- Benefits seen for patients who received pembrolizumab regimens up-front
- Provides support to use of immunotherapy in front-line setting



Harrington, ASCO 2020.

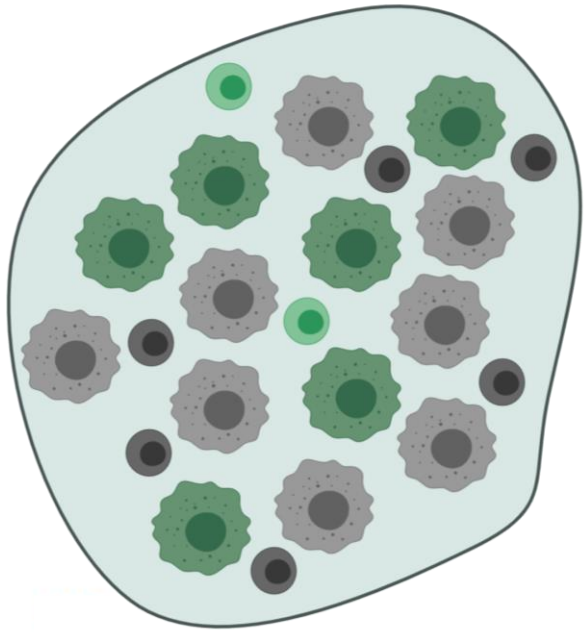
Outline

- Approved immunotherapies in head and neck cancers
- Biomarkers and immunotherapy responsiveness
- Unique considerations for head and neck cancers
- Future directions

PD-L1: TPS vs CPS

$$TPS = \frac{\#\ of\ \mathrm{PD{-}L1}\ positive\ tumor\ cells}{number\ of\ viable\ tumor\ cells} \times 100$$

$$CPS = \frac{\#\ of\ \mathrm{PD{-}L1}\ positive\ cells\ (tumor\ cells, lymphocytes, macrophages)}{total\ number\ of\ tumor\ and\ immune\ cells} \times 100$$



PD-L1-positive immune cell

PD-L1-negative immune cell

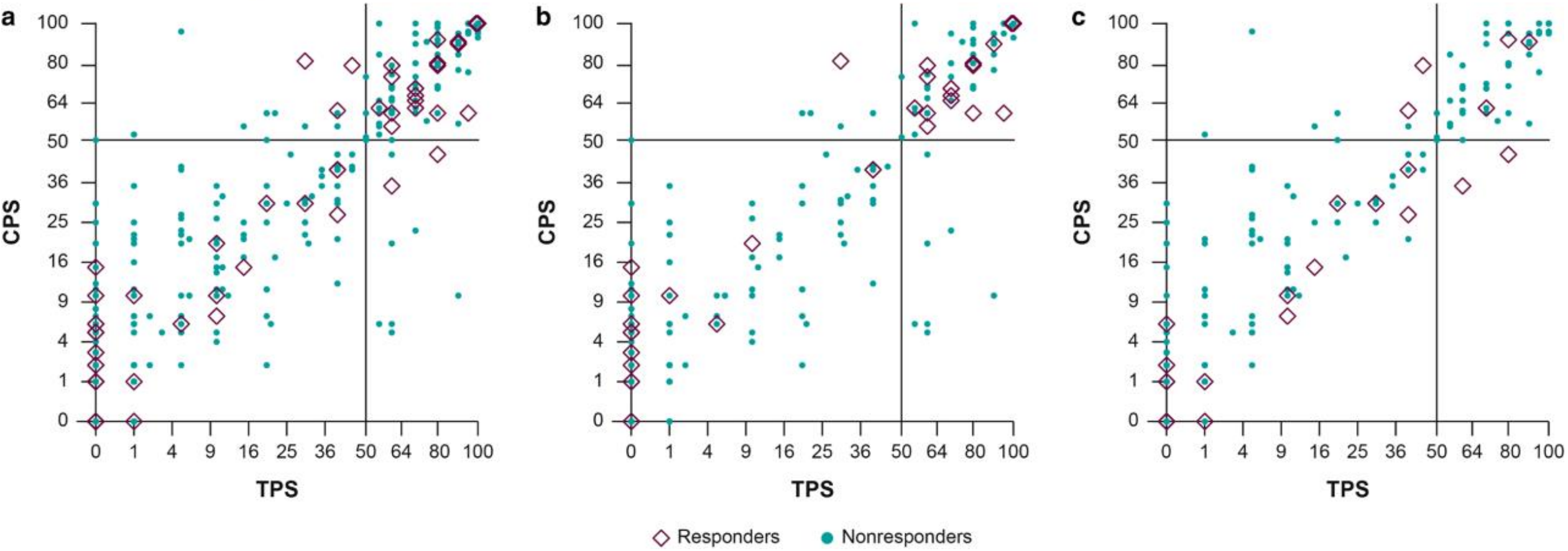
PD-L1-positive tumor cell

PD-L1-negative tumor cell

$$TPS = \frac{6\ positive\ tumor\ cells}{14\ total\ tumor\ cells} \times 100 = 43$$

$$CPS = \frac{6\ positive\ tumor\ cells + 2\ positive\ immune\ cells}{22\ total\ cells} \times 100 = 36$$

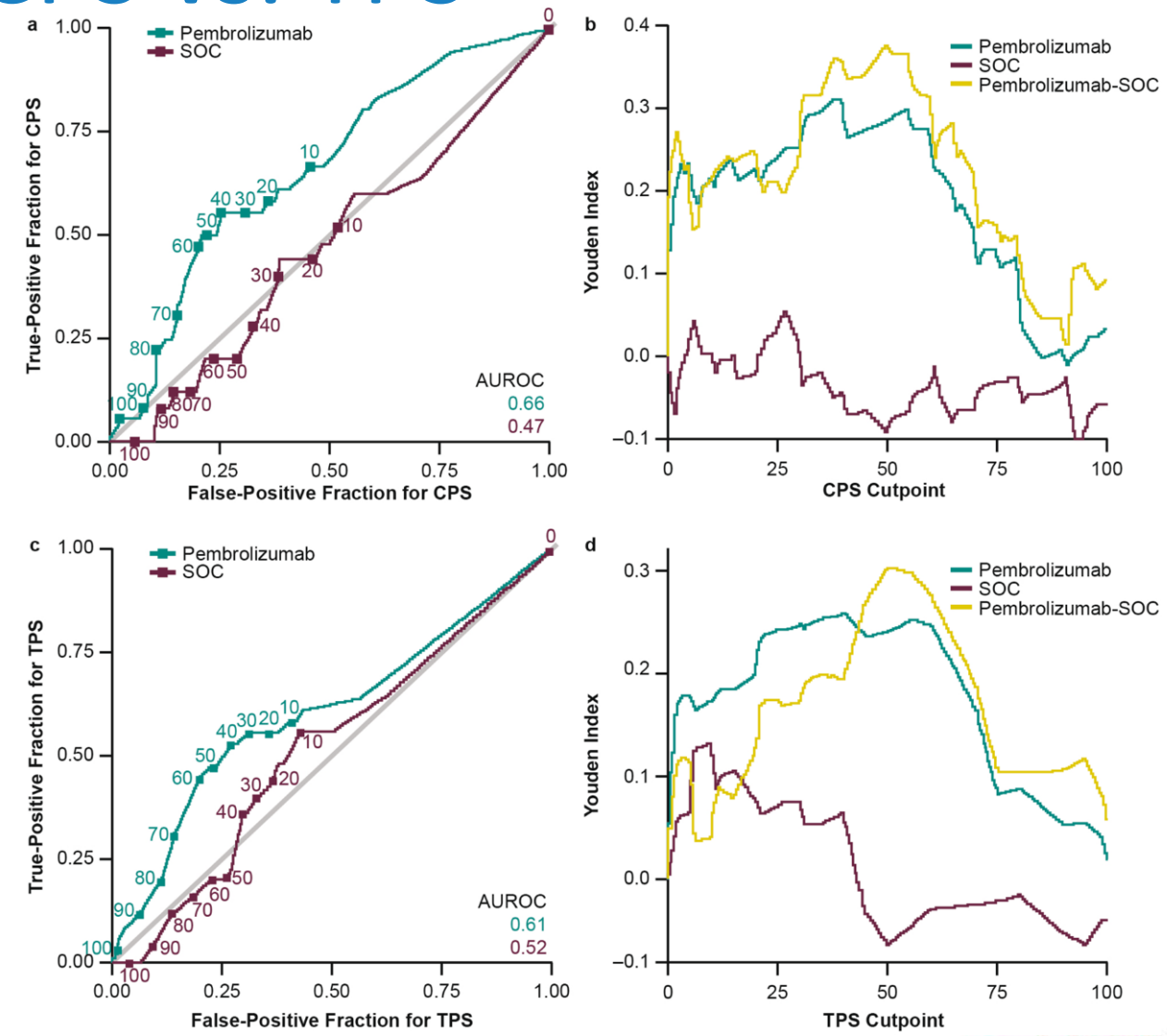
CPS vs. TPS



a All patients. b Pembrolizumab-treated patients. c SOC-treated patients

Mod Pathol. 2021 Mar;34(3):532-541

CPS vs. TPS



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Impact of PD-L1 in HNSCC

PD-L1 CPS

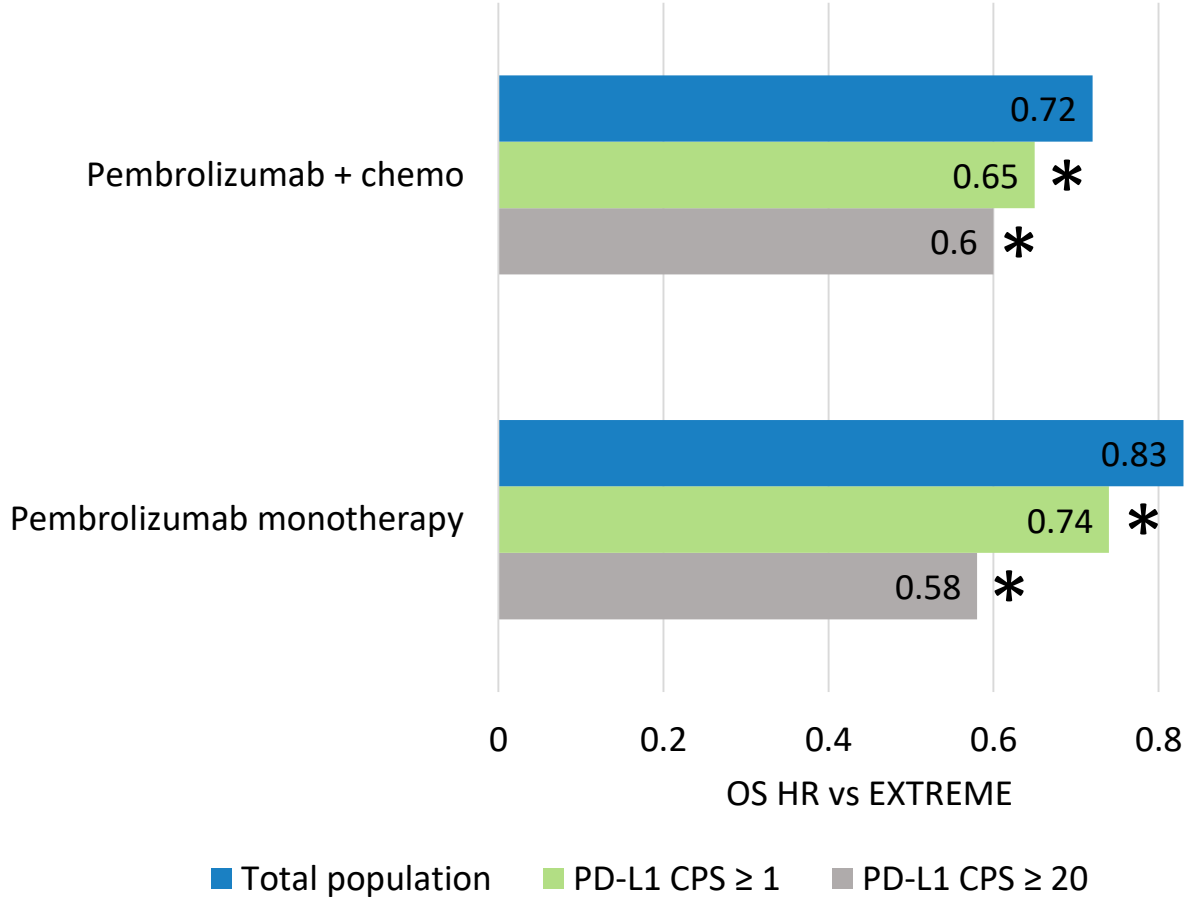
- KEYNOTE-048
  - First-line treatment
  - Approval of pembrolizumab monotherapy: CPS ≥ 1
- KEYNOTE-040
  - After platinum
  - Improved outcomes in PD-L1-positive patients (by CPS ≥ 1), no significance in total population

PD-L1 TPS

- CheckMate 141
  - After platinum
  - Greatest benefit seen for PD-L1-positive tumors (TPS ≥ 1%), but benefit regardless
- KEYNOTE-012
  - Second-line treatment
  - Higher response rate with PD-L1 CPS-positive tumors
  - No difference for PD-L1-positive tumors by TPS

KEYNOTE-048: Outcomes by PD-L1 status

- Greatest benefits seen in tumors with highest PD-L1 expression
- Approval requires PD-L1 expression (CPS) only for monotherapy
- For total population, only pembrolizumab + chemotherapy should be considered, not monotherapy



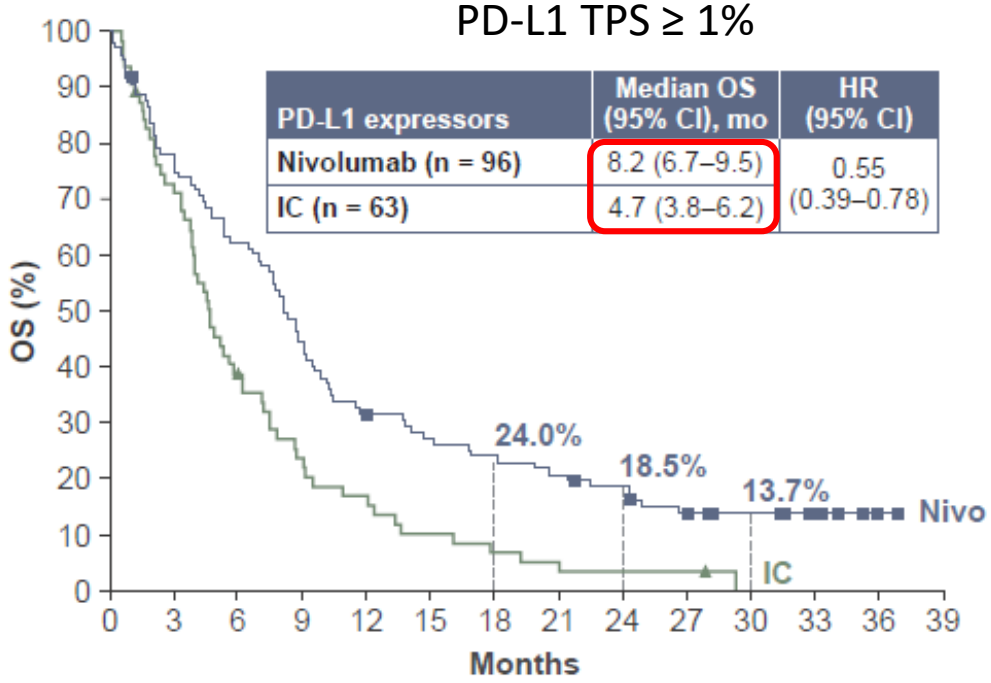
*superiority statistically demonstrated at interim or final analysis

Rischin, ASCO 2019.

CheckMate 141: Outcomes by PD-L1 status

CheckMate 141: 2 year update

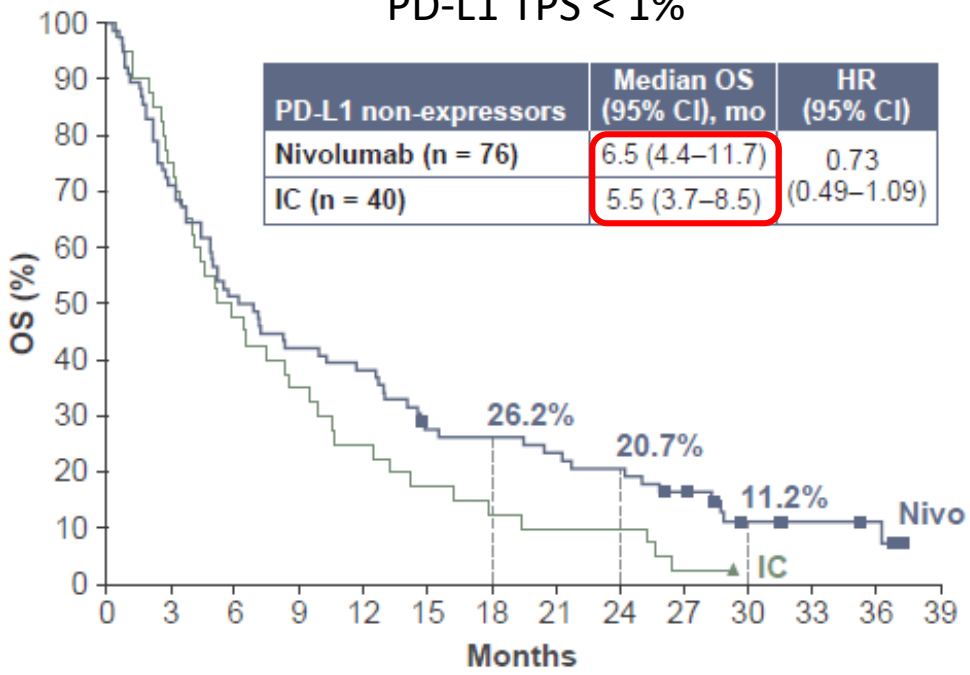
PD-L1 TPS ≥ 1%



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 TPS < 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.

Outline

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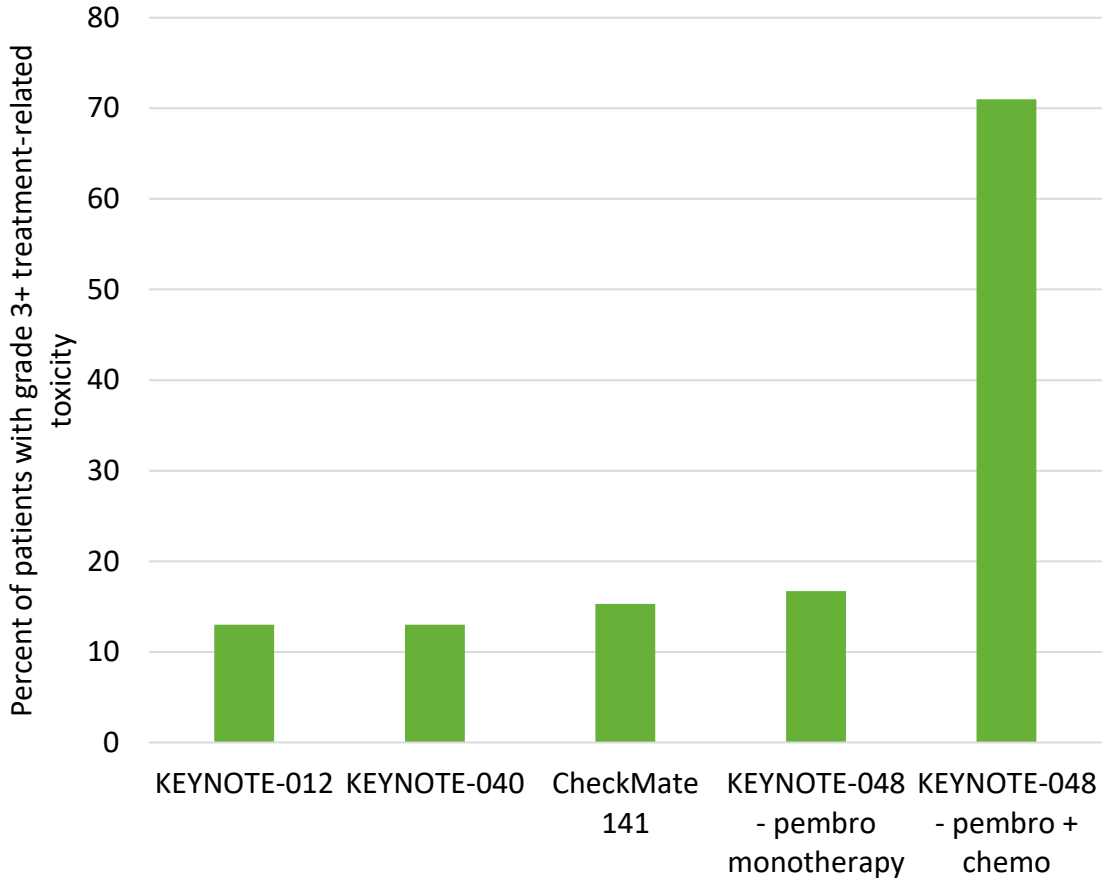
Toxicities in head and neck cancer patients

- Patients typically receive aggressive radiation treatment, with accompanying side effects
- Radiation in combination with chemotherapy, immunotherapy and/or surgery can further complicate toxicity profiles
- While combinations may have higher response rates, also have higher toxicity rates



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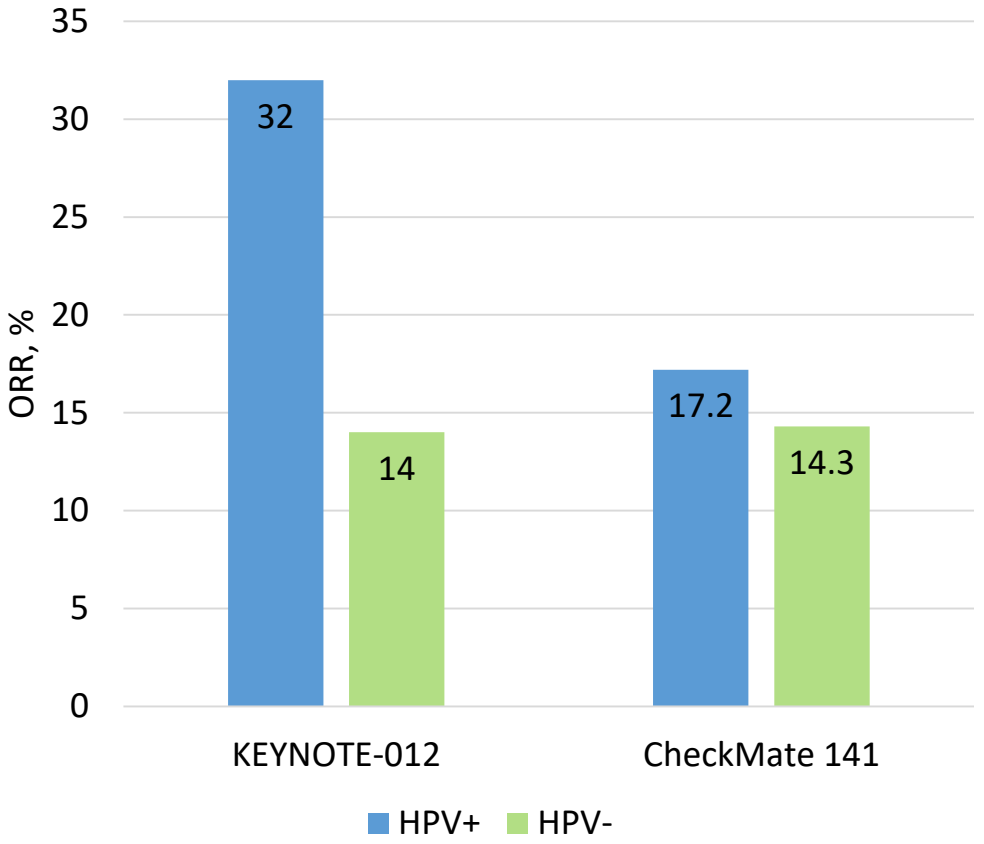
Viral infections in HNSCC

- Virally-associated cancers are biologically and clinically distinct
  - Human papillomavirus associated with oropharynx cancer
  - Epstein Barr virus associated with nasopharyngeal cancer
- Evidence that HPV+ tumors may perform better, but there is benefit with immunotherapy regardless of HPV status



Cohen, J Immunother Cancer 2019.

Combination immune checkpoint inhibition in HNSCC – *limited success to date*

Trial	Patient population	Treatment arms	ORR	Median OS (months)	Landmark OS
EAGLE	R/M HNSCC after platinum	Durvalumab	17.9%	7.6	24-months: 18.4%
		Durvalumab + tremelimumab	18.2%	6.5	24-months: 13.3%
		SoC	17.3%	8.3	24-months: 10.3%

Trial	Patient population	Treatment arms	Expected study completion
KESTREL	Untreated HNSCC	Durvalumab	February 2021
		Durvalumab + tremelimumab	
		SoC	
CheckMate 714	Platinum-refractory HNSCC	Nivolumab + ipilimumab	January 2024
		Nivolumab	
CheckMate 651	Untreated HNSCC	Nivolumab + ipiliumumab	February 2026
		EXTREME regimen	

Ferris, Ann Oncol 2020

Outline

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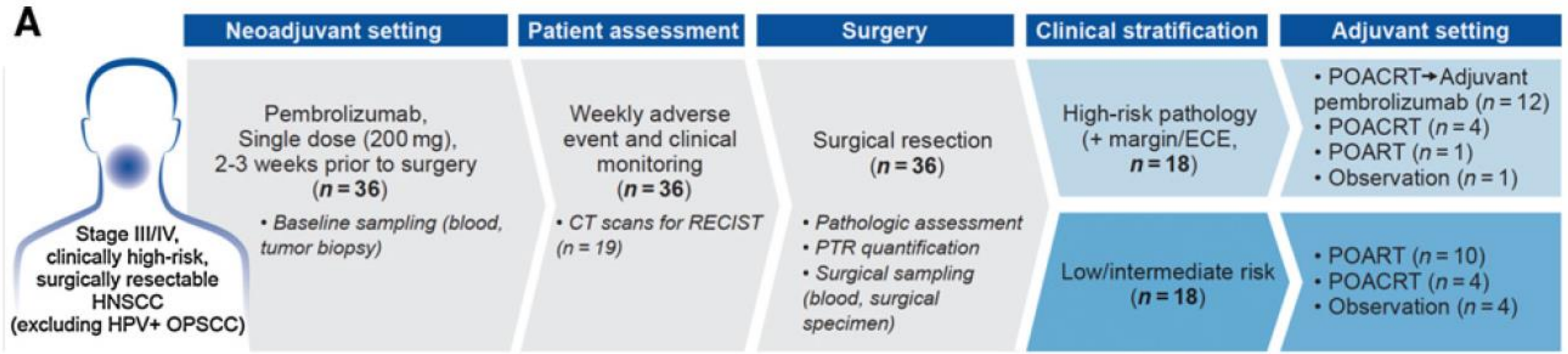
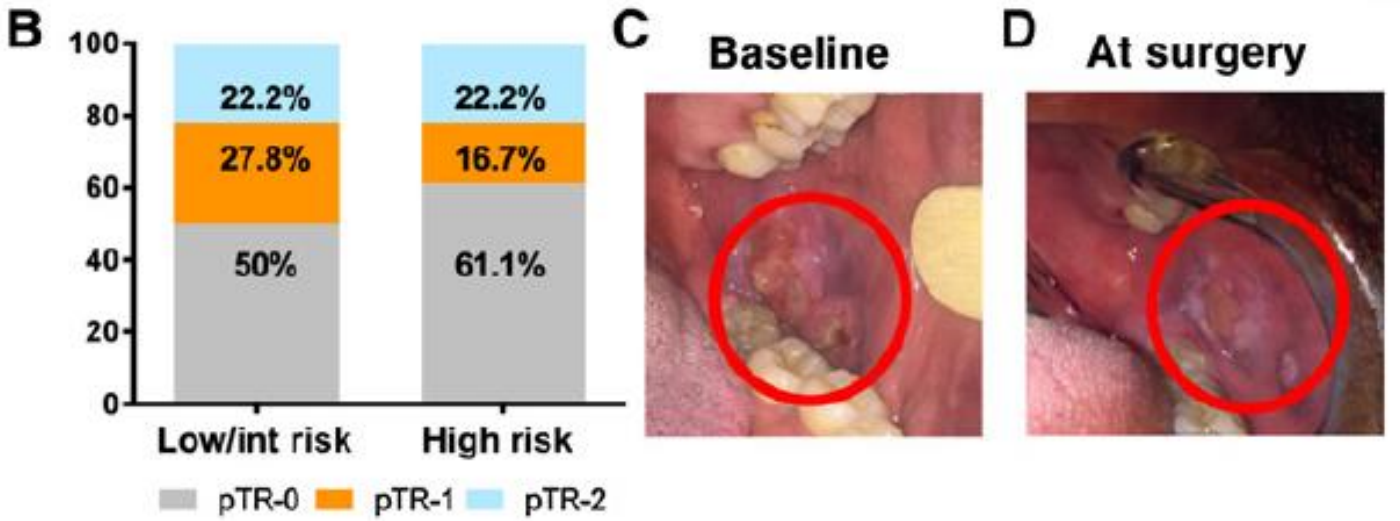
In development: Oral cavity cancer



Uppaluri, Clin Cancer Res 2020

In development: Oral cavity cancer

- No serious AEs or unexpected surgical complications/delays
- pTR-2: 22%
- pTR-1: 22%
- 1-year relapse rate: 16.7%



Uppaluri, Clin Cancer Res 2020

In development: Checkpoint inhibitors + radiotherapy as primary therapy

- KEYNOTE-412: pembrolizumab + chemoradiation
  - Phase III
  - Safety confirmed, estimated completion 2021
- **NEGATIVE**
- REACH: avelumab + cetuximab + radiotherapy
  - Phase III
  - Safety confirmed, estimated completion 2027

Leidner, AACR 2019.

In development: cetuximab + pembrolizumab for recurrent metastatic disease

- Cetuximab and pembrolizumab are both approved as monotherapies for HNSCC
- Phase II trial testing cetuximab + pembrolizumab:
  - Platinum refractory or ineligible disease
  - ORR: 45%
  - Median OS: 18.4 months
  - Safety profile consistent with individual drugs

Sacco, H&N Cancers Symposium 2020.

In development: Selected ongoing combination trials

Trial	Patient population	Treatment arms	Targets	Expected study completion
LEAP-010	Untreated recurrent/ metastatic PD-L1+ HNSCC (CPS ≥ 1)	Pembrolizumab + lenvatinib	PD-1 + multikinase inhibitor	April 2024
		Pembrolizumab	PD-1	
INDUCE-3	Untreated recurrent/ metastatic PD-L1+ HNSCC (CPS ≥ 1)	Pembrolizumab + GSK609	PD-1 + ICOS	July 2023
		Pembrolizumab	PD-1	
NCT02643550	HNSCC after 1-2 therapies, including progression on Pt	Monalizumab + cetuximab	NKG2A + EGFR	Phase 1/2: 2021 Phase 3: planned

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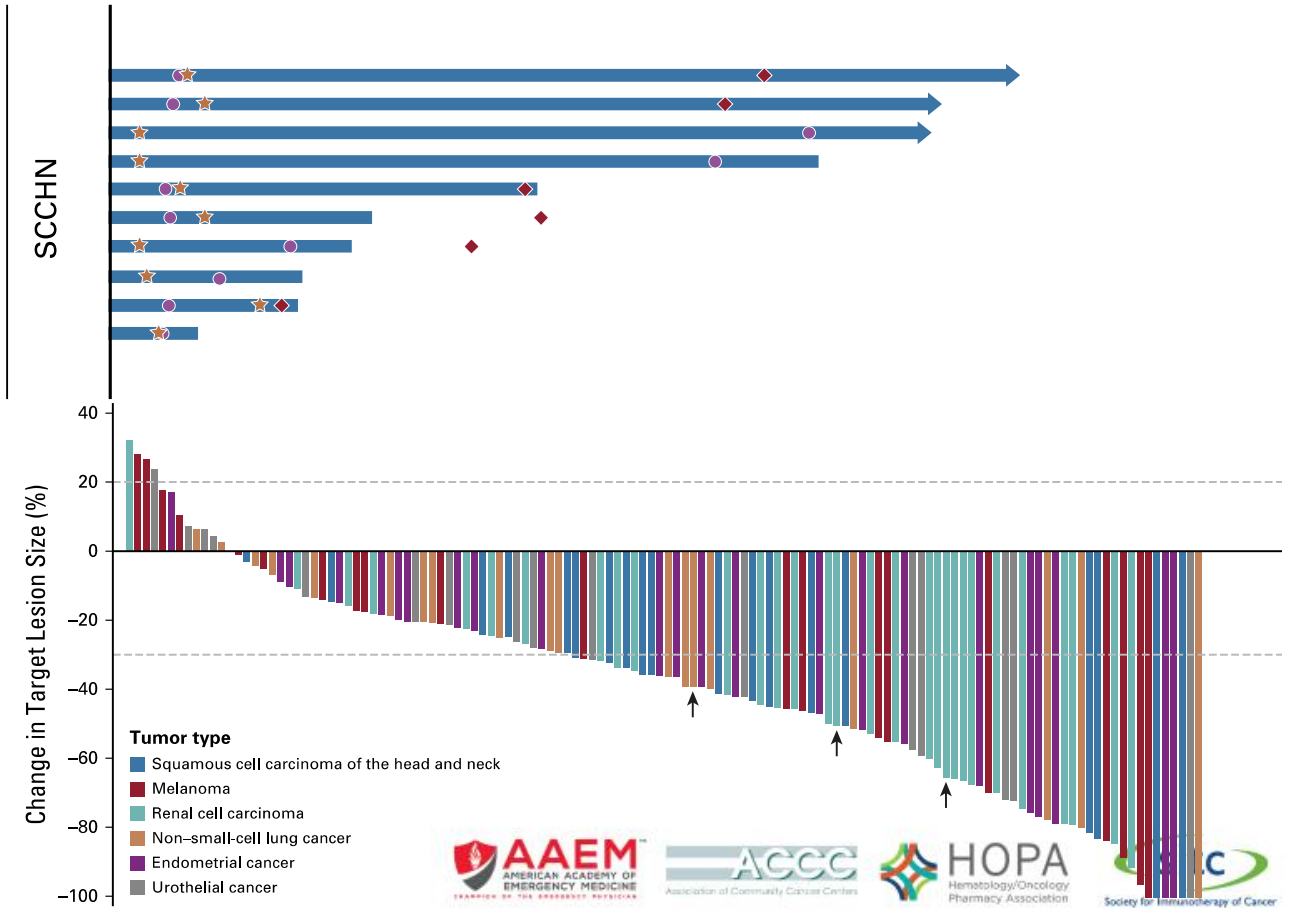
1154 Volume 38, Issue 11

Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors

Matthew H. Taylor, MD[1]; Chung-Han Lee, MD, PhD[2]; Vicky Makker, MD[2]; Drew Rasco, MD[3]; Corina E. Dutcus, MD[4]; Jane Wu, PhD[4]; Daniel E. Stepan, MD[5]; Robert C. Shumaker, PhD[4]; and Robert J. Motzer, MD[2]

TABLE 4. Efficacy Outcomes (investigator review, immune-related RECIST)

Parameter	RCC (n = 30)	Endometrial (n = 23)	SCCHN (n = 22)
Best overall response			
Complete response	0 (0)	2 (9)	1 (5)
Partial response	21 (70)	10 (44)	9 (41)
Stable disease	8 (27)	10 (44)	10 (46)
Progressive disease	1 (3)	1 (4)	0 (0)
Unknown	0 (0)	0 (0)	2 (9)
ORR[a]	21 (70)	12 (52)	10 (46)
(95% CI)	(50.6 to 85.3)	(30.6 to 73.2)	(24.4 to 67.8)
ORR_{Week24}	19 (63)	12 (52)	8 (36)
(95% CI)	(43.9 to 80.1)	(30.6 to 73.2)	(17.2 to 59.3)
Median DOR, months (95% CI)	20.0 (9.0 to 22.9)	NE (2.6 to NE)	8.2 (2.2 to 12.6)
Median PFS, months (95% CI)	19.8 (9.9 to 24.1)	9.7 (4.2 to NE)	4.7 (4.0 to 9.8)



LEAP-010 (NCT04199104) Study Design

Key Eligibility Criteria
- Adults with histologically confirmed R/M HNSCC with no curative treatment
- Measurable disease by RECIST v1.1
- No progression within 6 months of completion of prior CCRT
- PD-L1 CPS ≥1[a]
- Known p16 status in the oropharynx[b]
- ECOG PS 0 or 1

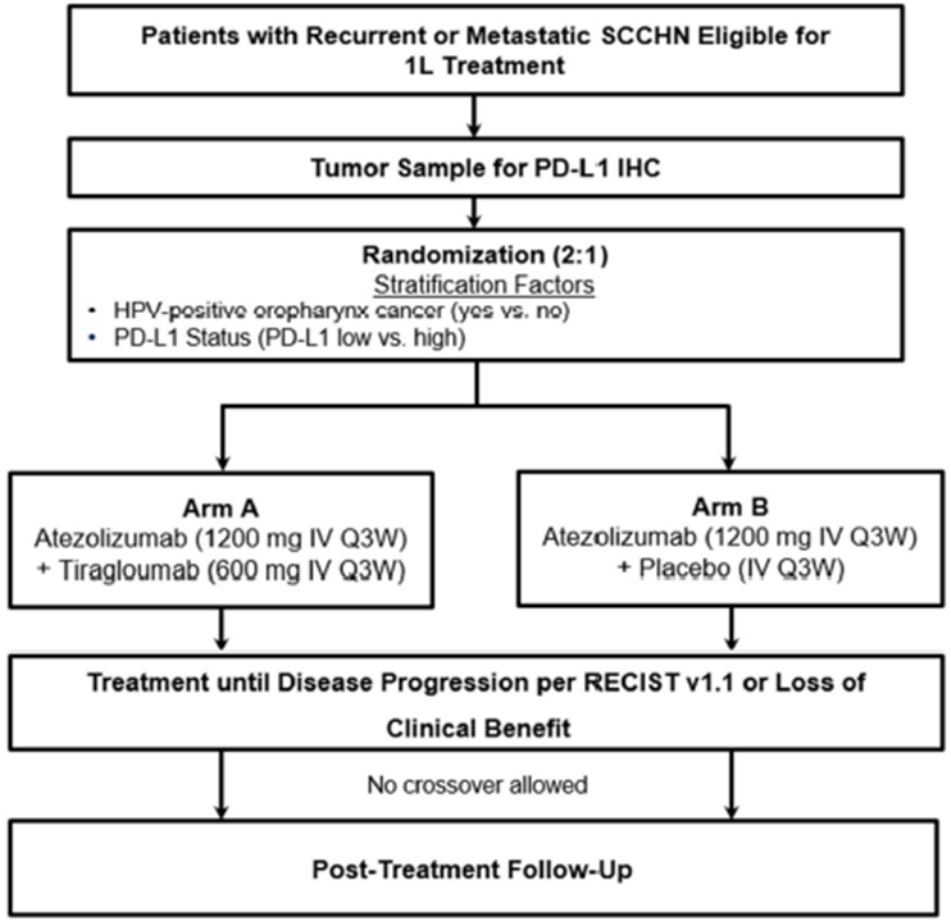
Stratification Factors
- PD-L1 expression (TPS <50% vs ≥50%[a])
- p16 status[b] (positive vs negative)
- ECOG PS (0 vs 1)

R (1:1)
N = 500

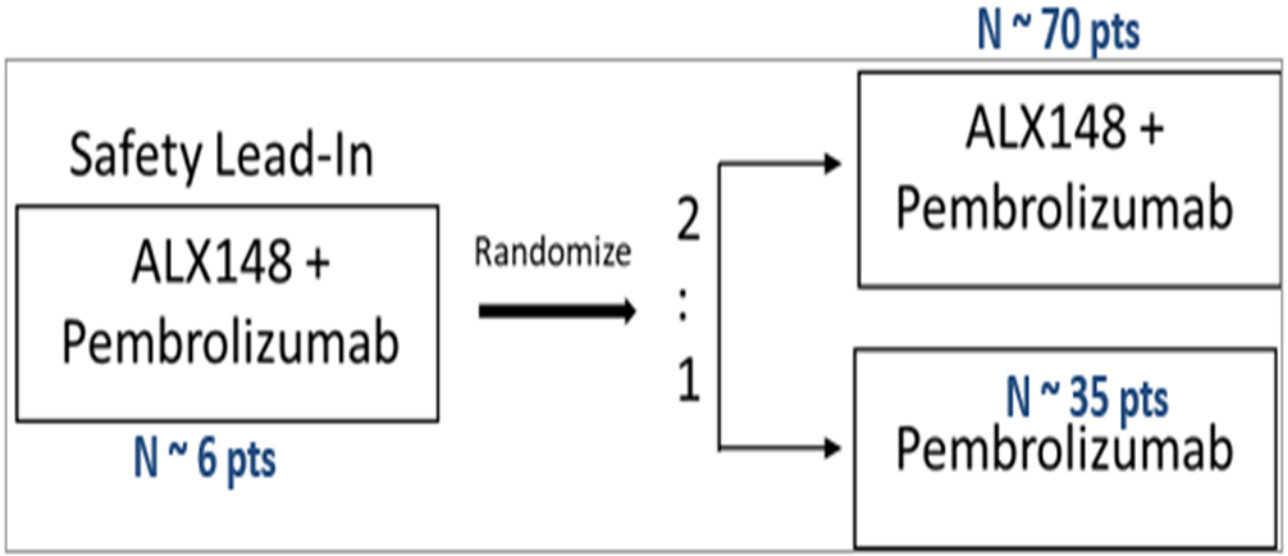
Pembrolizumab 200 mg IV Q3W (≤35 cycles) + Lenvatinib 20 mg PO QD → PD[c] → Pembrolizumab 200 mg IV Q3W (≤17 cycles) ± Lenvatinib 20 mg PO QD

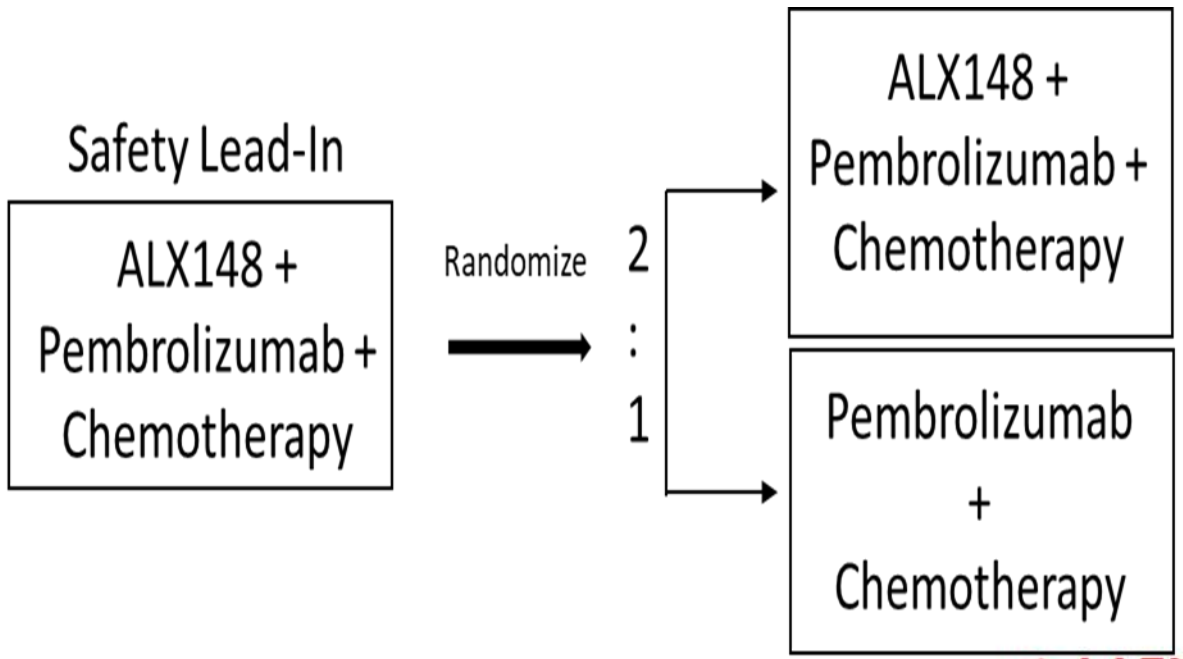
Pembrolizumab 200 mg IV Q3W (≤35 cycles) + Placebo PO QD → PD[c] → Pembrolizumab 200 mg IV Q3W (≤17 cycles) ± Placebo PO QD

CCRT, concomitant chemoradiotherapy; IV, intravenously; PD, progressive disease; PO, orally; QD, every day; Q3W, every 3 weeks; R, randomized; TPS, tumor proportion score.
[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent); [b]Assessed using the CINtec p16 histology assay; cutpoint for positivity ≥ 70%. HPV status for patients without oropharynx cancer is considered HPV negative ; [c]Patients who experience BICR-verified radiographic PD after stopping pembrolizumab treatment (for reasons other than PD or toxicity) after 35 cycles of pembrolizumab or after stopping treatment while experiencing stable disease, partial response, or complete response may receive a second course based on investigator decision.



HPV = Human papillomavirus; IHC = immunohistochemistry; IV = intravenous; Q3W = every 3 weeks; PD-L1 low = TIC 5% –19%; PD-L1 high = TIC ≥ 20%; SCCHN = squamous cell carcinoma of head and neck; RECIST = Response Evaluation Criteria in Solid Tumors.

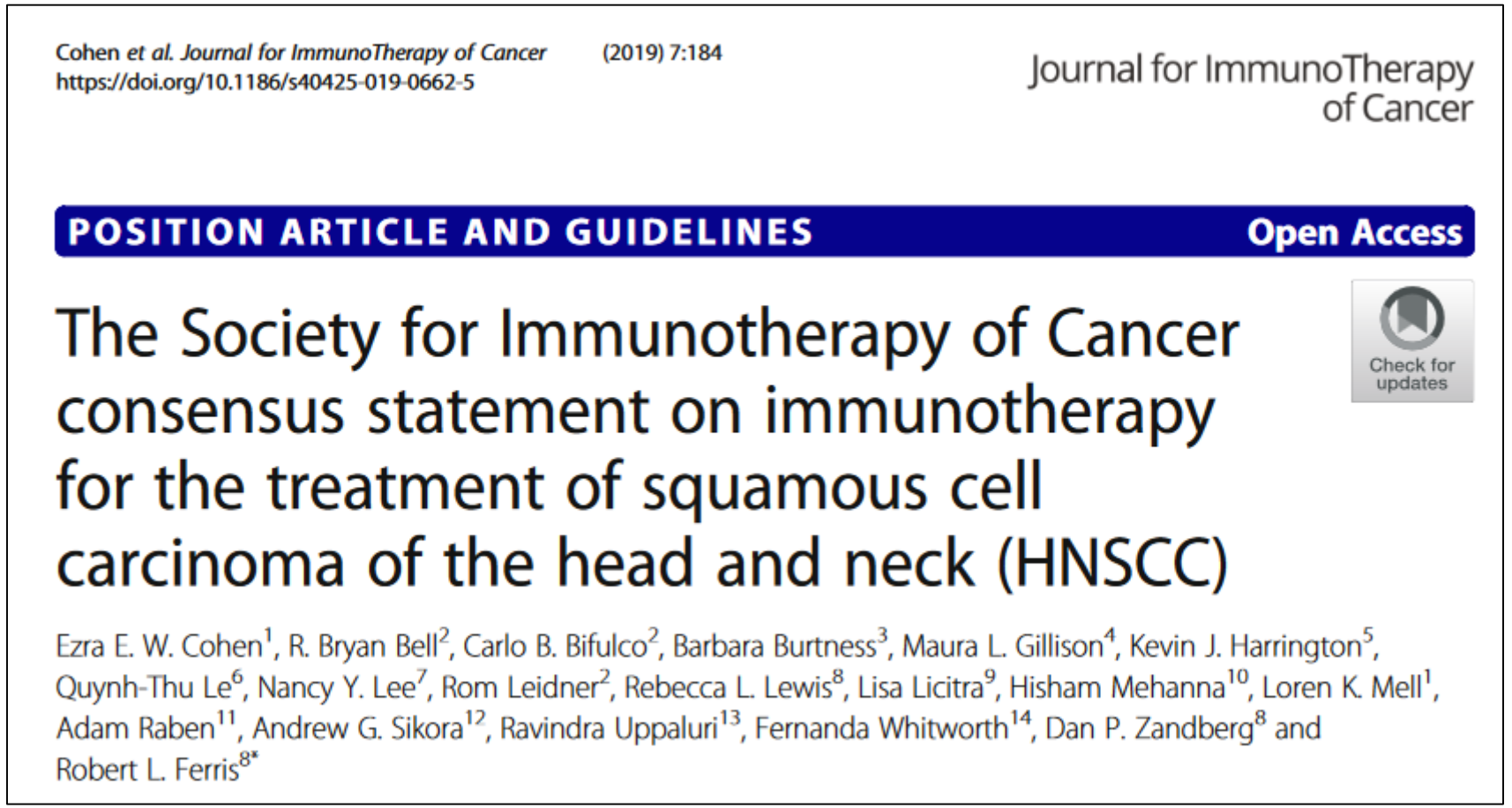




Conclusions

- Cytotoxic chemotherapy achieves limited survival in HNSCC 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 and development of predictive biomarkers.

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

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Case Studies

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

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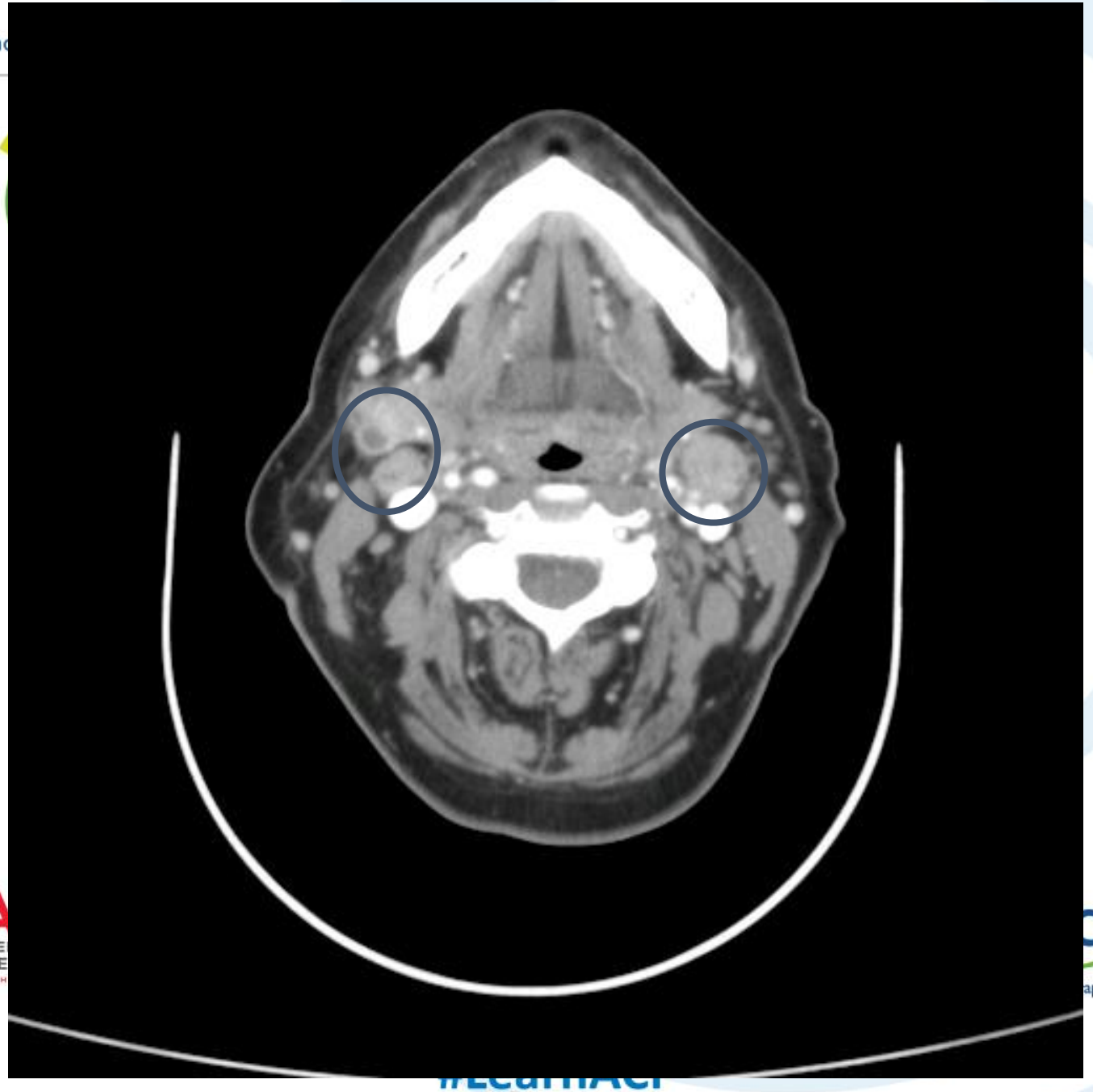
Case Presentation #1

59-year-old female patient with active lifestyle presents with otalgia, difficulty swallowing, and right neck mass



Case #1
Medical History

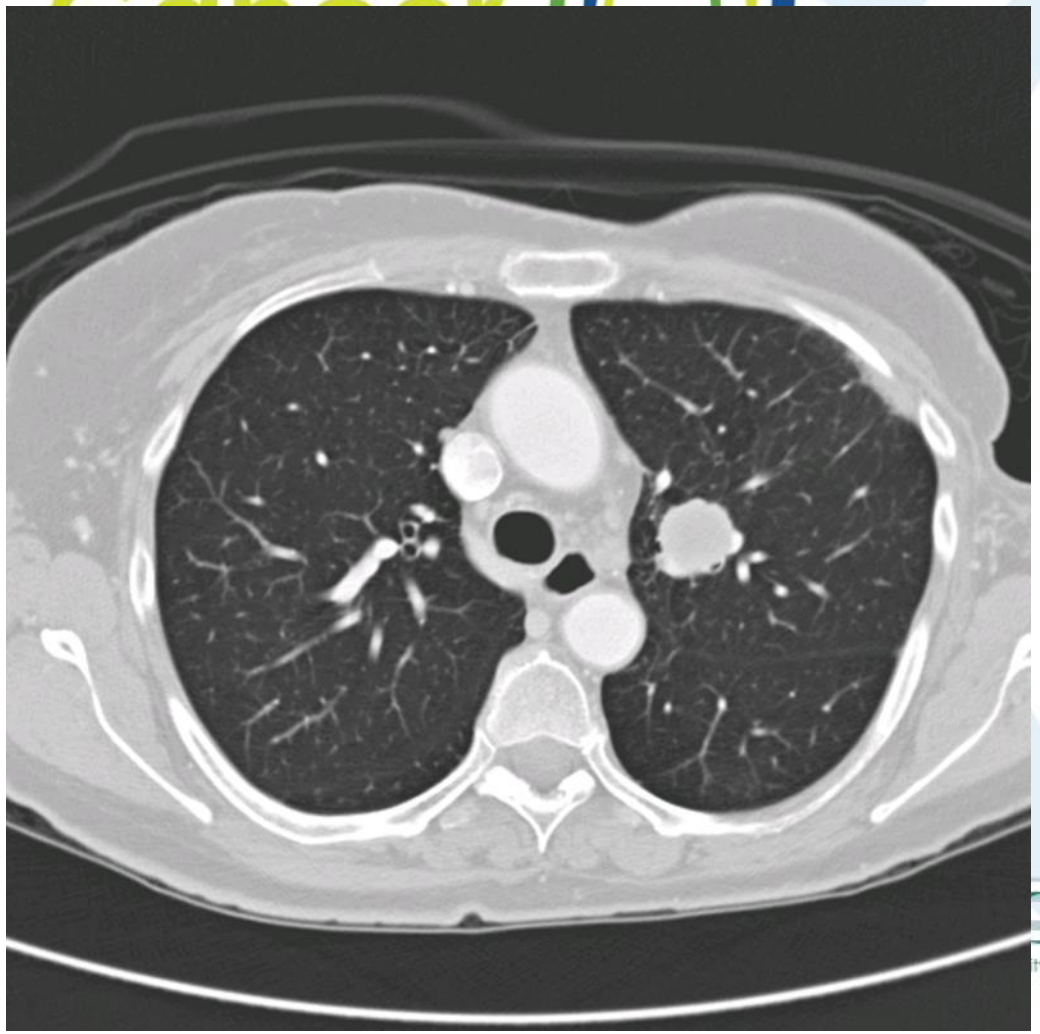
Treated for primary tumor of the oropharynx, at base of tongue, T2N2c, 13 months prior

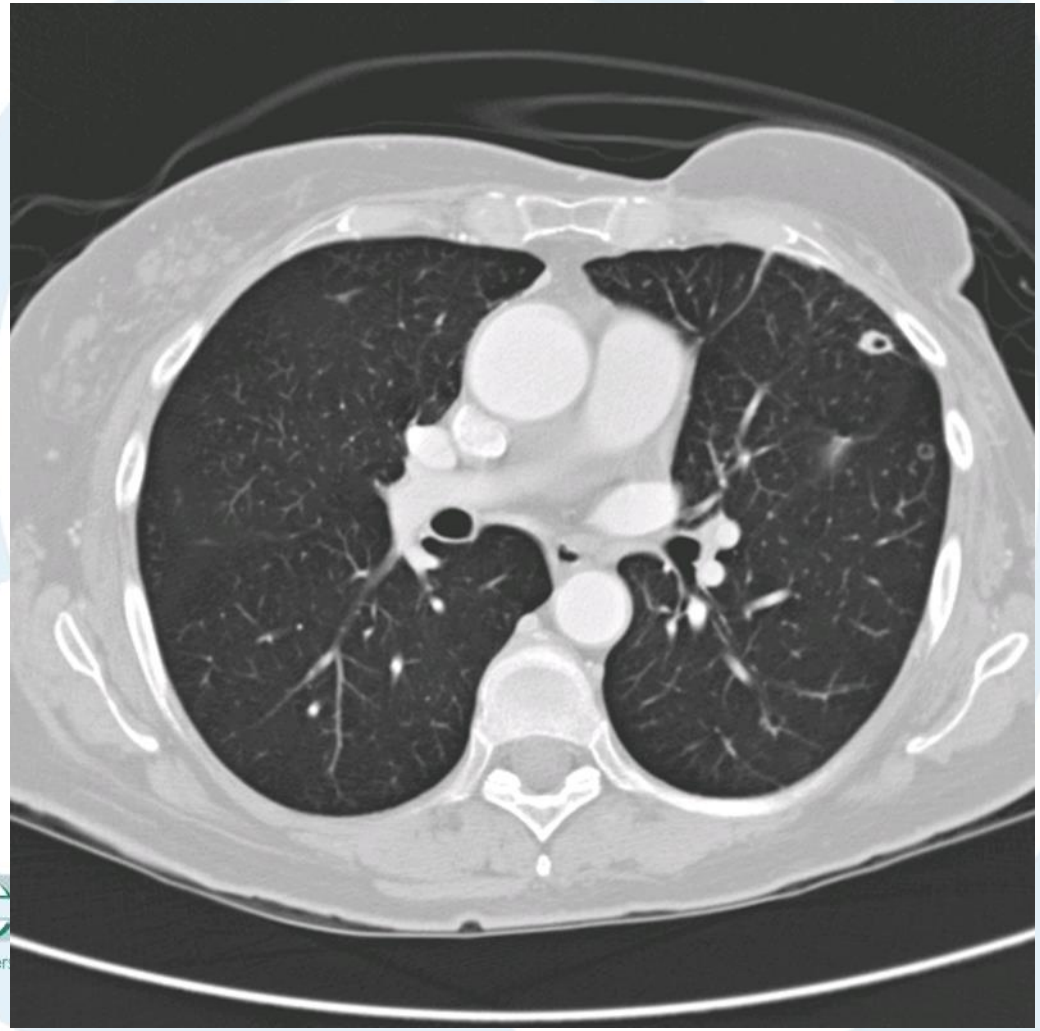
- Combination cisplatin with radiation
- Achieves a complete response after completing therapy

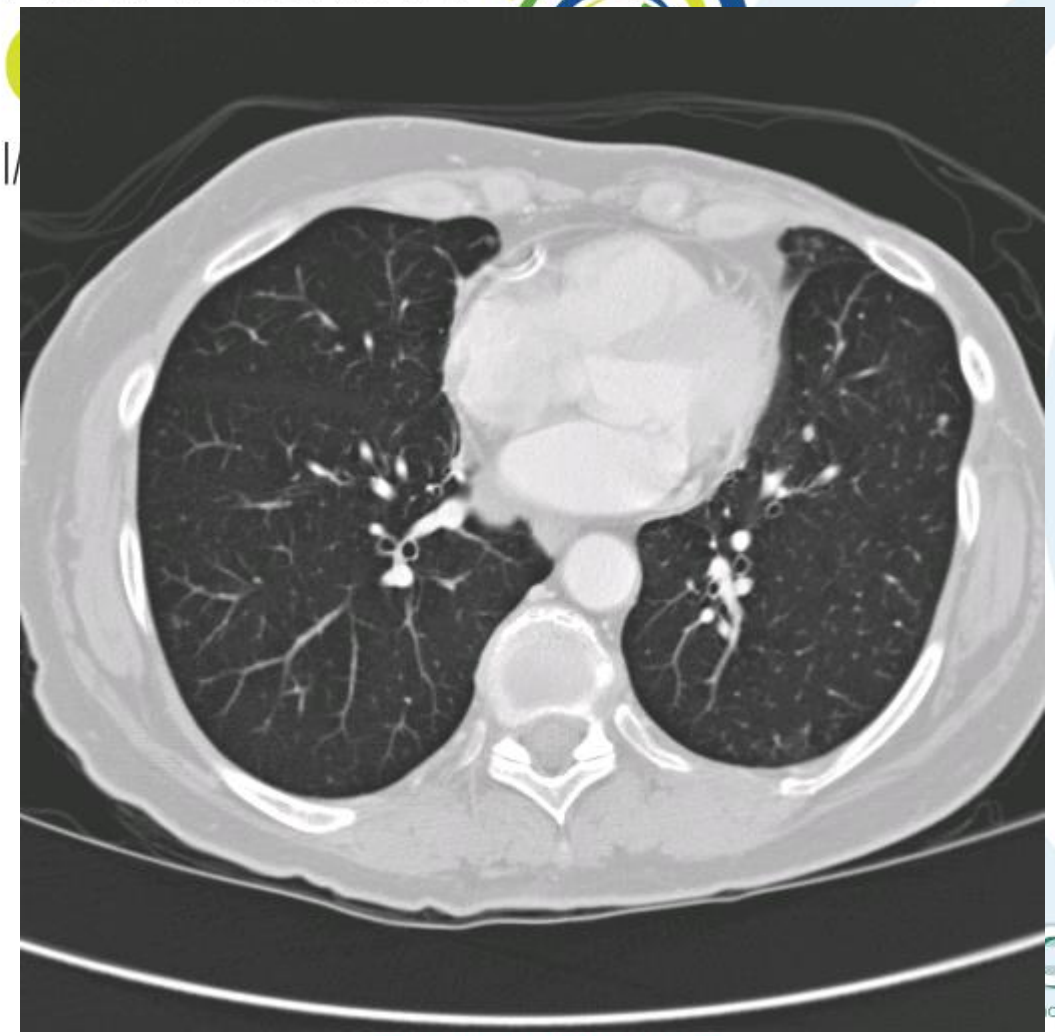
22 pack year history of smoking; quit 2 years prior

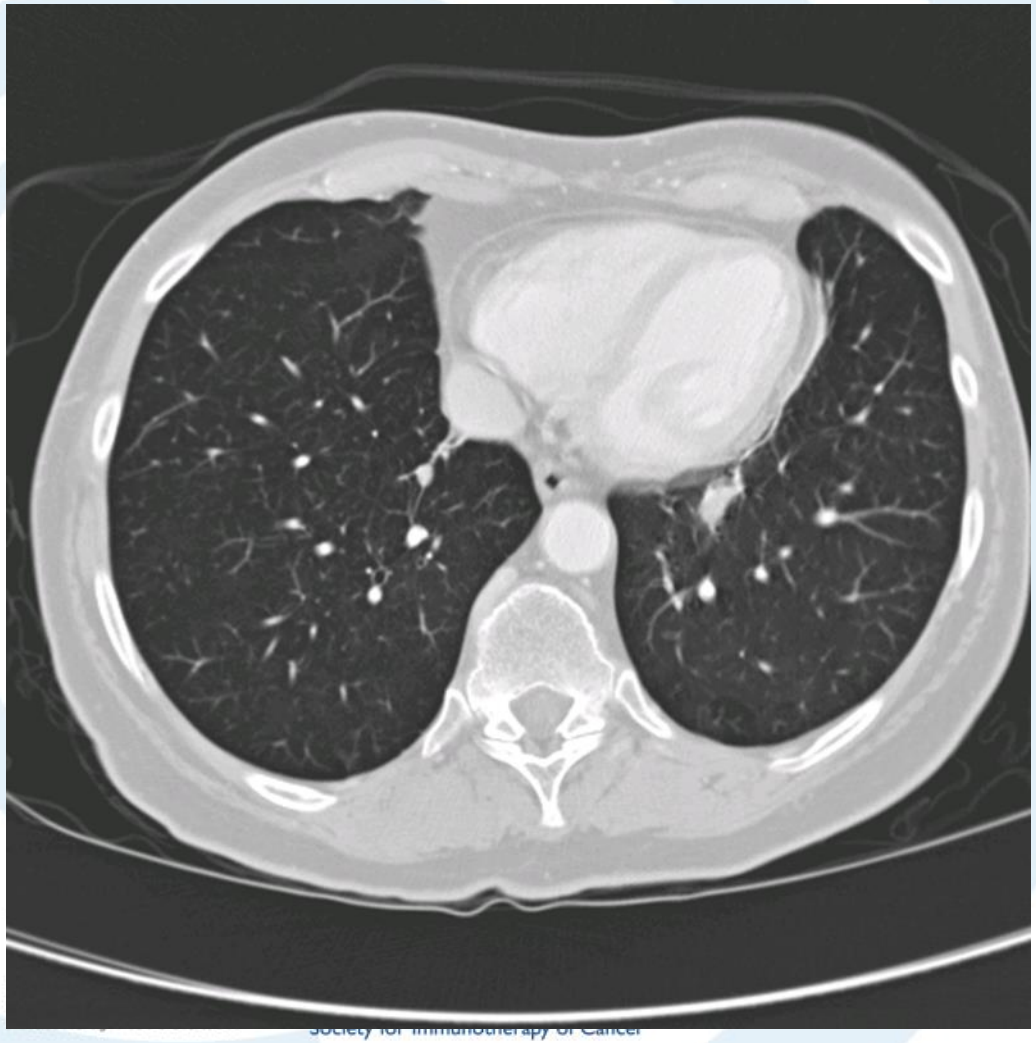
Hypertension controlled with diuretic

Case #1
Imaging 12 months after completing CRT









Case #1
Patient Function

- KPS: 80%
  - Lives with son's family, but maintains independence
  - Frequent golfer
- PDL1 CPS 5

Case Discussion #1

At this point, which treatment option would you pursue?

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Possible Options

- Pembrolizumab alone
- Pembrolizumab plus chemotherapy
- EXTREME regimen
- TPEx regimen
- Cetuximab alone

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Case Discussion #2

- 52 y/o man who initially presented to our clinic in January 2017 with recurrent oral tongue SCC
- Oncology history:
  - January 2010 presented with T1, N2b, underwent surgery including neck dissection
  - 2/10/2010 - 4/7/2010 underwent adjuvant CDDP/RT
  - August 2016 Relapse - Left tongue SCC
  - August 2016 - hemiglossectomy, lymph node dissection
  - November 2016 - new neck mass, FNA confirmed SCC
- Pain left head, neck, tongue; Mild dysphagia for liquids and some solids; Speech slurred
- CT chest demonstrates pulmonary nodules and intracardiac mass

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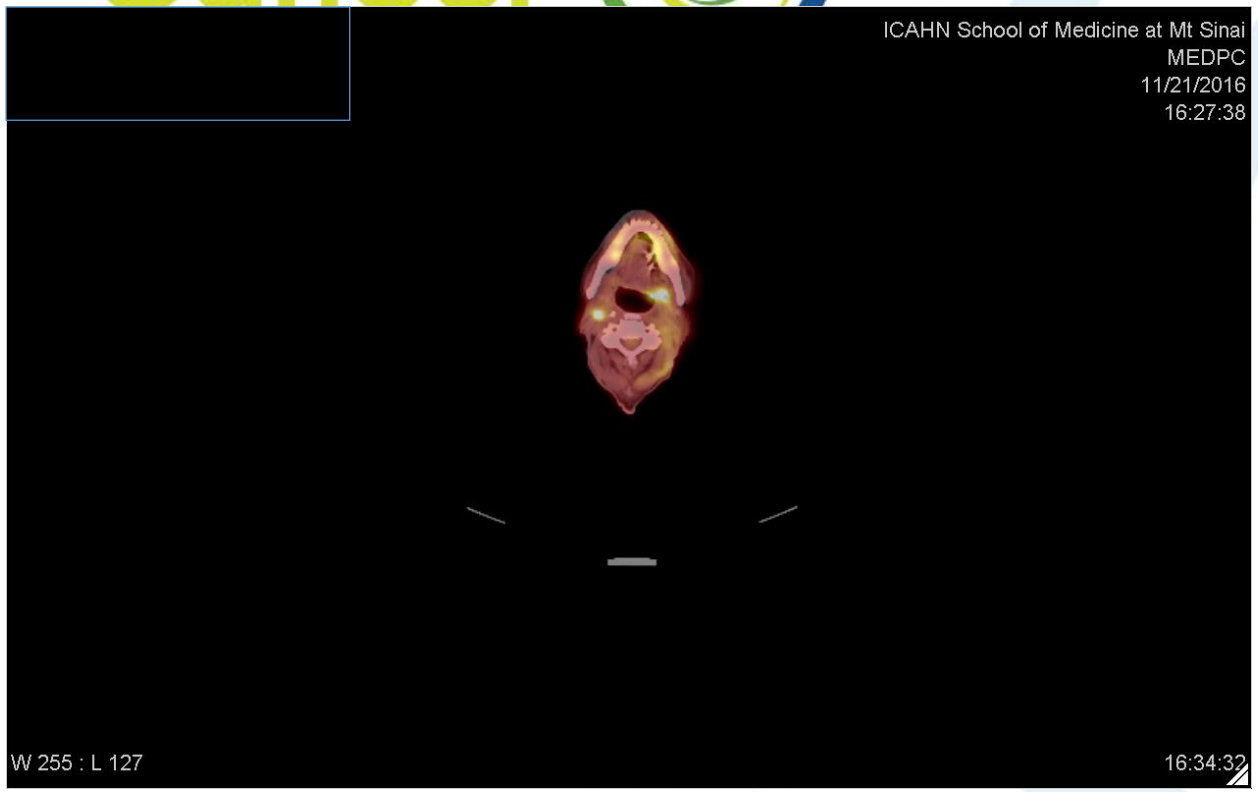

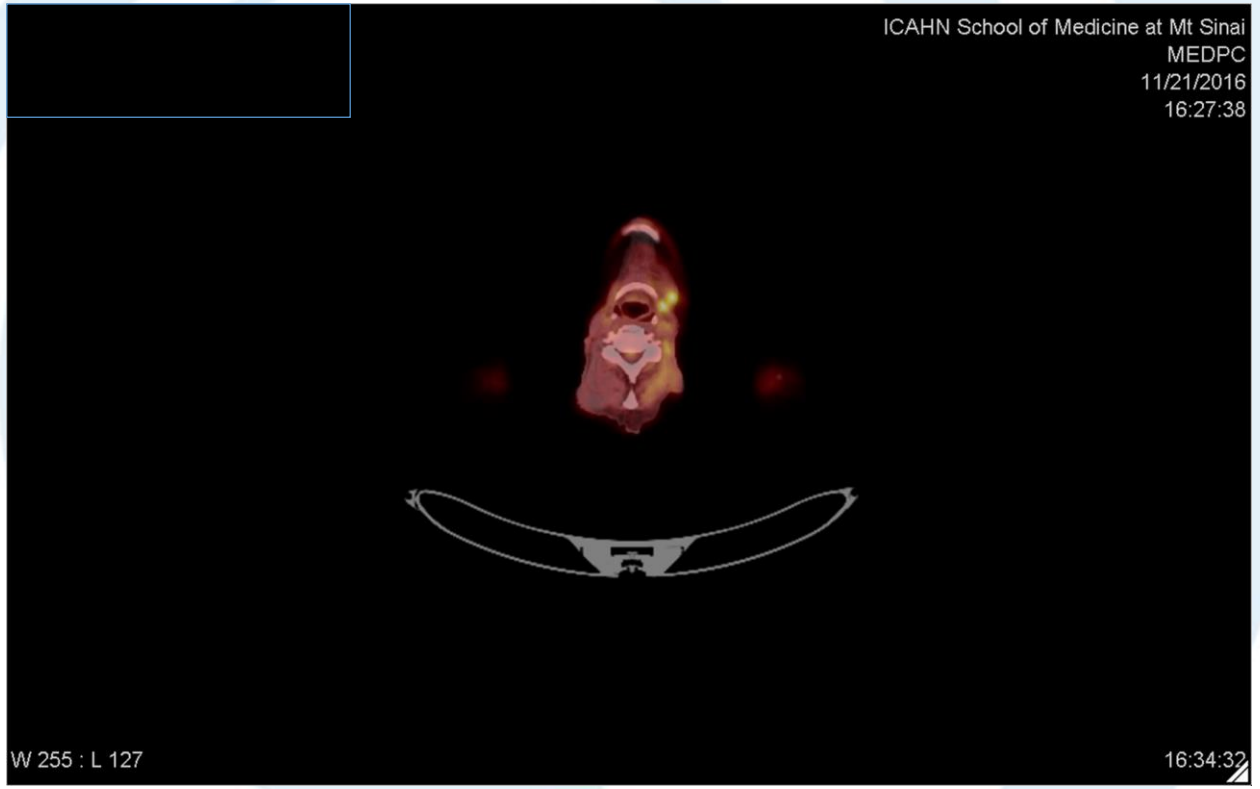

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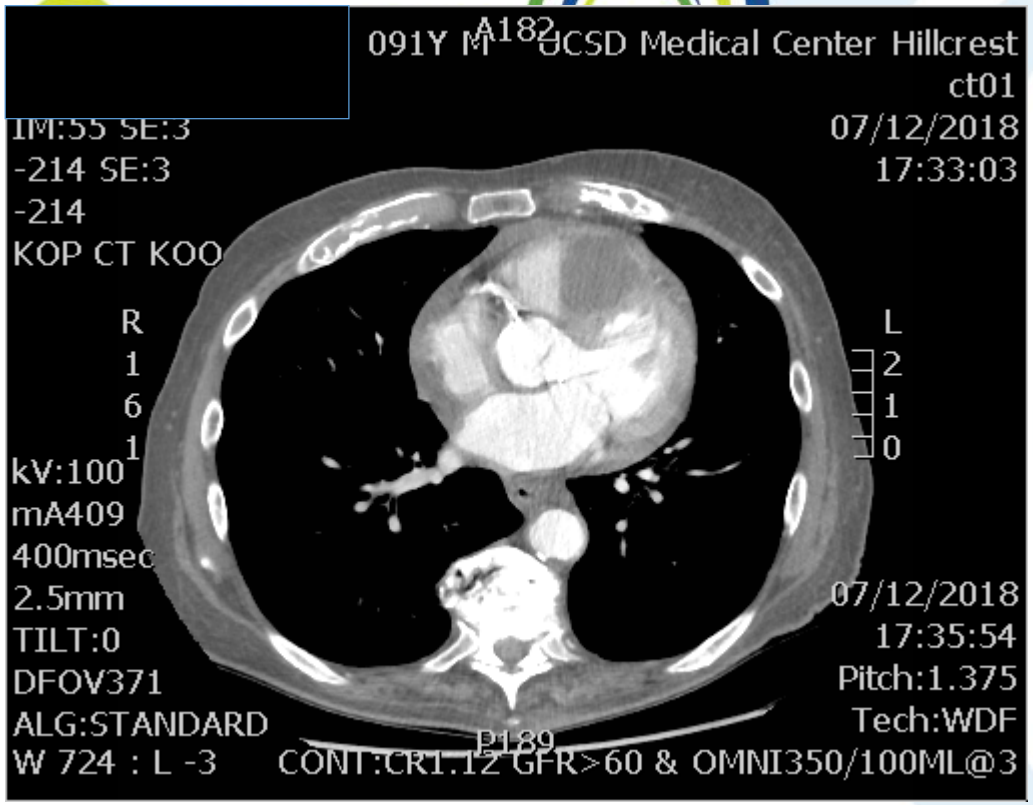

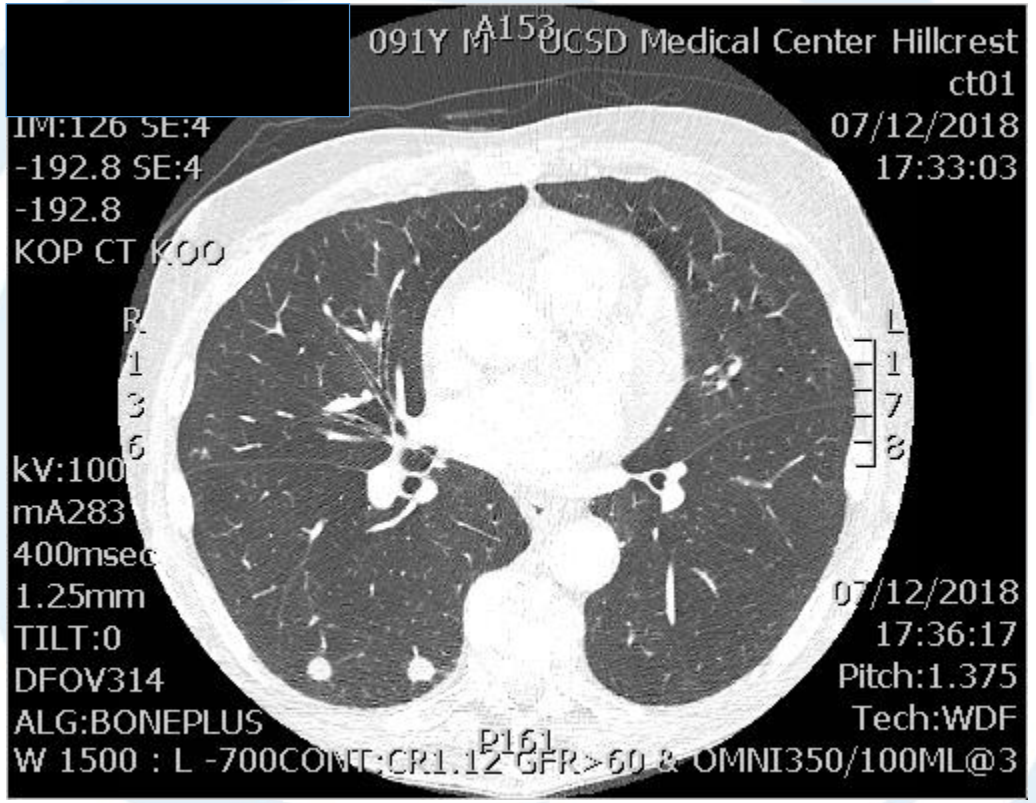

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Case Discussion

- PDL1 expression CPS 40 [secondary to gene amplification]

- Treated with pembrolizumab/chemotherapy → CR lasting 1 year