Management of Patients With Skin Cancers: Basal Cell Carcinoma and Melanoma

Daniel M. Siegel, MD, MS, FAAD, FACMS

SUNY Downstate Medical Center, Department of Dermatology

Brianna Hoffner, MS, ANP-BC, AOCNP®

University of Colorado Cancer Center

2016 JADPRO Live APSHO

Learning Objectives

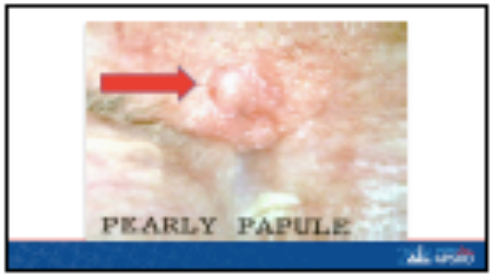
1. Demonstrate increased understanding of the MOAs of targeted and immunotherapy agents used in the treatment of advanced/metastatic melanoma and/or basal cell carcinoma, including the impact these unique agents have on patient outcomes
2. Apply new skill sets to guide and manage treatment expectations of patients and their families
3. Recognize and manage adverse events that occur with use of targeted therapies and immunotherapies in the treatment of advanced/metastatic melanoma and/or basal cell carcinoma
4. Discuss the pivotal role and necessary expertise of the AP as a vital part of the collaborative oncology team treating these skin cancers

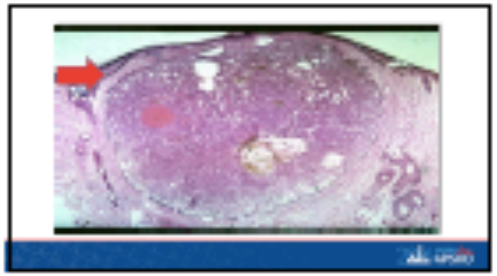
Financial Disclosure

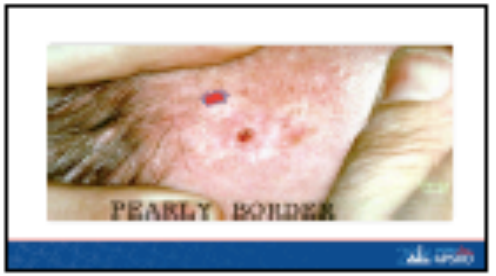
- Dr. Siegel has served on speakers bureaus and acted as an investigator for Genentech; acted as a consultant for Novartis; and participated in Castle Biosciences advisory boards.
- Ms. Hoffner has nothing to disclose.

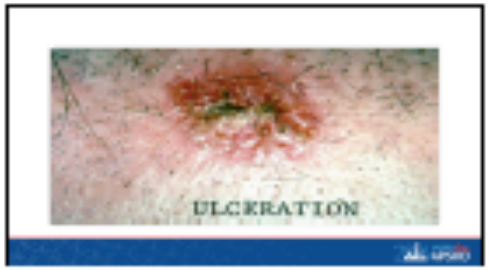
Basal Cell Carcinoma Diagnosis

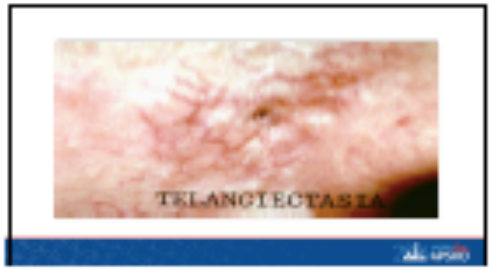
- Rodent ulcer
  - Central ulceration
  - Rolled border
  - Radial blood vessels going toward the center
- Raised hard pearly pink or gray lesion
- Nonhealing ulcer
- Nonhealing red scaly area
- Easily cut during shaving
- Why is this important? We are discussing advanced and metastatic basal cell carcinoma.
- Patients often have multiple primary tumors that may respond to therapy, which might increase the cost-benefit ratio of your approach!

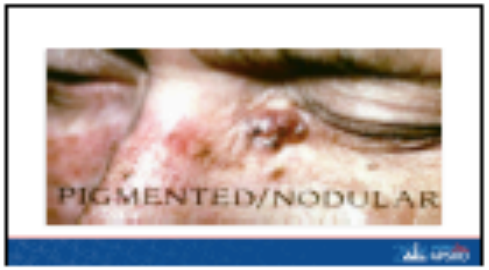


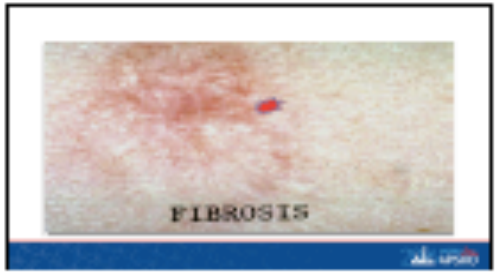


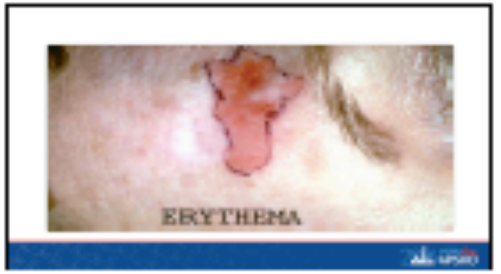












Images courtesy Dr. Daniel M. Siegel.

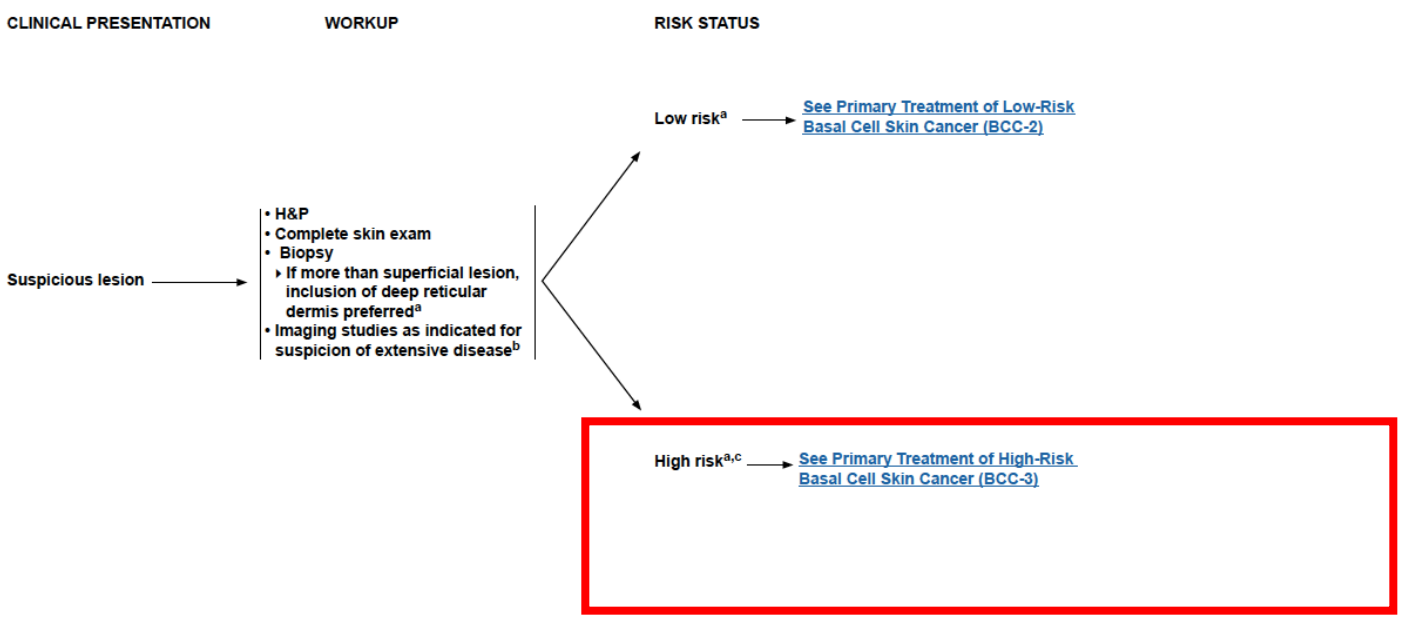
Advanced Basal Cell Carcinoma

- A new word in our vocabulary since the advent of hedgehog pathway inhibitors
- Has replaced a variety of less than scientific but nonetheless descriptive terms
- Gigundo, honker, train wreck, “crawled out from under a rock,” etc.
- All implied more than a typical day for the patient and the surgeon

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Basal Cell Skin Cancer

NCCN Guidelines Index
Basal Cell TOC
Discussion



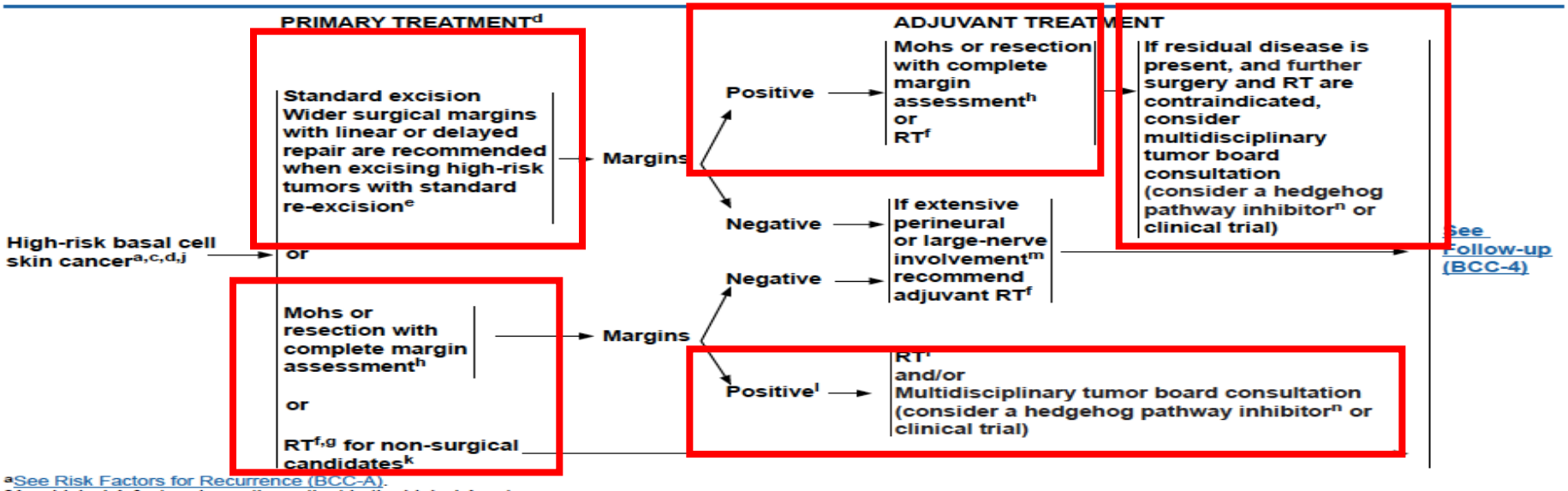
[a] See Risk Factors for Recurrence (BCC-A).
[b] Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease is suspected, MRI is preferred.
[c] Any high-risk factor places the patient in the high-risk category.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Basal Cell Skin Cancer

NCCN Guidelines Index
Basal Cell TOC
Discussion



[a] See Risk Factors for Recurrence (BCC-A).
[c] Any high-risk factor places the patient in the high-risk category.
[d] See Principles of Treatment for Basal Cell Skin Cancer (BCC-B).
[e] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[f] See Principles of Radiation Therapy for Basal Cell Skin Cancer (BCC-C).
[g] RT often reserved for patients over 60 years because of concerns about long-term sequellae.
[h] Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent section is an alternative to Mohs surgery.
[j] For complicated cases, consider multidisciplinary tumor board consultation.
[k] If surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy.
[l] Negative margins unachievable by Mohs surgery or more extensive surgical procedures.
[m] If large nerve involvement is suspected, consider MRI to evaluate extent and rule out base of skull involvement.
[n] Current FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RISK FACTORS FOR RECURRENCE

H&P	Low Risk	High Risk
Location/size	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm[1]	Area M ≥10 mm
	Area H <6 mm[1]	Area H ≥6 mm
Borders	Well defined	Poorly defined
Primary vs. Recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology		
Subtype	Nodular, superficial[2]	Aggressive growth pattern[3]
Perineural involvement	(-)	(+)

Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.
Area M = cheeks, forehead, scalp, neck, and pretibia.
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).

[1]Location independent of size may constitute high risk.
[2]Low-risk histologic subtypes include nodular, superficial, and other non-agressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
[3]Having morpheaform, basosquamous (metatypical), sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor. In some cases basosquamous (metatypical) tumors may be prognostically similar to SCC. Clinicopathologic consultation is recommended.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

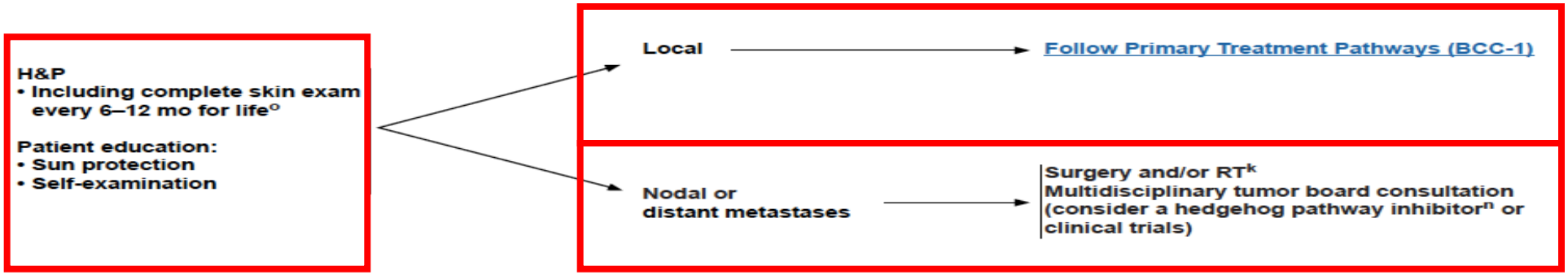
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Basal Cell Skin Cancer

NCCN Guidelines Index
Basal Cell TOC
Discussion

FOLLOW-UP

RECURRENCE



[k]If surgery and RT are contraindicated, consider multidisciplinary tumor board consultation and therapy.
[n]Current FDA-approved hedgehog pathway inhibitors include vismodegib and sonidegib.
[o]If no further skin cancers are identified in the first 2 years, then less frequent follow-up may be appropriate.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

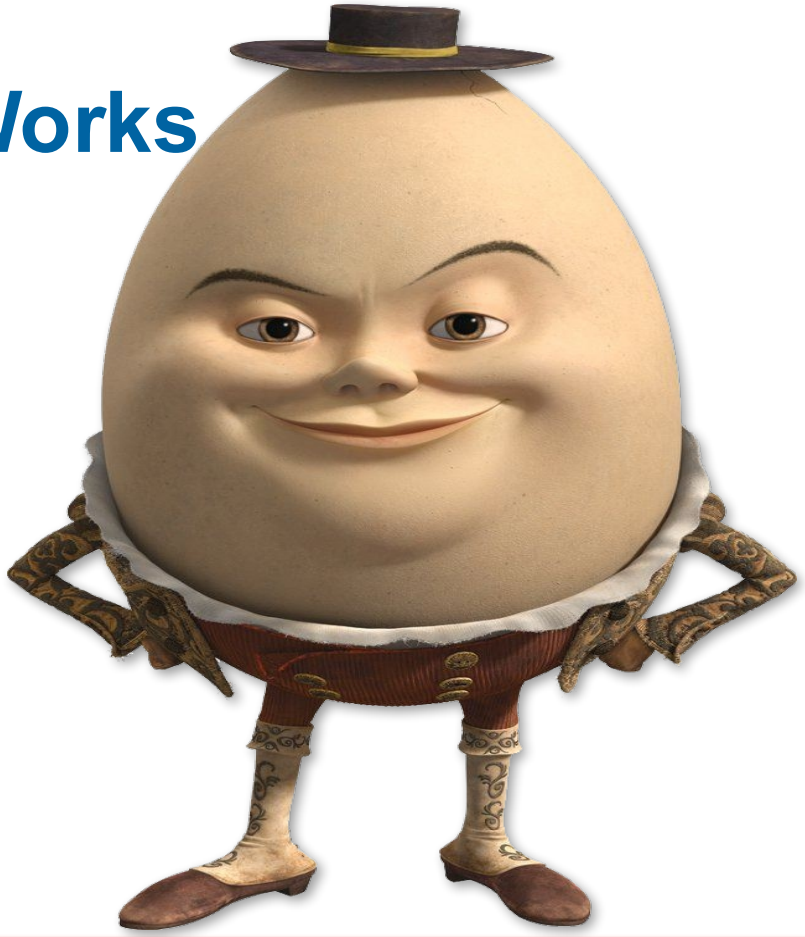
Drugs for BCC: Pre-January 30, 2012

- Systemic
  - Cisplatinum plus 5-FU, etc., mediocre
- Topical: Low-risk, superficial basal cell skin cancer
  - Topical therapies such as 5-FU, imiquimod, photodynamic therapy (e.g., amino levulinic acid [ALA], porfimer sodium), or vigorous cryotherapy may be considered, even though the cure rate may be lower
  - 84% 5-yr disease-free rate in superficial BCC

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Basal cell and squamous cell skin cancers. Version 2.2014. Available at NCCN.org

What's New?
Systemic Therapy That Works

- Factoid: There is money in bugs
- How do eggs grow bodies?



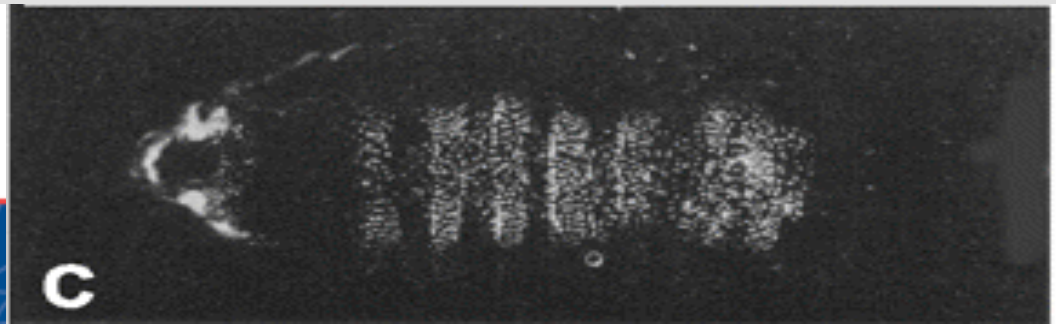
What's New? Systemic Therapy That Works

- Some hedgehog mutants result in abnormally shaped embryos that are unusually short and stubby compared to wild-type embryos
- The function of the hedgehog segment polarity gene has been studied in terms of its influence on the normally polarized distribution of larval cuticular denticles
- Not testicles—denticles
- Rough bits on the outside of the larvae

What's New? Systemic Therapy That Works

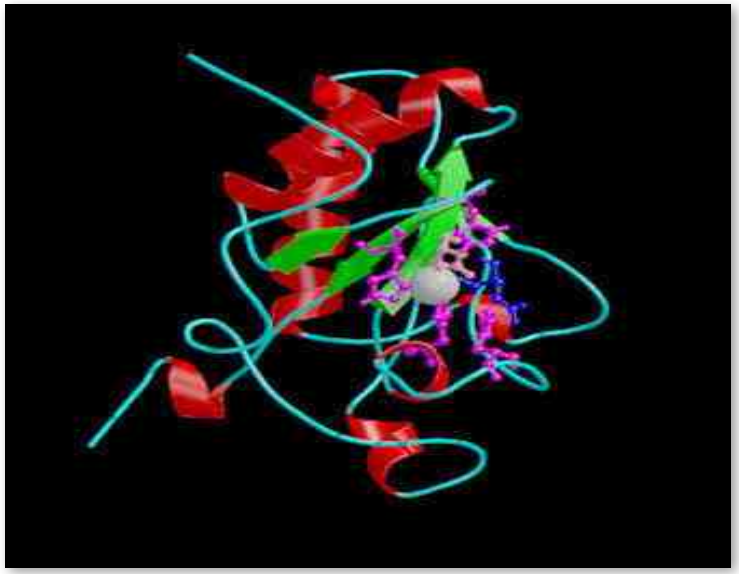
- 1970s: Nüsslein-Volhard and Wieschaus isolate mutations in genes that control development of the segmented anterior-posterior body axis of the fly
- Work results in discovery of a group of genes involved in the development of body segmentation
- 1995: They shared the Nobel Prize with Edward B. Lewis for their work studying genetic mutations in Drosophila embryogenesis
- Drosophila hedgehog (Hh) gene was identified as one of several genes important for creating the differences between the anterior and posterior parts of individual body segments


Click here to see
available babies!

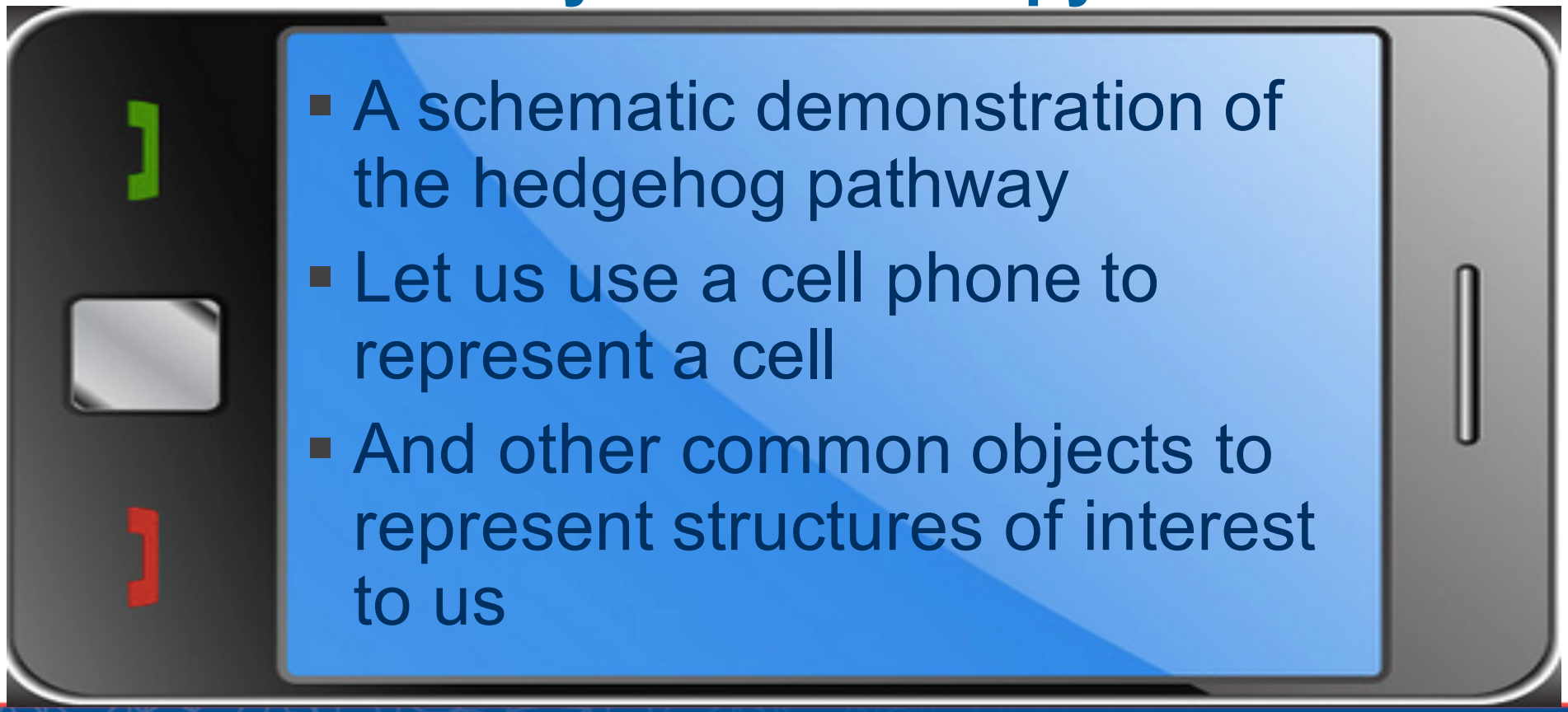


What's New? Systemic Therapy That Works

- Multiple flavors of hedgehog gene
- Of interest today is



What's New? Systemic Therapy That Works

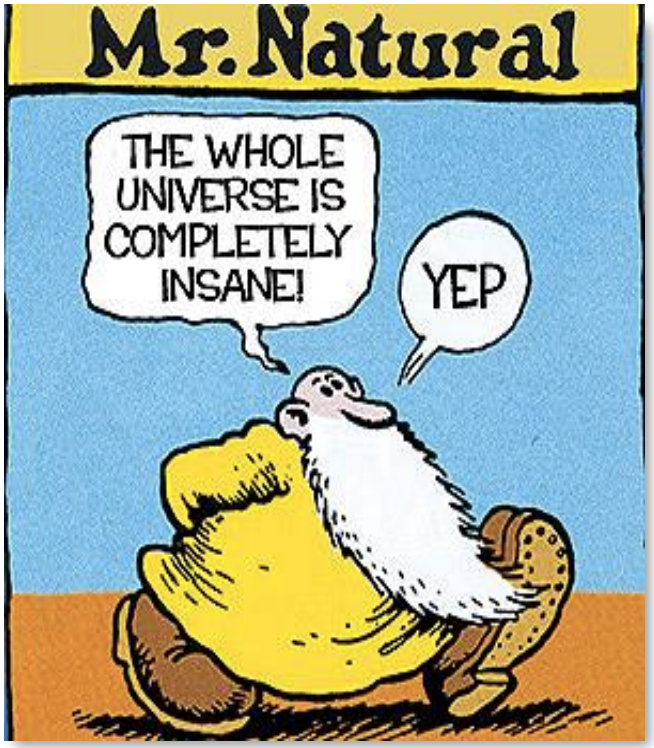


What's New? Systemic Therapy That Works

What's New? Systemic Therapy That Works

Oh Doctor, Is it Natural? No.

- …but it is modeled on nature
- Nature's own hedgehog pathway is cyclopamine (11-deoxojervine)
- Found in the California corn lily, aka, the California false hellebore and Western false hellebore
- *Veratrum californicum*
- Cyclopamine is a nasty poison that inhibits the Sonic Hedgehog pathway
- Causes birth defects such as…



Cyclopia, seen in both animals…

- http://naturespoisons.com/2014/05/06/cyclopamine-the-curious-case-of-cycloptic-sheep/

- **…and people**
- But a spark is lit
- Drum roll
- .
- .
- .
- .
- Oral hedgehog pathway inhibitors have a use when benefits outweigh the risks

mic Therapy That Works

The Clinical History

- Vismodegib was first to market January 2012.

Systemic Therapy That Works

- Phase II study of locally advanced (71) and metastatic (33) BCC
- 150 mg/day until disease progression or intolerable toxicity
- Results so good the drug makes it to market on a phase II study

The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma

Aleksandar Sekulic, M.D., Ph.D., Michael R. Migden, M.D., Anthony E. Oro, M.D., Ph.D., Luc Dirix, M.D., Ph.D., Karl D. Lewis, M.D., John D. Hainsworth, M.D., James A. Solomon, M.D., Ph.D., Simon Yoo, M.D., Sarah T. Arron, M.D., Ph.D., Philip A. Friedlander, M.D., Ph.D., Ellen Marmur, M.D., Charles M. Rudin, M.D., Ph.D., Anne Lynn S. Chang, M.D., Jennifer A. Low, M.D., Ph.D., Howard M. Mackey, Ph.D., Robert L. Yauch, Ph.D., Richard A. Graham, Ph.D., Josina C. Reddy, M.D., Ph.D., and Axel Hauschild, M.D.

N Engl J Med 2012; 366:2171-2179 | June 7, 2012 | DOI: 10.1056/NEJMoa1113713

Adverse Events: Common to the Class

Table 3. Commonly Reported Adverse Events, According to Grade.*

Event	Any Grade	Grade 1	Grade 2	Grade 3 or 4
		percentage of patients		
Muscle spasms	68	48	16	4
Alopecia	63	49	14	0
Dysgeusia	51	28	23	0
Decrease in weight	46	27	14	5
Fatigue	36	27	5	4
Nausea	29	21	7	1
Decrease in appetite	23	14	6	3
Diarrhea	22	16	5	1

Sekulic A, et al. *N Engl J Med*. 2012:366:2171-9.

More Adverse Events

- Other side effects
- Constipation, arthralgias, diarrhea, ageusia
- Amenorrhea: irreversible?
- Hyponatremia: 6 patients, 4%
- Hypokalemia: 2 patients, 1%
- Azotemia: 3 patients, 2%

Sekulic A, et al. *N Engl J Med* 2012:366:2171-9.

Management

- Spasms (Cramping, “pulls”, twitches), most common
  - Pickle juice
  - Massage
  - Valium
  - Cyclobenzaprine (Flexeril)
- Drug holidays: One-month treatment breaks mitigate and increase tolerability

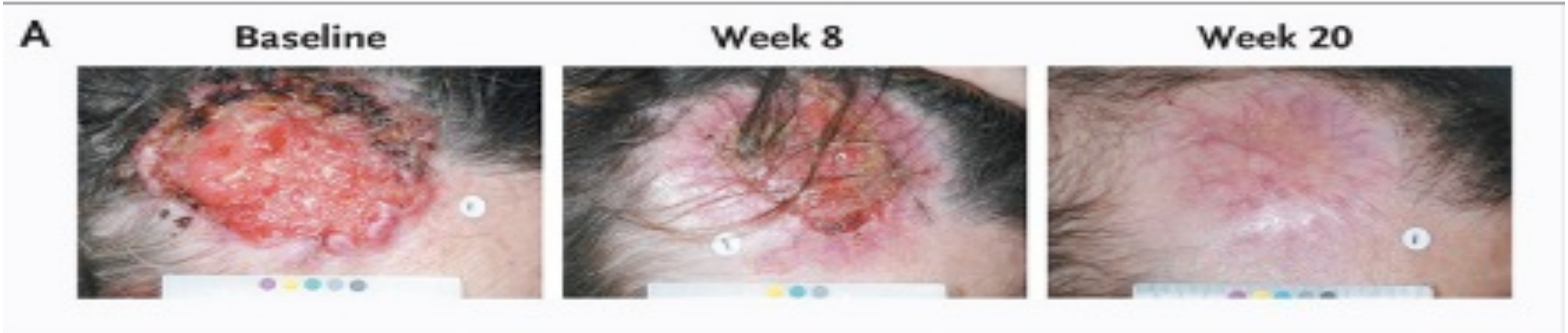
Sekulic A, et al. *N Engl J Med* 2012:366:2171-9.

Management

- No specific labs to follow
- Tell your patient if they get diarrhea or vomiting outside of what they might get for a typical bad meal or “bug,” let the provider know they might want to check electrolytes and BUN

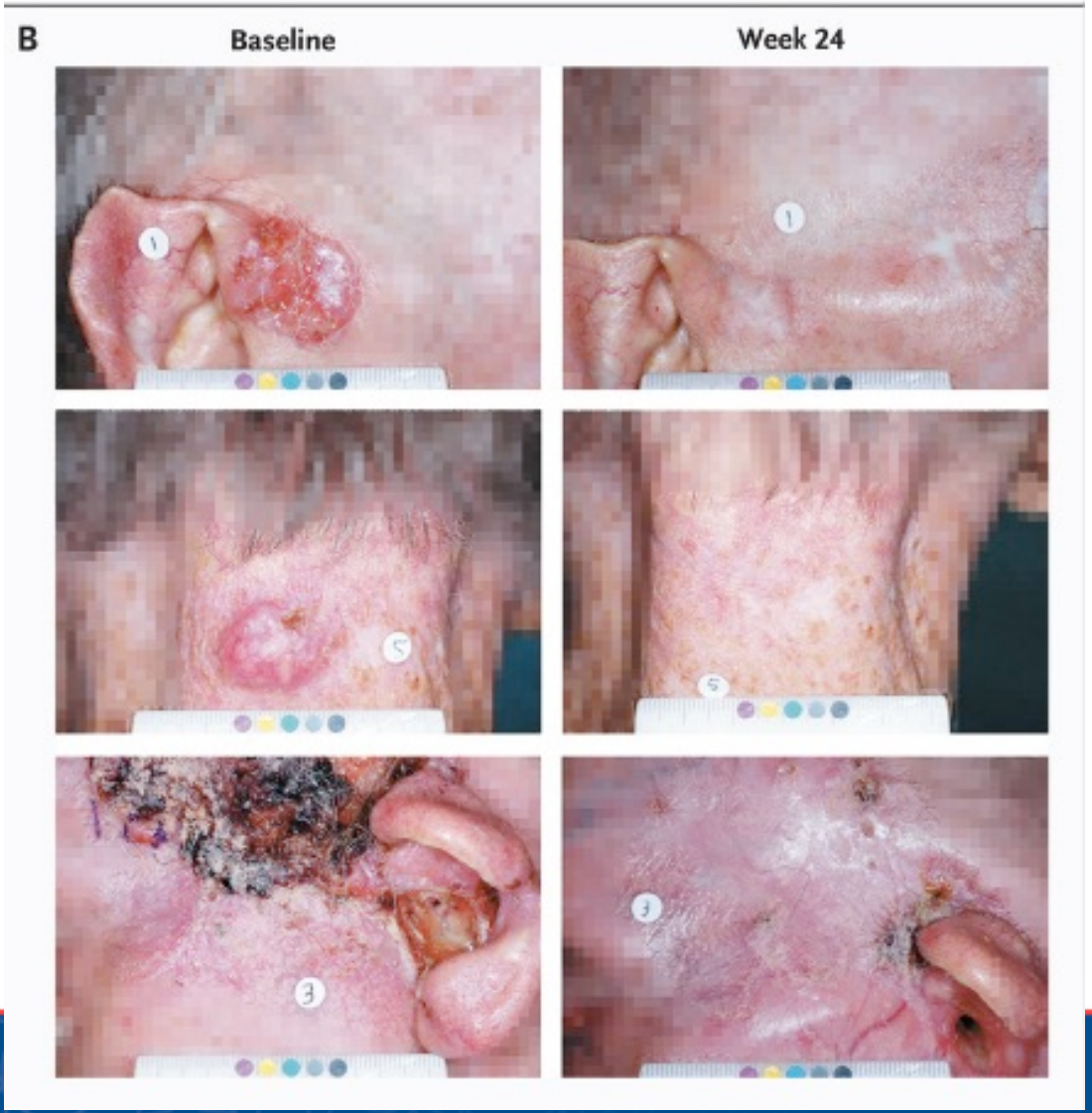
Sekulic A, et al. *N Engl J Med* 2012:366:2171-9.

Does it Work?



Sekulic A, et al. *N Engl J Med* 2012:366:2171-9.

Does it Work?



Sekulic A, et al. *N Engl J Med*. 2012:366:2171-9.

The Clinical History

- Vismodegib was first to market in January 2012
- Sonedegib came next in July 2015

Other Hh Inhibitors

- But others are in development and coming
  - **BMS-833923:** Currently being characterized in a phase 1b clinical trial in combination with dasatinib in CML patients
  - **PF-04449913; glasdegib:** Phase II for acute myeloid leukemia
  - **LY2940680; taladegib:** Phase I/II small cell lung cancer; phase I ovarian cancer and solid tumors; preclinical basal cell cancer

http://adisinsight.springer.com/

What's Gnu?

ASCO 2016: Let MIKIE Do it!

- **A randomized, double-blinded, regimen-controlled, phase II study to assess the efficacy and safety of two different vismodegib (V) regimens in patients with multiple BCCs**
- Regimen A: V 150 mg/d × 12 wk, then 3 alternating courses of placebo (P) × 8 wk followed by V × 12 wk
- Regimen B V 150 mg/d × 24 wk, then 3 alternating courses of P × 8 wk followed by V × 8 wk
- Primary objective was % reduction from baseline (BL) in number of BCCs at wk 73 (end of treatment)

Rogers G, et al. ASCO 2016, Abstract 9509.

ASCO 2016: Let MIKIE do it!

Conclusions

- Both treatment regimens were efficacious, with treatment interruptions not appearing to affect efficacy in either regimen
- Regimen A was associated with numerically better outcomes in terms of efficacy and discontinuation rate
- The safety profiles of both regimens were similar and consistent with previous clinical experience

Rogers G, et al. ASCO 2016, Abstract 9509.

ASCO 2016: STEVIE Is a Wonder!

- **Vismodegib, a hedgehog pathway inhibitor, in advanced basal cell carcinoma: STEVIE study primary analysis in 1215 patients**
- Open-label study focusing on safety of V in pts with aBCC in a real-world setting
- Adult pts (laBCC, mBCC) received oral VISMO 150 mg QD until progressive disease, unacceptable toxicity, or withdrawal
- Primary objective is safety; pts are followed for 12 months after last dose of VISMO; secondary objectives include efficacy and quality of life
- 1215 pts (laBCC, n = 1119; mBCC, n = 96) at 165 sites in 36 countries
- Median (range) age was 72.0 (18.0-101.0) years
- At the time of analysis, 375 (31%) patients remained on study
- Median (range) treatment duration was 8.6 (0-44) months

Hansson J, et al. ASCO 2016, Abstract 9532.

ASCO 2016: STEVIE Is a Wonder!

Conclusions

- The primary analysis of STEVIE, the largest ever clinical trial in pts with aBCC, confirms the previously observed safety profile and high response rates with VISMO, including many complete responses as well as durable responses

Hansson J, et al. ASCO 2016, Abstract 9532.

More at ASCO

- **Deep sequencing of metastatic cutaneous basal cell and squamous cell carcinomas to reveal distinctive genomic profiles and new routes to targeted therapies**
- Both mcBCC and mcSCC had high mutational load, high TP53 mutation frequency, similar mean genetic alterations (GA) and clincially relevant genetic alterations per sample and UV light associated DNA damage signals in all cases indicating possible benefit for immunotherapies
- mcSCC featured more cell-cycle dysregulations (CDKN2A loss) and NOTCH1 GA
- mcBCC had more sHH pathway alterations including PTCH1 primary GA and SMO GA associated with vismodegib resistance

Ross JS, et al. ASCO 2016, Abstract 9522.

More at ASCO

- **Efficacy and safety of sonidegib in patients (pts) with locally advanced (la) or metastatic (m) basal cell carcinoma (BCC): BOLT 30-month analysis**
- Sonidegib 200 mg was approved for use in pts with advanced BCC (aBCC; laBCC + mBCC) or laBCC not amenable to surgery/radiotherapy based on results from BOLT (NCT01327053); this is updated 30-month data
- Patients with laBCC or mBCC received sonidegib 200 or 800 mg daily
- Median duration of exposure was 11.0 mo (200 mg) and 6.6 mo (800 mg)
- laBCC ORRs were 56% (200 mg) and 45% (800 mg)
- Similar in pts with aggressive vs nonaggressive BCCs

Dummer R, et al. ASCO 2016, Abstract 9538.

More at ASCO

- Sonidegib 200 mg continued to have a more favorable safety profile than 800 mg, with fewer grade 3/4 adverse events (AEs; 43% vs 64%) and discontinuations due to AEs (30% vs 40%)
- The most common AEs (any grade) were muscle spasms (200/800 mg, 54%/69%), alopecia (49%/58%), and dysgeusia (44%/60%)
- Conclusions
  - Durable responses and long-term safety were demonstrated with sonidegib in the BOLT 30-month analysis

Dummer R, et al. ASCO 2016, Abstract 9538.

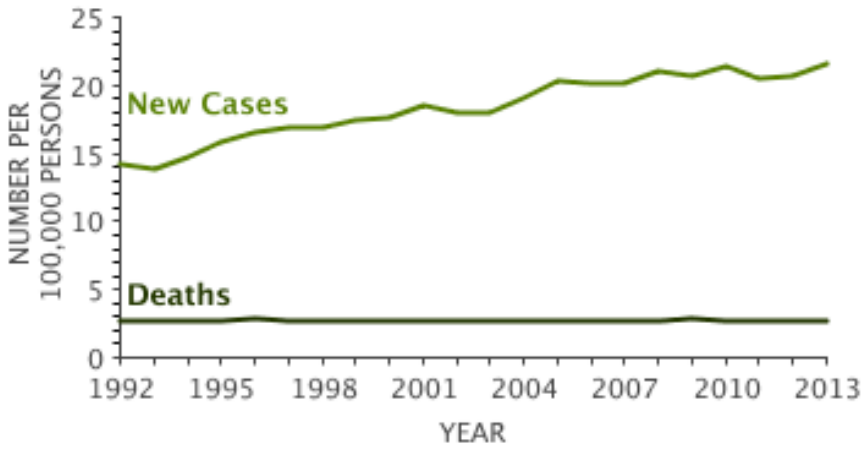
More at ASCO

- **Resistances to vismodegibs in a French case series of 207 patients with locally advanced basal cell carcinoma**
- 10 centers
- 4.7% (10) had primary resistance; 8.7% (18) developed secondary resistance and 9.2% (19) had stable disease

Basset-Seguin N, et al. ASCO 2016, Abstract 9562.

Melanoma Rising Incidence

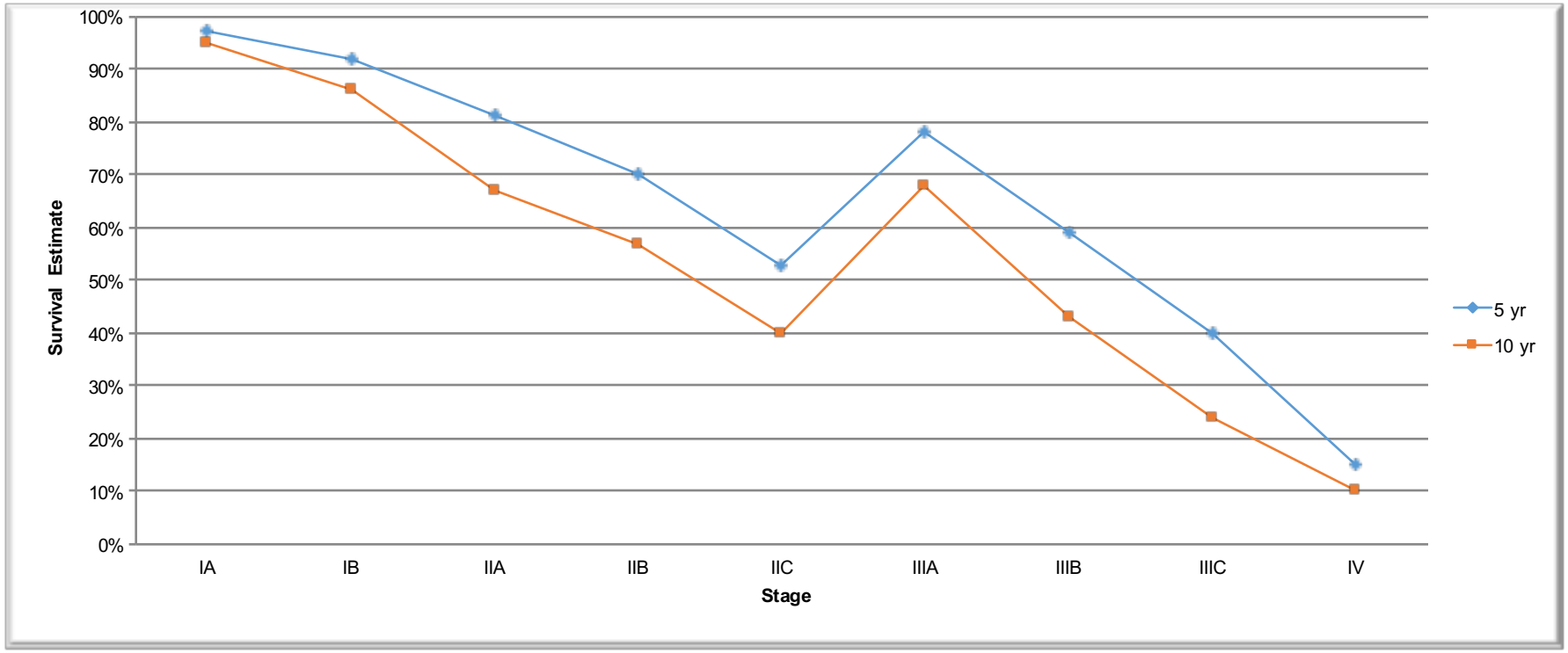
Estimated New Cases in 2016	76,380
% of All New Cancer Cases	4.5%
Estimated Deaths in 2016	10,130
% of All Cancer Deaths	1.7%



Percent Surviving 5 Years
91.5%
2006-2012

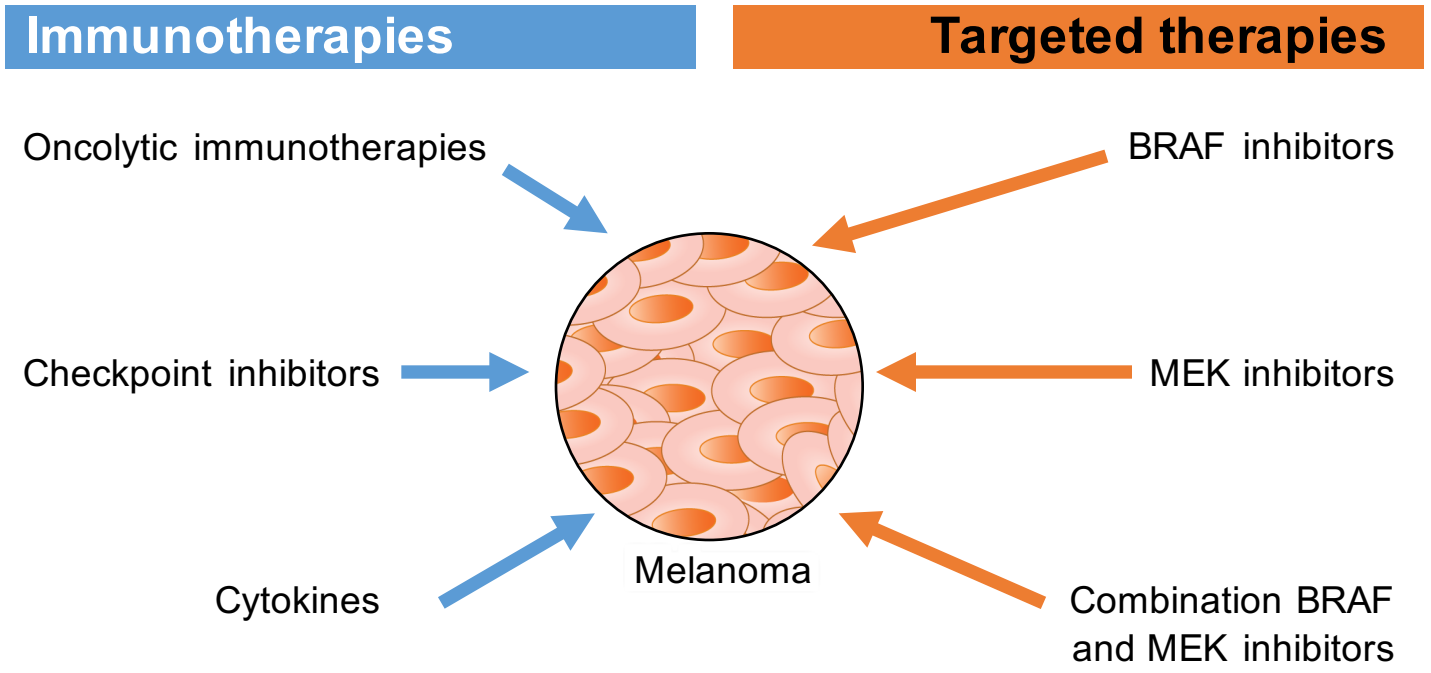
SEER Stat Fact Sheets: Melanoma of the Skin. http//seer.cancer.gov.

Survival by Stage



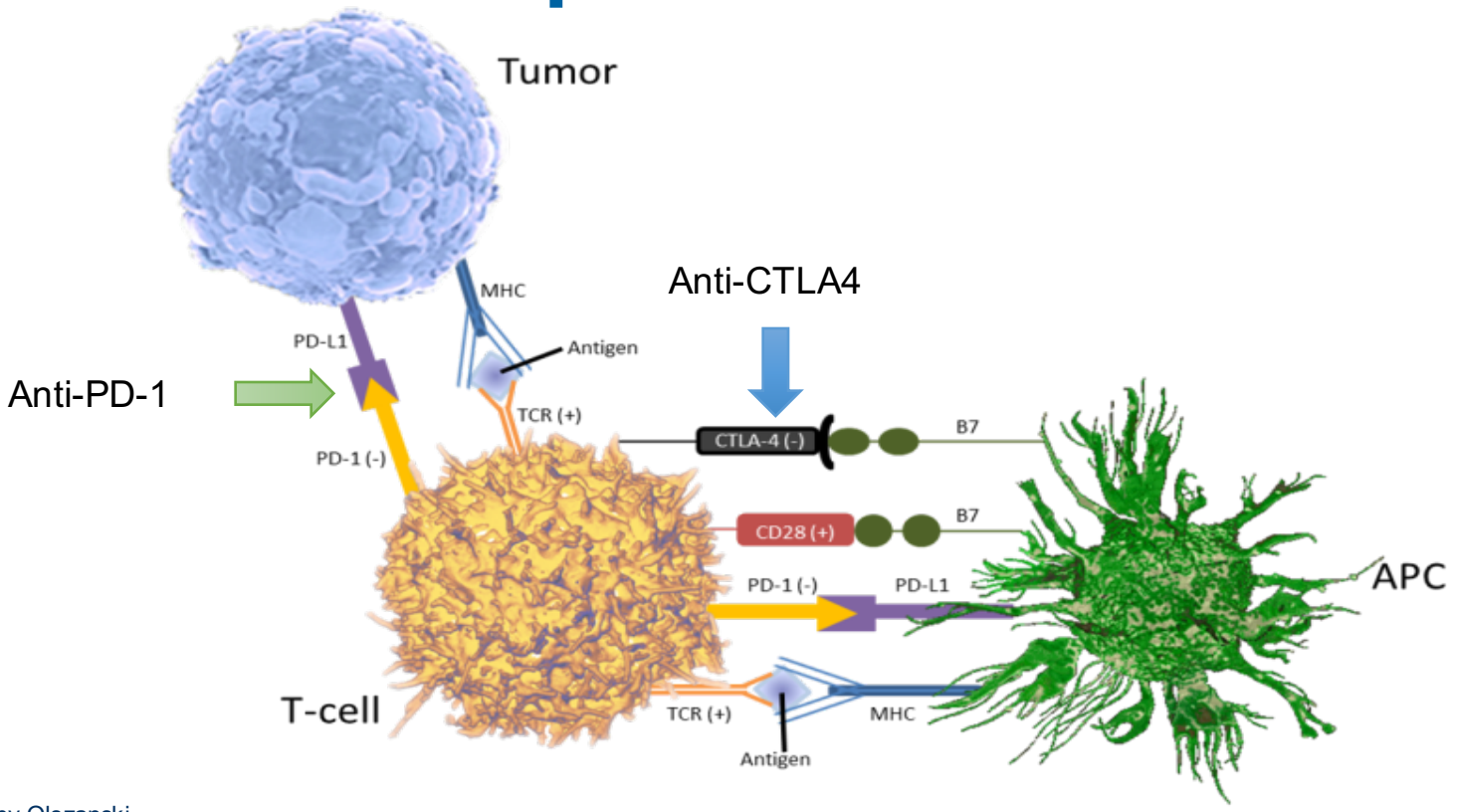
Graph courtesy Anthony Olszanski.

Treatment Targets in Melanoma

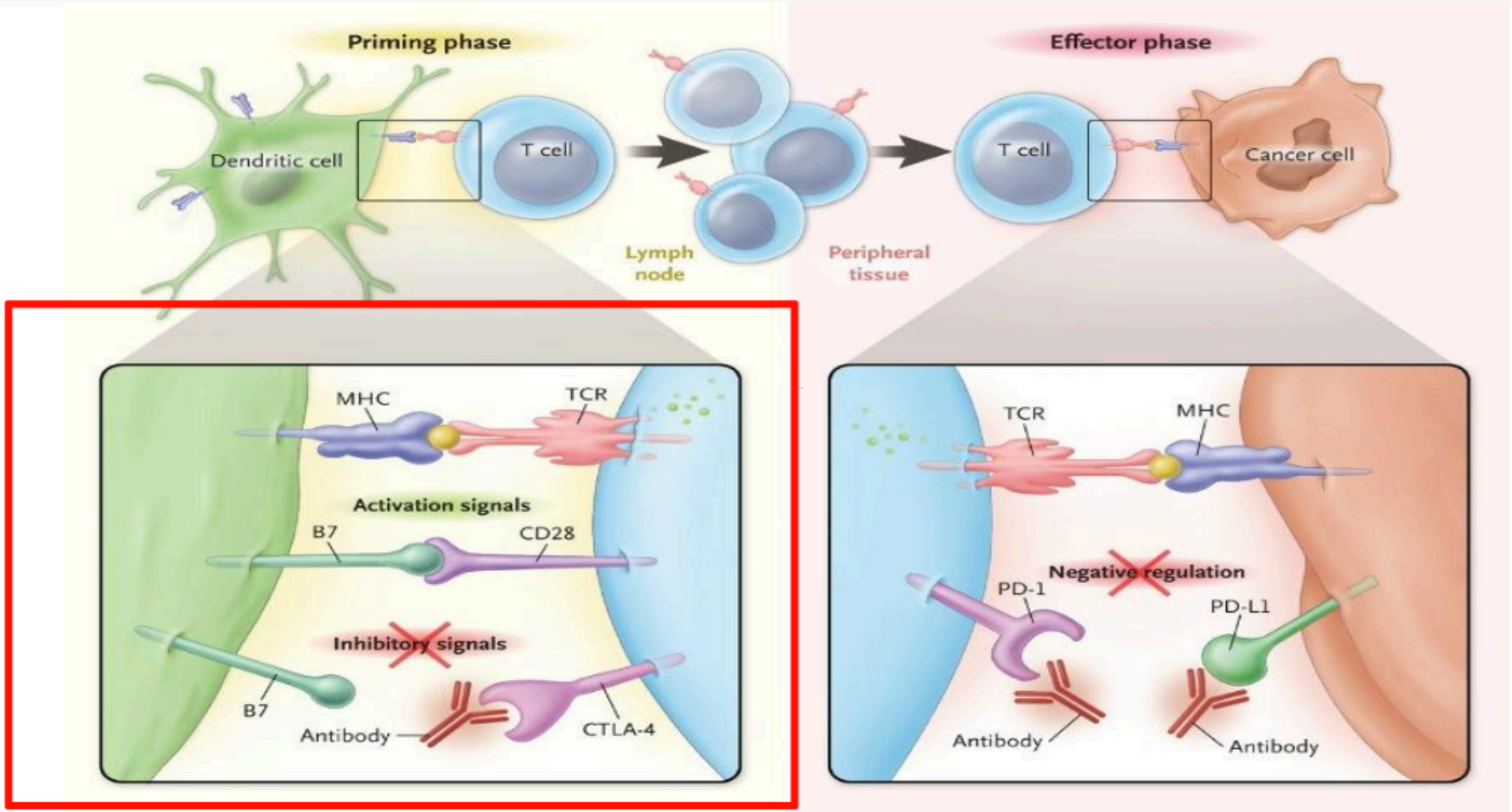


Batus M, et al. *Am J Clin Dermatol.* 2013;14:179-194.

Immune Checkpoints in Melanoma



Graphic courtesy Anthony Olszanski



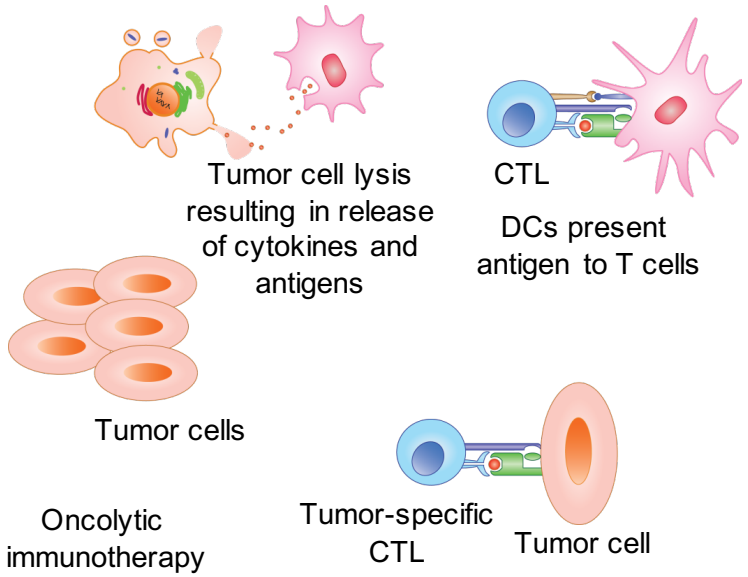
Ribas A. *N Engl J Med* 2012;366:2517-9.

TVEC: Oncolytic Immunotherapy

Definition

- Oncolytic immunotherapy involves a modified virus that has the potential to induce tumor cell lysis through selective replication and activate T cells for a possible specific, systemic immune response[1-4]
- Oncolytic immunotherapies are not vaccines, which are a form of active immunization designed to protect the body from tumor onset[5]

Proposed mode of action



CTL, cytotoxic T lymphocyte; DC, dendritic cell.

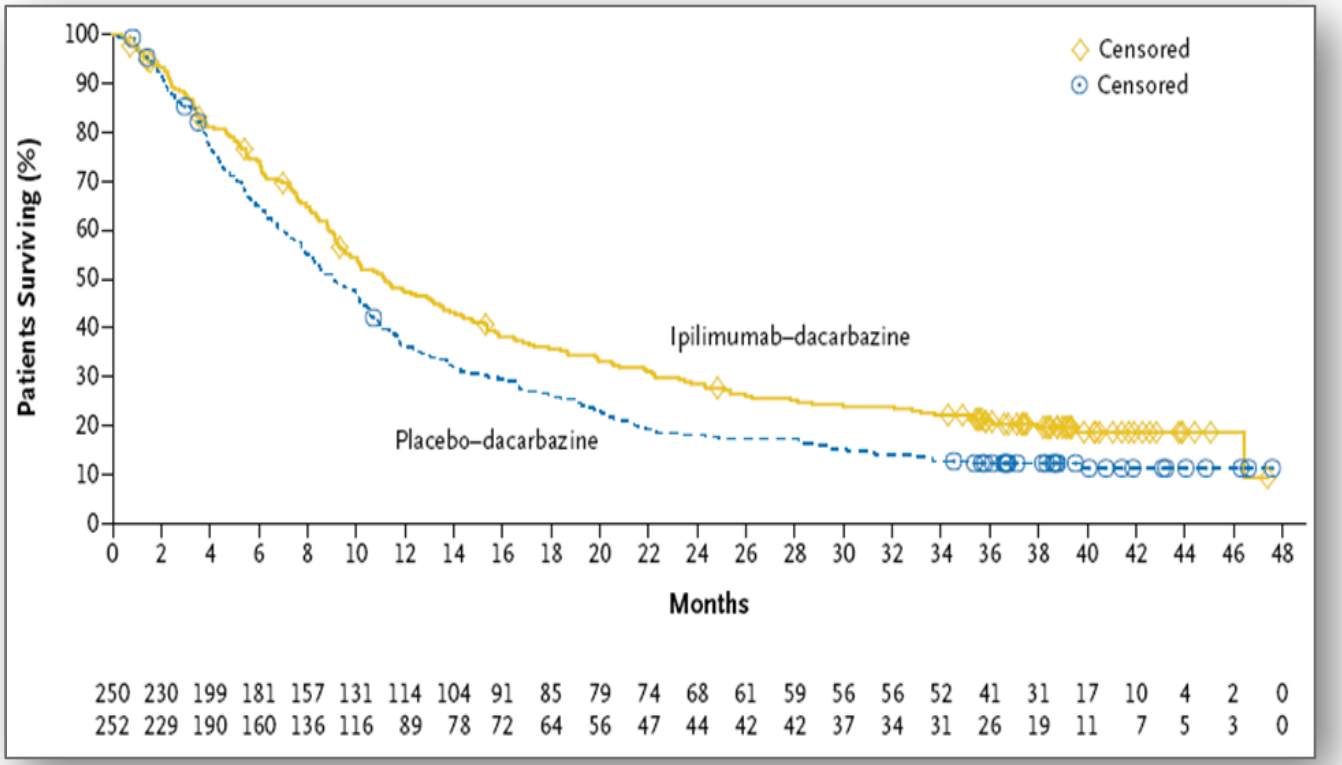
1. Pol JG, et al. *Virus Adapt Treat*. 2012;4:1-21. 2. Hawkins LK, et al. *Lancet Oncol*. 2002;3:17-26. 3. Mullen JT, et al. *Oncologist*. 2002;7:106-119. 4. Fukuhara H, et al. *Curr Cancer Drug Targets*. 2007;7:149-155. 5. Cavallo F, et al. *Cancer Immunol Immunother*. 2011;60:319-326. 6. Eager R, et al. *Mol Ther*. 2005;12:18-27.

Approved Immunotherapies

- High-dose IL-2
  - FDA approved 1992
- Ipilimumab
  - 03/2011 FDA approved for unresectable or metastatic melanoma
  - 10/2015 FDA approved in the adjuvant setting for stage III melanoma
- Pembrolizumab
  - 09/2014 FDA approved for unresectable or metastatic melanoma
- Nivolumab
  - 12/2014 FDA approved for unresectable or metastatic melanoma
- Ipilimumab + nivolumab
  - 09/2015 FDA approved for unresectable or metastatic melanoma
- T-VEC (talimogene laherparepvec)
  - 10/2015 FDA approved for unresectable melanoma

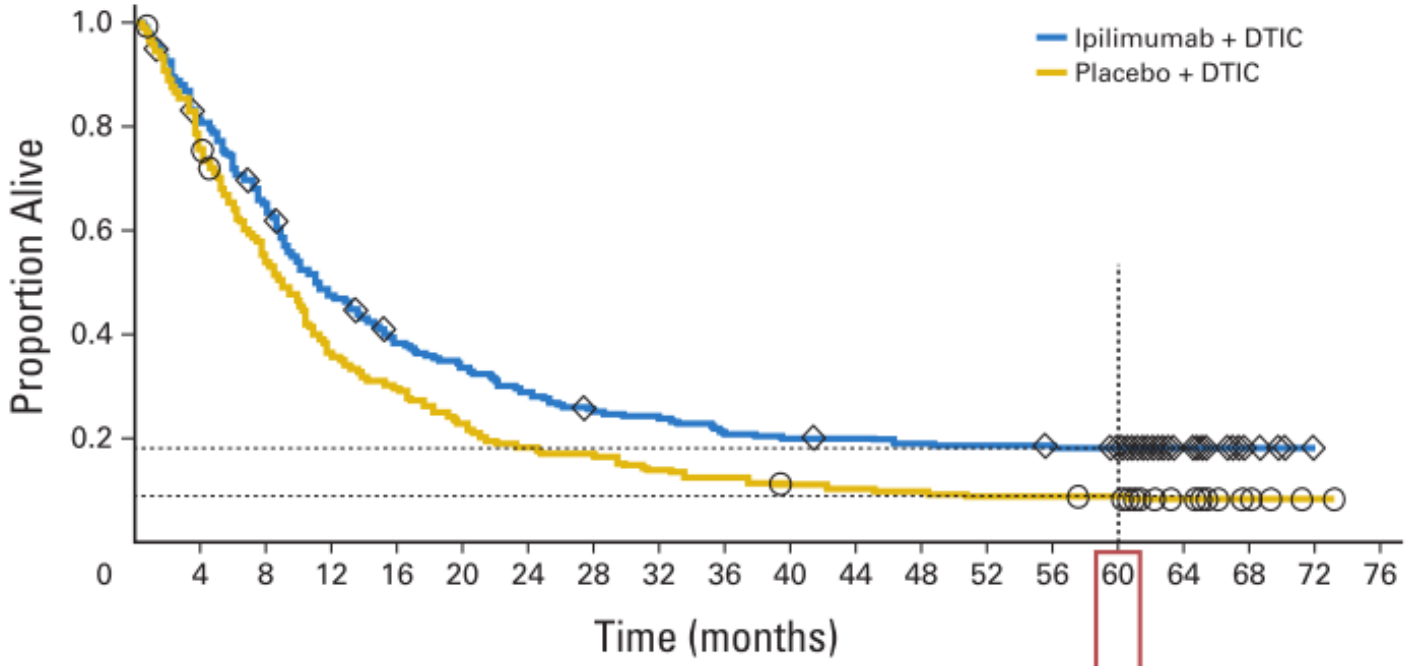
Survival in First-Line Setting

Ipilimumab Plus Dacarbazine vs. Dacarbazine: OS



Robert C, et al. *N Engl J Med* 2011;364:2517-26.

Long-Term Ipilimumab Survival

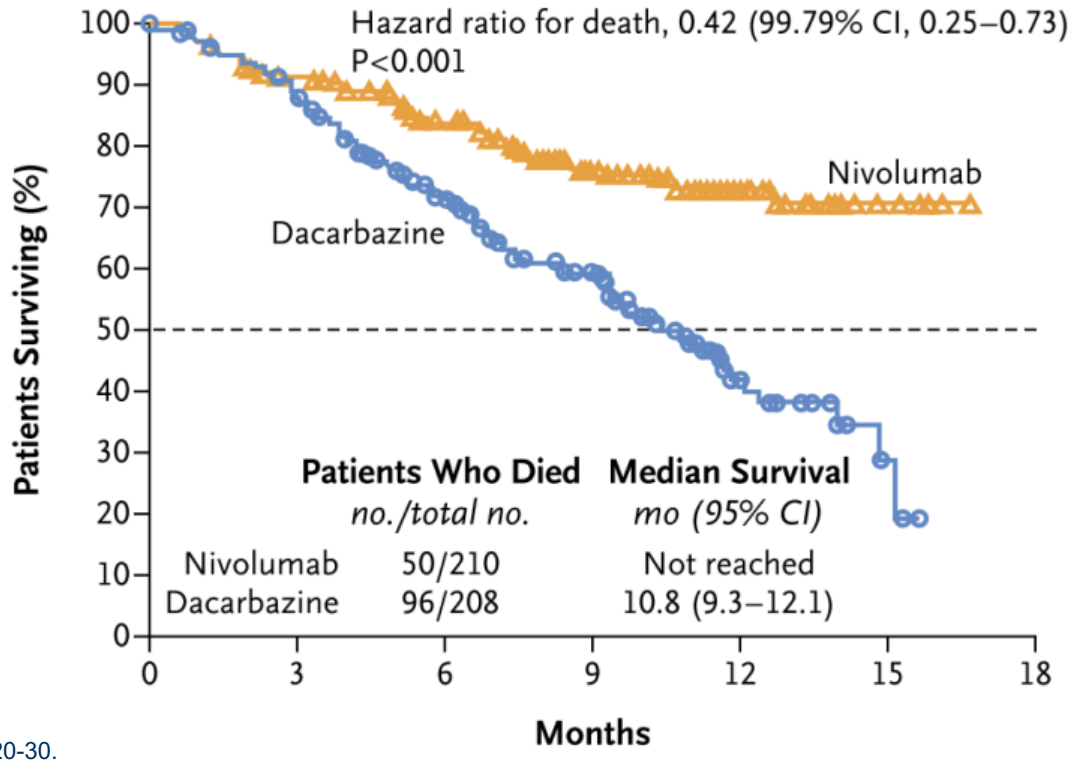


No. at risk

Ipilimumab + DTIC	250	200	159	116	92	80	69	60	57	50	47	46	44	43	42	40	17	6	0	0
Placebo + DTIC	252	192	136	90	73	56	44	42	34	30	26	24	23	21	21	20	9	4	1	0

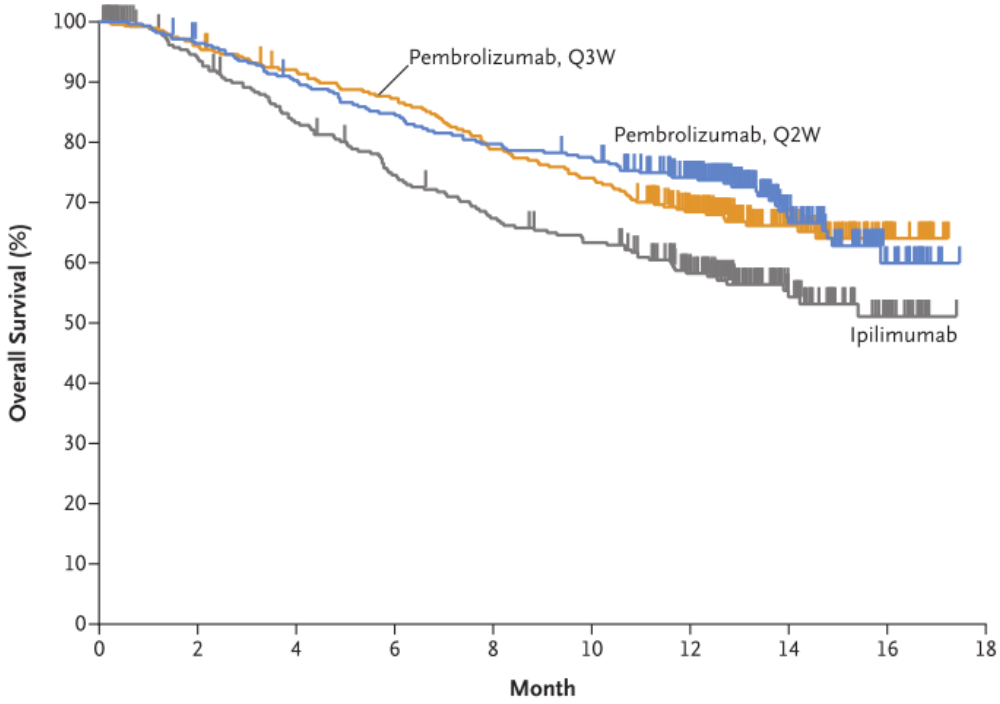
Maio M, et al. *J Clin Oncol* 2015;33:1191-6.

Nivolumab vs Dacarbazine First Line



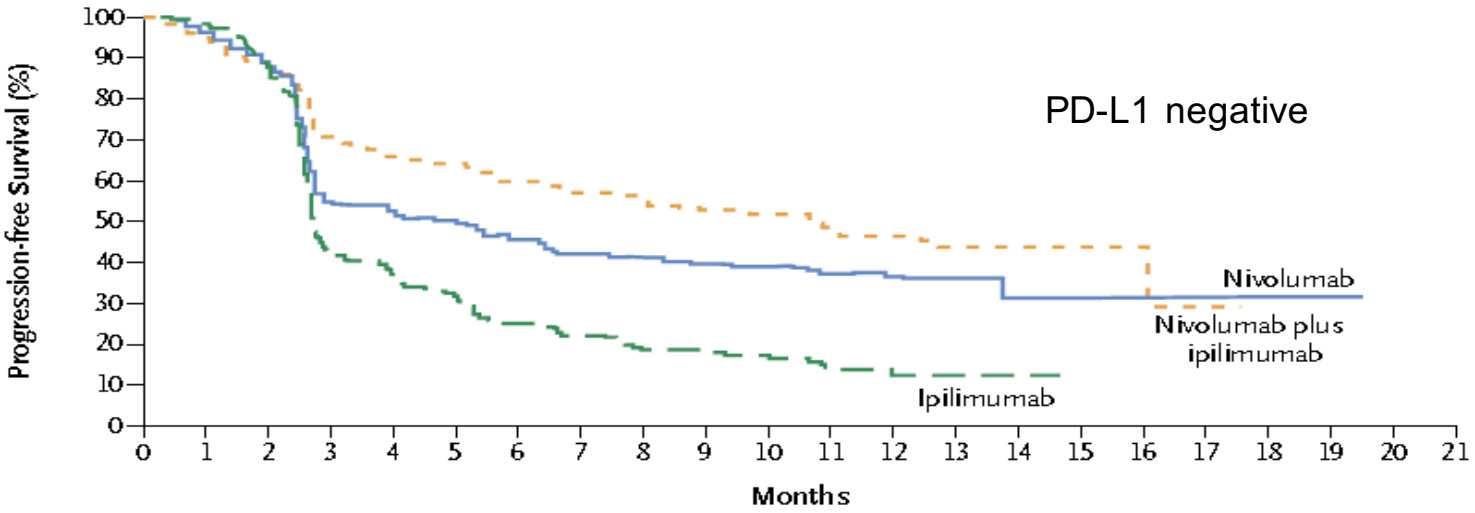
Robert C, et al. *N Engl J Med* 2015;372:320-30.

Pembrolizumab vs Ipilimumab



Robert C, et al. *N Engl J Med* 2015;25;372(26):2521-32.

CTLA4 Plus PD-1 vs Single Agent



- Combination is better than any single agent in unselected population
- PD-1 single agent may retain efficacy and decrease AEs in PD-L1 positive patients
- Nivolumab appears better than ipilimumab even in PD-L1 negative patients

Larkin J, et al. *N Engl J Med* 2015;373:23-34.

Immune-Related Adverse Events (irAEs)

- irAEs include any adverse event occurring as a result of the up-regulation of the immune system resulting in inflammation and off-target effects of the drug
- The suffix “itis” means inflammation, and irEAs can manifest as a variety of “itis’s” which most commonly include:
  - Hepatitis
  - Colitis
  - Dermatitis
  - Pruritus
  - Thyroiditis
  - Hypophysitis

Colitis

- Diarrhea and/or colitis is the most common and potentially most serious complication of anti-CTLA-4 therapy
  - Some trials report up to 31% of patients experiencing some grade of diarrhea, with 6% experiencing severe colitis[1]
  - Bowel perforation, sepsis, and death have been reported
- Diarrhea and/or colitis is less common with anti-PD1/PDL-1 therapy
  - Trials of anti-PD1 antibodies have reported the incidence of diarrhea to be approximately 17%, with just 1% experiencing grade 3/4 diarrhea[2]
- Higher incidence of more severe colitis with combination therapy
  - 12% overall, with approximately 8% grade 3 or 4[3]

1. Hodi FS, et al. *N Engl J Med* 2010;363(8):711-23; 2. Hamid O, et al. *N Engl J Med* 2013;369:134-44; Larkin *N Engl J Med* 2015;373:1270-1.

Colitis Management

- **Mild/Gr 1:** Less than 4 stools per day above baseline; manage symptomatically, i.e., bland diet, PPI, imodium/lomotil, consider delaying a dose until symptoms improve
- **Moderate/Gr 2:** Increase of 4 to 6 stools per day above baseline, consider colonoscopy; treatment with steroids should be initiated. Low-dose steroids may be sufficient 0.5 mg/kg per day of solumedrol or equivalent – but if no improvement within 24 hr would consider higher dose. Hold immunotherapy.
- **Severe/Gr 3 or higher:** Increase of 7 or more stools per day above baseline or other complications – initiate high-dose steroids 1 mg/kg of solumedrol or equivalent. Immunotherapy should be discontinued. For patients who do not respond to high doses steroids within 1 week or show clinical signs of worsening colitis, consider infliximab.
- **Prevention:** No known methods; budesonide was tested as a way to prevent immune-related colitis and a randomized phase II trial no benefit shown[1]

Weber J, et al. *Clin Cancer Res* 2009;15(17):Sept 1.

Hepatitis

- Less common than colitis, seen in 2 to 9% of patients and at least 1 death has been reported on anti-CLTA-4 therapy alone[1]
- Incidence with anti-PD1 closer to 0.5% (pembrolizumab PI); hepatotoxicity appears worse when ipilimumab combined other drugs including dacarbazine,[2] vemurafenib,[3] and anti-PD-1,[4] and should be used cautiously
- Combination therapy 15-18% overall and 6-8% grade 3-4[5]

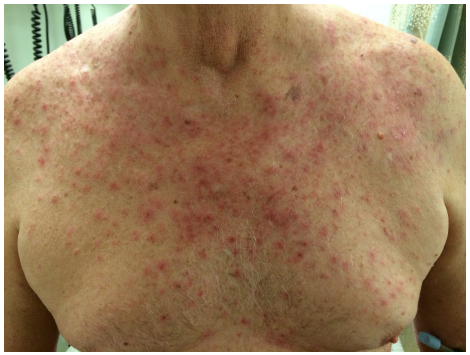
1. Hodi FS, et al. *N Engl J Med* 2010;363(8):711-23; 2. Robert C, et al. *N Engl J Med* 2011;364:2517-26; 3. Ribas A, et al. *N Engl J Med* 2013;368:1365-6; 4. Wolchok JD, et al. *N Engl J Med* 2013;369:122-33; 5. Larkin J, et al. *N Engl J Med* 2015;373:1270-1.

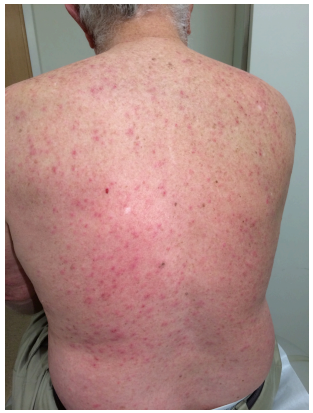
Hepatitis Management

- Rule out other causes of liver function test abnormalities
- Increase LFT monitoring until improvement
- Corticosteroid treatment should be used with grade 3 or higher elevations; prolonged taper may be required
- Mycophenolate may be useful in patients with persistent severe hepatotoxicity

Dermatitis

- Commonly seen with anti-CTLA-4 with up to 40% of patients reporting some grade of dermatologic side effect.[1] Seen in approximately 30% of patients on anti-PD1.[2] 40% of patients receiving combination therapy.[3]
  - Occasionally see severe rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis, full thickness dermal ulceration)
  - Median time to onset for moderate to severe dermatologic toxicity with anti-CTLA4 was 3 weeks[1]





Images courtesy Brianna Hoffner.

1. Hodi FS, et al. *N Engl J Med* 2010;363(8):711-23; 2. Keytruda (pembrolizumab) prescribing information; 3. Larkin J, et al. *N Engl J Med* 2015;373:1270-1.

Dermatitis Management

- Mild or moderate dermatitis (rash and pruritis) can be managed symptomatically
  - Topical non-steroidal anti-itch cream, antihistamines, oatmeal baths
- If rash persists for more than a week or interferes with ADLs would start moderate potency steroid creams (triamcinolone 0.1%) OR moderate dose parenteral steroids at 0.5 mg/kg/day of prednisone or equivalent
- Serious rashes require discontinuation of ipilimumab and management with high-dose steroids
- Rapid tapering of steroids not advised and may results in the recurrence or worsening of symptoms
- Antibiotics not helpful

Endocrinopathies

- A variety of autoimmune endocrinopathies have been reported[1] with immunotherapy and can be serious to fatal if not managed correctly.
- Hypophysitis first seen with anti-CLTA-4 therapy presented a new form of autoimmune pituitary disease.
- Hypophysitis, thyroid disease or abnormal thyroid function tests, and primary adrenal insufficiency has all been reported.
- Mechanism of injury not fully understood.
- Hypothyroidism is the most common endocrinopathy seen with anti-PD1 and occurs in approximately 8% of patients[2]
- Hypothyroidism in combination therapy occurs in approximately 15% of cases[3]

1. Corsello SM, et al. *J Clin Endocrinol Metab* 2013;98:1361-75; 2. Keytruda (pembrolizumab) prescribing information; 3. Larkin J, et al. *N Engl J Med* 2015;373:1270-1.

Endocrinopathies Symptom Surveillance

- Monitor patient for signs and symptoms associated with pituitary, thyroid, or adrenal disease
    - Often nonspecific but my include headache, fatigue, changes in mental status, abdominal pain, hypotension
- Check thyroid function tests at baseline and every 12 weeks while on treatment; TSH is the most sensitive test, but if symptoms would consider full panel including T3, T4, cortisol, and ACTH
- Time to onset may be much later: median 11 weeks with anti-CTLA-4[1] and 14 weeks with anti-PD1[2]

1. Hodi FS, et al. *N Engl J Med* 2010;363(8):711-23; 2. Keytruda (pembrolizumab) prescribing information.

Endocrinopathies Management

- Treatment of endocrinopathies requires appropriate hormone replacement, corticosteroids, and possibly stopping ipilimumab.
  - A cosyntropin stimulation test may be helpful prior to starting steroids.
  - Many endocrinopathies can be controlled and if hormone levels stable and at less than 7.5 mg of prednisone, then treatment can be continued

- Clinical Pearl: Does a pre-existing thyroid disorder put patient at higher risk of developing additional endocrinopathies? Not as far as we know.

Other IrAEs

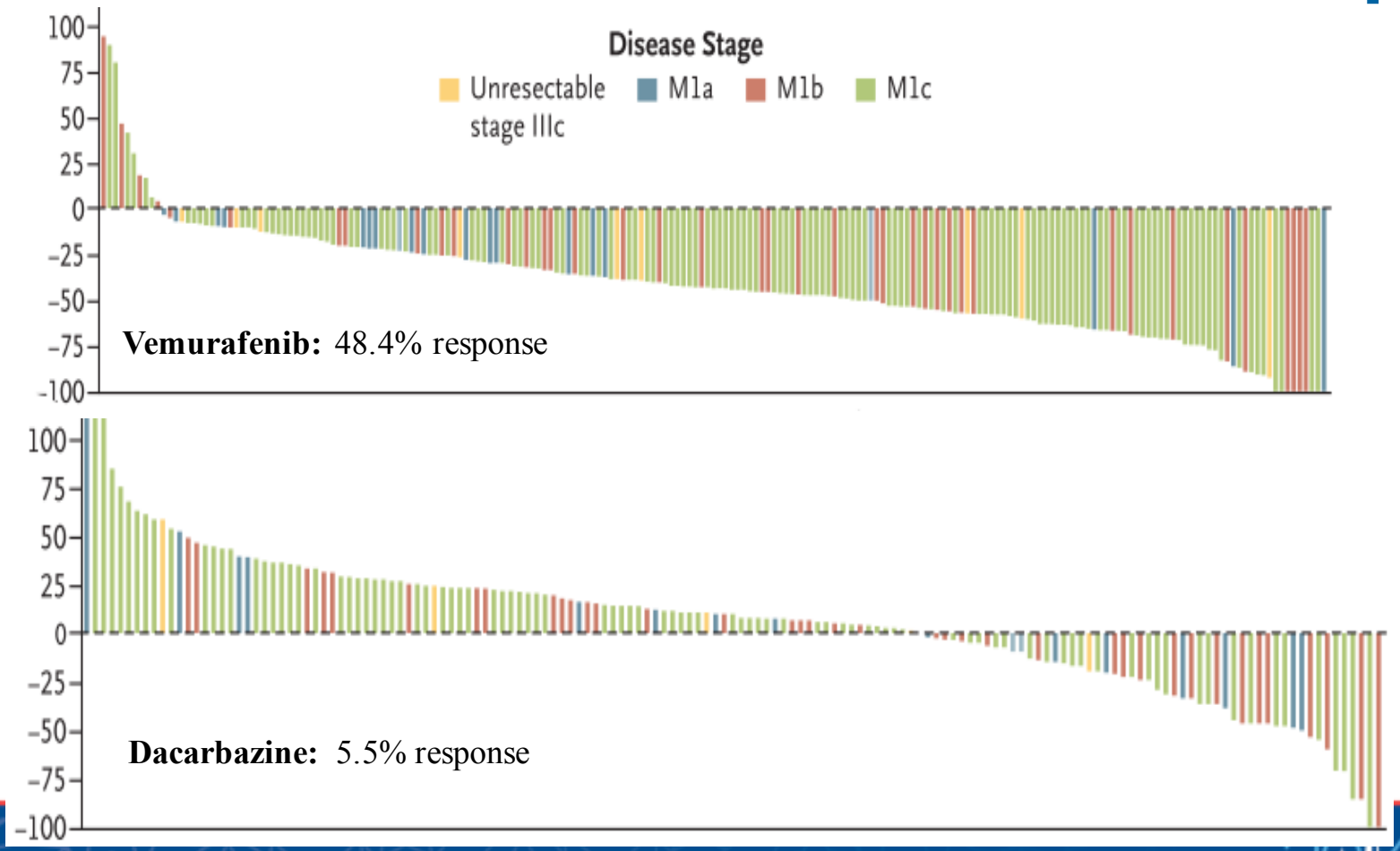
- Long list of other IMAEs
  - Ocular manifestations: conjunctivitis, uveitis, and scleritis
  - Pneumonitis
  - Neurologic complications: Guillian Barré syndrome, inflammatory myopathy, aseptic meningitis, temporal arteritis, posterior reversible encephalopathy syndrome
  - Sarcoidosis
  - Systemic vasculitis, including renal disease
  - Autoimmune pancreatitis
  - Red cell aplasia, pancytopenia, autoimmune neutropenia, acquired hemophilia A

General Guidelines for Managing irAEs

- Rule out all causes of adverse event, and if no other explanation, assume IMAE
- Consider symptomatic care when appropriate
- Consider holding or delaying a dose for mild toxicity
- Use steroids when necessary: not too early, not too late
- Moderate dose steroids for moderate toxicity, high doses for more serious toxicity; may need to add adjuvants to steroids if toxicity appear refractory, i.e., infliximab or mycophenolate
- When steroids are used for serious toxicity, taper over at least 30 days; rapid taper may result in recurrence or toxicity and may be more severe

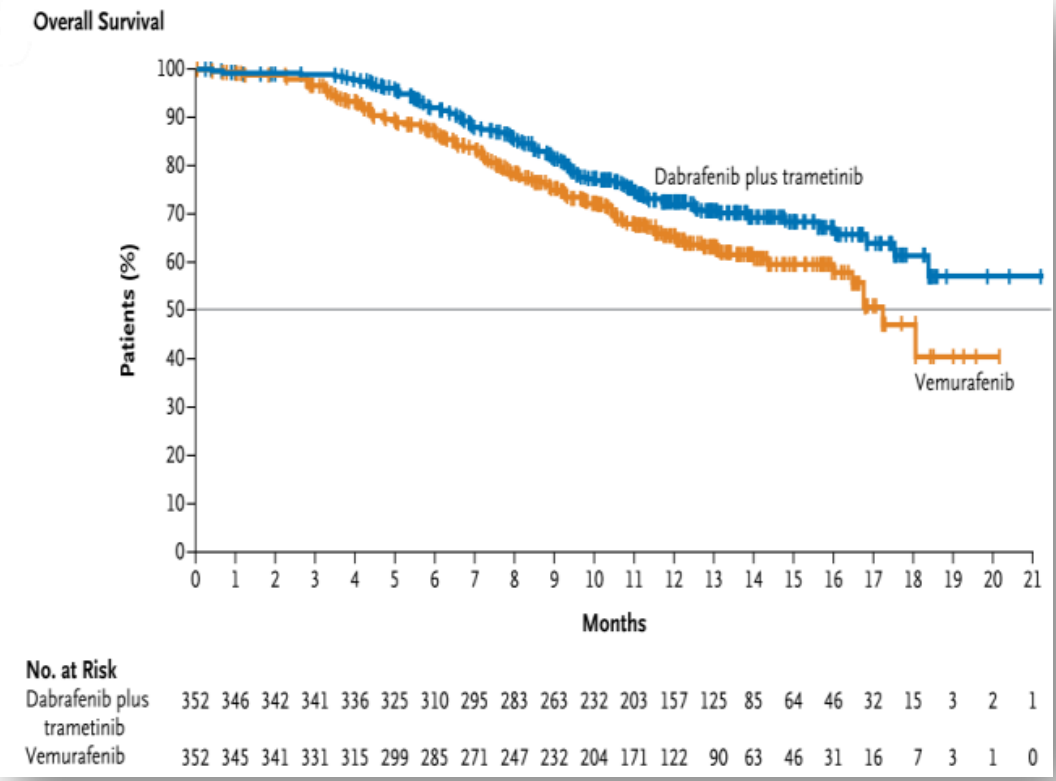
Targeted Therapies

Vemurafenib vs Dacarbazine: Best Response



Chapman PB, et al. *N Engl J Med* 2011;364:2507-16.

BRAF + MEK: Overall Survival



Overall response rate:
64% vs 51%

Duration of response:
13.8 vs 7.5 months

Robert C, et al. *N Engl J Med* 2015;372:30-9.

BRAF Mutations

- BRAF mutations found in approximately 50% of melanomas
- Portends more aggressive disease
- BRAF inhibitor therapy associated with 50% response rate and rapid response times
- Acquired resistance to BRAF therapy generally occurs at approximately 6 months
- BRAF and MEK inhibitors are effective only in patients with BRAF V600 mutations

BRAF Inhibition: Adverse Events

- Dermatologic
  - Potential for severe photosensitivity
  - Squamous cell carcinomas, keratoacanthomas
  - Rash
- Ocular
  - Uveitis
- Cardiac
  - QTc prolongation
- Hepatic
- General
  - Alopecia, arthritis, nausea, fatigue

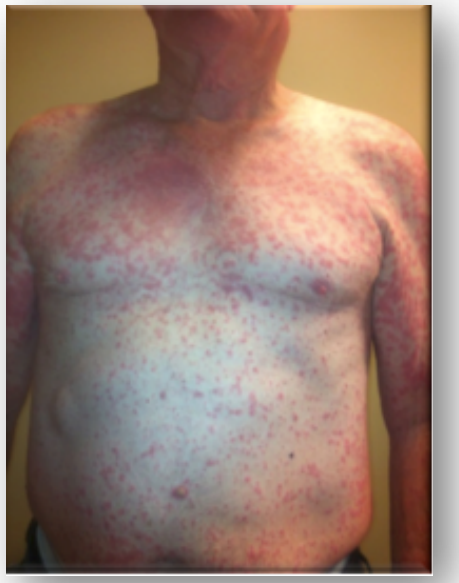


Photo courtesy of Brianna Hoffner

BRAF Inhibitors AE Management

- Dermatologic
  - Skin exam at baseline and every 2 months while on therapy
    - Cutaneous squamous cell carcinoma (SCC) is the most common grade 3 reaction but does not require a dose reduction
  - No sun exposure; use protection (avoidance, sunscreen, clothing)
- Ocular
  - Visual symptoms at each clinic visit
  - Steroid eye-drops for uveitis (ophthalmology evaluation)
- Cardiac
  - EKG at baseline, day 15, and monthly for 3 months, then every 3 months
  - Hold for QTc >500 ms or ≥60 ms above baseline (grade 3)
  - Restart at a reduced dose if QTc decreases to grade 2
- Hepatic
  - Monthly liver function tests (LFTs)
  - Hold for grade 3 LFT and dose-reduce when grade ≤2
- General
  - Nausea → anti-emetics
  - Arthralgias → NSAIDs or narcotics

MEK Inhibitors

- Lower single agent ORR ~25% (therefore, use in combination)
- Side effects similar to BRAF, but also include:
  - Ocular
    - Uveitis
    - Retinal-vein occlusion (discontinue therapy!)
    - Retinal pigment epithelial detachments
  - Cardiac
    - Cardiomyopathy
  - General
    - Peripheral edema (lymphedema, hypoalbuminemia)

MEK Inhibitors AE Management

- Ocular
  - Permanently discontinue therapy for patients with retinal vein occlusion
  - Perform ophthalmological exams any time a patient reports visual disturbances; dose-reduce for toxicities that resolve or improve
- Dermatologic
  - Dermatologic exam prior to starting therapy and every 2 months until 6 months after discontinuation of therapy
  - For grade 3 or 4 skin toxicity, hold MEK for up to 3 weeks; dose-reduce if symptoms improve
- Hepatic
  - Monitor LFTs baseline and at least monthly while on therapy; dose-reduce for toxicity
- Hematologic
  - Monitor CBC; discontinue for any hemorrhagic event
- Cardiac
  - Assess LVEF prior to initiation of therapy, 1 month after starting therapy and then at 2-3 month intervals during therapy
  - Withhold treatment for up to 4 weeks if absolute LVEF value decreases by 10% from pretreatment values and is less than the lower limit of normal.
- General
  - Diarrhea can be managed with antidiarrheal medications
  - Therapy should always be held for any intolerable grade 2 or grade 3/4 side effect; discontinue therapy for second occurrence of grade 4 side effect

BRAF + MEK

- Combination therapy with dabrafenib and trametinib approved in January 2014
- Response rates from phase I/II trial:
  - Overall response rate 76% for combination therapy vs 54% for single-agent dabrafenib
  - Median duration of response was 10.5 months in combination vs 5.6% months in dabrafenib monotherapy
- Side effects reported in phase I/II study:

Fever (71%)
Chills (58%)
Fatigue (53%)
Abdominal pain (33%)
Peripheral edema (31%)
Cough (29%)
Headache (29%)
Arthralgia (27%)
Night sweats (24%)
Decreased appetite (22%)
Constipation (22%)
Rash (45%)
Nausea (44%)
Vomiting (40%)
Diarrhea (36%)
Myalgia (22%)

Flaherty 2012.

Case #1

- 58-year-old female with IV melanoma with metastases to the liver and bone
- PMH: Hypertension, hypercholesterolemia, asthma
- PSH: Cholecystectomy
- Initiated on ipilimumab (3 mg/kg) + nivolumab (1 mg/kg)
  - C1D1: 7/1/16
  - C2D1: 7/22/16
  - C3D1: 8/19/16

Case #1 (cont)

- 8/27/16 patient presents to outside hospital complaining of fever, cough, and shortness of breath
- Vital signs: BP 125/86, HR 90, RR 22, O_2 90%, temp 100.1
- CXR: Read as RML pneumonia
- Patient initiated on Augmentin 875 mg/125 mg Q12

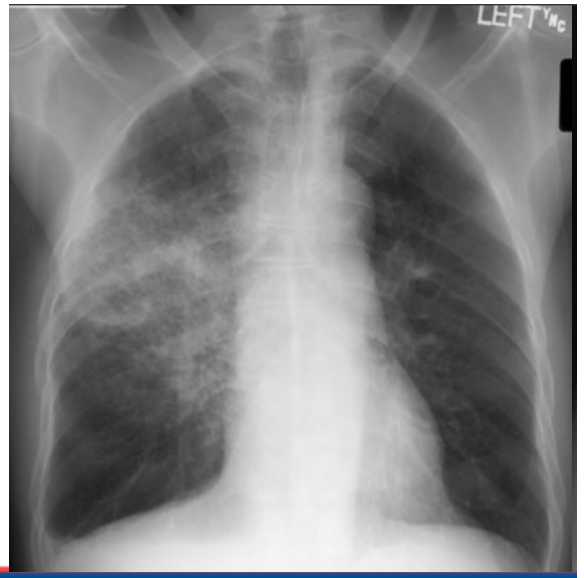


Image courtesy Brianna Hoffner.

Case #1 (cont)

- 8/30/16 patient presents to clinic with continued low-grade fever, cough, and diarrhea since 8/29/16
- Denies sick contacts, dietary changes
- Approximately 8 loose bowel movements per day (baseline 1 BM daily)
- No relief with Imodium
- Cough making it difficult to sleep at night

Case #1 (cont)

US Department of HHS. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

GASTROINTESTINAL

Page 2 of 10

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death

REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea.

ALSO CONSIDER: Dehydration; Hypotension.

PULMONARY/UPPER RESPIRATORY

Page 1 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death

ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).

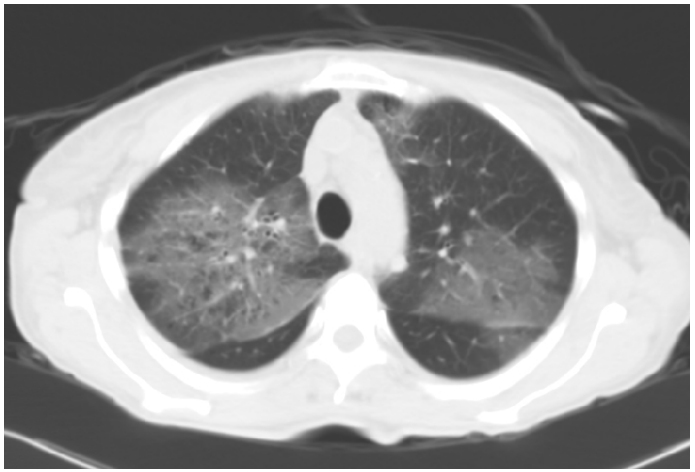
Case #1 (cont)

- Grade 3 diarrhea differential diagnoses
  - Infectious diarrhea (including C. diff)
  - Antibiotic associated diarrhea
  - Colitis secondary to immunotherapy

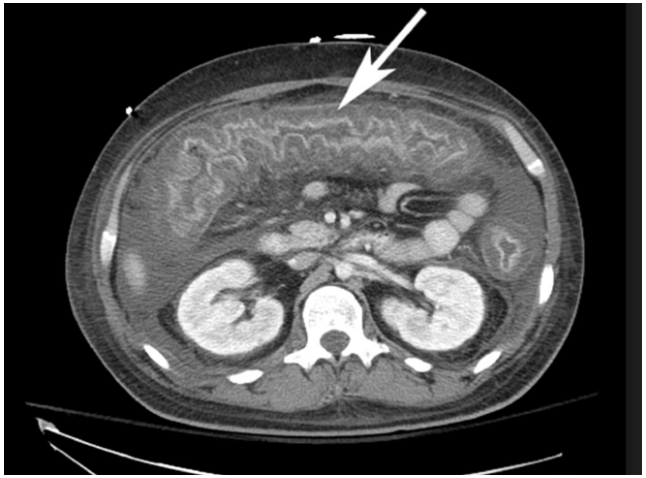
- Grade 3 Cough vs pneumonitis differential diagnoses:
  - Infectious
  - Inflammatory
  - Irritation

Case #1 (cont)

Chest CT scan



Abdominal CT scan



Images courtesy of Brianna Hoffner.

Case #1 (cont)

- Grade 3 colitis and grade 3 pneumonitis
  - Initiate steroid at 1 mg/kg of solumedrol or equivalent
  - Recommend IV steroid initially with colitis symptoms due to gut absorption issues
  - Taper slowly
  - Consider antibiotic prophylaxis during high-dose steroid
  - Discontinue immunotherapy

Case #2: Advanced BCC

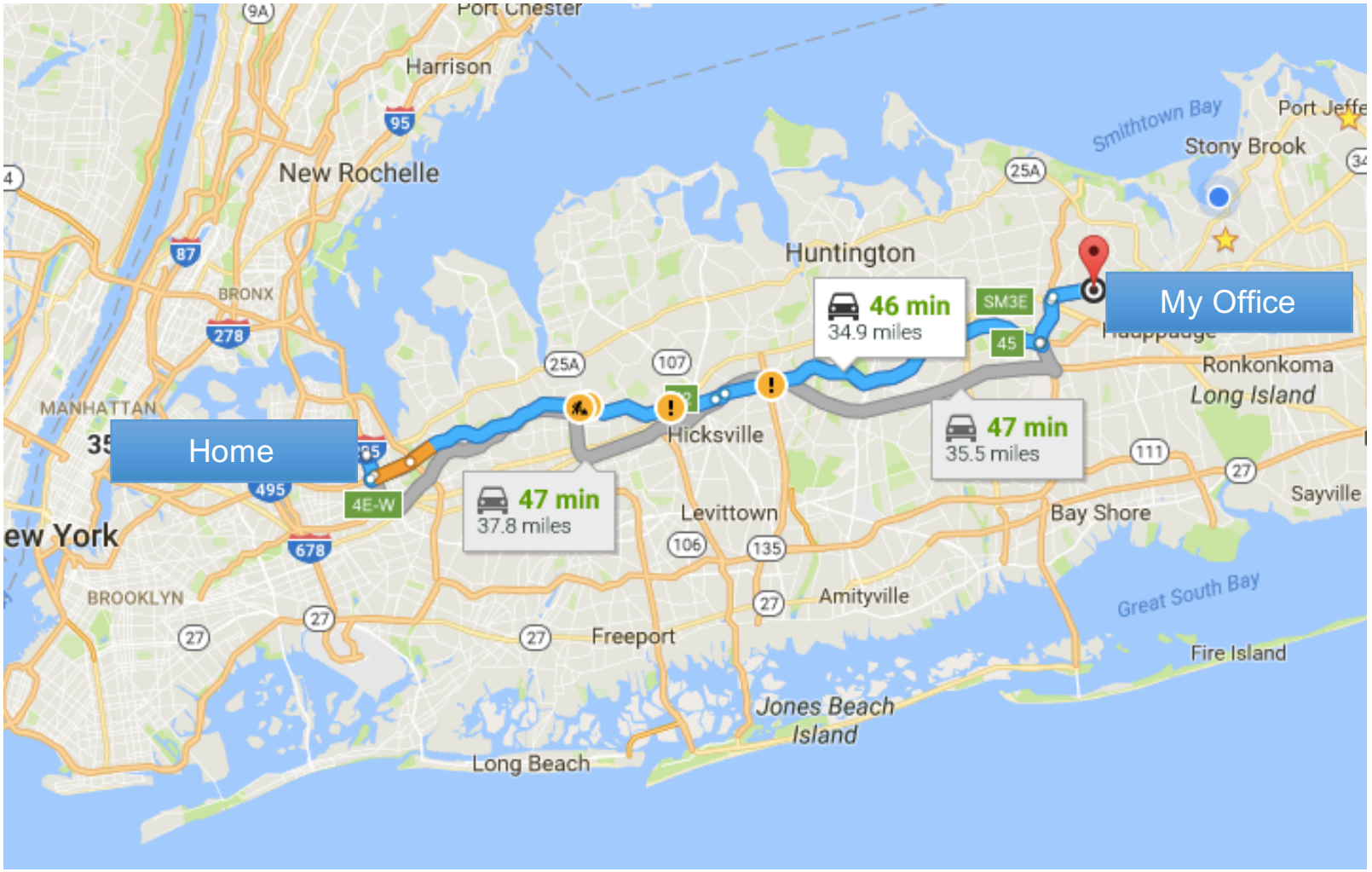
- 98-year-old white female with a BCC excised from her nose 8 years prior to presentation on August 29, 2013
- According to the patient, who was well oriented and communicative, and her two younger sisters who accompanied her, the surgeon told her the excision margins were positive but she need not return to him as it should not be a problem in her lifetime
- A year after surgery, she began to have bleeding along the suture line
- One subsequent surgery and RT over next 3 years

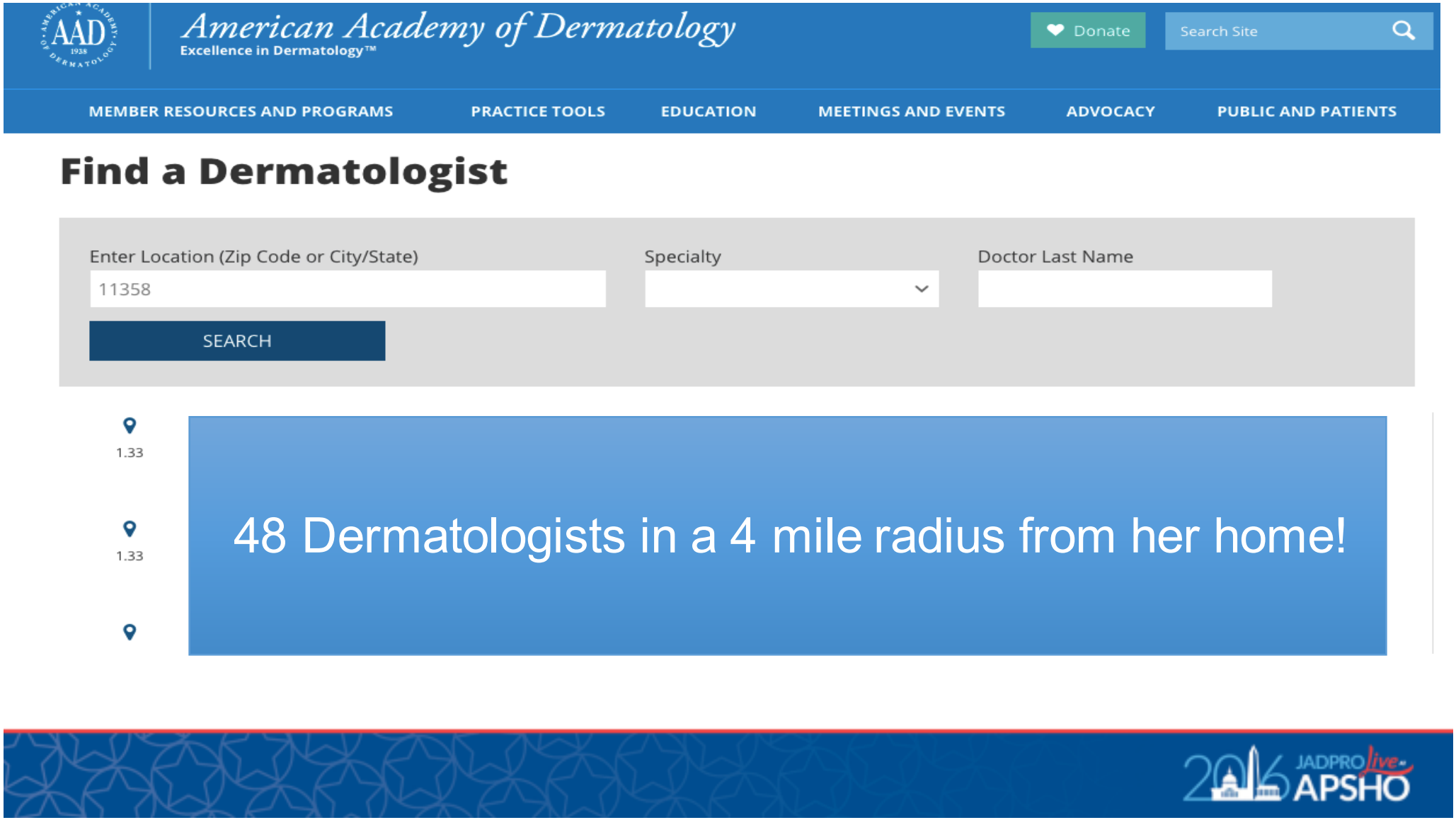
Case #2: Advanced BCC

- Past medical history
  - Pacemaker for “decades”
  - Congestive heart failure
  - Other non-melanoma skin cancers
- Medications
  - Warfarin
  - Folic acid
  - Atenolol
  - Digoxin

Case #2: Advanced BCC

- Over the preceding 5 years, she became reclusive as the appearance of the lesion and the associated odor deterred visitors. Family visits became infrequent.
- Only two sisters and her nephew had seen her in person in that time
- She was referred to me by the patient's nephew, a dermatologist who lives a few states away, because her primary dermatologist was not comfortable prescribing a hedgehog inhibitor due to her age
- I was the closest person he knew who would see her and treat her despite her age


Home
My Office
46 min
34.9 miles
47 min
37.8 miles
47 min
35.5 miles
Harrison
New Rochelle
Huntington
Hicksville
Levittown
Bay Shore
Amityville
Freeport
Long Beach
Jones Beach Island
Stony Brook
Smithtown Bay
Ronkonkoma
Long Island
Sayville
Great South Bay
Fire Island
MANHATTAN
BRONX
BROOKLYN


American Academy of Dermatology
Excellence in Dermatology™
Donate
Search Site
MEMBER RESOURCES AND PROGRAMS
PRACTICE TOOLS
EDUCATION
MEETINGS AND EVENTS
ADVOCACY
PUBLIC AND PATIENTS
Find a Dermatologist
Enter Location (Zip Code or City/State)
11358
Specialty
Doctor Last Name
SEARCH
1.33
1.33
48 Dermatologists in a 4 mile radius from her home!
2016 JADPRO Live APSHO

August 29, 2013

Images courtesy Dr. Daniel M. Siegel.

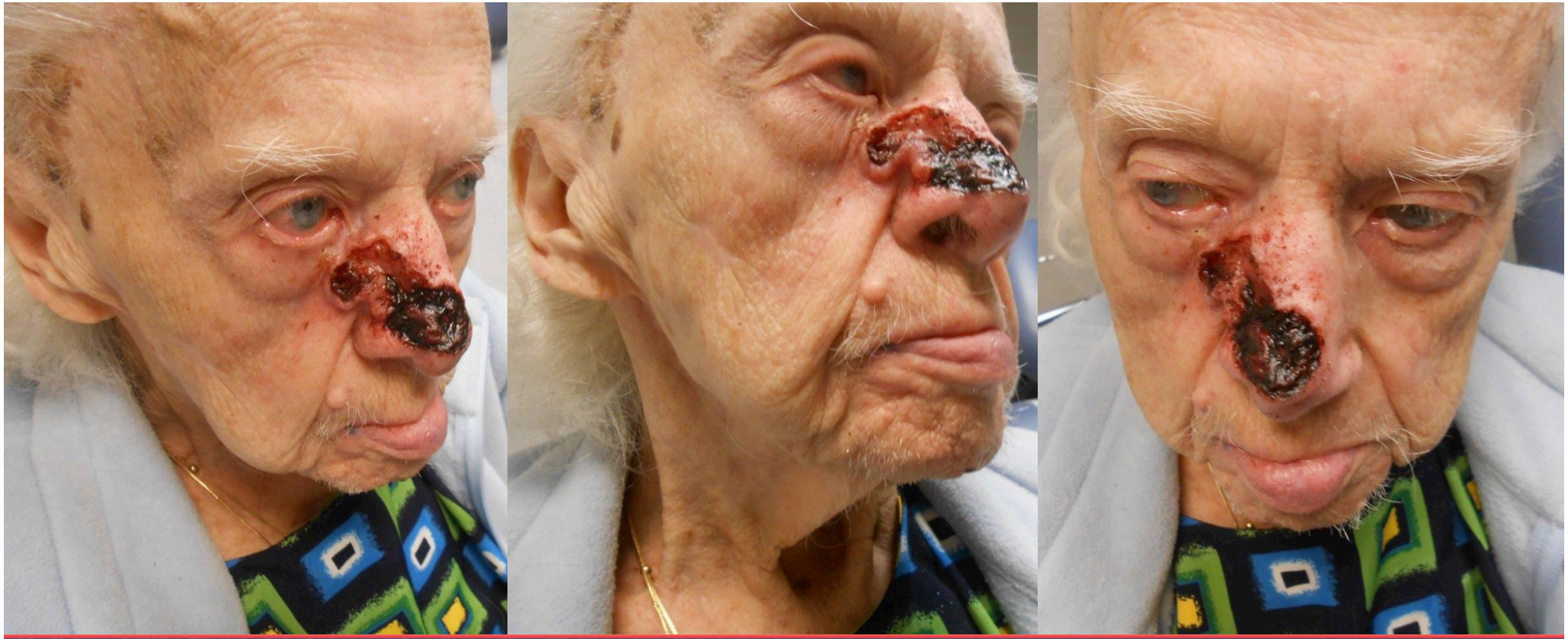


Image courtesy Dr. Daniel M. Siegel.

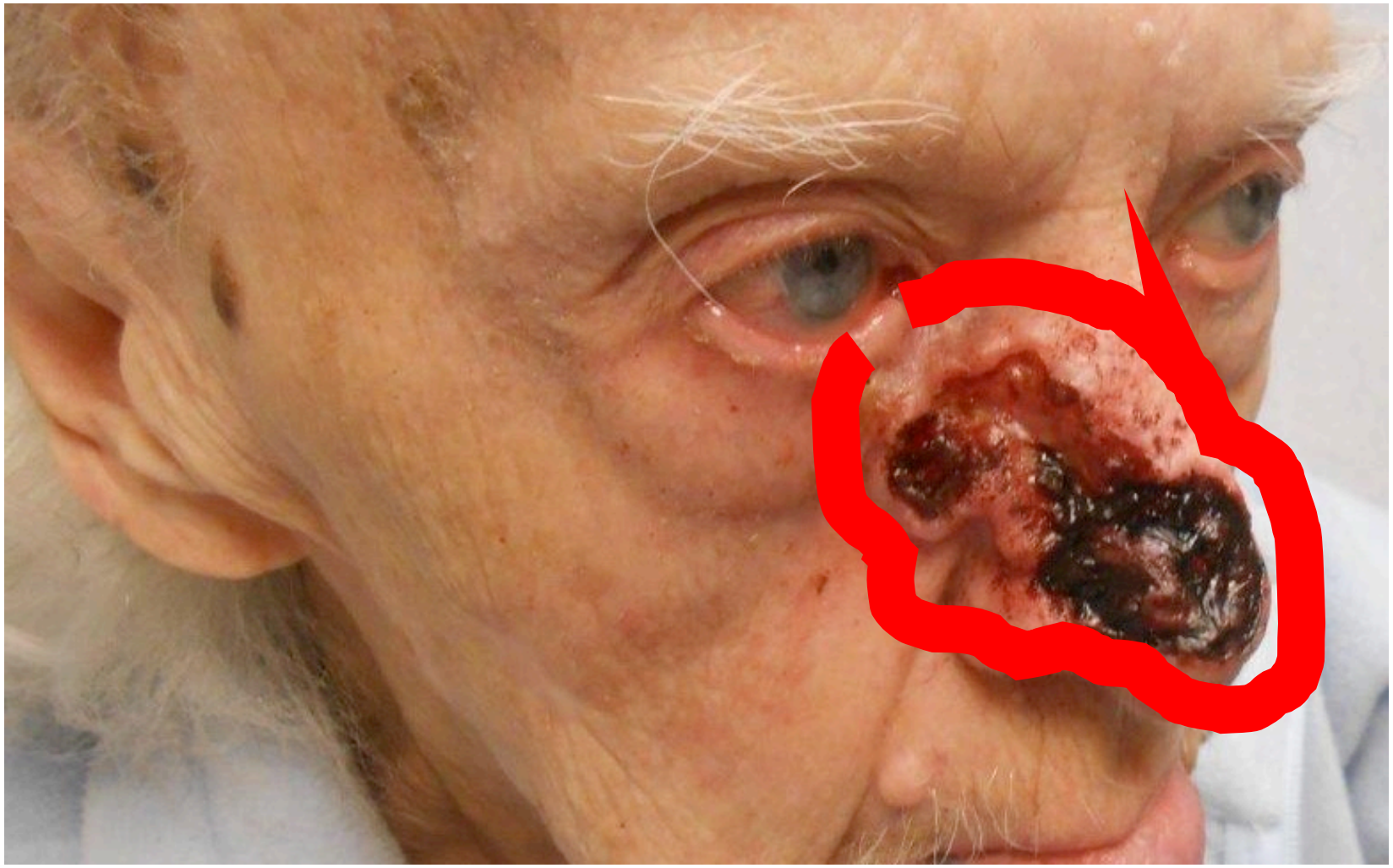


Image courtesy Dr. Daniel M. Siegel.

August 29, 2013

Discussion

- Age and cardiac status and likely extent of tumor would preclude surgery
- Removal of much of nose would likely result in decompensation of CHF due to loss of nasal valve function; adequate reconstruction would also be risky for the patient
  - In any event, patient refused surgery

August 29, 2013

Discussion

- Radiation: Already had maximal dose to area
- Patient left office with lots of info, annotated by me

September 2013

- A few phone calls over next few weeks to talk with patient and her two sisters who lived with her to answer questions.

October 7, 2013

Visit

- Sisters concerned the site is bleeding more over last few weeks
- Patient agrees to starts vismodegib150 mg per day
- Confirmatory biopsy obtained to confirm diagnosis and demonstrate not an SCC
- Biopsy showed infiltrative BCC
  - No surprise
- Begins treatment ~2 weeks post visit

October 7, 2013

Images courtesy Dr. Daniel M. Siegel.

Mid-December 2013

Phone call

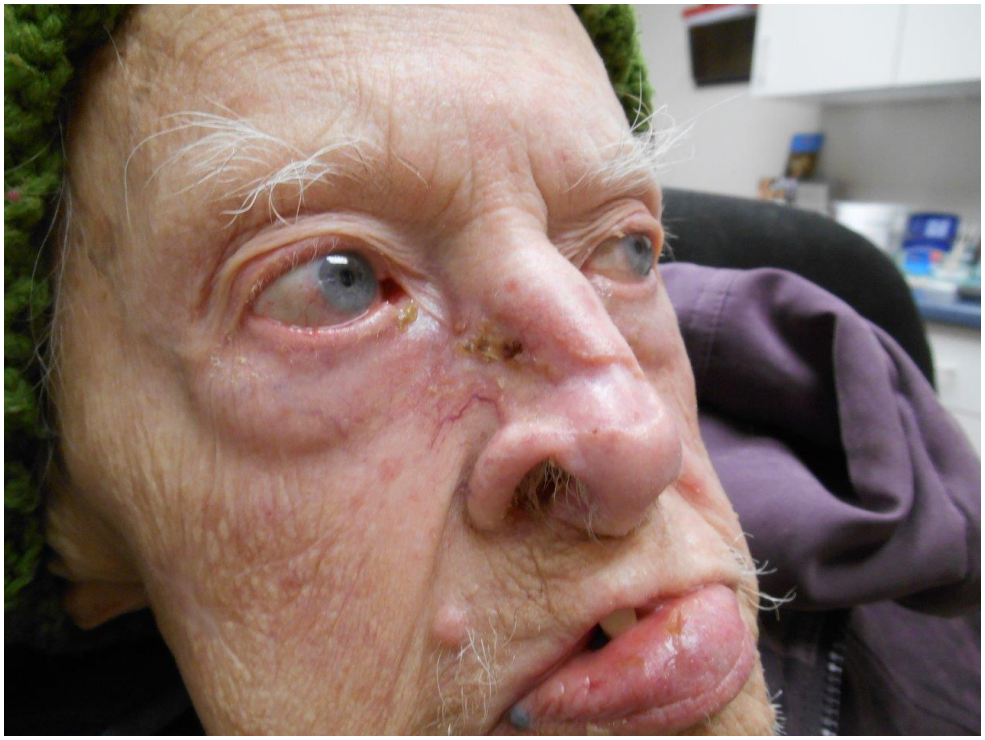
- Patient begins losing weight as appetite diminishes.
  - Major concern as she has been getting “fragile” over the past few years, per her sisters
- Hair loss not of concern
- No muscle spasms
- We all agree on a drug holiday for a month

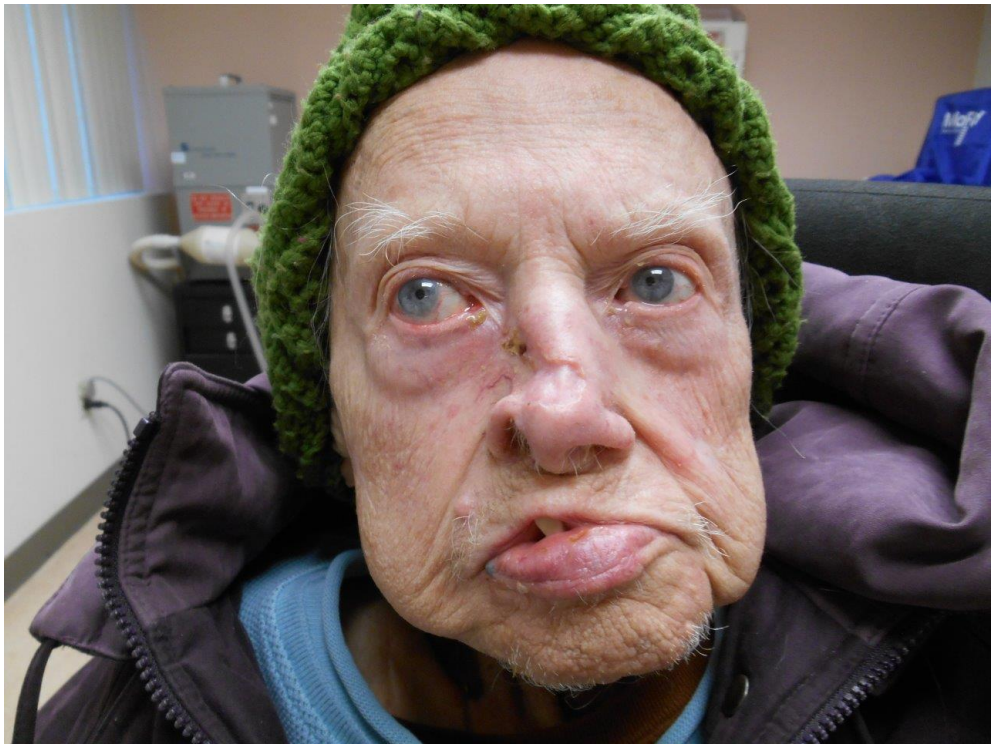
January 13, 2014

Office visit

- Happy patient who enjoyed the holidays with family and friends
- Spends 99th birthday with loved ones in early January
- Patients eating again
- Patients “feels good,” no desire to go back on drug
- Exam: Focal crusting; no palpable tumor. No LAD.

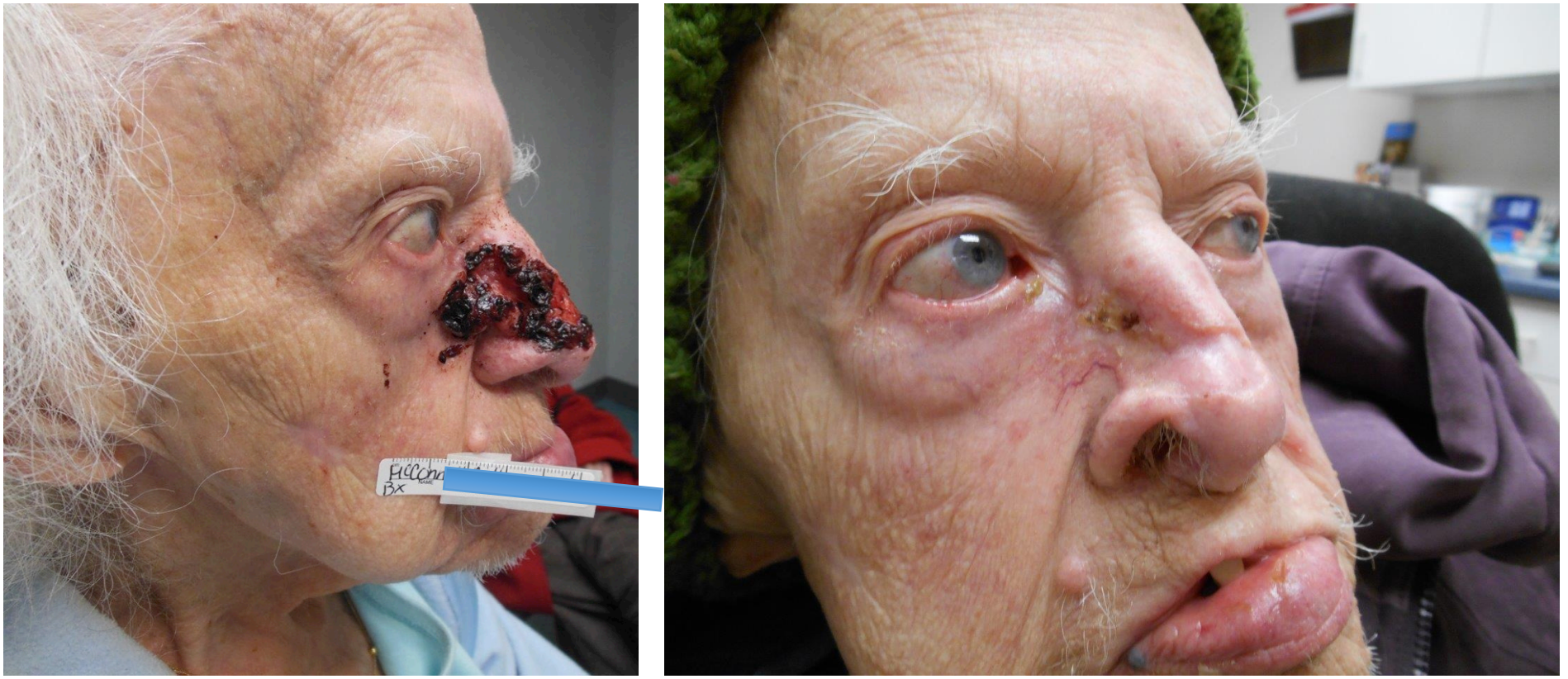
January 13, 2014





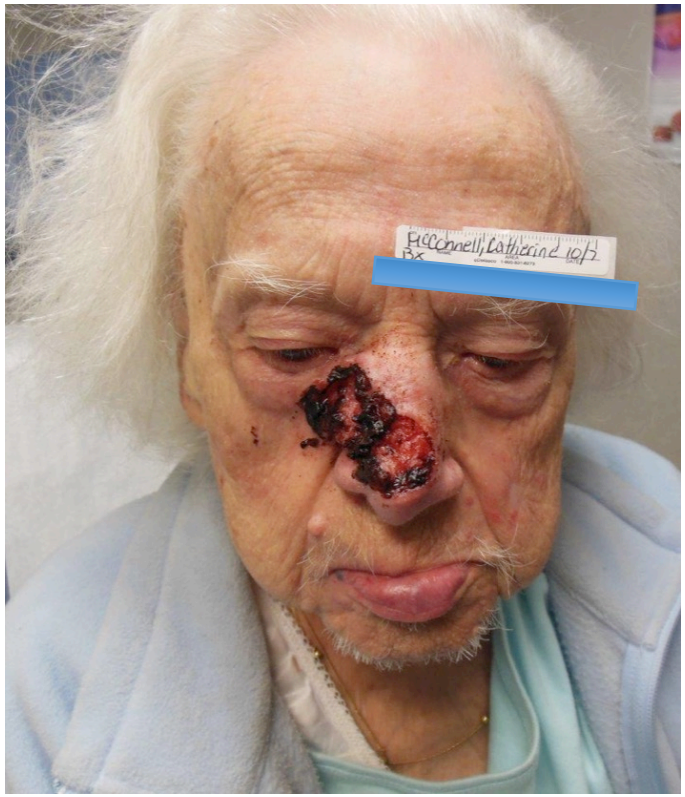
Images courtesy Dr. Daniel M. Siegel.

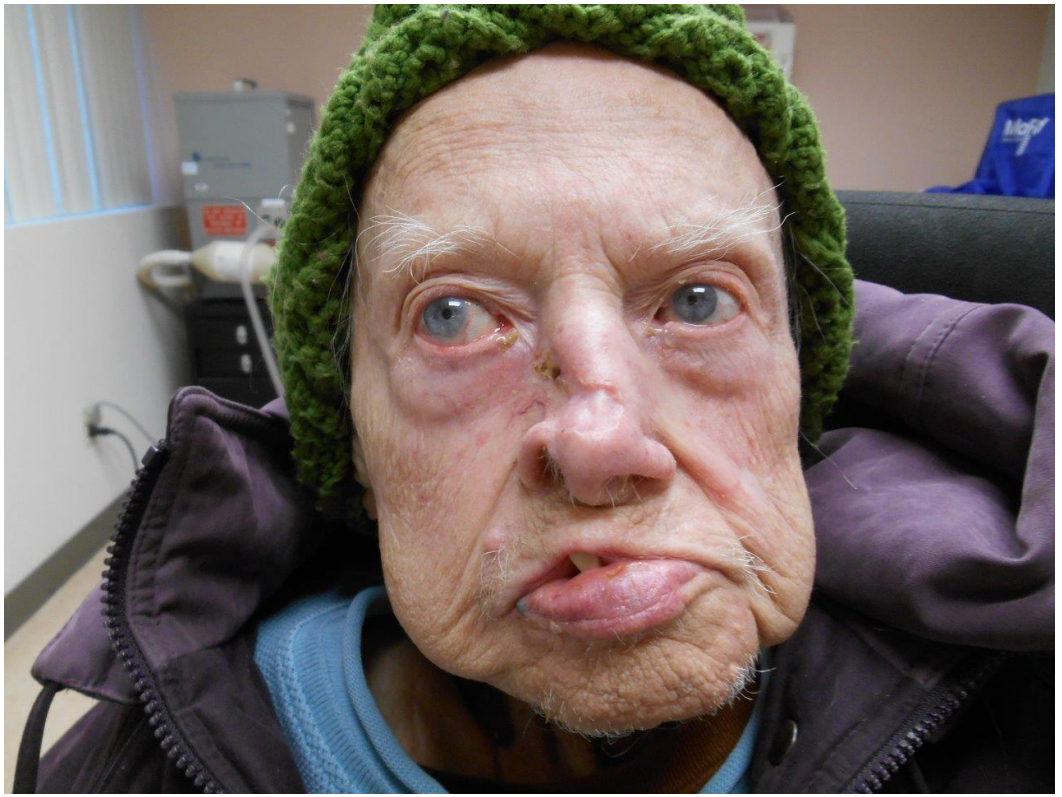
October 7, 2013 vs January 13, 2014



Images courtesy Dr. Daniel M. Siegel.

October 7, 2013 vs January 13, 2014





Images courtesy Dr. Daniel M. Siegel.

Epilogue

- Passed away in March 2014
- Family grateful to have had a few months to spend with patient in her twilight years after a multiyear interlude


SMARTIE
This has been a SMARTIE presentation.
SMARTIE participants, you can now visit the SMARTIE website to answer the post-session questions for this presentation.
If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.