

Investor KOL Event – Phase III

SGT-610: PATIDEGIB GEL, 2%



SOL-GEL



Forward Looking Statements

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding: the potential of SGT-610 (patidegib gel, 2%) as a treatment for Gorlin syndrome and other patient populations; the design, timing, progress and results of our clinical studies, including the expected timing of topline results from our Phase III study of SGT-610; the timing of submission of a New Drug Application and of, and our ability to obtain, regulatory approvals for our product candidates; the expected timing of commercial launch; the potential market opportunity, pricing, reimbursement and peak sales of SGT-610; our commercialization strategy, launch readiness, and the expected size and cost of our commercial infrastructure, including our reliance on third-party service providers; the scope and duration of patent protection and regulatory exclusivity, including any patent term extension; our plans for patient engagement and care initiatives, including our ICD-10 code application and centers of excellence; and the potential development of our other product candidates and the size of their potential markets. In some cases, you can identify forward-looking statements by terminology such as “believe,” “may,” “estimate,” “continue,” “anticipate,” “intend,” “should,” “plan,” “expect,” “predict,” “potential,” or the negative of these terms or other similar expressions. Forward-looking statements are based on information we have when those statements are made or our management’s current expectations and are subject to risks and uncertainties that could cause actual performance or results to differ materially from those expressed in or suggested by the forward-looking statements. Important factors that could cause such differences include, but are not limited to, the risk of a delay in reporting the top-line results of Sol-Gel’s pivotal Phase 3 clinical trial of SGT-610 (patidegib gel, 2%) for Gorlin syndrome, that we will not successfully complete the Gorlin syndrome Phase 3 clinical trial or that such clinical trial will fail to meet its primary endpoint or one or more of its secondary endpoints, as well as the following factors: (i) the adequacy of our financial and other resources, particularly in light of our history of recurring losses; (ii) our ability to complete the development of our product candidates; (iii) our ability to find suitable co-development partners; (iv) our ability to obtain and maintain regulatory approvals for our product candidates in our target markets, the potential delay in receiving such regulatory approvals and the possibility of adverse regulatory or legal actions relating to our product candidates even if regulatory approval is obtained; (v) our collaborators’ ability to commercialize our pharmaceutical product candidates; (vi) our ability to obtain and maintain adequate protection of our intellectual property; (vii) our collaborators’ ability to manufacture our product candidates in commercial quantities, at an adequate quality or at an acceptable cost; (viii) our collaborators’ ability to establish adequate sales, marketing and distribution channels; (ix) acceptance of our product candidates by healthcare professionals and patients; (x) the possibility that we may face third-party claims of intellectual property infringement; (xi) the timing and results of clinical trials that we may conduct or that our competitors and others may conduct relating to our or their products; (xii) intense competition in our industry, with competitors having substantially greater financial, technological, research and development, regulatory and clinical, manufacturing, marketing and sales, distribution and personnel resources than we do; (xiii) potential product liability claims; (xiv) potential adverse federal, state and local government regulation in the United States, China, Europe or Israel; (xv) loss or retirement of key executives and research scientists; (xvi) general market, political and economic conditions in the countries in which the Company operates; and (xvii) the security situation in Israel. These factors and other important factors discussed in the Company’s Annual Report on Form 20-F filed with the Securities and Exchange Commission (“SEC”) on March 19, 2026, and our other reports filed with the SEC, could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Except as required by law, we undertake no obligation to update any forward-looking statements contained in this presentation. This presentation contains information from third-party sources, including data from studies conducted by others and market data obtained from industry publications. Although we believe such information to be reliable, we have not independently verified any such information and make no representation as to its accuracy or completeness. Certain data in this presentation are derived from post hoc analyses of a prior Phase III study that did not meet its primary endpoint. These analyses were not prespecified, were not powered to detect statistically significant differences, and are exploratory and hypothesis-generating only. Reported p-values are nominal and have not been adjusted for multiple comparisons. These results may not be predictive of the results of our ongoing or future clinical trials. This presentation does not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any sale of securities in any jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of such jurisdiction.

Agenda

1.	WELCOME REMARKS	Mori Arkin <i>Chief Executive Officer, Chairman</i>
2.	SGT-610: PATIDEGIB GEL, 2%	Mori Arkin <i>Chief Executive Officer, Chairman</i>
3.	GORLIN SYNDROME ALLIANCE INTRODUCTION	Julie Breneiser, PA-C
4.	THE STORY OF HEDGEHOG SIGNALING AND HH INHIBITORS VS. BCCs	Ervin Epstein Jr., MD
5.	GORLIN SYNDROME DIAGNOSIS AND MANAGEMENT	Kavita Sarin, MD, PhD
6.	A CLINICIAN'S PERSPECTIVE	Elizabeth Billingsley, MD, FAAD, FACMS, FASDS
7.	PANEL DISCUSSION	Mori Arkin, Dr. Billingsley, Ms. Breneiser, Dr. Epstein, and Dr. Sarin
8.	Q&A SESSION	Mori Arkin, Dr. Billingsley, Ms. Breneiser, Dr. Epstein, and Dr. Sarin
9.	CLOSING REMARKS	Mori Arkin <i>Chief Executive Officer, Chairman</i>

The logo graphic consists of two overlapping, wavy, ribbon-like shapes. The top shape is a lighter teal color, and the bottom shape is a darker green color. They are positioned on the left side of the slide, with the text 'Sol-Gel' overlaid on them.

Sol-Gel

Focus on Skin Diseases with No Approved Treatments

Leading the way in Dermatological Advancements

Sol-Gel Technologies is an experienced dermatology company that leverages innovative approaches to develop advanced treatments for patients with severe skin conditions

Management Team



EYAL BEN-OR
Chief Financial Officer



MORI ARKIN
Chief Executive Officer, Chairman



MICHAEL GLEZIN
Chief Business Officer



DR. OFRA LEVY-HACHAM
VP, Clinical and Regulatory Affairs



DR. ITZIK YOSEF
Chief Operating Officer



DR. OFER TOLEDANO
VP, Research and Development

SGT-610 in Gorlin Syndrome

An investigational topical approach to preventing Basal Cell Carcinoma (BCC)

Target population

Adult patients with Gorlin syndrome

Mechanism

Patidegib is designed to block the Hedgehog signaling pathway

Development history

Patidegib gel, 2% (SGT-610) was acquired from PellePharm in January 2023 after the prior Phase III study did not meet its primary endpoint

U.S. designations

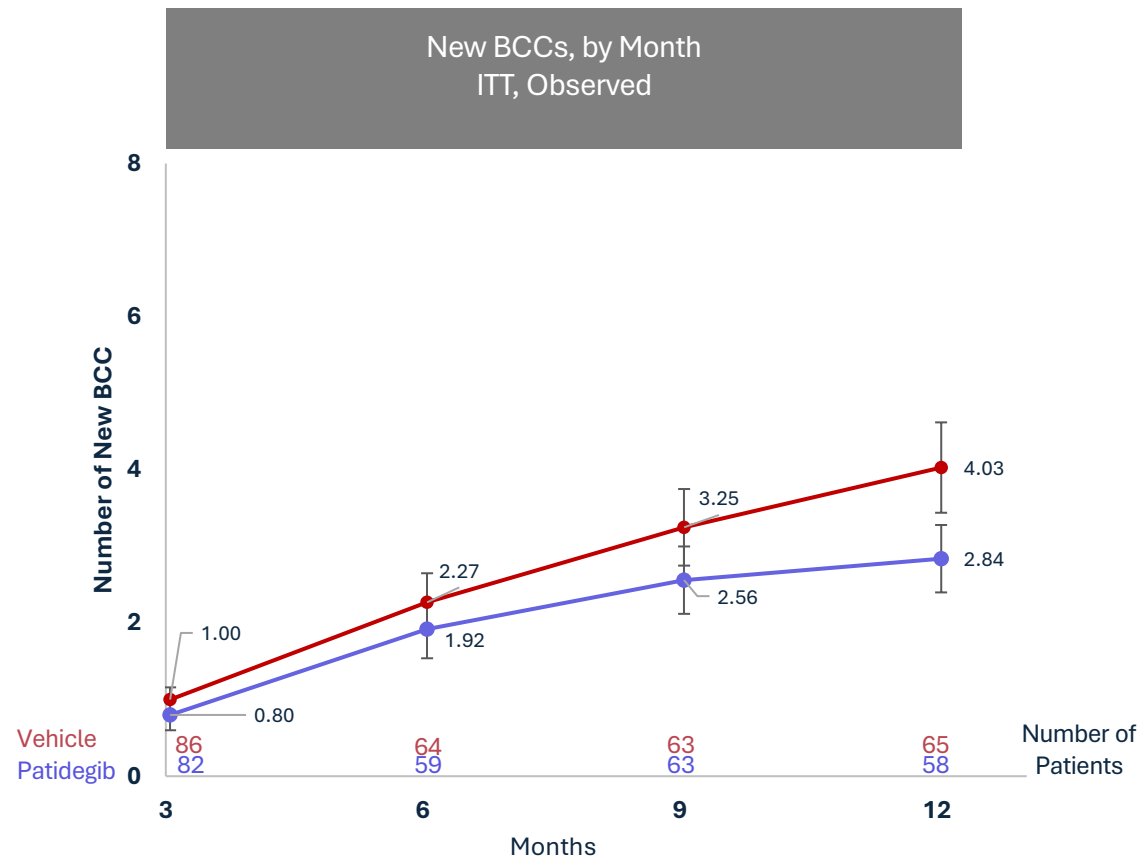
Orphan Drug and Breakthrough Therapy

If approved, SGT-610 will be the first therapy indicated for the prevention of BCCs in patients with Gorlin syndrome



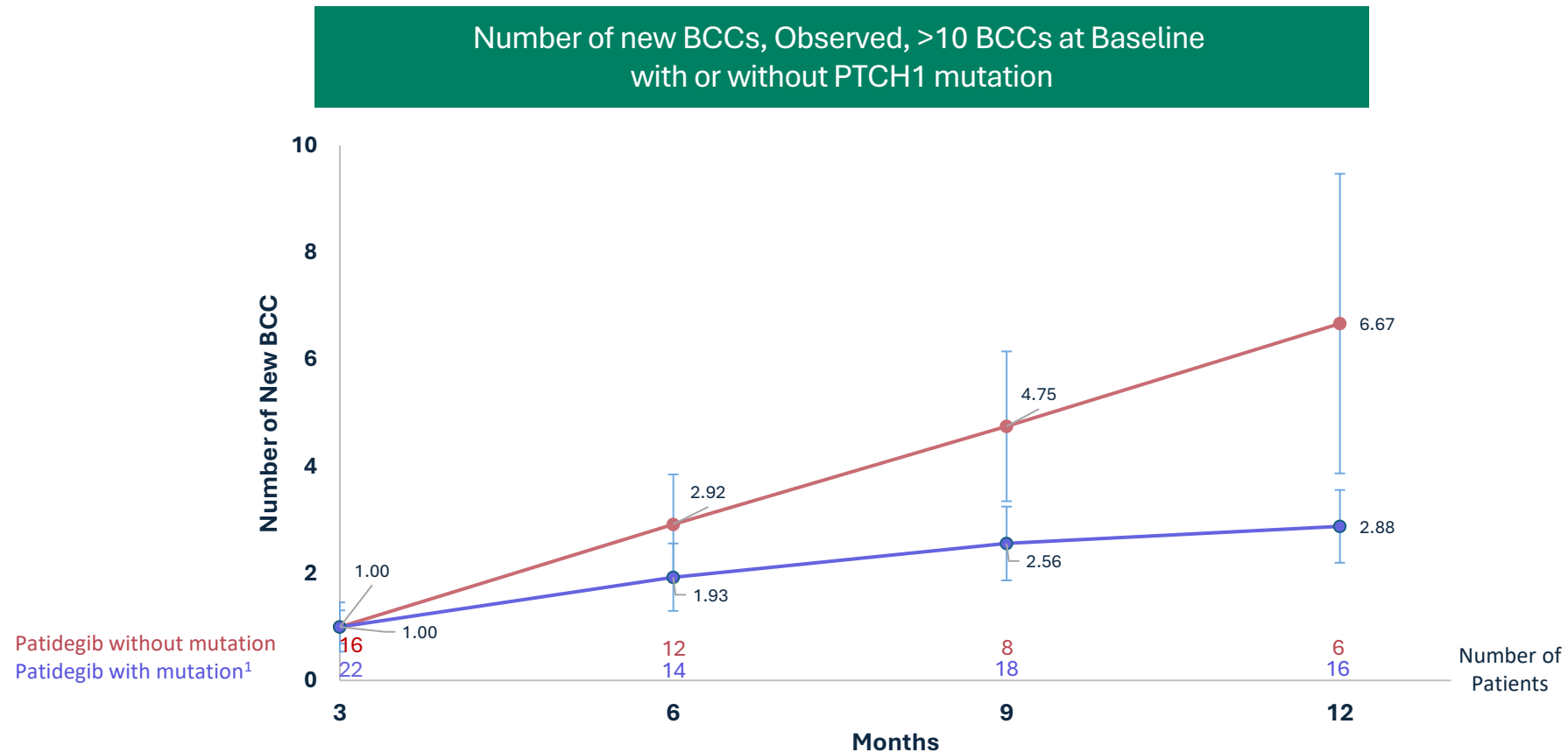
PellePharm Phase III

1. At least 3 BCCs at baseline in patients with Gorlin syndrome
2. Confirmation of PTCH1 mutation was not mandatory



What Did We Learn From the PellePharm study?

1. In the post hoc analysis, patients with Gorlin syndrome without a PTCH1 mutation showed no greater response to patidegib gel than to vehicle.

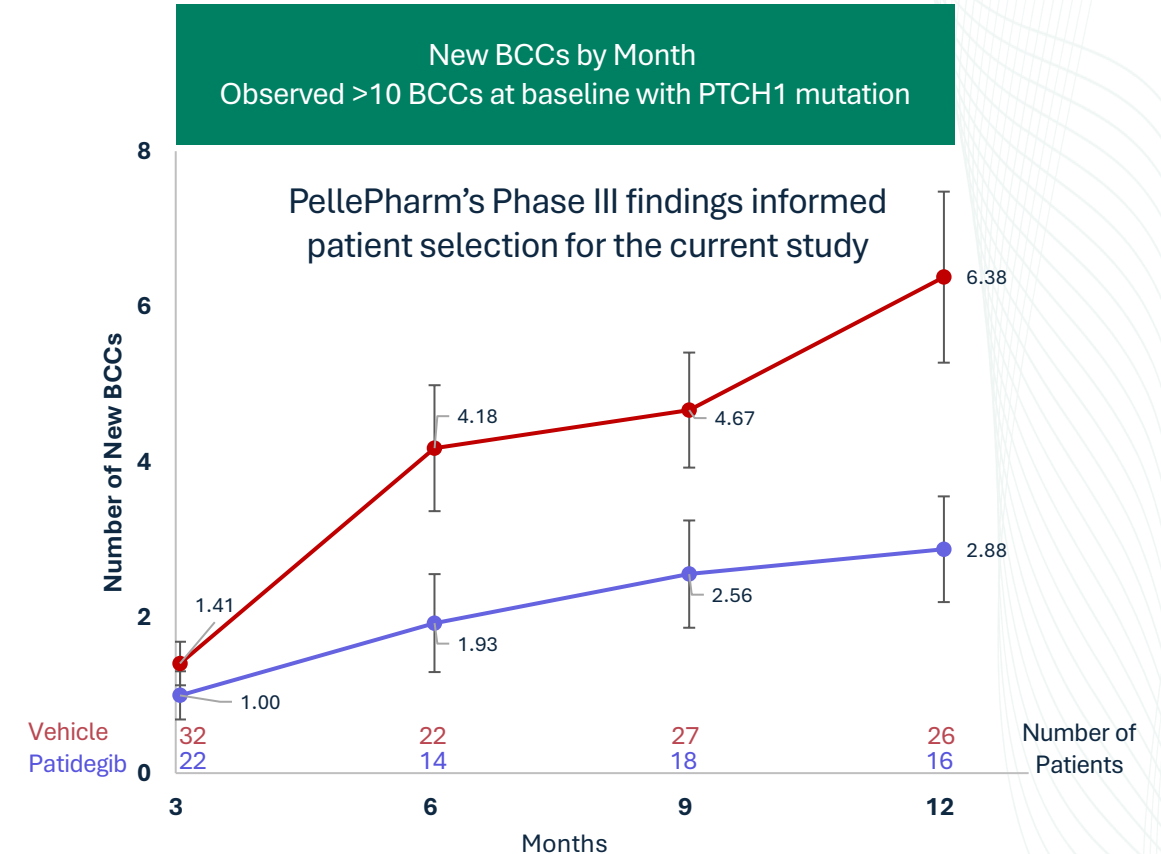
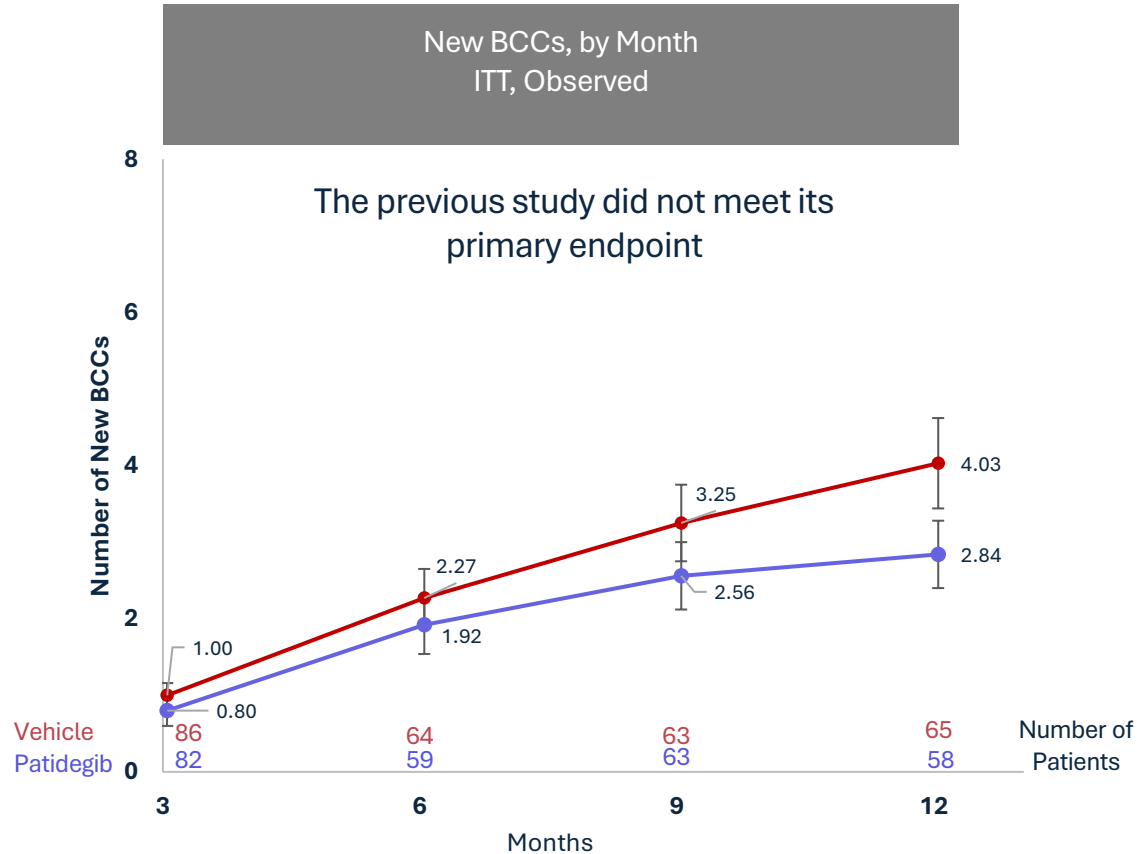


What Did We Learn From the PellePharm study?

2. In the post hoc analysis, a greater number of BCCs at baseline was associated with a larger treatment effect favoring patidegib over vehicle

Population – Month 12 ¹	Patidegib Mean ± SD (N)	Vehicle Mean ± SD (N)	% reduction	P-value
Baseline Total Lesions >6	2.78 ± 2.57 (32)	5.18 ± 5.47 (40)	46%	0.017
Baseline Total Lesions >8	2.96 ± 2.62 (25)	5.80 ± 5.57 (35)	48%	0.011
Baseline Total Lesions >10	2.88 ± 2.73 (16)	6.38 ± 5.60 (26)	55%	0.010

Post-hoc Analysis Findings Led to Current Study Design



Post hoc analysis: The left graph shows the number of new BCCs across the entire study population, including patients without the mutation and those with a low BCC burden. The mean number of new BCCs was approximately 30% lower with patidegib than with vehicle; however, the difference was not statistically significant.

The right graph shows the number of new BCCs among patients who had more than 10 BCCs at baseline and tested positive for a PTCH1 mutation. In this subgroup, the mean number of new BCCs was approximately 55% lower with patidegib than with vehicle, a statistically significant difference ($p = 0.010$).

FDA Feedback on Prior Study

(FDA response, May 2021):

*“We recommend conducting a new adequately-powered randomized, vehicle-controlled trial to support the efficacy of your product. However, it may be possible to identify study design elements from the completed trial that could be modified in a future trial to increase the power (**such as identifying a more sensitive patient population among Gorlin’s patients** or including a broader population such as subjects with non-Gorlin’s high frequency BCCs)”*

Summary: How We Applied These Findings in the New Phase III Study?

Conducted a more focused Phase III Study

Patient Selection

Criterion	Previous study  pellepharm	Current study  SOL-GEL
Facial BCCs	≥3 ¹	≥10
PTCH1 mutation	Patients without mutation were not excluded	Only patients with the mutation were enrolled
Gorlin syndrome inclusion criteria	No additional changes in study inclusion criteria were made	

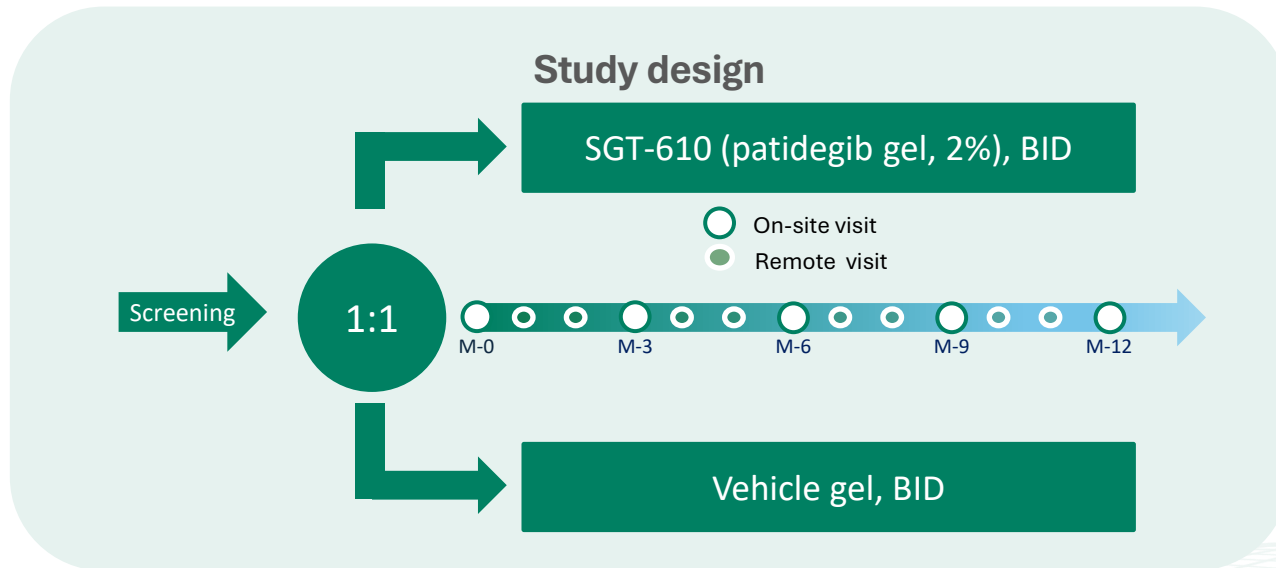
Operational Improvements

Dermoscopic assessment

Central photography review board

Only 6 on-site visits

SGT-610 Study Design - Update



Study Recruitment Summary:

41 sites
U.S., E.U. & U.K.

184 Patients Screened
113 Enrolled
102 Completed

More than 90% of enrolled
patients completed the study

Clinical Study Endpoints (Similar to Those in the Previous Study)

- Primary: Number of new BCCs
- Key Secondary: Number of new SEBs

SGT-610 Upcoming Milestones for the U.S. Market

2026		2027				2028
Q4		Q1	Q2	Q3	Q4	Q1
★	Topline Results					
		★	NDA submission			
					★	NDA Approval
						★ Launch

Future milestones are company targets, subject to regulatory review.

Strong IP Protection Until at Least 2044 of SGT-610

Patent and Regulatory Exclusivity

Oct, 2034 Orphan Drug Exclusivity

Apr, 2035 NCE Exclusivity with a 30-month stay (longer than ODE)

Jun, 2041 Formulation patent describing SGT-610 gel composition (granted)
including 5 years PTE

Jan, 2044 Method of use patent (granted)
Method of using topical patidegib in GS patients with PTCH1
mutation, also covers HF-BCC and neoadjuvant use

Jul, 2045 Composition of matter patent (pending)
Protects impurity levels in the patidegib API

Gorlin Syndrome SGT-610 Market Opportunity

~\$860M¹ U.S. only

Estimated peak sales opportunity

11,000 estimated U.S. patients with Gorlin syndrome²

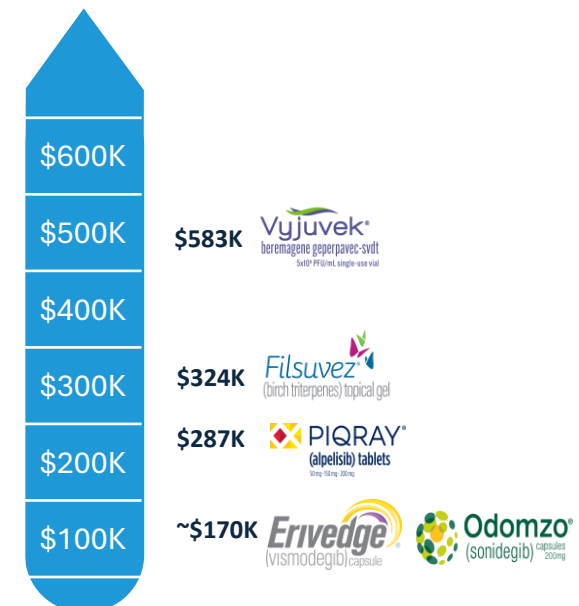
Estimated patients at peak	Patients
U.S. 	4,000

Potential Additional Market	Patients
E.U. 	3,200
Rest of world 	2,000

~\$270K Assessed by 

Expected annual net price of SGT-610

Comparative WAC benchmarks



SGT-610: Lean, Focused, Cost-Effective U.S. S&M Platform

Sol-Gel is expected to be launch-ready with a dedicated SGT-610 team, supported by a third-party commercialization service provider with proven rare-disease capabilities, while retaining full strategic control and economics

Operating Approach¹

35-45	Total platform personnel involved	• Core field, virtual & brand teams • Shared functional specialists included, field sales MSLs, • KAMs / NAMs leadership and access support
~20	Dedicated field FTEs	• Sales & field operations • Field market access & sales
\$40M-\$50M	Annual platform cost at launch	• Capital-efficient, without building full in-house infrastructure

New Commercialization initiatives at Sol-Gel:

1. Applied for an ICD-10 Code
2. Collaboration with GSA to Create Centers of Excellence



For the First Time: Sol-Gel applied for ICD-10 Code for Gorlin Syndrome

Sol-Gel plan to coordinate a research and care ecosystem that brings together specialized clinical care, longitudinal research, genomic data, patient engagement, and scientific collaboration

Patient partnership

- Patient education and navigation
- Referral gaps and patient feedback
- Center development and advocacy

Multidisciplinary Care

**Specialized
dermatology**

Mohs surgery

Genetics

Potential Expansion

Beyond the initial Gorlin program

¹ Journal of the American Academy of Dermatology, 2020; 84, 1493-1495

² Extrapolation of 5% of BCCs in the U.S.; Discov Oncol.. 2021; 12(1):31.

³ Based on Indegene quantitative analysis

⁴ 45.5% of patients with Gorlin develop OKC - Int J Women. Dermatol. 2022 Jun 15;8(2):e020

Future Development Opportunities

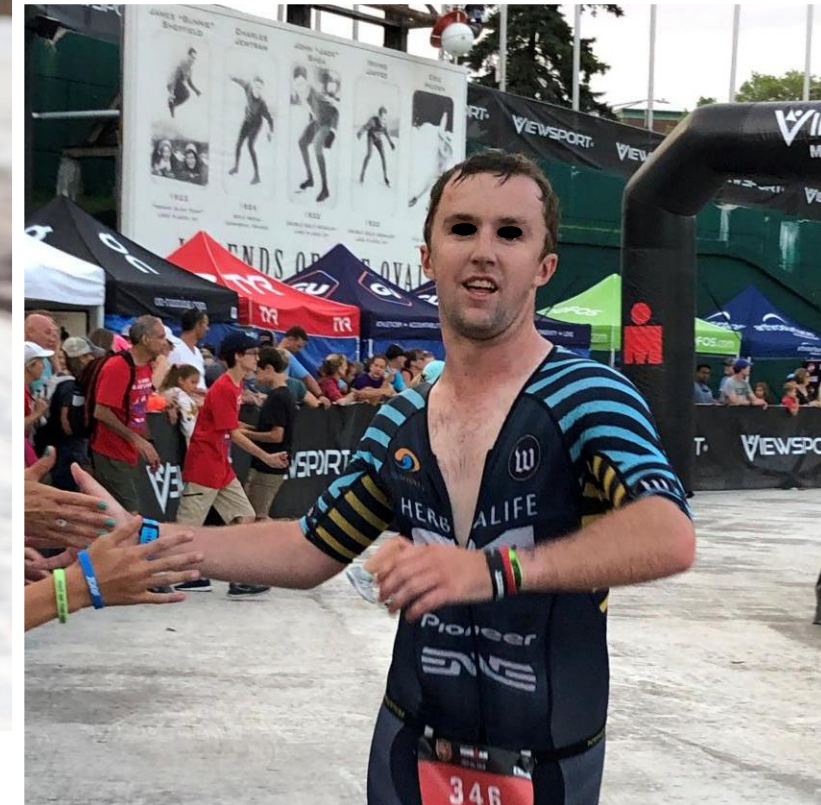
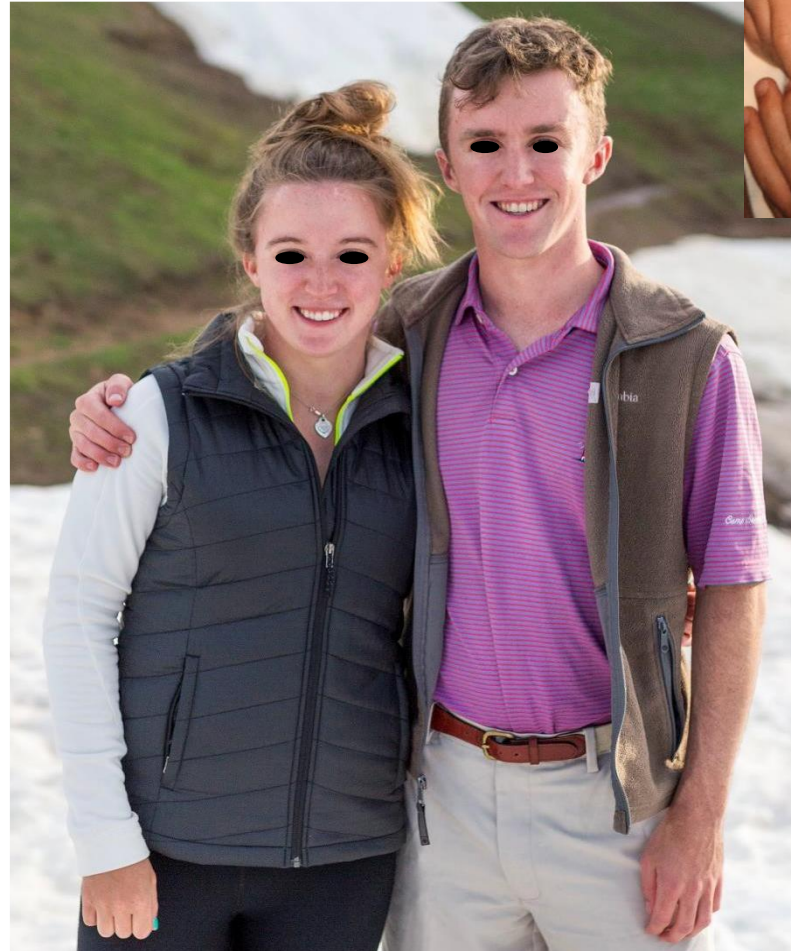
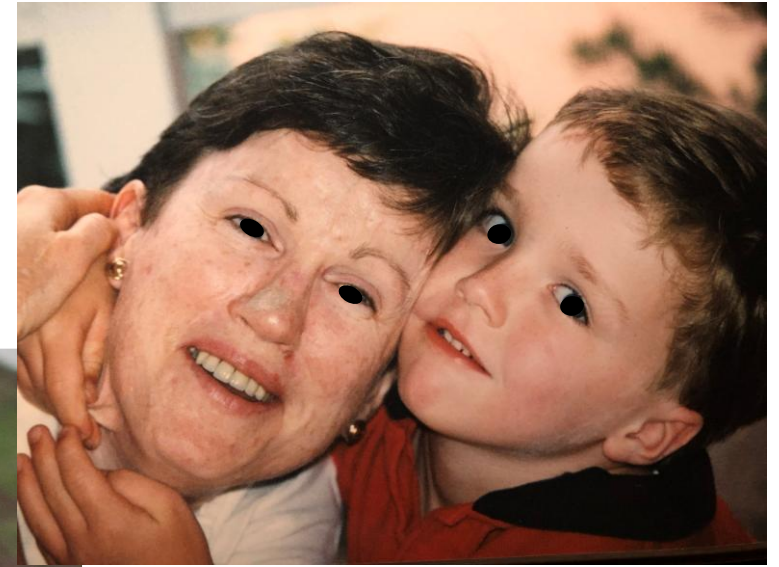
SGT-620		Prevention of new BCCs in patients with HF-BCC	124,000 patients in the U.S. ¹
SGT-630		Reduction in BCC size	100,000 patients in the U.S. ²
SGT-910		Scalp BCC in Gorlin syndrome	5,170 patients in the U.S. ³
SGT-810		Odontogenic keratocyst (OKC) to reduce surgical complications	5,000 patients in the U.S. ⁴ possibly 500 procedures each year

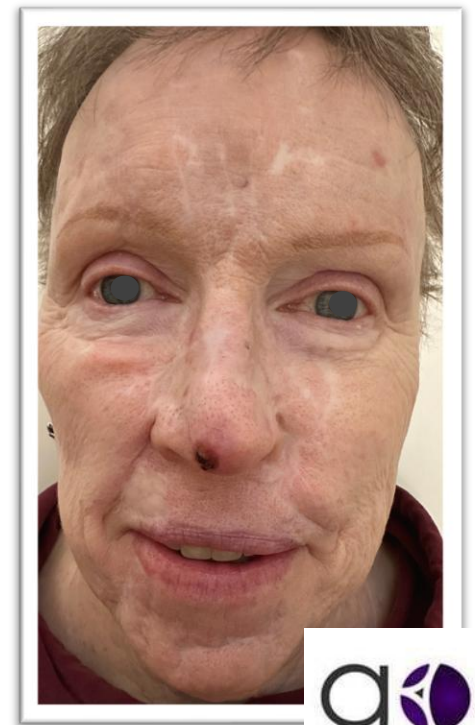
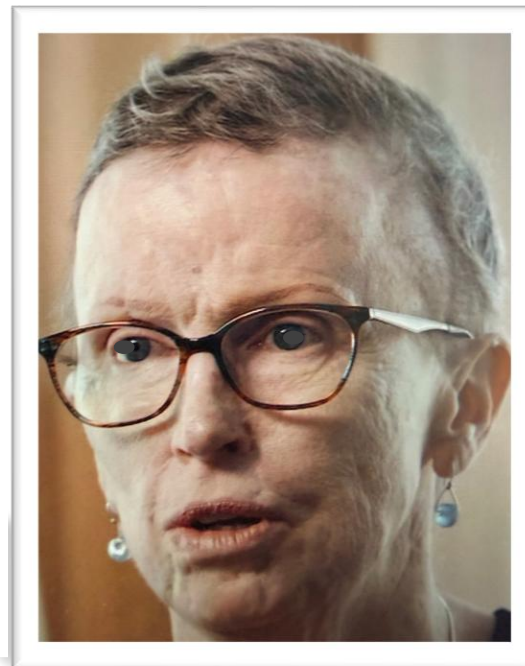
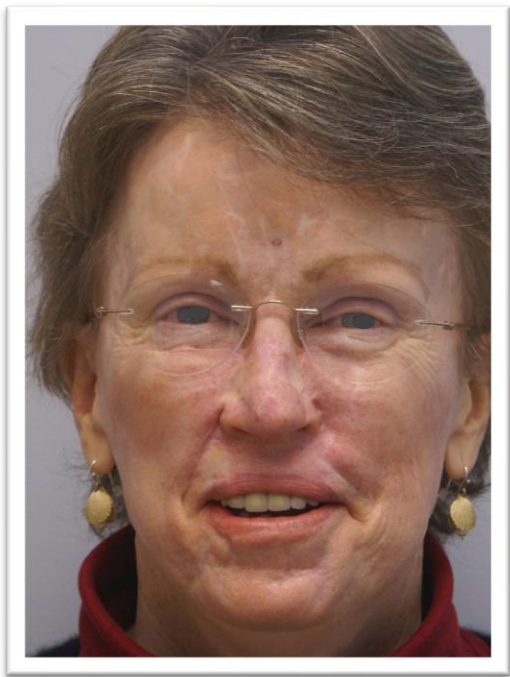
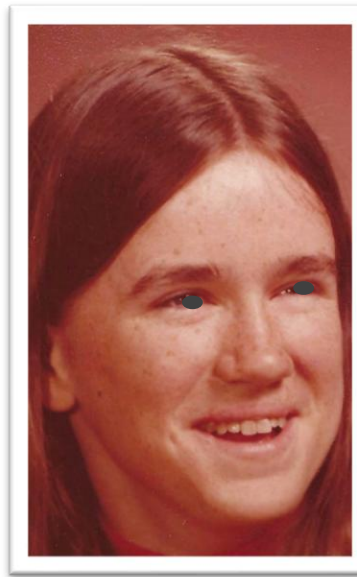
Julie Breneiser, Associate Director

Gorlin Syndrome Alliance

Affected mother of two adults with Gorlin Syndrome

Retired Physician Assistant





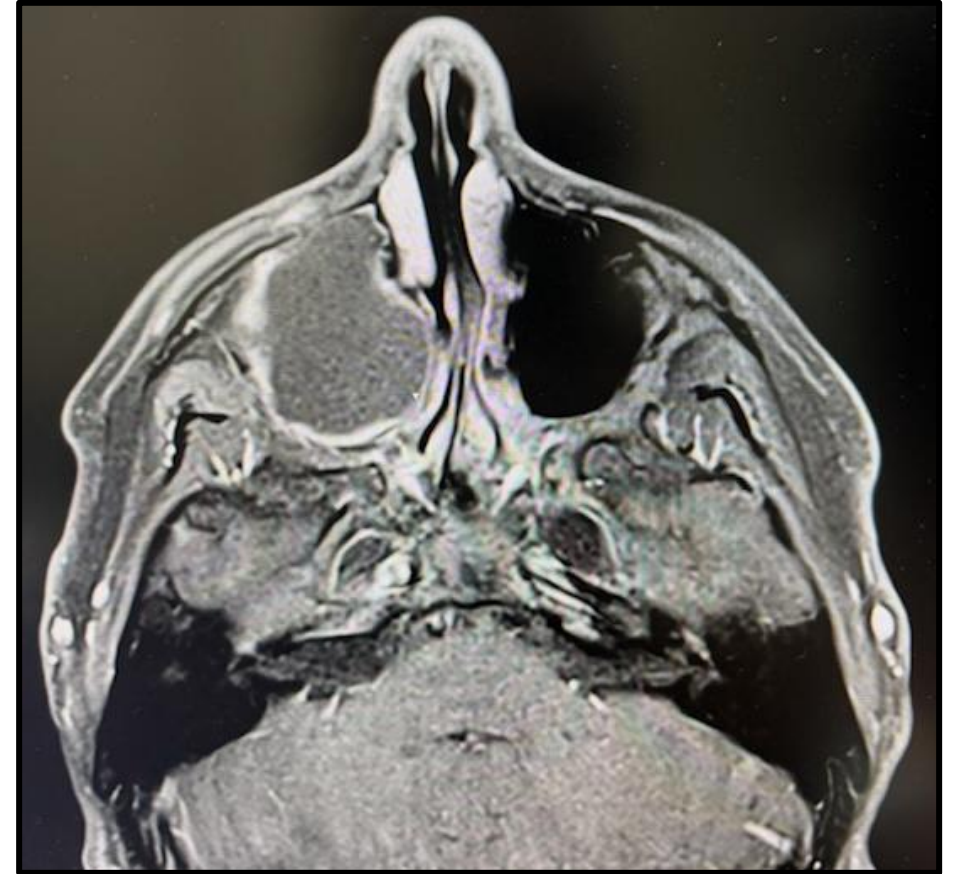
Gorlin Syndrome Fact Sheet

- Aka - Basal Cell (Carcinoma) Nevus Syndrome.
- Incidence: 1 in 31,000.
- Autosomal dominant genetic disorder (50% chance of passing it along). ~31 % spontaneous mutation rate.
- Can affect **every** organ system in the human body with over 100 possible manifestations.
- Most common manifestations:
 - a) **Basal cell carcinomas (BCCs)** – Some have over **1,000** in their lifetime.
 - b) **Odontogenic keratocysts (OKCs)** – Cysts of the jaw bones.
 - c) **Psychological burden** – Anxiety
 - d) Other manifestations
- **NO FDA APPROVED** treatments.



Odontogenic Keratocysts (OKCs)

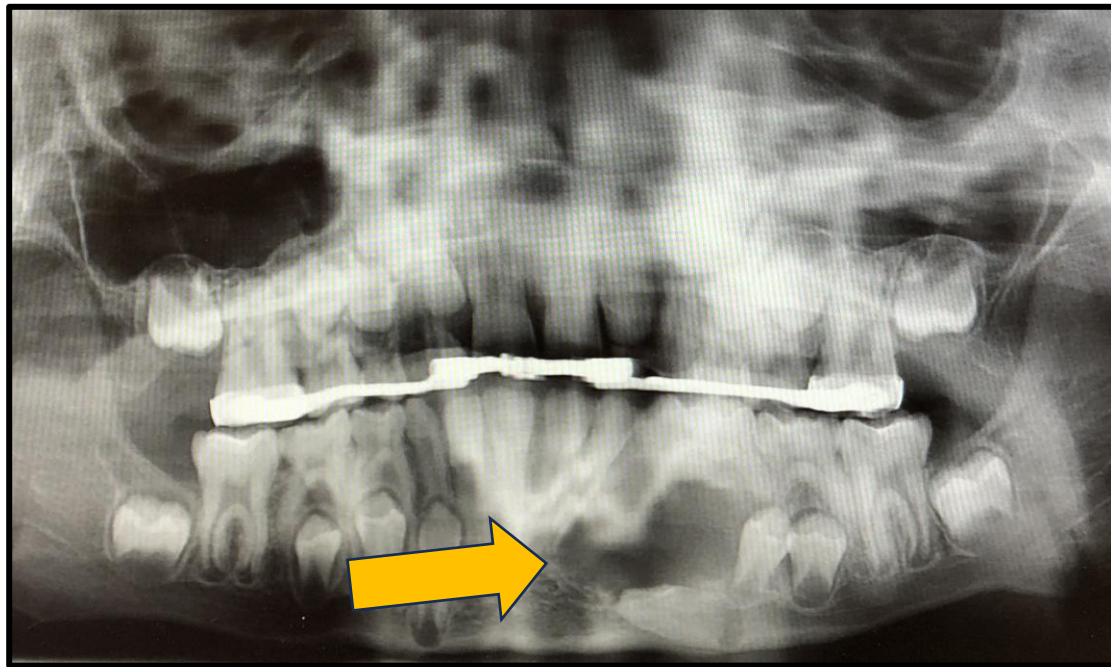
Boney cysts of the jaw bones with a **>40% recurrence rate**



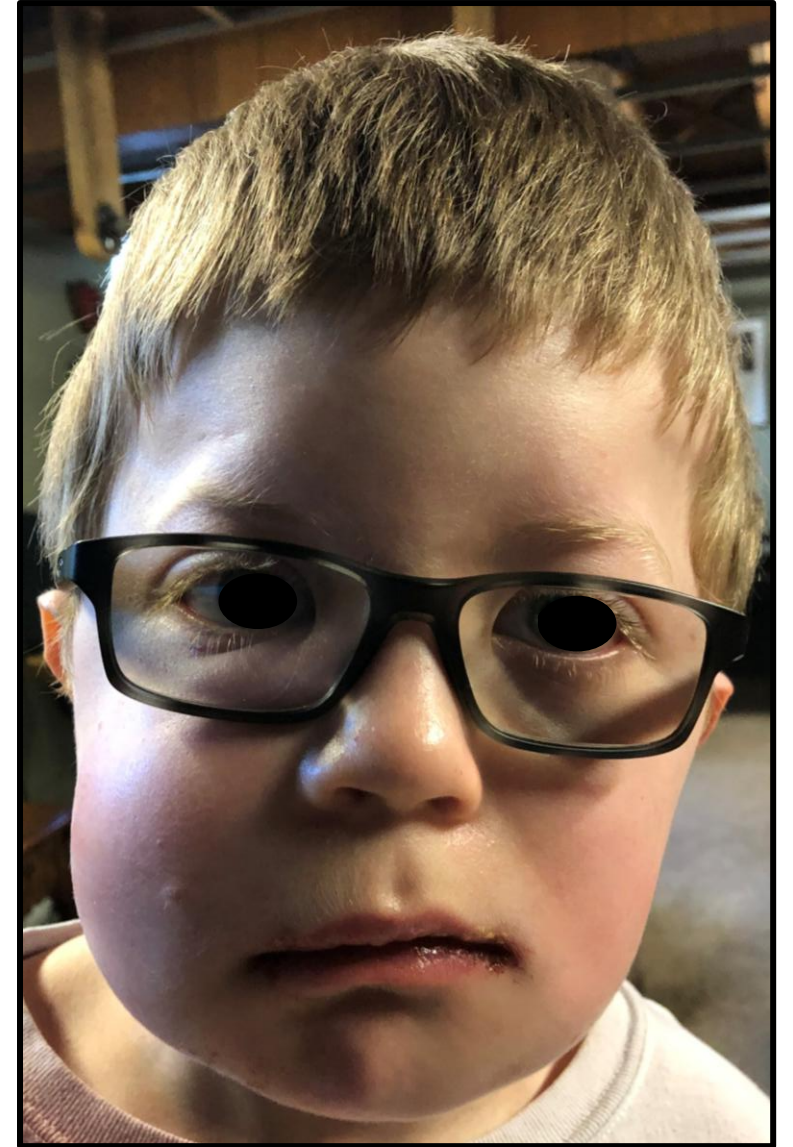
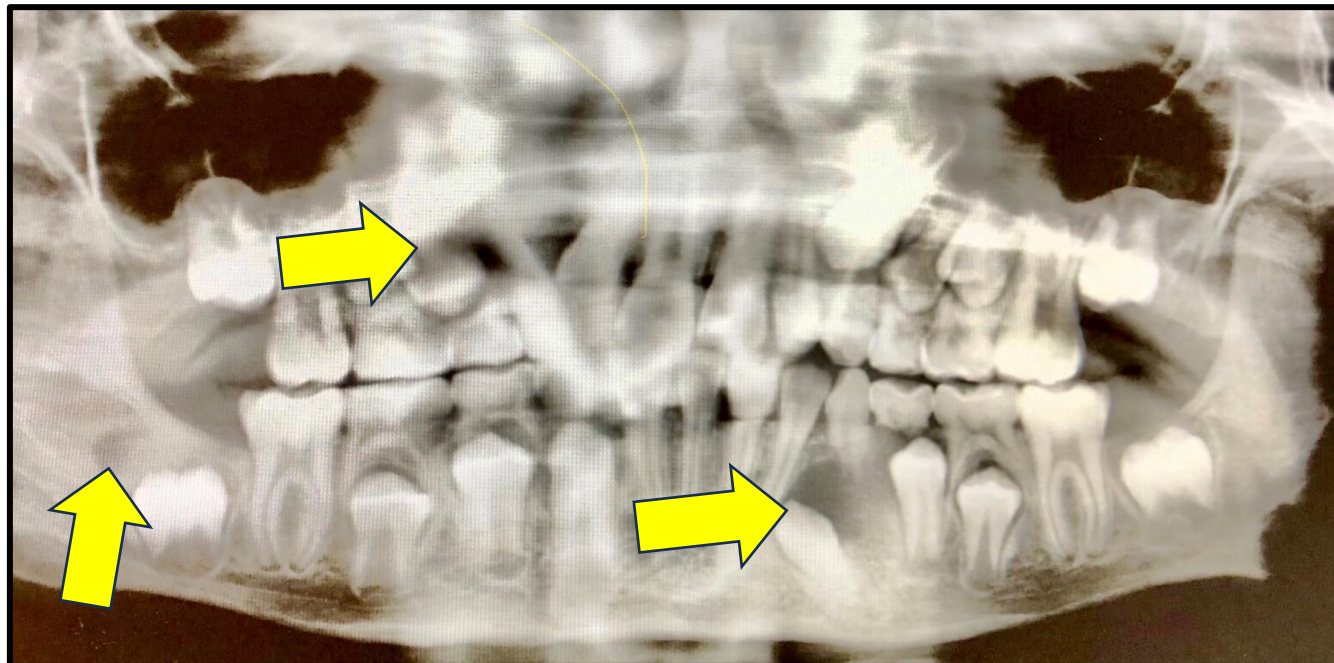
To reduce recurrences, surgical removal is *extensive & aggressive*.

Permanent teeth may be lost. Lip numbness may result.

Historically, cavity packed with gauze saturated with Carnoy Solution (now banned), currently, 5-fluorouracil. Recurrence reduction success: variable.



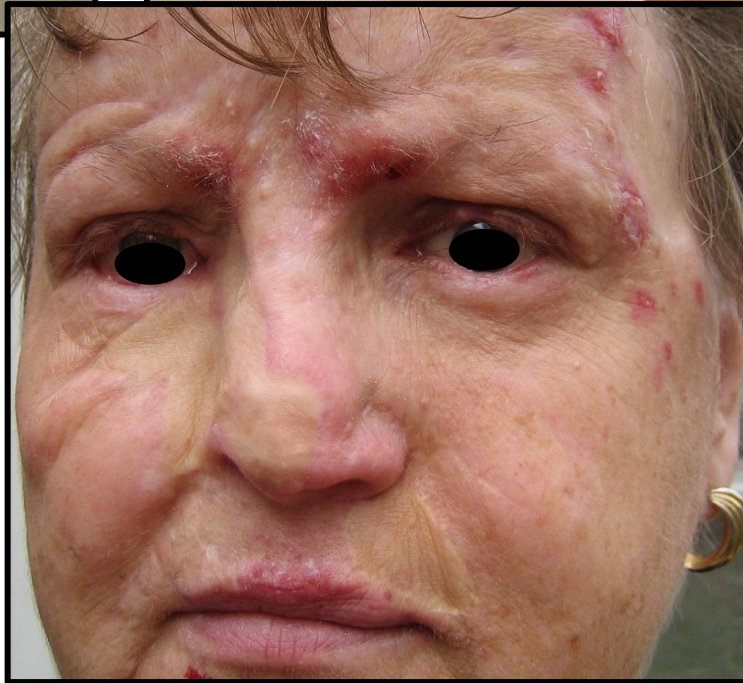
18 Months Later: *Recurrence* + 2 more OKCs



BEWARE:
Some may find images
on the next three slides to be
disturbing.

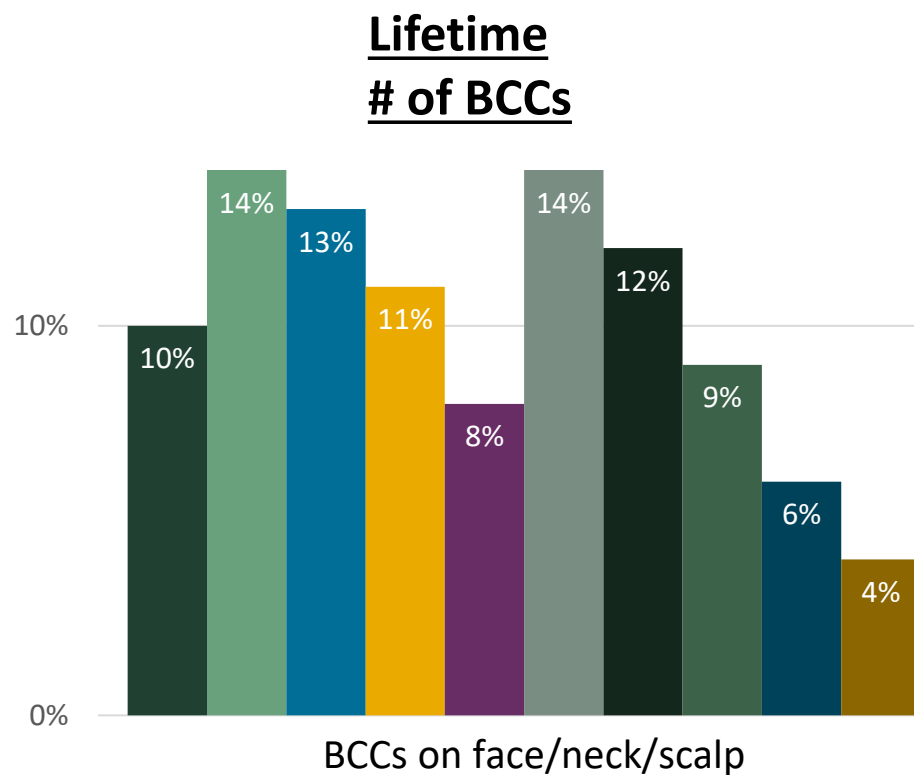




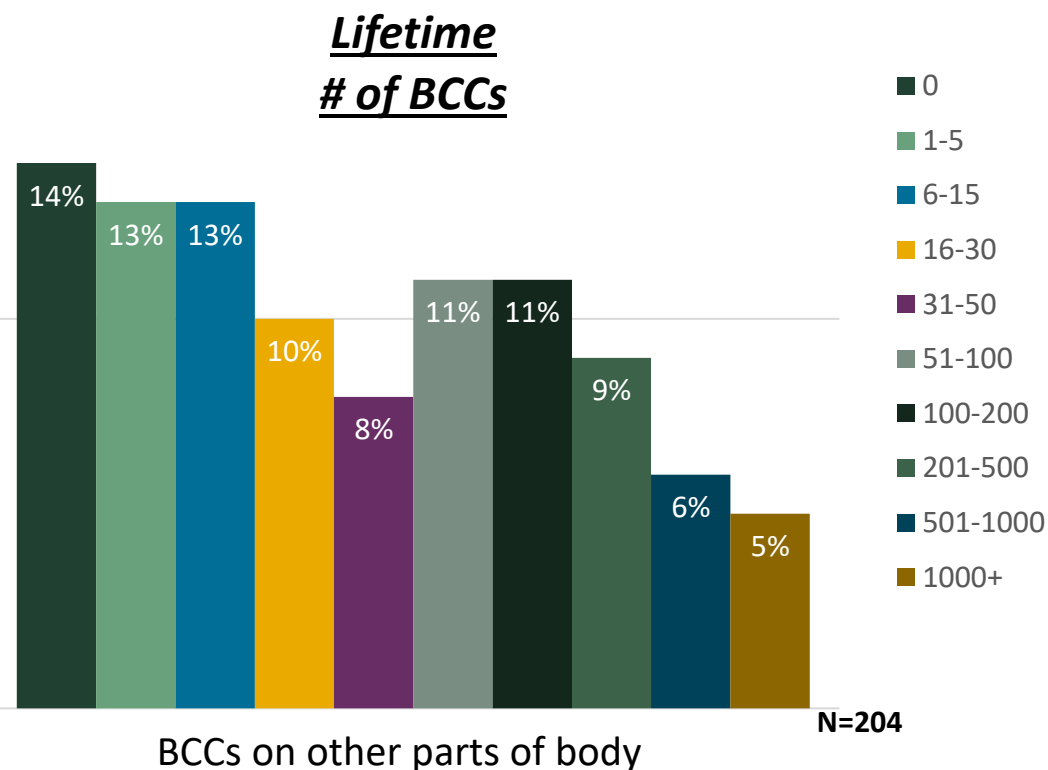




BCCs on face / neck / scalp:
45% of respondents >50 BCCs



BCCs on other parts of their body
42% respondents > 50,
5% had OVER 1,000



Gorlin Syndrome Alliance. *Patient Impact Report*. Unpublished report; 2021.
Available upon request from the Gorlin Syndrome Alliance (gorlinsyndrome.org).

CURRENT TREATMENT OPTIONS:

Surgical: *All cause pain, permanent scarring and disfigurement.*

Topical: *May cause pain, scabbing, scarring, treatment course lasts weeks.*

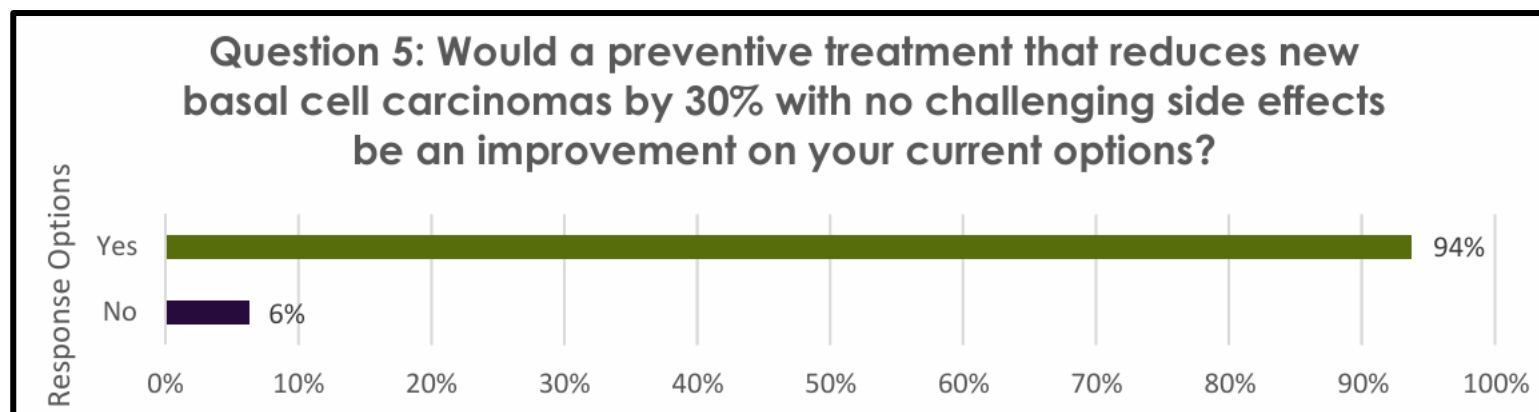
Oral: *Significant side effects (hair loss, muscle cramps,...) may lead to early termination.
BCCs return after medication stopped.*

Immunotherapy: *Side effects of currently available immunotherapy can be permanent and life threatening.*

Time lost from work / school / life activities for appointments, procedures, and recovery is
24.8 days annually.

The Gorlin Syndrome Alliance has surveyed our member community three times over the last five years.

Externally Led Patient Focused Drug Development Meeting for the FDA in 2021, patient audience response question:



A patient preferred and clinically meaningful reduction of the volume of BCCs by 30% is highly desired.

Gorlin Syndrome Alliance. *Voice of the Patient Report: Living with Gorlin Syndrome*. Gorlin Syndrome Alliance; 2022:46.
<https://gorlinsyndrome.org/hubfs/VOP%20WEBSITE.pdf>

We desperately need something that slows / interrupts the *constant* tide of BCC development and reduces the size of those present.

We will *never* be cancer survivors. We live with it every day.
We are considered **NEVER** cancer free and **NEVER** in remission.
“We can never ring the bell” indicating our treatments are done.



THANK YOU
for helping us to keep
scars
OFF
these smiling faces.



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jbreneiser@gorlinsyndrome.org

Ervin Epstein

Research Dermatologist/Cin Prof Dermatology UCSF (ret)
Sr Scientist Children's Hospital Oakland Res Inst (ret)
Co-Founder and Consultant (PellePharm)/Consultant (SGT)

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SOL-Gel Technologies NYC October 14, 2026

My Topic

Overall: The story of Hedgehog signaling and HH Inhibitors vs. BCCs

Specifically:

BCCs are driven by Excess Hedgehog Signaling

PTCH1-mutant BCCs are Susceptible to SMO-Binding Hedgehog
Inhibitors (e.g. Patidegib gel)

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Hedgehog signaling and HH Inhibitors vs. BCCs

1. How did we get from Gorlin syndrome to Hedgehog Signaling as the Driver of all BCCs??
 - i. 1960: Robert Gorlin DDS The Gorlin Syndrome - Phenotype: Basal Cell Carcinomas (NEJM)
 - ii. 1980: Nüsslein-Volhard/Wieschaus Fruit fly mutagenesis → Hedgehog phenotype (Nature → Nobel P)
 - iii. 1996: Global village: PTCH1 mutation → GS and Excess HH pathway signaling → "all" BCCs (Cell & Science)
2. What IS a Signaling pathway?

A: It's the "nervous system of the cell: Monitors the cell's environment →
Informs the cells' brain (aka nucleus) →
Behavioral Change
3. What specifically is the Hedgehog signaling pathway?

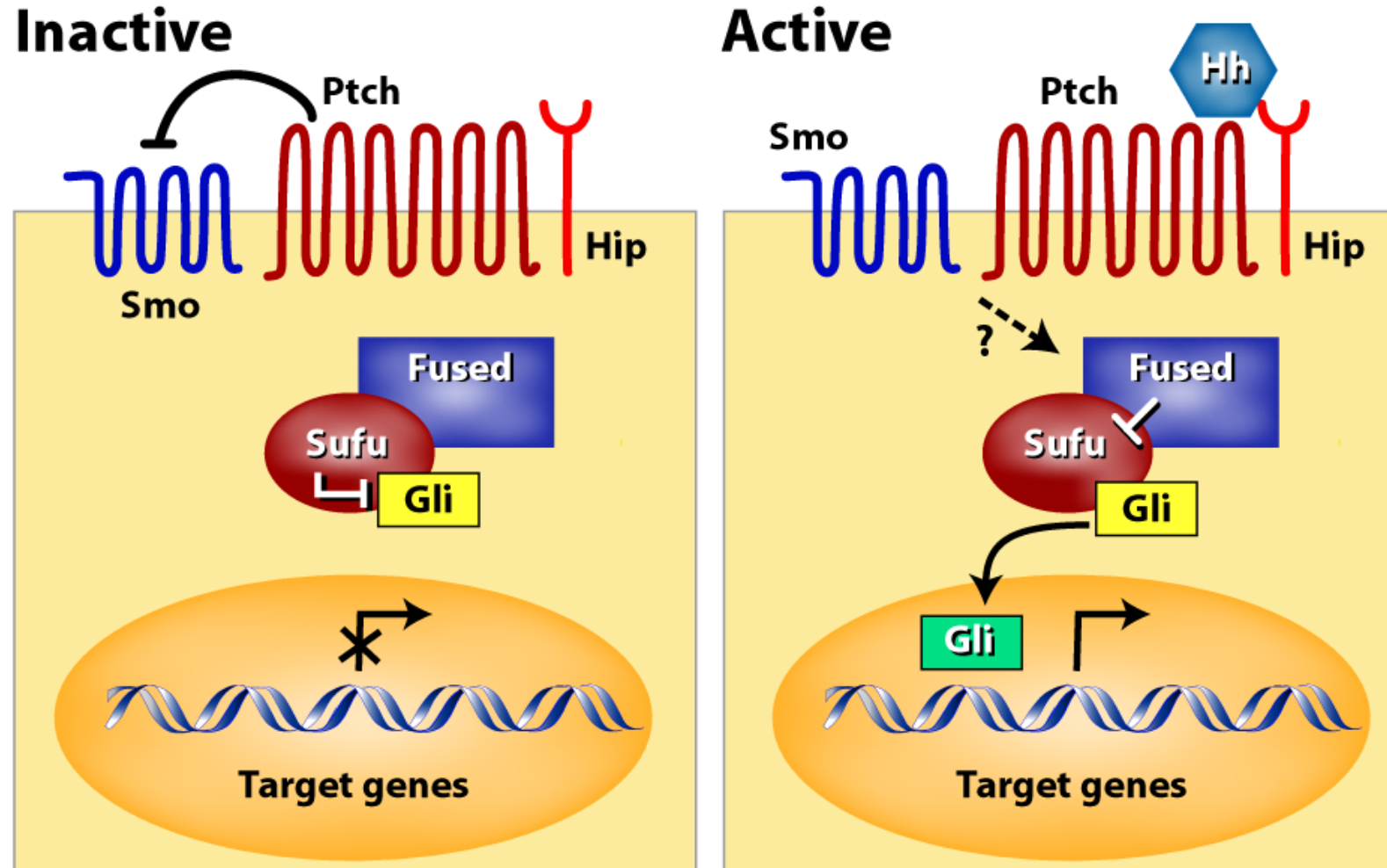
A: It is one of the crucial pathways by which one fertilized cell (Miracle!) → Multi-cellular newborn

Molecularly:

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Hedgehog Signaling Pathway

Hedgehog signalling pathway. In the absence of ligand, the HH signalling pathway is inactive (left). In this case, the transmembrane protein receptor Patched (PTCH1) inhibits the activity of Smoothed (SMO)

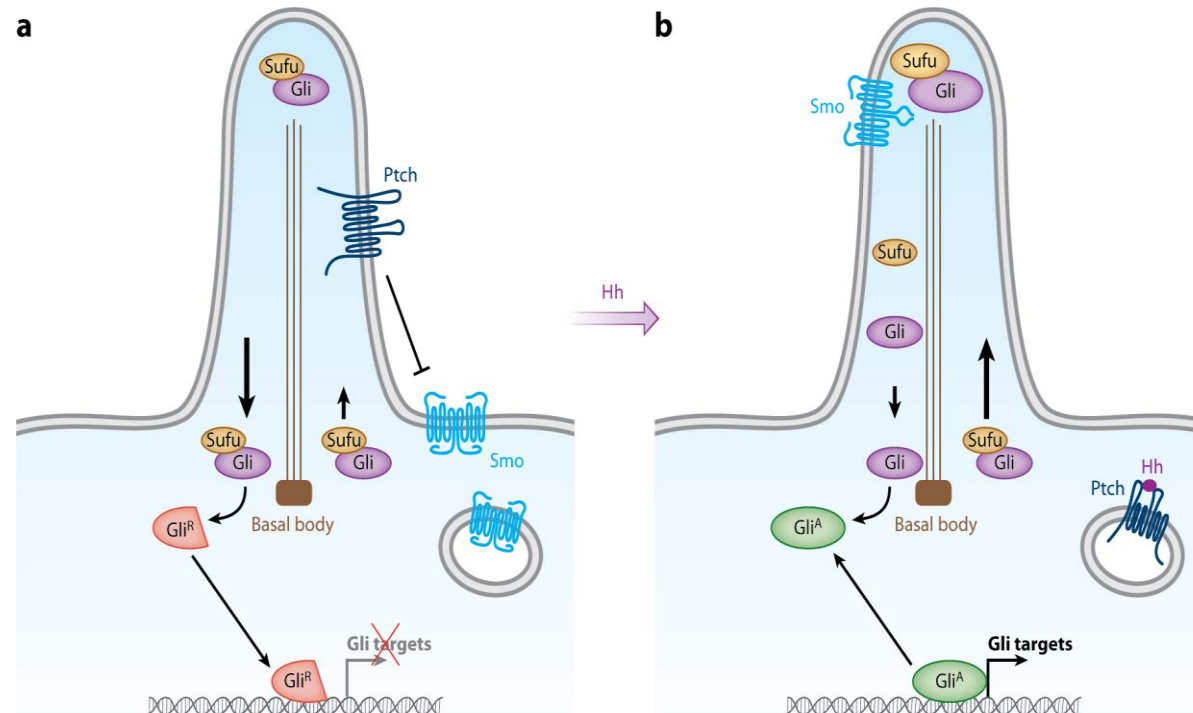


Nature Reviews Cancer volume 3, pages903–911 (2003)

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Hedgehog Signaling Pathway

Organization and Function of Hedgehog Signaling Complexes



Hui C-c, Angers S. 2011.
Annu Rev. Cell Dev. Biol. 27:513–37

In the absence of HH, (PTCH1) localizes to and prevents (SMO) from entering primary cilia.

HH signaling leads to the accumulation of SMO and increases the translocation of SUFU-Gli complexes to the tip of the primary cilium

BCCs are driven by Excess Hedgehog Signaling

- (i) **Familial linkage analysis: 1996 Global Village identified PTCH1 as the gene whose mutations underly Gorlin syndrome (H Hahn Cell; R Johnson Science)**
USA/EU: 85% of clinically-diagnosed GS pts have detectable PTCH1 mutation in histologically Normal tissue; <5% have SUFU mutation; 10% Unknown
- (ii) Engineered mutations in Hedgehog pathway genes (SHH, PTCH1, SMO) -> BCCs in mice
- (iii) Hedgehog signaling (assessed by *mRNA* encoding the Hedgehog target genes PTCH1, GLI1) is up-regulated in “all” human BCCs
- (iv) ORAL HH-inhibiting/SMO-binding drugs strongly inhibit BCC formation (prevention/interception) and shrink existing BCCs (treatment) in mouse and human skin

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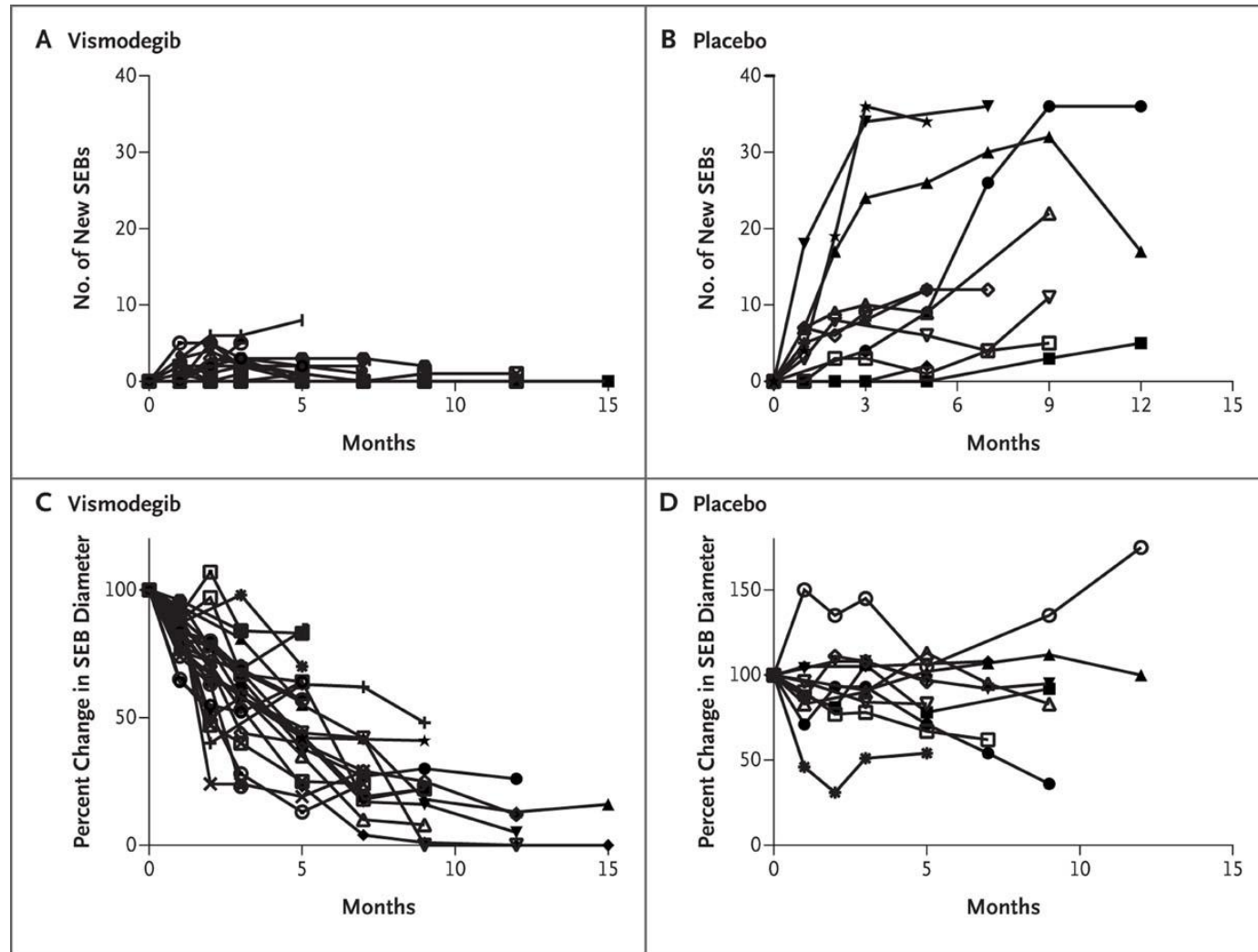
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Oral HH Inhibitor vs. Gorlin Patient BCCs



Prevent Appearance

Shrink Existing BCCs

New Eng J Med 2012

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- (iv) **ORAL HH-inhibiting/SMO-binding drugs strongly inhibit BCC formation (prevention/interception) and shrink existing BCCs (treatment) in mouse and human skin**

But – Why did we think that small molecules could inhibit Hedgehog signaling?

Small Molecules Can INHIBIT HH Signaling

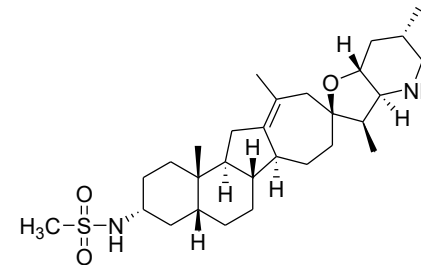
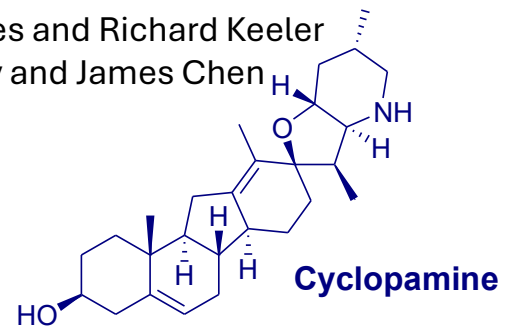


California Corn Lily
Veratrum californicum



1960's: Lynn James and Richard Keeler

1996: Phil Beachy and James Chen



Phase 2 trials:

- BCNS patients:
NCT02762084
- Nodular, sporadic BCC:
NCT02828111

SOL-Gel Technologies NYC October 14, 2026





The Cyclops

Polyphemus

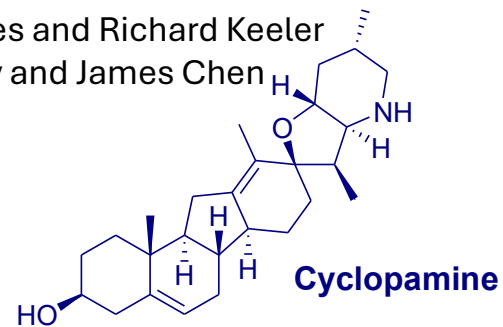
Small Molecules Can INHIBIT HH Signaling



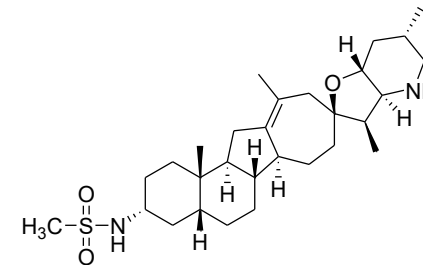
California Corn Lily
Veratrum californicum



1960's: Lynn James and Richard Keeler
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Cyclopamine



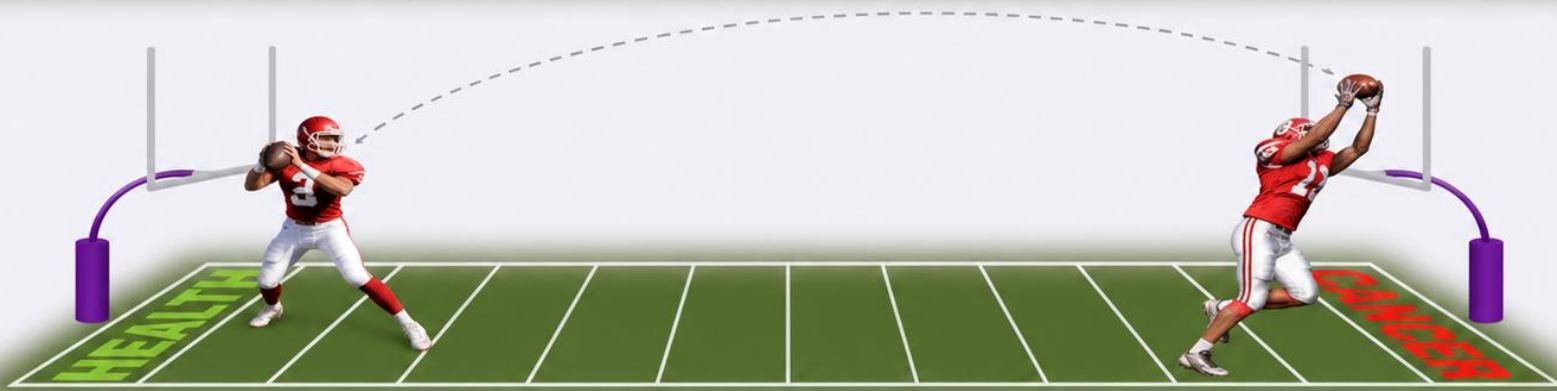
Patidegib

Phase 2 trials:

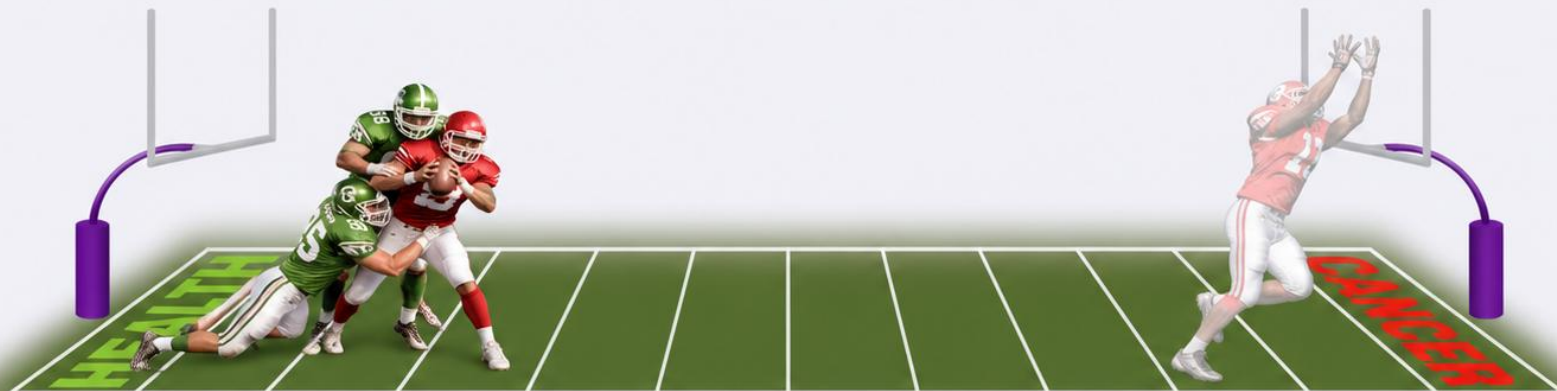
- BCNS patients:
NCT02762084
- Nodular, sporadic BCC:
NCT02828111

Reducing the BURDEN of BCCs

SOL-Gel Technologies NYC October 14, 2026



Normal Skin ->
 HH Up-Regulation ->
 Clonal Growth ->
BCCs



Prevention
 Achieving Skin Normality
 e.g. with Gene Therapy ->
NO BCCs



Interception:
 Stopping Clonal Growth Before it is
 Clinically Evident with Patidegib ->
NO BCCs

BCCs are driven by Excess Hedgehog Signaling

- (i) Familial linkage analysis: 1996 Global Village identified PTCH1 as the gene whose mutations underly Gorlin syndrome (H Hahn cell; R Johnson science)
USA: 85% of clinically-diagnosed GS pts have detectable PTCH1 mutation in histologically Normal tissue, <5% have SUFU mutation; 10% Unknown
- (ii) Engineered mutations in Hedgehog pathway genes (SHH, PTCH1, SMO) -> BCCs in mice
- (iii) Hedgehog signaling (assessed by *mRNA* encoding the Hedgehog target genes PTCH1, GLI1) is up-regulated in “all” human BCCs
- (iv) ORAL HH-inhibiting/SMO-binding drugs strongly inhibit BCC formation (prevention/interception) and shrink existing BCCs (treatment) in mouse and human skin,
Especially in PTCH1 mutant Patients with Gorlin Syndrome

And if it works so well Orally, “SURELY” it will do the same Topically!

Gorlin Syndrome Diagnosis and Management

Kavita Y. Sarin, MD, PhD

Director Skin Cancer Genetics Program, Stanford Cancer Institute

Department of Dermatology, Stanford University School of
Medicine

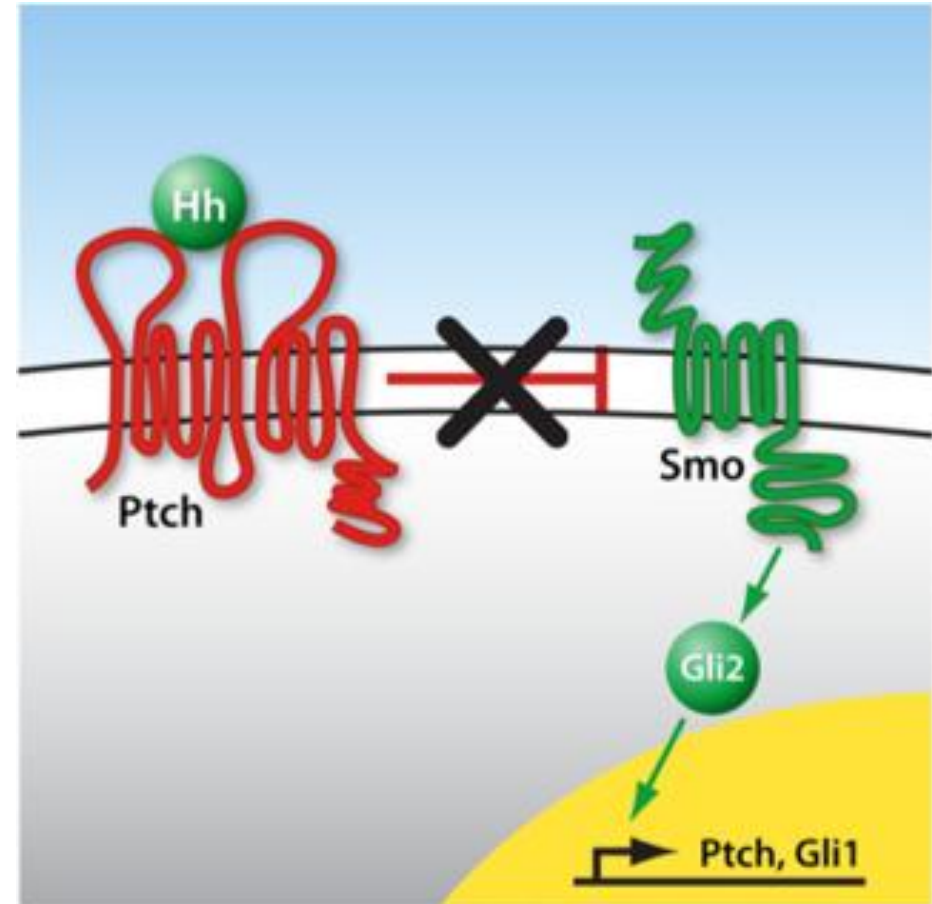
Sol-Gel investigator meeting October 2026



All clinical photographs are of my own patients, used with permission.

Gorlin syndrome: a genetic tumor predisposition syndrome

- Autosomal dominant tumor predisposition syndrome
- Estimated prevalence 1:31,000 to 1:256,000; 20–40% of cases are de novo.
- Tumors appear on sun-exposed and sun-protected skin, span every histologic subtype, are frequently pigmented, and start young.
- 51% of patients have their first BCC by age 20 and 72% by age 40. Some patients make more than 100 in a lifetime.
- PTCH1 variant is found in 85% of clinically diagnosed patients; SUFU accounts for approximately 5%.



Diagnostic clinical criteria: In practice

Diagnosis is established by 2 major criteria, or by 1 major + 2 minor criteria, or by 1 major criterion plus a pathogenic germline variant.

Major criteria	Minor criteria
BCC before age 20, or multiple BCCs	Rib anomalies — bifid, fused or splayed
Odontogenic keratocyst of the jaw before age 20	Macrocephaly
Palmar or plantar pitting	Cleft lip or palate
Lamellar calcification of the falx cerebri	Ovarian or cardiac fibroma
Medulloblastoma, desmoplastic variant	Lymphomesenteric cysts
First-degree relative with the syndrome	Ocular abnormalities — strabismus, coloboma, hypertelorism, cataract, glaucoma
	Vertebral anomalies, kyphoscoliosis, short 4th metacarpal, polydactyly

Despite the clinical criteria, I do not generally order radiographs for diagnostic purposes

This is a patient with a germline tumor-suppressor defect and can be radiosensitive; if the result will not change management, and the diagnosis can be confirmed on blood, I skip the film.

New Presentation of Gorlin Syndrome



Small pigmented papules, face



Shoulder — sun-protected skin

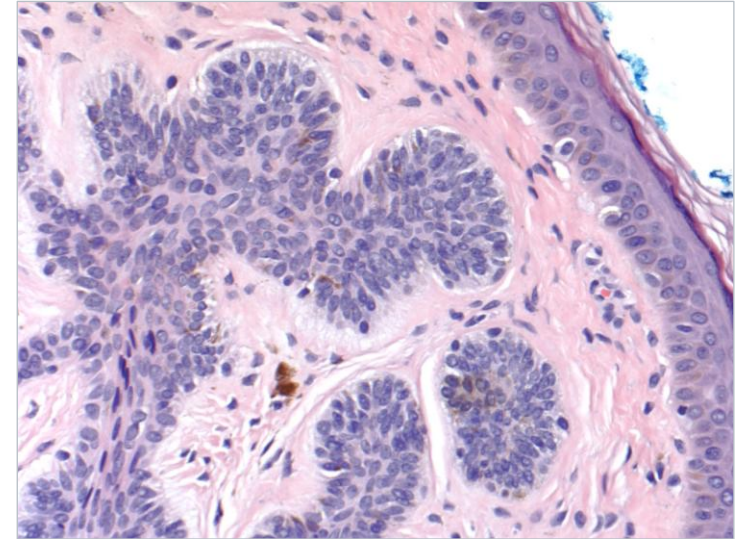


Plantar pits

Confirming the diagnosis



Panoramic radiograph: odontogenic keratocyst, right mandible



Biopsy: basaloid nests, peripheral palisading, stromal retraction

- Odontogenic keratocyst on the panorex — a second major criterion. Oral surgeons and orthodontists often see these years before dermatology does.
- Two major criteria met, so the clinical diagnosis was established. I still sent germline testing.

Genetic testing

Who I test

- Any BCC before age 20, or multiple BCCs before roughly age 40
- BCCs arising on sun-protected skin
- Multiple BCCs plus pits, jaw cysts, macrocephaly, falx calcification, ovarian or cardiac fibroma, or medulloblastoma
- A first-degree relative with the syndrome
- A history written as “recurrent BCC” that is really a series of numerous primary tumors

How I sequence the testing

- 1 PTCH1 and SUFU first — 85% of clinically diagnosed patients
- 2 Negative → sequence DNA from at least two separate BCCs for PTCH1 and SMO to look for postzygotic mosaicism

Why the gene matters:

Jaw surveillance

PTCH1: orthopantomogram every 2 years from age 8, annually after the first cyst, through about age 22. SUFU: no routine jaw screening.

Medulloblastoma

SUFU carries roughly 20 times the PTCH1 risk. SUFU or an unconfirmed clinical diagnosis in a child: baseline brain MRI, then every 4 months to age 3 and twice yearly to age 5.

The family

Autosomal dominant with 50% transmission. Cascade testing for parents, siblings and children, and it opens the door to prenatal testing and preimplantation diagnosis.

Therapeutic expectation

SMO inhibitors act upstream of SUFU. A SUFU-driven patient may not have the same response as a PTCH1 mutation for SMO inhibitors

Monitoring Gorlin

- Full skin examination every 3 to 6 months with discussion of photoprotection
- Total body photography and lesion mapping with numbered lesions
- Triage rather than treat-everything.
- The 2026 guideline severity assessment: number, size, growth rate, rate of new lesions, aggressive histology, functional impairment, disfigurement, and psychosocial impact.

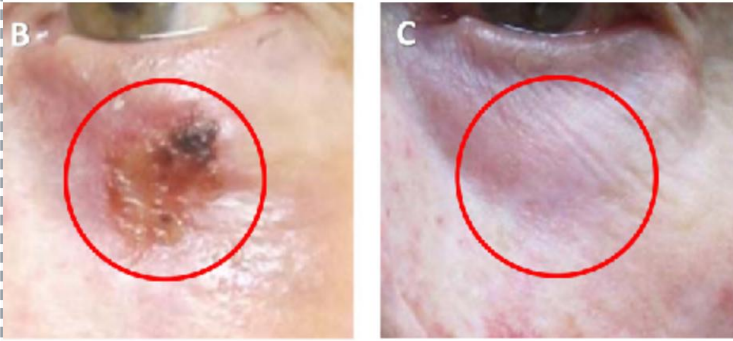


Every lesion measured and photographed at each visit, so change is documented rather than remembered

Imiquimod, 5-fluorouracil, and photodynamic therapy

Imiquimod 5%

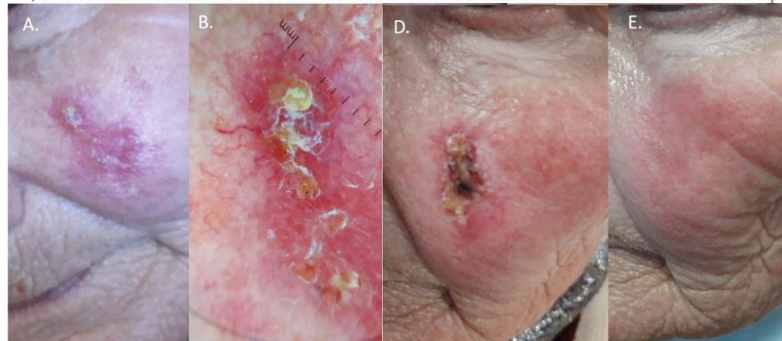
- 5 nights per week for 6 weeks for a biopsy-proven superficial BCC.
- Inflammatory reaction



Nahm, William J. et al. *Journal of drugs in dermatology : JDD* 20 3 (2021): 260-267 .

5-fluorouracil 5%

- Twice daily for 4 weeks.
- Easier to tolerate across a large field
- Irritating and turns skin red and crusty



Németh, C et al. Topical Fluorouracil Therapy for Basal Cell Carcinoma. In *Skin Cancer - Past, Present and Future*. IntechOpen2024

Photodynamic therapy

- Single treatment with 5-ALA
- 16 minutes under a blue light to activate treatment (painful)

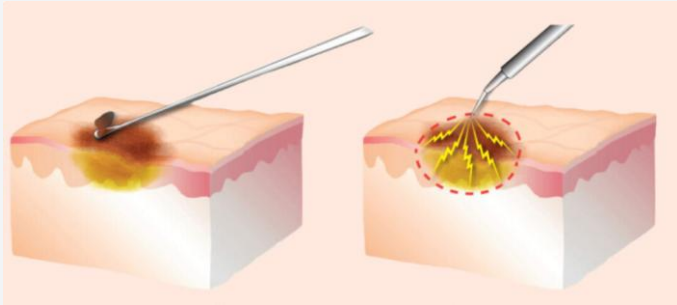


<https://www.sipderm.com/services/blue-light/>

- 5-year tumor-free survival in superficial BCC: 80.5% imiquimod, 70.0% 5-FU, 56.8% PDT (601-patient randomized trial)
- Biopsy-confirmed superficial tumors, trunk and extremities, and field treatment in the interval between surgical visits.
- Not for nodular, infiltrative or morpheaform tumors, not for recurrent tumors, and not on the central face.
- The purpose is to reduce the number of procedures and the cumulative scar

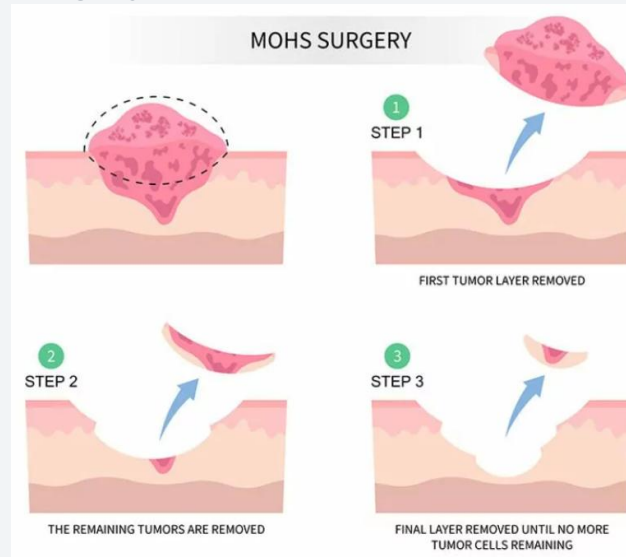
Procedural therapies for BCC

Electrodesiccation and curettage



- No sutures and no return visit for suture removal.
- Avoid the face, over terminal-hair-bearing scalp, and for recurrent or aggressive-histology tumors. The trade is a hypopigmented, atrophic scar, and these accumulate.

Excision and Mohs micrographic surgery



- High-risk anatomy (nose, periocular, ear, lip) aggressive histologic subtypes, and recurrent tumors.

Radiation therapy

- Relatively contraindicated. Irradiated skin in a patient with a germline PTCH1 defect develops dense fields of new BCCs within the treatment port.
- Absolutely contraindicated in children with Gorlin syndrome.
- Reserved for genuinely limited salvage or palliative situations

The role of oral hedgehog inhibitors

March 2022 · baseline



September 2022 · 6 months



July 2023 · 16 months



Oral hedgehog inhibitors have high efficacy

High Efficacy

2 vs **29**

new surgically eligible BCCs per patient-year on vismodegib versus placebo, in the randomized trial of 41 patients with the syndrome

- Existing tumors shrank substantially — but most surgically eligible BCCs regrew once the drug was stopped.
- In MIKIE (n=229), intermittent regimens reduced the number of clinically evident BCCs by 54–63% at week 73; intermittent dosing appears comparable in efficacy to continuous dosing.

Poor tolerability with continuous dosing

54%

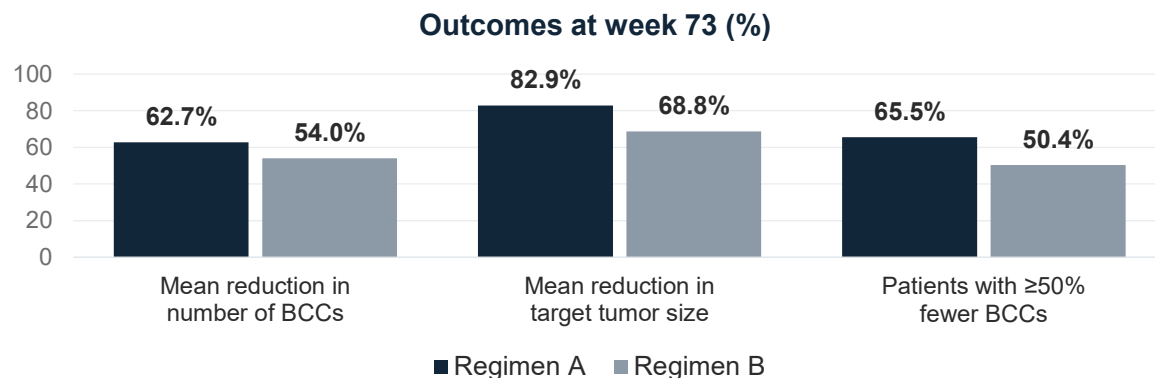
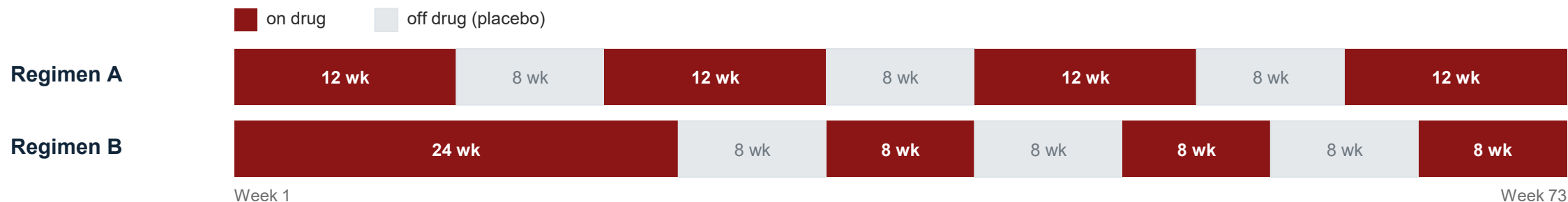
of patients discontinued vismodegib because of adverse events in that same prevention trial

- Muscle cramps and spasms, dysgeusia and loss of taste, alopecia, weight loss, fatigue, amenorrhea.
- Teratogenic — strict contraception required, which is a difficult conversation in a young, often reproductive-age population.
- Premature epiphyseal fusion rules out chronic use in growing children, the group with the longest disease ahead of them.

These are cumulative, non-life-threatening toxicities in patients who are not treating a lethal cancer. In practice, for Gorlin syndrome I use oral SMO inhibitors on intermittent schedules (3 weeks on / 3 weeks off) to reduce toxicity.

Intermittent dosing of hedgehog inhibitors: the MIKIE trial

Randomized, double-blind, regimen-controlled phase 2 trial · 229 patients, 52 centers, 10 countries · 85 with Gorlin syndrome · both arms received identical total drug exposure (48 weeks of drug, 24 of placebo)



Stopped treatment because of side effects

23%

MIKIE, pulsed dosing

54%

continuous daily dosing, Gorlin patients

But the toxicity is still there: 95% of patients had a drug-related side effect and 47% stopped for some reason. Muscle cramps 70%, loss of taste 65%, hair loss 64%.

Overview of the current state of the art

Surveillance and photography	Every patient, indefinitely	<i>Detects; does not prevent</i>
Topical 5-FU, imiquimod, PDT	Biopsy-proven superficial tumors, field disease	<i>Lesion-directed; weeks of local reaction</i>
Electrodesiccation and curettage	Low-risk nodular and superficial tumors, high volume	<i>Leaves a scar each time; scars accumulate</i>
Excision and Mohs surgery	High-risk sites and histology	<i>Definitive, but the most tissue and morbidity</i>
Oral hedgehog inhibitors	Intermittent dosing	<i>Systemic toxicity; discontinuation; not for children</i>
The gap	A tolerable therapy that lowers the rate of new tumors	<i>Nothing currently fills this</i>

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Professor of Dermatology
Penn State University College of Medicine
Penn State Health

Disclosure

Clinical Investigator/Principal Investigator

Regeneron Pharmaceuticals

Sol Gel Technologies

Consultant

Inhibitor Therapeutics

Phio Pharmaceuticals

Gorlin Syndrome -

- Tens to Hundreds of Basal Cell Carcinomas
- Lifelong condition with continual need for more treatment
- Numerous surgeries can lead to significant disfigurement
- Patients often give up/surgical fatigue leading to neglect and eventually larger more invasive procedures







Gorlin Syndrome Management

- Goal – prevent BCC development, growth, and need for surgery
- Topical treatments
- Oral medications
- Photodynamic therapy
- Surgery – gold standard
- Sun Prevention and Education
- Support

Gorlin Syndrome – Surgical Approach

Curettage (+/- electrodesiccation)

Excision

Mohs Surgery

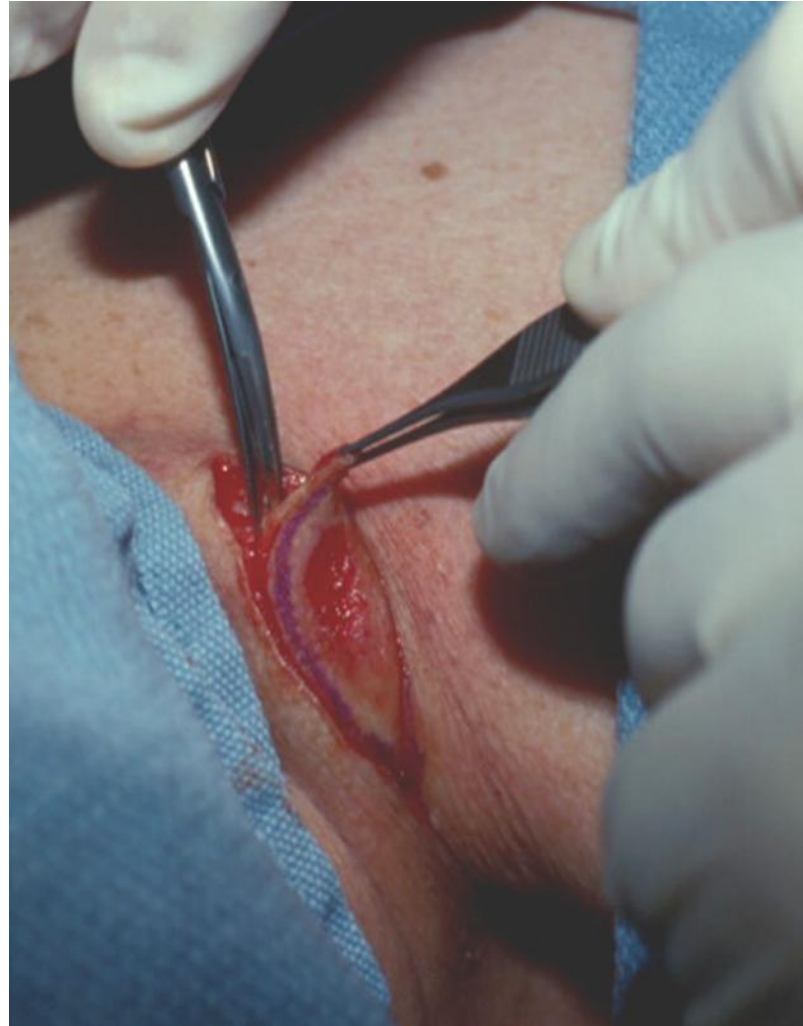
Curettage







Surgical Excision





Mohs Micrographic Surgery

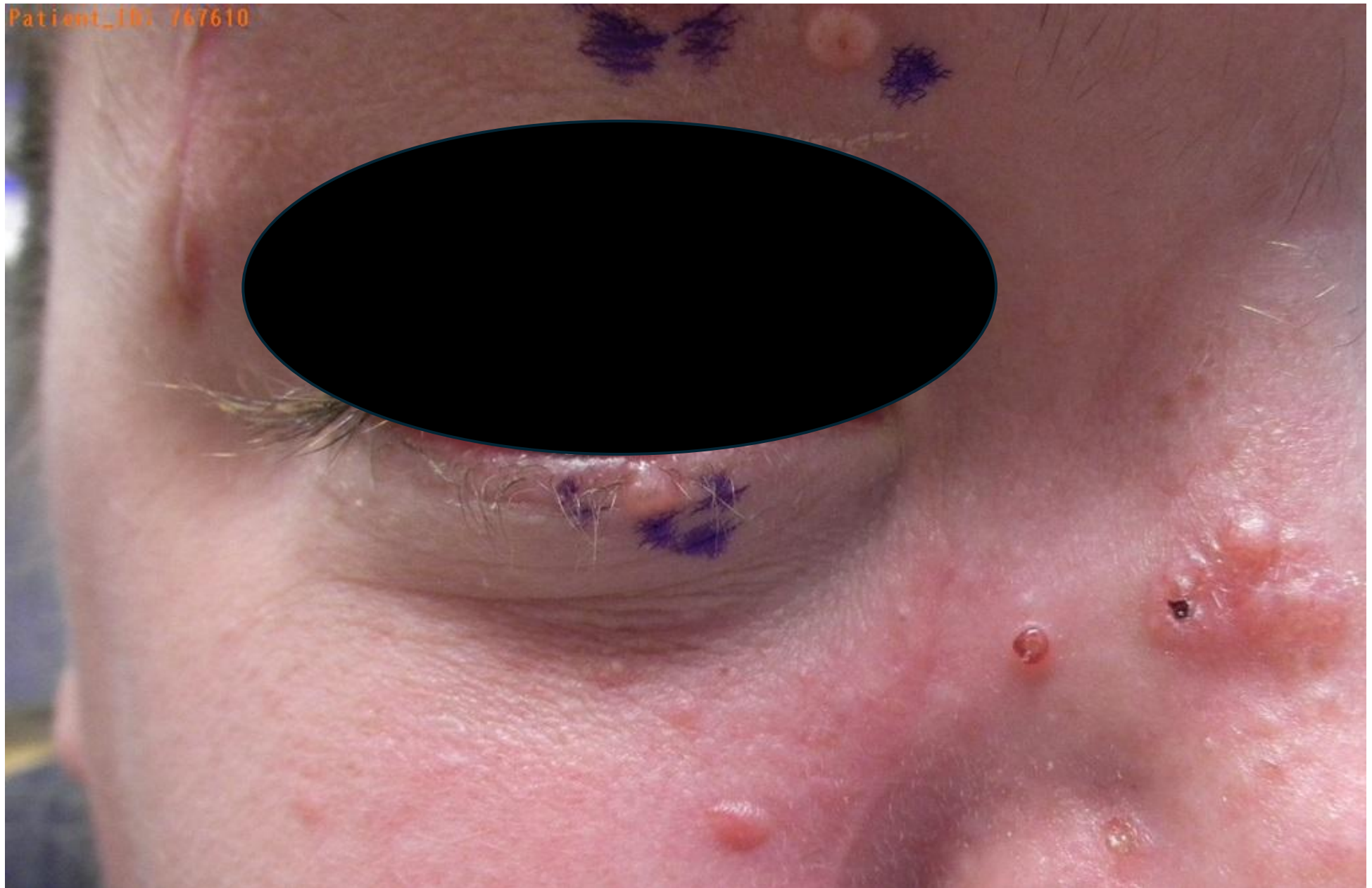
- Excision technique with frozen section analysis of surgical margins
- Allows 100% margin assessment
- Higher cure rate and tissue sparing
- Indications – recurrent lesions, tumors where tissue conservation is critical – eyelid, nose, lip, ear, etc, aggressive histology, Gorlin patients
- Time consuming - hours

Tissue Conservation





Patient_ID: 767610



Gorlin Syndrome – Surgeon's perspective

- Decrease the number and extent/size of surgeries
- Smaller lesions require less extensive surgeries
- Patients have different goals
- Team approach

Meaningful efficacy outcome

- Prevention of new lesions
 - Cure of small lesions
 - Reduction in size of larger lesions
-
- Fewer surgeries per patient
 - Fewer scars, smaller scars
 - Optimism and motivation for patients
-
- Decreasing the number of surgeries a patient needs by 30% would have significant impact in the management/care of a Gorlin individual

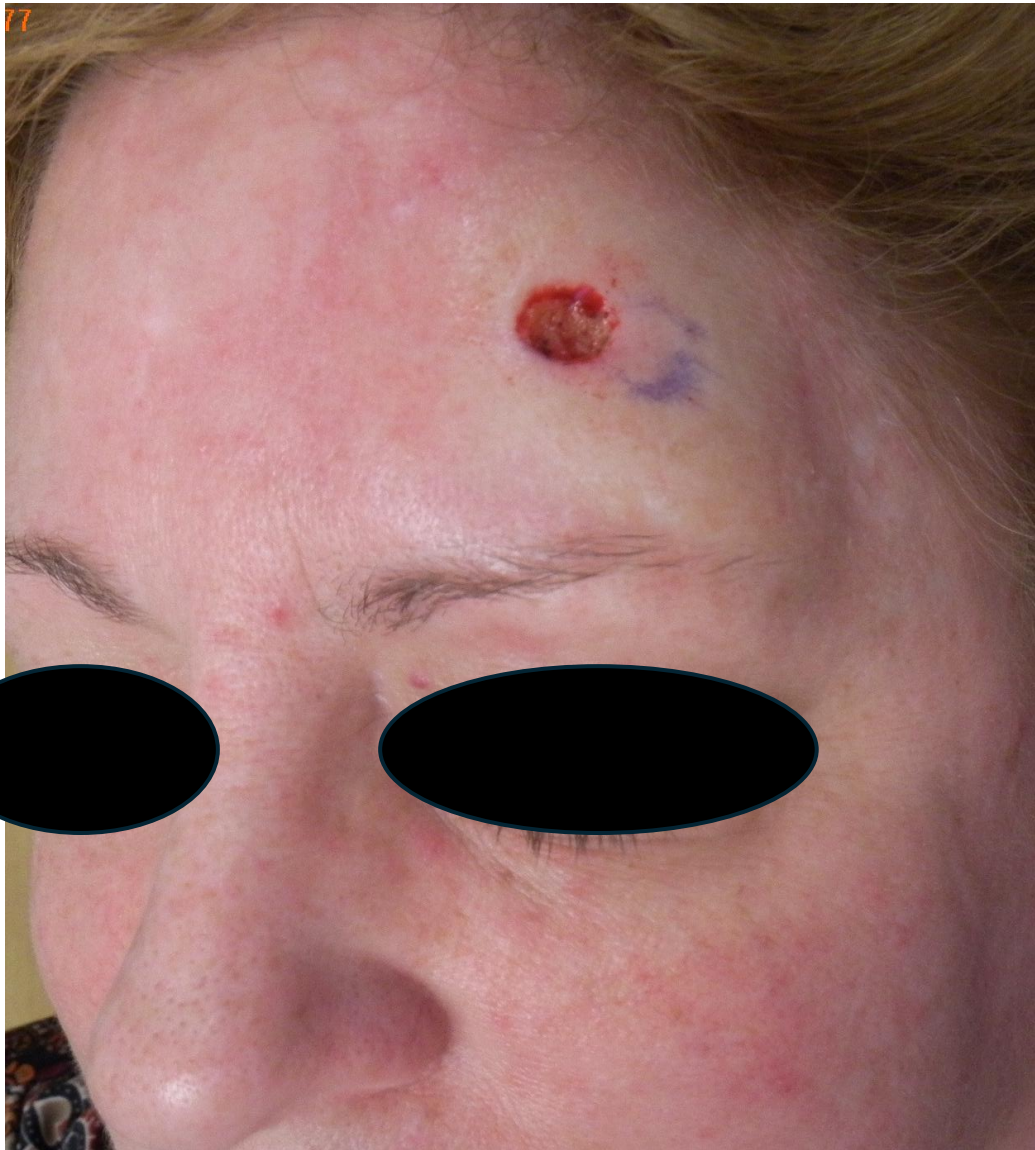


Surgeon's point of view

- Sometimes so numerous, many small lesions can run into each other – creating large defects
- Some tumors will not respond to this – some require surgery
- If can prevent small lesions/ shrink some lesions/ or cure some lesions – More normal skin preservation
- Allows easier reconstruction and less deformity
- Fewer surgeries and more options helps maintain the critical patient doctor relationship needed to help these patients keep the stamina needed to keep the disease in control

Why is this treatment important?

- One more option to decrease the number of surgeries, number of scars
- Easy and well-tolerated – patient motivation
- Builds into regimen of awareness and increased efforts
- Prevention, size reduction, and slowing progression are all meaningful outcomes









Gorlin Syndrome Management and Care

Optimize quality of life

Prevent need for so many surgeries

Decrease scarring and disfigurement

Multiple treatment options are needed to have long lasting impact

Panel Discussion



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Question and Answer Session



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