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Oral mucositis associated with targeted therapy and immunotherapy: what's old is new again
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HEALTHCARE

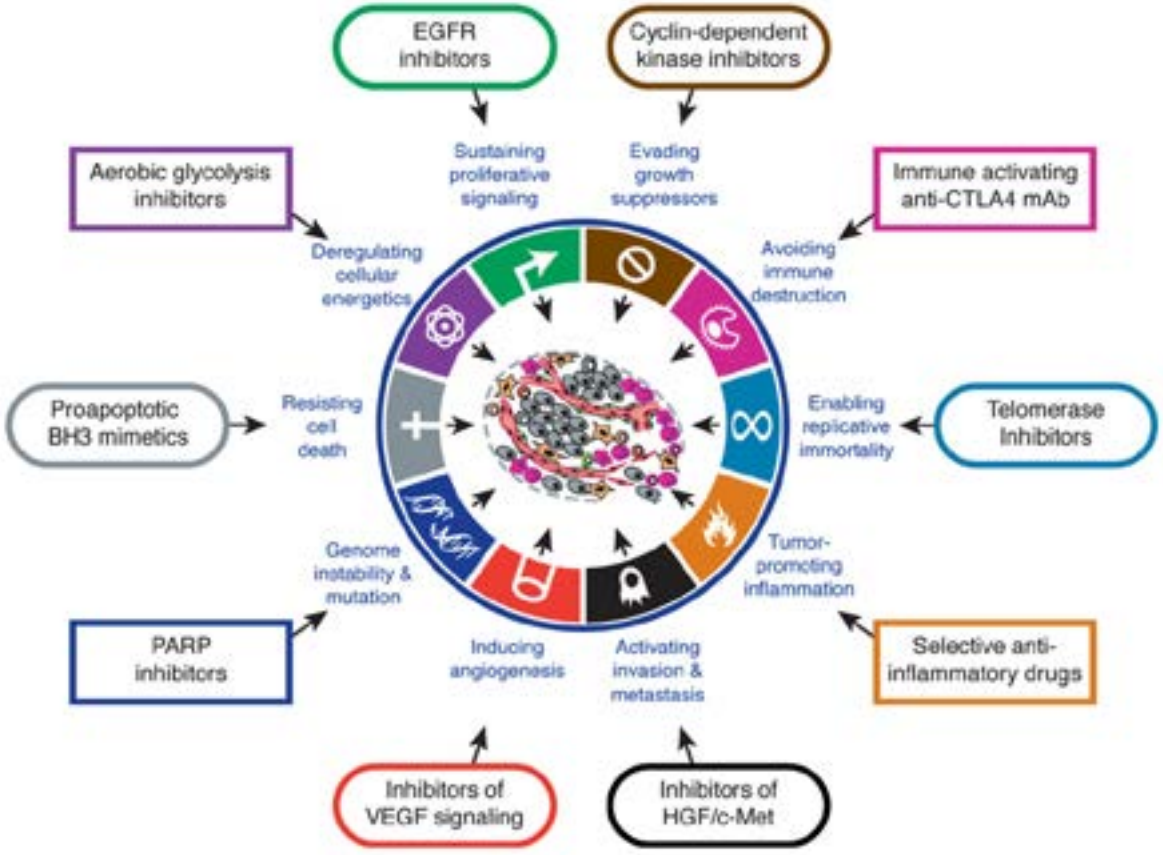
Faculty Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Midatech Pharma US			x					
Dermtreat ApS		x						

Outline

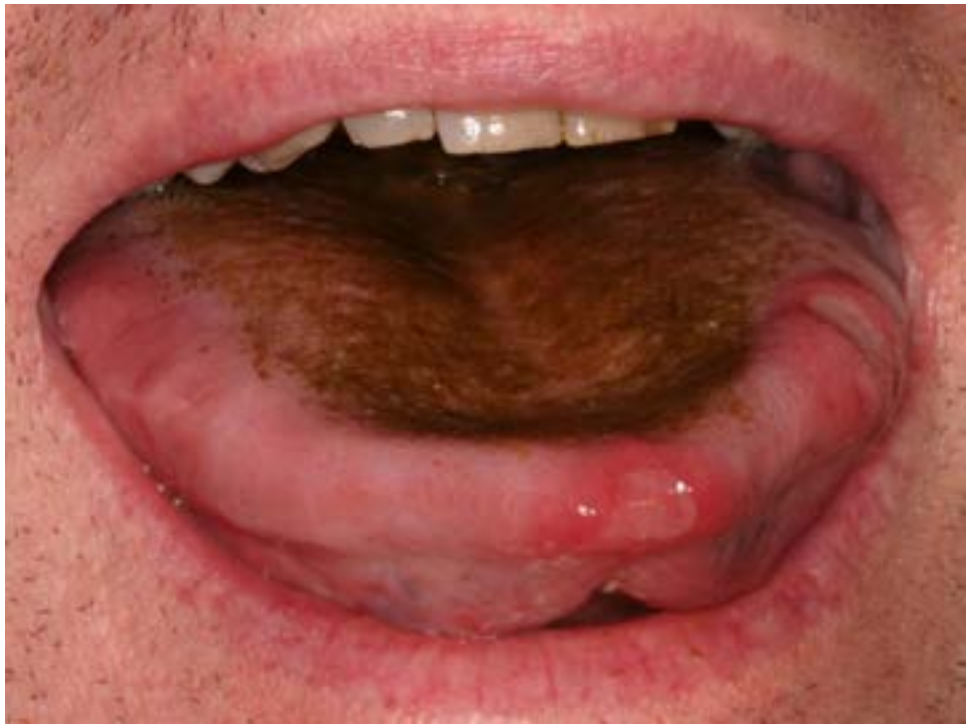
- Targeted therapies
  - mTOR inhibitors
  - MEK inhibitors
  - PI3K inhibitors
  - anti-VEGF TKIs
  - EGFR inhibitors
  - BRAF inhibitors
- Immune checkpoint inhibitors
  - CTLA4 inhibitors
  - PD-1/PDL-1 inhibitors



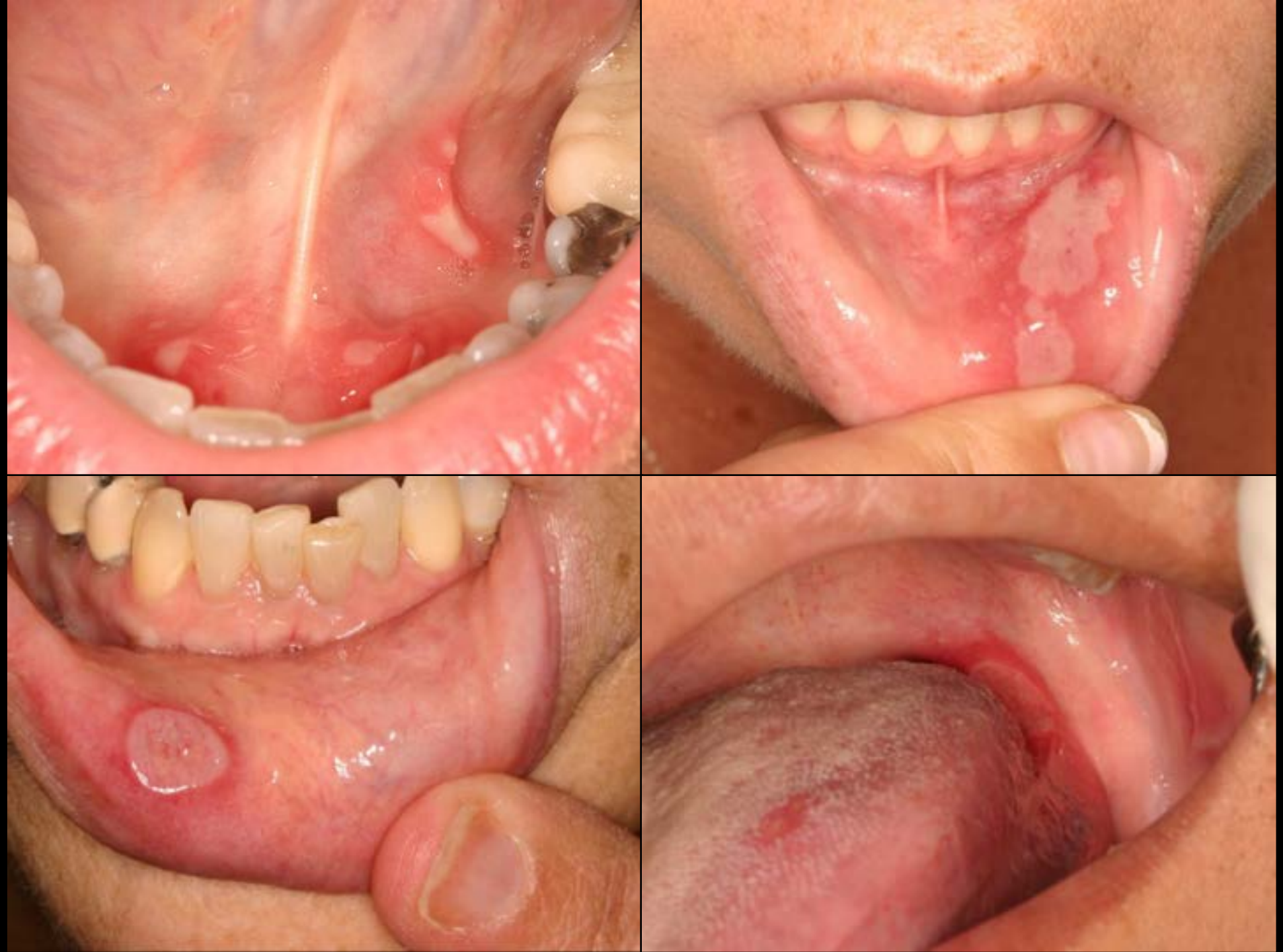
Hanahan D, Weinberg A. *Hallmarks of cancer*. Cell 2011;144:646-74

mTOR inhibitor-associated stomatitis

- mTOR pathway
  - PI3K/AKT/mTOR frequently upregulated, proliferation
  - sirolimus, temsirolimus, everolimus
- Clinical features
  - aphthous-like ulcers
  - acute onset, days to weeks
  - recurrent, diminish with time
  - dose dependent
- Management
  - topical steroids
  - palliative care
  - dose modification

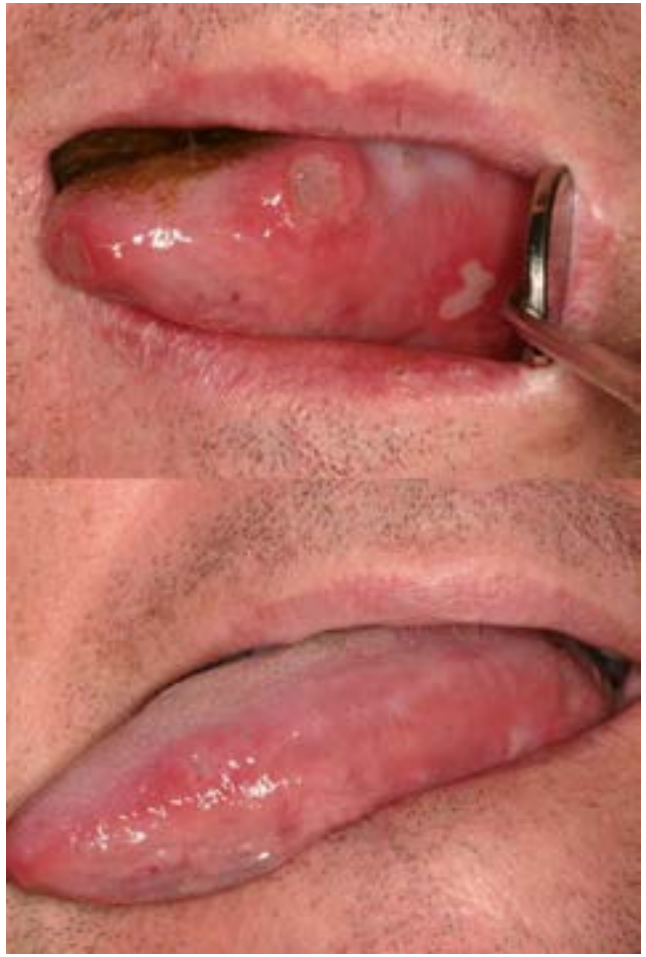


Sonis S, et al. Cancer 2010;116:210–5; Martins F, et al. Oral Oncology 2013;49:293–298; Shameem R, et al. Cancer Investigations 2015;33:70-7



mIAS management w/ corticosteroids

- Retrospective, open label phase 1/2 trials
  - 17 cancer patients, everolimus/ridaforolimus
  - 10 days median onset (4–25)
    - median pain = 7/10
    - 5 dose reductions, 1 DLT
  - improvement in ~90% w/ steroid therapy
    - topical (15), intralesional (5), systemic (1)
    - palliative treatments w/ limited benefit
- SWISH trial (n = 92), open label phase 2
  - advanced HR+/HER2+ breast ca
  - EVE 10 mg/EXE 25 mg
  - dexamethasone 0.5 mg/5 mL, 2 min, s/s, QID
  - incidence of ≥ grade 2 stomatitis at 8 wks compared w/ BOLERO-2:
    - 2.4% vs. 33% ($p < 0.001$), 21.2% vs. 67% all grades



de Oliveira MA, et al. Oral Oncology 2011;47:998–1003; Rugo H, et al. Lancet Oncol 2017;18:654-662

Aphthous stomatitis w/ other targeted therapies?

- PI3K inhibitors
  - idelalisib
    - multiple phase 1 and 2 studies, no mucositis
  - copanlisib
    - phase 1, 6/57 (11%) w/ “oral cavity mucositis”, table, no description

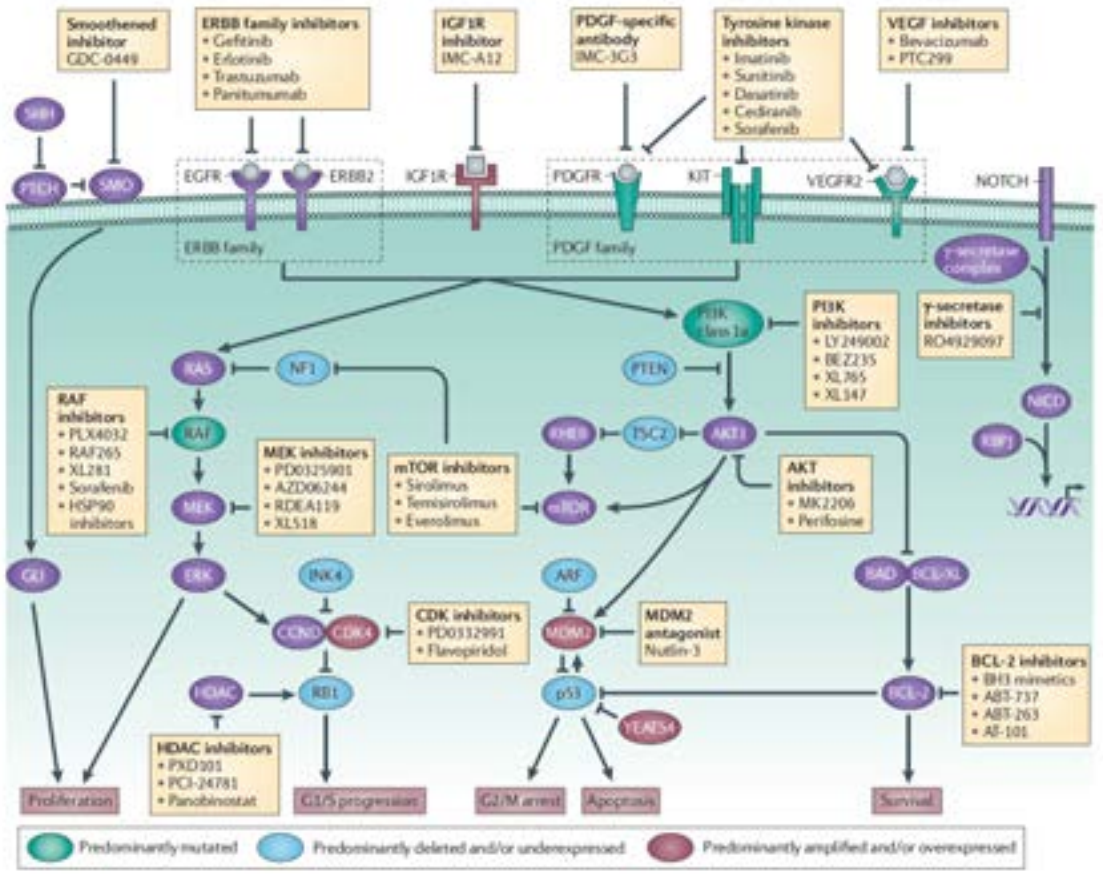
      Patnaik A, et al. Annals Oncol 2016;27:1928–40
- MEK inhibitors
  - trametinib (selumetinib, cobimetinib)
  - “mucositis”/”mucosal inflammation” reported infrequently (2-36%), aphthous-like? no description…

    Infante J, et al. Lancet Oncol 2012;13:773–81

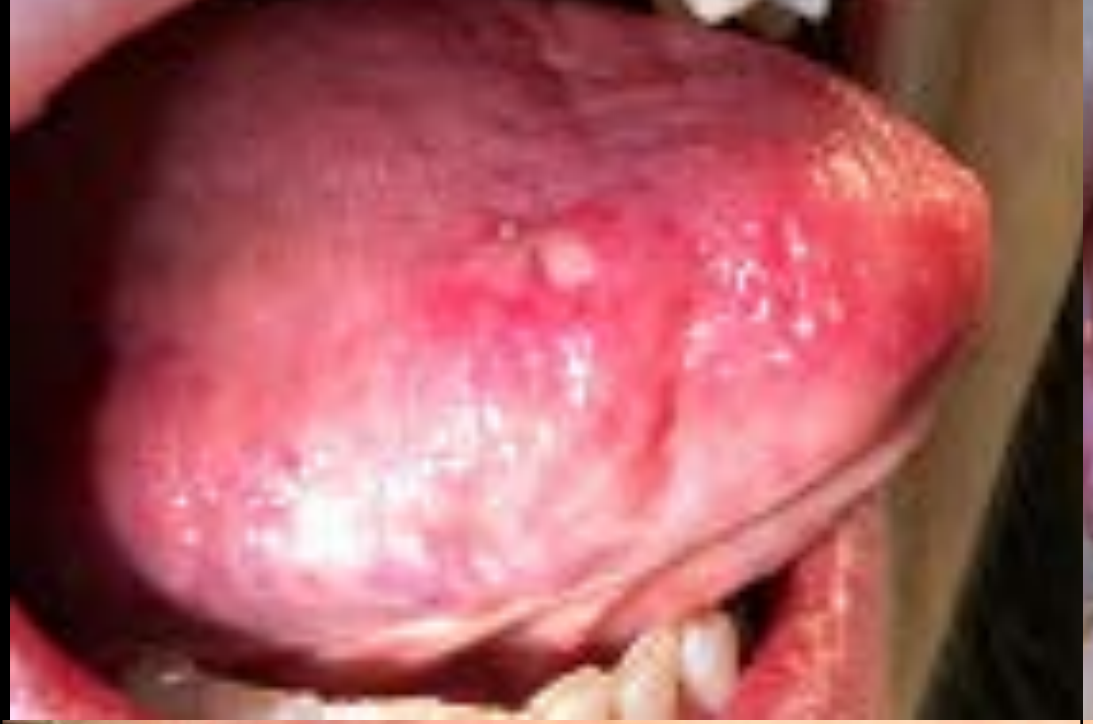
    Falchook G, et al. Lancet Oncol 2012;13:782–9

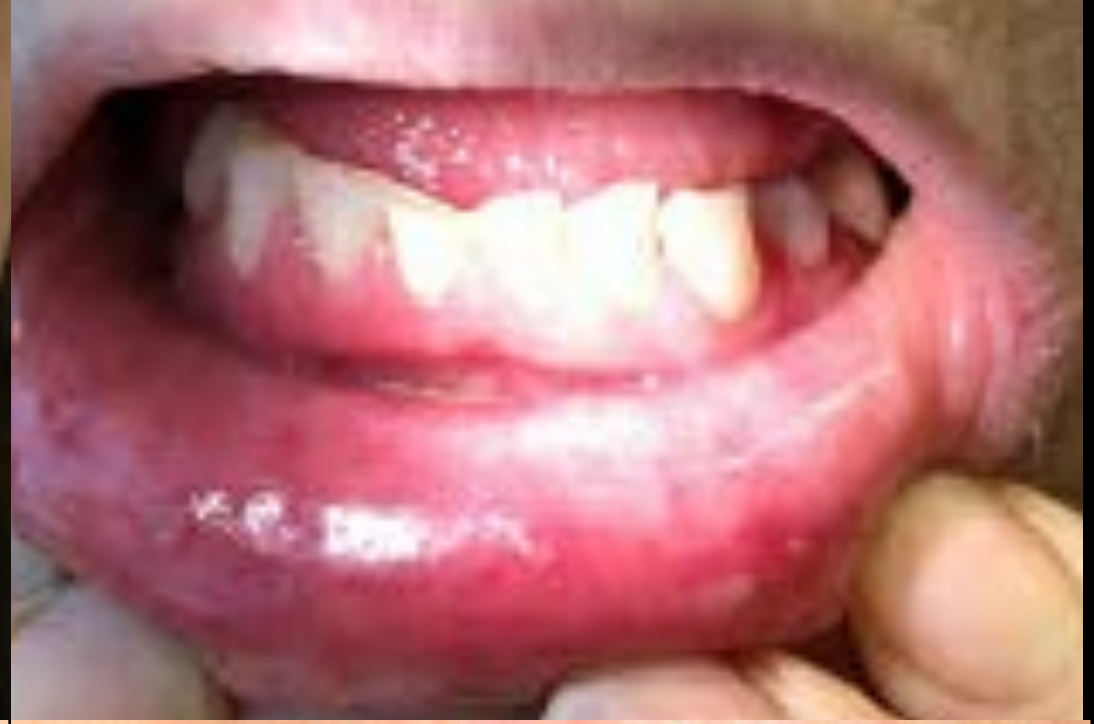
    Abdel-Rahman O, et al. Expert Rev Gastroenterol Hepatol 2015;9:1433–45
  - acneform rash common

    Anforth R, et al. Australasian J Dermatol 2014;55:250-4

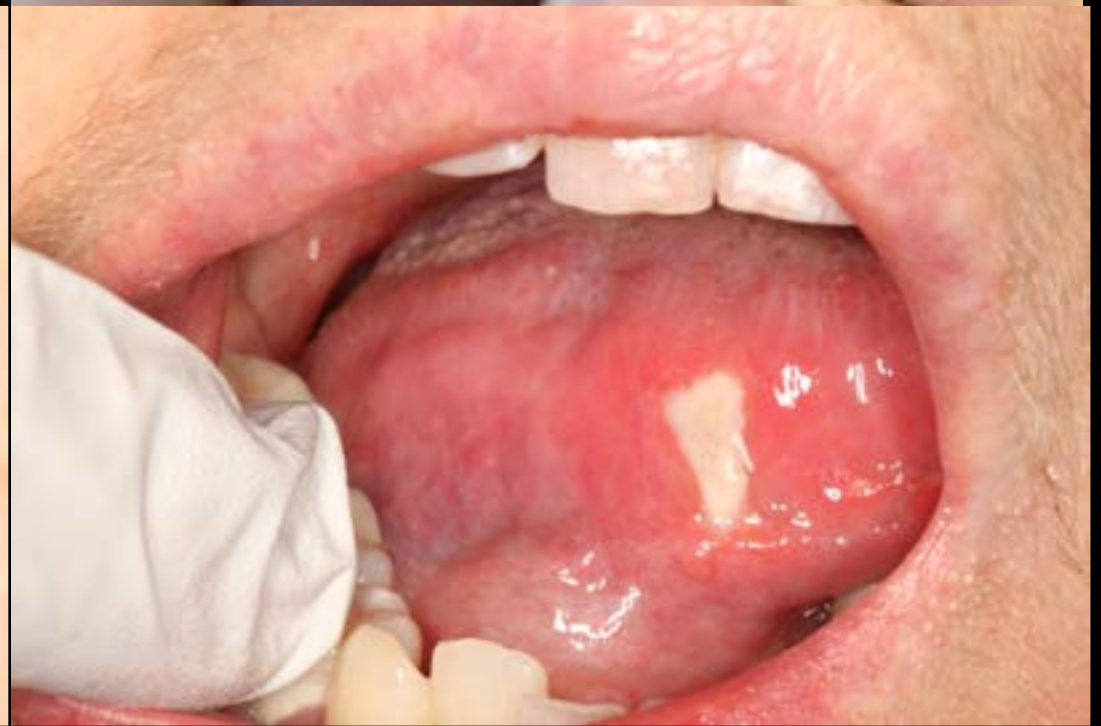


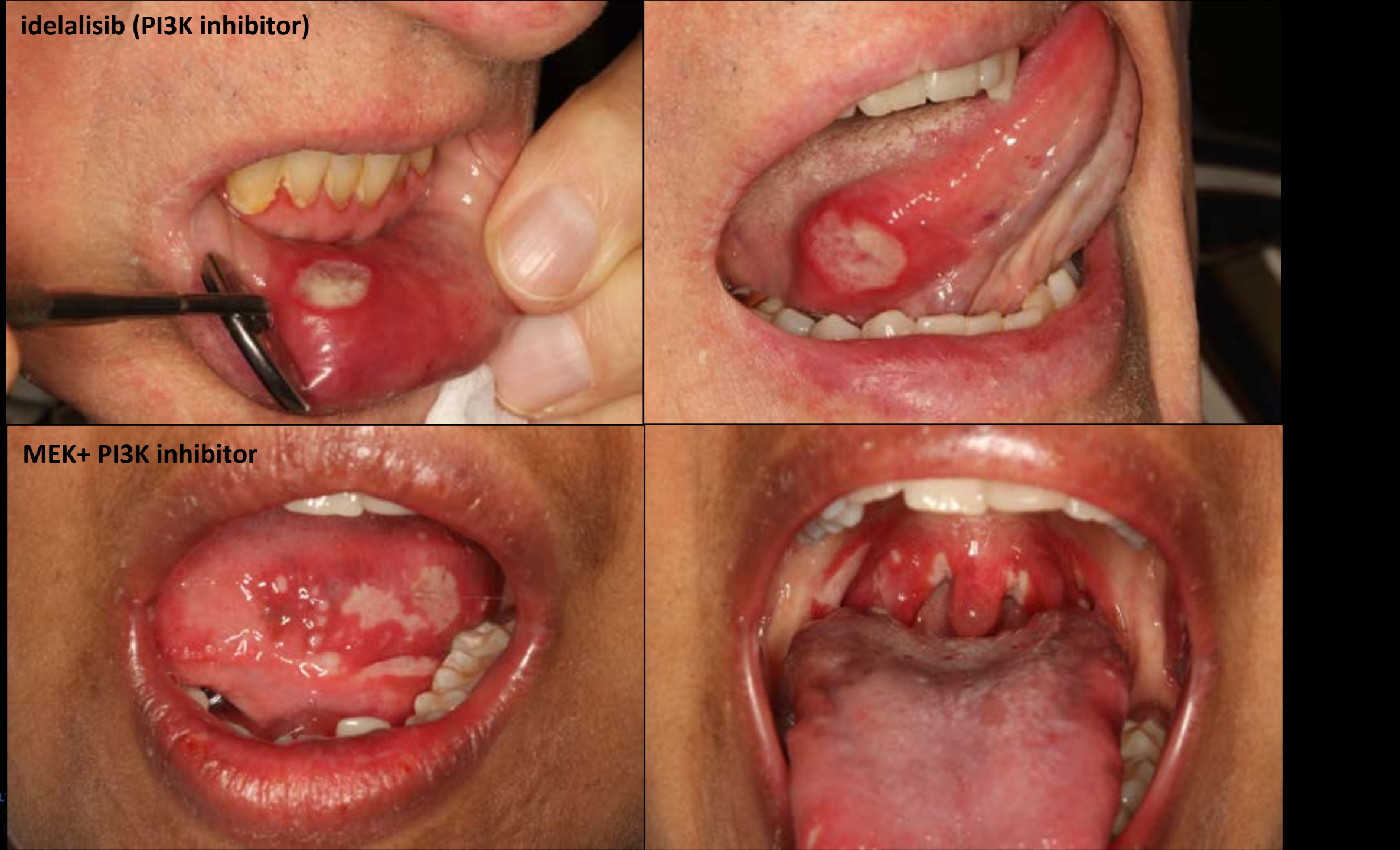
Taylor B, et al. Nat Rev Cancer 2011;11:541-7





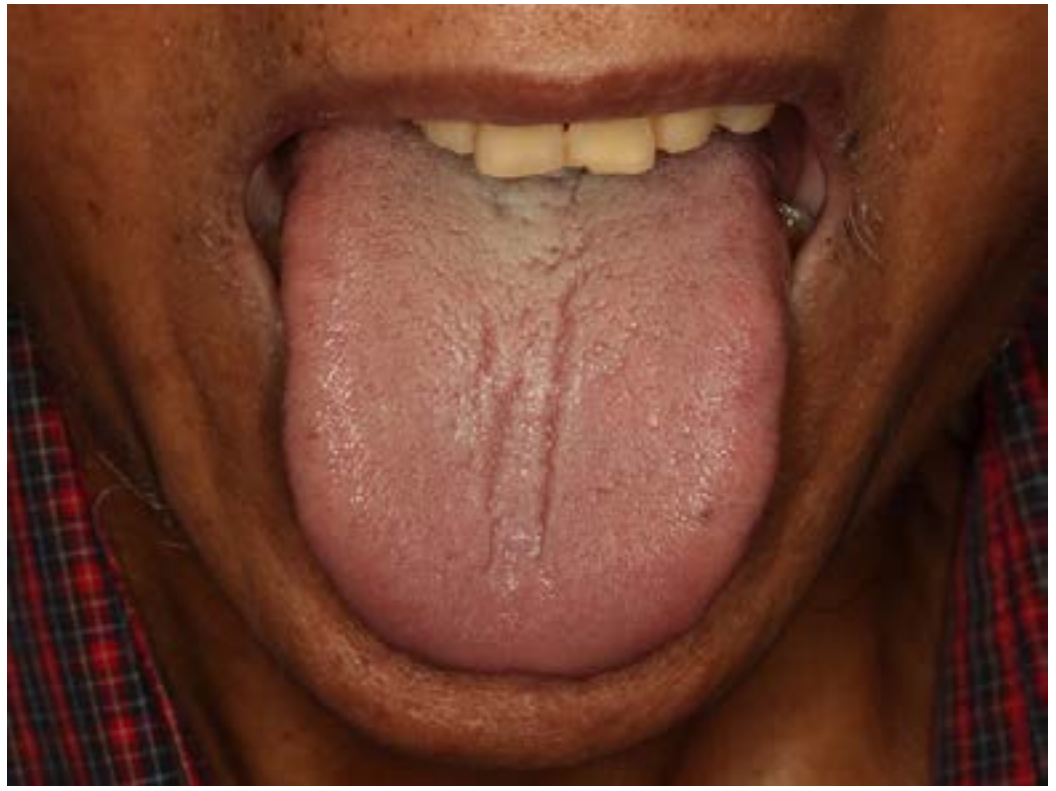
MEK inhibitors




idelalisib (PI3K inhibitor)
MEK+ PI3K inhibitor

Oral dysesthesia associated w/ TKIs

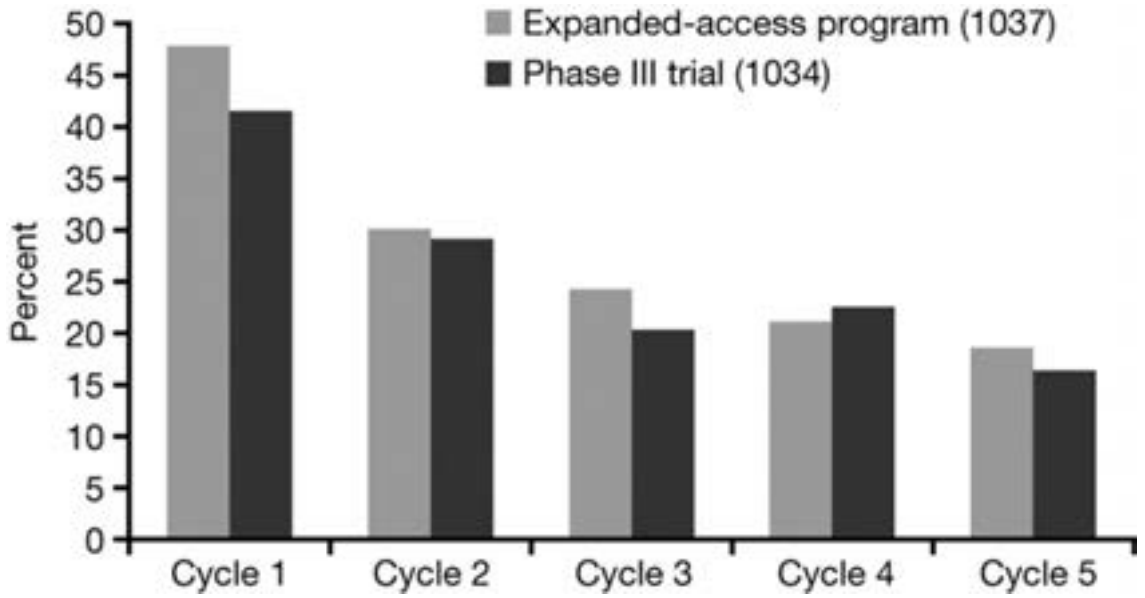
- Multi-targeted tyrosine kinase inhibitors
  - anti-VEGF
  - sunitinib, sorafebib, others
- Clinical features
  - *poorly described in literature*
  - normal appearing mucosa
  - oral/tongue sensitivity, dysesthesia, taste changes
  - association w/ hand-and-foot skin reaction, increasing severity
- Management?
  - treat as pain or dysesthesia?
  - diet modifications



Kollmannsberger et al. Oncologist 2011;16:543-53; Lee W, et al. Br J Dermatology 2009;161:1045-51; Yuan A, et al. Oral Oncology 2015;51:1026–33; Schmidinger M, et al. Oncologist 2017;22:1-10; Gerendesh B, et al. Oncotargets and Therapy 2017;10:5053-64

Sunitinib oral toxicity

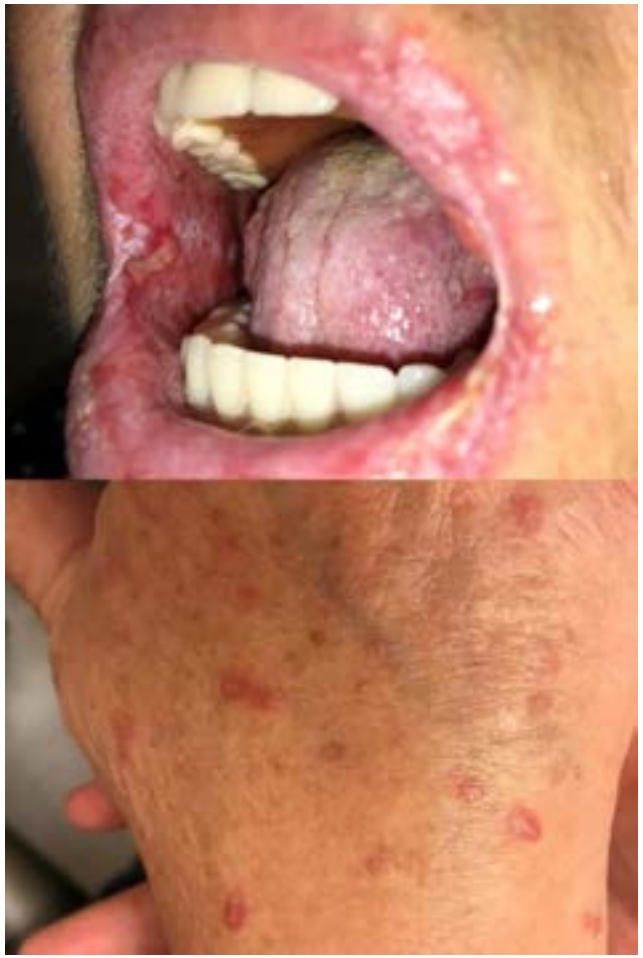
- Mucosal sensitivity
  - most ≤ grade 2
  - <10% required dose reduction
    - <1% required discontinuation
- Clinical course
  - 7-14 days after start/severity increases
  - resolves during 2 wk rest
  - recurs, severity lessens
- *Clinical findings normal*
  - single report of “bullous mucositis”(?)



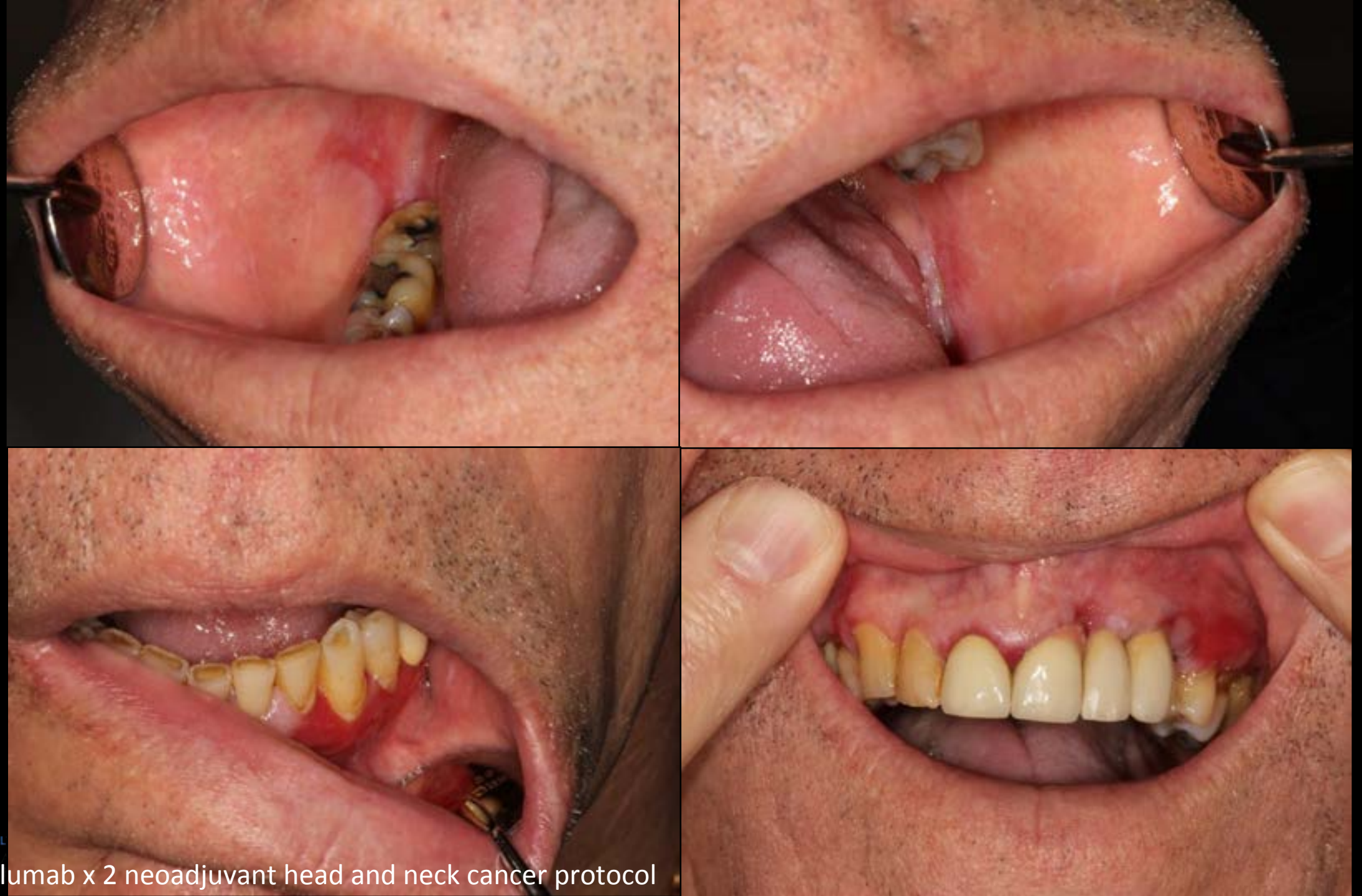
Kollmannsberger et al. Oncologist 2011;16:543-53; Mignogna M, et al. Ann Phamacother 2009;43:546-7

Immunotherapy-associated oral AEs

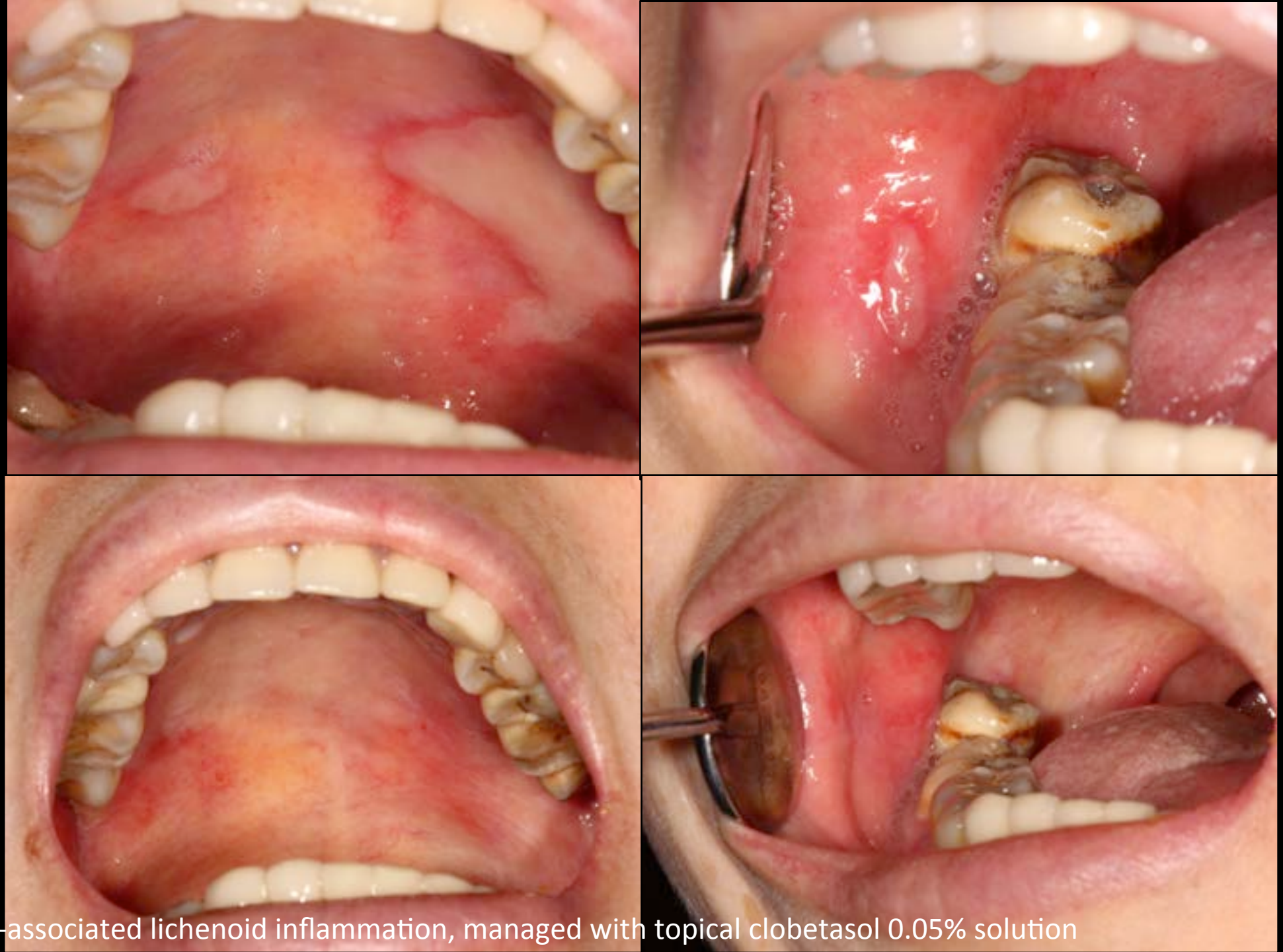
- Immune checkpoint inhibitors
  - block CTLA-4, PD-1/PD-L1; T cell activation
  - ipilimumab, nivolumab, pembrolizumab
- Clinical features
  - lichenoid inflammation, (bullous pemphigoid)
    - ~3 months mean onset (cutaneous); highly variable, case reports/series, multisystem possible
  - sicca syndrome (n=4, Hopkins, abrupt onset of severe hypofunction, timeframe variable)
  - GVHD after alloHSCT (relapse), potentially severe/ refractory
    - acute, overlap, chronic forms
  - combination therapy w/ higher rates
- Management
  - lichenoid – topical steroids, +/- modifications
  - sicca – palliative, sialogogues, dental
  - early recognition, referral



Curry J, et al. J Cutan Pathol 2017;44:158-76; Shi V, et al. JAMA Dermatol 2016;152:1128-36; Cappelli LC, et al. Ann Rheum Dis 2017;76:43–50; Haverkos B, et al. Blood. 2017;130:221-8; Sibaud V. Am J Clin Dermatol 2017; Sibaud V, et al. JEADV



nivolumab x 2 neoadjuvant head and neck cancer protocol



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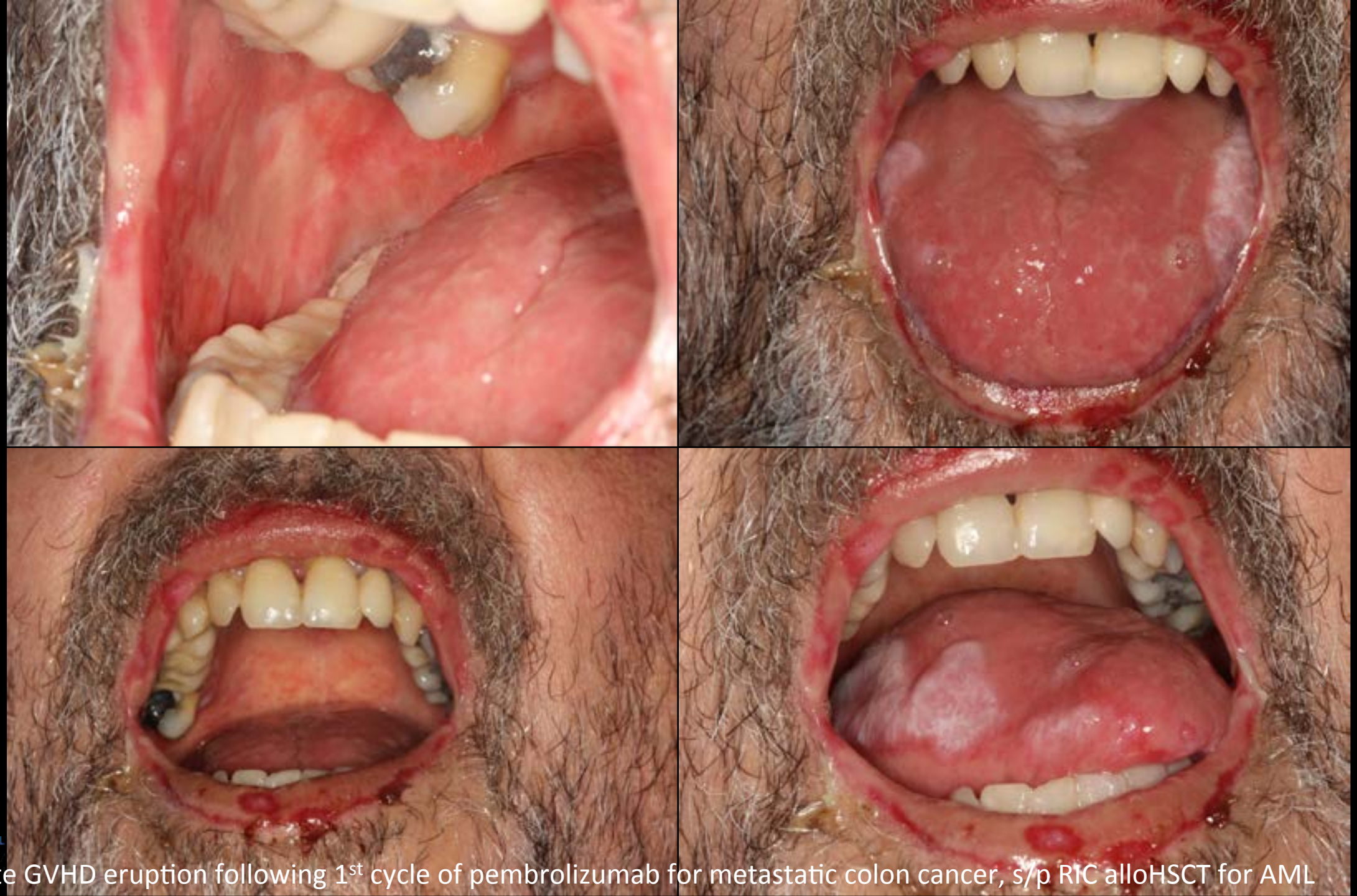
nivolumab-associated lichenoid inflammation, managed with topical clobetasol 0.05% solution



acute GVHD eruption following 1st cycle of pembrolizumab for metastatic colon cancer, s/p RIC alloHSCT for AML

Other reported oral toxicities

- Imatinib
  - lichenoid reactions, cheilitis, SJS
- EGF inhibitors
  - mucositis, 'which rarely includes aphthous ulcers', 'without mucosal changes'
- Vemurafenib
  - mucosal keratosis
    - symptomatic, gingiva, palate, linea alba, labial
    - regressed on discontinuation
  - SCC (lower lip, n = 1)
- Benign migratory glossitis/erythema migrans
  - bevacizumab, sunitinib, sorafenib (anti-VEGF?...)

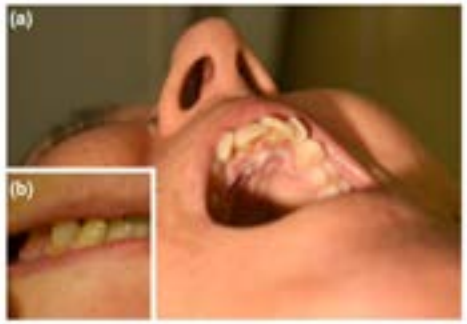


Figure 1 (a) painful erythematous hyperkerototic area set on the hard palate and (b) the lower gingiva.

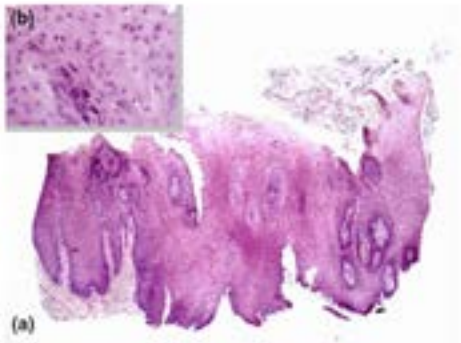
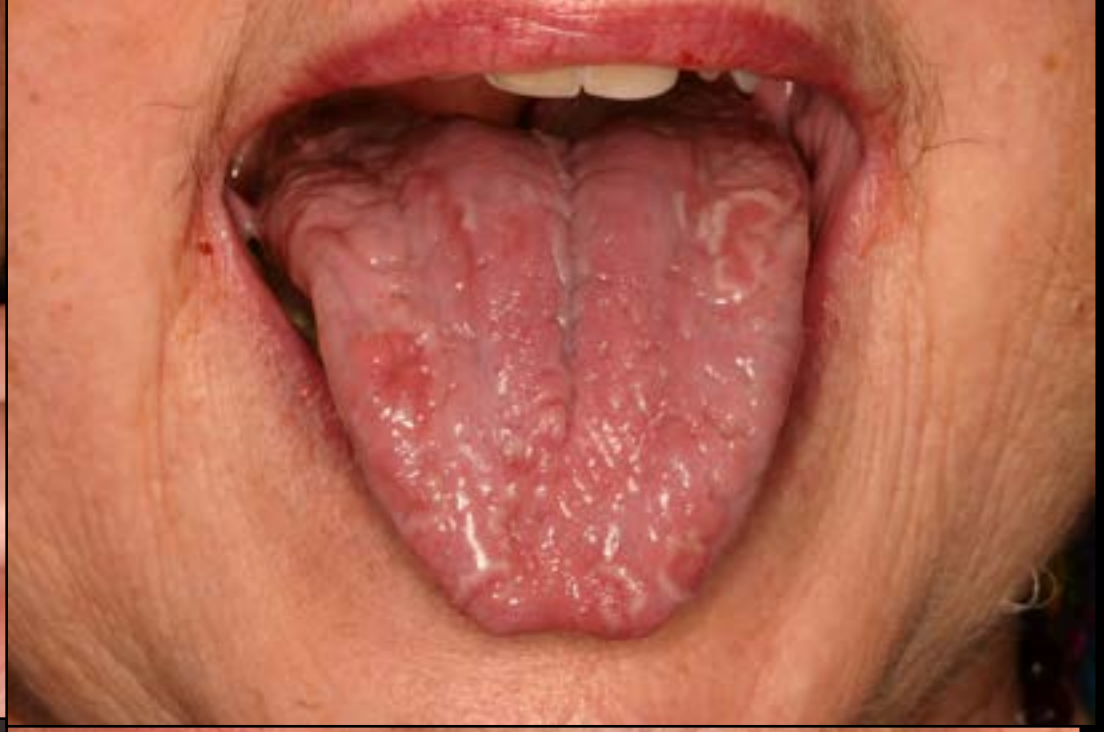
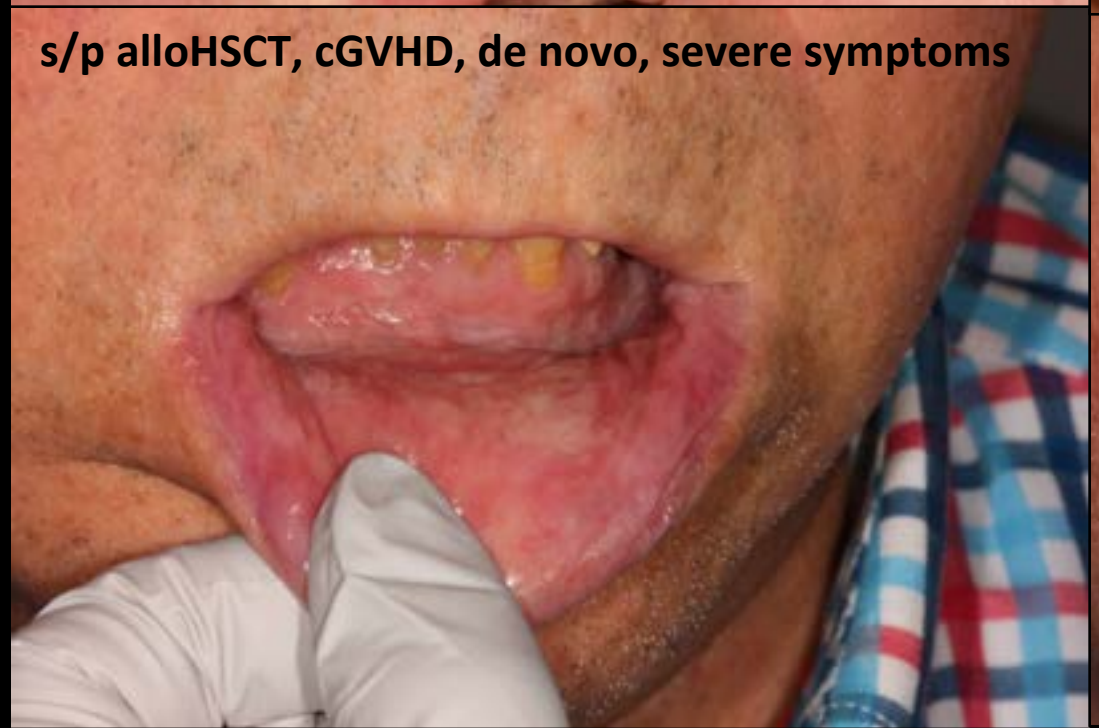


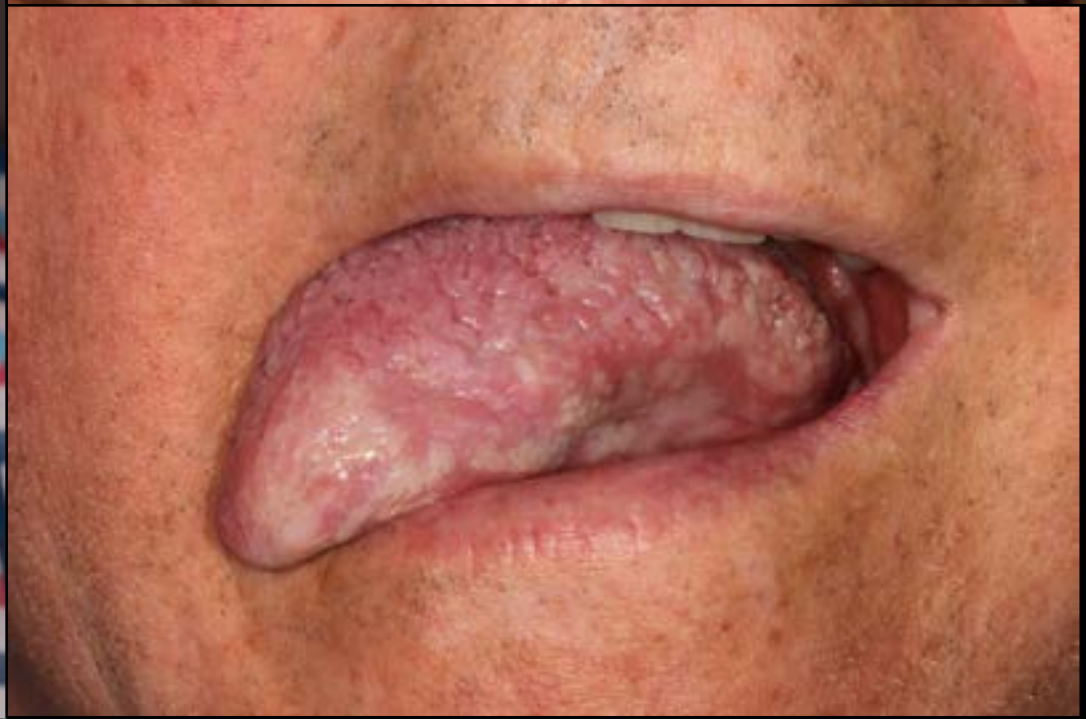
Figure 2 (a) hyperkeratotic verrucous proliferation, thickened granular zone, presence of koilocytes as well as dilated vessels in the corium (Haematoxylin and Eosin × 10). (b) koilocytes detail at higher scanning magnification (Haematoxylin and Eosin × 40).

Amitay-Laish I, et al. Dermatologic Therapy 2011;24:386-95; Pileri A, et al. JEADV 2016;30:10-25-67; Macdonald J, et al. J Am Acad Dermatol 2015;72:203-18; Hidalgo M, et al. J Clin Oncol 2001;19:3267-3279; Hubiche T, et al. Oncologist 2013;18:e16-e17; Gavrilovic I, et al. Oncologist 2012;17:274-8; Boussemart L, et al. Ann Oncol 2013;24:1691-7; Vigarios E, et al. Br J Dermatol 2015;172:1669-89


s/p alloHSCT, cGVHD, s/p IL-2, mild symptoms




s/p alloHSCT, cGVHD, de novo, severe symptoms



Summary

- Novel cancer therapies, novel oral toxicities, but mimic other conditions
- Understand risk, recognize early signs/symptoms
- Patient education, prevention, awareness
- Management depends on correct diagnosis, specialty referral
- Research opportunities abound