City of Hope®

Skin Tumor Board

Panel & Disclosures

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- Speaker Bureau for Regeneron, Sanofi Genzyme
- Advisory board participation: Merck, Regeneron, Sanofi Genzyme

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- Grant/Research Support from Genentech, Regeneron, RefleXion, Varian.
- Consultant for Regeneron/Sanofi.
- On the Speakers Bureau for AstraZeneca, and Takeda Pharmaceuticals.

Disclosure

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

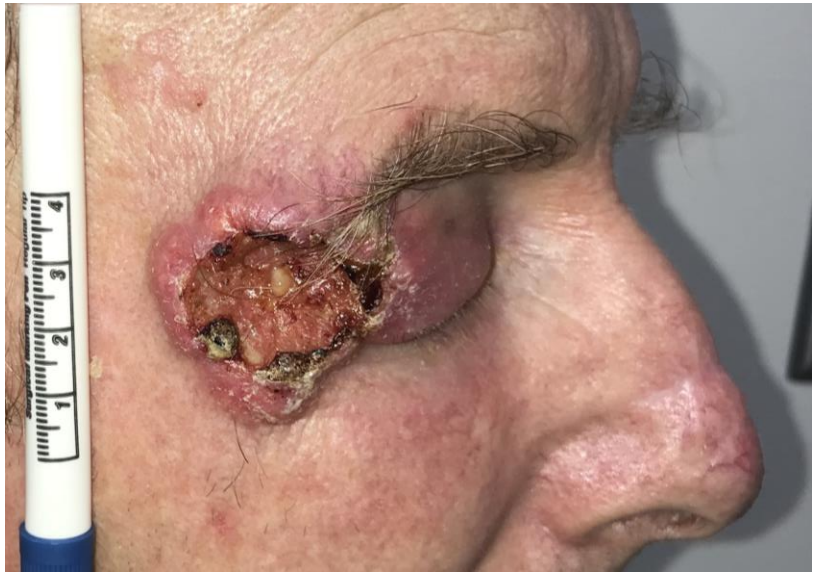
EXEMPTION:

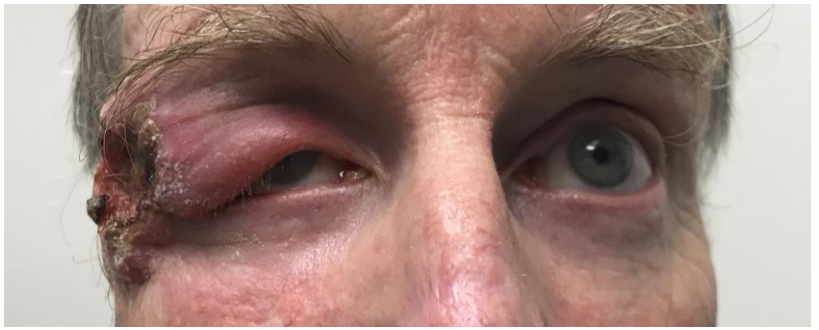
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Case: Locally Advanced cSCC

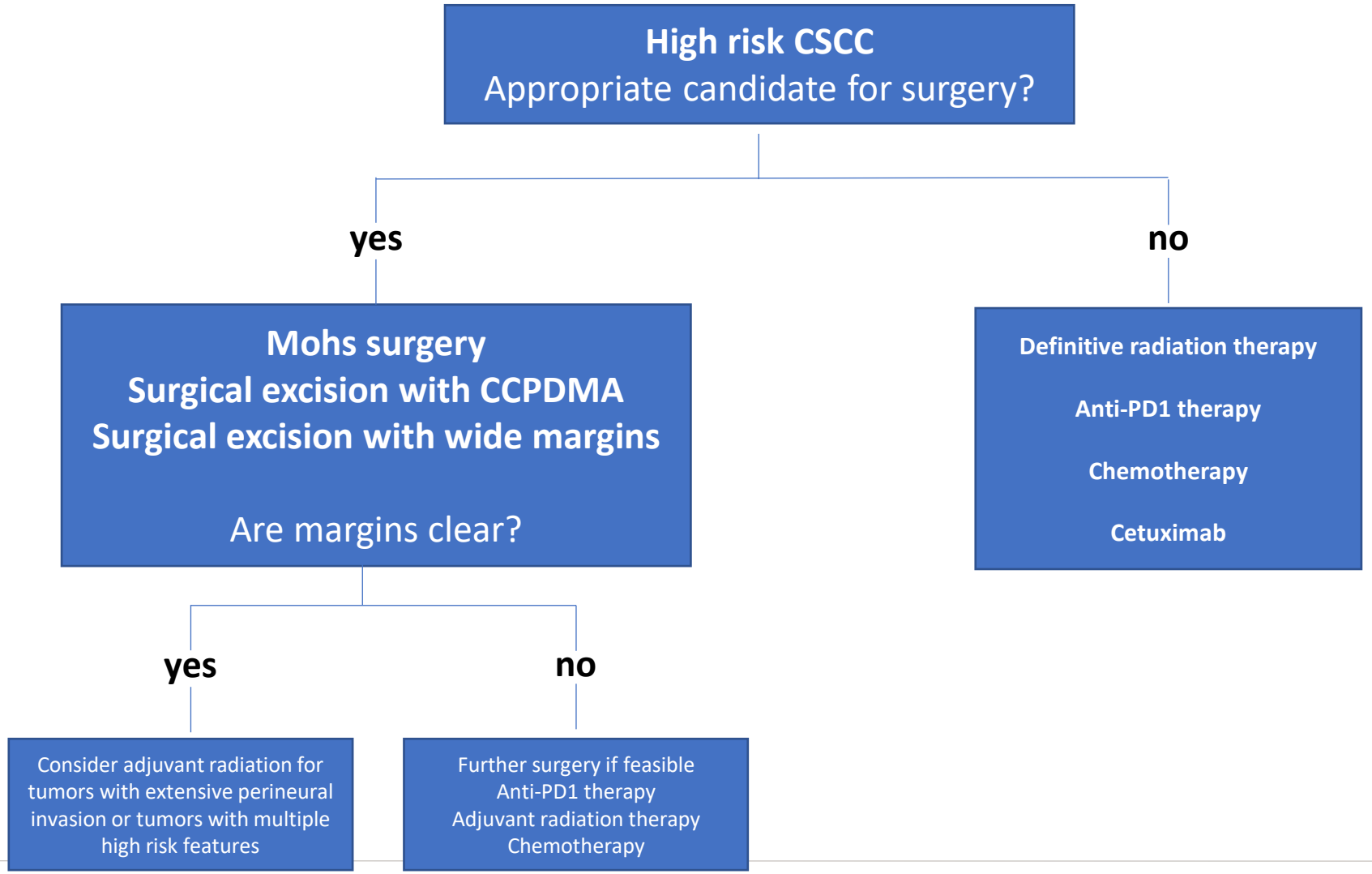
- 68yoM otherwise healthy with a rapidly growing, 3.5x3.5cm ulcerated plaque on the R temple and eyelid edema. Exam notable for intact intraocular eye movement and movement of ipsilateral forehead and cheek.
- Pathology results: moderately differentiated invasive cutaneous squamous cell carcinoma
- Imaging: FDG avid mass over the R orbit with invasion into the extraconal fat, lacrimal gland, and eyelid, abutting the right zygoma and right globe. No distant FDG-avid disease.

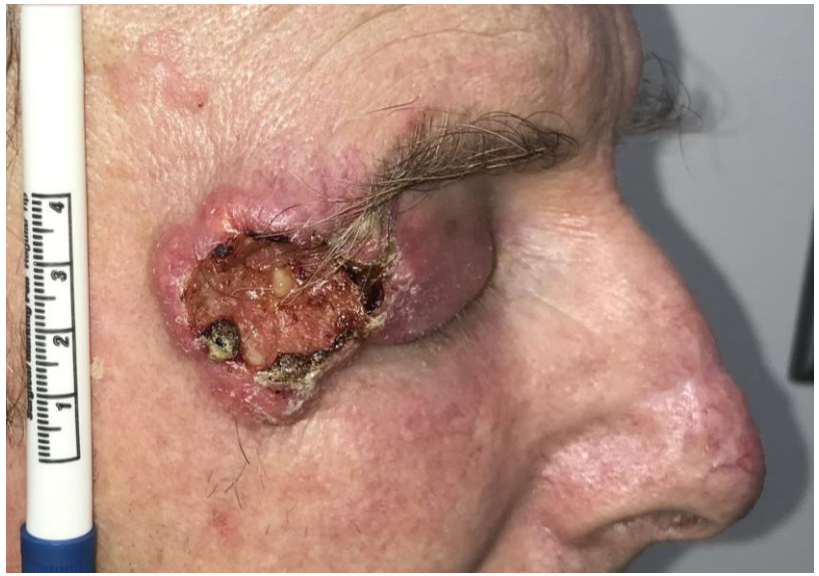


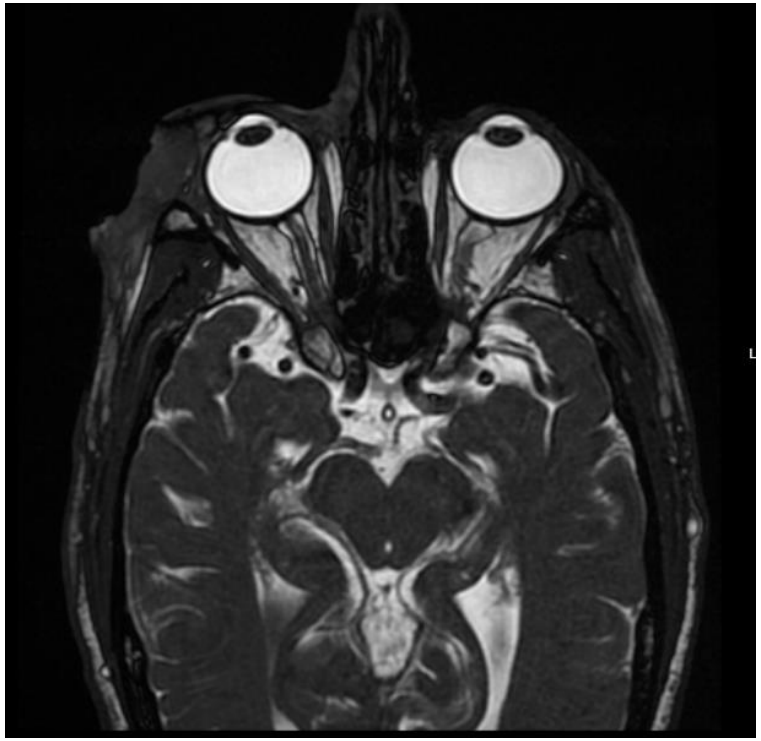


Dec 2018

Management approach for high risk CSCC







Surgery

Radiation

Systemic therapy

Immune checkpoint blockade for CSCC

- Both **cemiplimab** and **pembrolizumab** are FDA approved therapies for locoregionally advanced or metastatic CSCC that are not candidates for curative surgery or curative radiation

EMPOWER-CSCC1: Cemiplimab

	Group 1 (mCSCC) 3 mg/kg Q2W (n=59)	Group 2 (laCSCC) 3 mg/kg Q2W (n=78)	Group 3 (mCSCC) 350 mg Q3W (n=56)	Total (n=193)
Median duration of follow-up, months, (range)	18.5 (1.1–41.0)	15.5 (0.8–43.2)	17.3 (0.6–43.4)	15.7 (0.6–43.4)
ORR, %, (95% CI)	50.8 (37.5–64.1)	44.9 (33.6–56.6)	46.4 (33.0–60.3)	47.2 (39.9–54.4)
Complete response, n (%)	12 (20.3)	10 (12.8)	11 (19.6)	33 (17.1)
Partial response, n (%)	18 (30.5)	25 (32.1)	15 (26.8)	58 (30.1)
Median DOR, months (95% CI)	NR (20.7–NE)	41.9 (20.5–54.6)	41.3 (40.8–46.3)	41.3 (38.8–46.3)
Median PFS, months (95% CI)	18.4 (7.3–53.2)	18.5 (11.1–43.8)	21.7 (3.8–43.3)	22.1 (10.4–32.3)
Median OS, months (95% CI)	57.7 (29.3–NE)	NR (58.3–NE)	48.4 (29.5–NE)	NR (56.0–NE)

CI, confidence interval; DOR, duration of response; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

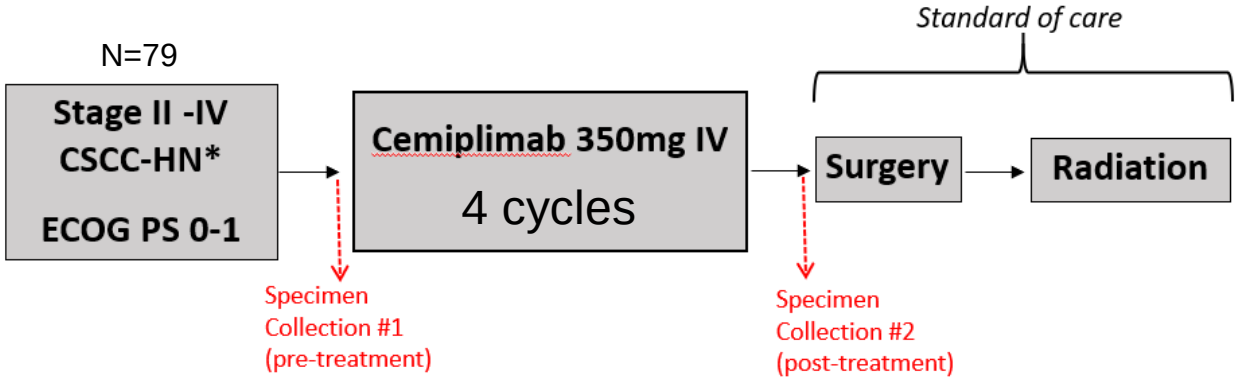
Migden, et al., presented at ESMO 2022. Final analysis of EMPOWER-CSCC-1, NCT 02760498.

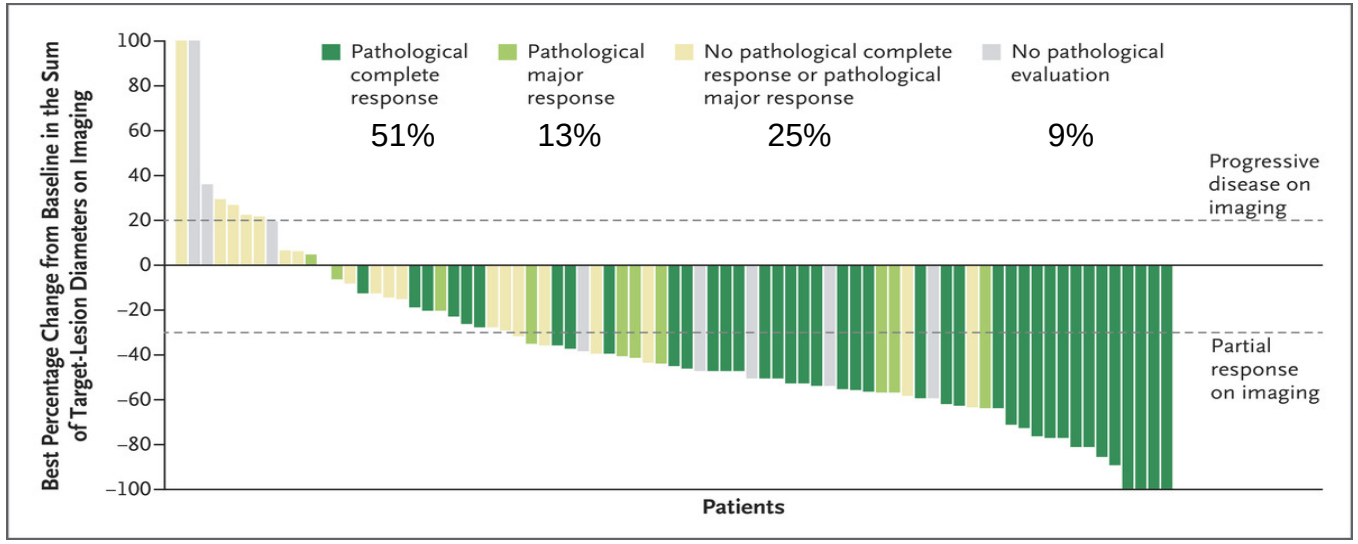
KEYNOTE-629: Pembrolizumab

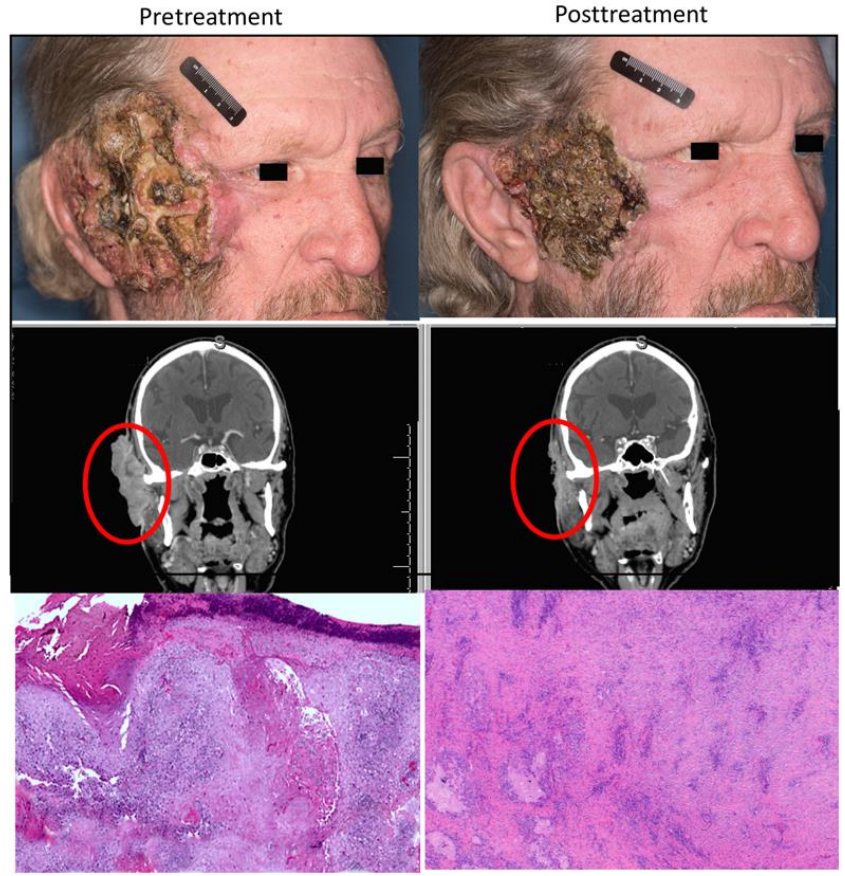
	Locally advanced (n=54)	Recurrent / metastatic (n= 105)	Total (N=159)
Median duration of follow up	14.9 (10.1-19.4) mo	27.2 (24.6-32.0) mo	Not reported
Overall response rate	50%	35.2%	40.3%
Complete Response	16.7%	10%	20 (12.6%)
Partial Response	33.3%	25%	44 (27.7%)
Duration of response, median months	Not reached	Not reached	Not reached
Grade 3-5 treatment related AEs			11.9%

Hughes, et al. "Pembrolizumab for locally…."Ann Oncol. 2021; 32(10):1276.
Grob, et al. "Pembrolizumab monotherapy for…." J Clin Oncol. 2020;38(25):2916.

Neoadjuvant immunotherapy



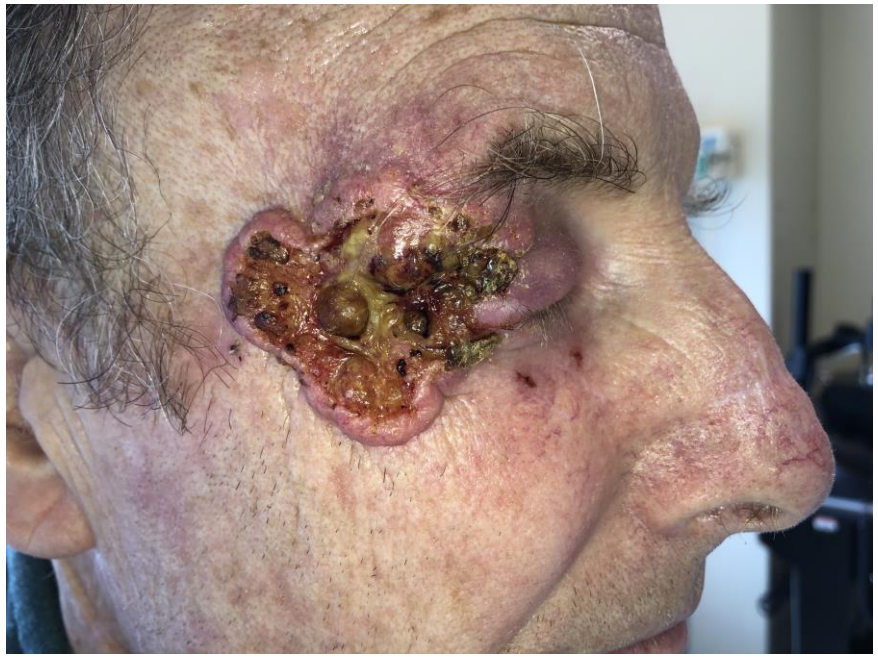




Ferrarotto, et al. Clin Cancer Res. 2021;27(16):4557-4565. doi:10.1158/1078-0432.CCR-21-0585
Gross, et al. NEJM. 2022; 387:1557-1568. DOI: 10.1056/NEJMoa2209813

Anti-PD1 therapy

- Cemiplimab initiated due to likely orbital exenteration outcome with surgery and dry eye with radiation. After 2 doses, he noted changes in the size of the tumor. The tumor appeared to flatten out.

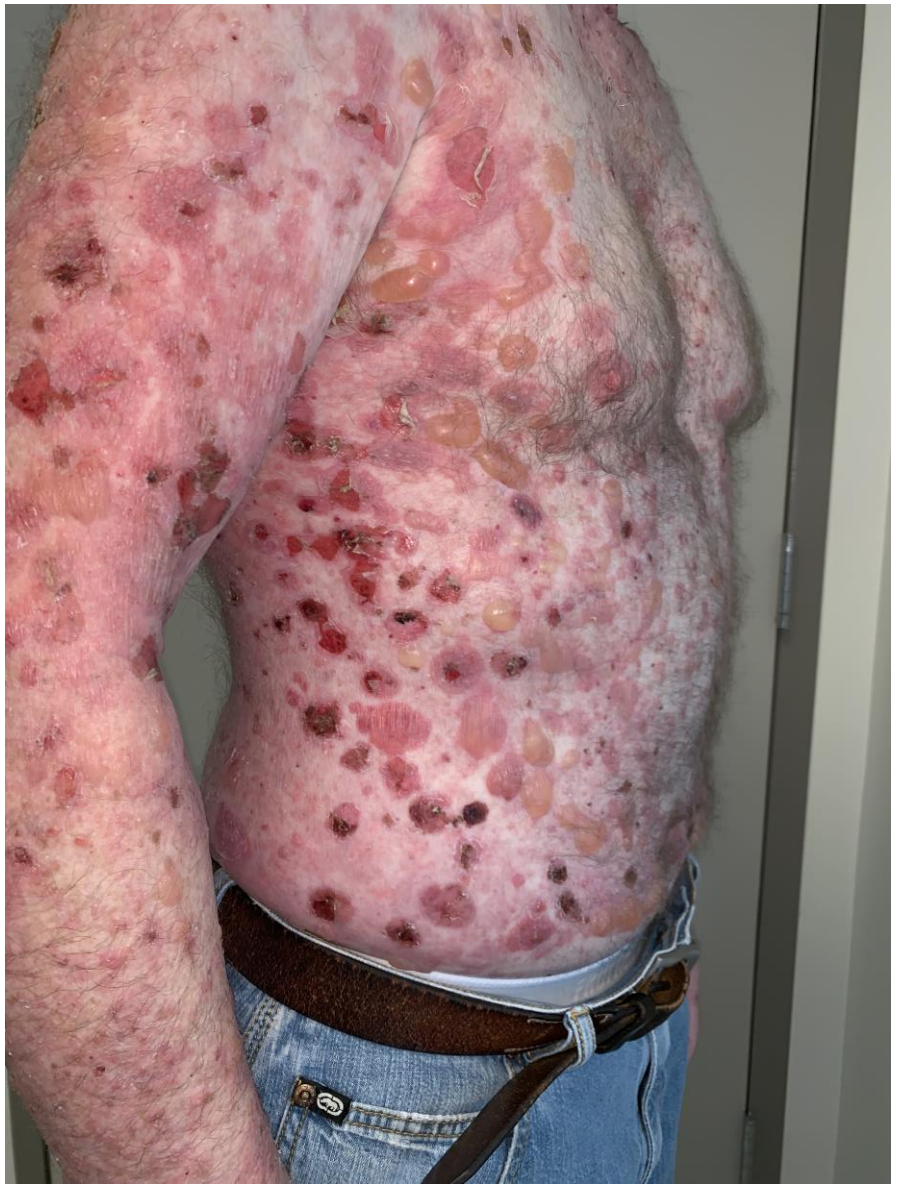


Feb 2019

Cemiplimab infusions

- Cemiplimab initiated due to likely orbital exenteration outcome with surgery and dry eye with radiation. After 2 doses, he noted changes in the size of the tumor. The tumor appeared to flatten out.

- However, after 3 infusions, he developed a severe immune related toxicity – PD1-inhibitor induced bullous pemphigoid – and had to discontinue cemiplimab

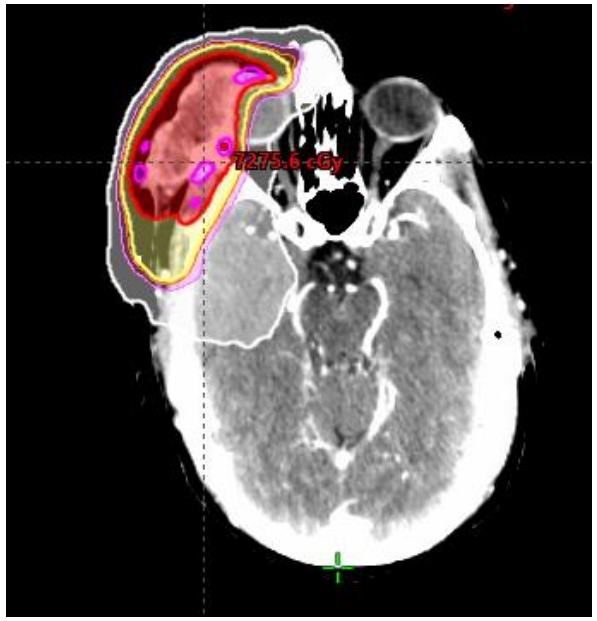


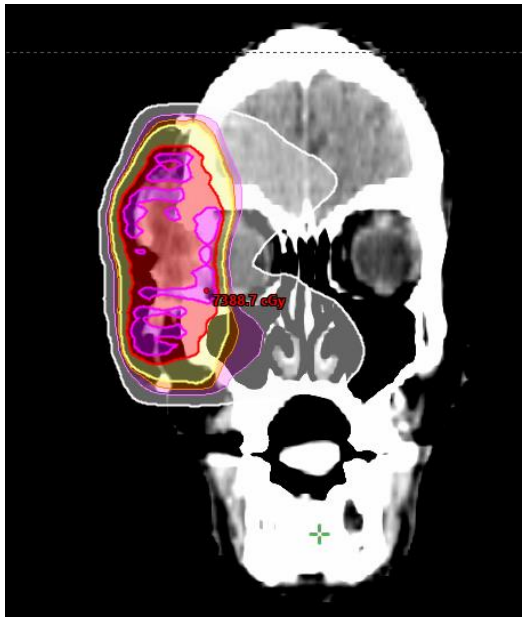
Feb 2019

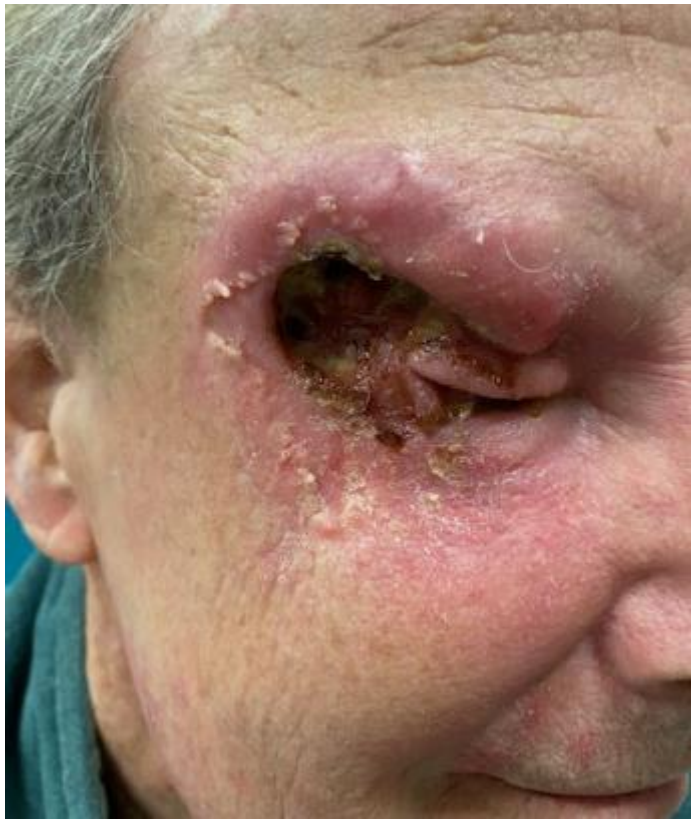
April 2019

Definitive radiation therapy

- Underwent definitive radiation therapy to the right orbit / temple, 70 Gy in 35 fractions, and showed a clinical response on exam and partial response on imaging.





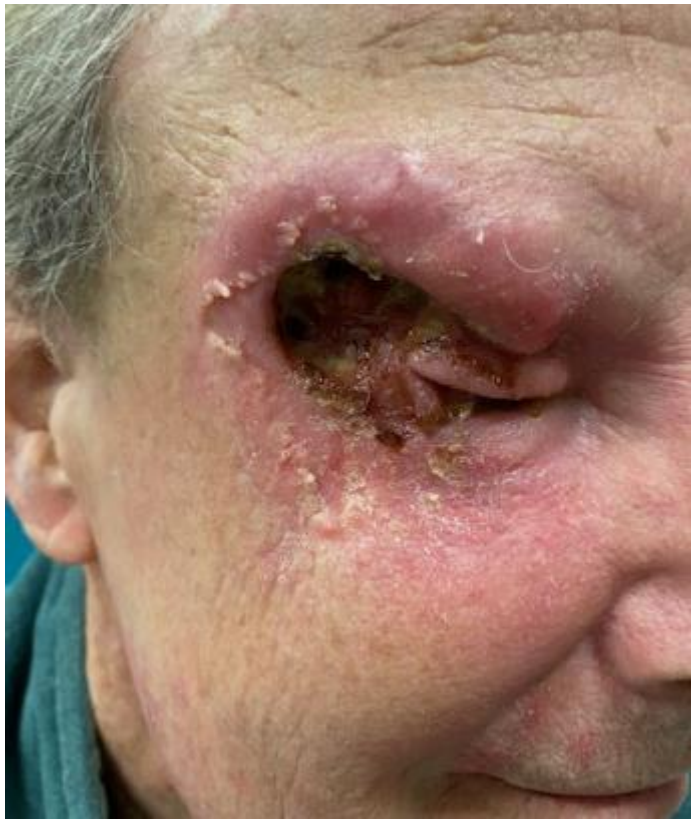


Feb 2019 — April 2019 — July 2019

Surgical resection

- 6 months post radiation, there was progressive tumor growth intra-orbitally on imaging. In addition, eyelid swelling had worsened, and he was unable to open his eyelid.

- Jan 2020: He consented to surgery and underwent radical orbitectomy with orbital exenteration, resection of periorbital soft tissue, and right selective neck dissection.



Dec
2019

Conclusions from CSCC case

- Surgery ultimately cured our patient
- Emerging data for role of anti-PD1 therapy in resectable CSCC, in which surgery and / or radiation may lead to high morbidity, neoadjuvant anti-PD1 therapy may play a role
- Immune related adverse events are important to recognize and present the major risk associated with anti-PD1 therapy
- Surgery remains first line treatment when possible without significant morbidity

Case: Melanoma

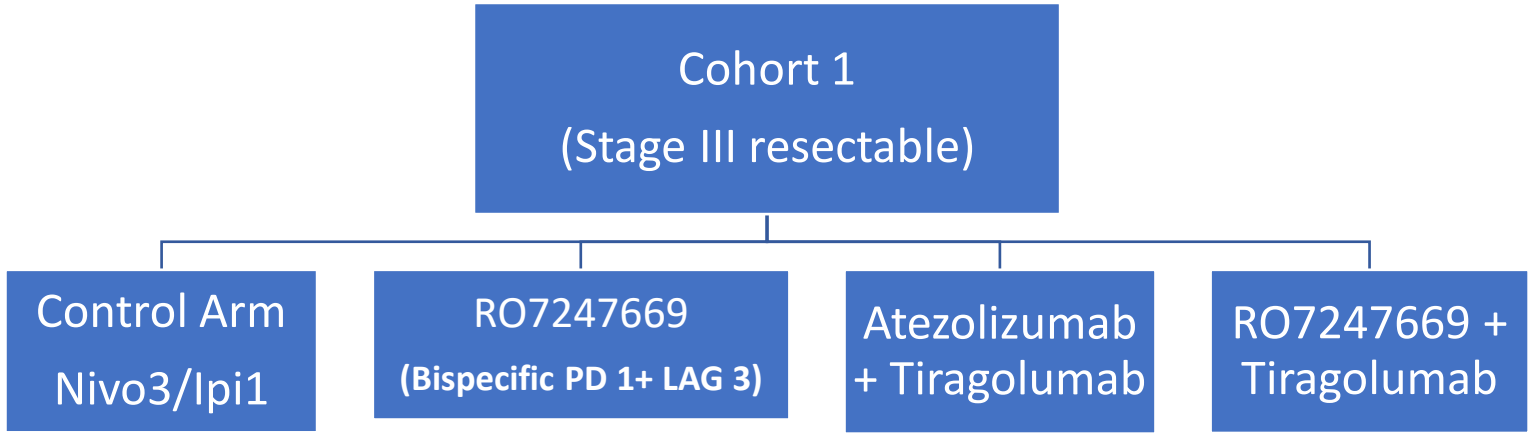
- **57yoM current smoker with diagnosed malignant melanoma of the scalp (10/29/21). Pt was incarcerated until 6/2021 and was s/p blunt force trauma to scalp during incarceration.**
- **Pathology results from OSH (10/29/2021): Malignant melanoma, vertical growth phase, with ulceration, tumor depth at least 16mm, Clark's level at least 4, mitotic rate 16/mm2, margins involved, history of pathologic stage pT4b.**
- **MRI brain face neck (12/28/21) demonstrated enlarged left intraparotid and left level 2 lymph node concerning for metastasis**
- **US guided soft tissue biopsy of left parotid lesion (1/13/22) with pathology demonstrating metastatic malignant melanoma.**
- **His care was delayed due to insurance constraints.**

LYMPH NODE, BIOPSY, SOFT TISSUE AND SALIVARY GLAND TISSUE

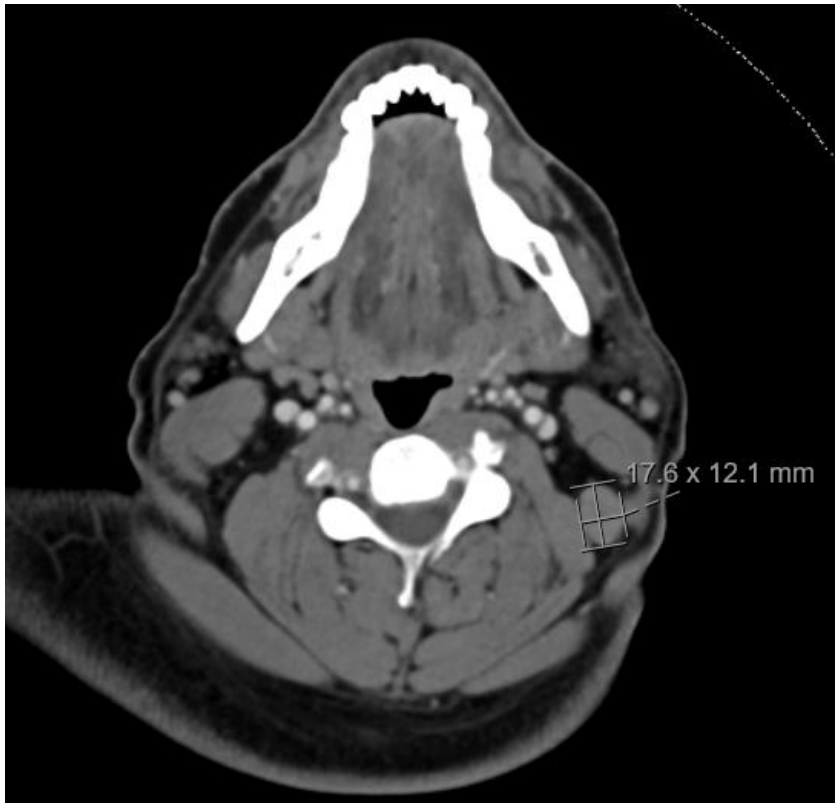
Genomic Alterations Detected	Allele Frequency	FDA-Approved Therapies in patient's tumor*	FDA-Approved Therapies in other tumor type*
AKT1 (c.118G>A; **p.E40K**)	**16%**	**None**	**None**
BRAF (c.1798_1799delGTinsAA; **p.V600K**)	**26%**	**Vemurafenib + Atezolizumab + Cobimetinib, Dabrafenib + Trametinib, Encorafenib + Binimetinib, Trametinib, Vemurafenib + Cobimetinib**	**None**
CDKN2A (c.322G>T; **p.D108Y**)	**32%**	**None**	**None**
ERBB4 (c.1630C>T; **p.R544W**)	**6%**	**None**	**None**
TERT (c.-124C>T)	**33%**	**None**	**None**

TUMOR MUTATIONAL BURDEN STATUS (TMB)
High
MICROSATELLITE STATUS (MSI)
Stable
PD-L1 22C3 FDA (KEYTRUDA) for Gastric/GEA STATUS
NO PD-L1 EXPRESSION
Combined Positive Score: 0

Clinical Trial: IRB #21507 (Morpheus-Melanoma)



- Neoadjuvant treatment for 2 cycles (6 weeks) and then surgery (CLND) in Week 7
- Key inclusion criteria: measurable disease (at least one target lesion) according to RECIST v1.1



3/2/22
CT Face Neck Chest Pelvis
(screen failure for Morpheus trial as the short axis of LN <1.5cm

SWOG S1801 - Neoadjuvant Therapy with Pembrolizumab

- **Patient was initiated neoadjuvant pembrolizumab**
- **Based on off protocol use in SWOG S1801 (Phase II trial randomized study in patients with resectable Stage III-IV melanoma)**

SWOG S1801: Background

- Tumor regression after PD-1 blockade depends on presence of antitumor cells located at tumor margin[1]
- Adjuvant anti–PD-1 therapy increases recurrence-free survival in patients with high-risk melanoma[2-4]
- Neoadjuvant anti–PD-1 therapy has previously been shown to increase proliferation of tumor-specific T-cells in preclinical and clinical models[5,6]
- Current analysis from the SWOG S1801 study compared safety, efficacy of neoadjuvant vs adjuvant pembrolizumab in patients with resectable stage III-IV melanoma[7]

1. Tumeh. Nature. 2014;515:568. 2. Weber. NEJM. 2017;377:1824. 3. Eggermont. NEJM. 2018;378:1789. 4. Grossman. Cancer Discov. 2022;12:644. 5. Liu. Cancer Discov. 2016;6:1382. 6. Blank. Nat Med. 2018;24:1655. 7. Patel. ESMO 2022. Abstr LBA6.

Slide credit: clinicaloptions.com

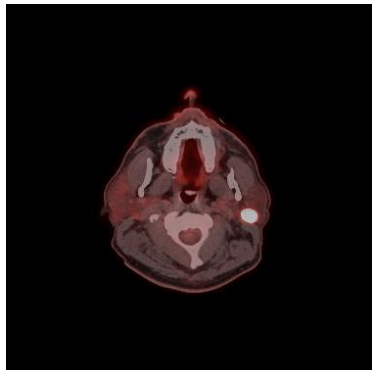
SWOG S1801: Investigator's Conclusions

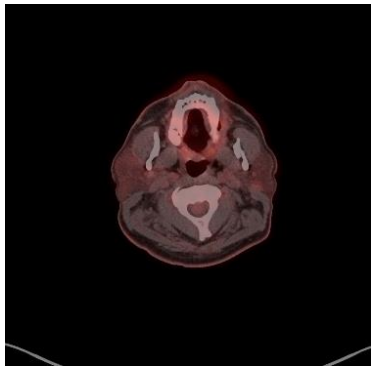
- In patients with resectable stage III-IV melanoma, neoadjuvant pembrolizumab increased EFS vs adjuvant pembrolizumab: HR = 0.58 (*P* = .004)
  - 2-yr EFS: 72% vs 49%
  - Disease progression prevented surgery in 8% of patients in neoadjuvant arm
  - Residual disease or metastasis occurred before adjuvant therapy in 6.5% of patients in neoadjuvant arm and 11% in adjuvant arm
  - Disease progression occurred in 20% of patients in neoadjuvant arm and 40% in adjuvant arm
- No significant difference in OS at this analysis; data are immature
- Safety in-keeping with prior data with similar TRAEs rates across arms
  - AEs in perioperative period were not increased with neoadjuvant pembrolizumab

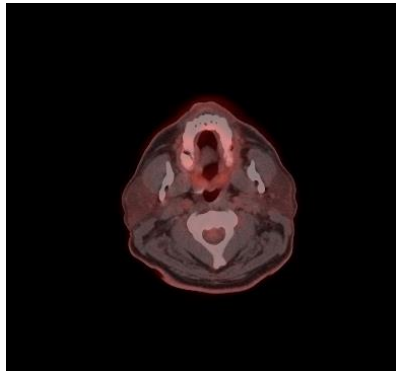
Patel. ESMO 2022. Abstr LBA6.

Slide credit: clinicaloptions.com

Melanoma case: Timeline of Events







1/28/22
Baseline
PET CT

5/16/22
1st restaging
PET CT (after C3)

8/1/22
2nd restaging
PET CT (after C6)

11/22/21
New patient visit with ENT (Dr. Kang)

2/8/22
Med Onc consult (Dr. Xing)

3/19/22
C1
Pembro

4/11/22
C2

5/2/22
C3

5/23/22
C4

6/13/22
C5

7/11/22
C6

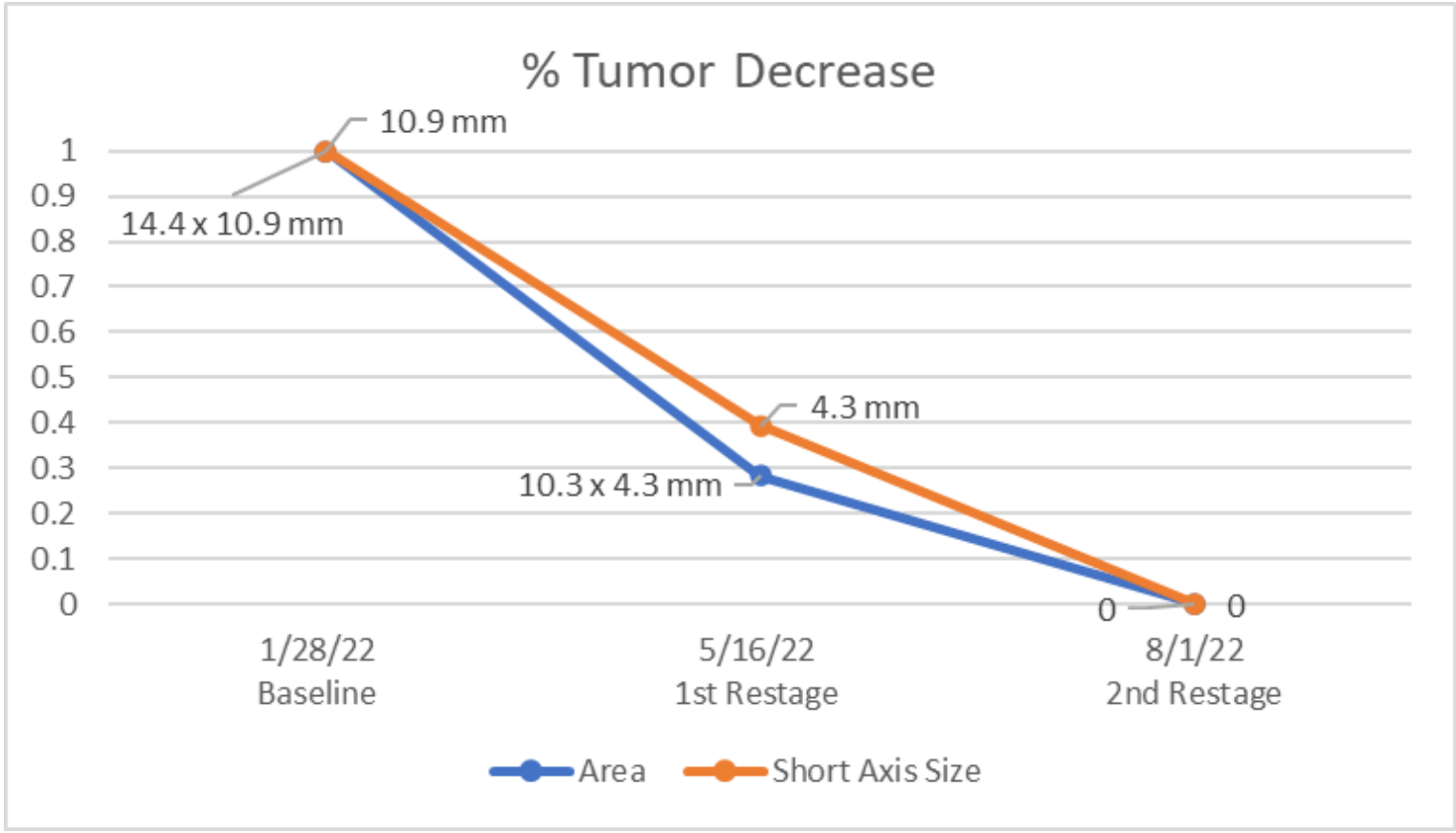
8/1/22
C7

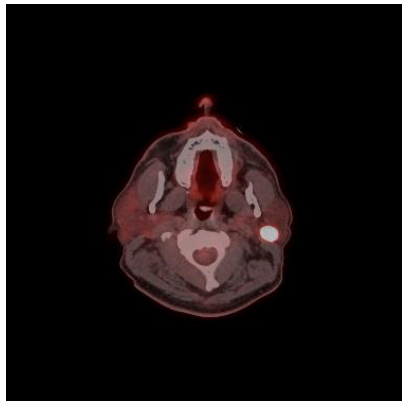
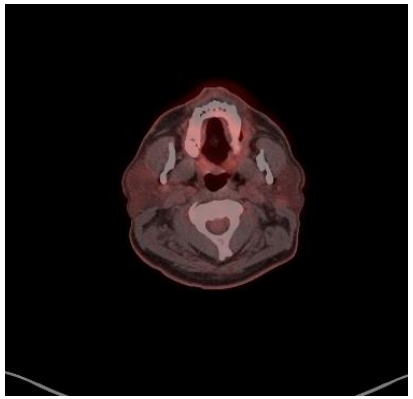
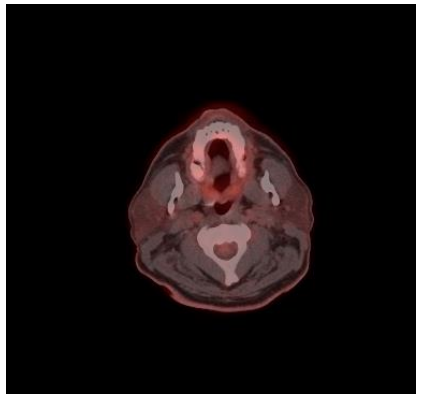
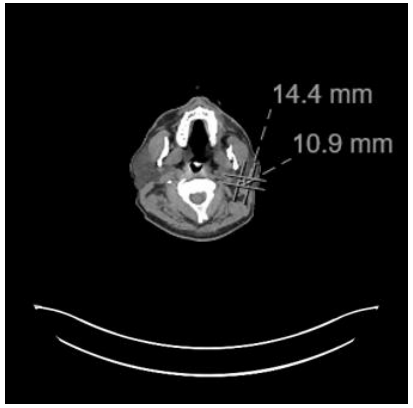
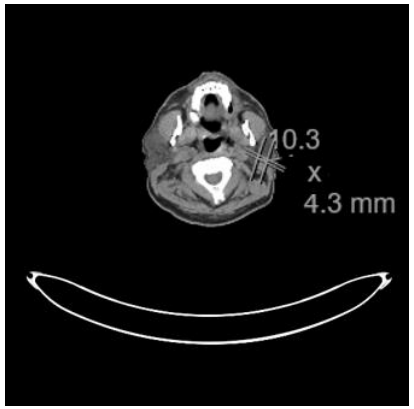
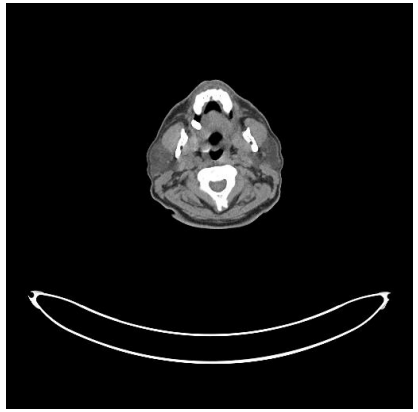
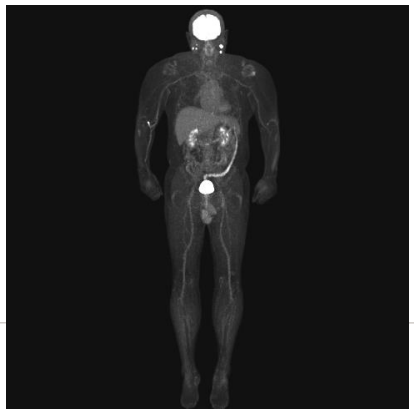
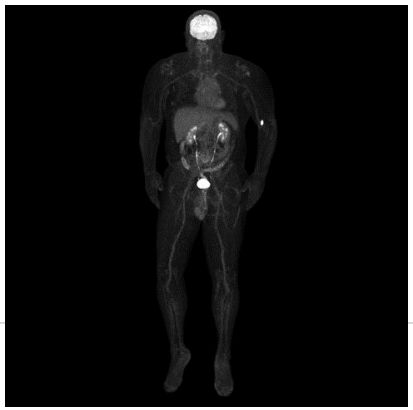
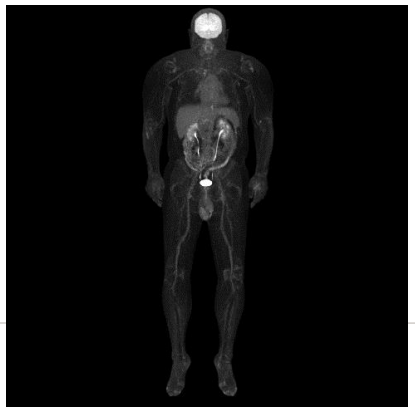
9/12/22
C8

10/3/22
C9

Tumor Regression with Neoadjuvant Pembrolizumab

- **Patient planned to complete 10 cycles of neoadjuvant pembrolizumab**
- **3rd restaging PETCT scheduled 11/4/22**
- **If PETCT shows patient remains in complete remission, recommend discontinuation of immunotherapy treatment per tumor board discussion**



1/28/22 Baseline	5/16/22 1st restaging after C3	8/1/22 2nd restaging after C6
		
		
		

We acknowledges the Pharmacy team (Sharon Xu) for her contributions to the slides.

Questions

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