ASSOCIATION OF COMMUNITY CANCER CENTERS

Multidisciplinary Advanced Cutaneous Squamous Cell Carcinoma Care

Rocky Mountain Oncology Society
Fall Dinner Symposia
Thursday, November 7th 2019

ACCC
Association of Community Cancer Centers

RMOS
ROCKY MOUNTAIN ONCOLOGY SOCIETY

Speakers

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Advanced Cutaneous Squamous Cell Carcinoma

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Disclosures

Dr. Misha Miller

I have no relevant disclosures.

Objectives

- To clinically identify cutaneous squamous cell carcinoma.
- To identify high risk features of cutaneous squamous cell carcinoma.
- To discuss Mohs micrographic surgery as a treatment option for cutaneous squamous cell carcinoma.
- To review case studies the highlight a multidisciplinary approach to treatment of cutaneous squamous cell carcinoma.

Cutaneous Squamous Cell Carcinoma (cSCC)

- 2nd most common malignancy of the skin
- Chronically sun-exposed skin
- #1 skin cancer on mucosa or hands
  - Lips, genitals

Cutaneous Squamous Cell Carcinoma

cSCC

- Immunocompromised at increased risk
- Renal transplant pts, risk of cSCC that is ↑18x
- May arise in chronic inflammation s/a burn (Marjolin's ulcer)
  - High rate of metastasis

Squamous Cell Carcinoma

Squamous cell carcinoma in situ - genitals

Seen in association with:

- HPV
- lack of circumcision
- chronic inflammation

May progress to invasive SCC

Erythroplasia of Queyrat

- Special type of SCCIS of penis
- Erythematous, moist & velvety
- ~ 30% may develop invasive SCC
- Metastasis in 20%
- One series found –
  - HPV 8 found in all eight cases studied
  - HPV 8 not found in classic SCCIS of penis

Erythroplasia of Queyrat

- Aggressive management
- Cooperation between dermatology (Mohs) and often urology
- Skip areas with urethral involvement are well-documented in the literature

Squamous Cell Carcinoma

- Histology (high risk features):
  - Breslow Depth >2mm
  - Clark level ≥ 4
  - Consider adjuvant treatment
    - Perineural Invasion (PNI)
      - Diameter ≥0.1 mm
    - Lymphovasular invasion

Lack of uniformity in reporting
Nonstandard tissue sampling make reporting difficult

Squamous Cell Carcinoma
High Risk features

- Tumor diameter >20 mm
- Location: Temple, ear, lip
- Poor differentiation
- Etiology (Marjolin's >> sunlight induced)

Mohs Micrographic Surgery (MMS)

- MMS is an out-patient based surgical procedure for treating skin cancer
  - Offers the highest cure rates for skin cancer
  - Preserves the greatest amount of normal, uninvolved tissue

- Dermatologist: both the surgeon and the pathologist

- Recommended as the first line treatment for the majority of high risk skin cancers or skin cancers in high risk locations

Mohs Micrographic Surgery vs. Excision

SURGICAL DERMATOLOGY

BJD
British Journal of Dermatology

Recurrence rates of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery vs. standard excision: a retrospective cohort study*

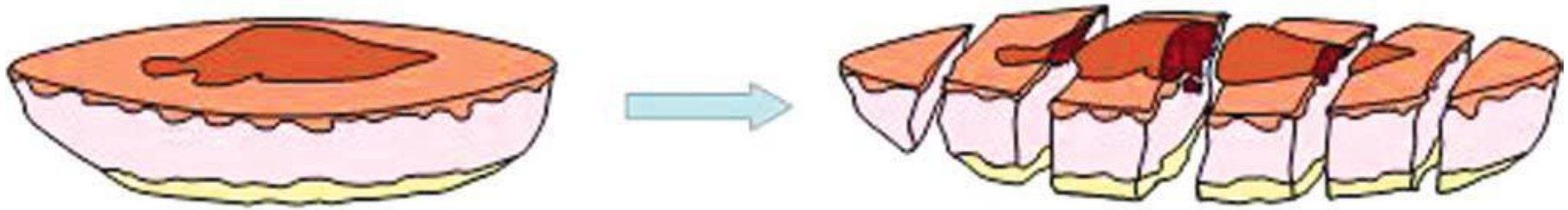
C.B. van Lee,[1] B.M. Roorda,[2] M. Wakkee,[1] Q. Voorham,[3] A.L. Mooyaart,[4] H.C. de Vijlder,[5] T. Nijsten[1] and R.R. van den Bos[1]

[1]Department of Dermatology and [4]Department of Pathology, Erasmus Medical Centre Cancer Institute, Rotterdam, the Netherlands
[2]Department of Dermatology, University Medical Centre Groningen, Groningen, the Netherlands
[3]PALGA: The Nationwide Network and Registry of Histology and Cytopathology, Houten, the Netherlands
[5]Department of Dermatology, Isala Hospital, Zwolle, the Netherlands

Recurrence rate of cSCC of 3% with MMS, 8% with standard excision

Mohs versus frozen sections

- Traditional tissue processing (formalin fixed paraffin embedded tissue)
  - Sectioned vertically “bread loafing”
  - Tissue excised at a 90-degree angle
  - Processing involves sampling random sections of tissue throughout the tissue block
  - Bread loafing is estimated to examine <1% of the total histologic margin

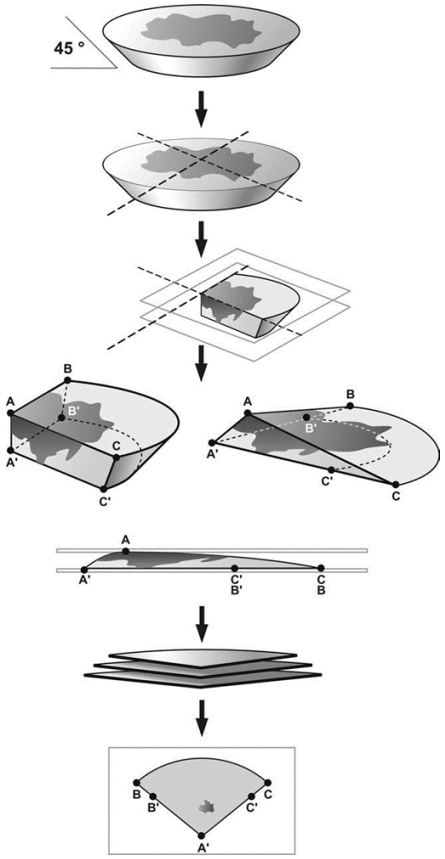


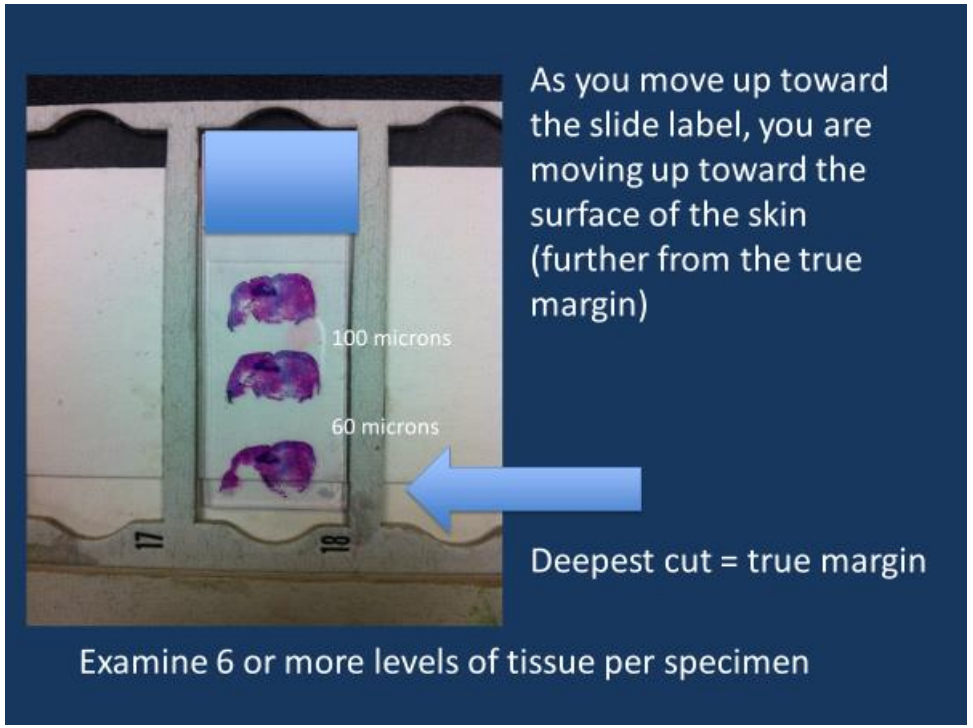
Van der Eerden et al. Laryngoscope. 2010; 120 (12) 2378- 84

Continued ….

- Mohs sectioning has higher cure rates because 100% of the margin can be examined
- Mohs also allows for the sparing of normal tissue
- There is no standard surgical “margin” in Mohs surgery. Tissue pathology examined is either clear of tumor or not clear of tumor.

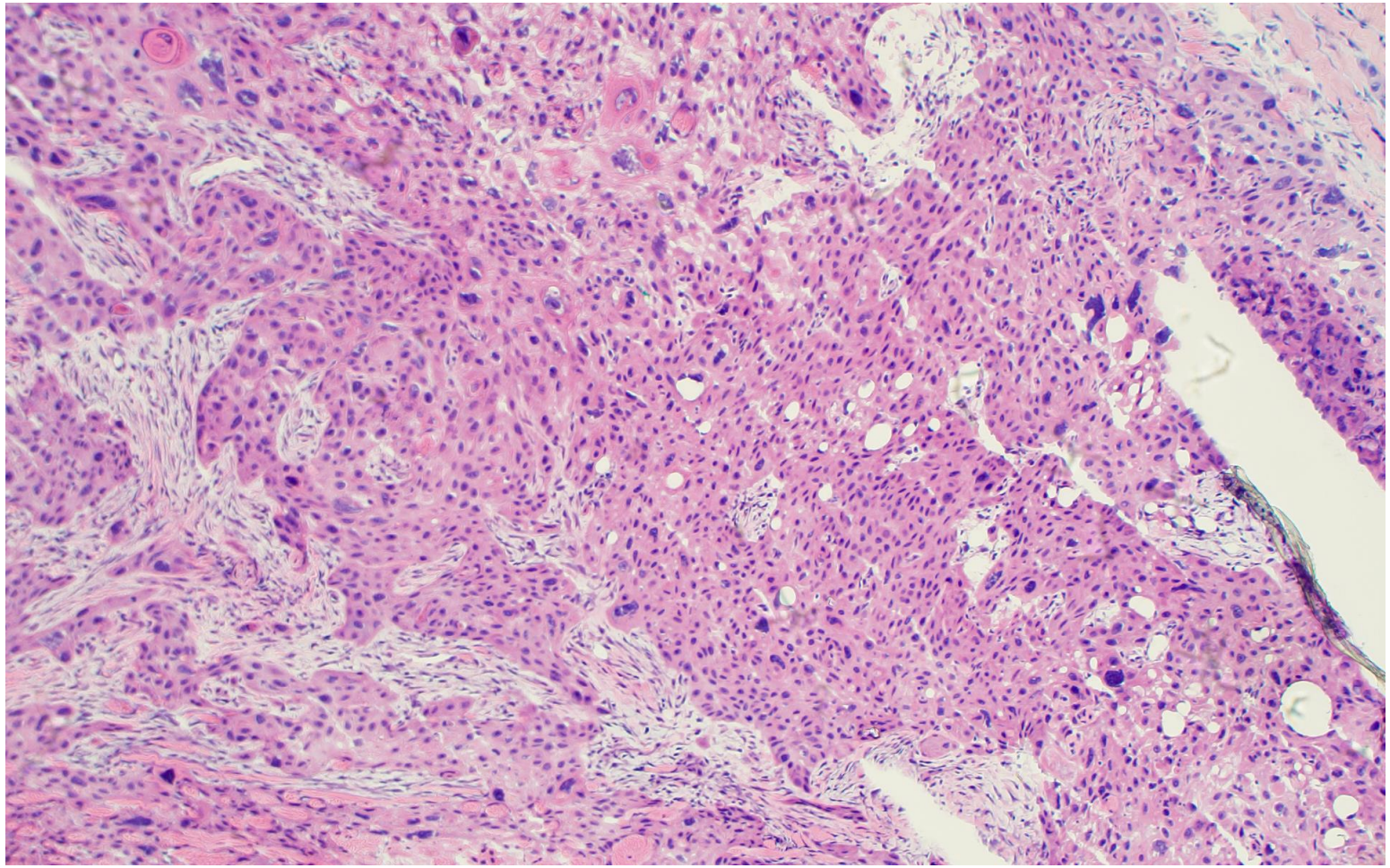
Mohs micrographic surgery - histopathology



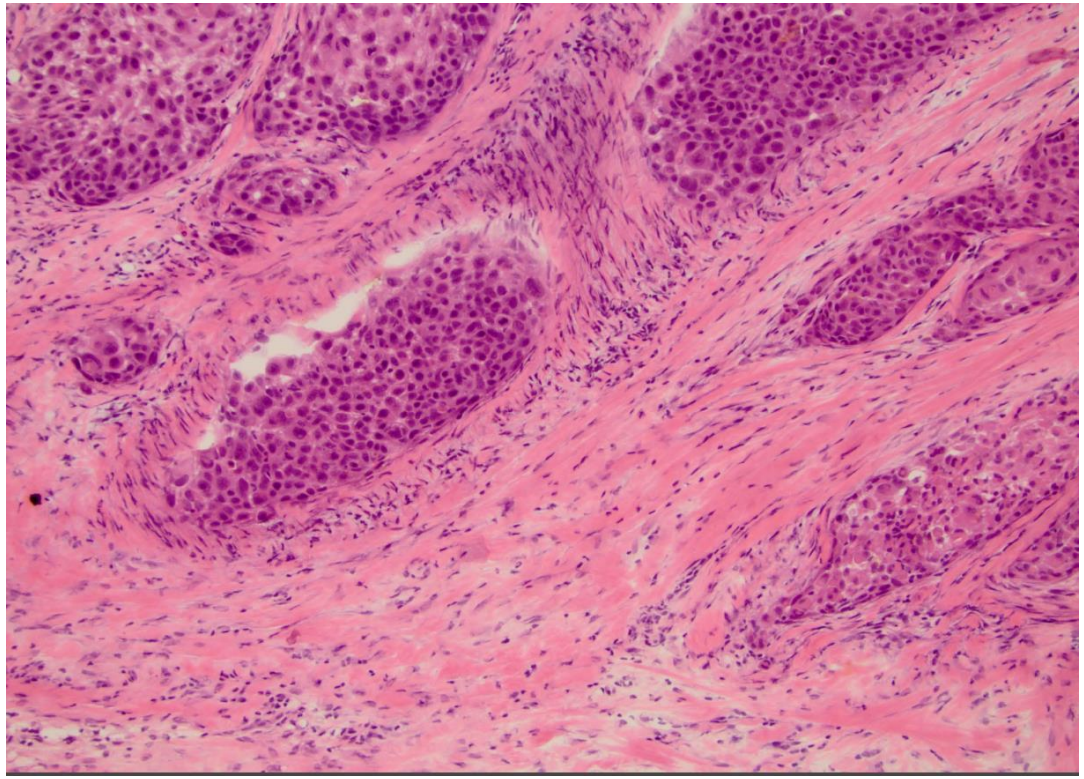


Van der Eerden et al. Laryngoscope. 2010; 120 (12) 2378- 84

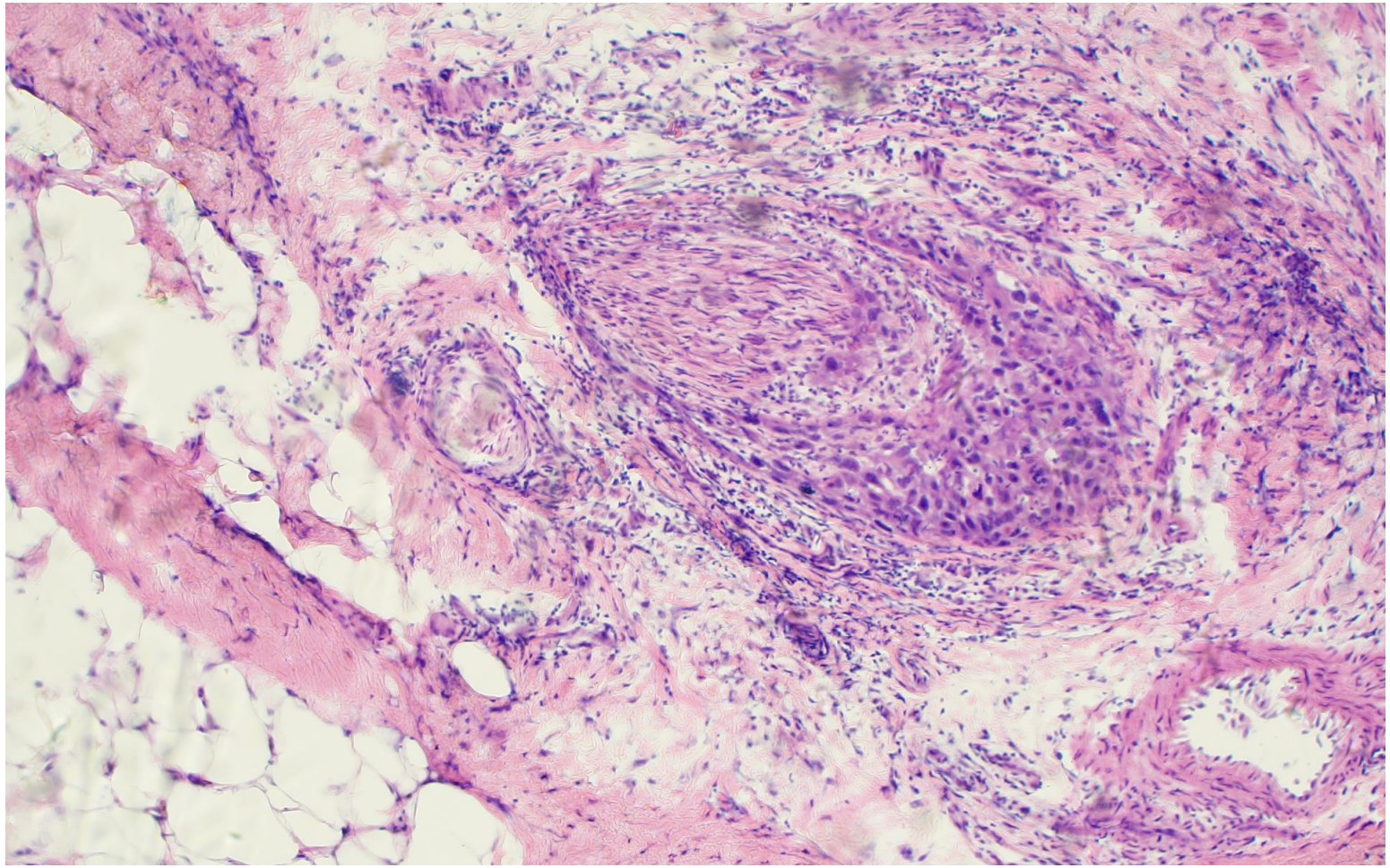
Moderately Differentiated cSCC



cSCC – Intravascular Invasion

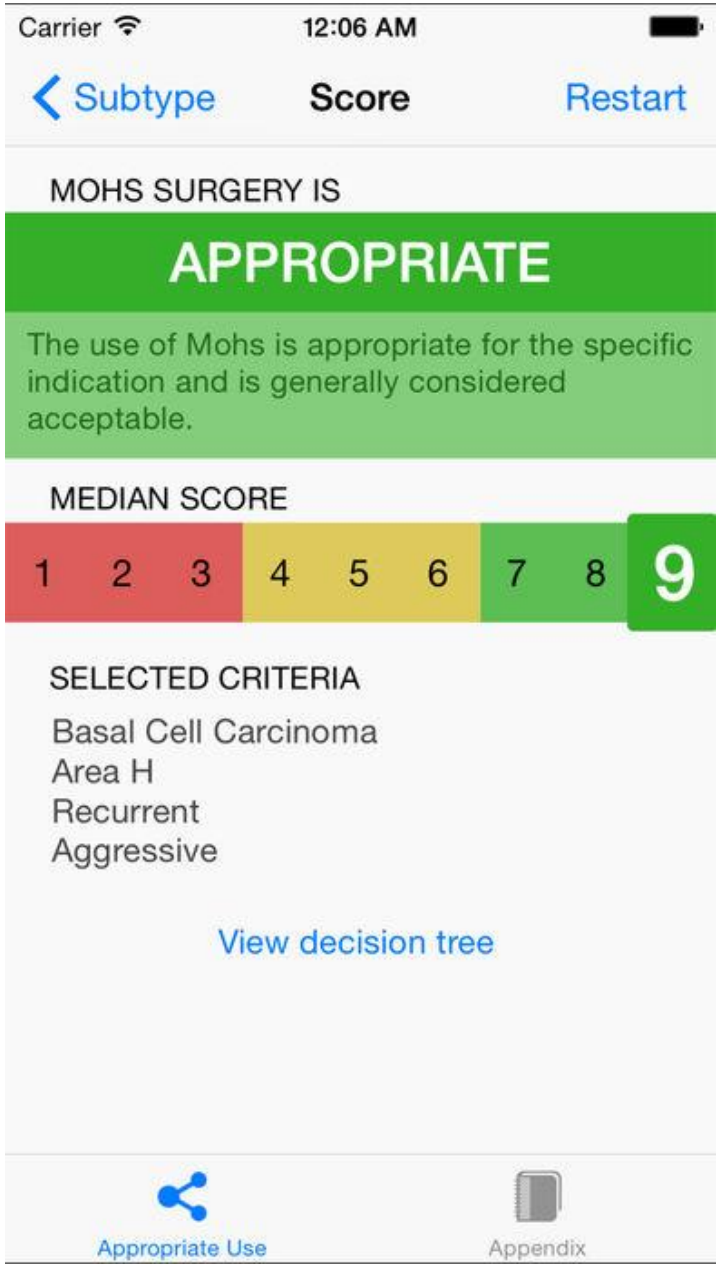


cSCC - Perineural Invasion



Clinical Scenarios for MMS

- Appropriate Use Criteria (AUC) developed in 2012 for 270 clinical scenarios
  - Designed to minimize overutilization of MMS
    - 400% increase from 1995-2009
    - 2 billion per year in Medicare $$
  - AUC stratifies tumors based on
    - Patient characteristics
    - Location
    - Recurrent/ non recurrent
    - Size
    - Histologic subtype
- Phone application available on iTunes


Carrier
12:06 AM
Subtype
Score
Restart
MOHS SURGERY IS
APPROPRIATE
The use of Mohs is appropriate for the specific indication and is generally considered acceptable.
MEDIAN SCORE
1 2 3 4 5 6 7 8 9
SELECTED CRITERIA
Basal Cell Carcinoma
Area H
Recurrent
Aggressive
View decision tree
Appropriate Use
Appendix

MMS Cost Effectiveness

- A study of 400 consecutive tumors in an out-patient setting showed the following average costs
  - Mohs surgery: $1,243
  - Primary excision with permanent sections: $1,167
  - Cost analysis included
    - Initial visit and histologic confirmation
    - Excision/Mohs
    - Repair
    - Estimated margin positivity and recurrence rates
- A review 10 years later found traditional excision and Mohs surgery to be equal in cost

Advances in Cutaneous Squamous Cell Carcinoma

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CU Specialty Care at Highlands Ranch | Cutaneous Oncology
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School of Medicine | Department of Medicine

Disclosures

Dr. Ryan Weight

Consultant

- Castle Biosciences Inc.
- ACCC-ICLIO
- Novartis
- SITC

Speakers Bureau

- Merck

cSCC Prevention

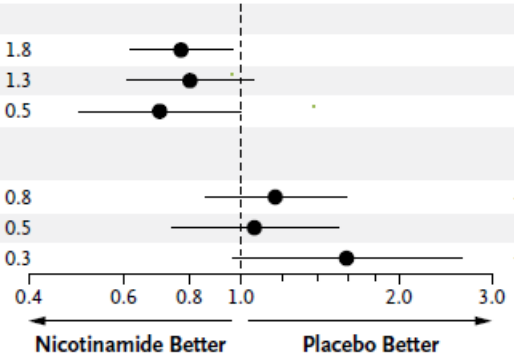
N = 386, randomized 1:1
At least 2 NMSCs past 5 years
500 mg nicotinamide BID vs placebo

The NEW ENGLAND JOURNAL of MEDICINE

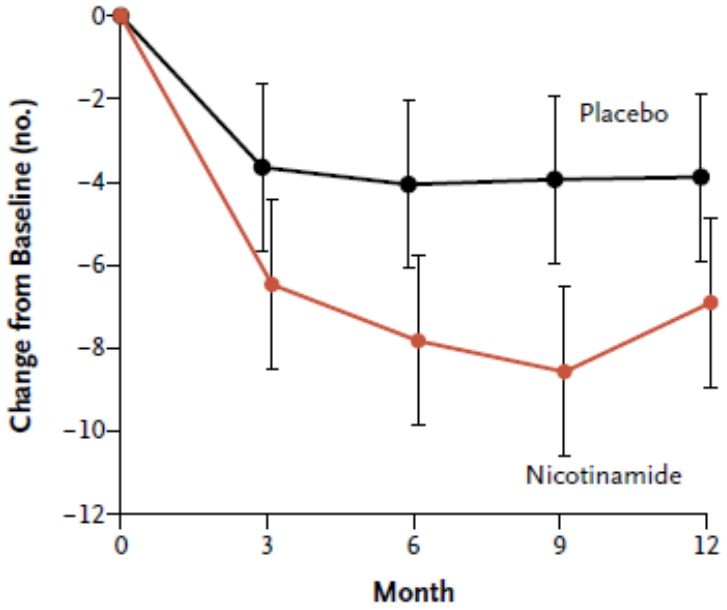
ORIGINAL ARTICLE

A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

Subgroup	Placebo (mean no. of lesions/person)	Nicotinamide (mean no. of lesions/person)	Relative Difference, % (95% CI)	P Value
12-mo intervention period				
NMSCs	2.4	1.8	23 (4 to 38)	0.02
BCCs	1.7	1.3	20 (−6 to 39)	0.12
SCCs	0.7	0.5	30 (0 to 51)	0.05
6-mo postintervention period				
NMSCs	0.8	0.8	−17 (−59 to 14)	0.33
BCCs	0.6	0.5	−6 (−53 to 26)	0.73
SCCs	0.3	0.3	−59 (−163 to 4)	0.07



Change from Baseline to Month 12 in Number of Actinic Keratoses

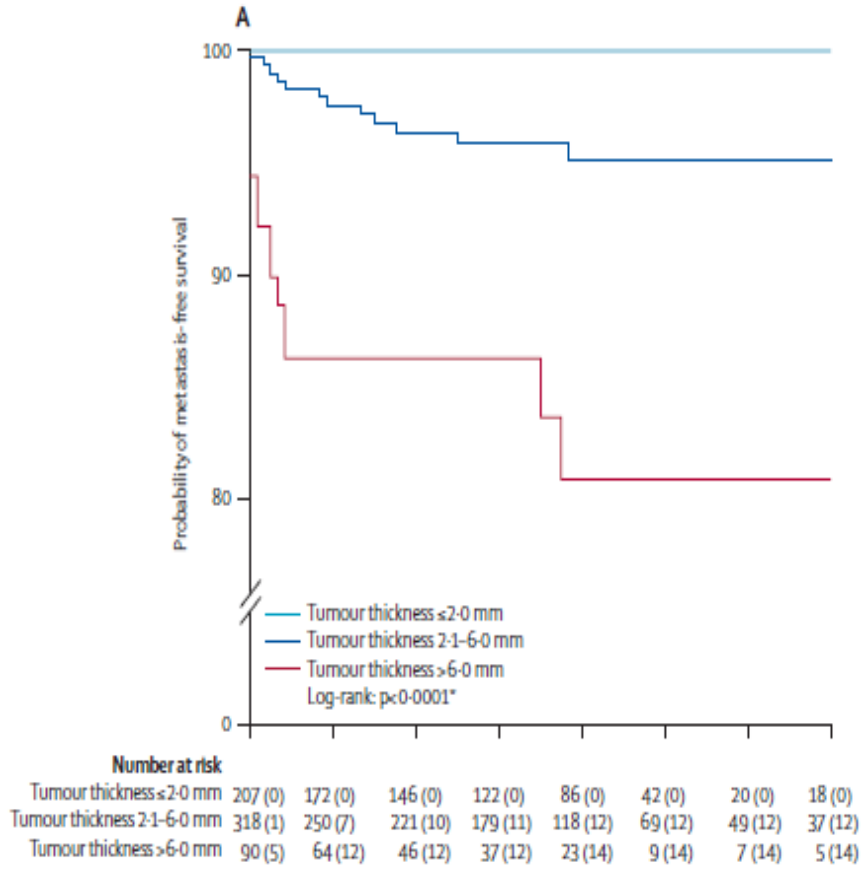


A. Chen et al. NEJM. 2015. 373(17): 1618-1626

cSCC Risk

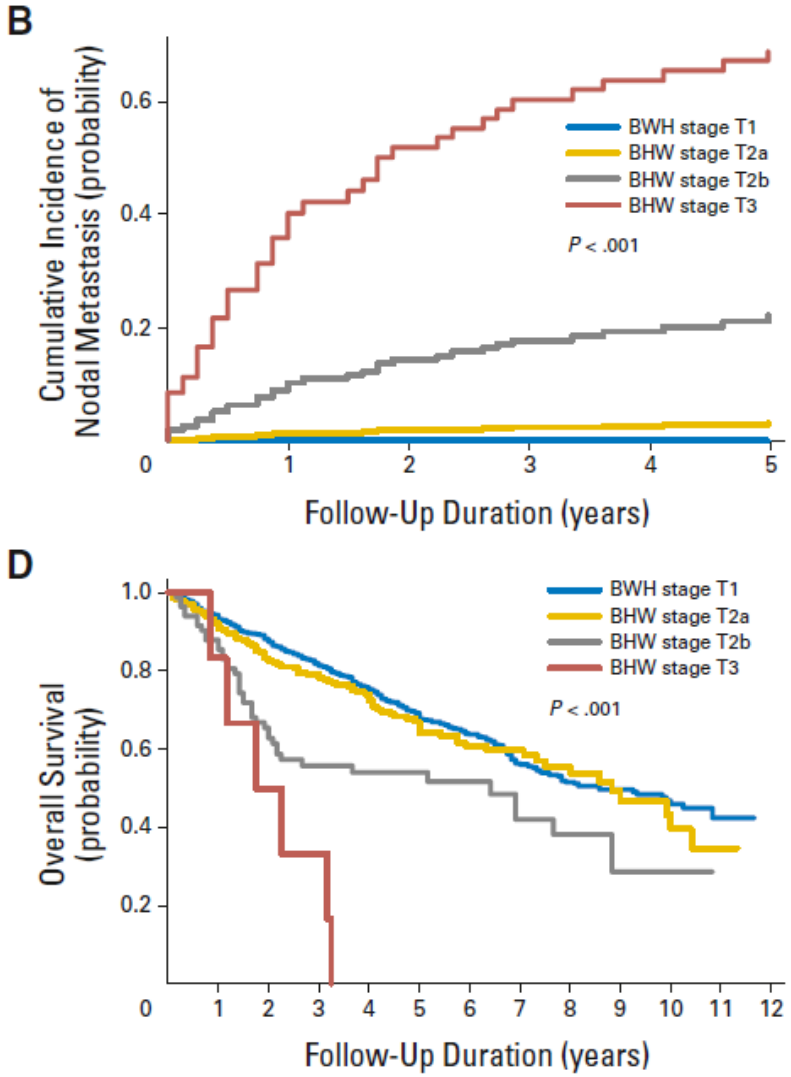
Prospective German Research Foundation Study

Brantsch K *et. al. Lancet Oncol.* 2008; 9: 713-20



AJCC - BWH Staging for cSCC

Karia P, *et. al. JCO*. 2014; 32(4): 327-334



BWH - Staging

Risk Factors

- Diameter > 2 cm
- Poorly differentiated
- PNI > 0.1 mm
- Invasion beyond fat

T1 - 0 risk factor
T2a - 1 risk factors
T2b - 2-3 risk factors
T3 - >4 risk factors or bone invasion

cSCC Stage III-IV Treatment

Adjuvant Chemotherapy / Radiotherapy

Historically: XRT +/- chemo-sensitizing Cisplatin

Current: anti-PD-1 (trials ongoing)

- No randomized confirmatory evidence justifying use
- Considered for ECE+, positive margins, multiple involved nodes, T3-4 local disease

Recurrent / Metastatic Chemotherapy

- Cohort series have shown activity of carboplatin, cisplatin, 5FU, capecitabine, bleomycin, MTX, doxorubicin, paclitaxel, docetaxel
- EGFR Antagonists (**Cetuximab**, Panitumumab, Erlotinib, Afatinib)
- In general 4-6 month PFS

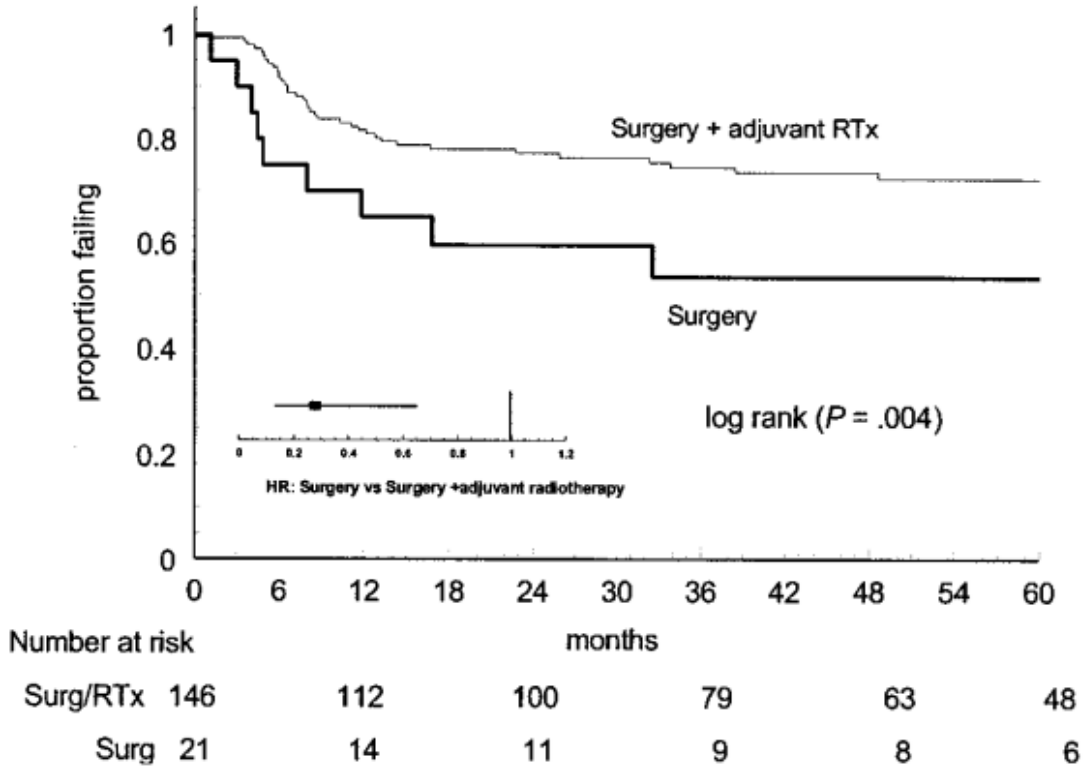
cSCC Stage III-IV Adjuvant

Surgery and Radiotherapy

- Retrospective chart review 1980 - 2000
- N = 167
- cSCC of the head and neck w/ nodal dz

Locoregional Failure

- 74% of recurrences
- 20% (Surg/RTx) vs 43% (Surg)



*RTOG 05.01 - Adjuvant high-risk cSCC RCT: RT 60 to 66 Gy or concurrent RT/weekly carboplatin (negative trial, accrual was held)

Veness *et. al.* *Laryngoscope*. 2005; 115:870-875

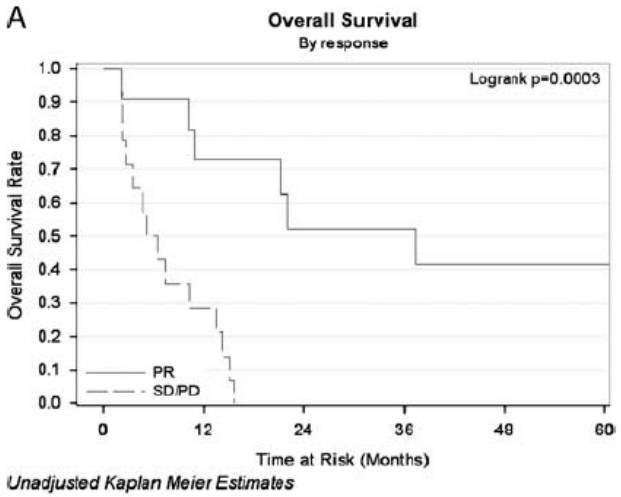
cSCC Stage III-IV Unresectable

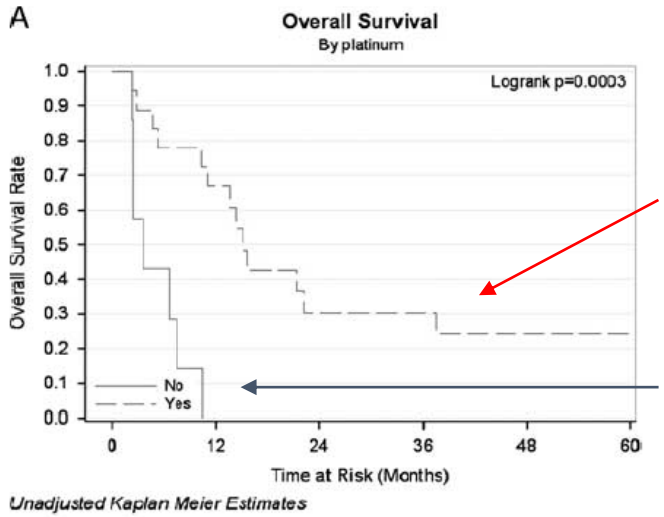
- N = 28

- Single institution

- Locoregional and metastatic disease

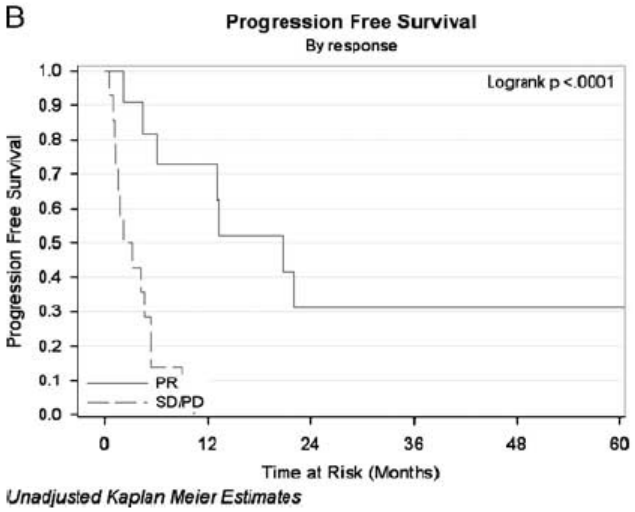
- Treatments included Cetuximab, Capecitabine, Platinum, Taxanes

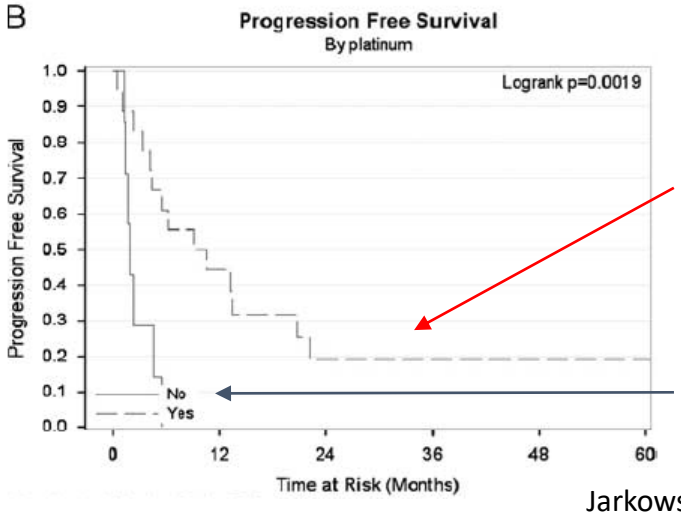




Received Platinum

Did not receive platinum





Received Platinum

Did not receive platinum

Jarkowski, A. *et. al. Am JCO*. 2016; 39(6): 545-548

cSCC Stage III-IV Unresectable

VOLUME 29 · NUMBER 25 · SEPTEMBER 1 2011

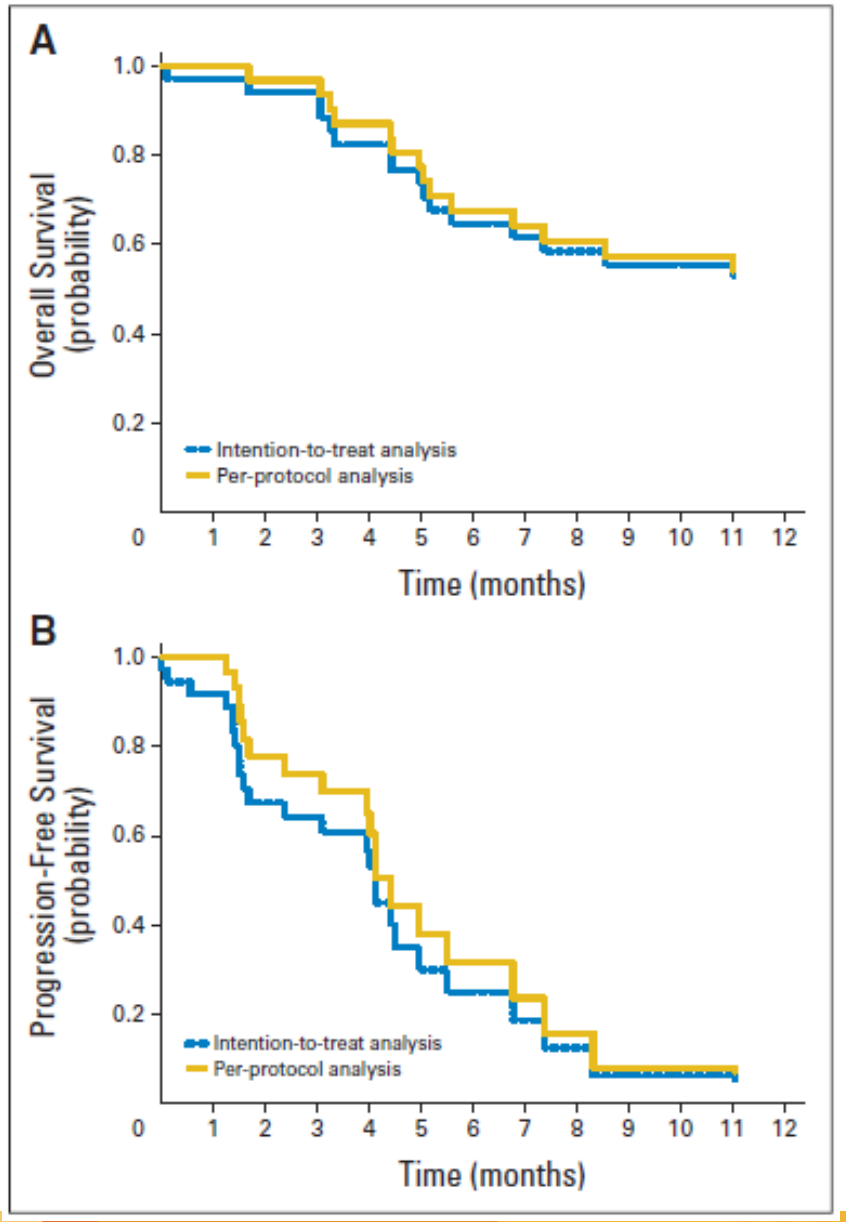
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase II Study of Cetuximab As First-Line Single-Drug Therapy in Patients With Unresectable Squamous Cell Carcinoma of the Skin

Eve Maubec, Peter Petrow, Isabelle Scheer-Senyarich, Pierre Duvillard, Ludovic Lacroix, Julien Gelly, Agnès Certain, Xavier Duval, Béatrice Crickx, Valérie Buffard, Nicole Basset-Seguin, Pierre Saez, Anne-Bénédicte Duval-Modeste, Henri Adamski, Sandrine Mansard, Florent Grange, Anne Dompmartin, Sandrine Faivre, France Mentré, and Marie-Françoise Avril

- N = 36
- Cetuximab 400 mg/m2 followed by weekly 250 mg/m2
- Endpoint: DCR at 6 weeks —> 69%

- EGFR IHC expression: 100%
- Previous studies show EGFR expression 80 - 100%



cSCC Stage III-IV Unresectable

C. Trodello, *et. al. Derm Surg*. 2017. 43(1): 40-49
A. Stratigos *et al. Euro. J. Cancer.* 2015. 51: 1989-2007

Efficacy of select drugs in metastatic cSCC

Reference	Drug	Sample Size	ORR (%)	PR (%)	CR (%)	PFS/DFS (mo.)
Trodello *et al.*	Cetuximab*	9	78	11	67	25
Trodello *et al.*	Cisplatin*	60	45	23	22	14

*Treatments included radiation and other systemic therapies

Reference	Drug	Sample Size	ORR (%)	PR (%)	CR (%)	SD (%)
Cartei *et al.*	Oral 5-FU	14	N/A	14	N/A	50
Sadek *et al.*	Cis, 5-FU + Bleo	14/13	N/A	54	30	16
Guthrie *et al.*	Cis + Doxorubicin	12	N/A	25	33	N/A

Case - 53 y/o Male with cutaneous lesion for 3 years

2 cycles of
Cisplatin/Docetaxel +
weekly Cetuximab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

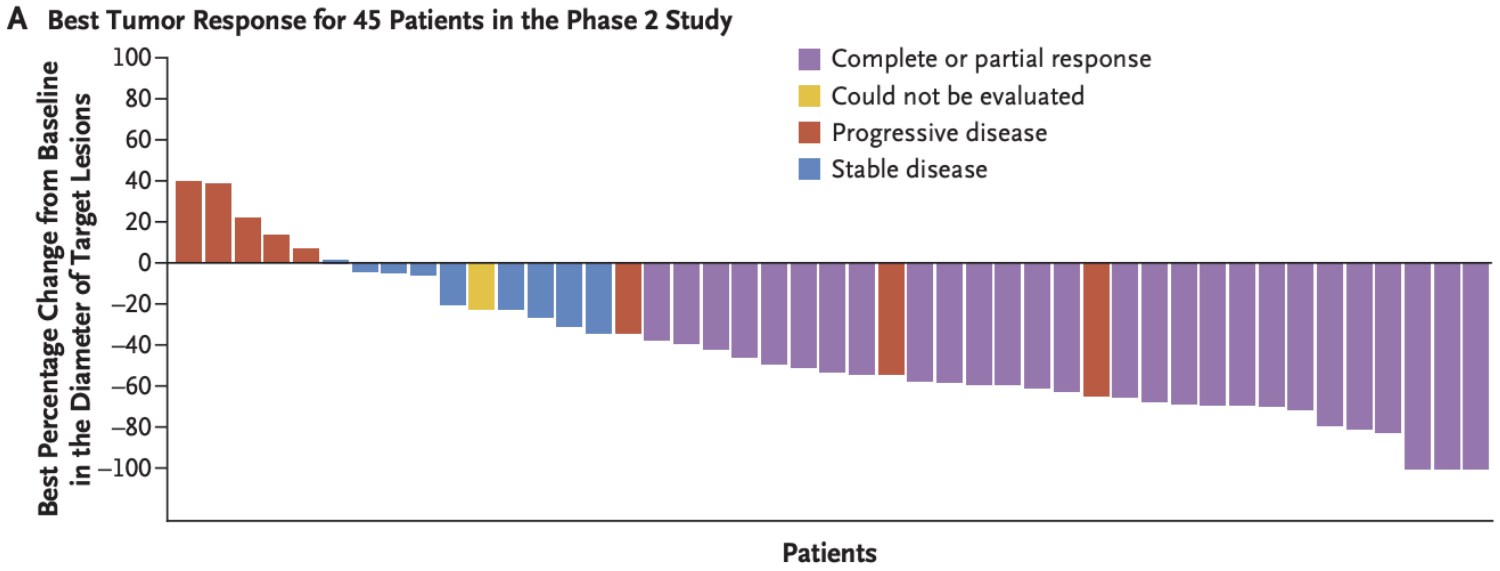
Migden, M, *et. al.* *N Engl J Med.* 2018; 379:341-351

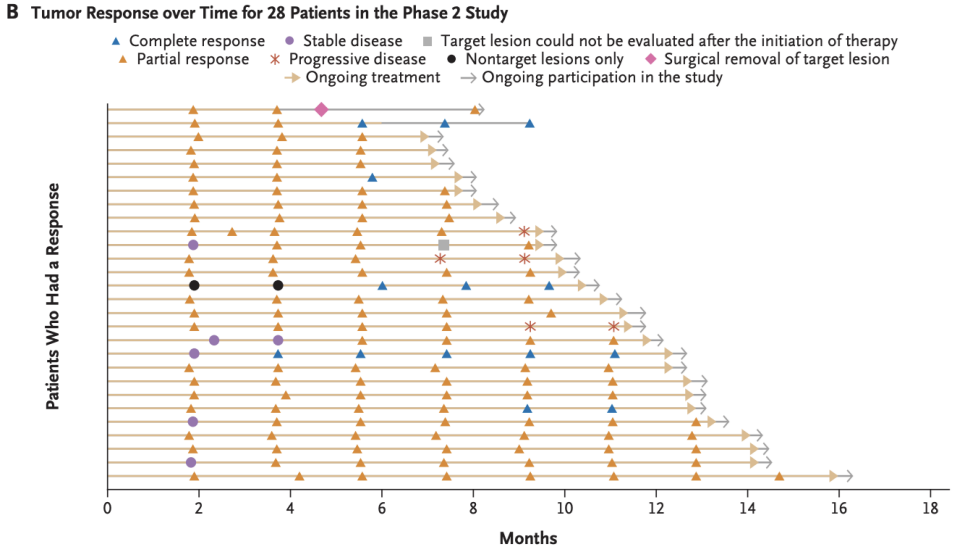
- N = 85
- Phase I - locally advanced or metastatic
- Phase 2 - distant and regionally metastatic

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Expansion Cohorts of the Phase 1 Study (N=26)	Metastatic-Disease Cohort of the Phase 2 Study (N=59)
Age		
Median (range) — yr	73 (55–88)	71 (38–93)
≥65 yr — no. (%)	21 (81)	43 (73)
Male sex — no. (%)	21 (81)	54 (92)
ECOG performance status score — no. (%)†		
0	10 (38)	23 (39)
1	16 (62)	36 (61)
Primary site of cutaneous squamous-cell carcinoma — no. (%)		
Head or neck	18 (69)	38 (64)
Arm or leg	5 (19)	12 (20)
Trunk	2 (8)	9 (15)
Penis	1 (4)	0
Previous systemic therapy for cutaneous squamous-cell carcinoma — no. of patients (%)‡		
No regimens	8 (31)	26 (44)
Any regimen	15 (58)	33 (56)
1 regimen	15 (58)	22 (37)
≥2 regimens	0	11 (19)
Previous radiotherapy for cutaneous squamous-cell carcinoma — no. (%)	20 (77)	50 (85)
Extent of cutaneous squamous-cell carcinoma — no. (%)		
Distant metastasis	8 (31)	45 (76)
Regional metastasis only	8 (31)	14 (24)
Locally advanced progression only	10 (38)	0

Cemiplimab (anti-PD-1) Approval





ORR - 47%

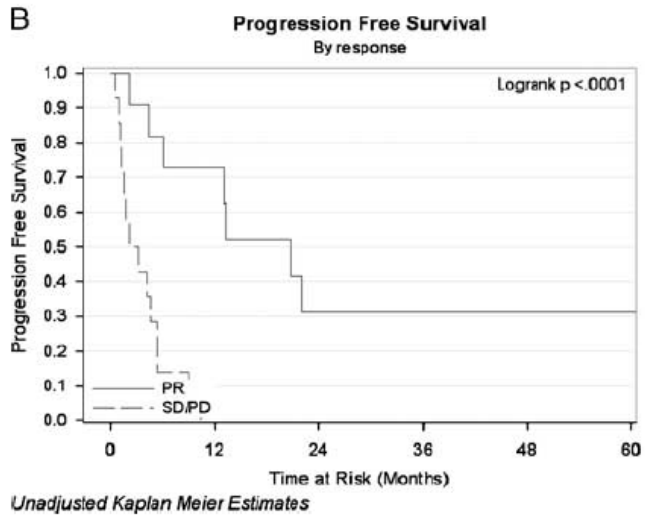
Clinical Benefit - ~70%

Previously Treated - 58%

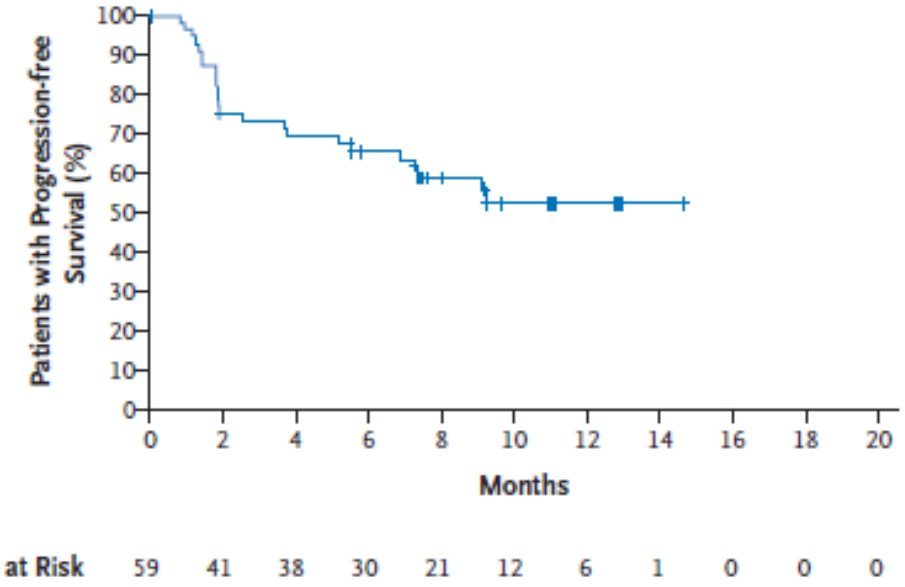
Approved 1st line metastatic, locally advanced SCC
September 28, 2018

Migden, M, *et. al.* *N Engl J Med.* 2018; 379:341-351

Cemiplimab (anti-PD1)



Progression Free Survival (53%)



Migden, M, *et. al.* *N Engl J Med.* 2018; 379:341-351

From Karl Lewis MD with permission

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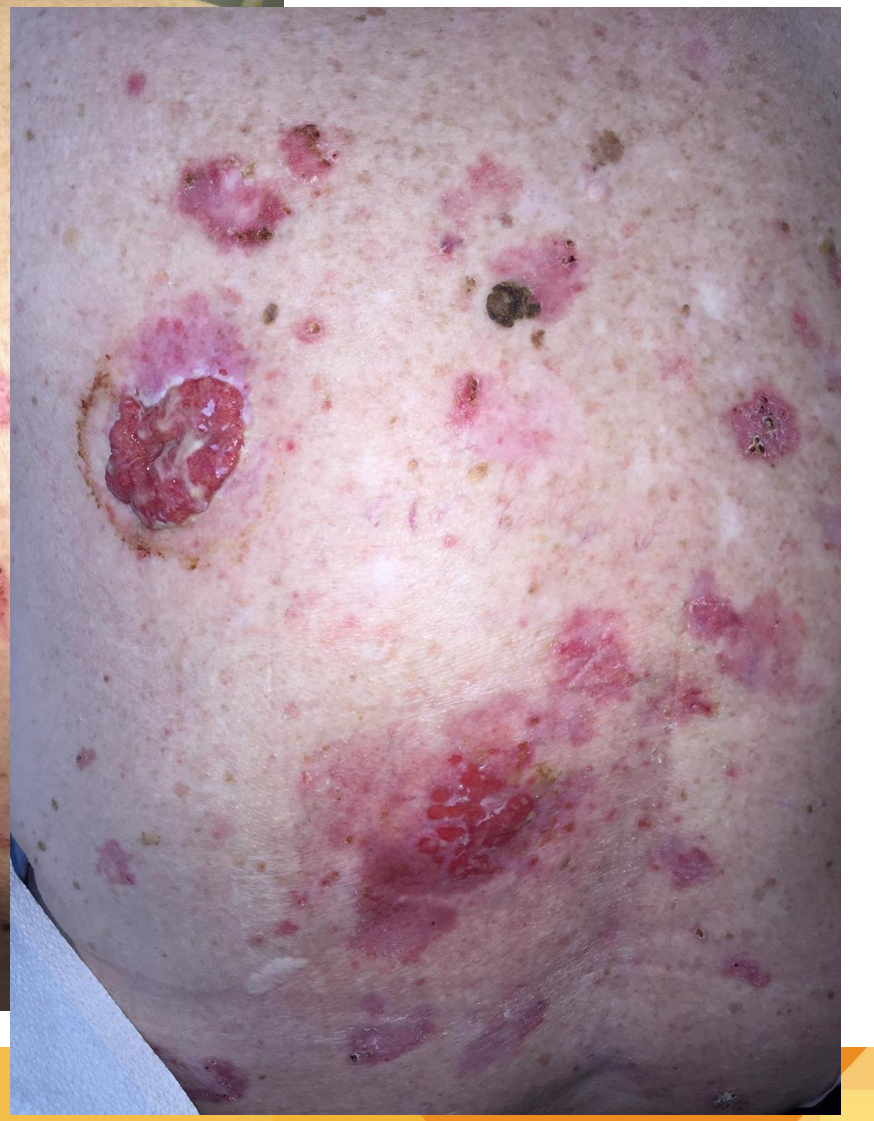
Case - 71 y/o F with multiple BCC and SCC in-situ

Case - After 10 weeks on anti-PD1



Immunotherapy Clinical Trials In cSCC (selected)

Trial / Drugs	Phase	Sponsor / Lead Site	NCT ID
Avelumab With or Without Cetuximab in Treating Patients With Advanced Skin Squamous Cell Cancer	II	Alliance for Clinical Trials in Oncology / NCI	NCT0394494
Tacrolimus, Nivolumab, and Ipilimumab in Treating **Kidney Transplant Recipients** With Selected Unresectable or Metastatic Cancers	I	NCI	NCT03816332
The **UNSCARRed** Study: UNresectable Squamous Cell Carcinoma Treated With **Avelumab** and **Radical Radiotherapy** (UNSCARRed)	II	Cross Cancer Institute	NCT03737721
Talimogene Laherparepvec and Nivolumab in Treating Patients With Refractory Lymphomas or Advanced or Refractory Non-Melanoma Skin Cancers	II	NCI	NCT02978625
MG1-MAGEA3 With Ad-MAGEA3 and Pembrolizumab in Patients With Previously Treated Metastatic Melanoma or Cutaneous Squamous Cell Carcinoma **(Pelican)**	I	Turnstone Biologics Inc.	NCT03773744
Pre-Operative Cemiplimab Administered Intralesionally for Patients With Recurrent Cutaneous Squamous Cell Carcinoma	I	Regeneron Pharmaceuticals	NCT03889912
Study of **Adjuvant Cemiplimab** Versus Placebo **After Surgery and Radiation** Therapy in Patients With High Risk Cutaneous Squamous Cell Carcinoma	III	Regeneron Pharmaceuticals	NCT03969004
Study Evaluating **Cemiplimab Alone and Combined With RP1 (Genetically Modified HSV1)** In Treating Advanced Squamous Skin Cancer **(CERPASS)**	II	Replimune Inc.	NCT04050436

clinicaltrials.gov queried 11.04.19

Clinical Trials Close To Home

- **Pembrolizumab** Versus Placebo **Following Surgery and Radiation** in Participants With Locally Advanced Cutaneous Squamous Cell Carcinoma **(KEYNOTE-630)**

Completely excised cSCC meeting the following criteria:

a) ECE + with either at least 1 lymph node >2 cm in greatest diameter or ≥2 lymph nodes involved.

b) Index tumor with ≥2 of the following high-risk features:
   i) Tumor ≥4 cm with a depth >6 mm
   ii) PNI
   iii) Poor differentiation and/or sarcomatoid histology
   iv) Recurrent disease
   v) Satellite lesions

c) Cortical bone invasion

- **REGN3767 (anti-LAG3 mAb)** Administered Alone or in Combination **With REGN2810 (anti-PD1 mAb)** in Patients With Advanced Malignancies

Anti-PD1/PDL1 experienced, locally advanced or metastatic, cSCC not appropriate for surgery

Multidisciplinary Cases

Case 1

- 77 yo male
- Referral VA
- Biopsy proven well differentiated SCC
- Left temple
- CT scan: ? Blurring of plane between tumor and frontal bone. ? invasion.

Clinical Multidisciplinary Course

- Mohs micrographic surgery
  - Tumor clearance at the periphery
- ENT
  - Burred the frontal bone
  - Reconstruction
- Radiation Oncology
  - Plan for EBRT
  - 1 session, then lost to follow up

Case 2

- 43 yo male
- Biopsy proven cSCC with clear cell features
- Left zygomatic cheek
- Rx: MMS, cleared in 2 stages
- Repair complex layered closure

Case 2

- Four Months later
- Left Parotid mass
- FNA + for malignant cells
  - Consistent with SCC

Case 2

- CT scan: positive pulmonary nodule
- Cemiplimab: 4 cycles
- Then parotid resection/ head and neck LND by ENT
  - No viable tumor in the parotid
  - 29 lymph nodes sampled: all negative
- ? Adjuvant Radiation
- Repeat CT: pending

Case 3

- 76 yo male
- History numerous basal cell carcinomas and squamous cell carcinomas
- History of cSCC 2017 (right face), neck LND, adjuvant radiation
- Sun exposure: summers at the Jersey Shore

Case 3

Case 3

After 7 Mohs procedures and 3 excisions in 1 year, referral placed to cutaneous oncology, presented at our multidisciplinary tumor board

Represented specialties: cutaneous oncology, dermatologis surgery, ENT, surgical oncology, dermatopathology, radiology, radiation oncology.

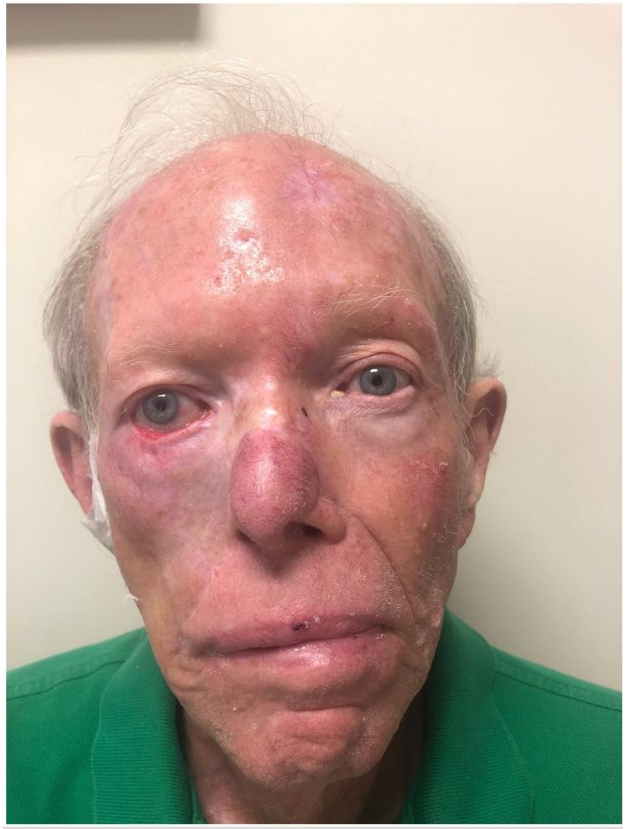
Started pembrolizumab

cSCCs with good response

Less BCCs, and continued to surgically treat BCCs

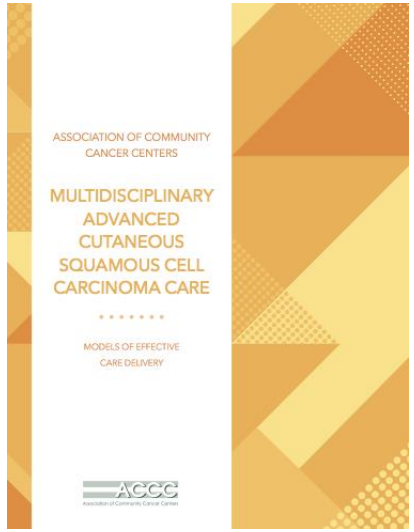
Patient offered vismodegib, refused.

Refuses more surgical treatment.



Importance of Multidisciplinary Care

- Emerging multidisciplinary care models across the country.
- Association of Community Cancer Centers education project on *Multidisciplinary Advanced Cutaneous Squamous Cell Carcinoma Care*.

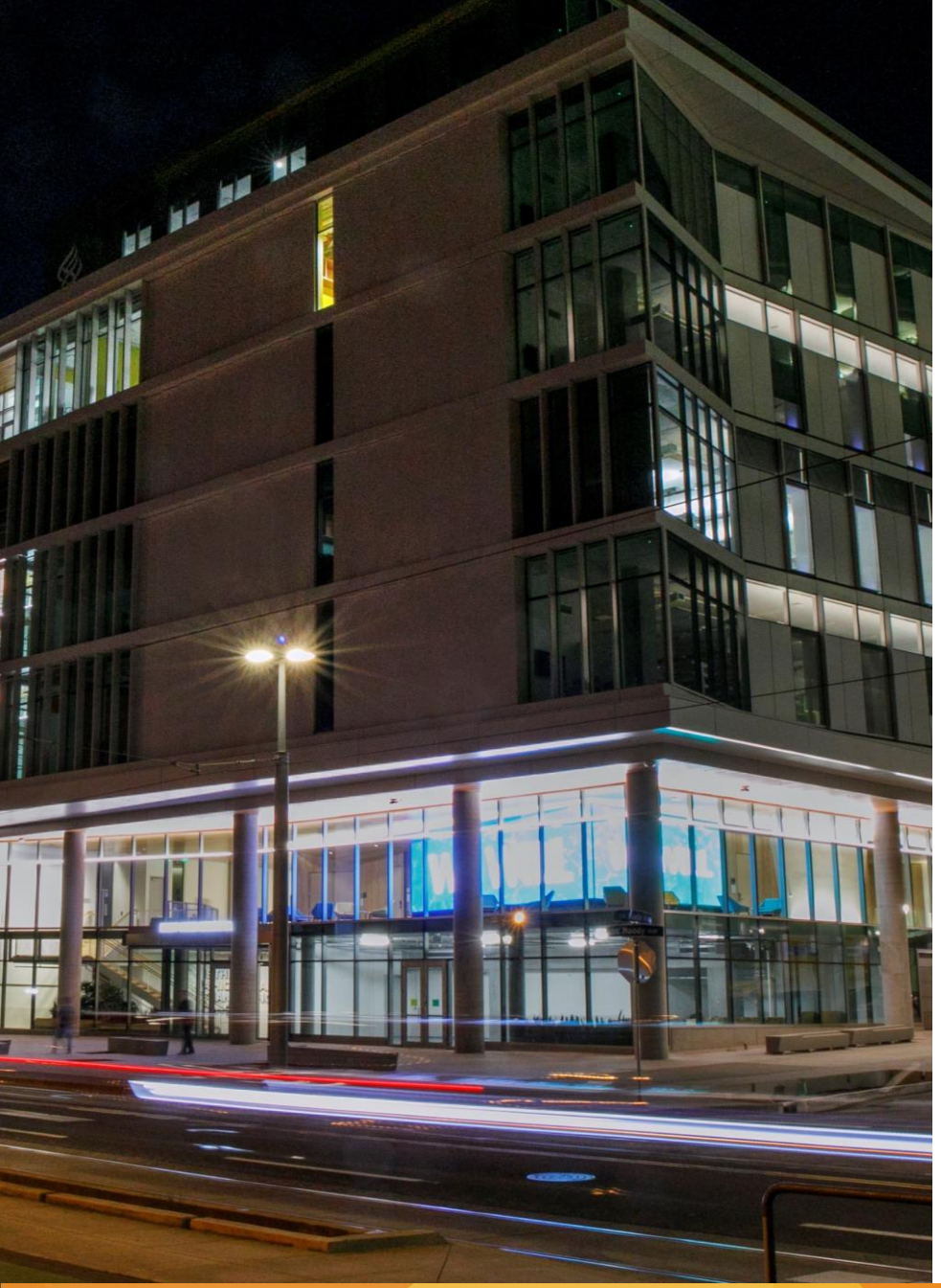


ACCC
Association of Community Cancer Centers

Publication available in print and online!

George Washington Cancer Center

- Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).
- **Newly developed** cutaneous oncology program.
- Multidisciplinary team **led by dermatologic surgeons**.
- Focus on **personalized care**.
- **Ongoing clinical trials** in adjuvant therapy.

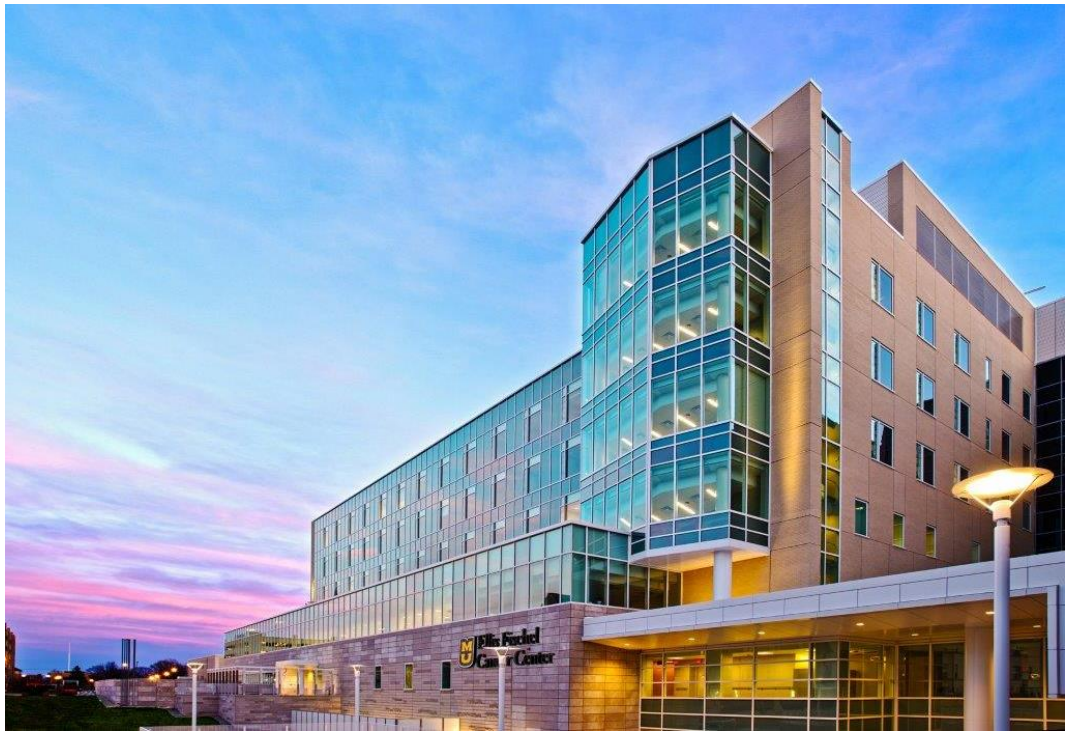


Oregon Health Services University Knight Cancer Institute

- NCI-designated Comprehensive Cancer Center.
- Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).
- Sees a **large volume** of high-risk cSCC patients.
- cSCC program **modeled after well-established melanoma program**.
- Expanding provider access via **virtual tumor boards**.
- Goal to increase access to clinical trials.

University of Missouri-Ellis Fischel Cancer Center

- Certified member of MD Anderson Cancer Care Network.
- Academic Comprehensive Cancer Program accredited by American College of Surgeons Commission on Cancer (CoC).
- **Emerging multidisciplinary cutaneous oncology team** with a dedicated cutaneous oncology tumor board and board-certified dermatopathologists.
- Team involves social work, pharmacy, patient, and nurse navigators.
- **Teledermatology** and the **ECHO platform**.
- **Ongoing clinical trials** in biomarker assessment.



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    - Julie Goddard, MD (ENT)
    - Adam Terella, MD (ENT)

Questions?

Thank You

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This lecture will be made available as an on-demand webinar.

For more information about this project:

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