Hedgehog Inhibitors, Optimizing Management and Treatment of Adverse Reactions

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South Beach Symposium
medical + aesthetic dermatology

GW School of Medicine & Health Sciences

Relevant Disclosures

Investigator/consultant and/or speaker:

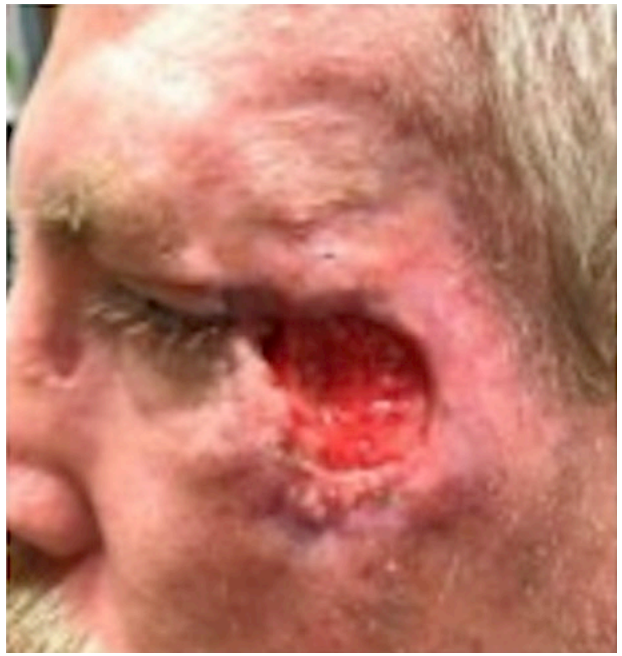
Almirall, Biofrontera, Galderma, Allergan (An Abbvie company), LEO Pharmaceuticals, SUN Pharmaceuticals, Regeneron, Pulse Biosciences

Community Dermatologist

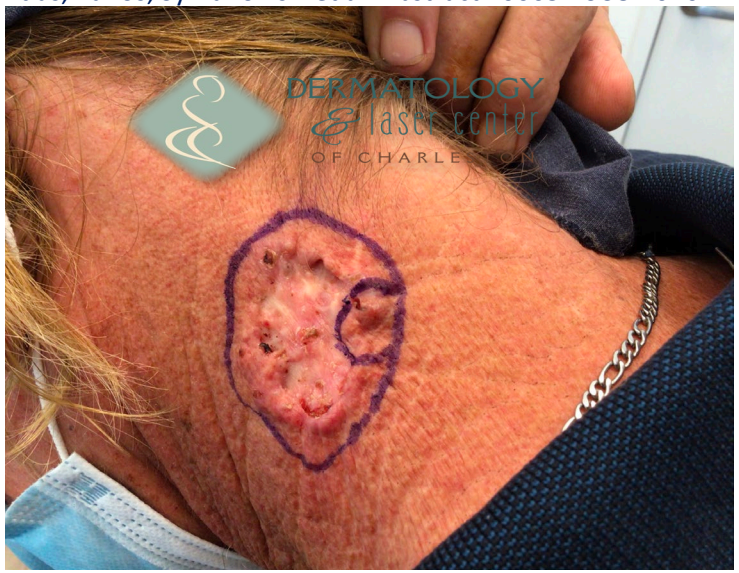
- **As such, I…**
- **Practice outside the academic setting**
- **Do not have Tumor Board (YET)**
- **Do not have centralized Electronic Health Record shared with other physicians**
- **However, I still see bad cancers (as do many of you)**

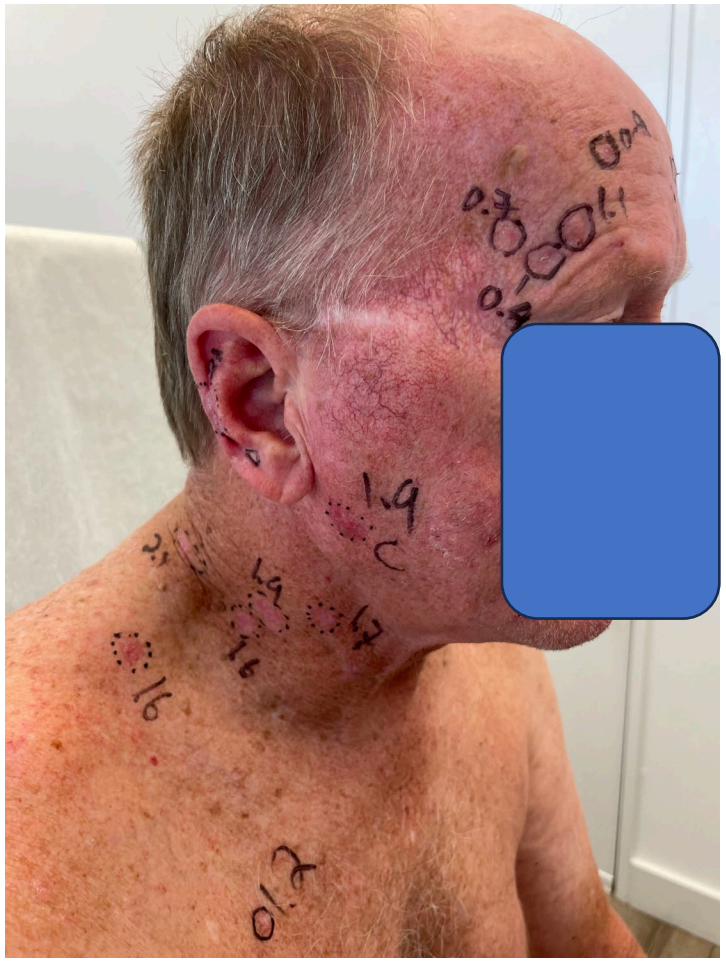
"Unfortunately it's inoperable. So I'm going to whack it with a hammer."

HIGH RISK TUMORS



Atlas, Kanos, Symanowski et al. Abstract 10065 ASCO 2020





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Major Classes of Approved Treatments for Advanced NMSC

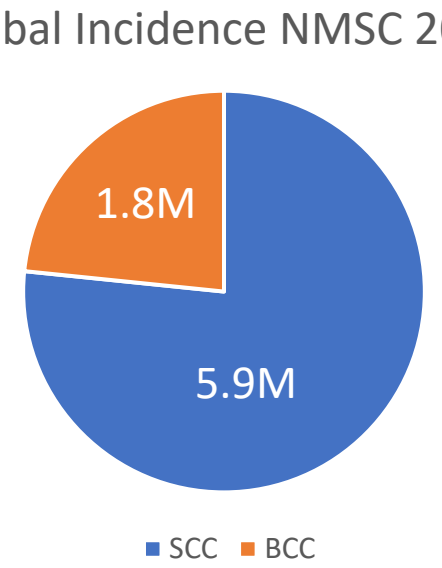
Hedgehog Pathway Inhibitors (FDA Approval Date)

- Vismodegib (30JAN2012) – mBCC or laBCC
  - Dosed 150mg PO daily
- Sonidegib (24JUL2015) – laBCC (mBCC outside USA)
  - Dosed 200mg PO daily (1 hr before or 2 hr after a meal)

PD-1 Inhibitors

- Cemiplimab
  - (28SEP2018) – laCSCC or mCSCC
  - (09FEB2021) - laBCC and mBCC - previously treated with HHI or not appropriate for HHI
  - Dosed IV 350mg every 3 weeks
- Pembrolizumab (24JUN2020) – recurrent or mCSCC and expanded to laSCC (01JUL2021)
  - Dosed IV 200mg every 3 weeks

Advanced BCC Incidence and Epidemiology



BCC: Locally advanced and metastatic cases in the US		
	laBCC	mBCC
% of all BCCs	0.83%	0.04%

Global Burden of Disease Cancer Collaboration. *JAMA Oncol*. 2019;5(12):1749-1768

Goldenberg G, et al. *J Am Acad Dermatol*. 2016;75(5):957-66.e2.

National Comprehensive Cancer Network®

PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced (laBCC), Nodal or Distant Metastatic Basal Cell Carcinoma (mBCC)

- Systemic therapy may be considered for laBCC. Locally advanced disease is defined by those that have primary or recurrent extensive disease where surgery and/or RT may not result in a cure or would possibly produce a significant functional limitation.
- Systemic therapy may be considered for cases of nodal or distant metastatic disease, especially if surgery and RT are not feasible.
- Multidisciplinary consultation may be required to determine the best treatment approach and deem the tumor not amendable to surgery or RT.
- Hedgehog pathway inhibitors (HHIs)
  - Due to frequency of intolerable side effects associated with HHIs, drug holidays or other alternatives to daily dosing can be used to reduce side effects to improve adherence to therapy and quality of life.
  - HHIs may be considered for diffuse BCC formation (eg, basal cell nevus syndrome or other genetic forms of multiple BCC). HHIs are not FDA approved for basal cell nevus syndrome; however, they may be used off-label and are effective based on a randomized controlled trial.[1]
- The role of adjuvant systemic therapy for resected BCC is unclear and thus, adjuvant systemic therapy is best performed in a clinical trial setting.

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Locally Advanced Disease - Neoadjuvant	• None	• Vismodegib[a,2] (category 2B)	• Cemiplimab-rwlc[b] (category 2B)
Locally Advanced Disease	• None	• Sonidegib[3] • Vismodegib[4,5]	• Cemiplimab-rwlc[b,c,6]
Nodal Disease	• None	• Vismodegib • Sonidegib[3] (category 2B)	• Cemiplimab-rwlc[b]
Metastatic Disease	• None	• Vismodegib[4,5]	• Cemiplimab-rwlc[b,6]

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Hedgehog Inhibitors (HHIs) Therapy for aBCC

Therapy	Vismodegib (150 mg orally once daily)[1*]		Sonidegib (200 mg orally once daily)[2]	
Phase 2 pivotal clinical study	**ERIVANCE** **Long-term analysis – INV**		**BOLT** **42-mo analysis – ICR**	
Diagnosis	**laBCC (N=63)**	**mBCC (N=33)**	**laBCC (N=66)**	**mBCC (N=13)**
ORR, % (95% CI) [n/N]	**60 (47–72)** [38/63]	**49 (31–66)** [16/33]	**56 (43–68)** [–/–]	**8 (0.2–36)** [–/–]
Median DoR, mo (range)	**26.2** (9.0–37.6)	**14.8** (5.6–17.0)	**26.1** (NE)	**24.0** (NE)
Median PFS, mo (95% CI)	**12.9** (10.2–28.0)	**9.3** (7.4–16.6)	**22.1** (NE)	**13.1** (5.6-33.1)
Serious AEs, any grade, % (n/N)	**35** (36/104)		**20** (16/79)	
Common AEs reported	**Muscle spasms, alopecia, taste disorder (dysgeusia), weight loss, fatigue, nausea, decreased appetite, and diarrhea**			

*Median follow-up for vismodegib: 29 months after accrual completion.

aBCC, advanced basal cell carcinoma; AE, adverse event; DoR, duration of response; HHI, hedgehog inhibitor; ICR, independent central review; INV, investigator review; laBCC, locally advanced BCC; mBCC, metastatic BCC; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

1. Sekulic A, et al. *BMC Cancer*. 2017;17:332. doi:10.1186/s12885-017-3286-5. 2. Dummer R, et al. *Br J Dermatol*. 2020;182:1369-1378.

COMPARING VISMODEGIB AND SONIDEGIB

	Vismodegib (ERIVANCE study)[19]	Sonidegib (BOLT study)[27]
Indication	Locally advanced BCC that has recurred following surgery, metastatic BCC, and patients who are not candidates for surgery or radiation	Locally advanced BCC that has recurred following surgery, and patients who are not candidates for surgery or radiation
Dose	150 mg once daily	200 mg once daily
Objective response rate (complete or partial response)	43% in locally advanced 30% in metastatic BCC	56% in locally advanced
Median duration of response	7.6 months	26.1 months
Progression-free survival	9.5 months	22.1 months
Common side effects	Muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, decreased appetite, and diarrhea	

- Half-life vismodegib is 4-12 days/sonidegib is 28 days
- Volume of distribution (VOD) for vismodegib is 16.4-26.6L and 9,166L for sonidegib
- What is the VOD of human blood?
- About 15.7L

Effects of Sonidegib Following Dose Reduction and Treatment Interruption in Patients with Advanced Basal Cell Carcinoma During 42-Month BOLT Trial.

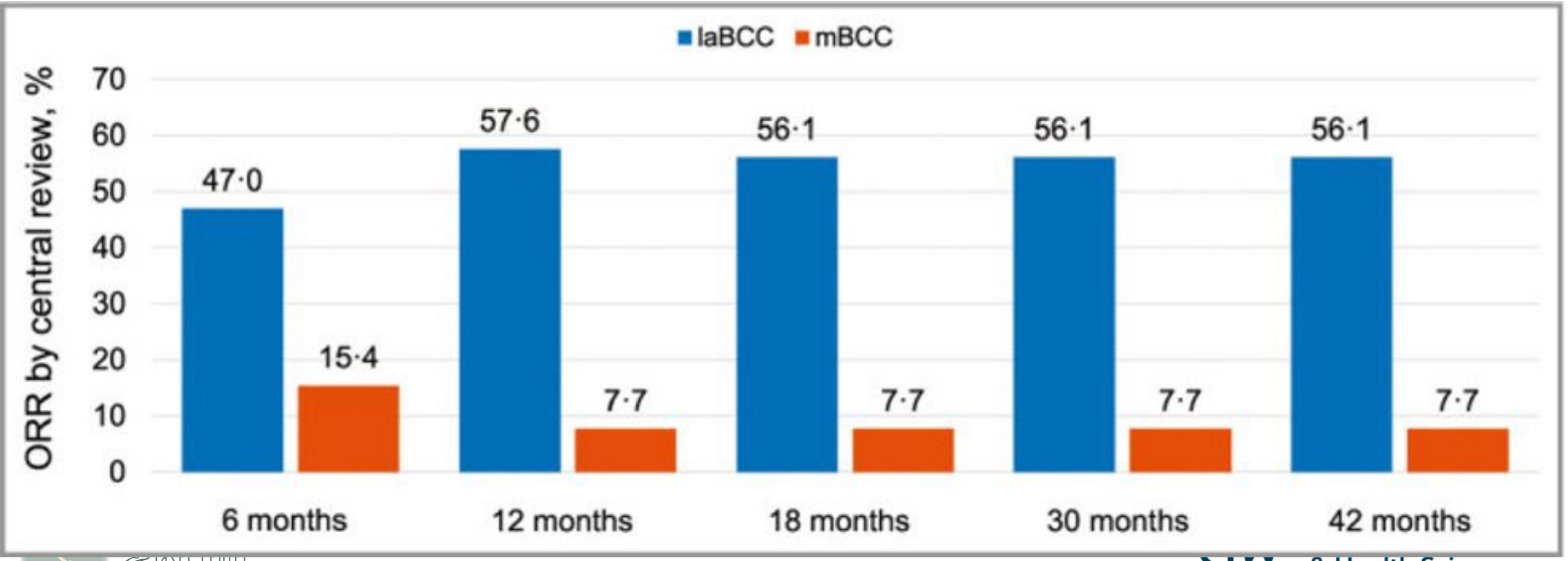
- Dose interruptions similar between 200- and 800-mg (68.4% vs 65.3%)
- Dose reductions more frequent in 800 mg (36.7%) than 200 mg (16.5%)
- ORR for 200 mg daily (48.1%) similar to patients without dose reduction or interruption (48.5%).

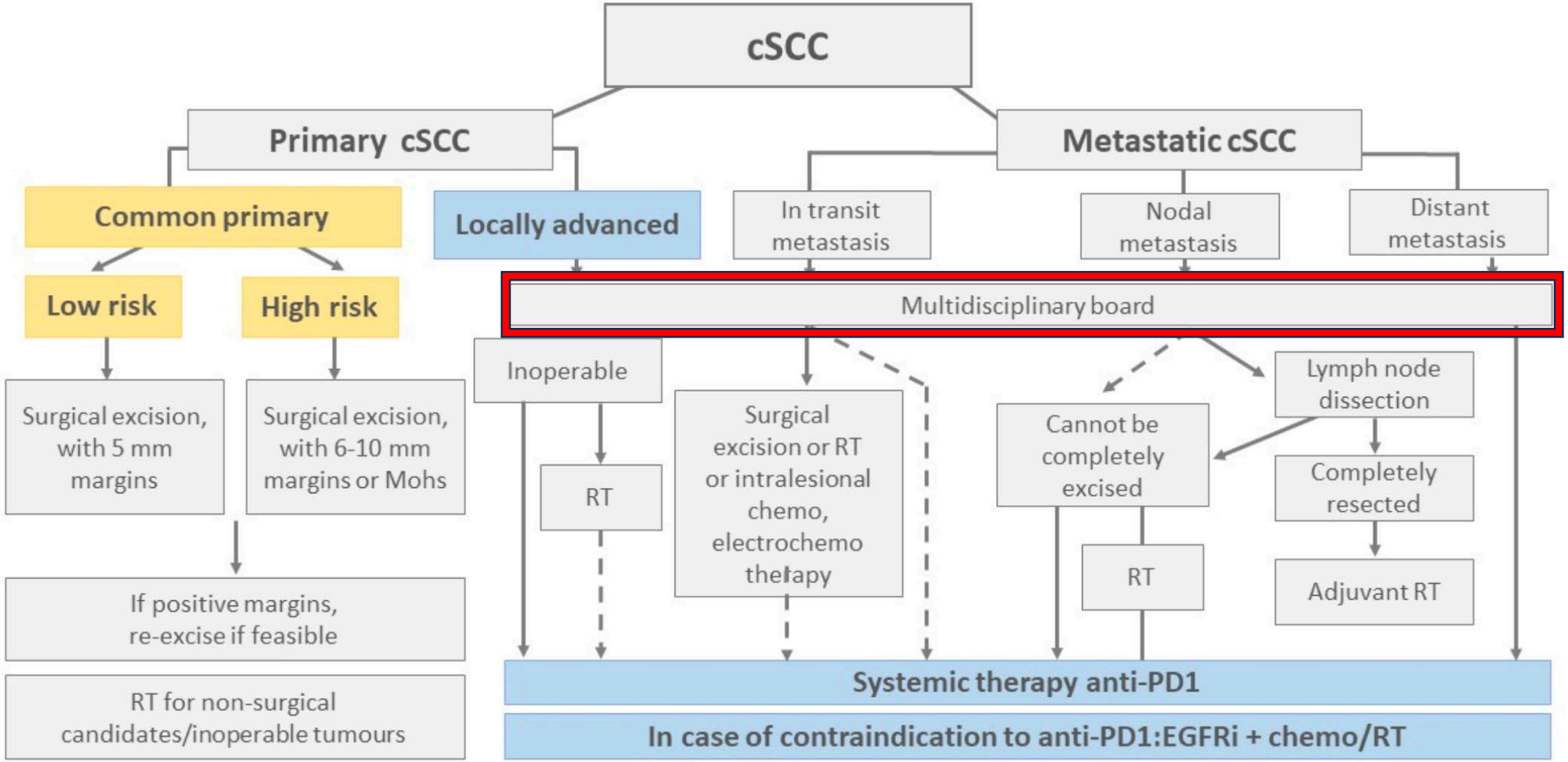
*Dose escalation may be tried for non-responders but may not improve outcomes.

Lewis K, Dummer R, Farberg AS, Guminski A, Squittieri N, Migden M. Dermatol Ther (Heidelb). 2021;11:2225-2234

The Oncologist 2016;21:1218–1229

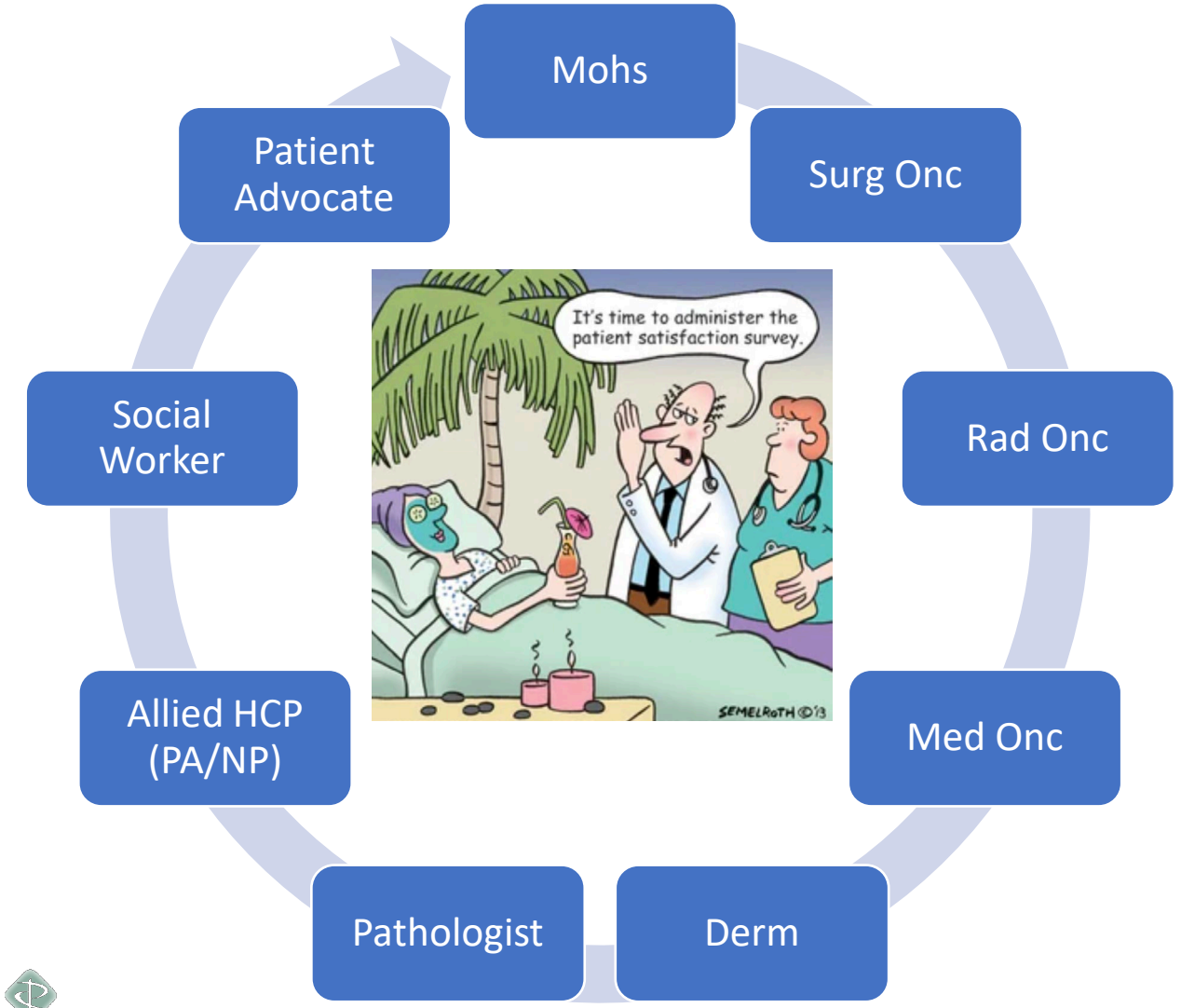
Objective response rates by central review across all BOLT (Basal Cell Carcinoma Outcomes with LDE225 Treatment) analyses in patients receiving sonidegib 200mg/day mg daily.



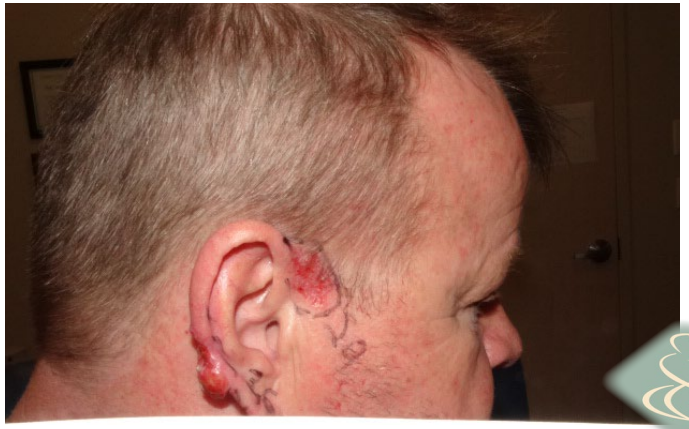


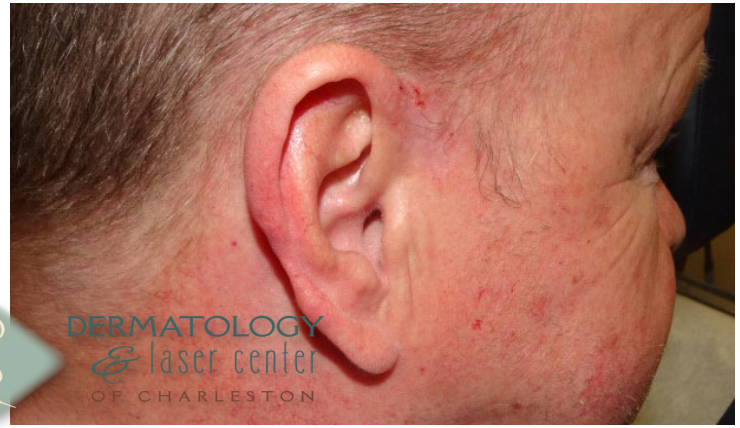
Stratigos AJ, Garbe C, Dessinioti C et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 2. Treatment. Eur J Cancer 2020; 128: 83–102

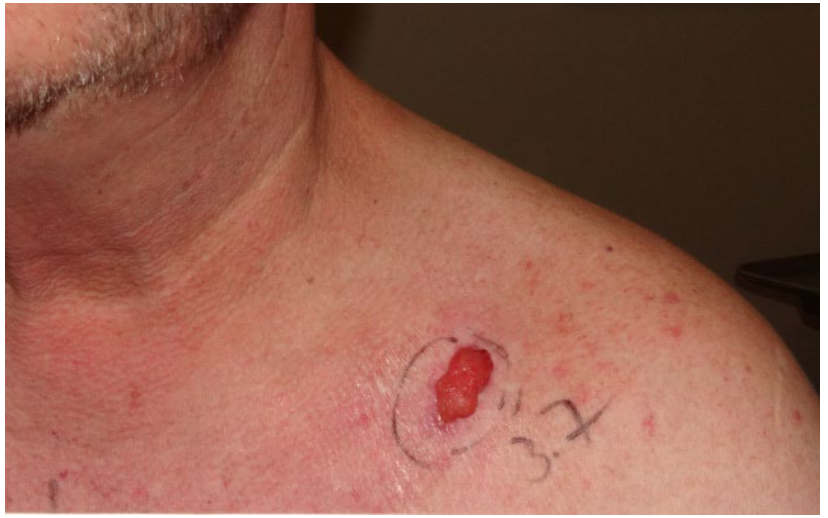
Who is on the MDT?

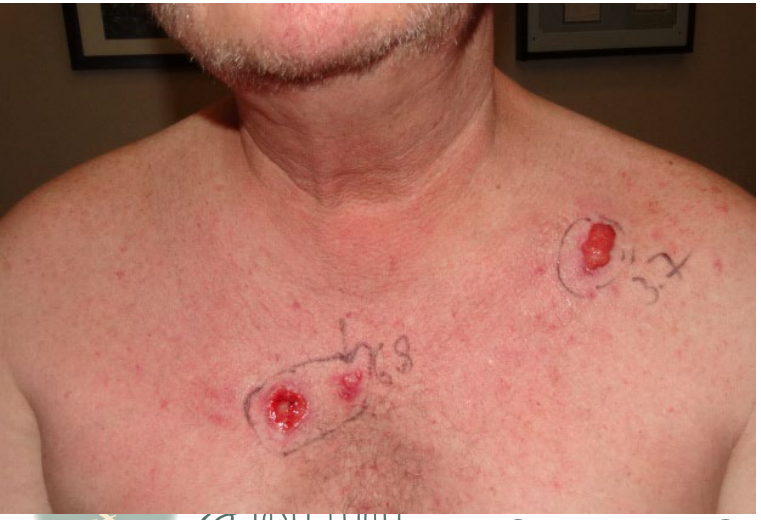


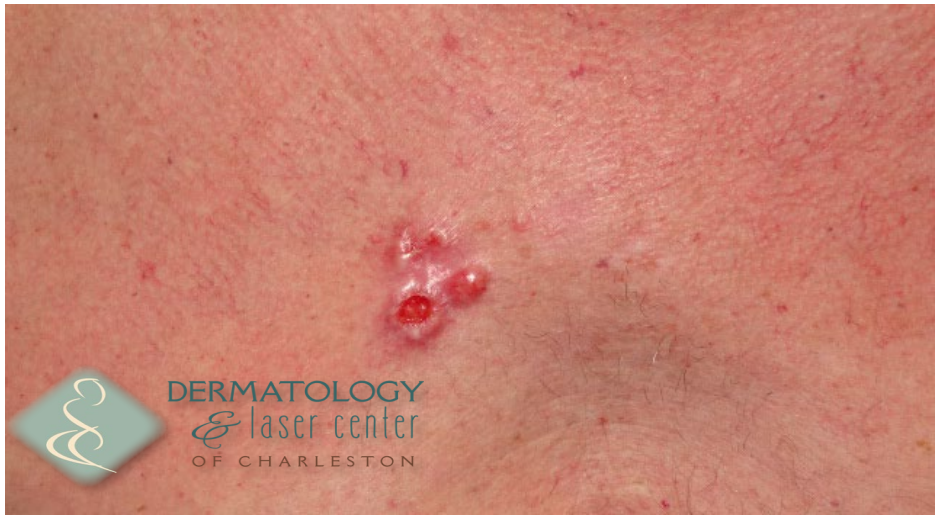
VISMODEGIB RESPONSES OVER 9 MONTHS

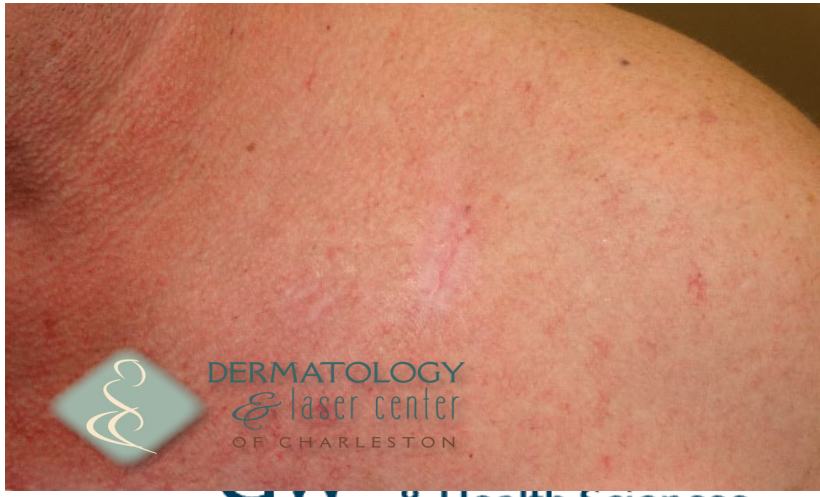




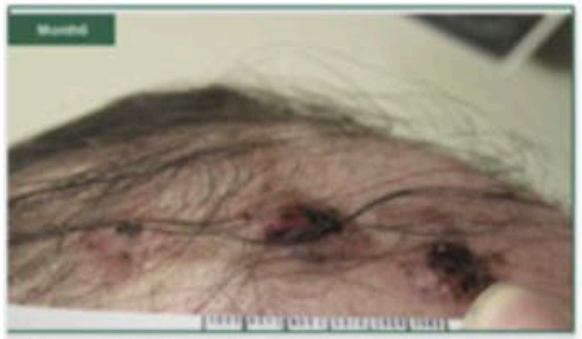








SONIDEGIB RESPONSES OVER 23 MONTHS



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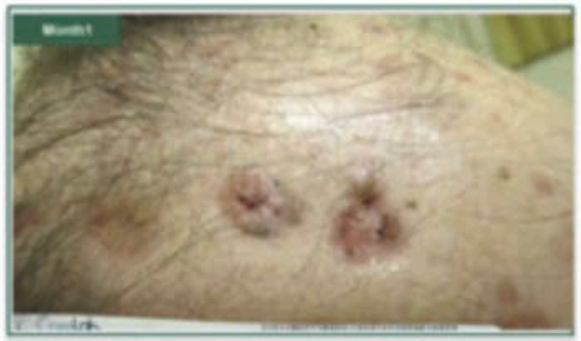

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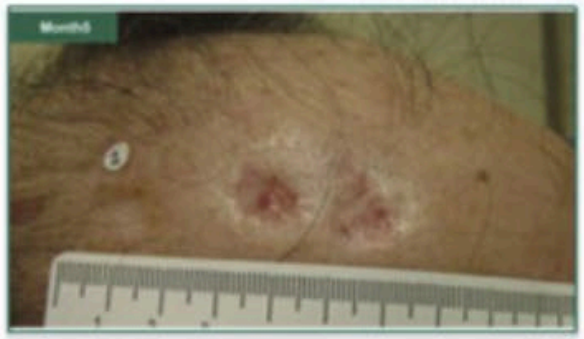
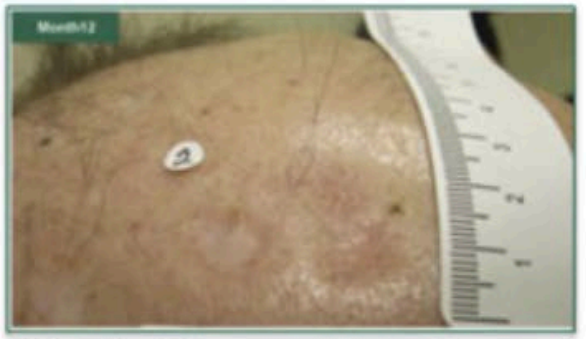


Month 5



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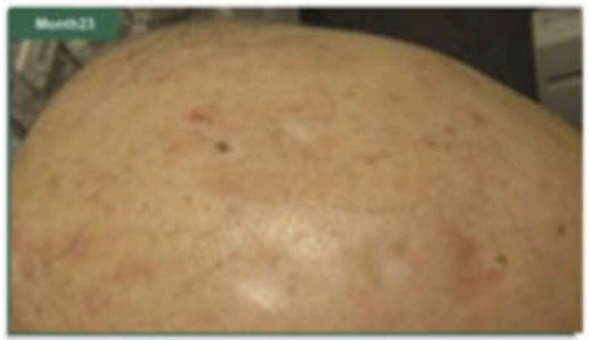
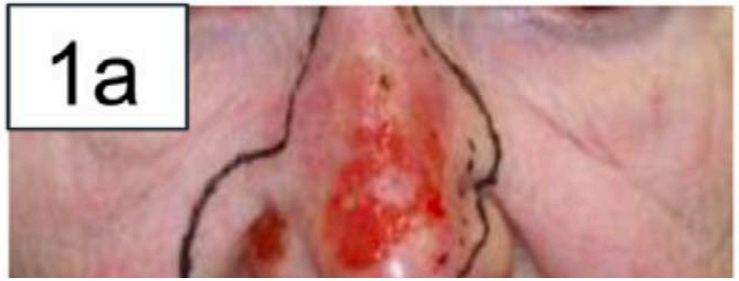
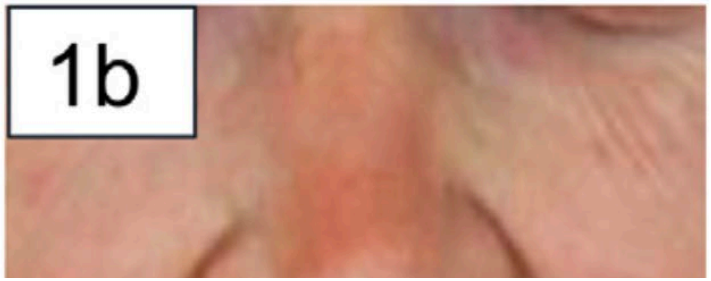


Month 23

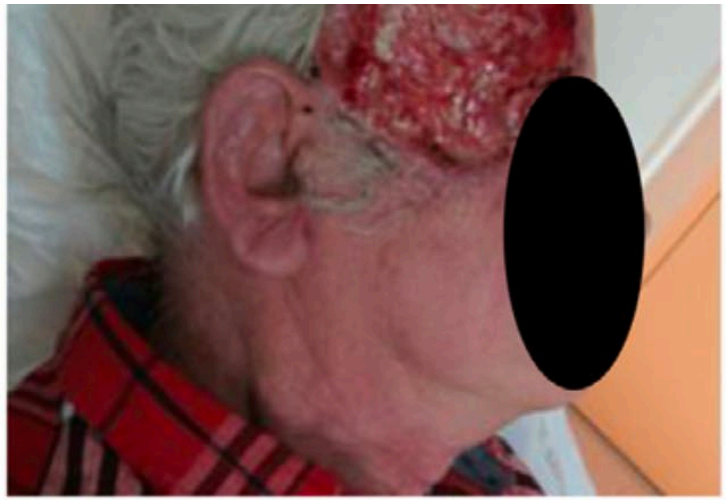


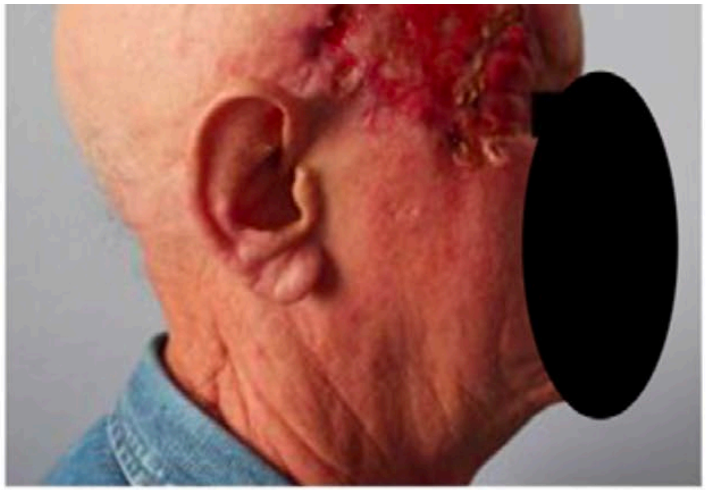


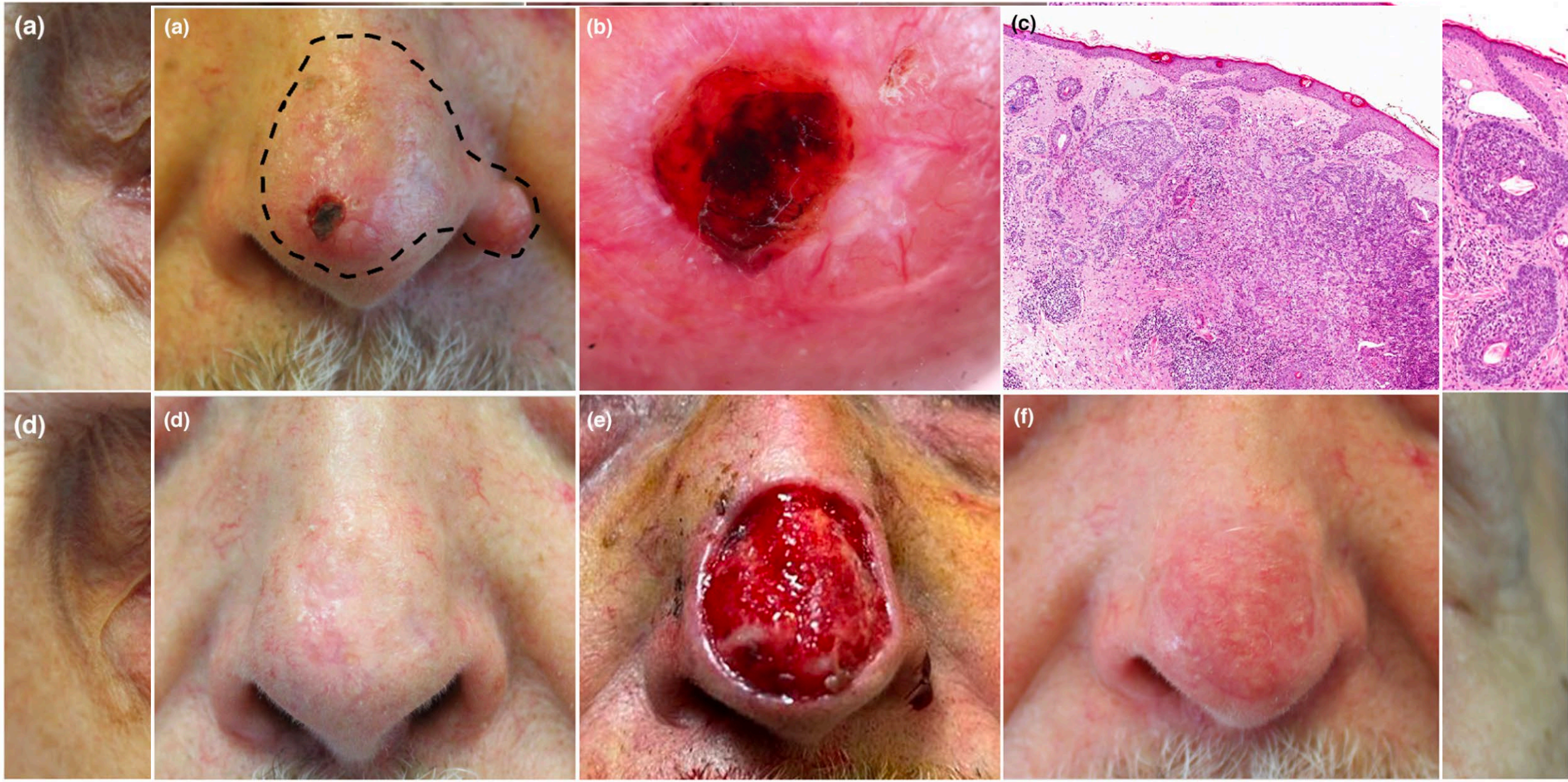
Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: First results of a multicenter, open-label, phase 2 trial (VISMONEO study)

Neoadjuvant Vismodegib in Locally Advanced Basal Cell Carcinoma

Nicolas Bertrand, MD[a,1,*], Pierre Guerreschi, MD, PhD[b,1], Nicole Basset-Seguin, MD, PhD[c], Philippe Saiag, MD, PhD[d], Alain Dupuy, MD, PhD[e], Sophie Dalac-Rat, MD[f], Véronique Dziwniel, PhD[g], César Depoortère, MD[b], Alain Duhamel, MD, PhD[h], Laurent Mortier, MD, PhD[i]






(a)
(a)
(b)
(c)
(d)
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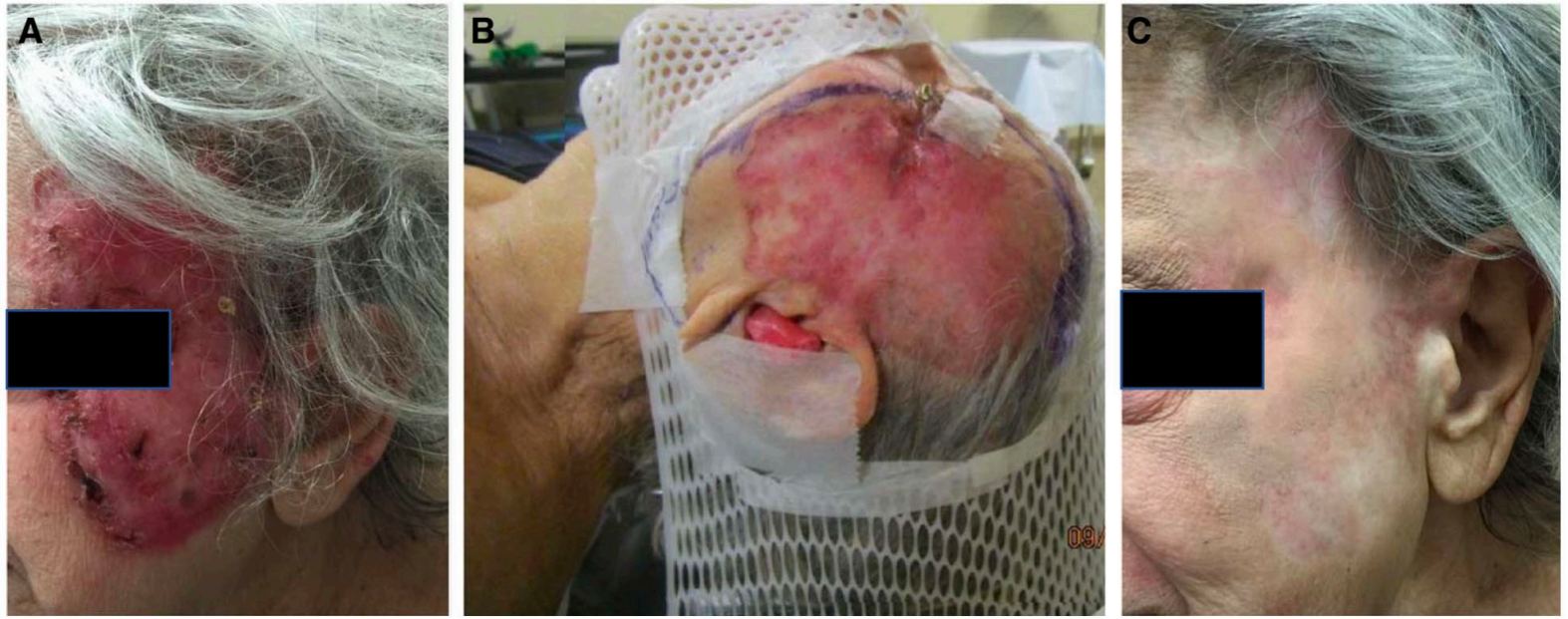
(e)
(f)

X HHI + XRT

- Case series n=12
- CR 100%/PFS 88.8% at 40 mos/16.6% relapse
- HHI may increase XRT induced cytotoxicity
- Induction with HHI may improve XRT response and durability with modest toxicity



Baseline 2.5 months 52 months

The Oncologist 2021;26:e2247–e2253

Melanoma and Cutaneous Malignancies

The Oncologist®

Hedgehog Inhibitor Induction with Addition of Concurrent Superficial Radiotherapy in Patients with Locally Advanced Basal Cell Carcinoma: A Case Series

Joshua P. Weissman,[a,b] Wolfram Samlowski,[b,c,d] Raul Meoz[b,c,d]

[a]Feinberg School of Medicine, Northwestern University, Evanston, Illinois, USA; [b]Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada, USA; [c]School of Medicine, University of Nevada, Las Vegas, Las Vegas, Nevada; [d]University of Nevada School of Medicine, Reno, Nevada, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-melanoma skin cancer • Keratinocyte carcinoma • Sonidegib • Vismodegib

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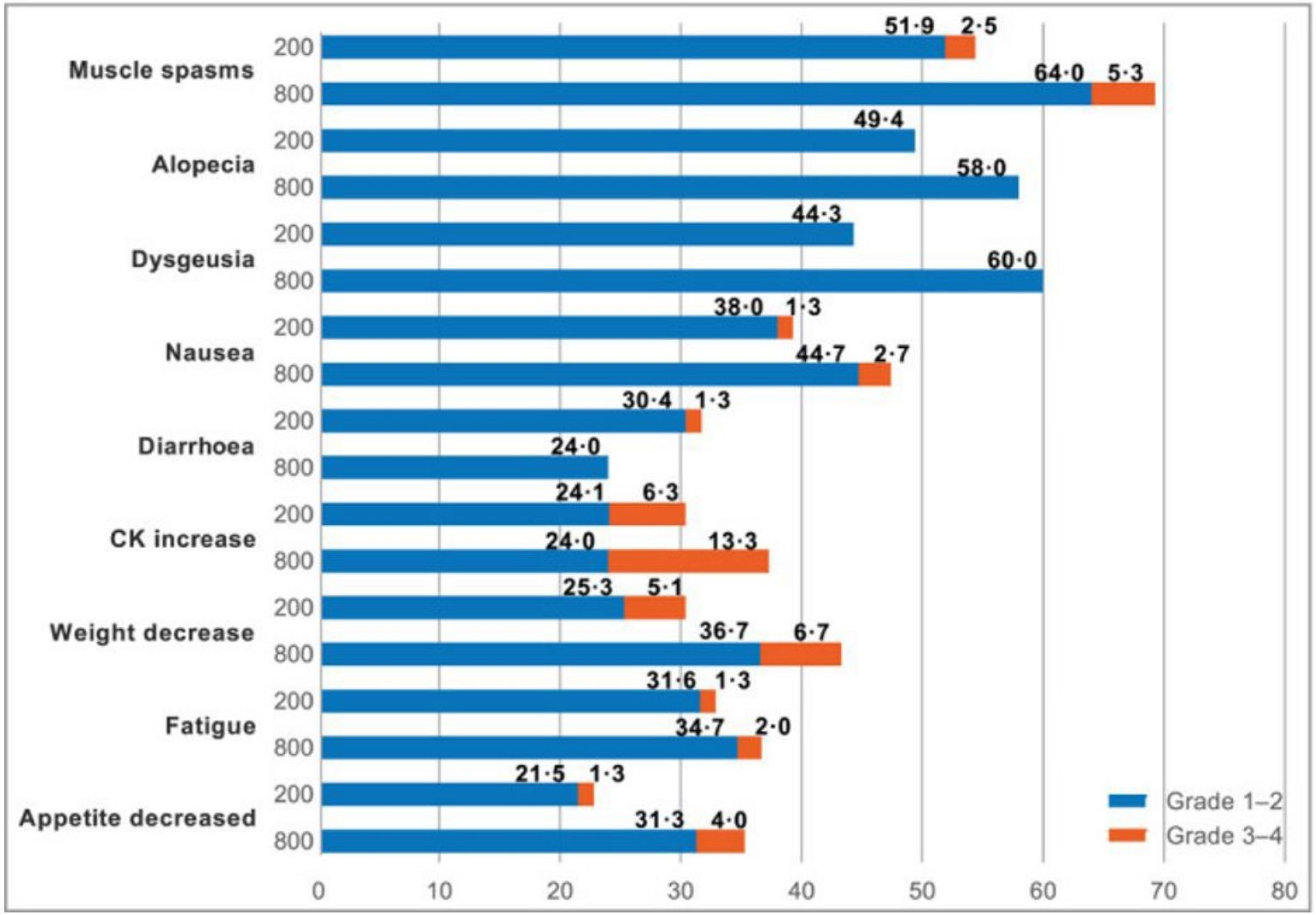
Three Treatment Cycle AE Rates Comparison

Adverse Effect	Vismodegib	Sonidegib
Muscle Spasms	60%	33%
Dysgeusia	60%	15%
Alopecia	25%	5%

30% Discontinuation Rate By Time of First Assessment

Weissman, J.P., Samlowski, W., Meoz, R., 2021. Hedgehog inhibitor induction with addition of concurrent superficial radiotherapy in patients with locally advanced basal cell carcinoma: A case series. Oncologist 26 (12), e2247–e2253.

Adverse Effect Profile of Sonidegib at Two Doses 200mg and 800mg



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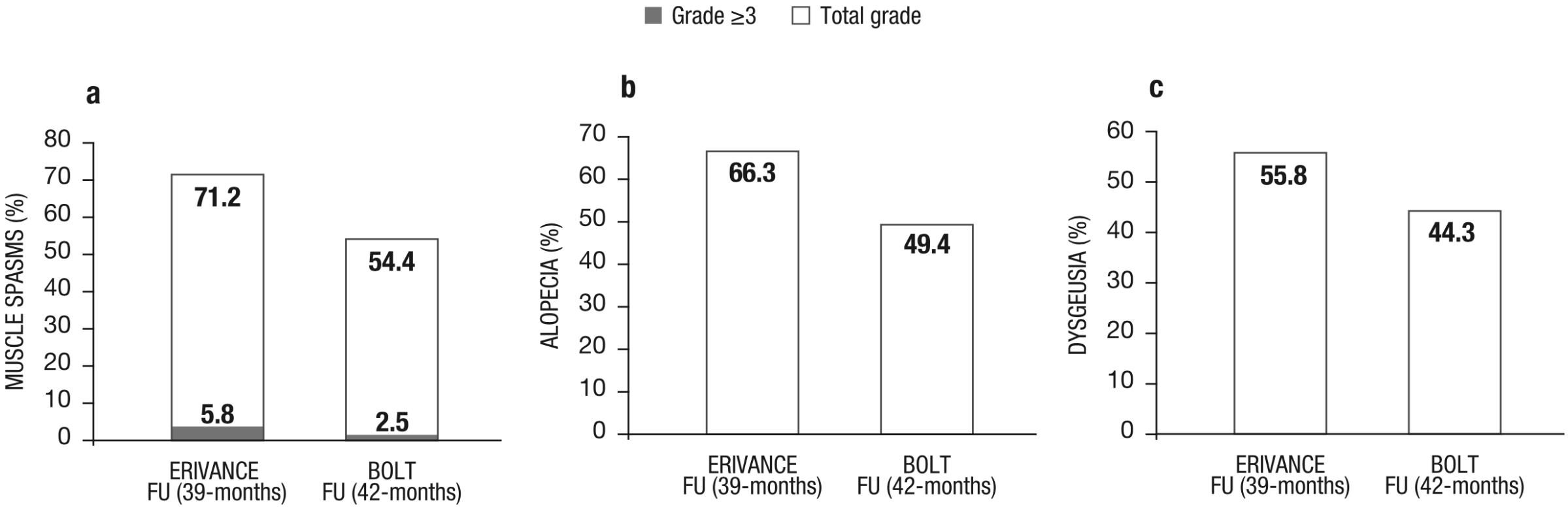
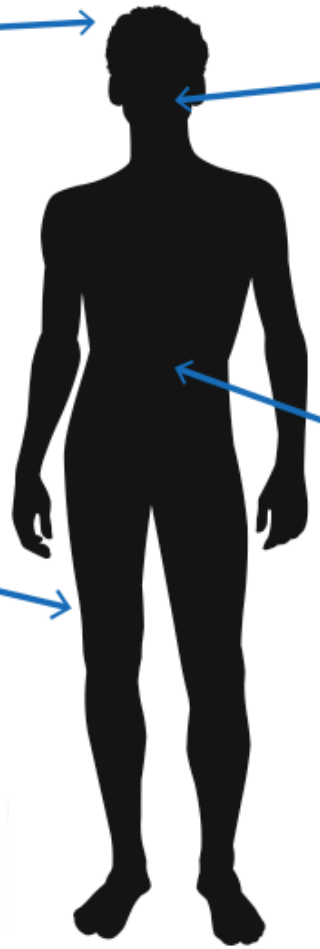
Cumulative Incidence of the Most Common AEs ERIVANCE AND BOLT



Principles of Management of HHI AEs

- Individualize medical decision making (elderly, comorbidities, mBCC, immunocompromised)
- Provide information on the most common AEs, that most are low grade and reversable after stopping
- Food intake must remain the same in the face of dysgeusia or ageusia, especially normal and underweight patients
- Supportive medications – used early
- Dose adjustments
  - On Label for Sonidegib
  - MIKIE Study for Vismodegib – Preplanned drug holidays
    - 23% Discontinuation Rate due to AEs

MANAGEMENT OF ADVERSE EVENTS HHIS



Alopecia
↓ Dermal papillae function/hair growth

Tx: Minoxidil 5% b.i.d.
Oral Minoxidil 1mg/day

Dysgeusia/Ageusia
↓ Bitter/sweet responsivity
↓ Taste buds

Tx: Nutrition consult
Flavor enhancers, spicy ingredients, recipes, zinc gluconate, delta 9 THC*

Muscle Spasms
↓ Myogenic factors
↓ Injury recovery

Tx: Amlodipine 10 mg/day

L-Carnitine 1000-2000 mg/day

Weight Loss
↑ Glucose uptake in muscle/brown adipocytes

Tx: Nutrition consult
Fish Oil megestrol acetate, corticosteroids

Fatigue/general:
Screen and Monitor (monthly): Usual labs plus: Creatine kinase (CK) and creatinine. Lipase may ↑ Methylphenidate*

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The Oncologist 2016;21:1218–1229

*limited data

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L-CARNITINE

L-Carnitine Reduces Muscle Cramps in Patients Taking Vismodegib

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[b]Department of Dermatology, University of Tennessee Health Science Center, Memphis, TN
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[d]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY

ABSTRACT

Vismodegib is an oral, small-molecule hedgehog pathway inhibitor (HHI) approved for the treatment of locally advanced and metastatic basal cell carcinoma. While an effective treatment option for these conditions, HHI therapy is associated with muscle cramps in a significant number of patients. This adverse effect negatively impacts patient quality of life and patient adherence to the prescribed treatment regimen.

Levocarnitine (L-carnitine) is a trimethylated amino acid known to play a critical role in lipid metabolism. It has antioxidant properties, and several studies have illustrated its effectiveness in lessening the severity of muscle cramps in various disease processes.

We present three patients who developed muscle cramping associated with vismodegib treatment for basal cell carcinoma. Each was started on L-carnitine therapy, and all three reported a significant decrease in the severity of their muscle cramps to the point that they were able to continue HHI therapy without taking a drug holiday. These cases illustrate a promising treatment option for the most common side effect associated with HHI treatment.

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Use and Monitoring for HPI - Recommendations

Table 4. Summary of Recommendations[21] for HPI Use

Indication	Recommendation	Grade of Recommendation[a]	Quality of Evidence[b]	Selected References
HPI for laBCC	Strong recommendation	1	A	Basset-Seguin et al[8] Chang et al[6] Migden et al[20] Sekulic et al[12]
HPI for mBCC	Strong recommendation	1	A	Basset-Seguin et al[8] Chang et al[6] Migden et al[20] Sekulic et al[12]
HPI for basal cell nevus syndrome	Recommendation	2A	B	Tang et al[3] Ozgur et al[17]
Use of a drug holiday or pulse dosing to mitigate adverse effects	Weak recommendation	2B	C	Dummer et al[22] Viscusi et al[15] Yang et al[23]
Monitor CPK	Strong recommendation[c]	A	A	Migden et al[20] Ally et al[24]
Monitor LFTS	Weak recommendation	2B	C	Ash et al[25] Ventarola et al[26]
Monitor electrolytes	Weak recommendation	2B	C	Simone et al[14]
Monitor bone density/lipids in premenopausal women	Weak recommendation	2B	C	Strasswimmer et al[27]
Monitor for pregnancy prevention	Strong recommendation	1	A	Kimura et al[28] Lipinski et al[29,30]
Monitor cardiovascular status	Weak recommendation	2B	C	Huizenga[31] Simone et al[14]

Overcoming drug resistance HPI

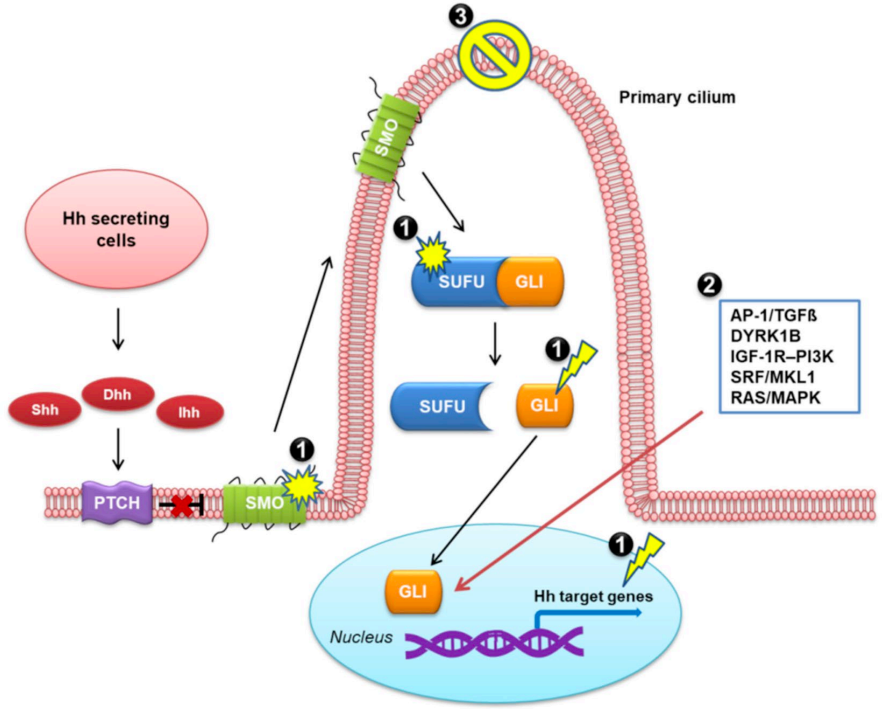
Occurs in 12.7% Vismodegib and 1.5% Sonidegib

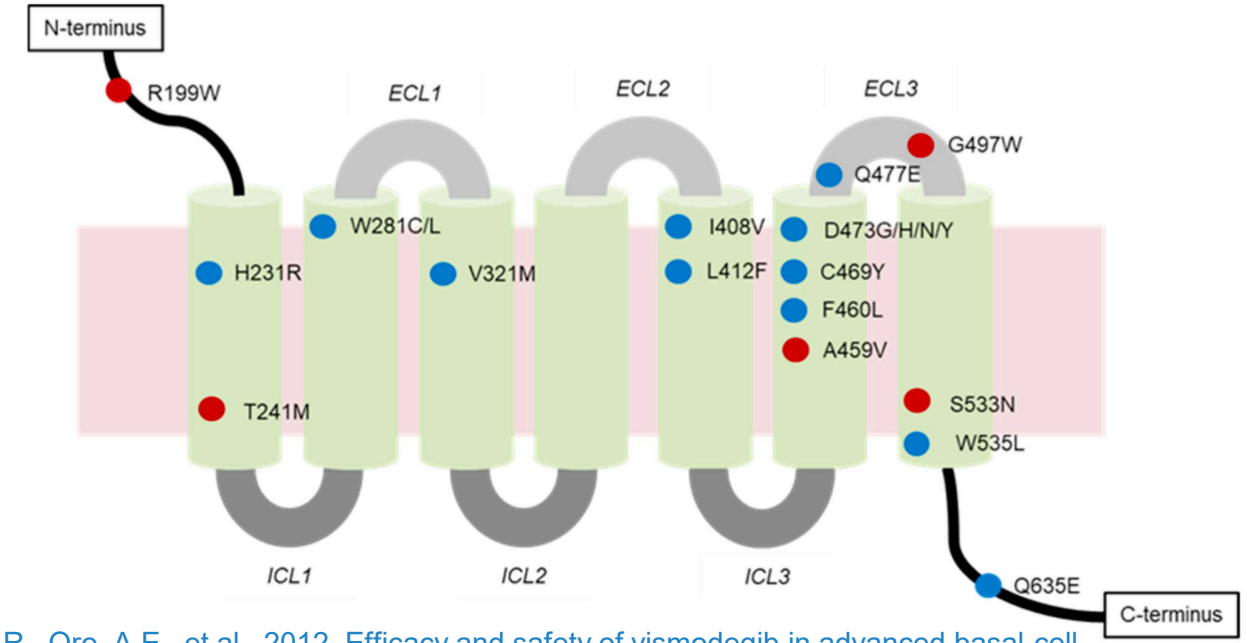
Develop novel and potent 2nd generation SMO inhibitors

Target downstream components of SMO in the Hh pathway or signaling molecules

Genetic pre-screening

Int. J. Mol. Sci. **2022**, *23*, 1733





Migden, M.R., Guminski, A., Gutzmer, R., et al., 2015. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. Lancet Oncol. 16, 716–728.

Sekulic, A., Migden, M.R., Oro, A.E., et al., 2012. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N. Engl. J. Med 366 (23), 2171–2179.

PubMed ▼ Peter Lee and vismodegib

Format: Abstract

Full text links

FULL TEXT JAMA Dermatology

JAMA Dermatol. 2017

JAMA Dermatol 2017:321-322

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

Becker LR[1], Aakhus AE[1], Reich HC[1], Lee PK[1].

"This study evaluates a novel alternate dosing regimen of vismodegib that has led to decreased toxicity and eliminates the need for a loading dose"

A hedgehog inhibitor dosed at 10 days per month is "*optimal maintenance*" for basal cell nevus syndrome (BCNS) patients

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
	11	12	13	14	15	16
17	18	19	20	21	22	23
24 / 31	25	26	27	28	29	30

Hedgehog Inhibitor Advantages

- Works quickly
- Its a pill, not an injection or an infusion
- Adverse events are unlikely to result in hospitalization or death
- Adverse events can be controlled by intermittent dosing and L-carnitine
- Can be given by dermatologist or dermatology provider
- Works better than advertised

Hedgehog Inhibitor Disadvantages

- Almost all patients get some adverse events
- Not sure when to discontinue
- Sometimes difficult to get to durable remission
  - Implies drug resistance

Conclusions

Drugs work better than advertised

Adverse effect profile unique to each class

Most patients at least respond

Work as a team, engage your MDT. Try to avoid going it alone

THANK YOU!

Hedgehog Inhibitors, Optimizing Management and Treatment of Adverse Reactions

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