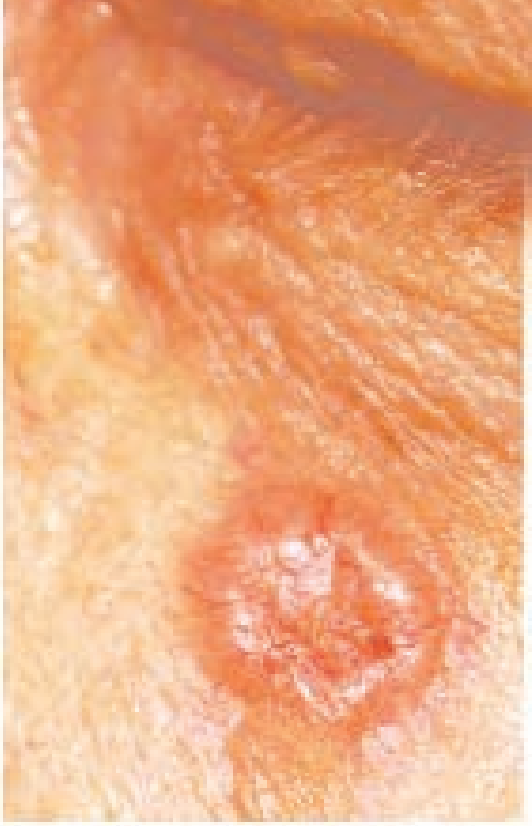

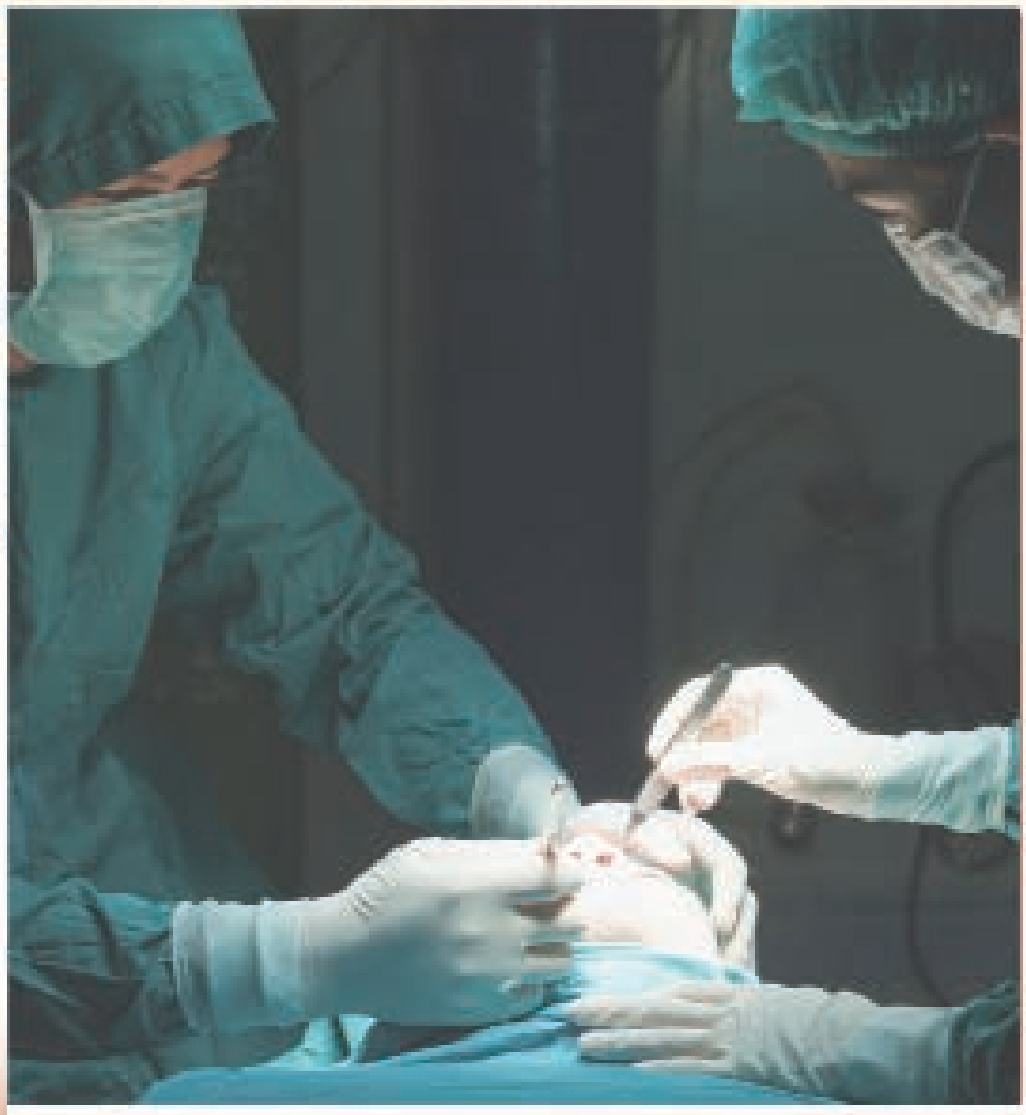

A3DVIEW

Addressing the Most Common Cancer:

The Pathology, Epidemiology, and Treatment Options of ADVANCED and METASTATIC BCC

THURSDAY, MAY 6, 2021

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM) and AMEDCO.
This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme.

Agenda

- Basal Cell Carcinoma: Introduction
  - Epidemiology/statistics
  - Prognostic factors
- Staging and Guidelines
  - Considerations for aggressive BCC
- BCC Failing or Not Amenable to Surgery or Radiation
  - Sonic hedgehog pathway
    - Vismodegib and sonidegib
  - Hedgehog side effects
  - Alternate dosing regimens
  - When disease progresses on hedgehog inhibition
    - Immunotherapy: the cancer/immunity cycle
    - Immune checkpoints and checkpoint inhibitors
      - Cemiplimab
      - Pembrolizumab and other investigational agents
- Case Study Presentations and Conclusions
- Q&A

A 3D View: Addressing the Most Common Cancer: The Pathology, Epidemiology, and Treatment Options of Advanced and Metastatic BCC

FACULTY

Anna Bar, MD
Associate Professor of Dermatology
Co-director of Mohs Micrographic Surgery
Oregon Health & Science University (OHSU)
Portland, OR

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Assistant Professor of Dermatology
Co-director of Mohs Micrographic Surgery
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Portland, OR

PROGRAM OVERVIEW

This case-based virtual activity will focus on treatment and management of patients with advanced/metastatic basal cell skin cancer.

TARGET AUDIENCE

This activity is designed to meet the educational needs of Mohs surgeons, onco-dermatologists, medical oncologists, dermatologists and other healthcare practitioners who care for patients with advanced/metastatic basal cell skin cancer.

LEARNING OBJECTIVES

On completing of the program, attendees should be able to:

- Discuss the pathogenic drivers of BCC including cellular signaling pathways and immune dysfunction
- Review the utility of Mohs micrographic surgery in the evaluation and therapeutic intervention in BCC
- Describe systemic therapeutic approaches in the treatment of locally advanced and metastatic BCC
- Summarize the clinical trial data for emerging immunotherapy agents for advanced or metastatic basal cell skin cancer

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NURSING CREDIT INFORMATION:
Purpose: This program would be beneficial for nurses involved in the care of patients with advanced/metastatic basal cell skin cancer. Credits: 1.0 ANCC Contact Hour.

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Anna Bar, MD receives consulting fees from Castle and Regeneron Pharmaceuticals. She received research funding to her institution from Castle, Pelle Pharm, and Polynoma.

Justin Leitenberger, MD has nothing to disclose.

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The reviewer of this activity has nothing to disclose.

CNE Content Review

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Live Learner Notification

Med Learning Group
A 3D View: Addressing the Most Common Cancer: The Pathology, Epidemiology, and Treatment Options of Advanced and Metastatic BCC
May 6, 2021
Online

Acknowledgement of Financial Commercial Support
Regeneron

Acknowledgement of In-Kind Commercial Support
No in-kind commercial support was received for this educational activity.

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Accreditation Statement

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Objectives - After Attending This Program You Should Be Able To
1. Discuss the pathogenic drivers of BCC including cellular signaling pathways and immune dysfunction.
2. Review the utility of Mohs micrographic surgery in the evaluation and therapeutic intervention in BCC.
3. Describe systemic therapeutic approaches in the treatment of locally advanced and metastatic BCC.

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Felecia Beachum	NA
Chris Drury	NA
Matthew Frese	NA
Christina Gallo	NA
Brianna Hanson	NA
Justin Leitenberger	NA
Scott McGee-Plys	NA
Lauren Welch	NA

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1. Go to http://mlg.cmecertificateonline.com
2. Click on **"5.6.21 A 3D View: Addressing the Most Common Cancer: The Pathology, Epidemiology, and Treatment Options of Advanced and Metastatic BCC**" link.
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4. Evaluate the meeting, click the provided link to open your credit certificate.

5. Print/save all pages of your certificate for your records.

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A 3D View: Addressing the Most Common Cancer: The Pathology, Epidemiology, and Treatment Options of Advanced and Metastatic BCC

Anna Bar, MD
Associate Professor of Dermatology

Justin Leitenberger, MD
Assistant Professor of Dermatology

Co-directors of Mohs Micrographic Surgery & Dermatologic Oncology
Oregon Health & Science University (OHSU)
Portland, OR

Disclosures

- **Dr. Bar** receives consulting fees from Castle and Regeneron Pharmaceuticals. She received research funding to her institution from Castle, Pelle Pharm and Polynoma.
- **Dr. Leitenberger** has nothing to disclose.

- During the course of this lecture, faculty may mention the use of medications for both US FDA-approved and non-FDA-approved indications
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This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme.

Learning Objectives

- Discuss the pathogenic drivers of BCC including cellular signaling pathways and immune dysfunction
- Review the utility of Mohs micrographic surgery in the evaluation and therapeutic intervention in BCC
- Describe systemic therapeutic approaches in the treatment of locally advanced and metastatic BCC
- Summarize the clinical trial data for emerging immunotherapy agents for advanced or metastatic basal cell skin cancer

Aggressive BCC

Is there such a thing?

Does BCC have a Risk of Metastasis?

- Rates of .0028% to 0.55% reported[1-3]
- In 1 study of predictive factors: 11,905 BCCs diagnosed between 2000 and 2009 at Brigham and Women's Hospital and Massachusetts General were screened[3]
- 248 cases ≥ 2 cm assessed for risk factors and metastasis/death[3]
- 248 cases < 2 cm randomly selected for comparison[3]

1. von Domarus H, Stevens PJ. *J Am Acad Dermatol*. 1984;10(6): 1043-1060. 2. Snow SN, et al. *Cancer*. 1994;73(2):328-335. 3. Morgan F, et al. *J Am Acad Dermatol*. 2020;83:832-838.

Factors predictive of recurrence, metastasis, and death from primary basal cell carcinoma 2 cm or larger in diameter

Frederick C. Morgan, BSPH,[a] Emily Stamell Ruiz, MD, MPH,[a] Pritesh S. Karia, MPH,[a,b] Robert J. Besaw, MPH,[a] Victor A. Neel, MD, PhD,[c] and Chrysalyne D. Schmults, MD, MSCE[a]
Boston, Massachusetts; Baltimore, Maryland; and Providence, Rhode Island

Multivariable logistic regression of ≥ 2 cm BCC tumors

Variable	Local Recurrence		Metastasis and/or Death	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Location				
Other	1 (reference)		1 (reference)	
Head and neck	9.7 (3.0-31.3)		5.3 (1.2-23.2)	.026
Diameter				
Other	—	—	1 (reference)	
≥ 4cm	—		11.9 (2.4-59.4)	.003
Tumor depth				
Other	1 (reference)		1 (reference)	
Beyond fat	3.1 (1.0-9.6)	.049	28.6 (6.7-121.0)	<.001
Treatment modality				
Other	1 (reference)		—	—
Mohs micrographic surgery	0.14 (.04-0.5)	.002	—	—

BCC > 4 cm on the head and neck, and invading beyond subcutaneous fat, may warrant more aggressive follow-up and radiologic imaging.

Morgan F, et al. *J Am Acad Dermatol*. 2020;83:832-838.

BCC Prognostic Factors

- < 2 cm group had no metastasis/death
- In ≥ 2 cm group, 3 significant predictors of metastasis/death
  - Diameter ≥ 4 cm or larger
  - Depth beyond subcutaneous fat
  - Head/neck location

Morgan F, et al. *J Am Acad Dermatol*. 2020;83:832-838.

Video 1
https://youtu.be/gizimT7MEok

Staging and Guidelines

Staging BCC

Tumor Staging System	Definition
AJCC 8th Edition T Staging for Cutaneous Carcinoma of the Head and Neck	
T1	< 2 cm in greatest diameter
T2	≥ 2 cm but < 4 cm in greatest diameter
T3	≥ 4 cm in greatest diameter or minor bone invasion or perineural invasion or deep invasion
T4a	Tumor with gross cortical bone and/or marrow invasion
T4b	Tumor with skull bone invasion and/or skull base foramen involvement
BWH T Staging for BCC	
T1	Tumor diameter < 2 cm or tumor diameter ≥ 2 cm with 0-1 risk factors
T2	Tumor diameter ≥ 2 cm with 2-3 risk factors

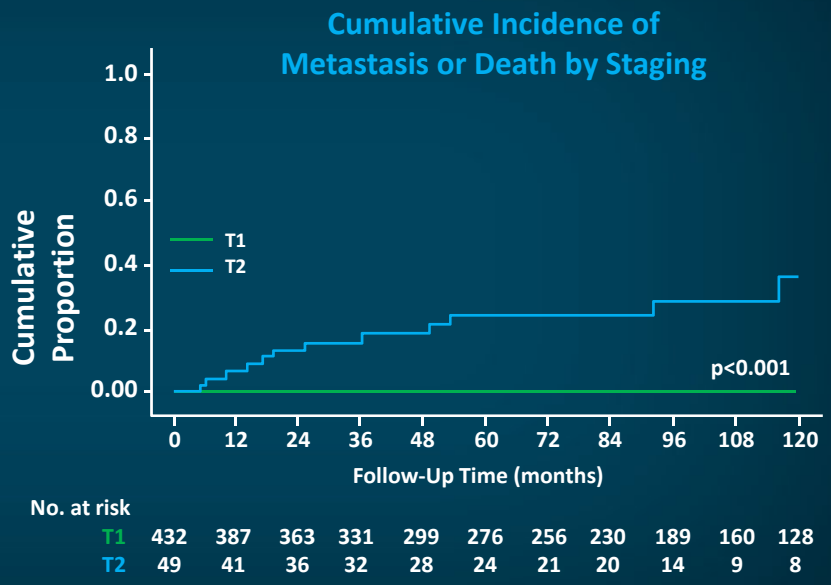
AJCC: American Joint Committee on Cancer. BWH: Brigham and Women's Hospital

Morgan F, Schmults C, et al. JAAD. 2021. doi: 10.1016/j.jaad.2021.01.052

Staging BCC

- BWH T2 BCC:
  - Local recurrence: 47% (28%-70%)
  - Metastasis/death: 37% (21%-60%)

BWH T2:
≥ 4 cm + depth beyond fat
≥ 4 cm + head/neck
≥ 2 cm + depth beyond fat + head/neck



Morgan F, Schmults C, et al. JAAD. 2021. doi: 10.1016/j.jaad.2021.01.052

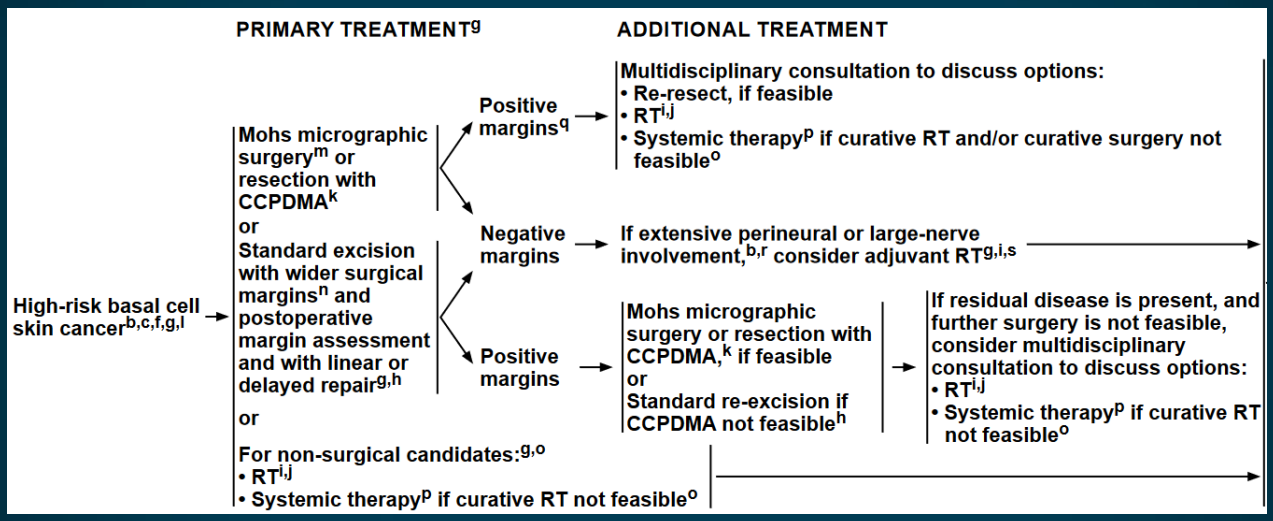
CCPDMA Cuts Recurrence Risk in Half for High-Risk BCC

	Recurrence Risk: Recurrent BCC, n (%)	Recurrence Risk: Aggressive Subtype BCC, n (%)
CCPDMA	132/2911 (4.5%)	97/3149 (3%)
SA	32/263 (12%)	17/234 (7%)
p value	p < .001	P < .001
Risk Ratio	.37 [.26-.54]	.42 [.26-.70]

CCPDMA = complete circumferential peripheral and deep margin assessment; SA = Standard Margin Assessment (vertical sections)

Fraga S, Waldman A. Complete marginal assessment in surgically excised keratinocyte carcinoma: A systematic review. Under review.

NCCN: Algorithm for High-Risk BCC



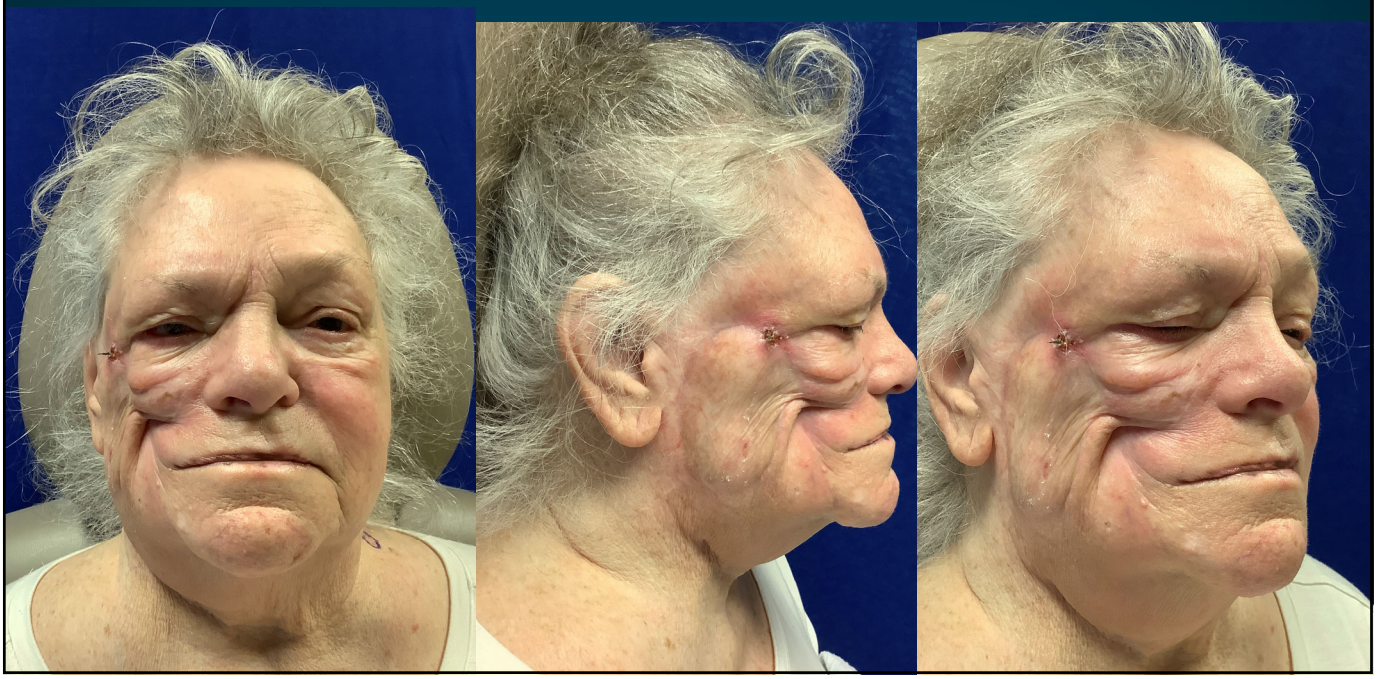
Schmults C, et al. NCCN Guidelines Version 2.2021: Basal Cell Skin Cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf.
Please see NCCN page above for footnotes and additional information/context for these guidelines.

Lack of Adherence to NCCN for High-Risk BCC/SCC

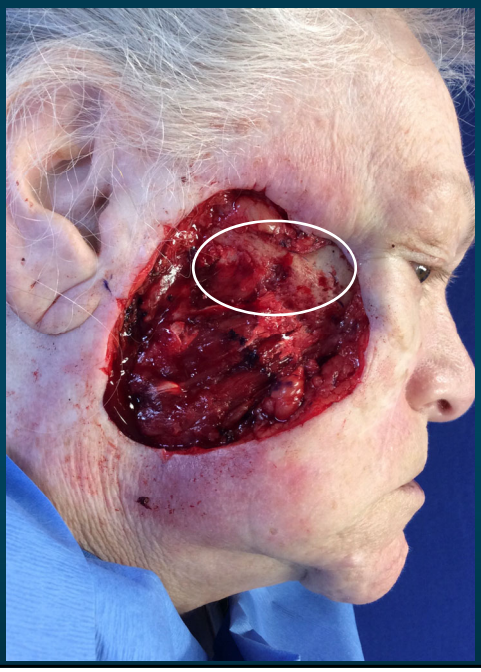
- Survey study of physicians from the 23 NCCN institutions
- ~50% response, N = 57
- Use of CCPDMA in a majority of NCCN high-risk cases
  - 14/15 Mohs surgeons
  - 10/16 other surgeons, dermatologists, radiation oncologists
  - 2/6 pathologists
- Reasons for not using CCPDMA
  - Surgeons defer to pathologists to determine appropriate margin assessment methods
  - Logistical difficulties (time-consuming, overnight stays, open wounds)

NCCN = National Comprehensive Cancer Network; SCC = squamous cell carcinoma.
Danesh M, et al. *Dermatologic Surgery*. 2020;46:1473-1480.

Multiply Recurrent BCC Treated with Several WLE/flaps



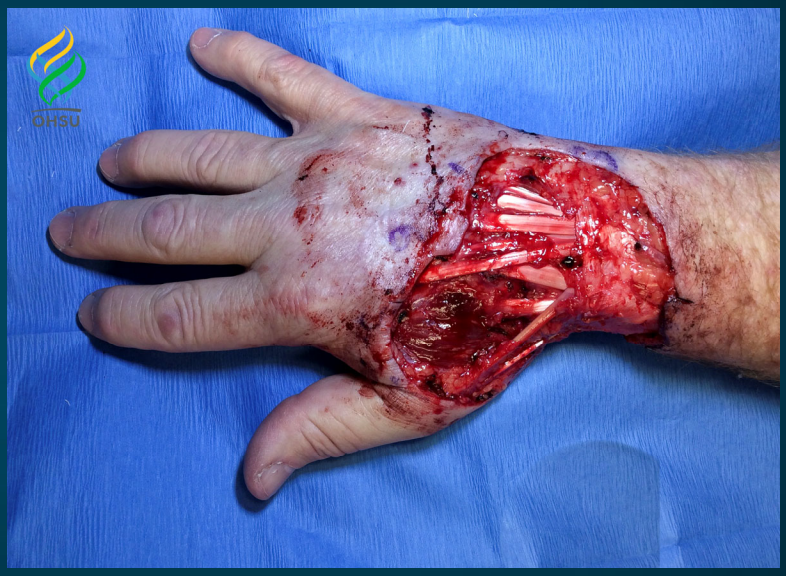
Mohs for Periphery and Deep Margin in OR



Tumor is going underneath the zygoma; sent to OR for zygoma removal

Mohs Surgery Attempted, but Tumor Found to be Deeply Invasive

Mohs surgery stopped as patient was going to lose function of the hand/need amputation



Attempt at Mohs Surgery Not Successful

Conclusions: Aggressive BCC

- BWH T2 BCC may have a risk of local recurrence and metastasis in excess of 20%
  - ≥ 4 cm + depth beyond fat
  - ≥ 4 cm + head/neck
  - ≥ 2 cm + depth beyond fat + head/neck
- Do Mohs surgery (or CCPDMA if needed, OR resection)
- Beware of multiply recurrent BCC
- Radiologic surveillance for recurrence
- Consider adjuvant systemic therapy in extreme or multiply recurrent cases

BCC Failing or Not Amenable to Surgery and Radiation

Video 2
Hedgehog Inhibitors and Immunotherapy
https://youtu.be/_EHC87kNtsk

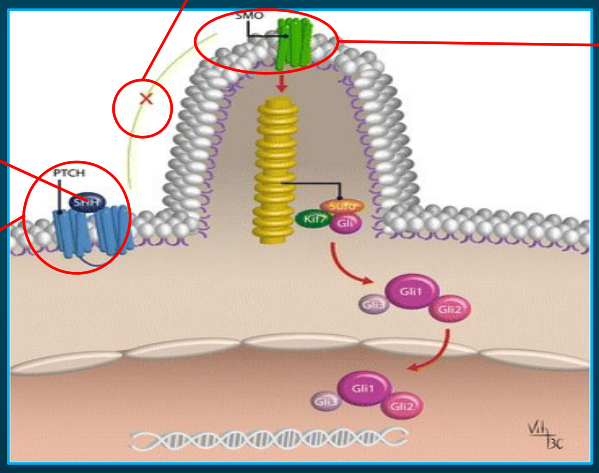
Sonic Hedgehog Pathway

4 Thus, blocking SHH attachment deactivates the carcinogenesis cascade

1 Pathway activation occurs when SHH binds to PTCH at the cell membrane.

2 In response to this binding, PTCH no longer inhibits SMO.

3 SMO accumulates at the primary cilium and initiates the downstream signaling cascade.



SHH = Sonic hedgehog; PTCH = Patched (a multitransmembrane protein); SMO = Smoothened (a key transmembrane protein).
Carballo G, et al. *Cell Commun Signal*. 2018;16:11.

Vismodegib

- Indications
  - Metastatic BCC
  - Locally advanced BCC that has recurred following surgery, or in those who are not candidates for surgery/radiation
- Dosage: oral; 150 mg once daily
- Contraindications: none
- Boxed warning: embryo-fetal toxicity

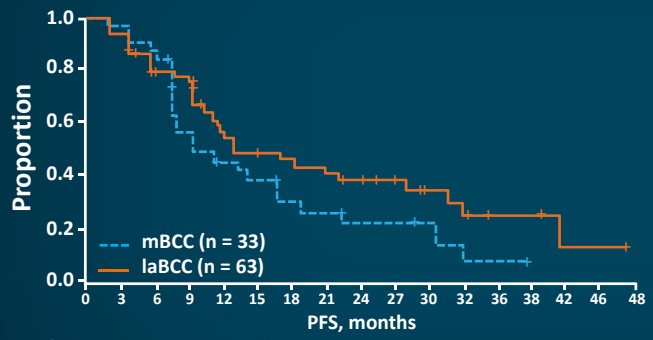
	mBCC (n = 33)	laBCC (n = 63)
ORR	30.3%	42.9%
Complete Response	0%	20.6%
Partial Response	30.3%	22.2%
Median Response Duration	7.6 months	7.6 months

mBCC = metastic BCC; laBCC = locally advanced BCC; ORR = objective response rate.

Sekulic A, et al. *N Eng J Med*. 2012;366:2171-2179. Vismodegib (Erivedge®) PI 2020 (https://www.gene.com/download/pdf/erivedge_prescribing.pdf). Accessed December 10, 2020.

Vismodegib: ERIVANCE BCC Trial

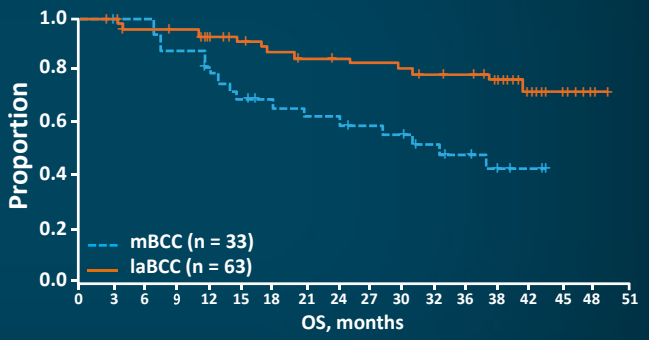
Progression Free Survival (PFS)



No. at risk

Metastatic	33	31	26	16	12	10	7	6	4	4	3	1	1	0	0	0	0
Locally Advanced	63	55	42	38	24	19	17	16	13	10	7	5	3	3	1	1	0

Overall Survival (OS)



	33	33	33	29	25	22	20	18	18	16	15	12	10	7	2	0	0	0
	63	61	58	56	52	48	45	43	42	41	40	38	37	25	13	8	2	0

Sekulic A, et al. *BMC Cancer*. 2017;17:332.

Sonidegib

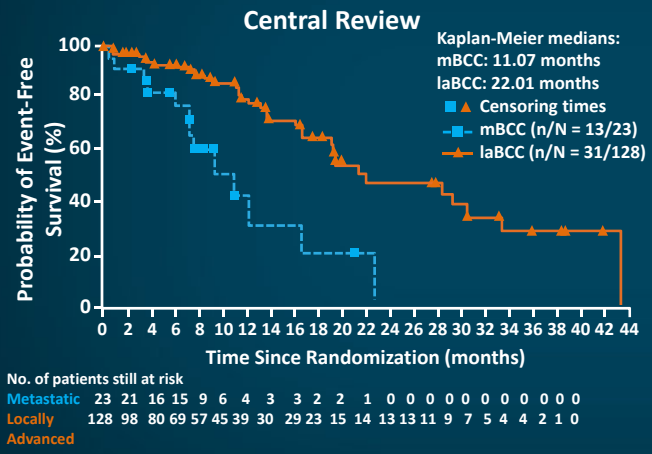
- Indications
  - Locally advanced BCC that has recurred following surgery, or in those who are not candidates for surgery/radiation
- Dosage: oral; 200 mg once daily
- Contraindications: none
- Boxed warning: embryo-fetal toxicity

	laBCC (n = 66)
ORR	56.0%
Complete Response	5%
Partial Response	52%
Median Response Duration	26.1 months

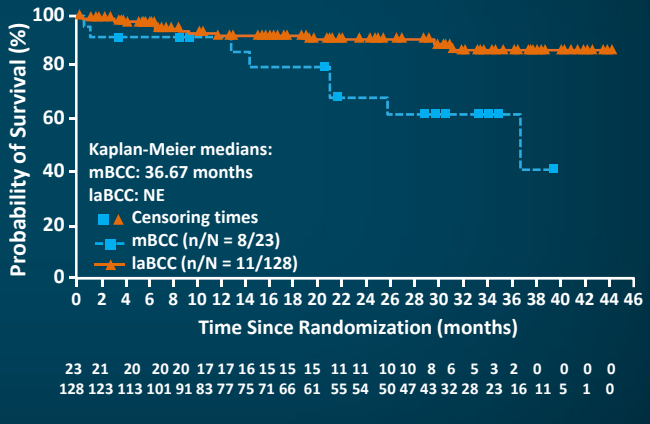
Sonidegib (Odomzo®) PI 2019 (https://www.odomzo.com/themes/custom/odomzo/global/pdfs/pi.pdf).

Sonidegib: BOLT Study

Progression Free Survival



Overall Survival



BOLT = Basal Cell Carcinoma Outcomes With LDE225 Treatment.
Lear JT, et al. *J Eur Acad Dermatol Venereol*. 2018;32(3):372-381.

Efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: A systematic review and meta-analysis

Pingxing Xie, MD, PhD, and Philippe Lefrançois, MD, PhD
Montreal, Canada

- 16 studies: quantitative meta-analysis of safety and efficacy
- Locally advanced BCC
  - Overall Response Rate: comparable for vismodegib and sonidegib (69% vs 57%)
  - Complete Response Rate: superior for vismodegib (31% vs 3%)
- Metastatic BCC
  - Overall Response Rate: superior for vismodegib (39% vs 15%)
- Side effects (combined prevalence)
  - 67%, 54%, and 58% for muscle spasms, dysgeusia, and alopecia, respectively; comparable for sonidegib and vismodegib
  - Upper GI distress more common in sonidegib than in vismodegib use
- Vismodegib favored over sonidegib in clinical practice

Xie P, Lefrançois P. *J Am Acad Dermatol* 2018;79:1089-1100.

Hedgehog Side Effects

- Hedgehog inhibitor side effects are not life-threatening but are nearly universal and often severe
- High rate of discontinuation in clinical trials (20%-50%)
  - Debilitating muscle pain/cramping
  - Loss of taste leading to major weight loss
  - Hair loss is often severe
- Alternatives to daily dosing are often used (though minimally studied)
  - A dosing regimen of 1 to 2 weeks on, 1 week off, is what we employ
  - Impact on efficacy unknown but such modifications are often needed to remain on treatment

Migden M, et al. *Lancet Oncology*. 2015;16:716-728. Dummer R, et al. *Br J Dermatol*. 2020;182(6):1369-1378. Sekulic A, et al. *BMC Cancer*. 2017;17:332. Sekulic A, et al. *N Eng J Med*. 2012;366:2171-2179. Villani A, et al. *Dermatol Ther*. 2020;10:401-412.

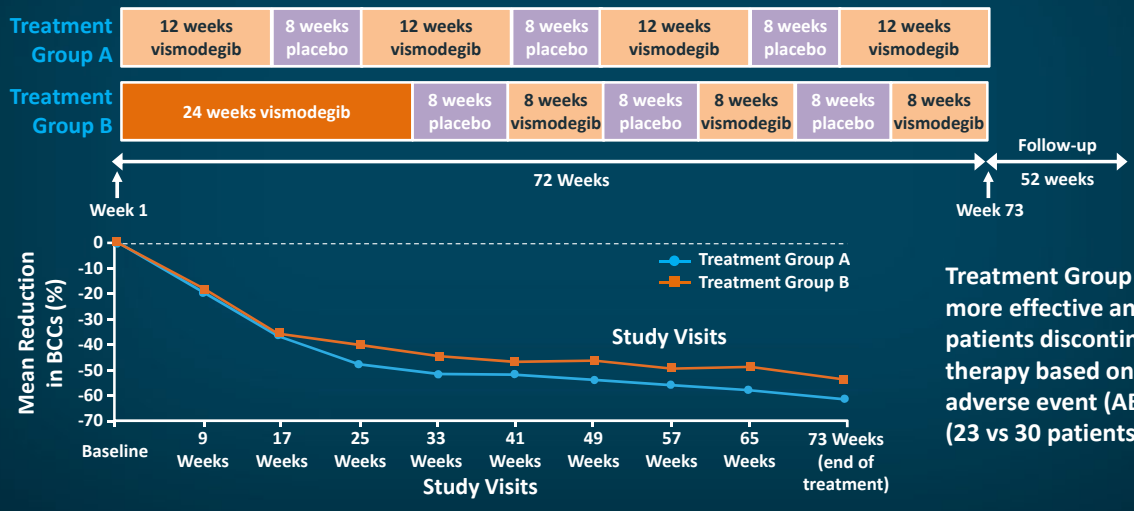
Alternate Dosing Regimens

- More tolerable than continuous therapy, with comparable effectiveness
- Impact on secondary resistance undefined
- BCC managed using hedgehog inhibitor (HHI) is comparable to chronic disease management or palliation
- May take months, weeks, or days off without loss of effectiveness

Dreno B, et al. *Lancet Oncol*. 2017;18(3):404-12. Becker L, et al. *JAMA Dermatol*. 2017;153(4):321-2.

Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial

Brigitte Dréno, Rainer Kunstfeld, Axel Hauschild, Scott Fosko, David Zloty, Bruno Labeille, Jean-Jacques Grob, Susana Puig, Frank Gilberg, Daniel Bergström, Damian R Page, Gary Rogers, Dirk Schadendorf



Treatment Group A was more effective and fewer patients discontinued therapy based on adverse event (AE) (23 vs 30 patients).

Dréno B, et al. *Lancet Oncol.* 2017; 18:404-412.

RESEARCH LETTER

A Novel Alternate Dosing of Vismodegib for Treatment of Patients With Advanced Basal Cell Carcinomas

Vismodegib Dosing Regimen, Response, and Adverse Effects

Patient No./Sex	BCC History	IVT Regimen (with/without medication = no. of cycles)	Length of Follow-Up, mo	BCC Response	Adverse Effects
1/M	>50 BCCs	1 wk/1 wk x 8 cycles; 1 wk/3 wks x 12 cycles	20	Decrease in number and size of lesions	Fatigue, arthralgia, arthritis, and alopecia; resolved after decreasing dose
2/M	Basal cell nevus syndrome	1 wk/2 wks x 10 cycles	12	Decrease in number and size of lesions	Fatigue, dysgeusia, and muscle aches
3/F	Multiple BCCs on the face	1 wk/1 wk x 6 cycles; 1 wk/2 wks x 7 cycles; 1 wk/3 wks x 14 cycles	24	Resolution	Alopecia; resolved with decreased dosage
4/M	Multiple recurrent and aggressive BCCs on face	1 wk/1 wk x 8 cycles; 1 wk/2 wks x 1 cycle; 1 wk/3 wks x 9 cycles	19	Resolution	Fatigue, dysgeusia, muscle spasms, and hand arthritis; improved with lowered dosage
5/F	Large periorbital BCC	1 wk/1 wk x 6 cycles; 1 wk/2 wks x 5 cycles	12	Decrease in BCC size	Fatigue, dysgeusia, muscle aches, and alopecia
6/M	Large BCC on nose	1 wk/1 wk x 6 cycles	7	Decrease in BCC size, followed by MMS	Fatigue, dysgeusia, diarrhea, and constipation
7/M	Incompletely excised periorbital BCC	1 wk/3 wks x 5 cycles	9	Resolution	Fatigue

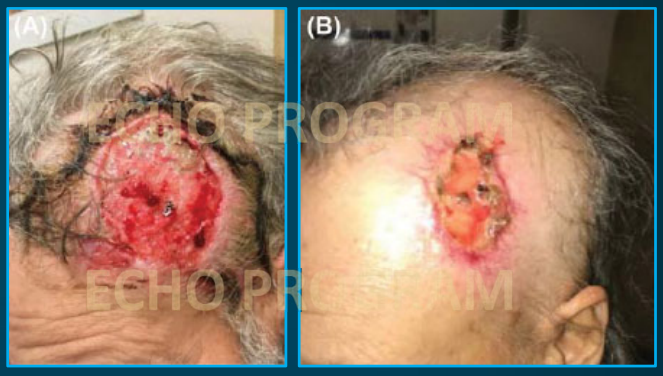
7 patients: 1 week on/1 to 3 weeks off based on tolerability; 3 BCC clinically resolved, 4 decreased in size
No patients discontinued therapy based on adverse effects.

IVT = intermittent vismodegib therapy; MMS = Mohs micrographic surgery.

Becker LR, et al. *JAMA Dermatol.* 2017; 153:321-322.

Outcomes for Basal Cell Carcinoma Treated With Vismodegib Extended Alternate Day Dosing

- 8 patients
- Vismodegib 150 daily x 3 months, then extended alternate day dosing as tolerated
  - Every other day to once weekly dosing
  - Mean reduction in tumor size: ~50%
  - 4 patients experienced no side effects, 4 experienced mild side effects that
    - improved/resolved with further extended alternate day dosing



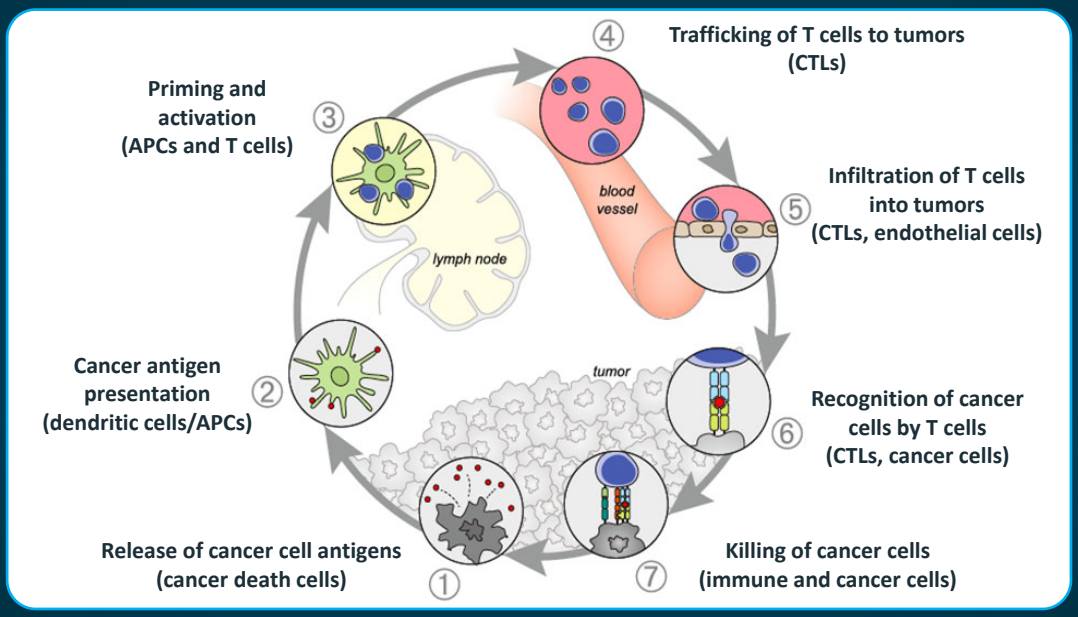
Before | Every 4 days x 10 months

Routt E, Ratner D. *Dermatol Surg.* 2020;46:1109-1112.

When Disease Progresses on Hedgehog Inhibition?

Justin Leitenberger, MD

Immunotherapy: The Cancer-Immunity Cycle

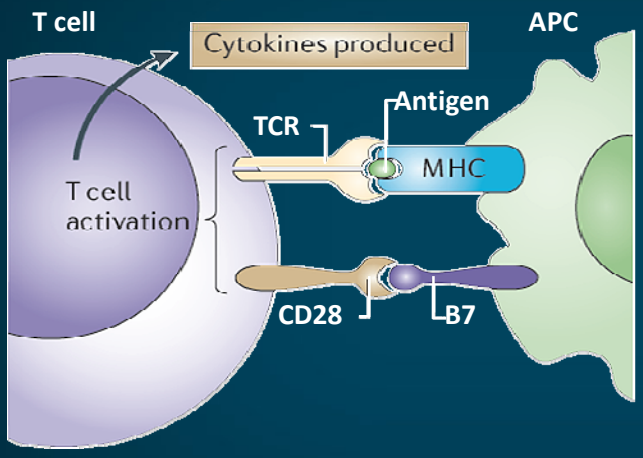


APCs = antigen-presenting cells; CTLs = cytotoxic T lymphocytes.

Chen DS, Mellman I. *Immunity.* 2013;39:1-10.

Immune Checkpoints

Activation of T lymphocytes

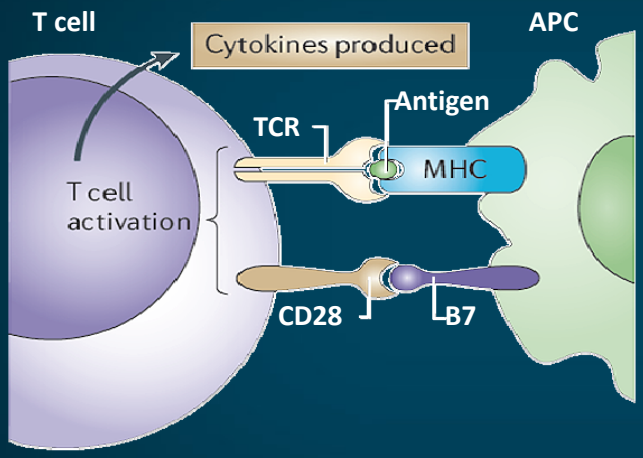


CTLA4 = cytotoxic T lymphocyte-associated protein 4; PD1 = programmed cell death 1; PDL1 = PD1 ligand 1; TIM3 = T cell immunoglobulin and mucin domain-containing protein 3; VISTA = V-domain immunglobulin suppressor of T cell activation.

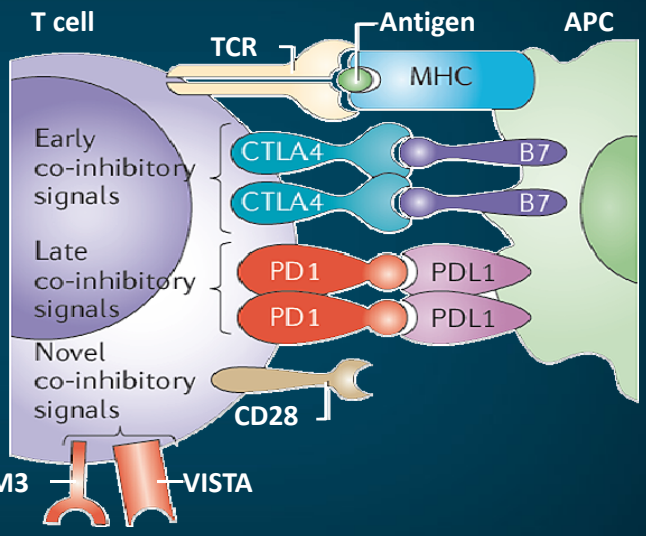
Sharma P et al. *Nat Rev Cancer*. 2011;11:805-812.

Immune Checkpoints

Activation of T lymphocytes



Inhibition of T lymphocytes



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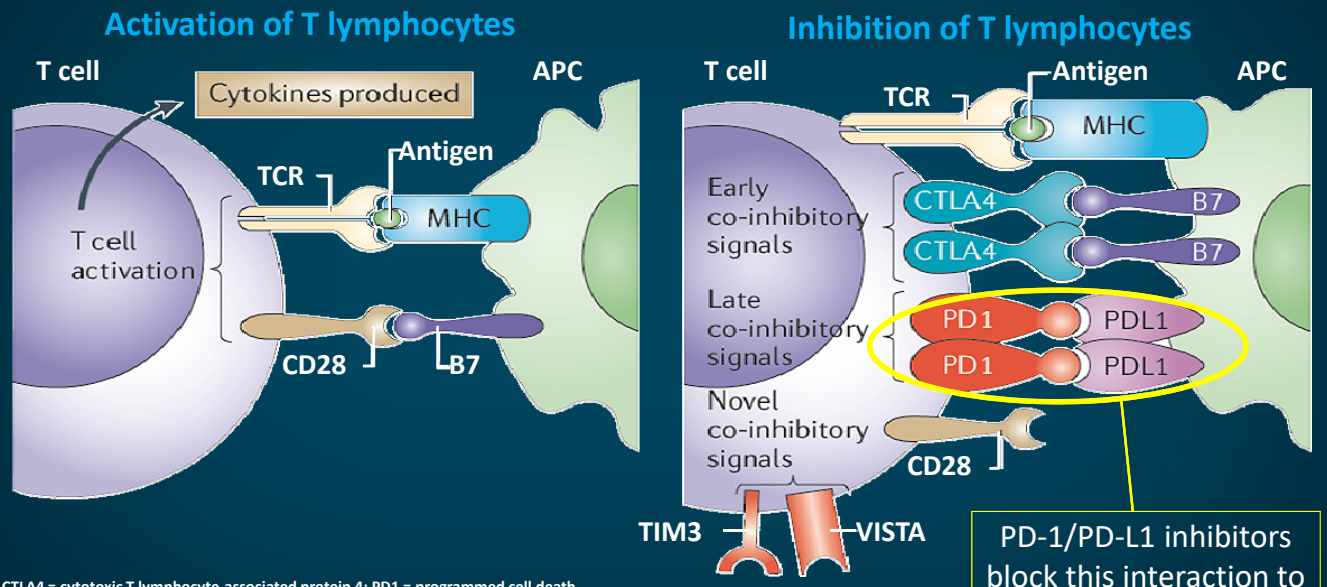

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Cemiplimab

- Feb 9, 2021: First FDA-approved immunotherapy for BCC (advanced cases previously treated with HHI)
  - Also indicated for metastatic cutaneous SCC and laSCC

Trial of cemiplimab for those not tolerating or progressing on HHI

	laBCC (n = 84)
ORR	31.0%
Complete Response	6.0%
Partial Response	25.0%
Response	85% responses ongoing at 12 months
Estimated PFS (all patients)	19 months

Stratigos AJ, et al. *Ann Oncology*. 2020;31:S1175-S1176.

Cemiplimab

- Median baseline TMB: 58.2 (responding; n = 18) and 23.5 (non-responding; n = 38) mutations/Mb
- Responses occurred at all TMB levels
- Downregulation of MHC-I expression identified as an immune evasion mechanism in non-responding BCCs with high TMB
- Adverse events: fatigue (30%), diarrhea (24%) and pruritus (21%)
- 17% of patients discontinued due to AEs

TMB = tumor mutational burden; MHC = major histocompatibility complex; Mb = megabase.

Stratigos AJ, et al. *Ann Oncology*. 2020;31:S1175-S1176.

Pembrolizumab With/Without Vismodegib for Advanced BCC

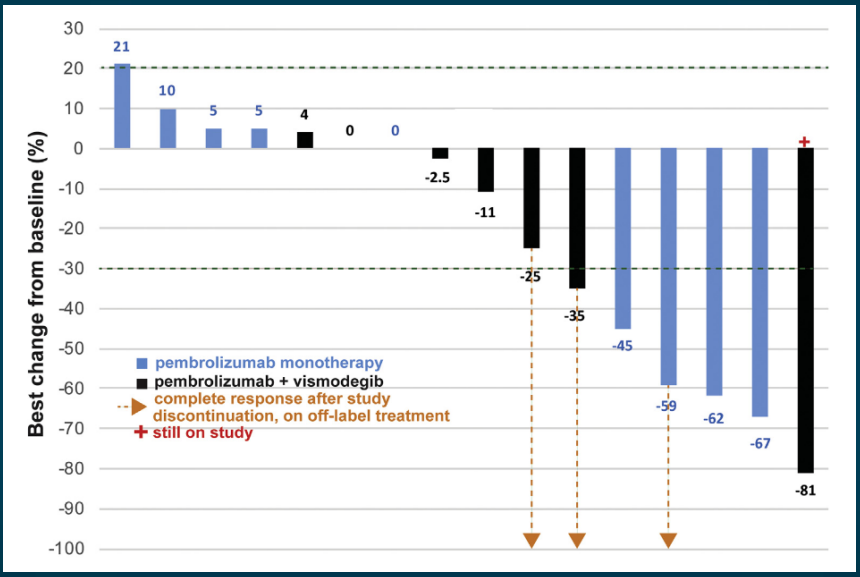
	All Participants (N = 16)	Pembrolizumab (n = 9)	Pembrolizumab + Vismodegib (n = 7)
ORR	38%	44%	29%
1-yr PFS	70%	62%	83%
1-yr OS	94%	89%	100%

- No life-threatening AEs or deaths during the study
- 3 grade 3 AEs occurred out of 98 AEs from 16 participants (1 case of hyponatremia attributed to pembrolizumab)
- 23 immune-related AEs (grade 1/2 dermatitis and fatigue most common)

Chang A, et al. *J Am Acad Dermatol*. 2019:564-566.

Not currently FDA approved for BCC

Pembrolizumab: Best % Change in BCC Diameter From Baseline



Chang A, et al. *J Am Acad Dermatol*. 2019:564-566.

Not currently FDA approved for BCC

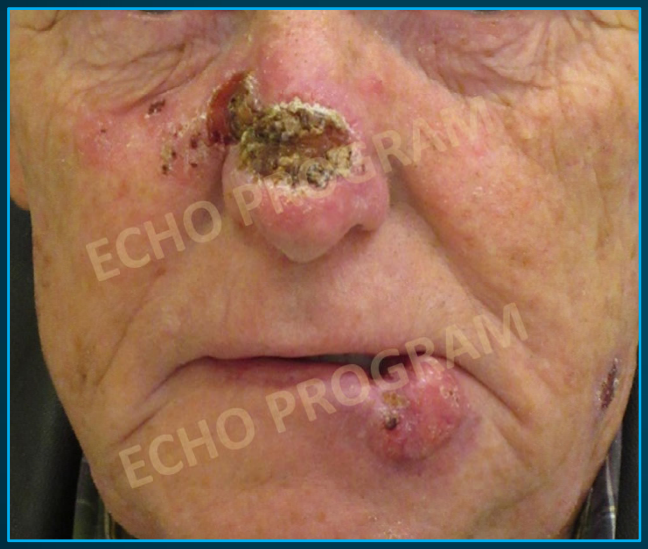
Summary

- Advanced BCC is best managed using multidisciplinary consultation
- Diameter > 4 cm, head/neck location, and/or invasion beyond subcutaneous fat significantly increase risk for local recurrence, metastasis, and death
- Vismodegib outperforms sonidegib in a recent meta-analysis on safety and efficacy
- Alternate dosing regimens can increase tolerability without compromising efficacy
- Immune checkpoint therapy is now approved (cemiplimab) and is useful in cases of hedgehog inhibitor progression or intolerance

Case Study 1

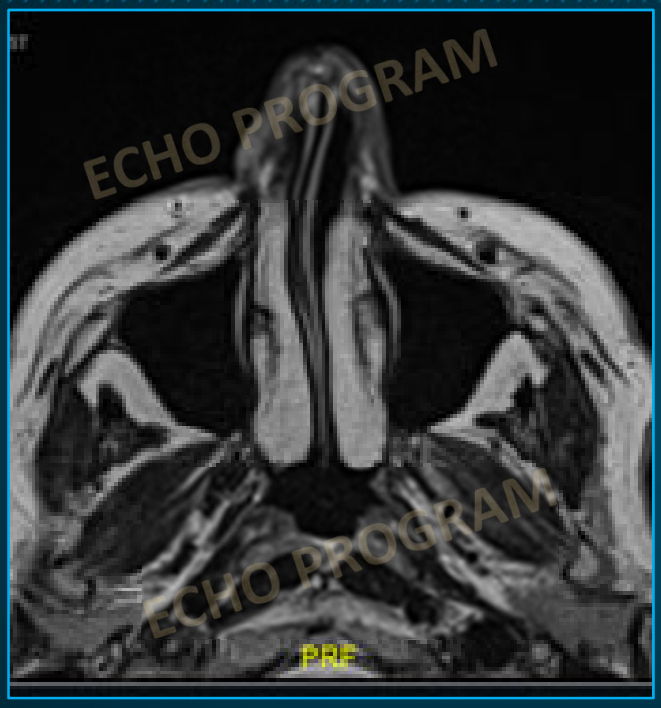
Locally Aggressive BCC: Case 1

Courtesy of Dr Emily Ruiz

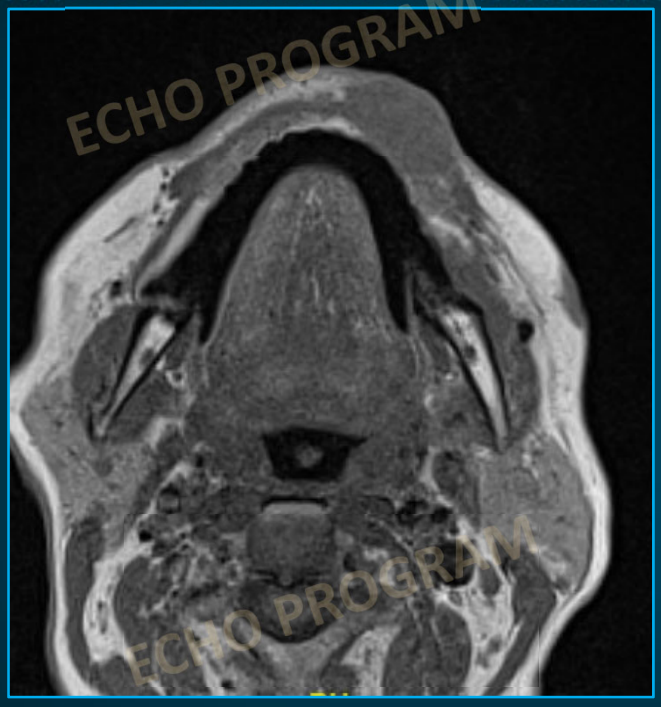


A 69-year-old healthy male presents with 2 BCCs.

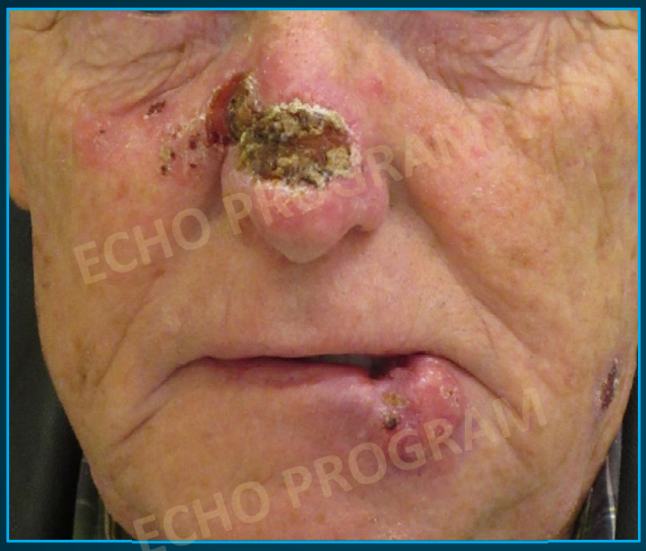
Next steps?



The tumor is inseparable from nasal bones and cartilage.



The tumor involves the maxilla and 2 submandibular lymph nodes.



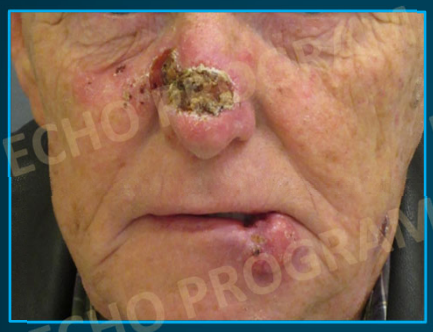
Nose
- Mohs surgery for peripheral and some deep margin
- Bone resection in OR
- Multistage flap

Lip
- Lip resection in OR
- Bilateral neck dissections
- Manibulectomy
- Fibula free flap
- Tracheosteomy
- Skin graft

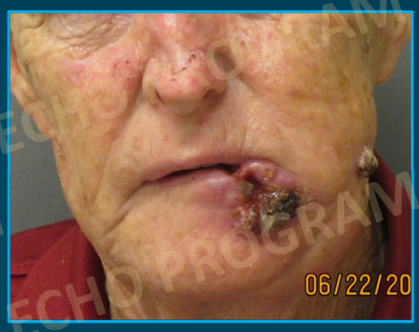
Surgery

Case 1: Next Steps

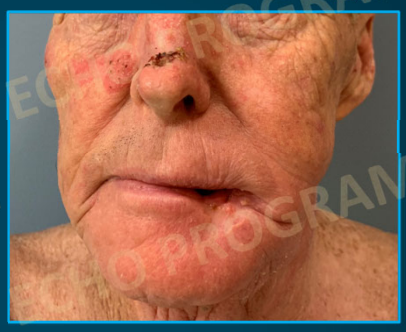
Before Vismodegib



S/P 3 Mo Vismodegib



Post Radiation Therapy



- Illustrates success but also imperfect response rate of hedgehog inhibitors
- Radiation may or may not be curative
- Cemiplimab can be considered if he fails radiation

Case Study 2

Locally Aggressive BCC: Case 2

Courtesy of Dr. Chrysalyne Schmults

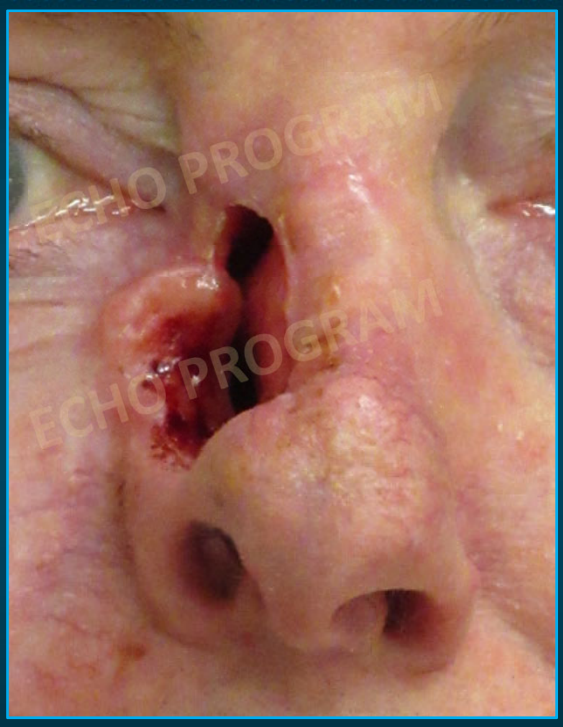
- A 58-year-old healthy man with BCC on right nasal sidewall initially presented in 2012
- Status post (S/P) radiation as primary therapy “to avoid bone resection near eye”

Aggressive BCC

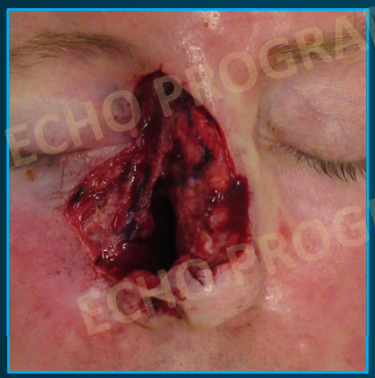
- 2015 to 2016: 5 subsequent recurrences excised by plastic surgeon with in-office frozen sections read by pathologist as clear
- At sixth recurrence the patient is referred for salvage radiation
- Radiation oncologist, in turn, referred the patient to the cancer center

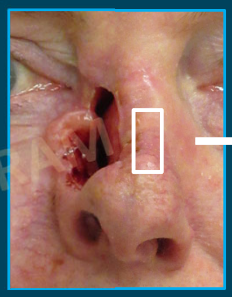
Aggressive BCC

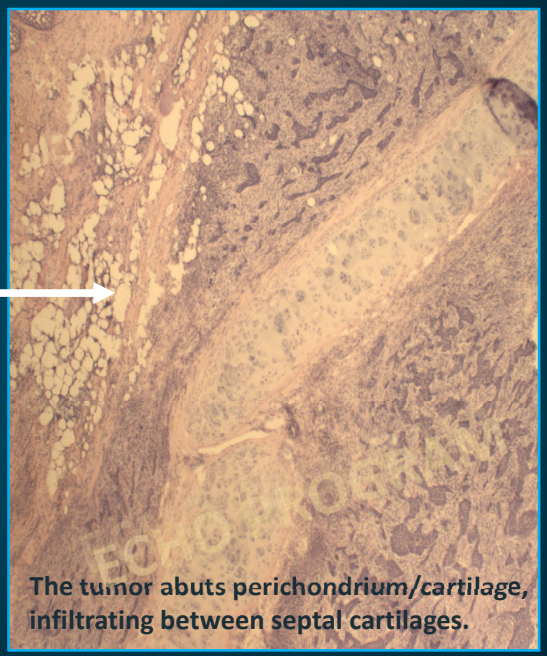
- Magnetic resonance imaging (MRI): tumor abuts bone, no sinus/orbit/nerve invasion
- No metastasis on neck/chest computed tomography (CT)



Mohs Pathology

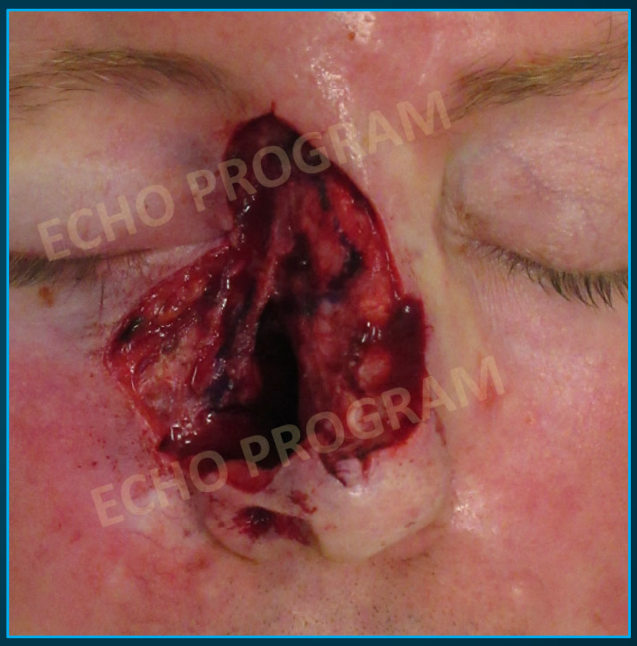






The tumor abuts perichondrium/cartilage, infiltrating between septal cartilages.

- Mohs cleared all but nasal bone and turbinate mucosa (purple outline)
- Head/neck surgeon Dr. Jason Kass requested en face assessment of posterior resection



- Mohs cleared all but nasal bone and turbinate mucosa (purple outline)
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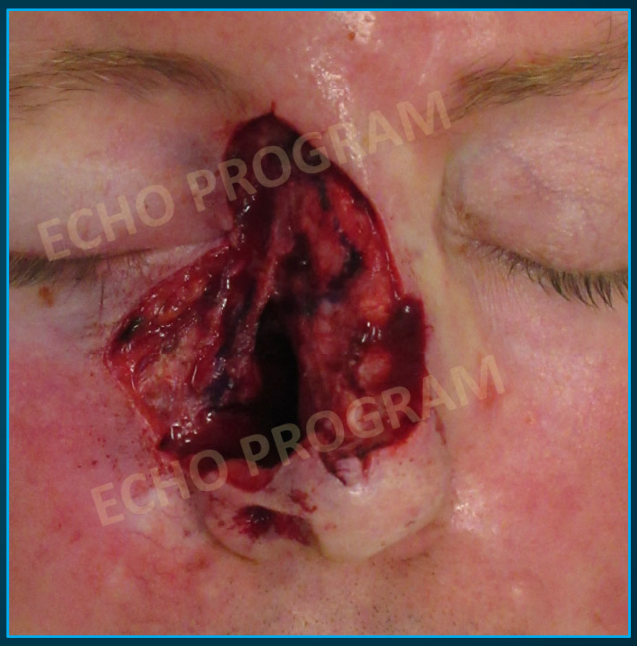
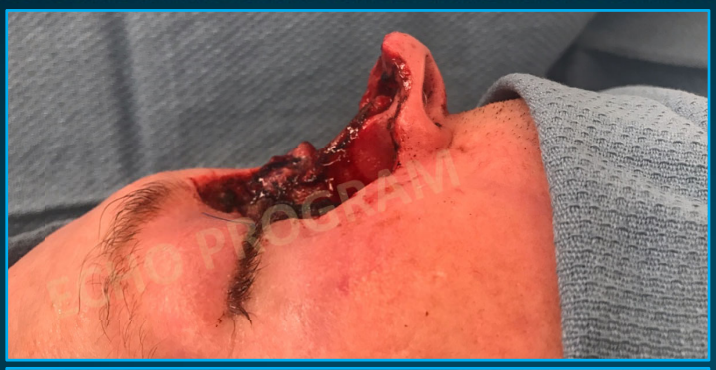
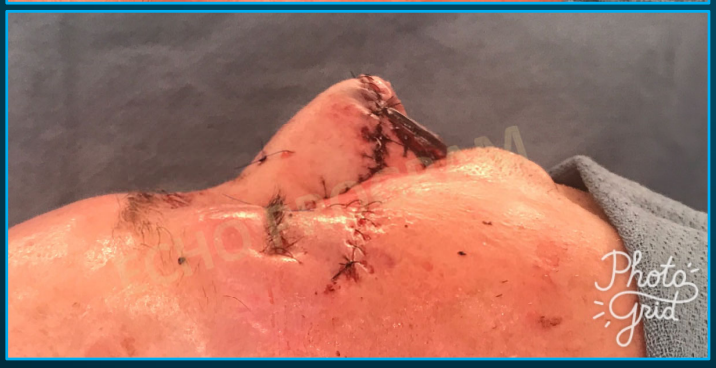
- **NCCN: Recommends CCPDMA for high-risk BCC that can't be closed primarily**

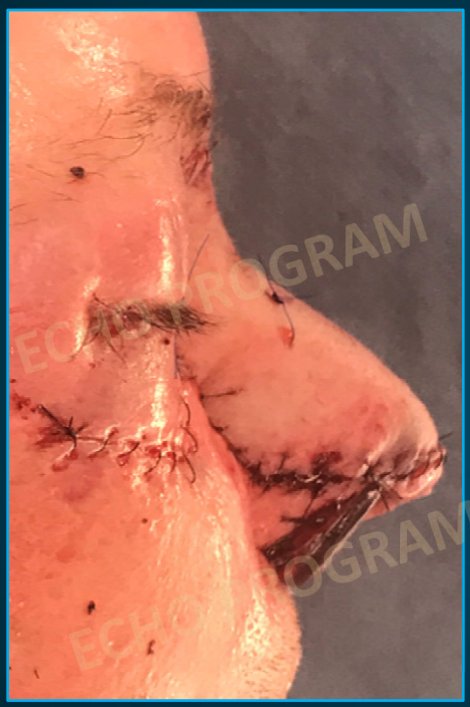






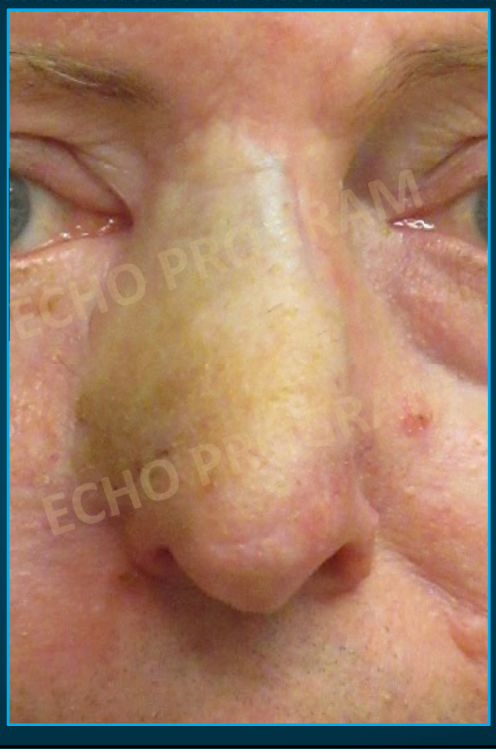
Margin clear but bony margin not processed en face

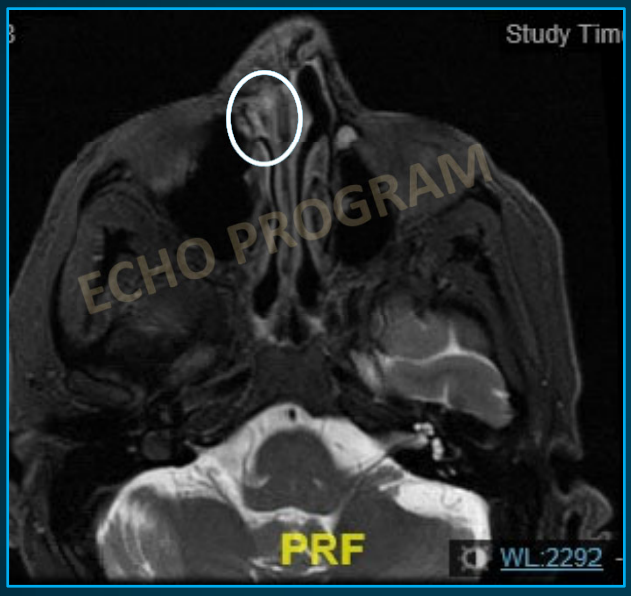
Septal bone graft (from radius) and free flap via Dr. Jason Kass



- Local recurrence: 47% (28%-70%)
- Metastasis: 37% (21%-60%)
- Adjuvant radiation?
  - No data on risk reduction
  - May compromise current reconstruction and make future surgery difficult
- Adjuvant vismodegib?
  - No data on risk reduction in adjuvant setting
  - Difficult side effect profile
  - Offered but declined
- Follow-up every 6 months with face MRI and neck CT every 2 to 3 years

At 1 year, the patient is doing well.





- At 1.5 years, notes nasal congestion, clotted blood
- Recurrent tumor focus, right ethmoid sinus, superior turbinate
- Recurred where couldn't complete Mohs resection
- Another OR resection planned

Despite Pre-Op Imaging and Multiple Scouting Biopsies to Aid Resection Planning, Margins Were Diffusely Positive

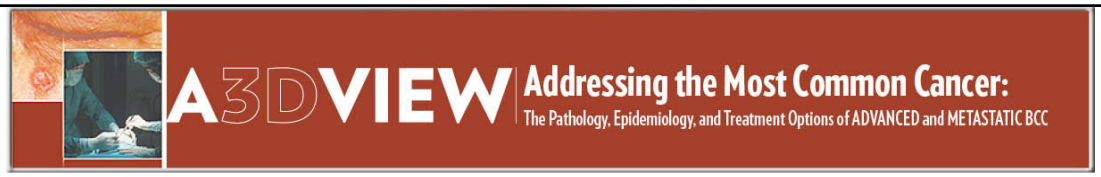
- In bone, underside of prior flap, lacrimal duct
- Patient declined rhinectomy and further maxilla resection

Next Steps for This Patient

- Vismodegib daily with complete response radiologically at 8 months but with extreme cachexia
- Tumor recurred during drug holiday
  - Again declined surgery
  - Currently weighing radiation vs vismodegib retrial vs cemiplimab

Questions/Answers

Thank you!



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Basal Cell Carcinoma: Identification and Management

Resource	Address
Ascierto PA, et al. Immunotherapy in non-melanoma skin cancer: Updates and new perspectives. *Drugs Context*. 2019;8:212583.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6434981/
Carballo GB, et al. A highlight on sonic hedgehog pathway. *Cell Commun Signal*. 2018;16:11.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5861627/
Cameron MC, et al. Basal cell carcinoma: Epidemiology; pathophysiology; clinical and histological subtypes; and disease associations. *J Am Acad Dermatol*. 2019;80:303-317.	https://pubmed.ncbi.nlm.nih.gov/29782900/
Cameron MC, et al. Basal cell carcinoma: Contemporary approaches to diagnosis, treatment, and prevention. *J Am Acad Dermatol*. 2019;80:321-339.	https://pubmed.ncbi.nlm.nih.gov/29782901/
Chang ALS, et al. Pembrolizumab for advanced basal cell carcinoma: An investigator-initiated, proof-of-concept study. *J Am Acad Dermatol*. 2019;80:564-566.	https://www.jaad.org/article/S0190-9622(18)32471-X/pdf
Chen DS, et al. Oncology meets immunology: The cancer-immunity cycle. *Immunity.* 2013;39:1-10.	https://pubmed.ncbi.nlm.nih.gov/23890059/
Danesh MJ, et al. Adherence to the National Comprehensive Cancer Network Criteria of Complete Circumferential Peripheral and Deep Margin Assessment in Treatment of High-Risk Basal and Squamous Cell Carcinoma. *Dermatologic Surg*. 2020;46:1473-1480.	https://pubmed.ncbi.nlm.nih.gov/32149872/
Dréno B, et al. Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): A randomised, regimen-controlled, double-blind, phase 2 trial. *Lancet Oncol.* 2017;18:404-412.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30072-4/fulltext
Dummer R, et al. Long-term efficacy and safety of sonidegib in patients with advanced basal cell carcinoma: 42-month analysis of	https://pubmed.ncbi.nlm.nih.gov/31545507/

the phase II randomized, double-blind BOLT study. *Br J Dermatol*. 2020;182:1369-1378.	
Hoorens I, et al. Mohs micrographic surgery for basal cell carcinoma: evaluation of the indication criteria and predictive factors for extensive subclinical spread. *Br J Dermatol*. 2016;174(4):847-52.	https://pubmed.ncbi.nlm.nih.gov/26595159/
Johnson TM, et al. Mohs surgery versus standard local excision for basal cell carcinoma, squamous cell carcinoma, and melanoma skin cancer. *Facial Plast Surg*. 2020;36(2):133-140.	https://pubmed.ncbi.nlm.nih.gov/32413920/
McDaniel B, et al. Basal Cell Carcinoma. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing. Updated November 20, 2020.	https://www.ncbi.nlm.nih.gov/books/NBK482439/
Migden MR, et al. Emerging trends in the treatment of advanced basal cell carcinoma. *Cancer Treat Rev*. 2018;64:1-10.	https://pubmed.ncbi.nlm.nih.gov/29407368/
Morgan FC, et al. Factors predictive of recurrence, metastasis, and death from primary basal cell carcinoma 2 cm or larger in diameter. *J Am Acad Dermatol*. 2020;83:832-838.	https://pubmed.ncbi.nlm.nih.gov/31600531/
Paulson KG, et al. Immunotherapy for skin cancer. *Int Immunol*. 2019;31:465-475.	https://pubmed.ncbi.nlm.nih.gov/30753483/
Sekulic A, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer*. 2017;17:332.	https://bmccancer.biomedcentral.com/articles/10.1186/s12885-017-3286-5
Sekulic A, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Eng J Med*. 2012;366:2171-2179.	https://www.nejm.org/doi/full/10.1056/nejmoa1113713
Stratigos AJ, et al. LBA47 Primary analysis of phase II results for cemiplimab in patients (pts) with locally advanced basal cell carcinoma (laBCC) who progress on or are intolerant to hedgehog inhibitors (HHIs). *Ann Oncology*. 2020;31(suppl 4):S1175-S1176.	https://www.annalsofoncology.org/article/S0923-7534(20)42359-2/abstract

Stratigos AJ, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 2. Treatment. *Eur J Cancer*. 2020;128:83-102.	https://pubmed.ncbi.nlm.nih.gov/32113942/
Tanese K. Diagnosis and management of basal cell carcinoma. *Curr Treat Options Oncol* 2019;20:13.	https://pubmed.ncbi.nlm.nih.gov/30741348/
Totonchy M, et al. Emerging concepts and recent advances in basal cell carcinoma. *F1000Res*. 2017;6:2085.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5717469/
Xie P, et al. Efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: A systematic review and meta-analysis. *J Am Acad Dermatol.* 2018;79:1089-1100.e17.	https://pubmed.ncbi.nlm.nih.gov/30003981/

Resources and Societies

Resource	Address
American Academy of Dermatology (AAD). *Skin Cancer.*	https://www.aad.org/media/stats-skin-cancer
American Cancer Society (ACS). *Basal and Squamous Cell Skin Cancer*.	https://www.cancer.org/cancer/basal-and-squamous-cell-skin-cancer.html
American College of Mohs Surgery	https://www.mohscollege.org/
American Society of Clinical Oncology (ASCO).	https://www.asco.org/
Centers for Disease Control and Prevention (CDC). *What Is Skin Cancer?*	https://www.cdc.gov/cancer/skin/basic_info/what-is-skin-cancer.htm
National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology. Basal Cell Skin Cancer. Version 1.2020.*	https://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf
Skin Cancer Foundation. *Basal Cell Carcinoma Overview.*	https://www.skincancer.org/skin-cancer-information/basal-cell-carcinoma/