Pembrolizumab/Cetuximab for the Treatment of Betel-Nut Associated Oral Cavity Cancer: A Case Series

Jonathan West MD[1], Daniel Kwon MD FACS[1], William Moss MD[2], Mark Wallace DO[2], Peter Brett MD[3]
[1]Caruso Department of Otolaryngology – Head and Neck Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA
[2]Division of Otolaryngology, Commonwealth Healthcare Corporation, Saipan, Commonwealth of the Northern Mariana Islands, USA
[3]Division of Medical Oncology, Commonwealth Healthcare Corporation, Saipan, Commonwealth of the Northern Mariana Islands, USA

BACKGROUND

- The Commonwealth of the Northern Mariana Islands (CNMI) is a remote, resource-limited US Territory with high rates of betel nut use and betel nut associated oral cavity carcinoma (BRA OC CA)[1]
- BNA OC CA in the CNMI is characterized by delayed presentation in younger patients, high rates of recurrence, and poor overall survival[2]
- BNA OC CA has a uniquely aggressive tumor phenotype that responds poorly to traditional chemotherapy and radiation with high rates of recurrence and metastasis[3]
- Platinum-based chemotherapy use is limited by patient comorbidities and surgical treatment of advanced tumors imparts significant functional and psychosocial morbidity
- Pembrolizumab/Cetuximab (Key/Erb) efficacy has been shown in a prior trial for recurrent/metastatic **non-betel nut associated** OC CA[4]

OBJECTIVES

- To evaluate the efficacy of Key/Erb treatment in the neoadjuvant, adjuvant, recurrent and metastatic settings for BNA OC CA by evaluating the rates of:
  1. Treatment response by clinical evaluation
  2. Overall survival (OS), progression-free survival (PFS)
  3. Grade 3-4 toxicity

METHODS

Design
- Retrospective case series (2019–2024)
- No clinical trials infrastructure available

Inclusion Criteria
- Patients with BNA OC CA cancer deemed unlikely to benefit from standard therapy

Treatment Cycle
- Pembrolizumab (Day 1) + Cetuximab (Days 1, 15, 29); repeated every 42 days up to 2 years or until toxicity

Treatment Response
- Classified into partial response (PR), complete response (CR), stable disease (SD), or progressive disease (PD)
- Determined by clinical evaluation

Endpoints
- Progression-free survival (PFS) (months) (mo)
- Overall survival
- Rate of grade 3-4 side effects

Statistical Analysis
- Kaplan Meier survival curves
- Swimmer plot

RESULTS

- **Patients**: 31 total (5 neoadjuvant, 26 adjuvant/recurrent/metastatic)
- **Histology**: 30 squamous, 1 verrucous cell carcinoma
- **Site**: 48% buccal mucosa, 35% tongue
- **Treatment duration**: Neoadjuvant – 3 months (2-6 mo); Adjuvant/recurrent/metastatic – 4 months (0.25 – 24 mo)
- **Treatment response:** 48% PR (all neoadjuvant cases PR); 32% PD
- **Median OS:** 15 months (95% CI 5–21)
- **Median PFS:** 10 months (95% CI 2–16)
- **Toxicity:** 65% had no grade 3–4 toxicity; 1 case of cetuximab anaphylaxis

CONTACT

Jonathan West, MD - jonathan.west@med.usc.edu

FIGURES

Figure 1: Pembrolizumab/Cetuximab treatment response (31 patients)

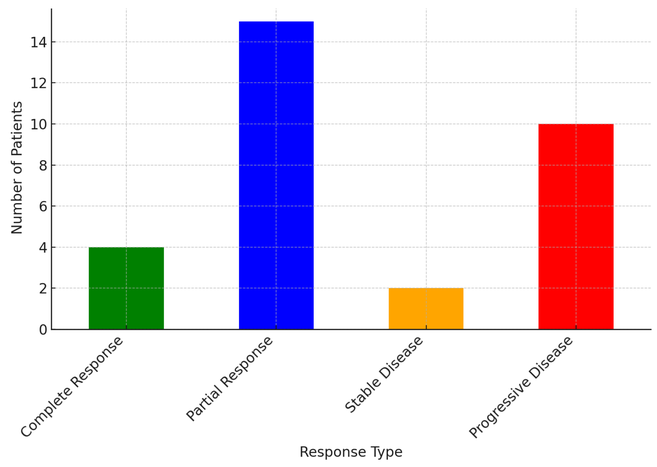


Figure 2: Example of tumor response after 2 years of Key/Erb treatment

Figure 3: Swimmer plot of overall survival and progression-free survival by primary site (from treatment start date)

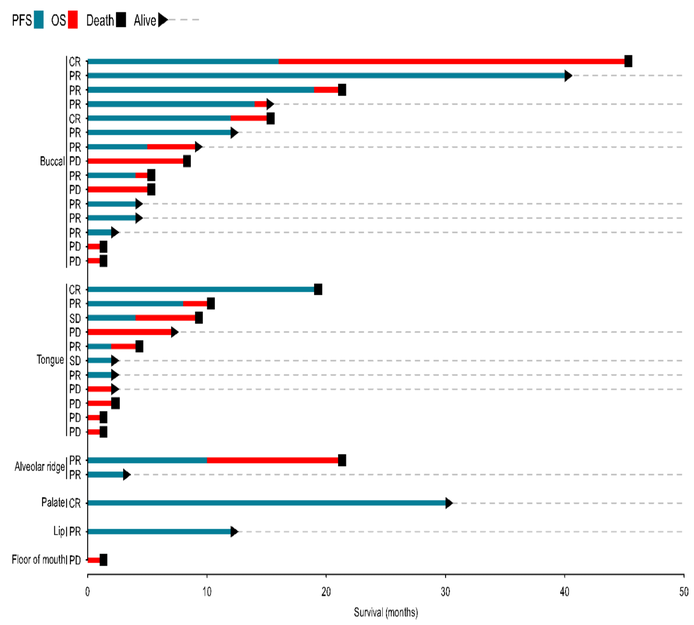
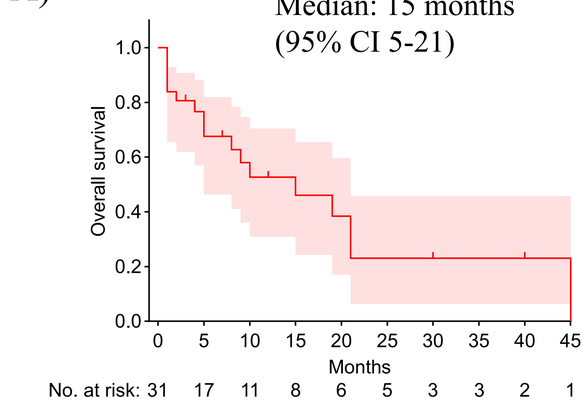
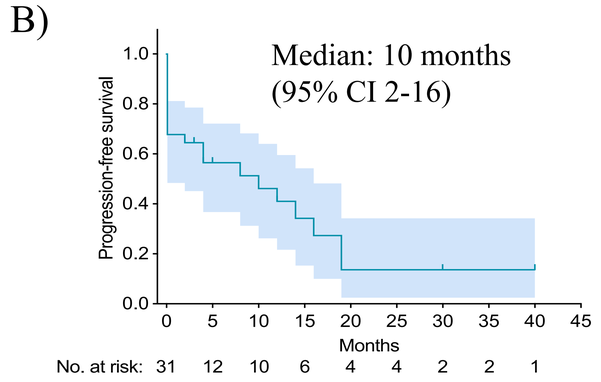


Figure 4: Kaplan Meier Curves of A) Overall Survival and B) Progression-Free Survival for all patients treated with Key/Erb (31)

A)



B)



DISCUSSION

Findings & Significance
- Key/Erb shows promising efficacy in BNA OC CA in numerous treatment settings with limited toxicity.
- Key/Erb presents a novel treatment approach for BNA OC CA that has the potential to improve oncologic outcomes and reduce surgical morbidity
- Most patients achieved disease stabilization or response, though 1/3 progressed, suggesting tumor heterogeneity warranting further study
- Our findings support further investigation of Key/Erb in the neoadjuvant, adjuvant and recurrent/metastatic settings

Limitations
- Retrospective design, no standardized treatment or monitoring protocol
- Treatment response defined by clinical impression. No objective measure applied (e.g. RECIST criteria)

Future Directions
- Conduct a randomized trial of Key/Erb treatment in the neoadjuvant, adjuvant and recurrent/metastatic settings
- Explore neoadjuvant Key/Erb use to reduce surgical morbidity and improve oncologic outcomes
- Investigate molecular mechanisms of betel-nut related malignancy to better predict immunotherapy response

REFERENCES

1. Paulino YC, Hurwitz EL, Ogo JC, Paulino TC, Yamanaka AB, Novotny R, Wilkens LR, Miller MJ, Palafox NA. Epidemiology of areca (betel) nut use in the mariana islands: Findings from the University of Guam/University of Hawai`i cancer center partnership program. Cancer Epidemiol. 2017 Oct;50(Pt B):241-246. doi: 10.1016/j.canep.2017.08.006. PMID: 29120831; PMCID: PMC5747254.
2. Narayanan AM, Finegersh AF, Chang MP, Orosco RK, Moss WJ. Oral Cavity Cancer Outcomes in Remote, Betel Nut-Endemic Pacific Islands. Ann Otol Rhinol Laryngol. 2020 Dec;129(12):1215-1220. doi: 10.1177/0003489420934846. Epub 2020 Jun 16. PMID: 32546006.
3. Li Y, Cheng A, Lee L, et al. Multifaceted mechanisms of areca nuts in oral carcinogenesis: the molecular pathology from precancerous condition to malignant transformation. J Cancer 2019; 10:4054-4062.
4. Sacco A, Chen R, Worden F, et al. Pembrolizumab plus cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma: an open-label, multi-arm, non-randomised, multicentre, phase 2 trial. Lancet Oncol 2021; 22:883-892.