Outside the Box:
Melanoma, BCC, SCC and The Patient With IBD

George Martin MD

Dr. George Martin Dermatology Associates

Kihei, Maui, Hawaii

drmauiderm@gmail.com

1

Dr. Martin: Conflict of Interest

- Almirall
- Athenex
- Biofrontera
- DUSA/SUN
- Abbvie
- Ortho/Bausch Health
- Galderma
- Pfizer
- LEO
- Lilly
- Celgene
- Janssen
- Pfizer
- Horizon

2

Case Study

- My patient MW: 70 yo WM w/ Crohn's beginning in his late 30's
- Referred to me: "increasing NMSC burden"
- Meds: prednisone; Inflixumab x "years"; Humira x 7 years up to the time of his initial visit)
- Surg Hx: multiple surgeries for fistula, colostomy & re-anastamosis
- Derm Hx: melanoma x 3 (Breslow: in-situ x 1; 0.6 and 0.8 mm); Had > 40 SCC & BCC in last 7 years over face, trunk and extremities
- Exam on initial visit: 5 SCC and 2 BCC w/ significant actinic damage

3

The Issue: Now to manage NMSC burden and a history of melanoma in a patient w/ IBD on a TNFi?

4

Today's Points of Discussion

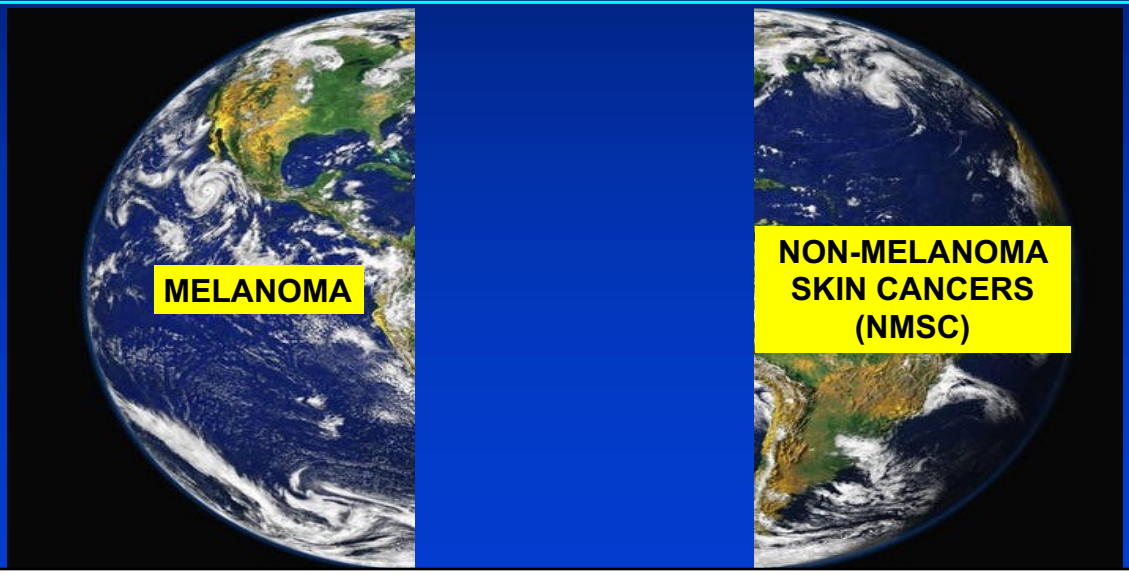
1. Primer on Melanoma and Non-melanoma skin cancer (NMSC)
2. How to treat the IBD patient who has a history of melanoma and NMSC and is "at risk" for more
3. How do we manage the IBD patient with Stage III or IV melanoma and advanced/metastatic NMSC

5

1. Primer on Melanoma & Non-Melanoma Skin Cancer (NMSC)

6

The World of Skin Cancers



7

Non-Melanoma Skin Cancer (NMSC)

8

Non-melanoma Skin Cancers (NMSC)

- Basal Cell Carcinoma: ~ 80% NMSC
- Squamous Cell Carcinoma: ~15-20% NMSC
- Rare: <1% of NMSC
  - Dermatofibroma sarcoma protuberans (DFSP)
  - Merkel Cell Carcinoma (equivalent to a mid level melanoma)
  - Sebaceous carcinoma
  - Angiosarcoma
  - Atypical Fibroxanthoma
  - Other eccrine, pilosebaceous and sarcoma malignancies

9

Non-Melanoma Skin Cancer (BCC/SCC)

- **No tumor registries are kept for BCC and SCC so data is extracted from insurance company data**

1. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. JAMA Dermatol. 2015;151(10):1081-1086.

10

BASAL CELL CARCINOMA (BCC)

11

Epidemiology: Basal Cell Carcinoma (BCC)

- Estimate that about 5.4 million BCC & SCC are diagnosed each year in about 3.3 million persons in the US[1]
- 80% of those being BCCs.
- The estimated ***lifetime risk for BCC*** in the **white population** is:
  - Men: 33-39%
  - Women: 23-28%
- BCC incidence doubles every 25 years

1. Amercian Cancer Society Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population, 2012. JAMA Dermatol. 2015;151(10):1081-1086.

12

CLINICAL & HISTOLOGIC FEATURES OF:

BASAL CELL CARCINOMA (BCC)

13

4 Basic Categories of BCC

1. Superficial BCC
2. Nodular BCC:
3. Infiltrative BCC
4. Locally Advanced/Metastatic BCC:

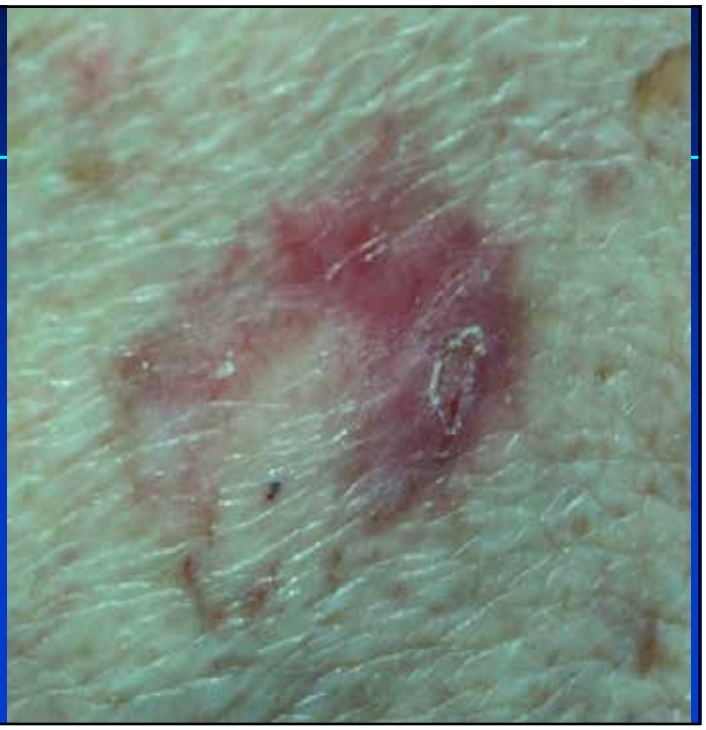
14

Superficial BCC

Clinical: typically an asymptomatic slow-growing pink or red, minimally elevated plaques

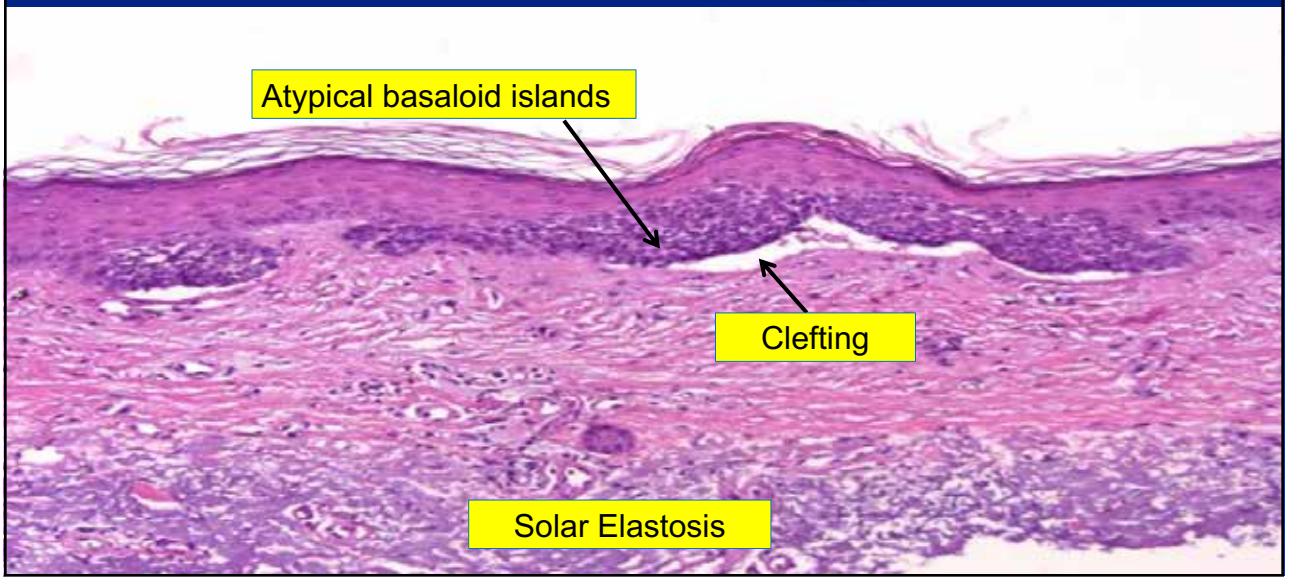
No risk of metastasis at this stage

Treatment: ED&C, topical agents, surgery



15

sBCC Histology



16

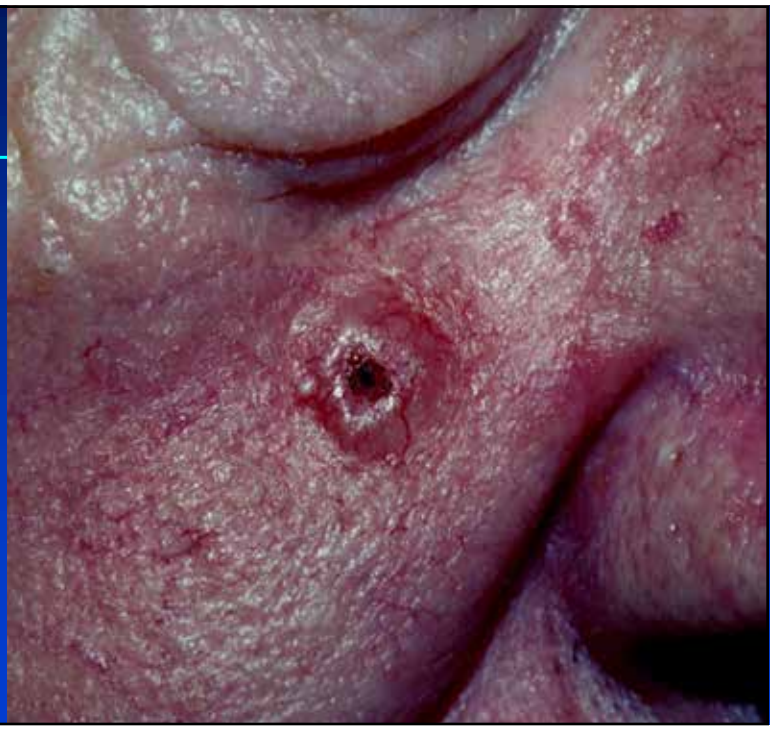
Nodular BCC

Clinical: Typically an asymptomatic waxy flesh color papule that can ulcerate or bleeds easily w/ minimal trauma

Slow growing; locally invasive

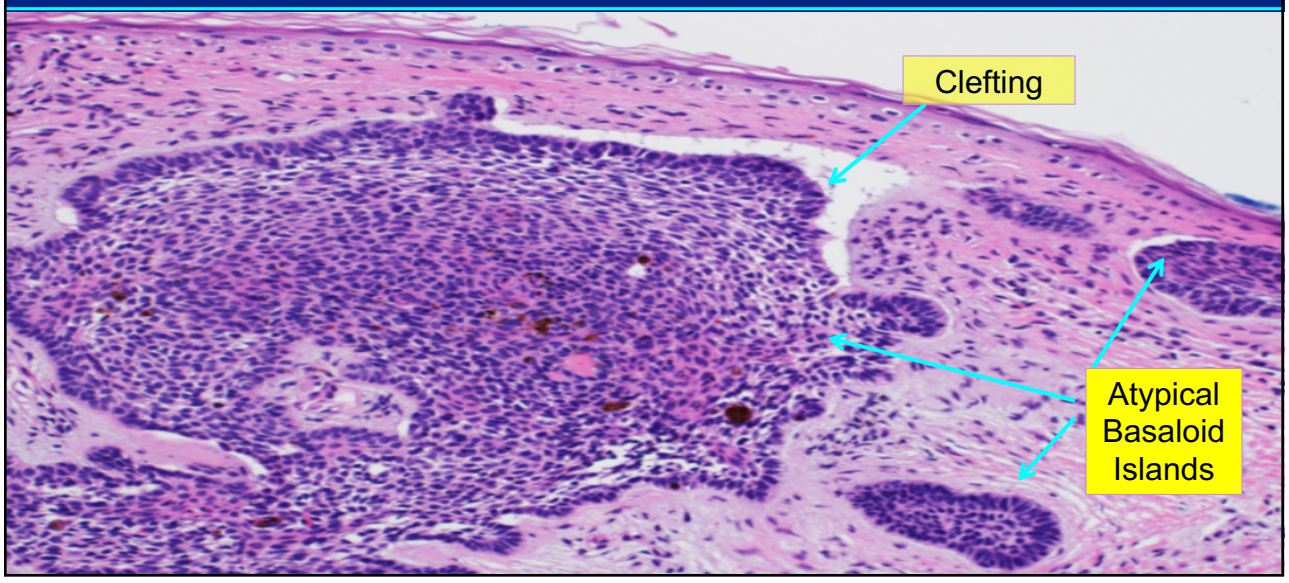
Treatment: surgical; XRT in non-surgical candidates

Risk of mets: exceedingly rare unless very large size



17

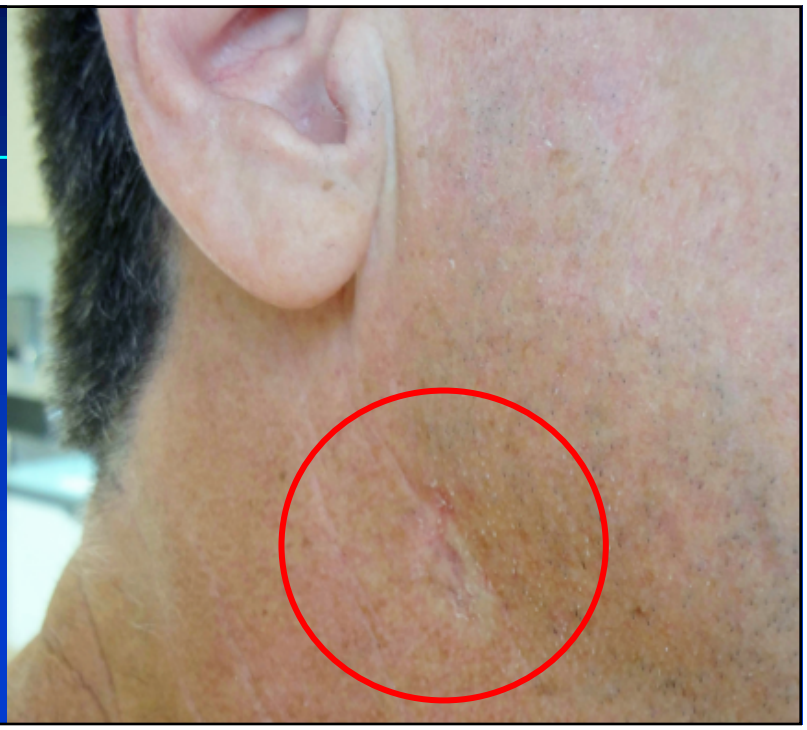
Nodular BCC Histology



18

Infiltrative or Sclerosing BCC

- Locally aggressive, deeply infiltrating asymptomatic lesion that extends on average 1 cm beyond the clinical margin
- Requires Mohs micrographic surgery to assess margin control
- Rare mets and only with large lesions



19

Infiltrative BCC (Invading the subcutis)

20

Locally Advanced & Metastatic Basal Cell Carcinoma

21

BCC Risk Stratification

- AJCC stage grouping (TNM: Tumor, Node, Metastasis) classification is rarely applied due to the ***exceedingly low incidence of BCC metastasis***

- ***Metastatic BCC is exceedingly rare***, with an estimated incidence of *0.0028% to 0.55%,* but has historically been associated with a very poor prognosis.

- Lymphatic metastasis to the regional lymph node basin followed by hematogenous spread to lung and bonen is the most common pathway of progression.

22

Management of Metastatic BCC

- Metastatic disease is limited to the regional lymph node basin:
  - Surgery and/or radiation therapy remain the most appropriate treatment, when possible.
- Distant metastases:
  - Multidisciplinary consultation is recommended to consider systemic therapy with ***hedgehog pathway inhibitors vismodegib, sonidegib)***
    - If this is not feasible:
      - PD-1 inhibitor: effective in small series
      - Platinum-based chemotherapy may be considered along with supportive care

23

Cutaneous Squamous Cell Carcinoma (cSCC)…..

It is NOT the same SCC as Head and Neck Mucosal SCC

24

EPIDEMIOLOGY OF cSCC

25

Squamous Cell Ca - Incidence

- 2nd most common skin cancer; *Double* the rate over the last 40 yrs
- *50%* will have a new SCC within 5 yrs of first
- **Aggressiveness varies wildly**
  - *SCC In Situ* may never progress
  - *Poorly differentiated SCC* have potential to metastasize
- 3-4% overall metastatic rate
  - >9,000 – 12,000 annual deaths of metastatic SCC in U.S.

26

CLINICAL & HISTOLOGIC FEATURES OF cSCC

29

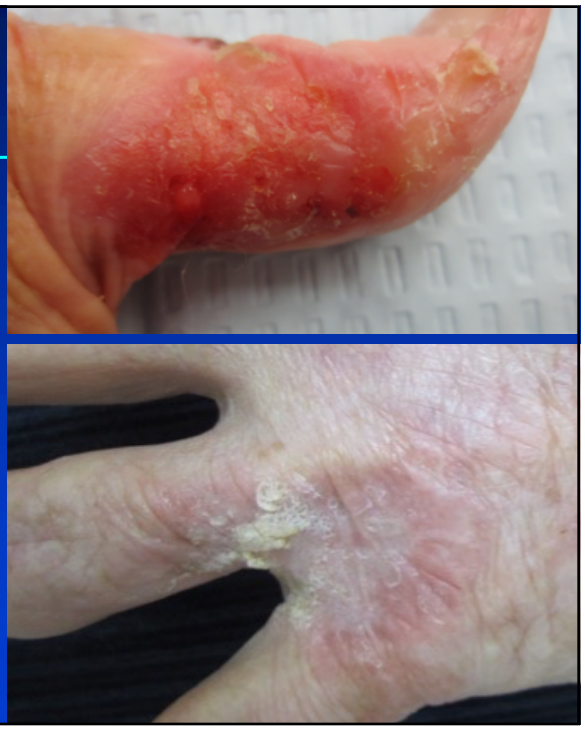
5 Basic Categories of cSCC

1. SCC in Situ (Bowen's Disease)
2. Keratocanthoma
3. Well differentiated SCC
4. Poorly Differentiated SCC
5. Advanced and Metastatic cSCC:

30

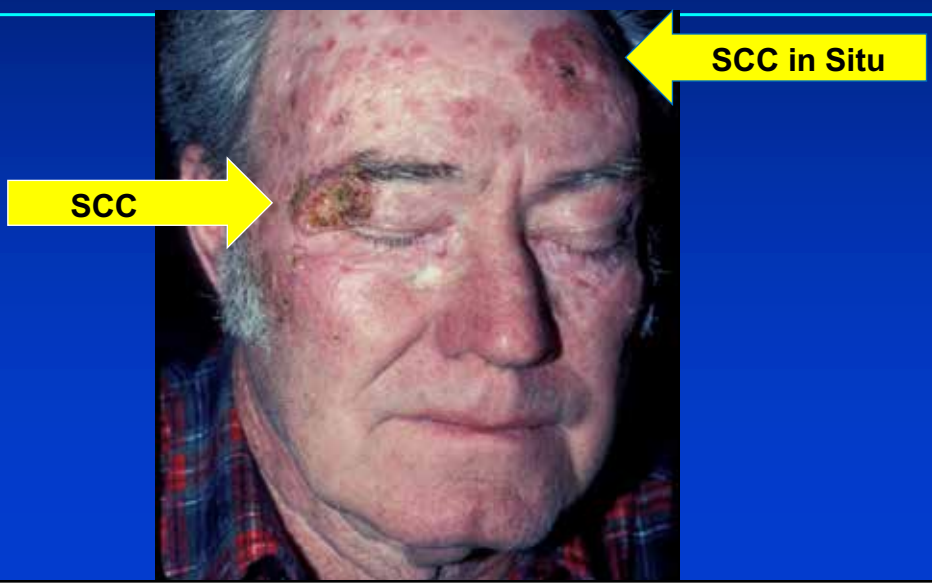
SCC in Situ….
aka “Bowens Disease”

- Red scaly plaque usually >1 cm
- Lesion confined to the epidermis
- No risk for mets until it beomes invasive
- Treated with ED&C, topicals, surgery



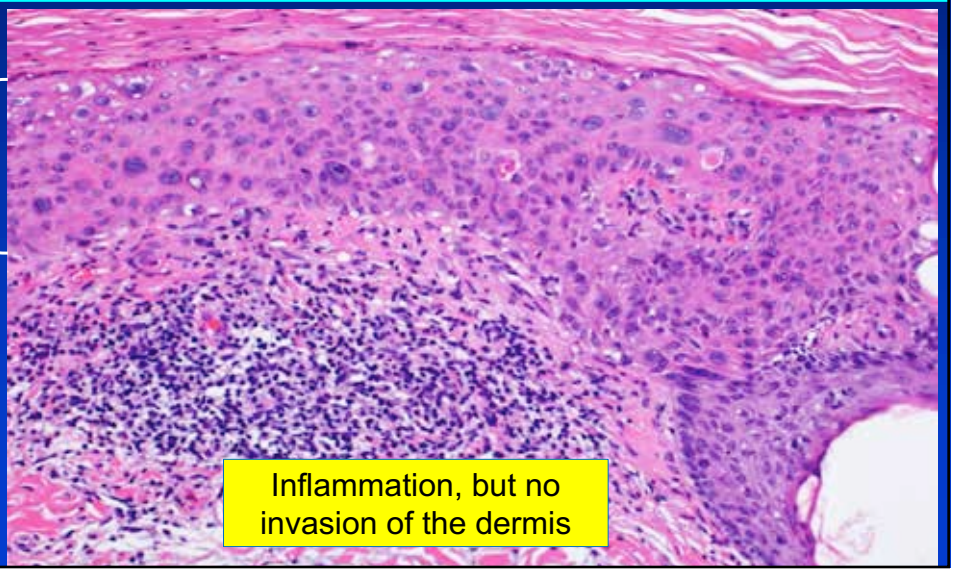
31

CLINICAL: SCC vs. SCC in SITU



32

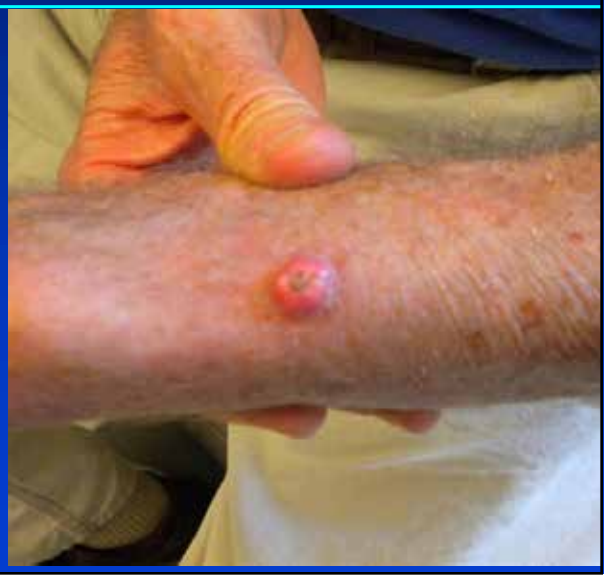
SCC in Situ



33

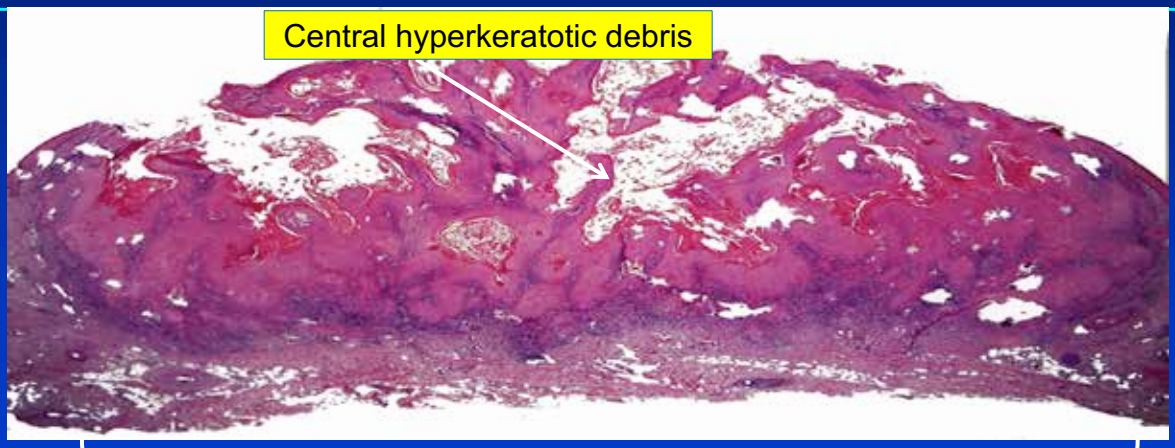
SCC - Keratocanthoma Type

- Subtype of SCC
- Rapidly growing “crater-like” nodule with a central keratinaceous core
- Generally self limiting but can rarely be aggressive



34

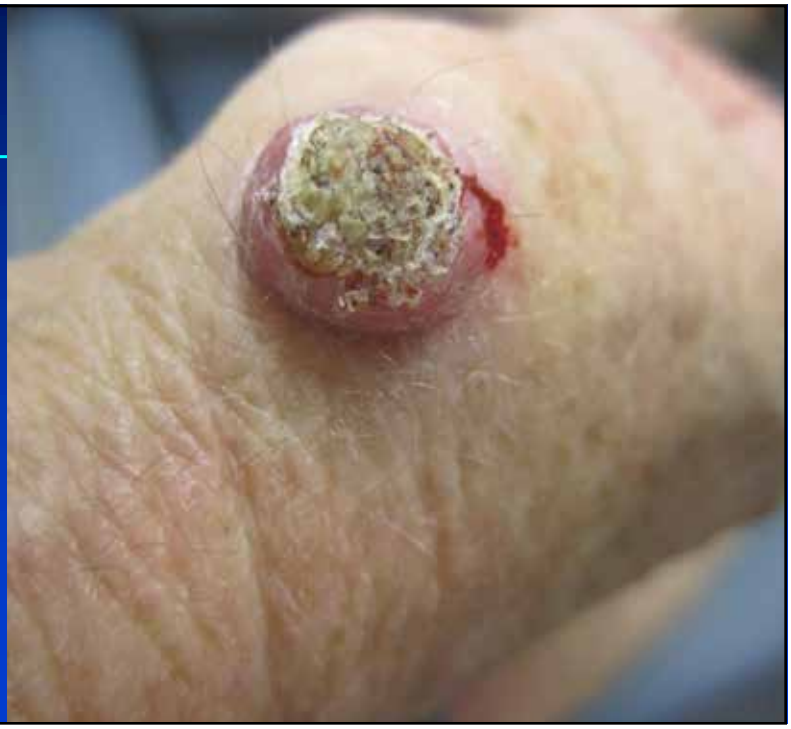
SCC - Keratoacanthoma Type



35

Well Differentiated SCC

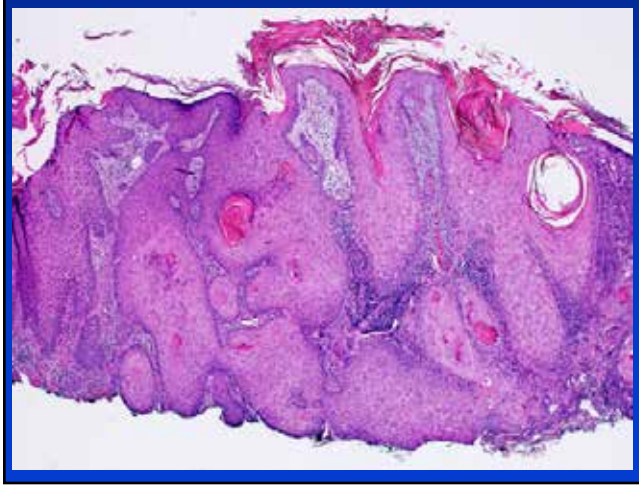
- Nodule with central crater filled w/ keratinous material
- Can be tender when it rapidly enlarges
- Well differentiated lesions (on histology) can metastasize
- Treatment: surgical excision; XRT in certain circumstances



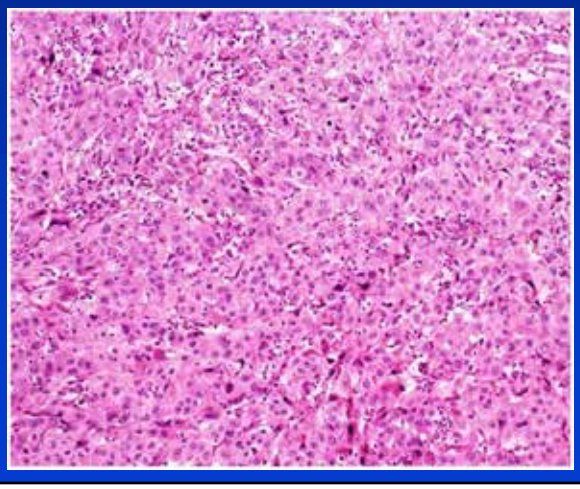
36

WELL vs. POORLY DIFFERENTIATED SCC

WELL DIFFERENTIATED SCC



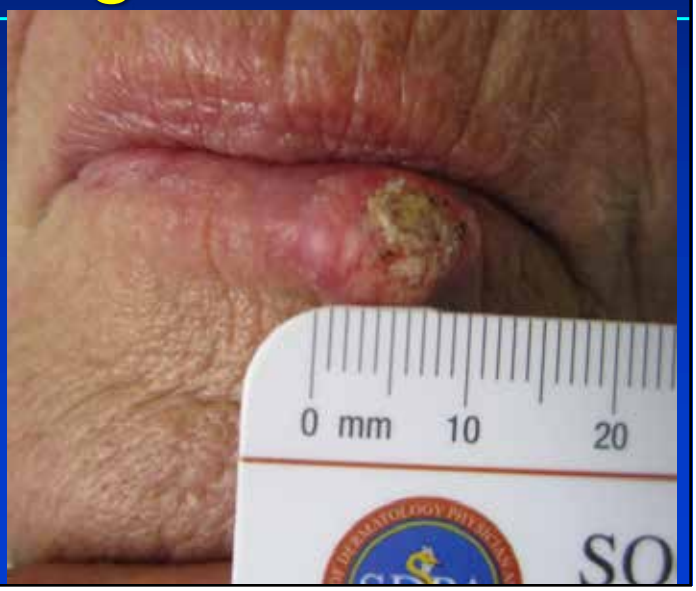
POORLY DIFFERENTIATED SCC



37

SCC – High Risk

- ***Mucosal lesions*** have a 5x higher rates of metastases
- Make sure to check *lymph nodes* in appropriate region

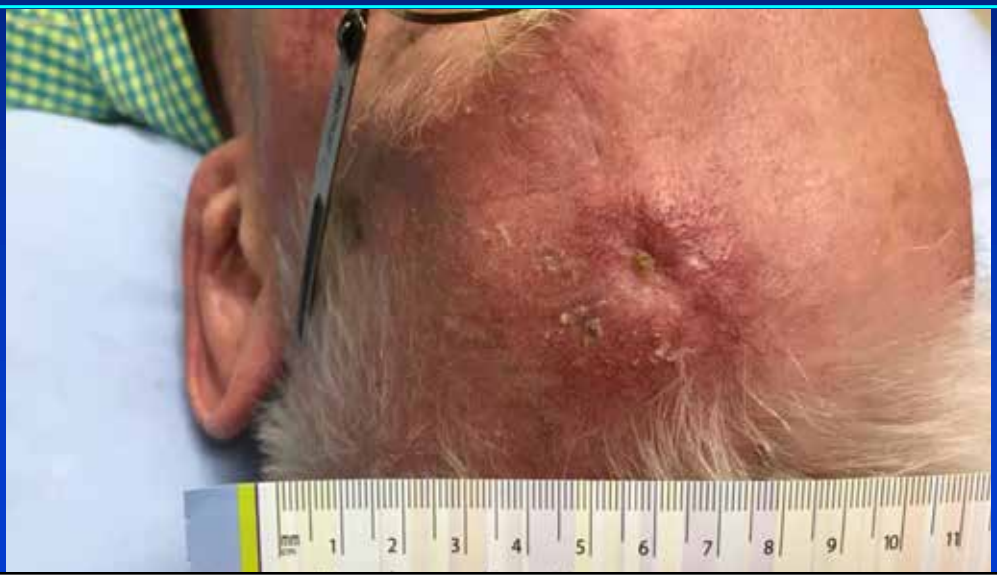


38

“High Risk” Poorly Differentiated SCC

39

Biopsy Proven Infiltrative cSCC: Fixed to Bone



40

Brigham and Women's Tumor Classification System: HIGH RISK SCC

Table II. Brigham and Women's Hospital tumor classification system

Category	Definition
T0	In situ SCC
T1	0 risk factors*
T2a	1 risk factor
T2b	2-3 risk factors
T3	4 risk factors or bone invasion

SCC, Squamous cell carcinoma.

*Risk factors include tumor diameter 2 cm or larger, poorly differentiated histology, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone, which automatically upgrades to T3).

RISK FACTORS FOR POOR OUTCOMES

- Tumor diameter > 2 cm
- Poorly differentiated histology
- Perineural invasion
- Tumor invasion beyond SQ fat (excluding bone, which automatically upgrades to T3)

Note: T2b and T3 make up only 5% of the original BWH cohort but account for 60% of the bad outcomes

41

Management of High Risk Cutaneous SCC

- **Mohs surgery** (and other methods of complete circumferential peripheral and deep margin assessment) are recommended by the NCCN for high risk CSCC
  - Cuts risks of local recurrence and death from disease by at least 50% as compared to wide excision with standard bread-loaf histology

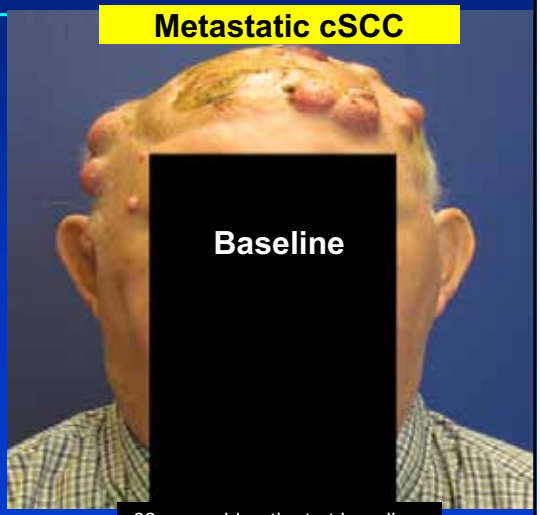
42

Metastatic and Advanced cSCC

43

Advanced and Metastatic cSCC

83-year-old patient, who had undergone multiple surgeries for CSCC



62-year-old patient at baseline.

Migden MR, Rischin D, et al. *N Engl J Med*. 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

44

Metastatic/Locally Advanced Cutaneous Squamous Cell Carcinoma

- More than 95% of patients with CSCC are cured with surgery;[4]
- ***In 2012, an estimated 3,900–8,700 patients in the US died from CSCC[5]***
- There is ***no approved systemic therapy for patients with advanced CSCC i.e. metastatic CSCC and locally advanced CSCC that is no longer amenable to surgery or radiation therapy***
- Patients with advanced CSCC are considered for palliative systemic therapy as part of routine clinical practice[9–11]
- CSCC has the clinical and molecular hallmarks of a tumor that is likely to be immune-responsive
  - The tumor mutation burden is high and the disease risk is increased among patients with immunosuppression[9–11]

1. Rogers HW et al. *JAMA Dermatol*. 2015;151:1081–1086. 2. Lomas A et al. *Br J Dermatol*. 2012;166:1069–1080. 3. Stratigos A et al. *Eur J Cancer*. 2015;51:1989–2007.
4. Kauvar AN et al. *Dermatol Surg*. 2015;41:1214–1240. 5. Karia PS et al. *J Am Acad Dermatol*. 2013;68:957–966. 6. Hillen U et al. *Eur J Cancer*. 2018;96:34–43.
7. Jarkowski A III et al. *Am J Clin Oncol*. 2016;39:545–548. 8. Cranmer LD et al. *Oncologist*. 2010;15:1320–1328. 9. Euvrard S et al. *N Engl J Med*. 2003;348:1681–1691.
10. Pickering CR et al. *Clin Cancer Res*. 2014; 20:6582–6592. 11. Chalmeers ZR et al. *Genome Med*. 2017;9:34.

45

PD-1 Blockade with *Cemiplimab* in Advanced Cutaneous Squamous Cell Carcinoma

Michael R. Migden,[1] Danny Rischin,[2] Chrysalyne D. Schmults,[3] Alexander Guminski,[4] Axel Hauschild,[5] Karl D. Lewis,[6] Christine H. Chung[7] Leonel Hernandez-Aya,[8] Annette M. Lim,[9] Anne Lynn S. Chang,[10] Guilherme Rabinowits,[11] Alesha A. Thai,[2] Lara A. Dunn,[12] Brett G.M. Hughes,[13] Nikhil I. Khushalani,[14] Badri Modi,[15] Dirk Schadendorf,[16] Bo Gao,[17] Frank Seebach,[18] Siyu Li,[17] Jingjin Li,[17] Melissa Mathias,[18] Jocelyn Booth,[17] Kosalai Mohan,[18] Elizabeth Stankevich,[17] Hani M. Babiker,[19] Irene Brana,[20] Marta Gil-Martin,[21] Jade Homsi,[22] Melissa L. Johnson,[23] Victor Moreno,[24] Jiaxin Niu,[25] Taofeek K. Owonikoko,[26] Kyriakos P. Papadopoulos,[27] George D. Yancopoulos,[18] Israel Lowy,[18] Matthew G. Fury[18]

[1]Departments of Dermatology and Head and Neck Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Medical Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia; [3]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Medical Oncology, Royal North Shore Hospital, St Leonards, Australia; [5]Schleswig-Holstein University Hospital, Kiel, Germany; [6]University of Colorado Denver, School of Medicine, Aurora, CO, USA; [7]Department of Head and Neck-Endocrine Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [8]Division of Medical Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA; [9]Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth, Australia; [10]Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA; [11]Formerly of Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [12]Department of Medicine, Head and Neck Medical Oncology, Memorial Sloan Kettering Cancer Center, New York City, NY, USA; [13]Royal Brisbane & Women's Hospital and University of Queensland, Brisbane, Australia; [14]Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, FL, USA; [15]Division of Dermatology, City of Hope, Duarte, CA, USA; [16]University Hospital Essen, Essen and German Cancer Consortium, Germany; [17]Regeneron Pharmaceuticals Inc., Basking Ridge, NJ, USA; [18]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; [19]University of Arizona Cancer Center, Tucson, AZ, USA; [20]Medical Oncology Department, Vall D'Hebron University Hospital, Barcelona, Spain; [21]Institut Català D'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain; [22]Formerly of Banner MD Anderson Cancer, Gilbert, AZ, USA; [23]Sarah Cannon Research Institute, Nashville, TN, USA; [24]START Madrid-FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain; [25]Department of Medical Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [26]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA; [27]START, San Antonio, TX, USA.

Migden MR, Rischin D, et al. *N Engl J Med*. 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

46

Effects of Cemiplimab in Patients with Advanced CSCC

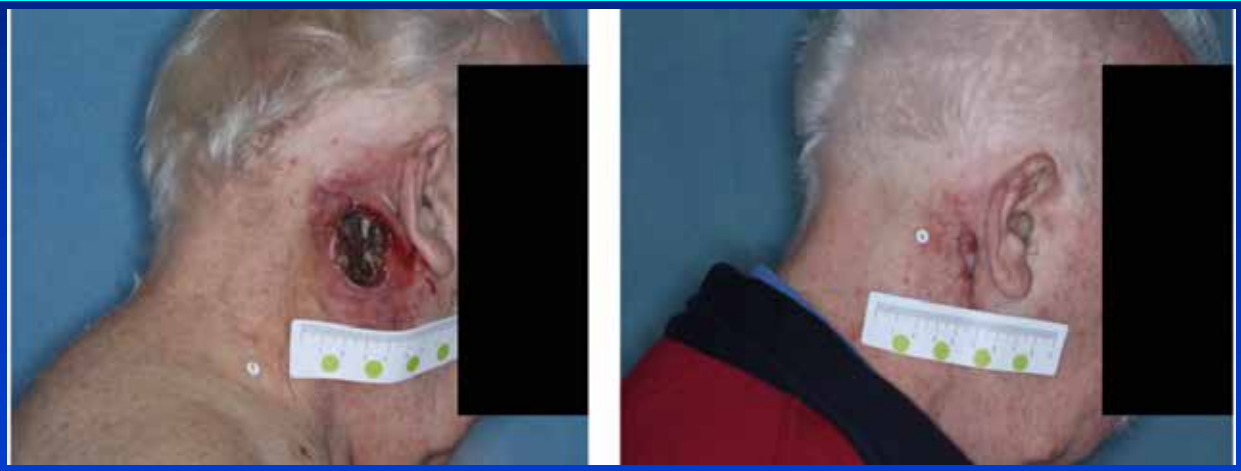
62-year-old patient at baseline and after 6 weeks of treatment with cemiplimab.

Migden MR, Rischin D, et al. *N Engl J Med*. 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

47

Effects of Cemiplimab in Patients with Advanced CSCC

Baseline Week 8

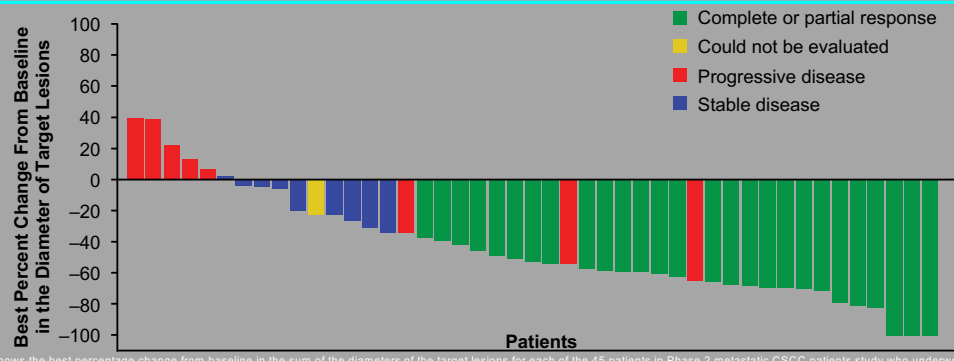


83-year-old patient, who had undergone multiple surgeries for CSCC, at baseline and after 8 weeks of treatment with cemiplimab.

Migden MR, Rischin D, et al. *N Engl J Med*. 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

48

Phase 2 Study: Best Percentage Change From Baseline in Target Lesions of Patients With Metastatic CSCC



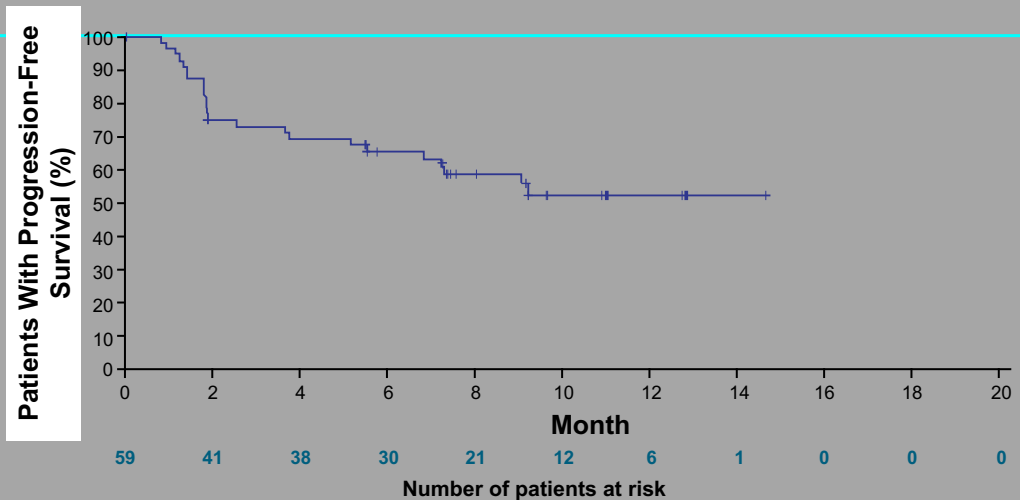
Plot shows the best percentage change from baseline in the sum of the diameters of the target lesions for each of the 45 patients in Phase 2 metastatic CSCC patients study who underwent imaging studies after the initiation of therapy, as well as the best response for each patient. The results of imaging studies were assessed by independent central review. Target lesions were lesions that could be measured according to RECIST, version 1.1; patients could have up to two target lesions per organ and five total target lesions. Nontarget lesions were lesions that could not be measured according to RECIST, version 1.1; patients with nontarget lesions only were considered to have a noncomplete response or nonprogressive disease, unless there was disappearance of all lesions or unequivocal progression. Measurements that were obtained after disease progression were excluded. A partial response was defined as a decrease in the sum of the target-lesion diameters of at least 30%, and progressive disease was defined as an increase in the sum of the target-lesion diameters of at least 20%. Three patients who had a decrease in the sum of the target-lesion diameters of at least 30% were classified as having progressive disease (red bars below baseline) because they had a new lesion or progression of a nontarget lesion. One patient had stable disease according to RECIST, version 1.1, but could not be evaluated overall (yellow bar) because the digital medical photographs could not be evaluated. The graph does not show data for the following patients (although they were included in the primary analysis): 3 patients who had new lesions or progression of nontarget lesions but had target lesions that could not be evaluated after the initiation of therapy, 1 patient who had a complete response but had nontarget lesions only at baseline, 4 patients who had nontarget lesions only, and 6 patients who had a target lesion that could not be evaluated after the initiation of therapy.

Migden MR, Rischin D, et al. *N Engl J Med*. 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

4

49

Phase 2 Study: Kaplan–Meier Curves for the Probability of Progression-Free Survival Among Patients With Metastatic CSCC

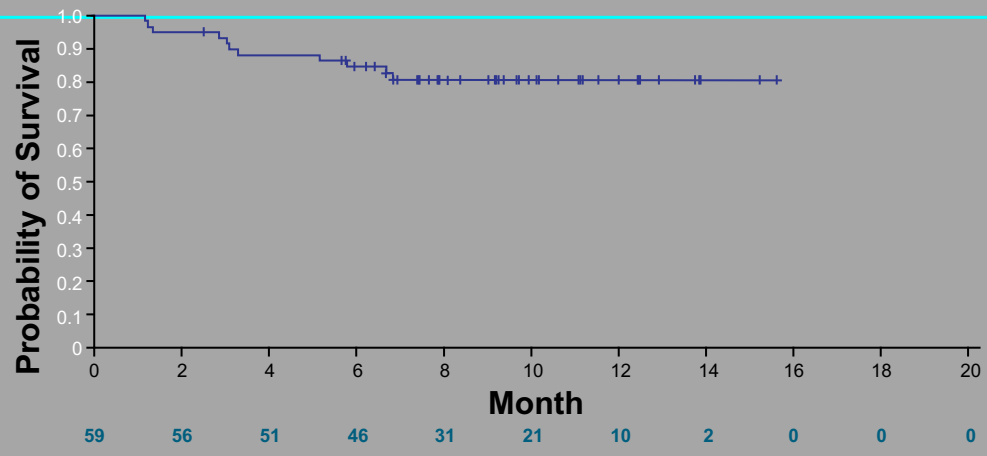


The median progression-free survival had not been reached at the time of data cutoff (October 27, 2017). The estimated probability of progression-free survival from baseline through 12 months was 53% (95% CI, 37 to 66), as assessed by independent central review.

Migden MR, Rischin D, et al. *N Engl J Med*. 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

50

Phase 2 Study: Kaplan–Meier Curves for the Probability of Overall Survival Among Patients With Metastatic CSCC



The median progression-free survival had not been reached at the time of data cutoff (October 27, 2017). The estimated probability of overall survival at 12 months was 81% (95% CI, 68 to 89).

Migden MR, Rischin D, et al. *N Engl J Med*. 2018. doi:10.1056/NEJMoa1805131 (epub ahead of print).

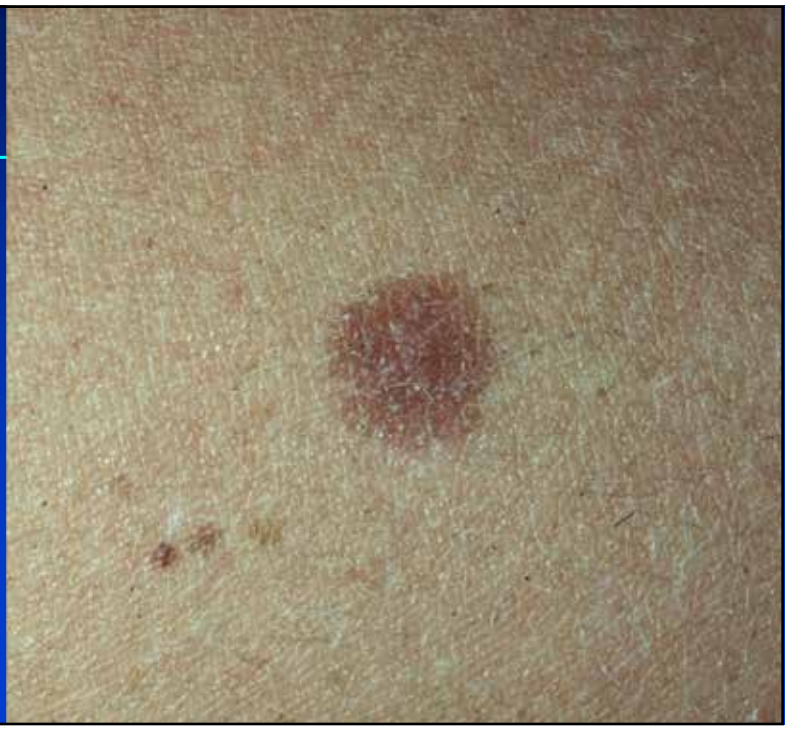
51

Melanoma

52

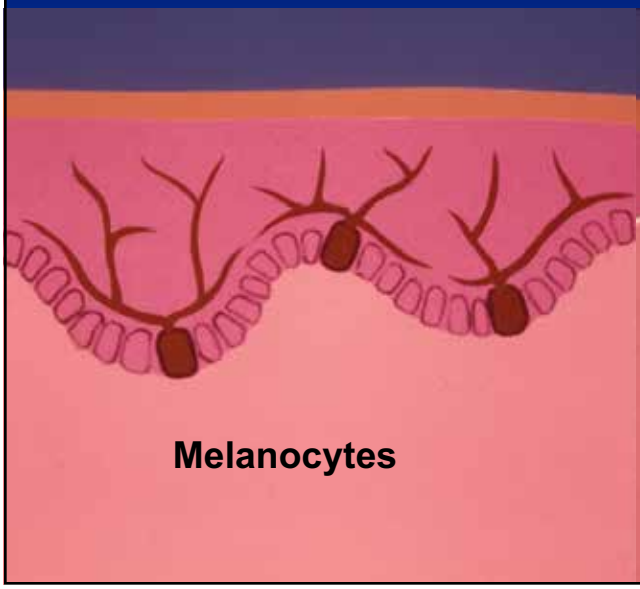
NEVI

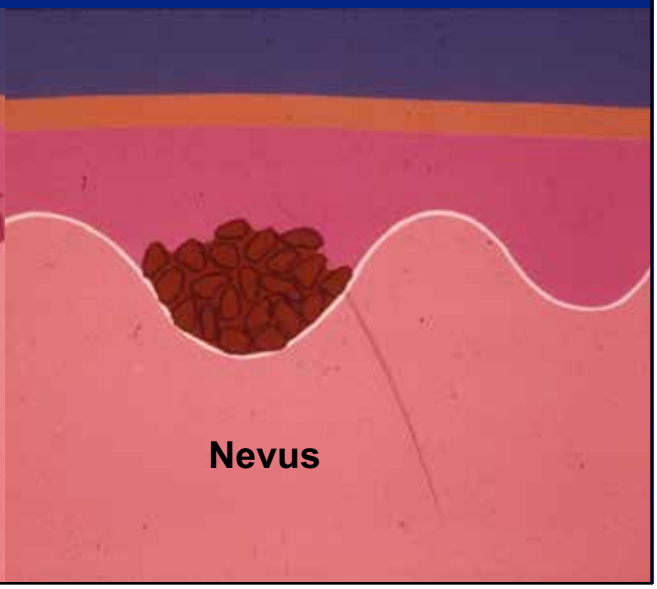
- Incidence of congenital nevi is 1%
- Acquired thru life – avg. individual has 30 moles by age 30



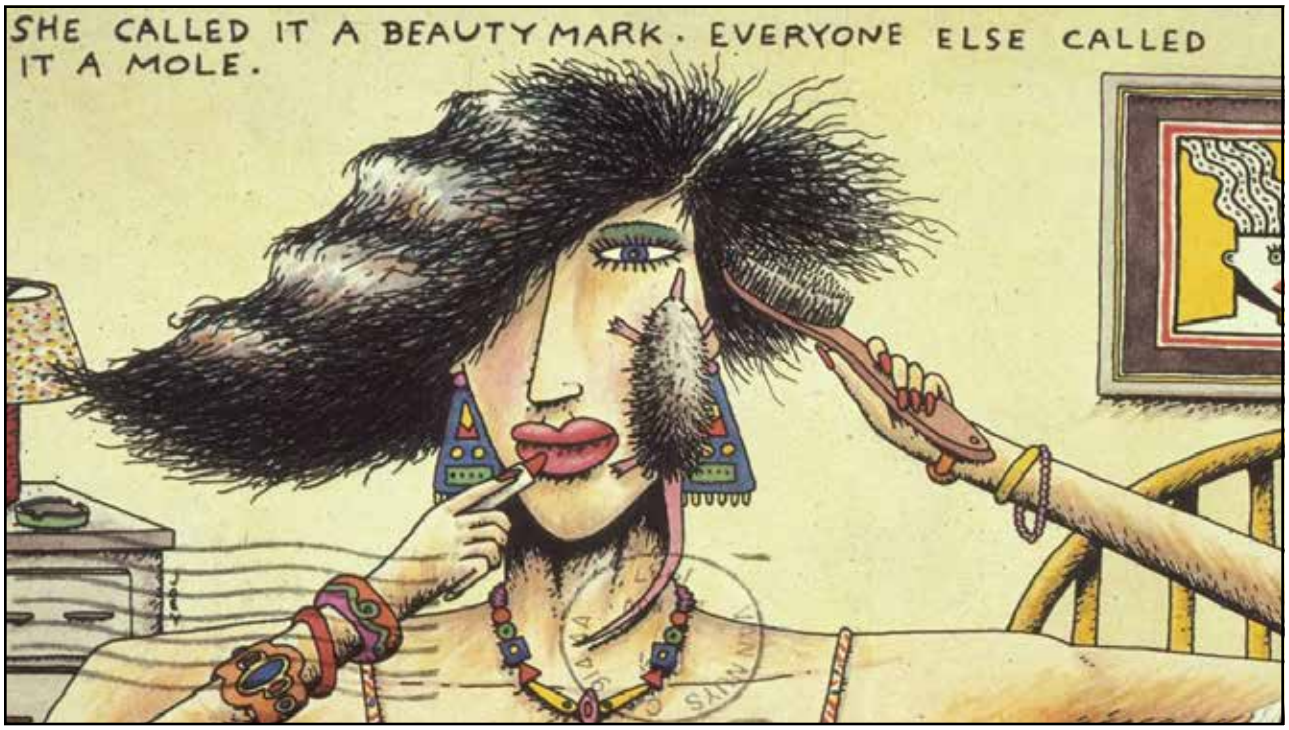
53

Melanocytes / Nevi



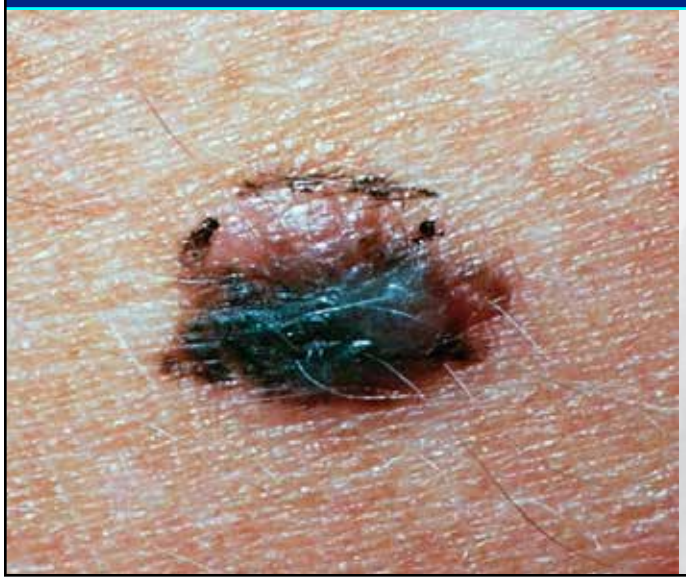


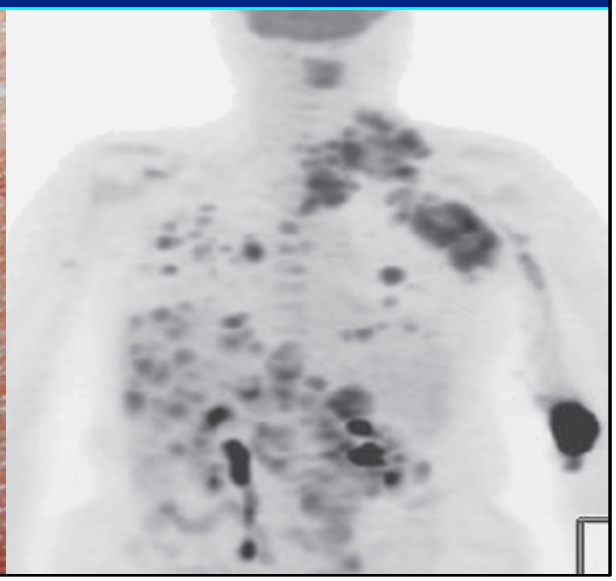
54



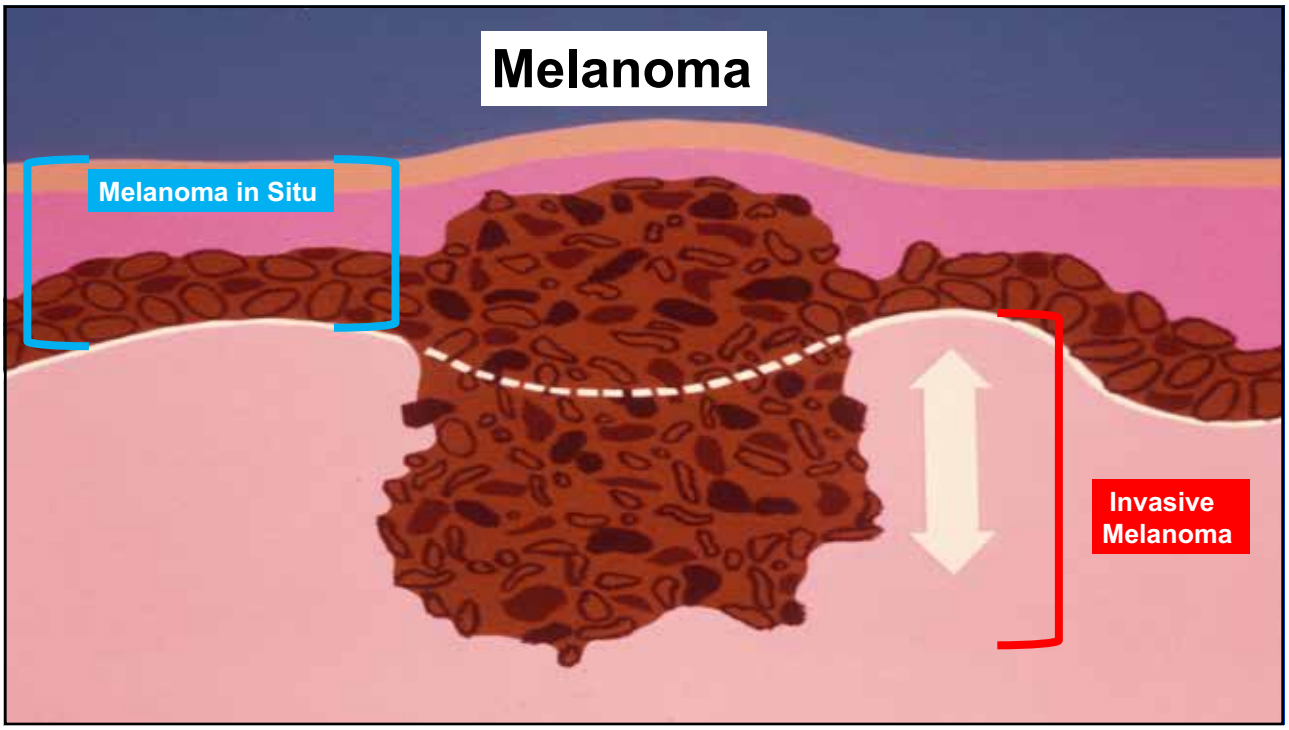
55

Melanoma





56



57

The Most Important Prognostic Factor In Melanoma Survival – Depth Of Invasion

- **Breslow Level:**
  - In situ
  - < 1mm
  - 1mm – 2mm
  - 2mm – 4mm
  - >4mm
- Clark's Level:
  - Based on anatomic location of melanoma cells
  - Replaced by Breslow Level

58

How Common is Melanoma in the U.S. ?

- The American Cancer Society's estimates for melanoma in the United States:
- In **2018: 91,270 new melanomas** will be diagnosed (about 55,150 in men and 36,120 in women).
- In **2020: 100,350 new melanomas** will be diagnosed (about 60,190 in men and 40,160 in women).

https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html

59

Risk Based on Skin Color

- Melanoma is more than 20 times more common in whites than in African Americans.
- **Lifetime risk of getting melanoma:**
  - White: 2.6% (1 in 38)
  - Black: 0.1% (1 in 1,000)
  - Hispanic: 0.6% (1 in 167)

https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html

60

Risk Factors

- The **risk** for each person can be affected by a number of different factors: fair skin, sunburns, tanning booths, family history, number of nevi, congenital nevi, immune status
- *Melanoma is more common in men overall*
  - *Before age 50* the rates are higher in women than in men.
- The risk of melanoma increases as people age.
  - The *average age* of people when it is diagnosed is ***65***
  - Not uncommon even among those younger than 30.
    - It's one of the most common (especially young women).

https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html

61

The Most Common Cancers in Young Adults Ages 20 to 39

- Breast cancer
- Lymphomas (non-Hodgkin and Hodgkin)
- ***Melanoma***
- Sarcomas (cancers of connective tissues like muscles and bones)
- Cancers of the female genital tract (cervix and ovary)
- Thyroid cancer
- Testicular cancer
- Colorectal cancer
- Brain and spinal cord tumors

https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html

62

Survival Figures Based On Breslow Level

Tumor Depth	Approximate 5 year Survival
< 1 mm	95–100%
1–2 mm	80–96%
2.1 – 4 mm	60–75%
> 4 mm	50%

British Association of Dermatologist Guidelines, 2002

63

Melanoma Survival

SEER stage	5-year relative survival rate
Localized	99%
Regional	65%
Distant	25%
All SEER stages combined	92%

64

Metastatic Melanoma

- **Until 2011**, the overall survival for **Stage IV melanoma:**
  - ***6% 5 year survival*** [1,2]
  - ***6 month median survival rate*** [1,2]
  - Surgical resection of isolated metastasis improves 5 yr. survival to 20% [3,4]

1. Dreiling L. et al Melanoma: Epidemiology, pathogenesis and new modes of treatment. Adv. Internal Med. 1996. 41: 553 – 604
2. Balch C.M., et al: Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 2001;19:35635-48
3. Essner R. et al Contemporary surgical treatment of advanced-stage melanoma. Arch Surg. 2004: 139: 961-6
4. Wong SL, et al Role of surgery in patients with Stage IV melanoma. Curr Opin Oncol. 2004; 16: 155-160.

65

AJCC TNM CLASSIFICATION FOR INVASIVE MELANOMA

T classification	
T1 ≤1.0 mm	a. <0.8 mm without ulceration b. <0.8 mm with ulceration *or* 0.8-1.0 mm with or without ulceration
T2 >1.0 to 2.0 mm	a. Without ulceration b. With ulceration
T3 >2.0 to 4.0 mm	a. Without ulceration b. With ulceration
T4 >4.0 mm	a. Without ulceration b. With ulceration
N and M classification	
N1: 1 node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	a. Clinically occult* b. Clinically detected† c. Intralymphatic metastases‡ *without* regional lymph node disease
N2: 2-3 nodes or in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node	a. Clinically occult* b. Clinically detected (≥1)† c. Intralymphatic metastases‡ with 1 occult or clinically detected regional LN
N3: ≥4 tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with ≥2 tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	a. ≥4 metastatic clinically occult nodes with *no* intralymphatic metastases b. ≥4 metastatic nodes (≥1 clinically detected), or matted nodes (any number) with *no* intralymphatic metastases c. ≥2 clinically occult or clinically detected nodes and/or presence of matted nodes (any number) *with* intralymphatic metastases
M1a: Distant skin, soft tissue (including muscle), and/or nonregional lymph nodes	With or without elevated LDH level
M1b: Lung metastasis with or without M1a	With or without elevated LDH level
M1c: Distant non-CNS visceral with or without M1a or M1b	With or without elevated LDH level
M1d: Distant metastasis to CNS with or without M1a, M1b, or M1c	With or without elevated LDH level

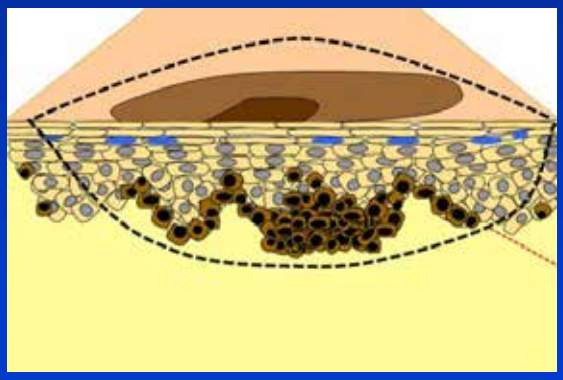
AJCC, American Joint Committee on Cancer; *CM*, cutaneous melanoma; *CNS*, central nervous system; *LDH*, lactate dehydrogenase; *LN*, lymph node; *TNM*, tumor, node, metastasis.
Adapted with permission of Springer International Publishing from Gershenwald et al.* Permission conveyed through Copyright Clearance Center, Inc.
*Clinically occult tumor-involved regional lymph nodes are microscopically diagnosed after sentinel lymph node biopsy.
†Clinically detected tumor-involved regional lymph nodes are defined as clinically evident nodal metastases confirmed by fine-needle aspiration, biopsy and/or therapeutic lymphadenectomy.
‡Intralymphatic metastases are defined by the presence of clinically apparent in-transit/satellite metastasis and/or histologically evident microsatellite metastases in the primary tumor specimen.

66

Not All Melanomas Are The Same:
(2019 Melanoma Estimates: 192,310 cases)

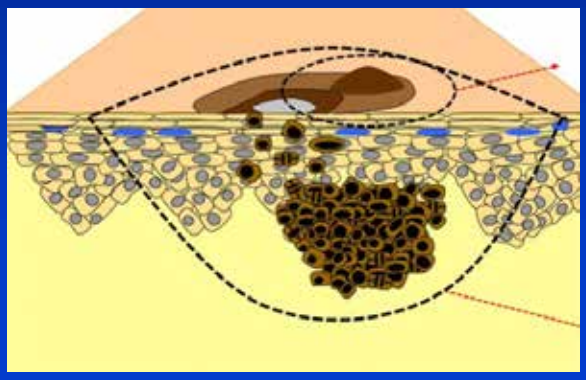
Melanoma in Situ

- 95,830 noninvasive (Melanoma in situ)



Invasive Melanoma

- 96,480 invasive melanomas



67

Surgical Management of Melanoma

- **Wide Excision:** Treatment of choice for primary cutaneous melanoma of ***any thickness*** is surgical excision with histologically negative margins[1].

1. Swelter S.M., et al Guidelines of care for the management of primary cutaneous melanomaJ Amer Acad Derm 2019 Vol 80, Issue 1, 208-250

68

Table IX. Surgical margin recommendations for primary cutaneous melanoma

Tumor thickness	Surgical margin*
In situ	0.5-1 cm†
≤1.0 mm	1 cm
>1.0 to 2.0 mm	1-2 cm
>2.0 mm	2 cm

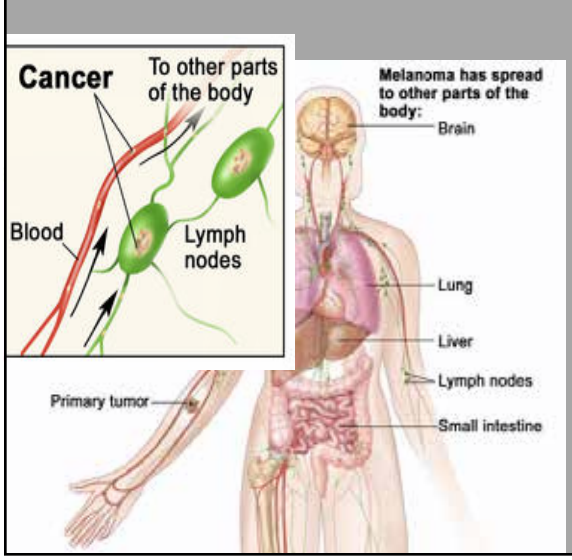
*Recommended surgical excision margins are clinically measured from the edge of the lesion or prior biopsy at the time of surgery; they are not histologic margins as measured by the pathologist. Margins may be modified for functional considerations or anatomic location.

†Margins larger than 0.5 cm may be necessary for melanoma in situ, lentigo maligna type.

Swelter S.M., et al Guidelines of care for the management of primary cutaneous melanomaJ Amer Acad Derm 2019 Vol 80, Issue 1, 208-250

69

Halstedian Model vs. Contemporary Model of Metastasis



Halstedian Model
Orderly progression

1 Primary (T) → 2 Nodal (N) → 3 Distant (M)

Contemporary Model
Alternate routes

Primary → Nodal / Distant

70

Surgical Management of Melanoma

- **Sentinel Lymph Node Biopsy:**
  - Only a "staging tool" – does not increase overall survival based on MSLT-1[1]
  - Recommended for melanomas > 0.8 mm in depth[2]

1. Morton DL, et al. Final Trial Report of Sentinel-Node Biopsy vs. Nodal Observation in Melanoma *N Engl J Med*. 2014; 370:599-609 DOI: 10.1056/NEJMoa1310460
2. Swelter S.M., et al Guidelines of care for the management of primary cutaneous melanomaJ Amer Acad Derm 2019 Vol 80, Issue 1, 208-250

73

Surgical Management of Melanoma

- **Completion Lymph Node Dissection:**
  - *NO longer recommended based on MSLT-2*[1,2]
  - Immediate completion lymph-node dissection was not associated with increased melanoma-specific survival among 1934 patients with data that could be evaluated in an intention-to-treat analysis or among 1755 patients in the per-protocol analysis.

1. Faries, B., et al Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma N Engl J Med 2017; 376:2211-2222DOI: 10.1056/NEJMoa1613210
2. Bello DM, Faries MB.The Landmark Series: MSLT-1, MSLT-2 and DeCOG (Management of Lymph Nodes)Ann Surg Oncol. 2020 Jan;27(1):15-21. doi: 10.1245/s10434-019-07830-w. Epub 2019 Sep 18. Review

74

2. Treating The IBD Patient Who Is "At Risk" For Melanoma and NMSC

75

What Did We Do For Our Patient?

- Considerations:
  - Maintain therapy and add acetretin (a systemic retinoid used in SOTR pts. to decrease NMSC burden)
  - Change to another biologic or oral systemic…and which one?

76

What are the inherent risks associated with immunosuppresive agents and TNFi?

1. New melanoma and NMSC development
2. Reactivation of melanoma and NMSC

77

Melanoma Risk: With Immunosuppressive, TNFi

- *TNFα inhibition and autoimmune disease alone do not significantly increase risk of melanoma.*
- *Immunosuppressive agents, high-dose corticosteroids, and topical immunosuppressants were associated with melanoma* (odds ratio [OR] 1.42 CI, 1.03-1.95, 3.30 CI, 2.44-4.48, and 1.87 CI, 1.06-3.28, respectively).

Damento G.M. et al TNF-Alpha Inhibition and Other Immunosuppressants in the Development of Uveal and Cutaneous Melanoma Mayo Clinic Proc. 2019 Jul;94(7):1287-1295. doi: 10.1016/j.mayocp.2018.11.033.

78

NMSC Risk: Immunosuppressives, TNFi

- This ***NMSC*** risk might also be elevated in patients who have used *cyclosporine.*
- Some studies also suggest an increased risk for ***NMSC*** in patients receiving ***TNFi.***
- Ustekinumab (12/23 inhibitor), IL-17 inhibitors, and IL-23 inhibitors, do not appear to alter malignancy risk…… BUT…..Larger and longer-term studies are necessary.

Damento G.M. et al TNF-Alpha Inhibition and Other Immunosuppressants in the Development of Uveal and Cutaneous Melanoma Mayo Clinic Proc. 2019 Jul;94(7):1287-1295. doi: 10.1016/j.mayocp.2018.11.033.

81

Suggested Cancer Screenings CDC

Breast cancer:
- Women age 50-74 years, average risk: mammogram every 2 years
- Women age 40-50 years, above average risk: consult with provider

Cervical cancer:
- Women age 21-65 years: Papanicolaou test every 3 years

Colore
- M … : screening
- M … ars: at risk p…
- Male and female patients age >75 years: consult with provider

What no skin exam?

Lung cancer:
- Male and female patients age 55-80 years: low-dose computed tomography if:
  - Smoking history of >30 pack years and
  - Currently smoke or have smoked within the past 15 years

From: Centers for Disease Control and Prevention, https://www.cdc.gov/cancer/dcpc/prevention/screening.htm.[184]

82

Recommendations For Skin & Ophthalmic Screening

- In patients receiving immunosuppressive treatments, physicians should consider monitoring with:
  - Full body skin examinations
  - Dilated ophthalmic exam

Damento G.M. et al TNF-Alpha Inhibition and Other Immunosuppressants in the Development of Uveal and Cutaneous Melanoma Mayo Clinic Proc. 2019 Jul;94(7):1287-1295. doi: 10.1016/j.mayocp.2018.11.033.

83

What About Reactivation Of His Melanoma on a TNFi

87

Paradigm Shift: *"Tumor Dormancy"*

88

A Case Of: *"Tumor Dormancy"*

- An organ donor had undergone surgery for a melanoma 16 years prior to her cerebral hemorrhage
- She had not had a local reoccurrence or metastasis, and she died from cerebral hemorrhage.
- Her two kidneys were transplanted to two recipients.
- *Both developed generalized melanoma and died from that malignancy*

MacKie RM, Reid R, Junor B. Fatal melanoma transferred in a donated kidney 16 years after melanoma surgery. N Engl J Med. 2003;348(6):567–568.

89

Late Metastasis (> 10 Years) From Melanoma

Table 3. List of nine publications on the frequency of late metastases (usually ≥10 years) from CMM.

REFERENCE	NO OF PATIENTS STUDIED	NO OF PATIENTS WITH LATE METASTASES (% IN BRACKETS)[1]
Crowley & Seigler[44]	7104	168 (2.4)
Schmid-Wendtzler et al[45]	6298	31 (0.5)
Brauer et al[46]	4196	70 (2.8)#
Leman & MacKie[47]	3822	25 (0.7)
Tsao et al[48]	2766	20 (0.7)##
Hohnheiser et al[49]	2487	34 (1.4)
Hansel et al[50]	1881	20 (1.1)
Shaw et al[51]	1283	34 (2.7)
Peters et al[52]	1015	36 (3.5)
Total	30852	438 (1.7)

Notes: [1] #: "Late" = 8 years, ##: "Late" = 15 years, "Ultra-late" metastases from CMM (≥20 years) have been reported, including metastases 41,[53] 46,[54] and 54 years.[55]

90

The risk of an inadvertently transmitted malignancy from a donor to an organ recipient

- Risk: very small (0.01%– 0.05%)
- Risk of dying during the first year while on the waiting list for a life-saving organ is considerably larger and ranges from 2% for kidney candidates to 17% for lung candidates (1)

1. Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. Br J Surg. 2014;101(7):768–774.

91

Most Frequent Types of Donor-Derived Malignant Tumors

HISTOLOGIC TYPE	PENN'S PUBLICATION (%)	XIAO ET AL'S PUBLICATION (%)
RCC Renal Cell CA	38	21
CMM Cutaneous Melanoma	18	18
LUNG	10	9
GMB Glioblastoma	7	5

RCC = Renal Cell Carcinoma; CMM = Cutaneous Malignant Melanoma; GMB: Glioblastoma Multiforme

Friberg and Nyström. Cancer Metastases: Early Dissemination and Late Recurrences. Cancer Growth and Metastasis 2015:8 43–49 doi:10.4137/CGM.S31244.

92

Conclusion

- 1. Disseminated tumor cells frequently exist in the original host prior to the detection of the primary tumor.
- 2. Metastatic cells can reside in organs that are not usually the site of secondary tumors, that is, the kidneys and the heart.
- 3. Metastatic cells in the original host can remain dormant for decades after the primary tumor has been removed.
- 4. The mechanisms capable of inducing dormancy may be reversible, leading to late recurrences.

Friberg and Nyström. Cancer Metastases: Early Dissemination and Late Recurrences. Cancer Growth and Metastasis 2015:8 43–49 doi:10.4137/CGM.S31244.

93

What Did We Do For Our Patient?

- We changed the patient to *vedolizumab*

94

3. Managing Patients on Immunotherapy and Systemic Therapy For Metastatic Melanoma and Advanced/Metastatic NMSC

95

U.S. FDA Approved Therapies for Metastatic Melanoma

- ***Immune Checkpoint Modulators***
  - Ipilimumab (Yervoy ®): approved 2011
  - Pembrolizumab (Keytruda ®) approved 2015
  - Nivolumab (Opdivo ®) approved 12/2014
- ***Growth Pathway Targeted Therapy***
  - **BRAF Inhibitors**
    - Vemurafenib (Zelboraf ®): approved 2011
    - Debrafenib (Tafinlar ®): approved 2013
  - **MEK Inhibition**
    - Tratenib (Mekinist®): approved 2013
    - Cobimetinib (Cotellic®) : approved 2015
  - **Combination BRAF & MEK Inhibition**
    - Encorafenib (BRAFi) Plus Binimetinib (MEKi): approved 9/2017

96

IMMUNE CHECKPOINT SIDE EFFECTS

Anti-PD-1 | Anti-PD-L1 | Ipilimumab

Agent, Patients (N), and Study [Reference]	Nivolumab N = 296[7]		Pembrolizumab N = 135[65]		MPDL3280A N = 171*[49]		BMS-936559 N = 207[17]		Ipilimumab N = 131[68]	
Adverse Event	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Pneumonitis	3%	1%	4%	0%	NR	0%	NR	NR	NR	NR
Diarrhea	11%	1%	20%	1%	26%	1%	9%	0%	32.8%	5.3%
Colitis	NR	NR	NR	NR	NR	NR	NR	NR	7.6%	5.3%
Rash	12%	0%	21%	2%	18%	1%	7%	0%	19.1%	0.8%
Pruritus	9%	< 1%	21%	1%	NR	NR	6%	0%	24.4%	0%
Vitiligo	3%	0%	9%	0%	NR	NR	2%	0%	2.3%	0%
ALT elevation	4%	1%	8%	0%	NR	3%	1%	0%	1.5%	0%
AST elevation	3%	1%	10%	1%	NR	NR	NR	NR	0.8%	0%
Infusion reaction/hyper-sensitivity	3%	< 1%	NR	NR	NR	NR	11%	< 1%	NR	NR
Fatigue	NR	NR	30%	1%	43%	4%	NR	NR	42%	6.9%
Hyperthyroidism/ hypothyroidism	3%	< 1%	8%	1%	NR	NR	3%	0%	1.5%	0%

Pneumonitis with anti-PD-1/ PD-L1

Most common and serious (Grade 3,4) side effects are related to colitis-death from ipilimumab

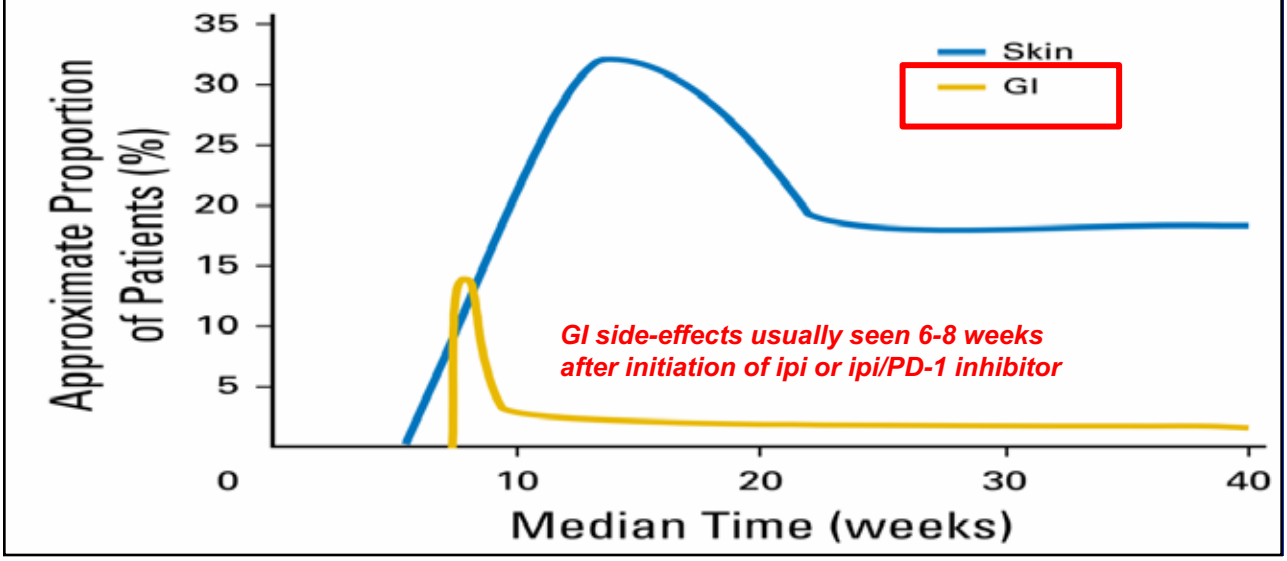
Vitiligo predicts good response

Thyroid and pituitary failure due to autoimmune attack

Oncology. 2014

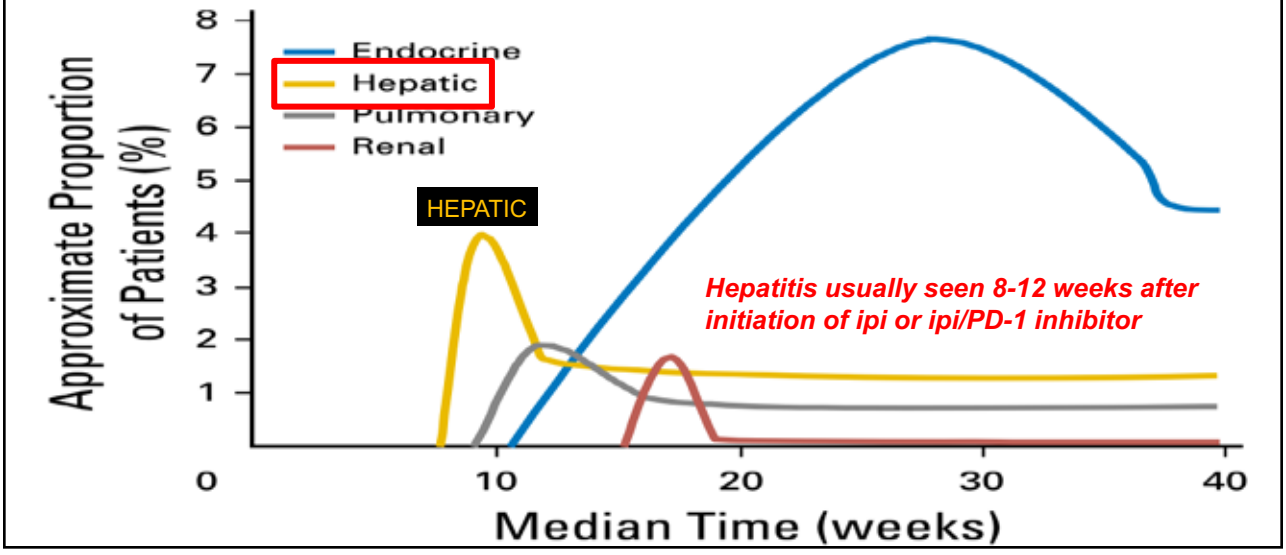
97

Timing of the Onset of Immune Related AEs (irAEs): GI and Skin



98

irAE: Hepatitis



99

General Principles of Management of Immune Related AEs

- Mainstay: immunosuppression with corticosteroids and immunosuppressives (inflixumab in the case of IBD flares)
- Most AEs resolve
- Temporary immunosuppression: does NOT seem to limit immune checkpoint inhibition (1,2)
- Prolonged immunosuppression (>4 weeks) with prednisone requires Pneumocystis carinii prophylaxis (NCCN guidelines) (3)

1. Horvat TZ, Adel NG, Dang T-O, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol. 2015;33(28): 3193-3198.
2. Weber JS, Antonia SJ, Topalian SL, et al. Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): a pooled analysis. J Clin Oncol. 2015;33(15 suppl):abstr 9018.
3. National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections(www.n ccn.org/org/professionals guidelines) /physician_gls/pdf/infections.pdf. Accessed June 2, 2016.

100

Annals of Internal Medicine

REVIEW

Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease

A Systematic Review

Noha Abdel-Wahab, MD, PhD; Mohsin Shah, MD; Maria A. Lopez-Olivo, MD, PhD; and Maria E. Suarez-Almazor, MD, PhD

Data Sources: MEDLINE, EMBASE, Web of Science, PubMed ePubs, and the Cochrane Central Register of Controlled Trials through September 2017 with no language restrictions.

Ann Intern Med. 2018;168:121-130. doi:10.7326/M17-2073

101

Inflammatory Bowel Dz: (n= 13 Patients) 8 w/ UC – 5 w/ Crohns

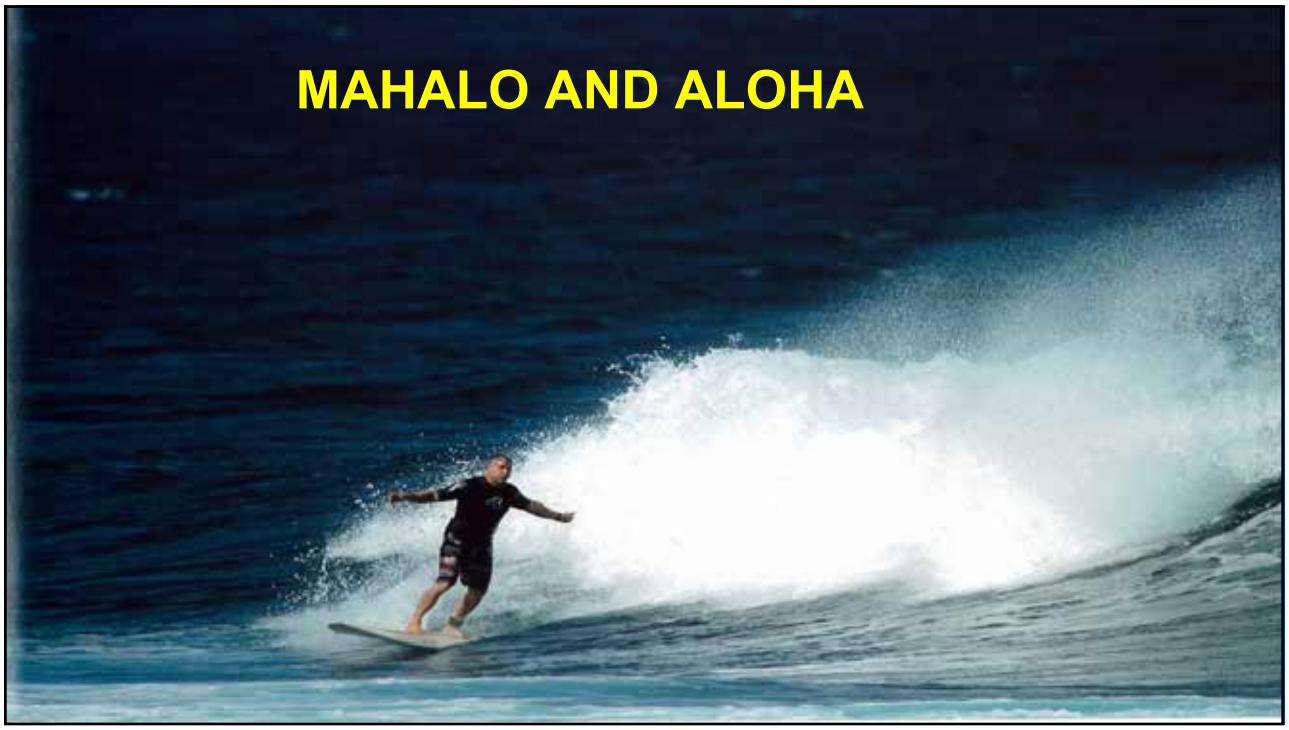
- 8 pts had an AE (62%)
- 5 had exacerbation (39%)
- 2 pts with Crohn's dz had de novo colitis (15%)
- 5 pts w/ active bowel sx at initiation of CPI tx – 3/5 had no AEs
- Tocilizumab and vedolizumab were administered concurrently w/ CPIs in 2 pts -> both developed colitis

102

Summary

- It is important that any IBD patient who is at risk for skin cancer be screened by a dermatologist
- Melanoma in situ: when excised w/ adequate margins is nearly 100% cure – immunosuppression **NOT** a critical issue
- Invasive melanoma: Immunosuppression is an important consideration
- Low risk SCC & BCC: immunosuppression **NOT** an issue
- High risk SCC & Locally advanced BCC: Immunosuppression is an important consideration
- Metastatic BCC,SCC and melanoma: Immunosuppression is an important consideration

103



104